Verbdg.-Nr.	Niedrigste Dosis (mg/kg)
3	23,3 (n=3)
4	1,7 (n=3)
5	2,3 (n=3)
6	16,7 (n=3)
10	0,2 (n = 3)
12	30,0 (n=3)
13	20,0 (n=2)
14	20,0 (n=2)

Tabelle 3; (n entspricht der Anzahl der in den Wert eingegangenen Versuche)

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz.

Es wurden mit anderen Verbindungen weitere Versuche unternommen.

Bei allen hier aufgelisteten Substanzen war eine Unterdrückung der Spontankontraktionen in den Ratten meßbar, wobei Tabelle 4 den Mittelwert der niedrigsten Dosis aus mindestens 2 Versuchen angibt, bei der erstmals Kontraktionen über einen Zeitraum von 10 min ausbleiben.

Tabelle 4:

Verbdg.-Nr.	Niedrigste Dosis (mg/kg)
27	115 (n=2)
28	16,7 (n=3)
29	23,3 (n=3)

Tabelle 4: (n entspricht der Anzahl der in den Wert eingegangenen Versuche)

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz.

Es wurden mit anderen Verbindungen weitere Versuche unternommen.

Bei allen hier aufgelisteten Substanzen war eine Unterdrückung der Spontankontraktionen in den Ratten meßbar, wobei Tabelle 5 den Mittelwert der niedrigsten Dosis aus mindestens 2 Versuchen angibt, bei der erstmals Kontraktionen über einen Zeitraum von 10 min ausbleiben.

Verbdg.-Nr.	Niedrigste Dosis (mg/kg)
18	0,2 (n=3)
19	0,1 (n=3)
20	0,5 (n=3)
23 (Tramadol)	5,3 (n=3)

Tabelle 5:(n entspricht der Anzahl der in den Wert eingegangenen Versuche)

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz und erscheinen darin auch gegenüber Tramadol überlegen.

Außerdem wurden die folgenden Substanzen mit dem in der Tabelle 6 dargestellten Ergebnis getestet:
Bei allen aufgelisteten Substanzen war eine Unterdrückung der Spontankontraktionen in den Ratten meßbar, wobei die Tabelle 6 den Mittelwert der niedrigsten Dosis aus 3 unabhängigen Experimenten angibt, bei der erstmals Kontraktionen über einen Zeitraum von 10 min ausbleiben.

Tabelle 6:

Verbindung	Niedrigste Dosis (mg/kg)
Tilidin	0,5 (n=3)

Meptazinol	1,0 (n=3)
Codein(Phosphat)	4,7 (n=3)

Tabelle 6; (n entspricht der Anzahl der in den Wert eingegangenen Versuche)

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz.

Beispiel 4: Testsystem Cystometrie an der wachen naiven Ratte

Es wurden cystometrische Untersuchungen an naiven, weiblichen Sprague-Dawley-Ratten nach der Methode von Ishizuka et. al. ((1997), Naunyn-Schmiedeberg's Arch. Pharmacol. 355: 787 – 793) durchgeführt. Drei Tage nach Implantation von Blasen- und venösen Kathetern wurden die Tiere im wachen Zustand, frei beweglich untersucht. Der Blasenkatheter wurde an einem Druckaufnehmer und eine Injektionspumpe angeschlossen. Die Tiere wurden in Stoffwechselkäfige gesetzt, die die Messung des Harnvolumens ermöglichten. Physiologische Kochsalzlösung wurde in die entleerte Blase infundiert (10 ml/Std.) und Blasendruck und Miktionsvolumen kontinuierlich aufgezeichnet. Nach einer Stabilisierungsphase wurde eine 20minütige Phase aufgezeichnet, die durch normale, reproduzierbare Miktionszyklen gekennzeichnet war. Es wurden unter anderem die folgenden Parameter bestimmt:

- Schwellendruck (threshold pressure TP, Blasendruck unmittelbar vor Miktion),
- Blasenkapazität (bladder capacity BC, Restvolumen nach vorhergehender Miktion plus Volumen der infudierten Lösung während der Füllungsphase),
- Interkontraktionsintervall (inter-contraction interval (ICI), das Zeitintervall zwischen den Miktionen).

Eine Erhöhung des Schwellendrucks (TP) zeigt eine wichtige therapeutische Wirkung bei einer der erfindungsgemässen Indikationen an. Auch das Interkontraktionsintervall (ICI) ist ein wichtiger Parameter zur Messung der physiologischen Wirksamkeit eines Stoffes in der Behandlung der Harninkontinenz, ebenso wie die Blasenkapazität (BC). Dabei ist es für eine Wirksamkeit aufgrund der sehr heterogenen Ursachen für die Symptomatik dieser Erkrankungsbilder nicht nötig, alle drei Parameter positiv zu beeinflussen. Es genügt daher völlig, wenn nur in einem dieser Parameter eine posive Wirkung festzustellen ist, um in der Harninkontinenz, erhöhter Miktionsfrequenz oder vermehrtem Harndrang einsetzbar zu sein.

Nach der Aufzeichnung von drei reproduzierbaren Miktionszyklen als Vorwert wurden 10 µg/kg Buprenorphin im Vehikel = 0,9 % NaCl i.v. appliziert und die Wirkung auf die cystometrischen Parameter 90 bis 120 Minuten aufgezeichnet. Im Wirkmaximum wurde der Mittelwert von 3 Miktionszyklen bestimmt und als prozentuale Veränderung gegenüber dem Vorwert dargestellt (Tabelle 7).

Die eingesetzte Konzentration entspricht dem ED_{50} in einem bekannten Analgesiemodell für Ratten, dem Tail Flick.

Buprenorphin	**TP** threshold pressure	**BC** bladder capacity	**ICI** inter-contraction interval
0,01 mg/kg iv (n=6)	+69,9% **	+3,6%	+10,9%

Tabelle 7: Beeinflussung der cystometrischen Parameter durch Buprenorphin (Veränderung zum Vorwert [%]); n entspricht der Anzahl der im Versuch eingesetzten Tiere. Signifikanz (Student T-Test): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Buprenorphin zeigt gerade beim TP eine positive Wirkung auf die Blasenregulation und ist damit prinzipiell geeignet zur Behandlung der

Harninkontinenz. Allerdings war die eingesetzte Konzentration, die analgetisch wirksam ist, offenbar zu hoch, da bei 2 der 6 Tiere bereits Tropf-Inkontinenz auftrat. Bei zwei niedrigeren Konzentrationen, 0,001 mg/kg i.v. und 0,005 mg/kg i.v. trat bei n=6 eine Steigerung des TP von + 27,6 % bzw. + 37,5% auf.

Beispiel 5: Testsystem Cystometrie an der wachen geschädigten Ratte

Dieses Modell simuliert die Dranginkontinenz im Tiermodell; das eingesetzte Oxyhemoglobin (OxyHb) induziert eine Blasenüberaktivität.

Es wurden cystometrische Untersuchungen an naiven, weiblichen Sprague-Dawley-Ratten nach der Methode von Pandita et al. (J. Urol. 2000, 164:545-550) durchgeführt. Drei Tage nach Implantation von Blasen- und venösen Kathetern wurden die Tiere im wachen Zustand, frei beweglich untersucht. Der Blasenkatheter wurde an einem Druckaufnehmer und eine Injektionspumpe angeschlossen. Die Tiere wurden in Stoffwechselkäfige gesetzt, die die Messung des Harnvolumens ermöglichten. Physiologische Kochsalzlösung wurde in die entleerte Blase infundiert (10 ml/Std.) und Blasendruck und Miktionsvolumen kontinuierlich aufgezeichnet. Nach einer Stabilisierungsphase wurde eine 20minütige Phase aufgezeichnet, die durch normale, reproduzierbare Miktionszyklen gekennzeichnet war. Es wurden unter anderem die folgenden Parameter bestimmt:

- Schwellendruck (threshold pressure TP, Blasendruck unmittelbar vor Miktion),
- Blasenkapazität (bladder capacity BC, Restvolumen nach vorhergehender Miktion plus Volumen der infudierten Lösung während der Füllungsphase),

- Interkontraktionsintervall (inter-contraction interval (ICI), das Zeitintervall zwischen den Miktionen).
- Miktionsdruck (micturition pressure MP, maximaler Blasendruck während einer Miktion).

Eine Erhöhung des Schwellendrucks (TP) zeigt eine wichtige therapeutische Wirkung bei einer der erfindungsgemässen Indikationen an. Auch das Interkontraktionsintervall (ICI) ist ein wichtiger Parameter zur Messung der physiologischen Wirksamkeit eines Stoffes in der Behandlung der Harninkontinenz, ebenso wie die Blasenkapazität (BC). Dabei ist es für eine Wirksamkeit aufgrund der sehr heterogenen Ursachen für die Symptomatik dieser Erkrankungsbilder nicht nötig, alle Parameter positiv zu beeinflussen. Es genügt daher völlig, wenn nur in einem dieser Parameter eine positive Wirkung festzustellen ist, um in der Harninkontinenz, erhöhter Miktionsfrequenz oder vermehrtem Harndrang einsetzbar zu sein.

Nach der Aufzeichnung von drei reproduzierbaren Miktionszyklen als Vorwert wurden $2.5x10^{-4}$M Oxyhämoglobin im Vehikel = 0,9% NaCl in die Blase infundiert. Die Wirkung auf die cystometrischen Parameter wurden etwa 20 Minuten aufgezeichnet. Im Wirkmaximum wurde der Mittelwert von 3 Miktionszyklen bestimmt und als prozentuale Veränderung gegenüber dem Vorwert dargestellt (Tabelle 8). Die Behandlung mit Oxyhämoglobin induziert eine charakteristische Veränderung der cystometrischen Parameter mit einer Erhöhung des Miktionsdrucks, einer Erniedrigung der Blasenkapazität und einer Verringerung des Interkontraktionsintervals. Diese Veränderungen bilden die Veränderungen ab, die bei Patienten mit Dranginkontinenz gefunden werden.

Die Applikation von 5 µg/kg Buprenorphin im Vehikel = 0,9 % NaCl i.v. vor der Applikation von Oxyhämoglobin ist in der Lage die Veränderungen, die durch Oxyhämoglobin induziert werden, zu unterdrücken und darüber hinaus noch einen Anstieg des Schwellendrucks zu induzieren (Tabelle 8).

Tabelle 8:

	MP Micturition pressure [cm H_2O]	**TP** threshold pressure [cm H_2O]	**BC** bladder capacity [ml]	**ICI** inter-contraction interval [min]
OxyHb				
2,5x10^{-4}M iv (n=5)	v: 59 ± 8 h: 97 ± 5 Dif.:+64,4% **	v: 8,72 ± 1,31 h: 9,84 ± 1,56 Diff.: +12,8%	v: 0,92 ± 0,10 h: 0,65 ± 0,06 Diff.: -29,3% **	v: 4,96 ± 0,33 h: 3,33 ± 0,18 Diff.: -32,9% **
OxyHb + Buprenorphin				
OxyHb: 2,5x10^{-4}M Buprenorphin: 0,005 mg/kg iv (n=6)	v: 54 ± 9 h: 37 ± 8 Diff.: -31,5% *	v: 9,07 ± 1,29 h: 14,28± 2,53 Diff.: +57,4 % *	v: 1,19 ± 0,12 h: 1,17 ± 0,13 Diff.: -1,7 %	v: 6,72 ± 0,73 h: 6,70 ± 0,88 Diff.: -0,3 %

Tabelle 8: Beeinflussung der cystometrischen Parameter durch Oxyhämoglobin (OxyHb) mit und ohne vorherige Gabe von Buprenorphin. Angegeben sind Durchschnittswerte mit Standardabweichungen vor (v) und nach (h) Anwendung der Substanzen sowie die Veränderung (Diff.) im Vergleich zum Vorwert [%]; n entspricht der Anzahl der im Versuch eingesetzten Tiere. Signifikanz (Student T-Test): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Es ist zu erkennen, daß OxyHb die Blasenparameter deutlich im Sinne einer Dranginkontinenz negativ beeinflußt. Diese negative Beeinflußung wird durch Buprenorphin aufgehoben und sogar verbessert. So sinkt der Miktionsdruck im Vergleich zu der durch OxyHb ausgelösten Dranginkontinenz und auch im Vergleich zur unbehandelten Kontrolle signifikant. Weiter normalisiert Buprenorphin in diesem Dranginkontinenzmodell das Interkontraktionsintervall und die Blasenkapazität vollkommen und bewirkt weiter eine signifikante und deutliche Erhöhung des Schwellendrucks.

Damit ist der Beweis angetreten, daß Buprenorphin, insbesondere im Bereich der Dranginkontinenz, für die das OxyHb-Modell als Standardmodell steht, eine hervorragende Wirkung zeigt und zwar auch bei Schädigung, also im Krankheitsfall.

Beispiel 6: Parenterale Applikationsform

20 g Tramadol und 1 g Venlafaxin wird in 1 l Wasser für Injektionszwecke bei Raumtemperatur gelöst und anschließend durch Zugabe von NaCl auf isotone Bedingungen eingestellt.

Patentansprüche:

1. Verwendung einer Wirkstoffkombination aus wenigstens einer der **Verbindungen A** und wenigstens einer der **Verbindungen B**, mit **Verbindung A** ausgewählt aus:

Gruppe a) enthaltend:

Tramadol, O-Demethyltramadol, oder O-desmethyl-N-mono-desmethyl-tramadol als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe b) enthaltend:

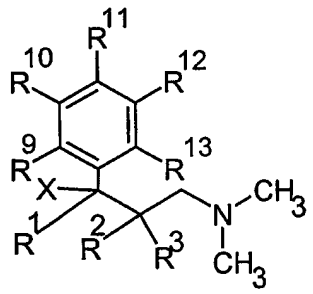
- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Tramadol
- Viminol
- Butorphanol

- Dextromoramid
- Dezocin
- Diacetylmorphin (Heroin)
- Hydrocodon
- Hydromorphon
- Ketobemidon
- Levomethadon
- Levomethadyl-Acetate (l-α-Acetylmethadol (LAAM))
- Levorphanol
- Morphin
- Nalorphin
- Oxycodon
- Pentazocin
- Piritramide
- Alfentanil
- Buprenorphin
- Etorphin
- Fentanyl
- Remifentanil
- Sufentanil

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe c) enthaltend:

1-Phenyl-3-dimethylamino-propanverbindungen gemäß allgemeiner **Formel I**



I

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^2 und R^3 jeweils unabhängig voneinander ausgewählt sind aus H oder C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^2 und R^3 zusammen einen gesättigten C_{4-7}-Cycloalkylrest bilden, unsubstituiert oder ein- oder mehrfach substituiert,

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

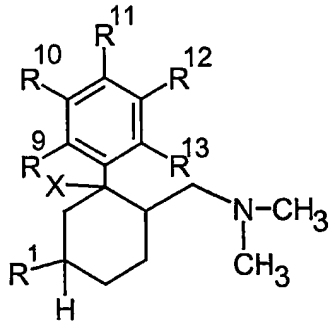
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe d) enthaltend:

substituierte 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel II**



II

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, Benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-Alkyl, Cl oder F und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt,

gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

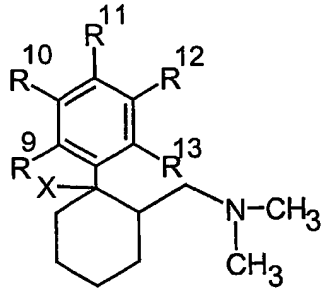
R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und/oder

Gruppe e) enthaltend:

6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel III**



III

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}$-

NHR^{18}, $CO-C_6H_4-R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

mit der Maßgabe, daß, wenn R^9, R^{11} und R^{13} H entsprechen, und einer von R^{10} oder R^{12} H und der andere OCH_3 entspricht, X nicht OH sein darf,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und mit wenigstens einer der **Verbindungen B**, ausgewählt aus:

Venlafaxin, Fesoterodin, Solifenacin (YM906), Cizolirtine, Resiniferatoxin, Nitro-Flurbiprofen, HCT1026, Talnetant, TAK-637, SL 251039, R 450, Rec 15/3079, (-)-DDMS, NS-8 und/oder DRP-001,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

zur Herstellung eines Arzneimittels zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz.

2. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe a)** ausgewählt ist aus:

Tramadol, (+)-Tramadol, (+)-O-Demethyltramadol oder (+)-O-desmethyl-N-mono-desmethyl-tramadol,
vorzugsweise Tramadol oder (+)-Tramadol,
insbesondere (+)-Tramadol.

3. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe b)** ausgewählt ist aus:

- Codein

- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Viminol
- Butorphanol
- Dezocin
- Nalorphin
- Pentazocin
- Buprenorphin

, vorzugsweise

- Codein
- Dextropropxyphen
- Dihydrocodein
- Meptazinol
- Nalbuphin
- Tilidin
- Buprenorphin

4. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe c)** ausgewählt ist aus Verbindungen gemäß **Formel I** für die gilt:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F, $OC(O)CH_3$ oder H,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise CH_3, C_2H_5, C_4H_9 oder t-Butyl, insbesondere CH_3 oder C_2H_5,

und/oder

R^2 und R^3 unabhängig voneinander ausgewählt sind aus

H, C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise H, CH_3, C_2H_5, i-Propyl oder t-Butyl, insbesondere H oder CH_3, vorzugsweise R^3 = H,

oder

R^2 und R^3 zusammen einen C_{5-6}-Cycloalkylrest bilden, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, vorzugsweise gesättigt und unsubstituiert, insbesondere Cyclohexyl.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OCH_3 oder SCH_3

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

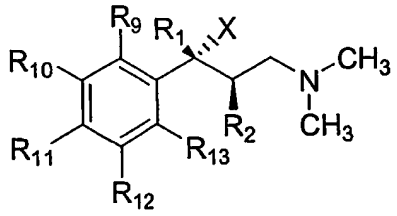
oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7.

5. Verwendung gemäß Anspruch 4, dadurch gekennzeichnet, daß Verbindungen der **Formel I** mit R^3 = H in Form der Diastereomeren mit der relativen Konfiguration Ia



Ia

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden

und/oder

daß die Verbindungen der **Formel I** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

6. Verwendung gemäß einem der Ansprüche 4 oder 5, dadurch gekennzeichnet, daß **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (2RS,3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-me-

thyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-Dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-Dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,
- (3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phe-nol,
- (+)-(1R,2R)-Essigsäure-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propylester,
- (1RS)-1-(1-Dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-phenyl)-propan-1-ol,
- (2RS, 3RS)-3-(4-Chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol und
- (+)-(2R,3R)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

vorzugsweise als Hydrochlorid.

7. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe d)** ausgewählt ist aus Verbindungen gemäß **Formel II** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere OH,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, CF_3, OH, O-C_{1-4}-Alkyl, Cl oder F, vorzugsweise OH, CF_3 oder CH_3,

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden,

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

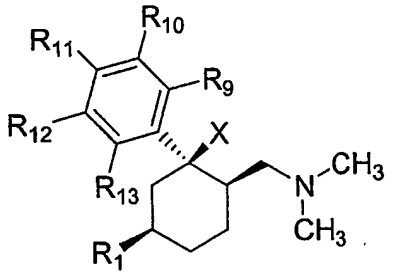
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

8. Verwendung gemäß Anspruch 7, dadurch gekennzeichnet, daß Verbindungen der **Formel II** in Form der Diastereomeren mit der relativen Konfiguration IIa



IIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden,

und/oder

daß die Verbindungen der **Formel II** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

9. Verwendung gemäß einem der Ansprüche 7 oder 8, dadurch gekennzeichnet, daß **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,3R,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol oder
- (1RS,2RS,5RS)-3-(2-Dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

10. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe e)** ausgewählt ist aus Verbindungen gemäß **Formel III** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere F oder H.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere dadurch gekennzeichnet, daß,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

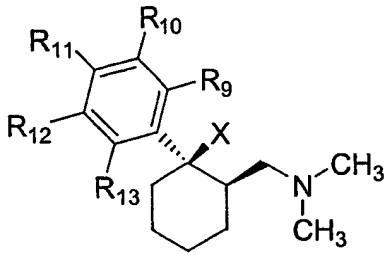
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

11. Verwendung gemäß Anspruch 10, dadurch gekennzeichnet, daß Verbindungen der **Formel III** in Form ihrer Diastereomeren mit der relativen Konfiguration IIIa



IIIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden

und/oder

, daß die Verbindungen der **Formel III** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

12. Verwendung gemäß einem der Ansprüche 10 oder 11, dadurch gekennzeichnet, daß **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (+)-(1R,2R)-3-(2-Dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,
- (+)-(1S,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol oder
- (-)-(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

13. Verwendung gemäß einem der Ansprüche 1 bis 12, dadurch gekennzeichnet, daß die **Verbindung B** ausgewählt ist aus:

Fesoterodin, Solifenacin (YM905), Cizolirtine, Resiniferatoxin oder Venlafaxin.

14. Wirkstoffkombination aus wenigstens einer der **Verbindungen A** und wenigstens einer der **Verbindungen B**, mit **Verbindung A** ausgewählt aus:

Gruppe a) enthaltend:

Tramadol, O-Demethyltramadol oder O-desmethyl-N-mono-desmethyl-tramadol als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe b) enthaltend:

- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)

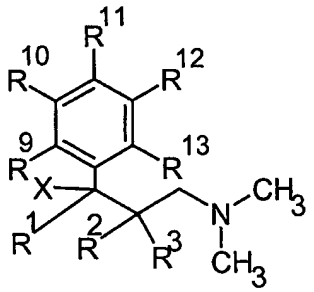
- Tilidin
- Tramadol
- Viminol
- Butorphanol
- Dextromoramid
- Dezocin
- Diacetylmorphin (Heroin)
- Hydrocodon
- Hydromorphon
- Ketobemidon
- Levomethadon
- Levomethadyl-Acetate (l-α-Acetylmethadol (LAAM))
- Levorphanol
- Morphin
- Nalorphin
- Oxycodon
- Pentazocin
- Piritramide
- Alfentanil
- Buprenorphin
- Etorphin
- Fentanyl
- Remifentanil
- Sufentanil

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder

Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe c) enthaltend:

1-Phenyl-3-dimethylamino-propanverbindungen gemäß allgemeiner **Formel I**



I

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^2 und R^3 jeweils unabhängig voneinander ausgewählt sind aus H oder C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^2 und R^3 zusammen einen gesättigten C_{4-7}-Cycloalkylrest bilden, unsubstituiert oder ein- oder mehrfach substituiert,

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder

mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

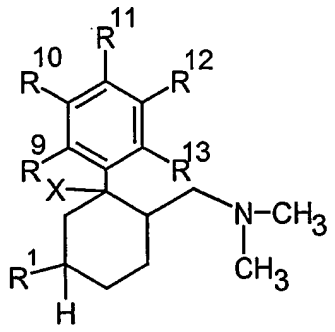
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe d) enthaltend:

substituierte 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel II**



II

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, Benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-Alkyl, Cl oder F und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert;

$PO(O\text{-}C_{1\text{-}4}\text{-Alkyl})_2$, $CO(OC_{1\text{-}5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1\text{-}3}\text{-Alkyl})$, $CO(C_{1\text{-}5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1\text{-}3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} $C_{1\text{-}4}$-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; $C_{1\text{-}6}$-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

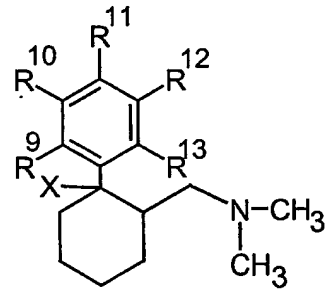
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,
als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und/oder

Gruppe e) enthaltend:

6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel III**



III

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

mit der Maßgabe, daß, wenn R^9, R^{11} und R^{13} H entsprechen, und einer von R^{10} oder R^{12} H und der andere OCH_3 entspricht, X nicht OH sein darf,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch

verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und mit wenigstens einer der **Verbindungen B**, ausgewählt aus:

Venlafaxin, Fesoterodin, Solifenacin (YM905), Cizolirtine, Resiniferatoxin, Nitro-Flurbiprofen, HCT1026, Talnetant, TAK-637, SL 251039, R 450, Rec 15/3079, (-)-DDMS, NS-8 und/oder DRP-001,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers.

15. Wirkstoffkombination gemäß Anspruch 14, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe a**) ausgewählt ist aus:

Tramadol, (+)-Tramadol, (+)-O-Demethyltramadol oder (+)-O-desmethyl-N-mono-desmethyl-tramadol,
vorzugsweise Tramadol oder (+)-Tramadol,
insbesondere (+)-Tramadol.

16. Wirkstoffkombination gemäß Anspruch 14, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe b**) ausgewählt ist aus:

- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Viminol
- Butorphanol
- Dezocin
- Nalorphin
- Pentazocin
- Buprenorphin

, vorzugsweise

- Codein
- Dextropropxyphen
- Dihydrocodein
- Meptazinol
- Nalbuphin
- Tilidin
- Buprenorphin

17. Wirkstoffkombination gemäß Anspruch 14, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe c**) ausgewählt ist aus Verbindungen gemäß **Formel I** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F, $OC(O)CH_3$ oder H,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise CH_3, C_2H_5, C_4H_9 oder t-Butyl, insbesondere CH_3 oder C_2H_5,

und/oder

R^2 und R^3 unabhängig voneinander ausgewählt sind aus

H, C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise H, CH_3, C_2H_5, i-Propyl oder t-Butyl, insbesondere H oder CH_3, vorzugsweise R^3 = H,

oder

R^2 und R^3 zusammen einen C_{5-6}-Cycloalkylrest bilden, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, vorzugsweise gesättigt und unsubstituiert, insbesondere Cyclohexyl.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OCH_3 oder SCH_3

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

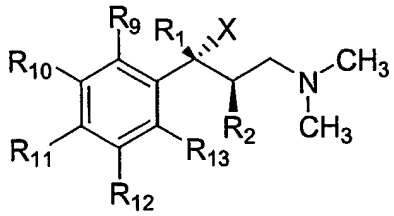
oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7.

18. Wirkstoffkombination gemäß Anspruch 17, dadurch gekennzeichnet, daß die Verbindungen der **Formel I** mit R^3 = H in Form der Diastereomeren mit der relativen Konfiguration Ia



Ia

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer

und/oder

daß die Verbindungen der **Formel I** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

19. Wirkstoffkombination gemäß einem der Ansprüche 17 oder 18, dadurch gekennzeichnet, daß die **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (2RS,3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-Dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-Dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,
- (3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phe-nol,
- (+)-(1R,2R)-Essigsäure-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propylester,
- (1RS)-1-(1-Dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-phenyl)-propan-1-ol,
- (2RS, 3RS)-3-(4-Chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol und
- (+)-(2R,3R)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

vorzugsweise als Hydrochlorid.

20. Wirkstoffkombination gemäß Anspruch 14, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe d)** ausgewählt ist aus Verbindungen gemäß **Formel II** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere OH,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, CF_3, OH, O-C_{1-4}-Alkyl, Cl oder F, vorzugsweise OH, CF_3 oder CH_3,

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden,

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

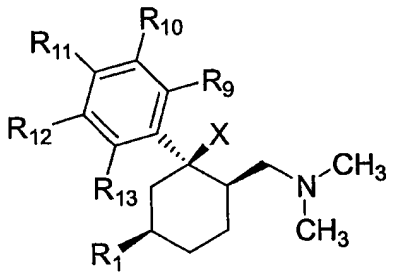
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

21. Wirkstoffkombination gemäß Anspruch 20, dadurch gekennzeichnet, daß die Verbindungen der **Formel II** in Form der Diastereomeren mit der relativen Konfiguration IIa



IIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer,

und/oder

daß die Verbindungen der **Formel II** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

22. Wirkstoffkombination gemäß einem der Ansprüche 20 oder 21, dadurch gekennzeichnet, daß **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,3R,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-me-

thyl-cyclohexyl)-phenol oder
- (1RS,2RS,5RS)-3-(2-Dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

23. Wirkstoffkombination gemäß Anspruch 14, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe e)** ausgewählt ist aus Verbindungen gemäß **Formel III** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere F oder H.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere dadurch gekennzeichnet, daß,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

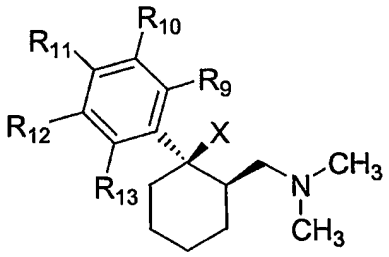
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

24. Wirkstoffkombination gemäß Anspruch 23, dadurch gekennzeichnet, daß die Verbindungen der **Formel III** in Form ihrer Diastereomeren mit der relativen Konfiguration IIIa



IIIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer

und/oder

, daß die Verbindungen der **Formel III** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

25. Wirkstoffkombination gemäß einem der Ansprüche 23 oder 24, dadurch gekennzeichnet, daß die **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (+)-(1R,2R)-3-(2-Dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,

- (+)-(1S,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol oder
- (-)-(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

26. Wirkstoffkombination gemäß einem der Ansprüche 14 bis 25, dadurch gekennzeichnet, daß die **Verbindung B** ausgewählt ist aus:

Fesoterodin, Solifenacin (YM905), Resiniferatoxin, Cizolirtine oder Venlafaxin.

27. Arzneimittel, vorzugsweise zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz, enthaltend eine Wirkstoffkombination gemäß einem der Ansprüche 14 bis 26 sowie gegebenenfalls geeignete Zusatz- und/oder Hilfsstoffe.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05529

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/135 A61K31/137 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 199 47 747 A (GRUENENTHAL GMBH) 12 April 2001 (2001-04-12) claims 1,2 ---	1,2, 13-15, 26,27
Y	PANDITA R K ET AL: "Actions of tramadol on the micturition reflex in awake, freely moving rats." NEUROUROLOGY AND URODYNAMICS, vol. 20, no. 4, 2001, pages 439-440, XP008020732 31st Annual Meeting of the International Continence Society;Seoul, South Korea; September 18-21, 2001 ISSN: 0733-2467 * Seite 440, Absatz "Conclusions" * --- -/--	1,2, 13-15, 26,27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2003	25/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beranová, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 658 908 A (MCNUTT JR ROBERT WALTON ET AL) 19 August 1997 (1997-08-19) column 6, line 22 - line 24 column 14, line 48	1,3,13, 14,16, 26,27
Y	MALINOVSKY J-M ET AL: "THE URODYNAMIC EFFECTS OF INTRAVENOUS OPIOIDS AND KETOPROFEN IN HUMANS" ANESTHESIA AND ANALGESIA, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 87, no. 2, August 1998 (1998-08), pages 456-461, XP001064299 ISSN: 0003-2999 * Seite 460, linke Spalte, letzter Absatz *	1,3,13, 14,16, 26,27
Y	PALMER K R ET AL: "DOUBLE-BLIND CROSS-OVER STUDY COMPARING LOPERAMIDE CODEINE AND DIPHENOXYLATE IN THE TREATMENT OF CHRONIC DIARRHEA" GASTROENTEROLOGY, SAUNDERS, PHILADELPHIA, PA,, US, vol. 79, no. 6, December 1980 (1980-12), pages 1272-1275, XP001065241 ISSN: 0016-5085 * Seite 1275, linke Spalte, letzter Absatz *	1,3,13, 14,16, 26,27
Y	DURAND A ET AL: "Drug therapy for urinary incontinence" PRESSE MEDICALE 06 MAY 2000 FRANCE, vol. 29, no. 16, 6 May 2000 (2000-05-06), pages 917-922, XP008020716 ISSN: 0755-4982 page 920, right-hand column, paragraph 2	1,3,13, 14,16, 26,27
Y	EP 1 072 260 A (NOVOSIS PHARMA AG) 31 January 2001 (2001-01-31) claims 1,18	1,13,14, 26,27
Y	RIPPLE MARY G ET AL: "Lethal combination of tramadol and multiple drugs affecting serotonin." AMERICAN JOURNAL OF FORENSIC MEDICINE AND PATHOLOGY, vol. 21, no. 4, December 2000 (2000-12), pages 370-374, XP008020715 ISSN: 0195-7910 page 372, left-hand column, paragraph 2	1,2, 13-15, 26,27

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KRONER BEVERLY A ET AL: "Pharmacotherapy trials of urinary incontinence in the geriatric patient: A review of current literature findings." JOURNAL OF GERIATRIC DRUG THERAPY, vol. 7, no. 1, 1992, pages 23-55, XP008020717 ISSN: 8756-4629 table 2 ----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP03/05529

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see supplemental Sheet additionnal matter PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box I.2

The current Claims 1, 13, 14, 26 and 27 relate to a disproportionately large number of possible compounds, of which only a small portion are supported by the description (PCT Article 6) and/or can be regarded as having been disclosed in the application (PCT Article 5). In the present case the claims lack the proper support and the application lacks the requisite disclosure to such an extent that it appears impossible to carry out a meaningful search covering the entire range of protection sought. The search was therefore directed to the parts of the claims that appear to be clear, supported and disclosed in the above sense, that is the compounds specified in the exemplary embodiments.

The applicant is advised that claims or parts of claims relating to inventions in respect of which no international search report has been established cannot normally be the subject of an international preliminary examination (PCT Rule 66.1(e)). In its capacity as International Preliminary Examining Authority the EPO generally will not carry out a preliminary examination for subjects that have not been searched. This also applies to cases where the claims were amended after receipt of the international search report (PCT Article 19) or where the applicant submits new claims in the course of the procedure under PCT Chapter II.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/05529

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19947747 A	12-04-2001	DE 19947747 A1	12-04-2001
		AU 7907600 A	10-05-2001
		CA 2386381 A1	12-04-2001
		WO 0124783 A2	12-04-2001
		EP 1217998 A2	03-07-2002
		HU 0202776 A2	28-02-2003
		JP 2003510350 T	18-03-2003
		US 2003069314 A1	10-04-2003
US 5658908 A	19-08-1997	AT 237597 T	15-05-2003
		AU 675928 B2	27-02-1997
		AU 3457393 A	01-09-1993
		CA 2129046 A1	05-08-1993
		DE 69332882 D1	22-05-2003
		DK 649414 T3	11-08-2003
		EP 0649414 A1	26-04-1995
		WO 9315062 A1	05-08-1993
		IL 104582 A	30-10-1998
		JP 3109832 B2	20-11-2000
		JP 7503247 T	06-04-1995
		NZ 246916 A	27-08-1996
		US 5681830 A	28-10-1997
		US 5574159 A	12-11-1996
		US 5854249 A	29-12-1998
		US 2002052007 A1	02-05-2002
		ZA 9300717 A	02-08-1994
EP 1072260 A	31-01-2001	DE 19934523 A1	25-01-2001
		EP 1072260 A1	31-01-2001

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 03/05529

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 A61K31/135 A61K31/137 A61K31/485

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der Internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	DE 199 47 747 A (GRUENENTHAL GMBH) 12. April 2001 (2001-04-12) Ansprüche 1,2 ---	1,2, 13-15, 26,27
Y	PANDITA R K ET AL: "Actions of tramadol on the micturition reflex in awake, freely moving rats." NEUROUROLOGY AND URODYNAMICS, Bd. 20, Nr. 4, 2001, Seiten 439-440, XP008020732 31st Annual Meeting of the International Continence Society;Seoul, South Korea; September 18-21, 2001 ISSN: 0733-2467 * Seite 440, Absatz "Conclusions" * --- -/--	1,2, 13-15, 26,27

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist
"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist
"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist
"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der Internationalen Recherche	Absendedatum des internationalen Recherchenberichts
21. August 2003	25/09/2003

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beranová, P

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	US 5 658 908 A (MCNUTT JR ROBERT WALTON ET AL) 19. August 1997 (1997-08-19) Spalte 6, Zeile 22 - Zeile 24 Spalte 14, Zeile 48 ---	1,3,13, 14,16, 26,27
Y	MALINOVSKY J-M ET AL: "THE URODYNAMIC EFFECTS OF INTRAVENOUS OPIOIDS AND KETOPROFEN IN HUMANS" ANESTHESIA AND ANALGESIA, WILLIAMS AND WILKINS, BALTIMORE, MD, US, Bd. 87, Nr. 2, August 1998 (1998-08), Seiten 456-461, XP001064299 ISSN: 0003-2999 * Seite 460, linke Spalte, letzter Absatz * ---	1,3,13, 14,16, 26,27
Y	PALMER K R ET AL: "DOUBLE-BLIND CROSS-OVER STUDY COMPARING LOPERAMIDE CODEINE AND DIPHENOXYLATE IN THE TREATMENT OF CHRONIC DIARRHEA" GASTROENTEROLOGY, SAUNDERS, PHILADELPHIA, PA,, US, Bd. 79, Nr. 6, Dezember 1980 (1980-12), Seiten 1272-1275, XP001065241 ISSN: 0016-5085 * Seite 1275, linke Spalte, letzter Absatz * ---	1,3,13, 14,16, 26,27
Y	DURAND A ET AL: "Drug therapy for urinary incontinence" PRESSE MEDICALE 06 MAY 2000 FRANCE, Bd. 29, Nr. 16, 6. Mai 2000 (2000-05-06), Seiten 917-922, XP008020716 ISSN: 0755-4982 Seite 920, rechte Spalte, Absatz 2 ---	1,3,13, 14,16, 26,27
Y	EP 1 072 260 A (NOVOSIS PHARMA AG) 31. Januar 2001 (2001-01-31) Ansprüche 1,18 ---	1,13,14, 26,27
Y	RIPPLE MARY G ET AL: "Lethal combination of tramadol and multiple drugs affecting serotonin." AMERICAN JOURNAL OF FORENSIC MEDICINE AND PATHOLOGY, Bd. 21, Nr. 4, Dezember 2000 (2000-12), Seiten 370-374, XP008020715 ISSN: 0195-7910 Seite 372, linke Spalte, Absatz 2 --- -/—	1,2, 13-15, 26,27

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	KRONER BEVERLY A ET AL: "Pharmacotherapy trials of urinary incontinence in the geriatric patient: A review of current literature findings." JOURNAL OF GERIATRIC DRUG THERAPY, Bd. 7, Nr. 1, 1992, Seiten 23-55, XP008020717 ISSN: 8756-4629 Tabelle 2 -----	

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 03/05529

Feld I Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt 2 auf Blatt 1)

Gemäß Artikel 17(2)a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. ☐ Ansprüche Nr.
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich

2. ☒ Ansprüche Nr. -
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich

siehe Zusatzblatt WEITERE ANGABEN PCT/ISA/210

3. ☐ Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

Feld II Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 3 auf Blatt 1)

Die internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. ☐ Da der Anmelder alle erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche.

2. ☐ Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchengebühr gerechtfertigt hätte, hat die Behörde nicht zur Zahlung einer solchen Gebühr aufgefordert.

3. ☐ Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche Nr.

4. ☐ Der Anmelder hat die erforderlichen zusätzlichen Recherchengebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

Bemerkungen hinsichtlich eines Widerspruchs

☐ Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.

☐ Die Zahlung zusätzlicher Recherchengebühren erfolgte ohne Widerspruch.

WEITERE ANGABEN **PCT/ISA/ 210**

Fortsetzung von Feld I.2

Die geltenden Patentansprüche 1, 13, 14, 26 und 27 beziehen sich auf eine unverhältnismäßig große Zahl möglicher Verbindungen, von denen sich nur ein kleiner Anteil im Sinne von Art. 6 PCT auf die Beschreibung stützen und als im Sinne von Art.5 PCT in der Patentanmeldung offenbart gelten kann. Im vorliegenden Fall fehlt den Patentansprüchen die entsprechende Stütze und fehlt der Patentanmeldung die nötige Offenbarung in einem solchen Maße, daß eine sinnvolle Recherche über den gesamten erstrebten Schutzbereich unmöglich erscheint. Daher wurde die Recherche auf die Teile der Patentansprüche gerichtet, welche im o.a. Sinne als gestützt und offenbart erscheinen, nämlich die Verbindungen, wie sie in den Ausführungsbeispielen angegeben sind.

Der Anmelder wird darauf hingewiesen, daß Patentansprüche, oder Teile von Patentansprüchen, auf Erfindungen, für die kein internationaler Recherchenbericht erstellt wurde, normalerweise nicht Gegenstand einer internationalen vorläufigen Prüfung sein können (Regel 66.1(e) PCT). In seiner Eigenschaft als mit der internationalen vorläufigen Prüfung beauftragte Behörde wird das EPA also in der Regel keine vorläufige Prüfung für Gegenstände durchführen, zu denen keine Recherche vorliegt. Dies gilt auch für den Fall, daß die Patentansprüche nach Erhalt des internationalen Recherchenberichtes geändert wurden (Art. 19 PCT), oder für den Fall, daß der Anmelder im Zuge des Verfahrens gemäß Kapitel II PCT neue Patentansprüche vorlegt.

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/EP 03/05529

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
DE 19947747 A	12-04-2001	DE 19947747 A1	12-04-2001
		AU 7907600 A	10-05-2001
		CA 2386381 A1	12-04-2001
		WO 0124783 A2	12-04-2001
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		US 2003069314 A1	10-04-2003
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		AU 675928 B2	27-02-1997
		AU 3457393 A	01-09-1993
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		US 5574159 A	12-11-1996
		US 5854249 A	29-12-1998
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		ZA 9300717 A	02-08-1994
EP 1072260 A	31-01-2001	DE 19934523 A1	25-01-2001
		EP 1072260 A1	31-01-2001

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number
WO 03/103637 A2

(51) International Patent Classification[7]: A61K 9/24, 9/26, 9/28, 9/52, 31/4965, 31/137

(21) International Application Number: PCT/IB03/02186

(22) International Filing Date: 9 June 2003 (09.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

617/DEL/2002	7 June 2002 (07.06.2002)	IN
1157/DEL/2002	15 November 2002 (15.11.2002)	IN
234/DEL/2003	6 March 2003 (06.03.2003)	IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19 Nehru Place, New Delhi 110 019, Maharashtra (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KUMAR, Pratik** [IN/IN]; c/o Dr. Neelam Singh, Shivpri, Damuchowk, 842001 Muzaffarpur, Bihar (IN). **JAIN, Girish, Kumar** [IN/IN]; 4, Sharda Niketan, Teachers Colony, Pitampura, 110034 Dehli (IN). **RAMPAL, Ashok** [IN/IN]; 14, Sewa Nagar, Ram Tirath Road, 143001 Amritsar, Punjab (IN). **NITHIYANANDAM, Ravikumar** [IN/IN]; No. 24, Bairavan Kovil Street, Dharapuram, Erode District, Periyar, Tamil Nadu 638 656 (IN). **RAMAKRISHNAN, Sankar** [IN/IN]; 24, River Bank Street, Madukkur, Thanjavur District, Tamil Nadu 614 903 (IN). **RAGHUVANSHI, Rajeev, Singh** [IN/IN]; D8/8131, Vasant Kunj, 110070 New Delhi, Delhi (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jayadeep, R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/103637 A2

(54) Title: MODIFIED RELEASE, MULTIPLE UNIT DRUG DELIVERY SYSTEMS

(57) Abstract: The invention relates to novel modified release multiple unit systems, and methods of preparing these systems, which can be easily compressed into tablets or filled into capsules or sachets without affecting the desired release characteristics of the pharmaceutical active ingredients incorporated within the systems. The multiple unit tablet includes multiple units. Each unit includes at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, one or more rate controlling polymers, and one or more one active pharmaceutical ingredients. The coating layer includes one or both of the one or more active pharmaceutical ingredients and the one or more rate controlling polymers. The tablet may further include an outer layer on the outer surface of the unit which includes a material that is one or both of elastic and compressible. The material may be a wax materials, such as polyethylene glycol's (PEGS).

MODIFIED RELEASE, MULTIPLE UNIT DRUG DELIVERY SYSTEMS

FIELD OF THE INVENTION

The technical field of the invention relates to modified release multiple unit systems, and methods of preparing these systems, which can be easily compressed into tablets or filled into capsules or sachets without affecting the desired release characteristics of the pharmaceutical active ingredients incorporated within the systems.

BACKGROUND OF THE INVENTION

The need to improve the clinical results of modified release formulations is well documented in the prior art. This is particularly important for drugs that have short half-lives, have region specific absorption, produce gastric irritation, or have other side effects at high plasma concentrations. One of the most common methods of achieving modified drug release involves the use of monolithic systems designed to have modified release characteristics. These monolithic systems vary from osmotic drug delivery systems to bioerodible or non-erodible matrix based systems.

Although a major portion of the modified release formulations currently prescribed are monolithic systems, they nonetheless suffer from a few serious drawbacks. Intentional or accidental breakdown of the delivery system is one of the limitations that may cause dose dumping. Dose dumping may lead to toxic or fatal effects, depending on the pharmaceutical compound. Further, the gastric emptying of the comparatively large monolithic systems is variable and is dependent on the presence or absence of food, as well as the type of food taken by the patient.

These disadvantages have prompted a shift in modified release technology from the use of monolithic systems to multiple unit systems, wherein each individual unit is formulated with modified release characteristics. The final dosage form consists of a collection of the multiple units, compressed into a tablet, or filled into a capsule or sachet. When administered, the individual units are dispersed freely into the gastrointestinal contents, avoiding the high local concentration of drug which may lead to irritation of gastrointestinal mucosa. Also, the performance of the dosage form is independent of inter- and intra-patient variability in gastric emptying time because of the small size of the individual units that make up the system. This technology has the added advantages of (1) allowing the production of numerous doses and strengths without the need for formulation

or process changes; (2) delivery of incompatible agents together in a single dosage form; and (3) delivery of particles or individual units that have different release characteristics to achieve desired release profile.

Each individual unit of the multiple unit system is either: (a) an inert core or pellet coated with one or more layers of drug and other release controlling polymeric substances; or (b) a drug-containing core or pellet optionally coated with one or more layers of release controlling polymeric substances.

A common problem with modified release, multiple unit systems is the rupturing or cracking of the release controlling layers or membrane of the core, or the fragmentation of the core, due to the mechanical stress generated during the compression of cores or individual units into a tablet or filling into a capsule or sachet. Various approaches are described in the prior art for formulating multiple unit systems with a desired mechanical strength. For example, U.S. Patent No. 4,713,248 discloses a water-based film comprising a homogenous combination of a water dispersible film forming agent and a polymeric substance that forms a film over a controlled release multiple unit formulation containing an active substance.

U.S. Patent No. 5,783,215 describes the use of inert and non-soluble cores of glass or sand particles and soluble cores, such as sugar spheres, which are capable of withstanding mechanical stress, in combination with a plasticizing layer of a hydrophilic polymer containing the drug, optionally with additional layers of the polymer not containing the drug, layered between the core and the release controlling membrane.

SUMMARY OF THE INVENTION

In one general aspect there is provided a multiple unit dosage form that includes multiple units. Each unit includes at least one core having an outer surface; a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, the coating layer including one or both of one or more active pharmaceutical ingredients and one or more rate controlling polymers; and an outer layer. The outer layer includes a material that is one or both of elastic and compressible.

Embodiments of the multiple unit dosage form may include one or more of the following features. For example, the core may include the one or more rate controlling polymers. The core may include the one or more active pharmaceutical ingredients. The

core may include the rate controlling polymer and the active pharmaceutical ingredient. The first coating layer may include the one or more active pharmaceutical ingredients.

The core may include one or more of sugar, a non-pareil seed, microcrystalline cellulose, celphere, sand silicon dioxide, glass, plastic, polystyrene, hydroxypropyl methylcellulose. The sugar may include one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose. The core may include one or more of an insoluble material, a soluble material, and a swellable material.

The rate controlling polymer may include one or more of cellulosic polymers, methacrylic acid polymers, and waxes. The rate controlling polymer may include one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, and hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

The one or more active pharmaceutical ingredients may include one or more of antidepressants, antidiabetics, antiulcers, analgesics, antihypertensives, antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents. The one or more active pharmaceutical ingredients may include one or more of enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts. The one or more active pharmaceutical ingredients may be one or both of glipizide and venlafaxine or their salts.

The multiple unit dosage form may further include one or more additional layers. The additional layers are positioned between (a) one or more of the core and the first coating layer and (b) surrounding at least a portion of the first coating layer. The one or more additional layers include one or more of a seal coat, a film forming layer, a rate controlling polymer, and an active pharmaceutical ingredient. The seal coat may be one or more of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, and methacrylic acid

copolymers. The film forming layer may be one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimellitate, cellulose acetate phthalate, waxes, polyethylene glycol, and methacrylic acid polymers.

The multiple unit dosage form may further include an outer layer on the outer surface of the unit and the outer surface includes a material that is one or both of elastic and compressible. The material in the outer layer may be one or more wax materials. The wax material may be one or more polyethylene glycols (PEGs). The PEGs may differ by molecular weight. The polyethylene glycol (PEG) may be one or more of PEG 600, PEG 4000, PEG 6000, PEG 8000, and PEG 20000. The waxy material may be from about 1% to about 15% by weight of the total tablet weight or from about 1% to about 100% by weight of the weight of the core and first coating layer. The waxy material may be applied to each unit as a solution, suspension, dispersion, or hot melt technique. The solution, suspension, or dispersion may be made using a solvent. The solvent may be one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water.

The active pharmaceutical ingredient may be glipizide and may be present in one or both of the core and the first coating layer. The multiple unit dosage form may further include a buffering agent with the glipizide in one or both of the core and the first coating layer. The buffering agent may be one or more of dibasic sodium phosphate, sodium ascorbate, meglumine, sodium citrate trimethanolamine, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, and L-lysine.

In the multiple unit dosage form, one or more of the core and the first coating layer may include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers, and coloring agents. The surfactants may include one or more of a non-ionic surfactant, an ionic surfactant, mono fatty acid esters of polyoxyethylene sorbitan, polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20), an anionic surfactant, sodium lauryl sulfate, polyoxyethylene castor oil derivative, polyoxyethyleneglycerol triiricinoleate castor oil, polyoxyl 35 castor

oil, Cremophor EL, and Vitamin E TPGS, d-alpha-tocopheryl polyethylene glycol 1000 succinate, polyethoxylated fatty acids and their derivatives, polyethylene glycol 400 distearate, polyethylene glycol - 20 dioleate, polyethylene glycol 4–150 mono dilaurate, polyethylene glycol –20 glyceryl stearate, alcohol – oil transesterification products, polyethylene glycol – 6 corn oil, polyglycerized fatty acids, polyglyceryl – 6 pentaoleate, propylene glycol fatty acid esters, propylene glycol monocaprylate, mono and diglycerides, glyceryl ricinoleate, sterol and sterol derivatives, sorbitan fatty acid esters and their derivatives, polyethylene glycol – 20 sorbitan monooleate and sorbitan monolaurate, polyethylene glycol alkyl ether or phenols, polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol, sugar esters, sucrose monopalmitate, polyoxyethylene – polyoxypropylene block copolymers, poloxamer, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine.

The binders may include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, and propylene glycol. The diluents may include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, and sugar confectioners. The disintegrants include one or more of starch, croscarmellose, crospovidone, and sodium starch glycolate. The lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, and white beeswax. The plasticizers include one or more of polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, and dibutyl sebacate. The stabilizers include one or more of antioxidants, buffers, and acids.

The multiple unit dosage form may further include one or more pharmaceutically acceptable excipients around the individual units. The dosage form may be a tablet and the tablet may be formed by application of a compressive force. The dosage form may be a capsule.

The active pharmaceutical ingredients of the multiple unit dosage form may be one or more of atorvastatin and amlodipine, metformin and glipizide, simvastatin and ramipril, simvastatin and amlodipine, metformin XL and glipizide XL, ramipril and atorvastatin, ramipril and amlodipine, metformin XL and glimiperide, fosinopril and amlodipine.

In another general aspect, there is provided a process for the preparation of a multiple unit dosage form. The process includes providing at least one core having an outer surface, forming a coated core by applying one or more coating layers to the core such that the one or more coating layers surround at least a portion of the outer surface of the core or the coating layers, forming an individual unit by applying a waxy material to the coated core to form a wax layer, and combining one or more units to form a multiple unit dosage form. One or both of the core and the coating layers includes one or more rate controlling polymers and active pharmaceutical ingredients.

Embodiments of the process may include one or more of the following features. For example, the process may further include applying one or both of a seal layer or a film forming layer between the core and the coating layer, between the one or more coating layers, and between the one or more coating layers and the wax layer. The waxy material may be one or more polyethylene glycols (PEGs) of one or more molecular weights. The polyethylene glycols (PEG) may be one or more of PEG 600, PEG 4000, PEG 6000, PEG 8000, and PEG 20000. The waxy material may be from about 1% to about 15% by weight of the total tablet weight. The waxy material may be from about 1% to about 100% by weight of the weight of the core and the one or more coating layers.

Applying the waxy material may include applying a coating of a solid waxy material by using a hot melt technique. Applying the waxy material may include applying a coating of waxy material by using as one or more of a solution, a suspension, and a dispersion. The solution or the suspension may be prepared in a solvent. The solvent may be selected from one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water.

The core may be an inert core. The core may include one or more pharmaceutically acceptable excipients. The core may include one or more active pharmaceutical ingredients. The one or more active pharmaceutical ingredients may be one or more of antidepressants, antidiabetics, antiulcers, analgesics, antihypertensives,

antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents. The one or more active pharmaceutical ingredients may be one or more of enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts. In particular, the active pharmaceutical ingredient may be venlafaxine or glipizide.

The core may be prepared by extrusion-spheronization. The extrusion-spheronization process may include granulating an inert core material with or without other pharmaceutical excipients with a binder solution to form a wet mass, passing the wet mass through an extruder to form extrudates, and spheronizing the extrudates. The core may be prepared by granulation. The granulation process may include wetting a dry mix of core material with or without other pharmaceutical excipients with a binder solution.

The units may be prepared by coating the cores with active pharmaceutical ingredients and rate controlling polymers. The units may be prepared by coating cores with a first layer comprising an active pharmaceutical ingredient and a second outer layer comprising a rate controlling polymer.

The process may further include applying a seal coat or a film forming layer between the core and the subsequent layers. The process may further include applying a seal coat or a film forming layer between a layer comprising an active pharmaceutical ingredient and a layer comprising a release rate controlling polymer

The rate controlling polymer may include one or more of cellulosic polymers, methacrylic acid polymers, and waxes. The rate controlling polymer may be one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

In another general aspect, a method for preparing a modified release multiple unit dosage form includes providing a core having a coating, forming individual units by coating the coated core with a coating material that is one or both of compressible and elastic, and forming the dosage form by combining one or more individual units. One or both of the core and the coating may be one or more rate controlling polymers and one or more active pharmaceutical ingredients.

Embodiments of the method of preparing a modified release multiple unit dosage form may include one or more of the following features, including any one or more of the features described above. For example, the coating material may be a waxy material. The coating material may be a polyethylene glycol. Combining one or more individual units may include filling the individual units into a capsule or sachet or compressing the individual units into a tablet.

In another general aspect, a method of treating a medical condition includes administering a multiple unit tablet for oral ingestion. Each unit includes a core, one or more layers surrounding the core, and an outer layer. The core includes one or more of a pharmaceutically acceptable excipient, an active pharmaceutical ingredient, and a rate controlling polymer. The one or more layers includes one or more of a pharmaceutically acceptable excipient, an active pharmaceutical ingredient, a rate controlling polymer, a sealing layer, and a film forming layer. The outer layer includes a material that is one or both of compressible or elastic to partially or completely absorb a compressive force exerted in combining the units.

Embodiments of the method of treating a medical condition may include one or more of the following features, including any one or more of the features described above. For example, the material of the outer layer may be a waxy material. The waxy material may be one or more polyethylene glycols of different molecular weights.

In another general aspect, a combination drug, multiple unit dosage form includes first units and second units. Each first unit includes at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, and an outer layer surrounding at least a portion of an outer surface of the first coating layer, the first coating layer including a first active pharmaceutical ingredient. Each second unit includes at least one core having an outer

surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, and an outer layer surrounding at least a portion of an outer surface of the first coating layer, the first coating layer including a second active pharmaceutical ingredient. One or both of the cores and the coating layers may include the rate controlling polymer. One or both of the outer layers may include a waxy material.

Embodiments of the combination drug, multiple unit dosage form may include one or more of the following features, including any one or more of the features described above. For example, waxy material may include one or more polyethylene glycols.

In another general aspect, a multiple unit dosage form includes multiple units. Each unit includes at least one core having an outer surface and comprising one or more one active pharmaceutical ingredients; and a coating layer surrounding at least a portion of the outer surface of the core, having an outer surface and comprising a waxy material.

Embodiments of the dosage form may include one or more of the following features. For example, the waxy material may be one or more polyethylene glycols of different molecular weights. The dosage form may be a tablet or a capsule.

In another general aspect, a multiple unit dosage form includes multiple units. Each unit includes at least one core having an outer surface and a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface. The coating layer includes glipizide or its pharmaceutically acceptable salt and optionally one or more rate controlling polymers.

In one embodiment, the pharmaceutically acceptable salt comprises one or more of mineral acid salts, organic acid salts, and organosulphonic acid salts.

In another general aspect, a modified release multiple unit system includes units of glipizide. The units include an inert core; a drug layer surrounding the inert core, the drug layer including glipizide; and a rate controlling polymer layer surrounding the drug layer.

Embodiments of the modified release multiple unit system may include one or more of the following features. For example, the system may be a tablet or a capsule.

In another general aspect, a modified release multiple unit system includes units of glipizide. The units include an inert core; a drug layer surrounding the inert core; a rate

controlling polymer layer surrounding the drug layer; and a waxy layer surrounding the drug layer.

Embodiments of the modified release multiple unit system may include one or more of the following features. For example, the system may be a tablet or a capsule. The units can be compressed into tablet, or filled into a capsule or a sachet; without affecting the desired release characteristics of drug.

In another general aspect, a modified release multiple unit system includes units of venlafaxine. The units include an inert core; a drug layer surrounding the inert core; and a rate controlling polymer layer surrounding the drug layer.

Embodiments of the modified release multiple unit system may include one or moreof the following features. For example, the system may be a tablet. The units can be compressed into tablet without affecting the desired release characteristics of drug.

In another general aspect, a modified release multiple unit system includes units of venlafaxine. The units include an inert core; a drug layer surrounding the inert core; a rate controlling polymer layer surrounding the drug layer; and a waxy layer surrounding the rate controlling polymer layer.

Embodiments of the modified release multiple unit system may include one or more of the following features. For example, the system may be a tablet. The units can be compressed into tablet without affecting the desired release characteristics of the venlafaxine.

In another general aspect, a modified release multiple unit system comprises units of a drug. The units include an inert core; a drug layer surrounding the inert core; a rate controlling polymer layer surrounding the drug layer; and a waxy layer surrounding the rate controlling polymer layer.

Embodiments of the modified release multiple unit system may include one or more of the following features. For example, the system may be compressed into tablet, or filled in capsule or sachet without affecting the desired release characteristics of drug.

In another general aspect, a process for the preparation of a modified release multiple unit system of a drug includes the steps of coating inert pellets with a drug and

rate controlling polymer layer; coating with a waxy layer; optionally blending with pharmaceutically acceptable excipients; compressing into a tablet, or filling into a capsule or a sachet of suitable size.

In another general aspect, a process for the preparation of a modified release multiple unit system of drug includes the steps of coating inert pellets with a drug and rate controlling polymer layer; coating with a waxy layer; optionally blending with pharmaceutically acceptable excipients; and compressing into tablet of suitable size.

Embodiments of the modified release multiple unit system may include one or more of the following features. For example, the drug may be venlafaxine or a pharmaceutically acceptable salt.

In another general aspect, a process for the preparation of modified release multiple unit system of drug includes the steps of coating drug containing cores with a rate controlling polymer layer; coating the rate controlling polymer layer with a waxy layer; optionally blending with pharmaceutically acceptable excipients; and compressing into a tablet, or filling into a capsule or a sachet of suitable size.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and claims.

DETAILED DESCRIPTION OF THE INVENTION

As described above with respect to the difficulties associated with prior art compositions, there exists a need for universally applicable, multiple unit dosage form or systems of desired mechanical strength. The difficulties in the prior art are believed to be addressed by the techniques, compositions, and concepts described herein for a modified release, multiple unit system that can be easily compressed into a tablet or filled into a capsule or sachet without affecting the desired release characteristics of the drug. To address the above described problems of the prior art associated with mechanical stress due to compression or filling, the inventors have found that there are benefits to providing an outermost coating of a waxy material to each unit of the multiple unit systems. The inventors have found that the application of a coating of waxy material to each unit provides favorable mechanical properties that withstand cracking. Specifically, the coating of waxy material withstands cracking of the release controlling membrane when

exposed to mechanical stress, for example, during compression into a tablet or filling into a capsule or sachet.

The inventors have applied the multiple unit dosage form or system techniques, compositions, and concepts to active pharmaceutical ingredients, including venlafaxine and glipizide. In so doing, the inventors have developed separate multiple unit dosage form or systems of venlafaxine and glipizide that are in the form of controlled release tablets in which the waxy layer is an optional component. These venlafaxine and glipizide controlled release, multiple unit tablets that include coated pellets of venlafaxine or glipizide, respectively, overcome the known problem of limited dosing associated with capsules. The term "controlled release" as used herein includes any type of modified release such as prolonged release, delayed release, sustained release, extended release and the like.

The waxy coating imparts a certain degree of elasticity or compressibility to the units and makes possible the compression of the multiple units into tablets or filling into capsules or sachets without altering the dissolution profile and hence the bioavailability and desired clinical effects. Further, this approach can be used over any types of pre-functional layers and irrespective of drug characteristics. Hence, the waxy coating provides a method for the preparation of modified or controlled release, multiple unit dosage forms or systems that include a final or outer coating of a waxy material and these units can be easily compressed into tablets, or filled into capsules or sachets without affecting the desired release characteristics of drug (e.g., dissolution profile, bioavailability, and clinical effects). In particular, the waxy layer can protect the release control polymer layer from cracking during compression, for example, during the production of tablets.

In general, the multiple units can be for use in any dosage forms, such as a tablet, capsule or sachet, and include a core or pellet, one or more layers around the pellet, and an outer waxy layer. The core or pellet can be entirely or partially an active pharmaceutical ingredient or an inert material, or a combination of both. The layers around the core may include one or more release or rate controlling polymers and/or active pharmaceutical ingredients. The layers also may be in the form of sealing or film forming layers around or between the polymer and active pharmaceutical ingredients. The various layers and

core may optionally contain pharmaceutically acceptable excipients. The outer waxy layer may consist entirely of a waxy material or may be a mixture of a waxy material and one or more pharmaceutically acceptable functional excipients.

The multiple units of the improved multiple unit systems may contain (1) inert pellets or cores or (2) drug containing pellets or cores in which the drug is incorporated within the pellets or cores. Cores and pellets generally are used interchangeably herein. The inert core of the improved multiple unit systems is either a commercially available product or prepared in the laboratory. The inert core may be of any geometric shape, although spherical beads have the advantage of providing ease of uniform coating. The bead diameter may vary from about 50 μm to 700 μm. The pellet weight may vary from about 3% to about 40% by weight of the total tablet weight.

The commercially available inert cores include sugar spheres, non pariel seeds, celpheres and the like. The laboratory or otherwise manufactured cores may be prepared according to any suitable method including:

a. Extrusion-Spheronization: The inert core material with or without drug and other pharmaceutical excipients is granulated by addition of a binder solution. The wet mass is passed through an extruder equipped with a screen. The extrudates are spheronized in a marumerizer. The resulting spheroids or pellets are dried and sieved for further applications.

b. Granulation: The inert core material with or without drug and other pharmaceutical excipients is dry-mixed and then the mixture is wetted by addition of a binder solution in a high shear-granulator/mixer. The granules are kneaded after wetting by the combined actions of mixing and milling. The resulting granules or pellets are dried and sieved for further applications.

The material from which the inert pellet or core is prepared may be selected from one or more of pharmaceutically inert insoluble, soluble, and/or swellable materials, with or without pharmaceutically acceptable excipients. The insoluble inert core material may be, for example, one or more of sand (silicon dioxide), glass, microcrystalline cellulose (e.g., celpheres) or plastic (e.g., polystyrene) material. The soluble inert core material may be, for example, one or more sugar such as glucose, mannitol, lactose, xylitol, dextrose,

sucrose, and the like. The swellable inert core material may be, for example, hydroxypropyl methylcellulose or a similar material. The core also can be a combination of two or more of these three general types of core materials.

Alternatively, drug-containing cores can also be prepared by completely or partially replacing the inert core material with one or more active pharmaceutical ingredients in the above two methods of preparing inert cores.

The improved, modified release multiple units may be prepared from inert cores by (a) coating the inert core with one or more drug and rate controlling polymer layers; or (b) coating the inert core with one or more drug layers and rate controlling polymer layers separately. Both of these options may contain a seal or film coat between the inert core and the drug layer and/or between the drug layer and the rate controlling polymer layer.

The improved, modified release multiple units also may be prepared from drug containing cores by (a) coating drug containing cores with rate controlling polymer; or (b) coating drug containing cores with drug and rate controlling polymer. Both of these options may contain a seal or film coat between the drug containing core and the polymer layer and/or over the polymer layer. The seal or film coat layer also can be formed between the drug containing core and the drug/polymer layer and/or over the drug/polymer layer.

The improved, modified release units are further processed by applying a final layer of a waxy material over each unit prepared by the above processes. Although the application of this waxy layer is the general rule, the inventors nonetheless have successfully formed tables from multiple units without the waxy layer. This may be dependent on, for example, the active pharmaceutical ingredient of the tablet.

The modified release units prepared by any of the above methods can be mixed with other pharmaceutically acceptable excipients, to the extent required or desired, and compressed into tablets or filled into capsules and sachets using techniques known in the art for these purposes. The final tablets or capsules may optionally be coated, if desired.

The drug layer of the improved multiple unit tablet includes one or more active pharmaceutical ingredients, and optionally includes other pharmaceutically acceptable excipients. The drug layer may be applied as an aqueous or non-aqueous solution or

dispersion of drug in water or organic solvent, or mixtures thereof. The one or more drugs may be selected from, for example, one or more of antidepressants, antidiabetics, antiulcers, analgesics, antihypertensives, antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents.

Illustrative examples of drugs of the above classes include enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts.

The rate controlling polymer layer includes one or more polymers with or without other pharmaceutically acceptable excipients. This layer may be applied as an aqueous or non-aqueous solution or dispersion of polymers in a water or organic solvent. Suitable rate controlling polymers include one or more of cellulosic polymers such as ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, and hydroxyethylcellulose; waxes; hydroxypropylmethyl phthalate; cellulose acetate phthalate; cellulose acetate trimellitate; and methacrylic acid polymers such as Eudragit ® RL and RS. The single drug and rate controlling layer may contain the above described drug and polymers in the same layer. Based on the desired release profile, the controlled release polymer layer weight may constitute from about 5% to about 75% of the total tablet weight.

The waxy material may be selected from, for example, a range of polyethylene glycols (PEGs) of various molecular weights, such as PEG 600, PEG 4000, PEG 6000, PEG 8000, PEG 20000 and the like. In general, the waxy material should be at least of approximately as compressible or elastic as PEG. The waxy material layer may constitute, for example, from about 1% to about 15% by weight of the total tablet weight, although the amount may be varied up or down if necessary. The amount of the waxy material may vary from about 1% to about 100% by weight of the weight of the core and coating layer or one or more coating layers. The waxy layer is applied as a solution or suspension using any conventional coating technique known in the art, including spray

coating in a conventional coating pan or fluidized bed processor, dip coating of each unit of a multiple unit system, or using a hot melt technique.

The solvents used for making a solution, dispersion, or suspension of the waxy material may be selected from, for example, one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water. In general, the solvent should adequately dissolve, disperse, or suspend whichever waxy material or materials is selected.

The seal coat may include suitable polymers, such as hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methacrylic acid copolymers and the like. The film forming coat or agents may include one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate, waxes such as polyethylene glycol, and methacrylic acid polymers such as Eudragit® RL and RS. Alternatively, the film forming layer or agents may be commercially available coating compositions including film-forming polymers marketed under various trade names, such as Opadry®. Film forming layers generally are provided for achieving a smooth surface and better appearance. Seal layer generally are applied to separate two incompatible layers, provide protection from moisture, etc. In general, the film forming layers and the seal layers may be the same or similar polymers used in different combinations or concentrations.

The other pharmaceutically acceptable excipients as used herein include surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers and coloring agents.

Suitable surfactants include one or more of non-ionic and ionic (i.e., cationic, anionic and Zwitterionic) surfactants suitable for use in pharmaceutical compositions. For example, suitable surfactants include non-ionic surfactants such as mono fatty acid esters of polyoxyethylene sorbitan (e.g., polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20)); anionic surfactants (e.g., sodium lauryl sulfate); polyoxyethylene castor oil derivatives (e.g., polyoxyethyleneglycerol triiricinoleate or polyoxyl 35 castor oil (Cremophor EL)); and Vitamin E TPGS (d-alpha-tocopheryl

polyethylene glycol 1000 succinate). Other suitable surfactants include polyethoxylated fatty acids and their derivatives (e.g., polyethylene glycol 400 distearate, polyethylene glycol - 20 dioleate, polyethylene glycol 4–150 mono dilaurate, and polyethylene glycol – 20 glyceryl stearate); alcohol – oil transesterification products (e.g., polyethylene glycol – 6 corn oil); polyglycerized fatty acids (e.g., polyglyceryl – 6 pentaoleate); propylene glycol fatty acid esters (e.g., propylene glycol monocaprylate); mono and diglycerides (e.g., glyceryl ricinoleate); sterol and sterol derivatives; sorbitan fatty acid esters and their derivatives (e.g., polyethylene glycol – 20 sorbitan monooleate and sorbitan monolaurate); polyethylene glycol alkyl ether or phenols (e.g., polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol); sugar esters (e.g., sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"); and ionic surfactants (e.g., sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine).

Suitable binders include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Suitable diluents include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and mixtures thereof.

Suitable disintegrants include one or more of starch, croscarmellose, crospovidone, sodium starch glycolate and the like. Suitable lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax and the like. Suitable plasticizers include one or more of polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, dibutyl sebacate and the like. Suitable stabilizers include one or more of antioxidants, buffers, acids and the like. Suitable coloring agents include any FDA approved colors for oral use.

The improved multiple unit systems described herein can be applied to most classes of drugs and most individual drugs. For example, two particular drugs that would benefit from an improved modified release multiple unit system are venlafaxine and glipizide. Venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and is a weak inhibitor of dopamine reuptake. It is widely indicated for the treatment of depression and generalized anxiety disorder. The term "venlafaxine" as used herein includes venlafaxine base as well as any pharmaceutically acceptable salt thereof. Examples of pharmaceutically acceptable venlafaxine salts include venlafaxine hydrochloride. The venlafaxine layer weight may constitute from about 15% to about 75% of the total tablet weight.

Venlafaxine has been administered in the form of immediate release compressed tablets in doses ranging from 75 to 350 mg/day, in divided doses, two to three times a day. Such therapeutic dosing leads to wide fluctuations in the blood plasma levels of venlafaxine, with high concentrations at one extreme leading to severe side effects, such as nausea and/or vomiting shortly after administration, and less than therapeutic levels at the other extreme. Moreover, requiring frequent administration of the drug (e.g., two to three doses per day) is associated with patient non-compliance. Most of these problems associated with frequent dosing can be overcome by formulating controlled or extended release dosage forms of venlafaxine.

Venlafaxine hydrochloride is available as an extended release, once per day capsule which is marketed by Wyeth under the trade name Effexor® XR. This capsule appears to be described in U.S. Patent No. 6,274,171, which discloses an extended release formulation of venlafaxine hydrochloride that includes spheroids of venlafaxine hydrochloride, microcrystalline cellulose, and optional hydroxypropyl methylcellulose coated with a mixture of ethylcellulose and hydroxypropyl methylcellulose. These film-coated spheroids are filled into capsules. However, these capsules suffer from a limitation that only a small number of coated beads or pellets can be put into a capsule of appropriate size that is convenient to swallow. Hence, there still exists a need for better controlled-release dosage forms of venlafaxine hydrochloride.

Glipizide is an oral blood glucose-lowering drug and is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptoms in patients with non-

insulin dependent diabetes mellitus. Glipizide stimulates secretion of insulin from the beta cells of pancreatic islet tissue and also exhibits extra-pancreatic action, including the ability to increase the number of insulin receptors. Chemically, glipizide is N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl] ethyl]-5-methylpyrazine carboxamide. Glipizide is a white, odorless powder with a pKa of 5.9, and is insoluble in both water and alcohol. These physicochemical properties of glipizide demand special techniques to formulate a dosage form that can be used to administer the drug at a controlled and predetermined rate.

Glipizide is available in the form of extended release oral tablets from Pfizer and is marketed under the trade name Glucotrol® XL. The extended release tablets are an osmotic drug delivery device that is based on push-pull technology. The delivery device includes a bi-layered core tablet that is coated with a semipermeable membrane having an orifice drilled on the coat for release of glipizide. The bilayered core tablet consists of a glipizide layer and a push layer of swellable polymers. When placed in dissolution media or gastrointestinal fluid, the device absorbs water through the semipermeable membrane, which leads to a swelling of the polymers in the push layer. This exerts a physical force on the drug layer forcing it out of the device through the orifice.

The glipizide layer of the pellets includes glipizide with or without other one or more of the pharmaceutically inert excipients described above. Optionally, this layer also may contain buffering agents. Buffers are used to maintain the pH of the glipizide layer and/or local environment surrounding the controlled release particles above to thereby aid in dissolution of glipizide in the dissolution media or gastrointestinal fluids. The buffering agents may be applied as an aqueous or non-aqueous solution or dispersion of drug in water/organic solvent, or mixtures thereof. Suitable buffering agents include one or more of dibasic sodium phosphate, sodium ascorbate, meglumine, sodium citrate trimethanolamine, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, and L-lysine.

The inventors have developed improved multiple unit, controlled release tablets of venlafaxine that advantageously (1) can be administered in one half tablet or one half dosage and (2) can be prepared with a large amount of drug by compressing into a tablet

of acceptable size that is easy to swallow. When administered, the controlled release tablet disintegrates rapidly into individual coated pellets of venlafaxine, which are dispersed into gastric fluid. Venlafaxine then is released in a controlled manner over a prolonged period of time from the individual coated pellets. Use of small controlled release coated pellets (i.e., units) decreases the chances of dose dumping and the performance of the units is also largely independent of gastric emptying time.

The improved multiple unit, controlled release tablet of venlafaxine can be prepared by processes known in the relevant art, e.g., comminuting, mixing, granulating, sizing, filling, molding, spraying, immersing, coating, compressing, etc.

In one of the embodiments, improved, multiple unit, controlled release tablets of venlafaxine can be prepared by coating inert pellets or cores with one or more venlafaxine layers which are further coated with a controlled release polymer layer. Optionally, the controlled release layer and/or venlafaxine layer may also be coated with a waxy layer to form the individual units. Further, these coated pellets or cores, or the units, may be blended with pharmaceutically acceptable excipients and compressed into suitably sized, multiple unit tablets.

Alternatively, the improved, multiple unit, controlled release tablets of venlafaxine can be prepared by coating inert pellets or cores with a single layer of venlafaxine and controlled release polymer. Optionally, the single layer of venlafaxine and polymer may be coated with a waxy layer to form the individual units. Further, these coated pellets or cores, or the units, may be blended with pharmaceutically acceptable excipients and compressed into suitably sized, multiple unit tablets.

The coating layers over the inert pellets or cores, or over the tablet, may be applied as a solution or dispersion of coating ingredients using any conventional technique known in the prior art, such as spray coating in a conventional coating pan or fluidized bed processor, dip coating, and the like. Alternatively, the layers over the inert pellet or core may be applied using a hot melt technique.

Optionally, the pellets or cores may be coated with one or more additional layers comprising film forming or sealing agents and/or pharmaceutically acceptable excipients between the above layers, over any of the layers, or over the inert pellet or core. The

multiple unit tablets also may be further coated, if desired. Optionally, these additional coating layers over the tablet may comprise the active pharmaceutical ingredient (e.g., venlafaxine, glipizide) for immediate release. These layers may comprise film forming or sealing agents with or without other pharmaceutically acceptable excipients.

The improved, multiple unit systems described above are further illustrated by the following examples. Although these examples are illustrative of the techniques, compositions, and concepts described herein, they are not intended to be limiting.

EXAMPLE 1

(A) Modified release multiple units:

	Example 1 (wt/tablet) mg
Inert Core	
Non pariel seeds	65
Drug Layer	
Venlafaxine hydrochloride	171 (equivalent to 150 mg of venlafaxine)
Magnesium stearate	15
Colloidal silica	25
Hydroxypropyl methylcellulose	15
Water	q.s
Rate controlling layer	
Ethyl cellulose	93.12
Hydroxypropyl methylcellulose	23.28
Triacetin	1% of total polymers
Wax layer	
Polyethylene glycol 6000	30.55

Procedure:

1. Venlafaxine was dissolved in water and colloidal silica and then magnesium stearate and hydroxypropyl methylcellulose were added under stirring.
2. Non-pareil seeds were loaded in a Glatt Wurster column and coated with the drug dispersion of Step 1.
3. The drug coated pellets of Step 2 were coated with a mixture of ethyl cellulose and hydroxypropyl methylcellulose dissolved in a mixture of isopropyl alcohol and methylene chloride.

4. The coated pellets of Step 3 then were coated with a solution of PEG 6000 in methylene chloride.

(B) Compressed tablet:

Ingredient	**Example 1 (wt/tablet) mg**
Modified release multiple units of (A)	438
Silicified microcrystalline cellulose	217
PEG 4000	80
Crospovidone	90
Magnesium Stearate	5

Procedure: The modified release multiple units of (A) were mixed with other excipients and compressed to form tablets.

The compressed tablets prepared according to Example 1 had an acceptable hardness of about 7-13 Kp and disintegration times of about five minutes. Table 1 illustrates the comparative release patterns *in vitro* for modified release multiple units and tablets prepared according to Example 1.

Table 1. Comparative *in vitro* release patterns of modified release multiple units and tablets using USP apparatus – II, at 50 rpm and pH 6.8.

Time (Hours)	Cumulative percentage release of venlafaxine	
	Modified release multiple units	Tablets
1	14	17
2	32	33
4	59	57
6	72	69
8	82	79
12	94	91
16	100	97
20	100	100

As shown in Table 1, the compression of modified release multiple units into tablets did not alter the sustained release pattern of venlafaxine.

EXAMPLE 2

(A) Modified release multiple units:

	Example 2 (wt/tablet) mg
Inert Core	
Non pariel seeds	65
Drug Layer	
Venlafaxine hydrochloride	171 (equivalent to 150 mg of venlafaxine)
Magnesium stearate	13.5
Colloidal silica	19.7
Hydroxypropyl methylcellulose	13.5
Water	q.s
Rate controlling layer	
Ethyl cellulose	93
Hydroxypropyl methylcellulose	24
Triacetin	1% of total polymers
Wax layer	
Polyethylene glycol 6000	30

Procedure:

1. Venlafaxine was dissolved in water and colloidal silica and then magnesium stearate and hydroxypropyl methylcellulose were added under stirring.
2. Non-pareil seeds were loaded in a Glatt Wurster column and coated with the drug dispersion of Step 1.
3. The drug coated pellets of Step 2 were coated with a mixture of ethyl cellulose and hydroxypropyl methylcellulose that was dissolved in a mixture of isopropyl alcohol and methylene chloride.

4. The coated pellets of Step 3 then were coated with a solution of PEG 6000 in methylene chloride.

(B) Compressed tablet:

Ingredient	Example 2 (wt/tablet) mg
Modified release multiple units of (A)	473
Silicified microcrystalline cellulose	288
PEG 6000	71
Crospovidone	102
Magnesium Stearate	6

Procedure: The modified release multiple units of A were mixed with other excipients and compressed to form tablets.

The compressed tablets prepared according to Example 2 had an acceptable hardness of about 7-13 Kp and disintegration times of about five minutes. Table 2 illustrates the comparative release patterns *in vitro* for modified release multiple units and tablets prepared according to Example 2.

Table 2. Comparative *in vitro* release patterns of modified release multiple units and tablets using USP apparatus – II, at 50 rpm and pH 6.8.

Time (Hours)	Cumulative percentage release of venlafaxine	
	Modified release multiple units	Tablets
1	7	7
2	18	20
4	43	44
8	65	71
12	75	80

As shown in Table 2, the compression of modified release multiple units into tablets did

not alter the sustained release pattern of venlafaxine.

EXAMPLE 3

(A) Modified release multiple units:

	Example 3 (wt/tablet) mg
Inert Core	
Celpheres	148
Drug Layer	
Glipizide	10
Polyethylene glycol	4.7
Hydroxypropyl methylcellulose	1.7
Polyvinyl pyrrolidone	3.0
Tween 80	0.5
Lactose	3.0
Rate controlling layer	
Ethyl cellulose	8
Hydroxypropyl methylcellulose	4
Triacetin	1.3
Talc	0.4
Wax layer	
Polyethylene glycol 6000	13.9

Procedure:

1. Polyethylene glycol, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, Tween and lactose were dissolved in water and glipizide then was dispersed in the solution.
2. Celpheres were loaded in a Glatt Wurster column and coated with the drug dispersion

of Step 1.

3. A solution of ethyl cellulose, hydroxypropyl methylcellulose and triacetin was prepared in a mixture of methylene chloride and isopropyl alcohol into which talc was dispersed.
4. The drug loaded pellets of Step 2 then were coated with the dispersion of Step 3 using a Glatt Wurster column.
5. The coated pellets of Step 4 then were coated with a solution of PEG 6000 in mixture of isopropyl alcohol and methylene chloride.

(B) Compressed tablet:

Ingredient	**Example 3 (wt/tablet) mg**
Modified release multiple units of (A)	197.4
Silicified microcrystalline cellulose	122.4
PEG 6000	29.6
Crospovidone	43.4
Magnesium Stearate	2.0

Procedure: The modified release multiple units of (A) were mixed with other excipients and compressed to form tablet

The compressed tablets prepared according to Example 3 had an acceptable hardness of about 8-10 Kp and disintegration time of about three minutes. Tables 3a and 3b illustrate the comparative release patterns *in vitro* for modified release multiple units and tablets, respectively, prepared according to Example 3.

Table 3a. *In vitro* release pattern of modified release multiple units using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from modified release multiple units
1	6
2	13
4	23
8	45
12	62
16	78
20	94
24	102

Table 3b. *In vitro* release pattern of tablets using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from tablets
0.3	3
2.3	18
6.3	44
10.3	65
14.3	83
18.3	100
22.3	107

As shown in Tables 3a and 3b above, the compression of modified release multiple units into tablets did not alter the sustained release pattern of glipizide.

The above examples illustrate that the techniques, compositions, and concepts described herein can provide modified release multiple unit systems that can withstand the mechanical stresses of tablet formation without affecting the desired release characteristics.

EXAMPLES 4-7

Additional formulations of controlled release tablets of venlafaxine prepared according to the compositions of Examples 4-7 are provided in Tables 4 and 5

Table 4. Composition of coated pellets

	Example 4 (wt/tablet) mg	Example 5 (wt/tablet) mg	Example 6 (wt/tablet) mg	Example 7 (wt/tablet) mg
Inert pellets				
Non pariel seeds	65	65	65	65
Venlafaxine layer				
Venlafaxine hydrochloride	171	171	171	171
Magnesium stearate	13.5	13.5	13.55	13.55
Colloidal silica	19.7	19.7	19.70	19.70
Hydroxypropyl methyl cellulose	13.5	13.5	13.55	13.55
Water	q.s	q.s	q.s	q.s
Controlled release polymer layer				
Ethyl cellulose	81.42	91.61	101.77	110.84
Hydroxypropyl methylcellulose	20.35	22.89	25.44	27.68
Triacetin	1.01	1.14	1.27	1.38
Waxy layer				
Polyethylene glycol 6000	28.8	30	30.72	33.27

Procedure:

1. A solution of venlafaxine hydrochloride was prepared in water. Colloidal silica, magnesium stearate and hydroxypropyl methylcellulose were added to the solution under stirring to form a uniform dispersion.
2. Non pareil seeds were loaded in a Glatt Wurster column and coated with the drug

dispersion of Step 1.

3. The venlafaxine coated pellets of Step 2 then were coated with a solution of ethyl cellulose and hydroxypropyl methylcellulose that was dissolved in a mixture of isopropyl alcohol and methylene chloride.
4. The coated pellets of Step 3 then were coated with a solution of Polyethylene glycol 6000 in isopropyl alcohol and methylene chloride.

Table 5. Composition of controlled release venlafaxine tablets

Ingredient	Example 4 (wt/tablet) mg	Example 5 (wt/tablet) mg	Example 6 (wt/tablet) mg	Example 7 (wt/tablet) mg
Coated Pellets	459	473	450	465
Silicified microcrystalline cellulose	288	288	276	285
Polyethylene glycol 6000	70	71	85	89
Crospovidone	102	102	98	100
Magnesium Stearate	6	6	6	6

Procedure:

The coated pellets were blended with silicified microcrystalline cellulose, polyethylene glycol 6000, and crospovidone; lubricated with magnesium stearate; and compressed into suitably sized tablets.

***In vitro* dissolution study**

The *in vitro* release of venlafaxine hydrochloride from controlled release tablets made according to the compositions of Examples 4-7 was studied in 900 ml of phosphate buffer (pH–6.8) using USP apparatus – II, at 50 rpm. The results of this testing are listed in Table 6.

Table 6: *In vitro* release of venlafaxine hydrochloride from controlled release tablets

Time (Hours)	Cumulative percentage (%) release of venlafaxine from tablets			
	Example 4	Example 5	Example 6	Example 7
1	7	7	4	3
2	24	20	12	11
4	51	44	34	30
8	79	71	57	53
12	91	80	68	64
14	95	84	72	68
16	98	88	75	71
18	101	90	76	74
20	102	91	79	76
24	102	95	82	80

***In Vivo* Bioavailability Study**

The *in vivo* performance of venlafaxine hydrochloride tablets prepared as per the composition of Examples 4 and 5 were evaluated with respect to the Effexor® XR 150mg capsules in 11 healthy male volunteers under fasting condition. The study protocol followed was open randomized 3 treatment, 3 period, 6 sequence cross over study with a wash out period of at least 5 days. Blood samples were collected at appropriate time intervals over a period of 48 hours and venlafaxine content analyzed using a validated inhouse LCMS - MS method. Pharmacokinetic parameters C_{max} (Maximum plasma concentration), T_{max} (Time to attain maximum plasma concentration), AUC_{0-t} (Area under the plasma concentration *vs* time curve from 0 hours to the time of last sample collected) and $AUC_{0-\alpha}$ (Area under the plasma concentration *vs.* time curve from 0 hours to infinity) were calculated from the data obtained. The results of the study are given in Table 7.

Table 7. Comparative pharmacokinetic data

Pharmacokinetic parameter	T_{max} (h)	C_{max} μg/ml	AUC_{0-t} (μg/ml) (h)	$AUC_{0-\infty}$ (μg/ml) (h)
Tablets of Example 4	4.85	114.31	1633.51	1795.72
Tablets of Example 5	5.091	130.56	1813.84	2006.79
Effexor® XR capsules	6.45	99.92	1719.49	2406.27

The controlled release tablets produced demonstrated comparable extent of absorption when compared to the reference Effexor® XR. It is within the skill of one ordinary skill in the art to develop a product with matching C_{max} and AUC_{0-t} with respect to the reference product. The controlled release tablets can provide therapeutic blood concentrations of venlafaxine over a period of at least twenty four hours.

Examples 8 and 9, described below, provide additional examples of controlled release, multiple unit formulations of glipizide that deliver glipizide over twenty four hours. In contrast to Example 3 of a glipizide formulation having a waxy layer, these glipizide examples have the rate controlling polymer layer but not the waxy layer.

EXAMPLE 8

Controlled release multiple units:

	Example 8 (wt/tablet) mg
Inert Core	
Celpheres	148
Drug Layer	
Glipizide	10
Polyethylene glycol	4.7
Hydroxypropyl methylcellulose	1.7
Polyvinyl pyrrolidone	3.0
Tween 80	0.5
Lactose	3.0
Rate controlling layer	
Ethyl cellulose	10
Hydroxypropyl methylcellulose	5
Triacetin	1.7
Talc	0.5

Procedure:

1. Polyethylene glycol, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, Tween and lactose were dissolved in water and glipizide then was dispersed in the solution.
2. Celpheres were loaded in a Glatt Wurster column and coated with the drug dispersion of Step 1.
3. A solution of ethyl cellulose, hydroxypropyl methylcellulose and triacetin was prepared in a mixture of methylene chloride and isopropyl alcohol into which talc was dispersed.

4. The drug loaded pellets of Step 2 then were coated with the dispersion of Step 3 using a Glatt Wurster column to prepare controlled release multiple units.

Table 8 illustrates the comparative release patterns *in vitro* for the controlled release multiple units prepared according to example 8.

Table 8. *In vitro* release pattern of controlled release multiple units using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from controlled release multiple units
1	10
2	18
4	29
8	46
12	62
16	74
20	89
24	98

EXAMPLE 9

Controlled release multiple units:

	Example 9 (wt/tablet) mg
Inert Core	
Celpheres	148
Drug Layer	
Glipizide	10.0
Polyethylene glycol	4.7
Hydroxypropyl methylcellulose	1.7
Polyvinyl pyrrolidone	3.0
Tween 80	0.5
Lactose	3.0
Rate controlling layer	
Ethyl cellulose	4.6
Hydroxypropyl methylcellulose	2.9
Triacetin	0.8
Talc	0.3

Procedure:

1. Polyethylene glycol, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, lactose and Tween were dissolved in water and glipizide then was dispersed in the solution.
2. Celpheres were loaded in a Glatt Wurster column and coated with the drug dispersion of Step 1.
3. A solution of ethyl cellulose, hydroxypropyl methylcellulose and triacetin was prepared in a mixture of methylene chloride and isopropyl alcohol into which talc was dispersed.

4. The drug loaded pellets of Step 2 then were coated with the dispersion of Step 3 using a Glatt Wurster column to prepare controlled release multiple units.

Table 9 illustrates the comparative release patterns *in vitro* for controlled release multiple units prepared according to Example 9.

Table 9. *In vitro* release pattern for controlled release multiple units using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from controlled release multiple units
1	26
2	37
4	55
8	74
12	86
16	93
20	97
24	98

Tables 8 and 9 indicate that controlled release, multiple unit systems of glipizide can be prepared that can provide therapeutic blood concentrations of glipizide over a period of at least twenty four hours.

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. For example, the waxy layer can, for example, affect the release of the units, or a mixture of a waxy material and a functional material, such as an active pharmaceutical ingredient or a functional pharmaceutical excipient. The mixture of waxy material and active pharmaceutical ingredients may provide an immediate release of the active pharmaceutical ingredient in the mixture. The waxy layer can be designed based on, for example, thickness or material to impart rate controlling properties to the units or pellets. The improved multiple unit systems also generally are intended for application to any active pharmaceutical ingredient and provide advantages to those that are primarily formulated as a capsule and/or are problematic to prepare as a tablet. Moreover, the multiple unit

systems can be prepared as a tablet, capsule, or sachet that includes a core and a coating of a waxy material. The core can consist of one or more active pharmaceutical ingredients and those pharmaceutically acceptable excipients necessary to form the core. The coating of waxy material allows the coated cores (i.e., units) to be compress as a tablet or filled into a capsule or sachet. In this manner, the dosage form can be immediate release. By adding a rate controlling polymer to the core, the dosage form can be an extended release. The dosage form also can be made from a mixture of immediate release and extended release units to provide immediate and extended release of the one or more active pharmaceutical ingredients.

Pharmaceutically acceptable salts of venlafaxine and glipizide may be used in the dosage forms, tablets, and capsules described herein. Pharmaceutically acceptable salts of venlafaxine and glipizide include mineral acid salts such as hydrochloride, hydroiodide, hydroflouride, sulphate, etc.; organic acid salts such as citrate, maleate, tartarate, etc.; and organosulphonic acid salts such as mesylate, besylate, tosylate, etc.

The improved multiple unit systems can be used to deliver combination drug products, such as combinations of atorvastatin and amlodipine, metformin and glipizide, simvastatin and ramipril, simvastatin and amlodipine, metformin XL and glipizide XL, ramipril and atorvastatin, ramipril and amlodipine, metformin XL and glimiperide, fosinopril and amlodipine. These combination drug products can be produced by separately forming individual units of each active pharmaceutical ingredient and then combining them into tablets, capsules, or sachets in a subsequent production step. In this manner, each of the active pharmaceutical ingredients can be fabricated to separately optimize the release of that active ingredient and then the final dosage form can be produced that has the desired ratio of each of the active ingredients. One or both of each of the active ingredients can be formed as units of one or more of an immediate release, a controlled release, a modified release, a delayed release, or an extended release form.

Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed inventions and be so described as a negative limitation. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

WE CLAIM:

1. A multiple unit dosage form comprising multiple units, each unit comprising: at least one core having an outer surface;

a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, the coating layer including one or both of one or more active pharmaceutical ingredients and one or more rate controlling polymers; and

an outer layer, the outer layer comprising a material that is one or both of elastic and compressible.

2. The multiple unit dosage form of claim 1, wherein the core includes the one or more rate controlling polymers.

3. The multiple unit dosage form of claim 1, wherein the core includes the one or more active pharmaceutical ingredients.

4. The multiple unit dosage form of claim 1, wherein the core includes one or more of sugar, a non-pareil seed, microcrystalline cellulose, celphere, sand silicon dioxide, glass, plastic, polystyrene, hydroxypropyl methylcellulose.

5. The multiple unit dosage form of claim 4, wherein the sugar comprises one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose.

6. The multiple unit dosage form of claim 1, wherein the core comprises one or more of an insoluble material, a soluble material, and a swellable material.

7. The multiple unit dosage form of claim 1, wherein the rate controlling polymer comprises one or more of cellulosic polymers, methacrylic acid polymers, and waxes.

8. The multiple unit dosage form of claim 1, wherein the rate controlling polymer comprises one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, and hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

9. The multiple unit dosage form of claim 1, wherein the one or more active pharmaceutical ingredients comprises one or more of antidepressants, antidiabetics,

antiulcers, analgesics, antihypertensives, antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents.

10. The multiple unit dosage form of claim 1, wherein the one or more active pharmaceutical ingredients comprise one or more of enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts.

11. The multiple unit dosage form of claim 1, wherein the one or more active pharmaceutical ingredients comprises one or both of glipizide and venlafaxine or their salts.

12. The multiple unit dosage form of claim 1, wherein the core includes the rate controlling polymer and the active pharmaceutical ingredient.

13. The multiple unit dosage form of claim 1, wherein the first coating layer further includes the active pharmaceutical ingredient.

14. The multiple unit dosage form of claim 1, wherein the first coating layer includes the one or more active pharmaceutical ingredients.

15. The multiple unit dosage form of claim 1, further comprising one or more additional layers, wherein the additional layers are positioned between (a) one or more of the core and the first coating layer and (b) surrounding at least a portion of the first coating layer,

wherein the one or more additional layers comprise one or more of a seal coat, a film forming layer, a rate controlling polymer, and an active pharmaceutical ingredient.

16. The multiple unit dosage form of claim 15, wherein the seal coat comprises one or more of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, and methacrylic acid copolymers.

17. The multiple unit dosage form of claim 15, wherein the film forming layer includes one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate, waxes, polyethylene glycol, and methacrylic acid polymers.

18. The multiple unit dosage form of claim 1, wherein the material in the outer layer comprises one or more wax materials.

19. The multiple unit dosage form of claim 18, wherein the wax material comprises one or more polyethylene glycols (PEGs).

20. The multiple unit dosage form of claim 19, wherein the one or more polyethylene glycols (PEGs) differ by molecular weight.

21. The multiple unit dosage form of claim 20, wherein the polyethylene glycol (PEG) comprises one or more of PEG 600, PEG 4000, PEG 6000, PEG 8000, and PEG 20000.

22. The multiple unit dosage form of claim 19, wherein the waxy material comprises from about 1% to about 15% by weight of the total dosage form weight.

23. The multiple unit dosage form of claim 19, wherein the waxy material comprises from about 1% to about 100% by weight of the weight of the core and the first coating layer.

24. The multiple unit dosage form of claim 19, wherein the waxy material is applied to each unit as a solution, suspension, dispersion, or hot melt technique.

25. The multiple unit dosage form of claim 24, wherein the solution, suspension, or dispersion is made using a solvent,

wherein the solvent comprises one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water.

26. The multiple unit dosage form of claim 1, wherein the active pharmaceutical ingredient comprises glipizide and is in one or both of the core and the first coating layer.

27. The multiple unit dosage form of claim 26, further comprising a buffering agent with the glipizide in one or both of the core and the first coating layer.

28. The multiple unit dosage form of claim 27, wherein the buffering agent comprises one or more of dibasic sodium phosphate, sodium ascorbate, meglumine, sodium citrate trimethanolamine, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, and L-lysine.

29. The multiple unit dosage form of claim 1, wherein one or more of the core and the first coating layer includes one or more pharmaceutically acceptable excipients.

30. The multiple unit dosage form of claim 29, wherein the pharmaceutically acceptable excipients includes surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers, and coloring agents.

31. The multiple unit dosage form of claim 30, wherein the surfactants include one or more of a non-ionic surfactant, an ionic surfactant, mono fatty acid esters of polyoxyethylene sorbitan, polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20), an anionic surfactant, sodium lauryl sulfate, polyoxyethylene castor oil derivative, polyoxyethyleneglycerol triiricinoleate castor oil, polyoxyl 35 castor oil, Cremophor EL, and Vitamin E TPGS, d-alpha-tocopheryl polyethylene glycol 1000 succinate, polyethoxylated fatty acids and their derivatives, polyethylene glycol 400 distearate, polyethylene glycol - 20 dioleate, polyethylene glycol 4–150 mono dilaurate, polyethylene glycol –20 glyceryl stearate, alcohol – oil transesterification products, polyethylene glycol – 6 corn oil, polyglycerized fatty acids, polyglyceryl – 6 pentaoleate, propylene glycol fatty acid esters, propylene glycol monocaprylate, mono and diglycerides, glyceryl ricinoleate, sterol and sterol derivatives, sorbitan fatty acid esters and their derivatives, polyethylene glycol – 20 sorbitan monooleate and sorbitan monolaurate, polyethylene glycol alkyl ether or phenols, polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol, sugar esters, sucrose monopalmitate,

polyoxyethylene – polyoxypropylene block copolymers, poloxamer, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine.

32. The multiple unit dosage form of claim 30, wherein the binders includes one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, and propylene glycol.

33. The multiple unit dosage form of claim 30, wherein the diluents include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, and sugar confectioners.

34. The multiple unit dosage form of claim 30, wherein the disintegrants include one or more of starch, croscarmellose, crospovidone, and sodium starch glycolate.

35. The multiple unit dosage form of claim 30, wherein the lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, and white beeswax.

36. The multiple unit dosage form of claim 30, wherein the plasticizers include one or more of polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, and dibutyl sebacate and the stabilizers include one or more of antioxidants, buffers, and acids.

37. The multiple unit dosage form of claim 1, wherein the dosage form comprises a tablet.

38. The multiple unit dosage form of claim 37, wherein the tablet further includes one or more pharmaceutically acceptable excipients around the individual units.

39. The multiple unit dosage form of claim 1, wherein the dosage form comprises a capsule.

40. The multiple unit dosage form of claim 1, wherein the active pharmaceutical ingredients comprise one or more of atorvastatin and amlodipine, metformin and glipizide, simvastatin and ramipril, simvastatin and amlodipine, metformin XL and glipizide XL, ramipril and atorvastatin, ramipril and amlodipine, metformin XL and glimiperide, fosinopril and amlodipine.

41. A process for the preparation of a multiple unit dosage form, the process comprising:

providing at least one core having an outer surface;

forming a coated core by applying one or more coating layers to the core such that the one or more coating layers surround at least a portion of the outer surface of the core or the coating layers;

forming an individual unit by applying a waxy material to the coated core to form a wax layer;

combining one or more units to form a multiple unit dosage form,

wherein one or both of the core and the coating layers includes one or more rate controlling polymers and active pharmaceutical ingredients.

42. The process of claim 41, further comprising applying one or both of a seal layer or a film forming layer between the core and the coating layer, between the one or more coating layers, and between the one or more coating layers and the wax layer.

43. The process of claim 41, wherein the waxy material comprises one or more polyethylene glycols (PEGs) of one or more molecular weights.

44. The process of claim 43, wherein the polyethylene glycols (PEG) comprise one or more of PEG 600, PEG 4000, PEG 6000, PEG 8000, and PEG 20000.

45. The process of claim 41, wherein the waxy material comprises from about 1% to about 15% by weight of the total dosage form weight.

46. The process of claim 41, wherein the waxy material comprises from about 1% to about 100% by weight of the weight of the core and the one or more coating layers.

47. The process of claim 41, wherein applying the waxy material comprises applying a coating of a solid waxy material by using a hot melt technique.

48. The process of claim 41, wherein applying the waxy material comprises applying a coating of waxy material by using as one or more of a solution, a suspension, and a dispersion.

49. The process of claim 48, wherein the solution or the suspension is prepared in a solvent.

50. The process of claim 49, wherein the solvent is selected from one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water.

51. The process of claim 41, wherein the core comprises an inert core.

52. The process of claim 41, wherein the core comprises one or more pharmaceutically acceptable excipients.

53. The process of claim 41, wherein the core comprises one or more active pharmaceutical ingredients.

54. The process of claim 41, wherein the one or more active pharmaceutical ingredients comprises one or more of antidepressants, antidiabetics, antiulcers, analgesics, antihypertensives, antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents.

55. The process of claim 41, wherein the one or more active pharmaceutical ingredients comprise one or more of enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts.

56. The process of claim 41, wherein the core is prepared by extrusion-spheronization.

57. The process of claim 56, wherein the extrusion-spheronization process comprises:

granulating an inert core material with or without other pharmaceutical excipients with a binder solution to form a wet mass;

passing the wet mass through an extruder to form extrudates; and

spheronizing the extrudates.

58. The process of claim 41, wherein the core is prepared by granulation.

59. The process of claim 58, wherein the granulation process comprises wetting a dry mix of core material with or without other pharmaceutical excipients with a binder solution.

60. The process of claim 41, wherein the units are prepared by coating the cores with active pharmaceutical ingredients and rate controlling polymers.

61. The process of claim 41, wherein the units are prepared by coating cores with a first layer comprising an active pharmaceutical ingredient and a second outer layer comprising a rate controlling polymer.

62. The process of claim 41, further comprising applying a seal coat or a film forming layer between the core and the subsequent layers or between a layer comprising an active pharmaceutical ingredient and a layer comprising a release rate controlling polymer

63. The process of claim 41, wherein the rate controlling polymer comprises one or more of cellulosic polymers, methacrylic acid polymers, waxes, ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, and hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

64. The process of claim 41, wherein the active pharmaceutical ingredient comprises venlafaxine.

65. The process of claim 41, wherein the active pharmaceutical ingredient comprises glipizide.

66. The process of claim 41, wherein the dosage form comprises a tablet.

67. The process of claim 41, wherein the dosage form comprises a capsule.

68. A method for preparing a modified release multiple unit dosage form, the method comprising:

providing a core having a coating, wherein one or both of the core and the coating include one or more of rate controlling polymers and active pharmaceutical ingredients;

forming individual units by coating the coated core with a coating material that is one or both of compressible and elastic; and

forming the dosage form by combining one or more individual units.

69. The method of claim 68, wherein combining one or more individual units comprises compressing the individual units into a tablet

70. The method of claim 68, wherein combining one or more individual units comprises filling the individual units into a capsule or sachet.

71. The method of claim 68, wherein the coating material comprises a waxy material.

72. The method of claim 68, wherein the coating material comprises a polyethylene glycol.

73. A method of treating a medical condition, the method comprising administering a multiple unit dosage form for oral ingestion, each unit comprising a core, one or more layers surrounding the core, and an outer layer, wherein

the core comprises one or more of a pharmaceutically acceptable excipients, an active pharmaceutical ingredient, and a rate controlling polymer,

the one or more layers comprises one or more of a pharmaceutically acceptable excipient, an active pharmaceutical ingredient, a rate controlling polymer, a sealing layer, and a film forming layer, and

the outer layer comprises a material that is one or both of compressible and elastic to partially or completely absorb a force exerted in forming the multiple unit dosage form by combining the units.

74. The method of claim 73, wherein the material of the outer layer comprises a waxy material.

75. The method of claim 74, wherein the waxy material comprises one or more polyethylene glycols of different molecular weights.

76. The method of claim 73, wherein the dosage form comprises a tablet.

77. The method of claim 73, wherein the dosage form comprises a capsule.

78. A multiple unit dosage form comprising multiple units, each unit comprising:

at least one core having an outer surface and comprising one or more one active pharmaceutical ingredients; and

a coating layer surrounding at least a portion of the outer surface of the core, having an outer surface and comprising a waxy material.

79. The multiple unit dosage form of claim 78, wherein the waxy material comprises one or more polyethylene glycols of different molecular weights.

80. The multiple unit dosage form of claim 78, wherein the dosage form comprises a tablet.

81. The multiple unit dosage form of claim 78, wherein the dosage form comprises a capsule.

82. A combination drug, multiple unit dosage form comprising:

first units; and

second units,

each first unit comprising at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, and an outer layer surrounding at least a portion of an outer surface of the first coating layer, the first coating layer including a first active pharmaceutical ingredient,

each second unit comprising at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, and an outer layer surrounding at least a portion of an outer surface of the first coating layer, the first coating layer including a second active pharmaceutical ingredient,

wherein one or both of the cores and the coating layers comprise a rate controlling polymer, and

one or both of the outer layers comprise a waxy material,.

83. The combination drug, multiple unit dosage form of claim 82, wherein the waxy material comprises one or more polyethylene glycols.

84. The combination drug, multiple unit dosage form of claim 82, wherein the dosage form comprises a tablet.

84. The combination drug, multiple unit dosage form of claim 82, wherein the dosage form comprises a capsule.

85. A multiple unit dosage form comprising multiple units, each unit comprising:

at least one core having an outer surface;

a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, the coating layer including glipizide or its pharmaceutically acceptable salt and optionally one or more rate controlling polymers.

86. The multiple unit dosage form of claim 85, wherein the pharmaceutically acceptable salt comprises one or more of mineral acid salts, organic acid salts, and organosulphonic acid salts.

87. The multiple unit dosage form of claim 85, wherein the core includes one or more of sugar, a non-pareil seed, microcrystalline cellulose, celphere, sand silicon dioxide, glass, plastic, polystyrene, hydroxypropyl methylcellulose.

88. The multiple unit dosage form of claim 87, wherein the sugar comprises one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose.

89. The multiple unit dosage form of claim 85, wherein the core comprises one or more of an insoluble material, a soluble material, and a swellable material.

90. The multiple unit dosage form of claim 85, wherein the rate controlling polymer comprises one or more of cellulosic polymers, methacrylic acid polymers, waxes, ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose,

carboxymethylcellulose, hydroxymethylcellulose, and hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

91. The multiple unit dosage form of claim 85, wherein the core includes rate controlling polymer and glipizide.

92. The multiple unit dosage form of claim 85, further comprising one or more additional layers, wherein the additional layers are positioned between (a) one or more of the core and the first coating layer and (b) surrounding at least a portion of the first coating layer,

wherein the one or more additional layers comprise one or more of a seal coat, a film forming layer, a rate controlling polymer, and an active pharmaceutical ingredient.

93. The multiple unit dosage form of claim 92, wherein the seal coat comprises one or more of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, and methacrylic acid copolymers and the film forming layer comprises one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate, waxes, polyethylene glycol, and methacrylic acid polymers.

94. The multiple unit dosage form of claim 85, further comprising an outer layer, the outer layer comprising a material that is one or both of elastic and compressible.

95. The multiple unit dosage form of claim 94, wherein the material in the outer layer comprises one or more wax materials.

96. The multiple unit dosage form of claim 95, wherein the wax material comprises one or more polyethylene glycols (PEGs).

97. The multiple unit dosage form of claim 85, further comprising a buffering agent with the glipizide in the first coating layer.

98. The multiple unit dosage form 97, wherein the buffering agent comprises one or more of dibasic sodium phosphate, sodium ascorbate, meglumine, sodium citrate trimethanolamine, sodium hydroxide, potassium hydroxide, calcium hydroxide,

magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, and L-lysine.

99. The multiple unit dosage form of claim 85, wherein the dosage form comprises a tablet.

100. The multiple unit dosage form of claim 85, wherein the dosage form comprises a capsule.

101. A modified release multiple unit system comprising units of glipizide, wherein the units comprise:

an inert core;

a drug layer surrounding the inert core, the drug layer comprising glipizide; and

a rate controlling polymer layer surrounding the drug layer.

102. The modified release multiple unit system of claim 101, wherein the system comprises a tablet.

103. The modified release multiple unit system of claim 101, wherein the system comprises a capsule.

104. A modified release multiple unit system comprising units of glipizide wherein the units comprise:

an inert core;

a drug layer surrounding the inert core;

a rate controlling polymer layer surrounding the drug layer; and

a waxy layer surrounding the drug layer.

105. The modified release multiple unit system of claim 104, wherein the units can be compressed into tablet, or filled into a capsule or a sachet; without affecting the desired release characteristics of drug.

106. The modified release multiple unit system of claim 104, wherein the system comprises a tablet.

107. The modified release multiple unit system of claim 104, wherein the system comprises a capsule.

108. A modified release multiple unit system comprising units of venlafaxine, wherein the units comprise:

an inert core;

a drug layer surrounding the inert core; and

a rate controlling polymer layer surrounding the drug layer.

109. The modified release multiple unit system of claim 108, wherein the system comprises a tablet.

110. A modified release multiple unit system comprising units of venlafaxine wherein the units comprise:

an inert core;

a drug layer surrounding the inert core;

a rate controlling polymer layer surrounding the drug layer; and

a waxy layer surrounding the rate controlling polymer layer.

111. The modified release multiple unit system of claim 110, wherein the units can be compressed into tablet without affecting the desired release characteristics of drug.

112. A modified release multiple unit system comprising units of a drug wherein the units comprise:

an inert core;

a drug layer surrounding the inert core;

a rate controlling polymer layer surrounding the drug layer; and

a waxy layer surrounding the rate controlling polymer layer.

113. The modified release multiple unit system of claim 112, wherein the units can be compressed into tablet, or filled in capsule or sachet; without affecting the desired release characteristics of drug.

114. A process for the preparation of a modified release multiple unit system of a drug, the process comprising the steps of:

coating inert pellets with a drug and rate controlling polymer layer;

coating with a waxy layer;

optionally blending with pharmaceutically acceptable excipients;

compressing into a tablet, or filling into a capsule or a sachet of suitable size.

115. A process for the preparation of a modified release multiple unit system of drug, the process comprising the steps of:

coating inert pellets with a drug and rate controlling polymer layer;

coating with a waxy layer;

optionally blending with pharmaceutically acceptable excipients;

compressing into tablet of suitable size.

116. The process of claim 115, wherein the drug comprises venlafaxine or a pharmaceutically acceptable salt.

117. A process for the preparation of modified release multiple unit system of drug comprising the steps of:

coating drug containing cores with a rate controlling polymer layer;

coating the rate controlling polymer layer with a waxy layer;

optionally blending with pharmaceutically acceptable excipients; and

compressing into tablet, or filling into capsule or sachet of suitable size.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number
WO 2003/103637 A3

(51) International Patent Classification[7]: A61K 9/24, 9/26, 9/28, 9/52, 31/4965, 31/137

(21) International Application Number: PCT/IB2003/002186

(22) International Filing Date: 9 June 2003 (09.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

617/DEL/2002	7 June 2002 (07.06.2002)	IN
1157/DEL/2002	15 November 2002 (15.11.2002)	IN
234/DEL/2003	6 March 2003 (06.03.2003)	IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19 Nehru Place, New Delhi 110 019, Maharashtra (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KUMAR, Pratik** [IN/IN]; c/o Dr. Neelam Singh, Shivpri, Damuchowk, 842001 Muzaffarpur, Bihar (IN). **JAIN, Girish, Kumar** [IN/IN]; 4, Sharda Niketan, Teachers Colony, Pitampura, 110034 Dehli (IN). **RAMPAL, Ashok** [IN/IN]; 14, Sewa Nagar, Ram Tirath Road, 143001 Amritsar, Punjab (IN). **NITHIYANANDAM, Ravikumar** [IN/IN]; No. 24, Bairavan Kovil Street, Dharapuram, Erode District, Periyar, Tamil Nadu 638 656 (IN). **RAMAKRISHNAN, Sankar** [IN/IN]; 24, River Bank Street, Madukkur, Thanjavur District, Tamil Nadu 614 903 (IN). **RAGHUVANSHI, Rajeev, Singh** [IN/IN]; D8/8131, Vasant Kunj, 110070 New Delhi, Delhi (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jayadeep, R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report: 13 May 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODIFIED RELEASE, MULTIPLE UNIT DRUG DELIVERY SYSTEMS

(57) Abstract: The invention relates to novel modified release multiple unit systems, and methods of preparing these systems, which can be easily compressed into tablets or filled into capsules or sachets without affecting the desired release characteristics of the pharmaceutical active ingredients incorporated within the systems. The multiple unit tablet includes multiple units. Each unit includes at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, one or more rate controlling polymers, and one or more one active pharmaceutical ingredients. The coating layer includes one or both of the one or more active pharmaceutical ingredients and the one or more rate controlling polymers. The tablet may further include an outer layer on the outer surface of the unit which includes a material that is one or both of elastic and compressible. The material may be a wax materials, such as polyethylene glycol's (PEGS).

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INTERNATIONAL SEARCH REPORT

PCT/IB 03/02186

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/24 A61K9/26 A61K9/28 A61K9/52 A61K31/4965 A61K31/137

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/12524 A (NYCOMED DANMARK A S ;BERTELSEN POUL (DK); SKINHOEJ ANNETTE (DK)) 18 March 1999 (1999-03-18) example 1 claim 51 page 33, line 31 - line 35	1-9,12, 29-35, 37-39, 68-70, 73,76,77
X	US 4 713 248 A (KJORNAES KIM ET AL) 15 December 1987 (1987-12-15) cited in the application examples 2,7 abstract	1-4,6-9, 12,37, 38,68, 69,73,76

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 September 2003	22 01. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sindel, U

INTERNATIONAL SEARCH REPORT

PCT/IB 03/02186

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 783 215 A (ARWIDSSON HANS ET AL) 21 July 1998 (1998-07-21) cited in the application claim 1 examples 1,5	1,4-6,9, 13,14, 29,30, 32,33, 37,38, 68,69, 73,76
X,P	WO 03/041692 A (KARMA PHARM LTD ;SELA YORAM (IL)) 22 May 2003 (2003-05-22) examples 1-4 claims 1,6	1,4-11, 13,14, 29,30, 32,73, 108

INTERNATIONAL SEARCH REPORT

PCT/IB 03/02186

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 73-77 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [X] Claims Nos.: 1, 41 (part.), 68, 73 (part.), 82
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-14, 18-40, 41-67 (part), 68-72, 73-77 (part), 101-103, 108-109, 114-117

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 41 (part.), 68, 73 (part.), 82

Present claims 1, 41 (part.), 68, 73 (part.) and 82 relate to an extremely large number of possible compounds and products. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and products claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the formulations mentioned in the examples.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14, 18-40, 41-67 (part.), 68-72, 73-77 (part.), 101-103, 108-109, 114-117

   Multiple unit dosage form, each unit comprising at least one core, a first coating layer and an outer layer

   ---

2. claims: 15-17, 41-67 (part.), 73-77 (part.), 104-107, 110-113

   Multiple unit dosage form, each unit comprising at least one core, a first coating layer, one or more additional layers and an outer layer

   ---

3. claims: 78-81, 85-100

   Multiple unit dosage form, each unit comprising at least one core and a coating layer

   ---

4. claims: 82-84

   Combination drug comprising two different multiple unit dosage forms

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INTERNATIONAL SEARCH REPORT

PCT/IB 03/02186

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number
WO 03/106421 A2

(51) International Patent Classification[7]: C07D 215/00

(21) International Application Number: PCT/EP03/06290

(22) International Filing Date: 16 June 2003 (16.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2002A001329 14 June 2002 (14.06.2002) IT

(71) Applicant *(for all designated States except IT)*: **RECORDATI S.A.** [CH/CH]; Piazza Boffalora 4, CH-6830 Chiasso (CH).

(71) Applicant *(for IT only)*: **RECORDATI INDUSTRIA CHIMICA E FARMACEUTICA SPA** [IT/IT]; Via Matteo Civitali, 1, I-20148 Milano (IT).

(72) Inventors: **LEONARDI, Amedeo**; Via Poliziano, 16, I-20154 Milano (IT). **MOTTA, Gianni**; Via Ungaretti, 10, I-20030 Barlassina (IT). **RIVA, Carlo**; Via Walder, 10, I-21100 Varese (IT). **GUARNERI, Luciano**; Via Canova, 18, I-20024 Garbagnate Milanese (IT).

(74) Agent: **SERJEANTS**; 25 The Crescent, King Street, Leicester LE1 6RX (GB).

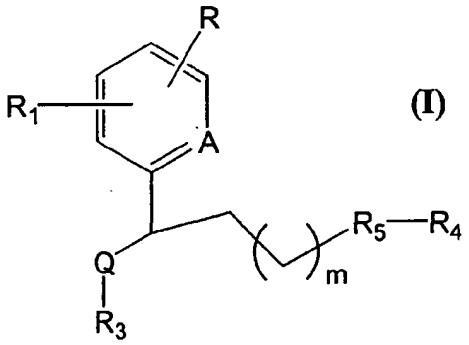
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

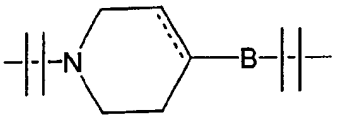
Published:
— *without international search report and to be republished upon receipt of that report*

[Continued on next page]

(54) Title: PHENYLALKYLAMINES AND PYRIDYLALKYLAMINES



(I)



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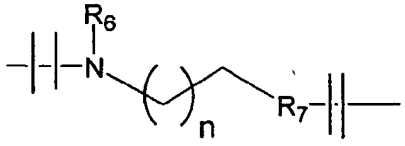


(III)

(57) Abstract: Compounds of formula (I): (A is CH or N, R and R_1 are a wide range of substituents, Q is CO, CHOH or $CHOR_2$, R_2 is alkyl, alkenyl, alkynyl or cycloalkyl group, each of which is optionally substituted, or is alkanoyl, alkanoyoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminothiocarbonyl, alkylaminothiocarbonyl or dialkylaminothiocarbonyl, R_3 is H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted, m is 1 or 2, R_4 is an aryl or heteroaryl group, either of which is optionally substituted, R_5 is either (II) or (III), wherein m is 1 or 2, R_6 is H or alkyl, R_7 is O, S, NR_6 or CH_2, B is a bond, O, S, NR_6 or CH_2 and ------- represents a single or double bond) have affinity for serotoninergic receptors. These compounds and their enantiomers, diastereoisomers, N-piperazine oxides, polymorphs, solvates and pharmaceutically acceptable salts are useful in the treatment of patients with neuromuscular dysfunction of the lower urinary tract and diseases related to 5-HT_{1A} receptor activity.

WO 03/106421 A2

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE

Phenylalkylamines and Pyridylalkylamines

DESCRIPTION

The invention relates to phenylalkylamines and pyridylalkylamines having affinity for serotoninergic receptors, pharmaceutical compositions thereof and uses for such compounds and compositions.

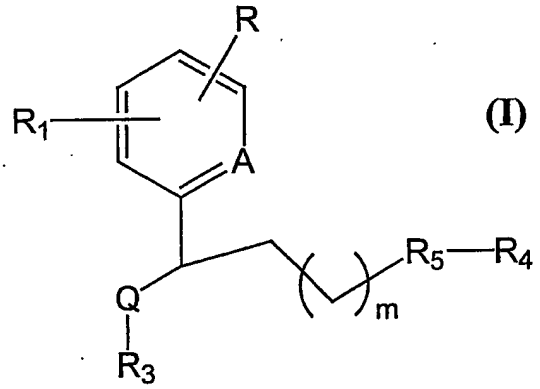
In mammals, micturition (urination) is a complex process that requires the integrated action of the bladder, its internal and external sphincters, the musculature of the pelvic floor and neurological control over these muscles at three levels (in the bladder wall or sphincter itself, in the autonomic centres of the spinal cord and in the central nervous system at the level of the pontine micturition centre (PMC) in the brainstem (pons) under the control of the cerebral cortex) (De Groat, *Neurobiology of Incontinence*, Ciba Foundation Symposium 151:27, 1990). Micturition results from contraction of the detrusor muscle, which consists of interlacing smooth-muscle fibres, under the control of the parasympathetic autonomic system originating from the sacral spinal cord. A simple voiding reflex is triggered by sensory nerves for pain, temperature and distension that run from the bladder to the sacral spinal cord. However, sensory tracts from the bladder reach the PMC too, generating nerve impulses that normally suppress the sacral spinal suppression of cortical inhibition of the reflex arc, and relaxing the muscles of the pelvic floor and external sphincter. Finally, the detrusor muscle contracts and voiding occurs. Abnormalities of lower-urinary tract function, e.g. dysuria, incontinence and enuresis, are common in the general population. Dysuria includes urinary frequency, nocturia and urgency, and may be caused by cystitis (including interstitial cystitis), prostatitis or benign prostatic hyperplasia (BPH) (which affects about 70% of elderly males), or by neurological disorders. Incontinence syndromes include stress incontinence, urgency incontinence, overflow incontinence and mixed incontinence. Enuresis refers to the involuntary passage of urine at night or during sleep.

Previously, treatment of neuromuscular dysfunction of the lower urinary tract involved administration of compounds that act directly on the bladder muscles, such as flavoxate, a spasmolytic drug (Ruffman, *J. Int. Med. Res.* 16:317, 1988) which is also active on the PMC (Guarneri *et al.*, *Drugs of Today*, 30:91, 1994), or anticholinergic compounds such as oxybutynin (Andersson, *Drugs* 36:477, 1988) and tolterodine

(Nilvebrant, *Life Sci.* 68(22-23): 2549, 2001). The use of α1-adrenergic receptor antagonists for the treatment of BPH is common too, but is based on a different mechanism of action (Lepor, *Urology*, 42:483, 1993). However, treatments that involve direct inhibition of the pelvic musculature (including the detrusor muscle) may have unwanted side effects, such as incomplete voiding or accommodation paralysis, tachycardia and dry mouth (Andersson, *Drugs* 35:477, 1988). Thus, it would be preferable to utilize compounds that act via the central nervous system to, for example, affect the sacral spinal reflex and/or the PMC inhibition pathways in a manner that restores normal functioning of the micturition mechanism.

EP 0982304 discloses 5-HT_{1A} binding agents which may be used in the treatment of CNS disorders, such as depression.

The invention provides compounds of formula I



(I)

wherein

R represents a hydrogen atom or one or more substituents selected from the group consisting of (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_1-C_6)-haloalkyl, (C_1-C_6)-haloalkoxy, (C_1-C_6)-hydroxyalkyl, alkoxy-(C_1-C_6)-alkyl, nitro, amino, (C_1-C_6)-aminoalkyl, N-(C_1-C_6)-alkylamino, N-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl, N, N-di-(C_1-C_6)-alkylamino, acylamino, (C_1-C_6)-alkylsulphonylamino, aminosulphonyl, (C_1-C_6)-alkylaminosulphonyl, cyano, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl, alkylcarbonyl-(C_1-C_6)-alkyl, formyl, alkanoyloxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkylaminocarbonylamino, (C_1-C_6)-alkylsulphinyl, (C_1-C_6)-alkylsulphonyl, and N, N-di-(C_1-C_6)-alkylaminosulphonyl groups;

R_1 is selected from the group consisting of hydrogen, cycloalkyl, aryl, aryloxy,

aralkyl, aralalkoxy, heterocyclic, heterocycloxy, heterocycloalkyl and heterocycloalkoxy groups, each group being optionally substituted with one or more substituent R, defined as above;

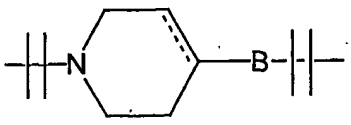
Q represents -C(O)- or -CH(OR_2)- where R_2 represents a member selected from the group consisting of hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl and cycloalkyl groups, wherein each group is optionally substituted with one or more groups selected from R_8 or R_9, where R_8 is selected from the group consisting of halo, (C_1-C_6)-alkoxy, (C_1-C_6)-haloalkoxy, cyano, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl, alkoxyalkyl, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl groups and R_9 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, and heteroarylalkoxy groups, each optionally substituted with R, or R_2 represents -C(O)-(C_1-C_6)-alkyl, -C(O)O-(C_1-C_6)-alkyl, -C(O)$NR_{10}R_{11}$ or -C(S)$NR_{10}R_{11}$ wherein R_{10} and R_{11} are independently hydrogen or (C_1-C_6)-alkyl;

R_3 represents (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, cycloalkyl, aryl or heterocycle, each being optionally substituted with one or more substituent R or R_1, defined as above;

R_4 represents aryl or heterocyclic, each being optionally substituted with one or more substituents R, defined as above;

A represents CH or N,

R_5 represents group (i) or group (ii)



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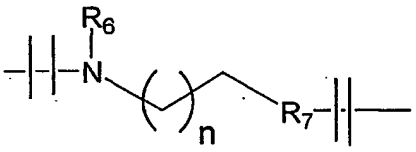


(ii)

(where R_4 is bound to the right of each group)

m and n are independently 1 or 2,

R_6 represents H or alkyl,

R_7 represents O, S, NR_6 or CH_2;

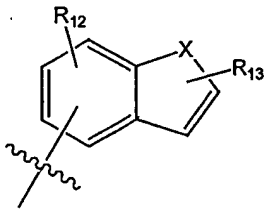
B represents a bond, O, S, NR_6 or CH_2; and

------- represents a single or double bond,

or an enantiomer, optical isomer, diastereomer, N-oxide (e.g., N-piperidine oxide), crystalline form, hydrate, solvate or pharmaceutically acceptable salt thereof.

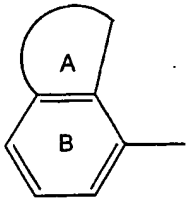
In certain embodiments, the invention provides compounds of formula I with the

proviso that the substituents of formula I are not such that simultaneously Q represents-C(O)- or -CH(OR_2)- where R_2 represents hydrogen; R represents a hydrogen atom or one or more substituents selected from the group consisting of (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_1-C_6)-haloalkyl, nitro, amino and cyano groups; R_1 is selected from the group consisting of hydrogen, unsubstituted phenyl, and alkylphenyl groups; R_3 represents cycloalkyl, aryl or heterocycle, each being optionally substituted with one or more substituent selected from the group consisting of (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_1-C_6)-haloalkyl, nitro, amino, cyano, unsubstituted phenyl, and alkylphenyl groups; R_5 represents group (i) wherein B represents a bond or CH_2; and R_4 represents the group



wherein X represents O, S, NH, N(C_1-C_6-alkyl), S(=O) or S(=O)$_2$, and R_{12} and R_{13} each represent one or more member selected independently from the group consisting of halo, hydroxy, alkyl, alkoxy, haloalkyl, alkylthio, nitro, amino, cyano, N-(C_1-C_6)-alkylamino, N, N-di-(C_1-C_6)-alkylamino, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl and acylamino groups.

In certain embodiments, the invention provides compounds of formula I with the proviso that the substituents of formula I are not such that simultaneously Q represents-C(O)-; R represents a hydrogen atom or one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, N, N-di-alkylamino, aminocarbonyl and alkoxycarbonyl groups; R_1 represents hydrogen; R_5 represents group (i) wherein B represents a bond or CH_2; R_4 represents an aryl or fully aromatic heteroaryl, each optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, N, N-di-alkylamino, aminocarbonyl and alkoxycarbonyl groups, or R_4 represents a bicyclic heteroaryl radical of formula



wherein A is a saturated or unsaturated ring having one or more heteroatoms, where rings A and B are each independently substituted with one or more substituent selected from the group consisting of alkyl, halo, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, alkanoyloxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, , amino, N-alkylamino and N,N,- di-alkylamino; and R_3 represents a saturated heterocyclic ring comprising a nitrogen atom, through which said saturated heterocyclic ring is bonded to the adjacent carbonyl group at Q, and which may optionally include a further hetero atom, and which may also be optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo and haloalkyl groups.

Preferred compounds of the invention include those whose preparation is described in the Examples below.

Compounds of formula I can exist as four stereoisomers, which may be present in racemic mixtures or in any other combination. Racemic mixtures can be resolved, i.e., subjected to enantiomeric enrichment, to yield compositions enriched with a particular enantiomer. Enantiomeric enrichment can be expressed as ee (enantiomeric excess) as defined below.

The invention also includes metabolites of the foregoing compounds having the same type of activity, hereinafter referred to as active metabolites.

The invention also contemplates prodrugs which are metabolized in the body to generate any of the foregoing compounds.

In another embodiment, the invention provides pharmaceutical compositions comprising compounds of formula I, enantiomers, diastereomers, N-oxides, crystalline forms, hydrates, solvates or pharmaceutically acceptable salts of such compounds of formula I, in admixture with pharmaceutically acceptable diluents or carriers such as those disclosed.

Yet another embodiment is a method for reducing the frequency of bladder contractions due to bladder distension in a mammal (such as a human) in need thereof by administering an effective amount of at least one compound of the present invention to reduce the frequency of bladder contractions due to bladder distension to the mammal.

Yet another embodiment is a method for increasing urinary bladder capacity in a mammal (such as a human) in need thereof by administering an effective amount of at least one compound of the present invention to increase urinary bladder capacity to the mammal.

Yet another embodiment is a method for treating disorders of the urinary tract in a mammal (such as a human) in need thereof by administering an effective amount of at least one compound of the present invention to ameliorate at least one condition among urinary urgency, overactive bladder, increased urinary frequency, decreased urinary compliance (decreased bladder storage capacity), cystitis (including interstitial cystitis), incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the bladder.

In yet other embodiments, the invention provides for methods of treating the above disorders, by administering a compound of formula I in combination with other agents such as, for example, one or more additional $5HT_{1A}$ antagonist, antimuscarinic drugs, α1-adrenergic antagonists, inhibitors of the cyclooxygenase enzyme, which may inhibit both COX1 and COX2 isozymes or which may, alternatively, be selective for COX2 isozyme, and NO donor derivatives thereof.

In yet another embodiment, the present invention provides a method for treating a mammal suffering from a central nervous system (CNS) disorder manifest in a serotoninergic dysfunction by administering an effective amount of at least one compound of the present invention to treat the CNS disorder. Such dysfunctions include, but are not limited to, anxiety, depression, hypertension, sleep/wake cycle disorders, feeding disorders, behaviour disorders, sexual dysfunction and cognition disorders in mammals (particularly in humans) associated with stroke, injury, dementia, and originated by neurological development, attention-deficit hyperactivity disorders (ADHD), drug addiction, drug withdrawal, irritable-bowel syndrome. Treatment may be effected by delivering a compound of the invention to the environment of a $5\text{-}HT_{1A}$ serotoninergic receptor, for example, to the extracellular medium (or by systemically or locally administering the compound to a mammal possessing such receptor) an amount of a compound of the invention effective to increase the duration of bladder quiescence with no contractions.

COMPOUNDS

The invention relates to compounds of formula I as disclosed above. The invention includes the enantiomers, diastereoisomers, N-oxides, crystalline forms, hydrates, solvates or pharmaceutically acceptable salts of these compounds, as well as active metabolites of these compounds having the same type of activity.

The term "haloalkyl" includes alkyl groups substituted by a single halogen atom (monohaloalkyl) and those substituted by more than one halogen atom (polyhaloalkyl). Examples of the latter are trifluoromethyl and 2,2,2-trifluoroethyl groups. The term haloalkoxy is to be interreted correspondingly. Preferred haloalkoxy groups include trifluoromethoxy and 2,2,2-trifluoroethoxy groups.

The term "aryl", alone or in combination, refers to a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.

The terms "heterocyclic" and "heterocyclo" refer to saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulphur and oxygen. Examples of saturated heterocyclic radicals include saturated heteromonocylic groups containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl); saturated heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., morpholinyl); saturated heteromonocyclic groups containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl). Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

The terms "heterocyclo" and "heterocyclic" encompass the term "heteroaryl," which refers to unsaturated heterocyclic radicals. Examples of "heteroaryl" radicals include unsaturated 5 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl) tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl); unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl); unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl; unsaturated 5 to 6-membered heteromonocyclic groups containing a sulphur atom, for example, 2-thienyl, 3-thienyl; unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl); unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., benzoxazolyl, benzoxadiazolyl); unsaturated 5 to 6-membered

heteromonocyclic groups containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl); unsaturated condensed heterocyclic groups containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl) and the like. The term "heteroaryl" also refers to radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" may have 1 to 3 substituents such as, for example and without limitation, lower alkyl, hydroxy, oxo, amino and lower alkylamino. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. Examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl.

The term "cycloalkyl" refers to saturated carbocyclic radicals having three to ten carbon atoms. Preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A most preferred cycloalkyl group is cyclohexyl.

The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from a carboxylic acid. Preferred acyl groups are alkanoyl groups, such as acetyl.

A "metabolite" of a compound disclosed herein is a derivative of a compound which is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolised. The term "metabolized" refers to the sum of the processes by which a particular substance is changed in the living body.All compounds present in the body are manipulated by enzymes within the body in order to derive energy and/or to remove them from the body. Specific enzymes produce specific structural alterations to the compound. Cytochrome P450, for example, catalyses a variety of oxidative and reductive reactions. Uridine diphosphate glucuronyltransferases , for example, catalyse the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphhydryl groups. Further information on metabolism may be obtained from *The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill (1996), pages 11-17.

The metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells or other *in vitro* systems such as cytochromes or microsomes, and analysis of the resulting compounds. Both methods are well known in the art.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. As used herein, the term "optical isomer" is equivalent to the term "enantiomer". Compounds that are stereoisomers of one another, but are not enantiomers of one another, are called diastereoisomers. The terms "racemate" or "racemic mixture" refer to a mixture of equal parts of enantiomers. The term "chiral center" refers to a carbon atom to which four different groups are attached. The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

$$ee = \frac{E1 - E2}{E1+E2} * 100$$

wherein E1 is the amount of the first enantiomer and E2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 50:30 is achieved, the ee with respect to the first enantiomer is 25%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. According to one embodiment of the invention, an ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is determined by one of ordinary skill in the art using standard techniques and procedures, such as high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is within the knowledge of one of ordinary skill in the art. In addition, the enantiomers of compounds of formula I can be resolved by one of ordinary skill in the art using standard techniques well known in the art, such as

those described by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981. Examples of resolutions include recrystallization techniques or chiral chromatography.

Diastereoisomers differ in both physical properties and chemical reactivity. A mixture of diastereomers can be separated into enantiomeric pairs based on solubility, fractional crystallization or chromatographic properties, e.g., thin layer chromatography, column chromatography or HPLC.

Purification of complex mixtures of diastereomers into enantiomers typically requires two steps. In a first step, the mixture of diastereomers is resolved into enantiomeric pairs, as described above. In a second step, enantiomeric pairs are further purified into compositions enriched for one or the other enantiomer or, more preferably resolved into composition comprising pure enantiomers. Resolution of enantiomers typically requires reaction or molecular interaction with a chiral agent, e.g., a solvent or column matrix. Resolution of enantiomers may be achieved, for example, by converting the mixture of enantiomers, e.g., a racemic mixture, into a mixture of diastereomers by reaction with a pure enantiomer of a second agent, i.e., a resolving agent. The two resulting diastereomeric products can then be separated. The separated diastereomers are then reconverted to the pure enantiomers by reversing the initial chemical transformation.

Resolution of enantiomers can also be accomplished by differences in their non-covalent binding to a chiral substance, e.g., by chromatography on homochiral absorbants. The noncovalent binding between enantiomers and the chromatographic adsorbant establishes diastereomeric complexes, leading to differential partitioning in the mobile and bound states in the chromatographic system. The two enantiomers therefore move through the chromatographic system, e.g, column, at different rates, allowing for their separation.

Chiral resolving columns are well known in the art and are commercially available (e.g., from MetaChem Technologies Inc., a division of ANSYS Technologies, Inc., Lake Forest, CA). Enantiomers can be analyzed and purified, for example,using chiral stationary phases (CSPs) for HPLC. Chiral HPLC columns tipically contain one form of an enantiomeric compound immobilized to the surface of a silica packing material. For chiral resolution to occur, there must be at least three points of simultaneous interaction between the CSP and one analyte enantiomer, with one or more of these interactions being stereochemically dependent.

D-phenylglycine and L-leucine are Type I CSPs and use combinations of p-p

interactions, hydrogen bonds, dipole-dipole interactions, and steric interactions to achieve chiral recognition. To be resolved on a Type I column, analyte enantiomers must contain functionality complementary to that of the CSP so that the analyte undergoes essential interactions with the CSP. The sample should preferably contain one of the following functional groups: p-acid or p-base, hydrogen bond donor and/or acceptor, or an amide dipole. Derivatization is sometimes used to add the interactive sites to those compounds lacking them. The most common derivatives involve the formation of amides from amines and carboxylic acids.

The MetaChiral ODM™ is a type II CSP. The primary mechanisms for the formation of solute-CSP complexes is through attractive interactions, but inclusion complexes also play an important role. Hydrogen bonding, pi-pi, and dipole stacking are important for chiral resolution on the MetaChiral™ ODM. Derivatization is often necessary when the solute molecule does not contain the groups required for solute-column interactions. Derivatization, usually to benzylamides, is also required of some strongly polar molecules like amines and carboxylic acids, which would otherwise interact too strongly with the stationary phase through non-stereo- specific interactions.

The invention provides compounds of formula I as set forth above.

In certain embodiments, formula I set forth above may include a proviso that excludes compounds represented by the generic formula disclosed in US 6436964.

In certain embodiments, formula I set forth above may include a proviso that excludes compounds represented by the generic formula disclosed in US 5585374.

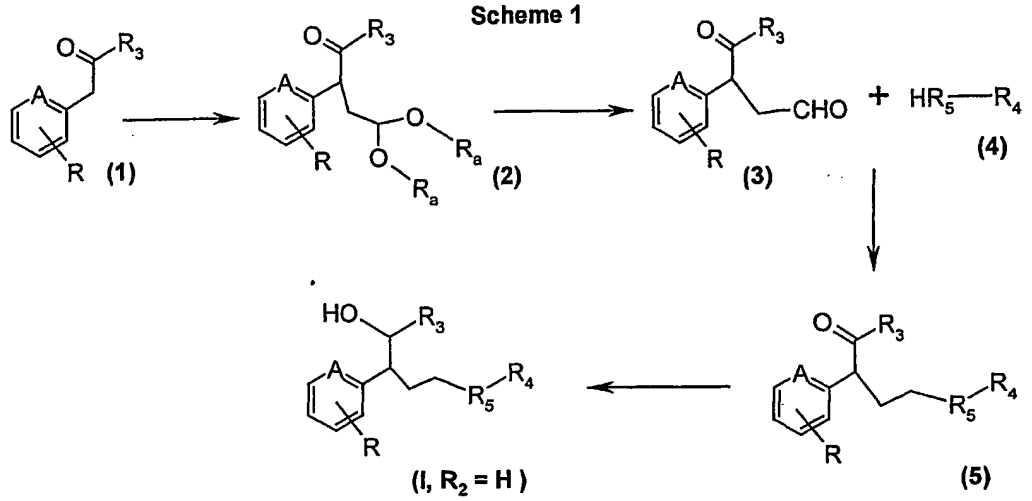
In certain embodiments, formula I set forth above may include a proviso that excludes compounds represented by the generic formulas disclosed in both US 6436964 and US 5585374.

Compounds of formula I can be separated into diastereomeric pairs by, for example, by separation by TLC.These diastereomeric pairs are referred to herein as diastereoisomer with upper TLC Rf; and diastereoisomer with lower TLC Rf. The diastereoisomers can further be enriched for a particular enantiomer or resolved into a single enantiomer using methods well known in the art , such as those described herein.

SYNTHESIS OF THE COMPOUNDS OF THE INVENTION

The compounds of the invention are generally prepared according to the following schemes:

Scheme 1



Group R is the same as (R+ R_1) as given in the general formula I. A, R_2, R_3, R_4 and R_5 have the same meanings as given in the general formula I and R_a is a lower alkyl group.

Starting material (1) is treated with a base, preferably potassium tert-butoxide, followed by alkylation with 2-bromoacetaldehyde dialkyl acetal or other carbonyl protected 2-haloacetaldehyde (e.g., the R_a alkyl groups can also be joined in a cycle to give a dioxolane or dioxane ring). Other alternative and appropriate bases to carry out the condensation include lithium amides, sodium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, cesium carbonate and the like with the aid or not of phase transfer catalysts. The reaction is preferably carried out in a solvent such as dimethyl sulfoxide or toluene at a temperature of 0°C to reflux.

The use of 3-bromopropionaldehyde dialkyl acetal or other carbonyl protected 3-halopropionaldehyde allow to obtain, by following the same reaction conditions described above in Scheme 1, compound I having m = 2 as foreseen in the general formula.

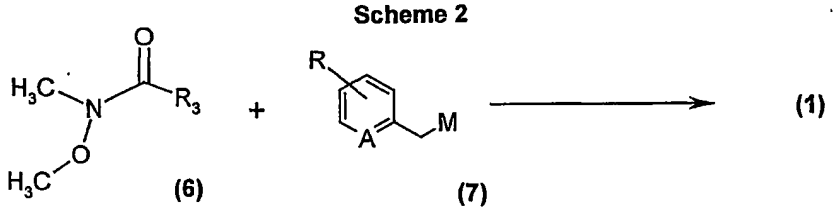
Treatment of (2) with an acid, such as hydrochloric acid or p-toluenesulfonic acid or trifluoroacetic acid in a suitable organic solvent, achieves aldehyde (3). Generally, the reaction is conducted in a protic solvent, such a mixture of aqueous acid and acetone or tetrahydrofuran, at temperatures of 5°C to 75°C, preferably at ambient temperature. A preferred similar method consists of carrying out the reaction in a mixture of aqueous trifluoroacetic acid in a chlorinated solvent at r.t.

Aldehyde (3) is coupled with the desired amine (4) by reductive amination procedure to prepare (5). The reaction is preferably carried out at ambient temperature in

a chlorinated solvent such as dichloroethane or methylene chloride or chloroform in the presence of sodium triacetoxyborohydride and is substantially complete in one to 24 hours (see for example A. F. Abdel-Magid et al., *J. Org. Chem.*, 61, 3849 (1996)) or can be carried out in a protic solvent (e.g., methanol) with the aid of sodium cyanoborohydride, optionally in the presence of molecular sieves.

Reduction of (5) to the alcohol (I) is readily accomplished using a reducing agent such as sodium borohydride or diisobutylaluminum hydride or other aluminum or boron hydride or other reduction method to carry out the conversion ketone to alcohol, well known to those skilled in the art, to prepare the hydroxy compound (I). The reaction is preferably carried out in an organic solvent such as methanol or methylene chloride or tetrahydrofuran at temperatures of -20°C to 0°C - ambient temperature.

Scheme 2



Starting material (1) is either commercially available or can be prepared by coupling the appropriate Weinreb amide (6) (See Nahm et al., *Tetrahedron Lett.*, 22, 3815, (1981)) with (7), as described in Scheme 2 above, where M is a metallic salt, such as lithium or magnesium halide. The reaction is preferably carried out under nitrogen atmosphere, in an aprotic solvent, such as tetrahydrofuran, at ambient or lower temperatures down to -78°C.

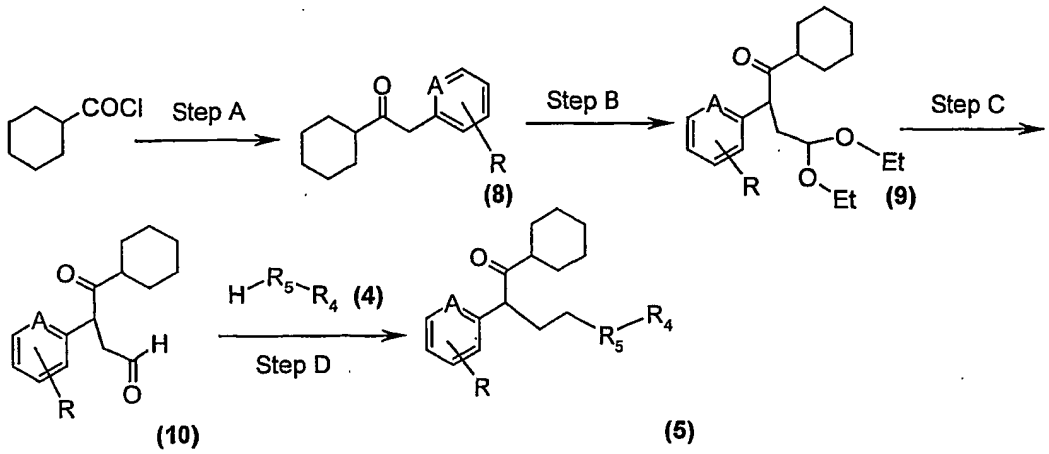
Alternatively, an ester of structure $R_3COOalkyl$ can be treated with a substituted benzylmagnesium chloride or benzylmagnesium bromide or lithium derivative under standard conditions well known in the art to provide the ketone of structure (1).

An alternative route to obtain compounds (1) consists of reacting the appropriate arylaldehyde with an alkylnitro derivative in a nitroaldol fashion, dehydration of the nitro alcohol thus obtained, followed by double bond reduction afford a 2-nitro(2–Ak)phenethyl derivative, which can undergo Nef reaction to yield the wished keto derivative 1. This kind of pathway is well documented in the experimental part and in the literature.

A preferred similar way of synthesis of (1) is the palladium catalysed coupling of an acyl halide with a compound (7) where M is Zn halide. More specifically, the compounds of formula (5) can be prepared following the procedure described in Scheme

3. All substituents, unless otherwise indicated, are as defined previously. The reagents and starting materials are readily available to one of ordinary skill in the art.

Scheme 3



In Scheme 3, step A, for example, cyclohexanecarbonyl chloride is added to a mixture of the suitable benzylzinc chloride(bromide) and an appropriate palladium catalyst, e.g., dichlorobis(triphenylphosphine)palladium (II) stirred at 0°C in a solvent such as tetrahydrofuran. Afterwards, stirring is continued at r.t. for 4-24 h. Then the reaction is quenched for example with an aqueous saturated solution of ammonium chloride. Typical work-up procedure by extraction provides the ketone **(8)**. Ketone **(8)** can be purified by techniques well known in the art, such as flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/hexane to provide the purified material. Alternatively, the crude ketone **(8)** can be used in step B without purification.

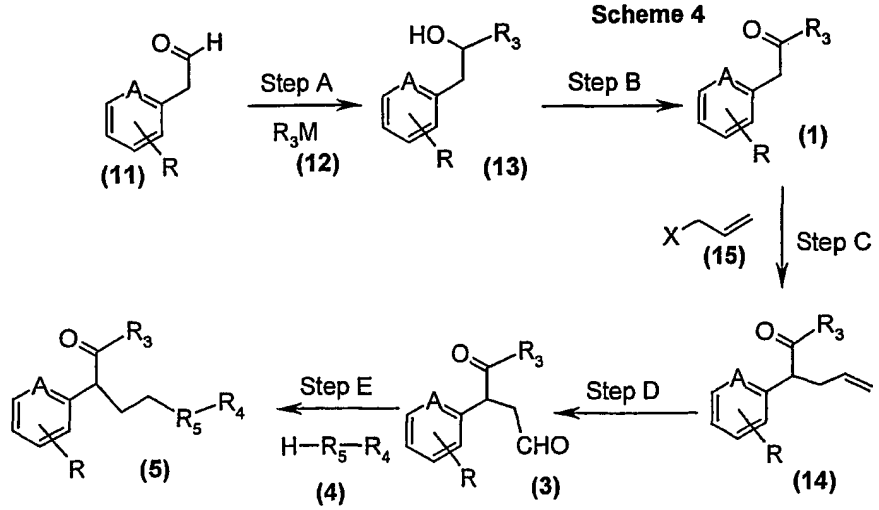
In Scheme 3, step B, ketone **(8)** is alkylated with bromoacetaldehyde diethyl acetal under conditions well known in the art to provide compound of structure **(9)**. For example, ketone **(8)** is dissolved in a suitable organic solvent, such as dimethyl sulfoxide or toluene and treated with a slight excess of a suitable base, such as potassium tert-butoxide. The reaction is stirred for about 15 to 30 minutes at a temperature of between 0°C and the reflux temp. of the solvent and bromoacetaldehyde diethyl acetal is added dropwise to the reaction. One of ordinary skill in the art would readily appreciate that bromoacetaldehyde dimethyl acetal, bromoacetaldehyde ethylene acetal and the like may be used in place of the corresponding diethyl acetal.

In Scheme 3, step C, compound **(9)** is hydrolyzed under acidic conditions to provide aldehyde **(10)** in a manner analogous to the procedure described in Scheme 1. More specifically, for example, compound **(9)** is dissolved in a suitable organic solvent,

such as dichloromethane and treated with a suitable acid, such as aq. trifluoroacetic acid. The reaction mixture is stirred for about 1 to 6 hours at room temperature. The reaction mixture is then diluted with the same solvent, washed with brine; the organic layer is separated, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to provide aldehyde (**10**). Aldehyde (**10**) can be purified by techniques well known in the art, such as flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/hexane. Alternatively, crude aldehyde (**10**) can be used directly in step D.

In Scheme 3, step D, aldehyde (**10**) is reductively aminated, under conditions well known in the art, with amine (**4**) to provide the ketone (**5**) in a manner analogous to the procedure described in Scheme 1. More specifically, for example, aldehyde (**10**) is dissolved in a suitable organic solvent, such as methylene chloride. To this solution is added about 1.05 or more equivalents of amine (**4**). Acetic acid may optionally be added to aid in dissolution of the amine (**4**). Then about 1.4 to 1.5 equivalents of sodium triacetoxyborohydride is added and the reaction is stirred at room temperature for about 3 to 5 hours. The reaction is then quenched by addition of a suitable base, such as aqueous sodium carbonate or hydroxide to provide a pH from 8 to about 12. The quenched reaction is then extracted with a suitable organic solvent, such as methylene chloride. The organic extracts are combined, washed with brine, dried, filtered and concentrated under vacuum to provide the compound of formula (**5**). This material can then be purified by techniques well known in the art, such as flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/petroleum ether or hexane.

Scheme 4



Alternatively, compounds of structure (**5**) can be prepared following the procedure described in Scheme 4. All substituents, unless otherwise indicated, are previously

defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

In Scheme 4, step A, aldehyde **(11)** is combined with a suitable organometallic reagent **(12)** under conditions well known in the art to provide alcohol **(13)**. Examples of suitable organometallic reagents include Grignard Reagents, alkyl lithium reagents, alkyl zinc reagents, and the like. Grignard Reagents are preferred. For examples of typical Grignard Reagents and reaction conditions, see J. March, "*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*", 2nd Edition, McGraw-Hill, pages 836-841 (1977). More specifically, aldehyde **(11)** is dissolved in a suitable organic solvent, such as tetrahydrofuran or toluene, cooled to about -5°C and treated with about 1.1 to 1.2 equivalents of a Grignard reagent of formula **(12)** wherein M is MgCl or MgBr. The reaction is stirred for about 0.5 to 6 hours, then quenched, and alcohol **(13)** is isolated by well-known work-up procedure.

In Scheme 4, step B, alcohol **(13)** is oxidized under standard conditions well know in the art, such as those described by J. March, "*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*", 2nd Edition, McGraw-Hill, pages 1082-1084 (1977), to provide ketone (1). (Ketone (1) is the starting material used in Scheme 1 above.)

For example, the above oxidation is also performed using standard Swern Oxidation conditions which are well known to one of ordinary skill in the art, or the alcohol **(13)** is dissolved in a suitable organic solvent, such as methylene chloride, the solution cooled with a wet ice-acetone bath, and treated with 2.5 to 3.0 equivalents of dimethyl sulfoxide. After stirring for about 30 minutes, the reaction is then treated with about 1.8 equivalents of P_2O_5. The reaction is stirred for about 3 hours and then, preferably, treated over about 30 minutes with about 3.5 equivalents of a suitable amine, such as triethylamine. The cooling bath is then removed and the reaction is stirred for about 8 to 16 hours. The ketone **(1)** is then isolated by standard extraction techniques well known in the art.

In Scheme 4, step C, ketone **(1)** is treated with a suitable base followed by addition of the alkene **(15)**, wherein X is a suitable leaving group, to provide compound **(14)**. For example, ketone **(1)** is combined with an excess of alkene **(15)** in a suitable organic solvent, such as tetrahydrofuran, and cooled with a wet ice acetone bath. Examples of suitable leaving groups are Cl, Br, I, tosylate, mesylate, and the like. Preferred leaving groups are Cl and Br. About 1.1 equivalents of a suitable base are added and the reaction is allowed to stir for about 2 hours at room temperature. Examples of

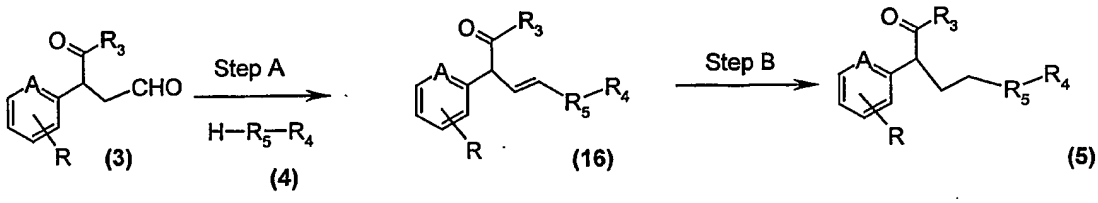
suitable bases are potassium tert-butoxide, sodium hydride, $NaN(Si(CH_3)_3)_2$, LDA, $KN(Si(CH_3)_3)_2$, $NaNH_2$, sodium ethoxide, sodium methoxide and the like. Potassium tert-butoxide is the preferred suitable base. The reaction is then quenched with aqueous acid and compound **(14)** is isolated by usual work-up procedure.

In Scheme 4, step D, compound **(14)** is treated with a suitable oxidizing agent to provide aldehyde **(3)**. (Aldehyde **(3)** is also prepared in Scheme 1.) Examples of suitable oxidizing agents are ozone, $NaIO_4$ /Osmium catalyst, and the like. Ozone is the preferred oxidizing agent. Examples of suitable oxidizing reagents and conditions are described by J. March, "*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*", 2nd Edition, McGraw-Hill, pages 1090-1096 (1977).

For example, compound **(14)** is dissolved in a suitable organic solvent, such as methanol, a small amount of Sudan III is added, and the solution is cooled to about -20°C. Ozone is bubbled into the solution for about 4 hours until the pink color turns to a pale yellow color. Then a reducing agent such as Me_2S or tributylphosphine is added. Concentration provides the intermediate dimethyl acetal of aldehyde **(3)**. This dimethyl acetal is readily hydrolyzed under standard acidic conditions to provide aldehyde **(3)**. Alternatively, direct acidic work-up of the crude reaction mixture provides aldehyde **(3)**. Alternatively, aldehyde **(3)** can be obtained directly by ozonolysis of **(14)** in a non-acetal forming solvent, such as methylene chloride.

In Scheme 4, step E, aldehyde **(3)** is reductively aminated under conditions analogous to those described above in Scheme 3, step D, to provide compound **(5)**. (Compound **5** is also prepared in Scheme 1.)

Scheme 5



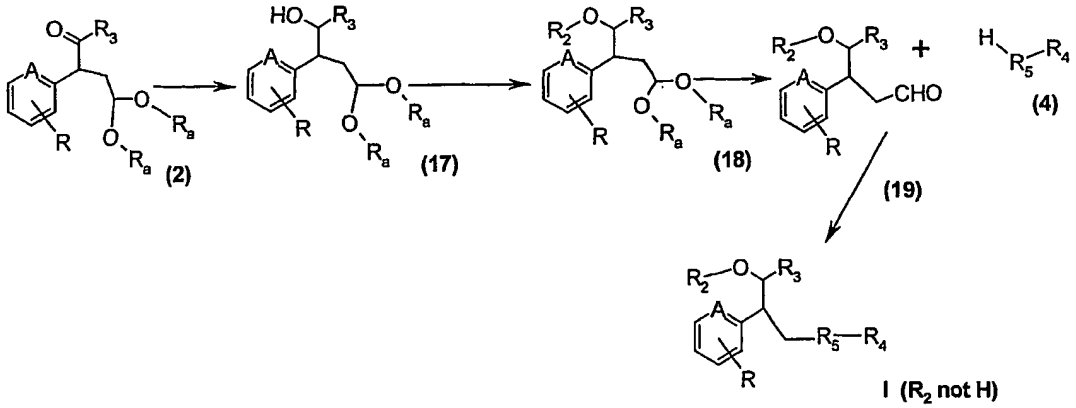
Scheme 5 provides an alternative synthesis for the preparation of ketone **(5)**. All substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

In Scheme 5, step A, aldehyde **(3)** is condensed with amine **(4)** under standard conditions well known in the art to provide the enamine **(16)**. For example, about 1.05 equivalents of aldehyde **(3)** dissolved in a suitable organic solvent, such as isopropyl

acetate or isopropanol, is added to neat amine (4), free base. Additional organic solvent is added to produce a slurry and the reaction is stirred for about 1 to 2 hours. The enamine (16) is then isolated by standard techniques, such as collection by filtration.

In Scheme 5, step B, the enamine (16) is hydrogenated under conditions well known to one of ordinary skill in the art to provide compound (5). For example, enamine (16) is combined with a suitable organic solvent, such as isopropyl alcohol and a catalytic amount of 5% palladium on carbon in a Parr bottle. The mixture is placed under 50 psi of hydrogen and shaken for about 2 days at room temperature. The slurry is then filtered to remove catalyst and the filtrate is concentrated to provide compound (5).

Scheme 6

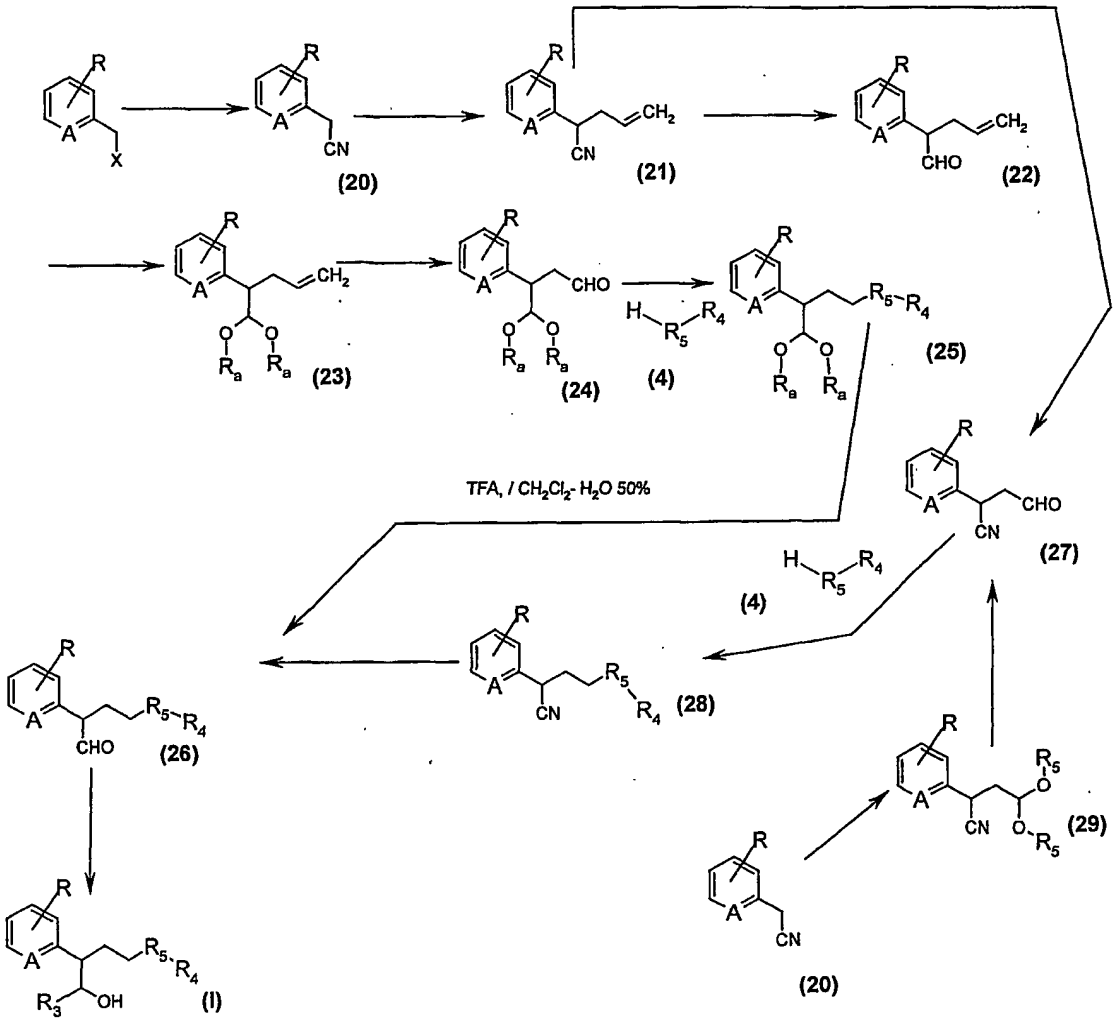


For the synthesis of compounds I where R_2 is different than H, the method given in Scheme 6 is used. Intermediate ketone (2) is reduced with the same reduction methods used above in scheme 1 for compound (5) affording intermediate (17), which is etherified by reaction with a base, for example NaH or potassium tert-butoxide or $NaNH_2$ or $LiNH_2$ or others in a suitable solvent e.g. tetrahydrofuran, affording the alkoxide, which is then reacted in situ with the appropriate R_2-X with X leaving group (halogen or mesylate or tosylate) at a temperature of from 0°C to the reflux temperature. The so obtained compounds (18) can undergo the same reactions described in scheme 1 affording product I with R_2 is not H.

Alternatively, compounds of formula I where R_2 is not a hydrogen atom, can be obtained by alkylating compounds of formula I where R_2 = H with the same methods described above for alkylating compound 17, limiting this procedure to the alkylation with very reactive halogenide or mesylate/tosylate (e.g., benzyl bromides) which can react under time/temperature controlled reaction condition, preferably at r.t.

Scheme 7 describes a double functionalization approach to the synthesis of Compound (I). This kind of approach can be useful for the synthesis of libraries of compounds (I) introducing different amine moieties and different R_3 goups at the same time.

Scheme 7



In scheme 7 R_a is a lower alkyl group or the two R_a groups are linked forming a 1,3-dioxolanyl or 1,3-dioxanyl group. An appropriate commercial benzyl derivative (with X = halogen or methanesulphonyloxy or p-toluenesulphonyloxy groups) can be reacted, as very well known to those skilled in the art, to afford the benzyl cyanide (20). These reactants can be converted following known alkylation methods into compounds

(21) or **(27)** respectively reacting them with allyl halogenides (or allyl mesylatese or tosylates) or haloalkylaldehydes in their carbonyl protected form (acetals or dioxolanyl derivatives or other).

These alkylation reactions can be carried out by the use of bases to generate the reactive benzyl carbanions. Example of used bases are lithium diisopropylamide (LDA) or tert-Butyl lithium or NaH or potassium tert-butoxide or sodium amide or potassium amide or others in an appropriate solvent such as THF or Et_2O or DMF or other at a temperature ranging from –78°C to the reflux temperature. A preferred method of alkylation include the use of hindered bases such as LDA in the presence of hexamethyl phosphorous triamide or DMPU at –78°C – r.t.

Compounds **(21)** can be in turn reduced by the use of diisobutylaluminum hydride (DIBAL-H) in an appropriate solvent (toluene, DMF, CH_2Cl_2 or other) at a temperature ranging from –78°C to the reflux of the solvent. The so obtained aldehydes **(22)** are then carbonyl protected following methods very well known to those skilled in the art to give compounds **(23)**, which can be catalytically osmilated (C. P. Forbes *J.C.S. Perkin Trans I* 1979, 906-910) or undergo ozonolysis to afford compounds **(24)**. Compounds **(24)** can be reductively aminated as described above to afford compounds **(25)**. Deprotection by common methods leads to the aldehydes **(26)**.

Compounds **(26)** can be alternatively obtained from compounds **(21)** applying the osmilation or ozonolysis procedure on them. The so obtained cyanopropionaldehydes **(27)** are then reductively aminated to compound **(28)**. Repeating the DIBAL-H reduction described above on these compounds affords the aldehydes **(26)**.

Compounds (27) are also easily obtained from compounds (29) by simple deprotection of the carbonyl functionality. The reaction of R_3-M (where M is a metallic salt, such as lithium or magnesium halide) with compounds **(26)** afford compounds **(I)**. A large number of organometallics such as litium or magnesium derivatives are commercially available or easily prepared and can be reacted in an appropriate solvent such as THF or Et_2O or others at –78°C – reflux.

Stereochemistry

In Schemes 1, 6 and 7 compounds I are obtained in syn/anti mixture of diastereoisomers with ratio depending on the reaction condition used. The diastereoisomers can be separated by usual tecniques known to those skilled in the art

including fractional crystallization of the bases or their salts or chromatografic tecniques such as LC or flash chromatography. For both the diastereoisomers, the (+) enantiomer of formula Ia can be separated from the (-) enantiomer using techniques and procedures well known in the art, such as that described by J. Jacques, et al., "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, Inc., 1981. For example, chiral chromatography with a suitable organic solvent, such as ethanol/acetonitrile and Chiralpak AD packing, 20 micron can also be utilized to effect separation of the enantiomers.

The free bases of formula I, their diastereoisomers or enantiomers can be converted to the corresponding pharmaceutically acceptable salts under standard conditions well known in the art. For example, the free base of formula I is dissolved in a suitable organic solvent, such as methanol, treated with one equivalent of maleic or oxalic acid for example, one or two equivalents of hydrochloric acid or methanesulphonic acid for example, and then concentrated under vacuum to provide the corresponding pharmaceutically acceptable salt. The residue can then be purified by recrystallization from a suitable organic solvent or organic solvent mixture, such as methanol/diethyl ether.

Combination treatments

In certain embodiments, disorders of the urinary tract are treated by administering a compound of formula I in combination with an additional 5-HT_{1A} antagonist or an antagonist of one or more additional class of receptors. In preferred embodiments a compound of formula I is administered in combination with an antagonist of an α1-adrenergic, or muscarinic receptor.

In further embodiments, lower urinary tract disease is treated by administering a compound of formula I in combination with one or more inhibitor of the cyclooxygenase enzyme, which may inhibit both COX1 and COX2 isozymes or which may, alternatively, be selective for COX2 isozyme, and NO donor derivatives thereof.

Examples of antimuscarinic drugs for administration in combination with a compound of formula I are oxybutynin, tolterodine, darifenacin, and temiverine.

A compound of formula I may be administered in combination with α1-adrenergic antagonists, for the therapy of lower urinary tract symptoms, whether or not these are associated with BPH. Preferred α1-adrenergic antagonists suitable for administration in combination with a compound of formula I are, for example, prazosin, doxazosin,

terazosin, alfuzosin, and tamsulosin. Additional α1-adrenergic antagonists suitable for administration in combination with a compound of formula I are described in U.S. Patents No. 5,798,362, 5,990,114; 6,306,861; 6,365,591; 6,387,909; and 6,403,594.

Examples of 5-HT_{1A} antagonists that may be administered in combination with a compound of formula I are found in Leonardi et al., *J. Pharmacol. Exp. Ther.* **299**: 1027-1037, 2001 (e.g., Rec 15/3079), U.S. Patent No. 6,071,920, other phenylpiperazine derivatives described in WO 99/06383 and pending U.S. Patent Applications Serial No. 10/266,088 and 10/266,104 filed on October 7, 2002. Additional 5-HT_{1A} antagonists include DU-125530 and related compounds described in U.S. Patent No. 5,462,942 and robalzotan and related compounds described in WO 95/11891.

Examples of selective COX2 inhibitors that may be administered in combination with a compound of formula I are, without limitation, nimesulide, meloxicam, rofecoxib, celecoxib, parecoxib and valdecoxib. Additional examples of selective COX2 inhibitors are described, without limitation, in US 6,440,963. Examples of non-selective COX1-COX2 inhibitors are, without limitation, acetylsalicylic acid, niflumic acid, flufenamic acid, enfenamic acid, meclofenamic acid, tolfenamic acid, thiaprophenic acid, ibuprofen, naproxen, ketoprofen, flurbiprofen, furprofen, indomethacin, acemethacin, proglumethacin, ketorolac, diclofenac, etodolac, sulindac, fentiazac, tenoxicam, lornoxicam, cynnoxicam, ibuproxam, nabumetone, tolmetin, amtolmetin. Accordingly, each of the foregoing are non-limiting examples of COX inhibitors that may be administered in combination with a compound of formula I.

Examples of derivatives of COX inhibitors that may be administered in combination with a compound of formula I are derivatives of COX inhibitors bearing nitrate (nitrooxy) or nitrite groups, such as those given , for example, in WO 98/09948, able to release NO in vivo.

Pharmaceutical Compositions

The invention further provides pharmaceutical compositions comprising a compound of formula I or an enantiomer, diastereomer, N-oxide, crystalline form, hydrate, solvate, active metabolite or pharmaceutically acceptable salt of the compound. The pharmaceutical composition may also include optional additives, such as a pharmaceutically acceptable carrier or diluent, a flavouring, a sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a colorant, a disintegrator, an excipient, a diluent, a lubricant, an absorption enhancer, a bactericide and the like, a

stabiliser, a plasticizer, an edible oil, or any combination of two or more of said additives.

Suitable pharmaceutically acceptable carriers or diluents include, but are not limited to, ethanol, water, glycerol, aloe vera gel, allantoin, glycerine, vitamin-A and E oils, mineral oil, phosphate buffered saline, PPG2 myristyl propionate, magnesium carbonate, potassium phosphate, vegetable oil, animal oil and solketal.

Suitable binders include, but are not limited to, starch, gelatine, natural sugars such as glucose, sucrose and lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, vegetable gum, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like.

Suitable disintegrators include, but are not limited to, starch such as corn starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Suitable lubricants include, but are not limited to, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

Suitable suspending agents include, but are not limited to, bentonite.

Suitable dispersing and suspending agents include, but are not limited to, synthetic and natural gums such as vegetable gum, tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone and gelatine.

Suitable edible oils include, but are not limited to, cottonseed oil, sesame oil, coconut oil and peanut oil.

Examples of additional additives include, but are not limited to, sorbitol, talc, stearic acid and dicalcium phosphate.

Unit Dosage Forms

The pharmaceutical composition may be formulated as unit dosage forms, such as tablets, pills, capsules, boluses, powders, granules, sterile parenteral solutions, sterile parenteral suspensions, sterile parenteral emulsions, elixirs, tinctures, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories. The unit dosage forms may be used for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation, transdermal patches, and a lyophilized composition. In general, any delivery of active ingredients that results in systemic availability of such ingredients can be used. Preferably the unit dosage form is an oral dosage form, most preferably a solid oral dosage; therefore the preferred dosage forms are tablets, pills and capsules. However, parenteral preparations are preferred too.

Solid unit dosage forms may be prepared by mixing the active agents of the present invention with a pharmaceutically acceptable carrier and any other desired

additives as described above. The mixture is typically mixed until a homogeneous mixture of the active agents of the present invention is obtained and the carrier and any other desired additives are formed, i.e. the active agents are dispersed evenly throughout the composition. In this case, the composition can be formed as dry or moist granules.

Dosage forms can be formulated as, for example, "immediate release" dosage forms. "Immediate release" dosage forms are typically formulated as tablets that release at least 60%-90% of the active ingredient within 30-60 min when tested in a drug dissolution test, e.g., U.S. Pharmacopeia standard <711>. In a preferred embodiment, immediate dosage forms release at 75% of active ingredient within about 45 min.

Dosage forms can also be formulated as, for example, "controlled release" dosage forms. "Controlled," "sustained," "extended" or "time release" dosage forms are equivalent terms that describe the type of active agent delivery that occurs when the active agent is released from a delivery vehicle at an ascertainable and manipulatable rate over a period of time, which is generally on the order of minutes, hours or days, typically ranging from about sixty minutes to about 3 days, rather than being dispersed immediately upon entry into the digestive tract or upon contact with gastric fluid. A controlled release rate can vary as a function of a multiplicity of factors. Factors influencing the rate of delivery in controlled release include the particle size, composition, porosity, charge structure, and degree of hydration of the delivery vehicle and the active ingredient(s), the acidity of the environment (either internal or external to the delivery vehicle), and the solubility of the active agent in the physiological environment, i.e., the particular location along the digestive tract. Typical parameters for dissolution test of controlled release forms are found in U.S. Pharmacopeia standard <724>.

Dosage forms can also be formulated to deliver active agent in multiphasic stages whereby a first fraction of an active ingredient is released at a first rate and at least a second fractions of active ingredient is released at a second rate. In a preferred embodiment, a dosage form can be formulated to deliver active agent in a biphasic manner, comprising a first "immediate release phase", wherein a fraction of active ingredient is delivered at a rate set forth above for immediate release dosage forms, and a second "controlled release phase," wherein the remainder of the active ingredient is released in a controlled release manner, as set forth above for controlled release dosage forms.

Tablets or pills can be coated or otherwise prepared so as to form a unit dosage

form that has delayed and/or sustained action, such as controlled release and delayed release unit dosage forms. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of a layer or envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release.

Biodegradable polymers for controlling the release of the active agents include, but are not limited to, polylactic acid, polyepsilon caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

For liquid dosage forms, the active substances or their physiologically acceptable salts are dissolved, suspended or emulsified, optionally with the usually employed substances such as solubilizers, emulsifiers or other auxiliaries. Solvents for the active combinations and the corresponding physiologically acceptable salts can include water, physiological salt solutions or alcohols, e.g. ethanol, propanediol or glycerol. Additionally, sugar solutions such as glucose or mannitol solutions may be used. A mixture of the various solvents mentioned may be used in the present invention too.

A transdermal dosage form is contemplated by the present invention too. Transdermal forms may be a diffusion transdermal system (transdermal patch) using either a fluid reservoir or a drug-in-adhesive matrix system. Other transdermal dosage forms include, but are not limited to, topical gels, lotions, ointments, transmucosal systems and devices, and iontophoretic (electrical diffusion) delivery systems. Transdermal dosage forms may be used for delayed release and sustained release of the active agents of the present invention.

The pharmaceutical compositions and unit dosage forms of the present invention for parenteral administration, and in particular by injection, typically include a pharmaceutically acceptable carrier, as described above. A preferred liquid carrier is vegetable oil. Injection may be, for example, intravenous, epidural, intrathecal, intramuscular, intraluminal, intratracheal or subcutaneous.

The active agents can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The active agents of the present invention may also be coupled with soluble

polymers such as targetable drug carriers. Such polymers include, but are not limited to, polyvinylpyrrolidone, pyran copolymers, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol, and polyethylenoxypolylysine substituted with palmitoyl residues.

Administration

The pharmaceutical composition or unit dosage forms of the present invention may be administered by a variety of routes, such as the oral and enteral, intravenous, intramuscular subcutaneous, transdermal, transmucosal (including rectal and buccal) and by inhalation routes. Oral or transdermal routes are preferred (e.g., solid or liquid formulations or skin patches, respectively).

The pharmaceutical composition or unit dosage forms comprising an effective amount of the present invention may be administered to an animal, preferably a human, in need of treatment of neuromuscular dysfunction of the lower urinary tract described by E. J. McGuire in "Campbell's UROLOGY", 5th Ed., 616-638, 1986, W.B. Saunders Company, and patients affected by any physiological dysfunction related to impairment of 5-HT_{1A} receptor function. Such dysfunctions include, without limitation, central-nervous-system disorders such as depression, anxiety, eating disorders, sexual dysfunction, addiction and related problems.

As used herein, the term "effective amount" refers to an amount that results in measurable amelioration of at least one symptom or parameter of a specific disorder. In a preferred embodiment, the compound treats disorders of the urinary tract, such as urinary urgency, overactive bladder, increased urinary frequency, reduced urinary compliance (reduced bladder storage capacity), cystitis (including interstitial cystitis), incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the bladder, or central nervous system disorders due to serotonergic dysfunction (such as anxiety, depression, hypertension, sleep/wake cycle disorders, feeding behaviour, sexual function and cognition disorders in mammals (particularly a human) associated to stroke, injury, dementia and due to neurological development, disorders from hyperactivity related to an attention deficit (ADHD), drug addiction, drug withdrawal, irritable bowel syndrome.

The pharmaceutical composition or unit dosage form of the present invention may be administered according to a dosage and administration regimen defined by routine testing in the light of the guidelines given above in order to obtain optimal activity while minimising toxicity or side effects for a particular patient. However, such fine tuning of the therapeutic regimen is routine in the light of the guidelines given herein.

The dosage of the active agents of the present invention may vary according to a variety of factors such as underlying disease conditions, the individual's condition, weight, sex and age, and the mode of administration. An effective amount for treating a disorder can easily be determined by empirical methods known to those of ordinary skill in the art, for example by establishing a matrix of dosages and frequencies of administration and comparing a group of experimental units or subjects at each point in the matrix. The exact amount to be administered to a patient will vary depending on the state and severity of the disorder and the physical condition of the patient. A measurable amelioration of any symptom or parameter can be determined by a person skilled in the art or reported by the patient to the physician. It will be understood that any clinically or statistically significant attenuation or amelioration of any symptom or parameter of urinary tract disorders is within the scope of the invention. Clinically significant attenuation or amelioration means perceptible to the patient and/or to the physician.

For example, a single patient may suffer from several symptoms of dysuria simultaneously, such as, for example, urgency and excessive frequency of urination or both, and these may be reduced using the methods of the present invention. In the case of incontinence, any reduction in the frequency or volume of unwanted passage of urine is considered a beneficial effect of the present method of treatment.

The amount of the agent to be administered can range between about 0.01 and about 25 mg/kg/day, preferably between about 0.1 and about 10 mg/kg/day and most preferably between 0.2 and about 5 mg/kg/day. It will be understood that the pharmaceutical formulations of the present invention need not necessarily contain the entire amount of the agent that is effective in treating the disorder, as such effective amounts can be reached by administration of a plurality of doses of such pharmaceutical formulations.

In a preferred embodiment of the present invention, the compounds are formulated in capsules or tablets, preferably containing 50 to 200 mg of the compounds of the invention, and are preferably administered to a patient at a total daily dose of 50 to 400 mg, preferably 150 to 250 mg and most preferably about 200 mg, for relief of urinary incontinence and dysfunctions under treatment with 5-HT_{1A} receptor ligand.

A pharmaceutical composition for parenteral administration contains from about 0.01% to about 100% by weight of the active agents of the present invention, based upon 100% weight of total pharmaceutical composition.

Generally, transdermal dosage forms contain from about 0.01% to about 100% by

weight of the active agents versus 100% total weight of the dosage form.

The pharmaceutical composition or unit dosage form may be administered in a single daily dose, or the total daily dosage may be administered in divided doses. In addition, co-administration or sequential administration of another compound for the treatment of the disorder may be desirable. For example, the compounds of the invention may be administered in combination with more antimuscarinic, α_1-adrenergic antagonist, 5-HT_{1A} receptor antagonist, or COX inhibitors or NO releasing derivatives thereof, for the therapy of lower urinary tract symptoms. Examples of antimuscarinics, α_1-adrenergic antagonists, 5-HT_{1A} receptor antagonist, COX inhibitors and NO releasing derivatives thereof are set forth above, without limitation.

For combination treatment where the compounds are in separate dosage formulations, the compounds can be administered concurrently, or each can be administered at separate staggered times. For example, the compound of the invention may be administered in the morning and the antimuscarinic compound may be administered in the evening, or vice versa. Additional compounds may be administered at specific intervals too. The order of administration will depend upon a variety of factors including age, weight, sex and medical condition of the patient; the severity and aetiology of the disorders to be treated, the route of administration, the renal and hepatic function of the patient, the treatment history of the patient, and the responsiveness of the patient. Determination of the order of administration may be fine-tuned and such fine-tuning is routine in the light of the guidelines given herein.

Uses-Methods for Treatment

Without wishing to be bound by theory, it is believed that administration of 5-HT_{1A} receptor antagonists prevents unwanted activity of the sacral reflex and/or cortical mechanisms that control micturition. Thus, it is contemplated that a wide range of neuromuscular dysfunctions of the lower urinary tract can be treated using the compounds of the present invention, including without limitation dysuria, incontinence and enuresis (overactive bladder). Dysuria includes urinary frequency, nocturia, urgency, reduced urinary compliance (reduced bladder storage capacity), difficulty in emptying the bladder, i.e. a suboptimal volume of urine is expelled during micturition. Incontinence syndromes include stress incontinence, urgency incontinence and enuresis incontinence, as well as mixed forms of incontinence. Enuresis refers to the involuntary passage of urine at night or during sleep.

The compounds of the present invention may also be useful for the treatment of central nervous system disorders due to serotonergic dysfunction.

The following examples represent typical syntheses of the compounds of formula I as described generally above. These examples are illustrative only and are not intended to limit the invention in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.

Example 1

8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-N-methyl-2-aminoethoxy}-quinoline

2-(2-Cyclohexyl-2-oxoethyl)-benzonitrile (Compound 1a)

To a solution of 0.47 g of 2-tolunitrile in 4 ml of THF was added 0.535 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (DMPU) and the mixture was cooled at –78°C; 2.22 ml of a 2M sol. of LDA in THF was then dropped during 5 min., then the reaction mixture was stirred at the same temperature for 15 min. followed by dropwise addition of 0.757 g of N-methyl-N-methoxycyclohexanecarboxamide in 4 ml of THF. After 1 h stirring at –78°C, the reaction mixture was quenched with a 10% aq. sol. of NH_4Cl. The temperature was allowed to rise at r.t. and the mixture was extracted with EtOAc (2x20ml), washed with 30 ml of brine, dried on Na_2SO_4 and evaporated to dryness in vacuo. The crude was purified by flash chromatography (PE – EtOAc 90:10) to afford 0.34 g of the title compound.

^{1}H-NMR (*$CDCl_3$, δ*): 1.10-2.05 (m ,10H); 2.45-2.60 (m, 1H); 4,00 (m, 2H); 7.20-7.43 (m, 2H); 7.48-7.70 (m, 2H);

3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyraldehyde diethyl acetal (Compound 1b)

To a suspension of 414 mg of 60% NaH oil dispersion in 10 ml of anhydrous DMF was added drop wise during 6 min under a nitrogen stream, a solution of 1.84 g of compound 1a in 5 ml of DMF and the reaction mixture was stirred at r.t. for 1 h; then was added 2.15 g of 2-bromoacetaldehyde diethyl acetal (97 %) in 5 ml of DMF; the mixture was stirred at r.t. for 15', then at 80°C for 5.5 h. Afterwards, the mixture was diluted with H_2O (250 ml), acidified with 2 N HCl, extracted with Et_2O (3 x 50 ml), washed with H_2O (40 ml), dried (Na_2SO_4) ed evaporated in vacuo, affording a crude (brownish oil), which was

purified by flash chromatography (PE - EtOAc 90:10) to yield 1.91 g of compound 1b as a yellowish oil.

^{1}H-NMR (*CDCl$_3$, δ*): 1.09-1.26 (m, 6H); 1.27-1.39 (m, 4H); 1.46-1.57 (m, 1H); 1.59-1.74 (m, 3H); 1.77-1.88 (m, 1H); 1.93-2.08 (m, 2H); 2.38-2.50 (m, 2H); 3.39-3.51 (m, 2H); 3.54-3.72 (m, 2H); 4.30-4.34 (m, 1H); 4.53-4.61 (m, 1H); 7.33-7.44 (m, 2H); 7.51-7.61 (m, 1H); 7.66-7.72 (m, 1H).

3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyraldehyde (Compound 1c)

A mixture of 1 g of the compound 1b, 9.5 ml of 50% aq. trifluoroacetic acid and 19 ml of CH_2Cl_2 was stirred for 2 h at r.t., then diluted with 8 ml of CH_2Cl_2. The organic layer was separated, washed with brine (2 x 15 ml), dried (Na_2SO_4) and evaporated to dryness in vacuo to afford a crude (0.788 g), used in the next step without further purification.

^{1}H-NMR (*CDCl$_3$, δ*): 1.01-2.11 (m, 10H); 2.31-2.43 (m, 1H); 2.64 (dd, 1H); 3.29-3.41 (m, 1H); 4.78 (dd, 1H); 7.25-7.37 (m, 1H); 7.39-7.53 (m, 2H); 7.61-7.64 (m, 1H); 9.62-9.68 (m, 1H).

8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-N-methyl-2-aminoethoxy}-quinoline

A mixture of 0.197 g of the compound 1c, 0.177 g of 8-(N-methyl-2-aminoethoxy)-quinoline, 0.31 g of sodium triacetoxyborohydride, 0.17 ml of AcOH and 6 ml of CH_2Cl_2 was stirred at r.t. for 1 h and alkalinised with 2 N NaOH. The organic layer was separated, washed with brine (2 x 15 ml), dried (Na_2SO_4) and evaporated to dryness in vacuo the give a crude which was purified by flash chromatography (CH_2Cl_2 - MeOH 95:5) affording the title compound (0.17 g; 52%).

^{1}H-NMR (*CDCl$_3$, δ*): 1.11-1.40 (m, 5H); 1.51-1.60 (m, 1H); 1.61-1.83 (m, 6H); 1.85-2.02 (m, 2H); 2.30-2.52 (m, 5H); 2.95-3.08 (m, 2H); 4.26-4.38 (m, 2H); 4.50-4.61 (m, 1H); 7.11 (d, 1H); 7.32-7.38 (m, 1H); 7.39-7.57 (m, 4H); 7.67 (d, 1H); 8.15 (d, 1H); 8.92-8.99 (m, 1H).

$[M+H]^+ = 456.25$

Example 2

8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-N-methyl-2-aminoethoxy}-quinoline

To a solution of 0.17 g of Compound of Example 1 in MeOH (5 ml), cooled at 0°C, 21.2 mg of $NaBH_4$ were added; the resulting mixture was stirred at 0°C for 30', then 1 h at r.t. Afterwards, the solvent was evaporated in vacuo and the crude poured into H_2O (10 ml) and extracted with CH_2Cl_2 (3x10 ml). The organic layer was separated, dried (Na_2SO_4) and evaporated to dryness in vacuo. The crude was purified by flash chromatography (EtOAc – 2 N methanolic ammonia 97:3) affording the title compound (55 mg; 32%).
$[M+H]^+ = 458.42$

Example 3

1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(2,6-dimethylphenyl)-piperidine

The title compound was obtained following the procedure described for the compound of Example 1, but using 4-(2,6-dimethylphenyl)-piperidine instead of 8-(N-methyl-2-aminoethoxy)-quinoline. Purification by flash chromatography (CH_2Cl_2 – MeOH 97:3) yielded the title compound (32.8%) as an oil.
^{1}H-NMR (*$CDCl_3$, δ*): 1.09-1.43 (m, 5H), 1.49-1.86 (m, 7H), 1.88-1.94 (m, 2H), 1.96-2.14 (m, 3H), 2.39-2.61 (m, 10H), 2.91-3.06 (m, 3H), 4.57-4.77 (m, 1H), 6.96-7.07 (m, 3H), 7.32-7.47 (m, 2H), 7.54-7.63 (m, 1H); 7.66-7.74 (m, 1H).
$[M+H]^+ = 443.33$

Example 4

1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-4-(2,6-dimethylphenyl)-piperidine

The title compound was obtained following the procedure described for the compound of Example 2, but using the compound of Example 3 as starting material instead of the compound of Example 1. Purification by flash chromatography (CH_2Cl_2 - MeOH / NH_3 97:3) yielded the title compound (20.9%) as an oil.
^{1}H-NMR (*$CDCl_3$, δ*): 1.09-1.43 (m, 5H), 1.49-1.86 (m, 7H), 1.88-1.94 (m, 2H), 1.96-2.14 (m, 3H), 2.39-2.61 (m, 10H), 2.91-3.06 (m, 3H), 4.57-4.77 (m, 1H), 6.96-7.07 (m, 3H), 7.32-7.47 (m, 2H), 7.54-7.63 (m, 1H); 7.66-7.74 (m, 1H).
$[M+H]^+ = 445.44$

Example 5

1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(4-fluoro-2-methoxyphenoxy)-piperidine

The title compound was obtained following the procedure described for the compound of Example 1, but using 4-(4-fluoro-2-methoxyphenoxy)-piperidine instead of 8-(N-methyl-2-aminoethoxy)-quinoline. Purification by flash chromatography (EP - EtOAc - MeOH / NH_3 7:3:0.2) yielded the title compound (12.3%)as an oil.
^{1}H-NMR (*$CDCl_3$, δ*): 1.06-1.33 (m, 5H), 1.41-2.90 (m, 16H), 2.58-2.76 (m, 2H), 3.74 (s, 3H); 3.98-4.11 (m, 1H), 4.89-4.54 (m, 1H), 6.43-6.52 (m, 1H); 6.54-6.60 (m, 1H); 6.73-6.81 (m, 1H); 7.22-7.33 (m, 1H); 7.35-7.53 (m, 2H); 7.57-7.69 (m, 1H).
$[M+H]^+ = 479.29$

Example 6 Radioligand binding to recombinant 5-HT_{1A} receptors

A. Method:

A Genomic clone G-21 coding for the human $5HT_{1A}$-serotonergic receptor is stably transfected in a human cell line (HeLa). HeLa cells are grown as monolayers in Dulbecco's modified Eagle medium (DMEM), containing 10% foetal bovine serum, gentamycin (0.1 mg/ml) and 5% carbon dioxide, at 37°C. The cells are detached from the growth flask at 95% confluence by a cell scraper and are lysed in cold 5 mM Tris and 5 mM EDTA buffer (pH 7.4). The homogenates are centrifuged at 40000 x *g* x 20 minutes and the pellets are resuspended in a small volume of cold 5 mM Tris and 5 mM EDTA buffer (pH 7.4) and immediately frozen and stored at –70°C until use. On the day of experiment, the cell membranes are resuspended in incubation buffer: 50 mM Tris HCl (pH 7.4), 2.5 mM $MgCl_2$, 10 mM pargyline (Fargin et al., *Nature* 335, 358-360, 1988). The membranes are incubated in a final volume of 1 ml for 30 minutes at 30°C with 1 nM [^{3}H]8-OH-DPAT, in the absence or presence of the test compounds. Non-specific binding is determined in the presence of 10 µM 5-HT. Incubation is stopped by addition of cold Tris-HCl buffer and rapid filtration through a 0.2%-polyethyleneimine-pretreated Whatman-GF/B or Schleicher-&-Schuell-GF52 filter.

B. Results

The affinity of the tested compounds is evaluated as inhibition of specific binding

of the radioligand to 5-HT_{1A} receptors (IC_{50}) by using the non-linear curve-fitting program Allfit (De Lean et al., *Am. J. Physiol.* **235**, E97-E102 (1978). The IC_{50} value is converted to an affinity constant (Ki) by the equation of Cheng & Prusoff (Cheng Y. C., et al., *Biochem. Pharmacol.* **22**, 3099-3108 (1973)).

Example 7 Effects on rhythmic bladder-voiding contractions induced by bladder filling in anaesthetised rats

A. Method:

Female Sprague-Dawley rats weighing 225-275 g (Crl: CD® (SD) IGS BR, Charles River Italia) are used. The animals are housed with free access to food and water and maintained on a forced 12-hour alternating light-dark cycle at 22-24°C for at least one week, except during the experiment. The activity on rhythmic bladder voiding contractions is evaluated according to the method of Dray (Dray J., *Pharmacol. Methods*, **13**:157, 1985), with some modifications as in Guarneri (Guarneri, *Pharmacol. Res.* **27**:173, 1993). Briefly, the rats are anaesthetised by subcutaneous injection of 1.25 g/kg (5 ml/kg) urethane, after which the urinary bladder is catheterised via the urethra using PE 50 polyethylene tubing filled with physiological saline. The catheter is tied in place with a ligature around the external urethral orifice and is connected to conventional pressure transducers (Statham P23 ID/P23 XL). The intravesical pressure is displayed continuously on a chart recorder (Battaglia Rangoni KV 135 with DCI/TI amplifier). The bladder is then filled via the recording catheter by incremental volumes of warm (37°C) saline until reflex bladder-voiding contractions occurred (usually 0.8-1.5 ml). For intravenous injection of bioactive compounds, PE 50 polyethylene tubing filled with physiological saline is inserted into the jugular vein.

From the cystometrogram, the number of contractions recorded 15 minutes before (basal values) and after treatment, as well as the mean amplitude of these contractions (mean height of the peaks in mmHg), is evaluated.

Since most compounds produce an effect that is relatively rapid in onset and leads to a complete cessation of bladder contractions, bioactivity is conveniently estimated by measuring the duration of bladder quiescence (i.e., the length of the time during which no contractions occurred). The number of tested animals showing a reduction in the number of contractions higher than 30% of that observed in the basal period is also recorded.

To compare the potency of tested compounds for inhibiting the bladder voiding

contractions, equieffective doses which result in the disappearance of contractions for a time of 10 minutes (ED_{10min}) are computed by means of linear regression using the least square method. The extrapolated doses which induce a reduction in the number of contractions greater than 30% in 50% of the treated rats (ED_{50}) is evaluated by the method of Bliss (Bliss C. I., *Quart J. Pharm. Pharmacol.* **11**, 192-216, 1938).

B. Results

The rapid distension of the urinary bladder in urethane-anaesthetised rats produces a series of rhythmic bladder-voiding contractions whose characteristics have been described (Maggi et al., *Brain Res.* 380:83, 1986; Maggi et al., *J. Pharmacol. Exp. Ther.*, **230**: 500, 1984). The frequency of these contractions is related to the sensory afferent arm of reflex micturition and to the integrity of the micturition centre, while their amplitude depends on the function of the reflex efferent arm. In this model system, compounds that act mainly on the central nervous system (such as morphine) cause a block in voiding contractions, whereas drugs that act at the level of the detrusor muscle, such as oxybutynin, lower the amplitude of the bladder contractions.

Example 8 Effect on cystometric parameters in conscious rats after oral administration

A. Method:

Male Sprague-Dawley rats [Crl: CD® (SD) IGS BR] of 300-400 g supplied by Charles River Italia are used. The animals are housed with free access to food and water and maintained on a forced 12-hour-light/12-hour-dark cycle at 22-24°C of temperature, except during the experiment. To quantify urodynamic parameters in conscious rats, cystometrographic studies is performed according to the procedure previously reported (Guarneri et al., *Pharmacol. Res.* **24**: 175, 1991).

Briefly, the rats are anaesthetised by intraperitoneal administration of 3 ml/kg of Equithensin solution (pentobarbital 30 mg/kg and chloral hydrate 125 mg/kg) and placed in a supine position. An approximately-10-mm-long midline incision is made in the shaved and cleaned abdominal wall. The urinary bladder is gently freed from adhering tissues, emptied and then cannulated via an incision in the bladder body, using a polyethylene cannula (0.58-mm internal diameter, 0.96-mm external diameter) which is permanently sutured with silk thread. The cannula is exteriorised through a subcutaneous

tunnel in the retroscapular area, where it is connected to a plastic adapter in order to avoid the risk of removal by the animal. For drug testing, the rats are utilised one day after implantation.

On the day of the experiment, rats are placed in modified Bollman cages, i.e., restraining cages, that are large enough to permit the rats to adopt a normal crouched posture, but narrow enough to prevent turning around. After a stabilisation period of about 20 minutes, the free tip of the bladder cannula is connected through a T-shaped tube to a pressure transducer (Statham P23XL) and to a peristaltic pump (Gilson minipuls 2) for continuos infusion of a warm (37°C) saline solution into the urinary bladder, at a constant rate of 0.1 ml/minute. The intraluminal-pressure signal during infusion of saline into the bladder is continuously recorded on a polygraph (Rectigraph-8K San-ei with BM614/2 amplifier from Biomedica Mangoni) .The cystometrogram is used to evaluate the urodynamic parameters of bladder volume capacity (BVC) and micturition pressure (MP). BVC (ml) is defined as the volume of saline infused into the bladder necessary to induce detrusor contraction followed by micturition. MP (mmHg) is defined as the maximal intravesical pressure caused by contraction during micturition. Basal BVC and MP values are evaluated as mean of the values observed in the cystometrograms recorded in an initial period of 30-60 minutes. Following determination of basal BVC and MP, the infusion is interrupted and the test compounds are administered orally by a stomach tube. Bladder infusion is resumed and changes in BVC and MP are evaluated from the mean values obtained in the cystometrograms observed during 1, 2, 3, 4 and 5 hours after treatment. Compounds are administered in a volume of 2 ml/kg and groups of control animals receive the same amount of vehicle (0.5% methocel in water) orally.

Statistical analysis

Data are expressed as mean ± standard error. The percent changes of BVC and MP *versus* the basal values, as well as Δ values (difference in ml or mmHg) of BVC and MP (BVC or MP at time "x" minus basal value), are evaluated for each rat/time. Data are reported as % changes *versus* basal values.

Statistical analysis on BVC and MP values, as well as on Δ values, is performed by S.A.S./STAT software, version 6.12. The observed differences between vehicle (control) and test treatments are evaluated on Δ values of BVC and MP, whereas the differences between the values at different times *versus* basal values are analyzed on

original BVC and MP data.

Example 9 Inhibition of stereotypy (rhythmic forepaw treading) induced by 8-OH-DPAT in rats (post-synaptic antagonism)

A. Method:

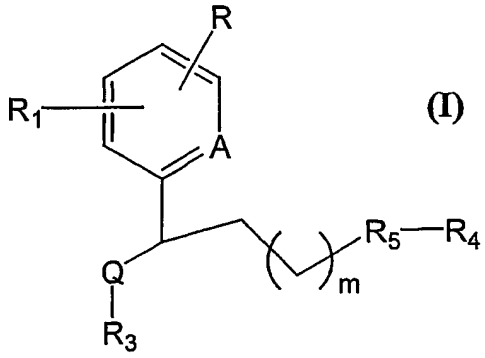
The inhibitory effect of 5-HT_{1A}-receptor antagonists on stereotyped forepaw treading induced in rats by subcutaneous injection of 8-OH-DPAT is evaluated by the method of Tricklebank (Tricklebank et al., *Eur. J. Pharmacol.*, 117: 15, 1985) with minor modifications as described below.

Male Sprague-Dawley rats [Crl: CD® (SD) IGS BR] weighing 150-175 g from Charles River Italia are used. The animals are housed with free access to food and water and maintained on a forced 12-hour-light/12-hour-dark cycle at 22-24°C of temperature. On the day of the experiment, the rats are placed singly in clear plastic containers, 10-15 minutes before administration of the vehicle or compounds to be tested. For evaluation of antagonistic activity after oral administration, the compounds are administered 1 and 4 hours before induction of stereotypy by 8-OH-DPAT (1 mg/kg subcutaneously). Observation sessions last 30 seconds and begin 3 min after 8-OH-DPAT treatment and were repeated every 3 minutes over a period of 15 minutes.

The appearance of the symptom induced by postsynaptic stimulation of 5-HT_{1A} receptors is noted, and the intensity is scored using an intensity scale in which: 0 = absent, 1 = equivocal, 2 = present and 3 = intense. Behavioural scores for treated rats are accumulated throughout the observation time (5 observation periods) and expressed as mean values of 4 rats/dose. Change in mean values of treated animals in comparison with control (vehicle) group, expressed as per-cent inhibition, was used to quantify the antagonistic activity.

CLAIMS

1. A compound having the general formula I



(I)

wherein

R represents a hydrogen atom or one or more halogen atoms or (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_1-C_6)-haloalkyl, (C_1-C_6)-haloalkoxy, (C_1-C_6)-hydroxyalkyl, alkoxy-(C_1-C_6)-alkyl, nitro, amino, (C_1-C_6)-aminoalkyl, (C_1-C_6)-alkylamino, N-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl, N, N-di-(C_1-C_6)-alkylamino, acylamino, (C_1-C_6)-alkylsulphonylamino, aminosulphonyl, (C_1-C_6)-alkylaminosulphonyl, cyano, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl, alkylcarbonyl-(C_1-C_6)-alkyl, formyl, alkanoyloxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkylaminocarbonylamino, (C_1-C_6)-alkylsulphinyl, (C_1-C_6)-alkylsulphonyl, and N, N-di-(C_1-C_6)-alkylaminosulphonyl groups;

R_1 represents a hydrogen atom or a cycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heterocyclic, heterocycloxy, heterocycloalkyl or heterocycloalkoxy group, each group being optionally substituted with one or more substituent R as above defined;

Q represents a carbonyl or hydroxymethylene group or a group of the formula -CH(OR_2)- where R_2 represents a (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl or cycloalkyl group, each of which is optionally substituted with one or more groups selected from R_8 and R_9, where R_8 is selected from the group consisting of halo, (C_1-C_6)-alkoxy, (C_1-C_6)-haloalkoxy, cyano, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl, alkoxyalkyl, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl groups and R_9 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, and heteroarylalkoxy groups, each optionally substituted with R, or R_2 represents -C(O)- (C_1-C_6)-alkyl, -C(O)O-(C_1-C_6)-

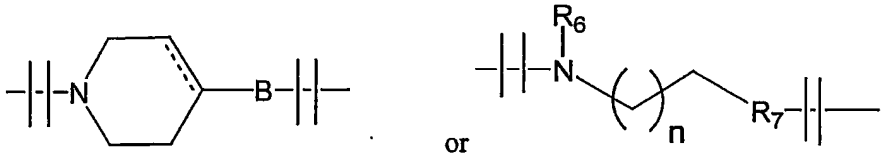
alkyl, -C(O)$NR_{10}R_{11}$ or -C(S)$NR_{10}R_{11}$ wherein each of R_{10} and R_{11} independently represents a hydrogen atom or a (C_1-C_6)-alkyl group;

R_3 represents a (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted with one or more substituent R or R_1, defined as above;

R_4 represents an aryl or heterocyclic group, each of which is optionally substituted with one or more substituents R, defined as above;

A represents CH or N,

R_5 represents



(where R_4 is bound to the right of each group)

m and n are independently 1 or 2,

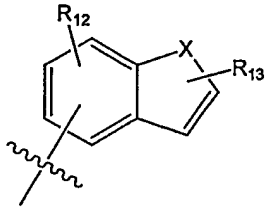
R_6 represents H or alkyl,

R_7 represents O, S, NR_6 or CH_2;

B represents a bond, O, S, NR_6 or CH_2; and

------ represents a single or double bond,

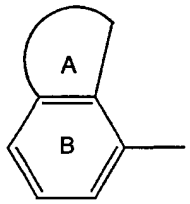
with a proviso that the substituents of formula I are not such that simultaneously Q represents-C(O)- or -CH(OH)-; R represents a hydrogen atom or one or more substituents selected from the group consisting of alkyl, alkoxy, alkylthio, hydroxy, halo, haloalkyl, nitro, amino or cyano groups; R_1 represents a hydrogen atom or a phenyl or alkylphenyl group; R_3 represents a cycloalkyl, aryl or heterocycic group, each of which is optionally substituted with one or more substituent selected from the group consisting of (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_1-C_6)-haloalkyl, nitro, amino, cyano, unsubstituted phenyl, and alkylphenyl groups; R_5 represents group (i) wherein B represents a bond or CH_2; and R_4 represents the group



wherein X represents O, S, NH, N(C_1-C_6-alkyl), S(=O) or $S(=O)_2$, and R_{12} and R_{13} each represent one or more member selected independently from the group consisting of halo,

hydroxy, alkyl, alkoxy, haloalkyl, alkylthio, nitro, amino, cyano, N-(C_1-C_6)-alkylamino, N, N-di-(C_1-C_6)-alkylamino, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl and acylamino groups, and

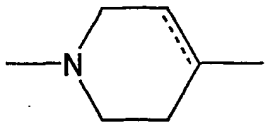
and further with the proviso that the substituents of formula I are not such that simultaneously Q represents-C(O)-; R represents a hydrogen atom or one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, N, N-di-alkylamino, aminocarbonyl, and alkoxycarbonyl groups; R_1 represents hydrogen; R_5 represents group (i) wherein B represents a bond or CH_2; R_4 represents an aryl or fully aromatic heteroaryl, each optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, N, N-di-alkylamino, aminocarbonyl and alkoxycarbonyl groups; or R_4 represents a bicyclic heteroaryl radical of formula



wherein A is a saturated or unsaturated ring having one or more heteroatoms, where rings A and B are each independently substituted with one or more substituent selected from the group consisting of alkyl, halo, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, alkanoyloxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, , amino, N-alkylamino and N,N,- di-alkylamino; and R_3 represents a saturated heterocyclic ring comprising a nitrogen atom, through which said saturated heterocyclic ring is bonded to the adjacent carbonyl group at Q, and which may optionally include a further hetero atom, and which may also be optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo and haloalkyl groups,

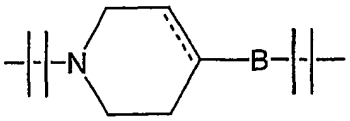
or an enantiomer, optical isomer, diastereomer, N-oxide, crystalline form, hydrate, solvate or pharmaceutically acceptable salt thereof.

2. A compound having the general formula I wherein R, R_1, R_3, R_4, R_5, Q, A and m are as defined in claim 1, provided that, if Q represents a carbonyl or hydroxymethyl group and R_5 represents a group of formula

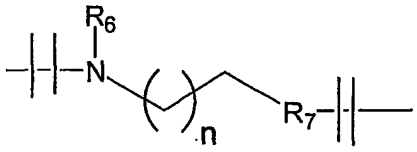


then R_3 is not a heterocyclic group attached to Q by a C-N bond and R_4 is not a substituted or unsubstituted 7-indolyl, 7-benzofuranyl or 7-benzothienyl group.

3. A compound according to claim 1 or claim 2 wherein R_5 represents



4. A compound according to claim 1 or claim 2 wherein R_5 represents



5. A compound according to any of claims 1 to 4 wherein R_3 represents a hydrogen atom or a $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl group, each group being optionally substituted with one or more substituent R or R_1 as defined in claim 1.

6. A compound according to claim 5 wherein R_3 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t.butyl, vinyl, allyl, prop-1-enyl, 1-methylvinyl, 2-methylallyl, ethynyl or prop-1-ynyl group.

7. A compound according to any of claims 1 to 4 wherein R_3 represents a cyclohexyl or 2-thienyl group.

8. A compound according to any of claims 1 to 7 wherein R_4 represents an unsubstituted heterocyclic group or a phenyl group substituted with one or more halogen atoms or $(C_1$-$C_6)$- alkyl, $(C_1$-$C_6)$-alkoxy or $(C_1$-$C_6)$-haloalkoxy groups.

9. A compound according to claim 8 wherein R_4 represents a 5-(2,3-dihydro-1,4-benzodioxinyl), 4-indolyl, 8-quinolyl, 2-methoxyphenyl, 2,6-dimethylphenyl, 4-fluoro-2-

methoxyphenyl or 2-(2,2,2-trifluoroethoxy)-phenyl group.

10. A compound according to claim 1, being

- 8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-N-methyl-2-aminoethoxy}-quinoline,
- 8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-N-methyl-2-aminoethoxy}-quinoline,
- 1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(2,6-dimethylphenyl)-piperidine,
- 1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-4-(2,6-dimethylphenyl)-piperidine or
- 1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(4-fluoro-2-methoxyphenoxy)-piperidine.

11. A pharmaceutical composition comprising a compound according to any of claims 1 to 10 or an enantiomer, optical isomer, diastereomer, N-oxide, crystalline form, hydrate, solvate or pharmaceutically acceptable salt of such a compound in admixture with a pharmaceutically acceptable diluent, excipient or carrier.

12. A method of reducing the frequency of urinary bladder contractions in a mammal in need of such treatment, the method comprising administering an effective amount of a compound according to any of claims 1 to 10 or of a composition according to claim 11 to said mammal.

13. A method of treating neuromuscular dysfunction of the lower urinary tract in a mammal in need of such treatment, the method comprising administering an effective amount of a compound according to any of claims 1 to 10 or of a composition according to claim 11 to said mammal.

14. A method according to claim 13 whereby one or more of the conditions or symptoms of urinary urgency, overactive bladder, increased urinary frequency, incontinence, mixed incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the urinary bladder is ameliorated.

15. A method according to any of claims 12 to 14 wherein said mammal is a human.

16. A method according to any of claims 12 to 15 wherein the compound or composition is administered by an oral, enteral, intravenous, intramuscular, subcutaneous, transmucosal, transdermal or by-inhalation route.

17. A method according to any of claims 12 to 16 wherein the compound or composition is administered in combination with an antimuscarinic or α_1 antagonist.

18. A method according to claim 17 wherein said antimuscarinic is oxybutynin, tolterodine, darifenacin or temiverine.

19. A method according to claim 17 wherein said α_1 antagonist is prazosin, doxazosin, terazosin, alfuzosin or tamsulosin.

20. A method for treating disorders of the central nervous system caused by serotonergic dysfunction, the method comprising delivering an effective amount of a compound according to any one of claims 1 to 10 or of a composition according to claim 11 to the environment of a 5-HT_{1A} serotonergic receptor.

21. A method according to claim 20 wherein said compound or composition is delivered via an extracorporeal route.

22. A method according to claim 21 wherein said compound or composition is delivered by administering the compound to a mammal possessing the 5-HT_{1A} serotonergic receptor.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number
WO 2003/106421 A3

(51) International Patent Classification[7]: C07D 211/14, 211/46, 215/26, A61K 31/445, 31/451, 31/47, A61P 13/00

(21) International Application Number: PCT/EP2003/006290

(22) International Filing Date: 16 June 2003 (16.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2002A001329 14 June 2002 (14.06.2002) IT

(71) Applicant *(for all designated States except IT)*: **RECORDATI S.A.** [CH/CH]; Piazza Boffalora 4, CH-6830 Chiasso (CH).

(71) Applicant *(for IT only)*: **RECORDATI INDUSTRIA CHIMICA E FARMACEUTICA SPA** [IT/IT]; Via Matteo Civitali, 1, I-20148 Milano (IT).

(72) Inventors: **LEONARDI, Amedeo**; Via Poliziano, 16, I-20154 Milano (IT). **MOTTA, Gianni**; Via Ungaretti, 10, I-20030 Barlassina (IT). **RIVA, Carlo**; Via Walder, 10, I-21100 Varese (IT). **GUARNERI, Luciano**; Via Canova, 18, I-20024 Garbagnate Milanese (IT).

(74) Agent: **SERJEANTS**; 25 The Crescent, King Street, Leicester LE1 6RX (GB).

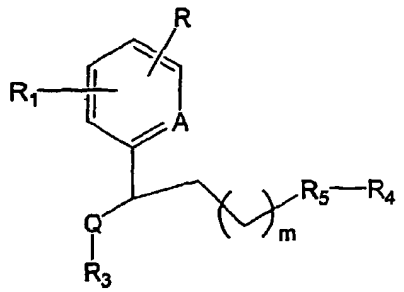
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

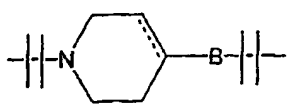
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

[Continued on next page]

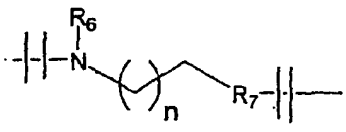
(54) Title: PHENYLALKYLAMINES AND PYRIDYLALKYLAMINES WITH SEROTONINERGIC RECEPTOR AFFINITY



(I)



(II)



(III)

(57) Abstract: Compounds of formula (I), (A is CH or N, R and R_1 are a wide range of substituents, Q is CO, CHOH or $CHOR_2$, R_2 is alkyl, alkenyl, alkynyl or cycloalkyl group, each of which is optionally substituted, or is alkanoyl, alkanoyoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminothiocarbonyl, alkylaminothiocarbonyl or dialkylaminothiocarbonyl, R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted, m is 1 or 2, R_4 is an aryl or heteroaryl group, either of which is optionally substituted, R_5 is either (II) or (III), wherein m is 1 or 2, R_6 is H or alkyl, R_7 is O, S, NR_6 or CH_2, B is a bond, O, S, NR_6 or CH_2 and ------ represents a single or double bond) have affinity for serotoninergic receptors. These compounds and their enantiomers, diastereoisomers, N-piperazine oxides, polymorphs, solvates and pharmaceutically acceptable salts are useful in the treatment of patients with neuromuscular dysfunction of the lower urinary tract and diseases related to 5-HT_{1A} receptor activity.

WO 2003/106421 A3

(88) Date of publication of the international search report:
17 June 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

nal Application No
PCT/EP 03/06290

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/14 C07D211/46 C07D215/26 A61K31/445 A61K31/451
A61K31/47 A61P13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BE 671 440 A (DR. KARL THOMAE GMBH) 1965 Starting material 17 in the table on page 6 corresponding to formula III on page 5 ---	1,2,4-6
X	EP 0 680 962 A (ZENECA LTD) 8 November 1995 (1995-11-08) claims 1,3,6,9; examples 17,19,20,24,26,27,29 ---	1-3,11
X	US 5 585 374 A (CLIFFE IAN A ET AL) 17 December 1996 (1996-12-17) cited in the application claims; example 5 ---	1-22
X	WO 96 16961 A (AMERICAN HOME PROD) 6 June 1996 (1996-06-06) page 5, line 23 - line 32; claims; examples 2-5 --- -/--	1-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 2004	23/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hanisch, I

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Ir ınal Application No
PCT/EP 03/06290

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 610 164 A (BAUDY REINHARDT B ET AL) 11 March 1997 (1997-03-11) column 3, line 11 - line 29; claims; example 2	1-22
X	EP 0 982 304 A (LILLY CO ELI) 1 March 2000 (2000-03-01) cited in the application claims 1-15,18-32; examples 1-52	1-22
X	US 5 610 295 A (CLIFFE IAN A ET AL) 11 March 1997 (1997-03-11) column 1, line 6 - line 13; claims 1-6,11,13	1-22
X	EP 0 924 205 A (LILLY CO ELI) 23 June 1999 (1999-06-23) paragraph '0010!; claims 1-16; examples 1-4,6-8	1-22

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP 03/06290

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 12-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/EP 03/06290

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
BE 671440	A		NONE		
EP 0680962	A	08-11-1995	DE	69531522 D1	25-09-2003
			EP	0680962 A2	08-11-1995
			JP	7304767 A	21-11-1995
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US 5610164	A	11-03-1997	NONE		
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			WO	9420481 A1	15-09-1994
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INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/EP 03/06290

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0924205 A		AU 1808399 A	05-07-1999
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		ZA 9811473 A	14-06-2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 March 2004 (11.03.2004)

PCT

(10) International Publication Number
WO 2004/019892 A3

(51) International Patent Classification[7]: A61F 13/00

(21) International Application Number:
PCT/US2003/027409

(22) International Filing Date:
2 September 2003 (02.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/407,009 30 August 2002 (30.08.2002) US

(71) Applicant *(for all designated States except US)*: **WATSON PHARMACEUTICALS, INC.** [US/US]; 311 Bonnie Circle, Corona, CA 92880 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **EBERT, Charles, D.** [US/US]; 1912 East Lakewood Dr., Salt Lake City, UT 84117 (US).

(74) Agents: **OSBORNE, David, W.** et al.; Thorpe North & Western LLP, P.O. Box 1219, Sandy, UT 84091-1219 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
1 July 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DRUG DELIVERY SYSTEM FOR TREATING URINARY INCONTINENCE

(57) Abstract: Methods for the prevention or amelioration of urinary incontinence are disclosed and described. One method includes the coadministration of an anticholinergic agent with either an SSRI, or an SNRI, or both.

WO 2004/019892 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/27409

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61F 13/00
US CL : 424/449, 443
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/449, 443

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/0010216 A1 (ROGOSKY et al.) 24 January 2002 (24.01.2002), abstract; page 1: 0012; page 3: 0033, 0035, 0037, 0039.	1-21, 23-32

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
11 February 2004 (11.02.2004)

Date of mailing of the international search report
04 MAY 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Isis Ghali
Telephone No. (703)308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/27409

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 22
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 22 depends on claim 20, which is reciting a transdermal patch; meanwhile the claim is directed to composition in the oral form.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Continuation of B. FIELDS SEARCHED Item 3:
WEST:ALL DATA BASES:
Search terms: transdermal, oral, oxybutynin, tolterodine, fluoxetine, paroxetine.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 March 2004 (11.03.2004)

PCT

(10) International Publication Number
WO 2004/019892 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/US2003/027409

(22) International Filing Date:
2 September 2003 (02.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/407,009 30 August 2002 (30.08.2002) US

(71) Applicant *(for all designated States except US)*: **WATSON PHARMACEUTICALS, INC.** [US/US]; 311 Bonnie Circle, Corona, CA 92880 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **EBERT, Charles, D.** [US/US]; 1912 East Lakewood Dr., Salt Lake City, UT 84117 (US).

(74) Agents: **OSBORNE, David, W.** et al.; Thorpe North & Western LLP, P.O. Box 1219, Sandy, UT 84091-1219 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/019892 A2

(54) Title: IMPROVED DRUG DELIVERY SYSTEM FOR TREATMENT OF URINARY INCONTINENCE

(57) Abstract: Methods for the prevention or amelioration of urinary incontinence are disclosed and described. One method includes the coadministration of an anticholinergic agent with either an SSRI, or an SNRI, or both.

IMPROVED DRUG DELIVERY SYSTEM FOR TREATMENT OF URINARY INCONTINENCE

PRIORITY DATA

This application claims priority to United States Provisional Patent Application Serial no. 60/407,009, filed on August 30, 2002, which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to coadministration of an anticholinergic agent with either a selective serotonin reuptake inhibitor (SSRI) or a selective norepinephrine reuptake inhibitor (SNRI), or both, for the treatment of urinary incontinence. Accordingly, this invention covers the fields of pharmaceutical sciences, medicine and other health sciences.

BACKGROUND OF THE INVENTION

Recently, an effective transdermal medication has been developed for the treatment of what has come to be known as overactive bladder which is ocassioned by an incontinence. Urge incontinence results from instability of the detrusor muscle, the muscle surrounding the bladder. The cholinergic receptors of the detrusor can be over-stimulated causing spasmodic contractions and a sensation of urgency to urinate, which may lead to an urgency to urinate, an increased micturation rate, and in extreme cases to incontinent episodes.

An oral sustained release technology is exemplified by Guittard et al., U.S. Patent 6,262,115 (Alza) discloses tablets of oxybutynin without any further pharmaceutical component which has hydroxypropylmethylcellulose present in a molecular weight of approximately 10,000 (herein: Guittard). An effective transdermal delivery system has been developed by Watson Pharmaceuticals, Inc., which comprises technology disclosed in Quan et al., U.S. Patent 5,834,010 (1998) (herein: "Quan"). Quan discloses transdermal technology for the delivery of oxybutynin. This application incorporates by reference in toto the complete disclosure of Quan. Quan teaches a transdermal medication that can be applied typically for twenty-four hours. It is recommended that such a transdermal medication be applied after a morning shower or bath, to thereby provide a twenty-four hour period of

protection against such overactive bladder condition until the following morning. Other attempts to provide a treatment in this area include Pharmacia PCT application 0162236 with U.S. priority of February 24, 2000, and Waki et al., European Patent Application 1174132 (2002). Waki et al. provide a recent time slice of the state of the art: "[T]he countermeasure for the bladder functional disorder such as urinary incontinence or pollakiuria associated with the increase in the population of the advanced age group is one of the most important question of vital interest in the medical treatment. Therefore, the development of the effective drugs in treating urinary incontinence or pollakiuria are to be desired, and various medicines in addition to oral drugs already available in the market are on their way to development. Oxybutynin hydrochloride used in the treatment of urinary incontinence and pollakiuria is well recognized as the excellent anticholinergic drug demonstrating its pharmacological effect through acetylcholine antagonism. An oral dosage form of the drug requires a comparatively small quantity of 2-3 mg per dose, but they have to be taken three times a day. In addition, the absorption of the drug through the intestinal tract is known to be good, but the higher hepatic metabolism is also reported (Pharmacopoeia 4 (5), 45-53, 1990). Regarding the routes of administration, the oral form has the advantage in not giving pain to patients as compared with the injection form, but it may not be easy to administer the medicine which has to be taken at the regular interval for the aged patients who may sometimes require the medical helper. Furthermore, the drug taken orally is inevitably absorbed into a hepatoportal vein through the intestinal tract, thereby being subjected to the first pass effect termed for the intense hepatic metabolism of the drug on its first passage and often leads to the marked decrease in biological availability in many cases. In order to maintain the effective concentration of the drug in the blood, it is necessary to administer a relatively large dose of drug, and as a result, an incidence in adverse effects naturally increases. From these standpoints, there is the urgent need for the development, of a preparation that is relatively easy to administer, long lasting in its effect, and yet with fewer adverse effects. In view of pharmacokinetics, a preparation that does not exhibit the behavior of a transitory drug concentration in the blood such that the blood concentration rapidly increases and then decreases as often observed in the general orally administrated preparation, but whose concentration increases gradually and its effective concentration in the blood can be continuously maintained over a long period of time is highly desired."

In an embodiment of the invention that utilizes the Quan technology, in such an embodiment, the matrix patch comprises about 0.1% to about 50% by weight triacetin, more preferably about 1% to about 40% by weight triacetin, and most preferably about 2% to about 20% by weight triacetin. The polymer layer is preferably an adhesive, but can also be laminated to an adhesive layer or used with an overlay adhesive. Suitable polymers include acrylics, vinyl acetates, natural and synthetic rubbers, ethylenevinylacetate copolymers, polysiloxanes, polyacrylates, polyurethanes, plasticized weight polyether block amide copolymers, plasticized styrene-rubber block copolymers, and mixtures thereof. Acrylic copolymer adhesives are preferred. The matrix patch can also contain diluents, excipients, emollients, plasticizers, skin irritation reducing agents, carriers, and mixtures thereof provided that such additives do not alter the basic characteristics of the matrix patch.

In aspects of the invention utilizing the Quan technology, suitable polymers that can be used in the biocompatible polymeric layer of the matrix patch include pressure-sensitive adhesives suitable for long-term contact with the skin. Such adhesives must be physically and chemically compatible with the drug and enhancer, and with any carriers and/or vehicles or other additives incorporated into the drug/enhancer composition. Suitable adhesives for use in the matrix patch include acrylic adhesives including cross-linked and uncross- linked acrylic copolymers; vinyl acetate adhesives; natural and synthetic rubbers including polyisobutylenes, neoprenes, polybutadienes, and polyisoprenes; ethylenevinylacetate copolymers; polysiloxanes; polyacrylates; polyurethanes; plasticized weight polyether block amide copolymers, and plasticized styrene-rubber block copolymers. Preferred contact adhesives for use in the matrix patch herein are acrylic adhesives, such as TSR (Sekisui Chemical Co., Osaka, Japan) and DuroTak. RTM. adhesives (National Starch & Chemical Co., Bridgewater, N.J.), and polyisobutylene adhesives such as ARcare.TM. MA-24 (Adhesives Research, Glen Rock, Pa.).

In use, the matrix patch contains a distal backing laminated on the polymer layer. The distal backing defines the side of the matrix patch that faces the environment, i.e., distal to the skin or mucosa. The backing layer functions to protect the matrix polymer layer and drug/enhancer composition and to provide an impenetrable layer that prevents loss of drug to the environment. Thus, the material chosen for the backing should be compatible with the polymer layer, drug, and enhancer, and should be minimally permeable to any components of the matrix patch.

Advantageously, the backing can be opaque to protect components of the matrix patch from degradation from exposure to ultraviolet light. Further, the backing should be capable of binding to and supporting the polymer layer, yet should be pliable to accommodate the movements of a person using the matrix patch. Suitable materials for the backing include metal foils, metalized polyfoils, composite foils or films containing polyester such as polyester terephthalate, polyester or aluminized polyester, polytetrafluoroethylene, polyether block amide copolymers, polyethylene methyl methacrylate block copolymers, polyurethanes, polyvinylidene chloride, nylon, silicone elastomers, rubber-based polyisobutylene, styrene, styrene-butadiene and styrene- isoprene copolymers, polyethylene, and polypropylene. A thickness of about 0.0005 to 0.01 inch is preferred. The release liner can be made of the same materials as the backing, or other suitable films coated with an appropriate release surface.

The matrix patch can further comprise various additives in addition to the polymer layer, basic drug, and triacetin-containing penetration enhancer that are the fundamental components of the transdermal drug delivery system. These additives are generally those pharmaceutically acceptable ingredients that are known in the art of drug delivery and, more particularly, in the art of transdermal drug delivery provided that such additive ingredients do not materially alter the basic and novel characteristics of the matrix patch. For example, suitable diluents can include mineral oil, low molecular weight polymers, plasticizers, and the like. Many transdermal drug delivery formulations have a tendency to cause skin irritation after prolonged exposure to the skin, thus addition of a skin irritation reducing agent aids in achieving a composition that is better tolerated by the skin. A preferred skin irritation reducing agent is glycerin, U.S. Pat. No. 4,855,294.

The matrix patch device containing a polymer layer, the drugs, and triacetin-containing penetration enhancer is brought in contact with the skin or mucosa at a selected application situs and is held in place by a suitable pressure-sensitive adhesive. Preferably, the polymer layer of the matrix patch is an adhesive, but the polymer layer can also be laminated to an adhesive layer or used with an overlay adhesive.

While Quan provides an excellent medication for cases of overactive bladder for most patients, an improvement is contemplated in the present invention for post-menopausal women.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides an improvement in the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with a greater resistance to active bladder reaction via the coadministration of a therapeutically effective amount of an anticholinergic agent with a therapeutically effective amount of an SSRI, or SNRI, or both. In one aspect, the anticholinergic agent may be oxybutynin and the SSRI may be fluoxitine.

There has thus been outlined, rather broadly, the more important features of the invention so that the detailed description thereof that follows may be better understood, and so that the present contribution to the art may be better appreciated. Other features of the present invention will become clearer from the following detailed description of the invention, taken with the accompanying claims, or may be learned by the practice of the invention.

DETAILED DESCRIPTION

Accordingly, there are several specific aspects of the present invention. In a first embodiment, there is provided an improvement in the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the coadministration therewith of an effective amount of FLUOXETINE whereby there is an enhanced resistance to said active bladder reaction.

In an aspect of this first embodiment, said coadministration is provided orally. In a still further aspect, the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction. In a further aspect, said coadministration is from a transdermal patch.

In a second aspect of the invention, an improvement is provided in the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the coadministration therewith of an effective amount of paroxetine whereby there is an enhanced resistance to said active bladder reaction. In an embodiment, said coadministration is

provided orally, and in a further embodiment thereunder, the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction. In an alternative embodiment of this aspect of the inventionsaid coadministration is from a transdermal patch.

In a third aspect of the invention, an improvement is provided in the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of Tolterodine, the improvement which comprises the coadministration therewith of an effective amount of fluoxetine whereby there is an enhanced resistance to said active bladder reaction. In an aspect of this embodiment, said coadministration is provided orally. In a still further aspect, the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction. In a further aspect, said coadministration is from a transdermal patch.

In a fourth aspect of the invention there is provided an improvement in the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of Tolterodine, the improvement which comprises the coadministration therewith of an effective amount of paroxetine whereby there is an enhanced resistance to said active bladder reaction. In an aspect of this embodiment, said coadministration is provided orally. In a still further aspect, the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction. In a further aspect, said coadministration is from a transdermal patch.

In further aspects of the invention, oral and transdermal delivery systems are provided for each of the aspects of the invention set forth above.

The range of drugs in the composition of the invention will vary within amounts necessary to provide the desired effect of a prophylaxis or treatment of urinary incontinence in post-menopausal women with weakened musculature in the area of the urinary tract.

In oral formulation embodiments of the invention with oxybutynin it is contemplated that oxybutynin will be used in the form of its hydrochloride .

In sustained release formulations with any of oxybutynin, Tolterodine, Fluoxetine and Paroxetine, it is contemplated that twice the dosage will be provided

vis a vis a regular (non-sustained release) tablet.

For Fluoxetine, the amount should vary from about 5 to about 120 mg. per dosage; in an embodiment, the range is 10 to 80 mg., and in an example the amount is 40 mg. A blood level that is continuously achieved for most of the period of delivery is to be achieved in accordance with the invention which should be from about 15 to 55 nanograms/ml;

For Paroxetine, the amount should vary from about 5 to 60 mg. per dosage unit; in an embodiment, the amount varies from about 10 to about 40 mg., and in a preferred embodiment the amount is 30 mg.

For oxybutynin or Tolterodine the amount is generally from about 2.5 to about 20 mg., and in an embodiment the amount is from about 5 to about 15 mg., whilst in an example the amount is 10 mg.

Hydroxypropylmethyl cellulose may be replaced with other sustained release vehicles. The amount and viscosity of each should be selected to provide a sustained release of the drug over a period of 24 hours.

The improvement of the invention in all aspects provides a post-menopausal woman with a protection against unwanted urination due to the frequent loss of muscle or sphinter control that accompanies the female aging process. A common example of this problem is leakage following a sneeze or a cough.

EXAMPLE I:

Using conventional tablet excipients and techniques, a rapidly dissolving tablet is provided which contains 3.9 mg. oxybutynin and 20 mg. fluoxetine.

The tablet provides a mature, post-menopausal woman with enhanced relief against incontinence vis a vis a tablet without the fluoxetine.

EXAMPLE II:

Using conventional tablet excipients and techniques, a rapidly dissolving tablet is provided which contains 3.9 mg. oxybutynin and 20 mg. paroxetine. The tablet provides a mature, post-menopausal woman with enhanced relief against incontinence vis a vis a tablet without the paroxetine.

EXAMPLES III-IV:

Oral sustained release technology is exemplified by Guitard Example 1 which

discloses "[a] therapeutic oxybutynin composition for administering to a patient *** prepared as follows: First, 103 grams of oxybutynin hydrochloride was dissolved in 1200 ml (milliliters) of anhydrous ethanol. Separately, 2,280 g of polyethylene oxide of 200,000 weight-average molecular weight, 150 g of hydroxypropylmethylcellulose of 9,200 average-number molecular weight and 450 g of sodium chloride were dry blended in a conventional blender for 10 minutes to yield a homogenous blend. Next, the oxybutynin ethanol solution was added slowly to the blend, with the blender continuously blending until all the ingredients were added to the three component dry blend, with the blending continued for another 8 to 10 minutes. The blended wet composition was passed through a 16 mesh screen and dried overnight at a room temperature of 72[deg] F. (22.2[deg]). Then, the dry granules were passed through a 20 mesh screen, 18 g of magnesium stearate was added, and all the ingredients blended again for 5 minutes. The fresh granules are ready for formulation into a therapeutic oxybutynin composition. The therapeutic composition comprises 3.4 wt % oxybutynin hydrochloride, 76 wt % polyethylene oxide of 200,000 weight-average molecular weight, 5 wt % of hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 15 wt % sodium chloride, and 0.6 wt % magnesium stearate." In accordance with the present invention, a sustained release tablet is provided by doubling the amounts of the two drug ingredients of Example I and II and incorporating this combination of drugs in place of the oxybutynin of Example 1 of Guittard. Each of the two tablets provides a 24 hour period of relief for incontinence.

EXAMPLE V:

Using conventional tablet excipients and techniques, a rapidly dissolving tablet is provided which contains 4.0 mg. Tolterodine and 20 mg. fluoxetine.
The tablet provides a mature, post-menopausal woman with enhanced relief against incontinence vis a vis a tablet without the fluoxetine.

EXAMPLE VI:

Using conventional tablet excipients and techniques, a rapidly dissolving tablet is provided which contains 4.0 mg. Tolterodine and 20 mg. paroxetine.
The tablet provides a mature, post-menopausal woman with enhanced relief against incontinence vis a vis a tablet without the paroxetine.

EXAMPLES VII-VIII:

Using the sustained release technology of Examples III-IV, a sustained release tablet is provided by doubling the amounts of the two drug ingredients of Example V and VI and otherwise following the procedure used in Examples III-IV. Each of the two tablets provides a 24 hour period of relief for incontinence.

EXAMPLE IX:

As a control, Example 1 of Quan is set forth: "Oxybutynin free base, pKa=10.3, is a strongly basic drug administered transdermally for antispasmodic and anticholinergic therapy. Matrix patches containing varying amounts of oxybutynin free base and penetration enhancers were prepared and tested as described above. The matrix systems consisted of 5 to 20% by weight of oxybutynin free base and 0 to 20% by weight of the enhancer contained in a medical grade acrylic copolymer adhesive.

"The matrix formulations were prepared as follows. First, the solids content of the adhesive was determined by weighing a small amount of the adhesive solution in a preweighed aluminum dish. The solvent was evaporated by overnight drying in a convection oven maintained at 80. degree. C. and the weight of the residue (dry adhesive) and percent solid adhesive content of the solution were determined. Once the solids content was determined, a known weight of the acrylic copolymer adhesive solution was weighed into a glass bottle. From the weight of the adhesive solution and the percent solid adhesive content, the amount of adhesive in the solution was calculated. Oxybutynin free base and enhancer were added to the bottle in proportions to yield the selected final composition. The bottle was then tightly capped, sealed with laboratory film, and rotated overnight until all ingredients had completely dissolved and the resultant solution was visually clear.

"Approximately 8 ml of the solution was then dispensed on a silanized polyester release liner and cast with a 10 mil gap casting knife. The casting was then dried in a convection oven at 70.degree. C. for 15 minutes to evaporate the solvent and to yield a dried film approximately 0.002 inch thick. A 0.003 inch thick polyethylene backing film was laminated onto the dried adhesive film with a rubber roller. These matrix laminates were then used to conduct in vitro skin flux studies that showed satisfactory results as explained in Table 1 of Quan.".

The transdermal matrix for the delivery of oxybutynin of Example 1 of Quan

is modified by incorporating therein 40 mg. of fluoxetine. Comparable results are achieved to those of Quan for patients other than post-menopausal women where the present invention provides a better retardation of active bladder response based upon weakened musculature.

EXAMPLE X:

The transdermal matrix for the delivery of oxybutynin of Example 1 of Quan is modified by incorporating therein 40 mg. of paroxetine. Comparable results are achieved to those of Quan for patients other than post-menopausal women where the present invention provides a better retardation of active bladder response based upon weakened musculature.

EXAMPLES XI-XII:

By replacing an equal amount of Tolterodine for the oxybutynin of Examples XIII and IX, a transdermal medication particularly suited for post-menopausal women is achieved that is designed to provide superior relief against active bladder caused by a weakened musculature.

EXAMPLES XIII:

The Waki et al. application discloses that "1.0 part of oxybutynin hydrochloride was dissolved in 200.0 parts of isoprapanol as the solvent, and then 20.0 parts of N-vinyl acetamide copolymer (PNVA GE167, a product of Showa Denko K.K.), 1.0 part of synthetic aluminum silicate and 1.0 part of borax were added and stir-mixed. The mixture solution containing 62.0 parts of glycerin and 15.0 parts of propylene glycol were added and continuously stirred.

"The solvent-type plaster with the desirable viscosity for the plaster is spread out over the non-woven fabric, then solvent is removed by heat drying (solvent drying) and the strippable film made of polyester was adhered. This was cut into the desirable size to obtain the transdermal absorption preparation containing oxybutynin hydrochloride."

By replacing the oxybutynin of the quoted Waki example with a combination of each of the drugs as set forth in Examples XIII-XI, a superior overall medication is contemplated for post-menopausal women with a weakened musculature.

CLAIMS

What is claimed is:

1. In the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the coadministration therewith of an effective amount of FLUOXETINE whereby there is an enhanced resistance to said active bladder reaction.

2. The method of claim 1 wherein said coadministration is provided orally.

3. The method of claim 2 wherein the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction.

4. The method of claim 1 wherein said coadministration is from a transdermal patch.

5. In the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the coadministration therewith of an effective amount of paroxetine whereby there is an enhanced resistance to said active bladder reaction.

6. The method of claim 6 wherein said coadministration is provided orally.

7. The method of claim 7 wherein the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction.

8. The method of claim 5 wherein said coadministration is from a transdermal patch.

9 In the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of Tolterodine, the improvement which

comprises the coadministration therewith of an effective amount of fluoxetine whereby there is an enhanced resistance to said active bladder reaction.

10. The method of claim 9 wherein said coadministration is provided orally.

11. The method of claim 10 wherein the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction.

12. The method of claim 11 wherein said coadministration is from a transdermal patch.

13. In the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of Tolterodine, the improvement which comprises the coadministration therewith of an effective amount of paroxetine whereby there is an enhanced resistance to said active bladder reaction.

14. The method of claim 13 wherein said coadministration is provided orally.

15. The method of claim 14 wherein the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction.

16. The method of claim 13 wherein said coadministration is from a transdermal patch.

17. A composition suitable for providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the providing a dosage form for the administration of an effective amount of paroxetine whereby there is an enhanced resistance to said active bladder reaction.

18. The composition of claim 17 in oral form.

19. The composition of claim 18 in a sustained release vehicle to provide a 24

hour delivery to the patient.

20. A transdermal patch containing the medication of claim 17.

21. A composition suitable for providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the providing a dosage form for the administration of an effective amount of fluoxetine whereby there is an enhanced resistance to said active bladder reaction.

22. The composition of claim 20 in oral form.

23. The composition of claim 20 in a sustained release vehicle to provide a 24 hour delivery to the patient.

24. A transdermal medication of claim 20.

25. A composition suitable for providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of Tolterodine, the improvement which comprises the providing a dosage form for the administration of an effective amount of fluoxetine whereby there is an enhanced resistance to said active bladder reaction.

26. The composition of claim 25 in oral form.

27. The composition of claim 25 in a sustained release vehicle to provide a 24 hour delivery to the patient.

28. A transdermal patch containing the medication of claim 25.

29. A composition suitable for providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of Tolterodine, the improvement which comprises the providing a dosage form for the administration of an effective amount

of paroxetine whereby there is an enhanced resistance to said active bladder reaction.

30. The composition of claim 29 in oral form.

31. The composition of claim 29 in a sustained release vehicle to provide a 24 hour delivery to the patient.

32. A transdermal patch containing the medication of claim 29.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 211/06, 215/54, 217/62, 237/30, 255/33, C07D 333/20, A61K 31/135, 31/33

A1

(11) International Publication Number: **WO 98/43942**

(43) International Publication Date: 8 October 1998 (08.10.98)

(21) International Application Number: PCT/SE98/00556

(22) International Filing Date: 26 March 1998 (26.03.98)

(30) Priority Data:
9701144-9 27 March 1997 (27.03.97) SE

(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN AB [SE/SE]; S-112 87 Stockholm (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: JOHANSSON, Rolf [SE/SE]; Daggstigen 8B, S-141 38 Huddinge (SE). HARALDSSON, Martin [SE/SE]; Runmästarvägen 8, S-183 72 Täby (SE). RINGBERG, Erik [SE/SE]; Gröna Gatan 23F, S-754 26 Uppsala (SE). VÅGBERG, Jan [SE/SE]; Karlslundsvägen 19, S-192 71 Sollentuna (SE). BEIERLEIN, Katarina [SE/SE]; Torbjörnsgatan 14, S-753 35 Uppsala (SE). EMOND, Rikard [SE/SE]; Mörtgatan 5, S-133 43 Saltsjöbaden (SE). SJÖBERG, Birger [SE/SE]; Trädgårdsvägen 98, S-191 46 Sollentuna (SE).

(74) Agents: WIDÉN, Björn et al.; Pharmacia & Upjohn AB, Patent Dept., S-751 82 Uppsala (SE).

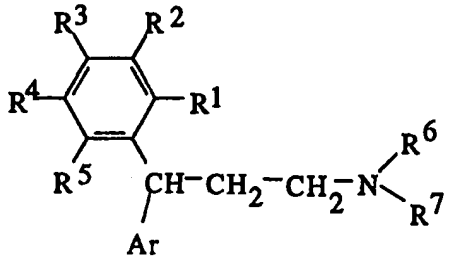
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL COMPOUNDS, THEIR USE AND PREPARATION

(57) Abstract

The invention relates to novel compounds of Formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and Ar are as defined in claim 1, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers. The compounds have anticholinergic activity, and the invention also relates to the compounds of Formula (I) for use as therapeutically active substances, pharmaceutical compositions containing compounds of Formula (I), the use of the compounds of Formula (I) for preparing anticholinergic drugs, the use of the compounds of Formula (I) for treating urinary incontinence, and methods for preparing the compounds of Formula (I).



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NOVEL COMPOUNDS, THEIR USE AND PREPARATION

TECHNICAL FIELD

The present invention relates to novel therapeutically active compounds, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

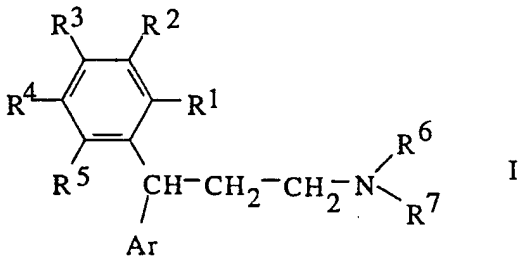
BACKGROUND OF THE INVENTION

WO 89/06644 and WO 94/11337 disclose tertiary 3,3-diphenylpropylamines having anticholinergic activity, especially for the treatment of urinary incontinence. SE-A-215499 discloses secondary 3,3-diphenylpropylamines having an advantageous effect on the heart and circulation. US-A-3,446,901, GB-A-1,169,944 and GB-A-1,169,945 disclose 3,3-diphenylpropylamines having antidepressant activity. DE-B1-1216318 discloses preparation of diphenylalkylamines having effect on the heart and circulation.

SUMMARY OF THE INVENTION

In accordance with the present invention, novel therapeutically active diarylpropylamines have been found which like the 3,3-diphenylpropylamines known from WO 89/06644 and WO 94/11337 above have favourable anticholinergic properties, and which therefore also can be used for the control of events mediated by acetylcholine, like urination.

In one aspect, the present invention provides novel compounds represented by the general formula I:



I

wherein:

R^1 is hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, halogen,

R^2 and R^3 independently are hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl,

R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, azido, alkyl of at least two carbon atoms, alkoxy of at least two carbon atoms, hydroxyalkyl of at least two carbon atoms,

R^5 is hydrogen, halogen, alkyl,

Ar is aryl or heteroaryl which may be mono- or independently disubstituted by alkyl, alkoxy, hydroxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl, and

R^6 and R^7 are hydrocarbyl groups which may be the same or different, together containing at least three carbon atoms, and which may carry one or more hydroxy groups, and wherein carbon atoms may be interconnected by oxygen atoms, and wherein R^6 and R^7 may form a ring together with the amine nitrogen,

with the provisos that (a) when:

(i) at least two of R^2, R^3 and R^5 are other than hydrogen, or

(ii) R^1 is other than hydroxy or methoxy, and Ar is other than phenyl that is ortho-substituted by hydroxy or methoxy, or

(iii) Ar is heteroaryl, or

(iv) at least one of R^6 and R^7 is aromatic hydrocarbyl or cycloalkyl, then

R^4 may also be hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, halogen, carbamoyl, sulphamoyl;

and (b), when Ar is unsubstituted phenyl, then R^1, R^2, R^3, R^4 and R^5 can not all be hydrogen;

their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

In another aspect, the present invention provides the compounds having the general Formula I above for therapeutical use, especially for the treatment of urinary incontinence related disorders.

In still another aspect, the present invention provides a pharmaceutical composition comprising one or more compounds of the general Formula I above as the active ingredient, preferably together with a pharmaceutically acceptable carrier and, if desired, other pharmacologically active agents.

In yet another aspect, the present invention provides a method of treating a patient (animals, including humans) suffering from a disorder related to urinary incontinence, which method comprises the step of administering to the said patient an effective amount of a compound having the general Formula I above.

In another aspect, the present invention provides the compounds according to Formula I for use as a pharmaceutically active substance, especially as an anticholinergic agent.

In yet another aspect, the present invention provides the use of the compounds having the general Formula I above for the manufacture of a medicament for the treatment of urinary incontinence related disorders.

In still another aspect, the present invention provides processes for preparing compounds having the general Formula I above.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises novel 3,3-diarylpropylamines and their pharmaceutically acceptable salts which are characterized by Formula I above and which

are useful as anticholinergic agents. The compounds are particularly useful for treatment of urinary incontinence.

One subgroup of compounds of Formula I is defined by the substituent R^4 being ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkyl-aminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyl-aminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, or azido.

In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, R^2, R^3 and R^5 are either all hydrogen or one of R^2, R^3 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

Another subgroup of the compounds of Formula I is defined by Ar being heteroaryl.

In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, and R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen.

Still another subgroup of the compounds of Formula I is defined by R^1 being hydrogen, alkyl, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, or halogen. Preferaby, Ar is then other than phenyl that is ortho-substituted by hydroxy or alkoxy.

In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

Yet another subgroup of the compounds of Formula I is defined by at least one of R^6 and R^7 being aromatic hydrocarbyl, cycloalkyl or a hydrocarbyl chain wherein carbon atoms are interconnected by an oxygen atom at one or more positions.

In a limited group of compounds within this subgroup, R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

In the compounds of Formula I, "alkyl", separately and in combinations, is preferably C_{1-8}alkyl, i.e. methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and isomeric forms thereof, more preferably C_{1-6}alkyl, especially C_{1-4}alkyl.

Similarly, "alkoxy", separately and in combinations, is preferably C_{1-8}alkoxy, i.e. methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptoxy, octoxy, and isomeric forms thereof, more preferably C_{1-6}alkoxy, especially C_{1-4}alkoxy.

"Aryl" means phenyl or naphthyl. "Heteroaryl" refers to a 5- or 6-membered heteroaromatic ring having from one to three heteroatoms, and which optionally may be fused to a homoaromatic ring, such as a benzene ring. Exemplary heteroaryl groups are morpholinyl, thienyl, furyl, piperazinyl, piperidinyl, imidazolinyl, pyridazolinyl, oxazolyl, isoxazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl.

"Halogen" includes fluoro, chloro, bromo and iodo.

When aryl is mono-substituted, it is preferably substituted in 2-position. When aryl is di-substituted, it is preferably substitued in positions 2 and 4. Preferred substituents are methyl, methoxy, hydroxy, hydroxymethyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl,

especially methyl, hydroxymethyl and halogen. Aryl is preferably phenyl.

Preferred heteroaryl groups are thienyl, pyrryl, thiazolyl, oxazolyl, methylthiazolyl and methylpyrryl.

R^1 is preferably hydroxy, halogen, trifluoromethyl, amino, methoxy or hydroxymethyl.

R^2 and R^3 are preferably selected from hydrogen, hydroxy and methoxy.

R^4 is preferably hydrogen, formyl, alkoxycarbonyl, alkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxamidoalkyl, carbamoylalkyl, aminoalkyl, amino, azido, cyanoalkyl, carboxy or carboxyalkyl. More preferably, R^4 is hydrogen, formyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethoxymethyl, methoxycarbonyl, amino, aminopropyl, acetyl, 1,2-hydroxyethyl, ethylaminomethyl, or hydroxyethoxyethyl-aminoethyl.

R^5 is preferably hydrogen.

R^6 and R^7 independently of each other preferably signify a saturated hydrocarbyl group, especially a saturated aliphatic hydrocarbyl group, such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^6 and R^7 together containing at least three, preferably at least four carbon atoms. R^6 and R^7 may carry one or more hydroxy groups and they may be joined to form a ring together with the nitrogen atom. It is preferred that at least one of R^6 and R^7 comprises a branched carbon chain.

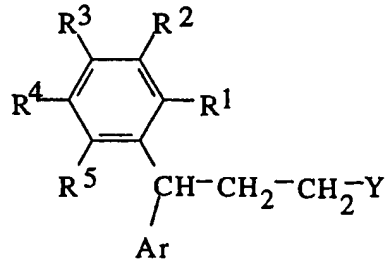
Exemplary groups $-NR^6,R^7$ are diethylamino, diisopropylamino, methyl-tert.-butylamino, methyl-tert.-pentylamino, piperidino, 2,2,6,6-tetramethylpiperidino, methylcyclobutylamino, methylcyclopentylamino, methylcyclohexylamino, methylcycloheptylamino, pyrrolidino, 2,2,5,5-tetramethylpyrrolidino, N-methyl-N-adamantylamino, especially diisopropylamino.

Representative compounds of Formula I are:
N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamine hydrochloride

N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(2-hydroxy-5-methyloxycarbonylphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine, and its 3(R)-isomer
N,N-diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxy-phenyl]-3-phenylpropanamine, and its 1(S*)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)phenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[5-(3-acetamidopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamine, and its (R)-isomer
N,N-diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)phenyl]-3-phenylpropanamine, and its (R)-isomer
N-cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine
N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamine
N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine, and its (R)-isomer

The compounds of Formula I may, in accordance with the present invention, be prepared by per se conventional methods, and especially by

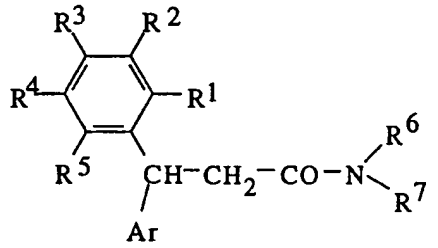
a) reacting a compound of Formula II



II

wherein R^1 to R^5 and Ar are as defined above for Formula I, and Y is a leaving group, with an amine HNR^6,R^7, wherein R^6 and R^7 are as defined above, or

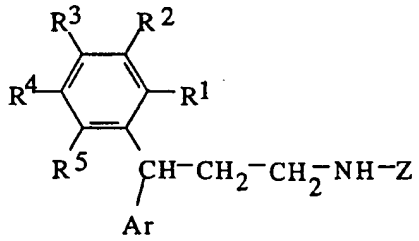
b) reducing a compound of Formula III



III

wherein R^1 to R^7 and Ar are as defined above for Formula I and any hydroxy groups may be protected, or

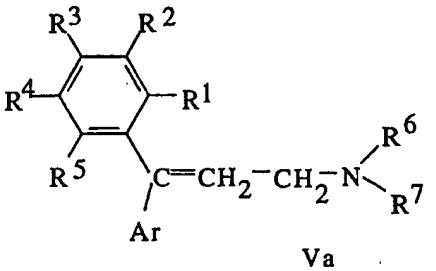
c) N-alkylating a secondary amine of Formula IV



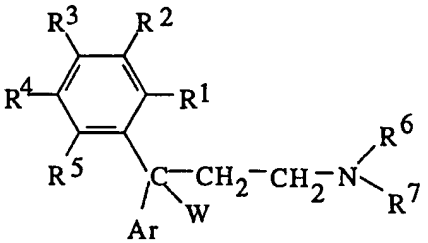
IV

wherein R^1 to R^5 and Ar are as defined above for Formula I and any hydroxy groups may be protected, and wherein Z has the same meaning as R^6 and R^7, or

d) reducing a compound of Formula Va or Vb



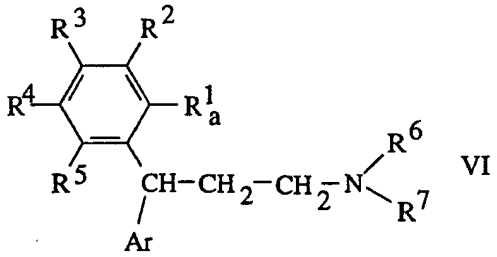
Va



Vb

wherein R^1 to R^7 and Ar are as defined above for Formula I and any hydroxy groups may be protected, and W signifies a hydroxy group or halogen, or

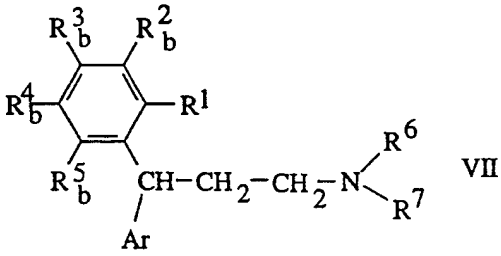
e) in a compound of Formula VI



VI

wherein R^2 to R^7 and Ar are as defined above for Formula I, and R^1a is carboxyl or alkoxy, converting R^1a to hydroxy, or

f) in a compound of Formula VII

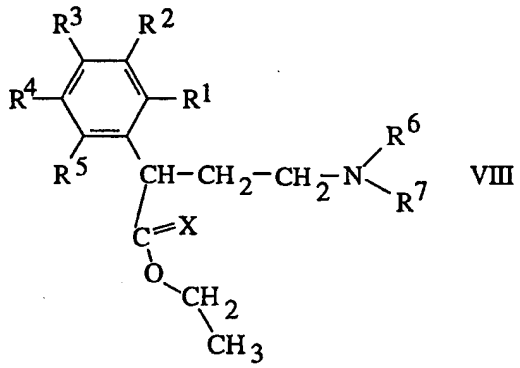


VII

wherein R^1, R^6, R^7 and Ar are as defined above for Formula I, and one of R^2b to R^5b is alkylene and the others are as defined above for R^2 to R^5, reducing alkylene to alkyl, hydroxyalkyl or dihydroxyalkyl, or

g) in a compound of Formula I as defined above, converting one or more of groups R^1 to R^5 to another or other groups R^1 to R^5, or

h) reacting a compound of Formula VIII

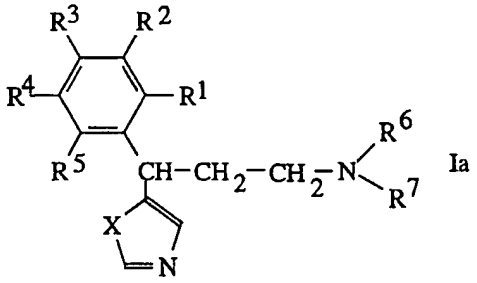


VIII

wherein R^1 to R^7 are as defined above for Formula I, and X is oxygen or sulphur, with a compound of Formula IX

$CH_3N{=}C:$ IX

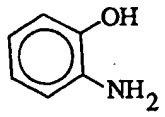
to form a compound of Formula Ia



Ia

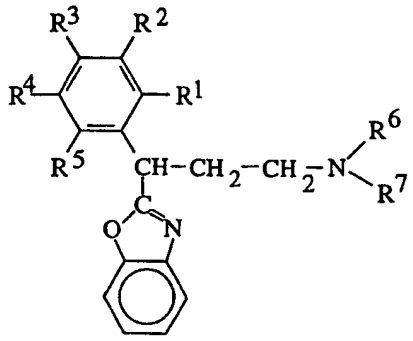
wherein R^1 to R^7 and X are as defined above, or

i) reacting a compound of Formula VIII above, wherein X is oxygen, with a compound of Formula X



X

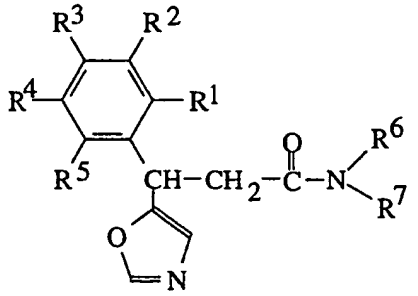
to form a compound of Formula Ib



Ib

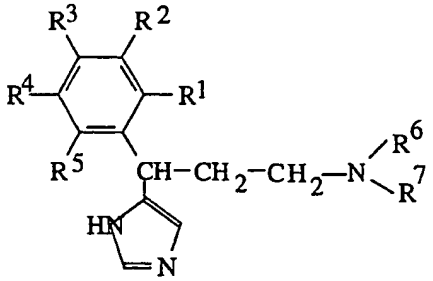
wherein R^1 to R^7 are as defined above for Formula I, or

j) converting a compound of Formula XI



XI

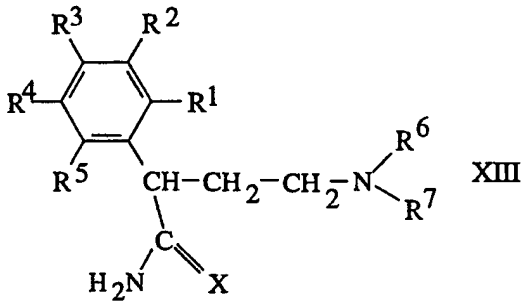
wherein R^1 to R^7 are as defined above for Formula I, to a compound of Formula XII



XII

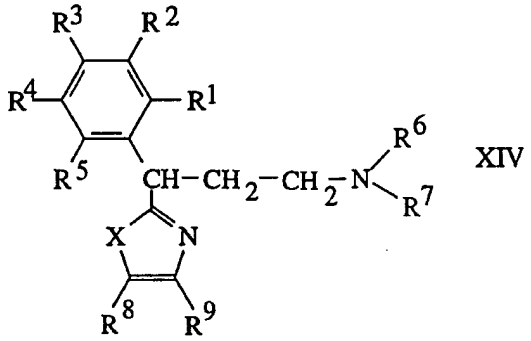
wherein R^1 to R^7 are as defined above for Formula I, or

k) converting a compound of Formula XIII



XIII

wherein R^1 to R^7 are as defined above for Formula I, and X is oxygen or sulphur, to a compound of Formula XIV



XIV

wherein R^1 to R^7 and X are as defined above for Formula I, and R^8 and R^9 independently are hydrogen or alkyl, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained,

ii) if desired converting the obtained bases of Formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or

iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers.

Appropriate reaction conditions in the above reactions may readily be selected by the skilled person with reference to analogous prior art methods and with due consideration of the specific Examples below. The necessary starting materials are either known or may be prepared in analogy with the preparation of known compounds.

The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by fractional crystallisation of salts with chiral acids or by chromatographic separation on chiral columns.

In accordance with the present invention, the compounds of Formula I, in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of Formula I in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds and compositions can, as mentioned above, be used for the same therapeutical indications as the compounds of the above-mentioned WO 89/06644 or WO 94/11337, i.e. for the treatment of acetylcholine-mediated disorders, such as urinary incontinence, especially urge incontinence. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the

condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 4 mg per kilo of body weight, administered singly or multiply in doses e.g. from about 0,05 mg to about 200 mg each.

The invention will be further illustrated by the following non-limiting example and pharmacological tests.

General

N.M.R data were acquired on a Jeol JNM-EX 270 or a Varian Unity 500 spectrometer. Spectra were recorded with tetramethylsilane (TMS) as internal standard at 30°C. Infrared spectra were recorded on a Perkin-Elmer Model Model 841 spectrophotometer. Non-corrected melting points were obtained on a Koeffler apparatus. Gas chromatography was performed on a HP 5940 instrument with a 10 m HP-1 column and the oven heated in the linear temperature gradient mode. All lithium aluminum hydride reductions were quenched by the use of the procedure according to V. Micovic and M. Mihailovic (J. Org. Chem. 18, 1190 (1953)).

EXAMPLE 1

N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

A solution of N-(5-hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (2.75 g, 7 mmol) in THF (40 mL) was added to lithium aluminum hydride (LAH) (0.50 g, 13 mmol) and the mixture was stirred at ambient temperature for 2 h. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 19:1). The title compound was crystallised by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 0.75 g (27%); mp 70-75°C. ^{1}H NMR (DMSO-d6) δ 1.17 (q, 3H), 1.23 (t, 3H), 2.18 (d, 3H), 2.47 (m, 2H), 2.84-3.07 (m, 2H), 3.15 (m, 1H), 3.37 (m, 1H), 3.42 (d, 2H), 3.46 (s, 2H), 3.67 (m, 1H), 3.74 (m, 2H), 4.30 (m, 1H), 4.76 (br, 1H), 6.71 (d, 1H), 6.80 (d, 1H), 7.06 (d, 1H), 7.16 (t, 1H), 7.27 (t, 2H), 7.33 (d, 2H), 9.29 (d, 1H) and 10.07 (br, 1H). Anal. ($C_{23}H_{33}NO_3 \cdot HCl$) C, H, N.

The starting compound N-(5-hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide was prepared as follows:

1.1 Trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid

A solution of triethyl phosphonoacetate (22.4 g, 0.10 mol) in THF (150 mL) was added to sodium hydride (80%, 2.7 g, 0.09 mol) under nitrogen during 15 min. The resulting mixture was refluxed for 15 min whereafter a solution of 2-benzyloxy-5-methyl-benzophenone (15.1 g, 0.05 mol) in THF (50 mL) was added. The reaction mixture was refluxed for 19 h. Water and sodium hydroxide (10 g, 0.25 mol) were added and most of the THF was distilled off. Ethanol was added until a clear solution was obtained and the reflux was continued for a few minutes. Water was added to a total volume of 1 L and the mixture was washed with diethyl ether. Hydrochloric acid was added to the water-phase and a crystalline mass was obtained. The pure trans-isomer was obtained by recrystallisation from ethanol. Yield 10.4 g (60%). ^{1}H NMR (DMSO-d6) δ 2.24 (s, 3H), 4.92 (s, 2H), 6.41 (s, 1H), 6.87 (d, 1H), 6.98 (d, 1H), 7.03 (m, 2H) 7.12 (m, 1H), 7.22 (m, 3H), 7.29 (m, 1H), 7,30 (m, 1H) and 7.33-7.39 (m, 3H).

1.2 trans-N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

A solution of DCC (5.2 g, 17 mmol) in THF (20 mL) was added to a solution of trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid (6.9 g, 20 mmol), 2-(2-isopropylaminoethoxy)-ethanol, triethylamine (2.5 g, 25 mmol) and hydroxysuccinimide (2.8 g, 24 mmol) in THF (50 mL). The reaction mixture was stirred for 20 h. The solvent was evaporated and the residue chromatographed on silica (gradient from toluene to ethyl acetate). Yield 5.9 g (62%).

1.3 trans-N-(5-Hydroxy-3-oxapentyl)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide

A solution of trans-N-(5-hydroxy-3-oxapentyl)-N-isopropyl-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (5.9 g, 12 mmol) in acetic acid (50 mL) was hydrogenatated over Pd/C (10 %, 0.5 g) for 16 h. Filtering and evaporation of solvent left a residue that was chromatographed on silica (ethyl acetate). Yield 2.83 g (61 %).

EXAMPLE 2

N-Cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

A solution of N-cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (0.93 g, 2.5 mmol) in THF (20 mL) was added to LAH (0.22 g, 5.6 mmol) and the mixture was stirred at reflux temperature for 30 min. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (chloroform-methanol 9:1). The amine salt was obtained by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 0.45 g (46%); mp. 230-232°C. ^{1}H NMR (DMSO-d6) δ 1.27-1.70 (m, 10H), 1.88 (br, 1H), 2.05 (d, 1H), 2.17 (s, 3H), 2.42 (br, 1H), 2.60 (s, 3H), 2.85 (br, 2H), 3.34 (m, 1H), 4.30 (t, 1H), 6.72 (d, 1H), 6.80 (dd, 1H), 7.05 (br, 1H), 7.15 (t, 1H), 7.27 (t, 2H), 7.31 (d, 2H), 9.31 (s, 1H) and 10.53 (br, 1H). Anal. ($C_{24}H_{33}NO \cdot HCl$) C, H, N.

The starting compound N-cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide was prepared as follows:

2.1 N-Cycloheptyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

A solution of DCC (5.2 g, 25 mmol) in THF (50 mL) was added to a solution of trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid (Example 1.1), (6.9 g,

20 mmol), cycloheptylamine (2.6 g, 23 mmol), triethylamine (2.0 g, 20 mmol) and hydroxysuccinimide (2.4 g, 21 mmol) in THF (50 mL). The reaction mixture was stirred for 1 h at room temperature. Another portion of cycloheptylamine (1.3 g) was added and the reaction mixture was left stirring for another 1 h. The mixture was filtered and the filtrate evaporated. The residue was dissolved in diethyl ether and washed with hydrochloric acid (1M), water and brine in subsequent order. After evaporation of the solvent, the residue was crystallised from toluene-hexane to give 7.3 g (83%). ^{1}H NMR ($CDCl_3$) δ 1.06 (br, 2H), 1.25-1.74 (m, 10H), 2.30 (s, 3H), 3.83 (m, 1H), 4.95 (s, 2H), 5.50 (d, 1H), 6.49 (s, 1H), 6.90-7.08 (m, 4H), and 7.12-7.44 (m, 9H).

2.2 N-Cycloheptyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

A solution of N-cycloheptyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (4.4 g, 10 mmol) and methyliodide (4 g, 30 mmol) in DMF (10 mL) was added to sodiumhydride (80 %, 1.2 g, 40 mmol) at ambient temperature and the mixture was stirred for 60 min. Excess sodium hydride was destroyed by adding methanol, and the reaction mixture was then partioned between toluene and water. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was crystallised from toluene-hexane to yield 4.4 g (97%). ^{1}H NMR ($CDCl_3$) (almost 1:1 mixture of rotameres) δ 1.20-1.80 (m, 12H), 2.30 (m, 3H) 2.61 (s, 1.5H), 2.71 (s, 1.5H), 3.93 (m, 0.5H), 4.46 (m, 0.5H), 4.81 (m, 1H), 6.43 (m, 1H), 6.81 (m, 2H) and 7.08-7.35 (m, 10H).

2.3 N-Cycloheptyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide

A solution of N-cycloheptyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (3.15 g, 7 mmol) in acetic acid (40 mL) was hydrogenated over Pd/C (10%, 0.2 g) for 72 h. The reaction mixture was filtered and the solvent evaporated. The residue was chromatographed

on silica (toluene-ethyl acetate 9:1). Yield 0.95 g (37%). ^{1}H NMR ($CDCl_3$) δ 1.26-1.98 (m, 12H), 2.02 (s, 3H), 2.12 (s, 3H), 2.28 (m, 1H), 2.52 (m, 1H), 2.71 (m, 1H), 4.36 (dd, 1H), 6.39 (s, 1H), 6.76 (s, 2H), 7.15 (m, 2H) and 7.25 (m, 5H).

EXAMPLE 3

N-Cyclohexyl-N-methyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine hydrochloride

A solution of N-cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide (4.0 g, 9 mmol) in THF (90 mL) was added to LAH (0.50 g, 13 mmol) in THF (5 mL) and the mixture was stirred at ambient temperature for 2.5 h. The reaction was quenched and the solvent evaporated. The resulting oil was hydrogenated over Pd/C (10%, 1g) in acetic acid (70 mL) for 20 h. After filtration and evaporation of the solvent, the residue was chromatographed on silica (chloroform:methanol 99:1). The amine salt was obtained by dissolving the free amine in diethyl ether and adding hydrogen chloride in diethyl ether. Yield 1.2 g (36%); mp. 179-183°C. ^{1}H NMR (DMSO-d6) δ 1.05 (m, 1H), 1.21-1.38 (m, 4H), 1.51 (d, 1H), 1.74 (br, 2H), 1.86 (br, 1H), 2.00 (d, 1H), 2.17 and 2.19 (s, 3H), 2.39-2.56 (m, 2H), 2.63 (m, 3H), 2.82 (m, 1H), 2.93 (m, 1H), 3.17 (m, 1H), 4.32 (q, 1H), 6.73 and 6.75 (d, 1H), 6.79 and 6.81 (t, 1H), 7.02 and 7.10 (d, 1H), 7.14-7.18 (m, 1H), 7.25-7.29 (m, 2H), 7.33 (t, 2H), 9.34 (br, 1H) and 10.78 (s, 1H). Anal. ($C_{23}H_{31}NO \cdot HCl$) C, H, N.

The starting compound N-cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide was prepared as follows:

3.1 N-Cyclohexyl-N-methyl-trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenamide

A solution of DCC (5.2 g, 25 mmol) in THF (50 mL) was added to a solution of trans-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropenoic acid (Example 1.1), (6.9 g,

20 mmol), N-methyl-cyclohexylamine (2.6 g, 23 mmol), triethylamine (2.0 g, 20 mmol) and hydroxysuccinimide (2.4 g, 21 mmol) in THF (50 mL). The reaction mixture was stirred for 2 h. A second portion of DCC (2.5 g, 13 mmol) and N-methyl-cyclohexylamine (1.5 g, 13 mmol) was added and the reaction mixture was left stirring for 16 h. Diethyl ether and hydrochloric acid (1M) were added and the organic phase was washed with brine. The organic layer was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate 9:1). Yield 5.5 g (63%). ^{1}H NMR (DMSO-d6) (almost 1:1 mixture of rotameres) δ 0.88-1.06 (m, 2H), 1.16-1.39 (m, 5H), 1.55 (t, 2H), 1.67 (br, 1H), 2.21 (s, 1.5H), 2.23 (s, 1.5H) 2.56 (s, 1.5H), 2.67 (s, 1.5H), 3.67 (m, 0.5H), 4.05 (m, 0.5H), 4.82 (s, 1H), 4.85 (s, 1H), 6.57 (s, 0.5H), 6.59 (s, 0.5H), 6.84 (dd, 1H), 6.87 (d, 0.5H), 6.89 (t, 1H), 6.95 (dd, 1H), 6.98 (d, 0.5H), 7.12 (dd, 1H), 7.17 (m, 3H), 7.27 (m, 2H), and 7.32 (m, 3H).

EXAMPLE 4

N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamine hydrochloride

Boran·SMe$_2$-complex in THF (7 mL, 14 mmol) was gently refluxed with a weak stream of nitrogen for 30 minutes. N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide (1.55 g, 4.2 mmol) was added to the refluxing solution and the reflux was continued for 1 h. The reaction mixture was partioned between diethyl ether and sodium hydroxide (1M). The solvent of organic layer was evaporated and the residue was chromatographed on silica (toluene-triethylamine 9:1) to yield the free amine. The hydrochloride salt was obtained by dissolving the amine in diethyl ether with the addition of hydrogen chloride in diethyl ether. The resulting oil produced crystals after some time stirring in diethyl ether. Yield 0.39 g (23%); mp. 143-144°C. ^{1}H NMR (DMSO-d6) δ 1.19 (q, 6H), 1.25 (dd, 6H), 2.53 (m, 1H), 2.70 (m, 1H), 2.87 (m, 2H), 3.59 (m, 2H), 4.38 (t, 1H), 7.24 (t, 1H), 7.35 (t, 2H), 7.39 (d,

2H), 7,45 (t, 1H), 7.68 (t, 1H), 7.74 (t, 2H) and 10.25 (br, 1H). Anal. ($C_{22}H_{28}NF_3 \cdot HCl$) C, H, N.

The starting compound N,N-diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide was prepared as follows:

4.1 Diethyl N,N-diisopropylacetamide phosphonate

A mixture of triethylphosphite (23 g, 0.14 mol) and N,N-diisopropyl 2-bromoacetamide (29 g, 0.13 mol) was heated to 110°C for 3 h to yield 35 g (97%). The product was used without purification.

4.2 N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropenamide

A solution of diethyl N,N-diisopropylacetamide phosphonate (8.4 g, 30 mmol) in THF (20 mL) was added dropwise to sodium hydride (80 %, 0.85 g, 29 mmol) during 30 min, keeping the temperature below 30°C. A solution of 2-trifluoromethyl-benzophenone (5.0 g, 20 mmol) in THF (20 mL) was added and the reaction mixture was heated to 50°C and kept at that temperature for 16 h. A second portion of the phosphorous ylide (15 mmol), prepared as above, was added. After another 24 h at 50°C the mixture was partioned between diethyl ether and water. The etheral layer was evaporated and the residue chromatographed on silica (toluene-ethyl acetate 9:1) yielding 3.0 g (41%) as a mixture of the E- and Z-isomers. Labels a and b refer to the different isomers. ^1H NMR ($CDCl_3$-d) δ 0.80 (d, 6Ha), 1.08 (d, 3Hb), 1.24 (t, 6Hb), 1.31 (d, 3Hb), 1.44 (d, 6Ha), 3.32 (m, 1Ha), 3.34 (m, 1Hb), 4.19 (m, 1Hb), 4.32 (m, 1Ha), 6.04 (s, 1Ha), 6.65 (s, 1Hb) and 7.18-7.75 (m, 9Ha, 9Hb).

4.3 N,N-Diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropanamide

A solution of N,N-diisopropyl-3-(2-trifluoromethylphenyl)-3-phenylpropenamide (2.95 g, 8.1

mmol) in ethanol (50 mL) was hydrogenated over Pd/C (10%, 300 mg) at normal pressure for 24 h. The catalyst was filtered off, the solvent partly evaporated and the product collected after crystallisation. Yield 1.78 g (60%). ^{1}H NMR ($CDCl_3$-d) δ 1.16 (m, 6H), 1.30 (m, 6H), 2.86 (dd, 1H), 3.11 (dd, 1H), 3.41 (m, 1H), 4.03 (m, 1H), 5.12 (m,1H) and 7.10-7.78 (m, 9H).

EXAMPLE 5

N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(3-pyridyl)-propanamine dihydrochloride

A solution of N,N-diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide (2.8 g, 8 mmol) in THF (25 mL) was added to LAH (1.3 g, 32 mmol). The reaction mixture was refluxed for 4 h whereafter the reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 99:1) to give 2.2 g. The product (1.3 g, 4 mmol) was dissolved in dichloromethane (20 mL) and the solution was cooled to -78°C and boron tribromide (1 g, 8 mmol) was added dropwise and the reaction mixture was allowed to reach room temperature during 1 h. The reaction mixture was washed with sodium hydroxide (1M) and brine and the organic phase was dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (toluene-triethylamine 9:1) to give 0.35 g. The free amine was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added to produce the dihydrochloride as crystals which soon rearranged to a hard glass. ^{1}H NMR (DMSO-d6) δ 1.22 (dd, 6H), 1.28 (dd, 6H), 2.60 (m,1H), 2.70 (m, 1H), 2.93 (m, 2H), 3.60 (m, 2H), 4.60 (t, 1H), 6.85 (t, 1H), 6.89 (d, 1), 7.11 (t, 1H), 7.38 (d, 1H), 7.96 (dd, 1H), 8.46 (d, 1H), 8.75 (d, 1H), 8.85 (s, 1H), 9.90 (br, 1H) and 10.14 (s, 1H).

The starting compound N,N-diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide was prepared as follows:

5.1 2-Methoxyphenyl-3-pyridyl-ketone

A solution of 2-bromoanisole (21 g, 0.11 mol) in diethyl ether (100 mL) was added to magnesium turnings during 45 minutes with heating. After the addition the reflux was continued for 15 min. The Grignard reagent was cooled to 0°C and a solution of 3-cyanopyridine (10 g, 0.10 mol) in diethyl ether (100 mL) was added dropwise. The mixture was refluxed for a few minutes. Hydrochloric acid (20 mL, 0.24 mol, conc.) and 2-propanol (20 mL) were added and the reflux was continued for 30 min. Water and diethyl ether were added and the phases separated. The water-phase was made alkaline (2M NaOH) and was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and evaporated to yield 17 g. The crude was chromatographed on silica (toluene-ethyl acetate 19:1) to give 3.75 g (19%). ^1H NMR ($CDCl_3$-d) δ 3.76 (s, 3H), 7.01 (d, 1H), 7.10 (t, 1H), 7.41 (dd, 1H), 7.46 (dd, 1H), 4.53 (m, 1H), 8.12 (d, 1H), 8.75 (s, 1H) and 8.94 (s,

5.2 N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(3-pyridyl)-propanamide

A solution of of diethyl N,N-diisopropylacetamide phosphonate (Example 4.1), (9.3 g, 33 mmol) in THF (40 mL) was added dropwise to sodium hydride (80 %, 1.0 g, 33 mmol) during 15 min. The mixture was heated to 40°C for 15 minutes and then cooled to 5°C whereafter a solution of 2-methoxyphenyl-3-pyridyl-ketone (4.5 g, 21 mmol) in THF (10 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for 16 h. The reaction mixture was partioned between diethyl ether and water and the organic phase was dried ($MgSO_4$) and evaporated to yield 7.1 g of solid material. The product was hydrogenated over Pd/C (10%, 0.2 g) in acetic acid (50 mL) for 48 h. The reaction mixture was filtered and the solvent evaporated. The residue was partioned between diethyl ether and hydrochloric acid (1 M) and the phases were separated. The water-phase was made alkaline (2 M

sodium hydroxide) and extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and filtered. Crystallisation began and the mixture was diluted with hexane. Filtration gave 2.9 g (40%). ^1H NMR ($CDCl_3$-d) δ 1.14 (dd, 6H), 1.28 (d, 6H), 3.04 (dd, 2H), 3.38 (m, 1H), 3.74 (s, 3H), 4.05 (m, 1H), 5.00 (t, 1H), 6.84 (d, 1H), 6.92 (t, 1H), 7.19 (m, 3H), 7.57 (d, 1H), 8.39 (m, 1 H) and 8.55 (d, 1H). 1H).

EXAMPLE 6

N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamine hydrochloride

A solution of N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide (3.1 g, 9.4 mmol) in THF (20 mL) was added to LAH (1.0 g, 25 mmol) and the reaction mixture was stirred at reflux temperature for 2 h. More LAH (0.5 g), was added and the reflux continued for another 2 h. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-ethyl acetate 3:1) to give 0.4 g of the free amine as a syrup. The amine was dissolved in isopropanol/diethyl ether and hydrogen chloride in diethyl ether was added to give the amine salt. Yield 0.32 g (10 %); mp 152-154 °C. ^1H NMR (DMSO-d6) δ 1.19 (dd, 6H), 1.26 (dd, 6H), 2.57 (m, 2H), 2.86 (m, 1H), 2.97 (m, 1H), 3.58 (m, 2H), 4.36 (t, 1H), 6.69 (dd, 1H), 7.14 (m, 1H), 7.22 (m, 2H), 7.29 (m, 1H), 7.32 (d, 2H), 7.33 (s, 2H), 7.54 (m, 1H) and 10.24 (br, 1H). Anal. ($C_{21}H_{28}NF \cdot HCl$) H, N; C: calcd, 72.1; found, 72.6.

The starting compound N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide was prepared as follows:

6.1 trans-N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropenamide

A solution of diethyl N,N-diisopropylacetamide phosphonate (Example 4.1), (8.4 g, 30 mmol) in THF (20 mL) was added dropwise to sodium hydride (80 %, 0.85 g, 25

mmol) during 30 min, keeping the temperature below 40°C. A solution of 2-trifluoromethyl-benzophenone (4.0 g, 20 mmol) in THF (10 mL) was added and the reaction mixture was stirred at ambient temperature for 30 min. The mixture was partioned between diethyl ether and brine. The organic layer was dried ($MgSO_4$) and evaporated to give a crystalline mass. Recrystallisation from hexane yielded 3.9 g (60 %). ^1H NMR ($CDCl_3$-d) δ 0.85 (d, 6H), 1.39 (d, 6H), 3.29 (m, 1H), 4.27 (m, 1H), 6.29 (s, 1H), 7.10 (m, 3H) and 7.30 (m, 6H).

6.2 N,N-Diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamide

A solution of trans-N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropenamide (3.25 g, 10 mmol) was hydrogenated over Pd/C (10%, 300 mg) in acetic acid (30 mL) for 24 h. The catalyst was filtered off and the solvent was evaporated to yield 3.15 g (96%). ^1H NMR ($CDCl_3$-d) δ 1.12 (q, 6H), 1.28 (q, 6H), 3.05 (d, 2H), 3.38 (m, 1H), 4.03 (m, 1H), 4.93 (t, 1H) and 6.94-7.32 (m, 9H).

EXAMPLE 7

(R)-N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

Hydrogen chloride in diethyl ether was added to a solution of (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine (0.81 g, 2.4 mmol) in diethyl ether and 2-propanol. Crystals were filtered to yield 0.4 g (45%); mp 178-179°C. $[\alpha]_{Hg}$ = -40° (c 1.1 in methanol). ^1H NMR (DMSO-d6) δ 1.16 (d, 3H), 1.20 (d, 3H), 1.24 (d, 3H), 1.27 (d, 3H), 2.54 (m, 2H), 2.84 (m, 1H), 2.97 (m, 1H), 3.58 (br, 2H), 4.38 (t, 1H), 7.08 (d, 1H), 7.22 (t, 1H), 7.32 (m,4H), 7.65 (dd, 1H), 7.83 (d, 1H), 9.80 (s, 1H), 9.86 (br, 1H) 10.99 (s, 1H). Anal. ($C_{22}H_{29}NO_2 \cdot HCl$) H, N; C: calcd, 70.3; found, 70.8.

The starting compound (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine was prepared as follows:

7.1 (R)-N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine

DDQ (1.1 eq) was added to a solution of (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine mandelate (prepared as described in WO 94/11337, Example 1) (2.46 g, 5 mmol), dichloromethane (20 mL) and phosphate buffer (pH 7) (0.1 mL). Thereafter, sodium hydroxide solution (20 mL, 1 M) and diethyl ether were added and the phases were separated. The water-phase was extracted twice with dichloromethane-diethyl ether (2:1). The organic phase was dried ($MgSO_4$) and evaporated. The residue was crystallised from ethyl acetate-hexane to yield 1.35 g (80 %).

EXAMPLE 8

(R)-N,N-Diisopropyl-3-[5-(7-hydroxy-2-aza-5-oxaheptyl)-2-hydroxyphenyl]-3-phenylpropanamine di-(S)-mandelate

Sodiumcyanoborohydride (0.25 g, 3.9 mmol) was added to a solution of (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine (Example 7.1), (1.25 g, 3.7 mmol) and 2-ethoxy-(2-amino)-ethanol (19.5 g, 18 mmol) in methanol (10 mL). Hydrochloric acid (conc) was added to adjust pH to about 3. After 3h, the pH was adjusted to about 1 and the solvent was evaporated. The residue was partioned between diethyl ether and water, whereafter the organic layer was evaporated and the residue chromatographed on silica (chloroform-triethylamine-methanol 88:10:2). The pure amine was dissolved in 2-propanol-diethyl ether with (S)-mandelic acid (2 eq), whereby the product crystallised (the crystals were unstable and an oily mass was soon obtained). Yield 0.2 g (7%); mp dec. ^1H NMR (free amine) ($CDCl_3$-d) δ 1.05 (d, 6H), 1.09 (d, 6H), 2.10 (m, 1H), 2.35 (m, 2H), 2.67 (m, 3H), 3.19 (m, 2H), 3.47 (m, 2H), 3.49 (t, 2H), 3.56 (d, 2H),

3.63 (t, 2H), 4.45 (dd, 1H), 6.75 (d, 1H), 6.79 (d, 1H), 6.95 (dd, 1H), 7.18 (m, 1H) and 7.26-7.33 (m, 4H).

EXAMPLE 9

(R)-N,N-Diisopropyl-3-(2-hydroxy-5-methyloxycarbonyl-phenyl)-3-phenylpropanamine hydrochloride

A solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-methyloxycarbonyl-phenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (0.92 g, 2 mmol) in ethanol (30 mL) was hydrogenated over Pd/C (10%, 50 mg) at room temperature for 2 h. The catalyst was filtered off and the solution was treated with hydrogen chloride to obtain the amine salt. Yield 0.66 g (81 %); mp 177-178°C; $[\alpha]_D$ = -23° (c 1.0, methanol). ^{1}H NMR (DMSO-d6) δ 1.19 (dd, 6H), 1.25 (dd, 6H), 2.48 (m, 2H), 2.85 (m, 1H), 2.95 (m, 1H), 3.58 (m, 2H), 3.78 (s, 3H), 4.38 (t, 1H), 6.98 (d, 1H), 7.20 (m, 1H), 7.31 (d, 2H), 7,32 (s, 2H), 7.69 (dd, 1H), 7.81 (d, 1H), 9.85 (br, 1H), 10.74 (s, 1H). Anal. ($C_{23}H_{31}NO_3 \cdot HCl$) H, N, C.

EXAMPLE 10

N,N-Diisopropyl-3-(2-hydroxymethyl)phenyl-3-phenylpropanamine hydrochloride

A solution of N,N-diisopropyl-3-(2-carboxyphenyl)-3-phenylpropanamine hydrochloride (1.88 g, 5 mmol) in THF (30 mL) was added to LAH (1.5 g, 38 mmol) and the reaction mixture was stirred att ambient temperature for 2 h. The reaction was quenched and the solvent evaporated. The residue was dissolved in hot diethyl ether-2-propanol (100 mL, 1:4), whereafter HCl in diethyl ether was added. After cooling the product was filtered and dried at 60°C (vacuum). Yield 1.2 g (68%); mp 223-224°C. ^{1}H NMR (DMSO-d6) δ 1.18 (t, 6H), 1.25 (q, 6H), 2.91 (m, 2H), 3.26 (disturbed by solvent, 2H), 3.57 (m, 2H), 4.38 (t, 1H), 4.43 (d, 1H), 4.74 (d, 1H), 5.22 (s, 1H), 7.20 (q, 2H), 7.25-7.35 (m, 5H), 7.40 (dd, 2H), 9.95 (s, 1H). Anal. ($C_{22}H_{31}NO \cdot HCl$) H, N, C.

EXAMPLE 11

(S)-N,N-Diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine hydrochloride

(S)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine (0.67 g, 1.5 mmol) was hydrogenated over Pd/C (10%, 67 mg) at atmospheric pressure overnight in ethanol (20 mL). The catalyst was filtered off and the solvent was evaporated. The residue was partioned between diethyl ether and sodium hydroxide (1 M). The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$) and the solvent was evaporated. The amine salt was obtained by dissolving the amine in diethyl ether-isopropanol and treatment with hydrogen chloride in diethyleter. Yield 0.37 g; mp 219-221 °C; $[\alpha]_D$ -11.4° (c=1.0, methanol); ^1H NMR (CD_3OD) δ 1.30 (d, 12H), 2.36-2.60 (m, 2H), 2.68 (t, 2H), 3.05 (t, 2H), 3.60-3.72 (m, 4H), 4.40 (t, 1H), 6.73 (d, 1H), 6.90 (dd, 1H), 7.0 (s, 1H), 7.17-7.38 (m, 5H). Anal. ($C_{23}H_{33}NO_2 \cdot HCl \cdot 0.2H_2O$) C, H, N.

The starting compound (S)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-hydroxy)ethylphenyl]-3-phenylpropanamine was prepared as follows:

11.1 (S)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine

A mixture of (S)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (8 g, 12.7 mmol), $Pd(OAc)_2$ (28 mg, 0.12 mmol), tri-o-tolyl-phosphine (74 mg, 0.14 mmol) and tributylamine (5.9 mL, 24.5 mmol) in dimethylacetamide (50 mL) was heated to 60 °C under nitrogen atmosphere. Ethene (g) was then added to 8 bars pressure. After stirring overnight the reaction mixture was allowed to cool to room temperature. Nitrogen was flushed through the reaction vessel, and toluene and water were added. The aqueous layer

was extracted with toluene and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was treated with sodium hydroxide (1 M) and extracted with diethyl ether and toluene. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica (gradient ethyl acetate-methanol 90:10 up to 0.06% NH_3 in ethyl acetate-methanol 90:10) Yield 1 g (18%); ^1H NMR ($CDCl_3$) δ 0.94 (d, 12H), 2.20 (br, 2H), 2.37 (br, 2H), 3.0 (br, 2H), 4.38 (t, 1H), 5.0 (s, 2H), 5.11 (d, 1H), 5.61 (d, 1H), 6.60-6.70 (m, 1H), 6.80 (d, 1H), 7.12-7.19 (m, 12H).

11.2 (S)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)-phenyl]-3-phenylpropanamine

(S)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (1 g, 2.34 mmol) in THF (25 mL) was added to 9-BBN (0.5 M in THF, 11.7 mL, 5.85 mmol) under nitrogen atmosphere at 0 °C. Additional 9-BBN (2.3 mL, 1.2 mmol) was added after 3 hours of stirring, the temperature was raised to room temperature and the mixture was stirred for 0.5 hour. It was then cooled to 0 °C and 1 M sodium hydroxide (10 mL) was added followed by H_2O_2 (30% in H_2O, 10 mL). After 1 hours stirring, water was added and the mixture was extracted with diethyl ether. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica (gradient of diethyl ether to 1% NH_3 in diethyl ether). Yield 0.67 g (64%). ^1H NMR ($CDCl_3$) δ 0.90 (d, 12H), 2.10-2.18 (m, 2H), 2.30-2.37 (m, 2H), 2.80 (t, 2H), 2.90-3.0 (m, 2H), 3.80 (br, 2H), 4.40 (t, 1H), 5.0 (s, 2H), 6.80 (d, 1H), 7.0 (m, 1H), 7.10-7.38 (m, 11H).

EXAMPLE 12

(R)-N,N-Diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine hydrochloride

The title compound as well as the starting compounds were prepared in an analogous manner to the preparation described in Example 11, with the exception that (S)-N,N-

diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was changed to (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1).

Yield 0.35 g (33%); mp 209-215 °C; $[\alpha]_D$ +9.8° (c=1.0, methanol); ^1H NMR (CD_3OD) δ 1.29 (d, 12H), 2.40-2.60 (m, 2H), 2.67 (t, 2H), 3.04 (t, 2H), 3.61-3.72 (m, 4H), 4.40 (t, 1H), 6.70 (d, 1H), 6.90 (dd, 1H), 7.0 (s, 1H), 7.18-7.40 (m, 5H). Anal. ($C_{23}H_{33}NO_2 \cdot HCl \cdot 0.2H_2O$) C, H, N.

Preparation of starting compounds:

12.1 (R)-N,N-Diisopropyl-3-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine

Yield 5.5 g (53%); ^1H NMR ($CDCl_3$) δ 0.94 (d, 12H), 2.20 (br, 2H), 2.37 (br, 2H), 3.0 (br, 2H), 4.38 (t, 1H), 5.0 (s, 2H), 5.11 (d, 1H), 5.61 (d, 1H), 6.60-6.70 (m, 1H), 6.80 (d, 1H), 7.12-7.19 (m, 12H).

12.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)-phenyl]-3-phenylpropanamine

Yield 1.2 g (75%); ^1H NMR ($CDCl_3$) δ 0.89 (d, 12H), 2.15 (m, 2H), 2.32 (m, 2H), 2.80 (t, 2H), 2.95 (m, 2H), 3.80 (br, 2H), 4.40 (t, 1H), 4.98 (s, 2H), 6.80 (d, 1H), 6.96 (m, 1H), 7.10-7.35 (m, 11H).

EXAMPLE 13

(R)-N,N-Diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

(R)-N,N-Diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine (1 g, 2.25 mmol) was treated as described in Example 11. Yield 0.6 g (68%); mp 105-115 °C; $[\alpha]_D$ -32.6° (c 1.02, methanol); ^1H NMR (DMSO-d_6) d 1.18-1.28 (m, 12H), 2.5 (m, 3H), 2.50-2.62 (m, 2H), 2.86 (m, 1H), 2.97 (m, 1H), 3.58 (m, 2H), 4.38 (t, 1H), 6.99 (d, 1H), 7.2 (m, 1H), 7.29-7.35 (m, 4H), 7.73 (dd, 1H), 7.85 (d, 1H), 9.90

(br, 1H), 10.70 (s, 1H). Anal. ($C_{23}H_{31}NO_2 \cdot HCl \cdot 0.4H_2O$) C, H, N.

The starting compound (R)-N,N-diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine was prepared as follows:

13.1 (R)-N,N-Diisopropyl-3-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine

To a stirred solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (Example 12) (10.2 g, 21.23 mmol) in DMF (100 mL) under nitrogen atmosphere at room temperature were sequentially added triethylamine (2.58 g, 25.47 mmol), TlOAc (6.15 g, 23.35 mmol), isobutylvinylether (14 mL, 106.14 mmol), DPPP (0.87 g, 2.12 mmol) and $Pd(OAc)_2$ (0.24 g, 1.06 mmol). The reaction temperature was raised to 100 °C and stirred for 3 hours, cooled to room temperature, filtered and treated with HCl (5%, 250 mL) and stirred for another 2 hours. The reaction mixture was repeatedly extracted with dichloromethane and the combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated. Triethylamine and DMF were destilled off under reduced pressure to yield 9 g (98%); ^1H NMR ($CDCl_3$) δ 1.22 (m, 12H), 2.52-2.70 (m, 7H), 3.40 (br, 2H), 4.34 (t, 1H), 5.10 (s, 1H), 6.90 (d, 1H), 7.17-7.40 (m, 10H), 7.82 (m, 1H) and 7.92 (s, 1H).

EXAMPLE 14

N,N-Diisopropyl-3(R)-[2-hydroxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine fumarate

N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)-phenyl]-3-phenylpropanamine (2.7 g, 6.05 mmol) was hydrogenated over Pd/C (0.27 g, 10%) in ethanol at atmospheric pressure for 2 hours. The catalyst was filtered off and the solvent was evaporated. The resulting oil was chromatographed on silica (toluene-triethylamine 90:10). Fumarate salt of the amine was afforded by adding fumaric acid (0.13 g, 1.13 mmol) dissolved in warm ethanol to a

solution of the free base in diethyl ether yielding white crystals (0.44 g, 83%); mp 240-244 °C; $[\alpha]_D$ +9.8° (c 1.02, methanol); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 1.26 (dd, 3H), 2.20-2.30 (m, 2H), 2.55-2.67 (m, 2H), 3.30 (m, 2H), 4.32 (t, 1H), 4.59 (q, 1H), 6.53 (s, 2H), 6.72 (dd, 1H), 6.93 (dd, 0.5H), 7.12-7.17 (m, 1H), 7.21-7.31 (m, 5H). Anal. ($C_{23}H_{33}NO_2 \cdot C_4H_4O_4 \cdot 0.3H_2O$) C, H, N.

The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)phenyl]-3-phenylpropanamine was prepared as follows:

14.1 N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1-hydroxyethyl)-phenyl]-3-phenylpropanamine

N,N-Diisopropyl-3(R)-(5-acetyl-2-benzyloxyphenyl)-3-phenylpropanamine, prepared as described in Example 13.1, (3.5 g, 7.90 mmol) dissolved in dry THF was added to $LiAlH_4$ (0.2 g, 5.41 mmol). After 2 hours of stirring, additional $LiAlH_4$ (50 mg, 1.32 mmol) was added and the reaction mixture was stirred for 1.5 hours. The reaction was quenched and the solvent evaporated. The residue was chromatographed on silica (toluene-E_3N 90:10) to give 2.74 g (78%) of an oil that crystallised slowly upon storage at room temperature.

EXAMPLE 15

(+)-N,N-Diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine fumarate

N,N-Diisopropyl-3(R)-[2-benzyloxy 5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine (0.55 g, 1.2 mmol) was treated in an analogous manner to that described in Example 14 above, which yielded white crystals, 0.32 g (55%); mp 196-200 °C; $[\alpha]_D$ +13.5° (c 1.0, methanol); ^{1}H NMR (CD_3OD) δ 1.28 (m, 12H), 2.40-2.48 (m, 1H), 2.52-2.60 (m, 1H), 3.03 (t, 2H), 3.55 (d, 2H), 3.66 (m, 2H), 4.42 (t, 1H), 4.57 (t, 1H), 6.7 (s, 2H), 6.79 (d, 1H), 7.05 (dd,

1H), 7.16-7.21 (m, 2H), 7.28 (m, 2H), 7.36 (m, 2H). Anal. ($C_{23}H_{33}NO_3 \cdot C_4H_4O_4$) C, H, N.

The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine was prepared as follows:

15.1 N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1(R*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine

To an ice-chilled solution of AD-mix-α (5.7 g) in H_2O (20 mL) and t-BuOH (10 mL) was added N,N-diisopropyl-3(R)-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (Example 12.1), (1.74 g, 4.1 mmol) dissolved in t-BuOH (10 mL). After 1 hour of stirring, the ice bath was removed and the reaction mixture was stirred for additional 21 hours. Na_2SO_3 (6 g) was then added and after 1 hours of stirring the reaction mixture was partioned between H_2O and ethyl acetate. The aqueous layer was extracted 3 times with ethyl acetate, the combined organic layers were dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (ethyl acetate-triethylamine, 90:10) to afford 0.55 g. ^1H NMR ($CDCl_3$) δ 0.9 (s, 6H), 0.95 (s, 6H), 2.15-2.20 (m, 2H), 2.30-2.38 (m, 2H), 2.96 (m, 2H), 3.60-3.70 (m, 2H), 4.41 (t, 1H), 4.75 (m, 1H), 5.0 (s, 2H), 6.85 (d, 1H), 7.10-7.35 (m, 12H).

EXAMPLE 16

(-)-N,N-Diisopropyl-3(R)-[5-(1(S*),2-dihydroxyethyl) 2-hydroxyphenyl]-3-phenylpropanamine fumarate

N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(1(S*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine (1.1 g, 2.4 mmol) was treated in an analogous manner to that described in Example 11 which yielded white crystals, 0.25 g (21%); mp 208-211 °C; $[\alpha]_D$ -8° (c 1.02, methanol); ^1H NMR (CD_3OD) δ 1.28 (m, 12H), 2.39-2.47 (m, 1H), 2.51-2.59 (m, 1H), 3.03 (t, 2H), 3.51-3.53 (m, 2H), 3.67 (m, 2H), 4.42 (t, 1H), 4.54 (dd, 1H), 6.68 (s, 2H), 6.78 (d, 1H), 7.06 (dd, 1H),

7.16-7.20 (m, 2H), 7.26 (m, 2H), 7.34-7.36 (m, 2H). Anal. ($C_{23}H_{33}NO_3 \cdot C_4H_4O_4$) C, H, N.

The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(1(S*),2-dihydroxyethyl)phenyl]-3-phenylpropanamine was obtained by treating N,N-diisopropyl-3(R)-(2-benzyloxy-5-ethenylphenyl)-3-phenylpropanamine (obtained in Example 12.1) as described in Example 15.1 above, but with AD-mix-β replacing AD-mix-α. Yield 1.2 g (44%).

EXAMPLE 17

(R)-[N,N-Diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)-phenyl]-3-phenylpropanamine hydrochloride

N,N-Diisopropyl-3(R)-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine (0.35 g, 0.72 mmol) was treated in an analogous manner to that described in Example 14. Yield 0.10 g (31%); mp 147-156 °C; $[\alpha]_D$ +8.2° (c 1.01, methanol); ^1H NMR (CD_3OD) δ 1.25-1.32 (m, 16H), 1.45-1.54 (m, 4H), 2.40-2.48 (m, 3H), 2.51-2.59 (m, 1H), 3.0-3.10 (m, 2H), 3.51 (t, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 6.72 (d, 1H), 6.86 (dd, 1H), 6.91 (d, 1H), 7.19 (m, 1H), 7.30 (t, 2H), 7.34-7.36 (m, 2H). Anal. ($C_{27}H_{41}NO_2 \cdot HCl \cdot 2H_2O$) C, N; H: calcd, 9.6; found, 8.3.

The starting compound (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine was prepared as follows:

17.1 (R)-N,N-Diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine

n-BuLi (2.5 M in hexane, 19 mL, 47.5 mmol) was added to a solution of to (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3- phenylpropanamine (prepared as described in WO 94/11337, Example 1) (8.9 g, 18.52 mmol) in dry diethyl ether (100 mL) kept at -40 °C under nitrogen atmosphere. After 1.5 hour of stirring, additional n-BuLi (10 mL, 25

mmol) was added and after 2 hours another n-BuLi (5 mL, 12.5 mmol) was added. The reaction was then stirred for 15 minutes and DMF (6 mL, 77.8 mmol) was added followed by additional DMF (5 mL, 64.8 mmol) after 20 minutes of stirring. The temperature was allowed to rise to room temperature and after 35 minutes of stirring, NH_4Cl (sat.) was added followed by water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica (toluene-triethylamine 90:10) to afford 8 g (100%) of a yellowish oil; ^1H NMR ($CDCl_3$) δ 0.90 (m, 12H), 2.12-2.40 (m, 4H), 2.95 (m, 2H), 4.44 (t, 1H), 5.10 (s, 2H), 6.95 (d, 1H), 7.15-7.36 (m, 10H), 7.70 (dd, 1H), 7.91 (s, 1H), 9.88 (s, 1H).

17.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy 5-(5-carboxypent-1-enyl)phenyl]-3-phenylpropanamine

To a slurry of 4-carboxybutyl triphenylphosphonium bromide (4.1 g, 9.31 mmol) in THF (25 mL) at -10 °C under nitrogen atmosphere was added potassium tert-butoxide (2.1 g, 18.62 mmol). The mixture turned orange and after 10 minutes stirring, (R)-N,N-diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine (2 g, 4.65 mmol) in THF (10 mL) was added. After 4 hours of stirring, hydrochloric acid (1M) and diethyl ether were added and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica (ethyl acetate-triethylamine 90:10 followed by methanol) to afford 3 g containing traces of triphenylphosphine. The product was used in the next step without further purification.

17.3 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(6-hydroxyhex-1-enyl)phenyl]-3-phenylpropanamine

(R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(5-carboxypent-1-enyl)phenyl]-3-phenylpropanamine was reduced as described in Example 10. Yield 0.35 g (15%).

EXAMPLE 18

(R)-N,N-Diisopropyl-3-[5-(2-diisopropylaminoethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

(R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine (0.6 g, 1.13 mmol) was refluxed with concentrated HCl (25 mL) overnight. The reaction mixture was then basified with 10 M sodium hydroxide and extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 0.5 g oil that was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). The pure fractions were pooled and extracted with diethyl ether and 10 M sodium hydroxide. The resulting diethyl ether solution was treated with hydrogen chloride in diethyl ether. Yield 50 mg (9%); $[\alpha]_D$ +1.4° (c 0.94, methanol); ^1H NMR (CD_3OD) δ 1.27-1.34 (m, 12H), 1.36-1.42 (m, 12H), 2.50-2.58 (m, 1H), 2.60-2.67 (m, 1H), 2.95 (t, 2H), 3.05 (m, 2H), 3.15-3.27 (m, 2H), 3.70 (m, 2H), 3.75 (m, 2H), 4.40 (t, 1H), 6.80 (d, 1H), 7.02 (dd, 1H), 7.13 (d, 1H), 7.20 (m, 1H), 7.31 (m, 1H), 7.39-7.41 (m, 1H). Anal. ($C_{29}H_{46}N_2O \cdot 2HCl \cdot 0.4H_2O$) C, H, N.

The starting compound N,N-diisopropyl-3(R)-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine was prepared as follows:

18.1 N,N-Diisopropyl-3(R)-(5-formylmethyl-2-benzyloxy-phenyl)-3-phenylpropanamine

DMSO (1.1 mL, 15.5 mmol) dissolved in dichloromethane was added dropwise to oxalyl chloride (0.64 mL, 7.74 mmol) at -78 °C under nitrogen atmosphere. After 10 minutes of

stirring, (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-hydroxyethyl)phenyl]-3-phenylpropanamine (Example 12.2) (2.3 g, 5.16 mmol) in dichloromethane was added and the reaction mixture was stirred for additional 1 h. Triethylamine (5.4 mL, 38.7 mmol) was then added and the temperature was allowed to rise to room temperature. The reaction mixture was taken up in water and dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated in vacuo and the product was used in the next step without further purification.

18.2 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-diisopropylaminoethyl)phenyl]-3-phenylpropanamine

Diisopropylamine (4.2 mL, 30 mmol) was dissolved in methanol (12 mL). 5 M HCl in methanol (2 mL) was added followed by N,N-diisopropyl-3(R)-(5-formylmethyl-2-benzyloxyphenyl)-3-phenylpropanamine (5 mmol) in methanol (10 mL) and sodium cyanoborohydride (0.22 g, 3.5 mmol). The reaction mixture was stirred at room temperature overnight. methanol was then evaporated, and diethyl ether and H_2O were added. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 3 g of a crude product that was chromatographed on silica (toluene-triethylamine 95:5). Yield 0.65 g (25%); ^1H NMR ($CDCl_3$) δ 0.88-0.91 (m, 18H), 1.20 (d, 9H), 2.10-2.20 (m, 2H), 2.30-2.38 (m, 2H), 2.87-3.10 (m, 4H), 4.34 (m, 1H), 4.98 (d, 2H), 6.75-6.97 (m, 2H), 7.10-7.30 (m, 11H).

EXAMPLE 19

(R)-N,N-Diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamine

(R)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethyl-phenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1) (3.9 g, 11.5 mmol) and Al_2O_3 (115 g, 1.13 mol) refluxed in ethyl acetate (0.5 L) for 60 hours. Al_2O_3 was filtered off and ethyl acetate was evaporated. Chromatography on silica (toluene-triethylamine, 90:10) of the residue yielded 2.5 g (59%). The fumarate salt was

obtained by adding fumaric acid (0.17 g, 1.48 mmol) dissolved in warm ethanol to the free base (0.55 g, 1.48 mmol) in diethyl ether; mp 174-177 °C; $[\alpha]_D$ +5.5° (c 1.02, methanol); ^{1}H NMR (CD_3OD) δ 1.15 (t, 3H), 1.27-1.30 (m, 12H), 2.41-2.49 (m, 1H), 2.52-2.60 (m, 1H), 3.04 (dd, 2H), 3.49 (q, 2H), 3.67 (m, 2H), 4.35 (s, 2H), 4.43 (t, 1H), 6.69 (s, 2H), 6.80 (d, 1H), 7.04 (dd, 1H), 7.12 (d, 1H), 7.18-7.37 (m, 4H). Anal. ($C_{24}H_{35}NO_2 \cdot C_4H_4O_4$) C, H, N.

EXAMPLE 20

N-Isopropyl-3-(5-carboxy-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine (1.3 g, 2.6 mmol) was dissolved in HOAc. Palladium (10%) on charcoal (0.13 g) was added and the mixture was hydrogenated at atmospheric pressure for 48 hours. The catalyst was then filtered off and the solvent was evaporated. The resulting oil was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). This purification was done in 16 portions with about 100 mg material each time. The pure fractions were pooled and freeze-dried to give 0.57 g of trifluoroacetic acid salt. The crystals were dissolved in 1 M HCl and freeze-dried to give 0.4 g (43%) of the hydrochloride salt as white crystals; mp 155-160 °C; ^{1}H NMR (DMSO-d_6) δ 1.17 (d, 3H), 1.19 (d, 3H), 2.30-2.38 (m, 1H), 2.38-2.46 (m, 1H), 2.72 (br, 1H), 2.80 (br, 1H), 3.25 (m, 1H), 4.40 (t, 1H), 6.94 (d, 1H), 7.18-7.22 (m, 1H), 7.29-7.33 (m, 4H), 7.66 (dd, 1H), 7.76 (d, 1H); Anal. ($C_{19}H_{23}NO_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

The starting compound N-benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine was prepared as follows:

20.1 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanal

3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanol (16.5 g, 41.5 mmol) (prepared as described in WO 94/11337, Example 1c) was reacted as described in Example 18.1. The combined organic layers were washed with 2 M HCl, 10% $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated to give 16 g (98%) of yellowish crystals of the product that was used in the next step without further purification; mp 99-100 °C; ^1H NMR ($CDCl_3$) δ 3.10 (dd, 2H), 5.0 (s, 2H), 4.98-5.10 (m, 1H), 6.76 (d, 1H), 7.16-7.38 (m, 12H), 9.65 (s, 1H).

20.2 N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

To a solution of N-benzylisopropylamine (34 mL, 0.20 mol) in methanol (80 mL) was added 5 M HCl in methanol (16.2 mL, 80.9 mmol) followed by 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanal (16.0 g, 40.5 mmol) in methanol (20 mL) and sodium cyanoborohydride (1.78 g, 28.3 mmol). The resulting solution was stirred for 17 hours. The solvent was evaporated and diethyl ether was added to the resulting syrup. The solution was washed 3 times with water, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (hexane-ethyl acetate, 75:25) giving 15.9 g of a syrup. The hydrochloride salt of the compound was prepared by dissolving the product in diethyl ether and adding HCl dissolved in diethyl ether. The resulting oil was washed with diethyl ether, dissolved in 10 M sodium hydroxide and extracted with diethyl ether 3 times. Purification by chromatography on silica (using a gradient of dichloromethane up to 1% triethylamine in dichloromethane) yielded 7 g (33%) of the product as a colourless oil. ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H), 0.90 (d, 3H), 2.02-2.12 (m, 2H), 2.38 (t, 2H), 2.90 (m, 1H), 3.50 (d, 2H), 4.50 (t, 1H), 4.95 (s, 2H), 6.70 (s, 1H), 7.10-7.35 (m, 17H).

20.3 N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine

A mixture of magnesium turnings (1.18 g, 48.6 mmol) and iodine (one small crystal) was warmed gently. A solution of N-benzyl-N-isopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (6.0 g, 11 mmol) and 1,2-dibromoethane (0.2 mL, 2.3 mmol) in dry THF (25 mL) was added dropwise under nitrogen atmosphere to the refluxing mixture. After 2 hours of refluxing, 1,2-dibromoethane (0.59 mL, 6.8 mmol) was added. The mixture was left overnight under nitrogen atmosphere. The mixture was then added together with 1,2-dibromoethane (0.93 mL, 10.8 mmol) to warmed magnesium turnings (1.18 g, 48.6 mmol) and iodine (one small crystal). After 30 minutes of refluxing, the mixture was cooled to room temperature and CO_2 (g) was bubbled through. After 3 hours, ammonium chloride (aq, 15%, 50 mL) was added followed by diethyl ether (100 mL). The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated to give 5.8 g of an oil. The crude product was chromatographed on silica (using a gradient of acetone up to 5% ethanol in acetone) to give the pure product (1.3 g, 23%) as an oil. N-benzyl-N-isopropyl-3-(2-benzyloxyphenyl)-3-phenylpropanamine (3.1 g) was obtained as a biproduct from the reaction. ^1H NMR ($CDCl_3$) δ 0.98 (d, 3H), 1.10 (d, 3H), 2.30-2.40 (m, 2H), 2.46-2.65 (m, 2H), 3.40 (br, 1H), 3.85 (br, 2H), 4.30 (br, 1H), 4.98 (br, 2H), 6.80 (d, 1H), 7.10-7.40 (m, 15H), 7.95 (d, 1H), 7.95 (d, 1H), 8.20 (s, 1H).

EXAMPLE 21

N-Benzyl-N-isopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

N-Benzyl-N-isopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropanamine, prepared as described in Example 20.3, (3.1 g, 6.90 mmol) was refluxed in concentrated HCl (30 mL) for 20 h. The reaction mixture was allowed to cool to room temperature and the liquid was poured off. The remaining oil was washed with water and diethyl ether and then

dissolved in 2-propanol. The solution was evaporated and treated with 10 M sodium hydroxide to give the free base. Chromatography on silica (hexane:ethyl acetate 75:25) afforded 0.5 g of the compound that was fractionated on a reversed-phase PEP-RPC HR 30/26 column using a gradient of acetonitrile (containing 0.1% TFA) and milliQ-water (containing 0.1% TFA). The pure fractions were pooled and extracted with diethyl ether and 10 M sodium hydroxide. To the resulting diethyl ether solution was added dropwise saturated diethyl ether-HCl (g). The resulting crystals of the hydrochloric salt were collected by filtration; mp 115-122 °C; ^{1}H NMR (DMSO-d_6) δ 1.28 (m, 6H), 2.27-2.38 (m, 1H), 2.48-2.55 (m, 1H), 2.72-2.97 (m, 2H), 3.55 (m, 1H), 4.23 (m, 2H), 4.35 (m, 1H), 6.68-6.74 (m, 1H), 6.82 (dt, 1H), 6.96-7.24 (m, 7H), 7.38-7.42 (m, 3H), 7.64-7.68 (m, 2H), 9.55 (d, 1H), 10.62 (br, 1H). Anal. ($C_{25}H_{29}NO\cdot HCl$) C, H, N.

EXAMPLE 22

(R)-N,N-Diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine dihydrochloride

(R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropanamine (3.20 g, 7.07 mmol) was dissolved in 100 % acetic acid and 10% Pd/C (0.52 g) was added. The mixture was hydrogenated (60 psi) overnight at room temperature. The catalyst was filtered off and the solvent was evaporated. The residue was dissolved in water, basified with sodium hydroxide (11 M), extracted with ethyl acetate, the organic phase was dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (toluene-ethyl acetate-triethylamine-methanol, 20:5:1.5:1). The amine was redissolved in diethyl ether and a HCl-saturated diethyl ether solution was carefully added. The precipitate was filtered off wich gave 0.30 g (10 %); ^{1}H NMR (CD_3OD) δ 1.29 (m, 12H), 1.88 (m, 2H), 2.51(m, 2H), 2.59 (t, 2H), 2.88 (t, 2H), 3.04 (t, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 4.55 (bs, 1H), 6.76 (d, 1H), 6.93 (d, 1H), 7.03 (s, 1H), 7.19 (t, 1H), 7.30 (t, 2H), 7.37 (d, 2H); mp.

226-228 °C; $[\alpha]_D$ +11.5° (c=1.0, methanol). Anal. ($C_{24}H_{36}N_2O*2HCl$) C, H, N.

The starting compound (R)-N,N-diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropanamine was prepared as follows:

22.1 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyano-ethenyl)phenyl]-3-phenylpropylamine

To a solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (13.87 g, 28.87 mmol) (prepared as described in WO 94/11337, Example 1) in DMF (140 mL) was added triethylamin (5.00 mL, 36.10 mmol), $Pd(OAc)_2$ (0.32 g, 1.44 mmol), tri(o-tolyl)phosphine (1.76 g, 5.77 mmol) and acrylonitrile (2.39 mL, 36.10 mmol). The reaction mixture was stirred overnight at 115 °C in a sealed flask equipped with a reflux condenser under nitrogen atmosphere. The resulting mixture was concentrated, and the residue was dissolved in diethyl ether, washed with aqueous 2 M sodium hydroxide and water. The organic phase was dried ($MgSO_4$) whereafter petroleum ether was added to the organic phase and a precipitate was formed. Recrystallisation from ethanol yielded 5.50 g (42%). ^1H NMR ($CDCl_3$) δ 0.90 (s, 6H), 0.95 (s, 6H), 2.15 (q, 2H), 2.35 (q, 2H), 2.95 (m, 2H), 4.40 (t, 1H), 5.05 (s, 2H), 5.70 (d, 1H), 6.85 (d, 1H), 7.10-7.50 (m, 13H).

EXAMPLE 23

(R)-N,N-Diisopropyl-3-[5-3-(acetamidopropyl)-2-hydroxy-phenyl]-3-phenylpropanamine hydrochloride

To a solution of (R)-N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, (Example 22), (0.45 g, 1.23 mmol) in methanol (45 mL) was added acetic anhydride (0.23 mL, 2.47 mmol). The mixture was stirred for 3 h at room temperature and then evaporated to dryness. The residue was dissolved in H_2O, basified with aqueous 11 M sodium hydroxide and extracted with toluene. The organic layer was dried with $MgSO_4$, filtered and

evaporated. The amine was dissolved in diethyl ether and a HCl-saturated diethyl ether solution was carefully added. The precipitate formed was filtered off to give 0.55 g (100 %). ^{1}H NMR (CD_3OD) δ 1.27 (m, 12H), 1.75 (m, 2H), 2.08 (s, 3H), 2.52 (m, 4H), 3.04 (t, 2H), 3.20 (t, 2H), 3.68 (m, 2H), 4.40 (t, 2H), 6.72 (d, 1H), 6.90 (d, 1H), 6.99 (s, 1H), 7.19 (t, 1H), 7.30 (m, 4H); mp. 171-175 °C; $[a]_D$ +3.6° (c=0.5, methanol). ($C_{26}H_{38}N_2O_2$*HCl) C, H, N.

EXAMPLE 24

(R)-N,N-Diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

(R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-cyanoethenyl)phenyl]-3-phenylpropylamine (Example 22.1), (4.00 g, 8.84 mmol) was treated as described in Example 22, but the hydrogenation was performed at atmospheric pressure. Yield 1.35 g (38 %); ^{1}H NMR (CD_3OD) δ 1.14 (s, 6H), 1.16 (s, 6H), 2.50 (m, 2H), 2.79 (t, 2H), 3.05 (t, 2H), 3.68 (m, 2H), 4.39 (t, 2H), 6,75 (d, 1H), 6.98 (d, 1H), 7.09 (s, 1H), 7.19 (t, 1H), 7.32 (m, 4H); mp. 156-159 °C; $[\alpha]_D$ +4.0° (c=0.5, methanol); Anal. ($C_{24}H_{32}N_2O$*1.0HCl*0.25H_2O) C, H; N: calcd, 6.9; found, 6.4.

EXAMPLE 25

(R)-N,N-Diisopropyl-3-[5-(2-carbamoylethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride.

A solution of (R)-N,N-diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine (Example 24), (2.00 g, 5.48 mmol), in conc. HCl was stirred at 50 °C for 2 h and then evaporated. The residue was dissolved in water, basified with aqueous 11 M sodium hydroxide and extracted with toluene. The organic layer was dried ($MgSO_4$), filtrated and evaporated. The residue was chromatographed on toluene-ethyl acetate-triethylamine-methanol, 7:2:1:1. The product was obtained from dietyl ether-hydrogen choride. Yield 0.9 g (39%); ^{1}H NMR (CD_3OD) δ 1.31 (m, 12H), 2.44 (t, 2H), 2.53 (m, 2H), 2.78 (t, 2H), 3.04 (t, 2H),

3.67 (m, 2H), 4.39 (t, 1H), 6.72 (d, 1H), 6.82 (d, 1H), 7.02 (s, 1H), 7.18 (t, 1H), 7.32 (m, 4H); mp. 200-202 °C; $[\alpha]_D$ +7.6° (c=0.5, methanol). Anal. ($C_{24}H_{34}N_2O_2$*1.0HCl *0.5H_2O) C, H, N.

EXAMPLE 26

(R)-N,N-Diisopropyl-3-[5-(2-carboxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine hydrochloride

To a solution of (R)-N,N-diisopropyl-3-[5-(2-carbamoylethyl)-2-hydroxyphenyl]-3-phenylpropanamine (obtained in Example 25), (0.50 g, 1.31 mmol) in ethanol (15 mL) and H_2O (10 mL) was added KOH (3.75 g, 66.8 mmol). The mixture was stirred overnight at 100 °C. The solvent was evaporated and the residue redissolved in H_2O and washed with diethyl ether. The aqueous layer was acidified with conc. HCl and the precipitate was collected by filtration and washed with 2 M HCl. The product was fractionated on a reversed-phase PEP RPC HR 30/26 (Pharmacia Biotech AB, Sweden) column using a gradient of 20-60% acetonitrile with 0.1% TFA. Fractions were pooled and hydrochloric acid (2 mL, conc.) was added and the solvent was evaporated. The residue was crystallised from methanol-diethyl ether to give 0.37 g (0.96 mmol, 74%); ^1H NMR (CD_3OD) δ 1.28 (m, 12H), 2.48 (m, 4H), 2.76 (t, 2H), 3.04 (t, 2H), 3.67 (m, 2H), 4.39 (t, 1H), 6.72 (d, 1H), 6.92 (d, 1H), 7.00 (s, 1H), 7.19 (t, 1H), 7.32 (m, 4H); mp. 205-207 °C; $[\alpha]_D$ +3.7° (c=1.0, methanol). Anal. ($C_{24}H_{33}NO_3$*1.0HCl) C, H, N.

EXAMPLE 27

(R)-(N,N-Diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine dihydrochloride

(R)-N,N-Diisopropyl-3-(5-azido-2-benzyloxyphenyl)-3-phenylpropanamine (0.90 g, 2.03 mmol) was dissolved in acetic acid and 10% Pd/C (210 mg, cat.) was added. The mixture was stirred and exposed to H_2 (1 atm.) at room temperature overnight. The Pd/C catalyst was filtered off,

and the filtrate evaporated. The residue was dissolved in water and basified with aqueous 11 M sodium hydroxide, extracted with diethyl ether, dried ($MgSO_4$) filtrated and evaporated. The crude residue was chromatographed on silica (n-hexane-ethanol-triethylamine, 7:3:1). The hydrochloride was obtained from dietyl ether hydrogen chloride. The resulting oil was freeze-dried from water. Yield 0.30 g (37 %); ^1H NMR (DMSO) δ 1.13 - 1.33 (m, 12H), 2.47 (m, 2H), 2.82 (br, 1H), 2.98 (br, 1H), 3.57 (br, 2H), 4.38 (t, 1H), 6.96 (d, 1H), 7.08 (d, 1H), 7.19 (s, 1H), 7.22 (m, 1H), 7.32 (m, 4H), 10.05 (br, 2H), 10.13 (s, 1H); mp. 180-183 °C; $[\alpha]_D$ +21.0° (c=0.1, methanol). Anal. ($C_{21}H_{30}N_2O*2.0HCl*0.5H_2O$) C, H, N.

The starting compound (R)-N,N-diisopropyl-3-(5-azido-2-benzyloxyphenyl)-3-phenylpropanamine was prepared as follows:

27.1 (R)-N,N-Diisopropyl-3-(5-azido-2-benzyloxyphenyl)-3-phenylpropanamine

To a mixture of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (10.00 g, 20.81 mmol) (prepared as described in WO 94/11337, Example 1) and Mg (1.57 g, 64.52 mmol) in THF (50 mL) was added 1,2-dibromoethane (3.59 mL, 41.63 mmol) and the solution was self-refluxing for a while. The mixture was refluxed for 1 h whereafter the solution was cooled and tosyl azide (4.10 g, 20.81 mmol) in diethyl ether (100 mL) was added with constant stirring while keeping the temperature at 0 °C wherafter the temperature was allowed to rise to room temperature for 4 h. A solution of tetra-sodium pyrophosphate decahydrate (4.46 g, 10.00 mmol) in 50 mL water was added. A precipitate was filtered off and the filtrate was evaporated. The residue was extracted with diethyl ether, the organic phase was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (n-hexane-ethanol, 8:2). The product was crystallised from ethanol to give 1.15 g (13 %); IR (KBr) 2116 (N_3) cm^{-1}; ^1H

NMR ($CDCl_3$) δ 0.92 (d, 12H), 2.10 (m, 2H), 2.33 (m, 2H), 2.95 (m, 2H), 4.40 (t, 1H), 5.00 (s, 2H), 6.81 (d, 2H), 6.97 (s, 1H), 7.10 - 7.40 (m, 10H).

EXAMPLE 28

(R)-N,N-Diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

To a solution of (R)-N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine (0.25 g, 0.76 mmol) in 0.78 M HCl (5.35 mL, 4.20 mmol) was added $NaNO_2$ (0.05 g, 0.76 mmol) dissolved in H_2O (0.4 mL) at -10 °C and the mixture was stirred for 20 minutes. To the mixture was added NaN_3, (57 mg, 0.88 mmol) dissolved in H_2O (0.4 mL), and the mixture was stirred at -10 °C for 30 minutes. The mixture was basified (pH 7-8) with aqueous 11 M sodium hydroxide and extracted with diethyl ether. The diethyl ether phase was dried ($MgSO_4$) and evaporated to give an oil, which was chromatographed on silica (toluene-ethyl acetate-triethylamine 7:2:1). The product was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added. The precipitate was filtered to give (0.07 g, 0.18 mmol, 24%) of light-brown crystals. IR (KBr) 2111 (N_3) cm^{-1}; ^1H NMR (CD_3OD) δ 1.29 (m, 12H), 2.50 (m, 2H), 3.04 (m, 2H), 3.68 (m, 2H), 4.40 (t, 1H), 6.68 (s, 1H), 6.81 (m, 2H), 7.23 (m, 1H), 7.35 (m, 4H); mp. 131-134 °C; $[\alpha]_D$ -5.0° (c=0.1, methanol).

The starting compound (R)-N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine was prepared as follows:

28.1 (R)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine

A solution of (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (prepared as described in WO 94/11337, Example 1)(7.30 g, 15.2 mmol) treated as described in Example 1.3 above. Yield 4.47 g (94 %).

28.2 (R)-N,N-Diisopropyl-3-[2-hydroxy-5-(4-methylphenylazo)phenyl]-3-phenylpropanamine

$NaNO_2$ (0.27 g, 4.30 mmol) was added to a mixture of hydrochloric acid (0.64 mL, 7.70 mmol, conc.) and p-methylaniline (0.41 g, 3.80 mmol) in ice-water (20 mL). The mixture was stirred at 0 °C for 10 min. and then added to an ice-cold solution of (R)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropanamine (1.00 g, 3.21 mmol) in THF (3mL), H_2O (12 mL) and sodium hydroxide (0.69 g, 17.32 mmol). After stirring the mixture for 20 minutes, it was extracted with toluene, dried ($MgSO_4$), and evaporated to give an oil, which was chromatographed on (toluene-ethyl acetate-triethylamine 8:1:1) to give 0.83 g, 1.93 mmol, (60%) of the title compound. ^1H NMR ($CDCl_3$) δ 1.12 (d, 6H), 1.19 (d, 6H), 2.22 (m, 1H), 2.43 (m, 5H), 2.79 (m, 1H), 3.32 (m, 2H), 4.57 (d, 1H), 6.98 (d, 1H), 7.24 (m, 3H), 7.36 (m, 4H), 7.66 (m, 4H).

28.3 (R)-N,N-Diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine

A solution of $Na_2S_2O_4$ (1.23 g, 12.8 mmol) in water (10 mL) was added to a solution of (R)-N,N-diisopropyl-3-[2-hydroxy-5-(4-methylphenylazo)phenyl]-3-phenylpropanamine (0.55 g, 1.28 mmol) in ethanol (50 mL) at 75 °C during 15 min. More dry $Na_2S_2O_4$ (1.23 g, 12.8 mmol) was added in 10 portions. Water was added to the solution which was then extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and evaporated to give an oil, which was chromatographed on silica (n-hexane-ethanol-triethylamine 7:3:1) to give an oil. The product was dissolved in ethanol and hydrogen chloride in diethyl ether was added. The solvent was evaporated, redissolved in water and vacuum-dried wich yielded 0.25 g (60%).

EXAMPLE 29

(R)-N,N-Diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)-phenyl]-3-phenylpropanamine hydrochloride

A solution of (R)-N,N-diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine (2.0 g, 4.86 mmol) in THF (50 mL) was added dropwise to LAH (0.28 g, 7.29 mmol). After stirring for 2 h, the reaction was quenched and the solvent evaporated. The residue was recrystallized from ethanol-water. The product was dissolved in ethanol and hydrogen chloride in diethyl ether was added. White crystals were filtered off to give 0.82 g (46%); mp. 204-207 °C; $[\alpha]_D$ +12.8° (c=1.0, methanol); ^1H NMR (DMSO) δ 1.18 (t, 6H), 1.24 (t, 6H), 1.63 (m, 2H), 2.47 (m, 4H), 2.87 (br, 2H), 3.38 (q, 2H), 3.57 (br, 2H), 4.32 (t, 1H), 4.42 (t, 1H), 6.74 (d, 1H), 6.83 (d, 1H), 7.03 (s, 1H), 7.17 (t, 1H), 7.30 (m, 4H) Anal. ($C_{24}H_{35}NO_2$*1.0HCl) C, H, N.

The starting compound (R)-N,N-diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine was prepared as follows:

29.1 (R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-ethoxycarbonylethyl)phenyl]-3-phenylpropanamine

A solution of triethyl phosphonoacetate (6.93 mL, 34.92 mmol) in THF (50 mL) was added dropwise to NaH (0.84 g, 29.10 mmol, 80%). The mixture was cooled to 0 °C and (R)-N,N-diisopropyl-3-(2-benzyloxy-5-formylphenyl)-3-phenylpropanamine, prepared as described in Example 17.1, (5.00 g, 11.64 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 3 h at 0 °C. The solvent was evaporated and the residue was redissolved in toluene and washed twice with water. The organic layer was dried ($MgSO_4$) and the solvent evaporated to give 5.0 g (86%).

29.2 (R)-N,N-Diisopropyl-3-[5-(2-ethoxycarbonylethyl)-2-hydroxyphenyl]-3-phenylpropanamine

(R)-N,N-Diisopropyl-3-[2-benzyloxy-5-(2-ethoxycarbonylethyl)phenyl]-3-phenylpropanamine (3.0 g, 5.98 mmol) was treated as described in Example 1.3. Yield 2.0 g (81%); ^{1}H NMR ($CDCl_3$) δ 1.08 (d, 6H), 1.12 (d, 6H), 1.18 (t, 3H), 2.05 (m, 2H), 2.37 (m, 4H), 2.72 (t, 2H), 3.22 (m, 2H), 4.03 (q, 2H), 4.48 (m, 1H), 6.55 (s, 1H), 6.86 (m, 2H), 7.28 (m, 5H).

EXAMPLE 30

N,N-Diisopropyl-3-(5-ethylaminomethyl-2-hydroxyphenyl)-3-phenylpropanamine

(R)-N,N-Diisopropyl-3-(5-formyl-2-hydroxyphenyl)-3-phenylpropanamine (prepared in Example 7.1) (1.23 g, 3.62 mmol) was dissolved in methanol (20 mL). Ethylamine [3.62 mL, 21.7 mmol (6M hydrochloric acid in methanol)] and sodium cyanoborohydride (0.14 g, 2.17 mmol) were added. The mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate-triethylamine 7:3:1). The product was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added. The resulting oil was stirred in diethyl ether over night to give crystals. Yield 0.70 g (44%); mp. 140-142 °C; $[\alpha]_D$ -5.0° (c=0.5, methanol); ^{1}H NMR (CD_3OD) δ 1.30 (m, 15H), 2.59 (m, 2H), 3.05 (m, 4H), 3.70 (m, 2H), 4.07 (s, 2H), 4.42 (t, 1H), 6.85 (d, 1H), 7.20 (m, 2H), 7.30 (t, 2H), 7.41 (d, 2H), 7.50 (s, 1H) Anal. ($C_{24}H_{36}N_2O*2.0HCl*0.5H_2O$) C,H,N.

EXAMPLE 31

N-Cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

A solution of N-cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (1.60 g, 3.44 mmol) was hydrogenated over Pd/C (160 mg, 10%) in acetic acid at room temperature overnight. The solution was basified with

sodium hydroxide (11 M) and the mixture was filtered. The filtrate was extracted with ethyl acetate, dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (toluen-triethylamine 9:1). The free amine was dissolved in diethyl ether and hydrogen chloride in diethyl ether was added to give an oil. The oil was crystallised in 2-propanol to give 0.90 g (79%); mp. 153-155 °C; ^1H NMR (CD_3OD) δ 1.78 (m, 2H), 2.22 (m, 4H), 2.48 (m, 2H), 2.72 (s, 3H), 2.95 (br, 2H), 3.68 (m, 1H), 4.44 (t, 1H), 6.78 (t, 1H), 6.79 (d, 1H), 7.03 (t, 1H), 7.12 (d, 1H), 7.18 (t, 1H), 7.28 (t, 2H), 7.34 (d, 2H); Anal. ($C_{20}H_{25}NO*1.0$ HCl*0.3 2-propanol) C, H, N.

The starting compound N-cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was prepared as follows:

31.1 N-Cyclobutyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

5 M HCl-methanol (3.50 mL, 17.71 mmol) was added to a solution of cyclobutylamine (4.50 mL, 53.15 mmol) in methanol (14 mL). The mixture was added to 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanal (Example 20.1), (3.50 g, 8.86 mmol), followed by sodium cyanoborohydride (0.389 g, 6.20 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed on silica (toluene-ethyl acetate-triethylamine 92:4:4).Yield 2.61 g (65%); ^1H NMR ($CDCl_3$) δ 1.57 (m, 5H), 2.14 (m, 4H), 2.47 (t, 2H), 3.16 (m, 1H), 4.45 (t, 1H), 5.00 (s, 2H), 6.75 (d, 1H), 7.10-7.47 (m, 12H).

31.2 N-Cyclobutyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

5 M HCl-methanol (0.46 mL, 2.32 mmol), formaldehyde (0.870 g, 28.97 mmol) and sodium cyanoborohydride (0.255 g, 4.056 mmol) were added to a solution of N-cyclobutyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (2.61 g, 5.79

mmol) in methanol (8 mL). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed on silica (hexane-triethylamine, 9:1). Yield 1.59 g (59%); ^{1}H NMR ($CDCl_3$) δ 1.59 (m, 2H), 1.73 (m, 2H), 1.91 (m, 2H), 2.06 (s, 3H), 2.16 (m, 4H), 2.68 (m, 1H), 4.38 (t, 1H), 5.00 (s, 2H), 6.72 (d, 1H), 7.12-7.58 (m, 12H).

EXAMPLE 32

N-Cyclopentyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine hydrochloride

N-Cyclopentyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (2.46 g, 5.14 mmol) was treated as described in Example 31. The crude was not chromatographed but crystallised from aqueous ethanol. Yield 1.24 g (70%) ^{1}H NMR (DMSO) δ 1.48 (br, 1H), 1.66 (br, 2H), 1.85 (br, 1H), 2.46 (br, 2H), 2.68 (s, 3H), 2.87 (br, 2H), 3.53 (m, 1H), 4.35 (t, 1H), 6.77 (t, 1H), 6.83 (d, 1H), 7.01 (t, 1H), 7.16 (t, 1H), 7.27 (t, 3H), 7.33 (d, 2H), 9.57 (br, 1H), 10.85 (br, 1H); mp 169-172 °C; Anal. ($C_{21}H_{27}NO*HCl$) C, H, N.

The starting compound N-cyclopentyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine was prepared as follows:

32.1 N-Cyclopentyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanal, prepared as described in Example 20.1, (7.00 g, 17.71 mmol) was treated with cyclopentylamine as described in Example 31.1. Yield 4.9 g (59%); ^{1}H NMR ($CDCl_3$) δ 1.20 (m, 2H), 1.40-1.80 (m, 6H), 2.18 (m, 2H), 2.55 (t, 2H), 2.98 (m, 1H), 4.45 (t, 1H), 5.00 (s, 2H), 6.75 (d, 1H), 7.10-7.45 (m, 12H).

32.2 N-Cyclopenthyl-N-methyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine

A solution of N-cyclopentyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanamine (3.50 g, 7.53 mmol) was treated as described in Example 31.2. Yield 2.46 g (68%); ^{1}H NMR ($CDCl_3$) δ 1.10-1.80 (m, 8H), 2.19 (m, 5H), 2.36 (m, 2H), 2.58 (m, 1H), 4.37 (t, 1H), 4.98 (s, 2H), 6.72 (d, 1H), 7.10-7.50 (m, 12H).

EXAMPLE 33

N,N-Diisopropyl-3-(2-aminophenyl)-3-phenylpropanamine hydrochloride

LAH (0.94 g, 24.8 mmol) was added to a solution of N,N-diisopropyl-3-(2-aminophenyl)-3-phenylpropenylamide (1.6 g, 4.98 mmol) in THF (90 mL). The mixture was stirred for 72 h at room temperature. The reaction was quenched and the solvent evaporated. The crude residue was fractionated on a reversed-phase PEP RPC HR 30/26 (Pharmacia Biotech AB, Sweden) column using 20 % acetonitrile with 0.1% TFA. Hydrochloric acid was added to the pure fractions and the solvent was evaporated. The residue was redissolved in water and freeze-dried giving 88 mg (5%); mp 138 - 142 °C; ^{1}H NMR (DMSO) δ 1.25 (m, 12H), 2.47 (m, 1H), 2.65 (m, 1H), 2.87 (m, 1H), 3.13, (m, 1H), 3.59 (br, 2H), 4.58 (t, 1H), 7.20 - 7.37 (m, 5H), 7.42 (m, 2H), 7.54 (d, 2H), 9.94 (br, 2H). Anal. ($C_{21}H_{30}N_2$*HCl*H_2O) C, N, H: calcd.8.5; found 7.9.

The starting compound N,N-diisopropyl-3-(2-aminophenyl)-3-phenylpropenylamide was prepared as follows:

33.1 2-(3,5-Dimethyl-4-hydroxyphenylazo)benzophenone

A slurry of ice (500 mL), hydrochloric acid (16.8 mL, 202 mmol, conc.), 2-aminobenzophenone (20.00 g, 101 mmol) and $NaNO_2$ (9.0 g, 131 mmol) were added to a stirred solution of 2,6-dimethylphenol (18.40 g, 151 mmol) and sodium hydroxide (16.20 g, 404 mmol) in ice-cold water (100 mL). After 20 minutes the mixture was extracted with

diethyl ether. The organic phase was washed with hydrochloric acid (6 M), $NaHCO_{3(aq)}$, dried ($MgSO_4$) and the solvent evaporated. The crude residue was chromatographed on silica (toluene) and pure fractions were pooled and evaporated to give a red oil. The oil was crystallised in hexane/toluene to give 7.73 g (23%).

33.2 2-(3,5-Dimethyl-4-tosyloxyphenylazo)benzophenone

A mixture of 2-(3,5-dimethyl-4-hydroxyphenylazo)-benzophenone (7.73 g, 23.41 mmol) and tosyl chloride (9.4 g, 49 mmol) in pyridine (20 mL) was stirred at 90 °C for 9 h. Water was added and the mixture was extracted with diethyl ether. The organic phase was washed with sodium hydroxide (2 M) and hydrochloric acid (2 M), dried ($MgSO_4$) and the solvent evaporated. The product was crystallised in ethanol to give 7.62 g (67%); ^1H NMR ($CDCl_3$) δ 2.08 (s, 6H), 2.49 (s, 3H), 7.05 (s, 2H), 7.37 (m, 4H), 7.48 (m, 1H), 7.62 (m, 3H), 7.82 (m, 5H).

33.3 N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-tosyloxyphenyl-azo)phenyl]-3-phenylpropenamide

2-(3,5-Dimethyl-4-tosyloxyphenylazo)benzophenone (7.22 g, 14.9 mmol) was treated as described in Example 4.2 but with 3 eq of N,N-diisopropylacetamide diethylphosphonate and sodium hydride. Yield 4.5 g (50%). ^1H NMR ($CDCl_3$) δ 0.72 (d, 3H), 0.82 (br, 3H), 1.28 (d, 3H), 1.42 (d, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 2.45 (s, 3H), 3.25 (m, 1H), 4.28 (m, 1H), 6.05 and 6.63 (s, 1H), 7.00 - 7.90 (m, 15H).

33.4 N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-hydroxyphenyl-azo)phenyl]-3-phenylpropenamide

A solution of potassium hydroxide (10.3 mL, 6 M) and N,N-diisopropyl-3-[2-(3,5-dimethyl-4-tosyloxyphenyl-azo)phenyl]-3-phenylpropenamide (3.5 g, 5.74 mmol) in ethanol (110 mL) was refluxed for 1 h. The mixture was acidified with hydrochloric acid (conc.) and the solvent evaporated. The residue was partioned between toluene and water. The organic layer was dried ($MgSO_4$) and the solvent

evaporated. The crude residue was chromatographed on silica (toluene-ethyl acetate 9:2). Yield 1.3 g (50%). ^{1}H NMR ($CDCl_3$) δ 0.71 (d, 3H), 0.80 (br, 3H), 1.27 (d, 3H), 1.40 (d, 3H), 2.20 (s, 3H), 2.23 (s, 3H), 3.25 (m, 1H), 4.35 (m, 1H), 5.52 (brd, 1H), 6.05 and 6.60 (s, 1H), 7.00 - 7.80 (m, 11H).

33.5 N,N-Diisopropyl-3-(2-aminophenyl)-3-phenylpropenamide

N,N-Diisopropyl-3-[2-(3,5-dimethyl-4-hydroxyphenyl-azo)phenyl]-3-phenylpropenamide (2.58 g, 5.68 mmol) was treated as described in Example 28.3. The crude residue gave crystals from aqueous ethanol. Yield 1.23g (67%).

EXAMPLE 34

N,N-Diisopropyl-3-(benzoxazol-2-yl)-3-phenylpropanamine, hydrochloride

A mixture of N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine (2.51 g, 8.6 mmol), 75% aqueous ethanol (15 mL) and 2 M NaOH (8.5 mL, 17 mmol) was refluxed over night. After evaporation of the solvent, the residue was made acidic with 2 M HCl and the solvent was evaporated. A mixture of the residual semicrystalline oil was heated with o-aminophenol (1.8 g, 16.5 mmol) and polyphosphoric acid (12 g) at 200°C for 2 hours under N_2. The somewhat cooled hard solid was dissolved in water and washed once with diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether/triethylamine 97:3). The pure amine was precipitated as hydrochloride from diethyl ether affording white crystals, 1.27 g (39%): mp 197-198°C; ^{1}H NMR ($CDCl_3$) δ 1.49 (m, 12H), 2.80-3.20 (m, 4H), 3.48 (br, 2H), 4.45 (t, 1H), 7.25-7.48 (m, 8H), 7.70 (m, 1H), 11.48 (br, 1H).

The starting compound N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine was prepared as follows:

34.1 N,N-Diisopropyl-3-cyano-3-phenylpropanamine

Sodium hydride, 80% in mineral oil (2.82 g, 94 mmol), was washed with petroleum ether and dried under a N_2-stream. Dry DMF (100 mL) was added. Benzyl cyanide (12.1 g, 103 mmol) was added to the stirred suspension over a period of 20 min. The temperature rose to approx. 45°C. The mixture was stirred for another 15 min. 2-Chloroethyl-diisopropylamine (15.4 g, 94 mmol) was added. All the amine was consumed within 30 min. Most of the DMF was evaporated under reduced pressure and the residue was dissolved in water/diethyl ether. The aqueous phase was extracted once with diethyl ether and the combined organic phases were extracted twice with 2 M HCl. The combined aqueous phases were made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were then dried (Na_2SO_4) and the solvent was evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine, 40:1), affording the title compound, 16.8 g (67%), as a colourless liquid. ^{1}H NMR ($CDCl_3$) δ 1.01 (m, 12H), 1.97 (m, 2H), 2.62 (m, 2H), 3.00 (m, 2H), 4.02 (dd, 1H), 7.17-7.40 (m, 5H).

34.2 N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamine

N,N-Diisopropyl-3-cyano-3-phenylpropanamine (11.6 g, 47.5 mmol) was mixed with H_2SO_4 (90%, 100 mL) and the mixture was stirred at 100°C for 30 min. The reaction mixture was poured on ice, made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated, affording the title compound as a colourless oil, 12.4 g (100%); ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 12H), 2.14 (m, 1H), 2.60 (m, 1H), 2.73 (t, 2H), 3.31 (m, 2H), 3.86 (t, 1H), 6.06 (br, 2H), 7.51- 7.61 (m, 5H).

34.3 N,N-Diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine

N,N-Diisopropyl-3-carbamyl-3-phenylpropanamine (26.5 g 0.100 mol) was added into aqueous ethanol (90%, 300 mL)

containing conc. HNO_3 (13.3 g, 0.21 mol) and refluxed for five days. Most of the solvent was evaporated under reduced pressure and the residue was mixed with water/diethyl ether. The organic phase was washed once with water. The combined aqueous phases were made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were then dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine, 97/3), to afford the title compound as a colourless liquid, 20.1 g (68.7%): ^1H NMR ($CDCl_3$) δ 0.96 (m, 12H), 1.21 (t, 3H), 1.81 (m, 1H), 2.22 (m, 1H), 2.40 (t, 2H), 3.66 (dd, 1H), 4.12 (m, 2H), 7.20-7.32 (m, 5H).

EXAMPLE 35

N,N-Diisopropyl-3-(oxazol-5-yl)-3-phenylpropanamine hydrochloride

Freshly distilled methylisonitrile (1.66 g, 40.4 mmol) was dissolved in dry THF (75 mL) under N_2-atmosphere and the mixture was cooled to -78°C. 1.4 M n-BuLi (29 mL, 40.5 mmol) was slowly added to the solution, followed by N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamine (4.71 g, 16.2 mmol) in THF (10 mL). The reaction temperature was allowed to rise to -20°C, at which the reaction was quenched with HOAc (10 mL). The solvent was evaporated and the residue was mixed with diethyl ether/water. The organic phase was washed once with water and the combined aqueous phases were made alkaline with 11 M NaOH and extracted twice with diethyl ether. The organic phases were put together, dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (chloroform-methanol-conc. ammonia, 490:10:1). The pure amine was precipitated with HCl-saturated diethyl ether, affording the title compound as a glassy oil, 1.4 g (48%). ^1H NMR (CD_3OD) δ 1.21-1.40 (m, 12H), 2.57 (m, 1H), 2.68 (m, 1H), 2.91 (m, 1H), 3.23 (m, 1H), 3.72 (m, 2H), 4.41 (dd, 1H), 7.39 (m, 5H), 7.52 (s, 1H), 9.13 (s, 1H).

EXAMPLE 36

N,N-Diisopropyl-3-(imidazol-4(5)-yl)-3-phenylpropanamine dihydrochloride

N,N-Diisopropyl-3-oxazol-5-yl-3-phenylpropanamide (0.76 g 2.6 mmol) was mixed with formamide (5 mL). The mixture was heated at 175°C for 6 hours. The solvent was evaporated under vacuum (1 mm Hg) and the residue was partitioned between 1 M HCl and diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The light brown oil was dissolved in diethyl ether and added to a suspension of lithium aluminium hydride (LAH) (0.70 g, 5.4 mmol) in diethyl ether. The reaction mixture was stirred at ambient temperature overnight. The reaction was quenched, and the solvent was evaporated. The crude amine was dissolved in EtOAc and precipitated as a hydrochloride salt with HCl-saturated diethyl ether to afford the title compound as hygroscopic crystals, 0.32 g (35%): ^{1}H NMR ($CDCl_3$) δ 1.38 (m, 12H), 2.80 (m, 2H), 3.00 (m, 1H), 3.16 (m, 1H), 3.64 (br, 2H), 4.41 (m, 1H), 6.89 (s, 1H), 7.27-7.41 (m, 5H), 8.78 (s, 1H), 10.32 (br, 2H).

The starting compound N,N-diisopropyl-3-oxazol-5-yl-3-phenylpropanamide (0.76 g 2.6 mmol) was prepared as follows:

36.1 3-Cyano-3-phenylpropanoic acid

Ethyl cinnamate (85.3 g, 0.484 mol), potassium cyanide (64.2 g, 0.986 mol) and ammonium chloride (38.9 g, 0.726 mol) were mixed with aqueous DMF (90%, 360 mL). The mixture was stirred at 105°C for 7 hours. The somewhat cooled mixture was filtered and most of the DMF was evaporated. The residue was taken up in diethyl ether and 1 M HCl. The aqueous phase was extracted twice with diethyl ether. The combined diethyl ether phases were evaporated and the black oil was suspended in EtOH (200 mL) and 2 M NaOH (250 mL) and stirred at ambient temperature for 2 hours. The mixture

was diluted with brine (200 mL) and water (400 mL) and washed twice with diethyl ether. After acidification (12 M HCl) the aqueous phase was extracted three times with diethyl ether. The pooled organic phases were dried (Na_2SO_4) and the solvent evaporated affording the title compound as a black oil, 74 g (87%): ^1H NMR ($CDCl_3$) δ 1.05 (d, 3H), 1.17 (d, 3H), 1.22 (d, 6H), 2.68 (dd, 1H), 3.16 (dd, 1H), 3.4 (br, 1H), 3.76 (m, 1H) 4.19 (dd, 1H), 7.31 (m, 5H), 8.9 (br, 1H).

36.2 N,N-Diisopropyl-3-cyano-3-phenylpropanamide

3-Cyano-3-phenylpropanoic acid (67.7 g, 0.389 mol) was dissolved in 2-PrOH. To the filtered acid solution was carefully added KOH (18.4 g, 0.33 mol) dissolved in 2-PrOH (200 mL), diethyl ether (100 mL) was added and the precipitate was filtered off. The dried acid salt (51.9 g, 0.24 mol) was suspended in benzene (400 mL) and oxalyl chloride was carefully added. The reaction mixture was stirred at 80°C for 2 hours. The solvent was evaporated and the residue was co-evaporated twice with benzene. The brown oil was dissolved in benzene (200 mL) and cooled in an ice-bath. A solution of diisopropylamine (82 g, 0.81 mol) in benzene (200 mL) was added to the stirred reaction mixture during 45 min. The mixture was left to slowly warm up to room temperature overnight. The solvent was evaporated and the residue was taken up in diethyl ether and 1 M HCl. The organic phase was washed once with water, once with 1 M NaOH, again with water, dried (Na_2SO_4) and the solvent evaporated to afford the title compound as a dark brown oil, 41.7 g (41%): ^1H NMR ($CDCl_3$) δ 1.07 (d, 3H), 1.17 (d, 3H), 1.36 (m, 6H), 2.77 (m, 1H), 2.97 (m, 1H), 3,51 (br, 1H), 3.81 (m, 1H), 4.50 (dd, 1H), 7.39 (m, 5H).

36.3 N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamide

N,N-Diisopropyl-3-cyano-3-phenylpropanamide (21.1 g, 82 mmol) was dissolved in EtOH (130 mL) and 2 M NaOH (100 mL). Hydrogen peroxide (30%, 20.2 mL, 200 mmol) was added and the mixture was stirred at ambient temperature for two

hours. The resulting precipitate was filtered, washed with water and dried, yielding the title compound as white crystals, 15.6 g (69%): ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3H), 1.19 (d, 3H), 1.31 (m, 6H), 2.51 (dd, 1H), 3.30 (dd, 1H), 3.41 (m, 1H), 4.02 (m, 1H), 4.18 (dd, 1H), 5.7 (br, 1H), 6.4 (br, 1H), 7.21-7.42 (m, 5H).

36.4 N,N-Diisopropyl-3-ethoxycarbonyl-3-phenylpropanamide

N,N-Diisopropyl-3-carbamoyl-3-phenylpropanamide was treated as described in Example 34:3 (two days of reflux and no chromatography) which gave the title compound as a colourless semicrystalline oil, 15.9 g (93%): ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 9H), 1.36 (m, 6H), 2.53 (dd, 1H), 3.18 (dd, 1H), 3.4 (br, 1H), 3.98 (m, 1H), 4.15 (m, 3H), 7.31 (m, 5H).

36.5 N,N-Diisopropyl-3-oxazol-5-yl-3-phenylpropanamide

The method described for Example 35 above was used, starting from N,N-diisopropyl-3-ethoxycarbonyl-3-phenylpropanamide. The crude was chromatographed on silica (petroleum ether-EtOAc, 3:2), affording the title compound as a light yellow oil, 0.77 g (46%): ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 3H), 1.14 (d, 3H), 1.29 (m, 6H), 2.98 (m, 2H), 3.4 (br, 1H), 3,93 (m, 1H), 4.79 (t, 1H), 6.82 (s, 1H), 7.28 (m, 5H), 7.76 (s, 1H).

EXAMPLE 37

N,N-Diisopropyl-3-(oxazol-2-yl)-3-phenylpropanamine hydrochloride

A mixture of N,N-diisopropyl-3-carbamoyl-3-phenylpropanamine, prepared in Example 34.2 (4.05 g, 15.4 mmol), 1,2-dichloroethyl ethyl ether (2,32 g, 16.2 mmol), water (0.300 g, 16.6 mmol) and formic acid (50 mL) was stirred at 75°C for 3 hours. The formic acid was evaporated and the residue was dissolved in water/diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were

dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (petroleum ether-triethylamine 97:3). The pure amine was precipitated as hydrochloride salt with HCl-saturated diethyl ether, affording the title compound as white crystals, 0.61 g (12%): mp 157-158°C; ^1H NMR (DMSO(d_6)) δ 1.11 (m, 12H), 2.35 (m, 1H), 2.63 (m, 1H), 3.03 (m, 2H), 3.56 (m, 2H), 4.45 (m, 1H), 7.21-7.40 (m, 6H) 8.06 (d, 1H), 10.20 (br, 1H).

EXAMPLE 38

N,N-Diisopropyl-3-phenyl-3-(thiazol-2-yl)propanamine hydrochloride

The title compound was prepared in an analogous manner to that described in Example 37. N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine (1.11 g, 4.0 mmol) yielded white crystals of the title compound, 1.12 g (82%): mp 155-156°C; ^1H NMR ($CDCl_3$) δ 1.37 (m, 12H), 2.75-3.15 (m, 4H), 3.60 (m, 2H), 4.45 (t, 1H), 7.25-7.36 (m, 6H), 7.71 (d, 1H), 11.30 (br, 1H).

The starting compound N,N-diisopropyl-3-phenyl-3-thiocarbamoylpropanamine was prepared as follows:

38.1 N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine

H_2S was bubbled into a solution of N,N-diisopropyl-3-cyano-3-phenylpropanamine, prepared in Example 34.1, (3.45 g, 14.3 mmol) and triethylamine (2.0 g, 20 mmol) in dry pyridine (10 mL) until saturation was achieved. The stirred reaction was held under H_2S-atmosphere at 65°C for 5 days. The pyridine was evaporated and the crude product was chromatographed on silica (chloroform-methanol-conc. ammonia 380:20:1), yielding the title compound as a colourless glassy oil, 3.1 g (78%): ^1H NMR ($CDCl_3$) δ 0.99 (m, 12H), 2.07 (m, 1H), 2.40 (m, 3H), 3.05 (m, 2H), 4.10 (t, 1H), 7.20-7.45 (m 5H), 7.7-8.1 (b, 1H), 8.0-8.5 (br, 1H).

EXAMPLE 39

N,N-Diisopropyl-3-(4-methylthiazol-2-yl)-3-phenyl-propanamine hydrochloride

The title compound was prepared in an analogous manner to that described in Example 37. N,N-Diisopropyl-3-phenyl-3-thiocarbamoylpropanamine, prepared in Example 38.1, (1.5 g, 5,4 mmol), and 2-chloroacetone (0.75 g, 8.1 mmol) yielded the title compound as a white amorphous substance, 1.1 g (56%): mp 178-181°C; ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 12H), 2.50 (s, 3H), 2.98 (m, 3H), 3.18 (m, 1H), 3.60 (m, 2H), 6.94 (d, 1H), 7.30-7.47 (m, 5H), 11.15 (br, 1H).

EXAMPLE 40

N,N-Diisopropyl-3-(thiazol-5-yl)-3-phenylpropanamine hydrochloride

The title compound was prepared in an analogous manner to that described in Example 35. Reaction with N,N-diisopropylamine-3-ethoxythiocarbonyl-3-phenylpropanamine (1.14 g, 3.7 mmol) gave a crude that was chromatographed on silica (petroleum ether-triethylamine 97:3), affording white crystals of the title compound, 0.19 g (30%): mp 193-194°C; ^{1}H NMR ($CDCl_3$) δ 1.1.34 (m, 12H), 2.85 (m, 4H), 5.56 (m, 2H), 4.29 (t, 1H), 7.26-7.39 (m, 5H), 7.73 (s, 1H), 8.71 (s, 1H) 11.61 (br, 1H).

The starting compound N,N-diisopropylamine-3-ethoxythiocarbonyl-3-phenylpropanamine was prepared as follows:

40.1 N,N-Diisopropyl-3-ethoxythiocarbonyl-3-phenyl-propanamine

HCl-gas was bubbled through an ice-cold solution of N,N-diisopropyl-3-cyano-3-phenylpropanamine (2.9 g, 12 mmol), prepared in Example 34.1, in dried ethanol (50 mL, molecular sieve 3 Å) until saturation. The stirred reaction was held under HCl-atmosphere at room temperature overnight. The solvent was carefully evaporated and the

remaining oil was dissolved in dry pyridine (100 mL). To this solution was added triethylamine (5.7 g, 56 mmol) and to the now thick suspension was bubbled H_2S until saturation was achieved. The dark olive-green reaction mixture was held under a H_2S-atmosphere at 65°C overnight. The solvent was evaporated and the residue was partioned between 1 M HCl and diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted twice with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was chromatographed on silica (chloroform-methanol-conc. ammonia, 198:1:1), affording the title compound as a straw-coloured liquid, 1.24 g (33%): ^1H NMR ($CDCl_3$) δ 0.95 (m, 12H), 1.34 (t, 2H), 1.97 (m, 1H), 2.37 (m, 3H), 2.98 (m, 2H), 4.10 (t, 1H) 4.46 (m, 2H), 7.13-7.39 (m, 5H).

EXAMPLE 41

N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)-propanamine fumarate

To a suspension of lithium aluminium hydride (LAH) (0.51 g 13.3 mmol) in THF (30 mL), N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide (2.0 g, 5.33 mmol) was added and warmed to 50°C overnight. The reaction mixture was quenched and the solvent was evaporated. The residue was dissolved in diethyl ether and extracted twice with 2 M HCl, and the combined aqueous phases were washed twice with diethyl ether. The aqueous phase was made alkaline (11 M NaOH) and extracted three times with diethyl ether, the combined organic phases were washed once with brine, dried ($MgSO_4$) and the solvent evaporated. The pure amine was crystallised from methanol as its fumarate, yielding the title compound as white crystals, 1.52 g (58%): mp 203-205°C; ^1H NMR (DMSO) δ 1.00 (d, 12H), 2.02 (q, 2H), 2.33 (m, 2H), 3.18 (m 2H), 4,62 (t, 1H), 6.50 (s, 1H), 6.68-7.18 (m, 6H), 7.28 (t, 1H).

The starting compound N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide was prepared as follows:

41.1 N,N-Diisopropyl-3-(2-thienyl)propenamide

2-Bromothiophene (2.28 g, 14.0 mmol), N,N-diisopropylacrylamide (1.55 g, 10.0 mmol), palladium(II)acetate (34 mg, 0.15 mmol), tri-o-tolylphosphine (183 mg, 0.6 mmol), tri-n-butyl amine (2.04 g, 11.0 mmol) and dry DMF (5 mL) were mixed under a N_2-atmosphere. The mixture was heated to 130°C for 9 hours. Diethyl ether and H_2O was added to the somewhat cooled mixture. The aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed twice with 2 M HCl, once with water, once with brine, and dried ($MgSO_4$), and the solvent was then evaporated. The crude product was chromatographed on silica (petroleum ether-ethyl acetate 4:1), affording a yellow oil, 1.58 g (66%): ^1H NMR ($CDCl_3$) δ 1.35 (br, 12H), 3.9 (br, 1H), 4.1 (br 1H), 6.65 (d, 1H), 7.00-7.30 (m, 3H), 7.72 (d, 1H).

41.2 2-Methoxyphenyllithium

2-Methoxybromobenzene (8.44 g 45.1 mmol) was dissolved in dry diethyl ether (15 mL). The mixture was cooled to -78°C. n-BuLi (17.8 mL, 45.0 mmol) was added and the mixture was stirred for one hour at -78°C and then for 20 min. at -10°C. The aryl lithium solution was used immediately.

41.3 N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamide

Copper(I)bromide dimethyl sulfide complex (4.63 g 22.5 mmol) was dissolved in dimethyl sulfide (18 mL), and diethyl ether (15 mL). The solution was cooled to 0°C, whereafter 2-methoxyphenyllithium (41.2) (45 mmol) was added. After 10 min., the temperature was lowered to -78°C. Trimethylsilylchloride (4.89 g, 45.0 mmol) was added, followed by N,N-diisopropyl-3-(2-thienyl)propenamide (41.1)

(3.56 g, 15 mmol) in diethyl ether (20 mL). The temperature was allowed to slowly rise to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and conc. ammonia (10 mL). Diethyl ether (80 mL) was added and the mixture was filtered through Celite. The aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed once with brine and dried ($MgSO_4$). The solvent was evaporated and the crude product was chromatographed on silica (petroleum ether-ethyl acetate 3:1), affording a yellow oil, 3.75 g (73%): ^1H NMR ($CDCl_3$) d 1.12 (t, 6H), 1.29 (t, 6H), 3.02 (m, 2H), 3.4 (br, 1H), 3.80 (s, 3H), 4.03 (m, 1H), 5.26 (t, 1H), 6.8-7.3 (m, 7H).

41.4 N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamide

A solution of N,N-diisopropyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamide (2.37 g, 6.9 mmol) in dichloromethane(35 mL) was cooled down to -78°C and boron tribromide (5.9 g 23.57 mmol) was added. The reaction mixture was allowed to slowly warm to room temperature. The reaction was quenched by slow addition of water (20 mL). The pH was adjusted to around 6 with $NaHCO_3$(s) and the mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed once with brine, dried ($MgSO_4$) and the solvent was evaporated. This crude product (2.46 g, 107%) was used without further purification. ^1H NMR ($CDCl_3$) δ 1.05 (d, 3H), 1.20 (m, 6H), 1.35 (d, 3H), 3.16 (m, 2H), 3.4 (br, 1H), 4.0 (m, 1H), 5.24 (dd. 1H), 6.7-7.2 (m, 7H).

Examples 42-54 and 57 and 58 were prepared with the methodology described for Example 41, starting with the appropriate acrylamides and aryl bromides.

EXAMPLE 42

N,N-Diisopropyl-3-(2,4-dihydroxyphenyl)-3-(2-thienyl)propanamine

The crude product was crystallised from petroleum ether/ethyl acetate affording the title compound, 0.41 g as slightly pink crystals: mp 102-109°C; ^{1}H NMR ($CDCl_3$) δ 1.11 (m, 12H), 2.01 (m, 1H), 2.41 (m, 2H), 2.72 (m, 1H), 3.26 (m, 2H), 4.66 (dd, 1H), 6.30 (dd, 1H), 6.45 (d, 1H), 6.73 (d, 1H), 6.91-7.00 (m, 2H), 7.17 (dd, 1H).

EXAMPLE 43

N,N-Diisopropylamine-3-(2-methoxyphenyl)-3-(2-thienyl)propanamine, fumarate

White crystals, 0.95 g: mp 153-155°C; ^{1}H NMR (CD_3OD) δ 1.28 (m, 12H), 2.48 (m, 2H), 3.05 (m, 2H), 3.68 (m, 2H), 3.85 (s, 3H), 4.71 (t, 1H), 6.68 (s, 2H), 6.89-7.03 (m, 4H), 7.20-7.30 (m, 3H).

EXAMPLE 44

N,N-Diisopropyl-3-(2,4-dimethoxyphenyl)-3-(2-thienyl)propanamine fumarate

White crystals, 1.52 g: mp 103-109°C; ^{1}H NMR (CD_3OD) δ 1.28 (m, 12H), 2.46 (m, 2H), 3.04 (m, 2H), 3.66 (m, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 4.60 (t, 1H), 6.46-6.58 (m, 2H), 6.68 (s, 2H), 6.91-6.97 (m, 2H), 7.09- 7.26 (m, 2H).

EXAMPLE 45

N,N-Diisopropyl-3-(3-methoxyphenyl)-3-(2-thienyl)propanamine hydrochloride

White crystals, 1.16 g: mp 95-97°C; ^{1}H NMR (CD_3OD) δ 1.28 (d, 12H), 2.49 (m, 2H), 2.96 (m, 1H), 3.13 (m, 1H), 3.68 (m, 2H), 3.77 (s, 3H), 4.31 (t, 1H), 6.83 (m, 1H), 6.68-7.02 (m, 4H), 7.27 (m, 2H).

EXAMPLE 46

N,N-Diisopropyl-3-(4-methoxyphenyl)-3-(2-thienyl)-propanamine hydrochloride

White amorphous substance, 0.50 g: mp 157-160°C; ^{1}H NMR (CD_3OD) δ 1.31 (m, 12H), 2.47 (m, 2H), 2.94 (m, 1H), 3.12 (m, 1H); 3.68 (br, 2H), 3.77 (s, 3H), 4.28 (t, 1H), 6.87-7.00 (m, 4H), 7.23-7.32 (m, 3H).

EXAMPLE 47

N-Isopropyl-N-methyl-3-(2-methoxyphenyl)-3-(2-thienyl)propanamine fumarate

White crystals, 1.32 g: mp 141-143°C; ^{1}H NMR (CD_3OD) δ 1.24 (m, 6H), 2.50 (m, 2H), 2.73 (s, 3H), 3.04 (m, 2H), 3.58 (m, 1H), 3.84 (s, 3H), 4.73 (t, 1H), 6.68 (s, 2H), 6.96 (m, 4H), 7.24 (m, 3H).

EXAMPLE 48

N,N-Diisopropyl-3-phenyl-3-(2-thienyl)propanamine, hydrochloride

White crystals, 0.74 g: mp 165-166°C; ^{1}H NMR (CD_3OD) δ 1.28 (d, 12H), 2.52 (m, 2H), 2.96 (m, 1H), 3.13 (m, 1H), 3.70 (br, 2H), 4.34 (t, 2H), 6.92-7.04 (m, 2H), 7.20-7.42 (m, 6H).

EXAMPLE 49

N-Cyclohexyl-N-methyl-3-phenyl-3-(2-thienyl)propanamine hydrochloride

White crystals, 1.1 g: mp 197-199°C; ^{1}H NMR (CD_3OD) δ 1.15-1.52 (br, 5H), 1.68 (br, 1H), 1.90 (br, 4H), 2.51 (br, 2H), 2.78 (s, 3H), 2.91-3.40 (m, 3H), 4.31 (t, 1H), 6.92-7.04 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 50

N,N-Diethyl-3-phenyl-3-(2-thienyl)propanamine fumarate

White crystals, 1.7 g (tot. 49 %): mp 135-137°C; ^{1}H NMR (CD_3OD) δ 1.22 (t, 3H), 2.50 (m, 2H), 2.90-3.26 (m, 6H),

4.30 (t, 1H), 6.68 (s, 2H), 6.92-7.03 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 51

N-Isopropyl-N-methyl-3-phenyl-3-(2-thienyl)propanamine hydrochloride

White crystals, 1.6 g: mp 139-144°C; ^{1}H NMR (CD_3OD) δ 1.24 (m, 6H), 2.52 (m, 2H), 2.75 (s, 3H), 3.03 (m, 2H), 3.59 (m, 1H), 4.32 (t, 1H), 6.92-7.04 (m, 2H), 7.20-7.40 (m, 6H).

EXAMPLE 52

N-[3-Phenyl-3-(2-thienyl)propyl]pyrrolidine fumarate

Crystallisation from 2-propanol, 1.1 g: mp 144-145°C; ^{1}H NMR (CD_3OD) δ 2.02 (m, 4H) 2.31 (m, 2H), 2.97-3.42 (m, 6H), 4.29 (t, 1H), 6.69 (s, 2H), 6.91-7.01 (m, 2H), 7.18-7.38 (m, 6H).

EXAMPLE 53

N-[3-Phenyl-3-(2-thienyl)propyl]piperidine hydrochloride

The hydrochloride was crystallised from ethylmethylketone, 0.84 g: mp 193-194°C; ^{1}H NMR (CD_3OD) δ 1.40-2.00 (b, 6H), 2.54 (m, 2H), 2.82-3.80 (m, 6H), 4.29 (t, 1H), 6.91-7.03 (m, 2H), 7.20-7.42 (m, 6H).

EXAMPLE 54

N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine hydrochloride

White crystals, 2.1 g: mp 205-210°C; ^{1}H NMR ($CDCl_3$) δ 1.36 (m, 12H), 2.18 (s, 3H), 2.63 (m, 2H), 2.95 (m, 2H), 3.54 (m, 4H), 4.61 (t, 1H), 6.76-7.01 (m, 5H), 7.16 (d, 1H).

EXAMPLE 55

(R*) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine

To the racemic free base of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-2-thienylpropanamine (20 g, 0.06 mol), prepared in Example 54, in abs. ethanol (50 g) was added L-(+)-tartaric acid (9.5 g 0.063 mol) in ethanol (60 g). The salt formed was filtered off and crystallised twice from ethanol/methanol 10/1, 10 mL per gram of crystals, affording the title compound as white crystals, (6.8 g, 14.1 mmol): mp 214-215°C; $[\alpha]_{Hg}$=+17.3° (c=3.82 in methanol).

EXAMPLE 56

(S*) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine

From the mother liquid from the first crystallisation to obtain (R*) N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine in Example 55, the free base was recovered. The amine was treated with a 5% excess of D-(-)-tartaric acid in ethanol as above, yielding the title compound as white crystals, 6.1 g (12.7 mmol): mp 214°C; $[\alpha]_{Hg}$=-17.5° (c=3.85 in methanol).

EXAMPLE 57

N,N-Diisopropyl-3-phenyl-3-(3-thienyl)propanamine hydrochloride

White crystals, 0.94 g: mp 141-142 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 12H), 2.87 (m, 4H), 3.56 (br, 2H), 3.98 (t, 1H), 6.94 (dd, 1H), 7.27 (m, 7H), 11.4 (br, 1H).

The starting compound was prepared as follows:

57.1 N,N-Diisopropyl-3-(3-thienyl)propenamide

Sodium hydride, 60% in mineral oil (3.9 g, 98 mmol), was washed several times with petroleum ether and dried under a stream of nitrogen. Sodium-dried THF was added

followed by diethyl N,N-diisopropyl acetamidephosphonate (27.4 g, 98 mmol). When the evolution of gas had ceased, thiophene-3-aldehyde (10.0 g, 89.2 mmol) in THF(50 mL) was added at such a rate that the temperature never exceeded 45°C. After one hour of stirring at ambient temperature, the reaction was quenched with 4 mL of water and stirred for another hour. The solvent was evaporated and the residue was taken up in diethyl ether/2M NaOH. The organic phase was washed once with water and once with brine, dried (Na_2SO_4) and evaporated. The crude was chromatographed on silica (petroleum ether-ethyl acetate 4:1) affording the title compound as a light-brown oil, 14.8 g (70%): ^{1}H NMR ($CDCl_3$) δ 1.37 (b, 12H), 3.86 (br, 1H), 4.10 (br, 1H), 6.68 (d, 1H), 7.27-7.41 (m, 3H), 7.59 (d, 1H).

EXAMPLE 58

N,N-Diisopropyl-3-(2-furanyl)-3-phenylpropanamine hydrochloride

White crystals, 60 mg: mp 139-141 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (br, 12H), 2.64 (m, 1H), 2.85 (m, 3H), 3.55 (m, 2H), 3.98 (t, 1H), 6.16 (d, 1H), 6.31 (dd, 1H), 7.30 (m, 6H), 11.4 (br, 1H).

The starting compound was prepared as follows:

58.1 N,N-Diisopropyl-3-(2-furanyl)propenamide

The title compound was obtained from furfural with the procedure described in Example 57.1, as a colourless oil, 11.2 g (75%): ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 12H), 4.0 (br, 2H), 6.41 (m, 2H), 6.76 (d, 1H), 7.38 (m, 2H).

EXAMPLE 59

N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-3-phenyl-propanamine fumarate

A solution of N,N-diisopropyl-3-(N-methyl-pyrr-2-yl)-3-phenyl-propanamide (4.92 g, 15.7 mmol) in THF (75 mL), was dropped into a stirred mixture of LAH (2.38 g, 62.8

mmol). Stirring was continued at 50 °C overnight. Standard work-up gave the amine as a yellow oil, which was isolated as the fumarate salt, 2.74 g (42 %): m.p. 134-6°C; ^{1}H NMR (CD_3OD) δ 1.27 (d, 6H), 1.29 (d, 6H), 2.24 (m, 1H), 2.48 (m, 1H), 2.97 (dt, 1H), 3.26 (dt, 1H), 3,32 (s, 3H), 3.69 (septet, 2H), 4.08 (t, 1H), 6.05 (t, 1H), 6.16 (m, 1H), 6.57 (dd, 1H), 6.71 (s, 2H) and 7.19-7.34 (m, 5H).

The starting compound was prepared as follows:

59.1 N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-propenamide

The title compound was prepared from N-methyl-2-pyrrolaldehyde and N,N-diisopropyl-dimethylphosphon acetamide analogously to Example 4.2, giving 7.61 g (92%): ^{1}H NMR($CDCl_3$) δ 1.32 (d, 6H), 1.35 (d, 6H), 3.68 (s, 3H), 4.00 (m, 2H), 6.13 (t, 1H), 6.55-6.66 (3H) and 7,57 (d, 1H).

59.2 N,N-Diisopropyl-3-(N-methylpyrrol-2-yl)-3-phenyl-propanamide

The title compound was prepared from N,N-diisopropyl-3-(N-methylpyrrol-2-yl)-propenamide by a method analogous to that described in Example 41.3, giving 4.92 g (78 %): ^{1}H NMR ($CDCl_3$) δ 0.85-1.32 (4d from rotamers, 12H), 2.91 (d, 2H), 3.31 (s, 3H) 3.45 (m, 1H), 3.88 (m, 1H), 4.65 (t, 1H), 6.07 (2H), 6.50 (dd, 1H) and 7.15-7.22 (5H).

EXAMPLE 60

3-(N-Methylpyrrol-2-yl)-3-phenyl-1-pyrrolidinopropane fumarate

The title compound was prepared analogously to Example 59, using N,N-tetramethylene-dimethylphosphon acetamide, yield 950 mg (36 % tot.): m.p. 194-5°C; ^{1}H NMR (CD_3OD) δ 1.27 (d, 12H), 2.2-2.6 (m, 2H) 3.05 (m, 2H), 3.66 (sept., 2H), 4.03 (t, 1H), 6.02 (two d, 2H), 6.64 (t, 1H), 6.69 (s, 2H) and 7.28 (m, 5H).

BIOLOGICAL EVALUATION

The pharmacological activity of compounds prepared in the Examples was tested using in vitro methods.

Functional in vitro studies

Male guinea pigs, weighing about 300 g, were killed by a blow on the neck and exsanguinated. Smooth muscle strips of the urinary bladder were dissected in a Krebs-Henseleit solution (pH 7.4). The strip preparations were vertically mounted between two hooks in thermostatically controlled (37°C) organ baths (5 ml). One of the hooks was adjustable and connected to a force transducer (FT 03, Grass Instruments). The Krebs-Henseleit solution was continuously bubbled with carbogen gas (93.5% O_2/6.5% CO_2) to maintain the pH at 7.4. Isometric tension was recorded by a Grass Polygraph (Model 79D). A resting tension of approximately 5 mN was initially applied on each muscle strip and the preparations were allowed to stabilise for at least 45 min. The resting tension was repeatedly adjusted and the preparations were washed several times during the stabilisation period.

Carbachol (carbamylcholine chloride) was used as the standard muscarinic receptor agonist. In each experiment, the viability of the preparations and the reproducibility of their contractile responses were initially tested by two consecutive additions of a submaximal concentration (3 x 10^{-6} M) of carbachol. A concentration-response curve to carbachol was then generated by cumulative addition of carbachol to the organ-bath (i.e., stepwise increase of the agonist concentration until the maximal contractile response was reached), followed by washing out and a resting period of at least 15 min. before a fix concentration of the test compound (antagonist) was added to the organ-bath. After 60 min. of incubation with the antagonist, a second cumulative concentration-response curve to carbachol was generated. Responses were expressed as per cent of the maximal response to carbachol. EC_{50}-values for carbachol in the absence (control) and presence of antagonist were graphically derived and dose ratios (r)

were calculated. Dissociation constants, K_B, for the antagonists were calculated using equation (1) (Schild, H.I., Br. J. Pharmacol. Chemother. 1949, 4, 277-280), where [A] is the concentration of test compound:

$$K_B = [A]/r-1 \quad (1)$$

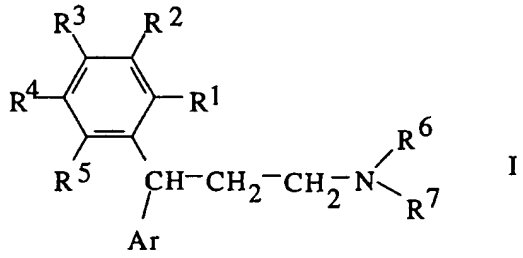
The KB values obtained are presented in Table 1 below.

Table 1

Example No.	K_B-value nM	Example No.	K_B-value nM	Example No.	K_B-value nM
1	499	23	1.05	45	51
3	236	24	1.91	46	286
4	132	27	7.1	47	91
5	336	28	8.55	48	31
6	10	29	1.5	49	590
7	13	30	139	50	154
8	26	31	14	51	118
9	3.8	32	36	52	350
10	171	33	56	53	154
11	431	34	803	55	2
12	1.18	35	1773	56	360
13	15	36	2640	59	690
14	4.5	37	520	60	707
15	15	38	207		
16	32	39	235		
17	3.5	40	814		
18	172	41	7.6		
19	2.9	42	286		
20	3315	43	29		
22	2.8	44	2285		

CLAIMS

1. A compound of Formula (I):



I

wherein:

R^1 is hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, halogen,

R^2 and R^3 independently are hydrogen, hydroxy, alkyl, alkoxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl,

R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, alkoxycarbonylalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, azido, alkyl having at least two carbon atoms, alkoxy having at least two carbon atoms, hydroxyalkyl having at least two carbon atoms,

R^5 is hydrogen, halogen, alkyl,

Ar is aryl or heteroaryl which may be mono- or independently disubstituted by alkyl, alkoxy, hydroxy, hydroxyalkyl, halogen, alkoxycarbonylalkyl, carbamoyl, sulphamoyl, and

R^6 and R^7 are hydrocarbyl groups which may be the same or different, together containing at least three carbon atoms, and which may carry one or more hydroxy groups, and wherein carbon atoms may be interconnected by oxygen atoms, and wherein R^6 and R^7 may form a ring together with the amine nitrogen;

with the provisos that (a) when:
(i) at least two of R^2, R^3 and R^5 are other than hydrogen, or
(ii) R^1 is other than hydroxy or methoxy, and Ar is other than phenyl that is ortho-substituted by hydroxy or methoxy, or
(iii) Ar is heteroaryl, or
(iv) at least one of R^6 and R^7 is aromatic hydrocarbyl or cycloalkyl, then
R^4 may also be hydrogen, methyl, methoxy, hydroxymethyl, hydroxy, halogen, carbamoyl, sulphamoyl;
and (b), when Ar is unsubstituted phenyl, then R^1, R^2, R^3, R^4 and R^5 can not all be hydrogen;
their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

2. The compound according to claim 1, wherein R^4 is ω-hydroxyalkoxy, ω-aminoalkoxy, ω-aminoalkylamino, alkoxyalkyl, hydroxyalkoxyalkylaminoalkyl, dihydroxyalkyl, formyl, alkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, carbamoylalkyl, carboxamidoalkyl, carboxyl, amino, nitro, cyano, nitrilo, cyanoalkyl, or azido.

3. The compound according to claim 2, wherein R^1 is hydrogen or methyl, R^2, R^3 and R^5 are either all hydrogen or one of R^2, R^3 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

4. The compound according to claim 1, wherein Ar is heteroaryl.

5. The compound according to claim 4, wherein R^1 is hydrogen or methyl, and R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and the others are hydrogen.

6. The compound according to claim 1, wherein R^1 is hydrogen, alkyl, hydroxyalkyl, trifluoromethyl, amino, alkylcarbonylamino, alkylcarbonyloxy, or halogen, and Ar is other than phenyl that is ortho-substituted by hydroxy or alkoxy.

7. The compound according to claim 6, wherein R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

8. The compound according to claim 1, wherein at least one of R^6 and R^7 is aromatic hydrocarbyl, cycloalkyl or a hydrocarbyl chain wherein carbon atoms are interconnected by an oxygen atom in at least one position.

9. The compound according to claim 8, wherein R^1 is hydrogen or methyl, R^2, R^3, R^4 and R^5 are either all hydrogen or one of R^2, R^3, R^4 and R^5 is methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and the others are hydrogen, and Ar is phenyl or phenyl which is mono- or independently disubstituted by methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen.

10. The compound according to any one of claims 1 to 9, wherein R^1 is hydroxy, halogen, trifluoromethyl, amino, methoxy or hydroxymethyl.

11. The compound according to any one of claims 1 to 10, wherein R^2 and R^3 independently are hydrogen, hydroxy or hydroxymethyl.

12. The compound according to any one of claims 1 to 10, wherein R^4 is hydrogen, formyl, alkoxycarbonyl, alkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxamidoalkyl, carbamoylalkyl, aminoalkyl, amino, azido, cyanoalkyl, carboxy or carboxyalkyl.

13. The compound according to claim 12, wherein R^4 is hydrogen, formyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethoxymethyl, methoxycarbonyl, amino, aminopropyl, acetyl, 1,2-hydroxyethyl, ethylaminomethyl, or hydroxyethoxyethyl-aminoethyl.

14. The compound according to any one of claims 1 to 13, wherein R^5 is hydrogen.

15. The compound according to any one of claims 1 to 14, wherein each of R^6 and R^7 independently signify a saturated hydrocarbyl group, especially a saturated aliphatic hydrocarbyl group such as C_{1-8}alkyl, especially C_{1-6}alkyl, or adamantyl, R^6 and R^7 together containing at least three, preferably at least four carbon atoms.

16. The compound according to any one of claims 1 to 14, wherein R^6 and R^7 taken together form a ring with the amine nitrogen.

17. The compound according to any one of claims 1 to 16, wherein at least one of R^6 and R^7 comprises a branched carbon chain.

18. The compound according to any one of claims 1 to 17, wherein Ar is thienyl, pyrryl, thiazolyl, oxazolyl, methylthiazolyl or methylpyrryl.

19. The compound according to claim 1, which is:
N,N-diisopropyl-3-(2-fluorophenyl)-3-phenylpropanamine hydrochloride,
N,N-diisopropyl-3-(5-formyl-2-hydroxy-phenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(2-hydroxy-5-methyloxycarbonyl-phenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-acetyl-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(2-hydroxyethyl)-phenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(1-hydroxyethyl)-phenyl]-3-phenylpropanamine, or its 3(R)-isomer,
N,N-diisopropyl-3(R)-[5-(1(R*),2-dihydroxyethyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its 1(S*)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(6-hydroxyhexyl)-phenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-ethoxymethyl-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[5-(3-aminopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[5-(3-acetamidopropyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[5-(2-cyanoethyl)-2-hydroxyphenyl]-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-amino-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-(5-azido-2-hydroxyphenyl)-3-phenylpropanamine, or its (R)-isomer,
N,N-diisopropyl-3-[2-hydroxy-5-(3-hydroxypropyl)-phenyl]-3-phenylpropanamine, or its (R)-isomer,
N-cyclobutyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropanamine,
N,N-diisopropyl-3-(2-hydroxyphenyl)-3-(2-thienyl)propanamine, or
N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-(2-thienyl)propanamine, or its (R)-isomer.

20. The compound according to any one of claims 1 to 19 for use as a pharmaceutically active substance, especially as an anticholinergic agent.

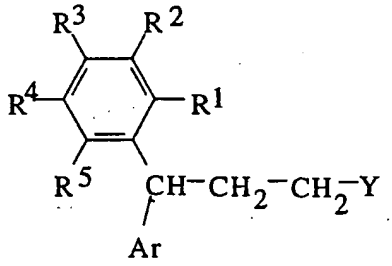
21. A pharmaceutical composition comprising a compound according to any one of claims 1 to 19, and preferably a compatible pharmaceutical carrier.

22. Use of a compound according to any one of claims 1 to 19 for preparing an anticholinergic drug.

23. A method of treating a living body suffering from a disorder related to urinary incontinence, which method comprises the step of administering to said living body an effective amount of a compound according to any one of claims 1 to 19.

24. A method of preparing a compound according to any one of claims 1 to 19, which comprises:

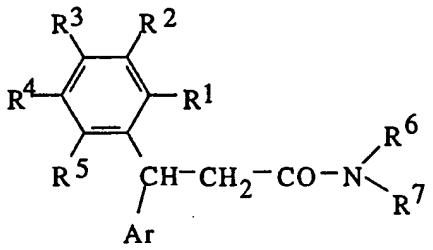
a) reacting a compound of Formula II



II

wherein R^1 to R^5 and Ar are as defined in claim 1, and Y is a leaving group, with an amine HNR^6,R^7, wherein R^6 and R^7 are as defined above, or

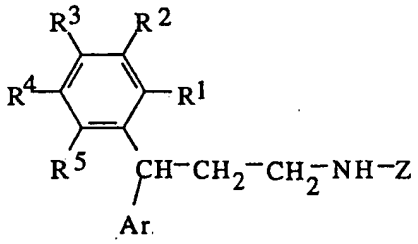
b) reducing a compound of Formula III



III

wherein R^1 to R^7 and Ar are as defined in claim 1 and any hydroxy groups may be protected, or

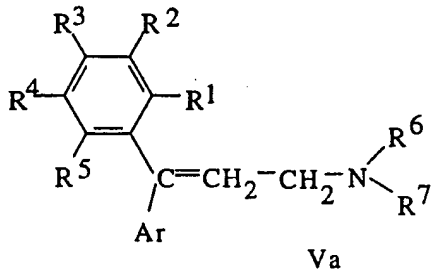
c) N-alkylating a secondary amine of Formula IV



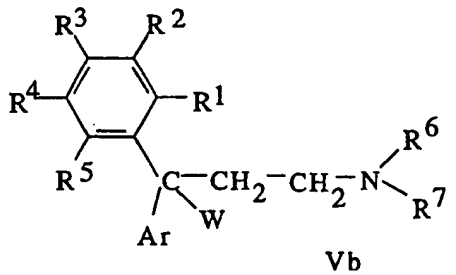
IV

wherein R^1 to R^5 and Ar are as defined in claim 1 and any hydroxy groups may be protected, and wherein Z has the same meaning as R^6 and R^7, or

d) reducing a compound of Formula Va or Vb



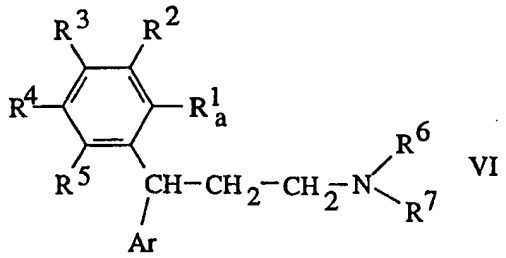
Va



Vb

wherein R^1 to R^7 and Ar are as defined in claim 1 and any hydroxy groups may be protected, and W signifies a hydroxy group or halogen, or

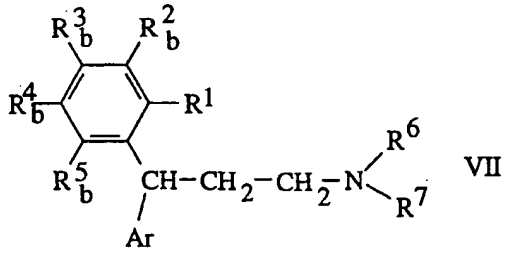
e) in a compound of Formula VI



VI

wherein R^2 to R^7 and Ar are as defined in claim 1, and R^1a is carboxyl or alkoxy, converting R^1a to hydroxy, or

f) in a compound of Formula VII

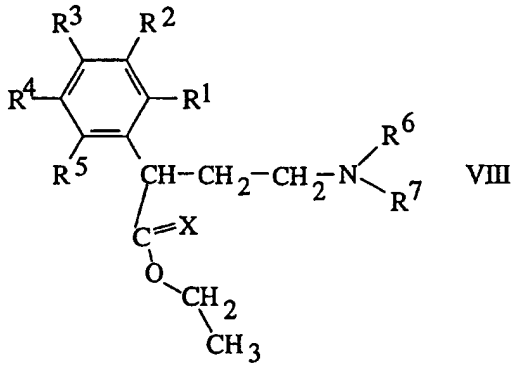


VII

wherein R^1, R^6, R^7 and Ar are as defined in claim 1, and one of R^2b to R^5b is alkylene and the others are as defined in claim 1 for R^2 to R^5, reducing alkylene to alkyl, hydroxyalkyl or dihydroxyalkyl, or

g) in a compound of Formula I as defined in claim 1, converting one or more of groups R^1 to R^5 to another or other groups R^1 to R^5, or

h) reacting a compound of Formula VIII

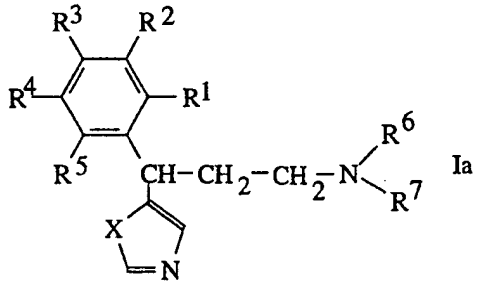


VIII

wherein R^1 to R^7 are as defined in claim 1, and X is oxygen or sulphur, with a compound of Formula IX

$$CH_3N{=}C: \qquad \text{IX}$$

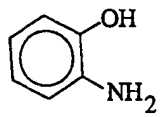
to form a compound of Formula Ia



Ia

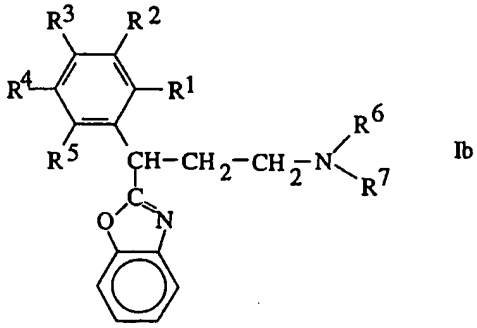
wherein R^1 to R^7 and X are as defined above, or

i) reacting a compound of Formula VIII above, wherein X is oxygen, with a compound of Formula X



X

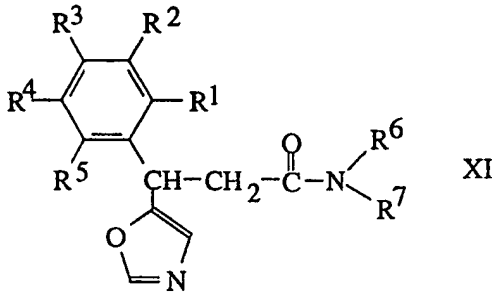
to form a compound of Formula Ib



Ib

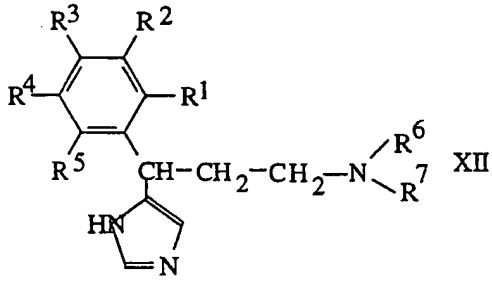
wherein R^1 to R^7 are as defined in claim 1, or

j) converting a compound of Formula XI



XI

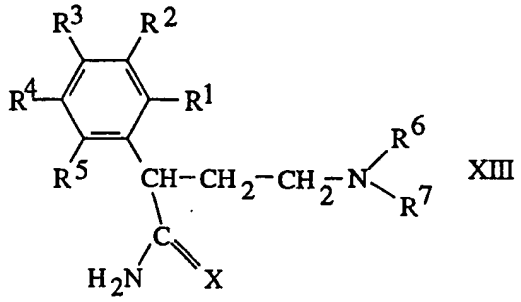
wherein R^1 to R^7 are as defined in claim 1, to a compound of Formula XII



XII

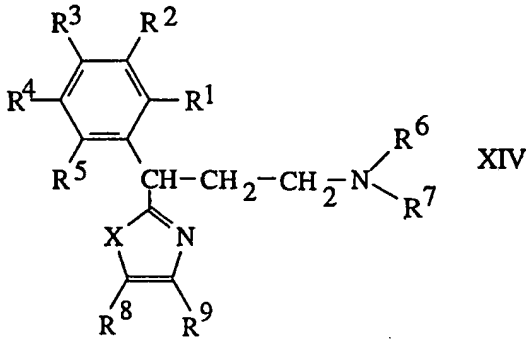
wherein R^1 to R^7 are as defined in claim 1, or

k) converting a compound of Formula XIII



XIII

wherein R^1 to R^7 are as defined in claim 1, and X is oxygen or sulphur, to a compound of Formula XIV



XIV

wherein R^1 to R^7 and X are as defined above, and R^8 and R^9 independently are hydrogen or alkyl, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained,

ii) if desired converting the obtained bases of Formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or

iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00556

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 211/06, C07C 215/54, C07C 217/62, C07C 237/30, C07C 255/33, C07D 333/20, A61K 31/135, A61K 31/33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07C, C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9411337 A1 (KABI PHARMACIA AB), 26 May 1994 (26.05.94) --	1-22,24
X	WO 8906644 A1 (KABIVITRUM AB), 27 July 1989 (27.07.89) --	1-22,24
X	DE 1216318 B1 (FARBWERKE HOECHST AKTIENGESELLSCHAFT VORMALS MEISTER LUCIUS & BRüNING), 12 May 1966 (12.05.66), column 4, line 1 - line 4, the claims --	1-21,24

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 June 1998	29 -06- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00556

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1169944 A (ED. GEISTLICH SÖHNE AG FüR CHEMISCHE INDUSTRIE), 5 November 1969 (05.11.69), page 1, line 10 - line 12, the claims ---	1-21,24
X	GB 1169945 A (ED GEISTLICH SÖHNE AG FüR CHEMISCHE INDUSTRIE), 5 November 1969 (05.11.69), page 1, line 10 - line 11, the claims --- --------	1-21,24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00556

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 23
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

09/06/98

International application No.
PCT/SE 98/00556

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		HU 9501329 D	00/00/00
		JP 8503208 T	09/04/96
		NO 951775 A	05/05/95
		SE 9203318 D	00/00/00
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WO 8906644 A1	27/07/89	AU 635493 B	25/03/93
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		EP 0354234 A	14/02/90
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GB 1169944 A	05/11/69	NONE	
GB 1169945 A	05/11/69	US 3446901 A	27/05/69

PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro
INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 : A61K 9/22 — A2

(11) Internationale Veröffentlichungsnummer: WO 98/56359

(43) Internationales Veröffentlichungsdatum: 17. Dezember 1998 (17.12.98)

(21) Internationales Aktenzeichen: PCT/DE98/01659

(22) Internationales Anmeldedatum: 12. Juni 1998 (12.06.98)

(30) Prioritätsdaten:
197 25 911.1 13. Juni 1997 (13.06.97) DE
60/068,977 30. Dezember 1997 (30.12.97) US

(71)(72) Anmelder und Erfinder: BODMEIER, Roland [DE/DE]; Ravenweg 18, D–14163 Berlin (DE). McGINITY, James, W. [US/US]; 4209 Dunning Lane, Austin, TX 78746 (US).

(74) Anwalt: SCHUBERT, Klemens; Im Schönower Park 1E, D–14167 Berlin (DE).

(81) Bestimmungsstaaten: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Veröffentlicht
Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.

(54) Title: COMPOUNDS WHICH DELAY THE RELEASE OF ACTIVE SUBSTANCES

(54) Bezeichnung: ZUSAMMENSETZUNGEN, DIE DIE WIRKSTOFFFREISETZUNG VERZÖGERN

(57) Abstract

The invention relates to compounds which delay the release of active substances. The invention also relates to a method for the production thereof. The compounds are produced, for instance, by wet or spray granulation, spray drying or extrusion of a conventional filling material (e.g. microcrystalline cellulose or lactose) and a carrier material (hydroxypropylmethyl cellulose or polyethylene oxide). The inventive composition can be processed together with the active substance and other auxiliary agents into a solid medicament form, e.g. a tablet, which releases the active substance in a delayed manner.

(57) Zusammenfassung

Es werden Zusammensetzungen, welche die Wirkstofffreisetzung verzögern, sowie Verfahren zu ihrer Herstellung beschrieben. Die Zusammensetzungen werden z.B. durch Feucht– oder Sprühgranulierung, Sprühtrocknung oder Extrusion aus einem üblichen Füllstoff (z.B. mikrokristalline Cellulose oder Lactose) und einem Trägermaterial (z.B. Hydroxypropylmethylcellulose oder Polyethylenoxid) hergestellt. Diese erfindungsgemäße Zusammensetzung kann zusammen mit dem Wirkstoff und anderen Hilfsstoffen in eine feste Arzneiform, z.B. eine Tablette, verarbeitet werden, die den Wirkstoff verzögert freigibt.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AL	Albanien	ES	Spanien	LS	Lesotho	SI	Slowenien
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CU	Kuba	KZ	Kasachstan	RO	Rumänien		
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EE	Estland	LR	Liberia	SG	Singapur		

Zusammensetzungen, die die Wirkstofffreisetzung verzögern

Die Erfindung betrifft Zusammensetzungen, die die Wirkstofffreisetzung verzögern.

Zur Tablettenherstellung werden verschiedene Hilfsstoffe wie Füllstoffe, Zerfallsmittel, Bindemittel, Schmiermittel usw. eingesetzt. Aufgrund der wenigeren Herstellungsschritte und geringeren Wirkstoffbelastung ist die Direkttablettierung der Naß- oder Trockengranulierung vorzuziehen. Für die Direkttablettierung sind jedoch Hilfsstoffe mit besonderen Eigenschaften notwendig. Die verwendeten Hilfsstoffe sollen zahlreiche, z. T. gegenläufige Anforderungen, wie gute Fließfähigkeit, gute Komprimierbarkeit bei geringem Druck, hohe Härte und Abriebsfestigkeit und gute Zerfallsneigung nach der Einnahme erfüllen. Die Verwendung von Füllstoffen wie mikrokristalliner Cellulose (MCC), Cellulose, Dicalciumphosphat, Lactose u.a. ist für die Tablettenherstellung weithin üblich. Die gewünschten Anforderungen werden von den handelsüblichen Füllstoffen nur mehr oder weniger gut erfüllt. Weitere Hilfsstoffe wie Gleitmittel, Bindemittel, Sprengmittel u.a. werden deshalb bei der Tablettenherstellung hinzugefügt.

Es ist daher wünschenswert, "bessere" Hilfsstoffe, die möglichst viele wünschenswerte Tablettiereigenschaften in sich vereinigen, zu entwickeln. In der Patentliteratur und der wissenschaftlichen Literatur sind einige Direkttablettiermittel, bestehend aus Mischungen verschiedener Hilfsstoffe, beschrieben. Dabei wird meist ein Füllstoff mit einem weiteren Hilfsstoff kombiniert und durch entsprechende Verfahren, z.B. Sprühtrocknung oder Sprühgranulierung, in einem bestimmten Verhältnis in Gra-

nulat- oder Pulverkörnchen fixiert. Dazu zählen z.B. bereits vermarktete Gemische aus MCC mit Lactose oder MCC mit Siliciumdioxid oder MCC mit Natriumcarboxymethylcellulose, die den oben genannten idealen Eigenschaften nahekommen und Vorteile gegenüber den Einzelkomponenten oder Gemischen der Einzelkomponenten besitzen.

Diese Zusammensetzungen werden meist in rasch zerfallenden festen Arzneiformen eingesetzt und haben selbst keinen retardierenden Effekt auf die Wirkstofffreisetzung.

Die Herstellung fester Arzneiformen mit verzögerter Wirkstofffreigabe kann durch verschiedene Maßnahmen erreicht werden. Dazu zählen vor allem das Überziehen der Arzneiform mit einer Diffusionsbarriere, meist einem Polymer und die Herstellung von Matrix-Systemen (z.B. Tabletten) auf der Basis wasserunlöslicher oder wasserlöslicher Trägermaterialien (Hilfsstoffe, welche die Wirkstofffreisetzung retardieren). Bei den letztgenannten Systemen werden der Wirkstoff und die Hilfsstoffe mit dem Trägermaterial gemischt und in eine feste Arzneiform, meist Tabletten, verarbeitet. Das Trägermaterial ist für die Verzögerung der Wirkstofffreisetzung verantwortlich. Als wasserlösliche Trägermaterialen werden unter anderem Cellulosederivate wie Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC) oder Polyethylenoxide eingesetzt. Diese Polymere quellen in Kontakt mit wäßrigen Medien. Der Arzneistoff wird z.B. aus Tabletten entweder durch Erosion der Gelschicht und/oder durch Diffusion durch die Gelschicht verzögert freigesetzt.

Den Trägermaterialien fehlen meist die oben beschriebenen idealen Tablettiereigenschaften, wie z.B. gute Fließeigenschaften oder Komprimierbarkeit. Die Tabletten werden daher meist über Granulierverfahren und unter Zusatz von Hilfsstoffen hergestellt.

Aufgabe der Erfindung ist es daher, Kombinationen des Trägermaterials mit geeigneten Hilfsstoffen zu entwikkeln, welche die genannten Anforderungen weitgehend erfüllen und eine Direkttablettierung mit dem Wirkstoff erlauben.

Die Aufgabe wird dadurch gelöst, daß eine Zusammensetzung zur Verfügung gestellt wird, welche aus einer innigen Mischung eines Hilfsstoffes und einem Trägermaterial besteht und die Wirkstofffreisetzung aus Zubereitungen retardiert.

Während die bekannten Hilfsstoff-Kombinationen die Wirkstofffreisetzung nicht oder nur unerheblich retardieren, sind die erfindungsgemäßen neuen Hilfsstoff-Trägermaterial-Kombinationen Zusammensetzungen, welche die Wirkstofffreisetzung verzögern.

Erfindungsgemäß ist vorgesehen, daß das Trägermaterial retardierende Eigenschaften aufweist.

Erfindungsgemäß bevorzugt ist es, daß das Trägermaterial ein hydrophiles Polymer, ein Cellulosederivat, Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Polyethylenoxid und/oder ein Vinylderivat (z.B. Polyvinylpyrrolidon, Polyvinylalkohol, Polyvinylacetate oder Copolymere) ist.

Erfindungsgemäß bevorzugt ist es, daß der Hilfsstoff ein Füllstoff ist. Besonders bevorzugt ist es dabei, daß der Hilfsstoff Cellulose oder mikrokristalline Cellulose, ein Zucker oder Zuckeralkohol, wie Sorbit oder Mannit, Lactose und/oder ein Calciumsalz ist.

Bevorzugt ist es ferner, daß weitere Hilfsstoffe vor der Herstellung der Zusammensetzung zugegeben werden.

Erfindungsgemäß ist es ferner, daß die Zusammensetzung in wesentlich frei von Wirkstoffen ist und ein retardierendes hydrophiles oder hydrophobes Trägermaterial und einen Hilfsstoff ausgewählt aus der Gruppe bestehend aus Cellulosen, Kohlenhydraten, Calciumsalzen oder Polyolen enthält, wobei das Trägermaterial und der Hilfsstoff in einem derartigen Verhältnis vorliegen, daß eine verzögerte Freisetzung eines Wirkstoffes erzielt wird, wenn man den Wirkstoff mit der Zusammensetzung formuliert.

Insbesondere bevorzugt ist es dabei, daß das retardierende Material aus der Gruppe bestehend aus Polyethylenoxid, Hydroxypropylmethylcellulose, Hydroxymethylcellulose, Acrylatpolymeren, Fetten, Wachsen, hydrierten Pflanzenölen, Lipiden, Fettsäuren, Fettalkoholen oder aus Kombinationen von zwei oder mehreren dieser Materialien ausgewählt ist.

Weiterhin bevorzugt ist es, daß das retardierende Material Polyethylenoxid umfaßt.

Bevorzugt sind ferner erfindungsgemäße Ausführungsformen, wobei das retardierende Material etwa 10 bis 90 Gew.-% der retardierenden Zusammensetzung umfaßt, besonders bevorzugt etwa 15 bis 35 Gew.-% der retardierenden Zusammensetzung umfaßt, insbesondere bevorzugt etwa 15 bis 85 Gew.-% der Zusammensetzung umfaßt. Ganz besonders bevorzugt ist es, daß das Polyethylenoxid etwa 20 Gew.-% der Zusammensetzung umfaßt.

Weiterhin bevorzugt ist es, daß der Hilfsstoff mikrokristalline Cellulose ist. Besonders bevorzugt ist hierbei, daß die mikrokristalline Cellulose etwa 15 bis 95 Gew.-%

der Zusammensetzung umfaßt, insbesondere etwa 65 bis 95 Gew.-% der Zusammensetzung umfaßt und ganz besonders bevorzugt etwa 70 Gew.-% der Zusammensetzung umfaßt.

Bevorzugterweise sind erfindungsgemäße Ausführungsformen, wobei das Wachs hydriertes Pflanzenöl, Glycerin, Carnaubawachs, Bienenwachs, ein Acrylatpolymer oder eine Mischung von zwei oder mehreren der genannten Stoffe ist. Hierbei ist es ferner bevorzugt, daß das Fett ein Monoglycerid, ein Diglycerid, ein Triglycerid oder eine Mischung von zwei oder mehreren der genannten Stoffe ist. Bevorzugt ist außerdem, daß das Polyol Xylit, Mannit, Sorbit oder eine Mischung aus zwei oder mehreren der genannten Stoffe ist. Ganz besonders bevorzugt ist es, daß das Wachs hydriertes Pflanzenöl ist.

Bevorzugt sind erfindungsgemäße Zusammensetzungen, die als Pulver oder Granulat vorliegen. Auch ist bevorzugt, daß das Wachs Glycerin ist.

Erfindungsgemäß bevorzugt ist es ferner, daß der Hilfsstoff mikrokristalline Cellulose ist und in einer Menge von etwa 50 Gew.-% in der Zusammensetzung vorliegt.

Bevorzugt ist auch, daß das retardierende Material eine wäßrige Polymerdispersion ist, insbesondere eine Cellulosepolymer oder eine Acrylatpolymerdispersion ist.

Ein weitere Gegenstand der vorliegenden Erfindung ist eine Zubereitung, enthaltend eine erfindungsgemäße Zusammensetzung. Dabei ist bevorzugt, daß die Zubereitung weiterhin mindestens einen Wirkstoff enthält.

Gegenstand der vorliegenden Erfindung ist auch eine Zubereitung, erhältlich durch Verpressen einer erfindungsge-

mäßen Zusammensetzung mit mindestens einem Wirkstoff und gegebenenfalls weiteren Hilfsstoffen.

Erfindungsgemäß ist die Freisetzung eines Wirkstoffes durch das Verhältnis von Wirkstoff zur erfindungsgemäßen Zusammensetzung kontrolliert und einstellbar.

Erfindungsgemäß ist es auch, daß man die Freisetzung eines Wirkstoffes durch das Verhältnis von Hilfsstoff zu Trägermaterial einer erfindungsgemäßen Zusammensetzung kontrolliert und einstellt. Erfindungsgemäß ist es ferner, daß man die Freisetzung eines Wirkstoffes durch Mischung zweier Zusammensetzungen gemäß Anspruch 1 mit voneinander unterschiedlichem Hilfsstoff-Trägermaterial-Verhältnis kontrolliert und einstellt.

Erfindungsgemäß ist es außerdem, daß man die Freisetzung eines Wirkstoffes durch Mischung zweier oder mehrerer Zusammensetzungen gemäß Anspruch 1 mit jeweils unterschiedlichen Trägermaterialien und/oder Hilfsstoffen kontrolliert und einstellt.

Ein weiterer Gegenstand der vorliegenden Erfindung ist auch ein Verfahren zur Herstellung einer erfindungsgemäßen Zubereitung, wobei man das retardierende Trägermaterial mit dem Hilfsstoff bei einer Temperatur trocken vermischt, bei welcher das retardierende Trägermaterial schmilzt oder erweicht, wobei man eine erfindungsgemäße Zusammensetzung erhält, und daß man der Zusammensetzung einen pharmakologisch wirksamen Stoff hinzufügt und vermischt und man die so erhaltene Mischung einer Schmelzextrusion unterwirft, wobei der Hilfsstoff der Zusammensetzung bei der Temperatur der Schmelzextrusion nicht schmilzt.

Bevorzugt ist es dabei, daß der Hilfsstoff ein Calciumsalz, ein Polyol oder ein Kohlenhydrat ist. Besonders bevorzugt ist es hierbei, daß man die Extrusion wasserfrei ausführt.

Die Herstellung der erfindungsgemäßen Zusammensetzungen erfolgt nach bekannten Methoden, z. B. durch Sprühgranulierung, Feuchtgranulierung, Extrusion oder Sprühtrocknung. Bei den erfindungsgemäßen Zusammensetzungen handelt es sich um eine innige Mischung der Hilfsstoffe und Trägermaterialien. Die Komponenten sind also in dieser Mischung in einem bestimmten Verhältnis fixiert und unterscheiden sich dadurch auch von einfachen physikalischen Mischungen der Einzelkomponenten. Es kann also nicht zur Entmischung während der weiteren Verarbeitung kommen, während physikalische Mischungen entmischbar sind.

Zu den Trägermaterialien zählen hydrophile Hilfsstoffe die in Kontakt mit wäßrigen Medien, z.B. Körperflüssigkeiten, die Wirkstofffreisetzung verzögern. Dazu gehören vor allem Polymere wie Cellulosederivate (z. B. Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose) Polysaccharide, Acrylatderivate, Polyethylenoxide, Vinylderivate (z.B. Polyvinylpyrrolidon, Polyvinylalkohol, Polyvinylacetate) und Derivate (z.B. vernetzte Polymere) oder Copolymere.

Die geeigneten Hilfsstoffe kommen in erster Linie aus der Gruppe der Füllstoffe. Füllstoffe wie mikrokristalline Cellulose, Cellulose, Dicalciumphosphat oder Lactose sind für die Tablettenherstellung weithin üblich. Als Füllstoffe können auch Zucker/Zuckeralkohole wie Saccharose, Mannit oder Sorbit verwendet werden. Es können auch Mischungen von Füllstoffen wie z. B. Lactose/mikrokristalline Cellulose verwendet werden.

Selbstverständlich können den Füllstoff-Trägermaterial-Mischungen auch noch andere Bestandteile zugesetzt werden, die während der Herstellung entsprechend mit eingearbeitet werden. Diese Bestandteile gehören zu den üblicherweise bei pharmazeutischen Zusammensetzungen verwendeten Hilfsstoffen, z. B. Schmiermittel, Gleitmittel, Geschmacksstoffe, Farbstoffe u.a.

Die Herstellung der Mischungen aus den verschiedenen Komponenten erfolgt nach bekannten Methoden, z. B. durch Sprühgranulierung, Feuchtgranulierung, Sprühtrocknung oder Extrusion.

Im Falle der Sprühgranulierung wird die Pulvermischung im Wirbelbett bei leicht erhöhter Temperatur vorgelegt und mit einer Flüssigkeit, meist Wasser oder Alkohol oder einer wäßrigen (organischen) Lösung eines entsprechenden Hilfsmittels besprüht, agglomeriert und dann getrocknet.

Zur Feuchtgranulierung mischt man beispielsweise den Hilfsstoff mit dem Trägermaterial in einem geeigneten Mischer, granuliert mit Wasser oder einer geeigneten Flüssigkeit und trocknet das Feuchtgut, nachdem es durch ein Sieb passiert wurde.

Bei den Granulierverfahren können die Hilfsstoffe und/oder Trägermaterialien oder Teilmengen auch in die Granulierflüssigkeit gegeben werden.

Bei der Sprühtrocknung wird eine flüssige Mischung der Komponenten in einer geeigneten Sprühvorrichtung bei erhöhten Temperaturen versprüht. Der Füllstoff kann dabei dispergiert (z. B. Cellulose, MCC oder Calciumsalze) oder gelöst (z. B. Lactose, Sorbit, Mannit) vorliegen.

Zur Retardierung der Freisetzung werden häufig HPMC-Typen mit hoher Molmasse eingesetzt. Diese HPMC-Typen bilden im Kontakt mit Wasser schon bei niedrigen Konzentrationen eine hochviskose Masse, die sich nur schwer verarbeiten läßt. Bei der Feuchtgranulierung wird daher meist nicht mit einer wäßrigen sondern mit einer alkoholischen Granulierflüssigkeit gearbeitet. Bei der Herstellung einer erfindungsgemäßen Zusammensetzung aus Füllstoff und HPMC, z.B. durch Sprühtrocknung, können daher nur sehr niedrig konzentrierte wäßrige HPMC-Lösungen versprüht werden. Alternativ kann mit organischen Lösungsmitteln und damit mit Dispersionen gearbeitet werden.

Ein besonderer Aspekt der Erfindung ist daher die Herstellung einer erfindungsgemäßen Zusammensetzung aus höherkonzentrierten wäßrigen Systemen von Celluloseethern wie HPMC. Die Löslichkeit von HPMC in Wasser nimmt mit steigender Temperatur ab. Bei erhöhten Temperaturen können höherkonzentrierte HPMC-Dispersionen hergestellt werden. HPMC ist also bei erhöhten Temperaturen überwiegend dispergiert und nicht mehr gelöst. Zusammen mit dem Füllstoff können nun höherkonzertrierte wäßrige Mischungen versprüht werden. Der Vorteil liegt in der Verarbeitung konzentrierterer flüssiger Systeme und damit kürzeren Prozeßzeiten und Kosteneinsparungen.

Bestimmte MCC- und Lactose-Typen werden industriell bereits durch Sprühtrocknung gewonnen. Das Trägermaterial könnte also den Hilfsstoffdispersionen oder -lösungen vor der Trocknung beigegeben werden.

Die Teilchengröße der Zusammensetzungen läßt sich durch entsprechende Auswahl der Prozeß- und Formulierungsparameter kontrollieren.

Die erfindungsgemäßen Mischungen haben bessere Tablettiereigenschaften als der reine Träger und zeichnen sich durch folgende Vorteile aus: gute Fließfähigkeit, gute Komprimierbarkeit, hohe Härte, geringer Abrieb. Durch die Vorabherstellung der innigen Mischung wird die nachfolgende Tablettierung durch Einsparung von Herstellungsschritten erleichtert.

Die erfindungsgemäßen Zusammensetzungen können dann mit dem Wirkstoff und anderen Hilfsstoffen vermischt werden und z.B. in eine Tablette verpreßt werden. Zu den Wirkstoffen zählen nieder- und höhermolekulare Arzneistoffe (z.B. auch Peptide, Proteine) zur human- und veterinärmedizinischen Anwendung und Substanzen, die in der Landwirtschaft, im Haushalt, in der Nahrungsmittel-, kosmetischen und chemischen Industrie und anderen Industriezweigen genutzt werden. Selbstverständlich können auch Kombinationen von Wirkstoffen verwendet werden.

Die Arzneistofffreisetzung aus Matrixsystemen basierend auf hydrophilen Trägermaterialien wird neben den Eigenschaften des Trägermaterials auch von den Eigenschaften des Wirkstoffes beeinflußt. Dazu zählen in erster Linie die notwendige Dosis und die Löslichkeit des Wirkstoffes. Um die gewünschten Freisetzungsprofile zu erhalten, kann der Wirkstoff mit erfindungsgemäßen Zusammensetzungen mit unterschiedlichem Hilfsstoff-Trägermaterial-Verhältnis verarbeitet werden. Die Freisetzung kann dabei durch das Hilfsstoff-Trägermaterial-Verhältnis variiert werden. Das für den jeweiligen Wirkstoff ideale Hilfsstoff-Trägermaterial Verhältnis kann auch durch Zusammenmischen zweier Hilfsstoff-Gemische unterschiedlicher Zusammensetzung erreicht werden, z.B. durch Mischen zweier mit Trägermaterial hoch und niedrig konzentrierten Zusammensetzungen.

Die neuen Tablettierhilfsstoffe können selbstverständlich auch in anderen Herstellungsverfahren von Retardsystemen eingesetzt werden, z.B. zur Pelletherstellung oder zur Befüllung von Kapseln.

Durch die nachfolgenden Beispiele wird die Erfindung erläutert, soll dadurch jedoch nicht eingeschränkt werden.

Beispiel 1

Der Hilfsstoff (z.B. Lactose, $Ca_3(PO)_4$ oder mikrokristalline Cellulose) und das Trägermaterial (Hydroxypropylmethylcellulose - HPMC K4M oder Polyethylenoxid - Polyox) werden mit einem wäßrigen oder alkoholisch-wäßrigen Medium in unterschiedlichen Verhältnissen feucht granuliert, durch ein Sieb gedrückt und anschließend zu Granulaten getrocknet.

Beispiel 2

Der Hilfsstoff (Lactose, $Ca_3(PO)_4$ oder mikrokristalline Cellulose) und das Trägermaterial (Hydroxypropylmethylcellulose - HPMC K4M) werden in heißem Wasser in einer Konzentration von 30% in unterschiedlichen Verhältnissen gelöst oder dispergiert und in einem Sprühtrockner bei einer Einlaßtemperatur von ca. 130 °C versprüht. Das getrocknete Agglomerat kann direkt verwendet werden.

Beispiel 3

Wie Beispiel 1, nur wurden die Granulate durch Sprühgranulierung in einem Sprühgranulator (Aeromatic) durch ein Top-Spray Verfahren hergestellt. Der Hilfsstoff (z.B. Lactose, $Ca_3(PO)_4$ oder mikrokristalline Cellulose) und das Trägermaterial (Hydroxypropylmethylcellulose - HPMC K4M oder Polyethylenoxid - Polyox) wurden vorgelegt und

durch Einsprühen der Lösungsmittel bei leicht erhöhten Temperaturen granuliert. Alternativ kann auch etwas Trägermaterial in die Granulierflüssigkeit eingearbeitet werden.

Beispiel 4

Das Beispiel beschreibt ein Verfahren zur Herstellung einer Zusammensetzung zur raschen Wirkstofffreisetzung unter Verwendung eines Schmelzextrusionsverfahrens.

Materialien:

	Gew.-%
MCC (mikrokristalline Cellulose)	82
Xylit	10
kreuzvernetztes PVP, Sprengmittel	5
Natriumstearylfumarat, Schmiermittel	3

Die Extrusion bei ca. 90 °C liefert rasch freisetzende Granulate enthaltend Füllstoffe, Bindemittel, Sprengmittel und Schmiermittel. Diese rasch freisetzenden Granulate werden dann mit trockenen Inhaltsstoffen nach Wahl, einschließlich Wirkstoffen, einem Gleitmittel und bei bestimmten Ausführungsformen der Erfindung gegebenenfalls mit erfindungsgemäßen Zusammensetzungen gemischt und zu Tabletten verpreßt.

Beispiel 5

Im folgenden wird eine exemplarische Liste von Füllstoffen wiedergegeben, welche in der Praxis erfindungsgemäß allein oder in Kombination mit den Zusammensetzungen der vorliegenden Erfindung verwendet werden können.

MCC (mikrokristalline Cellulose)
Calciumsulfat

Polyole (z.B. Mannit, Sorbit, Malit, Xylit)
Calciumphosphat
Calciumcarbonat
Dextrose, Lactose
Saccharose, Maltose
Fructose
Polysaccharide

Beispiel 6

Im folgenden wird eine exemplarische Liste von retardierenden Materialien wiedergegeben, welche in der Praxis der vorliegenden Erfindung verwendet werden können. Diese retardierenden Materialien, welche auch als Trägermaterial bezeichnet werden können, können erfindungsgemäß allein oder in Kombination mit anderen Trägermaterialien und/oder den Zusammensetzungen der vorliegenden Erfindung verwendet werden.

HPC
Polysaccharide
HPMC, Polyethylenoxid
Lipide und Triglyceride, Monoglyceride, Diglyceride
Wachse, Fettsäuren und hydrierte Pflanzenöle
Acrylatpolymere
Ethylcellulose
Carbomere (Carbopol® 97IP) Polycarbophil
HPMCAS und HPMCP

Andere Inhaltsstoffe:
Die Zusammensetzungen können ferner enthalten:0,1 bis 20% Zerfallsmittel oder Bindemittel (z. B. Natruimstärkeglycolut (Expoltab®, Prinojel®)
Natriumcroscarmellose (Ac-Di-Sol®)(Zerfallsmittel)
kreuzvernetztes PVP (Polyplasdone® XL10)

Veegum® und andere Tone, Stärken, Alginate, PVP und andere dem Fachmann bekannte Zerfallsmittel und Bindemittel.

Die erfindungsgemäße Zusammensetzung kann ferner Xylit, AHA's und andere wasserlösliche Materialien, Elektrolyten und Nichtelektrolyten enthalten, welche unterhalb 150 °C Schmelzen. Die Mittel wirken als porenbildende Stoffe in der erfindungsgemäßen Zusammensetzung.

Die erfindungsgemäße Zusammensetzung kann ferner Schmiermittel und Gleitmittel enthalten, welche den Fließvorgang in Tablettier- und Kapselfüllmaschinen unterstützen und auch ein gutes Fließen in Kapselzubereitungen fördern. Schmiermittel umfassen Magnesium- und Calciumstearat und Stearinsäure, Natriumstearlyfumarat und hydrierte Pflanzenöle.

Wichtige Inhaltsstoffe der Zusammensetzung:

1. HPC oder HPMC
2. MCC in einem Verhältnis 80:20 oder 50:50 (MCC:HPC oder MPMC:PE)in Kombination mit MCC im beschriebenen Verhältnis stellen eine beispielhafte Ausführungsform der erfindungsgemäßen Zusammensetzung dar.

Optionale Inhaltsstoffe:
Siliciumdioxid, Talkum, Stärke und Polyethylenglycol

Beispiel 7

Das Beispiel beschreibt ein Verfahren zur Anwendung bei der Schmelzextrusion der langsam freisetzenden Zusammensetzung.

Die Verfahrenstemperatur der Schmelzextrusion liegt typischerweise bei 60 bis 150 °C während 1 ½ bis 3 Minuten, abhängig von der Größe der Vorrichtung und der Chargen-

größe und den Eigenschaften der Stoffe der Pulvermischung.

Das Maß der Erosion und der verzögerten Freisetzung der Wirkstoffe aus einer Matrixtablette hängt vom Verhältnis der retardierenden Stoffe zu den Hilfsstoffen in der Zusammensetzung ab. Das Material wird ferner keinen hohen Temperaturen über längere Zeiträume ausgesetzt. Restfeuchte und Lösemittel sind daher nicht von Bedeutung.

Die Anwendung der Schmelzextrusion sichert eine hohe Gleichförmigkeit der Inhaltsstoffe in der Zusammensetzung, da eine zusätzlich Mischung in inneren des Extruders erfolgt. Entmischung, welche bei der direkten Verpressung auftritt, wird gleichfalls vermieden.

Die Vorteile der erfindungsgemäßen Zusammensetzung, welche mittel der Schmelzextrusion hergestellt werden, sind u. a.:

- kontinuierliches und rasches Verfahren
- keine Lösemittel oder Wasser
- durchführbar mit hohen Gehalten an Bindemitteln/retardierenden Stoffen
- Recycling und erneute Verarbeitung der Stoffe ist möglich
- anwendbar bei retardierenden Stoffen und Füllstoffen, wenn ein Inhaltsstoff bei der Verarbeitungstemperatur schmilzt oder erweicht
- gute Fließ- und physikalische Eigenschaften
- gleichförmige Verteilung der Komponenten in der fertigen Zusammensetzung
- Zusammensetzung ist trocken mischbar mit Wirkstoffpulver und -granulat
- weitere in der Tablettenformulierung enthaltene inaktive Stoffe können sein:
  Füllstoffe

Bindemittel
Zerfallsmittel
Farbstoffe
Puffer
Gleitmittel
Schmiermittel

Zusätzliche Schmiermittel oder Zerfallsstoffe können der Zusammensetzung gleichzeitig zusammen mit dem Wirkstoff oder der erfindungsgemäßen Zusammensetzung zugesetzt werden.

Beispiel 8

Sprühgranulations-, Sprühtrocknungs- und Feuchtgarnulationsverfahren

Die Verbindungen können mit Hilfe der dem Fachmann bekannten klassischen Verfahren zur Herstellung pharmazeutischen Formulierungen im Lichte der vorliegenden Offenbarung hergestellt werden. Derartige Verfahren umfassen beispielsweise Feucht- oder Sprühgranulation, Sprühtrocknung, Sprüherstarrung, Schmelzgranulation oder Kaltextrusion.

Bei der Sprühgranulation wird die Pulvermischung, bestehend aus dem retardierenden Trägermaterial und der Hilfsstoff in einem fluidisierten Bett mit einem Lösemittel/Lösemittelgemisch (z. B. Wasser oder Alkohol) granuliert. Ein Bindemittel oder das retardierende Trägermaterial oder Teile davon können dem Lösemittel/Lösemittelgemisch zugegeben werden.

Bei der Sprühtrocknung wird eine flüssige Lösung oder Dispersion der Komponenten durch Einsprühen in eine beheizte Luftkammer und Entfernung des Lösemittels in die

trocknen Komponenten überführt. Verschiedene direkt verpreßbare Zusammensetzungen (z. B. MCC, Lactose) wurden durch eine Sprühtrocknung hergestellt. Die Zusammensetzungen können durch Zugabe der Komponenten zur Flüssigkeit vor dem Versprühen hergestellt werden.

Bei der Schmelzgranulation wird das geschmolzene Trägermaterial mit anderen Hilfsstoffen gemischt und in einer beheizten Kammer zusammengegeben und dann gekühlt und gemahlen. Bei der Sprüherstarrung wird das geschmolzene Trägermaterial mit den anderen Hilfsstoffen dispergiert und dann in Partikel versprüht und gekühlt.

Bei der Sprüherstarrung wird der Hilfsstoff zum geschmolzenen retardierenden Trägermaterial hinzugefügt, gefolgt von der Sprüherstarrung der Masse in Partikel.

Lipide (Wachse, Triglyceride und dergleichen) könnten in die langsam freisetzende Zusammensetzung in Form eines Pulvers oder einer heißen Schmelze eingefügt werden, wobei die Zusammensetzung mit der heißen Schmelze granuliert wird.

Bei den wäßrigen Polymerdispersionen werden die Hilfsstoffe in der Dispersionsmischung gelöst oder dispergiert, gefolgt von einer Sprühtrocknung, oder der Hilfsstoff wird mit der Polymerdispersion granuliert. Plastifizierungsmittel können zur Spaltung der Polymerpartikel zugesetzt werden. Geeignete Polymerdispersionen enthalten entweder Celluluse- (Ethylcelluluose in Aquacoat oder Surelease) oder Acryl- (Eudragit) Polymere.

Die erfindungsgemäße Zusammensetzung besteht aus einer innigen Mischung des retardierenden Materials und des Hilfsstoffs in einem festgelegten Verhältnis. Diese Zu-

sammensetzungen entmischen sich nicht im Vergleich mit physikalischen Mischungen.

Die erfindungsgemäßen Zusammensetzungen weisen bessere Tablettierungseigenschaften auf, als die reinen retardierenden Materialien, einschließlich Fließverhalten, Kompressibilität, Härte und Abrieb.

Sprühtrocknung und Feuchtgranulation sind gebräuchliche Verfahren in der pharmazeutischen Industrie, um Granulate zum Verpressen zu Tabletten herzustellen. Da Tablettenformulierungen viele Komponenten enthalten, ermöglicht die erfindungsgemäße Zusammensetzung die Herstellung eines Granulats durch physikalisches Mischen des Wirkstoffs mit einer erfindungsgemäßen Zusammensetzung unter anschließendem Verpressen der Mischung zu einer langsam freisetzenden Matrixtablette.

Die hier beschriebenen Zusammensetzungen und Verfahren können vom Fachmann in einfacher Weise ohne großen experimentellen Aufwand nachvollzogen werden. Neben den ausführlich beschriebenen bevorzugten Ausführungsformen kann der Fachmann diese verändern und anpassen, ohne damit die erfinderische Idee zu verlassen. Es ist klar, daß neben den beschriebenen und verwendeten Materialien auch solche, dem Fachmann geläufige, verwendet werden können, die zu den gleichen oder vergleichbaren Ergebnissen führen und unter den Umfang der vorliegenden Erfindung fallen.

Patentansprüche

1. Zusammensetzung, dadurch gekennzeichnet, daß sie
a) aus einer innigen Mischung eines Hilfsstoffes und einem Trägermaterial besteht und
b) die Wirkstofffreisetzung aus Zubereitungen retardiert.

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß das Trägermaterial retardierende Eigenschaften aufweist.

3. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial ein hydrophiles Polymer ist.

4. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial ein Cellulosederivat ist.

5. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial Hydroxypropylmethylcellulose ist.

6. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial Hydroxypropylcellulose ist.

7. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial Polyethylenoxid ist.

8. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Trägermaterial ein Vinylderivat (z.B. Polyvinylpyrro-

lidon, Polyvinylalkohol, Polyvinylacetate oder Copolymere) ist.

9. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hilfsstoff ein Füllstoff ist.

10. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hilfsstoff Cellulose oder mikrokristalline Cellulose ist.

11. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hilfsstoff ein Zucker oder Zuckeralkohol, wie Sorbit oder Mannit ist.

12. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hilfsstoff Lactose ist.

13. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hilfsstoff ein Calciumsalz ist.

14. Zusammensetzung nach einem oder mehreren der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß weitere Hilfsstoffe vor der Herstellung der Zusammensetzung zugegeben werden.

15. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß die Zusammensetzung in wesentlich frei von Wirkstoffen ist und ein retardierendes hydrophiles oder hydrophobes Trägermaterial und einen Hilfsstoff ausgewählt aus der Gruppe bestehend aus Cellulosen, Kohlenhydraten, Calciumsalzen oder Polyolen enthält,

wobei das Trägermaterial und der Hilfsstoff in einem derartigen Verhältnis vorliegen, daß eine verzögerte Freisetzung eines Wirkstoffes erzielt wird, wenn man den Wirkstoff mit der Zusammensetzung formuliert.

16. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß das retardierende Material aus der Gruppe bestehend aus Polyethylenoxid, Hydroxypropylmethylcellulose, Hydroxymethylcellulose, Acrylatpolymeren, Fetten, Wachsen, hydrierten Pflanzenölen, Lipiden, Fettsäuren, Fettalkoholen oder aus Kombinationen von zwei oder mehreren dieser Materialien ausgewählt ist.

17. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß das retardierende Material Polyethylenoxid umfaßt.

18. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß das retardierende Material etwa 10 bis 90 Gew.-% der retardierenden Zusammensetzung umfaßt.

19. Zusammensetzung nach Anspruch 18, dadurch gekennzeichnet, daß das retardierende Material etwa 15 bis 35 Gew.-% der retardierenden Zusammensetzung umfaßt.

20. Zusammensetzung nach Anspruch 19, dadurch gekennzeichnet, daß das retardierende Material etwa 15 bis 85 Gew.-% der Zusammensetzung umfaßt.

21. Zusammensetzung nach Anspruch 17, dadurch gekennzeichnet, daß das Polyethylenoxid etwa 20 Gew.-% der Zusammensetzung umfaßt.

22. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß der Hilfsstoff mikrokristalline Cellulose ist.

23. Zusammensetzung nach Anspruch 22, dadurch gekennzeichnet, daß die mikrokristalline Cellulose etwa 15 bis 95 Gew.-% der Zusammensetzung umfaßt.

24. Zusammensetzung nach Anspruch 23, dadurch gekennzeichnet, daß die mikrokristalline Cellulose etwa 65 bis 95 Gew.-% der Zusammensetzung umfaßt.

25. Zusammensetzung nach Anspruch 24, dadurch gekennzeichnet, daß die mikrokristalline Cellulose etwa 70 Gew.-% der Zusammensetzung umfaßt.

26. Zusammensetzung nach Anspruch 16, dadurch gekennzeichnet, daß das Wachs hydriertes Pflanzenöl, Glycerin, Carnaubawachs, Bienenwachs, ein Acrylpolymer oder eine Mischung von zwei oder mehreren der genannten Stoffe ist.

27. Zusammensetzung nach Anspruch 15 oder 17, dadurch gekennzeichnet, daß das Fett ein Monoglycerid, ein Diglycerid, ein Triglycerid oder eine Mischung von zwei oder mehreren der genannten Stoffe ist.

28. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß das Polyol Xylit, Mannit, Sorbit oder eine Mischung aus zwei oder mehreren der genannten Stoffe ist.

29. Zusammensetzung nach Anspruch 16, dadurch gekennzeichnet, daß das Wachs hydriertes Pflanzenöl ist.

30. Zusammensetzung nach Anspruch 16, dadurch gekennzeichnet, daß diese als Pulver oder Granulat vorliegt.

31. Zusammensetzung nach Anspruch 16, dadurch gekennzeichnet, daß das Wachs Glycerin ist.

32. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß der Hilfsstoff mikrokristalline Cellulose ist und in einer Menge von etwa 50 Gew.-% in der Zusammensetzung vorliegt.

33. Zusammensetzung nach Anspruch 15, dadurch gekennzeichnet, daß das retardierende Material eine wäßrige Polymerdispersion ist.

34. Zusammensetzung nach Anspruch 33, dadurch gekennzeichnet, daß die wäßrige Polymerdispersion eine Cellulosepolymer oder eine Acrylatpolymerdispersion ist.

35. Verfahren zur Herstellung einer Zusammensetzung nach Anspruch 1, in dem man das Trägermaterial und den Hilfsstoff in inniger Weise mischt.

36. Verfahren nach Anspruch 35, dadurch gekennzeichnet, daß man eine Sprüh- oder Feuchtgranulierung durchführt.

37. Verfahren nach Anspruch 35, dadurch gekennzeichnet, daß man eine Extrusion durchführt.

38. Verfahren nach Anspruch 35, dadurch gekennzeichnet, daß man eine Sprühtrocknung durchführt.

39. Verfahren nach Anspruch 38, dadurch gekennzeichnet, daß man eine Lösung oder Dispersion des Hilfsstoffes

mit einem überwiegend dispergiertem Trägermaterial sprühtrocknet.

40. Verfahren nach einem oder mehreren der Ansprüche 35 bis 39, wobei als Flüssigkeit Wasser eingesetzt wird.

41. Verfahren nach einem oder mehreren der Ansprüche 35 bis 40, wobei eine Flüssigkeit eingesetzt wird, in der das Trägermaterial während der Herstellung der Zusammensetzung überwiegend nicht löslich ist.

42. Zubereitung, enthaltend eine Zusammensetzung nach Anspruch 1.

43. Zubereitung nach Anspruch 42, enthaltend weiterhin mindestens einen Wirkstoff.

44. Zubereitung nach einem der Ansprüche 42 oder 43, erhältlich durch Verpressen einer Zusammensetzung gemäß Anspruch 1 mit mindestens einem Wirkstoff und gegebenenfalls weiteren Hilfsstoffen.

45. Zubereitung nach einem oder mehreren der Ansprüche 42 bis 44, wobei die Freisetzung eines Wirkstoffes durch das Verhältnis von Wirkstoff zur Zusammensetzung gemäß Anspruch 1 kontrolliert und einstellbar ist.

46. Zubereitung nach einem oder mehreren der Ansprüche 42 bis 45, dadurch gekennzeichnet, daß man die Freisetzung eines Wirkstoffes durch das Verhältnis von Hilfsstoff zu Trägermaterial einer erfindungsgemäßen Zusammensetzung kontrolliert und einstellt.

47. Zubereitung nach einem oder mehreren der Ansprüche 42 bis 46, dadurch gekennzeichnet, daß man die Freisetzung eines Wirkstoffes durch Mischung zweier Zusam-

mensetzungen gemäß Anspruch 1 mit voneinander unterschiedlichem Hilfsstoff-Trägermaterial-Verhältnis kontrolliert und einstellt.

48. Zubereitung nach einem oder mehreren der Ansprüche 42 bis 47, dadurch gekennzeichnet, daß man die Freisetzung eines Wirkstoffes durch Mischung zweier oder mehrerer Zusammensetzungen gemäß Anspruch 1 mit jeweils unterschiedlichen Trägermaterialien und/oder Hilfsstoffen kontrolliert und einstellt.

49. Verfahren zur Herstellung einer Zubereitung nach Anspruch 42, dadurch gekennzeichnet, daß man das retardierende Trägermaterial mit dem Hilfsstoff bei einer Temperatur trocken vermischt, bei welcher das retardierende Trägermaterial schmilzt oder erweicht, wobei man eine Zusammensetzung gemäß Anspruch 1 erhält, und daß man der Zusammensetzung einen pharmakologisch wirksamen Stoff hinzufügt und vermischt und man die so erhaltene Mischung einer Schmelzextrusion unterwirft, wobei der Hilfsstoff der Zusammensetzung bei der Temperatur der Schmelzextrusion nicht schmilzt.

50. Verfahren gemäß Anspruch 49, dadurch gekennzeichnet, daß der Hilfsstoff ein Calciumsalz, ein Polyol oder ein Kohlenhydrat ist.

51. Verfahren nach einem der Ansprüche 49 oder 50, dadurch gekennzeichnet, daß man die Extrusion wasserfrei ausführt.

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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 : A61K 9/22 — A3

(11) Internationale Veröffentlichungsnummer: **WO 98/56359**

(43) Internationales Veröffentlichungsdatum: 17. Dezember 1998 (17.12.98)

(21) Internationales Aktenzeichen: PCT/DE98/01659

(22) Internationales Anmeldedatum: 12. Juni 1998 (12.06.98)

(30) Prioritätsdaten:

197 25 911.1	13. Juni 1997 (13.06.97)	DE
60/068,977	30. Dezember 1997 (30.12.97)	US

(71)(72) Anmelder und Erfinder: BODMEIER, Roland [DE/DE]; Ravenweg 18, D–14163 Berlin (DE). McGINITY, James, W. [US/US]; 4209 Dunning Lane, Austin, TX 78746 (US).

(74) Anwalt: SCHUBERT, Klemens; Im Schönower Park 1E, D–14167 Berlin (DE).

(81) Bestimmungsstaaten: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Veröffentlicht

Mit internationalem Recherchenbericht.

Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 18. März 1999 (18.03.99)

(54) Title: COMPOUNDS WHICH DELAY THE RELEASE OF ACTIVE SUBSTANCES

(54) Bezeichnung: ZUSAMMENSETZUNGEN, DIE DIE WIRKSTOFFFREISETZUNG VERZÖGERN

(57) Abstract

The invention relates to compounds which delay the release of active substances. The invention also relates to a method for the production thereof. The compounds are produced, for instance, by wet or spray granulation, spray drying or extrusion of a conventional filling material (e.g. microcrystalline cellulose or lactose) and a carrier material (hydroxypropylmethyl cellulose or polyethylene oxide). The inventive composition can be processed together with the active substance and other auxiliary agents into a solid medicament form, e.g. a tablet, which releases the active substance in a delayed manner.

(57) Zusammenfassung

Es werden Zusammensetzungen, welche die Wirkstofffreisetzung verzögern, sowie Verfahren zu ihrer Herstellung beschrieben. Die Zusammensetzungen werden z.B. durch Feucht– oder Sprühgranulierung, Sprühtrocknung oder Extrusion aus einem üblichen Füllstoff (z.B. mikrokristalline Cellulose oder Lactose) und einem Trägermaterial (z.B. Hydroxypropylmethylcellulose oder Polyethylenoxid) hergestellt. Diese erfindungsgemäße Zusammensetzung kann zusammen mit dem Wirkstoff und anderen Hilfsstoffen in eine feste Arzneiform, z.B. eine Tablette, verarbeitet werden, die den Wirkstoff verzögert freigibt.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DE 98/01659

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Y. KAWASHIMA ET AL.: "preparation of a directly tabletable controlled-release matrix filler with microcrystalline cellulose modified with hydroxypropylmethylcellulose" CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 41, no. 12, December 1993, pages 2156-2160, XP000422466 Tokyo (JP) see the whole document --- -/--	1-6,9, 10,15, 16, 18-20, 22-25, 30, 32-35, 38-46

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 January 1999	25/01/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DE 98/01659

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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INTERNATIONALER RECHERCHENBERICHT

Ir ationales Aktenzeichen
PCT/DE 98/01659

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K9/22

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	Y. KAWASHIMA ET AL.: "preparation of a directly tabletable controlled-release matrix filler with microcrystalline cellulose modified with hydroxypropylmethylcellulose" CHEMICAL & PHARMACEUTICAL BULLETIN, Bd. 41, Nr. 12, Dezember 1993, Seiten 2156-2160, XP000422466 Tokyo (JP) siehe das ganze Dokument --- -/--	1-6,9, 10,15, 16, 18-20, 22-25, 30, 32-35, 38-46

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

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Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/DE 98/01659

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie²	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	DATABASE WPI Week 9439 Derwent Publications Ltd., London, GB; AN 94-313633 XP002090093 & JP 06 239764 A (SHINETSU CHEM IND CO LTD), 30. August 1994 siehe Zusammenfassung ---	1-6,9, 10,15, 16, 18-20, 22-25, 30, 32-35, 38-46
X	EP 0 032 004 A (EURO-CELTIQUE S.A.) 15. Juli 1981 siehe Seite 1, Zeile 1 - Zeile 31 siehe Seite 28, Zeile 24 - Seite 30, Zeile 9 siehe Seite 31; Beispiel 1 ---	1,2,9, 15,16, 18-20, 30,35, 36,40-46
E	DE 196 51 734 A (MÜLLER) 2. Juli 1998 siehe das ganze Dokument siehe Spalte 6, Zeile 31 - Zeile 58 ---	1-6, 8-16, 18-20, 26,28, 30, 33-35, 38-46
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Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 1/00, 217/62, 217/48, 219/28, 219/22, C07D 207/06, 295/06, C07C 271/08, C07F 7/18, C07C 307/02, A61K 31/135, 31/325, 31/40, 31/435

A1

(11) International Publication Number: **WO 99/58478**

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/EP99/03212

(22) International Filing Date: 11 May 1999 (11.05.99)

(30) Priority Data:
98108608.5 12 May 1998 (12.05.98) EP

(71) Applicant *(for all designated States except US)*: SCHWARZ PHARMA AG [DE/DE]; Alfred–Nobel–Strasse 10, D–40789 Monheim (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MEESE, Claus [DE/DE]; Kreuzberger Strasse 50, D–40789 Monheim (DE). SPARF, Bengt [SE/SE]; Drottningstigen 6, S–142 65 Trångsund (SE).

(74) Agent: ALBRECHT, Thomas; Kraus & Weisert, Thomas–Wimmer–Ring 15, D–80539 Munich (DE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL DERIVATIVES OF 3,3–DIPHENYLPROPYLAMINES

(57) Abstract

The invention concerns novel derivatives of 3,3–diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

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Description

Novel derivatives of 3,3-diphenylpropylamines

The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions, but also the main part of the contractions in the overactive bladder resulting in symptoms such as urinary frequency, urgency and urge incontinence. For this reason, antimuscarinic drugs have been proposed for the treatment of bladder overactivity.

Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder overactivity. The effectiveness of oxybutynin has been demonstrated in several clinical studies, but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the most common experienced side effect which may be severe enough to

result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

Tolterodine is a new, potent and competitive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al., 1997, Tolterodine - a new bladder-selective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195-207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite are almost identical to those of tolterodine (Nilvebrant et al., 1997, Eur. J. Pharmacol. 327 (1997), 195-207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite gives a major contribution to the clinical effect in most patients.

WO 94/11337 proposes the active metabolite of tolterodine as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage com-

pared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

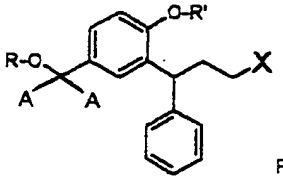
However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability, leading to pre-systemic side effects or interactions due to non-absorbed antimuscarinic drug. In a method to circumvent this disadvantage, different prodrugs of the metabolite have been synthesized and tested for their antimuscarinic activity, potential absorption through biological membranes and enzymatic cleavage.

It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is a further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption through biological membranes of the drugs or an unfavourable metabolism.

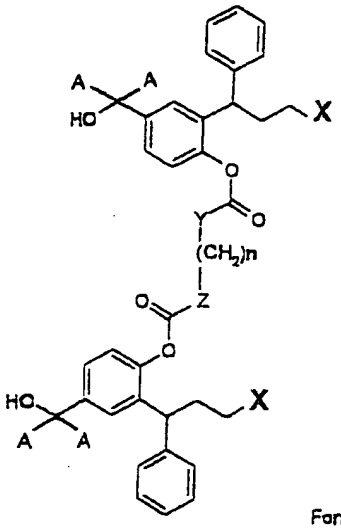
A further object of the invention is to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds

and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

According to the present invention, novel 3,3-diphenylpropylamines are provided, which are represented by the general formulae I and VII'



Formula I



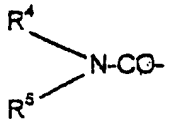
Formula VII'

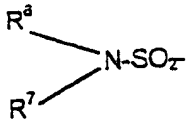
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

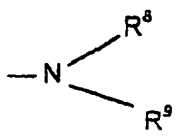
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unstubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

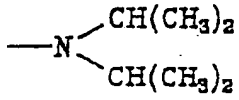
The aforementioned compounds can form salts with physiologically acceptable organic and inorganic acids. Furthermore, the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide and the like.

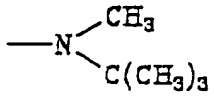
When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

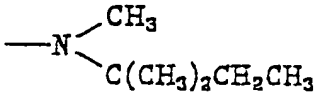
Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

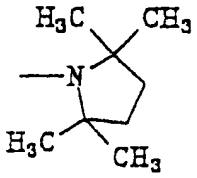
According to another embodiment of the invention, at least one of R^8 and R^9 comprises a branched carbon chain.

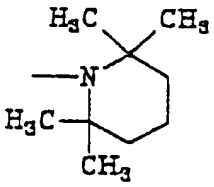
Presently preferred tertiary amino groups X in formula I include the following groups a) to h):

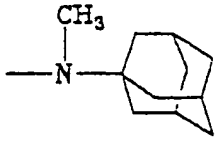
a) 

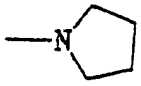
b) 

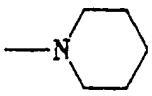
c) 

d) 

e) 

f) 

g) 

h) 

Group a) is particularly preferred.

The aforementioned tertiary amino groups X are described in WO 94/11337 and the compounds according to the present invention can be obtained by using the corresponding starting compounds.

In the compounds according to the present invention, the term "alkyl" preferably represents a straight-chain or branched-chain hydrocarbon group having 1 to 6 carbon atoms. Such hydrocarbon groups may be selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The term "cycloalkyl" denotes a cyclic hydrocarbon group having 3 to 10 carbon atoms which may be substituted conveniently.

The term "substituted or unsubstituted benzyl" denotes a benyl group $-CH_2-C_6H_5$ which is optionally substituted by one or more substituents on the phenyl ring. Suitable substituents are selected from alkyl, alkoxy, halogen, nitro and the like. Suitable halogen atoms are fluorine, chlorine and iodine atoms. Preferred substituted benzyl groups are 4-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 2-methoxybenzyl, 4-nitrobenzyl, 2-nitrobenzyl, 4-chlorobenzyl and 2-chlorobenzyl.

In the compounds according to the present invention the term "C_1-C_6 alkylcarbonyl" denotes a group R-C(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkylcarbonyl groups are selected from acetyl, propionyl, isobutyryl, butyryl, valeroyl and pivaloyl. The term "cycloalkylcarbonyl" denotes a group R-C(=O)- wherein R is a cyclic hydrocarbon group as defined hereinbefore. The same counts to the selected carbonyl groups.

The term "aryl" denotes an aromatic hydrocarbon group such as phenyl- (C_6H_5-), naphthyl- ($C_{10}H_7$-), anthryl- ($C_{14}H_9$-), etc. Preferred aryl groups according to the present invention are phenyl and naphthyl with phenyl being particularly preferred.

The term "benzoyl" denotes an acyl group of the formula -CO-C_6H_5 wherein the phenyl ring may have one or more substituents.

Preferred substituents of the aryl group and in particular of the phenyl group are selected from alkyl, alkoxy, halogen and *nitro*. As substituted benzoyl groups 4-methylbenzoyl, 2-methylbenzoyl, 4-methoxybenzoyl, 2-methoxybenzoyl, 4-chlorobenzoyl, 2-chlorobenzoyl, 4-nitrobenzoyl and 2-nitrobenzoyl may be mentioned.

The term "C_1-C_6 alkoxycarbonyl" refers to a group ROC(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkoxycarbonyl groups are selected from $CH_3OC(=O)$-, C_2H_5-OC(=O)-, $C_3H_7OC(=O)$- and $(CH_3)_3COC(=O)$- and alicyclic alkyloxycarbonyl.

The term "amino acid residue" denotes the residue of a naturally occurring or synthetic amino acid. Particularly preferred amino acid residues are selected from the group consisting of glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl.

The amino acid residue may be substituted by a suitable group and as substituted amino acid residues, benzoylglycyl and N-acetylglycyl may be mentioned.

The term "carbohydrate" denotes the residue of a polyhydroxy aldehyde or polyhydroxy ketone of the formula $C_nH_{2n}O_n$ or $C_n(H_2O)_n$ and correponding carbohydrate groups are, for example, described in Aspinal, The Polysaccharides, New York: Academic Press 1982, 1983. A preferred carbohydrate group in the compounds according to the present invention is a glucuronosyl group, in particular a 1β-D-glucuronosyl group.

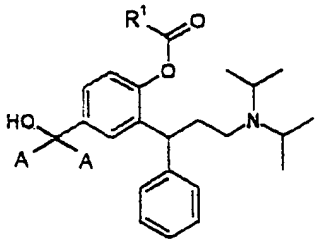
The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates, imidazolides and the like.

The term "Bn" as used herein denotes a benzyl group.

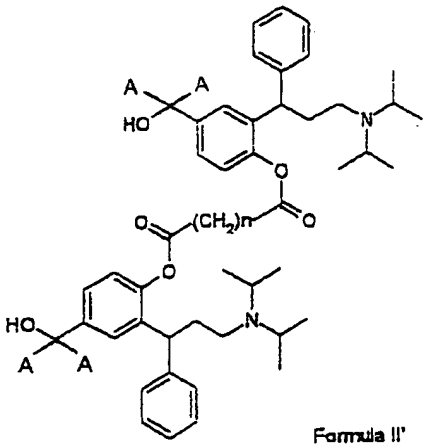
Suitable ester moieties of inorganic acids may be derived from inorganic acids such as sulfuric acid and phosphoric acid.

Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

Particularly preferred phenolic monoesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

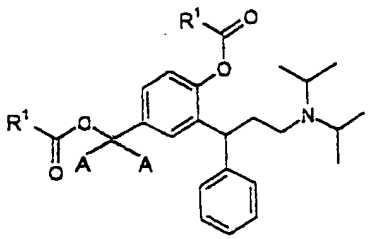
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

B) Identical diesters represented by the general formula III



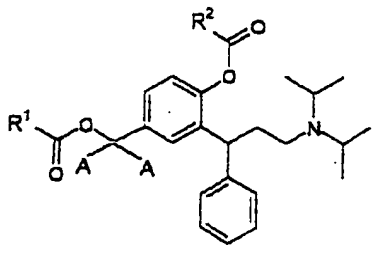
Formula III

wherein R^1 is as defined above.

Particularly preferred identical diesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diiso-propylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

C) Mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is as defined above

and

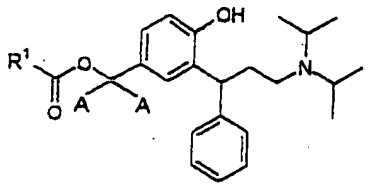
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

Particularly preferred mixed diesters are listed below:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diiso-propylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

D) Benzylic monoesters represented by the general formula V



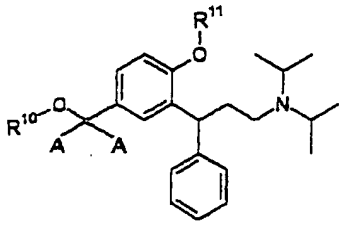
Formula V

wherein R^1 is as defined above.

Particularly preferred benzylic monoesters are listed below:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-propionic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

E) Ethers and silyl ethers represented by the general formula VI



Formula VI

wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined above and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

Particularly preferred ethers and silyl ethers are listed below:

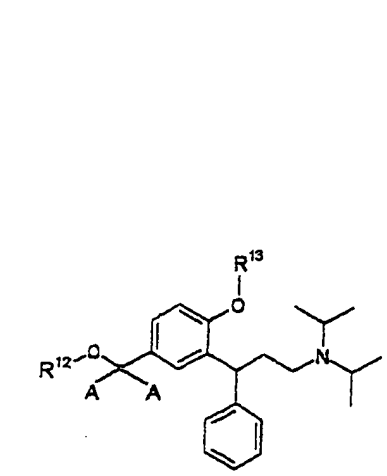
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,

(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,
(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

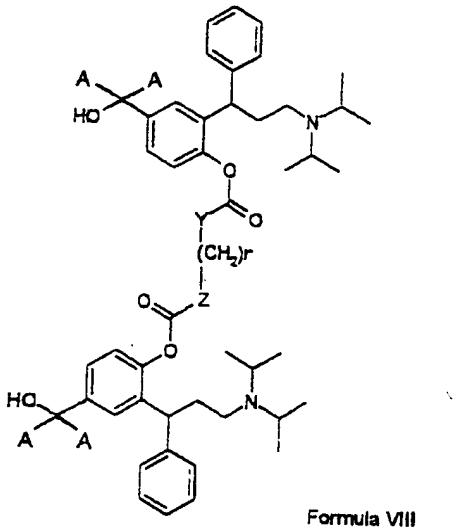
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

F) Carbonates and carbamates represented by the general formulae VII and VIII

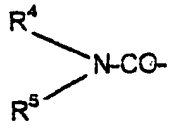


Formula VII



Formula VIII

wherein Y, Z and n are as defined above and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



wherein R^4 and R^5 are as defined above.

Particularly preferred carbonates and carbamates are listed below:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,

(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,

(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,

(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,

(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,

(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

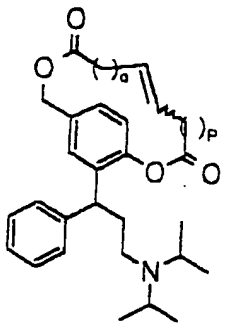
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,

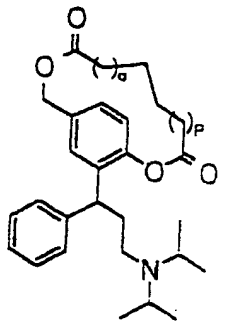
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



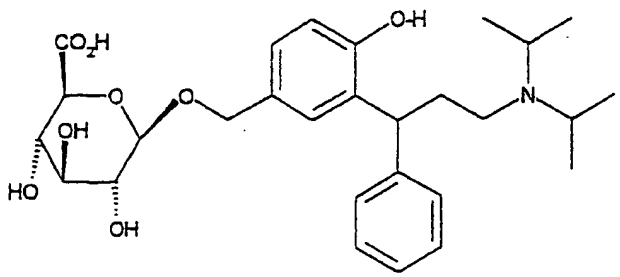
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $-CH_2-$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula

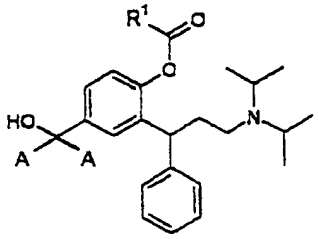


and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

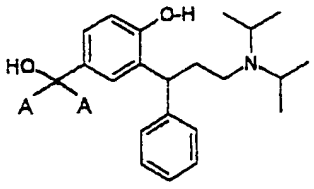
The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, the following processes are provided:

A process for the production of phenolic monoesters represented by the general formula II

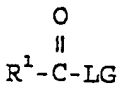


Formula II

as defined above, which comprises treatment of a compound of the formula

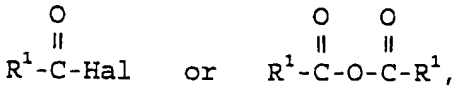


with an equivalent of an acylating agent selected from



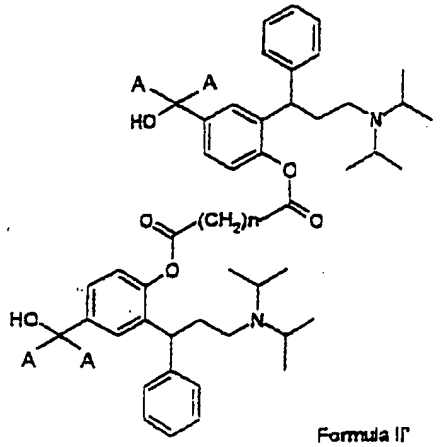
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined above, in an inert solvent in the presence of a condensating agent.

Preferably, the acylating agent is selected from



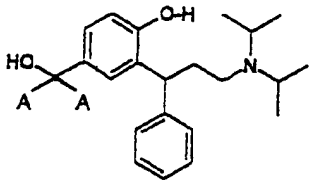
wherein Hal represents a halogen atom, preferably a chlorine atom, and R^1 is as defined above.

A process for the production of phenolic monoesters represented by the general formula II'

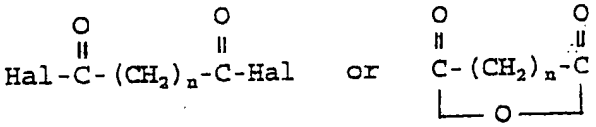


Formula II'

as defined above, which comprises treatment of two equivalents of a compound of the formula

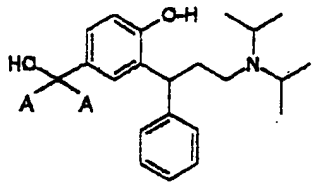


with an acylating agent selected from



wherein Hal represents a halogen atom, preferably a chlorine atom.

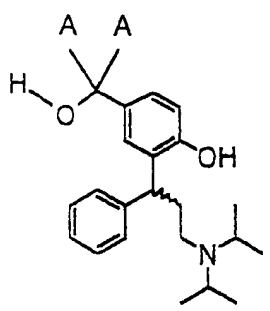
Hence, in these processes, an Intermediate B having the formula



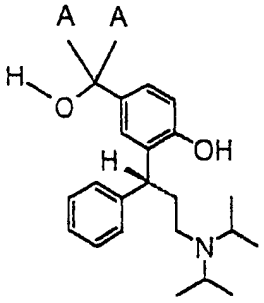
is treated with an equivalent of an acylating agent (e.g. an acyl halogenite or acyl anhydride) in an inert solvent and in the presence of a condensating agent (e.g. amine) to provide phenolic monoesters of formula II or formula II' (wherein n

is 0-12), respectively, if polyfunctional acylating agents (e.g. acid halides, preferably acid chlorides of dicarboxylic acids) are used.

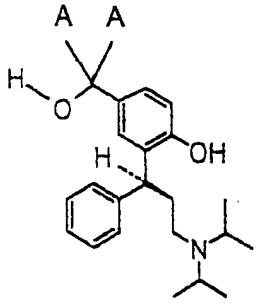
The Intermediate B as used in the processes for the production of the 3,3-diphenylpropylamines according to the present invention can be in the form of a racemic mixture or of optically active compounds in accordance with the formulae shown below:



Intermediate RS



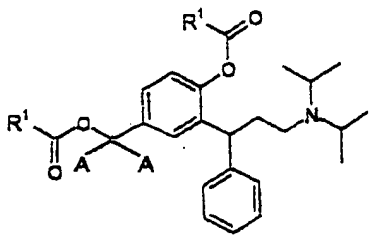
Intermediate R-(+)



Intermediate S-(-)

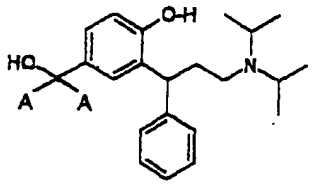
Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *"Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

The identical diesters represented by the general formula III



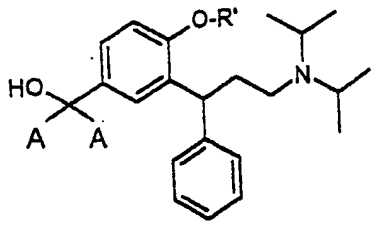
Formula III

as defined above can be prepared by a process which comprises treatment of a compound of the formula



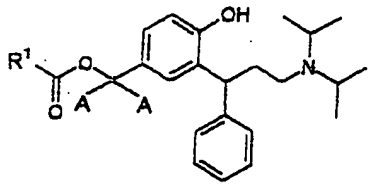
with at least two equivalents of the acylating agent R^1-C(=O)-LG as defined above.

Thus, the aforementioned di-acyl compounds are readily accessible if an at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In the above process, the following Intermediate A



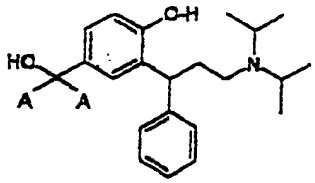
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

Benzylic monoestes represented by the general formula V



Formula V

wherein R^1 is as defined above can be prepared by a process which comprises treatment of a compound of the formula

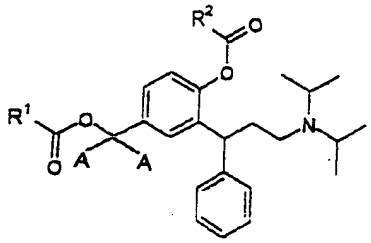


at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

Hence, this process relates to the preparation of phenols with *para* acyloxymethyl substituents (cf. formula V). These compounds can be prepared in several chemical steps from intermediates such as formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P.G.M. Wuts, "*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room tempera-

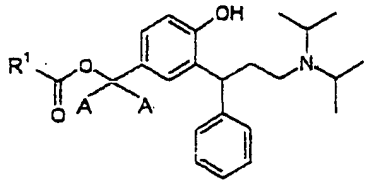
ture and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

The mixed diesters represented by the general formula IV



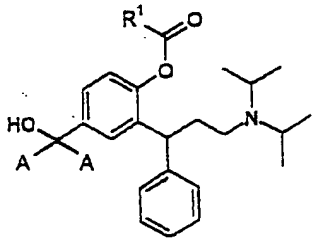
Formula IV

wherein R^1 and R^2 are as defined above can be prepared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V



Formula V

wherein R^1 is as defined above or of a phenolic monoester represented by the general formula II

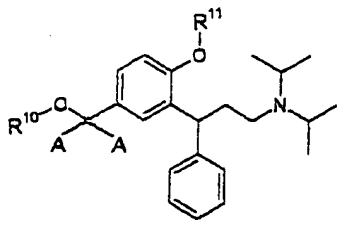


Formula II

as defined hereinbefore.

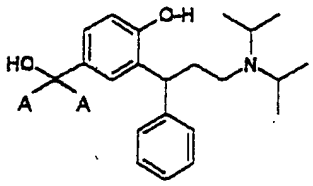
In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

Ethers represented by the general formula VI



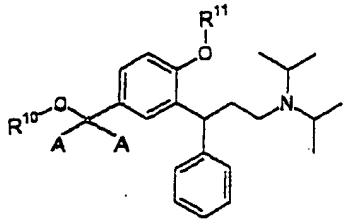
Formula VI

as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



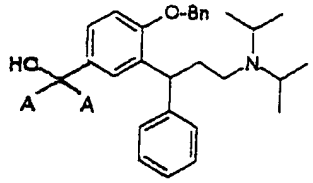
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

A further process for the preparation of ethers represented by the general formula VI

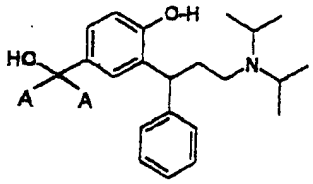


Formula VI

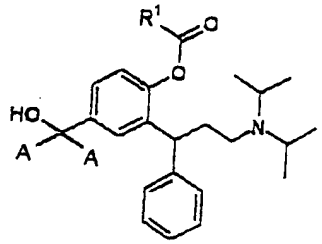
wherein R^{10} and R^{11} are as defined hereinbefore, comprises acid or base treatment of free benzylic alcohols selected from



and

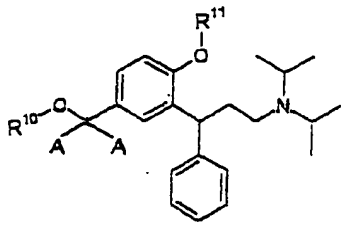


and



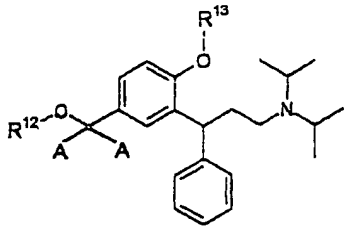
Formula II

or



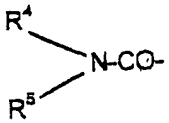
Formula VI

wherein R^{10} is hydrogen and R^{11} is as defined above or



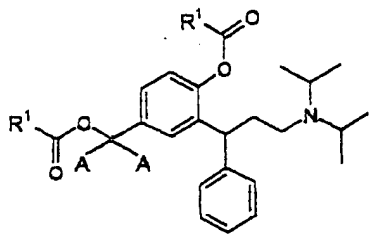
Formula VII

wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or

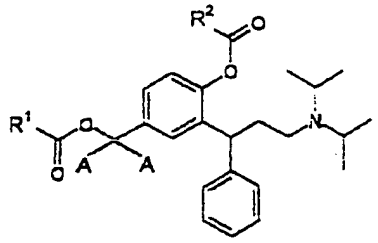


wherein R^4 and R^5 are as defined above

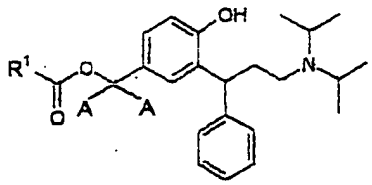
or of benzylic acylates selected from



Formula III



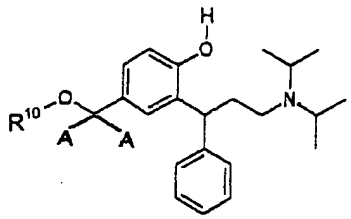
Formula IV



Formula V

wherein R^1 and R^2 are as defined hereinbefore in the presence of suitable hydroxy reagents.

Finally, ethers of formula VI can be prepared by a process which comprises treating a compound of the formula

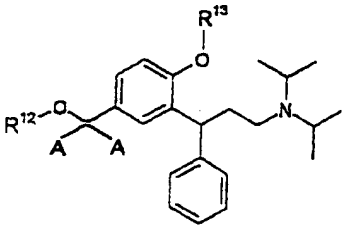


wherein R^{10} is as defined above with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

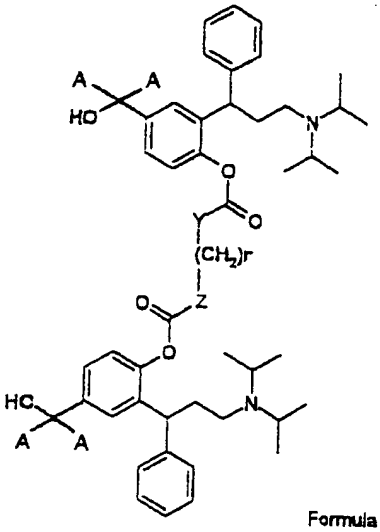
In summary, regioselective modification of the *benzylic hydroxy groups* is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J.M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P.M. Deya; J. Org. Chem. **53**: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or compounds of formulas II or VI (in which R^{10} is hydrogen) or formula VII (in which R^{12} is hydrogen) as well as benzylic acylates such as formulae III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. **30**: 1939-1942 [1989]).

Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^{11} = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis **1981**, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta **76**: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. **26**: 4307-4310 [1987]).

Carbonates and carbamates represented by the general formulae VII and VIII

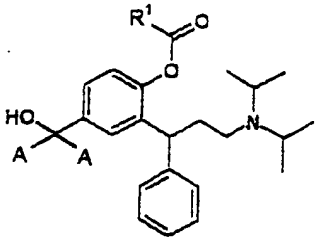


Formula VII

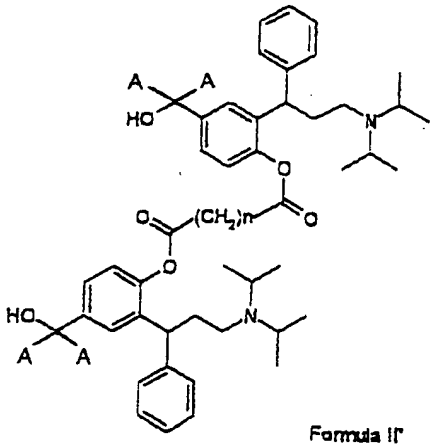


Formula VIII

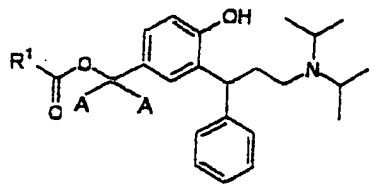
as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of



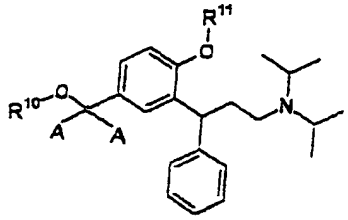
Formula II



Formula IT



Formula V



Formula VI

wherein R^1 is defined as above, n is 0 to 12, Bn is benzyl, R^{10} or R^{11} is hydrogen with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10°C to the refluxing temperature of the solvent or reagent used to provide compounds of the general formula VII where R^{12} represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and R^{13} represents $-C(=O)-Y-R^3$, wherein Y and R^3 represent O, S, NH and alkyl or aryl, respectively. Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of formula VIII where X, Y have the meaning of O, S, or NH and n is zero to twelve.

The invention, moreover, relates to pharmaceutical compositions comprising one or more of the aforementioned 3,3-diphenylpropylamines. In other words, the compounds according to the present invention can be used as pharmaceutically active substances, especially as antimuscarinic agents.

They can be used for preparing pharmaceutical formulations containing at least one of said compounds.

The compounds according to the present invention in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of claims 1 to 15 in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as water, gelatine, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in

the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0.05 mg to about 50 g each.

The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

I. Experimental

1. General

All compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy (Bruker DPX 200). The chemical shifts reported for ^{13}C NMR spectra (50 MHz, ppm values given) refer to the solvents $CDCl_3$ (77.10 ppm), dideuterio dichloromethane (CD_2Cl_2, 53.8 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm), respectively. ^{1}H NMR data (200 MHz, ppm) refer to internal tetramethylsilane).

Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution.
Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%); (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/triethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%); (7), cyclohexane/acetone/acetic acid (80/20/0.5, v/v-%).
Optical rotations were measured at 589.3 nm and room temperature on a Perkin Elmer Polarimeter Type 241.
Melting points (mp) reported are uncorrected and were determined on a Mettler FP 1 instrument.
IR spectra were taken from a Perkin-Elmer FTIR spectrometer Series 1610, resolution 4 cm^{-1}.
Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance (%) reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives.
Combined liquid chromatography-mass spectrometry (LC-MS): Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z values and relative abundance reported.

2. Synthesis of Intermediates A and B

3-Phenylacrylic acid 4-bromophenyl ester

An ice-cooled solution of 4-bromophenol (69.2 g) and cinnamoyl chloride (66.8 g) in dichloromethane (150 ml) was treated with triethylamine (40.6 g). After stirring for 18 hrs at

room temperature the mixture was washed with water (250 ml), 1 M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0 g, 99.8% yield), m.p. 113.3°C, tlc: (1) 0.83. NMR($CDCl_3$): 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

(±)-6-Bromo-4-phenylchroman-2-one

A portion of the ester (60.0 g) was dissolved in a mixture of acetic acid (60 ml) and concentrated sulphuric acid (18 ml) and refluxed for 2 hrs. After cooling, the reaction mixture was poured into ice water and the product was isolated by extraction with ethylacetate. Evaporation of the solvent and recrystallization of the residue from boiling ethanol (150 ml) yielded 26.3 g (43.8% yield) of pure, crystalline *(±)-6-bromo-4-phenylchroman-2-one*, m.p. 117.8°C, tlc: (1) 0.67. NMR ($CDCl_3$): 36.56, 40.51, 117.29, 118.87, 127.47, 127.89, 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester

A suspension consisting of (±)-6-bromo-4-phenylchroman-2-one (85.0 g), anhydrous potassium carbonate (46.7 g), sodium iodide (20.5 g) and benzyl chloride (40.6 g) in methanol (350 ml) and acetone (350 ml) was refluxed for 3 hrs. After evaporation of the solvents the residue was extracted with diethyl ether (2 x 300 ml) and the extract was washed with water (2 x 200 ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8 g (102.1% crude yield) of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* as a light yellow oil, tlc: (1) 0.77; NMR ($CDCl_3$): 39.22, 40.53, 51.63, 70.16, 113.10, 113.77, 126.46,

126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid

A solution of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* (0,391 g, 0,92 mmol) in ethanol (5 ml) was treated at 50°C with excess aqueous sodium hydroxide solution until the milky emulsion became clear. The reaction mixture was then acidified (pH 3), evaporated and extracted with dichloromethane. The organic extract was evaporated and the remaining oil was redissolved in a minimum of boiling ethanol. The precipitation formed after 18 hrs at 4°C was filtered off and dried in vacuo to yield 0,27 g (71.4%) of *(±)-3-(2-Benzyloxy)-5-bromophenyl)-3-phenylpropionic acid*, colourless crystals, m.p. 124.9°C; tlc: (1) 0.15 (starting material methyl ester 0.75); NMR ($CDCl_3$): 39.15, 40.26, 70.25, 113.21, 113.90, 126.62, 127.27, 127.98, 128.17, 128.47, 128.54, 130.46, 130.68, 134.34, 136.45, 142.16, 154.95, 177.65. LC-MS: 412/410 (14/11%, $M^{+\cdot}$), 394/392 (15/13%), 321/319 (17/22%), 304/302 (17/21%), 259 (24%), 194 (22%), 178 (21%), 167 (65%), 152 (49%), 92 (100%). IR (KBr): 3434, 3030, 1708, 1485, 1452, 1403, 1289, 1243, 1126, 1018, 804, 735, 698, 649. Calculated for $C_{22}H_{19}BrO_3$ (mol-wgt. 411.30): C 64.25%, H 4.66%, Br 19.43%, O 11.67%; found: C 63.72%, H 4.70%, Br 19.75%, O 11.80%.

Alternatively, the crude reaction mixture from the above described synthesis of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* was evaporated, redissolved in warm ethanol, and treated with excess aqueous potassium hydroxide solution. Acidification to pH 3 (conc. hydrochloric acid) and cooling to 4°C resulted in the formation of a solid, which was filtered off after 18 hrs, washed repeatedly

with water and dried to yield *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* in 82% yield.

a) **Resolution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid**

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
Warm solutions of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* (815.6 g, 1.85 mol) and 1S,2R-(+)-ephedrine hemihydrate (232.1 g, 1.85 mol) in 2000 ml and 700 ml, respectively, of absolute ethanol were combined and then allowed to cool to 0°C. The precipitate formed was collected, washed with cold ethanol and dried in vacuum to give 553.2 g of the ephedrinium salt of the title compound (m.p. 153°C, e.e. 65% as determined by NMR and HPLC). The salt was recrystallized twice from boiling ethanol to give *R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1S,2R-(+)-ephedrinium salt* in 75% yield, colourless crystalls, m.p. 158.6°C, e.e. 97.6% (HPLC). NMR ($CDCl_3$): 9.53, 30.90, 41.54, 42.83, 61.45, 70.15, 70.42, 113.05, 113.68, 125.89, 126.03, 127.33, 127.85, 128.19, 128.28, 128.45, 129.86, 130.70, 135.91, 136.65, 140.40, 144.09, 155.20, 178.94.

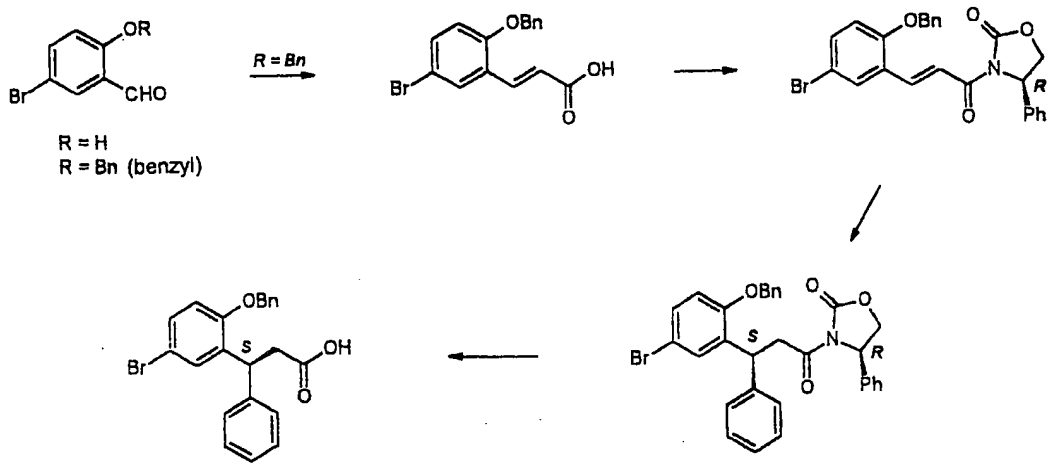
1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 ml) and dichloromethane (10 ml). The organic phase was separated, washed twice with water (2 ml), and evaporated to dryness to give *R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid* as a colourless oil which slowly solidified (0.4 g, 98% yield), m.p. 105.6°C (from ethyl acetate/n-

heptane); tlc: (7) 0.21; $[\alpha]_D^{20}$ = -21.1 (c = 1.0, ethanol), e.e. 99.9% (HPLC). NMR: identical with the racemic acid.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
The combined mother liquids from the above resolution and recrystallizations were treated under stirring and cooling (18°C) with excess conc. aqueous hydrochloric acid. The precipitate (ephedrinium hydrochloride) was filtered off, and the filtrate was evaporated to dryness. The residue was redissolved in dichloromethane (1.5 litre) and then washed with several portions of 1 M aqueous hydrochloric acid followed by water. After drying (Na_2SO_4), filtration, and evaporation 479 g of crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid were obtained as a yellow viscous oil. The pure S-(+) enantiomeric acid was converted into the 1R,2S-(-)-ephedrine salt as described above for the R-(-) acid. Two recrystallizations from boiling ethanol provided colourless crystals of *S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1R,2S-(-)-ephedrinium salt* in 83% yield, m.p. 158.7°C, e.e. 97.8% (HPLC). NMR ($CDCl_3$): 9.47, 30.85, 41.54, 42.92, 61.48, 70.13, 70.30, 113.04, 113.66, 125.89, 126.01, 127.32, 127.84, 128.18, 128.44, 129.83, 130.68, 135.94, 136.63, 140.44, 144.13, 155.19, 178.94.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid was obtained in quantitative yield from this ephedrinium salt by the method described above for the R-(-) acid, tlc: (7) 0.20, e.e. (NMR) > 99%, mp 105.5°C; $[\alpha]_D^{20}$ = +22.6 (c = 1.0, ethanol); NMR: identical with the racemic acid.

b) **Enantioselective Synthesis of R-(-)- and S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid**



2-Benzyloxy-5-bromobenzaldehyde

To a solution of 0.1 mol of 5-bromo-2-benzaldehyde in THF (150 ml) was added 0.1 mol of K_2CO_3 and 0.11 mol of benzyl bromide. The mixture was refluxed for 2 hrs and water (500 ml) was added. After addition of ethyl acetate (400 ml) and stirring the organic layer was washed with water, dried (sodium sulphate) and evaporated to dryness. The resulting slightly yellow solid of pure (tlc) 2-benzyloxy-5-bromo-benzaldehyde was used as such in the next step.

3-(2-Benzyloxy-5-bromophenyl)-acrylic acid

A mixture of 2-benzyloxy-5-bromobenzaldehyde (0.10 mol), malonic acid (15.0 g), and piperidine (2.0 ml) in 150 ml of pyridine was first heated at 90°C for 90 min and subsequently refluxed for 0.5 hrs. After cooling to room temperature, the reaction was poured on a mixture of ice (1 kg) and concentrated aqueous hydrochloric acid (250 ml). The solid

material that precipitated after stirring for 2 hrs. was collected by suction and recrystallized from a minimum of boiling methanol.

3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one

Pivaloylchloride (7 g) was added dropwise at -30°C to a stirred solution of 3-(2-benzyloxy-5-bromophenyl)-acrylic acid (50.0 mmol) and triethylamine (15.0 ml) in 200 ml of tetrahydrofuran. After an additional hour the temperature was lowered to -50°C and (R)-2-phenyloxazolidin-2-one (9.0 g) and lithium chloride (2.5 g) were added in one portion. The cooling bath was then removed and stirring was continued over 18 hrs. The reaction was diluted with water and 3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one was isolated by extraction with ethyl acetate.

3-[3-(2-Benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one

To a precooled (-30°C) mixture of copper-(I) chloride (21.0 g) and dimethylsulfide (45 ml) in dry tetrahydrofuran (150 ml) was added dropwise an ethereal solution of phenylmagnesiumbromide (0.3 mol). The mixture was stirred 20 min at the same temperature and then cooled to -40°C. A solution of 3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one (50.0 mmol) in dry tetrahydrofuran (150 ml) was added during 10 min. The cooling bath was removed and stirring was continued for 18 hrs. The mixture was quenched with half-saturated aqueous ammonium chloride solution and the product was isolated by extraction with ethyl acetate.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
A solution of the above described 3-[3-(2-benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one in tetrahydrofuran (300 ml) and water (100 ml) was cooled to 0°C and then treated with 30% aqueous hydrogen peroxide (20 ml) followed by solid lithium hydroxide (4.3 g). Water was added after 2 hrs and the chiral auxiliary was removed by extraction with ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (10%) and crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was extracted with tert.-butyl-methylether.

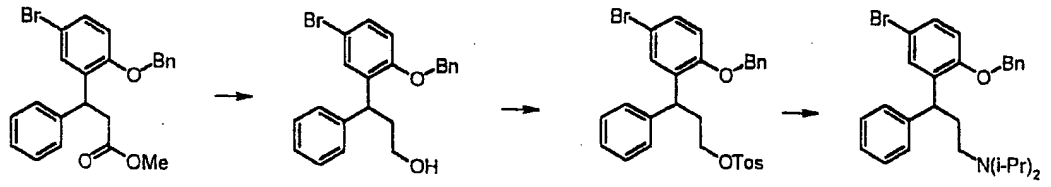
HPLC analysis (Chiralpak AD, mobile phase hexane/2-propanol/trifluoro acetic acid [92:8:0.1, vol/vol-%); flow 1.0 ml/min, detection 285 nm) indicated an enantiomeric ratio 93:7 (retention times 14.8 min and 11.5 min, respectively). The e.e. of 86% of the S-(+) enantiomer can be improved to >98.5% by recrystallization of the diastereomeric salts using "nitromix" (Angew. Chem. Int. Ed. Engl. 1998, Vol. 37, p. 2349) or (1R,2S)-(-)-ephedrine hemihydrate as described above. The S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was isolated after acidification of aqueous solutions of the diastereomeric salts. It forms colourless crystals which gave an optical rotation of $[\alpha]_D^{22}$ = +21.6 (c = 0.5, MeOH).

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
Conjugate organocuprate addition of phenylmagnesiumbromide to *3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4S)-4-phenoyloxazolidin-2-one* as described above for the S-(+)enantiomer gave crystalline R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid in an e.e. of 99.6% after two recrystalliza-

tions, $[\alpha]_D^{22}$ = -21.7 (c = 0.5, MeOH).

c) Synthesis of the R- and S- Enantiomers of Intermediate B

(i) Phenylpropanol Route



(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol

A solution of the methyl(±)-propionate (121.0 g) in 350 ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9 g) in tetrahydrofuran (350 ml). After stirring at room temperature for 18 hrs, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8 g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8°C, tlc: (1) 0.47, *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol*. NMR ($CDCl_3$): 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

The same product was obtained after reduction of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* with lithium aluminium hydride in tetrahydrofuran (30 min, 25°C), 31% yield.

(±)-Toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester

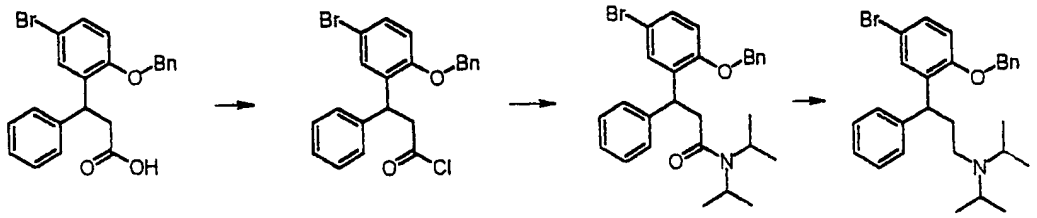
A cooled (5°C) solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0 g) in dichloromethane (300 ml) was treated with pyridine (79.4 ml) and then p-toluenesulphonyl chloride (60.6 g) in dichloromethane (200 ml). After 18 hrs. at room temperature the solvent was removed in vacuum and the residue was extracted with diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give *(±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester* as a light yellow oil after concentration under reduced pressure (140.3 g, 93.6% yield), tlc: (1) 0.66. NMR ($CDCl_3$): 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16, 155.07.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

A solution of the (±)-toluenesulphonate ((±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester, 139.3 g) in acetonitrile (230 ml) and N,N-diisopropylamine (256 g) was refluxed for 97 hrs. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500 ml) and aqueous sodium hydroxide (2 M, 240 ml). The organic phase was washed twice with water (250 ml) and then extracted with 1 M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500 ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *(±)-[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5 g, 77.9%

yield), tlc: (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70, 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

(ii) Phenylpropionamide Route



S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionyl chloride

Thionylchloride (4.5 g, 2.8 ml, 37.8 mmol) and some drops of dimethylformamide were added to a solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid (10.3 g, 25 mmol) in ethyl acetate (60 ml). The mixture was refluxed until tlc control indicated complete consumption of the starting material (2 hrs). Evaporation in vacuum gave the acid chloride as a light yellow liquid in almost quantitative yield (10.7 g). Conversion of an aliquot to the methyl ester showed a single spot in tlc (R_f 0.54, solvent system (7)).

S-(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

A solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionyl chloride (9.6 g, 22.3 mmol) in ethyl acetate (40 ml) was added dropwise to a stirred and cooled (3°C) solution of diisopropylamine (6.4 g, 49.0 mmol) in 60 ml of ethyl acetate. The reaction was stirred for 18 hrs at room temper-

ature and then washed with water, aqueous hydrochloric acid (1 M) and half saturated brine. The organic phase was dried (sodium sulphate) and evaporated to dryness. The colourless oily residue (10.7 g, 97% yield) of S-(+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide showed a single spot on tlc: (R_f 0.70 (4)). NMR ($CDCl_3$): 18.42, 20.46, 20.63, 20.98, 39.51, 41.44, 45.76, 48.63, 70.00, 112.84, 113.64, 126.10, 126.45, 127.34, 127.78, 128.20, 128.36. 129.93, 130.59, 135.18, 136.52, 143.52, 155.17, 169.61.

(±)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionamide

The amide was prepared from diisopropylamine and the racemic acid chloride as described above for the S-(+) enantiomer. The viscous colourless oil was dissolved in ethanol and the solution stored at -30°C. From this solution colourless crystals were obtained, m.p. 101.8°C.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diiso-propylamine

To a stirred solution of (±)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide (11.8 g) in 40 ml of dry tetrahydrofuran was added 1 M lithium aluminium hydride/tetrahydrofuran (36 ml). The reaction was refluxed for 4 hrs and then quenched with the dropwise addition of water. After removal of the precipitate the solvent was evaporated and the oily residue dissolved in diluted sulphuric acid. The aqueous phase was washed several times with diethyl ether, adjusted to pH 10-12 (aqueous NaOH), and extracted with diethyl ether. The extract was dried (sodium sulphate), filtered and evaporated to dryness in vacuum to leave 8.1 g (76.7%) of the title compound as a viscous colourless oil, tlc:(4) 0.86. The NMR spectrum corresponds to the product, obtained from the

tosylate precursor (see above).

S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = +18.5 (c = 10.0, ethanol), e.e. of a representative batch 99.4%

R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = -17.3 (c = 10.0, ethanol), e.e. of a representative batch 98.3%.

The optical purities were determined by chiral HPLC using Chiralpak OD columns.

(±)-4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride

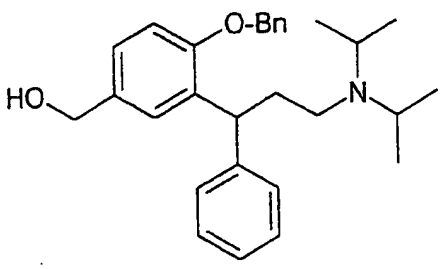
An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to -60°C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and the green reaction mixture was warmed to room temperature. After the addition of an aqueous solution of ammonium chloride (200 ml, 10%) and adjustment of the aqueous phase to

pH 0.95, a white solid was recovered by filtration to provide *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride* (14.7 g, 64.3% yield), m.p. 140°C (dec.), tlc: (2) 0.33. NMR (CD_3OD): 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol

Intermediate A (n = 1)

The (±)-hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free oily base thus obtained (28 g; tlc (2): R_f 0.46) was dissolved in dry diethyl ether (230 ml). This solution was slowly (2h) dropped under a nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8 g) in ether (140 ml). After stirring for 18 hrs, the reaction was quenched by the addition of water (4.7 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (26 g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4°C, tlc: (2) 0.32. NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



Intermediate A

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol

Intermediate d_2-A (n = 2)

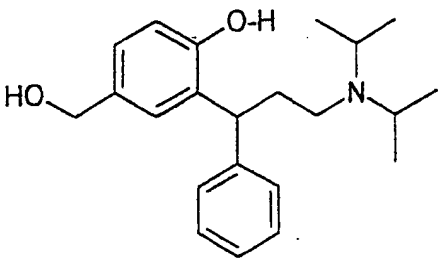
Repetition of the above described reduction of the methyl-ester of *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid* by the use of lithium aluminium deuteride gave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-[C^2H]methanol, colourless amorphous solid in 77% yield; tlc: (2) 0.33. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.96, 70.05, 111.76, 125.72, 127.34, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Intermediate B (n = 1)

A solution of Intermediate A (9.1 g) in methanol (100 ml) was hydrogenated over Raneynickel (4.5 g) under ambient conditions. After 5 hrs thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95 g, 96.5% yield) which gradually solidified, *(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol*, m.p. 50°C, tlc: (2) 0.15. NMR ($CDCl_3$): 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38.

Hydrochloride: colourless crystalls, m.p. 187-190°C (with decomposition)



Intermediate B

S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *S-(-)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 85% yield, colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol); NMR ($CDCl_3$): 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.

S-(+) hydrochloride: colourless, non-hygroscopic solid, m.p. 186.4°C (dec.); $[\alpha]_D^{22}$ = +6.6 (c = 0.5, water). NMR (DMSO-d_6): 16.58, 18.17, 31.62, 41.37, 45.90, 54.02, 63.07, 115.18, 126.05, 126.37, 128.03, 128.45, 129.04, 133.12, 143.88, 153.77.

R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 87% yield,

colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = +21.3 (c = 1.0, ethanol).

R-(-) hydrochloride: colourless, non-hygroscopic solid, m.p. 179.8°C (dec.); $[\alpha]_D^{22}$ = -7.2 (c = 0.5, water); NMR (DMSO-d_6): 16.59, 18.19, 31.64, 41.38, 45.92, 54.07, 63.08, 115.19, 126.07, 126.39, 128.04, 128.46, 129.05, 133.13, 143.89, 153.79.

S-(+)-mandelate: m.p. 139.7°C, $[\alpha]_D^{21}$ = +38.3 (c = 1.0, ethanol)

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

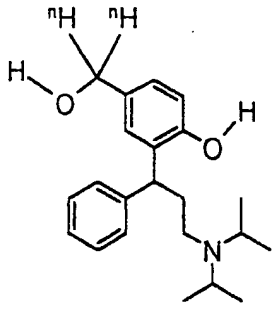
Intermediate d_2-B (n = 2)

A stirred suspension of lithium aluminium deuteride (0.1 g, 2.38 mmol) in 5 ml of dry diethyl ether was treated during 30 min at room temperature under an atmosphere of dry nitrogen with a solution of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid methyl ester (1.0 g, 2.17 mmol) in dry diethyl ether (5 ml). After an additional stirring at room temperature for 18 hrs the reaction was quenched by the dropwise addition of 0.17 ml of ^2H_2O. The resultant precipitation was filtered off, washed with small portions of ether, and the combined organic phases were evaporated to dryness in vacuum to leave

(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol

as slightly yellow, viscous oil which gradually crystallized, m.p. 84.1°C; tlc: (2) 0.33 (starting material 0.46), 0.725 g, 77.2% yield. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.30, 70.05, 111.76, 125.72, 125.94, 126.92, 127.34, 127.71, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

A solution of the above (±)-[4-benzyloxy-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol (0.129 g, 0.29 mmol) in a suspension of methanol (5 ml) and wet Raney-Nickel (0.1-0.2 g) was stirred at room temperature under an atmosphere of deuterium gas ($^2H_2$). After 1 hr tlc indicated complete disappearance of the starting material. The mixture was filtered, evaporated and the residue was redissolved in diethyl ether (5 ml). The solution was washed with water (2 x 5 ml), dried over sodium sulphate, filtered and evaporated to dryness to leave a pale yellow oil, 76.3 mg, in 74.6% yield, which gradually solidified to give a colourless solid of a m.p. range of 46-49°C. Tlc:(4) 0.57 (starting material 0.77). NMR ($CDCl_3$): 19.57, 19,94, 33.33, 39.56, 42.18, 48.07, 48.43, multiplett centred at 64.61, 118.47, 126.29, 126.58, 127.55, 127.94, 128.38, 132.53, 144.53, 155.37. GC-MS (P-CI, ammonia, TMS derivative): 488.43 (100%), 489.56 (70%), 490.56 (31%), 491.57 (8%).



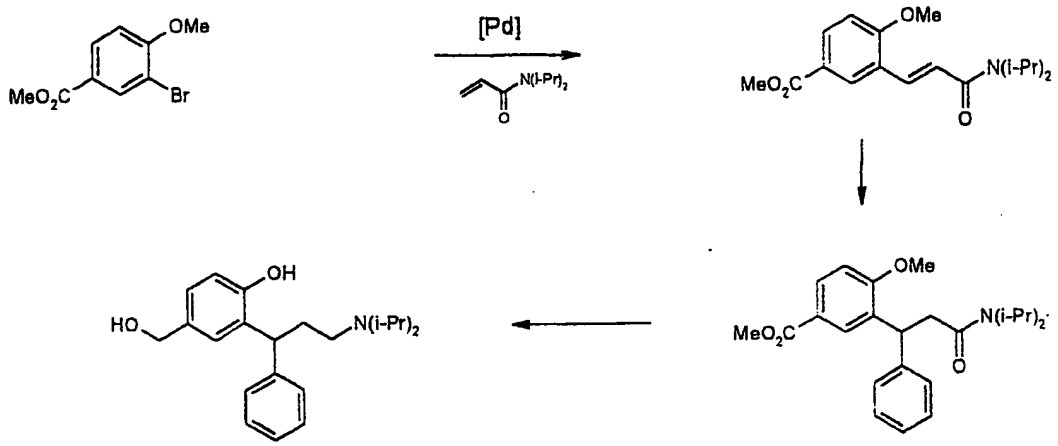
Intermediate d_2-B

n = 2, deuterium

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

Intermediate d_2-B

(iii) Heck-Cuprate-Route to Intermediate B



Intermediate B

N,N-Diisopropyl-acrylamide

A solution of acroyl chloride (42.2 g, 40.6 ml, 0.467 mol) in 125 ml of dichloromethane was slowly added to a cooled (0-5°C) solution of N,N-diisopropylamine in dichloromethane (500 ml). After 2 hrs the precipitated ammonium salt was filtered off and the filtrate was washed with 1M hydrochloric acid (3 x 100 ml), dried (sodium sulphate), and evaporated to dryness. N,N-diisopropyl-acrylamide was obtained as a slight yellow liquid in 48% yield and ca. 99% purity. NMR ($CDCl_3$): 20.54, 21.25, 45.66, 48.10, 125.62, 130.70, 166.17.

(E)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide

((E)-3-(2-Diisopropylcarbamoyl-vinyl)-4-methoxybenzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were

dried before use.

A stirred suspension consisting of N,N-dimethylglycine (6.0 mmol), anhydrous sodium acetate (40 mmol), methyl 3-bromo-4-methoxybenzoate (20 mmol, 4.90 g), N,N-diisopropylacrylamide (24 mmol, 3.72 g), bis-(benzonitrile)-palladium-II chloride (1.5 mol%), and 20 ml of N-methyl-2-pyrrolidinone was heated at 130°C until no starting material could be detected by tlc (starting material methyl 3-bromo-4-methoxybenzoate: R_f 0.73; N,N-diisopropylacrylamide: R_f 0.46; solvent system (1)). After cooling to room temperature 50 ml of an aqueous 2N HCl solution was added. The reaction was diluted with dichloromethane (50 ml) and the precipitated grey palladium metal was filtered off. The organic phase was washed with five portions (50 ml each) of 2N aqueous hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness. The remaining off-white solid was recrystallized from ethyl acetate/n-hexane to give 4.40 g (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide in 69% yield, m.p. 139-140°C, tlc: (1) R_f 0.40.

NMR (CD_2Cl_2): 21.22, 22.10, 46.39, 48.87, 52.59, 56.61, 111.42, 123.39, 123.78, 125.54, 130.32, 132.53, 135.07.

MS (EI, DI, 105°C): 319 ($M^{+\cdot}$, 22), 304 (6%), 276 (8%), 219 (100%), 187 (18%), 160 (7%).

(±)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

((±)-3-(2-Diisopropylcarbamoyl-1-phenylethyl)-4-methoxybenzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.

A dark green solution of lithium diphenylcuprate was prepared by addition of phenyllithium solution (12 ml, 24 mmol, cyclo-

hexane/diethyl ether) to a cooled (0°C) and stirred suspension of copper-I bromide dimethylsulphide adduct (2.71 g, 13 mmol) in diethyl ether (40 ml). This solution was cooled to -78°C and then subsequently solutions were added of trimethylchlorosilane (1.5 ml, 12 mmol) in diethyl ether (5 ml) followed by the above cinnamide (3.19 g, 10.0 mmol, (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide) in 10 ml of tetrahydrofuran. The reaction was stirred for one hour at -78°C, warmed to room temperature and then quenched by the addition of 150 ml of a saturated aqueous solution of ammonium chloride. After 90 min the organic phase was washed with two portions (100 ml) of half saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated to dryness. The yellow oily residue was dissolved in a minimum of ethyl acetate and purified by column chromatography on silica gel (mobile phase (1)). Evaporation of the combined fractions of the title compound gave

(±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

as a viscous slightly yellow syrup (1.8 g, 44% yield).
NMR (CD_2Cl_2): 19.45, 19.56, 19.74, 38.86, 44.87, 47.92, 50.80, 54.76, 109.41, 121.32, 125.53, 128.10, 128.43, 128.78, 132.03, 143.20, 159.95, 165.95, 168.87. MS (EI, DI, 105°C): 397 ($M^{+\cdot}$, 41%), 366 (5%), 322 (2%), 269 (3%), 255 (14%), 237 (7%), 165 (5%), 128 (12%), 91 (43%), 58 (100%).

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A solution of (±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide (0.79 g, 2.0 mmol) in 20 ml of tetrahydrofuran was cooled to 5°C and then treated with 2.5 ml of 1M $LiAlH_4$/THF. After stirring at room tem-

perature for 18 hrs. finely powdered aluminium chloride (0.3 g) was added and stirring was continued for additional 4 hrs. The reaction was quenched at 5°C by the dropwise addition of water followed by aqueous sodium hydroxide solution. The mixture was diluted with diethyl ether (150 ml) and the organic phase was washed with half saturated brine, dried (sodium sulphate), and evaporated to dryness to give the title compound as a solid off-white foam. Tlc (2) 0.16, m.p. 48-51°C. A portion of the material was converted into the hydrochloride (ethereal hydrochloric acid), m.p. 186-189°C (dec.).

Hydrogenolytic Deoxygenation of S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A mixture of *S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (683 mg, 2.0 mmol, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol)), platinium-on-carbon catalyst (120 mg) and acetic acid (1.0 ml) was diluted with ethyl acetate (50 ml) and then hydrogenated at room temperature under a pressure of 4 bar hydrogen gas for 5 hrs. The catalyst was filtered off and the filtrate was evaporated to leave an oil. The residue was redissolved in dichloromethane (25 ml) and the solution was washed with aqueous sodium hydrogencarbonate solution. The organic phase was concentrated to dryness and the oily residue taken up in ethanol (7 ml). Addition of D-(-)-tartaric acid (300 mg) and storage of the clear solution at -25°C gave colourless crystals (310 mg) of **S-(-)-2-(3-diisopropylamino-1-phenylpropyl)-4-methylphenol D-(-) hydrogentartrate** in 33% yield, tlc: (4): 0.66 (starting material 0.31), $[\alpha]_D^{22}$ = -26.7 (c = 1.0, methanol). NMR (CD_3OD): 17.98, 18.37, 20.69, 33.68, 43.12, 56.33, 74.17, 116.31, 127.51, 129.11, 129.50, 129.70, 129.89, 130.41, 144.57, 153.67, 176.88.

A portion of the tartrate was treated with aqueous sodium hydrogencarbonate solution and the free base was isolated in quantitative yield as a colourless oil by extraction with ethyl acetate and evaporation of the extract. $[\alpha]_D^{22}$ = -26.3 (c = 1.0, methanol).

Preferred intermediates in the processes for the preparation of the 3,3-diphenylpropylamines according to the present invention are:
(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
R-(-)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
S-(+)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol and their salts.

3. Examples

a) Phenolic monoesters

aa) General procedure

Esters of Carboxylic Acids
A stirred solution of (±)-*2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenol* (Intermediate B, 1.71 g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid mono-chloride for compounds of formula II, 2.50 mmol for compounds

of formula II') in 60 ml of dichloromethane was cooled to 0°C and then triethylamine (0.502 g, 4.96 mmol for compounds of formula II, 1.05 g, 9.92 mmol for compounds of formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 min. Stirring was continued for 18 hrs at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and at low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents.
The esters of formula II or II' were obtained as colourless to light yellow solids or viscous syrups in purities between 90% and 99% (tlc, HPLC, NMR).

Esters of N-Acylamino Acids

Phenolic Monoesters

To a solution of the respective amino acid (2.0 mmol) in 0.7 ml to 5 ml of N,N-dimethylformamide and 0.5 ml of triethylamine was added at 5°C in one portion methyl chloroformate (2.0 mmol, 288 mg). After stirring for 2 hrs. at the same temperature the cooling bath was removed and a solution of Intermediate B (2.0 mmol, 682 mg) in 5 ml of dichloromethane and triethylamine (0.5 ml) was added. The reaction was allowed to stir for 2-8 hrs and then diluted with diethyl ether (70 ml). Solid precipitates were filtered off and the mixture was washed with aqueous sodium hydrogen sulphate solution (5%) and water. After drying (sodium sulphate), filtration and evaporation in vacuum the residue was purified by flash chromatography on silica gel (eluent: solvent system (4)). N-acylamino acid esters were obtained as viscous oils or waxy solids in yields between 24% and 73%.

bb) Salt formation (Example hydrochloride)

A cooled (0°C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of formula II) or 9.4 mmol (diamines of formula II') ethereal (1 M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100°C (with decomposition).

The following compounds were prepared according to the method described above and their analytical data are listed below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.47 (4), NMR ($CDCl_3$): 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%)

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.52 (4); NMR ($CDCl_3$): 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%)

(±)-n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16,

43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-Cl (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-Cl (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36

R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.38 (4), starting material: 0.26; colourless oil (yield 95%); NMR ($CDCl_3$): 19.02, 19.14, 19.96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138,76, 143.93, 147.97, 175.39.
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +5.5 (c = 1.0, chloroform); NMR ($CDCl_3$): 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23, 34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40, 128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

(±)-2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.49 (1); NMR ($CDCl_3$): 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92, 128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; GC-MS/P-CI

(ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
((±)-2-[Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171.47, 173,82

(±)-Cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.66 (4), starting material Intermediate B (0.50), colourless oil, yield: 82%. NMR ($CDCl_3$): 20.42, 25.87, 30.25, 36.57, 41.89, 43.97, 47.15, 49.02, 64.63, 122.56, 125.60, 126.16, 126.81, 127.60, 127.94, 128.35, 128.77, 136.74, 138.88, 143.85, 147.92, 175.05.

(±)-Cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.67 (4), starting material Intermediate B (0.50), colourless oil, yield: 93%. NMR ($CDCl_3$): 20.27, 25.40, 25.74, 29.03, 29.16, 36.29, 41.82, 43.31, 44.08, 49.36, 64.62, 122.56, 125.68, 126.22, 126.92, 127.92, 128.38, 136.65, 139.00, 143.72, 147.86, 174.40.
(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.31 (4); colourless syrup (99% yield, purity > 95%);gradually crystallized upon refrigeration; NMR ($CDCl_3$): 20.41, 20.51, 36.65, 42.42, 43.85, 48.79, 64.70, 122.79, 125.74, 126.17, 126.83, 128.13, 128.28, 128.58, 129.48, 130.25, 133.62, 137.21, 139.10, 143.67, 148.00, 164.99.

*R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-*hydroxymethylphenyl ester
tlc R_f 0.30 (4); colourless syrup
Hydrochloride: colourless amorphous solid; $[\alpha]_D^{20}$ = +14.9 (c = 1.0, chloroform);
NMR ($CDCl_3$): 17.06, 17.53, 18.25, 18.61, 31.23, 42.19, 45.49, 54.26, 54.53, 64.09, 122.55, 126.77, 127.13, 127.58, 128.10, 128.50, 128.72, 128.78, 129.02, 130.17, 133.96, 134.27, 140.81, 142.13, 147.91, 165.40.

(±)-4-Methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.30 (4), starting material Intermediate B: 0.24; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.32, 20.50, 21.78, 36.13, 42.35, 43.98, 49.29, 64.66, 122.79, 125.81, 126.19, 126.70, 127.04, 128.30, 129.32, 129.76, 130.29, 136.94, 139.20, 143.61, 144.46, 148.04, 165.07.
LC-MS: 459 ($M^{+\cdot}$, 3.5%), 444 (17%), 223 (2.5%), 195 (2%), 119 (48%), 114 (100%).

(±)-2-Methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
viscous colourless oil, tlc: (4) 0.64 (starting material R_f 0.51), yield 84%. NMR ($CDCl_3$): 20.44, 20.53, 21.86, 22.01, 36.74, 42.36, 43.87, 48.81, 64.76, 122.93, 123.11, 125.71, 126.12, 126.88, 128.10, 128.48, 130.76, 131.26, 131.70, 132.03, 132.79, 137.28, 139.00, 141,73, 143.72, 148.04, 165.25. LC-MS: 459 ($M^{+\cdot}$, 21%), 444 (100%), 326 (1%), 223 (10%), 213 (6%), 195 (9%), 165 (14%), 115 (94%), 91 (99%).

(±)-2-Acetoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

colourless syrup, tlc: (4) 0.47 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.39, 20.57, 20.96, 36.92, 42.29, 43.88, 48.87, 64.64, 122.39, 122.64, 124.05, 125.80, 126.11, 126.75, 128.09, 128.32, 132.23, 134.66, 137.27, 139.32, 143.64, 147.63, 151.37, 162.72, 169.73. LC-MS: 503 ($M^{+\cdot}$, 7%), 488 (59%), 446 (6%), 326 (22%), 223 (9%), 213 (9%), 195 (9%), 163 (14%), 121 (100%), 114 (88%).

(±)-1-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

colourless viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.46, 20.58, 36.82, 42.46, 43.89, 48.76, 64.81, 122.98, 124.51, 125.64, 125.79, 125.98, 126.15, 126.44, 126.94, 128.12, 128.36, 128.65, 131.37, 131.82, 133.98, 134.45, 137.44, 139.08, 143.73, 148.13, 165.49. LC-MS: 495 ($M^{+\cdot}$, 8%), 480 (100%), 213 (7%), 165 (8%), 155 (95%), 127 (100%), 114 (90%).

(±)-2-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

colourless slightly yellow viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 71%. NMR ($CDCl_3$): 20.47, 20.59, 36.71, 42.59, 43.85, 48.81, 64.82, 122.89, 126.89, 127.89, 128.19, 128.41, 128.68, 129.50, 132.03, 132.55, 135.87, 137.22, 139.08, 143.83, 148.20, 165.14. LC-MS: 495 ($M^{+\cdot}$, 7%), 480 (98%), 223 (8%), 213 (6%), 195 (6%), 165 (8%), 155 (96%), 127 (100%), 114 (81%).

(±)-4-Chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.54 (4), starting material Intermediate B: 0.44; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.34, 20.50, 36.41, 42.51, 43.84, 48.93, 64.66, 122.72, 125.82, 126.88, 127.27, 128.06, 128.56, 128.96, 131.60, 133.80, 136.95, 139.30, 140.16, 143.60, 147.87, 164.10. LC-MS: 479 ($M^{+\cdot}$, 1.5%), 464 (10%), 223 (2%), 195 (2%), 165 (1.5%), 139 (25%), 114 (100%).

(±)-4-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.47 (4), starting material Intermediate B: 0.42; yield: 89%, viscous light yellow oil; NMR ($CDCl_3$): 20.31, 20.47, 36.43, 42.39, 43.90, 48.97, 55.53, 64.71, 121.79, 122.86, 125.72, 126.14, 126.79, 128.11, 128.27, 131.27, 131.77, 132.36, 132.84, 137.15, 139.01, 143.74, 148.08, 163.92, 164.71. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (20%), 223 (2%), 195 (2%), 135 (48%), 114 (100%).

(±)-2-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.40 (4), starting material Intermediate B: 0.42; yield: 98%, viscous light yellow oil; NMR ($CDCl_3$): 20.29, 20.42, 36.50, 41.92, 44.02, 49.09, 55.95, 64.72, 119.10, 120.20, 122.86, 125.64, 126.10, 126.82, 128.06, 128.30, 132.38, 134.32, 137.11, 139.01, 143.87, 148.00, 159.82, 164.40. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (18%), 223 (1%), 195 (1%), 135 (49%), 114 (100%).

(±)-4-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.44 (4), starting material Intermediate B: 0.42; yield: 78%, viscous yellow oil which slowly solidified; m.p. 123.6°C; NMR ($CDCl_3$): 20.47, 20.62, 36.52, 42.66, 43.70, 48.75, 64.69, 122.61, 123.72, 125.91, 126.33, 127.04, 128.02, 128.37, 131.32, 134.86, 136.83, 139.55, 143.56, 147.75, 150.93, 163.04. LC-MS: 490 ($M^{+\cdot}$, 1.5%), 475 (15%), 327 (0.8%), 223 (3%), 195 (3%), 150 (15%), 114 (100%).

(±)-2-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.32 (4), starting material Intermediate B: 0.42; yield: 92%, viscous yellow oil which slowly solidified; NMR ($CDCl_3$): 20.39, 20.50, 36.74, 42.14, 43.89, 48.71, 48.92, 64.59, 122.15, 123.95, 124.18, 125.89, 126.25, 127.23, 127.99, 128.39, 129.95, 132.95, 133.08, 136.72, 139.62, 143.64, 147.63, 148.15, 163.90. LC-MS: 490 ($M^{+\cdot}$, 1%), 475 (11%), 327 (2.5%), 223 (2.5%), 195 (3%), 165 (3%), 150 (7%), 114 (100%).

(±)-N-Acetylglycine 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester/(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ((±)-2-[Diisopropylamino-1-phenylpropyl]-4-(hydroxymethyl)-phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171,47, 173.82.

(±)-Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.38 (4); NMR ($CDCl_3$): 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23,

64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

(±)-Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.40 (4); NMR ($CDCl_3$): 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

(±)-Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 127.39, 127.99, 128.35, 129.31, 131.84, 136.98, 138.94, 143.80, 147.40, 169.05

(±)-Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

(±)-Identical diesters (formula III) were prepared and worked up as described above with the exception that 2.4 mmol of both triethylamine and acyl chloride (R^1-COCl) were used. The physical properties were similar to the bases and salts described above.
Diesters of N-acylaminoacids were prepared as described for phenolic monoesters with the exception that an additional molar equivalent of acylating agent (mixed acid anhydride) was used.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.65 (4). This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F. Reber, A. Lardon, T. Reichstein, *Helv. Chim. Acta* **37**: 45-58 [1954])

(±)-Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.76 (4); GC-MS/P-CI (ammonia): 426.3 (100%), 368.3 (22%); GC-MS/P-CI (methane, trimethylsilyl derivative): 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$)- 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80, 65.21, 123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, tlc: R_f 0.82 (4); NMR ($CDCl_3$): 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; GC-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%)

(±)-n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.86 (4); NMR ($CDCl_3$): 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76,

148.41, 171.68, 173.40; GC-MS/P-CI (ammonia): 482.8 (100%), 396.4 (67%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, tlc: R_f 0.83 (4), NMR ($CDCl_3$): 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%)

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, Tlc: R_f 0.96 (4); NMR ($CDCl_3$): 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%)

(±)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

(+)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

Hydrochloride: colourless solid; tlc: (4) 0.70, $[\alpha]_D^{20}$ = +24.2 (c = 1.0, chloroform). NMR (DMSO-d_6): 16.52, 17.99, 18.06, 26.99, 31.32, 53.94, 65.98, 123.58, 127.65, 127.98, 128.62, 128.90, 129.02, 129.45, 129.71, 130.10, 133.64, 134.32, 134.55, 135.60, 142.52, 148.37, 164.53, 165.76.

c) **Mixed diesters**

Mixed diesters (formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters. Working up and physical properties corresponded to the bases and salts described above.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.76 (4); NMR ($CDCl_3$): 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.70, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.74 (4); NMR ($CDCl_3$): 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
Viscous colourless oil, tlc: R_f 0.70 (4); NMR ($CDCl_3$): identical with R-(+) enantiomer, see below.

R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
tlc: R_f 0.70 (4)
Hydrochloride: colourless non-hygroscopic solid $[\alpha]_D^{20}$ = +27.1 (c = 1.0, chloroform). NMR ($CDCl_3$): 17.14, 18.53,

21.04, 31.51, 42.25, 46.27, 54.74, 65.58, 123.18, 127.07, 127.55, 127.61, 127.99, 128.80, 130.22, 134.14, 134.81, 135.27, 141.44, 148.54, 165.19, 170.81.

(±)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18

(+)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
colourless oil
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +14.6 (c = 1.0, chloroform); NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.54, 18.92, 19.06, 20.95, 31.49, 34.07, 41.64, 46.17, 54.55, 65.49, 122.91, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

(±)-2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropyl-amino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40

(±)-2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diiso-propylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.81 (4); NMR ($CDCl_3$): 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60

d) Benzylic monoesters

A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 g) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2 - 24 hrs complete disappearence of the starting material (R_f = 0.45 (3)). The mixture was filtered and then evaporated under high vacuum (< 40°C) to give the carboxylic acid (R^1-CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.25 (2); NMR ($CDCl_3$): 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32

(±)-Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.26 (2); NMR ($CDCl_3$): 19.45, 20.96, 33.26, 39.63, 42.27, 48.23, 63.59, 118.00, 127.36, 128.33, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44

(±)-Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.45 (2); NMR ($CDCl_3$): 19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22

(±)-Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.54 (2); NMR ($CDCl_3$): 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05

(±)-Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.56 (4); NMR ($CDCl_3$): 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.61 (4); NMR ($CDCl_3$): 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39

(±)-Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60

e) Ethers and silyl ethers

A mixture of Intermediate B (3.4 g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^{10}-OH (50-150 ml) was stirred at room temperature until no starting material was detectable (2-24 hrs). After evaporation to dryness (< 35°C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100-200 ml, 5%, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of formula VI (R^{11} = H) as colourless to light yellow oils.

Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for examples of the structure of formula IV.

Hydrochlorides:

Molar equivalents of bases of formula VI (R^{11} = H), dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile or acetone to give colourless crystalline material.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol, tlc: R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl

derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%);
hydrochloride: amorphous hygroscopic colourless solid;
m.p. 161°C; NMR (CD_3OD): 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 129.42, 129.55, 130.43, 144.32, 155.85

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol, tlc: R_f 0.72 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 444.8 (100%), 398.4 (6%);
hydrochloride: colourless non-hygroscopic crystals, m.p. 158-161°C, NMR (CD_3OD): 15.43, 17.12, 18.82, 33.80, 56.49, 66.49, 73.62, 116.19, 127.63, 128.99, 129.13, 129.36, 129.55, 130.58, 130.75, 144.32, 155.77

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol, NMR ($CDCl_3$): 18.62, 19.44, 23.10, 33.24, 39.61, 42.26, 48.22, 71.87, 73.94, 117.78, 124.95, 127.35, 127.57, 128.32, 128.47, 133.66, 134.23, 144.48, 155.25

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethyl-phenol, NMR ($CDCl_3$): 19.44, 22.32, 33.27, 39.65, 42.29, 48.25, 69.28, 72.10, 117.90, 127.38, 128.03, 128.41, 131.10, 133.76, 134.37, 144.51, 154.65.
Hydrochloride: colourless crystals, m.p. 140.4°C, tlc (4) 0.61. LC-MS: 383 (6%, $[M-HCl]^{+\cdot}$), 368 (11%), 324 (1%), 223 (6%), 195 (3%), 165 (2%), 155 (5%), 114 (100%). NMR (DMSO-d_6): 16.57, 18.09, 18.19, 22.29, 31.58, 41.25, 45.87, 53.97, 69.26, 69.92, 115.28, 126.34, 127.08, 127.25, 127.96, 128.45, 129.07, 129.70, 132.31, 143.88, 154.22.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol, NMR ($CDCl_3$): 13.75, 19.44, 19.75, 32.24, 33.28,

39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester, NMR ($CDCl_3$): 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128,35 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester, NMR ($CDCl_3$): 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol, NMR ($CDCl_3$): 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28

(±)-Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$): 0.10, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98

(±)-[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]methanol, NMR ($CDCl_3$): 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14, 155.06

(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxy-phenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09

(±)-Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxy-phenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28

(±)-[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$): -4.92, -5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.44, 128.48, 133.37, 135.74, 144.11, 155.20

(±)-4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diiso-propylamino-1-phenylpropyl)-phenol, tlc: R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85%), 470.43 (10%), 396.3 (31%)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, NMR ($CDCl_3$): -4.77, -4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95

(±)-{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-di-methylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropyl-amine, tlc: R_f 0.94 (3); GC-MS/N-CI (methane): 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7

(78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

(±)-Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$): 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94

(±)-Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.87 (4); NMR ($CDCl_3$): 20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05, 137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%)

(±)-Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01; GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%)

f) Carbamates and carbonates

Mono N-substituted carbamates

A solution of 4.0 mmol of Intermediate B, benzylic ether (formula VI, R^{11} = H) or monoester of formula II in dichloromethane (20 ml) was treated at room temperature for 16 hrs with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After

washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation oily residues or colourless solids of the free bases were obtained.

N-disubstituted carbamates

N,N-dialkyl-carbamoylchloride (4.4 mmol) was dissolved in dichloromethane and dropped into a cooled (0°C) and stirred mixture consisting of Intermediate B (4.0 mmol), dichloromethane (30 ml) and triethylamine (7.0 mmol, 0.71 mg, 1 ml). Stirring was continued for 6 hrs. The mixture was then washed with 5 portions (10 ml) of aqueous sodium hydrogen carbonate, dried (sodium sulphate), filtered and evaporated to give the carbamates as colourless oils or solids.

Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65°C over 18 hrs.
Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of formulae II to IV. Alkyl chloroformates were used as acylation reagents.

Hydrochlorides:

The oils or solids were redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m.p. 64°C (with decomposition); NMR (DMSO-d_6): 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52

(±)-N,N-Dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.34, 20.66, 30.51, 36.33, 36.77, 42.00, 48.28, 50.21, 65.65, 119.83, 123.44, 125.19, 126.60, 127.38, 127.54, 129.31, 136.62, 143.33, 150.99, 155.67.

(±)-N,N-Diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.54, 20.66, 30.49, 35.61, 42.42, 48.31, 50.20, 65.56, 119.43, 123.40, 125.33, 126.66, 126.99, 127.05, 136.30, 143.27, 149.13, 154.97

(±)-N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester; NMR ($CDCl_3$): 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]acetic acid ethyl ester hydrochloride
Tlc: R_f 0.14 (4); m.p. colourless crystals (from acetone, 21% yield); NMR ($CDCl_3$): 16.76, 16.86, 18.45, 20.96, 31.37, 42.20, 46.13, 54.56, 65.50, 123.10, 126.98, 127.66, 128.72,

130.14, 134.05, 134.72, 135.22, 141.37, 148.47, 165.12, 170.71

(±)-N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester, tlc: R_f 0.36 (3); NMR ($CDCl_3$): 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74

(±)-N,N-Dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 20.59, 20.66, 30.59, 35.96, 36.40, 36.74, 36.98, 42.03, 48.26, 50.09, 67.09, 119.04, 123.23, 123.49, 125.01, 126.67, 127.72, 129.33, 133.65, 143.43, 150.99, 155.63.

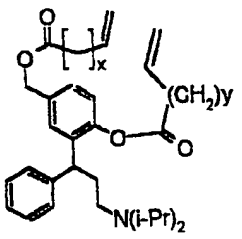
(±)-N,N-Diethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N,N-diethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 13.31, 13.64, 13.89, 20.33, 20.71, 31.57, 37.97, 41.55, 42.37, 48.46, 51.00, 67.23, 120.00, 123.39, 124.82, 126.31, 126.95, 127.33, 150.36, 157.18, 158.97.

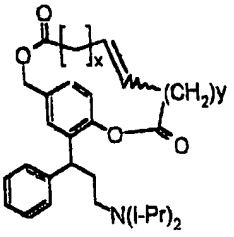
(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-methyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (formula VII', X = Y = NH, n = 4) tlc: R_f 0.60 (6); dihydrochloride m.p. 142.5-145.6°C

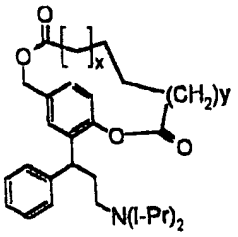
(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4)

g) **Intramolecular cyclic diesters via Ring Closing Metathesis (RCM)**







Example:

(±)-Pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester (x = y = 2)

A cooled (4°C) mixture of pent-4-enoic acid, isobutyl chloroformate, and triethylamine (each 5.84 mmol) in 10 ml of dichloromethane was stirred 5 hrs under an atmosphere of dry nitrogen gas. The cooling bath was then removed and both triethylamine (1.46 mmol) and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (1.46 mmol) were added in one portion. After 18 hrs the mixture was diluted with dichloromethane (30 ml), washed several times with water and finally aqueous 5% sodium hydrogen carbonate solution. After drying (sodium sulphate), filtration and evaporation the oily residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxy-*

methyl)-phenyl ester as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$): 18.95, 20.77, 27.75, 28.87, 33.58, 36.83, 42.13, 43.72, 48.71, 65.85, 70.55, 115.47, 115.99, 122.45, 126.26, 127.08, 127.96, 128.11, 128.83, 133.73, 136.38, 136.79, 137.04, 143.77, 148.46, 171.11, 172.78.

Intramolecular cyclic diesters of 1,ω-dioic acids and Intermediate B

Example

Intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Grubbs catalyst (benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium, 16 mg, 0.002 mmol, 2 mol-%) was added to a solution of *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester* (483 mg, 0.96 mmol) in dichloromethane (150 ml) and the mixture was refluxed for 96 hrs. under an atmosphere of nitrogen gas, after which all of the starting material was consumed as indicated by tlc. The mixture was filtered through a short pad of basic alumina, and the solvent was removed in vacuum. Flash chromatography (solvent system (4)) afforded the intermediate intramolecular cyclic diester of oct-4-ene-1,8-dioic acid and 2-(3-diisopropylamino)-1-(phenylpropyl)-4-hydroxymethyl-phenol (324 mg) as a colourless syrup (tlc: (4) R_f 0.68) in 71% yield, mixture of two geometrical isomers. NMR ($CDCl_3$, major isomer): 19.24, 20.61, 23.11, 25.62, 30.55, 33.53, 35.02, 42.41, 48.29, 50.20, 65.30, 114.46, 124.33, 125.58, 127.15, 128.70, 129.29, 131.10, 132.46, 139.54, 146.76, 147.98, 173.76, 174.39.

A portion of this material (140 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature in the

presence of palladium-on carbon catalyst to afford the *intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol* in essentially quantitative yield, 139 mg, colourless oil, tlc: (4) 0.71.

NMR ($CDCl_3$): 19.36, 20.73, 24.84, 25.28, 28.90, 29.70, 30.57, 33.72, 34.37, 42.39, 48.26, 50.20, 65.26, 114.45, 124.37, 127.11, 128.67, 129.29, 131.18, 132.45, 139.52, 146.77, 147.69, 173.90, 174.15.

Poly-co-DL-Lactides of Intermediate B

All reagents were dried over P_2O_5 in vacuum (< 1 mbar) and at room temperature. The reactions were carried out at room temperature in an atmosphere of dry, oxygen-free nitrogen.

Low Molecular Weight Copolymer

A 15% solution of n-butyllithium (0.36 ml) was injected through a rubber septum into a stirred solution of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol (100 mg, Intermediate B) and DL-dilactide (1.5 g) in 15 ml of dry toluene. The polymerization was allowed to proceed for 4 days at room temperature. Distilled water (10 ml) was then added in order to terminate the polymerization. The organic phase was separated and slowly dropped into 200 ml of methanol. The precipitated colourless oil was treated with water (100 ml) and then dried in high vacuum for 48 hrs.

The copolymer was obtained in 72.7% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 2000-4000 and a weight content of Intermediate B of about 8.4% (NMR). Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) analysis showed a Mw of 1108 and a Mn of 702.

High Molecular Weight Copolymer

The high molecular weight copolymer was prepared as described above with the exception that 3.0 g of DL-dilactide was used. Precipitation by methanol gave a fluffy white solid which was carefully washed with water and then dried as desribed to give the copolymer in 81% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 4000-8000 and a weight content of Intermediate B of about 2.0%. Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) showed a Mw of 9347 and a Mn of 6981. Differential scanning calorimetry (DSC) provided a Tg of 42.5°C.

NMR Analysis

The ^1H NMR resonance signals of the poly-lactyl chain were clearly separated from the copolymeric part of Intermediate B (solvent $CDCl_3$):

CH_3 resonances of the poly-lactyl chain: 1.30-1.60 ppm

CH resonances of the poly-lactyl chain: 5.10-5.30 ppm

CH resonances of the connecting lactyl units with the two hydroxy groups of Intermediate B: 4.8-5.0 ppm and 5.5-5.7 ppm.

Polymer bound Intermediate B: 1.06-1.11 (CH_3), 2.20-2.30 ($CH_2\underline{CH_2}$), 2.40-2.80 ($N\underline{CH_2}$), 3.30-3.50 ($N\underline{CH}$), 4.45-4.55 ($\underline{CH}CH_2$), 4.70-4.80 ($\underline{CH_2}$-OCO-lactyl), 6.70-7.30 (aryl $\underline{CH}$).

h) **Inorganic ester**

Example:

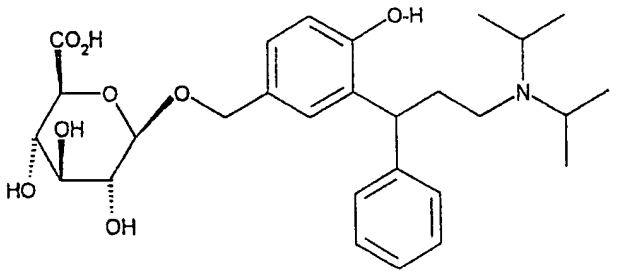
(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

Hydrochloride

To a stirred solution of chlorosulphonic acid (116 mg, 1.0 mmol) in 5 ml of dry diethyl ether was slowly added at 0°C a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester (445.6 mg, 1.0 mmol) in 3 ml of dry diethyl ether. The gel formed immediately during the addition was stirred at room temperature until it became a crystalline consistency (ca. 1 hr). The precipitate was washed several times with diethyl ether and then dried in vacuum to give 0.52 g (46% yield) colourless crystals, m.p. 63-65°C. NMR ($CDCl_3$): 16.85, 17.03, 18.32, 18.49, 32.01, 42.29, 46.23, 55.23, 55.50, 69.24, 122.52, 126.94, 127.15, 129.04, 129.76, 130.25, 133.89, 134.93, 136.85, 141.87, 147.80, 165.19.

i) **Benzylic 1-O-β-D-glucuronide of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol**

((±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol)



A solution of methyl 2,3,4-triacetyl-1-α-D-glucuronosyl-bromide (2.07 g, 4.64 mmol) in 24 ml of dry toluene was cooled to -25°C under an atmosphere of nitrogen and then treated with a solution of (±)-benzoic acid 2-(3-diisopropyl-amino-1-phenylpropyl)-4-hydroxymethylphenyl ester in 7 ml of toluene. To this mixture was added dropwise with stirring and under protection from light a solution of silver triflate in 14 ml of toluene (immediate formation of a white precipitate). The cooling bath was removed after 15 min and pyridine (0.38 ml) was added. The mixture was diluted with ethyl acetate (200 ml), filtered and the clear yellow filtrate was washed sequentially with aqueous solutions of sodium thiosulphate (5%), sodium hydrogen carbonate (5%), and sodium chloride (20%). The solution was dried with solid sodium sulphate, treated with charcoal, filtered and evaporated to dryness. The waxy residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(2,3,4-triacetyl-1β-D-glucuronosyloxymethyl)-phenyl ester*, colourless syrup, tlc (4) 0.70 (starting amine: 0.31, bromo glycoside: 0.23), yield 14%.

NMR ($CDCl_3$, mixture of diastereomers): 20.41, 20.50, 20.60, 20.65, 20.84, 36.49, 42.44, 43.65, 48.73, 52.91, 69.46, 70.43, 71.12, 72.11, 72.60, 73.99, 99.19, 122.91, 126.23, 126.38, 126.54, 127.60, 127.92, 128.06, 128.09, 128.31, 128.59, 129.38, 130.22, 133.67, 134.31, 137.41, 143.52, 148.46, 164.82, 167.26, 169.21, 169.39, 170.07.

A portion (350 mg) of the above described material was dissolved and hydrolyzed in a solvent mixture consisting of tetrahydrofuran/methanol/aqueous potassium hydroxide (excess, 12 hrs, 22°C). The mixture was evaporated, re-dissolved in 5 ml of water and the pH was adjusted to 8.3. This solution was applied to a chromatography column charged with prewashed XAD 2 resin (50 g). The column was washed with water (ca. 250 ml) and then eluted with methanol. Collection of the appropriate methanol fractions, and evaporation of the combined fractions in vacuum gave 111 mg of

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol, sodium salt,

amorphous colourless solid, m.p. ≅ 110-124°C (dec.), tlc (4) 0.12. NMR (CD_3OD, major isomer): 19.43, 19.67, 33.26, 39.63, 42.27, 48.23, 69.76, 73.55, 74.70, 75.95, 78.03, 107.64, 117.95, 125.51, 127.36, 128.33, 133.83, 134.77, 144.49, 155.36, 176.76.

II. Incubations of different compounds of the invention with human liver S 9-fraction

a) Incubation of unlabelled substrates

A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

The pooled human liver S 9-preparation was delivered by Gentest, Woburn, MA, USA.

In a routine assay, 25 µL of pooled human liver S9 (20 mg protein/mL, H961, Gentest, Woburn, MA, USA) was incubated

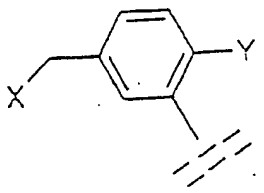
for 2 hrs at 37°C with 40 µM substrate in a 0.01 M potassium phosphate buffer in the presence of NADPH (1 mM). The reaction was quenched by the addition of concentrated perchloric acid and precipitating protein was removed by centrifugation. The supernatant was adjusted to pH 3 with concentrated potassium phosphate solution, centrifuged, and injected into the HPLC for analysis of the respective products.

The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

The incubation results expressed in (%) of theoretical turnover are presented in Fig. 1.

They ranged from 96 to 63.2%. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:
The prodrugs introduced in the assay show the following chemical structure:



chemical structure	X-/-Y	
AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and n-butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate

iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	n-butyrate
PropO-/-OProp	means	proprionate
HO-/-OProp	means	hydroxy and proprionate
HO-/-OAc	means	hydroxy and acetate
BzO-/-OBz	means	benzoate and benzoate
AcO-/-OiBut	means	acetate and isobutyrate
AcO-/-OBz	means	acetate and benzoate

b) Incubation of labelled substrates

The metabolic degradation of the unlabelled hydroxy metabolite (i.e. Intermediate B) and the deuteriated hydroxy-metabolite (Intermediate d_2B) were compared in vitro. Used were the respective enantiomers and the racemates.

The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate to produce the corresponding carboxylic acid.

The measurement was performed with an incubation time of 3 hrs at 37.0°C in a concentration of 40 µM. The formation of the carboxylic acid from the deuteriated hydroxy-metabolite showed a significantly decreased velocity of 10%.

These in-vitro experiments indicate a reduced metabolic turnover of the deuteriated compound in vitro, which may result in higher plasma levels.

c) Receptor binding study

WO 94/11337 discloses that the active metabolite has high affinity to muscarinic receptors in the guinea-pig bladder. Different compounds of the present invention were tested in

a well established standardized assay, measuring the binding of [^{3}H]-methylscopolamine to recombinant human M3 receptors. BSR-M3H cells transfected with a plasmid encoding the human muscarinic M3 receptor were used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. An aliquot of the membrane preparation was incubated with [^{3}H]-methylscopolamine in the presence or absence of different concentrations of several compounds of the invention for 60 minutes at 25°C. Nonspecific binding was estimated in the presence of 1 μM atropine. Membranes were filtered and washed three times and the filters were counted to determine the amount of [^{3}H]-methylscopolamine specifically bound. The following table shows the IC_{50} values of several compounds of the invention in the M3 receptor binding assay.

Interaction with human M3 receptors in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	8.7
(-)HO-/-OH	1300
(+)HO-/-OiBut	159
(+)HO-/-OBz	172
BzO-/-OBz	2400
AcO-/-OiBut	3600
AcO-/-OBz	5400

These data clearly showed that derivatization at the phenolic hydroxyl moiety results in an about 20 times less potent binding. If both functionalities are derivatized, the binding is even more dramatically reduced. Furthermore, it is demonstrated that the enantiomers of the active metabolite exhibit a marked difference in the binding characteristics to human M3 receptors.

The compounds were tested for their anticholinergic activity in a standard tissue assay, the guinea-pig ileum. A segment of ileum was obtained from Duncan Hartley guinea-pigs which were sacrified by cervical dislocation. The tissue was placed under 1 g tension in a 10 ml bath containing Krebs' solution (pH 7.4, 32°C) and the concentration-dependent ability of different compounds to reduce the methacholine-induced (0.6 μM) contractile response was recorded. The IC_{50} values for the different substances were calculated and examples are presented in the following table.

Anticholinergic activity in guinea-pig ileum in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	20
(-)HO-/-OH	680
(+)HO-/-OiBut	57
(+)HO-/-OBz	180
(+)BzO-/-OBz	220
(+)AcO-/-OiBut	240

These data confirm the results obtained in the receptor binding assays and demonstrate that the anticholinergic activity of the compounds decreases with increased derivatization.

d) Biological membranes

Different compounds of the invention were tested for their ability to penetrate the human skin (200 μm thick) in the "Flow through cell" at 32°C according to Tiemessen et al. (Acta Pharm. Technol. 1998; 34:99-101). Phosphate buffer (pH 6.2) was used as the acceptor medium. Samples were drawn at different time points and analysed by RP-HPLC with UV de-

tection (220 nm). Permeation profiles were plotted and mean flux rates of different substances were calculated by linear regression analysis. The data obtained for different compounds of the invention are summarized in the following table.

Penetration through human skin

Prodrug	Flux rate [$\mu g/cm^2/24hrs$]
HO-/-OH	3
HO-/-OiBut	150
iButO-/-OiBut	60
PropO-/-OProp	70

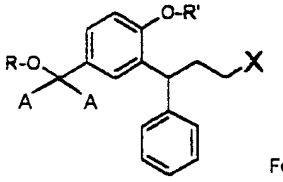
Disubstitution of the hydroxy group of HO-/-OH leads to a ≥ 20-fold increase in skin permeation in relation to the parent HO-/-OH. Suprisingly monosubstitution of the penolic hydroxy group resulted in even higher 50-fold penetration rate through human skin.

Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite, once they have entered the systemic circulation as shown by the in vitro metabolism by the human liver S9 preparation.

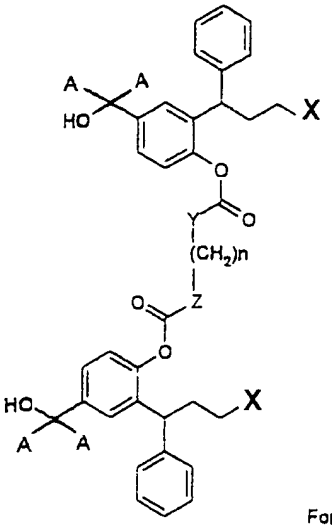
Thus, the antimuscarinic prodrugs according to this invention showed a profile that defines excellent prodrugs.

Claims

1. 3,3-Diphenylpropylamines of the general formulae I and VII':



Formula I



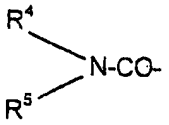
Formula VII'

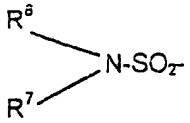
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

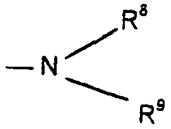
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R' is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

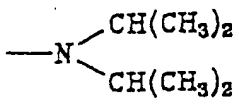
A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

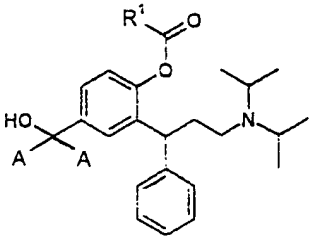
and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

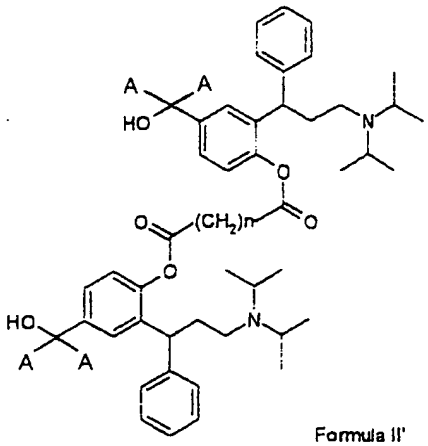
2. 3,3-Diphenylpropylamines as claimed in claim 1, wherein X is



3. 3,3-Diphenylpropylamines as claimed in claim 2 selected from phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

4. 3,3-Diphenylpropylamines as claimed in claim 3 selected from:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

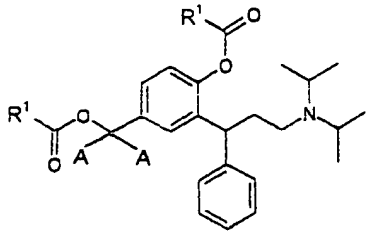
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester.

5. 3,3-Diphenylpropylamines as claimed in claim 2 selected from identical diesters represented by the general formula III



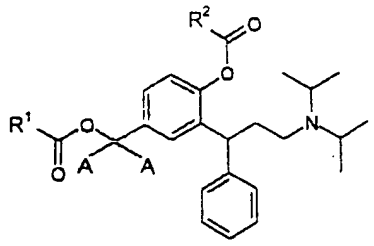
Formula III

wherein R^1 is defined as in claim 3.

6. 3,3-Diphenylpropylamines as claimed in claim 5 selected from:
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

7. 3,3-Diphenylpropylamines as claimed in claim 2 selected from mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is defined as in claim 3

and

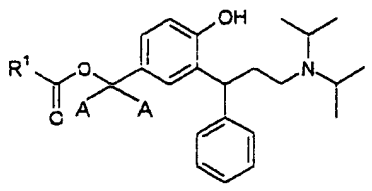
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

8. 3,3-Diphenylpropylamines as claimed in claim 7 selected from:
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

9. 3,3-Diphenylpropylamines as claimed in claim 2 selected from benzylic monoesters represented by the general formula V



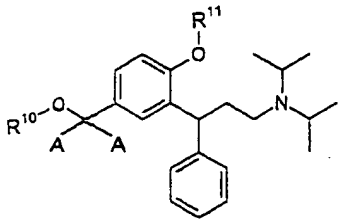
Formula V

wherein R^1 is defined as in claim 3.

10. 3,3-Diphenylpropylamines as claimed in claim 9 selected from:
(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. 3,3-Diphenylpropylamines as claimed in claim 2 selected from ethers and silyl ethers represented by the general formula VI



Formula VI

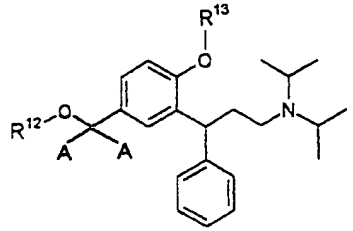
wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined in claim 1 and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

12. 3,3-Diphenylpropylamines as claimed in claim 11 selected from:
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,

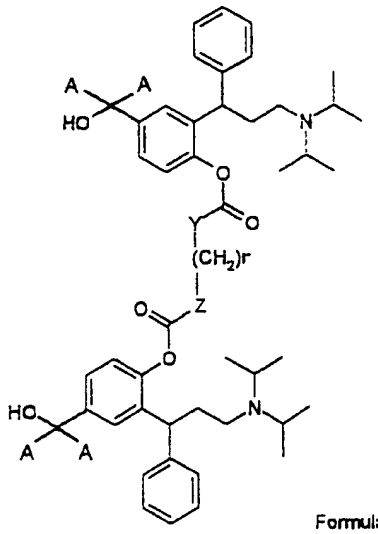
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxy-methylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-tri-methylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,

(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

13. 3,3-Diphenylpropylamines as claimed in claim 2 selected from carbonates and carbamates represented by the general formulae VII and VIII

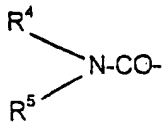


Formula VII



Formula VIII

wherein Y, Z and n are as defined in claim 1 and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



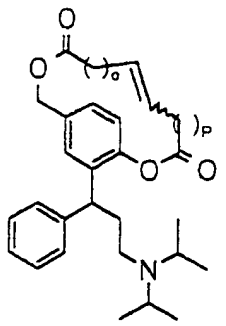
wherein R^4 and R^5 are as defined in claim 1.

14. 3,3-Diphenylpropylamines as claimed in claim 13 selected from:
(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,
(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester,
(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,
(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,
(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,
(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

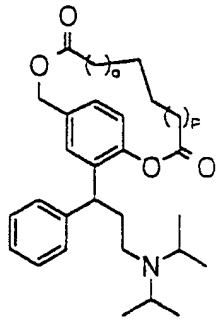
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

15. 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



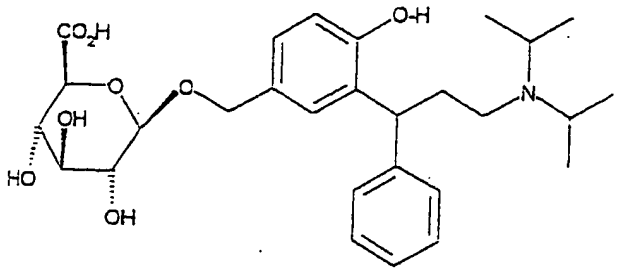
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $\frac{}{}CH_2\frac{}{}$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenyl-propyl)-4-hydroxymethyl-phenol

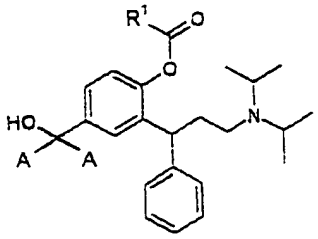
(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula



and

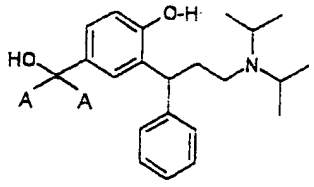
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

16. A process for the production of phenolic monoesters represented by the general formula II

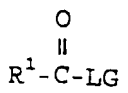


Formula II

as defined in claim 3, which comprises treatment of a compound of the formula

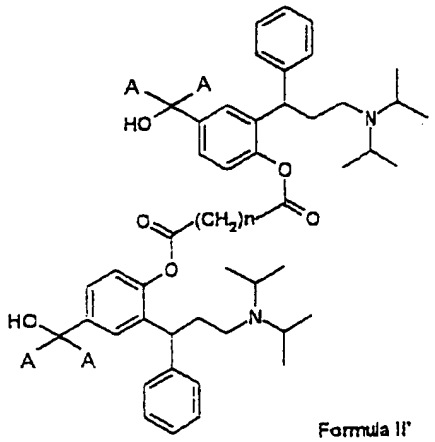


with an equivalent of an acylating agent selected from



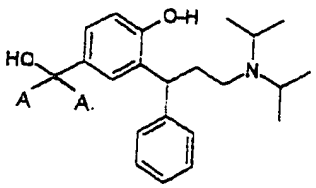
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined in claim 3, in an inert solvent in the presence of a condensating agent.

17. A process for the production of phenolic monoesters represented by the general formula II'

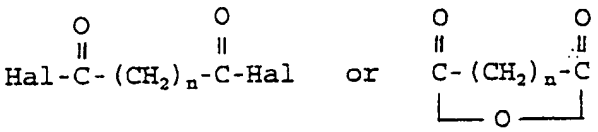


Formula II'

as defined in claim 3, which comprises treatment of two equivalents of a compound of the formula



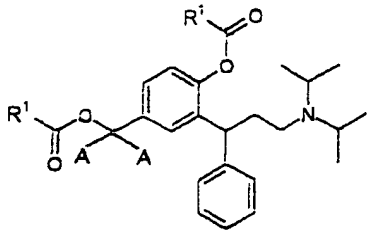
with an acylating agent selected from



or

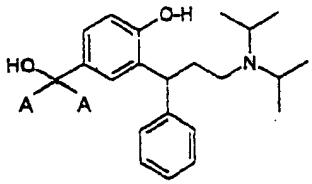
wherein Hal represents a halogen atom.

18. A process for the production of identical diesters represented by the general formula III



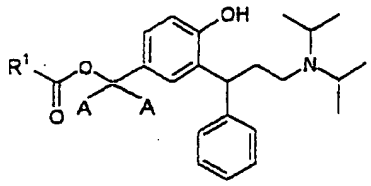
Formula III

as defined in claim 5, which comprises treatment of a compound of the formula



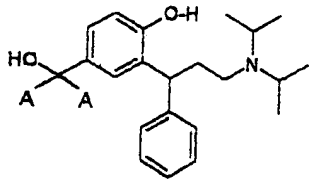
with at least two equivalents of the acylating agent as defined in claim 16.

19. A process for the preparation of benzylic monoesters represented by the general formula V



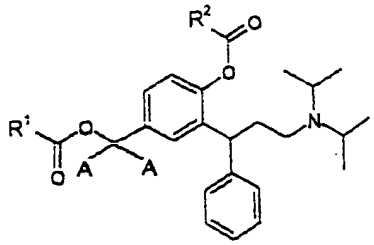
Formula V

as defined in claim 9, which comprises treatment of a compound of the formula



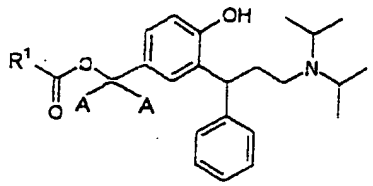
at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

20. A process for the preparation of mixed diesters represented by the general formula IV



Formula IV

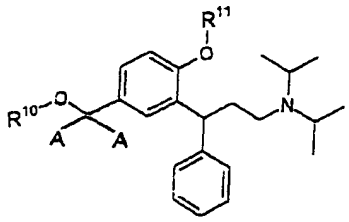
as defined in claim 7, which comprises acylation of a benzylic monoester represented by the general formula V



Formula V

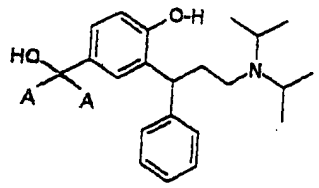
as defined in claim 9 or of a phenolic monoester represented by the formula II as defined in claim 3.

21. A process for the production of ethers represented by the general formula VI



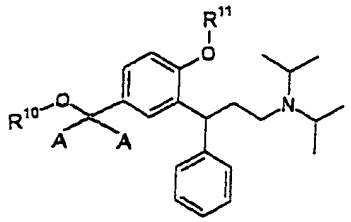
Formula VI

as defined in claim 11 wherein R^{11} is hydrogen which comprises reacting a compound of the formula



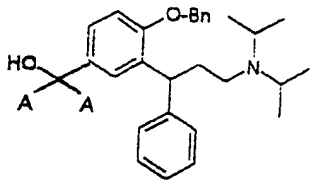
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

22. A process for the preparation of ethers represented by the general formula VI

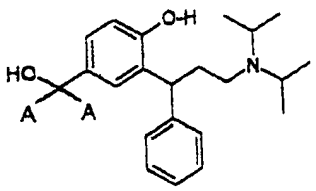


Formula VI

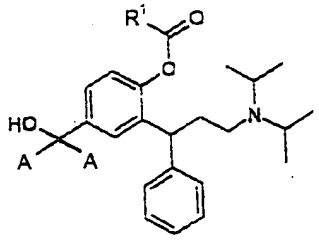
wherein R^{10} and R^{11} are as defined in claim 11, which comprises acid or base treatment of free benzylic alcohols selected from



and

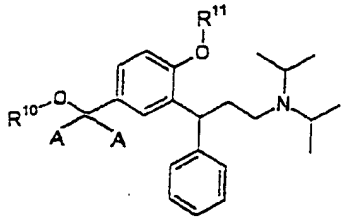


and



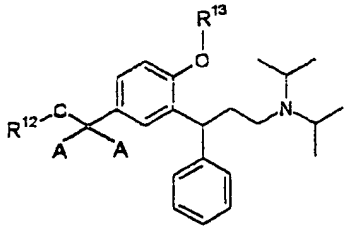
Formula II

or



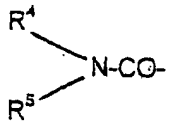
Formula VI

wherein R^{10} is hydrogen or

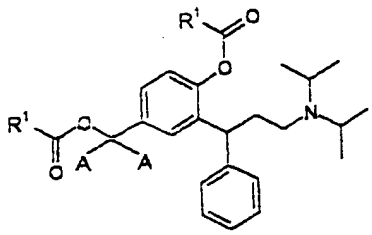


Formula VII

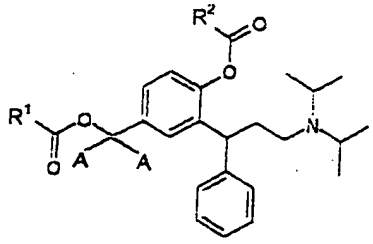
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



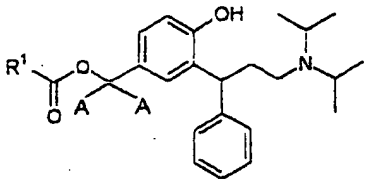
wherein R^4 and R^5 are as defined in claim 1 or of benzylic acylates selected from



Formula III



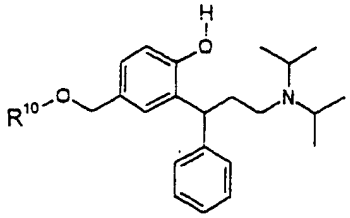
Formula IV



Formula V

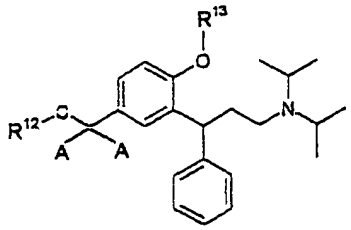
wherein R^1 and R^2 are as defined in claim 7 in the presence of suitable hydroxy reagents.

23. A process for the preparation of ethers of formula VI as defined in claim 11, which comprises treating a compound of the formula

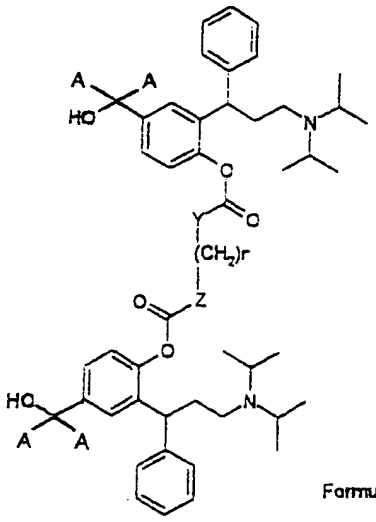


with an alkylating agent selected from alkyl halcgenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

24. A process for the preparation of carbonates and carbamates represented by the general formulae VII and VIII

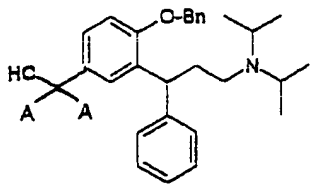


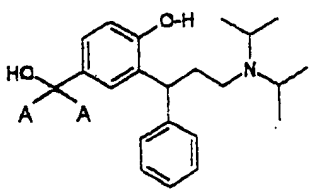
Formula VII

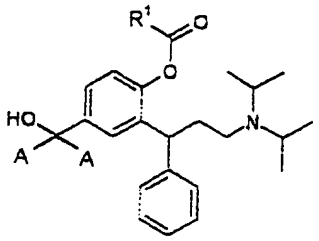


Formula VIII

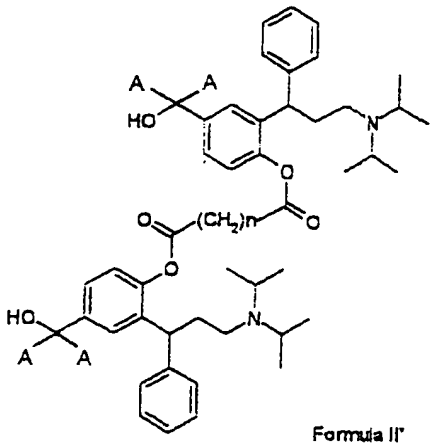
as defined in claim 13, which comprises reacting a compound selected from the group consisting of



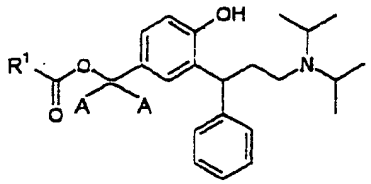




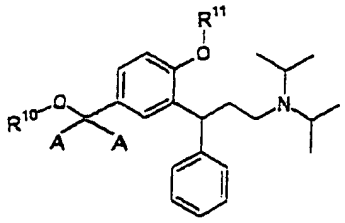
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as in claim 3, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is as defined in claim 11 with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

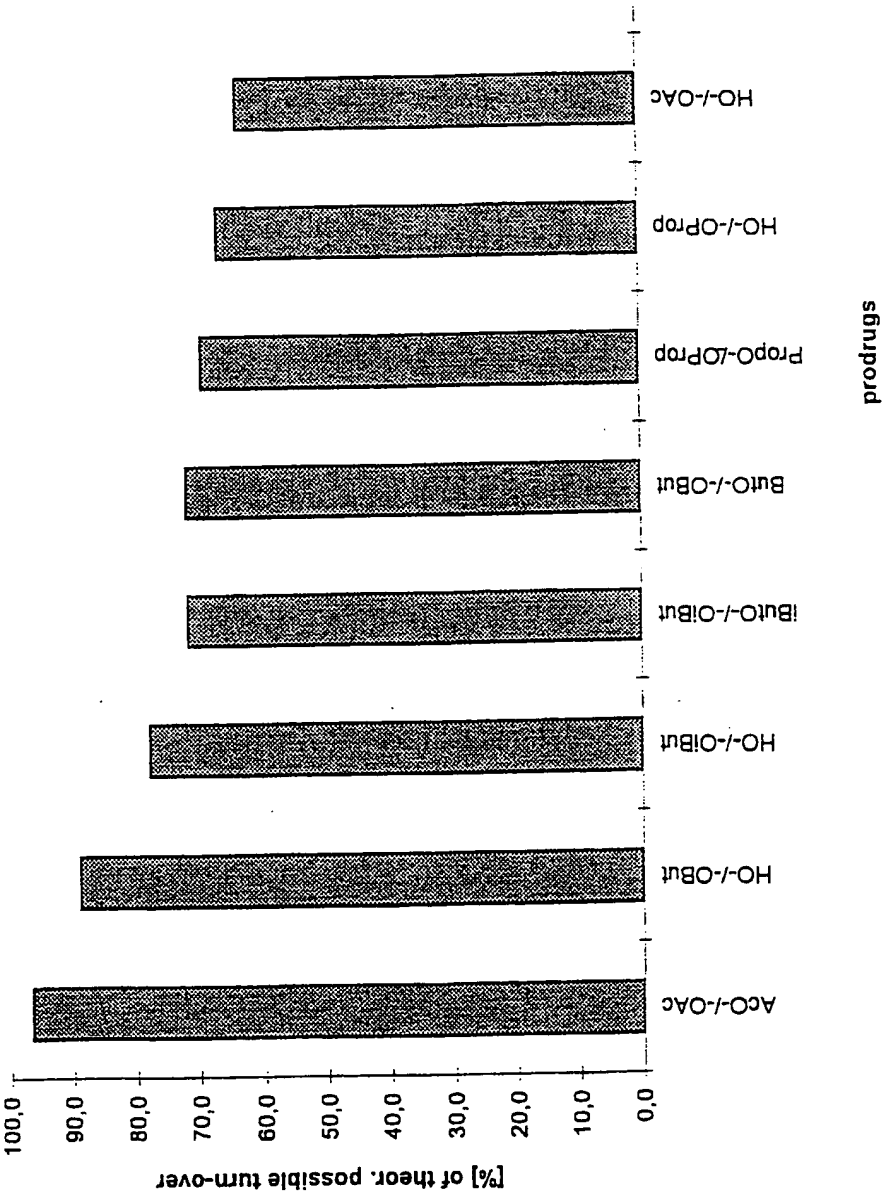
25. 3,3-Diphenylpropylamines as claimed in claims 1 to 15 for use as pharmaceutically active substances, especially as antimuscarinic agents.

26. A pharmaceutical composition comprising a 3,3-diphenylpropylamine as claimed in claim 1 to 15 and a compatible pharmaceutical carrier.

27. Use of a 3,3-diphenylpropylamine as claimed in claims 1 to 15 for preparing an antimuscarinic drug.

FIG. 1

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h



INTERNATIONAL SEARCH REPORT

Inter. onal Application No
PCT/EP 99/03212

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C1/00 C07C217/62 C07C217/48 C07C219/28 C07C219/22
C07D207/06 C07D295/06 C07C271/08 C07F7/18 C07C307/02
A61K31/135 A61K31/325 A61K31/40 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26 May 1994 (1994-05-26) cited in the application page 12, line 35 - page 13, line 15 ---	1-3,5,9, 25-27
A	WO 89 06644 A (KABIVITRUM AB) 27 July 1989 (1989-07-27) abstract ---	1-3, 25-27
A	LISBETH NILVEBRANT ET AL.: "Tolterodine - a new bladder-selective antimuscarinic agent" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 327, 1997, pages 195-207, XP002079629 cited in the application the whole document -----	1,25-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 July 1999	26/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rufet, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. onal Application No
PCT/EP 99/03212

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DE 69317898 T	15-10-1998
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Erteilt auf Grund der VO. vom 12. 5. 1943 – RGBl. II S. 150

AUSGEGEBEN AM
22. DEZEMBER 1952

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PATENTSCHRIFT

№ 766 207

KLASSE 12p GRUPPE 101

I 67372 IVc/12p

Nachträglich gedruckt durch das Deutsche Patentamt in München

(§ 20 des Ersten Gesetzes zur Änderung und Überleitung von Vorschriften auf dem Gebiet des gewerblichen Rechtsschutzes vom 8. Juli 1949)

Dr. Max Bockmühl, Dr. Gustav Ehrhart, Frankfurt/Main,
Dr. Otto Eisleb, Hofheim und Dr. Leonhardt Stein, Bad Soden (Taunus)
sind als Erfinder genannt worden

I. G. Farbenindustrie A. G., Frankfurt/Main

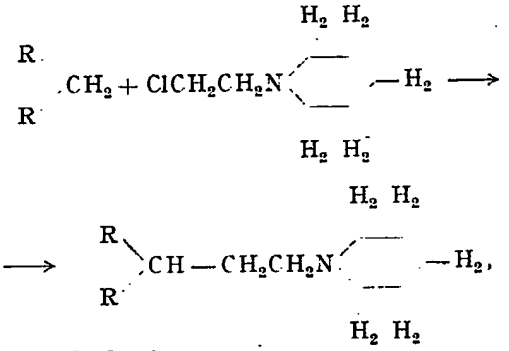
Verfahren zur Herstellung von basischen Verbindungen der Diarylmethanreihe

Patentiert im Deutschen Reich vom 9. Juli 1940 an
Der Zeitraum vom 8. Mai 1945 bis einschließlich 7. Mai 1950 wird auf die Patentdauer nicht angerechnet (Ges. v. 15. 7. 51)
Patenterteilung bekanntgemacht am 16. Oktober 1952

Es wurde gefunden, daß man zu basischen Verbindungen der Diarylmethanreihe, deren Arylreste auch untereinander verbunden sein können und die an dem die Arylreste tragenden Methankohlenstoff basische Alkylreste mit mindestens 2 C-Atomen in gerader Kette enthalten, auf folgende Weise gelangen kann:

Man kann ein Diarylmethan mit einem Aminoalkylhalogenid, dessen Aminogruppe durch Alkylgruppen substituiert sein kann, dessen halogentragende Alkylgruppe mindestens 2 C-Atome in gerader Kette enthält und in welchem zwei Alkylgruppen durch Brückenbindung miteinander verknüpft sein können, unter Verwendung halogenwasserstoffabspaltender Mittel umsetzen. Zum Beispiel erhält man durch Umsetzung von Diäthylaminoäthyl- oder Piperidinoäthylchlorid mit Diphenylmethan unter Verwendung von Natrium, Natriumamid, Phenylnatrium oder einer

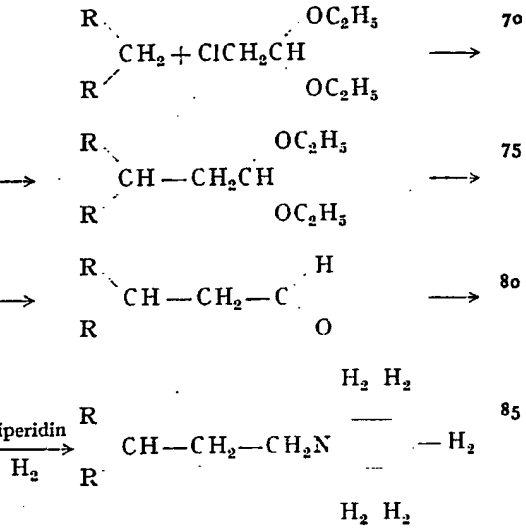
anderen geeigneten Alkaliverbindung als Halogenwasserstoffabspalter Diphenyldiäthylaminopropan bzw. Diphenylpiperidinopropan.



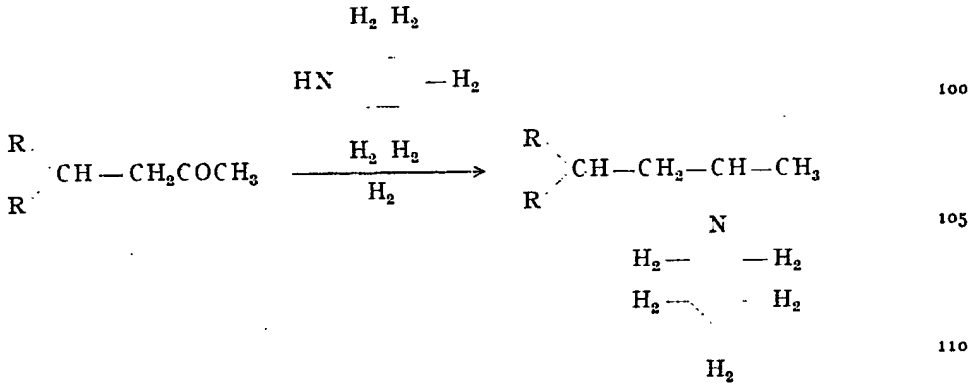
(R = Arylrest).

Ebenso lassen sich basische Alkylhalogenide mit verzweigter Kohlenstoffkette oder geeignete basische heterocyclische Halogenide, die obiger Definition entsprechen, verwenden, z. B. N-Methyl-β-halogenpiperidine. Auch läßt sich das Verfahren mit Diarylmethanen ausführen, deren Arylte miteinander verbunden sind, z. B. mit Fluoren.

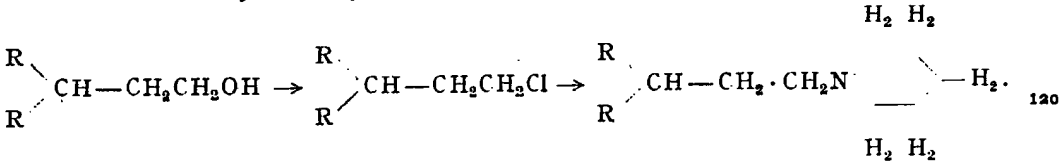
Man kann auch Diarylmethane, an deren Methankohlenstoff ein in geeignetem Abstand carbonylhaltiger Alkylrest steht, in Gegenwart von Ammoniak oder Aminen hydrieren. Zum Beispiel erhält man durch Einwirkung von Chloracetaldehydacetal auf Diphenylmethan unter Verwendung von Halogenwasserstoffabspaltern Diphenylpropionaldehydacetal, das sich durch Hydrolyse in den zugehörigen Aldehyd überführen läßt. Dieser gibt bei Hydrierung in Gegenwart von Ammoniak, primären oder sekundären Aminen die entsprechenden Diphenylpropylaminverbindungen.



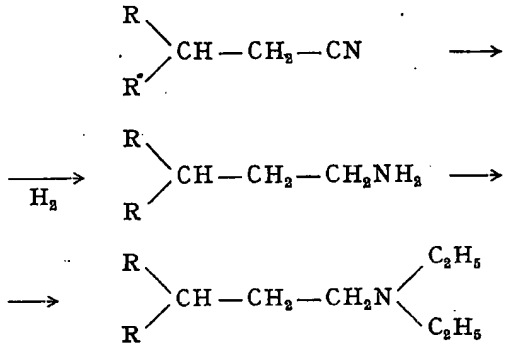
Geht man von Diphenyläthylmethylketon (Benzhydrylaceton) aus, so gelangt man beispielsweise durch Hydrierung in Gegenwart von Piperidin zu α. α-Diphenylpiperidinobutan.



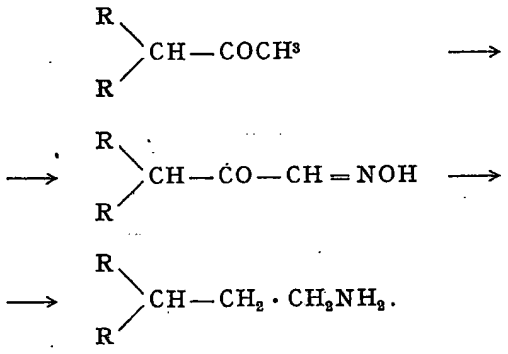
Ferner kann man geeignete Halogenalkyldiarylmethane mit Ammoniak oder Aminen umsetzen. Man führt beispielsweise Diphenylmethan vermittels Äthylenchlorhydrin in den Diphenylpropylalkohol über, wandelt diesen in das zugehörige Chlorid und letzteres vermittels Basen in die Diphenylpropylaminverbindungen um.



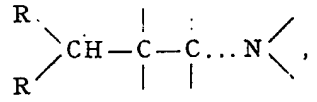
Auch kann man von einer nitrilhaltigen Diphenylmethanverbindung ausgehen, wie dem β,β-Diphenylpropionsäurenitril, welches man katalytisch zum Amin hydriert, worauf man gegebenenfalls die erhaltene Aminoverbindung alkyliert.



Endlich kann man Diaryl-alkylketone in die Isonitrosoverbindungen und letztere durch Reduktion in die zugehörigen Amine überführen, die gegebenenfalls noch alkyliert werden können. So kann man 1, 1-Diphenylaceton zum Diphenylisonitrosoketon nitrosieren, das sich durch Reduktion in das zugehörige Alkamin bzw. Amin überführen läßt.



Die Verfahrensprodukte bilden wasserlösliche Salze und zeigen sehr gute krampflösende Eigenschaften. Sie sollen daher als Arzneimittel oder zum Aufbau neuer Arzneistoffe verwendet werden. Sie besitzen die allgemeine Formel



in welcher also das Methankohlenstoffatom mit dem Stickstoffatom durch eine gerade Kette von mindestens 2 C-Atomen verbunden ist und diese Kette außerdem auch verzweigt sein kann.

Beispiele

1. Zu 101 g feingeschnittenem Natriumdraht in 100 ccm Benzol läßt man unter Rühren eine Mischung von 336 g Diphenylmethan und 235 g Chlorbenzol eintropfen. Die Temperatur wird zweckmäßig durch schwaches Kühlen auf etwa 35° gehalten. Nach etwa 7 bis 8 Stunden ist die Reaktion beendet. Dann läßt man ebenfalls bei 35° 240 g Piperidinoäthylchlorid eintropfen, rührt 1 Stunde bei Zimmertemperatur und kocht schließlich 1 Stunde unter Rückfluß. Die erkaltete Reaktionsmasse wird mit Wasser versetzt. Die benzolische Schicht wird abgetrennt und mit verdünnter Salzsäure ausgeschüttelt. Beim Alkalischmachen der sauren Lösung scheidet sich das α,α-Diphenyl-γ-piperidinopropan als Öl ab, welches unter 8 mm Druck bei 210 bis 220° siedet. Zur Darstellung des Chlorhydrats löst man die Base in Äther und säuert mit alkoholischer Salzsäure schwach an, wobei das zuerst ölig abgeschiedene Chlorhydrat sehr bald kristallinisch erstarrt. Durch Umkristallisieren aus Alkohol und Äther erhält man farblose Kristalle, die bei 214 bis 215° schmelzen.

2. Zu 11 g feingeschnittenem Natriumdraht in 100 ccm Benzol gibt man unter Rühren eine Mischung von 27 g Chlorbenzol und 34 g Diphenylmethan. Die Temperatur wird etwa 7 Stunden lang auf 35 bis 40° gehalten. Dann läßt man 21 g Morpholinoäthylchlorid unter schwacher Kühlung bei etwa 30 bis 35° eintropfen, rührt 1 Stunde bei Zimmertemperatur und kocht dann schließlich noch 1 Stunde unter Rückfluß. Man arbeitet wie im Beispiel 1 auf und erhält das α,α-Diphenyl-δ-morpholinopropan, welches unter 8 mm Druck bei 210 bis 220° siedet. Das Chlorhydrat bildet farblose Kristalle vom Schmelzpunkt 205 bis 206°.

3. Zu 10 g feingeschnittenem Natriumdraht in 100 ccm Benzol läßt man 25 g Chlorbenzol zutropfen. Die Temperatur steigt sehr bald und wird durch schwaches Kühlen auf 35° gehalten. Nach 2 Stunden ist die Reaktion beendet. Dann läßt man eine Lösung von 33 g Fluoren in 100 ccm Benzol zufließen, wobei nur geringe Temperaturerhöhung eintritt. Nach einstündigem Rühren bei Zimmertemperatur läßt man unter Kühlung 24 g Piperidinoäthylchlorid eintropfen. Zur Vervollständigung der Reaktion läßt man 1 Stunde bei Zimmertemperatur nachrühren und dann noch 1 Stunde unter Rückfluß kochen. Man erhält das α-Diphenylen-γ-piperidinopropan vom Kp. 230 bis 240° bei 7 mm Druck. Das Chlorhydrat schmilzt bei 205°.

4. Zu 5,5 g feingeschnittenem Natriumdraht in 50 ccm Benzol läßt man unter Rüh-

ren ein Gemisch von 13,5 g Chlorbenzol und 17 g Diphenylmethan eintropfen. Die Temperatur hält man 7 bis 8 Stunden lang auf 35 bis 40°. Dann läßt man bei 35° eine Lösung von 20 g 1, 3-Piperidinopropylbromid in 50 ccm Benzol eintropfen und kocht zur Vervollständigung der Reaktion noch 1 Stunde unter Rückfluß. Das erhaltene α, α-Diphenyl-δ-piperidinobutan siedet unter 8 mm Druck bei 225 bis 235°. Sein Chlorhydrat schmilzt bei 171°.

5. Zu 11 g feingeschnittenem Natriumdraht in 50 ccm Benzol läßt man unter Rühren ein Gemisch von 27 g Chlorbenzol und 34 g Diphenylmethan zutropfen. Man verfährt wie oben und läßt dann bei 35° 30 g α-Piperidino-β-chlorpropan zutropfen. Man erhält das α, α-Diphenyl-β-methyl-γ-piperidinopropan vom Kp. 220 bis 230° bei 13 mm Druck. Schmelzpunkt des Chlorhydrats 211 bis 212°.

6. Aus Diphenylmethan und N-Methyl-3-chlorpiperidin erhält man unter den gleichen Bedingungen das Diphenyl-[N-methylpiperidyl-(3)]-methan, welches unter 8 mm Druck bei 195 bis 200° siedet. Das Chlorhydrat schmilzt unscharf bei 110 bis 120° unter Zersetzung.

7. 67,2 g Diphenylmethan geben mit 60 g Chloracetaldehydacetal in benzolischer Lösung unter Verwendung von 20 g Natrium und 50 g Chlorbenzol das Diphenylpropionaldehydacetal, das durch einstündiges Erhitzen auf dem Dampfbad mit 100 ccm 2 n-Schwefelsäure unter Umschütteln in den freien Aldehyd übergeführt wird. Der Siedepunkt des Aldehyds ist 190 bis 200° bei 13 mm Druck. Zur Überführung des Aldehyds in das Amin werden 5,6 g Aldehyd in Gegenwart von 3 g Piperidin in alkoholischer Lösung und von Nickel als Katalysator hydriert. Das Hydrierungsprodukt wird wie üblich aufgearbeitet und stellt das α, α-Diphenyl-γ-piperidinopropan dar.

8. 84 g Diphenylmethan geben mit 61 g Essigsäurechloräthylester unter Verwendung von Chlorbenzol und Natrium den Essigsäure-1, 1-diphenylpropylester-(3), der bei 200° und 18 mm Druck destilliert. Zum Verseifen der Acetylverbindung werden 14 g Ester mit 40 ccm Alkohol und 20 g Ätzkali 2 Stunden auf dem Dampfbad erhitzt. Nach dem Abkühlen wird mit Wasser verdünnt, ausgeäthert und der Ätherrückstand im Vakuum abdestilliert. Das Diphenylpropanol, das auch durch Reduktion von β, β-Diphenylpropionsäureester mit Na und Alkohol gewonnen werden kann, siedet unter 18 mm Druck zwischen 180 und 190°. Zur Überführung in das Chlorid werden 10 g Diphenylpropanol mit 25 ccm Benzol und 10 g Thionylchlorid 2 Stunden auf dem Dampfbad gekocht. Das erhaltene Chlorid wird nach Entfernen der flüchtigen Stoffe mit 10 g Piperidin auf dem Dampfbad umgesetzt. Nach Aufarbeiten des Reaktionsproduktes erhält man das α, α-Diphenyl-γ-piperidinopropan.

9. 77 Gewichtsteile Diphenylmethan, 77 Gewichtsteile Toluol, 65 Gewichtsteile β-Chloräthyldiäthylamin und 20 Gewichtsteile fein pulverisiertes Natriumamid werden zusammen 6 Stunden unter Rückfluß gekocht. Nach dem Erkalten wird zur Auflösung des ausgeschiedenen Natriumchlorids Wasser zugesetzt; der abgetrennten Toluollösung wird die Base durch Ausschütteln mit verdünnter Salzsäure entzogen. Sie wird daraus mit Natronlauge als Öl abgeschieden, in Äther aufgenommen, abgetrennt und nach dem Trocknen über Kaliumcarbonat destilliert. Kp_4 170 bis 175°. Die Base, nämlich α, α-Diphenyl-γ-diäthylaminopropan, ist ein farbloses Öl. Das Hydrochlorid, aus der Base in Äther mit alkoholischer Salzsäure bereitet, ist ein farbloses Kristallpulver, das bei 143 bis 144° schmilzt.

10. 46 Gewichtsteile Fluoren, 80 Gewichtsteile Toluol, 37 Gewichtsteile β-Chloräthyldiäthylamin und 11 Gewichtsteile fein pulverisiertes Natriumamid werden zusammen unter Rühren erhitzt. Ab 60° beginnt die Reaktion. Das Gemisch wird langsam bis auf 100° erhitzt und 4 Stunden dabei gehalten. Nach dem Abkühlen wird verdünnte Salzsäure bis zur congosauren Reaktion zugesetzt. Aus der abgetrennten wäßrigen Salzlösung wird mit Natronlauge die Base gefällt, die unter 4 mm Druck bei 192 bis 210° als farbloses dickes Öl destilliert. Das Diäthylaminoäthylfluoren bildet ein gut kristallisierendes saures Sulfat, das sich aus Alkohol umkristallisieren läßt und in Wasser leicht löslich ist. Schmelzpunkt 217 bis 218°.

11. 13,7 g Benzhydrylaceton (Diphenyläthylmethylketon) werden in 200 ccm Alkohol mit 10 ccm 54%igem wäßrigem Methylamin in Gegenwart eines Nickelkatalysators bei 120° und 50 Atm. Druck mit Wasserstoff gerührt. Nach Beendigung der Wasserstoffaufnahme wird vom Nickel abgesaugt, der Alkohol abdestilliert und der Rückstand mit verdünnter Natronlauge und Äther behandelt. Die getrocknete ätherische Lösung wird mit ätherischer Salzsäure angesäuert, wobei sich sofort das α, α-Diphenyl-γ-methylaminobutanchlorhydrat abscheidet. Nach dem Umlösen aus Alkohol und Essigester erhält man farblose Prismen vom Schmelzpunkt 170 bis 172°.

12. Aus molekularen Mengen Diphenylmethan und Dimethylaminoäthylchlorid erhält man gemäß Beispiel 9 unter Verwendung von Natriumamid als halogenwasserstoffabspaltendem Mittel das α, α-Diphenyl-γ-dimethylaminopropan. Siedepunkt der Base 170

bis 173° unter 10 mm Druck. Das Chlorhydrat zeigt den Schmelzpunkt 168°.

13. Aus molekularen Mengen Diphenylmethan und Pyrrolidinoäthylchlorid (Kp_{35} 80 bis 81°) erhält man unter Verwendung von Natriumamid das α, α-Diphenyl-γ-pyrrolidinopropan vom Siedepunkt 190 bis 192° bei 4 mm Druck. Das primäre Phosphat schmilzt bei 160 bis 161°.

14. 19 g Benzhydrylaceton und 19 g Piperidin werden in alkoholischer Lösung in Gegenwart eines Nickelkatalysators bei 125° und etwa 50 atü hydriert. Das entstandene α, α-Diphenyl-γ-piperidinobutan zeigt den Siedepunkt 200 bis 203° unter 6 mm Druck. F. des Chlorhydrates 214°.

15. 11,9 g Natrium in 50 ccm Benzol und 29 g Chlorbenzol werden mit 43,3 g Diphenylmethan umgesetzt und dann mit 29 g 1-Chlor-2-piperidinopropan, dargestellt aus α-Brompropionsäureäthylester gemäß Helv. Chim. Acta Bd. 5, S. 476, umgesetzt. Das α, α-Diphenyl-γ-piperidinobutan siedet bei etwa 205° unter 6 mm Druck. Die Verbindung ist identisch mit der nach Beispiel 14 erhaltenen.

PATENTANSPRUCH:

Verfahren zur Herstellung von basischen Verbindungen der Diarylmethanreihe, deren Arylreste auch untereinander verbunden sein können und die im Methankohlenstoff basische Alkylreste von mindestens 2 Kohlenstoffatomen in gerader Kette enthalten, dadurch gekennzeichnet, daß man Diarylmethane mit Aminoalkylhalogeniden, deren Aminogruppe durch Alkylgruppen substituiert sein kann, deren halogentragende Alkylgruppe mindestens 2 C-Atome in gerader Kette enthält und in welchen zwei Alkylgruppen durch Brückenbindung miteinander verknüpft sein können, unter Verwendung von halogenwasserstoffabspaltenden Mitteln kondensiert; oder daß man Diarylmethane, an deren Methankohlenstoff ein in geeignetem Abstand carbonylhaltiger Alkylrest steht, in Gegenwart von Ammoniak, primären oder sekundären Basen hydriert; oder daß man Diarylalkylketone in die Isonitrosoverbindungen und letztere durch Reduktion in die zugehörigen Amine überführt und diese gegebenenfalls alkyliert; oder daß man geeignete Halogenalkyldiarylmethane mit Ammoniak oder Aminen umsetzt; oder daß man Diarylalkylmethane, die im aliphatischen Rest eine Nitrilgruppe enthalten, reduziert und die so erhaltenen Amine gegebenenfalls alkyliert.

5610 12.52

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 831 799 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
02.05.2003 Bulletin 2003/18

(21) Application number: **96918477.9**

(22) Date of filing: **07.06.1996**

(51) Int Cl.[7]: **A61K 31/135**, A61K 31/155, A61K 31/165, A61K 31/40, A61K 31/38, A61K 31/44, A61K 31/445

(86) International application number:
PCT/US96/10201

(87) International publication number:
WO 96/040097 (19.12.1996 Gazette 1996/55)

(54) **COMPOUNDS ACTIVE AT A NOVEL SITE ON RECEPTOR-OPERATED CALCIUM CHANNELS USEFUL FOR TREATMENT OF NEUROLOGICAL DISORDERS**

VERBINDUNGEN, DIE AN EINER NEUEN STELLE AUF REZEPTOR-STIMULIERTEN KALZIUMKANÄLEN WIRKSAM SIND, VERWENDBAR ZUR BEHANDLUNG VON NEUROLOGISCHEN KRANKHEITEN

COMPOSES ACTIFS AU NIVEAU D'UN NOUVEAU SITE DE CANAUX CALCIQUES ACTIVES PAR RECEPTEUR, UTILES DANS LE TRAITEMENT DE TROUBLES NEUROLOGIQUES

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **07.06.1995 US 485038**

(43) Date of publication of application:
01.04.1998 Bulletin 1998/14

(73) Proprietor: **NPS PHARMACEUTICALS, INC.**
Salt Lake City Utah 84108 (US)

(72) Inventors:
- **MUELLER, Alan, L.**
  Salt Lake City, UT 84105 (US)
- **MOE, Scott, T.**
  Salt Lake City, UT 84105 (US)
- **BALANDRIN, Manuel, F.**
  Sandy, UT 84093 (US)
- **DELMAR, Eric, G.**
  Salt Lake City, UT 84108 (US)
- **VANWAGENEN, Bradford, C.**
  Salt Lake City, UT 84124 (US)
- **ARTMAN, Linda, D.**
  Salt Lake City, UT 84105 (US)
- **BARMORE, Robert, M.**
  Salt Lake City, UT 84102 (US)
- **SMITH, Daryl, L.**
  Murray, UT 84123 (US)

(74) Representative: **VOSSIUS & PARTNER**
Siebertstrasse 4
81675 München (DE)

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Printed by Jouve, 75001 PARIS (FR)

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Description

Field of the Invention

[0001] This invention relates to compounds useful as neuroprotectants, anticonvulsants, anxiolytics, analgesics, muscle relaxants or adjuvants to general anesthetics. The invention relates as well to the use of such compounds for the preparation of a pharmaceutical composition for the treatment of neurological disorders and diseases, including, but not limited to, global and focal ischemic and hemorrhagic stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage such as in cardiac arrest or neonatal distress, epilepsy, anxiety, and neurodegenerative diseases such as Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis (ALS).

Background of the Invention

[0002] The following is a description of relevant art.

[0003] Glutamate is the major excitatory neurotransmitter in the mammalian brain. Glutamate binds or interacts with one or more glutamate receptors which can be differentiated pharmacologically into several subtypes. In the mammalian central nervous system (CNS) there are three main subtypes of ionotropic glutamate receptors, defined pharmacologically by the selective agonists *N*-methyl-D-aspartate (NMDA), kainate (KA), and α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA). The NMDA receptor has been implicated in a variety of neurological pathologies including stroke, head trauma, spinal cord injury, epilepsy, anxiety, and neurodegenerative diseases such as Alzheimer's Disease (Watkins and Collingridge, *The NMDA Receptor,* Oxford: IRL Press, 1989). A role for NMDA receptors in nociception and analgesia has been postulated as well (Dickenson, A cure for wind-up: NMDA receptor antagonists as potential analgesics. *Trends Pharmacol. Sci.* 11: 307, 1990). More recently, AMPA receptors have been widely studied for their possible contributions to such neurological pathologies (Fisher and Bogousslavsky, Evolving toward effective therapy for acute ischemic stroke. *J. Amer. Med. Assoc.* 270: 360, 1993; Yamaguchi *et al.,* Anticonvulsant activity of AMPA/kainate antagonists: Comparison of GYKI 52466 and NBQX in maximal electroshock and chemoconvulsant seizure models. *Epilepsy Res.* 15: 179, 1993).

[0004] When activated by glutamate, the endogenous neurotransmitter, the NMDA receptor permits the influx of extracellular calcium (Ca^{2+}) and sodium (Na^{+}) through an associated ion channel. The NMDA receptor allows considerably more influx of Ca^{2+} than do kainate or AMPA receptors (but see below), and is an example of a receptor-operated Ca^{2-} channel. Normally, the channel is opened only briefly, allowing a localized and transient increase in the, concentration of intracellular Ca^{2+} ($[Ca^{2+}]$), which, in turn, alters the functional activity of the cell. However, prolonged increases in $[Ca^{2+}]_1$, resulting from chronic stimulation of the NMDA receptor, are toxic to the cell and lead to cell death The chronic elevation in $[Ca^{2+}]_1$, resulting from stimulation of NMDA receptors, is said to be a primary cause of neuronal degeneration following a stroke (Choi, Glutamate neurotoxicity and diseases of the nervous system. *Neuron* 1: 623, 1988). Overstimulation of NMDA receptors is also said to be involved in the pathogenesis of some forms of epilepsy (Dingledine *et al.*, Excitatory amino acid receptors in epilepsy. *Trends Pharmacol. Sci.* 11: 334, 1990), anxiety (Wiley and Balster, Preclinical evaluation of *N*-methyl-D-aspartate antagonists for antianxiety effects: A review. In: *Multiple Sigma and PCP Receptor Ligands: Mechanisms for Neuromodulation and Neuroprotection?* NPP Books, Ann Arbor, Michigan, pp. 801-815, 1992), neurodegenerative diseases (Meldrum and Garthwaite, Excitatory amino acid neurotoxicity and neurodegenerative disease. *Trends Pharmacol. Sci.* 11: 379, 1990), and hyperalgesic states (Dickenson, A cure for wind-up: NMDA receptor antagonists as potential analgesics. *Trends Pharmacol. Sci.* 11: 307, 1990).

[0005] The activity of the NMDA receptor-ionophore complex is regulated by a variety of modulatory sites that can be targeted by selective antagonists. Competitive antagonists, such as the phosphonate AP5, act at the glutamate binding site, whereas noncompetitive antagonists, such as phencyclidine (PCP), MK-801 or magnesium (Mg^{2+}), act within the associated ion channel (ionophore). There is also a glycine binding site that can be blocked selectively with compounds such as 7-chlorokynurenic acid. There is evidence suggesting that glycine acts as a co-agonist, so that both glutamate and glycine are necessary to fully elicit NMDA receptor-mediated responses. Other potential sites for modulation of NMDA receptor function include a zinc (Zn^{2+}) binding site and a sigma ligand binding site. Additionally, endogenous polyamines such as spermine are believed to bind to a specific site and so *potentiate* NMDA receptor function (Ransom and Stec, Cooperative modulation of [^{3}H]MK-801 binding to the NMDA receptor-ion channel complex by glutamate, glycine and polyamines. *J. Neurochem.* 51: 830, 1988). The potentiating effect of polyamines on NMDA receptor function may be mediated via a specific receptor site for polyamines; polyamines demonstrating agonist, antagonist, and inverse agonist activity have been described (Reynolds, Arcaine is a competitive antagonist of the polyamine site on the NMDA receptor. *Europ. J. Pharmacol.* 177: 215, 1990; Williams *et al.*, Characterization of polyamines having agonist, antagonist, and inverse agonist effects at the polyamine recognition site of the NMDA receptor. *Neuron* 5: 199, 1990). Radioligand binding studies have demonstrated additionally that higher concentrations of polyamines *inhibit* NMDA receptor function (Reynolds and Miller, Ifenprodil is a novel type of NMDA receptor antag-

onist: Interaction with polyamines. *Molec. Pharmacol.* 36: 758, 1989; Williams *et al.*, Effects of polyamines on the binding of [^{3}H]MK-801 to the NMDA receptor: Pharmacological evidence for the existence of a polyamine recognition site. *Molec. Pharmacol.* 36: 575, 1989; Sacaan and Johnson, Characterization of the stimulatory and inhibitory effects of polyamines on [^{3}H]TCP binding to the NMDA receptor-ionophore complex. *Molec. Pharmacol.* 37: 572, 1990). This inhibitory effect of polyamines on NMDA receptors is probably a nonspecific effect (*i.e.*, not mediated via the polyamine receptor) because patch clamp electro-physiological studies have demonstrated that this inhibition is produced by compounds previously shown to act at the polyamine receptor as either agonists or antagonists (Donevan *et al.*, Arcaine Blocks *N*-Methyl-D-Aspartate Receptor Responses by an Open Channel Mechanism: Whole-Cell and Single-Channel Recording Studies in Cultured Hippocampal Neurons. *Molec. Pharmacol.* 41: 727, 1992; Rock and Macdonald, Spermine and Related Polyamines Produce a Voltage-Dependent Reduction of NMDA Receptor Single-Channel Conductance. *Molec. Pharmacol.* 42: 157, 1992).

[0006] Recent studies have demonstrated the molecular diversity of glutamate receptors (reviewed by Nakanishi, Molecular Diversity of Glutamate Receptors and Implications for Brain Function. *Science* 258: 597, 1992). At least five distinct NMDA receptor subunits (NMDAR1 and NMDAR2A through NMDAR2D), each encoded by a distinct gene, have been identified to date. Also, in NMDAR1, alternative splicing gives rise to at least six additional isoforms. It appears that NMDAR1 is a necessary subunit, and that combination of NMDAR1 with different members of NMDAR2 forms the fully functional NMDA receptor-ionophore complex. The NMDA receptor-ionophore complex, thus, can be defined as a hetero-oligomeric structure composed of at least NMDAR1 and NMDAR2 subunits; the existence of additional, as yet undiscovered, subunits is not excluded by this definition. NMDAR1 has been shown to possess binding sites for glutamate, glycine, Mg^{2+}, MK-801, and Zn^{2+}. The binding sites for sigma ligands and polyamines have not yet been localized on NMDA receptor subunits, although ifenprodil recently has been reported to be more potent at the NMDAR2B subunit than at the NMDAR2A subunit (Williams, Ifenprodil discriminates subtypes of the *N*-Methyl-D-aspartate receptor: selectivity and mechanisms at recombinant heteromeric receptors. Mol. Pharmacol. 44: B51, 1993).

[0007] Several distinct subtypes of AMPA and kainate receptors have been cloned as well (reviewed by Nakanishi, Molecular diversity of glutamate receptors and implications for brain function. *Science* 258: 597, 1992). Of particular relevance are the AMPA receptors designated GluR1, GluR2, GluR3, and GluR4 (also termed GluRA through GluRD), each of which exists in one of two forms, termed flip and flop, which arise by RNA alternative splicing. GluR1, GluR3 and GluR4, when expressed as homomeric or heteromeric receptors, are permeable to Ca^{2+}, and are therefore examples of receptor-operated Ca^{2+} channels. Expression of GluR2 alone or in combination with the other subunits gives rise to a receptor which is largely impermeable to Ca^{2+}. As most native AMPA receptors studied *in situ* are not Ca^{2+}-permeable (discussed above), it is believed that such receptors *in situ* possess at least one GluR2 subunit.

[0008] Furthermore, it is hypothesized that the GluR2 subunit is functionally distinct by virtue.of the fact that it contains an arginine residue within the putative pore-forming transmembrane region II; GluR1, GluR3 and GluR4 all contain a glutamine residue in this critical region (termed the Q/R site, where Q and R are the single letter designations for glutamine and arginine, respectively). The activity of the AMPA receptor is regulated by a number of modulatory sites that can be targeted by selective antagonists (Honore *et al.*, Quinoxalinediones: potent competitive non-NMDA glutamate receptor antagonists. *Science* 241: 701, 1988; Donevan and Rogawski, GYKI 52466, a 2,3-benzodiazepine, is a highly selective, noncompetitive antagonist of AMPA/kainate receptor responses. *Neuron* 10: 51, 1993). Competitive antagonists such as NBQX act at the glutamate binding site, whereas compounds such as GYKI 52466 appear to act noncompetitively at an associated allosteric site.

[0009] Compounds that act as competitive or noncompetitive antagonists at the NMDA receptor are said to be effective in preventing neuronal cell death in various *in vitro* neurotoxicity assays (Meldrum and Garthwaite, Excitatory amino acid neurotoxicity and neurodegenerative disease. *Trends Pharmacol. Sci.* 11: 379, 1990) and in *in vivo* models of stroke (Scatton, Therapeutic potential of NMDA receptor antagonists in ischemic cerebrovascular disease in *Drug Strategies* in the *Prevention and Treatment of Stroke,* IBC Technical Services Ltd., 1990). Such compounds are also effective anticonvulsants (Meldrum, Excitatory amino acid neurotransmission in epilepsy and anticonvulsant therapy in *Excitatory Amino Acids.* Meldrum, Moroni, Simon, and Woods (Eds.), New York: Raven Press, p. 655, 1991), anxiolytics (Wiley and Balster, Preclinical evaluation of *N*-methyl-D-aspartate antagonists for antianxiety effects: A review. In: *Multiple Sigma and PCP Receptor Ligands: Mechanisms for Neuromodulation and Neuroprotection?* NPP Books, Ann Arbor, Michigan, pp. 801-815, 1992), and analgesics (Dickenson, A cure for wind-up: NMDA receptor antagonists as potential analgesics. *Trends Pharmacol. Sci.* 11: 307, 1990), and certain NMDA receptor antagonists may lessen dementia associated with Alzheimer's Disease (Hughes, Merz' novel approach to the treatment of dementia. *Script* No. 1666: 24, 1991).

[0010] Similarly, AMPA receptor antagonists have come under intense scrutiny as potential therapeutic agents for the treatment of such neurological disorders and diseases. AMPA receptor antagonists have been shown to possess neuroprotectant (Fisher and Bogousslavsky, Evolving coward effective therapy for acute ischemic stroke. *J. Amer. Med. Assoc.* 270: 360, 1993) and anticonvulsant (Yamaguchi *et al.*, Anticonvulsant activity of AMPA/kainate antagonists: comparison of GYKI 52466 and NBQX in maximal electroshock and chemoconvulsant seizure models. *Epilepsy*

Res. 15: 179, 1993) activity in animal models of ischemic stroke and epilepsy, respectively.

[0011] The nicotinic cholinergic receptor present in the mammalian CNS is another example of a receptor-operated Ca^{2+} channel (Deneris *et al.*, Pharmacological and functional diversity of neuronal nicotinic acetylcholine receptors. *Trends Pharmacol.* Sci. 12: 34, 1991). Several distinct receptor subunits have been cloned, and these subunits can be expressed, in *Xenopus* oocytes for example, to form functional receptors with their associated cation channels. It is hypothesized that such receptor-ionophore complexes are heteropentameric structures. The possible role of nicotinic receptor-operated Ca^{2+} channels in the pathology of neurological disorders and diseases such as ischemic stroke, epilepsy and neurodegenerative diseases has been largely unexplored.

[0012] It has been demonstrated previously that certain spider and wasp venoms contain arylalkylamine toxins (also called polyamine toxins, arylamine toxins, acylpolyamine toxins or polyamine amide toxins) with activity against glutamate receptors in the mammalian CNS (for reviews see Jackson and Usherwood, Spider toxins as tools for dissecting elements of excitatory amino acid transmission. *Trends Neurosci.* 11: 278, 1988; Jackson and Parks, Spider Toxins: Recent Applications In Neurobiology. *Annu. Rev. Neurosci.* 12: 405, 1989; Saccomano et al., Polyamine spider toxins: Unique pharmacological tools. *Annu. Rep. Med. Chem.* 24: 287, 1989; Usherwood and Blagbrough, Spider Toxins Affecting Glutamate Receptors: Polyamines in Therapeutic Neurochemistry. *Pharmacol. Therap.* 52: 245, 1991; Kawai, Neuroactive Toxins of Spider Venoms. *J. Toxicol. Toxin Rev.* 10: 131, 1991). Arylalkylamine toxins were initially reported to be selective antagonists of the AMPA/kainate subtypes of glutamate receptors in 'the mammalian CNS (Kawai *et al.*, Effect of a spider toxin on glutaminergic synapses in the mammalian brain. *Biomed. Res.* 3: 353, 1982; Saito *et al.*, Spider Toxin (JSTX) blocks glutamate synapse in hippocampal pyramidal neurons. Brain Res. 346: 397, 1985; Saito *et al.*, Effects of a spider toxin (JSTX) on hippocampal CA1 neurons *in vitro. Brain Res.* 481: 16, 1989; Akaike *et al.*, Spider toxin blocks excitatory amino acid responses in isolated hippocampal pyramidal neurons. *Neurosci. Lett.* 79: 326, 1987; Ashe *et al.*, Argiotoxin-636 blocks excitatory synaptic transmission in rat hippocampal CAI pyramidal neurons. *Brain Res.* 480: 234, 1989; Jones *et al.*, Philanthotoxin blocks quisqualate-induced, AMPA-induced and kainate-induced, but not NMDA-induced excitation of rat brainstem neurones *in vivo. Br. J. Pharmacol.* 101: 968, 1990). Subsequent studies have demonstrated that while certain arylalkylamine toxins are both nonpotent and nonselective at various glutamate receptors, other arylalkylamines are both very potent and selective at antagonizing responses mediated by NMDA receptor activation in the mammalian CNS (Mueller *et al.*, Effects of polyamine spider toxins on NMDA receptor-mediated transmission in rat hippocampus *in vitro. Soc. Neurosci. Abst.* 15: 945, 1989; Mueller *et al.*, Arylamine spider toxins antagonize NMDA receptor-mediated synaptic transmission in rat hippocampal slices. *Synapse* 9: 244, 1991; Parks *et al.*, Polyamine spider toxins block NMDA receptor-mediated increases in cytosolic calcium in cerebellar granule neurons. *Soc. Neurosci. Abst.* 15: 1169, 1989; Parks *et al.*, Arylamine toxins from funnel-web spider (*Agelenopsis aperta*) venom antagonize *N*-methyl-D-aspartate receptor function in mammalian brain. *J. Biol. Chem.* 266: 21523, 1991; Priestley *et al.*, Antagonism of responses to excitatory amino acids on rat cortical neurones by the spider toxin, argiotoxin-636. *Br. J. Pharmacol.* 97: 1315, 1989; Draguhn *et al.*, Argiotoxin-636 inhibits NMDA-activated ion channels expressed in *Xenopus* oocytes. *Neurosci. Lett.* 132: 187, 1991; Kiskin *et al.*, A highly potent and selective *N*-methyl-D-aspartate receptor antagonist from the venom of the *Agelenopsis* aperta spider. *Neuroscience* 51: 11, 1992; Brackley *et al.*, Selective antagonism of native and cloned kainate and NMDA receptors by polyamine-containing toxins. *J. Pharmacol. Exp. Therap.* 266: 1573, 1993; Williams, Effects of *Agelenopsis aperta* toxins on the N-methyl-D-aspartate receptor: Polyamine-like and high-affinity antagonist actions. *J. Pharmacol. Exp. Therap.* 266: 231, 1993). Inhibition of nicotinic cholinergic receptors by the arylalkylamine toxin philanthotoxin has also been reported (Rozental *et al.*, Allosteric inhibition of nicotinic acetylcholine receptors of vertebrates and insects by philanthotoxin. *J. Pharmacol. Exp. Therap.* 249: 123, 1989).

[0013] Parks *et al.* (Arylamine toxins from funnel-web spider (*Agelenopsis aperta*) venom antagonize *N*-methyl-D-aspartate receptor function in mammalian brain. *J. Biol. Chem.* 266: 21523, 1991), describe arylalkylamine spider toxins (α-agatoxins) which antagonize NMDA receptor function in mammalian brain. The authors discuss the mechanism of action of arylalkylamine toxins, and indicate that an NMDA receptor-operated ion channel is the probable site of action of the α-agatoxins, and most probably other spider venom arylalkylamines. They state:

> "The discovery that endogenous polyamines in the vertebrate brain modulate the function of NMDA receptors suggests that the arylamine toxins may produce their antagonism via a polyamine-binding site on glutamate receptors. Brackley *et al.* studied the effects of spermine and philanthotoxin 433 on the responses evoked by application of excitatory amino acids in *Xenopus* oocytes injected with mRNA from rat or chick brain. These authors reported that, at concentrations below those that antagonize glutamate receptor function, both spermine and philanthotoxin potentiate the effects of excitatory amino acids and some other neurotransmitters. On the basis of these and other data, Brackley *et al.* concluded that the arylamine toxins may, by binding nonspecifically to the membranes of excitable cells, reduce membrane fluidity and alter receptor function. The validity of this intriguing idea for NMDA receptor function is not well supported by two recent binding studies. Reynolds reported that argiotoxin 636 inhibits the binding of [^{3}H]MK-801 to rat brain membranes in a manner that is insensitive to glutamate, glycine,

or spermidine. This author concluded that argiotoxin 636 exerts a novel inhibitory effect on the NMDA receptor complex by binding to one of the Mg^{2+} sites located within the NMDA-gated ion channel. Binding data reported by Williams *et al.* also support the conclusion that argiotoxin 636 does not act primarily at the polyamine modulatory site on the NMDA receptor, but rather acts directly to produce an activity-dependent block of the ion channel. It is already known that compounds such as phencyclidine and ketamine can block the ion channels associated with both arthropod muscle glutamate receptors and mammalian NMDA receptors. Thus, it seems possible that vertebrate and invertebrate glutamate receptors share additional binding sites for allosteric modulators of receptor function, perhaps related to divalent cation-binding sites. Clearly, considerable additional work will be needed to determine if the arylamines define such a novel regulatory site."

[0014] Usherwood and Blagbrough (Spider Toxins Affecting Glutamate Receptors: Polyamines in Therapeutic Neurochemistry. *Pharmacol. Therap.* 52: 245, 1991) describe a proposed intracellular binding site for arylalkylamine toxins (polyamine amide toxins) located within the membrane potential field referred to as the QUIS-R channel selectivity filter. The authors postulate that the binding site for polyamine amide toxins may occur close to the internal entrance of the channel gated by the QUIS-R of locust muscle. The authors also note that one such toxin, argiotoxin-636, selectively antagonizes the NMDA receptor in cultured rat cortical neurons.

[0015] Gullak *et al.* (CNS binding sites of the novel NMDA antagonist Arg-636. *Soc. Neurosci. Abst.* 15: 1168, 1989), describe argiotoxin-636 (Arg-636) as a polyamine (arylalkylamine) toxin component of a spider venom. This toxin *is* said to block NMDA-induced elevation of cGMP in a noncompetitive fashion. The authors state that:

"[^{125}I]Arg-636 bound to rat forebrain. membranes with K_d and B_{max} values of 11.25 μM and 28.95 pmol/mg protein (80% specific). The ability of other known polyamines and recently discovered polyamines from *Agelenopsis aperta* to inhibit binding paralleled neuroactivity as functional NMDA antagonists. No other compounds tested were able to block specific binding."

[0016] The authors then stated that polyamines (arylalkylamines) may antagonize responses to NMDA by interacting with membrane ion channels.

[0017] Seymour and Mena (*In vivo* NMDA antagonist activity of the polyamine spider venom component, argiotoxin-636. *Soc. Neurosci. Abst.* 15: 1168, 1989) describe studies that are said to show that argiotoxin-636 does not significantly affect locomotor activity at doses that are effective against audiogenic seizures in DBA/2 mice, and that it significantly antagonizes NMDA-induced seizures with a minimal effective dose of 32 mg/kg given subcutaneously (s.c.).

[0018] Herold and Yaksh (Anesthesia and muscle relaxation with intrathecal injections of AR636 and AG469, two acylpolyamine spider toxins, in rats. *Anesthesiology* 77: 507, 1992) describe studies that are said to show that the arylalkylamine argiotoxin-636 (AR636), but not agatoxin-489 (AG489). produces muscle relaxation and anesthesia following intrathecal administration in rats.

[0019] Williams (Effects of *Agelenopsis aperta* toxins on the *N*-methyl-D-aspartate receptor: Polyamine-like and high-affinity antagonist actions, *J. Pharmacol. Exp. Therap.* 266: 231, 1993) reports that the α-agatoxins (arylalkylamines) Agel-489 and Agel-505 enhance the binding of [^{3}H]MK-801 to NMDA receptors on membranes prepared from rat brain by an action at the stimulatory polyamine receptor; polyamine receptor agonists occluded the stimulatory effects of Agel-489 and Agel-505 and polyamine receptor antagonists inhibited the stimulatory effect of Agel-505. Higher concentrations of Agel-489 and Agel-505, and argiotoxin-636 at all concentrations tested, had inhibitory effects on the binding of [^{3}H]MK-801. In *Xenopus* oocytes voltage-clamped at -70 mV, Agel-505 inhibited responses to NMDA with an IC_{50} of 13 nM; this effect of Agel-505 occurred at concentrations approximately 10,000-fold lower than those that affected [^{3}H]MK-801 binding. Responses to kainate were inhibited only 11% by 30 nM Agel-505. The antagonism of NMDA-induced currents by Agel-505 was strongly voltage-dependent, consistent with an open-channel blocking effect of the toxin. Williams states:

"Although α-agatoxins can interact at the positive allosteric polyamine site on the NNDA receptor, stimulatory effects produced by this interaction may be masked in functional assays due to a separate action of the toxins as high-affinity, noncompetitive antagonists of the receptor."

[0020] Brackley et al. (Selective antagonism of native and cloned kainate and NMDA receptors by polyamine-containing toxins, *J. Pharmacol. Exp. Therap.* 266: 1573, 1993) report that the polyamine-containing toxins (arylalkylamines) philanthotoxin-343 (PhTX-343) and argiotoxin-636 (Arg-636) produce reversible, noncompetitive, partly voltage-dependent antagonism of kainate- and NMDA-induced currents in *Xenopus* oocytes injected with rat brain RNA. Arg-636 was demonstrated to be selective for NMDA-induced responses (IC_{50} = 0.04 μM) compared to kainate-induced responses (IC_{50} = 0.07 μM), while PhTX-343 was selective for kainate-induced responses (IC_{50} = 0.12 μM) compared to NMDA-induced responses (IC_{50} = 2.5 μM). Arg-636 more potently antagonized responses co NMDA in

Xenopus oocytes expressing cloned NMDAR1 subunits (IC_{50} = 0.09 μM) than responses to kainate in oocytes expressing either cloned GluR1 (IC_{50} = 3.4 μM) or GluR1+GluR2 subunits (IC_{50} ≈ 300 μM). PhTX-343, on the other hand, was equipotent at antagonizing NMDAR1 (IC_{50} = 2.19 μM) and GluR1 (IC_{50} = 2.8 μM), but much less potent against GluR1+GluR2 subunits (IC_{50} = 270 μM).

[0021] Raditsch *et al.* (Subunit-specific block of cloned NMDA receptors by argiotoxin-636. *FEBS Lett.* 324: 63, 1993) report that Arg-636 more potently antagonizes responses in *Xenopus* oocytes expressing NMDAR1+NMDAR2A subunits (IC_{50} = 9 nM) or NMDAR1+NMDAR2B subunits (IC_{50} = 2.5 nM) than NMDAR1+NMDAR2C subunits (IC_{50} = 460 nM), even though all of the receptor subunits contain an asparagine residue in the putative pore-forming transmembrane region II (the Q/R site, as discussed above). The authors state that the large difference in Arg-636 sensitivity between NMDAR1+NMDAR2A and NMDAR1+NMDAR2C channels "must be conferred by other structural determinants."

[0022] Herlitz *et al.* (Argiotoxin detects molecular differences in AMPA receptor channels. *Neuron* 10: 1131, 1993) report that Arg-636 antagonizes subtypes of AMPA receptors in a voltage- and use-dependent manner consistent with open-channel blockade. Arg-636 potently antagonizes Ca^{2+}-permeable AMPA receptors comprised of GluRAi (K_1 = 0.35 μM), GluRCi (K_1 = 0.23 μM), or GluRDi subunits (K_1 = 0.43 μM), while being essentially ineffective against Ca^{2+}-impermeable GluRBi subunits at concentrations up to 10 μM. Other data reported by these investigators strongly suggest that the Q/R site in the purative pore-forming transmembrane region II is of primary importance in determining Arg-636 potency and Ca^{2+} permeability.

[0023] Blaschke *et al.* (A single amino acid determines the subunit-specific spider toxin block of α-amino-3-hydroxy-5-methylisoxazole-4-propionate/kainate receptor channels. *Proc. Natl. Acad. Sci. USA* 90: 6528, 1993) report that the arylalkylamine JSTX-3 potently antagonizes responses to kainate in *Xenopus* oocytes expressing GluR1 (IC_{50} = 0.04 μM) or GluR3 (IC_{50} = 0.03 μM) subunits, but that expressed receptors in which a GluR2 subunit is present are essentially unaffected by the toxin. site-directed mutagenesis studies strongly implicate the Q/R site as the primary site influencing toxin potency.

[0024] Nakanishi *et al.* (Bioorganic studies of transmitter receptors with philanthotoxin analogs. *Pure Appl. Chem.*, in press) have synthesized a number of highly potent photoaffinity labeled philanthotoxin (PhTX) analogs. Such analogs have been studied on expressed nicotinic cholinergic receptors as a model system for receptor-operated calcium channels. These investigators suggest that these PhTX analogs block the ion channel with the hydrophobic headpiece of the toxin binding to a site near the cytoplasmic surface while the polyamine tail extends into the ion channel from the cytoplasmic side.

[0025] In US-A 4,018,895 aryloxy phenyl propylamines are disclosed which are useful as antidepressants, wherein the phenyl ring is not substituted.

[0026] US-A 5,281,624 pertains to N-alkyl-3-phenyl-3(2-substituted phenoxy) propylamines useful to treat more pinephinine imbalance associated neurological disorders

[0027] EP-A 0 399 504 discloses aryloxyphenyl propylamines which may be used for the treatment of anoxia, migrane, ischemia, traumatic injury and neurodegenerative disease.

Summary of the Invention

[0028] Applicant has determined that simplified arylalkylamines (see below) are potent, noncompetitive antagonists of the NMDA receptor-ionophore complex. For example, such compounds bind to the site labeled by [^{3}H]MK-801 at concentrations ranging approximately 1 to 400-fold higher - than those which antagonize NMDA receptor-mediated function. Such simplified arylalkylamines possess one or more of the following additional biological properties: significant neuroprotectant activity, significant anticonvulsant activity, significant analgesic activity, no PCP-like stereotypic behavior in rodents (hyperexcitabilicy and head weaving) at effective neuroprotectant, anticonvulsant and analgesic doses, no generalization to PCP in a PCP discrimination assay at effective neuroprotectant, anticonvulsant and analgetic doses, no neuronal vacuolization at effective neuroprotectant, anticonvulsant and analgesic doses, significantly less potent activity against voltage-sensitive calcium channels, and minimal hypotensive activity at effective neuroprotectant, anticonvulsant and analgesic doses. Such compounds may, however, inhibit the induction of LTP in rat hippocampal slices and may produce motor impairment at neuroprotectant, anticonvulsant and analgesic doses.

[0029] By "neurological disorder or disease" is meant a disorder or disease of the nervous system including, but not limited to, global and focal ischemic and hemorrhagic stroke, head trauma, spinal cord injury, spinal cord ischemia, ischemia- or hypoxia-induced nerve cell damage, hypoxia-induced nerve cell damage as in cardiac arrest or neonatal distress, epilepsy, anxiety, neuropsychiatric or cognitive deficits due to ischemia or hypoxia such as those that frequently occur as a consequence of cardiac surgery under cardiopulmonary bypass, and neurodegenerative disease. Also meant by "neurological disorder or disease" are those disease states and conditions in which a neuroprotectant, anticonvulsant, anxiolytic, analgesic, muscle relaxant and/or adjunct in general anesthesia may be indicated, useful, recommended or prescribed.

[0030] By "neurodegeneracive disease" is meant diseases including, but not limited to, Alzheimer's Disease, Huntington's Disease, Patkinson's Disease, and amyotrophic lateral sclerosis (ALS).

[0031] By "neuroprotectant" is meant a compound capable of preventing the neuronal damage or death associated with a neurological disorder or disease.

[0032] By "anticonvulsant" is meant a compound capable of reducing convulsions produced by conditions such as simple partial seizures, complex partial seizures, status epilepticus, and trauma-induced seizures such as occur following head injury, including head surgery.

[0033] By "anxiolytic" is means a compound capable of relieving the feelings of apprehension, uncertainty and fear that are characteristic of anxiety.

[0034] By "analgesic" is meant a compound capable of relieving pain by altering perception of nociceptive stimuli without producing anesthesia or loss of consciousness.

[0035] By "muscle relaxant" is meant a compound that reduces muscular tension.

[0036] By "adjunct in general anesthesia" is meant a compound useful in conjunction with anesthetic agents in producing the loss of ability to perceive pain associated with the loss of consciousness.

[0037] By "potent" or "active" is meant that the compound has activity at receptor-operated calcium channels, including NMDA receptors, Ca^{2+}-permeable AMPA receptors, and nicotinic cholinergic receptors, with an IC_{50} value less than 10 μM, more preferably less than 100 nM, and even more preferably less than 1 nM.

[0038] By "selective" is meant that the compound is potent at receptor-operated calcium channels as defined above, but is less potent by greater than 10-fold, more preferably 50-fold, and even more preferably 100-fold, at other neurotransmitter receptors, neurotransmitter receptor-operated ion channels, or voltage-dependent ion channels.

[0039] By "biochemical and electrophysiological assays of receptor-operated calcium channel function" is meant assays designed to detect by biochemical or electrophysiological means the functional activity of receptor-operated calcium channels. Examples of such assays include, but are not limited to, the fura-2 fluorimetric assay for cytosolic calcium in cultured rat cerebellar granule cells (see Example 1 and Example 2), patch clamp electrophysiolocial assays (see Example 3 and Example 27), rat hippocampal slice synaptic transmission assays, radioligand binding assays Example 21, Example 22, and Example 23), and *in vitro* neuroprotectant assays (see Example 3).

[0040] By "efficacy" is meant that a statistically significant level of the desired activity is detectable with a chosen compound; by "significant" is meant a statistical significance at the $p < 0.05$ level.

[0041] By "neuroprotectant activity" is meant efficacy in treatment of neurological disorders or diseases including, but not limited to, global and focal ischemic and hemorrhagic stroke, .head trauma, spinal cord injury, spinal cord ischemia, ischemia- or hypoxia-induced nerve cell damage, hypoxia-induced nerve cell damage as in cardiac arrest or neonatal distress, neuropsychiatric or cognitive deficits due to ischemia or hypoxia such as those that frequently occur as a consequence of cardiac surgery under cardiopulmonary bypass, and neurodegenerative diseases such as Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, and amyocropbic lateral sclerosis (ALS) (see Examples 4 and 5, below) .

[0042] By "anticonvulsant activity" is meant efficacy in reducing convulsions produced by conditions such as simple partial seizures, complex partial seizures, status epilepticus, and trauma-induced seizures such as occur following head injury, including head surgery (see Examples 6 and 7, below).

[0043] By "anxiolytic activity" is meant that a compound reduces the feelings of apprehension, uncertainty and fear that are characteristic of anxiety.

[0044] By "analgesic activity" is meant that a compound produces the absence of pain in response to a stimulus that would normally be painful. Such activity would be useful in clinical conditions of acute and chronic pain including, but not limited- to the following: preemptive preoperative analgesia; peripheral neuropathies such as occur with diabetes mellitus and multiple sclerosis; phantom limb pain; causalgia; neuralgias such as occur with herpes zoster; central pain such as that seen with spina cord lesions; hyperalgesia; and allodynia.

[0045] By "causalgia" is meant a painful disorder associated with injury of peripheral nerves.

[0046] By "neuralgia" is meant pain in the distribution of a nerve or nerves.

[0047] By "central pain" is meant pain associated with a lesion of the central nervous system.

[0048] By "byperalgesia" is meant an increased response to a stimulus that is normally painful.

[0049] By "allodynia" is meant pain due to a stimulus that does not normally provoke pain (see Examples 8 through 11, below).

[0050] By "induction of long-term potentiation in rat hippocampal slices" is meant the ability of tetanic electrical stimulation of afferent Schaffer collateral fibers to elicit long-term increases in the strength of synaptic transmission at the Schaffer collateral-CA1 pyramidal cell pathway in rat hippocampal slices maintained *in vitro* (see Example 16).

[0051] By "therapeutic dose" is meant an amount of a compound that relieves to some extent one or more symptoms of the disease or condition of the patient. Additionally, by "therapeutic dose" is meant an amount that rerurns to normal, either partially or completely, physiological or biochemical parameters associated with or causative of the disease or condition. Generally, id is an amount between about 1 nmole and 1 μmole of the compound, dependent on its EC_{50}

(IC_{50} in the case of an antagonist) and on the age, size, and disease associated with the patient.

[0052] By "impair cognition" is meant the ability to impair the acquisition of memory or the performance of a learned task (see Example 17). Also by "impair congnition" is meant the ability to interfere with normal rational thought processes and reasoning.

[0053] By "disrupt motor function" is meant the ability to significantly alter locomotor activity (see Example 12) or elicit significant ataxia, loss of the righting reflex, sedation or muscle relaxation (see Example 13).

[0054] By "locomotor activity" is meant the ability to perform normal ambulatory movements.

[0055] By "loss of the righting reflex" is meant the ability of an animal, typically a rodent, to right itself after being placed in a supine position.

[0056] By "neuronal vacuolization" is meant the production of vacuoles in neurons of the cingulate cortex or retrosplenial cortex (see Example 15).

[0057] By "cardiovascular activity " is meant the ability to elicit significant changes in parameters including, but not limited to, mean arterial blood pressure and heart rate (see Examples 18 and 19).

[0058] By "hyperexcitability" is meant an enhanced susceptibility to an excitatory stimulus. Hyperexcitability is often manifested as a significant increase in locomotor activity in rodents administered a drug (see Example 12).

[0059] By "sedation" is meant a calmative effect, or the allaying of activity and excitement. Sedation is often manifested as a significant decrease in locomotor activity in rodents administered a drug (see Example 12).

[0060] By "PCP-like abuse potential" is meant the potential of a drug to be wrongfully used, as in the recreational use of PCP (i.e., "angel dust") by man. It is believed that PCP-like abuse potential can be predicted by the ability of a drug to generalize to PCP in rodents trained to discriminate PCP from saline (see Example 14.)

[0061] By "generalization to PCP" is meant that a compound is perceived as being PCP in rodents trained to discriminate PCP from saline (see Example 14).

[0062] By "PCP-like psychotomimetic activity" is meant the ability of a drug to elicit in man a behavioral syndrome resembling acute psychosis, including visual hallucinations, paranoia, agitation, and confusion. It is believed that PCP-like psychotomimetic activity can be predicted in rodents by the ability of a drug to produce PCP-like stereotypic behaviors including ataxia, head weaving, hyperexcitability, and generalization to PCP in rodents trained to discriminate PCP from saline (see Example 12, Example 13, and Example 14).

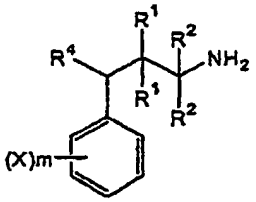
[0063] By "ataxia" is meant a deficit in muscular coordination.

[0064] By "head weaving" is meant the stereotypic behavior elicited in rodents by PCP in which the head is repeatedly moved slowly and broadly from side to side.

[0065] By "pharmaceutical composition" is meant a therapeutically effective amount of a compound of the present invention in a pharmaceutically acceptable carrier, *i.e.*, a formulation to which the compound can be added to dissolve or otherwise facilitate administration of the compound. Examples of pharmaceutically acceptable carriers include water, saline, and physiologically buffered saline. Such a pharmaceutical composition is provided in a suitable dose. Such compositions are generally those which are approved for use in treatment of a specified disorder by the FDA or its equivalent in non-U.S. countries.

[0066] Treatment involves the steps of first identifying a patient that suffers from a neurological disease or disorder by standard clinical methodology and then treating such a patient with a composition of the present invention.

[0067] One aspect of the present invention features the use of a compound having the formula:



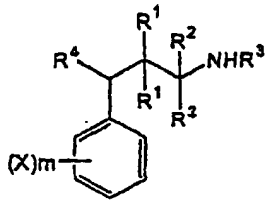
wherein:

X is independently selected from the group consisting of -Br, -Cl, -F, -I, $-CF_3$, alkyl, -OH, $-OCF_3$, -O-alkyl, and -O-acyl;
R_1 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and -O-acyl;
R_2 is independently selected from the group consisting of -H, alkyl, and hydroxyalkyl, or both R_2s together are imino;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, $-CF_3$, alkyl, -OH,- OCF_3 -O-alkyl, or -O-acyl; and
m is independently an integer from 0 to 5; and pharmaceutically acceptable salts and complexes thereof provided that said compound is not:

3-(p-isopropoxyphenoxy)-3-phenylpropylamine
3-(2'-methyl-4',5'-dichlorophenoxy)-3-phenylpropylamine
3-(p-t-butylphenoxy)-3-phenylpropylamine
3-(2',4'-dichlorophenoxy)-3-phenyl-2-methyl propylamine
3-(o-ethylphenoxy)-3-phenylpropylamine
3-(o-methoxyphenoxy)-3-phenylpropylamine
3-phenoxy-3-phenylpropylamine

for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

[0068] Another aspect features the use of a compound having the formula

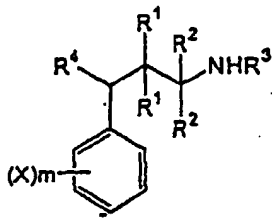


wherein:

X is independently selected from the group consisting of -F, -Cl, -Br, -I, -CF_3 alkyl, -OH, -OCF_3, -O-alkyl, and -O-acyl;
R_1 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and -O-acyl;
R_2 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and hydroxyalkyl, or both R_2s together are imino;
R_3 is selected from the group consisting of methyl and ethyl;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH, -OCF_3, -O-alkyl, or -O-acyl;
and m is independently an integer from 0 to 5; and pharmaceutically acceptable salts and complexes thereof provided that said compound is not
N-methyl 3-(o-chloro-p-tolyloxy)-3-phenyl-1-methylpropylamine
N-methyl 3-(p-tolyloxy)-3-phenylpropylamine
N-methyl 3-(o-chloro-p-isopropylphenoxy)-3-phenyl-2-methylpropylamine
N-methyl 3-(p-iodophenoxy)-3-phenyl-propylamine
N-methyl 3-(3-n propylphenoxy)-3-phenyl-propylamine
N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine
N-methyl 3-(m-chlorophenoxy)-3-phenylpropylamine
N-methyl 3-(p-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-(p-methoxyphenoxy)-3-phenylpropylamine
N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine
N-methyl 3-(o-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-(o-tolyloxy)-3-phenylpropylamine
N-methyl 3-(p-chlorophenoxy)-3-phenylpropylamine
N-methyl 3-(m-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-phenoxy-3-phenyl-2-methylpropylamine
N-methyl 3-phenoxy-3-phenyl-1-methylpropylamine
N-methyl 3-phenoxy-3-phenylpropylamine
N-methyl 3-(o-trifluoromethylphenoxy)-3-phenylpropylamine
N-methyl 3-(m-methoxyphenoxy)-3-phenylpropylamine
N-ethyl 3-(o-iodophenoxy)-3-phenylpropylamine
N-ethyl-3-(o-chlorophenoxy)-3-phenylpropylamine
N-methyl-3-(o-bromophenoxy)-3-phenylpropylamine
N-methyl-3-(o-bromophenoxy)-3-phenylpropylamine

for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

[0069] A third aspect features the use of a compound having the formula:



wherein:

(X)m is selected from the group consisting of meta-fluoro; meta-chloro, ortho-O-C_1-C_4 alkyl, ortho-methyl, ortho-fluoro, ortho-chloro, meta-O-C_1-C_4 alkyl, meta-methyl, ortho-OH, and meta-OH;
R_1 is H;
R_2 is H;
R_3 is selected from the group consisting of methyl and ethyl;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH, -OCF_3, -O-alkyl, or -O-acyl; and pharmaceutically acceptable salts and complexes thereof, for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

[0070] The compounds of the present invention are active at an NMDA receptor.

[0071] By "patient" is meant any animal that has a cell with an NMDA receptor. Preferably, the animal is a mammal. Most preferably, the animal is a human.

[0072] By "alkyl" is meant a branched or unbranched hydrocarbon chain containing between 1 and 6, preferably between 1 and 4, carbon atoms, such as, e.g., methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, 2-methylpentyl, cyclopropylmethyl, allyl, and cyclobutylmethyl.

[0073] By "lower alkyl" is meant a branched or unbranched hydrocarbon chain containing between 1 and 4 carbon atoms, of which examples are listed herein.

[0074] By "hydroxyalkyl" is meant an alkyl group as defined above, substituted with a hydroxyl group.

[0075] By "alkylphenyl" is meant an alkyl group as defined above, substituted with a phenyl group.

[0076] By "acyl" is meant -C(O)R, where R is H or alkyl as defined above, such as, e.g., formyl, acetyl, propionyl, or butyryl;

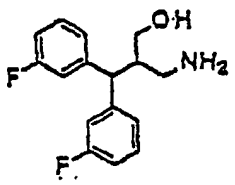
or R is -O-alkyl such as in alkyl carbonates or R is N-alkyl such as in alkyl carbamates.

[0077] By "cycloalkyl" is meant a branched or unbranched cyclic hydrocarbon chain containing between 3 and 12 carbon atoms.

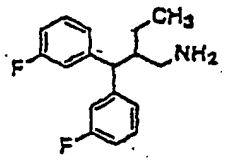
[0078] Preferred aspects are those embodiments in which (X) m is independently selected from the group consisting of meta-fluoro, meta-chloro, ortho-O-lower alkyl, ortho-methyl, ortho-fluoro, ortho-chloro, meta-O-lower alkyl, meta-methyl, ortho-OH, and meta-OH.

[0079] Especially preferred aspects are those embodiments in which (X)m is meta-fluoro; NR^3 is selected from the group consisting of NH and N-methyl; and each R^1 and R^2 is -H;

[0080] Other preferred embodiments of the present invention relate to the use of a compound which is selected from the group consisting of



Compound 54



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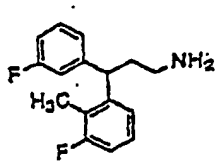

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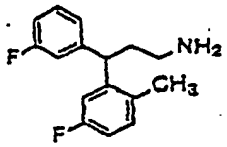

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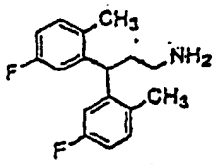

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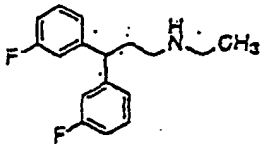

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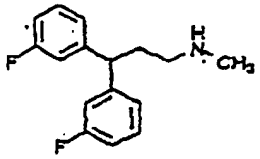

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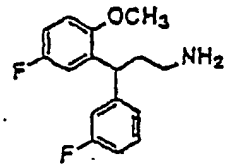

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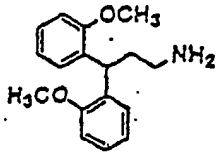

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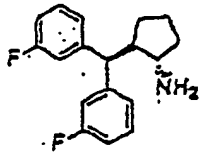

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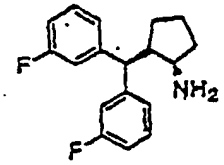

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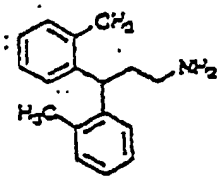

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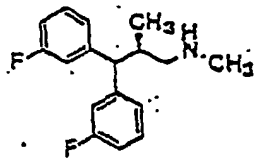

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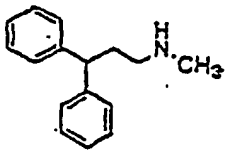

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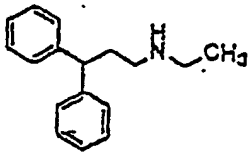

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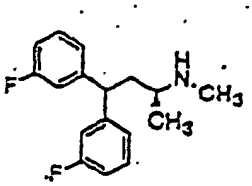

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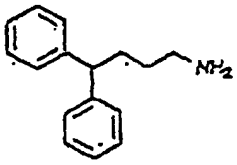

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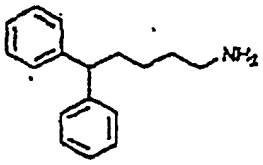

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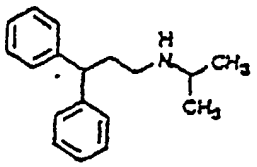

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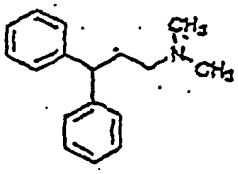

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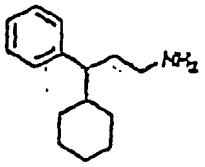

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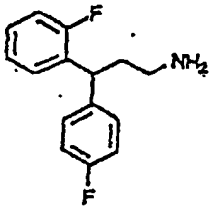

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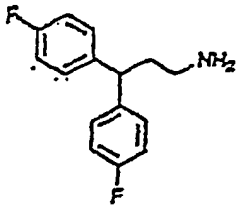

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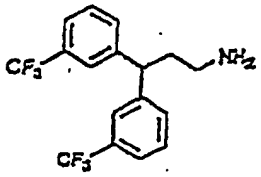

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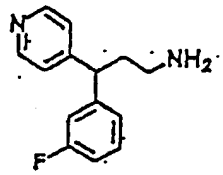

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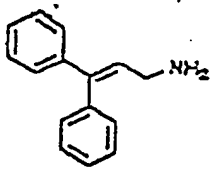

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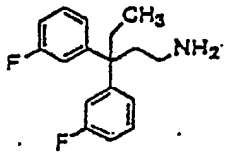

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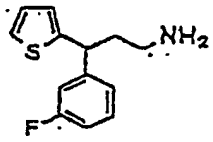

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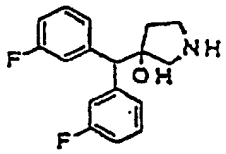

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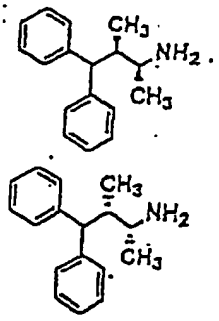
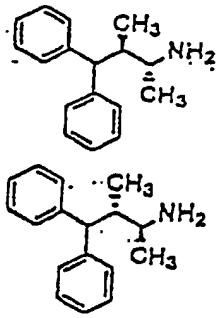
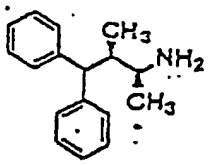


Compound 85
(mixture of 2
compounds)



Compound 86
(mixture of 2
compounds)



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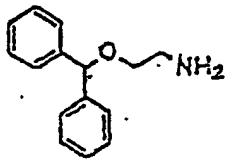

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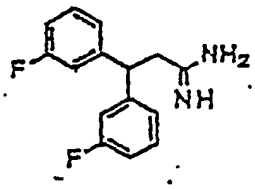

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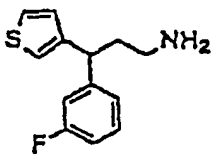

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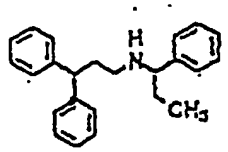

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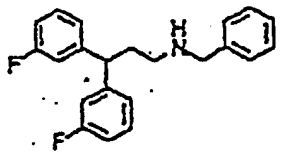

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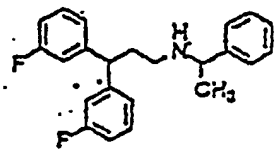

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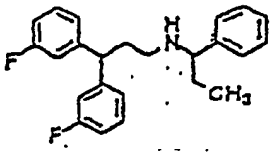
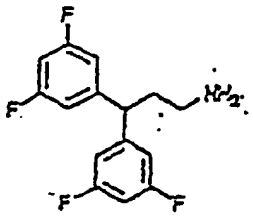
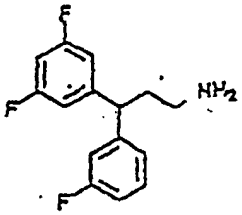


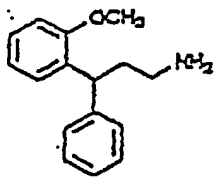
Compound 94



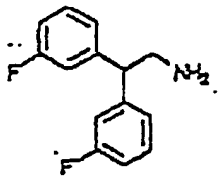
Compound 95



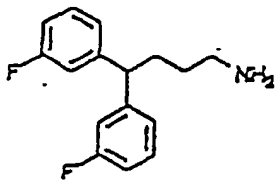
Compound 96



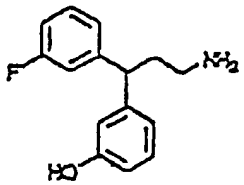
Compound 97



Compound 98



Compound 100



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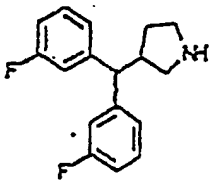
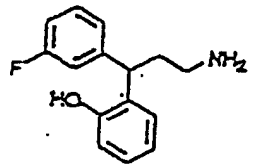
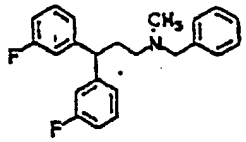


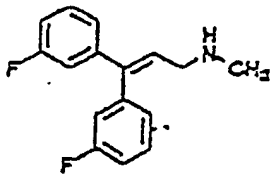
Compound 102



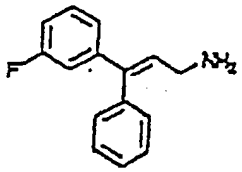
Compound 103

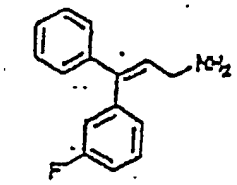


Compound 105

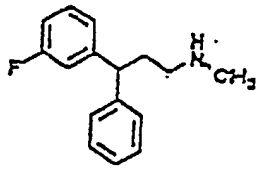


Compound 106

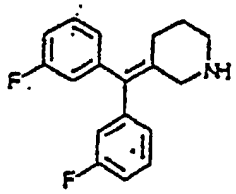




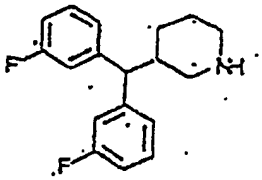
Compound 107
(mixture of 2
compounds)



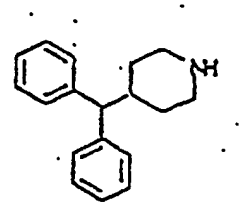
Compound 108



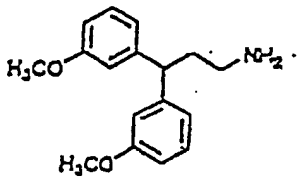
Compound 109



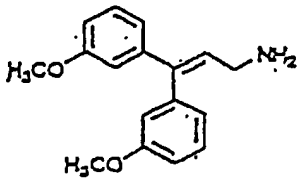
Compound 111



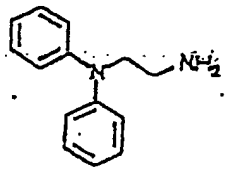
Compound 114



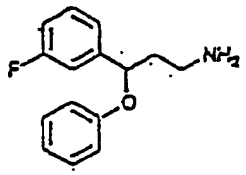
Compound 115



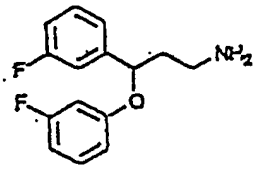
Compound 116



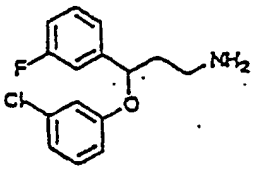
Compound 117



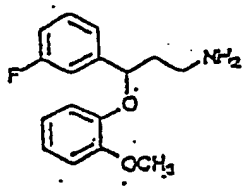
Compound 118



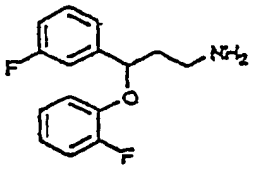
Compound 119



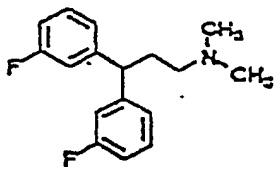
Compound 120



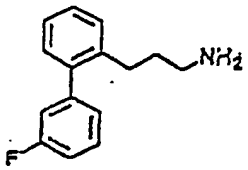
Compound 121



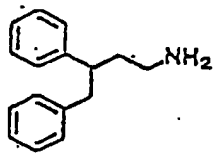
Compound 122



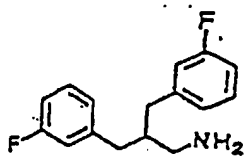
Compound 123



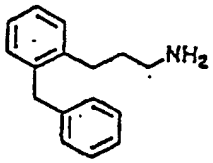
Compound 124



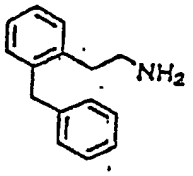
Compound 125



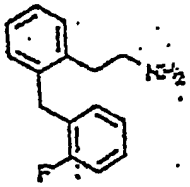
Compound 126



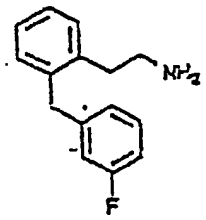
Compound 127



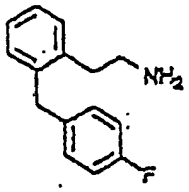
Compound 128



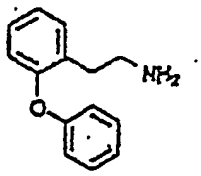
Compound 129



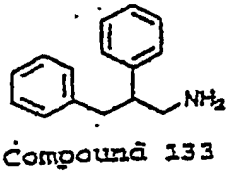
Compound 130



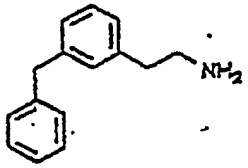
Compound 131



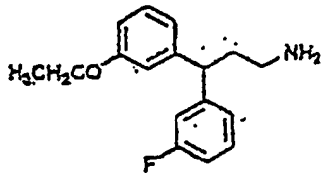
Compound 132



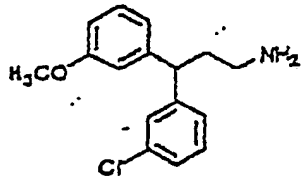
Compound 133



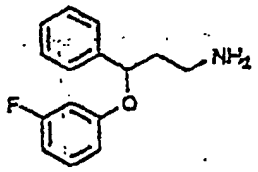
Compound 134



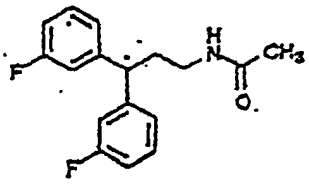
Compound 135



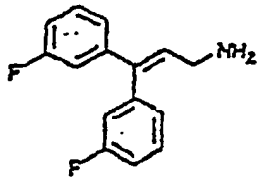
Compound 136



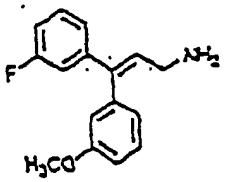
Compound 137



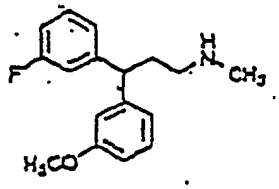
Compound 138



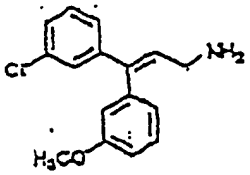
Compound 139



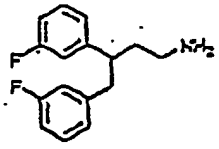
Compound 141



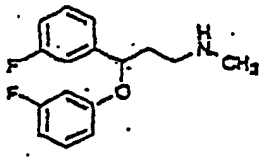
Compound 142



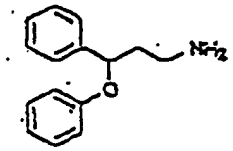
Compound 143



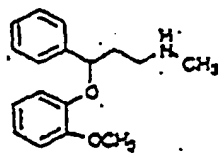
Compound 144



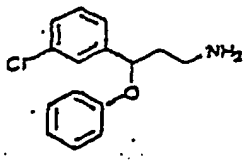
Compound 145



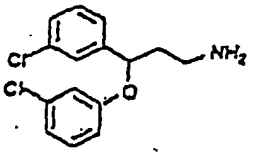
Compound 146



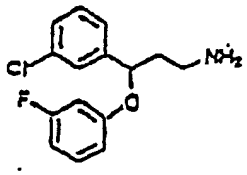
Compound 147



Compound 148



Compound 149



Compound 150

, and pharmaceutically acceptable salts and complexes thereof for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

[0081] Preferably, the compound to be administered has an $IC_{50} \leq 10$ μM at an NMDA receptor, more preferably ≤ 2.5 μM, and most preferably ≤ 0.5 μM at an NMDA receptor.

[0082] In further preferred embodiments, the invention uses compounds with an I.C. $_{50} \leq 10$μm at an MMDA receptor selected from the group consisting of Compound 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 75, 76, 77, 78, 79, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, ,96, 97, 98, 100, 101, 102, 103, 105, 106, 107, 108, 109, 111, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138 (potential prodrug), 139, 141, 142, 143, 144, 145, 146, 147, 148, 149, and 150, and pharmaceutically acceptable salts and complexes thereof.

[0083] In more preferred embodiments, the invention uses compounds with an $IC_{50} \leq 2.5$ μM at an NMDA receptor selected from the group consisting of Compound 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 70, 75, 76, 81, 82, 83, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 100, 101, 102, 103, 105, 106, 108, 109, 111, 115, 118, 119, 120, 121, 122, 125, 126, 127, 128, 129, 130, 131, 132, 133, 135, 136, 137, 138 (potential prodrug), 139, 142, 144, 145, 146, 147, 148, 149, and 150, and pharmaceutically acceptable salts and complexes thereof. In other embodiments, the compound is selected from the group consisting of Compound 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 76, 82, 83, 88, 89, 90-, 92, 93, 94, 95, 96, 101, 102, 103, 105, 109, 111, 115, 118, 119, 120, 121, 122, 125, 126, 127, 129, 130, 131, 135, 136, 137, 138, 139, 142, 144, 145, 148, 149, and 150, and pharmaceutically acceptable salts and complexes thereof.

[0084] In particularly preferred embodiments, the invention uses a compound with an $IC_{50} \leq 0.5$ μM at an NMDA receptor selected from the group consisting of Compound 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 65, 82, 83, 89, 90, 91, 93, 94, 95, 96, 97, 103, 111, 118, 119, 120, 122, 126, 135, 136, 137, 138 (potential prodrug), 142, 144, 145, 147, 148, 149, and 150, and pharmaceutically acceptable salts and complexes thereof.

[0085] In more preferred embodiments, the invention uses a compound selected from the group consisting of Compound 60, 66, 69, 103, 111, 118, 119, 120, 122, 136, 137, 138 (potential prodrug), 142, 144, 145, 148, 149, and 150, and pharmaceutically acceptable salts and complexes thereof.

[0086] In particularly preferred embodiments, the invention uses a compound selected from the group consisting of Compound 60, 119, and 144, and pharmaceutically acceptable salts and complexes thereof.

[0087] In other particularly preferred embodiments, the invention uses a compound selected from the group consisting of Compound 60, 119, and 144, and pharmaceutically acceptable salts and complexes thereof.

[0088] The present invention further provides simplified arylalkylamines as defined in the attached claims.

[0089] Preferably, the compound has an $IC_{50} \leq 10$ μM at an NMDA receptor. More preferably, the compound has an $IC_{50} \leq 5$ μM, more preferably ≤ 2.5 μM, and most preferably ≤ 0.5 μM at an NMDA receptor.

[0090] In preferred embodiments, the compound has an $IC_{50} \leq 10$ μM at an NMDA receptor and is selected from the group consisting of Compounds 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 76, 78, 79, 82, 83, 84, 88, 89, 90, 92, 93, 94, 95, 96, 98, 101, 102, 103, 105, 107, 108, 109, 111, 115, 116, 118, 119, 120, 121, 122, 124, 125, 126, 127, 129, 130, 131, 134, 135, 136, 137, 138 (potential prodrug), 139, 141, 142, 143, 144, 145, 148, 149, and 150. In other embodiments, the compound is selected from the group consisting of 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 76, 82, 83, 88, 89, 90, 92, 93, 94, 95, 96, 101, 102, 103, 105, 109, 111, 115, 118, 119, 120, 121, 122, 125, 126, 127, 129, 130, 131, 135, 136, 137, 138, 139, 142, 144, 145, 148, 149, and 150.

[0091] In more preferred embodiments, the compound has an $IC_{50} \leq 2.5$ μM at an NMDA receptor and is selected from the group consisting of Compound 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 76, 82, 83, 88, 89, 90, 92, 93, 94, 95, 96, 101, 102, 103, 105, 108, 109, 111, 115, 118, 119, 120, 121, 122, 125, 126, 127, 129, 130, 131, 135, 136, 137, 138 (potential prodrug), 139, 142, 144, 145, 148, 149, and 150.

[0092] In particularly preferred embodiments, the compound has an $IC_{50} \leq 0.5$ μM at an NMDA receptor and is selected from the group consisting of Compound 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 82, 83, 89, 90, 93, 94, 95, 96, 103, 111, 118, 119, 120, 122, 126, 135, 136, 137, 138 (potential prodrug), 142, 144, 145, 148, 149, and 150.

[0093] In preferred embodiments, the compound is selected from the group consisting of Compound 60, 66, 69, 103, 111, 118, 119, 120, 122, 136, 137, 138, 142, 144, 145, 148, 149, and 150.

[0094] In particularly preferred embodiments, the compound is selected from the group consisting of Compound 60, 119, and 144.

[0095] In more particularly preferred embodiments, the compound is selected from the group consisting of Compound 60, 119, and 144.

[0096] Also provided in an aspect of the invention are pharmaceutical compositions useful for treating a patient having a neurological disease or disorder as defined in the attached claims. The pharmaceutical compositions are provided in a pharmaceutically acceptable carrier and appropriate dose. The pharmaceutical compositions may be in the form of pharmaceutically acceptable salts and complexes, as is known to those skilled in the art'.

[0097] Preferably, the compound has an $IC_{50} \leq 10$ μM at an NMDA receptor. More preferably the compound has an $IC_{50} \leq 5$ μM, more preferably ≤ 2.5 μM, and most preferably ≤ 0.5 μM at an NMDA receptor.

[0098] In further preferred embodiments, the pharmaceutical composition comprises a compound with an $IC_{50} \leq$ 10μM at an NMDA receptor and is selected from the group consisting of Compound 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 75, 76, 77, 78, 79, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, ,96, 97, 98, 100, 101, 102, 103, 105, 106, 107, 108, 109, 111, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138 (potential prodrug), 139, 141, 142, 143, 144, 145, 146, 147, 148, 149, and 150. Preferably, the compound is selected from the'group consisting of 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 76, 78, 79, 82, 83, 84, 88, 89, 90, 92, 93, 94, 95, 96, 98, 101, 102, 103, 105, 107, 108, 109, 111, 115, 116, 118, 119, 120, 121, 122, 124, 125, 126, 137, 129, 130, 131, 134, 135, 136, 137, 138 (potential prodrug), 139, 141, 142, 143, 144, 145, 148, 149, and 150.

[0099] In other embodiments, the-compound is selected from the group consisting of 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 76, 82, 83, 88, 89, 90, 92, 93, 94, 95, 96, 101, 102, 103, 105, 109, 111, 115, 118, 119, 120, 121, 122, 125, 126, 127, 129, 130, 131, 135, 136, 137, 138, 139, 142, 144, 145, 148, 149, and 150.

[0100] In more preferred embodiments, the pharmaceutical composition comprises a compound with an $IC_{50} \leq 2.5$ μM at an NMDA receptor and is selected from the group consisting of Compound 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 70, 75, 76, 81, 82, 83, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 100, 101, 102, 103, 105, 106, 108, 109, 111, 115, 118, 119, 120, 121, 122, 125, 126, 127, 128, 129, 130, 131, 132, 133, 135, 136, 137, 138 (potential prodrug), 139, 142, 144, 145, 146, 148, 149, and 150. Preferably, the compound is selected from the group consisting of 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 76, 82, 83, 88, 89, 90, 92, 93, 94, 95, 96, 101, 102, 103, 105, 108, 109, 111, 115, 118, 119, 120, 121, 122, 125, 126, 127, 129, 130, 131, 135, 136, 137, 138 (potential prodrug), 139, 142, 144, 145, 148, 149, and 150.

[0101] In particularly preferred embodiments, the pharmaceutical composition comprises a compound with an $IC_{50} \leq 0.5$ μM at an MMDA receptor and is selected from the group consisting of Compound 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 82, 83, 89, 90, 93, 94, 95, 96, 97, 103, 111, 118, 119, 120, 122, 126, 135, 136, 137, 138 (potential prodrug), 142, 144, 145, 148, 149, and 150. Preferably, the compound is selected from the group consisting of 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 69, 82, 83, 89, 90, 93, 94, 95, 96, 103, 111, 118, 119, 120, 122, 126, 135, 136, 137, 138 (potential prodrug), 142, 144, 145, 148, 149, and 150.

[0102] In more preferred embodiments, the pharmaceutical composition comprises a compound selected from the group consisting of Compound 60, 66, 69, 103, 111, 118, 119, 120, 122, 136, 137, 138, 142, 144, 145, 148, 149, and 150. Preferably, the compound is selected from the group consisting of Compound 60, 66, 69, 103, 111, 118, 119, 120,

122, 136, 137, 138, 142, 144, 145, 148, 149, and 150.

[0103] In most particularly preferred embodiments, the pharmaceutical composition comprises a compound selected from the group consisting of Compound 60, 119, and 144.

[0104] Preferably, the compound is selected from the group consisting of 60, 119, and 144.

[0105] Structural modifications can be made to compounds such as 60 which do not add materially to the structure-activity relationships (SAR) illustrated here. For example, successful bioisosteric replacement or substitution of optionally substituted phenyl'groups, such as those occurring in compound 60, can be accomplished with other lipophilic or semi-polar aromatic (e.g., naphthyl, naphthoxy, benzyl, phenoxy, phenylthio), aliphatic (alkyl, e.g., isopropyl), cycloaliphatic (cycloalkyl, e.g., cyclohexyl), heterocyclic [e.g., pyridyl, furanyl, thiofuranyl (thiophenyl)], or other functional groups or systems, as is well known in the art, will afford clinically useful compounds (structural homologs, analogs, and/or congeners) with similar biopharmaceutical properties and activity at the NMDA receptor (e.g., *cf.* compounds 75, 79, 83, 89, 119-122, 125, 126, 128, 130, 132, 137, 144, and 145). For example, such replacements or substitutions have been used to great effect in the development of SAR among other groups of highly clinically and commercially successful synthetic pharmaceutical agents such as the classical H_1 -antihistamines, anticholinergics (antimuscarinics; e.g., anti-Parkinsonians), antidepressants (including tricyclic compounds), and opioid analgesics [See, Foye *et al.* (Eds.), *Principles of Medicinal Chemistry,* 4th ed., Lea and Febiger/Williams and Wilkins, Philadelphia, PA, 1995, pp. 233, 265, 281-282, 340-341, 418-427, and 430; Prous, J.R., *The Year's Drug News, Therapeutic Targets - 1995 Edition,* Prous Science Publishers, Barcelona, Spain, 1995, pp. 13, 55-56, 58-59, 74, 89, 144-145, 152, 296-297, and 317]. Similarly, bioisosteric replacement or substitution of the methylene or methine groups in the propyl backbone of compounds such as 60 with, e.g., oxygen, sulfur, or nitrogen, will afford clinically useful NMDA receptor-active compounds . with similarly useful biopharmaceutical properties, such as 88 (a modified "classical H_1-antihistamine-type" structure), which can be further optimized for activity at the NMDA receptor by preparing, e.g., the corresponding compound(s) containing, e.g., (bis) (3-fluorophenyl) group (s), as taught by the present invention. The propyl backbone of compounds such as **60** may also be modified successfully by the incorporation of ring systems (as in compounds **102** and **111**) and/or unsaturation (e.g., a double bond, as in compounds **81, 106, 109,** and **139**) to afford further clinically useful NMDA receptor-active compounds of the present invention (cf. compounds cited above).

[0106] The method for making a therapeutic agent may comprise the steps of screening for said agent by determining whether said agent is active on a receptor-operated calcium channel, and synthesizing said therapeutic agent in an amount sufficient to provide said agent in a therapeutically effective amount to a patient. Said screening may be performed by methods known to those of ordinary skill in the art, and may, for example be performed by the methods set out herein. Those skilled in the art are also familiar with methods used to synthesize therapeutic agents in amounts sufficient to be provided in a therapeutically effective amount.

[0107] In a preferred aspect, said receptor-operated calcium channel is an NMDA receptor. In a more preferred aspect, said method further comprises the step of adding a pharmaceucically acceptable carrier to said agent.

[0108] Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Description of the Preferred Embodiments

Assays for Potent and Selective Antagonists of Receptor-Operated Calcium Channels in the Mammalian CNS

[0109] Desired properties of a drug include: high affinity and selectivity for receptor-operated Ca^{2-} channels, such as those present in NMDA, AMPA and nicotinic cholinergic receptor-ionophore complexes (compared to responses mediated via other neurotransmitter receptors, neurotransmitter receptor-operated ion channels, or voltage-dependent ion channels) and a noncompetitive antagonism of said receptor-operated Ca^{2+} channels.

[0110] The MMDA receptor-ionophore complex is utilized as an example of a receptor-operated Ca^{2+} channel. Activation of the NMDA receptor opens a cation-selective channel that allows the influx of extracellular Ca^{2+} and Na^{+}, resulting in increases in $[Ca^{2+}]_i$ and depolarization of the cell membrane Measurements of $[Ca^{2+}]_i$ were used as primary assays for detecting the activity of arylalkylamine compounds on NMDA receptors. Purified arylalkylamines, synthetic aryl-alkylamines, and synthetic analogs of arylalkylamines were examined for activity in in vitro assays capable of measuring glutamate receptor activity. simplified synthetic analogs generally consist of suitably substituted aromatic chromophoric groups attached to an alkyl(poly)amine moiety (see Compounds **54** through **69** below).

[0111] A primary assay that provides a functional index of glutamate receptor activity and that allows high-throughput screening was developed. Primary cultures of rat cerebellar granule cells loaded with the fluorimetric indicator fura-2 were used to measure changes in $[Ca^{2+}]_i$ elicited by NMDA and its coagonist glycine. This assay provides an extremely sensitive and precise index of NMDA receptor activity. Increases in $[Ca^{2+}]_i$ evoked by NMDA are dependent on the presence of glycine, and are blocked by extracellular Mg^{2+} or antagonists acting at the glutamate, glycine, or MK-801 binding sites. Increases in $[Ca^{2+}]_i$ elicited by NMDA/glycine are readily distinguished from those resulting from depo-

larization by their refractoriness to inhibition by blockers of voltage-sensitive Ca^{2+} channels. The fidelity with which measurements of $[Ca^{2+}]_1$ corroborate results obtained by electrophysiological and ligand-binding studies suggests that such measurements mirror closely activation of the NMDA receptor-ionophore complex.

Example 1: Potent noncompetitive inhibition of NMDA receptor function

[0112] Preferential inhibitory effects of arylalkylamines on NMDA receptor-mediated increases in $[Ca^{2+}]_i$ in cultured rat cerebellar granule cells were measured. Increases in $[Ca^{2+}]_i$ were elicited by the addition of NMDA/glycine (50 μM/ l μM) in the presence or absence of different concentrations of each test compound. The IC_{50} values were derived for each test compound using from 2 to 8 separate experiments per test compound, and the standard error level was less than 10% of the mean value for each compound.

[0113] All of the arylalkylamines tested blocked increases in $[Ca^{2+}]_i$ in cerebellar granule cells elicited by NMDA/ glycine. Many of the arylalkylamines tested were more potent than competitive antagonists such as AP5 (IC_{50} = 15 μM). The inhibitory effects of the arylalkylamines were not overcome by increasing the concentrations of NMDA or glycine. That is, no change was observed in the EC_{50} for either NMDA or glycine. The arylalkylamines are thus non-competitive antagonists at the NMDA receptor-ionophore complex, and act neither at the glutamate nor the glycine binding sites.

Example 2: Activity against Kainate and AMPA receptor function

[0114] Measurements of $[Ca^{2+}]_i$ in cerebellar granule cells can also be used to monitor activation of the native kainate or AMPA receptors present in this tissue. Although the increases in $[Ca^{2+}]_i$ evoked by these agonists are of a lesser magnitude than those evoked by NMDA/glycine, such responses are robust and can be used to precisely assess the specificity of action of arylalkylamines on pharmacologically defined glutamate receptor subtypes. Comparative measurements of $[Ca^{2+}]_i$ revealed a clear distinction in the receptor selectivity of the arylalkylamines. Some, like JSTX-3 (Joro Spider toxin from the spider *Nephila clavata*), were more potent antagonists of responses elicited by kainate (100 μM) or AMPA (30 μM).

Neuroprotectant activity

[0115] Desired properties of a neuroprotectant drug include the following. (1) The drug can be administered by oral or injectable routes (*i.e.*, it is not significantly broken down in the stomach, intestine or vascular system and thus reaches the tissues to be treated in a therapeutically effective amount). Such drugs are easily tested in rodents to determine their bioavailability. (2) The drug exhibits neuroprotectant activity (*i.e.*, efficacy) when given after an ischemic insult (stroke, asphyxia) or traumatic injury (head trauma, spinal cord injury). (3) The drug is devoid of or has minimal side effects such as impairment of cognition, disruption of motor performance, sedation or hyperexcitability, neuronal vacuolization, cardiovascular activity, PCP-like abuse potential, or PCP-like psychotomimetic activity.

[0116] Although glutamate is the physiological synaptic transmitter, chronic exposure to glutamate leads to neuronal cell death. Much of the neurodegeneration caused by glutamate appears to be mediated by MKDA receptors and results directly from chronically elevated levels of cytosolic Ca^{2+}. There is now extensive experimental support for the view that NMDA and AMPA receptors play a major role in mediating the neuronal degeneration following a stroke and other ischemic/hypoxic events (Choi, Glutamate neurotoxicity and diseases of the nervous system. *Neuron* **1**: 623, 1988). Most of this evidence is based on the ability of competitive or noncompetitive antagonists of the NMDA or AMPA receptor to effectively block neuronal cell death in both in vitro and *in vivo* models of stroke.

Example 3: Cortical neuron protection

[0117] To assess the *in vitro* neuroprotectant effect of arylalkylamines, mouse cortical neurons grown in culture were exposed for 5 minutes to NMDA, and cell death after 24 hours was monitored by measuring the release of lactate dehydrogenase (LDH), a cytoplasmic enzyme that is released from dying cells (Choi *et al.*, Glutamate neurotoxicity in cortical cell culture. *J. Neurosci.* **7**: 357, 1987).

[0118] More rigorous testing to determine potential therapeutic efficacy involved *in vivo* stroke models. In these models, the blood supply is temporarily blocked by clamping the main arteries to the brain.

Example 4: Bilateral carotid artery occlusion

[0119] The first assay was the bilateral common carotid artery occlusion model of forebrain ischemia performed in the gerbil (Karpiak *et al.*, Animal models for the study of drugs in ischemic stroke. *Ann. Rev. Pharmacol. Toxicol.* **29**:

403, 1989; Ginsberg and Busto, Rodent models of cerebral ischemia. *Stroke* **20**: 1627, 1989). Blood flow to the brain was interrupted for 7 minutes by clamping the carotid arteries. The test compounds were administered as a single dose given intraperitoneally (i.p.) 30 minutes after reinstating blood flow. During the course of these experiments, the core body temperature of the animals was maintained at 37°C to prevent any hypothermia reaction. It has been shown that many NMDA receptor antagonists cause hypothermia and this effect can account for much of the protective effect of these compounds. The brains were examined for neuronal cell death 4 days later by silver staining sections of the brain and quantifying death by morphometric analysis.

Example 5: Middle cerebral artery occlusion

[0120] The middle cerebral artery model of stroke performed in the rat (Karpiak *et al.*, Animal models for the study of drugs in ischemic stroke. *Ann. Rev. Pharmacol. Toxicol.* **29**: 403, 1989; Ginsberg and Busto, Rodent models of cerebral ischemia. *Stroke* **20**: 1627, 1989) is different from the gerbil model because it results in a more restricted brain infarct, and thereby approximates a different kind of stroke (focal thrombotic stroke). In the first study using this stroke model, one cerebral artery was permanently occluded by surgical ligation. The test compounds were administered 30 minutes after the occlusion by a single intraperitoneal (i.p.) injection. During the course of these experiments, the core body temperature of the animals was maintained at 37°C to prevent any hypothermic reaction. Brains were assessed histologically for neuronal cell loss 24 hours later. Infarct volumes were calculated using the area of histological pallor from 10 slides and integrating the distance between each successive section.

[0121] In the second study of focal cerebral ischemia in the rat, the middle cerebral artery was permanently occluded by passing a small piece of suture thread through the carotid artery to the region of the middle cerebral artery. Core body temperature was maintained at 37°C.

[0122] In a third model of focal cerebral ischemia in the rat, an ischemic infarct was produced by a photothrombotic method using the dye Rose Bengal.

[0123] In a fourth model of focal cerebral ischemia in the rat, the middle cerebral artery was temporarily occluded by passing a small piece of suture thread through the carotid artery to the region of the middle cerebral artery. The suture thread was withdrawn after an ischemic period of 2 hr. Core body temperature was maintained at 37°C.

Anticonvulsant activity

[0124] Desired properties of an anticonvulsant drug include: the drug can be administered by oral or injectable routes, the drug exhibits effective anticonvulsant activity against several seizure types, including, but not limited to, simple partial seizures, complex partial seizures; status epilepticus, and trauma-induced seizures such as occur following head injury, including head surgery; and the drug is devoid of or has minimal side effects such as impairment of cognition, disruption of motor performance, sedation or hyperexcitability, neuronal vacuolization, cardiovascular activity, PCP-like abuse potential, or PCP-like psychotomimetic activity.

[0125] Glutamate is the major excitatory transmitter in the brain, and thus may play at major role in seizure activity, and contribute to the pathogenesis of epilepsy. Much of the evidence favoring a major role for glutamate receptors in epilepsy derives from pharmacological studies demonstrating that glutamate receptor agonists elicit seizures, and that NMDA and AMPA receptor antagonists are effective anticonvulsants when administered *in vivo.* There are numerous *in vivo* models involving different kinds of seizures and behavioral effects that are relevant for clinically distinct forms of epilepsy. It is thus prudent to test for effects in several models, because it may be an oversimplification to suppose that the same mechanism underlies all forms of seizure activity.

Example 6: Convulsant blocking activity

[0126] In initial studies, the ability of arylalkylamines to block seizures induced by kainate, picrotoxin or bicuculline were examined. Each of these convulsants acts through a different mechanism and seizures elicited by kainate are qualitatively different from those elicited by picrotoxin or bicuculline. In these experiments, a fraction of *Agelenopsis aperta* venom containing several arylalkylamine toxins was administered intravenously (iv) 5 min before picrotoxin or bicuculline, and 5 min after kainate administration. The arylalkylamines diminished the seizures induced by all three of these agents. The effects of picrotoxin or bicuculline were so severe that all 19 control animals died within 25 minutes. In contrast, there were no deaths in the 9 animals pretreated with the arylalkylamines. In fact, only about half the animals treated with the arylalkylamines showed any convulsions at all and those symptoms abated within an hour. These results demonstrate clear anticonvulsant effects of arylalkylamines and prompted further studies using purified arylalkylamines and their analogs.

Example 7: Seizure stimuli

[0127] Three different seizure-inducing test paradigms were used initially in this second group of studies and arylalkylamines proved to be effective anticonvulsants in two such paradigms. The first two models used DBA/2 mice which are prone to audiogenic seizures. Seizures were elicited by sound (bell tone at 109 dBs) or the intraperitoneal (ip) administration of NMDA (56 mg/kg). The test substances were administered 15-30 min before the convulsant stimulus. The number of clonic seizures was recorded for 1 min following the audiogenic stimulus or for 15 min following the administration of NMDA.

Analgesic activity

[0128] Desired properties of an analgesic drug include: the drug can be administered by oral or injectable routes, the drug exhibits analgesic activity, the drug is devoid of or has minimal side effects such as impairment of cognition, disruption of motor performance, sedation or hyperexcitability, neuronal vacuolization, cardiovascular activity, PCP-like abuse potential, or PCP-like psychotomimetic activity.

[0129] Glutamate and NMDA receptor-mediated responses may play a role in certain kinds of pain perception (Dickenson, A cure for wind up: NMDA receptor antagonists as potential analgesics. *Trends Pharmacol. Sci.* **11**: 302, 1990).

Example 8: Writhing response test

[0130] In the first series of experiments, the animals were administered an unpleasant stimulus (2-phenyl-1,4-benzoquinone, PBQ) which elicits a writhing response (abdominal stretching). Typically, the number of writhes occurring in a 5 min observation period is recorded. Classic analgesic drugs, such as morphine, are effective at decreasing the number of PBQ-elicited writhes (100% block of the writhing response at 4 mg/kg i.p.). Nonsteroidal antiinflammatory agents are likewise effective in this model.

Example 9: Hot plate test

[0131] In this model of analgesic activity, mice were administered test substances s.c. 30 min before being placed on a hot plate (50°C). The time taken to lick the feet or jump off the plate is an index of analgesic activity, and effective analgesics increase the latency to licking or jumping. Morphine (5.6 mg/kg) increased the latency to jump by 765%.

Example 10: Tail flick test

[0132] In this standard assay, the thermal nociceptive stimulus was 52°C warm water with the latency to tail flick or withdrawal taken as the endpoint.

Example 11. Formalin test

[0133] Male Sprague-Dawley rats were habituated to an observation chamber for at least 1 hr before receiving an injection of dilute formalin (5%) in a volume of 50 µl into the left rear paw. Behavioral responses were monitored immediately after s.c. injection of formalin into the dorsal surface of the paw by counting the number of flinches exhibited by the animal. Behaviors were monitored for at least 50 min after formalin injection and'were recorded as early phase responses (0 - 10 min post-formalin) and late phase responses (20 - 50 min post-formalin). Compounds were injected intrathecally (i.th.) 10 min prior to formalin (pre-treatment) or 10 min after formalin (post-treatment) in a volume of 5 µl.

[0134] Intraplantal administration of formalin produced a typical biphasic response of flinching behavior, commonly described as the early and late phase responses.

[0135] Taken together, the results obtained with the hot plate, tail flick and formalin assays demonstrate that arylalkylamines have significant analgesic activity in several rodent models of acute pain. The formalin assay additionally demonstrates that arylalkylamines are effective in an animal model of chronic pain. Importantly, the arylalkylamines possess significant analgesic activity when administered after the formalin stimulus. This profile of activity -clearly distinguishes the arylalkylamines from standard NMDA receptcr antagonists such as MK-801.

Side effects of arylalkylamines

[0136] Given the important role NMDA receptors play in diverse brain functions, it is not surprising to find that antagonists of this receptor are typically associated with certain unwelcome side effects. In fact, it is this property that provides the major obstacle to developing therapies that target NMDA receptors. The principal side effects, which

characterize both competitive and noncompetitive antagonists, are a PCP-like psychotomimetic activity, impairment of motor performance, sedation or hyperexcitability, impairment of cognitive abilities, neuronal vacuolization, or cardiovascular effects (Willetts *et al.*, The behavioral pharmacology of NMDA receptor antagonists. *Trends Pharmacol. Sci.* **11**: 423, 1990; Olney *et al.*, Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science* **244**: 1360, 1989). The psychotomimetic effect associated with inhibition of NMDA receptor-mediated responses is epitomized in the response to phencyclidine (PCP) or "angel dust" which acts at the MK-801 binding site. Impairment of cognitive ability is associated with the important role that NMDA receptors normally play in learning and memory.

[0137] Relatively less is known concerning the side effect profile of AMPA receptor antagonists. However, it is becoming clear that such compounds also elicit motor impairment, ataxia and profound' sedation.

[0138] The activity of arylalkylamines was examined in animal models that index motor impairment, sedation and psychotomimetic activity as well as both *in vitro* and *in vivo* models of learning and memory.

(a) PCP-like Psychotomimetic Activity

[0139] In rodents, both competitive and noncompetitive antagonists of the NMDA receptor produce a PCP-like stereotypic behavior characterized by hyperactivity, head-weaving, and ataxia (Willetts *et al.*, The behavioral pharmacology of MMDA receptor antagonists. *Trends Pharmacol. Sci.* **11**: 423, 1990; Snell and Johnson, In: *Excitatory* Amino *Acids in Health and Disease,* John Wiley & Sons, p. 261, 1988). We investigated whether the arylalkylamines would elicit such behaviors. In addition, we investigated whether the arylalkylamines would substitute for PCP in rats trained to discriminate PCP from saline (Willetts *et al.*, The behavioral pharmacology of MMDA receptor antagonists. *Trends Pharmacol. Sci.* **11**: 423, 1990), and whether the arylalkylamines would elicit a PCP-like neuronal vacuolization (Olney *et al.*, Pathological changes induced in cerebrocortical, neurons by phencyclidine and related drugs. *Science* **244**: 1360, 1989).

Example 12: Locomotor activity

[0140] The first assay simply monitors locomoter activity during the first hour following peripheral (s.c. or i.p.) administration of test substance.

Example 13: Motor impairment

[0141] In the first assay, generalized motor impairment, was examined in the inverted grid assay. In this assay, animals are placed on a wire-holed grid suspended from a rotating metal bar which can be inverted. The animals are then scored for their ability to climb to the top or hang on to the grid: Animals with severe motor impairment fall off the grid. This assay provides an index of "behavioral disruption" that may result from ataxia, loss of the righting reflex, sedation, or muscle relaxation.

[0142] The second assay of acute motor impairment was the rotorod assay. In this assay, Frings and CF1 mice were injected with test compound and placed on a knurled rod which rotated at a speed of 6 rpm. The ability of the mice to maintain equilibrium for long periods of time was determined; those mice that were unable to maintain equilibrium on the rotorod for 1 min in each of 3 trials were considered impaired.

Example 14. PCP discrimination

[0143] In this assay, rats who have been trained to lever press for food reinforcement must select which of two levers in their cages is correct. The only stimulus they have for selecting the correct lever is their ability to detect whether they received a PCP or vehicle injection. After about two months of training, rats become very good at discriminating PCP from vehicle injections and can then be tested with other drugs to determine if they are discriminated as PCP. When tested in this procedure, other drugs which are known to produce a PCP-like intoxication substitute for PCP. These drugs include various PCP analogs such as ketamine and the noncompetitive NMDA receptor antagonist, MK-801.

Example 15

[0144] The administration of compounds such as PCP and MK-801 to rats produces a neurotoxic effect termed neuronal vacuolization. Following a single dose of such compounds, vacuoles are found in particular central neurons, especially those in the cingulate cortex and retrosplenial cortex.

[0145] Taken together, the results on locomotor activity, motor impairment, PCP discrimination and neuronal vacu-

olization strongly suggest that arylalkylamines will be devoid of PCP-like side effects in man.

(b) **Cognitive impairment**

[0146] One of the major reasons for postulating a role of NMDA receptors in memory and learning derives from cellular studies on long-term potentiation (LTP) in the rat hippocampus. LTP is a long-lasting increase in the magnitude of synaptic responses produced by brief yet incense synaptic stimulation. Since the discovery of this phenomenon, it has become the preeminent cellular model of learning in the vertebrate brain (Teyler and Discenna, Long-term potentiation. *Annu. Rev. Neurosci.* **10**: 131, 1987). Transmission at synapses formed by Schaffer collaterals onto CA1 pyramidal cells is mediated by NMDA and AMPA receptors. Following a brief tetanizing stimulus, the magnitude of the population spike (a measure of synaptic transmission) is greatly increased and remains so for hours. It has been shown that all known competitive and noncompetitive antagonists of NMDA recepcors block LTP in the rat hippocampus, whereas antagonists of non-NMDA receptors are without effect (Collingridge and Davis, In: *The NMDA Receptor*, IRL Press. p. 123, 1989). This supports a role of NMDA receptors in memory and learning.

Example 16: LTP assay

[0147] The effects of selected arylalkylamines and literature standards were examined for effects on LTP in slices of rat hippocampus. As anticipated, all the conventional competitive (AP5 and AP7) and noncompetitive (MK-801 and ifenprodil) NMDA receptor antagonists inhibited the induction of LTP in the hippocampus. Slices of rat hippocampus were superfused for 30-60 min with a test compound before delivering a tetanizing stimulus consisting of 3 trains, separated by 500 msec, of 100 Hz for 1 sec each. The response amplitude was monitored for an additional 15 minutes post-tetanus. The tetanizing stimulus caused a mean 95% increase in the amplitude of the synaptic response. The induction of LTP was significantly blocked ($p < 0.05$) by competitive (AP5, AP7) or noncompetitive (MK-801, ifenprodil) NMDA receptor antagonists. Quite surprisingly, none of the arylalkylamines tested blocked the induction of LTP ($p > 0.05$), even when used at high concentrations (100-300 μM) that caused some inhibition of the control response.

[0148] These results highlight yet another unique and important feature of arylalkylamines. Arylalkylamines are the first, arid at present the only, class of compounds shown to be selective and potent antagonists of the NMDA receptor that do not block the induction of LTP. This likely reflects the novel mechanism and site of action of arylalkylamines and suggests that drugs which target the novel site on the NMDA receptor will similarly lack effects on LTP. As LTP is the primary cellular model for learning and memory in the mammalian CNS, it additionally suggests that such drugs will lack deleterious effects on cognitive performance.

Example 17: Learning tests

[0149] In this test, rats were trained to alternate turning in a T maze for a food reward. MK-801 was included for comparison. Test compounds were administered i.p. 15 min before testing. Control animals made the correct choice about 80% of the time. Increasing doses of MK-801 progressively decreased the number of correct choices and this decrement in behavior was accompanied by hyperactivity.

[0150] Although MK-801 decreased learning performance in parallel with increases in locomotor activity, other studies using different paradigms in rodents and primates have shown a clear dissociation between the effects on learning and locomotion. Thus, both competitive and noncompetitive NMDA receptor antagonists impair learning at doses which do not cause any overt change in motor behavior. This demonstrates that conventional NMDA receptor antagonists impair learning independently of other side effects. The result's of the T-maze assay demonstrate that arylalkylamines, do not impair learning even at doses that cause some decrease in locomotor activity.

[0151] In a second series of experiments, the effect on learning in the Morris water maze task was evaluated. In this test, a hidden platform was placed in a fixed location in a circular steel tank, and submerged 2 cm below the surface of the water. Each rat was given 3 trials per day with a 10 min intertrial interval for 5 days. A trial was initiated by placing the rat in the water, nose facing the wall of the tank, at one of three predetermined starting locations. The order of the start location was varied daily. Learning was measured as a decrease in time required to swim to the platform. If an animal failed to locate the platform within 60 sec after the start of the trial, the rat was hand-guided to it. The animals remained on the platform for 10 sec before being removed from the tank. Ten min after the last training trial on day 5, the animals received a probe test. The platform was removed for this 1 trial task and the animals were allowed to swim for 60 sec to assess the spatial bias for the platform location. Two measures were recorded from this task: latency to first crossing the area where the platform had been, and total number of crossings.

[0152] The results of these learning tasks are encouraging. They suggest that arylalkylamines lack the learning and memory deficits that typify other NMDA receptor antagonists. In fact, there is a suggestion that the arylalkylamines may even be nootropic (memory enhancers).

(c) Cardiovascular effects

[0153] *In vivo* studies with certain arylalkylamines revealed a hypotensive effect of these compounds, especially at high doses. On the basis of these results, a systematic study of the effects of arylalkylamines on cardiovascular function was performed.

Example 18: Ca^{2+} channel inhibition

[0154] We have discovered that some of the arylalkylamines are quite potent inhibitors of voltage-sensitive Ca^{2+} channels, specifically those sensitive to inhibition by dihydropyridines (L-type channels). Such effects on vascular smooth muscle would be expected to dilate blood vessels and cause a drop in blood pressure, thus producing hypotension.

[0155] The ability of arylalkylamines to inhibit dihydropyridine-sensitive Ca^{2+} channels was examined in cerebellar granule cells and a rat aortic smooth muscle cell line, A_7r5 cells. Overall, we have observed a wide range of potencies against voltage-sensitive Ca^{2+} channels that does not correlate with potency against NMDA receptors. This strongly suggests that further structure-activity work based on chemical modification of the arylalkylamine molecule will lead to the development of compounds that are very potent NMDA antagonists with low potency against voltage-sensitive Ca^{2+}channels.

[0156] Arylalkylamines are not, however, indiscriminate blockers of voltage-sensitive Ca^{2+} channels. They do not, for example, affect voltage-sensitive Ca^{2+} channels in cerebellar Purkinje cells (P-type channels), or those channels thought to be involved in neurotransmitter release (N-channels). The arylalkylamines that do block voltage-sensitive Ca^{2+} channels appear to target specifically L-type Ca^{2+} channels. Moreover, as mentioned above, there is a high degree of structural specificity in this effect. For example, one arylalkylamine is 57 times more potent than another arylalkylamine in blocking Ca^{2+} influx through L-type channels, where the only structural difference between the compounds is the presence or absence of a hydroxyl group.

Example 19: *In vivo* cardiovascular studies

[0157] On the basis of these studies, it is anticipated that chemical efforts will minimize the cardiovascular side effects by (1) enhancing the uptake of arylalkylamine into the brain such that lower doses are required for neuroprocection, and (2) increasing the selectivity (potency ratio) of arylalkylamines for receptor-operated Ca^{2+} channels over voltage-sensitive Ca^{2+} channels.

Example 20: Biological activity of Compound 54 and analogs

[0158] Compounds **54** - **139** had high potencies against NMDA-induced increases in $[Ca^{2+}]_1$ in rat cerebellar granule cells grown in culture (Table 1). Compounds **54** - **147** inhibited [^{3}H]MK-801 binding in membranes prepared from rat hippocampal and cortical tissue (Table 1).

[0159] Compound **57** possessed the following additional biological activities: significant anticonvulsant activity against sound-induced seizures in a genetically susceptible mouse model of reflex epilepsy (Frings mice) following i. p. administration (ED_{50} = 1 mg/kg and TD_{50} (motor impairment) between 6 and 8 mg/kg).

[0160] Compound **58** possessed the following additional biological activities: significant anticonvulsant activity against sound-induced seizures in a genetically susceptible mouse model of reflex epilepsy (Frings mice) following i. p. administration (ED_{50} = 0.9 mg/kg and TD_{50} (motor impairment) = 14.5 mg/kg); no significant neuroprotectant activity in a rat model of focal ischemic stroke following i.p. administration of 2 mg/kg 30 min prior to vessel occlusion and 2 mg/kg 3 hr post-occlusion; and no significant cardiovascular activity in anesthetized rats at doses up to 2 mg/kg i.v.

[0161] Compound **59** possessed the following additional biological activities: significant anticonvulsant activity against sound-induced seizures in a genetically susceptible mouse model of reflex epilepsy (Frings mice) following i. p. administration (ED_{50} = 2.7 mg/kg and TD_{50} (motor impairment) = 7.8 mg/kg); a reduction in seizure threshold as indexed by the i.v. Metrazol test in mice at the dose of. 11.7 mg/kg i.p.; no significant neuroprotectant activity in a rat model of focal ischemic stroke following i.p. administration of 2 mg/kg 30 min prior to vessel occlusion and 2 mg/kg 3 hr pose-occlusion; and no significant cardiovascular activity in anesthetized rats at doses up to 10 mg kg i.v.

[0162] Compound **60** possessed the following additional biological activities: significant anticonvulsant activity against sound-induced seizures in a genetically susceptible mouse model of reflex epilepsy (Frings mice) following i. p. administration (ED_{50} = 4.4 mg/kg and TD_{50} (motor impairment) = 9.2 mg/kg); significant anticonvulsant activity against sound-induced seizures in a genetically susceptible mouse model of reflex epilepsy (Frings mice) following oral administration (ED_{50} = 10 mg/kg and TD_{50} (motor impairment) = 25.6 mg/kg); significant anticonvulsant activity against maximal electroshock-induced seizures in mice following i.p. administration (ED_{50} = 8.17 mg/kg and TD_{50}

(rotorod) = 17.30 mg/kg); no effect on seizure threshold as indexed by the i.v. Metrazol test in mice at the doses of 1 and 4 mg/kg i.p.; a reduction in seizure threshold as indexed by the i.v. Metrazol test in mice at the doses of 8 and 17 mg/kg i.p.; significant neuroprotectant activity in a rat model of temporary focal ischemic stroke following i.p. administration of 2 mg/kg 30 min prior to vessel occlusion and 2 mg/kg 3 hr post-occlusion; significant neuroprotectant activity in a rat model of temporary focal ischemic stroke following i.p. or i.v. administration of 1 mg/kg 2 hr and again 8 hr post-occlusion; significant neuroprotectant activity in a rat model of temporary focal ischemic stroke following i.v. administration of 1 mg/kg 2 hr post-occlusion; no significant neuroprotectant activity in a rat photothrombotic model of focal ischemia following the administration of 10 mg/kg i.p. at 15 min, 3 hr, and again 6 hr post-occlusion; no neuronal vacuolization when administered at doses of 20 mg/kg i.p. or 10 mg/kg i.v.; no significant cardiovascular activity in conscious beagle dogs at the dose of 0.3 mg/kg i.v. (60 sec bolus injection); transient increases in mean arterial pressure in conscious beagle dogs at the doses of 1 and 3 mg/kg i.v., with larger magnitude and longer duration effects seen at the dose of 10 mg/kg i.v. (60 sec bolus injection); transient increases in heart rate in conscious beagle dogs at the doses of 3 and 10 mg/kg i.v. (60 sec bolus injection); no significant changes in the ECG in conscious beagle dogs at doses ranging from 0.3 to 10 mg/kg i.v. (60 sec bolus injection); no significant behavioral effects in conscious beagle dogs at the doses of 0.3 and 1 mg/kg i.v. (60 sec bolus injection); a slight increase in respiratory rate in conscious beagle dogs at the dose of 3 mg/kg i.v. (60 sec bolus injection); dilated pupils, whole body tremors, salivation, and urination in conscious beagle dogs at the dose of 10 mg/kg i.v. (60 sec bolus injection); no significant behavioral effects in conscious male Wistar rats at doses up to 4 mg/kg i.v.; excitation, stereotypies, increased reactivity to touch, increased muscle tone, and tremor in conscious male Wistar rats at the dose of 8 mg/kg i.v.; Straub tail, convulsions, and death in conscious male Wistar rats at the dose of 16 mg/kg i.v.

[0163] Taken together, the results obtained with these simplified synthetic arylalkylamines suggest that such simplified molecules do not interact specifically with the arylalkylamine binding site on receptor-operated Ca^{2+} channels as do Compounds 1, 2 and 3. Specifically, Compounds **54** - **147** bind to the site labeled by [^{3}H]MK-801 at concentrations ranging approximately 1 to 400-fold higher than those which antagonize the function of the MMDA receptor-ionophore complex. The fact that Compounds **54** - **147** at therapeutic doses do not generally produce PCP-like stereotypic behavior, substitute for PCP in drug discrimination assays, or elicit neuronal vacuolization suggests, however, that such compounds might be useful either as lead compounds or drug candidates for neurological disorders and diseases. It has been reported that compounds which bind with low affinity (relative to MK-801) to the site labeled by [^{3}H]MK-801 might possess therapeutic utility and possess a more favorable side effect profile than that possessed by a high affinity antagonise such as MK-801 itself (Rogawski, Therapeutic potential of excitatory amino acid antagonists: channel blockers and 2,3-benzodiazepines. *Trends Pharmacol. Sci.* **14**: 325, 1993). The low affinity of certain compounds within the group of Compounds **54** - **147** (relative to MK-801) for the site labeled by [^{3}H]MK-801 may place these compounds into this general class of low affinity noncompetitive antagonists.

Identification of a novel modulatory site on receptor-operated calcium channels

[0164] Having identified arylalkylamines which have therapeutically useful properties as defined above, compounds can now be identified which act at the critical arylalkylamine binding site on receptor-operated Ca^{2+} channels, such as those present within NMDA, AMPA and nicotinic cholinergic receptor-ionophore complexes.

[0165] Examples of suitable tests now follow:

Example 21: Radioligand binding in rat cortex or cerebellum.

[0166] The following assay can be utilized as a high throughput assay to screen product libraries (e.g., natural product libraries and compound files at major pharmaceutical companies) to identify new classes of compounds with activity at this unique arylalkylamine site. These new classes of compounds are then utilized as chemical lead structures for a drug development program targeting the arylalkylamine binding site on receptor-operated Ca^{2+} channels. The compounds identified by this assay offer a novel therapeutic approach to treatment of neurological disorders or diseases. Examples of such compounds include those provided in the generic chemical formulae above. Routine experiments can be performed to identify those compounds having the desired activities.

[0167] Rat brain membranes are prepared according to the method of Williams *et al.* (Effects of polyamines on the binding of [^{3}H]MK-801 to the NMDA receptor: Pharmacological evidence for the existence of a polyamine recognition site. *Molec. Pharmacol.* **36**: 575, 1989) with the following alterations: Male Sprague-Dawley rats (Harlan Laboratories) weighing 100-200 g are sacrificed by decapitation. The cortex or cerebellum from 20 rats are cleaned and dissected. The resulting brain tissue is homogenized at 4°C with a polytron homogenizer at the lowest setting in 300 ml 0.32 M sucrose containing 5 mM K-EDTA (pH 7.0). The homogenate is centrifuged for 10 min at 1,000 x *g* and the supernatant removed and centrifuged at 30,000 x *g* for 30 minutes. The resulting pellet is resuspended in 250 ml 5 mM K-EDTA (pH 7.0) stirred on ice for 15 min, and then centrifuged at 30,000 x g for 30 minutes. The pellet is resuspended in 300

ml 5 mM K-EDTA (pH 7.0) and incubated at 32°C for 30 min. The suspension is then centrifuged at 100,000 x *g* for 30 min. Membranes are washed by resuspension in 500 ml 5 mM K-EDTA (pH 7.0), incubated at 32°C for 30 min, and centrifuged at 100,000 x *g* for 30 minutes. The wash procedure, including the 30 min incubation, is repeated. The final pellet is resuspended in 60 ml 5 mM K-EDTA (pH 7.0) and stored in aliquots at -80°C. The extensive washing procedure utilized in this assay was designed in an effort to minimize the concentrations of glutamate and glycine (co-agonists at the NMDA receptor-ionophore complex) present in the membrane preparation.

[0168] To perform a binding assay with [^{3}H]arylalkylamine, aliquots of SPMs (Synaptic Plasma Membranes) are thawed, resuspended in 30 mls of 30 mM EPPS/1mM K-EDTA, pH 7.0, and centrifuged at 100,000 x *g* for 30 minutes. SPMs are resuspended in buffer A (30 mM EPPS/l mM K-EDTA, pH 7.0). The [^{3}H]arylalkylamine is added to this reaction mixture. Binding assays are carried out in polypropylene test tubes. The final incubation volume is 500 µl. Nonspecific binding is determined in the presence of 100 µM nonradioactive arylalkylamine. Duplicate samples are incubated at 0°C for 1 hour. Assays are terminated by the addition of 3 ml of ice-cold buffer A, followed by filtration over glass-fiber filters (Schleicher & Schuell No. 30) that are presoaked in 0.33% polyethyleneimine (PEI). The filters are washed with another 3 x 3 ml of buffer A, and radioactivity is determined by scintillation counting at an efficiency of 35-40% for ^{3}H.

[0169] In order to validate the above assay, the following experiments are also performed:

(a) The amount of nonspecific binding of the [^{3}H]arylalkylamine to the filters is determined by passing 500 µl of buffer A containing various concentrations of [^{3}H]arylalkylamine through the presoaked glass-fiber filters. The filters are washed with another 4 x 3 ml of buffer A, and radioactivity bound to the filters is determined by scintillation counting at an efficiency of 35-40% for ^{3}H. In filters that are not pretreated with 0.33% PEI, it was found that 87% of the ^{3}H-ligand was bound to the filter. Presoaking with 0.33% PEI reduces the nonspecific binding to 0.5 - 1.0% of the total ligand added.

(b) A saturation curve is constructed by resuspending SPMs in buffer A. The assay buffer (500 µl) contains 60 µg of protein. Concentrations of [^{3}H]arylalkylamine are used, ranging from 1.0 nM to 400 µM in half-log units. A saturation curve is constructed from the data, and an apparent K_D value and B_{max} value determined by Scatchard analysis (Scatchard, The attractions of proteins for small molecules and ions. Ann. *N.Y. Acad. Sci.* **51**: 660, 1949). The cooperativity of binding of the [^{3}H]arylalkylamine is determined by the construction of a Hill plot (Hill, A new mathematical treatment of changes of ionic concentrations in muscle and nerve under the action of electric currents, with a theory to their mode of excitation. J. *Physiol.* **40**: 190, 1910).

(c) The dependence of binding on protein (receptor) concentration is determined by resuspending SPMs in buffer A. The assay buffer (500 µl) contains a concentration of [^{3}H]arylalkylamine equal to its K_D value and increasing concentrations of protein. The specific binding of [^{3}H]arylalkylamine should be linearly related to the amount of protein (receptor) present.

(d) The time course of ligand-receptor binding is determined by resuspending SPMs in buffer A. The assay buffer (500 µl) contains a concentration of [^{3}H]arylalkylamine equal to its K_D value and 100 µg of protein. Duplicate samples are incubated at 0°C for varying lengths of time; the time at which equilibrium is reached is determined, and this time point is routinely used in all subsequent assays.

(e) The pharmacology of the binding site can be analyzed by competition experiments. In such experiments, the concentration of [^{3}H]arylalkylamine and the amount of protein are kept constant, while the concentration of test (competing) drug is varied. This assay allows for the determination of an IC_{50} and an apparent K_D for the competing drug (Cheng and Prusoff, Relationship between the inhibition constant (K_1) and the concentration of inhibitor which causes 50 percent inhibition (IC_{50}) of an enzymatic reaction. *J. Biochem. Pharmacol.* **22**: 3099, 1973). The cooperativity of binding of the competing drug is determined by Hill plot analysis.

Specific binding of the [^{3}H]arylalkylamine represents binding to a novel site on receptor-operated Ca^{2+}-channels such as those present within NMDA-, AMPA- and nicotinic cholinergic receptor-ionophore complexes. As such, other arylalkylamines should compete with the binding of [^{3}H]arylalkylamine in a competitive fashion, and their potencies in this assay should correlate with their inhibitory potencies in a functional assay of receptor-operated Ca^{2+} channel antagonism (*e.g.*, inhibition of NMDA receptor-induced increases in $[Ca^{2+}]_1$ in cultures of rat cerebellar granule cells). Conversely, compounds which have activity at the other known sites on receptor-operated Ca^{2+} channels (*e.g.*, MK-801, Mg^{2+}, polyamines) should not displace [^{3}H]arylalkylamine binding in a competitive manner. Rather, complex allosteric modulation of [^{3}H]arylalkylamine binding, indicative of noncompetitive interactions, might be expected to occur. In preliminary experiments, MK-801 did not displace [^{3}H]arylalykylamine binding at concentrations up to 100 µM.

(f) Studies to estimate the dissociation kinetics are performed by measuring the binding of [^{3}H]arylalkylamine after it is allowed to come to equilibrium (see (d) above), and a large excess of nonradioactive competing drug is added to the reaction mixture. Binding of the [^{3}H]arylalkylamine is then assayed at various time intervals. With this assay, the association and dissociation rates of binding of the [^{3}H]arylalkylamine are determined (Titeler, Multiple

Dopamine Receptors: Receptor Binding Studies *in Dopamine Pharmacology.* Marcel Dekker, Inc., New York, 1983). Additional experiments involve varying the reaction temperature (0°C to 37°C) in order to understand the temperature dependence of this parameter.

Example 22: Radioligand binding in cerebellar granule cells

[0170] Primary cultures of cerebeiiar granule neurons are obtained from 8-day-old rats and plated onto Squares of Aclar plastic coated with poly-L-lysine. The plastic squares are placed in 24-well culture plates, and approximately 7.5 X 10^5 granule cells are added to each well. Cultures are maintained in Eagles' medium (HyClone Laboratories) containing 25 mM KCl, 10% fetal calf serum (HyClone Laboratories), 2 mM glucamine, 100 µg/ml gentamicin, 50 U/ml penicillin, and 50 µg/ml streptomycin at 37°C in a humid atmosphere of 5% CO_2 in air for 24 hr before the addition of cytosine arabinoside (10 µM, final). No changes of culture medium are made until the cells are used for receptor binding studies 6-8 days after plating.

[0171] To perform a binding assay with [^{3}H]arylalkylamine, the reaction mixture consists of 200 µl of buffer A (20 mM K-HEPES, 1 mM K-EDTA, pH 7.0) in each well of the 24-well plate. The [^{3}H]arylalkylamine is added to this reaction mixture. Nonspecific binding is determined in the presence of 100 µM nonradioactive arylalkylamine. Triplicate samples are incubated at 0°C for 1 hour. Assays are terminated by manually scraping the cells off the Aclar squares and placing them into polypropylene test tubes. The membranes prepared from whole cells in this manner are suspended in 10 ml of ice-cold buffer A, and filtered over glass-fiber filters (Schleicher & Schuell No. 30) that are presoaked in 0.33% PEI. The filters are washed with another 3 x 3 ml of buffer A, and radioactivity on the filters is determined by scintillation counting at an efficiency of 35-40% for ^{3}H. The assay may be terminated by centrifugation rather than filtration in order to minimize nonspecific binding.

[0172] Specific experiments to characterize and validate the assay are performed essentially as above, except that cells are used in place of membranes for the initial binding. The binding assay allows for the determination of an IC_{50}, value and an apparent K_D for the competing drug as described by Scatchard analysis (The attractions of proteins for small molecules and ions. *Ann. N.Y. Acad. Sci.* **51**: 660, 1949). Cooperativity of binding of the competing drug is determined by Hill plot analysis (A new mathematical treatment of changes of ionic concentrations in muscle and nerve under the action of electric currents, with a theory .to their mode of excitation. *J. Physiol.* **40**: 190, 1910). The specific binding of the [^{3}H]arylalkylamine represents binding, to a novel site on receptor-operated calcium channels.

Example 23: Patch-clamp electrophysiology assay

[0173] The following assay is performed for selected compounds identified in the above-mentioned radioligand binding assays as interacting in a highly potent and competitive fashion at the novel arylalkylamine binding site on receptor-operated Ca^{2+} channels, such as those present in NMDA-, AMPA- or nicotinic cholinergic receptor-ionophore complexes. This patch-clamp assay provides additional relevant data about the site and mechanism of action of said previously selected compounds. Specifically, the following pharmacological and physiological properties of the compounds interacting at the arylalkylamine binding site are determined, utilizing the NMDA receptor-ionophore complex as an example of receptor-operated Ca^{2+} channels: potency and efficacy at blocking MMDA receptor-mediated ionic currents, the noncompetitive nature of block with respect to glutamate and glycine, use-dependence of action, voltage-dependence of action, both with respect to onset and reversal of blocking, the kinetics of blocking and unblocking (reversal), and open-channel mechanism of blocking. Such data confirm that the compounds interacting at the arylalkylamine binding site retain the unique biological profile of the arylalkylamines, and do not have their primary activity at the known sites on the NMDA receptor-ionophore complex (glutamate binding site, glycine binding site, MK-801 binding site, Mg^{2+} binding site, Zn^{2+} binding site, sigma binding site, polyamine binding site).

[0174] Patch-clamp recordings of mammalian neurons (hippocampal, cortical, cerebellar granule cells) are carried out utilizing standard procedures (Donevan *et al.,* Arcaine blocks N-methyl-D-aspartate receptor responses by an open channel mechanism: whole-cell and single-channel recording studies in cultured hippocampal neurons. *Molec. Pharmacol.* **41**: 727, 1992; Rock and Macdonald, Spermine and related polyamines produce a voltage-dependent reduction of NMDA receptor single-channel conductance. *Molec. Pharmacol.* **42**: 157, 1992).

[0175] Alternatively, patch-clamp experiments can be performed on *Xenopus* oocytes or on a stably transfected mammalian cell line (*e.g.*, HEK 293 cells) expressing specific subunits of receptor-operated Ca^{2+} channels. In this manner, for example, potency and efficacy at various glutamate receptor subtypes (*e.g.*, NMDAR1, NMDAR2A through NMDAR2D, GluR1 through GluR4) can be determined. Further information regarding the site of action of the arylalkylamines on these glutamate receptor subtypes can be obtained by using site-directed mutagenesis.

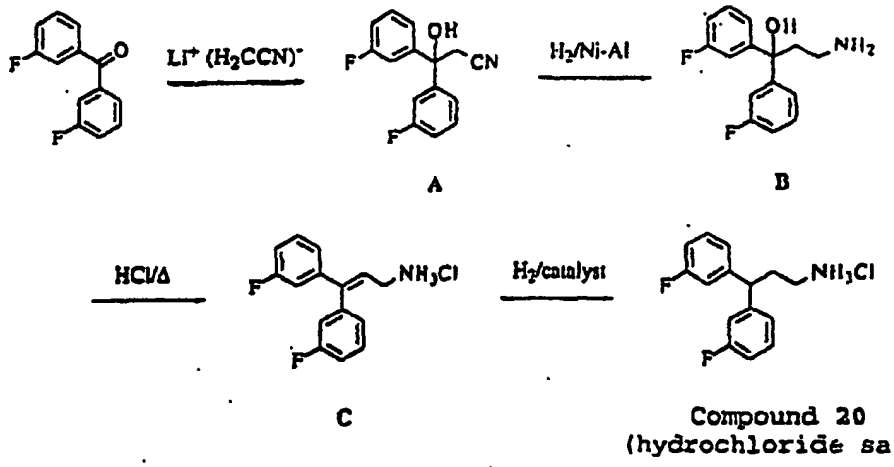
Example 24: Synthesis of simplified arylalkylamines

[0176] Synthesis of Compound **20** (Reference Compound) was accomplished as follows.

[0177] A solution of sodium hydride (1.21 g, 50 mmol) in dimethoxyethane was treated with diethyl cyanomethylphosphonate (8.86 g, 50 mmol) and the reaction stirred 4 hr at room temperature. To this was added 3,3'-difluorobenzophenone (10 g, 46 mmol) in DME. The reaction was stirred 24 hr at room temperature, quenched with H_2O, and partitioned between diethyl ether and water. The ether fraction was dried over Na_2SO_4 and concentrated. GC/MS of this material showed 90% of the product A and 10% starting benzophenone.

[0178] A solution of this material in ethanol with a catalytic amount of $Pd(OH)_2$ was hydrogenated at 55 psi hydrogen for 4 hr at room temperature. The reaction was filtered and the catalyst washed with ethanol (3x). The filtrate and ethanol washes were combined and concentrated. GC/MS of this material showed 90% of the product B and 10% of the starting benzophenone.

[0179] A solution of this material in THF was treated with. 70 ml 1 M B_2H_6 (70 mmol) in THF and refluxed 1 hr. After cooling the reaction was treated with 6 N HCl (50 ml) and refluxed an additional hour. After cooling the reaction was basified to pH 14 with 10 N NaOH and equilibrated with ether. The ether layer was removed and washed with 10% HCl (3x). The acidic washes were combined, basified to pH 14 with 10 N NaOH and extracted with dichloromethane (3x). The organic washes were combined, dried over Na_2SO_4, and concentrated to yield an oil. GC/MS of this material showed 100% Compound **20**. GC/EI-MS (R_t =7.11 min) m/z (relative intensity) **247** (M^+, 31), **230** (100), **215** (30), **201** (52), **183** (63), **134** (23), **121** (16), **101** (21), **95** (15), **77** (15). This material in diethyl ether was filtered and treated with 35 ml 1 M HCl in ether. The precipitate was collected, dried, and recrystallized from water-ethanol to afford 1.045 g of Compound **20**, as the hydrochloride salt. ^{1}H-NMR ($CDCl_3$) d 8.28 (3H, br s), 7.28-7.17 (2 H, m), 7.02-6.86 (6 H, m), 4.11 (1H). t, J=8 Hz), 2.89 (2H, br t, J=8 Hz), 2.48 (2H, br t, J=7 Hz); ^{13}C-NMR ($CDCl_3$) d 164.6, 161.3, 144.8, 144.7, 130.4, 130.3, 123.3, 123.2, 114.7, 114.5, 114.1, 113.8, 47.4, 38.4, 32.7.



[0180] Synthesis of Compound **21**, Compound **33** and Reference Compounds was accomplished as follows.

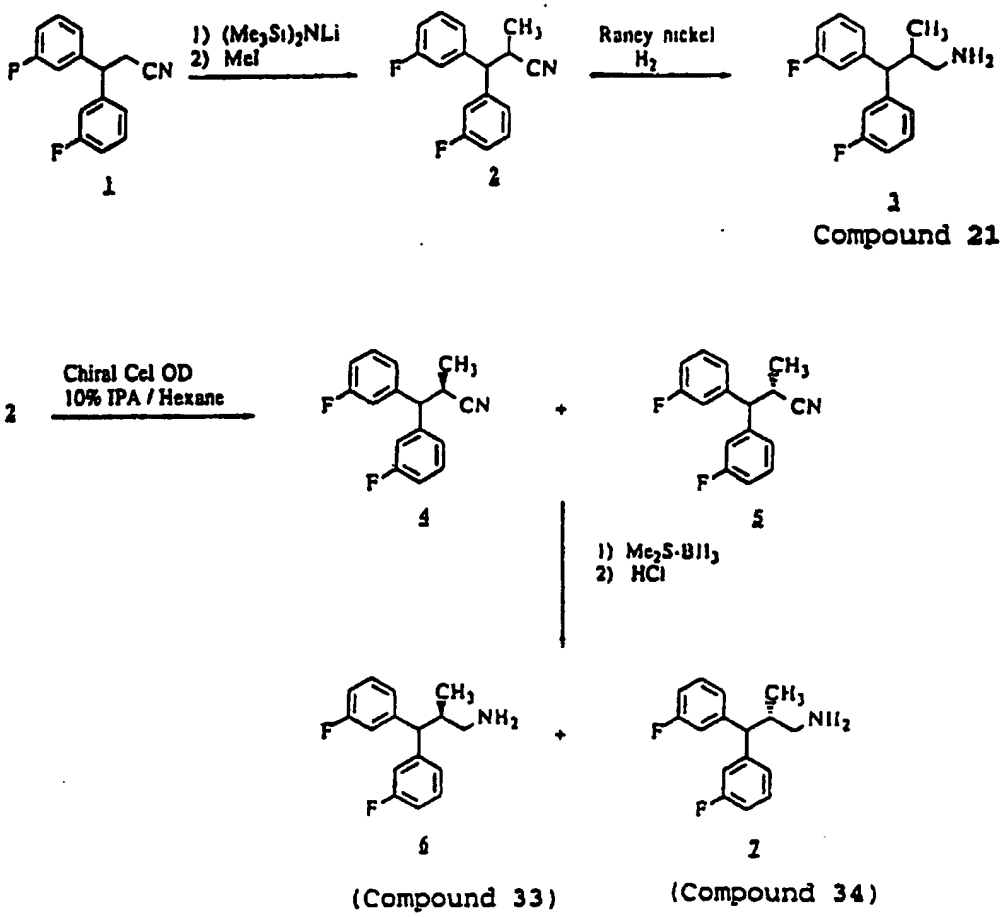
[0181] A 100 ml round-bottomed flask equipped with stir bar, septa, and argon source was charged with compound **1** (2.43 g, 10 mmol) in 30 ml THF. The solution was cooled to -78°C and treated dropwise with 11 ml lithium bis(trimethylsilyl)amide (1M in THF) (11 mmol). The reaction was stirred at -78°C for 30 min and created dropwise with excess iodomethane (3.1 ml, 50 mmol). The reaction was stirred 30 min at -58°C. GC/EI-MS analysis of an aliquot from the reaction showed consumption of the starting nitrile **1**. The reaction was quenched with water, diluted with diethyl ether and transferred to a separatory funnel. The ether layer was washed with 10% HCl (3X), brine (1X), dried with anhydrous $MgSO_4$, and concentrated to a brown oil. This material was distilled (Kugelrohr, 100°C) at reduced pressure to afford 1.5 g of a clear oil. GC/EI-MS of this material showed it to contain the desired product **2** , (R_t=7.35 min) *m/z* (rel. int.) 257 (M^+, 3), 203 (100), 183 (59), 170 (5), 133 (4), 109 (3) ; ^{1}H-NMR ($CDCl_3$) d 7.4-6.9 (8H, m), 4.01 (1H, d, J=10 Hz), 3.38 (1H, dq, J=7, 10 Hz), 1.32 (3H, d, J=7 Hz); ^{13}C-NMR ($CDCl_3$) d 19.4, 30.5, 54.2, 114.5, 114.6, 114.7, 114.9, 115.0, 115.3, 123.3, 123.4, 123.6, 123.7, 130.5, 130.6, 131.7.

[0182] Product **3** was synthesized by the catalytic reduction of **2** using Raney nickel in 95:5 EtOH:aqueous sodium

hydroxide (2 Eq.) under 60 psi hydrogen. GC/EI-MS (R_t=7.25 min) *m/z* (rel. int.) 261 (M', 20), 244 (35), 229 (16), 215 (17), 201 (80), 183 (100), 133 (42), 115 (27), 109 (47), 95 (20); ^{1}H-NMR ($CDCl_3$) d 7.3-6.8 (8H, m), 3.62 (1H, d, J=10 Hz), 2.70 (1H, M), 2.40 (2H, m), 1.73 (2H, m), 0.91 (3H, d, J=7 Hz). Note that product **3** in this reaction sequence corresponds to Compound **21**.

[0183] Product **2** in 10% IPA-hexane (100 mg/ml was chromatographed, in 500 µl aliquots, through Chiral Cel OD (2.0 x 25 cm) using 10% IPA-hexane at 10 ml/min measuring optical density at 254 nm. This afforded the two optically pure enantiomers **4** and **5** (as determined by analytical chiral HPLC; Note, the stereochemistry of these two compounds has not been assigned at this time). These two compounds were identical in their GC/EI-MS and ^{1}H-NMR spectra as product **2** (data above)

[0184] Each of the enantiomers **4** and **5** was reduced separately using dimethyl sulfideborane complex in the following manner. A solution of compound (**4** or **5**) in THF was heated to reflux and treated with excess (2 Eq.) 1M (in THF). dimethyl sulfideborane complex and the reaction refluxed 30 min. After this time the reaction was cooled to 0°C and treated with 6 N HCl. The reaction was set to reflux for 30 min. After this time the reaction was transferred to a separatory funnel, basified to pH > 12 with 10N NaOH; and the product (**6**) extracted into ether. The ether layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated to an oil. The product was purified by prep-TLC using 5% methanol-chlorform. Each of the individual enantiomers (**6** and **7**) were found to be identical in their GC/EI-MS and ^{1}H-NMR spectra as product **3** (data above). Note that product **6** in this scheme corresponds to Compound 33 . Compound 33-HCl: mp = 260-270°C (dec), $[a]_{369}26$ = +6.6 (c 1.0 in EtOH), $[a]_D26$ = +0.4 (c 1.0 in EtOH). Compound 33·HI: The free base of Compound 33 was dissolved in EtOH and 47% hydriodic acid (1.1 equvt.) was added. The solvent was evaporated under vacuum and the resulting solid hydroiodide was recrystallized twice from heptane/EtOAc by slow evaporation: mp = 195-197°C. The absolute configuration of compound 33·HI was determined to be R by single crystal (monoclinic colorless needle, 0.50 x 0.05 x 0.03 mm) X-ray diffraction analysis using a Siemens R3*m/V* diffractometer (3887 observed reflections).



[0185] Synthesis of Compound **24** (Reference Compound) was accomplished as described below. Compounds **25** (Reference Compound) **65, 76-78, 83, 90, 96-97, 115,** and **135-136** were prepared in a similar manner.

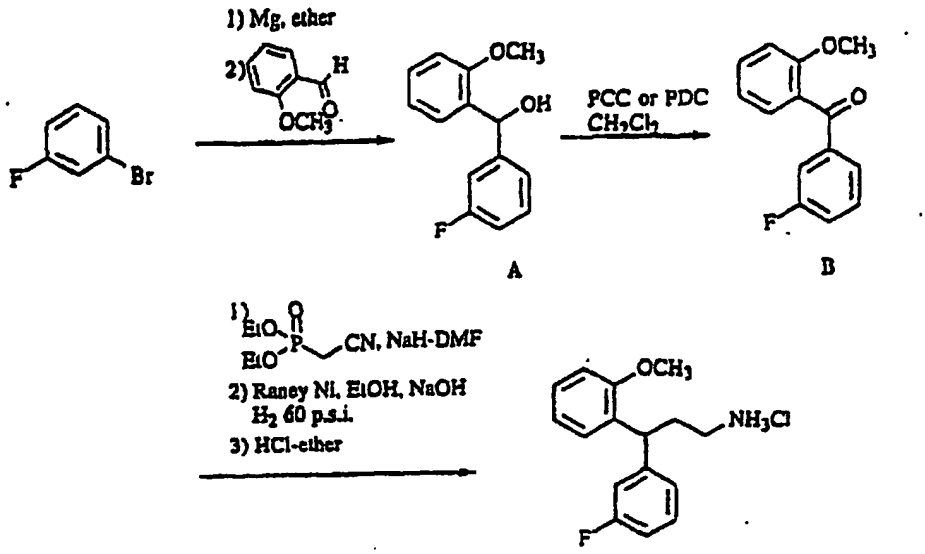
[0186] A suspension of magnesium turnings (0.95 g, 39.2 mmol) in 150 ml anhydrous diethyl ether was treated with 1-bromo-3-fluorobenzene (6.83 g, 39.2 mmol) dropwise via syringe. After 1.5 hr the solution was transfered via cannula to a flask containing o-anisaldehyde (5.0 g, 36.7 mmol) in 100 ml anhydrous diethyl ether at 0°C and stirred 2hr. The reaction mixture was quenched with water and partitioned between water and ether. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate to afford 7.90g (93% yield) of product **A**.

[0187] Pyridinium dichromate (16.0 g, 42.5 mmol) was added to a solution of the alcohol **A** (7.90 g, 34.0 mmol) in dichloromethane (100 ml), and the reaction was stirred 12 hr. Diethyl ether (300 ml) was added to the reaction mixture and the black solution was filtered through a silica gel plug (30 cm) and washed with an additional 500 ml ether. After evaporation of the solvent *in vacuo*, the solid was recrystallized from acetone to give 7.45 g (95% yield) of product **B**.

[0188] Diethyl cyanomethylphosphonate (7.0 g, 39.5 mmol) was slowly added to a suspension of sodium hydride (1.58 g, 39.5 mmol) in 100 ml N,N-dimethylformamide. After 30 minutes the ketone **B** was added to the solution and stirred an additional 2 hr. The reaction mixture was quenches with water, and partitioned between water and ether. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* to give a pale yellow oil.

[0189] In a glass bomb, the oil was dissolved in 100 ml ethanol and 20 ml 10N NaOH. A catalytic amount of Raney Nickel suspened in water (ca. 15 mol percent) was added to the solution. The reaction mixture was shaken under 60 psi H_2 for 12 hr on a Parr Hydrogenator. After filtering off excess Raney Nickel, the solution was extracted with chloroform. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. After

filtration, the oil was run through a silica gel column in chloroform and methanol. The solvent was evaporated *in vacuo* to give a pale yellow oil. GC/EI-MS (R_t=8.10 min) *m/z* (rel. intensity) **259** (100), **242** (44), **213** (48), **183** (42), **136** (50), **109** (94), **91** (60), **77** (25). The oil was then acidified with hydrogen chloride in diethyl ether. Evaporation of the ether afforded a pale yellow solid that was recrystallized in hot acetonitrile to afford 3.45 g (42.1% yield) white needles of Compound **24**, as the hydrochloride salt.



Compound 24 (HCl salt)

[0190] Compounds **101** and **103** were synthesized from compounds **25** and **24**, respectively, by cleavage of their *O*-methyl ethers with borane tribromide in the normal manner.

[0191] Compound **32** (Reference compound) was synthesized according to standard procedures as described above.

[0192] Compounds **107, 116, 139,** and **143** were prepared as synthetic intermediates used in the preparation of Compounds **32, 115, 20,** and **25,** respectively.

[0193] Compound **50** (Reference Compound) was also prepared using the chiral synthesis described below.

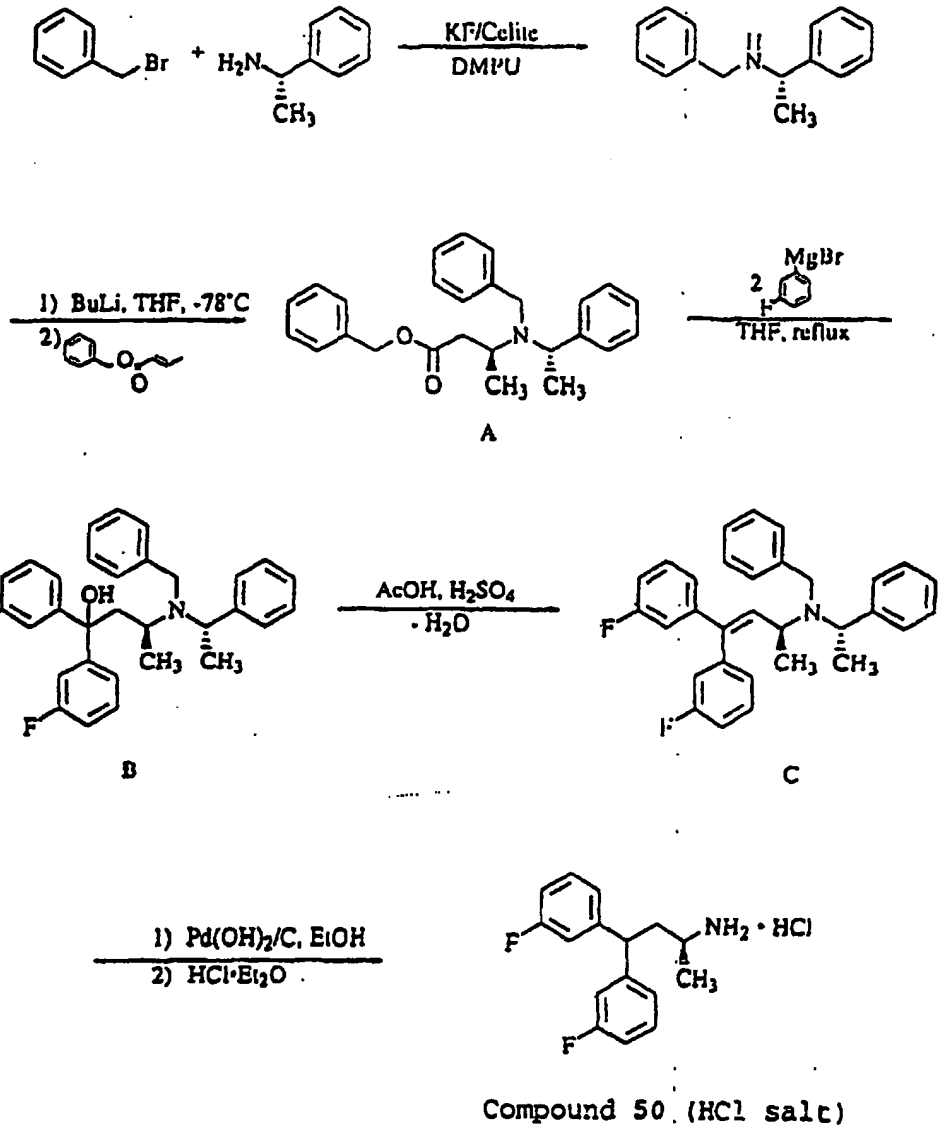
[0194] To an ice cold solution of *N*-benzyl-(*S*)-a-methylbenzylamine (18.0 g, 85.2 mmol) in THF (75 ml) was added butyl lithium (2.5 M in hexane) (37.5 ml, 93.8 mmol) via a syringe over a period of 10 min at such a rate as to keep the reaction temperature below 10°C during the addition. The reaction was then stirred at 0°C for 15 min. The reaction was cooled to -78°C in a dry ice/isopropanol bath and then a solution of benzyl crotonate (15.0 g, 85.2 mmol) in THF (100 ml) was added dropwise over a period of 45 min. The reaction was stirred at -78°C for 15 min, and then saturated NH_4Cl (50 ml) was added. The reaction mixture was then quickly transferred to a separatory funnel containing saturated NaCl (500 ml) and ether (200 ml). The layers were separated and the aqueous layer extracted with ether (200 ml). The combined organic layers were dried, evaporated, and chromatographed on silica gel (50 mm x 30 cm) (hexane/ethyl acetate [20:1]) to yield 21.0 g, 63.7% of product A. ^{1}H-NMR showed that the diastereoselectivity of the reaction is > 90%.

[0195] A mixture of magnesium (2.58 g, 106 mmol), THF (200 ml), and 1-bromo-3-fluorobenzene (18.60 g, 106.3 mmol) was refluxed for 45 min. While still under reflux, product **A** (16.45 g, 42.45 mmol) was added via syringe with THF (25 ml) over a 2 min period. The reaction was refluxed for 1 hr, and then allowed to cool to room temperature. Saturated NH_4Cl(aq) (200 ml) was added. The reaction mixture was then transferred to a separatory funnel containing saturated NaCl(aq) (500 ml) and diethyl ether (200 ml). The layers were separated and the aqueous layer extracted with ether (200 ml). The combined organic layers were dried over sodium sulfate and evaporated to give 21.41 g of product **B** as a yellow liquid.

[0196] Product **B** (20.02 g, 42.45 mmol, theoretical) was dissolved in acetic acid (120 ml) and sulfuric acid (30 ml). The reaction was stirred at 90°C for 1 hr. The acetic acid was rotary evaporated giving a brown sludge. This material was placed in an ice bath and cold water (400 ml) was added. The product immediately precipitated. To the reaction was slowly added 10 N NaOH (150 ml) to neutral pH. Diethyl ether (200 ml) was added to this mixture. The mixture

was shaken until there was no undissolved material. The ether layer was separated, washed with water (2 x 100 ml), dried over sodium sulfate, and rotary evaporated yielding 13.14 g (68.2% based on ester) of a thick brown oil. This oil was taken up in ether and converted to the hydrochloride salt with hydrogen chloride in diethyl ether to give product **C** as a yellow-white solid.

[0197] Product **C** (7.17 g, 14.6 mmol) was taken up in absolute ethanol (200 ml). Pearlman's catalyst ($Pd(OH)_2/C$; 2.00 g) was added. The reaction was shaken under 70 psi hydrogen gas at 70°C for 20 hr, and the reaction mixture was filtered through Celite. The filtrate was rotary evaporated to give 3.54 g of a light yellow glass. This material was taken up in diethyl ether (100. ml) and was basified with 1 N MaOH (25 ml). The ether layer was washed with water (1 x 25 ml), dried over sodium sulfate, and rotary evaporated to give 2.45 g of a light yellow oil. This material was Kugelrohr distilled (90-100°C, 1 mm Hg) to give 1.17 g of a colorless liquid. This material was taken up in diethyl ether and converted to the hydrochloride salt with ethereal hydrogen chloride. After rotary evaporation, the salt was recrystallized from 0.12 N HCl (200 mg/ml). The crystals were filtered off and were washed with cold 0.12 N HCl yielding 0.77 g (18%) of Compound 50 as silvery white crystals (as the hydrochloride salt).



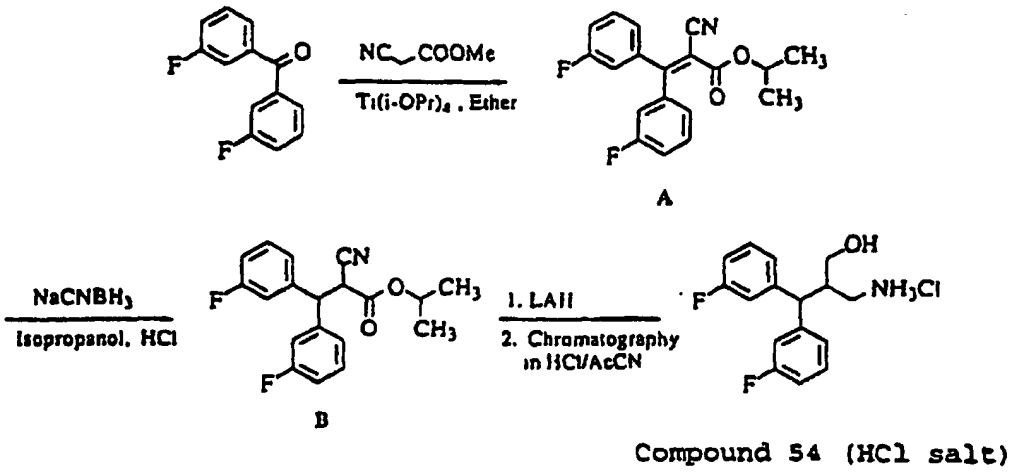
Compound 50 (HCl salt)

[0198] Synthesis of Compound **54** was accomplished as described below.

[0199] To a solution of 3,3'-difluorobenzophenone (5 g, 22.9 mmol) and methyl cyanoacetate (3.4 g, 34.4 mmol) in 15 ml of ether was added titanium isopropoxide (16.9 g ml, 57.25 mmol). This solution was stirred for 6 days at room temperature then quenched with 0.5 mol of HCl in 300 ml of water. The mixture was diluted with 100 ml of ether, and the layers separated. The ether layer was washed with 5% HCl and saturated brine, then dried over sodium sulfate. The solvents were evaporated *in vacuo* to give 8 g of product **A**.

[0200] Compound A was dissolved in 50 ml of isopropanol, followed by the addition of a small amount of bromocresol green. Sodium cyanoborohydride (1.52 g, 24.2 mmol) was added all at once followed immediately with the dropwise addition of concentrated HCl, added at such a rate as to keep the solution yellow. After 2 hours the reaction was worked up by partitioning between ether and water. The ether layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated to give the product **B**.

[0201] To a solution of lithium aluminum hydride (30.4 ml, 30.4 mmol) in THF was added product **B** (1 g, 3.04 mmol) in 2 ml of THF over a period of 30 seconds. This solution was stirred overnight at room temperature, then quenched with the addition of 20 ml of ethyl acetate. The solvents were then removed *in vacuo*, and the resulting oil was dissolved in aqueous HCl and acetonitrile. The product was then purified on a C-18 column with a gradient of 0.1% HCl to acetonitrile to give 82 mg of Compound **54**, as the hydrochloride salt. EI-MS *m/z* (relative intensity) 277 (M^+, 100), 260 (2.4), 242 (8.6), 229 (28), 215 (11.7), 204 (16), 183 (12), 133 (9.5), 124 (14), 109 (6.8), 30 (22).



[0202] Compound 55 was synthesized analogously to Compound **21** except that ethyl iodide was used in the alkylation step. GC/EI-MS (R_t = 7.43 min) *m/z* (relative intensity) 275 (M^+, 100), 258 (66), 229 (63), 204 (57), 201 (72), 183 (84 , 134 (57), 124 (68), 109 (98), 72 (72).

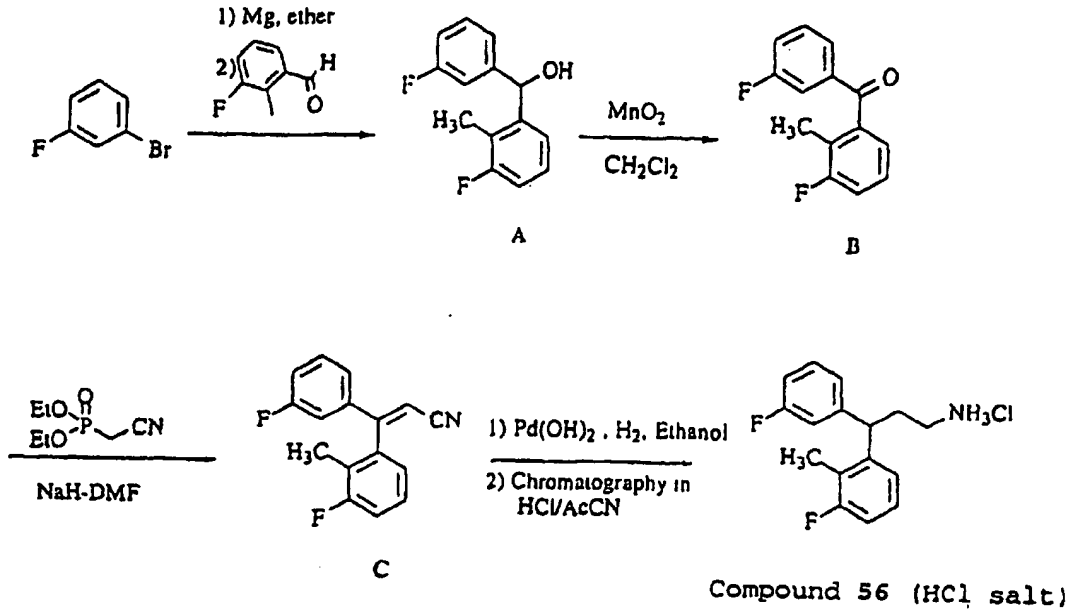
[0203] The synthesis of Compound 56 was accomplished as follows.

[0204] The alcohol **A** was synthesized from 3-fluorobromobenzene and 3-fluoro-2-methylbenzaldehyde as described for product **A** in the synthesis of Compound **24.**

[0205] The alcohol A (8.4 g, 36.2 mmol) was stirred with manganese dioxide (12.6 g, 144.8 mmol) in 100 ml of dichloromethane for 4 days. The reaction mixture was then diluted with ether and filtered through a 0.2 micron teflon membrane filter. The filtrate was concentrated to give 7.6 g of the ketone **B**.

[0206] The substituted acrylonitrile C was synthesized as described for product **A** in the Compound **20** synthesis.

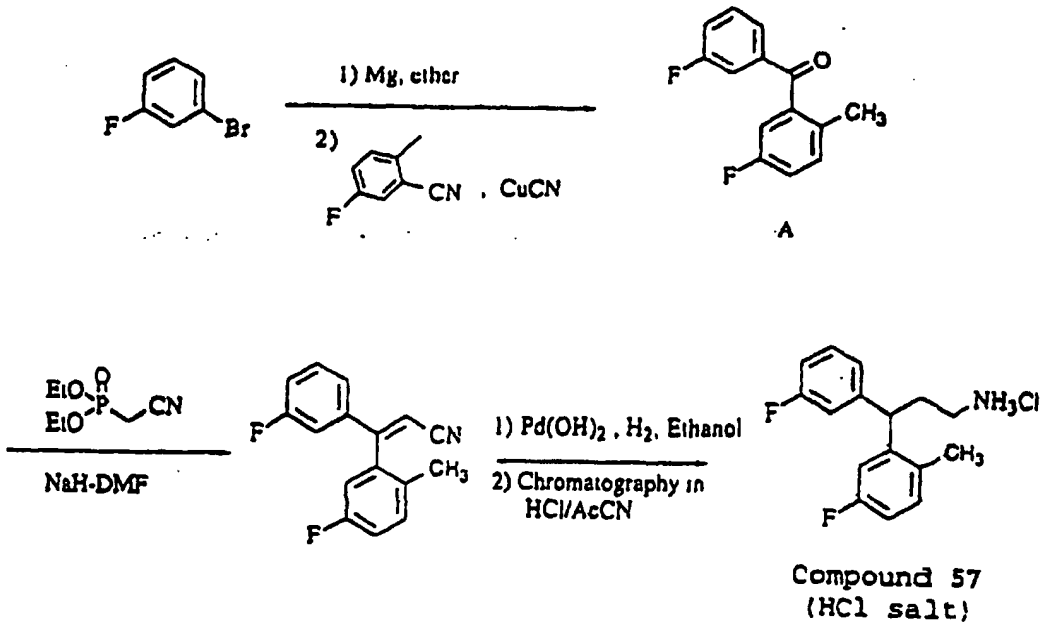
[0207] To the nitrile C (4 g, 15.7 mmol) in 240 ml of ethanol was added 2 g of 10% palladium dihydroxide on carbon. This mixture was hydrogenated at 60-40 psi for 3 days. The reaction, mixture was then filtered and concentrated. The resulting oil was dissolved in chloroform and chromatographed on silica gel (30% methanol/5% isopropylamine in chloroform) to give the amine. This amine was dissolved in aqueous HCl/acetonitrile and purified *via* HPLC on C-18 (10% acetonitrile/0.1% HCl to 50% acetonitrile/0.1% HCl over 60 min) then lyophilized to give 800 mg of Compound **56**, as the hydrochloride salt. GC/EI-MS (R_t = 7.39 min) *m/z* (relative intensity) 261 (M^+, 64), 244 (56), 229 (57), 215 (100), 203 (53), 183 (21), 133 (39), 122 (31), 109 (32).



[0208] The synthesis of Compound **57** was accomplished as follows.

[0209] To a solution of 5-fluoro-2-methylbenzonitrile (5 g, 37 mmol) in 50 ml of THF was added 3-fluorophenylmagnesium bromide (46 ml, 40 mmol) and copper (I) cyanide (0.072 g, 0.8 mmol). This solution was refluxed for 4 hours, then poured into ether/20% HCl and stirred for a further 2 hours. The layers were separated, and the ether layer washed with water and saturated brine. The solution was dried over sodium sulfate and concentrated. The crude oil was purified on silica (hexane to 50% dichloromethane in hexane over 60 min) to give 6.7 g of the ketone **A**.

[0210] The ketone **A** was converted to Compound **57** as described for Compound **56**. GC/EI-MS (R_t = 7.35 min) *m/z* (relative intensity) 261 (M^+, 52), 244 (41), 229 (67), 215 (100), 203 (42), 201 (42), 183 (21), 133 (45), 122 (28), 109 (26).



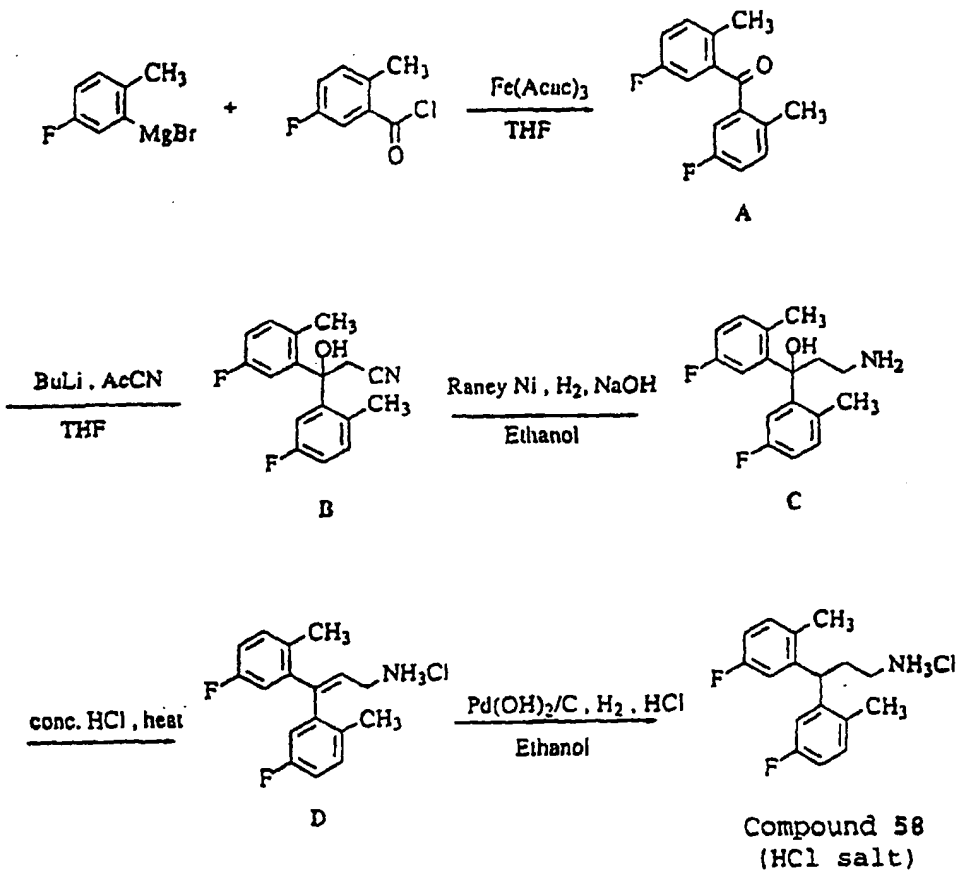
[0211] The synthesis of Compound 58 was accomplished as follows.

[0212] To a solution of 5-fluoro-2-methylbenzoyl chloride (2.24 g, 13 mmol) in 10 ml of dry THF was added iron III acetylacetonate (0.16 g, 0.44 mmol). The solution was cooled to 0°C, and a THF solution of 5-fluoro-2-methylphenyl-magnesium bromide (20 ml, 15.5 mmol) was added by syringe over a period of 30 min. The reaction was stirred for another 30 min, then poured slowly into ether/5% HCl. The ether layer was separated, washed with saturated brine, dried over sodium sulfate, and concentrated to give 3.2 g of ketone **A**.

[0213] Dry THF (30 ml) was cooled to -78°C followed by the addition of butyl lithium (5.85 ml, 14.6 mmol, 2.5 M solution in hexanes). Acetonitrile (0.76 ml, 14.62 mmol) was then added over a period of 2 min, then allowed to stir at -78°C for 15 min. To this solution was added ketone **A** (3 g, 12.2 mmol) in 5 ml of THF. The solution was stirred for 30 min at -78°C then allowed to warm to room temperature and stirred overnight. The reaction mixture was partitioned between ether and 5% HCl. The ether layer was separated, washed with saturated brine, dried over sodium sulfate, and concentrated to give 2.2 g of the nitrile **B**.

[0214] The nitrile **B** (1 g, 3.48 mmol) was dissolved in 30 ml of ethanol and 3 ml of 10 N sodium hydroxide. To this solution was added 1 g of a 50% aqueous slurry of Raney nickel, and the mixture was hydrogenated at 60 psi for 2C hours. The reaction was filtered and concentrated to a white solid. This residue was taken up in ether/water and the ether layer separated. The ether solution was dried over sodium sulfate and concentrated to give 0.96 g of the hydroxy amine **C**.

[0215] The hydroxy amine C (0.96 g, 3.3 mmol) was taken up in concentrated HCl and heated to 70°C which caused brief solution, and then precipitation of the alkene **D**. The alkene was collected by filtration and dissolved in 30 ml of ethanol and 1 ml of conc. HCl. Palladium dihydroxide on carbon (0.4 g) was added to the solution, and the mixture hydrogenated at 60 psi for 24 hours. The product was isolated by filtering off the catalyst and evaporating the solvent. The residue was dissolved in 0.1% HCl and acetonitrile, and purified on C-18 (15% acetonitrile/0.1% HCl to acetonitrile) to give 0.6 g of Compound **58**, as the hydrochloride salt. GC/EI-MS (R_t = 7.82 min) m/z (relative intensity) 275 (M^+, 100), 258 (20), 243 (74), 229 (38), 214 (65), 201 (31), 196 (32), 183 (20), 148 (35), 138 (42), 133 (48), 122 (69), 109 (41).



[0216] Synthesis of Compound **59** was accomplished as follows.

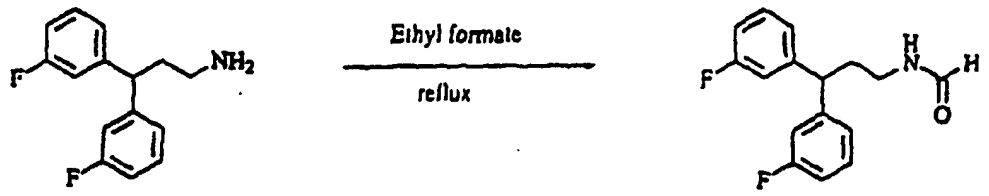
[0217] Compound **20** (2.0 g, 7.05 mmol) was dissolved in abs. EtOH (200 ml) and cooled to 5-10°C in an ice bath. Acetaldehyde (0.395 ml, 7.05 mmol, cooled to -4°C) was added followed by nickel-aluminum alloy (200 mg, Fluka Chemika), and the reaction was hydrogenated on a Parr apparatus at 50 psi for 2 hr. GC/MS showed 75% yield of the product and 2% of the *N,N*-diethyl side-reaction product. The reaction mixture was filtered through diatomaceous earth and the filtrate was evaporated under reduced pressure. The crude product was dissolved in isopropanol (5 ml)/ether (60 ml)/ethereal HCl (1 M), and then hexane (5 ml) was added to the cloud point. The cloudy mixture was filtered through paper, then hexane (10 ml) was added to the cloud point, and the solution was filtered again. The filtrate-was stoppered and the product was allowed to crystallize at room temperature. The crystals were collected and dried to provide 0.325 g (14.8% yield) of Compound 59, as the hydrochloride salt (colorless needles).

[0218] The synthesis of Compound **60** was accomplished as follows. Compounds **66, 69, 108, 123, 142,** and **145** can be synthesized in a similar manner starting from Compounds **33, 50, 32, 60, 25** and **119**, respectively.

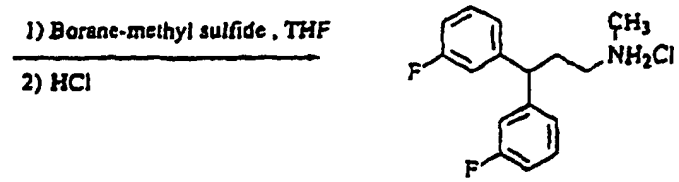
[0219] Compound **20** (as the free base) (1.0 g, 4.0 mmol was refluxed in ethyl formate (150 ml) for 2 hr. The solvent was then removed under reduced pressure to provide 1.1 g, 99% yield of formamide **A** as a colorless oil. GC/MS showed the product to be 100.0% pure and was used in the following step without further purification.

[0220] The formamide **A** (1.1 g, 4.0 mmol) was dissolved in dry THF (100 ml) and heated to reflux (no condenser). Borane-methyl sulfide complex (1.2 ml, 12 mmol, 10.5 M) was added dropwise over a period of 3 min to the refluxing solution. Reflux was maintained for approximately 15 min, open to the air, until the reaction volume was reduced to approximately 30 ml. The reaction was then cooled in an ice bath, and ice (5 g, small pieces) was carefully added followed by H_2O (25 ml) and conc. HCl (25 ml). The acidic solution was refluxed for 30 min. The reaction mixture was then cooled in an ice bath, basified with NaOH (10N), extracted with ether (3 X 100 ml), dried (Na_2SO_4, anhydrous), and evaporated under reduced pressure. The crude product was dissolved in ether (10 ml)/hexane (50 ml) and ethereal

HCL (1 M) was added dropwise to precipitate the hydrochloride salt. The salt was collected and recrystallized from isopropanol (3 ml)/ether (40 ml) to provide 0.5 g of Compound **60**, as the hydrochloride salt.



Compound 20 (as free base) **A**



Compound 60 (HCl salt)

[0221] Alternatively, Compound **60** was synthesized from commercially available starting materials in the following four step reaction sequence. The first intermediate in this synthetic route, ethyl-*N*-benzyl-*N*-methyl-3-aminopropionate. was prepared by conjugate addition of *N*-benzylmethylamine to ethyl acrylate. The ester functionality of the first intermediate was then reacted with two equivalents of Griguard reagent (prepared from 1-bromo-3-fluorobenzene) to provide *N*-benzyl-*N*-methyl-3-hydroxy-3- (bis-3-fluorophenyl) propylamine. The Grignard reaction product was then dehydrated in a mixture of 6N HCl/acetic acid to yield *N*-benzyl-*N*-methyl-3-(bis-3-fluorophenyl)-2-propenamine. Catalytic hydrogenation of this material as its hydrochloride salt in ethanol over Pearlman's catalyst [$Pd(OH_2)/C$] provided, after recrystallization from ethyl acetate, colorless, needles of Compound 60 as the hydrochloride salt.

[0222] In a 500-mL, 3-necked flask equipped with thermometer, reflux condenser, and a 125-mL addition funnel [charged with ethyl acrylate (88.3 mL, 81.5 g, 0.815 mol)] was placed *N*-benzylmethylamine (100 mL, 94.0 g, 0.776 mol). The ethyl acrylate was added dropwise to the stirring reaction mixture over a period of 80 min. After stirring for 18 h at room temperature, the product was vacuum distilled and the fraction containing product was collected at 78-95°C (0.12-0.25 mm Hg), (138 g, 80% yield): Bp 78-95°C (0.12-0.25 mm Hg) ; TLC, R_f = 0.23 [hexane-EtOAc (5:1)], R_f = 0.57 [MeOH-$CHCl_3$ (100:5)]; GC, t_R = 6.06 min; MS, 221 (M^+), 206 (M-CH_3), 192 (M-C_2H_5), 176 (M-OC_2H_5), 144 (M-C_6H_5), 134 [$CH_2N(CH_3)CH_2Ph$], 120 [$N(CH_3)CH_2Ph$], 91 (CH), 77 (CH), 42 (CH_2CH_2N); ^1H NMR (free base, $CDCl_3$) d 1.25 ppm (t, J = 7.1, 3H, CH_2CH_3), 2.20 (s, 3H, NCH_3), 2.51 (t, *J* = 7.3, 2H, $COCH_2$), 2.74 (t, *J* = 7.2, 2H, CH_2N), 3.51 (s, 2H, NCH_2Ph), 4.13 (q, *J* = 7.1, 2H, OCH_2CH_3), 7.18-7.35 (m, 5H, ArH); ^{13}C NMR (free base, $CDCl_3$ d 15.2 (CH_2CH_3), 34.0 ($COCH_2$), 42.9 (NCH_3), 53.8 (NCH_2), 61.4 (OCH_2CH_3), 63.1 (CH_2Ph), 128.0 (CH), 129.2 (CH), 130.0 (CH), 139.9 (q), 173.7 (q).

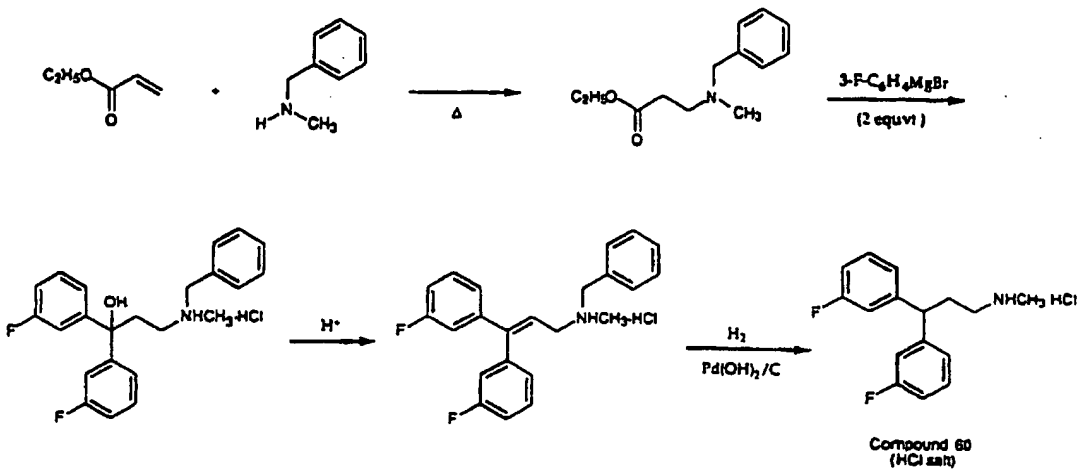
[0223] In a 5-L, four-necked, round-bottom flask, under nitrogen, was placed Mg [51.5 g, 2.12 mol, turnings, washed with THF (2 x 300 mL)] and THF (2 L). An addition funnel was charged with 1-bromo-3-fluorobenzene (neat, 392.8 g, 2.24 mol). One-twentieth of the bromide was added to the magnesium suspension followed by one crystal of iodine. After initiation of the Grignard reaction the remaining 1-bromo-3-fluorobenzene was then added to the refluxing mixture over a period of 50 min. The reaction was refluxed for an additional 45 min. To the refluxing solution of Grignard reagent was added a solution of ethyl N-benzyl-*N*-methyl-3-aminopropionate (187.5 g, 0.847 mol) in THF (100 mL) over a period of 20 min. After the ester addition was complete, the reaction was refluxed for 1h. The reaction was then cooled in an ice bath. Saturated NH_4Cl (aq., 400 mL) and H_2O (400 mL) were added and the mixture was transferred to a

separatory funnel. The organic layer was separated and the aqueous layer was extracted once with THF (400 mL). The combined organic layers were washed with said. NaCl (2 x 200 mL, aq.), dried (anh. Na_2SO_4), filtered through paper, and rotary evaporated vacuum to yield 281.6 g (90%) of crude product as an orange, viscous oil. This material (281.6 g, 0.766 mol) was dissolved in acetonitrile (1.4 L). Concentrated hydrochloric acid (65.0 mL, 0.786 mol, 12N) was added to the stirring filtrate. The crystallizing mixture was then cooled to -20 °C for 17 h. The product was collected, washed with cold acetonitrile (800 mL), and dried to provide a white solid, 235.6 g (69% yield from the ester). For analytical purposes, the hydrochloride salt was further purified by recrystallization from acetonitrile: Mp 194-197 °C (uncorr.); TLC, R_f = 0.23 [hexane-EtOAc (5:1)], R_f = 0.85 [MeOH-$CHCl_3$ (100:5)], R_f = 0.72 [MeOH-$CHCl_3$ (100:3)]; GC, t_R = 10.93 min; MS, 367 (M^+), 272 (M-C_6H_4F), 258 (M-CH_2Ph-H_2O), 219 [$(C_6H_4F)_2CH$], 148 [$CH_2CH_2N(CH_3)CH_2Ph$], 134 [$CH_2N(CH_3)CH_2Ph$], 91 (C_7H_7), 42 (CH_2CH_2N); ^{1}H NMR (free base, $CDCl_3$) d 2.18 (s, 3H, NC<u>H</u>$_3$), 2.41 (m, 2H, CHC<u>H</u>$_2$), 2.58 (m, 2H, C<u>H</u>$_2$N), 3.42 (s, 2H, C<u>H</u>$_2$Ph), 6.86 (dt, J_1 = 8.5, J_2 = 1.8, 2H, Ar-H), 7.18-7.30 (m, 10H. Ar-H), 8.33 (bs, 1H, O<u>H</u>); ^{13}C NMR (free base, $CDCl_3$) d 35.6 (CH<u>C</u>H$_2$), 41.5 (CH_3, N<u>C</u>H$_3$), 54.3 (CH_2, <u>C</u>H$_2$N), 62.6 (CH_2, <u>C</u>H$_2$Ph), 113.1 (d, J = 23, CH, Ar-$C_{5,5'}$), 113.5 (d, J = 23, CH), 121.2 (d, J = 3, CH), 127.5 (CH), 128.5 (CH), 129.2 (CH), 129.5 (CH), 129.6 (CH), 137.0 (q), 150.2 (q), 162.8 (d, J = 243, q, Ar-$C_{3,3'}$).

[0224] In a 5-L, 3-necked reaction vessel, equipped with an overhead mechanical stirrer, reflux condenser, and thermometer, was placed *N*-benzyl-*N*-methyl-3-hydroxy-3-bis (3-fluorophenyl)propylamine hydrochloride (225.4 g, 0.559 mol), 6N HCl (1392 mL) and glacial HOAc (464 mL). The suspension was heated in a water bath (80-85 °C) and stirred for 18 h. After 18 h of heating, the reaction mixture was cooled in an ice/MeOH bath. Ethyl acetate (500 mL) was added to the cooled reaction mixture. NaOH (10*N*, 1.7 L) was then added to the cooled mixture over a period of 25 min at such a rate as to keep the temperature below 40 °C. The mixture was transferred to a 6-L separatory funnel. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with satd. NaCl (2 x 100 mL, aq.), dried Na_2SO_4 (250 g), rotary evaporated, and then dried under vacuum to provide 185.6 g (95% yield) of the free base as a fluid, brownish-colored oil.

[0225] The material above was stirred with hexane (1.5 L). The resulting solution was filtered through paper. 4M HCl in dioxane (146 mL) was added dropwise with stirring to the filtrate over a period of 5 min. The semi-translucent solvent was then decanted away from the light-yellow colored, semisolid precipitate. The crude hydrochloride salt was dissolved in refluxing ethyl acetate (600 mL) and was filtered. The filtrate was then thoroughly cooled in an ice bath, and hexane (110 mL) was slowly added, with vigorous stirring. After cooling in an ice bath for 2 h, the entire flask filled with a white crystalline solid. This material was collected on a filter funnel, washed with ice-cold hexane/ethyl acetate [(1:4), 400 mL], and dried to yield 128.7 g, 59.7% of a white solid. On standing the mother liquor precipitated another 14.8 g of an off-white solid. Total yield 128.7 g + 14.8 g = 143.5 (67%). Mp 141-142 °C (uncorr.); TLC, R_f = 0.20 [hexane-EtOAc (5:1)], R_f = 0.75 [MeOH-$CHCl_3$ (100:5)], R_f = 0.49 [MeOH-$CHCl_3$ (100:3)]; GC, t_R = 10.40 min; MS, 349 (M^+), 330, 301, 281, 258 (M-CH_2Ph), 240, 229 [M-N(CH_3)CH_2Ph], 201, 183, 146, 133, 109, 91 ($CH_2C_6H_5$), 65, 42 (CH_2NHCH_3); ^{1}H NMR (free base, $CDCl_3$) d 2.20 ppm (s, 3H, NC<u>H</u>$_3$), 3.08 (d, J = 6.8, 2H, C<u>H</u>$_2$N), 3.47 (d, J < 1, 2H, C<u>H</u>$_2$Ph), 6.29 (t, J = 6.8, 1H, C<u>H</u>), 6.85-7.04 (m, 6H, ArH), 7.19-7.35 (m, 7H, ArH).

[0226] *N*-Benzyl-*N*-methyl-3-bis(3-fluorophenyl) allylamine hydrochloride (120.0 g, 0.311 mol) was dissolved in abs. EtOH (1250 mL). $Pd(OH)_2$/charcoal (10,0 g, ~20% Pd, Fluka Chemical) was added. The reaction mixture was stirred under a steady flow of hydrogen gas for 18 h at 25 °C (atmospheric pressure). The mixture was then filtered through Celite®/fritted glass, the catalyst was washed with EtOH (2 x 50 mL), and the solvent was removed under reduced pressure to yield 95.4 g, 103% of crude product. This material was dissolved in refluxing ethyl acetate (300 mL) with vigorous stirring and filtered. The flask was allowed to stand for 2 h at 25 °C, during which time the hydrochloride salt began to crystallize as needles. The flask was then cooled, the product was collected, washed with ice-cold ethyl acetate (20 mL), and dried to yield 73.7 g, 80%, of Compound 60 as a white, crystalline solid. Mp 129-130 °C; UV/Vis, e = 2.1 x 10^3 L·mol^{-1}cm^{-1} (264 nm, EtOH, 25 °C, linear range: 0.05-0.20 mg/mL); TLC, R_f = 0.00 [hexane-EtOAc (5:1)], R_f = 0.07 [MeOH-$CHCl_3$ (100:5)], R_f = 0.19 [MeOH-$CHCl_3$-NH_4OH (100:5:1)]; GC, t_N = 7.45 min; MS, 261 (M^+), 229, 215, 201, 183, 164, 150, 138, 122, 101, 83, 75, 57, 42 [CH_2NHCH_3]; ^{1}H NMR (HCl salt, $CDCl_3$ + 1 gtt MeOD) δ 2.56 (m, 2H, NC<u>H</u>$_2$), 2.60 (s, 3H, NC<u>H</u>$_3$), 2.85 (t, J = 8.0, 2H, CHC<u>H</u>$_2$), 4.11 (t, J = 8.0, 1H, C<u>H</u>), 6.87-6.98 (m, 4H, ArH), 7.06 (d, J = 7.7, 2H, $Ar_{2,2'}$H), 7.25 (dd, J_1 = 6, J_2 = 8, ArH); ^{13}C NMR (HCl salt, $CDCl_3$ + 1 gt MeOD) δ 30.9 (CH_2, CH<u>C</u>H$_2$), 32.7 (CH_3, N<u>C</u>H$_3$), 47.6 (CH, <u>C</u>HCH$_2$), 47.8 (CH_2, <u>C</u>H$_2$N), 113.9 (J = 21, $ArC_{2,2'}$ or $ArC_{4,4'}$), 114.5 (d, J = 22, $ArC_{2,2'}$ or $ArC_{4,4'}$), 123.2 (d, J = 3, Ar-$C_{6,6'}$), 130.3 (d, J = 9, Ar-$C_{5,5'}$), 144.7 (d, J = 7, Ar-$C_{1,1'}$), 162.9 (d, J = 245, Ar-$C_{3,3'}$); IR: KBr pellet (cm^{-1}), 3436.9, 2963.4, 2778.5, 2453.7, 1610.6, 1589.3, 1487.0, 1445.3, 1246.0, 764.5; solubility: 2 g/mL (H_2O), 1 g/mL (EtOH); anal. calcd. for $C_{16}H_{17}NF_2$.HCl (Karl Fischer: 0.26% H_2O): C, 64.37; H, 6.11; N, 4.69; found: C, 64.14; H, 6.13; N, 4.69.



[0227] Compound **105** was prepared by selective reduction of its corresponding alkene by catalytic hydrogenation over Pd/C.

[0228] Compound **61** was prepared from 2-bromo-4-fluoroanisole and 3-fluorobenzaldehyde as described for Compound **24**. GC/EI-MS (R_t = 9.22 min) *m/z* (relative intensity) 277 (M^+, 74), 260 (46), 245 (35), 231 (44), 229 (34), 217 (24), 203 (28), 201 (31), 183 (28), 154 (24), 133 (19), 109 (100).

[0229] Compound 62 was prepared from 2-bromoanisole and 2-methoxybenzaldehyde as described for Compound **24.** GC/EI-MS (R_t = 9.30 min) *m/z* (relative intensity) 271 (M', 100), 254 (17), 240 (23), 225 (40), 223 (45), 207 (22), 181 (32), 165 (31), 136 (48), 121 (98), 91 (83).

[0230] The synthesis of Compound **63** was accomplished as follows.

[0231] Alcohol **A** was obtained from 3-fluorobenzaldehyde as described for product **A** of the Compound **24** synthesis.

[0232] To alcohol **A** (10.275 g, 47 mmol) in 200 ml of ethanol was added 1.6 g of 10% Pd/C and 1 ml of concentrated HCl. This mixture was hydrogenated for 3 hr at 60 psi, then filtered and concentrated to give the diphenylmethane **B**.

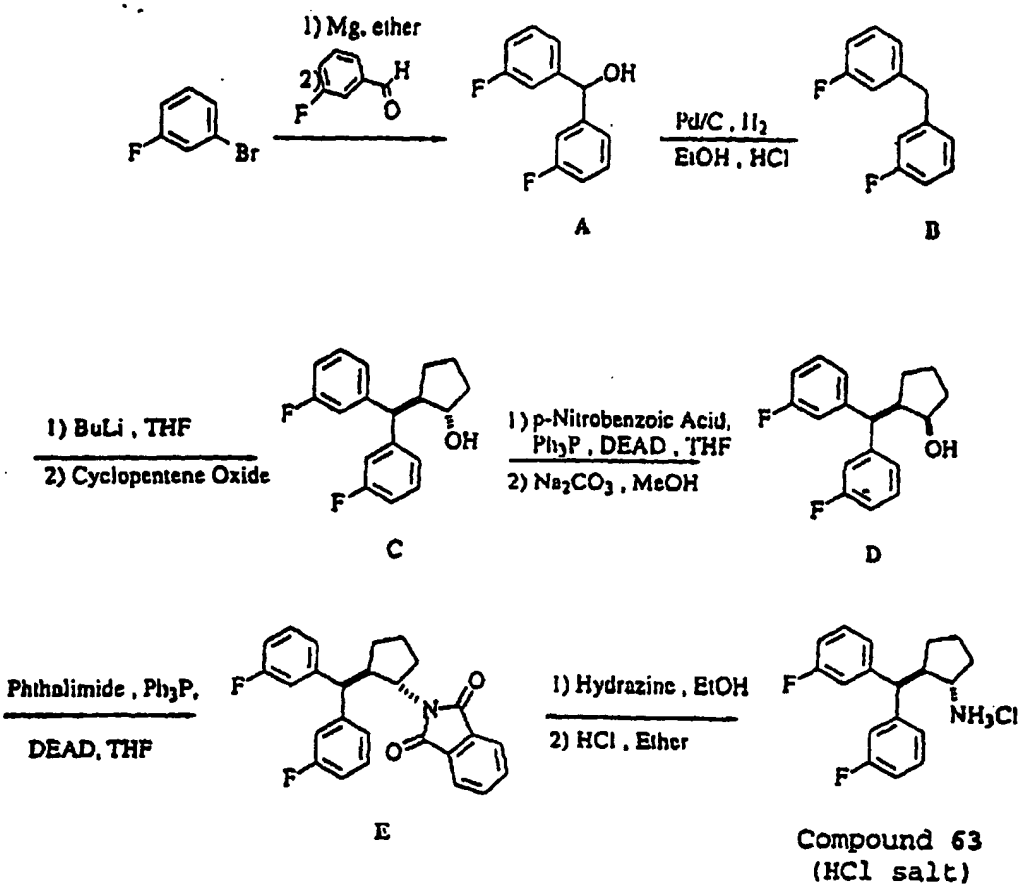
[0233] Product **B** (2.01 g, 9.86 mmol) was dissolved in 20 ml of THF and cooled to -78°C. Butyl lithium (4.4 ml, 10.8 mmol, 2.5 M in hexanes) was added slowly by syringe, and then the reaction stirred for another 30 min at -7.8°C. To this orange solution was added cyclopentene oxide (0.9 ml, 10.3 mmol). The reaction was allowed to stir 3 hours while warming slowly to room temperature. The reaction was quenched with 150 ml of 10% HCl and extracted 3 times with ether. The ether layer was dried over sodium sulfate and concentrated to give 2.5 g of the alcohol **C**.

[0234] To the alcohol C (1 g, 3.5 mmol) in 10 ml of dry THF was added triphenylphosphine (1.37 g, 5.2 mmol) in 5 ml of THF and p-nitrobenzoic acid (0.87 g, 5.2 mmol) in 5 ml of THF. This solution was cooled to 0°C followed by the addition of DEAD (0.82 ml, 5.2 mmol), and allowed to stir overnight. The reaction was partitioned between water and ether. The ether was removed *in vacuo* and the resulting oil was chromatographed on silica gel in hexane/ethyl acetate to yield 365 mg of the cis-ester. This ester was hydrolyzed in methanol with potassium carbonate by stirring overnight. After removal of the methanol, the residue was taken up in ether, washed with water, dried over sodium sulfate and concentrated to give 250 mg of the *cis* alcohol **D**.

[0235] To the alcohol D (.25 g, 0.9 mmol) in 5 ml of dry THF was added triphenylphosphine (342 mg, 1.3 mmol) in 5 ml of THF and phthalimide (191.3 mg, 1.3 mmol) in 5 ml of THF. This solution was cooled to 0°C followed by the addition of DEAD (0.205 ml, 1.3 mmol), and allowed to stir overnight. The reaction was partitioned between water and ether. The ether was removed *in vacuo* and the resulting oil was chromatographed on silica gel in hexane/ethyl acetate to yield 100 mg of the phthalimide **E**.

[0236] To a solution of the phthalimide **E** (100 mg) in 20 ml of ethanol was added 8.8 mg of hydrazine hydrate. The solution was refluxed for 5 hours then stirred at room temperature overnight. The reaction was worked up by adding 1 ml of conc. HCl and filtering off the white solid. The resulting solution was concentrated to dryness and the solid taken up in ether and aqueous sodium hydroxide. The ether layer was dried over sodium sulfate and concentrated to a white solid. This was taken up in a small amount of ether and treated with 10 drops of 1M HCl in ether. After stirring overnight, the white solid was collected by filtration and dried to give 50 mg of Compound **63**, as the hydrochloride salt. GC/EI-MS (R_t = 9.22 min) *m/z* (relative intensity) 287 (M^+, 45), 270 (12), 201 (63), 183 (81), 133 (38), 109 (43),

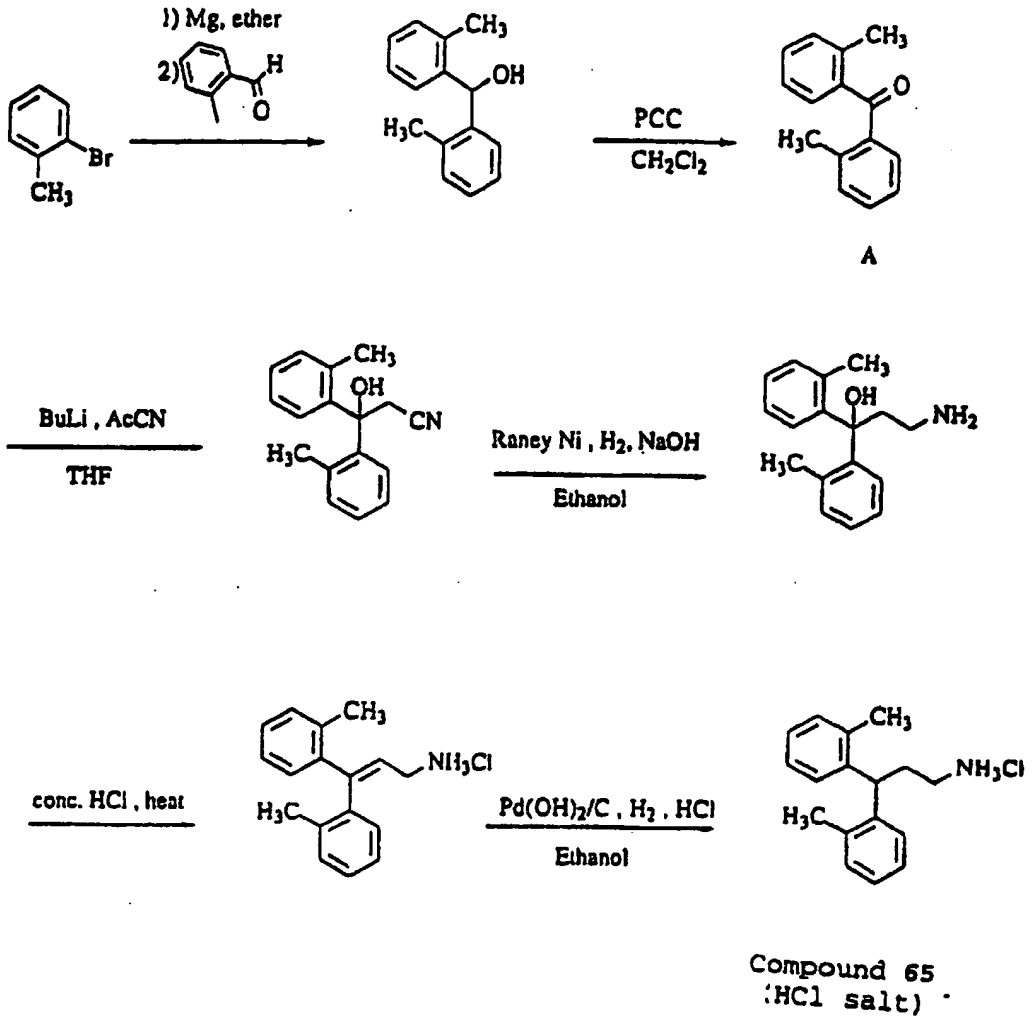
83 (44), 56 (100), 43 (37).



[0237] The synthesis of Compound **64** was done as described for Compound **63** except that the inversion step (product **C** to **D**) was omitted in order to obtain the cis amine as the final product. GC/EI-MS (R_t = 8.28 min) *m/z* (relative intensity) 287 (M^+, 15), 270 (4), 201 (13), 183 (15), 133 (11), 109 (16), 84 (43), 56 (100), 43 (32).

[0238] The synthesis of Compound **65** was accomplished as follows.

[0239] The ketone **A** was synthesized similarly to ketone **B** in the Compound **24** synthesis using 2-methylphenylmagnesium bromide and 2-methylbenzaldehyde as starting materials. This ketone was converted to the final product using the procedure outlined for Compound **58.** GC/EI-MS (R_t = 7.84 min) m/z (relative intensity) 239 (M^+, 88), 222 (14), 207 (100), 193 (46), 178 (71), 165 (60), 130 (39), 120 (40), 115 (51), 104 (40), 91 (38), 77 (21).



Compound **119** was synthesized in a seven-step reaction sequence starting from commercially-available *trans*-3-fluorocinnamic acid. This synthetic route is conceptually similar to that reported in the literature [U.S. Patent 4,313,896 (1982)] for related analogs. However, the three final steps were performed using a significantly different reaction sequence than that reported. The cinnamic acid was reduced and chlorinated in three steps to the corresponding 3-(3-fluorophenyl)propylchloride. This compound was brominated with NBS (*N*-bromosuccinimide) and the resulting trihalide was then reacted with 3-fluorophenol. The resulting ether was converted to the final product using a Gabriel synthesis.

[0240] *Trans*-3-fluorocinnamic acid (25.0 g, 150.4 mmol) was dissolved in abs. EtOH (250 mL) and hydrogenated over 10% Pd/C (2.5 g) in a Parr apparatus at 60 psig, 50°C, for 1 h (hydrogen uptake: calcd. 245 psig; found 260 psig). The reaction mixture was filtered and evaporated to yield a crystalline product (23.0 g, 89%). GC, t_f = 4.43 min; MS, 168 (M^+).

[0241] Under a stream of dry nitrogen, at 0-10°C, a solution of 3-fluorohydrocinnamic acid (22.0 g, 131 mmol) in THF (100 mL) was added dropwise, over a period of 15 min, to a suspension of $LiAlH_4$ (4.23 g, 111 mmol) in THF (200 mL). The reaction was heated to reflux for a period of 1 h and then worked-up according to Fieser & Fieser's Reagents for Organic Synthesis (Vol. 1, 1967) to provide a white solid (20.1 g, 99%). GC, t_R = 3.74 min; MS, 154 (M^+).

[0242] A solution of 3-(3-fluorophenyl)-1-propanol (15.0 g, 97.4 mmol) and triphenylphosphine (36.0 g, 137.3 mmol) in CCl_4 (150 mL) was refluxed for 19 h. Additional $P(C_6H_5)_3$ (3 x 3.0 g, 3 x 11.4 mmol) was added periodically over a period of 24 h. The resulting precipitate was removed by filtration and the solids were washed with hexane. The filtrate

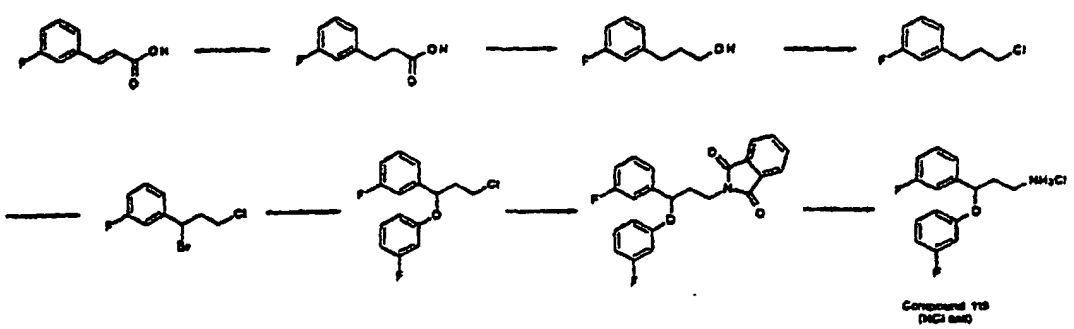
was evaporated under vacuum and the residue was suspended in hexane (200 mL) and then filtered. Evaporation of the filtrate provided 16.0 g (95.1%) of crude product which was purification by silica gel flash chromatography, elution with hexane, to provide 14.7 g (87%) of a colorless liquid. GC, t_R = 3.63 min; MS, 172/174 (M^+).

[0243] A solution of the above chloride (12.0 g, 69.5 mmol), *N*-bromosuccinimide (17.3 g, 97.2 mmol), and dibenzoyl peroxide (0.06 g) in CCl_4 (75 mL) was refluxed for 1 h. The reaction mixture was then cooled in an ice bath, filtered, and the solids were washed with hexane. The filtrate was evaporated to provide 17.9 g (100%) of product. GC, t_R = 5.21 min; MS, 251/253 (M^+).

[0244] A mixture of 3-bromo-3-(3-fluorophenyl) -1-propylchloride (4.0 g, 15.9 mmol), 3-fluorophenol (1.98 g, 17.7 mmol), and K_2CO_3 (2.65 g, 19.2 mmol) suspended in acetone (80 mL) was refluxed for 15 h. The volatiles were then removed under vacuum and the resulting residue was suspended in a mixture of hexane (200 mL) and NaOH (0.1N, 100 mL). The layers were separated and the organic layer washed, 0.1N NaOH (100 mL and H_2O (100 mL), dried (anh. Na_2SO_4), and evaporated *in vacuuo*. The resulting residue was chromatographed on silica gel, elution with hexane followed by hexane/EtOAc (100:1] then [40:1] to provide 1.64 g (37%) of product as a colorless oil. GC, t_R = 7.28 min; MS, 282/283 (M^+); TLC r_f= 0.3, hexane/EtOAc [40:1].

[0245] A solution of 3-(3-fluorophenyl)-3-(3-fluorophenoxy)-1-propylchloride (1.52 g, 5.38 mmol) and potassium phthalate (1.20 g, 6.48 mmol) was heated to 90°C in DMF (30 mL) for a period of 2 h in a nitrogen atmosphere. The reaction mixture was then cooled and poured into H_2O (100 mL). The resulting solution was extracted with Et_2O (2 x 100 mL). The organic extract was washed, sat. NaCl (100 mL) and H_2O (2 x 100 mL), dried (anh. Na_2SO_4), and evaporated under vacuum to provide 2.17 g of crude product. The material was chromatographed on silica gel, elution with hexane/EtOAc [40:1] and then [20:1] to provide after evaporation 1.81 g (86%) of product as a glass.

[0246] A solution of *N*-phthaloyl-3-(3-fluorophenyl)-3 -(fluorophenoxy)-1-propylamine (1.74 g, 4.42 mmol) and anh. hydrazine (1.43 g, 44.6 mmol) in abs. EtOH (30 mL) was refluxed for 1 h. The reaction was cooled and evaporated under vacuum. The resulting material was suspended in Et_2O (75 mL) and washed with 0.2N NaOH (2 x 25 mL). The organic layer was dried (anh. Na_2SO_4), and evaporated under vacuum to provide 1.04 g (89.3%) which was purified by reverse-phase chromatography [Vydac Prep. C18; 264 nm; 50 mL/min; gradient elution ACN/0.1% HCl aq., 10%-50% over 20 min; r_t = 17.4 min], to yield 0.89 g (67%) of Compound **119** as a hygroscopic hydrochloride salt.



[0247] Compounds **118, 120-122** and **137** were prepared in a manner similar to the procedures used for the preparation of Compound **119.**

[0248] Compound **113** was synthesized from commercially available 4,4-diphenylcyclohexenone in three steps. First, the alkene in the starting material was reduced by means of catalytic hydrogenation. Methoxylamine formation followed by reduction using standard procedures.

[0249] Compounds **67-68, 70-75, 79-82, 84-89, 91-95, 98-100, 102, 105-106, 109-114, 117, 124-134, 138,** and **141-150** were synthesized by standard procedures known to those skilled in the art, as described above.

Gas Chromatography of Simplified Arylalkylamines

[0250] Gas chromatographic and mass spectral data were obtained on a Hewlett-Packard 5890 Series II Gas Chromatograph equipped with a 5971 Series Mass Selective Detector [Ultra-2 Ultra Performance Capillary Column (cross-linked 5% phenyl methyl silicone); column length, 25 m, column i.d., 0.20 mm; The flow rate, 60 mL/min; injector temp., 250°C; gradient temperature program, 20°C/min from 125 to 325°C for 1C min, then held constant at 325°C for 6 min].

[0251] Compound **20**. (Rt = 7.34 min), m/z (rel. int.) 247 (M+,27), 231 (16). 230 (100), 229 (45), 215 (29), 214 (14),

204 (43), 203 (37), 202 (13), 201 (47), 184 (14), 183 (58), 181 (8), 151 (9), 135 (13), 134 (31), 133 (25), 124 (18), 122 (16), 121 (19), 109 (15), 101 (29), 96 (18), 95 (11), 83 (11), 75 (20), 57 (10), 42 (9)

[0252] Compound **24.** (Rt = 8.21 min), m/z (rel. int.) 259 (M+,122), 260 (23), 242 (44), 241 (15), 228 (15), 227 (49), 216 (15), 213 (56), 212 (16), 211 (55), 195 (32), 196 (22), 185 (34), 184 (19), 183 (67), 171 (16), 170 (38), 165 (44), 151 (20), 150 (16), 146 (13), 136 (46), 134 (17), 133 (37), 123 (15), 121 (22), 120 (13), 109 (100), 91 (34), 77 (29), 51 (15)

[0253] Compound **25.** (Rt = 8.49 min), m/z (rel. int.) 259 (M+,39), 243 (16), 242 (95), 241 (25), 227 (27), 217 (15), 216 (100), 215 (27), 212 (13), 211 (50), 201 (14), 200 (11), 199 (15), 196 (15), 185 (20), 184 (19), 183 (50), 171 (24), 170 (28), 165 (15), 146 (10), 136 (11), 134 (12), 133 (23), 121 (21), 77 (9)

[0254] Compound **32.** (Rt = 7.30 min), m/z (rel. int.) 229 (M+,21), 213 (16), 212 (100), 211 (61), 197 (33), 196 (19), 194 (14), 186 (26), 185 (30), 184 (19), 183 (69), 170 (17), 166 (16), 165 (77), 134 (25), 133 (23), 116 (17), 115 (17), 103 (18), 101 (11), 78 (13), 77 (23), 75 (13), 51 (18), 43 (13), 42 (13)

[0255] Compound **33.** (Rt = 7.56 min), m/z (rel. inc.) 261 (M+,68), 245 (18), 244 (100), 229 (43), 215 (16), 214 (15), 204 (57), 203 (43), 202 (15), 201 (64), 184 (14), 183 (73), 148 (16), 136 (13), 135 (46), 133 (60), 124 (51), 115 (27), 111 (14), 109 (96), 107 (16), 96 (14), 83 (27), 75 (20), 58 (96), 57 (33), 56 (23), 41 (35)

[0256] Compound **50.** (Rt = 7.37 min), m/z (rel. int.) 261 (M+,2), 244 (9), 229 (4), 204 (7), 203 (11), 201 (8), 183 (11), 101 (5). 58 (7), 44 (100), 42 (7)

[0257] Compound **55.** (Rt = 7.86 min), m/z (rel. int.) 275 (M+,98), 276 (20), 258 (59), 229 (58), 216 (31), 215 (22), 214 (19), 204 (49), 203 (41), 202 (21), 201 (82), 184 (18), 183 (100), 181 (14), 150 (21), 135 (33), 133 (55), 124 (41), 115 (13), 109 (90), 101 (15), 83 (20), 75 (16), 72 (23), 57 (13), 56 (24)

[0258] Compound **56.** (Rt = 7.79 min), m/z (rel. int.) 261 (M+,67), 262 (12), 244 (54), 229 (56), 218 (27), 217 (16), 216 (19), 215 (100), 214 (45), 203 (50), 202 (32), 201 (51), 197 (16), 196 (26), 183 (24), 138 (17), 135 (20), 134 (17), 133 (39), 122 (26), 121 (13), 109 (30), 101 (17), 96 (14), 83 (16), 75 (13)

[0259] Compound **57.** (Rt = 7.65min), m/z (rel. int.) 261 (M+,62), 244 (50), 229 (50), 218 (24), 217 (13), 216 (18), 215 (100), 214 (36), 203 (42), 202 (19), 201 (33), 197 (14), 196 (19), 183 (17), 138 (19), 135 (16), 134 (12), 133 (29), 122 (29), 109 (25), 101 (13)

[0260] Compound **58.** (Rt = 8.15 min), m/z (rel. int.) 275 (M+,134), 276 (26), 258 (23), 244 (19), 243 (100), 232 (25), 229 (53), 217 (51), 216 (23), 215 (67), 214 (97), 201 (44), 197 (21), 196 (43), 183 (23), 148 (38), 147 (21), 138 (46), 135 (46), 134 (18), 133 (64), 125 (25), 123 (28), 122 (81), 115 (27), 109 (54), 107 (17), 83 (27), 44 (19), 43 (19)

[0261] Compound **59.** (Rt = 7.61 min), m/z (rel. int.) 275 (M+,27), 204 (8), 203 (10), 201 (19), 183 (25), 109 (8), 101 (7), 58 (100), 57 (8), 56 (8), 44 (9)

[0262] Compound **60.** (Rt = 7.34 min), m/z (rel. int.) 261 (M+,55), 262 (10), 204 (16), 203 (15), 201 (31), 183 (35), 133 (11), 122 (11), 121 (10), 109 (9), 101 (16), 96 (11), 75 (10), 57 (9), 44 (100), 42 (11)

[0263] Compound **61.** (Rt = 8.07min;, m/z (rel. int., 277 (M+,68), 278 (13), 260 (31), 246 (11), 245 (25), 234 (12), 231 (32), 229 (26), 217 (20), 203 (23), 201 (24), 188 (12), 183 (22), 154 (24), 151 (15), 150 (10), 133 (18), 124 (10), 109 (100), 95 (11), 44 (14)

[0264] Compound **62.** (Rt = 8.93 min), m/z (rel. int.) 271 (M+,115), 272 (22), 254 (16), 239 (22), 225 (36), 223 (40), 181 (33), 165 (34), 153 (13), 152 (24), 136 (39), 132 (13), 131 (16), 123 (20), 122 (13), 121 (89), 119 (13), 115 (23), 105 (17), 91 (100), 77 (22)

[0265] Compound **63.** (Rt = 8.47min), m/z (rel. int.) 287 (M+,31., 241 (9), 204 (27), 203 (20), 202 (9), 201 (30), 183 (38), 150 (13), 133 (20), 109 (27), 84 (45), 83 (43), 82 (11), 57 (18), 56 (100), 43 (25)

[0266] Compound **64.** (Rt = 8.57 min), m/z (rel. int.) 287 (M+,63,, 288 (13), 270 (14), 242 (16), 241 (17), 215 (17), 214 (18), 204 (35), 203 (27), 202 (18), 201 (70), 183 (86), 150 (18), 147 (16), 146 (17), 135 (16), 133 (45), 109 (45), 84 (31), 83 (38), 82 (13), 75 (15), 57 (21), 56 (100), 43 (44)

[0267] Compound **65.** (Rt = 8.18 min), m/z (rel. int.) 239 (M+,88), 240 (17), 222 (12), 208 (18), 207 (100), 195 (24), 193 (48), 192 (11), 181 (33), 180 (32), 179 (57), 178 (72), 166 (16), 165 (60), 152 (13), 130 (36), 129 (17), 120 (40), 117 (34), 116 (14), 115 (53), 107 (20), 105 (19), 104 (42), 103 (11), 91 (37), 77 (20), 65 (17)

[0268] Compound **66.** (Rt = 7.46 min), m/z (rel. int.) 275 (M+,7), 201 (5), 183 (6), 133 (3), 109 (6), 71 (3), 45 (3), 44 (100), 42 (3)

[0269] Compound **67.** (Rt = 7.56 min), m/z (rel. int.) 225 (M+,24), 194 (8), 193 (12), 179 (6), 168 (10), 167 (12), 166 (6), 165 (20), 152 (9), 120 (8), 116 (6), 115 (7), 103 (7), 77 (8), 51 (5), 44 (100)

[0270] Compound **68.** (Rt = 7.85 min), m/z (rel. int.) 239 (M+,22), 194 (5), 193 (10), 168 (10), 167 (12), 166 (6), 165 (19), 152 (9), 134 (6), 116 (5), 115 (7), 91 (7), 77 (6), 59 (5), 58 (100), 44 (8)

[0271] Compound **69.** (Rt = 7.35min), m/z (rel. int.) 275 (M+,11), 203 (24), 202 (7), 201 (23), 183 (35), 122 (6), 121 (6), 101 (9), 58 (100), 57 (8), 56 (10)

[0272] Compound **72.** (Rt = 7.90 min), m/z (rel. int.) 253 (M+,25), 238 (9), 193 (7), 168 (8), 167 (14), 165 (17), 152 (9), 115 (7), 91 (11), 73 (8), 72 (100), 58 (45), 56(7), 44 (6), 43 (9), 42 (8)

[0273] Compound **73.** (Rt = 7.29 min), m/z (rel. int.) 239 (M+,9), 240 (2), 167 (2), 165 (5), 152 (2), 115 (2), 77 (2), 59 (5), 58 (100), 44 (3), 42 (5)

[0274] Compound **79**. (Rt = 7.89 min), m/z (rel. int.) 230 (M+,37), 214 (15), 213 (100), 212 (62), 201 (26), 200 (72), 198 (21), 195 (12), 188 (17), 187 (85), 186 (46), 185 (42), 184 (9), 157 (12), 135 (9), 133 (24), 109 (10), 107 (20), 106 (62), 80 (14), 79 (32), 78 (9), 51 (20)

[0275] Compound **81**. (Rt = 7.40 min), m/z (rel. int.) 209 (M+, 89), 210 (14), 208 (100), 193 (17), 192 (56), 191 (42), 189 (12), 178 (20), 166 (11), 165 (45), 152 (12), 132 (86), 131 (10), 130 (53), 117 (22), 115 (48), 106 (22), 105 (10), 104 (12), 103 (16), 91 (16), 77 (22), 51 (15)

[0276] Compound **82**. (Rt = 7.93min), m/z (rel. int.) 275 (M+, 124), 276 (25), 232 (33), 215 (12), 214 (16), 204 (14), 203 (100), 201 (24), 196 (8), 183 (20), 150 (14), 138 (9), 136 (14), 135 (44), 133 (26), 125 (9), 124 (71), 123 (29), 121 (14), 115 (14), 111 (72), 110 (9), 109 (84), 101 (14), 83 (9), 75 (8)

[0277] Compound **83**. (Rt = 7.22 min), m/z (rel. int.) 235 (M+,10), 219 (17), 218 (100), 217 (62), 203 (20), 192 (10), 191 (38), 190 (7), 189 (14), 185 (17), 183 (7), 171 (9), 165 (8), 147 (10), 146 (11), 134 (12), 133 (17), 121 (8), 109 (8), 97 (8), 45 (7)

[0278] Compound **85**. (Rt = 7.73 min), m/z (rel. int.) 239 (M+, 7), 222 (15), 179 (8), 178 (9), 168 (16), 167 (33), 166 (12), 165 (43), 161 (9), 152 (20), 146 (17), 129 (7), 120 (15), 118 (7), 117 (19), 115 (25), 91 (25), 77 (7), 72 (9), 44 (100), 42 (6)

[0279] Compound **86**. (Rt = 7.66 min), m/z (rel. int.) 239 (M+,3), 222 (4), 168 (4), 167 (11), 166 (4), 165 (14), 152 (7), 120 (6), 117 (6), 115 (8), 91 (9), 72 (5), 44 (100), 42 (3)

[0280] Compound **87**. (Rt = 7.33 min), m/z (rel. int.) 239 (M+,4), 222 (9), 179 (9), 178 (11), 168 (11), 167 (27), 166 (13), 165 (48), 161 (7), 152 (22), 146 (14), 128 (7), 120 (11), 118 (8), 117 (21), 115 (31), 91 (29), 77 (9), 72 (8), 51 (7), 44 (100), 42 (9)

[0281] Compound **88**. (Rt = 7.4 min), m/z (rel. int.) 227 (M+,.0), 183 (10), 168 (18), 167 (100), 166 (32), 165 (83), 164 (10), 163 (6), 153 (6), 152 (35), 139 (6), 115 (8), 105 (9), 77 (12), 51 (7), 45 (23)

[0282] Compound **89**. (Rt = 8.74 min), m/z (rel. int.) 260 (M+,220), 261 (39), 259 (89), 242 (18), 203 (17), 202 (16), 201 (61), 183 (58), 165 (100), 150 (20), 148 (25), 138 (24), 137 (61), 122 (73), 121 (31), 111 (47), 101 (23), 96 (16), 75 (16), 44 (17), 43 (29)

[0283] Compound **90**. (Rt = 7.32min), m/z (rel. int.) 235 (M+,9), 219 (16), 218 (100), 217 (42), 206 (17), 205 (9), 204 (7), 203 (21), 202 (8), 193 (12), 192 (71), 191 (62), 190 (9), 189 (19), 185 (13), 171 (14), 159 (9), 147 (14), 146 (16), 134 (10), 133 (17), 121 (14), 109 (11), 101 (8), 97 (17), 45 (15)

[0284] Compound **91**. (Rt = 10.67 min), m/z (rel. int.) 329 (M+,6), 301 (20), 300 (81), 167 (18), 166 (6), 165 (18), 152 (10), 132 (5), 120 (45), 119 (21), 118 (11), 117 (9), 115 (11), 106 (6), 105 (5), 104 (12), 103 (5), 92 (8), 91 (100), 77 (10), 41 (6)

[0285] Compound **92**. (Rt = 10.37min), m/z (rel. int.) 337 (M+,30), 338 (7), 204 (7), 203 (7), 201 (7), 183 (10), 133 (6), 121 (8), 120 (70), 106 (6), 92 (9), 91 (100)

[0286] Compound **93**. (Rt = 10.25 min), m/z (rel. int.) 351 (M+,28), 352 (7), 337 (9), 336 (39), 203 (10), 201 (11), 183 (17), 135 (6), 134 (20), 133 (6), 132 (6), 120 (11), 118 (5), 109 (18), 106 (12), 105 (100), 104 (13), 103 (8), 91 (14), 79 (11), 77 (12)

[0287] Compound **94**. (Rt = 10.48 min), m/z (rel. int.) 365 (M+,2), 337 (25), 336 (100), 203 (8), 201 (8), 183 (14), 133 (5), 132 (6), 120 (14), 119 (13), 118 (9), 115 (5), 109 (20), 106 (5), 104 (10), 91 (52)

[0288] Compound **95**. (Rt = 6.68min), m/z (rel. int.) 283 (M+,59), 284 (11), 267 (11), 266 (71), 265 (19), 251 (24), 250 (9), 241 (14), 240 (100), 239 (48), 237 (30), 232 (10), 220 (17), 219 (65), 199 (9), 152 (12), 151 (18), 142 (20), 140 (13), 139 (20), 127 (22), 119 (24), 114 (12), 101 (10), 63 (10), 44 (9)

[0289] Compound **96**. (Rt = 6.93 min), m/z (rel. int.) 265 (M+,46), 249 (16), 248 (100), 247 (34), 233 (27), 232 (11), 223 (9), 222 (65), 221 (39), 220 (10), 219 (36), 202 (14), 201 (54), 152 (15), 151 (14), 133 (9), 124 (12), 119 (9), 109 (9), 101 (14), 75 (9)

[0290] Compound **97**. (Rt = 8.10 min), m/z (rel. int.) 241 (M+,101), 242 (18), 224 (50), 223 (19), 210 (11), 209 (37), 197 (12), 196 (10), 195 (55), 194 (16), 193 (60), 181 (29), 178 (20), 167 (38), 166 (16), 165 (52), 153 (12), 152 (36), 136 (27), 133 (12), 132 (14), 116 (12), 115 (25), 103 (13), 91 (100), 77 (18)

[0291] Compound **98**. (Rt = 6.69 min), m/z (rel. int.) 232 (M+,3), 204 (11), 203 (37), 202 (30), 201 (100), 188 (9), 184 (14), 183 (84), 182 (10), 181 (15), 170 (9), 109 (17), 107 (10), 83 (10), 75 (8), 57 (7)

[0292] Compound **100**. (Rt = 7.66 min). m/z (rel. int.) 261 (M+,150), 262 (29), 217 (11), 216 (70), 215 (28), 214 (11), 203 (30), 202 (31), 201 (100), 196 (10), 184 (15), 183 (90), 181 (11), 133 (20), 124 (12), 122 (20), 109 (39), 101 (14), 83 (10), 75 (10), 45 (43)

[0293] Compound **101**. (Rt = 7.72 min), m/z (rel, int.) 245 (M+,20). 229 (16), 228 (100), 227 (36), 213 (21), 211 (22), 202 (57), 201 (30), 199 (21), 183 (50), 181 (14), 171 (15), 170 (26), 165 (12), 152 (21), 134 (19), 133 (35), 122 (28), 120 (19), 120 (13), 119 (12), 109 (20), 107 (20), 106 (18), 101 (15), 94 (15), 91 (20), 77 (18), 74 (15), 65 (20), 63 (14), 55 (14), 51 (15), 44 (27), 43 (17), 42 (14)

[0294] Compound **102**. (Rt = 8.33 min), m/z (rel. int.) 273 (M+,19), 204 (16), 203 (16), 201 (15), 183 (18), 177 (9), 133 (8), 109 (13), 70 (41), 69 (100), 68 (20), 43 (25), 42 (5), 41 (5)

[0295] Compound **103.** (Rt = 8.59 min), m/z (rel. int.) 245 (M+,118), 246 (20), 229 (15), 228 (100), 227 (85), 213 (27), 211 (23), 209 (15), 207 (12), 202 (19), 201 (32), 200 (17), 199 (84), 196 (10), 183 (38), 181 (15), 171 (13), 170 (23), 152 (19), 151 (15), 150 (10), 134 (18), 133 (32), 131 (12), 122 (36), 119 (15), 109 (24), 107 (10), 106 (12), 91 (19), 77 (12)

[0296] Compound **105.** (Rt = 10.24 min), m/z (rel. int.) 351 (M+,7), 201 (5), 183 (7), 135 (9), 134 (79), 133 (4), 109 (5), 92 (8), 91 (100), 65 (8), 42 (7)

[0297] Compound **106.** (Rt = 7.52 min), m/z (rel. int.) 259 (M-,77:, 260 (14), 258 (31), 244 (30), 228 (13), 227 (28), 214 (14), 201 (24), 165 (12), 164 (100), 162 (29), 133 (56), 109 (44), 75 (13), 44 (80), 42 (56)

[0298] Compound **107**. (Rt = 7.45 min), m/z. (rel. int.) 227 (M+,101), 228 (16), 226 (100), 211 (22), 210 (68), 209 (49), 207 (13), 196 (22), 184 (15), 183 (62), 150 (50), 148 (31), 133 (44), 132 (53), 130 (45), 117 (15), 115 (29), 106 (14), 77 (18), 75 (13), 51 (14)

[0299] Compound **108.** (Rt = 7.46 min), m/z (rel. int.) 243 (M+,34), 244 (6), 212 (6), 211 (9), 197 (6), 186 (12), 185 (10), 184 (5), 183 (19), 165 (15), 133 (6), 120 (6), 103 (5), 77 (6), 44 (100), 42 (6)

[0300] Compound **109**. (Rt = 8.68 min), m/z (rel. int.) 285 (M+,110), 286 (22), 284 (27), 256 (16), 228 (37), 227 (27), 225 (10), 220 (11), 207 (15), 201 (27), 191 (14), 190 (100), 163 (11), 162 (85), 161 (10), 147 (11), 146 (11), 133 (32), 109 (20), 83 (12), 82 (36)

[0301] Compound **111.** (Rt = 8.81 min), m/z (rel. int.) 287 (M+,29), 214 (9), 204 (15), 203 (18), 202 (9), 201 (34), 183 (42), 135 (9), 133 (28), 109 (28), 84 (47), 83 (100), 82 (19), 75 (5), 70 (16), 68 (13), 57 (18), 56 (28), 44 (16), 43 (25), 42 (14)

[0302] Compound **114.** (Rt = 8.71 min), m/z (rel. int.) 237 (M+,197), 238 (37), 236 (67), 193 (15), 179 (30), 178 (40), 165 (41), 159 (43), 158 (26), 132 (24), 130 (16), 116 (17), 115 (37), 106 (21), 103 (34), 91 (50), 77 (48), 57 (68), 56 (100), 51 (32), 43 (50), 42 (34)

[0303] Compound **115.** (Rt = 9.45 min), m/z (rel. int.) 271 (M+,34), 255 (12), 254 (67), 253 (14), 239 (23), 229 (16), 228 (100), 227 (18), 224 (16), 223 (68), 213 (9), 212 (10), 211 (10), 197 (34), 196 (17), 195 (11), 181 (18), 169 (10), 165 (22), 153 (19), 152 (27), 146 (16), 145 (13), 141 (12), 139 (10), 136 (22), 134 (11), 133 (41), 122 (16), 121 (31), 115 (30), 91 (18), 77 (15), 65 (11), 63 (10), 44 (10)

[0304] Compound **116**. (Rt = 9.50 min), m/z (rel. int.) 269 (M-,41), 268 (32), 254 (8), 253 (21), 252 (100), 251 (14), 238 (23), 237 (18), 221 (10), 209 (9), 178 (8), 165 (19), 162 (22), 160 (19), 152 (18), 147 (11), 146 (8), 145 (18), 110 (9), 130 (11), 115 (10)

[0305] Compound **117.** (Rt = 7.64 min), m/z (rel. int.) 212 (M+, 13), 183 (16), 182 (100), 180 (7), 167 (7), 152 (3), 104 (27), 91 (7), 78 (4), 77 (41), 51 (13)

[0306] Compound **118.** (Rt = 7.46 min), m/z (rel. int.) 245 (M+,4), 153 (8), 152 (43), 150 (9), 135 (6), 133 (10), 124 (5), 123 (36), 122 (38), 121 (17), 109 (16), 101 (14), 96 (24), 95 (16), 94 (100), 93 (7), 83 (7), 77 (21), 75 (11), 66 (15), 65 (30), 63 (10), 51 (14), 50 (6)

[0307] Compound **119.** (Rt = 7.39 min), m/z (rel. int.) 263 (M+,7), 171 (14), 170 (14), 152 (74), 151 (13), 150 (20), 141 (55), 135 (10), 133 (23), 123 (20), 122 (100), 121 (49), 120 (11), 113 (9), 112 (92), 111 (9), 109 (41), 107 (12), 103 (13), 102 (11), 101 (40), 97 (9), 96 (66), 95 (51), 94 (9), 84 (28), 83 (88), 82 (8), 81 (16), 77 (14), 75 (54), 74 (10), 70 (10), 69 (10), 64 (10), 63 (23), 57 (62), 56 (13), 51 (15), 50 (12), 42 (8)

[0308] Compound **120.** (Rt = 8.48 min), m/z (rel. int.) 279 (M+,4), 159 (16), 157 (49), 153 (11), 152 (100), 150 (12), 133 (11), 130 (27), 128 (73), 123 (12), 122 (57), 121 (23), 111 (10), 109 (25), 101 (23), 99 (16), 96 (26), 95 (10), 83 (9), 75 (28), 73 (10), 65 (12), 64 (11), 63 (22), 51 (9), 50 (8)

[0309] Compound **121.** (Rt = 8.30 min), m/z (rel. int.) 275 (M+,2), 152 (15), 125 (B), 124 (100), 122 (14), 121 (7), 109 (35), 96 (7), 95 (10), 81 (14), 77 (9), 65 (7), 52 (11)

[0310] Compound **122.** (Rt = 7.39 min), m/z (rel. int.) 263 (M+,.1), 170 (12), 152 (66), 151 (10), 150 (18), 141 (68), 135 (10), 133 (19), 123 (16), 122 (76), 121 (39), 112 (100), 111 (18), 109 (36), 107 (11), 103 (11), 102 (9), 101 (33), 96 (56), 95 (32), 92 (11), 83 (96), 81 (13), 77 (13), 75 (43), 64 (25), 63 (26), 57 (61), 56 (14), 51 (14), 50 (11)

[0311] Compound **123.** (Rt = 5.88 min), m/z (rel. int.) 275 (M+,46), 276 (9), 202 (8), 201 (30), 183 (28), 133 (8), 109 (9), 101 (9), 71 (9), 59 (12), 58 (100), 44 (8), 42 (26)

[0312] Compound **124.** (Rt = 7.05 min), m/z (rel. int.) 229 (M+,15), 213 (15), 212 (89), 211 (13), 196 (20), 197 (100), 196 (24), 186 (12), 185 (21), 184 (29), 183 (87), 179 (7), 178 (8), 177 (13), 176 (5), 171 (7), 170 (18), 169 (4), 166 (5), 165 (20), 152 (5), 133 (7), 75 (4), 63 (4), 57 (9), 56 (4)

[0313] Compound **125.** (Rt = 7.54 min), m/z (rel. int.) 225 (M+, 57), 226 (13), 209 (13), 208 (75), 193 (13), 180 (14), 179 (21), 178 (20), 165 (22), 130 (34), 117 (59), 115 (28), 105 (18), 104 (94), 103 (45), 91 (100), 78 (30), 77 (38), 65 (36), 63 (13), 51 (20), 45 (17)

[0314] Compound **126.** (Rt = 7.81 min). m/z (rel. int.) 261 (M+,12), 244 (31), 152 (27), 151 (17), 150 (9), 136 (11), 135 (100), 133 (21), 122 (24), 115 (5), 110 (13), 109 (90), 107 (6), 96 (7), 83 (27), 56 (7)

[0315] Compound **127**. (Rt = 7.93 min), m/z (rel. int.) 225 (M+,23), 208 (20), 207 (6), 193 (13), 181 (7), 180 (37), 179 (100), 178 (36), 167 (9), 166 (12), 165 (36), 152 (9), 134 (30), 130 (26), 129 (9), 117 (16), 115 (22), 104 (6), 91

(38), 77 (7), 65 (7)

[0316] Compound **128.** (Rt = 7.42 min), m/z (rel. int.) 211 (M+,83), 212 (15), 194 (36), 193 (18), 182 (62), 181 (20), 180 (17) 179 (53), 178 (60), 176 (11), 167 (57), 166 (44), 165 (100), 152 (24), 120 (39), 116 (12), 115 (28), 104 (22), 103 (15), 91 (46), 89 (16), 78 (10), 77 (20), 65 (15), 63 (12), 51 (12)

[0317] Compound **129.** (Rt = 7.39 min), m/z (rel. int.) 229 (M+,104), 230 (19), 212 (28), 211 (14), 201 (13), 200 (85), 199 (22), 198 (14), 197 (50), 196 (58), 185 (73), 184 (45), 183 (100), 179 (43), 178 (55), 177 (17), 176 (17), 170 (18), 165 (33), 152 (12), 133 (22), 120 (57), 115 (17), 109 (44), 104 (23), 103 (17), 91 (32), 89 (16), 83 (20), 78 (12), 77 (22), 63 (16), 51 (13)

[0318] Compound **130.** (Rt = 7.38 min), m/z (rel. int.) 229 (M+,133), 230 (24), 212 (27), 211 (14), 200 (54), 199 (17), 198 (16), 197 (53), 196 (64), 185 (49), 184 (43), 183 (100), 179 (28), 178 (29), 177 (14), 170 (19), 165 (26), 133 (22), 120 (35), 115 (19), 109 (32), 104 (17), 103 (18), 91 (38), 89 (17), 83 (18), 77 (24), 63 (16)

[0319] Compound **131.** (Rt = 7.40 min), m/z (rel. int.) 229 (N+,146), 230 (26), 212 (48), 211 (23), 200 (51), 199 (17), 198 (16), 197 (61), 196 (70), 185 (50), 184 (43), 183 (100), 179 (28), 178 (28), 170 (20), 165 (23), 133 (21), 120 (35), 115 (20), 109 (59), 104 (25), 103 (17), 91 (27), 89 (17), 83 (22), 77 (22)

[0320] Compound **132.** (Rt = 7.03 min), m/z (rel. int.) 0 (M+,.0), 185 (14), 184 (100), 183 (23), 181 (17), 165 (18), 155 (12), 153 (14), 152 (12), 120 (85), 119 (67), 115 (10). 106 (16), 91 (19), 89 (14), 78 (12), 77 (25), 51 (16)

[0321] Compound **133.** (Rt = 7.09 min), m/z (rel. int.) 211 (M+,13), 195 (16), 194 (100), 181 (27), 180 (70), 179 (31), 178 (28), 166 (25), 165 (40), 152 (9), 120 (14), 119 (14), 118 (12), 115 (10), 104 (26), 103 (53), 102 (12). 91 (62), 89 (10), 78 (13), 77 (42), 65 (17), 51 (13)

[0322] Compound **134.** (Rt = 7.45 min), m/z (rel. int.) 211 (M^+,14), 183 (15), 182 (100), 181 (14), 179 (13), 178 (18), 167 (27), 166 (18), 165 (46), 152 (10), 115 (8), 104 (8), 103 (6), 91 (29), 89 (7), 78 (5), 77 (7), 65 (7)

[0323] Compound **135.** (Rt = 8.60 min), m/z (rel. int.) 273 (M+,34), 257 (14), 256 (76), 231 (16), 230 (100), 228 (18), 227 (57), 213 (14), 211 (37), 202 (30), 201 (40), 199 (26), 184 (13), 183 (50), 181 (12), 171 (17), 170 (20), 152 (15), 150 (19), 134 (15), 133 (31), 122 (14), 121 (29), 109 (16), 107 (13), 106 (17), 91 (12), 65 (12)

[0324] Compound **136.** (Rt = 9.26 min), m/z (rel. int.) 275 (M+,44), 277 (15), 260 (28), 259 (19), 258 (81), 257 (13), 243 (15), 234 (33), 233 (19), 232 (100), 231 (13), 229 (15), 227 (42), 224 (15), 223 (86), 208 (13), 197 (45), 196 (26), 195 (13), 182 (14), 181 (33), 179 (11), 178 (18), 166 (22), 165 (60), 164 (12), 163 (10), 153 (32), 152 (55), 151 (18), 149 (10), 139 (11), 137 (17), 136 (19), 121 (13), 115 (25), 102 (11), 91 (16), 77 (17)

[0325] Compound **137.** (Rt = 7.42 min), m/z (rel. int.) 245 (M+,1), 153 (8), 152 (7), 141 (64), 135 (10), 134 (100), 132 (11), 117 (6), 115 (12), 112 (56), 105 (15), 104 (55), 103 (32), 95 (8), 91 (16), 84 (8), 83 (15), 78 (24), 77 (24), 75 (9), 65 (6), 63 (8), 57 (10), 51 (9)

[0326] Compound **138.** (Rt = 9.24 min), m/z (rel. int.) 289 (M+,77), 290 (16), 230 (20), 229 (21), 215 (15), 203 (22), 201 (32), 183 (36), 134 (10), 133 (13), 124 (10), 121 (9), 109 (10), 101 (10), 73 (100), 43 (23)

[0327] Compound **139.** (Rt = 7.25 min), m/z (rel. int.) 245 (M+,92), 246 (15), 244 (67), 229 (16), 228 (63), 227 (46), 225 (10), 224 (15), 214 (13), 201 (39), 183 (13), 151 (13), 150 (100), 149 (14), 148 (58), 135 (22), 133 (54), 124 (14), 122 (12), 109 (18), 101 (15), 75 (13) (20). 131 (10)

[0328] Compound **141.** (R_t = 8.44 min), m/z (rel. int.) 257 (M+,48), 258 (8), 256 (36), 241 (21), 240 (100), 239 (19), 226 (2-2), 225 (20), 209 (11), 197 (14), 196 (18), 183 (25), 170 (16), 162 (19), 160 (10), 150 (28), 148 (26), 147 (9), 146 (8), 145 (13), 133 (20), 130 (8), 121 (10)

[0329] Compound **142.** (R_t = 8.47 min) , m/z (rel. int.) 273 (M+,14), 217 (5), 216 (31), 215 (5), 183 (8), 170 (4), 150 (5), 121 (4), 58 (5), 45 (5), 44 (100)

[0330] Compound **143.** (R_t = 9.39 min), m/z (rel. int.) 273 (M+,47), 275 (16), 274 (19), 272 (36), 258 (39), 257 (26), 256 (100), 255 (17), 242 (25), 241 (15), 221 (23), 178 (25), 177 (11), 176 (14), 168 (14), 167 (11), 166 (54), 165 (34), 164 (34), 163 (16), 162 (45), 160 (19), 152 (28), 151 (22), 149 (19), 147 (18), 145 (24), 139 (11), 136 (15), 131 (15), 130 (35), 121 (15), 115 (14), 111 (11), 103 (13), 102 (19), 89 (11), 77 (16), 75 (14), 63 (16), 51 (12)

[0331] Compound **148.** (Rt = 8.43 min), m/z (rel. int.) 261 (M+, 3), 170 (14), 169 (5), 168 (44), 153 (4), 151 (4), 140 (6), 139 (4), 138 (15), 132 (6), 125 (7), 123 (40), 115 (6), 103 (24), 102 (8), 101 (5), 95 (7), 94 (100), 89 (5), 77 (22), 75 (6), 66 (8), 65 (16), 63 (7), 51 (10), 50 (4).

[0332] Compound **149.** (Rt = 9.28 min), m/z (rel. int.) 295 (M+,4), 170 (32), 169 (12), 169 (100), 166 (8), 159 (22), 157 (66), 152 (11), 140 (16), 139 (11), 138 (41), 132 (11), 130 (32), 129 (8), 128 (82), 127 (10), 125 (16), 115 (12), 111 (15), 103 (55), 102 (18), 101 (15), 99 (19), 89 (10), 77 (26), 76 (8), 75 (27), 73 (11), 65 (11), 64 (10), 63 (22), 51 (11).

[0333] Compound **150.** (Rt = 8.32 min), m/z (rel. int.) 279 (M+,4), 171 (9), 170 (37), 169 (13), 168 (100), 166 (8), 142 (8), 141 (88), 140 (19), 139 (12), 138 (42), 132 (12), 130 (7), 125 (16), 115 (12), 113 (10), 112 (89), 111 (11), 104 (8), 103 (60), 102 (19), 101 (12), 95 (14), 89 (11), 84 (11), 83 (24), 77 (29), 76 (6), 75 (24), 63 (13), 57 (17), 51 (11).

Example 30: Biological properties of synthesized arylalkylamines

[0334] Compounds synthesized as described in Example 28 and Example 29 were tested for various biological

properties detailed in the examples.

Table 1

Compound	IC_{50} (μm)vs. NMDA[a]	IC_{50} (μm)vs. [^{1}H]MK-801[c]
Compound **54**	0.036 (4)	0.046 (3)
Compound **55**	0.035 (3)	0.153 (2)
Compound **56**	0.218 (4)	0.955 (2)
Compound **57**	0.028 (4)	0.063 (2)
Compound **58**	0.028 (2)	0.203 (3)
Compound **59**	0.272 (2)	0.453 (3)
Compound **60**	0.416 (11)	0.641 (9)
Compound **61**	0.134 (4)	0.324 (2)
Compound **62**	0.177 (5)	0.617 (1)
Compound **63**	0.093 (6)	0.245 (3)
Compound **64**	0.309 (3)	0.851 (2)
Compound **65**	0.167 (3)	2.0 (1)
Compound **66**	0.236 (4)	1.2 (2)
Compound **67**	10.95 (2)	2.9 (1)
Compound **68**	2.9 (1)	not tested
Compound **69**	0.224 (2)	0.366 (1)
Compound **70**	1.7 (1)	not tested
Compound **71**	6.35 (2)	not tested
Compound **72**	7.4 (1)	not tested
Compound **73**	12.6 (1)	not tested
Compound **75**	0.94 (2)	not tested
Compound **76**	0.73 (2)	not tested
Compound **77**	5.5 (2)	not tested
Compound **78**	10.2 (1)	not tested
Compound **79**	12.6 (4)	10.2 (2)
Compound **81**	1.4 (1)	6.1 (2)
Compound **82**	0.106 (5)	0.794 (1)
Compound **83**	0.342 (4)	0.794 (1)
Compound **84**	7.9 (2)	23.4 (1)
Compound **85**	1.2 (3)	3.5 (1)
Compound **86**	1.2 (3)	6.0 (1)
Compound **87**	0.657 (4)	3.0 (1)
Compound **88**	2.5 (3)	10.6 (2)

[a]:Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1). (# in parentheses indicates the number of experiments).
[b]:TFA salt.
[c]:Inhibition of [^{3}H]MK-801 binding in rat cortical/ hippocampal washed membrane preparations (see Example 4).
[d]:IC_{50} study incomplete. % inhibition at the stated concentration.

Table 1 (continued)

Compound	IC_{50} (μm)vs. NMDA[a]	IC_{50} (μm)vs. [^{1}H]MK-801[c]
Compound **89**	0.240 (3)	1.2 (2)
Compound **90**	0.270 (4)	1.4 (2)
Compound **91**	0.162 (3)	14.1 (2)
Compound **92**	1.3 (3)	20.2 (2)
Compound **93**	0.486 (3)	26.9 (2)
Compound **94**	0.248 (4)	22.6 (2)
Compound **95**	0.311 (3)	3.0 (2)
Compound **96**	0.187 (5)	1.1 (2)
Compound **97**	0.410 (3)	2.6 (1)
Compound **98**	7.9 (1)	52.5 (2)
Compound **100**	0.602 (2)	3.2 (1)
Compound **101**	0.912 (2)	2.0 (1)
Compound **102**	1.01 (2)	3.3 (1)
Compound **103**	0.380 (4)	0.661 (2)
Compound **105**	1.03 (1)	> 3 (1)
Compound **106**	0.767 (1)	1.31 (1)
Compound **107**	2.67 (1)	3.83 (1)
Compound **108**	1.06 (1)	0.942 (1)
Compound **109**	2.0 (2)	0.882 (1)
Compound **111**	0.790 (3)	0.137 (1)
Compound **114**	5.25 (1)	not tested
Compound **115**	1.9 (1)	not tested
Compound **116**	4.47 (1)	not tested
Compound **117**	15.83 (3)	5.73 (1)
Compound **118**	0.498 (2)	0.336 (1)
Compound **119**	0.122 (2)	0.137 (1)
Compound **120**	0.112 (2)	0.128 (1)
Compound **121**	0.835 (2)	0.773 (1)
Compound **122**	0.275 (1)	not tested
Compound **123**	9.6 (7)	> 3 (2)
Compound **124**	3.5 (1)	14.3 (3)
Compound **125**	1.7 (1)	6.7 (2)
Compound **126**	0.398 (3)	6.0 (1)
Compound **127**	1.2 (3)	17.5 (2)

[a]:Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1). (# in parentheses indicates the number of experiments).
[b]:TFA salt.
[c]:Inhibition of [^{3}H]MK-801 binding in rat cortical/ hippocampal washed membrane preparations (see Example 4).
[d]:IC_{50} study incomplete. % inhibition at the stated concentration.

Table 1 (continued)

Compound	IC_{50} (μm)vs. NMDA[a]	IC_{50} (μm)vs. [^{1}H]MK-801[c]
Compound **128**	0.646 (4)	5.5 (1)
Compound **129**	1.26 (2)	not tested
Compound **130**	0.851 (2)	not tested
Compound **131**	1.23 (2)	not tested
Compound **132**	1.3 (1)	6.4 (1)
Compound **133**	0.760 (1)	3.0 (1)
Compound **134**	2.5 (1)	> 10 (1)
Compound **135**	0.403(2)	not tested
Compound **136**	0.226(2)	not tested
Compound **137**	0.346(2)	not tested
Compound **138**	138.0(1)	not tested
Compound **139**	1.97(2)	not tested
Compound **141**	5.2(1)	not tested
Compound **142**	not tested	not tested
Compound **143**	3.1(1)	not tested
Compound **144**	not tested	not tested
Compound **145**	not tested	not tested
Compound **146**	1.1(1)	0.372(1)
Compound **147**	0.894(2)	not tested
Compound **148**	not tested	not tested
Compound **149**	not tested	not tested
Compound **150**	not tested	not tested

[a]:Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1). (# in parentheses indicates the number of experiments).
[b]:TFA salt.
[c]:Inhibition of [^{3}H]MK-801 binding in rat cortical/ hippocampal washed membrane preparations (see Example 4).
[d]:IC_{50} study incomplete. % inhibition at the stated concentration.

[0335] The simplified arylalkylamines exemplified by Compounds 54 - 150 bind to the site labeled by [^{3}H]MK-801 at concentrations ranging approximately 1 to 400-fold higher than those which antagonize NMDA receptor-mediated function in the rat cerebellar granule cell assay.

[0336] Some of the simplified arylalkylamines disclosed have structural features similar to portions of other compounds which are utilized as, for example, anticholinergics, antiparkinsonians, antihistamines, antidepressants, calcium channel blockers, coronary vasodilators, opiate analgesics, and antiarrhythmics. However, when certain of these compounds were evaluated for NMDA receptor antagonist potency (Example 1), as can be seen in Table 2, none of the compounds tested, with the exception of (R)- and (S)-fendiline and nisoxetine, had IC_{50} values less than 1 μM. These data are summarized in Table 2.