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(54) Title: PROCESS FOR PREPARING MULTICYCLIC OXY-CONTAINING RING COMPONENTS (57) Abstract This invention relates to stereospecific processes for the preparation, separation and purification of multicyclic oxy-containing ring system compounds such as dibenzofuran and benzoxocine-type compounds which exhibit 5HT ₃ -antagonist properties including unique CNS, anti-emetic and gastric prokinetic activity and which are void of any significant D ₂ receptor binding affinity.		

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⁺ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

PROCESS FOR PREPARING MULTICYCLIC OXY-CONTAINING RING COMPONENTS

BACKGROUND OF THE INVENTION

This is a continuation-in-part application of copending application, United States Serial Number 07/620,240 filed November 29, 1990.

Field of the Invention

This invention relates to multicyclic oxy-containing ring system compounds such as dibenzofuran and benzoxocine-type compounds which exhibit 5HT₃-antagonist properties including unique CNS, anti-emetic and gastric prokinetic activity and which are void of any significant D₂ receptor binding affinity. This invention relates also to stereospecific processes for the preparation, separation and purification of said compounds.

5-Hydroxytryptamine, abbreviated "5-HT", is commonly known as serotonin. Serotonin found throughout the body including the gastrointestinal tract, platelets, spleen and brain, appears to be involved in a great number of physiological processes such as neurotransmission at certain neurones in the brain, and is implicated in a number of central nervous system (CNS) disorders. Additionally, serotonin appears to act as a local hormone in the periphery; it is released in the gastrointestinal tract, where it increases small intestinal motility, inhibits stomach and colon motility, and stimulates stomach acid production. Serotonin is most likely involved in normal intestinal peristalsis.

The various physiological activities exerted by serotonin are related to the variety of different receptors found on the surface membrane of cells in different body tissue. The first classification of serotonin receptors included two pharmacologically distinct receptors discovered in the guinea pig ileum.

The "D" receptor mediates smooth muscle contraction and the "M" receptor involves the depolarization of cholinergic nerves and release of acetylcholine. Three different groups of serotonin receptors have since been identified and the following assignment of receptors has been proposed: D-receptors are 5-HT₂-receptors; M-receptors are termed 5-HT₃-receptors; and all other receptors, which are clearly not 5-HT₂ or 5-HT₃, have been referred to as 5-HT₁-like and work is being continued on this classification.

5-HT₃-receptors have been located in non-neurological tissue, brain tissue, and a number of peripheral tissues related to different responses. It has been reported that 5-HT₃-receptors are located on peripheral neurones where they are related to serotonin's (excitatory) depolarizing action. The following subtypes of 5-HT₃-receptor activity have been reported: action involving postganglionic sympathetic and parasympathetic neurones, leading to depolarization and release of noradrenaline and acetylcholine, respectively (5-HT_{3B} subtype); action on enteric neurones, where serotonin may modulate the level of acetylcholine (5-HT_{3C} subtype); and action on sensory nerves such as those involved in the stimulation of heart nerve endings to produce a reflex bradycardia (5-HT_{3A} subtype), and also in the perception of pain.

Highly selective 5-HT₃-antagonists have been shown to be very effective at controlling and preventing emesis (vomiting) induced by chemotherapy and radiotherapy in cancer patients. The anti-emetic effects of 5-HT₃-antagonists in animals exposed to cancer chemotherapy or radiation are similar to those seen following abdominal vagotomy. The antagonist compounds are believed to act by blocking 5-HT₃-receptors situated on the cell membranes of the tissue forming the vagal afferent input to the emetic coordinating areas on the brain stem.

Serotonin is also believed to be involved in the disorder known as migraine headache. Serotonin released locally within the blood vessels of the head is believed to interact with elements of the perivascular neural plexus of which the afferent, substance P-containing fibers of the trigeminal system are believed relevant to the condition. By activating specific sites on sensory neuronal terminals, serotonin is believed to generate pain directly

and also indirectly by enhancing the nociceptive effects of other inflammatory mediators, for example bradykinin. A further consequence of stimulating the afferent neurones would be the local release of substance P and possibly other sensory mediators, either directly or through an axon reflex mechanism, thus providing a further contribution to the vascular changes and pain of migraine. Serotonin is known to cause pain when applied to the exposed blister base or after an intradermal injection; and it also greatly enhances the pain response to bradykinin. In both cases, the pain message is believed to involve specific 5-HT₃-receptors on the primary afferent neurones.

5-HT₃-antagonists are also reported to exert potential antipsychotic effects, and are believed to be involved in anxiety. Although not understood well, the effect is believed to be related to the indirect blocking of serotonin 5-HT₃-mediated modulation of dopamine activity.

Many workers are investigating various compounds having 5-HT₃-antagonist activity.

The development of 5-HT₃ agents originated from work carried out with metoclopramide (Beecham's Maxolon, A.H. Robins' Reglan), which is marketed for use in the treatment of nausea and vomiting at high doses. Metoclopramide is a dopamine antagonist with weak 5-HT₃-antagonist activity, which becomes more prominent at higher doses. It is reported that the 5-HT₃ activity and not the dopamine antagonism is primarily responsible for its anti-emetic properties. Other workers are investigating this compound in connection with the pain and vomiting accompanying migraine.

Merrell Dow's compound MDL-72222 is reported to be effective as an acute therapy for migraine, but toxicity problems have reportedly ended work on this compound. Currently four compounds, A.H. Robins' Zacopride, Beecham's BRL-43694, Glaxo's GR-38032F and Sandoz' ICS-205-930 are in clinical trials for use in chemotherapy-induced nausea and vomiting. GR-38032F is also in clinical trials in anxiety and schizophrenia, and reportedly, Zacopride in anxiety, while ICS-205-930 has been shown to be useful in treating carcinoid syndrome.

Compounds reported as gastroprokinetic agents include Beecham's BRL-24924, which is a serotonin-active agent for use in gut motility disorders such as gastric paresis, audition reflux esophagitis, and is known to have also 5-HT₃-antagonist activity.

Metoclopramide, Zacopride, Cisapride and BRL-24924 are characterized by a carboxamide moiety situated para to the amino group of 2-chloro-5-methoxy aniline. BRL-43694, ICS-205-930, GR-38032F and GR-65630 are characterized by a carbonyl group in the 3-position of indole or N-methyl indole. MDL-72222 is a bridged azabicyclic 2,4-dichlorobenzoate, while Zacopride, BRL-24924, BRL-43694 and ICS-205-930 have also bridged azabicyclic groups in the form of a carboxamide or carboxylic ester.

Bicyclic oxygen containing carboxamide compounds wherein the carboxamide is ortho to the cyclic oxygen moiety are reported to have antiemetic and antipsychotic properties in EPO Publ. No. 0234872.

Among the reported compounds are stereoisomers which are synthesized by using chiral synthesis, i.e., asymmetric induction methods of synthesis. Speaking generally, syntheses with asymmetric induction have been known in the prior art. A synthesis with asymmetric induction is commonly defined as a process in which a chiral unit in an ensemble of substrate molecules induces, by a reaction with achiral units, resulting molecules in such a manner that the stereoisomeric products are produced in unequal amounts. Such an asymmetric synthesis may be of great economic value for excluding or reducing the amount of unwanted isomers when only one of the diastereomers is of use or interest.

The reactants used in an asymmetric synthesis can be at least one chiral component consisting of a chemical reagent, solvent or catalyst. Alternatively, by selection of specific enantiomers as starting compounds, the preferred stereoisomer in a predominant amount can be induced. However, selection of enantiomerically pure intermediates does not always result in a stereoselective synthesis since chirality of an intermediate could be lost due to racemization under one or more sets of reaction conditions. Consequently, synthetic processes typically involve extra reaction steps to

accomplish the stereoselective result as well as involve a tedious recrystallization step.

Reported Developments

A chromatographic separation and crystallization step has been reported for the preparation of enantiomeric dibenzofurancarboxamides and 2-carboxamidesubstituted benzoxepines reported to have 5-HT₃-antagonist and gastroprokinetic activity in U.S. Patent Nos. 4,859,683, 4,857,517, 4,924,010 and 4,863,921, all of which are assigned to the same assignee as the present application.

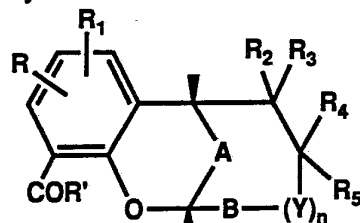
In U.S. Patent No.: 4,863,921, the synthesis of the dibenzofuran-carboxamides proceeds via condensation of a substituted dibenzofuran-4-carboxylic acid or a 6,7,8,9-tetrahydrodibenzofuran-4-carboxylic acid or a 5a,6,7,8,9,9a-hexahydrodibenzofuran-4-carboxylic acid or their acid halides or esters with an amine of the formula H₂N-R which results in the corresponding carboxamide. The process terminates with flash chromatographic separation of the isomers and a recrystallization step in a relatively poor overall yield. This synthesis is made difficult by the presence of an acid sensitive chiral center which racemizes under mild acidic conditions.

The present invention is based on a discovery that acid sensitive intermediates can be used in a stereoselective synthesis using conditions which do not affect the product's chiral centers. Using the present process invention, specific stereoisomers of two basic fused and bridged ring systems can be prepared without recourse to known separation techniques to obtain the desired enantiomers. Compounds prepared by this process are disclosed and claimed in co-pending U.S. Patent Application Serial No. 07/620,241 assigned to the same assignee and filed November 29, 1990.

Summary of the Invention

This invention relates to a process for the preparation of a substantially optically pure compound comprising a multicyclic oxy-containing ring system having at least two chiral centers at either fused or

bridged ring positions. The preferred compounds prepared by the present processes are described by formula I:



Formula I

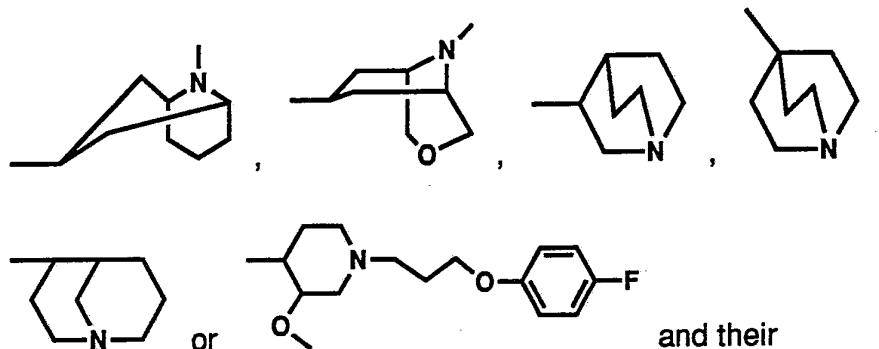
where

one of A or B is CHR_6 and the other A or B is a bond;

Y is CHR ;

n is 0, 1 or 2;

R' is hydroxy, alkoxy, aralkoxy, halo, OM where M is an alkali or alkaline earth metal, or NH-X where X is hydrogen, alkyl, acyl or Z where Z is



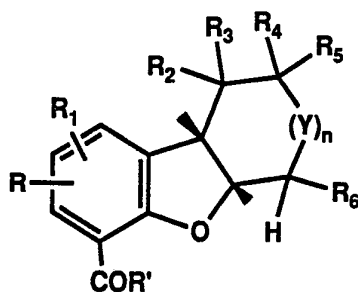
stereoisomers;

R and R_1 are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl, haloalkyl, amino, alkylamino, sulfonyl, alkylsulfamyl or alkylsulfonyl; and

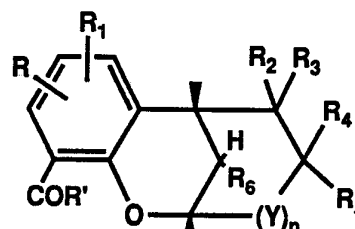
R_2 , R_3 , R_4 , R_5 and R_6 are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl or haloalkyl; and vicinal R_2 , R_3 , R_4 , R_5 and R_6 groups may together form double bonds.

The compounds of formula I are preferably prepared by subjecting a salicyclic acid, ester, amide, acid halide or acid salt having a chiral center-containing cycloalkenyl in the 3-position to acidic cyclization conditions which do not racemize said chiral center-containing cycloalkenyl substituent.

A preferred aspect of the present process invention is the stereospecific synthesis of a compound of either formula II or III below:

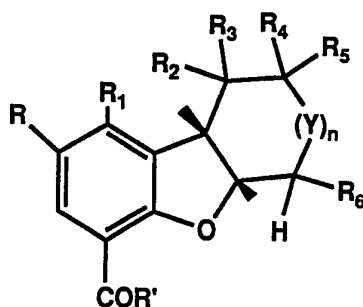


Formula II

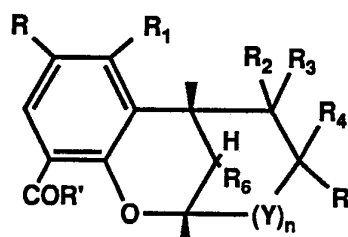


Formula III

A more preferred aspect of the invention is the stereospecific synthesis of an intermediate compound of either formula IV or V



Formula IV



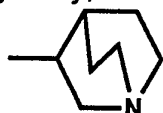
Formula V

where

Y is CH₂;

n is 1;

R' is hydroxy, alkoxy or NH-X where X is Z and Z is



and its stereoisomers;

R is hydrogen or halo;

R₁ are independently hydrogen, amino or mono- and dialkylamino ;

and

R₂, R₃, R₄, R₅ and R₆ are hydrogen; and

vicinal R₂, R₃, R₄, R₅ and R₆ groups may together form a double bond;

comprising subjecting a salicyclic acid, ester, amide or derivative thereof having a chiral center-containing cycloalkenyl in the 3-position to acidic

cyclization conditions which do not racemize said chiral center-containing cycloalkenyl substituent.

DETAILED DESCRIPTION OF THE INVENTION

As employed above and throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

— and — indicate the configuration at the chiral center;

"Alkyl" means, either alone or within the various substituents, defined hereinbefore, a hydrocarbon having one to about 10 carbon atoms. "Lower alkyl" means alkyl having one to about six carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, amyl and hexyl. Preferred lower alkyl includes methyl, ethyl and propyl.

"Halo" means Cl, Br, I and F. Preferred halo are Cl and Br.

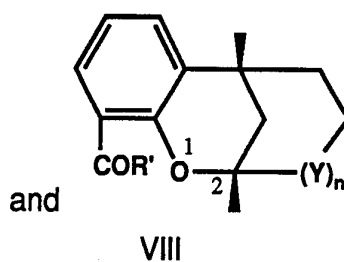
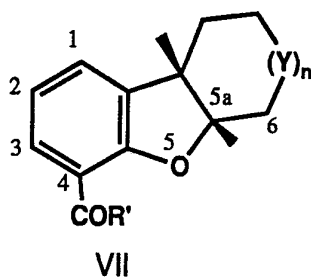
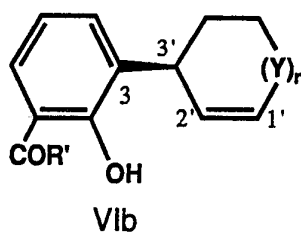
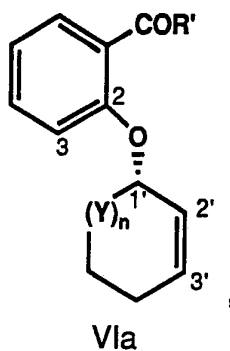
"Aryl" means a mononuclear and polynuclear aromatic hydrocarbon radical which can be substituted or unsubstituted. Examples of preferred aryl groups include phenyl and naphthyl. Preferred substituents include hydrogen, alkyl, alkoxy, amino, halo, aryl, aryloxy, carboalkoxy, nitro, dialkylamino, trifluoromethyl, thioalkyl and carbamoyl.

"Aralkyl" means an alkyl group substituted by an aryl radical. The preferred aralkyl groups are benzyl and phenethyl.

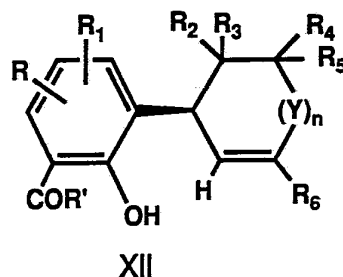
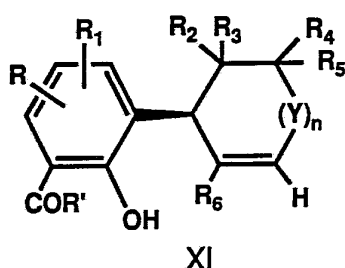
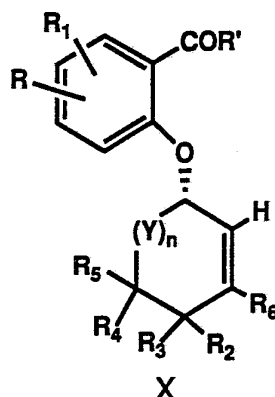
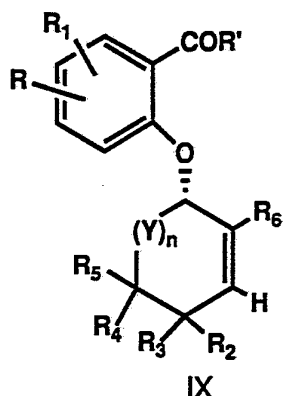
"Multicyclic" denotes a substituted or unsubstituted polynuclear aromatic hydrocarbon group in which one or more ring carbons have been replaced by a nitrogen, oxygen or sulfur atom.

Alkali or alkaline earth metals include those metals capable of forming a salt with a carboxylic acid. Preferred metals include Na, K, Ca, Mg, Li and Cs.

The nomenclature used throughout this invention is shown in Formulae VIa, - VIII:



The present invention involves the process of manipulating acid sensitive chiral compounds under acid conditions and permits the surprising synthesis of bridged or fused ring multicyclic compounds which retain their chiral character. The more preferred compounds used in this process are acid sensitive carboxylic acid, ester and amide chiral compounds described by Formulae IV and V. By choosing the appropriate acid cyclization conditions, the present process can result in either the formation of compounds of Formulae IV and/or V starting from the 3-cyclohexenyl salicylates of Formulae XI and XII, which are in turn prepared from chiral intermediates of Formulae IX and X below.

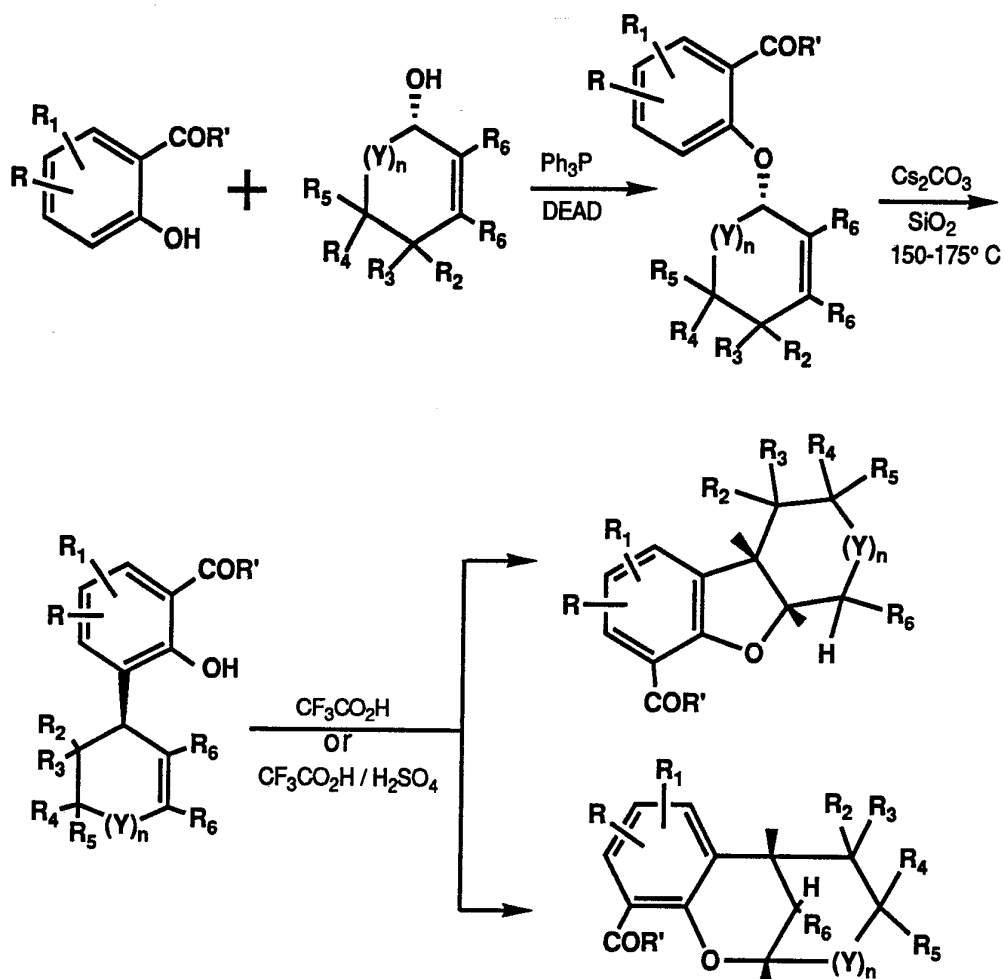


The bridged ring compounds of Formula V are prepared by subjecting the corresponding compound of Formulae XI or XII to sulfuric acid conditions, preferably about 10 - about 50% aqueous sulfuric acid, and most preferably about 35% aqueous sulfuric acid for a time of about 5 minutes to about 12 hours, and most preferably 30 minutes to about 2 hours.

The fused ring compounds of Formula IV are prepared by utilizing a weak acid, such as trifluoroacetic acid, alone or in admixture with a strong acid such as sulfuric acid. By varying the amount of weak acid to strong acid present, the ratio of fused product IV to bridged product V prepared can be manipulated from 6:1 to 1:1.

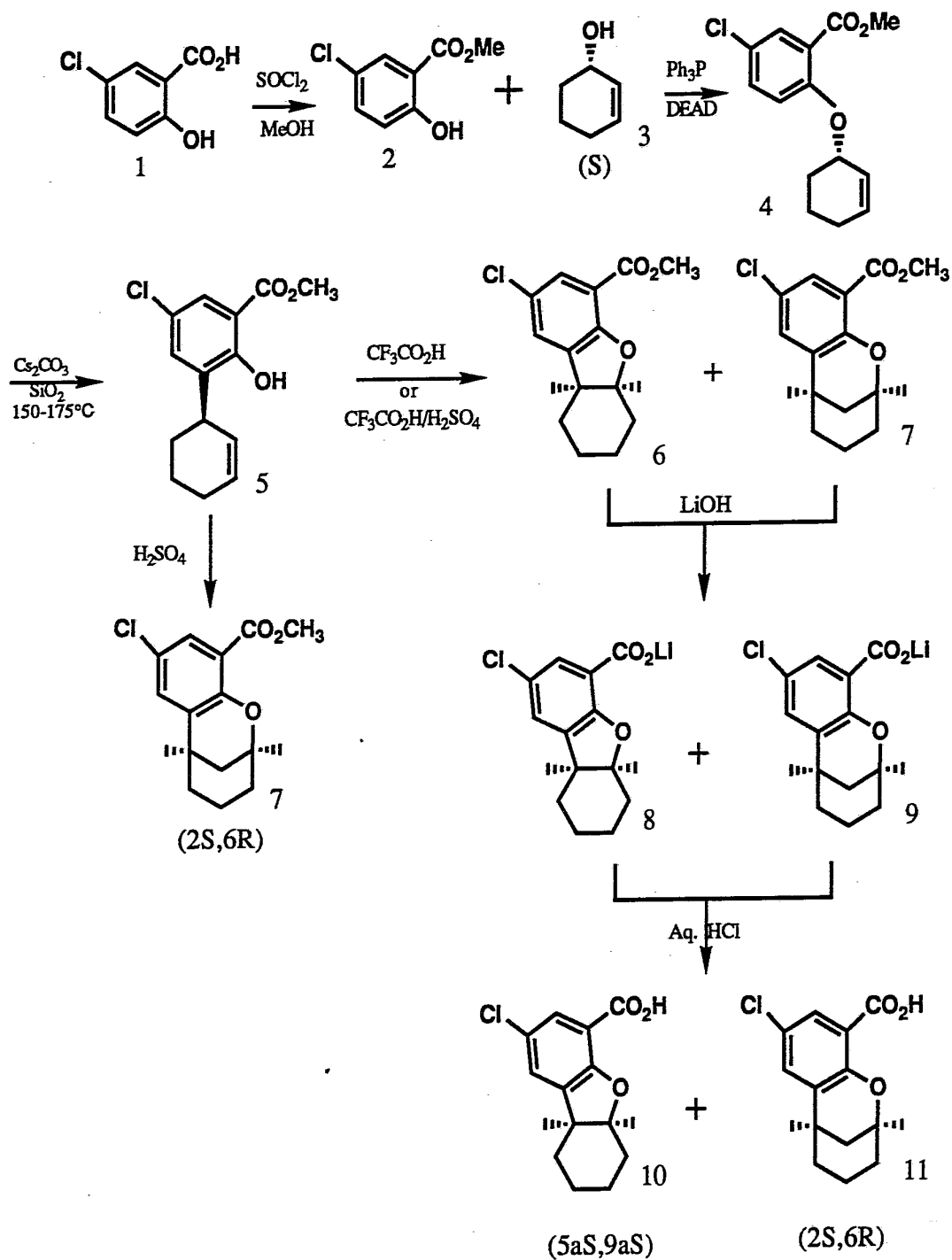
Further, the fused compounds of Formula IV may be converted into the bridged compounds V by using strong acid conditions.

The following reaction schemes illustrate the processes of the compounds of the present invention:

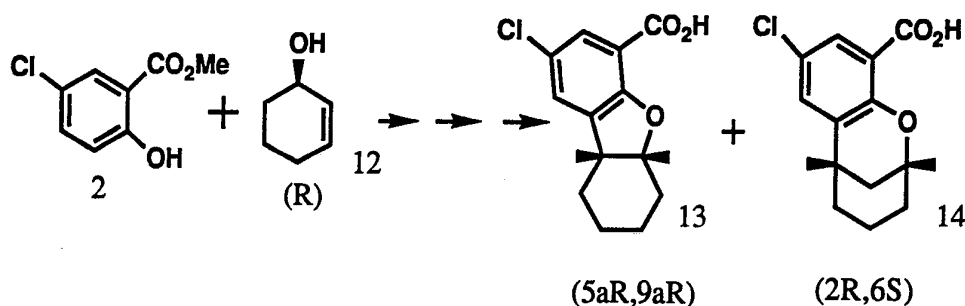


where at least one of R_6 is hydrogen.

The following sequence further illustrates the process of this invention.



This scheme is summarized below for the (R) chiral stereoisomers.



Referring to the above reaction scheme, the stereospecific synthesis is described below:

- a) esterifying 5-chloro salicylic acid (1) gives the corresponding phenol (2);
- b) treating said phenol with triphenyl phosphine and dialkylazodicarboxylate (preferably diethyl or diisopropylazodicarboxylate) in a nonhydroxylic non racemizing polar medium (such as THF, DMF, acetonitrile, etc.) with chirally pure cyclohexen-3-(S)-ol (3) results in the chiral phenol cyclohexenyl ether (4);
- c) treating said phenol cyclohexenyl ether at high temperature (100-250°C and preferably 150-200°C) in the presence of a base and catalyst (such as Cs_2CO_3 and SiO_2) effects the Claisen rearrangement of transferring chirality to a new stereocenter in the 3-(3'-cyclohexene)salicylate (5);
this may also be carried out neat or in the presence of high boiling solvents such as mono- and di-substituted anilines, such as dimethyl or diethylaniline or aromatic amines;
- d) effecting ring closure of said 3-(3'-cyclohexenyl)salicylate by refluxing with a weak acid such as acetic acid or trifluoroacetic acid, or by treatment with a weak acid such as trifluoroacetic acid and a strong acid such as sulfuric acid, hydrochloric acid, nitric acid, etc. at temperatures ranging from -15-150°C (preferably at slightly raised temperatures (20-35°C)) gives the chiral 5a,6,7,8,9,9a-hexahydrodibenzofuran ester (6) and the chiral 2,6-methano-2H-[3,4,5,6-tetrahydro]-1-benzoxocine-10-ester (7);

when this ring closure is carried out using sulfuric acid alone then the sole product prepared is the chiral 2,6-methano-2H-[3,4,5,6-tetrahydro]-1-benzoxocine-10-ester (7);

e) hydrolyzing said esters is preferably carried out in the presence of an aqueous organic media (such as dioxane, diglyme, THF, DMF, DMSO, etc.) with an alkali base (preferably with an aqueous base such as NaOH, KOH, LiOH, etc. however LiOH is most preferred) which selectively isolates the dibenzofuran acid as a salt (8) from the benzoxocine acid salt (9); and

f) treating the respective salts with a non-oxidizing mineral or organic acid such as hydrochloric acid, sulfuric acid, trifluoroacetic acid, etc. to obtain the chiral dibenzofuran acid (5aS,9aS) (10) and the chiral benzoxocine acid (2S,6R) (11).

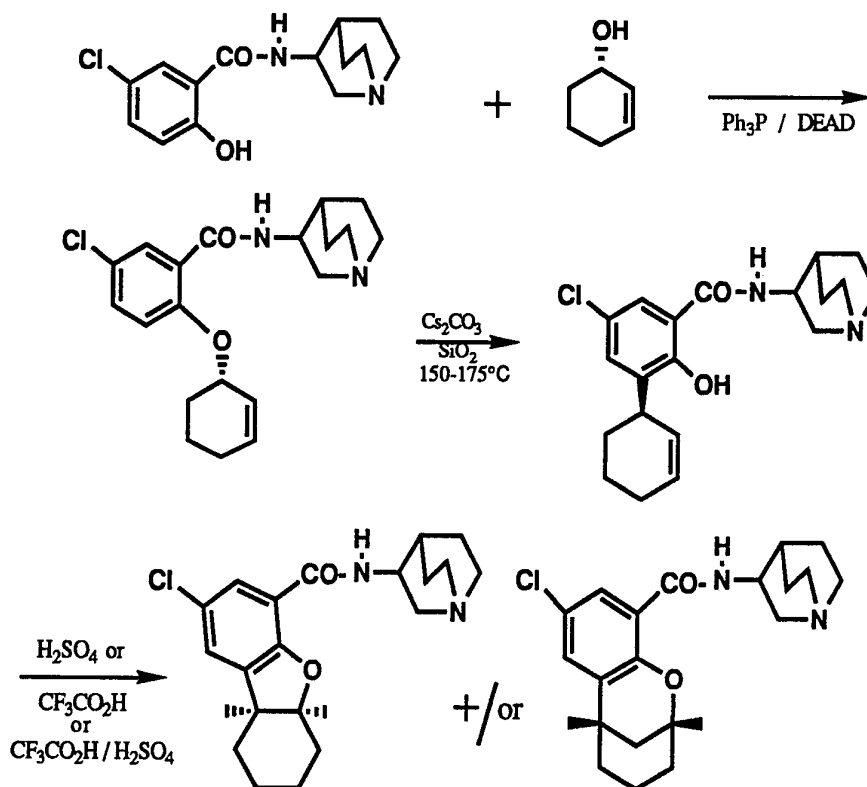
More specifically, it is most preferred to carry out this process using the desired ester, which can then be converted to the acid, amide, acid halide or acid salt under known reaction conditions.

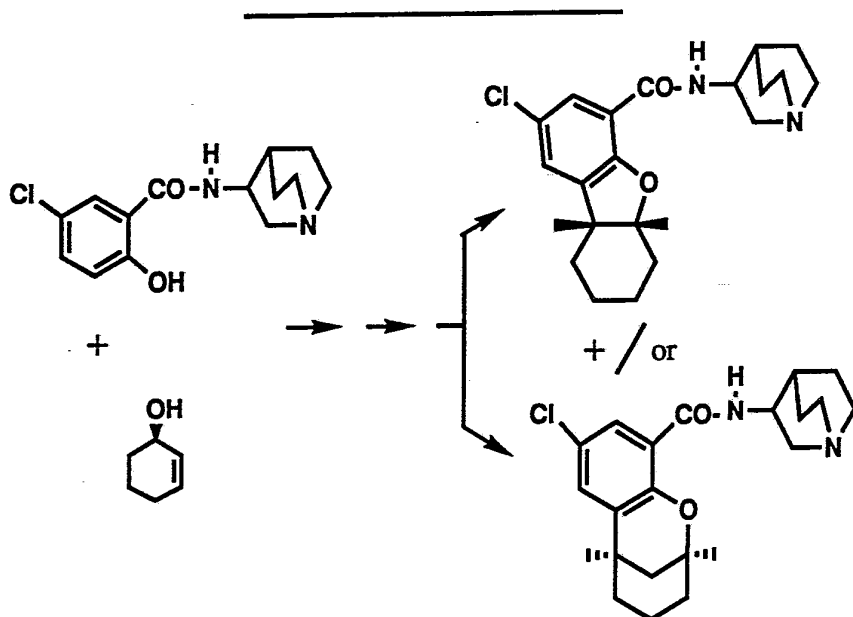
Repeating the above-described steps and using the chirally pure 2-cyclohexen-1-(R)-ol (12) instead of the chirally pure 2-cyclohexen-1-(S)-ol (3) in step b), the final chiral acids produced are the dibenzofuran acid (5aR,9aR) (13) and the chiral benzoxocine acid (2R,6S) (14).

Thus, the process is enabling for synthesizing all four possible stereoisomers of not only the dibenzofuran acids (10) and (13) and the benzoxocine acids (11) and (14) without the necessity of separating the desired enantiomers by cumbersome techniques, but also the corresponding esters, amides, acid halides and acid salts as well.

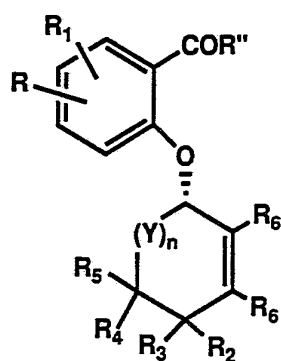
The resolution of the compounds of this invention and their starting materials may be carried out by known procedures. Incorporation by reference is hereby made to U.S. Patent No. 4,863,921 and the four volume compendium Optical Resolution Procedures for Chemical Compounds: Optical Resolution Information Center, Manhattan College, Riverdale, New

York. Such procedures are useful in the practice of this invention. A further useful reference is Enantiomers, Racemates and Resolutions: Jean Jacques, Andre Collet and Samuel H. Wilen; John Wiley & Sons, Inc., New York, 1981. Basically, the resolution of the compounds is based on the differences in the physical properties of diastereomers. Conversion of the racemates into a mixture of diastereomers by attachment of an enantiomerically pure moiety results in forms that are separable by fractional crystallization, distillation or chromatography. Alternately, another chiral center can be incorporated into the desired products, such as shown below.

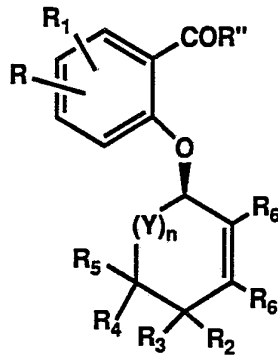




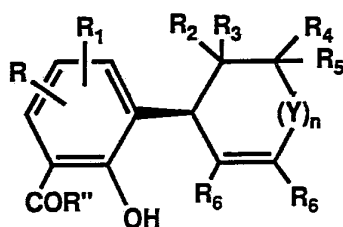
Novel intermediate compounds of this invention include those compounds of Formulae XIII-XVI.



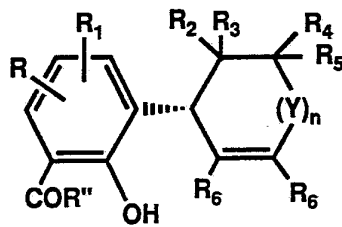
XIII



XIV



XV



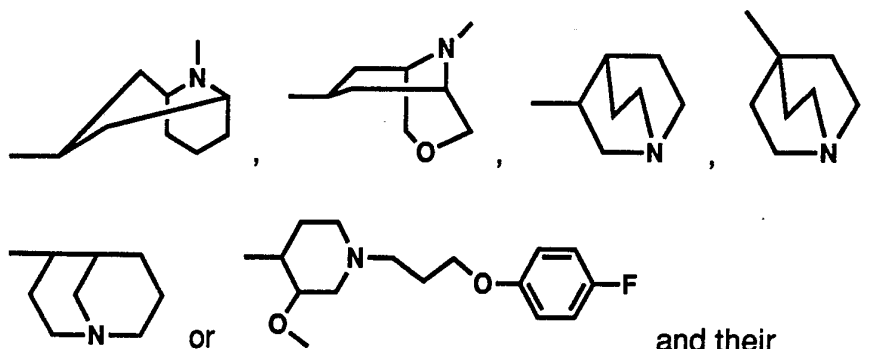
XVI

where Y is CHR;

n is 0, 1 or 2;

R'' is halo, OM where M is an alkali or alkaline earth metal, or NH-X

where X is hydrogen, alkyl, acyl or Z where Z is



stereoisomers;

R and R₁ are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl, haloalkyl, amino, alkylamino, sulfonyl, alkylsulfamyl or alkylsulfonyl; and

R₂, R₃, R₄, R₅ and R₆ are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl or haloalkyl provided at least one of R₆ is hydrogen; and vicinal R₂, R₃, R₄, R₅ and R₆ groups may together form double bonds;

The compounds and process of the present invention are more fully illustrated by the following representative examples.

EXAMPLE 1

Methyl 5-chlorosalicylate

Thionyl chloride (900.0g, 7.46 mol) is added dropwise to methanol (1977.0g, 61.72 mol) at 20°C over a period of 1 hour, maintaining the temperature between 15-25°C with an ice bath. The cooling bath is removed and 5-chlorosalicylic acid (1000.0g, 5.8 mol) is added in one portion, then slowly heated to reflux. On completion of the reaction the solution is cooled to -5°C for 1 hour. The methyl 5-chlorosalicylate is filtered, washed with cold (-5°C) methanol (150 ml) and deionized water (2 x 1.0 L). The solid is dried under house vacuum at 30°C for 24 hours to give 934.1g (86%) of methyl 5-chlorosalicylate; m.p. 44-46°C. Anal. (C₈H₇ClO₃) C, H, calculated Cl: 19.00; found Cl: 18.50. HPLC 97.87A%.

EXAMPLE 2

Methyl 5-chloro-2-(1'(S)-cyclohex-2'-enyl)salicylate

0.38g of methyl-5-chlorosalicylate and 0.4g of triphenylphosphine are placed in a dry 3 neck flask and anhydrous THF (20 ml) is added by cannula

under nitrogen pressure. A portion of 2-cyclohexen-1(S)-ol (0.2g) is added by syringe and the reaction is cooled to 0°C. A solution of THF (10 ml) and diethylazodicarboxylate (0.23g) is added dropwise over 1 hour, holding the temperature at 0°C. The reaction is held at 0°C for 30 minutes after the addition and is then allowed to warm to room temperature. Stirring is continued for 3 hours. TLC (hexane:ethyl acetate; 3:1) shows no starting material at this point. Evaporation of the solvent under reduced pressure and filtration of the oil through neutral alumina yields 0.42g (80%) of methyl 5-chloro-2-(1'(S)-cyclohex-2'-enyl)salicylate as an amber oil. Anal. Calcd. for $C_{14}H_{15}ClO_3$: C 63.04; H, 5.67. Found C, 62.61; H, 5.67. EI-MS m/z: 266, 268 (M+Cl pattern); 234, 236 (M+OMe); 80 [∞]RTD=+101 (C=0.1, MeOH).

EXAMPLE 3

Methyl 5-chloro-3-(3'(R)-cyclohex-2'-enyl)salicylate

0.42g of the product from Example 2 above is sealed in a tube under nitrogen with 0.5g of silica gel and 0.2g of cesium carbonate. The tube is placed in an oil bath and is heated to 150°C for 5 hours. TLC (hexane:ethyl acetate; 3:1) shows the product and 5-chlorosalicylic acid. A 5 ml quantity of isopropanol is added to the reaction mixture and it is filtered through a bed of celite. The celite bed is then washed with another 5 ml of isopropanol. The isopropanol solutions are combined, evaporated to one third its volume and placed in the freezer. After 12 hours, 0.2g (50% yield) of chiral methyl 5-chloro-3-(3'(R)-cyclohex-2'-enyl)salicylate is obtained. Anal. Calcd. for $C_{14}H_{15}ClO_3$: C, 63.04; H, 5.67. Found: C, 64.18; H, 5.88. EI-MS m/z: 266, 268 (M+Cl pattern); 234, 236 (M+OMe); 206, 208 (M+CO₂CH₃). [∞]RTD= -95 (C=0.1, MeOH).

EXAMPLE 4

Methyl 2-chloro-[5a(S)-9a(S)-(5a.6.7.8.9.9a-hexahydro)]dibenzofuran-4-carboxylate

Methyl 8-chloro-[2(S)-6(R)-methano-2H-3.4.5.6-tetrahydro]-1-benzoxocine-10-carboxylate

0.2g of the product from Example 3 above is dissolved in 6 ml of trifluoroacetic acid. Then 0.2g of sulfuric acid is added. The solution turns violet and the temperature rises from 20°C to 25°C. After stirring for 45 minutes TLC (hexane:ethyl acetate; 4:1) shows only the product. 20 ml of

water is added to the reaction, stirred for 10 minutes and then the mixture is extracted with 25 ml of toluene. The toluene solution is dried, filtered and evaporated under reduced pressure to yield 0.2g of the furan ester as an amber oil. NMR shows this to be a 3:1 mixture of methyl 2-chloro-[5a(S)-9a(S)-(5a,6,7,8,9,9a-hexahydro)]-dibenzofuran-4-carboxylate and methyl 8-chloro-[2(S)-6(R)-methano-2H-3,4,5,6-tetrahydro]-1-benzoxocine-10-carboxylate products.

EXAMPLE 5

2-chloro-[5a(S)-9a(S)(5a,6,7,8,9,9a-hexahydro)]dibenzofuran-4-carboxylic acid

To 0.2g of the 3:1 mixture from Example 4 above is dissolved in 2 ml of dioxane, 4 ml of 1N LiOH is added and the mixture is heated to 60°C. After 2 hours, TLC (hexane: ethyl acetate; 4:1) shows only the presence of the acid. The reaction is cooled in the refrigerator overnight to obtain 90 mg of solids which are then acidified with aqueous acetic acid. Extraction of the acetic acid solution with ethyl acetate yields 60 mg of 2-chloro-[5a(S)-9a(S)(5a,6,7,8,9,9a-hexahydro)]dibenzofuran-4-carboxylic acid. N.O, 150-153°C. Anal. Calcd. for C₁₃H₁₃ClO₃: C, 61.79; H, 5.19. Found: C, 61.74; H, 5.16. EI-MS m/z: 252, 254 (M+Cl pattern); 206, 208. [∞]RTD= -28 (C=0.1, MeOH).

EXAMPLE 6

8-chloro-[2(S)-6(R)-methano-2H-3,4,5,6-tetrahydro]-1-benzoxocine-10-carboxylic acid

When the LiOH solution from Example 5 is treated with aqueous acetic acid (20ml) and extracted with ethyl acetate then the product obtained is 8-chloro-[2(S)-6(R)-methano-2H-3,4,5,6-tetrahydro-1-benzoxocine]-10-carboxylic acid.

EXAMPLE 7

When the ring closure of Example 4 is carried out only using sulfuric acid, then methyl 8-chloro-[2(S)-6(R)-methano-2H-3,4,5,6-tetrahydro]-1-benzoxocine-10-carboxylate is formed. Basic hydrolysis gives the salt which is converted to the free acid on treatment with mineral or organic acid. M.P. 120-122°C. Anal. Clcd. for C₁₃H₁₃ClO₃: C, 61.79; H, 5.19. Found: C, 61.57; H, 5.12. [∞]RTD= 21 (C=0.1, MeOH).

EXAMPLE 8

5-Chlorosalicyl[N-(1-azabicyclo[2.2.2]oct-3(S)-yl)]carboxamide

To a solution of 3-aminoquinuclidine (1.3g, 0.01 mol.) in methylene chloride (25ml) is added a solution of dicyclohexylcarbodiimide (2.1g, .011 mol) in methylene chloride (5ml). The mixture is then cooled to 0°C and 5-chlorosalicylic acid (1.7g, .0098 mol) in methylene chloride is added and stirred overnight. Acetic acid (1ml) is added to destroy the excess dicyclohexylcarbodiimide and the dicyclohexylurea, which precipitates, is filtered off. The filtrate is washed with 1N sodium hydroxide and water, dried and concentrated to yield the desired amide. The (S) and (R) enantiomers are then resolved.

EXAMPLE 9

5-Chloro-2-(1'(S)-cyclohex-2'-enyl)salicyl[N-(1-azabicyclo[2.2.2]oct-3(S)-yl)]-carboxamide

5-Chlorosalicyl[N-(1-azabicyclo[2.2.2]oct-3(S)-yl)]carboxamide (0.56 grams .002 mol) and triphenylphosphine (0.4g) is charged to a dry 3 neck flask and 20 ml of anhydrous THF is added by canula under nitrogen pressure. A 0.2g portion of 2-cyclohexen-1(S)-ol is added by syringe and the reaction is cooled to 0°C. A solution of 10 ml of THF and 0.23g of diethylazodicarboxylate is added dropwise over 1 hour, holding the temperature at 0°C. The reaction is held at 0°C for 30 minutes after the addition and then allowed to warm to room temperature. Stirring is continued for 3 hours. Evaporation of the solvent under reduced pressure and filtration of the oil through neutral alumina yields 5-chloro-2-(1'(S)-cyclohex-2'-enyl)salicyl[N-(1-azabicyclo[2.2.2]oct-3(S)-yl)]-carboxamide.

EXAMPLE 10

5-Chloro-3-(3'(R)-cyclohex-2'-enyl)salicyl[N-(1-azabicyclo[2.2.2]oct-3(S)-yl)]-carboxamide

The 0.59g (.0016mol) of 5-chloro-2-(1'(S)-cyclohex-2'-enyl)salicyl[N-(1-azabicyclo[2.2.2]oct-3(S)-yl)]carboxamide is sealed in a tube under nitrogen with 0.5 g of silica gel and 0.2 g of cesium carbonate. The tube is placed in an oil bath and heated to 150°C for 5 hours. A 5ml quantity of toluene is added to the reaction mixture and it is filtered through a bed of celite. The celite bed is then washed with another 5ml of toluene. The

toluene solutions are combined, washed with 1N sodium hydroxide, and water, dried and evaporated to yield
 5-chloro-3-(3'(R)-cyclohex-2'-enyl)salicyl[N-(1-azabicyclo[2.2.2]oct-3(S)-yl)]-carboxamide.

EXAMPLE 11

2-Chloro-[5a(S)-9a(S) (5a,6,7,8,9,9a-hexahydro)]dibenzofuran-4-[N-(1-azabicyclo[2.2.2.]oct-3(S)-yl)]carboxamide.

8-Chloro-[2(S)-6(R)-methano-2H-3,4,5,6-tetrahydro]-1-benzoxocine-10-[N-(1-azabicyclo[2.2.2.]oct-3(S)-yl)]carboxamide

5-Chloro-3-(3'(R)-cyclohex-2'-enyl)salicyl[N-(1-azabicyclo[2.2.2]oct-3(S)-yl)]carboxamide (0.28g .0007 mol) is dissolved in 6ml of trifluoroacetic acid and 0.4g of sulfuric acid is added. After stirring for 45 minutes 20ml of water is added to the reaction which is stirred for 10 minutes, and then extract with 25 ml of toluene. The toluene solution is dried and evaporated under reduced pressure to yield a mixture of 2-chloro-[5a(S)-9a(S) (5a,6,7,8,9,9a-hexahydro)]dibenzofuran-4-[N-(1-azabicyclo[2.2.2.]oct-3(S)-yl)]carboxamide and 8-chloro-[2(S)-6(R)-methano-2H-3,4,5,6-tetrahydro]-1-benzoxocine-10-[N-(1-azabicyclo[2.2.2.]oct-3(S)-yl)]carboxamide, which are separated by HPLC.

EXAMPLE 12

When the procedures of Examples 8-11 are followed and 3-aminoquinuclidine is replaced by 3(R)-aminoquinuclidine then the products prepared are 2-chloro-[5a(S)-9a(S) (5a,6,7,8,9,9a-hexahydro)]dibenzofuran-4-[N-(1-azabicyclo[2.2.2.]oct-3(R)-yl)]carboxamide and 8-chloro-[2(S)-6(R)-methano-2H-3,4,5,6-tetrahydro]-1-benzoxocine-10-[N-(1-azabicyclo[2.2.2.]oct-3(R)-yl)]carboxamide.

EXAMPLE 13

When the procedures of Examples 1-12 are followed and methyl 5-chlorosalicylate of Example 2 is replaced by the compounds of Table I, below, then the corresponding compounds are prepared.

Table I

methyl 5-bromosalicylate
 methyl 5-methylsulfonylsalicylate
 methyl 2-methoxy-4-amino-5-chlorobenzoate

methyl 2-methoxy-4-acetylamino-5-chlorobenzoate
 methyl 4-acetylamino-5-chlorosalicylate
 methyl 2-methoxy-4-aminobenzoate
 methyl 2-methoxy-4-methylamino-5-chlorobenzoate
 methyl 2-methoxy-5-sulfamylbenzoate
 methyl 2-methoxy-5-methylsulfamylbenzoate

EXAMPLE 14

When the procedures of Examples 8-13 are followed and 3(S)-amino-quinuclidine in Example 8 is replaced by the compounds of Table II, below, then the corresponding compounds are prepared.

Table II

3-aminoquinuclidine
 4-amino-1-azabicyclo[3.3.1.]nonane
 4-amino-1-azabicyclo[2.2.2.]octane
 3-amino-9-methyl-9-azabicyclo[3.3.1.]nonane
 3-amino-7-oxo-9-methyl-9-azabicyclo[3.3.1.]nonane
 1-(p-fluorophenoxypropyl)-3-methoxy-4-aminopiperidine
 and the stereoisomers of the above compounds.

EXAMPLE 15

When the procedure of Example 4 is followed and the ratio of weak acid (trifluoroacetic acid) to strong acid (sulfuric acid) is varied according to the Table III below, then the corresponding amount of fused product(dibenzofuran) to bridged product (benzoxacine) is shown.

Table III

Reaction time hrs.	Acid	Temperature	Fused/Bridged
1	TFA/sulfuric 20:1	-5°C	6/1
1	TFA/sulfuric 100:1	-5°C	6/1
2	TFA/sulfuric 20/1	-15°C	6/1
1	acetic/sulfuric 20/1	25°C	1/1

EXAMPLE 16**A. Methyl 8-chloro-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxocin-10-carboxylate**

To concentrated sulfuric acid (519ml) is added in portions methyl-5-chloro-3-(3'cyclohexenyl)salicylate (345g, 1.3mol), keeping the temperature below 50°C. After stirring at room temperature for 1 hour the mixture is poured into water (4.2L), followed by neutralization with 50% aqueous sodium hydroxide (843ml). This basic mixture is extracted with toluene (2.5L), the toluene dried with sodium sulfate, filtered and evaporated to dryness to give 351.6g (102%) of methyl-8-chloro-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxocin-10-carboxylate as an oil which is used directly in the next step.

B. 8-Chloro-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxocin-10-carboxylic acid

methyl 8-chloro-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxocin-10-carboxylate (351.6g) is added to a solution of lithium hydroxide monohydrate, (131.0g, 3.12mol) in water (2.6L) and the mixture heated to reflux for 1.5 hours which results in the formation of a heavy precipitate. The reaction mixture is cooled to room temperature, ethyl acetate (1.7L) is added, followed by acidification with concentrated hydrochloric acid (276ml). The ethyl acetate is removed and the acidic aqueous layer is further extracted with ethyl acetate (500ml). The ethyl acetate extracts are combined, dried with sodium sulfate, filtered and evaporated to dryness to give 327.7g of material. Recrystallization from acetonitrile gives 253.6g of 8-chloro-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxocin-10-carboxylic acid: mp 110°-120°C; ¹H NMR (CDCl₃) δ 10.94(s, 1H), 7.98(d, 1H), 7.22(d,1H),4.98(s, 1H), 3.10(s, 1H), 1.2-2.3(m, 8H). Achiral HPLC 99.53A%.

EXAMPLE 17**Conversion of 2-chloro-cis-5a,6,7,8,9,9a-hexahydrodibenzofuran-4-carboxylic acid to 8-chloro-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxocin-10-carboxylic acid**

A mixture of the 2-chloro-cis-5a,6,7,8,9,9a-hexahydrodibenzofuran-4-carboxylic acid (300mg, 1.19mmol) and concentrated sulfuric acid (25ml) are stirred at room temperature for 1 hour. The solution turns dark amber as the acid dissolves. The mixture is cooled in an ice-bath and water (50ml) is

added in portions at 25°C. The cloudy mixture is extracted with toluene (2 x 50ml), the toluene is dried with sodium sulfate, filtered and evaporated to dryness to give a glassy solid. The NMR shows this product to be the 8-chloro-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxocin-10-carboxylic acid. ^1H NMR CDCl_3 δ 10.2(s, 1H), 7.9(d, 1H), 7.2(d, 1H), 4.9(m, 1H), 3.3(m, 1H), 1.2-2.4(m, 8H).

Compounds of this invention may be readily converted to their non-toxic acid addition salts by customary methods used in the art. The non-toxic salts of this invention are those salts the acid component of which is pharmacologically acceptable in the intended dosages, including those prepared from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid, and from organic acids such as methane sulfonic acid, benzenesulfonic acid, acetic acid, propionic acid, maleic acid, succinic acid, glycolic acid, lactic acid, salicylic acid, benzoic acid, nicotinic acid, phthalic acid, stearic acid, oleic acid, etc.

Compounds within the scope of this invention exhibit useful gastric prokinetic and anti-emetic properties and lack D_2 receptor binding activity. As such they possess therapeutic value in the treatment of upper bowel motility and gastro-esophageal reflux disorders. Further, the compounds of this invention may be useful in the treatment of disorders related to impaired gastrointestinal motility such as retarded gastric emptying, dyspepsia, flatulence, esophageal reflux, peptic ulcer and emesis. Compounds within the scope of this invention exhibit 5-HT_3 antagonism and are considered to be useful in the treatment of psychotic disorders such as schizophrenia and anxiety and in the prophylaxis treatment of migraine and cluster headaches. Compounds of this invention are selective in that they have little or no dopaminergic antagonist activity.

Various tests in animals can be carried out to show the ability of the compounds of this invention to exhibit pharmacological responses that can be correlated with activity in humans. These tests involve such factors as the effect of the compounds of Formulae V and VI on gastric motility, emesis, selective antagonism of 5-HT_3 receptors and their D_2 dopamine receptor binding properties.

It has been found that the compounds of this invention when tested in the above variety of situations show a marked activity.

One such test is the "Rat Gastric Emptying: Amberlite Bead Method". This test is carried out as follows:

The study is designed to assess the effects of a test agent on gastric emptying of a solid meal in the rat. The procedure is a modification of those used in L.E. Borella and W. Lippmann (1980) Digestion 20: 26-49.

Procedure:

Amberlite® beads are placed in a phenol red solution and allowed to soak for several hours. Phenol red serves as an indicator, changing the beads from yellow to purple as their environment becomes more basic. After soaking, the beads are rinsed with 0.1 NaOH to make them purple and then washed with deionized water to wash away the NaOH.

The beads are filtered several times through 1.18 and 1.4mm sieves to obtain beads with diameters in between these sizes. This is done using large quantities of deionized water. The beads are stored in saline until ready to use.

Male Sprague-Dawley rats are fasted 24 hours prior to the study with water ad libitum. Rats are randomly divided in treatment groups with an N of 6 or 7.

Test agents are prepared in 0.5% methylcellulose and administered to the rats orally in a 10 ml/kg dose volume. Control rats receive 0.5% methylcellulose, 10 ml/kg p.o. One hour after dosing, rats are given 60 Amberlite® beads intragastrically. The beads are delivered via a 3 inch piece of PE205 tubing attached to a 16 gauge tubing adapter and syringe. A small piece of PE 50 tubing is placed inside the tubing adapter to prevent the beads from being pulled back into the syringe. The beads are flushed into each rat's stomach with 1 ml saline.

Rats are sacrificed 30 minutes after receiving the beads and their stomachs are removed. The number of beads remaining in each stomach is counted after rinsing the beads with NaOH.

The number of beads remaining in each stomach is subtracted from 60 to obtain the number of beads emptied. The mean number of beads $\pm$ S.E.M. is determined for each treatment group. The percent change from control is calculated as follows:

$$\frac{\text{Mean Control Group} - \text{Mean Test Agent Group}}{\text{Mean Control Group}} \times 100$$

Statistical significance may be determined using a t-test for independent samples with a probability of 0.05 or less considered to be significant.

In order to demonstrate the ability of the compounds of this invention as anti-emetic agents, the following test for "Cisplatin-Induced Emesis in the Ferret" may be used. This test is a modified version of a paper reported by A. P. Florezyk, J. E. Schurig and W. T. Brodner in Cancer Treatment Reports: Vol. 66, No. 1, January 1982.

Cisplatin had been shown to cause emesis in the dog and cat. Florczyk, et al. have used the ferret to demonstrate the same effects.

Procedure:

Male castrated, Fitch ferrets, weighing between 1.0 and 1.5 kg have an indwelling catheter placed in the jugular vein. After a 2-3 day recovery period, the experimental procedure is begun.

30 minutes prior to administration of cisplatin, ferrets are dosed with the compound in 0.9% saline (i.v.) at a dose volume of 2.0 ml/kg.

45 minutes after administration of cisplatin, ferrets are again dosed with the 0.9% saline (i.v.) mixture at a dose volume of 2.0 ml/kg.

Cisplatin is administered (i.v.) 30 minutes after the first dosing with 0.9% saline. Cisplatin, 10 mg/kg is administered in a dose volume of 2.0 ml/kg.

The time of cisplatin administration is taken as time zero. Ferrets are observed for the duration of the experiment (4 hours). The elapsed time to the first emetic episode is noted and recorded, as are the total number of periods of emesis.

An emetic (vomiting) episode is characterized by agitated behavior, such as pacing around the cage and rapid to and fro movements. Concurrent with this behavior are several retching movements in a row, followed by a single, large, retch which may or may not expulse gastric contents. Immediately following the single large retch, the ferret relaxes. Single coughs or retches are not counted as vomiting episodes.

D-2 Dopamine Receptor Binding Assay

The D-2 dopamine receptor binding assay has been developed with slight modifications using the method of Ian Cresse, Robert Schneider and Solomon H. Snyder, Europ. J. Pharmacol. 46: 377-183 (1977). Spiroperidol is a butyrophenone neuroleptic whose affinity for dopamine receptors in brain tissue is greater than that of any other known drug. It is a highly specific D-1 dopamine (non-cyclase linked) receptor agent with K_1 values of 0.1-0.5 for D-2 inhibition and 300 nM for D-1 inhibition.

Sodium ions are important regulators of dopamine receptors. The affinity of the D-2 receptor is markedly enhanced by the presence of millimolar concentrations of sodium chloride. The K_d in the absence and presence of 120 mM sodium chloride is 1.2 and 0.086 nM respectively. Sodium chloride (120 mM) is included in all assays as a standard condition.

The caudate nucleus (corpus striatum) is used as the receptor source because it contains the highest density of dopamine receptors in the brain and periphery.

Procedure:

Male Charles-River rats weighing 250-300g are decapitated and their brain removed, cooled on ice, and caudate dissected immediately and frozen on dry ice. Tissue can be stored indefinitely at -70°C. For assay caudate is homogenized in 30 ml of tris buffer (pH 7.7 at 25°C) using the polytron homogenizer. The homogenate is centrifuged at 40,000g (18,000-19,000 RPM in SS-34 rotor) for 15 minutes. Pellet is resuspended in fresh buffer and centrifuged again. The final pellet is resuspended in 150 volumes of assay buffer.

Specific ^3H -spiroperidol binding is assayed in a total 2 ml reaction volume consisting of 500 μl of caudate homogenate, 50 mM tris buffer (pH 7.4 at 35°C), 5 mM MgSO_4 , 2 mM EDTA $\cdot$ 2NA, 120 mM NaCl, 0.1% ascorbic acid, 0.4 nM ^3H -spiroperidol and test compound or assay buffer. When catecholamines are included in the assay, 10 μM pargyline should be included in the reaction mixture to inhibit monoamine oxidase. Samples are incubated at 37°C for 30 minutes followed by addition of 5 ml ice cold 50 mM TRIS (pH 7.7 at 25°C) and filtration through GF/B glass fiber filters on a Brandel Receptor Binding Filtration apparatus. Filters are washed twice with an additional 5 ml of tris buffer each. Assay groups are performed in triplicate and 1 μM d(+) butaclamol is used to determine nonspecific binding. Filters are placed in vials containing 10 ml of Ecoscint phosphor, shaken for 30 minutes and dpm determined by liquid scintillation spectrophotometry using a quench curve. Proteins are determined by the method of Bradford, M.; Anal. Biochem. 72, 248 (1976) using Bio-Rad's coomassie blue G-250 dye reagent. Bovine gamma globulin supplied by Bio-Rad is used as the protein standard.

Bezold-Jarisch Effect in Anaesthetized Rats

Male rats 260-290 g are anaesthetized with urethane 1.25 g/kg $^{-1}$ i.p., and trachea cannulated. The jugular vein is cannulated for intravenous (i.v.) injection of drugs. Blood pressure is recorded from a cannula in the left carotid artery and connected to a heparin/saline-filled pressure transducer. Continuous heart rate measurements are taken from the blood pressure recordings. The Bezold-Jarisch effect is evoked by rapid, bolus i.v.

injections of 5-HT and measurements are made of the fall in heart rate. In each rate, consistent responses are first established with the minimum dose of 5-HT that evokes a clear fall in heart rate. Injections of 5-HT are given every 12 minutes and a dose-response curve for the test compound is established by injecting increasing doses of compound 5 minutes before each injection of 5-HT. The effect of the compound on the 5-HT-evoked bradycardia is calculated as a percent of the bradycardia evoked by 5-HT before injection of compound.

In separate experiments to measure the duration of 5-HT antagonism caused by the compounds of this invention, a single dose of compound is injected 5 minutes before 5-HT, and the effects of 7 repeated challenges with 5-HT are then monitored. The effects of the compound on the efferent vagal limb of the Bezold-Jarisch reflex are checked by electrically stimulating the peripheral end of a cut vagus nerve. Unipolar electrical stimulation is applied every 5 minutes via a pair of silver electrodes, using 1 ms rectangular pulses in 5 strains with a maximally-effective voltage (20 V at 10 Hz). Pulse frequency may vary from 5-30 Hz and frequency-response curves are constructed before and 10 minutes after i.v. injection of a single dose of compound.

The results of these above tests indicate that compounds within the scope of this invention exhibit a valuable balance between the peripheral and central action of the nervous system and may be useful in the treatment of disorders related to impaired gastro-intestinal motility such as gastric emptying, dyspepsia, flatulence, esophageal reflux and peptic ulcer and in the treatment of disorders of the central nervous system such as psychosis.

The compounds of the present invention can be administered to a mammalian host in a variety of forms adapted to the chosen route of administration, i.e., orally, or parenterally. Parenteral administration in this respect includes administration by the following routes: intravenous, intramuscular, subcutaneous, intraocular, intrasynovial, transepithelially including transdermal, ophthalmic, sublingual and buccal; topically including ophthalmic, dermal, ocular, rectal and nasal inhalation via insufflation and aerosol and rectal systemic.

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, trochees, capsules, elixirs, suspensions, syrups, wafers and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 6% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 50 and 300 mg of active compound.

The tablets, trochees, pills, capsules and the like may also contain the following: 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 and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

The active compound may also be administered parenterally or intraperitoneally. Solutions of the active compound as a freebase or pharmacologically acceptable salt can be prepared in water suitably mixed

with a surfactant such as hydroxy-propylcellulose. Dispersion can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and 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, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. For prolonged absorption of the injectable compositions, agent delaying absorption, for example, aluminum monostearate and gelatin may be incorporated.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with the various other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying technique which yields a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

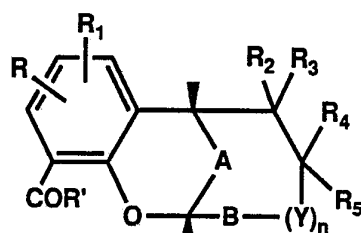
The therapeutic compounds of this invention may be administered to a mammal alone or in combination with pharmaceutically acceptable

carriers, as noted above, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice.

The physician will determine the dosage of the present therapeutic agents which will be most suitable for prophylaxis or treatment and will vary with the form of administration and the particular compound chosen, and also, it will vary with the particular patient under treatment. He will generally wish to initiate treatment with small dosages and, if necessary, increase the dosage by small increments until the optimum effect under the circumstances is reached. The therapeutic dosage will generally be from 0.1 to 20 mg or from about 0.01 mg to about 50 mg/kg of body weight per day and higher although it may be administered in several different dosage units from once to several times a day. Higher dosages are required for oral administration.

WHAT IS CLAIMED IS:

1. A process for the preparation of a substantially optically pure compound comprising a multicyclic oxy-containing ring system having at least two chiral centers at either fused or bridged ring positions comprising subjecting a phenol with an ortho chiral center-containing cycloalkenyl to acidic cyclization conditions which do not racemize said chiral center-containing cycloalkenyl substituent.
2. A process according to claim 1 comprising selecting acidic conditions for the preparation of a fused oxy-containing ring system.
3. A process according to claim 1 comprising selecting acidic conditions for the preparation of a bridged oxy-containing ring system.
4. A process according to claim 1 comprising forming said chiral center-containing cycloalkenyl phenol from a chiral center-containing cycloalkenyl phenyl ether.
5. A process according to claim 1 for the preparation of a substantially optically pure compound of the formula



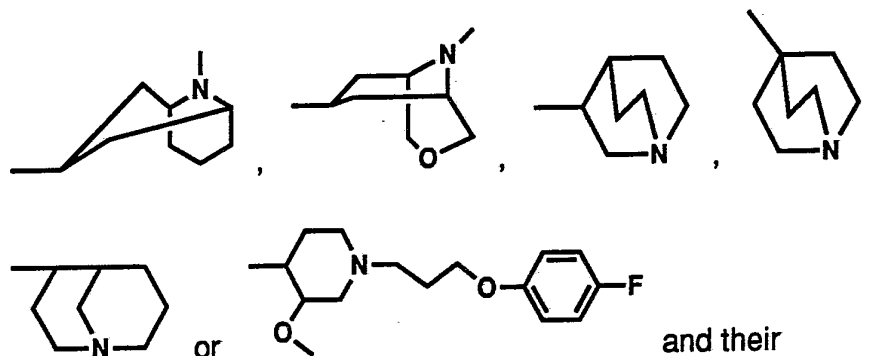
where

one of A or B is CHR_6 and the other A or B is a bond;

Y is CHR ;

n is 0, 1 or 2;

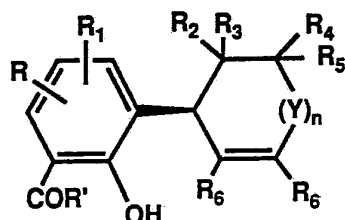
R' is hydroxy, alkoxy, aralkoxy, halo, OM where M is an alkali or alkaline earth metal, or NH-X where X is hydrogen, alkyl, aralkyl, acyl or Z where Z is



stereoisomers;

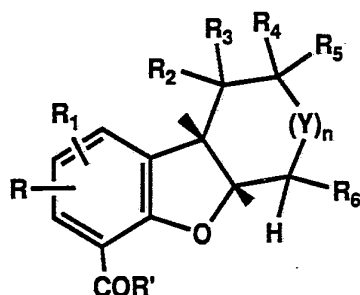
R and R₁ are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl, haloalkyl, amino, alkylamino, sulfonyl, alkylsulfamyl or alkylsulfonyl; and

R₂, R₃, R₄, R₅ and R₆ are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl or haloalkyl; and vicinal R₂, R₃, R₄, R₅ and R₆ groups may together form double bonds; which comprises treating a compound of the formula

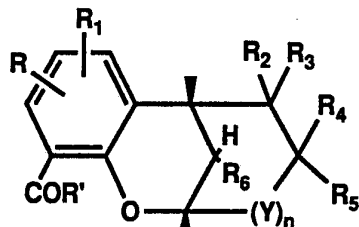


where at least one R₆ is hydrogen; with trihaloacetic acid or a mixture of trihaloacetic acid and sulfuric acid and isolating the compounds formed.

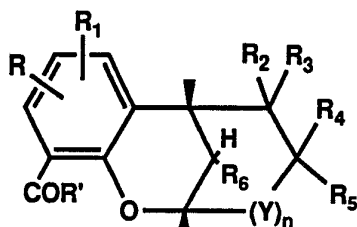
6. A process according to claim 5 for the preparation of a compound of the formula



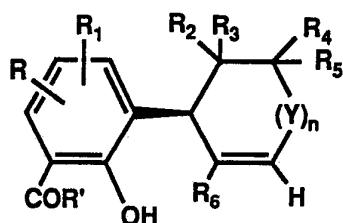
7. A process according to claim 5 for the preparation of a compound of the formula



8. A process according to claim 3 for the preparation of a compound of the formula

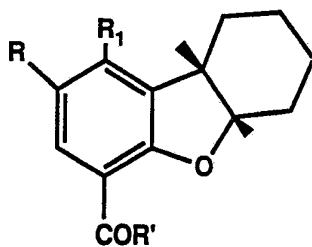


by treating a compound of the formula

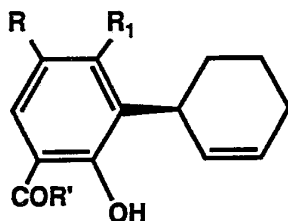


with sulfuric acid .

9. A process according to claim 6 for the preparation of a compound of the formula

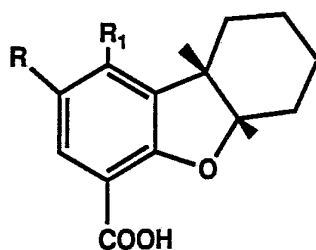


by treating a compound of the formula



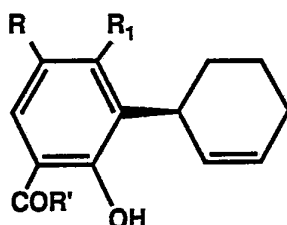
with trihaloacetic acid or a mixture of trihaloacetic acid and sulfuric acid.

10. A process for the preparation of a compound according to Claim 9 of the formula



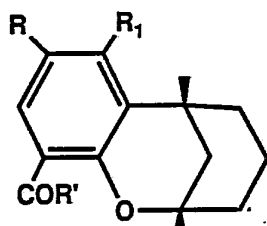
where R is hydrogen or halo and R₁ is hydrogen, amino or mono- or dialkylamino;

by treating a compound of the formula

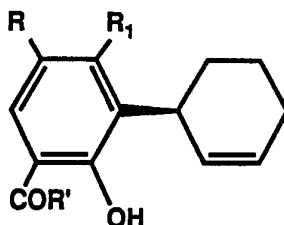


where R is hydrogen or halo, R₁ is hydrogen, amino or mono- or dialkylamino and R' is alkoxy; with trifluoroacetic acid or a mixture of trifluoroacetic acid and sulfuric acid and hydrolyzing the resultant ester.

11. A process according to Claim 3 for the preparation of a compound of the formula

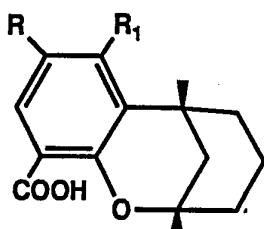


by treating a compound of the formula

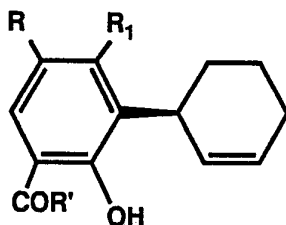


with sulfuric acid or a mixture of trihaloacetic acid and sulfuric acid.

12. A process according to Claim 11 for the preparation of a compound of the formula

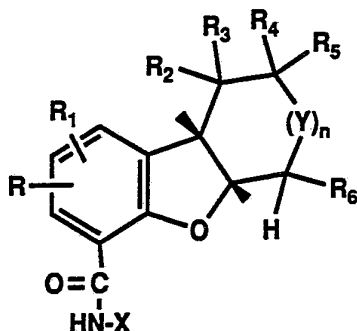


where R is hydrogen or halo and R₁ is hydrogen, amino or mono- or dialkylamino; by treating a compound of the formula



where R is hydrogen or halo and R₁ is hydrogen, amino or mono- or dialkylamino and R' is alkoxy; with sulfuric acid or a mixture of trifluoroacetic acid and sulfuric acid and hydrolyzing the resultant ester.

13. A process according to Claim 5 for the preparation of a compound of the formula



where

one of A or B is CHR_6 and the other A or B is a bond;

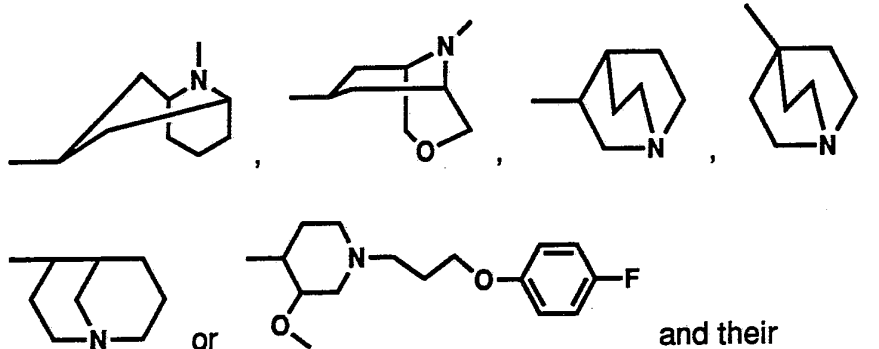
Y is CHR;

n is 0, 1 or 2;

R and R_1 are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl, haloalkyl, amino, alkylamino, sulfonyl, alkylsulfamyl or alkylsulfonyl; and

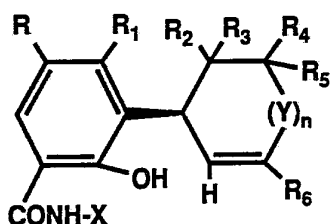
R_2 , R_3 , R_4 , R_5 and R_6 are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl or haloalkyl; and vicinal R_2 , R_3 , R_4 , R_5 and R_6 groups may together form double bonds; and

X is Z where Z is



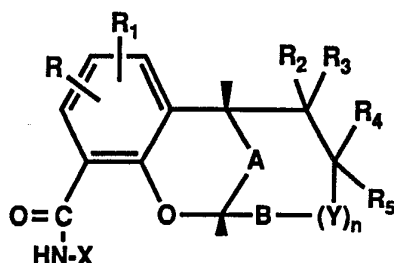
stereoisomers;

by treating a compound of the formula



with trihaloacetic acid or a mixture of trihaloacetic acid and sulfuric acid.

14. A process according to Claim 8 for the preparation of a compound of the formula



where

one of A or B is CHR₆ and the other A or B is a bond:

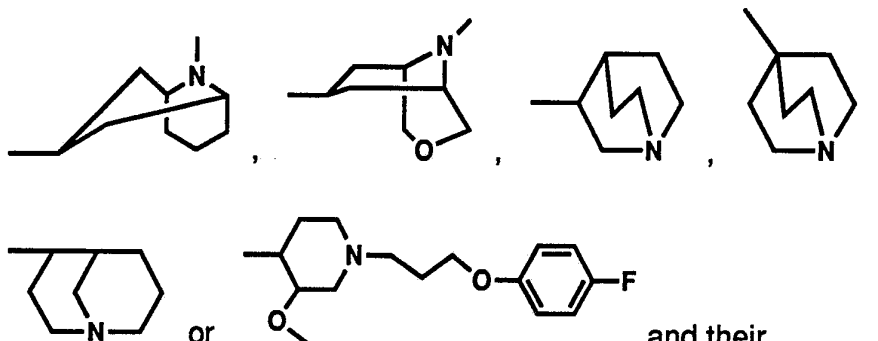
Y is CHR;

n is 0, 1 or 2;

R and R₁ are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl, haloalkyl, amino, alkylamino, sulfonyl, alkylsulfamyl or alkylsulfonyl; and

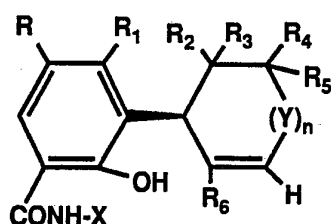
R₂, R₃, R₄, R₅ and R₆ are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl or haloalkyl; and vicinal R₂, R₃, R₄, R₅ and R₆ groups may together form double bonds; and

X is Z where Z is



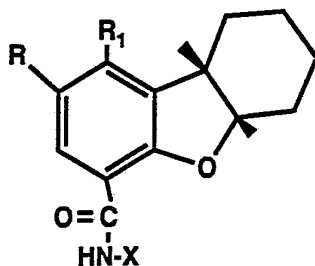
stereoisomers;

by treating a compound of the formula

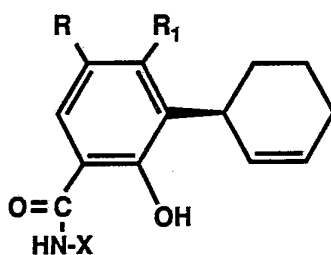


with sulfuric acid or a mixture of trihaloacetic acid and sulfuric acid.

15. A process according to Claim 13 for the preparation of a compound of the formula

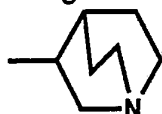


where R is hydrogen or halo and R₁ is hydrogen, amino or mono- or dialkylamino and X is Z;
by treating a compound of the formula



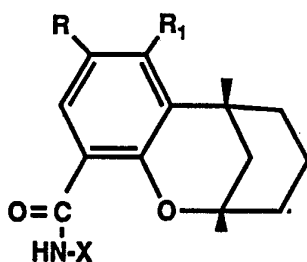
where R is hydrogen or halo, R₁ is hydrogen, amino or mono- or dialkylamino and X is Z;
with trifluoroacetic acid or a mixture of trifluoroacetic acid and sulfuric acid.

16. A process according to Claim 15 where R is chloro, R₁ is hydrogen



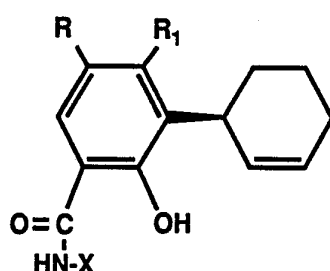
and X is Z where Z is and its stereoisomers; thus forming 2-chloro-[5a(S)-9a(S) (5a,6,7,8,9,9a-hexahydro]dibenzofuran-4-[N-(1-azabicyclo[2.2.2.]oct-3-yl)carboxamide.

17. A process according to Claim 14 for the preparation of a compound of the formula



where R is hydrogen or halo and R₁ is hydrogen, amino or mono- or dialkylamino and X is Z;

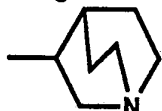
by treating a compound of the formula



where R is hydrogen or halo and R₁ is hydrogen, amino or mono- or dialkylamino and X is Z;

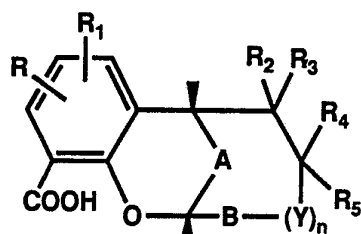
with sulfuric acid or a mixture of trifluoroacetic acid and sulfuric acid.

18. A process according to Claim 15 where R is chloro, R₁ is hydrogen



and X is Z where Z is and its stereoisomers; thus forming 8-chloro-[2(S)-6(R)-methano-2H-3,4,5,6-tetrahydro]-1-benzoxocine-10-[N-(1-azabicyclo[2.2.2]oct-3(S)-yl)]carboxamide.

19. A process for the preparation of a compound of the formula



where

one of A or B is CHR₆ and the other A or B is a bond;

Y is CHR;

n is 0, 1 or 2;

R and R₁ are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl, haloalkyl, amino, alkylamino, sulfonyl, alkylsulfamyl or alkylsulfonyl; and

R₂, R₃, R₄, R₅ and R₆ are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl or haloalkyl; and vicinal groups may together form double bonds comprising the steps of:

esterifying a substituted or unsubstituted salicylic acid to obtain a phenol;

treating said phenol with triphenyl phosphine and diethylazodicarboxylate in a polar medium with chirally pure 2-cyclohexen-1-(S)-ol to obtain a chiral phenol cyclohexenyl ether;

treating said phenol cyclohexenyl ether at high temperature to effect the Claisen rearrangement of transferring chirality to a new stereocenter in the 3-(3'-cyclohexenyl)salicylate;

effecting ring closure of said 3-(3'-cyclohexenyl)salicylate with an acid to obtain the chiral [5a(S)-9a(S)-(5a,6,7,8,9,9a-hexahydro]dibenzofuran-4-carboxylate and the chiral [2(S)-6(R)-methano-2H-3,4,5,6-tetrahydro]-1-benzoxocine-10-carboxylate;

hydrolyzing said esters with an aqueous base to selectively isolate the dibenzofuran acid as a salt from the benzoxocine acid salt; and

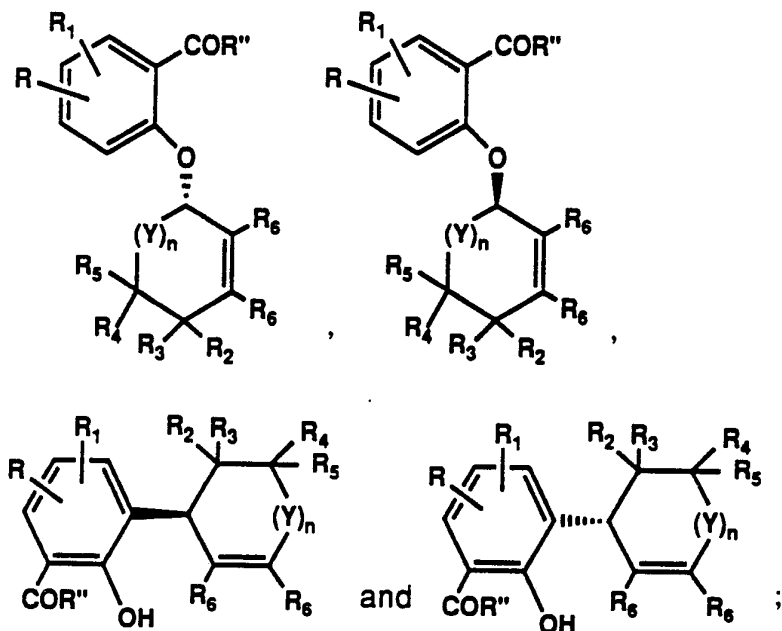
treating the respective salts with a mineral or organic acid to obtain the chiral dibenzofuran acid (S,S) and the chiral benzoxocine acid (R,S).

20. The process of claim 19 wherein said ring closure is affected by refluxing with trifluoroacetic acid.

21. The process of claim 19 wherein said ring closure is affected by treatment with a mixture of trifluoroacetic acid and sulfuric acid.

22. The process of claim 19 wherein said ring closure is effected by sulfuric acid.

23. A compound selected from the group consisting of:

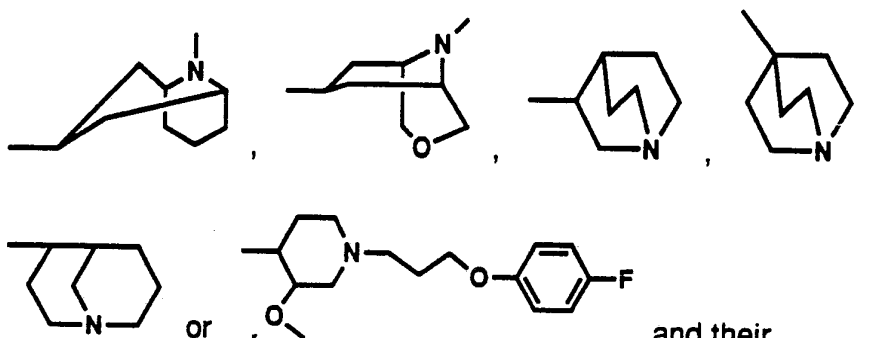


where Y is CHR;

n is 0, 1 or 2;

R'' is halo, OM where M is an alkali or alkaline earth metal, or NH-X

where X is hydrogen, alkyl, acyl or Z where Z is



stereoisomers;

R and R₁ are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl, haloalkyl, amino, alkylamino, sulfonyl, alkylsulfamyl or alkylsulfonyl; and

SUBSTITUTE SHEET

R₂, R₃, R₄, R₅ and R₆ are independently hydrogen, alkyl, halo, alkoxy, aryl, aralkyl or haloalkyl provided at least one of R₆ is hydrogen; and vicinal R₂, R₃, R₄, R₅ and R₆ groups may together form double bonds.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/06610

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5): C07D 307/79 US CL : 549/458		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
U.S.	549/458	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US, A, 4,863,921 (YOUSSEFYEH ET AL.) 05 SEPTEMBER 1989. See column 4, lines 30-41.	10
A	US, A, 4,668,690 (SHUTSKE) 26 MAY 1987	10
A	US, A, 4,924,010 (YOUSSEFYEH ET AL.) 08 MAY 1990	10
¹⁰ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION ¹⁴		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
09 JANUARY 1992	03 FEB 1991	
International Searching Authority	Signature of Authorized Officer	
ISA/US	BRIAN M. BURN	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

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

1. ☐ Claim numbers _____, because they relate to subject matter ¹² not required to be searched by this Authority, namely:

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹³, specifically:

3. ☐ Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

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

See attached continuation

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
1,2,5-10 as they read on cl. 10 [first-claimed invention]
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

ATTACHMENT # 1

THIS INTERNATIONAL SEARCHING AUTHORITY CONSIDERS THAT THE ABOVE-IDENTIFIED INTERNATIONAL APPLICATION DOES NOT COMPLY WITH THE REQUIREMENTS OF UNITY OF INVENTION. REASONS WITH RELEVANT CLAIMS FOR EACH INVENTION ARE:

- I. Process of preparing a multicyclic oxy-containing ring system of 7-10 members, classified in class 549, subclass 354.
- II. Process of preparing a compound containing a bicyclo-morpholino substituent, classified in class 544, subclass 105.
- III. Process of preparing a compound containing a quinuclidine substituent, classified in class 546, subclass 135.
- IV. Process of preparing a multicyclic oxy-containing ring system wherein $R^1 = -OH$, - or, classified in class 546, subclass 206.
- V. Process of preparing a multicyclic oxy-containing ring system wherein $R^1 = \text{aralkoxy}$, halo, classified in class 546, subclass 205.
- VI. A compound containing a carboxylic halide, classified in class 562, subclass 840.
- VII. A compound containing an acyl fluoride moiety, classified in class 562, subclass 849.
- VIII. Oxy-containing carboxylic acids wherein the aromatic rings are bonded to each other. ($R^{11} = OM$), classified in class 562, subclass 469.
- IX. Oxy-containing aromatic acids, wherein the carboxyl group is bonded directly to a ring ($R^{11} = OM$), classified in class 562, subclass 473.
- X. Oxy-containing aromatic acyl halides, wherein the carboxyl group is bonded directly to a ring ($R^{11} = OM$), classified in class 562, subclass 474.
- XI. Oxy-containing aromatic carboxylic acids, classified in class 562, subclass 465.
- XII. Sulfur-containing carboxamides, classified in class 564, subclass 162 ($R^{11} = HNX$).
- XIII. Sulfur and hydroxy-containing carboxamides, classified in class 564, subclass 169.

ATTACHMENT # 2

THIS INTERNATIONAL SEARCHING AUTHORITY CONSIDERS THAT THE ABOVE-IDENTIFIED INTERNATIONAL APPLICATION DOES NOT COMPLY WITH THE REQUIREMENTS OF UNITY OF INVENTION. REASONS WITH RELEVANT CLAIMS FOR EACH INVENTION ARE:

XIV. Carbaryl-containing carboxamides, classified in class 564, subclass 169.

XV. Carboxamides wherein a benzene ring is bonded directly to the carbaryl, classified in class 564, subclass 176.

XVI. Multicyclic carboxamides, classified in class 564, subclass 171.

XVII. Acyclic sulfonamides, classified in class 564, subclass 99 ($R^{11} = \text{HNX}$).

XVIII. Oxy-containing compounds containing isomeric quinuclidine substituents, classified in class 546, subclass 133.

XIX. Oxy-containing compounds containing a bicyclomorpholine substituent, classified in class 546, subclass 116.

XX. Oxy-containing compounds containing a piperidinyl ether substituent, classified in class 546, subclass 220.

Inventions I-V are generic to claims 1-23. Inventions VI-XX are generic to claim 24. The compounds are being separated from the process claims, because materially different products (from those claim 4) result from the instant process as claimed. The claims as filed lack a single general inventive concept, and a search of all 20 inventions would be unduly burdensome on the international searching authority (as is evidenced by the various subclasses under which all 20 inventions fall). If applicant elects not to pay for any additional inventions, the narrowest process (claim 10) will be examined; first-claimed invention.