



This invention relates to novel [3-(4-phenylpiperazin-1-yl)propyl]-, [3-(4-phenylpiperazin-1-yl)-2,2-dimethylpropyl]- and [1-(4-phenylpiperazin-1-yl-methyl)cycloprop-1-ylmethyl]-2,4(1H,3H)-pyrimidinedione, 2,4,6(1H,3H,5H)-pyrimidinetrione, 5,6-dihydro-2,4(1H,3H)-pyrimidinedione, 1,2,4-triazine-3,5(2H,4H)-dione and 5,6,7,8-tetrahydro-2,4(1H,3H)-quinazolin-2(1H)-one derivatives as α_1 -adrenoceptor antagonists, their uses as therapeutic agents, and the methods of their making.

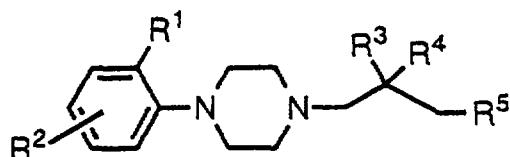
10 α_1 -Adrenoceptors mediate the contractile state of smooth muscle tissue. For example, hypersympathetic activity produces contraction of vascular smooth muscle which leads to elevated blood pressures. Thus, α_1 -adrenoceptor antagonists find use as anti-hypertensive agents. α_1 -Adrenoceptor stimulation also
15 produces contraction of urethral and bladder neck smooth muscle, leading to increased resistance in urinary outflow. Thus, α_1 -adrenoceptor antagonists are useful in treating conditions which relate directly or indirectly to obstructive uropathies, particularly obstruction due to benign prostatic
20 hyperplasia (BPH) (Lepor, H. *The Prostate Supplement*. 1990, 3, 75-84). However, the amount of α_1 -adrenoceptor antagonist required to produce a therapeutic effect with regard to urinary outflow, can produce an excessive decrease of blood pressure and/or an inhibition of the mechanism by which normal
25 blood pressure is maintained during changes in posture (i.e., postural hypotension). Thus, α_1 -antagonists which can selectively reduce α_1 -adrenoceptor hyperactivity in prostatic and/or lower urinary tract smooth muscle, without affecting blood pressure or causing postural hypotension, are desirable.

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In a first aspect this application relates to a compound of Formula I:

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I

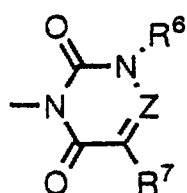
in which:

R^1 is acetylamino, amino, cyano, trifluoroacetylamino, halo, hydro, hydroxy, nitro, methylsulfonylamino, 2-propynyloxy, a group selected from (C_{1-6}) alkyl, (C_{3-6}) cycloalkyl, (C_{3-6}) -cycloalkyl (C_{1-4}) alkyl, (C_{1-6}) alkyloxy, (C_{3-6}) cycloalkyloxy, (C_{3-6}) cycloalkyl (C_{1-4}) alkyloxy and (C_{1-4}) alkylthio (which group is optionally further substituted with one to three halo atoms) or a group selected from aryl, aryl (C_{1-4}) alkyl, heteroaryl, heteroaryl (C_{1-4}) alkyl, aryloxy, aryl (C_{1-4}) -alkyloxy, heteroaryloxy and heteroaryl (C_{1-4}) alkyloxy (which aryl and heteroaryl are optionally further substituted with one to two radicals independently selected from halo and cyano);

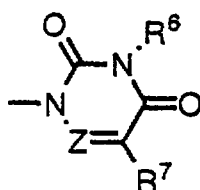
R^2 is cyano, halo, hydro, hydroxy or a group selected from (C_{1-6}) alkyl and (C_{1-6}) alkyloxy (which group is optionally further substituted with one to three halogen atoms);

R^3 and R^4 are both hydro or methyl or together are ethylene;

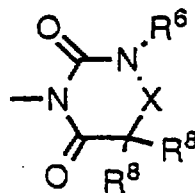
R^5 is a group selected from Formulae (a), (b), (c) and (d):



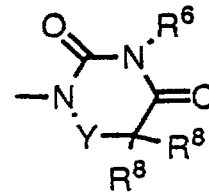
(a)



(b)



(c)



(d)

in which:

X is $C(O)$, CH_2 or $CH(OH)$;

Y is CH_2 or $CH(OH)$;

Z is N or $C(R^9)$, wherein R^9 is hydro, (C_{1-6}) alkyl or hydroxy;

R^6 is hydro, a group selected from (C_{1-6}) alkyl, $(C_{3-}$

6)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl (which group is optionally further substituted with one to three halo atoms) or a group selected from aryl, heteroaryl, aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are
5 optionally further substituted with one to three radicals selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and aryl);
R⁷ is (C₁₋₆)alkanoyl, carbamoyl, cyano, di(C₁₋₆)alkylamino, halo, hydro, hydroxy, hydroxyiminomethyl, (C₁₋₆)alkylsulfonyl,
10 (C₁₋₄)alkylthio, a group selected from (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₁₋₆)alkyloxy and (C₁₋₆)alkyloxy(C₁₋₄)alkyl (which group is optionally further substituted with one to three radicals selected from halo, hydroxy or (C₁₋₆)alkyloxy) or a group selected from aryl, heteroaryl, aryl(C₁₋₄)alkyl and
15 heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are optionally further substituted with one to three radicals selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and aryl) or R⁷ and R⁹ together are tetramethylene; and each R⁸ is independently hydro, hydroxy, methyl or ethyl; and the
20 pharmaceutically acceptable salts and N-oxides thereof.

A second aspect of this invention is a pharmaceutical composition which contains a compound of Formula I in admixture with one or more suitable excipients.
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A third aspect of this invention is the processes for preparing compounds of Formula I.

Unless otherwise stated, the following terms used in the
30 specification and claims have the meanings given below:

"Alkyl", as in (C₁₋₄)alkylthio, (C₁₋₆)alkyl or (C₁₋₆)alkyloxy, means a straight or branched saturated hydrocarbon radical having from one to the number of carbon
35 atoms designated optionally substituted with one to three halo atoms (e.g., optionally substituted (C₁₋₄)alkylthio includes methylthio, ethylthio, 2,2,2-trifluoroethylthio, etc.; optionally substituted (C₁₋₆)alkyl includes methyl, trifluoro-



methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc.; and optionally substituted (C₁₋₆)alkyloxy includes methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.).

"Alkanoyl" means the radical -C(O)R having from one to the number of carbon atoms designated (e.g., formyl, acetyl, propionyl, butyryl, etc.).

10

"Cycloalkyl", as in (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl-(C₁₋₄)alkyl, (C₃₋₆)cycloalkyloxy or (C₃₋₆)cycloalkyl-(C₁₋₄)alkyloxy, means a saturated monocyclic hydrocarbon radical having from three to the number of carbon atoms designated (e.g., (C₃₋₆)cycloalkyl includes the radicals cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; and (C₃₋₆)cycloalkyloxy includes the radicals cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy).

20

"Aryl", as in aryl, aryl(C₁₋₄)alkyl, aryloxy and aryl(C₁₋₄)alkyloxy, means an organic radical derived from an aromatic hydrocarbon containing 6 to 14 carbon atoms and includes monocyclic or condensed carbocyclic aromatic rings (e.g., phenyl, naphthyl, anthracenyl, phenanthrenyl, etc.) optionally substituted with one to two radicals independently selected from halo and cyano.

25

"Heteroaryl", as in heteroaryl, heteroaryl(C₁₋₄)alkyl, heteroaryloxy and heteroaryl(C₁₋₄)alkyloxy, means an organic radical derived from an aromatic hydrocarbon containing 5 to 14 atoms, 1 to 5 of which are hetero atoms chosen from N, O, or S, and includes monocyclic, condensed heterocyclic and condensed carbocyclic and heterocyclic aromatic rings (e.g., thienyl, furyl, pyrrolyl, pyrimidinyl, isoxazolyl, oxazolyl, indolyl, benzo[b]thienyl, isobenzofuranyl, purinyl, isoquinolyl, pteridinyl, perimidinyl, imidazolyl, pyridyl, pyrazolyl, pyrazinyl, etc.) optionally substituted with one to two radicals independently selected from halo and cyano.

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"Carbamoyl" means aminocarbonyl.

"Halo" means fluoro, chloro, bromo, or iodo.

5

"Tetramethylene" means the radical $-\text{CH}_2 \cdot (\text{CH}_2)_2 \cdot \text{CH}_2-$.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group
10 displaceable under alkylating conditions, and includes halogen and alkane- or arenesulfonyloxy, such as methanesulfonyloxy, ethanesulfonyloxy, benzenesulfonyloxy and tosyloxy, and thienyloxy, dihalophosphinoyloxy, tetrahalophosphaoxy, and the like.

15

"Organometallic base" means a base capable of reacting with an organic compound to give a "metalated" compound of the formula R-Met^1 in which Met^1 is any monovalent electro
positive metal element, typically an alkylmetallic base and
20 preferably an alkyl alkali metal base (e.g., n-butyllithium, n-butylnatrium, n-butympotassium and the like)..

"Animal" includes humans, non-human mammals, e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, and deer,
25 and non-mammals, e.g., birds and the like.

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to, medical or
30 veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that
35 the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "which group is optionally substituted with one to three halo atoms" means that the group referred to



may or may not be substituted in order to fall within the scope of the invention.

"Protective group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., a group which selectively blocks one reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site and which can be readily removed after the selective reaction is completed.

"Protective agent" means an agent which will react with a multifunctional compound and create a protective group at reactive nitrogen atoms.

"Protected" in reference to a compound or a group means a derivative of compound or group in which a reactive site or sites are blocked with protective groups.

"Deprotecting" refers to removing any protective groups present after the selective reaction has been carried out.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid and the like; or with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, p-chlorobenzene-sulfonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, 1,2-ethane-disulfonic acid, ethanesulfonic acid, fumaric acid,



glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hexanoic acid, heptanoic acid, o-(4-hydroxybenzoyl)-benzoic acid, 2-hydroxyethanesulfonic acid, hydroxynaphthoic acid, lactic acid, lauryl sulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), muconic acid, 2-naphthalenesulfonic acid, oxalic acid, 3-phenylpropionic acid, propionic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiary butylacetic acid, p-toluenesulfonic acid, trimethylacetic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide. Acceptable organic bases include diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine and the like.

"N-Oxide", when referring to a compound of Formula I, means such compound in which nitrogens are in an oxidized state, i.e., O_N. The N-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

The term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

"Treating" or "treatment" of a disease includes:

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- (1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display symptoms of the disease,
- 5 (2) inhibiting the disease, i.e., arresting its development, or
- (3) relieving the disease, i.e., causing regression of the disease.

10

Isomerism is the phenomenon wherein compounds have identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

15 Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes optical isomers. A carbon atom bonded to four nonidentical substituents is termed a "chiral center".

20

A compound with one chiral center has two enantiomeric forms of opposite chirality and may exist as either an individual enantiomer or as a mixture of enantiomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture".

25

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When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the Sequence Rule of Cahn,

35



Ingold and Prelog and the absolute descriptor *R* or *S* is cited in parentheses followed by a hyphen and the chemical name of compound.

5 Compounds of Formula I can exist as individual stereoisomers or mixtures of stereoisomers. For example, compounds of Formula I in which R^5 is a group of Formula (c) or (d) can contain chiral centers at the 5- and/or 6-positions of the 5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione moiety. When
10 chiral centers are present at both the 5- and 6-positions two enantiomeric pairs are possible (i.e., the 5*R*,6*S*/5*S*,6*R* enantiomeric pair, also referred to as the *cis*-isomers, and the 5*R*,6*R*/5*S*,6*S* enantiomeric pair, also referred to as the *trans*-isomers). For the purposes of the present application
15 when referring to a compound of Formula I by name or by formula and the configuration is not designated, it is to be understood that the reference is to all possible configurations of the compound.

20 The compounds of Formula I are named in accordance with acceptable nomenclature rules generally consistent with "Chemical Abstracts". For example, the compound of Formula I in which R^1 is methoxy and R^2 , R^3 and R^4 are each hydro: is named 3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-
25 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione when R^5 is a group of Formula (a), wherein *Z* is CH and R^7 is methyl; is named 3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione when R^5 is a group of Formula (a), wherein *Z* is C(R^9) and R^7 and R^9
30 together are tetramethylene; is named 4-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-6-methyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione when R^5 is a group of Formula (a), wherein *Z* is N and R^7 is methyl; and is named 3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-
35 5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione when R^5 is a group of Formula (c) and each R^8 is methyl.



PRESENTLY PREFERRED EMBODIMENTS:

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formula I are preferred. For example, preferred compound of Formula I are those in which R^1 is (C_1-6) alkyloxy (optionally further substituted with one to three fluorine atoms) or heteroaryl; R^2 is hydro, halo, hydroxy or (C_1-6) alkyl; and R^5 is a group selected from Formulae (a), (b) and (c), in which R^6 is hydro, (C_1-6) alkyl, (C_3-6) cycloalkyl (C_1-4) alkyl, heteroaryl (C_1-4) alkyl or a group selected from benzyl and phenyl (which group is optionally further substituted with one to three radicals selected from halo, (C_1-6) alkyloxy, (C_1-6) alkyl and aryl) and R^7 is carbamoyl, cyano, halo, hydro, hydroxyiminomethyl, hydroxymethyl or (C_1-6) alkyl (which alkyl is optionally substituted with one to three fluorine atoms) or together with R^9 is tetramethylene.

Particularly preferred compounds of Formula I are those in which R^1 is methoxy, ethoxy, 2,2,2-trifluoroethoxy, oxazolyl or pyrrolyl; R^2 is hydro, chloro, fluoro, hydroxy or methyl; and R^5 is a group selected from Formulae (a), (b) or (c), in which R^6 is hydro, methyl, cyclohexylmethyl, pyridylmethyl, pyrazinylmethyl, furylmethyl, thienylmethyl, biphenylmethyl or a group selected from benzyl and phenyl (which group is optionally further substituted with one to three radicals selected from chloro, fluoro, methyl or methoxy) and R^7 is carbamoyl, cyano, halo, hydro, hydroxyiminomethyl, hydroxymethyl, methyl, ethyl, propyl, trifluoromethyl or together with R^9 is tetramethylene; X is CH_2 and each of the R^8 radicals are hydro or X is $CH(OH)$ and one of the R^8 radicals is hydroxy.

Most preferred compounds of Formula I are those in which R^1 is 2,2,2-trifluoroethoxy; R^2 is hydro, chloro, fluoro, hydroxy or methyl; R^3 and R^4 are each hydro; R^5 is a group of Formula (a) in which R^7 is hydro or methyl and Z is $C(R^9)$, wherein R^9 is hydro or methyl, or a group of Formula (c) in



which X is CH(OH), one of the R⁸ radicals is hydroxy and the other is methyl; and R⁶ is hydro, methyl, cyclohexylmethyl, pyridylmethyl, pyrazinylmethyl, furylmethyl, thienylmethyl, biphenylmethyl or a group selected from benzyl and phenyl
5 (which group is optionally further substituted with one to three radicals selected from chloro, fluoro, methyl or methoxy).

PHARMACOLOGY AND UTILITY:

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The α_1 -adrenoceptor pharmacology of the compounds of this invention was determined by art-recognized procedures. *In vitro* assays for measuring the relative effect of test compounds on α_1 -adrenoceptor mediated contraction of rat
15 isolated aortic and rabbit isolated urinary bladder smooth muscle are described in Example 38. *In vitro* assays for measuring the relative effect of test compounds on α_1 -adrenoceptor mediated contraction of human isolated arterial, prostatic and urinary bladder smooth muscle are
20 described in Example 39. An *in vivo* assay for measuring the blood pressure lowering effects of test compounds in normotensive and spontaneously hypertensive rats is described in Example 40. An *in vivo* assay for measuring the effect of test compounds on the reflex maintenance of basal blood
25 pressure in response to postural change from supine to vertical is described in Example 41. An *in vivo* assay for measuring the relative effect of test compounds on α_1 -adrenoceptor mediated increases in blood and intraurethral pressures is described in Example 42.

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In summary, the compounds of this invention were tested by the procedures described above and found to selectively inhibit the α_1 -adrenoceptors which mediate the contractile state of prostatic and lower urinary tract smooth muscle. The
35 compounds of this invention will decrease resistance in urinary outflow, without producing the blood pressure lowering effects and/or the postural hypotension that are associated with previously described α_1 -adrenoceptor antagonists.



Accordingly, the compounds of this invention are useful in treating conditions which relate directly or indirectly to obstructive uropathies, particularly obstruction due to benign prostatic hyperplasia.

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ADMINISTRATION AND PHARMACEUTICAL COMPOSITION:

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another compound of Formula I or with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. Therapeutically effective amounts of compounds of Formula I may range from 0.1 micrograms per kilogram body weight ($\mu\text{g/kg}$) per day to 1 milligram per kilogram body weight (mg/kg) per day, typically 1 $\mu\text{g/kg/day}$ to 10 $\mu\text{g/kg/day}$. Therefore, a therapeutically effective amount for a 80 kg human may range from 8 $\mu\text{g/day}$ to 800 mg/day, typically 80 $\mu\text{g/day}$ to 0.8 mg/day.

One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease.

In general, compounds of Formula I will be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable



excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of Formula I. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient
5 that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium
10 stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral
15 oil, sesame oil, etc.). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

Compressed gases may be used to disperse the compound of Formula I in aerosol form. Inert gases suitable for this
20 purpose are nitrogen, carbon dioxide, nitrous oxide, etc. Other suitable pharmaceutical carriers and their formulations are described in A.R. Alfonso Remington's *Pharmaceutical Sciences* 1985, 17th ed. Easton, Pa.: Mack Publishing Company.

25

The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In
30 general, the final composition will comprise from 0.000001%w to 10.0%w of the compound of Formula I, preferably 0.00001%w to 1.0%w, with the remainder being the excipient or excipients.

35 Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical



formulations containing a compound of Formula I are described in Example 37.

CHEMISTRY:

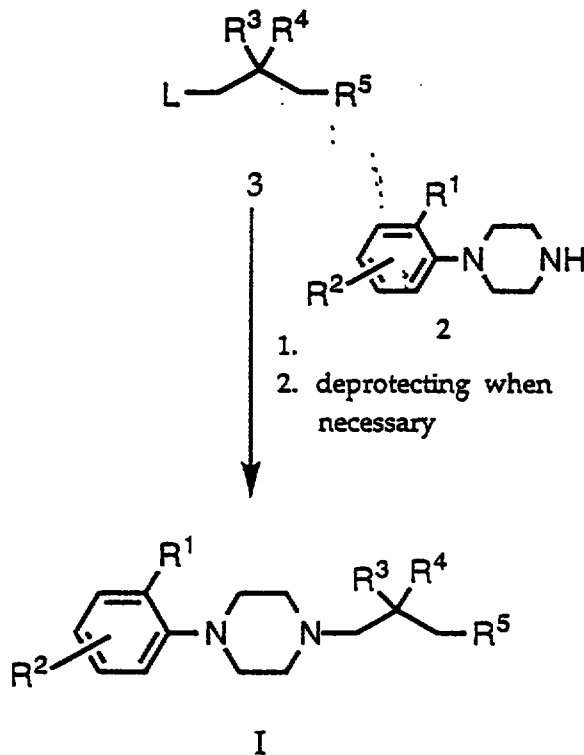
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Compounds of Formula I:

Compounds of Formula I can be prepared by the process depicted in the following Reaction Scheme I:

10

Scheme I



in which L is a leaving group and each R¹, R², R³, R⁴ and R⁵ are as defined in the Summary of the Invention with respect to Formula I.

15

In general, compounds of Formula I can be prepared by alkylating an optionally substituted 1-phenylpiperazine of Formula 2 with a compound of Formula 3, or a protected derivative thereof, and then deprotecting when necessary. The alkylation can be carried out neat at 100 to 250°C, typically

20



at 150 to 200°C and preferably at 180 to 190°C, requiring 1 to 3 hours (for further details see Example 24, *infra.*). Alternatively, the reaction can be carried out in a suitable inert organic solvent (e.g., acetonitrile, *N,N*-dimethyl-
5 formamide (DMF), *N*-methylpyrrolidione (NMP), any appropriate mixture of suitable solvents, etc., preferably acetonitrile) with a suitable base present (e.g., sodium carbonate, potassium carbonate, cesium carbonate, 2,4,6-trimethyl-
pyridine, etc., preferably potassium carbonate) and optionally
10 an iodide salt present (e.g., sodium iodide, lithium iodide, tetraalkylammonium iodides such as tetramethyammonium iodide and the like, etc., preferably sodium iodide) at 40 to 90°C, typically at 70 to 85°C and preferably at reflux, requiring 6 to 72 hours (for further details see Example 25, *infra.*).

15

Deprotection when a nitrogen protective group is present can be effected by any means which removes the protective group and gives the desired product in reasonable yield. A detailed description of the techniques applicable to
20 protective groups and their removal can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981. For example, a convenient method of deprotection when the protective group is 2-(trimethylsilyl)-ethoxymethyl is carried out with tetrabutylammonium fluoride
25 in a suitable inert organic solvent (e.g., tetrahydrofuran (THF), hexamethylphosphoramide (HMPA), any appropriate mixture of suitable solvents, etc., preferably THF) at 10 to 65°C, typically at 20 to 25°C and preferably at approximately 25°C, and requires 8 to 24 hours (for further details see
30 Example 27, *infra.*). Deprotection when the protective group is methoxymethyl can be effected with concentrated hydrochloric acid in a suitable solvent, typically water/alcohol (9:1-1:9) mixture (e.g., water/methanol, /ethanol, /isopropanol, /any appropriate mixture of suitable alcohols,
35 etc.) and preferably water/isopropanol (7:1), at 20 to 100°C, typically at 70 to 90°C and preferably at approximately reflux, requiring 2 to 14 hours.

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In addition, any hydroxy groups present in the compound of Formula 2 or 3 should be protected with a suitable protective group (e.g., benzyl, para-methoxybenzyl, 1-naphthylmethyl, etc., preferably benzyl). A convenient
5 method of deprotecting a benzyl protected hydroxy group is by catalytic hydrogenation. The hydrogenation is carried out with a suitable catalyst (e.g., 10% palladium on carbon (10% Pd/C), palladium hydroxide, palladium acetate, etc. preferably 10% Pd/C) in the presence of ammonium formate and
10 in an appropriate solvent, typically an alcohol (e.g., ethanol, methanol, isopropanol, any appropriate mixture of alcohols, etc.) and preferably methanol, at 50 to 66°C, typically at 63 to 66°C and preferably at reflux. Alternatively, the benzyl group is removed by treating the
15 protected compound with the catalyst under a hydrogen atmosphere at 0 to 50 psi, typically at 10 to 20 psi and preferably at approximately 15 psi, at 20 to 50°C, typically at 23 to 27°C and preferably at 25°C;

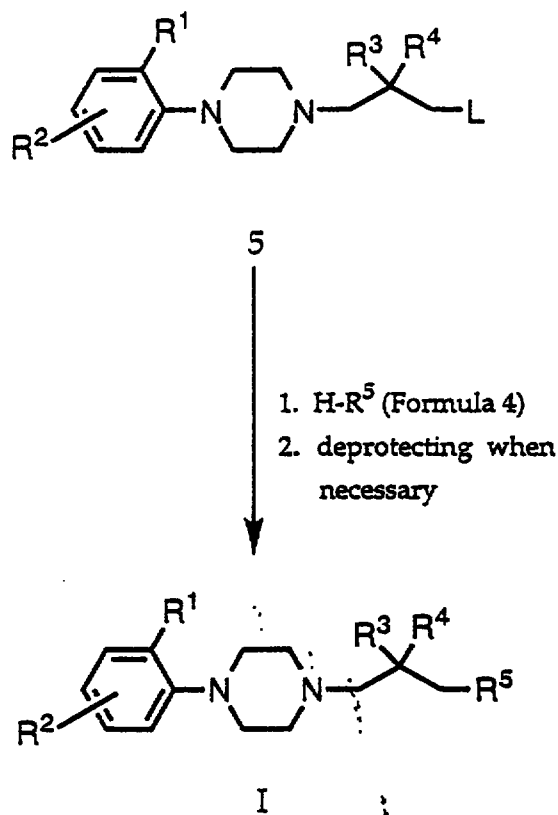
20 Alternatively, compounds of Formula I in which R⁵ can be prepared by the process depicted in the following Reaction Scheme II:

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Scheme II



in which L is a leaving group and each R¹, R², R³, R⁴ and R⁵ are as defined in the Summary of the Invention with respect to Formula I.

An alternative method for preparing compounds of Formula I comprises alkylating a compound of the formula H-R⁵ (Formula 4), or the protected derivative thereof, with a compound of Formula 5 and then deprotecting when necessary. The alkylation is carried out in the presence of a suitable base (e.g., sodium carbonate, tetrabutylammonium fluoride, benzyltrimethylammonium chloride with sodium hydroxide, tetrabutylammonium hydroxide, potassium carbonate, cesium carbonate, sodium hydride, etc., preferably potassium carbonate) and in a suitable inert organic solvent (e.g., DMF, THF, acetonitrile, mixtures of toluene and water, any appropriate mixture of suitable solvents, etc., preferably THF) at 10 to 40°C, typically at 20 to 25°C and preferably at approximately 20°C, and requires 1 to 24 hours (for further details see Examples 30 and 31, *infra*). The deprotection is



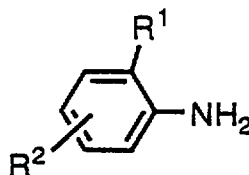
carried out as set forth in Reaction Scheme I.

Alternatively, the alkylation of the compound of Formula 4 is effected by treating the compound of Formula 4 with a suitable silylating agent (e.g., 1,1,1,3,3,3-hexamethyl-disilazane (HMDS), *N,O*-bistrimethylsilylacetamide, hexamethylsiloxane, etc., preferably HMDS) in a suitable inert organic solvent (e.g., trifluoromethanesulfonic acid, DMF, NMP, THF, DME, toluene, any appropriate mixture of suitable solvents, etc., preferably trifluoromethanesulfonic acid) at 100 to 180°C, typically at 150 to 180°C and preferably at approximately 90°C, for 6 to 24 hours and then reacting with 1 molar equivalent of the compound of Formula 5 neat or in a suitable inert organic solvent (e.g., trifluoro-methane-sulfonic acid, dry benzene, toluene, 1,2-dichlorobenzene, any appropriate mixture of suitable solvents, etc., preferably trifluoromethanesulfonic acid) at 60 to 150°C, typically at 60 to 110°C and preferably at approximately 70°C, for 0.25 to 15 hours. Proceeding as described above the following compound of Formula I was prepared:

1-(3-{4-[2-methoxyphenyl]piperazin-1-yl}propyl)-5,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione fumarate, m.p. 216-218°C;
Anal.: Calcd. for $C_{20}H_{28}N_4O_3 \cdot C_2H_2O_2$: C, 59.01; H, 6.60; N, 11.47%; Found: C, 58.95; H, 6.61; N, 11.36%.

Compounds of Formula 2:

Compounds of Formula 2 are commercially available or can be prepared by methods known to those of ordinary skill in the art. For example, compounds of Formula 2 can be prepared by reacting a compound of Formula 6:



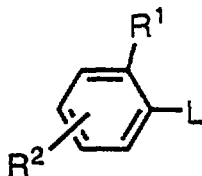
6

in which each R¹ and R² are as defined in the Summary of the Invention with respect to Formula I, with bis(chloroethyl)-

amine hydrochloride. The reaction can be carried out with a suitable base present, typically a nitrogen base (e.g., triethylamine, *N,N*-diisopropylethylamine, etc.) or a carbonate salt base (e.g., potassium carbonate, sodium carbonate, cesium carbonate, etc.) and preferably potassium carbonate, and optionally an iodide salt present (e.g., sodium iodide, lithium iodide, tetraalkylammonium iodides such as tetramethylammonium iodide and the like, etc., preferably sodium iodide) in a suitable inert organic solvent (e.g., *n*-butanol, *tert*-butanol, 2-methoxyethyl ether (diglyme), 2-ethoxyethanol, xylene, any appropriate mixture of suitable solvents, etc., preferably diglyme) at 110 to 170°C, typically at 140 to 165°C and preferably at reflux, requiring 2 to 24 hours (for further details see Example 13, *infra*). Alternatively, the reaction can be carried out neat at 150 to 300°C, typically at 180 to 200°C and preferably at approximately 180°C, requiring 2 to 5 hours.

Preferably, the reaction is carried out by reacting the bis(chloroethyl)amine hydrochloride with an acid addition salt of the compound of Formula 6, preferably the hydrochloride salt, in a suitable solvent (e.g., xylenes, diglyme, *o*-dichlorobenzene, *n*-hexanol, any appropriate mixture of suitable solvents, etc., preferably *o*-dichlorobenzene/*n*-hexanol (10:1)) at 140 to 180°C, typically at 160 to 180°C and preferably at reflux, requiring 1 to 8 hours (for further details see Example 14, *infra*).

Compounds of Formula 2 also can be prepared by reacting a compound of Formula 7:



7

in which L is a leaving group, typically a halogen atom and preferably fluoro, and each R¹ and R² are as defined in the

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Summary of the Invention with respect to Formula I, with an optionally protected 1-metalated piperazine, typically a protected lithium 1-piperazinide and preferably lithium 4-benzyl-1-piperazinide, and then deprotecting. The protected
5 1-metalated piperazine is prepared by cooling a solution of protected piperazine in a suitable inert organic solvent, preferably an ether (e.g., THF, diethyl ether, monoglyme, diglyme, any appropriate mixture of suitable solvents, etc., preferably THF), to between -70 and 10°C, typically to between
10 -35 to 5°C and preferably to approximately 0°C, adding an organometallic base, typically an alkylmetallic base and preferably an alkyl alkali metal base (e.g., n-butyllithium, n-butylna, n-butylna, n-butylna, etc., preferably n-butyl-lithium), at a rate such that the reaction temperature remains
15 below 15°C, preferably below 5°C, and then allowing the reaction to proceed at -70 to 45°C, typically at -10 to 35°C and preferably at approximately 25°C, for 10 minutes to 1 hour.

20 The reaction with the compound of Formula 7 is carried out by cooling a solution containing the 1-metalated piperazine to between -60 and 15°C, typically to between -45 and 10°C and preferably to approximately 0°C, adding the compound of Formula 7 and then allowing the
25 reaction to proceed at -10 to 30°C, typically at 15 to 25°C and preferably at approximately 25°C, for 30 minutes to 48 hours. A convenient method of deprotection when the protective group is benzyl is by treating with a suitable catalyst (e.g., 10% palladium on carbon (10% Pd/C), palladium
30 hydroxide, palladium acetate, etc. preferably 10% Pd/C) under a hydrogen atmosphere at 0 to 50 psi, typically at 10 to 20 psi and preferably at approximately 15 psi, and in an appropriate solvent, typically an alcohol (e.g., ethanol, methanol, isopropanol, any appropriate mixture of alcohols,
35 etc.) and preferably methanol, at 20 to 50°C, typically at 23 to 27°C and preferably at 25°C. Further details of the reaction steps set forth in this and the preceding paragraph are provided in Example 16, infra.



A convenient method for preparing a compound of Formula 2 in which R¹ is pyrrol-1-yl comprises reacting a protected 4-(2-aminophenyl)piperazine, preferably 4-(2-aminophenyl)-piperazine-1-carbaldehyde, with 2,5-dimethoxytetrahydrofuran and then deprotecting. The reaction with the 1-carbaldehyde is carried out in a suitable solvent, typically an acid (e.g., concentrated acetic acid, propionic acid, trifluoroacetic acid, any appropriate mixture of suitable acids, etc.) and preferably concentrated acetic acid, at 100 to 150°C, typically at 110 to 120°C and preferably at reflux, and requires 1 to 3 hours. The deprotection can be effected with a strong base (e.g., sodium hydroxide, lithium hydroxide, potassium hydroxide, any appropriate mixture of bases, etc., preferably sodium hydroxide) in a suitable solvent, typically an alcohol (e.g., ethanol, methanol, isopropanol, any appropriate mixture of alcohols, etc.) and preferably methanol, at 20 to 65°C, typically at 50 to 55°C and preferably at approximately 50°C, requiring 3 to 6 hours.

20

The 4-(2-aminophenyl)piperazine-1-carbaldehyde can be prepared by reacting 1-chloro-2-nitrobenzene with piperazine-1-carbaldehyde to give 4-(2-nitro-phenyl)piperazine-1-carbaldehyde and then reducing. The reaction between the 1-carbaldehyde and the 2-nitrobenzene is carried out in a suitable solvent (e.g., DMF, NMP, acetonitrile, any appropriate mixture of suitable solvents, etc., preferably DMF) at 50 to 100°C, typically at 60 to 80°C and preferably at approximately 100°C, and requires 20 to 50 hours. The reduction can be effected with a suitable chemical reducing agent (e.g., nickel boride, stannous chloride, etc., preferably nickel boride) in a suitable solvent, typically an alcohol (e.g., ethanol, methanol, isopropanol, any appropriate mixture of alcohols, etc.) and preferably methanol, at 20 to 65°C, typically at 50 to 65°C and preferably at approximately 60°C, requiring 1 to 20 hours. Alternatively, the reduction can be effected under a hydrogen atmosphere at 0 to 50 psi, typically at 10 to 20 psi and preferably at

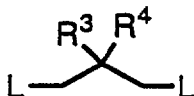


approximately 15 psi, with a suitable catalyst (e.g., 10% palladium on carbon (10% Pd/C), palladium hydroxide, palladium acetate, etc. preferably 10% Pd/C) and in an appropriate solvent, typically an alcohol (e.g., ethanol, methanol, isopropanol, any appropriate mixture of alcohols, etc.) and preferably methanol, at 20 to 50°C, typically at 23 to 27°C and preferably at 25°C, requiring 5 to 40 hours. Further details of the reaction steps set forth in this and the preceding paragraph are provided in Example 17, *infra*.

A convenient method for preparing a compound of Formula 2 in which R² is hydroxy comprises de-methylating a compound of Formula 2 in which R² is methoxy. The de-methylation is effected by heating in a suitable aqueous acid (e.g., aqueous hydrobromic acid, pyridine hydrochloride, any appropriate mixture of suitable acids, etc., preferably aqueous hydrobromic acid) at 100 to 200°C, typically at 120 to 140°C and preferably at reflux, for 5 to 20 hours (for further details see Example 18, *infra*).

Compounds of Formula 3:

In general, compounds of Formula 3 can be prepared by alkylating a compound of the formula H-R⁵ (Formula 4), or a protected derivative thereof, with a compound of Formula 8:



8

in which each L is a leaving group and R³ and R⁴ are as defined in the Summary of the Invention with respect to Formula I, and then deprotecting when necessary. The reaction is carried out in the presence of a suitable base (e.g., tetraalkylammonium halide such as tetra-*n*-butylammonium fluoride, tetra-*n*-butylammonium bromide, benzyltrimethylammonium chloride and the like, tetraalkylammonium hydroxide, tetraalkylammonium chloride with potassium hydroxide,



potassium carbonate, etc., preferably tetra-n-butylammonium bromide) and in a suitable inert organic solvent (e.g., THF, DMF, acetonitrile, mixtures of toluene and water, any appropriate mixture of suitable solvents, etc., preferably
5 DMF) at 10 to 40°C, typically at 20 to 30°C and preferably at approximately 25°C, and requires 1 to 24 hours (for further details see Example 19, *infra.*). The alkylation may direct at either or both of the two secondary ring nitrogens present in the compound of Formula 3. A suitable nitrogen protective
10 group can facilitate the direction of the alkylation. Suitable protective groups include methoxymethyl, 2-(trimethylsilyl)-ethoxy-methyl, tert-butyloxycarbonyl, benzyloxycarbonyl, etc., preferably methoxymethyl. Deprotection is carried out by proceeding as described above with respect to Reaction Scheme
15 I (for further details see Example 20, *infra.*).

Compounds of Formula 3 in which R⁶ is hydro can be prepared by de-benzylating the corresponding compound of Formula 3 in which R⁶ is benzyl. The de-benzylation is carried
20 out with ammonium formate in the presence of a palladium catalyst (e.g., 10% palladium on carbon (10% Pd/C), wet 20% palladiumhydroxide on carbon, palladium black, etc., preferably 10% Pd/C) and in a suitable solvent, typically an alcohol (e.g., methanol, ethanol, 2-ethoxyethanol, any
25 appropriate mixture of suitable alcohols, etc.) and preferably methanol, at 50 to 66°C, typically at 62 to 66°C and preferably at reflux, and requires 3 to 96 hours (for further details see Example 21, *infra.*).

30 Compounds of Formula 3 in which R⁵ is a group of Formula (a) wherein R⁶ is (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl or a group selected from aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are optionally further substituted with one to three radicals
35 selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and aryl) can be prepared by reacting a corresponding compound of Formula 3 in which R⁶ is hydro with 1 molar equivalent of an appropriate alkylating agent (e.g., iodomethane, benzyl



bromide, 4-methylbenzyl bromide, cyclohexylmethyl bromide, pyrazin-2-ylmethyl bromide, thien-2-ylmethyl bromide, fur-3-ylmethyl bromide, biphenyl-2-ylmethyl bromide, etc.) in the presence of a suitable base (e.g., sodium carbonate, potassium
5 carbonate, cesium carbonate, sodium hydride, etc., preferably potassium carbonate). The reaction is carried out in a suitable solvent (e.g., DMF, NMP, THF, DME, any appropriate mixture of suitable solvents, etc., preferably DMF) at 22 to 70°C, typically at 40 to 65°C and preferably at
10 approximately 40°C, and requires 5 to 24 hours.

Compounds of Formula 3 in which L is hydroxy and R³ and R⁴ together are ethylene can be prepared by hydrolyzing a corresponding 3- or 1-(1-cyanocycloprop-1-ylmethyl)-
15 2,4(1H,3H)-pyrimidinedione or 1-(1-cyanocycloprop-1-ylmethyl)-2,4,6(1H,3H,5H)-pyrimidinetrione, respectively, to give the corresponding 1-cyclopropanecarboxylic acid, reacting the carboxylic acid with methyl chloroformate to give the corresponding methoxycarbonyl carboxylate and then reducing
20 the carboxylate. The hydrolysis can be effected by heating the nitrile with acid (e.g., concentrated hydrochloric acid, acetic acid, sulfuric acid, trifluoroacetic acid, any appropriate mixture of suitable acids, etc., typically a mixture of concentrated acetic acid and concentrated
25 hydrochloric acid and preferably approximately 20% v/v acetic acid/concentrated hydrochloric acid) at 50 to 150°C, typically at 100 to 120°C and preferably at reflux, for 1 to 5 hours.

Conversion of the carboxylic acid to the methoxycarbonyl
30 carboxylate is carried out in a suitable inert organic solvent (e.g., THF, methylene chloride, 1,2-dichloroethane, ether, any appropriate mixture of suitable solvents, etc., preferably THF) under an inert atmosphere (e.g., argon, nitrogen, etc.) at -20 to 20°C, typically at 0 to 10°C and preferably at
35 approximately 0°C, and requires 0.2 to 2 hours. Reduction of the carboxylate can be effected with a suitable chemical reducing agent (e.g., sodium borohydride, lithium borohydride, etc., preferably sodium borohydride) at 0 to 25°C, typically



at 10 to 20°C and preferably at approximately 20°C, requiring 1 to 3 hours. Compounds of Formula 3 in which L is methanesulfonyloxy and R³ and R⁴ together are ethylene can be prepared by treating the corresponding compound of Formula 3
5 in which L is hydroxy with methanesulfonyl chloride in a suitable inert organic solvent (e.g., methylene chloride, dichloroethane, pyridine, any appropriate mixture of suitable solvents, etc., preferably methylene chloride) at 0 to 25°C, typically at 0 to 10°C and preferably at approximately 0°C,
10 requiring 0.5 to 2 hours.

The appropriate 3- and 1-(1-cyanocycloprop-1-ylmethyl)-2,4(1H,3H)-pyrimidinediones or 1-(1-cyanocycloprop-1-ylmethyl)-2,4,5(1H,3H,5H)-pyrimidinetriones are prepared by
15 alkylating a compound of the formula H-R⁵, or the protected derivative thereof, with 1-cyanocycloprop-1-yl-methyl methanesulfonate. The alkylation is carried out in the presence of a base (e.g., sodium hydride, potassium hydride, potassium carbonate, lithium hexamethyldisilazide, etc.,
20 preferably sodium hydride) and in a suitable inert organic solvent (e.g., DMF, THF, acetonitrile, any appropriate mixture of suitable solvents, etc., preferably DMF) at 20 to 70°C, typically at 50 to 60°C and preferably at approximately 50°C, and requires 4 to 24 hours.

25

The 1-cyanocycloprop-1-ylmethyl methanesulfonate is prepared by treating 1-cyanocycloprop-1-ylmethanol with methanesulfonyl chloride in a suitable inert organic solvent (e.g., methylene chloride, dichloroethane, pyridine, any
30 appropriate mixture of suitable solvents, etc., preferably methylene chloride) at 0 to 25°C, typically at 0 to 10°C and preferably at approximately 0°C, requiring 0.5 to 2 hours.

The 1-cyanocycloprop-1-ylmethanol is prepared by
35 converting 1-cyano-propane-1-carboxylic acid to methoxycarbonyl 1-cyanopropane-1-carboxylate and then reducing the carboxylate. The conversion of the carboxylic acid to the methoxycarbonyl carboxylate and its subsequent reduction to



the corresponding alcohol are both carried out in a manner similar to that described above for preparing compounds of Formula 3 from the corresponding 1-cyclopropanecarboxylic acid. Further details of the reaction steps set forth in this and the three preceding paragraphs are provided in Example 22, *infra*.

The 1-cyanocyclopropane-1-carboxylic acid can be prepared by reacting 1,2-dibromoethane with ethyl cyanoacetate. The reaction is carried out in the presence of a aqueous quaternary ammonium hydroxide (e.g., triethylbenzyl-ammonium hydroxide, tetrabutylammonium hydroxide, etc., preferably triethylbenzylammonium hydroxide) at 0 to 50°C, typically at 10 to 30°C and preferably at approximately 22°C, requiring 0.5 to 2 hours (for further details see R.K. Singh, S. Danishefsky, *J. Org. Chem.* (1975) 40, 2969).

The *N*-oxides of the compounds of Formula 3 can be prepared by treating an unoxidized form of the compound of Formula 3 with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, 3-chloroperoxybenzoic acid, etc.) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as methylene chloride) preferably methylene chloride) at -10 to 25°C, typically at 0 to 10°C and preferably at approximately 0°C, requiring 1 to 14 hours (for further details see Example 23, *infra*).

Compounds of Formula 4:

Compounds of Formula 4 are commercially available or can be prepared by methods known to those of ordinary skill in the art. For example, compounds of Formula 4 in which R⁶ is hydro can be prepared by reacting an acetic acid ester of the formula R⁷CH₂C(O)OR in which R⁷ is as defined in the Summary of the Invention with respect to Formula I (e.g., ethyl isovalerate, methyl methoxyacetate, etc.) with ethyl formate to give a corresponding 3-oxopropionate, reacting the 3-oxopropionate with thiourea to give the corresponding



2-thioxo-4(1*H*,3*H*)-pyrimidineone and then converting the thioxopyrimidineone to the corresponding pyrimidinedione. The reaction between the acetic acid ester and ethyl formate is carried out in the presence of a suitable base (e.g., sodium, sodium hydride, potassium hydride, sodium ethoxide, etc.) in a suitable solvent (e.g., diethyl ether, ethanol, THF, any appropriate mixture of suitable solvents, etc., preferably diethyl ether) at -10 to 40°C, typically at 0 to 25°C and preferably at approximately 10°C, requiring 20 to 90 hours.

10 The reaction with the thiourea is carried out in a suitable solvent, typically an alcohol (e.g., ethanol, methanol, isopropanol, any appropriate mixture of alcohols, etc.) and preferably ethanol, at 20 to 100°C, typically at 50 to 80°C and preferably at approximately 75°C, requiring 1 to 10 hours.

15 The conversion of the thioxopyrimidineone to the pyrimidinedione is effected with aqueous acid (e.g., concentrated hydrochloric acid) in a suitable solvent (e.g., water, ethanol, DMSO, any appropriate mixture of suitable solvents, etc.) at 50 to 120°C, typically at 70 to 110°C and preferably at approximately 100°C, and requires 2 to 12 hours (for further details see Example 2, *infra*).

20

Compounds of Formula 4 in which R⁵ is a group of Formula (a) wherein R⁶ is (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl or a group selected from aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are optionally further substituted with one to three radicals selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and aryl) can be prepared by reacting a corresponding compound of Formula 4 in which R⁶ is hydro with 1 molar equivalent of an appropriate alkylating agent in the presence of a suitable base. The reaction is carried out by proceeding as described above for alkylating compounds of Formula 3 in which R⁶ is hydro (for further details see Example 5, *infra*).

30

35

Alternatively, compounds of Formula 4 in which R⁵ is a group of Formula (a) wherein R⁶ is (C₁₋₆)alkyl, heterocyclo-(C₁₋₄)alkyl, aryl(C₁₋₄)alkyl or heteroaryl(C₁₋₄)alkyl and



certain protected derivatives of compounds of Formula 4 in which R^5 is a group of Formula (a) can be prepared by treating a corresponding compound of Formula 4 in which R^6 is hydro with a suitable silylating agent (e.g., 1,1,1,3,3,3-hexamethyldisilazane (HMDS), *N,O*-bistrimethylsilylacetamide, 5 hexamethylsiloxane, etc., preferably HMDS) in a suitable inert organic solvent (e.g., trifluoromethanesulfonic acid, DMF, NMP, THF, DME, toluene, any appropriate mixture of suitable solvents, etc., preferably trifluoromethanesulfonic acid) at 10 100 to 180°C, typically at 150 to 180°C and preferably at approximately 90°C, for 6 to 24 hours and then reacting with 1 molar equivalent of the alkylating agent (e.g., methoxymethyl acetate, benzyl bromide, etc.) neat or in a suitable inert organic solvent (e.g., trifluoromethanesulfonic acid, 15 dry benzene, toluene, 1,2-dichlorobenzene, any appropriate mixture of suitable solvents, etc., preferably trifluoromethanesulfonic acid) at 60 to 150°C, typically at 60 to 110°C and preferably at approximately 70°C, for 0.25 to 15 hours (for further details see Example 6, *infra.*).

20

Compounds of Formula 4 in which R^5 is a group of Formula (a) in which R^7 is cyano can be prepared by reacting (Z)-1-cyano-2-ethoxy-*N*-ethoxycarbonyl-acrylamide with a compound of the formula NH_2R^6 , or a protected derivative thereof, in which 25 R^6 is as defined in the Summary of the Invention with respect to Formula I. The reaction is carried out in a suitable solvent (e.g., water, ethanol, 2-methoxyethanol, any appropriate mixture of suitable solvents, etc., preferably water) at 30 to 100°C, typically at 50 to 70°C and preferably 30 at approximately 60°C, and requires 0.1 to 2 hours (for further details see Example 1, *infra.*).

Protected compounds of Formula 4 in which R^5 is a group of Formula (a) can be prepared by reacting a corresponding 35 compound of Formula 4 in which R^6 is hydro with a suitable protecting agent (e.g., 2-(trimethylsilyl)ethoxymethyl chloride, di-*tert*-butyldicarbonate, etc.). For example, a protected compound of Formula 4 wherein the protective group



is 2-(trimethylsilyl)ethoxymethyl can be prepared by reacting the unprotected compound with 2-(trimethylsilyl)ethoxy-methyl chloride in the presence of a suitable base (e.g., diisopropylethylamine, diethylaniline, potassium carbonate, sodium hydride, etc., preferably sodium hydride) in a suitable solvent (e.g., methylene chloride, THF, DMF, NMP,, etc., preferably DMF) at 0 to 30°C, typically at 20 to 30°C and preferably at approximately 22°C, requiring 1 to 16 hours (for further details see Example 7, *infra.*).

10

A compound of Formula 4 in which R⁵ is a group of Formula (a) wherein Z is C(R⁹), R⁷ and R⁹ together are -(CH₂)₄- and R⁹ is hydro (i.e., 5,6,7,8-tetrahydro-2,4(1H,3H)-quinazoline-dione) can be prepared by hydrolyzing 4-ethoxy-5,6,7,8-hexahydro-2(3H)-quinazolineone. The hydrolyzation is carried out with acid (e.g., hydrochloric acid) in a suitable solvent, typically an alcohol (e.g., ethanol, methanol, isopropanol, any appropriate mixture of alcohols, etc.) and preferably ethanol, at 50 to 85°C, typically at 60 to 70°C and preferably at approximately 65°C, and requires 0.5 to 5 hours (for further details see C. Bischoff and E. Schröder, *J. f. prakt. Chemie* 1985, 327, 129-132). The 4-ethoxy-5,6,7,8-hexahydro-2(3H)-quinazolineone is prepared by reacting ethyl 2-oxocyclohexanecarboxylate with cyanamide. The reaction with the cyanamide is carried out in a suitable solvent, typically an alcohol (e.g., ethanol, methanol, isopropanol, any appropriate mixture of alcohols, etc.) and preferably ethanol, at 25 to 100°C, typically at 50 to 80°C and preferably at approximately 75°C, and requires 1 to 40 hours.

30

Compounds of Formula 4 in which R⁵ is a group of Formula (b) can be prepared by alkylating a corresponding compound of the formula P-R⁵ in which P is a protective group (e.g., benzyl, 2-(trimethylsilyl)ethoxymethyl, tert-butyloxycarbonyl, etc.) and R⁵ is a group of Formula (b) wherein R⁶ is hydro with an appropriate alkylating agent (e.g., iodomethane, benzyl bromide, 4-methylbenzyl bromide, cyclohexylmethyl bromide, pyrazin-2-ylmethyl bromide, thien-2-ylmethyl bromide,



fur-3-ylmethyl bromide, biphenyl-2-ylmethyl bromide, etc.) and then deprotecting. In a similar fashion, a compound of Formula 4 in which R^5 is a group of Formula (b) and R^6 is benzyl can be prepared by alkylating a corresponding compound of Formula 4 in which R^6 is hydro with benzyl bromide and then deprotecting.

The alkylation is carried out with at least 2 molar equivalents of the alkylating agent in the presence of an excess amount of a suitable base (e.g., sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, etc., preferably sodium hydride) and in a suitable solvent (e.g., DMF, NMP, THF, DME, any appropriate mixture of suitable solvents, etc., preferably DMF) at 20 to 80°C, typically at 30 to 50°C and preferably at approximately 50°C, requiring 4 to 40 hours.

The deprotection can be effected by any means which removes the protective group without removing the radical designated by R^6 . For example, deprotection when the protective group is benzyl can be effected under conditions similar to those described above for de-benzylating a compound of Formula 3 in which R^6 is benzyl (for further details see Example 9, *infra.*). Deprotection when the protective group is 2-(trimethylsilyl)ethoxymethyl can be effected under the conditions described above for deprotecting a similarly protected compound of Formula I.

Compounds Formula 4 in which R^7 is hydroxymethyl can be prepared by reacting a corresponding compound of Formula 4 in which R^7 is hydro with paraformaldehyde. The reaction is carried out in the presence of an aqueous base (e.g., aqueous sodium hydroxide, aqueous potassium hydroxide, etc.) at 20 to 100°C, typically at 40 to 60°C and preferably at approximately 50°C, and requires 40 to 90 hours (for further details see Example 3, *infra.*).

Compounds of Formula 4 in which R^7 is hydroxyiminomethyl



can be prepared by converting a corresponding compound of Formula 4 in which R^7 is hydro to a 2,4-dioxo-5(1H,3H)-pyrimidinecarbaldehyde derivative via a modified Reimer-Tiemann reaction (see Gupta, V.S. and Huennekens, F.M. (1967), *Biochemistry*, 6(7), 2168) and then reacting the carbaldehyde with hydroxylamine hydrochloride. The conversion to the carbaldehyde is carried out with chloroform in the presence of aqueous sodium hydroxide at 10 to 100°C, typically at 60 to 80°C and preferably at reflux, and requires 0.5 to 15 hours. The reaction with the hydroxylamine hydrochloride is carried out in the presence of potassium acetate in a suitable solvent (e.g., water, methanol, 1/1 water/methanol, any appropriate mixture of suitable solvents, etc., preferable a 1/1 water/methanol) at 20 to 100°C, typically at 60 to 90°C and preferably at reflux, and requires 0.2 to 5 hours. Further details of the reaction steps set forth above are provided in Example 4, *infra*.)

Compounds of Formula 4 in which R^6 is optionally substituted aryl or heteroaryl can be prepared by reacting a compound of Formula 4 in which R^6 is hydro with an appropriate alkylating agent (e.g., 1-fluoro-4-iodobenzene, bromobenzene, 2-bromopyridine, etc.) in the presence of a suitable copper source (e.g., copper(I) oxide, copper bronze, copper(I) bromide, etc., preferably copper(I) oxide) in a suitable inert organic solvent (e.g., 2,4,6-trimethylpyridine, diethyl-aniline, NMP, any appropriate mixture of suitable solvents, etc., preferably 2,4,6-trimethylpyridine) at 100 to 180°C, typically at 150 to 175°C and preferably at reflux, requiring 4 to 20 hours (for further details see Example 8, *infra*.)

Compounds of Formula 4 in which R^5 is a group of Formula (c) wherein X is C(O) can be prepared by reacting a compound of the formula $H_2NC(O)NHR^6$ (e.g., urea, benzylurea, etc.) with an alkyl malonate of the formula $(R^8)_2C(COOR)_2$, wherein each R^6 and R^8 are as defined in the Summary of the Invention with respect to Formula I. The reaction is carried out in the presence of a base (e.g., sodium methoxide, potassium tert-



butoxide, sodium hydride, etc. preferably sodium methoxide) in a suitable solvent, typically an alcohol (e.g., ethanol, methanol, isopropanol, any appropriate mixture of alcohols, etc.) and preferably methanol, at 50 to 100°C, typically at 60 to 70°C and preferably at reflux (for further details see Example 10, infra.).

Compounds of Formula 5:

In general, compounds of Formula 5 are prepared by reacting a compound of Formula 2 with a compound of Formula 8. The reaction is carried out in the presence of a suitable base (e.g., sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, etc., preferably potassium carbonate) and in a suitable inert organic solvent (e.g., acetonitrile, DMF, NMP, any appropriate mixture of suitable solvents, etc., preferably acetonitrile) at 50 to 85°C, typically at 70 to 80°C and preferably at reflux, and requires 2 to 16 hours (for further details see Example 28, infra.).

20

Compounds of Formula 5 in which L is hydroxy and R³ and R⁴ are both methyl can be prepared by acylating a compound of Formula 2 with a protected 3-hydroxy-2,2-dimethylpropionyl halide (e.g., 3-benzyloxy-2,2-dimethylpropionyl chloride) to give the corresponding protected 3-hydroxy-2,2-dimethyl-1-(4-phenylpiperazin-1-yl)-1-propanone and then reducing and deprotecting to give the corresponding 2,2-dimethyl-3-(4-phenylpiperazin-1-yl)-1-propanol. The acylation is carried out in a suitable solvent (e.g., benzene, methylene chloride, any appropriate mixture of suitable solvents, etc.) and requires 0.1 to 6 hours at approximately 0°C. The reduction can be effected with a suitable chemical reducing agent (e.g., lithium aluminum hydride, etc.) in a suitable solvent (e.g., THF, any appropriate mixture of suitable solvents, etc.) requiring 1 to 30 hours at reflux. Deprotection when the protective group is benzyl is conveniently carried out by phase-transfer catalytic hydrogenation (e.g. ammonium formate, Pd/C; etc.) in a



suitable solvent, typically an alcohol (e.g., methanol, any appropriate mixture of suitable alcohols, etc.), for 2 to 14 hours at reflux. The 1-propanol can be converted to the corresponding 1-chloro-2,2-dimethyl-3-(4-phenylpiperazin-
5 1-yl)propane by reacting it with a suitable halogenating agent (e.g., p-toluenesulfonyl chloride, etc.) in a suitable solvent (e.g., methylene chloride, pyridine, any appropriate mixture of suitable solvents, etc.) requiring 0.1 to 12 hours at approximately 25°C.

10

The protected 3-hydroxy-2,2-dimethylpropionyl halide is prepared by methylating ethyl cyanoacetate to give 2-cyano-2-methylpropionic acid, reducing the propionic acid and protecting to give protected 3-hydroxy-2,2-dimethyl-
15 propanenitrile, hydrolyzing the protected 3-hydroxy-2,2-dimethylpropanenitrile to give protected 3-hydroxy-2,2-dimethylpropionic acid and then converting the propionic acid to a corresponding acid halide. The methylation can be effected with a suitable methylating agent (e.g., iodomethane,
20 etc.) in the presence of a base (e.g., triethylbenzyl ammonium hydroxide, etc.) in a suitable solvent (e.g., water, any appropriate mixture of suitable solvents, etc.) requiring 1 to 12 hours at approximately 20°C. The reduction is carried out by reacting the propionic acid with methyl chloroformate
25 for 0.1 to 2 hours at -5 to 0°C and then reacting with a suitable chemical reducing agent (e.g., sodium borohydride, etc.) in a suitable solvent (e.g., THF, any appropriate mixture of suitable solvents, etc.) for 1 to 4 hours at approximately 20°C. Protecting wherein the protective group
30 is benzyl can be effected by reacting the unprotected 3-hydroxy-2,2-dimethylpropanenitrile with benzyl bromide for 1 to 4 hours at approximately -5°C. The hydrolyzation can be effected with an aqueous base (e.g., 10% sodium hydroxide, etc.) in a suitable solvent, typically an alcohol (e.g.,
35 methanol, any appropriate mixture of suitable alcohols, etc.), for 2 to 12 hours at reflux. Conversion to the acid halide can be effected with a suitable halogenating agent (e.g., oxalyl chloride, etc.) in a suitable solvent (e.g., benzene,



methylene chloride, any appropriate mixture of suitable solvents, etc.) requiring 1 to 6 hours at approximately 25°C. Further details of the reaction steps set forth in this and the preceding paragraph are provided in Example 29, *infra*.

5

Compounds of Formula 6:

The compounds of Formula 6 can be prepared by reducing a corresponding nitrobenzene. The reduction can be effected with a suitable chemical reducing agent or by catalytic
10 hydrogenation and is carried out in a manner similar to that described above for reducing 4-(2-nitrophenyl)-1-piperazinecarbaldehyde in preparing the compound of Formula 2 in which R¹ is pyrrol-1-yl. Nitrobenzenes suitable for preparing compounds of Formula 6 are commercially available or
15 can be prepared by methods known to those of ordinary skill in the art. For example, suitable 2-oxynitrobenzenes can be prepared by reacting 2-fluoronitrobenzene with an appropriate alcohol (e.g., a (C₁₋₆)alcohol such as methanol, ethanol, 2,2,2,-trifluoroethanol and the like; a (C₃₋₆)cycloalcohol
20 such as cyclopropylmethanol, 2-cyclohexylethanol and the like; an arylalcohol such as phenol and the like; an aryl(C₁₋₄)-alcohol such as benzylalcohol and the like; a heteroalcohol such as 2-pyridinol and the like; a hetero(C₁₋₄)alcohol such as 2-pyridinemethanol and the like; etc.) in the presence of a
25 strong base (e.g., potassium *tert*-butoxide, sodium hydride, potassium hydride, lithium hexamethyldisilazide, etc., preferably potassium *tert*-butoxide). The reaction is carried out in a suitable solvent (e.g., 1,2-dimethoxyethane, THF, *tert*-butylmethylether, any appropriate mixture of solvents,
30 etc., preferably 1,2-dimethoxyethane) at -30 to 30°C, typically at -20 to 20°C and preferably at approximately -10°C, and requires 0.2 to 2 hours (for further details see Example 11, *infra*)).

35 Alternatively, suitable 2-oxynitrobenzenes can be prepared by reacting a corresponding 2-nitrophenol with a compound of the formula R-L, in which L is a leaving group (typically methanesulfonyloxy) and R¹ is 2-propynyl, a group



selected from (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl and (C₃₋₆)cyclo-
alkyl(C₁₋₄)alkyl (which group is optionally further
substituted with one to three halo atoms) or a group selected
from aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and
5 heteroaryl are optionally further substituted with one to
three radicals selected from halo, cyano, (C₁₋₆)alkyloxy,
(C₁₋₆)alkyl and aryl), in the presence of a suitable base,
typically a nitrogen base (e.g., triethylamine,
N,N-diisopropylethylamine, etc.) or a carbonate salt base
10 (e.g., potassium carbonate, sodium carbonate, cesium
carbonate, etc.) and preferably potassium carbonate, in a
suitable inert organic solvent (e.g., DMF, NMP, THF, DMSO, any
appropriate mixture of suitable solvents, etc., preferably
DMF) at 60 to 160°C, typically at 140 to 160°C and preferably
15 at approximately 150°C, requiring 10 to 24 hours (for further
details see Example 12, infra.).

Compounds of Formula 7:

Compounds of Formula 7 are commercially available or can
20 be prepared by methods known to those of ordinary skill in the
art. For example, a compound of Formula 7 in which L is
fluoro, R¹ is oxazol-2-yl and R² is hydro (i.e., 2-fluoro-
1-oxazol-2-ylbenzene) can be prepared by reacting
2-fluorobenzoic acid chloride with 2-bromoethylamine
25 hydrobromide to give 2-fluoro-1-(4,5-dihydrooxazol-2-
yl)benzene and then oxidizing. The reaction with the 2-
bromoethylamine hydrobromide is carried out in the presence of
a suitable base, typically a nitrogen base (e.g., triethyl-
amine, N,N-diisopropylethylamine, etc., preferably
30 triethylamine) and in a suitable solvent (e.g., benzene,
methylene chloride, DMF, toluene, THF, any appropriate mixture
of suitable solvents, etc., preferably benzene) at
50 to 110°C, typically at 100 to 110°C and preferably at
reflux, and requires 2 to 20 hours. The oxidation can be
35 carried out with a suitable oxidizing agent (e.g., nickel
peroxide hydrate, manganese dioxide, etc., preferably nickel
peroxide hydrate) in a suitable solvent (e.g., benzene,
methylene chloride, 1,2-dichloroethane, decalin, any



appropriate mixture of suitable solvents, etc., preferably benzene) at 20 to 150°C, typically at 50 to 120°C and preferably at reflux, and requires 2 to 40 hours. Further details of the process steps set forth in this paragraph are
5 provide in Example 15, infra.

Additional Processes:

Compounds of Formula I in which R⁵ is a group of Formula (c), wherein X is CH(OH) and one R⁸ is *cis*-hydroxy, or a group
10 of Formula (d), wherein one R⁸ is *cis*-hydroxy, can be prepared by hydroxylating a corresponding compound of Formula I in which R⁵ is a group of Formula (a) or (b), respectively, wherein Z is CH. The hydroxylation can be carried out by treating with acid (e.g., formic acid, trifluoroacetic acid,
15 etc.) and *N*-bromosuccinimide in a suitable aqueous solvent (e.g., 9:1 to 1:9 aqueous mixtures of DMSO, DMF, etc., preferably 5:1 DMSO/water) at 0 to 40°C, typically at 10 to 25°C and preferably at approximately 20°C, requiring 4 to 24 hours, followed by neutralization to pH 7-8 by
20 treating with a suitable aqueous base (e.g., aqueous sodium bicarbonate, potassium bicarbonate, disodium hydrogen phosphate, etc., preferably aqueous sodium bicarbonate) at -10 to 30°C, preferably at approximately 10°C for 10 to 30 minutes (for further details see Example 35, infra.).

25

Compounds of Formula I in which R⁶ is hydro can be prepared by de-benzylating a compound of Formula I in which R⁶ is benzyl. The de-benzylation is carried out under conditions similar to those described above for de-benzylating a compound
30 of Formula 3(a) in which R⁶ is benzyl (for further details see Example 32, infra.).

Compounds of Formula I in which R⁶ is (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl or a group selected
35 from aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are optionally further substituted with one to three radicals selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl or aryl) can be prepared by reacting a compound of



Formula I in which R^6 is hydro with an appropriate alkylating agent (e.g., dimethylsulfate, benzyl bromide, 4-methylbenzyl bromide, cyclohexylmethyl bromide, pyrid-2-ylmethyl chloride, 1,6-dimethylbenzyl chloride, 4-chlorobenzyl chloride, pyrazin-
5 2-yl-methyl bromide, thien-2-ylmethyl bromide, fur-3-ylmethyl bromide, biphenyl-2-yl-methyl bromide, etc.). Typically the reaction is carried out in the presence of a suitable base (e.g., tetraalkylammonium halide such as tetrabutylammonium fluoride, benzyltrimethylammonium chloride and the like,
10 tetraalkylammonium hydroxide, tetraalkylammonium chloride with potassium hydroxide, potassium carbonate, etc., preferably tetrabutylammonium fluoride) and in a suitable inert organic solvent (e.g., THF, DME, DMF, any appropriate mixture of suitable solvents, etc., preferably THF) at 10 to 50°C,
15 typically at 20 to 25°C and preferably at approximately 20°C, and requires 1 to 20 hours (for further details see Example 33, infra.).

Compounds of Formula I in which R^6 is optionally
20 substituted aryl or heteroaryl can be prepared by reacting a compound of Formula I in which R^6 is hydro with an appropriate alkylating agent (e.g., 1-fluoro-4-iodobenzene, bromobenzene, 2-bromopyridine, etc.) in the presence of a suitable copper source (e.g., copper(I) oxide, copper bronze, copper(I)
25 bromide, etc., preferably copper(I) oxide) in a suitable inert organic solvent (e.g., 2,4,6-trimethylpyridine, diethyl-aniline, NMP, any appropriate mixture of suitable solvents, etc., preferably 2,4,6-trimethylpyridine) at 100 to 180°C, typically at 150 to 170°C and preferably at reflux, requiring
30 4 to 24 hours.

Compounds of Formula I in which R^7 is carbamoyl can be prepared by treating a compound of Formula I in which R^7 is cyano with acid (e.g., trifluoroacetic acid (TFA),
35 concentrated sulfuric acid, any appropriate mixture of suitable acids, etc., preferably TFA) at 50 to 100°C, typically at 70 to 85°C and preferably at reflux, for 0.1 to 96 hours (for further details see Example 34, infra.).



Compounds of Formula I in which R^1 is amino can be prepared by hydrogenating a compound of Formula I in which R^1 is nitro. The hydrogenation is carried out with a suitable catalyst (e.g., 10% Pd/C, palladium hydroxide, palladium acetate, etc., preferably 10% Pd/C) in a suitable alcohol solvent (e.g., ethanol, methanol, any appropriate mixture of suitable alcohols, etc., preferably ethanol) at 20 to 40°C, typically at 20 to 30°C and preferably at approximately 25°C, and 15 to 40 psi, typically at 15 to 30 psi and preferably at approximately 15 psi, and requires 4 to 24 hours.

Compounds of Formula I in which R^1 is acetylamino, trifluoroacetylamino or methylsulfonylamino can be prepared by reacting a compound of Formula I in which R^1 is amino with acetic anhydride, trifluoroacetic anhydride or methanesulfonyl chloride, respectively. The reaction is carried out in a suitable inert organic solvent (e.g., pyridine, 2,6-dimethylpyridine, dichloromethane, triethylamine, any appropriate mixture of suitable solvents, etc., preferably pyridine) at 0 to 40°C, typically at 0 to 10°C and preferably at approximately 0°C, and requires 0.5 to 3 hours.

Compounds of Formula I in which R^1 , R^2 and/or R^5 is hydroxy can be prepared by demethylating a compound of Formula I in which R^1 , R^2 and/or R^5 is methoxy. The de-methylation can be carried out with an appropriate demethylating agent (e.g., sodium cyanide, boron tribromide, boron trichloride, etc., preferably sodium cyanide) in a suitable inert organic solvent (e.g., dimethyl sulfoxide (DMSO), NMP, HMPA, methylene chloride, 1,2-dichloroethane, any appropriate mixture of suitable solvents, etc., preferably DMSO) at 80 to 180°C, typically at 100 to 160°C and preferably at reflux, and requires 2 to 24 hours. Alternatively, the de-methylation can be effected with a suitable aqueous acid (e.g., aqueous hydrobromic acid, pyridine hydrochloride, any appropriate mixture of suitable acids, etc., preferably aqueous hydrobromic acid) at reflux, for 5 to 20 hours. Proceeding as



described above the following compound of Formula I was prepared: 3-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl}propyl)-5-hydroxy-2,4(1H,3H)-pyrimidine-dione, m.p. 192-194; Anal.: Calcd. for

5 $C_{19}H_{22}F_4N_4O_4 \cdot (C_2H_2O_2)_{1.5}$: C, 48.39; H, 4.55; N, 9.03%;
Found: C, 48.20; H, 4.67; N, 9.18%.

Compounds of Formula I in which R^2 is halo can be prepared by halogenating a compound of Formula I in which R^2 is hydro. The halogenation can be carried out with a suitable
10 halogenating agent (e.g., NCS, NBS, etc.) in a suitable inert organic solvent (e.g., DMF, DMSO, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), NMP, any appropriate mixture of suitable solvents, etc., preferably DMF) at
15 0 to 100°C, typically at 20 to 60°C and preferably at approximately 20°C, requiring 1 to 48 hours.

Compounds of Formula I in which R^2 is cyano can be prepared by cyano-de-halogenation of a compound of Formula I
20 in which R^2 is halo. The reaction is carried out with copper(I) cyanide in a suitable inert organic solvent (e.g., NMP, DMPU, DMF, any appropriate mixture of suitable solvents, etc., preferably NMP) under an inert atmosphere (e.g., argon, nitrogen, etc.) at 150 to 220°C, preferably at approximately
25 200°C, and requires 8 to 24 hours.

Compounds of Formula I may be prepared as pharmaceutically acceptable acid addition salts by reacting the free base forms of a compound of Formula I with a
30 pharmaceutically acceptable inorganic or organic acid. Alternatively, the pharmaceutically acceptable base addition salts of compounds of Formula I may be prepared by reacting the free acid forms of compounds of Formula I with pharmaceutically acceptable inorganic or organic bases.
35 Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this application. Alternatively, the salt forms of



the compounds of Formula I may be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, compounds of Formula I in an acid addition salt form may be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, etc.). Compounds of Formula I in a base addition salt form may be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

The *N*-oxides of the compounds of Formula I can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, meta-chloroperoxybenzoic acid, etc.) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as methylene chloride) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, etc.) in a suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, etc.) at 0 to 80°C.

As will be apparent to one of ordinary skill in the art, compounds of Formula I may be prepared as individual isomers or mixtures of isomers. Isomers which are diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are readily separated by taking advantage of these dissimilarities. For example, diastereomers can be separated by chromatography or,



preferably, by separation/resolution techniques based upon differences in solubility. Optical isomers can be separated by reacting the racemic mixture with an optically active resolving agent to form a pair of diastereomeric compounds.

5 The isomers are then separated by any of the techniques described above for the separation of diastereomers and the pure optical isomer recovered, along with the resolving agent, by any practical means that would not result in racemization. While resolution of optical isomers can be carried out using

10 covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred, e.g., crystalline diastereomeric salts. Suitable resolving acids include tartaric acid, o-nitrotartranilic acid, mandelic acid, malic acid, the 2-arylpropionic acids in general, and

15 camphorsulfonic acid.

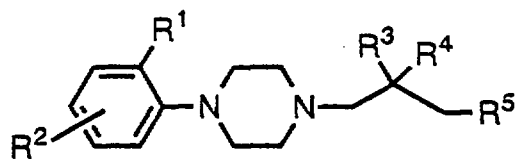
Individual isomers of compounds of Formula I can also be separated by such methods as direct or selective crystallization or by any other method known to one of

20 ordinary skill in the art. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds of Formula I can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981). Alternatively,

25 individual isomers of compounds of Formula I can be prepared using the isomeric forms of the starting materials.

In summary, an aspect of this invention is a process for preparing a compound of Formula I:

30



I

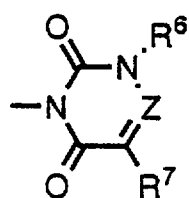
in which:

R¹ is acetylamino, amino, cyano, trifluoroacetylamino, halo,

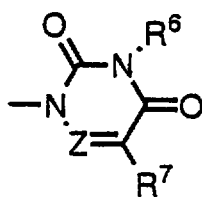
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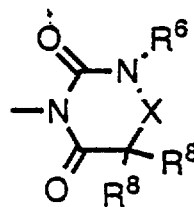
- hydro, hydroxy, nitro, methylsulfonylamino, 2-propynyloxy, a group selected from (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl, (C₁₋₆)alkyloxy, (C₃₋₆)cycloalkyloxy, (C₃₋₆)cycloalkyl(C₁₋₄)alkyloxy and (C₁₋₄)alkylthio (which group is optionally further substituted with one to three halo atoms) or a group selected from aryl, aryl(C₁₋₄)alkyl, heteroaryl, heteroaryl(C₁₋₄)alkyl, aryloxy, aryl(C₁₋₄)alkyloxy, heteroaryloxy and heteroaryl(C₁₋₄)alkyloxy (which aryl and heteroaryl are optionally further substituted with one to two radicals independently selected from halo and cyano);
- R² is cyano, halo, hydro, hydroxy or a group selected from (C₁₋₆)alkyl and (C₁₋₆)alkyloxy (which group is optionally further substituted with one to three halogen atoms);
- R³ and R⁴ are both hydro or methyl or together are ethylene; and
- R⁵ is a group selected from Formulae (a), (b), (c) and (d):



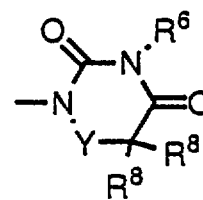
(a)



(b)



(c)



(d)

20

in which:

X is C(O), CH₂ or CH(OH);

Y is CH₂ or CH(OH);

Z is N or C(R⁹), wherein R⁹ is hydro, (C₁₋₆)alkyl or hydroxy;

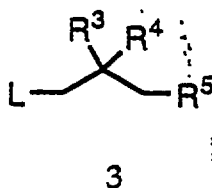
- R⁶ is hydro, a group selected from (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl (which group is optionally further substituted with one to three halo atoms) or a group selected from aryl, heteroaryl, aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are optionally further substituted with one to three radicals selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and aryl);

R⁷ is (C₁₋₆)alkanoyl, carbamoyl, cyano, di(C₁₋₆)alkylamino,

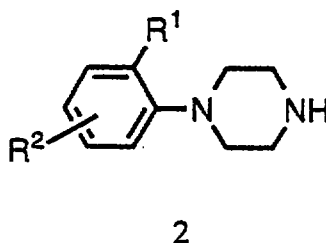


halo, hydro, hydroxy, hydroxyiminomethyl, (C₁₋₆)alkylsulfonyl, (C₁₋₆)alkylthio, a group selected from (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₁₋₆)alkyloxy and (C₁₋₆)alkyloxy(C₁₋₄)alkyl (which group is optionally further substituted with one to three radicals selected from halo, hydroxy or (C₁₋₆)alkyloxy) or a group selected from aryl, heteroaryl, aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are optionally further substituted with one to three radicals selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and aryl) or R⁷ and R⁹ together are tetramethylene; and each R⁸ is independently hydro, hydroxy, methyl or ethyl; and the pharmaceutically acceptable salts and N-oxides thereof, which process comprises:

(a) alkylating a compound of Formula 3:



or a protected derivative thereof, in which L is a leaving group and each R³, R⁴ and R⁵ are as defined above with respect to Formula I, with a compound of Formula 2:

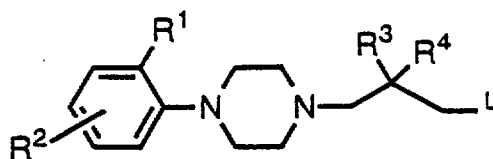


or a protected derivative thereof, in which each R¹ and R² are as defined above with respect to Formula I, and then deprotecting when necessary; or

(b) alkylating a compound of the formula H-R⁵ with a compound of Formula 5:

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5

in which L is a leaving group and each R¹, R², R³ and R⁴ are as defined above with respect to Formula I; and

5

(c) optionally further de-benzylating a compound of Formula I in which R⁶ is benzyl to give a compound of Formula I in which R⁶ is hydro;

- 10 (d) optionally further alkylating a compound of Formula I in which R⁶ is hydro to give a compound of Formula I in which R⁶ is (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl or a group selected from aryl, heteroaryl, aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are
- 15 optionally further substituted with one to three radicals selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and aryl);

- (e) optionally further oxidizing a compound of Formula I to
- 20 give an N-oxide derivative;

(f) optionally further reducing an N-oxide derivative of a compound of Formula I to unoxidized form;

- 25 (g) optionally further converting a compound of Formula I into a pharmaceutically acceptable salt; and

(h) optionally further converting a salt form of a compound of Formula I to non-salt form.

30

In any of the above processes, a reference to Formula I refers to such Formula wherein Z, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined in their broadest definitions set forth in the Summary of the Invention, with the processes applying



particularly well to the presently preferred embodiments.

EXAMPLES:

5

EXAMPLE 1

1-(4-Methoxybenzyl)-5-cyano-2,4(1H,3H)-pyrimidinedione

The following is the preparation of a compound of Formula
10 4 in which R⁵ is a group of Formula (a) wherein Z is CH,
R⁶ is 4-methoxybenzyl and R⁷ is cyano.

A mixture of (Z)-1-cyano-2-ethoxy-N-ethoxycarbonylacryl-
amide (1 g, 4.71 mmol), 4-methoxybenzylamine (1.29 g,
15 9.42 mmol) and water (15 ml) was heated 10 minutes at
approximately 70°C. The reaction mixture was cooled and
treated with 10 N hydrochloric acid (1 ml). The solids were
collected, washed with water, dried in vacuo and
recrystallized from ethanol/chloroform to give 1-benzyl-5-
20 cyano-1-(4-methoxybenzyl)-2,4(1H,3H)-pyrimidinedione (788 mg,
3.06 mmol).

EXAMPLE 2

25

5-prop-2-yl-2,4(1H,3H)-pyrimidinedione

The following is the preparation of a compound of Formula
4 in which R⁵ is a group of Formula (a) wherein Z is CH,
R⁶ is hydro and R⁷ is prop-2-yl.

30

A suspension of sodium (2.84 g, 123.5 mmol) in dry
diethyl ether (27 ml) was cooled to 0°C and a mixture of ethyl
isovalerate (23.04 ml, 153 mmol), ethyl formate (16.65 ml,
206 mmol) and dry diethyl ether (19 ml) was added dropwise.
35 The mixture was cooled 48 hours at 0°C and allowed to stand
24 hours at 25°C and then concentrated in vacuo. The residue
was stirred 7 hours at reflux with thiourea (5.95 g, 78 mmol)
and absolute ethanol (44 ml). The mixture was concentrated



and the residue was dissolved in water (40 ml). The solution was washed with diethyl ether, treated with concentrated hydrochloric acid and cooled to 0°C. The solids were collected and recrystallized from ethanol. The crystals were
5 suspended in 10% aqueous chloroacetic acid (11 ml) and the suspension was heated 8 hours at reflux and then cooled. The solids were collected and recrystallized from ethanol to give 5-prop-2-yl-2,4(1H,3H)-pyrimidinedione, m.p. 284-286°C.

10 Proceeding as in Example 2, but substituting methyl methoxyacetate for ethyl isovalerate gave 5-methoxy-2,4(1H,3H)-pyrimidinedione.

EXAMPLE 3

15

5-Hydroxymethyl-2,4(1H,3H)-pyrimidinedione

The following is the preparation of a compound of Formula 4 in which R⁵ is a group of Formula (a) wherein which Z is CH,
20 R⁶ is hydro and R⁷ is hydroxymethyl.

A mixture of uracil (9 g, 80.3 mmol), paraformaldehyde (3 g) and 0.42 N potassium hydroxide (125 ml) was heated 90 hours at 50°C. The reaction mixture was diluted with water
25 (350 ml), stirred with Dowex® 50 ion-exchange resin (30 g, H form, 100-200 mesh), filtered, concentrated in vacuo to a volume of 20 ml and refrigerated. The solids were collected and recrystallized from water (50 ml) to give 5-hydroxymethyl-2,4(1H,3H)-pyrimidinedione (9.5 g, 65.04 mmol), m.p. 260-300°C
30 (dec).

EXAMPLE 4

5-Hydroxyiminomethyl-2,4(1H,3H)-pyrimidinedione

35

The following is the preparation of a compound of Formula 4 in which R⁵ is a group of Formula (a) wherein Z is CH, R⁶ is hydro and R⁷ is hydroxyiminomethyl.



A mixture of uracil (6 g, 53.5 mmol), 50% sodium hydroxide (12 ml, 150 mmol) and chloroform (5 ml) was heated at reflux and additional chloroform (20 ml) was added over 15 minutes. The mixture was heated 4 hours at reflux and then concentrated at 50°C using a water aspirator. The residue was dissolved in water (5 ml) and the solution was treated with 5 N hydrochloric acid. The solution was chromatographed on Dowex® 50 eluting with water to give 2,4-dioxo-5(1H,3H)-pyrimidinecarbaldehyde (1.79 g, 11.2 mmol).

A mixture of 2,4-dioxo-5(1H,3H)-pyrimidinecarbaldehyde (1.79 g, 12.8 mmol), methanol (35 ml) and water (35 ml) was heated at reflux and then a mixture of hydroxylamine hydrochloride (905 mg, 13 mmol), potassium acetate (1.28 g, 13 mmol) and water (15 ml) was added. The mixture was cooled and the solids were collected, washed with water and recrystallized from water/methanol to give 5-hydroxyimino-methyl-2,4(1H,3H)-pyrimidinedione (1.68 g, 10.8 mmol).

20

EXAMPLE 5

1-Benzyl-5-methyl-2,4(1H,3H)-pyrimidinedione

25 The following is the preparation of a compound of Formula 4 in which R⁵ is a group of Formula (a) wherein Z is CH, R⁶ is benzyl and R⁷ is methyl.

A mixture of thymine (7.68 g, 61 mmol), benzyl bromide (10.55 g, 61 mmol), potassium carbonate (17.05 g, 123 mmol) and DMF (90 ml) was stirred 12 hours at 25°C. The reaction mixture was poured into water (500 ml) and extracted with ethyl acetate (3x 200 ml). The combined extract was washed with water (5x 100 ml), dried (Na₂SO₄) and concentrated in vacuo. The residue was crystallized from hexane/ethyl acetate to give 1-benzyl-5-methyl-2,4(1H,3H)-pyrimidinedione (9.4 g, 43.9 mmol), m.p. 170-173°C.

35

This Sheet Has Been Replaced



Proceeding as in Example 5, but substituting a different starting material for benzyl bromide and/or 5-methyl-2,4(1H,3H)-pyrimidinedione gave the following compounds of Formulae 3 and 4:

- 5 substituting 3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione and pyrid-4-ylmethyl chloride gave 3-(3-chloropropyl)-5-methyl-1-pyrid-4-ylmethyl-2,4(1H,3H)-pyrimidinedione;
- 10 substituting 5-ethyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-5-ethyl-2,4(1H,3H)-pyrimidinedione, m.p. 154-155°C; substituting 5-propyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-5-propyl-2,4(1H,3H)-pyrimidinedione; substituting 5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione gave
- 15 1-benzyl-5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione, m.p. 194-195°C; substituting 6-methyl-1,2,4-triazine-3,5(2H,4H)-dione gave 4-benzyl-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione, m.p. 143-146°C;
- 20 substituting 2,4-dioxo-5(1H,3H)-pyrimidinecarbaldehyde gave 1-benzyl-2,4-dioxo-5(1H,3H)-pyrimidinecarbaldehyde; substituting 6-cyano-5-methyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-6-cyano-5-methyl-2,4(1H,3H)-pyrimidinedione; substituting 2,4(1H,3H)-pyrimidinedione gave 1-benzyl-
- 25 2,4(1H,3H)-pyrimidinedione; substituting 4-methoxybenzyl bromide gave 1-(4-methoxybenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione; substituting 2,4-dimethylbenzyl bromide gave 1-(2,4-dimethylbenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione;
- 30 substituting 2-methylbenzyl bromide gave 1-(2-methylbenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione; substituting biphenyl-3-ylmethyl bromide gave 1-biphenyl-3-ylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione; substituting cyclohexylmethyl bromide gave 1-cyclohexylmethyl-
- 35 5-methyl-2,4(1H,3H)-pyrimidinedione; substituting pyrazin-2-ylmethyl chloride gave 1-pyrazin-2-ylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione; substituting pyrid-4-ylmethyl chloride gave 1-pyrid-4-



ylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione;
substituting pyrid-3-ylmethyl chloride gave 1-pyrid-3-
ylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione;
substituting fur-2-ylmethyl chloride gave 1-fur-2-ylmethyl-
5 5-methyl-2,4(1H,3H)-pyrimidinedione;
substituting fur-3-ylmethyl chloride gave 1-fur-3-ylmethyl-
5-methyl-2,4(1H,3H)-pyrimidinedione;
substituting thien-2-ylmethyl chloride gave 1-thien-2-
ylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione; and
10 substituting methyl iodide gave 1,5-dimethyl-2,4(1H,3H)-
pyrimidinedione.

EXAMPLE 6

15 1-Methoxymethyl-5-methyl-2,4(1H,3H)-pyrimidinedione

The following is the preparation of a protected
derivative compound of Formula 4 in which R⁵ is a group of
Formula (a) wherein Z is C(CH₃), R⁷ is methyl and the
20 protective group is methoxymethyl.

A mixture of thymine (100 g, 0.79 mol), trifluoromethane-
sulfonic acid (2 ml, 20 mmol) and HMDS (418 ml, 1.98 mol) was
heated 16 hours with stirring at 90°C and briefly at reflux
25 and then distilled in vacuo at 80°C to remove the excess HMDS.
The mixture was treated with trifluoromethanesulfonic acid
(1.5 ml, 20 mmol) and then methoxymethyl acetate (88 ml,
0.89 mol) was added at a rate such that the reaction
temperature did not exceed 95°C. The mixture was heated
30 20 minutes at 70°C and then distilled in vacuo to remove the
trimethylsilyl acetate formed as byproduct. The reaction
mixture was poured into isopropanol (800 ml) and stirred 18
hours. The solids were collected, washed with ethyl acetate
and dried to give 1-methoxymethyl-5-methyl-
35 2,4(1H,3H)-pyrimidinedione (116 g, 0.68 mol).

Proceeding similarly as in Example 5, but substituting
different starting materials for thymine and/or methoxymethyl



acetate, gave the following compounds of Formula 4:

- substituting 5,6-dimethyl-2,4(1H,3H)-pyrimidinedione and benzyl bromide gave 1-benzyl-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione, m.p. 187-189°C;
- substituting 5-methoxymethyl-2,4(1H,3H)-pyrimidinedione and benzyl bromide gave 1-benzyl-5-methoxymethyl-2,4(1H,3H)-pyrimidinedione, m.p. 134-136°C;
- substituting 6-methyl-2,4(1H,3H)-pyrimidinedione and benzyl bromide gave 1-benzyl-6-methyl-2,4(1H,3H)-pyrimidinedione, m.p. 228-230°C;
- substituting 5-hydroxyiminomethyl-2,4(1H,3H)-pyrimidinedione and benzyl bromide gave 1-benzyl-5-hydroxyiminomethyl-2,4(1H,3H)-pyrimidinedione, m.p. 172-174°C; and
- substituting 2,2,2-trifluoroethyl p-toluenesulfonate gave 1-(2,2,2-trifluoro-ethoxy)-5-methyl-2,4(1H,3H)-pyrimidine-dione.

EXAMPLE 7

1-[2-(Trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione

The following is a of the preparation of a protected compound of Formula 4 in which R⁵ is a group of Formula (a) wherein Z is CH, R⁷ is hydro and the protective group is 2-(trimethylsilylethoxy)methylbenzyl.

A solution of 60% sodium hydride (2 g, 50 mmol) in mineral oil was washed with hexanes (2x 20 ml) and cooled to 0°C. The solution was diluted with DMF (200 ml) and then uracil (5.6 g, 50 mmol) was added portionwise over 30 minutes. The mixture was treated with 2-(trimethylsilyl)ethoxymethyl chloride (8.8 ml, 50 mmol) and allowed to warm to 25°C and stand 4 hours. The reaction mixture was diluted with water (500 ml) and extracted with diethyl ether (4x 100 ml). The combined extract was washed with brine, dried (Na₂SO₄), filtered and concentrated. The residue was purified by chromatography on silica gel eluting with hexanes/ethyl



acetate (2:1) to give 1-[2-(trimethylsilyl)ethoxymethyl]-
2,4(1H,3H)-pyrimidinedione (1.8 g, 7.4 mmol), m.p. 120-122°C.

Proceeding as in Example 7, but a different starting
5 material for uracil and/or 2-(trimethylsilyl)ethoxymethyl
chloride gave the following protected compounds of Formula 4:

substituting 5-prop-2-yl-2,4(1H,3H)pyrimidinedione and di-
tert-butyl dicarbonate gave tert-butyl 5-prop-2-yl-2,4-dioxo-
10 (1H,3H)-1-pyrimidinecarboxylate;
substituting 5-methylthio-2,4(1H,3H)pyrimidinedione and di-
tert-butyl dicarbonate gave tert-butyl 5-methylthio-2,4-dioxo-
(1H,3H)-1-pyrimidine-carboxylate;
substituting 5-fur-2-yl-2,4(1H,3H)pyrimidinedione and di-tert-
15 butyl dicarbonate gave tert-butyl 5-fur-2-yl-2,4-dioxo-
(1H,3H)-1-pyrimidinecarboxylate;
substituting 5-methoxy-2,4(1H,3H)-pyrimidinedione gave
1-[2-(trimethylsilyl)ethoxymethyl]-5-hydroxymethyl-
2,4(1H,3H)-pyrimidinedione; and
20 substituting 5-hydroxymethyl-2,4(1H,3H)-pyrimidinedione gave
1-[2-(trimethylsilyl)ethoxymethyl]-5-hydroxymethyl-
2,4(1H,3H)-pyrimidinedione.

EXAMPLE 8

25 1- and 3-(4-Fluorophenyl)-5-methyl-2,4(1H,3H)-pyrimidinedione

The following is the preparation of a compound of Formula
4 in which R⁵ is a group of Formula (a) wherein Z is CH,
30 R⁶ is 4-fluorophenyl and R⁷ is methyl and a compound of
Formula 4 in which R⁵ is a group of Formula (b) wherein Z is
CH, R⁶ is 4-fluorophenyl and R⁷ is methyl.

A mixture of thymine (5 g, 39.6 mmol), 1-fluoro-
35 4-iodobenzene (9.68 g, 5 ml, 43.6 mmol), copper(I) oxide
(6.24 g, 43.6 mmol) and 2,4,6-trimethylpyridine (200 ml) was
heated 12 hours at reflux with stirring and under an argon
atmosphere. The reaction mixture then was cooled to 25°C,



diluted with methylene chloride (300 ml), washed with 5% sulfuric acid (5x 300 ml) and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to give 1-(4-fluoro-phenyl)-
5 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (1.85 g, 9.2 mmol), m.p. 212-214°C, and 3-(4-fluorophenyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (2.39 g, 10.2 mmol), m.p. 229-231°C.

10 Proceeding as in Example 8, but substituting bromobenzene for 1-fluoro-4-iodobenzene gave 5-methyl-1-phenyl-2,4(1*H*,3*H*)-pyrimidinedione, m.p. 200-202°C, and 5-methyl-3-phenyl-2,4(1*H*,3*H*)-pyrimidinedione, m.p. 258-260°C.

15

EXAMPLE 9

3-Benzyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione

The following is the preparation of a compound of Formula
20 4 in which R⁵ is a group of Formula (b) wherein Z is CH, R⁶ is benzyl and R⁷ is methyl.

A mixture of 1,3-dibenzyl-5-methyl-2,4(1*H*,3*H*)-pyrimidine-
dione (2 g, 6.5 mmol), 5% palladium on carbon (3 g) and
25 0.4 N ammonium formate (250 ml in methanol) was heated 1.5 hours at reflux. The reaction mixture then was filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with methylene chloride/methanol (95:5) to give 3-benzyl-5-methyl-2,4(1*H*,3*H*)-pyrimi-
30 dinedione, m.p. 208-210°C.

Proceeding as in Example 9, but substituting different starting materials for 1,3-dibenzyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione, the following compounds of Formula 4 were
35 prepared:

substituting 2,4-dibenzyl-6-methyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione gave 2-benzyl-6-methyl-1,2,4-triazine-



3,5(2H,4H)-dione, m.p. 141-142°C;
substituting 1,3-dibenzyl-5,6-dimethyl-2,4(1H,3H)-pyrimidine-
dione gave 3-benzyl-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione;
and
5 substituting 1,3-dibenzyl-6-methyl-2,4(1H,3H)-pyrimidinedione
gave 3-benzyl-6-methyl-2,4(1H,3H)-pyrimidinedione.

EXAMPLE 10

10 1-Benzyl-5,5-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione

The following is the preparation of a compound of Formula
4 in which R⁵ is a group of Formula (c) wherein X is C(O), R⁶
is benzyl and each R⁸ is methyl.

15

A mixture of sodium methoxide (0.343 g, 14.9 mmol),
benzylurea (1.6 g, 10.6 mmol), diethyl dimethylmalonate
(1.9 g, 10 mmol) and methanol (15 ml) was heated 6 hours at
reflux. The reaction mixture was concentrated and the residue
20 was stirred with water (30 ml) at 5°C and then hydrochloric
acid was added. The solids were collected, washed with water
and dried to give 1-benzyl-5,5-dimethyl-
2,4,6(1H,3H,5H)-pyrimidinetrione, m.p. 136-137°C.

25

EXAMPLE 11

4-Fluoro-2-(2,2,2-trifluoroethoxy)aniline

30 The following is the preparation of a compound of Formula
6 in which R¹ is 2,2,2-trifluoromethoxy and R² is fluoro at
the 4-position.

A solution of trifluoroethanol (88 g, 64 ml, 88 mol) was
35 added to a slurry of potassium tert-butoxide (98.8 g, 0.88
mol) in 1,2-dimethoxyethane (145 ml) such that the reaction
temperature remained below 11°C. The mixture then was cooled
1.5 hours at 0 to 5°C and added over 2.5 hours to a solution



of 2,4-difluoronitrobenzene (135 g, 0.85 mol) in
1,2-dimethoxyethane (150 ml) at -10°C. The mixture was cooled
1 hour at -10°C and then aqueous potassium dihydrogen
phosphate solution (13 g, 130 ml) was added. The mixture was
5 warmed to 25°C and solid potassium dihydrogen phosphate (7 g)
was added. The mixture was diluted with methyl *tert*-butyl
ether (600 ml) and water (300 ml) and the organic layer was
separated, diluted with methyl *tert*-butyl ether (100 ml),
washed with water (2x 400 ml), filtered through celite (2 g)
10 and concentrated in vacuo to give 4-fluoro-2-(2,2,2-
trifluoroethoxy)nitrobenzene (13 g, 57.2 mmol)

A slurry of 20% palladium hydroxide on carbon (30 mg) in
ethyl acetate (3 ml) was hydrogenated 17 hours with stirring
15 and then a solution of 4-fluoro-2-trifluoroethoxynitrobenzene
(3 g, 13 mmol) in ethyl acetate (6 ml) was added. The mixture
was hydrogenated 16 hours with stirring, filtered on celite,
washed with ethyl acetate (10 ml), diluted with 4.3 M hydrogen
chloride (3 ml, 13 mmol in isopropanol) and concentrated in
20 vacuo. The residue was taken up in ethyl acetate (25 ml) and
the slurry was concentrated, diluted with ethyl acetate
(25 ml), reconcentrated and diluted with ethyl acetate (5 ml).
The slurry was stirred 17 hours, diluted with ethyl acetate
(10 ml) and stirred 5 hours. The solids were collected,
25 washed with ethyl acetate (3 ml) and dried in vacuo at 60°C to
give 4-fluoro-2-(2,2,2-trifluoroethoxy)aniline hydrochloride
(2.5 g, 10.4 mmol), m.p. 203-204°C.

EXAMPLE 12

30

2-(2,2,2-Trifluoroethoxy)aniline

The following is the preparation of a compound of Formula
6 in which R¹ is 2,2,2-trifluoromethoxy and R² is hydro.

35

A mixture of 2-nitrophenol (18.8 g, 135 mmol),
2,2,2-trifluoroethyl *para*-toluenesulfonate (34.36 g,
135 mmol), potassium carbonate (18.7 g, 135 mmol) and DMF



(200 ml) was heated 16 hours at 140°C. The reaction mixture then was cooled, diluted with water (600 ml) and extracted with ether/hexanes (1:1; 3x 400 ml). The combined extracts were washed with saturated sodium bicarbonate (3x 100 ml) and
5 brine, dried (NaSO₄), filtered and concentrated to give 1-(2,2,2-trifluoroethoxy)-2-nitrobenzene (27 g, 117 mmol) as an oil.

A mixture of 1-(2,2,2-trifluoroethoxy)-2-nitrobenzene
10 (15 g, 68 mmol), platinum oxide hydrate (100 mg) and absolute ethanol (80 ml) was hydrogenated 18 hours with stirring at 25°C and 15 psi of pressure. The reaction mixture then was filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate
15 (9:1) to give 2-(2,2,2-trifluoroethoxy)aniline (10.4 g, 54.5 mol), m.p. 49-50°C.

EXAMPLE 13.

20 1-[2-(2,2,2-Trifluoroethoxy)phenyl]piperazine

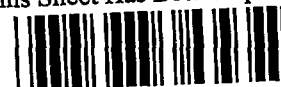
The following is the preparation of a compound of Formula 2 in which R¹ is 2,2,2-trifluoroethoxy and R² is hydro.

25 A mixture of 2-(2,2,2-trifluoroethoxy)aniline (2.85 g, 14.9 mmol), bis(2-chloroethyl)amine hydrochloride (2.66 g, 14.9 mmol), potassium carbonate (2.06 g, 14.9 mmol), sodium iodide (0.45 g, 3 mmol) and bis(2-methoxyethyl) ether (7.3 ml) was heated 8 hours at reflux. The reaction mixture then was
30 cooled, treated with concentrated ammonium hydroxide, poured into water (30 ml) and extracted with ethyl acetate (3x 30 ml). The combined extracts were washed with water (2x 30 ml) and brine (1x 30 ml), dried (MgSO₄) and concentrated in vacuo. The residue was purified by column
35 chromatography on silica gel eluting with methylene chloride/methanol (95:5) to give 1-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazine (2.93 g, 11.2 mmol), m.p. 107-108°C.



Proceeding as in Example 13, but substituting different starting materials for 2-(2,2,2-trifluoroethoxy)aniline the following compounds of Formula 2 were prepared:

- 5 substituting 4-chloro-2-methoxyaniline gave 1-(4-chloro-2-methoxyphenyl)-piperazine as an oil;
substituting 4-chloro-2-(2,2,2-trifluoroethoxy)aniline gave 1-[4-chloro-2-(2,2,2-trifluoroethoxy)phenyl]piperazine as a foam;
- 10 substituting 4-fluoro-2-(2,2,2-trifluoroethoxy)aniline and recrystallizing from a solution of hydrochloric acid in alcohol gave 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazine hydrochloride 206-208°C;
substituting 5-fluoro-2-methoxyaniline gave 1-(5-fluoro-2-methoxyphenyl)-piperazine, m.p. 181-183°C;
- 15 substituting 4-fluoro-2-ethoxyaniline gave 1-(4-fluoro-2-ethoxyphenyl)piperazine as an oil;
substituting 2-(trifluoromethoxy)aniline gave 1-(2-trifluoromethoxyphenyl)-piperazine as an oil;
- 20 substituting 4-fluoro-2-methoxyaniline and recrystallizing from a solution of hydrochloric acid in alcohol gave 1-(4-fluoro-2-methoxyphenyl)piperazine hydrochloride, m.p. 202-204°C;
substituting 5-chloro-2-methoxyaniline gave 1-(5-chloro-2-methoxyphenyl)-piperazine;
- 25 substituting 5-chloro-2-(2,2,2-trifluoroethoxy)aniline gave 1-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]piperazine;
substituting 2-aminobiphenyl gave 1-biphenyl-2-ylpiperazine as an oil;
- 30 substituting 4-methyl-2-(2,2,2-trifluoroethoxy)aniline and recrystallizing from a solution of hydrochloric acid in alcohol gave 1-[4-methyl-2-(2,2,2-trifluoroethoxy)phenyl]piperazine, m.p. 215°C (dec);
- 35 substituting 4-methoxy-2-(2,2,2-trifluoroethoxy)aniline gave 1-[4-methoxy-2-(2,2,2-trifluoroethoxy)phenyl]piperazine;
substituting 2-trifluoromethylaniline gave 1-(2-trifluoromethylphenyl)-piperazine;



- substituting 2-n-propylaniline gave 1-(2-n-propylphenyl)-piperazine, m.p. 213-215°C;
substituting 2-neopentoxylaniline gave 1-(2-neopentoxyphenyl)-piperazine;
- 5 substituting 2-(2-propynyloxy)aniline gave 1-[2-(2-propynyloxy)phenyl]-piperazine;
substituting 2-cyclopropylaniline gave 1-(2-cyclopropylphenyl)piperazine dihydrochloride, m.p. 124-133°C;
substituting 2-benzylaniline gave 1-(2-benzylphenyl)-
- 10 piperazine;
substituting *N*-(2-aminophenyl)acetamide gave *N*-(2-piperazin-1-ylphenyl)-acetamide;
substituting *N*-(2-aminophenyl)trifluoroacetamide gave *N*-(2-piperazin-1-ylphenyl)trifluoroacetamide;
- 15 substituting 4-methyl-2-methoxyaniline gave 1-(4-methyl-2-methoxyphenyl)-piperazine, m.p. 207-224°C;
substituting 2-bromo-4-fluoroaniline gave 1-(2-bromo-4-fluorophenyl)piperazine;
substituting 2,4-di(2,2,2-trifluoroethoxy)aniline gave
- 20 1-[2,4-di(2,2,2-trifluoroethoxy)phenyl]piperazine; and
substituting 2-(2,2,2-trifluoroethoxy)-2-methylaniline gave 1-[2-(2,2,2-trifluoroethoxy)-4-methylphenyl]piperazine.

EXAMPLE 14

25

1-[4-Fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazine

The following is the preparation of a compound of Formula 2 in which R¹ is 2,2,2-trifluoroethoxy and R² is fluoro at the

30 4-position.

A mixture of bis(2-chloroethyl)amine hydrochloride (14.3 g, 80 mmol), 2-(4-fluoro-2,2,2-trifluoroethoxyaniline hydrochloride (20 g, 81 mmol), prepared as in Example 11,

35 o-dichlorobenzene (40 ml) and *n*-hexanol (4 ml) was heated 4 hours at reflux. The reaction mixture was allowed to cool to 80°C, then slowly diluted with ethyl acetate (100 ml) and allowed to cool to 25°C. The solids were collected, washed



with ethyl acetate (20 ml) and dried in vacuo at 60 to 65°C to give 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazine dihydrochloride (20.1 g, 56.4 mmol), m.p. 208-210°C.

5

EXAMPLE 15

2-Fluoro-1-oxazol-2-ylbenzene

The following is the preparation of a compound of Formula
10 7 in which L is fluoro, R¹ is oxazol-2-yl and R² is hydro.

A mixture of 2-fluorobenzoic acid (4.5 g, 32.14 mmol), oxalyl chloride (4.1 ml, 48.2 ml), DMF (2 drops) and methylene chloride (40 ml) was heated 2 hours at reflux. The reaction
15 mixture was allowed to cool to 25°C, then stirred approximately 12 hours and concentrated. The residue was slowly added to a suspension of 2-bromoethylamine hydrobromide (5.7 g, 28 mmol), triethylamine (21 ml, 160 mmol) and benzene (200 ml). The mixture was heated 12 hours at reflux, allowed
20 to cool to 25°C, stirred an additional 12 hours and diluted with water. The aqueous layer was separated and extracted with methylene chloride (2x 50 ml). The combined extracts were dried (MgSO₄) and concentrated. The residue was purified on silica gel by column chromatography eluting with
25 hexanes/ethyl acetate (5:1) to give 2-fluoro-1-(4,5-dihydro-oxazol-2-yl)benzene (1.96 g, 11.9 mmol).

A mixture of 2-fluoro-1-(4,5-dihydrooxazol-2-yl)benzene (4.5 g, 27.3 mmol), nickel peroxide hydrate (7 g) and benzene
30 (40 ml) was heated 24 hours at reflux. The reaction mixture was allowed to cool to 25°C, then filtered and concentrated by rotary evaporation. The residue was purified on silica gel by column chromatography eluting with hexanes/ethyl acetate (5:1) to give 2-fluoro-1-oxazol-2-ylbenzene (0.5 g, 3.07 mmol).

35

This Sheet Has Been Replaced



EXAMPLE 16

1-(2-Oxazol-2-ylphenyl)piperazine

5 The following is the preparation of a compound of Formula 2 in which R¹ is oxazol-2-yl and R² is hydro.

10 A mixture of *N*-benzylpiperazine (3.56 g, 20.2 mmol) and THF (25 ml) was cooled to 0°C and *n*-butyllithium (2.5 M in hexanes, 7.6 ml, 19 mmol) was added. The mixture was cooled 30 minutes with stirring at 0°C, stirred 1 hour at 25°C, then cooled to 0°C and 2-fluoro-1-oxazol-2-ylbenzene (1.1 g, 6.75 mmol) was added slowly. The reaction mixture was allowed to warm to 25°C, then stirred 90 minutes and diluted with 15 water. The aqueous layer was separated and extracted with ethyl acetate (3x 30 ml). The combined extracts were washed with brine, dried (MgSO₄) and concentrated. The residue was purified on silica gel by column chromatography eluting with hexanes/ethyl acetate (9:1) to give 4-benzyl-1-(2-oxazol-2-ylphenyl)piperazine (0.805 g, 2.52 mmol). 20

25 A mixture of the 4-benzyl-1-(2-oxazol-2-ylphenyl)-piperazine (0.906 g, 2.84 mmol), obtained as in the proceeding paragraph, 10% palladium on carbon (1 g) and methanol (20 ml) was stirred 4 hours at 25°C under a hydrogen atmosphere (15 psi). The reaction mixture then was filtered and concentrated by rotary evaporation to give 1-(2-oxazol-2-ylphenyl)piperazine (0.480 g, 2.1 mmol).

30 Proceeding as in Example 16, but substituting 2,4-difluoro-1-oxazol-2-yl-benzene gave 1-(4-fluoro-2-oxazol-2-ylphenyl)piperazine.

This Sheet Has Been Replaced



EXAMPLE 17

1-(2-pyrrol-1-ylphenyl)piperazine

5 The following is the preparation of a compound of
Formula 2 in which R¹ is pyrrol-1-yl and R² is hydro.

A mixture of 1-chloro-2-nitrobenzene (6.54 g, 41.5 mmol),
piperazine-1-carboxaldehyde (4.7 g, 41.5 mmol) and DMF (18 ml)
10 was heated 48 hours at 100°C. The reaction mixture then was
cooled, diluted with water and extracted with ethyl acetate
(3x). The combined extracts were washed with water, dried
(MgSO₄), filtered and concentrated. The residue was purified
by column chromatography on silica gel eluting with methylene
15 chloride/methanol (98:2) to give 4-(2-nitrophenyl)piperazine-
1-carbaldehyde (3.2 g, 13.7 mmol).

A mixture of the 4-(2-nitrophenyl)piperazine-1-
carbaldehyde (3.57 g, 15.2 mmol), obtained as in the
20 proceeding paragraph, 10% palladium on carbon and ethanol
(50 ml) was stirred approximately 12 hours at 25°C under a
hydrogen atmosphere (15 psi). The reaction mixture then was
filtered and concentrated to give 4-(2-aminophenyl)piperazine-
1-carbaldehyde (2.91 g, 14.1 mmol), m.p. 129-133°C.

25 A mixture of 4-(2-aminophenyl)piperazine-1-carbaldehyde
(1.27 g, 6.2 mmol), 2,5-dimethoxytetrahydrofuran (1.13 g,
8.6 mmol) and concentrated acetic acid (4 ml) was heated
1.75 hours at reflux. The reaction mixture then was cooled in
30 an ice-bath, diluted with water/ice and extracted with
methylene chloride. The methylene chloride extract was washed
with aqueous sodium hydroxide and then water, dried (MgSO₄),
filtered and concentrated. The residue was purified by column
chromatography on silica gel eluting with methylene chloride/
35 methanol (97.5/2.5) to give 4-(2-pyrrol-1-ylphenyl)-
piperazine-1-carbaldehyde (1.12 g, 4.4 mmol) as an oil.



A mixture of 4-(2-pyrrol-1-ylphenyl)piperazine-1-carbaldehyde (1.12 g, 4.4 mmol), sodium hydroxide (440 mg, 11 mmol) and methanol (10 ml) was heated 14 hours at 50°C. The reaction mixture was allowed to cool to approximately 25°C and then partitioned between water (20 ml) and dichloroethane (30 ml). The aqueous layer was separated and extracted with dichloroethane (3x 30 ml). The combined dichloroethane was washed with brine and dried (K₂CO₃). The residue was purified by column chromatography on silica gel eluting with a gradient of 1 to 5% methanol/0.1% triethylamine/dichloroethane to give 1-(2-pyrrol-1-yl-phenyl)piperazine (0.77 g, 3.4 mmol).

Proceeding as in Example 17, but substituting 4-chloro-3-nitrotoluene for 1-chloro-2-nitrobenzene gave 1-(4-methyl-2-pyrrol-1-ylphenyl)piperazine.

EXAMPLE 18

1-[2-(2,2,2-trifluoroethoxy)-4-hydroxyphenyl]piperazine

The following is the preparation of a compound of Formula 2 in which R¹ is 2,2,2-trifluoroethoxy and R² is hydro.

A mixture of 1-[2-(2,2,2-trifluoroethoxy)-4-methoxyphenyl]piperazine (1.87 g, 6.4 mmol) and 48% aqueous hydrobromic acid (5 ml) was heated 17 hours at reflux. The reaction mixture was allowed to cool and then concentrated in vacuo. The residue was dissolved in ethanol (10 ml) at approximately 55°C and the solution was cooled to 0°C. The solids were collected, washed with cold ethanol (3x 10 ml) and dried in vacuo at approximately 80°C to give 1-[2-(2,2,2-trifluoroethoxy)-4-hydroxyphenyl]piperazine hydrobromide, m.p. 190-194. Anal.: Calcd. for C₁₂H₁₄F₃N₂O₂•(HBr)_{0.5}•H₂O: C, 43.00; H, 5.27; N, 8.37%; Found: C, 43.41; H, 4.97; N, 8.36%.

This Sheet Has Been Replaced



EXAMPLE 19

1-methoxymethyl-3-(3-chloropropyl)-5-methyl-
2,4(1H,3H)-pyrimidinedione

5

The following is the preparation of a protected derivative of a compound of Formula 3 in which L is chloro, R³ and R⁴ are each hydro and R⁵ is a group of Formula (a) wherein Z is CH, R⁷ is methyl and the protective group is methoxymethyl.

A mixture of 1-methoxymethyl-5-methyl-2,4(1H,3H)-pyrimidinedione (115 g, 0.68 mol), prepared as in Example 6, sodium hydroxide (29.7 g, 0.74 mol), tetra-n-butylammonium bromide (10.9 g, 30 mmol) and DMF (350 ml) was heated with vigorous stirring at 25 to 35°C until a nearly homogeneous solution was obtained. The mixture then was cooled to 25°C and 1-bromo-3-chloropropane (73.5 ml, 0.75 mol) was added. The mixture was heated 16 hours with stirring at 25 to 35°C and then partitioned between ethyl acetate (250 ml) and water (600 ml). The aqueous layer was extracted with ethyl acetate (4x 50 ml) and the combined extracts were washed with dilute sodium hydroxide and water, dried (MgSO₄), filtered and concentrated in vacuo to give 1-methoxymethyl-3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione (154.5 g, 0.63 mol) as an oil.

Proceeding as in Example 19, but substituting a different starting material for 1-methoxymethyl-5-methyl-2,4(1H,3H)-pyrimidinedione, gave the following compounds of Formula 3 or a protected derivative thereof:

substituting 1-benzyl-5-methyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidine-dione, m.p. 48-50°C;

substituting 4-benzyl-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione gave 2-(3-chloropropyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione;

substituting 2-benzyl-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione



- gave 4-(3-chloropropyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione;
- substituting 1-(4-methoxybenzyl)-5-cyano-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-1-(4-methoxybenzyl)-5-cyano-
- 5 2,4(1H,3H)-pyrimidinedione;
- substituting 1-benzyl-5-ethyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-chloropropyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione as an oil;
- substituting 1-benzyl-5-propyl-2,4(1H,3H)-pyrimidinedione gave
- 10 1-benzyl-3-(3-chloropropyl)-5-propyl-2,4(1H,3H)-pyrimidine-dione as an oil;
- substituting 1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-1-[2-(trimethylsilyl)-ethoxymethyl]-2,4(1H,3H)-pyrimidinedione as an oil;
- 15 substituting 1-benzyl-6-methyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-chloropropyl)-6-methyl-2,4(1H,3H)-pyrimidine-dione;
- substituting 3-benzyl-6-methyl-2,4(1H,3H)-pyrimidinedione gave 3-benzyl-1-(3-chloropropyl)-6-methyl-2,4(1H,3H)-pyrimidine-
- 20 dione;
- substituting 5-methyl-1-phenyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-5-methyl-1-phenyl-2,4(1H,3H)-pyrimidine-dione;
- substituting 5-methyl-3-phenyl-2,4(1H,3H)-pyrimidinedione gave
- 25 1-(3-chloropropyl)-5-methyl-3-phenyl-2,4(1H,3H)-pyrimidine-dione;
- substituting 1-(4-fluorophenyl)-5-methyl-2,4(1H,3H)-pyrimi-dinedione gave 3-(3-chloropropyl)-1-(4-fluorophenyl)-5-methyl-2,4(1H,3H)-pyrimidinedione;
- 30 substituting 3-(4-fluorophenyl)-5-methyl-2,4(1H,3H)-pyrimi-dinedione gave 1-(3-chloropropyl)-3-(4-fluorophenyl)-5-methyl-2,4(1H,3H)-pyrimidinedione;
- substituting 1-benzyl-5-cyano-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-chloropropyl)-5-cyano-2,4(1H,3H)-pyrimidine-
- 35 dione;
- substituting 1-biphenyl-3-ylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione gave 1-biphenyl-3-ylmethyl-3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione;



- substituting 1-(2-methylbenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-1-(2-methylbenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione;
- substituting 1-(2,4-dimethylbenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-1-(2,4-dimethylbenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione;
- substituting 1-(4-methoxybenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-1-(4-methoxybenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione;
- substituting 1-cyclohexylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-1-cyclohexylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione;
- substituting 5-methyl-1-pyrazin-2-yl-2,4(1H,3H)-pyrimidine-dione gave 3-(3-chloropropyl)-5-methyl-1-pyrazin-2-yl-2,4(1H,3H)-pyrimidinedione;
- substituting 1-benzyl-2,4-dioxo-5(1H,3H)-pyrimidine-carbaldehyde gave 1-benzyl-3-(3-chloropropyl)-2,4-dioxo-5(1H,3H)-pyrimidinecarbaldehyde;
- substituting 1-fur-2-yl-5-methyl-2,4(1H,3H)-pyrimidinedione gave 1-fur-2-yl-3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione;
- substituting 1,5-dimethyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-1,5-dimethyl-2,4(1H,3H)-pyrimidinedione;
- substituting 5-methyl-1-thien-2-yl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-5-methyl-1-thien-2-yl-2,4(1H,3H)-pyrimidinedione;
- substituting 1-fur-3-yl-5-methyl-2,4(1H,3H)-pyrimidinedione gave 1-fur-3-yl-3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione;
- substituting 5-methyl-1-pyrid-4-yl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-5-methyl-1-pyrid-4-yl-2,4(1H,3H)-pyrimidinedione;
- substituting 1-benzyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-chloropropyl)-2,4(1H,3H)-pyrimidinedione;
- substituting 5-methyl-1-pyrid-3-yl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-5-methyl-1-pyrid-3-yl-2,4(1H,3H)-pyrimidinedione;
- substituting 5-methyl-1-pyrid-2-yl-2,4(1H,3H)-pyrimidinedione

gave 3-(3-chloropropyl)-5-methyl-1-pyrid-2-yl-2,4(1H,3H)-
pyrimidinedione;
substituting 3-benzyl-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione
gave 3-benzyl-1-(3-chloropropyl)-5,6-dimethyl-2,4(1H,3H)-
5 pyrimidinedione;
substituting 1-benzyl-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione
gave 1-benzyl-3-(3-chloropropyl)-5,6-dimethyl-2,4(1H,3H)-
pyrimidinedione, m.p. 72-74°C;
substituting 3-benzyl-5-methyl-2,4(1H,3H)-pyrimidinedione gave
10 3-benzyl-1-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidine-
dione, as an oil;
substituting 1-benzyl-5-trifluoromethyl-2,4(1H,3H)-pyrimidine-
dione gave 1-benzyl-3-(3-chloropropyl)-5-trifluoromethyl-
2,4(1H,3H)-pyrimidinedione, m.p. 100-101°C;
15 substituting 5-hydroxymethyl-1-[2-(trimethylsilyl)ethoxy-
methyl]-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-
5-hydroxymethyl-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-
pyrimidinedione;
substituting 1-[2-(trimethylsilyl)ethoxymethyl]-5-methoxy-
20 2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-
1-[2-(trimethylsilyl)ethoxymethyl]-5-methoxy-2,4(1H,3H)-
pyrimidinedione;
substituting tert-butyl 5-prop-2-yl-2,4-dioxo-(1H,3H)-1-
pyrimidinecarboxylate gave tert-butyl 3-(3-chloropropyl)-
25 5-prop-2-yl-2,4-dioxo-(1H,3H)-1-pyrimidine-carboxylate;
substituting 1-(2,2,2-trifluoroethoxy)-5-methyl-2,4(1H,3H)-
pyrimidinedione gave 3-(3-chloropropyl)-1-(2,2,2-trifluoro-
ethoxy)-5-methyl-2,4(1H,3H)-pyrimidinedione;
substituting tert-butyl 5-methylthio-2,4-dioxo-(1H,3H)-1-
30 pyrimidinecarboxylate gave tert-butyl 3-(3-chloropropyl)-
5-methylthio-2,4-dioxo-(1H,3H)-1-pyrimidine-carboxylate; and
substituting tert-butyl 5-fur-2-yl-2,4-dioxo-(1H,3H)-1-
pyrimidinecarboxylate gave tert-butyl 3-(3-chloropropyl)-
5-fur-2-yl-2,4-dioxo-(1H,3H)-1-pyrimidine-carboxylate.

35

This Sheet Has Been Replaced



EXAMPLE 20

3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione

5 The following is the preparation of a compound of
Formula 3 in which L is chloro, R³ and R⁴ are each hydro and
R⁵ is a group of Formula (a) wherein Z is CH, R⁶ is hydro and
R⁷ is methyl.

10 A mixture of 1-methoxymethyl-3-(3-chloropropyl)-5-methyl-
2,4(1H,3H)-pyrimidinedione (40.4 g, 0.16 mol) and isopropanol
(200 ml) was heated to 60°C and added to refluxing
concentrated hydrochloric acid (200 ml) at a rate such that
the reaction mixture remained at gentle reflux. The mixture
15 was heated 3 hours at reflux and then distilled to remove
methanol byproduct. The mixture was heated 4.5 hours at 92°C,
cooled to 25°C, poured into water (650 ml), saturated with
sodium hydroxide and extracted with ethyl acetate (5x 300 ml).
The combined extracts were washed with sodium bicarbonate and
20 water and concentrated in vacuo. The residue was
recrystallized from toluene/isopropanol (10:1, 55 ml) and the
solids were collected, washed with hexanes and dried at 60°C
(15 g 1st crop). The mother liquors were concentrated and the
solids were collected, dried (2nd crop) and combined with the
25 first crop to give 3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-
pyrimidinedione (19.8 g, 94 mmol), m.p. 145-147°C.

EXAMPLE 21

30 3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione

 The following is the preparation of a compound of
Formula 3 in which L is chloro, R³ and R⁴ are each hydro and
R⁵ is a group of Formula (a) wherein Z is CH, R⁶ is hydro and
35 R⁷ is methyl.

 A mixture of 1-benzyl-3-(3-chloropropyl)-5-methyl-
2,4(1H,3H)-pyrimidinedione (1 g, 3.41 mmol), prepared as in

Example 19, 10% palladium on carbon (1 g) and 0.1 M ammonium formate/methanol (340 ml) was heated 3 hours at reflux under argon. The reaction mixture was allowed to cool to 25°C, then filtered and concentrated in vacuo. The residue was purified
5 by column chromatography on silica gel eluting with hexane-ethyl acetate (1:1) to give 3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione (0.52 g, 2.57 mmol), m.p. 117-121°C.

10 Proceeding as in Example 21, but substituting different a starting material for 1-benzyl-3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione, gave the following compounds of Formula 3 or a protected derivative thereof:

15 substituting 4-benzyl-2-(3-chloropropyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione gave 2-(3-chloropropyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione;
substituting 2-benzyl-2-(3-chloropropyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione gave 4-(3-chloropropyl)-
20 6-methyl-1,2,4-triazine-3,5(2H,4H)-dione;
substituting 3-benzyl-1-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave 1-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione;
substituting 3-benzyl-1-(3-chloropropyl)-5,6-dimethyl-
25 2,4(1H,3H)-pyrimidinedione gave 1-(3-chloropropyl)-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione;
substituting 3-benzyl-1-(3-chloropropyl)-6-methyl-2,4(1H,3H)-pyrimidinedione gave 1-(3-chloropropyl)-6-methyl-2,4(1H,3H)-pyrimidinedione;
30 substituting 1-benzyl-3-(3-chloropropyl)-5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione;
substituting 1-benzyl-3-(3-chloropropyl)-6-methyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-6-methyl-
35 2,4(1H,3H)-pyrimidinedione;
substituting 1-benzyl-3-(3-chloropropyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione;



substituting 1-benzyl-5-methyl-2,4,6(1H,3H,5H)-pyrimidine-
trione gave 5-methyl-2,4,6(1H,3H,5H)-pyrimidinetrione; and
substituting 1-benzyl-3-(3-chloropropyl)-5-methyl-
2,4(1H,3H)-pyrimidinedione gave 3-(3-chloropropyl)-5-methyl-
5 2,4(1H,3H)-pyrimidinedione.

EXAMPLE 22

10 1-(1-Benzyl-5-methyl-2,4-dioxo-(1H,3H)-pyrimidin-3-
ylmethyl)cycloprop-1-ylmethyl methanesulfonate

The following is the preparation of a compound of
Formula 3 in which L is methanesulfonyloxy, R³ and R⁴ together
are tetramethylene and R⁵ is a group of Formula (a) wherein Z
15 is CH, R⁶ is benzyl and R⁷ is methyl.

A mixture of 1-cyano-1-propanecarboxylic acid (2 g,
18 mmol), dry triethylamine (3.3 ml, 23.5 mmol) and THF
(25 ml) was cooled to between -5°C and 0°C and a mixture of
20 methyl chloroformate (1.7 ml, 21.5 mmol) and THF (10 ml) was
added at a rate such that the temperature of the reaction
mixture remained between -5°C and 0°C. The mixture was
stirred 30 minutes, cooled to 0°C and filtered (washing
through with THF (5x 10 ml)). The combined filtrate was
25 cooled to 0°C under argon and added to a mixture of sodium
borohydride (2.04 g, 53.9 mmol) and water (12.5 ml) at <10°C.
The mixture was stirred 2 hours at 25°C, treated with
10% hydrochloric acid and concentrate. The residual mixture
was treated with 10% sodium bicarbonate and extracted with
30 ethyl acetate. The organic layer was washed with brine, dried
(MgSO₄) and concentrated to dryness. The residue was purified
by flash chromatography on silica gel eluting with hexane/
ethyl acetate (7:3) to give 1-cyanocyclo-prop-1-ylmethanol
(1.16 g, 11.9 mmol) as an oil.

35

A mixture of 1-cyanocycloprop-1-ylmethanol (4.31 g,
44.4 mmol), obtained as in the preceding paragraph,
triethylamine (9.04 ml, 64.8 mmol) and methylene chloride



(78 ml) was cooled under argon to between 0 and 5°C and methanesulfonyl chloride (4.67 ml, 59.9 mmol) was added slowly. The mixture was cooled 3 hours with stirring at 0 to 5°C, then diluted with water and extracted with methylene
5 chloride. The extract was washed with 5% sodium bicarbonate, dried (MgSO₄) and concentrated to dryness to give 1-cyano-cycloprop-1-ylmethyl methanesulfonate.

A mixture of the 1-cyanocycloprop-1-ylmethyl
10 methanesulfonate and DMF (78 ml) was added to a mixture of 1-benzyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (9.1 g, 42.2 mmol), 60% sodium hydride (1.95 g, 48.8 mmol) and DMF (117 ml) at 0 to 5°C. The mixture was heated 20 hours at 45 to 55°C, then diluted with water (20 ml) and saturated
15 ammonium chloride (20 ml) and extracted with ethyl acetate. The extract was washed with water and then brine, dried (MgSO₄) and concentrated to dryness. The residue was purified by flash chromatography on silica gel eluting with hexane/
ethyl acetate (1:1) to give 1-benzyl-3-(1-cyanocycloprop-1-ylmethyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (10.4 g,
20 35.2 mmol).

A mixture of 1-benzyl-3-(1-cyanocycloprop-1-ylmethyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (10.4 g, 35.2 mmol),
25 acetic acid (37.4 ml) and concentrated hydrochloric acid (164.4 ml) was heated 2 hours at reflux. The reaction mixture then was diluted with water (150 ml) and extracted with methylene chloride. The extract was extracted with 5% sodium hydroxide (3x). The combined aqueous phase was treated with
30 10% hydrochloric acid and extracted with methylene chloride. The methylene chloride extract was washed with water, dried (MgSO₄) and concentrated to dryness to give 1-(1-benzyl-5-methyl-2,4-dioxo-(1*H*,3*H*)-pyrimidin-3-ylmethyl)-1-cyclopropanecarboxylic acid (11.03 g, 35.1 mmol).

35

A mixture of 1-(1-benzyl-5-methyl-2,4-dioxo-(1*H*,3*H*)-pyrimidin-3-ylmethyl)-1-cyclopropanecarboxylic acid (11 g, 35 mmol), triethylamine (6.46 ml, 45.6 mmol) and THF



(138 ml) was cooled to 0°C under argon and a mixture of methyl chloroformate (3.23 ml, 42 mmol) and THF (20 ml) was added at a rate such that the temperature of the reaction mixture remained at 0°C. The mixture was cooled 30 minutes with stirring at 0 to 2°C and then filtered (washing through with THF (3x 50 ml)). The combined filtrate was cooled to 0°C under argon and added to a mixture of sodium borohydride (3.29 g, 87 mmol) and water (23.3 ml) at <10°C. The mixture was stirred 2 hours, diluted with water (20 ml), treated with 10% hydrochloric acid, diluted with brine (40 ml) and extracted with ethyl acetate (4x 100 ml). The combined extracts were washed with brine, dried (MgSO₄) and concentrated to dryness. The residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (7:3) to give 1-(1-benzyl-5-methyl-2,4-dioxo-(1*H*,3*H*)-pyrimidin-3-ylmethyl)cycloprop-1-ylmethanol (9.52 g, 31.7 mmol), m.p. 81.5°C.

A mixture of 1-(1-benzyl-5-methyl-2,4-dioxo-(1*H*,3*H*)-pyrimidin-3-ylmethyl)-cycloprop-1-ylmethanol (1.95 g, 6.5 mmol), triethylamine (1.32 ml, 9.5 mmol) and methylene chloride (20 ml) was cooled to between 0 and 5°C under argon and methanesulfonyl chloride (0.69 ml, 8.85 mmol) was added slowly. The mixture was stirred cooled 2 hours at 0 to 5°C, then diluted with water (20 ml) and extracted with methylene chloride. The extract was washed with 5% sodium bicarbonate, dried (MgSO₄) and concentrated to give 1-(1-benzyl-5-methyl-2,4-dioxo-(1*H*,3*H*)-pyrimidin-3-ylmethyl)cycloprop-1-ylmethyl methanesulfonate.

EXAMPLE 23

3-(3-Chloropropyl)-5-methyl-2,4-dioxo-(1*H*,3*H*)-pyrimidin-1-ylmethylpyridine 1-oxide

The following is the preparation of a compound of Formula 3 in which L is chloro, Z is CH, R³ and R⁴ are each hydro and R⁵ is a group of Formula (a) wherein





R⁶ is 1-oxidopyrid-4-ylmethyl and R⁷ is methyl.

A mixture of 3-(3-chloropropyl)-5-methyl-1-pyrid-4-yl-2,4-(1*H*,3*H*)-pyrimidinedione (0.54 g, 1.84 mmol), prepared as
5 in Example 4, and methylene chloride (20 ml) was cooled to 0°C, treated with 3-chloroperoxybenzoic acid (tech. grade 0.55 g, 2.2 mmol), stirred 10 hours and then partitioned between aqueous sodium bicarbonate (20 ml) and methylene chloride (50 ml). The organic layer was separated, washed
10 with 10% sodium sulfate (1x 10 ml) and brine (1x 10 ml) and concentrated in vacuo to give 3-(3-chloropropyl)-5-methyl-2,4-dioxo-(1*H*,3*H*)-pyrimidin-1-yl-methylpyridine 1-oxide (0.53 g, 1.7 mmol).

15

EXAMPLE 24

3-{3-[4-(4-chloro-2-methoxyphenyl)piperazin-1-yl]propyl}-
5-methyl-2,4(1*H*,3*H*)-pyrimidinedione

20 The following is the preparation of a compound of Formula I in which R¹ is methoxy, R² is chloro at the 4-position, R³ and R⁴ are each hydro and R⁵ is a group of Formula (a) wherein Z is CH, R⁶ is hydro and R⁷ is methyl.

25 A mixture of 3-(3-chloropropyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (223 mg, 0.98 mmol), prepared as in Example 19, and 1-(4-chloro-2-methoxy-phenyl)piperazine (200 mg, 0.98 mmol), prepared as in Example 12, was heated 2 hours with stirring at 180 to 190°C, allowed to cool to 25°C and then
30 purified by preparative thin layer chromatography on silica gel eluting with methylene chloride/(methylene chloride/methanol/ammonium hydroxide-60:10:1) (7:3) to give 3-{3-[4-(4-chloro-2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione. The free base was
35 recrystallized from a solution of hydrogen chloride in methanol to give 3-{3-[4-(4-chloro-2-methoxyphenyl)-piperazin-1-yl]propyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 182-184°C. Anal.: Calcd. for



$C_{19}H_{25}ClN_4O_3 \cdot (HCl)_2$: C, 48.25; H, 5.92; N, 11.84%;
Found: C, 48.55; H, 5.81; N, 11.85%.

Proceeding as in Example 24, but substituting a different
5 starting material for 4-(4-chloro-2-methoxyphenyl)piperazine
and/or 3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione,
gave the following compounds of Formula I:

substituting 1-[4-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-
10 piperazine and recrystallizing from a solution of fumaric acid
in alcohol gave 3-{3-[4-(4-chloro-2-(2,2,2-trifluoro-
ethoxy)phenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-
pyrimidinedione fumarate, m.p. 180-182°C; Anal.: Calcd. for
 $C_{20}H_{24}ClN_4O_3 \cdot C_4H_4O_4$: C, 49.19; H, 4.84; N, 9.57%; Found: C,
15 49.29; H, 4.78; N, 9.40%; substituting 1-(2-fur-2-
ylphenyl)piperazine and 1-tert-butyl 3-(3-chloropropyl)-
5-methyl-2,4-dioxo-(1H,3H)-1-pyrimidinecarboxylate and
recrystallizing from a solution of oxalic acid in alcohol gave
3-{3-[4-(2-fur-2-ylphenyl)-piperazin-1-yl]propyl}-5-methyl-
20 2,4(1H,3H)-pyrimidinedione oxalate, m.p. 225-226°C;
substituting 1-(4-fluoro-2-hydroxyphenyl)piperazine and
1-tert-butyl 3-(3-chloropropyl)-5-methyl-2,4-dioxo-
(1H,3H)-1-pyrimidinecarboxylate and recrystallizing from a
solution of hydrobromic acid in alcohol gave 3-{3-[4-(4-
25 fluoro-2-hydroxyphenyl)piperazin-1-yl]propyl}-5-methyl-
2,4(1H,3H)-pyrimidinedione hydrobromide, m.p. 265-268°C;
Anal.: Calcd. for $C_{18}H_{23}FN_4O_3 \cdot HBr$: C, 41.24; H, 4.81; N,
10.69%; Found: C, 41.44; H, 4.91; N, 10.61%; substituting
1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazine and
30 1-tert-butyl 3-(3-chloropropyl)-5-methylthio-2,4-dioxo-
(1H,3H)-1-pyrimidine-carboxylate gave 3-{3-[4-(4-fluoro-
2-(2,2,2-trifluoroethoxyphenyl)-piperazin-1-yl]propyl}-
5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride,
m.p. 183-186°C (dec); Anal.: Calcd. for $C_{20}H_{25}F_4N_4O_3 \cdot HCl$: C,
35 46.83; H, 4.91; N, 10.92%; Found: C, 46.91; H, 5.01;
N, 10.78%;
substituting 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-
piperazine and tert-butyl 3-(3-chloropropyl)-5-prop-2-yl-2,4-



dioxo-(1*H*,3*H*)-1-pyrimidine-carboxylate gave 3-{3-[4-(2-(4-fluoro-2,2,2-trifluoroethoxy)phenyl)-piperazin-1-yl]-propyl}-5-prop-2-yl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 204-206°C; Anal.: Calcd. for

5 $C_{22}H_{28}F_4N_4O_3 \cdot (HCl)_{1.5} \cdot (H_2O)_{0.5}$: C, 49.28; H, 5.73; N, 10.45%; Found: C, 49.57; H, 5.62; N, 10.42%; and

substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and tert-butyl 3-(3-chloropropyl)-5-fur-2-yl-2,4-dioxo-(1*H*,3*H*)-1-pyrimidinecarboxylate and recrystallizing from a

10 solution of oxalic acid in alcohol gave 3-{3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]propyl}-5-fur-2-yl-2,4(1*H*,3*H*)-pyrimidinedione oxalate, m.p. 202-206°C; Anal.: Calcd. for $C_{23}H_{25}F_3N_4O_2 \cdot C_2H_2O_4$: C, 52.81; H, 4.78; N, 9.85%; Found: C, 52.68; H, 4.89; N, 9.61%.

15

EXAMPLE 25

1-Benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione

20

The following is the preparation of a compound of Formula I in which R¹ is methoxy, R², R³ and R⁴ are each hydro and R⁵ is a group of Formula (a) wherein Z is CH, R⁶ is benzyl and R⁷ is methyl.

25

A mixture of 1-benzyl-3-(3-chloropropyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (550 mg, 1.87 mmol), prepared as in Example 19, 1-(2-methoxyphenyl)piperazine (367 g, 1.87 mmol), sodium iodide (623 g, 3.75 mmol), potassium carbonate (260 mg, 1.81 mmol) and acetonitrile (50 ml) was stirred 8 hours at
30 reflux. The reaction mixture then was poured into water (200 ml) and extracted with methylene chloride (3x 100 ml). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography on
35 silica gel eluting with hexane/ethyl acetate (1:1) to give 1-benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (800 mg, 1.78 mmol) as an oil. The free base was recrystallized from a solution of



hydrochloric acid in alcohol to give 1-benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 195-198°C. Anal.: Calcd. for $C_{26}H_{32}N_4O_3 \cdot (HCl)_2$: C, 59.88; H, 6.57; N, 10.74%; Found: C, 59.71; H, 6.64; N, 10.73%.

Proceeding as in Example 25, but substituting different starting materials for 3-(3-chloropropyl)-1-benzyl-5-methyl-2,4(1H,3H)-pyrimidinedione and/or 1-(2-methoxyphenyl)-piperazine the following compounds of Formula I or the protected derivatives thereof were prepared:

substituting 3-benzyl-1-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave 3-benzyl-1-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 209-211°C; Anal.: Calcd. for $C_{26}H_{32}N_4O_3 \cdot (HCl)_2$: C, 59.88; H, 6.57; N, 10.74%; Found: C, 59.85; H, 6.57; N, 10.70%;

substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine gave 1-benzyl-3-{3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)-piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 87-89°C; Anal.: Calcd. for $C_{27}H_{31}F_3N_4O_3 \cdot HCl$: C, 55.91; H, 6.08; N, 9.66%; Found: C, 56.20; H, 5.96; N, 9.33%;

substituting 1-(5-fluoro-2-methoxyphenyl)piperazine gave 1-benzyl-3-{3-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 165-167°C; Anal.: Calcd. for $C_{26}H_{31}FN_4O_3 \cdot (HCl)_2$: C, 57.88; H, 6.16; N, 10.38%; Found: C, 57.67; H, 6.20; N, 10.30%;

substituting 1-[4-chloro-2-(2,2,2-trifluoroethoxy)phenyl]piperazine and recrystallizing from a solution of fumaric acid in alcohol gave 1-benzyl-3-{3-[4-(4-chloro-2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 156-158°C; Anal.: Calcd. for $C_{27}H_{30}F_3N_4O_3 \cdot C_4H_4O_4$: C, 55.07; H, 5.22; N, 8.29%; Found: C, 55.22; H, 5.16; N, 8.30%;

substituting 3-(3-chloropropyl)-1-benzyl-5,6-dimethyl-

- 2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 239-241°C; Anal.: Calcd. for $C_{27}H_{34}N_4O_3 \cdot (HCl)_2$: C, 60.55; H, 6.77; N, 10.46%; Found: C, 60.33; H, 6.79; N, 10.37%;
- substituting 1-(4-fluoro-2-methoxyphenyl)piperazine gave 1-benzyl-3-(3-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 178-180°C; Anal.: Calcd. for $C_{26}H_{31}FN_4O_3 \cdot (HCl)_2$: C, 57.50; H, 6.20; N, 10.32%; Found: C, 57.42; H, 6.14; N, 10.13%;
- substituting 1-(4-chloro-2-methoxyphenyl)piperazine gave 1-benzyl-3-(3-[4-(4-chloro-2-methoxyphenyl)piperazin-1-yl]propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 184-186°C; Anal.: Calcd. for $C_{26}H_{31}ClN_4O_3 \cdot (HCl)_2$: C, 55.86; H, 5.96; N, 10.00%; Found: C, 55.53; H, 5.85; N, 9.95%;
- substituting 3-(3-chloropropyl)-1-benzyl-5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 240-241°C; Anal.: Calcd. for $C_{26}H_{29}F_3N_4O_3 \cdot (HCl)_2$: C, 54.26; H, 5.43; N, 9.73%; Found: C, 53.97; H, 5.40; N, 9.59%;
- substituting 3-(3-chloropropyl)-5-cyano-1-(4-methoxybenzyl)-2,4(1H,3H)-pyrimidinedione gave 5-cyano-1-(4-methoxybenzyl)-3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 248-249°C (dec); Anal.: Calcd. for $C_{27}H_{31}N_5O_4 \cdot (HCl)_{1.5}$: C, 57.67; H, 6.18; N, 12.46%; Found: C, 57.68; H, 6.02; N, 12.36%;
- substituting 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazine and recrystallizing from a solution of fumaric acid in alcohol gave 1-benzyl-3-(3-[4-(4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 145-146°C; Anal.: Calcd. for $C_{27}H_{30}F_4N_4O_3 \cdot C_4H_4O_4$: C, 57.22; H, 5.26; N, 8.61%; Found: C, 57.07; H, 5.28; N, 8.46%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloro)-propyl-1-(2,4-dimethylbenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave



- 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-1-(2,4-dimethyl-benzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 113-115°C; Anal.: Calcd. for $C_{29}H_{37}F_3N_4O_3 \cdot (HCl)_2$: C, 55.04; H, 6.16; N, 8.85%; Found: C, 55.33; H, 6.00; N, 8.64%;
- 5 substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloro)-propyl-1-(2-methylbenzyl)-2,4(1H,3H)-pyrimidine-dione gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-1-(2-methyl-benzyl)-2,4(1H,3H)-pyrimidinedione
- 10 hydrochloride, m.p. 172-174°C; Anal.: Calcd. for $C_{28}H_{34}F_3N_4O_3 \cdot HCl$: C, 57.93; H, 6.16; N, 9.65%; Found: C, 57.86; H, 6.02; N, 9.55%;
- substituting 3-(3-chloropropyl)-1-benzyl-5-propyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-[4-(2-methoxyphenyl)-
- 15 piperazin-1-yl]propyl)-5-propyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 202-204°C; Anal.: Calcd. for $C_{28}H_{36}N_4O_3 \cdot HCl$: C, 65.30; H, 7.28; N, 10.88%; Found: C, 65.07; H, 7.24; N, 10.74%;
- substituting 3-(3-chloropropyl)-1-benzyl-5-ethyl-2,4(1H,3H)-
- 20 pyrimidinedione gave 1-benzyl-3-(3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 183-185°C; Anal.: Calcd. for $C_{27}H_{34}N_4O_3 \cdot (HCl)_2$: C, 60.55; H, 6.77; N, 10.46%; Found: C, 60.40; H, 6.86; N, 10.25%;
- 25 substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-biphenyl-3-yl-methyl-3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave 1-biphenyl-3-ylmethyl-3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}-
- 30 propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 93-94°C; Anal.: Calcd. for $C_{33}H_{35}F_3N_4O_3 \cdot HCl$: C, 63.06; H, 5.77; N, 8.92%; Found: C, 61.66; H, 5.90; N, 8.50%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloropropyl)-1-benzyl-5-ethyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)-
- 35 piperazin-1-yl]propyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 180-181°C; Anal.: Calcd. for $C_{28}H_{33}F_3N_4O_3 \cdot HCl$: C, 58.56; H, 6.11; N, 9.76%; Found: C, 58.83; H, 6.11; N, 9.77%;





substituting 1-(4-fluoro-2-methoxyphenyl)piperazine and 1-(3-chloropropyl)-3-benzyl-5-methyl-2,4(1H,3H)-pyrimidinedione gave 3-benzyl-1-(3-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, 5 m.p. 210-212°C; Anal.: Calcd. for $C_{26}H_{31}FN_4O_3 \cdot (HCl)_2$: C, 57.88; H, 6.16; N, 10.38%; Found: C, 57.50; H, 6.18; N, 10.62%;

substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloropropyl)-1-benzyl-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl)-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 221-222°C; Anal.: Calcd. for $C_{28}H_{33}F_3N_4O_3 \cdot (HCl)_{1.1}$: C, 58.37; H, 6.06; N, 9.72%; Found: C, 58.38; H, 5.96; N, 9.58%;

15 substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-(3-chloropropyl)-3-benzyl-5-methyl-2,4(1H,3H)-pyrimidine-dione gave 3-benzyl-1-(3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl)-5-methyl-2,4(1H,3H)-pyrimidine-dione hydrochloride, m.p. 168-169°C; Anal.: Calcd. for $C_{27}H_{31}F_3N_4O_3 \cdot (HCl)_{1.9}$: C, 55.01; H, 5.69; N, 9.50%; Found: C, 54.95; H, 5.59; N, 9.43%;

substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloropropyl)-1-cyclohexylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione gave 1-cyclohexylmethyl-3-(3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 130-132°C; Anal.: Calcd. for $C_{27}H_{37}F_3N_4O_3 \cdot HCl$: C, 57.99; H, 6.88; N, 10.02%; Found: C, 58.01; H, 6.80; N, 9.87%;

substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 30 3-(3-chloropropyl)-1-pyrazin-2-ylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl)-5-methyl-1-pyrazin-2-ylmethyl-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 149-151°C; Anal.: Calcd. for $C_{25}H_{29}F_3N_6O_3 \cdot C_4H_4O_4$: C, 53.08; H, 5.44; N, 12.81%; Found: C, 52.87; H, 5.13; N, 12.83%;

substituting 1-(4-chloro-2-methoxyphenyl)piperazine and 3-benzyl-1-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidine-

- dione gave 3-benzyl-1-(3-[4-(4-chloro-2-methoxyphenyl)-piperazin-1-yl]propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 194-195°C; Anal.: Calcd. for $C_{26}H_{31}ClN_4O_3 \cdot (HCl)_2$: C, 55.63; H, 6.03; N, 9.98%;
- 5 Found: C, 55.82; H, 5.94; N, 9.85%;
- substituting 1-[4-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazine and 3-benzyl-1-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave 3-benzyl-1-(3-[4-[4-chloro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl)-
- 10 5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 251-252°C; Anal.: Calcd. for $C_{27}H_{30}F_3ClN_4O_3 \cdot HCl$: C, 53.55; H, 5.49; N, 9.25%; Found: C, 53.74; H, 5.26; N, 9.37%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-benzyl-3-(3-chloropropyl)-5-propyl-2,4(1H,3H)-pyrimidine-
- 15 dione gave 1-benzyl-3-(3-[4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl]propyl)-5-propyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 178°C; Anal.: Calcd. for $C_{29}H_{35}F_3N_4O_3 \cdot HCl$: C, 59.03; H, 6.32; N, 9.49%;
- Found: C, 59.08; H, 6.26; N, 9.52%;
- 20 substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-benzyl-3-(3-chloropropyl)-5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl)-5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 125-127°C;
- 25 Anal.: Calcd. for $C_{27}H_{28}F_6N_4O_3 \cdot HCl$: C, 52.65; H, 4.91; N, 9.10%; Found: C, 52.44; H, 4.79; N, 8.92%;
- substituting 1-benzyl-3-(3-chloropropyl)-2,4-dioxo-5(1H,3H)-pyrimidine-carbaldehyde and recrystallizing from a solution of fumaric acid in alcohol gave 1-benzyl-
- 30 3-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]-2,4-dioxo-5(1H,3H)-pyrimidinecarbaldehyde fumarate, m.p. 198°C; Anal.: Calcd. for $C_{26}H_{30}N_4O_4 \cdot (C_4H_4O_4)_{0.5}$: C, 64.37; H, 6.16; N, 10.72%; Found: C, 64.07; H, 6.25; N, 11.12%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and
- 35 1-benzyl-3-(3-chloropropyl)-5-cyano-2,4(1H,3H)-pyrimidinedione gave 1-benzyl-3-(3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl]propyl)-5-cyano-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 142-143°C; Anal.: Calcd. for



- $C_{27}H_{28}F_3N_5O_3 \cdot (HCl)_{1.2} \cdot (H_2O)_{0.5}$: C, 57.50; H, 5.18; N, 12.42%;
Found: C, 55.93; H, 5.22; N, 11.94%;
substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and
3-(3-chloropropyl)-1-fur-2-ylmethyl-5-methyl-2,4(1H,3H)-
5 pyrimidinedione gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)-
phenyl]piperazin-1-yl}propyl)-1-fur-2-yl-methyl-5-methyl-
2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 132-134°C;
Anal.: Calcd. for $C_{25}H_{29}F_3N_4O_4 \cdot (HCl)_2$: C, 51.81; H, 5.39; N,
9.66%; Found: C, 51.89; H, 5.44; N, 9.55%;
- 10 substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and
3-(3-chloropropyl)-5-trifluoromethyl-2,4(1H,3H)-pyrimidine-
dione gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-
1-yl}propyl)-5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione
hydrochloride, m.p. 225-226°C; Anal.: Calcd. for
15 $C_{20}H_{22}F_6N_4O_3 \cdot (HCl)_2$: C, 43.06; H, 4.43; N, 10.04%;
Found: C, 43.12; H, 4.59; N, 9.81%;
substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and
3-(3-chloropropyl)-1,5-dimethyl-2,4(1H,3H)-pyrimidinedione
gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-
20 yl}propyl)-1,5-dimethyl-2,4(1H,3H)-pyrimidinedione
hydrochloride, m.p. 212-213°C; Anal.: Calcd. for
 $C_{21}H_{27}F_3N_4O_3 \cdot (HCl)_2$: C, 49.12; H, 5.69; N, 10.91%;
Found: C, 48.97; H, 5.68; N, 10.77%;
substituting 1-(4-fluoro-2-methoxyphenyl)piperazine and
25 1-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave
1-{3-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]propyl}-
5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride,
m.p. 196-197°C; Anal.: Calcd. for $C_{19}H_{25}FN_4O_3 \cdot (HCl)_2$: C,
49.79; H, 6.16; N, 12.22%; Found: C, 50.13; H, 6.37;
30 N, 12.27%;
substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and
1-(3-chloropropyl)-3-benzyl-5,6-dimethyl-2,4(1H,3H)-pyrimi-
dinedione and recrystallizing from a solution of fumaric acid
in alcohol gave 1-(3-{4-[2-(2,2,2-trifluoroethoxy)-
35 phenyl]piperazin-1-yl}propyl)-3-benzyl-5,6-dimethyl-
2,4(1H,3H)-pyrimidinedione fumarate, m.p. 125-127°C;
Anal.: Calcd. for $C_{28}H_{33}F_3N_4O_3 \cdot C_2H_2O_2$: C, 58.62; H, 5.84; N,
8.55%; Found: C, 58.63; H, 5.67; N, 8.42%;





- substituting 1-[4-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazine and 1-(3-chloropropyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 1-(3-{4-[4-chloro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 205-206°C; Anal.: Calcd. for $C_{20}H_{24}ClF_3N_4O_3 \cdot (HCl)_2$: C, 43.53; H, 5.10; N, 10.15%; Found: C, 43.77; H, 5.10; N, 10.13%;
- substituting 1-(4-chloro-2-methoxyphenyl)piperazine and 1-(3-chloropropyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 1-(3-[4-(4-chloro-2-methoxyphenyl)piperazin-1-yl]propyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 154-155°C; Anal.: Calcd. for $C_{19}H_{25}ClN_4O_3 \cdot (HCl)_2$: C, 44.05; H, 6.37; N, 10.81%; Found: C, 44.26; H, 6.08; N, 10.46%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloropropyl)-5-methyl-1-thien-2-ylmethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5-methyl-1-thien-2-yl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 103-106°C; Anal.: Calcd. for $C_{25}H_{29}SF_3N_4O_3 \cdot (HCl)_2$: C, 53.03; H, 5.48; N, 9.89%; Found: C, 53.25; H, 5.31; N, 9.52%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-benzyl-3-(3-chloropropyl)-2,4-dioxo-5(1*H*,3*H*)-pyrimidine-carbaldehyde and recrystallizing from a solution of fumaric acid in alcohol gave 1-benzyl-3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-2,4-dioxo-5(1*H*,3*H*)-pyrimidinecarbaldehyde fumarate, m.p. 175°C; Anal.: Calcd. for $C_{27}H_{29}F_3N_4O_4 \cdot C_4H_4O_4$: C, 57.58; H, 5.14; N, 8.66%; Found: C, 57.42; H, 5.13; N, 8.61%;
- substituting 1-[4-hydroxy-2-(2,2,2-trifluoroethoxy)phenyl]-piperazine and 3-(3-chloropropyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-(3-{4-[4-hydroxy-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 232-242°C; Anal.: Calcd. for $C_{20}H_{25}F_3N_4O_4 \cdot HCl$: C, 49.63; H, 5.59; N, 11.02%; Found: C, 49.62; H, 5.65; N, 10.66%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloropropyl)-1-fur-3-ylmethyl-5-methyl-2,4(1*H*,3*H*)-



- pyrimidinedione gave 3-(3-(4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)propyl)-1-fur-3-yl-methyl-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 128-131°C; Anal.: Calcd. for $C_{25}H_{29}F_3N_4O_4 \cdot (HCl)_2$: C, 50.26; H, 5.57; N, 9.38%; Found: C, 50.55; H, 5.25; N, 9.22%;
- 5 substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-(3-chloropropyl)-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 1-(3-(4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-
- 10 yl)propyl)-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 201-203°C; Anal.: Calcd. for $C_{21}H_{27}F_3N_4O_3 \cdot C_4H_4O_4$: C, 53.95; H, 5.61; N, 10.06%; Found: C, 53.92; H, 5.71; N, 10.00%;
- substituting 3-(3-chloropropyl)-5-methyl-1-pyrid-4-ylmethyl-
- 15 2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave di(3-(3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl)-5-methyl-1-pyrid-4-ylmethyl-2,4(1H,3H)-pyrimidinedione) fumarate, m.p. 210-212°C; Anal.: Calcd. for $(C_{25}H_{31}N_5O_3)_2 \cdot C_4H_4O_4$: C, 66.33; H, 6.59; N, 13.68%;
- 20 Found: C, 63.49; H, 6.65; N, 13.58%;
- substituting 3-benzyl-1-(3-chloropropyl)-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-benzyl-1-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-5,6-dimethyl-2,4(1H,3H)-
- 25 pyrimidinedione fumarate, m.p. 164-166°C; Anal.: Calcd. for $C_{27}H_{34}N_4O_3 \cdot C_4H_4O_4$: C, 64.35; H, 6.62; N, 9.68%; Found: C, 64.57; H, 6.67; N, 9.71%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloropropyl)-5-methyl-1-pyrid-4-ylmethyl-2,4(1H,3H)-
- 30 pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-(4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)propyl)-5-methyl-1-pyrid-4-ylmethyl-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 122-124°C; Anal.: Calcd. for $C_{26}H_{30}F_3N_5O_3 \cdot C_4H_4O_4$: C, 56.07; H, 5.49; N, 10.90%; Found: C, 56.36; H, 5.55; N, 10.61%;
- 35 substituting 3-(3-chloropropyl)-6-methyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-6-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride,

m.p. 232-234°C; Anal.: Calcd. for $C_{19}H_{26}N_4O_3 \cdot (HCl)_2$: C, 51.19; H, 6.68; N, 12.56%; Found: C, 51.11; H, 6.47; N, 12.44%; substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-benzyl-3-(3-chloropropyl)-2,4(1H,3H)-pyrimidinedione gave

5 1-benzyl-3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-2,4(1H,3H)-pyrimidinedione hydrochloride; Anal.: Calcd. for $C_{26}H_{29}F_3N_4O_3 \cdot (HCl)_2$: C, 53.43; H, 5.52; N, 9.59%; Found: C, 53.22; H, 5.34; N, 9.37%; substituting 1-[4-methyl-2-(2,2,2-trifluoroethoxy)phenyl]-

10 piperazine and 3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of hydrobromic acid in alcohol gave 3-(3-{4-[4-methyl-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrobromide, m.p. 86-90°C; Anal.: Calcd. for

15 $C_{21}H_{27}F_3N_4O_3 \cdot HBr$: C, 48.38; H, 5.41; N, 10.75%; Found: C, 48.73; H, 5.62; N, 10.51%; substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloropropyl)-6-methyl-2,4(1H,3H)-pyrimidinedione gave

20 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-6-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 218-220°C; Anal.: Calcd. for $C_{20}H_{25}F_3N_4O_3 \cdot (HCl)_2$: C, 48.10; H, 5.44; N, 11.22%; Found: C, 47.85; H, 5.48; N, 11.08%; substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and

25 3-(3-chloropropyl)-5-methyl-1-pyrid-3-ylmethyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5-methyl-1-pyrid-3-ylmethyl-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 158-160°C;

30 Anal.: Calcd. for $C_{26}H_{30}F_3N_5O_3 \cdot C_4H_4O_4$: C, 56.55; H, 5.93; N, 10.30%; Found: C, 56.27; H, 5.82; N, 10.05%; substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloropropyl)-5-methyl-1-phenyl-2,4(1H,3H)-pyrimidine-

35 dione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-5-methyl-1-phenyl-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 190-192°C; Anal.: Calcd. for $C_{26}H_{29}F_3N_4O_3 \cdot C_4H_4O_4$: C, 58.25; H, 5.38; N, 9.06%;





Found: C, 58.11; H, 5.45; N, 9.20%;
substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and
1-(3-chloropropyl)-5-methyl-3-phenyl-2,4(1*H*,3*H*)-pyrimidine-
dione and recrystallizing from a solution of fumaric acid in
5 alcohol gave 1-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]-
piperazin-1-yl}propyl)-5-methyl-3-phenyl-2,4(1*H*,3*H*)-pyrimi-
dinedione fumarate; Anal.: Calcd. for $C_{26}H_{29}F_3N_4O_3 \cdot C_4H_4O_4$: C,
57.41; H, 5.46; N, 8.93%; Found: C, 57.37; H, 5.45; N, 8.63%;
substituting 1-(3-chloropropyl)-6-methyl-2,4(1*H*,3*H*)-pyrimi-
10 dinedione gave 1-(3-[4-(2-methoxyphenyl)piperazin-1-
yl}propyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride,
m.p. 228-230°C; Anal.: Calcd. for $C_{19}H_{26}N_4O_3 \cdot (HCl)_2$: C, 51.39;
H, 6.66; N, 12.62%; Found: C, 51.14; H, 6.36; N, 12.38%;
substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and
15 1-(3-chloropropyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave
1-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-
yl}propyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride,
m.p. 217-219°C; Anal.: Calcd. for $C_{20}H_{25}F_3N_4O_3 \cdot (HCl)_2$: C,
48.10; H, 5.44; N, 11.22%; Found: C, 47.96; H, 5.46;
20 N, 11.15%;
substituting 1-(4-fluoro-2-methoxyphenyl)piperazine and
3-(3-chloropropyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave
3-{3-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl}propyl}-
6-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride,
25 m.p. 235-237°C; Anal.: Calcd. for $C_{19}H_{25}FN_4O_3 \cdot (HCl)_2$: C,
49.20; H, 6.21; N, 12.08%; Found: C, 49.02; H, 6.22;
N, 12.01%;
substituting 1-(4-fluoro-2-methoxyphenyl)piperazine and
3-(3-chloropropyl)-5-methyl-1-pyrid-3-ylmethyl-2,4(1*H*,3*H*)-
30 pyrimidinedione and recrystallizing from a solution of fumaric
acid in alcohol gave 3-{3-[4-(4-fluoro-2-methoxyphenyl)-
piperazin-1-yl}propyl}-5-methyl-1-pyrid-3-ylmethyl-
2,4(1*H*,3*H*)-pyrimidinedione fumarate; Anal.: Calcd. for
 $C_{25}H_{30}FN_5O_3 \cdot C_4H_4O_4$: C, 57.90; H, 6.03; N, 11.64%;
35 Found: C, 58.07; H, 5.93; N, 11.34%;
substituting 1-(4-fluoro-2-ethoxyphenyl)piperazine and
3-(3-chloropropyl)-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione and
recrystallizing from a solution of hydrobromic acid in alcohol

gave 3-{3-[4-(4-fluoro-2-ethoxyphenyl)-piperazin-1-yl]propyl}-5-ethyl-2,4(1H,3H)-pyrimidinedione hydrobromide, m.p. 224-227°C; Anal.: Calcd. for $C_{21}H_{29}FN_4O_3 \cdot HBr$: C, 44.54; H, 5.52; N, 9.89%; Found: C, 44.22; H, 5.48; N, 9.76%;

5 substituting 1-(4-fluoro-2-oxazol-2-ylphenyl)piperazine and 3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of oxalic acid in alcohol gave 3-{3-[4-(4-fluoro-2-oxazol-2-ylphenyl)-piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione oxalate, m.p. 207-210°C;

10 Anal.: Calcd. for $C_{21}H_{24}FN_5O_3 \cdot C_2H_2O_4$: C, 54.86; H, 5.20; N, 13.91%; Found: C, 54.71; H, 5.30; N, 13.93%;

substituting 1-(2-oxazol-2-ylphenyl)piperazine and 3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of oxalic acid in alcohol gave

15 3-{3-[4-(2-oxazol-2-ylphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione oxalate, m.p. 214-215°C; Anal.: Calcd. for $C_{21}H_{25}N_5O_3 \cdot C_2H_2O_4$: C, 55.13; H, 6.11; N, 13.85%; Found: C, 55.22; H, 5.70; N, 14.15%;

substituting 3-(3-chloropropyl)-5-methyl-1-pyrid-2-ylmethyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl}-5-methyl-1-pyrid-2-ylmethyl-2,4(1H,3H)-pyrimidinedione fumarate as a foam; Anal.: Calcd. for $C_{25}H_{31}N_5O_3 \cdot (C_4H_4O_4)_{1.5} \cdot (H_2O)_{0.25}$: C, 59.27; H, 6.02; N, 11.15%; Found: C, 59.25; H, 6.13; N, 11.27%;

25 substituting 1-(4-fluoro-2-methoxyphenyl)piperazine and 3-(3-chloropropyl)-6-methyl-2,4(1H,3H)-pyrimidinedione gave 3-{3-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]propyl}-6-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 227-229°C; Anal.: Calcd. for $C_{19}H_{25}FN_4O_3 \cdot (HCl)_2$: C, 48.82; H, 6.20; N, 11.98%; Found: C, 48.72; H, 5.87; N, 11.72%;

substituting 2-(3-chloropropyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione and recrystallizing from a solution of

35 fumaric acid in alcohol gave di(2-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl}-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione) fumarate, m.p. 235-237°C; Anal.: Calcd. for $(C_{18}H_{25}N_5O_3)_2 \cdot C_4H_4O_4$: C, 56.93; H, 6.57; N, 16.60%;



- Found: C, 56.97; H, 6.59; N, 16.54%;
substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and
4-(3-chloropropyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione
and recrystallizing from a solution of fumaric acid in alcohol
5 gave di[4-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione] fumarate,
m.p. 242-245°C; Anal.: Calcd. for $(C_{19}H_{24}F_3N_5O_3)_2 \cdot C_4H_4O_4$:
C, 51.48; H, 5.45; N, 14.29%; Found: C, 51.20; H, 5.29;
N, 14.20%;
- 10 substituting 4-(3-chloropropyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione and recrystallizing from a solution of fumaric acid in alcohol gave 4-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl}-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione) fumarate, m.p. 204-206°C; Anal.: Calcd. for
15 $C_{18}H_{25}N_5O_3 \cdot C_4H_4O_4$: C, 54.54; H, 6.24; N, 14.45%;
Found: C, 54.28; H, 6.38; N, 14.65%;
- substituting 1-(4-fluoro-2-methoxyphenyl)piperazine and
4-(3-chloropropyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione
and recrystallizing from a solution of fumaric acid in alcohol
20 gave 4-{3-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]propyl}-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione) fumarate,
m.p. 193-195°C; Anal.: Calcd. for $C_{18}H_{25}N_5O_3 \cdot C_4H_4O_4$: C, 51.75;
H, 5.90; N, 13.72%; Found: C, 51.93; H, 5.56; N, 13.91%;
- substituting 1-(2-trifluoromethoxyphenyl)piperazine and
25 3-(3-chloropropyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione and
recrystallizing from a solution of hydrobromic acid in alcohol
gave 3-(3-[4-(2-trifluoromethoxyphenyl)-piperazin-1-yl]propyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione hydrobromide,
m.p. 64-73°C; Anal.: Calcd. for $C_{20}H_{25}F_3N_4O_3 \cdot (HBr)_{0.25}$: C,
30 53.78; H, 5.70; N, 12.54%; Found: C, 54.39; H, 6.09;
N, 12.61%;
- substituting 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazine and 3-(3-chloropropyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy-phenyl)piperazin-1-yl]propyl}-5-ethyl-2,4(1H,3H)-pyrimidine-
35 dione hydrochloride, m.p. 186-188°C; Anal.: Calcd. for $C_{21}H_{27}F_4N_4O_3 \cdot (HCl)_2$: C, 47.46; H, 5.31; N, 10.54%;
Found: C, 47.67; H, 5.34; N, 10.64%;





- substituting 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazine and 3-(3-chloropropyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy-phenyl)piperazin-1-yl]propyl}-6-methyl-2,4(1*H*,3*H*)-pyrimidine-
5 dione hydrochloride, m.p. 225-228°C; Anal.: Calcd. for $C_{20}H_{24}F_4N_4O_3 \cdot (HCl)_2$: C, 46.12; H, 5.06; N, 10.83%; Found: C, 46.28; H, 4.98; N, 10.66%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-(1-benzyl-5-methyl-2,4-dioxo-(1*H*,3*H*)-pyrimidin-3-ylmethyl)cycloprop-1-ylmethyl methanesulfonate gave 1-benzyl-
10 3-(1-{4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-ylmethyl)cycloprop-1-ylmethyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione as an oil;
- substituting 1-(4-fluoro-2-methoxyphenyl)piperazine and
15 1-benzyl-3-(3-chloro-propyl)-5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione and recrystallizing from a solution of fumaric acid in alcohol gave 1-benzyl-3-{3-[4-(4-fluoro-2-methoxy-phenyl)piperazin-1-yl]propyl}-5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione fumarate, m.p. 168-169°C;
20 Anal.: Calcd. for $C_{27}H_{33}FN_4O_4 \cdot (C_4H_4O_4)_{0.5} \cdot (H_2O)_{0.5}$: C, 61.80; H, 6.44; N, 9.94%; Found: C, 61.72; H, 6.25; N, 10.02%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-benzyl-3-(3-chloropropyl)-5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione and recrystallizing from a solution of
25 fumaric acid in alcohol gave 1-benzyl-3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione fumarate, m.p. 176-177°C;
Anal.: Calcd. for $C_{28}H_{33}F_3N_4O_4 \cdot C_4H_4O_4$: C, 58.00; H, 5.63; N, 8.45%; Found: C, 58.20; H, 5.62; N, 8.48%;
- 30 substituting 1-benzyl-3-(3-chloropropyl)-5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione and recrystallizing from a solution of fumaric acid in alcohol gave 1-benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione fumarate, m.p. 184°C;
35 Anal.: Calcd. for $C_{27}H_{34}N_4O_4 \cdot C_4H_4O_4 \cdot (CH_4O)_{0.5}$: C, 61.95; H, 6.60; N, 9.171%; Found: C, 62.00; H, 6.89; N, 9.45%;
- substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-(3-chloropropyl)-3-(4-fluorophenyl)-5-methyl-2,4(1*H*,3*H*)-

- pyrimidinedione gave 1-(3-(4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)propyl)-3-(4-fluorophenyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 220-222°C; Anal.: Calcd. for $C_{26}H_{28}F_4N_4O_3 \cdot (HCl)_2 \cdot (H_2O)_{0.1}$: C, 52.46; H, 5.11; N, 9.41%; Found: C, 52.21; H, 4.91; N, 9.26%;
- 5 substituting 1-(4-fluoro-2-methoxyphenyl)piperazine and 3-(3-chloropropyl)-1-pyrid-4-ylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-[4-(4-fluoro-2-methoxyphenyl)-piperazin-1-yl]propyl)-1-pyrid-4-ylmethyl-5-methyl-2,4(1H,3H)-pyrimidinedione fumarate as a foam; Anal.: Calcd. for $C_{25}H_{30}FN_5O_3 \cdot (C_4H_4O_4)_{1.5}$: C, 58.03; H, 5.65; N, 10.91%; Found: C, 57.92; H, 5.71; N, 11.00%;
- 10 substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloropropyl)-1-(4-fluorophenyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl}propyl)-1-(4-fluorophenyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 166-168°C; Anal.: Calcd. for $C_{26}H_{28}F_4N_4O_3 \cdot HCl \cdot (C_4H_{10}O)_{0.3}$: C, 56.34; H, 5.56; N, 9.66%; Found: C, 56.06; H, 5.76; N, 9.36%;
- 20 substituting 1-(2-pyrrol-1-ylphenyl)piperazine and 3-(3-chloropropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione gave 3-{3-[4-(2-pyrrol-1-ylphenyl)piperazin-1-yl]-propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione hydrobromide, m.p. 249-252°C; Anal.: Calcd. for $C_{22}H_{27}N_5O_2 \cdot HBr$: C, 55.60; H, 5.95; N, 14.80%; Found: C, 55.49; H, 6.10; N, 14.04%;
- 25 substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 3-(3-chloropropyl)-5-methyl-2,4-dioxo-(1H,3H)-pyrimidin-1-ylmethylpyridine 1-oxide gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5-methyl-2,4-dioxo-(1H,3H)-pyrimidin-1-ylmethylpyridine 1-oxide fumarate, m.p. 120-122°C. Anal.: Calcd. for $C_{26}H_{30}F_3N_5O_4 \cdot (C_4H_4O_4)_{1.5}$: C, 54.31; H, 5.13; N, 9.906%; Found: C, 54.55; H, 5.15; N, 9.93%;
- 30 substituting 1-(4-fluoro-2-methoxyphenyl)piperazine and 3-(3-chloropropyl)-1-(2,2,2-trifluoroethoxy)-5-methyl-2,4(1H,3H)-pyrimidinedione gave 3-{3-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]propyl}-1-(2,2,2-trifluoro-





ethoxy)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrobromide,
m.p. 179-181°C; Anal.: Calcd. for $C_{21}H_{26}F_4N_4O_3 \cdot HBr$: C, 46.76;
H, 5.05; N, 10.39%; Found: C, 47.13; H, 5.15; N, 10.21;
substituting 3-(3-chloropropyl)-1-[2-(trimethylsilyl)ethoxy-
5 methyl]-2,4(1H,3H)-pyrimidinedione gave 3-(3-{4-[2-(2,2,2-
trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-1-[2-
(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione;
substituting 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-
piperazine and 3-(3-chloropropyl)-1-[2-(trimethylsilyl)ethoxy-
10 methyl]-2,4(1H,3H)-pyrimidinedione gave 3-(3-{4-[4-fluoro-
2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-
1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione;
substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and
2-(3-chloropropyl)-6-methyl-4-[2-(trimethylsilyl)ethoxy-
15 methyl]-1,2,4-triazine-3,5(2H,4H)-dione gave 2-(3-{4-[2-
(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-
6-methyl-4-[2-(trimethylsilyl)ethoxymethyl]-1,2,4-triazine-
3,5(2H,4H)-dione;
substituting 1-(4-fluoro-2-methoxyphenyl)piperazine and
20 2-(3-chloropropyl)-6-methyl-4-[2-(trimethylsilyl)ethoxy-
methyl]-1,2,4-triazine-3,5(2H,4H)-dione gave 2-{3-[4-(4-
fluoro-2-methoxyphenyl)piperazin-1-yl]propyl}-6-methyl-
4-[2-(trimethylsilyl)ethoxymethyl]-1,2,4-triazine-3,5(2H,4H)-
dione;
25 substituting 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-
piperazine and 3-(3-chloropropyl)-5-hydroxymethyl-
1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione
gave 3-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-
piperazin-1-yl}propyl)-5-hydroxymethyl-1-[2-(trimethyl-
30 silyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione;
substituting 1-(2-chlorophenyl)piperazine and 3-(3-chloro-
propyl)-5-methyl-1-[2-(trimethylsilyl)ethoxymethyl]-
2,4(1H,3H)-pyrimidinedione gave 3-{3-[4-(2-chlorophenyl)-
piperazin-1-yl]propyl}-5-methyl-1-[2-(trimethylsilyl)ethoxy-
35 methyl]-2,4(1H,3H)-pyrimidinedione;
substituting 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-
piperazine and 3-(3-chloropropyl)-5-fluoro-1-[2-(trimethyl-
silyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione gave



3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)propyl)-5-fluoro-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione;
substituting 1-[2-(4-fluoro-2,2,2-trifluoroethoxy)phenyl]-piperazine and 3-(3-chloropropyl)-5-chloro-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione gave 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)propyl)-5-chloro-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione;
substituting 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazine and 1-[2-(trimethylsilyl)ethoxymethyl]-5-methoxy-2,4(1H,3H)-pyrimidinedione gave 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-1-[2-(trimethylsilyl)ethoxymethyl]-5-methoxy-2,4(1H,3H)-pyrimidinedione as an oil;
substituting 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine and 1-[2-(trimethylsilyl)ethoxymethyl]-5-hydroxymethyl-2,4(1H,3H)-pyrimidinedione gave 3-(3-(4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-1-[2-(trimethylsilyl)ethoxymethyl]-5-hydroxymethyl-2,4(1H,3H)-pyrimidinedione as an oil; and
substituting 1-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazine and 2-(3-chloropropyl)-6-methyl-4-[2-(trimethylsilyl)ethoxymethyl]-1,2,4-triazine-3,5(2H,4H)-dione gave 2-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-6-methyl-4-[2-(trimethylsilyl)ethoxymethyl]-1,2,4-triazine-3,5(2H,4H)-dione.

EXAMPLE 26

30

3-(3-(4-[4-Fluoro-2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)propyl)-5-dimethylamino-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione

35

The following is the preparation of a protected derivative of a compound of Formula I in which R¹ is 2,2,2-trifluoroethoxy, R² is fluoro at the 4-position, R³ and R⁴ are each hydro and R⁵ is a group of Formula (a) wherein Z



is CH, R⁷ is dimethyl amino and the protective group is 2-(trimethylsilyl)ethoxy-methyl.

A mixture of 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)-phenyl]-piperazin-1-yl)propyl)-5-chloro-1-[2-(trimethylsilyl)-ethoxymethyl]-2,4(1H,3H)-pyrimidinedione (0.5 g, 0.84 mmol), prepared as in Example 25, aqueous dimethylamine (40%, 3 ml) and ethanol (3 ml) was heated in a sealed tube 3 hours at 130°C. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel eluting with methylene chloride/methanol (95:5 + 3% ammonium hydroxide) to give 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-5-dimethylamino-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione (0.26 g, 0.44 mmol).

EXAMPLE 27

3-(3-(4-(2-(2,2,2-Trifluoroethoxyphenyl)piperazin-1-yl)propyl)-2,4(1H,3H)-pyrimidinedione

The following is the preparation of a compound of Formula I in which R¹ is 2,2,2-trifluoroethoxy, R², R³ and R⁴ are each hydro and R⁵ is a group of Formula (a) wherein Z is CH and R⁶ and R⁷ are each hydro.

A mixture of the 3-(3-(4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)-propyl)-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione (273 mg, 0.5 mmol), prepared as in Example 25, tetrabutylammonium fluoride (2 mmol) and THF (5 ml) was stirred 24 hours at 25°C. The reaction mixture then was concentrated and the residue was purified by column chromatography on silica gel eluting with ethyl acetate to give 3-(3-(4-[2-(2,2,2-trifluoroethoxy)-phenyl]-piperazin-1-yl)propyl)-2,4(1H,3H)-pyrimidinedione (160 mg, 0.39 mmol). The free base was recrystallized from a solution of hydrogen chloride in ethanol to give 3-(3-(4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-



2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 247-249°C.

Anal.: Calcd. for $C_{19}H_{23}F_3N_4O_3 \cdot (HCl)_2$: C, 47.01; H, 5.19; N, 11.54%; Found: C, 46.84; H, 5.18; N, 11.34%.

5 Proceeding as in Example 27, but substituting a different starting material for 3-(3-(4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)propyl)-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione gave the following compounds of Formula I:

10

substituting 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)-propyl)-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 187°C.

15

Anal.: Calcd. for $C_{19}H_{22}F_4N_4O_3 \cdot C_4H_4O_4$: C, 50.55; H, 4.80; N, 10.25%; Found: C, 50.46; H, 4.75; N, 10.13%;

20

substituting 2-(3-(4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-6-methyl-4-[2-(trimethylsilyl)ethoxymethyl]-1,2,4-triazine-3,5(2H,4H)-dione and recrystallizing from a solution of fumaric acid in alcohol gave di[2-(3-(4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione] fumarate, m.p. 213-215°C;

25

Anal.: Calcd. for $(C_{19}H_{24}F_3N_5O_3)_2 \cdot C_4H_4O_4$: C, 51.96; H, 5.40; N, 14.43%; Found: C, 52.23; H, 5.38; N, 14.35%;

30

substituting 2-(3-(4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl)propyl)-6-methyl-4-[2-(trimethylsilyl)ethoxymethyl]-1,2,4-triazine-3,5(2H,4H)-dione and recrystallizing from a solution of fumaric acid in alcohol gave 2-(3-(4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl)propyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione fumarate, m.p. 201-203°C;

35

substituting 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)-propyl)-5-hydroxymethyl-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-5-hydroxymethyl-2,4(1H,3H)-pyrimidine-

dione fumarate, m.p. 181°C;; Anal.: Calcd. for $C_{20}H_{24}F_4N_4O_4 \cdot (C_4H_4O_4)_{0.5}$: C, 50.18; H, 5.49; N, 10.18%; Found: C, 49.98; H, 5.49; N, 10.01%; substituting 3-(3-[4-(2-chlorophenyl)piperazin-1-yl]propyl)-5-methyl-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione gave 3-(3-[4-(2-chlorophenyl)piperazin-1-yl]propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 240-242°C;; Anal.: Calcd. for $C_{18}H_{23}ClN_4O_2 \cdot HCl \cdot (H_2O)_{0.75}$: C, 52.37; H, 6.23; N, 13.57%; Found: C, 52.14; H, 6.03; N, 13.54%; substituting 3-(3-[4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]-propyl)-5-fluoro-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione gave 3-(3-[4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]-propyl)-5-fluoro-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 187-189°C;; Anal.: Calcd. for $C_{19}H_{21}F_5N_4O_3 \cdot (HCl)_2$: C, 43.77; H, 4.44; N, 10.74%; Found: C, 43.52; H, 4.35; N, 10.83%; substituting 3-(3-[4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]-propyl)-5-chloro-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-[4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]-propyl)-5-chloro-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 210-212°C;; Anal.: Calcd. for $C_{19}H_{21}F_4N_4O_3 \cdot C_4H_4O_4 \cdot (CH_4O)_{0.5}$: C, 47.28; H, 4.56; N, 9.39%; Found: C, 47.44; H, 4.28; N, 9.08%; substituting 3-(3-[4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]-propyl)-5-dimethylamino-1-[2-(trimethylsilyl)ethoxymethyl]-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-[4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]-propyl)-5-dimethylamino-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 182-184°C;; Anal.: Calcd. for $C_{21}H_{27}F_4N_5O_3 \cdot C_4H_4O_4$: C, 50.93; H, 5.30; N, 11.88%; Found: C, 50.82; H, 5.35; N, 11.62%; substituting 3-(3-[4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]-propyl)-1-[2-(trimethylsilyl)ethoxymethyl]-5-methoxy-2,4(1H,3H)-pyrimidinedione gave



- 3-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5-methoxy-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 188-189°C; Anal.: Calcd. for $C_{20}H_{24}F_4N_4O_4 \cdot (HCl)_2$: C, 45.04; H, 4.91; N, 10.51%; Found: C, 44.88; H, 4.87; N, 10.40%;
- substituting 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-1-[2-(trimethylsilyl)ethoxymethyl]-5-hydroxymethyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave
- 10 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5-hydroxymethyl-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 143°C; Anal.: Calcd. for $C_{20}H_{25}F_3N_4O_4 \cdot C_2H_2O_2$: C, 51.41; H, 5.34; N, 9.89%; Found: C, 51.15; H, 5.56; N, 10.29%; and
- 15 substituting 2-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}-propyl)-6-methyl-4-[2-(trimethylsilyl)ethoxymethyl]-1,2,4-triazine-3,5(2H,4H)-dione and recrystallizing from a solution of fumaric acid in alcohol gave 2-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione fumarate, m.p. 204-206°C;; Anal.: Calcd. for $C_{19}H_{23}F_4N_5O_3 \cdot (C_4H_4O_4)_{0.5}$: C, 49.63; H, 4.92; N, 13.15%; Found: C, 49.03; H, 5.12; N, 13.19%.

25

EXAMPLE 28

1-Bromo-3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propane

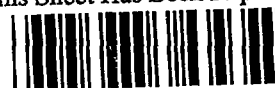
30

The following is the preparation of a compound of Formula 5 in which L is bromo, R^1 is 2,2,2-trifluoroethoxy and R^2 , R^3 and R^4 are each hydro.

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A mixture of 4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine (2.37 g, 9.1 mmol), 1-bromo-3-chloropropane (14.34 g, 91.1 mmol), potassium carbonate (1.88 g, 13.6 mmol) and acetonitrile (40 ml) was heated 16 hours at reflux under argon. The reaction mixture was allowed to cool





to 25°C, then filtered and concentrated in vacuo. The residue was further concentrated at 60°C in vacuo to remove excess 1-bromo-3-chloropropane. The residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to give a mixture of 1-chloro- and 1-bromo-3-{4-[2-(2,2,2-trifluoro-ethoxy)phenyl]piperazin-1-yl}propane (1.4 g).

EXAMPLE 29

10 1-Chloro-2,2-dimethyl-3-{4-[2-(2,2,2-trifluoro-ethoxy)phenyl]piperazin-1-yl}propane

The following is the preparation of a compound of Formula 5 in which L is chloro, R¹ is 2,2,2-trifluoroethoxy and R² is hydro and R³ and R⁴ are each methyl.

A mixture of ethyl cyanoacetate (5 g, 44 mmol), triethylbenzylammonium chloride (10.05 g, 44 mmol), iodomethane (11 ml, 177 mmol) and 50% sodium hydroxide (88 ml) was stirred 2 hours at 20°C. The reaction mixture then was diluted with water (220 ml) and the aqueous phase was separated, washed with diethyl ether, treated with concentrated hydrochloric acid and extracted with diethyl ether (3x 50 ml). The combined extracts were washed with brine (1x 50 ml), dried (MgSO₄) and concentrated to give 2-cyano-2-methylpropionic acid (4.3 g, 37.5 mmol).

A mixture of 2-cyano-2-methylpropionic acid (4.1 g, 36.1 mmol), dry triethylamine (6.6 ml, 46.9 mmol) and THF (70 ml) was cooled to between -5° and 0°C under argon and methyl chloroformate (3.4 ml, 43.3 mmol) was added. The mixture was stirred 1 hour, filtered at 0°C (washing through with THF), and recooled to 0°C under argon and then a mixture of sodium borohydride (4.1 g, 108 mmol) and cold water (25 ml) was added at a rate such that the reaction mixture remained below 10°C. The mixture was stirred 2.5 hours at 20°C, treated with 10% hydrochloric acid, washed with brine (1x 40 ml) and extracted with ethyl acetate (4x 40 ml). The combined extracts were

washed with brine, dried (MgSO_4) and concentrated. The residue was purified by chromatography on silica gel eluting with hexanes/ethyl acetate (7:3) to give 3-hydroxy-2,2-dimethyl-propanenitrile (2.7 g, 27.1 mmol).

5

A solution of 60% sodium hydride (367.1 mg, 15.3 mmol) was washed with hexane (3x 2 ml) and suspended in DMF (2 ml). The suspension was cooled to -10°C and then a mixture of 3-hydroxy-2,2-dimethylpropanenitrile (1.4 g, 13.9 mmol) and 10 DMF (8 ml) was added. The mixture was cooled 2.5 hour with stirring stirred at -10 to -5°C and then benzyl bromide (1.7 ml, 13.9 mmol) was added. The mixture was cooled 2 hours with stirring at -5°C , diluted with water (10 ml) and extracted with diethyl ether (3x 10 ml). The combined 15 extracts were washed with water (1x 10 ml) and brine (1x 10 ml), dried (MgSO_4) and concentrated to give 3-benzyloxy-2,2-dimethylpropanenitrile (2.5 g, 13.2 mmol).

A mixture of 3-benzyloxy-2,2-dimethylpropanenitrile 20 (2.5 g, 13.2 mmol), 10% aqueous sodium hydroxide (10 ml) and methanol (150 ml) was heated 8 hours at reflux and then concentrated. The residue was dissolved in water (30 ml) and the solution was washed with dichloromethane (2x 10 ml), treated with 10% hydrochloric acid and extracted with ethyl 25 acetate (4x 20 ml). The combined extracts were washed with water and brine, dried (MgSO_4) and concentrated to give 3-benzyloxy-2,2-dimethylpropionic acid (1.6 g, 7.5 mmol).

A mixture of 3-benzyloxy-2,2-dimethylpropionic acid 30 (1.6 g, 7.5 mmol), benzene (10 ml) and DMF (2 drops) was cooled to between 0 and 5°C and then oxalyl chloride (0.98 ml, 11.2 mmol) was added slowly. The mixture was stirred 1.5 hours at between 20 and 25°C and concentrated. The residue was dissolved in benzene (10 ml) and the solution 35 reconcentrated (repeated once). The residue then was dissolved in benzene (6 ml) and the solution was cooled to 0°C and added to a cold (0°C) mixture of 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine (2.1 g, 8.24 mmol) and benzene





(6 ml). The mixture was cooled 15 hours at 0°C and then triethylamine (3 ml, 21.3 mmol) was added. The mixture was stirred an additional 20 minutes, diluted with 10 ml of saturated sodium carbonate and extracted with methylene chloride (3x 15 ml). The combined extracts were washed with water (1x 10 ml), dried (MgSO₄) and concentrated. The residue was purified by chromatography on silica gel eluting with hexanes/ethyl acetate (8:2) to give 3-benzyloxy-2,2-dimethyl-1-(4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)-1-propanone (2.8 g, 6.4 mol).

A suspension of lithium aluminum hydride (0.49 g, 12.8 mmol) and THF (5 ml) was cooled to 0°C and added to a solution of 3-benzyloxy-2,2-dimethyl-1-(4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)-1-propanone (2.8 g, 6.4 mol) in 12 ml of THF. The mixture was heated 2 hours at reflux, slowly diluted with water, filtered and concentrated. The residue was dissolved in water and the solution was extracted with methylene chloride (4x 30 ml). The combined extracts were washed with water (1x 25 ml), dried (MgSO₄) and concentrated. The residue was purified by chromatography on silica gel eluting with hexanes/ethyl acetate (8:2) to give 3-benzyloxy-2,2-dimethyl-1-(4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)propane (2.6 g, 6.2 mol).

A mixture of 3-benzyloxy-2,2-dimethyl-1-(4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl)propane (2.5 g, 6 mol), 10% palladium on carbon (2.8 g), ammonium formate (3.8 g, 59.6 mmol) and methanol (130 ml) was heated 1 hour at reflux. The reaction mixture was allowed to cool to approximately 25°C, then filtered over celite (washing through with methanol and saturated sodium carbonate (20 ml)) and concentrated. The residue was dissolved in water and the solution was extracted with methylene chloride (3x 20 ml). The combined extracts were dried (MgSO₄) and concentrated. The residue was purified by chromatography on silica gel eluting with hexanes/ethyl acetate (8:2) to give 2,2-dimethyl-3-(4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)-1-propanol (1.6 g, 5.1 mol).

A mixture of 2,2-dimethyl-3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}-1-propanol (991 mg, 2.9 mol), triethylamine (0.4 ml, 2.9 mmol), p-toluenesulfonyl chloride
5 (678 mg, 3.4 mmol), 4-dimethylaminopyridine (35 mg, 0.29 mmol) and methylene chloride (15 ml) was stirred 8 hours at 20 to 25°C. The reaction mixture then was filtered and concentrated and the residue was purified by chromatography on silica gel eluting with hexanes/ethyl acetate (95:5) to give 1-chloro-
10 2,2-dimethyl-3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propane (238 mg, 0.67 mol).

EXAMPLE 30

15 3-(3-{4-[2-(2,2,2-Trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5,6,7,8-tetrahydro-2,4(1H,3H)-quinazolinedione

The following is the preparation of a compound of Formula I in which R¹ is methoxy, R², R³ and R⁴ are each hydro and R⁵
20 is a group of Formula (a) wherein Z is C(R⁹), R⁶ is benzyl and R⁷ and R⁹ together are tetramethylene.

A mixture of 5,6,7,8-tetrahydro-2,4(1H,3H)-quinazoline-dione (665 mg, 4 mmol), 1-chloro- and 1-bromo-3-{4-[2-(2,2,2-
25 trifluoroethoxy)phenyl]-piperazin-1-yl}propane (1.4 g), prepared as in Example 28, potassium carbonate (552 mg, 4 mmol) and dry DMF (20 ml) was heated 16 hours at 65°C under argon. The reaction mixture then was cooled to 25°C, filtered, washed with methylene chloride and concentrated at 70°C
30 in vacuo. The residue was purified by preparative thin layer chromatography on silica gel eluting with methylene chloride/methanol (95:5) to give 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-5,6,7,8-tetrahydro-2,4(1H,3H)quinazolinedione (838 mg, 1.8 mmol), m.p. 148-150°C.
35 Anal.: Calcd. for C₂₃H₃₀F₃N₄O₃·HCl·(H₂O)_{2.5}: C, 49.56; H, 5.97; N, 10.05%; Found: C, 47.26; H, 5.90; N, 9.55.





Proceeding as in Example 30, but substituting a different starting material for 1-chloro- and 1-bromo-3-(4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propane gave the following compounds of Formula I:

5

substituting 1-chloro- and 1-bromo-3-[4-(4-fluoro-2-methoxyphenyl)-piperazin-1-yl]propane gave 3-{3-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]-propyl}-5,6,7,8-tetrahydro-2,4(1H,3H)quinazolinedione, m.p. 230-232°C;

10 Anal.: Calcd. for $C_{20}H_{29}FN_4O_3 \cdot (HCl)_2 \cdot (H_2O)_{0.5}$: C, 53.99; H, 6.38; N, 11.45%; Found: C, 52.75; H, 6.28; N, 11.03; and substituting 1-chloro- and 1-bromo-3-[4-(2-methoxyphenyl)-piperazin-1-yl]propane gave 3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl}-5,6,7,8-tetrahydro-2,4(1H,3H)quina-
15 zolinedione, m.p. 212-214°C; Anal.: Calcd. for $C_{22}H_{30}N_4O_3 \cdot (HCl)_2 \cdot (H_2O)_{0.3}$: C, 55.41; H, 6.89; N, 11.75%; Found: C, 55.19; H, 6.95; N, 11.55.

EXAMPLE 31

20

1-Benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-hydroxyiminomethyl-2,4(1H,3H)-pyrimidinedione

The following is the preparation of a compound of Formula
25 I in which R^1 is methoxy, R^2 , R^3 and R^4 are each hydro and R^5 is a group of Formula (a) wherein Z is CH, R^6 is benzyl and R^7 is hydroxyiminomethyl.

A mixture of 1-bromo-3-[4-(2-methoxyphenyl)piperazin-1-yl]propane (1.09 g, 3.5 mmol), prepared as in Example 25,
30 1-benzyl-5-hydroxyiminomethyl-2,4(1H,3H)-pyrimidinedione (0.86 g, 3.5 mmol), tetrabutylammonium fluoride (4.5 g, 17.5 mmol) and acetonitrile (50 ml) was stirred 24 hours at 25°C. The reaction mixture then was concentrated in vacuo and
35 the residue was dissolved in ethyl acetate (50 ml). The solution was washed with water (3x 50 ml) and brine (1x 50 ml) and purified by preparative thin layer chromatography on silica gel eluting with methylene chloride/methanol (95:5) and



1% ammonium hydroxide to give 1-benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-hydroxyimino-methyl-2,4(1*H*,3*H*)-pyrimidinedione (250 mg, 0.6 mmol). The free base was recrystallized from a solution of fumaric acid in alcohol to give 1-benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-hydroxyiminomethyl-2,4(1*H*,3*H*)-pyrimidinedione fumarate, m.p. 198-200°C; Anal.: Calcd. for C₂₆H₃₁N₅O₄·C₄H₄O₄: C, 59.78; H, 6.02; N, 11.62%; Found: C, 59.74; H, 6.03; N, 11.83%.

10

Proceeding as in Example 31, but substituting a different starting material for 1-bromo-3-[4-(2-methoxyphenyl)piperazin-1-yl]propane and/or 1-benzyl-5-hydroxyiminomethyl-2,4(1*H*,3*H*)-pyrimidinedione gave the following compounds of

15 Formula I:

substituting 1-chloro-3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propane and 5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione and recrystallizing from a solution of hydrochloric acid in alcohol gave 3-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 186-189°C; Anal.: Calcd. for C₁₉H₂₄F₄N₅O₃·(HCl)₂: C, 44.10; H, 5.06; N, 10.83%; Found: C, 43.99; H, 5.16;

25 N, 10.78%; and

substituting 1-chloro-2,2-dimethyl-3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propane and 1-benzyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 1-benzyl-3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}-2,2-dimethylpropyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione.

30

EXAMPLE 32

3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-
5-methyl-2,4(1*H*,3*H*)-pyrimidinedione

35

The following is the preparation of a compound of Formula I in which R¹ is methoxy, R², R³ and R⁴ are each hydro and R⁵



is a group of Formula (a) wherein Z is CH, R⁶ hydro and R⁷ is methyl.

A mixture of 1-benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione (809 mg, 1.8 mmol), prepared as in Example 25, 10% palladium on carbon (800 mg) and of 0.1N ammonium formate (180 ml, 18 mmol in methanol) was heated 10 hours at reflux. The reaction mixture then was filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (30 g) eluting with ethyl acetate to give 3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione (459 mg, 1.28 mmol), m.p. 168-170°C. The free base was recrystallized from a solution of hydrochloric acid in methanol to give 3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 245-248°C. Anal.: Calcd. for C₁₉H₂₆N₄O₃·(HCl)₂: C, 50.99; H, 6.71; N, 12.52%; Found: C, 51.06; H, 6.47; N, 12.58%.

Proceeding as in Example 32, but substituting other starting materials for 1-benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione, the following compounds of Formula I were prepared:

substituting 1-benzyl-3-{3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]-propyl}-5-propyl-2,4(1H,3H)-pyrimidinedione gave 3-{3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl}-5-propyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 135-137°C; Anal.: Calcd. for

C₂₂H₂₉F₃N₄O₃·(HCl)₂: C, 48.85; H, 6.06; N, 10.36%; Found: C, 48.84; H, 5.95; N, 10.21%;

substituting 3-benzyl-1-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione gave 1-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 239-242°C; Anal.: Calcd. for C₁₉H₂₆N₄O₃·(HCl)₂: C, 52.90; H, 6.54; N, 12.98%; Found: C, 53.32; H, 6.53; N, 13.13%;

substituting 1-benzyl-3-{3-[4-(4-fluoro-2-methoxyphenyl)-



- piperazin-1-yl]propyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-{3-[4-(4-fluoro-2-methoxyphenyl)-piperazin-1-yl]propyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 240-242°C; Anal.: Calcd. for $C_{19}H_{25}FN_4O_3 \cdot (HCl)_2$: C, 50.78; H, 6.05; N, 12.46%; Found: C, 50.60; H, 6.03; N, 12.22%;
- substituting 1-benzyl-3-{3-[4-(2-(2,2,2-trifluoroethoxy)-phenyl)piperazin-1-yl]propyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidine-dione gave 3-{3-[4-(2-(2,2,2-trifluoro-ethoxy)phenyl)-piperazin-1-yl]propyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 169-171°C; Anal.: Calcd. for $C_{20}H_{25}F_3N_4O_3 \cdot (HCl)_2$: C, 47.93; H, 5.47; N, 11.18%; Found: C, 48.06; H, 5.52; N, 10.88%;
- substituting 1-benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl}-5,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 237-239°C; Anal.: Calcd. for $C_{20}H_{28}N_4O_3 \cdot (HCl)_2$: C, 53.93; H, 6.78; N, 12.58%; Found: C, 53.73; H, 6.77; N, 12.36%;
- substituting 1-benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-methoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl}-5-methoxymethyl-2,4(1*H*,3*H*)-pyrimidinedione fumarate as a foam; Anal.: Calcd. for $C_{20}H_{28}N_4O_4 \cdot C_4H_4O_4$: C, 56.13; H, 6.47; N, 10.91%; Found: C, 56.22; H, 6.47; N, 11.02%;
- substituting 1-benzyl-3-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]propyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-{3-[4-(5-fluoro-2-methoxyphenyl)-piperazin-1-yl]propyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 270°C (dec); Anal.: Calcd. for $C_{19}H_{25}FN_4O_3 \cdot (HCl)_2$: C, 55.27; H, 6.35; N, 13.57%; Found: C, 55.03; H, 6.30; N, 13.56%;
- substituting 1-benzyl-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-5-trifluoromethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-{3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl}-5-trifluoro-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 257°C (dec); Anal.: Calcd. for $C_{19}H_{23}F_3N_4O_3 \cdot (HCl)_{1.1}$: C, 50.42;



- H, 5.36; N, 12.38%; Found: C, 50.36; H, 5.62; N, 12.21%; substituting 1-benzyl-3-(3-[4-(4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl)-piperazin-1-yl]propyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-[4-(4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]propyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione fumarate, m.p. 190-192°C; Anal.: Calcd. for $C_{20}H_{24}N_4O_3 \cdot C_4H_4O_4$: C, 51.40; H, 5.03; N, 9.99%; Found: C, 51.45; H, 5.07; N, 9.92%;
- 10 substituting 1-benzyl-3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]-propyl)-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 244-246°C; Anal.: Calcd. for $C_{20}H_{28}N_4O_3 \cdot (HCl)_2$: C, 52.87; H, 6.88; N, 12.33%; Found: C, 53.06; H, 6.71; N, 12.27%;
- 15 substituting 1-benzyl-3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]-propyl)-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)-piperazin-1-yl]propyl)-5-ethyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 169-171°C; Anal.: Calcd. for $C_{21}H_{27}N_4O_3 \cdot (HCl)_2$: C, 49.13; H, 5.69; N, 10.91%; Found: C, 49.01; H, 5.82; N, 11.20%;
- 20 substituting 3-benzyl-1-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]-propyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione gave 1-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]propyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 202-203°C; Anal.: Calcd. for $C_{20}H_{25}F_3N_4O_3 \cdot (HCl)_2$: C, 47.25; H, 5.54; N, 11.02%; Found: C, 46.98; H, 5.73; N, 10.82%;
- 25 substituting 1-benzyl-3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]-propyl)-5-propyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride, m.p. 237-238°C; Anal.: Calcd. for $C_{21}H_{30}N_4O_3 \cdot (HCl)_2$: C, 59.63; H, 7.38; N, 13.24%; Found: C, 53.24; H, 6.70; N, 11.54%;
- 30 substituting 1-benzyl-3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]-propyl)-5,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione gave 3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)-
- 35

- piperazin-1-yl]propyl}-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 198-199°C; Anal.: Calcd. for $C_{21}H_{27}F_3N_4O_3 \cdot (HCl)_2$: C, 48.28; H, 5.78; N, 10.72%; Found: C, 48.26; H, 5.81; N, 10.77%;
- 5 substituting 1-benzyl-3-(3-{4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl}-propyl)-5,5-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl}propyl)-5,5-dimethyl-
- 10 2,4,6(1H,3H,5H)-pyrimidinetrione fumarate, m.p. 200°C; Anal.: Calcd. for $C_{21}H_{27}F_3N_4O_4 \cdot (C_4H_4O_4)_{0.5} \cdot (CH_4O)_{1.5}$: C, 52.31; H, 6.27; N, 9.96%; Found: C, 51.95; H, 5.91; N, 10.35%; substituting 1-benzyl-3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-5,5-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione and
- 15 recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl)-5,5-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione fumarate, m.p. 196°C; Anal.: Calcd. for $C_{20}H_{28}N_4O_4 \cdot C_4H_4O_4 \cdot (H_2O)_{0.5}$: C, 56.13; H, 6.48; N, 10.91%; Found: C, 56.02; H, 6.43;
- 20 N, 10.85%;
- substituting 1-benzyl-3-(3-{4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl}-2,2-dimethylpropyl)-5-methyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-{4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl}-2,2-dimethylpropyl)-5-methyl-
- 25 2,4(1H,3H)-pyrimidinedione fumarate, m.p. 143-144°C; Anal.: Calcd. for $C_{22}H_{29}F_3N_4O_3 \cdot C_4H_4O_4$: C, 54.73; H, 5.83; N, 9.82%; Found: C, 54.77; H, 5.81; N, 9.78%;
- substituting 1-benzyl-3-(3-[4-(4-fluoro-2-methoxyphenyl)-piperazin-1-yl]propyl)-5,5-dimethyl-2,4,6(1H,3H,5H)-pyrimi-
- 30 dinetrione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-[4-(4-fluoro-2-methoxyphenyl)-piperazin-1-yl]propyl)-5,5-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione fumarate, m.p. 171°C; Anal.: Calcd. for
- 35 $C_{20}H_{27}FN_4O_4 \cdot (C_4H_4O_4)_{0.5} \cdot (H_2O)_{1.25}$: C, 54.26; H, 6.52; N, 11.50%; Found: C, 54.07; H, 6.35; N, 11.39%;
- substituting 1-benzyl-3-(1-{4-[2-(2,2,2-trifluoroethoxy)-phenyl]piperazin-1-yl-methyl}cycloprop-1-yl-methyl)-5-methyl-





- 2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(1-{4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-ylmethyl}cycloprop-1-yl-methyl)-5-methyl-2,4(1H,3H)-pyrimidinedione fumarate as a foam;
- 5 Anal.: Calcd. for $C_{22}H_{27}F_3N_4O_3 \cdot (C_4H_4O_4)_{1.5}$: C, 53.67; H, 5.31; N, 8.94%; Found: C, 53.61; H, 5.50; N, 8.90%;
- substituting 1-benzyl-3-{1-[4-(2-methoxyphenyl)piperazin-1-ylmethyl]cycloprop-1-yl-methyl}-5-methyl-2,4(1H,3H)-pyrimidinedione and recrystallizing from a solution of fumaric
- 10 acid in alcohol gave 3-{1-[4-(2-methoxyphenyl)piperazin-1-ylmethyl]cycloprop-1-yl-methyl}-5-methyl-2,4(1H,3H)-pyrimidinedione fumarate as a foam; Anal.: Calcd. for $C_{21}H_{28}N_4O_3 \cdot C_4H_4O_4$: C, 58.11; H, 6.59; N, 10.84%; Found: C, 58.38; H, 6.50; and N, 10.52%;
- 15 substituting 1-benzyl-3-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5,5-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-
- 20 5,5-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione fumarate, m.p. 132°C; Anal.: Calcd. for $C_{21}H_{26}F_4N_4O_4 \cdot (C_4H_4O_4)_{0.5} \cdot (H_2O)_{1.25}$: C, 49.77; H, 5.54; N, 10.09%; Found: C, 49.69; H, 5.44; N, 9.96.

25

EXAMPLE 33

3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-
1,5-dimethyl-2,4(1H,3H)-pyrimidinedione

30

The following is the preparation of a compound of Formula I in which R^1 is methoxy, R^2 is hydro, R^3 and R^4 are hydro and R^5 is a group of Formula (a), wherein Z is CH and R^6 and R^7 are each methyl.

35

A mixture of 3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione (550 mg, 1.53 mmol), prepared as in Example 32, dimethyl sulfate (193 mg, 1.53 mmol) and 0.1 N tetrabutylammonium fluoride



(100 ml, 10 mmol in THF) was stirred 4 hours at 25°C. The reaction mixture then was concentrated in vacuo and the residue was purified by column chromatography on silica gel eluting with ethyl acetate to give 3-{3-[4-(2-methoxyphenyl)-
5 piperazin-1-yl]propyl}-1,5-dimethyl-2,4(1H,3H)-pyrimidine-
dione, as an oil. The free base was recrystallized from a solution of hydrochloric acid in alcohol to give
3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-1,5-dimethyl-
2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 256-258°C.
10 Anal.: Calcd. for $C_{20}H_{28}N_4O_3 \cdot (HCl)_2$: C, 53.93; H, 6.79; N, 12.58%; Found: C, 54.05; H, 6.87; N, 12.58%.

Proceeding as in Example 33, but substituting other starting materials for 3-{3-[4-(2-methoxyphenyl)piperazin-1-
15 yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione and/or dimethyl sulfate, the following compounds of Formula I were prepared:

substituting 1-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-
5-methyl-2,4(1H,3H)-pyrimidinedione gave 1-{3-[4-(2-methoxy-
20 phenyl)piperazin-1-yl]propyl}-3,5-dimethyl-2,4(1H,3H)-
pyrimidinedione hydrochloride, m.p. 242-244°C; Anal.: Calcd. for $C_{20}H_{28}N_4O_3 \cdot (HCl)_2$: C, 53.93; H, 6.78; N, 12.58%;
Found: C, 53.70; H, 6.92; N, 12.58%;

substituting 3-{3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)-
25 piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione and
4-chlorobenzyl chloride gave 1-(4-chlorobenzyl)-3-{3-[4-(2-
(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]propyl}-
5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride,
m.p. 170-172°C; Anal.: Calcd. for $C_{27}H_{30}ClF_3N_4O_3 \cdot HCl$: C,
30 55.20; H, 5.31; N, 9.53%; Found: C, 55.01; H, 5.24; N, 9.56%;

substituting 3-{3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)-
piperazin-1-yl]propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione and
3-chlorobenzyl chloride gave 1-(3-chlorobenzyl)-3-{3-[4-(2-
(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl]propyl}-
35 5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride,
m.p. 142-144°C; Anal.: Calcd. for $C_{27}H_{30}ClF_3N_4O_3 \cdot HCl$: C,
55.03; H, 5.33; N, 9.50%; Found: C, 54.80; H, 5.27; N, 9.46%;
substituting 3-{3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)-

- piperazin-1-yl}propyl}-5-methyl-2,4(1H,3H)-pyrimidinedione and 2-picolyl chloride hydrochloride and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl}propyl)-5-methyl-
- 5 1-pyrid-2-ylmethyl-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 134-135°C; Anal.: Calcd. for $C_{26}H_{30}F_3N_5O_3 \cdot C_4H_4O_4$: C, 56.07; H, 5.49; N, 10.90%; Found: C, 55.82; H, 5.64; N, 11.05%;
- substituting 3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)-
- 10 piperazin-1-yl}propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione and 2-chlorobenzyl chloride gave 1-(2-chlorobenzyl)-3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl}-propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride, m.p. 152-153°C; Anal.: Calcd. for $C_{27}H_{30}ClF_3N_4O_3 \cdot HCl$: C, 55.20; H, 5.31; N, 9.53%; Found: C, 54.99; H, 5.38; N, 9.56%;
- 15 substituting 3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)-piperazin-1-yl}propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione and 2,6-dimethylbenzyl chloride and recrystallizing from a solution of fumaric acid in alcohol gave 3-(3-[4-(2-(2,2,2-
- 20 trifluoroethoxy)phenyl)piperazin-1-yl}propyl)-5-methyl-1-(2,6-dimethylbenzyl)-2,4(1H,3H)-pyrimidinedione fumarate, m.p. 121-124°C; Anal.: Calcd. for $C_{29}H_{35}F_3N_4O_3 \cdot C_4H_4O_4$: C, 58.40; H, 6.09; N, 8.26%; Found: C, 58.63; H, 6.14; N, 8.36%; and
- 25 substituting 3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)-piperazin-1-yl}propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione and 4-methylbenzyl chloride gave 3-(3-[4-(2-(2,2,2-trifluoroethoxy)phenyl)piperazin-1-yl}propyl)-1-(4-methylbenzyl)-5-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride,
- 30 m.p. 141-143°C; Anal.: Calcd. for $C_{28}H_{33}F_3N_4O_3 \cdot (HCl)_2$: C, 55.89; H, 5.99; N, 9.12%; Found: C, 56.18; H, 5.99; N, 9.31%.

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EXAMPLE 34

1-(4-Methoxybenzyl)-3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-2,4-dioxo-5(1H,3H)-pyrimidinecarboxamide

5

The following is the preparation of a compound of Formula I in which R¹ is methoxy, R², R³ and R⁴ is hydro and R⁵ is a group of Formula (a) wherein Z is CH, R⁶ is 4-methoxyphenyl and R⁷ is carbamoyl.

10

A mixture of 5-cyano-1-(4-methoxybenzyl)-3-(3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl)-2,4(1H,3H)-pyrimidine-dione (450 mg, 0.92 mmol), prepared as in Example 25, and trifluoroacetic acid (4 ml) was heated 4 days at reflux. The reaction mixture then was concentrated in vacuo and the residue was dissolved in methylene chloride. The solution was washed with 10% aqueous sodium hydroxide and then water, dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel eluting with methylene chloride/methanol (97:3) to give 1-(4-methoxybenzyl)-3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-2,4-dioxo-5(1H,3H)-pyrimidinecarboxamide as a foam. The free base was recrystallized for a solution of hydrochloric acid in alcohol to give 1-(4-methoxybenzyl)-3-(3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl)-2,4-dioxo-5(1H,3H)-pyrimidinecarboxamide hydrochloride, m.p. 157-158°C. Anal.: Calcd. for C₂₇H₃₃N₅O₅·(HCl)₂: C, 53.06; H, 6.30; N, 11.46%; Found: C, 53.35; H, 5.90; N, 11.12%.

30

EXAMPLE 35

cis-3-(3-(4-[4-Fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl)propyl)-5,6-dihydroxy-5-methyl-5,6-dihydro-2,4(1H,3H)-pyrimidinedione

35

The following is the preparation of the *cis*-isomers of a compound of Formula I in which R¹ is 2,2,2-trifluoroethoxy, R² is fluoro in the 4-position, R³ and R⁴ are each hydro and R⁵

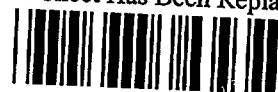
is a group of Formula (c) wherein X is CH(OH), R⁶ is hydro and one of the R⁸ radicals is hydroxy and the other is methyl.

A mixture of 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)-
5 phenyl]-piperazin-1-yl}propyl)-5-methyl-2,4(1H,3H)-pyrimidine-
dione (1.12 g, 2.52 mmol), prepared as in Example 32,
trifluoroacetic acid (0.86 g, 7.56 mmol), water (0.82 ml) and
DMSO (22 ml) was cooled to between 0 and 5°C and N-bromo-
succinimide (3.02 g/ml, 0.58 ml, 10.08 mmol) was added. The
10 mixture was stirred in the dark at 25°C, treated with
5% sodium bicarbonate, stirred 1 hour, diluted water (10 ml)
and then extracted with ethyl acetate (4x 20 ml). The
combined extracts were washed with water/brine (1:1,
1x 30 ml), dried (MgSO₄) and concentrated. The residue was
15 purified by flash chromatography on silica gel eluting with
methylene chloride/methanol (93:7) to give *cis*-3-(3-(4-[4-
fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-
5,6-dihydroxy-5-methyl-5,6-dihydro-2,4(1H,3H)-pyrimidinedione
(0.49 g, 1.03 mmol), m.p. 110°C. Free base (0.49 mg, 1.01)
20 was recrystallized from a solution of fumaric acid in methanol
to give *cis*-3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)-
phenyl]-piperazin-1-yl}propyl)-5,6-dihydroxy-5-methyl-
5,6-dihydro-2,4(1H,3H)-pyrimidinedione fumarate (493 mg,
0.83 mmol), m.p. 155°C; Anal.: Calcd. for
25 C₂₀H₂₆F₄N₄O₅•C₄H₄O₄: C, 48.49; H, 5.09; N, 9.42%;
Found: C, 48.33; H, 5.08; N, 9.61%.

Proceeding as in Example 35, but substituting
3-(3-(4-[2-(2,2,2-trifluoro-ethoxy)phenyl]piperazin-1-
30 yl}propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione for
3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-
piperazin-1-yl}propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione
gave *cis*-3-(3-(4-[2-(2,2,2-trifluoro-ethoxy)phenyl]piperazin-
1-yl}propyl)-5,6-dihydroxy-5-methyl-5,6-dihydro-
35 2,4(1H,3H)-pyrimidinedione fumarate, m.p. 125-126°C.
Anal.: Calcd. for C₂₀H₂₇F₃N₄O₅•(C₄H₄O₄)_{0.5}•(H₂O)_{0.75}: C,
49.67; H, 5.78; N, 10.53%; Found: C, 49.73; H, 5.55;
N, 10.48%.

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Example 35A

cis-3-(3-{4-[4-Fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-
5 piperazin-1-yl}propyl)-5,6-dihydroxy-5-methyl-5,6-dihydro-
2,4(1H,3H)-pyrimidinedione fumarate, prepared as above, was
dissolved in ethanol to a concentration of 20 mg/ml. A 2.0 ml
fraction was injected onto a Chiralpak AS (2 x 250 cm) column,
and was eluted with hexane/ethanol/diethylamine (90:9.9:0.1)
10 at 8.0 ml/min, monitoring the eluate by UV absorption at
238 nm. The (+)-enantiomer eluted first, and the (-)-enantiomer
second.

After repeated injections and elutions, the fractions
15 highly enriched in the (+)-enantiomer were pooled and
concentrated to give 610 mg (1.28 mmol) of the free base. This
material was dissolved in warm methanol (10 ml), and fumaric
acid (148 mg, 1.28 mmol) added and dissolved. A suspension of
a fine powder was obtained on the addition of ethyl acetate
20 (15 ml). The suspension was aged at room temperature, filtered
and dried in vacuo, and the solids recrystallized to give
400 mg of the (+)-enantiomer of cis-3-(3-{4-[4-fluoro-2-
(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-5,6-
dihydroxy-5-methyl-5,6-dihydro-2,4(1H,3H)-pyrimidinedione
25 fumarate: m.p. 183.5-192.1°C, $[\alpha]_D +13.2^\circ$ (c=0.34, MeOH). The
product was analyzed using an analytical Chiralpak AS column,
and found to consist of 94.9% (+)-enantiomer and 5.1%
(-)-enantiomer.

30 Similarly, the fractions highly enriched in the (-)-
enantiomer were pooled and concentrated to give 540 mg of the
free base. This material was dissolved in warm methanol
(10 ml), and fumaric acid (130 mg) added and dissolved. A
suspension of a fine powder was obtained on the addition of
35 ethyl acetate (15 ml). The suspension was aged at room
temperature, filtered and dried in vacuo, to give 356 mg of
the (-)-enantiomer of cis-3-(3-{4-[4-fluoro-2-(2,2,2-
trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-5,6-dihydroxy-

5-methyl-5,6-dihydro-2,4(1H,3H)-pyrimidinedione fumarate: m.p. 169.5-178.0°C, $[\alpha]_D -15.6^\circ$ ($c=0.48$, MeOH). The product was analyzed using an analytical Chiralpak AS column, and found to consist of 91.9% (-)-enantiomer and 8.1% (+)-enantiomer.

5

EXAMPLE 36

trans-3-(3-{4-[4-Fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5,6-dihydroxy-5-methyl-5,6-dihydro-2,4(1H,3H)-pyrimidinedione

10

The following is the preparation of the trans-isomers of a compound of Formula I in which R^1 is 2,2,2-trifluoroethoxy, R^2 is fluoro in the 4-position, R^3 and R^4 are each hydro and R^5 is a group of Formula (c) wherein X is CH(OH), R^6 is hydro and one of the R^8 radicals is hydroxy and the other is methyl.

15

A mixture of cis-3-(3-{4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-5,6-dihydroxy-5-methyl-5,6-dihydro-2,4(1H,3H)-pyrimidinedione (600 mg, 1.42 mmol), prepared as in Example 35, para-toluenesulfonic acid monohydrate (1.2 g, 6.3 mmol) and DMSO (46 ml) was heated 14 hours at 50°C. The mixture was allowed to cool to approximately 25°C, render neutral pH by treating with saturated sodium bicarbonate and extracted with ethyl acetate (4x 30 ml). The combined extracts were washed with water (1x 20 ml) and brine, dried (MgSO₄) and concentrated. The residue was purified by loading onto preparative silica plates and developing twice with methylene chloride/methanol (93:7) to give trans-3-(3-{4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl}propyl)-5,6-dihydroxy-5-methyl-5,6-dihydro-2,4(1H,3H)-pyrimidinedione (102 mg, 0.21 mmol) as a foam.

20

25

30

EXAMPLE 37

35

The following are representative pharmaceutical formulations containing a compound of Formula I.

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ORAL FORMULATION

A representative solution for oral administration contains:

5	Compound of Formula I	100-1000 mg
	Citric Acid Monohydrate	105 mg
	Sodium Hydroxide	18 mg
	Flavoring	
10	Water	q.s. to 100 ml

INTRAVENOUS FORMULATION

A representative solution for intravenous administration contains:

	Compound of Formula I	10-100 mg
	Dextrose Monohydrate	q.s. to make isotonic
	Citric Acid Monohydrate	1.05 mg
20	Sodium Hydroxide	0.18 mg
	Water for Injection	q.s. to 1.0 ml

TABLET FORMULATION

A representative tablet form of a compound of Formula I may contain:

	Compound of Formula I	1%
	Microcrystalline Cellulose	73%
30	Stearic Acid	25%
	Colloidal Silica	1%

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EXAMPLE 38

α_1 -Adrenoceptor In Vitro, Functional Assay
in Tissue Isolated from Rabbit and Rat

5

The following describes *in vitro* assays for measuring the relative effect of test compounds on α_1 -adrenoceptor mediated contraction of rat, isolated aortic smooth muscle and rabbit, isolated urinary bladder smooth muscle.

10

Thoracic aorta were isolated from rats and immediately immersed in Krebs' solution (comprising in mM concentrations: NaCl, 118.5; NaHCO₃, 25; dextrose, 5; KCl, 4.8; CaCl₂, 2.5; MgSO₄, 1.2; KH₂PO₄, 1.2; cocaine, 0.03; corticosterone, 0.03; propranolol, 0.001; ascorbic acid, 0.1; and indomethacin, 0.01). The aortas were dissected free from extraneous tissue and then a cross sectional ring approximately 3 mm in length was cut from the most proximal segment. The aortic rings were suspended vertically in 10 ml tissue baths and bathed in
15
20
Kreb's solution maintained at 37°C and constantly aerated with a 95% O₂ and 5% CO₂ gas mixture. A resting tension of 1 g was applied to each aortic ring and thereafter periodically readjusted to maintain a 1 g resting tension throughout the duration of the assay.

25

Urinary bladders were emptied and isolated from rabbits. Bladders were dissected free from extraneous tissue and then a cross sectional ring of bladder neck tissue was cut above the urethra to approximately one third of the way up the bladder.
30
The bladder neck was cut parallel to the longitudinal muscle fibers to give flat section of muscle tissue and then the flat section was cut parallel to the longitudinal muscle to give several flat strips. Strips of bladder tissue were suspended vertically in 10 ml tissue baths and bathed in Kreb's solution
35
maintained at 33°C and constantly aerated with a 95% O₂ and 5% CO₂ gas mixture. A resting tension of 5 g was applied to each urinary bladder strip. The strips were allowed to relax to a resting tension of 1 g and thereafter periodically

readjusted to maintain the 1 g resting tension throughout the duration of the assay.

5 The aortic ring or urinary bladder strip preparations were allowed to equilibrate for 60 minutes during which period the bath solution was replaced every 15 minutes. The tissue was then exposed to bath solution containing norepinephrine (0.1 to 10 μ M) and once a steady state contraction was produced the tissue was exposed to bath solution free of
10 norepinephrine, replacing the solution twice every 5 minutes for 30 minutes. The aortic rings were exposed to norepinephrine and the urinary bladder strips to phenylephrine in a cumulative concentration fashion. That is, the isolated tissue was exposed to bath solution containing a threshold
15 concentration of either norepinephrine or phenylephrine until a steady state contractile response was attained and then the concentration of agonist was cumulatively increased by 0.5 log increments until a maximal or near maximal response was attained. Norepinephrine produced a concentration-dependent,
20 α_1 -adrenoceptor mediated contraction of the aortic rings. Phenylephrine produced a concentration-dependent, α_1 -adrenoceptor mediated contraction of the urinary bladder strips.

25 The tissue was then exposed to solution free of agonist, replacing the solution twice every 5 minutes for 30 minutes. After baseline tension was established and readjusted to 1 g, the tissue was exposed to bath solution containing the test compound, replacing the solution every 15 minutes for
30 60 minutes. In the presence of the test compound, the tissue again was exposed to either norepinephrine or phenylephrine in a cumulative concentration fashion, increasing the agonist concentration until a maximal or near maximal response was achieved.

35

The concentration ratio (CR) of agonist necessary to produce equiactive responses in the absence and presence of the test compound was determined.

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Relying on the concentration ratio, the assay concentration (molar) of the test compound, and the relationship:

5
$$pA_2 = - \log \frac{[\text{test compound}]}{CR - 1}$$

the negative log of the dissociation constant (pA_2) for each test compound at α_1 -adrenoceptors were estimated for both
10 aortic tissue and urinary bladder tissue.

Proceeding as in Example 38, compounds of Formula I were tested and found to selectively inhibit the α_1 -adrenoceptor mediated contractions of rabbit, isolated urinary bladder
15 smooth muscle. In contrast, prazosin, an α_1 -adrenoceptor antagonist that has been proscribed for treating BPH, selectively inhibited the α_1 -adrenoceptor mediated contractions of rat, isolated aortic smooth muscle.

20 EXAMPLE 39

α_1 -Adrenoceptor *In Vitro*, Functional Assay
in Tissue Isolated from Human

25 The following describes *in vitro* assays for measuring the relative effect of test compounds on α_1 -adrenoceptor mediated contractions of human, isolated arterial and urinary bladder smooth muscle.

30 Human arterial blood vessels were obtained post-mortem and immediately immersed in cold physiological saline solution. Within 24 hours of removal the isolated arterial tissue was placed in Krebs' solution (comprising in mM concentrations: NaCl, 118.5; NaHCO₃, 25; dextrose, 5; KCl,
35 4.8; CaCl₂, 2.5; MgSO₄, 1.2; KH₂PO₄, 1.2; cocaine, 0.03; corticosterone, 0.03; propranolol, 0.001; ascorbic acid, 0.1; and indomethacin, 0.01). The arteries were dissected free from extraneous tissue and then cut into cross sectional rings approximately 3 mm in length. The arterial rings were



suspended vertically in 10 ml tissue baths and bathed in
Kreb's solution maintained at 37°C and constantly aerated with
a 95% O₂ and 5% CO₂ gas mixture. A resting tension of
1 to 1.5 g was applied to each ring and thereafter
5 periodically readjusted to maintain a 1 g resting tension
throughout the duration of the assay.

Human prostatic and bladder neck smooth muscle tissue was
obtained following radical cystoprostatectomies or radical
10 prostatectomies and immediately immersed in Krebs' solution.
The prostatic and bladder tissue was dissected free from
extraneous tissue and then strips of tissue 0.8 to 1.2 cm in
length and 3 to 5 mm in width were cut and suspended
vertically in 10 ml tissue baths and bathed in Kreb's solution
15 maintained at 37°C and constantly aerated with a 95% O₂ and
5% CO₂ gas mixture. A resting tension of 0.75 to 1 g was
applied to each muscle strip and thereafter periodically
readjusted to maintain a 1 g resting tension throughout the
duration of the assay.

20

The arterial ring and prostatic and bladder neck strip
preparations were allowed to equilibrate for 60 minutes during
which period the bath solution was replaced every 15 minutes.
The tissue was then exposed to bath solution containing
25 norepinephrine (1 to 10 μM) and once a steady state
contraction was produced the tissue was exposed to bath
solution free of norepinephrine, replacing the solution twice
every 5 minutes for 30 minutes. The arterial ring and
prostatic and bladder neck strip preparations were exposed to
30 norepinephrine in a cumulative concentration fashion. That
is, the isolated tissue was exposed to bath solution
containing a threshold concentration of norepinephrine until a
steady state contractile response was attained and then the
concentration of norepinephrine was cumulatively increased by
35 0.5 log increments until a maximal or near maximal response
was attained. Norepinephrine produced a concentration-
dependent, α₁-adrenoceptor mediated contraction of the
arterial ring and of the prostatic and bladder neck strip

preparations.

The tissue was then exposed to solution free of norepinephrine, replacing the solution twice every 5 minutes for 30 minutes. After baseline tension was established and readjusted to 1 g, the tissue was exposed to bath solution containing the test compound, replacing the solution every 15 minutes for 60 minutes. In the presence of the test compound, the tissue again was exposed to norepinephrine in a cumulative concentration fashion, increasing the norepinephrine concentration until a maximal or near maximal response was achieved.

The concentration ratio (CR) of norepinephrine necessary to produce equiactive responses in the absence and presence of the test compound was determined. Relying on the concentration ratio, the assay concentration (molar) of the test compound, and the relationship:

$$pA_2 = - \log \frac{[\text{test compound}]}{CR - 1}$$

the negative log of the dissociation constant (pA_2) for each test compound at α_1 -adrenoceptors were estimated for the arterial ring and prostatic and bladder neck strip preparations.

Proceeding as in Example 39, compounds of Formula I were tested and found to selectively inhibit the α_1 -adrenoceptor mediated contractions of human, isolated prostatic and bladder neck smooth muscle. In contrast, prazosin non-selectively inhibited the α_1 -adrenoceptor mediated contractions of both human, isolated prostatic/bladder neck smooth muscle and isolated arterial smooth muscle.

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Example 40

Rat In Vivo, Blood Pressure Assay

5 The following describes an *in vivo* assay for measuring the effect of test compounds on blood pressure in normotensive and spontaneously hypertensive rats.

Normotensive or spontaneously hypertensive rats
10 (0.25 to 0.45 kg) were fasted for 18 hours and anesthetized with ether. The right femoral vein was isolated and cannulated with a fluid filled polyethylene cannulae for bolus administration of test substances. The right femoral artery
15 cannula connected to an external pressure transducer for monitoring mean arterial blood pressure (MAP).

The rats were placed in restrainers and allowed to recover from anesthesia. Following a 30 minute period for
20 stabilization, test compounds or vehicle were administered, i.v., and blood pressure was monitored continuously for at least 4 hours post-administration.

Proceeding as in Example 40, compounds of Formula I were
25 tested and found to be considerably less potent than prazosin at producing blood pressure lowering effects.

Example 41

30 Rat In Vivo, Tilt-Response Assay

The following describes an *in vivo* assay in normotensive rats for measuring the propensity of test compounds to inhibit the reflex maintenance of basal blood pressure levels in
35 response to vertical tilt.

Normotensive rats (0.25 to 0.45 kg) were fasted for 18 hours and anesthetized with ether. The right femoral vein



was isolated and cannulated with a fluid filled polyethylene cannulae for bolus administration of test substances. The right femoral artery was isolated and cannulated with a fluid filled polyethylene cannula connected to an external pressure transducer for monitoring mean arterial blood pressure (MAP).

The rats were restrained in a supine position and allowed to recover from anesthesia. Following a 30 minute period for stabilization, test compounds or vehicle were administered, i.v., and blood pressure was monitored continuously while the rats were tilted vertically at 30 to 60 degrees from supine at 15, 30 and 45 minutes post-administration.

Proceeding as in Example 41, compounds of Formula I were tested and found to be considerably less potent than prazosin at inhibiting the reflex maintenance of basal blood pressure levels in response to vertical tilt.

Example 42

20

Dog In Vivo, Blood and Intraurethral Pressure Assay

The following describes an *in vivo* assay for measuring the relative effect of test compounds on hypogastric nerve stimulation-induced increases in intraurethral pressure and phenylephrine-induced increases in diastolic blood pressure in anesthetized dog.

Mongrel dogs (10 to 20 kg) were fasted for 12 to 18 hours and anesthetized with pentobarbital sodium (35 mg/kg, i.v.). An endotracheal tube was inserted and thereafter the lungs were mechanically ventilated with room air. The right femoral vein was isolated and cannulated with two polyethylene cannulae, one for the administration of a continuous infusion of pentobarbital sodium (5 to 10 mg/kg/hr) and the other for bolus administration of test substances. The right femoral artery was isolated and cannulated to the abdominal aorta with a fluid filled polyethylene cannula connected to an external

pressure transducer for monitoring diastolic aortic pressure (DAP). The bladder was exposed via a ventral midline abdominal incision and emptied of urine through a 22 gauge needle. The bladder was cannulated through a stab incision
5 with a water filled balloon catheter connected to an external pressure transducer for monitoring prostatic intraurethral pressure (IUP). The right hypogastric nerve (HGN) was carefully isolated and attached to a Dastre's electrode for nerve stimulation.

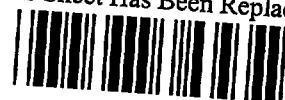
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The preparation was allowed to stabilize for a least 30 minutes and must have had a stable basal IUP for not less than 15 minutes prior to commencement of the assay protocol. The HGN was stimulated (20-50 V, 10 Hz, 10 msec pulse train for
15 10 sec) to induce a measurable increase in IUP and then phenylephrine (PE) was administered by bolus injection (0.5 to 0.6 µg/kg, i.v.) to induce a measurable increase in IUP. The HGN stimulation and PE bolus injection were repeated every 5 minutes until three consecutive reproducible increases in
20 IUP and DAP were achieved. Vehicle (0.1 to 0.3 ml/kg) was administered and 20 minutes later the HGN stimulation and PE bolus injection were repeated. Test compound was then administered and 20 minutes later the HGN stimulation and PE bolus injection were repeated. Test compound was
25 administered approximately every 20 minutes, increasing the dose until maximal or near maximal inhibition of the increases in IUP and DAP was attained.

Proceeding as in Example 42, compounds of Formula I were
30 tested and found to selectively inhibit the HGN stimulation-induced increases in IUP. In contrast, prazosin inhibited increases in IUP and DAP in a similar fashion.

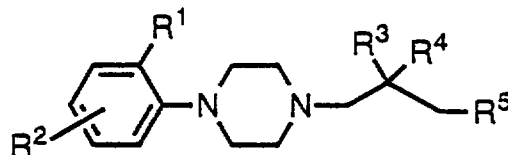
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Claims

1. A compound of Formula I:

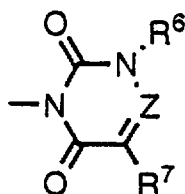


I

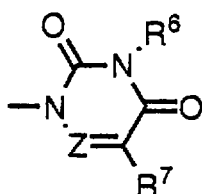
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in which:

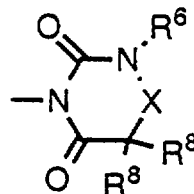
- R^1 is acetylamino, amino, cyano, trifluoroacetylamino, halo, hydro, hydroxy, nitro, methylsulfonylamino, 2-propynyloxy, a group selected from (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl, (C₁₋₆)alkyloxy, (C₃₋₆)cycloalkyloxy, (C₃₋₆)cycloalkyl(C₁₋₄)alkyloxy and (C₁₋₄)alkylthio (which group is optionally further substituted with one to three halo atoms) or a group selected from aryl, aryl(C₁₋₄)alkyl, heteroaryl, heteroaryl(C₁₋₄)alkyl, aryloxy, aryl(C₁₋₄)alkyloxy, heteroaryloxy and heteroaryl(C₁₋₄)alkyloxy (which aryl and heteroaryl are optionally further substituted with one to two radicals independently selected from halo and cyano);
- R^2 is cyano, halo, hydro, hydroxy or a group selected from (C₁₋₆)alkyl and (C₁₋₆)alkyloxy (which group is optionally further substituted with one to three halogen atoms);
- R^3 and R^4 are both hydro or methyl or together are ethylene; and
- R^5 is a group selected from Formulae (a), (b), (c) and (d):



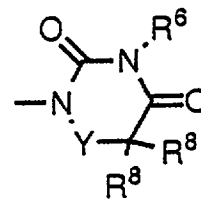
(a)



(b)



(c)



(d)

in which:





X is C(O), CH₂ or CH(OH);
Y is CH₂ or CH(OH);
Z is N or C(R⁹), wherein R⁹ is hydro, (C₁₋₆)alkyl or hydroxy;
R⁶ is hydro, a group selected from (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl (which group is optionally further substituted with one to three halo atoms) or a group selected from aryl, heteroaryl, aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are optionally further substituted with one to three radicals selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and aryl);
R⁷ is (C₁₋₆)alkanoyl, carbamoyl, cyano, di(C₁₋₆)alkylamino, halo, hydro, hydroxy, hydroxyiminomethyl, (C₁₋₆)alkylsulfonyl, (C₁₋₆)alkylthio, a group selected from (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₁₋₆)alkyloxy and (C₁₋₆)alkyloxy(C₁₋₄)alkyl (which group is optionally further substituted with one to three radicals selected from halo, hydroxy or (C₁₋₆)alkyloxy) or a group selected from aryl, heteroaryl, aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are optionally further substituted with one to three radicals selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and aryl) or R⁷ and R⁹ together are tetramethylene; and each R⁸ is independently hydro, hydroxy, methyl or ethyl; and the pharmaceutically acceptable salts and N-oxides thereof.

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2. The compound of Claim 1 in which R¹ is (C₁₋₆)alkyloxy (optionally further substituted with one to three fluorine atoms) or heteroaryl; R² is hydro, halo, hydroxy or (C₁₋₆)alkyl; and R⁵ is a group selected from formulae (a), (b) and (c), in which R⁶ is hydro, (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl, heteroaryl(C₁₋₄)alkyl or a group selected from benzyl and phenyl (which group is optionally further substituted with one to three radicals selected from halo, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and aryl) and R⁷ is carbamoyl, cyano, halo, hydro, hydroxyiminomethyl, hydroxymethyl or (C₁₋₆)alkyl (which alkyl is optionally substituted with one to three fluorine atoms) or together with R⁹ is tetramethylene.





3. The compound of Claim 2 in which R^1 is methoxy, ethoxy, 2,2,2-trifluoroethoxy, oxazolyl or pyrrolyl; R^2 is hydro, chloro, fluoro, hydroxy or methyl; R^6 is hydro, methyl, cyclohexylmethyl, pyridylmethyl, pyrazinylmethyl, furylmethyl, thienylmethyl, biphenylmethyl or a group selected from benzyl and phenyl (which group is optionally further substituted with one to three radicals selected from chloro, fluoro, methyl or methoxy) and R^7 is carbamoyl, cyano, halo, hydro, hydroxy-
10 iminomethyl, hydroxymethyl, methyl, ethyl, propyl, trifluoromethyl or together with R^9 is tetramethylene; X is CH_2 and each of the R^8 radicals are hydro or X is $CH(OH)$ and one of the R^8 radicals is hydroxy.

15 4. The compound of Claim 3 in which R^1 is 2,2,2-trifluoroethoxy; R^3 and R^4 are each hydro; and R^5 is a group of Formula (a) in which R^7 is hydro, hydroxymethyl or methyl and Z is $C(R^9)$, wherein R^9 is hydro or methyl, or a group of Formula (c) in which X is $CH(OH)$, one of the R^8
20 radicals is hydroxy and the other is methyl.

5. The compound of Claim 4 in which R^1 is 2,2,2-trifluoroethoxy, Z is CH, R^2 is hydro, R^6 is hydro and R^7 is methyl, namely 3-(3-(4-(2-(2,2,2-trifluoroethoxy)-
25 phenyl]piperazin-1-yl)propyl)-5-methyl-2,4(1H,3H)-pyrimidine-
dione and the pharmaceutically acceptable salts thereof.

6. The compound of Claim 5 which is 3-(3-(4-(2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-5-methyl-
30 2,4(1H,3H)-pyrimidinedione hydrochloride.

7. The compound of Claim 4 in which R^1 is 2,2,2-trifluoroethoxy, Z is CH, R^2 is fluoro at the 4-position, R^6 is hydro and R^7 is methyl, namely
35 3-(3-(4-(4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione and the pharmaceutically acceptable salts thereof.





8. The compound of Claim 7 which is 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione fumarate.

5 9. The compound of Claim 4 in which R¹ is 2,2,2-trifluoroethoxy, Z is CH, R² is fluoro at the 4-position, R⁶ is hydro and R⁷ is ethyl, namely 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione and the
10 pharmaceutically acceptable salts thereof.

10. The compound of Claim 9 which is 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione hydrochloride.

15 11. The compound of Claim 4 in which R¹ is oxazol-2-yl, Z is CH, R² is fluoro at the 4-position, R⁶ is hydro and R⁷ is methyl, namely 3-(3-(4-(4-fluoro-2-oxazol-2-ylphenyl)-piperazin-1-yl)propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione and
20 the pharmaceutically acceptable salts thereof.

12. The compound of Claim 11 which is 3-(3-(4-(4-fluoro-2-oxazol-2-ylphenyl)piperazin-1-yl)propyl)-5-methyl-2,4(1H,3H)-pyrimidinedione oxalate.

25 13. The compound of Claim 4 in which R¹ is 2,2,2-trifluoroethoxy, Z is CH, R² is fluoro at the 4-position, R⁶ is hydro and R⁷ is hydroxymethyl, namely 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-5-hydroxymethyl-2,4(1H,3H)-pyrimidinedione and the
30 pharmaceutically acceptable salts thereof.

14. The compound of Claim 13 which is 3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl)propyl)-5-hydroxymethyl-2,4(1H,3H)-pyrimidinedione fumarate.

15. The compound of Claim 4 in which R¹ is 2,2,2-trifluoroethoxy; R² is fluoro at the 4-position; R³ and R⁴ are





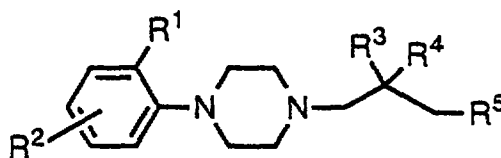
each hydro; R^5 is a group of formula (c) in which X is CH(OH), one of the R^8 radicals is hydroxy and the other is methyl, namely cis-3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-5,6-dihydroxy-5-methyl-5,6-dihydro-
 5 2,4(1H,3H)-pyrimidinedione and the pharmaceutically acceptable salts thereof.

16. The compound of Claim 15 which is (+)-enantiomer of cis-3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-
 10 piperazin-1-yl}propyl)-5,6-dihydroxy-5-methyl-5,6-dihydro-2,4(1H,3H)-pyrimidinedione fumarate.

17. The compound of Claim 15 which is (-)-enantiomer of cis-3-(3-(4-[4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-
 15 piperazin-1-yl}propyl)-5,6-dihydroxy-5-methyl-5,6-dihydro-2,4(1H,3H)-pyrimidinedione fumarate.

18. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of
 20 claims 1 to 17 in combination with a pharmaceutically acceptable excipient.

19. A process for preparing a compound of Formula I:



I

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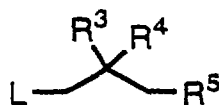
in which R^1 , R^2 , R^3 , R^4 , R^5 are as defined in claim 1 and the pharmaceutically acceptable salts and N-oxides thereof, which process comprises:

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(a) alkylating a compound of Formula 3:

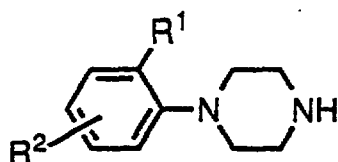


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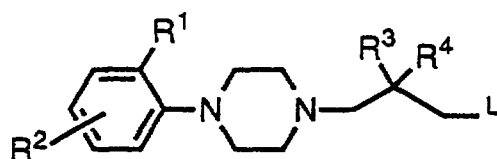
or a protected derivative thereof, in which L is a leaving group and each R³, R⁴ and R⁵ are as defined in claim 1 with respect to Formula I, with a compound of Formula 2:



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or a protected derivative thereof, in which each R¹ and R² are as defined in claim 1 with respect to Formula I, and then deprotecting when necessary; or

(b) alkylating a compound of the formula H-R⁵, in which R⁵ is as defined in claim 1, with a compound of Formula 5:



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in which L is a leaving group and each R¹, R², R³ and R⁴ are as defined in claim 1 with respect to Formula I; and

(c) optionally further de-benzylating a compound of Formula I in which R⁶ is benzyl to give a compound of Formula I in which R⁶ is hydro;

(d) optionally further alkylating a compound of Formula I in which R⁶ is hydro to give a compound of Formula I in which R⁶ is (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkyl





or a group selected from aryl, heteroaryl, aryl(C₁₋₄)alkyl and heteroaryl(C₁₋₄)alkyl (which aryl and heteroaryl are optionally further substituted with one to three radicals selected from halo, cyano, (C₁₋₆)alkyloxy, (C₁₋₆)alkyl and
5 aryl);

(e) optionally further oxidizing a compound of Formula I to give an *N*-oxide derivative;

10 (f) optionally further reducing an *N*-oxide derivative of a compound of Formula I to unoxidized form;

(g) optionally further converting a compound of Formula I into a pharmaceutically acceptable salt; and
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(h) optionally further converting a salt form of a compound of Formula I to non-salt form.

20. Compounds according to any one of claims 1-17
20 whenever prepared according to the process claimed in claim 19 or by an obvious chemical equivalent thereof.

21. Compounds according to any one of claims 1-17 as pharmaceutically active substances, particularly for the
25 treatment of a disease involving directly or indirectly an obstruction of the lower urinary tract caused by benign prostatic hyperplasia.

22. The novel compounds, pharmaceutical compositions,
30 processes and methods substantially as described herein.

23. The use of compounds in accordance with any one of claims 1-17 in the manufacture of medicaments, particularly for the treatment of a disease involving directly or
35 indirectly an obstruction of the lower urinary tract caused by benign prostatic hyperplasia.



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