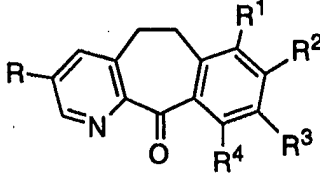
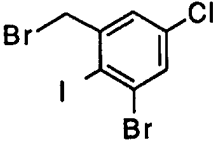




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(54) Title: SYNTHESIS OF INTERMEDIATES USEFUL IN PREPARING TRICYCLIC COMPOUNDS		
(57) Abstract		
<p>The invention relates to a process for preparing a compound of formula (I), comprising reacting a bromo-substituted pyridine with an amine of the formula NHR^5R^6, reacting the resulting amide with an iodo-halomethyl-substituted compound and cyclizing the resultant product, wherein R, R¹, R², R³ and R⁴ are as defined in the specification; also claimed are a compound of formula (a), and a process for preparing it from the corresponding halo-substituted benzoic acid.</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(a)</p> </div> </div>		

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10 SYNTHESIS OF INTERMEDIATES USEFUL IN PREPARING
TRICYCLIC COMPOUNDS

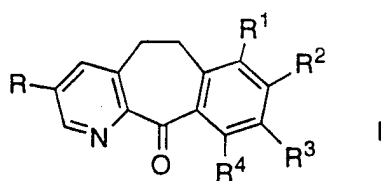
BACKGROUND OF THE INVENTION

15 This invention provides an improved process for preparing intermediates useful in the preparation of tricyclic compounds known as antihistamines and as inhibitors of farnesyl protein transferase (FPT). In particular, the compounds of this invention are useful in the preparation of antihistamines such as those disclosed in U.S. Patents 4,282,233 and 5,151,423, and of FPT inhibitors disclosed in International Application No. PCT/US96/19603, filed December 19, 1996.

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SUMMARY OF THE INVENTION

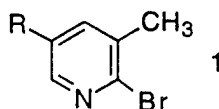
This invention provides a process for preparing a compound of the formula



25 wherein:

R, R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen and halo;
 comprising:

(a) reacting a compound of formula 1

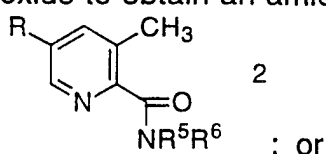


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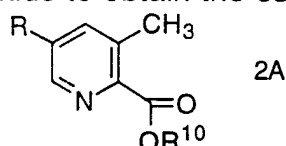
(i) with an amine of the formula NHR⁵R⁶, wherein R⁵ is hydrogen and R⁶ is C₁-C₆ alkyl, aryl or heteroaryl; R⁵ is C₁-C₆ alkyl, aryl or heteroaryl and R⁶ is hydrogen; R⁵ and R⁶ are independently

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- selected from the group consisting of C₁-C₆ alkyl and aryl; or R⁵ and R⁶, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms or comprising 3 to 5 carbon atoms and one hetero moiety selected from the group consisting of -O- and -NR⁹-, wherein R⁹ is H, C₁-C₆ alkyl or phenyl; in the presence of a palladium catalyst and carbon monoxide to obtain an amide of formula 2:

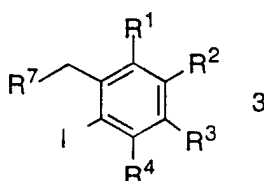


- (ii) with an alcohol of the formula R¹⁰OH, wherein R¹⁰ is C₁-C₆ lower alkyl or C₃-C₆ cycloalkyl, in the presence of a palladium catalyst and carbon monoxide to obtain the ester of formula 2A

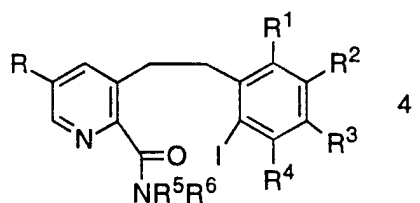


followed by reacting the compound of 2A with an amine of formula NHR⁵R⁶ to obtain the amide of formula 2;

- (b) reacting the amide of formula 2 with an iodo-substituted compound of formula 3



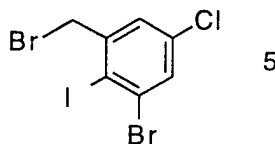
wherein R¹, R², R³ and R⁴ are as defined above and R⁷ is Cl or Br, in the presence of a strong base to obtain a compound of formula 4



- (c) cyclizing a compound of formula 4 with a reagent of the formula R⁸MgL, or when none of R, R¹, R², R³ and R⁴ are bromo, with a reagent of the formula R⁸Li, wherein R⁸ is C₁-C₈ alkyl, aryl or heteroaryl and L is Br or Cl; provided that prior to cyclization, compounds wherein R⁵ or R⁶ is hydrogen are reacted with a suitable N-protecting group.

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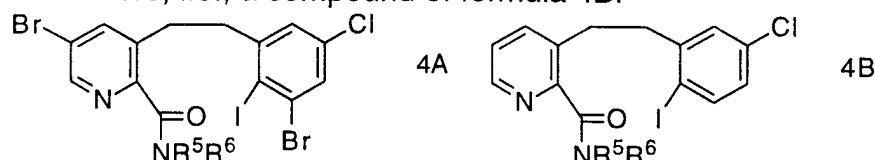
This invention also claims the intermediate compound of formula 3, in particular a compound of formula 3 wherein R¹ and R³ are hydrogen, R² is chloro, and each of R⁴ and R⁷ are bromo, i.e., a compound of formula 5:



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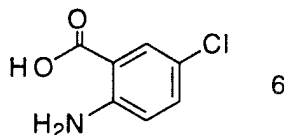
This invention also claims the intermediate compound of formula 4, in particular a compound of formula 4 wherein R¹ and R³ are hydrogen, R² is chloro, and each of R and R⁴ are bromo, i.e., a compound of formula 4A, or wherein R¹, R², R³ and R⁴ are hydrogen and R² is chloro, i.e., a compound of formula 4B:

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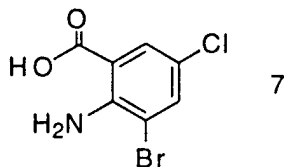
Also claimed herein is a process for preparing a compound of formula 5 comprising:

i) brominating 2-amino chlorobenzoic acid of formula 6

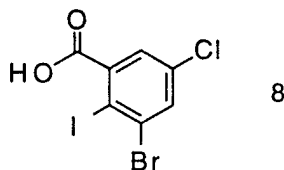


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to obtain 2-amino-3-bromo-5-chlorobenzoic acid of formula 7



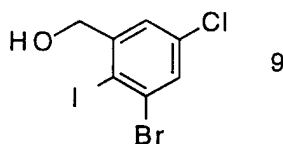
ii) iodinating the compound of formula 7 to obtain 2-iodo-3-bromo-5-chlorobenzoic acid of formula 8



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iii) reducing the carboxylic acid of the halo-substituted benzoic acid of formula 8 to obtain the corresponding hydroxy-methyl compound of formula 9

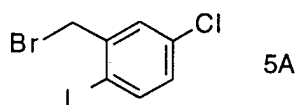
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; and

iv) brominating the compound of formula 9.

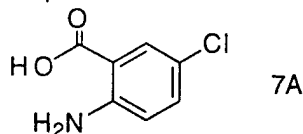
Also claimed herein is a process for preparing a compound of formula 5A



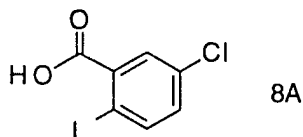
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comprising:

i) iodonating the compound of formula 7A

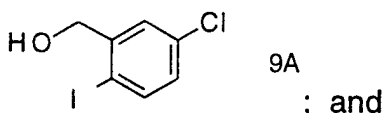


to obtain 2-iodo-5-chlorobenzoic acid of formula 8A



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ii) reducing the carboxylic acid of the halo-substituted benzoic acid of formula 8A to obtain the corresponding hydroxy-methyl compound of formula 9A



; and

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iii) brominating the compound of formula 9A.

Preferred compounds of formula I are those wherein R^2 is halo. Also preferred are compounds wherein R^1 and R^3 are each hydrogen. Another group of preferred compounds is that wherein R, R^1 , R^3 and R^4 are hydrogen and R^2 is halo. Still another group of preferred compounds is that wherein R^1 and R^3 are each hydrogen and R and R^2 are independently selected from the group consisting of halo. Yet another group of preferred compounds is that wherein R^1 and R^3 are each hydrogen and R, R^2 and R^4 are independently selected from the group consisting of halo. Halo is preferably Cl or Br.

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DETAILED DESCRIPTION

As used herein, the terms "alkyl" and "lower alkyl," where not otherwise defined, mean straight or branched alkyl chains of 1 to 6 carbon atoms.

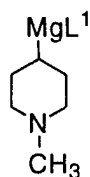
5 "Halo" refers to fluorine, chlorine, bromine or iodine radicals.

"Aryl" means phenyl, substituted phenyl wherein the substituents are 1 to 3 substituents independently selected from the group consisting of C₁ to C₆ alkyl and C₁ to C₆ alkoxy, benzyloxy or naphthyl.

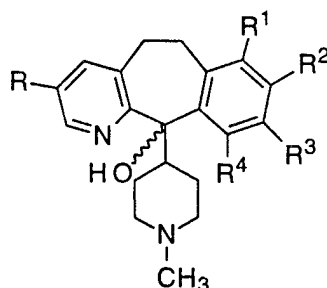
10 "Heteroaryl" means a 5- or 6-membered aromatic ring comprising one or two nitrogen atoms, e.g., pyridyl, pyrimidyl, imidazolyl or pyrrolyl.

When R⁵ and R⁶, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms, the rings so produced are exemplified by pyrrolidinyl, piperidinyl and perhydroazepine. When R⁵ and R⁶, together with the nitrogen to which they are attached, form a ring comprising 4 to 5 carbon atoms and a heteroatom, the rings so produced are exemplified by piperazinyl, N-methyl-piperazinyl, N-phenyl-piperazinyl and morpholinyl.

The compounds prepared by the process disclosed above are useful as intermediates in the procedures described in
 20 PCT/US96/19603 and U.S. 5,151,423 to obtain the desired compounds wherein the piperidinyl ring is N-substituted. Using those procedures, the compounds of the present invention are reacted with a substituted piperidine of the formula



25 wherein L¹ is a leaving group selected from the group consisting of Cl and Br, to obtain a compound of the formula



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This compound is converted to the corresponding piperidylidene, the nitrogen is deprotected, and the compound is reduced to the piperidyl form. The piperidinyll nitrogen can then be reacted with a variety of compounds, e.g., an acyl compound such as an ester or acyl chloride to form the desired amide.

By using the intermediates prepared by the process of this invention, the desired tricyclic antihistamines and FPT inhibitors described above can be made by a seven-step process rather than the fifteen-step process disclosed in the art. The present process allows halo substitution at any of R¹, R², R³ and/or R⁴, while previously disclosed procedures were not operative for preparing compounds wherein R⁴ is halogen. Moreover, the present process, employing the iodo-substituted intermediate of formula 3, is regioselective, producing the compound of formula 4 in high yield; without the iodo substituent, the reaction of step (b) produces undesirable mixtures of products, for example compounds wherein two compounds of formula 2 react in the presence of the strong base to produce a compound wherein the methyl group of one molecule joins to the carbonyl group of the other.

In step (a), the bromo-substituted pyridine of formula 1 is reacted with the amine NHR⁵R⁶ or with the alcohol of formula R¹⁰OH in the presence of a palladium catalyst, carbon monoxide (CO) and a base; when reacted with the alcohol, the product is then converted to an amide by reaction with an amine of the formula NHR⁵R⁶.

As defined above, the amines of formula NHR⁵R⁶ are exemplified by aniline, N-methylaniline, pyrrolidine, piperidine, perhydroazepine, piperazine, N-methyl-piperazine, N-phenyl-piperazine and morpholine. Preferred amines are aniline and N-methylaniline, with aniline being most preferred. The amount of amine (NHR⁵R⁶) reacted ranges from 1 to 4 equivalents, and is preferably 1 to 1.5 equivalents.

Palladium catalysts are exemplified by PdX₂/ligand at ratios of 1:0.5 to 1:3, preferably 1:1 to 1:2, at a range of 0.5 to 40 mol%, preferably 1 to 10 mol%, and most preferably 1 to 5 mol%; Pd(PPh₃)₄; (R¹¹)₃P/ Pd₂(dba)₃; and Pd/C, wherein X is OAc or Cl, ligand refers to P(R¹¹)₃ or a nitrogen-based ligand such as dipyridyl, 2-aminopyridine, 2-cyanopyridine, 2-dimethylaminopyridine, 1,10-phenanthroline, 2-

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methoxypyridine or (S)-(-)-nicotine, and wherein Ac is acetyl, R¹¹ is C₁ to C₆ alkyl or aryl, Ph is phenyl, and dba is dibenzylidene acetone. Preferred catalysts are Pd(OAc)₂/dipyridyl, Pd(OAc)₂/P(R¹¹)₃ and (PPh₃)₂PdCl₂.

- 5 Suitable bases include, but are not limited to, C₁ to C₁₀ alkyl amines such as triethylamine (Et₃N), t-butylamine and 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU), and inorganic bases such as K₂CO₃, Na₂CO₃, Na₂HPO₄ and NaOH. Preferred bases are K₂CO₃, DBU and Et₃N, with 1,8-DBU being preferred for use with Pd(OAc)₂/dipyridyl and
- 10 Et₃N being preferred for use with (PPh₃)₂PdCl₂.

- Suitable solvents are tetrahydrofuran (THF), dimethyl-formamide (DMF), acetonitrile (CH₃CN) and toluene or a combination thereof. CH₃CN is preferred for reaction with an amine and a combination of CH₃CN and toluene is preferred for reaction with an alcohol. The
- 15 temperature range for the reaction is 35°C to 100°C, preferably about 55°C for reaction with the amine and preferably about 80°C for reaction with an alcohol. The reaction is carried out at a pressure of 5 psi to 500 psi, preferably 40 to 200 psi, and most preferably at 50 to 150 psi. The time for reaction ranges from 2 hours to 4 days, preferably 4 hours to 2
- 20 days, and most preferably 16 to 48 hours.

 Conversion of the ester of formula 2A to the amide of formula 2 is accomplished by methods well known in the art, for example by reacting the ester directly with the amine or by using the conditions described by Basha et al in Tetrahedron Letters, (1977), p. 4171.

- 25 In step (b), the amide formed in step (a) is reacted with the iodo-substituted compound of formula 3 in a solvent such as THF, t-butyl methyl ether (t-BuOMe), diethyl ether (Et₂O), diglyme or a mixture thereof, preferably a mixture of THF and t-butyl methyl ether, in the presence of a strong base such as lithium diisopropylamide (LDA),
- 30 lithium hexamethyldisilylamide or sodium amide, preferably LDA. The concentration of the base ranges from 2.0 to 4.0 equivalents, preferably 2.0 to 2.2 equivalents. The iodo compound of formula 3 is reacted in a concentration range of 1.0 to 1.5 equivalents, preferably 1.1 equivalents. The reaction is carried out in a temperature range of -78°C to -20°C,
- 35 preferably -50°C to -30°C.

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In step (c), the product of step (b) is cyclized by treating with 1.0 to 3.0 equivalents, preferably 1.1 equivalents, of a reagent of the formula R^8MgL , wherein R^8 is C_1 - C_6 alkyl such as iso-propyl; aryl such as phenyl, 2,4,6-trimethylphenyl, 2-methylphenyl, 2-methoxy-phenyl, 2-methoxy-5-methylphenyl or 2,5-dimethoxyphenyl; or heteroaryl such as N-methyl-piperidyl and L is Br or Cl. Typical reagents of the formula R^8MgL are isopropylmagnesium chloride, 2-mesitylmagnesium bromide, o-tolyl-magnesium bromide, 2-methoxy-phenylmagnesium bromide, 2-methoxy-5-methylphenylmagnesium bromide, 2,5-dimethoxyphenyl-magnesium bromide and N-methyl-piperidylmagnesium bromide. A preferred reagent of formula R^8MgL is one wherein R^8 is 2-methoxy-phenyl, e.g., 2-methoxyphenylmagnesium bromide. For compounds wherein none of R, R^1 , R^2 , R^3 and R^4 are bromo, the cyclization reagent can also be R^8Li , wherein R^8 is as defined above. Preferred R^8Li reagents are n-, sec- and tert-butyllithium, methyllithium and phenyllithium. Suitable solvents include t-BuOMe, Et₂O, THF and toluene, with THF being preferred. The temperature range for the reaction is -78°C to 25°C, preferably 0 to -40°C, and most preferably -25 to -15°C.

Before cyclization, a protecting step is necessary when one of R^5 or R^6 is hydrogen. A protecting group can be added either after step (a) or after step (b). A compound of formula 2 or 4 is suitably protected by methods well known in the art, using protecting groups well known in the art, for example by reacting with CH₃I and a base such as NaNH₂, LDA, butyl lithium, NaH, CaH₂ or NaOH with a phase transfer catalyst, preferably NaH or NaOH with a phase transfer catalyst. Suitable phase transfer catalysts include C_1 to C_8 tertiary alkyl amine salts such as tetrabutylammonium bromide, tetrabutylammonium chloride or tetraoctylammonium bromide, benzyltriethylammonium chloride, trialkylsulfates, phosphorus salts and crown ethers. Base concentration ranges from 1 to 3 equivalents, preferably 1.5 equivalents, and phase transfer catalyst concentration ranges from 1.0 to 50 mol%, preferably 10 mol%. CH₃I concentration ranges from 1.0 to 5 equivalents, preferably 1.5 equivalents. Suitable solvents for the methylation step are THF, DMF, N,N-dimethyl-acetamide and dimethylsulfoxide (DMSO),

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with DMF being preferred. The temperature range for the reaction is -20°C to 20°C, preferably -10°C.

In the process for preparing the intermediate of formula 5, step (i) comprises brominating an amino,halo-substituted benzoic acid of formula 6 to obtain the corresponding 3-bromo-substituted benzoic acid of formula 7 by treating the compound of formula 6 with 1.0 to 2.0 equivalents, preferably 1.5 equivalent of bromine and an acid such as acetic acid (HOAc), HCl, CF₃CO₂H, CH₃SO₃H or CF₃SO₃H, preferably HOAc. The reaction is carried out at a temperature of 0 to 40°C, preferably 10 to 20°C.

In step (ii), the brominated benzoic acid of formula 7 is iodinated to obtain a compound of formula 8 by reacting with NaNO₂ or KNO₂, preferably NaNO₂, in an acid such as HCl, H₂SO₄, CH₃SO₃H or CF₃CO₂H, preferably H₂SO₄, and then treating the resultant product with KI, NaI or tetrabutylammonium iodide, preferably KI, in water. The nitrite concentration ranges from 1.0 to 4.0 equivalents, preferably 2.2 equivalents, and the iodide concentration ranges from 2 to 10 equivalents, preferably 5 to 7 equivalents. The reaction temperature ranges from -10 to 40°C, with a preferred range of -5 to 5°C.

In step (iii), the chloro-bromo-iodo benzoic acid of formula 8 is reduced to the corresponding alcohol by methods well known in the art. Suitable reducing agents include, but are not limited to, BH₃•THF and B(OCH₃)₃, BH₃•(CH₃)₂S (BMS) and B(OCH₃)₃, NaBH₄/SOCl₂, KBH₄/SOCl₂, NaBH₄/AlCl₃ and NaBH₄/TiCl₄. Preferred reagents are BH₃•THF or BMS in combination with B(OCH₃)₃ or NaBH₄ in combination with SOCl₂. As an example, the concentration of BMS ranges from 1.0 to 4.0 equivalents, preferably 2.5 to 3.0 equivalents, and the concentration of B(OCH₃)₃ ranges from 5 to 20 equivalents, preferably 10 to 16 equivalents. The temperature range for the reaction is from 0 to 30°C, preferably 15 to 25°C.

In step (iv) of the process for preparing the intermediate, the hydroxysubstituted compound is converted to the corresponding bromo-substituted compound by treatment with a brominating reagent such as SOBr₂, PPh₃ and Br₂, or Br₃P, preferably PPh₃ and Br₂. The amount of PPh₃ and Br₂ ranges from 1.0 to 2.0 equivalents, preferably being 1.1 to

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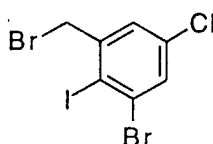
1.4 equivalents. Suitable solvents are THF, CH₃CN, EtCN and CH₂Cl₂, with CH₃CN being preferred. The temperature range for the reaction is 0 to 20°C, preferably 3 to 8°C.

In the process for preparing the intermediate of formula 5A, the benzoic acid of formula 7A is iodinated to obtain a compound of formula 8A, reduced to the alcohol of formula 9A, and brominated in the same manner as that described for the preparation of the compound of formula 5.

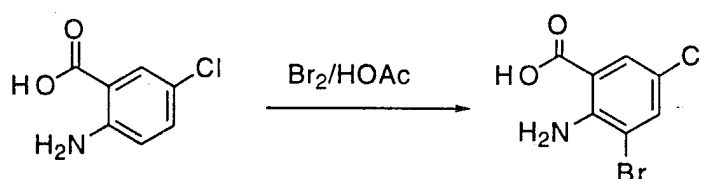
Starting materials of formula 1, NHR⁵R⁶, R⁸MgL and R⁸Li are known in the art or can readily be prepared by one skilled in the art. Starting materials of formula 3 are known in the art or, where the starting material is of formula 5 or 5A, can be prepared by methods disclosed herein.

Following are specific examples of the procedures in the various steps of the process of this invention for preparing compounds of formula I and formula 3, although those skilled in the art will appreciate that similar procedures within the scope of the process of this invention can be used to prepare other compounds of formula I and formula 3.

Preparation 1



Step (i):

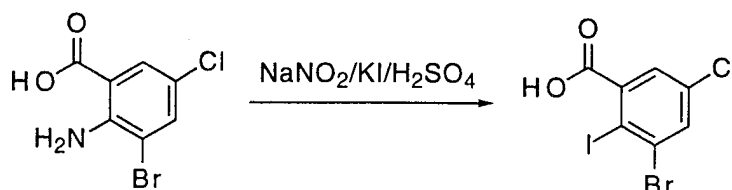


To a solution of 200 g (1.05 mol) of 2-amino-5-chlorobenzoic acid in 3.4 L of HOAc at 15°C was added dropwise 184 g (1.15 mol) of Br₂. The mixture was stirred at 15°C for 4 hrs, quenched slowly into 8 L of water, and extracted with 2 X 2 L of t-BuOMe. The combined extract was washed with water, dried over MgSO₄ and concentrated. The crude product was treated with hot hexane, filtered and dried to give 210 g (80%) of 2-amino-3-bromo-5-chlorobenzoic acid as white solid. Mp. 225-228°C. ¹H NMR (DMSO-d₆): δ 7.70 (d, J = 2.6 Hz, 1 H), 7.69 (d, J =

-11-

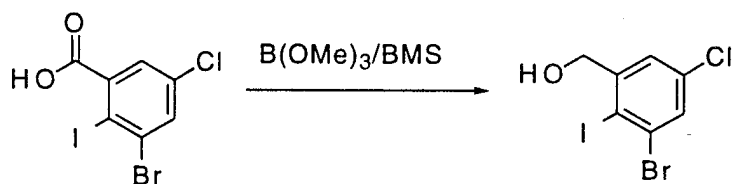
2.6 Hz, 1 H), 6.8 (bs, 2 H). ^{13}C NMR (DMSO- d_6): δ 168.16, 147.06, 136.25, 130.19, 118.22, 112.35, 110.34. IR: 3480 (m), 3350 (m), 2920 (s), 1670 (s) cm^{-1} . Analysis calcd. for $\text{C}_7\text{H}_5\text{BrClINO}_2$: C, 33.53, H, 2.00, N, 5.59; Found: C, 33.63, H, 2.12, N, 5.70.

5 Step (ii):



To 40 g (159 mmol) of the product of step (i) in 160 mL of conc. H_2SO_4 at 0°C 24.1 g (350 mmol) of NaNO_2 was added slowly. The mixture was mechanically stirred at that temperature for 3 hrs and
10 quenched into 1 L ice with strong agitation. The resulting solution was added slowly into 158 g (954 mmol) of KI in 2 L ice water and extracted with 2 X 1 L of EtOAc. The combined extract was washed with NaHSO_3 , dried over MgSO_4 and concentrated. To the residue was added hexane and the precipitate was filtered and dried to give 50.4 g (87%) of 2-iodo-3-bromo-5-chlorobenzoic acid as white solid. Mp. $174\text{--}176^\circ\text{C}$. ^1H NMR (DMSO- d_6): δ 7.98 (d, $J = 2.4$ Hz, 1 H), 7.60 (d, $J = 2.4$ Hz, 1 H).
15 ^{13}C NMR (DMSO- d_6): δ 168.08, 144.23, 134.13, 133.08, 132.53, 126.91, 99.88. IR: 3150 (m), 2920 (s), 1720 (s), 1650 (m) cm^{-1} .

Step (iii):



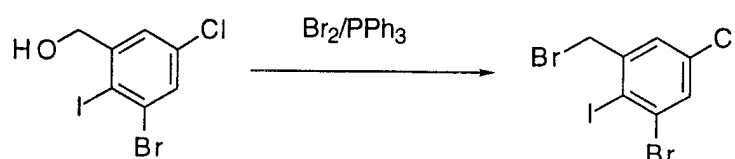
20

To a 2 L flask with a mechanical stirrer, a thermometer, and an addition funnel, at r.t. were added sequentially 50 g (138 mmol) of the product of step (ii), 500 mL of THF, 229 mL (2.01 mol) of 2.0 M $(\text{CH}_3\text{O})_3\text{B}$ and 193 mL (386.4 mmol) of 2.0 M $\text{BH}_3 \cdot (\text{CH}_3)_2\text{S}$. The reaction mixture
25 was stirred at r.t. for 18 hrs, quenched with 500 mL of CH_3OH and concentrated. The residue was dissolved with 1 L EtOAc, washed with brine, dried over MgSO_4 , and concentrated to give 47 g (98%) of 2-iodo-3-bromo-5-chlorobenzyl alcohol as a white solid.

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Alternatively, the acid was reduced following a two-step, one-pot procedure: first, the acid was converted to its corresponding acid chloride and then treated with NaBH_4 . Mp. 99-101°C. ^1H NMR (CDCl_3): δ 7.55 (d, $J = 2.4$ Hz, 1 H), 7.39 (d, $J = 2.4$ Hz, 1 H), 4.61 (s, 2 H), 2.48 (bs, 1 H). ^{13}C NMR (CDCl_3): δ 146.70, 134.93, 130.84, 130.48, 125.74, 100.45, 69.99. IR: 3200 (s), 2920 (s) cm^{-1} . Anal. calcd. for $\text{C}_7\text{H}_7\text{ClBrIO}$: C, 24.03, H, 2.00; Found: C, 24.35, H, 2.19.

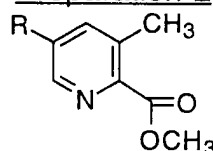
Step (iv):



To a 500 mL flask with a mechanical stirrer at 5°C were added 9.7 g (37 mmol) of PPh_3 , 100 mL CH_3CN and 6 g (37 mmol) of Br_2 . The reaction mixture was stirred at 5°C for 1 hr, and 10 g (28.7 mmol) of the alcohol of step (iii) in 100 mL of CH_3CN was added dropwise. The reaction mixture was allowed to warm to r.t., agitated for 1 hr, and concentrated. The residue was extracted with 2 X 400 mL CH_2Cl_2 , washed with brine, dried over MgSO_4 and concentrated. The phosphoxide was filtered after addition of hexane. The filtrate was passed through a pad of silica gel and concentrated to give 11.3 g (96%) of 2-iodo-3-bromo-5-chlorobenzylbromide as a white solid.

Alternatively, the alcohol was converted either to the bromide using SOBr_2 in 90% yield, or to the corresponding chloride using SOCl_2 . Mp. 75-77°C. ^1H NMR (CDCl_3): δ 7.54 (d, $J = 2.4$ Hz, 1 H), 7.36 (d, $J = 2.4$ Hz, 1 H), 4.60 (s, 2 H). ^{13}C NMR (CDCl_3): δ 143.94, 134.66, 131.98, 131.58, 128.15, 104.71, 39.52. IR: 2920 (s), 1540 (m) cm^{-1} .

Preparation 2

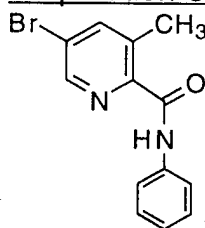


To a 400 mL autoclave was charged 1.6 g (6.06 mmol) of 2,5-dibromo-3-methylpyridine, 0.45 g (0.64 mmol) of $(\text{PPh}_3)_2\text{PdCl}_2$, 30 mL of toluene/ CH_3CN (1:1), 0.33 mL (95 mmol) of Et_3N and 4 eq. of

-13-

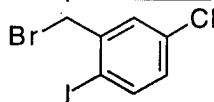
CH₃OH. The autoclave was sealed, evacuated, flushed with nitrogen three times and charged with carbon monoxide to 80 psi. The autoclave was heated to 80°C for 16 hrs, cooled to r.t. and the excess carbon monoxide was evacuated under vacuum. The conversion was about 55% as determined by NMR. The contents of the autoclave were transferred into a flask for concentration. The residue was then purified on a silica gel column, eluting with hexane:EtOAc to give the ester as a white solid. M.p. 61-62°C. ¹H NMR (CDCl₃): δ 8.58 (d, J = 1.9 Hz, 1H), 7.78 (d, J = 1.9 Hz, 1H), 3.96 (s, 3H), 2.58 (s, 3H). ¹³C NMR (CDCl₃): δ 165.82, 147.94, 145.17, 142.20, 137.63, 123.56, 52.74, 19.96. IR: 1715 cm⁻¹.

Preparation 3



To a 4 L autoclave were added sequentially 250 g (949 mmol) of 2,5-dibromo-3-methylpyridine, 6.7 g (30 mmol) of Pd(OAc)₂, 5.0 g (32 mmol) of dipyrldyl, 10 L of toluene, 127 mL (1.1 mol) of aniline, and 277 mL (2.0 mol) of DBU. The autoclave was sealed, evacuated, purged with nitrogen, and charged with carbon monoxide to 80 psi. The reaction mixture was heated to 65°C for about 2 days with periodical refilling as necessary, and then cooled to r.t. The contents of the autoclave was vented under vacuum and flushed with nitrogen, then transferred to a 10 L flask with the aid of water and EtOAc. The mixture was concentrated and filtered through a pad of celite. The filtrate was extracted with 2 X 1 L of toluene. The combined extract was washed with brine, filtered and concentrated. The residue was recrystallized from hot *i*-PrOH and the precipitate was filtered, washed with M.L., and dried at 50°C to give 220 g (76%) of the amide as white solid.

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Preparation 4

Step (i):



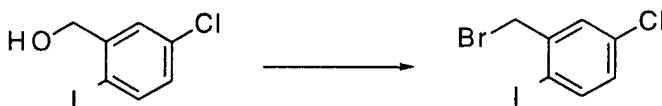
- 5 To 75 g (394 mmol) of 2-amino-5-chlorobenzoic acid (90%) in 300 mL of conc. H_2SO_4 at 0°C was added slowly 60 g (870 mmol) of NaNO_2 . The mixture was mechanically stirred at that temperature for 5 hrs and at rt for 12 hrs, then quenched into 2 L ice with strong agitation. The resulting solution was added slowly into 393 g (2.37 mol) of KI in 2 L
- 10 ice water and extracted with 2 X 1 L of EtOAc. The combined extract was washed with NaHSO_3 , dried over MgSO_4 , concentrated and dried to give 124 g (>100%) of 2-iodo-5-chlorobenzoic acid as white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 7.91 (d, $J = 8.5$ Hz, 1H), 7.66 (d, $J = 2.6$ Hz, 1H), 7.26 (dd, $J = 8.5, 2.6$, 1H).

15 Step (ii):



- To a 2 L flask with a mechanical stirrer, a thermometer, and an addition funnel at r.t. were added sequentially 124 g (0.4 mol) of the product of Step (i), 700 mL of THF, 500 g (4.85 mol) of $(\text{CH}_3\text{O})_3\text{B}$, and
- 20 560 mL (1.12 mol) of 2.0 M $\text{BH}_3 \cdot \text{Me}_2\text{S}$. The reaction mixture was stirred at r.t. for 18 hrs., quenched with 500 mL of CH_3OH and concentrated. The residue was dissolved with 1 L EtOAc, washed with brine, dried over MgSO_4 , and concentrated to give 121 g (>100%) of 2-iodo-5-chlorobenzyl alcohol as white solid. ^1H NMR (CDCl_3): δ 7.64 (d, $J = 8.3$ Hz, 1H), 7.41 (d, $J = 2.5$ Hz, 1H), 6.93 (dd, $J = 8.3, 2.5$, 1H), 4.57 (s, 2H).

25 Step (iii):

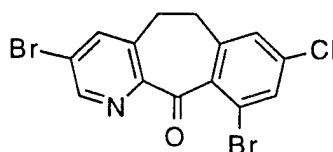


-15-

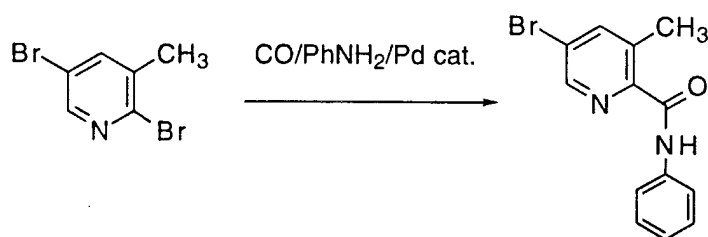
To a 500 mL flask with a mechanical stirrer at 5°C were added 140 g (0.53 mol) of PPh₃, 1100 mL CH₃CN, and 85 g (0.53 mol) of Br₂. The reaction mixture was stirred at 5°C for 1 hr, and 121 g (about 0.4 mmol) of the alcohol of Step (ii) was added portionwise. The reaction mixture was allowed to warm to r.t., agitated for 1 hr, and concentrated. The residue was extracted with 2 X 400 mL CH₂Cl₂, washed with brine, dried over MgSO₄, and concentrated. The phosphoxide was filtered after addition of hexane. The filtrate was passed through a pad of silica gel and concentrated to give 2-iodo-5-chlorobenzylbromide as white solid (about 95% yield). ¹H NMR (CDCl₃): δ 7.68 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 2.5 Hz, 1H), 6.90 (dd, J = 8.5, 2.5 Hz, 1H), 4.44 (s, 2H).

Alternatively, the alcohol was converted either to the bromide using SOBr₂ in 90% yield, or to the corresponding chloride using SOCl₂.

Example 1



Step 1:

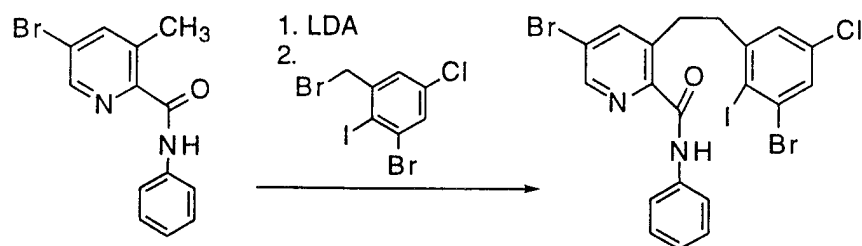


To a 4 L autoclave were added sequentially 250 g (949 mmol) of 2,5-dibromo-3-methylpyridine, 21 g (30 mmol) of (Ph₃P)₂PdCl₂, 2 L of CH₃CN, 100 mL (1.1 mol) of aniline, and 154 mL (1.5 mol) of Et₃N. The autoclave was sealed, evacuated, purged with nitrogen and charged with carbon monoxide to 80 psi. The reaction mixture was heated to 60°C for about 3 days with periodical refilling as necessary, and then cooled to r.t. The contents of the autoclave was vented under vacuum, flushed with nitrogen and transferred to a 10 L flask with the aid of water and EtOAc. The mixture was concentrated and filtered through a pad of celite. The filtrate was extracted with 2 X 1 L of EtOAc. The combined extract was washed with brine, dried over MgSO₄, filtered and

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concentrated. The residue was recrystallized from hot i-PrOH and the precipitate was filtered, washed with mother liquor and dried at 50°C to give 162 g (59%) of the amide as white solid. The solution yield was determined to be 71%. Mp. 103-104°C. ¹H NMR (CDCl₃): δ 10.00 (bs, 1H), 8.49 (d, J = 2.1 Hz, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.72 (d, J = 7.5 Hz, 2H), 7.37 (dd, J = 7.5, 7.4 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 2.79 (s, 3H). ¹³C NMR (CDCl₃): δ 162.79, 146.34, 145.21, 143.29, 137.91, 137.72, 128.96, 124.18, 123.12, 119.61, 20.68. IR: 3320 (w), 2920 (s), 1700 (m) cm⁻¹. Elemental analysis: calcd for C₁₃H₁₁BrN₂O: C, 53.60, H, 3.78, N, 9.62; found: C, 53.50, H, 3.79, N, 9.51.

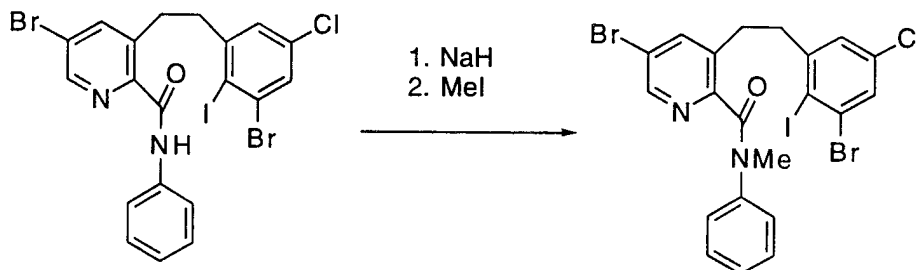
Step 2:



To a solution of 0.98 mL (7 mmol) of i-Pr₂NH in 5 mL t-BuOMe at -40°C was added 2.8 mL (7 mmol) of 2.5 M n-BuLi in hexanes. To a mixture of 1 g (3.44 mmol) of the product of Step 1 in 4 mL of THF and 10 mL of t-BuOMe at -50°C was added dropwise the LDA solution. The resulting purple solution was added dropwise at -40°C into 1.4 g (3.61 mmol) of the product of Preparation 1 in 10 mL of t-BuOMe. The mixture was allowed to warm to 0°C and was quenched with a solution of NH₄Cl. The precipitate was filtered, washed with brine and hexanes, and dried to give 1.47 g (69%) of the desired product. An analytical sample was purified on a silica gel column. Mp. 186-187°C. ¹H NMR (CDCl₃): δ 10.02 (s, 1H), 8.54 (d, J = 2.1 Hz, 1H), 7.78 (d, J = 2.1 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 2.4 Hz, 1H), 7.39 (dd, J = 7.4, 8.4 Hz, 2H), 7.29 (d, J = 2.4 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 3.44-3.40 (m, 2H), 3.28-3.18 (m, 2H). ¹³C NMR (CDCl₃): δ 162.40, 148.14, 147.14, 145.20, 142.84, 140.16, 137.62, 135.04, 131.48, 130.33, 129.10, 128.14, 124.44, 123.43, 119.83, 105.42, 44.21, 33.67. IR: 2920 (s), 1680 (m) cm⁻¹. HRMS: Calc'd for C₂₀H₁₅Br₂ClN₂O: 620.8265, Found: 620.8262 (MH⁺).

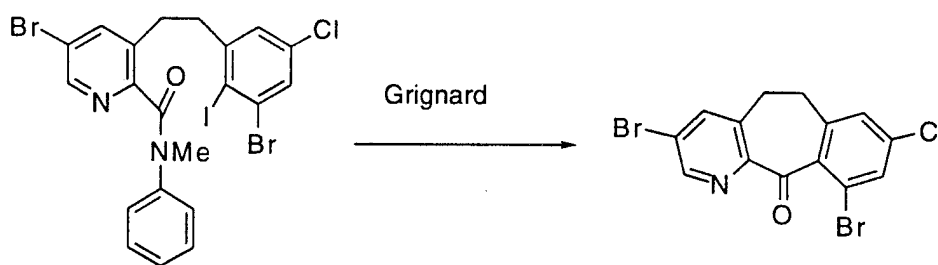
-17-

Step 3:



To 27.7 g (44.2 mmol) of the product of Step 2 in 750 mL of DMF at -10°C was added 1.5 g 80% NaH (66.3 mmol). After stirring at -10°C for 1 hr, 4.1 mL (66.3 mmol) of CH_3I was added to the flask. The mixture was mechanically stirred at -10°C for 1 hr, then quenched carefully into 2 L ice. The precipitate was filtered, washed with water and dried to give 23.7 g (85%) of the desired product as an off-white solid. Mp. $180\text{--}181^{\circ}\text{C}$. NMR indicates two rotamers. ^1H NMR (CDCl_3): δ 8.26 (d, $J = 1.8$ Hz, 1H), 7.53 (d, $J = 1.8$ Hz, 1H), 7.52 (s, 1H), 7.18–7.10 (m, 6H), 3.15 (s, 3H), 3.17–3.10 (m, 2H), 2.83–2.79 (m, 2H). ^{13}C NMR (CDCl_3): δ 167.61, 152.35, 147.94, 147.59, 142.87, 139.41, 135.11, 131.79, 130.51, 129.06, 129.04, 127.98, 127.04, 126.65, 120.21, 105.08, 43.97, 37.26, 31.96. IR: 2920 (s), 1650 (m) cm^{-1} . HRMS: Calc'd for $\text{C}_{21}\text{H}_{17}\text{Br}_2\text{ClIN}_2\text{O}$: 634.8420, Found: 634.8423 (MH^+).

Step 4:



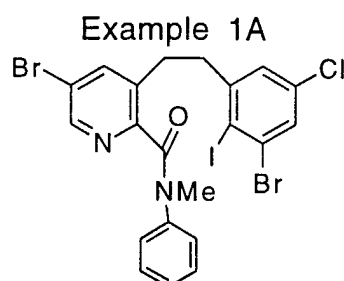
To a solution of 2 g (3.15 mmol) of the product of Step 3 in 40 mL of THF at -20°C was added dropwise 4.8 mL of 0.72 M 2- $\text{CH}_3\text{OC}_6\text{H}_4\text{MgBr}$ (3.5 mmol) in THF. The mixture was stirred at -20°C for 20 min. and quenched with 5 mL of saturated NH_4Cl . The quenched solution was stirred at r.t. for 16 hrs. to complete the hydrolysis, concentrated and extracted with 2 X 10 mL of EtOAc. The combined extract was washed with brine, dried over MgSO_4 and concentrated. The residue was chromatographed on silica gel, eluting with

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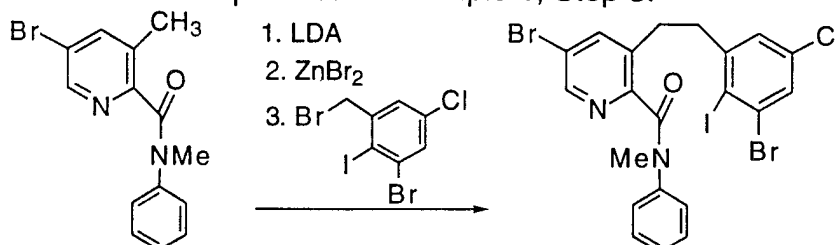
hexane/EtOAc (9:1) to give 0.84 g (66%) of the azoketone. The solution yield was determined to be 82% by HPLC. Mp. 198-200°C.

^1H NMR (CDCl_3): δ 8.74 (d, $J = 1.8$ Hz, 1 H), 7.75 (d, $J = 1.8$ Hz, 1 H), 7.55 (d, $J = 1.8$ Hz, 1 H), 7.20 (d, $J = 1.8$ Hz, 1 H), 3.25-3.19 (m, 2 H), 3.15-3.09 (m, 2 H). ^{13}C NMR (CDCl_3): δ 194.17, 150.21, 149.39, 140.90, 140.73, 139.18, 137.69, 136.54, 131.48, 126.79, 123.33, 119.88, 32.78, 31.59. IR: 2920 (s), 1690 (m) cm^{-1} . Elemental analysis: Calcd. for $\text{C}_{14}\text{H}_8\text{Br}_2\text{Cl}$ NO: C, 41.84, H, 1.99, N, 3.49; Found: C, 42.11 H, 2.07, N, 3.64.

10



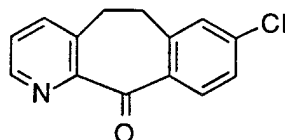
Alternative route to the product of Example 1, Step 3:



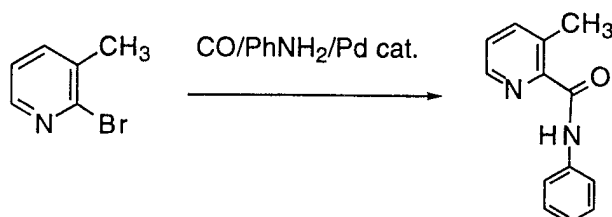
To a solution of 2.5 mL (18 mmol) of diisopropylamine in 10 mL dry THF at -60°C was added dropwise 7.2 mL (18 mmol) of 2.5 M *n*-BuLi. To another flask containing 5 g (16.4 mmol) of the N-methyl amide starting material (prepared in a manner similar to that described in Example 1, Step 1) in 50 mL THF at -78°C was added the above LDA solution. After stirring at -78°C for 5 min., 20.8 mL (18 mmol) of a freshly prepared solution of ZnBr_2 was added. To the resulting mixture was added 6.7 g (16.4 mmol) of 5-chloro-3-bromo-2-iodobenzyl bromide in 10 mL THF. The reaction was heated to reflux for 2 hrs, quenched slowly into saturated NH_4Cl and extracted with toluene. The combined extract was washed with brine, dried over MgSO_4 and concentrated. The precipitate was filtered to give 4.6 g (44%) of the N-methylated product. The HPLC solution yield was determined to be 60%.

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Example 3



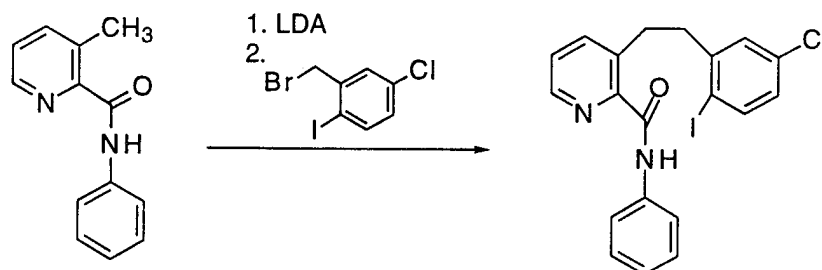
Step 1:



- 5 In a 150 mL autoclave were added sequentially 10 g (55 mmol) of 2-bromo-3-methylpyridine, 1.2 g (1.7 mmol) of $(\text{Ph}_3\text{P})_2\text{PdCl}_2$, 50 mL of CH_3CN , 8 mL (87 mmol) of aniline, and 18 mL (116 mmol) of DBU. The autoclave was sealed, evacuated, purged with nitrogen and charged with carbon monoxide to 80 psi. The reaction mixture was heated to
- 10 65°C for 9 h with periodical refilling of carbon monoxide as necessary, and then cooled to r.t. The contents of the autoclave was vented under vacuum, flushed with nitrogen and transferred into a separatory funnel with the aid of water and EtOAc. The phases were separated and the aqueous phase was extracted with 100 mL of EtOAc. The combined
- 15 extract was washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was recrystallized from hot *i*-PrOH and water and the precipitated was filtered and dried at 50°C to give 6.9 g (59%) of the amide as white solid. The solution yield was determined to be 76%. Mp. $66\text{--}67^\circ\text{C}$. ^1H NMR (CDCl_3): δ 10.23 (bs, 1H), 8.37 (dd, $J = 4.6$ Hz,
- 20 0.8 Hz, 1H), 7.71 (m, 2H), 7.62 (dd, $J = 6.95$ Hz, 1H), 7.31–7.36 (m, 3H), 7.10 (t, $J = 7.42$ Hz, 1H), 2.79 (s, 3H). ^{13}C NMR (CDCl_3): δ 163.52, 146.70, 145.21, 141.28, 138.02, 136.13, 128.94, 125.95, 123.97, 119.62, 20.80. R: 3330 (w), 2920 (s), 1680 (m) cm^{-1} . Analysis. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}$: C, 73.58, H, 5.66, N, 13.21; found: C, 73.29, H, 5.76, N,
- 25 12.81.

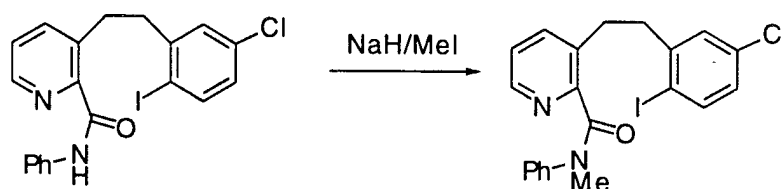
-20-

Step 2:



To a solution of 10 mL (70 mmol) of *i*-Pr₂NH in 40 mL *t*-BuOCH₃ at -40°C was added 28 mL (70 mmol) of 2.5 M *n*-BuLi in hexanes. To a mixture of 7.0 g (33.0 mmol) of the product of Step 1 in 30 mL of THF and 70 mL of *t*-BuOCH₃ at -30°C was added dropwise the above LDA solution. The resulting purple solution was added dropwise at -30°C into 11.0 g (33.0 mmol) of 3-chloro-6-iodo benzyl bromide in 20 mL of THF and 50 mL of *t*-BuOCH₃. The mixture was allowed to warm to 0°C and quenched with a solution NH₄Cl. The phases were separated and the aqueous phase was extracted with 100 mL of *t*-BuOCH₃. The combined organic solution was washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was used directly in the following step without further purification. ¹H NMR (CDCl₃): δ 10.24 (s, 1H), 8.43 (dd, J = 4.57 Hz, J = 1.6 Hz, 1H), 7.71 (m, 2H), 7.52 (dd, J = 7.8 Hz, 1.59 Hz, 1H), 7.29-7.35 (m, 2H), 7.24 (d, J = 2.61 Hz, 1H), 7.08 (t, J = 7.43 Hz, 1H), 6.81 (dd, J = 8.4 Hz, J = 2.6 Hz, 1H), 3.40-3.44 (m, 2H), 3.03-3.07 (m, 2H).

Step 3:



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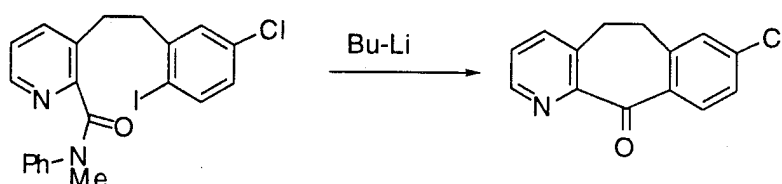
To the residue (~33 mmol) of the product of Step 2 in 70 mL of DMF at 0°C was added 2.6 g 60% NaH (66 mmol). After stirring at 0°C for 1 hr, 2.5 mL (40 mmol) of CH₃I was added to the flask. The mixture was mechanically stirred at 0°C for 15 min, then quenched carefully by ice. EtOAc (200 mL) was added and the solution was washed with water (100 x 5). The organic layer was concentrated to give 16 g residue, which was separated by column chromatography

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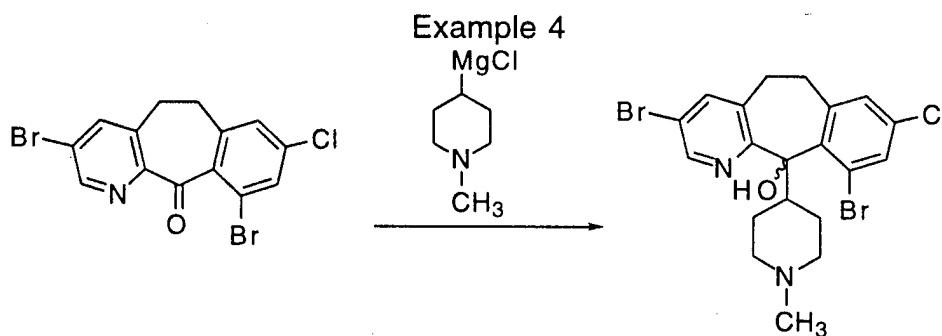
-21-

(hexane/EtOAc) to give 10 g product, 64% yield, in two steps. Mp. 106-107°C. NMR indicate two rotamers. ¹H NMR (CDCl₃): δ 8.17 (d, J = 4.6 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 6.96 - 7.1 (m, 6H), 6.86 (dd, J = 8.5, 2.4 Hz, 1H), 3.49 (s, 3H),
 5 2.90 - 2.96 (m, 2H), 2.74 - 2.80 (m, 2H). ¹³C NMR (CDCl₃): δ 168.4, 153.9, 146.5, 145.4, 143.1, 140.4, 137.0, 134.6, 133.2, 129.7, 128.8, 128.3, 126.7, 126.6, 123.3, 97.2, 41.4, 37.1, 32.1.

Step 4:



10 To a solution of 2 g (4.2 mmol) of the product of Step 3 in 20 mL of THF at -78°C was added dropwise 2.52 mL of 2.0 n-BuLi (5.0 mmol) in cyclohexane. The mixture was stirred at -78°C for 10 min. and quenched with 30 mL of saturated NH₄Cl. The quenched solution was
 15 extracted with 2 X 50 mL of EtOAc. The combined extract was washed with brine, dried over MgSO₄ and concentrated. The residue was passed through silica gel, eluting with hexane/EtOAc (6:4) to give 1.02 g (78%) of the title compound. ¹H NMR (CDCl₃): δ 8.60 (dd, J = 4.6, 1.5 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.55 (dd, J = 7.7, 1.5 Hz, 1H), 7.29 (dd, J = 7.7, 4.6 Hz, 1H), 7.24 (dd, J = 8.5, 2.0 Hz, 1H), 7.17 (d, J = 2.0, 1H),
 20 3.15-3.20 (m, 4H). ¹³C NMR (CDCl₃): δ 194.1, 155.3, 149.4, 143.9, 139.6, 138.2, 137.4, 136.4, 133.6, 130.3, 127.9, 126.8, 35.2, 33.1.



25 To a solution of 1.88 g (4.68 mmol) of the product of Example 1 in 10 mL THF at -20°C was added dropwise 5.72 mL (5.15 mmol) of 0.9 M of the Grignard. The reaction was stirred at that temperature for 1 hr,

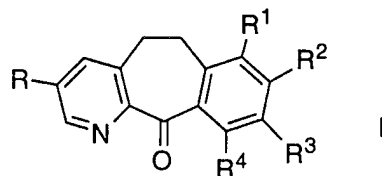
-22-

quenched into NH_4Cl and extracted with EtOAc. The combined extract was washed with brine, dried over MgSO_4 and concentrated. The residue was chromatographed on silica gel, eluting with EtOAc/hexane to give 1.4 g (60%) product as fluffy solid. Mp. 98-100°C. ^1H NMR (5 CDCl_3): δ 8.45 (d, $J = 2.1$ Hz, 1 H), 7.64 (d, $J = 2.1$ Hz, 1 H), 7.62 (d, $J = 2.2$ Hz, 1 H), 7.07 (d, $J = 2.2$ Hz, 1 H), 6.86 (s, 1H), 3.68-3.58 (m, 1 H), 3.48-3.39 (m, 1 H), 3.06-2.8 (m, 4 H), 2.66-2.57 (m, 1 H), 2.23 (s, 3 H), 1.85-1.75 (m, 2 H), 1.68-1.58 (m, 1 H), 1.40-1.36 (m, 1 H), 0.91-0.85 (m, 1 H). ^{13}C NMR (10 CDCl_3): δ 156.54, 145.04, 141.25, 140.57, 139.09, 135.32, 134.65, 132.52, 130.42, 122.35, 119.64, 80.50, 56.07, 55.70, 45.94, 44.98, 34.27, 30.83, 26.20, 26.09. IR: 3300 (w), 2920 (s), 1570 (w) cm^{-1} .

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We claim:

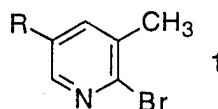
1. A process for preparing a compound of the formula



5 wherein:

R, R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen and halo; comprising:

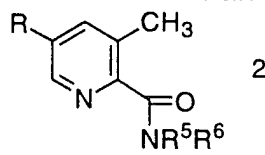
- (a) reacting a compound of formula 1



10

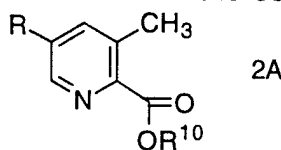
- (i) with an amine of the formula NHR⁵R⁶, wherein R⁵ is hydrogen and R⁶ is C₁-C₆ alkyl, aryl or heteroaryl; R⁵ is C₁-C₆ alkyl, aryl or heteroaryl and R⁶ is hydrogen; R⁵ and R⁶ are independently selected from the group consisting of C₁-C₆ alkyl and aryl; or R⁵ and R⁶, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms or comprising 3 to 5 carbon atoms and one hetero moiety selected from the group consisting of -O- and -NR⁹-, wherein R⁹ is H, C₁-C₆ alkyl or phenyl; in the presence of a palladium catalyst and carbon monoxide to obtain an amide of formula 2:

20



; or

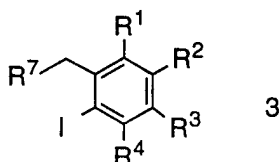
- (ii) with an alcohol of the formula R¹⁰OH, wherein R¹⁰ is C₁-C₆ lower alkyl or C₃-C₆ cycloalkyl, in the presence of a palladium catalyst and carbon monoxide to obtain the ester of formula 2A



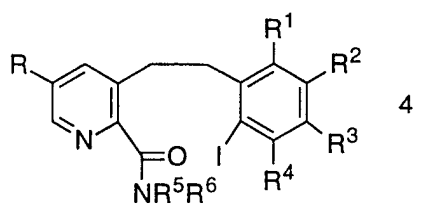
- 25 followed by reacting the compound of 2A with an amine of formula NHR⁵R⁶ to obtain the amide of formula 2;

-24-

(b) reacting the amide of formula 2 with an iodo-substituted compound of formula 3

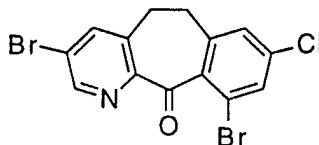


wherein R¹, R², R³ and R⁴ are as defined above and R⁷ is Cl or Br, in the presence of a strong base to obtain a compound of formula 4



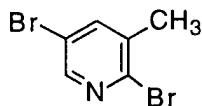
(c) cyclizing a compound of formula 4 with a reagent of the formula R⁸MgL, or when none of R, R¹, R², R³ and R⁴ are bromo, with a reagent of the formula R⁸Li, wherein R⁸ is C₁-C₈ alkyl, aryl or heteroaryl and L is Br or Cl, provided that prior to cyclization, compounds wherein R⁵ or R⁶ is hydrogen are reacted with a suitable N-protecting group.

2. A process of claim 1 for preparing a compound of the formula



comprising:

(a) reacting a compound of the formula

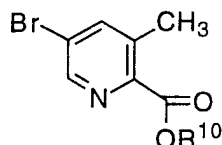


(i) with an amine of the formula NHR⁵R⁶, wherein R⁵ is hydrogen and R⁶ is C₁-C₆ alkyl, aryl or heteroaryl; R⁵ is C₁-C₆ alkyl, aryl or heteroaryl and R⁶ is hydrogen; R⁵ and R⁶ are independently selected from the group consisting of C₁-C₆ alkyl and aryl; or R⁵ and R⁶, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms or comprising 3 to 5 carbon atoms and one hetero moiety selected from the group consisting of -O- and -NR⁹-, wherein R⁹ is H, C₁-C₆ alkyl or phenyl; in the presence of a palladium catalyst and carbon monoxide to obtain an amide of the formula:

-25-



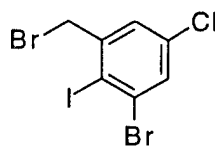
(ii) with an alcohol of the formula R^{10}OH , wherein R^{10} is $\text{C}_1\text{-C}_6$ lower alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl, in the presence of a palladium catalyst and carbon monoxide to obtain the ester of the formula



5

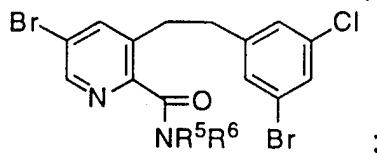
followed by reacting the ester with an amine of formula NHR^5R^6 to obtain the amide of step (i);

(b) reacting the amide of step (a) with an iodo-substituted compound of the formula



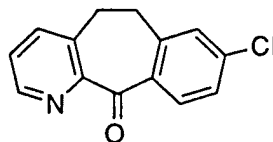
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in the presence of a strong base to obtain a compound of the formula



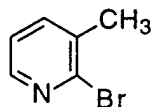
(c) cyclizing a compound of step (b) with a reagent of the formula R^8MgL , wherein R^8 is $\text{C}_1\text{-C}_8$ alkyl, aryl or heteroaryl and L is Br or Cl ,
 15 provided that prior to cyclization, compounds wherein R^5 or R^6 is hydrogen are reacted with a suitable N-protecting group.

3. A process of claim 1 for preparing a compound of the formula



20 comprising:

(a) reacting a compound of the formula



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- (i) with an amine of the formula NHR^5R^6 , wherein R^5 is hydrogen and R^6 is $\text{C}_1\text{-C}_6$ alkyl, aryl or heteroaryl; R^5 is $\text{C}_1\text{-C}_6$ alkyl, aryl or heteroaryl and R^6 is hydrogen; R^5 and R^6 are independently selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl and aryl; or R^5 and R^6 , together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms or comprising 3 to 5 carbon atoms and one hetero moiety selected from the group consisting of $-\text{O}-$ and $-\text{NR}^9-$, wherein R^9 is H, $\text{C}_1\text{-C}_6$ alkyl or phenyl; in the presence of a palladium catalyst and carbon monoxide to obtain an amide of the formula:

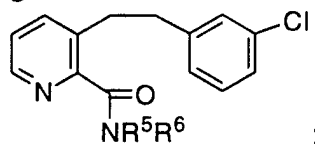
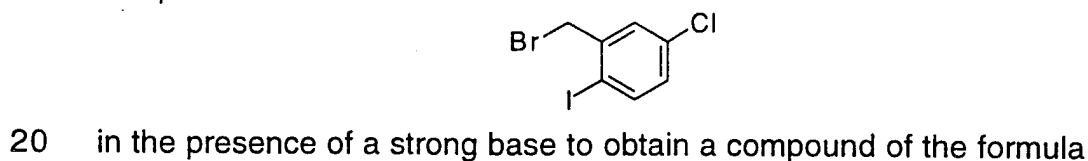


- (ii) with an alcohol of the formula R^{10}OH , wherein R^{10} is $\text{C}_1\text{-C}_6$ lower alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl, in the presence of a palladium catalyst and carbon monoxide to obtain the ester of the formula



- 15 followed by reacting the ester with an amine of formula NHR^5R^6 to obtain the amide of step (i);

- (b) reacting the amide of step (a) with an iodo-substituted compound of the formula



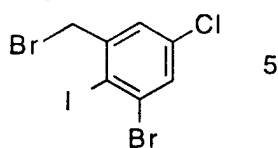
- (c) cyclizing a compound of step (b) with a reagent of the formula R^8MgL or R^8Li , wherein R^8 is $\text{C}_1\text{-C}_8$ alkyl, aryl or heteroaryl and L is Br or Cl, provided that prior to cyclization, compounds wherein R^5 or R^6 is hydrogen are reacted with a suitable N-protecting group.
- 25

4. The process of any of claims 1, 2 or 3 wherein R^5 is phenyl and R^6 is hydrogen.

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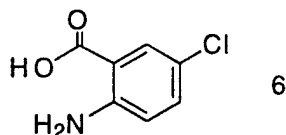
5. The process of any of claims 1, 2, 3 or 4 wherein the palladium catalyst is $\text{PdX}_2/\text{ligand}$; $\text{Pd}(\text{PPh}_3)_4$; $(\text{R}^{11})_3\text{P}/\text{Pd}_2(\text{dba})_3$; or Pd/C , wherein X is OAc or Cl, ligand is $\text{P}(\text{R}^{11})_3$, dipyridyl, 2-aminopyridine, 2-cyano-pyridine, 2-dimethylaminopyridine, 1,10-phenanthroline, 2-methoxy-pyridine or (S)-(-)-nicotine, and wherein Ac is acetyl, R^{11} is C_1 to C_6 alkyl or aryl, Ph is phenyl, and dba is dibenzylidene acetone.
6. The process of any of claims 1, 2, 3, 4 or 5 wherein R^8MgL is isopropylmagnesium chloride, 2-mesitylmagnesium bromide, o-tolylmagnesium bromide, 2-methoxy-phenylmagnesium bromide, 2-methoxy-5-methylphenyl-magnesium bromide, 2,5-dimethoxyphenyl-magnesium bromide or N-methyl-piperidylmagnesium bromide.
7. A process of any of claims 1, 3, 4 or 5 wherein R^8Li is n-butyl-lithium, sec-butyllithium, tert-butyllithium, methyllithium or phenyllithium.
8. A process of claim 7 wherein R^6 is reacted with a protecting group after step (a) or wherein R^6 is reacted with a protecting group after step (b).

9. A process for preparing a compound of the formula 5

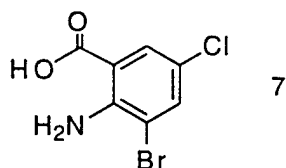


comprising:

- i) brominating 2-amino chlorobenzoic acid of formula 6

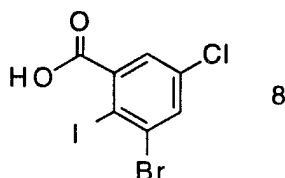


to obtain 2-amino-3-bromo-5-chlorobenzoic acid of formula 7

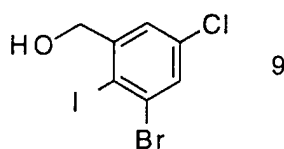


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ii) iodinating the compound of formula 7 to obtain 2-iodo-3-bromo-5-chlorobenzoic acid of formula 8



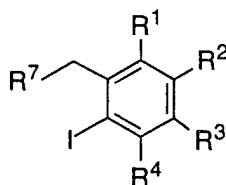
5 iii) reducing the carboxylic acid of the halo-substituted benzoic acid of formula 8 to obtain the corresponding hydroxy-methyl compound of formula 9



; and

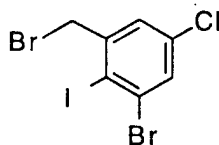
iv) brominating the compound of formula 9.

10 10. A compound of the formula

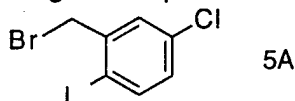


wherein R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen and halo; and R⁷ is Cl or Br.

15 11. A compound of claim 10 which is



12. A process for preparing a compound of formula 5A

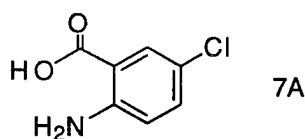


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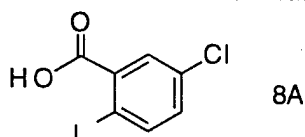
comprising:

i) iodinating the compound of formula 7A

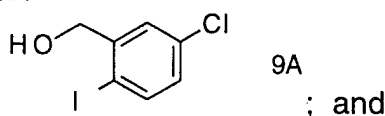
-29-



to obtain 2-iodo-5-chlorobenzoic acid of formula 8A



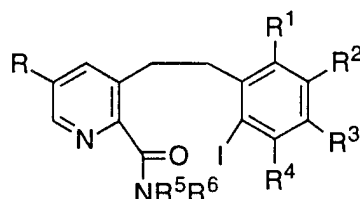
- 5 ii) reducing the carboxylic acid of the halo-substituted benzoic acid of formula 8A to obtain the corresponding hydroxy-methyl compound of formula 9A



; and

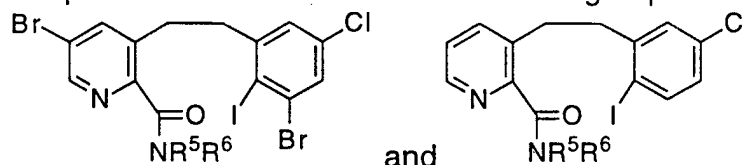
- iii) brominating the compound of formula 9A.

- 10 13. A compound of the formula



- wherein R, R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen and halo; and wherein R⁵ is hydrogen and R⁶ is C₁-C₆ alkyl, aryl or heteroaryl; R⁵ is C₁-C₆ alkyl, aryl or heteroaryl and R⁶ is hydrogen; R⁵ and R⁶ are independently selected from the group consisting of C₁-C₆ alkyl and aryl; or R⁵ and R⁶, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms or comprising 3 to 5 carbon atoms and one hetero moiety selected from the group consisting of -O- and -NR⁹-, wherein R⁹ is H, C₁-C₆ alkyl or phenyl.

14. A compound of claim 13 selected from the group consisting of



INTERNATIONAL SEARCH REPORT

In ternational Application No

PCT/US 98/03812

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D221/16 C07D213/81 C07C25/02 C07C17/16

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 396 083 A (SCHERING CORPORATION) 7 November 1990 see page 25, line 55 - page 28, line 20 ---	1-8, 13, 14
A	WO 96 31478 A (SCHERING CORPORATION) 10 October 1996 see page 29 - page 32 ---	1-8, 13, 14
X	GB 2 094 790 A (SPOFA VEREINIGTE PHARMA WERKE) 22 September 1982 see page 16, line 41 - line 60 ---	9-12
X	EP 0 011 858 A (HOFFMANN LA ROCHE) 11 June 1980 see page 11; example 1 ---	10
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

26 June 1998

Date of mailing of the international search report

09/07/1998

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Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

In. .tional Application No

PCT/US 98/03812

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KAREL SINDELAR ET AL: "Tricyclic psychotropic agents containing two chalcogen atoms in the central ring : derivatives of 11H-dibenz'b,f!-1,4-oxathiepin"</p> <p>COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS.,</p> <p>vol. 47, no. 3, 1982, PRAGUE CS,</p> <p>pages 967-983, XP002069467</p> <p>see pages 970,975, compounds XVI,XVII</p> <p>---</p>	10,12
X	<p>PELZ K ET AL: "NEUROTROPE UND PSYCHOTROPE SUBSTANZEN XXII WEITERE CHLORDERIVATE DES 10-(4-METHYLPYPERAZINO)-10,11-DIHYDRODIBENZO' b,f!THIEPINS UND EINIGE VERWANDTE STOFFE"</p> <p>COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS,</p> <p>vol. 33, no. 6, 1 January 1968,</p> <p>pages 1852-1872, XP000560349</p> <p>see page 1869 ,preparation of 5-chlor-2-jod benzosäure</p> <p>-----</p>	12

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 98/03812

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Information on patent family members

In International Application No

PCT/US 98/03812

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0011858 A		US 4360511 A	23-11-1982