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APPLICANTS

MICHAEL N. FISHER, RINGOES, NJ; DONG OK, EDISON, NJ; ELIZABETH M. NAYLOR, SCOTCH PLAINS, NJ; ANN E. WEBER, SCOTCH PLAINS, NJ.

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MOLLIE M. YANG
PATENT DEPT.
MERCK & CO., INC.
P.O. BOX 2000
RAHWAY, NJ 07065-0907

TITLE

SUBSTITUTED SULFONAMIDES AS SELECTIVE BETA3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

U.S. DEPT. of COMM.-Pat. & TM Office-PTO-436L (rev. 10-78)

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C. Blyle 3-27-95
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Supervisory Patent Examiner
Group 1200-AU 1203
Primary Examiner

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U.S. PATENT APPLICATION

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CONTINUING DATA********
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08/233166

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

P 30635 05/12/94 08233166

13-2755 030 101 710.00CH 19203

PTO-1556
(5/87)

TITLE OF THE INVENTION

SUBSTITUTED SULFONAMIDES AS SELECTIVE β3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

BACKGROUND OF THE INVENTION

β-Adrenoceptors have been subclassified as β1 and β2 since 1967. Increased heart rate is the primary consequence of β1-receptor stimulation, while bronchodilation and smooth muscle relaxation typically result from β2 stimulation. Adipocyte lipolysis was initially thought to be solely a β1-mediated process. However, more recent results indicate that the receptor-mediating lipolysis is atypical in nature. These atypical receptors, later called β3-adrenoceptors, are found on the cell surface of both white and brown adipocytes where their stimulation promotes both lipolysis (breakdown of fat) and energy expenditure.

Early developments in this area produced compounds with greater agonist activity for the stimulation of lipolysis (β3 activity) than for stimulation of atrial rate (β1) and tracheal relaxation (β2). These early developments disclosed in Ainsworth et al., U.S. Patents 4,478,849 and 4,396,627, were derivatives of phenylethanolamines.

Such selectivity for β3-adrenoceptors could make compounds of this type potentially useful as antiobesity agents. In addition, these compounds have been reported to show antihyperglycemic effects in animal models of non-insulin-dependent diabetes mellitus.

A major drawback in treatment of chronic diseases with β3 agonists is the potential for stimulation of other β-receptors and subsequent side effects. The most likely of these include muscle tremor (β2) and increased heart rate (β1). Although these phenylethanolamine derivatives do possess some β3 selectivity, side effects of this type have been observed in human volunteers. It is reasonable to expect that these side effects resulted from partial β1 and/or β2 agonism.

More recent developments in this area are disclosed in Ainsworth et al., U.S. Patent 5,153,210, Caulkett et al., U.S. Patent

4,999,377, Alig et al., U.S. Patent 5,017,619, Lecount et al., European Patent 427480 and Bloom et al., European Patent 455006.

Even though these more recent developments purport to describe compounds with greater β_3 selectivity over the β_1 and β_2 activities, this selectivity was determined using rodents, in particular, rats as the test animal. Because even the most highly selective compounds, as determined by these assays, still show signs of side effects due to residual β_1 and β_2 agonist activity when the compounds are tested in humans, it has become apparent that the rodent is not a good model for predicting human β_3 selectivity.

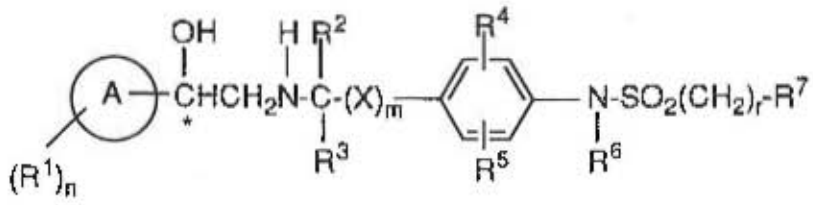
Recently, assays have been developed which more accurately predict the effects that can be expected in humans. These assays utilize cloned human β_3 receptors which have been expressed in Chinese hamster ovary cells. See Emorine et al, Science, 1989, 245:1118-1121; and Liggett, Mol. Pharmacol., 1992, 42:634-637. The agonist and antagonist effects of the various compounds on the cultivated cells provide an indication of the antiobesity and antidiabetic effects of the compounds in humans.

SUMMARY OF THE INVENTION

The instant invention is concerned with substituted sulfonamides which are useful as antiobesity and antidiabetic compounds. Thus, it is an object of this invention to describe such compounds. It is a further object to describe the specific preferred stereoisomers of the substituted sulfonamides. A still further object is to describe processes for the preparation of such compounds. Another object is to describe methods and compositions which use the compounds as the active ingredient thereof. Further objects will become apparent from reading the following description.

DESCRIPTION OF THE INVENTION

The present invention provides compounds having the formula I:



I

where

n is 0 to 5;

m is 0 or 1;

r is 0 to 3;

A is phenyl, a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, a benzene ring fused to a C_3-C_8 cycloalkyl ring, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, or a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen;

R^1 is hydroxy, oxo, halogen, cyano, NR^8R^8, SR^8 trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, SO_2R^9, $OCOR^9$, NR^8COR^9, COR^9, $NR^8SO_2R^9$, $NR^8CO_2R^8$, or C_1-C_6 alkyl substituted by hydroxy, halogen, cyano, NR^8R^8, SR^8, trifluoromethyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, phenyl, NR^8COR^9, COR^9, SO_2R^9, $OCOR^9$, $NR^8SO_2R^9$ or $NR^8CO_2R^8$;

R^2 and R^3 are independently hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl with 1 to 3 substituents selected from hydroxy, C_1-C_6 alkoxy, and halogen;

X is $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$ or $-CH_2O-$;

R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, halogen, NHR^8, OR^8, SO_2R^9 or $NHSO_2R^9$;

R^6 is hydrogen or C_1-C_6 alkyl;

R^7 is $Z-(R^{1a})_n$;

R^{1a} is R^1, C_3-C_8 cycloalkyl, phenyl, or 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to three groups independently selected from oxo, R^8 and NR^8R^8;

Z is phenyl, naphthyl, a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, a benzene ring fused to a C_3-C_8 cycloalkyl ring, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, or a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen;

R^8 is hydrogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, Z optionally having 1 to 3 substituents selected from halogen, C_1-C_6 alkyl and C_1-C_6 alkoxy, or C_1-C_{10} alkyl having 1 to 3 substituents selected from hydroxy, halogen, CO_2H, CO_2-C_1-C_6 alkyl, SO_2-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, and Z optionally substituted by from 1 to 3 of halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

R^9 is R^8 or NR^8R^8; or

a pharmaceutically acceptable salt thereof.

Preferred compounds of the instant invention are realized when in the above structural formula I:

R^2 and R^3 are hydrogen or methyl;

X is $-CH_2-$;

n is 0 to 3;

m is 1;

r is 0 to 2; and

R^4, R^5 and R^6 are hydrogen.

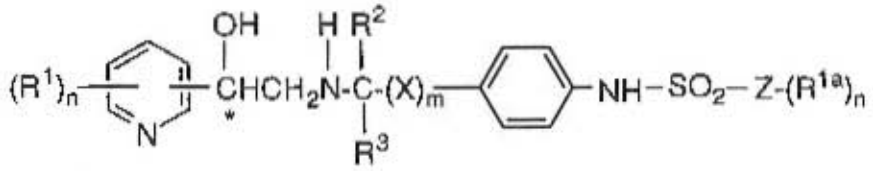
Other preferred compounds of the instant invention are realized when in the above structural formula I:

A is phenyl or a 6-membered heterocyclic ring with 1 or 2 nitrogen atoms;

R^1 is hydroxy, halogen, cyano, trifluoromethyl, NR^8R^8, $NR^8SO_2R^9$, NR^8COR^9, $NR^8CO_2R^8$, C_1-C_6 alkyl optionally substituted by hydroxy; and

r is 0 or 2.

More preferred compounds are represented by the formula Ia:



Ia

wherein

n is 0 to 3;

m is 1

R^1 is halogen or NR^8R^8;

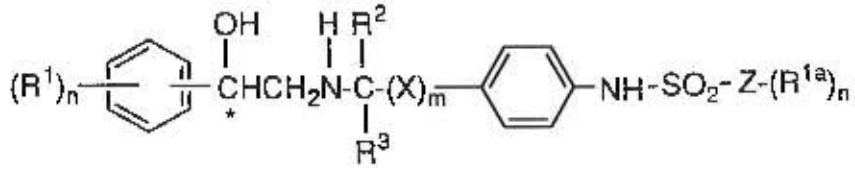
R^{1a} is halogen, C_1-C_6 alkyl, NR^8R^8, NR^8COR^9, $NR^8CO_2R^8$, $OCOR^9$, or 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to three groups independently selected from oxo, R^8 and NR^8R^8;

Z is phenyl, naphthyl or benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen;

X is $-CH_2-$; and

R^2, R^3 are independently hydrogen or methyl .

Other more preferred compounds are represented by formula Ib:



Ib

wherein

n is	0 to 3;
m is	1
R^1 is	hydroxy, NR^8R^8 or halogen;
R^{1a} is	halogen, C_1-C_6 alkyl, NR^8R^8, NR^8COR^9, $NR^8CO_2R^8$, $OCOR^9$, or 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to three groups independently selected from oxo, R^8 and NR^8R^8;
Z is	phenyl, naphthyl or benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen;
X is	$-CH_2-$; and

R^2 and R^3 are independently hydrogen or methyl.

Representative antiobesity and antidiabetic compounds of the present invention include the following:

N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide

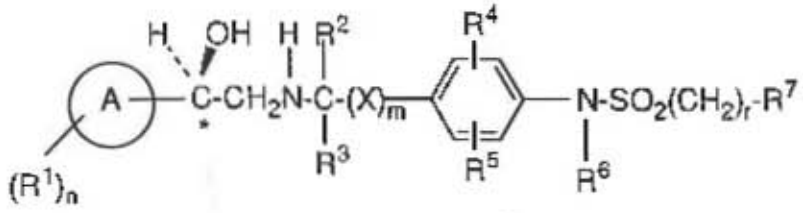
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-5-benzisoxazolesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(dimethylaminocarbonyl)amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-isopropylbenzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-2-naphthalenesulfonamide
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-4-iodobenzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-2-naphthalenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-3-quinolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-chlorophenyl)ethyl]amino]ethyl]phenyl]-3-isopropylbenzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-chlorophenyl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-chlorophenyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in structural Formula I. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule, in particular, R^2 and R^3. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention. In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the compound in which the hydroxy substituent is above the plane of the structure, as seen in Formula Ic, is more active and thus more preferred over the compound in which the hydroxy substituent is below the plane of the structure.

The following stereospecific structure represents the preferred stereoisomers of the instant invention:



Ic

where n, m, r, A, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as defined above under formula I.

Throughout the instant application, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

Examples of 5 and 6-membered heterocycles and fused heterocycles of A, Z and R^{1a} include pyridyl, quinolinyl, pyrimidinyl, pyrrolyl, thienyl, imidazolyl, thiazolyl, benzimidazolyl, thiadiazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzoxazinyl, benzisoxazolyl, benzothiazolyl, tetrahydronaphthyl, dihydrobenzofuranyl, tetrahydroquinolinyl, furopyridine and thienopyridine.

The preferred values of A and Z are phenyl, naphthyl or heterocycles with from 1 to 4 heteroatoms independently selected from one of oxygen or sulfur, and/or 1 to 4 nitrogen atoms.

The more preferred values of A are phenyl, pyridyl, quinolinyl, pyrimidinyl, pyrrolyl, thienyl, imidazolyl, and thiazolyl.

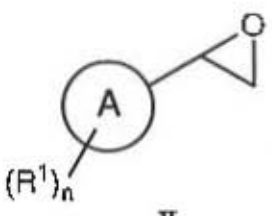
The more preferred values of Z are phenyl, naphthyl, quinolinyl, thienyl, benzimidazolyl, thiadiazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzoxazinyl, benzisoxazolyl, benzothiazolyl, tetrahydronaphthyl, dihydrobenzofuranyl, and tetrahydroquinolinyl.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other; thus for example, NR^8R^8 may represent NH_2, $NHCH_3$, $N(CH_3)CH_2CH_3$, and the like.

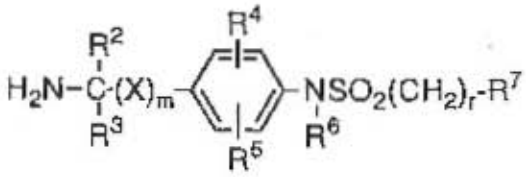
The following abbreviations are used throughout the specification:

Boc	: tert-butyloxycarbonyl
Cbz	: carbobenzyloxy
DIP-Cl	: diisopinocampheylchloroborane
DMF	: dimethylformamide
DMSO	: dimethylsulfoxide
HPLC	: high pressure liquid chromatography
Me	: methyl
MPLC	: medium pressure liquid chromatography
Ms	: methanesulfonyl (mesyl)
NBS	: N-bromosuccinimide
NCS	: N-chlorosuccinimide
nHex	: n-hexyl
TFA	: trifluoroacetic acid
THF	: tetrahydrofuran

The compounds (I) of the present invention can be prepared from epoxide intermediates such as those of formula II and amine intermediates such as those of formula III. The preparation of these intermediates is described in the following schemes.



II

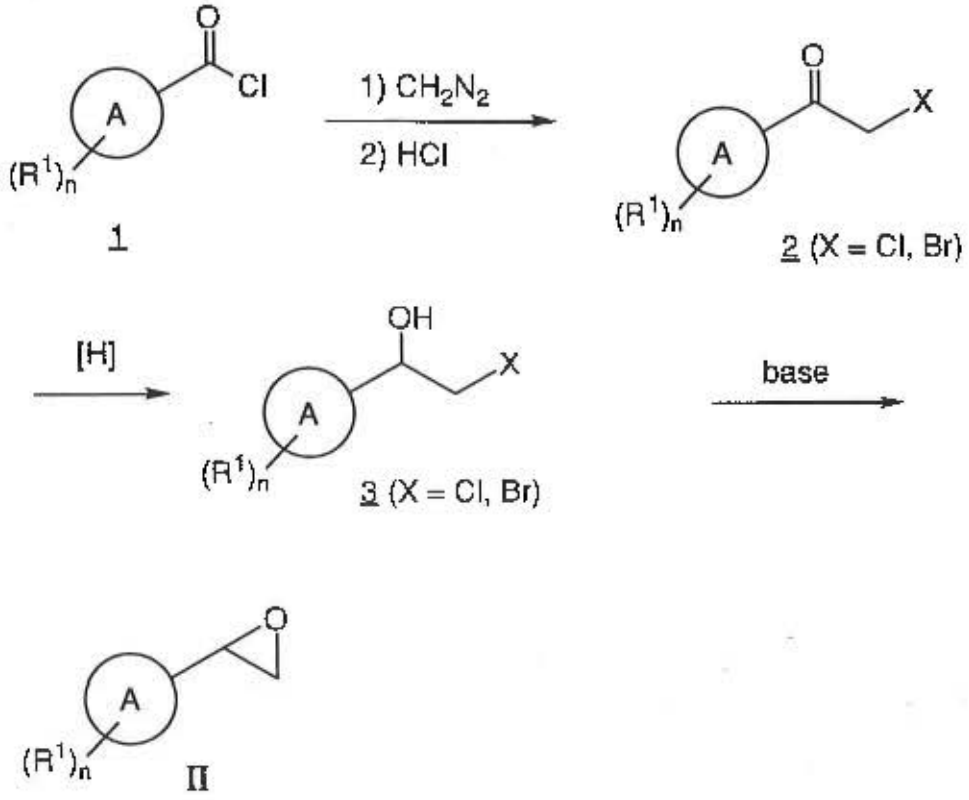


III

where n, m, r, A, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as defined above.

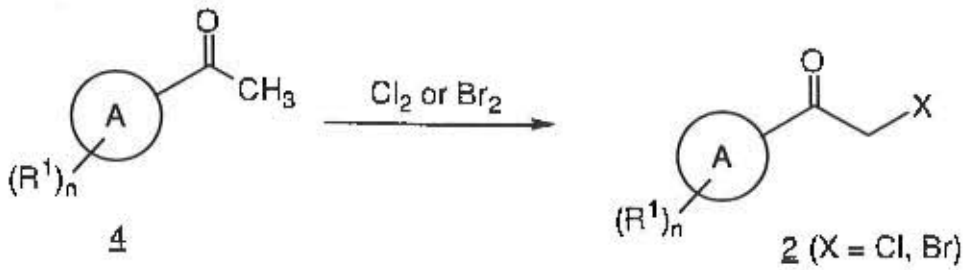
Compounds II are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route is illustrated in Scheme 1. Acid chloride 1, which may be commercially available or readily prepared from the corresponding acid by treatment with, for example, thionyl chloride or oxalyl chloride, is treated with diazomethane in a solvent such as diethyl ether. The resultant diazoketone is then treated with hydrogen chloride to give chloroketone 2 (X = Cl). The haloketone 2 is then reduced with a reducing agent such as sodium borohydride. The resultant alcohol 3 is treated with base such as potassium carbonate in refluxing acetone to provide the desired epoxide II. The enantiomerically enriched (*R*) and (*S*) epoxides II are readily available by asymmetric reduction of haloketones 2 using chiral reducing agents such as (-) or (+)-DIP-Cl, (*R*) or (*S*)-Alpine borane or (*R*) or (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole-borane ((*R*) or (*S*)-OAB•BH_3).

SCHEME 1



An alternate route to the desired haloketones 2 is illustrated in Scheme 2. Methylketone 4 may be converted to the corresponding haloketone using a variety of reagents known to those in the art and summarized in Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, 369-372. Conveniently, methylketone 4 is treated with chlorine or *N*-chlorosuccinimide in acetic acid with an additional acid source such as hydrogen chloride or aluminum chloride. For the synthesis of 2 (X = Br), bromine or NBS with hydrogen bromide or aluminum bromide may be used. In some cases, the chloro or bromoketones 2 may be commercially available.

SCHEME 2

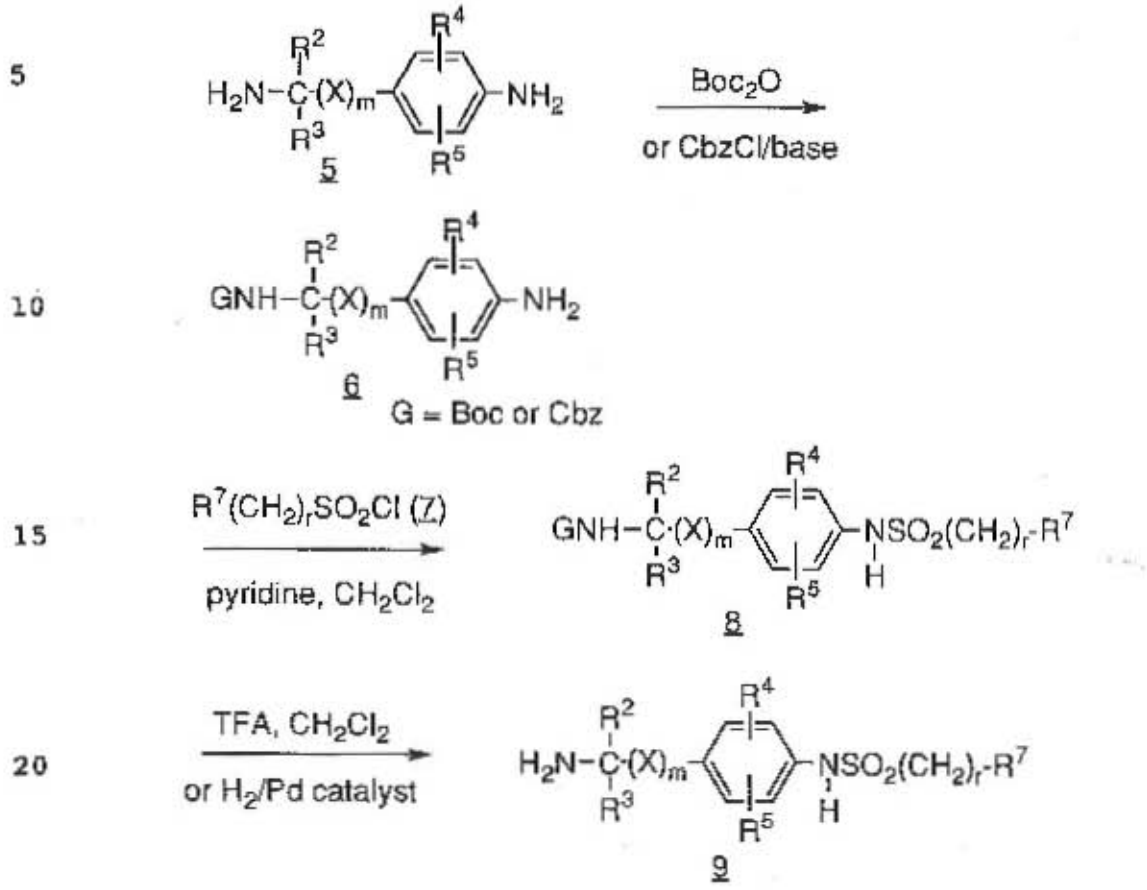


4 2 (X = Cl, Br)

Many of the methylketones 4 are commercially available or readily prepared by methods described in the literature and known to those skilled in the art. R^1 substituents on the acid chlorides 1 or methylketones 4 may need to be protected during the subsequent procedures. A description of such protecting groups may be found in: Protective Groups in Organic Synthesis, 2nd Ed., T. W. Greene and P. G. M. Wuts, John Wiley and Sons, New York, 1991.

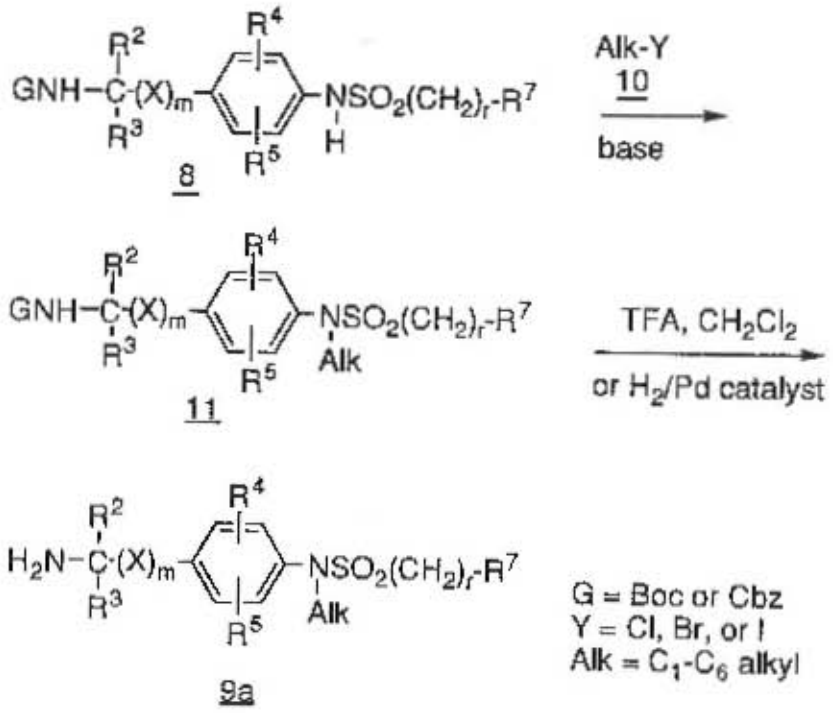
Compounds III can be conveniently prepared by a variety of methods familiar to those skilled in the art. A convenient route for their preparation when R^6 is hydrogen is illustrated in Scheme 3. Compound 5 is selectively protected as a suitable carbamate derivative 6 with, for example, di-*tert*-butyl dicarbonate or carbobenzyloxy chloride. This compound is then treated with a sulfonyl halide, preferably the sulfonyl chloride 7, and a base such as pyridine in an anhydrous solvent such as dichloromethane or chloroform for 0.5 to 24 hours at temperatures of -20 to 50°C, preferably 0°C, to provide the sulfonamide 8. The protecting group is then removed with, for example, trifluoracetic acid in the case of Boc or catalytic hydrogenation in the case of Cbz, to give the desired amine 9.

SCHEME 3.



Compounds III where R^6 is not hydrogen may be conveniently prepared as illustrated in Scheme 4. Sulfonamide 8, prepared as described above, is alkylated with an appropriate alkylating agent 10 in the presence of base to provide sulfonamide 11. Removal of the protecting group as above gives the desired compound 9a.

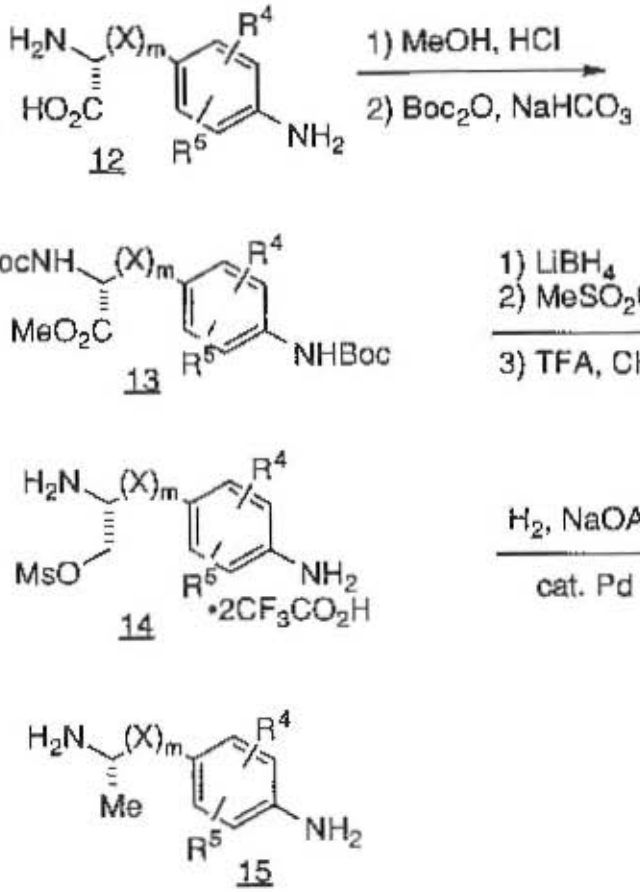
SCHEME 4



The sulfonyl chlorides 7, many of which are commercially available, can also be readily prepared by a number of methods familiar to those skilled in the art. One suitable method involves the addition of an organolithium reagent or a Grignard reagent to sulfuryl chloride following the procedure of S. N. Bhattacharya, et. al., J. Chem. Soc. (C), 1265-1267 (1969). Another convenient method involves the treatment of a thiol with sulfuryl chloride and a metal nitrate according to the procedure of Y. J. Park, et. al., Chemistry Letters, 1483-1486 (1992). Sulfonic acids are also conveniently converted to the corresponding sulfonyl chloride by treatment with PCl_5, PCl_3 or $SOCl_2$ (J. March, Advanced Organic Chemistry, 4th Ed., John Wiley and Sons, New York: 1992, p1297 and references sited therein). Aromatic and heteroaromatic compounds may be chlorosulfonylated directly by treatment with Vilsmeier's reagent or chorosulfonic acid (Organic Synthesis, I, 8).

The diamines 5 are commercially available or readily prepared by methods described in the literature or known to those skilled in the art. Compound 5 where R^2 or R^3 is methyl can be prepared from the corresponding amino acid following the method of J. D. Bloom, et. al., J. Med. Chem., 35, 3081-3084 (1992). As illustrated in Scheme 5 for R^3 = methyl, the appropriate (*R*) amino acid 12 is esterified, conveniently by treatment with methanolic hydrochloric acid, and then treated with di-*tert*-butyl dicarbonate to give compound 13. The ester group is reduced with a hydride source such as lithium borohydride and the resultant alcohol is converted to a leaving group such as a mesylate. Removal of the Boc protecting groups gives diamine 14. This compound is subjected to catalytic hydrogenation in the presence of base such as sodium acetate to give the desired α-methyl amine 15. The other enantiomer is available through an analogous sequence starting with the corresponding (*S*) amino acid.

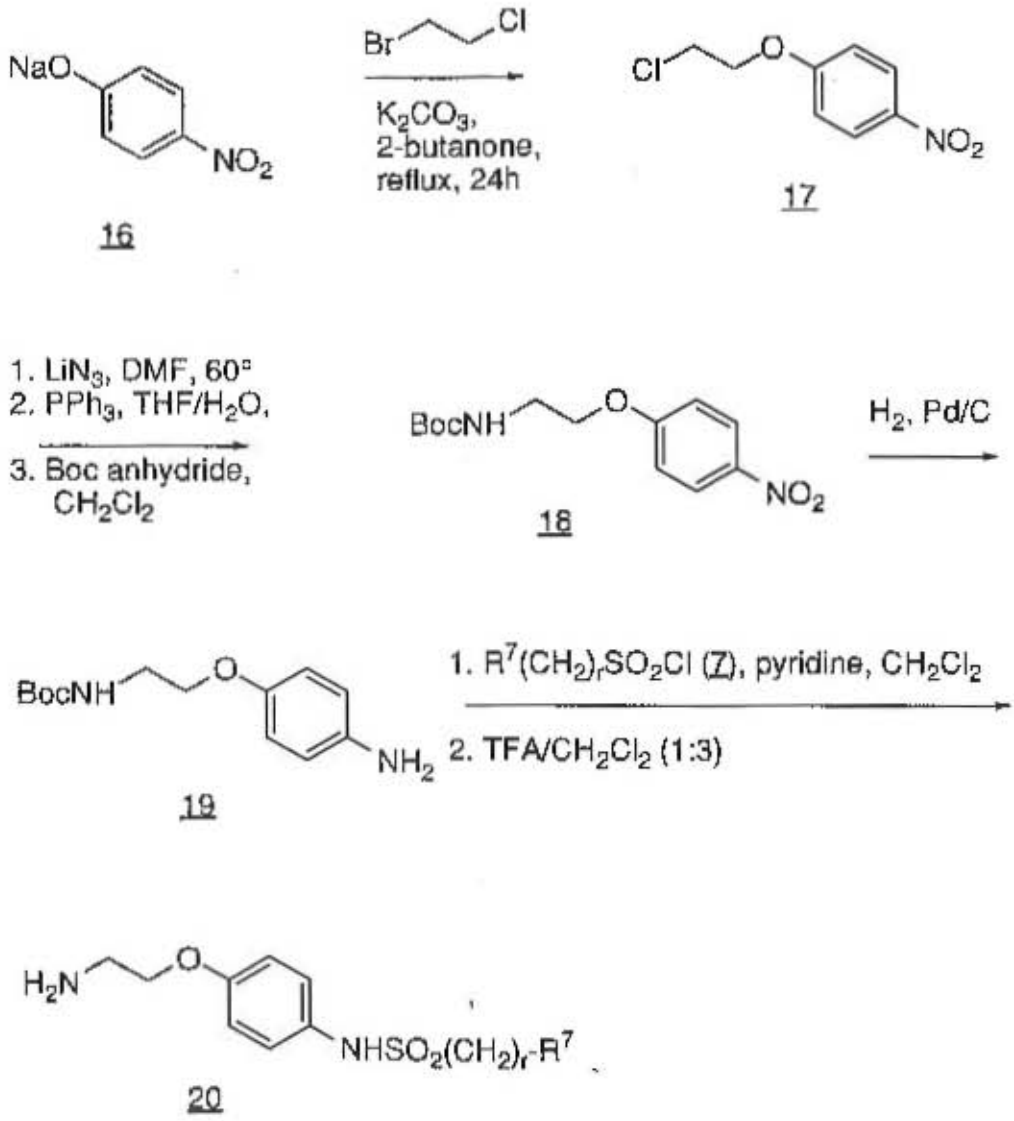
SCHEME 5



Diamines 5 or sulfonamide amines 9 where X is -CH_2O- and m is 1 are also readily prepared by methods described in the literature or known to those skilled in the art. For example, as shown in Scheme 6, the sodium salt of 4-nitrophenol 16 is alkylated with 1-bromo-2-chloroethane, conveninetly in refluxing 2-butanone with a base such as potassium carbonate to give chloro derivative 17. The chloride is converted to the corresponding amine by treatment with lithium azide followed by reduction with, for example, triphenylphosphine in aqueous tetrahydrofuran. Protection of the resultant amine, conveniently as its t-butyl carbamate by treatment with di-tert-butyldicarbonate, gives derivative 18. The nitro group is then reduced, for example, by

catalytic hydrogenation to provide amine 19. Acylation of intermediate 19 with sulfonyl chloride 7, followed by deprotection with acid such as trifluoroacetic acid gives the desired intermediate 20.

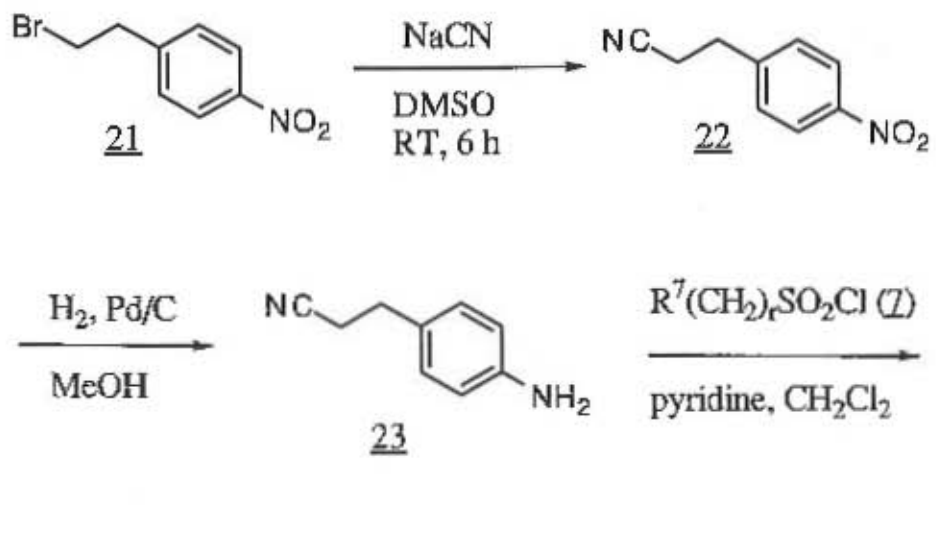
SCHEME 6



Alternatively, diamine 5 where X is $-CH_2O-$ and m is 1 is available from intermediate 19 by treatment with trifluoroacetic acid. This diamine may then be modified as illustrated in Scheme 3.

Diamines 5 and sulfonamide amines 9 where X is $-CH_2CH_2-$ and m is 1 are also readily prepared by methods described in the literature or known to those skilled in the art. For example, as shown in Scheme 7, bromo derivative 21 is treated with sodium cyanide to provide nitrile 22. The nitro group is selectively reduced by treatment with hydrogen and catalytic palladium to provide amine 23. Amine 23 is acylated with sulfonyl chloride 7 to give the corresponding sulfonamide 24. Reduction of compound 24 with cobalt chloride and sodium borohydride provides the desired amine 25.

SCHEME 7

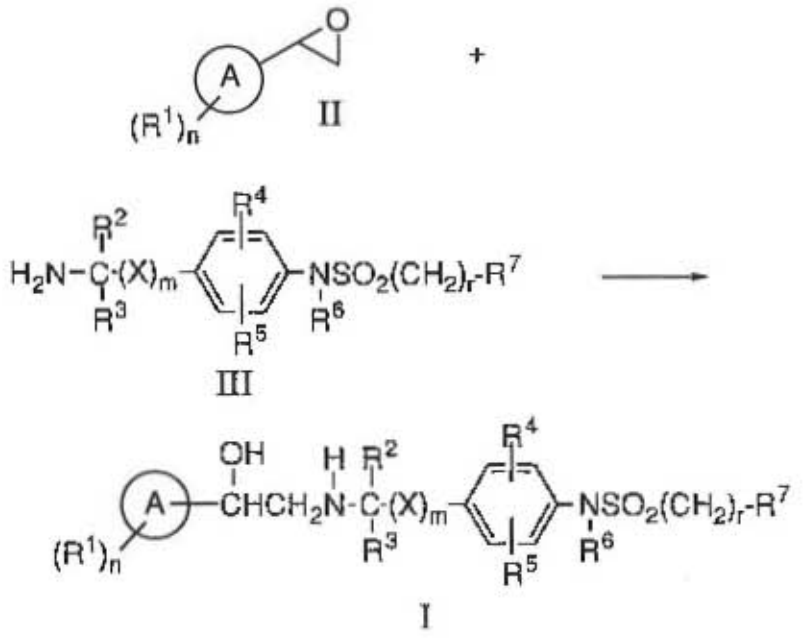


Alternatively, diamine 5 where X is -CH_2CH_2- and m is 1 is available from intermediate 23 by reduction of the nitrile group with, for example, cobalt chloride and sodium borohydride. This diamine may then be modified as illustrated in Scheme 3.

Intermediates II and III are coupled by heating them neat or as a solution in a polar solvent such as methanol, acetonitrile, tetrahydrofuran, dimethylsulfoxide or *N*-methyl pyrrolidinone for 1 to 24 hours at temperatures of 30 to 150°C to provide compounds I as shown in Scheme 8. The reaction is conveniently conducted in refluxing methanol. Alternatively, a salt of amine III, such as the

trifluoroacetate or hydrochloride salt, may be used. In these cases, a base such as sodium bicarbonate or diethylisopropylamine is added to the reaction mixture. The product is purified from unwanted side products by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel as described by W. C. Still, et. al., J. Org. Chem. 43, 2923 (1978), medium pressure liquid chromatography, or HPLC. Compounds which are purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner.

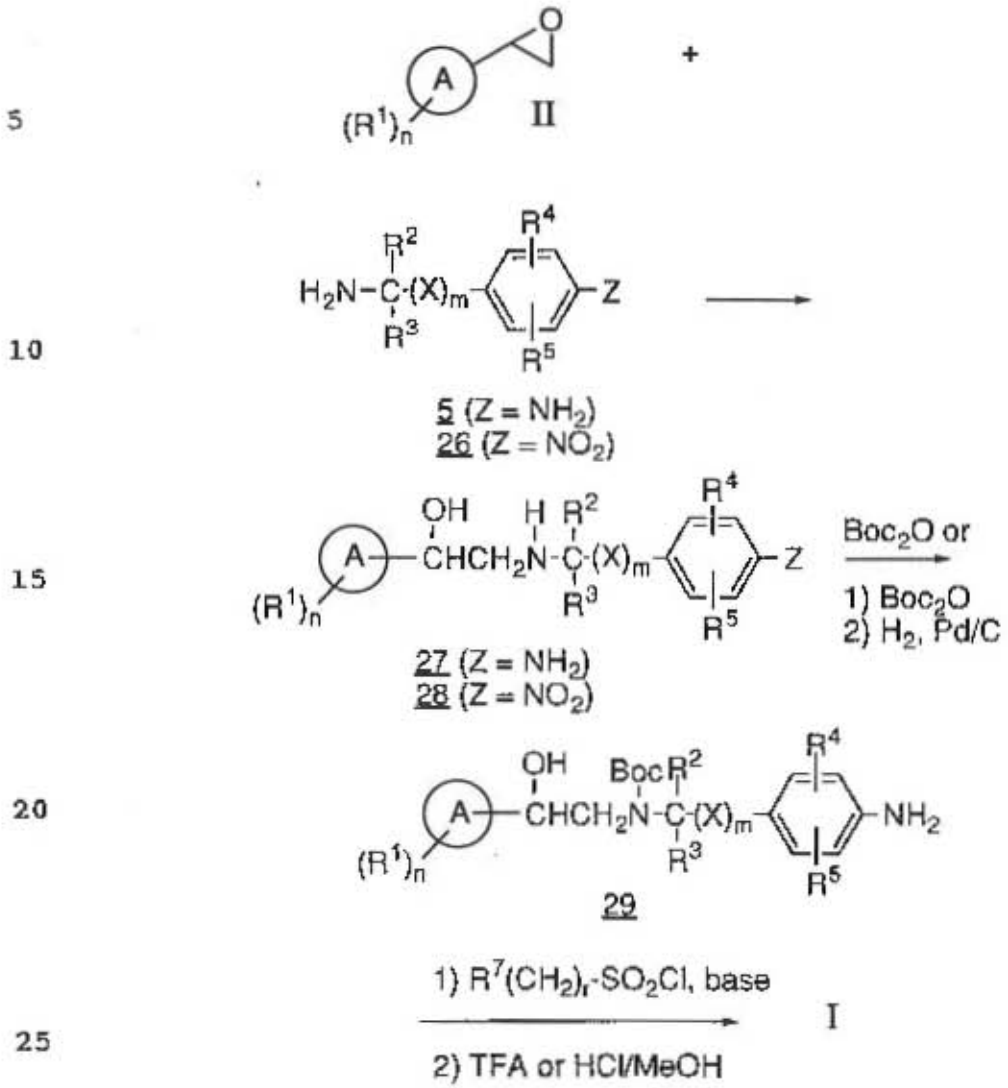
SCHEME 8



In some cases, the coupling product I from the reaction described in Scheme 8 may be further modified, for example, by the removal of protecting groups or the manipulation of substituents on, in particular, R^1 and R^7. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

An alternate method for the synthesis of compound I is illustrated in Scheme 9. Epoxide II is coupled to amine 5 as described above for coupling intermediates II and III (Scheme 8) to give aniline derivative 27. The secondary amine is selectively protected, for example, as a carbamate by treatment with di-*tert*-butyldicarbonate to provide carbamate 29. Alternatively, nitro amine 26 is used in the coupling reaction to provide 28. Following protection as described above, the nitro group is reduced, for example, by catalytic hydrogenation, to provide intermediate 29. Treatment with a sulfonyl chloride in the presence of a base such as pyridine followed by removal of the protecting group with, in the case of a *tert*-butylcarbamate, acid such as trifluoroacetic acid or methanolic hydrogen chloride, provides the sulfonamide I.

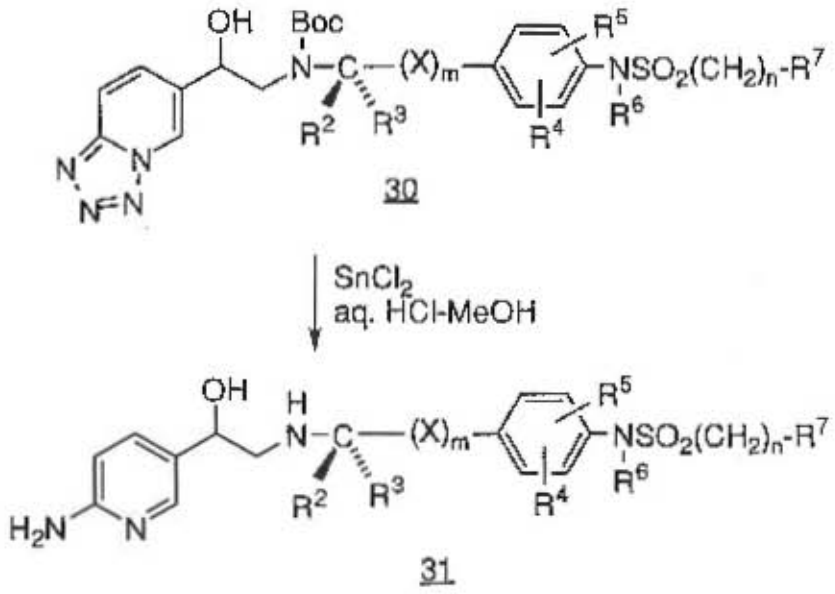
SCHEME 9



In some cases, compound I from the reaction sequence illustrated in Scheme 9 may be further modified, for example, by the removal of protecting groups or the manipulation of substituents on, in particular, R1 and R7, as described above. In addition, manipulation of substituents on any of the intermediates in the reaction sequence illustrated in Scheme 9 may occur. One such example is illustrated in Scheme 10. Compound 30, which is prepared as outlined in Scheme 9 from the corresponding epoxide, is subjected to reduction using tin(II)

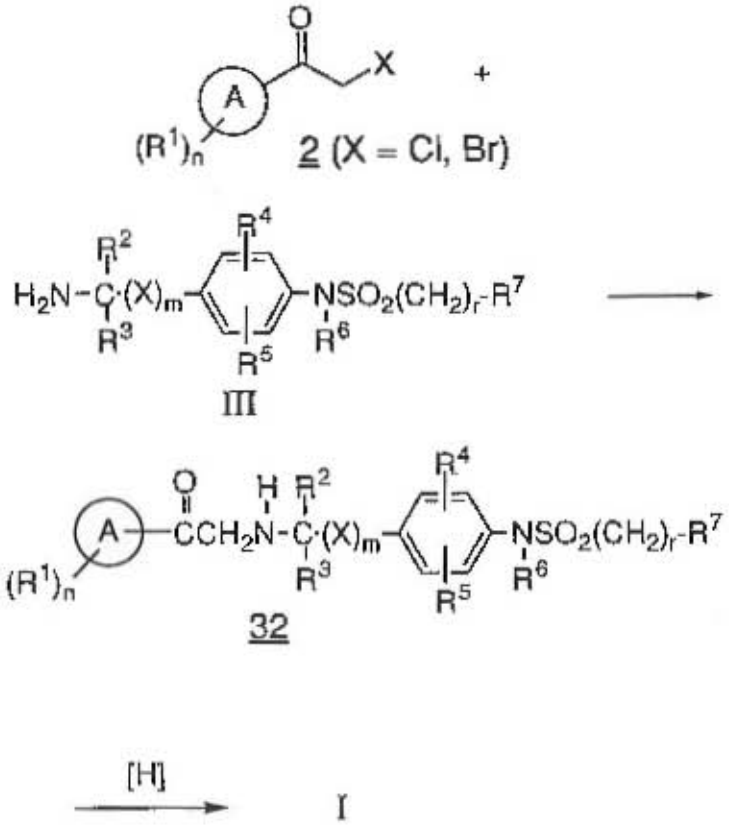
chloride to provide compound 31. Other examples of substituents on compound I which may be reduced to the corresponding amine by methods commonly known to those skilled in the art include nitro groups, nitriles, and azides.

SCHEME 10



The compounds (I) of the present invention can also be prepared from amine intermediates such as those of formula III and haloketone intermediates such as those of formula 2, as shown in Scheme 11. Amine III is alkylated with haloketone derivative 2, conveniently by treatment of a mixture of III and 2 with base such as potassium carbonate or triethylamine in a polar solvent such as acetonitrile, acetone or dimethylformamide. The resultant aminoketone 32 is reduced with, for example, sodium borohydride in methanol to give the desired aminoalcohol I.

SCHEME 11



In some cases, the product I from the reaction described in Scheme 11 may be further modified, for example, by the removal of protecting groups or the manipulation of substituents on, in particular, R^1 and R^7. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

Compounds of the general Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials of known configuration.

The instant compounds can be isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function such as a carboxy or tetrazole, can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

As previously indicated, the compounds of the present invention have valuable pharmacological properties.

The present invention also provides a compound of the general Formula I or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance.

In one aspect, the present invention provides a compound of the general Formula I or a pharmaceutically acceptable ester thereof: or a pharmaceutically acceptable salt thereof for use in the treatment of obesity in human or non-human animals.

The present invention further provides a compound of the general Formula I, or a pharmaceutically acceptable ester thereof; or pharmaceutically acceptable salt thereof, for use in the treatment of hyperglycemia (diabetes) in human or non-human animals.

The disease diabetes mellitus is characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels. The result of these defects is elevated blood glucose or hyperglycemia. Research on the treatment of diabetes has centered on attempts to normalize fasting and postprandial blood glucose levels. Treatments have included parenteral administration of exogenous insulin, oral administration of drugs and dietary therapies.

Two major forms of diabetes mellitus are now recognized. Type I diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-independent diabetes, often occurs in the face of normal, or even elevated levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type II diabetics are also obese.

In addition the compounds of the present invention lower triglyceride levels and cholesterol levels and raise high density lipoprotein levels and are therefore of use in combatting medical conditions wherein such lowering (and raising) is thought to be beneficial. Thus they may be used in the treatment of hyper-triglyceridaemia, hypercholesterolaemia and conditions of low HDL (high density lipoprotein) levels in addition to the treatment of atherosclerotic disease such as of coronary, cerebrovascular and peripheral arteries, cardiovascular disease and related conditions.

Accordingly, in another aspect the present invention provides a method of lowering triglyceride and/or cholesterol levels and/or increasing high density lipoprotein levels which comprises administering, to an animal in need thereof, a therapeutically effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof. In a further aspect the present invention provides a method of treating atherosclerosis which comprises administering, to an animal in need thereof; a therapeutically effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof. The compositions are formulated and administered in the same general manner as detailed below for treating diabetes and obesity. They may also contain other active ingredients known for use in the treatment of atherosclerosis and related conditions, for example fibrates such as clofibrate, bezafibrate and gemfibrozil; inhibitors of cholesterol biosynthesis such as HMG-CoA reductase inhibitors for example lovastatin, simvastatin and pravastatin; inhibitors of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide;

anion exchange resins for example cholestyramine, colestipol or a dialkylaminoalkyl derivatives of a cross-linKed dextran; nicotinyl alcohol, nicotinic acid or a salt thereof; vitamin E; and thyromimetics.

The compounds of the instant invention also have the effect of reducing intestinal motility and thus find utility as aiding in the treatment of various gastrointestinal disorders such as irritable bowel syndrome. It has been proposed that the motility of non-sphincteric smooth muscle contraction is mediated by activity at β_3 adrenoreceptors. The availability of a β_3 specific agonist, with little activity at β_1 and β_2 receptors will assist in the pharmacologic control of intestinal motility without concurrent cardiovascular effects. The instant compounds are administered generally as described below with dosages similar to those used for the treatment of diabetes and obesity.

It has also been found unexpectedly that the compounds which act as agonists at ß3 adrenoreceptors may be useful in the treatment of gastrointestinal disorders, especially peptic ulcerations, esophagitis, gastritis and duodenitis, (including that induced by H. pylori), intestinal ulcerations (including inflammatory bowel disease, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal ulcerations.

In addition, β_3 receptors have been indicated to have an effect on the inhibition of the release of neuropeptides in certain sensory fibers in the lung. As sensory nerves may play an important role in the neurogenic inflammation of airways, including cough, the instant specific β_3 agonists may be useful in the treatment of neurogenetic inflammation , such as asthma, with minimal effects on the cardio-pulmonary system.

β_3 adrenoreceptors are also able to produce selective antidepressant effects by stimulating the β_3 receptors in the brain and thus an additional contemplated utility of the compounds of this invention are as antidepressant agents.

The active compounds of the present invention may be orally administered as a pharmaceutical composition, for example, with an inert diluent, or with an assimilable edible carrier, or they may be

enclosed in hard or soft shell capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, which includes sublingual administration, these active compounds may be incorporated with excipients and used in the form of tablets, pills, capsules, ampules, sachets, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated.

When treating diabetes mellitus and/or hyperglycemia generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

When treating obesity, in conjunction with diabetes and/or hyperglycemia, or alone, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from 1 milligram to about 1000 milligrams per kilogram of animal body weight, preferably given in divided doses two to six times a day, or in sustained release form. For most large mammals, the total

daily dosage is from about 10 milligrams to about 10,000 milligrams, preferably from about 10 milligrams to about 500 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 70 milligrams to about 3500 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

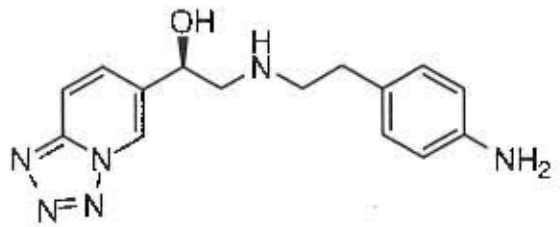
These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and

liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The following examples are provided so that the invention might be more fully understood. They should not be construed as limiting the invention in any way.

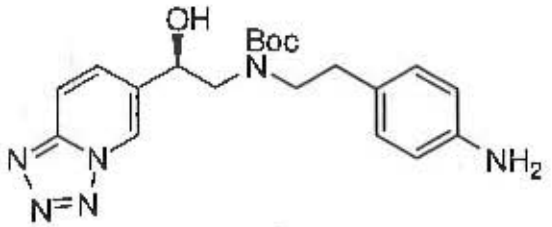
EXAMPLE 1



(R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(tetrazolo[1,5-a]pyrid-6-yl)ethylamine

A solution of 1.62 g (10 mmol) of (R)-2-(tetrazolo[1,5-a]pyrid-6-yl)oxirane (See Fisher and Wyvratt, European Patent Application 0 318 092 A2 for the synthesis of this compound.) and 4.1 g (30 mmol) of 2-(4-aminophenyl)ethylamine in 30 mL of methanol was heated at reflux for 5h. The reaction mixture was concentrated and the residue chromatographed on silica gel (2% methanol/98% methylene chloride) to give 1.69 g (56%) of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 (d, 1H, J =1.3 Hz), 8.02 (d,1 H, J = 9.2 Hz), 7.82 (dd, 1H, J = 1.3, 9.2 Hz), 6.94 (d, 2H, J = 6.3 Hz), 6.63 (d, 2H, J = 6.3 Hz), 4.91 (m, 1H), 2.82 (m, 4H), 2.67 (t, 2 H, J = 7.1Hz).

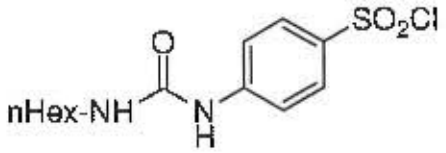
EXAMPLE 2



(R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(tetrazolo[1,5-a]pyrid-6-yl)ethylcarbamic acid 1,1-dimethylethyl ester

A solution of 1.69 g (56.7 mmol) of the amine from Example 1 and 1.23 g (56.7 mmol) of di-tert-butyl dicarbonate in 10 mL of tetrahydrofuran (THF) at 0° C was stirred for 2 h. The reaction mixture was concentrated and the residue chromatographed on silica gel (4% methanol/96% methylene chloride) to afford 2.2 g (97%) of the title compound: ^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (s, 1H), 8.05 (m, 2H), 7.85 (m, 2H), 6.93 (dd, 2H, J = 7.7, 8.3 Hz), 6.66 (d, 2H, J = 8.3 Hz), 4.99 (m, 1H), 3.49 (m, 4H), 2.70 (t, 2H, J =6.5 Hz), 1.26 (s, 9H).

EXAMPLE 3

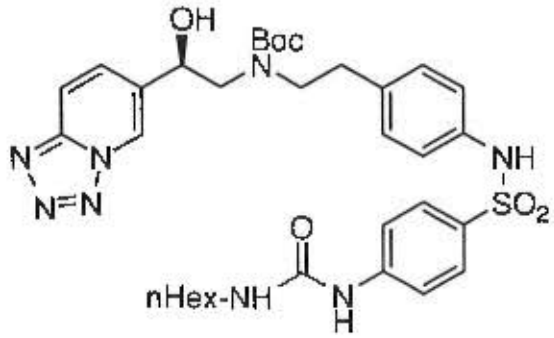


4-(Hexylaminocarbonylamino)benzenesulfonyl chloride

Hexylamine, 12.15 ml (9.2 mmol), was added dropwise to a solution of 10 ml (9.2 mmol) of phenyl isocyanate in THF (150 ml) at 0°C, and stirring was continued for 1 h. The solvent was removed *in vacuo*, and the resultant hexyl phenyl urea was used without further purification.

A 6-g (2.7 mmol) portion was added over 20 min to chlorosulfonic acid at 0°C, followed by heating at 60°C for 2h. After cooling, the mixture was added to ice/water (100ml) and the aqueous phase extracted with EtOAc (3x100 ml). The combined organic phase was washed with brine (50 ml), dried with $MgSO_4$, concentrated, and purified by flash chromatography (silica gel, 75% hexane/ 25% ethyl acetate) to give 6 g (70%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 2H, J = 9.6 Hz), 7.54 (d, 2H, J = 9.6 Hz), 6.79 (br.s, 1H), 4.71(br. s, 1H), 3.23 (t, 2H, J = 8 Hz), 1.54-1.44 (m, 2H), 1.33-1.20 (m, 6H), 0.91-0.79 (m, 3H).

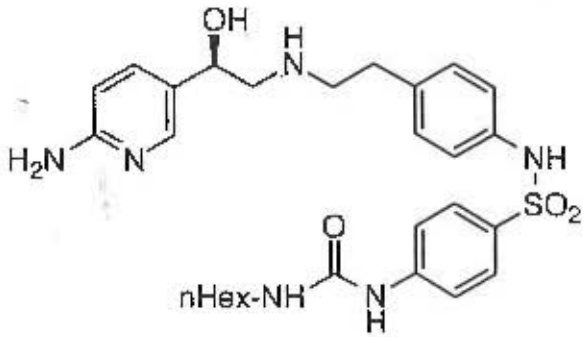
EXAMPLE 4



(R)-N-[4-[2-[N-(1,1-dimethylethoxycarbonyl)-N-[2-hydroxy-2-(tetrazolo[1,5-a]pyrid-6-yl)]ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

To a stirred solution of 0.200 g (0.502 mmol) of the Boc-compound from Example 2 in 3 mL of methylene chloride was added 80 mg (1.00 mmol) of pyridine followed by 0.16 g (0.75 mmol) of the sulfonyl chloride from Example 3. After being stirred for 5h, the reaction mixture was concentrated and the residue chromatographed on silica gel (10% methanol/90% methylene chloride) to afford 0.303 g (88%) of the title compound: ^{1}H NMR (400 Hz, CD_3OD) δ 8.95 (s, 1H), 8.0-8.08 (m, 1H), 7.75-7.87 (m, 1H), 7.40-7.62 (m, 4H), 7.00 (m, 4H), 4.95 (m, 2H), 3.47 (m, 2H), 3.15 (m, 2H), 2.75 (m, 2H), 1.52 (t, 2H, J = 6.0 Hz), 1.33 (m, 8H), 1.21 (s, 9H), 0.90 (t, 3H, J = 6.0 Hz).

EXAMPLE 5

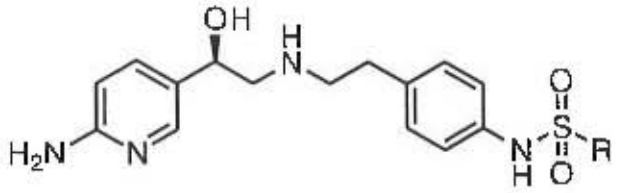


(R)-N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

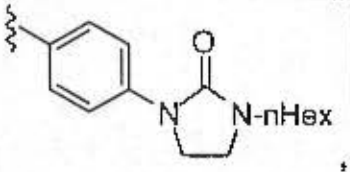
A mixture of 0.302 g (0.44 mmol) of the tetrazine from Example 4, 0.20 g (0.88mol) of tin(II) chloride dihydrate and 0.3 ml of concentrated aqueous hydrochloric acid in 2 mL of methanol was heated at reflux for 5 h. The reaction mixture was concentrated and the residue purified by reverse-phase MPLC (C8, 47%methanol/53 0.1% trifluoroacetic acid buffer) to give 0.32 g (78%) of the title compound as its bistrifluoroacetate salt: ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (dd, 1H, J = 2.0, 9.2 Hz), 7.86 (d, 1H, J = 2.0 Hz), 7.59 (d, 2H, J = 8.8 Hz), 7.43 (d, 2H, J = 8.8 Hz), 7.14 (d, 2H, J = 8.4 Hz), 7.07 (d, 2H, J = 8.4 Hz), 7.03 (d, 1H, J = 9.2 Hz), 4.92 (m, 1H), 3.23 (m, 2H), 3.15 (m, 2H), 2.93 (m, 2H, 4.0 Hz), 1.49 (t, 2H, J = 6.0Hz), 1.32 (m, 8H), 0.91 (t, 3H, J = 6.0 Hz); CI MS *m/z* 555(M+1).

Following the procedures outlined for Examples 1-5, the compounds listed in Table 1 were prepared.

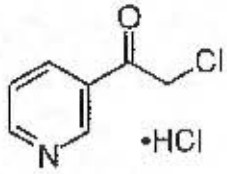
TABLE 1



Example	R	Selected ^{1}H NMR (CD_3OD) Data
6	Ph, trifluoroacetate salt	7.74 (m,2H), 7.53 (m, 1H), 7.45 (m, 2H).
7	2-naphthyl, trifluoroacetate salt	7.93 (m, 4H), 7.75 (d, 1H, J = 1.7 Hz), 7.61 (m, 2H)
8	3-quinolinyl, trifluoroacetate salt	9.00 (d, 1H, J = 2.3 Hz), 8.06 (m, 2H), 7.94 (m, 2H), 7.72 (t, 1H, J = 7.2 Hz)

9	1,2-benzisoxazol-5-yl, trifluoroacetate salt	9.02 (s, 1H), 8.30 (d, 1H, J = 1.3 Hz), 7.90 (m, 1H), 7.77 (m, 1H)
10	4-iodophenyl, trifluoroacetate salt	7.83 (d, 2H, J = 8.6 Hz), 7.46 (d, 2H, J = 8.6 Hz)
11	4-[(N-hexyl,N-methyl-aminocarbonyl)amino]-phenyl, trifluoroacetate salt	7.62 (d, 2H, J = 4.6 Hz), 7.48 (d, 2H, J = 4.6Hz), 2.99 (s, 3H)
12	4-[(N,N-dimethyl-aminocarbonyl)amino]-phenyl, trifluoroacetate salt	3.0 (s, 6H)
13	 trifluoroacetate salt	3.88-3.83 (m, 2H), 3.57-3.50 (m, 2H), 2.89-2.95 (m, 2H), 1.61-1.52 (m, 2H), 1.37-1.30 (m, 6H), and 0.93-0.88 (m,3H)

EXAMPLE 14

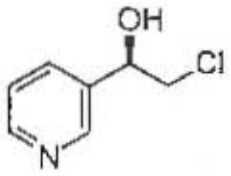


3-(2-Chloroacetyl)pyridine hydrochloride

To a solution of 12 g (11 mL, 100 mmol) of 3-acetylpyridine in 100 mL of ethyl ether was added 100 mL of 1 M ethereal hydrogen chloride. The resultant precipitate was filtered and 15.0 g (95.2 mmol) was collected and placed in a 500-mL round bottom flask equipped with a magnetic stir bar. To this was added 95 mL of 1 M hydrogen chloride in acetic acid. After the mixture was stirred until all the solid had dissolved, 12.7 g (95.2 mmol) of N-chlorosuccinimide (NCS) was added in one portion. The solution turned yellow and the

NCS gradually dissolved. After 4 h, a white precipitate had formed. The mixture was allowed to stir for 2.5 days. It was then filtered. The solid collected was washed with 10 mL of acetic acid and 200 mL of ethyl ether to give 15.2 g (83%) of the title compound as a white solid: ^{1}H NMR (200 MHz, d_6-DMSO) δ 9.22 (t, 1H, J = 1 Hz), 8.29 (dd, 1H, J = 1.6, 5.1 Hz), 8.55 (td, 1H, J = 2, 8.1 Hz), 7.82 (ddd, 1H, J = 0.8, 5.1, 8.1 Hz), 5.27 (s, 2H).

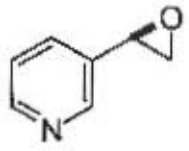
EXAMPLE 15



(R)-α-Chloromethyl-3-pyridinemethanol

To a stirred solution of 3.67 g (11.5 mmol) of (-)-B-chlorodiisopinocampheylborane [(-)-DIP-Cl] in 11 mL of THF at -25 °C was added a slurry of 1.00 g (5.21 mmol) of the product from Example 14 in 5 mL of THF via a cannula. Following the addition of 0.80 mL (5.79 mmol) of triethylamine, the reaction mixture was stirred at -25 °C for 4 days. To the mixture was added 10 mL of water which was then allowed to warm to room temperature. To the mixture was added 20 mL of ethyl acetate and the organic phase separated. The aqueous phase was neutralized with saturated $NaHCO_3$ solution then extracted six times with ethyl acetate. The combined organic phase was concentrated in vacuo to afford a yellow oil. Flash chromatography (silica gel, 75 - 100% ethyl acetate-hexanes) afforded 561 mg (68%) of the title compound as a pale yellow oil: ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (d, 1H, J = 1.8 Hz), 8.46 (dd, 1H, J = 4.9, 1.5 Hz), 7.90 (d, 1H, J = 7.9 Hz), 7.44 (dd, 1H, J = 7.9, 4.9 Hz), 4.93 (m, 1H), 3.75 (m, 2H).

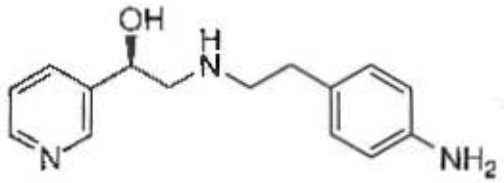
EXAMPLE 16



(R)-(Pyrid-3-yl)oxirane

To a solution of 557 mg (3.55 mmol) of the product from Example 15 in 16 mL of acetone was added 1.80 g of potassium carbononate. The mixture was heated at reflux for 20 h then cooled to room temperature. The mixture was filtered and the filtrate evaporated in vacuo. Flash chromatography (silica gel, 2% methanol-methylene chloride) afforded 262 mg (61%) of the title compound as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.54 (m, 2H), 7.52 (m, 1H), 7.24 (m, 1H), 3.86 (dd, 1H, J = 4.0, 2.5 Hz), 3.17 (dd, 1H, J = 5.4, 4.0 Hz), 2.80 (dd, 1H, J = 5.4, 2.5 Hz).

EXAMPLE 17

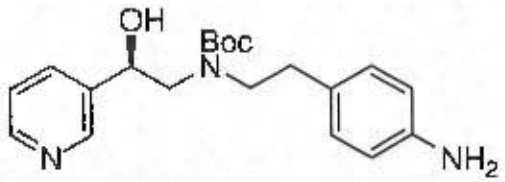


(R)-N-[2-[4-(Aminophenyl)lethyl]-2-hydroxy-2-(pyrid-3-yl)ethylamine

To a stirred solution of 377 mg (2.44 mmol) of 4-aminophenethylamine in 10 mL of methanol was added a solution of 300 mg (2.48 mmol) of the product from Example 16 in 15 mL of methanol. The mixture was heated at reflux for 16 h then cooled to room temperature. The methanol was removed in vacuo and the residue chromatographed (silica gel, 6 - 8% methanol, 1% ammonia-methylene chloride) to afford 101 mg (16%) of the title compound together with 279 mg of a mixture that was rechromatographed (5% methanol, 1% ammonia-methylene chloride) to give a further 54 mg (9%) of the title

compound as an off-white solid: ^{1}H NMR (500 MHz, CD_3OD) δ 8.52 (d, 1H, J = 1.8 Hz), 8.43 (dd, 1H, J = 4.8, 1.4 Hz), 7.81 (m, 1H), 7.40 (m, 1H), 6.95 (d, 2H, J = 8.3 Hz), 6.67 (d, 2H, J = 8.3 Hz), 4.81 (m, 1H), 2.90-2.65 (m, 6H).

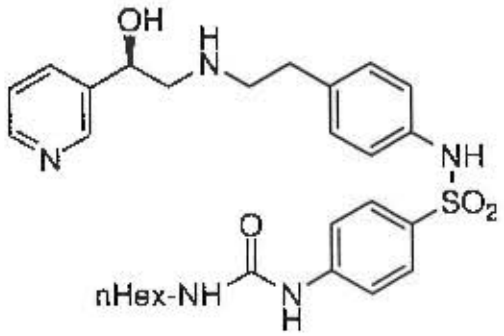
EXAMPLE 18



(R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(pyrid-3-yl)ethylcarbamic acid 1,1-dimethylethyl ester

A solution of 386 mg (1.77 mmol) of di-tert-butyl dicarbonate in 3.5 mL of THF was added, via a cannula, to a stirred slurry of 456 mg (1.77 mmol) of the product from Example 17 in 3.6 mL of THF cooled to 0 °C. The yellow solution was stirred at 0 °C for 3 h, then the THF was removed in vacuo. Flash chromatography (silica gel, 10% methanol, 1% ammonia-methylene chloride) afforded 549 mg (87%) of the title compound as an off white solid: ^{1}H NMR (500 MHz, CD_3OD, mixture of rotomers) δ 8.45 (m, 2H), 7.83 (d, 0.6H, J = 7.4 Hz), 7.78 (d, 0.4H, J = 6.9 Hz), 7.41 (m, 1H), 6.94 (d, 0.8H, J = 8.0 Hz), 6.89 (d, 1.2H, J = 7.8 Hz), 6.66 (d, 2H, J = 7.3 Hz), 4.89 (m, 1H), 3.42-3.21 (m, 4H), 2.67 (m, 2H), 1.39 (s, 5.4H), 1.36 (s, 3.6H).

EXAMPLE 19



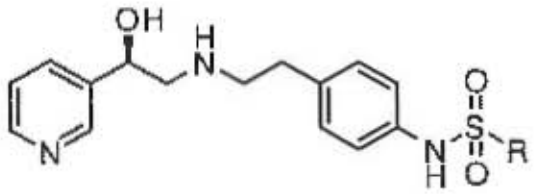
(R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

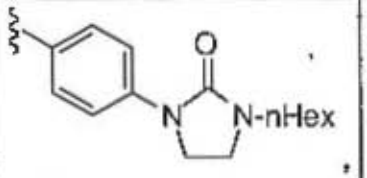
To a solution of 302 mg (0.845 mmol) of the product from Example 18 and 137 µL (1.69 mmol) of pyridine in 10 mL of methylene chloride was added 296 mg (0.928 mmol) of 4-(hexylaminocarbonylamino)benzenesulfonyl chloride from Example 3. The reaction was stirred for 12 h then the solvent removed in vacuo. Flash chromatography (silica gel, 6% methanol, 0.5% ammonia-methylene chloride) afforded 468 mg (87%) of the BOC-protected title compound.

A solution of 468 mg (0.731 mmol) of BOC-protected title compound in 5 mL of methylene chloride and 5 mL of trifluoroacetic acid was stirred for 30 min then the volatile components removed in vacuo. The residue was azeotroped twice with 10% methanol/toluene, twice with methanol, then dried in vacuo to give 521 mg (93%) of the title compound as its trifluroracetate salt: ^{1}H NMR (400 MHz, CD3OD) δ 8.88 (s, 1H), 8.79 (d, 1H, J = 5.5 Hz), 8.53 (d, 1H, J = 8.2 Hz), 7.99 (m, 1H), 7.59 (dd, 2H, J = 6.9, 1.9 Hz), 7.43 (dd, 2H, J = 6.9, 1.9 Hz), 7.15 (dd, 2H, J = 8.6, 2.1 Hz), 7.08 (dd, 2H, J = 8.6, 2.1 Hz); 5.23 (m, 1H), 3.40-3.10 (m, 6H), 2.94 (m, 2H), 1.49 (m, 2H), 1.32 (m, 6H), 0.90 (m, 2H).

Following the procedures outlined for Examples 14-19, the compounds listed in Table 2 were prepared.

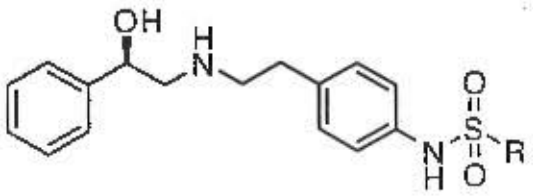
TABLE 2



Example	R	Selected ^{1}H NMR (CD_3OD) Data
20	4-isopropylphenyl	7.64 (d, 2H, J = 8.0 Hz), 7.33 (d, 2H, J = 8.0 Hz), 4.80 (m, 1H), 2.95-2.70 (m, 7H), 1.22 (d, 6H, J = 6.7 Hz)
21	4-iodophenyl, trifluoroacetate salt	7.84 (d, 2H, J = 8.6 Hz), 7.47 (d, 2H, J = 8.6 Hz), 5.19 (dd, 1H, J = 10.1, 3.0 Hz), 3.40-3.20 (m, 4H), 2.96 (m, 2H)
22	2-naphthyl	8.28 (s, 1H), 7.94 (m, 3H), 7.72 (dd, 1H, J = 8.7, 1.9 Hz), 7.60 (m, 2H)
23	3-quinolinyl, trifluoroacetate salt	9.01 (d, 1H, J = 2.3 Hz), 8.76 (d, 1H, 1.8 Hz), 8.08 (d, 1H, J = 8.7 Hz), 8.04 (d, 1H, J = 8.0 Hz), 7.93 (m, 1H), 7.73 (m, 1H)
24	4-[(N-hexyl,N-methyl-aminocarbonyl)amino]-phenyl, trifluoroacetate salt	5.12 (d, 1H, J = 8.7 Hz), 3.40-3.10 (m, 6H), 2.99 (s, 3H), 2.95 (m, 2H), 1.56 (m, 2H), 1.31 (m, 6H), 0.88 (m, 3H)
25	 trifluoroacetate salt	5.15 (m, 1H), 3.85 (m, 2H), 3.53 (m, 2H), 3.40-3.15 (m, 6H), 2.94 (m, 2H), 1.55 (m, 2H), 1.32 (m, 6H), 0.89 (m, 3H).

Starting with commercially available (R)-styrene epoxide and following the procedures outlined for Examples 17-19, the compounds listed in Table 3 were prepared.

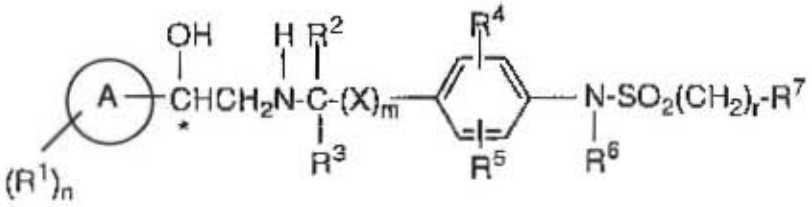
TABLE 3



Example	R	Selected 1H NMR (CD3OD) Data
26	4-iodophenyl, trifluoroacetate salt	7.84 (d, 2H, J = 8.6 Hz), 7.45 (d, 2H, J = 8.5 Hz)
27	2-naphthyl, trifluoroacetate salt	8.31 (s, 1H), 7.96-7.90 (m, 3H), 7.74 (dd, 1H, J = 1.8, 8.7 Hz), 7.63 (t, 1H), 7.58 (t, 1H)
28	3-quinolinyl, trifluoroacetate salt	9.01 (d, 1H, J = 2.2 Hz), 8.75 (d, 1H, J = 2.1 Hz), 8.07 (d, 1H, J = 8.4 Hz), 8.03 (d, 1H, J = 8.3 Hz), 7.92 (t, 1H, J = 7.0 Hz), 7.72 (t, 1H, J = 7.1 Hz)

WHAT IS CLAIMED IS:

1. A compound having the formula I:



I

where

n is 0 to 5;

m is 0 or 1;

r is 0 to 3;

A is ~~phenyl,~~ a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, ~~a benzene ring fused to a C3-C8 cycloalkyl ring,~~ a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, or a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen;

R1 is hydroxy, oxo, halogen, cyano, NR^8R^8, SR^8 trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, SO_2R^9, $OCOR^9$, NR^8COR^9, COR^9, $NR^8SO_2R^9$, $NR^8CO_2R^8$, or C_1-C_6 alkyl substituted by hydroxy, halogen, cyano, NR^8R^8, SR^8, trifluoromethyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, phenyl, NR^8COR^9, COR^9, SO_2R^9, $OCOR^9$, $NR^8SO_2R^9$ or $NR^8CO_2R^8$;

R^2 and R^3 are independently hydrogen, C_1-C_6 alkyl or C_1-C_6 alkyl with 1 to 3 substituents selected from hydroxy, C_1-C_6 alkoxy, and halogen;

X is $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$ or $-CH_2O-$;

R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, halogen, NHR^8, OR^8, SO_2R^9 or $NHSO_2R^9$;

R^6 is hydrogen or C_1-C_6 alkyl;

R^7 is $Z-(R^{1a})_n$;

R^{1a} is R^1, C_3-C_8 cycloalkyl, phenyl, or 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to three groups independently selected from oxo, R^8 and NR^8R^8;

Z is phenyl, naphthyl, a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, a benzene ring fused to a C_3-C_8 cycloalkyl ring, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, or a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen;

R^8 is hydrogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, Z optionally having 1 to 3 substituents selected from halogen, C_1-C_6 alkyl and C_1-C_6 alkoxy, or C_1-C_{10} alkyl having 1 to 3 substituents selected from hydroxy, halogen, CO_2H, CO_2-C_1-C_6 alkyl, SO_2-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, and Z optionally substituted by from 1 to 3 of halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

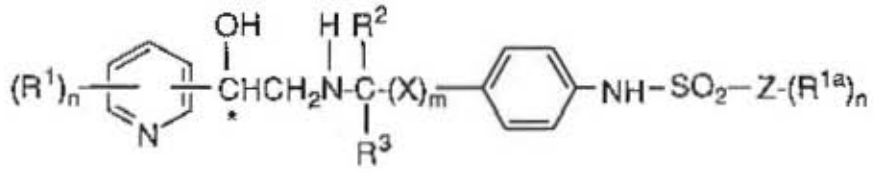
R^9 is R^8 or NR^8R^8; or

a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 where

n is 0 to 3;
m is 1;
r is 0 to 2;
A is ~~phenyl, or~~ a 5- or 6-membered heterocyclic ring with from 1 to 4 nitrogen atoms;
X is $-CH_2-$;
R^1 is hydroxy, halogen, cyano, trifluoromethyl, NR^8R^8, $NR^8SO_2R^9$, NR^8COR^9, $NR^8CO_2R^8$, C_1-C_6 alkyl optionally substituted by hydroxy;
R^2, R^3 are independently hydrogen or methyl;
R^4, R^5 and R^6 are each hydrogen; and
Z and R^{1a} are as defined in Claim 1.

3. A compound of Claim 1 having the formula Ia:



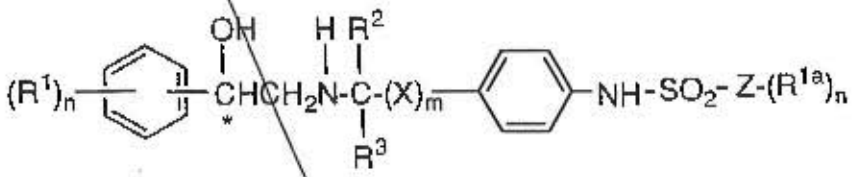
Ia

wherein
n is 0 to 3;
m is 1
R^1 is halogen or NR^8R^8;
R^{1a} is halogen, C_1-C_6 alkyl, NR^8R^8, NR^8COR^9, $NR^8CO_2R^8$, $OCOR^9$, or 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to three groups independently selected from oxo, R^8 and NR^8R^8;
Z is phenyl, naphthyl or benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen;
X is $-CH_2-$; and

R^2, R^3 are independently hydrogen or methyl.

4. A compound of Claim 3 wherein R^2 and R^3 are each hydrogen.

5. A compound of Claim 1 having the formula Ib:



Ib

wherein

n is 0 to 3;

m is 1

R^1 is hydroxy, NR^8R^8 or halogen;

R^{1a} is halogen, C_1-C_6 alkyl, NR^8R^8, NR^8COR^9, $NR^8CO_2R^8$, $OCOR^9$, or 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to three groups independently selected from oxo, R^8 and NR^8R^8;

Z is phenyl, naphthyl or benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen;

X is $-CH_2-$; and

R^2 and R^3 are independently hydrogen or methyl.

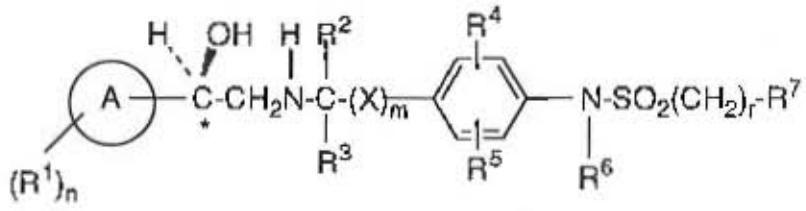
6. A compound of Claim 5 wherein R^2 and R^3 are each hydrogen.

7. A compound of Claim 1 selected from the group consisting of:

N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide;
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-5-benzisoxazolesulfonamide;
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(dimethylaminocarbonyl)amino]benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(4-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-isopropylbenzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide;
~~N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-4-iodobenzenesulfonamide;~~

N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-2-naphthalenesulfonamide, and
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-3-quinolinesulfonamide.

8. A compound of Claim 1 with the structural formula Ic:



Ic

where n, m, r, A, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as defined in Claim 1.

9. A method for the treatment of diabetes which comprises administering to a diabetic patient an effective amount of a compound of Claim 1.

10. A method for the treatment of obesity which comprises administering to an obese patient an effective amount of a compound of Claim 1.

11. A method for lowering triglyceride levels and cholesterol levels of raising high density lipoprotein levels which comprises administering to a patient needing lower triglyceride and cholesterol levels or higher high density lipoprotein levels an effective amount of a compound of Claim 1.

12. A method for decreasing gut motility which comprises administering to a patient in need of decreased gut motility, an effective amount of a compound of Claim 1.

13. A method for reducing neurogenic inflammation of airways which comprises administering to a patient in need of reduced neurogenic inflammation, an effective amount of a compound of Claim 1.

14. A method for reducing depression which comprises administering to a depressed patient an effective amount of a compound of Claim 1.

15. A method for treating gastrointestinal disorders which comprises administering to a patient with gastrointestinal disorders an effective amount of a compound of Claim 1.

16. A composition for the treatment of diabetes or obesity or for lowering triglyceride or cholesterol levels or increasing high density lipoprotein levels or for decreasing gut motility or for reducing neurogenic inflammation or for treating depression or for treating gastrointestinal disorders which comprises an inert carrier and an effective amount of a compound of Claim 1.

TITLE OF THE INVENTION

SUBSTITUTED SULFONAMIDES AS SELECTIVE β3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

ABSTRACT OF THE INVENTION

Substituted sulfonamides are selective β3 adrenergic receptor agonists with very little β1 and β2 adrenergic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to decrease gut motility. In addition, the compounds can be used to reduced neurogenic inflammation or as antidepressant agents. The compounds are prepared by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for increasing gut motility are also disclosed.


MAIL ROOM
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PATENT Case No. 19203

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
DECLARATION AND POWER OF ATTORNEY

Commissioner of Patents and Trademarks
Washington, D.C. 20231

As a below-named inventor, I hereby declare that I believe I am the:

☐ original, first and sole inventor; or

☒ an original, first and joint inventor along with the other inventors listed below, of the subject matter which is claimed and for which a patent is sought on the invention entitled

SUBSTITUTED SULFONAMIDES AS SELECTIVE BETA 3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

the specification of which ☒ is attached hereto;

☐ was filed on _____ as Application Serial No. _____ and was amended through _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended as indicated above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate for the same invention having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

				Priority Claimed	
				☐	☐
Country	Number	Date Filed	Attorney Docket	Yes	No
				☐	☐
Country	Number	Date Filed	Attorney Docket	Yes	No

DECLARATION AND POWER OF ATTORNEY

PATENT Case NO. 19203

Prior United States Filing

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date(s) of the prior application(s) and the national or PCT international filing date of this application:

Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket

And I hereby appoint

MOLLIE M. YANG Reg. No. 32,718

DAVID L. ROSE Reg. No. 26,332

Reg. No.

respectively and individually, as my attorneys or agents with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Please address all communications to:

Mollie M. Yang
Patent Department
Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907

Telephone No. (908) 594- 6343

DECLARATION AND POWER OF ATTORNEY

PATENT Case NO. 19203

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1.00

Full name of sole or joint inventor	Michael H. Fisher
Inventor's Signature	Michael H Fisher
Date	April 26, 1994
Residence	Ringoes, New Jersey 08551 NJ
Citizenship	United States
Post Office Address (if different from above)	P.O. Box 2000 Rahway, New Jersey 07065-0907

3.00

Full name of joint inventor	Elizabeth M. Naylor
Inventor's Signature	Elizabeth M. Naylor
Date	April 25 1994
Residence	Scotch Plains, New Jersey 07076 NJ
Citizenship	United Kingdom
Post Office Address (if different from above)	P.O. Box 2000 Rahway, New Jersey 07065-0907

2.00

Full name of joint inventor	Dong Ok
Inventor's Signature	Dong Ok
Date	April 26, 1994
Residence	Edison, New Jersey 08820 NJ
Citizenship	United States
Post Office Address (if different from above)	P.O. Box 2000 Rahway, New Jersey 07065-0907

4.00

Full name of joint inventor	Ann E. Weber
Inventor's Signature	Ann E Weber
Date	April 25, 1994
Residence	Scotch Plains, New Jersey 07076 NJ
Citizenship	United States
Post Office Address (if different from above)	P.O. Box 2000 Rahway, New Jersey 07065-0907

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

08/233,166

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/233,166	04/26/94	FISHER	M 19209

EXAMINER
NORTHINGTON DAVIS, J

12M2/0805

MOLLIE M. YANG
PATENT DEPT.
MERCK & CO., INC.
P.O. BOX 2000
RAHWAY, NJ 07065-0907

ART UNIT	PAPER NUMBER
1203	2

DATE MAILED: 08/05/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-16 are pending in the application.
   Of the above, claims 5 and 6 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-4 and 7-16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-93)

1. This application contains claims directed to the following patentably distinct species of the claimed invention: A and R^7.

The radicals within the definition of A and R^7 are diverse in scope. A prior art reference which anticipates one member of A or R^7 such as phenyl under 35 USC 102 would not render obvious another member such as pyridinyl under 35 USC 103. Accordingly, the radicals are independent and patentably distinct.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 1 is generic.

Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. M.P.E.P. § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

2. During a telephone conversation with Mollie Yang on July 20, 1994 a provisional election was made with traverse to prosecute the invention of Example 25, claims 1-4 and 7-16 . Affirmation of this election must be made by applicant in responding to this Office action. Claims 5 and 6 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

4. Claims 1-4 and 7-16 are Markush claims which are generic to the elected invention. These Markush claims lack unity of invention for the reasons outlined above. Accordingly, the Markush type claim will be examined fully with respect to the elected species and further to the extent

necessary to determine patentability. See MPEP 803.02.

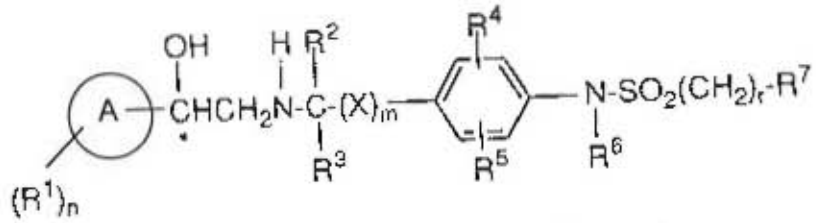
5. Claims 1-4 and 7-16 are rejected on the grounds that the claims are drawn to an improper Markush group. In re Harnish, 206 USPQ 300, states that a unity of invention exists where compounds included within a Markush group(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility. In the instant case, the claimed subject matter does not share a substantial structural feature disclosed as being essential to that utility.

The requirement for a proper Markush claim is that it include only substances that in their physical, chemical and physiological characteristics are functionally equivalent. The members of the instant Markush groups possess widely different, physical and chemical properties. The compounds are not considered functionally equivalent and are so diverse that they demonstrate dissimilar and unrelated properties. The mere fact that there is structural similarity in pharmaceutical agents is not in itself reason to render all the embodiments functionally equivalent.

The improper Markush groups are A and R^7.

6. The examined subject matter is as follows:

A compound having the formula I:



I

where A is pyridinyl;

R^7 is Z-(R^{1a})n;

R^{1a} is R^1, C_3-C_8 cycloalkyl, phenyl;

Z is phenyl, naphthyl;

The radicals not recited above are as defined in claim 1.

Amending the claims to the examined subject matter would overcome the improper Markush rejection.

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how the make the claimed invention.

The phrases "A or Z is a 5 or 6- membered heterocyclic ring with form 1 to 4 heteroatoms..sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring"and "R^{1a} is 5 or 6-membered heterocycle with form 1 to 3 heteroatoms...groups independently selected form oxo" appear at claim 1. A hypothetical compound can be embraced by the claim 1 definition, for instance, if A is pyridinyl, Z is benzene fused to a pyridinyl, R^{1a} is pyridinyl and n is 5. The specification does not adequately teach how to prepare such a bulky compound. Undue experimentation would be involved to prepare such a compound. Thus the Examiner concludes that the specification fails to teach how to prepare the claimed compounds.

8. Claims 1- 4 and 7-16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

9. The prior art references are cited to show the state of the art . The references do not anticipate nor render obvious the examined subject matter.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zinna N. Davis whose telephone number is (703) 308-4699.

A facsimile center has been established in Group 1200, room 3C10. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine is (703) 308-4556 or 305-3592.

DAVIS:tcj
July 27, 1994

C. Warren Ivy
Supervisory Patent Examiner
Group 120

TO SEPARATE, HOLD AT TOP AND BOTTOM EDGES, SNAP–APART AND DISCARD CARBON

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

NOTICE OF REFERENCES CITED

SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
08/~~233~~,166	1203	2

APPLICANT(S)
Fisher et al.

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A	3,452,037	6-24-69	Santilli	514	507	
	B	4,396,627	8-2-83	Ainsworth et al.	424	309	
	C	4,478,849	10-23-84	Ainsworth et al.	424	285	
	D	4,999,377	3-12-91	Caulkett et al.	514	507	
	E	5,017,619	5-21-91	Alig et al	514	523	
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R

S

T

U

EXAMINER	DATE
Z. Dawson	7-20-94

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

PATENT

Sheet 1 of 1

FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
19203	08/233,166
APPLICANT(S)	
MICHAEL H. FISHER, ET AL	
FILING DATE	GROUP ART UNIT
Apr 26, 1994	1203

94 AUG -1 GROUP 120

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	3,816,516	6/11/74	D.A. COX, ET AL	546	344	
	4,000,193	12/28/76	L.H.C. LUNTS, ET AL	546	344	
	~~4,396,627~~	~~8/2/83~~	~~A.T. AINSWORTH, ET AL~~			
	~~4,478,849~~	~~10/23/84~~	~~A.T. AINSWORTH, ET AL~~			
	~~4,999,377~~	~~3/12/91~~	~~P.W.R. CAULKETT, ET AL~~			
	~~5,017,619~~	~~5/21/91~~	~~L. ALIG, ET AL~~			
	5,153,210	10/6/92	A.T. AINSWORTH, ET AL	546	344	

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	0, 068,669	1/6/83	EPO	546	344		
	0,427,480	5/15/91	EPO	546	344		
	0,455,006	11/6/91	EPO	546	344		
	1,565,080	4/16/80	GREAT BRITAIN	546	344		
	1,108,577	4/3/68	GREAT BRITAIN	546	344		

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	1	A.A. Larsen, et al, Journal Medicinal Chemistry, Vol. 10, 3 pg. 462-472

EXAMINER [signature] DATE CONSIDERED 1-12-95

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.

26
12x
7-27-94
Worthington

PATENT
Case No. 19203

Opp185
3
8/12/94
SW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: MICHAEL H. FISHER, ET AL

MAIL ROOM
JUL 29 1994
PAT. & TRADEMARK OFF.

Serial No. 08/233,166
Filed: April 26, 1994
For: SUBSTITUTED SULFONAMIDES AS SELECTIVE BETA3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

Art Unit: 1205
Examiner: Z. DAVIS

94 AUG -1 AM 9:22
GROUP: 120

The Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR 1.97

Sir:

1. Applicant(s) submit(s) on the attached PTO-1449 herewith a list of patents, publications or other information of which they are aware, which they believe may be pertinent to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. 1.56. This Information Disclosure Statement is not an admission that any patent, publication or other information referred to herein is "prior art" for this invention unless specifically designated as such.

2. In accordance with 37 C.F.R. 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made.

3. If the captioned case is a continuing application of an earlier filed parent application, the Examiner is respectfully requested to refer to any art cited to the earlier filed parent application. If this is inconvenient, additional copies will be submitted upon request.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date appearing below.

MERCK & CO., INC.

By Kelly Bogdansky Date July 26, 1994

REV.3/18/93

PATENT
Case No. 19203

INFORMATION DISCLOSURE STATEMENT

4. Copies of the following references listed on PTO-1449 are not enclosed because they have been submitted in a related application as follows:

	RELATED APPLICATION		
REFERENCE	SN	FILING DATE	MERCK CASE

94 AUG -1 AM 9:22
GROUP: 120

5. In accordance with 37 C.F.R. 1.97, (check one)

☑ the attached information is filed within three months of the filing date of the captioned case.

☐ the undersigned certifies that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Statement.

☐ the undersigned certifies that no item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application or, to the knowledge of the person signing the certification after making reasonable inquiry, was known to any individual designated under 37 C.F.R. 1.56(c) more than three months prior to the filing of the statement.

Respectfully submitted,

By: MOLLIE M. YANG
Attorney For Applicant(s)
Reg. No. 32,718
MERCK & CO., INC.
Patent Dept.
P.O. Box 2000
Rahway, N.J. 07065-0907
(908)594- 6343

Date: July 26, 1994

REV. 3/18/93

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Michael Fisher et al		
Serial No.:	08/233,166	Case No.: 19203	Art Unit: 1203
Filed:	April 26, 1994		Examiner: Davis
For:	Substituted Sulfonamides as Selective β3 Agonists for the Treatment of Diabetes and Obesity		

The Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

AMENDMENT UNDER 37 C.F.R.1.111

Sir:

There is an outstanding Office Action mailed August 5, 1994 for which a response is due by November 7, 1994. Reconsideration of the application is respectfully requested in view of the following remarks.

REMARKS

Status of the Claims

Claims 1-16 are pending in the application. Claims 5-6 have been withdrawn from consideration.

Election of Species

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date appearing below.

MERCK & CO., INC.

By: _____ Date: 11/4/94

Applicants hereby affirmed the election of the compound of Example 25. Claims readable thereon are 1-4, 7-16.

Improper Markush Group

Claims 1-4 and 7-16 stand rejected as allegedly being drawn to improper Markush group. Applicants respectfully disagree.

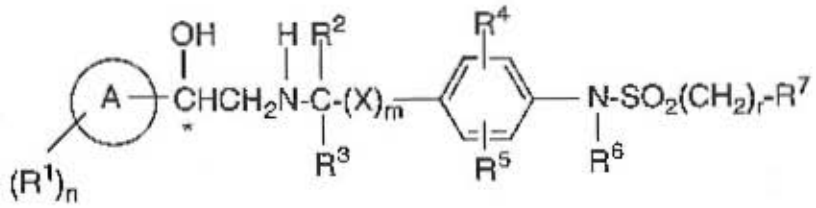
The guidelines set forth in M.P.E.P §706.03(y) for examining Markush-type claims states that "[w]here a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by a consideration of the compound as a whole, and does not depend on there being a community of properties in the members of the Markush expression." In the instant case, the claimed compounds as a whole possess a common utility, that as β3 agonists, and a common core, that of an N-phenylsulfonamide in which the phenyl group is linked to a β-hydroxyethanamino group via a linker.

In In re Harnisch 206 U.S.P.Q. 300 (C.C.P.A. 1980) - a case cited by the Examiner, the claimed compounds all had a common function (dyestuffs) and a common core (coumarin), and there the Court held that under the circumstances, the Markush groupings were proper even though the substituents on the coumarin core varied widely. As the facts in the instant case are analogous to those in Harnisch, a similar conclusion of proper Markush groupings must also be reached here.

Applicants respectfully submit that the improper Markush grouping rejection is untenable and request its withdrawal. Applicants further urge that the Examiner adhere to the examination guidelines set forth in M.P.E.P. §803.02 in the examination of the Markush-type claims.

The Examiner indicates that amending the claims to the examined subject matter would overcome the improper Markush rejection. The examined subject matter is said to be as follows:

"A compound having the formula I



I

where

A is pyridinyl;

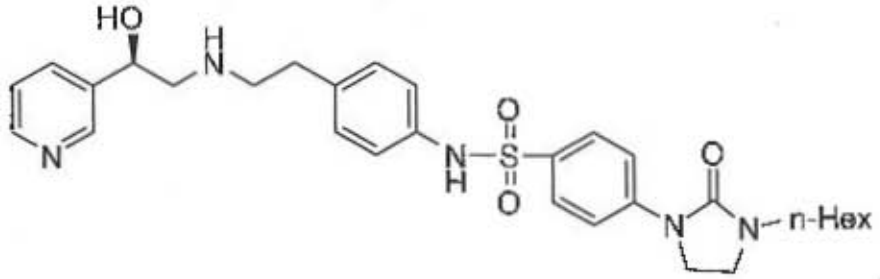
R^7 is $Z\text{-}(R^{1a})_n$;

R^{1a} is R^1, C3-C8 cycloalkyl, phenyl;

Z is phenyl, naphthyl.

The radicals not recited above are as defined in claim 1."

Regrettably, Applicants cannot so amend the claims as the above definition of R^{1a} does not encompass the elected species, which is the compound having the structure 1



1

The substituted imidazolidone moiety of structure 1 is not embraced by the above-defined R^{1a}.

Objection/Rejection Under 35 U.S.C. §112, first paragraph

The specification is objected to and claims 1-4 and 7-16 are rejected as allegedly failing to adequately teach how to make the claimed invention. Applicants respectfully traverse.

It is well established that a "specification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding in scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with enabling requirement of first paragraph of 35 USC 112 unless there is reason to doubt objective truth therein which must be relied on for enabling support.....[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of statement in supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with contested statement." In re Marzocchi, 169 U.S.P.Q. 367, 369, 370 (C.C.P.A., 1971).

In the present case, the specification on pages 10-26 provides detailed teachings on how to make the compounds of the present invention in terms corresponding to those used in the claims, and the Examiner has failed to put forth any evidence or reasoning to support the rejection under 35 USC §112, first paragraph. Bare assertion of non-enablement without more is insufficient to sustain this ground of rejection under the prevailing legal standard.

The Examiner states that

> A hypothetical compound can be embraced by the claim 1 definition, for instance, if A is pyridinyl, Z is benzene fused to a pyridinyl, R1a is pyridinyl and n is 5. The specification does not adequately teach how to prepare such a bulky compound. Undue experimentation would be involved to prepare such a compound.

The Examiner has imposed an impossible, and erroneous, standard of enablement by implicitly requiring the specification disclosure to teach each and every possible species within the generic claim. Applicants respectfully submit that it is not a function of the claims to specifically exclude possible inoperative substances (see e.g. Atlas Powder v. DuPont de Nemours, 224 USPQ 409, 414 (CAFC 1984)); in fact it would be impossible to do so. Since the claims are addressed to persons skilled in the art, compliance with the enablement requirement must be determined from that perspective. As the Patent Office Board of Appeal has said "[I]t is always possible to theorize some combination of circumstances which would render a claimed composition...inoperative, but the art-skilled would assuredly not choose such a combination." (Ex Parte Cole 223 USPQ 94, 95, 96

(POBA, 1983)). Therefore, even though the Examiner can come up with "hypothetical" compounds, a person skilled in the art would know to avoid those compounds.

In view of the above arguments, Applicants respectfully submit that the objection to the specification, and rejection of the claims under 35 USC§112, first paragraph are in error, and request that the Examiner withdraw the same.

Applicants acknowledge that the references in FORM PTO-892 dated 7/20/94 are cited by the Examiner to show the state of the art, and do not anticipate or render obvious the examined subject matter.

Applicants believe that the application is now in condition for allowance. An early favorable action is respectfully requested.

Respectfully submitted,

By _____
Mollie M. Yang
Reg. No. 32,718
Attorney for Applicants
Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(908) 594-6343

Date: November 4, 1994

PATENT
CASE NO. 19203

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

In re application of: MICHAEL FISHER, ET AL
Serial No. 08/233,166
Filed April 26, 1994
Group Art Unit 1203
Examiner DAVIS

For: SUBSTITUTED SULFONAMIDES AS SELECTIVE BETA-3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

Transmitted herewith is an amendment in the above-identified application.

☒ No additional fee is required.

☐ The fee has been calculated as shown below.

CLAIMS AS AMENDED

(1)	(2) Claims remaining after amendment	(3)	(4) Highest Number Previously Paid For	(5) Present Extra	(6) Rate	(7) Additional fee
Total Claims	* 16	-	** 20 =	0 X	$22	= 0.00
Independent Claims	* 1	-	*** 3 =	0 X	$76	= 0.00
Multiple Dependent Claims				0	$240****	= 0.00
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT →			0.00

* If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
** If the "Highest Number Previously Paid For" in this space is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" in this space is less than 3, write "3" in this space.
**** Add this fee only if application is amended to include multiple dependent claims (regardless of number) and no multiple dependent claims were originally filed.

Charge $ 0.00 to Deposit Account No. 13-2755. Please charge any additional fees or credit overpayment to Deposit Account No. 13-2755. Duplicate copies of this sheet are enclosed.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date appearing below.
MERCK & CO., INC.
By _____
Date 11/4/94

Respectfully,

By: Mollie M. Yang
Attorney for Applicant(s)
Reg. No. 32,718
MERCK & CO., INC.
Patent Dept.
P.O. Box 2000
Rahway, N.J. 07065-0907
(908)594- 6343
Date: November 4, 1994

IN TRIPLICATE
REV. 10/1/94

PATENT
CASE NO. 19203

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

In re application of: MICHAEL FISHER, ET AL
Serial No. 08/233,166
Filed April 26, 1994
Group Art Unit 1203
Examiner DAVIS
For: SUBSTITUTED SULFONAMIDES AS SELECTIVE BETA-3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

Transmitted herewith is an amendment in the above-identified application.

☒ No additional fee is required.

☐ The fee has been calculated as shown below.

CLAIMS AS AMENDED

(1)	(2) Claims remaining after amendment	(3)	(4) Highest Number Previously Paid For	(5) Present Extra	(6) Rate	(7) Additional fee
Total Claims	* 16	-	** 20 =	0 X	$22	= 0.00
Independent Claims	* 1	-	*** 3 =	0 X	$76	= 0.00
Multiple Dependent Claims				0	$240****	= 0.00
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT			0.00

* If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
** If the "Highest Number Previously Paid For" in this space is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" In this space is less than 3, write "3" in this space.
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MERCK & CO., INC.
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Respectfully,

By: Mollie M. Yang
Attorney for Applicant(s)
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MERCK & CO., INC.
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Date: November 4, 1994

IN TRIPLICATE
REV. 10/1/94

PATENT
CASE NO. 19203

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Commissioner of Patents and Trademarks
Washington, D.C. 20231

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Independent Claims	* 1	-	*** 3 =	0 X	$76	= 0.00
Multiple Dependent Claims				0	$240****	= 0.00
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT			0.00

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MERCK & CO., INC.
By _____
Date 11/4/94

Respectfully,

By: Mollie M. Yang
Attorney for Applicant(s)
Reg. No. 32,718

MERCK & CO., INC.
Patent Dept.
P.O. Box 2000
Rahway, N.J. 07065-0907
(908)594- 6343

Date: November 4, 1994

IN TRIPLICATE
REV. 10/1/94

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

08/233,166

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/233,166	04/26/94	FISHER	MW

M 13203
EXAMINER
NORTHINGTON DAVIS, Z

12M2/0202

MOLLIE M. YANG
PATENT DEPT.
MERCK & CO., INC.
P.O. BOX 2000
RAHWAY, NJ 07065-0907

ART UNIT	PAPER NUMBER
1209	5

DATE MAILED: 02/02/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 11-8-94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire ONE month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-16 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☐ Claims _____ are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-16 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
    ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters; prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Part III DETAILED ACTION

1. Pursuant to Applicant's remarks based on the improper Markush group and election of species, restriction is now required.

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1, 2, 5, and 7-16, drawn to compounds, composition, and method of use wherein A represents phenyl or a benzene fused to a C_3-C_8 cycloalkyl ring.

II. Claims 1-4 and 7-16, drawn to compounds, composition, and method of use wherein A represents a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur, and nitrogen, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur, and nitrogen, or a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur, and nitrogen fused to a 5- or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur, and nitrogen.

The inventions are distinct, each from the other because of the following reasons:

The radicals within the definition of A are diverse in scope. A prior art reference which anticipates one member of A such as phenyl under 35 USC 102 would not render obvious another member such as pyridinyl under 35 USC 103. Accordingly, the radicals are independent and patentably distinct.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

A telephone call was made to Ms. Mollie Yang on January 23, 1995 to request an oral election to the above restriction requirement, but did not result in an election being made.

2. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

A facsimile center has been established in Group 1200, room 3C10. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machines are (703) 308-4556 or 305-3592.

3. Any inquiry concerning this communication should be directed to Zinna N. Davis at telephone number (703) 308-4699.

Zinna N. Davis
Patent Examiner
Group 1200- ART UNIT 1203

DAVIS:jd
January 27, 1995

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

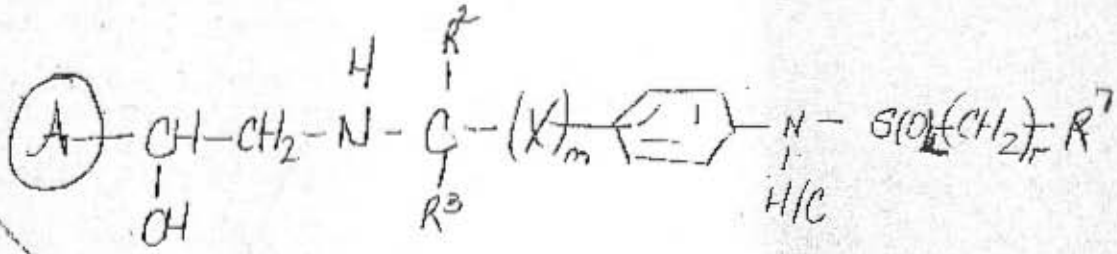
ONLINE SEARCH REQUEST FORM

USER Zinna N. DAVIS SERIAL NUMBER 08/233166

ART UNIT 1203 PHONE X41679 DATE 7-7-94

Please give a detailed statement of requirements. Describe as specifically as possible the subject matter to be searched. Define any terms that may have special meaning. Give examples or relevant citations, authors, or keywords, if known.

You may include a copy of the broadest and or relevant claim(s).



A = carbocyclic/heterocyclic

X = $-CH_2-$ / $-CH_2CH_2-$ / $-CH=CH-$ / $-CH_2O-$

m = 0 or 1

n = 0-5

r = 0-3

$R^7 \rightarrow Z(R^{1a})_n$

Z = carbocyclic/heterocyclic

R^{1a} → open

STAFF USE ONLY

COMPLETED 7/8

SEARCHER Mary 4258

ONLINE TIME 12 TOTAL TIME

(in minutes)

NO. OF DATABASES

SYSTEMS

✓ CAS ONLINE

DARC/QUESTEL

DIALOG

SDC

OTHER

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FILE 'MEDLINE'
L9              0 L6

FILE 'EMBASE'
L10             0 L6

TOTAL FOR ALL FILES
L11             0 L6

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FILE 'CA' ENTERED AT 12:14:22 ON 08 JUL 94
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FILE COVERS 1967 - 25 Jun 1994 (940625/ED)  VOL 120 ISS 26

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  HCA File when conducting SmartSELECT searches with large
  numbers of terms.

THIS IS THE BETTER CA FILE.  SEE NEWS FOR DETAILS.


L12             1 L6/P


L13             0 L6/D

=> s l12 not l7
L14             0 L12 NOT L7
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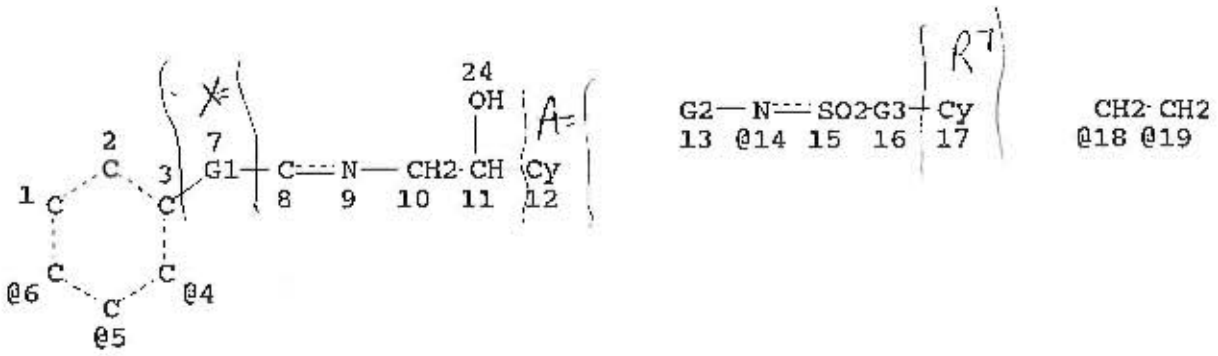
northington-davis



CH≡CH
@20 @21

CH2 O
@22 @23

X= VAR G1=CH2/18-3 19-8/20-3 21-8/22-8 23-3/22-3 23-8
VAR G2=H/C
REP G3=(0-3) CH2
VPA 14-4/5/6 U
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

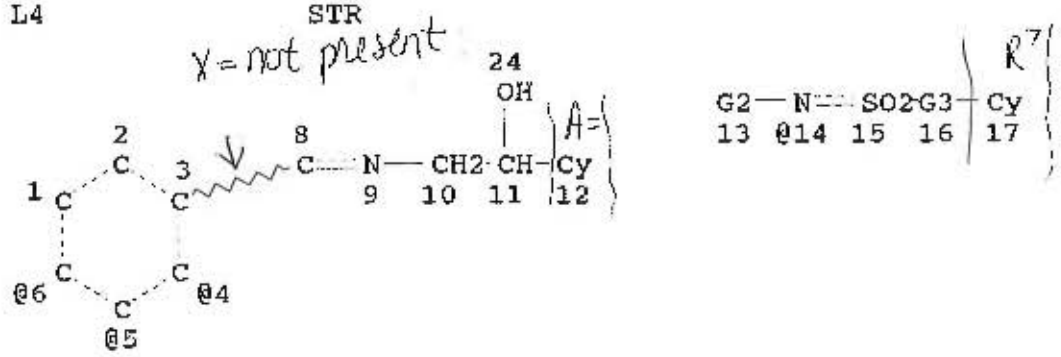
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE
L3 0 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 16202 ITERATIONS 0
ANSWERS
SEARCH TIME: 00.00.53

L4 STR

X = not present



northington-davis

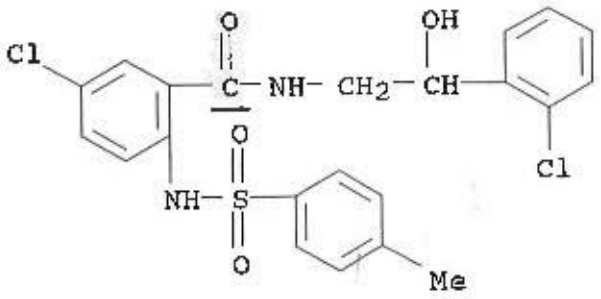
VAR G2=H/C
REP G3=(0-3) CH2
VPA 14-4/5/6 U
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 17

STEREO ATTRIBUTES: NONE
L6 2 SEA FILE=REGISTRY SSS FUL L4

100.0% PROCESSED 8814 ITERATIONS 2
ANSWERS
SEARCH TIME: 00.00.48

L6 ANSWER 1 OF 2 REGISTRY COPYRIGHT 1994 ACS
RN 25233-68-5 REGISTRY
CN Benzamide,
5-chloro-N-(o-chloro-.beta.-hydroxyphenethyl)-2-p-
toluenesulfonamido- (7CI, 8CI) (CA INDEX NAME)
FS 3D CONCORD
MF C22 H20 Cl2 N2 O4 S
LC STN Files: BEILSTEIN*, CA, CAOLD, IFICDB, IFIPAT, IFIUDB
(*File contains numerically searchable property data)



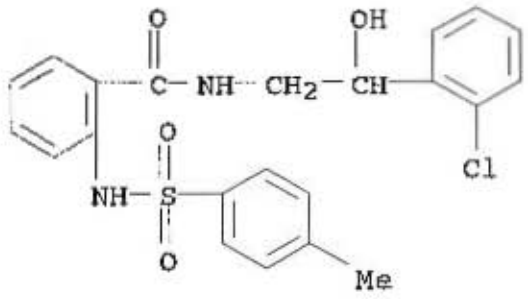
$R^2 = H$
$R^3 = H$

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: P 71:81338

L6 ANSWER 2 OF 2 REGISTRY COPYRIGHT 1994 ACS

RN 23595-56-4 REGISTRY
CN Benzamide, N-(o-chloro-.beta.-hydroxyphenethyl)-o-(p-toluenesulfonamido)- (8CI) (CA INDEX NAME)
FS 3D CONCORD
MF C22 H21 Cl N2 O4 S



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THIS IS THE BETTER CA FILE. SEE NEWS FOR DETAILS.

L7 1 L6

=> d .mh

L7 ANSWER 1 OF 1 CA COPYRIGHT 1994 ACS
TI Tranquilizer N-[o-(2-oxazolin-2-yl)phenyl] alkyl or aryl sulfonamides and intermediates
SO U.S., 5 pp.
CODEN: USXXAM
IN Santilli, Arthur A.; Osdene, Thomas S.
PI US 3452037 690624
AI US 631213 - 661003
PY 1969
AB Prepd. from I are the title compds. (II) having tranquilizer,
antidepressant, anticonvulsant, and analgesic activities.
I are

prepd. from an isatoic anhydride. Thus, 9.85 g. 5-chloroisatoic anhydride (III) and 4 g. HOCH2CH2NH2 heated in 50 ml. H2O at 100.degree. for 20 min. gave I (A = R = H, X = Cl) (IV), m. 121-2.5.degree. (H2O). Addn. of 10.3 g. 4-Me-C6H4SO2Cl in portions to 5.8 g. IV in 30 ml. dry pyridine at 0.degree. and, after standing in the cold overnight, addn. of H2O gave 9.6 g. solid, m. 112-19.degree.. This was heated with 30 ml. EtOH over steam to give II (A = 4-MeC6H4SO2, R = H, X = Cl), m. 174-6.degree. (EtOH). Thus prepd. were the following II (A, R, X, m.p., and yield % yield given): Ph, H, H, 66-8.degree. (aq. EtOH), -; MeSO2, H, H, 164-5.degree. (benzene), -; MeSO2, Me, Cl, 114-16.degree. (aq. EtOH), 24; MeSO2, Ph, Cl, 157-8.degree., 83; PhCH2SO2, Ph, Cl, 139-40.degree. (cyclohexane), 80 (crude); 4-MeC6H4SO2, H, H (V), 197-9.degree. (EtOH), -; 4-MeC6H4SO2, Me, Cl, 122-4.degree. (MeOH), 16 (50% crude); 4-MeC6H4SO2, Ph, Cl, 132-3.degree. (MeOH), 100 (crude); 4-MeC6H4SO2, 2-ClC6H4, H, 152-3.degree. (EtOH), 79 (crude); 4-MeC6H4SO2, 2-ClC6H4, Cl, 167-8.degree. (benzene-petroleum ether), 40. V (1 g.) and 1 g. P2S5 after 2 hrs. reflux in 15 ml. dry pyridine, hydrolysis (50 ml. hot H2O), and neutralization (30% HCl) gave N-[o-(2-thiazolin-2-yl)phenyl]-p-toluenesulfonamide, m. 160-3.degree. (aq. pyridine). Intermediate I described were (A, X, R, and m.p. given): Ph, H, H, 77-9.degree. (benzene-cyclohexane); H, Cl, Me, 109-10.5.degree. (benzene); H, Cl, Ph, 119-21.degree. (benzene). Addnl. prepns. were given. Thus, refluxing 2 hrs. of 134 g. 2-ClC6H4CH(OH)CN and 82 g. Ac2O gave 107 g. 2-ClC6H4CHOAcCN, b0.cntdot.25 110-1.degree., which was added dropwise to 37.8 g. LiAlH4 stirred in 800 ml. anhyd. tetrahydrofuran. Reflux (2 hrs.), dropwise addn. of 100 ml. H2O and then 200 ml. 20% NaOH, and work up

on the next day gave 56 g. 2-ClC6H4-CH(OH)CH2NH2 (IIIa), b0.cntdot.25 108-12.degree.. Mixts. of IIIa (18.9 and 18.8 g., resp.) with 19.7 g. III or 16.3 g. isatoic anhydride, both in 50 ml. EtOH, heated 15 min. gave, resp., the I (A = H, R = 2-ClC6H4) (Ia), (X = H), m. 103-5.degree. (benzene.cyclohexane) and Ia (X = Cl), m. 105-7.degree. (benzene.cyclohexane), N-(p-toluenesulfonyl deriv. (by action of 2 equiv. 4-MeC6H4SO2Cl in abs. pyridine overnight at 0.degree., crude yield 78%) m. 165-6.degree. (benzene). The last was converted to the corresponding oxazoline I (above) by the action of MeSO2Cl. Alternately, refluxing a soln. of 3.4 g. 2,5-(H2N)ClC6H3CONHCH2CH2OH in 25 ml. SO2Cl2 for 1 hr., evapn., and treatment of crude product (3 g.) in 10 ml. hot H2O with 10% Na2CO3 gave 2,5-(H2N)ClC6H3CONHCH2CH2Cl (IIIb), m. 115-16.degree. (cyclohexane). Addn. of 4 g. finely powd. Na2CO3 to 6.2 g. IIIb in 15 ml. Me2NCHO and heating at reflux 1.5 hrs. gave 3.2 g. II (A = R = H, X = Cl), m. 76-8.degree. (hexane). Also described was the prepn. (reflux of 5 g. 2-PhNHC6H4CO2H in 20 ml. EtO2CCl for 10 hrs.) of N-phenylisatoic anhydride, m. 177-9.degree. (EtOH).

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AN   71:81338  CA

=> fil .biotech;s l6
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FILE 'BIOSIS'
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L1                TR
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DAVIS
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#6/A
3/14/95
CHS

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Michael Fisher et al		
Serial No.:	08/233,166	Case No.: 19203	Art Unit:1203
Filed:	April 26, 1994		Examiner:Davis
For:	Substituted Sulfonamides as Selective β3 Agonists for the Treatment of Diabetes and Obesity		

The Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

RESTRICTION REQUIREMENT

Sir:

There is an outstanding Office Action mailed February 2, 1995 for which a response is due by March 2, 1995. Kindly amend the application as follows:

In the Claims:

AMEND the following claims

Claim 1, page 42, line 17: after "A is" delete "phenyl, ".

Claim 1, page 42, line 19: after "nitrogen" delete "a benzene ring fused to a C3-C8 cycloalkyl ring".

Claim 2, page 44, line 4: after "A is" delete "phenyl, or ".

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date appearing below.

MERCK & CO., INC.

By: _____ Date: 2/28/95

Claim 7, page 46: delete the lines 33 to 34 (i.e. the last and penultimate lines on page 46).

Claim 7, page 47: delete lines 1-4.

CANCEL claims 5 and 6.

REMARKS

The claims have been restricted as follows:

Group I: claims 1, 2, 5 and 7-16 drawn to compounds, compositions, and method of use wherein A represents phenyl or a benzene fused to a C3-C8 cycloalkyl ring.

Group II: claims 1-4 and 7-16 drawn to compounds, compositions, and method of use where A represents a heterocyclic moiety as defined in the claims.

Applicants hereby elect the invention of Group II without traverse. In accordance with this election claims 1, 2 and 7 have been amended, and claims 5 and 6 have been canceled.

Applicants believe that the application is now in condition for allowance. An early favorable action is respectfully requested.

Respectfully submitted,

By _____
Mollie M. Yang
Reg. No. 32,718
Attorney for Applicants
Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(908) 594-6343

Date: February 28, 1995

PATENT
CASE NO. 19203

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

In re application of: MICHAEL FISHER, ET AL
Serial No. 08/233,166
Filed April 26, 1994
Group Art Unit 1203
Examiner DAVIS

For: SUBSTITUTED SULFONAMIDES AS SELECTIVE B3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

Transmitted herewith is an amendment in the above-identified application.

☒ No additional fee is required.

☐ The fee has been calculated as shown below.

CLAIMS AS AMENDED

(1)	(2) Claims remaining after amendment	(3)	(4) Highest Number Previously Paid For	(5) Present Extra	(6) Rate	(7) Additional fee
Total Claims	* 14	-	** 16 =	0 X	$22	= 0.00
Independent Claims	* 1	-	*** 1 =	0 X	$76	= 0.00
Multiple Dependent Claims				0	$240****	= 0.00
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT			0.00

* If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
** If the "Highest Number Previously Paid For" in this space is less than 20, write "20" in this space.
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**** Add this fee only if application is amended to include multiple dependent claims (regardless of number) and no multiple dependent claims were originally filed.

Charge $ 0.00 to Deposit Account No. 13-2755. Please charge any additional fees or credit overpayment to Deposit Account No. 13-2755. Duplicate copies of this sheet are enclosed.

Respectfully,

By: Mollie M. Yang
Attorney for Applicant(s)
Reg. No. 32,718
MERCK & CO., INC.
Patent Dept.
P.O. Box 2000
Rahway, N.J. 07065-0907
(908)594- 6343
Date: February 28, 1995

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MERCK & CO., INC.
By
Date 2/28/95

IN TRIPLICATE
REV. 10/1/94

PATENT
CASE NO. 19203

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

In re application of: MICHAEL FISHER, ET AL
Serial No. 08/233,166
Filed April 26, 1994
Group Art Unit 1203
Examiner DAVIS
For: SUBSTITUTED SULFONAMIDES AS SELECTIVE B3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

Transmitted herewith is an amendment in the above-identified application.

☒ No additional fee is required.

☐ The fee has been calculated as shown below.

CLAIMS AS AMENDED

(1)	(2) Claims remaining after amendment	(3)	(4) Highest Number Previously Paid For	(5) Present Extra	(6) Rate	(7) Additional fee
Total Claims	* 14	-	** 16 =	0 X	$22	= 0.00
Independent Claims	* 1	-	*** 1 =	0 X	$76	= 0.00
Multiple Dependent Claims				0	$240****	= 0.00
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT			0.00

* If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
** If the "Highest Number Previously Paid For" in this space is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" in this space is less than 3, write "3" in this space.
**** Add this fee only if application is amended to include multiple dependent claims (regardless of number) and no multiple dependent claims were originally filed.

Charge $ 0.00 to Deposit Account No. 13-2755. Please charge any additional fees or credit overpayment to Deposit Account No. 13-2755. Duplicate copies of this sheet are enclosed.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date appearing below.
MERCK & CO., INC.
By _____
Date 2/28/95

Respectfully,

By: Mollie M. Yang
Attorney for Applicant(s)
Reg. No. 32,718
MERCK & CO., INC.
Patent Dept.
P.O. Box 2000
Rahway, N.J. 07065-0907
(908)594- 6343
Date: February 28, 1995

IN TRIPLICATE
REV. 10/1/94

PATENT
CASE NO. 19203

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

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			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT			0.00

* If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
** If the "Highest Number Previously Paid For" in this space is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" in this space is less than 3, write "3" in this space.
**** Add this fee only if application is amended to include multiple dependent claims (regardless of number) and no multiple dependent claims were originally filed.

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MERCK & CO., INC.
By _____
Date 2/28/95

Respectfully,

By: Mollie M. Yang
Attorney for Applicant(s)
Reg. No. 32,718
MERCK & CO., INC.
Patent Dept.
P.O. Box 2000
Rahway, N.J. 07065-0907
(908)594- 6343
Date: February 28, 1995

IN TRIPLICATE
REV. 10/1/94

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

08/233,160

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/233,166	04/26/94	FISHER	M 19233

EXAMINER: NORTHINGTON DAVIS, Z

12M1/0327

MOLLIE M. YANG
PATENT DEPT.
MERCK & CO., INC.
P.O. BOX 2000
RAHWAY, NJ 07065-0907

ART UNIT	PAPER NUMBER
1203	7

DATE MAILED: 03/27/95

NOTICE OF ALLOWABILITY

PART I.

1. ☒ This communication is responsive to Amendment A filed February 28, 1995
2. ☒ All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. ☒ The allowed claims are 1-4 and 7-16 (now 1-14, respectively)
4. ☐ The drawings filed on _____ are acceptable.
5. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [_] been received. [ ] not been received. [ ] been filed in parent application Serial No. _____, filed on _____
6. ☐ Note the attached Examiner's Amendment.
7. ☐ Note the attached Examiner Interview Summary Record, PTOL-413.
8. ☐ Note the attached Examiner's Statement of Reasons for Allowance.
9. ☐ Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. ☐ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. ☐ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. ☐ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. ☐ Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER

Attachments:

- _ Examiner's Amendment
- _ Examiner Interview Summary Record, PTOL-413
- _ Reasons for Allowance
- _ Notice of References Cited, PTO-892
- _ Information Disclosure Citation, PTO-1449
- _ Notice of Informal Application, PTO-152
- _ Notice re Patent Drawings, PTO-948
- _ Listing of Bonded Draftsmen
- _ Other

Ap Davis
(703)308-4679

C. Warren Ivy
Supervisory Patent Examiner
Group 120

PTOL-37 (REV. 4-89) *

USCOMM DC 56-9769

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/233,166	04/26/94	FISHER M	19203

75F1/0817

MOLLIE M. YANG
PATENT DEPT.
MERCK & CO., INC.
P.O. BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
NORTHINGTON DAVIZ	
ART UNIT	PAPER NUMBER
1203	8

DATE MAILED: 08/17/95

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant's failure to respond to the Office letter, mailed _____.
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☒ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of 5-24-95 of the Notice of Allowance.
   - ☐ The issue fee was received on _____.
   - ☐ The issue fee has not been received in Allowed Files Branch as of _____.

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   - ☐ The corrected and/or substitute drawings were received on _____.
6. ☐ The reason(s) below.

DIRECT ANY INQUIRIES TO :
PUBLISHING DIVISION
MARCIA CAMPBELL
(703) 305-8190
OR
PRISCILLA FULLER
(703) 305-8283

PTO-1432 (REV. 5-83)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: Box ISSUE FEE
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

12M1/0327

MOLLIE M. YANG
PATENT DEPT.
MERCK & CO., INC.
P.O. BOX 2000
RAHWAY, NJ 07065-0907

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

☐ Note attached communication from the Examiner
☐ This notice is issued in view of applicant's communication filed _____

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/232,166	04/26/94	014	HORTINGTON DAVI, Z	1203 03/27/95

First Named Applicant: FISHER, MICHAEL H.

TITLE OF INVENTION: SUBSTITUTED SULFONAMIDES AS SELECTIVE BETA3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
19202	514-357.000	K09	UTILITY	NO	$1210.00	06/27/95

THE APPLICATION IDENTIFIES ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY Status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the patent and Trademark Office of the change in status, or
B. If the Status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:
A. Pay FEE DUE shown above, or
B. File verified statement of Small Entity Status before, or with, pay of 1/2 the FEE DUE shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.

III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (REV. 12-93) (0651-0033)

4. PATIENT AND TRADEMARK OFFICE COPY

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 1992

Application or Docket Number: 233166

CLAIMS AS FILED - PART I

	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
FOR							
BASIC FEE				$355.00	OR		$710.00
TOTAL CLAIMS	16 minus 20 =	*	x$11=		OR	x$22=	
INDEPENDENT CLAIMS	1 minus 3 =	*	x 37=		OR	x 74=	
MULTIPLE DEPENDENT CLAIM PRESENT			+115=		OR	+230=	
			TOTAL		OR	TOTAL	710

* If the difference in column 1 is less than zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
Total	*	Minus	**	=	x$11=		OR	x$22=	
Independent	*	Minus	***	=	x 37=		OR	x 74=	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+ 115=		OR	+230=	
					TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
Total	*	Minus	**	=	x$11=		OR	x$22=	
Independent	*	Minus	***	=	x 37=		OR	x 74=	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+ 115=		OR	+ 230=	
					TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
Total	*	Minus	**	=	x$11=		OR	x$22=	
Independent	*	Minus	***	=	x 37=		OR	x 74=	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+115=		OR	+230=	
					TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875
(Rev.10-92)

Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Form PTO 1130
(REV 2/94)

PACE DATA ENTRY CODING SHEET

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

1ST EXAMINER Jones 108 DATE 5/20/94
2ND EXAMINER DATE

APPLICATION NUMBER	TYPE APPL	FILING DATE MONTH DAY YEAR	SPECIAL HANDLING	GROUP ART UNIT	CLASS	SHEETS OF DRAWING
08/233166	1	04 26 94	D	1205	514	10

TOTAL CLAIMS	INDEPENDENT CLAIMS	SMALL ENTITY?	FILING FEE	FOREIGN LICENSE	ATTORNEY DOCKET NUMBER
16	1	D	710	Y	19203

CONTINUITY DATA

CONT CODE	STATUS CODE	PARENT APPLICATION SERIAL NUMBER	PCT APPLICATION SERIAL NUMBER	PARENT PATENT NUMBER	PARENT FILING DATE MONTH DAY YEAR
			PCT/ /		
			PCT/ /		
			PCT/ /		
			PCT/ /		
			PCT/ /		

PCT/FOREIGN APPLICATION DATA

FOREIGN PRIORITY CLAIMED	COUNTRY CODE	PCT/FOREIGN APPLICATION SERIAL NUMBER	FOREIGN FILING DATE MONTH DAY YEAR

TITLE OF INVENTION

ATTORNEY REGISTRATION NUMBERS

CORRESPONDENCE NAME AND ADDRESS

APPLICANT/INVENTOR DATA

AUTHORITY CODE			
FAMILY NAME		NAME SUFFIX	
GIVEN NAME		STATE/CTRY CODE	
CITY			

AUTHORITY CODE			
FAMILY NAME		NAME SUFFIX	
GIVEN NAME		STATE/CTRY CODE	
CITY			

MORE

08/233166
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Deposit Acct. 13-2755
MERCK & CO., INC.
Our Case Docket No. 19203

Transmitted herewith for filing is
the patent application of Inventor(s): MICHAEL H. FISHER, DONG OK, ELIZABETH M. NAYLOR AND ANN E. WEBER

For: SUBSTITUTED SULFONAMIDES AS SELECTIVE BETA 3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

Enclosed are also:

☐ _____ sheets of drawing.

☐ An assignment of the invention to

☐ A certified copy of a application.

For	Number Filed	Number Extra	Rate	Basic Fee $710
Total Claims	16 - 20 =	0 X	$22	= 0.00
Independent Claims	1 - 3 =	0 X	$74	= 0.00
Multiple Dependent Claims		-	$230	= 0.00
* Add this fee if application contains any multiple dependent claims, regardless of number.		TOTAL FILING FEE →		$710.00

Please charge my Deposit Account No. 13-2755 in the amount of $ 710.00 . The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. 13-2755. Duplicate copies of this sheet are enclosed.

EXPRESS MAIL CERTIFICATE
DATE OF DEPOSIT April 26, 1994
EXPRESS MAIL NO. EG292851015US
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231
MAILED BY Kelly L. Koslosky
DATE April 26, 1994

Respectfully,

By: Mollie M. Yang
Attorney For Applicant(s)
Reg. No. 32,718
MERCK & CO., INC.
Patent Dept.
P.O. Box 2000
Rahway, N.J. 07065-0907
(908) 594- 6343

Date: April 26, 1994

REV.6/14/93 IN TRIPLICATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE 08/233166 PATENT

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Deposit Acct. 13-2755
MERCK & CO., INC.
Our Case Docket No. 19203

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☐ A certified copy of a application.

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Multiple Dependent Claims					$230	= 0.00
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MAILED BY Kelly J. Bosbury
DATE April 26, 1994

Respectfully,

Mollie M. Yang

By: Mollie M. Yang
Attorney For Applicant(s)
Reg. No. 32,718
MERCK & CO., INC.
Patent Dept.
P.O. Box 2000
Rahway, N.J. 07065-0907
(908) 594- 6343

Date: April 26, 1994

REV.6/14/93

IN TRIPLICATE

08/233166

APPROVED FOR LICENSE ☑

INITIALS MAY 1 8 94 3.5

CONTENTS

Date Entered or Counted		Date Received or Mailed
	1. Application ____ papers.	
7-21-94	2. Rej 3	8-5-94
	3. Prior Art	7/29/94
	4. Reg for Recon	11/8/94
1/23/95	5. Rest (1)	2.2.95
	6. Amdt A	3/6/95 - 3/28/95
3-24-95	7. Notice of Abandonment	3/27/95
	8. ABANDONED	AUG 17 1995
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(FRONT)

STAPLE AREA

☆U.S.G.P.O.: 1994 - 378-972

PATENT NUMBER	ORIGINAL CLASSIFICATION	
	CLASS	SUBCLASS
	514	357

APPLICATION SERIAL NUMBER
08/233,166

APPLICANT'S NAME (PLEASE PRINT)
Fisher et al

IF REISSUE, ORIGINAL PATENT NUMBER

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)			
514	300	341	362	
546	117	276	311	312
546	338			

INTERNATIONAL CLASSIFICATION

C	0	7	D	213	02
A	6	1	K	31	44

GROUP ART UNIT: 1203

ASSISTANT EXAMINER (PLEASE STAMP OR PRINT FULL NAME)
ZINNA N. DAVIS (ZND)

PRIMARY EXAMINER (PLEASE STAMP OR PRINT FULL NAME)
C. Warren Ivy
Supervisory Patent Examiner
Group 120

PTO 270 - (REV. 5-91)

ISSUE CLASSIFICATION SLIP

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

Staple Issue Slip Here

POSITION		ID NO.	DATE
CLASSIFIER		7	5-18-99
EXAMINER		341	5/20/99
TYPIST		359	5/20/99
VERIFIER		342	5-25
CORPS CORR.			
SPEC. HAND			
FILE MAINT.			
DRAFTING			

INDEX OF CLAIMS

Claim Final	Claim Original	Date
1	1	✓
2	2	✓
3	3	✓
4	4	✓
	5	N
	6	N
5	7	✓
6	8	✓
7	9	✓
8	10	✓
9	11	✓
10	12	✓
11	13	✓
12	14	✓
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SYMBOLS

- ✓ ..... Rejected
- = ... Allowed
- - (Thereby numbered) Cancelled
- + ... Restricted
- N ..... Not elected
- I ..... Interference
- A ..... Appeal
- O ..... Objected

Claim Final	Claim Original	Date
	51	
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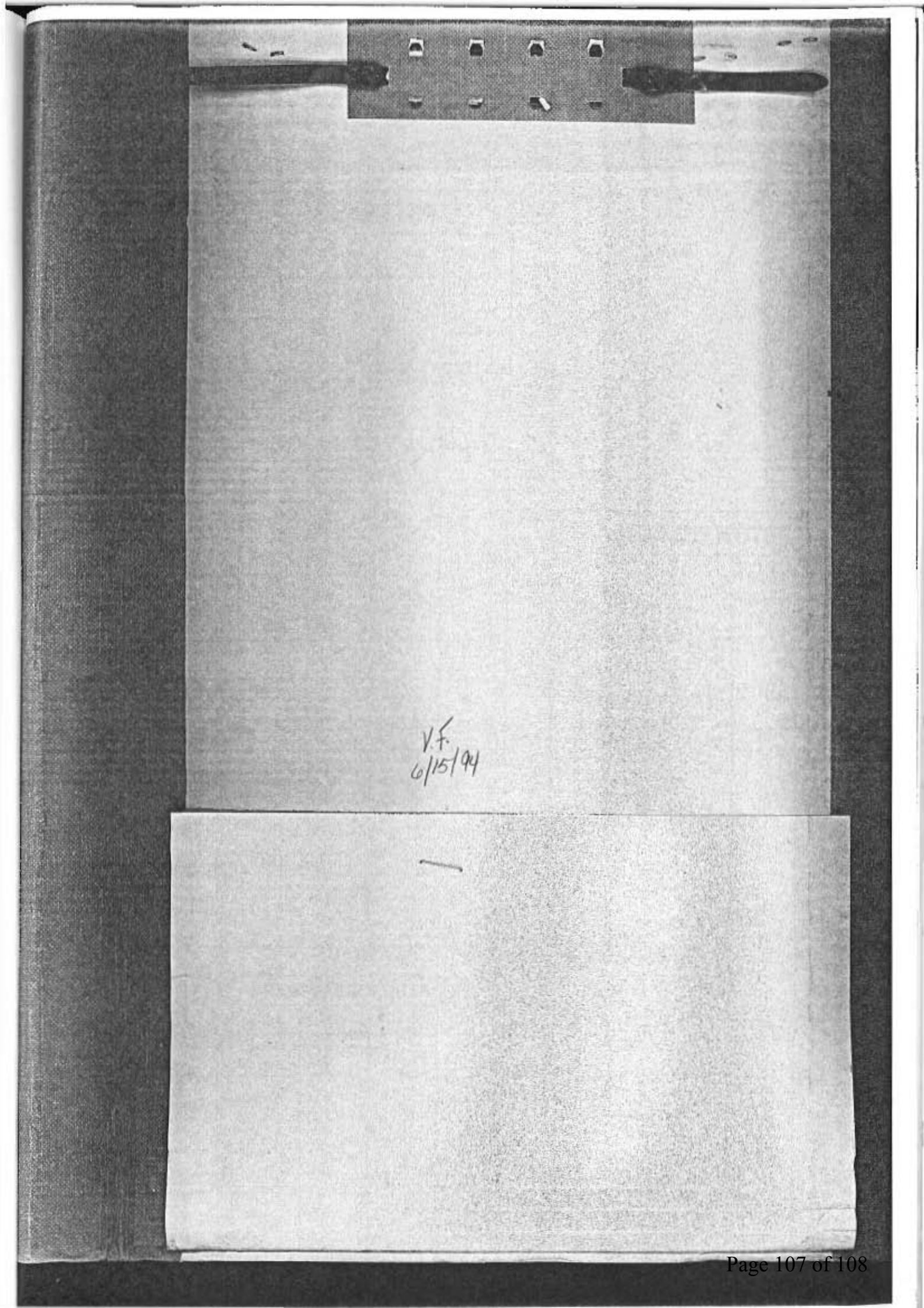
V.f.
6/15/94

SEARCHED

Class	Sub.	Date	Exmr.
546	334,337	7-20-94	JKO
514	357,352		
	344,350		
Search	10		
Date	+		
546	117, 311	3-25-95	JKO
	312,338		

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
SAME AS ABOVE		3-25-95	JKO

SEARCH NOTES

	Date	Exmr.
CAS Computer Search		
1966 - 10 Date	7-7-94	JKO

(RIGHT OUTSIDE)