US005202333A

United States Patent [19]

Berger et al.

[11] Patent Number: 5,202,333

[45] Date of Patent: Apr. 13, 1993

[54] TRICYCLIC 5-HT$_3$ RECEPTOR ANTAGONISTS

[75] Inventors: **Jacob Berger**, Los Altos Hills; **Robin D. Clark**, Palo Alto; **Richard M. Eglen**, Mountain View; **William L. Smith**, Sunnyvale; **Klaus K. Weinhardt**, San Francisco, all of Calif.

[73] Assignee: **Syntex (U.S.A.) Inc.**, Palo Alto, Calif.

[21] Appl. No.: **704,565**

[22] Filed: **May 22, 1991**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 442,082, Nov. 28, 1989, abandoned.

[51] **Int. Cl.**[5] **C07D 471/08**; A61K 31/55; A61K 31/455

[52] **U.S. Cl.** **514/296**; 514/211; 514/872; 540/520; 546/99; 546/100

[58] **Field of Search** 546/99, 100; 540/520; 514/211, 296

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,341,528	9/1967	Shavel, Jr.	546/98
3,896,132	7/1975	Bernauer	260/289 R
4,309,543	1/1982	Keeley	546/98
4,571,396	1/1986	Hutt	546/156
4,959,367	9/1990	King et al.	514/243

FOREIGN PATENT DOCUMENTS

0093488	11/1983	European Pat. Off. .
430190	6/1991	European Pat. Off. .
88-04292	6/1988	World Int. Prop. O. .

OTHER PUBLICATIONS

Reynolds, J. C. 1989, Prokinetic Agents: A Key in the Future of Gastroenterology, Gastroenterology Clinics of North America, 18:437–457.

1989, Drugs Acting on 5-Hydroxytryptamine Receptors, The Lancet, pp. 717–719.

Scholtysik, G. 1988, 5-Hydroxytryptamine Antagonist ICS 205-930 Blocks Cardiac Potassium, Sodium and Calcium Channels, J. of Pharmacol. Exp. Ther. 245, 3:773–778.

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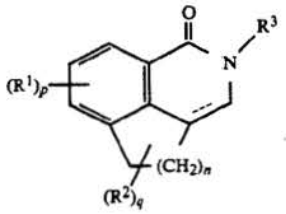
Primary Examiner—Mark L. Berch

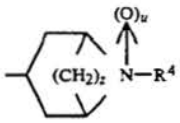
[57] **ABSTRACT**

The present invention is directed to 5-HT$_3$ receptor antagonist compounds of formula I:

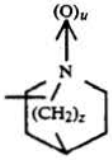


I

in which
the dashed line denotes an optional double bond;
n is 1, 2 or 3;
p is 0, 1, 2 or 3;
q is 0, 1 or 2;
each R^1 is independently selected from halogen, hydroxy, lower alkoxy, lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;
each R^2 is lower alkyl; and
R^3 is a group selected from Formulae (a), (b), (c) and (d):



(a)



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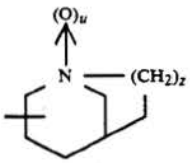

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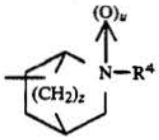

(d)

in which
u is 0 or 1;
z is 1, 2 or 3; and
R^4 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, or a group $(CH_2)_tR^5$ where t is 1 or 2 and R^5 is thienyl, pyrrolyl, or furyl, each optionally further substituted by one or two substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C_{1-4} alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C_{1-4} alkyl optionally substituted by hydroxy, C_{1-4} alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acyloxy; and the ph
individual isomers, m
preparation, compo

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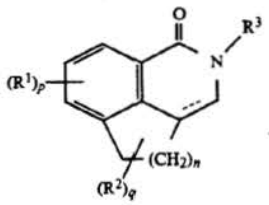
Primary Examiner—Mark L. Berch
Attorney, Agent, or Firm—Wayne W. Montgomery; Derek P. Freyberg; Tom M. Moran

[57] **ABSTRACT**

The present invention is directed to 5-HT$_3$ receptor antagonist compounds of formula I:



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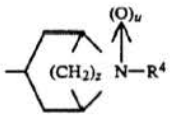
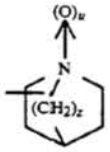
in which
the dashed line denotes an optional double bond;
n is 1, 2 or 3;
p is 0, 1, 2 or 3;
q is 0, 1 or 2;
each R^1 is independently selected from halogen, hydroxy, lower alkoxy, lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;
each R^2 is lower alkyl; and
R^3 is a group selected from Formulae (a), (b), (c) and (d):



(a)



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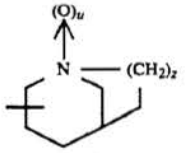

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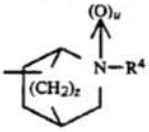

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R^4 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, or a group $(CH_2)_tR^5$ where t is 1 or 2 and R^5 is thienyl, pyrrolyl, or furyl, each optionally further substituted by one or two substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C_{1-4} alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C_{1-4} alkyl optionally substituted by hydroxy, C_{1-4} alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acyloxy; and the pharmaceutically acceptable salts, individual isomers, mixtures of isomers, processes for preparation, compositions, and methods of use thereof.

TRICYCLIC 5-HT$_3$ RECEPTOR ANTAGONISTS

This application is a continuation-in-part of copending application, Ser. No. 07/442,082, filed Nov. 28, 1989 and now abandoned.

FIELD OF THE INVENTION

This invention relates to novel compounds which are 5-HT$_3$ receptor antagonists, pharmaceutical compositions containing them and methods for their use and methods for preparing these compounds. In particular, it relates to tricyclic 5-HT$_3$ receptor antagonists containing a bridged bicyclic amine substituent. The invention also relates to novel intermediates for making the 5-HT$_3$ receptor antagonists.

BACKGROUND OF THE INVENTION

Serotonin, a neurotransmitter with mixed and complex pharmacological characteristics, was first discovered in 1948 and subsequently has been the subject of substantial research. Serotonin, also referred to as 5-hydroxytryptamine (5-HT), acts both centrally and peripherally on discrete 5-HT receptors. 5-HT Receptors are presently delineated into three major subclassifications - 5-HT$_1$, 5-HT$_2$ and 5-HT$_3$ - each of which may also be heterogeneous. Receptors of the 5-HT$_3$ subclass pervade autonomic neurons and appear to regulate the release of a variety of neurotransmitters in the gastrointestinal, cardiovascular and central nervous systems.

5-HT$_3$ receptors are located in high densities on neurons associated with the emetic reflex and drugs which block the interactions of serotonin at the 5-HT$_3$ receptor level, i.e., 5-HT$_3$ receptor antagonists, possess potent antiemetic properties. Such antagonists demonstrate utility for counteracting the emetic effects of cancer chemotherapy and radiotherapy (see Drugs Acting on 5-Hydroxytryptamine Receptors: *The Lancet* Sep. 23, 1989 and refs. cited therein).

Functional bowel disorders are prevalent in much of the industrialized world. Chronic gastroesophageal reflux disease alone may be present in as much as 15% of the population. Use of prokinetic agents is one of the most effective methods known for treating such disorders. Because many 5-HT$_3$ antagonists possess prokinetic properties and are relatively free from side effects they are particularly useful in the treatment of gastrointestinal diseases (see Reynolds R. C. Prokinetic Agents: A Key in the Future of Gastroenterology. *Gastroenterology Clinics of North America* 1989, 18, 437–457).

5-HT$_3$ receptors are present in those areas of the brain which control mood, emotion, reward and memory. 5-HT$_3$ receptor antagonists reduce mesolimbic dopamine levels, a necessary property for antipsychotic activity. Such antagonists also increase cholinergic tone in the limbic-cortical region, which may explain their cognitive enhancing effects. In addition, 5-HT$_3$ antagonists possess anxiolytic properties, demonstrate potential for use in the treatment of dependency disorders and are under investigation in patients with schizophrenia (see article from *The Lancet* previously cited).

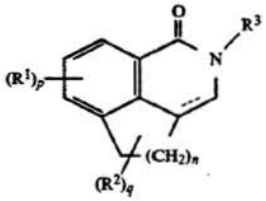
There is evidence that 5-HT$_3$ receptors mediate nociceptive input to afferent neurons (see Glaum, S.; Proudfit, H. K.; Anderson, E. G. *Neurosci. Lett.* 1988, 95, 313). 5-HT$_3$ antagonists may therefore be of value in the control of pain, particularly migraine (see Peatfield R.; Drugs and the Treatment of Migraine. *Trends. Pharmacol. Sci.* 1988, 9, 141).

The 5-HT$_3$ receptor antagonist ICS 205-930 inhibits arrhythmias in a variety of animal models and exerts mixed class III and class I antiarrhythmic properties in ventricular myocytes (see Scholtysik, G.; Imoto, Y.; Yatani, A; Brown, A. M. *J. Pharmacol. Exp. Ther.* 1988, 245, 773 and references therein). 5-HT$_3$ antagonists may therefore be of use in treating or preventing arrhythmias.

The disclosures of these and other documents referred to throughout this application, e.g., in the Pharmacology section of the Detailed Description of the Invention, are incorporated herein by reference.

SUMMARY OF THE INVENTION

The first aspect of this invention is the compounds of Formula I:



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each R^1 is independently selected from halogen, hydroxy, lower alkoxy, lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;

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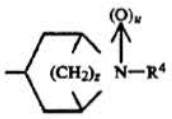
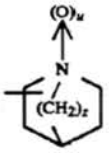


(a)



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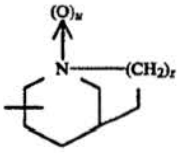

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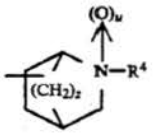

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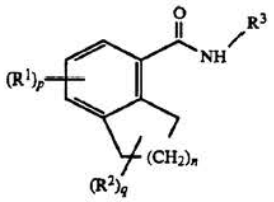
A second aspect of this invention is a pharmaceutical composition containing a compound of Formula I in admixture with one or more suitable excipients.

A third aspect of this invention is a method of treating diseases involving emesis, gastrointestinal disorders, CNS disorders, cardiovascular disorders or pain by administering a therapeutically effective amount of a compound of Formula I to a subject afflicted with such a condition.

A fourth aspect of this invention is the compounds of Formula II:



II

in which n, p, q, R^1, R^2 and R^3 are as defined for Formula I, which are useful intermediates in preparing compounds of Formula I.

A fifth aspect of this invention are the processes for preparing compounds of Formula I and is set forth in the "Detailed Description Of The Invention."

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"Alkyl" means a straight, branched, or cyclic saturated hydrocarbon radical having from one to the number of carbon atoms designated. For example C_{1-7} alkyl is alkyl having at least one but no more than seven carbon atoms, e.g., methyl, ethyl, i-propyl, n-propyl, n-butyl, cyclopropylmethyl, pentyl, cyclohexyl, heptyl and the like.

"Alkoxy" means the radical —OR wherein R is alkyl having from one to the number of carbon atoms designated, e.g., C_{1-7} alkoxy includes, e.g., methoxy, ethoxy, i-propoxy, n-propoxy, n-butoxy, pentoxy, hexoxy and the like.

"Alkonyl" means the radical —C(O)R wherein R is alkyl having from one to the number of carbon atoms designated, e.g., C_{1-7} alkonyl includes ethanoyl, propanoyl, i-butanoyl, n-butanoyl, pentanoyl, hexanoyl and the like.

"Lower" modifies alkyl, alkoxy and alkonyl and refers to those alkyl radicals or R groups in alkoxy and alkonyl radicals containing 1 to 6 carbon atoms.

"Halogen" means fluorine, chlorine, bromine, or iodine.

"Esterified carboxy" means the ester group —COOR wherein R is C_{1-8} alkyl.

"In vivo hydrolyzable acyloxy" means a group —OC(O)R, wherein R is C_{1-8} alkyl, capable of undergoing enzymatic hydrolysis within a living organism.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under alkylating conditions, and includes halogen and alkane- or arenesulfonyloxy such as mesyloxy, ethanesulfonyloxy, benzenesulfonyloxy, tosyloxy and the like.

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, and deer) and non-mammals (e.g., birds and the like).

"Cytotoxic agents" include platinum anti-cancer agents such as cisplatin (cis-diamminedichloroplatinum), as well as non-platinum anti-cancer drugs such as cyclophosphamide (cytoxin), vincristrine (leurocristine), procarbazine (N-(1-methylethyl)-4-[(2-methylhydrazino)methyl]benzamide), methotrexate, fluorouracil, mechlorethamine hydrochloride (2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride), doxorubicin, adriamycin, dactinomycin (actinomycin-D) cytarabine, carmustine, dacarbazine, and others listed at page 1143 of the *Journal of Clinical Oncology* 1989; 7(8): 1143.

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy. Thus, "disease" here includes the emesis caused by therapy with agents having emetogenic side effects, in particular by therapy for cancer, such as chemotherapy with cytotoxic agents and radiotherapy.

"Emesis", for the purposes of this application, will have a meaning that is broader than the normal, dictionary definition and includes not only vomiting, but also nausea and retching.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optional bond" means that the bond may or may not be present and that the description includes both single bonds and double bonds; "optionally converting a compound of Formula I to a corresponding pharmaceutically acceptable salt" means that the conversion may or may not be carried out in order for the process described to fall within the invention, and the invention includes those processes wherein the compound of Formula I is converted to the salt and those processes in which it is not.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological

activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.-2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, i.e., arresting its development, or

(3) relieving the disease, i.e., causing regression of the disease.

Compounds that have identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space are termed "isomers". Isomers that differ in the nature or sequence of bonding of their atoms are termed "constitutional isomers". Isomers that differ only in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diasteromers" and stereoisomers that are mirror images are termed "enantiomers" or sometimes "optical isomers". Stereoisomers that are superimposable upon their mirror images are termed "achiral" and those not superimposable are termed "chrial". A carbon atom bonded to four different groups is termed a "chiral center" or alternatively an "asymmetric carbon".

When a compound has a chiral center, a pair of enantiomers of opposite chirality is possible. An enantiomer can be characterized by the absolute configuration of its chiral center and described by the R- and S-sequencing rules of Cahn and Prelog (i.e., as (R)- and (S)-isomers) or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+)- and (−)-isomers, respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is termed a "racemic mixture" or "racemate" and may be described as the (RS)- or (±)-mixture thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 3rd edition March, Jerry, John Wiley and Sons, New York, 1985).

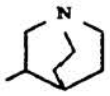
Certain compounds of Formulae I and II can exist as stereoisomers. For example, certain compounds possess a chiral center at the ring carbon of the R^3 substituent which is bonded to the amide nitrogen and, when the optional bond is absent, at the 3a-position and therefore can exist as (R)- or (S)-isomers. In addition, certain compounds can exist as the (endo)- or (exo)-isomers, e.g., when the R^3 substituent is 1-azabicyclo[3.3.1]non-4-yl.

When a compound of Formula I or II possesses one chiral center, a pair of enantiomers exists. When two chiral centers are present in a compound of Formula I, four separate steroisomers exist (i.e., two separate pairs of enantiomers). When a compound of Formula I possesses two chiral centers and can exist as endo or exo, eight separate stereoisomers are possible (i.e., two separate pairs of enantiomers in the endo or exo form).

It is to be understood that when referring to Formula I, II, (a), (b), (c) or (d) in this application, a straight line depicting the covalent bond between the R^3 substituent and the amide nitrogen represents the possible geometric isomers and enantiomers or the mixtures, racemic or otherwise, thereof. Similarly, when referring to Formula I in which the optionally bond is absent, a straight line depicting the covalent bond between carbons 3a and 4 represents either the R or S configurations or a mixture racemic, or otherwise, thereof. For purposes of the present application when referring to a compound by name or by formula and the configuration is not designated, it is to be understood that the reference is to all possible forms.

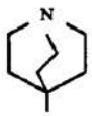
Certain R^3 substituents described in this application are of particular interest and are therefore defined specifically as the following:

(1) Formula (b) where z is 2 and u is 0 having the specific formula



is referred to as 1-azabicyclo[2.2.2]oct-3-yl;

(2) Formula (b) where z is 2 and u is 0 having the specific formula



is referred to as 1-azabicyclo[2.2.2]oct-4yl;

(3) Formula (a) where z is 3, u is 0 and R^4 is methyl having the specific formula

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