

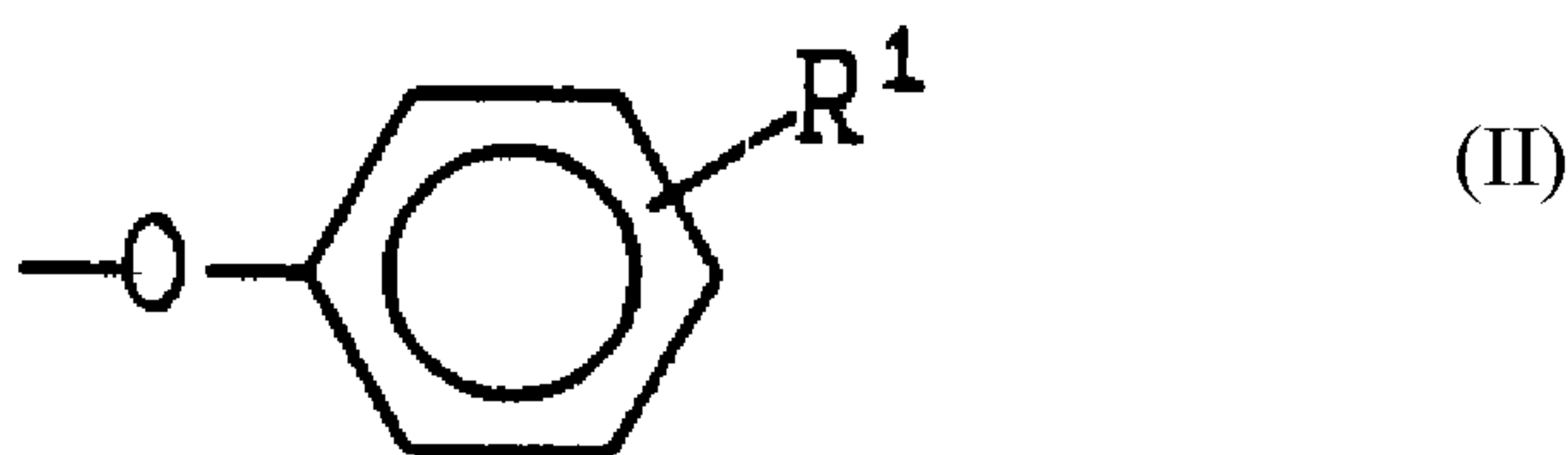
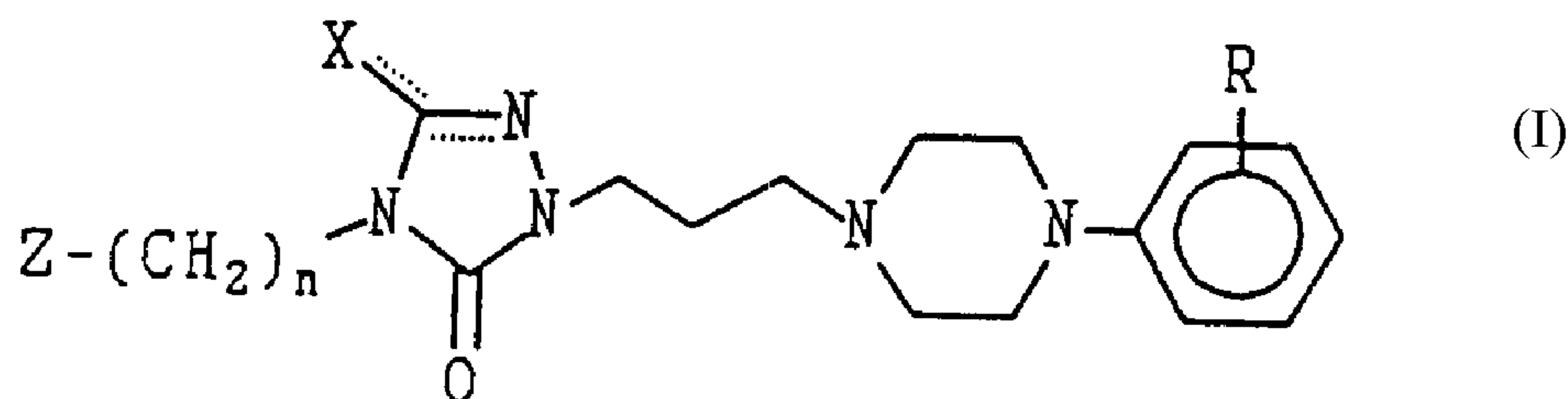


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(54) **DERIVES ANTIDEPRESSEURS 3-**

**HALOPHENYLPIPERAZINYLPROPYLE DE TRIAZOLONES
ET DE TRIAZOLDIONES SUBSTITUEES**

(54) **ANTIDEPRESSANT-3-HALOPHENYLPIPERAZINYL-PROPYL
DERIVATIVES OF SUBSTITUTED TRIAZOLONES AND
TRIAZOLDIONES**

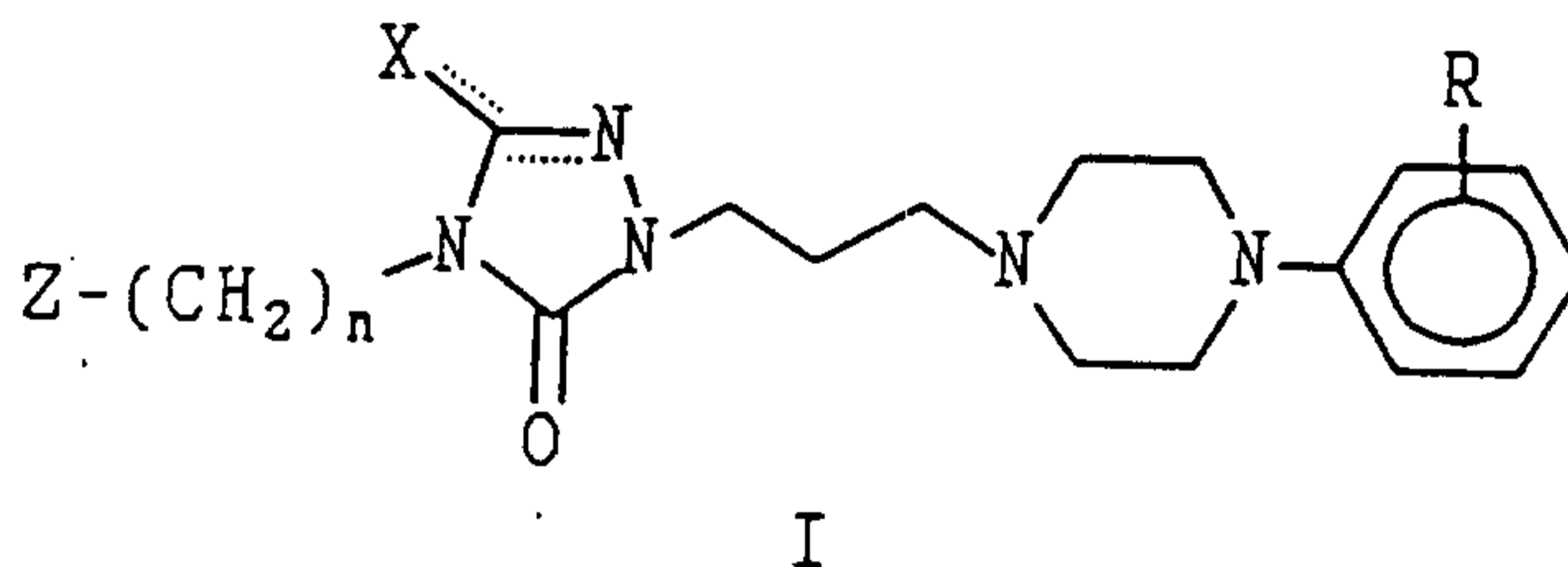


(57) 2-(3-[4-(3-Halophenyl)-1-piperazinyl]propyl derivatives of certain 4-alkyl-or 4-phenoxyalkyl-2,4-dihydro-3H-1,2,4-triazol-3-ones and triazol-3,5-diones are psychotropic agents having promise as antidepressants by virtue of their receptor site binding affinity profiles and animal pharmacology. Compounds of Formula I and their acid addition salts and/or hydrates are disclosed: (see formula I). In the foregoing structural formula the symbol R denotes halogen, preferably chloro, or trifluoromethyl; Z is hydrogen or (see formula II) with R¹ being hydrogen, halogen, C₁₋₄ alkoxy and trifluoromethyl; and n is an integer from 2-4. The symbol X is either an oxygen atom, providing a carbonyl moiety; or is an acetyl group. The single and dotted lines represent either a covalent single bond or a double bond. The compounds of Formula I exist then in two structural subclasses, Ia and Ib.

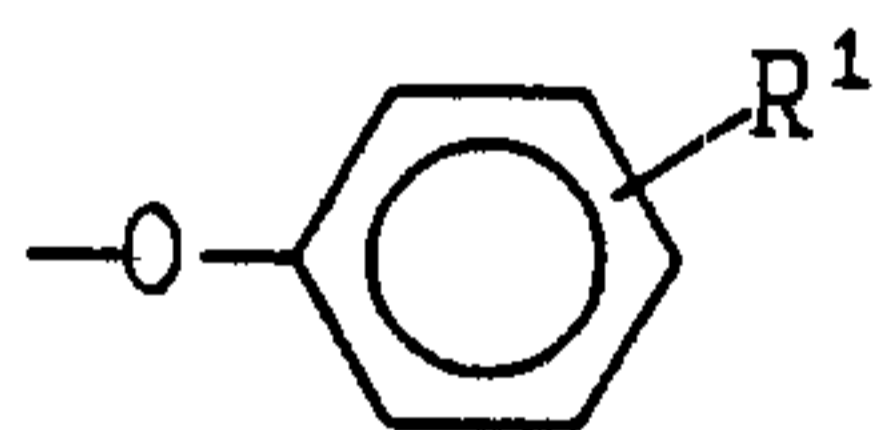


Abstract

2-(3-[4-(3-Halophenyl)-1-piperazinyl]propyl derivatives of certain 4-alkyl-or 4-phenoxyalkyl-2,4-dihydro-3H-1,2,4-triazol-3-ones and triazol-3,5-diones are psychotropic agents having promise as antidepressants by virtue of their receptor site binding affinity profiles and animal pharmacology. Compounds of Formula I and their acid addition salts and/or hydrates are disclosed:



15 In the foregoing structural formula the symbol R denotes halogen, preferably chloro, or trifluoromethyl; Z is hydrogen or



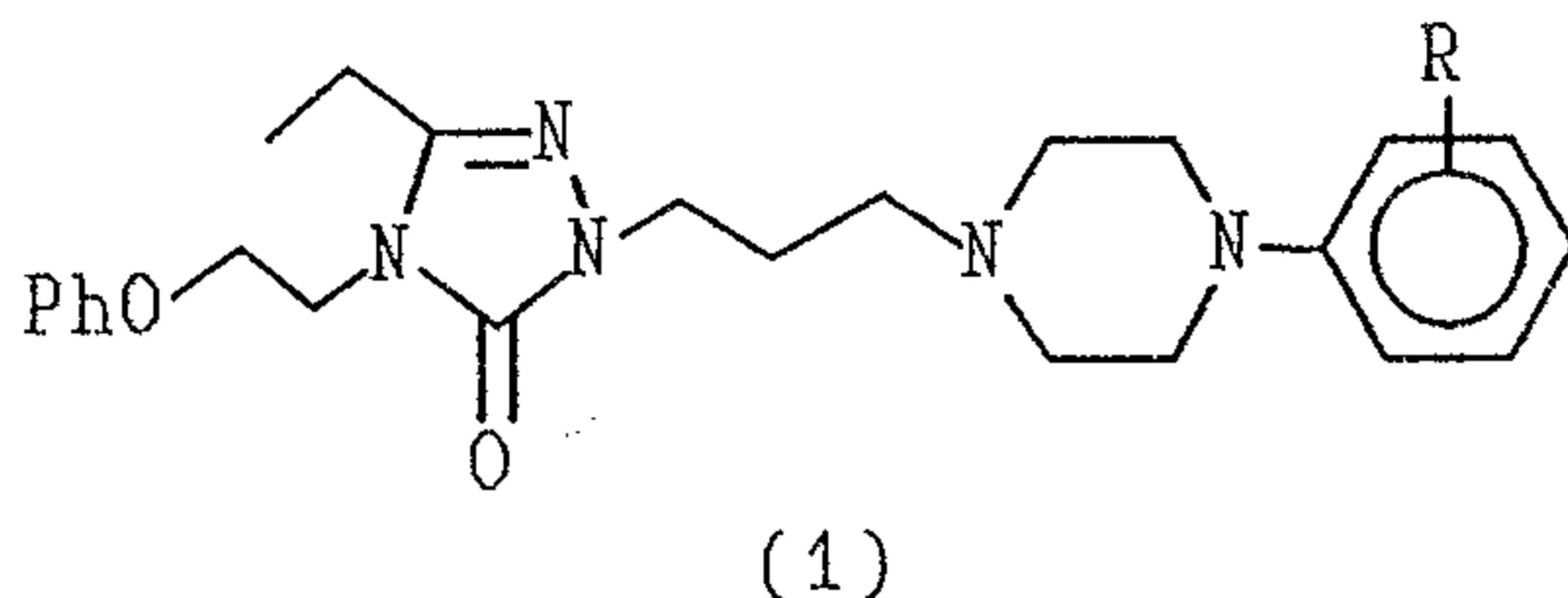
with R¹ being hydrogen, halogen, C₁₋₄ alkoxy and trifluoromethyl; and n is an integer from 2-4. The symbol X is either an oxygen atom, providing a carbonyl moiety; or is an acetyl group. The single and dotted lines represent either a covalent single bond or a double bond. The compounds of Formula I exist then in two structural subclasses, Ia and Ib.

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Background of The Invention

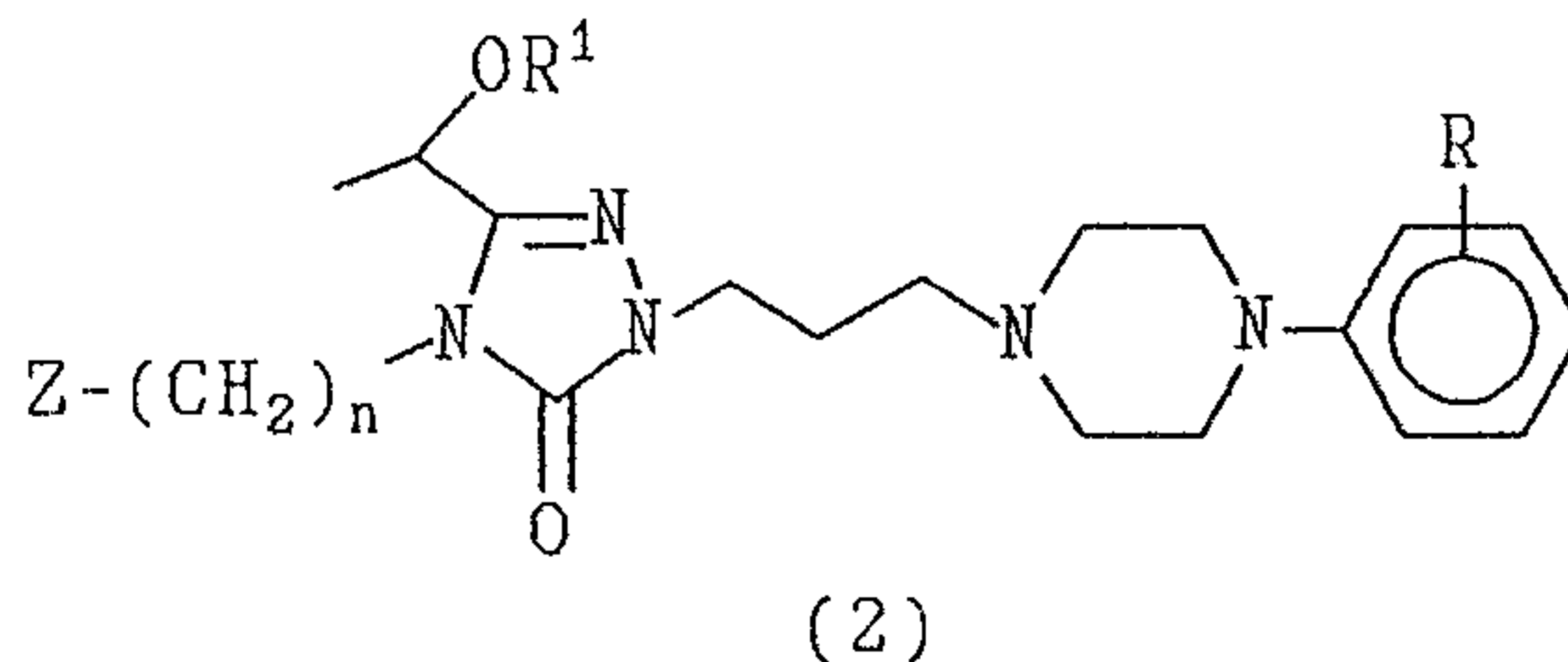
The present invention relates to 1,2,4-triazole heterocyclic carbon compounds, their preparation, metabolic transformations and use. More particularly, the invention relates to keto and triazoldione analogs of the antidepressant agent nefazodone.

Nefazodone is a member of a series of compounds having structure (1) as disclosed by Temple, Jr., et al. in U.S. 4,338,317.



15 Nefazodone (R is meta-chloro) has been extensively studied clinically as an antidepressant agent.

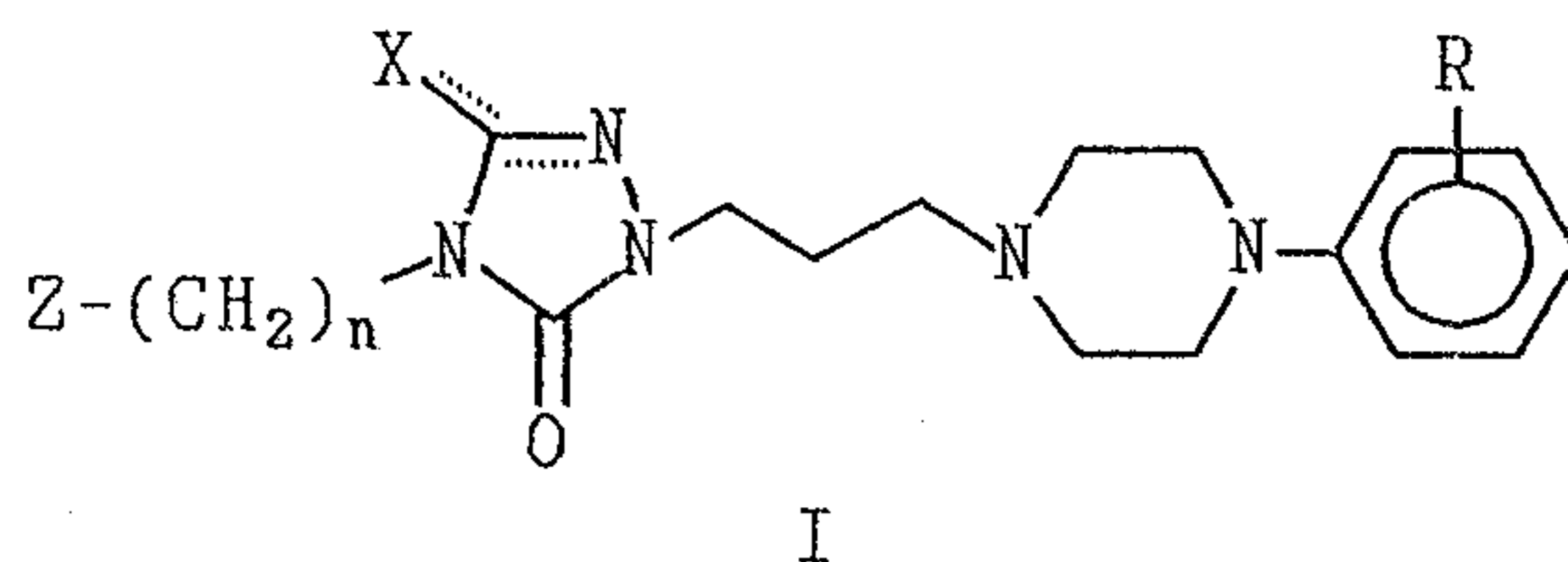
A major metabolic pathway for nefazodone and related analogs involves α -carbon hydroxylation of the ethyl group attached to the 5-position of the triazolone ring. These antidepressant compounds as well as certain ether and ester derivatives were disclosed and claimed in U.S. 4,613,600 as structure (2). In these compounds, Z is



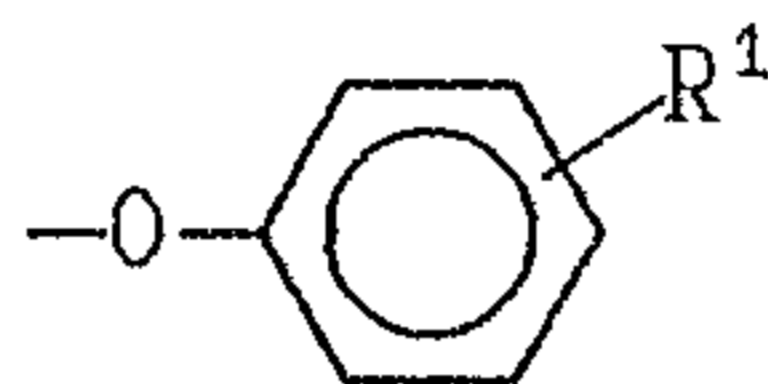
hydrogen or phenoxy and R¹ is, inter alia, an alkyl or acyl moiety.

Summary and Detailed Description of the Invention

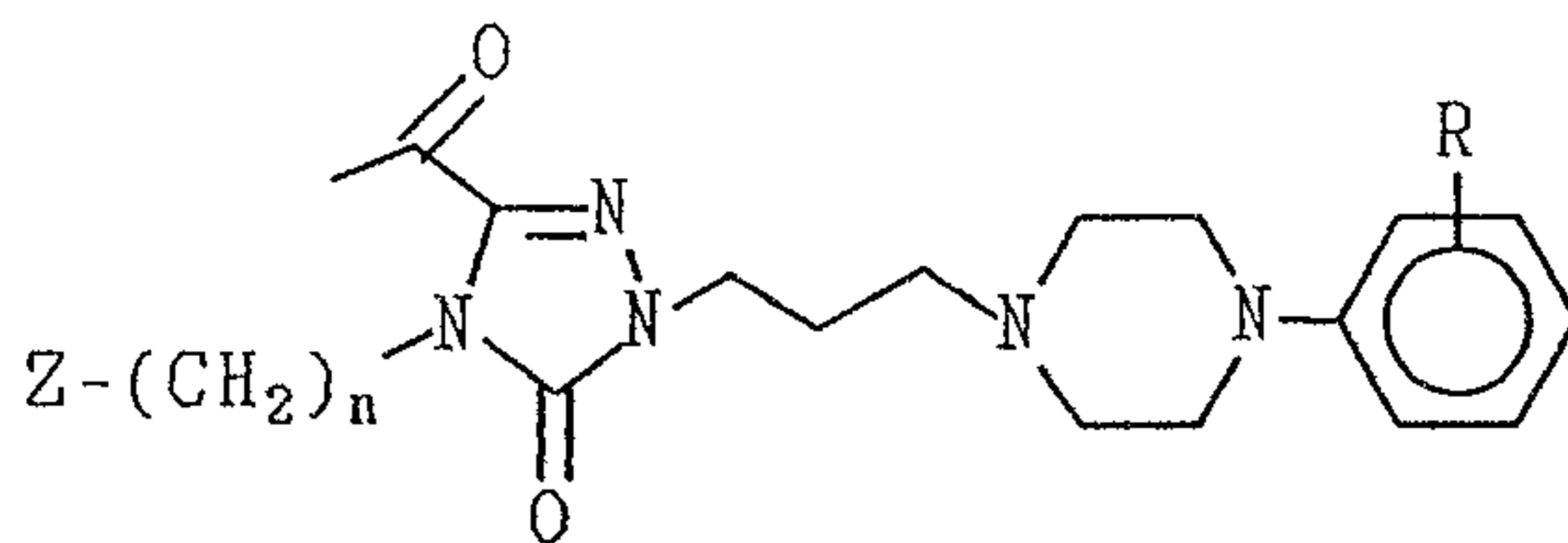
The present invention concerns compounds of Formula I and their acid addition salts and/or hydrates.



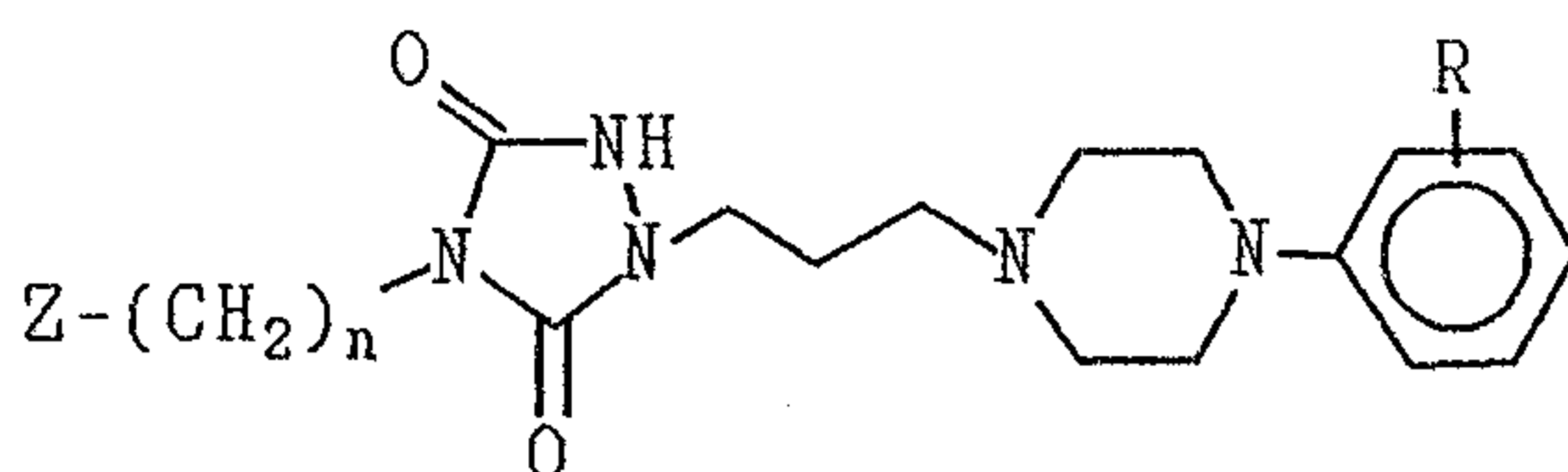
10 In the foregoing structural formula the symbol R denotes halogen, preferably chloro, and trifluoromethyl; Z is hydrogen and



with R¹ being hydrogen, halogen, C₁₋₄ alkoxy and trifluoromethyl; and n is an integer from 2-4. The symbol X is either an oxygen atom, providing a carbonyl moiety; or is an acetyl group. The single and dotted lines represent either a covalent single bond or a double bond. The compounds of Formula I exist then in two structural subclasses, Ia and Ib.



Ia

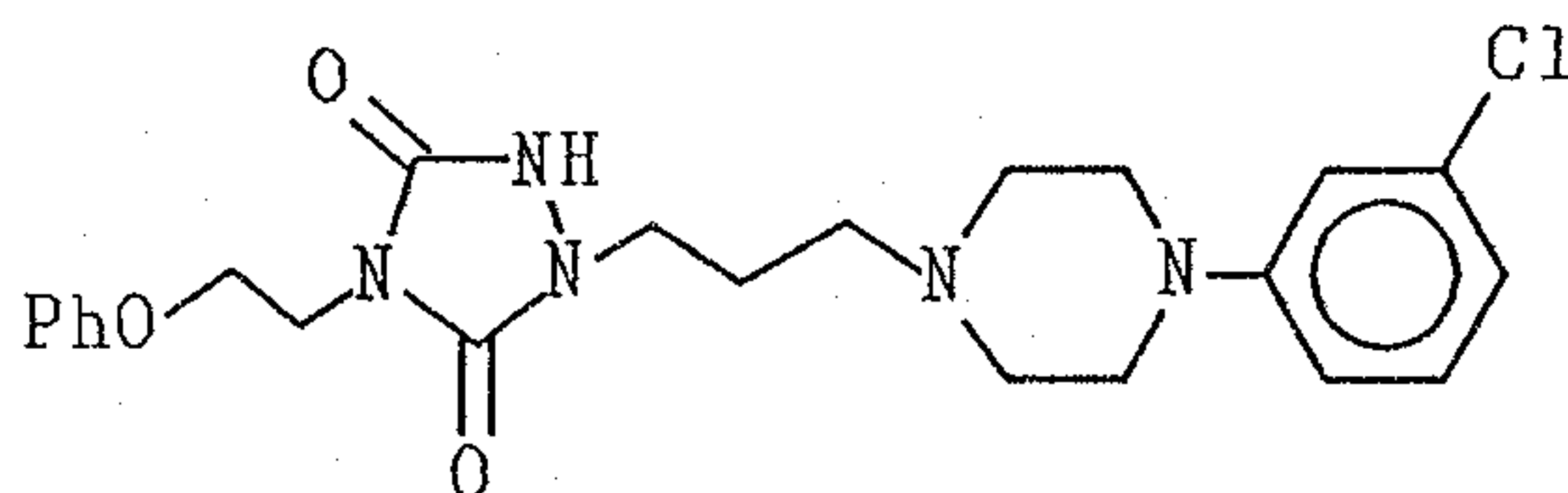


Ib

Compounds of formula I arose from investigations of the metabolism of the antidepressant drug nefazodone.

15 Blood levels of a new and uncharacterized major metabolite of nefazodone were observed following nefazodone administration to humans and animals (rat and dog). No indication of this circulating

20 metabolite had been seen in urine or bile samples. Subsequently, this new major metabolite was isolated and identified as having the following structure:



Nefazodone triazoldione metabolite.

XIb

30 In its broadest aspect, the instant invention is concerned with structural variation at the 5-position of the 3H-1,2,4-triazol-3-one ring of nefazodone and its related analogs. The compounds of the present invention are characterized by replacement of the 5-ethyl-group by an acetyl group (Ia) or by

transformation of the 5-position to a carbonyl moiety (Ib). The invention also concerns the discovery that compounds of the present invention are psychotropic agents displaying selective central nervous system effects which are associated with useful antidepressant activity. The more preferred compounds of the present series have the structures of Formula XIb, and in the most preferred compounds of Formula XIb, Z is a phenoxy moiety.

For medicinal use, the pharmaceutically acceptable acid addition salts, those salts in which the anion does not contribute significantly to toxicity or pharmacological activity of the organic cation, are preferred. The acid addition salts are obtained either by reaction of an organic base of structure I with an inorganic or organic acid, preferably by contact in solution, or by any of the standard methods detailed in the literature and available to any practitioner skilled in the art. Examples of useful organic acids are carboxylic acids such as maleic acid, acetic acid, tartaric acid, propionic acid, fumaric acid, isethionic acid, succinic acid, pantoic acid, cyclamic acid, tannic acid, and the like; useful inorganic acids are hydrohalic acids such as HCl, HBr, HI; sulfuric acid, phosphoric acid; and the like.

The Formula I compounds are useful pharmacologic agents with psychotropic properties. In this regard they exhibit selective central nervous system effects which are associated with antidepressant activity. The effects are demonstrated by means of conventional in vitro binding characteristics in certain CNS receptor site test systems and in a selected in vivo model which has been shown to be correlative of the

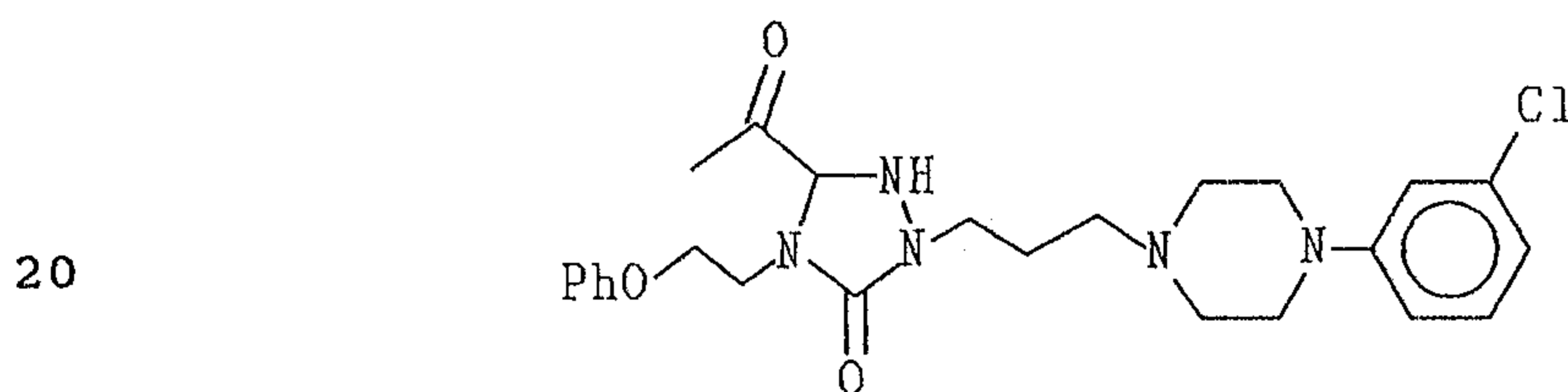
antidepressant activity associated with the structurally-related agents, nefazodone and its 5-hydroxyethyl metabolite.

Specifically, nefazodone triazoldione (XIb, "nef-triazoldione") was comparatively tested with nefazodone and the 5-hydroxyethyl metabolite ("OH-nefazodone"). Both of these agents possess useful antidepressant properties (Cf: US 4,338,317 and US 4,613,600). According to in vitro binding testing, nef-triazoldione displays affinity for serotonin receptors as does nefazodone and OH-nefazodone. Similarly, nef-triazoldione was relatively inactive with respect to dopamine receptor binding, cholinergic receptor binding, and alpha-receptor binding, in general these binding activities fall between those for nefazodone and OH-nefazodone. The binding of nef-triazoldione at serotonin type 2 receptors was not as robust as for both nefazodone and OH-nefazodone; however nef-triazoldione displayed lower affinity at alpha-receptor binding sites than the two reference compounds. The latter observation is significant in that agents with low affinity for alpha-receptors relative to serotonin type 2 receptors are less likely to elicit certain undesirable side effects, such as sedation and lowering of blood pressure. Thus nef-triazoldione, a representative of the instant XIb compounds, displayed a binding profile similar to related antidepressant agents.

The efficacy of nef-triazoldione at serotonin type 2 receptor sites in vivo was determined by examining its acute effect in a rat model based on the 5-HT₂-mediated DOI (chemically, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane)-induced headshake response. Cf: Bedard and Pycock, Neuropharmacology

16: 663-670 (1977). A modest inhibition of the DOI-
induced headshake response was produced and in this
regard the XIb compound appeared to be less potent
than either nefazodone or OH-nefazodone in this in
5 vivo test. These results were comparable to the in
vitro binding potencies of the test compounds at
serotonin type 2 receptors. Thus the in vivo results
which correlate with selective in vitro binding are
indicative of useful antidepressant effects following
10 systemic administration of these compounds.

In regard to compounds of Formula Ia (5-acetyl-
triazolones), experimental data indicate that they are
metabolic precursors of Formula Ib triazoldione
compounds. Using an in vitro human liver microsomal
15 preparation with "keto-nefazodone" (Formula XIa) as
substrate in a metabolite conversion experiment,



keto-nefazodone
XIa

25 nefazodone triazoldione (XIb) was produced and
isolated.

Examination of HPLC chromatographs of plasma from
dogs given nefazodone shows small amounts of a
compound with the same HPLC retention times as keto-
nefazodone. The similarity of HPLC retention times
30 for both keto-nefazodone and the parent drug
nefazodone in many HPLC systems, as well as the small
amount of the compound complicate the detection of
this putative metabolite. As demonstrated with the in

vitro liver enzyme experiments, Ia compounds may be expected to act as metabolic precursors for Ib compounds following systemic administration and portal circulation. As compound Ib precursors, Ia compounds inherently possess useful antidepressant activity.

Another aspect then of the instant invention provides a method for treating a mammal afflicted with depression which comprises administering systemically to said mammal a therapeutically effective antidepressant amount of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof. The use and administration of the compounds of the instant invention is considered to be done in the same fashion as for the reference drugs nefazodone or trazodone. An effective antidepressant dose ranges from 1 to 40 mg/kg of body weight with a dosage dependent on effects sought, manner of administration, and to some extent with the particular Formula I compound selected. A preferred dosage range is 5 to 10 mg/kg body weight. Systemic administration refers to oral, sublingual, buccal, transdermal, transnasal, rectal, and parenteral (i.e. intramuscular, intravenous and subcutaneous). Generally it will be found that when a compound of the present invention is administered orally, a larger quantity of the active agent is required to produce the same effect as a smaller quantity given parenterally. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level that will produce effective antidepressant effects without causing any harmful or untoward side effects.

The compounds of the present invention may be administered for antidepressant purposes either as

individual therapeutic agents or as mixtures with other therapeutic agents. Therapeutically, the instant compounds are generally given as pharmaceutical compositions comprised of an
5 antidepressant amount of a compound of Formula I or a pharmaceutically acceptable salt and/or hydrate thereof and a pharmaceutically acceptable carrier. Pharmaceutical compositions which provide from about 1 to 750 mg of the active ingredient per unit dose are
10 preferred and are conventionally prepared as tablets, lozenges, capsules, powders, aqueous or oily suspensions, syrups, elixirs, and aqueous solutions.

The nature of the pharmaceutical composition employed will, of course, depend on the desired route
15 of administration. For example, oral compositions may be in the form of tablets or capsules and may contain conventional excipients such as binding agents (e.g. syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone), fillers (e.g. lactose, sugar,
20 maize-starch, calcium phosphate, sorbitol or glycine), lubricants (e.g. magnesium stearate, talc, polyethylene glycol or silica) disintegrants (e.g. starch) and wetting agents (e.g. sodium lauryl sulfate). Solutions or suspensions of a Formula I
25 compound with conventional pharmaceutical vehicles are employed for parenteral compositions such as an aqueous solution for intravenous injection or an oily suspension for intramuscular injection.

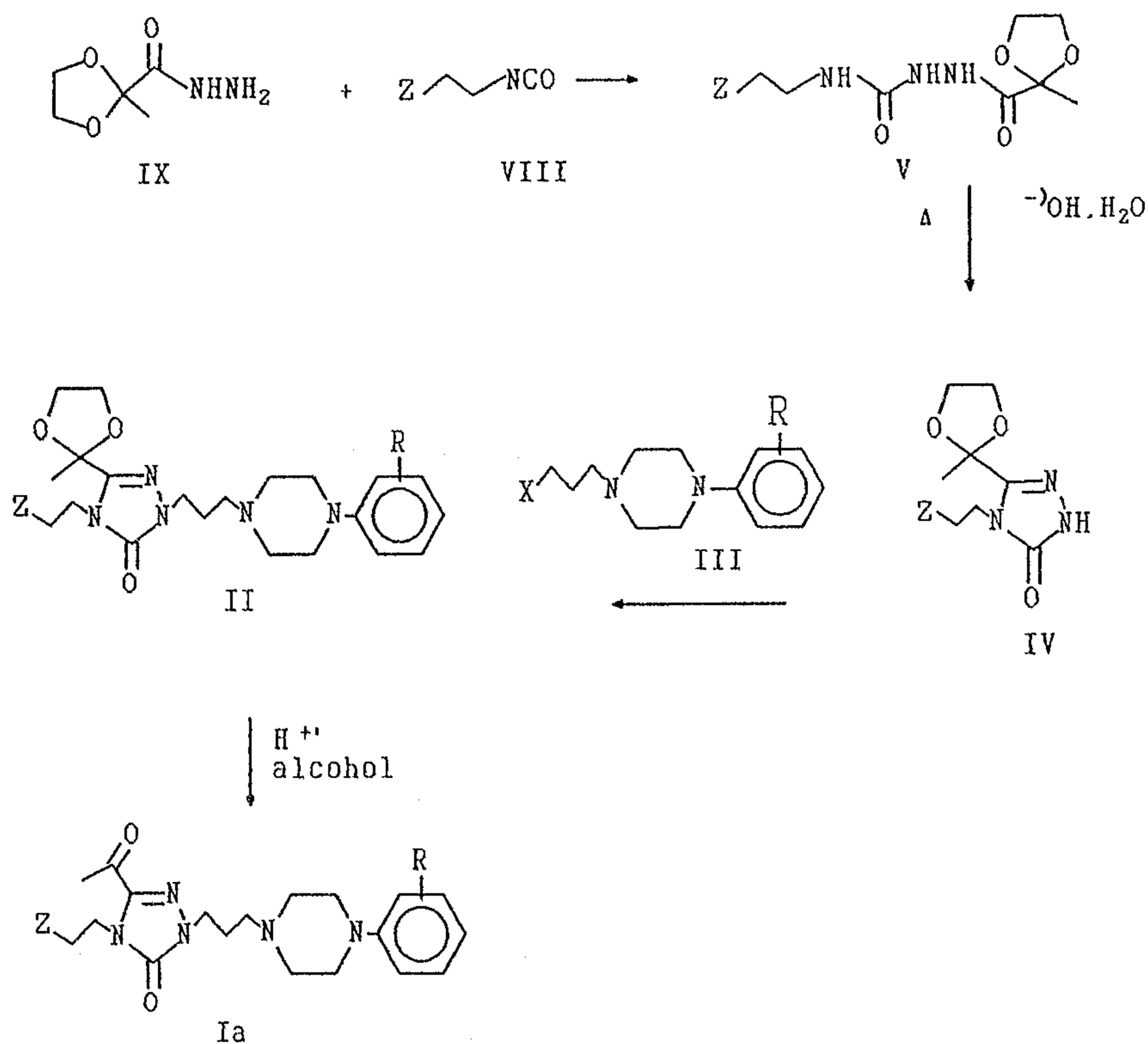
Such compositions having the desired clarity,
30 stability and adaptability for parenteral use are obtained by dissolving from about 0.1% to 10% by weight of a Formula I compound or one of its salt forms in water or a vehicle consisting of a polyhydric aliphatic alcohol such as glycerine, propylene glycol,

and the polyethylene glycols or mixtures thereof. The polyethylene glycols consist of a mixture of non-volatile, usually liquid, polyethylene glycols which are soluble in both water and organic liquids and
5 which have molecular weights from about 200 to 1500.

When transnasal application is intended, the Formula I compound pharmaceutical composition is formulated in a pharmaceutical composition which enhances penetration of the nasal mucosa. Such
10 formulations normally employ fatty acid salts of the Formula I base compound and their preparation and use would be known to one skilled in the pharmaceutical arts.

The general procedures for preparation of Formula
15 I compounds are outlined in Schemes 1 and 2.

Scheme 1
Preparation of Formula Ia Compounds



In Scheme 1, the ethylene ketal of pyruvic acid
 5 hydrazide (IX), prepared by treating an alcoholic
 solution of the ethylene ketal of ethyl pyruvate with
 hydrazine hydrate; is reacted with an appropriate
 isocyanate (VIII) in toluene solution to provide the
 semicarbazide intermediate compound (V). The
 10 semicarbazide is ring-closed in aqueous hydroxide to

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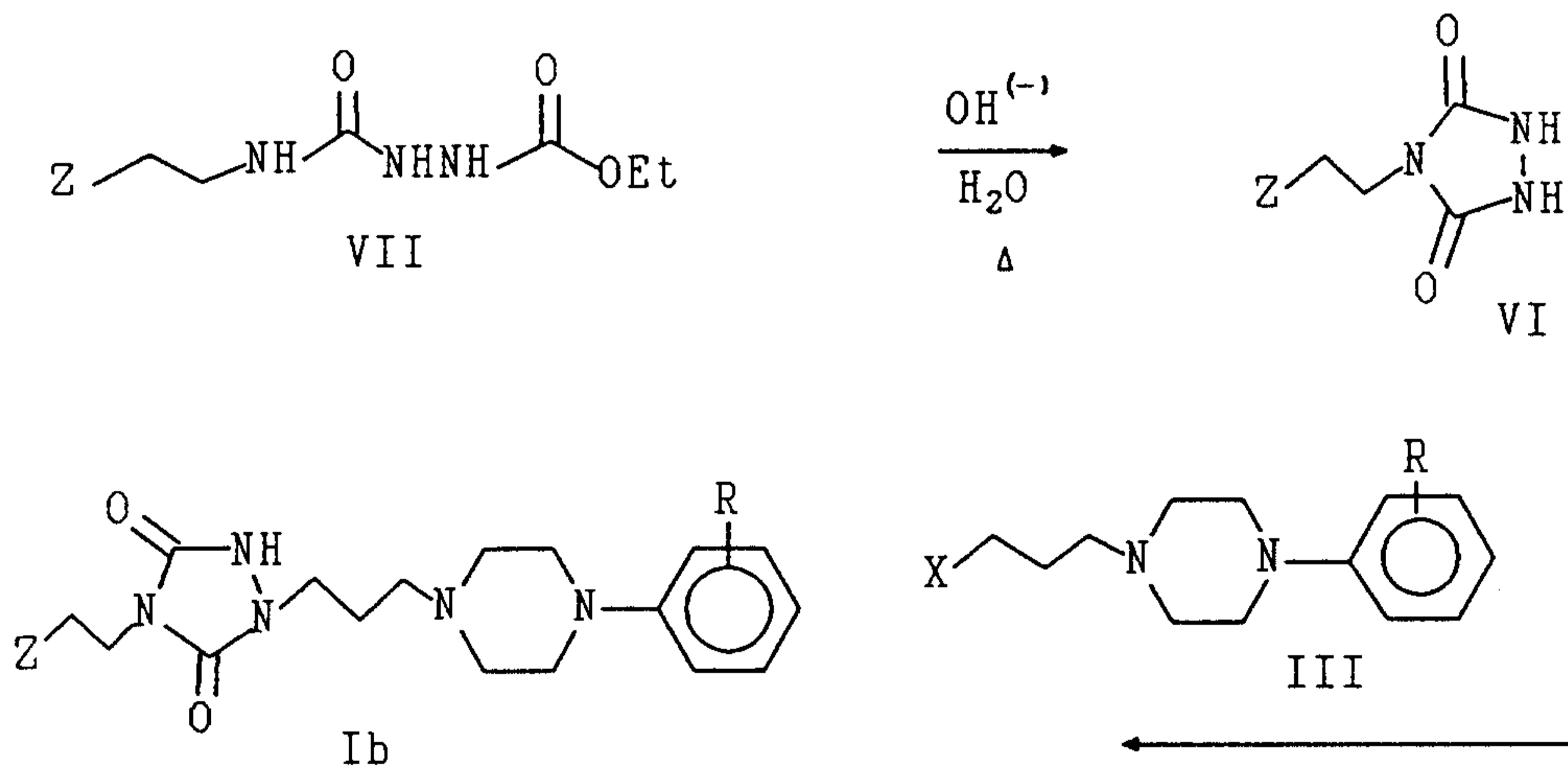
provide the triazolone ketal (IV) which is alkylated at the 2-position of the ring with a phenylpiperazine of Formula III, such as 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine, to provide the ketal derivative (II). Hydrolysis of II in acidic media results in the product of Formula Ia.

Intermediate compound (III) is prepared according to the synthetic process disclosed in the nefazodone patent of Temple, Jr., *et al.*, US 4,338,317.

10

Scheme 2

Preparation of Formula Ib Compounds



15

In Scheme 2, the semicarbazide of Formula VII, prepared by treating a toluene solution of an appropriate isocyanate (VIII) with ethyl carbazate; is ring-closed in aqueous hydroxide to give the 1,2,4-triazolidine-3,5-dione intermediate of Formula VI. Alkylation of VI with a phenylpiperazine (III), such as 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine

20

provides the triazoldione product Ib. The formation of a bis-alkylated adduct was not a problem as its formation did not occur to any appreciable extent.

5 In both of these synthetic schemes, R and Z are the same as defined supra. The symbol X denotes an organic synthetic leaving group such as chloro, bromo, iodo, mesyl, tosyl, and the like; all of which are familiar to one skilled in organic synthesis. The starting materials used to prepare compounds VII and
10 IX are common synthetic reagents and are commercially available or easily prepared according to well known procedures well known to those skilled in the pertinent art.

15 It should be appreciated that compound Ib could also be obtained by enzymatic (human liver microsomes) conversion of compound Ia in vitro. Administration of nefazodone or structural analogs to mammals will result in significant plasma levels of the related Ib compounds. By "significant plasma levels" is meant
20 that these levels are from one to several-fold higher than those of the parent drug.

Regarding the molecular structure of compounds of Formula Ib, NMR spectral analysis indicates that these compounds exist almost completely in the dione form as
25 opposed to the enol forms.

Description of Specific Embodiments

The compounds which constitute this invention and their methods of preparation will appear more full
30 from a consideration of the following examples which are given for the purpose of illustration only and are not to be construed as limiting the invention in sphere or scope. All temperatures are understood to be in degree C. when not specified.

The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed as parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), doublet (d), doublet of doublets (dd), or quartet (q). Abbreviations employed are DMSO- d_6 (deuterio-dimethylsulfoxide), $CDCl_3$ (deuteriochloroform), and are otherwise conventional. The infra-red (IR) spectral descriptions include only absorption wave numbers (cm^{-1}) having functional group identification value. The IR determinations were employed using potassium bromide (KBr) as diluent. The elemental analyses are reported as percent by weight.

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. All 1H NMR spectra were recorded on a Bruker 360 MHz spectrometer using TMS as an internal standard. Thin layer chromatography (TLC) were carried out on precoated silica gel GF (250 μ) plates (Analtech) and visualized using UV light (254 nm). Flash chromatography was performed using finely divided silica gel (32-63 μ) obtained from ICN Biochemicals.

Synthesis of Intermediates

30

A. Intermediates For Synthesis of Ia Compounds

Example 1

Ethylene Ketal of Pyruvic Acid Hydrazide (IX)

Ethyl pyruvate (5.09 g, 4.81mL, 43 mmole) and ethylene glycol (5.39 g, 4.84 mL, 87 mmole) were
5 combined in 4.5 mL benzene, to which p-toluenesulfonic acid monohydrate (113 mg) was added, and the resulting mixture was stirred at reflux temperature for 18 hr. with the water of reaction being collected in a Dean-Stark trap. Following concentration in vacuo, the
10 residual yellow oil was taken up in 40 mL abs. ethanol, treated with hydrazine monohydrate (3.23 g; 3.13 mL; 65 mmol) and this reaction solution was heated at reflux for about 7 hr. Concentration in vacuo yielded a white solid which was recrystallized
15 in about 20 mL isopropanol to provide, after drying in vacuo, crystalline product IX as 3.65 g (58%) of white needles, mp 120-122°.

Example 2

20 Phenoxyethyl semicarbazide intermediate (V)

A solution of sodium nitrite (9.90 g, 144 mmole) in 30 mL H₂O was added dropwise over 6.5 min. to a well-stirred mixture of 3-phenoxypropionyl hydrazide hydrochloride (28.0 g, 129 mmole) in 155 mL H₂O and 78
25 mL toluene being kept at 5° by ice-bath cooling. The temperature rose to 13°. After the temperature receded to 5° the mixture was stirred for an additional hr., Celite® was added and the mixture was filtered through a Celite® pad. The organic layer was
30 separated and the aqueous phase was extracted with toluene (2 x 20 ml). The combined extracts were dried (Na₂SO₄) and filtered through a MgSO₄ pad. The toluene filtrate was slowly added dropwise, under a N₂ atmosphere, into a 250 mL 3-necked reaction flask

sitting in an oil bath heated to 100°. The azide decomposed slowly and the toluene solution was stirred and heated until gas evolution ceased.

The isocyanate VIII solution was cooled to 18° and the pyruvic acid ketal hydrazide (IX; 18.9 g, 129 mmole) was added in one portion. The reaction mixture was stirred at ambient temperature for 16 hr. (during the first half-hour the reaction mixture temperature rose to 31° before subsiding). Solid precipitated during this time and the resulting thick mixture was cooled and filtered. The yellow solid was rinsed with additional toluene and dried in vacuo to yield 36.1 g (90.5%) of semicarbazide intermediate V, mp 103-111°.

NMR spectral analysis was consistent with the desired product structure.

Example 3

5-(2-Methyl-1,4-dioxolan-2-yl)-4-(2-phenoxyethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (IV)

The phenoxyethyl semicarbazide intermediate V (30.5 g, 98.6 mmole; as prepared in Example 2) was introduced into a hot (95°) stirred solution of KOH (6.37 g of 87% KOH pellets, 98.6 mmole) in 600 mL H₂O and stirred at gentle reflux for 6 hr. The mixture was filtered and the basic filtrate was cooled (ice bath) and neutralized (9.0 mL conc. HCl) and a yellow solid slowly precipitated during an additional 2 hr. of chilling and stirring. The mixture was filtered and the solid was rinsed with H₂O and then dried in vacuo (over P₂O₅) to provide 14.07 g (49%) of Formula IV product, mp 142-144°.

NMR spectral analysis was consistent with the desired structure.

Example 4

2-(3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl)-5-(2-methyl-1,4-dioxolan-2-yl)-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one (II)

5 The hydrochloride salt of 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine (III; 9.35 g; 30.2 mmole) was converted to the base form with 40% NaOH solution. Extraction of the basic aqueous liquid with CH₂Cl₂ and concentration in vacuo of the CH₂Cl₂ extracts gave
10 8.5 g of the base as an oil. The oil was combined with triazolone ketal intermediate IV (prepared in Example 3; 8.00 g, 2.75 mmole), K₂CO₃ (11.4 g, 82.5 mmole) and KI (1.0 g) in 100 mL acetonitrile which was stirred at reflux for 24 hr. Filtration of the hot
15 mixture and rinsing of the residue with additional acetonitrile gave a filtrate which was concentrated in vacuo to 16.3 g of a yellow orange viscous oil which was used as is for hydrolysis in the subsequent step.

20 B. Intermediates For Synthesis of Ib Compounds

Example 5

1-Carbethoxy-4-(2-phenoxyethyl)semicarbazide (VII)

25 A solution of sodium nitrite (7.72 g, 0.112 mol) in deionized water (23.2 mL was added dropwise over 6.5 min. to a well stirred mixture of 3-phenoxypropionyl hydrazide hydrochloride¹ (22.00 g, 0.102 mol), deionized water (110 mL) and toluene (55 mL) that was cooled to 5°C in an ice bath. The
30 temperature rose to 13°C. After the mixture was stirred at 5°C for one hr., Celite® was added and the mixture was filtered through a pad of Celite®. The

1. Prepared according to U.S. 4,487,773, Example 5.

organic layer was separated and the aqueous phase was extracted with toluene (2 x 20 mL). The combined extracts were dried over Na₂SO₄ and filtered through a pad of MgSO₄.

5 The clear, bright yellow toluene solution containing the intermediate azide was added dropwise, under a nitrogen atmosphere, to a 250 mL, 3-neck reaction flask setting in an oil bath that had been heated to 100°C (oil bath temp.). The azide
10 decomposed slowly and stirring and heating were continued until gas evolution ceased. The yellow isocyanate solution was then cooled to 15°C and treated all at once with an equimolar amount (10.90 g, 0.102 mol) of ethyl carbazate. The resultant thick
15 mixture was stirred at ambient temperature for one hour (temperature gradually rose to 33°C) and the reaction was completed by heating to 90°C (pot temp.). Finally the mixture was cooled to 10°C and filtered. The product was rinsed with fresh toluene and dried in
20 vacuo to yield 21.36 g (78%) of VII as a white solid; mp 170-173°C. ¹H NMR (DMSO-d₆) was consistent.

Anal. Calcd for C₁₂H₁₇N₃O₄:

C, 53.92; H, 6.41; N, 15.72.

Found: C, 54.04; H, 6.37; N, 15.55.

25

Example 6

4-(2-Phenoxyethyl)-1,2,4-triazolidine-3,5-dione (VI)

The 1-(ethoxycarbonyl)semicarbazide VII (10.28 g, 0.0385 mol) was added to a solution of potassium
30 hydroxide (4.96 g, 0.0769 mol) in water (105 mL) and the suspension was stirred and heated in an oil bath at 95°C (oil bath temp.) for one hour. The yellow mixture was cooled to 25°C and filtered. The filtrate was further cooled in an ice bath and neutralized by

the slow addition of 6.72 ml (0.0807 mol) of conc. HCl. After 15 min. a white precipitate of VI was collected by filtration, washed with water and dried to constant weight. Yield: 6.56 g (77%); mp 187-
 5 189°C. ¹H NMR (DMSO-d₆): δ = 10.15 (s, 2H, equivalent NH's).

Anal. Calcd for C₁₀H₁₁N₃O₃:

C, 54.29; H, 5.01; N, 19.00.

Found: C, 54.23; H, 4.92; N, 18.60.

10

Synthesis of Formula I Products

A. Formula Ia

Example 7

15 2-(3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl)-5-acetyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride (Ia)

The ethylene ketal precursor (II; 14.50 g; 27.5 mmole) was dissolved in a mixture of 3N HCl (14 mL) and ethanol (100 mL) and heated at reflux for 4 hr.
 20 Progress of the reaction was monitored with TLC (silica gel; CH₂Cl₂/MeOH, 96:4). The reaction solution was concentrated in vacuo and the residue was partitioned between H₂O (40 mL) and CH₂Cl₂ (50 mL).
 25 This mixture was made basic with 4N NaOH (12 mL) and the organic layer separated. The aqueous layer was extracted with a 30 mL portion of CH₂Cl₂. The combined CH₂Cl₂ portions were dried (Na₂SO₄) and concentrated to 16.5 g of crude Ia product as an oil which was
 30 purified by flash chromatography on silica gel (120 g of 32-63μ size) eluting with CH₂Cl₂-1% MeOH. The appropriate fractions were combined and concentrated to provide 8 g (59.9% yield from Compound IV) of the base as a gum.

The base was converted into a crystalline salt by taking up the gum in *n*-propanol (80 mL) and acidifying with 4N HCl (4.15 mL, one equivalent). Removal of the propanol and trituration of the residual solid in acetone provided a crystalline HCl salt which weighed 7.4 g after isolation and drying in vacuo (P_2O_5), mp 162-165°.

NMR and IR spectral analyses conformed to the assigned structure.

10 Anal Calcd for $C_{25}H_{30}ClN_5O_3 \cdot HCl$:
C, 57.69; H, 6.00; N, 13.46; Cl, 13.62.
Found: C, 57.76; H, 6.10; N, 13.25; Cl, 13.90.

Example 8

15 2-(3-[4-(3-Chlorophenyl)-1-piperazinylpropyl]-4-(2-phenoxyethyl)-4H-1,2,4-triazole-3,5(1H,2H)-dione hydrochloride (Ib)

1-(3-Chloropropyl)-4-(3-chlorophenyl)piperazine hydrochloride (III) (13.58 g, 0.0438 mol) was suspended in water, layered with methylene chloride and made strongly basic with 40% aqueous NaOH while stirring and cooling in an ice bath. The organic layer was separated and the aqueous phase was extracted once more with methylene chloride. The combined extracts were washed once with water, dried (Na_2SO_4) and the solvent was evaporated to leave a clear amber oil.

30 A mixture of the triazolidine-3,5-dione (VI) (9.70 g, 0.0438 mol), the free base of (III) (11.96 g, 0.0438 mole) and pulverized sodium hydroxide pellets (1.75 g, 0.0438 mol) were combined in 2-propanol (340 mL) and heated at reflux for 3.5 hr. The mixture was filtered while hot and concentrated in vacuo to leave a cloudy amber oil. The crude product was then

purified by flash chromatography on silica gel (225 g) using a gradient mixture of 2-4.5% methanol/methylene chloride as the eluent. Fractions containing pure product were identified by TLC (silica gel, 4%
5 CH₃OH/CH₂Cl₂), combined and evaporated to dryness to yield 12.58 g (63%) of pale yellow gum.

The free base (12.58 g, 0.0274 mol) was dissolved in 2-propanol (175 mL) and treated with one equivalent of 2N HCl (13.70 mL). The salt quickly began to
10 precipitate from solution. The mixture was cooled and filtered to yield 10.21 g (47%) of Ib as a white solid after drying in vacuo over P₂O₅; mp 201-204°C. ¹H NMR (DMSO-d₆): δ = 7.04 (s, 1H, NH).

Anal. Calcd for C₂₃H₂₈N₅O₃·HCl:

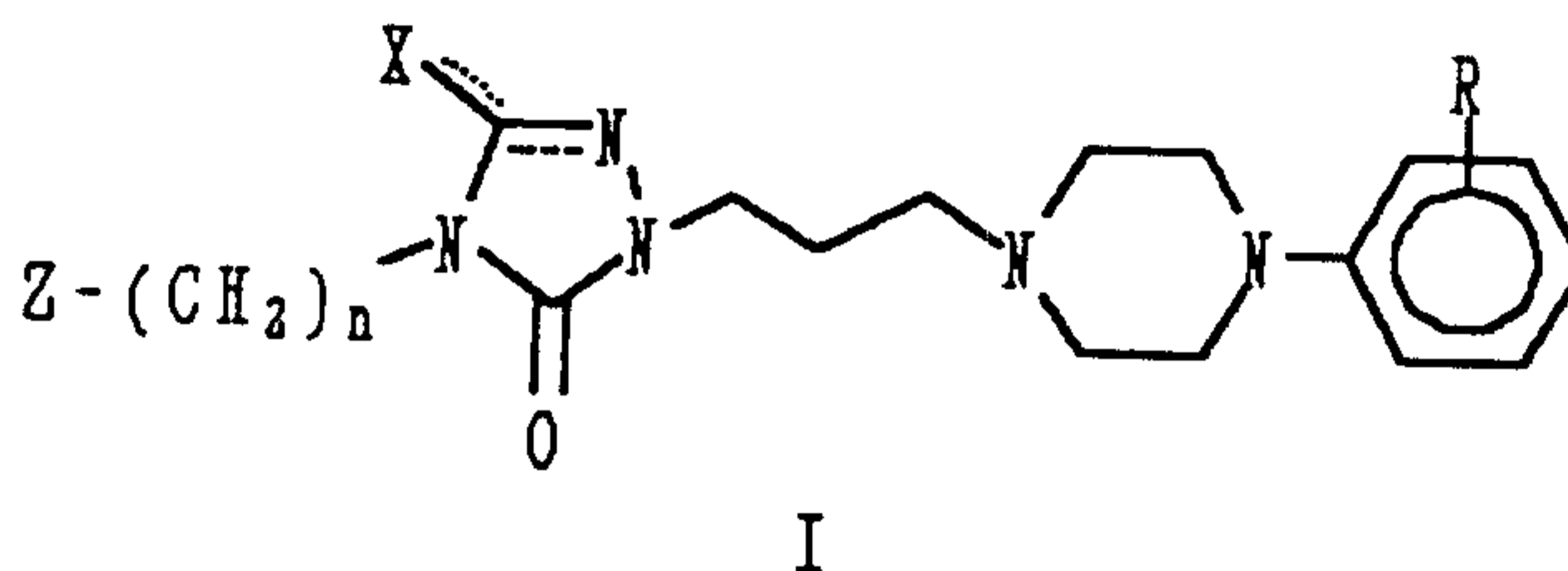
15 C, 55.87; H, 5.91; N, 14.17; Cl, 14.34.

Found (corrected for H₂O and IPA):

C, 56.13; H, 5.78; N, 14.24; Cl, 14.04.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound of Formula I



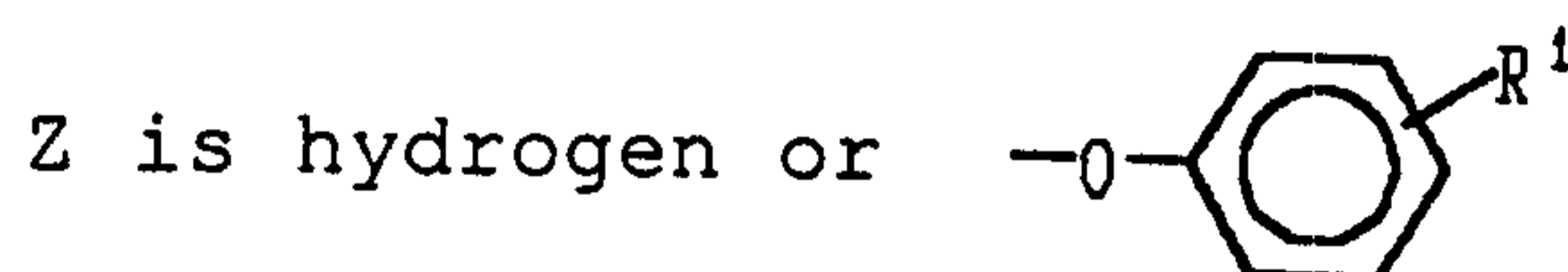
10 or a pharmaceutically acceptable acid addition salt and/or hydrate thereof wherein

R is halogen or trifluoromethyl;

X is oxygen or acetyl;

15 the single and dotted lines represent either a covalent single or double bond;

n is an integer from 2 to 4; and



in which R¹ is hydrogen, halogen, C₁₋₄ alkoxy or trifluoromethyl.

2. The compound of claim 1 wherein X is acetyl.

3. The compound of claim 1 wherein X is oxygen.

25 4. The compound of claim 1 wherein Z is

5. The compound of claim I wherein R is 3-chloro.

30 6. The compound of claim 4 wherein R¹ is hydrogen.

7. The compound of claim 2, 2-(3-[4-(3-chlorophenyl)-1-piperazinyl]propyl)-5-acetyl-2,4-dihydro-4-(2-phenoxy ethyl)-3H-1,2,4-triazol-3-one.

8. The compound of claim 3, 2-(3-[4-(3-chlorophenyl)-1-piperazinyl]propyl)-4-(2-phenoxyethyl)-4H-1,2,4-triazole-3,5(1H,2H)-dione.

9. A pharmaceutical formulation which comprises
5 a compound of Formula I, as claimed in any one of claims 1 to 8, associated with one or more pharmaceutically acceptable carriers, excipients, or diluents therefor.

10. A compound of Formula I as claimed in any one of claims
10 1 to 8 for use as an antidepressant agent.

11. The use of a pharmaceutical compound of formula I as set out in any one of claims 1 to 8, as an antidepressant agent.

12. The use of a pharmaceutical compound of formula I as
15 set out in any one of claims 1 to 8 in the manufacture of a medicament for the treatment of depression.