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ATTORNEYS FOR PLAINTIFF
SCHERING CORPORATION

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SCHERING CORPORATION,

Plaintiff,

v.

ANDRX CORPORATION,
ANDRX PHARMACEUTICALS, INC.
and ANDRX PHARMACEUTICALS LLC,

Defendants.

Civil Action
No. 01-0049 (JGp)

COMPLAINT

Plaintiff Schering Corporation, for its Complaint against Defendants Andrx Corporation, Andrx Pharmaceuticals, Inc. and Andrx Pharmaceuticals LLC, hereby alleges as follows:

The Parties

1.A. Plaintiff Schering Corporation ("Schering") is a New Jersey corporation having its principal place of business at 2000 Galloping Hill Road, Kenilworth, New Jersey 07033.

1.B. Upon information and belief, Defendant Andrx Corporation ("Andrx Corp.") is a Florida corporation having its principal place of business at 4001 Southwest 47th Avenue, Fort Lauderdale, Florida 33314.

1.C. Upon information and belief, Defendant Andrx Pharmaceuticals, Inc. ("Andrx Inc.") is a wholly-owned subsidiary of Andrx Corp. organized under Florida law and having its principal place of business at 4001 Southwest 47th Avenue, Fort Lauderdale, Florida 33314. Upon information and belief, Andrx Inc. is wholly owned and controlled by, and is an operating entity and alter-ego of, Andrx Corp.

1.D. Upon information and belief, Andrx Pharmaceuticals LLC ("Andrx LLC") is a wholly-owned subsidiary of Andrx Inc. organized under Virginia law. Andrx LLC has represented that it has a place of business at 707 East Main Street, 11th Floor, Richmond, Virginia 23219, but it has no such place of business at that address. Upon information and belief, Andrx LLC has no employees, no legitimate place of business and is wholly owned and controlled by, and is a non-operating shell entity and alter-ego of, Andrx Corp.

1.E. Upon information and belief, Andrx Inc. and Andrx LLC are both wholly owned and controlled by, and are alter-egos of, Andrx Corp. Andrx Corp., Andrx Inc. and Andrx LLC are effectively the same entity and are referred to collectively hereinafter as Andrx.

Nature of the Action

2. This is a civil action for the willful infringement of United States Patent No. 4,659,716 ("the '716 patent"). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 100 <u>et seq</u>.

Jurisdiction and Venue

3. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

4. This Court has personal jurisdiction over Andrx Corp. by virtue of, <u>inter alia</u>: (1) its presence in New Jersey through its wholly-owned subsidiaries and alter-egos, which maintain facilities and employ personnel in New Jersey; (2) its systematic and continuous contacts with New Jersey, including its wholly-owned subsidiaries and alter-egos' sale of prescription drugs in New Jersey and registration of prescription drugs in the *New Jersey Formulary*; (3) its performance of tortious acts that have caused foreseeable harm within New Jersey; and (4) its previous consent to this Court's jurisdiction for determining its infringement of the '716 patent.

5. This Court has personal jurisdiction over Andrx Inc. by virtue of, inter alia: (1) the fact that it is an alter-ego of Andrx Corp. and is subject to personal jurisdiction wherever Andrx Corp. is subject to personal jurisdiction; (2) its presence in New Jersey; (3) its systematic and continuous contacts with New Jersey, including its sale of prescription drugs in New Jersey and registration of prescription drugs in the *New Jersey Formulary;* (4) its performance of tortious acts that have caused foreseeable harm within New Jersey; and (5) its previous consent to this Court's jurisdiction for determining its infringement of the '716 patent.

6. This Court has personal jurisdiction over Andrx LLC by virtue of, inter alia: (1) the fact that it is an alter-ego of Andrx Corp. and is subject to personal jurisdiction wherever Andrx Corp. is subject to personal jurisdiction; (2) its performance of tortious acts that have caused foreseeable harm within New Jersey; and (3) its previous consent to this Court's jurisdiction for determining its infringement of the '716 patent.

7. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1400(b).

The Patents

8. On April 21, 1987, the '716 patent, entitled "Antihistaminic 8-(Halo)-Substituted 6,11-Dihydro-11-(4-Piperidylidene)-5H-Benzo[5,6]Cyclohepta[1,2-b]Pyridines," was duly and legally issued to Schering as assignee. Since that time, Schering has been, and continues to be, the sole owner of the '716 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '716 patent is attached hereto as Exhibit A.

9. On September 5, 1989, United States Patent No. 4,863,931 ("the '931 patent"), entitled "Antihistaminic Fluoro Substituted Benzocycloheptapyridines" was duly and legally issued to Schering as assignee. Since that time, Schering has been, and continues to be, the sole owner of the '931 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '931 patent is attached hereto as Exhibit B. Andrx has represented that it will not infringe the '931 patent. If this representation proves to be incorrect, it may be necessary to expand the above-captioned civil action to include a claim for willful infringement of the '931 patent.

Acts Giving Rise to this Action

10. Upon information and belief, on or before November 21, 2000, Andrx submitted Abbreviated New Drug Application ("ANDA") 75-990 to the United States Food and Drug Administration ("the FDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). Andrx's ANDA seeks the FDA approval necessary for Andrx to engage in the commercial manufacture, use, offer for sale and sale of generic, orally-disintegrating tablets containing 10 milligrams of loratadine per tablet ("the Generic Product"). Andrx's ANDA specifically seeks FDA approval to market the Generic Product prior to the expiration of the '716 patent.

11. Within its ANDA, Andrx alleged under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '716 patent are either invalid, unenforceable or not infringed by the manufacture, use or sale of the Generic Product. Schering received written notification of Andrx's ANDA and § 505(j)(2)(A)(vii)(IV) allegation on November 22, 2000.

12. Andrx's submission of said ANDA to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '716 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Andrx commercially manufactures, uses, offers for sale or sells the Generic Product, or induces or contributes to

such conduct, it would further infringe the '716 patent under 35 U.S.C. § 271(a), (b) and/or (c).

13. Even if Andrx Corp., Andrx Inc. and Andrx LLC are not treated as a single entity for purposes of this action, which they should be, each of them is nonetheless jointly and severally liable for the infringement of the '716 patent.

14. Andrx Corp. is jointly and severally liable for the infringement of the '716 patent, regardless of which Andrx entity actually filed ANDA 75-990. This is so because, upon information and belief, Andrx Corp. caused, participated in, contributed to, aided, abetted and induced the submission of ANDA 75-990 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA, as evidenced by, <u>inter</u> <u>alia</u>, the fact that the statement of factual and legal basis supporting the § 505(j)(2)(A)(vii)(IV) allegation was prepared and signed by an Andrx Corp. in-house attorney, Ted Whitlock.

15. Andrx Corp.'s causing, participation in, contribution to, aiding, abetting and inducement of the submission of said ANDA and § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '716 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Andrx Corp. commercially manufactures, uses, offers for sale or sells the Generic Product, or induces or contributes to such conduct, it would further

infringe the '716 patent under 35 U.S.C. § 271(a), (b) and/or (c).

16. Andrx Inc. is jointly and severally liable for the infringement of the '716 patent, regardless of whether it is treated as an alter-ego of Andrx Corp. for purposes of this action. This is so because, upon information and belief, Andrx Inc. participated in, contributed to, aided, abetted and induced the submission of ANDA 75-990 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA.

17. Andrx Inc.'s participation in, contribution to, aiding, abetting and inducement of the submission of said ANDA and § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '716 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Andrx Inc. commercially manufactures, uses, offers for sale or sells the Generic Product, or induces or contributes to such conduct, it would further infringe the '716 patent under 35 U.S.C. § 271(a), (b) and/or (c).

18. Andrx LLC is jointly and severally liable for the infringement of the '716 patent, regardless of whether it is treated as an alter-ego of Andrx Corp. for purposes of this claim. This is so because, upon information and belief, Andrx LLC is now the named applicant on ANDA 75-990, including its § 505(j)(2)(A)(vii)(IV) allegation regarding the '716 patent, rendering it jointly and severally liable for the infringement of

the '716 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Andrx LLC commercially manufactures, uses, offers for sale or sells the Generic Product, or induces or contributes to such conduct, it would further infringe the '716 patent under 35 U.S.C. § 271(a), (b) and/or (c).

19. Andrx had actual and constructive notice of the '716 patent prior to filing ANDA 75-990. Accordingly, Andrx's infringement of the '716 patent has been, and continues to be, willful.

20. Schering will be irreparably harmed by these infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Prayer for Relief

WHEREFORE, Schering prays for judgment as follows:

A. That Andrx has willfully infringed the '716 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA 75-990 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the expiration date of the '716 patent, including any extensions;

C. That Andrx, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially using, offering for sale or selling the Generic Product, and any other product that infringes or induces or contributes to the infringement of the '716 patent, prior to the expiration of that patent, including any extensions;

D. That Schering be awarded monetary relief if Andrx commercially uses, offers for sale or sells the Generic Product, or any other product that infringes or induces or contributes to the infringement of the '716 patent, within the United States prior to the expiration of that patent, including any extensions, and that any such monetary relief be trebled and awarded to Schering with prejudgment interest;

E. That Schering be awarded the attorney fees, costs and expenses that it incurs prosecuting this action; and

F. That Schering be awarded other and further relief as this Court deems just and proper.

Dated: January 4, 2001

Respectfully submitted,

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United States Patent [19]
Villani et al.

[11] **Patent Number:** 4,659,716
[45] **Date of Patent:** Apr. 21, 1987

[54] **ANTIHISTAMINIC 8-(HALO)-SUBSTITUTED 6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINES**

[75] Inventors: **Frank J. Villani**, Fairfield; **Jesse K. Wong**, Union, both of N.J.

[73] Assignee: **Schering Corporation**, Madison, N.J.

[21] Appl. No.: **838,974**

[22] Filed: **Mar. 12, 1986**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 580,304, Feb. 15, 1984, abandoned.

[51] **Int. Cl.^{4}** **A61K 31/445; C07D 401/08**
[52] **U.S. Cl.** **514/290; 546/93**
[58] **Field of Search** 546/93; 514/290

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,326,924	6/1967	Villani	546/93
3,717,647	2/1973	Villani	546/315
4,282,233	8/1981	Villani	546/93 X

FOREIGN PATENT DOCUMENTS

46-20387	6/1971	Japan	546/93

OTHER PUBLICATIONS

PDR, 1984, pp. 515, 529, 557, 558, 566, 593, 594, 611, 631, 633, 648, 664, 667, 668, 709.
Scrip No. 1026, 8/19/85.
Burger's Medicinal Chemistry, 4th Ed, Part III, Wiley-Interscience, NY, 1981, pp. 818-819.
Brandon, M., et al., *Annals of Allergy*, 44, 71-75 (1980).
Business Week, 5/2/83, pp. 60-61.
Villani, F., et al., *Arzneim.-Forsch.*, 36(11), Nr. 9 1986, pp. 1311-1314.
Villani, F. et al., *J. Med. Chem.*, 15(7), 750-754 (1972).
Goodman and Gilman's, *The Pharmacological Basis of Therapeutics*, MacMillan, New York, 1980, p. 626.
PDR, 1985, pp. 888, 889, 964, 1425, 1426, 1485, 1612, 1613, 1725, 1726, 1872, 1873, 1879, 1965, 1966, 2276, 2277.

Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—James R. Nelson; Stephen I. Miller; Richard C. Billups

[57] **ABSTRACT**

Disclosed are 7- and/or 8-(halo or trifluoromethyl)-substituted-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines and the pharmaceutically acceptable salts thereof, which possess antihistaminic properties with substantially no sedative properties. Methods for preparing and using the compounds and salts are described.

16 Claims, No Drawings

ANTIHISTAMINIC 8-(HALO)-SUBSTITUTED 6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BENZO[5,6]CYCLOHEPTA[1,2-B]PYRIDINES

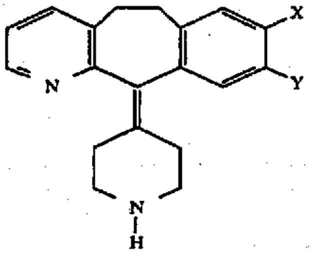
The present application is a continuation-in-part of U.S. application Ser. No. 580,304, filed Feb. 15, 1984, now abandoned, the benefit of which is claimed pursuant to the provisions of 35 U.S.C. 120.

BACKGROUND OF THE INVENTION

U.S. Pat. Nos. 3,326,924, 3,717,647 and 4,282,233 describe certain 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines.

SUMMARY OF THE INVENTION

The present invention is directed to compounds having structural formula I:



I

or pharmaceutically acceptable salts thereof, wherein X and Y independently represent H, halo (i.e., fluoro, chloro, bromo or iodo), or trifluoromethyl with the proviso that at least one of X and Y is halo or trifluoromethyl. Particularly, preferred compounds are those wherein X is F and Y is H and wherein X is Cl and Y is H.

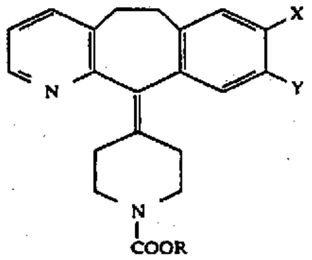
The compounds of the invention have unexpectedly been found to possess advantageous antihistaminic activity and low central nervous system (CNS) activity indicative of non-sedation. The compounds can thus be employed in pharmaceutical compositions in combination with pharmaceutically acceptable carriers and in methods of treating allergic reactions in a mammal.

DESCRIPTION OF THE INVENTION

The compounds of the invention can form salts with pharmaceutically acceptable acids such as hydrochloric, methanesulfonic, sulfuric, acetic, maleic, fumaric, phosphoric and the like. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base form may be regenerated by treating the salt forms with a base. For example, dilute aqueous base solutions may be utilized. Dilute aqueous sodium hydroxide, potassium carbonate, ammonia, and sodium bicarbonate solutions are suitable for this purpose. The free base form differs from the respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but the salts are otherwise equivalent to the respective free base form for purposes of the invention.

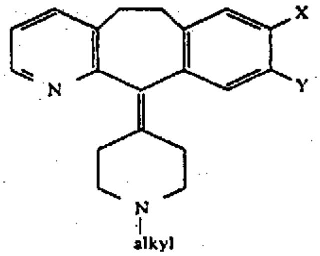
The compounds of the invention and their corresponding salts can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

The compounds of the invention can be prepared by decarbalkoxylation of a compound of the formula II:



II

wherein R is an alkyl group (preferably ethyl) and X and Y are as defined above. The compounds of formula II can be prepared by procedures described in U.S. Pat. No. 4,282,233 from the corresponding N-alkyl (preferably N-methyl) compounds of formula III

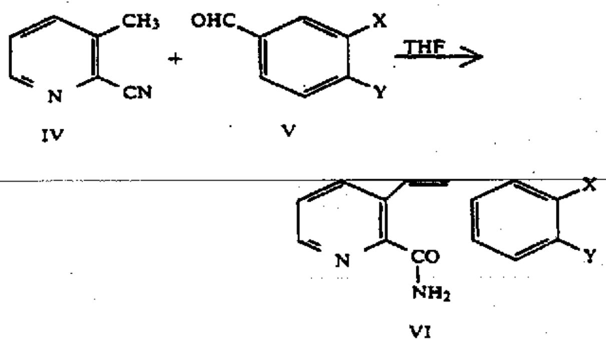


III

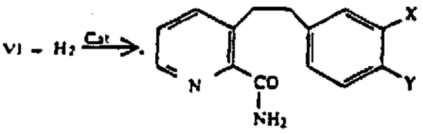
by employing appropriate starting materials having the desired X and Y substituents.

Alternatively, the compounds of the invention can be prepared by dealkylation of compounds of formula III, e.g., by reaction with cyanogen bromide and subsequent hydrolysis of the N-cyano product with, for example, aqueous acid solution to provide the compounds of formula I.

The compounds of formula III can be produced by the procedures described in U.S. Pat. No. 3,326,924 by employing the appropriately X and Y substituted starting materials. For example, 2-cyano-3-picoline of formula IV can be reacted with an appropriate benzaldehyde of formula V in the presence of a strong base such as potassium butoxide to give an ortho-phenethenyl pyridine carboxamide of formula VI

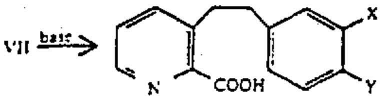


which is then hydrogenated, e.g., by employing a noble metal on carbon catalyst such as palladium or platinum on carbon, to the corresponding ortho-phenethyl pyridine carboxamide of formula VII



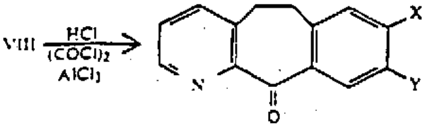
VII

which in turn is hydrolyzed, e.g. with base such KOH, to the otho-phenethyl pyridine carboxylic acid of formula VIII



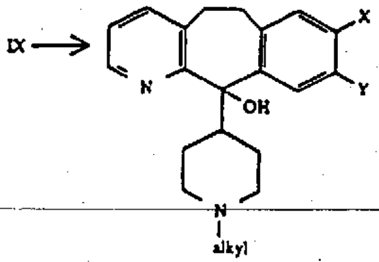
VIII

The compound of formula VIII can be cyclized, e.g., with oxalyl chloride and aluminum trichloride, to a compound of formula IX



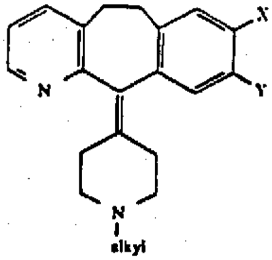
IX

which is reacted with, for example, a Grignard reagent prepared from a 4-halo-N-alkyl-piperidine to produce the compound of formula X



X

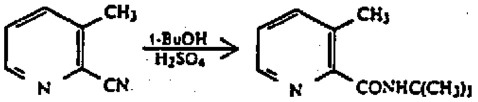
which in turn is dehydrated, e.g., by acid such as polyphosphoric acid or sulfuric acid, to the compound of formula III:



III

The compound of formula IX may also be reacted with Na in liquid NH_3 and a 4-halo-N-alkyl-piperidine to produce the compound of formula X.

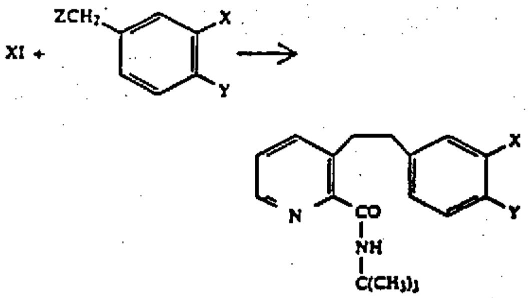
In an alternative method 2-cyano-3-methylpyridine can be reacted in a Ritter reaction with a tertiary butyl compound in an acid such as concentrated sulfuric acid or concentrated sulfuric acid in glacial acetic acid to form a compound of formula XI



IV XI

Suitable tertiary butyl compounds include, but are not limited to, t-butyl alcohol, t-butyl chloride, t-butyl bromide, t-butyl iodide, isobutylene or any other compound which under hydrolytic conditions forms t-butyl carboxamides with cyano compounds. The temperature of the reaction will vary depending on the reactants, but generally the reaction is conducted in the range of from about 50° C. to about 100° C. with t-butyl alcohol. The reaction may be performed with inert solvents but is usually run neat.

The product of the Ritter reaction (formula XI) can be reacted with an appropriate 3 and/or 4-halo or trifluoromethyl-substituted benzyl halide, in the presence of a base to form the compound of formula XII

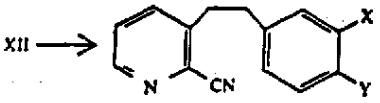


XII

wherein Z is chloro, bromo or iodo. Examples of appropriate benzyl halides include, but are not limited to, 3-chloro-benzyl chloride, 3-fluoro-benzyl bromide, 3,4-dichloro-benzyl chloride, 4-fluoro-benzyl chloride, 3-trifluoromethyl-benzyl chloride, 3-bromobenzyl chloride, etc. Any suitable base can be employed e.g., an alkyl lithium compound such as n-butyl lithium in tetrahyrofuran (THF). Preferably the base has a pK_a of greater than 20 and more preferably greater than 30.

This reaction can be conducted at any suitable temperature, e.g., temperatures of from about −78° C. to about 30° C., preferably from about −40° C. to about −30° C. The reaction can be performed in any suitable inert solvent such as THF, diethyl ether, etc.

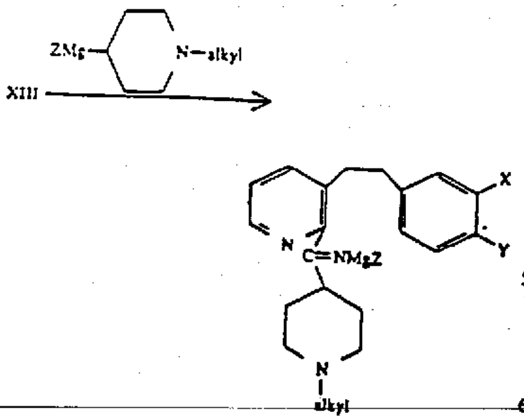
The tertiary-butyl amide of formula XII can be converted to the cyano compound of formula XIII



XIII

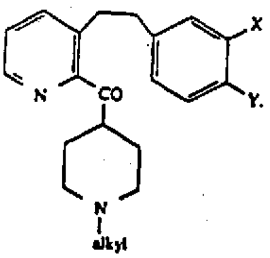
by the use of a suitable dehydrating agent such as $POCl_3$, $SOCl_2$, P_2O_5, toluene sulfonyl chloride in pyridine, oxalyl chloride in pyridine, etc. This reaction can be performed in the absence of or with a co-solvent such as xylene. The dehydrating agent such as $POCl_3$ is employed in equivalent amounts or greater and preferably in amounts of from about 2 to about 15 equivalents. Any suitable temperature and time can be employed for performing the reaction, but generally heat is added to speed up the reaction. Preferably, the reaction is performed at or near reflux.

The cyano compound of formula XIII can then be reacted with a Grignard reagent prepared from the appropriate 1-alkyl-4-halopiperidine. This reaction is generally performed in an inert solvent such as an ether, toluene or tetrahydrofuran. This reaction is performed under the general conditions for a Grignard reaction, e.g., at temperatures of from about 0° C. to about 75° C. The resulting compound of formula XIV



XIV

(wherein Z is again chloro, bromo or iodo) is hydrolyzed, e.g., by reaction with aqueous acid such as aqueous HCl to prepare the corresponding ketone of formula XV

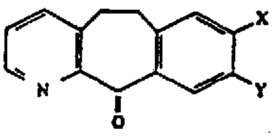


XV

The compound of formula XV can be ring-closed to form the desired cycloheptene ring system by treating the compound XV with a super acid having a Hammett acidity function of less than about minus 12, e.g., minus 13, minus 14, etc., to produce a compound of formula III. This measure of acidity is defined in Hammett, Louis P., and Deyup, Alden J., *Journal of the American Chemical Society*, Vol. 54, 1932, p. 2721. Suitable super acids for this purpose include, for example, HF/BF_3, CF_3SO_3H, CH_3SO_3H/BF_3, etc. The reaction can be performed in the absence of or with an inert co-solvent such as CH_2Cl_2. The temperature and time of the reaction vary with the acid employed. For example, with HF/BF_3 as the super acid system the temperature may be controlled so as to minimize side reactions, such as HF addition to the double bond of the rings. For this purpose, the temperature is generally in the range of from about +5° C. to −50° C., preferably from about −30° C. to −35° C. With CF_3SO_3H as the super acid system, the reaction may be run at elevated temperatures, e.g., from about 25° C. to about 150° C. and at lower temperatures but the reaction then takes longer to complete.

Generally the super acid is employed in excess, preferably in amounts of from about 1.5 to about 30 equivalents. For example, with HF/BF_3 as the super acid system the molar ratio of HF to the compound of formula XV in the reaction mixture is preferably from about 30 to about 1.5, more preferably 2.5 to 1.5. In such system, the molar ratio of BF_3 to the compound of formula XV in the reaction mixture is preferably from about 15 to about 0.75, more preferably from about 1 to about 0.75.

As another alternative, a compound of formula XII above can be cyclized by use of super acid such as CF_3SO_3H or HF/BF_3 to produce a compound of formula IX.



IX

The compounds of formula IX may then be converted to the desired compounds of the invention as described above.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 5 to about 20 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethyl-cellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and therey solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternately, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration, for example,

liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

The composition of the invention may also be deliverable transdermally, e.g., with a transdermally acceptable carrier. The transdermal compositions can take the form of creams, lotions and/or emulsions, can be included in an appropriate adhesive for application to the skin or can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the transdermally acceptable composition is utilized to prepare a "reservoir type" or "matrix type" patch which is applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of a compound of formula I through the skin. Most preferably, the patch of the invention will be worn for a period of about 24 hours and provide a total daily dosage of about 1 mg to about 40 mg, preferably from about 5 mg to about 10 mg, of a compound of the invention. The patch may then be replaced if necessary with a fresh patch, thereby providing a constant blood level of a compound of formula I to the patient in need thereof.

The utilization of this new transdermal dosage form and its prescribed regimen will provide the advantages described above. Other frequencies of dosage application are anticipated, for example, a once every 3 day frequency or a once every 7 day frequency. Although a once a day dosage regimen may be preferred, it is not intended that the invention be limited to any particular regimen.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet or tablet itself or it can be the appropriate number of any of these packaged form.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 1000 mg according to the particular application. The compositions can, if desired, also contain other therapeutic agents, such as decongestants.

The dosages may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The compounds of the invention possess antihistaminic properties. The antihistaminic properties of these compounds may be demonstrated by use of standard pharmacological testing procedures. For example, the ability of the compounds to reduce histamine-induced paw edema in mice may be measured by use of the following method.

Male CF_1 mice, 25–30 g, are housed under conditions of controlled temperature and humidity with a 12 hour dark/light cycle. Food and water are allowed ad libitum. The mice are randomly assigned to the treatment groups. One hour after treatment with a compound of the invention or vehicle, the mice are lightly anesthetized with ether. The left hind paw of each mouse serves as a control and is injected with 25 μl of isotonic saline. The right hind paw serves as the experimental paw and is injected with 25 μl of isotonic saline containing 13 μg histamine dihydrochloride. Thirty minutes later the mice are killed by cervical dislocation and both hind paws of each mouse are removed by cutting at the tarsal joint. The weight of each paw is recorded and the difference in weight between the compound-treated and the placebo-treated groups is evaluated using Student's "t" test. The ED_{50} values (the dose causing 50% inhibition of histamine-induced edema) and 95% confidence limits are determind by the Linear Least Square Dose-Response method [Brownlee, K. A., "Statistical Theory And Methodology In Science and Engineering", 2nd Ed., J. Wiley and Sons, New York, 1965, pp. 346–349]. The compounds of 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (Compound A) and 8-fluoro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (Compound B) were tested by this procedure with the results shown in Table 1 below:

TABLE 1

Treatment	Oral Dose mg/kg	No. of Animals	Increased Paw Weight (mg) Mean	% Inhibition	Oral ED_{50} (mg/kg)
Placebo	—	7	22.3	—	—
Compound A	0.03	8	19.9	11	
	0.1	7	13.0	42	
	0.3	8	6.1	73	
	1.0	8	2.5	89	0.15
Compound B					<1

Compounds A and B were also tested for antihistaminic activity by the procedures set forth in paragraph A below and for CNS activity by the procedures set forth in paragraphs B, C, and D below.

A. Prevention of histamine-induced lethality in guinea pigs. Compounds A and B were evaluated for their ability to protect female albino guinea pigs (250–350 g) against death induced by the intravenous injection of histamine dihydrochloride at 1.1 mg/kg, which is approximately twice the LD_{99}. Doses of the antagonists were administered orally to separate groups of fasted animals 1 hour prior to the challenge with histamine and protection from death recorded for 30 minutes after histamine. ED_{50} values were determined for each drug by prohibit analysis.

B. Antagonism of Physostigmine Lethality. The physostigmine-induced lethality test used was a modification of the technique reported by COLLIER et al., *Br. J. Pharmac.*, 32, 295–310 (1968). Physostigmine salicylate (b 1.0 mg/kg s.c.) produces 100% lethality when administered to mice grouped 10 per plastic cage (11×26×13 cm). Test agents were administered orally 30 minutes prior to physostigmine. The number of survivors were counted 20 minutes after physostigmine administration.

C. Antagonism of Acetic Acid Writhing. The acetic acid writhing test used was essentially that described by HENDERSHOT and FORSAITH, *J. Pharmac. Exp. Ther.*, 125, 237–240 (1959), except that acetic acid rather than phenylquinone was used to elicit writhing. Mice were injected with 0.6% aqueous acetic acid at 10 mg/kg i.p. 15 minutes after oral administration of the test drug. The number of writhes for each animal was counted during a 10 minute period starting 3 minutes after acetic acid treatment. A writhe was defined as a sequence of arching of the back, pelvic rotation and hind limb extension.

D. Antagonism of Electro-Convulsive Shock (ECS). For the ECS test, a modification of the method of TOMAN et al., *J. Neurophysiol.*, 9, 231–239 (1946), was used. One hour after oral administration of the test drug or vehicle, mice were administered a 13 mA, 60 cycle a.c. electroconvulsant shock (ECS) for 0.2 seconds via corneal electrodes. This shock intensity produces tonic convulsions, defined as extension of the hind limbs, in at least 95% of vehicle-treated mice.

Of the above test procedures for measuring CNS activity of antihistamines, the physostigmine-induced lethality test is believed to be a major index of non-sedating characteristics, since it reflects mainly central anticholinergic potency which is believed to contribute to sedative activity.

The results from the above test procedures are set forth in Table 2 below:

TABLE 2

	Antihistaminic Activity	CNS Activity		
	A. G. pig.	B. Physostigmine	C. Acetic	D. ECS
Compound	p.o. ED_{50} (mg/kg)	lethality ED_{50} (mg/kg)	writhing ED_{50} (mg/kg)	test ED_{50} (mg/kg)
A	0.15	320	147	160
B	.09	320	320	320

The above results demonstrate that the compounds of the invention are a potent antihistamines having low CNS activity indicative of non-sedation. Specifically, Compounds A and B are relatively inactive in all of the CNS test procedures, and in particular, they provide an ED_{50} in the physostigmine-induced lethality test of greater than 320.

Compound A was also tested to assess its sedative effects in another procedure:

Acute behavioral, neurologic and autonomic effects of Compound A were evaluated in mice by a modification of the method of Irwin [Irwin S., Drug Screening And Evaluation Of New Drugs In Animals, in *Animal And Clinical Pharmacologic Techniques in Drug Evaluation.* Nodine JM and Siegler PE (Eds)., Year Book Medical Publishers Inc., Chicago 1964, pp 36–54]. After oral administration of vehicle or drug, mice (CFI males, 20–24 g) were observed and manipulated to evaluate behavorial, neurologic and autonomic changes. A semi-quantitative scoring scale was used where signs normally present (e.g., spontaneous activity, alertness, pupil size) were assigned a "normal" score of 0 and scores of +1, +2 and +3 indicated slight, moderate and marked increases and scores of −1, −2 and −3 indicated slight, moderate and marked decreases from "normality". When a sign occurred that is not normally present (e.g., convulsions, tremors), its magnitude was graded on a 1-3 scale. Each treatment group consisted of 6 animals and evaluations were conducted 1 hour after dosing. Additional observations for lethality were made for up to 24 hours after dosing. Incidence is defined as the observation occurring in an animal with a score of 2 or greater according to the scoring method defined above.

Effects of Compound A on behavior, neurologic function and automatic function in mice

Measurement	MED, mg/kg pc*
Lethality	300
Reactivity	300
Decreased motor activity	300
Decreased muscle tone	300
Tremors/convulsions	300
Ataxia	300
Mydriasis	300
Ptosis	300

*Minimal effective dose, defined as the lowest dose that produced a score of 2 or greater according to Irwin (supra) in at least 3 of 6 animals tested at each dose.

From the above test results, it may be concluded that the compounds of the invention would be essentially non-sedating at a clinically useful antihistamic dosage. Compound B (i.e., the 8-fluoro compound) is particularly preferred because it has also shown very low toxicity.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptom being treated. A typical recommended dosage regimen is oral administration of from 5 to 100 mg/day, preferably 10 to 20 mg/day, in two to four divided doses to achieve relief of the symptoms.

The following examples are intended to illustrate, but not to limit, the present invention.

EXAMPLE I

A.

N-(1,1-Dimethylethyl)-3-methyl-2-pyridine carboxamide

2-cyano-3-methyl pyridine (400 g) is suspended in t-BuOH (800 mL) and the mixture heated to 70° C. Concentrated sulphuric acid (400 mL) is added dropwise over 45 minutes. The reaction is complete after a further 30 minutes at 75° C. The mixture is then diluted with water (400 mL), charged with toluene (600 mL) and brought to pH 10 with concentrated aqueous ammonia. The temperature is kept at 50°-55° C. during the work up. The toluene phase is separated, the aqueous layer reextracted and the combined toluene phases are washed with water. Removal of the toluene yields an oil, N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide, from which solid product may crystallize. Product yield of 97% is determined by internal standard assay on gas chromatograph.

B.

3-[2-(3-Fluorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide

Tetrahydrofuran (125 mL) and N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide (1 equivalent) are charged and cooled to −40° C. under nitrogen. Two equivalents of n-butyllithium are then added over 40 minutes. When half the n-butyllithium is added the mixture turns purple. Sodium bromide (1.3 g) is added and then 3-fluoro-benzyl bromide (1.05 equivalents) is added dropwise (1:1 solution in tetrahydrofuran) over 40-50 minutes while the temperature is maintained at −40° C. After 30 minutes at −40° C., the mixture is diluted with water (250 mL) and the organic phase separated. This phase is dried over sodium sulphate and the solvent removed yielding an oil from which solid product, 3-[2-(3-fluorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide, may crystallize.

C.

3-[2-(3-Fluorophenyl)ethyl]-2-pyridine-carbonitrile

A solution of 3-[2-(3-fluorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (36.4 g, 0.121 mole) in 123 mL (202.3 g, 1.32 mole) of phosphorous oxychloride is heated at 110° C. for 3.5 hours and stirred at ambient temperature an additional 15 hours. The reaction is quenched with ice and water and the pH of the solution is brought to 8 by the addition of a saturated aqueous solution of potassium carbonate. The product is extracted into ethyl acetate and the solution is concentrated to a residue. Following purification by silica gel chromatography and trituration with pentane, 16.2 g (0.072 mole) of product is obtained in 60% yield.

D.

(1-Methyl-4-piperidinyl)[3-[2-(3-fluorophenyl)ethyl]-2-pyridinyl]methanone

To a solution of 3-[2-(3-fluorophenyl)ethyl]-2-pyridine carbonitrile (28.0 g, 0.123 mole) in 150 mL of dry THF is added 92 mL (1.48 moles/liter, 0.136 mole) of N-methylpiperidyl magnesium chloride over 10 minutes maintaining the temperature of 45°-50° C. The reaction is maintained at 40° C. to 50° C. for another 10 minutes and at ambient temperature for 45 minutes. The reaction is quenched to below pH 2 and aqueous hydrochloric acid and the resulting solution is stirred at 25° C. for 1 hour. The pH of the solution is adjusted to about 8, the product is extracted with ethylacetate, and the solution is concentrated to a residue. Following purification by silica gel chromatography, 38.3 g of product is obtained as a brown oil.

E.

8-Fluoro-11-(1-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

A solution of (1-methyl-4-piperidinyl)[3-[2-(3-fluorophenyl)ethyl]-2-piperidinyl]methanone (15.0 g, 0.046 mole) in 74 mL (125.5 g, 0.837 mole) of trifluoromethanesulfonic acid is stirred at ambient temperature for 18 hours. The reaction is quenched with ice-water and the solution made basic with potassium hydroxide. The product is extracted into ethyl acetate. The ethyl acetate solution is filtered to remove insolubles and the filtrate is concentrated to a residue. Following purification by silica gel chromatography, 5.4 g (0.0175 mole) of product is obtained in 38% yield.

F.

8-Fluoro-11(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To a stirred solution of 8-fluoro-11-(1-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (10.5 g, 34 mmol) and triethylamine (5.2 g, 52 mmol) in dry toluene (120 mL) at 80° C. under an argon atmosphere, was added ethylchloroformate (18.5 g, 170 mmol) via a syringe. The reaction mixture was allowed to stir at this temperature for 30 minutes and at room temperature for one hour. The reaction mixture was then filtered and solvent was removed. The residue was triturated with pentane to give 10.1 grams (yield = 81%) of the title compound, m.p. = 116°-118° C.

G.

8-Fluoro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridine

8-Fluoro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (3.6 g, 9.8 mmol.) was refluxed with KOH (4.5 g) in 50 mL of ethanol/water (1:1) for 66 hours under an argon atmosphere. The reaction mixture was poured into a brine solution and extracted twice with ethyl acetate. The extracts were combined and then dried over Na_2SO_4 and filtered. Solvent was removed to give 2.76 grams (yield = 95%) of the title compound, m.p. = 133.5°-134.5° C.

EXAMPLE II

A.

3-[2-(3-Fluorophenyl)ethenyl]-picolinamide

A solution of 2-cyano-3-picoline (142 g, 1.2 mole) and 3-fluorobenzaldehyde (164 g, 1.32 mole) in 750 mL of dry tetrahydrofuran (THF) is prepared. This solution is added dropwise to a solution of 162.0 grams of potassium t-butoxide (1.44 mole) dissolved in 750 mL of dry THF at −15° C. to −20° C.

The addition requires ¾ hour, and the temperature is maintained below −15° C. The mixture is stirred at −15° to −20° C. for 1 hour, then at 0° to 5° C. for 2 hours.

Saturated NH_4Cl solution (400 mL) is added to the mixtured followed by 250 mL of H_2O. The mixture is stirred for ½ hour, and the aqueous layer is separated and extracted with 300 mL of CH_2Cl_2, which is combined with the THF layer. The organic solution is washed with 400 mL of saturated NH_4Cl solution, dried over Na_2SO_4, treated with charcol and filtered through diatomaceous earth.

The solvent is removed on a rotary evaporator, and the oily residue is dissolved in 350 mL of boiling toluene. The mixture is filtered hot to remove impurities and cooled overnight at 0° to 5° C. The off-white solid that precipitates is filtered, washed twice with 100 mL of cold toluene, and dried at 60° C. for 6 hours, yielding 122.1 grams (42.1%) of the title compound, m.p. = 153°-155° C.

B.

3-[2-(3-Fluorophenyl)ethyl]-picolinamide

A solution is prepared by dissolving 121 grams of 3-[2-(3-fluorophenyl)ethenyl]-picolinamide (0.5 mole) in 500 mL of acetic acid. To the solution is added 8.0 grams of 5% Pd/C and the mixture is placed on a Parr hydrogenator overnight. A theoretical amount of H_2 is absorbed, and mixture is filtered through diatomaceous earth and poured into 4 liters of H_2O. The off-white suspension is stirred for 2 hours and cooled at 0° to 5° C. for 20 hours.

The solid product 3-[2-(3-fluorophenyl)ethyl]-picolinamide is filtered and washed three times with 100 mL of H_2O and dried at 60° C. for 20 hours, yielding 108 grams (yield = 88.6%) of the title compound, m.p. = 102°-104° C.

C.

3-[2-(3-Fluorophenyl)ethyl]-picolinic acid

A suspension of 73.2 grams of 3-[2-(3-fluorophenyl)ethyl]-picolinamide (0.3 mole) in 500 mL of ethanol and 125 grams of 45% KOH (1.0 mole) is prepared. H_2O (200 mL) is added, and the mixture is refluxed for 20 hours. TLC shows complete conversion to the acid.

The alcohol is removed by distillation until the vapor temperature reaches 100° C. The suspension is cooled to room temperature, 100 mL of H_2O is added and the solution is brought to a pH of 4–4.5 with 12N HCl (110 mL). The suspension is stirred for 1 hour and cooled overnight. The solid is filtered, washed three times with 100 mL of H_2O and dried at 65° C. for 24 hours, yielding 69.6 grams (yield = 94.8%) of the title compound, m.p. = 118°-122° C.

D.

8-Fluoro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta[1,2-b]pyridin-11-one

A solution of 61.3 grams of 3-[2-(3-fluorophenyl)ethyl]-picolinic acid (0.25 mole) in 900 mL of tetrachloroethane is prepared. Anhydrous HCl gas is passed through the solution at room temperature for 1½ hours. Oxalylchloride (48.3 grams, 0.38 mole) is carefully added, and stirred for 24–26 hours at room temperature (slight heating at 35°-40° C. for 4 hours is needed to obtain a dark solution). The solution is cooled to 0°-5° C., and 67 grams of $AlCl_3$ (0.5 mole) are slowly added over ½ hour. The mixture is stirred at 0° to 5° C. for 18 hours. An additional 17 grams of $AlCl_3$ (0.125 mole) is added, and mixture is stirred for 2 hours.

Then 500 mL of 3.7% HCl is added, and the mixture is stirred for ½ hour and filtered through diatomaceous earth. The top aqueous layer is separated, and the organic layer is washed twice with 500 mL of 3.7N HCl. The combined aqueous layer is washed twice with 500 mL of ether.

Benzene (1 liter) is added. The mixture is cooled to 5°-10° C. and brought to pH > 9 with slow addition of 390 grams of 50% NaOH. The mixture is stirred for ½ hour and filtered through diatomaceous earth. The aqueous layer is separated and washed twice with 300 mL of benzene, which are combined with the first benzene layer.

The combined organic layers are washed with 250 mL of 5% $NaHCO_3$ and 250 mL of saturated NaCl solution. The organic layer is dried over Na_2SO_4, and solvent is removed leaving 49.6 grams of a yellow solid. The solid is dissolved in 100 mL of butyl acetate (hot) and cooled for 24–48 hours at 0° to 5° C. The solid is filtered, washed twice with 30 mL of cold ethyl acetate, and dried at 60° C. for 20 hours, yielding 38.8 grams (yield = 68.5%) of the title compound, m.p. = 116°-119° C.

E.

1-Methyl-4-[8-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]piperidin-11-OL

A suspension is prepared by mixing 22.7 grams of 11-oxo-8-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (0.1 mole) with 500 mL of liquid NH_3, and 5.1 grams of Na (0.22 mole) are added. The resulting blue mixture is stirred for ¾ hour. A solution containing 15.9 grams of 4-chloro-N-methyl-piperidine (0.12 mole) in 400 mL of dry THF is slowly added over ½ hour and stirred for 2 hours at −25° C.

NH_4Cl (17.5 grams, 0.33 mole) is added, and the mixture is stirred for ½ hour until the mixture warms to 0° C. Saturated NH_4Cl solution (200 mL) is added, followed by 50 mL of H_2O, and mixture is stirred for ½ hour.

The aqueous layer is separated and extracted with 200 mL of CH_2Cl_2, which is combined with the THF layer. The combined organic layer is washed with 250 mL of saturated NH_4Cl solution, and dried over Na_2SO_4. The solvent is removed, leaving 34.7 grams of an oil, which crystallizes upon cooling.

The solid material is dissolved in 65 mL of hot n-butyl acetate and cooled overnight. The solid obtained is filtered, washed twice with 15 mL of cold ethyl acetate, and then dried at 75° C. for 6 hours, yielding 15.8 grams of the title compound, m.p.=123.5°–125° C.

The solvent is removed from the filtrate, leaving 11.0 grams of a yellow solid, which is dissolved in 20 mL boiling ethyl acetate, filtered hot, and cooled at 0°–5° C. for 4 hours. The solid obtained is filtered, washed twice with 5 mL of ethyl acetate, and dried at 60° C. for 5 hours, yielding 4.3 grams (total yield=61.7%).

F.

8-Fluoro-11-(1-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cylohepta[1,2-b]pyridine

A solution of 13.1 grams of 1-methyl-4-[8-fluoro-6,11-dihydro-11-hydroxy-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-yl]piperidine (0.04 mole) in 40 mL of 93% H_2SO_4 is prepared. The solution is stirred overnight at room temperature. CH_2Cl_2 (200 mL) is added, and with external cooling, the mixture is neutralized to pH>9 using 50% NaOH, while maintaining the temperature below 30° C. The aqueous layer is separated and re-extracted twice with 150 mL of CH_2Cl_2, which is combined with the first layer. The combined organic layer is washed with 150 mL of saturated $NaHCO_3$ solution and 150 mL of saturated NaCl solution, dried over Na_2SO_4, treated with charcoal and filtered through diatomaceous earth. The solvent is removed on a rotary evaporator leaving 12.9 grams of a yellow oil, which solidified upon standing.

The oil is dissolved in 70 mL of hot diisopropyl ether (6 parts) and poured into a hot solution of 9.5 grams of maleic acid (0.082 mole) dissolved in 60 mL of diisopropyl ether. The solution is cooled to 0°–5° C. with stirring and a yellow oil forms. The mixture is cooled overnight at 0°–5° C. with a yellow solid forming. The solid is filtered, washed twice with 20 mL of cold diisopropyl ether, and dried at 60° C. for 4 hours, yielding 18.2 grams.

This solid is dissolved in 2 parts boiling diisopropyl ether and filtered hot. The filtrate is cooled at 0°–5° C. with stirring for 1 hour with a heavy white precipitate forming. The suspension is cooled at 0°–5° C. for 6 hours. The solid formed is filtered, washed three times with 15 mL of cold diisopropyl ether and dried at 75°–80° C. for 48 hours, yielding 15.6 grams (yield=72.2%) of the title compound, m.p.=151°–152° C.

The product of step F above can then be employed in the process described in Example 1.F. and 1.G. to provide 8-fluoro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

and 8-fluoro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, respectively.

EXAMPLE III

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine acetic acid salt

To 12 grams of sodium hydroxide in 30 mL ethyl alcohol (70%) add 6 grams of 8-chloro-6,11-dihydro-11-(1-ethoxy-carbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (prepared as described in U.S. Pat. No. 4,282,233) and reflux with stirring for 24 hours. After about the first 6–8 hours an additional 30 mL of 70% ethyl alcohol may be added.

Remove about 50% of the solvent by distillation in vacuo. Add a small amount of ice water and acidify with glacial acetic acid.

Extract with chloroform (6–8×), since the product precipitates from the acetic acid solution as a thick emulsion which cannot be filtered.

Concentrate the chloroform extracts to a small volume and precipitate the product with hexane. Crude m.p. 197°–200° C.

Recrystallize from benzene-hexane to obtain the product, m.p. 199°–200° C. Yield 4.0–4.5 grams.

EXAMPLE IV

B.

3-[2-(3-Chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide

31.5 g of N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide (e.g., as prepared in step A of Example I above) is dissolved in 600 mL of dry tetrahydrofuran and the resulting solution is cooled to −40° C. Two equivalents of n-butyllithium in hexane are added while the temperature is maintained at −40° C. The solution turned deep purple-red. 1.6 g of sodium bromide is added and the mixture is stirred. A solution of 26.5 g (0.174 mole) m-chlorobenzylchloride in 125 mL of tetrahydrofuran is added while the temperature is maintained at −40° C. The reaction mixture is stirred until the reaction is complete as determined by thin layer chromatography. Water is added to the reaction until the color is dissipated. The reaction mixture is extracted with ethyl acetate, washed with water, and concentrated to a residue. A yield of 92% for the product is shown by chromatography.

C.

3-[2-(3-Chlorophenyl)ethyl]-2-pyridine-carbonitrile

A solution of 3-[2-(3-chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (175 g, 0.554 mole), in 525 mL (863 g, 5.63 mole) of phosphorous oxychloride is heated at reflux for 3 hours. Completion of the reaction is determined by thin layer chromatography. Excess phosphorous oxychloride is removed by distillation at reduced pressure and the residue is quenched into a mixture of water and isopropanol. The pH is brought to 5–7 by addition of 50% aqueous sodium hydroxide solution while maintaining the temperature below 30° C. The crystalline slurry of crude product is filtered and washed with water. Crude product is purified by slurrying the wet cake in hot isopropanol followed by cooling at 0°–5° C. The product is filtered, washed with hexane and dried at below 50° C. Yield: 118 g (HPLC purity 95.7%), m.p. 72°–73° C., 89.4% of theory.

D.

(1-Methyl-4-piperidinyl)[3-[2-(3-chlorophenyl)ethyl]-2-pyridinyl]methanone hydrochloride

To a solution of product of Step C above (118 g. 0.487 mole) in 1.2 L of dry tetrahydrofuran is added 395 mL (2.48 mole/liter, 0.585 mole, 1.2 eg.) of N-methylpiperidyl magnesium chloride over about 15 minutes maintaining the temperature at 45° C.–50° C. by cooling with water as necessary. The reaction is maintained at 40° C. to 50° C. for about another 30 minutes. Completion of the reaction is determined by thin-layer chromatography. The reaction is quenched to pH below 2 with 2N hydrochloric acid and the resulting solution is stirred at about 25° C. for 1 hour. The bulk of the tetrahydrofuran is removed by distillation and the resulting solution is adjusted to pH 3.5 by the addition of aqueous sodium hydroxide. After cooling to 0° to 5° C., the crystalline hydrochloride salt product is filtered off, washed with ice cold water and dried to constant weight at 60° C. Yield: 168.2 g (HALC purity 94%), m.p. 183°–185° C., 89% of theory.

E.

8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidylindene)5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To a solution of a product of Step D above (59 g, 0.15 mole) in 120 mL (120 g, 6.0 mole) of hydrofluoric acid at −35° C. is added boron trifluoridine (44.3 g, 0.66 mole) over 1 hour. Completeness of the reaction is determined by thin-layer chromatography. The reaction is quenched using ice, water and potassium hydroxide to a final pH of 10. The product is extracted into toluene and the toluene solution is washed with water and brine. The toluene solution is concentrated to a residue, which is dissolved in hot hexane. Insolubles are removed by filtration and the filtrate is concentrated to an off-white powder. Yield: 45.7 g (HPLC purity: 96%), 92% of theory.

Alternative Step E

8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

A solution of 177 g (0.49 mole) of a product of Step D above in 480 mL (814.1 g, 5.31 mole) of trifluoromethanesulfonic acid at 90°–95° C. for 18 hours under nitrogen. Completeness of the reaction is determined by thin-layer chromatography. The cooled reaction is quenched with ice-water and the pH is adjusted to 6 with barium carbonate. The product is extracted into methylene chloride, which is concentrated under reduced pressure to about 1 liter and washed with water. The product is extracted into 1N hydrochloric acid, which is treated with 30 g of Darco, and filtered through celite. The pH of the filtrate is adjusted to 10 with 50% aqueous sodium hydroxide and the product is extracted into methylene chloride, which is removed under reduced pressure. The residue is dissolved in hot hexane, which is filtered to remove insolubles. The filtrate is concentrated to a residual beige powder. Yield: 126 g (HPLC purity 80%), 65% of theory.

EXAMPLE V

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

The acetic acid salt prepared as in Example II is dissolved in a minimum amount of water and the solution is made basic with a dilute aqueous solution of potassium carbonate. A pink colored oil separates.

Extract the organic material with chloroform, wash with water and remove the solvent. Triturate the residue with hexane. Recrystallize from a large volume of hexane after charcoal decolorization to obtain the product, m.p. 151°–152° C.

EXAMPLE VI

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta [1,2-b]pyridine

A.

8-chloro-6,11-dihydro-11-(1-cyano-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

Dissolve 16.2 grams (0.05 mole) of 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5H-benzo[5,6-]cyclohepta[1,2-b]pyridine (prepared by the methods described in U.S. Pat. No. 3,326,924) in 300 mL of dry benzene. To this solution, add slowly under nitrogen a solution of cyanogen bromide (6.4 g) dissolved in 75 mL of benzene. Allow this mixture to stir at room temperature overnight (approximately 20 hours).

Filter the solution, and concentrate the filtrate in vacuo to a small volume and precipitate the product by the addition of petroleum ether or hexane until precipitation is complete. Filter and recrystallize from ethanol/water to yield the product 15 grams (89%), m.p. 140°–142° C.

Anal. Calcd. for $C_{20}H_{18}N_3Cl$: C,71.53; H,5.40; N,12.51. Found, C,71.73; H,5.43; N,12.27.

B.

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

A solution of 14 grams of the N-cyano compound from part A in 60 mL of concentrated hydrochloric acid, 600 mL of glacial acetic acid and 400 mL of water is refluxed with stirring for 20 hours. The solvents are removed in vacuo and the residue dissolved in water and neutralized with ammonium hydroxide. The material is extracted several times with chloroform, the chloroform extracts washed with water and concentrated to dryness, and the residue triturated with petroleum ether or hexane to yield 11.5 grams (93%) m.p. 149°–151° C. After recrystallization from hexane, the product melts at 150°–151° C.

Anal. Calcd. for $C_{19}H_{19}N_2Cl$: C,73.42; H,6.16; N,9.01. Found: C,73.19; H,6.14; N,8.91.

EXAMPLE VII

A.

N-(1,1-dimethylethyl)-3-[2-(4-fluorophenyl)ethyl]-2-pyridine carboxamide

To a cooled (−40° C.) solution of N-(1,1-dimethylethyl)-3-methyl-2-pyridinecarboxamide (38.4 g, 0.2 mole) in dry THF (250 mL) is added n-butyl lithium (185 mL, 0.44 mole). Then sodium bromide (1.9 g, 18 mmol.) is added and is allowed to stir for 15 minutes. 4-Fluorobenzylchloride (31.8 g. 0.22 mole) was added and the reaction is allowed to stir for 2½ hours while warming up to −5° C. The reaction is then quenched with water and the product is extracted twice with ethyl acetate followed by washing twice with brine. The organic phase is dried over Na_2SO_4, filtered and solvent is removed to give desired compound (60.0 g) in 99% yield, m.p. 59°-61° C.

By a similar procedure, the corresponding 3-fluorophenyl, 3,4-dichlorophenyl, 3-bromophenyl, 4-chlorophenyl and 3,4-dibromophenyl analogs can be prepared by employing the appropriate substituted benzyl chloride.

B.

3-[2-(4-Fluorophenyl)ethyl]-2-pyridine-carbonitrile

The product of previous Step A (60.0 g, 0.2 mole) in $POCl_3$ (200 mL) is heated at 110° C. under an argon atmosphere for 3½ hours. The reaction mixture is poured onto ice and basified with 50% NaOH solution. It is then extracted three times with ethyl acetate, washed with water and brine, and dried over Na_2SO_4. Solvent is removed and the residue is passed through a coarse SiO_2 (60-200 mesh) column to give the desired product as a white solid (40 g) in 88% yield, m.p. 48°-49° C.

C.

9-Fluoro-5,6-dihydro-(1H)-benzo[5,6]cyclohepta[1,2-b]-pyridin-11-one

The product of Step B hereof (31.5 g, 139 mmol) is cyclized in polyphosphoric acid (1.24 kg) at 200° C. for 5½ hours. The hot reaction is poured into ice and then basified with 50% NaOH solution. The product is extracted three times with $CHCl_3$ and then washed with brine. The organic phase is dried (Na_2SO_4), filtered, and solvent is removed to give the desired product (20.4 g) in 64% yield, m.p. 78°-81° C. after recrystallization from diisopropyl ether.

D.

9-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinyl)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-OL

A solution of the product of previous Step C above (10.0 g, 44 mmol) in THF (100 mL) is added slowly to a cooled (−40° C.) solution of the Grignard reagent prepared from N-methyl-4-chloro-piperidine (57.9 mL, 88 mmol) in THF (70 mL). This is allowed to stir for about 1 hour while warming up to 0° C. The reaction is then quenched with NH_4Cl solution and then extracted twice with ethyl acetate. The organic phase is washed with brine, dried over Na_2SO_4, filtered and solvent removed. The residue is flash chromatographed and eluted with 5% methanol in $CHCl_3$ to give the desired compound (10.1 g) in 70% yield as white granular crystals, m.p. 126°-127° C. after recrystallization from diisopropyl ether.

E.

9-Fluoro-11-[1-methyl-4-piperidylene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To an ice-bath-cooled acid (146 mL) of H_2SO_4 and CF_3SO_3H (1:1) is added the product of previous Step D (7.3 g, 22.3 mmol). The reaction mixture is allowed to stir for ½ hour at ice bath temperature and then at room temperature for 1½ hour. The reaction mixture is poured onto ice and then basified with 50% NaOH solution. The product is extracted three times with ethyl acetate and washed with brine. The organic phase is desired (Na_2SO_4), filtered and solvent is removed to give a crude oil which is charcoaled and recrystallized from ethyl acetate and isopropyl ether to give the desired product (5.6 g) in 82% yield, m.p. 134.5°-135.5° C.

F.

9-fluoro-11-[1-ethoxycarbonyl-4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To a stirred solution of the product of previous Step E (5.0 g, 16.2 mmol) and triethylamine (2.6 g, 26 mmol) in dry toluene (60 mL) at 80° C. under an argon atmosphere, is added ethylchloroformate (9.8 g, 90 mmol) via a syringe. The reaction is allowed to stir at this temperature for 30 minutes and at room temperature for an hour. The reaction is filtered and solvent is removed. The residue is passed through coarse SiO_2 (60-200 mesh), eluted with $CHCl_3$ to give the desired product (4.5 g) in 76% yield as a white solid, m.p. 112°-114° C. after trituration wih pentane.

G.

9-Fluoro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

The product of previous Step F (3.83 g, 10.4 mmol) is refluxed with KOH (4.6 g) in 50 mL of ethanol/H_2O (1:1) for 4 hours under an argon atmosphere. The reaction mixture is poured into a brine solution and extracted twice with ethyl acetate. It is then dried over Na_2SO_4 and filtered. Solvent is removed to give the named compound (2.86 g) in 90% yield, m.p. 138°-140° C.

EXAMPLE VIII

A.

3-[2-(3,4-Dichlorophenyl)ethyl]-2-pyridinecarbonitrile

A solution of 3-[2-(3,4-dichlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (37.8 g, 0.107 mole) in 120 mL (197.4 g, 1.29 mole) of phosphorous oxychloride is heated at 110° C. for 4.5 hours. Completion of the reaction is determined by thin-layer chromotography. The reaction is quenched with ice and H_2O and the pH of the solution is brought to 8 by the addition of a saturated solution of potassium carbonate. The product is extracted into ethylacetate. The solution is concentrated to a solid residue which upon recrystallization from diethyl ether/ethyl acetate provides the desired product, (27.1 g, 0.098 mole), in 91.6% yield.

B.

(1-Methyl-4-piperidinyl)-[3-[2-(3,4-dichlorophenyl)ethyl]-2-piperidinyl]methanone

To a solution of the product of previous Step A (21.2 g, 0.0765 mole) in 140 mL of dry tetrahydrofuran at reflux is added 50 mL (1.48 mole/liter, 0.074 mole) of N-methylpiperidyl magnesium chloride over about 10 minutes. The reaction is maintained at reflux for an additional 10 minutes. The reaction is quenched to pH below 2 with aqueous hydrochloric acid and the resulting solution is stirred at 25° C. for 1 hour. The pH of the solution is adjusted to about 8, the product is extracted with ethyl acetate and the solution is concentrated to a residue. Following purification by silica gel chromatography and crystallization from diisopropyl ether, the desired product (19.86 g, 0.0526 mole) is obtained in 69% yield.

C.

8,9-Dichloro-6,11-dihydro-11-(1-methyl-4-piperidylidene-5H-benzo[5,6]-cyclohepta[1,3-b[pyridine

A solution of the product of previous Step B (9.8 g. 0.0259 mole) in 100 mL (169.6 g. 1.13 mole) of trifluoromethanesulfonic acid is heated at 85° C. for 48 hours. The reaction is quenched with ice-water and the solution made basic with potassium hydroxide. The product is extracted into ethyl acetate and the solution is concentrated to a residue. Following purification by reverse phase HPLC and crystallization from acetone/pentane, the desired product (2.38 g. 0.0066 mole) is obtained in 25.5% yield.

D.

8,9-Dichloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

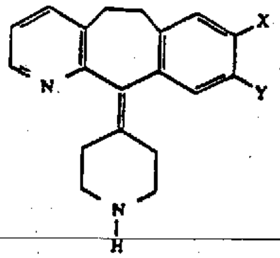
Ethyl chloroformate (1.9 mL. 2.16 g: 0.020 mole) in 10 mL of toluene is slowly added at 80° C. to a solution of the product of previous Step C (1.44 g. 0.004 mole) and triethylamine (1.5 mL. 1.09 g. 0.011 mole) in 50 mL of toluene. Folowing complete addition, the temperature is maintained at 80° C. for 2.5 hours. Insolubles in the reaction mixture are removed by filtration, and the filtrate is concentrated to a residue. Following silica gel chromotography and crystallization from pentane, the desired product (1.2 g. 0.0029 mole) is obtained in 72.5% yield.

E.

8,9-Dichloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

A solution of the product of previous Step D (0.925 g. 0.0022 mole) and potassium hydroxide (1.5 g. 0.039 mole) in 7.5 mL of water and 8.5 mL of ethanol is heated at reflux for 27 hours. The reaction mixture is diluted with water and the product is extracted into ethyl acetate. The solution is concentrated to a residue and the named compound (0.685 g. 0.0020 mole) is obtained from crystallization with toluene. Yield 91%.

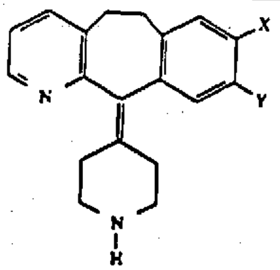
By employing the appropriately substituted benzyl chloride in Example I. B. above in place of 3-fluorobenzyl chloride, the following compounds of formula I or their pharmaceutically acceptable salts may also be prepared:



I

Compound No.	X	Y
1	H	Cl
2	H	Br
3	H	I
4	H	CF$_3$
5	Br	H

-continued



I

Compound No.	X	Y
6	I	H
7	CF$_3$	H
8	F	F
9	Br	Br
10	Cl	F
11	Cl	Br
12	F	Cl
13	Br	Cl
14	F	Br
15	Br	F

The following formulations exemplify some of the dosage forms of the compositions of this invention. In each, the term "active compound" designates a compound of the invention, e.g., Compound A or Compound B, or a pharmaceutically acceptable salt or solvate thereof.

PHARMACEUTICAL DOSAGE FORM EXAMPLES

EXAMPLE A

Tablets

No	Ingredient	mg/tablet	mg/tablet
1.	Active Compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix item nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with item no. 3. Mill the damp granules through a coarse screen (e.g., ¼") if needed. Dry the damp granules. Screen the dried granules if needed and mix with item no. 4 and mix for 10–15 minutes. Add item no. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active Compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade,	40	70
4.	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix item nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add item no. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

EXAMPLE C

	Parenteral	
Ingredient	mg/vial	mg/vial
Active Compound Sterile Powder	100	500

Add sterile water for injection or bacteriostatic water for injection, for reconstitution.

EXAMPLE D

Injectable	
Ingredient	mg/vial
Active Compound	100
Methyl para-hydroxybenzoate	1.8
Propyl para-hydroxybenzoate	0.2
Sodium Bisulfite	3.2
Disodium Edetate	0.1
Sodium Sulfate	2.6
Water for Injection q.s. ad	1.0 mL

Method of Manufacture

1. Dissolve the para-hydroxybenzoates in a portion (85% of the final volume) of the water for injection at 65°-70° C.
2. Cool to 25°-35° C. Charge and dissolve the sodium bisulfite, disodium edetate and sodium sulfate.
3. Charge and dissolve active compound.
4. Bring the solution to final volume by adding water for injection.
5. Filter the solution through a 0.22 membrane and fill into appropriate containers.
6. Finally, sterilize the units by autoclaving.

The following examples illustrate formulations including a compound of formula I for transdermal application. Compound A refers to 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, but again other compounds of formula I such as compound B above may be employed in its place.

EXAMPLE E

Ointment	mg/g
Compound A	200
White Petrolatum	800

EXAMPLE F

Ointment	mg/g
Compound A	200
Propylene glycol	200
White Petrolatum	600

EXAMPLE G

Cream	mg/g
Compound A	200
Mineral Oil	48
White Petrolatum	120
Cetostearyl Alcohol	57.6
Polyethylene glycol 1000 monocetylether	18.0
Propylene glycol	80
Water	476.4

EXAMPLE H

Gel	mg/g
Compound A	200
Pluronic F-127	250
Ethanol	200
Water	350

EXAMPLE I

Cream	mg/g
Compound A	100.00
Mineral Oil	54.0
White Petrolatum	135.0
Cetostearyl Alcohol	65.0
Ceteth 20	20.0
Propylene Glycol	100.0
Water q.s. ad	1.0 g

The formulations of Examples E-I above can be packaged to produce a "reservoir type" transdermal patch with or without a rate-limiting patch membrane. The size of the patch and or the rate limiting membrane can be chosen to deliver the transdermal flux rates desired. Such a transdermal patch can consist of a polypropylene or polyester impervious backing member heat sealed to a polypropylene porous/permeable membrane to from a reservior therebetween. The patch can include a pharmaceutically acceptable adhesive (such as a acrylate adhesive) on the membrane layer to adhere the patch to the skin of the host, e.g., a mammal such as a human. A release liner such as a polyester release liner can also be provided to cover the adhesive layer prior to application of the patch to the skin as is conventional in the art. This patch assembly can be packaged in an aluminum foil or other suitable pouch again as is conventional in the art.

Alternatively, a compound of formula I or a salt thereof can be formulated into a "matrix-type" transdermal patch as in Examples J and K below. Drug Delivery Systems Characteristics and Biomedical Application, R. L. Juliano, ed., Oxford University Press, N.Y. (1980); and Controlled Drug Delivery Vol. I Basic Concepts, Stephen D. Bruck (1983) described the theory and application of methods useful for transdermal delivery systems. The relevant teachings of these texts are herein incorporated by reference. The drug-matrix could be formed utilizing various polymers, e.g. silicone, polyvinyl alcohol, polyvinyl chloride-vinyl acetate copolymer. The "drug matrix" may then be packaged into an appropriate transdermal patch.

EXAMPLE J

Patch	mg/g
Compound A	200
silicone polymer	800

EXAMPLE K

Patch	mg/g
Compound A	300
Polyvinyl chloride vinyl acetate co-polymer	700

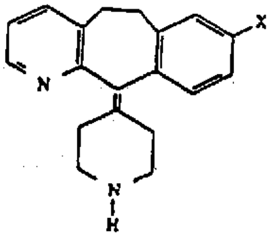
The invention also contemplates a package which contains a specific number of transdermal patches that may be utilized to complete a specified course of treatment. For example a package containing 7, 24 hour patches would be utilized to complete a one week course of therapy.

The relevant teachings of all published references cited herein as incorporated by reference.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

We claim:

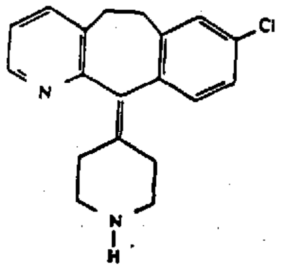
1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein X represents Cl or F.

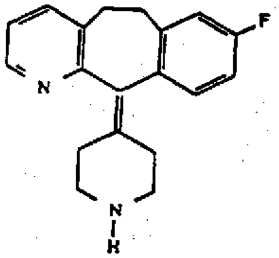
2. A compound defined in claim 1 in the form of the acetic acid salt.

3. A compound having the structural formula



or a pharmaceutically acceptable salt thereof.

4. A compound having the structural formula



or a pharmaceutically acceptable salt thereof.

5. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of a compound as defined in claim 1 in combination with a pharmaceutically acceptable carrier.

6. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of the compound defined in claim 2 in combination with a pharmaceutically acceptable carrier.

7. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of the compound defined in claim 3 in combination with a pharamaceutically acceptable carrier.

8. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of the compound defined in claim 4 in combination with a pharmaceutically acceptable carrier.

9. A composition as defined in claim 7 in unit dosage form.

10. A composition as defined in claim 8 in unit dosage form.

11. A transdermally acceptable pharmaceutical composition comprising an anti-allergic effective amount of a compound as defined in claim 1 and a pharamaceutically acceptable transdermal carrier.

12. A transdermally acceptable pharamaceutical composition comprising a anti-allergic effective amount of a compound as defined in claim 3 and a pharmaceutically acceptable transdermal carrier.

13. A transdermally acceptable pharmaceutical composition comprising an anti-allergic effective amount of a compound as defined in claim 4 and a pharmaceutically acceptable transdermal carrier.

14. A method for treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of a compound as defined in claim 1.

15. A method of treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of a compound as defined in claim 3.

16. A method for treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of a compound as defined in claim 4.

* * * * *

United States Patent [19]
Schumacher et al.

[11] **Patent Number:** **4,863,931**
[45] **Date of Patent:** **Sep. 5, 1989**

[54] **ANTIHISTAMINIC FLUORO SUBSTITUTED BENZOCYCLOHEPTAPYRIDINES**

[75] Inventors: Doris P. Schumacher, Florham Park; Bruce L. Murphy, Glen Ridge; Jon E. Clark, Highland Park, all of N.J.

[73] Assignee: Schering Corporation, Kenilworth, N.J.

[21] Appl. No.: 244,768

[22] Filed: Sep. 15, 1988

[51] Int. Cl.^{4} A61K 31/445; C07D 401/04
[52] U.S. Cl. 514/290; 546/93
[58] Field of Search 546/93; 514/290

[56] **References Cited**

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3,717,647	2/1973	Villani	546/315
4,282,233	8/1981	Villani	514/290
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F. Villani et al., *J. Med. Chem.*, vol. 15, No. 7, pp. 750–754 (1972).

F. Villani et al., *Arzneim-Forsch.*, vol. 36, pp. 1311–1314 (1986).

Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—Henry P. Nowak; James R. Nelson

[57] **ABSTRACT**

Certain benzocycloheptapyridine compounds with fluorine substitution across the exocyclic double bond are prepared and they are useful as antihistaminic agents.

14 Claims, No Drawings

ANTIHISTAMINIC FLUORO SUBSTITUTED BENZOCYCLOHEPTAPYRIDINES

BACKGROUND OF THE INVENTION

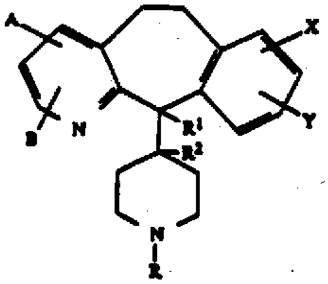
The present invention relates to certain benzocycloheptapyridines having fluoro substitution across an exocyclic double bond.

Numerous benzocycloheptapyridine compounds having substitution on the tricyclic ring system and having hydrogenated exocyclic double bonds have been disclosed. See, for example, U.S. Pat. Nos. 3,326,924, 3,717,647 and 4,282,233, European published Application No. 0042544, Villani et al., *Journal of Medicinal Chemistry,* Vol. 15, No. 7, pp 750–754 (1972) and *Arzneim. Forsch.,* 36, pp 1311–1314 (1986). However, fluoro-substitution across the exocyclic double bond has not previously been disclosed or suggested.

U.S. Pat. No. 4,731,447 in column 8, lines 31–35 discloses that in the preparation of certain benzocycloheptapyridine compounds using HF/BF_3 the temperature may be controlled so as to minimize side reactions, such as HF addition to the double bond of the rings.

SUMMARY OF THE INVENTION

It has now surprisingly been found that antihistamine activity is possessed by compounds represented by structural formula I



I

or a pharmacuetically acceptable salt thereof, wherein:

A, B, X and Y may be the same or different, and each independently represents H, halo, $-CF_3$, $-C(O)R^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, alkyl, alkenyl or alkynyl, which alkyl or alkenyl groups may be substituted with halo, $-OR^{10}$, or $-CO_2R^{10}$;

each R^{10} independently represents H, alkyl or aryl;

R^{11} represents alkyl or aryl;

R^1 and R^2 represent H and F respectively or F and H respectively; and

R represents H, alkyl or $-C_2R^{10}$ wherein R^{10} is as previously defined.

The invention also relates to a pharmaceutical composition comprising a compound of formula I in combination with a pharmaceutically acceptable carrier and to a method of treating allergic reactions by administering to a mammal in need of such treatment an antihistaminic effective amount of a compound of formula I.

In a preferred embodiment of the invention, one of A, B, X and Y is halo, e.g., chloro or fluoro, and the other groups are H.

In another preferred embodiment of the invention, R is $-CO_2R^{10}$, where R^{10} is H or alkyl, and most preferably alkyl, e.g., ethyl. In yet another preferred embodiment of the invention, R^1 is fluoro, and R^2 is H.

Preferred species falling within the scope of formula I include: ethyl 4-[8-chloro-6,11-dihydro-5H-benzo[5,6-]cyclohepta[1,2-b]pyridin-11-yl]-4-fluoro-1-piperidinecarboxylate; and

ethyl 4-[8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidine-carboxylate.

DETAILED DESCRIPTION OF THE INVENTION

Certain compounds of formula I may exist in different isomeric as well as conformational forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures.

The compounds of formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemihydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of the invention.

Certain compounds of formula I will be acidic in nature, e.g. those compounds which possess a carboxylic or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic compounds of formula II also form pharmaceutically acceptable salts, e.g., acid addition salts and quaternary ammonium salts. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to product a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The quaternary ammonium salts are prepared by conventional methods, e.g., by reaction of a tertiary amino group in a compound of formula II with a quaternizing compound such as an alkyl iodide, etc. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid, base and quaternary salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

When utilized herein, the terms below, unless otherwise indicated, have the following scope:

halo—represents fluoro, chloro, bromo and iodo;

alkyl (including the alkyl portions of alkoxy, alkylamino and dialkylamino)—represents straight or branched carbon chains, which contain from 1 to 6 carbon atoms;

alkenyl—represents straight or branched carbon chains having at least one carbon to carbon double bond and preferably having from 2 to 6 carbon atoms;

alkynyl—represents straight or branched carbon chains having at least one carbon to carbon triple bond and preferably having from 2 to 6 carbon atoms;

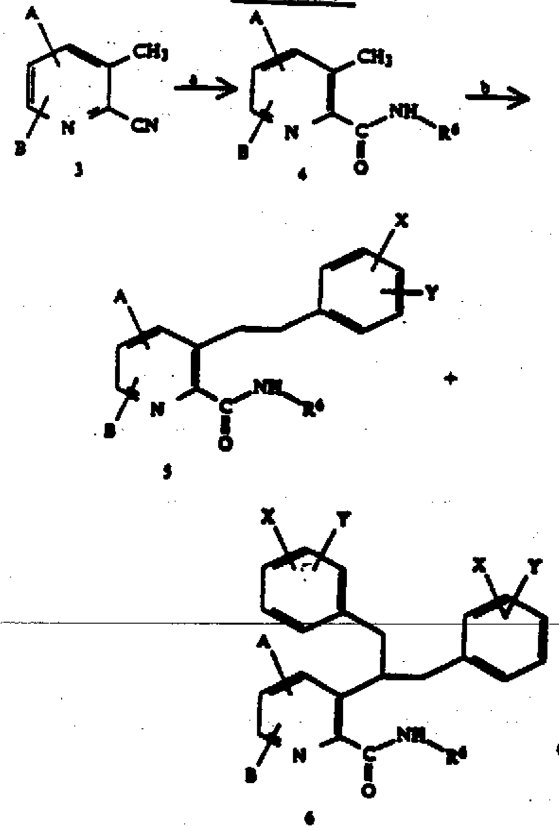
aryl—represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., a phenyl or fused benzene ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted with 1 to 3 groups, each independently selected from halo, alkyl, hydroxy, alkoxy, phenoxy, amino, alkylamino, dialkylamino. Preferred aryl groups include phenyl and 4-chlorophenyl.

The lines drawn from the groups A, B, X and Y into the pyridine and benzene rings of formula I are intended to indicate that such groups may be substituted on any carbon of such rings.

Compounds A and B above were prepared as side-products of the reactions described in U.S. Pat. No. 4,731,447. The methods described in that patent may be employed to prepare the compounds of the invention as described further below.

Compounds of general formula I may be prepared as shown in Scheme 1 below wherein A, B, X, Y, R^1, R^2, R^{10} and R^{11} are as defined above and R^6 and R^a are as defined below. The general method for producing compounds of general formula I from compounds of general formula 3 is outlined by reactions (a) through (g) in Scheme 1. Compounds of general formula 3 may be readily prepared as described in March, J. *Advanced Organic Chemistry*, 3rd Edition, John Wiley & Sons (1985), pp. 496–97; Villani et al, *J. Heterocyclic Chem.*, 8, 73 (1971) or may be obtained from commercial sources, e.g. Reilly Tar and Chemical.

SCHEME 1



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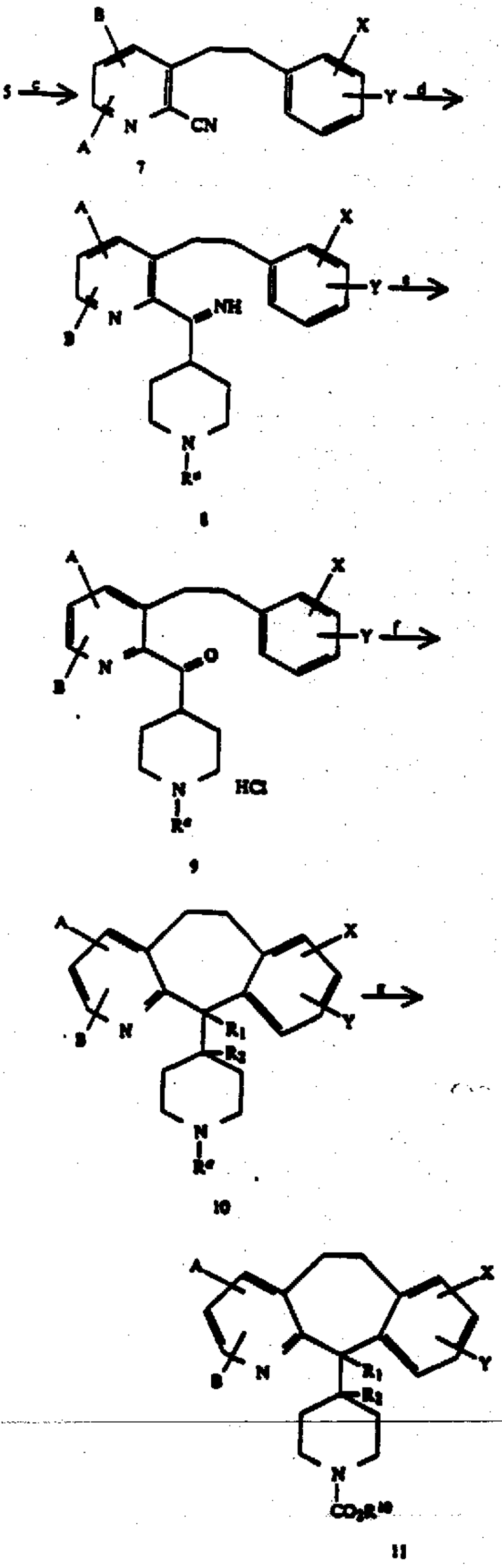
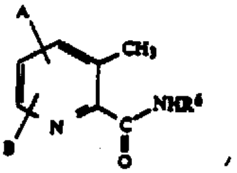
SCHEME 1



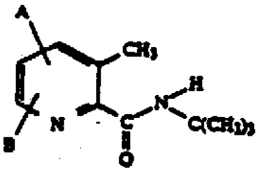
Reaction (a): A compound of formula 3, e.g., an unsubstituted or substituted 2-cyano-3-methyl-pyridine, can be converted into the corresponding carboxylic acid, e.g., an appropriate 3-methyl-2-pyridine carboxylic acid or activated ester thereof, e.g., a succinimide or hydroxysuccinimide ester, by reactions conventional in the art e.g., hydrolysis or esterification. The carboxylic acid or activated ester thereof can then be reacted with the appropriate amino compound of formula NH_2R^6 to form a compound of formula 4



(4)

wherein R^6 is a protecting group that will protect the N of the group $CONHR^6$ in formula 4 from reaction with an alkylating agent. Preferably the protecting group is a tertiary butyl group.

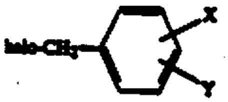
. A compound having such an R^6 tertiary butyl group can also be obtained directly from a compound of formula 3, for example, by a Ritter reaction in which a tertiary butyl compound is reacted with a 2-cyano-3-methyl-pyridine compound to produce a compound of formula 4a.



(4a)

This reaction is generally performed in an acid such as concentrated sulfuric acid or concentrated sulfuric acid in glacial acetic acid. Suitable tertiary butyl compounds include, but are not limited to, t-butyl iodide, t-butyl chloride, t-butyl bromide, t-butyl iodide, isobutylene or any other compound which under hydrolytic conditions forms t-butyl carboxamides with cyano compounds. The temperature of the reaction will vary depending on the reactants, but generally is conducted in the range of from about 50° to about 100° C. with t-butyl alcohol. The reaction may be performed with inert solvents but is usually run neat.

Reaction (b): The compound of formula 4 may be reacted with an appropriate benzyl halide of the formula



in the presence of a base to form the compound of formula 5 above. The halide is preferably Cl, Br or I, more preferably Cl. Examples of appropriate benzyl halides include, but are not limited to, benzyl chloride, 3-chlorobenzyl chloride, 3-fluorobenzyl chloride, 3,4-dichlorobenzylchloride, 4-fluorobenzyl chloride, 3-nitrobenzyl chloride, 3-methylbenzyl chloride, etc. Any suitable base can be employed, e.g., an alkyl lithium compound such as n-butyl lithium in tetrahydrofuran (THF). Preferably the base has a pK_a of greater than 20 and more preferably greater than 30. This reaction can

be conducted at any suitable temperature, e.g., temperatures of from about −78° C. to about 30° C., preferably from about −40° C. to about −30° C. The reaction can be performed in any suitable inert solvent such as THF, diethyl ether, etc.

Reaction (c): The amide of formula 5 may be converted to the cyano compound of formula 6 by the use of a suitable dehydrating agent such as $POCl_3$, $SOCl_2$, P_2O_5, toluene sulfonyl chloride in pyridine, oxalyl chloride in pyridine, etc. This reaction can be performed in the absence of or with an inert co-solvent such as xylene. The dehydrating agent such as $POCl_3$ is employed in equivalent amounts or greater and preferably in amounts of from about 2 to about 15 equivalents. Any suitable temperature and time can be employed for performing the reaction, but generally heat is added to speed up the reaction. Preferably, the reaction is performed at or near reflux.

Reaction (d): The cyano compound of formula 6 may be reacted with a Grignard reagent prepared from the appropriate 1-(N-protected)-4-halopiperidine. Any suitable N-protecting group known in the art to protect the piperidinyl nitrogen atom from reaction during formation of the Grignard reagent can be employed. Suitable N-protecting groups include alkyl (e.g. methyl), aryl (e.g. phenyl or substituted phenyl), alkyloxyalkyl (e.g. methoxymethyl), benzyloxyalkyl (e.g. benzyloxymethyl), substituted benzyloxyalkyl (e.g. (di-p-methoxyphenyl) methyl), triphenylmethyl, tetrahydropyranyl, diphenyl phosphinyl, benzene sulfenyl, etc. The N-protecting group can be later removed by conventional means once the Grignard reagent has been reacted with the compound of formula 6.

The reaction between compounds of formula 6 and the Grignard reagent are generally performed in an inert solvent such as an ether, toluene or tetrahydrofuran. This reaction is performed under the general conditions for a Grignard reactions, e.g., at temperatures of from about 0° C. to about 75° C.

Reaction (e): The resulting intermediate of formula 8, wherein R^6 is an alkyl group, may be hydrolyzed, e.g., with aqueous acid such as aqueous HCl, to prepare the corresponding ketone of formula 9.

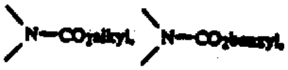
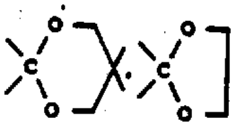
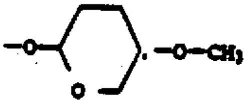
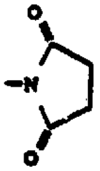
Reaction (f): The compound of formula 9 can be ring-closed to form the desired cycloheptene ring system (formula 10) by treating the compound 9 with a super acid having a Hammett acidity function of less than about minus 12, e.g., minus 13, minus 14, etc. This measure of acidity is defined in Hammett, Louis P., and Deyrup, Alden J., "Journal of the American Chemical Society", Vol. 54, 1932, p. 2721. Suitable super acids for this purpose include, for example, HF/BF_3. The reaction can be performed in the absence of or with a suitable inert co-solvent such as CH_2Cl_2. The temperature and time of the reaction vary with the acid employed.

The temperature may be controlled so as to maximize the side reaction of HF addition to the exocyclic double bond. Consequently, the temperature is generally in the range of from about +5° to −50° C., preferably from about 0° to +5° C.

Generally, the super acid is employed in excess, preferably in amount of from about 1.5 to about 30 equivalents. For example, with HF/BF_3 as the super acid system the volume/weight ratio of HF to the compound of formula IX in the reaction mixture is preferably from about 30 to about 1.5, more preferably 2.5 to 1.5. In such system, the weight/weight ratio of BF_3 to the compound of formula 9 in the reaction mixture is preferably from about 15 to about 0.75, more preferably from about 1 to about 0.75.

Reaction (g): The alkyl group (R^4) on the piperidyl ring (when it is methyl) may be converted to the alkyl esters of the formula Ia by reacting a compound of general formula 10 with an alkyl chloroformate, preferably ethyl chloroformate as described in Villani et al., Arzneim.—Forsch/Drug Research 1986, 36, 1311–1314 and in U.S. Pat. No. 4,731,447.

In the above processes a-g, it is sometimes desirable and/or necessary to protect certain A, B, X, Y, etc., groups during the reactions. Conventional protecting groups are operable. For example, the groups listed in column 1 of the following table may be protected as indicated in column 2 of the table:

1. Group to be protected	2. Protected Group
—COOH	—COOalkyl, —COObenzyl, —COOphenyl
	
	
	
—OH	
—NH$_2$	

Of course, other protecting groups well known in the art may be used. After the reaction or reactions, the protecting groups may be removed by standard procedures.

Conversion of compounds of formula Ia to compounds of formula I wherein R is H can be accomplished by hydrolysis the —CO_2R^{10} group. Hydrolysis may occur in an organic or inorganic polar solvent by refluxing in the presence of a base or acid. A typical hydrolyzing reaction utilizes 30% HCl solution in ethanol.

The compounds of the present invention can be used as antihistamines. One method of measuring the antihistamine activity of the compounds of the present invention in vitro utilizes isolated preparation of guinea pig ileum as described below and in Tozzi et al., Agents and Actions, 4(4):264 (1974).

Guinea Pig Ileum

Antagonists were evaluated for their ability to inhibit the spasmogenic doses of histamine dihydrochloride (1.8×10^{6}M) and acetylcholine chloride (1.3×10^{-7}M) on separate ileal segments of guinea-pig intestine according to the classical isotonic technique described in Magnus, Pflugers Arch. Ges. Physiol., 102:123 (1904). Freshly cut 2 cm segments of ileum were removed from male albino guinea-pigs (300–500 g) and suspended in 10 ml perfusion baths containing Tyrode solution warmed to 32° C. and constantly aerated with 95% O_2 and 5% CO_2. Tissues were adjusted to 0.5–1 g tension and allowed to equilibrate for a period of 30 minutes. All responses were recorded by means of a Harvard smooth muscle transducer connected to a Harvard electronic recorder. Utilizing 3–4 logarithmically-spaced doses of the antagonist, a graded inhibition of the smooth muscle response to histamine or acetylcholine was obtained by alternating the dose of agonist with increasing doses of antagonist. The agonists, in volumes of 0.1 ml, were added to the bath and kept in contact with the tissues for 45 seconds before they were removed by washing. In general, 3 control contractions of approximately equal height were obtained prior to studying the antagonist. The antagonist, in volumes between 0.1 and 0.3 ml, was added to the bath and allowed to remain for 3 minutes before the agonist was added. Then both were removed by washing and the next log increment of the antagonist was used.

At least 5 separate dose-response patterns were attained in each drug assay utilizing 2–5 segments. The average percent inhibition of agonist in all trials was then calculated. The results for the compound 8-chloro-6,11-dihydro-11-fluoro-11-(1-methyl-4-piperidinyl)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine are shown in Table 1.

TABLE 1

Molar Conc. of Histamine	% of Maximum Response for Histamine	% of Maximum Response for Histamine in the Presence of Test Compound
10^{-8}	11 ± 3	2 ± 0.9
3×10^{-8}	17 ± 4	5 ± 1
10^{-7}	33 ± 7	8 ± 1
3×10^{-7}	56 ± 4	18 ± 4
10^{-6}	81 ± 7	32 ± 3
3×10^{-6}	96 ± 3	42 ± 3

The following test procedure may be used to demonstrate antihistaminic activity of compounds of formula I. Protection against histamine lethality in the following assay is indicative of strong antihistaminic properties.

Prevention of Histamine-Induced Lethality in Guinea Pigs

Compounds may be evaluated for antihistamine activity by their ability to protect female albino guinea pigs (250–350 g) against death induced by the intravenous injection of histamine dihydrochloride at 1.1 mg/kg, which is approximately twice the LD_{99}. Doses of the antagonists were administered orally to separate groups of fasted animals 1 hour prior to the challenge with histamine and protection from death recorded for 30 minutes after histamine.

At a dose of 1 mg/kg p.o. of ethyl 4-[8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta [1,2-b]pyridin-11-yl]-1-piperidinecarboxylate, 4 of 5 animals survived the dose of histamine dihydrochloride.

The compounds of formula I can be administered in any number of conventional dosage forms. Solid dosage forms include capsules, tablets, pills, powders, suspensions, solutions, cachets or suppositories. Parenteral preparations include sterile solutions or suspensions. Inhalation administration can be in the form of a nasal or oral spray, or by insufflation. Topical dosage forms can be creams, ointments, lotions, transdermal devices (e.g., of the conventional patch or matrix type) and the like.

The formulations and pharmaceutical compositions contemplated by the above dosage forms can be prepared with conventional pharmaceutically acceptable excipients and additives, using conventional techniques. Such pharmaceutically acceptable excipients and additives are intended to include carriers, binders, flavorings, buffers, thickeners, color agents, stabilizing agents, emulsifying agents, dispersing agents, suspending agents, perfumes, preservatives, lubricants, etc.

When used orally or parenterally as antihistamines, the compounds of the invention can be administered in an amount ranging from about 0.1 mg/kg to about 100 mg/kg, preferably from 0.01 mg/kg to about 25 mg/kg per day. Determination of the proper dosage of a compound of the invention for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of formula I and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the disease being treated.

The following examples illustrate specific embodiments of the present invention including preparation of compounds, intermediates and starting materials.

EXAMPLE 1

A.
N-(1,1-dimethylethyl)-3-methyl-2-pyridinecarboxamide

A suspension of 2-cyano-3-methyl pyridine (400 g; 3.4 mol) in 800 mL of t-butanol was heated at 70° C. Concentrated sulfuric acid (400 mL) was added over 45 min. The reaction was complete after a further 30 min. at 75° C. The reaction mixture was diluted with water (400 mL) and toluene (600 mL) and brought to pH 10 with concentrated aqueous ammonia. The temperature was kept at 50°–55° C. during work-up. The toluene phase was separated, the aqueous layer extracted again with toluene and the combined toluene phases were washed with water. Removal of the toluene yielded 633 g (97%) of crystalline N-(1,1-dimethylethyl)-3-methyl-2-pyridinecarboxamide: m.p. 56°–58° C.; NMR 9200 MHz, $CDCl_3$)δ1.52 (s,9H); 2.75 (s,3H); 7.25 (dd,1H, J=7.5, 5 Hz); 7.58 (dd,1H, J=7.5, 1.2 Hz); 8.08 (br s, 1H); 8.40 (dd,1H, J=5), 1.2 Hz); mass spectrum, m/e (rel intensity) 192M+ (12), 177 (49). Anal. Calcd for $C_{11}H_{16}N_2O$: C,68.68; H, 8.13; N,14.40. Found: C,68.71; H,8.39; N,14.57.

B.
3-[2-(3-Chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide

To a cold (−40° C.) solution of N-(1,1-dimethylethyl)-3-methyl-2-pyridinecarboxamide (31.5 g; 0.16 mol) in 600 mL of dry tetrahydrofuran was added n-butyllithium in hexanes (2.5 mol; 131 mL) while the temperature was maintained at −40° C. The solution turned deep red after one equivalent was added. Sodium bromide (1.6 g) was added and the mixture was stirred for 10 min. A solution of m-chlorobenzyl-chloride (26.5 g; 0.174 mol) in 125 mL of dry tetrahydrofuran (THF) was added while the temperature was again maintained at −40° C. The reaction mixture was stirred for a further 30 min. after which water was carefully added until the color dissipated. The product was isolated by extraction into ethyl acetate which was washed with water, dried ($MgSO_4$) and concentrated to give 53.6 g (HPLC purity 89%; yield 92%) of 3-[2-(3-chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide as an oil. This oil may be used directly in the next step or crystallized from hexanes to give 3-[2-(3-chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide as a white solid: m.p. 45°–46° C.; NMR (200 MHz,$CDCl_3$)δ1.50 (s,9H), 2.96 (t,2H,J=8 Hz); 3.40 (t,2H,J=8 Hz); 7.0–7.3 (m,5H); 7.39 (dd,1H,J=8, 2 Hz); 7.98 (br s, 1H); 8.30 (dd,1H, J=4, 1 Hz); mass spectrum, m/e (rel intensity) 316M+ (19). Anal. Calcd for $C_{18}H_{21}N_2OCl$: C,68.22; H,6.68; N,8.88; Cl,11.19. Found: C,68.25; H,6.59; N,8.78; Cl,11.10.

C. 3-[2-(3-Chlorophenyl)ethyl]-2-pyridinecarbonitrile

A solution of 3-[2-(3-chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (175 g; 0.55 mol) in 525 mL (5.6 mol) of phosphorous oxychloride was heated at reflux for 3 h. Excess phosphorus oxychloride (−300 mL) was removed by distillation and the remaining solution was carefully poured into ice-water. The pH of the solution was adjusted to 8 with 50% aqueous sodium hydroxide while the temperature was maintained at 25°–30° C. The mixture was stirred for 2h during which time the pH was maintained at 8. The product was collected by filtration, washed with water and dried in a vacuum oven at 50° C. to give 127 g (95%) of crystalline 3-[2-(3chlorophenyl)ethyl]-2-pyridinecarbonitrile: m.p. 72°–73° C.; NMR (200 MHz, $CDCl_3$)δ2.9–3.1 (m,2H), 3.1–3.2 (m,2H), 7.0–7.1 (m,1H), 7.1–7.3 (m,3H), 7.42 (dd,1H,J=7.3, 5 Hz); 7.56 (dd,1H,J=7.3, 1.2 Hz), 8.48 (dd,J=5, 1.2 Hz); mass spectrum, m/e (rel intensity) 242 M+ (18). Anal. Calcd for $C_{14}H_{11}N_2Cl$: C,69.28; H,4.59; N,11.54; Cl 14.61. Found: C,69.37; H,4.48; N,11.39; Cl,14.48.

D.
[3-[2-(3-chlorophenyl)ethyl]-2-pyridinyl]-1-methyl-4-piperidinyl methanone hydrochloride

To a solution of compound 3-[2-(3-chlorophenyl) ethyl]-2-pyridinecarbonitrile (118 g; 0.49 mol) in 1.2 L of dry THF was added 395 mL (2.48 N; 0.59 mol) of N-methyl-piperidyl magnesium chloride over 0.5 h while the temperature was maintained at 40°–50° C. by cooling with water as necessary. The reaction mixture was maintained at 40°–50° C. for an additional 0.5 h. The reaction was quenched to below pH 2 by the addition of 2N hydrochloric acid and the resulting solution was stirred at 25°–30° C. for 1 h. The bulk of the THF was removed by distillation and the pH of the solution adjusted to 3.5 by the addition of aqueous sodium hydroxide. The mixture was cooled to 5° C. and the product was collected by filtration, washed with cold water and dried under vacuum at 60° C. to give 168 g (91%) of [3-[2-(3-chlorophenyl) ethyl]-2-pyridinyl]-1-methyl-4-piperidinyl methanone hydrochloride as a crystalline solid: mp 183°-185° C.; NMR (200 MHz, DMSO)δ2.72 (s,3H), 2.8-2.9 (m,2H) 3.0-3.2 (m,4H), 3.3-3.5 (m,3H), 3.9-4.1 (m,1H), 7.2-7.3 (m,1H), 7.3-7.4 (m,3H), 7.57 (dd,1H,J=6, 4Hz), 7.84 (dd,1H, J=6, 1.2 Hz), 8.59 (dd,1H,J=4, 1.2 Hz), 10.95 (br s, 1H); mass spectrum m/e (rel intensity) 345M^{+2} (32), 343M+ (100). Anal. Calcd for $C_{20}H_{24}N_2OCl_2$: C,63.32; H,6.38; N,7.39; Cl,18.69. Found: C,63.45; H,6.47; N,7.40; Cl, 18.49.

E.
8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To a solution of [3-[2-(3-chlorophenyl)ethyl]-2-pyridinyl]-1-methyl-4-piperidinyl methanone hydrochloride (59.0 g; 0.15 mol) in 120 mL (120 g; 6.0 mol) of hydrofluoric acid at −35° C. was added boron trifluoride (44.3 g; 0.66 mol) over 1 h. The reaction was quenched using ice water and potassium hydroxide to a final pH of 10. The product was extracted into toluene which was washed with water and brine. The toluene solution was concentrated to a residue which was triturated with hot hexanes. Insoluble salts were removed by filtration and the filtrate was concentrated to give as a main product 45.7 g (HPLC purity 96%, yield 91%) of 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine as an off-white solid: mp 116°-119° C.; NMR (200 MHz, $CDCl_3$)δ2.0-2.2 (m,2H), 2.27 (s,3H), 2.3-2.6 (m,4H), 2.6-3.0 (m,4H), 3.3-3.6 (m,2H), 7.0-7.2 (m,4H), 7.44 (dd,1H,J=8, 2 Hz), 8.42 (dd,1H,J=3, 2 Hz); mass spectrum, m/e (rel intensity) 327M^{+3} (28), 325M^{+1} (100) Anal. Calcd. for $C_{20}H_{21}N_2Cl$: C,73.94; H,6.52; N,8.63; Cl,10.92. Found: C,73.88; H,6.48; N,8.69; Cl10.80. This material was found to include the two corresponding fluoro-substituted compound of the invention as discussed further below.

F.
8-Chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

Ethyl chloroformate (40.4 mL; 45.9 g; 0.423 mol) was added slowly to a hot (-80° C) toluene solution (320 mL) of the 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (45.7 g; 0.141 mol) from Example 1E containing the two corresponding fluoro-substituted compounds of the invention. Following complete addition, the temperature was maintained at 80° C. for 1 h. The reaction mixture was cooled to ambient temperature and the toluene solution washed with water which was adjusted to pH 10 with aqueous sodium hydroxide. The organic layer was concentrated to a residue which was dissolved in hot acetonitrile and decolorized with charcoal. The solution was concentrated to a crystalline slurry which was cooled (5° C). 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6-]cyclohepta [1,2-b]pyridine containing the two corresponding fluoro-substituted compounds of the invention as discussed in Examples 1G below was isolated by filtration yielding 42.4 g: m.p. 134.5°-136° C.; NMR (400 MHz, $CDCl_3$)δ1.25 (t,3H,J=8 Hz), 2.3-2.4 (m,3H), 2.4-2.5 (m,1H), 2.7-2.9 (m,2H), 3.1-3.2 (m,2H), 3.3-3.4 (m,2H), 3.81 (br s, 2H), 4.13 (q,2H,J=8 Hz), 7.1-7.3 (m,4H), 7.43 (dd,1H,J=9,2 Hz), 8.40 (d,1H,J=5 Hz); mass spectrum, m/e (relative intensity) 385M^{+3} (35), 383 M+1 (100). Anal. Calcd. for $C_{22}H_{23}N_2ClO_2$: C,69.00; H,6.05; N,7.32; Cl9.26. Found: C,69.37; H,6.09; N,7.35; Cl 9.37.

G. Isolation of Ethyl 4-[8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-4-fluoro-1-piperidenecarboxylate and ethyl 4-[8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidenecarboxylate

The mother liquor from Example 1F (9.8 g) was dissolved in methanol and chromatographed on 2 C-18 cartridges on a Waters Prep 500 eluted with 3:7 (pH 7.8 phosphate buffer:MeOH). Appropriate fractions were combined and concentrated to an aqueous solution. The products were extracted into methylene chloride which was dried ($MgSO_4$) and concentrated to a residue. This resulted in 1.0 g of ethyl 4-[8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-4-fluoro-1-piperidenecarboxylate (Compound A) and 2.5 of ethyl 4-[8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidinecarboxylate (Compound B). These compounds had the characteristics as described in Example 2 and 3.

EXAMPLE 2

Characterization of Ethyl 4-[8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-4-fluoro-1-piperidenecarboxylate

m.p. 149°-153° C.; NMR (200 MHz, $CDCl_3$)δ1.24 (t,3H,J=6 Hz); 1.6-1.9 (m,4H); 2.7-3.2 (m,4H); 3.4-4.1 (m,4H); 4.14 (q,2H,J=6 Hz); 4.35 (d,1H,J=32 Hz); 7.0-7.2 (m,4H); 7.48 (dd,1H,J=8,1 Hz); 8.34 (dd,1H,J=4, 1Hz); mass spectrum, m/e (rel intensity) 403M+1 (34) Anal. Calcd. for $C_{22}H_{24}N_2O_2ClF$: C,65.91; H,5.90; N,6.70; Cl8.94. Found: C,66.00; H,5.91; N,6.78; Cl 8.94.

EXAMPLE 3

Characterization of Ethyl 4-[8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidinecarboxylate

m.p. 62-73° C.; NMR (400 MHz, $CDCl_3$)δ1.22 (t,3H,J=7 Hz); 1.2-1.3 (m,1H); 1.4-1.5 (m,1H); 1.5-1.7 (m,1H); 1.68 (s,2H); 2.5-2.7 (br s, 2H); 2.8-3.1 (m,2H); 3.3-3.5 (m,2H); 4.08 (q,3H,J=7 Hz); 4.1-4.2 (m,1H); 7.1-7.2 (m,2H); 7.25 (s,1H); 7.45 (d,1H,J=6 Hz); 7.63 (d,1H,J=6 Hz); 8.55 (s,1H). Mass spectrum, m/e (rel intensity) 403M^{+1} (72) Anal. Calcd for f$C_{22}H_{24}N_2O_2ClF$: C,65.91; H,5.90; N,6.70; Cl8.94. Found: C,65.58; H,6.00; N,6.95; Cl8.80.

The following examples illustrate the preparation of tablets and capsules using as the active compound any of the compounds of formula I, e.g., Compound A or B above.

Example 4

Pharmaceutical Dosage Form Examples

Example A

No.	Ingredient	mg/tablet	mg/tablet
1.	Active Compound	100	500
2.	Lactose USP	122	133
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix items nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with item no. 3. Mill the damp granules through a coarse screen (e.g., ¼") if needed. Dry the damp granules. Screen the dried granules if needed and mix with item no. 4 and mix for 10–15 minutes. Add item no. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

Example B

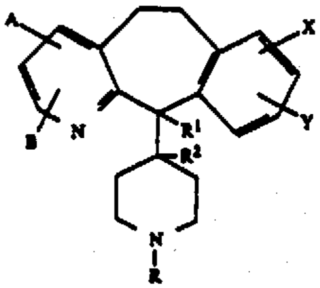
Capsules			
No.	Ingredient	mg/capsule	mg/capsule
1.	Active Compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade,	40	70
4.	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture Mix item nos. 1, 2 and 3 in a suitable blender for 10–15 minutes. Add item no. 4 and mix for 1–3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in connection with certain specific embodiments thereof, it will evident to one of ordinary skill in the art that many alternatives, modifications and variations may be made. All such alternatives, modifications and variations are intended to be included within the spirit and scope of the invention.

We claim:

1. A compound represented by structural formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

A, B, X and Y may be the same or different, and each independently represents H, halo, $-CF_3$, $-OR^{10}$, $-C(O)R^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, alkyl, alkenyl or alkynyl, alkyl, alkenyl or alkynyl, which alkyl or alkenyl groups may be substituted with halo, $-OR^{10}$, or $-CO_2R^{10}$;

R^{10} represents H, alkyl or aryl;

R^{11} represents alkyl or aryl;

R^1 and R^2 may be H and F respectively or F and H respectively; and

R is H, alkyl or $-CO_2R^{10}$ wherein R^{10} is as previously defined.

2. A compound of claim 1 wherein A, B, X and Y may be the same or different and each independently represents H or halo.

3. A compound of claim 2 wherein one of A, B, X and Y is halo and the others are H.

4. The compound of claim 3 wherein one of X or Y is halo and A, B and the other of X or Y are H.

5. The compounds of claim 4 wherein the halo X or Y is chlorine.

6. A compound according to claim 4 wherein R is CO_2R^{10}.

7. The compounds of claim 6 wherein R^{10} is selected from H or alkyl.

8. The compounds of claim 7 wherein R^{10} is alkyl.

9. The compounds of claim 8 wherein R^{10} is ethyl.

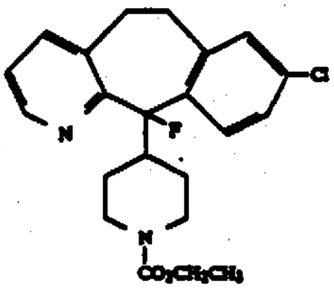
10. The compounds of claim 9 wherein R^1 is fluorine and R^2 is H.

11. A compound of claim 1 having the name:

ethyl 4-[8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-4-fluoro-1-piperidine carboxylate; or

ethyl 4-[8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidine carboxylate.

12. A compound of claim 10 having the formula:



13. A pharmaceutical composition which comprises a compound having structural formula I as defined in claim 1, in combination with a pharmaceutically acceptable carrier.

14. A method for treating allergic reactions in a mammal comprising administering to said mammal an antihistaminic effective amount of a compound as claimed in claim 1.

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