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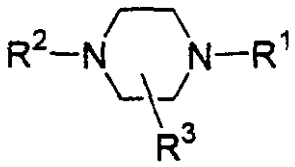
(54) **Title:** NOVEL SYNTHESIS OF PIPERAZINE RING

(57) **Abstract**

A novel process for preparing a compound of formula (I) wherein R^1 denotes substituted or unsubsituted alkyl, alkoxy, aryl, aryloxy or arylalkoxy; R^2 denotes substituted or unsubstituted alkyl, alkoxy, aryl, aryloxy, arylalkoxy, tosyl, formyl, acetyl or amine; and R^3 denotes substituted or unsubstituted alkyl, alkoxy, aryl, aryloxy or arylalkoxy is disclosed. These compounds are useful in the synthesis of the antidepressant mirtazapine and other tetracyclic compounds.



(I)

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NOVEL SYNTHESIS OF PIPERAZINE RING

RELATED APPLICATION

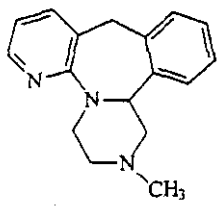
This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional application, Serial No. 60/130,048, filed April 19, 1999.

FIELD OF THE INVENTION

The present invention relates to methods for the synthesis of piperazine rings, particularly for the preparation of heterocyclic compounds useful as intermediates in the synthesis of piperazinoazepines such as the antidepressant mirtazapine.

BACKGROUND OF THE INVENTION

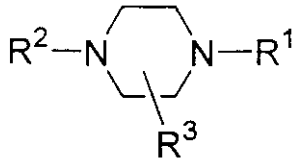
Mirtazapine, also known as 1,2,3,4,10,14b-hexahydro-2-methylpyrazine [2,1-a]pyrido[2,3-c] benzazepine, is an antidepressant suitable for oral administration. It has a tetracyclic chemical structure unrelated to other classes of antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclics or monoamine oxidase inhibitors. Mirtazapine belongs to the piperazinoazepine group of compounds, and has the following structural formula.



Known methods for the preparation of piperazine ring derivatives have low yields (9-30%), expensive reagents, and many reaction steps (Roderick, W.R. et al., J. Med. Chem 9, 1966, 181-185). It is desirable to have methods for preparing piperazine ring derivatives with fewer steps, high yields and inexpensive raw materials.

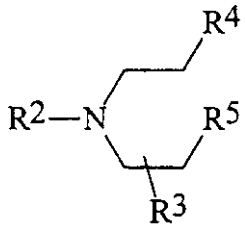
SUMMARY OF THE INVENTION

The present invention relates to a novel process for preparing a compound of the formula I:



wherein

R^1 denotes substituted or unsubstituted alkyl, aryl, arylalkoxy, tosyl, formyl, benzoyl, acetyl or amine; R^2 denotes substituted or unsubstituted alkyl, alkoxy, aryl, aryloxy or arylalkoxy; and R^3 denotes substituted or unsubstituted alkyl, alkoxy, aryl, aryloxy or arylalkoxy; by reacting a compound of the formula



II

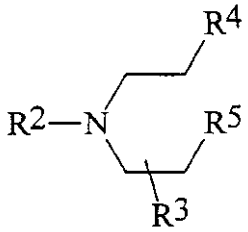
wherein R^2 and R^3 are as defined above and R^4 and R^5 are independently selected from the group consisting of fluoro, chloro, bromo and iodo,

with a compound of the formula H_2N-R^1, wherein R^1 is as defined above. Preferably the reaction is performed in the presence of a solvent. Polar aprotic solvents such as, dimethyl formamide, dimethylacetamide and dimethylsulfoxide are preferred.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a new process for preparing piperazine rings suitable for use in the synthesis of the antidepressant mirtazapine and other tetracyclic compounds such as those disclosed in U.S. Patent No. 4,062,848 to van der Burg, the contents of which are incorporated herein by reference.

The process of the present invention comprises the steps of reacting a compound of formula II:

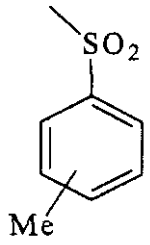


II

wherein

R^4 and R^5 are independently any of the of radicals selected from the group that consists of fluoro, chloro, bromo and iodo; and R^2 and R^3 are as defined above;

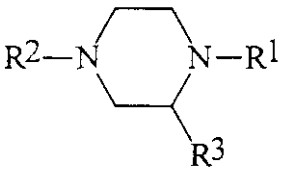
with a compound of the formula $H_2N\text{-}R^1$, wherein R^1 is as defined above. Preferably, R^1 denotes aryl, acetyl, formyl, benzoyl, amine, or tosyl. Most preferably, R^1 is tosyl. In order to remove any doubt, the tosyl radical is defined as the group of formula VI:



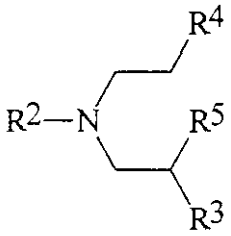
VI

wherein Me represents a methyl group. Preferably R^2 denotes methyl, R^3 denotes phenyl, R^4 denotes chloro, and R^5 denotes chloro.

Preferably, the compounds of formulae I and II are compounds of formulae IV and V accordingly:

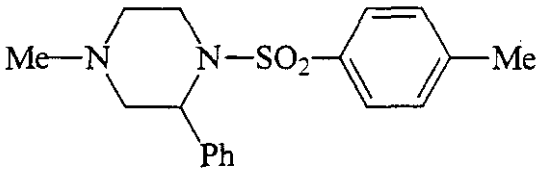


IV



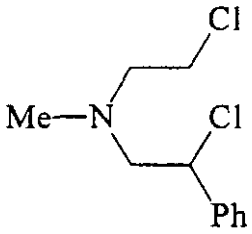
V

In a preferred embodiment, the present invention relates to a process for preparing a compound of formula XI:



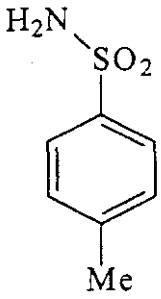
XI

wherein Ph represents a phenyl group, which comprises reacting a compound of formula XII:



XII

with a compound of formula XIII:

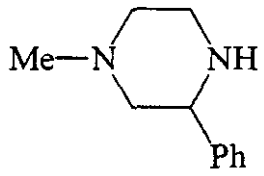


XIII

Preferably this reaction takes place in the presence of a strong base such as sodium hydroxide (NaOH), sodium hydride (NaH), potassium hydroxide (KOH), potassium hydride (KH), sodium methoxide (NaOMe) and sodium amide ($NaNH_2$). Sodium hydroxide and sodium hydride are preferred.

Preferred solvents for the above reaction are any one or more of the solvents selected from the group that consisting of dimethyl formamide (DMF), dimethyl acetamide (DMAC), dimethyl sulfoxide (DMSO), xylene, benzene, ethylbenzene, acetonitrile, toluene and ethers with high boiling points such as ethyleneglycol dimethyl ether, diethyleneglycol dimethyl ether, and propyleneglycol dimethyl ether.

The compound of formula XI may be further hydrolized to give the compound of formula XIV:

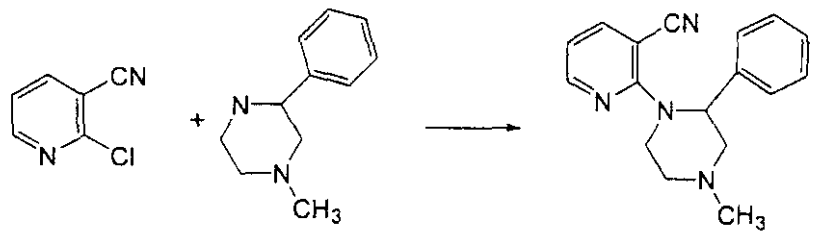


XIV

The compound of formula XIV is known as 4-methyl-2-phenylpiperazine. Compounds of formula XI may be hydrolyzed by reacting a compound of the formula XI with acid to give compounds of the formula XIV. Preferred acids for the reaction are strong acids such as sulfuric acid (H_2SO_4), hydrochloric acid (HCl), phosphoric acid (H_3PO_4) and p-toluene sulfonic acid. A more preferred acid is sulfuric acid with a concentration of about 98%. Preferably the reaction is carried out in aqueous solution.

The compound of formula XIV may be used in the preparation of the mirtazapine (1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine), as shown in Schemes 1 and 2 below.

Scheme 1

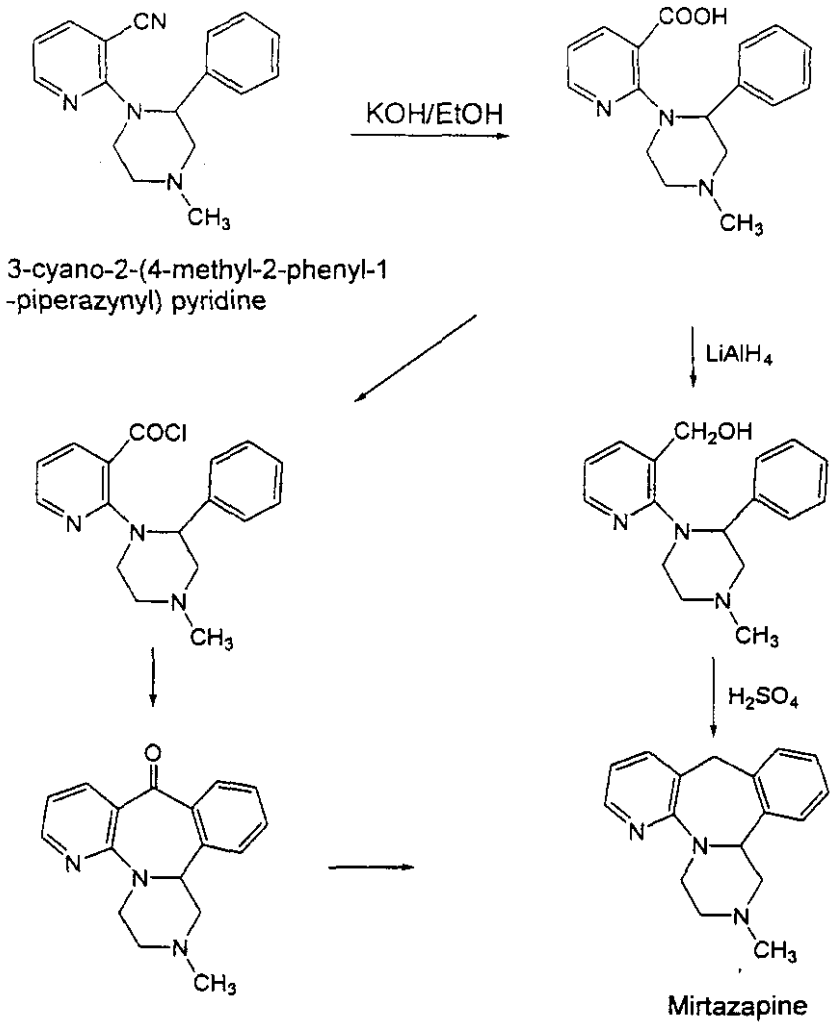


2-chloro-3-cyano-pyridine | 4-methyl-2-phenyl peperazine | 3-cyano-2-(4-methyl-2-phenyl-1-piperazynyl) pyridine

As shown in Scheme 1, the compound 3-cyano-2-(4-methyl-2-phenyl-1-piperazynyl) pyridine may be prepared starting from 2-chloro-3-cyano-pyridine and 4-methyl-2-phenyl-piperazine.

Starting from 3-cyano-2-(4-methyl-2-phenyl-1-piperazynyl)pyridine, mirtazapine can be prepared by two routes, which are further presented in Scheme 2:

Scheme 2

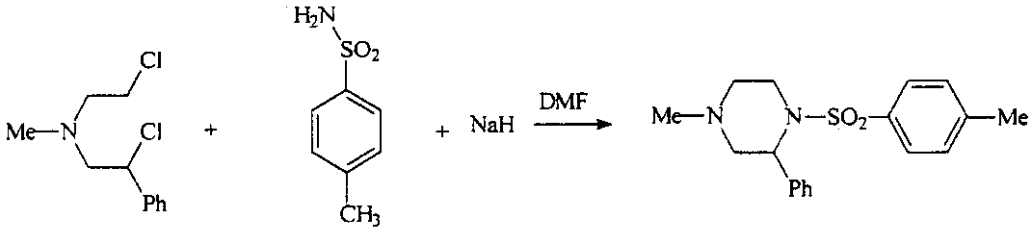


In accordance with the present invention, mirtazapine produced by the process of the present invention may be prepared as pharmaceutical compositions that are particularly useful for the treatment of depression. Such compositions comprise mirtazapine with pharmaceutically acceptable carriers and/or excipients known to one of skill in the art.

EXAMPLES

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

EXAMPLE 1



3g 2.2g 1.1g

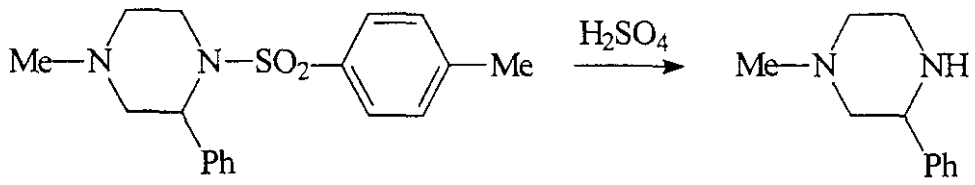
A suspension of sodium hydride (60%, 1.1 g) in DMF (20 mL) was prepared. p-Toluenesulfonamide (2.2 g) was dissolved in DMF (10 mL) and added continuously to the sodium hydride suspension. After mixing at room temperature the suspension was heated to 60-70°C.

After that, the solution of beta-chloro-N-methyl-N-chloroethyl phenylethylamine (3 g) in DMF (10 mL) was added dropwise and mixed overnight. The reaction mixture was poured into a mixture of water (21 g) and ice (40 g).

After 4 hours the precipitate was filtered, washed with water (2 x 30 mL) and dried in an oven to give 3.3 g of the product.

EXAMPLE 2

Preparation of 4-methyl-2-phenyl piperazine



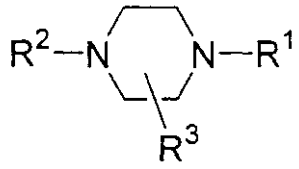
Tosyl piperazine (1.2 g) was dissolved in water (1g) and H_2SO_4 (98%, 3 mL) while heating to 110°C. After 20 minutes at 110-120°C the reaction mixture was poured into water (10 mL) and ice (20 g).

The solution was alkalized to pH 13 with NaOH (47%) and the product was extracted into ether. After phase separation the organic phase was evaporated to dryness to give the 4-methyl-2-phenyl piperazine in 75% yield.

Although certain presently preferred embodiments of the invention have been described herein, it will be apparent to those skilled in the art to which the invention pertains that variations and modifications of the described embodiment may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rules of law.

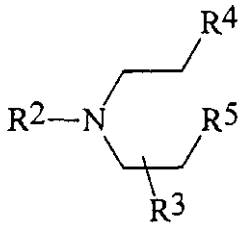
WE CLAIM:

1. A method for preparing a compound of the formula



wherein R^1 denotes substituted or unsubstituted alkyl, aryl, arylalkoxy, tosyl, benzoyl, formyl, acetyl or amine; R^2 denotes substituted or unsubstituted alkyl, alkoxy, aryl, aryloxy or arylalkoxy; and R^3 denotes substituted or unsubstituted alkyl, alkoxy, aryl, aryloxy or arylalkoxy,

comprising the step of reacting a compound of the formula



II

wherein R^2 and R^3 are as defined above and R^4 and R^5 are independently selected from the group consisting of fluoro, chloro, bromo and iodo,

with a compound of the formula H_2N-R^1, wherein R^1 is as defined above.

2. The method of claim 1, wherein R^1 is selected from the group consisting of aryl, acetyl, formyl, benzoyl, amine and tosyl.

3. The method of claim 2, wherein R^1 is tosyl.

4. The method of claim 1, wherein R^2 is methyl.

5. The method of claim 1, wherein R^3 is phenyl.

6. The method of claim 1, wherein R^4 is chloro.

7. The method of claim 1, wherein R^5 is chloro.

8. The method of claim 1, wherein the reaction is performed in a solvent selected from the group consisting of DMF, DMAC, ethers, ethyleneglycol dimethyl ether, diethyleneglycol dimethyl ether, propyleneglycol dimethyl ether, DMSO, xylene, benzene, ethylbenzene, acetonitrile and toluene.

9. The method of claim 8, wherein said solvent is DMF.

10. The method of claim 1, further comprising the step of adding a strong base.

11. The method of claim 10, wherein said strong base is selected from the group consisting of sodium hydroxide, sodium hydride, potassium hydroxide, potassium hydride, sodium methoxide and sodium amide.

12. The method of claim 11, wherein the base is sodium hydroxide.

13. The method of claim 11, wherein the base is sodium hydride.

14. The method of claim 1, further comprising the step of removing R^1 by hydrolysis.

15. The method of claim 14, wherein R^1 is removed by hydrolysis using a strong acid.

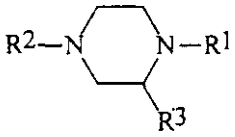
16. The method of claim 15, wherein the acid is selected from the group consisting

of sulfuric acid, hydrochloric acid, phosphoric acid and p-toluene sulfonic acid.

17. The method of claim 16, wherein the acid is sulfuric acid.

18. The method of claim 17 wherein the sulfuric acid has a concentration of about 98%.

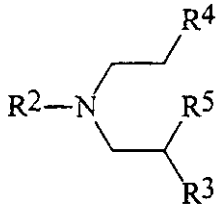
19. A method for preparing a compound of the formula:



IV

wherein R^1 denotes substituted or unsubstituted alkyl, aryl, arylalkoxy, tosyl, formyl, benzoyl, acetyl or amine; R^2 denotes substituted or unsubstituted alkyl, alkoxy, aryl, aryloxy or arylalkoxy; and R^3 denotes substituted or unsubstituted alkyl, alkoxy, aryl, aryloxy or arylalkoxy,

comprising the step of reacting a compound of the formula



V

wherein R^2 and R^3 are as defined above and R^4 and R^5 are independently selected from the group consisting of fluoro, chloro, bromo and iodo,

with a compound of the formula $H_2N\text{-}R^1$, wherein R^1 is as defined above.

20. The method of claim 19, wherein R^1 is selected from the group consisting of aryl, acetyl, formyl, benzoyl, amine and tosyl.

21. The method of claim 20, wherein R^1 is tosyl.

22. The method of claim 19, wherein R^2 is methyl.

23. The method of claim 19, wherein R^3 is phenyl.

24. The method of claim 19, wherein R^4 is chloro.

25. The method of claim 19, wherein R^5 is chloro.

26. The method of claim 19, wherein the reaction is performed in a solvent selected from the group consisting of DMF, DMAC, ethers, ethyleneglycol dimethyl ether, diethyleneglycol dimethyl ether, propyleneglycol dimethyl ether, DMSO, xylene, benzene, ethylbenzene, acetonitrile and toluene.

27. The method of claim 26, wherein said solvent is DMF.

28. The method of claim 19, further comprising the step of adding a strong base.

29. The method of claim 28, wherein the base is selected from the group consisting of sodium hydroxide, sodium hydride, potassium hydroxide, potassium hydride, sodium methoxide and sodium amide.

30. The method of claim 29 wherein the base is sodium hydride.

31. The method of claim 29, wherein the strong base is sodium hydroxide.

32. The method of claim 19, further comprising the step of removing R^1 by hydrolysis.

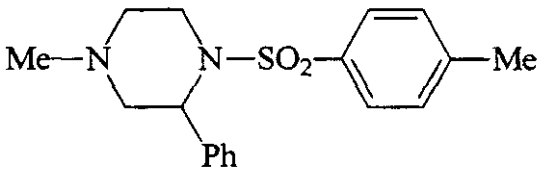
33. The method of claim 32, wherein R^1 is removed by hydrolysis using a strong acid.

34. The method of claim 33, wherein the acid is selected from the group consisting of sulfuric acid, hydrochloric acid, phosphoric acid and p-toluene sulfonic acid.

35. The method of claim 34, wherein the acid is sulfuric acid.

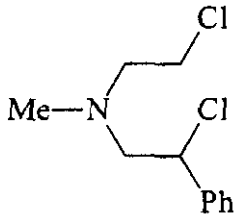
36. The method of claim 35 wherein the sulfuric acid has a concentration of about 98%.

37. A method for preparing a compound of the formula:



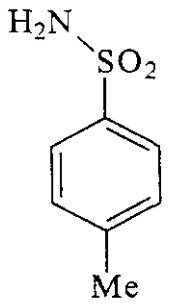
XI

which comprises the step of reacting a compound having the formula:



XII

with a compound having the formula:



XIII

38. The method of claim 37, wherein the reaction is done in a solvent selected from the group consisting of DMF, DMAC, ethers, ethyleneglycol dimethyl ether, diethyleneglycol dimethyl ether, propyleneglycol dimethyl ether, DMSO, xylene, benzene, ethylbenzene, acetonitrile and toluene.

39. The method of claim 38, wherein said solvent is DMF.

40. The method of claim 37, further comprising the step of adding a strong base.

41. The method of claim 40, wherein said strong base is selected from the group consisting of sodium hydroxide, sodium hydride, potassium hydroxide, potassium hydride, sodium methoxide and sodium amide.

42. The method of claim 41, wherein the base is sodium hydroxide.

43. The method of claim 41, wherein the strong base in sodium hydroxide.

44. The method of claim 37, further comprising the step of removing the tosyl group by hydrolysis.

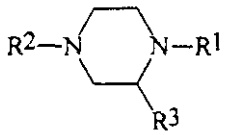
45. The method of claim 44, wherein the tosyl group is removed by hydrolysis using a strong acid.

46. The method of claim 45, wherein the acid is selected from the group consisting of sulfuric acid, hydrochloric acid, phosphoric acid and p-toluene sulfonic acid.

47. The method of claim 46, wherein the acid is sulfuric acid.

48. The method of claim 47 wherein the sulfuric acid has a concentration of about 98%.

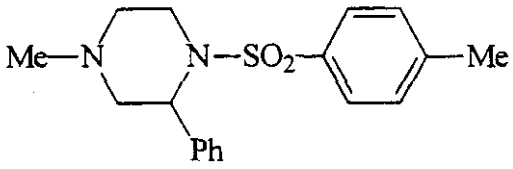
49. A compound of the formula:



IV

wherein R^1 denotes substituted or unsubstituted alkyl, aryl, arylalkoxy, tosyl, formyl, benzoyl, acetyl or amine; R^2 denotes substituted or unsubstituted alkyl, alkoxy, aryl, aryloxy or arylalkoxy; and R^3 denotes substituted or unsubstituted alkyl, alkoxy, aryl, aryloxy or arylalkox.

50. A compound of the formula:



XI

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/09418

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07D 241/04
US CL : 544/383

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)

U.S. : 544/383

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 practicable, search terms used)

CAS ONLINE STRUCTURE SEARCH

C. *DOCUMENTS CONSIDERED TO BE RELEVANT*

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,025,513 A (OLIVIE) 24 May 1977, col. 3, and example 1.	1, 2, 4-10, 19-20, 22-28, 49 --- 11-13, 29-31
Y	US 4,935,515 A (WINKLEY et al) 19 June 1990, col. 6 to col. 7, lines 1-6.	10-13, 28-31
X	US 4,918,190 A (TODA et al) 17 April 1990, col. 3, lines 14-15.	49

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 18 JULY 2000	Date of mailing of the international search report 02 AUG2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EMILY BERNHARDT Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

哌嗪环的新合成方法

本发明公开了用于制备分子式(I)的化合物的新方法，其中R^1代表取代或未取代的烷基、烷氧基、芳基、芳氧基或芳基烷氧基；R^2代表取代或未取代的烷基、烷氧基、芳基、芳氧基、芳基烷氧基、甲苯磺酰基、甲酰基、乙酰基或胺；且R^3代表取代或未取代的烷基、烷氧基、芳基、芳氧基或芳基烷氧基。这些化合物在抗抑郁药米氮平和其它四环化合物的合成中有用。