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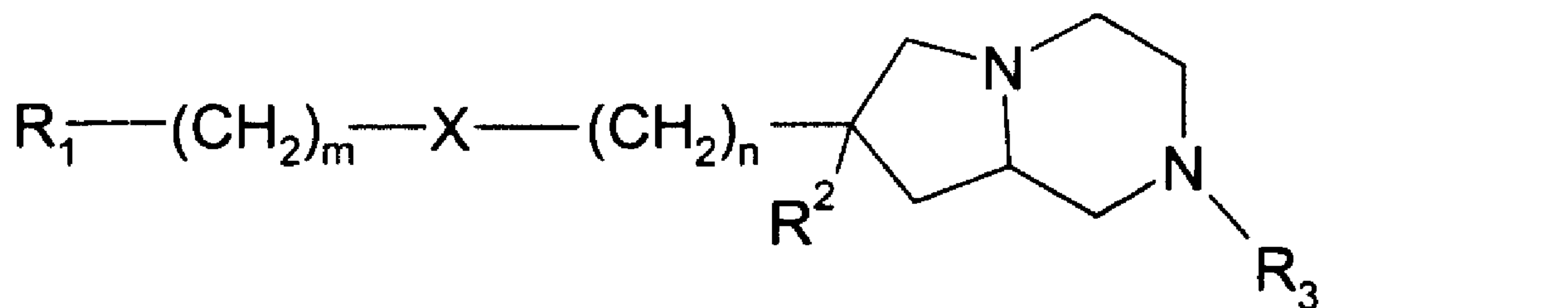
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(54) Titre : DERIVES DE LA PYRROLO[1,2-a]PYRAZINE UTILISES COMME LIGANDS DU 5HT1A

(54) Title: PYRROLO[1,2-a]PYRAZINE DERIVATIVES AS 5HT1A LIGANDS



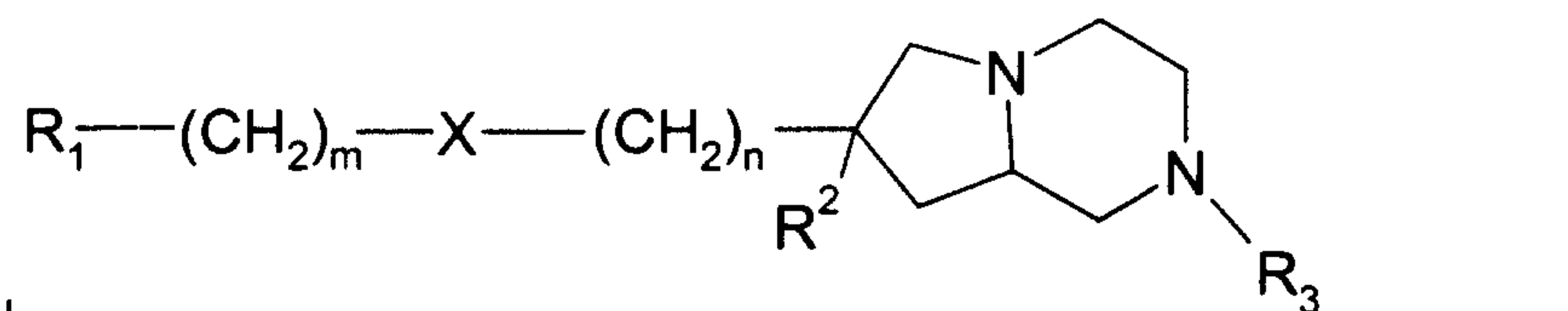
(57) **Abrégé/Abstract:**

This invention relates to the use of compounds of formula I (see formula I) wherein R_1 , R_2 , R_3 , X, m and n are defined as in the specification, and their pharmaceutically acceptable salts, for the treatment of disorders of the serotonin system.



2,7-SUBSTITUTED OCTAHYDRO-PYRROLO[1,2-a]PYRAZINE DERIVATIVESAbstract

This invention relates to the use of compounds of formula I



wherein R_1 , R_2 , R_3 , X , m and n are defined as in the specification, and their pharmaceutically acceptable salts, for the treatment of disorders of the serotonin system.

5

PYRROLO[1,2-a]PYRAZINE DERIVATIVES AS 5HT_{1A} LIGANDS**Background of the Invention**

The present invention relates to the use of pharmacologically active 2,7-substituted octahydro-1H-pyrrolo[1,2-a]pyrazine derivatives, and their acid addition salts. The compounds of this invention are ligands for serotonin receptor subtypes, especially the 5HT_{1A} receptor, and are therefore useful in the treatment of disorders that can be treated by altering (i.e., increasing or decreasing), serotonin mediated neurotransmission.

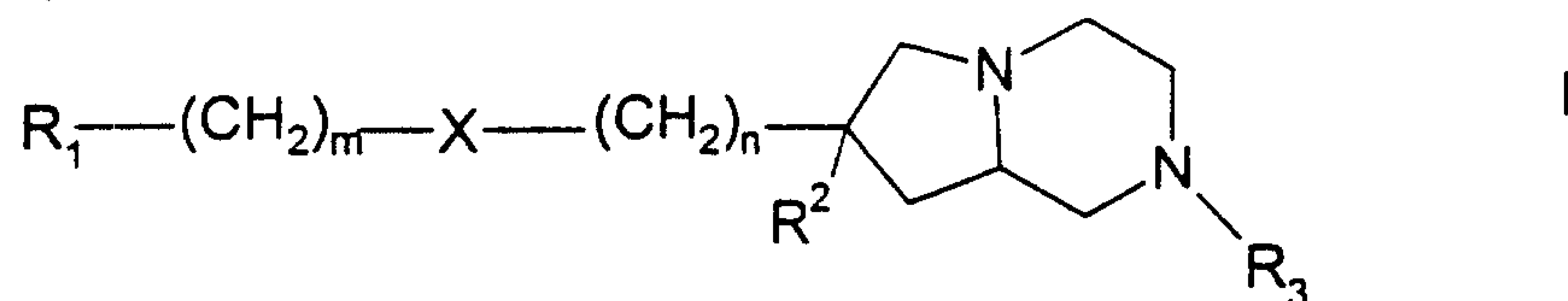
The pharmacologically active 2,7-substituted octahydro-1H-pyrrolo[1,2-a]pyrazine derivatives of the formula I, as defined below, are also ligands for dopamine receptor subtypes, especially the dopamine D4 receptor. They are useful in treating disorders that can be treated by altering (i.e., increasing or decreasing) dopamine mediated neurotransmission. The dopamine receptor binding activity of such compounds is referred to in World Patent Application WO 97/23482, which designates the United States and was published on July 3, 1997.

Serotonin plays a role in several psychiatric disorders, including anxiety, Alzheimer's disease, depression, nausea and vomiting, eating disorders, and migraine. (See Rasmussen et al., "Chapter 1. Recent Progress in Serotonin (5HT)_{1A} Receptor Modulators", in Annual Reports in Medicinal Chemistry, Section I, 30, pp. 1-9, 1995, Academic Press, Inc.; Antigas et al., Trends Neurosci., 19 (9), 1996, pp. 378-383; and Wolf et al., Drug Development Research, 40, 1997, pp. 17-34.) Serotonin also plays a role in both the positive and negative symptoms of schizophrenia. (See Sharma et al., Psychiatric Annals., 26 (2), February, 1996, pp. 88-92.)

Summary of the Invention

This invention relates to a medicine (i.e., pharmaceutical composition or formulation) for treating a disorder that can be treated by altering (e.g., increasing or decreasing) serotonin mediated neurotransmission in a mammal including a human.

The medicine comprises (a) a pharmaceutically acceptable carrier or diluent and (b) an amount of a compound of formula I:



wherein

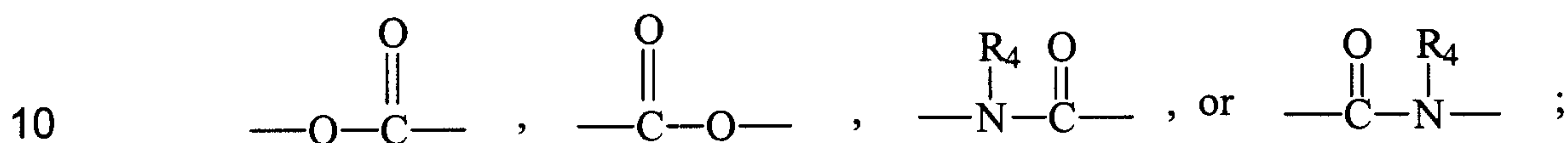
R₁ is phenyl, naphthyl, benzoxazolonyl, indolyl, indolonyl, benzimidazolyl, quinolyl, furyl, benzofuryl, thienyl, benzothienyl, oxazolyl, benzoxazolyl;

35 R₂ is H or (C₁-C₆)alkyl;

R₃ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl;

wherein each group of R_1 and R_3 may be independently and optionally substituted with one to four substituents independently selected from the groups consisting of fluoro, chloro, bromo, iodo, cyano, nitro, thiocyano, $-SR_4$, $-SOR_4$, $-SO_2R_4$, $-NHSO_2R_4$, (C_1-C_6) alkoxy, $-NR_4R_5$, $-NR_4COR_5$, $-CONR_4R_5$, phenyl,
 5 $-COR_4$, $-COOR_4$, (C_1-C_6) alkyl, (C_1-C_6) alkyl substituted with one to six halogens, (C_3-C_6) cycloalkyl, and trifluoromethoxy;

X is O, S, SO, SO_2 , NR_4 , $C=O$, $CH(OH)$, CHR_4 ,



R_4 is H or (C_1-C_6) alkyl;

R_5 is H or (C_1-C_6) alkyl;

m is 0, 1 or 2; and

15 n is 0, 1 or 2; or

a pharmaceutically acceptable salt thereof;

that is effective in treating such disorder.

Preferably, R_1 is phenyl, naphthyl, benzoxazolonyl, indolyl, indolonyl, benzimidazolyl, or quinolyl; and R_1 and R_3 may be independently substituted with up
 20 to three substituents independently selected from the group consisting of fluoro, chloro, bromo, iodo, cyano, $-NR_4R_5$, (C_1-C_6) alkoxy, $-COOR_4$, $-CONR_4R_5$, (C_1-C_6) alkyl, (C_1-C_6) alkyl substituted with one to six halogens, (C_3-C_6) cycloalkyl, and trifluoromethyl;

R_2 is H or CH_3 ;

25 X is O, $C=O$, $CHOH$, $-C(=O)O-$, or CH_2 ,

m is 0, or 1; and

n is 0 or 1.

In another preferred embodiment,

R_1 is phenyl or substituted phenyl;

30 R_3 is substituted or unsubstituted phenyl, pyridinyl, or pyrimidinyl; and

X is O, $-C(=O)O-$, or CH_2 .

In another preferred embodiment,

R_2 is H;

X is O;

35 m is 0; and

n is 1.

3

In another preferred embodiment,

R₁ is fluorophenyl, cyanophenyl or (trifluoromethyl)phenyl;

R₃ is chloropyridinyl.

In another preferred embodiment,

5 R₁ is fluorophenyl, cyanophenyl or (trifluoromethyl)phenyl;

R₃ is fluoropyrimidinyl.

In another preferred embodiment,

R₃ is 5-chloro-2-pyridinyl.

In another preferred embodiment,

10 R₃ is 5-fluoro-2-pyrimidinyl.

Examples of preferred methods of this invention are those that employ one of the following compounds of the formula I or a pharmaceutically acceptable salt thereof:

15 (7S,8aS)-7-(4-fluorophenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine;

(7S,8aS)-7-(3-cyanophenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine;

20 (7S,8aS)-7-(4-fluorophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine;

(7S,8aS)-7-(3-(trifluoromethyl)phenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine;

25 (7S,8aS)-7-(3-cyanophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine; and

5 (7S,8aS)-7-(4-cyanophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine.

The term "treating", as used herein, refers to retarding or reversing the progress of, or alleviating or preventing either the disorder or condition to which the term "treating" applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein,
10 refers to the act of treating a disorder or condition, as the term "treating" is defined above.

The chemist of ordinary skill will recognize that certain combinations of substituents included within the scope of formula I may be chemically unstable and will avoid these combinations or alternatively protect sensitive groups with well known protecting groups.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated
15 monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, unless otherwise indicated, refers to radicals having the formula -O-alkyl, wherein "alkyl" is defined as above.

The compounds of formula I contain one or more chiral centers and therefore exist in
20 different enantiomeric and diastereomeric forms. Formula I, as defined above, includes, and this invention relates to the use of, all optical isomers and other stereoisomers of compounds of the formula I and mixtures thereof.

Preferably, the disorder to be treated is, migraine, headache or cluster headache in a mammal.

25 Also preferably, the disorder is selected from depression (e.g., dysthymia, major depressive disorder, pediatric depression, recurrent depression, single episode depression, post partum depression, depression in Parkinson's patients, cancer patients, and post myocardial infarction patients, and subsyndromal symptomatic depression), generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder,
30 avoidant personality disorder, borderline personality disorder and phobias in a mammal, including a human.

The disorder may be of cognition, memory or learning, such as age related memory disorder or neurodegenerative diseases such as Alzheimer's disease in a mammal, including a human.

5 The disorder may further be attention deficit hyperactivity disorder (ADHD) in a mammal, including a human.

The disorder may further be an eating disorder (e.g., bulimia or anorexia nervosa), or a chemical dependency or addiction, (e.g., a dependency on, or addiction to, alcohol, nicotine, cocaine, heroin, phenolbarbitol or a benzodiazepine), in a mammal, including a human.

10 The disorder may be anxiety or depression associated with senile dementia or Alzheimer's disease in a mammal, including a human.

The disorder may still be cancer, such as prostate cancer in a mammal.

The disorder may further be cerebral infarct such as that caused by stroke, ischemia or traumatic head injury in a mammal, including a human.

15 The disorder may be a sexual disorder such as paraphilias, premature ejaculation or sexual dysfunction in a mammal, including a human.

The disorder may further be dizziness in a mammal, including a human.

The disorder may be peptic ulcer in a mammal, including a human.

20 In the medicine, the compound of the formula I, as defined above, or pharmaceutically acceptable salt thereof, may be combined with a serotonin reuptake inhibitor (SRI)(e.g., sertraline, fluoxetine, fenfluramine, or fluvoxamine). This means that the compound of formula I or pharmaceutically acceptable salt thereof may be administered in the form of a pharmaceutical composition that also contains an SRI, or that such compound or salt is administered in a separate pharmaceutical
25 composition from that in which the SRI is administered, but as part of a dose regimen that calls for the administration of both active agents for treatment of a particular disorder or condition.

30 The disorder to be treated may further be cerebral infarct such as that caused by stroke, ischemia or traumatic head injury in a mammal, wherein the compound of the formula I, as defined above, or pharmaceutically acceptable salt thereof, is used in combination with a serotonin-2 (5HT₂) receptor antagonist (e.g., ketanserin, pelanserin, pipamperone, spiperone, pirenperin or ritanserin) or a pharmaceutically acceptable salt thereof. Other 5HT₂ receptor antagonists that can be used in this invention are referred to in U.S. Patent 5,364,857, which issued on November 15,
35 1994.

The pharmaceutically acceptable acid addition salts of compounds of the formula I may used, as referred to above, in various formulations of this invention. The compounds of formula I are basic in nature and are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used

5 to prepare pharmaceutically acceptable acid addition salts of those compounds of formula I are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate,

10 ascorbate, succinate, maleate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, and p-toluenesulfonate.

For practical use, the medicine according to the present invention may be put in a commercial package. Such a commercial package usually includes a written

15 matter which states that the medicine can or should be used for the purposes described in this specification.

The term "one or more substituents", as used herein, includes from one to the maximum number of substituents possible based on the number of available bonding sites.

5 The term "disorders of the serotonin system", as referred to herein, refers to disorders, the treatment of which can be effected or facilitated by altering (i.e., increasing or decreasing) serotonin mediated neurotransmission.

 Formula I above includes compounds identical to those depicted but for the fact that one or more atoms (for example, hydrogen, carbon or fluorine atoms) are replaced by
10 radioactive isotopes thereof. Such radiolabelled compounds are useful as research and diagnostic tools in, for example, metabolism studies, pharmacokinetic studies and binding assays.

 This invention also relates to a method, such as positron emission tomography (PET), of obtaining images of a mammal, including a human, to which a radiolabelled compound of
15 the formula I, or pharmaceutically acceptable salt thereof, has been administered.

 The compounds of formula I that are employed in the present invention, being ligands for serotonin receptor subtypes, especially the 5HT_{1A} receptor, within the body, are accordingly of use in the treatment of disorders of the serotonin system.

Detailed Description of the Invention

20 The compounds of formula I and their pharmaceutically acceptable salts (hereinafter also referred to, collectively, as "the therapeutic compounds used in the methods of this invention") can be prepared as described in World Patent Application WO 97/23482, which designates the United States and was published on July 3, 1997.

25 Compounds of formula I in which one or more atoms are radioactive may be prepared by methods known to a person of ordinary skill in the art.

 For example, compounds of formula I wherein the radioactive atom is tritium may be prepared by reacting an aryl halide Ar-X, wherein the halogen is chlorine, bromine or iodine, with gaseous ³H₂ and a noble metal catalyst, such as palladium suspended on carbon, in a
30 suitable solvent such as a lower alcohol, preferably methanol or ethanol. Compounds of formula I wherein the radioactive atom is ¹⁸F may be prepared by reacting an aryl trialkyl stannane Ar-SnR₃, wherein R is lower alkyl, preferably methyl or n-butyl, with ¹⁸F-enriched fluorine (F₂), OF₂ or CF₂OOF in a suitably inert solvent (cf M. Namavari, *et al.*, *J. Fluorine Chem.*, 1995, 74, 113).

35 Compounds of formula I wherein the radioactive atom is ¹¹C or ¹⁴C may be prepared by reacting an aryl halide Ar-X, wherein X is preferably bromine or iodine, or an aryl trifluoromethane sulfonate (Ar-OSO₂CF₃) with potassium [¹¹C]cyanide or potassium [¹⁴C]cyanide and a noble metal catalyst, preferably tetrakis(triphenylphosphine)palladium, in a reaction inert solvent such as water or tetrahydrofuran, and preferably a mixture of water and

5 tetrahydrofuran. (See Y. Andersson, B. Langstrom, *J. Chem. Soc. Perkin Trans. 1*, 1994, 1395).

The utility of radioactive agents with affinity for 5HT_{1A} receptors for visualizing organs of the body either directly or indirectly has been documented in the literature. For example, C.-Y. Shiue *et al.*, *Synapse*, 1997, 25, 147 and S. Houle *et al.*, *Can. Nucl. Med. Commun*,
10 1997, 18, 1130, describe the use of 5HT_{1A} receptor ligands to image 5HT_{1A} receptors in the human brain using positron emission tomography (PET).

The therapeutic compounds of formula I used in this invention can be administered orally, buccally, transdermally (e.g., through the use of a patch), parenterally or topically. Oral administration is preferred. In general, these compounds are most desirably administered in
15 dosages ranging from about 1 mg to about 1000 mg per day, preferably from about 10 to about 200 mg per day, although variations may occur depending on the weight and condition of the person being treated and the particular route of administration chosen. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any
20 harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

When used in the same oral, parenteral or buccal pharmaceutical composition as an SRI, the daily dose of the compound of formula I or pharmaceutically acceptable salt thereof will be within the same general range as specified above for the administration of such
25 compound or salt as a single active agent. The daily dose of the SRI in such a composition will generally be within the range of about 1 mg to about 400 mg, preferably from about 10 to about 100 mg.

When used in the same oral, parenteral or buccal pharmaceutical composition as a 5HT₂ antagonist, the daily dose of the compound of formula I or pharmaceutically acceptable salt thereof will be within the same general range as specified above for the administration of
30 such compound or salt as a single active agent. The daily dose of the 5HT₂ antagonist in such a composition will generally be within the range of about 0.1-10 parts by weight, relative to 1.0 part by weight of the compound of formula I.

The therapeutic compounds of formula I used in this invention may be formulated with pharmaceutically acceptable carriers or diluents into compositions adapted to be administered
35 by either of the two routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the therapeutic compounds used in this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, elixirs, syrups, and the like. Such carriers include solid

5 diluents or fillers, sterile aqueous media and various non-toxic organic solvents, for example. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or
10 tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as
15 high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

20 For parenteral administration, solutions of a therapeutic compound used in the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intramuscular and
25 subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is also possible to administer the therapeutic compounds used in the present invention topically when treating inflammatory conditions of the skin
30 and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The activity of the compounds of the present invention with respect to 5HT_{1A} binding ability can be determined according to the following procedure. Binding assays using membranes derived from HeLa cells expressing the human 5HT_{1A} receptor or from
35 membranes derived from rat brain tissue can be performed according to standard procedures. For example, HeLa cells expressing the human 5HT_{1A} receptor can be grown in culture to confluence and then harvested by replacing the media with phosphate buffered saline containing 5 mM EDTA and centrifuging at 1000 x g for 10 minutes at 4° C. The pellet is homogenized in a 50 mM Tris buffer containing 4 mM CaCl₂ and having a pH of 7.7, using a

5 Brinkman Polytron^{*} at setting 6 for 20 seconds and centrifuged at 48,000 x g for 10 minutes at 4° C. Membranes are stored frozen at -78° C until the time of assay. On the day of the experiment, the membranes are resuspended in a 50 mM Tris buffer (pH 7.7) containing 4 mM CaCl₂ and 10 μM pargyline to a final tissue concentration of 2.5 mg/mL and added to test tubes containing an incubation buffer, various concentrations of test drug, and [³H]-8-OH-
 10 DPAT. Non-specific binding is defined in the presence of a saturating concentration of 5HT. Assay tubes are incubated for 30 minutes at 37° C to attain equilibrium, and incubations are terminated by rapid filtration through Whatman GF/B filters using a Brandel cell harvester. The membranes are washed three times with 4 mL aliquots of an ice-cold buffer (without CaCl₂ or pargyline). Membrane-bound ligand is determined by liquid scintillation counting of
 15 the filters in Ready-Safe^{*} scintillation cocktail. The dissociation constant (K_D) for the radioligand, previously determined by saturation analysis, is used to calculate apparent K_i's by means of the Cheng-Prusoff equation (Cheng and Prusoff, 1973). The IC₅₀ concentrations (concentration of compound required to displace specific binding by 50%) can be calculated by linear regression analysis of the concentration-response curves from competition binding
 20 studies. The preferred compounds of this invention bind to the human 5HT_{1A} receptor with a K_i less than 1.0 micromolar.

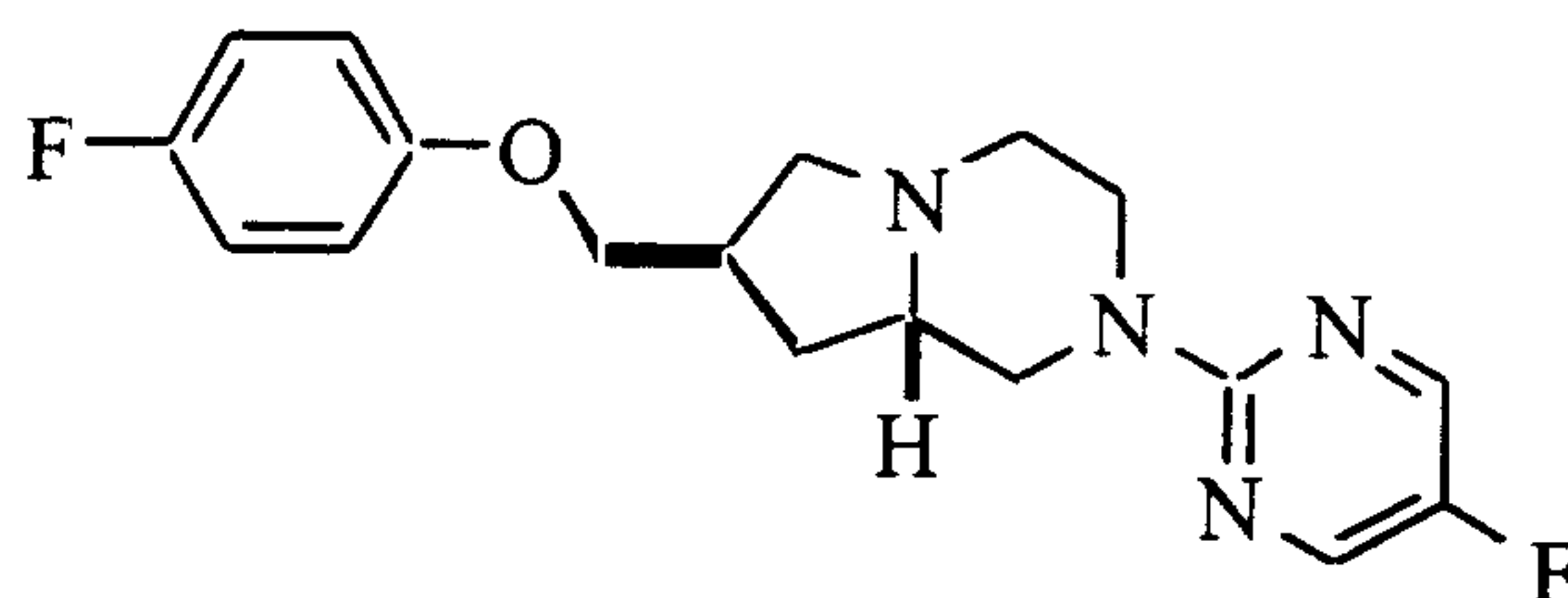
The agonist and antagonist activities of the therapeutic compounds used in the methods of this invention at 5-HT_{1A} receptors can be determined using a single saturating concentration according to the following procedure. Male Hartley guinea pigs are decapitated and 5-HT_{1A}
 25 receptors are dissected out of the hippocampus, while receptors are obtained by slicing at 350 μm on a McIlwain^{*} tissue chopper and dissecting out the substantia nigra from the appropriate slices. The individual tissues are homogenized in a 5 mM HEPES buffer containing 1 mM EGTA (pH 7.5) using a hand-held glass-Teflon® homogenizer and centrifuged at 35,000 x g for 10 minutes at 4°C. The pellets are resuspended in a 100 mM HEPES buffer containing 1 mM
 30 EGTA (pH 7.5) to a final protein concentration of 20 μg of protein per tube. The following agents are added so that the reaction mix in each tube contained 2.0 mM MgCl₂, 0.5 mM ATP, 1.0 mM cAMP, 0.5 mM IBMX, 10 mM phosphocreatine, 0.31 mg/mL creatine phosphokinase, 100 μM GTP and 0.5-1 microcuries of [³²P]-ATP (30 Ci/mmol: NEG-003^{*} - New England Nuclear). Incubation is initiated by the addition of tissue to siliconized microfuge tubes (in triplicate) at 30°C
 35 for 15 minutes. Each tube receives 20 μL tissue, 10 μL drug or buffer (at 10X final concentration), 10 μL 32 nM agonist or buffer (at 10X final concentration), 20 μL forskolin (3 μM final concentration) and 40 μL of the preceding reaction mix. Incubation is terminated by the addition of 100 μL 2% SDS, 1.3 mM cAMP, 45 mM ATP solution containing 40,000 dpm [³H]-cAMP (30 Ci/mmol: NET-275^{*} - New England Nuclear) to monitor the recovery of cAMP from the
 *Trade-mark

5 columns. The separation of [^{32} P]-ATP and [^{32} P]-cAMP is accomplished using the method of Salomon *et al.*, *Analytical Biochemistry*, **1974**, 58, 541-548. Radioactivity is quantified by liquid scintillation counting. Maximal inhibition is defined by 10 μ g (R)-8-OH-DPAT for 5-HT_{1A} receptors. Percent inhibition by the test compounds is then calculated in relation to the inhibitory effect of (R)-8-OH-DPAT for 5-HT_{1A} receptors. The reversal of agonist induced inhibition of
10 forskolin-stimulated adenylate cyclase activity is calculated in relation to the 32 nM agonist effect.

The following Examples are provided solely for the purposes of illustration and do not limit the invention which is defined by the claims.

Example 1

15 (7RS,8aSR)-7-(4-Fluorophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine

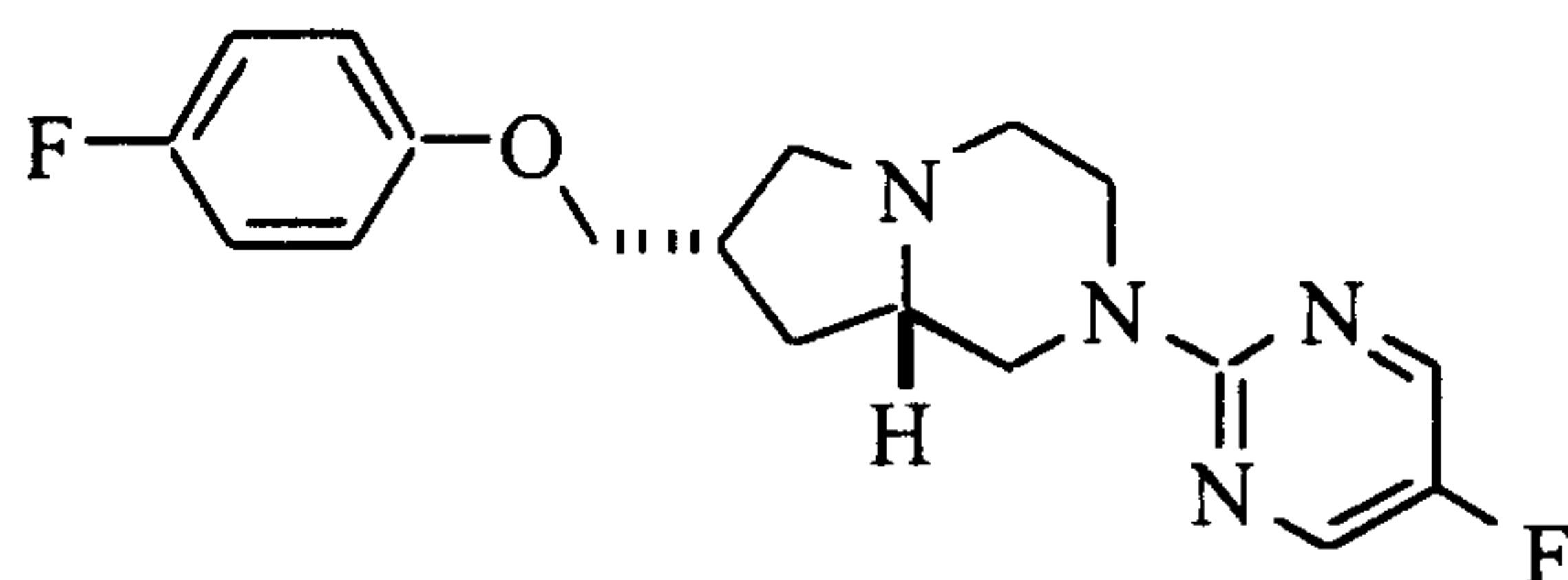


A solution of 2.00 g (5.9 mmol) of (7RS,8aSR)-7-(4-fluorophenoxy)methyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 2) and 4.1 mL
20 (20.6 mmol) of 5M aqueous ammonium formate in 50 mL methanol was treated with an aqueous slurry of 0.200 g of 10% Pd/C. The reaction was refluxed for 48 hours. The mixture was filtered and the solvent removed *in vacuo* to give an oily residue. The crude (7RS,8aSR)-7-(4-fluorophenoxy)methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine was combined with 1.2 g (9.1 mmol) of 2-chloro-5-fluoropyrimidine (Dunaiskis, A. *et al.*, *Org. Prep. Proc. Int.*,
25 1995, 27, 600-602), 2.0 g (9.1 mmol) of sodium carbonate in 100 mL of water, and the mixture was gently refluxed for 16 hours. After cooling to room temperature, the mixture was extracted with methylene chloride (3x). The combined organic layers were dried (magnesium sulfate), filtered, and evaporated. Purification by flash silica gel chromatography eluting with 90:10 ethyl acetate:hexane gave 0.744 g (27%) of the title compound. Mp ($\cdot$ HCl) 120-122 $^{\circ}$ C.
30 ^{13} C NMR (base, CDCl₃): δ 31.4, 35.3, 43.8, 49.0, 51.5, 57.6, 61.5, 71.4, 115.39, 115.50, 115.62, 115.92, 144.96, 145.24, 149.9, 153.2, 155.1, 155.7, 158.8. Anal. calc'd for C₁₈H₂₀F₂N₄O: C, 62.41; H, 5.82; N, 16.18. Found: C, 62.05, H, 5.99; N, 16.33.

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Example 2

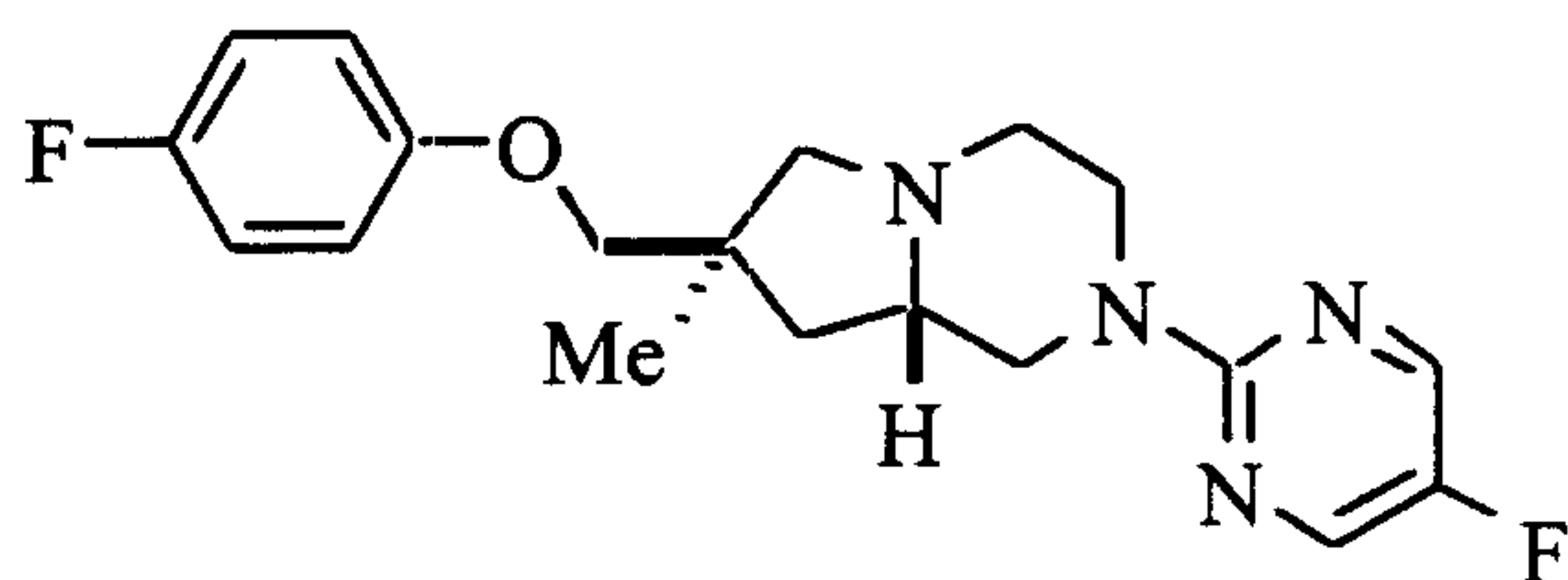
(7SR,8aSR)-7-(4-Fluorophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



A solution of 0.870 g (2.6 mmol) of (7SR,8aSR)-7-(4-fluorophenoxy)methyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 2) and 1.8 mL (8.9 mmol) of 5M aqueous ammonium formate in 50 mL methanol was treated with an aqueous slurry of 0.100 g of 10% Pd/C. The reaction was refluxed for 24 hours. The mixture was filtered and the solvent removed *in vacuo* to give an oily residue. The crude (7SR,8aSR)-7-(4-fluorophenoxy)methyl-1,2,3,4,6,7, 8,8a-octahydro-pyrrolo[1,2-a]pyrazine was combined with 0.373 g (2.8 mmol) of 2-chloro-5-fluoropyrimidine (Dunaïskis, A. *et al.*, *Org. Prep. Proc. Int.*, **1995**, 27, 600-602), 0.650 g (6.1 mmol) of sodium carbonate in 50 mL of water, and the mixture was gently refluxed for 16 hours. After cooling to room temperature, the mixture was extracted with methylene chloride (3x). The combined organic layers were dried (magnesium sulfate), filtered, and evaporated. Purification by silica gel flash chromatography eluting with 85:15 ethyl acetate:hexane gave 0.444 g (50%) of the title compound. Mp ($\cdot$ HCl) 211-213°C. ^{13}C NMR (base, CDCl_3): δ 31.7, 35.2, 43.8, 49.1, 51.4, 56.6, 62.3, 72.5, 115.45, 115.56, 115.89, 144.95, 145.24, 149.9, 153.2, 155.1, 155.6, 158.79, 158.90. Anal. calc'd for $\text{C}_{18}\text{H}_{20}\text{F}_2\text{N}_4\text{O}$: C, 62.41; H, 5.82; N, 16.18. Found: C, 62.15, H, 5.99; N, 16.38.

Example 3

(7RS,8aSR)-7-(4-Fluorophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-7-methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



A solution of 0.745 g (2.80 mmol) of (7RS,8aSR)-7-hydroxymethyl-2-(5-fluoropyrimidin-2-yl)-7-methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 5) and 0.43 mL (3.08 mmol) of triethylamine in 30 mL of dry methylene chloride was chilled to 0°C, and treated with methanesulfonyl chloride (0.228 mL, 2.94 mmol) in 15 mL of dry

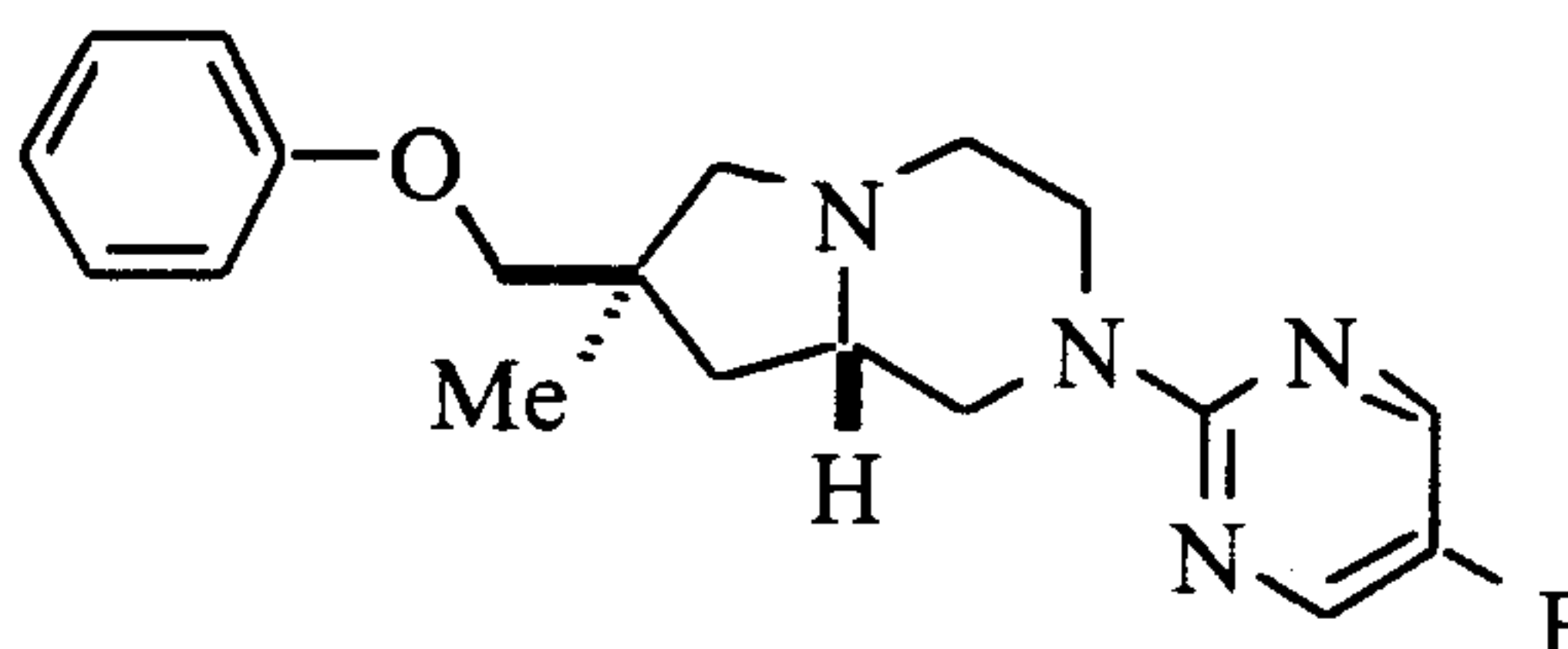
-13-

5 methylene chloride. After 1 hour, the solution was washed with water (2x), dried (magnesium sulfate), filtered and evaporated to give 0.915g (95%) of mesylate as a pale yellow solid.

A solution of 0.23 g (2.0 mmol) of 4-fluorophenol in 10 mL of dry DMF was treated with 0.096 g (2.4 mmol) of sodium hydride (60% oil dispersion), and the mixture heated at 50 °C for 1 hour. A solution of 0.25 g (0.73 mmol) of mesylate in 10 mL of dry DMF was added
 10 and the solution heated at 100 °C for 72 hours. The mixture was cooled to room temperature, diluted with water, and extracted with diethyl ether (2x). The organic phase was dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography eluting with 2:1 petroleum ether:diethyl ether gave 0.15 g (58%) of the title compound. Mp ($\cdot$ HCl) 158-160 °C. ^{13}C NMR (base, CDCl_3): δ 26.4, 39.9, 40.6, 43.8, 49.1, 51.6, 62.8, 64.5, 76.0, 115.3, 115.5, 115.6, 115.9, 145.0, 145.2, 149.9, 153.2, 155.4, 155.7, 158.8, 158.9.
 15 HRMS calc'd for $\text{C}_{19}\text{H}_{23}\text{F}_2\text{N}_4\text{O}$ (MH^+): 361.1840; found: 361.1861.

Example 4

(7RS,8aSR)-7-Phenoxymethyl-2-(5-fluoropyrimidin-2-yl)-7-methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



20

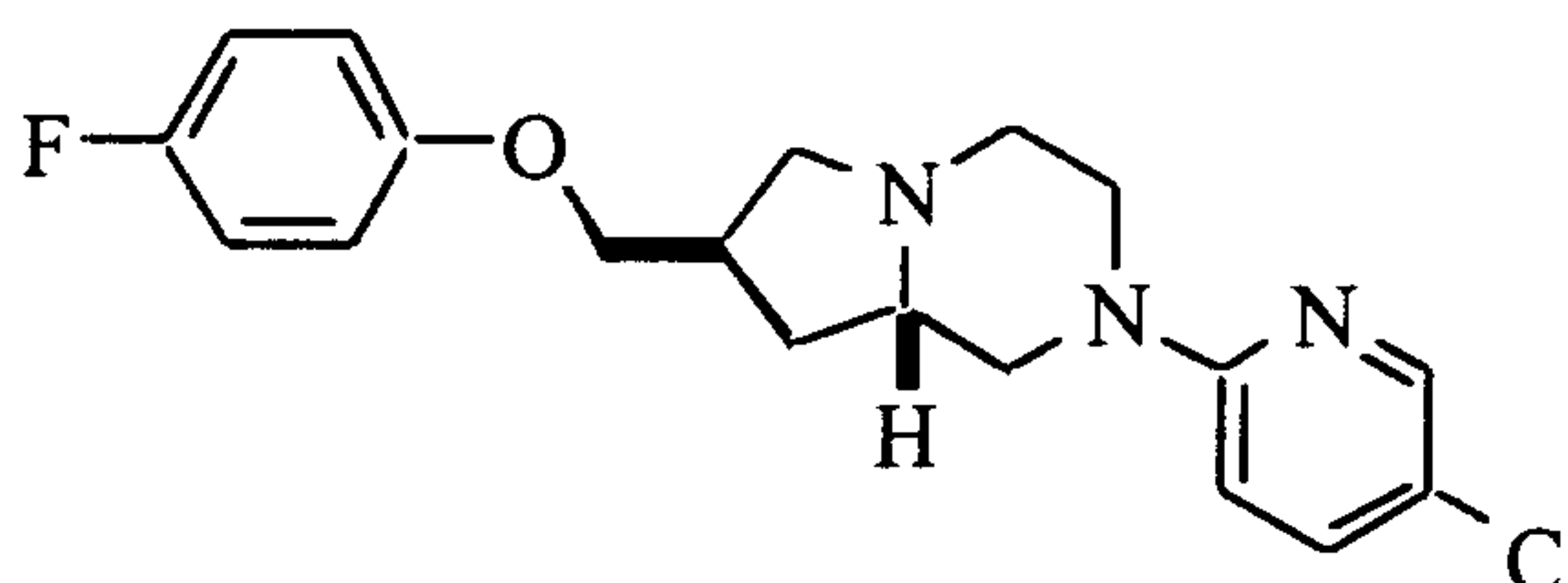
A solution of 0.745 g (2.80 mmol) of (7RS,8aSR)-7-hydroxymethyl-2-(5-fluoropyrimidin-2-yl)-7-methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 5) and 0.43 mL (3.08 mmol) of triethylamine in 30 mL of dry methylene chloride was chilled to 0 °C, and treated with methanesulfonyl chloride (0.228 mL, 2.94 mmol) in 15 mL of dry
 25 methylene chloride. After 1 hour, the solution was washed with water (2x), dried (magnesium sulfate), filtered and evaporated to give 0.915 g (95%) of mesylate as a pale yellow solid.

A solution of 0.19 g (2.0 mmol) of phenol in 10 mL of dry DMF was treated with 0.096 g (2.4 mmol) of sodium hydride (60% oil dispersion), and the mixture heated at 50 °C for 1 hour. A solution of 0.25 g (0.73 mmol) of mesylate in 10 mL of dry DMF was added and the
 30 solution heated at 100 °C for 72 hours. The mixture was cooled to room temperature, diluted with water, and extracted with diethyl ether (2x). The organic phase was dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography eluting with petroleum ether:diethyl ether (2:1) gave 0.18 g (72%) of the title compound. Mp ($\cdot$ HCl) 189-191 °C. ^{13}C NMR (base, CDCl_3): δ 26.4, 40.0, 40.6, 43.8, 49.1, 51.6, 62.8, 64.5, 75.3, 114.5,

5 120.7, 129.4, 145.0, 145.2, 149.9, 153.2, 158.9, 159.3. HRMS calc'd for $C_{19}H_{23}FN_4O$ (MH⁺): 343.1934; found: 343.1951.

Example 5

(7RS,8aSR)-7-(4-Fluorophenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



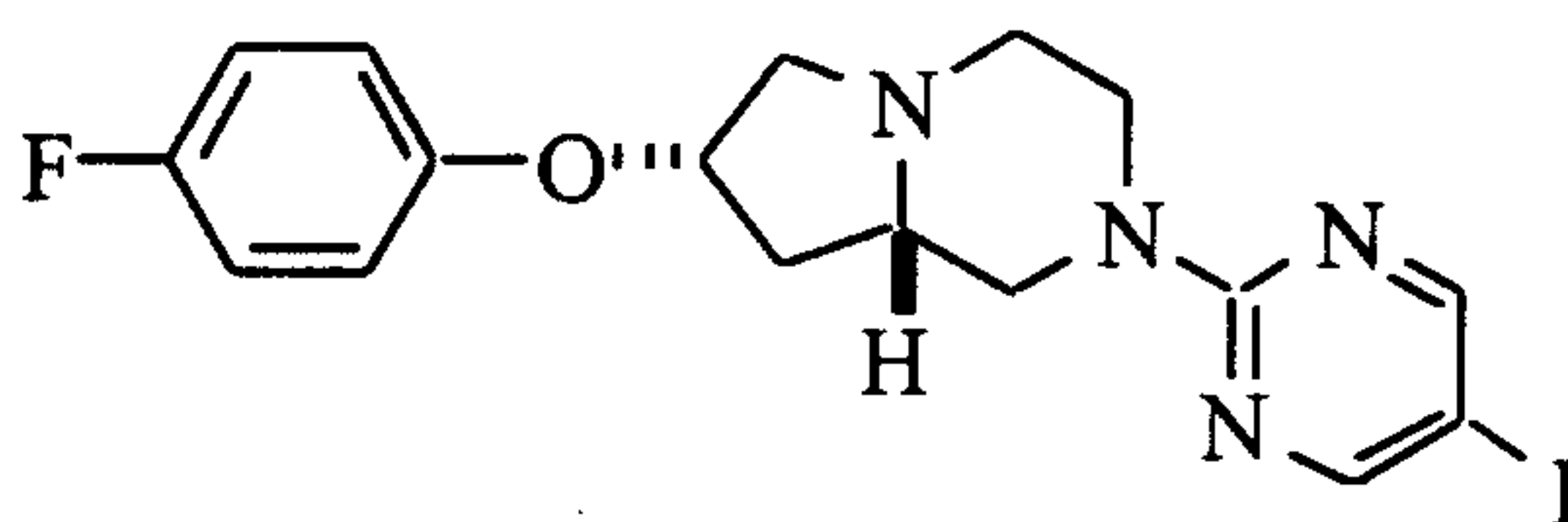
10

A mixture of 3.8 g (26 mmol) of 2,5-dichloropyridine, 1.3 g (12 mmol) of sodium carbonate, 1.3 g (5.2 mmol) of (7RS,8aSR)-7-(4-fluorophenoxy)methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 2), and 20 mL of isoamyl alcohol was heated at reflux for 18 hours. The solvent was evaporated, the residue taken up in water and ethyl acetate, and the pH adjusted to 11 with sodium carbonate. The layers were separated and the organic phase was dried (magnesium sulfate), filtered, and evaporated. Purification by medium pressure silica gel chromatography with ethyl acetate gave 35 mg (2%) of the title compound. Mp (·HCl) 202-206°C. HRMS calc'd for $C_{19}H_{21}ClFN_3O$ (MH⁺): 362.1435, found: 362.1451.

20

Example 6

(7S,8aS)-7-(4-Fluorophenoxy)-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



A solution of 0.971 g (4.18 mmol) of (7R,8aS)-7-hydroxy-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Diafi, L. *et al.*, *J. Het. Chem.*, **1990**, 27, 2181), 0.703 g (6.27 mmol) of 4-fluorophenol and 1.32 g (5.02 mmol) of triphenylphosphine in 20 mL of dry THF was treated with 0.79 mL (5.02 mmol) of diethyl azodicarboxylate and the solution stirred at room temperature for 21 hours. Excess HCl (g) in diethyl ether was added, the precipitate was collected on a Büchner funnel, washing with ethyl acetate. The gummy residue was dissolved in a mixture of ethyl acetate and aqueous ammonium hydroxide, the layers were separated, the aqueous phase was extracted with more ethyl acetate (2x), the combined organic phase was dried (magnesium sulfate), filtered and evaporated. Purification

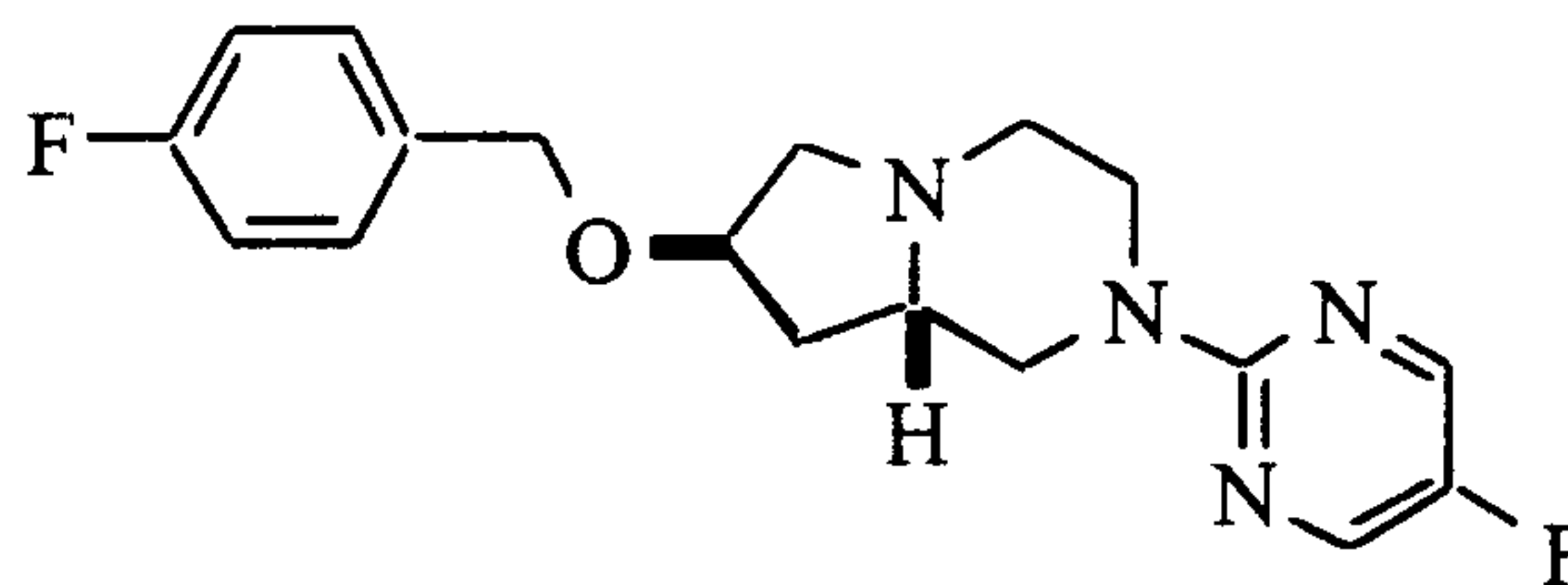
30

5 by silica gel MPLC with 95:5 ethyl acetate:methanol gave 1.3 g (95%) of (7S,8aS)-7-(4-fluorophenoxy)-2-phenylmethyl-1,2,3,4, 6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine.

A solution of 0.83 g (2.5 mmol) of (7S,8aS)-7-(4-fluorophenoxy)-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine in 10 mL of methanol and 1.8 mL of aqueous ammonium formate (5 M) was treated with an aqueous slurry of 0.325 g of 10%
 10 palladium on carbon and the mixture was stirred at room temperature for 24 hours. The mixture was filtered through Celite, evaporated, re-evaporated with another 100 mL of chloroform, dissolved in 100 mL of chloroform, dried (magnesium sulfate), filtered and evaporated. The crude amine (0.61 g, ca. 2.5 mmol), 0.50 g (3.75 mmol) of 2-chloro-5-fluoropyrimidine (Dunaïskis, A. *et al.*, *Org. Prep. Proc. Int.*, **1995**, 27, 600-602), 0.86 g (6.2
 15 mmol) of potassium carbonate and 15 mL of 2-propanol were refluxed for 5.5 hours. The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3x). The combined organic phase was washed with water (2x) and brine (1x), dried (magnesium sulfate), filtered and evaporated. Purification by silica gel MPLC starting with 70:30 ethyl acetate:hexane and ramping to 50:50 ethyl acetate:hexane at 30 minutes, gave
 20 0.30 g (36%) of the title compound. Mp ($\cdot$ HCl) 90-95°C. ^{13}C NMR (base, CDCl_3): δ 36.6, 43.6, 48.7, 60.5, 62.1, 75.6, 115.67, 115.98, 116.08, 116.18, 144.97, 145.26, 149.9, 153.2, 153.8, 155.6, 158.8. HRMS calc'd for $\text{C}_{17}\text{H}_{19}\text{F}_2\text{N}_4\text{O}$ (MH $^{+}$): 333.1527, found: 333.1556.

Example 7

25 (7R,8aS)-7-(4-Fluorobenzyl)oxy-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



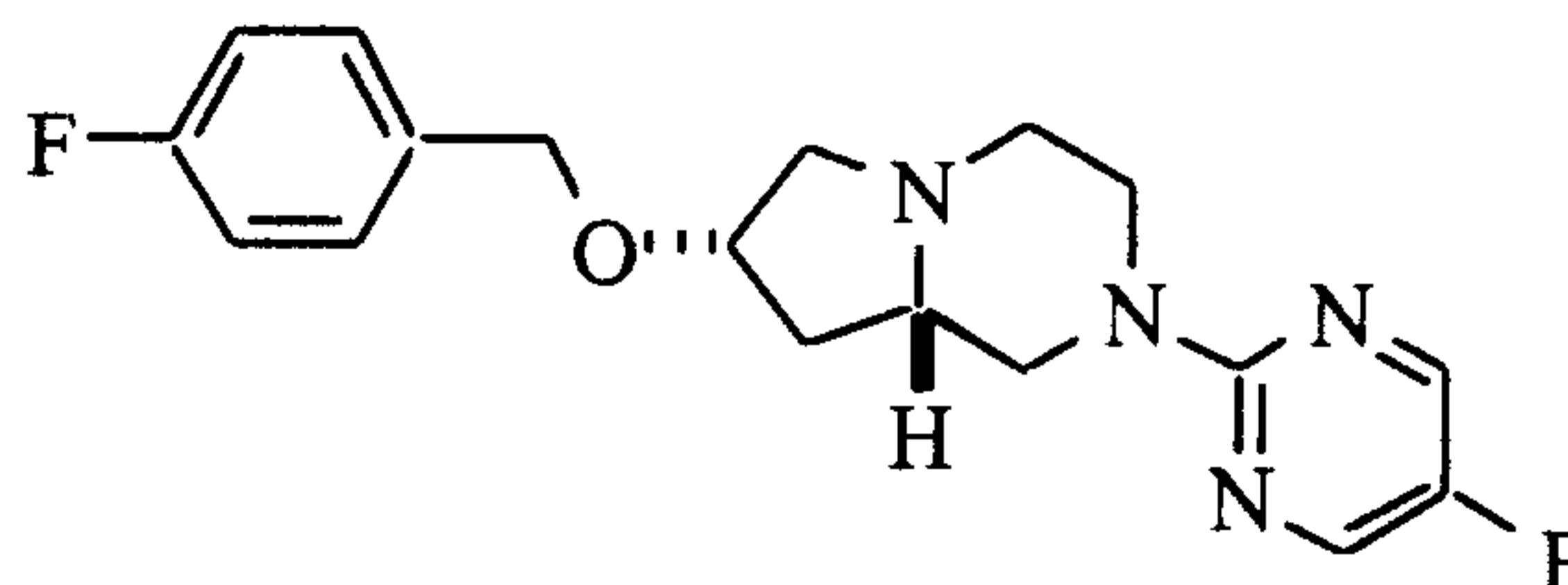
A solution of 0.75 g (3.15 mmol) of (7R,8aS)-7-hydroxy-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 6) and 0.79 mL (6.3 mmol) of 4-fluorobenzyl bromide in 30 mL of dry DMF was treated with 0.15 g (3.8 mmol) of sodium
 30 hydride (60% oil dispersion), and the mixture was heated at 100°C for 18 hours. The mixture was cool, diluted with water, and extracted with diethyl ether (5x). The combined organic phase was dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatograph with 50:50 ethyl acetate:hexane gave 0.090 g (8%) of the title compound. Mp ($\cdot$ HCl) 74-79°C. ^{13}C NMR (base, CDCl_3): δ 35.6, 43.9, 48.9, 51.2, 60.4, 60.7, 70.7, 76.7,

-16-

- 5 115.1, 115.4, 129.35, 129.46, 133.9, 144.9, 145.2, 149.9, 153.2, 158.9, 164.0. HRMS calc'd for $C_{18}H_{20}F_2N_4O$ (MH⁺): 347.1683, found: 347.1671.

Example 8

(7S,8aS)-7-(4-Fluorobenzyl)oxy-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine

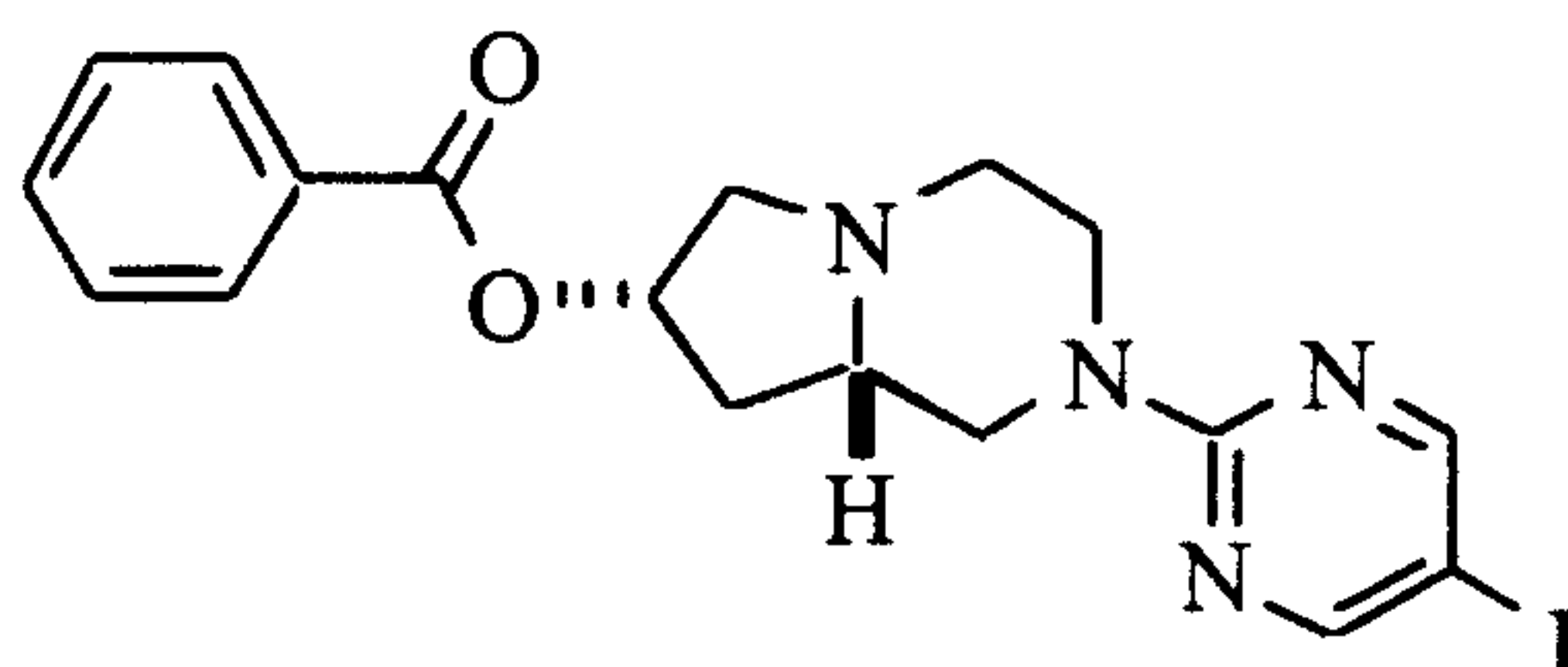


10

- A solution of 1.15 mL (10.2 mmol) of 4-fluorobenzyl alcohol in 35 mL of dry DMF was treated with 0.48 g (12 mmol) of sodium hydride (60% oil dispersion), and the mixture was stirred at 50°C for 30 minutes. A solution of 1.15 g (3.64 mmol) of (7R,8aS)-7-methanesulfonyloxy-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 7) in 35 mL of dry DMF was added and the solution stirred at 100°C for 18 hours. The solution was cooled, diluted with water, and extracted with diethyl ether (2x). The combined organic phase was dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography with ethyl acetate gave 0.25 g (20%) of the title compound. Mp (·D-(-)-tartrate) 76-81°C. ¹³C NMR (base, CDCl₃): δ 36.3, 43.6, 48.8, 51.3, 60.2, 61.9, 70.4, 76.6, 115.0, 115.3, 129.43, 129.53, 134.0, 144.9, 145.2, 149.9, 153.2, 158.9, 160.6, 163.9. HRMS calc'd for $C_{18}H_{20}F_2N_4O$ (MH⁺): 347.1683, found: 347.1706.
- 15
- 20

Example 9

(7S,8aS)-2-(5-Fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazin-7-yl benzoate



25

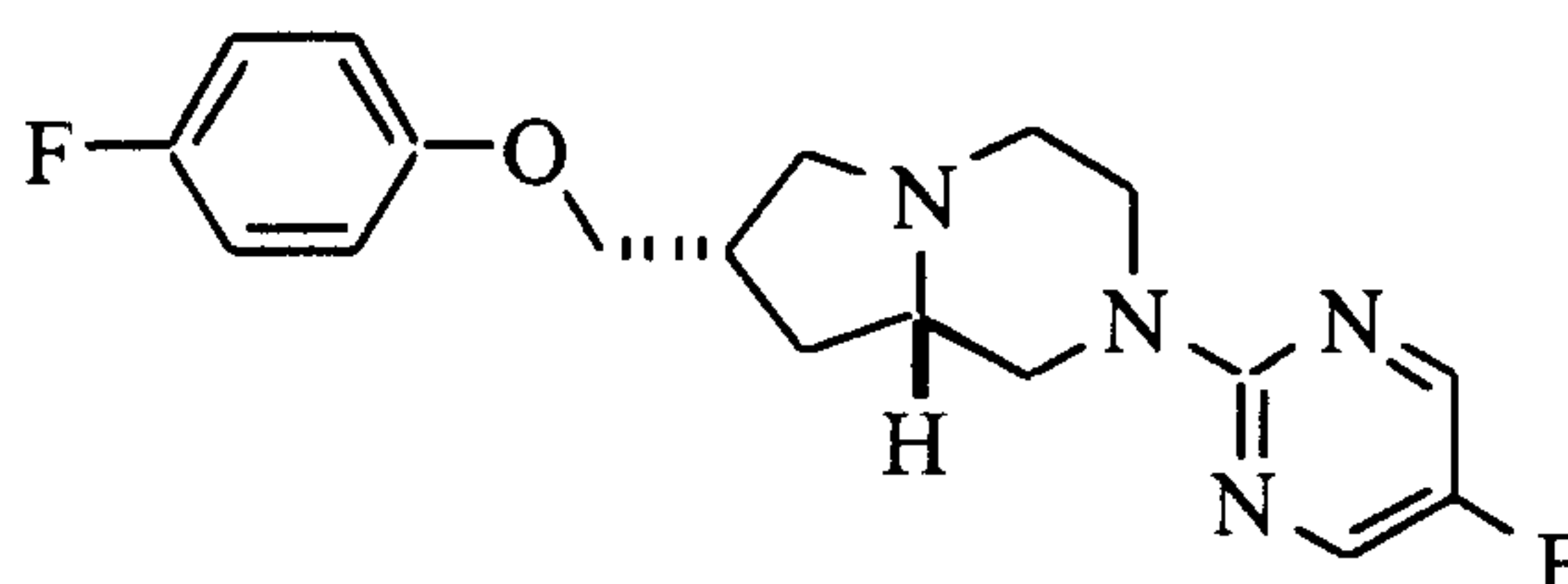
- A solution of 2.0 g (8.4 mmol) of (7R,8aS)-7-hydroxy-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 6), 1.54 g (12.6 mmol) of benzoic acid, 2.65 g (10.1 mmol) of triphenylphosphine, and 1.59 mL (10.1 mmol) of diethyl azodicarboxylate (DEAD) in 85 mL of THF was stirred at ambient temperature for 16 hours. The solvent was evaporated, and flash silica gel chromatography with 1:1 hexane:ethyl acetate gave 2.5 g of partially purified material. A second chromatography with 10:1 methylene chloride:methanol gave 1.68 g (59%) of the title compound. Mp (·HCl) 134-
- 30

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- 5 135.5°C. ^{13}C NMR (base, CDCl_3): δ 36.1, 43.7, 48.7, 51.2, 60.4, 61.8, 73.2, 128.3, 129.7, 130.1, 133.0, 145.0, 145.3, 150.0, 153.1, 158.9, 166.7. HRMS calc'd for $\text{C}_{18}\text{H}_{20}\text{FN}_4\text{O}$ (MH^+): 343.1570, found: 343.1585.

Example 10

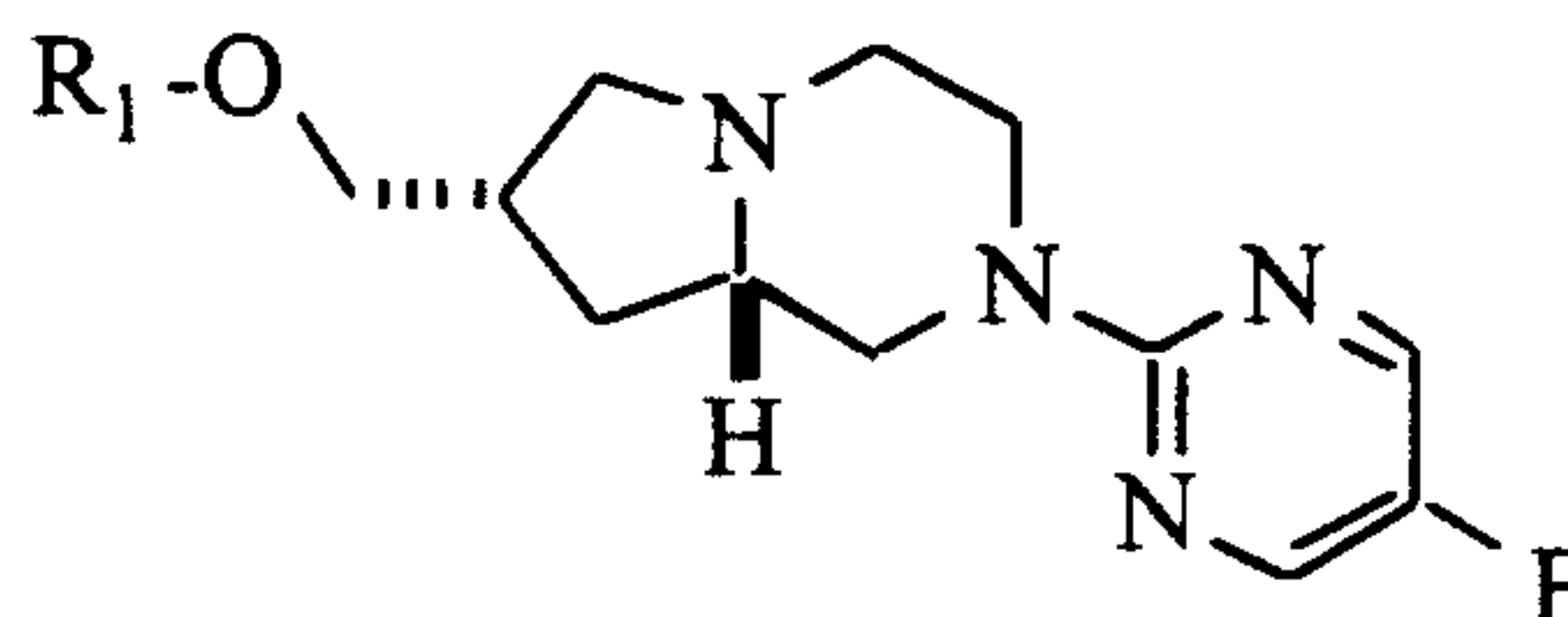
- 10 (7S,8aS)-7-(4-Fluorophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



- 15 A solution of 0.25 g (0.99 mmol) of (7S,8aS)-7-hydroxymethyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 13), 0.167 g (1.49 mmol) of 4-fluorophenol, 0.31 g (1.19 mmol) of triphenylphosphine and 0.19 mL (1.2 mmol) of diethyl azodicarboxylate (DEAD) in 10 mL of dry THF was stirred at ambient temperature for 16 hours. The solvent was evaporated, the residue was dissolved in chloroform and washed with 1M sodium hydroxide. The organic phase was dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography with 1:1 hexane:ethyl acetate and a second chromatography with 3:1 hexane:ethyl acetate gave 0.185 g (54%) of the title
- 20 compound. Mp ($\cdot\text{HCl}$) 207.5-208°C. ^{13}C NMR (base, CDCl_3): δ 31.7, 35.2, 43.8, 49.1, 51.4, 56.6, 62.3, 72.5, 115.5, 115.6, 115.9, 144.9, 145.2, 149.9, 153.2, 155.1, 155.6, 158.8, 158.9. m/z (MH^+) 347.

Example 11

- 25 (7S,8aS)-7-(Substituted-phenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazines



The following compounds were prepared from (7S,8aS)-7-hydroxymethyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 13) and the appropriate phenol according to the method described in Example 10.

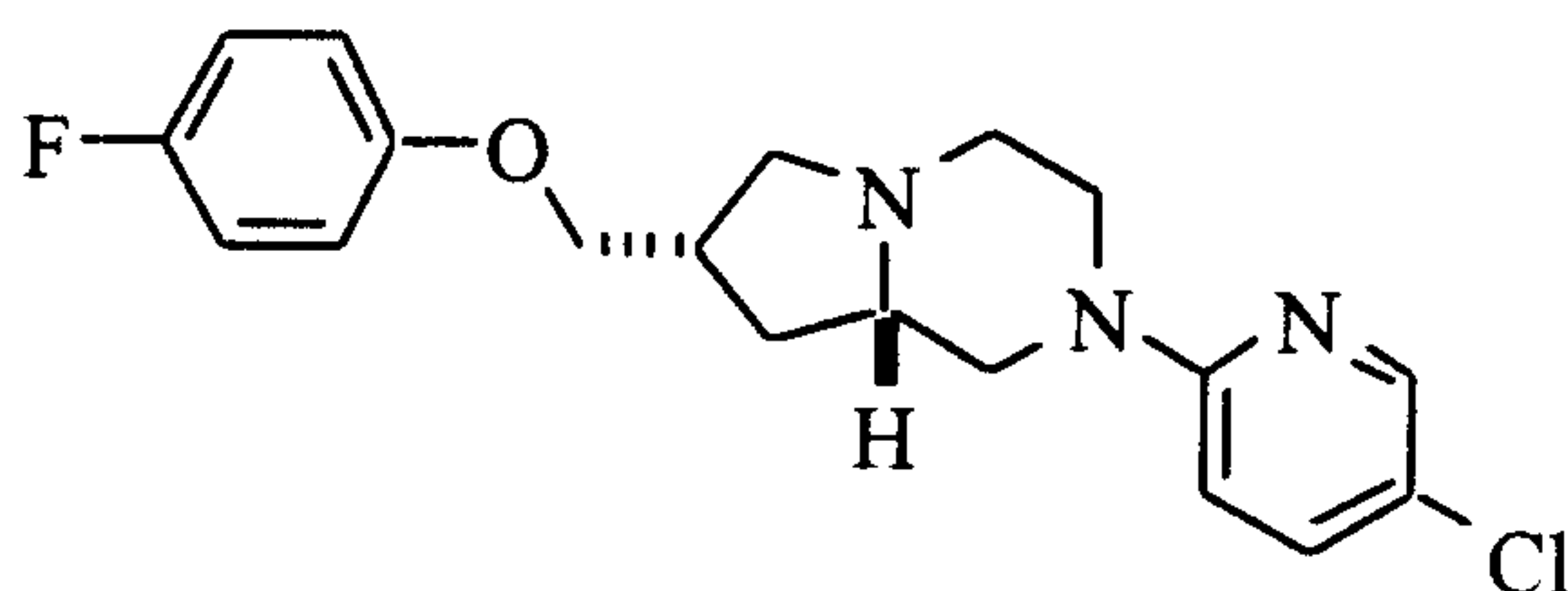
- 30 11a. 7S,8aS)-7-(3-Cyanophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot\text{HCl}$) 83-85°C. HRMS calc'd for $\text{C}_{19}\text{H}_{21}\text{FN}_5\text{O}$ (MH^+): 354.1730, found: 354.1716.

- 5 11b. (7S,8aS)-7-(4-Cyanophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 183-185°C. HRMS calc'd for $C_{19}H_{21}FN_5O$ (MH⁺): 354.1730, found: 354.1719.
- 11c. (7S,8aS)-7-(3,5-Difluorophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 205-206°C. HRMS calc'd for
10 $C_{18}H_{20}F_3N_4O$ (MH⁺): 365.1589, found: 365.1592.
- 11d. (7S,8aS)-7-(2-Nitrophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 151-153°C. HRMS calc'd for
 $C_{18}H_{21}FN_5O_3$ (MH⁺): 374.1628, found: 374.1638.
- 11e. (7S,8aS)-7-(3-Nitrophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-
15 1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 92-9°C. HRMS calc'd for
 $C_{18}H_{21}FN_5O_3$ (MH⁺): 374.1628, found: 374.1647.
- 11f. (7S,8aS)-7-(4-Nitrophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 189-191°C. HRMS calc'd for
 $C_{18}H_{21}FN_5O_3$ (MH⁺): 374.1628, found: 374.1647.
- 20 11g. (7S,8aS)-7-(3-(Trifluoromethyl)phenoxy)methyl-2-(5-fluoropyrimidin-
2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: HRMS calc'd for $C_{19}H_{21}F_4N_4O$ (MH⁺):
397.1651, found: 397.1642.
- 11h. (7S,8aS)-7-(4-(Cyanomethyl)phenoxy)methyl-2-(5-fluoropyrimidin-2-
yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 65-67°C. HRMS calc'd for
25 $C_{20}H_{23}FN_5O$ (MH⁺): 368.1887, found: 368.1898.
- 11i. (7S,8aS)-7-(4-((Methoxycarbonyl)methyl)phenoxy)methyl-2-(5-
fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 50-52°C.
HRMS calc'd for $C_{21}H_{25}FN_4O_3$ (MH⁺): 401.1989, found: 401.1965.
- 11j. (7S,8aS)-7-(3-(Methoxycarbonyl)phenoxy)methyl-2-(5-
30 fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 74-79°C.
HRMS calc'd for $C_{20}H_{24}FN_4O_3$ (MH⁺): 387.1832, found: 387.1866.
- 11k. (7S,8aS)-7-(3-(Ethynyl)phenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 73-76°C. HRMS calc'd for
 $C_{20}H_{22}FN_4O$ (MH⁺): 353.1778, found: 353.1805.
- 35 11l. (7S,8aS)-7-(3-(Ethoxy)phenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 169-17 °C. HRMS calc'd for
 $C_{20}H_{26}FN_4O_2$ (MH⁺): 373.2040, found: 373.2016.

- 5 11m. (7S,8aS)-7-(Phenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 76-79°C. HRMS calc'd for
C₁₈H₂₂FN₄O (MH⁺): 329.1778, found: 329.1784.

Example 12

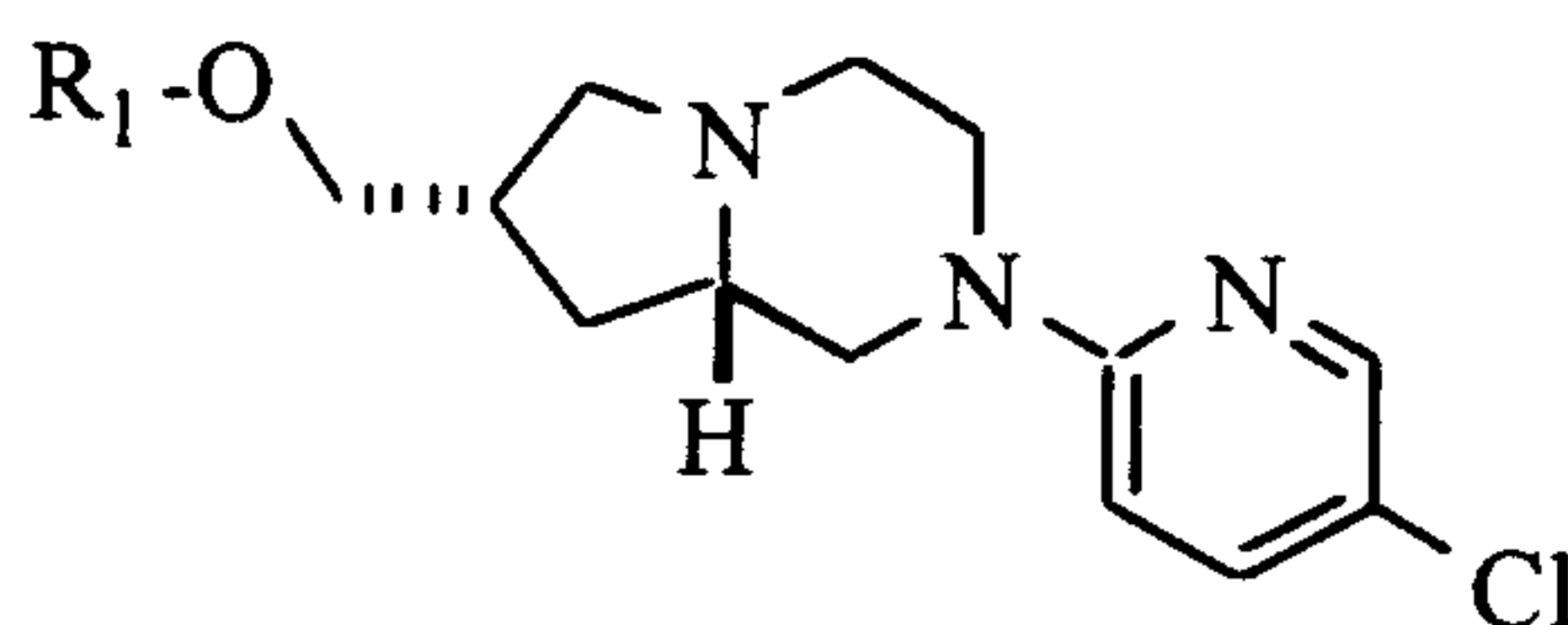
- 10 (7S,8aS)-7-(4-Fluorophenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-
octahydro-pyrrolo[1,2-a]pyrazine



- A solution of 0.25 g (0.93 mmol) of (7S,8aS)-7-hydroxymethyl-2-(5-chloropyridin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 14), 0.157 g (1.40 mmol) of 4-
fluorophenol, 0.29 g (1.12 mmol) of triphenylphosphine and 0.18 mL (1.1 mmol) of diethyl
15 azodicarboxylate (DEAD) in 10 mL of dry THF was stirred at ambient temperature for 16
hours. The solvent was evaporated, the residue was dissolved in chloroform and washed with
1M sodium hydroxide. The organic phase was dried (magnesium sulfate), filtered and
evaporated. Purification by flash silica gel chromatography with 1:1 hexane:ethyl acetate
gave 0.24 g (71%) of the title compound. Mp ($\cdot$ HCl) 221-224°C. HRMS calc'd for
20 C₁₉H₂₂ClFN₃O (MH⁺): 362.1435, found: 362.1415.

Example 13

- (7S,8aS)-7-(Substituted-phenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-
octahydro-pyrrolo[1,2-a]pyrazines



- 25 The following compounds were prepared from (7S,8aS)-7-hydroxymethyl-2-(5-
chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 14) and the
appropriate phenol according to the method described in Example 12.

- 13a. (7S,8aS)-7-(3-Cyanophenoxy)methyl-2-(5-chloropyridin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 220-224°C. HRMS calc'd for
30 C₂₀H₂₂CIN₄O (MH⁺): 369.1482, found: 369.1472.

- 13b. (7S,8aS)-7-(4-Cyanophenoxy)methyl-2-(5-chloropyridin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine. Purification by flash silica gel

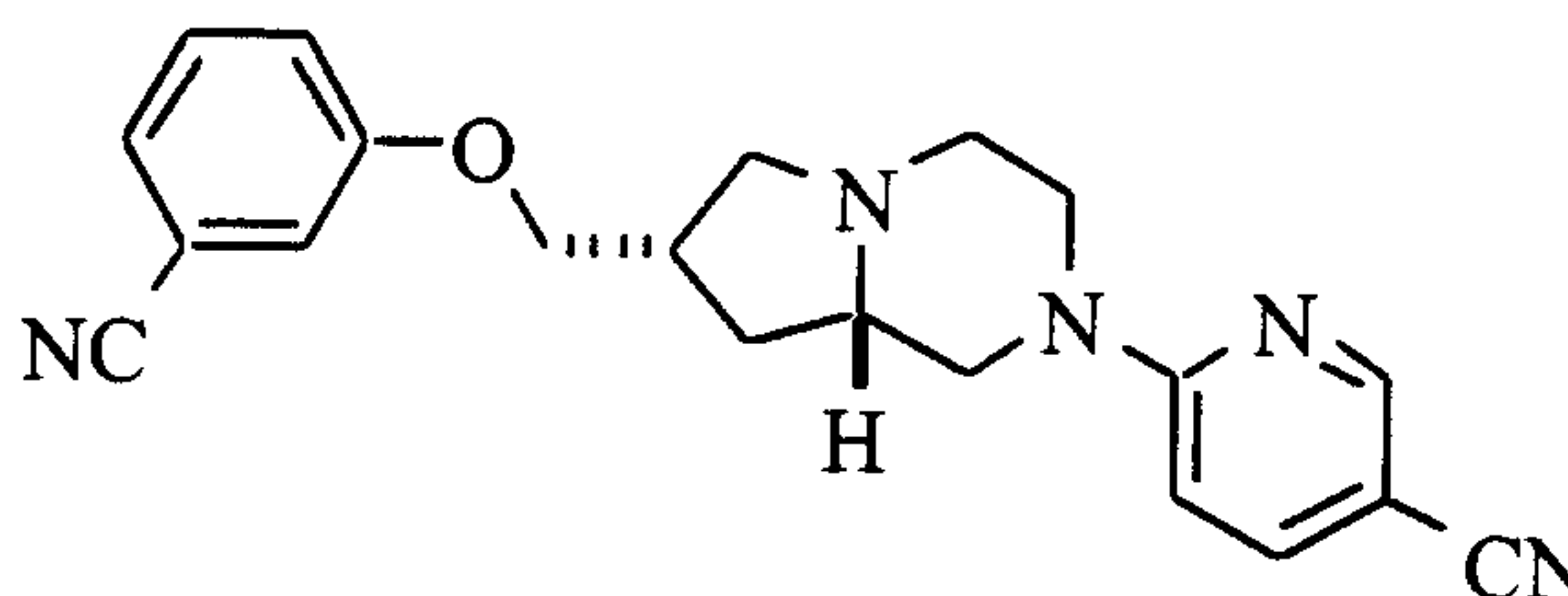
5 chromatography with ethyl ether. Mp ($\cdot$ HCl) 245°C (dec). HRMS calc'd for $C_{20}H_{22}ClN_4O$ (MH⁺): 369.1482, found: 369.1465.

13c. (7S,8aS)-7-(3,5-Difluorophenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine. Purification by flash silica gel chromatography with 65:35 diethyl ether:petroleum ether. Mp ($\cdot$ HCl) 220°C (dec). HRMS
10 calc'd for $C_{19}H_{21}ClF_2N_3O$ (MH⁺): 380.1341, found: 380.1309.

13d. (7S,8aS)-7-(4-(Methoxycarbonyl)methylphenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: Mp ($\cdot$ HCl) 186-189°C. HRMS calc'd for $C_{22}H_{27}ClN_3O_3$ (MH⁺): 416.1741, found: 416.1765.

Example 14

15 (7S,8aS)-7-(3-Cyanophenoxy)methyl-2-(5-cyanopyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



A solution of 1.0 g (6.4 mmol) of (7S,8aS)-7-hydroxymethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 13, Step A), 1.77 g (12.8 mmol) of 2-chloro-5-cyanopyridine and 2.71 g (25.6 mmol) of sodium carbonate in 50 mL of isoamyl alcohol was
20 heated at reflux for 18 hours. The mixture was cooled to room temperature, diluted with ethyl acetate and water, the pH was adjusted to 11 with sodium carbonate, the layers were separated, and the aqueous layer extracted with ethyl acetate. The combined organic phase was dried (magnesium sulfate), filtered and evaporated to give (7S,8aS)-7-hydroxymethyl-2-
25 (5-cyanopyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine.

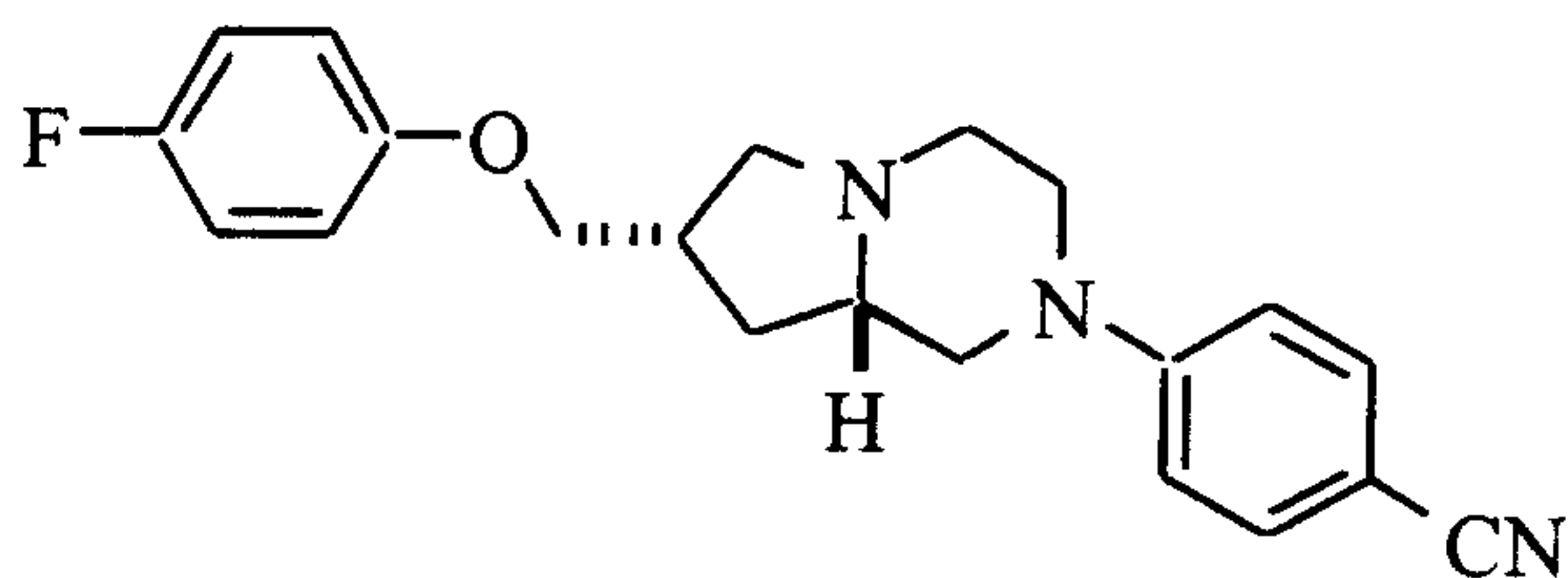
The (7S,8aS)-7-hydroxymethyl-2-(5-cyanopyridin-2-yl)-1,2,3,4, 6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine, 1.6 g (13.4 mmol) of 3-cyanophenol, and 2.8 g (11 mmol) of triphenylphosphine were dissolved in 20 mL of dry THF, the solution was treated with 1.7 mL (11 mmol) of diethyl azodicarboxylate (DEAD), and the reaction stirred at ambient
30 temperature for 16 hours. The solvent was evaporated, the residue taken up in ethyl acetate, and washed with 1M NaOH (sodium hydroxide). The organic phase was extracted with 1M HCl (3x), and the aqueous acid was washed with ethyl acetate (1x). The aqueous phase was made basic with 1M NaOH, extracted with ethyl acetate (3x), and the combined organic phase dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel

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- 5 chromatography with 75:25 ethyl acetate:hexane gave 0.603 g (19%) of the title compound. Mp ($\cdot$ HCl) 197-200°C. HRMS calc'd for $C_{21}H_{22}N_5O$ (MH⁺): 360.1824, found: 360.1802.

Example 15

(7S,8aS)-7-(4-Fluorophenoxy)methyl-2-(4-cyanophenyl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



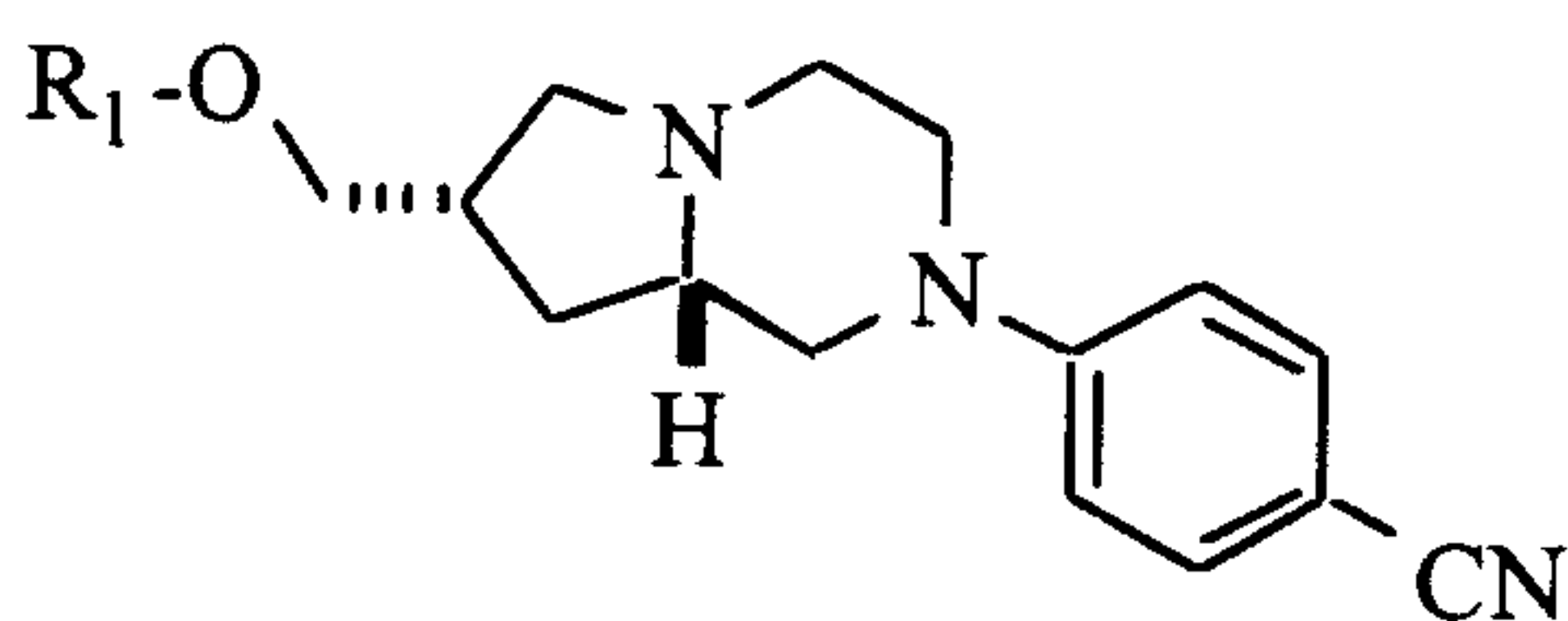
10

- A solution of 0.25 g (0.97 mmol) of (7S,8aS)-7-hydroxymethyl-2-(4-cyanophenyl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 16), 0.164 g (1.46 mmol) of 4-fluorophenol, 0.31 g (1.15 mmol) of triphenylphosphine in 10 mL of THF was treated with 0.18 mL (1.15 mmol) of diethyl azodicarboxylate and the solution stirred at ambient temperature for 16 hours. The solvent was removed by rotary evaporation, and the residue partitioned between chloroform and 1M sodium hydroxide. The layers were separated, and the organic phase was dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography with 1:1 ethyl acetate:hexane gave 0.225 g (66%) of the title compound. Mp ($\cdot$ HCl) 81-85°C. HRMS calc'd for $C_{21}H_{23}FN_3O$ (MH⁺): 352.1825, found: 352.1817.

20

Example 16

(7S,8aS)-7-(Substituted-phenoxy)methyl-2-(4-cyanophenyl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



- The following compounds were prepared from (7S,8aS)-7-hydroxymethyl-2-(4-cyanophenyl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 16) and the appropriate phenol according to the method described in Example 15.

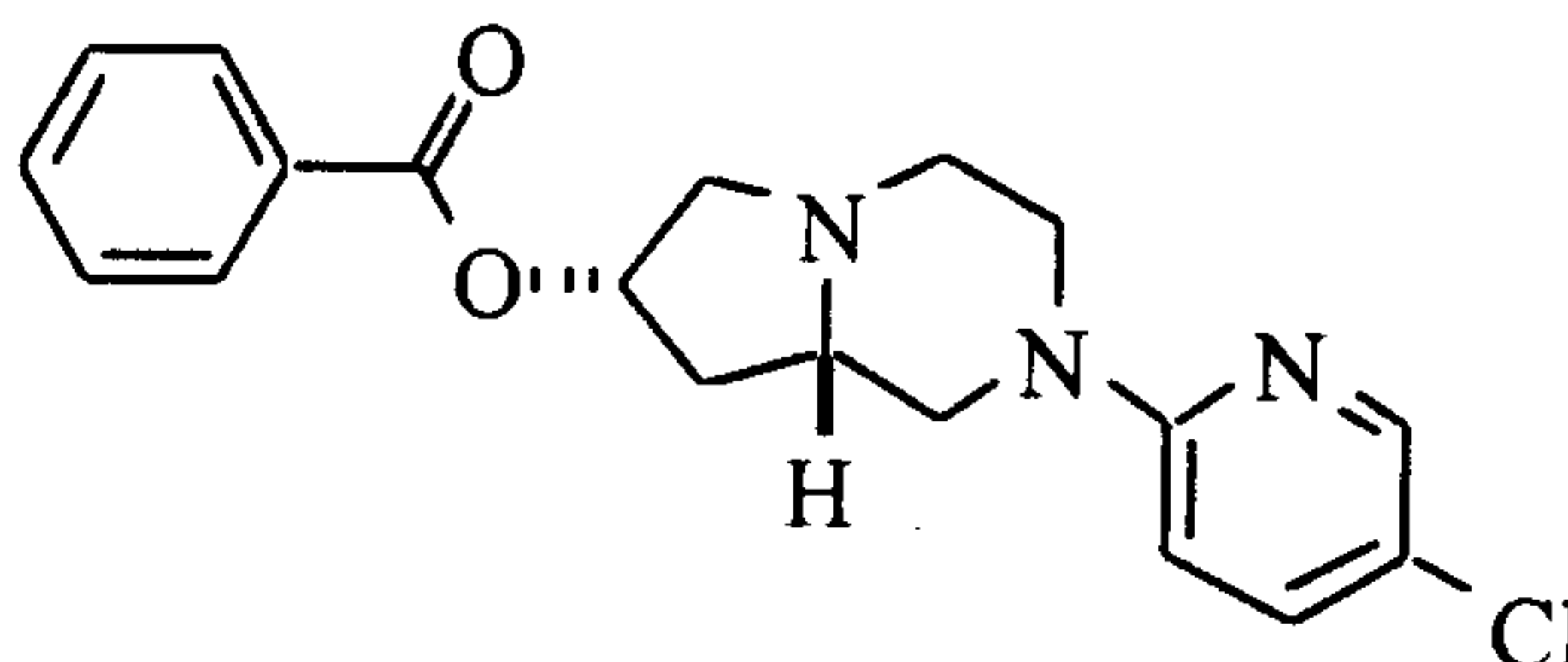
- 16a. (7S,8aS)-7-(3-Cyanophenoxy)methyl-2-(4-cyanophenyl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine. Mp 114-118°C. HRMS calc'd for $C_{22}H_{23}N_4O$ (MH⁺): 359.1872, found: 359.1877.
- 16b. (7S,8aS)-7-(4-Cyanophenoxy)methyl-2-(4-cyanophenyl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine. Mp 128-135°C. HRMS calc'd for $C_{22}H_{23}N_4O$ (MH⁺): 359.1872, found: 359.1879.

30

- 5 16c. (7S,8aS)-7-(3-Ethoxyphenoxy)methyl-2-(4-cyanophenyl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine. Mp 94-98°C. HRMS calc'd for $C_{23}H_{28}N_3O_2$
(MH⁺): 378.2182, found: 378.2145.

Example 17

- 10 (7S,8aS)-2-(5-Chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazin-7-yl
benzoate

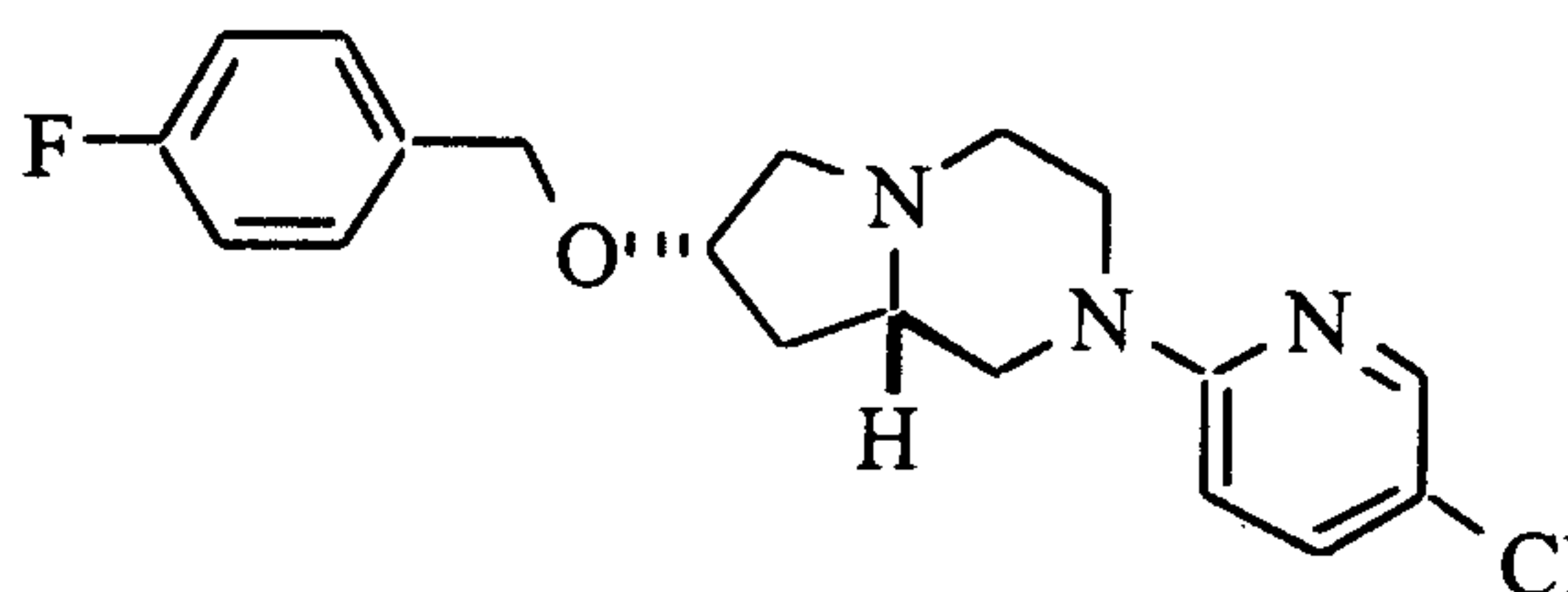


- 15 A solution of 0.595 g (2.35 mmol) of (7R,8aS)-7-hydroxy-2-(5-chloropyridin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 17), 0.430 g (3.52 mmol) of
benzoic acid and 0.738 g (2.81 mmol) of triphenylphosphine in 25 mL of dry THF was treated
with 0.44 mL (2.8 mmol) of diethyl azodicarboxylate, and the mixture stirred at ambient
temperature for 16 hours. The solvent was evaporated and the residue purified by flash silica
gel chromatography with 10:1 methylene chloride:acetone. A second chromatography of the
major fraction with the same system gave 0.63 g (75%) of the title compound. Mp (·HCl) 202-
205°C. HRMS calc'd for $C_{19}H_{21}ClN_3O_2$ (MH⁺): 358.1322, found: 358.1320.

20

Example 18

- (7S,8aS)-7-(4-Fluorobenzyl)oxy-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-
pyrrolo[1,2-a]pyrazine



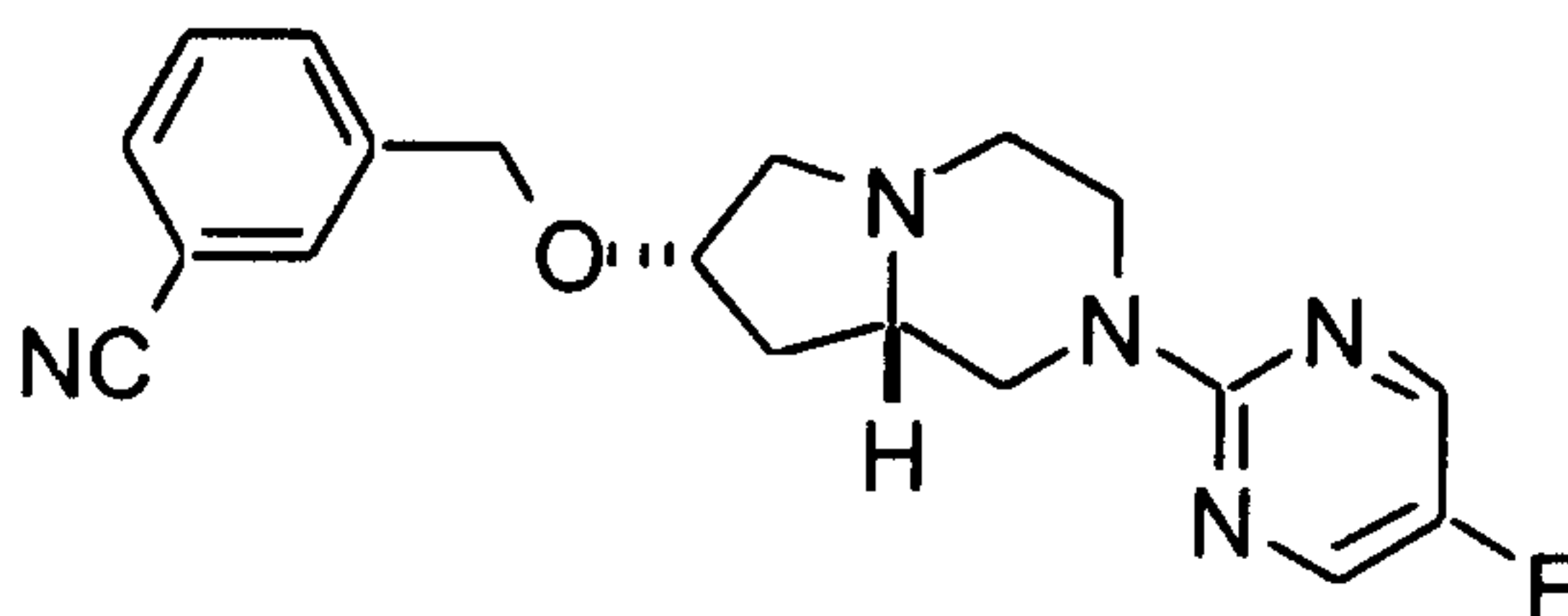
- 25 A solution of 0.23 g (0.91 mmol) of (7S,8aS)-7-hydroxy-2-(5-chloropyridin-2-yl)-
1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 18) in 10 mL of dry THF was
treated with 40 mg (1.0 mmol) of sodium hydride (60% oil dispersion), followed by 0.125 mL
(1.0 mmol) of 4-fluorobenzyl bromide and 17 mg (0.05 mmol) of tetra-n-butylammonium
iodide. The mixture was stirred at ambient temperature for 16 hours, and warmed to 50 °C for
4 hours. The suspension was cooled, the solvent was evaporated, and the residue partitioned
30 between ethyl acetate and water. The layers were separated, and the organic phase was
dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel

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5 chromatography with 95:5 chloroform: methanol gave 0.135 g (41%) of the title compound. Mp ($\cdot$ HCl) 165-168°C. HRMS calc'd for $C_{19}H_{22}ClFN_3O$ (MH⁺): 362.1435, found: 362.1451.

Example 19

(7S,8aS)-7-(3-Cyanobenzyl)oxy-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



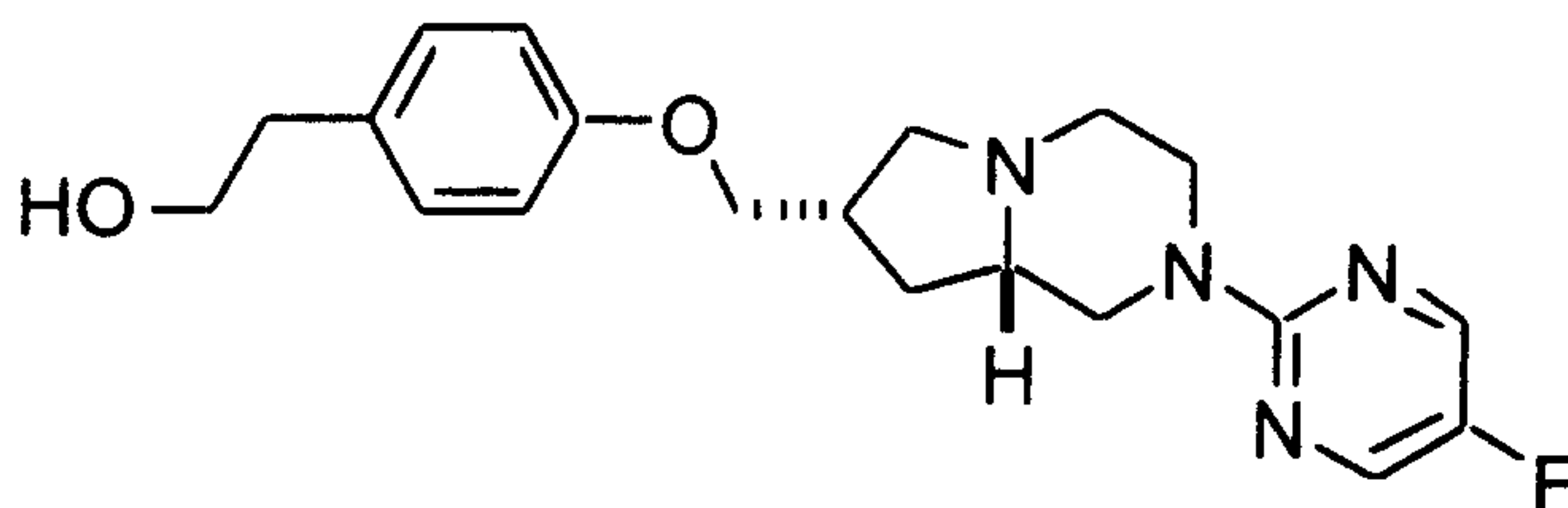
10

A solution of 0.60 g (2.5 mmol) of (7S,8aS)-7-hydroxy-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 15) in 30 mL of THF was treated with 0.41 g (10 mmol) of sodium hydride (60% oil dispersion), followed by 0.75 g (3.8 mmol) of 3-cyanobenzyl bromide and 30 mg (0.1 mmol) of tetra-n-butylammonium iodide. The mixture was stirred 50°C for 16 hours, cooled to room temperature, the solvent was evaporated, and the residue partitioned between ethyl acetate and water. The layers were separated, the organic phase was washed with water and brine, dried (magnesium sulfate), filtered and evaporated. Purification by MPLC silica gel chromatography with ethyl acetate gave 0.11 g (12%) of the title compound. Mp ($\cdot$ HCl) 95-100°C. HRMS calc'd for $C_{19}H_{21}FN_5O$ (MH⁺): 345.1730; found: 345.1739.

20

Example 20

(7S,8aS)-7-(4-(2-Hydroxyethyl)phenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



25

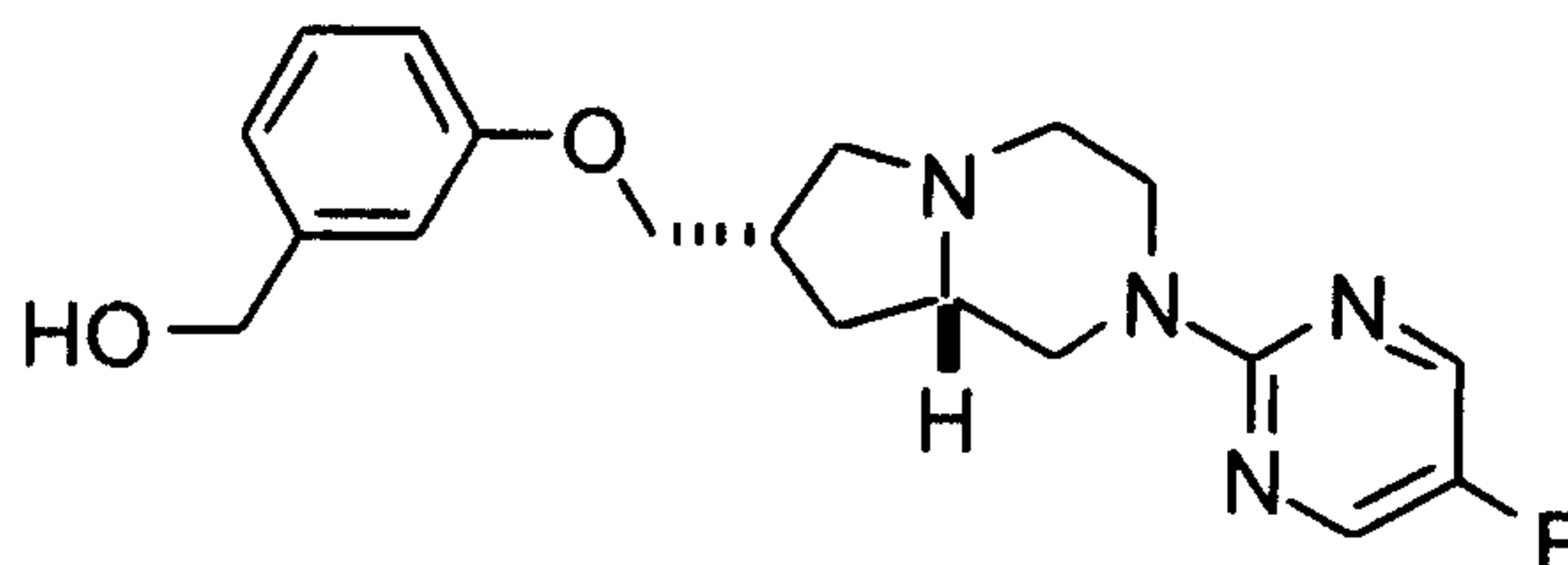
A solution of 0.13 g (0.33 mmol) of (7S,8aS)-7-(4-((methoxycarbonyl)methyl)phenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Example 11i) in 15 mL of anhydrous ethyl ether was added dropwise to an ice-cold suspension of 0.025 g (0.65 mmol) of lithium aluminum hydride in 15 mL of anhydrous ethyl ether and the mixture stirred for 30 minutes. The reaction was carefully quenched at 0°C with 0.025 mL of water, 0.025 mL of 15% sodium hydroxide, and 0.075 mL of water. The precipitate which formed was filtered through Celite, the filtrate concentrated *in vacuo*, and purification of the residue by flash silica gel chromatography with 95:5 ethyl

30

- 5 acetate:methanol gave 0.075 g (63%) of the title compound. Mp ($\cdot$ HCl) 145-147°C. HRMS calc'd for $C_{20}H_{26}FN_4O_2$ (MH⁺): 373.2040, found: 373.2054.

Example 21

(7S,8aS)-7-(3-(Hydroxymethyl)phenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



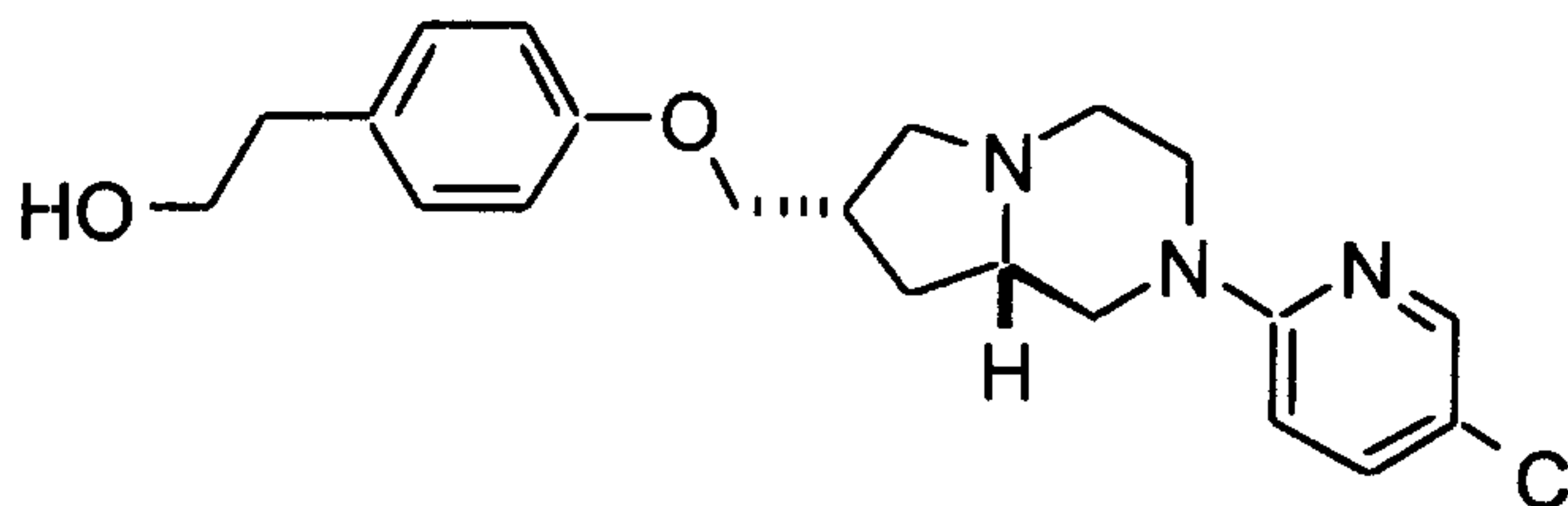
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- A solution of 0.15 g (0.39 mmol) of (7S,8aS)-7-(3-(methoxycarbonyl)phenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Example 11j) in 15 mL of anhydrous ethyl ether was added dropwise to an ice-cold suspension of 0.029 g (0.78 mmol) of lithium aluminum hydride in 15 mL of anhydrous ethyl ether and the mixture stirred for 30 min. The reaction was carefully quenched at 0°C with 0.029 mL of water, 0.029 mL of 15% sodium hydroxide, and 0.087 mL of water. The precipitate which formed was filtered through Celite, the filtrate concentrated *in vacuo*, and purification of the residue by flash silica gel chromatography with 95:5 chloroform:methanol gave 0.099 g (72%) of the title compound. Mp ($\cdot$ HCl) 85-89°C. HRMS calc'd for $C_{19}H_{24}FN_4O_2$ (MH⁺): 359.1883, found: 359.1895.

20

Example 22

(7S,8aS)-7-(4-(2-Hydroxyethyl)phenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



25

- A solution of 0.15 g (0.33 mmol) of (7S,8aS)-7-(4-((methoxycarbonyl)methyl)phenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Example 13d) in 15 mL of anhydrous ethyl ether was added dropwise to an ice-cold suspension of 0.027 g (0.65 mmol) of lithium aluminum hydride in 15 mL of anhydrous ethyl ether and the mixture stirred for 30 minutes. The reaction was carefully quenched at 0°C with 0.027 mL of water, 0.027 mL of 15% sodium hydroxide, and 0.081 mL of water. The precipitate which formed was filtered through Celite, the filtrate concentrated *in*

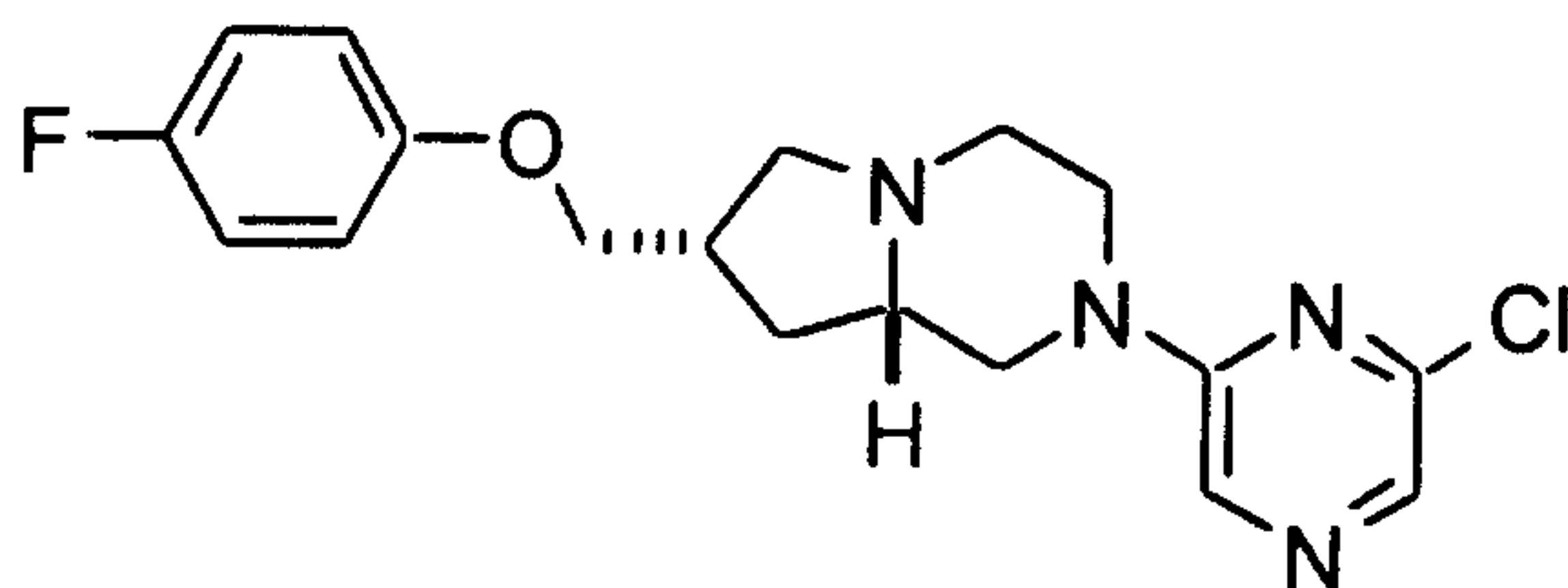
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-25-

5 *vacuo*, and purification of the residue by flash silica gel chromatography with 95:5 chloroform:methanol gave 0.13 g (95%) of the title compound. Mp ($\cdot$ HCl) 199-202°C. HRMS calc'd for $C_{21}H_{27}ClN_3O_2$ (MH⁺): 388.1792, found: 388.1807.

Example 23

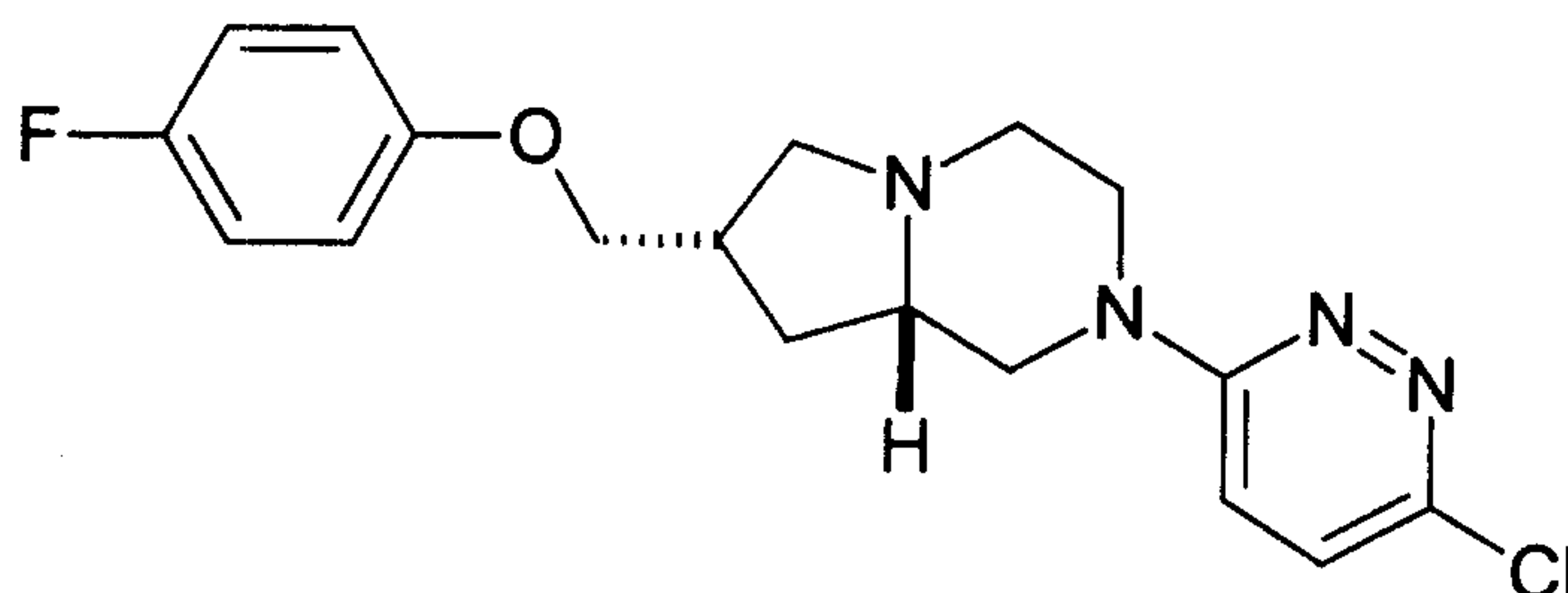
10 (7S,8aS)-7-(4-Fluorophenoxy)methyl-2-(6-chloropyrazin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



A mixture of 0.500 g (2.00 mmol) of (7SR,8aSR)-7-(4-fluorophenoxy)methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 3), 1.49 g (10.0 mmol) of 2,6-dichloropyrazine, and 0.508 g (4.79 mmol) of sodium carbonate in 50 mL of isoamyl alcohol
15 was heated to reflux for 16 hours. The reaction was cooled to ambient temperature, the solvent removed *in vacuo*, the residue taken up in ethyl acetate and water, the pH was adjusted to 11 with sodium carbonate and the layers were separated. The aqueous phase was extracted with ethyl acetate, and the combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography with 90:10
20 ethyl acetate:hexane gave 0.491 g (68%) of the title compound. Mp ($\cdot$ HCl) 209-212°C. HRMS calc'd for $C_{18}H_{21}ClFN_4O$ (MH⁺): 363.1388, found: 363.1384.

Example 24

(7S,8aS)-7-(4-Fluorophenoxy)methyl-2-(6-chloropyridazin-3-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



25

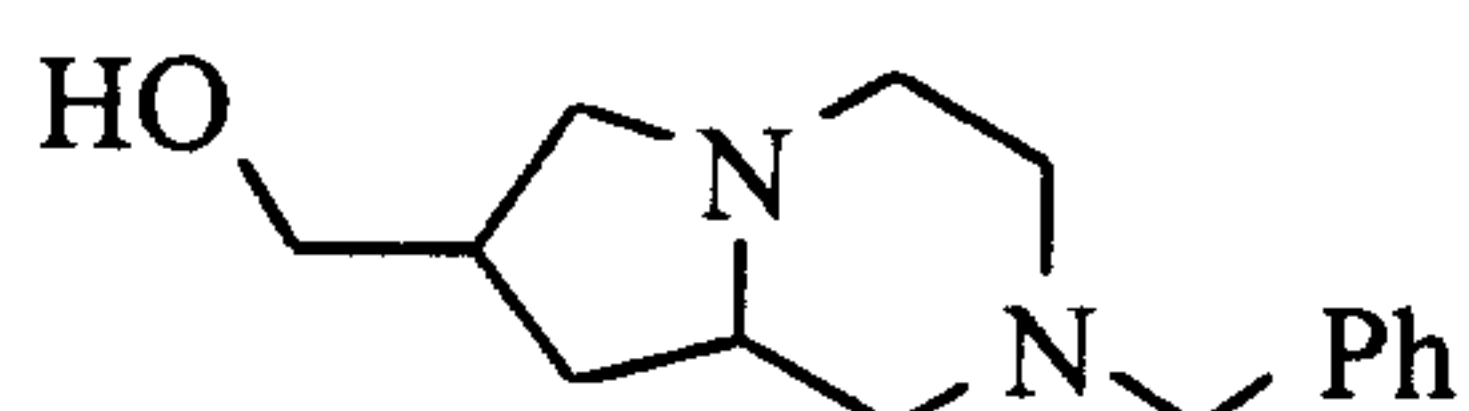
A mixture of 0.500 g (2.00 mmol) of (7SR,8aSR)-7-(4-fluorophenoxy)methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 3), 1.49 g (10.0 mmol) of 3,6-dichloropyridazine, and 0.508 g (4.79 mmol) of sodium carbonate in 50 mL of isoamyl alcohol was heated to reflux for 48 hours. The reaction was cooled to ambient temperature, the
30 solvent removed *in vacuo*, the residue taken up in ethyl acetate and water, the pH was adjusted to 11 with sodium carbonate and the layers were separated. The aqueous phase

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5 was extracted with ethyl acetate, and the combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography with 90:10 ethyl acetate:hexane gave 0.478 g (66%) of the title compound. Mp ($\cdot$ HCl) 229°C (dec). HRMS calc'd for $C_{18}H_{21}ClFN_4O$ (MH⁺): 363.1388, found: 363.1404.

Preparation 1

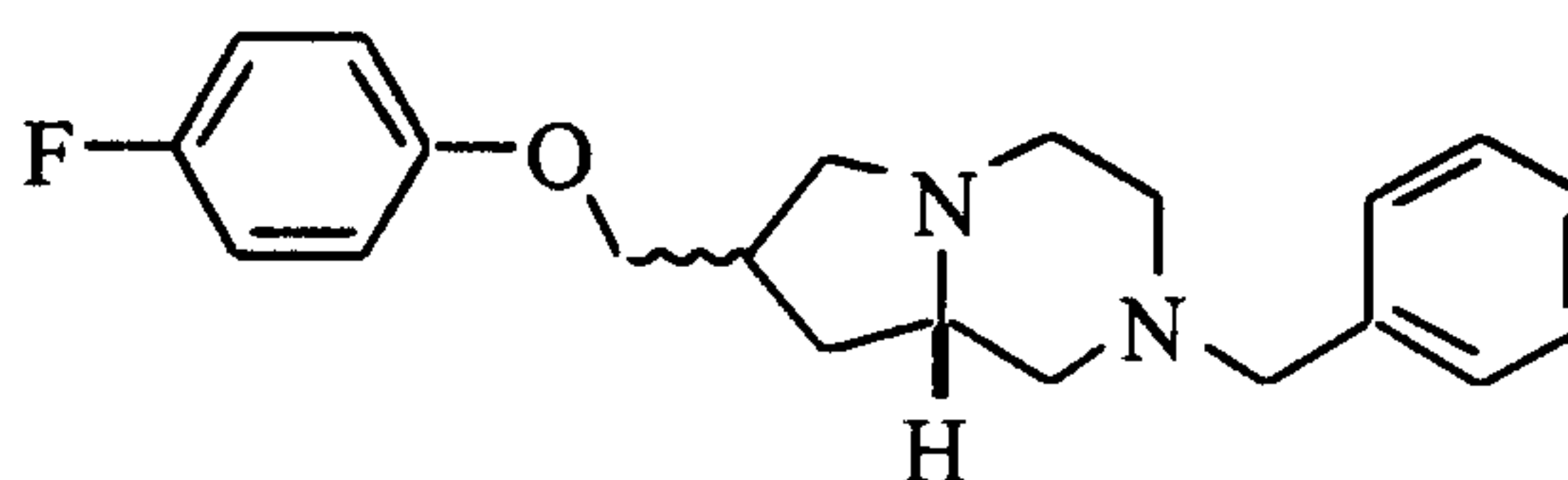
10 7-Hydroxymethyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



A suspension of 3.20 g (84.3 mmol) of lithium aluminum hydride in 30 mL of dry THF was cooled to 0°C and treated dropwise with a solution of 8.00 g (27.7 mmol) of 7-methoxycarbonyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazin-1-one (Jones, R. C. F., Howard, K. J., *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2391) in 80 mL of dry THF. After 30 min the reaction was carefully quenched with 3 mL of water, 3 mL of 15% NaOH and 9 of mL water. The mixture was filtered, the filtrate evaporated, the residue taken up in ethyl acetate and washed with brine. The organic layer was dried (magnesium sulfate), filtered, and evaporated to give 6.09 g (89%) of the title compound as a mixture of (7RS,8aSR)- and (7SR,8aSR)- isomers of sufficient purity for use in the next reaction (Preparation 2). m/z (MH⁺) 247.

Preparation 2

(7RS,8aSR)- and (7SR,8aSR)-7-(4-Fluorophenoxy)methyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



25 A solution of 6.00 g (24.35 mmol) of 7-hydroxymethyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 1), 4.10 g (36.5 mmol) of 4-fluorophenol and 7.70 g (29.4 mmol) of triphenylphosphine in 50 mL dry THF at 0°C was treated dropwise with 4.6 mL (29.3 mmol) of diethyl azodicarboxylate. The reaction was allowed to warm to room temperature and stirred for 24 hours. The solvent was evaporated, the residue taken up in ethyl acetate and washed with 1M NaOH (3x). The organic layer was dried (magnesium sulfate), filtered, and evaporated to give the crude product as a dark oil. Purification by flash silica gel chromatography eluting with 95:5 ethyl acetate:methanol gave 2.27 g (27%) of the (7RS,8aSR)- isomer and 0.410 g (5%) of the (7SR,8aSR)- isomer.

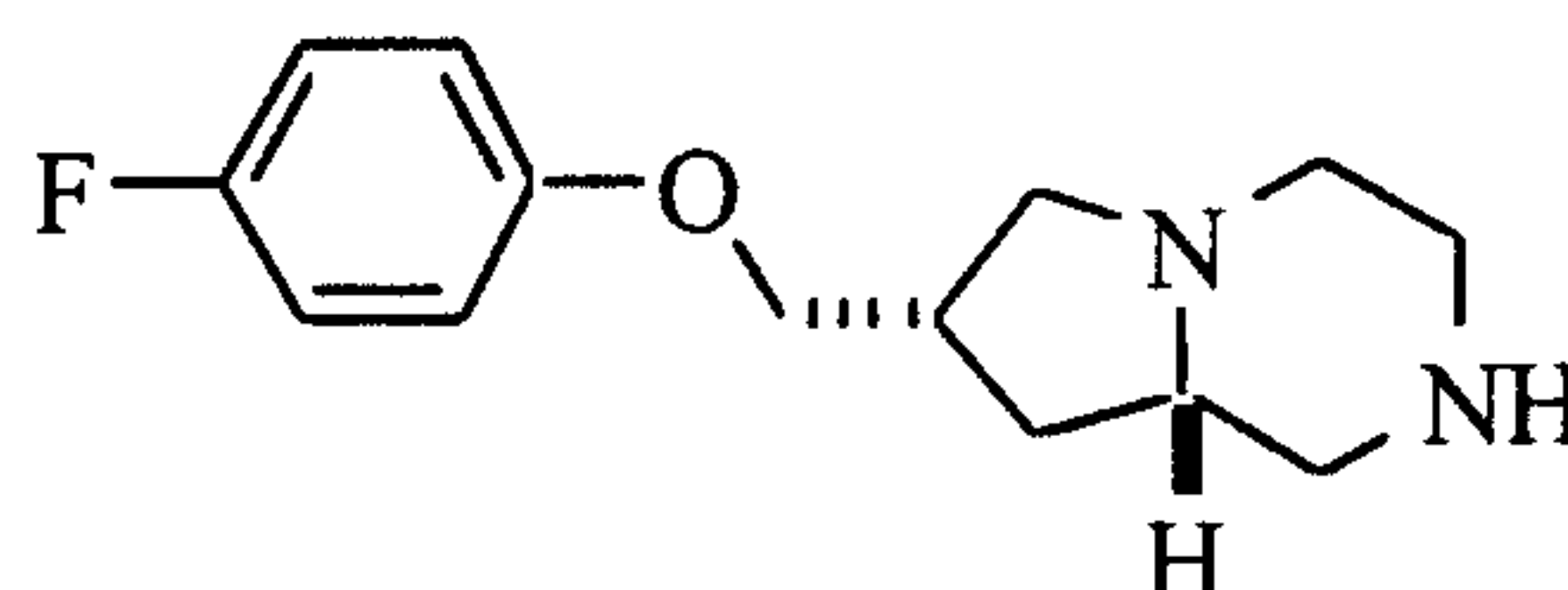
-27-

5 (7RS,8aSR)-7-(4-fluorophenoxy)methyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: ^{13}C NMR (CDCl_3): δ 32.0, 35.5, 51.5, 52.5, 56.4, 57.7, 62.7, 62.9, 72.7, 115.45, 115.55, 115.86, 127.0, 128.2, 129.2, 138.3, 155.1, 155.6, 158.8.

(7SR,8aSR)-7-(4-fluorophenoxy)methyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine: ^{13}C NMR (CDCl_3): δ 31.6, 35.4, 51.6, 52.5, 57.4, 57.6, 61.7, 62.9, 71.6,
10 115.40, 115.51, 115.60, 115.91, 127.0, 128.2, 129.2, 138.2, 155.13, 155.15, 155.7, 158.8.

Preparation 3

(7SR,8aSR)-7-(4-Fluorophenoxy)methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine

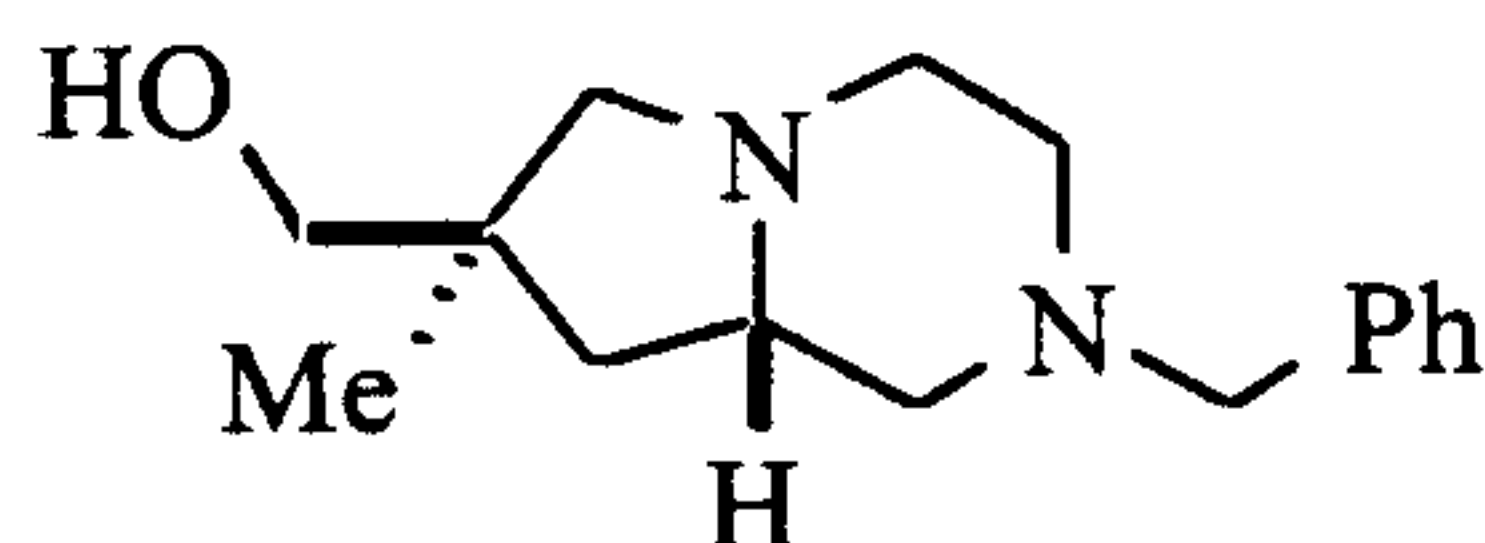


15 A mixture of 1.20 g (3.53 mmol) of (7SR,8aSR)-7-(4-fluorophenoxy)methyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 2), 30 mL of methanol and 2.5 mL of 5.0 M ammonium formate was treated with an aqueous slurry of 0.15 g of 10% palladium on carbon. The mixture was heated at reflux for 48 hours, cooled to ambient temperature, filtered through Celite, and the filtrate was evaporated. The residue was
20 taken up in dilute aqueous ammonium hydroxide and extracted with chloroform (3x). The combined organic phase was dried (magnesium sulfate), filtered and evaporated to give 0.874 g (99%) of the title compound. ^{13}C NMR (CDCl_3): δ 32.0, 34.5, 45.2, 50.9, 53.4, 57.0, 63.7, 72.6, 115.4, 115.5, 115.8, 155.1, 155.6, 158.7. HRMS calc'd for $\text{C}_{14}\text{H}_{20}\text{FN}_2\text{O}$ (MH^+): 251.156, found: 251.155.

25

Preparation 4

(7RS,8aSR)-7-Hydroxymethyl-7-methyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



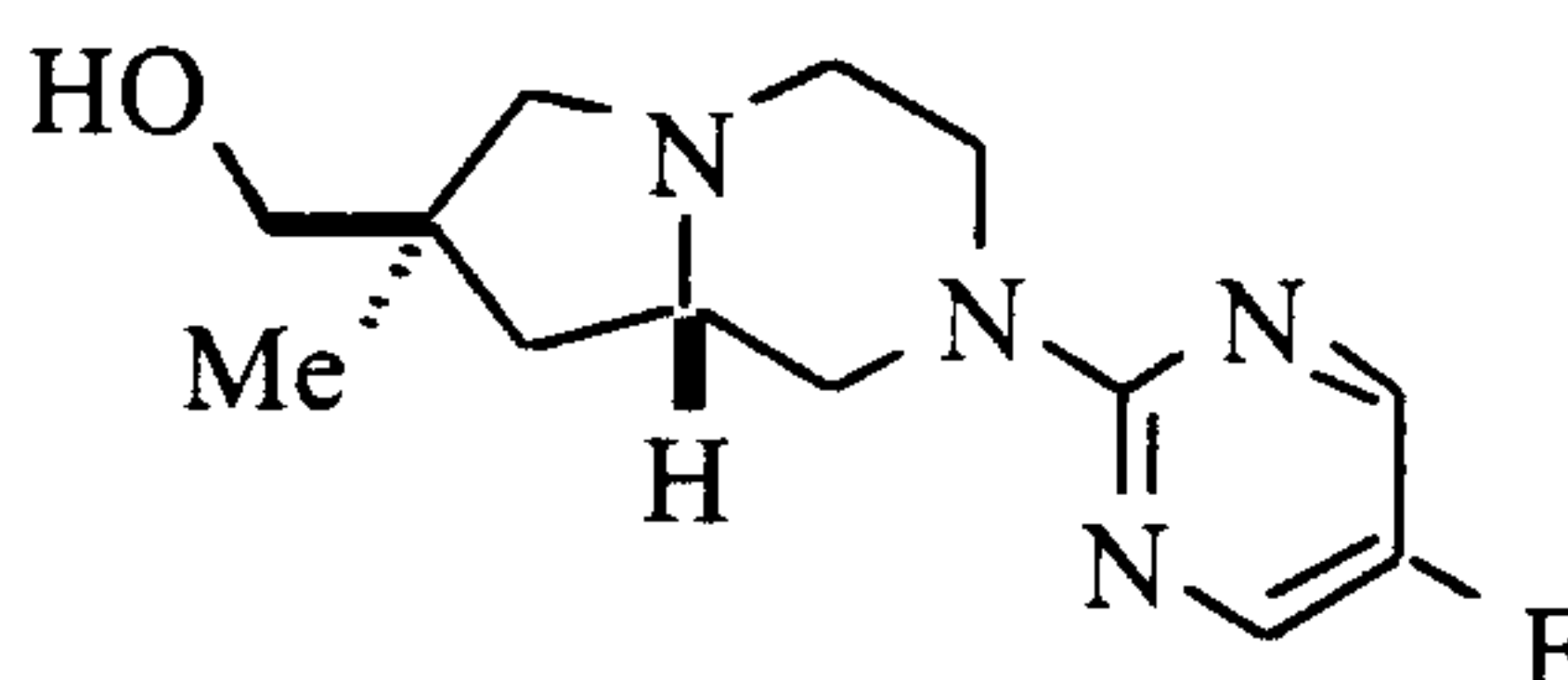
A solution of 3.33 g (11 mmol) of (7RS,8aSR)-7-methoxycarbonyl-7-methyl-2-phenyl-
30 methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazin-1-one (Jones, R. C. F., Howard, K. J., *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2391) in 125 mL of dry THF was added dropwise to a stirred suspension of 1.26 g (33 mmol) of lithium aluminum hydride in 125 mL of dry THF. The solution was stirred for 2 hours at room temperature, and carefully quenched with 1.26 mL of water, 1.26 mL of 15% NaOH, and 3.78 mL of water. After stirring for 30 minutes, the mixture

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- 5 was filtered through Celite, dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography eluting with 9:1 chloroform:methanol gave 1.67g (58%) of the title compound. ^{13}C NMR (base, CDCl_3): δ 25.3, 39.7, 41.8, 51.1, 51.6, 57.1, 62.3, 62.9, 63.3, 71.3, 127.0, 128.2, 128.7, 129.2, 138.3. m/z (MH^+) 261.

Preparation 5

- 10 (7RS,8aSR)-7-Hydroxymethyl-7-methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine

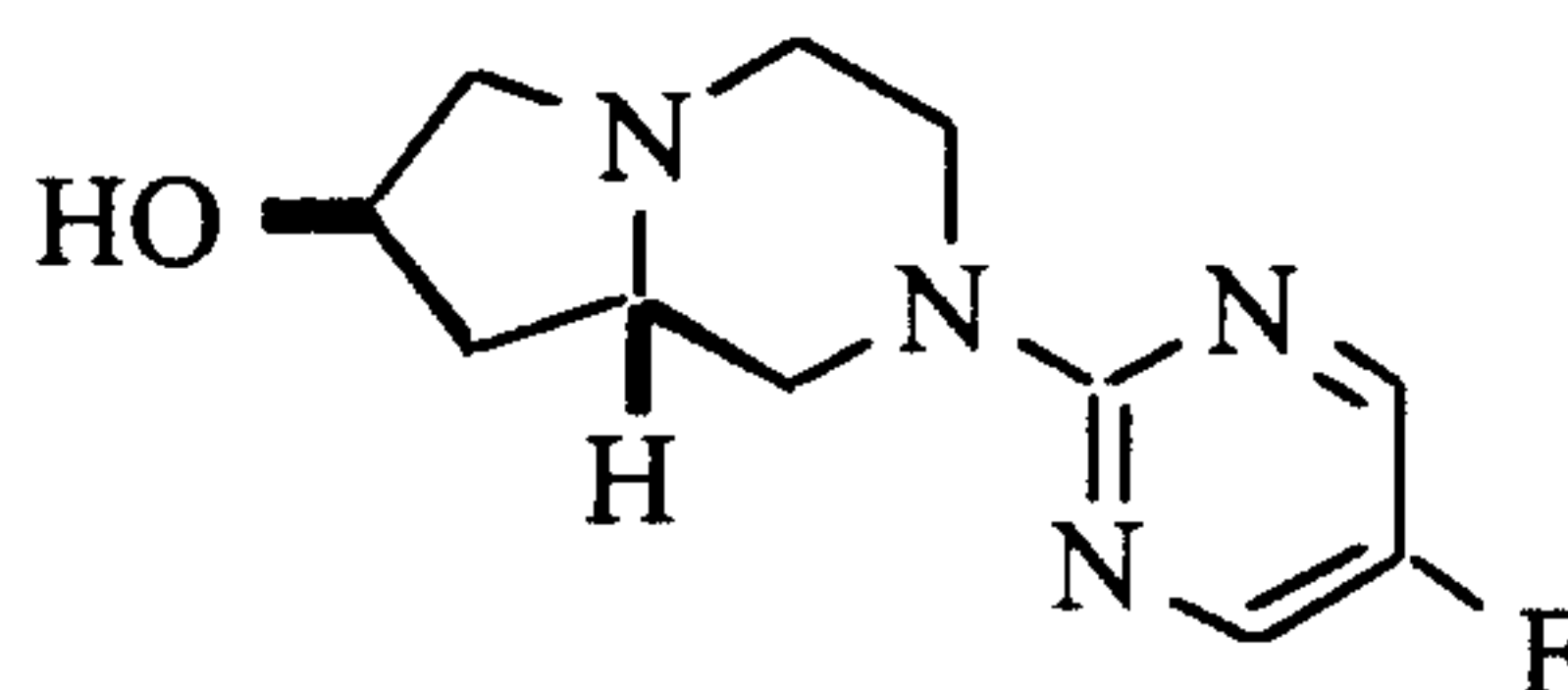


- 15 A solution of 1.65 g (6.35 mmol) of (7RS,8aSR)-7-hydroxymethyl-7-methyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 4) in 20 mL of methanol was mixed with 4.44 mL (22.2 mmol) of 5M aqueous ammonium formate, an aqueous slurry of 0.825 g of 10% palladium on carbon was added and the mixture was stirred at ambient temperature overnight. The solution was filtered through Celite and evaporated to give (7RS,8aSR)-7-hydroxymethyl-7-methyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine of sufficient purity for use in the next step.

- 20 A mixture of (7RS,8aSR)-7-hydroxymethyl-7-methyl-1,2,3,4,6, 7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (1.08g, 6.35 mmol), 0.925 g (6.98 mmol) of 2-chloro-5-fluoropyrimidine (Dunaiskis, A. *et. al.*, *Org. Prep. Proc. Int.*, **1995**, 27, 600-602), and 1.48 g (13.96 mmol) of sodium carbonate and 65 mL of water was heated at 90°C for 72 hours. The solution was cooled and extracted with chloroform (3x). The combined organic layers were dried
25 (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography eluting with chloroform:methanol (95:5) gave 0.80 g (47%) of the title compound. ^{13}C NMR (CDCl_3): δ 25.5, 39.5, 41.7, 43.3, 48.7, 51.2, 62.3, 63.8, 71.0, 144.9, 145.2, 149.8, 153.1, 158.9. m/z (MH^+) 267.

Preparation 6

- 30 (7R,8aS)-7-Hydroxy-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



Step A

5 A solution of 9.75 g (42.0 mmol) of (7R,8aS)-7-hydroxy-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Diafi, L. *et al.*, *J. Het. Chem.*, **1990**, *27*, 2181) and 29.4 mL of 5M ammonium formate in 140 mL of methanol was treated with an aqueous slurry of 4.9 g of 10% palladium on carbon and the mixture was stirred at ambient temperature for 18 hours. The mixture was filtered through Celite and evaporated to give
10 (7R,8aS)-7-hydroxy-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine as a clear oil.

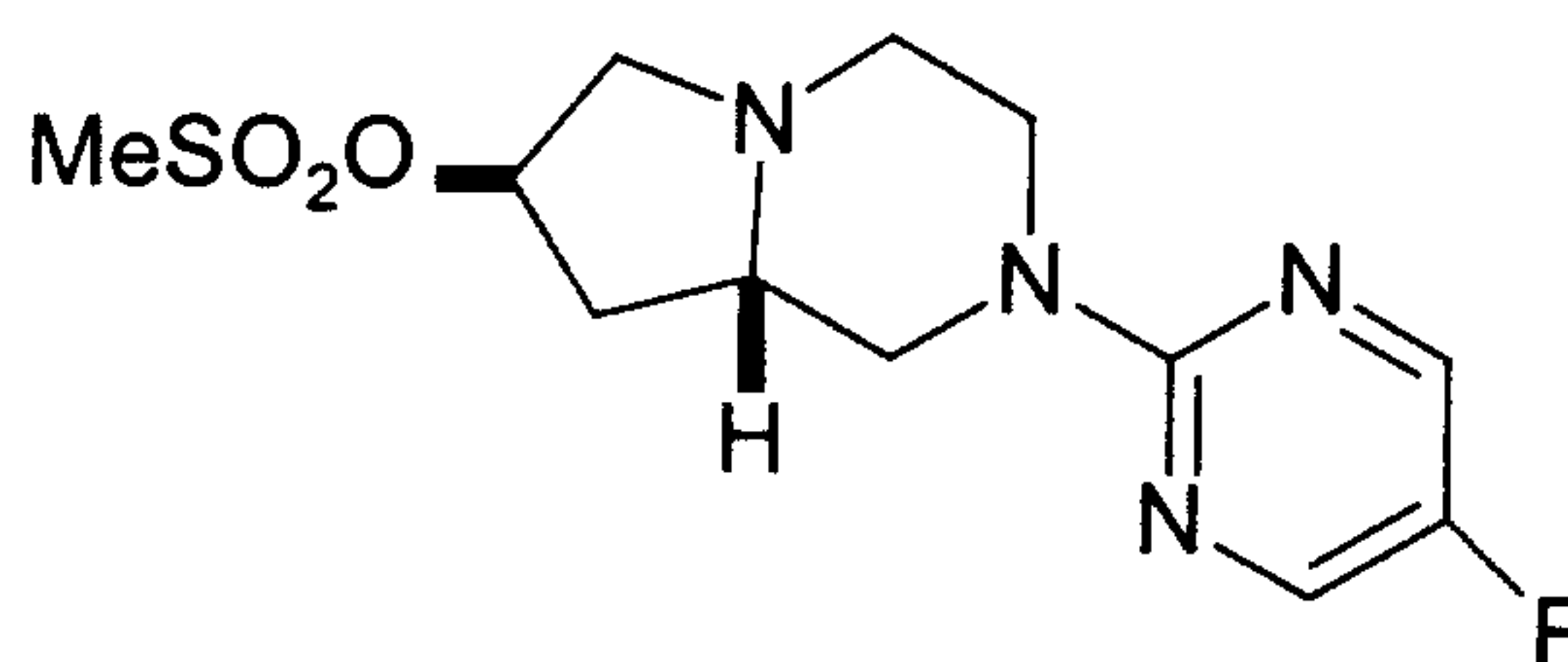
Step B

A mixture of the crude (7R,8aS)-7-hydroxy-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine, 9.96 g (52.5 mmol) of 2-chloro-5-fluoropyrimidine (Dunauskis, A. *et al.*, *Org. Prep. Proc. Int.*, **1995**, *27*, 600-602), 13.4 g (126 mmol) of sodium carbonate and 450 mL of water
15 was heated at 95°C for 72 hours. The mixture was cooled, extracted with chloroform (2x), and the combined organic phase was dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography with 95:5 ethyl acetate:methanol gave 8.54 g (85%) of the title compound. ¹³C NMR (base, CDCl₃): δ 39.1, 43.7, 48.7, 51.0, 60.2, 62.9, 69.4, 144.95, 145.24, 149.9, 153.2, 158.9. m/z (MH⁺) 239.

20

Preparation 7

(7R,8aS)-7-Methanesulfonyloxy-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine

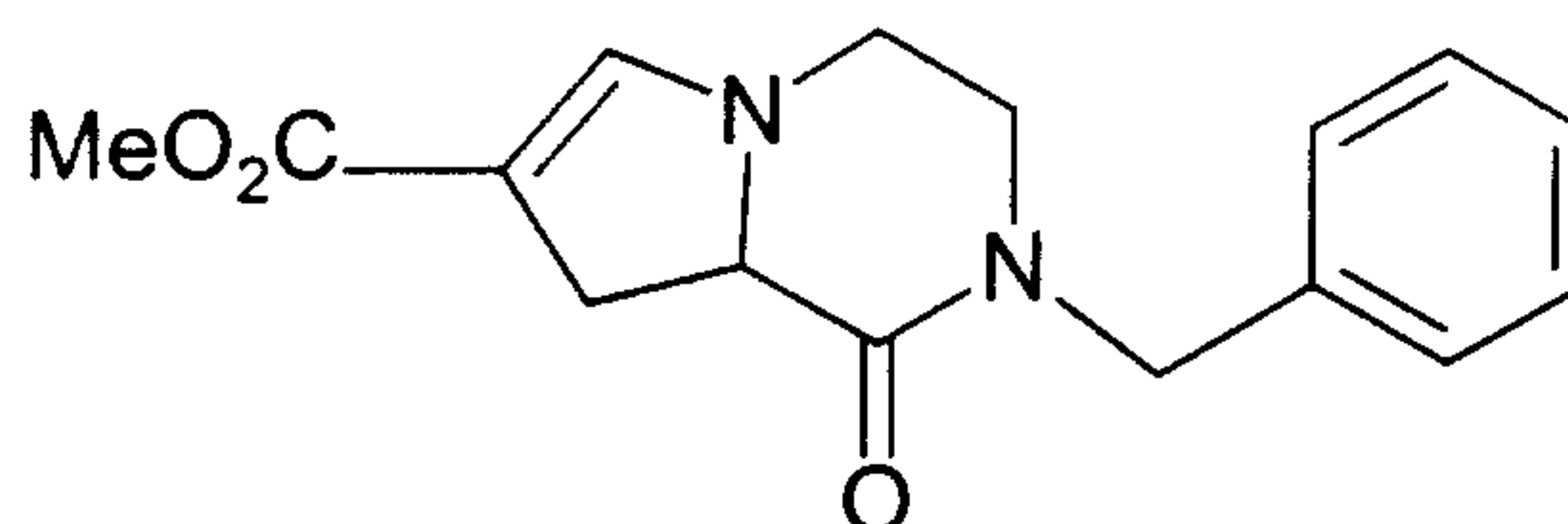


A solution of 1.00 g (4.20 mmol) of (7R,8aS)-7-hydroxy-2-(5-fluoropyrimidin-2-yl)-
25 1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 6) and 0.644 mL (4.62 mmol) of triethylamine in 40 mL of methylene chloride was chilled to 0°C and 0.34 mL (4.41 mmol) of methanesulfonyl chloride in 20 mL of methylene chloride was added slowly. After 30 minutes, water was added and the pH adjusted to 10 with 1M NaOH. The layers were separated, the organic phase was washed with water (2x), dried (magnesium sulfate), filtered and
30 evaporated to give 1.15 g (86%) of the title compound of sufficient purity for use in subsequent reactions. m/z (MH⁺) 317.

5

Preparation 8

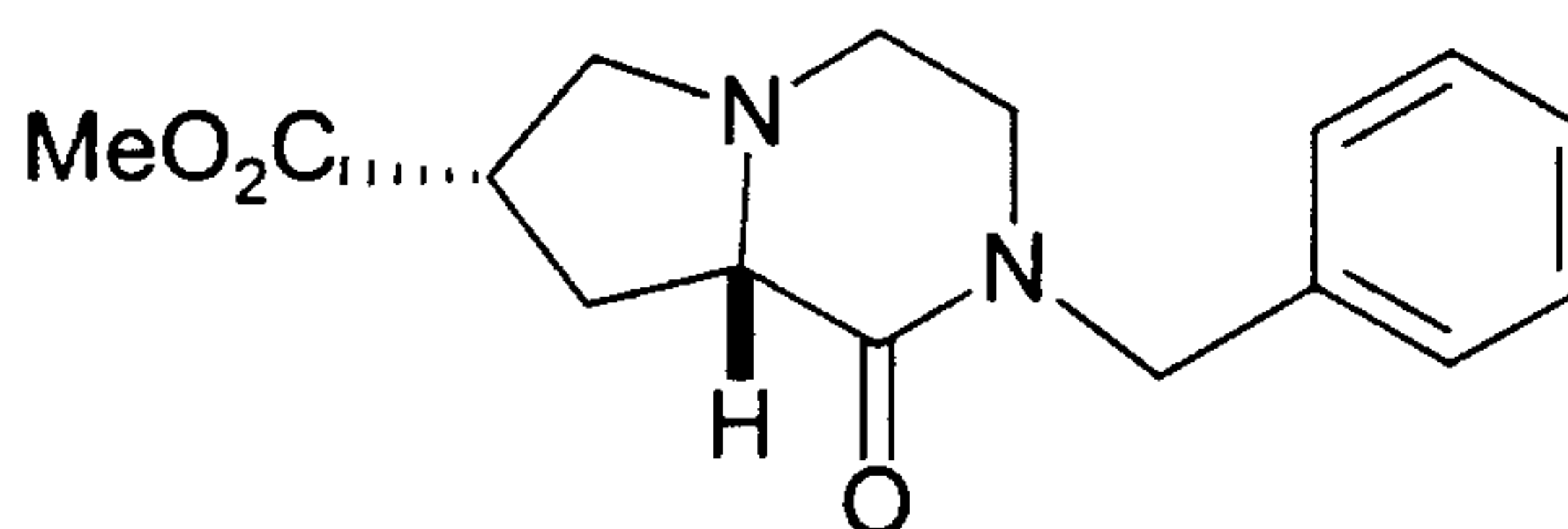
7-Methoxycarbonyl-2-phenylmethyl-1,2,3,4,8,8a-hexahydro-pyrrolo[1,2-a]pyrazin-1-one



A solution of 8.6 g (27 mmol) of dimethyl 2-phenylmethyl-2,3,5,6,7,7a-hexahydro-1H-pyrrolo[1,2-c]imidazol-5,7-dioate (Jones, R. C. F., Howard, K., *J. J. Chem. Soc. Perkin Trans. 1*, **1993**, 2391) and 2.0 mL (13 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 150 mL of methanol was heated at reflux for 16 hours. The solvent was evaporated, the residue was dissolved in ethyl acetate and washed with water (2x), dried (magnesium sulfate), filtered and evaporated to give 6.45 g (84%) of the title compound. ¹³C NMR (CDCl₃): δ 32.9, 43.9, 45.6, 50.5, 50.8, 63.1, 106.0, 127.7, 128.0, 128.8, 136.2, 148.1, 165.7, 170.0. HRMS calc'd for C₁₆H₁₉N₂O₃ (MH⁺): 287.1396, found: 287.1406.

Preparation 9

(7SR,8aSR)-7-Methoxycarbonyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazin-1-one



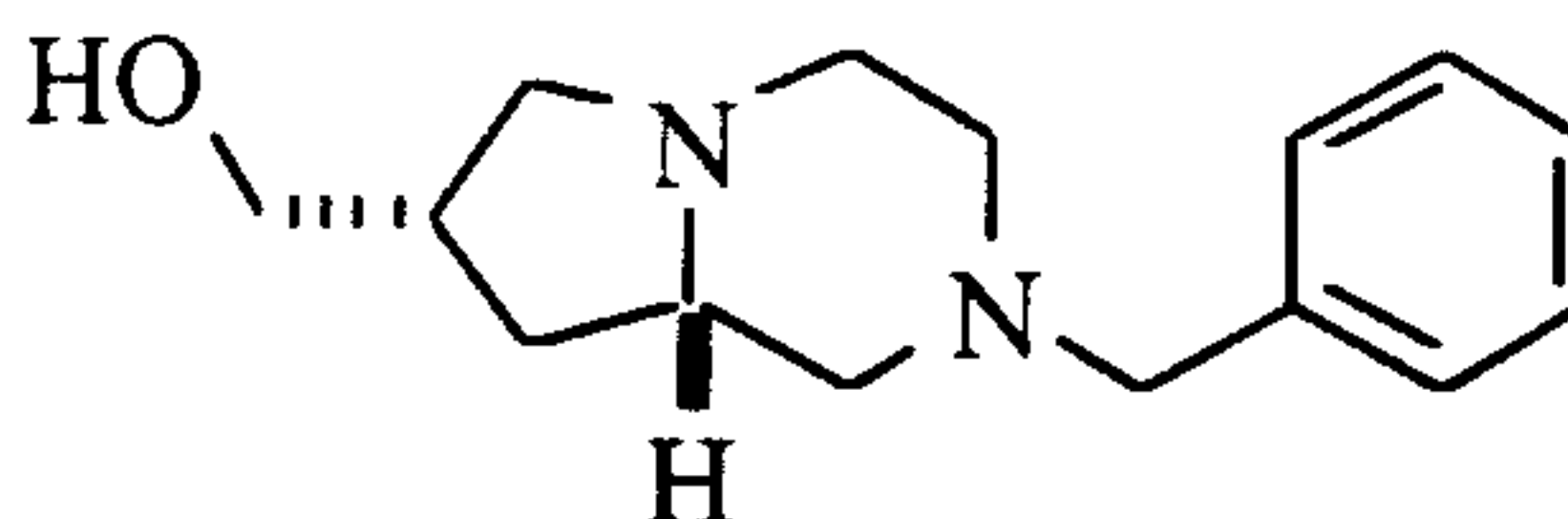
20

A mixture of 40.0 g (140 mmol) of 7-methoxycarbonyl-2-phenylmethyl-1,2,3,4,8,8a-hexahydro-pyrrolo[1,2-a]pyrazin-1-one (Preparation 8) and 10 g of 5% Pd on charcoal in 600 mL of ethyl acetate was shaken in a Parr apparatus under 50 psi of hydrogen gas for 6.5 hours. The mixture was filtered through Celite, and the filtrate was evaporated to give 38.4 g (95%) of the title compound. ¹³C NMR (CDCl₃): δ 31.8, 41.4, 44.8, 46.5, 49.6, 52.1, 55.2, 64.0, 127.5, 128.1, 128.7, 128.8, 136.6, 169.6, 174.8. HRMS calc'd for C₁₆H₂₂N₂O₃ (MH⁺): 289.1552, found: 289.1549.

5

Preparation 10

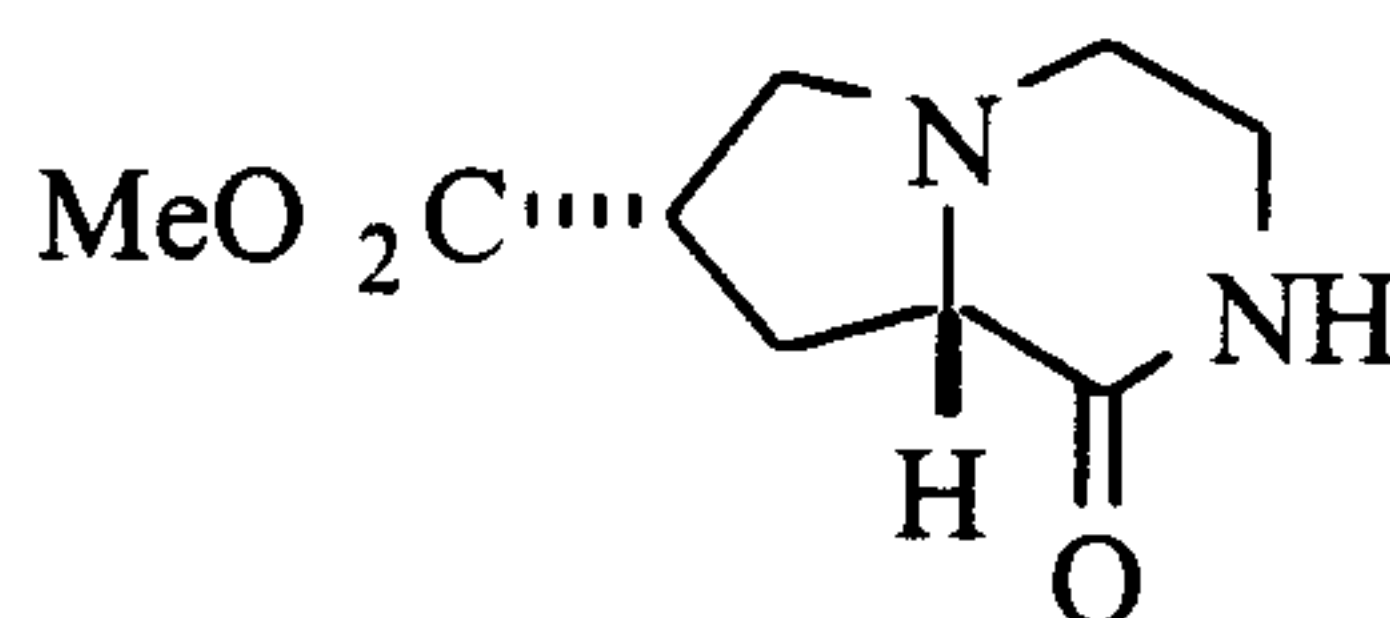
(7SR,8aSR)-7-Hydroxymethyl-2-phenylmethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



A three-neck flask fitted with a reflux condenser and dropping funnel was charged
 10 with 100 mL of dry THF and 2.4 g (63 mmol) of lithium aluminum hydride (LAH), and a
 solution of 6.0 g (21 mmol) of (7SR,8aSR)-7-methoxycarbonyl-2-phenylmethyl-
 1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazin-1-one (Preparation 9) in 60 mL of dry THF
 was placed in the dropping funnel. The LAH suspension was heated to reflux and the ester
 solution was added over a 30-60 minutes period. Reflux continued for another 4 hours, the
 15 reaction was cooled in an ice bath and quenched by careful addition of 2.4 mL of water, 2.4
 mL of 15% sodium hydroxide, and 7.2 mL of water. Stirring continued until a white precipitate
 formed, the mixture was filtered through Celite, and the filtrate was evaporated to give 5.0 g
 (97%) of the title compound of sufficient purity for use in subsequent reactions. ¹³C NMR
 (CDCl₃): δ 31.1, 37.2, 51.3, 52.6, 57.4, 62.8, 62.9, 67.4, 127.0, 128.2, 129.2, 138.2. HRMS
 20 calc'd for C₁₅H₂₃N₂O (MH⁺) 247.1810, found: 247.1800.

Preparation 11

(7S,8aS)-7-Methoxycarbonyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazin-1-one



A mixture of 77.3 g (16 mmol) of N-benzyloxycarbonyl-*cis*-4-carboxy-L-proline
 25 dimethyl ester (Bridges, R. J. *et al.*, *J. Med. Chem.*, **1991**, 34, 717) and 169 mL (55 mmol) of
 5M ammonium formate in 1000 mL of methanol was treated with an aqueous slurry of 15.5 g
 of 10% palladium on carbon. After 4 hours, the mixture was filtered through Celite, the filtrate
 was concentrated to about 500 mL, saturated with sodium bicarbonate, and extracted with
 chloroform (5x). The aqueous layer was saturated with sodium chloride and extracted with
 30 chloroform (3x). The combined organic phase was dried (magnesium sulfate), filtered and
 evaporated to give 39.8 g (88%) of *cis*-4-carboxy-L-proline dimethyl ester.

A mixture of 39.8 g (213 mmol) of *cis*-4-carboxy-L-proline dimethyl ester, 40.2 g (213
 mmol) of 2-(phthalimido)acetaldehyde (Preparation 12), and 17.5 g (213 mmol) of anhydrous
 sodium acetate in 2150 mL of dry methylene chloride was treated with 67.7 g (319 mmol) of
 35 sodium (triacetoxo)borohydride in small portions over a 1 hour period. The solution was

-32-

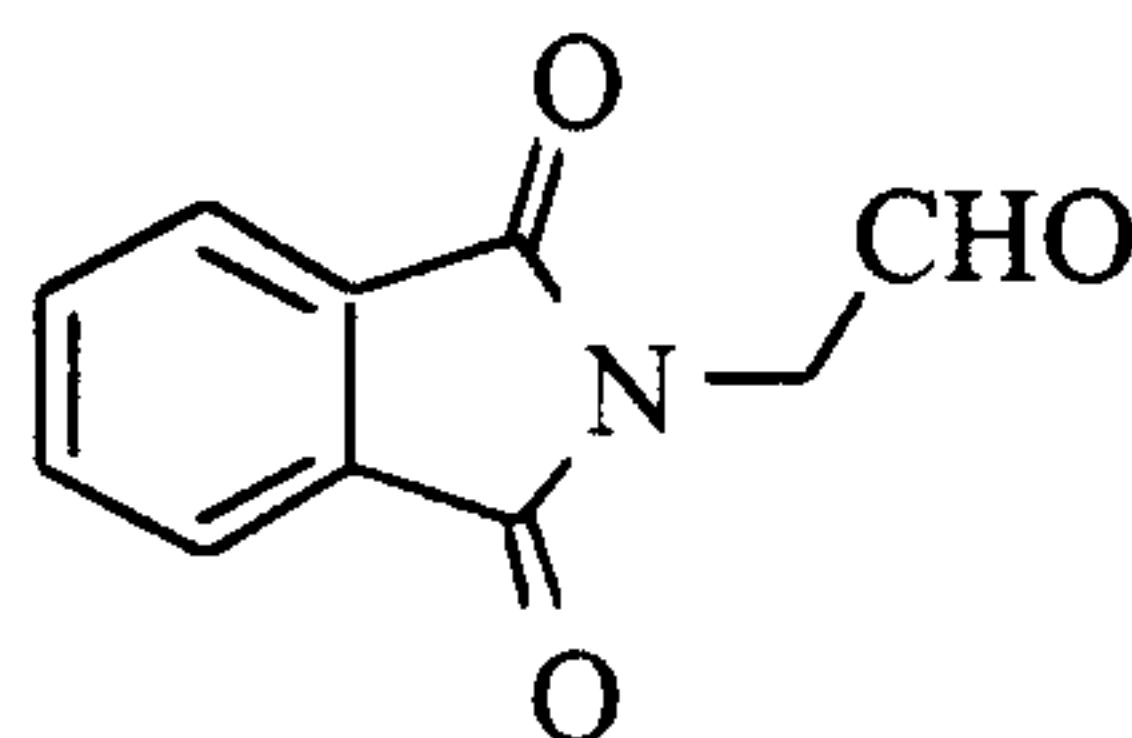
5 stirred for 16 hours, water was added, and the pH adjusted to 10 with 1M sodium hydroxide. The organic phase was separated, dried (magnesium sulfate), filtered and evaporated to give 73.8 g (96%) of N-(2-(phthalimido)ethyl-*cis*-4-carboxy-L-proline dimethyl ester.

A solution of 73.8 g (205 mmol) of N-(2-(phthalimido)ethyl-*cis*-4-carboxy-L-proline dimethyl ester and 44.1 mL (513 mmol) of 40% aqueous methyl amine in 3100 mL of methanol was stirred at ambient temperature for 16 hours. The solvent was evaporated and the crude product purified by flash silica gel chromatography starting with 4:1 diethyl ether:methanol and ending with 2:1 diethyl ether: methanol to give 37.0 g (91%) of the title compound of sufficient purity for use in subsequent reactions. m/z (MH⁺) 199.

Another sample of the title compound was purified further by flash silica gel chromatography with ethyl ether:methanol (9:1 to 8:2) and formed a white solid on standing. Mp 70-74°C. ¹³C NMR (d₆-DMSO): δ 32.2, 40.5, 42.4, 46.6, 52.6, 55.8, 64.0, 173.9, 176.2. HRMS calc'd for C₉H₁₅N₂O₃ (MH⁺):199.1083, found: 199.1091.

Preparation 12

2-(Phthalimido)acetaldehyde



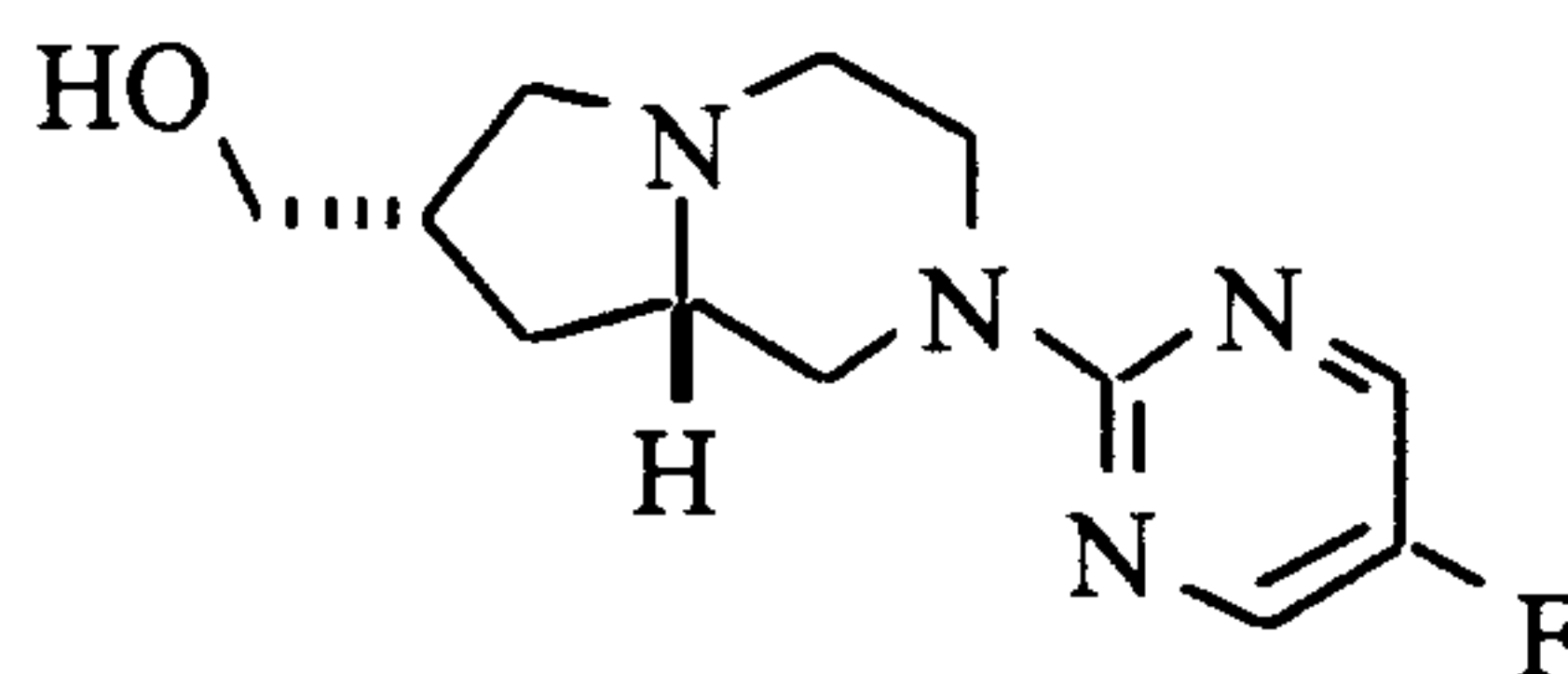
20

A solution of 50.0 g (190 mmol) of 2-(phthalimido)acetaldehyde diethyl acetal in 300 mL of toluene was treated with 150 mL of 50% aqueous trifluoroacetic acid and the mixture was stirred vigorously at ambient temperature for 72 hours. The solution was concentrated *in vacuo* and 100 mL of ethyl acetate was added. The white precipitate was filtered off and washed with ice-cold ethyl acetate (100 mL) to give 30.0 g (78%) of the title compound.

25

Preparation 13

(7S,8aS)-7-Hydroxymethyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



30

Step A

A solution of 1.75 g (8.84 mmol) of (7S,8aS)-7-methoxycarbonyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazin-1-one (Preparation 11) in 100 mL of THF was added dropwise to a suspension of 0.67 g (18 mmol) of lithium aluminum hydride in 100 mL of refluxing

-33-

5 tetrahydrofuran (THF). After stirring for 1 hour, the solution was cooled and carefully quenched with 0.67 mL of water, 0.67 mL of 15% sodium hydroxide, and 2.0 mL of water. The precipitate was filtered and the filtrate was concentrated to give 1.4 g of (7S,8aS)-7-hydroxymethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine of sufficient purity for use in subsequent reactions.

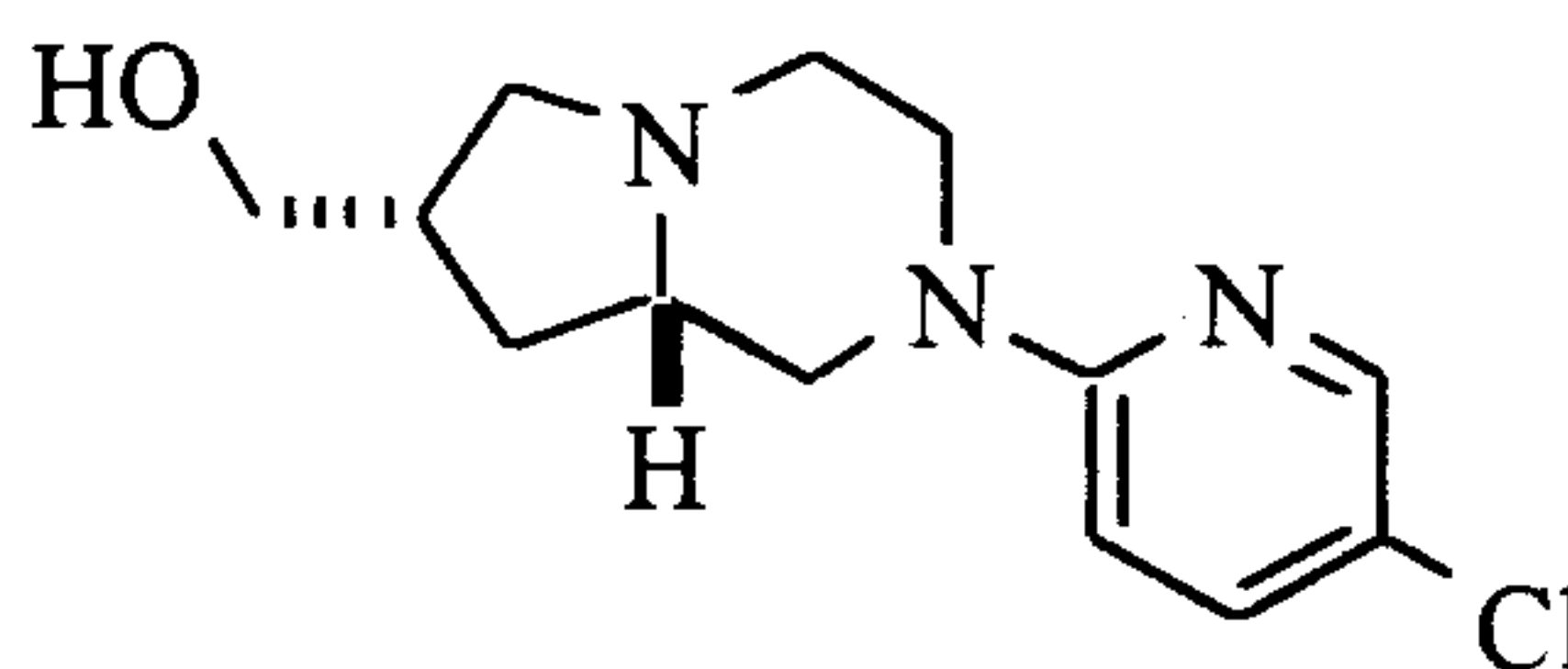
10 Step B

A mixture of 1.38 g (8.84 mmol) of (7S,8aS)-7-hydroxymethyl-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine, 1.30 g (9.87 mmol) of 2-chloro-5-fluoropyrimidine (Dunaïskis, A. et al., *Org. Prep. Proc. Int.*, 1995, 27, 600-602), and 2.85 g (26.9 mmol) of sodium carbonate and 90 mL of water was heated at 95 °C for 16 hours. The solution was
 15 cooled and extracted with chloroform (2x), the combined organic phase was dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography with 9:1 chloroform:methanol gave 0.97 g (43%) of the title compound. Mp 123-124°C. m/z (MH⁺) 253. ¹³C NMR (CDCl₃): δ 30.9, 37.1, 43.8, 48.8, 51.3, 57.5, 62.6, 67.2, 144.9, 145.2, 149.9, 153.2, 158.8.

20

Preparation 14

(7S,8aS)-7-Hydroxymethyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine

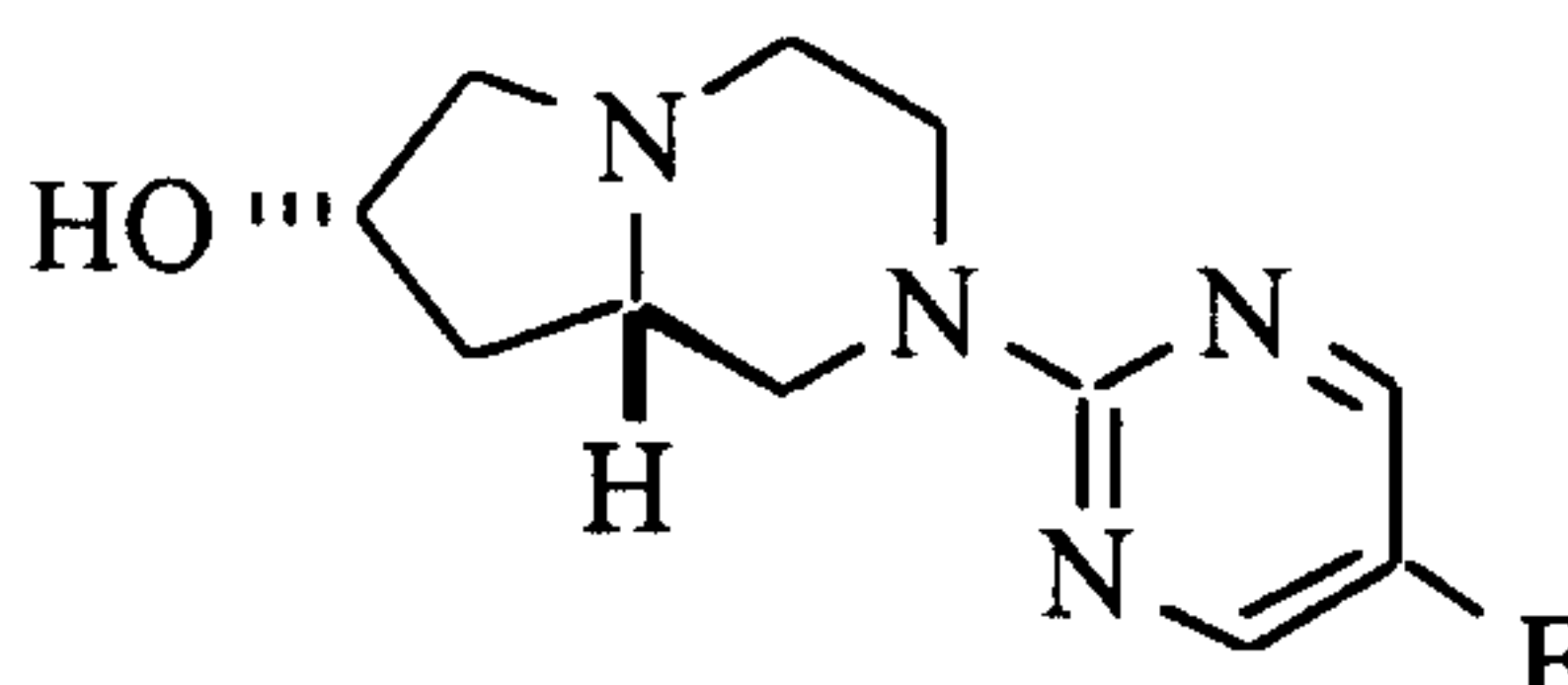


A mixture of 0.50 g (3.2 mmol) of (7S,8aS)-7-hydroxymethyl-1,2,3,4,6,7,8,8a-
 25 octahydro-pyrrolo[1,2-a]pyrazine (Preparation 13, Step A), 2.37 g (16.0 mmol) of 2,5-dichloropyridine, 0.85 g (8.0 mmol) of sodium carbonate and 35 mL of isoamyl alcohol was refluxed for 48 hours. The hot solution was filtered and the filtrate evaporated. Purification by flash silica gel chromatography with 9:1 chloroform:methanol gave 0.25 g (29%) of the title compound. ¹³C NMR (CDCl₃): δ 31.1, 37.3, 44.7, 49.7, 51.2, 57.2, 62.5, 66.9, 107.9, 119.9,
 30 137.1, 146.1, 157.6. m/z (MH⁺) 268.

5

Preparation 15

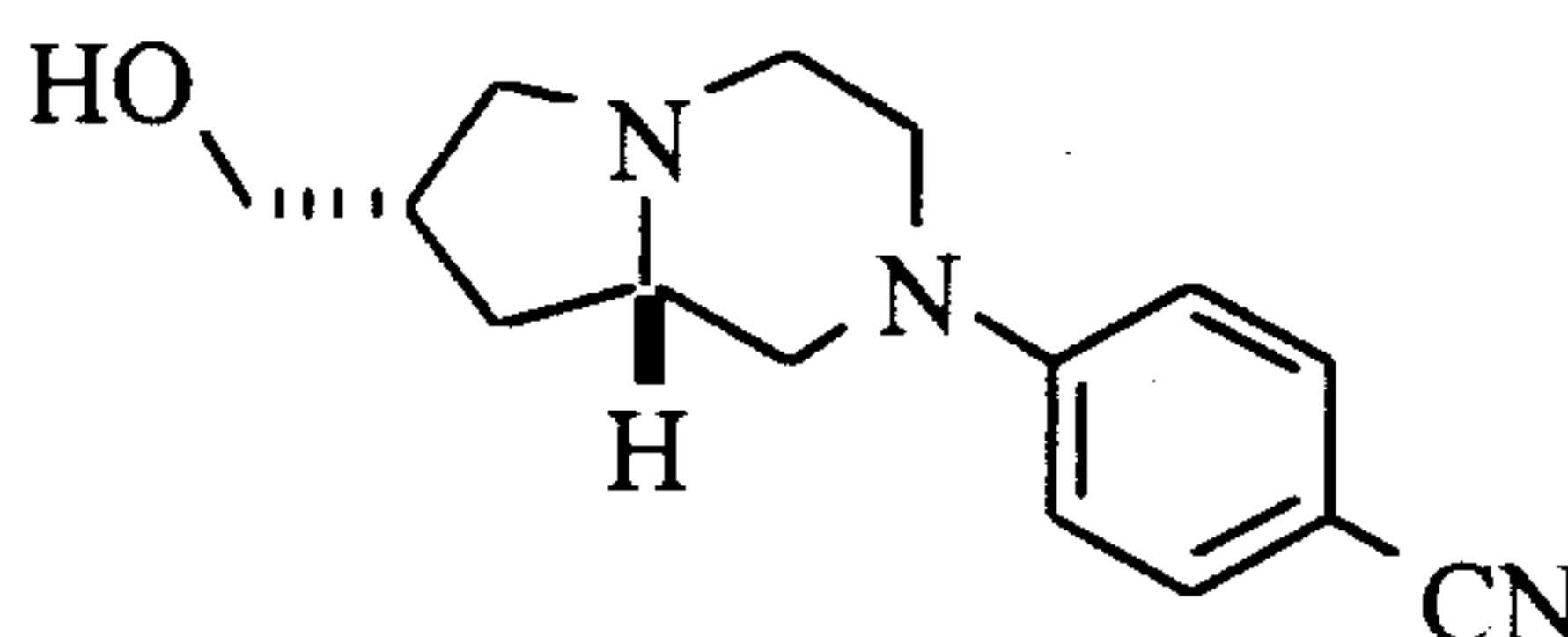
(7S,8aS)-7-Hydroxy-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



A solution of 1.58 g (4.61 mmol) of (7S,8aS)-2-(5-fluoropyrimidin-2-yl)-
 10 1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazin-7-yl benzoate (Example 9) in 200 mL of
 methanol was treated with 50 mL of 15% aqueous sodium hydroxide. After 30 minutes, the
 solvent was removed and the residue partitioned between water and ethyl acetate. The layers
 were separated, the organic phase was dried (magnesium sulfate), filtered and evaporated to
 give 0.922 g (84%) of the title compound. ¹³C NMR (CDCl₃): δ 39.4, 43.7, 49.0, 51.2, 62.2,
 15 63.6, 69.9, 144.9, 145.2, 149.9, 153.2, 158.9. m/z (MH⁺) 239.

Preparation 16

(7S,8aS)-7-Hydroxymethyl-2-(4-cyanophenyl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine

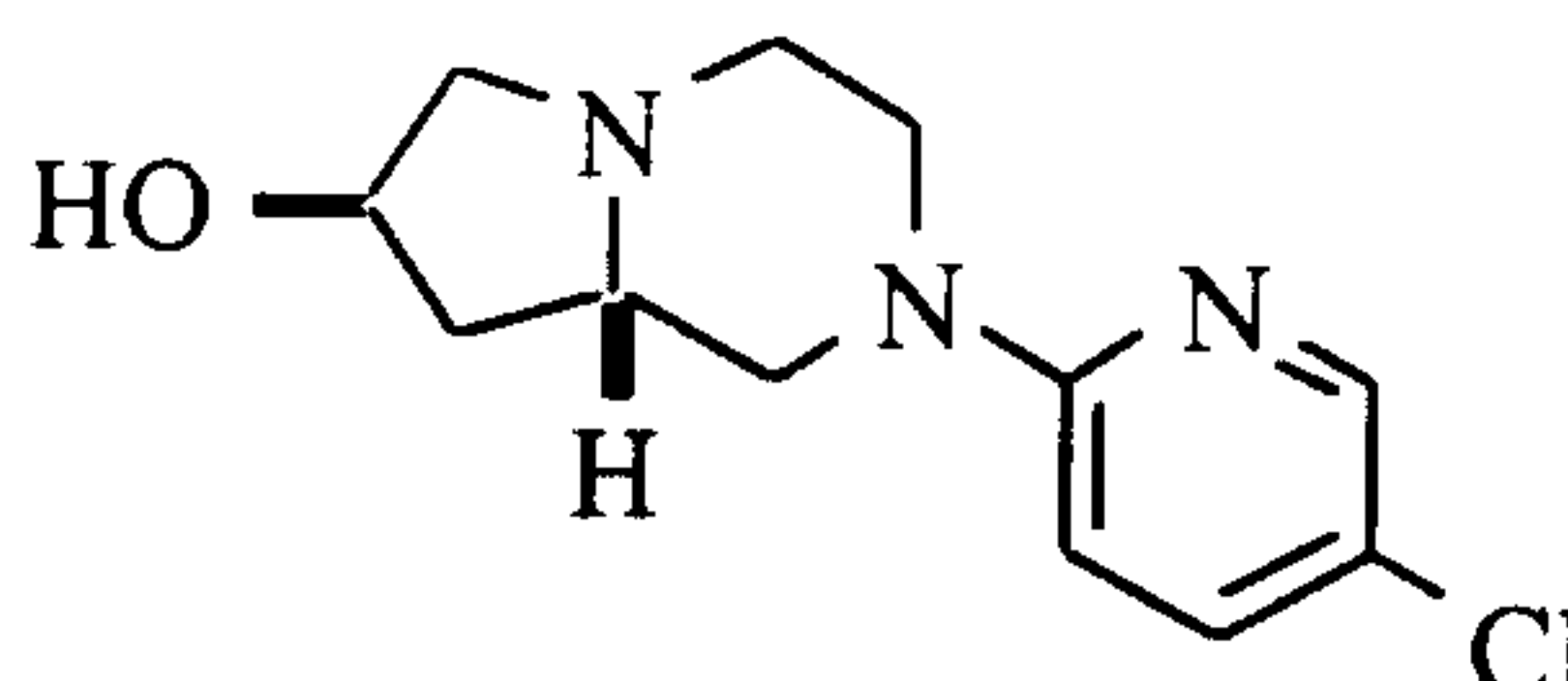


A mixture of 1.5 g (9.6 mmol) of (7S,8aS)-7-hydroxymethyl-1,2,3,4,6,7,8,8a-
 20 octahydro-pyrrolo[1,2-a]pyrazine (Preparation 13, Step A), 1.75 g (14.4 mmol) of 4-
 fluorobenzonitrile and 2.04 g (19.2 mmol) of sodium carbonate in 10 mL of DMSO was heated
 at 80°C for 16 hours. The solution was cooled to room temperature, diluted with water and
 extracted with 1:1 ethyl acetate:diethyl ether (3x). The combined organic phase was dried
 25 (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography
 with 9:1 chloroform: methanol gave 0.925 g (37%) of the title compound. ¹³C NMR (CDCl₃):
 δ 31.1, 37.2, 46.7, 51.0, 51.8, 57.6, 62.3, 67.3, 100.1, 114.3, 120.0, 133.5, 153.4. m/z (MH⁺)
 258.

5

Preparation 17

(7R,8aS)-7-Hydroxy-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine

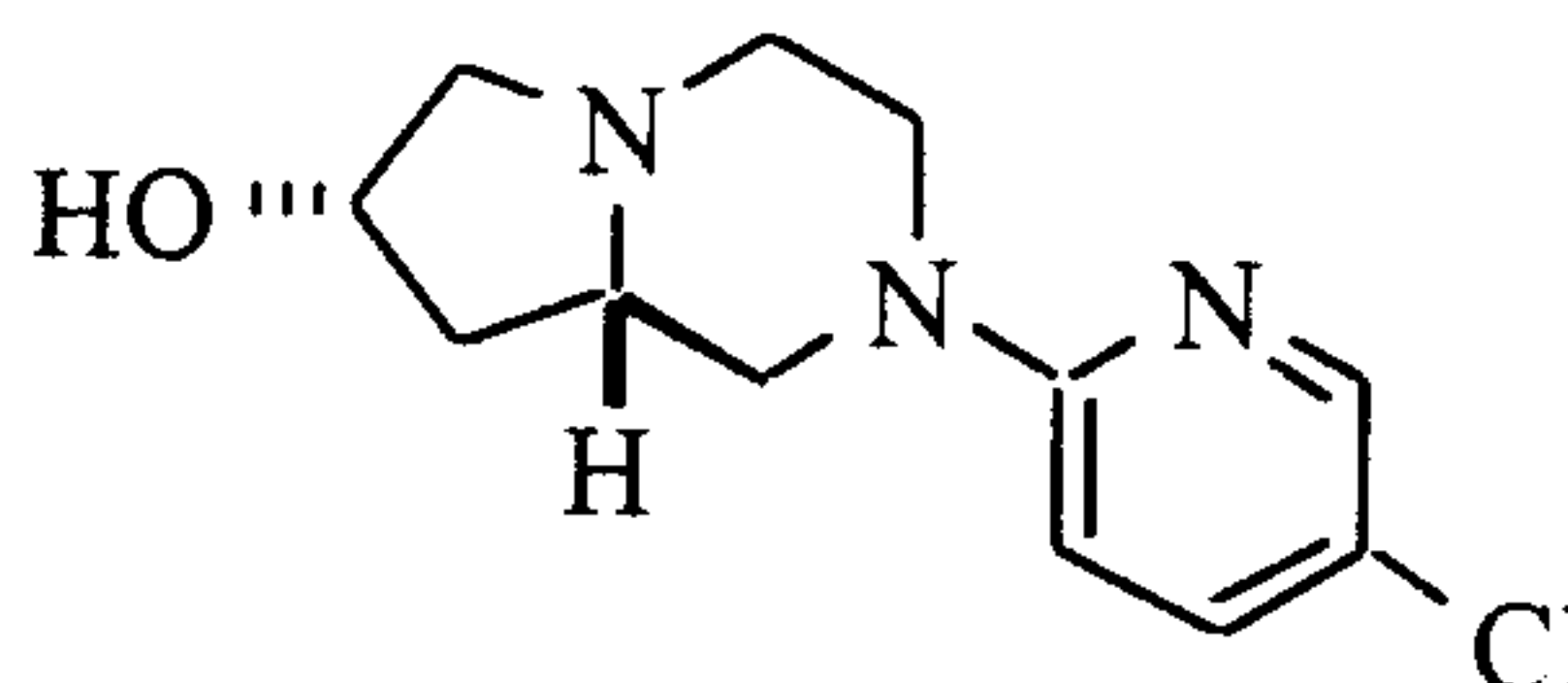


A mixture of 3.81 g (26.8 mmol) of (7R,8aS)-7-hydroxy-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine (Preparation 6, Step A), 19.8 g (134 mmol) of 2,5-dichloropyridine, 7.10 g (67.0 mmol) of sodium carbonate and 275 mL of isoamyl alcohol was heated at reflux for 72 hours. The mixture was cooled to about 100°C, filtered hot, and the filtrate concentrated *in vacuo*. Purification of the residue by flash silica gel chromatography with 9:1 chloroform:methanol gave 0.63 g (9%) of the title compound of sufficient purity for use in subsequent reactions. m/z (MH⁺) 254.

15

Preparation 18

(7S,8aS)-7-Hydroxy-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine



A solution of 0.52 g (1.45 mmol) of (7S,8aS)-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazin-7-yl benzoate (Example 17) in 50 mL of methanol was treated with 50 mL of 15% aqueous sodium hydroxide and stirred at ambient temperature for 30 minutes. The solvent was concentrated by half *in vacuo* and the residue extracted with chloroform (3x). The combined organic phase was dried (magnesium sulfate), filtered and evaporated. Purification by flash silica gel chromatography with 9:1 chloroform:methanol gave 0.25 g (68%) of the title compound. Mp (base) 167-168°C. m/z (MH⁺) 254.

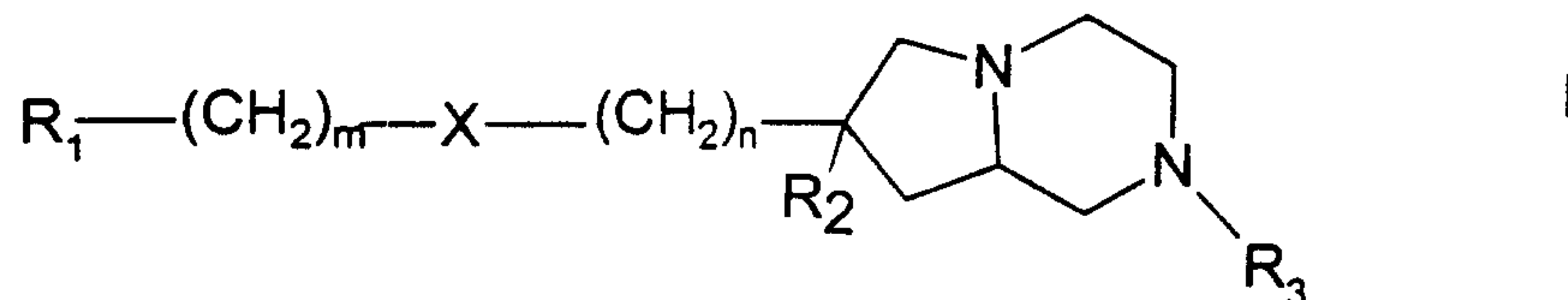
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25

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A medicine for treating a disorder or condition that can be treated by altering serotonin mediated neurotransmission in a mammal which comprises:

- (a) a pharmaceutically acceptable carrier or diluent, and
- (b) an amount effective in treating such disorder or condition of a compound of formula I:



(wherein R_1 is phenyl, naphthyl, benzoxazolonyl, indolyl, indolonyl, benzimidazolyl, quinolyl; furyl, benzofuryl, thienyl, benzothienyl, oxazolyl or benzoxazolyl;

R_2 is H or (C₁-C₆)alkyl;

R_3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl;

wherein each group of R_1 and R_3 may be independently and optionally substituted with one to four substituents independently selected from the groups consisting of fluoro, chloro, bromo, iodo, cyano, nitro, thiocyno, -SR₄, -SOR₄, -SO₂R₄, -NHSO₂R₄, (C₁-C₆)alkoxy, -NR₄R₅, -NR₄COR₅, -CONR₄R₅, phenyl, -COR₄, -COOR₄, (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one to six halogens, (C₃-C₆)cycloalkyl, and trifluoromethoxy;

X is O, S, SO, SO₂, NR₄, C=O, CH(OH), CHR₄,



R_4 is H or (C₁-C₆)alkyl;

R_5 is H or (C₁-C₆)alkyl;

m is 0, 1 or 2; and

n is 0, 1 or 2); or a pharmaceutically acceptable salt thereof.

2. A medicine according to claim 1, wherein R_1 is phenyl, naphthyl, benzoxazolonyl, indolyl, indolonyl, benzimidazolyl, or quinolyl; and R_1 and R_3 may be independently substituted with up to three substituents independently selected from the group consisting of fluoro, chloro, bromo, iodo, cyano, -NR₄R₅,

(C₁-C₆)alkoxy, -COOR₄, -CONR₄R₅, (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one to six halogens, (C₃-C₆)cycloalkyl, and trifluoromethoxy;

R₂ is H or CH₃;

X is O, C=O, CHOH, -C(=O)O-, or CH₂;

m is 0, or 1; and

n is 0 or 1.

3. A medicine according to claim 2, wherein:

R₁ is phenyl or substituted phenyl;

R₃ is substituted or unsubstituted phenyl, pyridinyl, or pyrimidinyl; and

X is O, -C(=O)O-, or CH₂.

4. A medicine according to claim 3, wherein:

R₂ is H;

X is O;

m is 0; and

n is 1.

5. A medicine according to claim 4, wherein:

R₁ is fluorophenyl, cyanophenyl or (trifluoromethyl)phenyl; and

R₃ is chloropyridinyl.

6. A medicine according to claim 4, wherein:

R₁ is fluorophenyl, cyanophenyl or (trifluoromethyl)phenyl; and

R₃ is fluoropyrimidinyl.

7. A medicine according to claim 5, wherein:

R₃ is 5-chloro-2-pyridinyl.

8. A medicine according to claim 6, wherein:

R₃ is 5-fluoro-2-pyrimidinyl.

9. A medicine according to claim 1, wherein the compound of formula I is

(7S,8aS)-7-(4-fluorophenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine.

10. A medicine according to claim 1, wherein the compound of formula I is

(7S,8aS)-7-(3-cyanophenoxy)methyl-2-(5-chloropyridin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine.

11. A medicine according to claim 1, wherein the compound of formula I is (7S,8aS)-7-(4-fluorophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine.
12. A medicine according to claim 1, wherein the compound of formula I is (7S,8aS)-7-(3-(trifluoromethyl)phenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine.
13. A medicine according to claim 1, wherein the compound of formula I is (7S,8aS)-7-(3-cyanophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine.
14. A medicine according to claim 1, wherein the compound of formula I is (7S,8aS)-7-(4-cyanophenoxy)methyl-2-(5-fluoropyrimidin-2-yl)-1,2,3,4,6,7,8,8a-octahydro-pyrrolo[1,2-a]pyrazine.
15. A medicine according to any one of claims 1 to 14, which is in a dosage unit form for human use, and contains the compound of formula I or salt thereof at a daily dose of 1 to 1,000 mg.
16. A medicine according to any one of claims 1 to 15, which is for treating migraine, headache or cluster headache.
17. A medicine according to any one of claims 1 to 15, which is for treating a disorder selected from anxiety, depression, dysthymia, major depressive disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, avoidant personality disorder, borderline personality disorder and phobias.
18. A medicine according to any one of claims 1 to 15, which is for treating a disorder of cognition, memory or learning.
19. A medicine according to any one of claims 1 to 15, which is for treating anxiety or depression associated with senile dementia or Alzheimer's disease.

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20. A medicine according to any one of claims 1 to 15, which is for treating cancer.

21. A medicine according to claim 20, wherein the cancer is prostate cancer.

5 22. A medicine according to any one of claims 1 to 15, which is for treating cerebral infarct, ischemia or traumatic head injury.

23. A medicine according to claim 22, which further comprises a (5HT₂) receptor antagonist, or a
10 pharmaceutically acceptable salt thereof.

24. A medicine according to any one of claims 1 to 15, which is for treating a sexual disorder.

25. A medicine according to any one of claims 1 to 15, which is for treating dizziness.

15 26. A medicine according to any one of claims 1 to 15, which is for treating an eating disorder.

27. A medicine according to any one of claims 1 to 15, which is for treating pain.

28. A medicine according to claim 17, which further
20 comprises a serotonin reuptake inhibitor.

29. A medicine according to claim 19, which further comprises a serotonin reuptake inhibitor.

30. A medicine according to any one of claims 1 to 15, which is for treating attention deficit hyperactivity
25 disorder.

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31. A medicine according to claim 23, wherein the (5HT₂) receptor antagonist is ketanserin, pelanserin, pipamperone, spiperone, pirenperin or ritanserin.

32. A medicine according to claim 23 or 31, which is in a dosage unit form for human use and contains the compound of formula I or salt thereof at a daily dose of 10 to 200 mg and the 5HT₂ receptor antagonist or salt thereof in an amount of 0.1-10 parts by weight per part by weight of the compound of formula I or salt thereof.

33. A medicine according to claim 28, wherein the serotonin reuptake inhibitor is sertraline, fluoxetine, fenfluramine, or fluvoxamine.

34. A medicine according to claim 33, which is in a dosage unit form for human use and contains the compound of formula I or salt thereof at a daily dose of 10 to 200 mg and the serotonin reuptake inhibitor at a daily dose of 10 to 100 mg.

35. A medicine according to claim 29, wherein the serotonin reuptake inhibitor is sertraline, fluoxetine, fenfluramine, or fluvoxamine.

36. A medicine according to claim 35, which is in a dosage unit form for human use and contains the compound of formula I or salt thereof at a daily dose of 10 to 200 mg and the serotonin reuptake inhibitor at a daily dose of 10 to 100 mg.

37. A commercial package which comprises the medicine according to any one of claims 1 to 15 and a written matter which states that the medicine is to be used for treating a disorder or condition that can be treated by altering serotonin mediated neurotransmission.

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38. A commercial package which comprises the medicine according to claim 16 and a written matter which states that the medicine is to be used for treating migraine, headache or cluster headache.

5 39. A commercial package which comprises the medicine according to claim 17, 28, 33 or 34 and a written matter which states that the medicine is to be used for treating a disorder selected from anxiety, depression, dysthymia, major depressive disorder, panic disorder, obsessive-compulsive
10 disorder, posttraumatic stress disorder, avoidant personality disorder, borderline personality disorder and phobias.

40. A commercial package which comprises the medicine according to claim 18 and a written matter which states that the medicine is to be used for treating a disorder of
15 cognition, memory or learning.

41. A commercial package which comprises the medicine according to claim 19, 29, 35 or 36 and a written matter which states that the medicine is to be used for treating anxiety or depression associated with senile dementia or
20 Alzheimer's disease.

42. A commercial package which comprises the medicine according to claim 20 and a written matter which states that the medicine is to be used for treating cancer.

43. A commercial package which comprises the medicine according to claim 22, 23, 31 or 32 and a written matter which states that the medicine is to be used for treating cerebral infarct, ischemia or traumatic head injury.
25

44. A commercial package which comprises the medicine according to claim 24 and a written matter which states that
30 the medicine is to be used for treating a sexual disorder.

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45. A commercial package which comprises the medicine according to claim 25 and a written matter which states that the medicine is to be used for treating dizziness.

46. A commercial package which comprises the medicine
5 according to claim 26 and a written matter which states that the medicine is to be used for treating an eating disorder.

47. A commercial package which comprises the medicine according to claim 27 and a written matter which states that the medicine is to be used for treating pain.

10 48. A commercial package which comprises the medicine according to claim 30 and a written matter which states that the medicine is to be used for treating attention deficit hyperactivity disorder.

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