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(54) Titre : COMPOSES MULTICYCLIQUES QUE L'ON UTILISE COMME ANTAGONISTES DE L'HORMONE DE
CONCENTRATION DE MELANINE DANS LE TRAITEMENT DE L'OBESITE ET DU DIABETE

(54) Title: MULTICYCLIC COMPOUNDS FOR USE AS MELANIN CONCENTRATING HORMONE ANTAGONISTS IN
THE TREATMENT OF OBESITY AND DIABETES

(57) **Abrégé/Abstract:**

The present invention relates to a melanin concentrating hormone antagonist compound of formula I: (I); or a pharmaceutically acceptable salt, solvate, enantiomer or prodrug thereof useful in the treatment, prevention or amelioration of symptoms associated with obesity and related diseases.



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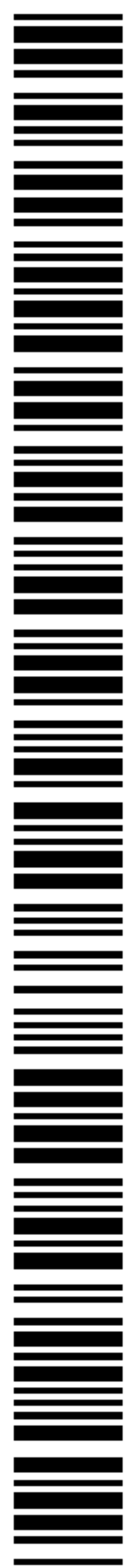
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(57) Abstract: The present invention relates to a melanin concentrating hormone antagonist compound of formula I: (I); or a pharmaceutically acceptable salt, solvate, enantiomer or prodrug thereof useful in the treatment, prevention or amelioration of symptoms associated with obesity and related diseases.



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CONTENANT LES PAGES 1 À 357

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MULTICYCLIC COMPOUNDS FOR USE AS MELANIN CONCENTRATING HORMONE ANTAGONISTS
IN THE TREATMENT OF OBESITY AND DIABETES**Field of Invention**

The present invention is in the field of medicine, particularly in the treatment of
5 obesity and diseases caused by or exacerbated by obesity. More specifically, the present
invention relates to antagonists of melanin concentrating hormone useful in the
prevention and treatment of obesity and related diseases.

Background of the Invention

10 The affluence of the 90's along with the exponential increase in food production
particularly in Western and Asian economies has resulted in feeding patterns that lead to
obesity. Obesity is defined as being excessively overweight. Excessive weight is
generally characterized by excessive body fat, because unused energy is stored in the
adipose tissues as fat.

15 Obesity has associated with it, economic and social costs. Obese people, an
increasing proportion of developed and developing societies, are regarded as having out
of control feeding habits often associated with low self-esteem. Moreover, obese persons
are more likely to have medical problems associated with or exacerbated by the excess
body weight. Examples of medical conditions caused, exacerbated or triggered by
20 excessive weight include bone fractures, pains in the knee joints, arthritis, increased risk
of hypertension, arteriosclerosis, stroke, diabetes, etc.

Background of the invention

Melanin concentrating hormone (MCH) is a 19 amino acid neuropeptide produced
25 in the lateral hypothalamic area and zona incerta, although MCH-expressing neurons
project to numerous regions of the brain. MCH is processed from a larger pre-prohormone
that also includes a second peptide, NEL, and possibly a third, NGE (Nahon, Crit Rev in
Neurobiology, 8:221-262, 1994). MCH mediates its effects through at least two G
protein-coupled receptors, MCHR1 and MCHR2 (Saito et al. Nature 400: 265-269, 1999;
30 Hill et al., J Biol Chem 276: 20125-20129, 2001). Both receptors are expressed in regions
of the brain consistent with MCH neuronal projection and known MCH physiologic

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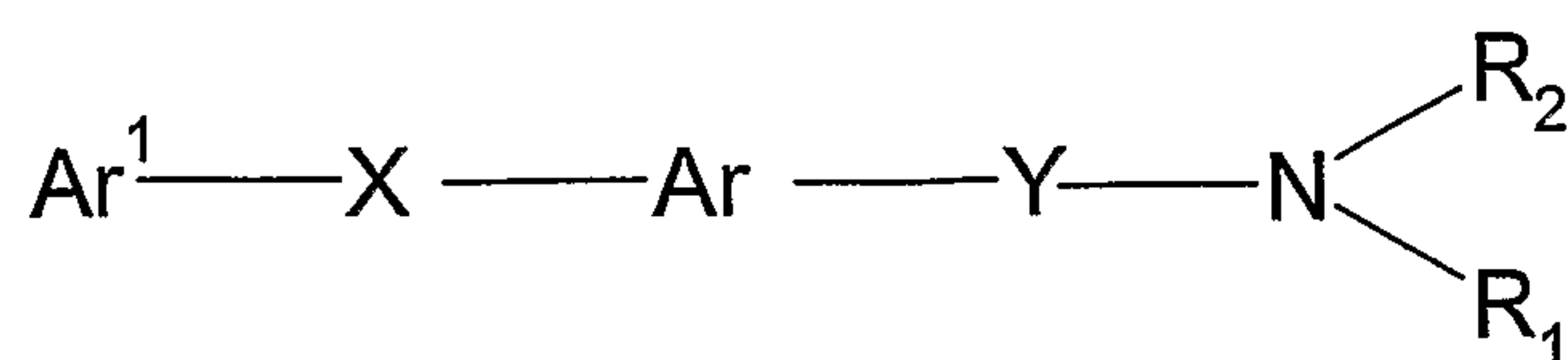
function (Hervieu et al., Eur J Neuroscience 12: 1194-1216, 2000; Hill et al., J Biol Chem 276: 20125-20129, 2001; Sailer et al., Proc Nat Acad Sci 98: 7564-7569, 2001).

Extensive evidence exists to support the orexigenic activity of MCH. MCH mRNA is elevated in rodent models of obesity and in the fasted state (Qu et al., Nature 380: 243-247, 1996). Intracerebroventricularly administered MCH increases feeding and blocks the anorexic effect of α -melanocyte stimulating hormone (Ludwig et al., Am J Physiol 274: E627-E633, 1998). MCH knock-out mice (MCH^{-/-} mice) are lean, hypophagic and hypometabolic (Shimada et al., Nature 396: 670-674, 1998), while MCH over-expressing transgenic mice are obese and insulin resistant (Ludwig et al., J Clin Invest 107: 379-386, 2001). MCHR1^{-/-} mice have recently been reported to be lean and hypermetabolic, indicating that the R1 isoform mediates at least some of the metabolic effects of MCH (Marsh et al., Proc Nat Acad Sci 99: 3240-3245, 2002; Chen et al., Endocrinology, 2002, in press).

In addition to its effects on feeding, MCH has been implicated in regulation of the hypothalamic-pituitary-adrenal axis through modulation of CRF and ACTH release (Bluet-Pajot et al., J Neuroendocrinol 7: 297-303, 1995). MCH may also play a role in the modulation of reproductive function (Murray et al., J Neuroendocrinol 12: 217-223, 2000) and memory (Monzon et al., Peptides 20: 1517-1519, 1999).

The current preferred treatment for obesity as well as Type II non-insulin dependent diabetes is diet and exercise with a view toward weight reduction and improved insulin sensitivity for diabetics. Patient compliance, however, is usually poor. The problem is compounded by the fact that there are currently only two medications approved for the treatment of obesity (sibutramine, or MeridiaTM and orlistat, or XenicalTM).

PCT application number WO 01/21577 (JP00/06375) filed September 19, 2000, discloses compounds reportedly useful as antagonists of the MCH receptor. In particular the WO 01/21577 application claims a compound of formula A



(A)

wherein:

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Ar¹ is a cyclic group that may have substituents;

X is a spacer having a main chain of 1 to 6 atoms;

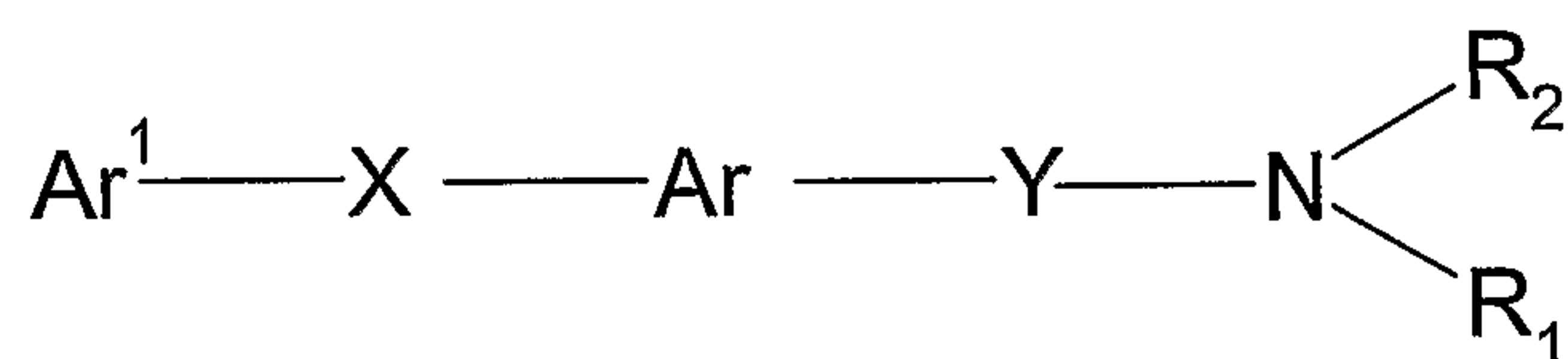
Y is a bond or a spacer having a main chain of 1 to 6 atoms;

Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;

R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents;

R¹ and R² together with the adjacent nitrogen atom may form a nitrogen-containing hetero ring which may have Substituents; R² may form a spiro ring together with Ar; or R², together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or salts thereof.

PCT application number WO 01/82925, filed April 26, 2001, also discloses compounds reportedly useful as antagonists of the MCH receptor. In particular the WO 01/82925 application claims a compound of formula B



(B)

wherein:

Ar¹ is an optionally substituted cyclic group;

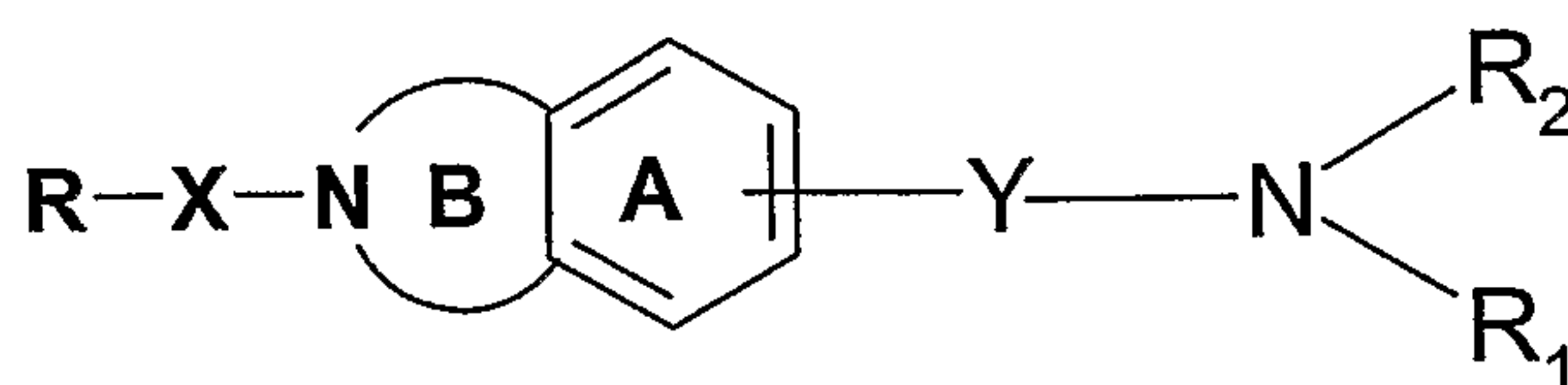
X and Y are independently a spacer having a C₁₋₆ main chain;

Ar is an optionally substituted fused polycyclic aromatic ring;

R¹ and R² are independently hydrogen atom or an optionally substituted hydrocarbon group; or alternatively R¹ and R² together with the nitrogen atom adjacent thereto may form a nitrogenous heterocycle, or R² together with the nitrogen atom adjacent thereto and Y may form an optionally substituted nitrogenous heterocycle, or R² together with the nitrogen atom adjacent thereto, Y, and Ar may form a fused ring.

PCT application number WO 01/87834, filed May 15, 2001, also discloses compounds reportedly useful as antagonists of the MCH receptor. In particular the WO 01/87834 application claims a compound of formula C.

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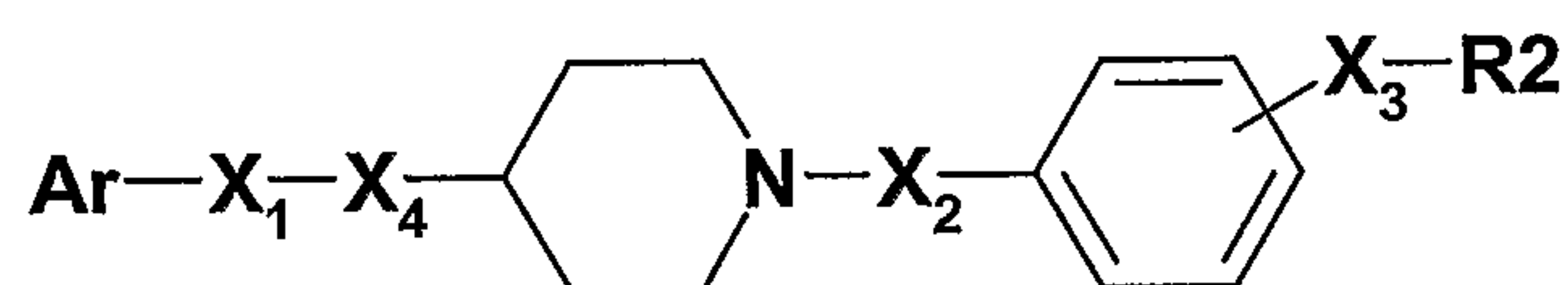


(C)

Wherein;

R represents hydrogen, halogen, or an optionally substituted cyclic group; X represents a
 5 bond or a spacer in which the main chain has one to ten atoms; Y represents a spacer in
 which the main chain has one to six atoms; ring A represents a benzene ring which may
 have other substituents; ring B represents a five- to nine-membered nitrogenous
 nonaromatic heterocycle which may have other substituents; and R^1 and R^2 are the same
 or different and each represents hydrogen, an optionally substituted hydrocarbon group, or
 10 an optionally substituted heterocyclic group, or R^1 and R^2 may form an optionally
 substituted nitrogenous heterocycle in cooperation with the adjacent nitrogen atom and R^2
 may form an optionally substituted nitrogenous heterocycle in cooperation with the
 adjacent nitrogen atom and Y.

Japanese patent application number JP2001-226269A also discloses compounds
 15 reportedly useful as antagonists of the MCH receptor. In particular the JP2001-226269A
 application claims a compound of formula D.



(D)

Wherein:

20 Ar is a substituted group-contg. arom. ring, X_1 is a substituted group-contg. divalent main
 chain of 1-5 atoms, X_2 , X_3 and X_4 are linking arms, and R_2 is a basic substituting group,
 and its salts.

Current treatments targeted at obesity have side effects. Examples of such
 treatments include phen-phen, and various over-the-counter appetite suppressants. These
 25 agents have not been proven effective for all patients and for sustainable periods of time.
 Similarly, the approved treatments, sibutramine (Meridia™) and orlistat (Xenical™) have
 been associated with side effects which may compromise compliance and may preclude
 long term use for sustained weight loss for certain patient populations.

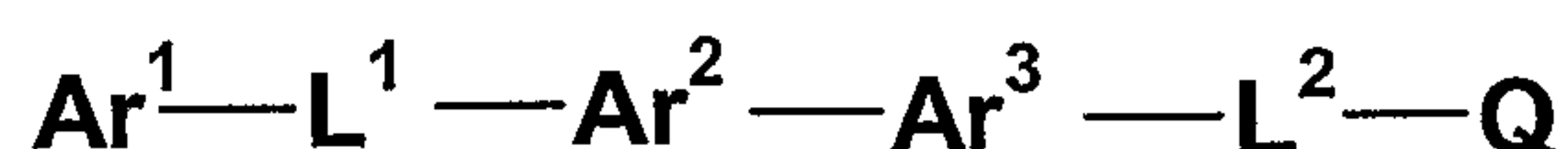
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Therefore, there is a need for new and/or improved therapeutically effective agents useful as antagonist of melanocortin releasing hormone to better control the dietary habits, minimize the preponderance of obesity and treat, prevent and/or ameliorate the effects of obesity including for example diabetes.

5

Summary of Invention

The present invention relates to a compound of formula I:



(I)

10 or a pharmaceutically acceptable salt, solvate, enantiomer, diastereomer or mixture of diastereomers or prodrug thereof wherein:

Ar¹ is a cyclic group optionally substituted with one to five groups selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, hydroxy, C₁-C₈ alkoxy, C₁-C₈ alkylaryl, phenyl, -O-aryl, heteroaryl, cycloalkyl, C₁-C₈ alkylcycloalkyl, cyano, -(CH₂)_nNR⁶R⁶, C₁-C₈ haloalkyl, C₁-C₈ haloalkoxy, halo, (CH₂)_nCOR⁶, (CH₂)_nNR⁵SO₂R⁶, -(CH₂)_nC(O)NR⁶R⁶, heterocyclic, and C₁-C₈ alkylheterocyclic; wherein the cycloalkyl, phenyl, aryl, and heterocyclic substituents are each optionally substituted with one to three groups selected from hydroxy, C₁-C₈ alkoxyalkyl, C₁-C₈ haloalkoxy, C₁-C₈ alkyl, halo, C₁-C₈ haloalkyl, nitro, cyano, amino, carboxamido, phenyl, aryl, alkylheterocyclic, heterocyclic, and oxo;

20 L¹ is a bond or a divalent linker having a main chain of 1 to 10 atoms; or represented by the formula X₂-(CR³R⁴)_m-X₃ where X₂ is attached to Ar¹ and X₃ is attached to Ar² wherein R³ and R⁴ are independently selected from a bond, hydrogen, C₁-C₈ alkyl, C₂-C₈ alkylene, C₂-C₈ alkynyl, phenyl, aryl, C₁-C₈ alkylaryl; wherein the alkyl, alkenyl, phenyl, and aryl groups are optionally substituted with one to five substituents independently selected from oxo, nitro, cyano, C₁-C₈ alkyl, aryl, halo, hydroxy, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, (CH₂)_nC(O)R⁶, and (CH₂)_nCONR⁶R⁶;

25 X₂ is independently oxygen, -CH, -CONH(CR³R⁴)_m, -NHCO(CR³R⁴)_m, - (CR³R⁴)_m, -CHR⁶, -NR⁵, S, SO, SO₂, -O(CR³R⁴)_m, or -S(CR³R⁴)_m;

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X_3 is independently oxygen, -C, -CH, -CHR⁶, - (CR³R⁴)_m, -CONH(CR³R⁴)_m, -NHCO(CR³R⁴)_m, -NR⁵, -NR⁵(CR³R⁴)_m, S, SO(CR³R⁴)_m, SO₂(CR³R⁴)_m, S(CR³R⁴)_m, SO, or SO₂; -O(CR³R⁴)_m, or -S(CR³R⁴)_m;

Ar² is a 5-member monocyclic heterocyclic aromatic group or positional isomer thereof, having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; and optionally substituted with one to three substituents selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, hydroxy, C₁-C₈ alkoxy, C₁-C₈ alkylaryl, phenyl, aryl, C₃-C₈ cycloalkyl, C₁-C₈ alkylcycloalkyl, cyano, C₁-C₈ haloalkyl, halo, (CH₂)_nC(O)R⁶, (CH₂)_nC(O)OR⁶, (CH₂)_nNR⁵SO₂R⁶, (CH₂)_nC(O)NR⁶R⁶, and C₁-C₈ alkylheterocyclic;

Ar³ is a 6-member monocyclic, aromatic, carbocyclic or heterocyclic ring having 0, 1, 2, or 3 heteroatoms selected from nitrogen, oxygen and sulfur and which is optionally substituted with one to three substituents independently selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, halo, -NHR⁵, C₁-C₈ haloalkyl, C₃-C₈ cycloalkyl, hydroxy, alkoxy, (CH₂)_nC(O)R⁶, (CH₂)_nC(O)OR⁶, (CH₂)_nNR⁵SO₂R⁶, (CH₂)_nC(O)NR⁶R⁶, phenyl, C₁-C₈ alkylaryl, and aryl;

L² is a divalent linker having a chain length of between 1 and 10 atoms in the main chain or is represented by the formula:



wherein X₄ is attached to Ar³ and is selected from the group consisting of C, -CH, CHR⁶, -CO, O, -NR⁵, -NC(O)-, -NC(S), -C(O)NR⁵-, -NR⁶'C(O)NR⁶, -NR⁶'C(S)NR⁶, -SO₂NR⁷, -NRSO₂R⁷, and -NR⁶'C(NR⁵)NR⁶;

X₅ is selected from the group consisting of -CH₂, -CH, -O(CR³R⁴)_m, NR³(CR³R⁴)_m, SO, SO₂, S, and SCH₂; wherein the group X₄-(CR³R⁴)_m-X₅ imparts stability to the compound of formula (1) and may be a saturated or unsaturated chain or divalent linker.

Q is a basic group or a group represented by -NR¹R²; wherein

R¹ and R² are independently hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₈ cycloalkane, C₁-C₈ alkylaryl, -C(O)C₁-C₈ alkyl, -C(O)OC₁-C₈ alkyl, C₁-C₈ alkylcycloalkane, (CH₂)_nC(O)OR⁵, (CH₂)_nC(O)R⁵, (CH₂)_nC(O)NR⁶R⁶, and (CH₂)_nNSO₂R⁵; wherein each of the alkyl, alkenyl, aryl are each optionally substituted with one to five groups

independently selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, phenyl, and alkylaryl; and wherein R¹ and R² may combine together, and with the nitrogen atom to which they are attached or with 0, 1, 2 or 3 atoms adjacent to the nitrogen atom to form a nitrogen

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containing heterocycle which may have 1, or 2 substituents independently selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₈ cycloalkane, C₁-C₈ alkylaryl, -C(O)C₁-C₈ alkyl, -C(O)OC₁-C₈ alkyl, C₁-C₈ alkylcycloalkane, oxo, halo amino, and (CH₂)_nC(O)NR⁶R⁶; provided that L²-Q is not CONH₂; wherein R¹ and R² may combine with the nitrogen atom to which they are attached to form an imine; and provided that Q is not a substituent on an amide;

R⁵ is hydrogen, CN, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₅-C₈ alkylaryl, (CH₂)_nNSO₂C₁-C₈ alkyl, (CH₂)_nNSO₂phenyl, (CH₂)_nNSO₂aryl, -C(O)C₁-C₈ alkyl, or -C(O)OC₁-C₈ alkyl; and R⁶ and R^{6'} are each independently hydrogen, C₁-C₈ alkyl, phenyl, aryl, C₁-C₈alkylaryl, or C₃-C₈cycloalkyl;

R⁷ is hydrogen, C₁-C₈ alkyl, phenyl, aryl, C₁-C₈alkylaryl, or C₃-C₈cycloalkyl, and wherein m is an integer from 1 to 8; and n is an integer from 0 to 8.

The present invention also relates to pharmaceutical formulations containing, a compound of formula I.

In another embodiment, the pharmaceutical formulation of the present invention may be adapted for use in treating obesity and related diseases.

The present invention also relates to methods for treating obesity in a patient in need thereof, wherein such treatment comprises administering to said patient a therapeutically effective amount of a compound of formula I in association with a pharmaceutically acceptable carrier, diluent or excipient.

The present invention also relates to a method for antagonizing the binding of MCH to MCH receptors for the treatment of diseases caused, or exacerbated by melanin concentrating hormone.

The present invention provides the use of a compound of formula I as an appetite suppressant and/or as a weight loss agent.

The present invention is related to the use of a compound of formula I for the manufacture of a medicament for treating obesity and related diseases.

Detailed Description

For the purposes of the present invention, as disclosed and claimed herein, the following terms are defined below.

The term “main chain” as used herein describes the number of atoms in the shortest distance between two ends of a variable or radical and includes the distance in number of atoms when traversing a straight chain, branched chain or atoms in a mono or bicyclic ring from one end of the variable or radical to the other.

5 The term “C₁-C₈ alkyl” represents a straight, branched hydrocarbon moiety having from one to eight carbon atoms, including but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclobutyl, pentyl, hexyl, and the like.

10 The term “C₃-C₈ cycloalkyl” as used herein refers to a cyclic hydrocarbon radical or group having from 3 to 8 carbon atoms and having no double bonds. Examples of C₃-C₈ cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl.

15 The term “C₃-C₈ cycloalkenyl” as used herein refers to a cyclic hydrocarbon radical or group having from 3 to 8 carbon atoms and having from 1 to 3 double bonds. Specific examples of C₃-C₈ cycloalkenyl include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, tetrahydrothiophene, tetrahydrofuran,

The term “halo” means halogens including iodo, chloro, bromo and fluoro.

20 The term “C₁-C₄ haloalkyl” refers to a C₁-C₄ alkyl group substituted with one, two or three halogen atoms as possible and appropriate. Examples of C₁-C₄ haloalkyl include but are not limited to trifluoromethyl, chloroethyl, and 2-chloropropyl. Similarly, a “C₁-C₈ haloalkyl” group is a C₁-C₈ alkyl moiety substituted with up to six halo atoms, preferably one to three halo atoms.

25 A “C₁-C₈ alkoxy” group is a C₁-C₈ alkyl moiety connected through an oxy linkage. The term includes “optionally halogenated C₁-C₈ alkoxy” groups including for example, C₁-C₈ alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentyloxy, etc.), which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples of alkoxy groups include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy.

30

The term "cyclic" as used herein refers to substituted or unsubstituted aromatic and non-aromatic ring structures containing hydrocarbon groups, and substituted or unsubstituted aromatic and non-aromatic heterocyclic groups. Cyclic groups may also be monocyclic, bicyclic or polycyclic unless otherwise specified. Examples of aromatic groups include, for example, benzene, thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrimidine, pyrazine, pyrimidine, pyridazine, naphthyl, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4,-thiadiazole, 1,3,4-thiadiazole, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, tetrahydrothiazole, tetrahydroisothiazole, tetrahydrooxazole, tetrahydroisoxazole, piperidine, tetrahydropyridine, dihydropyridine, piperazine, morpholine, thiomorpholine, tetrahydropyrimidine, tetrahydropyridazine, hexamethyleneimine, benzofuran, benzimidazole, benzoxazole, benzothiophene, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, isoquinoline, quinoline, indole, quinoxaline, phenanthridine, phenothiazine, phenoxathlin, phenoxazine, naphthylidene, quinazoline, carbazole, b-carboline, acridine, phenazine, phthalimide, and thioxanthene each of which may be optionally substituted.

The term "alkylcycloalkyl" as used herein refers to an alkyl group on which a cycloalkyl group is substituted. Exemplary of alkylcycloalkyl groups are methylcyclopropyl, methylcyclohexyl, methylcycloheptyl, ethylcyclopropyl, etc. The alkylcycloalkyl group may optionally be substituted independently with one to five groups selected from C₁-C₈ alkyl, phenyl, aryl, halo, amino, alkylsulfonyl, alkylsulfonamide, haloalkyl, carboxyalkyl, carboxamide, alkoxy, and perfluoroalkoxy.

The term "optionally substituted" as used herein and unless otherwise specified, means an optional substitution of one to five, preferably one to two groups independently selected from halo, hydroxy, oxo, cyano, nitro, phenyl, benzyl, triazolyl, tetrazolyl, 4,5-dihydrothiazolyl, halo, C₁-C₆ alkyl, C₁-C₄ haloalkyl, C₁-C₆ or a pharmaceutically acceptable salt, solvate, enantiomer, mixture of enantiomers or prodrug thereof wherein

Ar¹ is a cyclic group optionally substituted with one to five groups selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, hydroxy, C₁-C₈ alkoxy, C₁-C₈ alkylaryl, phenyl, -O-aryl, heteroaryl, cycloalkyl, C₁-C₈ alkylcycloalkyl, cyano, -(CH₂)_nNR⁶R⁶, C₁-C₈ haloalkyl, C₁-C₈ haloalkoxy, halo, (CH₂)_nCOR⁶, (CH₂)_nNR⁵SO₂R⁶, -(CH₂)_nC(O)NR⁶R⁶,

heterocyclic, and C₁-C₈ alkylheterocyclic; wherein the cycloalkyl, phenyl, aryl, and heterocyclic substituents are each optionally substituted with one to three groups selected from hydroxy, C₁-C₈ alkoxyalkyl, C₁-C₈ haloalkoxy, C₁-C₈ alkyl, halo, C₁-C₈ haloalkyl, nitro, cyano, amino, carboxamido, phenyl, aryl, alkylheterocyclic, heterocyclic, and oxo;

L¹ is a bond or a divalent linker having a main chain of 1 to 10 atoms; or represented by the formula X₂-(CR³R⁴)_m-X₃ where X₂ is attached to Ar¹ and X₃ is attached to Ar² wherein R³ and R⁴ are independently selected from a bond, hydrogen, C₁-C₈ alkyl, C₂-C₈ alkylene, C₂-C₈ alkynyl, phenyl, aryl, C₁-C₈ alkylaryl; wherein the alkyl, alkenyl, phenyl, and aryl groups are optionally substituted with one to five substituents independently selected from oxo, nitro, cyano, C₁-C₈ alkyl, aryl, halo, hydroxy, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, (CH₂)_nC(O)R⁶, and (CH₂)_nCONR⁶R⁶;

X₂ is independently oxygen, -CH, -CONH(CR³R⁴)_m, -NHCO(CR³R⁴)_m, - (CR³R⁴)_m, -CHR⁶, -NR⁵, S, SO, SO₂, -O(CR³R⁴)_m, or -S(CR³R⁴)_m;

X₃ is independently oxygen, -C, -CH, -CHR⁶, - (CR³R⁴)_m, -NR⁵, S, SO, or SO₂;

Ar² is a 5-member monocyclic heterocyclic aromatic group or positional isomer thereof, having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; and optionally substituted with one to three substituents selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, hydroxy, C₁-C₈ alkoxy, C₁-C₈ alkylaryl, phenyl, aryl, C₃-C₈ cycloalkyl, C₁-C₈ alkylcycloalkyl, cyano, C₁-C₈ haloalkyl, halo, (CH₂)_nC(O)R⁶, (CH₂)_nC(O)OR⁶, (CH₂)_nNR⁵SO₂R⁶, (CH₂)_nC(O)NR⁶R⁶, and C₁-C₈ alkylheterocyclic;

Ar³ is a 6-member monocyclic, aromatic, carbocyclic or heterocyclic ring having 0, 1, 2, or 3 heteroatoms selected from nitrogen, oxygen and sulfur and which is optionally substituted with one to three substituents independently selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, halo, -NHR⁵, C₁-C₈ haloalkyl, C₃-C₈ cycloalkyl, hydroxy, alkoxy, (CH₂)_nC(O)R⁶, (CH₂)_nC(O)OR⁶, (CH₂)_nNR⁵SO₂R⁶, (CH₂)_nC(O)NR⁶R⁶, phenyl, C₁-C₈ alkylaryl, and aryl;

L² is a divalent linker having a chain length of between 1 and 10 atoms in the main chain or is represented by the formula:

X₄-(CR³R⁴)_m-X₅;

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wherein X_4 is selected from the group consisting of C, $-\text{CH}$, CHR^6 , $-\text{CO}$, O, $-\text{NR}^5$, $-\text{NC}(\text{O})-$, $-\text{NC}(\text{S})$, $-\text{C}(\text{O})\text{NR}^5$, $-\text{NR}^{6'}\text{C}(\text{O})\text{NR}^6$, $-\text{NR}^{6'}\text{C}(\text{S})\text{NR}^6$, $-\text{SO}_2\text{NR}^7$, $-\text{NRSO}_2\text{R}^7$, and $-\text{NR}^{6'}\text{C}(\text{NR}^5)\text{NR}^6$;

X_5 is selected from the group consisting of $-\text{CH}_2$, $-\text{CH}$, $-\text{O}(\text{CR}^3\text{R}^4)_m$, $\text{NR}^3(\text{CR}^3\text{R}^4)_m$, SO , SO_2 , S, and SCH_2 ; wherein the group $X_4-(\text{CR}^3\text{R}^4)_m-X_5$ imparts stability to the compound of formula (1) and may be a saturated or unsaturated chain or divalent linker.

Q is a basic group or a group represented by $-\text{NR}^1\text{R}^2$; wherein

R^1 and R^2 are independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_8 cycloalkane, C_1 - C_8 alkylaryl, $-\text{C}(\text{O})\text{C}_1$ - C_8 alkyl, $-\text{C}(\text{O})\text{OC}_1$ - C_8 alkyl, C_1 - C_8 alkylcycloalkane, $(\text{CH}_2)_n\text{C}(\text{O})\text{OR}^5$, $(\text{CH}_2)_n\text{C}(\text{O})\text{R}^5$, $(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^6\text{R}^6$, and $(\text{CH}_2)_n\text{NSO}_2\text{R}^5$; wherein each of the alkyl, alkenyl, aryl are each optionally substituted with one to five groups independently selected from C_1 - C_8 alkyl, C_2 - C_8 alkenyl, phenyl, and alkylaryl; and wherein R^1 and R^2 may combine together, and with the nitrogen atom to which they are attached or with 0, 1, 2 or 3 atoms adjacent to the nitrogen atom to form a nitrogen containing heterocycle which may have 1, or 2 substituents independently selected from C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_8 cycloalkane, C_1 - C_8 alkylaryl, $-\text{C}(\text{O})\text{C}_1$ - C_8 alkyl, $-\text{C}(\text{O})\text{OC}_1$ - C_8 alkyl, C_1 - C_8 alkylcycloalkane, oxo, halo amino, and $(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^6\text{R}^6$; provided that L^2 -Q is not CONH_2 ; wherein R^1 and R^2 may combine with the nitrogen atom to which they are attached to form an imine; and provided that Q is not a substituent on an amide;

R^5 is hydrogen, CN, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_5 - C_8 alkylaryl, $(\text{CH}_2)_n\text{NSO}_2\text{C}_1$ - C_8 alkyl, $(\text{CH}_2)_n\text{NSO}_2$ phenyl, $(\text{CH}_2)_n\text{NSO}_2$ aryl, $-\text{C}(\text{O})\text{C}_1$ - C_8 alkyl, or $-\text{C}(\text{O})\text{OC}_1$ - C_8 alkyl; and

R^6 and $\text{R}^{6'}$ are independently hydrogen, C_1 - C_8 alkyl, phenyl, aryl, C_1 - C_8 alkylaryl, or C_3 - C_8 cycloalkyl; wherein m is an integer from 1 to 8; and n is an integer from 0 to 8.

where R^7 is independently at each occurrence H, C_1 - C_6 alkyl, phenyl or benzyl and R^8 is independently at each occurrence C_1 - C_6 alkyl, phenyl or benzyl.

The term "heterocycle or heterocyclic" represents a stable, saturated, partially unsaturated, fully unsaturated or aromatic 4, 5, or 6 membered ring, said ring having from one to three heteroatoms that are independently selected from the group consisting of sulfur, oxygen, and nitrogen. The heterocycle may be attached at any point which affords a stable structure. Representative heterocycles include 1,3-dioxolane, 4,5-dihydro-1H-imidazole, 4,5-dihydrooxazole, furan, imidazole, imidazolidine, isothiazole, isoxazole,

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morpholine, oxadiazole, oxazole, oxazolidinedione, oxazolidone, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, tetrazole, thiadiazole, thiazole, thiophene and triazole.

The heterocycle is further optionally substituted with one to three, preferably one
 5 or two groups independently selected from halo, hydroxy, oxo, cyano, nitro, phenyl, benzyl, triazolyl, tetrazolyl, 4,5-dihydrothiazolyl, C₁-C₆ alkyl, C₁-C₄ haloalkyl, C₁-C₆ alkoxy, COR⁷, CONR⁷R⁷, CO₂R⁷, NR⁷R⁷, NR⁷COR⁷, NR⁷SO₂R⁸, OCOR⁸, OCO₂R⁷, OCONR⁷R⁷, SR⁷, SOR⁸, SO₂R⁷ and SO₂(NR⁷R⁷), where R⁷ is independently at each
 occurrence H, C₁-C₆ alkyl, phenyl or benzyl and R⁸ is independently at each occurrence
 10 C₁-C₆ alkyl, phenyl or benzyl.

The term "alkylheterocyclic" as used herein refers to an alkyl group further substituted with a heterocyclic group. Examples of alkylheterocycles include but are not limited to 2-methylimidazoline, N-methylmorpholinyl, N-methylpyrrolyl and 2-methylindolyl.

15 The term "basic group" refers to an organic radical which is a proton acceptor. The term "basic group" also refers to an organic group containing one or more basic radicals. Illustrative basic radicals are amidino, guanidino, amino, piperidyl, pyridyl, etc, and excludes amides.

Suitable basic radicals contain one or more nitrogen atoms and include amino,
 20 imino, amidino, N-alkylamidines, N, N'-dialkylamidines, N-arylamidines, aminomethyleneamino, iminomethylamino, guanidino, aminoguanidino, alkylamino, dialkylamino, trialkylamino, alkylideneamino, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indoliziny, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinoliziny, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl,
 25 quinazolinyl, cinnolinyl, amide, thioamide, benzamidino, pteridinyl, 4H-carbazolyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, or any of the preceding substituted with amino, imino, amidino,
 30 aminomethyleneamino, iminomethylamino, guanidino, alkylamino, dialkylamino,

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trialkylamino, tetrahydroisoquinoline, dihydroisoindole, alkylideneamino, groups, or a group represented by the formula NR^1R^2 .

The term “suitable solvent” refers to any solvent, or mixture of solvents, inert to the ongoing reaction, that sufficiently solubilizes the reactants to afford a medium within
5 which to effect the desired reaction.

As used herein, the term “patient” includes human and non-human animals such as companion animals (dogs and cats and the like) and livestock animals. Livestock animals are animals raised for food production. Ruminants or “cud-chewing” animals such as cows, bulls, heifers, steers, sheep, buffalo, bison, goats and antelopes are
10 examples of livestock. Other examples of livestock include pigs and avians (poultry) such as chickens, ducks, turkeys and geese. Yet other examples of livestock include fish, shellfish and crustaceans raised in an aquaculture. Also included are exotic animals used in food production such as alligators, water buffalo and ratites (e.g., emu, rheas or ostriches). The preferred patient of treatment is a human.

15 The terms “treating” and “treat”, as used herein, include their generally accepted meanings, *i.e.*, preventing, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, or reversing the progression or severity of a pathological condition, or sequela thereof.

The terms “preventing”, “prevention of”, “prophylaxis”, “prophylactic” and
20 “prevent” are used herein interchangeably and refer to reducing the likelihood that the recipient of a compound of formula I will incur or develop any of the pathological conditions, or sequela thereof, described herein.

As used herein, the term “effective amount” means an amount of a compound of formula I that is sufficient for treating or preventing a condition, or detrimental effects
25 thereof, herein described, or an amount of a compound of formula I that is sufficient for antagonizing the MCHR1 receptor to achieve the objectives of the invention.

The term “pharmaceutically acceptable” is used herein as an adjective and means substantially non-deleterious to the recipient patient.

The term “formulation”, as in pharmaceutical formulation, is intended to encompass a
30 product comprising the active ingredient(s) (compound(s) of formula I), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the

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ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical formulations of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutical carrier, or a
5 compound of the formula I and a pharmaceutically acceptable co-antagonist of MCHR1 useful for the treatment and/or prevention of obesity or a related disease where antagonism of a MCH receptor may be beneficial.

The terms "diseases related to obesity" or "related diseases" as used herein refers to such symptoms, diseases or conditions caused by, exacerbated by, induced by, or
10 adjunct to the condition of being obese. Such diseases, conditions and/or symptoms include but are not limited to eating disorders (bulimia, anorexia nervosa, etc.), diabetes, diabetic complications, diabetic retinopathy, sexual/reproductive disorders, depression, anxiety, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleeping disorders, atherosclerosis, rheumatoid arthritis, stroke, hyperlipidemia,
15 hypertriglycemia, hyperglycemia, and hyperlipoproteinemia.

The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other non-human animals (as described above), each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

20 Because certain compounds of the invention contain an acidic moiety (e.g., carboxy), the compound of formula I may exist as a pharmaceutical base addition salt. Such salts include those derived from inorganic bases such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines such as aliphatic and aromatic amines, aliphatic
25 diamines, hydroxy alkamines, and the like.

Because certain compounds of the invention contain a basic moiety (e.g., amino), the compound of formula I may also exist as a pharmaceutical acid addition salt. Such salts include the salicylate, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate,
30 chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4 dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate,

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hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β -hydroxybutyrate, oxalate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and like salts. Preferred acid addition salts include the hydrochloride and oxalate salts. Acid addition salts are typically formed by reacting an equivalent amount of acid (based on moles of available basic i.e free pairs of electrons on nitrogen atoms, or a slight excess thereof) with the free base compound of the invention. The addition salt product is often isolated as the crystallization product. The crystallization may be spontaneous or may be facilitated by cooling and/or seeding. Other methods of isolating the acid addition salts are known to one of skill in the art.

Preferred Compounds of the Invention

Certain compounds of the invention are particularly interesting and preferred. The following listing sets out several groups of preferred compounds. It will be understood that each of the listings may be combined with other listings to create additional groups of preferred compounds.

Preferred Ar¹

Preferred Ar¹ groups are cyclic groups selected from cycloalkyl and cycloalkene groups such as the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl. Also preferred are groups selected from tetrahydrothiophene, tetrahydrofuran, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, tetrahydrothiazole, tetrahydroisothiazole, tetrahydrooxazole, phenyl, tetrahydroisoxazole, piperidine, tetrahydropyridine, benzothiophene, benzofuran, naphthyl, dihydropyridine, piperazine, morpholine, thiomorpholine, tetrahydropyrimidine, tetrahydropyridazine, hexamethyleneimine, each optionally substituted with C₁-C₆ alkyl, C₁-C₆ cycloalkyl, C₁-C₆ haloalkyl, hydroxy, alkoxyalkyl, cyano, halo, aryl, carboxamide, and C₁-C₆ carboxyalkyl. More preferred Ar¹ groups include cycloalkyl, cycloalkenyl, substituted or unsubstituted phenyl, benzothiophene, benzofuran and naphthyl.

Preferred L¹ groups

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Preferred as L^1 are groups having between 3 to 8 carbon atoms in the main chain. Also preferred are L^1 groups selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{SCH}_2-$, $-\text{OCH}_2-$, $-\text{CH}_2\text{SCH}_2-$, $-\text{CH}_2\text{OCH}_2-$, $-\text{OCH}_2\text{CH}_2\text{SCH}_2-$, $-\text{OCH}_2\text{CH}_2\text{OCH}_2-$, $-\text{O}(\text{CH}_2)_3\text{SCH}_2-$, $-\text{OCH}(\text{Et})\text{CH}_2\text{CH}_2\text{SCH}_2-$, $-\text{OCH}(\text{iPr})\text{CH}_2\text{CH}_2\text{SCH}_2-$, $-\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{SCH}_2-$, $-\text{O}(\text{CH}_2)_3\text{SCH}(\text{CH}_3)-$, $-\text{O}(\text{CH}_2)_2\text{SCH}(\text{CF}_3)-$, $-\text{OCH}_2\text{CH}(\text{NO}_2)\text{SCH}_2-$, $-\text{OCH}(\text{CN})\text{CH}_2\text{SCH}_2-$, $-\text{OCH}_2\text{CH}(\text{NH}_2)\text{SCH}_2-$, $-\text{CH}_2\text{O}(\text{CH}_2)_3\text{CH}_2\text{O}-$, and $-\text{CH}_2\text{O}(\text{CH}_2)_2\text{CH}_3\text{O}-$.

Preferred X_2 group

Also preferred is an L^1 group having the formula $X_2-(\text{CR}^3\text{R}^4)_m-X_3$ wherein a preferred X_2 group is selected from O, S, and $-\text{NR}^6$, and wherein R^6 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_8 cycloalkyl, phenyl, benzyl, C_1 - C_8 alkylamine, and aryl.

Preferred X_3 Groups

Also preferred is an L^1 group wherein, when L^1 is $X_2-(\text{CR}^3\text{R}^4)_m-X_3$; wherein X_3 is a group selected from $-\text{OCH}_2$, $-\text{SCH}_2$, $-\text{NR}^6\text{C}(\text{O})\text{CH}_2$, $-\text{NHCH}_2$, wherein R^6 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_8 cycloalkyl, phenyl, benzyl, and aryl. More preferred is an X_3 group selected from $-\text{OCH}_2$, and $-\text{SCH}_2$.

Also preferred is a compound of formula I wherein L^1 is $X_2-(\text{CR}^3\text{R}^4)_m-X_3$, and wherein the chain between X_2 and X_3 i.e., $-(\text{CR}^3\text{R}^4)_m-$ is an alkyl chain of 3 to 8 carbon atoms, or an alkenyl chain of 3 to 8 carbon atoms and optionally contains an alkyl, phenyl, amino, or cycloalkyl group as a side chain.

Preferred Ar^2 Groups

A preferred Ar^2 group is a 5-member monocyclic aromatic heterocyclic group having 1, 2, or 3 heteroatoms selected from oxygen, sulfur, and nitrogen. More preferred is a heterocyclic group selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, 2-pyraziline, pyrazolidine, isoxazole, isothiazole, 1,3,4-oxadiazole, 1,2,3-triazole, 1,3,4-thiadiazole and 1,3,4-oxadiazole. Most preferred Ar^2 are the oxadiazolyl or oxazolyl groups, and positional isomers thereof.

Preferred Ar³ Groups

Preferred Ar³ group is a 6-member carbocyclic or heterocyclic group having 0, 1, 2, or 3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and optionally substituted with one to two groups. More preferred is a cyclic group selected from phenyl, pyran, piperidine, pyridine, pyridazine, and piperazine. Most preferred Ar³ is phenyl.

Preferred L² groups

Preferred L² groups include a divalent group having between 3 and 8 atoms in the main chain. Also preferred are L² groups selected from the group consisting of –OCH₂CH₂–, –O(CH₂)₃–, –CH₂–, –CH₂CH₂–, –CH₂CH₂CH₂–, –CH=CH–, –CH₂CH₂CH=CH– and X₄–(CR³R⁴)_m–X₅.

15 Preferred X₄ Groups

Preferred X₄ groups include divalent groups, radicals, or fragments of the formula –C(O)NR⁶ wherein R⁶ is selected from the group consisting of hydrogen, C₁–C₆ alkyl, C₂–C₆ alkenyl, C₃–C₈ cycloalkyl, phenyl, benzyl, C₁–C₈ alkylamine, and aryl.

Also preferred is an X₄ group selected from O, S, –NR⁶C(O)NR⁶, –C(S)NR⁶, NR⁶C(S)NR⁶, NR⁶C(NR⁶)NR⁶, –NR⁶SO₂–, wherein R⁶ is independently selected from the group consisting of hydrogen, C₁–C₆ alkyl, C₂–C₆ alkenyl, C₃–C₈ cycloalkyl, phenyl, benzyl, C₁–C₈ alkylamine, and aryl.

Preferred X₅ Groups

Preferred is an X₅ group selected from –OCH₂–, –SCH₂–, O, –NR⁶C(O)–, –NR⁶C(S)–, –C(O)NR⁶–, –C(S)NR⁶–, NR⁶C(S)NR⁶–, NC(NR⁶)N–, NR⁶C(O)NR⁶–, –NR⁶SO₂– wherein R⁶ is independently selected from the group consisting of hydrogen, C₁–C₆ alkyl, C₂–C₆ alkenyl, C₃–C₈ cycloalkyl, phenyl, benzyl, C₁–C₈ alkylamine, and aryl. More preferred is an X₅ group selected from –OCH₂–, SCH₂– and O.

Also preferred is a compound of formula I wherein the chain between X₄ and X₅ is preferably an alkyl chain of 2 to 8 carbon atoms, or an alkenyl chain of 2 to 8 carbon atoms and optionally containing an alkyl, phenyl, or cycloalkyl group as a side chain.

Preferred Q groups:

The substituent Q of formula I is a basic group. A basic group is an organic group containing one or more basic radicals. Preferred Q groups are those represented by
5 the formula $-NR^1R^2$

Preferred R^1 and R^2 Groups

Preferred R^1 and R^2 groups are independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_8 cycloalkyl, C_3 - C_8
10 alkylcycloalkyl, phenyl, benzyl, COR^9 , SO_2R^9 , and $(CH_2)_nSO_2R^6$.

Also preferred are R^1 and R^2 groups which combine with each other, the nitrogen atom to which they are attached to form a heterocycle selected from morpholino, thiomorpholino, pyrrole, 2H-pyrrole, 2-pyrroline, pyrrolidine, oxazole, thiazole, imidazoline, imidazolidine, pyrazole, pyrazoline, piperazinyl, piperadinyl, pyrazinyl,
15 pyrimidine each optionally substituted with a C_1 - C_8 alkyl group.

Also preferred is a compound of the invention having R^1 and R^2 groups wherein the R^1 and R^2 groups combine with the nitrogen atom to which they are attached and with a carbon atom one or two atoms removed from the nitrogen atom to form a cycle such as for example, azepine, diazepine, pyridine, piperidine, indolyl, N-
20 methylpyrrolidinyl, pyrrolidinyl, morpholino, piperidinyl, and the like.

Also preferred are compounds of formula I wherein R^1 and R^2 combine together with the nitrogen atom to which they are attached to form an imine or substituted imine.

Most preferred are R_1 and R_2 which singly or in combination with each other
25 and/or the nitrogen atom to which they are attached form the groups independently selected from methyl, ethyl, propyl, isopropyl, isobutyl, cyclopentyl, cyclohexyl, N-morpholino, azepane, diazepine, pyridine, pyrrolidine, piperidine, N-methylpiperidine, and N-methylpiperazine.

30 Preferred R^3 and R^4 groups:

Preferred R^3 and R^4 are independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkylene, C_2 - C_8 alkynyl, phenyl, aryl, C_1 - C_8 alkylaryl, $(CH_2)_nNR^5SO_2R^6$,

$(\text{CH}_2)_n\text{C}(\text{O})\text{R}^6$, $(\text{CH}_2)_n\text{CONR}^6\text{R}^6$ and $(\text{CH}_2)_n\text{C}(\text{O})\text{OR}^6$; wherein the alkyl, alkenyl, phenyl, and aryl groups are optionally substituted with one to three substituents independently selected from oxo, nitro, cyano, C_1 - C_8 alkyl, aryl, halo, hydroxy, C_1 - C_8 alkoxy, C_1 - C_8 haloalkyl, $(\text{CH}_2)_n\text{C}(\text{O})\text{R}^6$, $(\text{CH}_2)_n\text{CONR}^6\text{R}^6$ and $(\text{CH}_2)_n\text{C}(\text{O})\text{OR}^6$.

5 Most preferred R^3 and R^4 substituents are independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkylene, C_2 - C_8 alkynyl, phenyl, and benzyl; and wherein n is 0, or 1, and wherein R^5 is hydrogen, C_1 - C_8 alkyl, phenyl or benzyl; and wherein R^6 is hydrogen, C_1 - C_8 alkyl, phenyl or benzyl.

10 Preferred R^5 groups

A preferred R^5 group is a group independently selected from hydrogen, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, C_2 - C_8 alkenyl, C_5 - C_8 alkylaryl, $(\text{CH}_2)_n\text{NSO}_2\text{C}_1$ - C_8 alkyl, $(\text{CH}_2)_n\text{NSO}_2$ phenyl, $(\text{CH}_2)_n\text{NSO}_2$ aryl, $-\text{C}(\text{O})\text{C}_1$ - C_8 alkyl, $-\text{C}(\text{O})\text{OC}_1$ - C_8 alkyl; and

15 Preferred R^6 groups

A preferred R^6 or $\text{R}^{6'}$ is independently selected from hydrogen, C_1 - C_8 alkyl, phenyl, aryl, alkylaryl, and C_3 - C_8 cycloalkyl.

An example of a preferred compound of the present invention is a compound
 20 selected from the group consisting of: 1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-dimethylamino-ethyl)-urea,
 1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,
 1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,
 25 1-(3-{4-[5-(Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidine,
 Cyclohexyl-ethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
 30 4-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-morpholine,
 1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azepane,

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- Diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
- 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-piperidine,
- 5 (3-{2-Chloro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,
- 1-Methyl-4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-piperazine,
- (3-{2-Fluoro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,
- 10 Ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
- Cyclopentyl-methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
- 15 1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azocane,
- Diethyl-(2-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-amine,
- Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
- Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-4-yl]-phenoxy}-propyl)-amine,
- 20 2-{4-[2-(1-Methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole,
- 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propenyl)-phenyl]-[1,3,4]oxadiazole,
- 25 Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-furan-2-yl]-phenoxy}-propyl)-amine,
- 4-Dimethylamino-N-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-butyramide,
- 1-(2-Dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- 30 1-(3-Dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

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Dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine,

1-(2-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-piperidine,

5 Dimethyl-(5-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-pent-4-enyl)-amine,

2-(2-Dimethylamino-ethoxy)-N-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-acetamide,

10 Dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine,

1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidine,

Diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,

15 1-(4-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-piperidine,

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(4-pyrrolidin-1-yl-butoxy)-phenyl]-[1,3,4]oxadiazole,

20 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-azepane,

1-(2-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-azepane,

Methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,

25 Diethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine,

1-(2-Dimethylamino-ethyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-

30 [1,3,4]oxadiazole,

1-(5-Dimethylamino-pentyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

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- 1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,
 1-(4-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-azepane,
 5 Diethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine,
 1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,
 1-(2-Dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
 10 (3-{4-[5-(Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,
 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(5-pyrrolidin-1-yl-pent-1-enyl)-phenyl]-[1,3,4]oxadiazole,
 15 1-(5-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-pent-4-enyl)-piperidine,
 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidin-4-one,
 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazole,
 20 Dimethyl-(2-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-amine,
 1-(2-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-piperidine,
 1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-piperidine,
 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-oxazole,
 Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-amine,
 25 Dimethyl-(6-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-hex-5-enyl)-amine,
 Dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-but-3-enyl)-amine,
 30 Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenoxy}-propyl)-amine,

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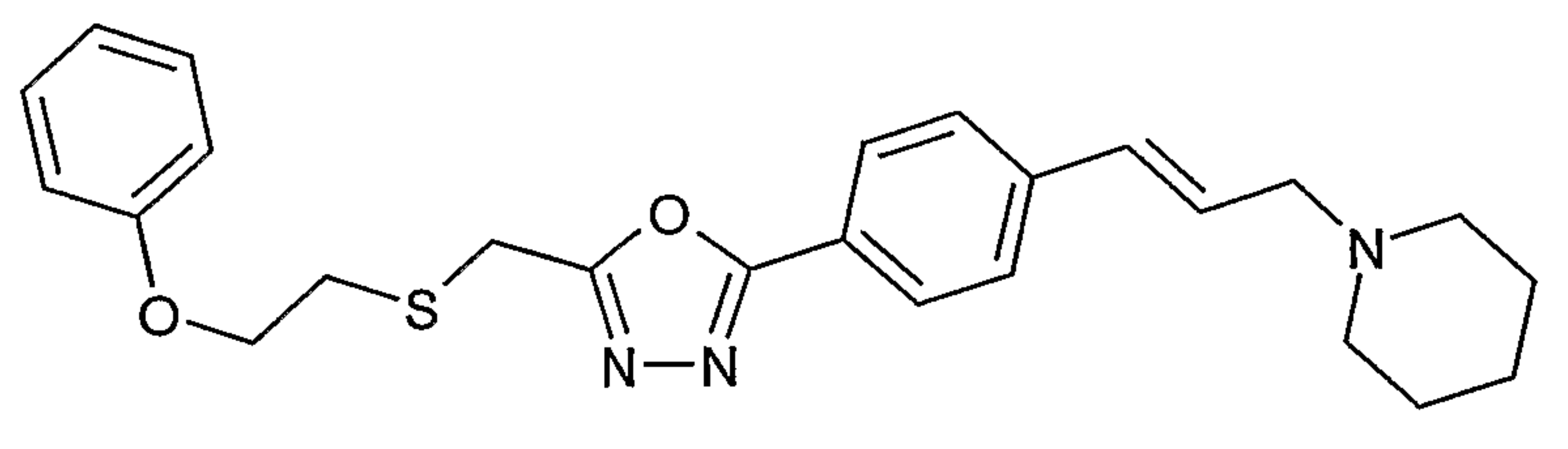
- (3-{4-[5-(Benzo[b]thiophen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,
- Dimethyl-(3-{4-[5-(naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,
- 5 Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,
- 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,3,4]oxadiazole,
- 2-[4-(3-Azetidin-1-yl-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole,
- 10 1-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,
- 1-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,
- 15 1-(2-Dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-urea,
- 1-(2-Dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-urea,
- 1-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea,
- 20 1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea,
- N,N-dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-ethane-1,2-diamine,
- 25 N,N-Dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-propane-1,3-diamine,
- 1-Methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy-methyl}-piperidine,
- 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propenyl)-phenyl]-oxazole,
- 30 1-(2-Diethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

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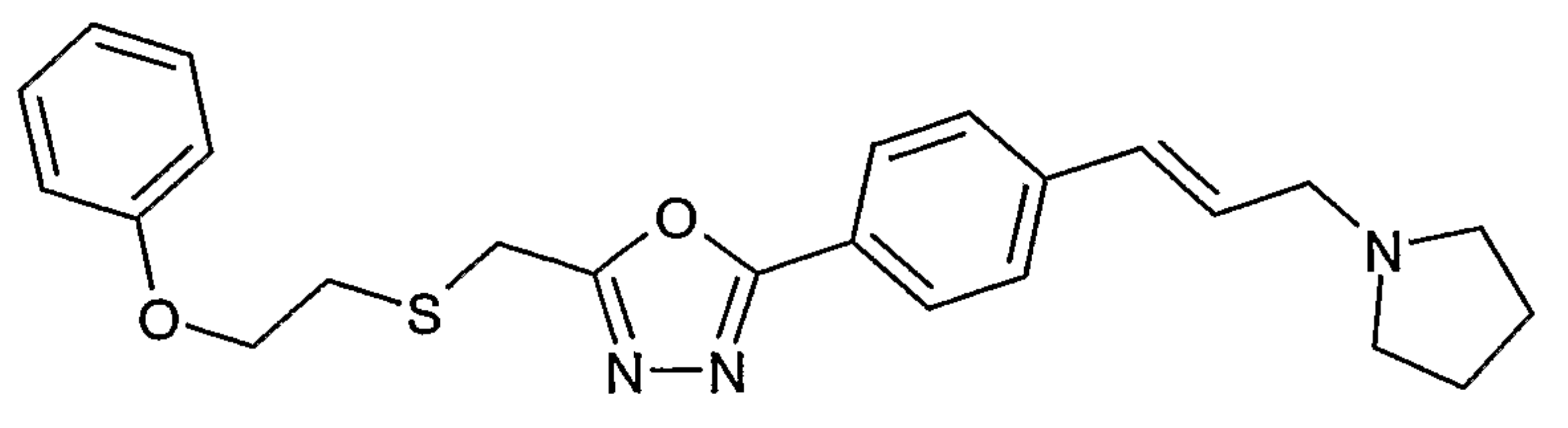
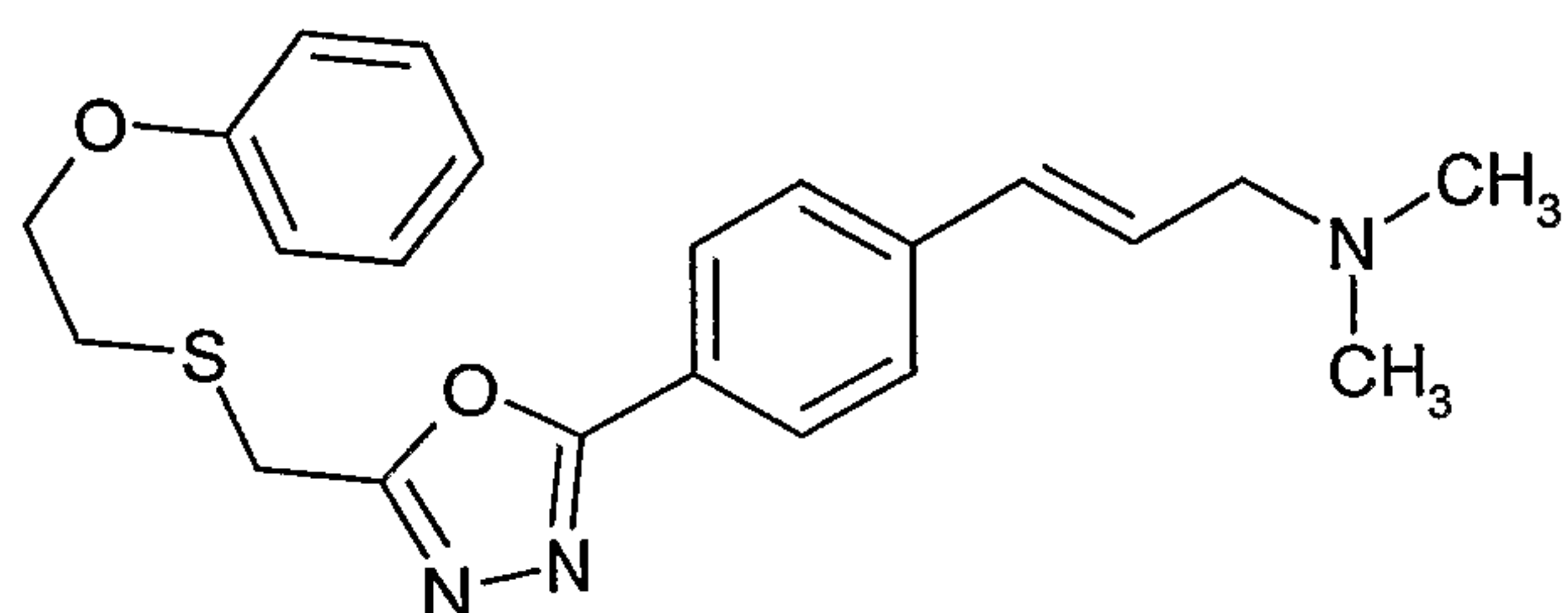
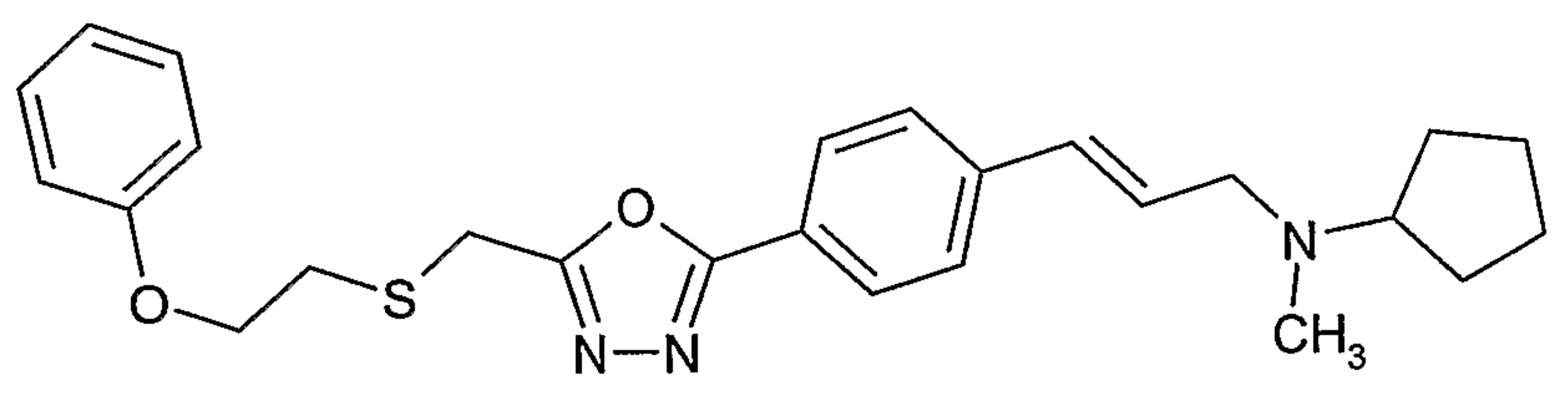
5-(2-Phenoxy-ethylsulfanylmethyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-
[1,2,4]oxadiazole,

Dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenoxy}-
ethyl)-amine, and pharmaceutically acceptable salts, solvates, enantiomers, diastereomers
5 and mixture of enantiomers thereof.

A most preferred compound of the present invention is selected from the group
consisting of:

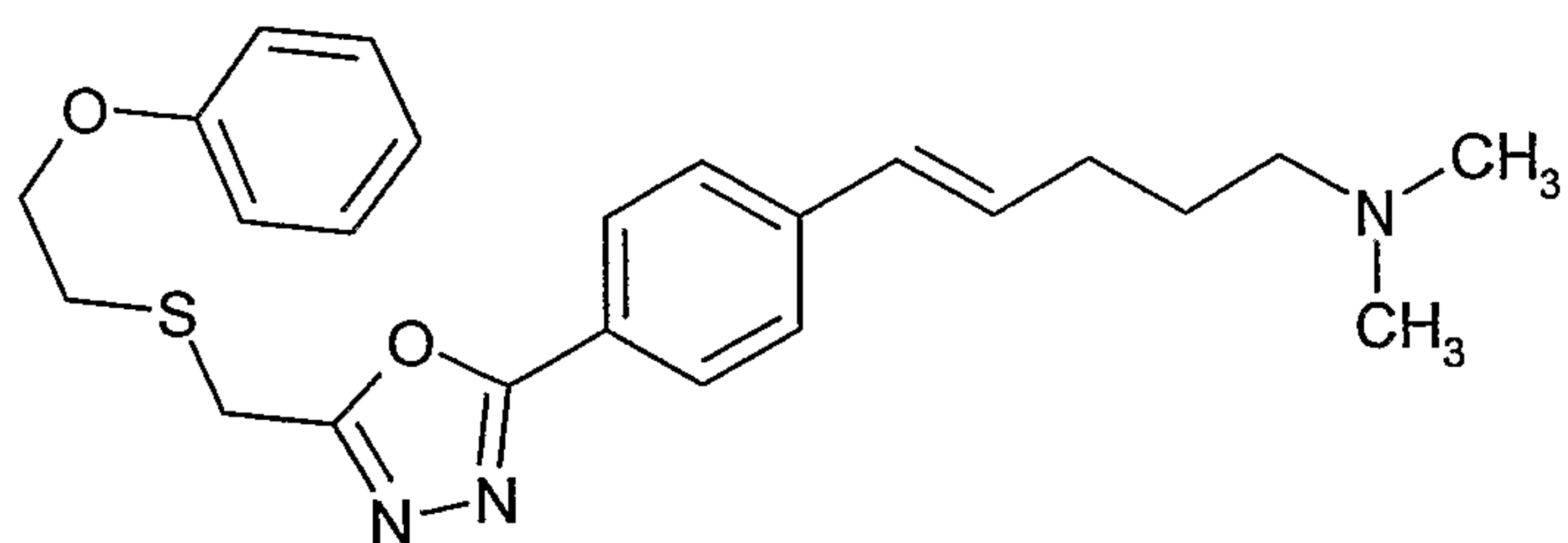


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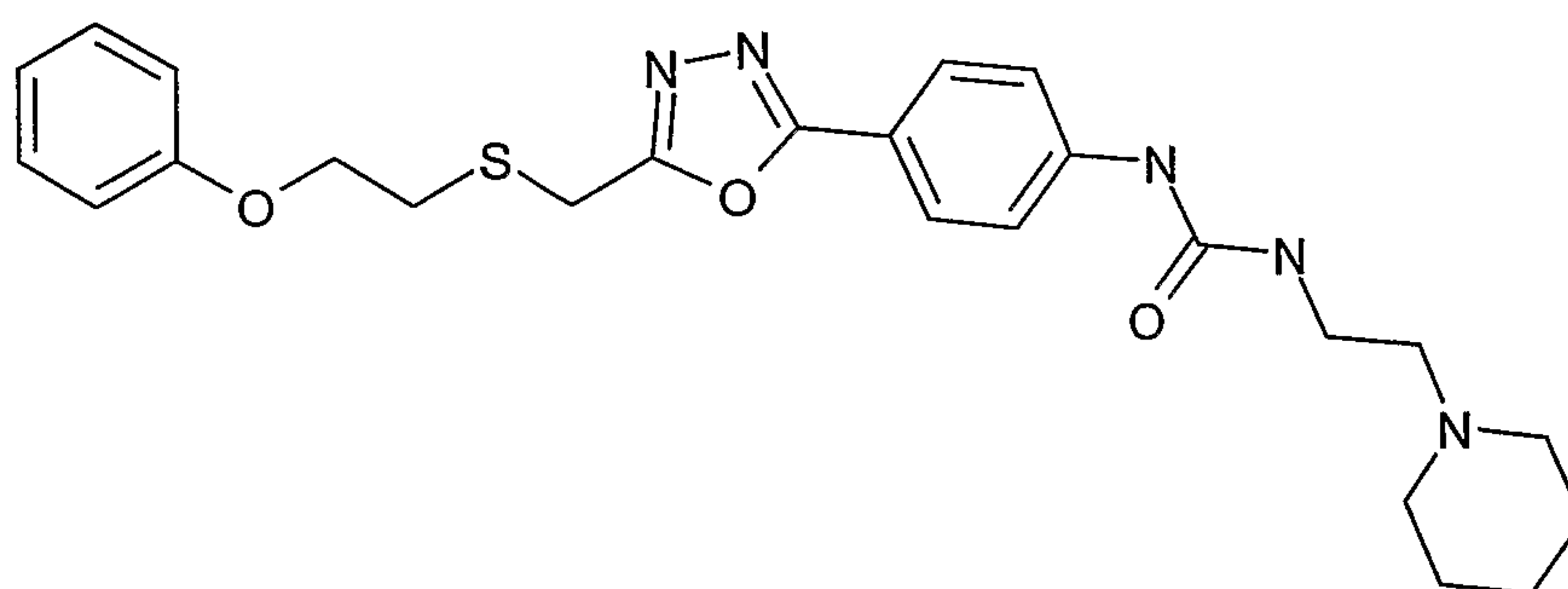


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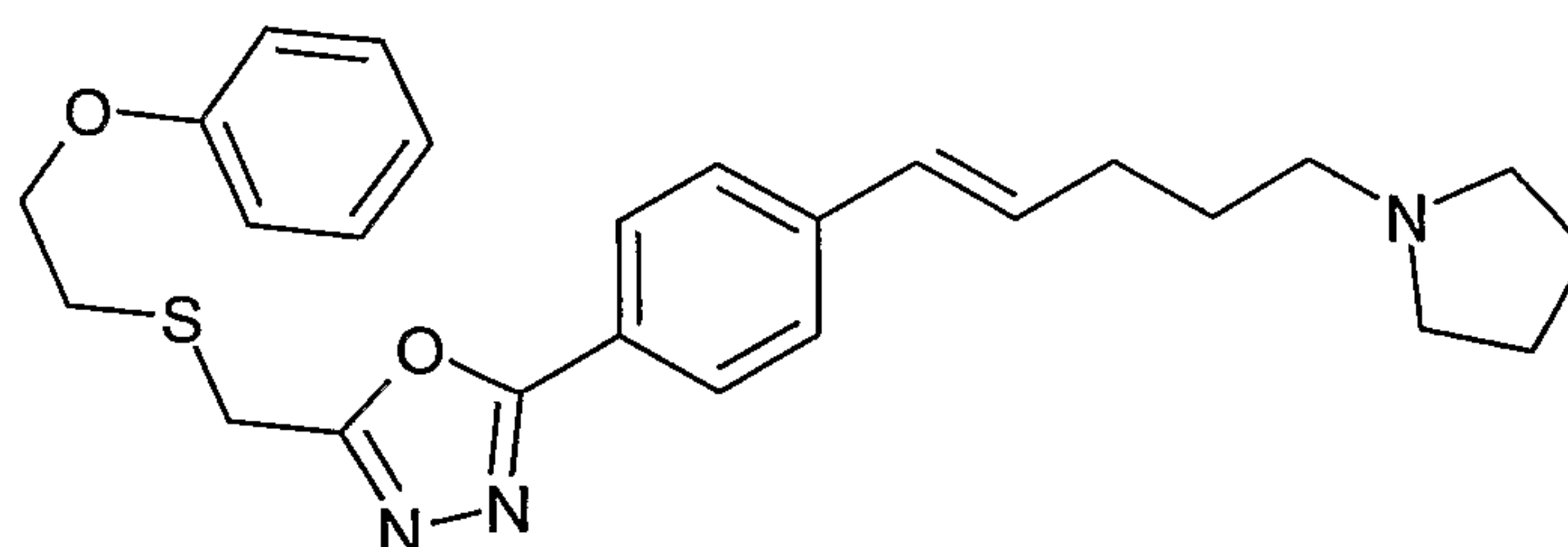
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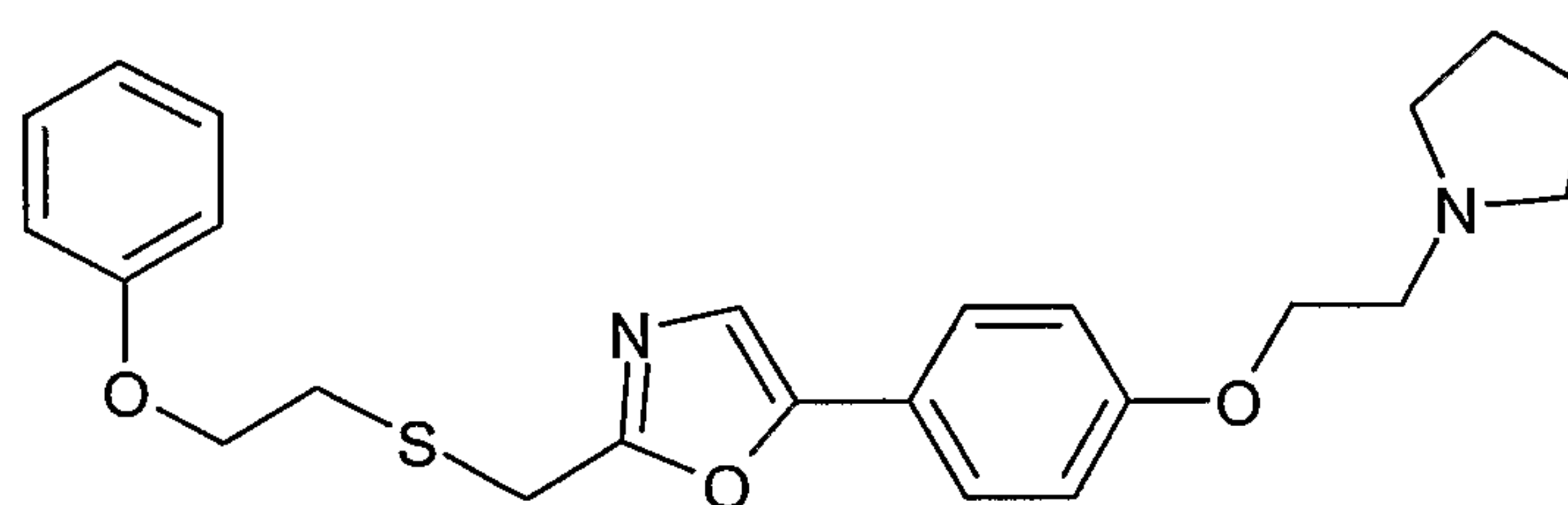
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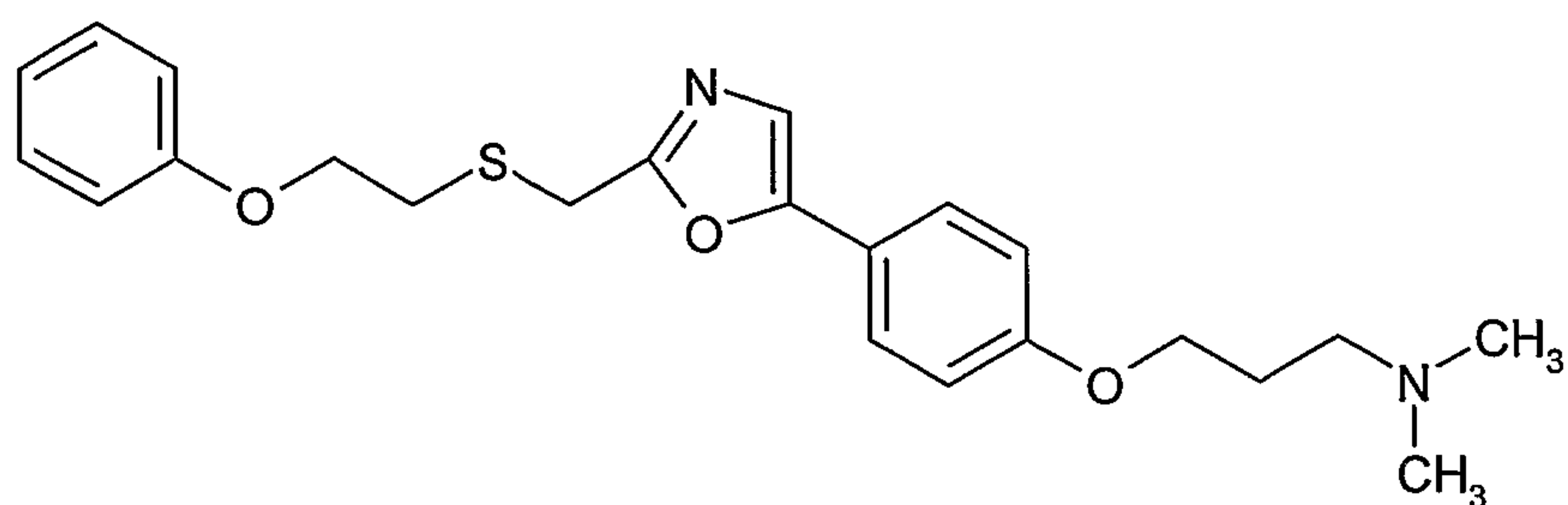
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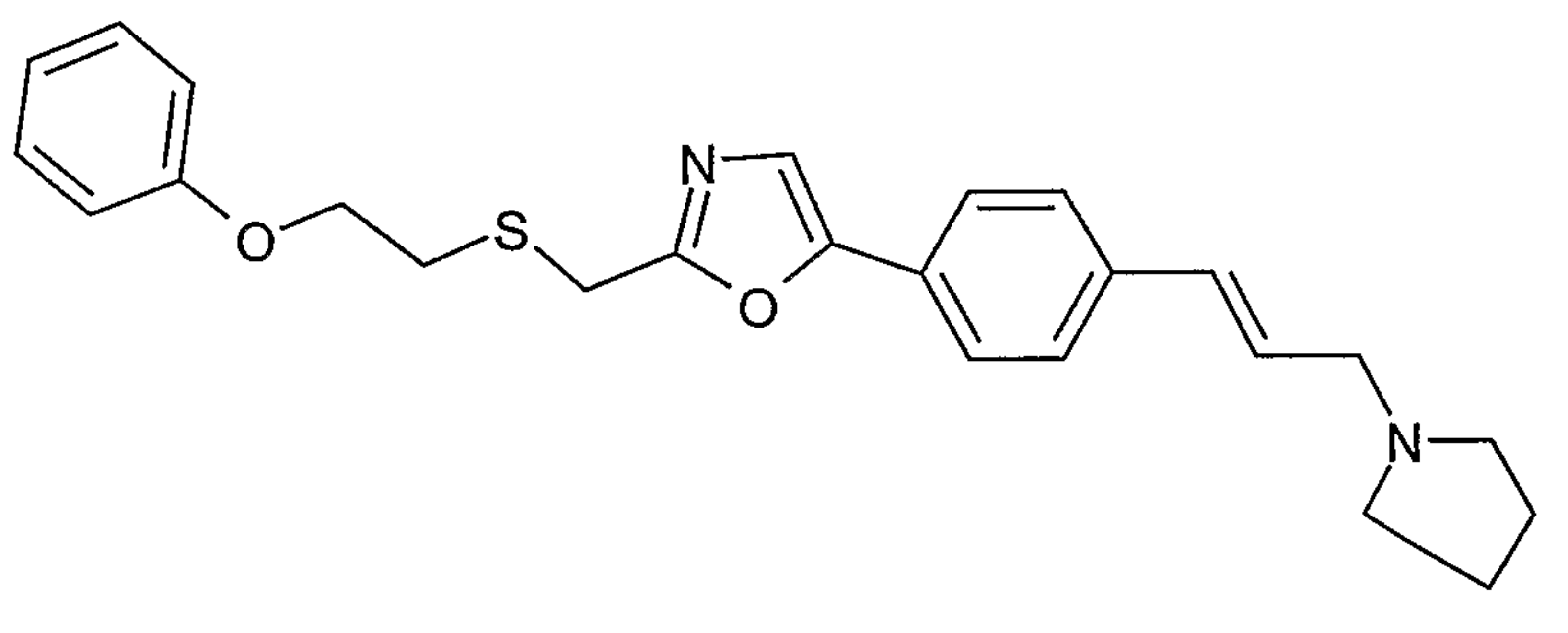


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or a pharmaceutically acceptable salt, solvate, prodrug, enantiomer, or mixture of enantiomers thereof.

5

Preparing Compounds of the Invention

Compounds of formula I may be prepared as described in the following Schemes and Examples. Precursors to the compounds of the invention are prepared by methods known to one of skill in the art. The compounds employed as initial starting materials in the synthesis of the compounds of the invention are well known and, to the extent not commercially available, are readily synthesized by standard procedures commonly employed by those of ordinary skill in the art. More particularly, the compounds of the invention are produced in accordance with the General Methods 1 through 5 that are described in detail below, or analogous methods thereto. These reactions are often carried out in accordance with per se known methods, or analogous methods thereto. Examples of such known methods include the methods described in general reference texts such as Organic Functional Group Preparations, 2nd Edition, 1989; Comprehensive Organic Transformations, VCH Publishers Inc, 1989; Compendium of Organic Synthetic Methods, Volumes 1-10, 1974-2002, Wiley Interscience; March's Advanced Organic Chemistry, Reactions Mechanisms, and Structure, 5th Edition, Michael B. Smith and Jerry March, Wiley Interscience, 2001, Advanced Organic Chemistry, 4th Edition, Part B, Reactions and Synthesis, Francis A. Carey and Richard J. Sundberg, Kluwer Academic / Plenum Publishers, 2000, etc., and references cited therein.

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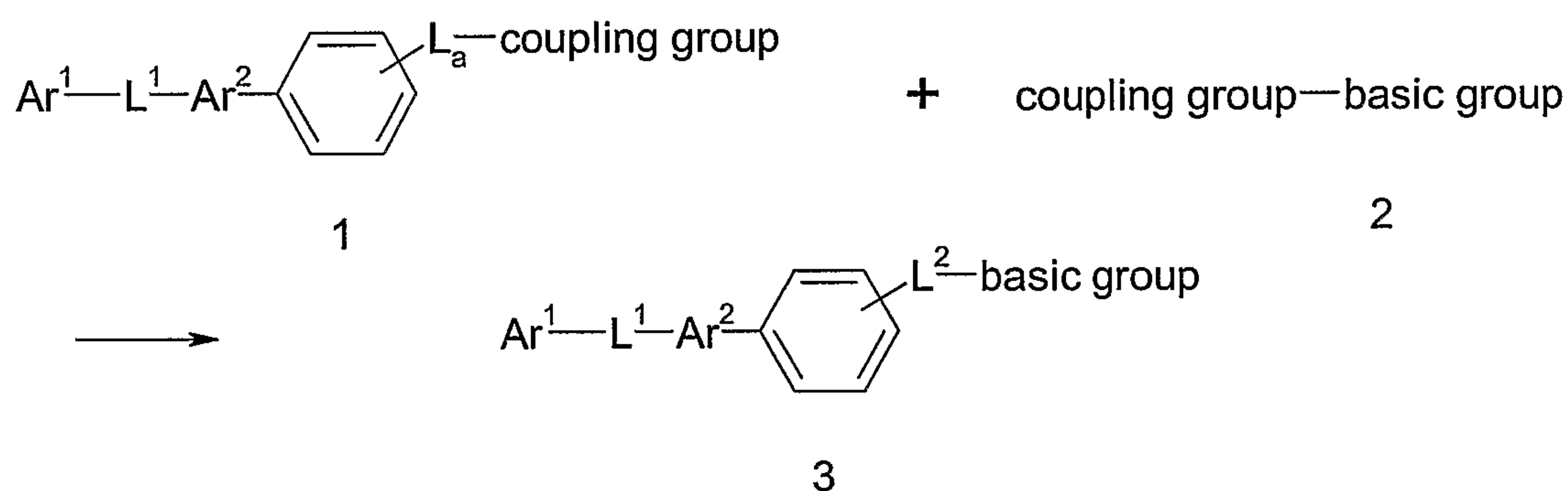
General Method 1: Coupling of the basic group

The compounds of Formula 3 can be prepared by the General Method 1, described in General Scheme 1, via coupling of a compound of Formula 2 containing a basic group with a group of Formula 1, where during the course of the coupling reaction the coupling groups are retained or lost to form the linker L² between the basic group and the phenyl

25

ring. Ar¹, L¹, Ar², L², and basic group are defined as above. In the schemes that follow Ar³ of formula I has been depicted as a phenyl group for convenience only and is not intended to be limiting. Also, L_a is defined as a group that when the coupling process occurs results in the formation of the linker L² defined above. Furthermore, in the schemes that follow, the group L¹ is depicted by the combination of group or groups interspacing or linking the groups Ar¹ and Ar². Similarly, the group L² is depicted by the combination of group or groups interspacing or linking the groups Ar³ and the basic group. The basic group of the compounds of the following schemes in general mean the group -N(R¹R²) unless otherwise indicated. Examples of the General Method 1 are a Displacement Process (Scheme 1a) and a Reductive Amination Process (Scheme 1b).

General Scheme 1: Coupling of Basic group



As outlined in Scheme 1a below, the coupling process of General Method 1 may consist of a displacement process whereby nucleophilic displacement of a leaving group, such as, but not limited to, halogen, triflate, tosylate, brosylate, mesylate, nosylate, nonaflate, tresylate, and the like, of Formula 4, by a nucleophilic basic group of Formula 5 affords the compounds of the invention. A leaving group is defined in one or more of the general reference texts described previously.

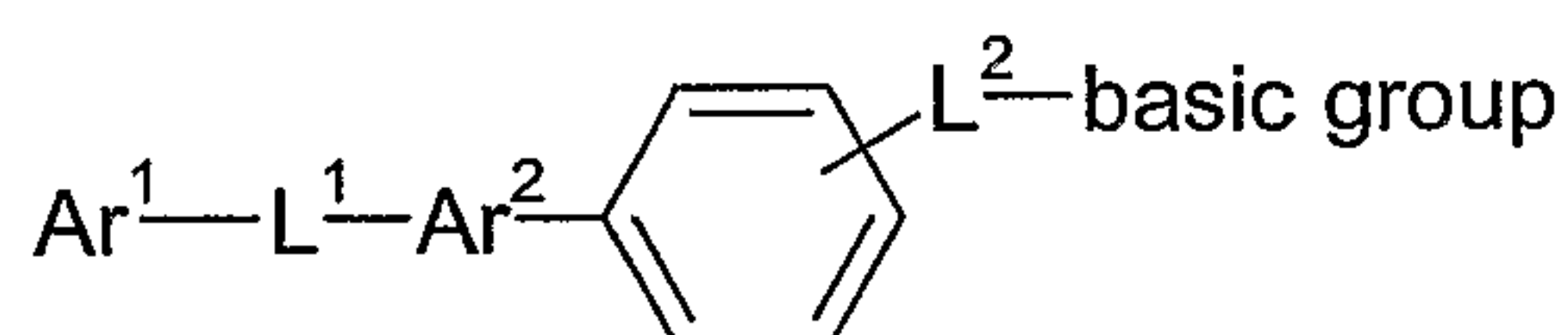
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Scheme 1a: Displacement Process

X = Leaving group (e.g., Cl, Br, I, OMs, OTs, etc)

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One to five equivalents of the nucleophilic basic group of Formula 5 and one to five equivalents of the reactive derivative of Formula 4 may be reacted in the presence, or absence, of an inert solvent. If necessary, the reaction may be carried out in the presence of a catalytic quantity to about five equivalents of a non-interfering base. A non-interfering base is a base suitable for the intended reaction by virtue of the base not deleteriously affecting the reaction. One to two equivalents of base is normally preferable. The reaction is normally carried out between 0 °C and 120 °C. Reaction time is normally 4 to 24 hours.

Nucleophilic basic groups would include, but would not be limited to ammonia, primary and secondary amines, guanidines, and the like. Specific nucleophilic basic groups include ammonia, methylamine, dimethylamine, diethylamine, diisopropylamine, pyrrolidine, piperidine, morpholine, azetidine, thiomorpholine, piperazine, imidazole, and the like. Among the above nucleophilic basic groups dimethylamine, pyrrolidine, and piperidine are preferable.

If necessary, the reaction can be carried out with nucleophilic basic group synthon, i.e., a group that could readily be converted to a basic group by methods known to one skilled in the art. Nucleophilic basic group synthons would include, but would not be limited to, azide, phthalimide, protected amines, hexamethylenetetramine, cyanamide, cyanide anion, and the like. Following the displacement reaction, these groups would then be unmasked under standard conditions to afford the basic group. For example, displacement with potassium phthalimide followed by removal of the phthalimide group

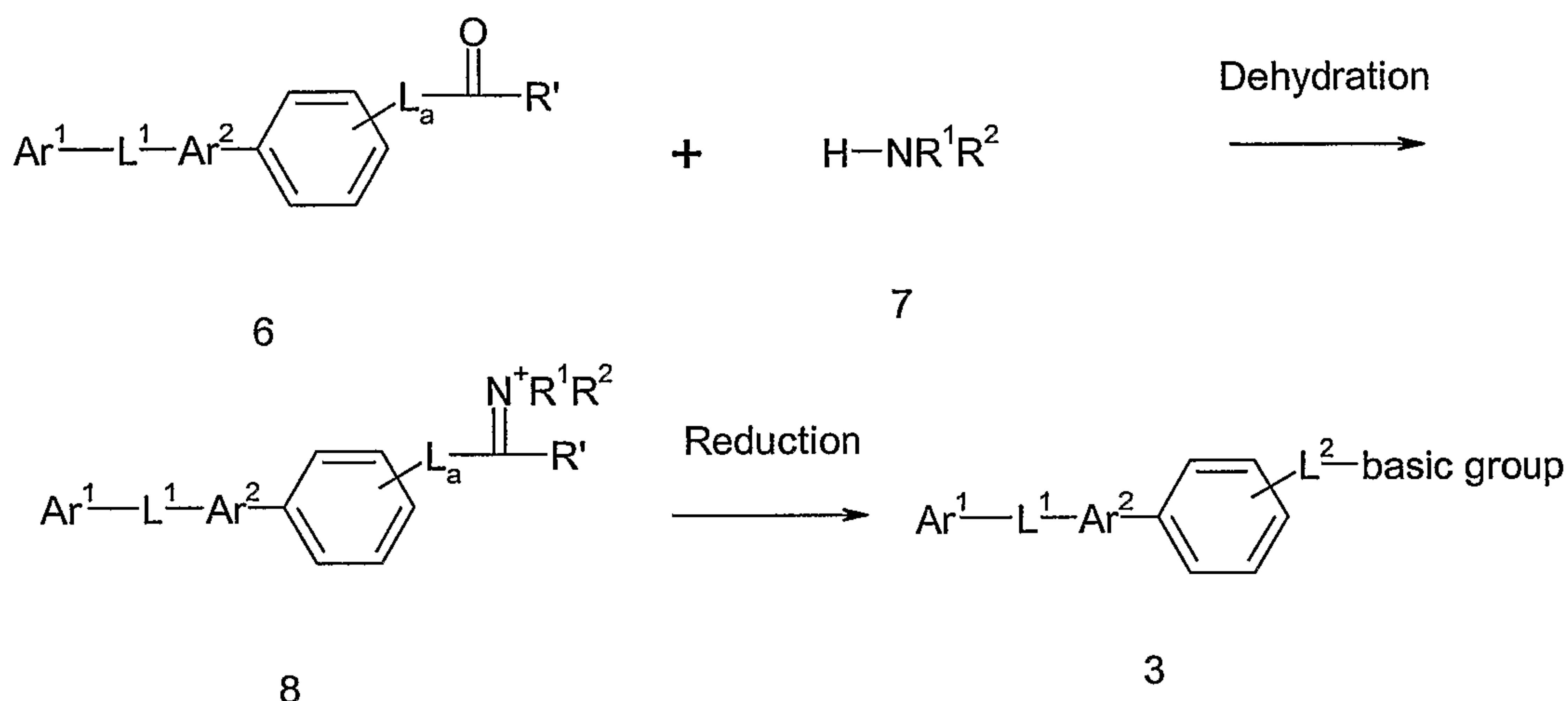
to afford the primary amine as in the Gabriel synthesis (see, March's Advanced Organic Chemistry, Reactions Mechanisms, and Structure, 5th Edition, Michael B. Smith and Jerry March, Wiley Interscience, 2001, Chapter 10, and references cited therein). Application of the synthon equivalent to the basic group applies to the processes described in all of the
5 General Methods 1 through 5.

Examples of "inert solvent" includes amide solvents (preferably DMF or DMAC), sulfoxide solvents (preferably DMSO), sulfone solvents (preferably sulfolane or dimethylsulfone), nitrile solvents (preferably acetonitrile), halogenated hydrocarbon solvents (preferably dichloromethane), aromatic solvents (preferably toluene or benzene),
10 ether solvents (preferably diethylether or THF), ketone solvents (preferably acetone), ester solvents (preferably ethyl acetate), alcohol solvent (preferably MeOH or EtOH), etc. Two or more of the solvents can be mixed in an appropriate ratio for use. Among the above solvents, DMF and DMSO are preferable.

Examples of "base" include, for instance, hydrides of alkali metals and alkaline
15 earth metals (e. g., lithium hydride, sodium hydride, potassium hydride, and the like), amides of alkali metals and alkaline earth metals (e. g., sodium amide, lithium diisopropyl amide, lithium hexamethyldisilazide, and the like), alkoxides (e. g. sodium methoxide, sodium ethoxide, potassium t-butoxide, and the like), inorganic bases, such as hydroxides of alkali metals or alkaline earth metals (e. g., sodium hydroxide, lithium hydroxide,
20 potassium hydroxide, and the like), carbonates and hydrogen carbonates of alkali metals or alkaline earth metals (e. g., potassium carbonate, sodium bicarbonate, sodium carbonate, cesium carbonate, and the like), amine bases (such as, N-methylmorpholine, DBU, DBN, pyridine, 2,6-lutidine, triethylamine, diisopropylethylamine, and the like). Among the above bases, sodium hydride, potassium carbonate, and cesium carbonate are
25 preferable.

As outlined in Scheme 1b below, the coupling process can consist of a Reductive Amination Process. A compound of Formula 6 is condensed with ammonia, or a primary, or secondary amine under dehydration / reduction conditions. Scheme 1b is a process analogous to that described in for example, Chem Pharm Bull 1999, 47 (8), 1154-1156;
30 Synlett 1999, (11), 1781-1783; and J Med Chem 1999, 42 (26), 5402-5414 and references cited therein.

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Scheme 1b: Reductive Amination Process

The carbonyl compound of Formula 6 is reacted with an amine of Formula 7 in an inert solvent under conditions that form the iminium species of Formula 8. The iminium species is reduced *in-situ* to form the compounds of Formula 3. The reaction is normally done in the presence of a dehydrating agent and a reducing agent. Amines of Formula 7 include, but are not be limited to ammonia, primary and secondary amines, and the like. Specific amine groups include ammonia, methylamine, dimethylamine, diethylamine, diisopropylamine, pyrrolidine, piperidine, morpholine, azetidine, thiomorpholine, piperazine, imidazole, and the like. One to five equivalents of the amine group of Formula 7 and one to five equivalents of the reactive derivative of Formula 6 are reacted in the presence, or absence, of an inert solvent. The use of an excess of dehydrating agent is normally preferable. The reaction is carried out in the presence of one to hundred equivalents of a reducing agent. One to three equivalents of reducing agent is preferable. The reaction is normally carried out between 0 °C and 120 °C. Reaction time is normally 4 to 24 hours. For the above amination reaction, MeOH and EtOH are preferable as inert solvents.

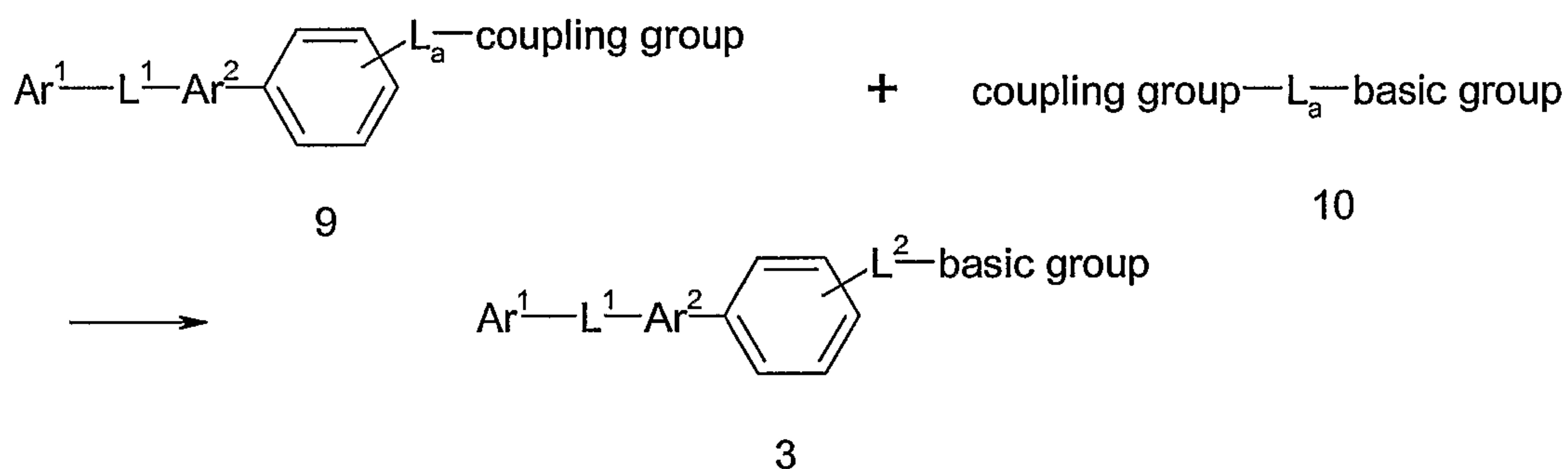
Examples of “dehydrating agents” may be anhydrous molecular sieves beads, anhydrous molecular sieve pellets, powdered anhydrous molecular sieves, anhydrous molecular sieves on supports (such as zeolite), anhydrous magnesium sulfate, anhydrous sodium sulfate, and the like. Among the above dehydrating agents, anhydrous molecular sieves pellets and powdered anhydrous molecular sieves are preferable.

Examples of “reducing agents” include hydrogen gas or hydrogen gas precursor and a hydrogenation catalyst. Other “reducing agents” include sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, sodium borohydride/Ti (Oi-Pr)₄, borohydride-exchange resin, and the like. Examples of “hydrogen gas precursors” include formic acid, 1,4-cyclohexadiene, and the like. Examples of “hydrogenation catalyst” include palladium on carbon, platinum on carbon, rhodium, ruthenium, nickel and the like. The metal can be used as a finely dispersed solid or absorbed on a support, such as carbon or alumina. Among the above reducing agents, sodium cyanoborohydride and sodium triacetoxyborohydride are preferred.

General Method 2: Coupling of the linker group

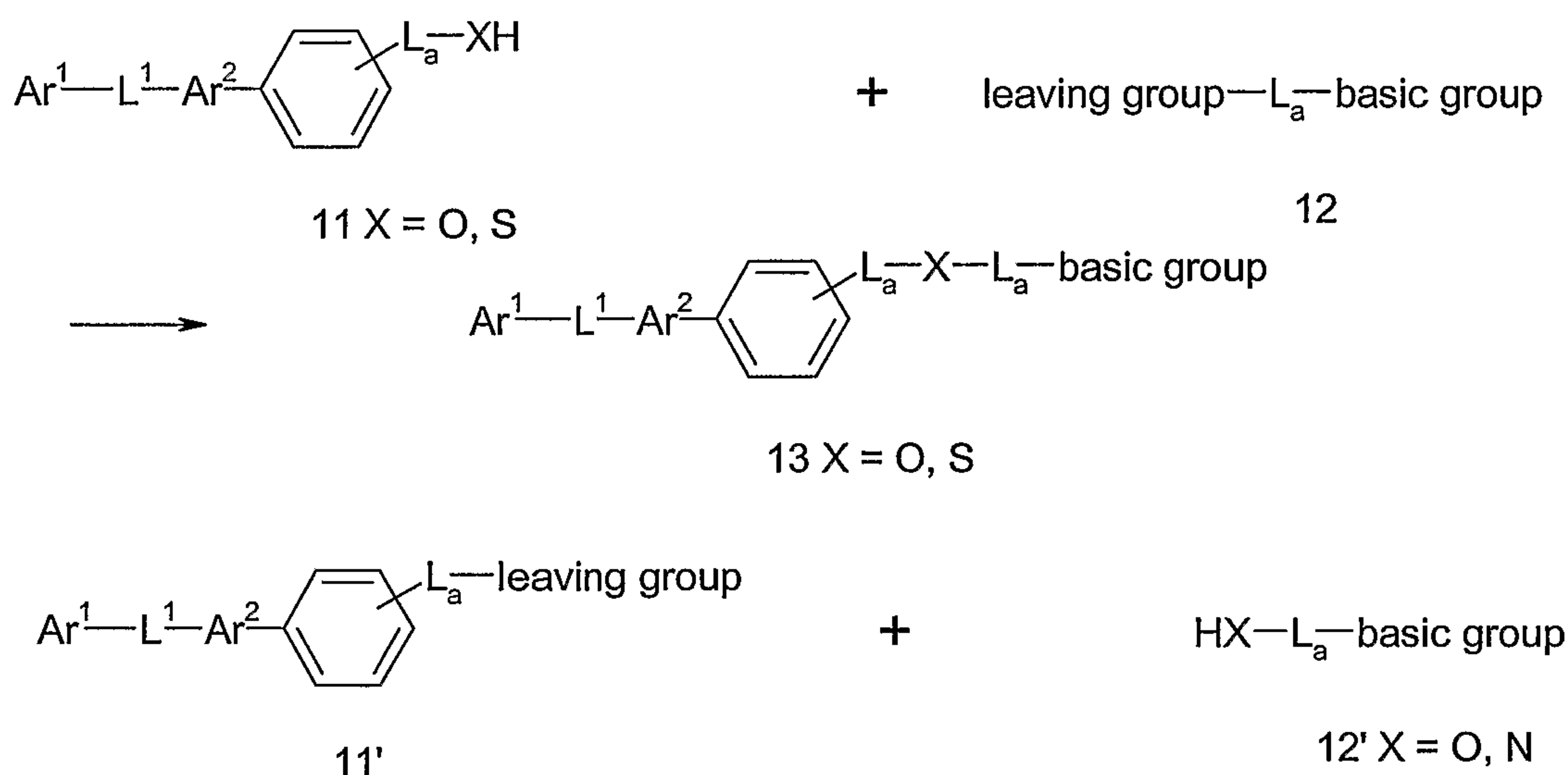
The compounds of Formula 3 can be prepared by the General Method 2, described in General Scheme 2, via reaction of the coupling group of Formula 9 with a coupling group of Formula 10.

General Scheme 2



Examples of the General Method 2 are an Ether/Thioether Alkylation Process (Scheme 2a), an Acylation/Sulfonylation Process (Scheme 2b), Urea/Thiourea/Guanidine Coupling Process (Scheme 2c1, 2c2, 2c3), an Organometallic Process (Scheme 2d), and a Wittig-type Coupling (Scheme 2e). As outlined in Scheme 2a below, the coupling process of General Method 2 can consist of a Ether/Thioether Alkylation Process. Nucleophilic displacement by an alcohol or thiol-containing compound of Formula 11 (or Formula 11') with a compound of Formula 12 (or Formula 12') containing a leaving group affords the ether and thioether compounds of Formula 13. Scheme 2a is a process analogous to that described in The Chemistry of the Ether Linkage; Patai, Wiley, 1967, 446, 460; and in March's Advanced Organic Chemistry, Reactions Mechanisms, and Structure, 5th Edition, Michael B. Smith and Jerry March, Wiley Interscience, 2001, Chapter 10.

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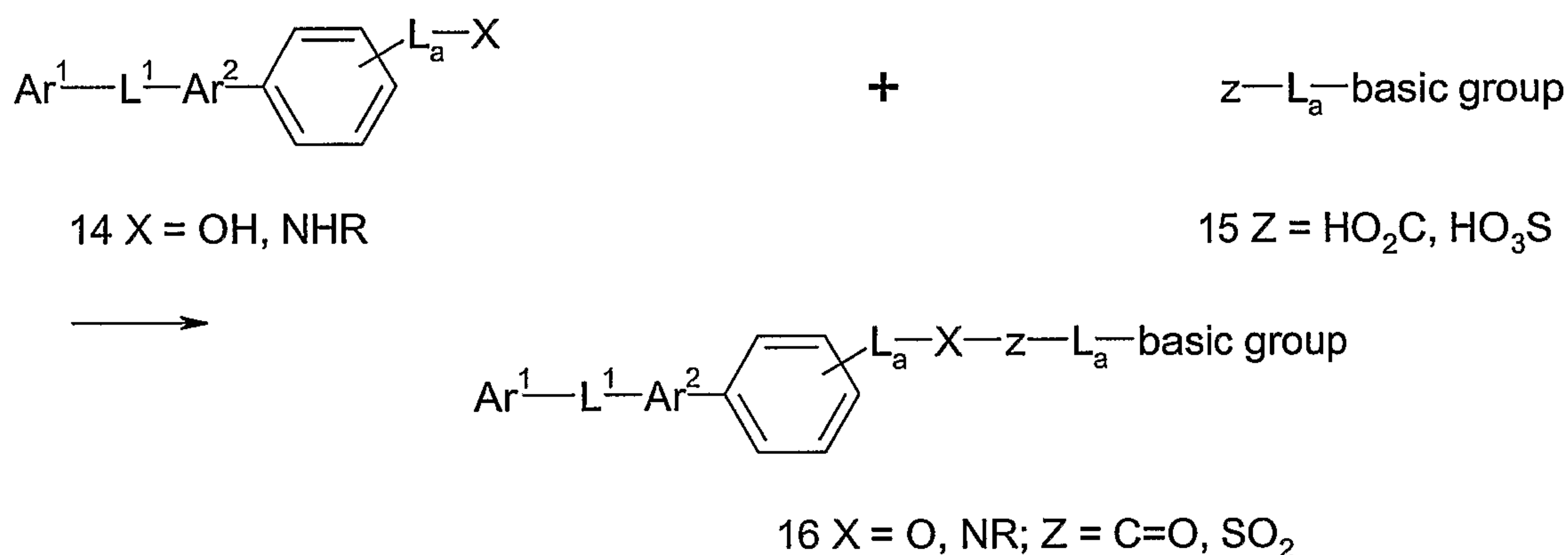
Scheme 2a: Ether/Thioether alkylation process

One to five equivalents of the alcohol or thiol of Formula 11 (or Formula 11') and one to five equivalents of the reactive derivative of Formula 12 (or Formula 12') are reacted in the presence, or absence, of an inert solvent. If necessary, the reaction can be carried out in the presence of a catalytic quantity to ten equivalents of a non-interfering base. One to three equivalents of base is normally preferable. The reaction is typically carried out between 0 °C and 120 °C. Reaction time is typically 4 to 24 hours, but may be longer depending on the particular substrate. Preferred bases for the above reaction include sodium hydride, potassium carbonate and cesium carbonate. If necessary, the reaction may be carried out with basic group synthon incorporated as the basic group in Formula 12, i.e., a group that could readily be converted to a basic group by methods known to one skilled in the art. Basic group synthons would include, but not be limited to, halogen, protected amine, nitrile, aldehyde, and the like. Following the ether/thioether alkylation reaction, these groups would then be unmasked or converted under standard conditions to afford the basic group. For example, alkylation with 1-iodo-4-chloro-butane would give a 4-chlorobutane derivative of compound 11. The chloride could then be converted by the Displacement Process, described above in Scheme 1a, into the basic group of a compound of Formula 13. Among the inert solvents, DMF and DMSO are preferable.

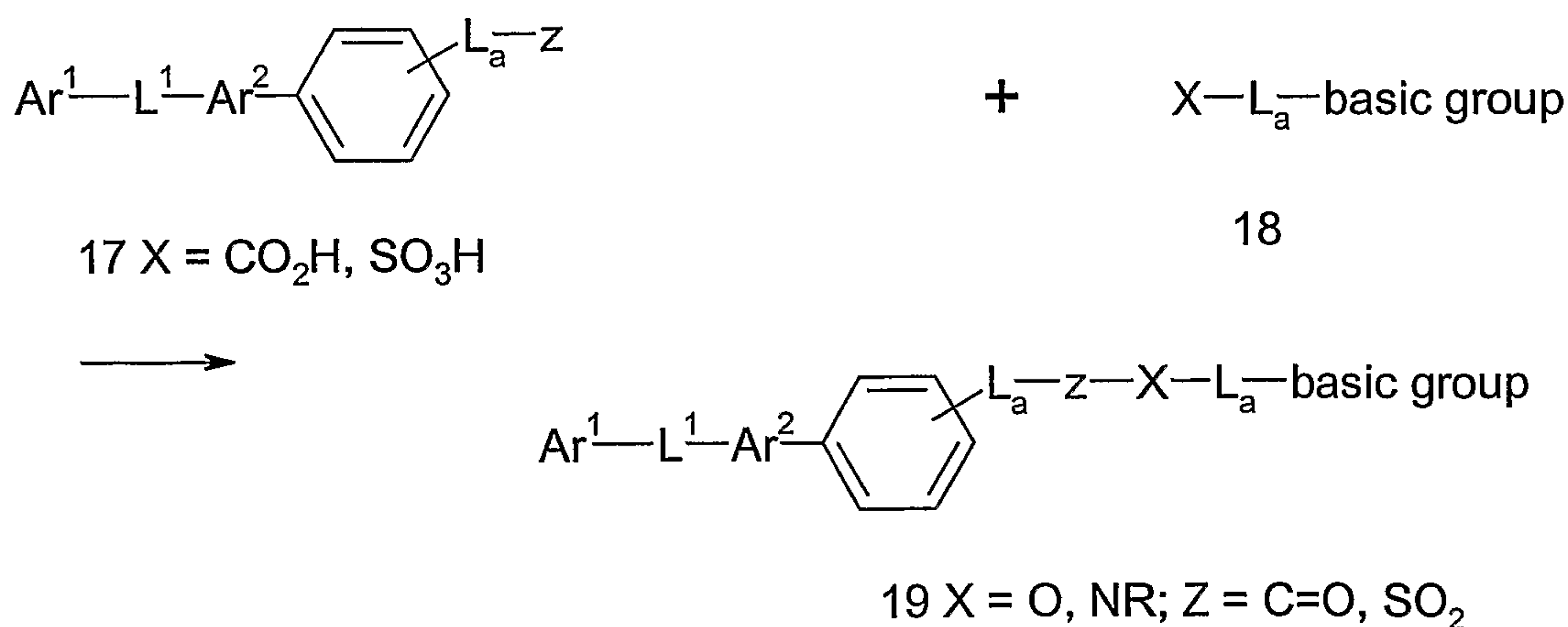
As outlined in Scheme 2b below, the coupling process of General Method 2 can consist of a Acylation/Sulfonylation Process. Acylation or sulfonylation of an alcohol or amine compound of Formula 14 with a carboxylic acid or sulfonic acid compound of Formula 15, affords the ester, amide, sulfonic ester, or sulfonamide compounds of

Formula 16. Alternatively, acylation or sulfonylation of an alcohol or amine compound of Formula 18 with a carboxylic acid or sulfonic acid compound of Formula 17 affords the ester, amide, sulfonic ester, or sulfonamide compounds of Formula 19. If necessary, the reaction can be carried out with a basic group synthon incorporated as the basic group in Formula 15 or Formula 18, i.e., a group that could readily be converted to a basic group by methods known to one skilled in the art. Basic group synthons would include, but not be limited to, halogen, protected amine, nitrile, aldehyde, and the like. Following the Acylation/Sulfonylation reaction, these groups would then be unmasked or converted under standard conditions to afford the basic group.

10

Scheme 2b: Acylation/sulfonylation process

or,



The carboxylic acid (or sulfonic acid) residue of compound 15 (or compound 17) is activated for coupling as a “reactive acylating agent.” “Reactive acylating agents” are described in detail in Advanced Organic Chemistry, 4th Edition, Part B, Reactions and

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Synthesis, Francis A. Carey and Richard J. Sundberg, Kluwer Academic / Plenum Publishers, 2000, Chapter 3, and references cited therein. The "reactive acylating agent" can be formed and isolated, then reacted with the compound of Formula 14 (or 18), or formed *in situ* and reacted with the compound of Formula 14 (or 18), to form the
5 compound of Formula 16 (or 19).

One to five equivalents of the "reactive acylating agent" of compound 15 (or compound 17) and one to five equivalents of compound of Formula 14 (or 18) are reacted in an inert solvent. If necessary the reaction may be carried out in the presence of one to five equivalents of 1-hydroxybenzotriazole, 1-hydroxy-7-azabenzotriazole, and (or) a
10 catalytic quantity to five equivalents of a base. The reaction is normally carried out between 0 °C and 120 °C. Reaction time is normally 4 to 48 hours.

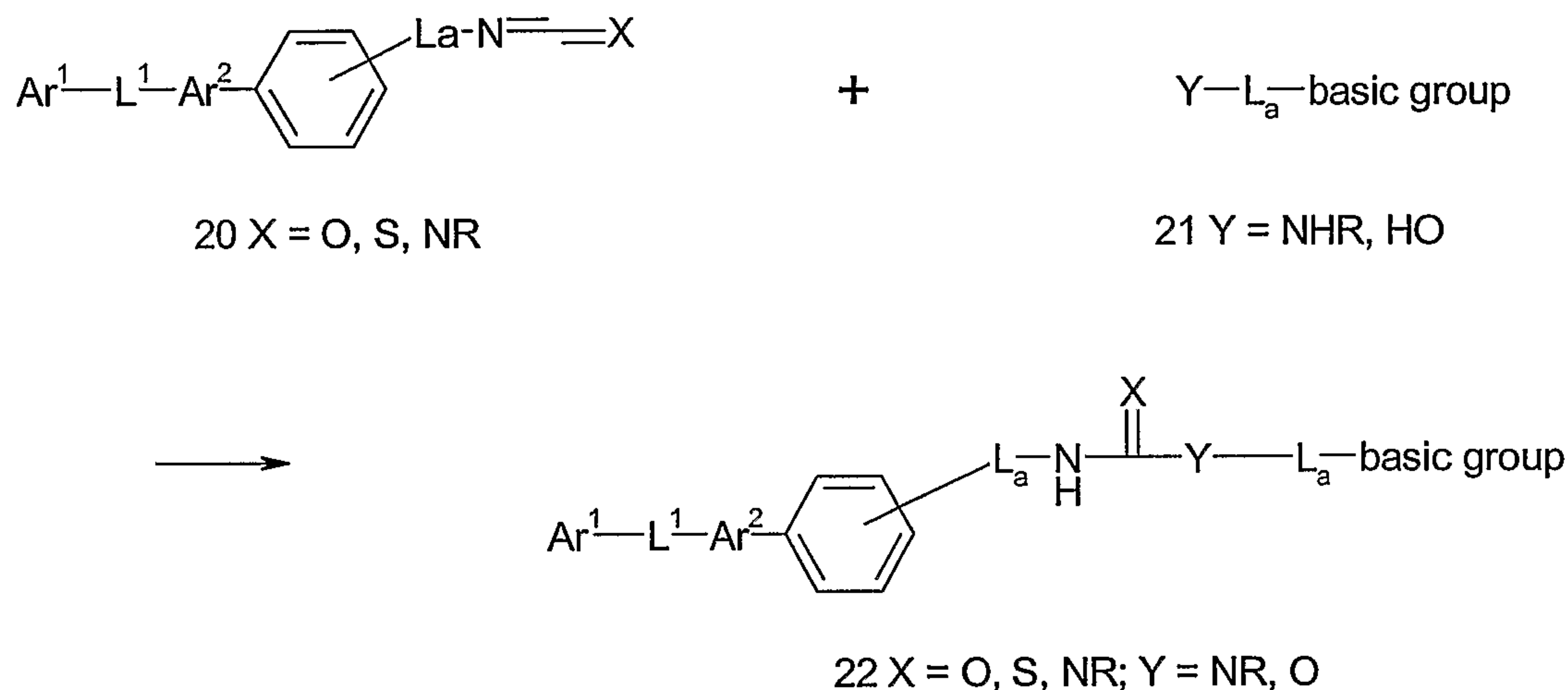
Examples of "reactive acylating agent" of compound 15 (or compound 17) include acid halides (e.g., acid chloride, acid bromide, and the like), mixed acid anhydrides (e. g., acid anhydrides with C₁-C₆ alkyl-carboxylic acid, C₆-C₁₀ aryl-carboxylic acid, and the
15 like), activated esters (e. g., esters with phenol which may have substituents, 1-hydroxybenzotriazole, N-hydroxysuccinimide, 1-hydroxy-7-azabenzotriazole, and the like), thioesters (such as, 2-pyridinethiol, 2-imidazolethiol, and the like), N-acylimidazoles (e.g., imidazole, and the like), etc.

A "reactive acylation agent" may also be formed reacting the carboxylic acid (or
20 sulfonic acid) residue of compound 15 (or compound 17) with a dehydration/condensation agent. Examples of a "dehydration/condensation agent" include dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), and the like. Preferred solvents for the above reaction include acetonitrile, THF, and dichloromethane.

25 Preferred bases for the above reaction include triethylamine, pyridine, and dimethylaminopyridine are preferable.

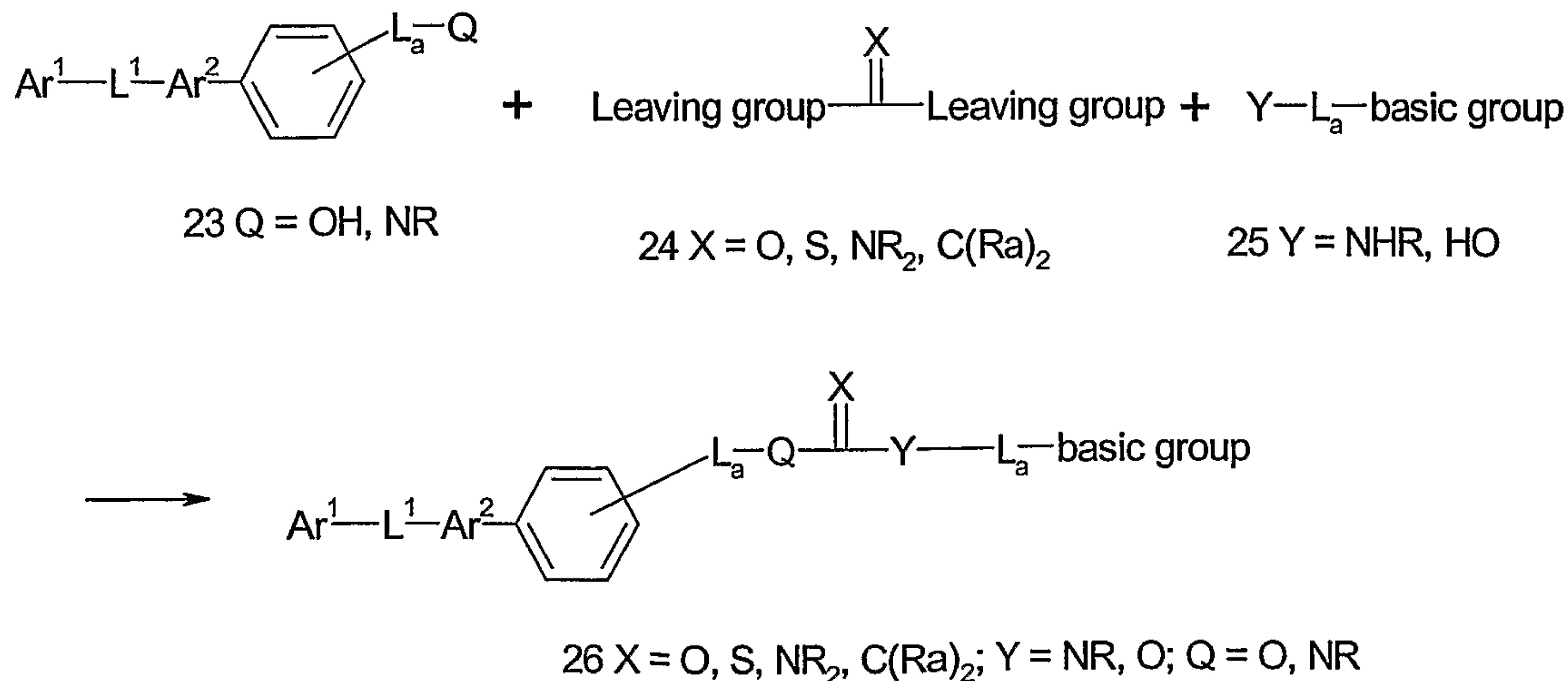
As outlined in Scheme 2c1, Scheme 2c2, and Scheme 2c3 below, the coupling process of General Method 2 can consist of a Urea/Thiourea/Guanidine/Carbamate-Type Coupling Process. The processes described are analogous to that described in US Patents 5,849,769
30 and 5,593,993, and references cited therein.

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Scheme 2c1: Urea/Thiourea/Guanidine/Carbamate-Type coupling

One to five equivalents of the isocyanate, isothiocyanate, carbodiimide of Formula 20 and one to five equivalents of compound of Formula 21 are reacted in an inert solvent. The reaction is typically carried out between 0 °C and 150 °C. Preferred reaction time is
 5 between 4 to 48 hours. Preferred solvents for the above reaction include acetonitrile, DMF, DMSO, THF, and dichloromethane.

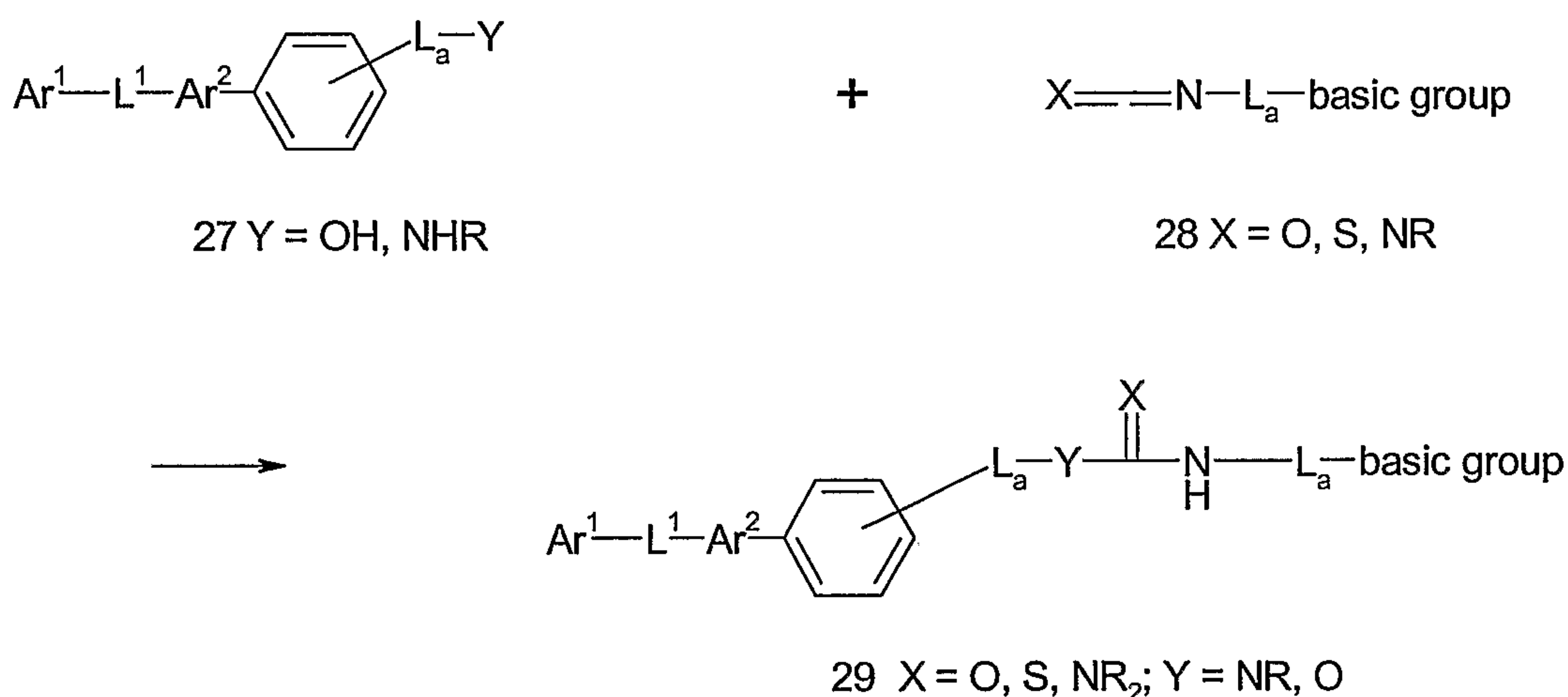
If necessary, the reaction can be carried out with a basic group synthon incorporated as the basic group wherein a synthon is as described earlier. Following the Urea/Thiourea/Guanidine/Carbamate-Type Coupling Process, these groups would then be
 10 unmasked or converted under standard conditions to afford the basic group.

Scheme 2c2: Urea/Thiourea/Guanidine/Carbamate-Type coupling

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Approximately one equivalent of the compound of Formula 23 and one equivalent of compound of Formula 24 and one equivalent of the compound of Formula 25 are reacted in an inert solvent. The reaction is typically carried out between 0 °C and 150 °C. Reaction time is normally 4 to 48 hours. The sequence of addition depends upon the reactivity of the individual reagents. The intermediate addition product may be isolated and subsequently be condensed with the second reagent. The reaction may or may not require the addition of a catalyst. Preferred solvents for the above reaction include acetonitrile, DMF, DMSO, THF, toluene, isopropanol, and dichloromethane. Acids and bases as described previously may be used to catalyze the above reaction.

10 **Scheme 2c1: Urea/Thiourea/Guanidine/Carbamate-Type coupling**

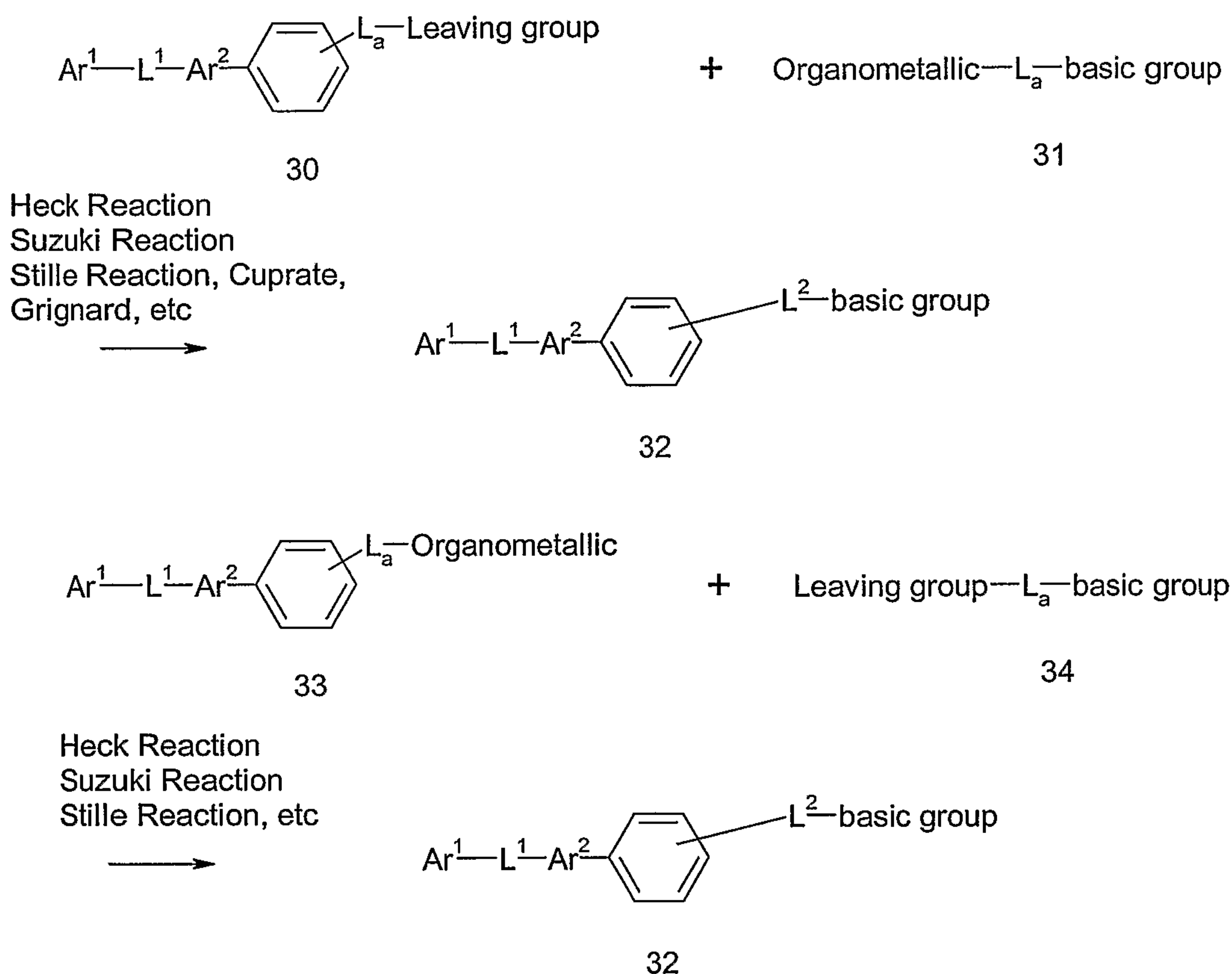


One to five equivalents of the isocyanate, isothiocyanate, carbodiimide of Formula 28 and one to five equivalents of compound of Formula 27 are reacted in an inert solvent. The reaction is normally carried out between 0 °C and 150 °C. Reaction time is normally 4 to 48 hours.

As outlined in Schemes 2d below, the coupling process of General Method 2 may consist of a Organometallic Coupling Process.

Scheme 2d: Organometallic Coupling Process

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The compound of Formula 30 (or Formula 34) is coupled with an organometallic compound of Formula 31 (or Formula 33) (containing a basic group, or basic group precursor) in an Organometallic Coupling Process to afford the compounds of the invention of Formula 32.

“Organometallic Coupling Processes” include “palladium-catalyzed cross coupling reactions,” such as, Heck-type coupling reactions, Suzuki-type coupling reactions and Stille-type coupling reactions. Other organometallic coupling reactions include, organocuprate coupling reactions, Grignard coupling reactions, and the like. A general description of Organometallic Coupling is given in detail in Advanced Organic Chemistry, 4th Edition, Part B, Reactions and Synthesis, Francis A. Carey and Richard J. Sundberg, Kluwer Academic / Plenum Publishers, 2000, Chapters 7 and 8, and references cited therein.

In Scheme 2d. the compound of Formula 30 (or Formula 34) is coupled with the organometallic reagent of Formula 31 (or Formula 33) in the presence, or absence, of a transition metal catalyst, and/or a phosphine or arsine, and/or a base in an inert solvent. Other additives, such as, copper salts, silver salts, and the like may be added. Approximately one equivalent of the compound of Formula 30 (or Formula 34) is reacted

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with one to five equivalents of the compound of Formula 31 (or Formula 33) with the appropriate additives in an inert solvent. The reaction is normally carried out between -78 °C and 200 °C for between 4 to 72 hours.

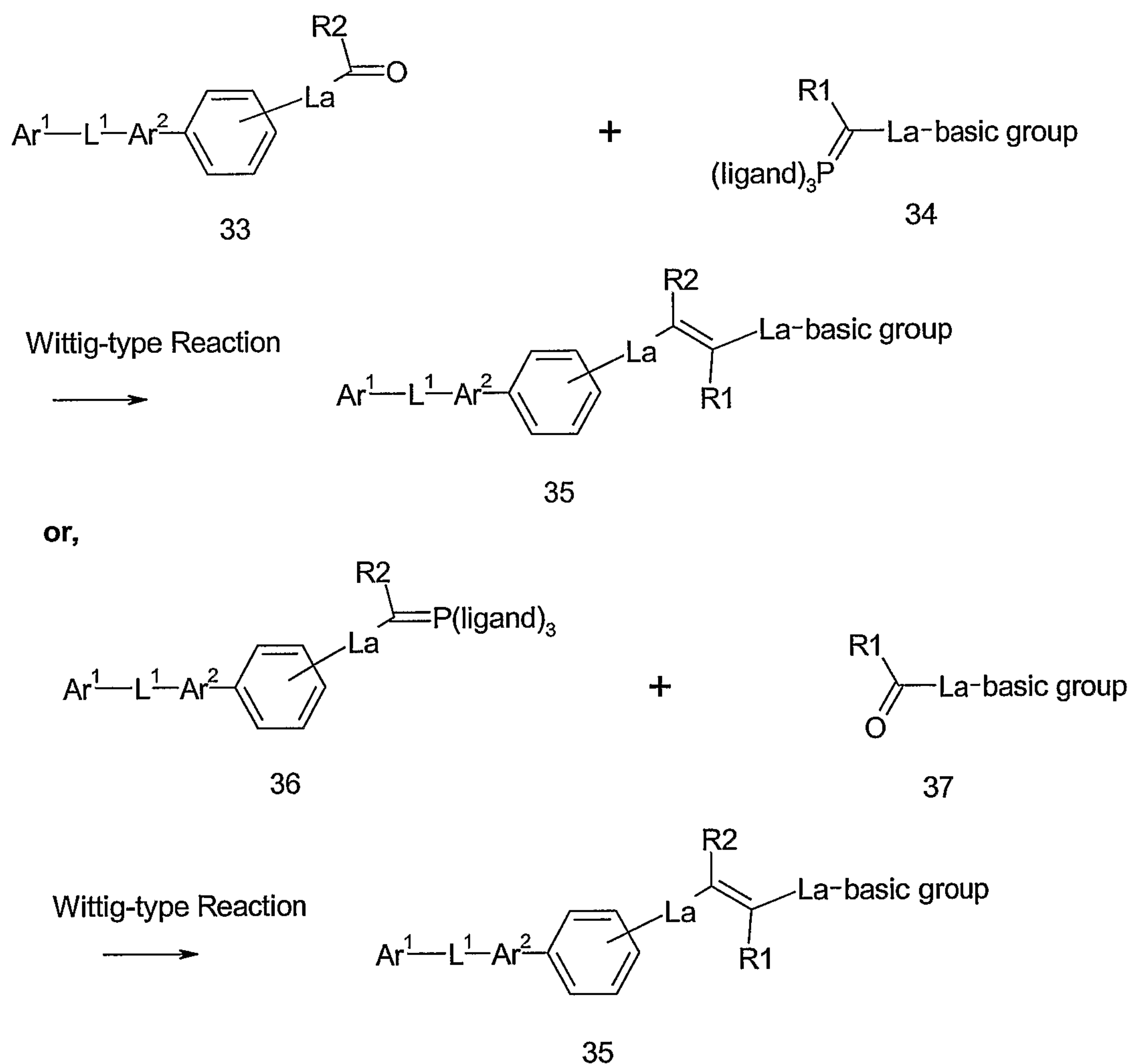
Examples of "organometallic reagents" include, organomagnesium, organozinc, mixed organocuprate, organostannane, or organoboron compounds, and the like. Examples of "transition metal catalysts" include, palladium and nickel catalysts, such as, Pd(OAc)₂, Pd (PPh₃)₄, PdCl₂, Pd(PPh₃)Cl₂, Pd(OCOCF₃)₂, (CH₃C₄H₅P)₂PdCl₂, [(CH₃CH₂)₃P]₂PdCl₂, [(C₆H₁₁)₃P]₂PdCl₂, [(C₆H₅)₃P]₂PdBr₂, Ni(PPh₃)₄, (C₆H₄CH=CHCOCH=CHC₆H₅)₃Pd, and the like. Among the above transition metal catalysts, Pd(OAc)₂, Ni(PPh₃)₄, and Pd(PPh₃)₄ are preferable.

Examples of "phosphines or arsines" include, a trialkyl or triarylphosphine or arsine, such as triisopropylphosphine, triethylphosphine, tricyclopentylphosphine, triphenylphosphine, triphenylarsine, 2-furylphosphine, tri-o-tolylphosphine, tricyclohexylphosphine, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, 2-(Di-*t*-butylphosphino)biphenyl, and the like. Among the above "phosphines and arsines," tri-o-tolylphosphine, triphenylarsine, and tricyclohexylphosphine are preferable.

Examples of "other additives" include, copper salts, zinc salts, lithium salts, ammonium salts and the like. Among the above "other additives," CuI, LiCl, and n-Bu₄N⁺Cl⁻ are preferable. If necessary, the reaction can be carried out with a basic group synthon incorporated as the basic group as described previously. As outlined in Schemes 2e below, the coupling process of General Method 2 can consist of a Wittig-type Coupling Process. The compound of Formula 33 (or Formula 37) is coupled with the phosphorus ylene (or ylide) reagent of Formula 34 (or Formula 36) to afford the compounds of Formula 35 of the invention. A general description of Wittig-type Coupling Reactions is given in detail in general reference texts such as Advanced Organic Chemistry, 4th Edition, Part B, Reactions and Synthesis, Francis A. Carey and Richard J. Sundberg, Kluwer Academic / Plenum Publishers, 2000, Chapter 2, and references cited therein.

Scheme 2e: Wittig-type couplings

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The compound of Formula 33 (or Formula 37) is coupled with the phosphorus ylene (or ylide) reagent of Formula 34 (or Formula 36) in the presence, or absence, a base in an inert solvent to form the compounds of the invention of Formula 35. Other additives, such as, lithium salts, sodium salts, potassium salts, and the like may be added.

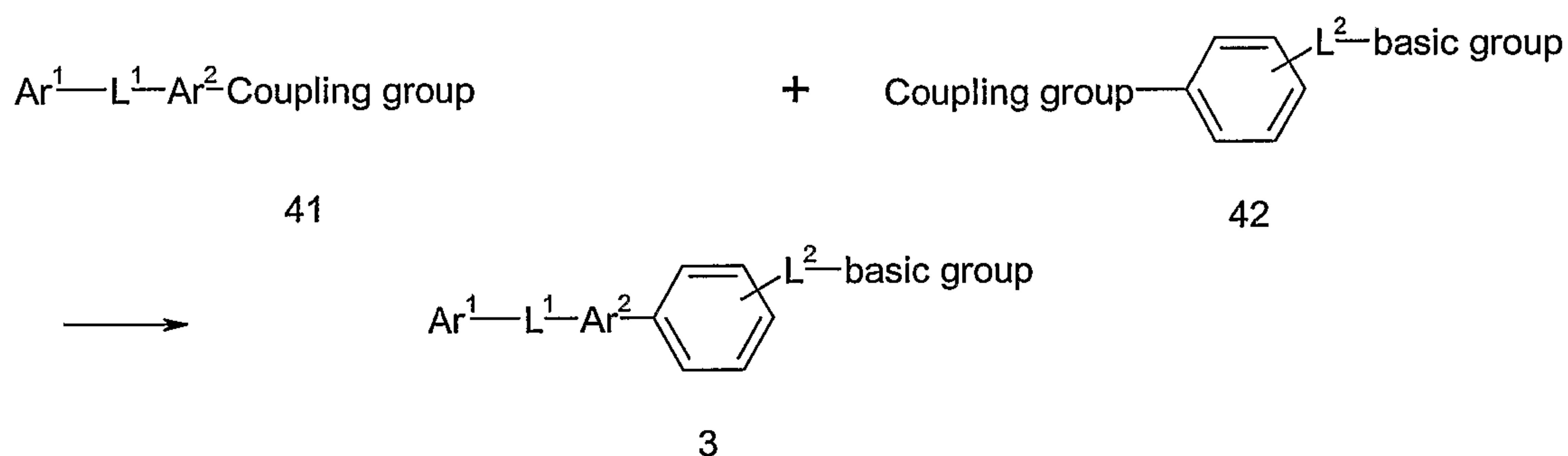
Approximately one to five equivalents of the compound of Formula 33 (or Formula 37) is reacted with one to five equivalents of the compound of Formula 34 (or Formula 36) with the appropriate additives in an inert solvent. The reaction is normally carried out between 78 °C and 120 °C for between 2 to 72 hours. The Wittig reaction product may be reduced to form other compounds of the invention using reducing agents known to one of skill in the art and/or described previously. Preferred bases for the above organometallic reactions include, sodium hydride, DBU, potassium t-butoxide, and lithium hexamethyldisilazide.

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General Method 3: Coupling of the five-membered ring heterocycle and phenyl groups

The compounds of Formula 3 can be prepared by the General Method 3, described in General Scheme 3, via coupling of the compounds of Formula 38 with a compound of Formula 39. An example of the General Method 3 is a Aryl Coupling Process (Scheme 3a). The aryl-coupling reaction is carried out in accordance with per se known methods, or analogous methods thereto, such as those described in the general reference texts discussed previously.

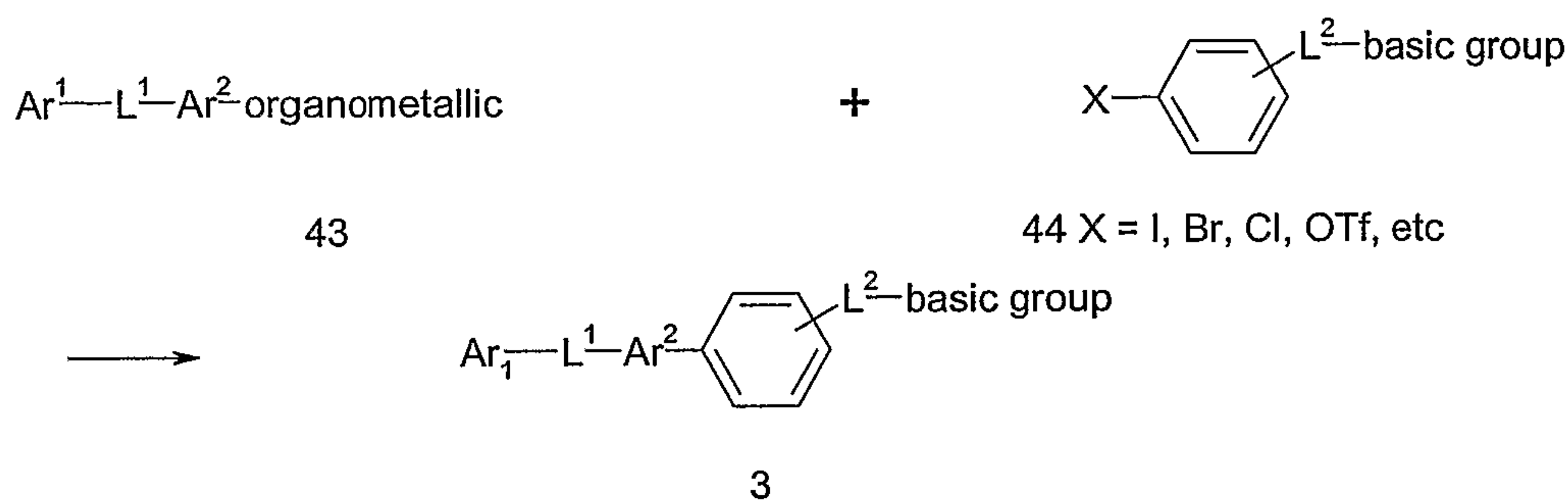
General Scheme 3: Aryl-coupling process



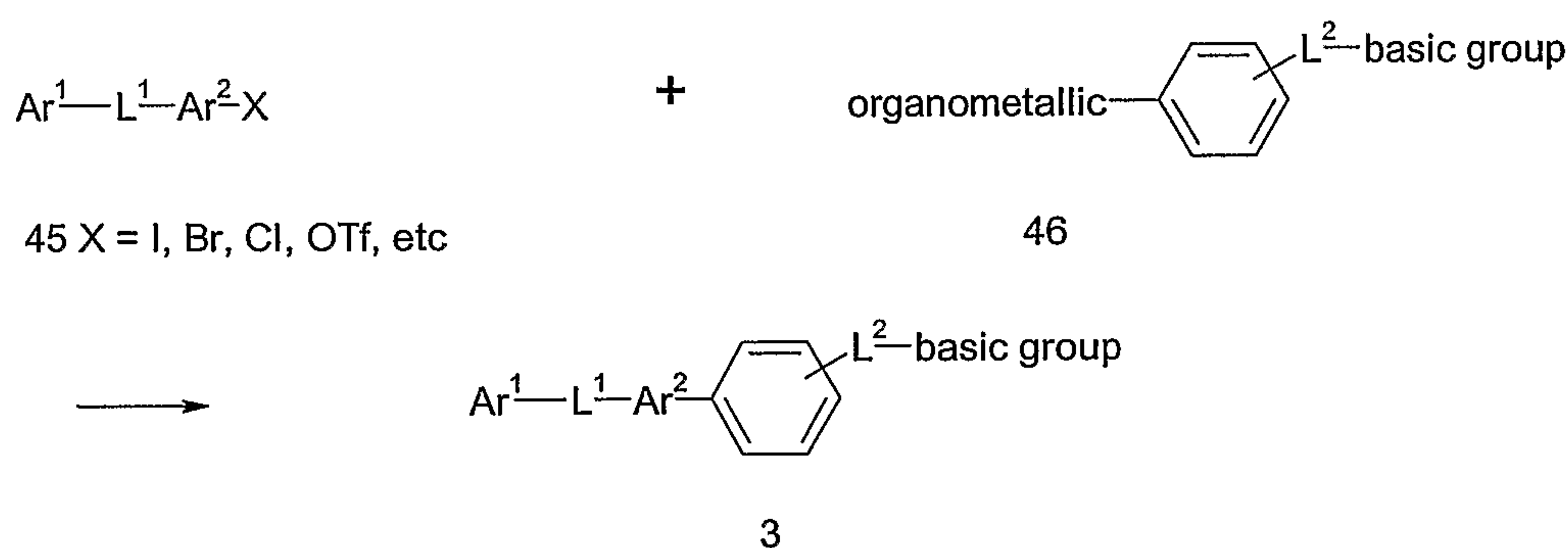
The compound of Formula 44 (or Formula 45) is coupled with an organometallic compound of Formula 43 (or Formula 46) in an Aryl Coupling Process to afford the compounds of the invention of Formula 3.

General Scheme 3a: Aryl Coupling

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or,



The compound of Formula 44 (or Formula 45) is coupled with the organometallic reagent of Formula 43 (Formula 46) in the presence, or absence, of a transition metal catalyst, and (or) a phosphine or arsine, and (or) a base in an inert solvent. Other additives, such as, copper salts, silver salts, and the like may be added. Approximately one equivalent of the compound of Formula 44 (or Formula 45) is reacted with one to five equivalents of the compound of Formula 43 (Formula 46) with the appropriate additives in an inert solvent. The reaction is normally carried out between -78°C and 200°C for between 4 to 72 hours. Examples of “organometallic reagents”, “transition metal catalysts”, “phosphines or arsines”, “other additives” and “base” have been described previously.

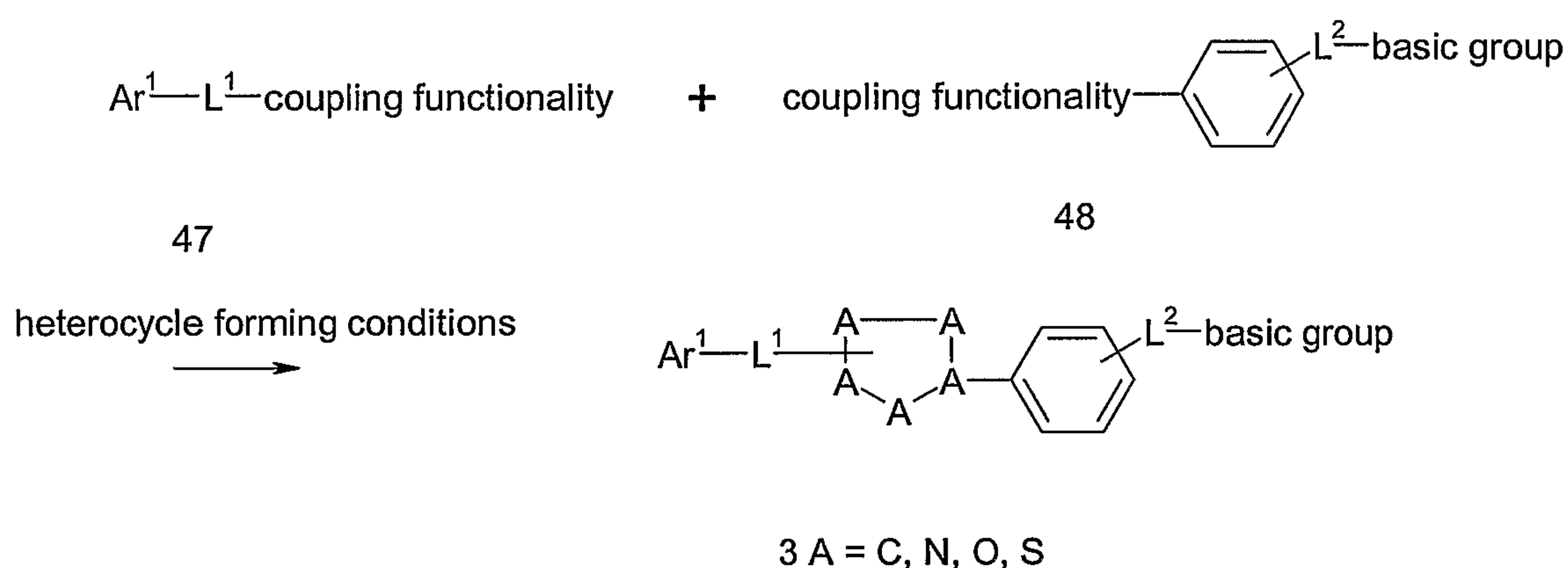
General Method 4: Heterocycle Formation

The compounds of Formula 3 can be prepared by the General Method 4, described in General Scheme 4, via reaction of the compound of Formula 47 containing a coupling group with a compound of Formula 48 containing a coupling group, where during the course of the coupling reaction the coupling groups form the 5-membered ring heterocycle between the linker L^1 and the phenyl ring. Ar^1 , L^1 , Ar^2 , L^2 , and basic group are defined as above. Examples of heterocyclic ring forming reactions are given in

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Comprehensive Heterocyclic Chemistry, Volumes 1-8, A. P. Katritzky and C. W. Rees Eds, Pergamon Press, 1984; Heterocyclic Chemistry, 3rd Ed, Thomas L. Gilchrist, Addison-Wesley-Longman Ltd, 1997; An Introduction to the Chemistry of Heterocyclic Compounds, 3rd Ed, R. M. Acheson, Wiley Interscience, 1976; etc, and references cited
 5 therein. Specific examples of the General Method 4 include an Oxadiazole Process (Schemes 4a and 4b), a Thiadiazole Process (Scheme 4c), and an Oxazole Process (Scheme 6 a-e). If necessary, the reaction can be carried out with a basic group synthon incorporated as the basic group, i.e., a group that could readily be converted to a basic
 10 group by methods known to one skilled in the art. Basic group synthons would include, but not be limited to, halogen, protected amine, nitrile, aldehyde, and the like. Following the Heterocycle Formation Process, these groups would then be unmasked or converted under standard conditions to afford the basic group.

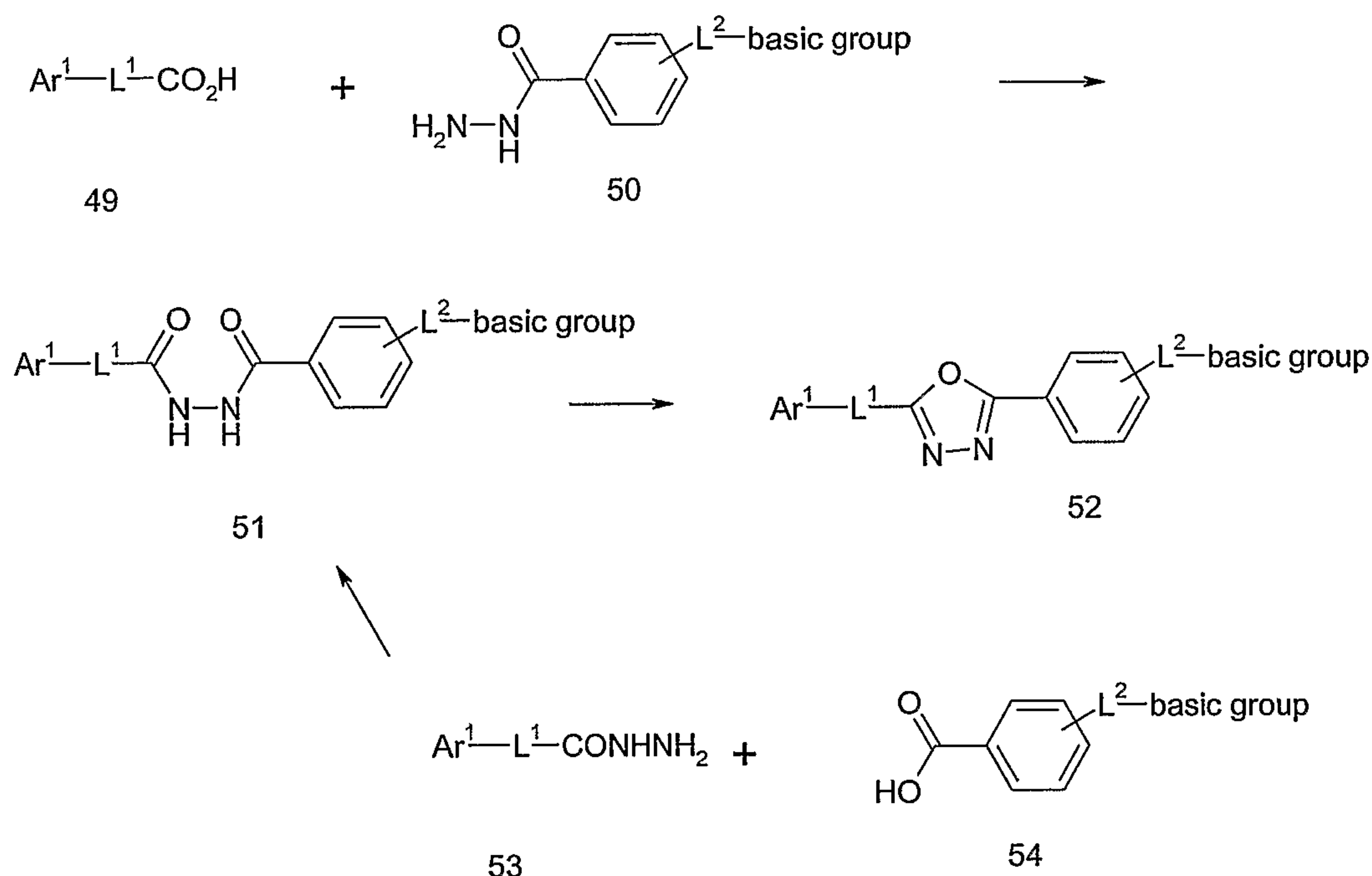
General Scheme 4: Heterocycle formation



As outlined in Scheme 4a below, the coupling process of General Method 4 can
 15 consist of a Oxadiazole Process. The diacylhydrazide compound of Formula 51 is produced by acylation of an acylhydrazide of Formula 50 (or Formula 53) by a carboxylic acid derivative of Formula 49 (or Formula 54). The acylation process is carried out in accordance with the above Acylation/Sulfonylation Process of the General Method 2. The
 20 diacylhydrazide is cyclized to the oxadiazole compounds of the invention of Formula 52 utilizing dehydration processes analogous to that described in J Org Chem 1999, 64 (19), 6989-6992; and Chem Heterocycl Compd 1999, 35 (3), 275-280.

Scheme 4a: Oxadiazole Process

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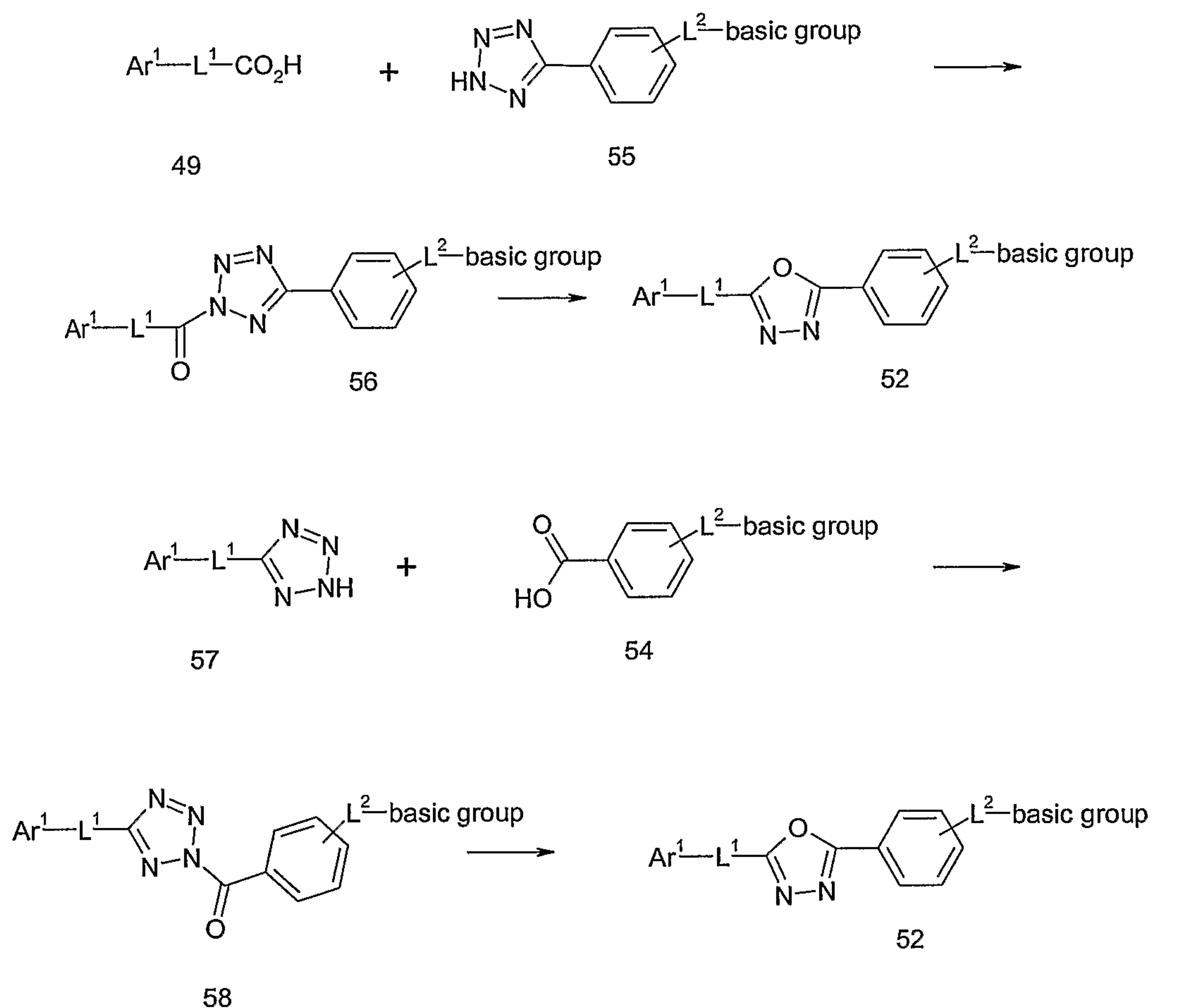


One equivalent of compound of Formula 51 is reacted with one to equivalents of a dehydrating agent in the presence, or absence, a base in an inert solvent. The reaction is normally carried out between 25 °C and 250 °C for between 4 to 72 hours. Examples of “dehydrating agents” include, SOCl₂, H₃PO₄, POCl₃, PCl₅, Tf₂O, Ac₂O, PPh₃-I₂, PPh₃-Br₂, PPh₃-Cl₂, PPh₃-CBr₄, PPh₃-CCl₄, PPA, NH(Tms)₂, P₂O₅, Me₂SiCl₂, PhOPCl₂, H₂SO₄, and the like.

As outlined in Scheme 4b below, an alternative Oxadiazole Process may be utilized to prepare the oxadiazole compounds of the invention of Formula 52. The carboxylic acid derivative of Formula 49 (or 54) is activated for coupling as a “reactive acylating agent.” The acylation process is carried out in accordance with the above Acylation/Sulfonylation Process of the General Method 2. The acylated intermediate is converted to the oxadiazole compounds of the invention of Formula 52. The process is analogous to that described in Synth Commun 1994, 24 (11), 1575-1582; J Org Chem 1961, 26, 2372; Synthetic Commun 24(11),1575-1582 (1994); etc, and references cited therein.

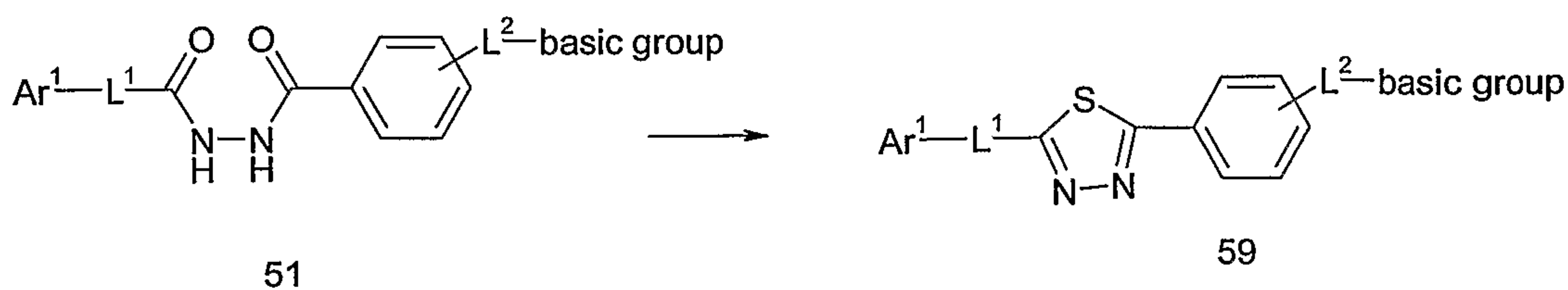
Scheme 4b: Oxadiazole Process

-44-



One to five equivalents of the “reactive acylating agent” of compound 49 (or compound 54) and one to five equivalents of compound of Formula 55 (or 57) are reacted in an inert solvent. If necessary the reaction can be carried out in the presence of a one to five equivalents of 1-hydroxybenzotriazole, 1-hydroxy-7-azabenzotriazole, and (or) a catalytic quantity to five equivalents of a base. The reaction intermediate of Formula 56 (or 58) may, or may not, be isolated. The reaction is normally carried out between 0 °C and 200 °C. Reaction time is normally 4 to 48 hours. Reactive acylation agents have been discussed and may similarly be prepared for compounds 49 and/or 55 as described previously.

Scheme 4c: Thiadiazole Process



One equivalent of compound of Formula 51 is reacted with one to five equivalents of a thiol dehydrating agent in the presence, or absence, a base in an inert solvent. The reaction is normally carried out between 25 °C and 250 °C for between 4 to 72 hours. Examples of "thiol dehydrating agents" include, P₂S₅, Lawesson reagent, and the like.

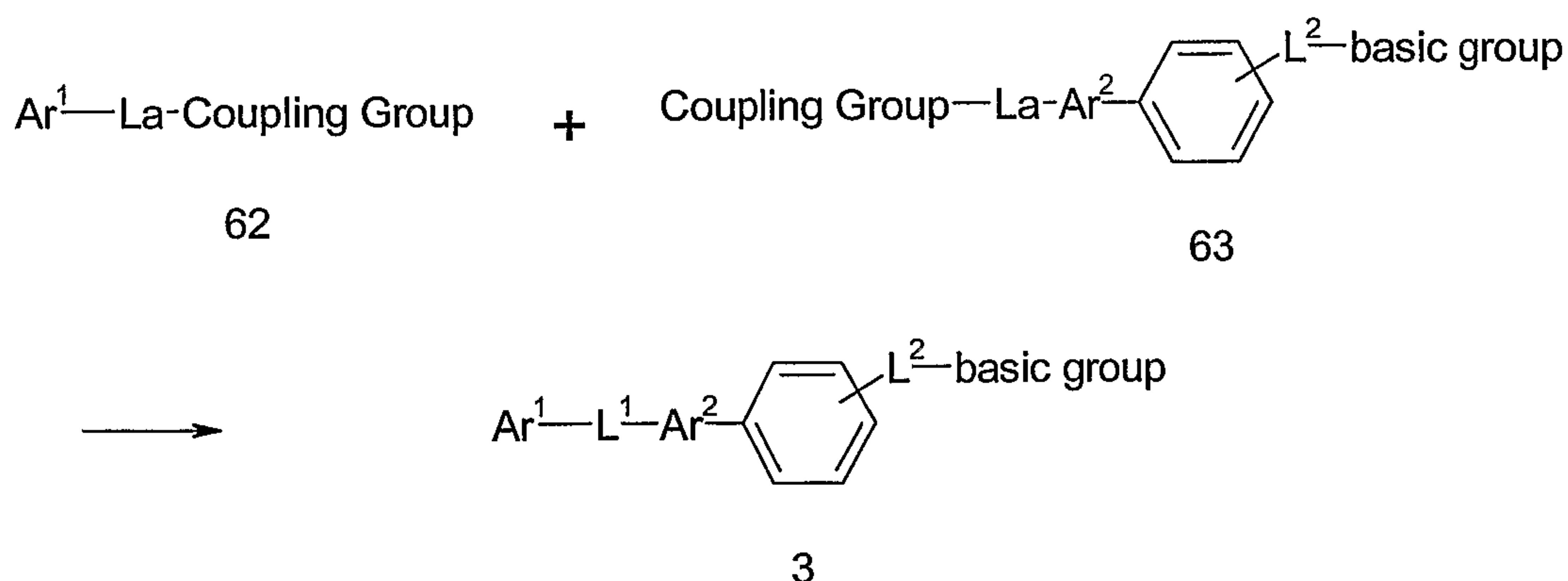
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General Method 5: Coupling of the linker group L¹

The compounds of Formula 3 can be prepared by the General Method 5, described in General Scheme 5, via reaction of the coupling group of Formula 62 with a coupling group of Formula 63, where during the course of the coupling reaction the coupling groups are retained, or lost, to form the linker L¹ between the 5-membered ring heterocyclic group and Ar¹. Ar¹, L¹, Ar², L², and basic group are defined as above. La is defined as a group that when the coupling process occurs results in the formation of the linker L² defined above. Examples of the General Method 5 are an Ether/Thioether Alkylation Process (Scheme 5a), an Acylation/Sulfonylation Process (Scheme 5b), an Urea/Thiourea/Guanadine Coupling Process (Scheme 5c1, 5c2, 5c3), an Organometallic Process (Scheme 5d), and a Wittig-type Coupling (Scheme 5e).

If necessary, the reactions below may be carried out with a basic group synthon incorporated as the basic group, as described previously. Following the Coupling of the Linker Group (L¹) Process, these groups would then be unmasked or converted under standard conditions to afford the basic group.

General Scheme 5: Coupling of Linker Group L₁



As outlined in Scheme 5a below, the coupling process of General Method 5 can consist of a Ether/Thioether Alkylation Process. Nucleophilic displacement by an alcohol or thiol-containing compound of Formula 64 (or Formula 68) with a compound of

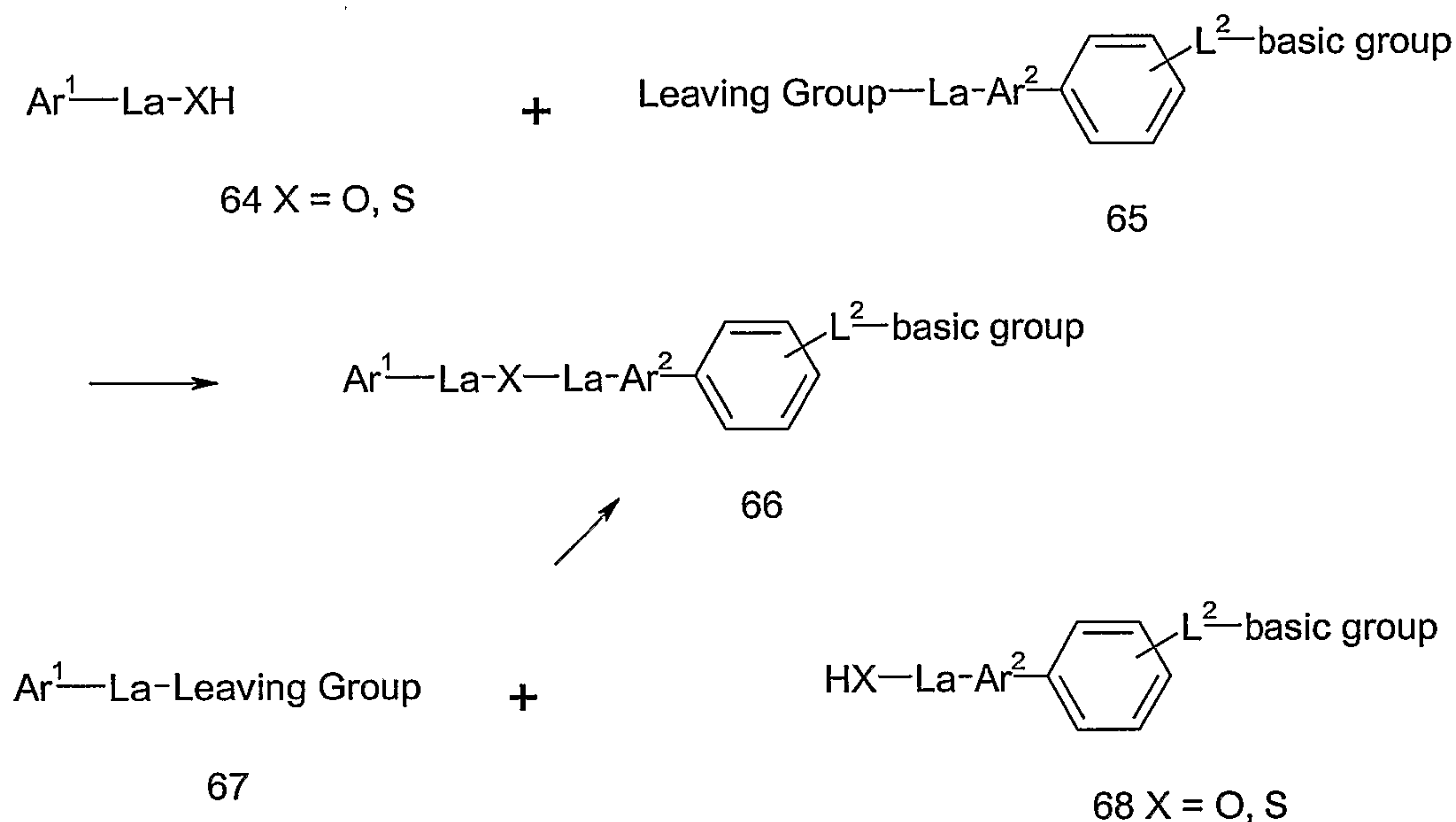
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Formula 65 (or Formula 67) containing a leaving group affords the ether and thioether compounds of Formula 66 of the invention. The processes are analogous to the process described for the General Method 2, described in Scheme 2a, and carried out in accordance with the above method.

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Scheme 5a: Ether/Thioether alkylation process

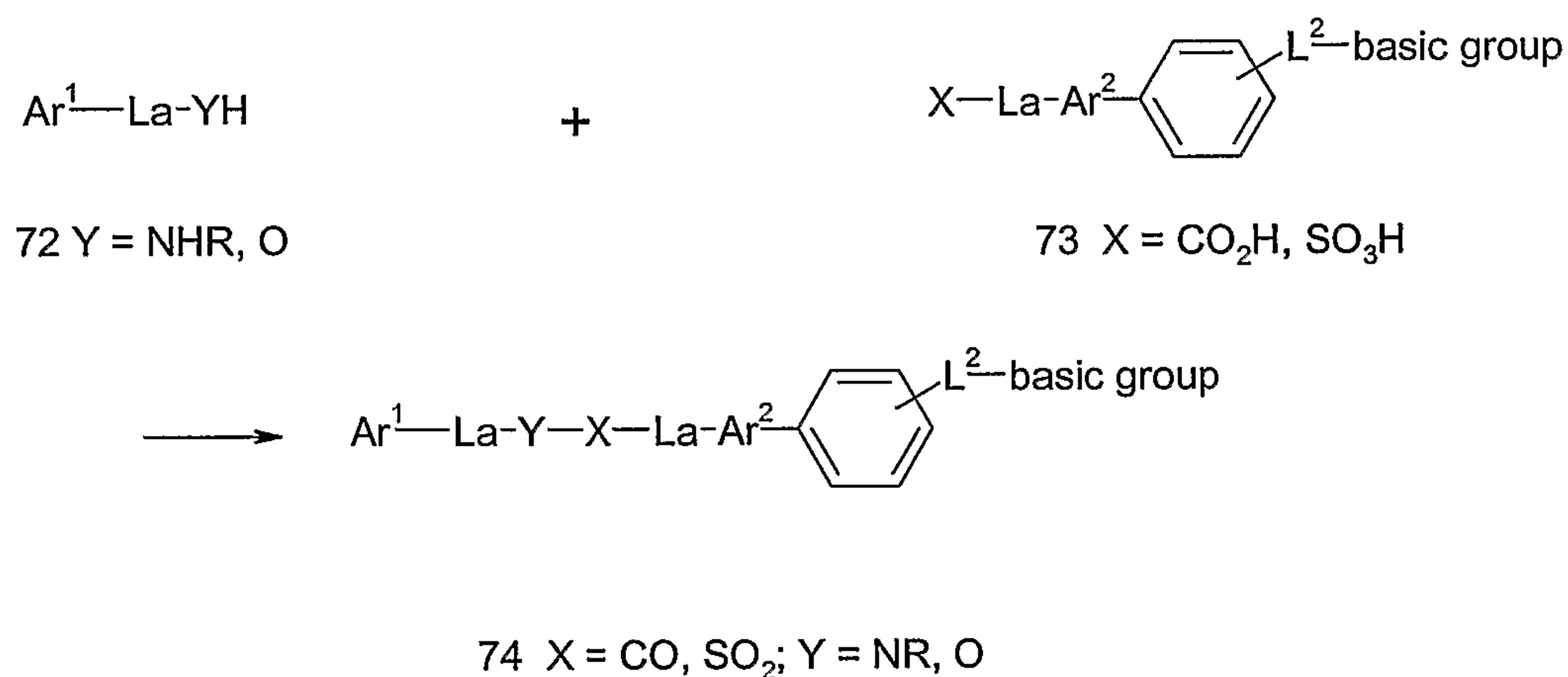
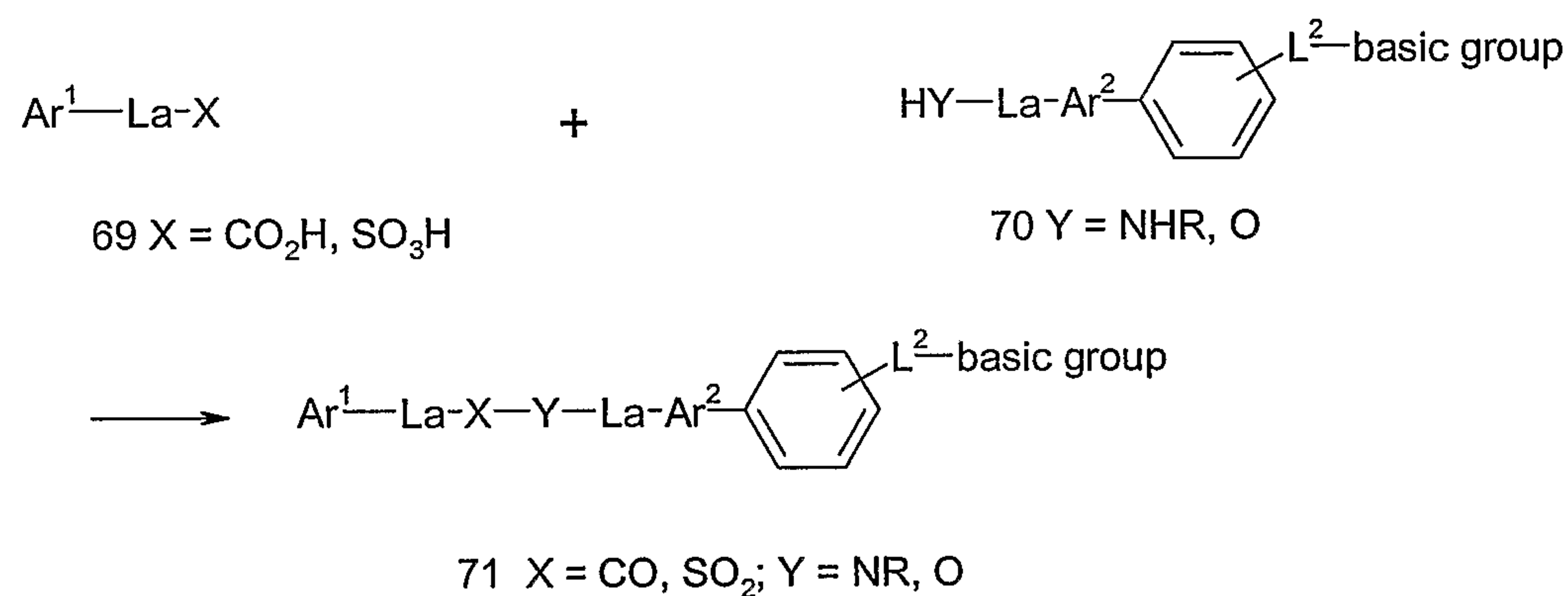


As outlined in Scheme 5b below, the coupling process of General Method 5 can consist of an Acylation/Sulfonylation Process. Acylation or sulfonylation of an alcohol or amine compound of Formula 70 with a carboxylic acid or sulfonic acid compound of Formula 69, affords the ester, amide, sulfonic ester, or sulfonamide compounds of Formula 71. Alternatively, acylation or sulfonylation of an alcohol or amine compound of Formula 72 with a carboxylic acid or sulfonic acid compound of Formula 73 affords the ester, amide, sulfonic ester, or sulfonamide compounds of Formula 74.

The processes are analogous to the process described for the General Method 2, described in Scheme 2b, is carried out in accordance with the above method.

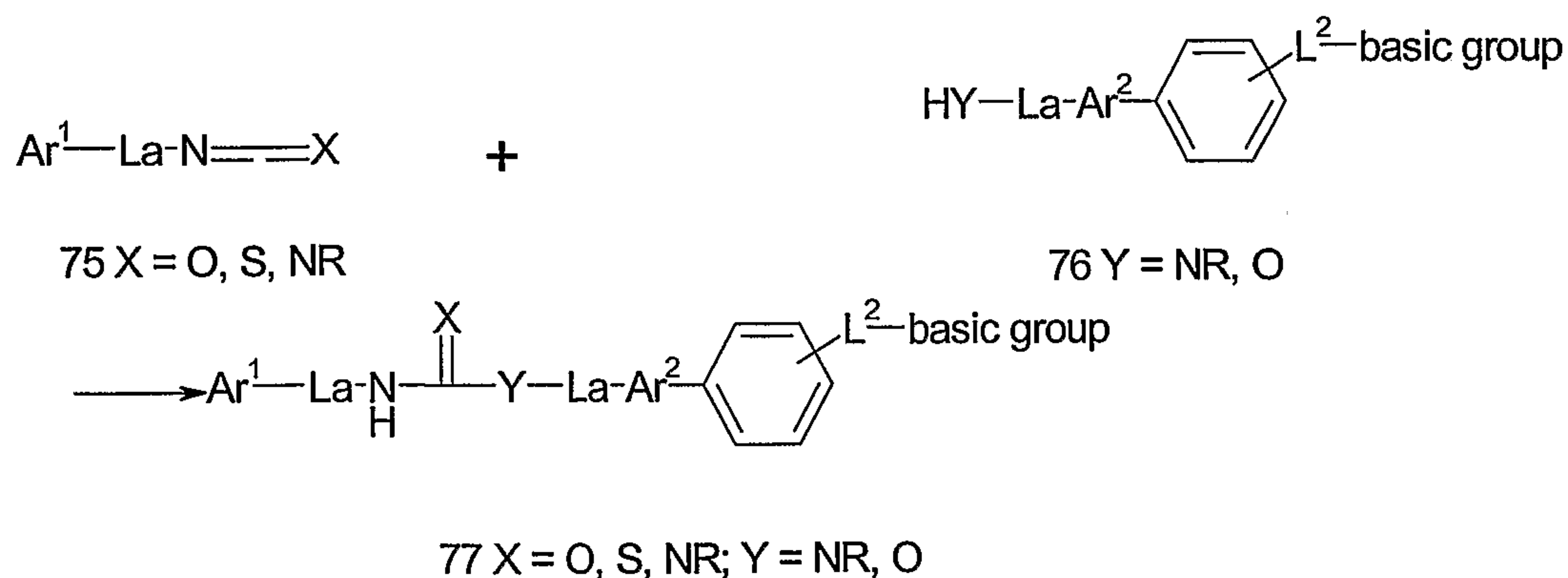
Scheme 5b: Acylation/Sulfonylation Process

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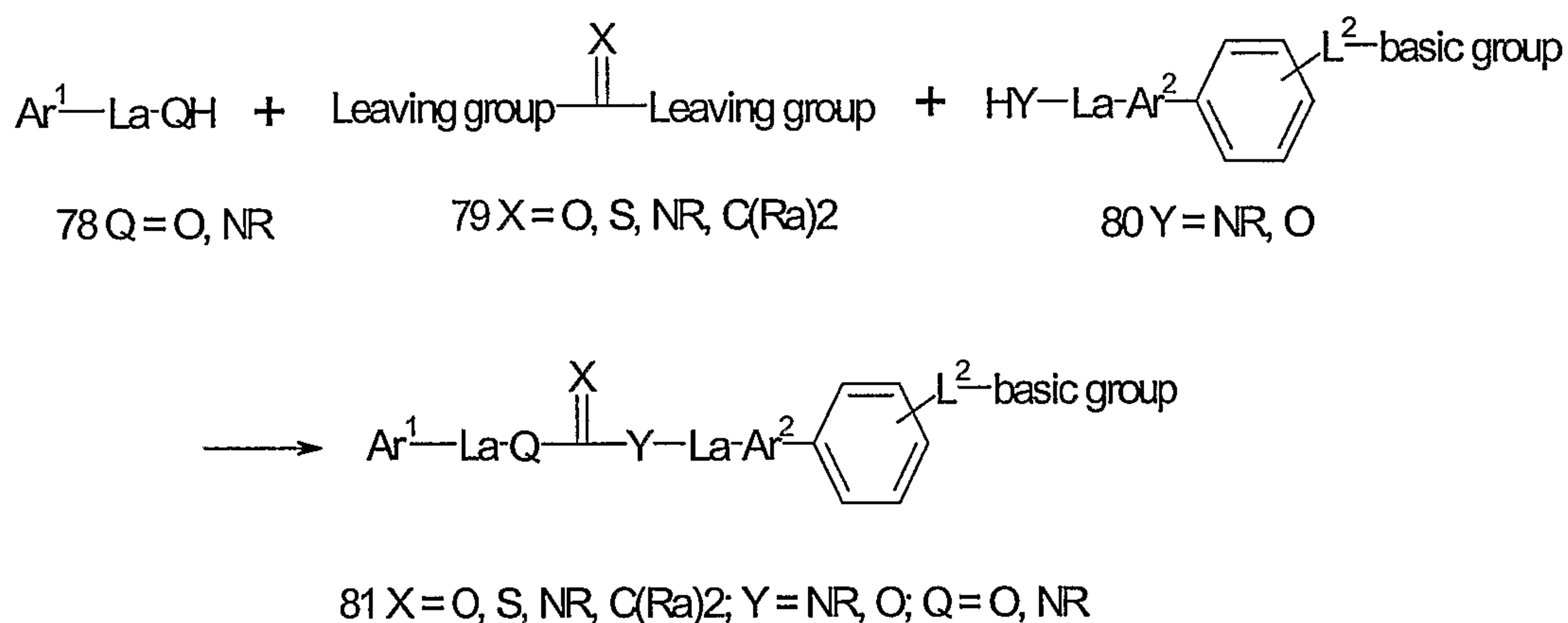
As outlined in Schemes 5c1, 5c2, and 5c3, below, the coupling process of General Method 5 can consist of a Urea/Thiourea/Guanidine/Carbamate-Type Coupling Process to afford the compounds of Formula 77, 81, and 84 of the invention. The processes are analogous to the processes described for the General Method 2, described in Schemes 2c1, 2c2, and 2c3, are carried out in accordance with the above method.

Scheme 5c1: Urea/Thiourea/Guadinine/Carbamate-Type Coupling

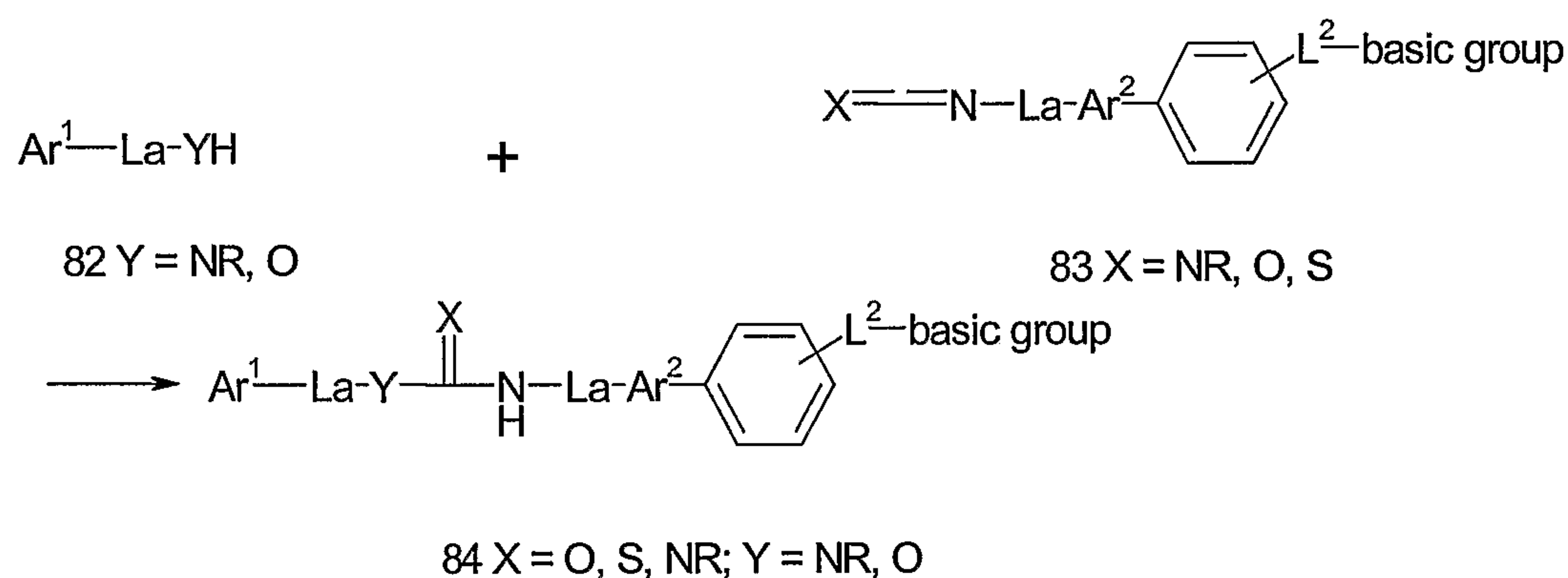


Scheme 5c2: Urea/Thiourea/Guadinine/Carbamate-Type Coupling

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Scheme 5c3: Urea/Thiourea/Guadine/Carbamate-Type Coupling



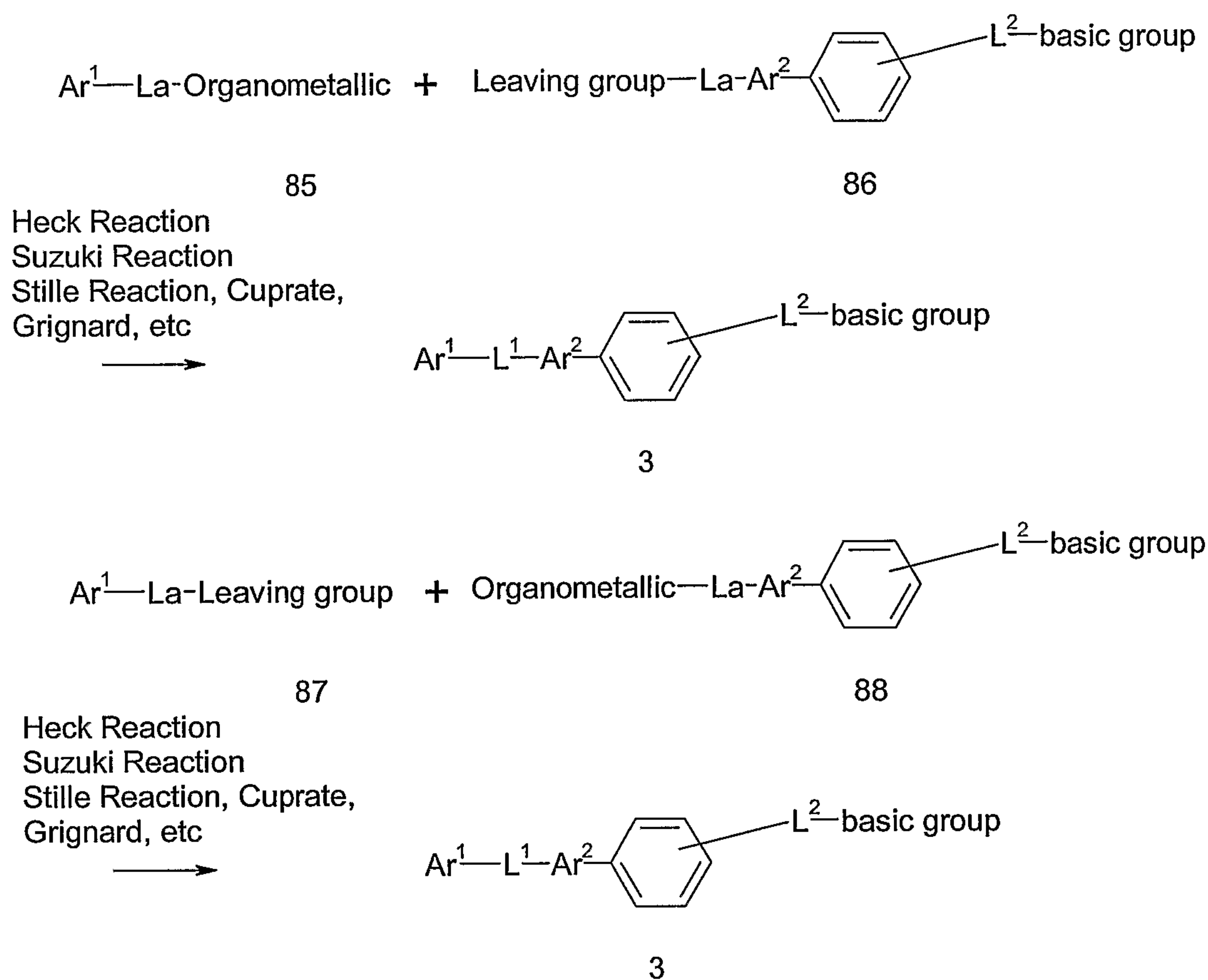
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As outlined in Schemes 5d below, the coupling process of General Method 5 can consist of a Organometallic Coupling Process. The compound of Formula 86 (or Formula 87) is coupled with an organometallic compound of Formula 85 (or Formula 88) in an Organometallic Coupling Process to afford the compounds of Formula 3 of the invention.

10 The processes are analogous to the processes described for the General Method 2, described in Scheme 2d, and are carried out in accordance with the above methods.

Scheme 5d: Organometallic Coupling Process

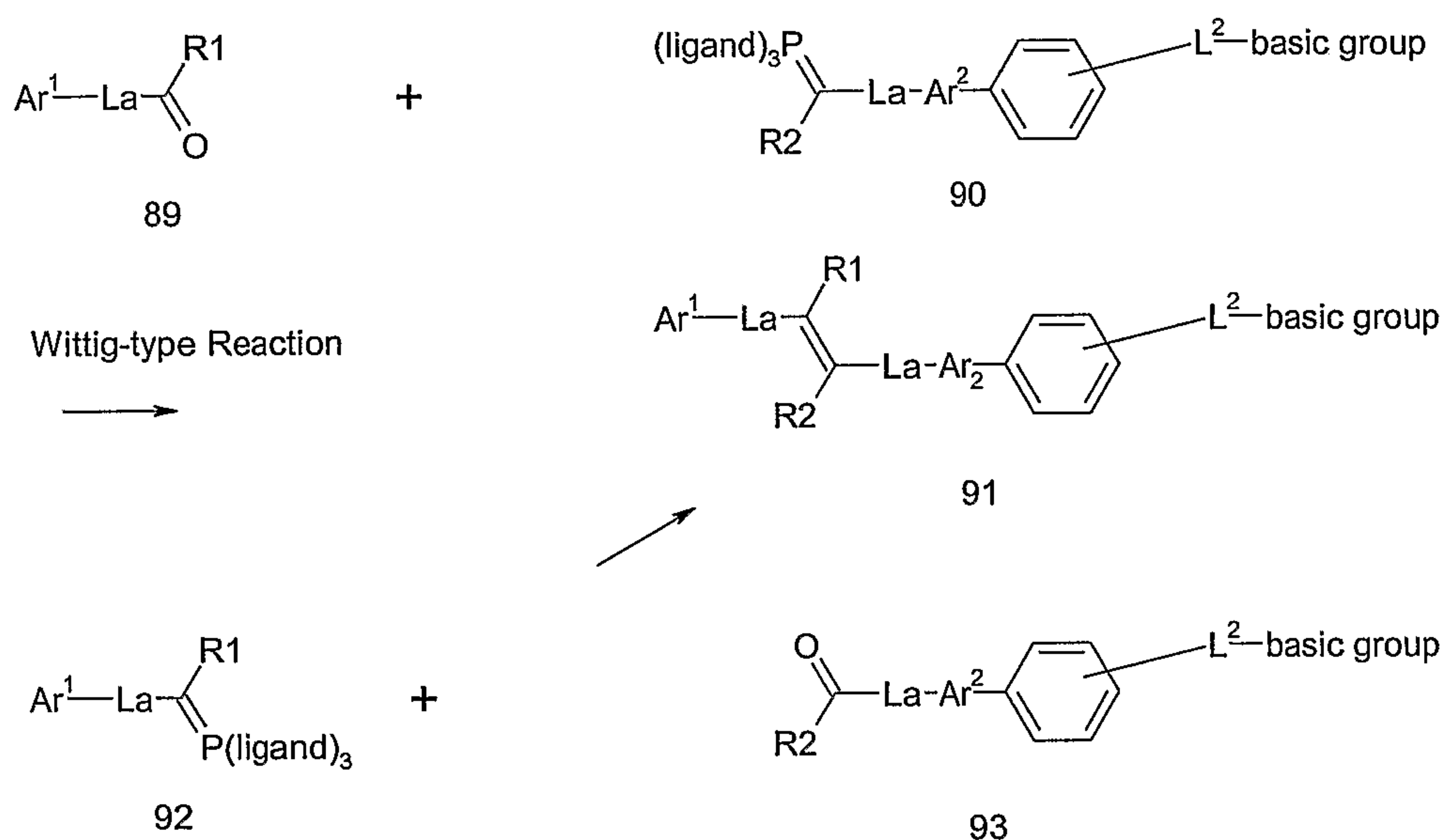
-49-



As outlined in Schemes 5e below, the coupling process of General Method 2 can consist of a Wittig-type Coupling Process. The compound of Formula 89 (or Formula 93) is coupled with the phosphorus ylene (or ylide) reagent of Formula 90 (Formula 92) to afford the compounds of Formula 91 of the invention. The processes are analogous to the processes described for the General Method 2, described in Scheme 2e, and are carried out in accordance with the above methods.

Scheme 5e: Wittig-type couplings

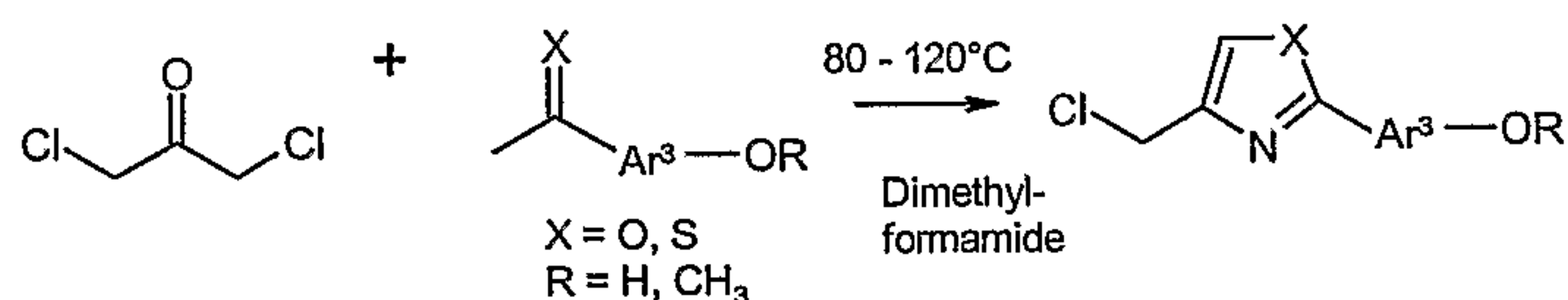
-50-



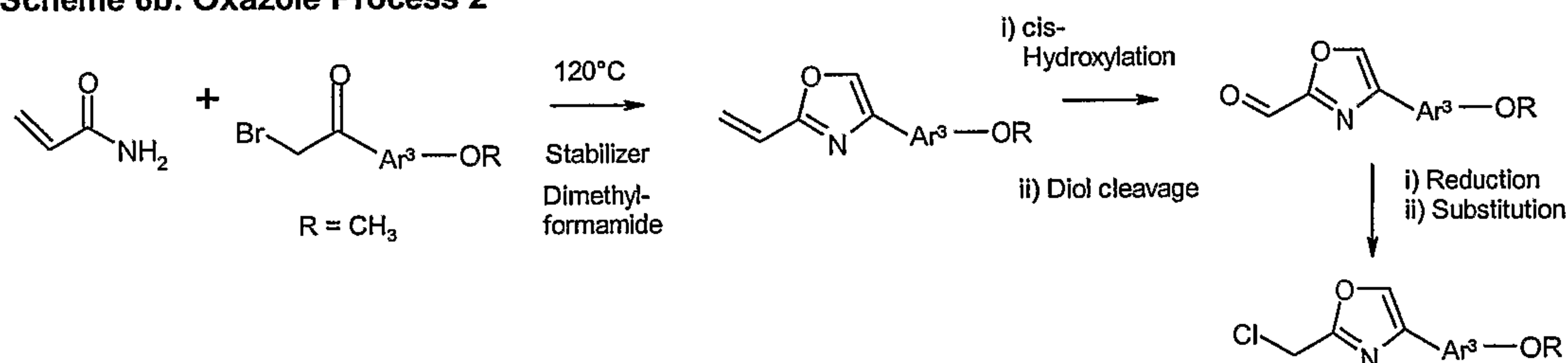
Preparation of Oxazole and Oxathiazole compounds

As outlined in schemes 6a-c (below) the formation of oxazoles and thiazoles require elevated temperatures from 80 – 120°C in solvents like dimethylformamide (scheme 6a + b) or phosphoryl chloride (scheme 6c).

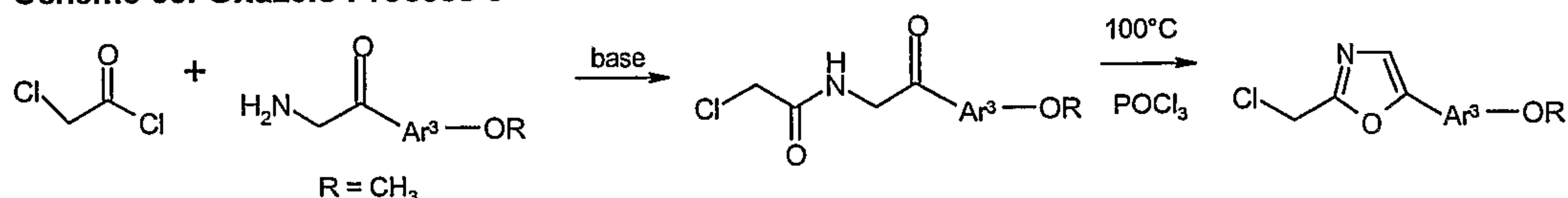
Scheme 6a: Oxazole and Thiazole Process 1



Scheme 6b: Oxazole Process 2



Scheme 6c: Oxazole Process 3

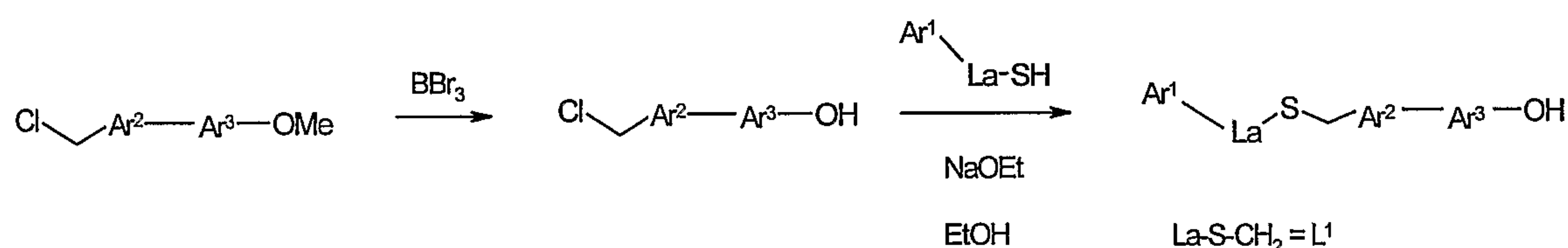


These heterocyclic cyclisations result either in chloromethyl substituted oxazoles and thiazoles (scheme 6 a + c) or in vinyl substituted oxazole (scheme 6b). After cis-hydroxylation of the later vinyl substituted oxazole, followed by diol cleavage, as known to the art, the resulting formyl substituted oxazole can be converted via reduction

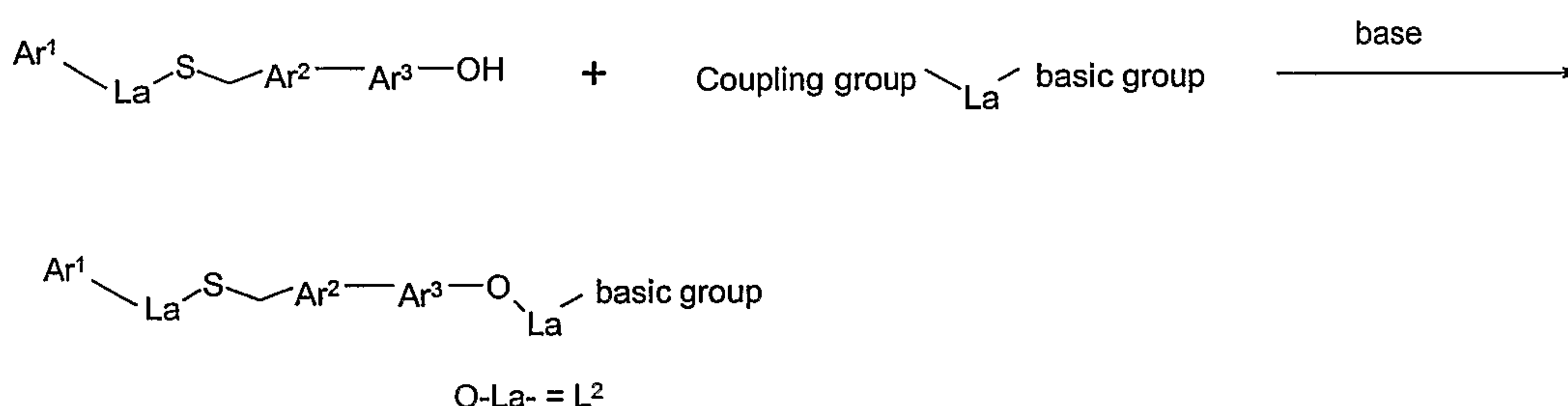
-51-

and substitution to the chloro methyl substituted oxazole (scheme 6b). The cyclisation of α -bromoketone with acrylamide (scheme 6b) is preferably performed in the presence of a stabiliser (such as 2,6 di-tert.-butyl-4-methyl-phenol) to prevent polymerisation of the acrylamide. As outlined in scheme 6c, the condensation of 2-chloro acetyl chloride with an α -aminoketone in presence of a base such as, for example, triethylamine, affords a product in high yield that can be cyclised in phosphoryl chloride to result in formation of an oxazole. Unlike general scheme 4, these heterocyclic formations of oxazoles and thiazoles do not work as desired in the presence of $\text{Ar}^1\text{-L}^1$ - nor in the presence of -L^2 - basic group, so that these groups have to be introduced later, as outlines in schemes 6d and 6e.

Scheme 6d: Formation of the Linker Group L_1



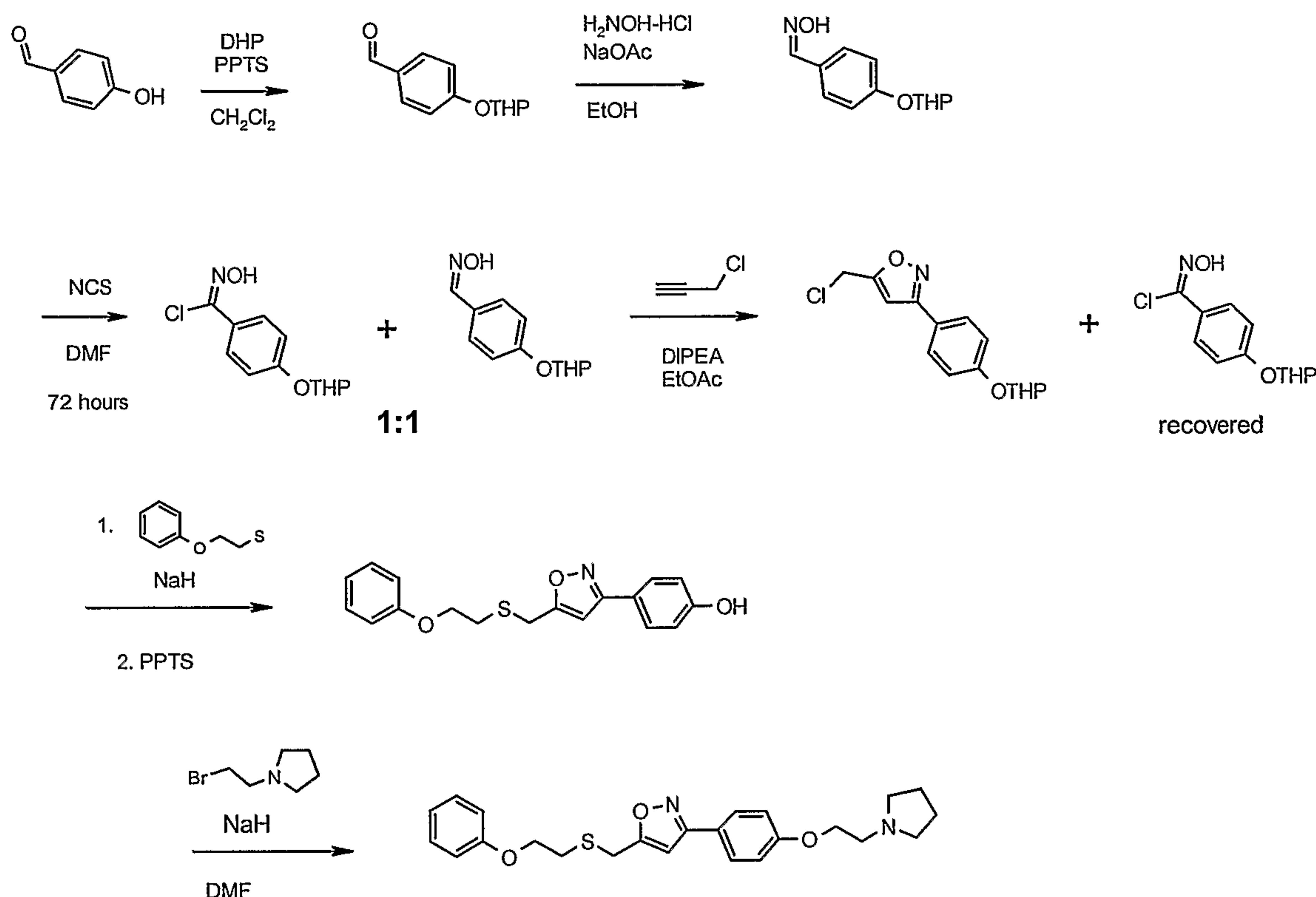
Scheme 6e: Formation of the Linker Group L_2



In order to achieve formation of the linker L^1 , the chloromethyl substituted oxazoles or thiazoles from scheme 6a-c can be used as alkylation substrates for thiolates (scheme 6d). Therefore, a thiol is treated with a base, like sodium ethoxide in ethanol, before addition of the chloro methyl substituted oxazole. This alkylation proceeds in the presence of an unprotected phenol. The unprotected phenol can be incorporated into linker L^2 in a subsequent reaction, as outlined in scheme 6e in solvents such as dimethylformamide and involving bases such as potassium carbonate. As outlined in scheme 6d, the phenol may be obtained from the Lewis-acid mediated cleavage of a methylether with Lewis-acids, preferably, borontribromide in solvents such as dichloromethane.

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For compounds wherein Ar² is oxazole, positional isomers of the oxazole group (e.g isoxazole) may be made as shown in Scheme 7.

Scheme 7

5

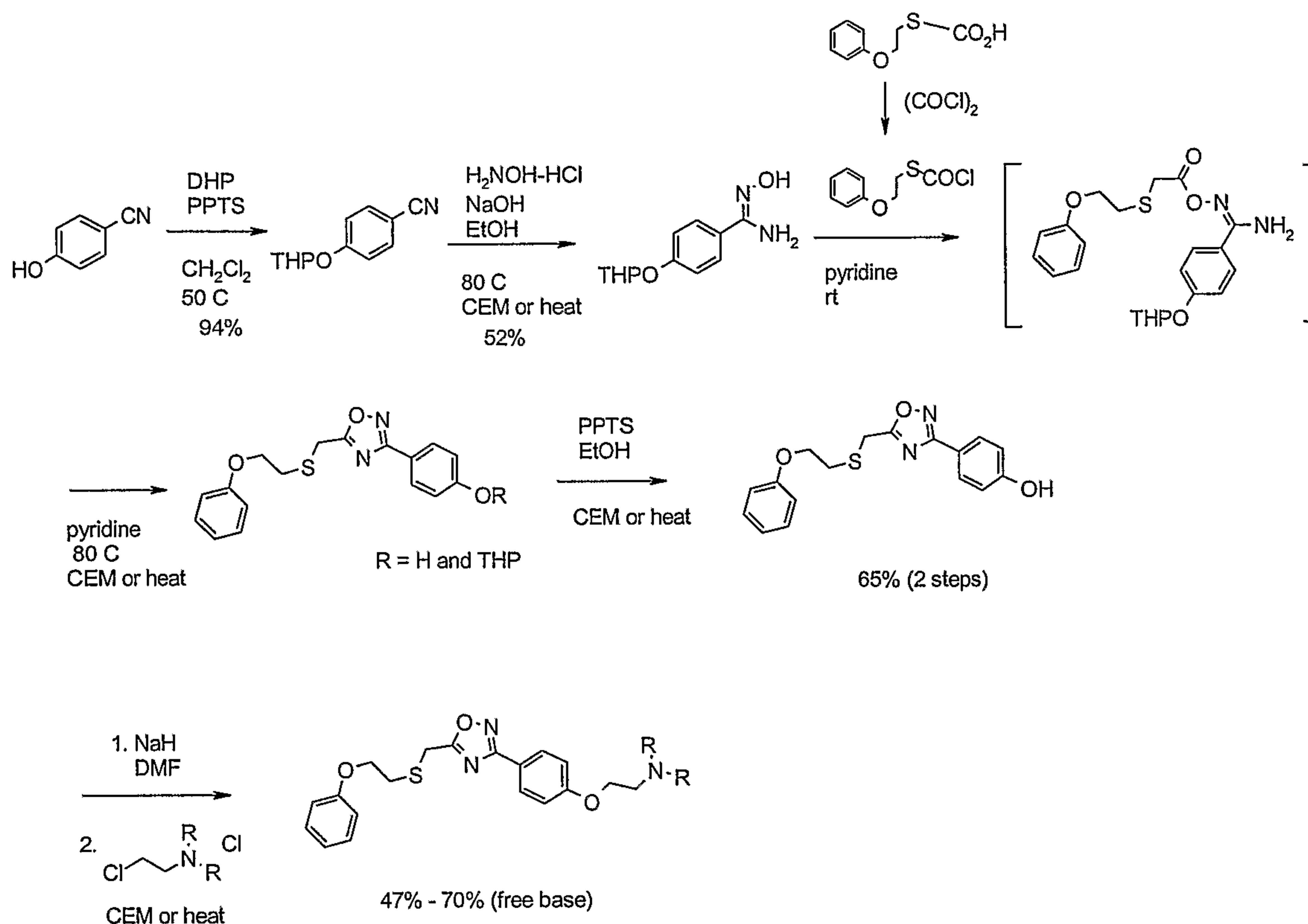
4-Hydroxy-benzaldehyde is protected as the tetrahydropyran (THP) ether, using dihydropyran and p-toluenesulfonic acid (PPTS) in dichloromethane. The aldehyde functionality is converted to an oxime with hydroxylamine hydrochloride and sodium acetate in ethanol. The oxime is then converted to a chloro-oxime with NCS in DMF.

- 10 Dipolar cycloaddition of the chloro-oxime and 3-chloropropyne in ethyl acetate using DIPEA as catalyst gives the intermediate 5-chloromethyl-3-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-isoxazole. This is then used to alkylate 2-phenoxy-ethanethiol. This intermediate is deprotected with PPTS to give 4-[5-(2-phenoxy-ethylsulfanylmethyl)-isoxazol-3-yl]-phenol. The phenol is alkylated with 1-(2-chloro-ethyl)-pyrrolidine hydrochloride to give the final product, 5-(2-phenoxy-ethylsulfanylmethyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-isoxazole.
- 15

The 1,2,4-oxadiazole simer may be prepared following the procedure of Scheme as shown in Scheme 8 for the particular example.

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Scheme 8



- 5 As shown, 4-Cyanophenol is protected as the Tetrahydropyran (THP) ether using dihydropyran and dihydropyran and p-toluenesulfonic acid (PPTS) in dichloromethane. The cyano functionality is converted to an amidoxime functionality by reaction with hydroxylamine hydrochloride and NaOH in ethanol in a microwave chamber at 80 °C. A mixture of the amidoxime and (2-phenoxy-ethylsulfanyl)-acetyl chloride in pyridine is microwaved at 80 °C to give the isoxazole intermediate as a mixture of protected THP ether and deprotected phenol. After removal of pyridine under vacuum, the reaction products are treated with PPTS in ethanol and microwaved at 75 °C to deprotect any remaining THP ether, giving 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenol. The phenol is alkylated with 1-(2-chloro-ethyl)-pyrrolidine hydrochloride to give the final product, 5-(2-phenoxy-ethylsulfanylmethyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,2,4]oxadiazole hydrochloride.

One of skill in the art is aware that other compounds within the scope of the invention may be made as shown or by modifications to the procedures provided which are not cumbersome and are known to one of skill in the art or accessible in the general reference

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texts or literature available to one of skill in the art. Furthermore, in addition to the discursive procedures herein, detailed examples are provided which would further assist one of skill in the art to make the appropriate modifications to arrive at compounds within the scope that are not specifically exemplified.

5

Demonstration of Function

In order to demonstrate that compounds of the present invention have the capacity to bind to and inhibit the function of MCHR1, binding and functional assays were established. All ligands, radioligands, solvents and reagents employed in these
10 assays are readily available from commercial sources or can be readily prepared by those skilled in the art.

The full-length cDNA for human MCHR1 was cloned from a human adult brain cDNA library (Edge Biosystems, Cat. 38356) by standard polymerase chain reaction (PCR) methodology employing the following primers: sense, 5'-GCCACCATGGACCT
15 GGAAGCCTCGCTGC-3'; anti-sense, 5'-TGGTGCCCTGACTTGGAGGTGTGC-3'. The PCR reaction was performed in a final volume of 50 μ l containing 5 μ l of a 10x stock solution of PCR buffer, 1 μ l of 10 mM dNTP mixture (200 μ M final), 2 μ l of 50 mM Mg(SO₄) (2 mM final), 0.5 μ l of 20 μ M solutions of each primer (0.2 μ M final), 5 μ l of template cDNA containing 0.5 ng DNA, 0.5 μ l of Platinum Taq High Fidelity DNA
20 polymerase (Gibco Life Technologies) and 36 μ l of H₂O. PCR amplification was performed on a Perkin Elmer 9600 thermocycler. After denaturation for 90 sec at 94°C, the amplification sequence consisting of 94°C for 25 sec, 55°C for 25 sec and 72°C for 2 min was repeated 30 times, followed by a final elongation step at 72°C for 10 min. The desired PCR product (1.1 Kb) was confirmed by agarose gel electrophoresis and the band
25 was extracted from the gel by Geneclean (Bio101) following the manufacturer's instructions. Following extraction, the cDNA fragment was cloned into pCR2.1-TOPO plasmid (Invitrogen) to confirm the identity and sequence.

In order to generate cell lines stably expressing MCHR1, the insert was then subcloned into the Xba I and Not I sites of pcDNA(+)-3.1-neomycin (Invitrogen).
30 After purification by Qiagen Maxi-prep kit (QIAGEN, Inc.), the plasmid was transfected by Fugene 6 (Roche Applied Science) into AV12 cells that had been previously transfected with the promiscuous G protein G α_{15} . The transfected cells were selected by

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G418 (800 µg/ml) for 10-14 days and single colonies were isolated from culture plates. The G418-resistant colonies were further selected for MCHR1 expression by measuring MCH-stimulated Ca^{2+} transients with a fluorometric imaging plate reader (FLIPR, Molecular Devices).

5 Typically, individual clones are plated out in 96-well plates at 60,000 cells per well in 100 µl of growth medium (Dulbecco's modified Eagle's medium (DMEM), 5% fetal bovine serum, 2 mM L-glutamine, 10 mM HEPES, 1 mM sodium pyruvate, 0.5 mg/ml Zeocin, and 0.5 mg/ml Geneticin). After 24 hrs at 37°C, medium is removed and replaced with 50 µl of dye loading buffer (Hank's balanced salt solution (HBSS)
10 containing 25 mM HEPES, 0.04% Plurionate 127 and 8 µM Fluo3 Both from Molecular Probes)). After a 60 min loading period at room temperature, dye loading buffer is aspirated and replaced with 100 µl of HEPES/HBBS. Plate is placed in FLIPR and basal readings are taken for 10 sec, at which point 100 µl of buffer containing 2 µM MCH (1 µM final) is added and measurements are taken over 105 sec. To correct for variations
15 between clones in numbers of cells per well, the MCH response is normalized to the response induced by epinephrine.

Both the ^{125}I -MCH binding and functional $\text{GTP}\gamma^{35}\text{S}$ binding assays employed membranes isolated from a clone designated as clone 43. Typically, cells from 20 confluent T225 flasks were processed by washing the monolayers in cold phosphate-buffered saline (PBS), scraping the cells into same and re-suspending the cell pellet in 35
20 ml of 250 mM Sucrose, 50 mM HEPES, pH 7.5, 1 mM MgCl_2 , 24 µg/ml DNase I, and protease inhibitors (1 Complete® tablet, per 50 ml of buffer prepared, Roche Diagnostics). After incubation on ice for 5 min, cells were disrupted with 20-25 strokes of a Teflon/Glass homogenizer attached to an overhead motorized stirrer, and the
25 homogenate was centrifuged at 40,000 rpm in Beckman Type 70.1 Ti rotor. The pellets were re-suspended in 250 mM Sucrose, 50 mM HEPES, pH 7.5, 1.5 mM CaCl_2 , 1 mM MgSO_4 and protease inhibitors by Teflon/Glass homogenization to achieve a protein concentration of ~3-5 mg/ml (Pierce BCA assay with Bovine serum albumin as standard). Aliquots were stored at -70°C.

30 Binding of compounds to MCHR1 was assessed in a competitive binding assay employing ^{125}I -MCH, compound and clone 43 membranes. Briefly, assays are carried out

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in 96-well Costar 3632 white opaque plates in a total volume of 200 μ l containing 25 mM HEPES, pH 7.5, 10 mM CaCl_2 , 2 mg/ml bovine serum albumin, 0.5% dimethyl sulfoxide (DMSO), 4 μ g of clone 43 membranes, 100 pM ^{125}I -MCH (NEN), 1.0 mg of wheat germ agglutinin scintillation proximity assay beads (WGA-SPA beads, Amersham) and a
5 graded dose of test compound. Non-specific binding is assessed in the presence of 1 μ M unlabeled MCH. Bound ^{125}I -MCH is determined by placing sealed plates in a Microbeta Trilux (Wallac) and counting after a 5 hr delay.

IC_{50} values (defined as the concentration of test compound required to reduce specific binding of ^{125}I -MCH by 50%) are determined by fitting the concentration-
10 response data to a 4-parameter model (max response, min response, Hill coefficient, IC_{50}) using Excel. K_i values are calculated from IC_{50} values using the Cheng-Prusoff approximation as described by Cheng *et al.* (Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction, *Biochem. Pharmacol.*, 22: 3099-3108 (1973)). The K_d for ^{125}I -MCH
15 is determined independently from a saturation binding isotherm.

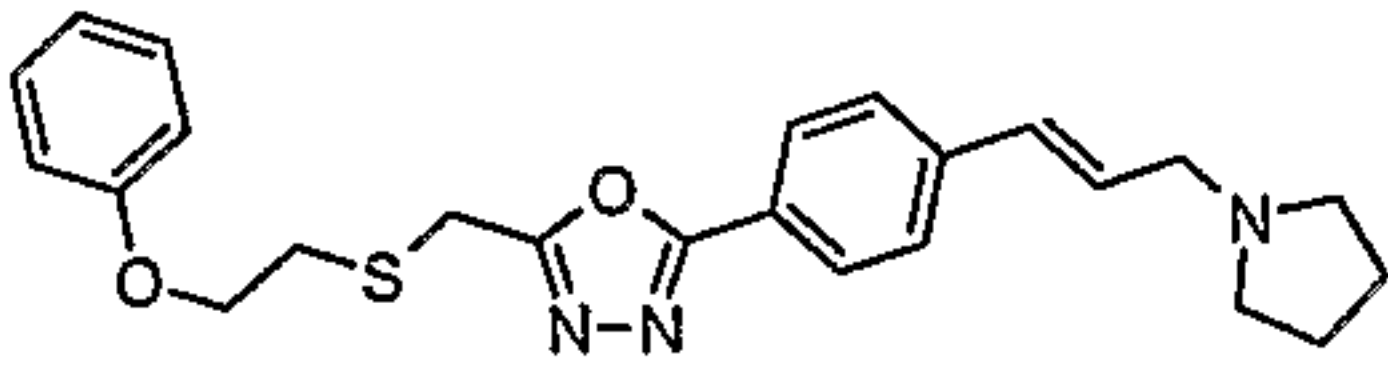
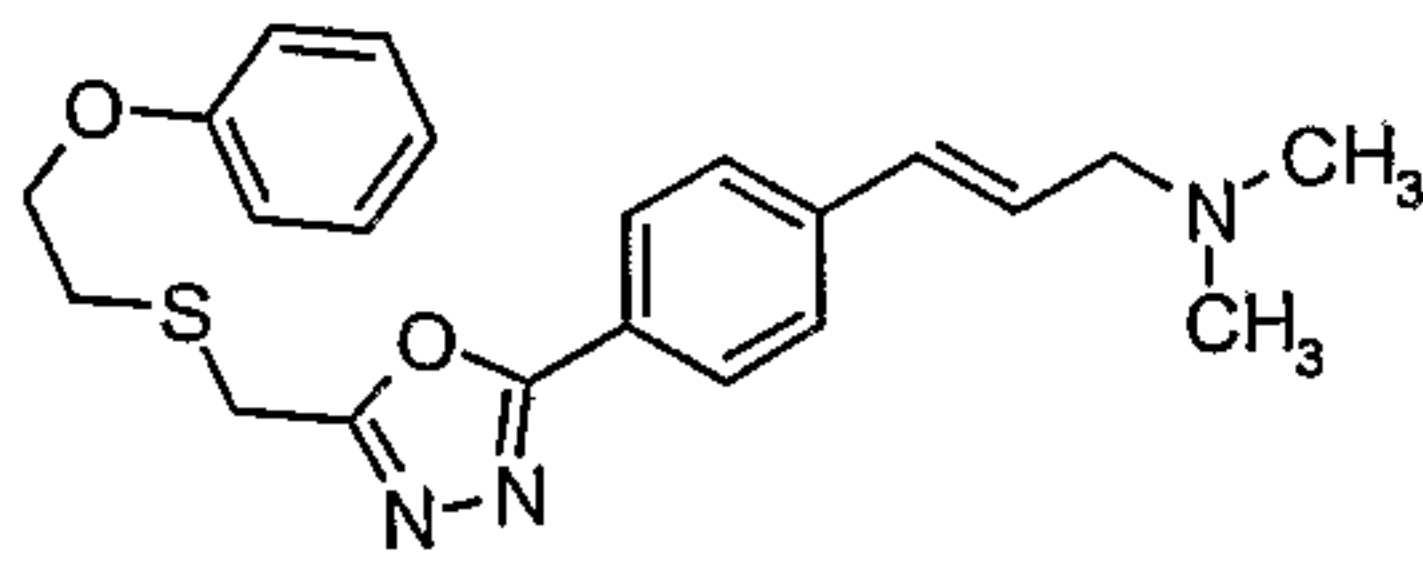
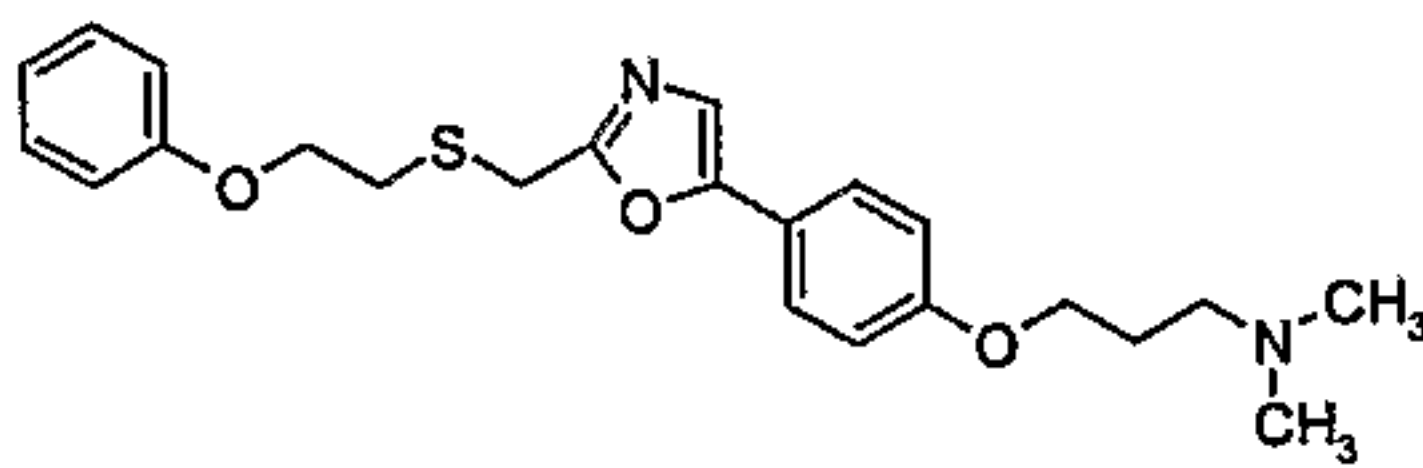
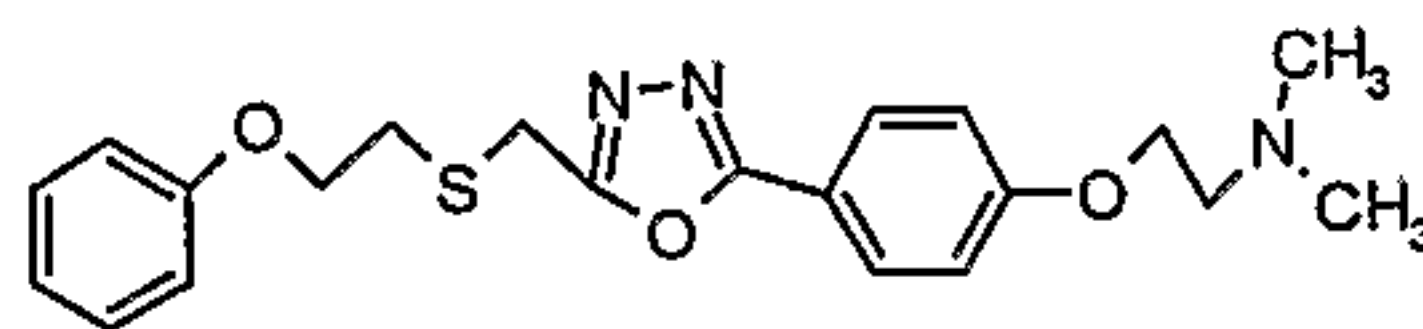
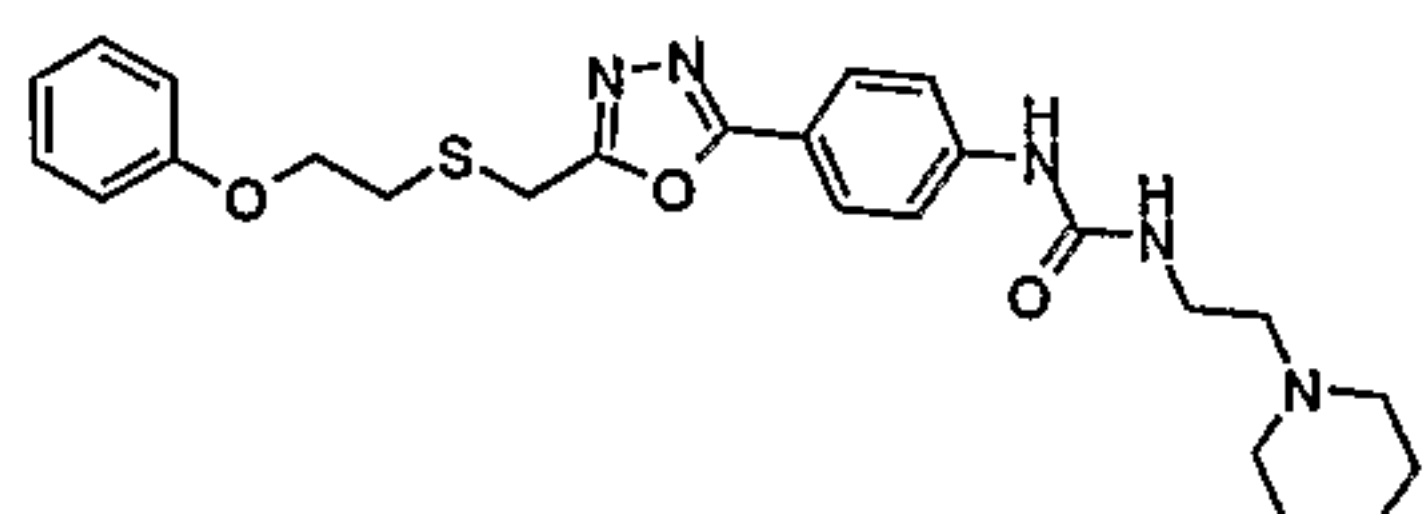
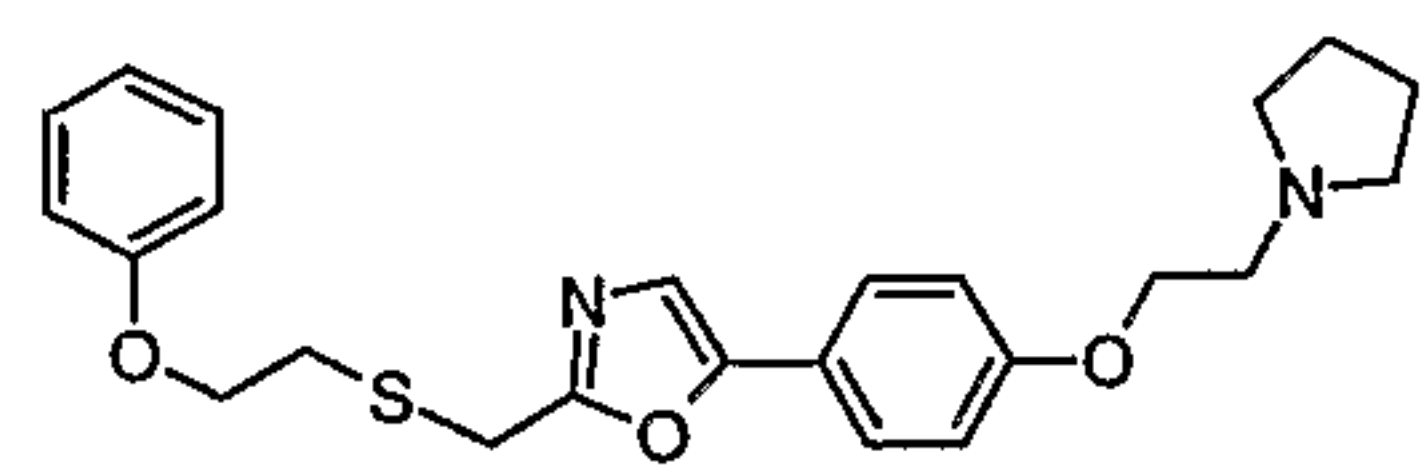
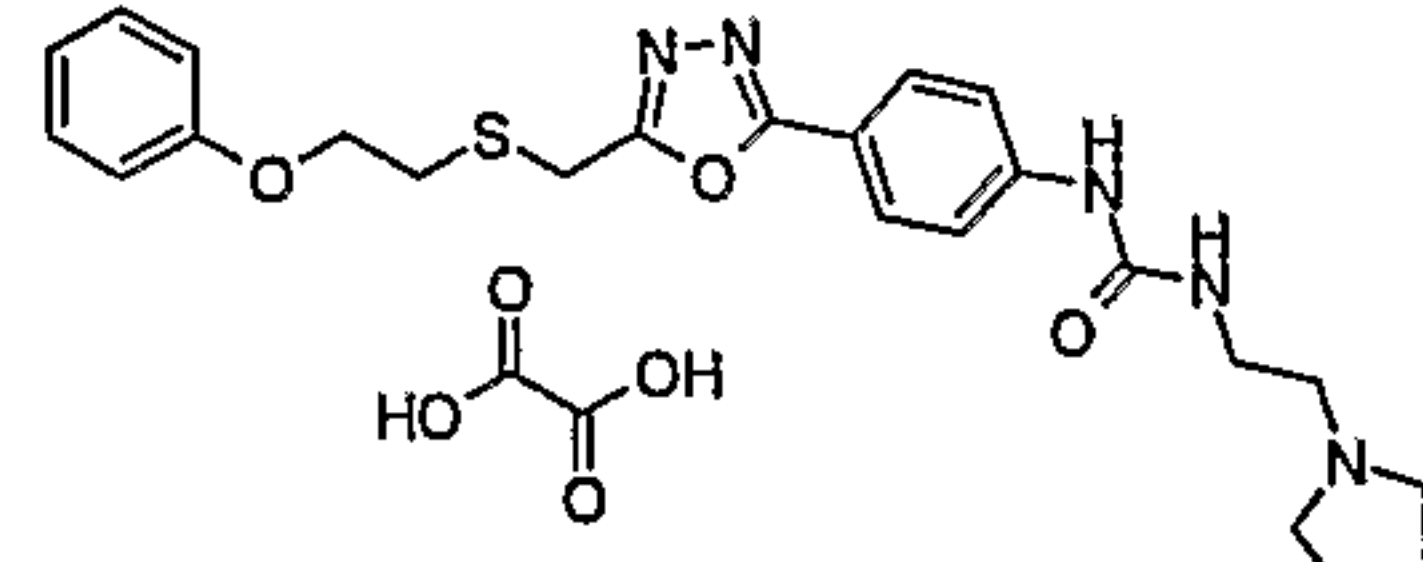
Functional antagonism of MCH activity is assessed by measuring the ability of test compound to inhibit MCH-stimulated binding of $\text{GTP}\gamma^{35}\text{S}$ to clone 43 membranes. Briefly, assays are carried out in Costar 3632 white opaque plates in a total volume of 200 μ l containing 25 mM Hepes, pH 7.5, 5 mM MgCl_2 , 10 μ g/ml saponin, 100 mM NaCl, 3
20 μ M GDP, 0.3 nM $\text{GTP}\gamma^{35}\text{S}$, 40 nM MCH (approximately equal to EC_{90}), 20 μ g of clone 43 membranes, 1.0 mg of wheat germ agglutinin scintillation proximity assay beads (WGA-SPA beads, Amersham) and a graded dose of test compound. The plates are sealed and left for 16-18 hrs at 4°C. After a 1 hr delay to allow plates to equilibrate to ambient temperature, bound $\text{GTP}\gamma^{35}\text{S}$ is determined by counting in a Microbeta Trilux (Wallac).

25 IC_{50} values (defined as the concentration of test compound required to reduce MCH-stimulated $\text{GTP}\gamma^{35}\text{S}$ binding by 50%) are determined by fitting the concentration-response data to a 4-parameter model (max response, min response, Hill coefficient, IC_{50}) using Excel. K_b values are calculated from IC_{50} values using a modification of the Cheng-Prusoff approximation as described by Leff and Dougal (Further concerns over Cheng-
30 Prusoff analysis, *Trends Pharmacol. Sci.* 14: 110-112 (1993)) after verifying competitive antagonism by Schild analysis. The EC_{50} for MCH alone is determined independently.

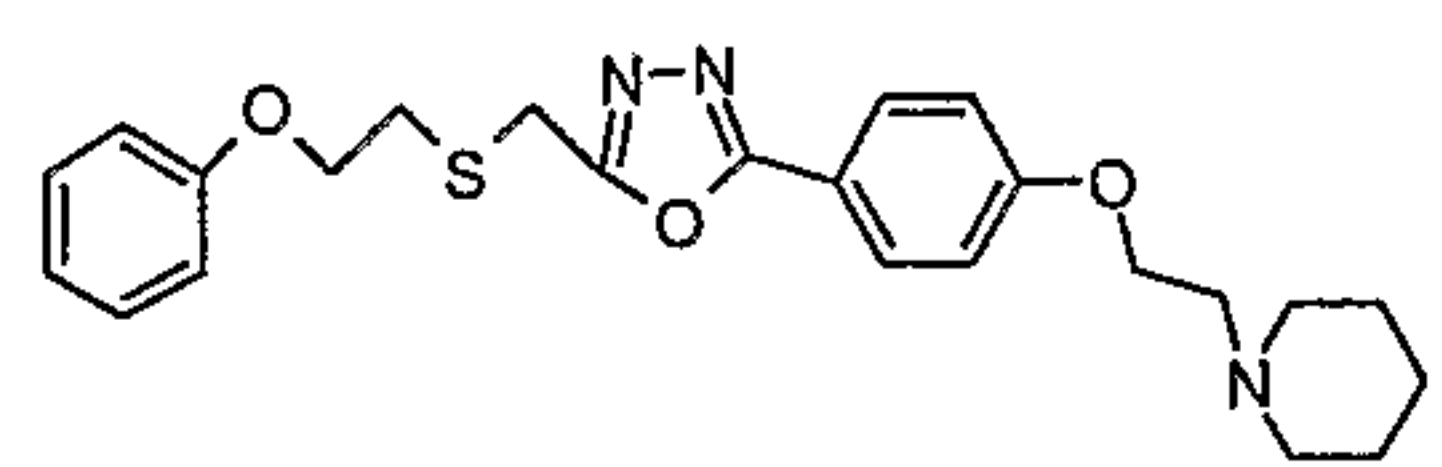
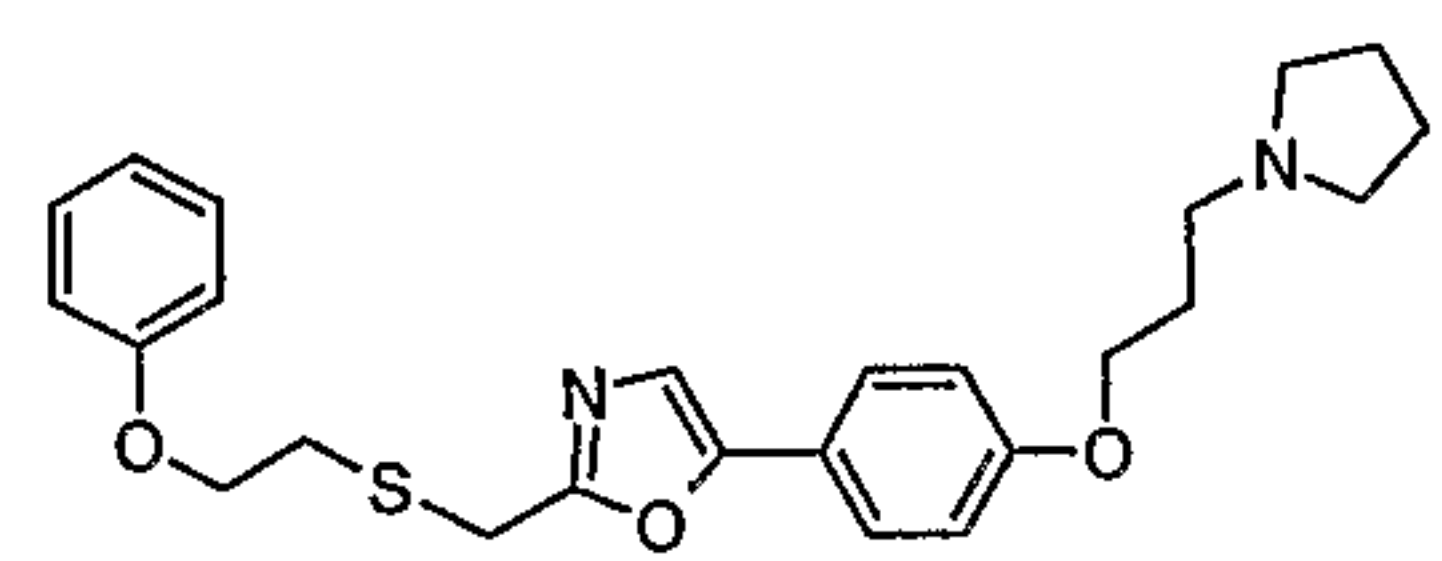
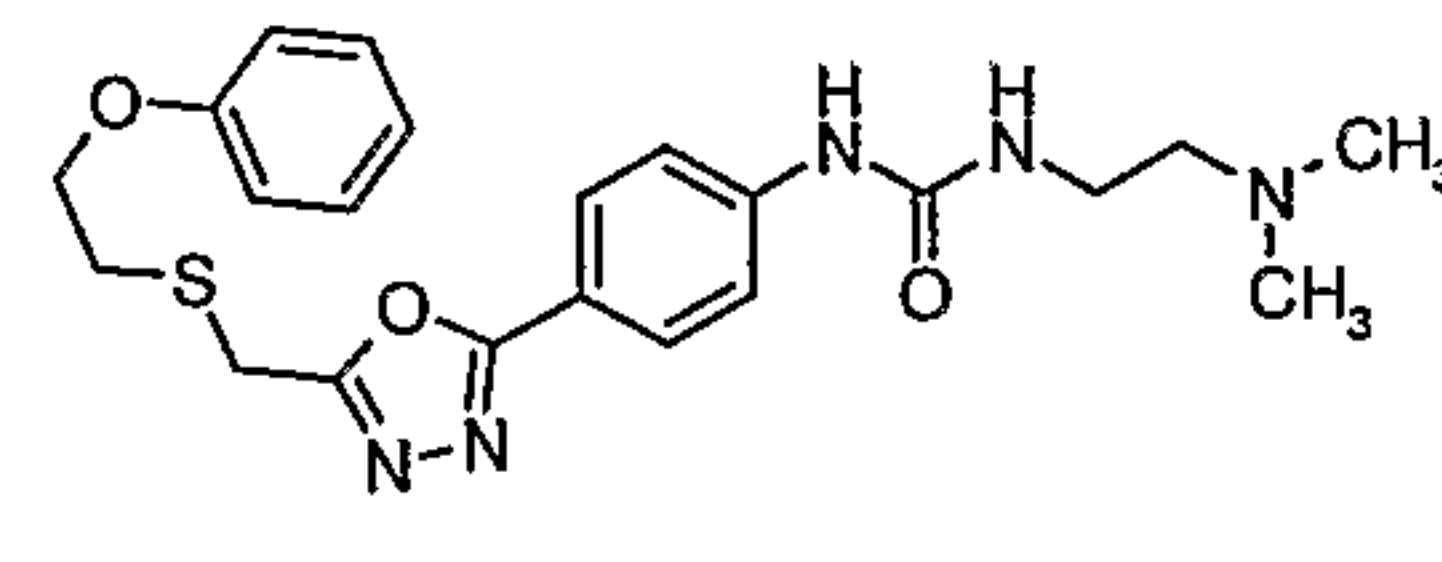
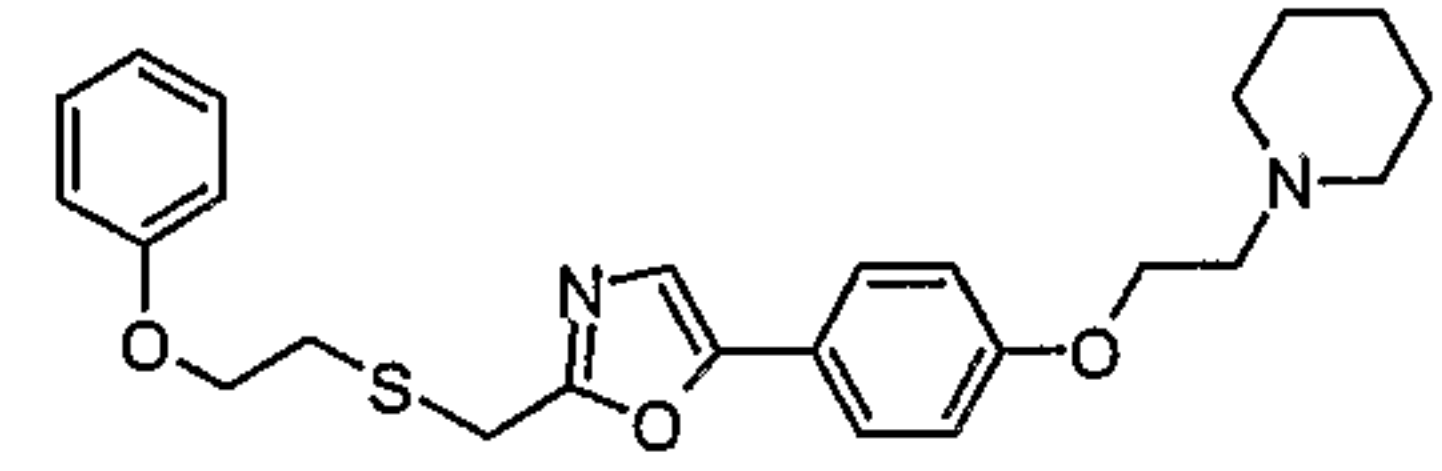
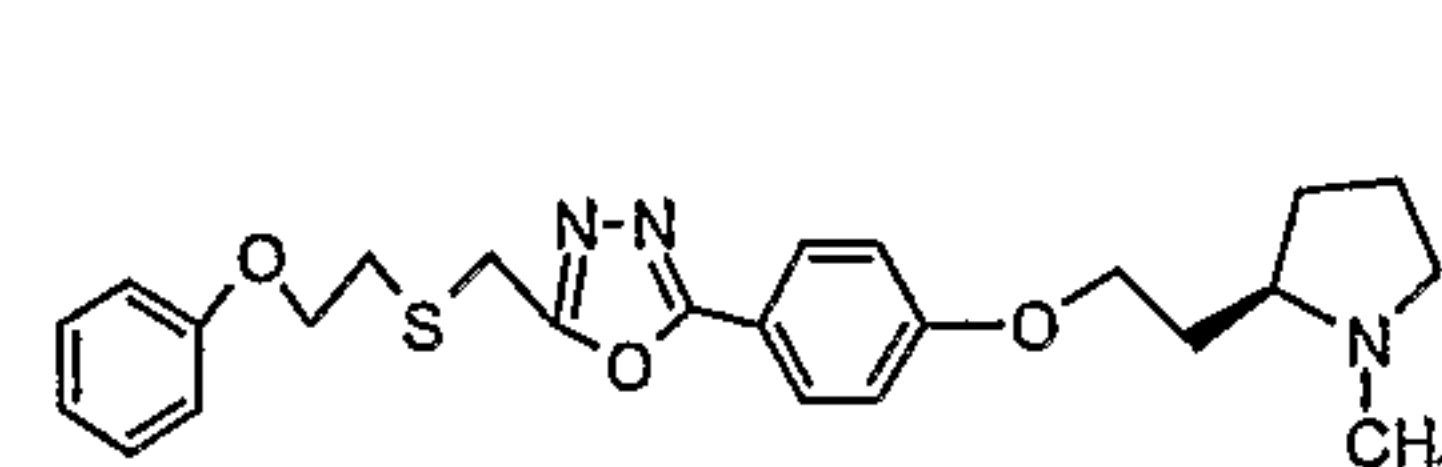
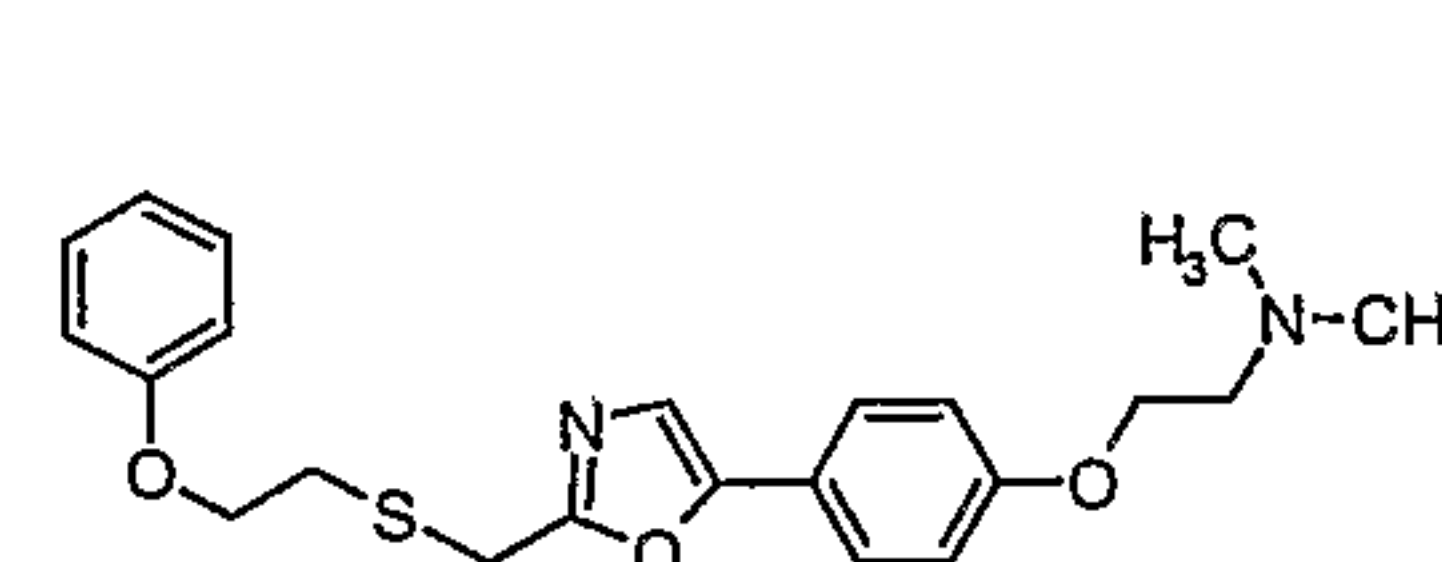
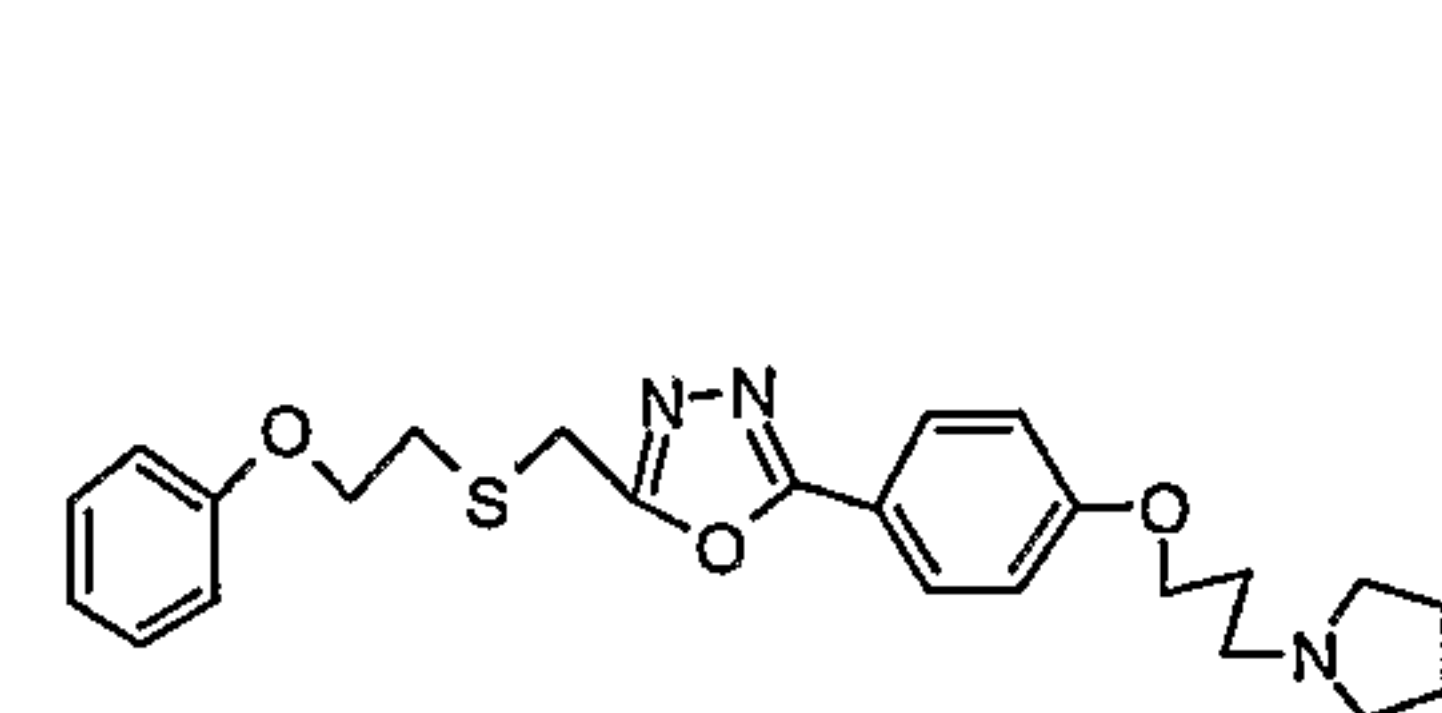
-57-

The MCHR1 binding and functional activities of 24 compounds in the oxadiazole series (tested in duplicate) are shown in Table 1

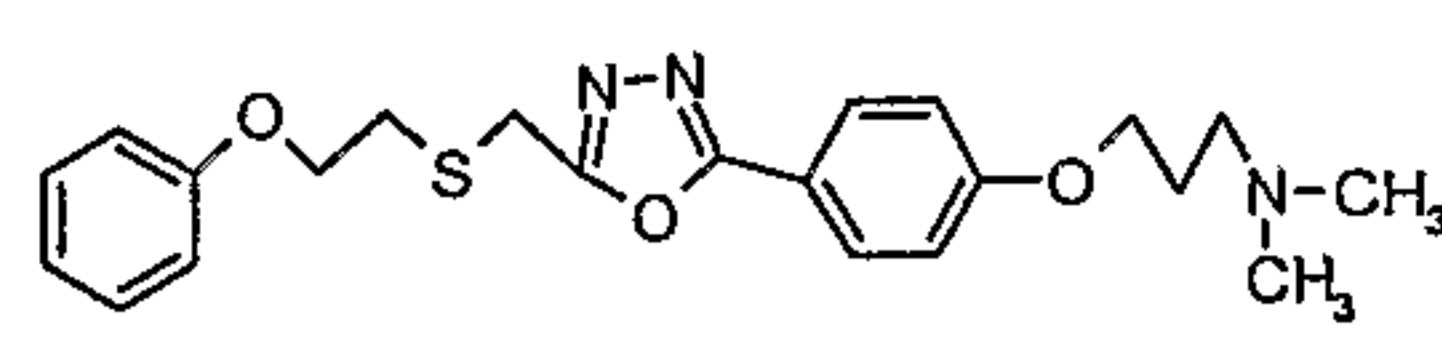
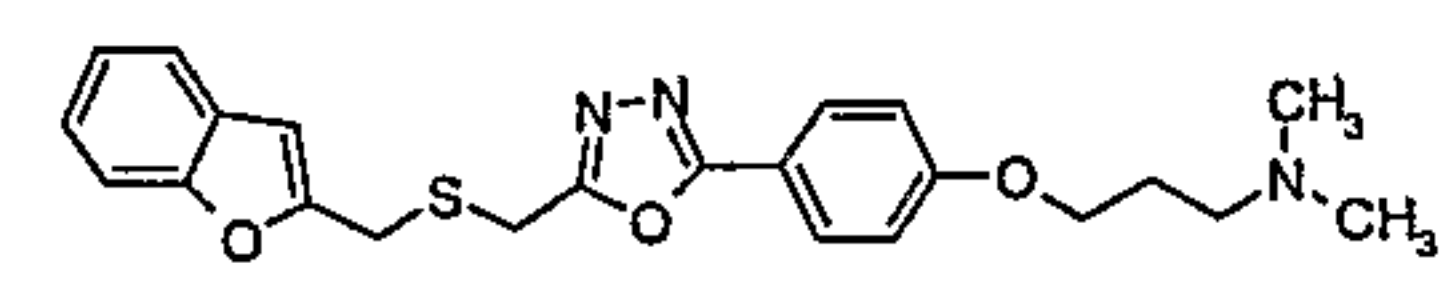
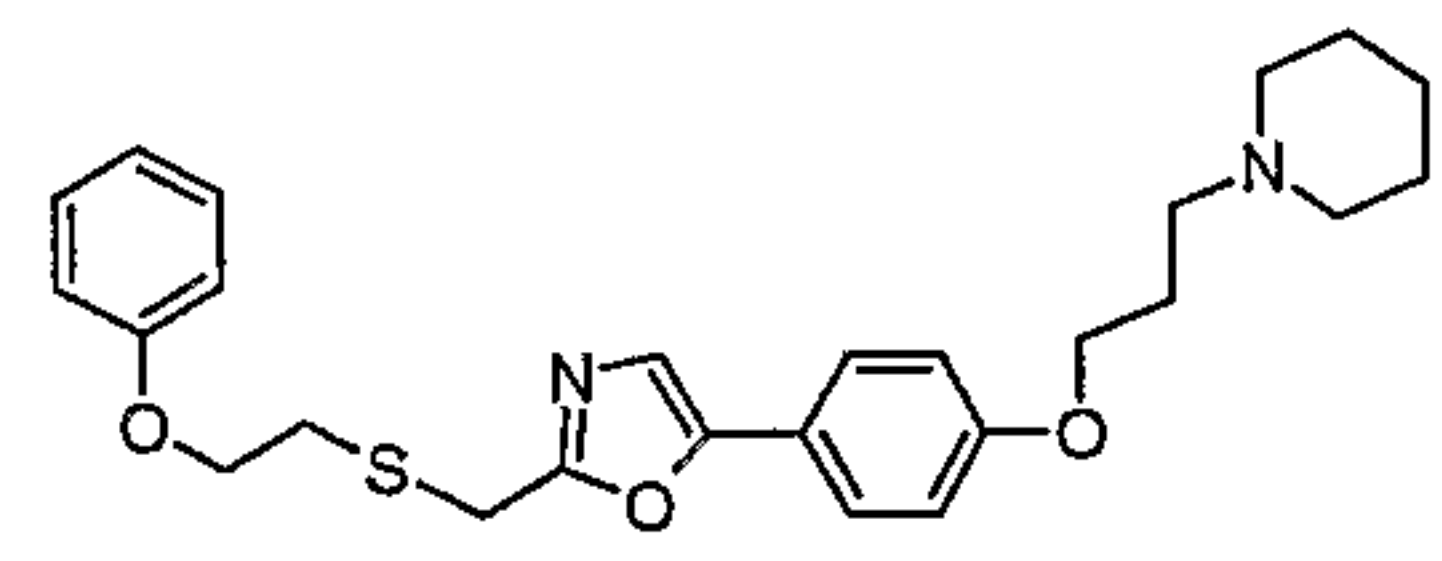
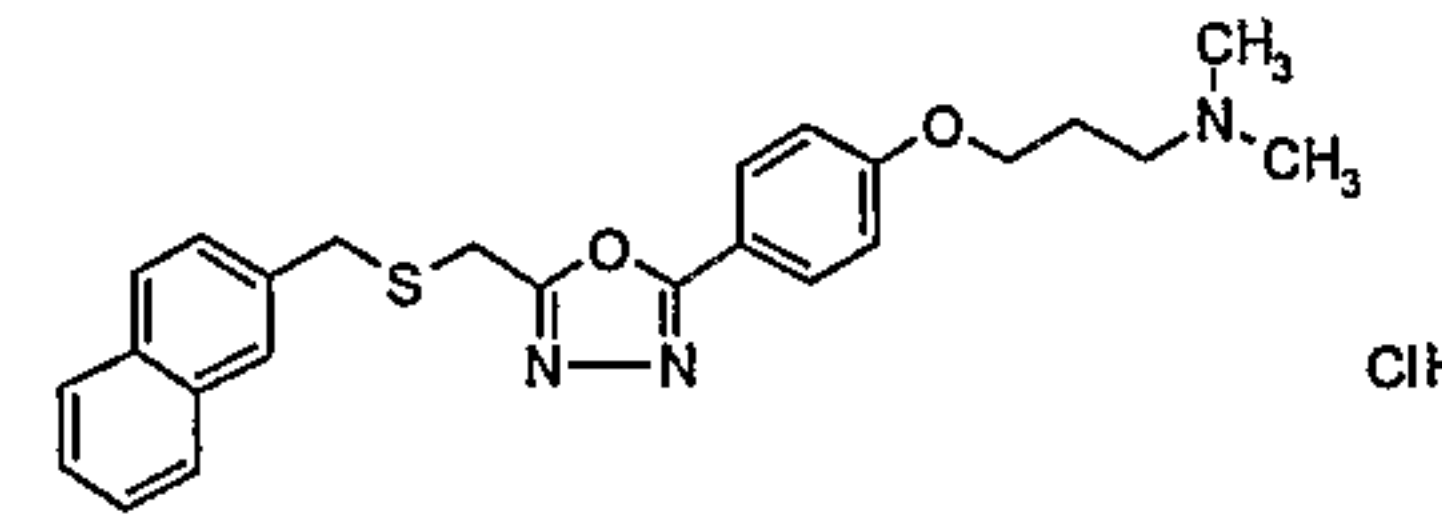
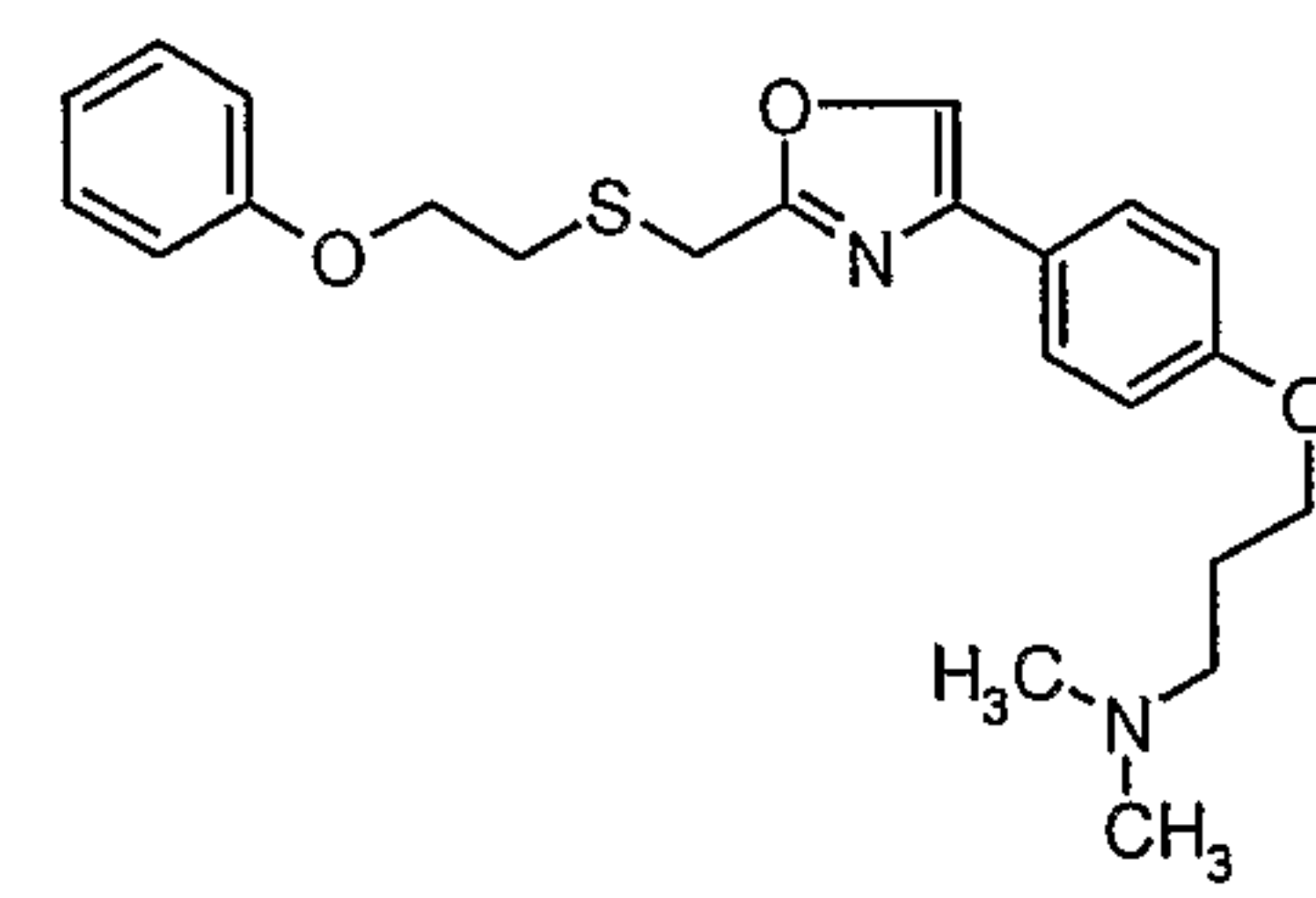
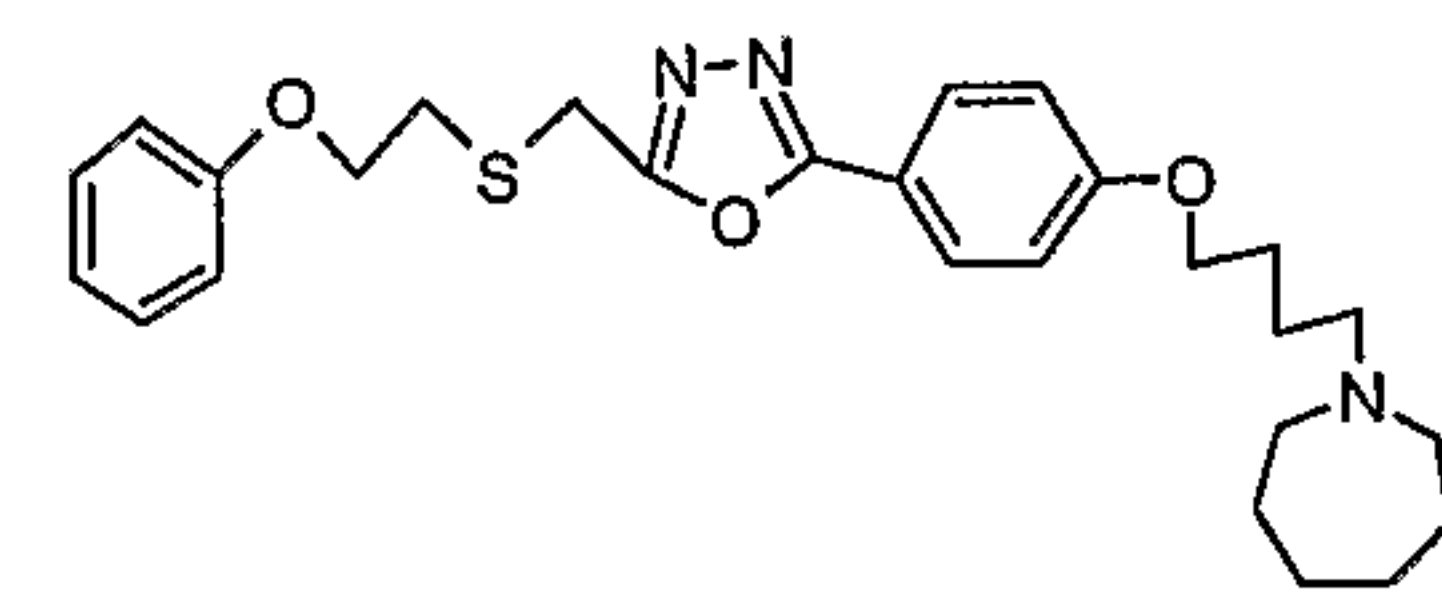
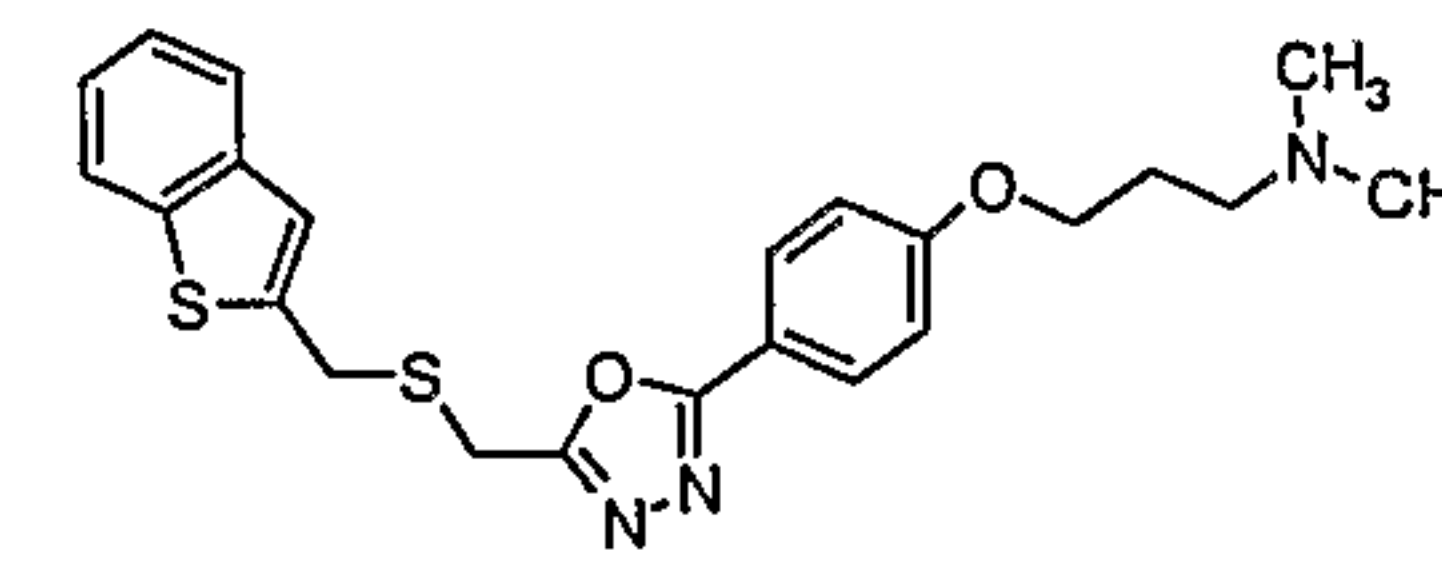
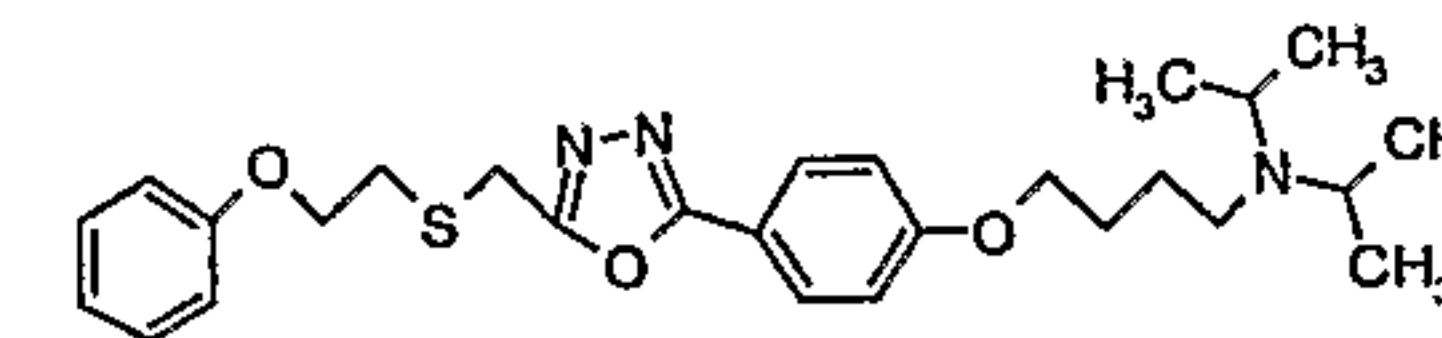
Table 1

Structure	K _i (nM)	K _b (nM)
	1.9	6.0
	3.7	11.6
	4.3	15.0
	5.3	13.6
	5.6	14.7
	5.8	12.0
	9	20.0

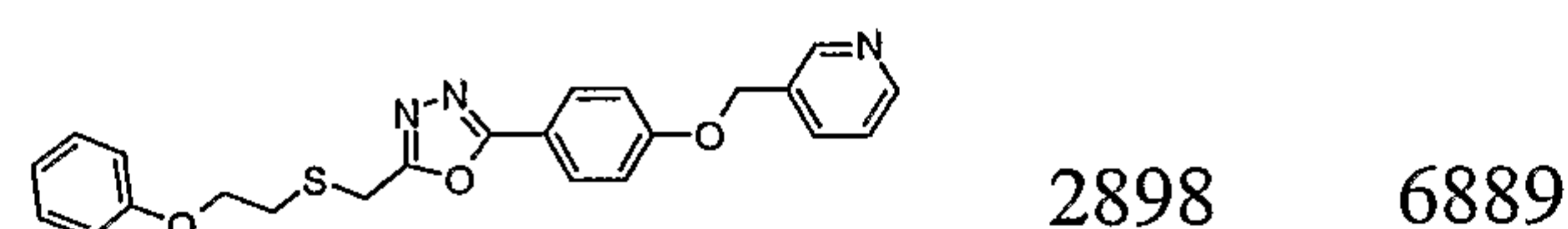
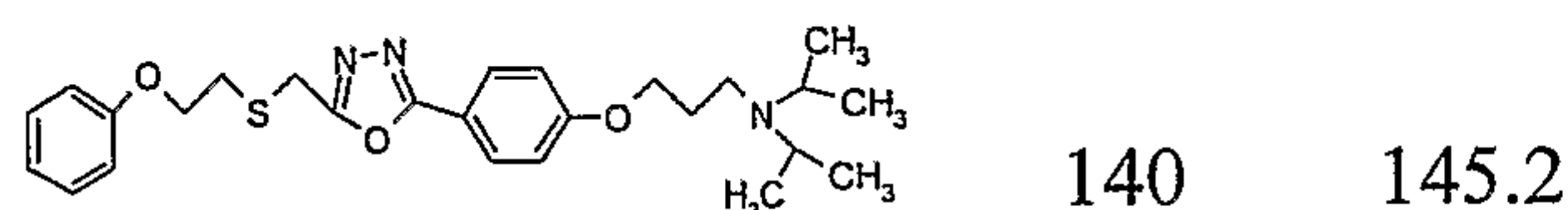
-58-

	9.2	19.8
	10.2	16.5
	10.4	16.2
	11.6	7.3
	12.9	39.6
	13.3	9.4
	14.3	18.1

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	16	11.9
 CO ₂ H-CO ₂ H	16.1	35.4
	17.9	15.9
 ClH	22.4	50.6
	35	41.5
	37.9	31.3
	48.4	139.5
	63.3	52.1

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In order to demonstrate in vivo efficacy of this series of compounds, compound of example 136 was injected intracerebro-ventricularly in the absence or presence of 2.1 nmol MCH, and its ability to block the effect of exogenous MCH was assessed. Diet-

5 induced obese male Long-Evans rats (Harlan, IN) weighing 500-550g at time of surgery were anesthetized with isoflurane. Stainless steel cannula guides (5mm length, 26 gauge, Plastics One, VA) were stereotaxically implanted in the lateral ventricle anteroposteriority: 0.8mm caudal to bregma; and lateral: 1.5mm from midline suture.

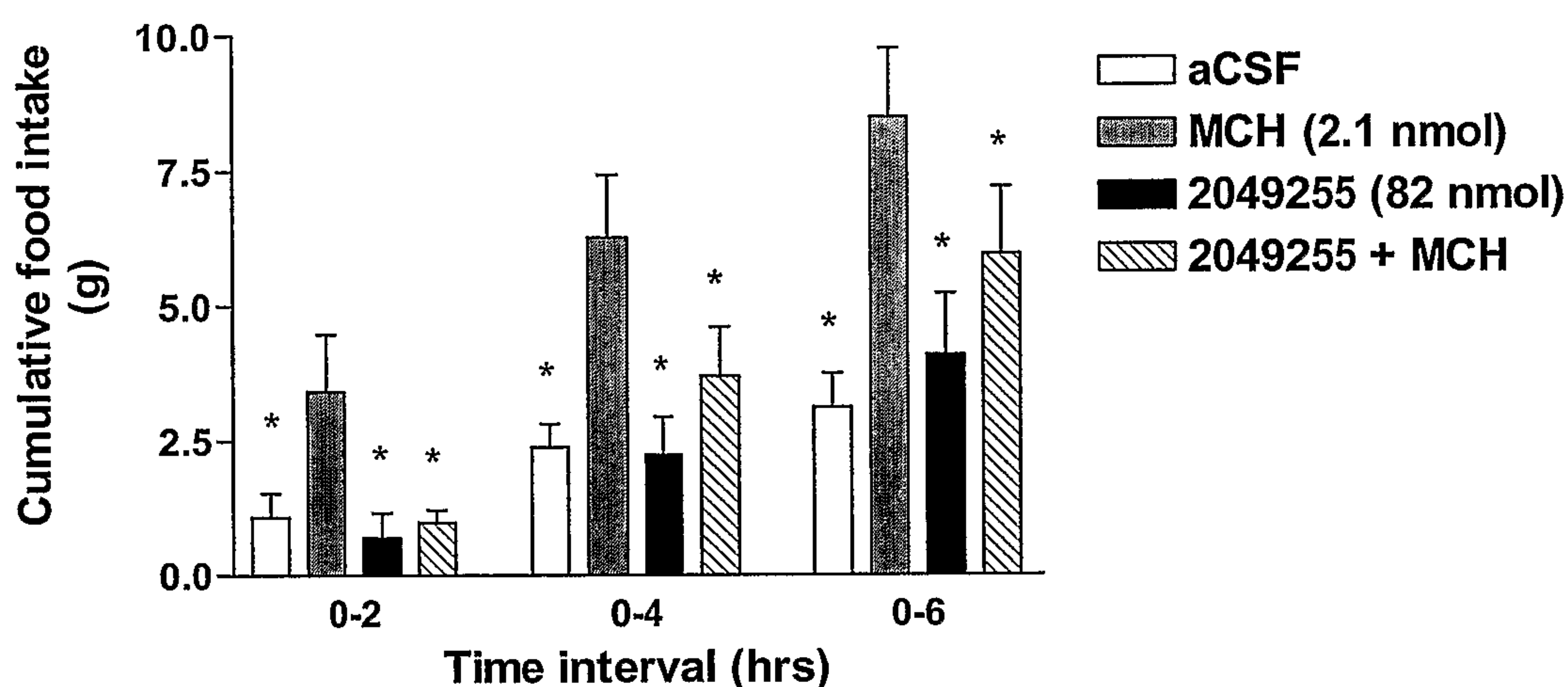
Animals were individually housed in a temperature regulated room (24°C) with a reverse

10 12 hour light/dark cycle (dark 10:00/22:00). Water and food (Teklad 95217, Harlan, WI) were available ad libitum. After surgery, animals were allowed to recover 7 days before experimental use. On test day, food was removed 1 hr prior to testing and animals (4 groups, n = 6 per group) were injected between 0900 and 1000 with 5μl of vehicle (artificial CSF), 2.1 nmol MCH, 82 nmol of compound of example 136, and MCH plus

15 compound of example 136. Cumulative food intake was measured at 2, 4 and 6 hours after injection. The results are shown in Fig. 1. Treatment with compound of example 136 completely blocked the orexigenic effect of exogenous MCH (* p < 0.05 vs. MCH alone).

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Fig.1



Utility

5 As antagonists of the MCHR1 binding, a compound of the present invention is useful in treating conditions in human and non-human animals in which the the MCHR1 receptor has been demonstrated to play a role. The diseases, disorders or conditions for which compounds of the present invention are useful in treating or preventing include, but are not limited to, diabetes mellitus, hyperglycemia, obesity, hyperlipidemia,

10 hypertriglyceridemia, hypercholesterolemia, atherosclerosis of coronary, cerebrovascular and peripheral arteries, gastrointestinal disorders including peptid ulcer, esophagitis, gastritis and duodenitis, (including that induced by *H. pylori*), intestinal ulcerations (including inflammatory bowel disease, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal ulcerations, neurogenic inflammation of airways, including cough,

15 asthma, depression, prostate diseases such as benign prostate hyperplasia, irritable bowel syndrome and other disorders needing decreased gut motility, diabetic retinopathy, neuropathic bladder dysfunction, elevated intraocular pressure and glaucoma and non-specific diarrhea dumping syndrome. By inhibiting the MCH activity the compounds of the invention provide anorexic effects. That is, the compounds of the invention are useful

20 as appetite suppressants and/or weightloss agents. Compounds of the present invention have also shown some affinity for the R2 isoform of MCHR. The compounds of the invention may also be used in combination with other approved therapeutic agents for the treatment and/or prevention of obesity and related diseases. In this format, the

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compounds of the present invention _____ the ositive effects of such approval combination treatments while minimizing the side effects due to the potential requirement of lower doses of such combination compounds. Such combination therapies may be delivered individually or in a combined formulation. Examples of compounds potentially
5 useful in combination with compounds of formula I include weight loss agents (Mevidia™, Xenical™), cholesterol lowering agents, glucose level control or modulating agents and the like.

In treating non-human, non-companion animals, the compounds of the present invention are useful for reducing weight gain and/or improving the feed utilization
10 efficiency and/or increasing lean body mass.

Formulation

The compound of formula I is preferably formulated in a unit dosage form prior to administration. Therefore, yet another embodiment of the present invention is a
15 pharmaceutical formulation comprising a compound of formula I and a pharmaceutical carrier.

The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the formulations of the present invention, the active ingredient (formula I compound) will usually be mixed with a
20 carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a liquid, tablet, capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions,
25 syrups, aerosol (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone,
30 cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents,

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sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

5

Formulation ExamplesFormulation 1

Tablets

Ingredient	Quantity (mg/tablet)
Active Ingredient	5 – 500
Cellulose, microcrystalline	200 - 650
Silicon dioxide, fumed	10 - 650
Stearate acid	5 - 15

10

The components are blended and compressed to form tablets.

Formulation 2

Suspensions

15

Ingredient	Quantity (mg/5 ml)
Active Ingredient	5 – 500 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to	5 ml

The medicament is passed through a No. 45 mesh U.S. sieve (approximately 355 micron opening) and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth

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paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 3

5

Intravenous Solution

Ingredient	Quantity
Active Ingredient	25 mg
Isotonic saline	1,000 ml

The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 ml per minute.

10

Dose

The specific dose administered is determined by the particular circumstances surrounding each situation. These circumstances include, the route of administration, the prior medical history of the recipient, the pathological condition or symptom being treated, the severity of the condition/symptom being treated, and the age and sex of the recipient. However, it will be understood that the therapeutic dosage administered will be determined by the physician in the light of the relevant circumstances, or by the veterinarian for non-human recipients.

15

Generally, an effective minimum daily dose of a compound of formula I is about 5, 10, 15, or 20 mg. Typically, an effective maximum dose is about 500, 100, 60, 50, or 40 mg. Most typically, the dose ranges between 5 mg and 60 mg. The exact dose may be determined, in accordance with the standard practice in the medical arts of "dose titrating" the recipient; that is, initially administering a low dose of the compound, and gradually increasing the dose until the desired therapeutic effect is observed.

20

25

Route of Administration

The compounds may be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, topical, intravenous, intramuscular or intranasal routes.

Combination Therapy

A compound of formula I may be used in combination with other drugs or
5 therapies that are used in the treatment/prevention/suppression or amelioration of the
diseases or conditions for which compounds of formula I are useful. Such other drug(s)
may be administered, by a route and in an amount commonly used therefor,
contemporaneously or sequentially with a compound of formula I. When a compound of
formula I is used contemporaneously with one or more other drugs, a pharmaceutical unit
10 dosage form containing such other drugs in addition to the compound of formula I is
preferred. Accordingly, the pharmaceutical compositions of the present invention include
those that also contain one or more other active ingredients, in addition to a compound of
formula I. Examples of other active ingredients that may be combined with a compound
of formula I, either administered separately or in the same pharmaceutical compositions,
15 include, but are not limited to:

- (a) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g.
troglitazone, pioglitazone, englitazone, MCC-555, BRL49653 and the like),
and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847;
20 (ii) biguanides such as metformin and phenformin;
- (b) insulin or insulin mimetics;
- (c) sulfonylureas such as tolbutamide and glipizide;
- (d) alpha-glucosidase inhibitors (such as acarbose);
- (e) cholesterol lowering agents such as
25 i. HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin,
fluvastatin, atorvastatin, and other statins),
ii. sequestrants (cholestyramine, colestipol and a dialkylaminoalkyl
derivatives of a cross-linked dextran),
iii. nicotiny alcohol nicotinic acid or a salt thereof,
30 iv. proliferator-activator receptor a agonists such as fenofibric acid derivatives
(gemfibrozil, clofibrat, fenofibrate and benzafibrate),

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- v. inhibitors of cholesterol absorption for example β -sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide,
- vi. probucol,
- vii. vitamin E, and
- 5 viii. thyromimetics;
- (f) PPAR δ agonists such as those disclosed in WO97/28149;
- (g) antiobesity compounds such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, and other β_3 adrenergic receptor agonists;
- 10 (h) feeding behavior modifying agents such as neuropeptide Y antagonists (e.g. neuropeptide Y5) such as those disclosed in WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822 and WO 97/20823;
- (i) PPAR α agonists such as described in WO 97/36579 by Glaxo;
- (j) PPAR γ antagonists as described in WO97/10813; and
- 15 (k) serotonin reuptake inhibitors such as fluoxetine and sertraline
- (l) antipsychotic agents such as for example olanzapine.

Examples

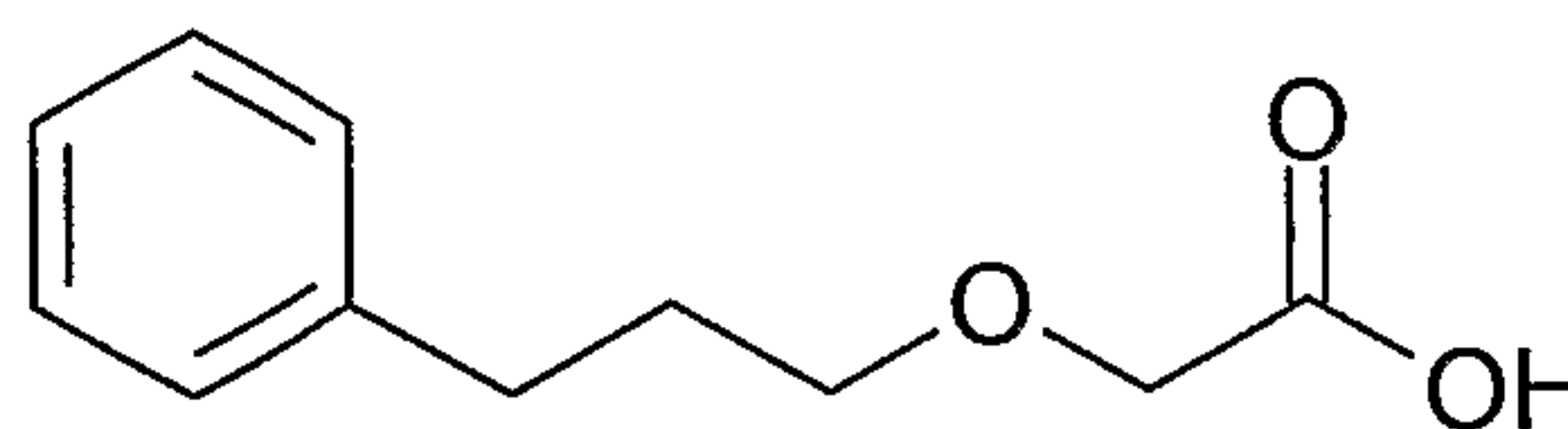
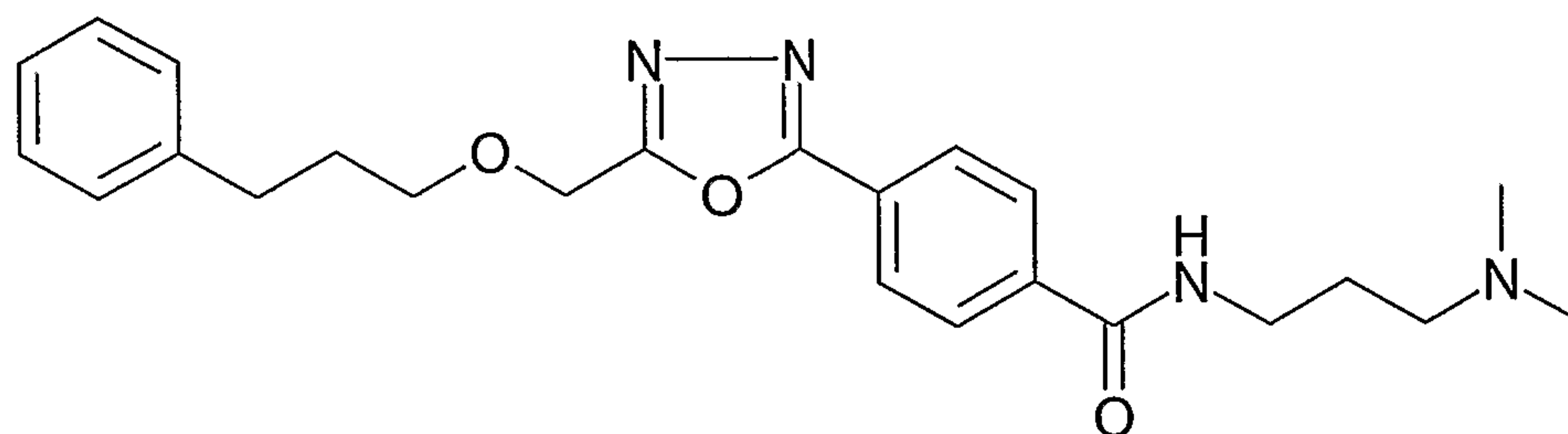
The following examples are only illustrative of the preparation protocols and Applicants' ability to prepare compounds of the present invention based on the schemes presented or modifications thereof. The examples are not intended to be exclusive or exhaustive of compounds made or obtainable .

20

Example 1

25 Preparation of *N*-(3-Dimethylaminopropyl)-4-[5-(3-phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 3-phenyl-1-propanol

-67-



a) (3-Phenylpropoxy)acetic acid

To a solution of 3-phenyl-1-propanol (5.0 g, 36.7 mmol) in 36 mL THF at room temperature was added, in portions, sodium hydride (1.54 g, 38.5 mmol). After 30

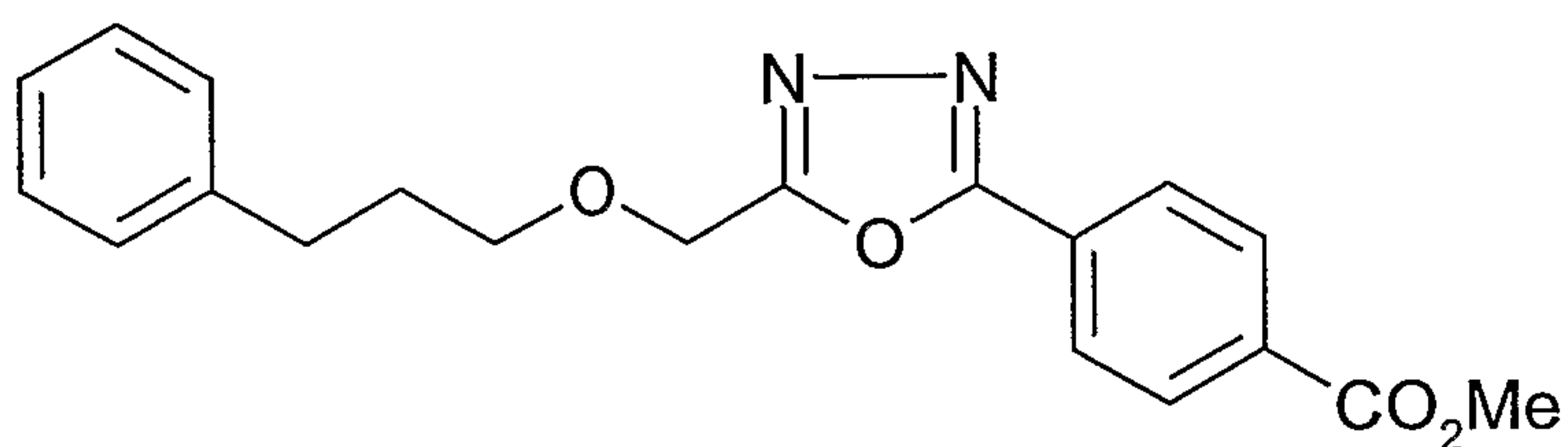
5 minutes, a solution of methyl bromoacetate (6.18 g, 40.4 mmol) in 18 mL THF was added and the resultant mixture stirred at room temperature for 4.1 hours. Next, the mixture was diluted with 20 mL H₂O, then lithium hydroxide (2.64 g, 110 mmol) was added and the biphasic solution was heated at 60°C for 1.5 hours. The mixture was then cooled to room temperature, diluted with Et₂O and washed three times with H₂O. The combined aqueous

10 phases were acidified with concentrated HCl until pH < 2. The resultant mixture was extracted three times with Et₂O. The organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated to afford an oil. Purification by flash filtration chromatography on silica gel (elution with CH₂Cl₂ followed by 9:1 CH₂Cl₂:MeOH) afforded 2.7 g (38%) of (3-phenylpropoxy)acetic acid as an oil.

15 ¹H NMR (DMSO-d₆) δ 7.30-7.15 (m, 5H), 3.99 (s, 2H), 3.5 (t, 2H, J=6 Hz), 2.63 (t, 2H, J=7 Hz), 1.76-1.85 (m, 2H). IR (CHCl₃, cm⁻¹) 3027, 3019, 3013, 2948, 1779, 1732, 1454, 1246, and 1136. MS (ES) m/e 193. Anal. Calcd for C₁₁H₁₄O₃: C, 68.02; H, 7.27. Found C, 68.58; H, 6.91

20 b) 4-[5-(3-Phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester

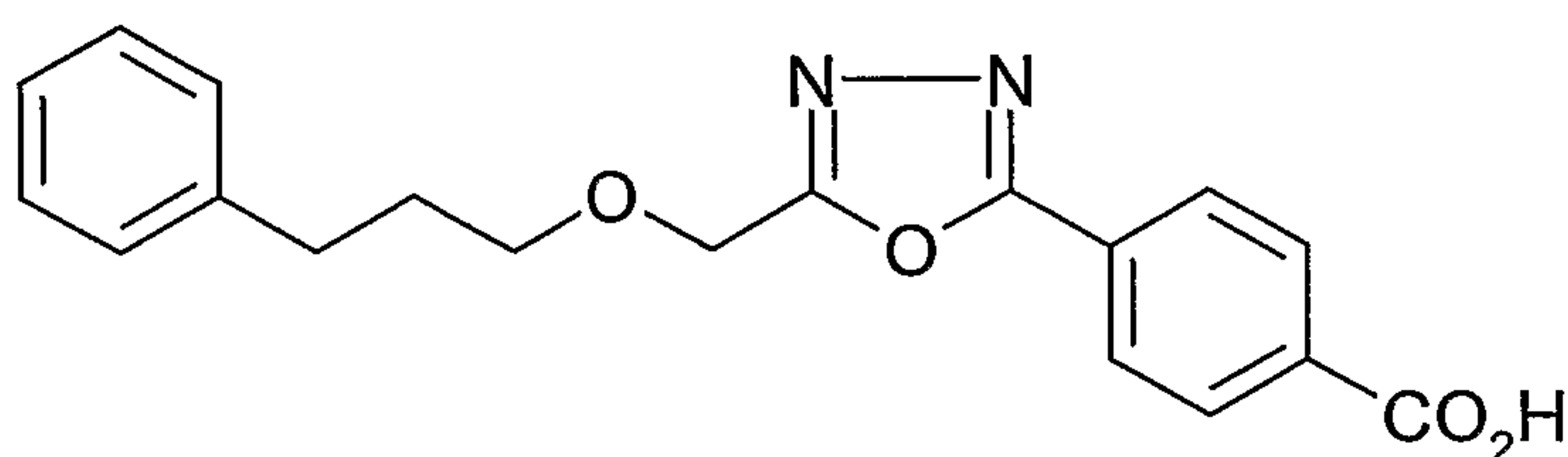
-68-



To a solution of (3-phenylpropoxy)acetic acid (1.11 g, 5.7 mmol) in 14.6 mL toluene at room temperature was added 1,3-dicyclohexylcarbodiimide (1.11 g, 5.7 mmol). After five minutes, 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.16 g, 5.7 mmol) was added and the suspension was heated at 100°C for thirty minutes, then at 130°C for thirty minutes. The mixture was cooled to room temperature then diluted with CH₂Cl₂ and filtered. Concentration of the filtrate afforded a solid. Purification by radial chromatography on silica gel (elution with 50% EtOAc:hexane) followed by crystallization of the isolated material from Et₂O:hexane afforded 0.921 g (46%) of 4-[5-(3-Phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester.

¹H NMR (DMSO-d₆) δ 8.17 (s, 4H), 7.1-7.3 (m, 5H), 4.8 (s, 2H), 3.9 (s, 3H), 3.6 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=8 Hz), 1.8-1.9 (m, 2H). IR (CHCl₃, cm⁻¹) 1722, 1438, 1283, 1111. MS (ES) m/e 353. Anal. Calcd for C₂₀H₂₀N₂O₄: C, 68.17; H, 5.72; N, 7.95. Found C, 67.78; H, 5.69; N, 7.74.

c) 4-[5-(3-Phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid

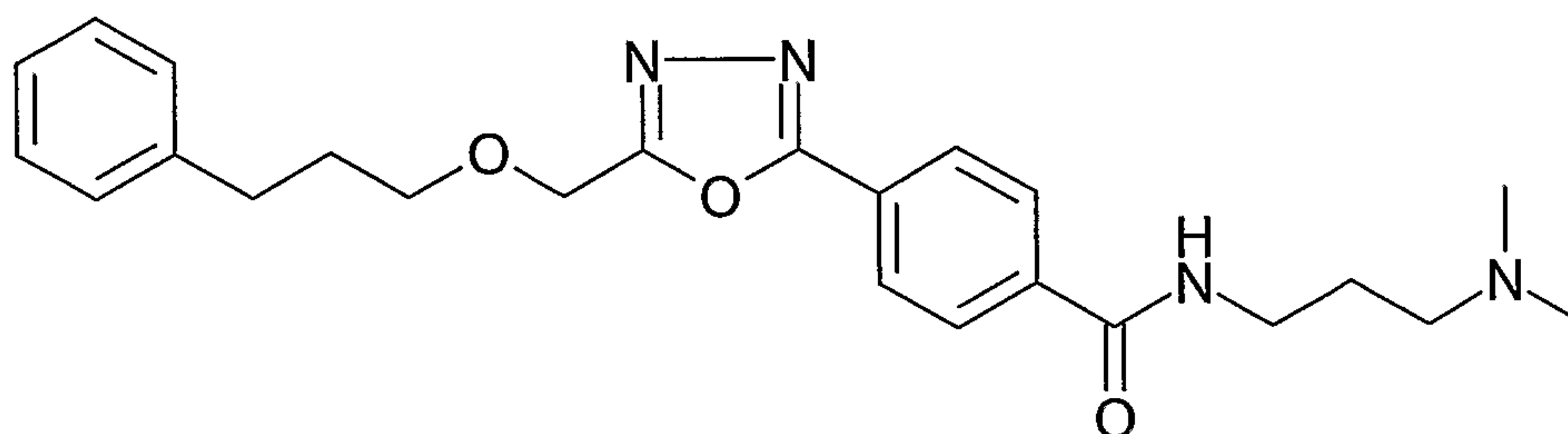


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A mixture of 4-[5-(3-phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.866 g, 2.5 mmol) and lithium hydroxide (0.177 g, 7.4 mmol) in 3.85 mL THF and 1.65 mL H₂O was stirred at 60°C for 1 hour. Upon cooling to room temperature the mixture was acidified with concentrated HCl (0.421 mL) and reduced in volume to
 5 remove the THF. The resulting insoluble material was collected by filtration to afford 0.760 g (91%) of 4-[5-(3-phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid.

¹H NMR (DMSO-d₆) δ 8.1 (m, 4H), 7.1-7.3 (m, 5H), 4.8 (s, 2H), 3.6 (t, 2H, J=6Hz) 2.6 (t, 2H, J=7Hz), 1.8-1.9 (m, 2H). IR (CHCl₃, cm⁻¹) 3097, 3028, 2944, 2856, 2675, 2559, 1706, 1685, 1583, 1551, 1433, 1292, 1108, 874, 719. MS (ES) m/e 339, 337
 10 Anal. Calcd for C₁₉H₁₈N₂O₄: C, 67.45; H, 5.36; N, 8.28. Found C, 66.34; H, 5.31; N, 8.18.

d) *N*-(3-Dimethylaminopropyl)-4-[5-(3-phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide



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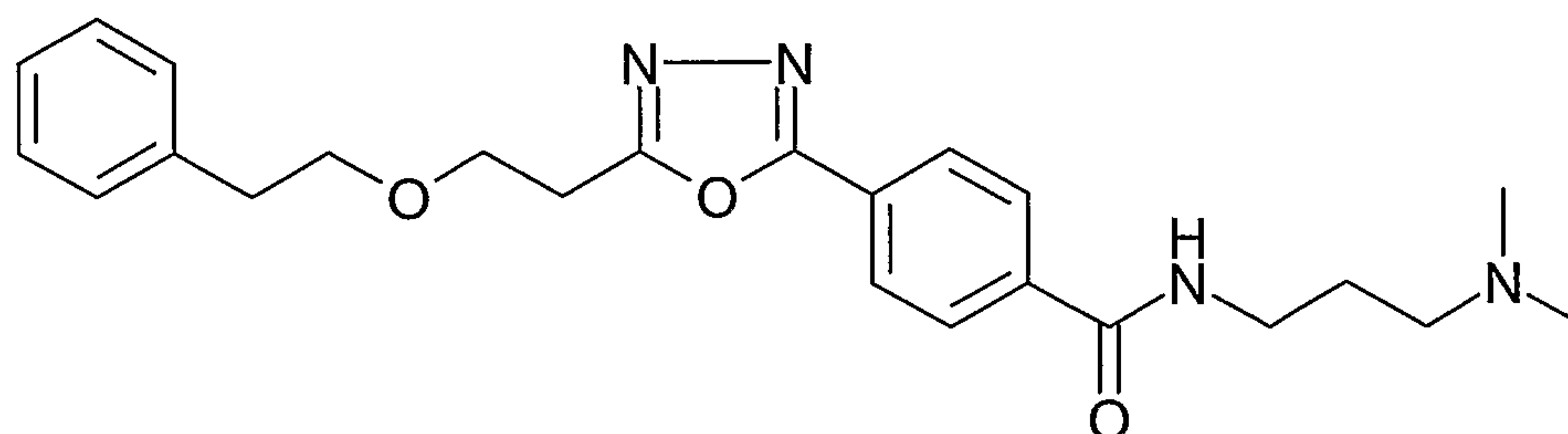
A mixture of 4-[5-(3-phenylpropoxymethyl)-[1,3,4] oxadiazol-2-yl]benzoic acid (0.730 g, 2.2 mmol) and 1,1'-carbonyldi-imidazole (0.367 g, 2.3 mmol) was stirred in 18 mL THF at 60°C for 45 minutes. After stirring an additional 45 minutes at room temperature, 3-(dimethylamino)propylamine (0.265 g, 2.59 mmol) was added. After
 20 stirring approximately 24 h at room temperature, the mixture was concentrated to an oil. The oil was treated with Et₂O and the resultant suspension was filtered. The filtrate was treated with hexane and the resultant crystals were collected by filtration to afford 0.451 g (49%) of *N*-(3-dimethylaminopropyl)-4-[5-(3-phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

25 ¹H NMR (DMSO-d₆) δ 8.7 (d, 1H, J=5Hz), 8.1 (d, 2H, J=8Hz), 8.0 (d, 2H, J=8Hz), 7.1-7.3 (m, 5H), 4.8 (s, 2H), 3.5 (t, 2H, J=6Hz), 3.32 (m, 2H), 2.62 (t, 2H, J=7Hz), 2.27 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.86 (m, 2H), 1.67 (m, 2H).

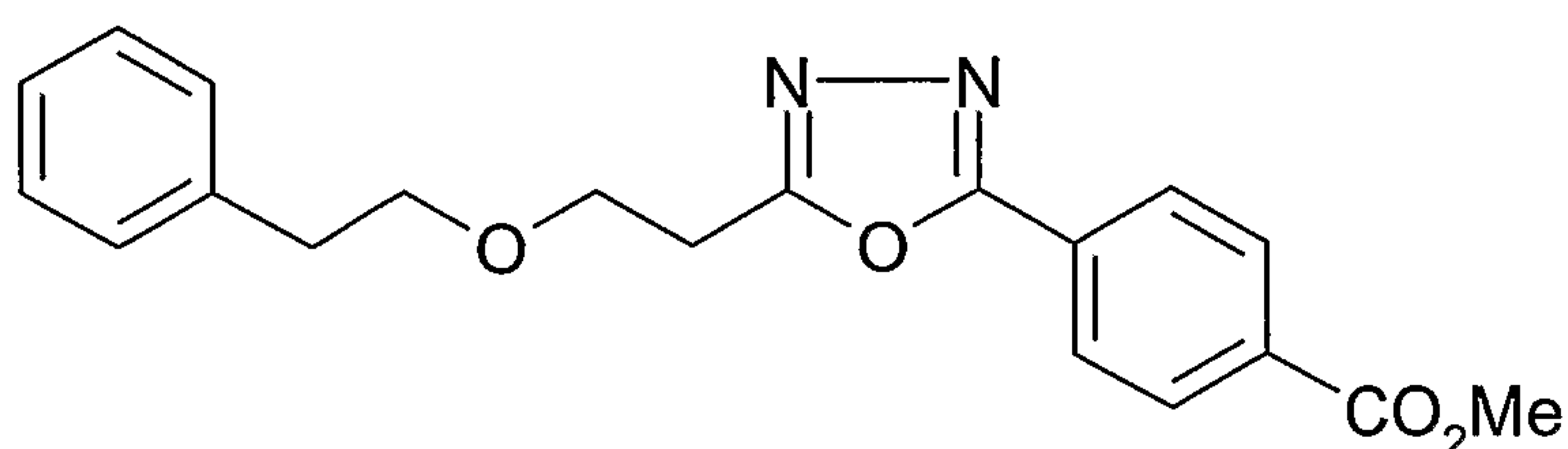
-70-

MS (ES) m/e, 423, 421. Anal. Calcd for $C_{24}H_{30}N_4O_3$: C, 68.22; H, 7.16; N, 13.26. Found C, 67.89; H, 7.09; N, 13.15. Mp($^{\circ}$ C)=90.

Example 2 N-(3-Dimethylaminopropyl)-4-[5-(2-phenethyloxyethyl)-[1,3,4-oxadiazol-2-yl]benzamide from 3-Phenethyloxypropionic acid



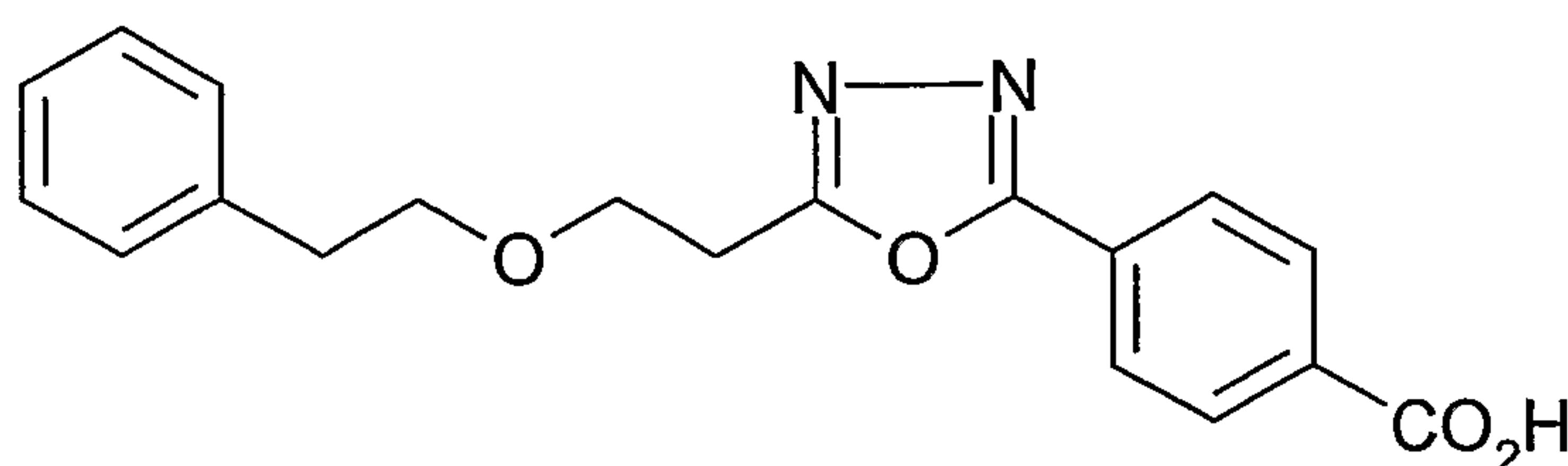
a) 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 3-Phenethyloxy propionic acid (1.02 g, 5.3 mmol), 1,3-dicyclohexylcarbodiimide (1.08 g, 5.3 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.06 g, 5.2 mmol) to afford 0.79 g (43%) of 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as a crystalline solid.

^1H NMR (DMSO- d_6) δ 8.09-8.18 (m, 4H), 7.07-7.17 (m, 5H), 3.91 (s, 3H), 3.85 (t, 2H, $J=6\text{Hz}$), 3.65 (t, 2H, $J=7\text{Hz}$), 3.20 (t, 2H, $J=6\text{Hz}$), 2.78 (t, 2H, $J=7\text{Hz}$). IR (CHCl_3 , cm^{-1}) 3009, 2954, 2871, 1721, 1438, 1282, 1111. MS (ES) m/e, 353. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found C, 68.38; H, 5.66; N, 8.01.

b) 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid

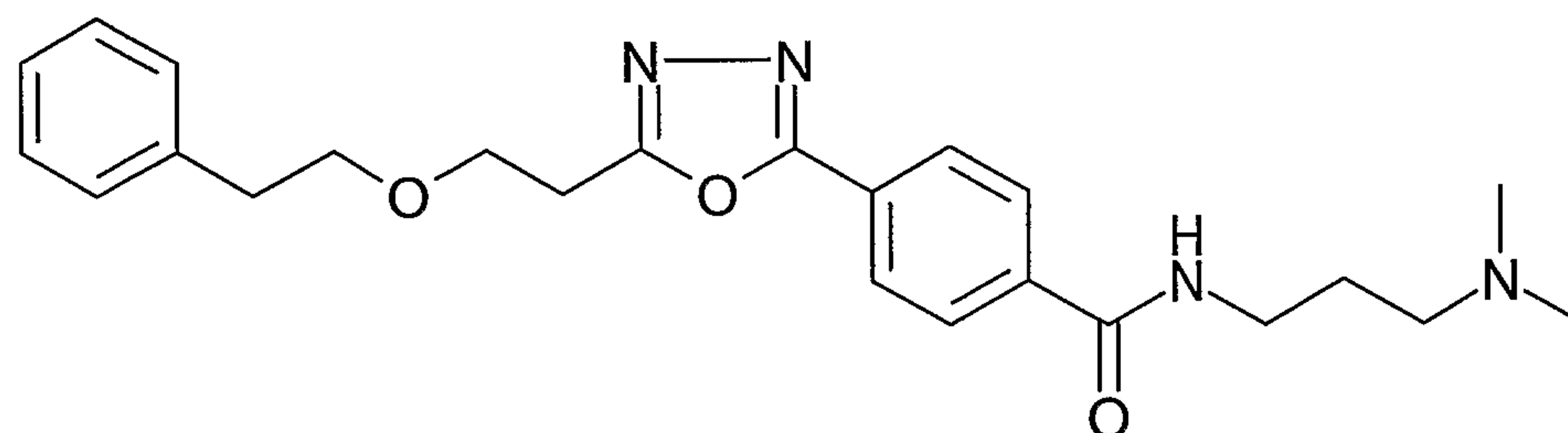


-71-

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester 0.724 g, 2.1 mmol) and lithium hydroxide (0.148 g, 6.2 mmol) to afford 0.558 g (80%) of 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid as solid.

^1H NMR (DMSO- d_6) δ 8.05-8.16 (m, 4H), 7.07-7.17 (m, 5H), 3.85 (t, 2H, $J=6\text{Hz}$), 3.65 (t, 2H, $J=7\text{Hz}$), 3.20 (t, 2H, $J=6\text{Hz}$), 2.78 (t, 2H, $J=7\text{Hz}$). IR (KBr, cm^{-1}) 3431, 1705, 1685, 1434, 1290, 1118, 715. MS (ES) m/e , 339, 337. Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$: C, 67.45; H, 5.36; N, 8.28. Found C, 64.37; H, 5.08; N, 9.05.

c) N-(3-Dimethylaminopropyl)-4-[5-(2-phenethyloxyethyl)-[1,3,4-oxadiazol-2-yl]benzamide

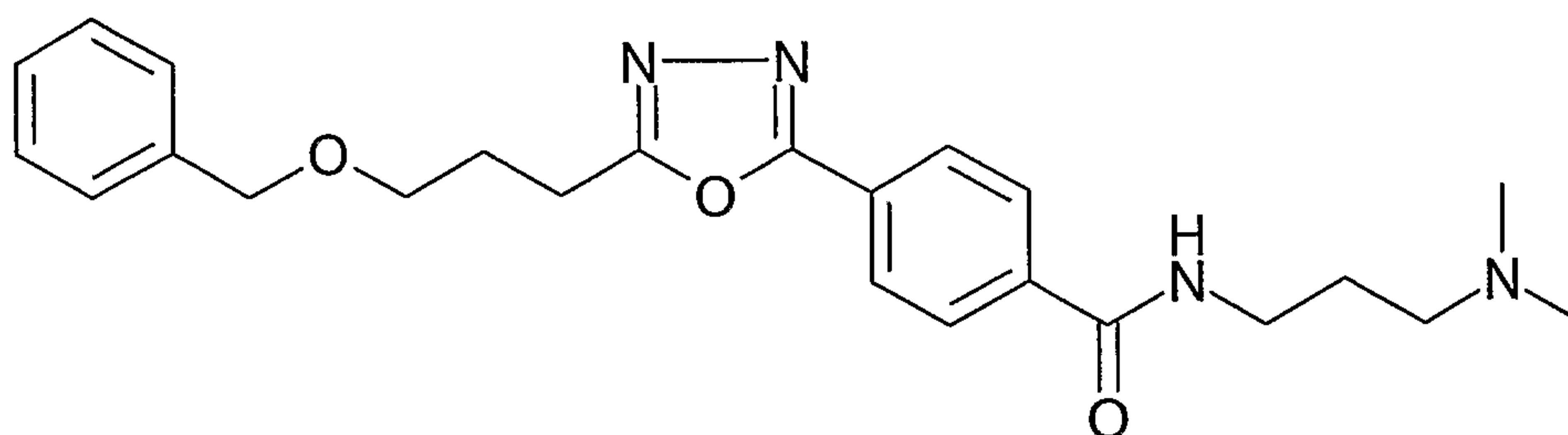


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.528 g, 1.6 mmol), 1,1'-carbonyldiimidazole (0.266 g, 1.6 mmol) and 3-(dimethylamino)propylamine (0.392 g, 3.8 mmol) to afford 0.309g (47%) of N-(3-Dimethylaminopropyl)-4-[5-(2-phenethyloxyethyl)-[1,3,4-oxadiazol-2-yl]benzamide as a crystalline solid.

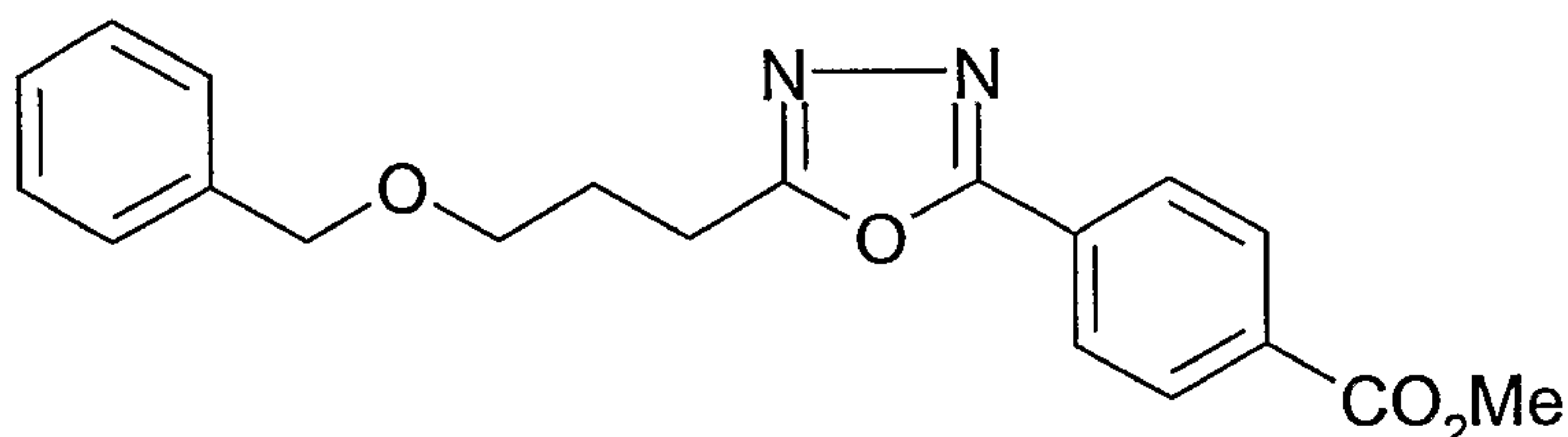
^1H NMR (DMSO- d_6) δ 8.71 (t, 1H, $J=5\text{Hz}$), 8.05 (d, 2H, $J=9\text{Hz}$), 8.02 (d, 2H, $J=9\text{Hz}$), 7.09-7.17 (m, 5H), 3.85 (t, 2H, $J=9\text{Hz}$), 3.65 (t, 2H, $J=7\text{Hz}$), 3.29 (m, 2H), 3.19 (t, 2H, $J=6\text{Hz}$), 2.78 (t, 2H, $J=7\text{Hz}$), 2.26 (t, 2H, $J=7\text{Hz}$), 2.14 (s, 6H), 1.66 (m, 2H). IR (CHCl_3 , cm^{-1}) 3307, 2942, 2879, 2761, 1631, 1540, 1116, 858, 699. MS (ES) m/e , 423, 421. Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_3$: C, 68.22; H, 7.16; N, 13.26. Found C, 67.83; H, 7.24; N, 13.19. $\text{Mp}(\text{°C})=92$.

Example 3 Preparation of 4-[5-(3-Benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzamide from 4-benzyloxybutyric acid

-72-



a) 4-[5-(3-Benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzoic acid methyl ester

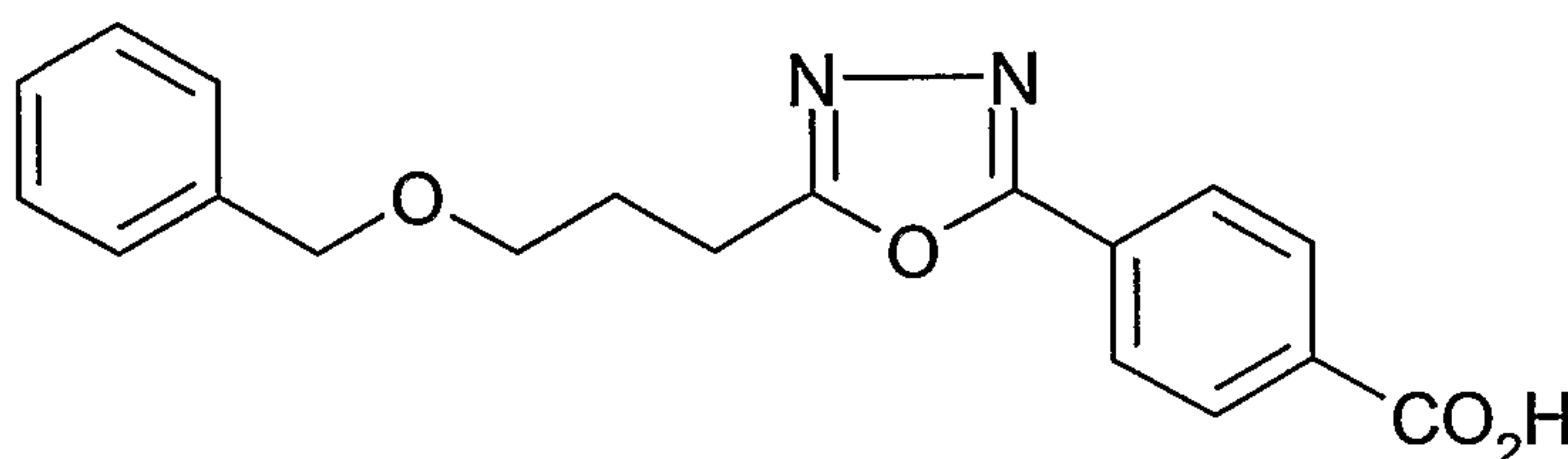


5 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 4-benzyloxybutyric acid (0.725 g, 3.7 mmol), 1,3-dicyclohexylcarbodiimide (0.771 g, 3.7 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.755 g, 3.7 mmol) to afford 0.733 g (56%) of 4-[5-(3-benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzoic acid methyl ester as a
10 crystalline solid.

¹H NMR (DMSO-*d*₆) δ8.09-8.16 (m, 4H), 7.23-7.30 (m, 5H), 4.46 (s, 2H), 3.90 (s, 3H), 3.56 (t, 2H, *J*=6Hz), 3.03 (t, 2H, *J*=7Hz), 2.07 (m, 2H). IR (CHCl₃, cm⁻¹) 1721, 1438, 1282, 1111. MS (ES) *m/e*, 353. Anal. Calcd for C₂₀H₂₀N₂O₄: C, 68.17; H, 5.72; N, 7.95. Found C, 68.10; H, 5.79; N, 8.03.

15

b) 4-[5-(3-Benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzoic acid



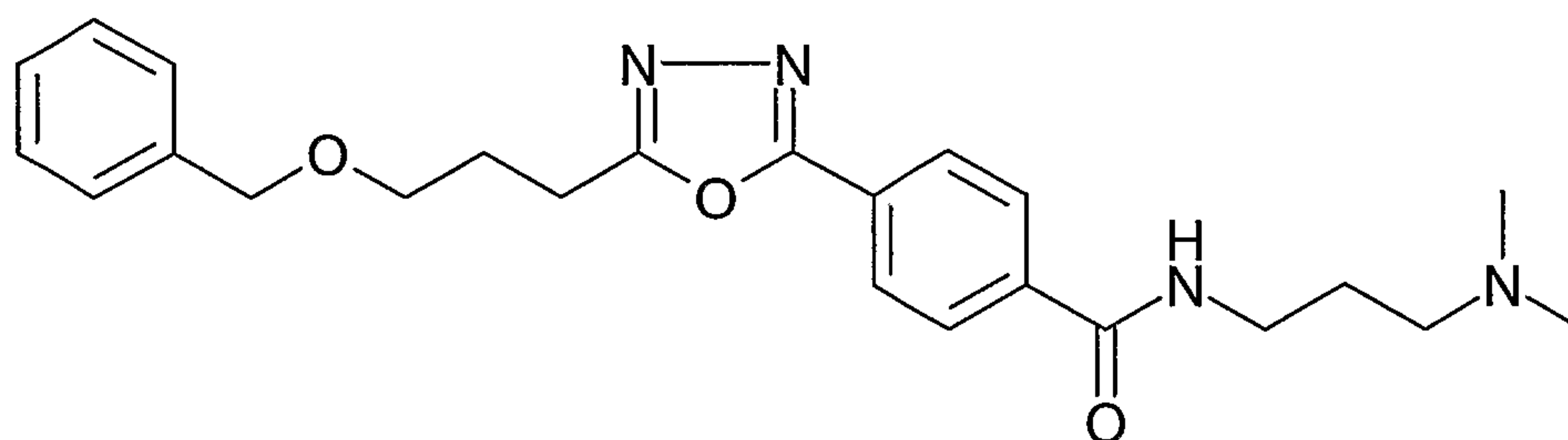
The above compound was prepared in a manner similar to that exemplified for the
20 preparation of Example 1c, from 4-[5-(3-benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethyl aminopropyl)benzoic acid methyl ester (0.669 g, 1.9 mmol) and lithium

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hydroxide (0.136 g, 5.7 mmol) to afford 0.610 g (95%) 4-[5-(3-benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzoic acid as a solid.

¹H NMR (DMSO-d₆) δ 8.06-8.14 (m, 4H), 7.23-7.29 (m, 5H), 4.46 (s, 2H), 3.56 (t, 2H, J=6Hz), 3.03 (t, 2H, J=7Hz), 2.02-2.11 (m, 2H). IR (KBr, cm⁻¹) 2859, 1681, 1428, 1321, 1292, 1119, 720. MS (ES) m/e, 339, 337. Anal. Calcd for C₁₉H₁₈N₂O₄: C, 67.45; H, 5.36; N, 8.28. Found C, 67.15; H, 5.36; N, 8.32.

c) 4-[5-(3-Benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzamide

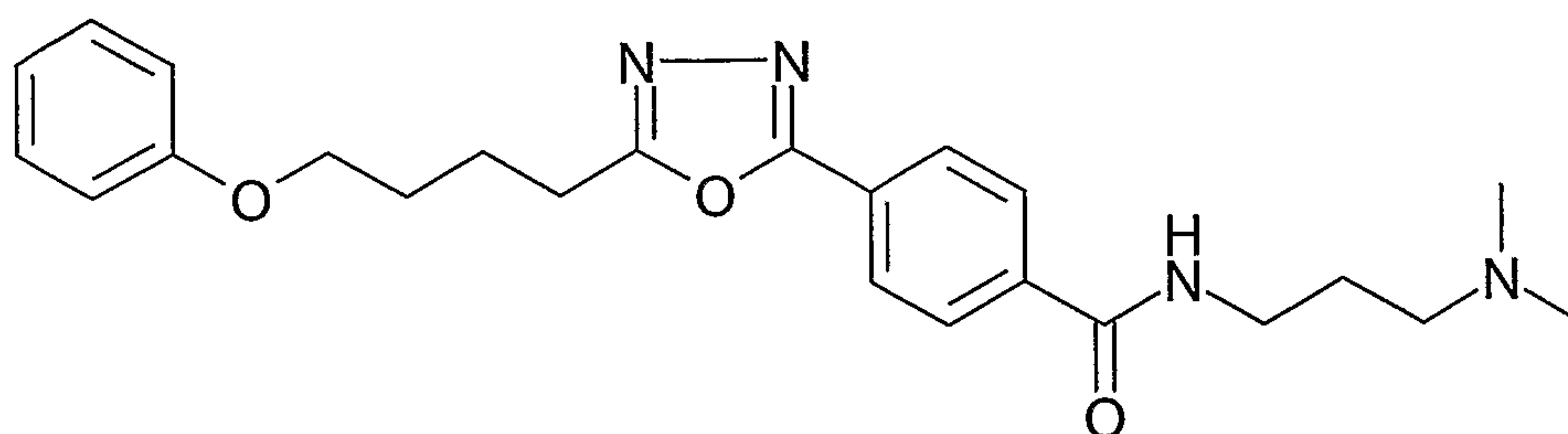


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from (4-[5-(3-Benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethyl aminopropyl)benzoic acid (0.580 g, 1.7 mmol), 1,1'-carbonyl diimidazole (0.291 g, 1.8 mmol) and 3-(dimethylamino)propyl amine (0.210 g, 2.1 mmol) to afford 0.408 g (56%) 4-[5-(3-benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethyl aminopropyl)benzamide as a crystalline material.

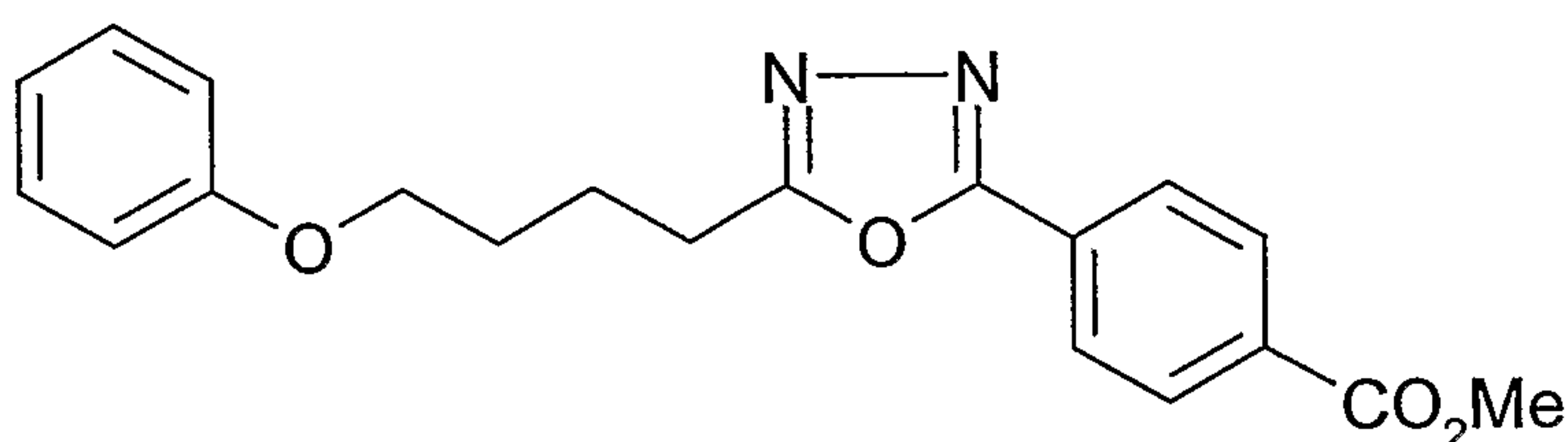
¹H NMR (DMSO-d₆) δ 8.69 (m, 1H), 7.99-8.07 (m, 4H), 7.28 (m, 5H), 4.46 (s, 2H), 3.55 (t, 2H, J=6Hz), 3.30 (m, 2H), 3.02 (t, 2H, J=7Hz), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 2.06 (m, 2H), 1.66 (m, 2H). IR (CHCl₃, cm⁻¹) 3008, 2864, 2827, 1651, 1587, 1556, 1494, 1093. MS (ES) m/e, 423, 421. Anal. Calcd for C₂₄H₃₀N₄O₃: C, 68.22; H, 7.16; N, 13.26. Found C, 67.24; H, 6.01; N, 12.84. Analytical HPLC: 100% purity. Mp(°C)= 106

Example 4 Preparation of N-(3-Dimethylaminopropyl)4-[5-(4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzamide from 5-phenoxypentanoic acid

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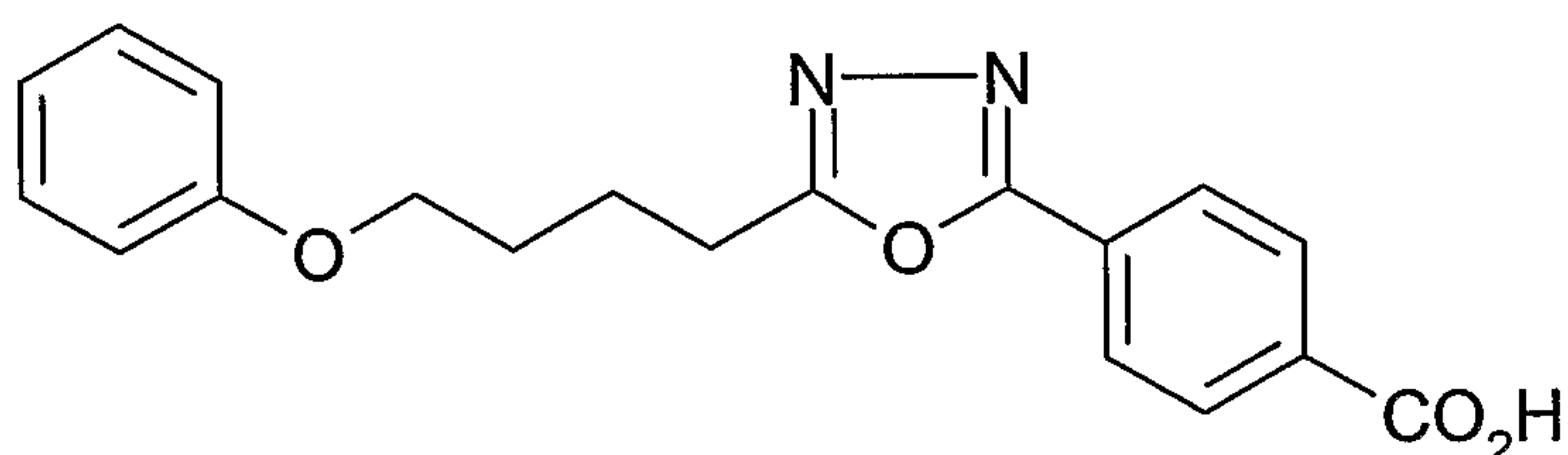
a) 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 5-phenoxybutanoic acid (1.02 g, 5.3 mmol), 1,3-dicyclohexylcarbodiimide (1.08 g, 5.3 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.06 g, 5.2 mmol) to afford 0.639 g (38%) of 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as a crystalline material.

¹H NMR (DMSO-d₆) δ 8.10 (m, 4H), 7.23-7.29 (m, 2H), 6.88-6.94 (m, 3H), 4.02 (t, 2H, J=6Hz), 3.90 (s, 3H), 3.04 (t, 2H, J=7Hz), 1.83-1.98 (m, 4H). IR (CHCl₃, cm⁻¹) 1721, 1587, 1498, 1438, 1283, 1245, 1111. MS (ES) m/e, 353. Anal. Calcd for C₂₀H₂₀N₂O₄: C, 68.17; H, 5.72; N, 7.95. Found C, 67.89; H, 5.58; N, 7.91.

b) 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



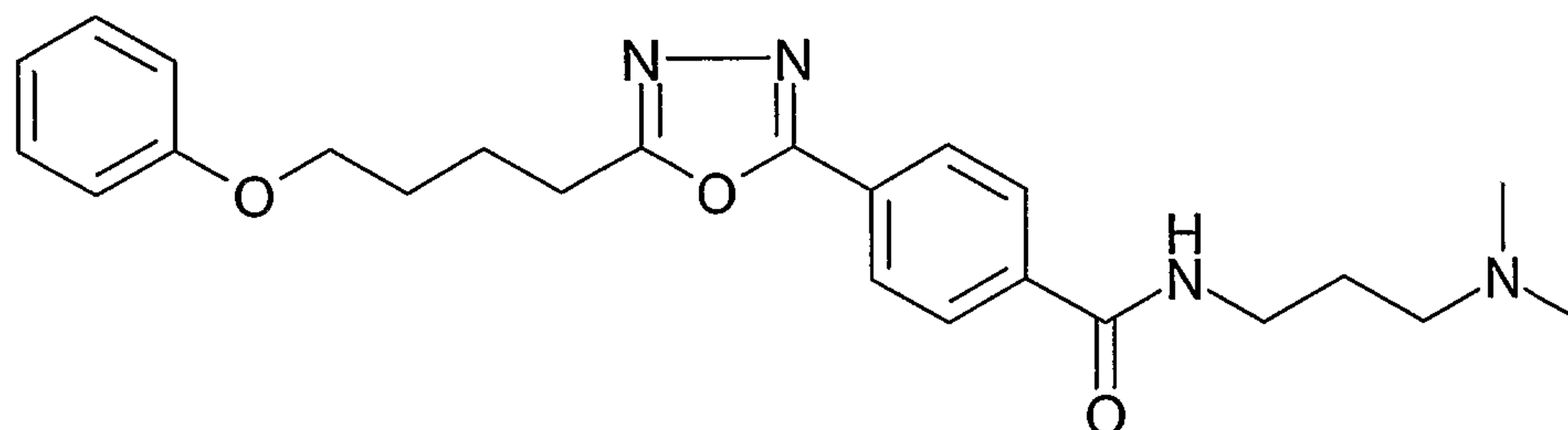
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.560 g, 1.6 mmol) and lithium hydroxide (0.114 g, 4.8 mmol) to afford 0.491 g (91%) of 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid as a solid.

¹H NMR (DMSO-d₆) δ 8.08-8.15 (m, 4H), 7.23-7.30 (m, 2H), 6.88-6.94 (m, 3H), 4.02 (t, 2H, J=6Hz), 3.04 (t, 2H, J=7Hz), 1.81-2.00 (m, 4H). IR (KBr, cm⁻¹) 1684, 1585,

-75-

1501, 1321, 1292, 1256, 723. MS (ES) m/e, 339, 337. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found C, 66.79; H, 5.40; N, 8.27.

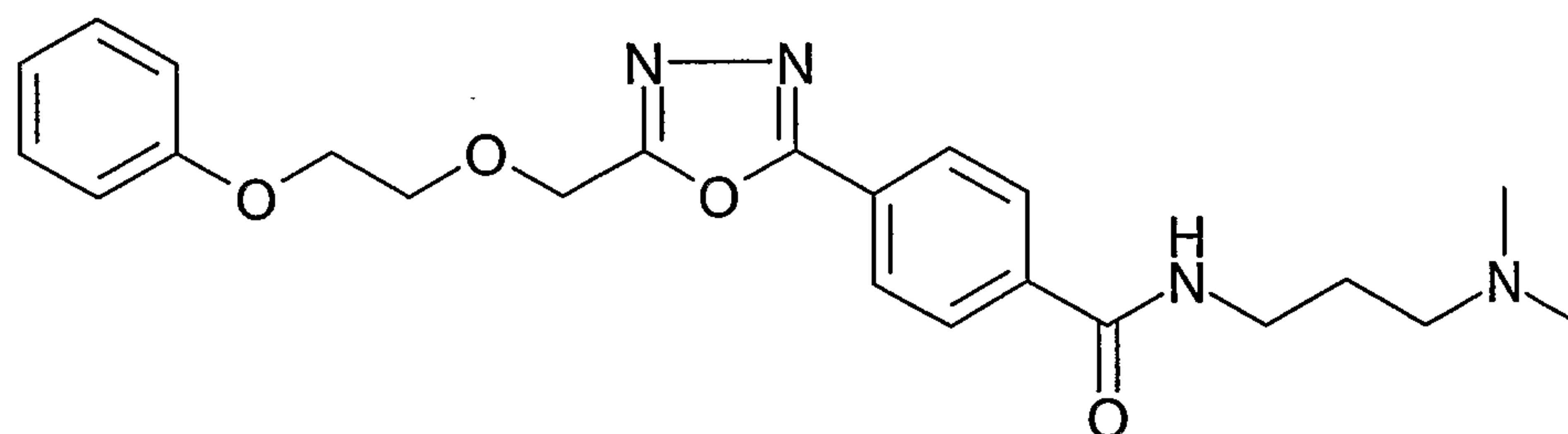
c) N-(3-Dimethylaminopropyl)4-[5-(4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzamide
5



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.461 g, 1.4 mmol), 1,1'-carbonyldiimidazole (0.231 g, 1.4 mmol) and 3-(dimethylamino)propylamine (0.167 g, 1.6 mmol) to afford the title compound as a crude mixture. Crystallization of the material from EtOAc afforded 0.237 g (40%) of N-(3-dimethyl-aminopropyl)4-[5-(4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzamide.

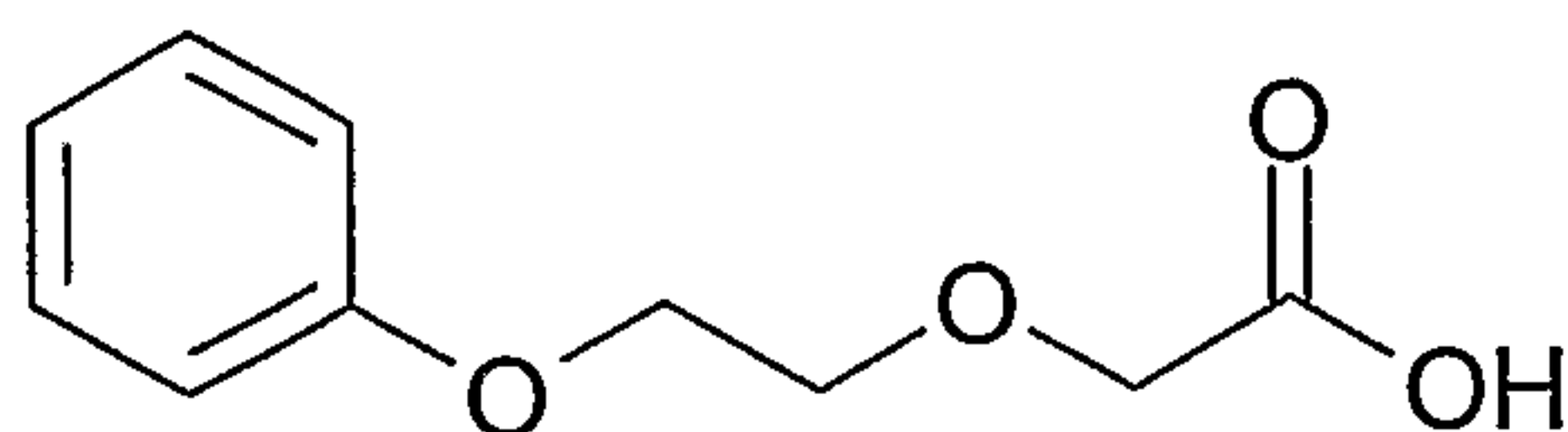
^1H NMR (DMSO- d_6) δ 8.70 (m, 1H), 8.00-8.08 (m, 4H), 7.23-7.30 (m, 2H), 6.88-6.94 (m, 3H), 4.02 (t, 2H, J=6Hz), 3.32 (m, 2H), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.83-1.98 (m, 4H), 1.62-1.72 (m, 2H). IR (KBr, cm^{-1}) 3310, 2953, 2763, 1634, 1563, 1540, 1498, 1253, 1249, 1010, 855, 749. MS (ES) m/e, 423, 421. Anal. Calcd for $C_{24}H_{30}N_4O_3$: C, 68.22; H, 7.16; N, 13.26. Found C, 68.25; H, 7.21; N, 12.82. Analytical HPLC: 100% purity. Mp($^{\circ}C$)=114.

20 Example 5 Preparation of N-(Dimethylaminopropyl)4-[5-(2-phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 2-phenoxyethanol



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a) 2-(Phenoxyethoxy)acetic acid

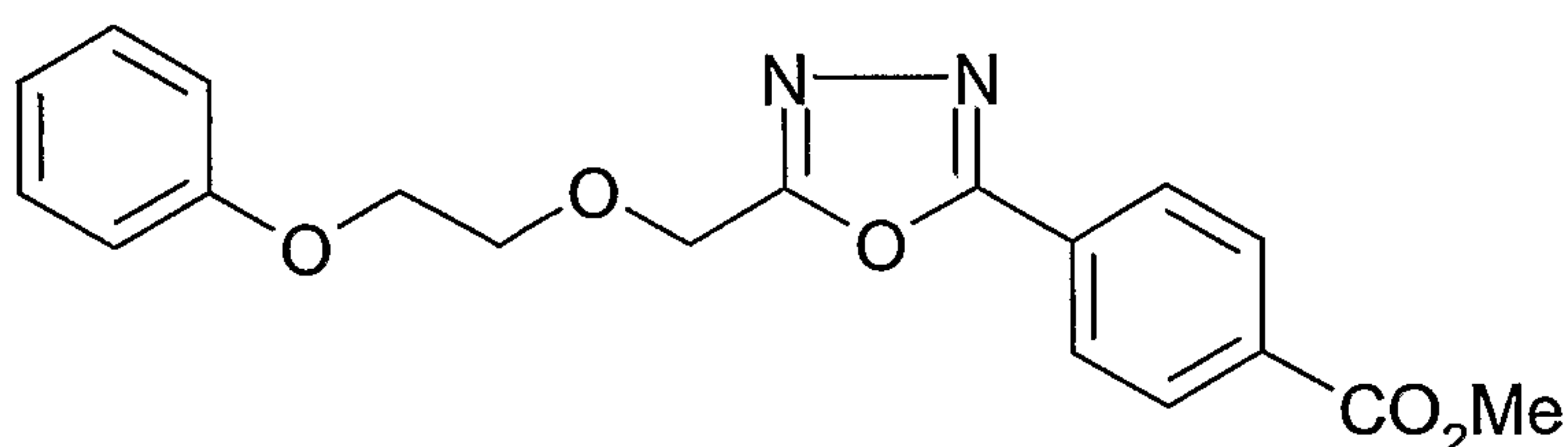


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1a, from 2-phenoxyethanol (5.4 g, 38.9 mmol) and methyl
 5 bromoacetate (6.55 g, 42.8 mmol), then, using lithium hydroxide (2.78 g 116.1 mmol) to afford 5.9 g (77%) of 2-(phenoxyethoxy)acetic acid as an oil.

^1H NMR (DMSO- d_6) δ 7.25-7.31 (m, 2H), 6.93 (m, 3H), 4.11 (m, 4H), 3.81 (m, 2H). IR (CHCl_3 , cm^{-1}) 1733, 1600, 1589, 1498, 1245, 1144. MS (ES) m/e , 197, 195. Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{O}_4$: C, 61.22; H, 6.16. Found C, 61.49; H, 5.70.

10

b) 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester

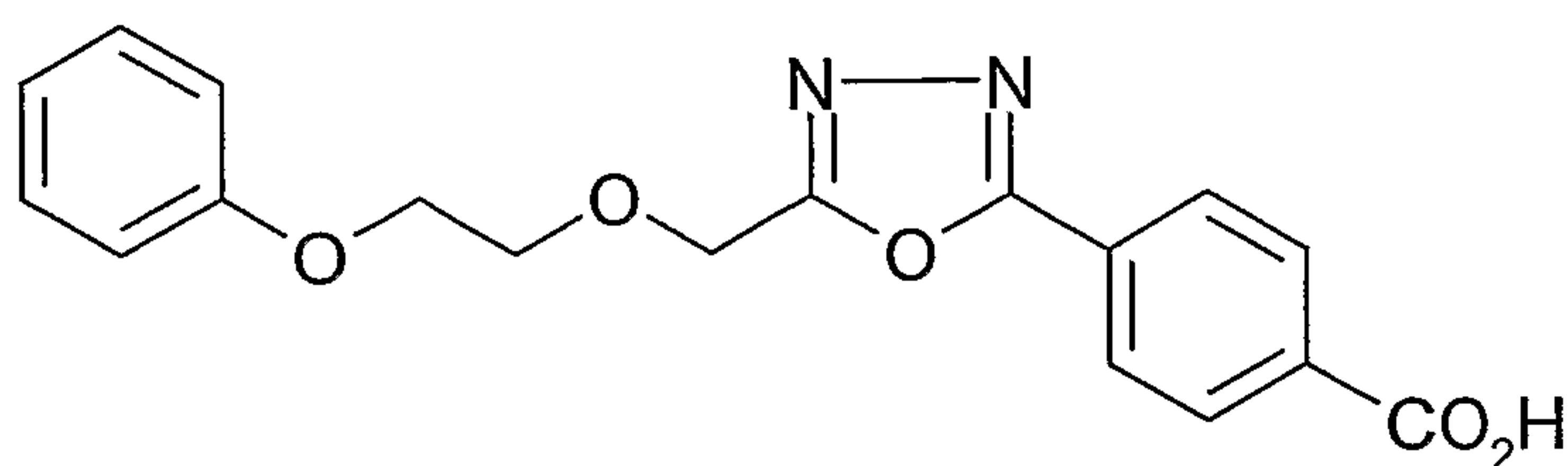


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 2-(phenoxyethoxy)acetic acid (1.08 g, 5.5 mmol), 1,3-
 15 dicyclohexylcarbodiimide (0.957 g, 4.6 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.938 g, 4.6 mmol) to afford 0.559 g (35%) of 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as a crystalline solid contaminated with 1,3-dicyclohexylurea.

^1H NMR (DMSO- d_6) δ 8.15 (m, 4H), 7.22-7.29 (m, 2H), 6.89-6.94 (m, 3H), 4.92
 20 (s, 2H), 4.15 (m, 2H), 3.92-4.17 (m, 2H), 3.91 (s, 3H). IR (CHCl_3 , cm^{-1}) 3328, 2850, 1719, 1601, 1565, 1441, 1296, 1282, 1254, 1146, 1137, 1112, 759, 715. MS (ES) m/e , 355. Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_5$: C, 64.40; H, 5.12; N, 7.91. Found C, 64.72; H, 5.66; N, 8.37.

25 c) 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid

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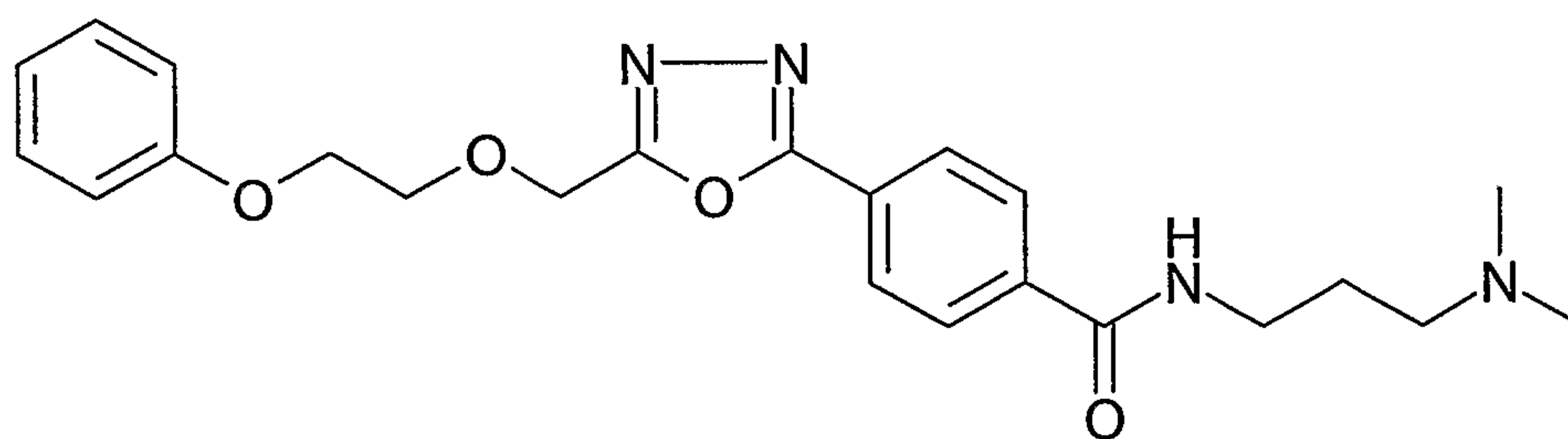


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.500 g, 1.4 mmol) and lithium hydroxide (0.101 g, 4.2 mmol) to afford 0.366 g (76%) as a solid contaminated with 1,3-dicyclohexylurea.

^1H NMR (DMSO- d_6) δ 7.95-8.06 (m, 4H), 7.26-7.32 (m, 2H), 6.91-6.98 (m, 3H), 4.14-4.19 (m, 4H), 3.88 (m, 2H).

IR (KBr, cm^{-1}) 3327, 2928, 2850, 1700, 1685, 1625, 1608, 1246, 1132, 691. MS (ES) m/e , 339. Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_5$: C, 63.53; H, 4.74; N, 8.23. Found C, 61.01; H, 5.65; N, 8.32.

d) N-(Dimethylaminopropyl)4-[5-(2-phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide



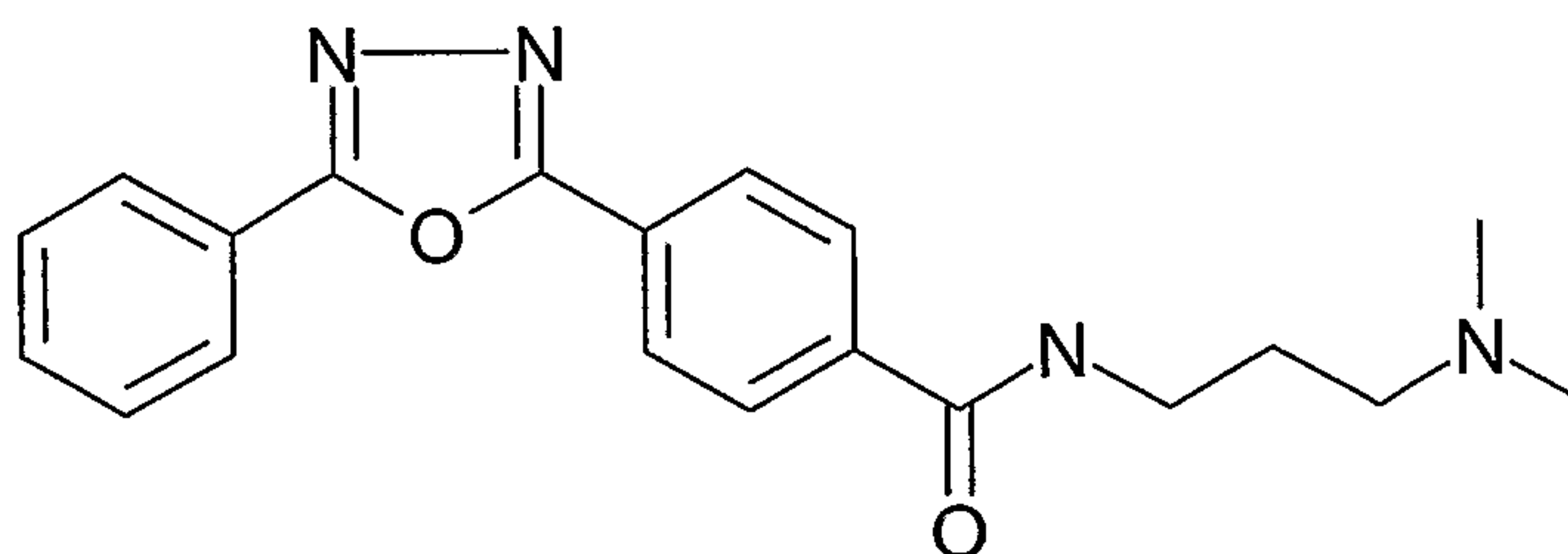
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid 0.333 g, 0.98 mmol), 1,1'-carbonyldiimidazole (0.160 g, 0.99 mmol) and 3-(dimethylamino)propylamine (0.099 g, 1.0 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (eluted with 10% 2M NH_3 in $\text{MeOH}:\text{CHCl}_3$) afforded 0.03 g (7%) of N-(dimethylamino propyl)4-[5-(2-phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide as a solid.

^1H NMR (DMSO- d_6) δ 8.72 (t, 1H, $J=5\text{Hz}$), 8.01-8.10 (m, 4H), 7.23-7.29 (m, 2H), 6.89-6.96 (m, 3H), 4.19 (s, 2H), 4.15 (m, 2H), 3.93 (m, 2H), 3.31 (m, 2H), 2.26 (t, 2H, $J=7\text{Hz}$), 2.14 (s, 6H), 1.62-1.72 (m, 2H). IR (CHCl_3 , cm^{-1}) 4446, 2936, 2763, 1637,

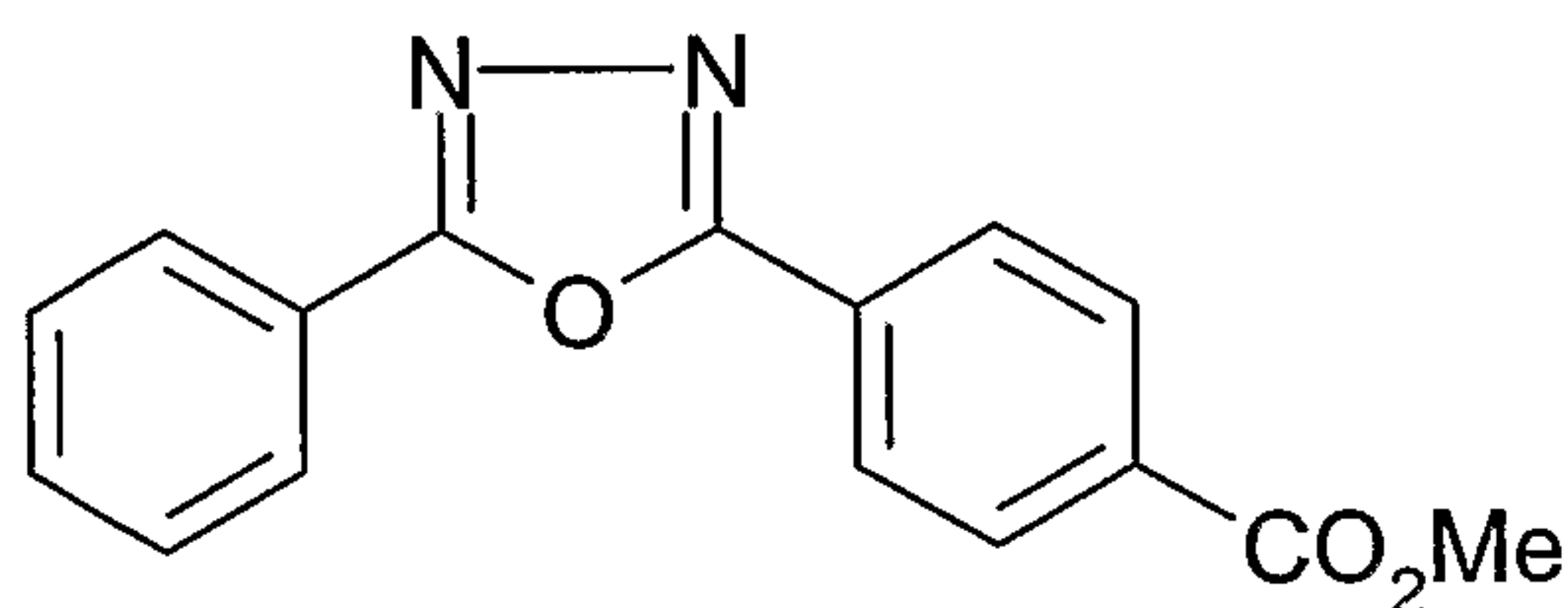
-78-

1530, 1490, 1253, 1047, 752. MS (ES) m/e, 425, 423. Anal. Calcd for $C_{23}H_{28}N_4O_4$: C, 65.08; H, 6.65; N, 13.20. Found C, 64.74; H, 6.58; N, 12.98. Mp($^{\circ}$ C)=146.

Example 6 Preparation of N-(3-Dimethylaminopropyl)-4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzamide from benzoyl chloride.



a) 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester

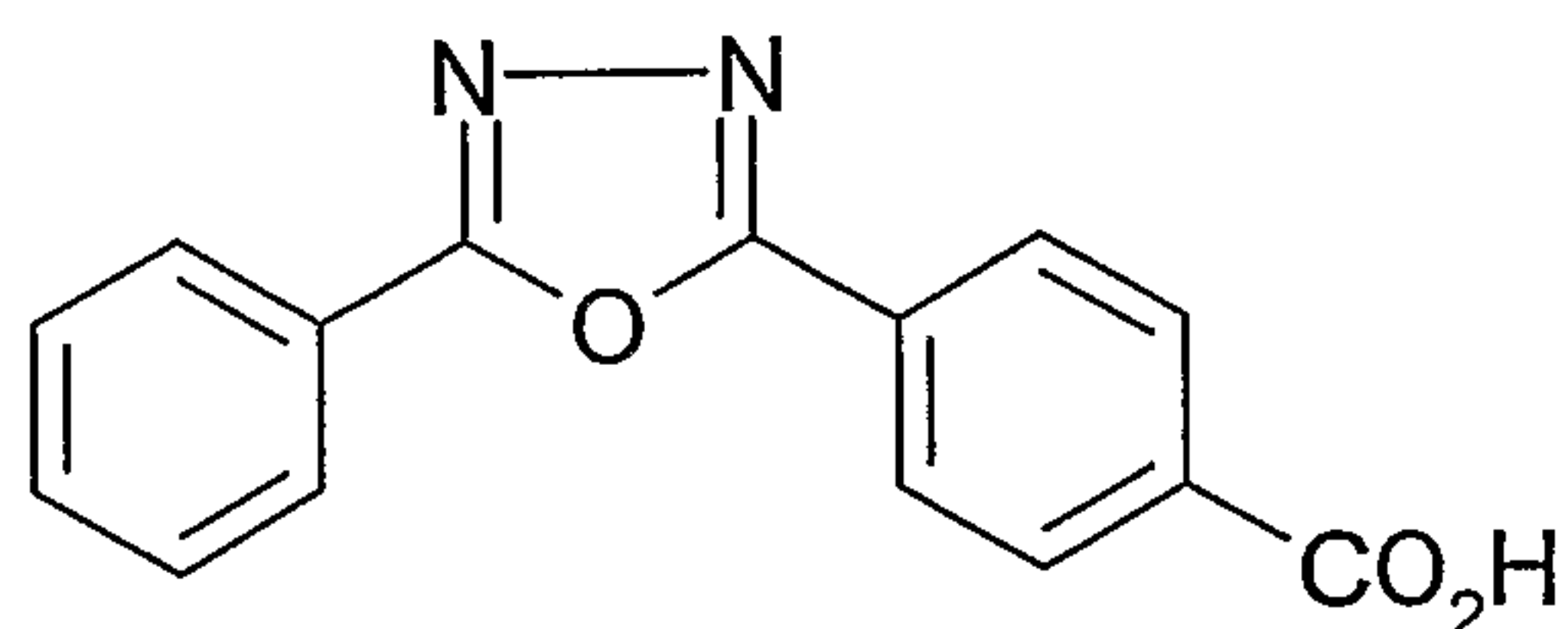


A suspension of 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.00 g, 4.9 mmol) and pyridine (0.391 g, 5.0 mmol) in 7.3 mL toluene stirring at room temperature was added benzoyl chloride. The resultant heavy white suspension was heated at 100 $^{\circ}$ C for twenty minutes then at 140 $^{\circ}$ C for twenty minutes. After cooling to room temperature the mixture was treated with EtOAc and H₂O. The suspension was triterated then filtered to afford 0.652 g (48%) of 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester. The filtrate phases were separated. The organic phase was dried over sodium sulfate, filtered, concentrated to afford a solid. The solid was crystallized from acetone: diethyl ether to afford 0.371 (27%) of 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.

^{1} H NMR (DMSO-*d*₆) δ 8.27 (m, 2H), 8.16 (m, 4H), 7.62-7.71 (m, 3H), 3.91 (s, 3H). IR (KBr, cm^{-1}) 1723, 1545, 1447, 1442, 1280, 1118, 1110, 1018, 780, 717, 688. MS (ES) m/e, 281. Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99. Found C, 68.47; H, 4.42; N, 10.03.

b) 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid

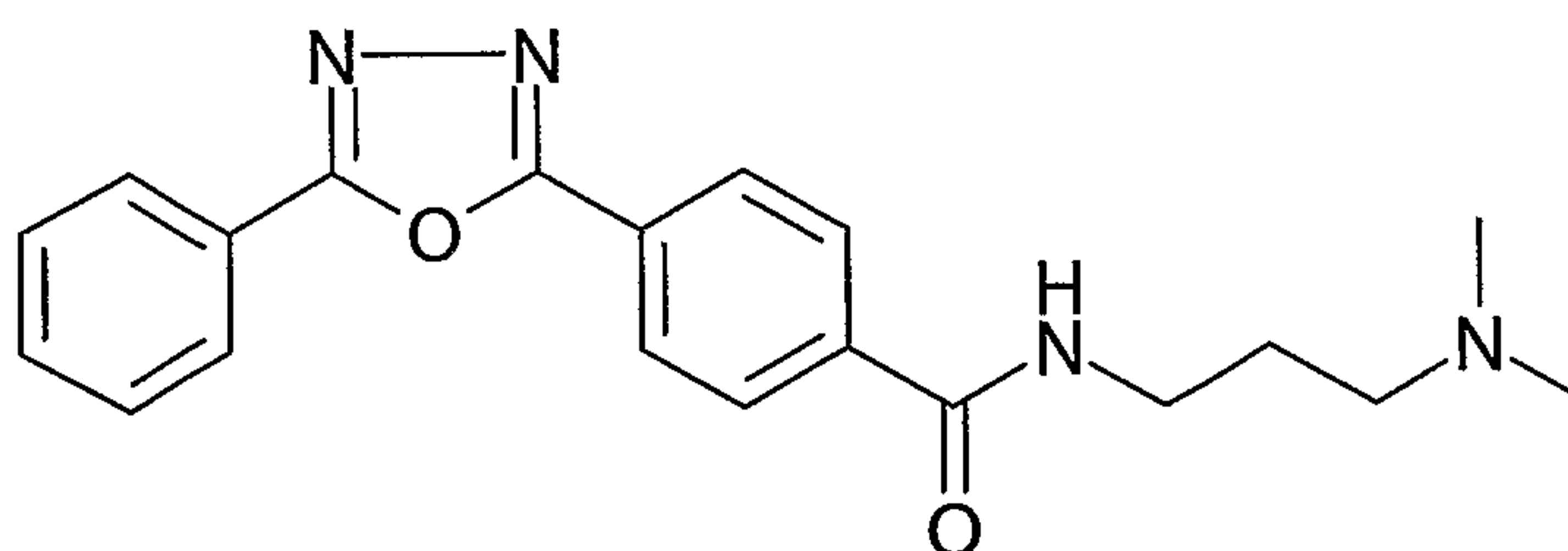
-79-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester (0.938 g, 3.3 mmol) and lithium hydroxide (0.240 g, 10.0 mmol) to afford 0.889 g (100%) of 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid as a solid.

^1H NMR (DMSO- d_6) δ 13.29 (bs, 1H), 8.21-8.28 (m, 2H), 8.13-8.19 (m, 4H), 7.61-7.69 (m, 3H). IR (KBr, cm^{-1}) 3436, 1683, 1547, 1425, 1287, 718, 689. MS (ES) m/e , 267, 265. Anal. Calcd for $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_3$: C, 67.67; H, 3.79; N, 10.52. Found C, 64.26; H, 3.76; N, 9.94.

c) N-(3-Dimethylaminopropyl)-4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzamide

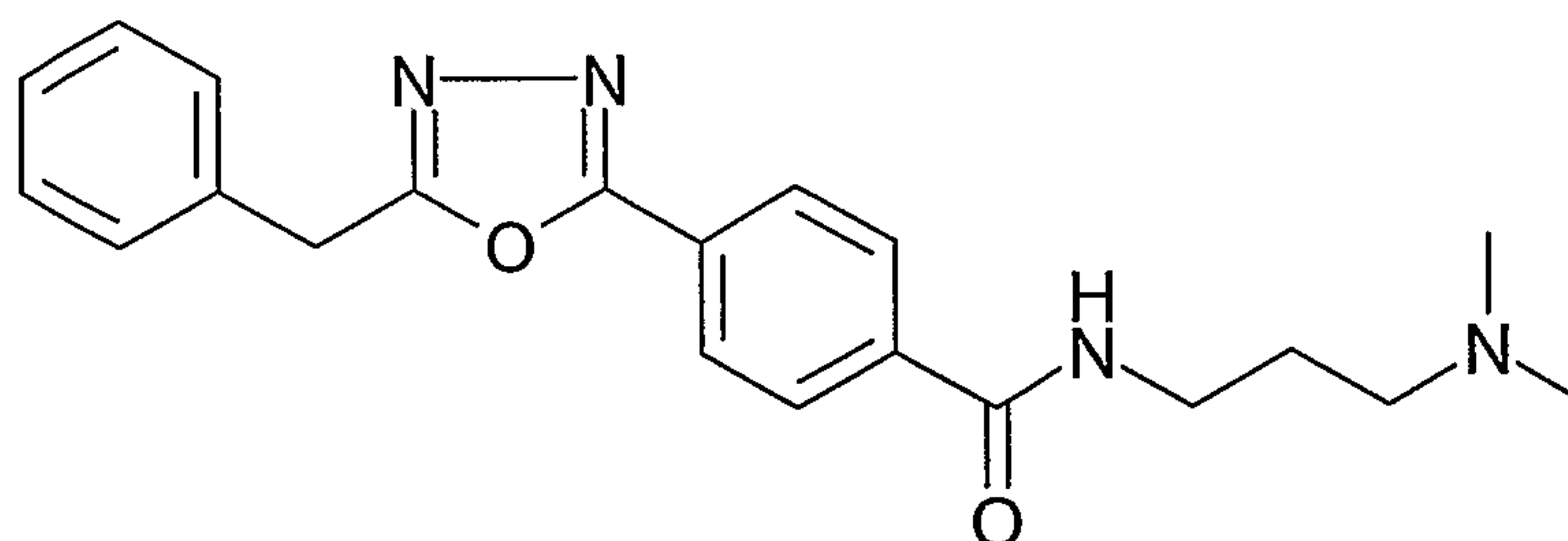


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid (0.536 g, 2.0 mmol), 1,1'-carbonyldiimidazole (0.3300 g, 2.0 mmol) and 3-(dimethylamino)propylamine (0.412 g, 4.0 mmol) and 1.3 mL DMF to afford a solid. Crystallization from methanol:diethyl ether afforded 0.286 g (41%) of N-(3-Dimethylaminopropyl)-4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzamide.

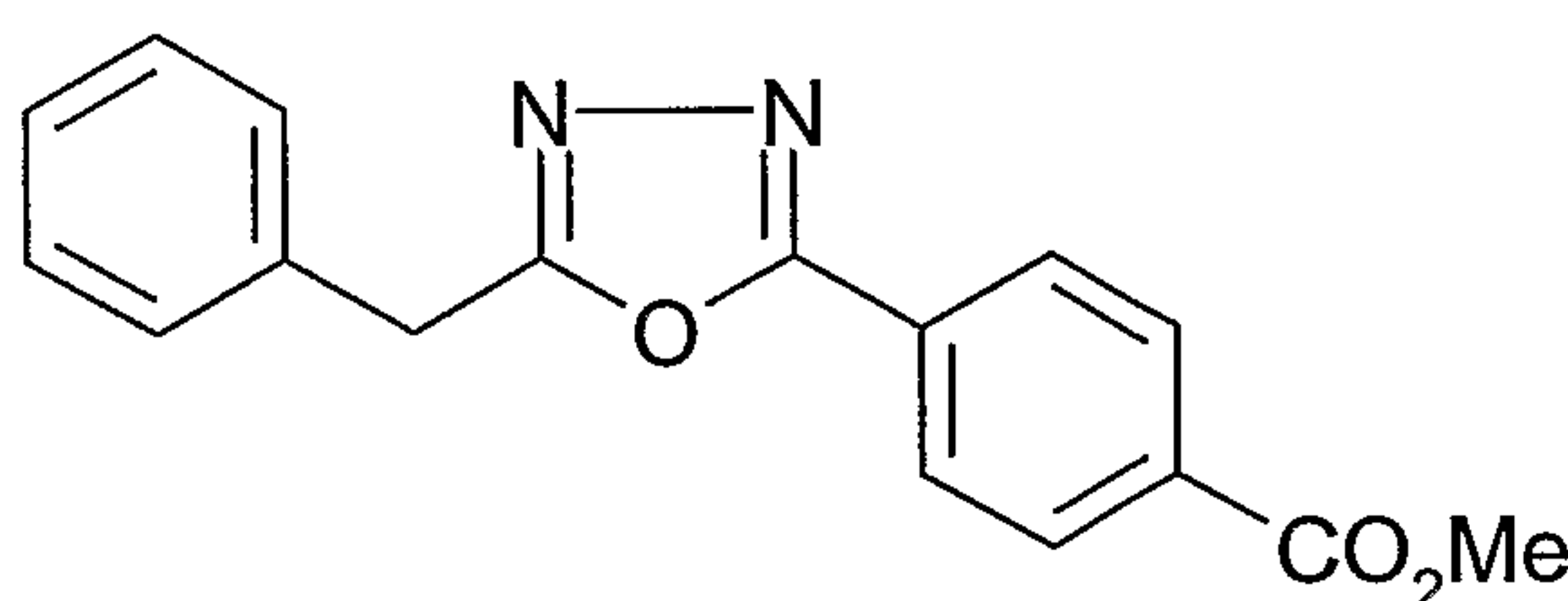
^1H NMR (DMSO- d_6) δ 8.73 (t, 1H, $J=5\text{Hz}$), 8.23 (d, 2H, $J=7\text{Hz}$), 8.15-8.20 (m, 2H), 8.05 (d, 2H, $J=7\text{Hz}$), 7.61-7.69 (m, 3H), 3.31 (m, 2H), 2.27 (t, 2H, $J=7\text{Hz}$), 3.31 (m, 2H), 1.63-1.73 (m, 2H). IR (KBr, cm^{-1}) 3330, 2941, 2763, 1667, 1646, 1547, 1492, 715. MS (ES) m/e , 351, 349. Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2$: C, 68.55; H, 6.33; N, 15.99. Found C, 68.08; H, 6.29; N, 15.90. $\text{Mp} (^{\circ}\text{C})=130$.

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Example 7 Preparation of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylaminopropyl)benzamide from phenylacetic acid.



a) 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester



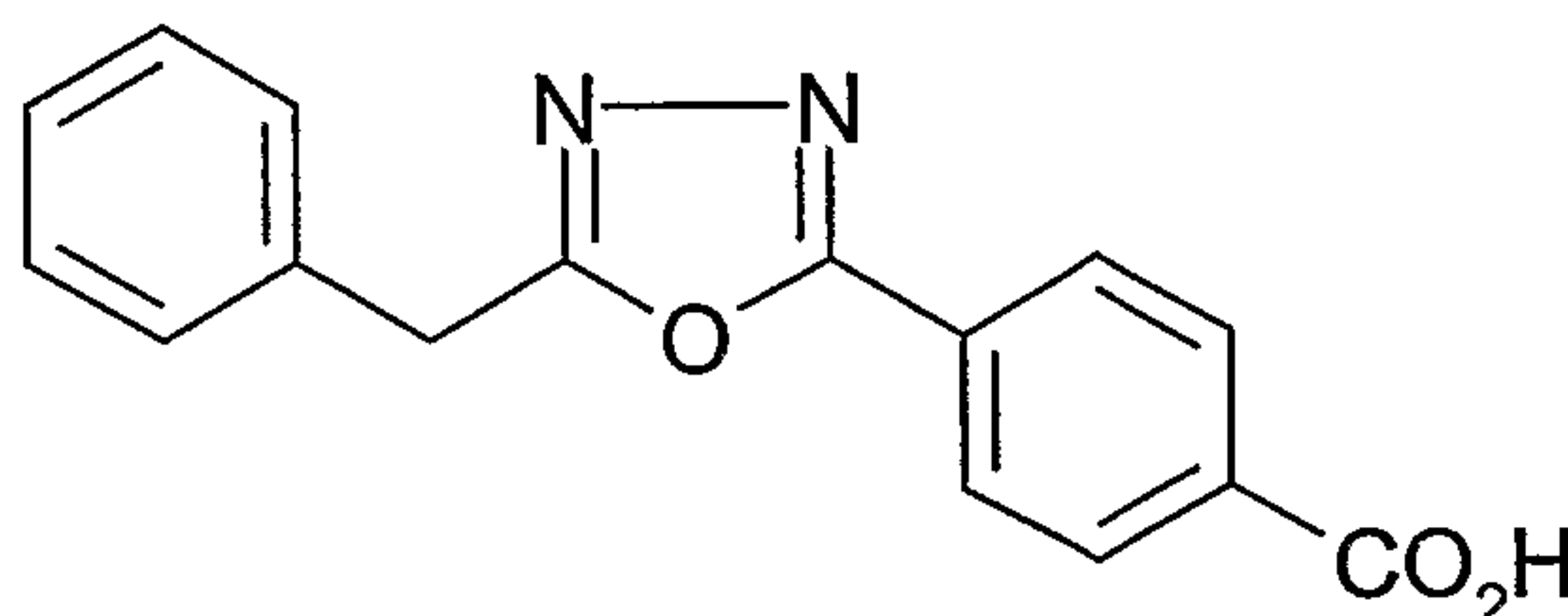
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The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from phenyl acetic acid (0.470 g, 3.5 mmol), 1,3-dicyclohexylcarbodiimide (0.710 g, 3.5 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.700 g, 3.5 mmol) to afford the title compound as a crude mixture.

10 Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc:hexane) followed by crystallization of the isolated material from diethyl ether afforded 0.421 g (69%) of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.

¹H NMR (DMSO-d₆) δ 8.08-8.16 (m, 4H), 7.28-7.41 (m, 5H), 4.39 9s, 2H), 3.89 (s, 3H). IR (KBr, cm⁻¹) 1716, 1559, 1551, 1435, 1276, 1111, 779, 728, 723, 710. MS (ES) 15 m/e, 295. Anal. Calcd for C₁₇H₁₄N₂O₃: C, 69.38; H, 4.79; N, 9.52. Found C, 69.27; H, 4.78; N, 9.52.

b) 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid



20

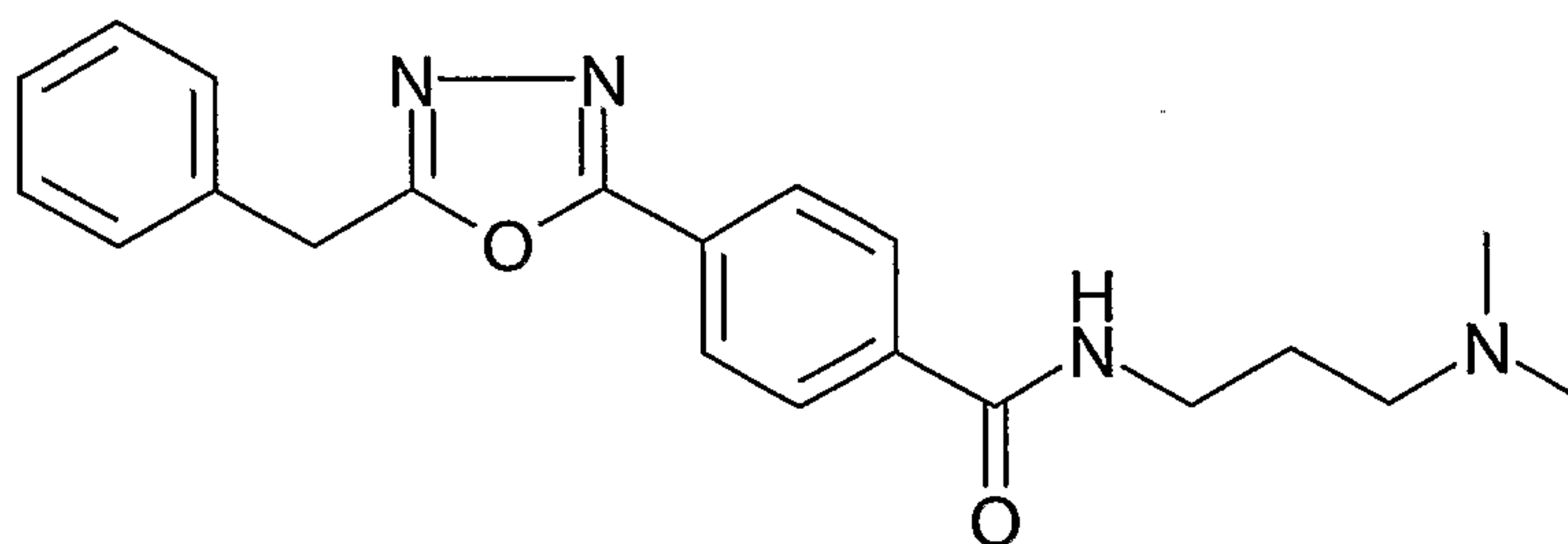
A mixture of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester (0.413 g, 1.4 mmol) and lithium hydroxide (0.125 g, 5.2 mmol) in 4.1 mL THF and 1.8 mL H₂O

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was stirred at room temperature for four hours. Next, concentrated HCl (450 μ L, 5.2 mmol) was added. The resultant suspension was reduced in volume then filtered to afford 0.393 g (85%) of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid.

^1H NMR (DMSO- d_6) δ 13.33 (bs, 1H), 8.06-8.14 (m, 4H), 7.27-7.42 (m, 5H), 4.39 (s, 2H). IR (KBr, cm^{-1}) 1706, 1685, 1583, 1563, 1552, 1432, 1323, 1290, 872, 716, 706. MS (ES) m/e , 281, 279. Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3$: C, 68.57; H, 4.32; N, 9.99. Found C, 68.38; H, 4.43; N, 9.99.

c) 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylaminopropyl)benzamide



10

A suspension of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid (0.255 g, 0.91 mmol), 1-hydroxybenzotriazole (0.123 g, 0.91 mmol), 4-dimethylamino pyridine (0.011 g, 0.09 mmol) and 1,3-dicyclohexylcarbodiimide (0.206 g, 1.00 mmol) in 26 mL CH_2Cl_2 was stirred at room temperature for fifteen minutes. Next, 3-(dimethylamino)propyl amine (0.093 g, 0.91 mmol) was added and the reaction was stirred 21 hours at room temperature. The suspension was filtered and the filtrate was reduced in volume. Purification by radial chromatography on silica gel (elution with 90:10:1 CH_2Cl_2 :MeOH: NH_4OH) followed by crystallization of the isolated material from ethanol:diethyl ether afforded 0.054 g (16%) of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylaminopropyl)benzamide. A second lot of crystals was obtained to afford 0.017 g (5%) of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylamino-propyl)benzamide.

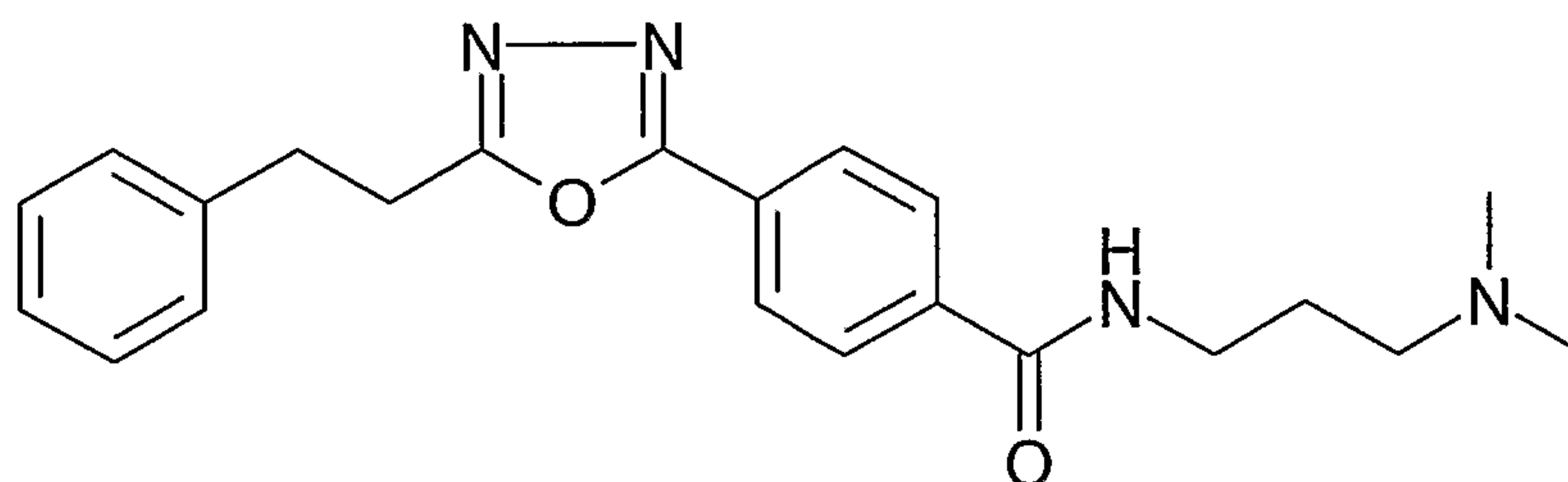
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^1H NMR (DMSO- d_6) δ 8.70 (t, 1H, $J=5\text{Hz}$), 8.04 (d, 2H, $J=9\text{Hz}$), 8.00 (d, 2H, $J=9\text{Hz}$), 7.29-7.41 (m, 5H), 4.38 (s, 2H), 3.31 (m, 2H), 2.25 (t, 2H, $J=7\text{Hz}$), 2.13 (s, 6H), 1.61-1.70 (m, 2H). IR (KBr, cm^{-1}) 3298, 2943, 2768, 1937, 1636, 1555, 1324, 1087, 863, 721, 706. MS (ES) m/e , 365, 363. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_2$: C, 69.21; H, 6.64; N, 15.37. Found C, 68.91; H, 6.71; N, 15.38. $\text{Mp}(\text{°C})=110$.

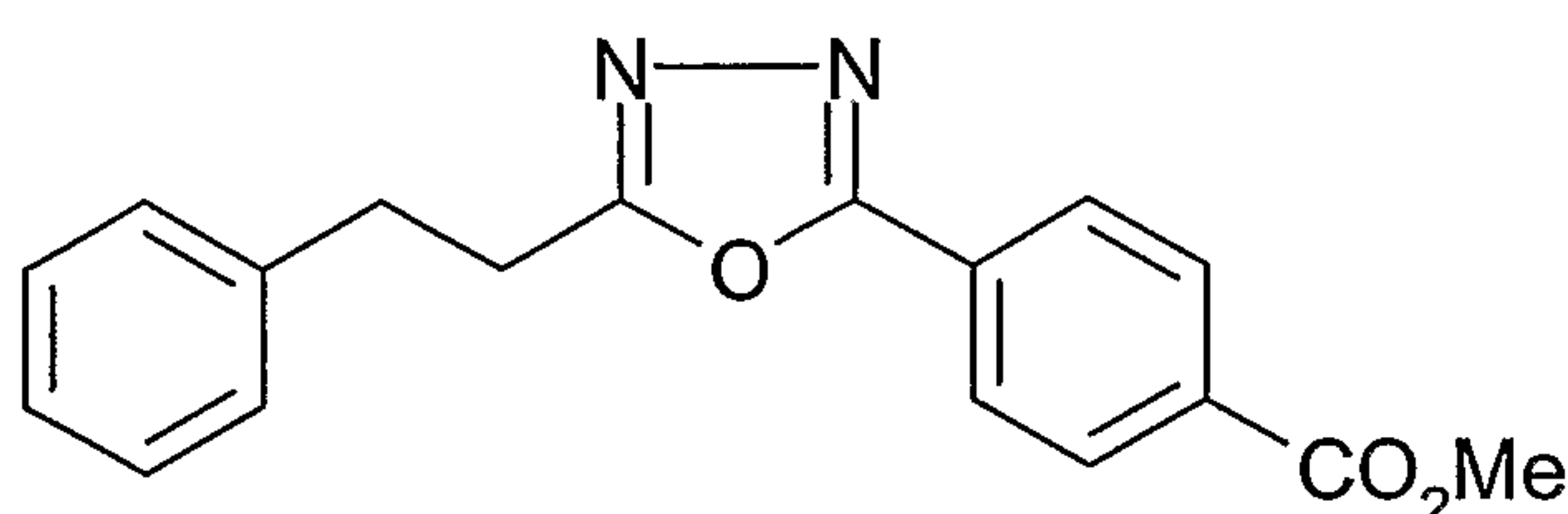
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Example 8 Preparation of N-(3-dimethylaminopropyl)-4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzamide from hydrocinnamoyl chloride



a) 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester



5

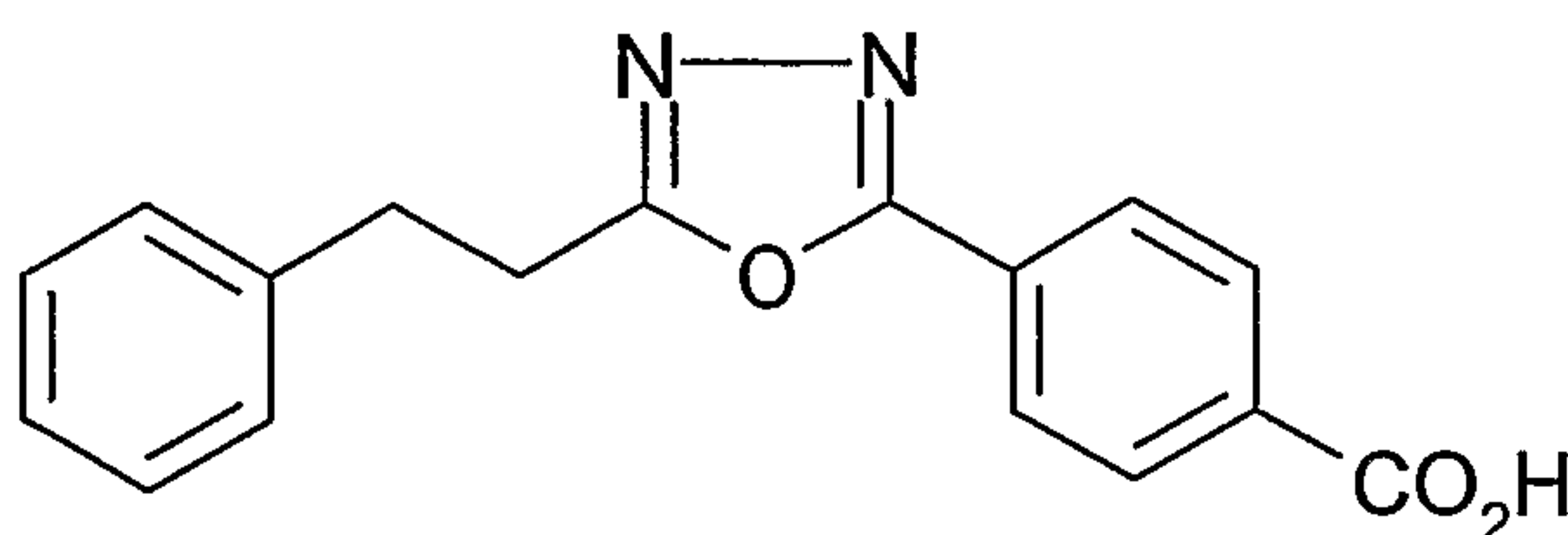
A solution of 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.00 g, 4.9 mmol) and hydrocinnamoyl chloride (0.826 g, 4.9 mmol) in 10 mL toluene was heated at 100 °C for five hours. The mixture was then concentrated to an oil. The oil was dissolved into CH₂Cl₂ and washed with 0.1 N HCl. The aqueous phase was extracted with CH₂Cl₂. The combined organic phases were dried over sodium sulfate, filtered and concentrated to afford a solid. Purification by HPLC on silica gel (eluted with a linear gradient of 10 to 25% EtOAc:toluene over a thirty minute period) afforded 0.604 g (40%) of 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester as a white solid.

10

¹H NMR (DMSO-d₆) δ 8.15 (d, 2H, J=9Hz), 8.09 (d, 2H, J=9Hz), 7.18-7.31 (m, 5H), 3.90 (s, 3H), 3.28 (t, 2H, J=7Hz), 3.12 (t, 2H, J=7Hz). IR (KBr, cm⁻¹) 1714, 1415, 1278, 1111, 774, 713, 696. MS (ES) m/e, 309. Anal. Calcd for C₁₈H₁₆N₂O₃: C, 70.12; H, 5.23; N, 9.09. Found C, 69.55; H, 5.14; N, 9.03.

15

b) 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid



20

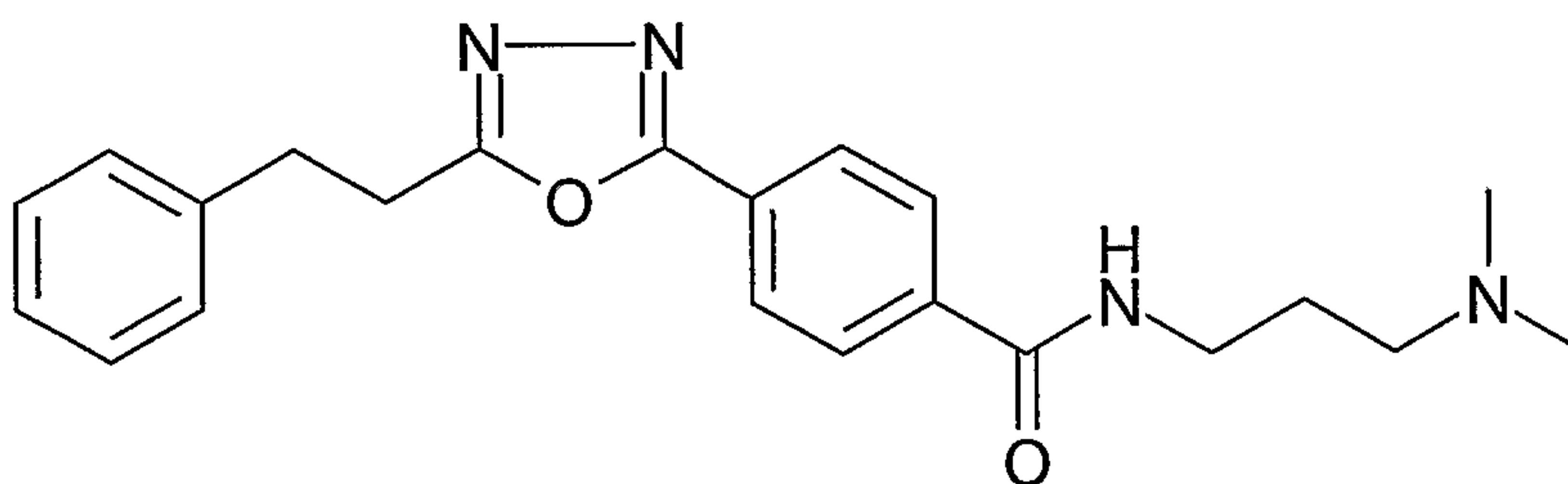
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid

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methyl ester (0.600 g, 2.0 mmol) and lithium hydroxide (0.140 g, 5.8 mmol), to afford 0.510 g (89%) of 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid.

¹H NMR (DMSO-d₆) δ 13.33 (bs, 1H), 8.13 (d, 2H, J=9Hz), 8.07 (d, 2H, J=9Hz), 7.18-7.33 (m, 5H), 3.28 (t, 2H, J=7Hz), 3.12 (t, 2H, J=7Hz). IR (CHCl₃, cm⁻¹) 1670, 1568, 1555, 1420, 1280, 1017. MS (ES) m/e, 295, 293. Anal. Calcd for C₁₇H₁₄N₂O₃: C, 69.38; H, 4.79; N, 9.52. Found C, 68.95; H, 4.57; N, 9.40.

c) N-(3-dimethylaminopropyl)-4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzamide



10

A suspension of 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid (0.480 g, 1.6 mmol), 1-hydroxybenzotriazole (0.337 g, 2.5 mmol), 3-(dimethylamino)propyl amine (0.286 g, 2.8 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.597 g, 3.11 mmol) in 46 mL THF was stirred at room temperature for twenty four hours. The resultant suspension was filtered and the filtrate was concentrated to an oil. The oil was dissolved into EtOAc then washed with 2N sodium hydroxide (2 x 25 ml), water then brine. The organic phase was dried over sodium sulfate, filtered, concentrated to afford a white solid. Crystallization of this material from methanol:diethyl ether afforded 0.354 g (57%) of N-(3-dimethylaminopropyl)-4-(5—phenethyl)-[1,3,4]oxadiazol-2-yl)benzamide.

15

¹H NMR (DMSO-d₆) δ 8.70 (t, 1H, J=5Hz), 8.04 (d, 2H, J=9Hz), 8.01 (d, 2H, J=9Hz), 7.19-7.30 (m, 5H), 3.26-3.33 (m, 4H), 3.12 (t, 2H, J=8Hz), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.62-1.71 (m, 2H). IR (CHCl₃, cm⁻¹) 3346, 2973, 2942, 2813, 2764, 1636, 1585, 1564, 1552, 1530, 1496, 1496, 1287. MS (ES) m/e, 379, 377. Anal. Calcd for C₂₂H₂₆N₄O₂: C, 69.82; H, 6.92; N, 14.80. Found C, 69.62; H, 6.84; N, 14.80.

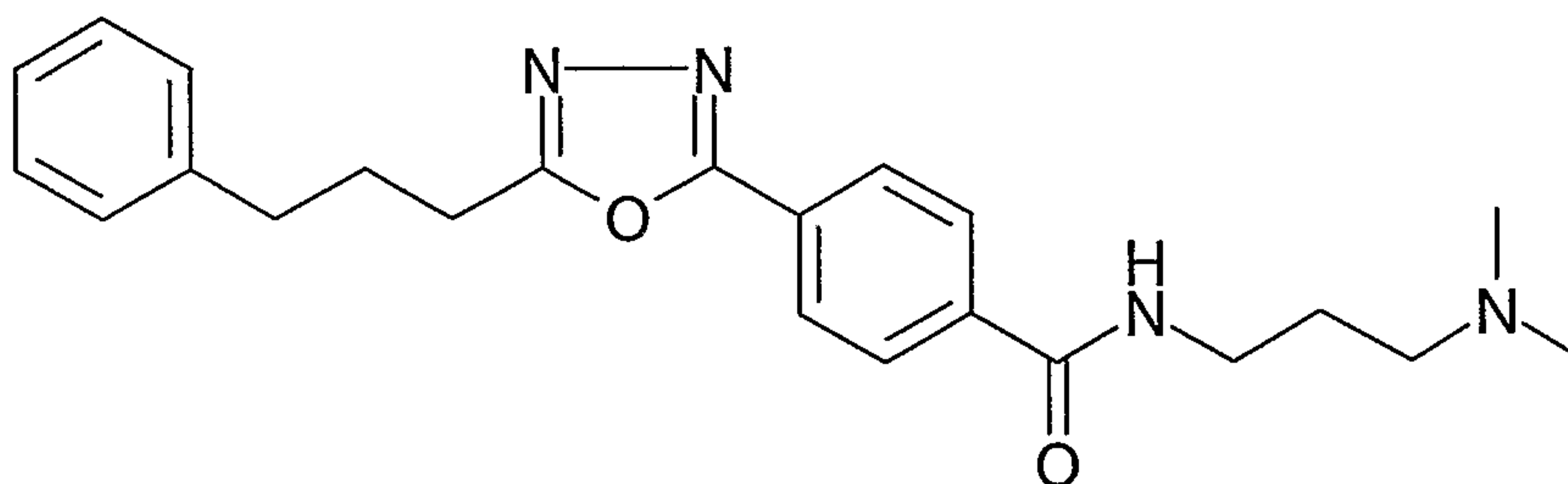
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Mp(°C)=126.

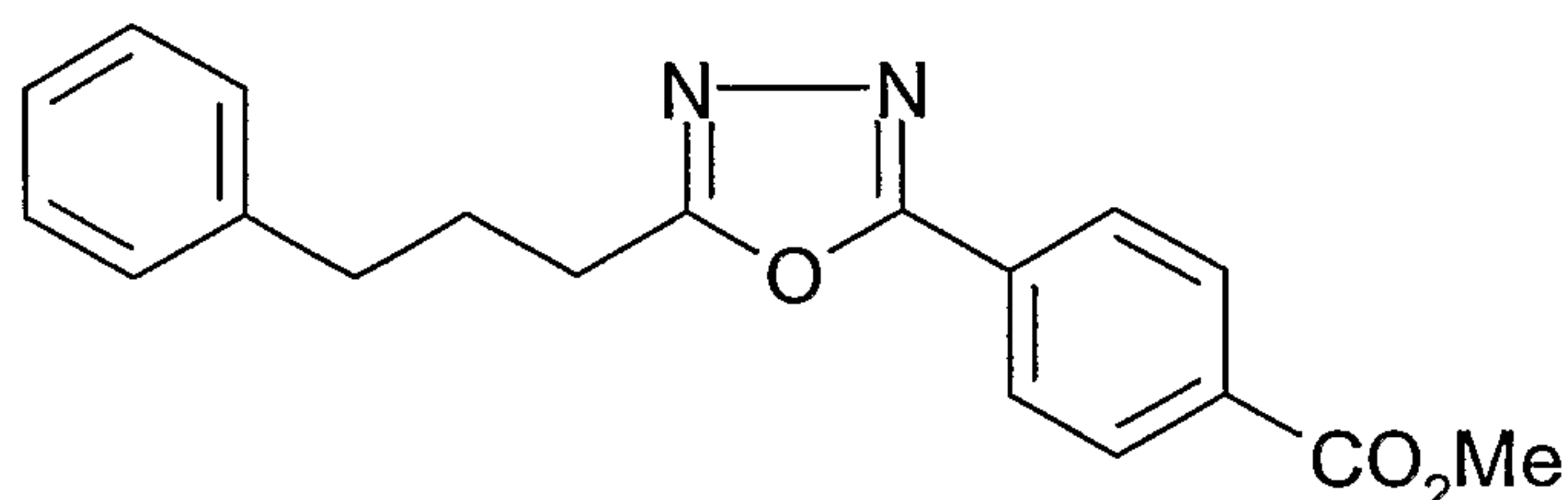
25

Example 9 Preparation of N-(3-dimethylaminopropyl)-4-(5-phenylpropyl)-[1,3,4]oxadiazol-2-yl)benzamide from 4-phenylbutyric acid

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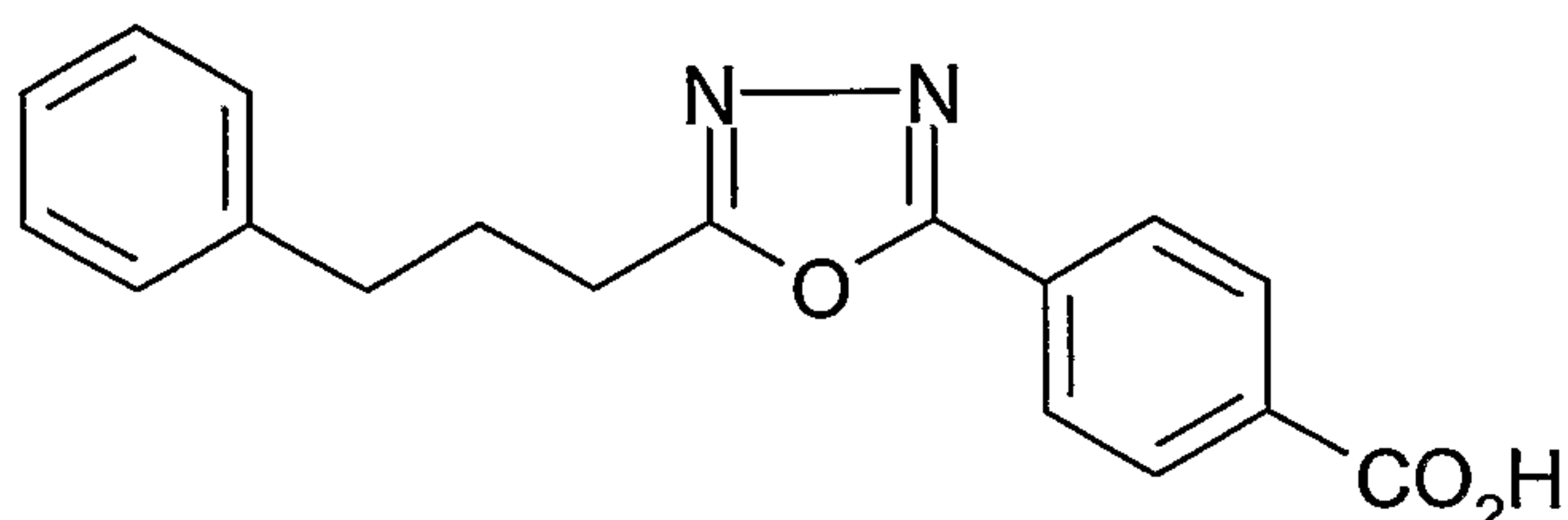
a) 4-[5—(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 4-phenylbutyric acid (0.470 g, 3.5 mmol), 1,3-dicyclohexylcarbodiimide (0.710 g, 3.5 mmol), 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.700 g, 3.4 mmol) and 5.1 mL toluene to afford the title compound as a crude material. Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc:hexane) followed by crystallization of the isolated material from diethyl ether afforded 0.554 g (50%) of 4-[5—(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester.

¹H NMR (DMSO-*d*₆) δ 8.14 (d, 2H, *J*=6Hz), 8.11 (d, 2H, *J*=6Hz), 7.15-7.32 (m, 5H), 3.90 (s, 3H), 2.95 (t, 2H, *J*=7Hz), 2.72 (t, 2H, *J*=7Hz), 2.04-2.14 (m, 2H). IR (KBr, cm⁻¹) 1724, 1713, 1587, 1572, 1415, 1281, 1275, 1114, 1107, 751, 718. MS (ES) *m/e*, 323. Anal. Calcd for C₁₉H₁₈N₂O₃: C, 70.79; H, 5.63; N, 8.69. Found C, 70.60; H, 5.65; N, 8.71.

b) 4-[5—(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



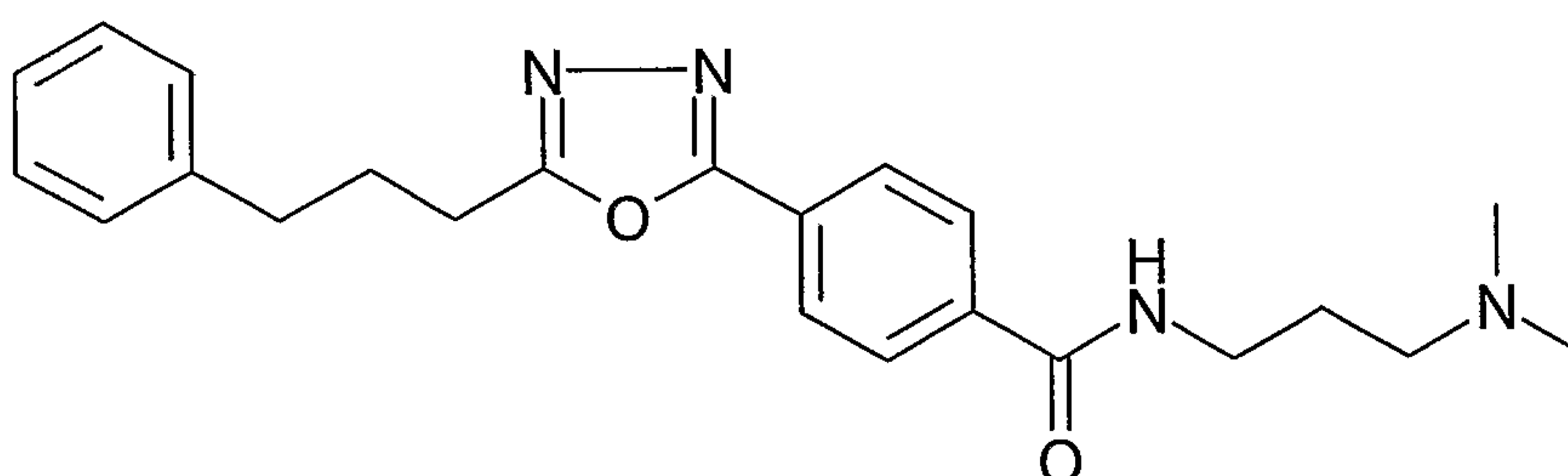
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 4-[5-(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl]benzoic

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acid methyl ester (0.512 g, 1.6 mmol) and lithium hydroxide (0.092 g, 3.8 mmol) to afford 0.333 g (85%) of 4-[5-(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl]benzoic acid.

¹H NMR (DMSO-d₆) δ 13.33 (bs, 1H), 8.12 (d, 2H, J=9Hz), 8.08 (d, 2H, J=9Hz), 7.15-7.32 (m, 5H), 2.95 (t, 2H, J=7Hz), 2.72 (t, 2H, J=7Hz), 2.04-2.14 (m, 2H). IR (KBr, cm⁻¹) 1685, 1565, 1322, 1302, 1287, 722. MS (ES) m/e, 309, 307. Anal. Calcd for C₁₈H₁₆N₂O₃: C, 70.12; H, 5.23; N, 9.09. Found C, 70.05; H, 5.20; N, 9.00.

c) N-(3-dimethylaminopropyl)-4-(5-phenylpropyl)-[1,3,4]oxadiazol-2-ylbenzamide

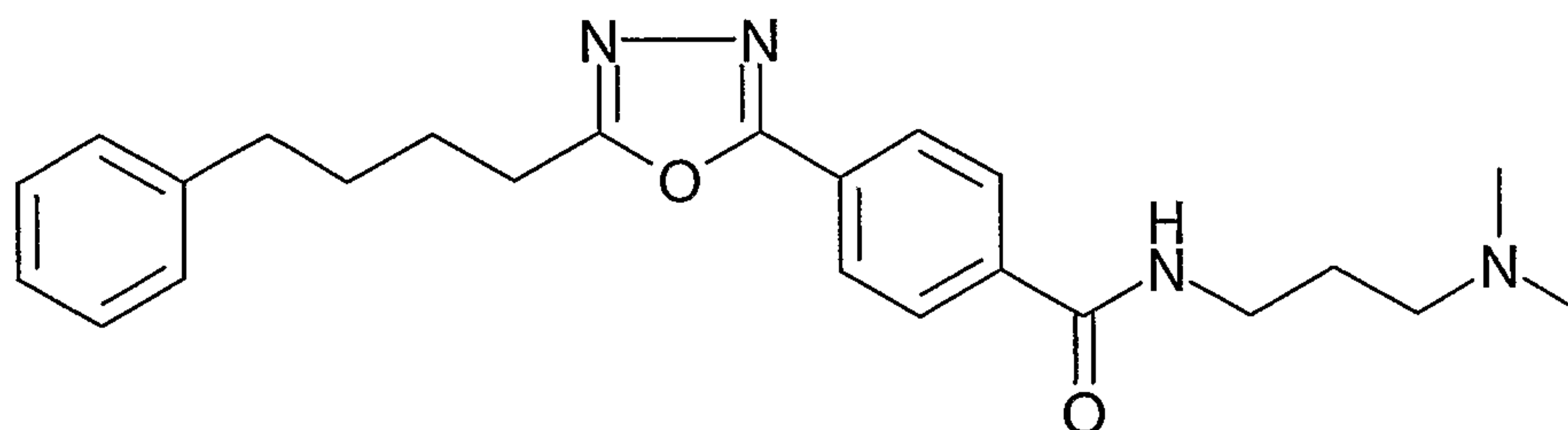


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.430 g, 1.39 mmol), 1-hydroxybenzotriazole (0.188 g, 1.39 mmol), 4-dimethylamino pyridine 0.150 g, 1.46 mmol), 3-(dimethylamino)propylamine (0.150 g, 1.46 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (eluted with 10% 2M ammonium:CH₂Cl₂) followed by crystallization of the isolated material from ethanol:diethyl ether afforded 0.274 g (50%) of N-(3-dimethylaminopropyl)-4-(5-phenylpropyl)-[1,3,4]oxadiazol-2-ylbenzamide.

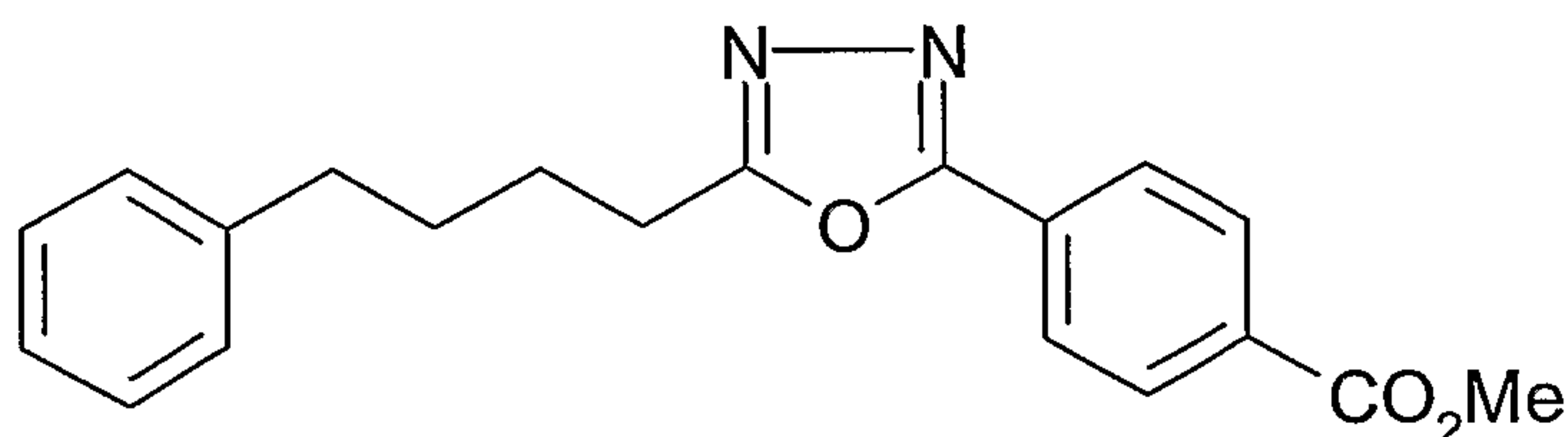
¹H NMR (DMSO-d₆) δ 8.70 (t, 1H, J=5Hz), 7.99-8.08 (m, 4H), 7.16-7.33 (m, 5H), 3.53 (m, 2H), 3.30 (t, 2H, J=7Hz), 2.72 (t, 2H, J=7Hz), 2.27 (t, 2H, J=7Hz), 2.13 (s, 6H), 2.04-2.11 (m, 2H), 1.63-1.72 (m, 2H). IR (CHCl₃, cm⁻¹) 3008, 2950, 2827, 1652, 1586, 1567, 1557, 1529, 1495, 1243, 1089. MS (ES) m/e, 393, 391. Anal. Calcd for C₂₃H₂₈N₄O₄: C, 70.38; H, 7.19; N, 14.27. Found C, 69.78; H, 7.04; N, 14.04. Analytical HPLC: 100% purity. Mp(°C)>200.

Example 10 Preparation of N-(3-dimethylaminopropyl)-4-(5-phenylbutyl)-[1,3,4]oxadiazol-2-ylbenzamide from 5-phenylvaleric acid

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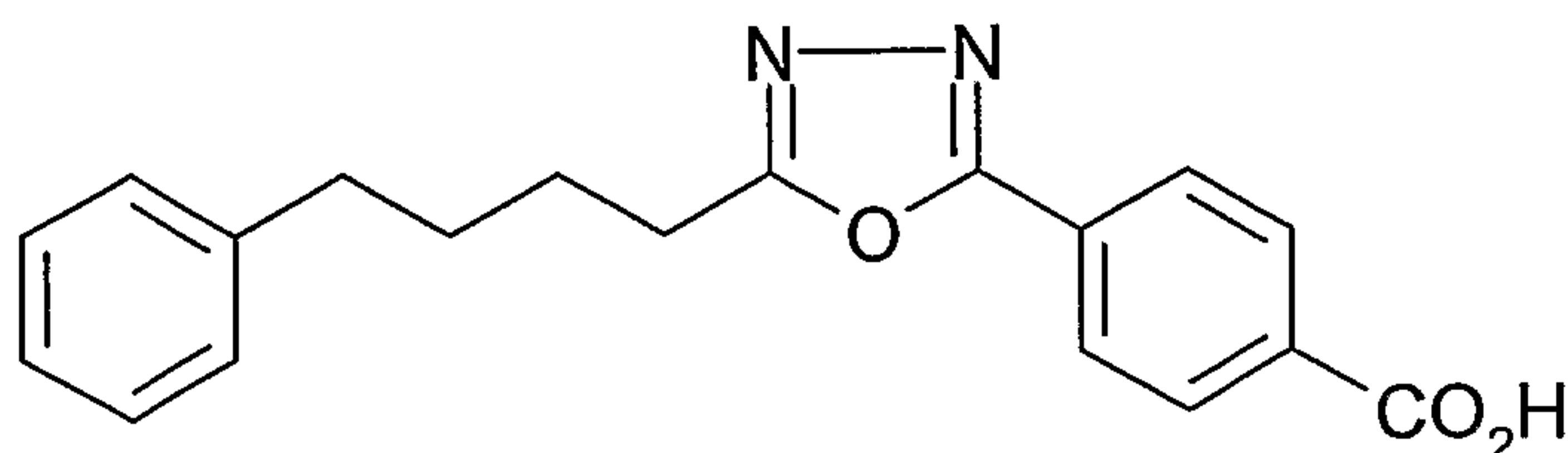
a) 4-[5-(3-phenylbutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester.



5 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 5-phenylvaleric acid (0.620 g, 3.5 mmol), 1,3-dicyclohexylcarbodiimide (0.710 g, 3.5 mmol), 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.700 g, 3.4 mmol) and 5.1 mL toluene to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 25% to 50%
10 EtOAc : hexane) followed by crystallization of the isolated material from diethyl ether afforded 0.463 g (40%) of 4-[5-(3-phenylbutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester.

¹H NMR (DMSO-*d*₆) δ 8.09-8.17 (m, 4H), 7.14-7.30 (m, 5H), 3.90 (s, 3H), 2.99 (t, 2H, J=7Hz), 2.64 (t, 2H, J=7Hz), 1.65-1.85 (m, 4H). IR (KBr, cm⁻¹) 1723, 1568, 1413,
15 1277, 1111, 716, 697. MS (ES) *m/e*, 337. Anal. Calcd for C₂₀H₂₀N₂O₃: C, 71.41; H, 5.99; N, 8.33. Found C, 71.36; H, 5.90; N, 8.29.

b) 4-[5-(3-phenylbutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



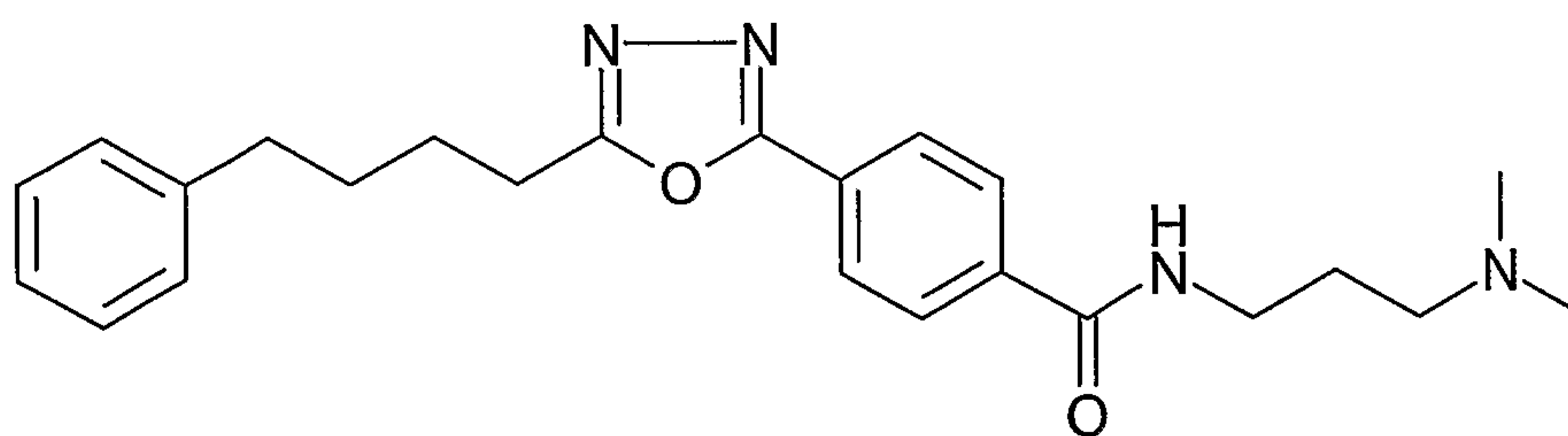
20 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, using 4-[5-(3-phenylbutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid

-87-

methyl ester (0.380 g, 1.16 mmol) and lithium hydroxide (0.081 g, 3.4 mmol) to afford 0.360 g (99%) of 4-[5-(3-phenylbutyl)-[1,3,4]oxa-diazol-2-yl]benzoic acid.

^1H NMR (DMSO- d_6) δ 13.38 (bs, 1H), 8.04-8.14 (m, 4H), 7.14-7.30 (m, 5H), 2.99 (t, 2H, $J=7\text{Hz}$), 2.64 (t, 2H, $J=7\text{Hz}$), 1.64-1.85 (m, 4H). IR (KBr, cm^{-1}) 2946, 1686, 1586, 1567, 1551, 1429, 1413, 1320, 1288, 740, 716. MS (ES) m/e , 323, 321. Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$: C, 70.79; H, 5.63; N, 8.69. Found C, 70.33; H, 5.38; N, 8.41.

c) 4[5-(3-dimethylaminopropyl)-4-(5-phenylbutyl)-[1,3,4]oxadiazol-2-yl]benzamide

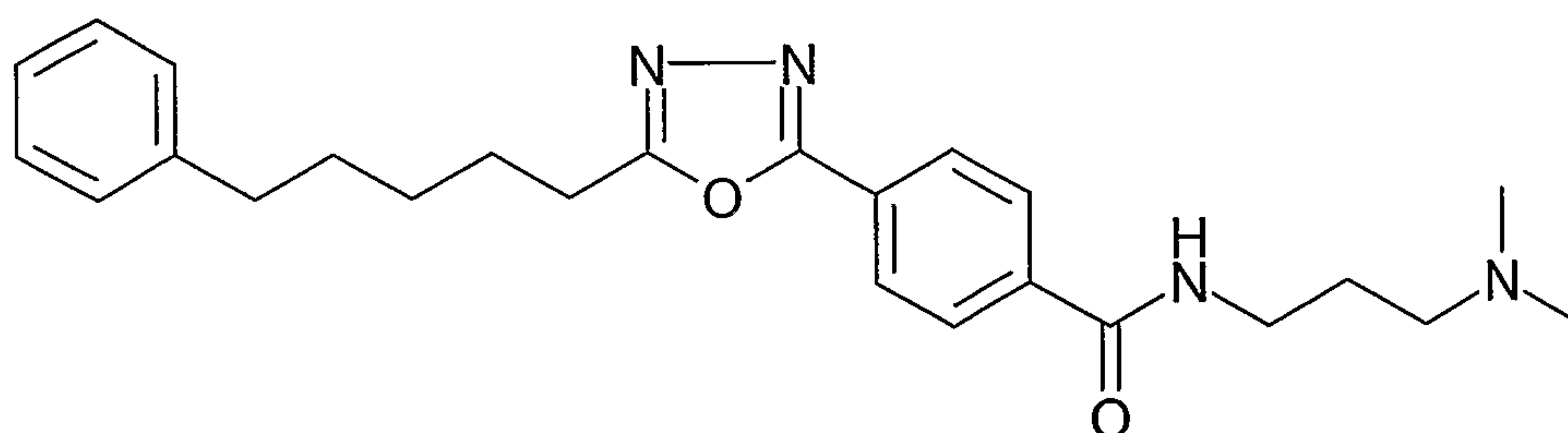


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(3-phenylbutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.342 g, 1.0 mmol), 1-hydroxybenzotriazole 0.136 g, 1.0 mmol), 4-dimethylamino pyridine (0.012 g, 0.10 mmol), 3-(dimethylamino)propylamine (0.108 g, 1.06 mmol) and 29 mL CH_2Cl_2 . Purification by radial chromatography on silica gel (eluted with 10% 2M ammonium: CH_2Cl_2) followed by crystallization of the isolated material from ethanol:diethyl ether afforded 0.226 g (55%) of 4[5-(3-dimethylaminopropyl)-4-(5-phenylbutyl)-[1,3,4]oxadiazol-2-yl]benzamide.

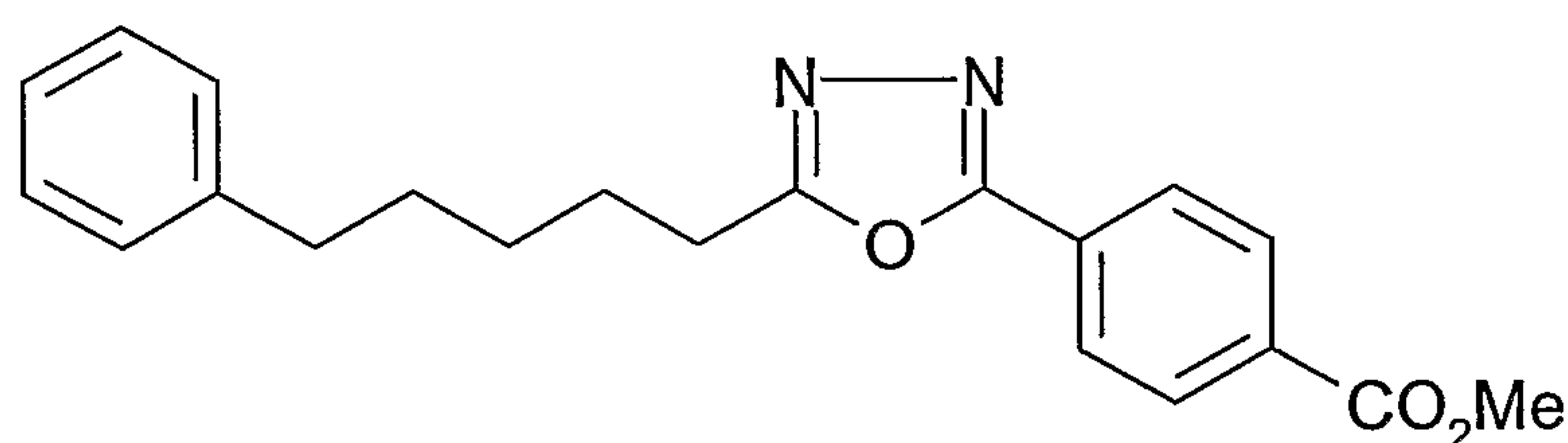
^1H NMR (DMSO- d_6) δ 8.71 (t, 1H, $J=5\text{Hz}$), 7.99-8.06 (m, 4H), 7.14-7.30 (m, 5H), 3.32 (m, 2H), 2.98 (t, 2H, $J=7\text{Hz}$), 2.64 (t, 2H, $J=7\text{Hz}$), 2.26 (t, 2H, $J=7\text{Hz}$), 2.14 (s, 6H), 1.62-1.82 (m, 6H). IR (CHCl_3 , cm^{-1}) 3008, 2947, 1652, 1586, 1567, 1556, 1529, 1495. MS (ES) m/e , 407, 405. Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_2$: C, 70.91; H, 7.44; N, 13.78. Found C, 70.66; H, 7.35; N, 13.67. $\text{Mp}(\text{°C})=84$.

Example 11 Preparation of N-(3-dimethylaminopropyl)-4-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]benzamide from 6-phenylhexanoic acid

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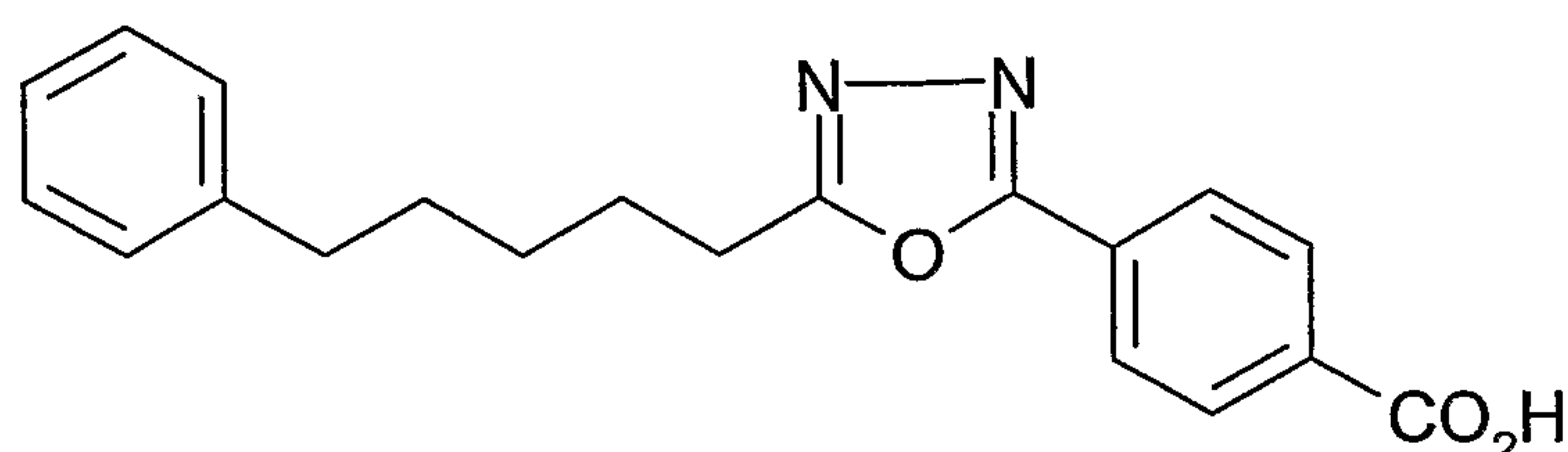
a) 4-[5-(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester.



5 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 6-phenylhexanoic acid (0.960 g, 5.0 mmol), 1,3-dicyclohexylcarbodiimide (1.01 g, 5.0 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.01 g, 4.95 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc :
10 hexane) afforded 0.766 g (44%) of 4-[5-(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester.

¹H NMR (DMSO-d₆) δ 8.10-8.17 (m, 4H), 7.11-7.28 (m, 5H), 3.90 (s, 3H), 2.95(t, 2H, J=7Hz), 2.59 (t, 2H, J=8Hz), 1.81 (dt, 2H, J=8Hz), 1.63 (dt, 2H, J=8Hz), 1.35-1.45 (m, 2H). IR (CHCl₃, cm⁻¹) 3010, 2938, 2860, 1721, 1569, 1438, 1282, 1119, 1111. MS
15 (ES) m/e, 351. Anal. Calcd for C₂₁H₂₂N₂O₃: C, 71.98; H, 6.33; N, 7.99. Found C, 72.04; H, 6.32; N, 8.00.

b) 4-[5—(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



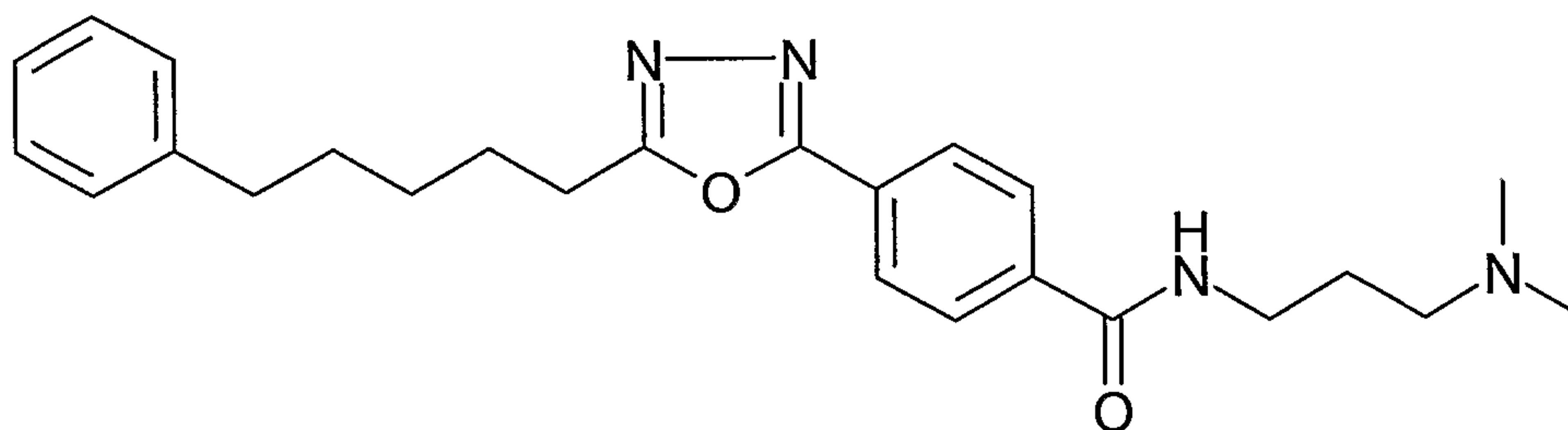
20 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 4-[5-(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl]benzoic

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acid methyl ester (0.725 g, 2.1 mmol), lithium hydroxide (0.149 g, 6.2 mmol) to afford 0.685 g (98%) of 4-[5-(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl]benzoic acid.

^1H NMR (DMSO- d_6) δ 13.33 (bs, 1H), 8.07-8.15 (m, 4H), 7.12-7.28 (m, 5H), 2.95 (t, 2H, $J=7\text{Hz}$), 2.59 (t, 2H, $J=7\text{Hz}$), 1.74-1.86 (m, 2H), 1.56-1.70 (m, 2H), 1.35-1.45 (m, 2H). IR (KBr, cm^{-1}) 2949, 2919, 2856, 1683, 1570, 1321, 1291, 732, 720. MS (ES) m/e , 337, 335. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$: C, 71.41; H, 5.99; N, 8.33. Found C, 70.86; H, 5.96; N, 8.26.

c) 4[5-(3-dimethylaminopropyl)-4-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]benzamide



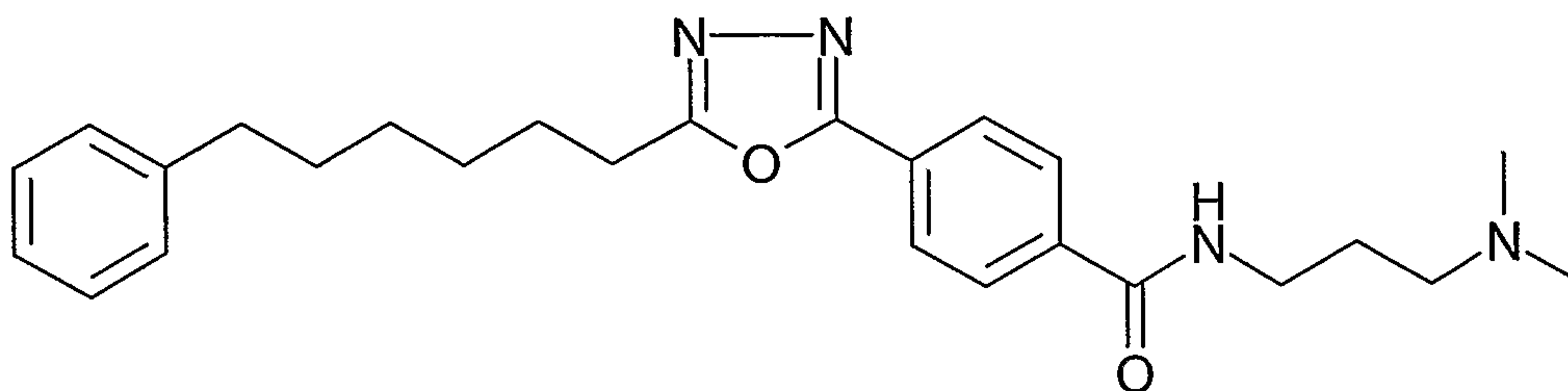
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.500 g, 1.49 mmol), 1-hydroxybenzotriazole (0.201 g, 1.49 mmol), 4-dimethylamino pyridine (0.018 g, 0.15 mmol), and 3-(dimethylamino)propylamine (0.159 g, 1.56 mmol) to afford the title compound as a crude mixture. Purification by chromatography on silica gel (eluted with a linear gradient of 2 to 10% 2M ammonium: CH_2Cl_2 over a thirty minute period) followed by crystallization of the isolated material from ethanol:diethyl ether afforded 0.209 g (33%) of 4[5-(3-dimethylaminopropyl)-4-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]benzamide. A second crop of crystals afforded 0.085g (13%) of the title compound.

^1H NMR (DMSO- d_6) δ 8.71 (t, 1H, $J=5\text{Hz}$), 8.00-8.07 (m, 4H), 7.12-7.28 (m, 5H), 3.30 (m, 2H), 2.94 (t, 2H, $J=7\text{Hz}$), 2.59 (t, 2H, $J=7\text{Hz}$), 2.26 (t, 2H, $J=7\text{Hz}$), 2.14 (s, 6H), 1.76-1.86 (m, 2H), 1.58-1.71 (m, 4H), 1.37-1.45 (m, 2H). IR (CHCl_3 , cm^{-1}) 3007, 1652, 1586, 1555, 1529, 1494. MS (ES) m/e , 421, 419. Anal. Calcd for $\text{C}_{25}\text{H}_{32}\text{N}_4\text{O}_2$: C, 71.40; H, 7.67; N, 13.32. Found C, 71.16; H, 7.64; N, 13.23. Mp°C =116.

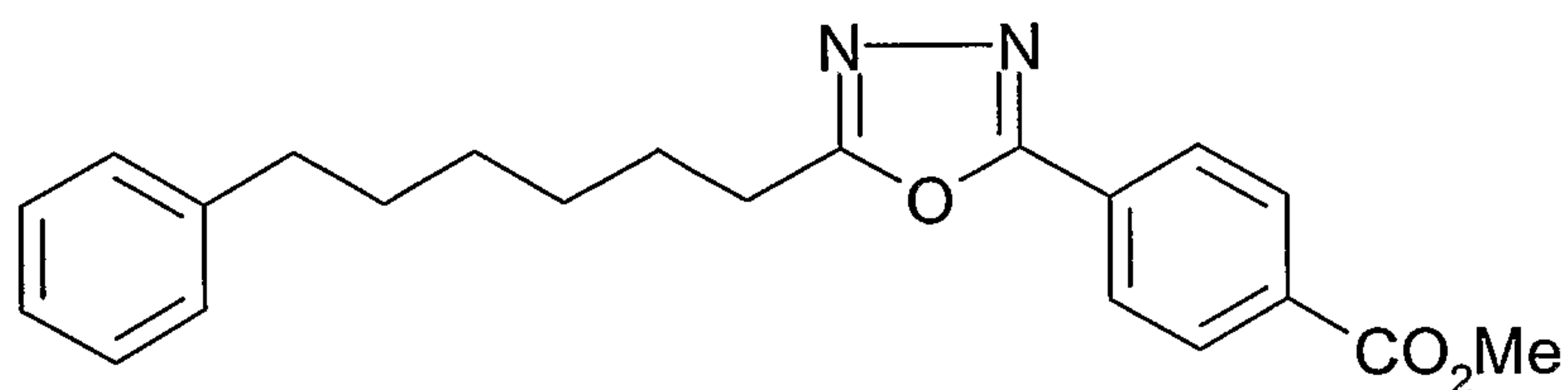
Example 12

-90-

Preparation of N-(3-dimethylaminopropyl)-4-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzamide from 7-phenylheptanoic acid



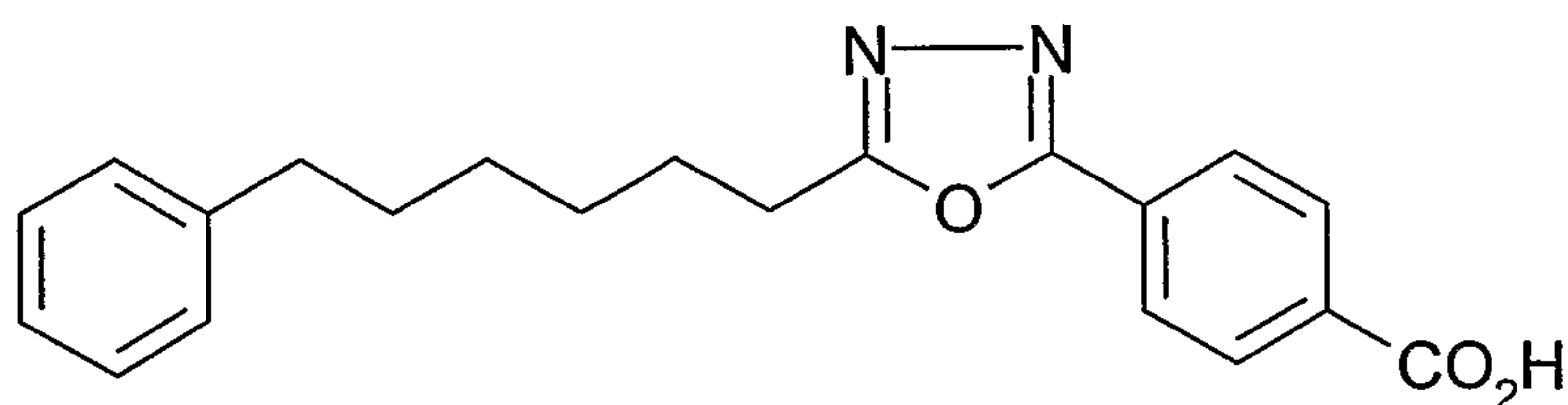
a) 4-[5-(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzoic acid
5 methyl ester.



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 7-phenylheptanoic acid (0.714 g, 3.46 mmol), 1,3-dicyclohexylcarbodiimide (0.714 g, 3.46 mmol), 4-(1*H*-tetrazole-5-yl)benzoic acid methyl
10 ester (0.700 g, 3.43 mmol) and 5.1 mL toluene to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc:hexane) afforded 0.738 g (59%) of 4-[5-(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.

¹H NMR (DMSO-*d*₆) δ 8.10-8.17 (m, 4H), 7.12-7.28 (m, 5H), 3.90 (s, 3H), 2.94 (t, 2H, J=7Hz), 2.56 (t, 2H, J=7Hz), 1.72-1.82 (m, 2H), 1.53-1.63 (m, 2H), 1.28-1.46 (m, 4H). IR (KBr, cm⁻¹) 2952, 2930, 2856, 1723, 1565, 1414, 1280, 1264, 1110, 778, 717, 698. MS (ES) *m/e*, 365. Anal. Calcd for C₂₂H₂₄N₂O₃: C, 72.51; H, 6.64; N, 7.69. Found C, 72.83; H, 6.59; N, 7.62.

20 b) 4-[5—(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzoic acid

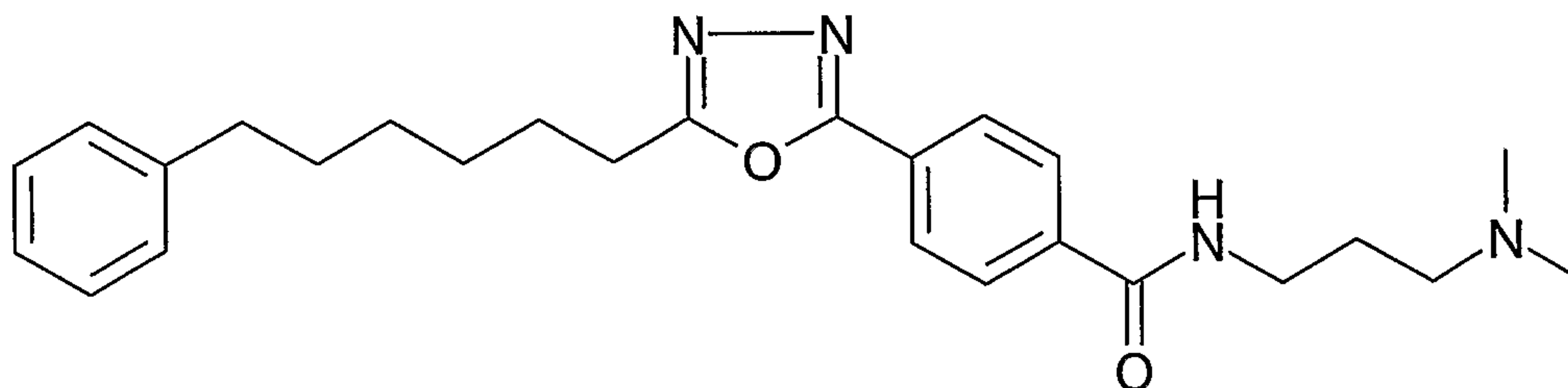


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The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 4-[5-(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.676 g, 1.93 mmol) and lithium hydroxide (0.139 g, 5.79 mmol) to afford 0.616 g (95%) of 4-[5-(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl]benzoic acid.

¹H NMR (DMSO-d₆) δ 8.05-8.13 (m, 4H), 7.12-7.28 (m, 5H), 2.93 (t, 2H, J=7Hz), 2.56 (t, 2H, J=8Hz), 1.72-1.82 (m, 2H), 1.50-1.63 (m, 2H), 1.26-1.46 (m, 4H). IR (KBr, cm⁻¹) 2942, 2924, 2853, 1686, 1573, 1429, 1287, 715. MS (ES) m/e, 351, 349. Anal. Calcd for C₂₁H₂₂N₂O₃: C, 71.98; H, 6.33; N, 7.99. Found C, 71.59; H, 6.45; N, 7.86.

c) 4[5-(3-dimethylaminopropyl)-4-(5-phenylhexyl)-[1,3,4]oxadiazol-2-yl]benzamide



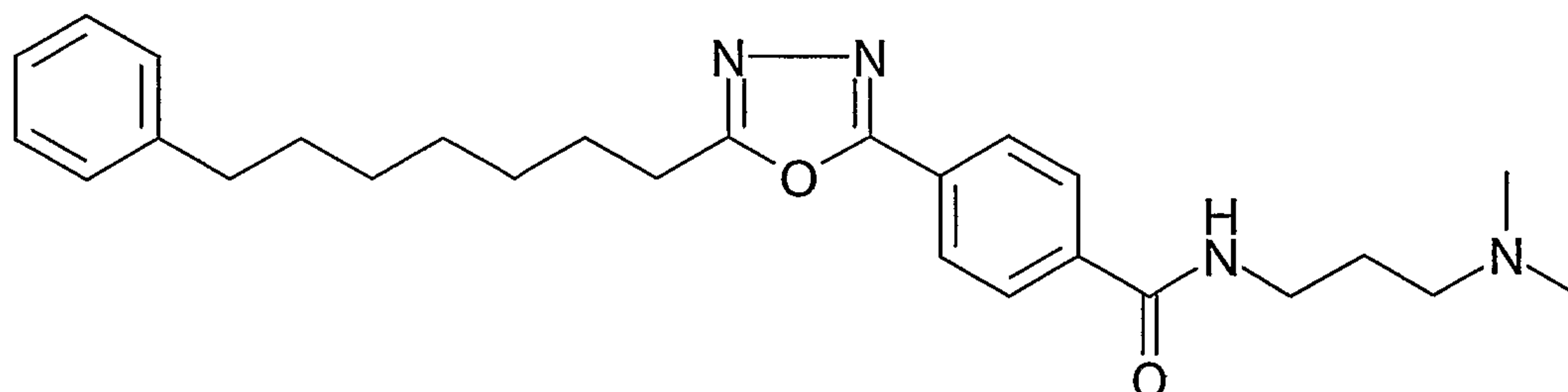
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.488 g, 1.39 mmol), 1-hydroxybenzotriazole (0.188 g, 1.39 mmol), 4-dimethylamino pyridine (0.017 g, 0.14 mmol) and 3-(dimethylamino)propylamine (0.149 g, 1.46 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (eluted with a 10% 2M ammonium :CH₂Cl₂) followed by crystallization of the isolated material from ethanol:diethyl ether afforded 0.152 g (25%) of 4[5-(3-dimethylaminopropyl)-4-(5-phenylhexyl)-[1,3,4]oxadiazol-2-yl]benzamide.

¹H NMR (DMSO-d₆) δ 8.71 (t, 1H, J=5Hz), 8.00-8.08 (m, 4H), 7.12-7.238 (m, 5H), 3.31 (m, 2H), 2.93 (t, 2H, J=7Hz), 2.56 (t, 2H, J=8Hz), 2.27 (t, 2H, J=7Hz), 2.13 (s, 6H), 1.53-1.79 (m, 6H), 1.30-1.44 (m, 4H). IR (KBr, cm⁻¹) 2936, 2861, 1652, 1586, 1567, 1556, 1529, 1495, 1302. MS (ES) m/e, 435, 433. Anal. Calcd for C₂₆H₃₄N₄O₂: C, 71.86; H, 7.89; N, 12.89. Found C, 71.59; H, 7.69; N, 12.72. Mp(°C)=91.

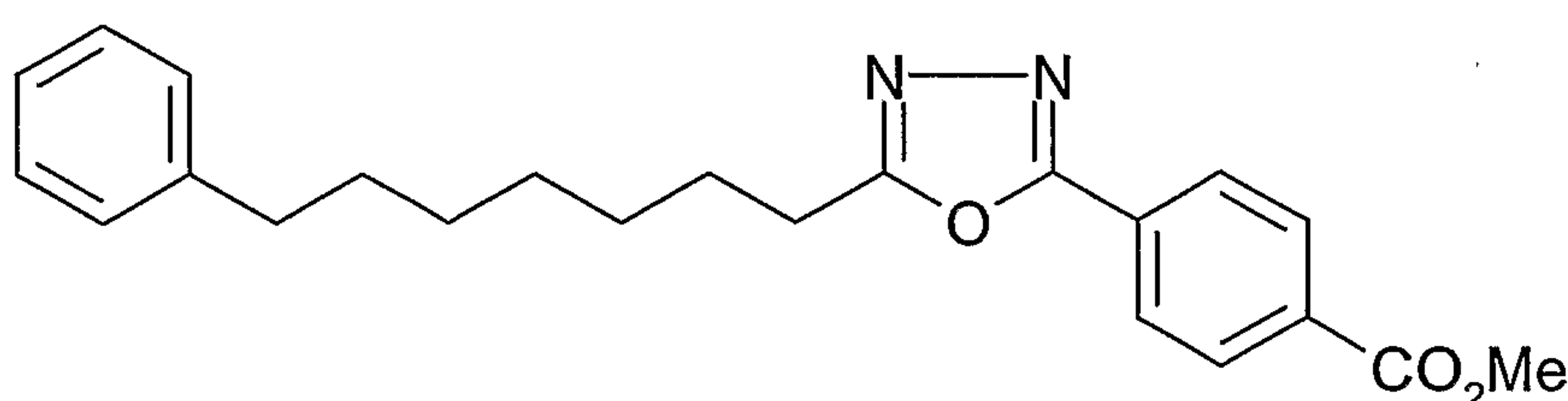
Example 13

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Preparation of N-(3-dimethylaminopropyl)-4-(5-phenylheptyl)-[1,3,4]oxadiazol-2-yl)benzamide from 8-phenyloctanoic acid



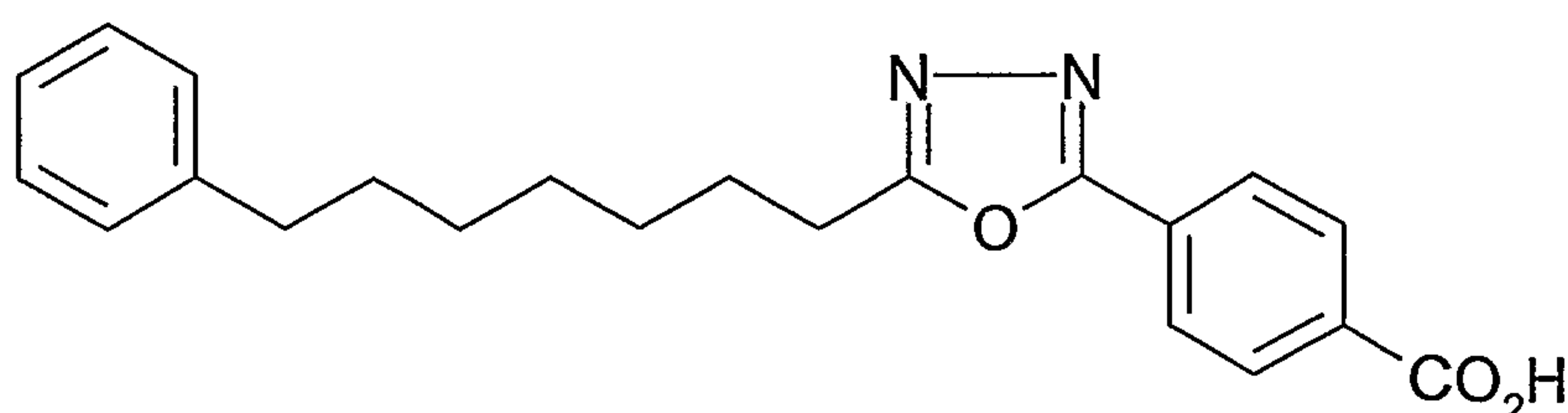
a) 4-[5-(3-phenylheptyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 8-phenyloctanoic acid (0.763 g, 3.46 mmol), 1,3-dicyclohexylcarbodiimide (0.714 g, 3.46 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.700 g, 3.43 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc :hexane) followed by crystallization of the isolated material from diethyl ether afforded 0.522 g (40%) of 4-[5-(3-phenylheptyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.

¹H NMR (DMSO-d₆) δ 8.13 (m, 4H), 7.12-7.28 (m, 5H), 3.90 (s, 3H), 2.94 (t, 2H, J=7Hz), 2.56 (t, 2H, J=7Hz), 1.63-1.81 (m, 2H), 1.44-1.61 (m, 2H), 1.22-1.41 (m, 6H). IR (KBr, cm⁻¹) 2926, 1724, 1570, 1437, 1280, 1110, 712. MS (ES) m/e, 379. Anal. Calcd for C₂₃H₂₆N₂O₃: C, 72.99; H, 6.92; N, 7.40. Found C, 73.11; H, 7.08; N, 7.68.

b) 4-[5-(3-phenylheptyl)-[1,3,4]oxadiazol-2-yl)benzoic acid



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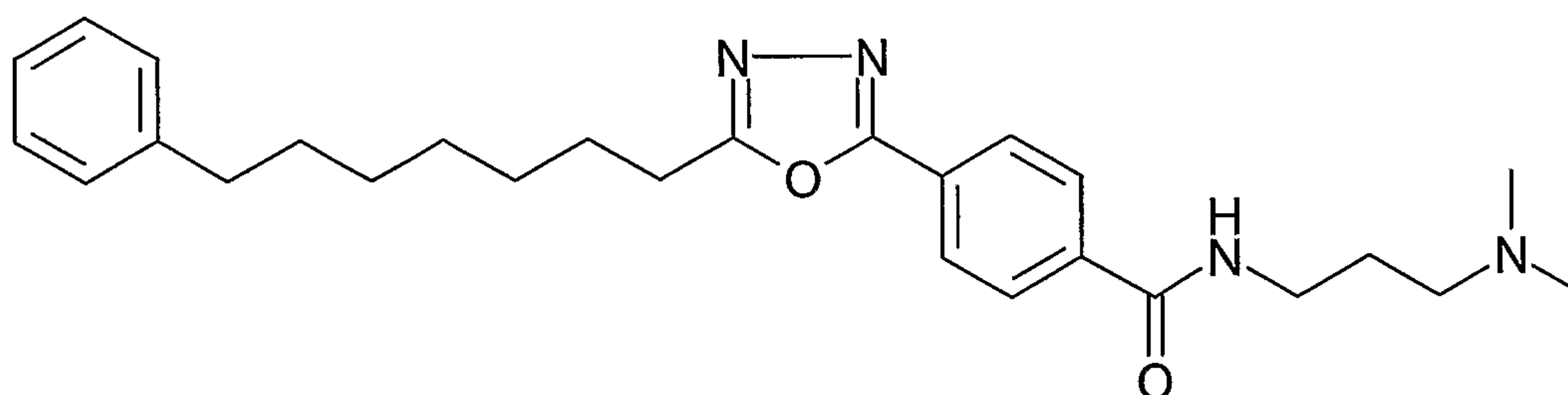
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 4-[5-(3-phenyl heptyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.467 g, 1.23 mmol) and lithium hydroxide (0.089 g, 3.70 mmol), in THF (5.4 mL) and water (1.0 mL) to afford 0.435 g (97%) of 4-[5-(3-phenylheptyl)-

5 [1,3,4]- oxadiazol-2-yl]benzoic acid.

¹H NMR (DMSO-d₆) δ 8.06-8.14 (m, 4H), 7.12-7.28 (m, 5H), 2.94 (t, 2H, J=7Hz), 2.56 (t, 2H, J=7Hz), 1.69-1.81 (m, 2H), 1.50-1.61 (m, 2H), 1.23-1.41 (m, 6H). IR (KBr, cm⁻¹) 2928, 2922, 2850, 1688, 1585, 1571, 1434, 1321, 1291, 722. MS (ES) m/e, 365, 363. Anal. Calcd for C₂₂H₂₄N₂O₃: C, 72.51; H, 6.64; N, 7.69. Found C, 69.19; H,

10 6.35; N, 7.47.

c) 4[5-(3-dimethylaminopropyl)-4-(5-phenylheptyl)-[1,3,4]oxadiazol-2-yl]benzamide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(3-phenylheptyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.399 g, 1.14 mmol), 1-hydroxybenzotriazole (0.154 g, 1.14 mmol), 4-dimethylamino pyridine (0.014 g, 0.11 mmol) and 3-(dimethylamino)propylamine (0.122 g, 1.20 mmol) to afford the title compound as a crude mixture. Purification by silica gel radial chromatography (eluted with a 10% 2M ammonium: CH₂Cl₂) followed by

20 crystallization of the isolated material from ethanol:diethyl ether afforded 0.103 g (20%) of 4[5-(3-dimethylaminopropyl)-4-(5-phenylhexyl)-[1,3,4]oxadiazol-2-yl]benzamide.

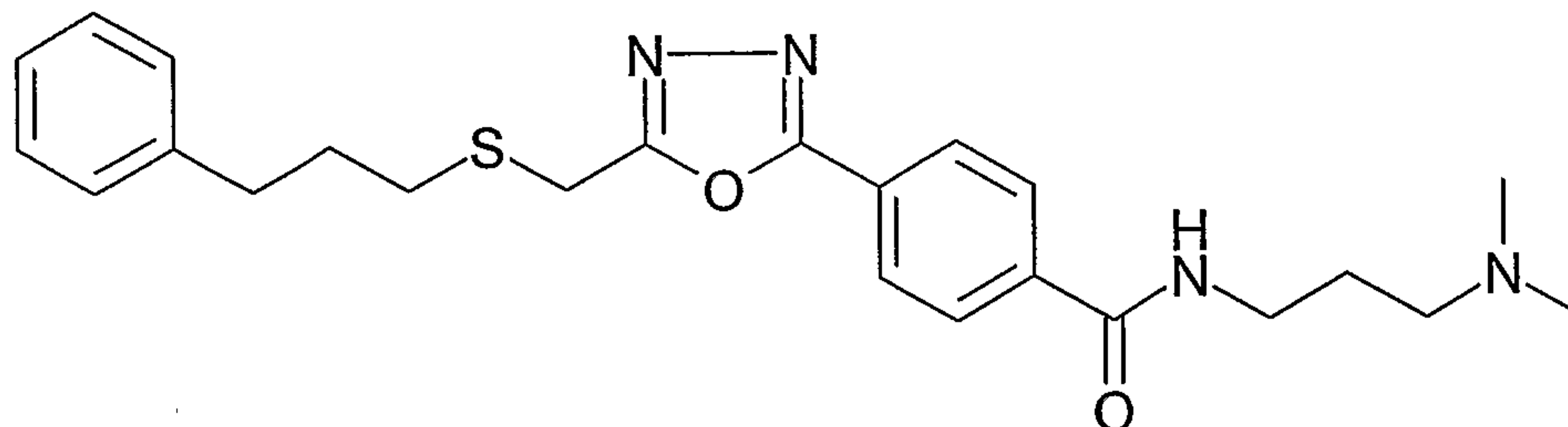
¹H NMR (DMSO-d₆) δ 8.71 (t, 1H, J=5Hz), 8.00-8.08 (m, 4H), 7.12-7.28 (m, 5H), 3.32 (m, 2H), 2.93 (t, 2H, J=7Hz), 2.56 (t, 2H, J=8Hz), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.44-1.77 (m, 6H), 1.27-1.40 (m, 6H). IR (CHCl₃, cm⁻¹) 3008, 2934, 2859, 2827, 1652, 1586, 1556, 1495. MS (ES) m/e, 449. Anal. Calcd for C₂₇H₃₆N₄O₂: C, 72.29; H, 8.09; N, 12.49. Found C, 72.21; H, 8.05; N, 12.50. Mp(°C)=108.

25

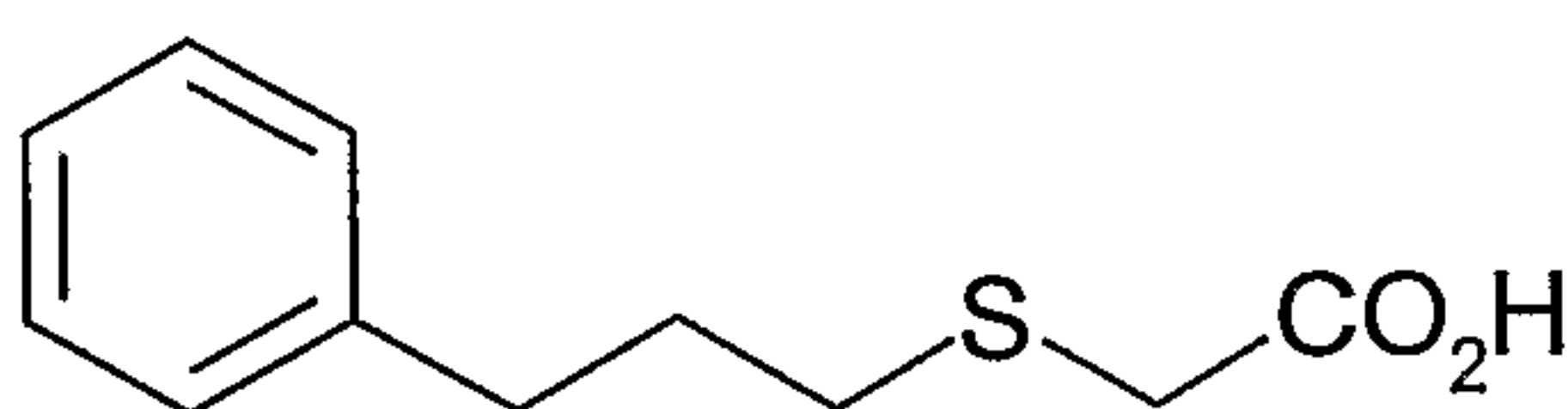
Example 14

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Preparation of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 3-phenylpropylmercaptan



a) (3-phenylpropylsulfanyl)acetic acid



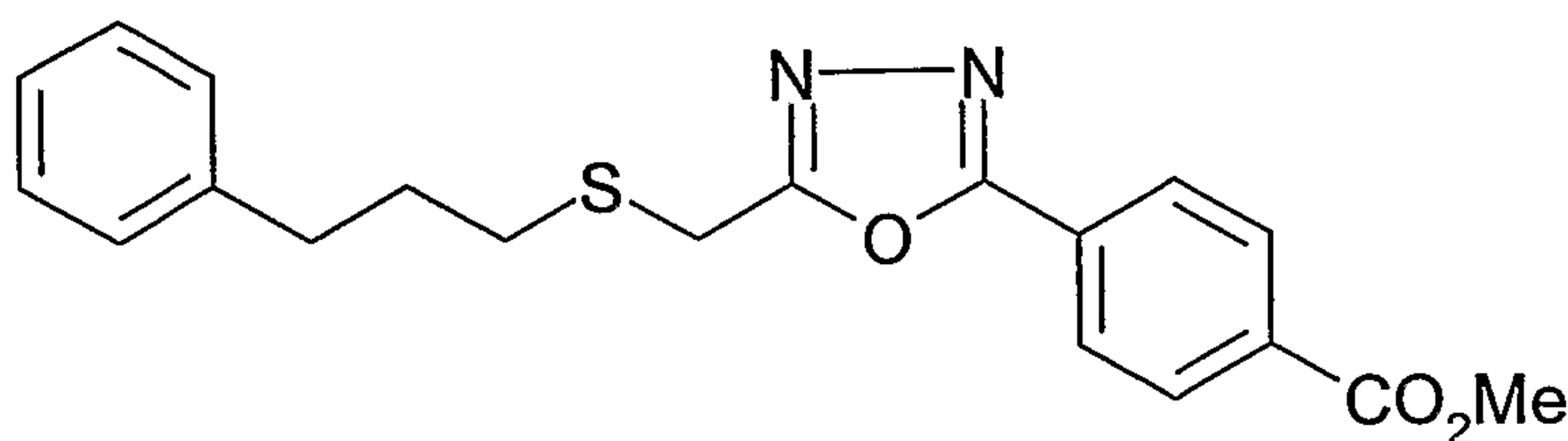
5

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1a, from 3-phenylpropylmercaptan (3.13 g, 20.6 mmol), sodium hydride (0.823 g, 20.6 mmol), and methyl bromoacetate (2.86 g, 18.7 mmol) to afford the title compound as a crude mixture. Purification by flash filtration chromatography on silica gel (elution with 4 x 250 mL 15% EtOAc:hexane followed by 3 x 250 mL EtOAc) afforded 3.83 g, (89%) of (3-phenylpropylsulfanyl)acetic acid.

¹H NMR (DMSO-d₆) δ 12.51 (bs, 1H), 7.15-7.30 (m, 5H), 3.23 (s, 2H), 2.65 (t, 2H, J=8Hz), 2.58 (t, 2H, J=7Hz), 1.78-1.88 (m, 2H). IR (CHCl₃, cm⁻¹) 3029, 3011, 1710, 1601, 1454, 1423, 1295, 1197. MS (ES) m/e, 209. Anal. Calcd for C₁₁H₁₄O₂S: C, 62.83; H, 6.71. Found C, 62.70; H, 6.52.

15

b) 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



20

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from (3-phenylpropylsulfanyl)acetic acid (0.975 g, 4.6 mM), 1,3-dicyclohexylcarbodiimide (0.957 g, 4.6 mmol), and 4-(1H-tetrazole-5-yl)benzoic acid

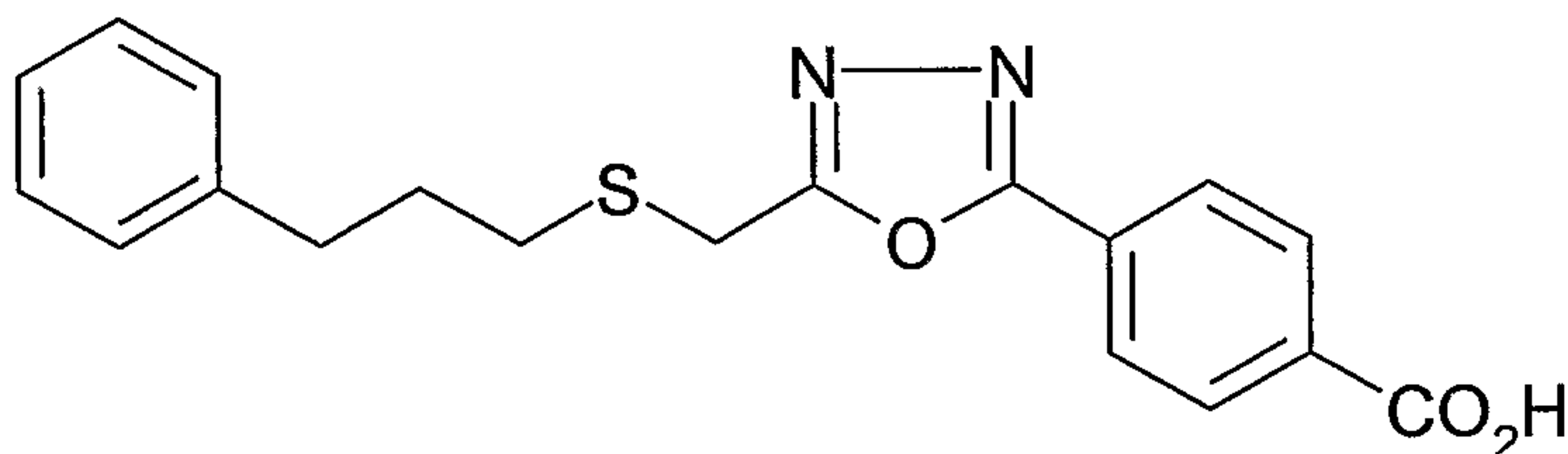
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methyl ester (0.789 g, 3.9 mmol) to afford the title compound as a crude mixture.

Purification by radial chromatography on silica gel followed by crystallization from diethyl ether afforded a total of 0.668 g (47%) of 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl] benzoic acid methyl ester.

¹H NMR (DMSO-d₆) δ 8.09-8.18 (m, 4H), 7.12-7.26 (m, 5H), 4.14 (s, 2H), 3.91 (s, 3H), 2.62-2.67 (m, 4H), 1.80-1.90 (m, 2H). IR (CHCl₃, cm⁻¹) 1721, 1554, 1438, 1299, 1283, 1119, 1111. MS (ES) m/e, 369. Anal. Calcd for C₂₀H₂₀N₂O₃S: C, 65.20; H, 5.47; N, 7.60. Found C, 65.05; H, 5.48; N, 7.67.

c) 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.600 g, 1.63 mmol) and lithium hydroxide (0.117 g, 4.89 mmol) to afford 0.522 g (90%) of 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid.

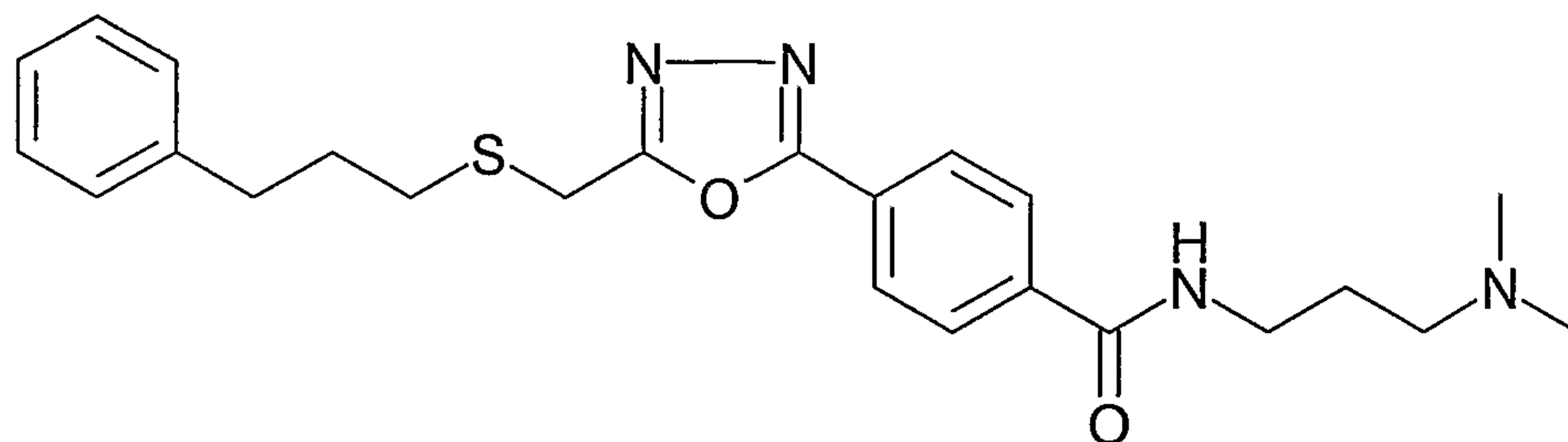
¹H NMR (DMSO-d₆) δ 8.03-8.16 (m, 4H), 7.11-7.28 (m, 5H), 4.14 (s, 2H), 2.66 (dt, 4H, J=7Hz), 1.79-1.88 (m, 2H).

IR (KBr, cm⁻¹) 1706, 1685, 1551, 1433, 1324, 1293, 715, 699.

MS (ES) m/e, 355, 353. Anal. Calcd for C₁₉H₁₈N₂O₃S: C, 64.39; H, 5.12; N, 7.90. Found C, 63.29; H, 4.95; N, 7.81.

d) N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide

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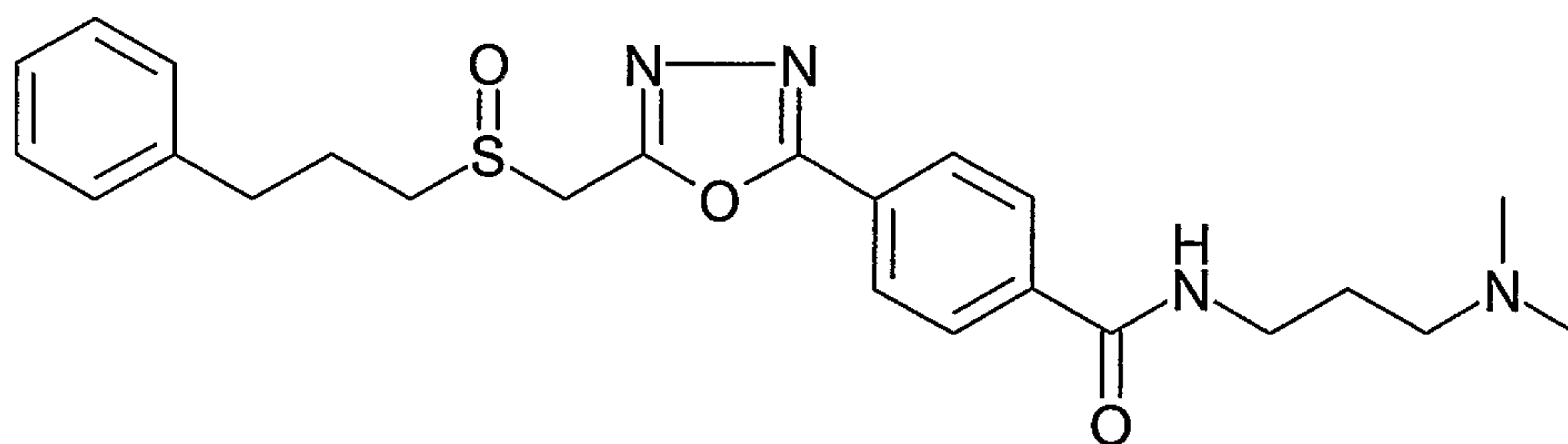


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.492 g, 1.39 mmol), 1,1'-carbonyldiimidazole (0.236 g, 1.46 mmol) and 3-(dimethylamino)propylamine (0.170 g, 1.67 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M ammonia in MeOH:CHCl₃) afforded 0.392 g (64%) of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

¹H NMR (DMSO-d₆) δ 8.72 (t, 1H, J=5Hz), 8.01-8.07 (m, 4H), 7.12-7.26 (m, 5H), 4.13 (s, 2H), 2.62-2.67 (m, 4H), 2.27 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.75-1.86 (m, 2H), 1.63-1.72 (m, 2H). IR (KBr, cm⁻¹) 3338, 2939, 2813, 2761, 1638, 1581, 1552, 1534, 1496, 1456, 1288, 712. MS (ES) m/e, 439, 437. Anal. Calcd for C₂₄H₃₀N₄O₂S: C, 65.73; H, 6.89; N, 12.77. Found C, 65.82; H, 6.94; N, 12.74. Mp(°C)=112.

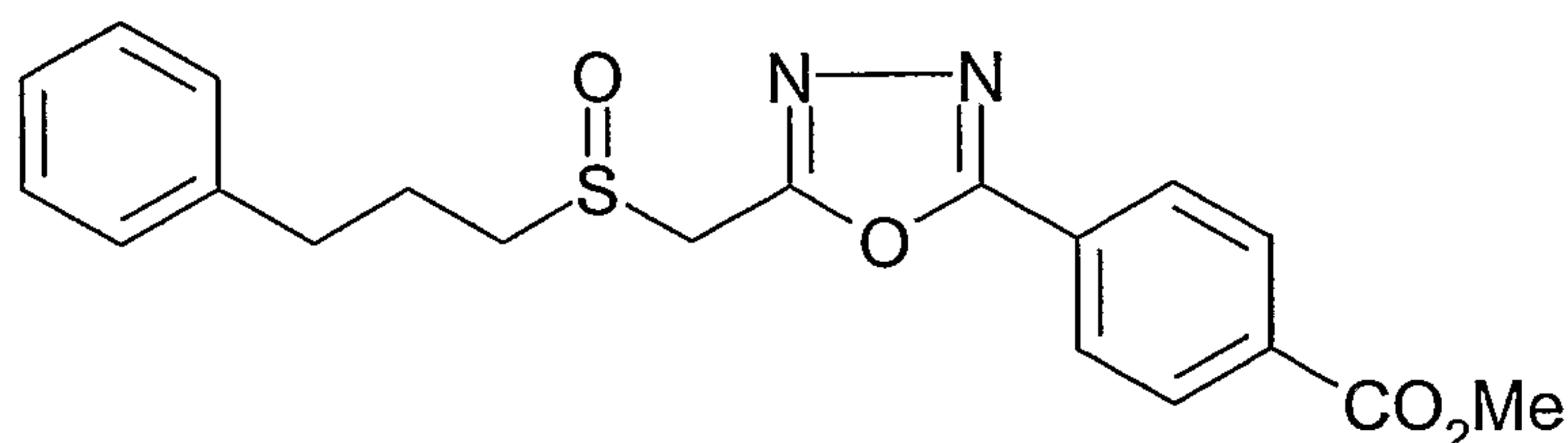
Example 15

Preparation of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



a) 4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester

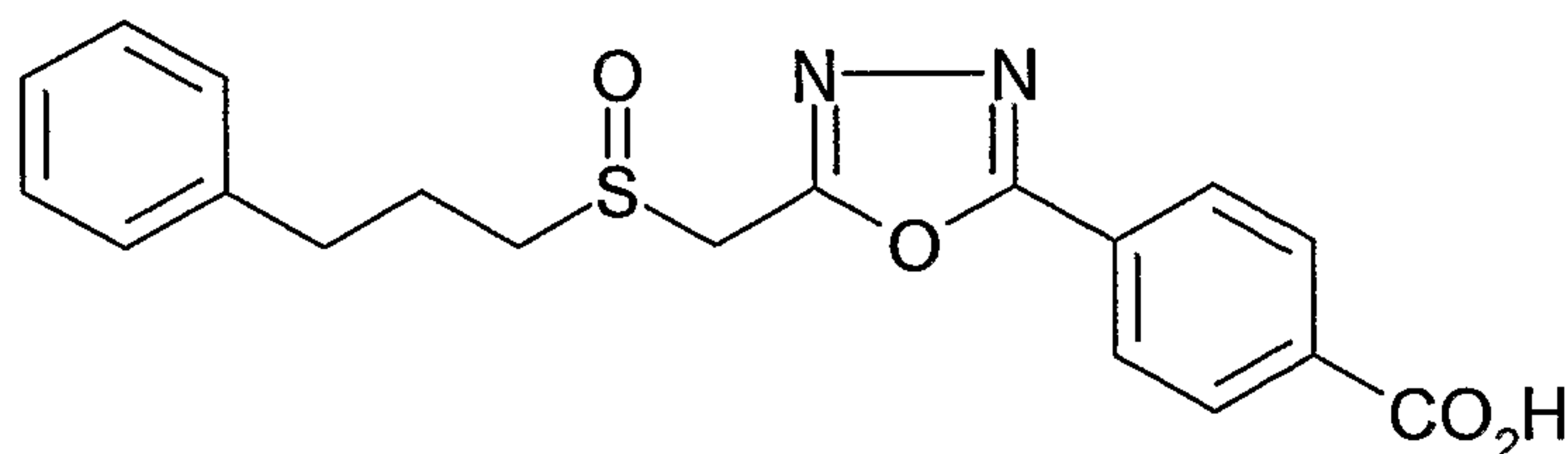
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A solution of 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.870 g, 2.4 mmol) in 12 mL CH₂Cl₂ stirring at 0 °C was added dropwise and peracetic acid (0.673 g, 2.8 mmol). After 2.1 hours the mixture was stirred at room temperature for 20 minutes before additional peracetic acid (0.036 g, 0.47 mmol) was added. Fifty minutes later additional peracetic acid (0.036 g, 0.47 mmol) was added. Twenty minutes after the second addition, the reaction was quenched with 5 mL saturated aqueous solution of sodium sulfite. The mixture was diluted with water then extracted with CH₂Cl₂. The organic phase was washed twice with H₂O, once with brine, dried over sodium sulfate, filtered, concentrated to afford a solid. Crystallization from acetone afforded 0.660 g (73%) of 4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester.

¹H NMR (DMSO-d₆) δ 8.11-8.20 (m, 4H), 7.16-7.32 (m, 5H), 4.73-4.78 (m, 1H), 4.51-4.56 (m, 1H), 3.90 (s, 3H), 2.88-3.05 (m, 2H), 2.72-2.77 (m, 2H), 1.95-2.05 (m, 2H). IR (CHCl₃, cm⁻¹) 1722, 1551, 1438, 1283, 1111. MS (ES) m/e, 385. Anal. Calcd for C₂₀H₂₀N₂O₄S: C, 62.16; H, 5.74; N, 7.25. Found C, 62.11; H, 5.22; N, 7.31.

b) 4-[5-(3-phenylpropane-1-sulfinylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid



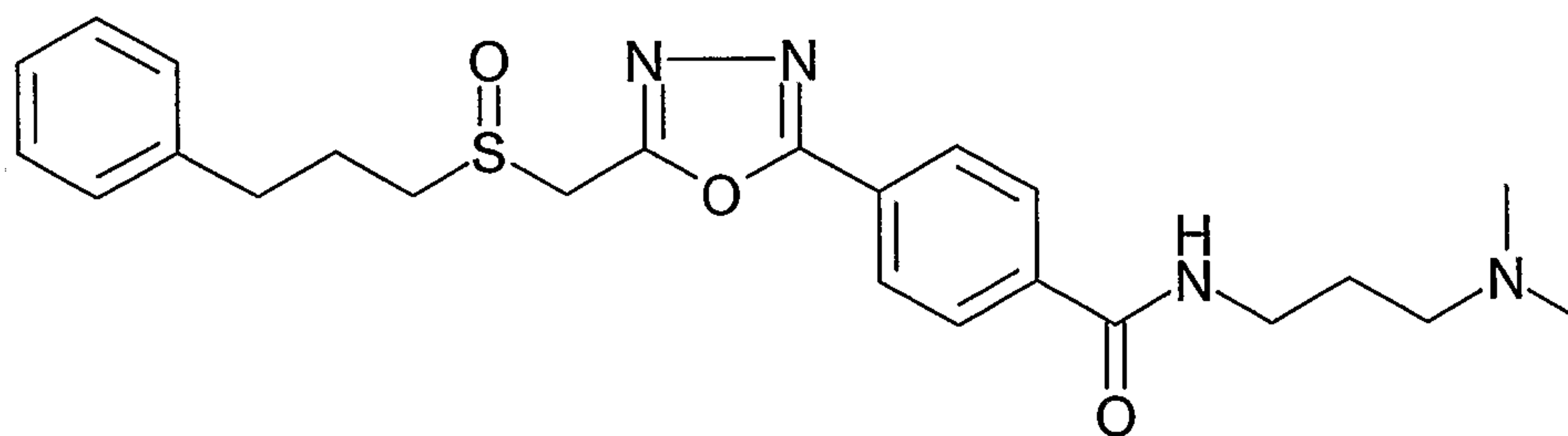
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.599 g, 1.56 mmol) and lithium hydroxide (0.112 g, 4.67 mmol) to afford 0.457 g (79%) of 4-[5-(3-phenylpropane-1-sulfinylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid.

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^1H NMR (DMSO- d_6) δ 13.40 (bs, 1H), 8.03-8.17 (m, 4H), 7.16-7.23 (m, 5H), 4.75 (d, 1H, $J=14\text{Hz}$), 4.54 (d, 1H, $J=14\text{Hz}$), 2.88-3.05 (m, 2H), 2.70-2.80 (m, 2H), 1.96-2.09 (m, 2H). IR (KBr, cm^{-1}) 2923, 1706, 1685, 1554, 1434, 1324, 1292, 1044, 1012, 873, 716, 697. MS (ES) m/e , 371. Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: C, 61.27; H, 5.41; N, 7.52.

5 Found C, 60.74; H, 4.79; N, 7.43.

c) N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide



10 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(3-phenylpropane-1-sulfinylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid (0.448 g, 1.20 mmol), 1,1'-carbonyldiimidazole (0.205 g, 1.26 mmol) and 3-(dimethylamino)propylamine (0.147 g, 1.44 mmol) to afford the title compound as a crude mixture. Crystallization of the crude
15 material from methanol:diethyl ether afforded 0.284 g (45%) of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

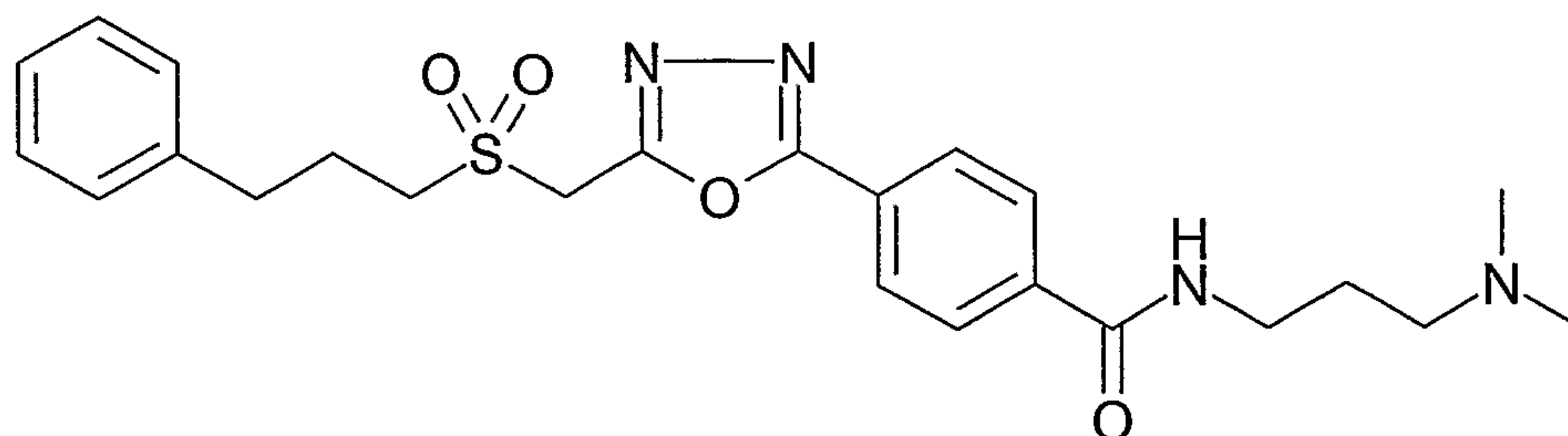
^1H NMR (DMSO- d_6) δ 8.73 (t, 1H, $J=5\text{Hz}$), 8.05 (m, 4H), 7.17-7.32 (m, 5H), 4.73 (d, 1H, $J=14\text{Hz}$), 4.52 (d, 1H, $J=14\text{Hz}$), 3.32 (m, 2H), 2.84-3.03 (m, 2H), 2.62-2.70
20 (m, 2H), 2.27 (t, 2H, $J=7\text{Hz}$), 2.14 (s, 6H), 1.94-2.06 (m, 2H), 1.62-1.72 (m, 2H). IR (KBr, cm^{-1}) 3334, 1645, 1585, 1554, 1536, 1304, 1047, 859 MS (ES) m/e , 455, 453. Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_3\text{S}$: C, 63.41; H, 6.65; N, 12.32. Found C, 62.86; H, 6.58; N, 12.14. Analytical HPLC: 100% Purity. $\text{Mp}(\text{°C})=127$.

25

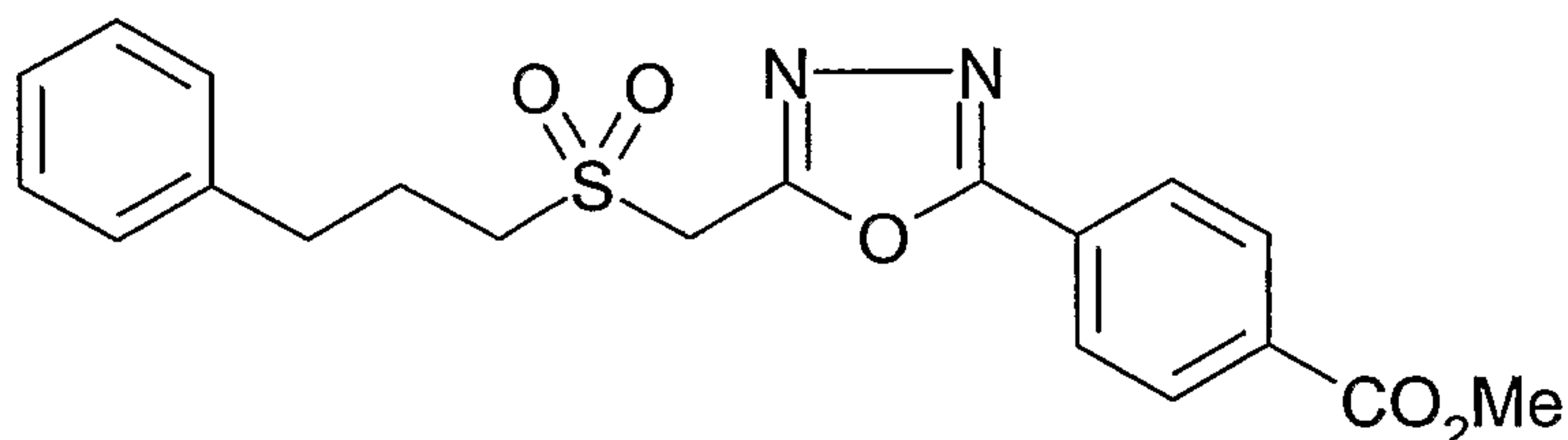
Example 16

Preparation of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 4-[5-(3-phenylpropylsulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester

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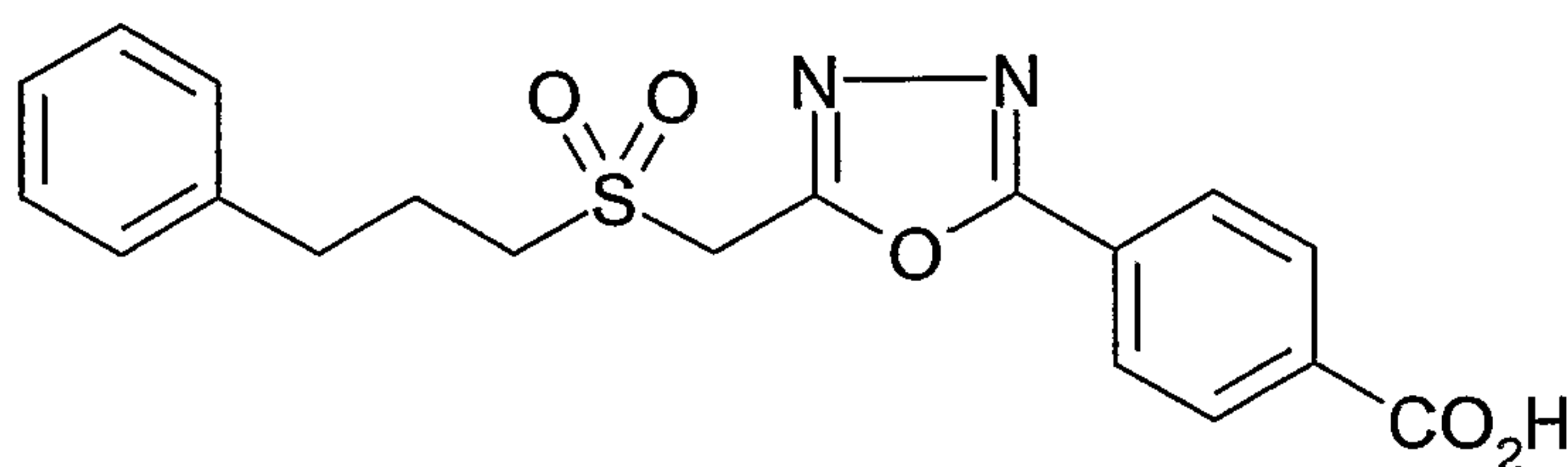
a) 4-[5-(3-phenylpropane-1-sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



5 A solution of 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.970 g, 2.63 mmol) and m-chloroperoxybenzoic acid (1.82 g, 5.8 mmol) in 14 mL CH₂Cl₂ was stirred at room temperature for 4.5 hours. The mixture was then quenched with 5 mL saturated aqueous solution of sodium sulfite. The mixture was diluted with water then extracted with CH₂Cl₂. The organic phase was washed twice with
10 H₂O, once with brine, dried over sodium sulfate, filtered, concentrated to afford a solid. Crystallization from acetone afforded 0.733 g (70%) of 4-[5-(3-phenylpropane-1-sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester.

¹H NMR (DMSO-d₆) δ 8.11-8.20 (m, 4H), 7.18-7.33 (m, 5H), 5.25 (s, 2H), 3.91 (s, 3H), 3.38 (t, 2H, J=8Hz), 2.74 (t, 2H, J=8Hz), 2.02-2.13 (m, 2H). IR (CHCl₃, cm⁻¹)
15 1722, 1438, 1333, 1299, 1284, 1112. MS (ES) m/e, 401, 399. Anal. Calcd for C₂₀H₂₀N₂O₅S: C, 59.99; H, 5.03; N, 7.00. Found C, 59.93; H, 5.12; N, 6.95.

b) 4-[5-(3-phenylpropane-1-sulfonylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid



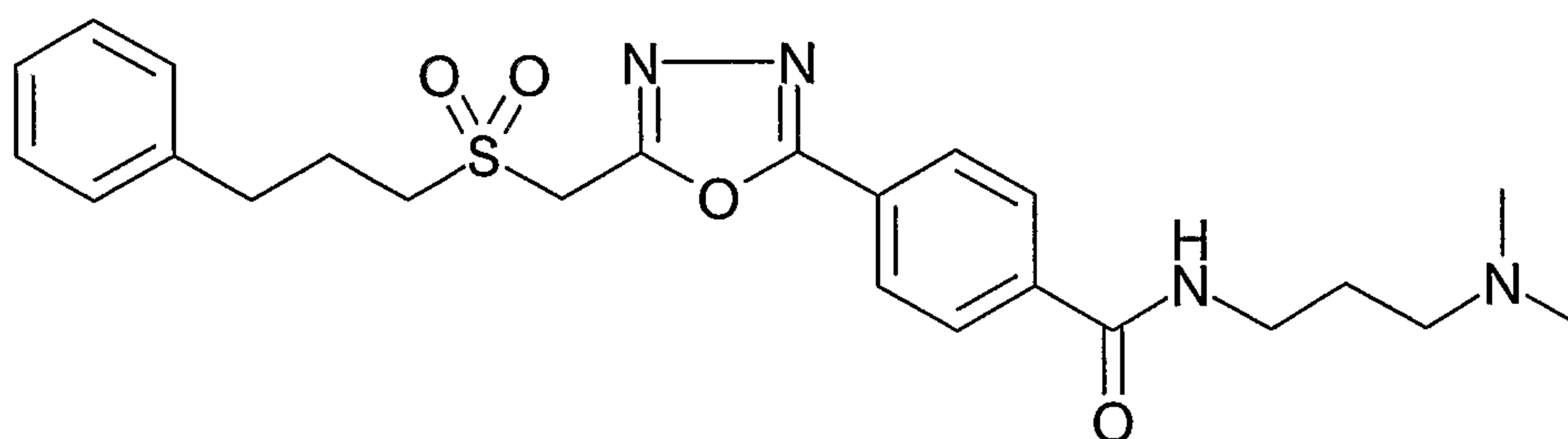
20 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(3-phenylpropane-1-sulfonylmethyl)-

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[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.667 g, 1.67 mmol) and lithium hydroxide (0.120 g, 5.00 mmol) to afford 0.559 g (87%) of 4-[5-(3-phenylpropane-1-sulfonylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid.

¹H NMR (DMSO-d₆) δ 13.38 (bs, 1H), 8.08-8.18 (m, 4H), 7.18-7.34 (m, 5H), 5.25 (s, 2H), 3.38 (t, 2H, J=8Hz), 2.75 (t, 2H, J=8Hz), 2.01-2.13 (m, 2H). IR (KBr, cm⁻¹) 2995, 2675, 2555, 1706, 1685, 1551, 1433, 1321, 1294, 1137, 1131, 1121, 717. MS (ES) m/e, 387. Anal. Calcd for C₁₉H₁₈N₂O₅S: C, 59.06; H, 4.70; N, 7.25. Found C, 58.42; H, 4.69; N, 7.11.

10 c) N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide



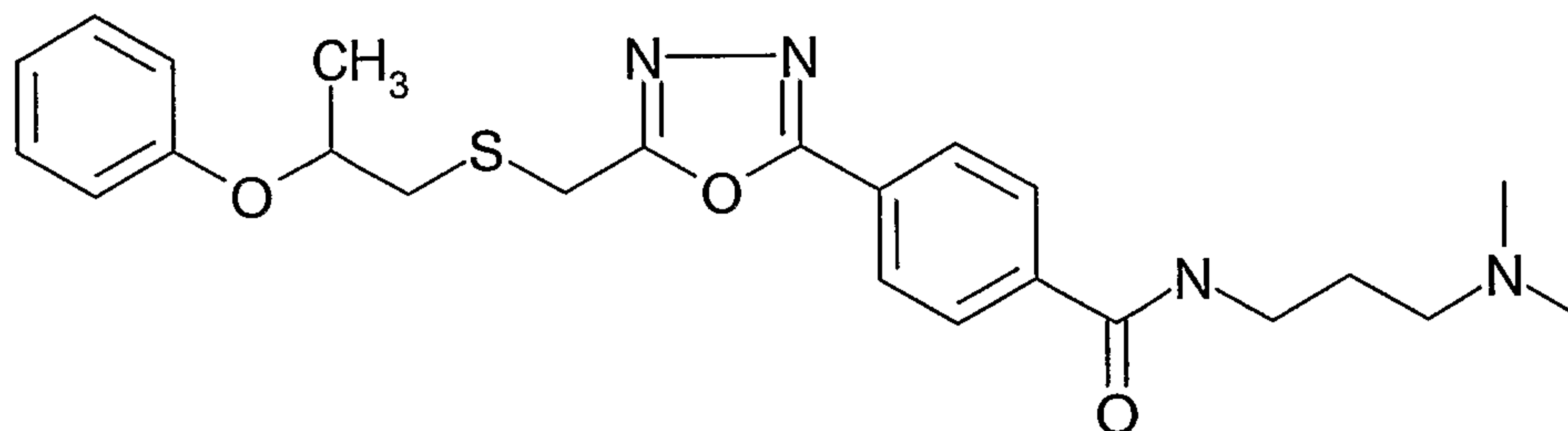
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(3-phenylpropane-1-sulfonylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid (0.550 g, 1.42 mmol), 1,1'-carbonyldiimidazole (0.242 g, 1.49 mmol) and 3-(dimethylamino)propylamine (0.175 g, 1.71 mmol) to afford the title compound as a crude mixture. Crystallization of the crude material from methanol:diethyl ether afforded 0.378 g (56%) of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

¹H NMR (DMSO-d₆) δ 8.74 (t, 1H, J=5Hz), 8.05 (m, 4H), 7.18-7.34 (m, 5H), 5.23 (s, 2H), 3.28-3.40 (m, 4H), 2.74 (t, 2H, J=8Hz), 2.27 (t, 2H, J=7Hz), 2.14 (s, 6H), 2.02-2.10 (m, 2H), 1.63-1.72 (m, 2H). IR (KBr, cm⁻¹) 3264, 2941, 2763, 1634, 1555, 1320, 1166, 1115, 697. MS (ES) m/e, 469. Anal. Calcd for C₂₄H₃₀N₄O₄S: C, 61.26; H, 6.43; N, 11.91. Found C, 61.38; H, 6.52; N, 11.94. Mp(°C)=157.

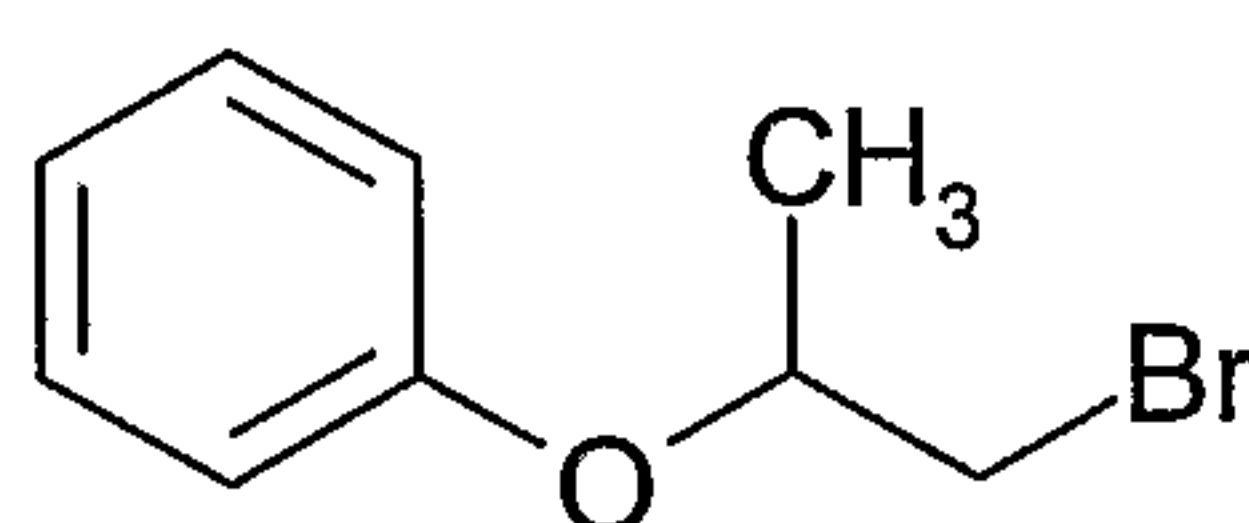
Example 17

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Preparation of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 2-phenoxypropanol



a) (2-Bromo-1-methylethoxy)benzene



5

A solution of triphenylphosphine (8.63 g, 32.9 mmol) in 94 mL CH_2Cl_2 stirring at room temperature was added dropwise, bromine (5.26 g, 32.9 mmol) over a twenty minute period. The resultant suspension was stirred at room temperature for 15 minutes then a solution of 2-phenoxypropanol (5.01 g, 32.9 mmol) and imidazole (2.69 g, 39.5 mmol) in 70 mL CH_2Cl_2 was added over a 15 minute period. The mixture was stirred at room temperature for 2.5 hours then subjected to filtration. The filtrate was concentrated in vacuo to afford an oil. Purification by flash filtration chromatography on silica gel (elution with 15%EtOAc:hexane) afforded 4.80 g (68%) of (2-Bromo-1-methylethoxy)benzene.

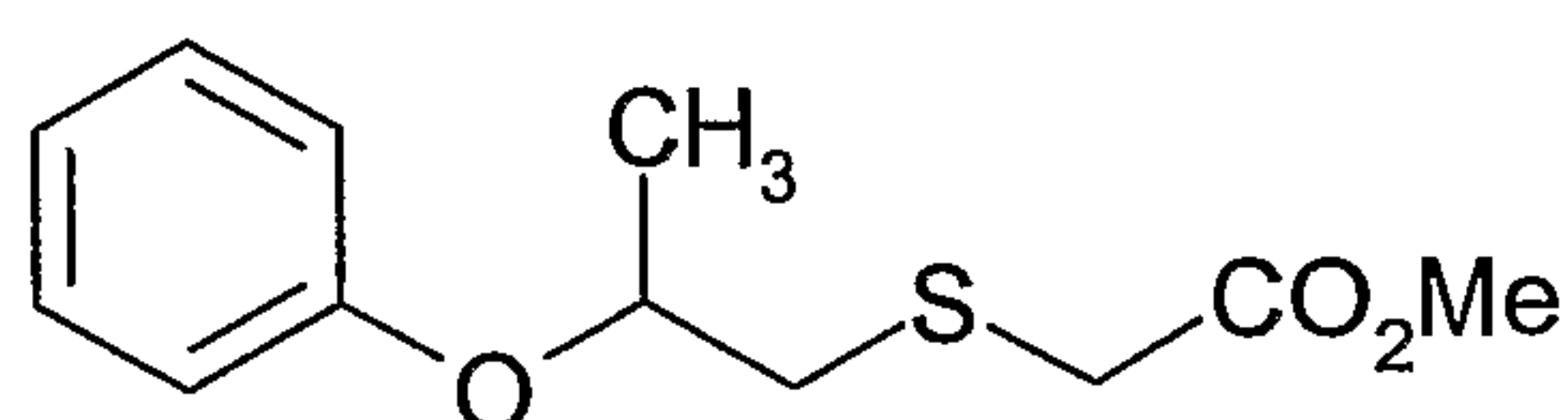
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^1H NMR (DMSO-d_6) δ 7.32-7.39 (m, 2H), 6.92-6.99 (m, 3H), 4.63-4.72 (m, 1H), 3.69 (ddd, 2H, $J=5, 11$ and 22Hz), 1.33 (d, 3H, $J=6\text{Hz}$). IR (CHCl_3 , cm^{-1}) 1600, 1588, 1495, 1062. MS (ES) m/e , 214. Anal. Calcd for $\text{C}_9\text{H}_{11}\text{BrO}$: C, 50.26; H, 5.15. Found C, 44.83; H, 4.51.

20

b) (2-Phenoxypropylsulfanyl)acetic acid methyl ester



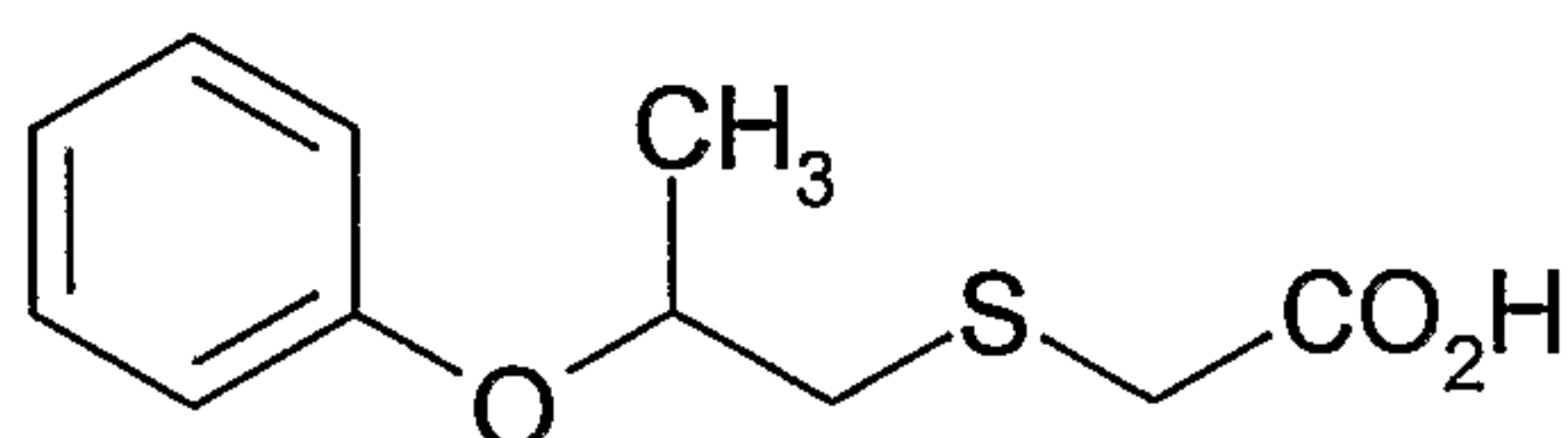
A solution of methyl thioglycolate (1.64 g, 15.4 mmol) in 61 mL THF stirring at room temperature was added sodium hydride (0.62 g, 15.4 mmol). The mixture was stirred fifteen minutes before a solution of 2-bromo-1-methylethoxy)benzene (3.02 g, 14.0

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mmol) in 3.0 mL THF was added. The mixture was stirred at room temperature for two days. The reaction mixture was diluted with 100 mL EtOAc then washed three times with water, brine, dried over sodium sulfate, filtered, concentrated to afford an oil. Purification by chromatography on silica gel (elution with a linear gradient of 10 to 25% Et₂O:hexane) afforded 2.20 g (65%)(2-phenoxypropylsulfanyl)acetic acid methyl ester.

¹H NMR (DMSO-d₆) δ 7.24-7.30 (m, 2H), 6.90-6.94 (m, 3H), 4.60-4.66 (m, 1H), 3.61 (s, 3H), 3.45 (d, 2H, J=3Hz), 2.76 (ddd, 2H, J=6, 14, 38Hz), 1.30 (d, 3H, J=6Hz). IR (CHCl₃, cm⁻¹) 1735, 1599, 1587, 1495, 1438, 1289, 1173, 1132. MS (ES) m/e, 241. Anal. Calcd for C₁₂H₁₆O₃S: C, 59.97; H, 6.71. Found C, 49.24; H, 5.39.

c) (2-Phenoxypropylsulfanyl)acetic acid

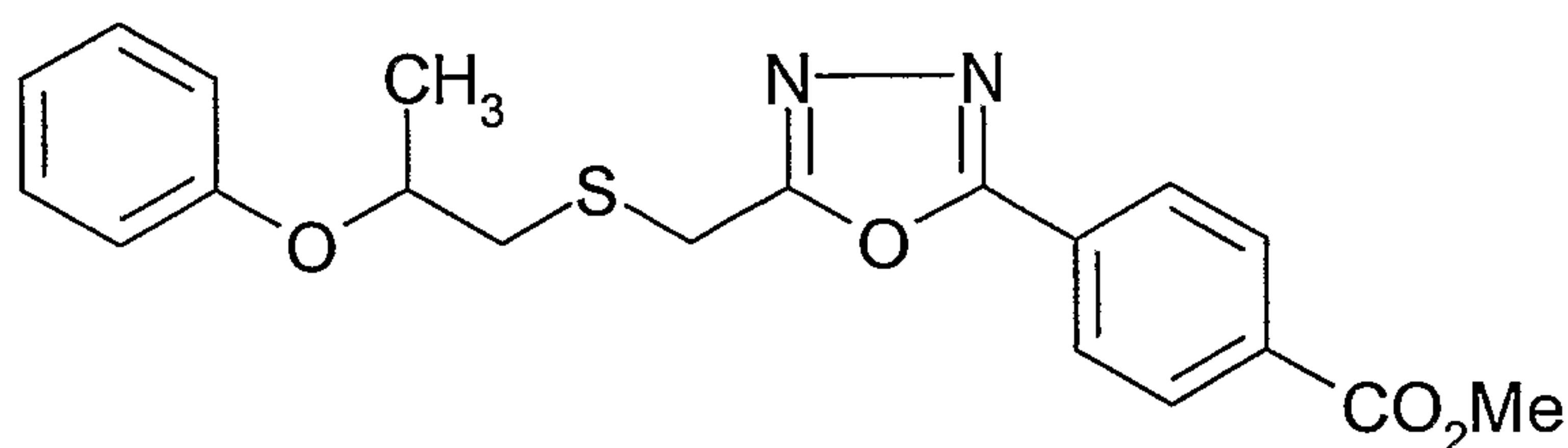


A mixture of 2-phenoxypropylsulfanyl)acetic acid methyl ester (1.93 g, 8.0 mmol) and lithium hydroxide (0.577 g, 24.1 mmol) was stirred at room temperature for 5.5 hours. The reaction mixture was quenched with concentrated HCl (2.02 mL, 8.0 mmol), diluted with EtOAc and water. The phases were separated and the aqueous phase extracted once with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, concentrated to afford 1.22 g (67%) of (2-Phenoxypropylsulfanyl)acetic acid.

¹H NMR (DMSO-d₆) δ 7.24-7.31 (m, 2H), 6.89-6.96 (m, 3H), 4.59-4.69 (m, 1H), 3.28-3.39 (m, 2H), 2.76-2.95 (m, 2H), 1.30 (d, 3H, J=6Hz). IR (CHCl₃, cm⁻¹) 2982, 2931, 1711, 1599, 1587, 1495, 1291, 1239, 1173, 1131. MS (ES) m/e, 227, 225. Anal. Calcd for C₁₁H₁₄O₃S: C, 58.38; H, 6.24. Found C, 58.80; H, 6.00.

d) 4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester

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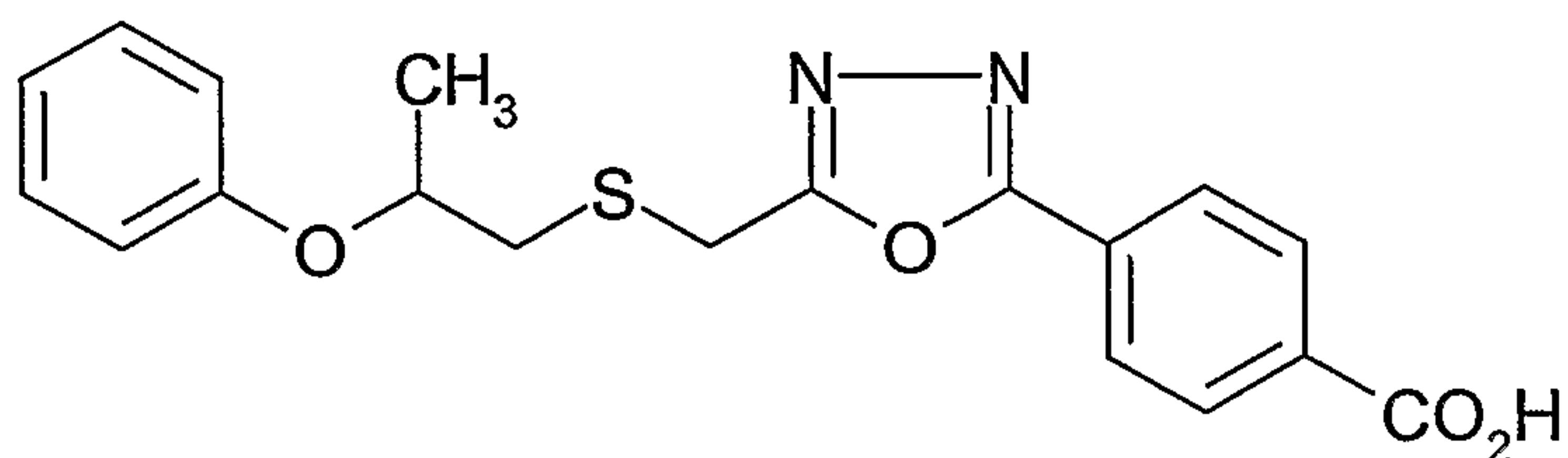


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from (2-phenoxypropylsulfanyl)acetic acid (0.950 g, 4.2 mM), 1,3-dicyclohexylcarbodiimide (0.866 g, 4.2 mmol), and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.857 g, 4.2 mmol) to afford the title compound as a crude mixture. Purification three times by radial chromatography on silica gel (elution with 50% EtOAc:hexane) afforded 0.631 g (39%) of 4-[5-(2-phenoxypropyl sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as an oil that slowly crystallized out.

¹H NMR (DMSO-*d*₆) δ 8.07-8.16 (m, 4H), 7.20-7.27 (m, 2H), 6.86-6.94 (m, 3H), 4.62-4.68 (m, 1H), 4.16-4.27 (m, 2H), 3.91 (s, 3H), 2.89-2.95 (m, 2H), 1.29 (d, 2H, *J*=6Hz).

MS (ES) *m/e*, 385. Anal. Calcd for C₂₀H₂₀N₂O₄S: C, 62.48; H, 5.24; N, 7.29. Found C, 62.25; H, 5.00; N, 6.71.

e) 4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid

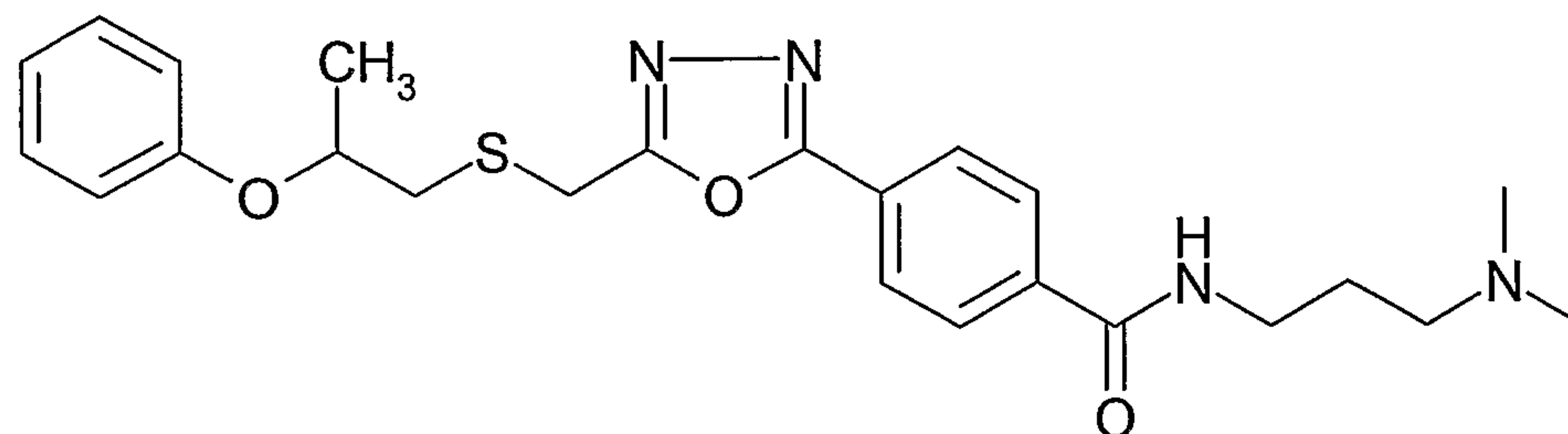


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17c, from 4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.611 g, 1.59 mmol) and lithium hydroxide (0.114 g, 4.76 mmol) to afford 0.573 g (97%) of 4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid.

¹H NMR (DMSO-*d*₆) δ 13.35 (bs, 1H) 8.04-8.14 (m, 4H), 7.21-7.30 (m, 3H), 6.87-6.94 (m, 3H), 4.58-4.71 (m, 2H), 4.16-4.27 (m, 2H), 2.88-3.00 (m, 2H), 1.29 (d, 3H, *J*=6Hz). IR (CHCl₃, cm⁻¹) 1700, 1587, 1495, 1240. MS (ES) *m/e*, 371, 369.

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f) N-(3-dimethylaminopropyl)-4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide

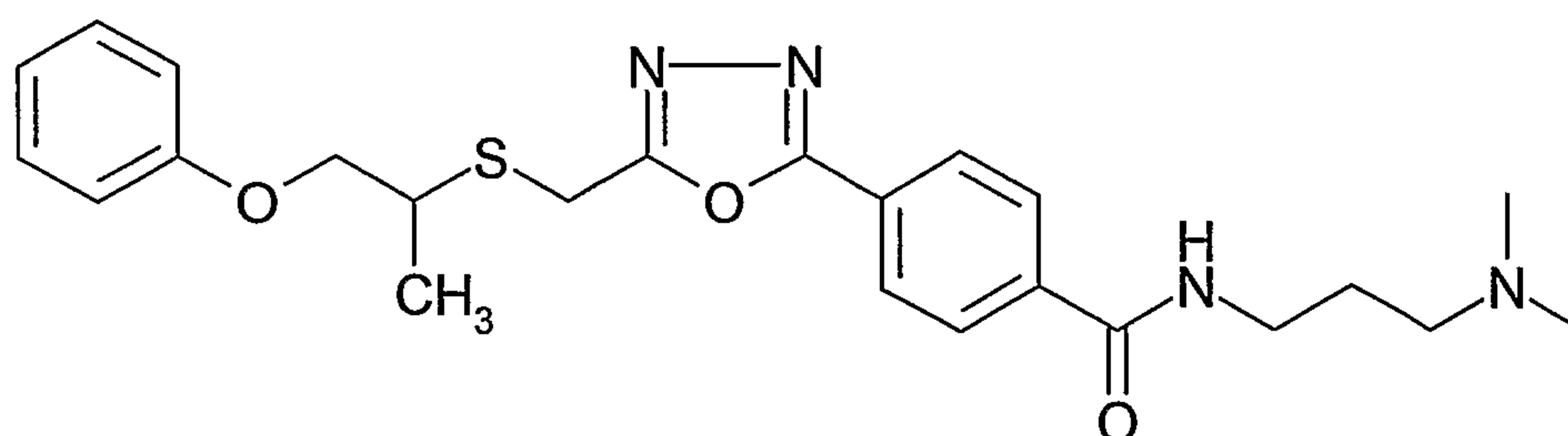


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.541 g, 1.46 mmol), 1,1'-carbonyldiimidazole (0.249 g, 1.53 mmol) and 3-(dimethylamino)propylamine (0.157 g, 1.53 mmol) to afford the title compound as a crude material. Purification by silica gel radial chromatography (elution with 10% 2M NH₃ in MeOH:CH₂Cl₂) followed by treatment of the isolated material with oxalic acid in acetone afforded the oxalate salt of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

¹H NMR (DMSO-d₆) δ 8.85 (t, 1H, J=6Hz), 8.04 (s, 4H), 7.18-7.27 (m, 2H), 6.87-6.93 (m, 3H), 4.63-4.69 (m, 1H), 4.16-4.27 (m, 2H), 3.32-3.39 (q, 2H, J=6Hz), 3.00-3.10 (m, 2H), 2.87-2.98 (m, 2H), 2.75 (s, 6H), 1.86-1.95 (m, 2H), 1.29 (d, 2H, J=6Hz). IR (CHCl₃, cm⁻¹) 3009, 1778, 1656, 1599, 1586, 1495, 1302, 1239, 1012. MS (ES) m/e, 455, 453. Anal. Calcd for C₂₄H₃₀N₄O₃S·C₂H₂O₄: C, 57.34; H, 5.92, N, 10.29. Found C, 56.92; H, 5.81; N, 10.22. Mp(°C)=117.

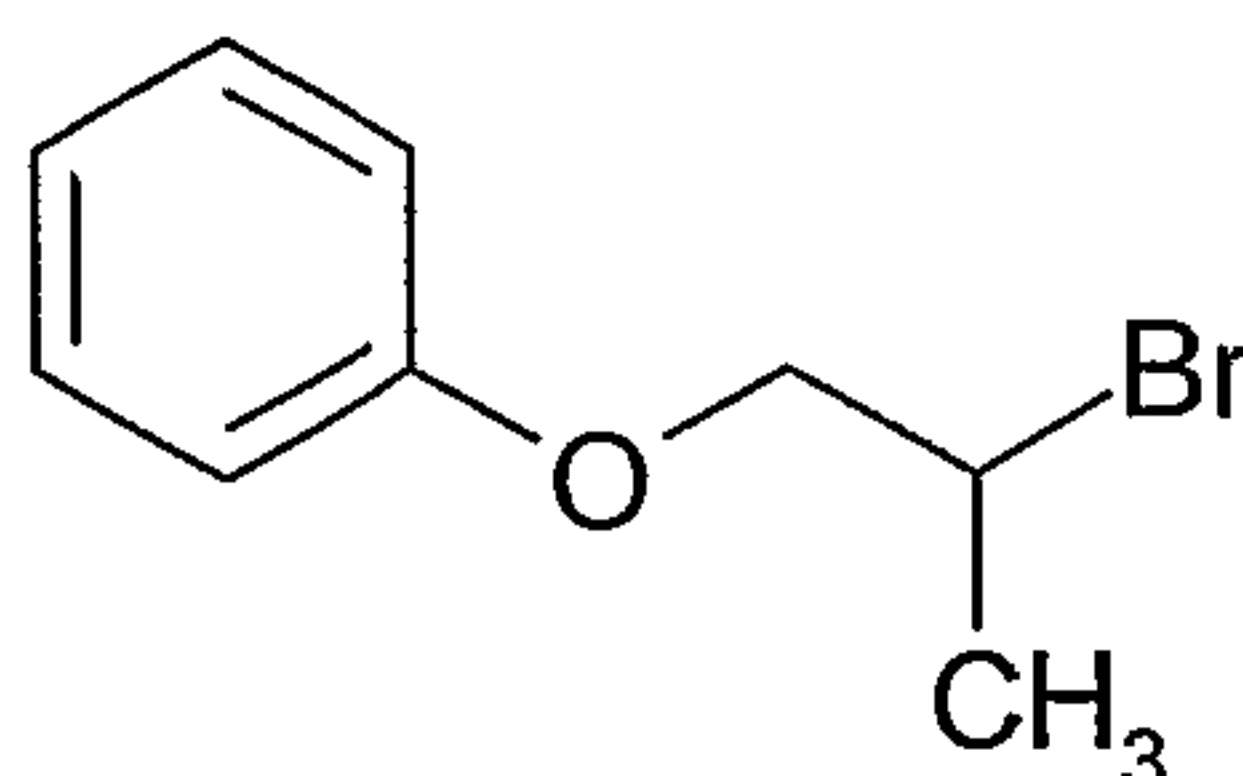
Example 18

Preparation of N-(3-dimethylaminopropyl)-4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 1-phenoxy-2-propanol



-105-

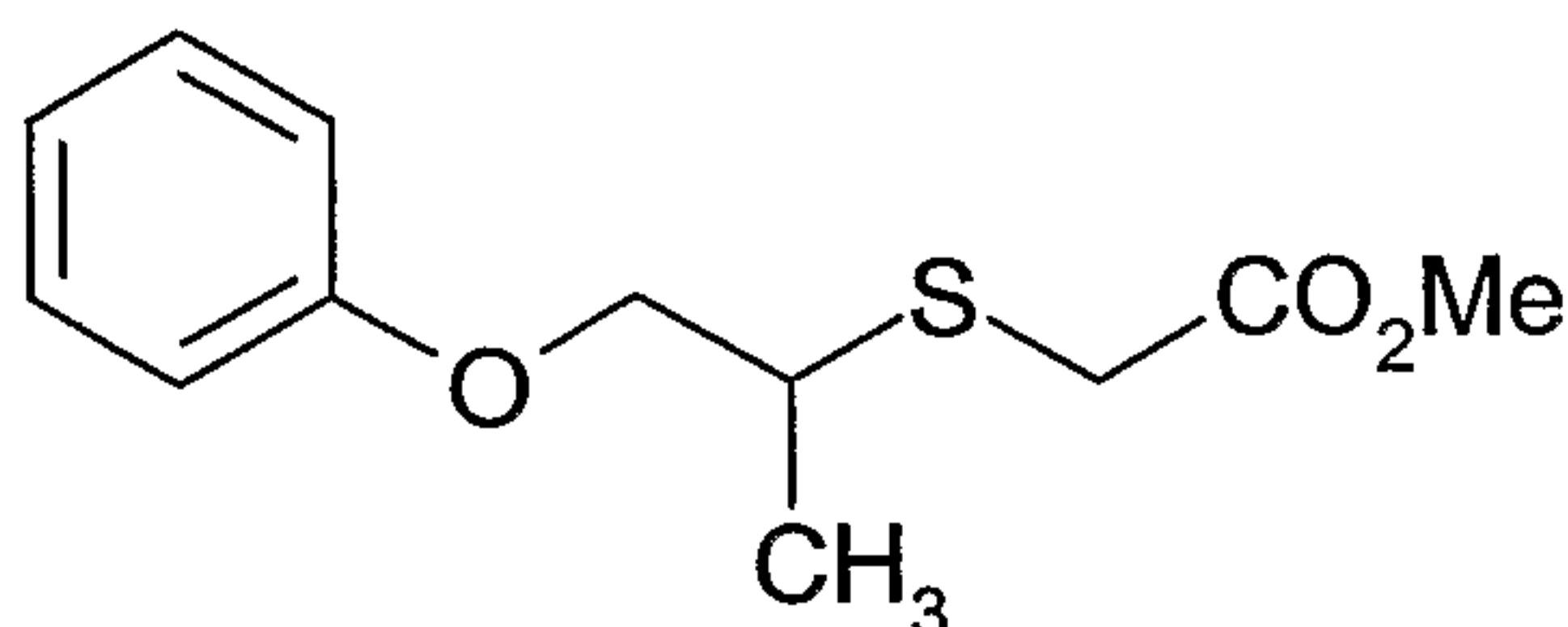
a) (2-bromopropoxy)benzene



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17a, from 1-phenoxy-2-propanol (7.01 g, 46.1 mmol)(containing approximately 10% 2-phenoxypropanol), triphenylphosphine (12.08 g, 46.1 mmol), bromine (7.36 g, 46.1mM) and imidazole (3.76 g, 55.3 mmol) to afford 9.23 g (93%) of (2-bromopropoxy)benzene as an oil which is contaminated with approximately 10% (2-bromo-1-methylethoxy)benzene.

^1H NMR (DMSO- d_6) δ 7.26-7.33 (m, 2H), 6.92-6.98 (m, 3H), 4.47-4.56 (m, 1H), 4.13-4.24 (m, 2H), 1.72 (d, 3H, $J=7\text{Hz}$). IR (CHCl_3 , cm^{-1}) 15600, 1588, 1497, 1244, 1035. MS (ES) m/e , 216, 214. Anal. Calcd for $\text{C}_9\text{H}_{11}\text{BrO}$: C, 50.26; H, 5.15. Found C, 41.53; H, 4.64.

b) (1-Methyl-2-phenoxyethylsulfanyl)acetic acid methyl ester



15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from (2-bromopropoxy)benzene (3.90 g, 18.1 mmol), methylthioglycolate (2.12 g, 19.9 mmol), and sodium hydride (0.798 g, 19.9 mmol) to afford 2.30 g (53%) of (1-Methyl-2-phenoxyethylsulfanyl) acetic acid methyl ester as an oil.

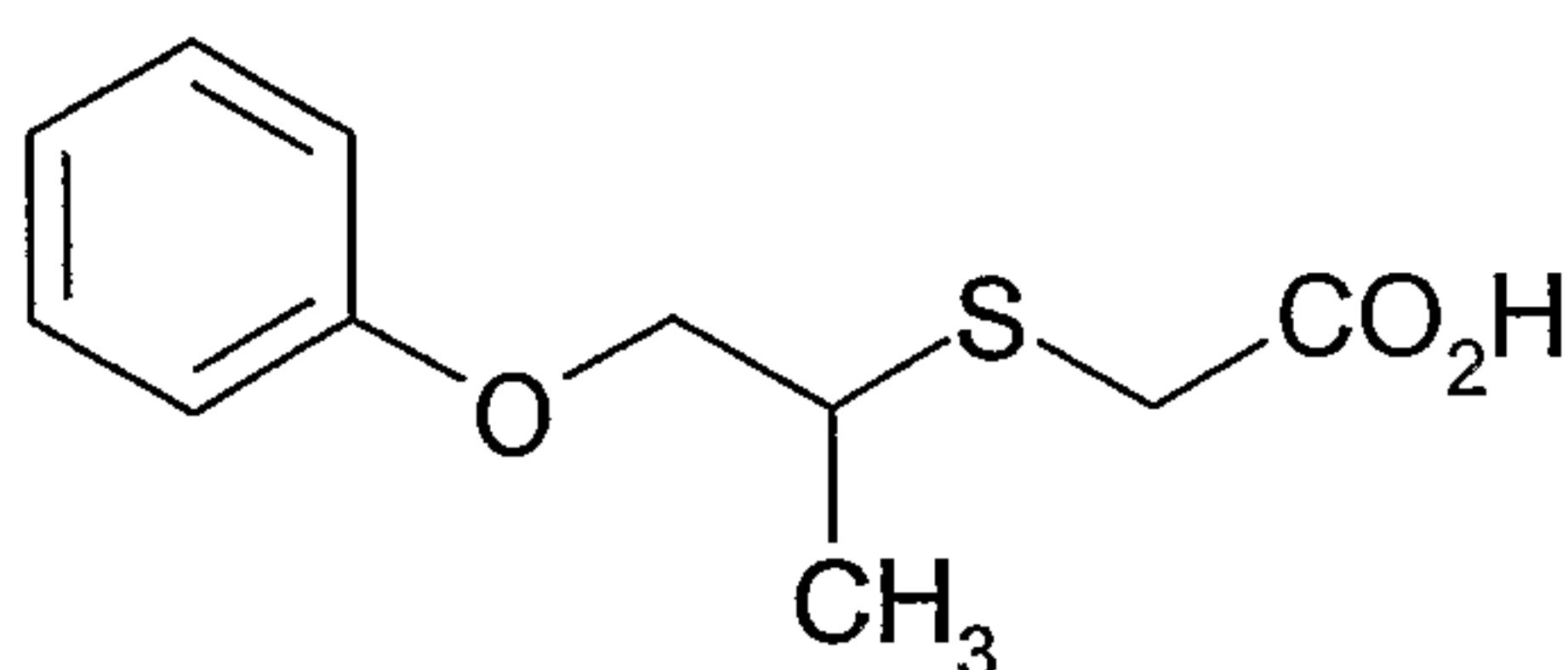
20

^1H NMR (DMSO- d_6) δ 7.25-7.32 (m, 2H), 6.90-6.96 (m, 3H), 4.10 (dd, 1H, $J=6,10\text{Hz}$), 3.94 (dd, 1H, $J=7, 10\text{Hz}$), 3.44-3.62 (m, 5H), 3.24-3.31 (m, 1H), 1.29 (d, 3H, $J=7\text{Hz}$). IR (CHCl_3 , cm^{-1}) 1735, 1600, 1497, 1289, 1243. MS (ES) m/e , 241. Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3\text{S}$: C, 59.97; H, 6.71. Found C, 59.61; H, 6.63.

25

c) (1-Methyl-2-phenoxyethylsulfanyl)acetic acid

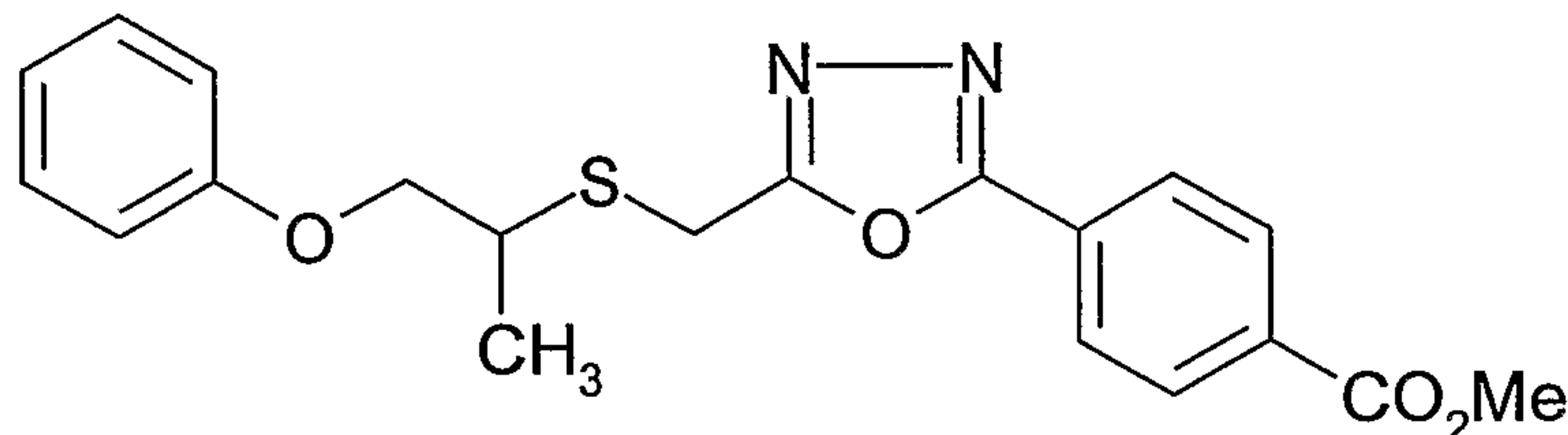
-106-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17c, from (1-Methyl-2-phenoxyethylsulfanyl)acetic acid methyl ester (2.01 g, 8.36 mmol) and lithium hydroxide (0.601 g, 25.1 mmol) to afford 1.84 g (97%) of (1-Methyl-2-phenoxyethylsulfanyl)acetic acid as an oil.

^1H NMR (DMSO- d_6) δ 12.51 (bs, 1H), 7.24-7.32 (m, 2H), 6.90-6.95 (m, 3H), 4.11 (dd, 1H, $J=5, 10\text{Hz}$), 3.93 (dd, 1H, $J=7, 10\text{Hz}$), 3.23-3.48 (m, 3H), 1.33 (d, 3H, $J=11\text{Hz}$). IR (CHCl_3 , cm^{-1}) 3010, 1712, 1600, 1587, 1497, 1300, 1291, 1243. MS (ES) m/e , 225. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3\text{S}$: C, 58.38; H, 6.24. Found C, 58.34; H, 6.08.

d) 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester

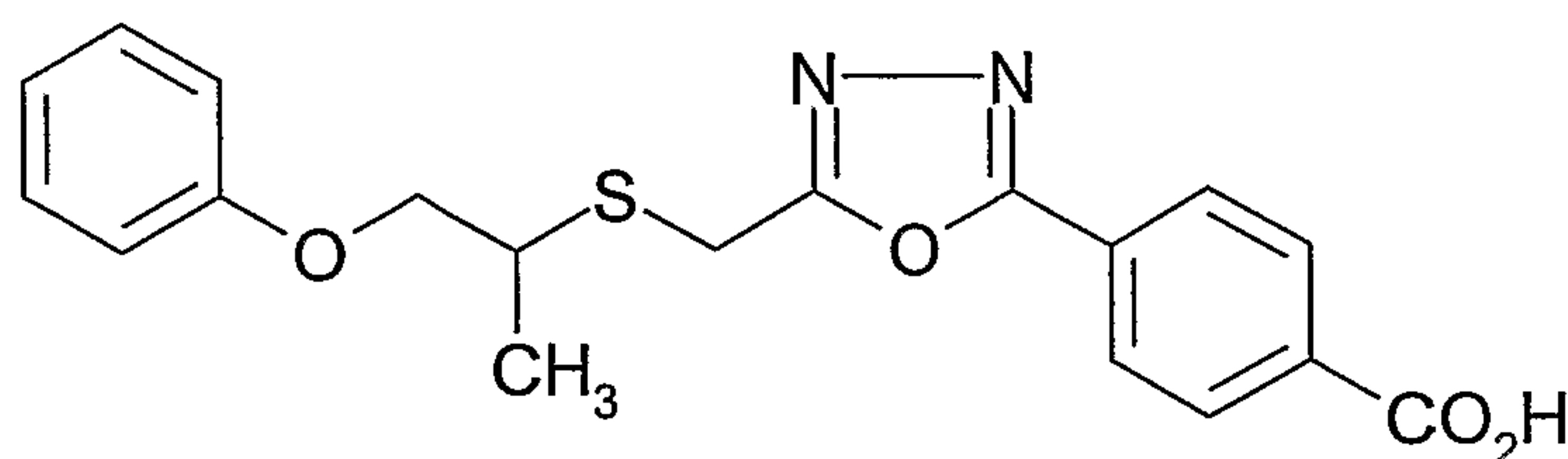


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from (1-Methyl-2-phenoxyethylsulfanyl)acetic acid (1.44 g, 6.4 mM), 1,3-dicyclohexylcarbodiimide (1.31 g, 6.4 mmol), and 4-(1H-tetrazole-5-yl)benzoic acid methyl ester (1.30 g, 6.4 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 50% EtOAc:hexane) afforded 1.21 g (49%) of 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as an oil that crystallizes out.

^1H NMR (DMSO- d_6) δ 8.07-8.16 (m, 4H), 7.20-7.31 (m, 2H), 6.89-6.96 (m, 3H), 4.29 (m, 2H), 4.11-4.15 (m, 1H), 4.00 (dd, 1H, $J=7, 10\text{Hz}$), 3.91 (s, 3H), 3.21-3.33 (m, 1H), 1.33 (d, 3H, $J=7\text{Hz}$). MS (ES) m/e , 385, 383. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: C, 62.48; H, 5.24, N, 7.29. Found C, 63.52; H, 5.95; N, 6.91.

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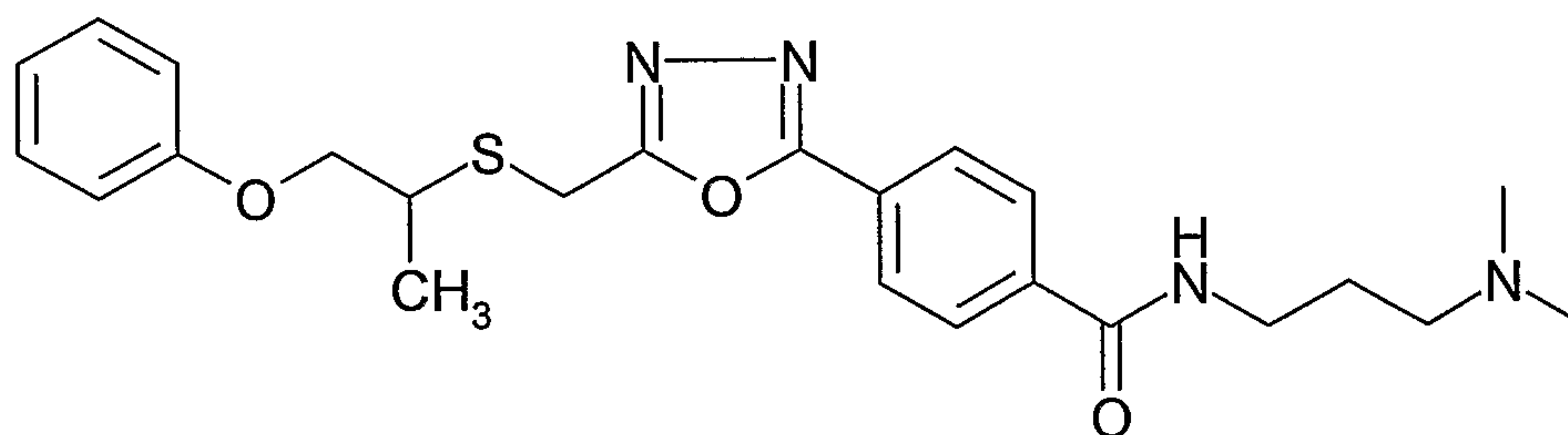
e) 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17c, from 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (1.19 g, 3.1 mmol), and lithium hydroxide (0.222 g, 9.3 mmol) to afford 1.06 g (92%) of 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid as a solid.

^1H NMR (DMSO- d_6) δ 13.36 (bs, 1H), 8.05-8.14 (M, 4h), 7.20-7.28 (m, 2H), 6.88-6.96 (m, 3H), 4.22-4.37 (m, 2H), 4.13 (dd, 1H, $J=6, 10\text{Hz}$), 4.00 (dd, 1H, $J=6, 10\text{Hz}$), 3.25-3.37 (m, 1H), 1.34 (d, 3H, $J=7\text{Hz}$). IR (CHCl_3 , cm^{-1}) 3010, 2934, 2859, 1700, 1600, 1587, 1497, 1286, 1266, 1242. MS (ES) m/e , 371, 369.

f) N-(3-dimethylaminopropyl)-4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide



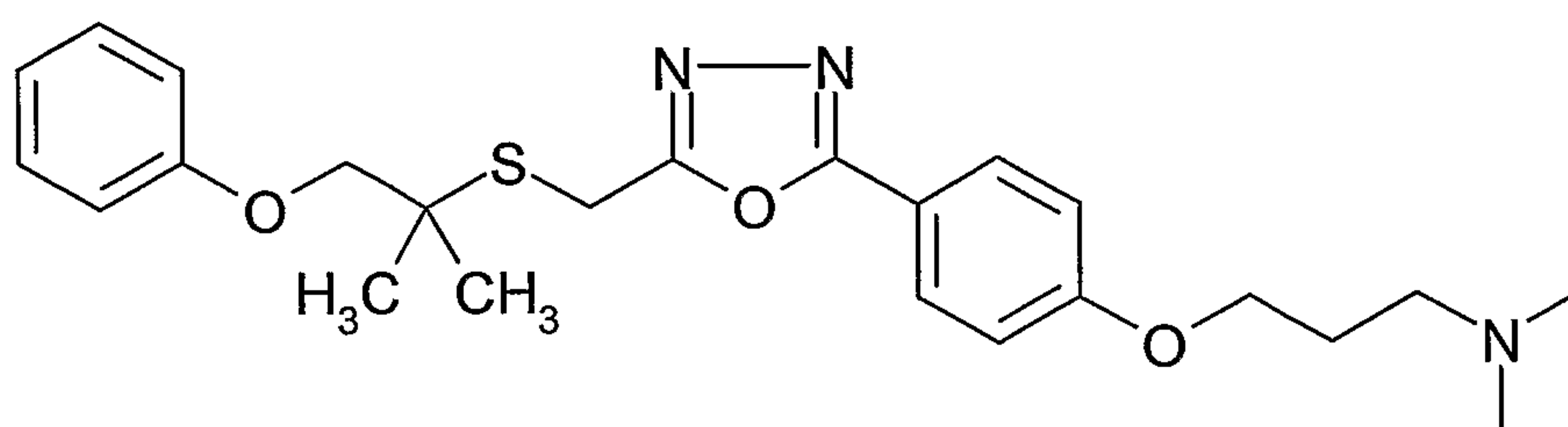
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (1.04 g, 2.8 mmol), 1,1'-carbonyldiimidazole (0.477 g, 2.9 mmol) and 3-(dimethylamino)propylamine (0.301 g, 2.9 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 in $\text{MeOH}:\text{CH}_2\text{Cl}_2$) followed by crystallization with $\text{EtOH}:\text{Et}_2\text{O}$ afforded 0.404 g (32%) of N-(3-dimethylamino propyl)-4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

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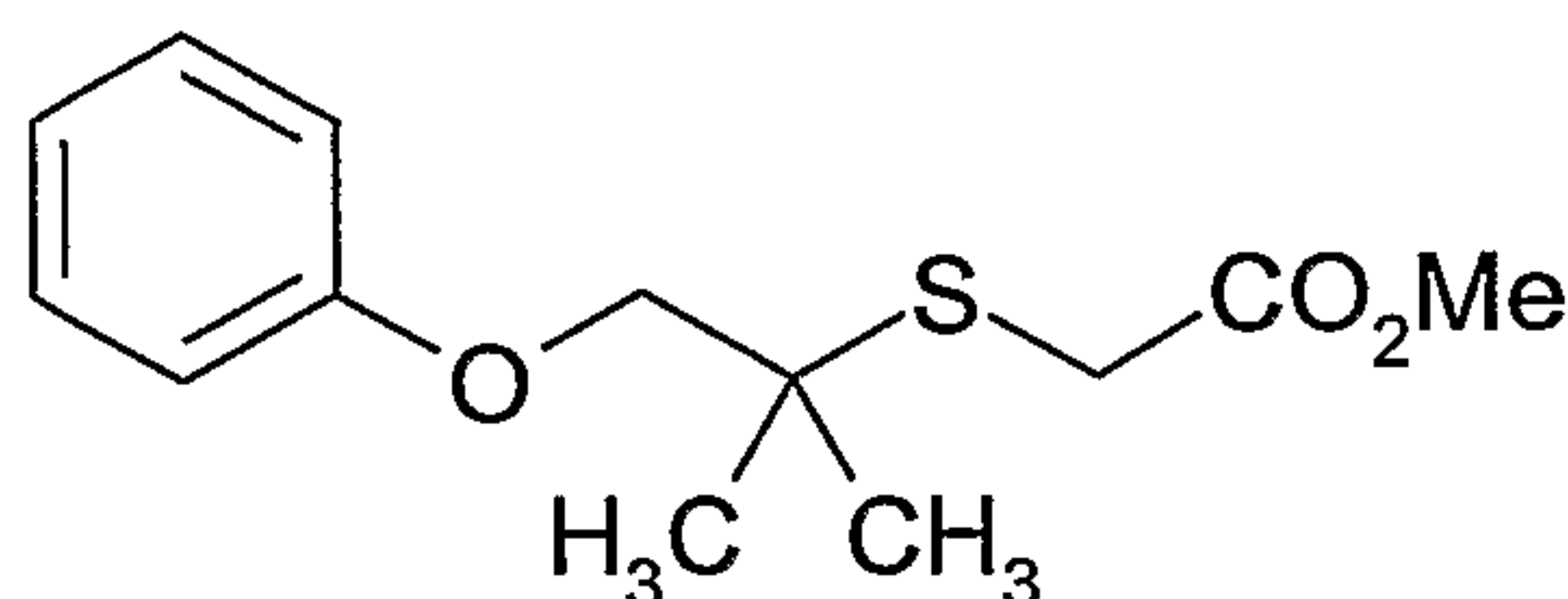
^1H NMR (DMSO- d_6) δ 8.72 (t, 1H, $J=5\text{Hz}$), 7.99-8.06 (m, 4H), 7.23-7.28 (m, 2H), 6.89-6.94 (m, 3H), 4.22-4.37 (m, 2H), 4.14 (dd, 1H, $J=6$ and 10Hz), 4.01 (dd, 1H, $J=7$ and 10Hz), 3.27-3.38 (m, 4H), 2.27 (t, 2H, $J=7\text{Hz}$), 2.14 (s, 6H), 1.62-1.72 (m, 2H), 1.33 (d, 3H, $J=7\text{Hz}$). IR (CHCl_3 , cm^{-1}) 307, 2951, 2827, 1652, 1585, 1550, 1496, 1243, 1012. MS (ES) m/e , 455, 453. Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_3\text{S}$: C, 63.41; H, 6.65, N, 12.32. Found C, 63.57; H, 6.62; N, 12.28. $\text{Mp}(\text{°C})=84$.

Example 19

Preparation of 3—{4-[5-1,1-dimethyl-2-phenoxyethyl
sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)
dimethylamine from isobutylene sulfide



a) (1,1-dimethyl-2-phenoxyethylsulfanyl) acetic acid methyl ester



A suspension of sodium hydride (0.416 g, 10.4 mmol) (washed twice with hexane) in 30 mL THF stirring at room temperature was added dropwise a solution of phenol (0.978 g, 10.4 mmol) in 3.5 mL THF. The resultant solution was added to a suspension of chloro(triphenylphosphine)gold (5.14 g, 10.4 mmol) in 30 mL THF over an 80 minute period. The temperature of the mixture was maintained between -30 °C and 10 °C (dry ice/ CH_3CN) during the addition of the sodium phenolate. The reaction was then stirred at room temperature for 3.5 hours before isobutylene sulfide (0.962 g, 10.9 mmol) was added. The reaction continued stirring at room temperature for approximately 4 hours then methyl boromacetate (1.75 g, 11.4 mmol) was added. The reaction was stirred overnight at room temperature. The suspension was treated with Celite, filtered through a pad of Celite and rinsed with diethyl ether. The filtrate was concentrated to an oil which

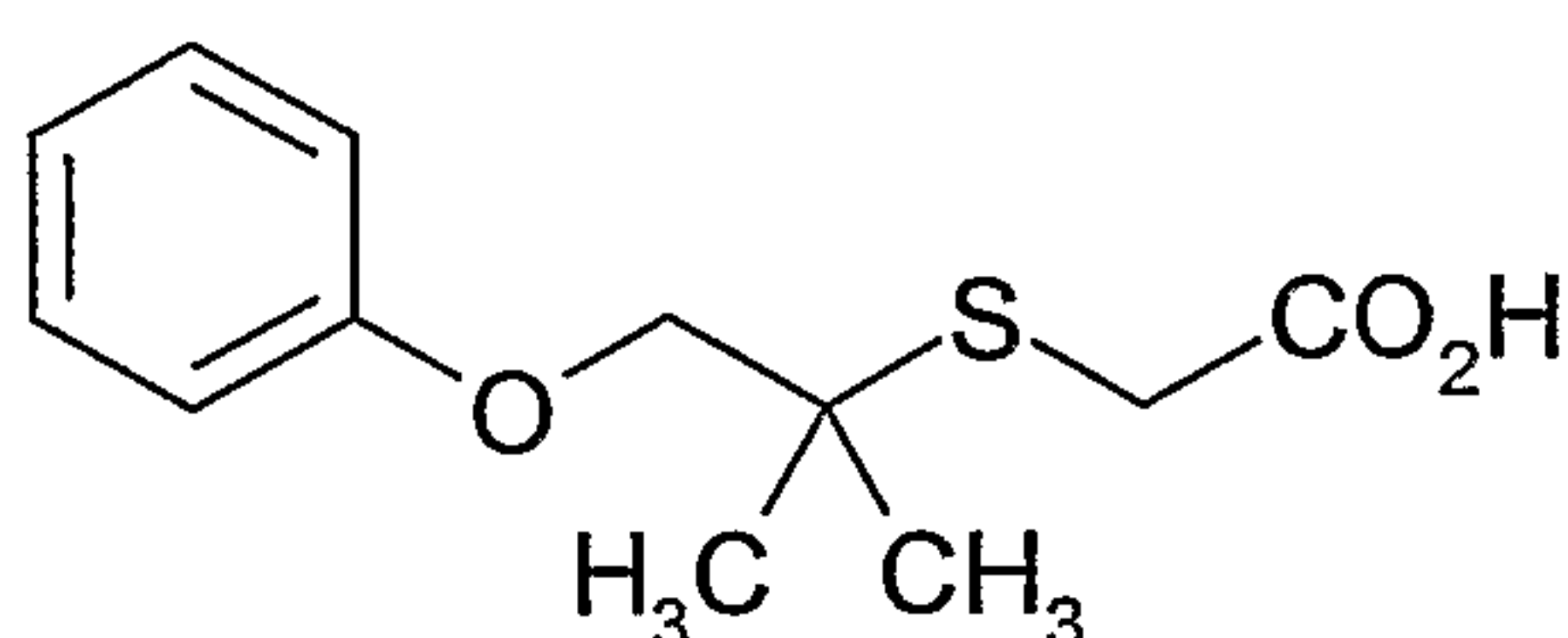
-109-

slowly turns into a suspension. The suspension was diluted with hexane, filtered and the filtrate concentrated to a yellow oil. Purification by chromatography on silica gel (elution with CH₂Cl₂) afforded 1.66 g (54%) of (1,1-dimethyl-2-phenoxyethylsulfanyl) acetic acid methyl ester a yellow oil.

¹H NMR (DMSO-d₆) δ 7.26-7.31 (m, 2h), 6.91-6.96 (m, 3H), 3.91 (s, 2H), 3.57 (s, 3H), 3.51 (s, 2H), 1.35 (s, 6H).

IR (CHCl₃, cm⁻¹) 3004, 2954, 2932, 2869, 1736, 1600, 1498, 1466, 1290, 1245, 1172, 1135. MS (ES) m/e, 255. Anal. Calcd for C₁₃H₁₈O₃S: C, 61.39; H, 7.13. Found C, 61.40; H, 7.17.

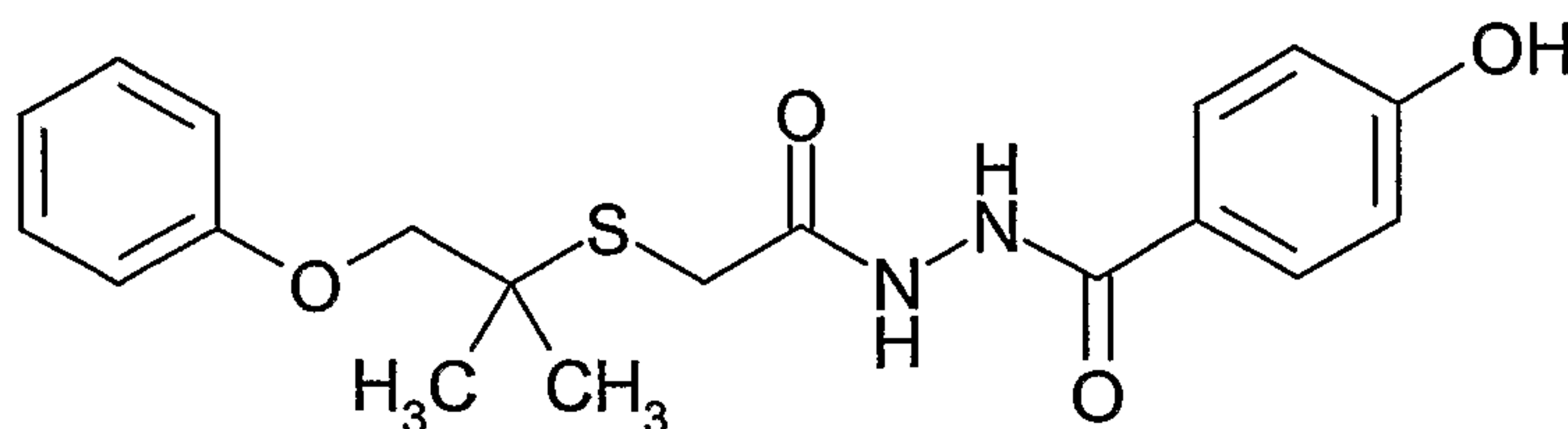
b) (1,1-dimethyl-2-phenoxyethylsulfanyl) acetic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from (1,1-dimethyl-2-phenoxyethylsulfanyl) acetic acid methyl ester (1.85 g, 7.3 mmol), lithium hydroxide (0.522 g, 21.8 mmol) to afford 1.28 g (73%) of (1,1-dimethyl-2-phenoxyethyl sulfanyl) acetic acid as an oil.

¹H NMR (DMSO-d₆) δ 7.25-7.31 (m, 2H), 6.91-6.95 (m, 3H), 3.92 (s, 2H), 3.40 (s, 2H), 1.35 (s, 6H). IR (CHCl₃, cm⁻¹) 2969, 2930, 2871, 1713, 1600, 1587, 1498, 1466, 1301, 1291, 1245, 1173. MS (ES) m/e, 240, 239. Anal. Calcd for C₁₂H₁₆O₃S: C, 59.97; H, 6.71. Found C, 43.43; H, 4.94.

c) 4-Hydroxybenzoic acid-N-[2-(1,1-dimethyl-2-phenoxyethyl sulfanyl)acetyl]hydrazide



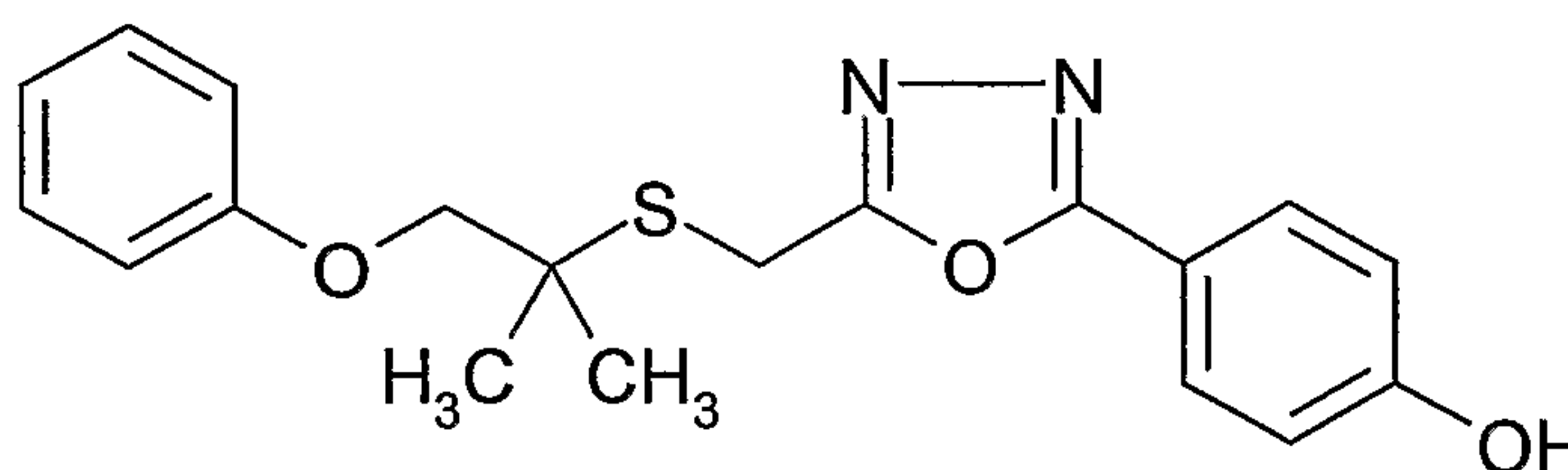
A solution of (1,1-dimethyl-2-phenoxyethylsulfanyl) acetic acid (1.19 g, 4.95 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.22 g, 4.95 mmol) in 25 mL

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CH₃CN and 6 mL THF was stirred at room temperature for 1 hour. The mixture was then treated with 4-hydroxybenzoic hydrazide (0.753 g, 4.95mM). The suspension was stirred at room temperature for 28 hours. The suspension was filtered, insolubles rinsed with CH₃CN and the filtrate concentrated to an oil. Purification by chromatography on silica gel (elution with 50% EtOAc:hexane followed by 75%EtOAc:hexane) afforded 0.910 g(49%) of 4-Hydroxybenzoic acid-N-[2-(1,1-dimethyl-2-phenoxyethylsulfanyl)acetyl]hydrazide as a white foam.

¹H NMR (DMSO-d₆) δ 9.98-10.15 (m, 2H), 7.75 (d, 2H, J=9Hz), 7.25-7.31 (m, 2H), 6.91-7.00 (m, 3H), 6.81 (d, 2H, J=9Hz), 3.96 (s, 2H), 3.40 (s, 2H), 1.39 (s, 6H). IR (CHCl₃, cm⁻¹) 1685, 1632, 1610, 1600, 1588, 1498, 1467, 1456, 1245, 1172. MS (ES) m/e, 375, 373. Anal. Calcd for C₁₉H₂₂N₂O₄S: C, 60.94; H, 5.92, N, 7.48. Found C, 60.76; H, 5.91; N, 7.24.

d) 4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol



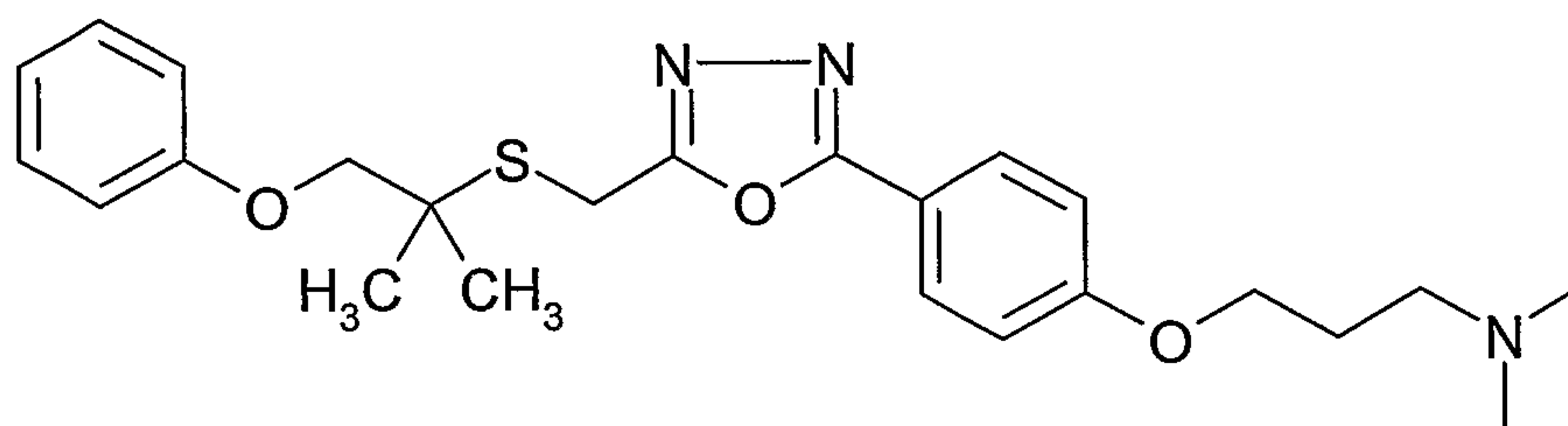
A mixture of 4-Hydroxybenzoic acid-N-[2-(1,1-dimethyl-2-phenoxyethylsulfanyl)acetyl]hydrazide (0.860 g, 2.3 mmol), triphenylphosphine (1.21 g, 4.6 mmol), triethyl amine (0.837 g, 8.3 mmol) and carbon tetrachloride (1.45 g, 8.3 mmol) in 24 mL CH₃CN was stirred at room temperature for 6.25 hours. The mixture was then concentrated to an oil. The oil was dissolved into EtOAc and washed three times with water and once with brine. The organic phase was dried over sodium sulfate, filtered, concentrated in vacuo to afford an oil. Purification by silica gel chromatography (elution with a linear gradient of 0 to 5% methanol:CHCl₃ over a twenty minute period) afforded 4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol and triphenyl phosphine oxide as an oil that slowly crystallizes out. The mixture was diluted with diethyl ether then filtered. The filtrate was concentrated to an oil. Purification by silica gel radial chromatography (elution with 50% Et₂O:hexane) followed by

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crystallization from MeOH:Et₂O afforded 0.499 g (61%) of 4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol.

¹H NMR (DMSO-d₆) δ 10.30 (bs, 1H), 7.76 (m, 2H), 7.73 (m, 2H), 7.21-7.28 (m, 2H), 6.90-6.94 (m, 3H), 4.23 (s, 2H), 3.96 (s, 2H), 1.40 (s, 6H). IR (KBr, cm⁻¹) 3158, 1610, 1598, 1588, 1499, 1467, 1286, 1244, 1173, 757. MS (ES) m/e, 357, 355. Anal. Calcd for C₁₉H₂₀N₂O₃S: C, 64.02; H, 5.66; N, 7.86. Found C, 63.91; H, 5.65; N, 7.77.

e) 3-{4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine



10

To a solution of 4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.205 g, 1.3 mmol) in 16.4 mL DMF stirring at room temperature was added sodium hydride (0.109 g, 2.7 mmol). The mixture was stirred 5 minutes then 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.205 g, 1.3 mmol) was added. The reaction was heated at 100 °C for 1.45 hours. After cooling to room temperature, the mixture was diluted with 50% EtOAc:hexane and 50% brine:H₂O. The phases were separated and the aqueous phase was extracted with 50% EtOAc:hexane. The combined organic phases were washed with 50% brine:H₂O the brine. The organic phase was dried over sodium sulfate, filtered, concentrated to afford 0.533 g an oil. The oil was dissolved into diethyl ether. To this solution was added dropwise a solution of EtOH in Et₂O that was treated with 0.103 mL acetyl chloride. The resultant precipitate was collected by filtration to afford 0.154 g (27%) of 3-{4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine as the hydrochloride salt.

¹H NMR (DMSO-d₆) δ 7.86-7.88 (m, 2H), 7.210-7.28 (m, 2H), 7.10-7.15 (m, 2H), 6.90-6.94 (m, 3H), 4.25 (s, 2H), 4.16 (t, 2H, J=6Hz), 3.96 (s, 2H), 3.19-3.24 (m, 2H), 2.79 (s, 6H), 2.13-2.22 (m, 2H), 1.40 (s, 6H). IR (CHCl₃, cm⁻¹) 2970, 1615, 1500,

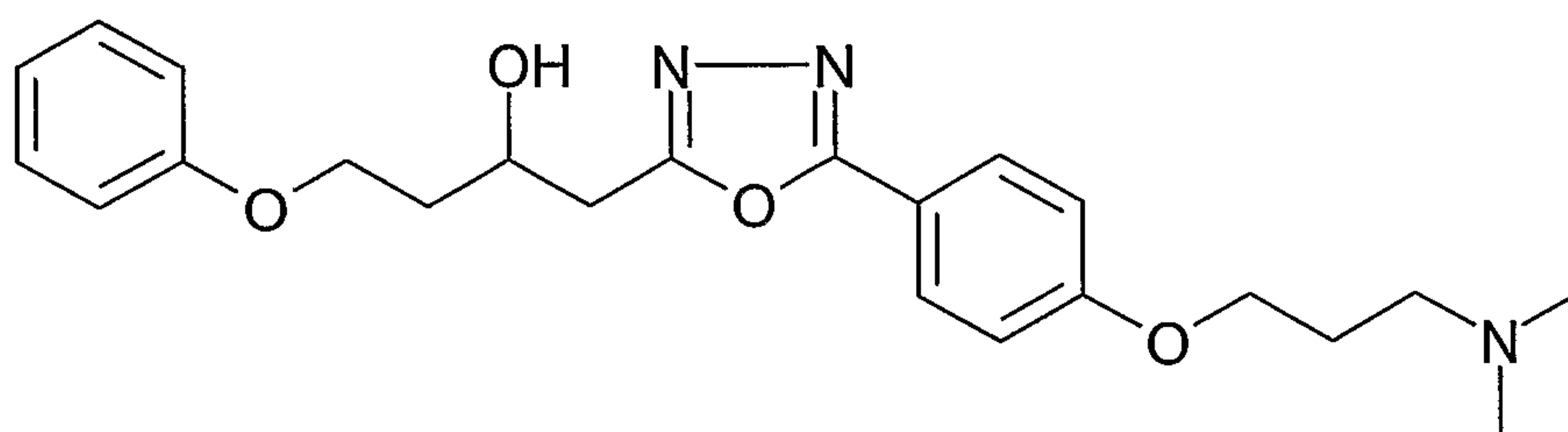
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-112-

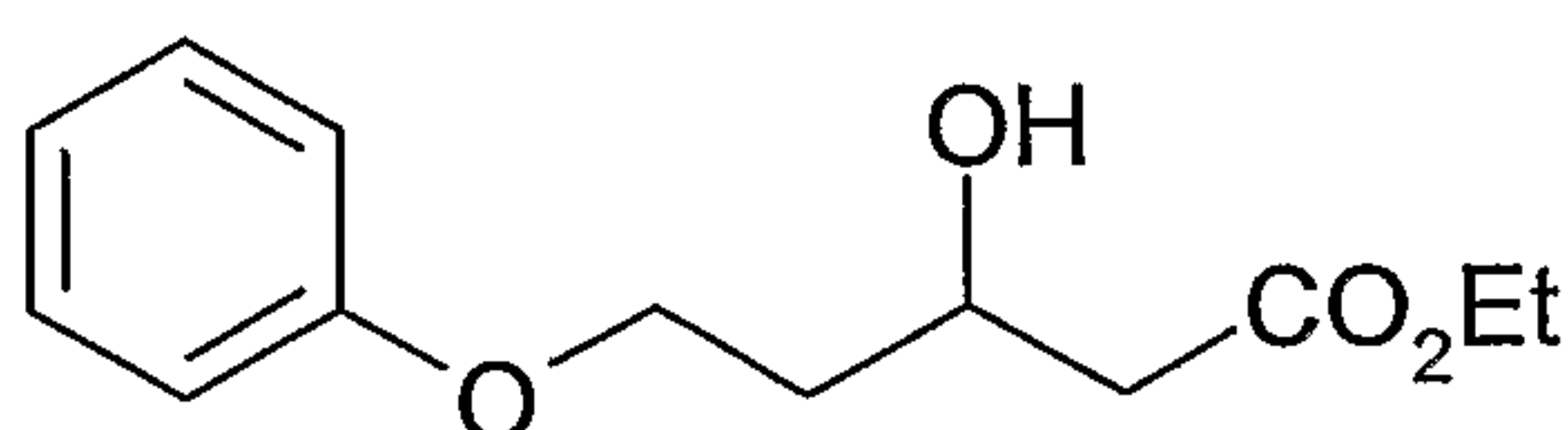
1245, 1224, 1175. MS (ES) m/e, 442. Anal. Calcd for $C_{24}H_{31}N_3O_3S \cdot HCl$: C, 60.30; H, 6.75; N, 8.79. Found C, 59.96; H, 6.59; N, 8.64. Mp($^{\circ}C$)=134.

Example 20

- 5 Preparation of 1-{5-[4-(3-Dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl}-4-phenoxybutan-2-ol from 3-Oxo-5-phenoxy-pentanoic acid ethyl ester



- a) 3-hydroxy-5-phenoxy-pentanoic acid ethyl ester

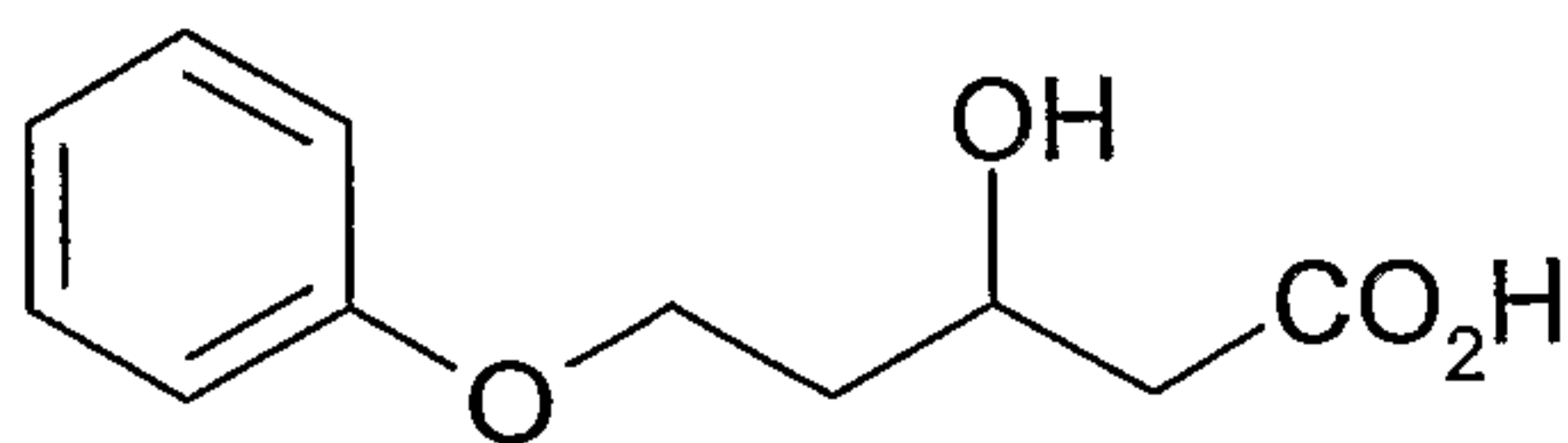


- 10 A solution of 3-Oxo-5-phenoxy-pentanoic acid ethyl ester 910.23 g, 43.3 mmol) in 122 mL EtOH and sodium borohydride (0.573 g, 15.2 mmol) was stirred at room temperature for 2.0 hours. The mixture was then treated with H_2O and reduced in volume. EtOAc and 1N HCl were added, phases separated and the organic phase was washed with brine, dried over sodium sulfate, filtered, concentrated to afford an oil. Purification by
15 HPLC on silica gel (elution with a linear gradient of 20 to 35% EtOAc:hexane over a 30 minute period) afforded 6.55 g (63%) of 3-hydroxy-5-phenoxy-pentanoic acid ethyl ester as an oil.

- ^1H NMR (DMSO- d_6) δ 7.24-7.31 (m, 2H), 6.88-6.93 (m, 3H), 4.90 (d, 1H, $J=6Hz$), 3.94-4.11 (m, 5H), 2.50 (dd, 1H, $J=5$ and 15Hz), 2.37 (dd, 1H, $J=8$ and 15Hz),
20 1.71-1.88 (m, 2H), 1.18 (t, 3H, $J=7Hz$). IR ($CHCl_3$, cm^{-1}) 3554, 3003, 2983, 2932, 1718, 1600, 1498, 1470, 1301, 1245, 1173. MS (ES) m/e, 239. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found C, 65.32; H, 7.42.

- b) 3-hydroxy-5-phenoxy-pentanoic acid

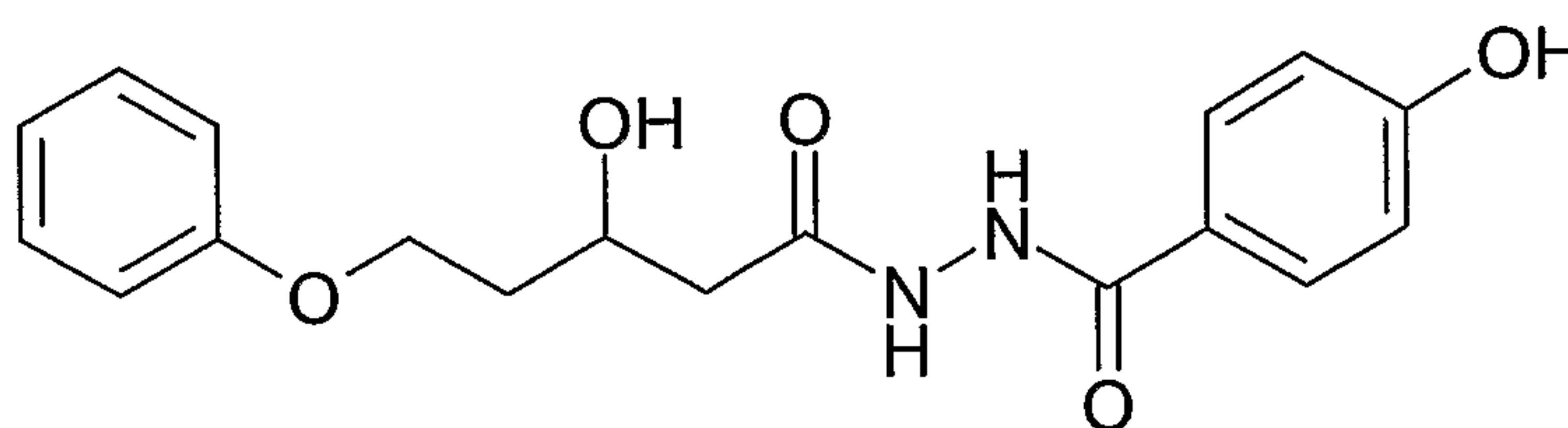
-113-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 8b, from 3-hydroxy-5-phenoxypentanoic acid ethyl ester (6.35 g, 26.6 mmol) and lithium hydroxide 1.91 g, 79.9 mmol) to afford 5.08 g (91%) of 3-hydroxy-5-phenoxypentanoic acid as a white solid.

^1H NMR (DMSO- d_6) δ 7.24-7.31 (m, 2H), 6.88-6.94 (m, 3H), 3.94-4.09 (m, 3H), 2.41 (dd, 1H, $J=5, 15\text{Hz}$), 2.30 (dd, 1H, $J=8, 15\text{Hz}$), 1.65-1.93 (m, 2H). IR (CHCl_3 , cm^{-1}) 3516, 3028, 2952, 2932, 2883, 1710, 1600, 1498, 1423, 1244, 1230, 1173. MS (ES) m/e , 211, 209. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_4$: C, 62.85; H, 6.71. Found C, 63.03; H, 6.59.

c) 4-Hydroxybenzoic acid-N-(3-hydroxy-5-phenoxypentanoyl)hydrazide

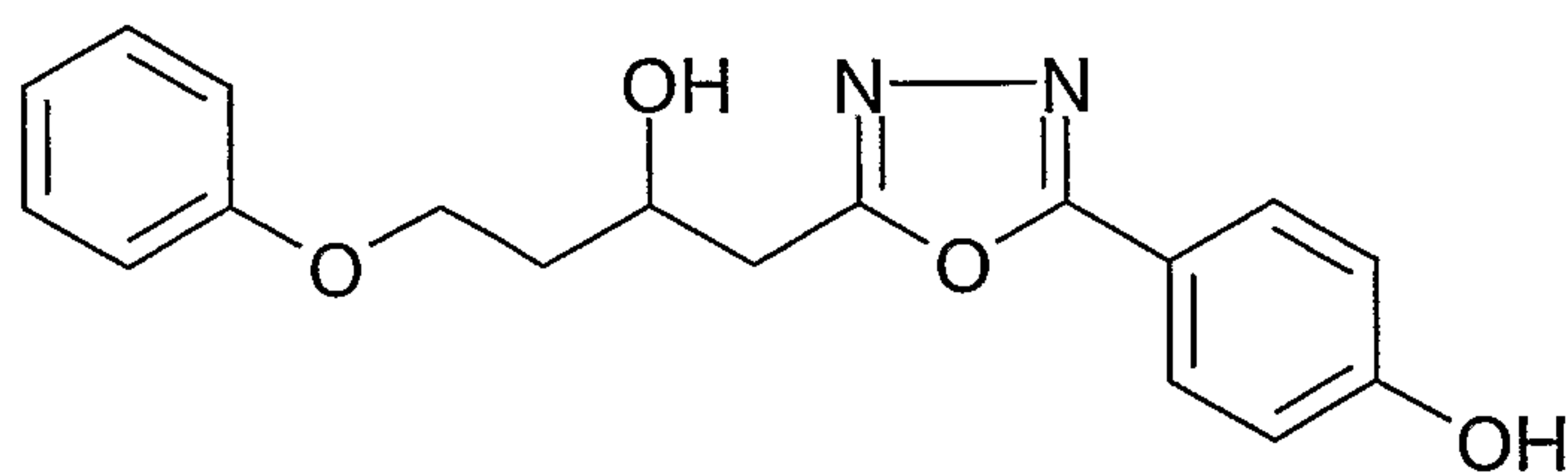


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 3-hydroxy-5-phenoxypentanoic acid (2.35 g, 8.0 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.97 g, 8.0 mmol) and 4-hydroxybenzoic hydrazide (1.21 g, 8.0 mmol) to afford 2.33 g (85%) of 4-Hydroxybenzoic acid-N-(3-hydroxy-5-phenoxypentanoyl)hydrazide as a solid.

^1H NMR (DMSO- d_6) δ 10.07 (bs, 2H), 9.77 (bs, 1H), 7.74 (d, 2H, $J=9\text{Hz}$), 7.22-7.31 (m, 2H), 6.89-6.95 (m, 3H), 6.89-6.95 (m, 3H), 6.80 (d, 2H, $J=9\text{Hz}$), 4.84 (d, 1H, $J=5\text{Hz}$), 4.01-4.16 (m, 3H), 2.29-2.43 (m, 2H), 1.89-2.02 (m, 1H), 1.68-1.82 (m, 1H). IR (KBr, cm^{-1}) 3413, 3207, 2949, 2875, 1661, 1601, 1579, 1475, 1469, 1244, 1056, 835. MS (ES) m/e , 345, 343. Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_5$: C, 62.78; H, 5.85, N, 8.13. Found C, 62.68; H, 5.83; N, 8.26.

d) 4-[5-(2-Hydroxy-4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]phenol

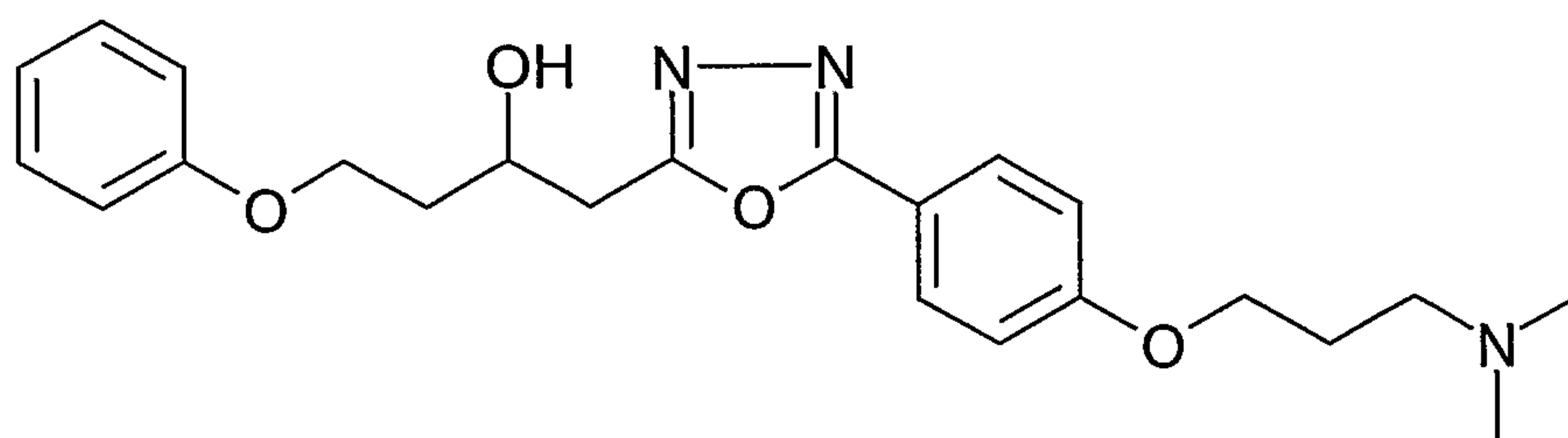
-114-



To a heavy suspension of 4-Hydroxybenzoic acid-N-(3-hydroxy-5-phenoxybutanoyl)hydrazide (0.900 g, 2.6 mmol) in 6 mL chlorobenzene stirring at room temperature was added 1,1,3,3-hexamethyldisilazane (1.31 g, 8.1 mmol) followed by trifluoromethane sulfonic acid (0.392 g, 2.6 mmol). The mixture was then heated at 120°C for 6 hours. After cooling to room temperature the suspension was filtered. The filtrate was treated with methanol then concentrated to an oil. The oil was dissolved into EtOAc and washed twice with 5N HCl. The aqueous phases were combined then extracted twice with EtOAc. The organic phases were combined, dried over sodium sulfate, filtered and concentrated to afford an oil. Purification by chromatography on silica gel (elution with 50% EtOAc:hexane) afforded 0.280g (33%) of 4-[5-(2-Hydroxy-4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]phenol as a solid.

¹H NMR (DMSO-d₆) δ 10.24 (bs, 1H), 7.78-7.82 (m, 2H), 7.24-7.31 (m, 2H), 6.89-6.96 (m, 5H), 5.14 (d, 1H, J=6Hz), 4.02-4.21 (m, 3H), 3.11 (dd, 1H, J=5, 15Hz), 2.99 (dd, 1H, J=8, 15Hz), 1.74-2.05 (m, 2H). IR (CHCl₃, cm⁻¹) 3204, 1617, 1599, 1587, 1501, 1473, 1279, 1244, 1173, 844, 754, 739. MS (ES) m/e, 327. Anal. Calcd for C₁₈H₁₈N₂O₄: C, 66.25; H, 5.56; N, 8.58. Found C, 60.90; H, 4.97; N, 6.95.

e) 1-{5-[4-(3-Dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl}-4-phenoxybutan-2-ol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-[5-(2-Hydroxy-4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]phenol (0.260 g 0.8 mmol), sodium hydride (0.064g, 1.6 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.126 g, 0.8 mmol) to afford the title compound as a

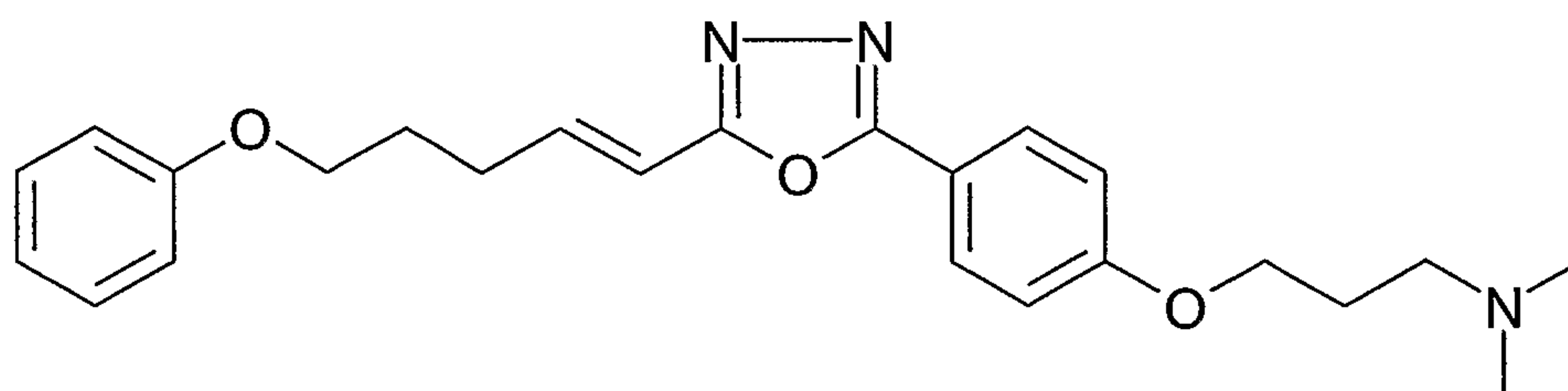
-115-

crude mixture. Purification by chromatography on silica gel (elution with 10% 2M NH₃ in MeOH:Et₂O) followed by crystallization from MeOH:Et₂O afforded 0.129 g (39%) of 1-{5-[4-(3-Dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl}-4-phenoxybutan-2-ol.

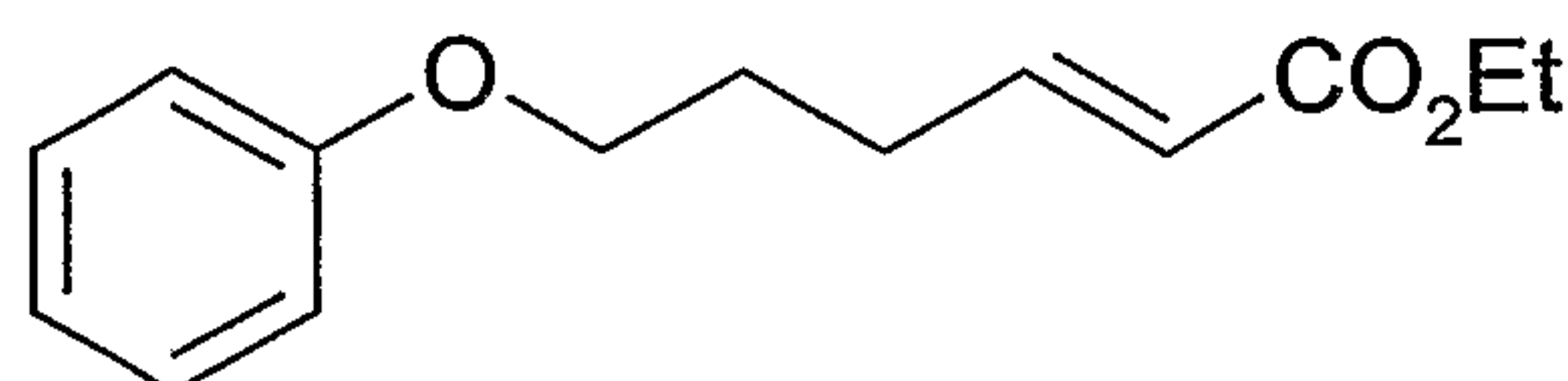
¹H NMR (DMSO-d₆) δ 7.88-7.91 (m, 2H), 7.24-7.30 (m, 2H), 7.12 (d, 2H, J=9Hz), 6.89-6.95 (m, 3H), 5.15 (d, 1H, J=6Hz), 4.07-4.21 (m, 5H), 3.12 (dd, 1H, J=5,15Hz), 3.00 (dd, 1H, J=8, 15Hz), 2.35 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.77-2.05 (m, 4H). IR (CHCl₃, cm⁻¹) 3535, 3019, 2953, 2825, 2777, 1614, 1500, 1470, 1255, 1174. MS (ES) m/e, 412. Anal. Calcd for C₂₃H₂₉N₃O₄: C, 67.13; H, 7.10, N, 10.21. Found C, 66.98; H, 6.96; N, 10.19. Mp(°C)=93.

Example 21

Preparation of Dimethyl-(3-{4-[5-(5-phenoxy-pent-1-enyl)-[1,3,4]-oxadiazol-2-yl]phenoxy}propyl)amine from 4-Phenoxybutan-1-ol



a) 6-Phenoxyhex-2-enoic acid ethyl ester



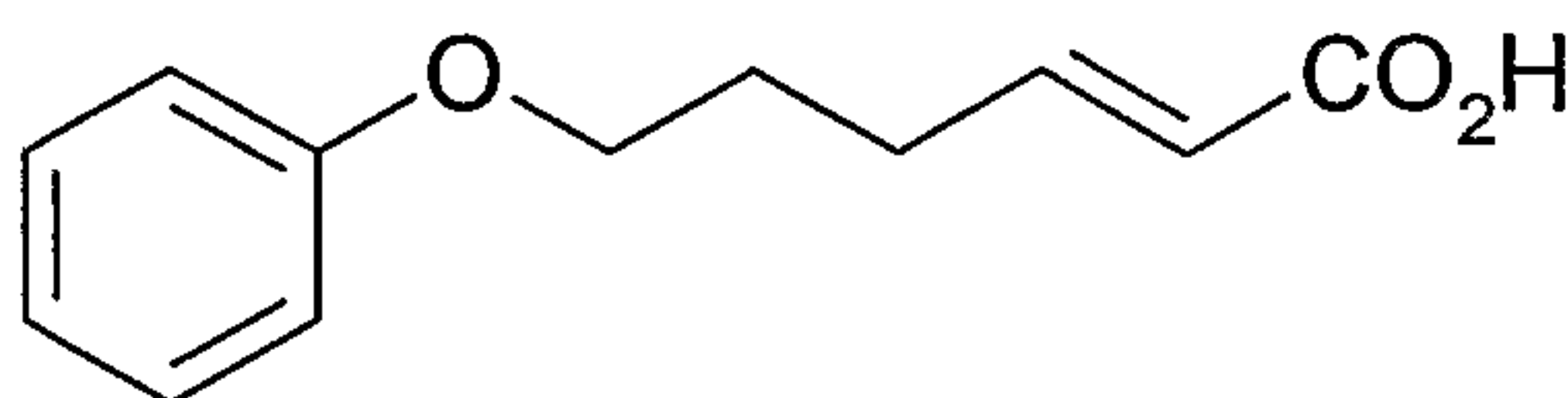
To a solution of oxalyl chloride (5.39 g, 42.5 mmol) in 500 mL CH₂Cl₂ at -78 °C was added dimethyl sulfoxide (6.64 g, 85.0 mmol). The reaction was stirred 10 minutes before a solution of 4-Phenoxybutan-1-ol (6.42 g, 38.6 mmol) in 40 mL CH₂Cl₂ was added dropwise over a 25 minute period. The reaction was continued stirring at -78 °C for 30 minutes before triethylamine (19.54 g, 193.1 mmol) was added. The cooling bath was removed allowing the reaction to gradually warm to room temperature. Upon warming, at approximately -40 °C (carboethoxymethylene)triphenylphosphorane was added directly followed by 250 mL CH₂Cl₂. The resultant solution was stirred approximately 18 hours at room temperature before being concentrated to an oil. Treatment of the oil with diethyl ether followed by sonication resulted in crystal

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formation. Crystals were collected by filtration and discarded. The filtrate was concentrated to an oil and the above process was repeated to remove additional triphenylphosphine oxide. Purification by chromatography on silica gel (elution with 10% Et₂O:hexane) afforded 7.05 g (78%) of *trans*-6-Phenoxyhex-2-enoic acid ethyl ester and 0.520 g (6%) of *cis*-6-Phenoxyhex-2-enoic acid ethyl ester as oils.

¹H NMR (DMSO-d₆) δ 7.24-7.31 (m, 2H), 6.89-7.00 (m, 4H), 5.88 (dt, 1H, J=1 and 15Hz), 4.10 (q, 2H, J=7Hz), 3.96 (t, 2H, J=6Hz), 2.36 (ddd, 2H, J=1, 7 and 16Hz), 1.82-1.92 (m, 2H), 1.20 (t, 3H, J=7Hz). IR (CHCl₃, cm⁻¹) 1711, 1600, 1498, 1277, 1246, 1172, 1041. MS (ES) m/e, 235. Anal. Calcd for C₁₄H₁₈O₃: C, 71.77; H, 7.74. Found C, 71.30; H, 7.73.

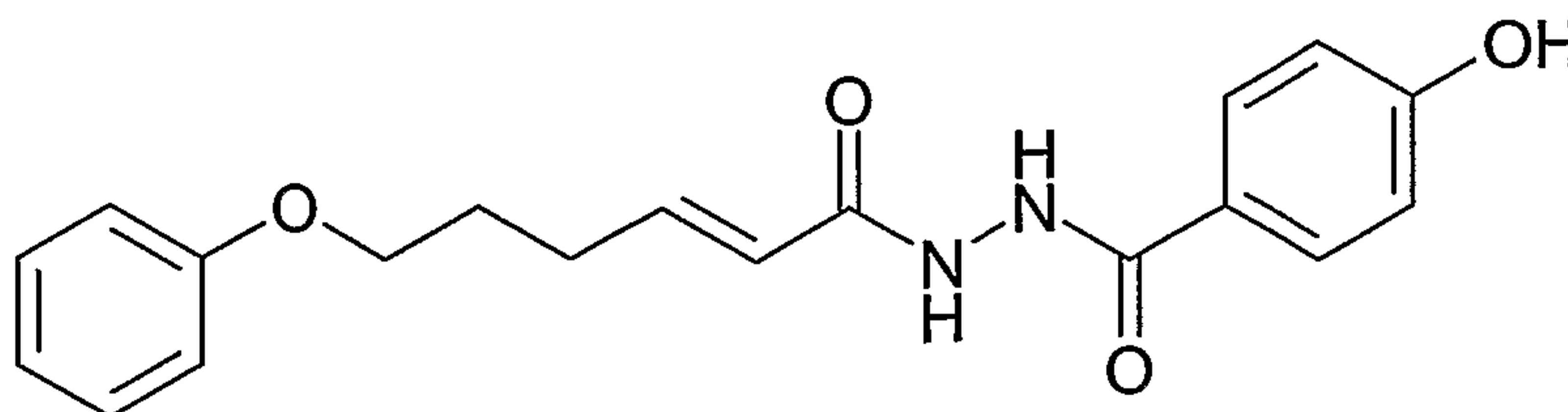
b) *trans*-6-Phenoxyhex-2-enoic acid



A solution of *trans*-6-Phenoxyhex-2-enoic acid ethyl ester (2.25 g, 9.6 mmol) in 48 mL acetone and 48 mL 1N lithium hydroxide was stirred at room temperature for 2.5 hours. The mixture was then quenched with 4.14 mL concentrated HCl, reduced in volume and set aside at 5 °C to allow for crystal formation. Collection of the crystals by filtration afforded 1.43 g (72%) of *trans*-6-phenoxyhex-2-enoic acid.

¹H NMR (DMSO-d₆) δ 12.10 (bs, 1H), 7.24-7.31 (m, 2H), 6.83-6.93 (m, 4H), 5.77-5.83 (m, 1H), 3.96 (t, 2H, J=6Hz), 2.30-2.38 (m, 2H), 1.81-1.91 (m, 2H). IR (KBr, cm⁻¹) 3441, 2942, 1693, 1642, 1291, 1252, 1242, 758. MS (ES) m/e, 205. Anal. Calcd for C₁₂H₁₄O₃: C, 69.89; H, 6.84. Found C, 70.02; H, 7.06.

c) 4-Hydroxybenzoic acid-N-(6-phenoxyhex-2-enoyl)hydrazide



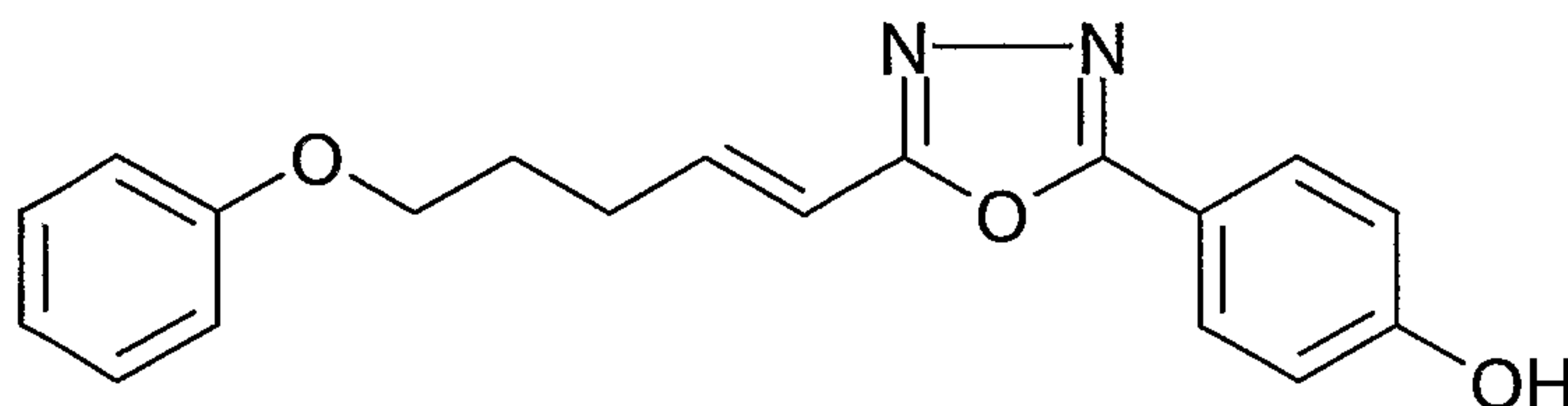
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from *trans*-6-phenoxyhex-2-enoic acid (1.30 g, 6.3 mmol),

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2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.56 g, 6.3 mmol) and 4-hydroxybenzoic hydrazide (0.959 g, 6.3 mmol) to afford the title compound as a crude mixture. Purification by crystallization (MeOH:Et₂O) afforded 1.05 g (49%) of 4-Hydroxybenzoic acid-N-(6-phenoxyhex-2-enoyl)hydrazide.

¹H NMR (DMSO-d₆) δ 10.09 (bs, 2H), 9.87 (bs, 1H), 7.74 (d, 2H, J=9Hz), 7.22-7.32 (m, 2H), 6.89-6.95 (m, 3H), 6.76-6.86 (m, 3H), 6.02-6.07 (m, 1H), 3.99 (t, 2H, J=6Hz), 2.35 (q, 2H, J=7Hz), 1.88 (m, 2H). IR (KBr, cm⁻¹) 3284, 3210, 3007, 1693, 1618, 1610, 1600, 1585, 1518, 1492, 1291, 1245, 1173, 937, 758. MS (ES) m/e, 341, 339. Anal. Calcd for C₁₉H₂₀N₂O₄: C, 67.05; H, 5.92; N, 8.23. Found C, 66.90; H, 6.03; N, 8.57.

d) 4-[5-(5-phenoxy-pent-1-enyl)-[1,3,4]oxadiazol-2-yl]phenol

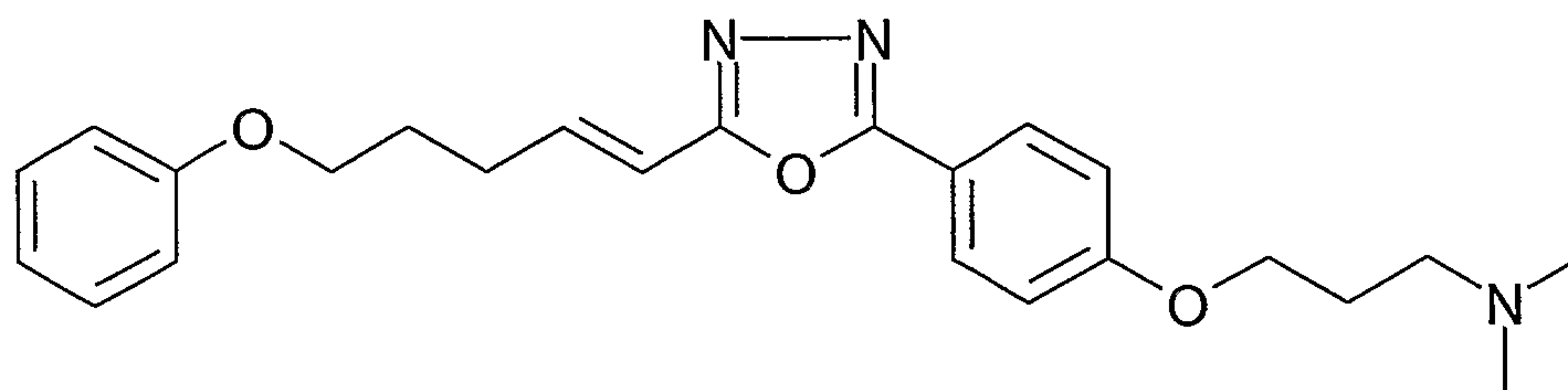


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-Hydroxybenzoic acid-N-(6-phenoxyhex-2-enoyl)hydrazide (0.915 g, 2.7 mmol), triphenylphosphine (1.41 g, 5.4 mmol), triethylamine (0.544 g, 5.4 mmol) and carbon tetrabromide (1.78 g, 5.4 mmol) to afford the title compound as a crude mixture. Crystallization of this material from EtOAc afforded 0.224 g (26%) of 4-[5-(5-phenoxy-pent-1-enyl)-[1,3,4]oxadiazol-2-yl]phenol.

¹H NMR (DMSO-d₆) δ 10.31 (bs, 1H), 7.84-7.89 (m, 2H), 7.25-7.31 (m, 2H), 6.89-6.99 (m, 6H), 6.54-6.59 (m, 1H), 4.03 (t, 2H, J=6Hz), 2.45-2.50 (m, 2H), 1.91-2.00 (m, 2H). IR (KBr, cm⁻¹) 2945, 2612, 1656, 1588, 1441, 1288, 1243, 1173, 1034, 845. MS (ES) m/e, 323, 321. Anal. Calcd for C₁₉H₁₈N₂O₃: C, 70.79; H, 5.63; N, 8.64. Found C, 70.70; H, 5.78; N, 8.64.

e) Dimethyl-(3-{4-[5-(5-phenoxy-pent-1-enyl)-[1,3,4]-oxadiazol-2-yl]phenoxy}propyl)amine from 4-Phenoxybutan-1-ol

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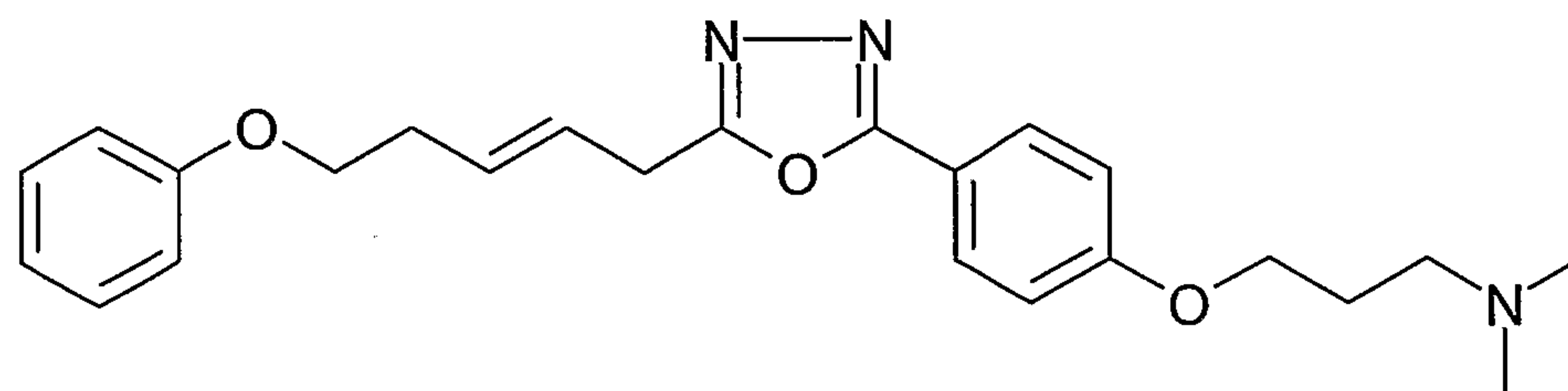


A suspension of 4-[5-(5-phenoxy-1-enyl)-[1,3,4]oxadiazol-2-yl]phenol (0.207 g 0.6 mmol), cesium carbonate (0.418g, 1.3 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.102 g, 0.6 mmol) in 8.5 mL DMF was heated at 90 °C for 3.5 hours. After cooling to room temperature the reaction was diluted with water then extracted three times with EtOAc. The organic phases were combined, washed with brine then concentrated an oil. Purification by radial chromatography on silica gel (elution with 10% 2M NH₃ in MeOH:CHCl₃) afforded 0.153 g of the title compound as an oil. Treatment of the oil, dissolved in acetone, with oxalic acid afforded 0.147 g (46%) of the oxalate salt of dimethyl-(3-{4-[5-(5-phenoxy-1-enyl)-[1,3,4]-oxadiazol-2-yl]phenoxy}propyl)amine.

¹H NMR (DMSO-d₆) δ 7.97 (d, 2H, J=9Hz), 7.23-7.31 (m, 2H), 7.15 (d, 2H, J=9Hz), 6.90-7.03 (m, 4H), 6.56-6.62 (m, 1H), 4.15 (t, 2H, J=6Hz), 4.01-4.05 (m, 2H), 2.76 (s, 6H), 2.04-2.17 (m, 2H), 1.87-1.99 (m, 2H). IR (CHCl₃, cm⁻¹) 1776, 1658, 1609, 1493, 1471, 1255, 1172. MS (ES) m/e, 408. Anal. Calcd for C₂₄H₂₉N₃O₃·C₂H₂O₄: C, 62.77; H, 6.28, N, 8.45. Found C, 62.47; H, 6.26; N, 8.32. Mp(°C)=163.

Example 22

Preparation of Dimethyl(3-{4-[5-(5-phenoxy-2-enyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from Hex-3-enedioic acid monomethyl ester



a) 6-Hydroxyhex-3-enoic acid methyl ester

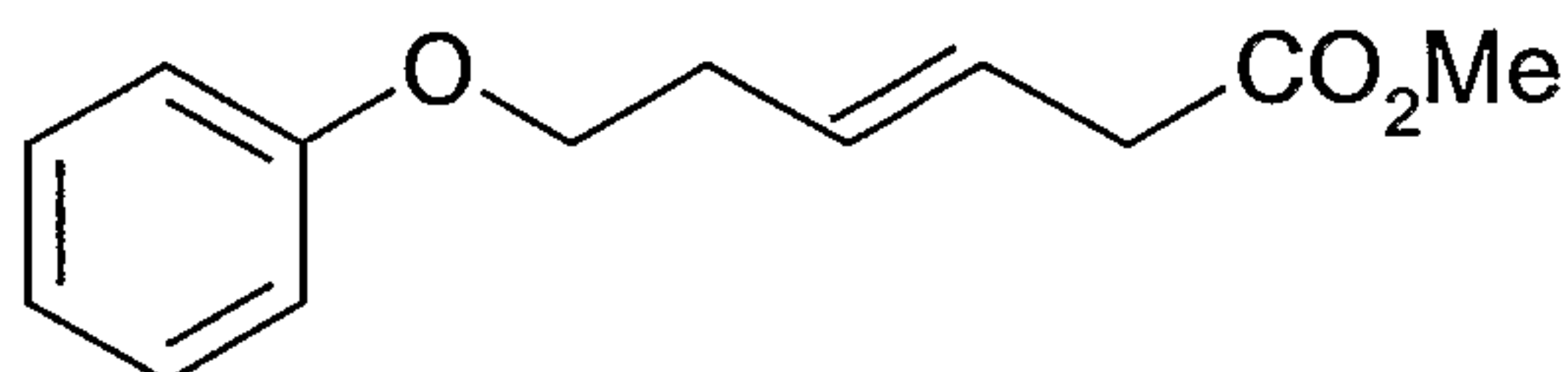


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To a solution of hex-3-enedioic acid monomethyl ester (8.49 g, 53.7 mmol) in 23 mL THF at -10°C was added a 1.0 M solution of borane in THF over a 140 minute period. The resultant suspension was stirred at room temperature approximately 24 hours. Next, the mixture was treated with 1:1 Acetic acid: H_2O then concentrated to an oil. The oil was added dropwise to a 100 mL saturated solution of sodium bicarbonate. This mixture was extracted with EtOAc. The organic phase was washed twice with the saturated solution of sodium bicarbonate. The combined aqueous phases were acidified with 5N HCl then extracted three times with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, concentrated in vacuo to afford 4.09 g (53%) of 6-Hydroxyhex-3-enoic acid methyl ester as an oil.

^1H NMR ($\text{DMSO}-d_6$) δ 5.45-5.60 (m, 2H), 4.47 (t, 1H, $J=5\text{Hz}$), 3.59 (s, 3H), 3.40 (ddd, 2H, $J=5,7,12\text{Hz}$), 3.04 (d, 2H, $J=6\text{Hz}$), 2.14 (q, 2H, $J=6\text{Hz}$). IR (CHCl_3 , cm^{-1}) 3620, 3465, 3023, 2955, 2884, 1733, 1438, 1169, 1044, 971. MS (ES) m/e , 126. Anal. Calcd for $\text{C}_7\text{H}_{12}\text{O}_3$: C, 58.32; H, 8.39. Found C, 57.43; H, 7.99.

b) 6-Phenxoyhex-3-enoic acid methyl ester

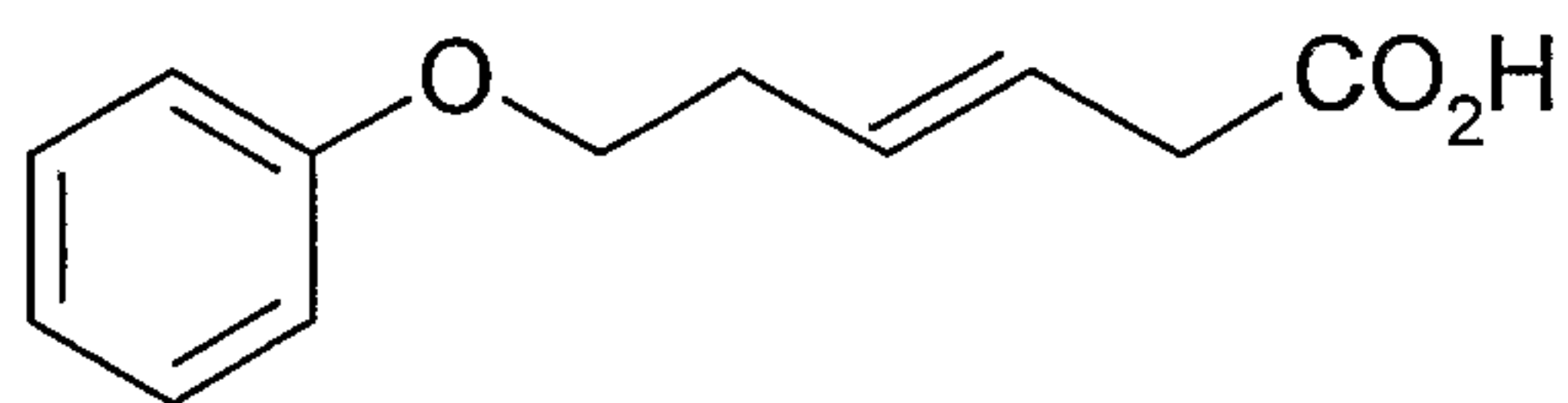


To a solution of 6-hydroxyhex-3-enoic acid methyl (1.30 g, 9.0 mmol) and phenol (1.27 g, 13.5) in 81 mL THF stirring at room temperature was added, in portions, 3,3-dimethyl-1,2,5-thiadiazolidine-1,1-dioxide triphenylphosphine adduct (reference: Castro, J. L., Matassa, V. G., *J. Org. Chem.* 1994, 59, 2289-2291) over a twenty minute period. After stirring approximately 24 hours, the reaction was diluted with EtOAc then washed three times with 1N sodium hydroxide, brine, dried over sodium sulfate, filtered, concentrated to a solid. Purification by chromatography on silica gel (elution with 10% Et_2O :hexane) afforded 0.987 g (50%) of 6-phenxoyhex-3-enoic acid methyl ester as an oil.

^1H NMR ($\text{DMSO}-d_6$) δ 7.24-7.31 (m, 2H), 6.89-6.94 (m, 3H), 5.62-5.65 (m, 2H), 3.97 (t, 2H, $J=7\text{Hz}$), 3.60 (s, 3H), 3.09 (m, 2H), 2.42-2.49 (m, 2H). IR (KBr, cm^{-1}) 3013, 2954, 1734, 1601, 1497, 1438, 1290, 1245, 1173, 1037, 970. MS (ES) m/e , 220. Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$: C, 70.89; H, 7.32. Found C, 56.90; H, 5.84.

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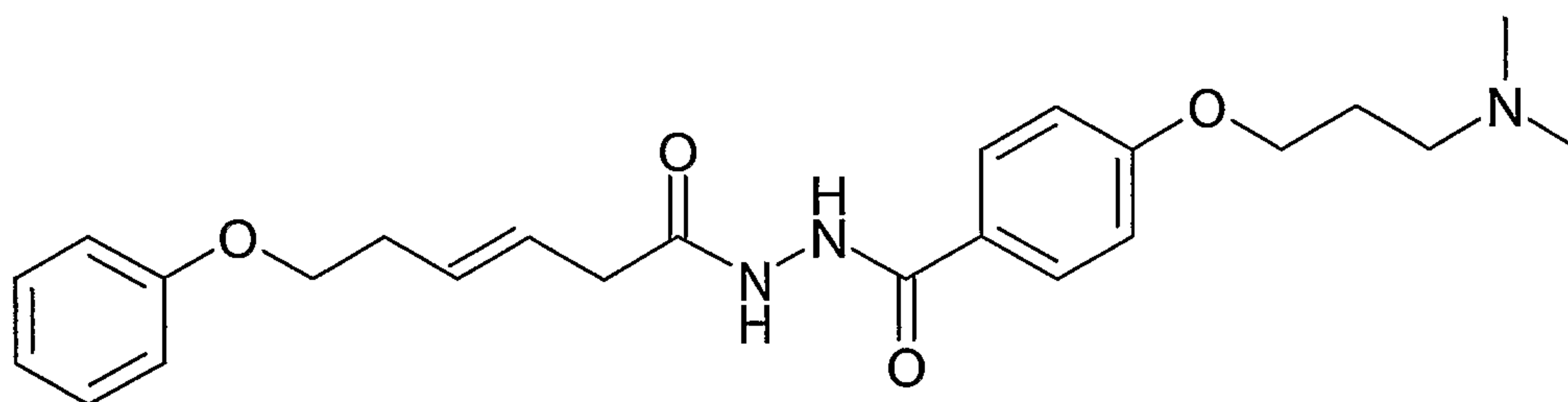
c) 6-Phenxoyhex-3-enoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17c, from 6-phenxoyhex-3-enoic acid methyl ester (0.960 g, 4.4 mmol) and lithium hydroxide (0.313 g, 13.1 mmol) to afford 0.760 g (85%) of 6-phenxoyhex-3-enoic acid as an oil that slowly crystallized out upon standing.

^1H NMR (DMSO- d_6) δ 12.29 (bs, 1H), 7.20-7.32 (m, 2H), 6.88-6.96 (m, 3H), 5.54-5.66 (m, 2H), 3.97 (t, 2H, $J=7\text{Hz}$), 2.99 (m, 2H), 2.43-2.48 (m, 2H). IR (KBr, cm^{-1}) 1713, 1601, 1471, 1398, 1246, 1225, 1039, 968, 758, 694. MS (ES) m/e , 205. Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_3$: C, 69.89; H, 6.84. Found C, 69.30; H, 6.64.

d) 4-(3-Dimethylaminopropoxy)benzoic acid-N-(6-phenoxyhex-3-enoyl)hydrazide



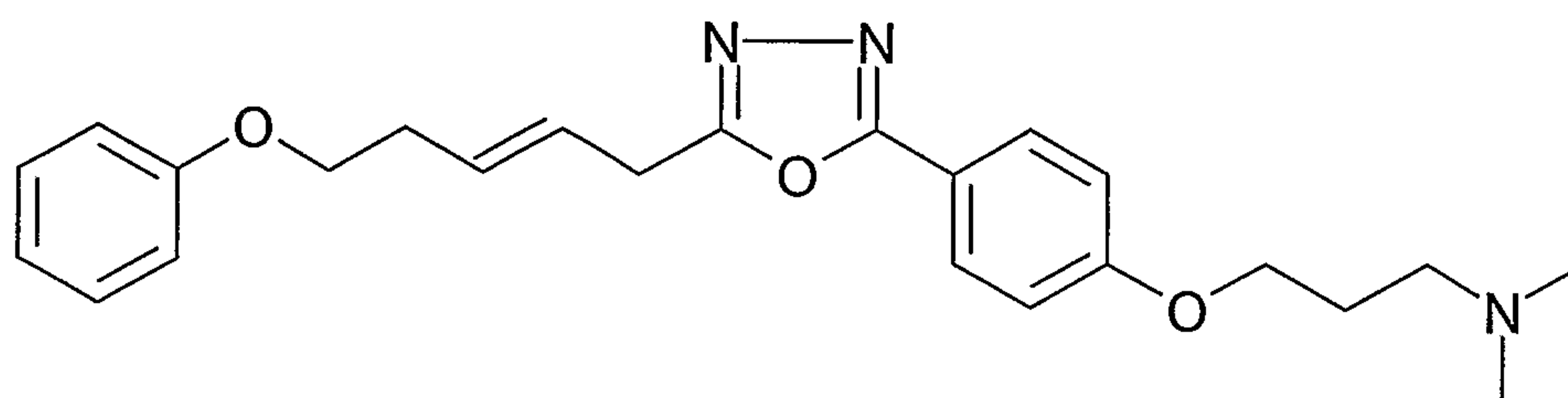
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 6-phenxoyhex-3-enoic acid (0.760 g, 3.7 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.911 g, 3.7 mmol) and 4-(3-dimethylaminopropoxy)benzoic hydrazide (0.874 g, 3.7 mmol) to afford the title compound as an oil. Treatment of the oil with EtOAc followed by 1N HCl resulted in crystal formation in the aqueous phase. The crystals were collected by filtration to afford 0.364 g (23%) of 4-(3-Dimethylaminopropoxy)benzoic acid-N-(6-phenoxyhex-3-enoyl)hydrazide.

^1H NMR (DMSO- d_6) δ 10.17 (s, 1H), 9.86 (s, 1H), 7.85 (d, 2H, $J=9\text{Hz}$), 7.24-7.31 (m, 2H), 7.03 (d, 2H, $J=9\text{Hz}$), 6.90-6.95 (m, 3H), 5.57-5.69 (m, 2H), 4.13 (t, 2H, $J=6\text{Hz}$), 3.99 (t, 2H, $J=7\text{Hz}$), 3.17-3.23 (m, 2H), 2.96 (d, 2H, $J=3\text{Hz}$), 2.44-2.48 (m, 2H), 2.11-2.20 (m, 2H). IR (KBr, cm^{-1}) 3201, 3010, 2591, 2563, 2519, 2468, 1683, 1666, 1642, 1609,

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1493, 1477, 1467, 1307, 1263, 1166, 978, 762. MS (ES) m/e, 426, 424. Anal. Calcd for $C_{24}H_{31}N_3O_4$: C, 62.40; H, 6.98; N, 9.10. Found C, 61.74; H, 6.83; N, 8.72.

e) Dimethyl(3-{4-[5-(5-phenoxyent-2-enyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine



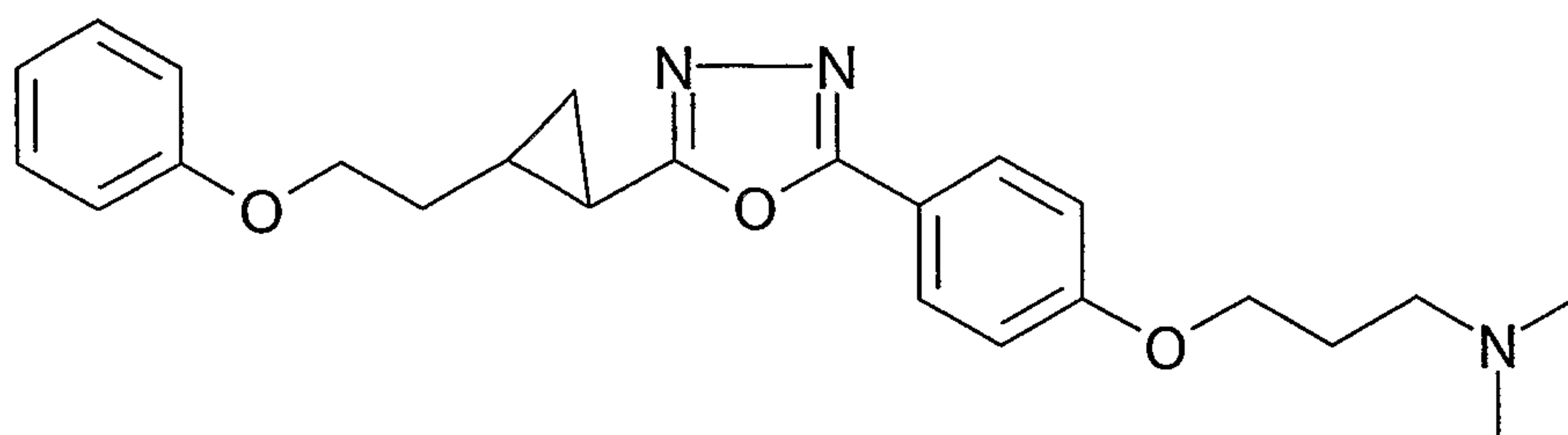
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-(3-Dimethylaminopropoxy)benzoic acid-N-(6-phenoxyhex-3-enoyl)hydrazide (0.348 g, 0.8 mmol), triphenylphosphine (0.217 g, 0.8 mmol), triethyl amine (0.160 g, 1.6 mmol) and carbon tetrabromide (0.275 g, 0.8 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (10% 2M NH_3 in MeOH: $CHCl_3$) afforded 0.224 g of material. The material was dissolved into diethyl ether. To this solution was added dropwise a solution of EtOH in Et₂O that was treated with 0.047 mL acetyl chloride. The resultant precipitate was collected by filtration to afford 0.176 g (53%) of dimethyl(3-{4-[5-(5-phenoxyent-2-enyl)-[1,3,4] oxadiazol-2-yl]-phenoxy}propyl)amine as the hydrochloride salt.

¹H NMR (DMSO-d₆) δ 7.87-7.93 (m, 2H), 7.23-7.29 (m, 2H), 7.11-7.16 (m, 2H), 6.89-6.94 (m, 3H), 5.78-5.82 (m, 2H), 4.16 (t, 2H, J=6Hz), 4.01 (t, 2H, J=7Hz), 3.71 (d, 2H, J=5Hz), 3.18-3.24 (m, 2H), 2.78 (s, 6H), 2.47-2.53 (m, 2H), 2.13-2.22 (m, 2H). IR (KBr, cm⁻¹) 2936, 2675, 2658, 2614, 2477, 1617, 1501, 1473, 1257, 1175, 972, 839, 769. MS (ES) m/e, 408. Anal. Calcd for $C_{24}H_{29}N_3O_3 \cdot HCl$: C, 64.93; H, 6.81, N, 9.46. Found C, 63.76; H, 6.75; N, 9.24. Analytical HPLC: 100% Purity. Mp(°C)=145.

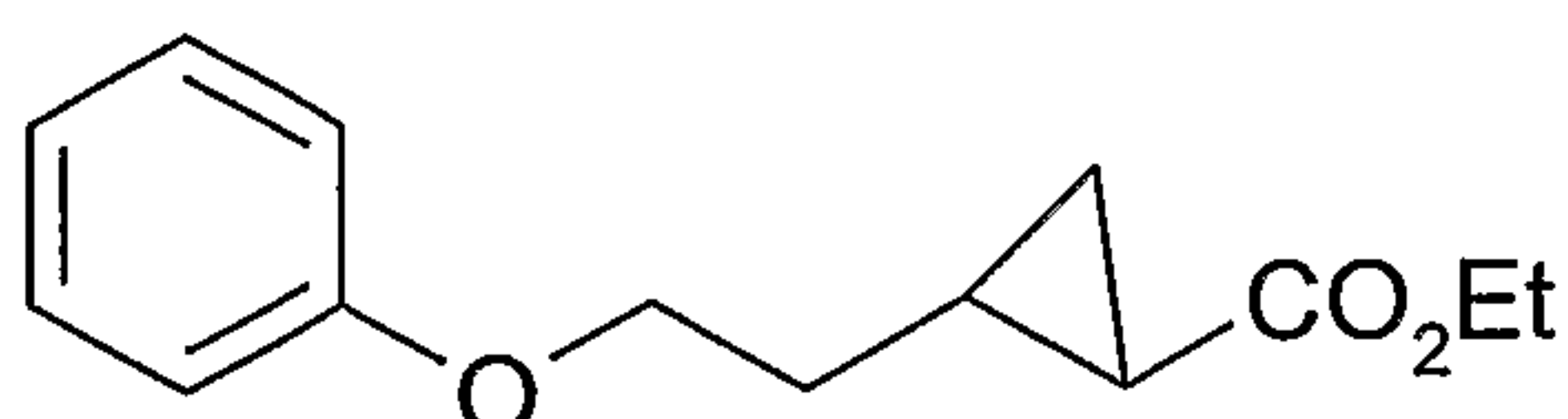
Example 23

Preparation of Dimethyl-[3(4-{5-[2-(2-phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenoxoy)propyl]amine from 4-phenoxybutene

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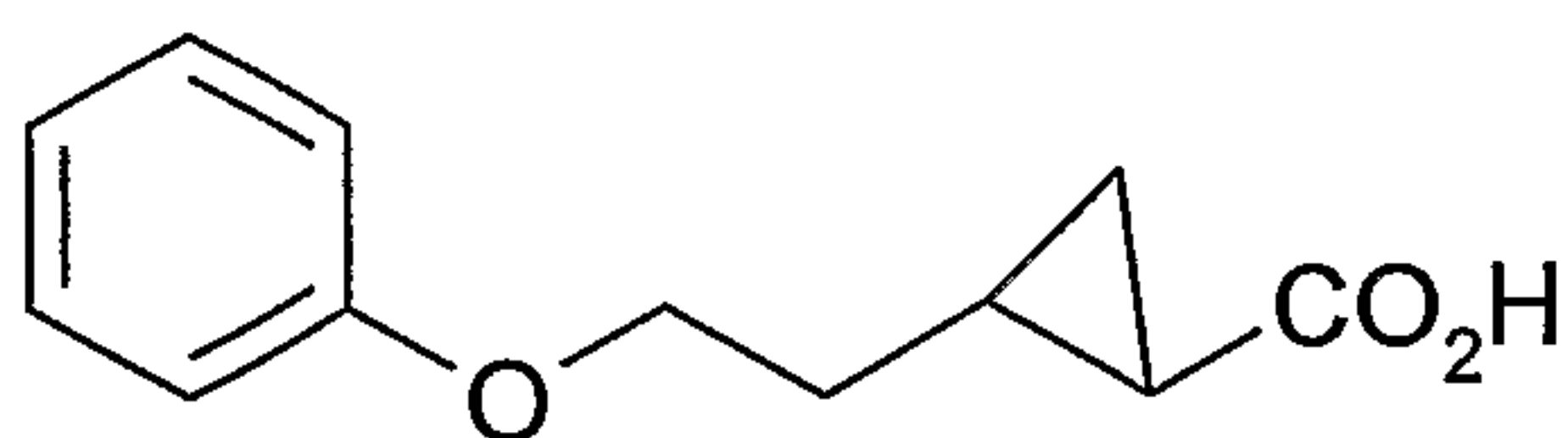
a) 2-(2-Phenoxyethyl)cyclopropanecarboxylic acid methyl ester



To a light suspension of 4-phenoxybutene (4.95 g, 33.4 mmol) and rhodium acetate (0.147 g, 0.33 mmol) in 295 mL CH₂Cl₂ stirring at room temperature was added a solution of ethyl diazo acetate (3.81 g, 33.4 mmol) in 48 mL CH₂Cl₂ over a four hour period. Stirring continued for an additional 30 minutes before the mixture was washed twice with 1N HCl, brine, dried over sodium sulfate, filtered, concentrated to afford an oil. Purification by chromatography on silica gel (elution with CH₂Cl₂) afforded 1.29 g (16%) of 2-(2-phenoxyethyl)cyclopropanecarboxylic acid methyl ester.

¹H NMR (CDCl₃) δ 7.28 (m, 2H), 6.90-6.94 (m, 3H), 4.12 (m, 2H), 4.02 (ddd, 2H, J=7,9,13Hz), 1.82 (ddd, 1H, J=7,14,21Hz), 1.76 (ddd, 1H, J=6, 13, 21Hz), 1.55 (m, 1H), 1.48 (dd, 1H, J=5,8Hz), 1.26 (t, 3H), 1.22 (ddd, 1H, 4,4,9Hz), 0.79 (ddd, 1H, J=4,6,8Hz). IR (CHCl₃, cm⁻¹) 3009, 2984, 2941, 2873, 1717, 1600, 1498, 1302, 1246, 1182, 1039. MS (EI) m/e, 234. Anal. Calcd for C₁₄H₁₈O₃: C, 71.77; H, 7.74. Found C, 69.01; H, 7.53.

b) 2-(2-Phenoxyethyl)cyclopropanecarboxylic acid



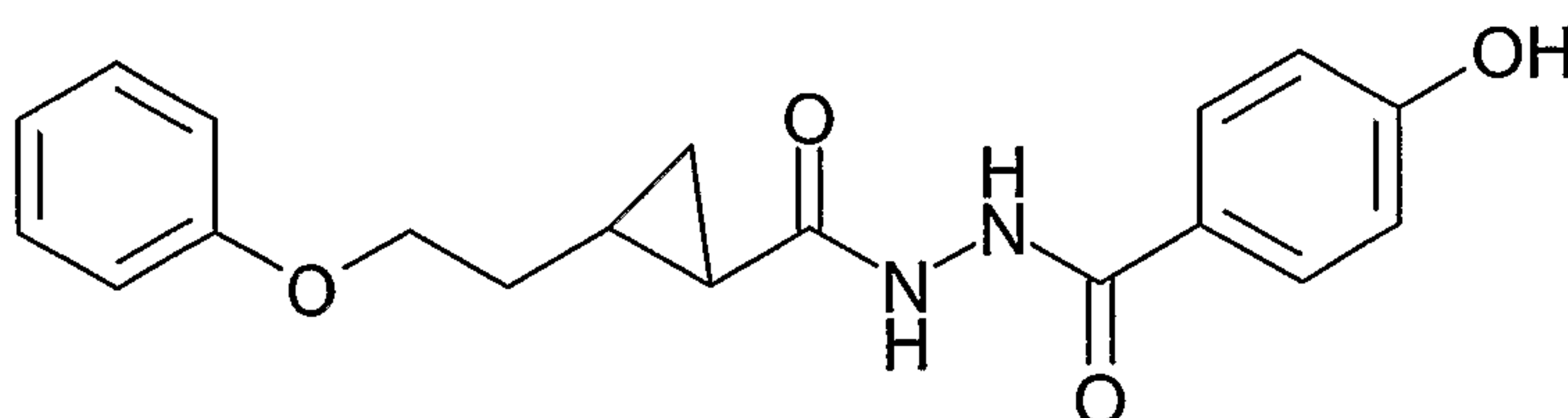
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 2-(2-Phenoxyethyl)cyclopropanecarboxylic acid methyl ester (1.07 g, 4.5 mmol) and lithium hydroxide (0.33 g, 13.6 mmol) to afford the title compound as a crude mixture. The material was treated with water then extracted twice with EtOAc. The organic phases were combined, dried over sodium sulfate, filtered,

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concentrated to afford 0.771 g (82%) 2-(2-Phenoxyethyl)cyclopropanecarboxylic acid as a solid.

¹H NMR (DMSO-d₆) δ 12.13 (bs, 1H), 7.24-7.31 (m, 2H), 6.89-6.95 (m, 3H), 3.94-4.06 (m, 2H), 1.66-1.75 (q, 2H, J=7Hz), 1.31-1.45 (m, 2H), 1.00 (ddd, 1H, J=4,8,17Hz), 0.78 (ddd, 1H, J=4,6,8Hz). IR (CHCl₃, cm⁻¹) 3020, 2943, 1696, 1600, 1498, 1246. MS (ES) m/e, 205. Anal. Calcd for C₁₂H₁₄O₃: C, 69.89; H, 6.84. Found C, 69.50; H, 6.90.

c) 4-Hydroxybenzoic acid-N-[2-(2-phenoxyethyl)cyclopropane
10 carbonyl]hydrazide



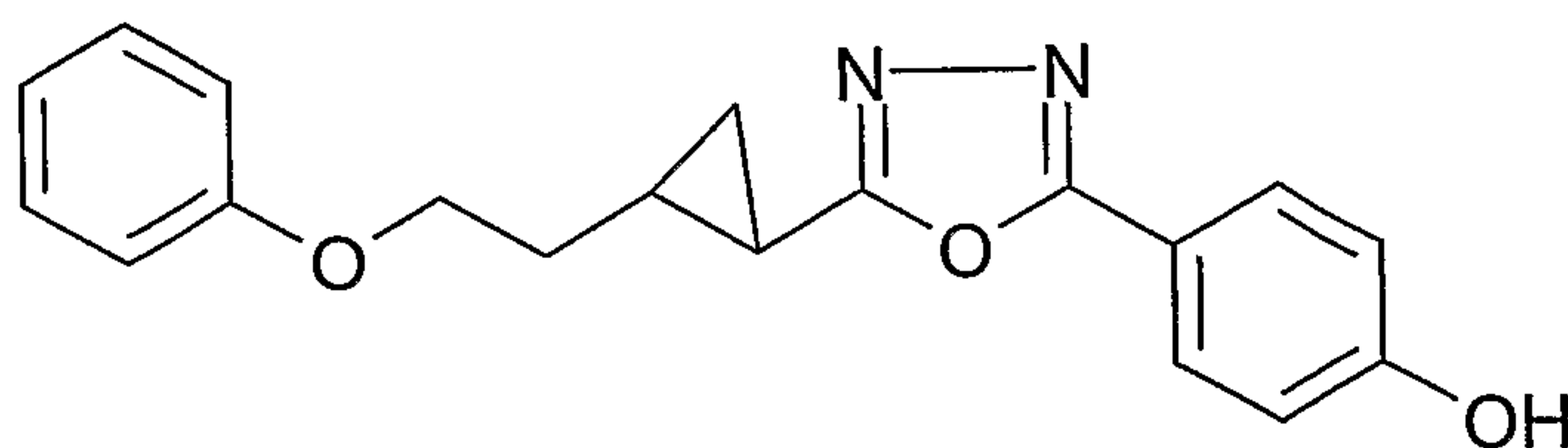
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 2-(2-Phenoxyethyl)cyclopropanecarboxylic acid (0.750 g, 3.6 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.899 g, 3.6 mmol) and
15 4-hydroxybenzoic hydrazide (0.553 g, 3.6 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% MeOH:CHCl₃) followed by crystallization from MeOH:EtOAc afforded 0.336 g (27%) of 4-hydroxybenzoic acid-N-[2-(2- phenoxyethyl)-cyclopropanecarbonyl]hydrazide.

¹H NMR (DMSO-d₆) δ 10.06-9.97 (M, 3H), 7.80-7.71 (m, 2H), 7.32-7.21 (m, 2H), 6.90-6.96 (m, 3H), 6.79-6.83 (m, 2H), 4.02 (t, 2H, J=6Hz), 1.68-1.79 (m, 2H), 1.55-1.61 (m, 1H), 1.28-1.36 (m, 1H), 0.92-0.98 (m, 1H), 0.74-0.80 (m, 1H). IR (KBr, cm⁻¹) 3301, 3226, 1696, 1620, 1610, 1584, 1518, 1498, 1290, 1248, 1173, 756. MS (ES) m/e, 341, 339. Anal. Calcd for C₁₉H₂₀N₂O₄: C, 67.05; H, 5.92; N, 8.23. Found C, 66.78; H, 5.76; N, 8.26.

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d) 4-{5-[2-(2-Phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenol

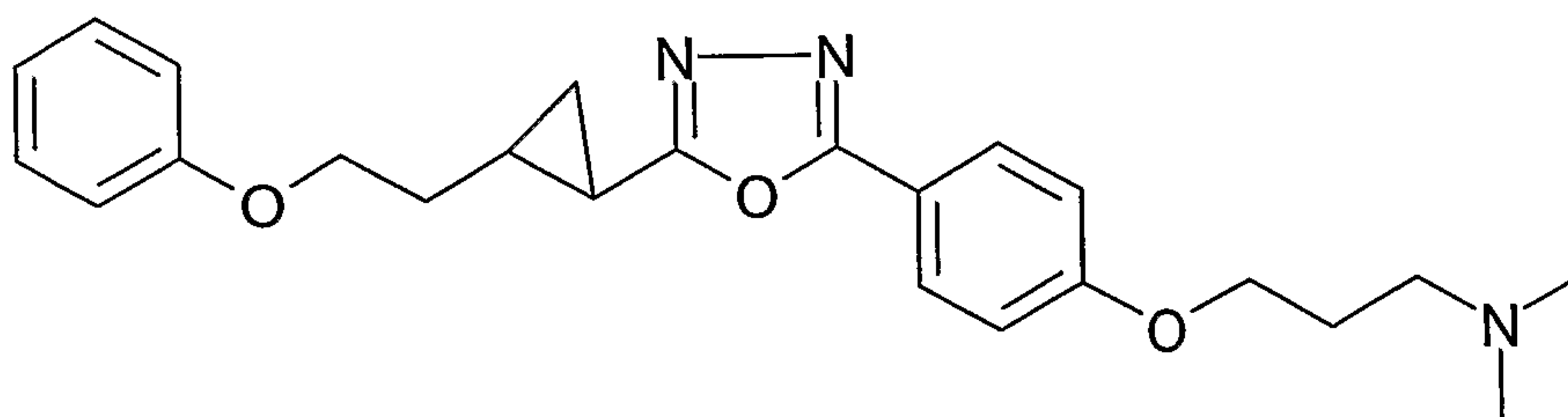
-124-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-N-[2-(2-phenoxyethyl)cyclopropanecarbonyl]hydrazide (0.308 g, 0.9 mmol), triphenylphosphine (0.285 g, 1.1 mmol), triethyl amine (0.110 g, 1.1 mmol) and carbon tetrabromide (0.360 g, 1.1 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with EtOAc) afforded 0.247 mg (85%) of (4-{5-[2-(2-Phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenol 0.247 g (85%) as a white foam.

¹H NMR (DMSO-d₆) δ 10.23 (bs, 1H), 7.73-7.81 (m, 2H), 7.24-7.31 (m, 2H), 6.88-6.96 (m, 5H), 4.05-4.12 (m, 2H), 2.16-2.22 (m, 1H), 1.77-1.90 (m, 2H), 1.56-1.64 (m, 1H), 1.26-1.32 (m, 1H), 1.06-1.14 (m, 1H). IR (KBr, cm⁻¹) 3422, 3092, 3027, 2954, 2813, 2684, 2606, 1615, 1601, 1585, 1565, 1500, 1478, 1381, 1287, 1269, 1249, 1175, 1167, 1078, 1032, 1008, 835, 752, 741, 689. MS (ES) m/e, 323, 321. Anal. Calcd for C₁₉H₁₈N₂O₃: C, 70.79; H, 5.63; N, 8.69. Found C, 69.53; H, 5.51; N, 8.28.

e) Dimethyl-[3(4-{5-[2-(2-phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenoxoy)propyl]amine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-{5-[2-(2-Phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenol (0.227 g 0.7 mmol), cesium carbonate (0.459g, 1.4 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.111 g, 0.7 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M NH₃ in MeOH:Et₂O) afforded an oil. Treatment of the oil, in

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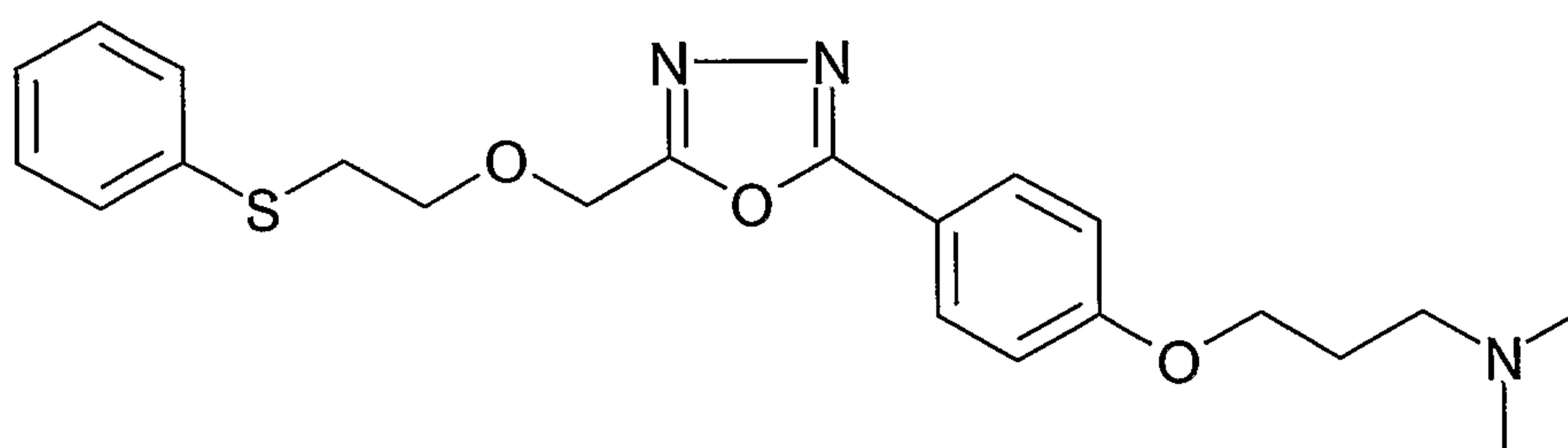
acetone, with oxalic acid afforded 0.214 g (61%) of dimethyl-[3(4-{5-[2-(2-phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenoxo)propyl]amine as the oxalate salt.

¹H NMR (DMSO-d₆) δ 7.87 (d, 2H, J=9Hz), 7.24-7.31 (m, 2H), 7.11 (d, 2H, J=9Hz), 6.89-6.96 (m, 3H), 4.05-4.15 (m, 4H), 3.13-3.18 (m, 2H), 2.75 (s, 6H), 2.01-2.20 (m, 3H), 1.78-1.90 (m, 2H), 1.54-1.68 (m, 1H), 1.28-1.34 (m, 1H), 1.15 (ddd, 1H, J=5,6,8Hz). IR (CHCl₃, cm⁻¹) 3000, 1777, 1655, 1615, 1501, 1302, 1250, 1224, 1175. MS (ES) m/e, 408. Anal. Calcd for C₂₄H₂₉N₃O₃: C, 62.77; H, 6.28, N, 8.45. Found C, 62.58; H, 6.28; N, 8.44. Mp(°C)=148.

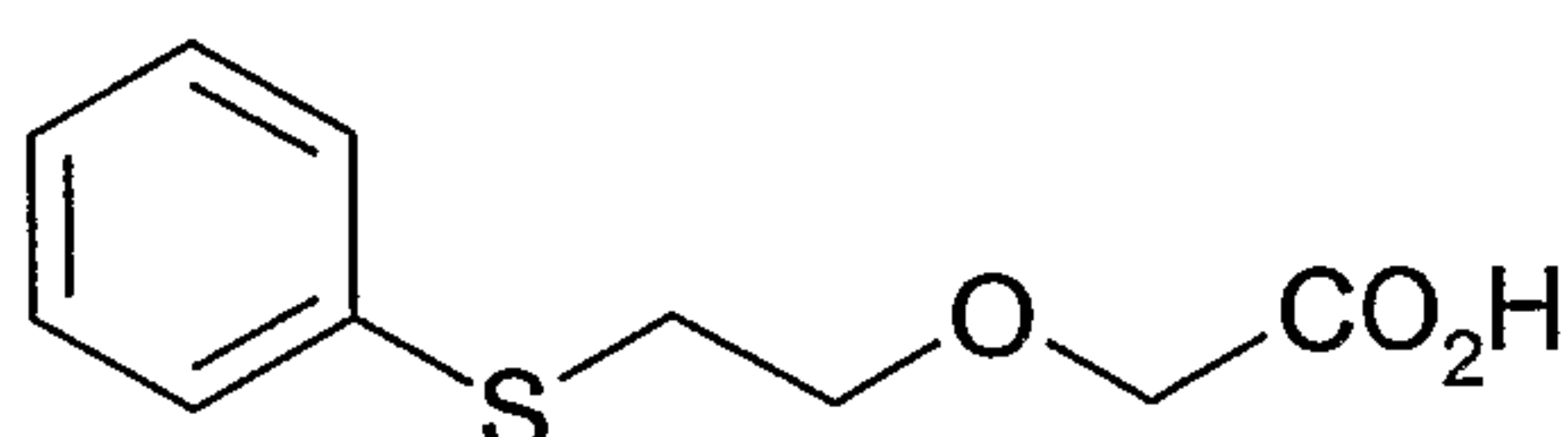
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Example 24

Dimethyl-(3-{4-[5-(2-phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from 2-(phenylthio)ethanol



15 a) (2-Phenylsulfanylethoxy)acetic acid



A suspension of sodium hydride (1.15 g, 28.9 mmol)(washed once with hexane) and 2-(phenylthio)ethanol (4.45 g, 28.9 mmol) in 104 mL DMF was stirred at room temperature for 30 minutes. Next, methyl bromoacetate (4.86 g, 31.7 mmol) was added and the stirring continued for 6.5 hours. The reaction was quenched with water then extracted twice with both hexane followed by EtOAc. The organic phases were combined, washed twice with water, once with brine, dried over sodium sulfate, filtered, concentrated to an oil. The oil was dissolved into 40 mL THF and 20 mL water then treated with lithium hydroxide (2.07 g, 86.6 mmol). The biphasic solution was heated with stirring at 60°C for 1 hour. Upon cooling to room temperature the reaction was quenched with 7.56 mL concentrated HCl. The reaction was extracted with EtOAc then the

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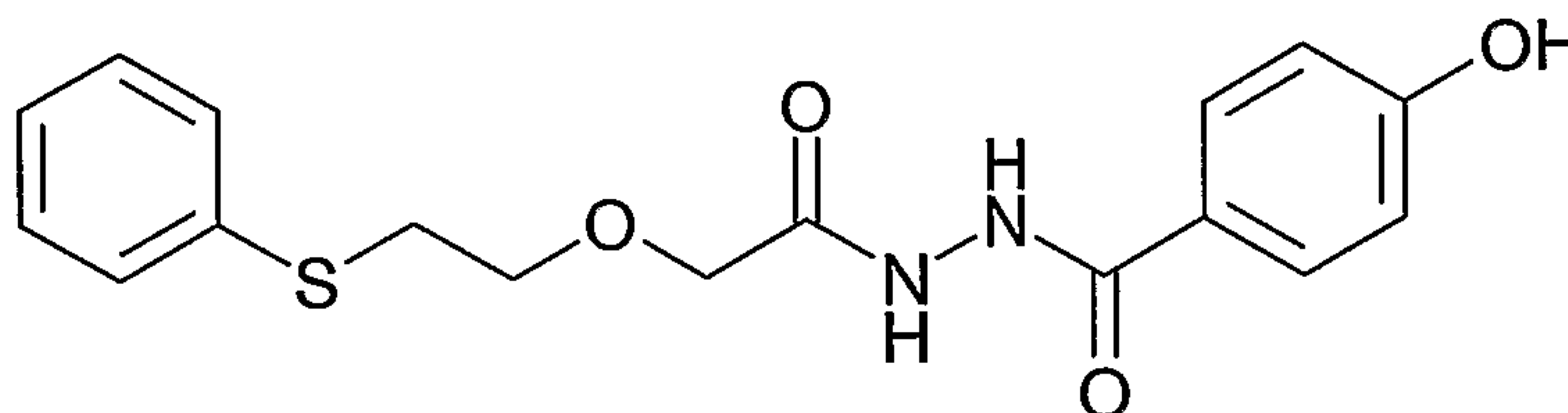
organic phase was washed twice with water, once with brine, dried over sodium sulfate, filtered, concentrated to afford an oil. Purification by chromatography on silica gel (elution with 10% MeOH containing 1% AcOH:CH₂Cl₂) afforded 0.903 g (15%) of (2-phenylsulfanylethoxy)acetic acid.

¹H NMR (DMSO-d₆) δ 7.29-7.36 (m, 4H), 7.16-7.24 (m, 1H), 3.77 (s, 2H), 3.63 (t, 2H, J=7Hz), 3.14 (t, 2H, J=7Hz).

IR (CHCl₃, cm⁻¹) 3051, 1603, 1481, 1440, 1428, 1409, 1116.

MS (ES) m/e, 211. Anal. Calcd for C₁₀H₁₂O₃S: C, 56.58; H, 5.70. Found C, 52.81; H, 5.54.

b) 4-Hydroxybenzoic acid N'-[2-(2-phenylsulfanylethoxy)]hydrazide

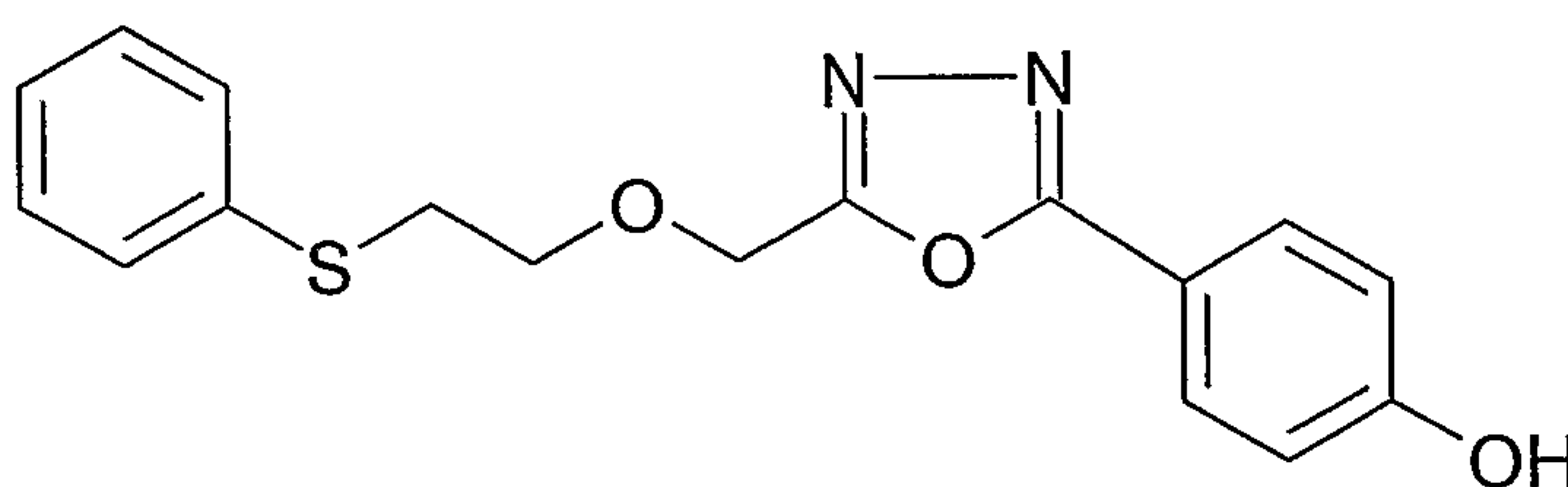


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (2-Phenylsulfanylethoxy)acetic acid (0.800 g, 3.8 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.932 g, 3.8 mmol) and 4-hydroxybenzoic hydrazide (0.573 g, 3.8 mmol) to afford the title compound as a crude mixture. Purification by HPLC on silica gel (elution with a linear gradient of 2 to 5% MeOH:CHCl₃) afforded 0.183 g (14%) of 4-hydroxybenzoic acid N'-[2-(2-phenylsulfanylethoxy)]hydrazide.

¹H NMR (DMSO-d₆) δ 10.07 (bs, 2H), 9.68 (bs, 1H), 7.74 (d, 2H, J=9Hz), 7.30-7.40 (m, 4H), 7.16-7.22 (m, 1H), 6.81 (d, 2H, J=8Hz), 4.04 (s, 2H), 3.71 (t, 2H, J=7Hz), 3.23 (t, 2H, J=7Hz). IR (KBr, cm⁻¹) 3209, 1692, 1640, 1608, 1507, 1439, 1281, 1236, 1173, 1127, 850, 742, 692. MS (ES) m/e, 347, 345. Anal. Calcd for C₁₇H₁₈N₂O₄S: C, 58.94; H, 5.24; N, 8.09. Found C, 58.52; H, 4.96; N, 8.01.

c) 4-[5-(2-Phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenol

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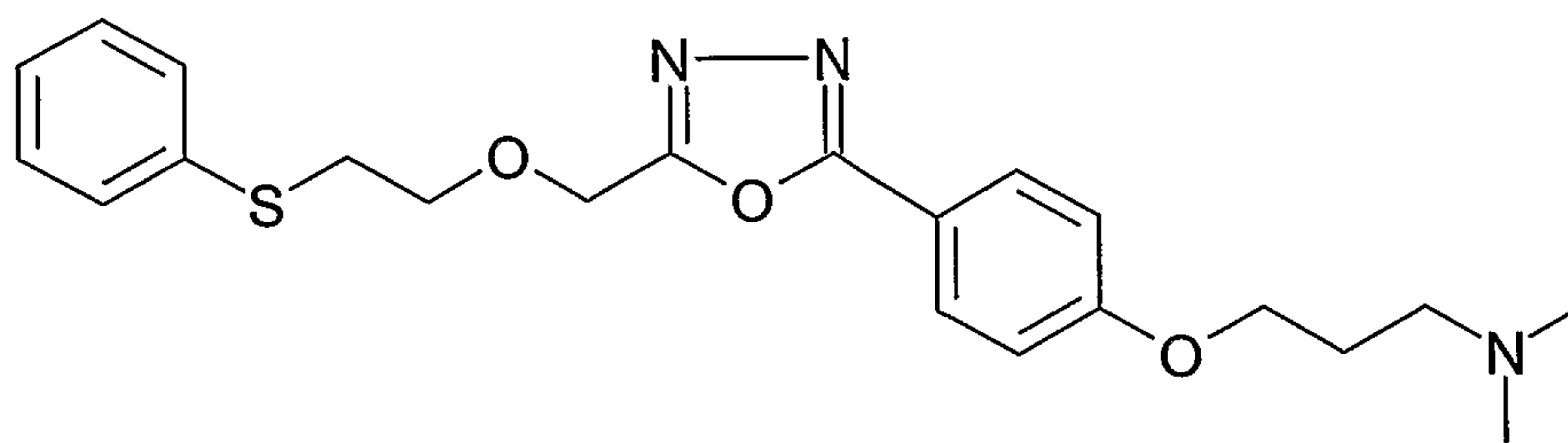


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-Hydroxybenzoic acid N'-[2-(2-phenylsulfanylethoxy)hydrazide (0.161 g, 0.7 mmol), triphenylphosphine (0.244 g, 0.9 mmol), triethyl amine (0.094 g, 0.9 mmol) and carbon tetrabromide (0.308 g, 0.9 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 75% EtOAc:hexane) afforded 0.135 g (88%) of 4-[5-(2-Phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenol.

¹H NMR (DMSO-d₆) δ 10.35 (bs, 1H), 7.82 (d, 2H, J=9Hz), 7.25-7.36 (m, 4H), 7.14-7.20 (m, 1H), 6.95 (d, 2H, J=9Hz), 4.78 (s, 2H), 3.73 (t, 2H, J=7Hz), 3.20 (t, 2H, J=7Hz).

IR (KBr, cm⁻¹) 3586, 3005, 1615, 1603, 1505, 1498, 1482, 1440, 1283, 1171, 1112, 1085, 843. MS (ES) m/e, 329, 327. Anal. Calcd for C₁₇H₁₆N₂O₃S: C, 62.18; H, 4.91; N, 8.53. Found C, 61.90; H, 4.88; N, 8.35.

d) Dimethyl-(3-{4-[5-(2-phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(2-phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.114 g 0.4 mmol), cesium carbonate (0.226 g, 0.7 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.055g, 0.4 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M NH₃ in MeOH:CHCl₃) followed by treatment of the isolated material with oxalic acid in

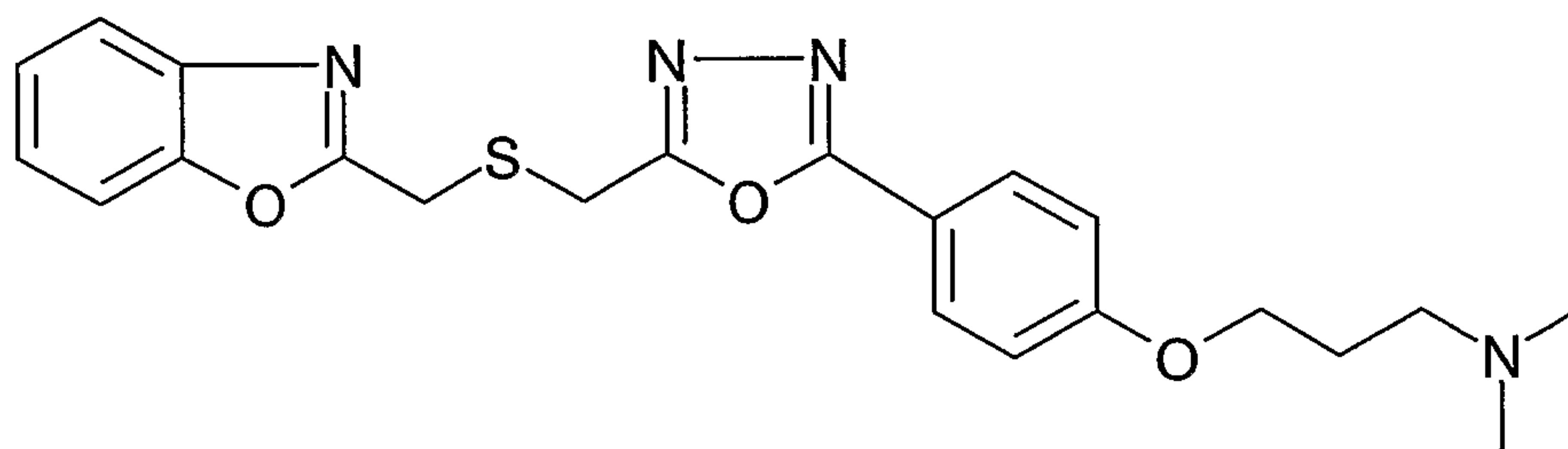
-128-

acetone afforded 0.130 g (74%) of Dimethyl-(3-{4-[5-(2-phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine as the oxalate salt.

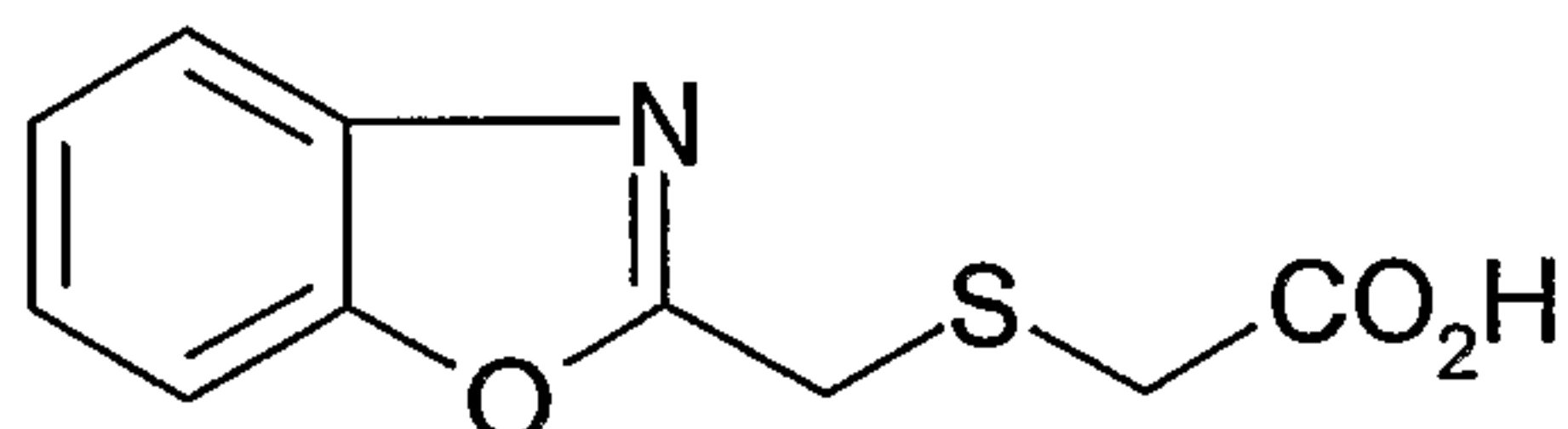
¹H NMR (DMSO-d₆) δ 7.93 (d, 2H, J=7Hz), 7.25-7.36 (m, 4H), 7.13-7.20 (m, 3H), 4.80 (s, 2H), 4.15 (t, 2H, J=6Hz), 3.74 (t, 2H, J=6Hz), 3.14-3.23 (m, 4H), 2.76 (s, 6H), 2.09-2.18 (m, 2H). IR (KBr, cm⁻¹) 3432, 3037, 2930, 2874, 1726, 1611, 1496, 1258, 1109, 742. MS (ES) m/e, 414. Anal. Calcd for C₂₂H₂₇N₃O₃S·C₂H₂O₄: C, 57.24; H, 5.80; N, 8.34. Found C, 57.14; H, 5.71; N, 8.27. Mp(°C)=143.

Example 25

10 Preparation of (3-{4-[5-(Benzooxazol-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine from 2-Chloromethylbenzoxazole



a) (Benzooxazol-2-ylmethylsulfanyl)acetic acid

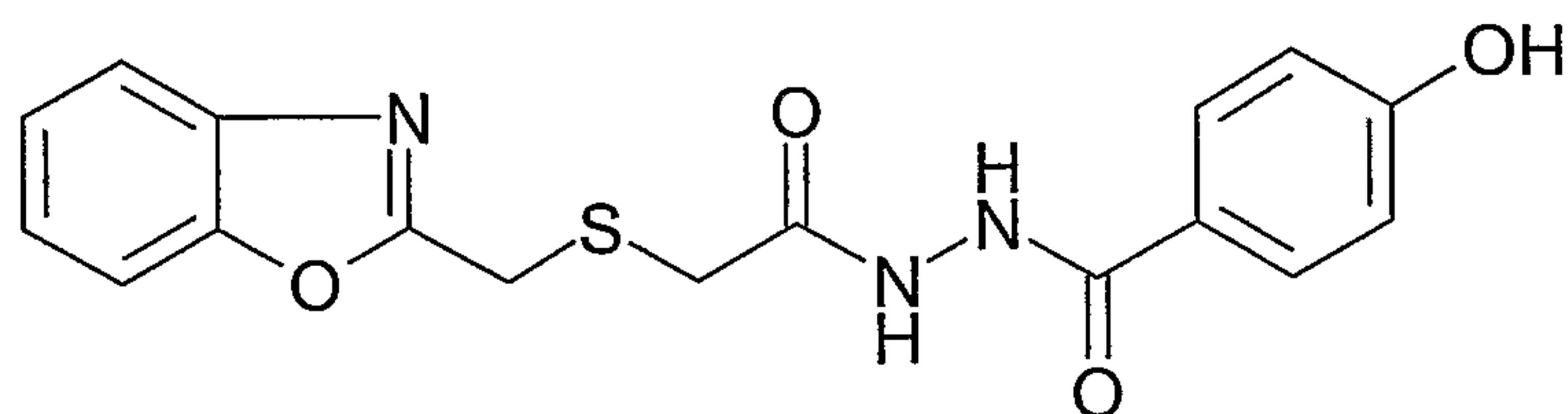


15 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from 2-Chloromethylbenzoxazole (1.57 g, 9.4 mmol), methylthio-glycolate (0.994 g, 9.4 mmol), and sodium hydride (0.375 g, 9.4 mmol) to afford the title compound as a crude mixture. Purification by crystallization with Et₂O afforded 1.12 g (54%) of (Benzo-oxazol-2-ylmethylsulfanyl)acetic acid.

20 ¹H NMR (DMSO-d₆) δ 12.71 (bs, 1H), 7.68-7.75 (m, 2H), 7.34-7.43 (m, 2H), 4.14 (s, 2H), 3.45 (s, 2H). IR (KBr, cm⁻¹) 2933, 2542, 1725, 1606, 1571, 1454, 1236, 1191, 1133, 840, 767. MS (ES) m/e, 224. Anal. Calcd for C₁₀H₉NO₃S: C, 53.80; H, 4.06; N, 6.27. Found C, 53.53; H, 4.02; N, 6.17.

25 b) 4-Hydroxybenzoic acid-*N*'-[2-benzooxazol-2-ylmethylsulfanyl]acetyl]hydrazide

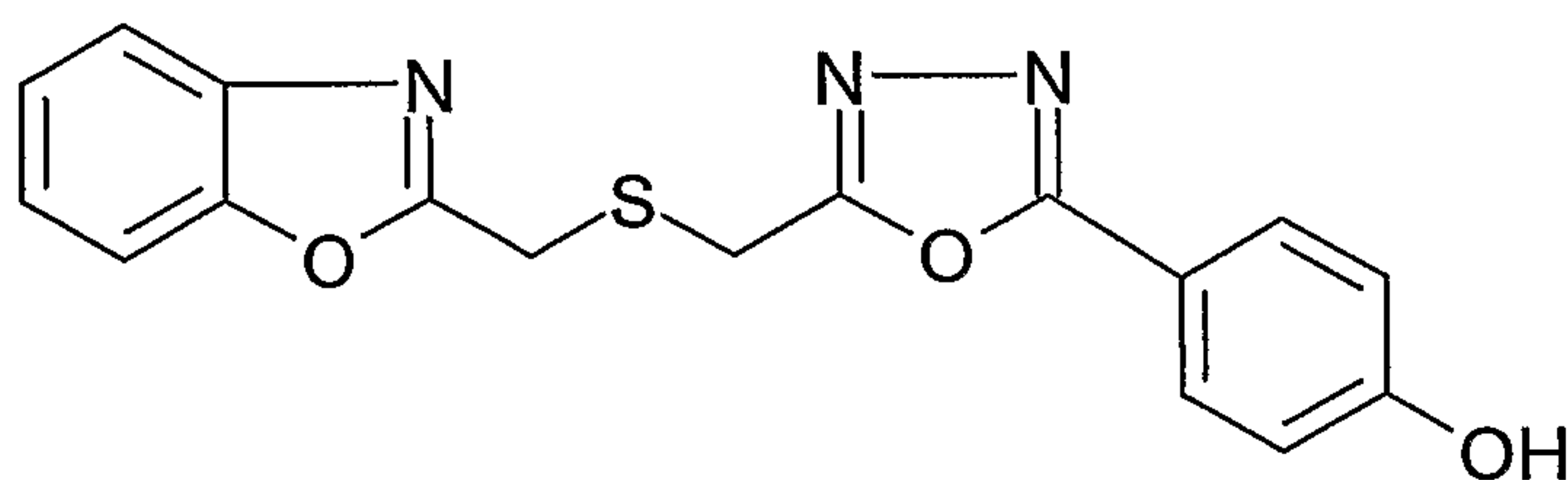
-129-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (benzooxazol-2-ylmethylsulfanyl)acetic acid (0.822 g, 3.7 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.911 g, 3.7 mmol) and 4-hydroxybenzoic hydrazide (0.560 g, 3.7 mmol) to afford the title compound as a crude material. Purification by HPLC on silica gel (elution with a linear gradient of 2 to 10% 2M NH₃ in MeOH:CHCl₃) afforded 0.190 g (14%) of 4-hydroxy benzoic acid-*N'*-[2-benzooxazol-2-ylmethylsulfanyl]acetyl] hydrazide as a white foam.

¹H NMR (DMSO-d₆) δ 10.27 (bs, 1H), 9.83 (bs, 1H), 9.38 (bs, 1H), 7.71-7.86 (m, 3H), 6.68-6.94 (m, 5H), 4.20 (s, 2H), 3.61 (s, 2H). IR (KBr, cm⁻¹) 3208, 1658, 1612, 1598, 1497, 1456, 1368, 1282, 1239, 1172, 843, 752. MS (ES) m/e, 358, 356. Anal. Calcd for C₁₇H₁₅N₃O₄S: C, 57.13; H, 4.23; N, 11.76. Found C, 56.82; H, 4.08; N, 11.71.

c) 4-[5-(Benzooxazol-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol



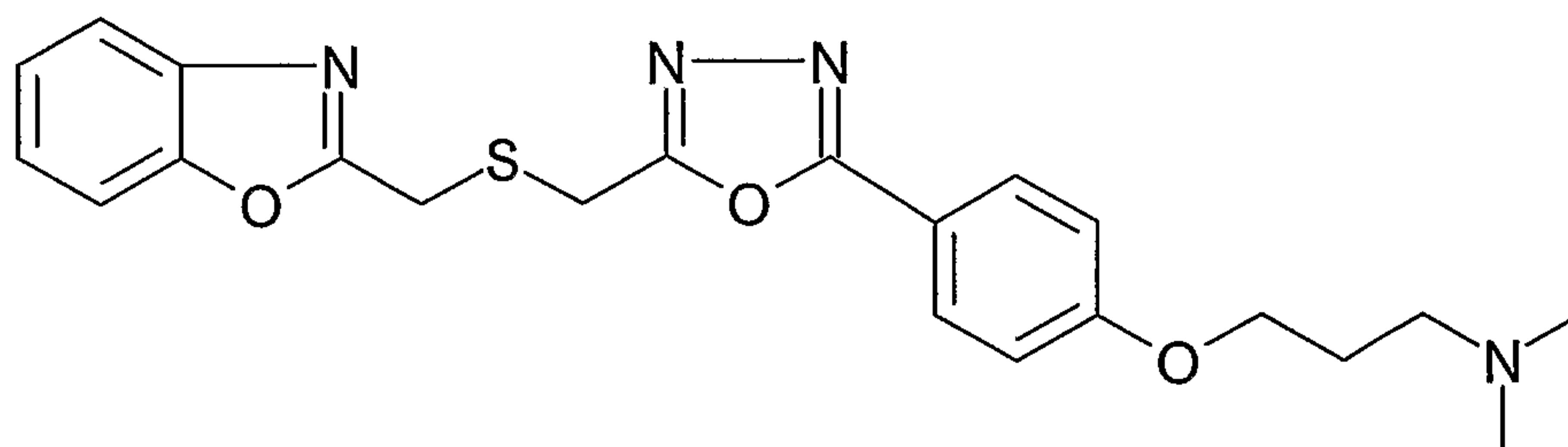
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N'*-[2-benzooxazol-2-ylmethylsulfanyl]acetyl]hydrazide (0.190 g, 0.5 mmol), triphenylphosphine (0.279 g, 1.1 mmol), triethyl amine (0.108 g, 1.1 mmol) and carbon tetrabromide (0.353 g, 1.1 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 50% EtOAc:hexane) afforded 0.150 g of 4-[5-(Benzooxazol-2-ylmethyl sulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenol along with triphenylphosphine as a contaminant.

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^1H NMR (DMSO- d_6) δ 10.29 (bs, 1H), 7.52 (m, 4H), 7.30-7.39 (m, 2H), 6.88-6.93 (m, 2H), 4.24 (d, 4H). IR (KBr, cm^{-1}) 3227, 1609, 1561, 1497, 1452. MS (ES) m/e , 340, 338. Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_3\text{S}$: C, 60.17; H, 3.86; N, 12.38. Found C, 63.51; H, 4.23; N, 9.32.

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d) (3-{4-[5-(Benzooxazol-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine



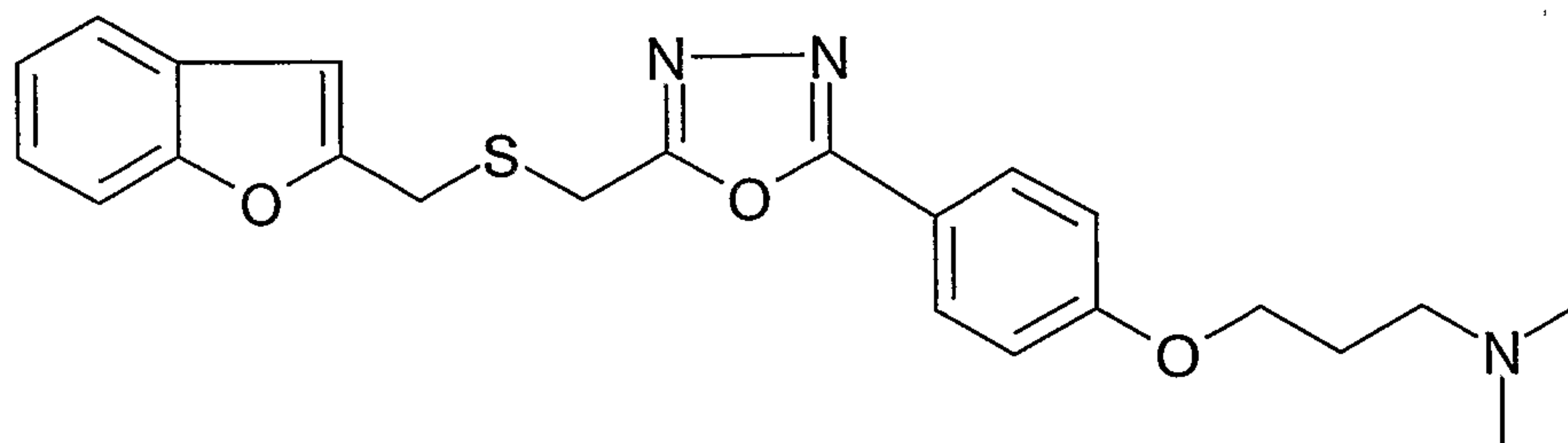
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(Benzooxazol-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.131 g, 0.4 mmol), cesium carbonate (0.252 g, 0.8 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.061g, 0.4 mmol) to afford the title compound as a crude material. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 in $\text{MeOH}:\text{CHCl}_3$) followed by treatment of the isolated material with oxalic acid in acetone afforded 0.026 g (13%) of (3-{4-[5-(Benzooxazol-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine as the oxalate salt.

^1H NMR (DMSO- d_6) δ 7.81 (d, 2H, $J=9\text{Hz}$), 7.60-7.64 (m, 2H), 7.29-7.38 (m, 2H), 7.10 (d, 2H, $J=9\text{Hz}$), 4.25 (d, 4H), 4.14 (t, 2H, $J=6\text{Hz}$), 3.15-3.20 (m, 2H), 2.77 (s, 6H), 2.08-2.17 (m, 2H). IR (KBr, cm^{-1}) 3007, 1777, 1656, 1614, 1500, 1455, 1302, 1254, 1176, 839. MS (ES) m/e , 425. Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_3\text{S}\cdot\text{C}_2\text{H}_2\text{O}_4$: C, 56.02; H, 5.09; N, 10.89. Found C, 55.28; H, 4.84; N, 10.74. $\text{Mp}(^{\circ}\text{C})=120$.

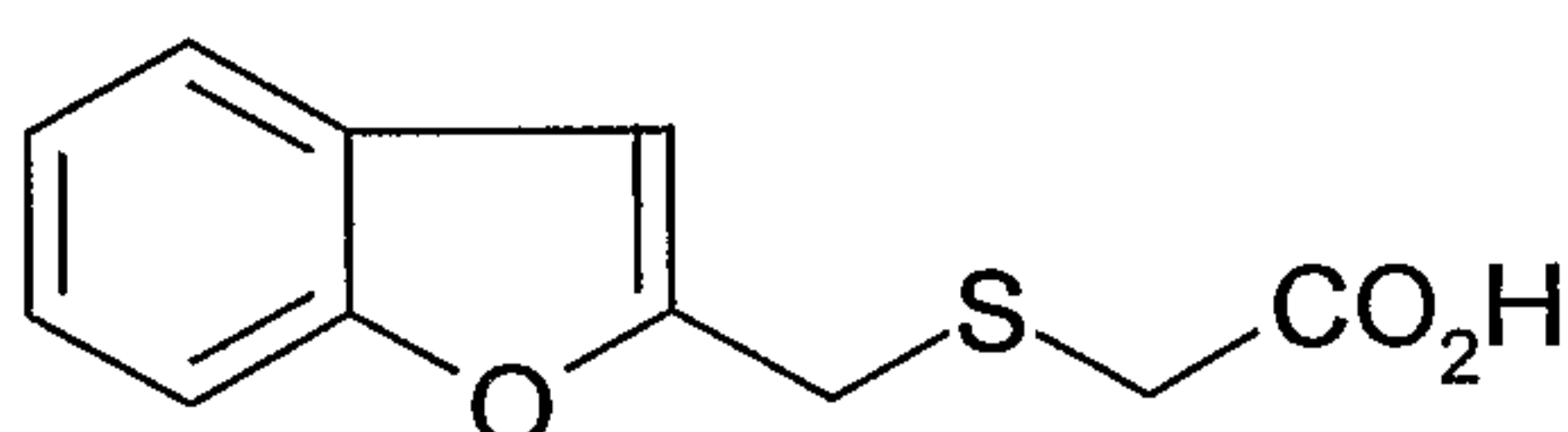
Example 26

Preparation of (3-{4-[5-Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine from 2-Bromomethylbenzofuran

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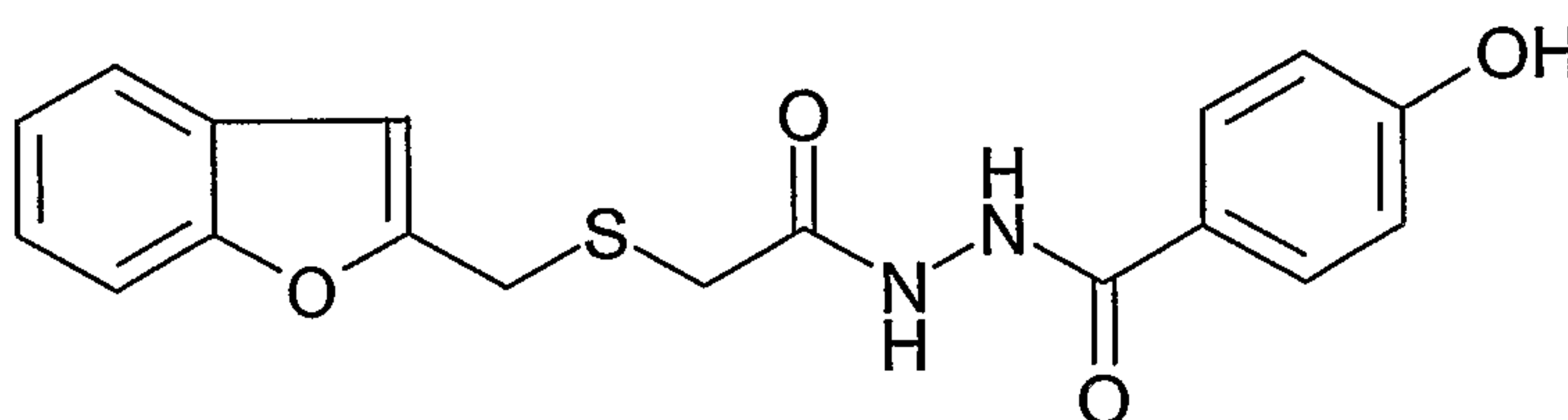


a) (Benzofuran-2-ylmethylsulfanyl)acetic acid



The above compound was prepared in a manner similar to that exemplified for the
 5 preparation of Example 17b, from 2-Bromomethylbenzofuran (3.34 g, 15.8 mmol),
 methylthioglycolate (2.02 g, 19.0 mmol), and sodium hydride (0.760 g, 19.0 mmol) to
 afford the title compound as a crude material. Purification by HPLC on silica gel (elution
 with a linear gradient of 2 to 10% MeOH:CHCl₃) afforded 1.46 g of (Benzofuran-2-
 ylmethylsulfanyl)acetic acid along with other coeluting impurities. Material was taken on
 10 to next step without further purification.

b) 4-Hydroxybenzoic acid-*N'*-[2-benzofuran-2-ylmethylsulfanyl)acetyl]hydrazide



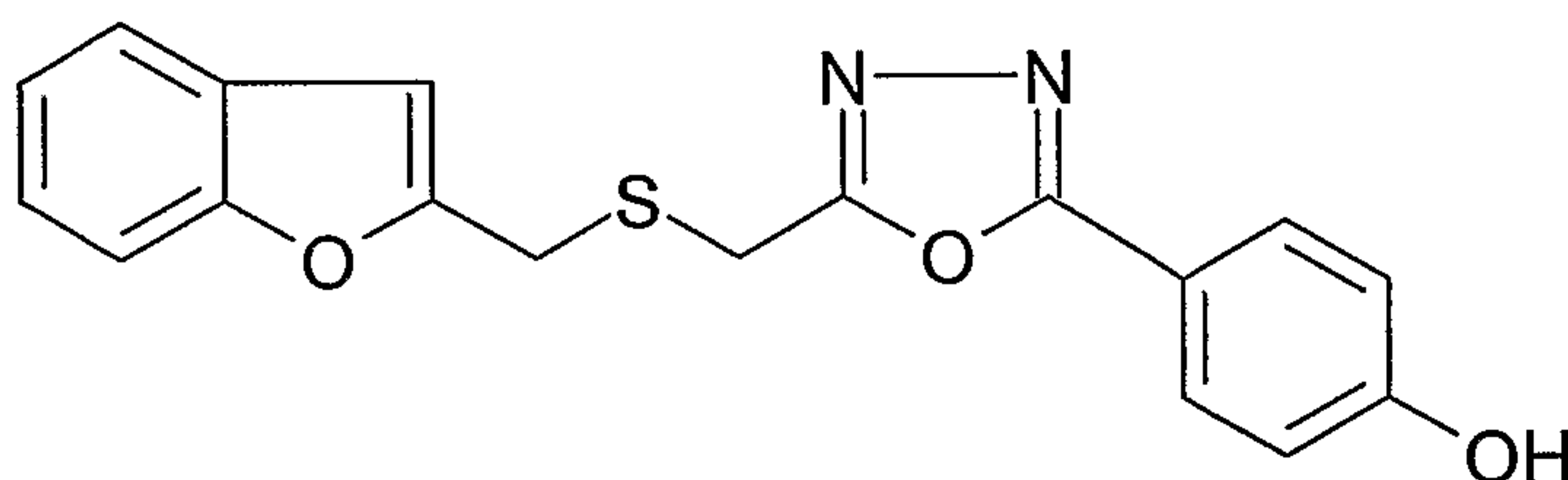
To a solution of benzofuran-2-ylmethylsulfanyl)acetic acid (1.46 g, 6.6 mmol) in
 15 100 mL THF stirring at room temperature was added 1,1'-carbonyldiimidazole (1.07 g,
 6.6 mmol). The reaction was heated at 60 °C for one hour. After cooling to room
 temperature, the mixture was treated with and 4-hydroxybenzoic hydrazide (1.50 g, 9.9
 mmol). After stirring for approximately 4 hours the reaction was concentrated to a solid
 material. The material was partitioned between EtOAc and 1N HCl. The phases were
 20 separated and the organic phase was washed twice with 1N HCl, brine, dried over sodium
 sulfate, filtered, concentrated to afford an oil. Treatment of the oil with CHCl₃ followed
 by sonication afforded 0.854 g (36%) of 4-Hydroxybenzoic acid-*N'*-[2-benzofuran-2-
 ylmethylsulfanyl)acetyl]hydrazide as a filterable solid.

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^1H NMR (DMSO- d_6) δ 10.02 (bs, 1H), 7.76 (d, 2H, $J=8\text{Hz}$), 7.53-7.61 (m, 2H), 7.20-7.31 (m, 2H), 6.83 (m, 3H), 4.09 (s, 2H), 3.27 (s, 2H). IR (KBr, cm^{-1}) 3296, 3211, 3007, 1687, 1625, 1584, 1515, 1452, 1281, 1173, 956, 745. MS (ES) m/e , 357, 355. Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$: C, 60.66; H, 4.53; N, 7.86. Found C, 58.53; H, 4.43; N, 7.93.

5

c) 4-[5-(benzofuran-2-ylmethylsulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol

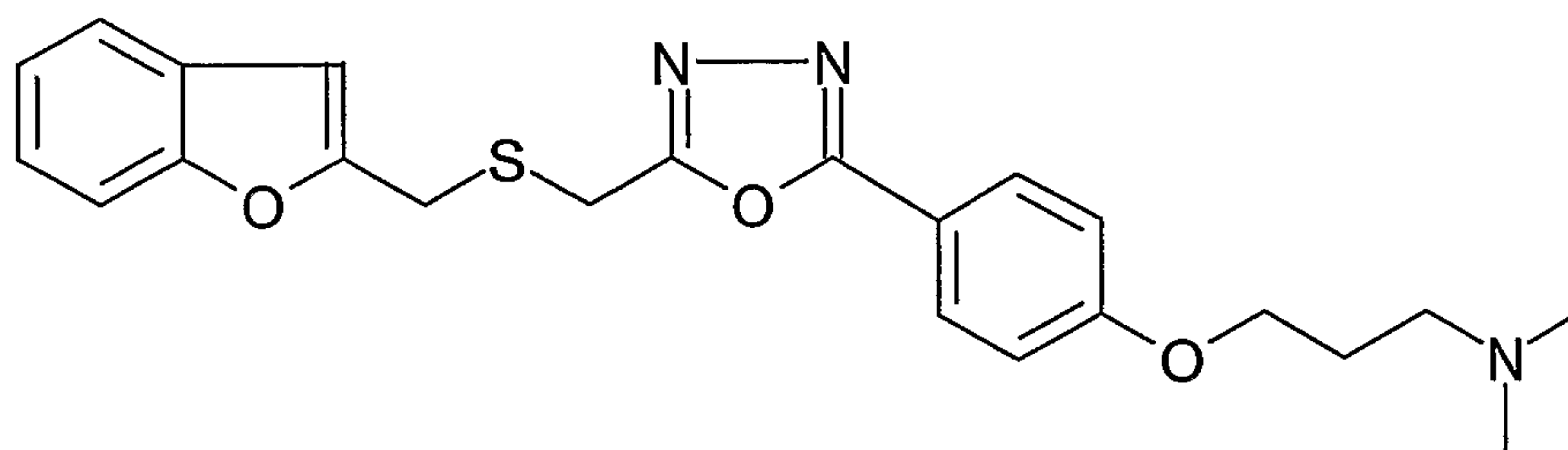


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid- N' -[2-benzofuran-2-ylmethylsulfanyl]acetyl]hydrazide (0.753 g, 2.1 mmol), triphenylphosphine (0.665g, 2.5 mmol), triethyl amine (0.256 g, 2.5 mmol) and carbon tetrabromide (0.841 g, 2.5 mmol) to afford the title compound as a crude material. Purification by radial chromatography on silica gel (elution with 75% EtOAc:hexane) afforded 0.550 g (77%) of 4-[5-(benzofuran-2-ylmethyl sulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol as an oil that slowly crystallized out.

^1H NMR (DMSO- d_6) δ 10.29 (s, 1H), 7.72 (d, 2H, $J=8\text{Hz}$), 7.46-7.57 (m, 2H), 7.17-7.28 (m, 2H), 6.79 (s, 1H), 6.79 (s, 1H), 4.10 (s, 2H), 4.08 (s, 2H). IR (KBr, cm^{-1}) 3429, 3053, 2936, 1611, 1595, 1575, 1452, 1293, 1176, 1097, 953, 844, 757. MS (ES) m/e , 339, 337. Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$: C, 63.89; H, 4.17; N, 8.28. Found C, 63.05; H, 4.34; N, 7.26.

20

d) (3-{4-[5-Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine



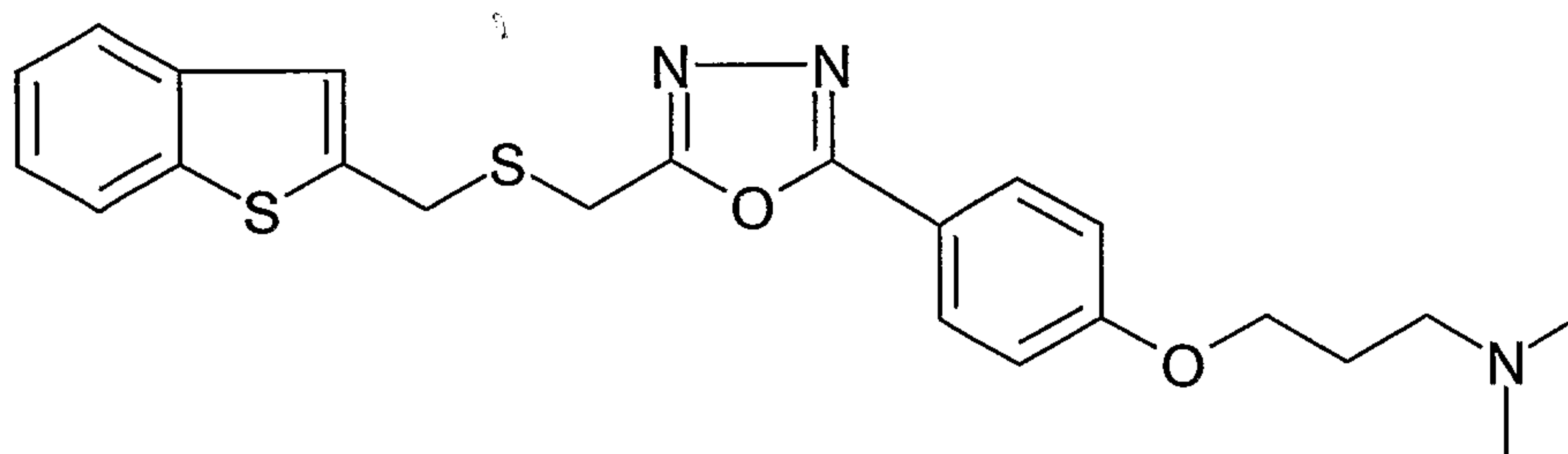
-133-

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(benzofuran-2-ylmethylsulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol (0.510 g, 1.5 mmol), cesium carbonate (0.982 g, 3.0 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.238g, 1.5 mmol) to afford the title compound as a crude material. Purification by radial chromatography on silica gel (elution with 10% 2M NH₃ in MeOH:CHCl₃) followed by treatment of the isolated material with oxalic acid in acetone afforded 0.364 g (47%) of (3-{4-[5-Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine as the oxalate salt.

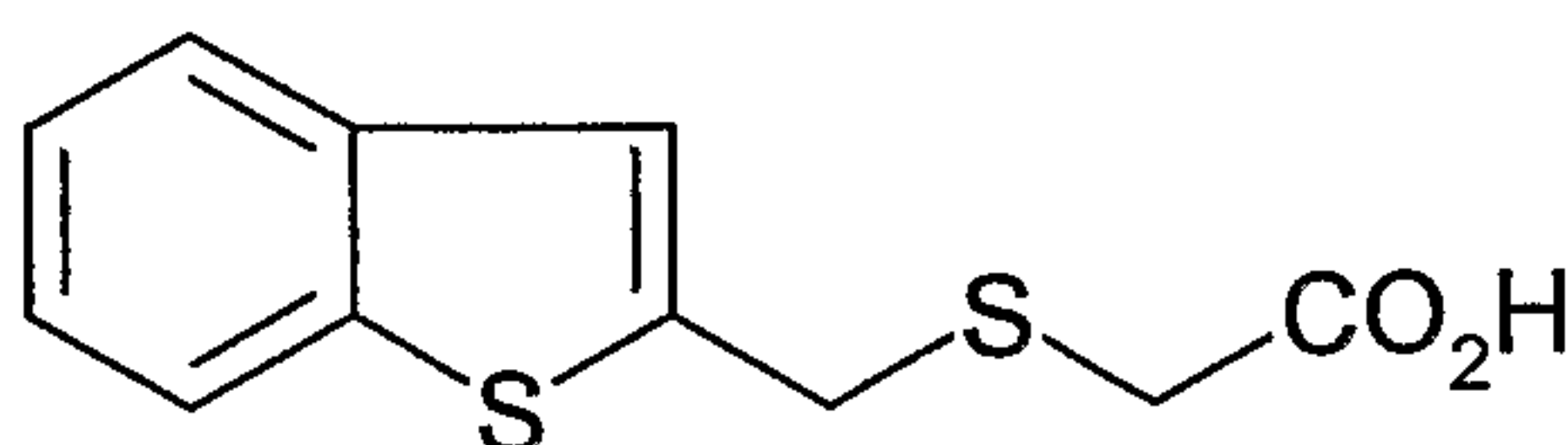
¹H NMR (DMSO-d₆) δ 7.83 (d, 2H, J=9Hz), 7.45-7.56 (m, 2H), 7.17-7.27 (m, 2H), 7.10 (d, 2H, J=9Hz), 6.79 (s, 1H), 4.09-4.16 (m, 6H), 3.15-3.20 (m, 2H), 2.77 (s, 6H), 2.09-2.18 (m, 2H). IR (KBr, cm⁻¹) 1615, 1500, 1255, 1175, 949, 754, 707. MS (ES) m/e, 424. Anal. Calcd for C₂₃H₂₅N₃O₃S·C₂H₂O₄: C, 58.47; H, 5.30; N, 8.18. Found C, 58.08; H, 5.22; N, 8.08. Mp(°C)=144.

Example 27

Preparation of (3-{4-[5-Benzo[*b*]thiophene-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine from 2-bromomethylbenzo[*b*]thiophene



a) (Benzo[*b*]thiophene-2-ylmethylsulfanyl)acetic acid



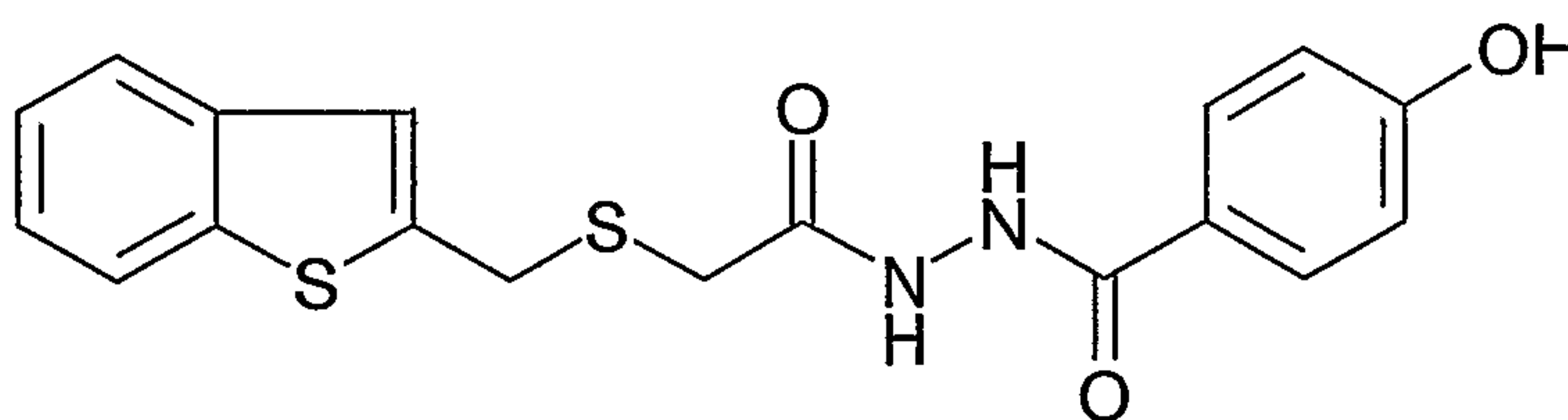
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from 2-bromomethylbenzo[*b*]thiophene (2.21 g, 9.7 mmol), methylthioglycolate (1.03 g, 9.7 mmol), and sodium hydride (0.389 g, 9.7 mmol) to afford the title compound as a crude mixture. Purification by HPLC on silica gel (elution with a linear gradient of 2 to 10% MeOH:CHCl₃) followed by crystallization of the isolated

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material from Et₂O:hexane afforded 1.16 g (50%) of (benzo[*b*]thiophene-2-ylmethylsulfanyl)acetic acid.

¹H NMR (DMSO-d₆) δ 12.65 (bs, 1H), 7.89-7.92 (m, 1H), 7.76-7.80 (m, 1H), 7.29-7.38 (m, 3H), 4.16 (s, 2H), 3.24 (s, 2H). IR (CHCl₃, cm⁻¹) 3010, 2917, 2673, 2568, 1710, 1458, 1436, 1297, 1132. MS (ES) m/e, 237. Anal. Calcd for C₁₁H₁₀O₂S₂: C, 55.44; H, 4.23. Found C, 55.41; H, 4.13.

b) 4-Hydroxybenzoic acid-*N'*-[2-benzo[*b*]thiophen-2-ylmethylsulfanyl]acetyl]hydrazide



10

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (benzo[*b*]thiophene-2-ylmethylsulfanyl)acetic acid (1.00 g, 4.2 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.04 g, 4.2 mmol) and 4-hydroxybenzoic hydrazide (0.638 g, 4.2 mmol) to afford the title compound. The resultant crystals that had formed upon concentration of the crude material were collected by filtration to afford 0.982 g (63%) of 4-Hydroxybenzoic acid-*N'*-[2-benzo[*b*]thiophen-2-ylmethylsulfanyl]acetyl]hydrazide.

¹H NMR (DMSO-d₆) δ 10.17 (bs, 1H), 10.09 (bs, 1H), 9.99 (bs, 1H), 7.89-7.93 (m, 1H), 7.75-7.79 (m, 3H), 7.22-7.38 (m, 3H), 6.82 (d, 2H, J=9Hz), 4.24 (s, 2H), 3.24 (s, 2H).

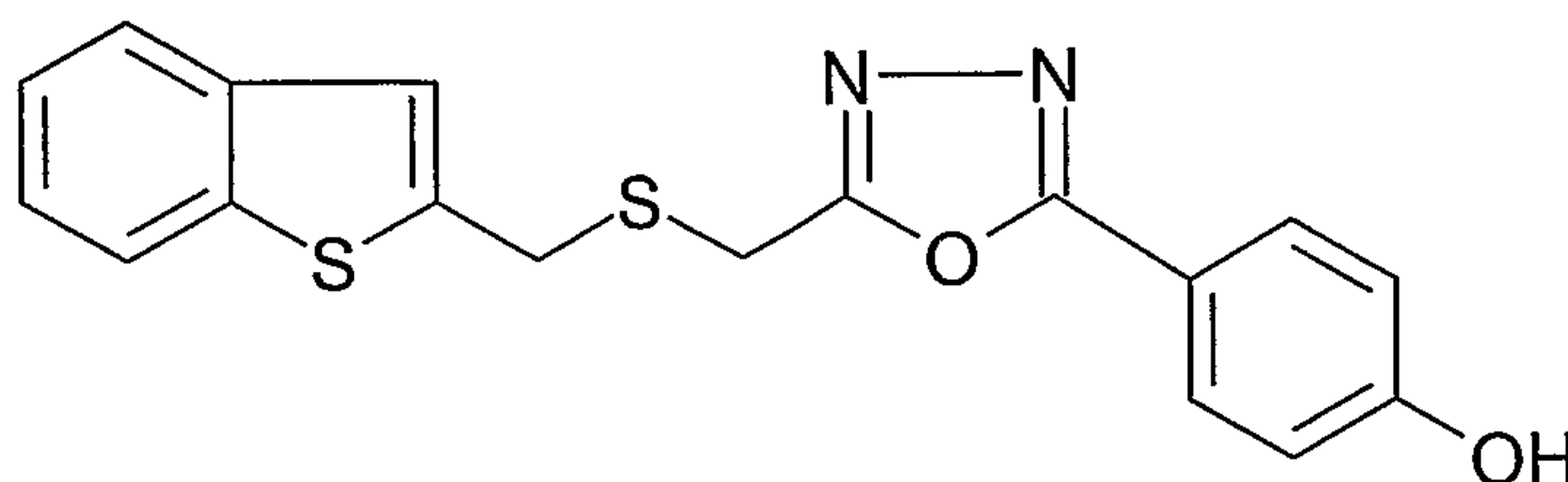
20

IR (KBr, cm⁻¹) 3311, 3200, 3004, 1685, 1624, 1610, 1585, 1547, 1518, 1495, 1331, 1285, 1234, 1175, 1109, 747. MS (ES) m/e, 373. Anal. Calcd for C₁₈H₁₈N₂O₃S₂: C, 57.73; H, 4.84; N, 7.48. Found C, 57.95; H, 4.09; N, 7.29.

c) 4-[5-(benzo[*b*]thiophene-2-ylmethylsulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol

25

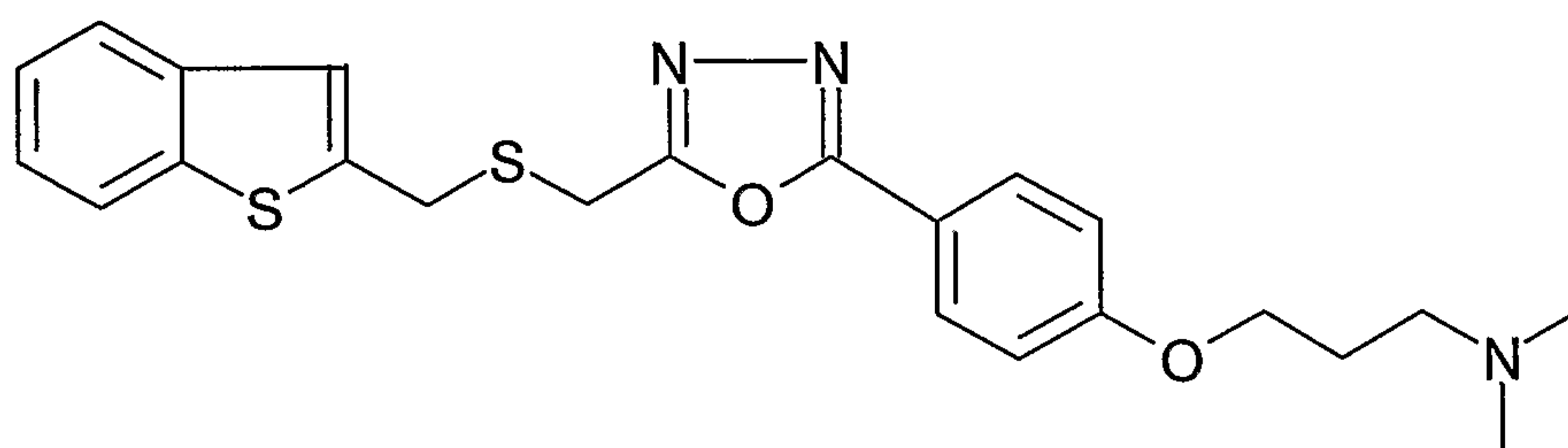
-135-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N'*-[2-benzo[*b*]thiophen-2-ylmethylsulfanyl]acetylhydrazide (0.611 g, 1.6 mmol), triphenylphosphine (0.860g, 3.3 mmol), triethyl amine (0.332 g, 3.3 mmol) and carbon tetrabromide (1.09 g, 3.3 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 50% EtOAc:hexane) followed by the filtration of the resultant crystals in the eluent afforded 0.208 g (36%) of 4-[5-(benzo[*b*]thiophene-2-ylmethylsulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol.

¹H NMR (DMSO-*d*₆) δ 10.29 (s, 1H), 7.87-7.90 (m, 1H), 7.72-7.78 (m, 3H), 7.28-7.37 (m, 3H), 6.92 (d, 2H, *J*=9Hz), 4.22 (s, 2H), 4.04 (s, 2H). IR (KBr, cm⁻¹) 3160, 2982, 2932, 1609, 1599, 1565, 1498, 1457, 1282, 1221, 1175, 742. MS (ES) *m/e*, 355. Anal. Calcd for C₁₈H₁₆N₂O₃S₂: C, 60.65; H, 4.52; N, 7.86. Found C, 61.72; H, 4.26; N, 7.31.

d) (3-{4-[5-Benzo[*b*]thiophene-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(benzo[*b*]thiophene-2-ylmethylsulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol (0.178 g, 0.5 mmol), cesium carbonate (0.325 g, 1.0 mmol) and 3-chloro-*N,N*-dimethylpropyl amine hydrochloride (0.079g, 0.5 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M NH₃ in MeOH:CHCl₃) followed by crystallization of the isolated

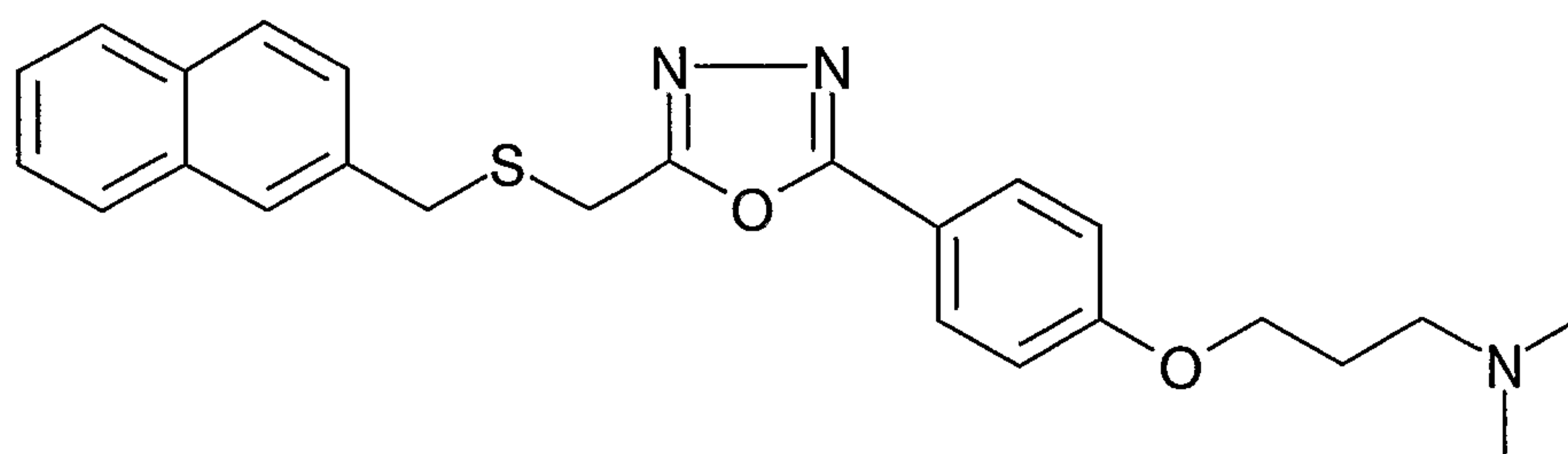
-136-

material from Et₂O afforded 0.115 g (52%) of (3-{4-[5-benzo[*b*]thiophene-2-ylmethylsulfanylmethyl]-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)dimethylamine.

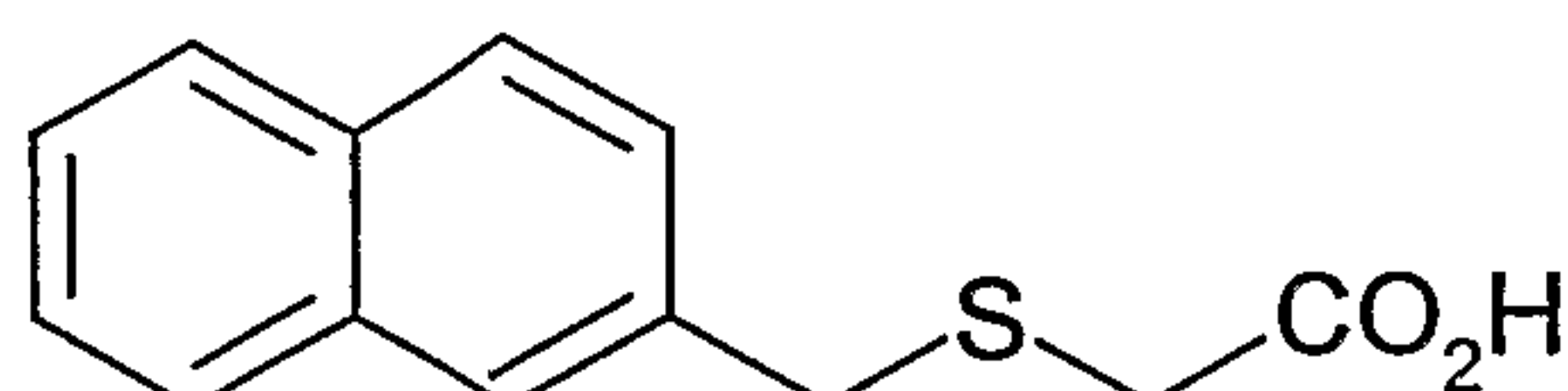
¹H NMR (DMSO-*d*₆) δ 7.74-7.89 (m, 4H), 7.27-7.36 (m, 3H), 7.08 (d, 2H, J=9Hz), 4.23 (s, 2H), 4.05-4.11 (m, 4H), 2.36 (t, 2H, J=7Hz), 2.15 (s, 6H), 1.88 (m, 2H).
 5 IR (KBr, cm⁻¹) 3432, 2940, 2814, 2761, 1587, 1616, 1563, 1500, 1469, 1428, 1305, 1256, 1177, 1153, 1088, 1051, 821, 740, 728. MS (ES) *m/e*, 438. Anal. Calcd for C₂₃H₂₅N₃O₃S₂: C, 62.15; H, 5.62; N, 9.24. Found C, 62.84; H, 5.73; N, 9.56. Mp(°C)=93.

Example 28

10 Preparation of Dimethyl-(3-{4-[5(naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from 2-Bromomethylnaphthalene



a) (Naphthalen-2-ylmethylsulfanyl)acetic acid



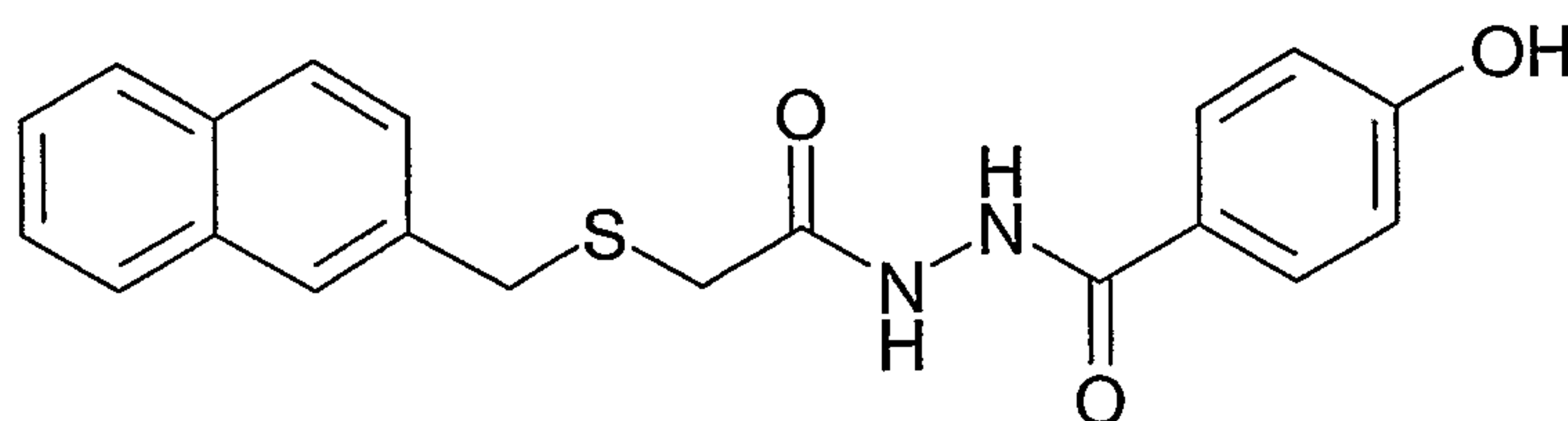
15 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from 2-bromomethylnaphthalene (1.86 g, 8.4 mmol), methylthioglycolate (0.982 g, 9.3 mmol), and sodium hydride (0.370 g, 9.3 mmol) to afford the title compound as a crude mixture. Crystallization from Et₂O afforded 1.01 g (52%) of (Naphthalen-2-ylmethylsulfanyl)acetic acid.

20 ¹H NMR (DMSO-*d*₆) δ 12.60 (bs, 1H), 7.86-7.91 (m, 3H), 7.78 (s, 1H), 7.46-7.54 (m, 3H), 3.98 (s, 2H), 3.13 (s, 2H).

IR (CHCl₃, cm⁻¹) 3059, 3019, 3010, 1709, 1601, 1510, 1422, 1295, 1230, 1126, 820. MS (ES) *m/e*, 231. Anal. Calcd for C₁₃H₁₂O₂S: C, 67.22; H, 5.21. Found C, 73.11; H, 4.83.

25 b) 4-Hydroxybenzoic acid-*N*'-[2-(naphthalen-2-ylmethylsulfanyl)acetyl]hydrazide

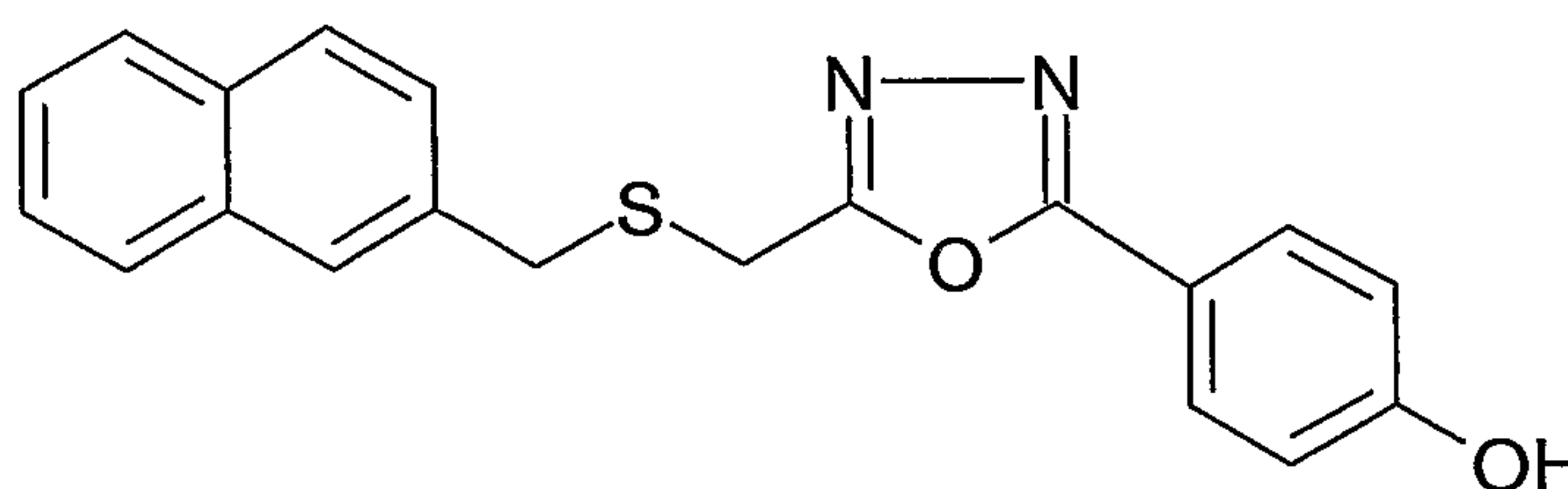
-137-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (Naphthalen-2-ylmethylsulfanyl)acetic acid (1.00 g, 4.3 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.06 g, 4.3 mmol) and 4-hydroxybenzoic hydrazide (0.655 g, 4.3 mmol) to afford the title compound. The resultant crystals that had formed upon concentration of the crude material were collected by filtration to afford 0.761 g (48%) of 4-hydroxybenzoic acid-*N'*-[2-(naphthalen-2-ylmethylsulfanyl)acetyl]hydrazide

¹H NMR (DMSO-d₆) δ 10.18 (bs, 1H), 10.09 (bs, 1H), 9.99 (bs, 1H), 7.83-7.97 (m, 4H), 7.77 (d, 2H, J=9Hz), 7.45-7.55 (m, 3H), 6.83 (d, 2H, J=9Hz), 4.06 (s, 2H), 3.15 (s, 2H). IR (KBr, cm⁻¹) 3206, 3055, 3005, 1688, 1622, 1610, 1584, 1549, 1517, 1495, 1289, 1234, 1173, 750. MS (ES) m/e, 367, 365. Anal. Calcd for C₂₀H₁₈N₂O₃S: C, 65.56; H, 4.95; N, 7.64. Found C, 65.74; H, 4.69; N, 7.58.

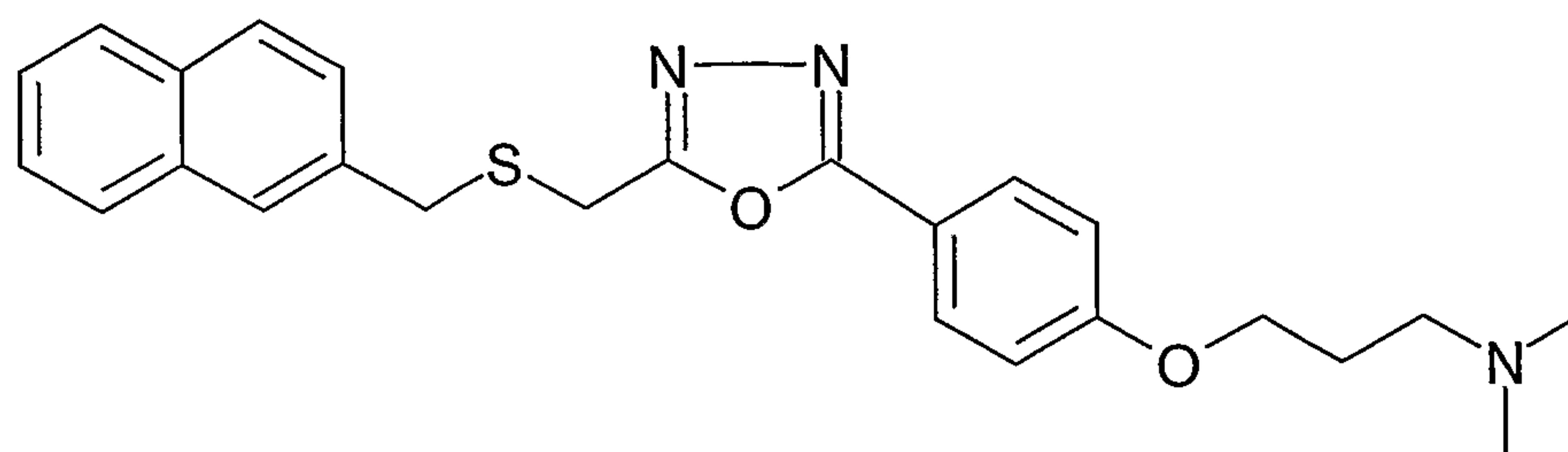
c) 4-[5-(Naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N'*-[2-(naphthalen-2-ylmethylsulfanyl)acetyl]hydrazide (0.562 g, 1.5 mmol), triphenylphosphine (0.805g, 3.1 mmol), triethyl amine (0.310 g, 3.1 mmol) and carbon tetrabromide (1.02 g, 3.1 mmol) to afford the title compound as a crude mixture. Attempts to purify material by silica gel radial chromatography failed. Material taken on to next step without further purification.

d) Dimethyl-(3-{4-[5(naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine

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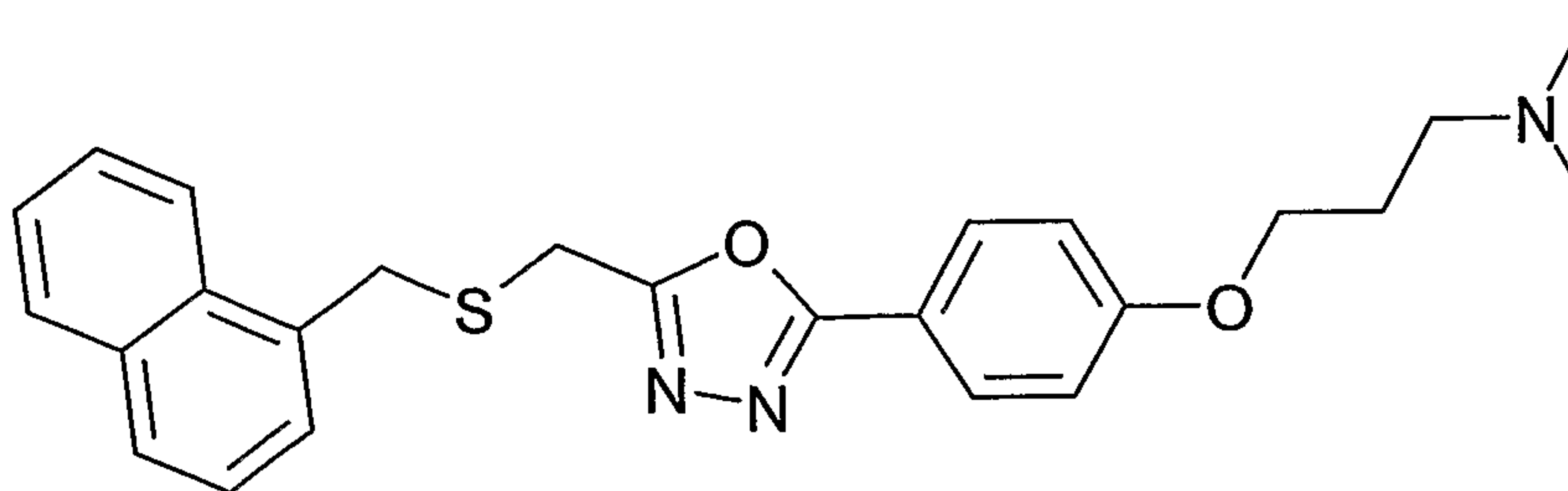
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(Naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.534 g, 1.5 mmol), cesium carbonate (0.999 g, 3.1 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.242g, 1.5 mmol) to afford the title compound. Purification by radial chromatography on silica gel (elution with 10% 2M NH₃ in MeOH:CHCl₃) afforded 0.155 g of the title compound as a solid. This material was dissolved into Et₂O then treated with a solution of EtOH that was treated with acetyl chloride (0.030 mL, 0.43 mmol). The resultant precipitate was collected by filtration to afford 0.103 g (16%) of dimethyl-(3-{4-[5(naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine as the hydrochloride salt.

¹H NMR (DMSO-d₆) δ 7.89-7.82 (m, 6H), 7.46-7.53 (m, 3H), 7.11 (d, 2H, J=9Hz), 4.16 (t, 2H, J=6Hz), 4.05 (s, 2H), 3.99 (s, 2H), 3.21 (m, 2H), 2.78 (s, 6H), 2.13-2.22 (m, 2H). IR (KBr, cm⁻¹) 3428, 3015, 2956, 2605, 2482, 1613, 1567, 1498, 1486, 1473, 1473, 1428, 1392, 1309, 1260, 1243, 1182, 1088, 1055, 941, 832, 752, 734. MS (ES) m/e, 434. Anal. Calcd for C₂₅H₂₇N₃O₂S·HCl: C, 63.88; H, 6.00; N, 8.94. Found C, 63.05; H, 5.88; N, 8.65. Analytical HPLC: 100% Purity. Mp(°C)=194.

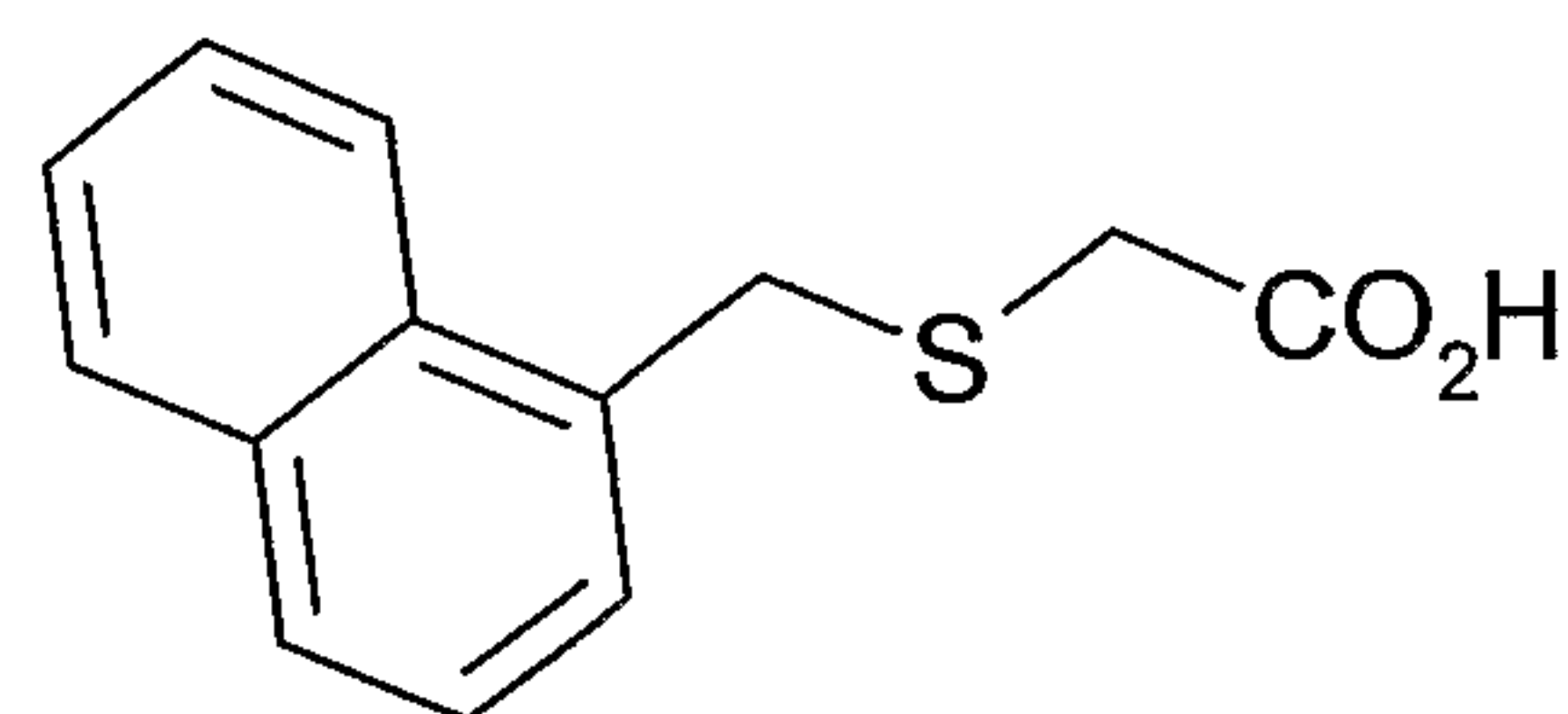
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Example 29

Preparation of Dimethyl-(3-{4-[5(naphthalen-1-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from 1-bromomethylnaphthalene.



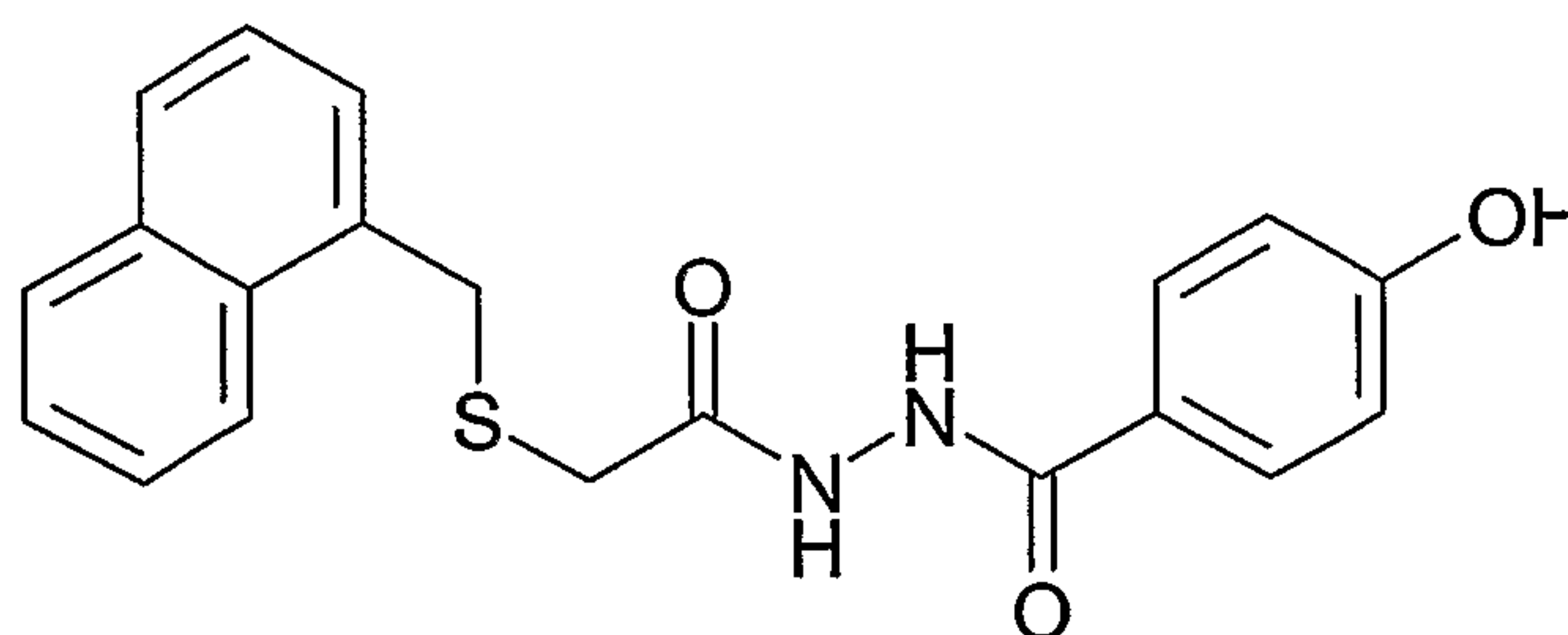
-139-



a) (Naphthalen-2-ylmethylsulfanyl)acetic acid

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from 1-bromomethylnaphthalene (10.71 g, 48.4 mmol), methylthio glycolate (3.57 g, 38.3 mmol), and sodium hydride (3.10 g, 77.5 mmol) to afford the title compound as a crude mixture. Purification by flash filtration chromatography on silica gel (elution with 3 x 500 mL CH₂Cl₂, 3 x 500 mL 10% MeOH:CH₂Cl₂) afforded 6.76 g (75%) of (naphthalen-1-yl- methylsulfanyl)acetic acid.

¹H NMR (DMSO-d₆) δ 12.68 (bs, 1H), 8.16-8.20 (m, 1H), 7.90-7.97 (m, 1H), 7.83-7.88 (m, 1H), 7.50-7.60 (m, 2H), 7.41-7.48 (m, 2H), 4.30 (s, 2H), 3.20 (s, 2H). IR (KBr, cm⁻¹) 3065, 3050, 3001, 2928, 1709, 1597, 1512, 1426, 1399, 1295, 802. MS (EI) m/e, 232

b) 4-Hydroxybenzoic acid-*N'*-[2-(naphthalen2-ylmethylsulfanyl)acetyl]hydrazide

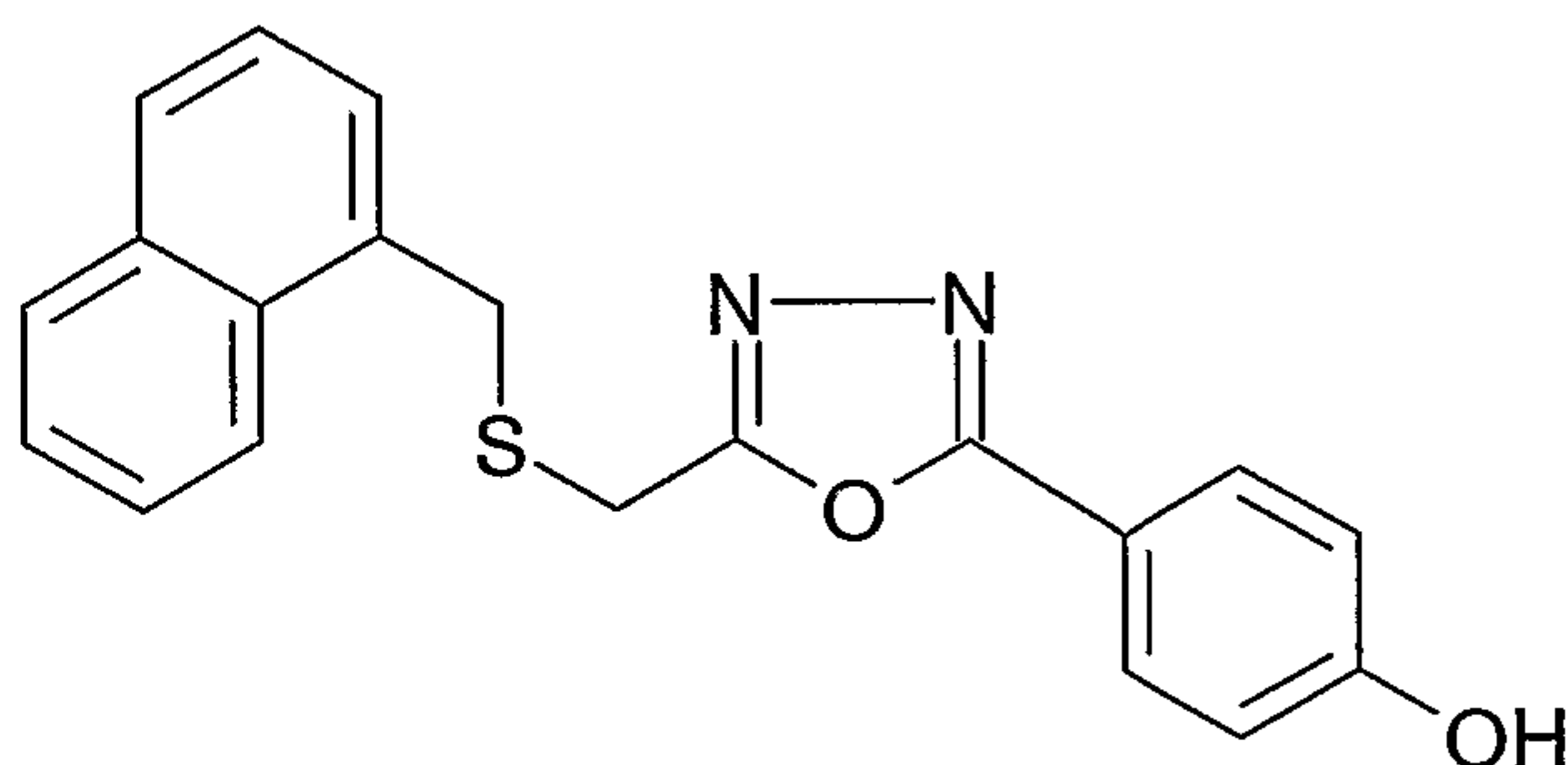
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (Naphthalen-1-ylmethylsulfanyl)acetic acid (1.77 g, 7.6 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.89 g, 7.6 mmol) and 4-hydroxybenzoic hydrazide (1.16 g, 7.6 mmol) to afford the title compound as a crude mixture. Crystallization from MeOH:Et₂O afforded 1.57 g (56%) of 4-hydroxybenzoic acid-*N'*-[2-(naphthalen-1-ylmethylsulfanyl) acetyl]hydrazide.

¹H NMR (DMSO-d₆) δ 10.24-10.04 (m, 3H), 8.22 (d, 1H, J=8Hz), 7.94 (d, 1H, J=8Hz), 7.85 (d, 1H, J=8Hz), 7.78 (d, 2H, J=9Hz), 7.43-7.61 (m, 4H), 6.83 (d, 2H, J=9Hz), 4.40 (s, 2H), 3.22 (s, 2H). IR (KBr, cm⁻¹) 3364, 3173, 3017, 1693, 1654, 1610,

-140-

1571, 1511, 1495, 1294, 1285, 1237, 1175, 778. MS (ES) m/e, 367, 365. Anal. Calcd for $C_{20}H_{18}N_3O_3S$: C, 65.56; H, 4.95; N, 7.64. Found C, 63.99; H, 4.74; N, 7.33.

c) 4-[5-(Naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol



5

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, using 4-hydroxybenzoic acid-*N'*-[2-(naphthalen-1-ylmethylsulfanyl)acetyl]hydrazide (0.898 g, 2.5 mmol), triphenylphosphine (1.93g, 7.4 mmol), triethyl amine (0.744 g, 7.4 mmol) and carbon tetrabromide (2.44 g, 7.4 mmol) to afford the title compound. Purification by silica gel flash filtration (elution with 50% Et₂O:hexane followed by Et₂O) afforded 0.420 g (49%) of 4-[5-(Naphthalen-1-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol as a white solid.

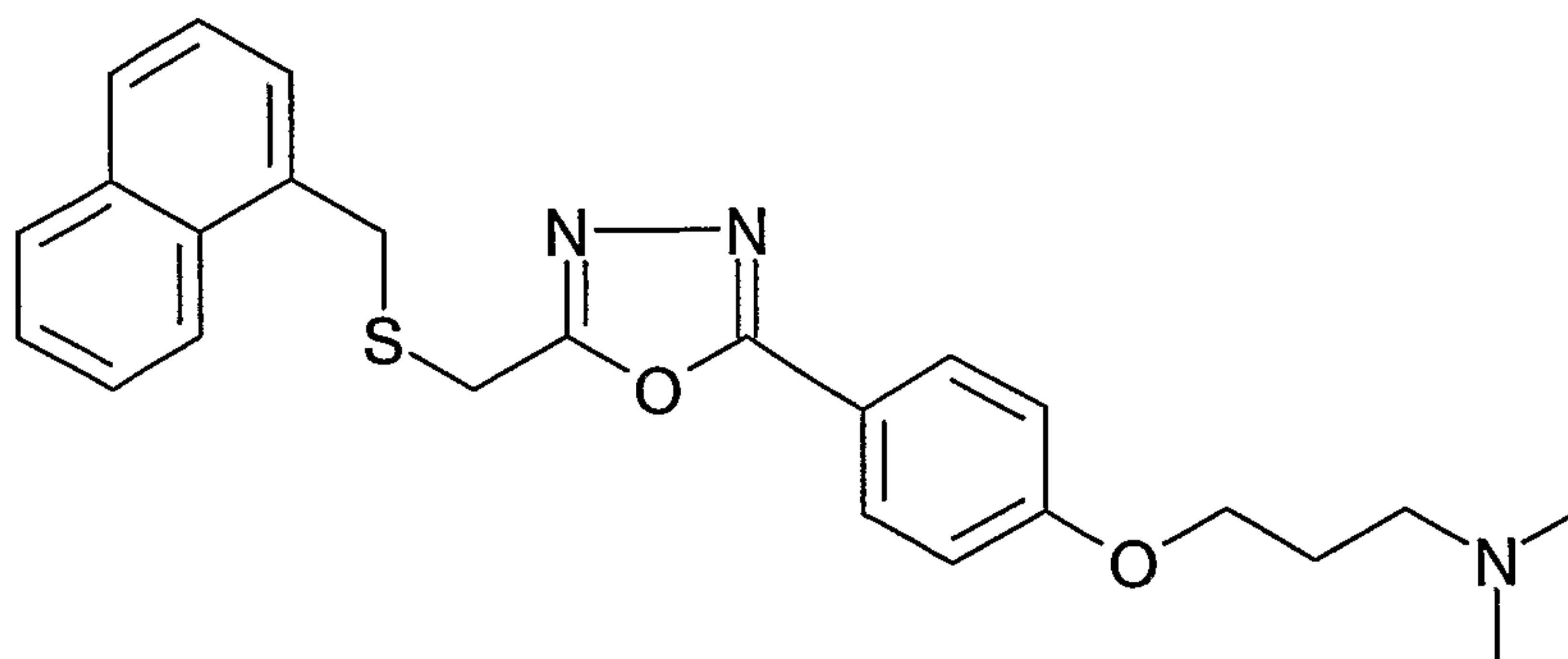
10

15

¹H NMR (DMSO-d₆) δ 10.31 (s, 1H), 8.13-8.17 (m, 1H), 7.91-7.95 (m, 1H), 7.84 (d, 1H, J=8Hz), 7.77 (d, 2H, J=8Hz), 7.38-7.57 (m, 4H), 6.94 (d, 2H, J=8Hz), 4.35 (s, 2H), 4.01 (s, 2H). IR (KBr, cm⁻¹) 3057, 1613, 1594, 1577, 1446, 1293, 1177, 773. MS (ES) m/e, 349, 347. Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.95; H, 4.63; N, 8.04. Found C, 67.72; H, 4.54; N, 7.74.

20

d) Dimethyl-(3-{4-[5(naphthalen-1-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine



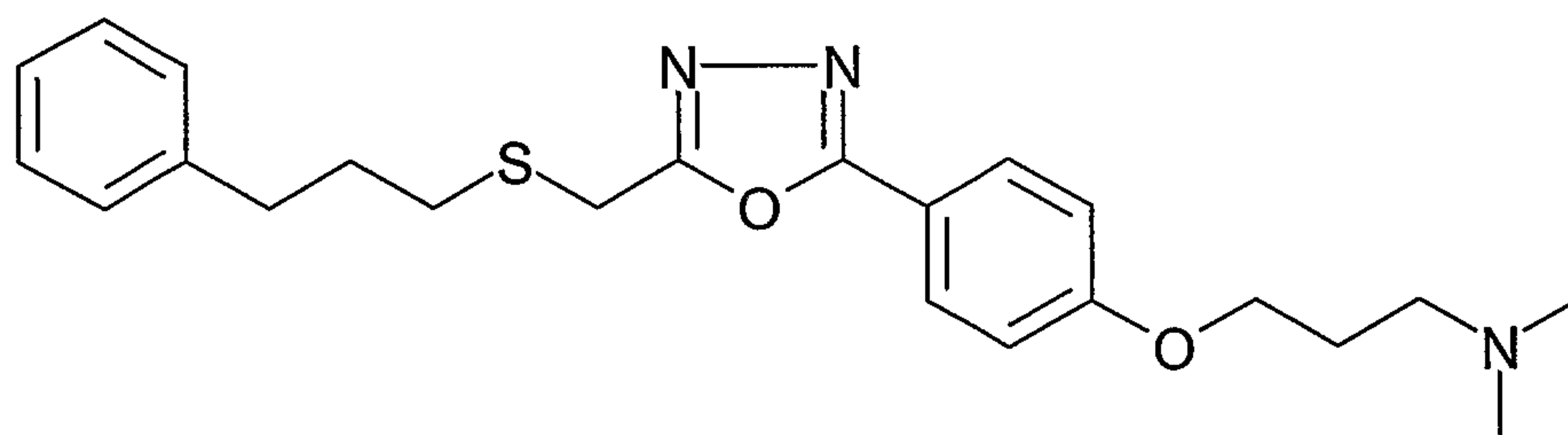
-141-

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(Naphthalen-1-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.400 g, 1.1 mmol), cesium carbonate (0.748 g, 2.3 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.181g, 1.1 mmol) to afford the title compound. Purification by silica gel radial chromatography (elution with 5% 2M NH₃ in MeOH:CHCl₃) afforded 0.374 g of the title compound as a solid. Crystallization from Et₂O afforded 0.374 g (75%) of Dimethyl-(3-{4-[5(naphthalen-1-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine.

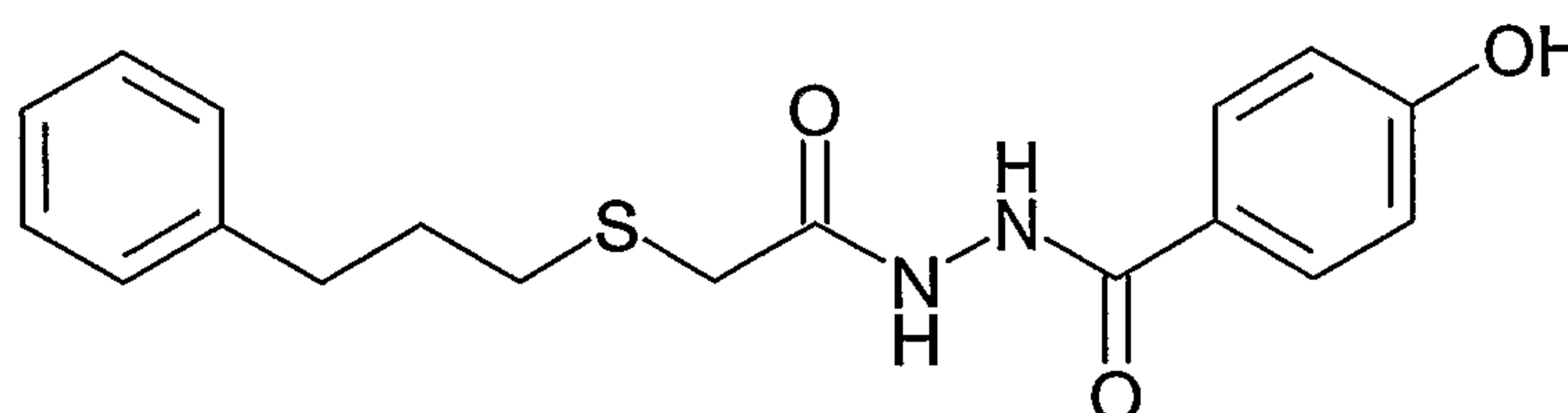
¹H NMR (DMSO-d₆) δ 8.16—8.13 (m, 1H), 7.92-7.95 (m, 1H), 7.84-7.88 (m, 3H), 7.41-7.57 (m, 4H), 7.12 (d, 2H, J=9Hz), 4.36 (s, 2H), 4.10 (t, 2H, J=7Hz), 2.15 (s, 6H), 1.84-1.93 (m, 2H). IR (KBr, cm⁻¹) 1614, 1500, 1469, 1257, 1175, 839. MS (ES) m/e, 434. Anal. Calcd for C₂₅H₂₇N₃O₂S: C, 69.26; H, 6.28; N, 9.69. Found C, 68.35; H, 6.16; N, 9.59. Mp(°C)=96.

Example 30

Preparation of Dimethyl-(3-{4-[5-(3-phenylpropylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from 3-Phenylpropyl mercaptan.



a) 4-Hydroxybenzoic acid *N*'-[2(3-phenylpropylsulfanyl) acetyl]hydrazide



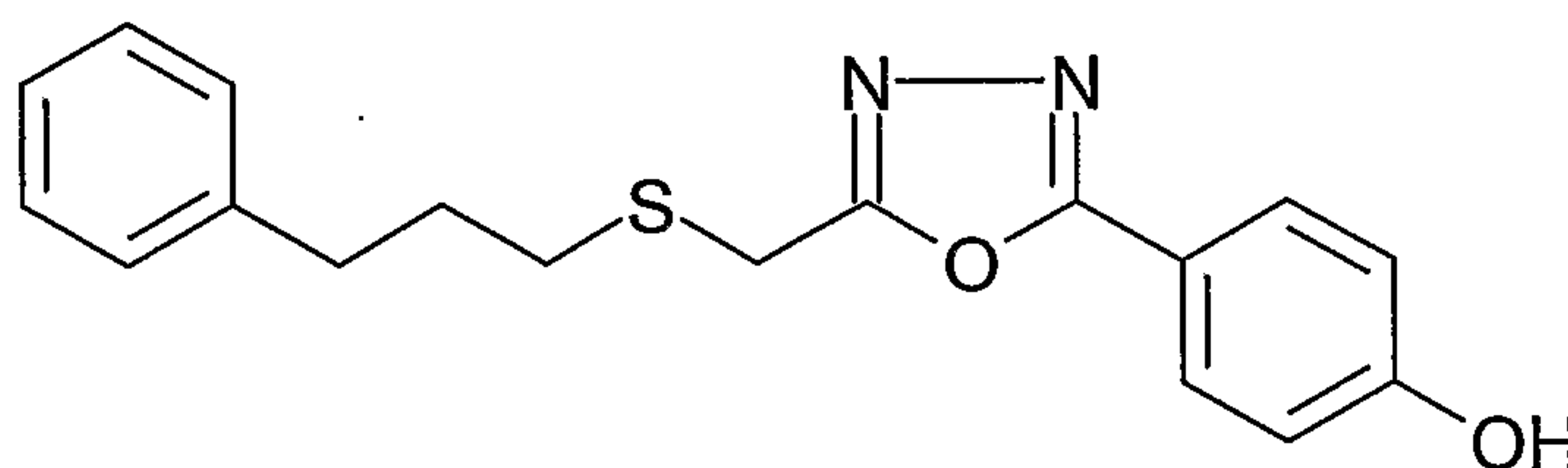
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (3-phenyl propylsulfanyl)acetic acid (2.00 g, 9.5 mmol), 4-hydroxy benzoic hydrazide (1.45 g, 9.5 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (2.35 g, 9.5 mmol) to afford the title compound as a crude mixture.

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Crystallization from methanol and diethyl ether afforded 2.15g (66%) of 4-hydroxybenzoic acid *N*'-[2(3-phenyl propyl sulfanyl) acetyl]hydrazide.

¹H NMR (DMSO-d₆) δ 10.02-10.13 (m, 2H), 9.94-9.97 (bs, 1H), 7.74 (d, 2H, J=8Hz), 7.14-7.31 (m, 5H), 6.81 (d, 2H, J=9Hz), 3.21 (s, 2H), 2.63-2.69 (m, 4H), 1.80-1.92 (m, 2H).
IR (KBr, cm⁻¹) 3311, 3208, 2859, 1695, 1625, 1609, 1585, 1517, 1495, 1284, 1175, 1115, 848, 694, 567. MS (ES) m/e, 345, 343. Anal. Calcd for C₁₈H₂₀N₂O₃S: C, 62.77; H, 5.85; N, 8.13. Found C, 62.37; H, 5.86; N, 8.03.

10 b) 4-[5(3-Phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol

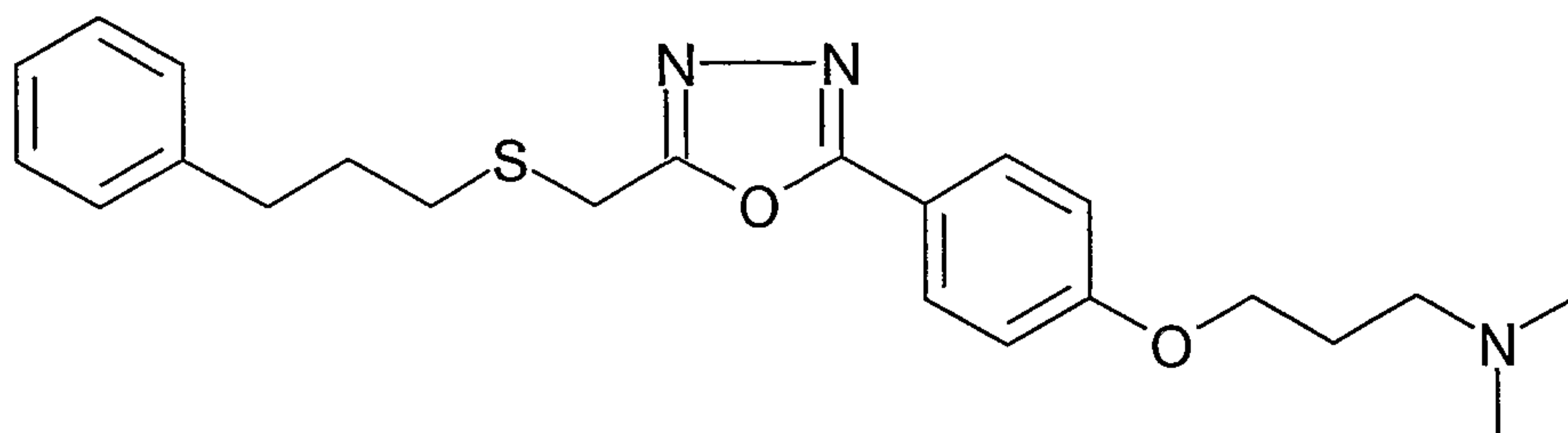


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N*'-[2(3-phenylpropyl sulfanyl)acetyl] hydrazide (1.94 g, 5.6 mmol), triphenyl phosphine (2.95 g, 11.3 mmol), triethylamine (2.05 g, 20.2 mmol) and carbon tetrabromide (3.55 g, 23.1 mmol) to afford the title compound as a crude material. Purification by flash filtration chromatography on silica gel (elution with 50% acetone:hexane) followed by crystallization of the isolated product from EtOH afforded 0.973 g (53%) of 4-[5(3-phenylpropyl sulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenol.

20 ¹H NMR (DMSO-d₆) δ 10.31 (s, 1H), 7.78 (d, 2H, J=9Hz), 7.14-7.27 (m, 5Hz), 6.94 (d, 2H, J=9Hz), 4.07 (s, 2H), 2.60-2.67 (m, 4H), 1.79-1.89 (m, 2H). IR (KBr, cm⁻¹) 3143, 3024, 2938, 1611, 1601, 1499, 1232. MS (ES) m/e, 327, 325. Anal. Calcd for C₁₈H₁₈N₂O₂S: C, 66.23; H, 5.56; N, 8.58. Found C, 65.87; H, 5.47; N, 8.44.

25 c) Dimethyl-(3-{4-[5-(3-phenylpropylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine

-143-

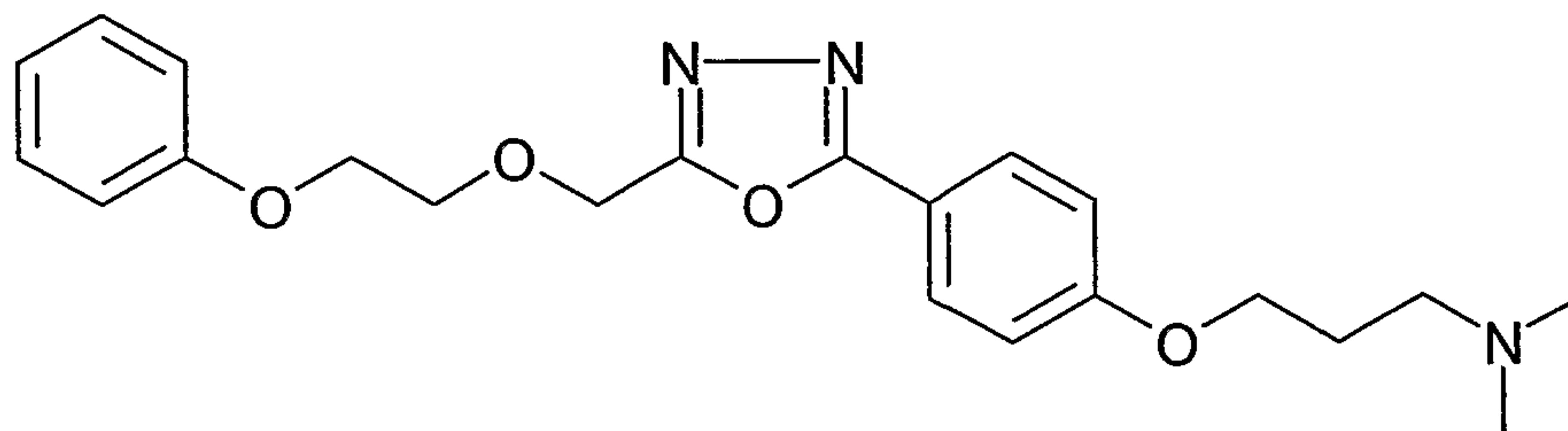


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-[5(3-phenylpropyl sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.800 g, 2.5 mmol), sodium hydride (0.225 g, 5.6 mmol), and 3-chloro-N,N-dimethylpropylamine HCl (0.426 g, 2.7 mmol) to afford the title compound as a crude material. Purification by radial chromatography on silica gel (elution with 10% 2M NH₃ IN MeOH:CHCl₃) afforded 0.602 g of an oil. The oil was dissolved in diethyl ether. To this solution was added dropwise, a solution of EtOH in Et₂O that was treated with 0.116 mL acetyl chloride. The resultant precipitate was collected by filtration to afford 0.533 g (50%) of dimethyl-(3-{4-[5-(3-phenylpropylsulfanyl methyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)amine as the hydrochloride salt.

¹H NMR (DMSO-d₆) δ 7.90 (d, 2H, J=9JHz), 7.22-7.27 (m, 2H), 7.13-7.18 (m, 5H), 4.17 (t, 2H, J=6Hz), 4.09 (s, 2H), 3.19-3.21 (m, 2H), 2.78 (s, 6H), 2.60-2.67 (m, 4H), 2.13-2.22 (m, 2H), 1.79-1.89 (m, 2H). IR (CHCl₃, cm⁻¹) 2970, 2337, 1615, 1570, 1500, 1474, 1254, 1176. MS (ES) m/e, 412. Anal. Calcd for C₂₃H₂₉N₃O₂S·HCl: C, 61.66; H, 6.75; N, 9.38. Found C, 61.30; H, 6.76; N, 9.13. Mp(°C)=148.

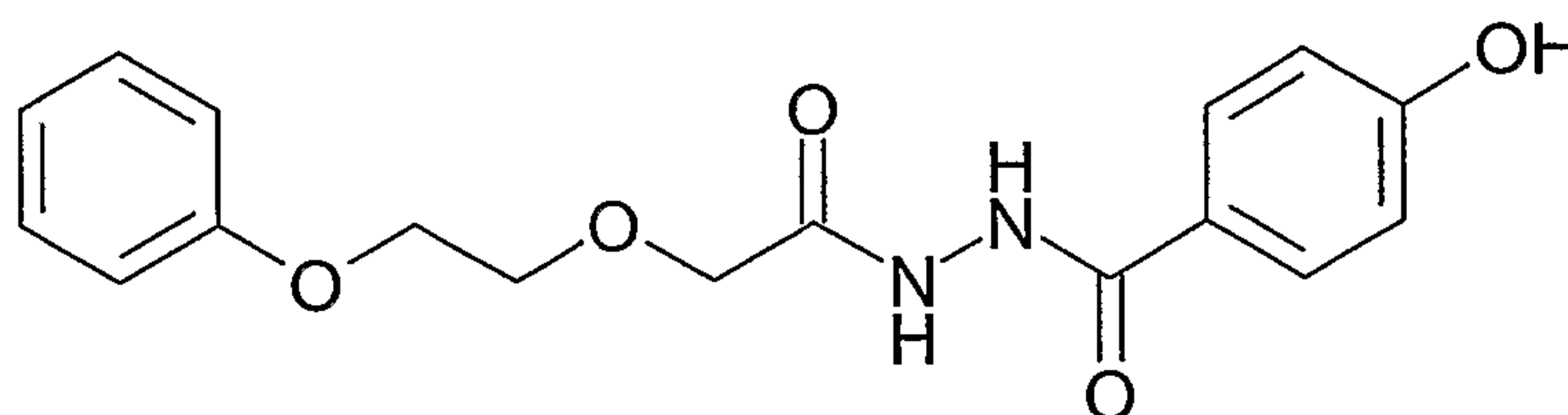
Example 31

Preparation of Dimethyl-(3-{4-[5-(2-phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from 2-(Phenoxyethoxy)acetic acid



a) 4-Hydroxybenzoic acid *N*'-[2-(2-phenoxyethoxy) acetyl] hydrazide

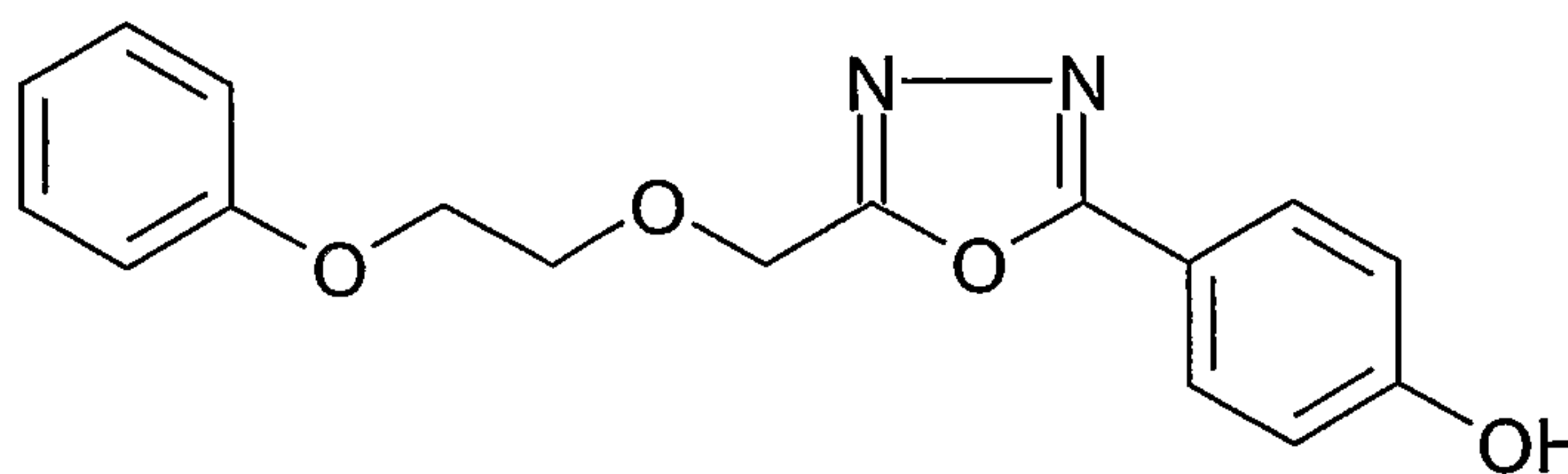
-144-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 2-(phenoxyethoxy)acetic acid (2.0g, 10.2 mmol), 4-hydroxy benzoic hydrazide (1.55 g, 10.2 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (2.52 g, 10.2 mmol) to afford the title compound as a crude mixture. Purification by HPLC on silica gel (elution with a linear gradient of 0 to 10% MeOH:CHCl₃ over a thirty minute period) followed by crystallization of the isolated material from MeOH:Et₂O afforded 1.02 g (30%) of 4-hydroxybenzoic acid *N'*-[2-(2-phenoxyethoxy) acetyl] hydrazide.

¹H NMR (DMSO-d₆) δ 10.08 (bs, 2H), 9.76 (bs, 1H), 7.74 (d, 2H, J=9Hz), 7.24-7.32 (m, 2H), 6.91-6.97 (m, 3H), 6.81 (d, 2H, J=9Hz), 4.16-4.19 (m, 2H), 4.11 (s, 2H), 3.85-3.89 (m, 2H). IR (KBr, cm⁻¹) 3229, 1695, 1647, 1627, 1609, 1588, 1574, 1507, 1498, 1246, 1140, 755. MS (ES) m/e, 331, 329. Anal. Calcd for C₁₇H₁₈N₂O₅: C, 61.81; H, 5.49; N, 8.48. Found C, 61.26; H, 5.51; N, 8.46.

b) 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]-oxadiazol-2-yl] phenol



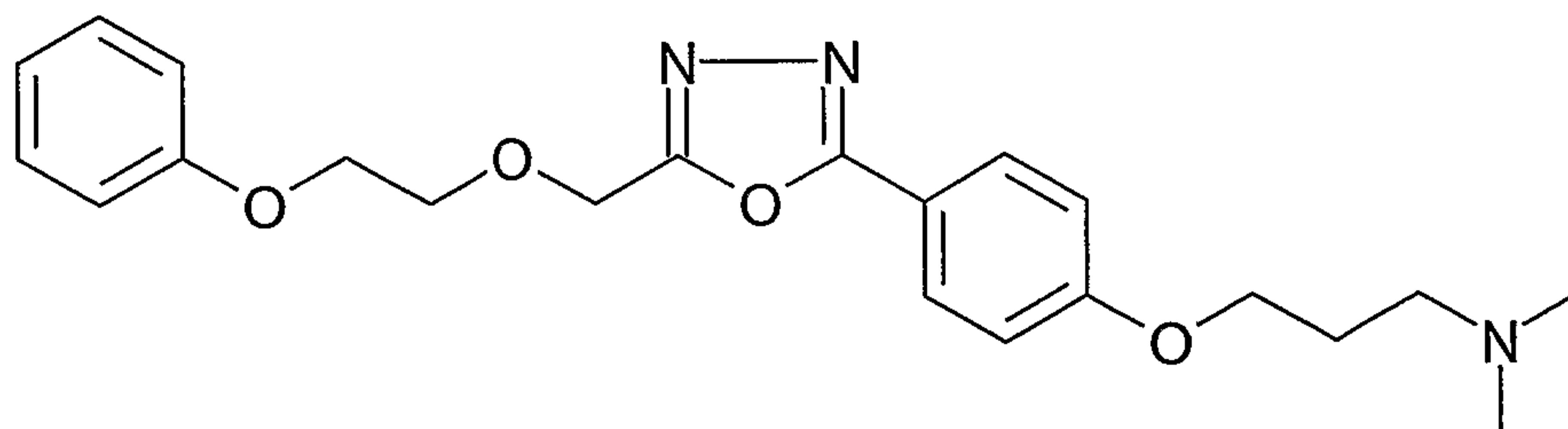
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid *N'*-[2-(2-phenoxyethoxy) acetyl] hydrazide (0.961 g, 2.9 mmol), triphenylphosphine (1.53 g, 5.8 mmol), triethylamine (1.06 g, 10.5 mmol) and carbon tetrabromide (1.83 g, 11.9 mmol) to afford the title compound as a crude mixture. Purification by flash filtration chromatography on silica gel (elution with 50% acetone:hexane) followed by crystallization of the isolated product from EtOH afforded 0.473 g (52%) of 4-[5-(2-phenoxyethoxymethyl)-[1,3,4]-oxadiazol-2-yl] phenol.

-145-

^1H NMR (DMSO- d_6) δ 10.32 (bs, 1H), 7.81 (d, 2H, $J=9\text{Hz}$), 7.23-7.30 (m, 2H), 6.89-6.97 (m, 5H), 4.85 (s, 2H), 4.13-4.16 (m, 2H), 3.89-3.92 (m, 2H). IR (KBr, cm^{-1}) 3120, 1609, 1600, 1497, 1218, 1244, 1251, 1116, 753. MS (ES) m/e , 313, 311. Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$: C, 65.38; H, 5.16; N, 8.97. Found C, 65.00; H, 5.10; N, 8.65.

5

c) Preparation of Dimethyl-(3-{4-[5-(2-phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-[5-(2-phenoxyethoxy methyl)-[1,3,4]-oxadiazol-2-yl]phenol (0.420 g, 1.3 mmol), sodium hydride (0.124 g, 3.1 mmol), and 3-chloro-N,N-dimethylpropylamine HCl (0.234 g, 1.5 mmol) to afford the title compound as a crude mixture. Crystallization from hexane: Et_2O afforded 0.321 g (60%) of dimethyl-(3-{4-[5-(2-phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl) amine.

15

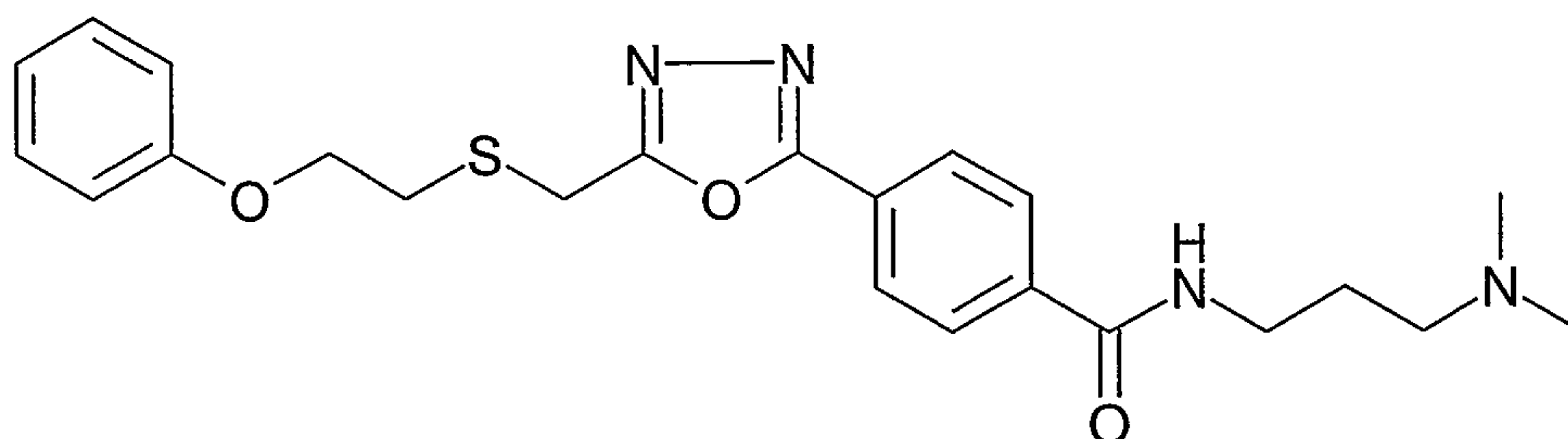
^1H NMR (DMSO- d_6) δ 7.90 (d, 2H, $J=9\text{Hz}$), 7.24-7.29 (m, 2H), 7.12 (d, 2H, $J=9\text{Hz}$), 6.89-6.94 (m, 3H), 4.86 (s, 2H), 4.07-4.16 (m, 4H), 3.90-3.93 (m, 2H), 2.36 (t, 2H, $J=7\text{Hz}$), 2.14 (s, 6H), 1.83-1.92 (m, 2H). IR (CHCl_3 , cm^{-1}) 2948, 2824, 2777, 1614, 1600, 1589, 1499, 1469, 1302, 1256, 1175, 1087, 839. MS (FD) m/e , 397. Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_4$: C, 66.48; H, 6.85; N, 10.57. Found C, 66.10; H, 6.83; N, 10.44. Mp°C =77.

20

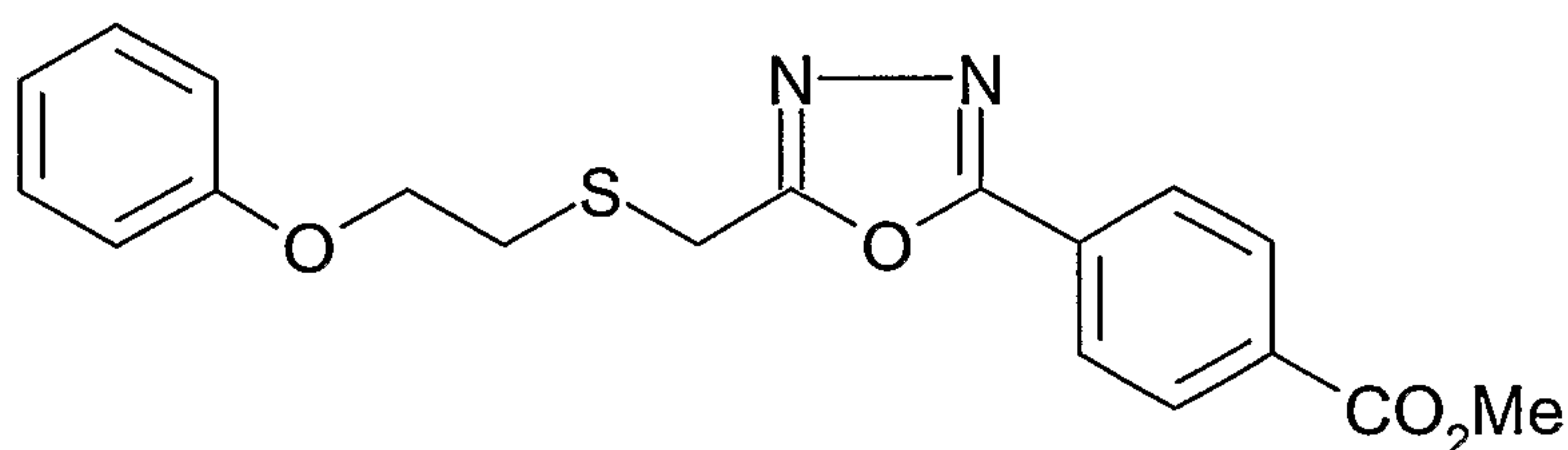
Example 32

Preparation of *N*-(3-Dimethylaminopropyl)-4-[5-(2-phenoxyethoxysulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from (2-Phenoxyethylthio)acetic acid

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a) 4-[5-(2-Phenoxyethoxysulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



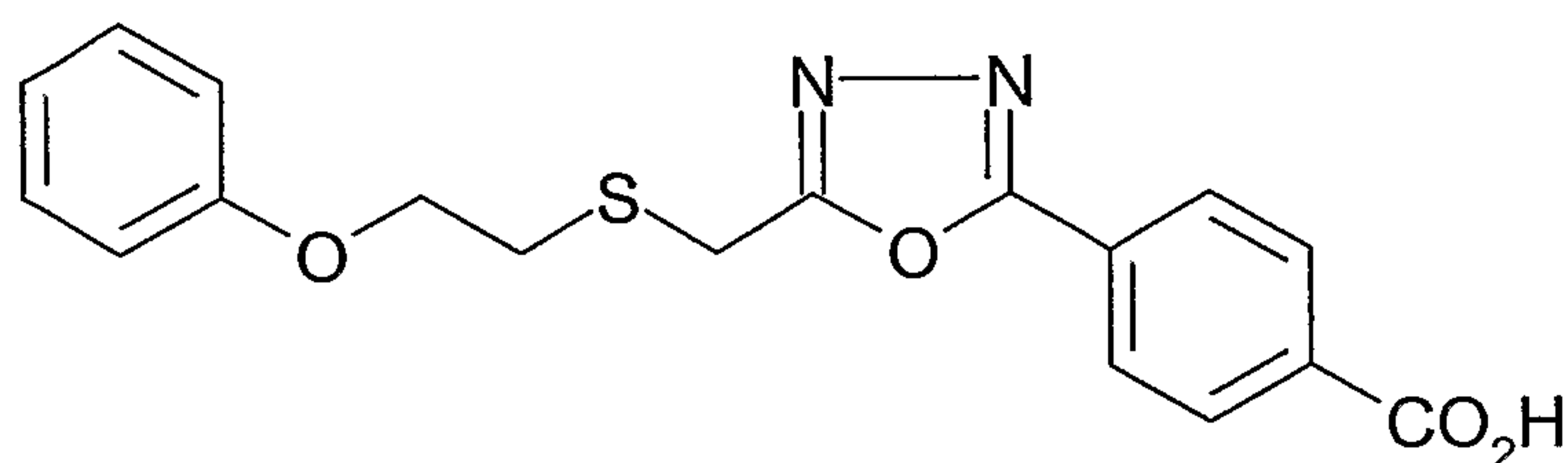
5 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from (2-phenoxyethylthio)acetic acid (2.21 g, 10.4 mmol), 1,3-dicyclohexylcarbodiimide (2.15 g, 10.4 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (2.13 g, 10.4 mmol) to afford the title compound as a crude mixture. Purification by flash filtration chromatography on silica gel (elution with 1 x 250 mL
10 CH₂Cl₂, 3 x 250 mL 50% EtOAc:hexane) afforded 0.990 g (26%) of 4-[5-(2-phenoxyethoxy sulfanyl methyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as a crystalline solid. Purification of the remaining contaminated fractions by HPLC on silica gel (elution with a linear gradient of 25 to 40% EtOAc:hexane over a thirty minute period) afforded 0.841 g (22%) of 4-[5-(2-phenoxy ethoxy sulfanyl methyl)-[1,3,4]
15 oxadiazol-2-yl]benzoic acid methyl ester.

¹H NMR (DMSO-d₆) δ 8.09-8.16 (m, 4H), 7.23-7.30 (m, 2H), 6.90-6.94 (m, 3H), 4.26 (s, 2H), 4.20 (t, 2H, J=6Hz), 3.91 (s, 3H), 3.04 (t, 2H, J=6Hz). IR (CHCl₃, cm⁻¹) 1721, 1498, 1283, 1243. MS (ES) m/e, 371. Anal. Calcd for C₁₉H₁₈N₂O₄S: C, 61.61; H, 4.90; N, 7.56. Found C, 61.54; H, 4.91; N, 7.56.

20

b) 4-[5-(2-Phenoxyethoxysulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid

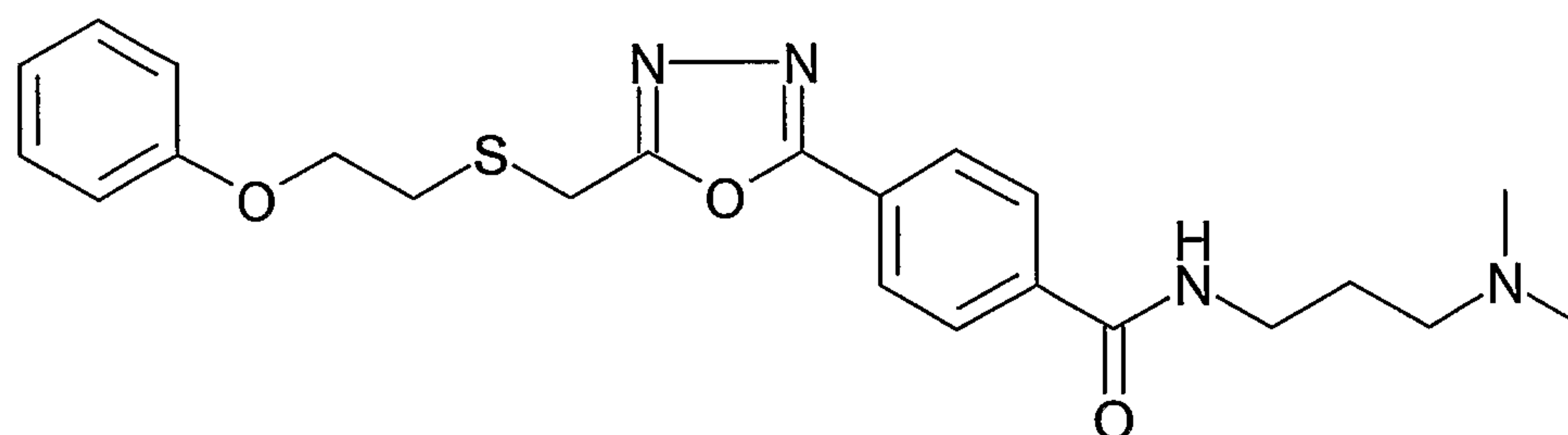
-147-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(2-phenoxy ethoxy sulfanyl methyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (1.00 g, 2.7 mmol), and lithium hydroxide
 5 (0.194 g, 8.1 mmol) to afford 0.868 g (90%) of 4-[5-(2-phenoxyethoxy sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid as a white solid.

¹H NMR (DMSO-d₆) δ 13.35 (bs, 1H), 8.06-8.14 (m, 4H), 7.23-7.30 (m, 2H), 6.90-6.98 (m, 3H), 4.26 (s, 2H), 4.20 (t, 2H, J=6Hz), 3.04 (t, 2H, J=6Hz). IR (CHCl₃, cm⁻¹) 1700, 1587, 1497, 1243. MS (ES) m/e, 357, 355. Anal. Calcd for C₁₈H₁₆N₂O₄S: C,
 10 60.66; H, 4.53; N, 7.86. Found C, 60.29; H, 4.51; N, 7.80.

c) *N*-(3-Dimethylaminopropyl)-4-[5-(2-phenoxyethoxysulfanyl methyl)-[1,3,4]oxadiazol-2-yl]benzamide



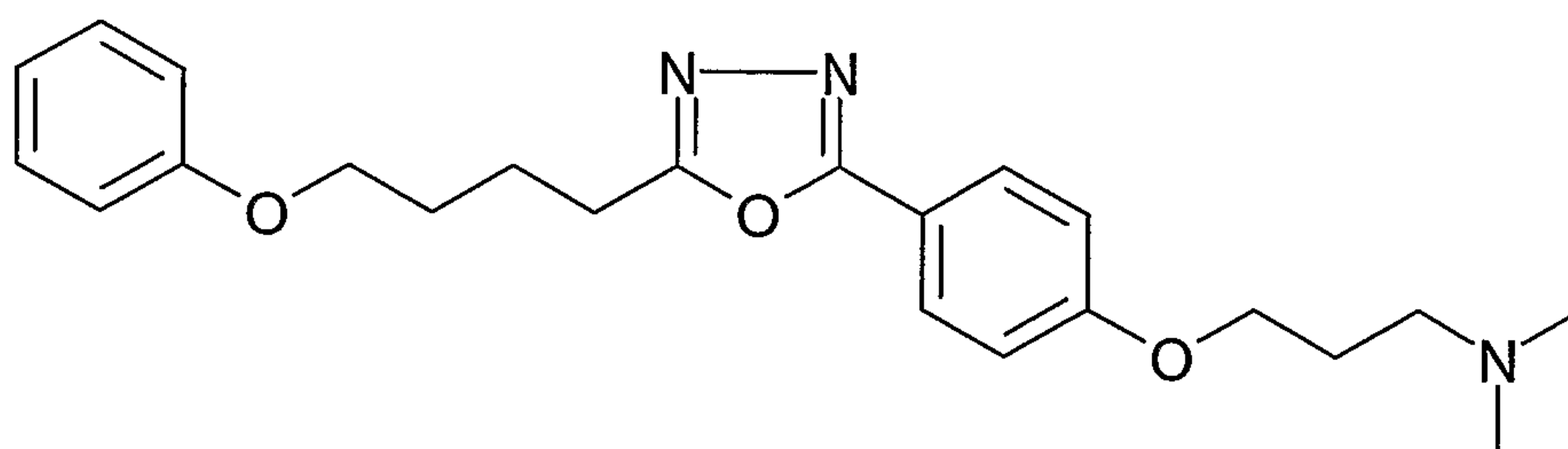
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(2-phenoxyethoxy sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.600 g, 1.68 mmol), 1-hydroxybenzotriazole (0.227 g, 1.68 mmol), 4-dimethylamino pyridine (0.021 g, 0.17 mmol), 3-(dimethylamino)propyl amine (0.181 g, 1.77 mmol) and 1,3-dicyclohexyl carbodiimide (0.365 g, 1.77 mmol) to
 20 afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M NH₃ in MeOH:CH₂Cl₂) followed by crystallization of the isolated material from EtOH:Et₂O afforded 0.335 g (45%) of *N*-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethoxysulfanyl methyl)-[1,3,4]oxadiazol-2-yl] benzamide.

-148-

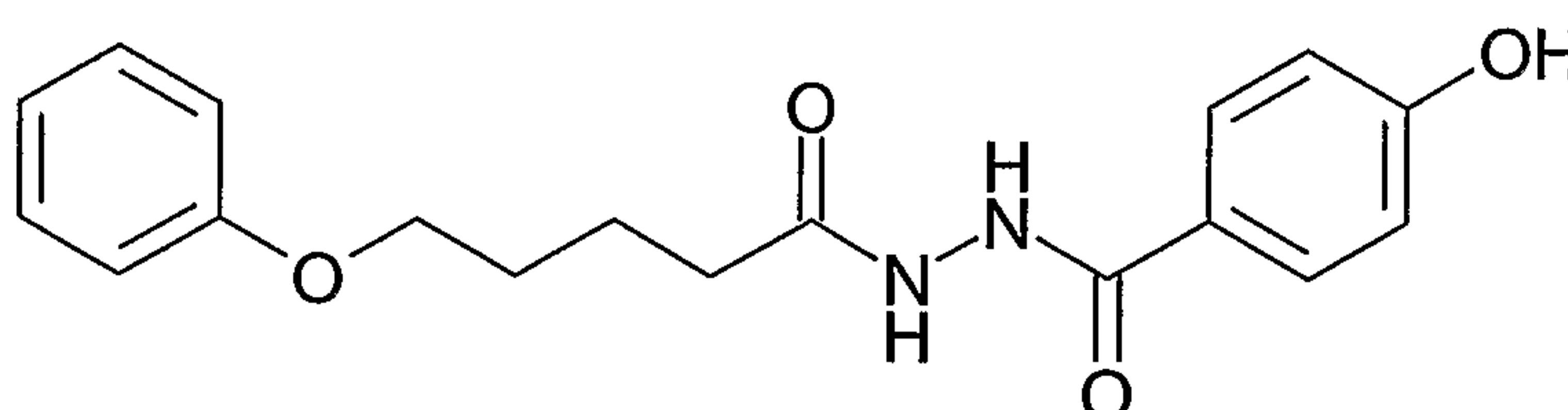
¹H NMR (DMSO-d₆) δ 8.72 (t, 1H, J=5Hz), 8.00-8.07 (m, 4H), 7.23-7.29 (m, 2H), 6.90-6.94 (m, 3H), 4.25 (s, 2H), 4.20 (t, 2H, J=6Hz), 3.30 (q, 2H, J=6Hz), 3.04 (t, 2H, J=6Hz), 2.66 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.62-1.72 (m, 2H). IR (CHCl₃, cm⁻¹) 3008, 2951, 2827, 1652, 1585, 1555, 1497, 1243, 1011. MS (ES) m/e, 441, 439. Anal. Calcd for C₂₃H₂₈N₄O₃S: C, 62.70; H, 6.41; N, 12.72. Found C, 62.33; H, 6.31; N, 12.62. Mp(°C)=96.

Example 33

Preparation of Dimethyl-(3-{4-[5-(4-phenoxybutyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)amine from 5-phenoxybutanoic acid



a) 4-Hydroxybenzoic acid-*N'*-(5-phenoxybutanoyl)hydrazide

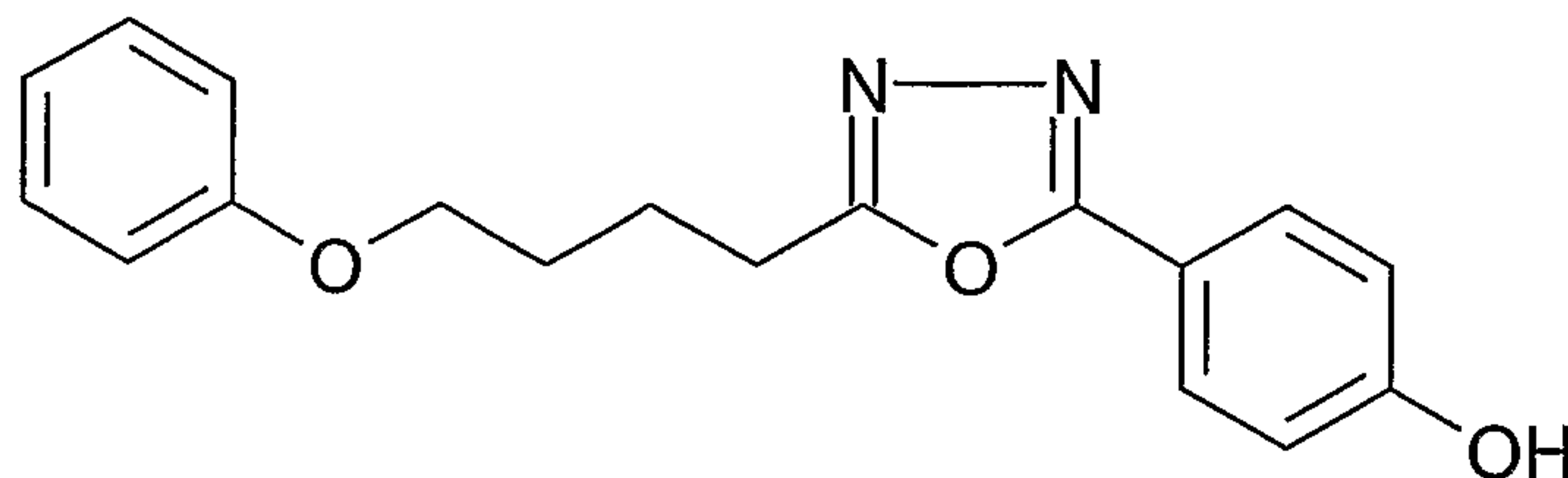


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 5-phenoxybutanoic acid (2.00 g, 10.3 mmol), 4-hydroxybenzoic hydrazide (1.57 g, 10.3 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (2.55 g, 10.3 mmol) to afford the title compound as a crude mixture. Purification by HPLC on silica gel (elution with a linear gradient of 0 to 10% MeOH:CHCl₃ over a thirty minute period) afforded 2.03 g (60%) of 4-hydroxybenzoic acid-*N'*-(5-phenoxybutanoyl)hydrazide as a white foam.

¹H NMR (DMSO-d₆) δ 10.06 (bs, 1H), 10.02 (bs, 1H), 9.75 (bs, 1H), 7.74 (d, 2H, J=9Hz), 7.21-7.31 (m, 2H), 6.87-6.95 (m, 3H), 6.81 (d, 2H, J=9Hz), 3.98 (t, 2H, J=6Hz), 2.24 (t, 2H, J=7Hz), 1.62-1.83 (m, 4H). IR (KBr, cm⁻¹) 3269, 1663, 1608, 1577, 1496, 1472, 1280, 1248, 848, 754. MS (ES) m/e, 329, 327. Anal. Calcd for C₁₈H₂₀N₂O₄: C, 65.84; H, 6.14; N, 8.53. Found C, 65.53; H, 6.19; N, 8.36.

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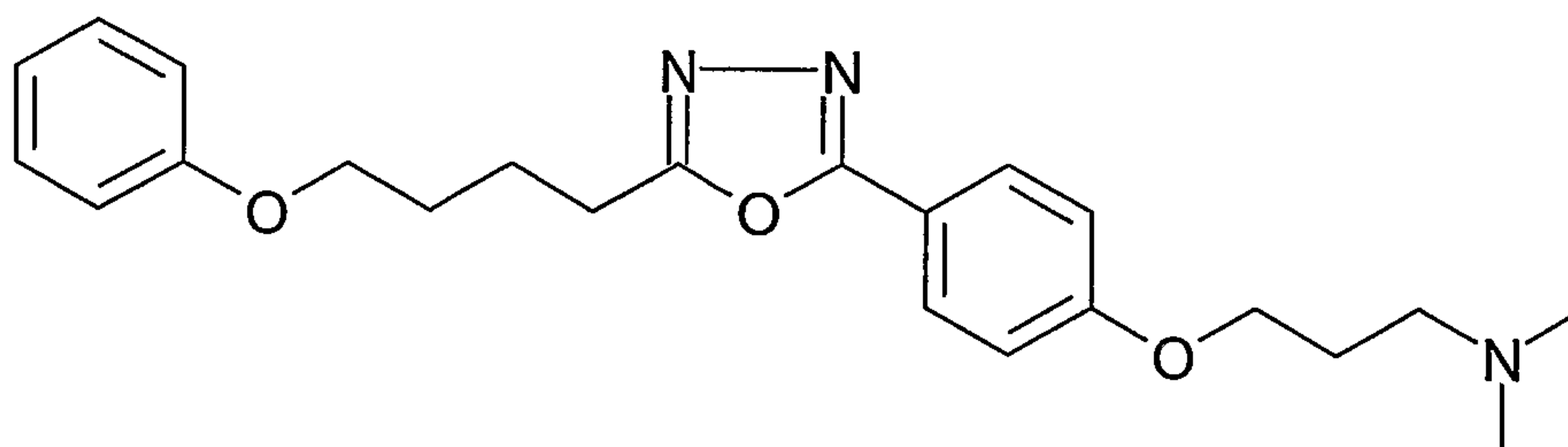
b) 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N'*-(5-phenoxybutanoyl)hydrazide (1.90 g, 5.8 mmol), triphenyl phosphine (11.6 g, 3.04 mmol), triethylamine (2.11 g, 20.8 mmol) and carbon tetrachloride (3.65 g, 23.7 mmol) to afford the title compound as a crude mixture. Purification by flash filtration chromatography on silica gel (elution with 50% acetone:hexane) followed by crystallization of the isolated product from ethanol afforded 1.71 g (65%) of 4-[5-(4-phenoxy butyl)-[1,3,4]oxadiazol-2-yl]phenol.

¹H NMR (DMSO-d₆) δ 10.25 (bs, 1H), 7.78-7.82 (m, 2H), 7.23-7.31 (m, 2H), 6.88-6.96 (m, 5H), 4.02 (t, 2H, J=6Hz), 2.98 (t, 2H, J=7Hz), 1.78-1.97 (m, 4H). IR (KBr, cm⁻¹) 3061, 2935, 2870, 1611, 1601, 1499, 1283, 1245, 1229, 1174, 1035, 750, 689. MS (ES) m/e, 311, 309. Anal. Calcd for C₁₈H₁₈N₂O₃: C, 69.66; H, 5.85; N, 9.03. Found C, 69.81; H, 5.85; N, 8.76.

c) Dimethyl-(3-{4-[5-(4-phenoxybutyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)amine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-[5-(4-phenoxy butyl)-[1,3,4]oxadiazol-2-yl]phenol (0.865 g, 2.8 mmol), sodium hydride (0.256 g, 6.4 mmol), and 3-chloro-N,N-dimethyl propylamine HCl (0.485 g, 3.1 mmol) to afford the title compound as a crude mixture.

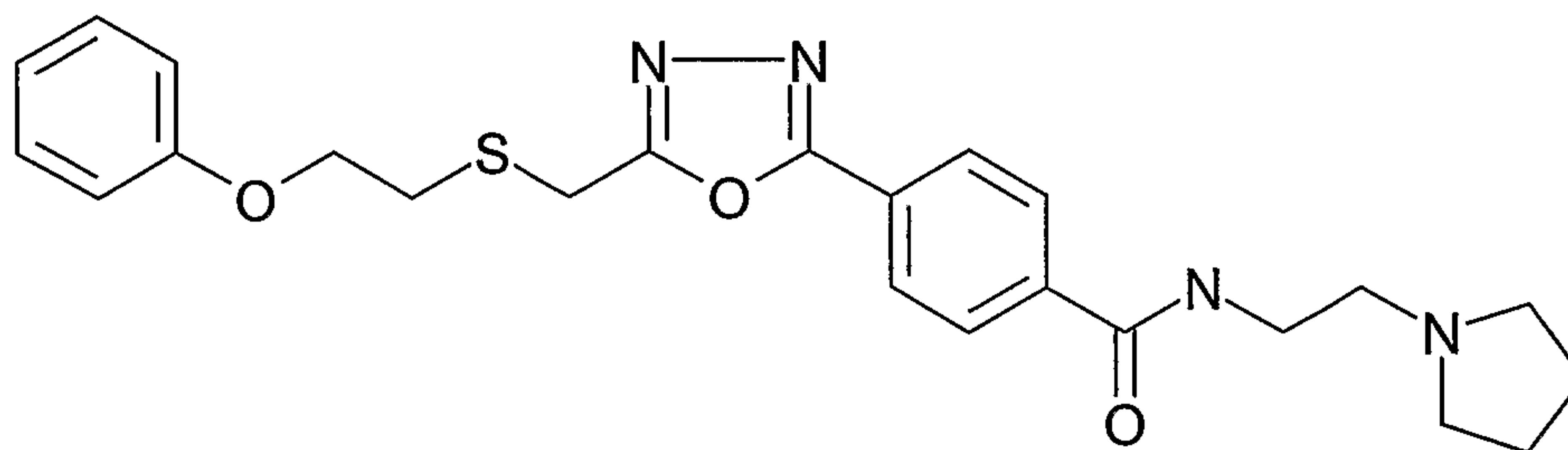
-150-

Crystallization from hexane:Et₂O afforded 0.769 g (70%) of dimethyl-(3-{4-[5-(4-phenoxybutyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)amine.

¹H NMR (DMSO-d₆) δ 7.88 (d, 2H, J=9Hz), 7.23-7.30 (m, 2H), 7.10 (d, 2H, J=9Hz), 6.89-6.94 (m, 3H), 4.08 (t, 2H, J=7Hz), 4.02 (t, 2H, J=6Hz), 2.99 (t, 2H, J=7Hz),
 5 2.35 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.81-1.95 (m, 6H). IR (CHCl₃, cm⁻¹) 2952, 2873, 2825, 2777, 1615, 1589, 1500, 1470, 1248, 1174. MS (FD) m/e, 395. Anal. Calcd for C₂₃H₂₉N₃O₃: C, 69.85; H, 7.39; N, 10.62. Found C, 69.87; H, 7.54; N, 10.26. Mp(°C)=78.

Example 34

10 Preparation of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N-(2-aminoethyl)pyrrolidine



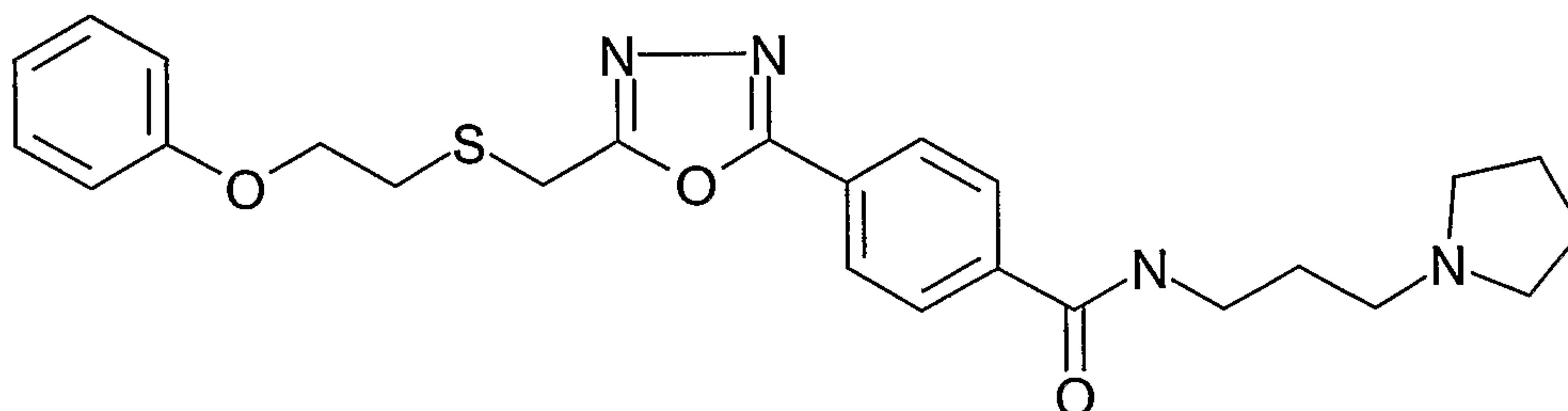
To a slurry of the 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.054 g, 0.15 mmole), 1-hydroxybenzotriazole hydrate (0.024 g, 0.18 mmole), and N-(2-aminoethyl)pyrrolidine (0.023 ml, 0.18 mmole) in 2 ml dichloromethane at room temperature was added diisopropylcarbodiimide (0.047 ml, 0.30 mmole). The reaction was stirred 16 h at ambient temperature, then polystyrene methylisocyanate (0.06 mmole) and dichloromethane were added and the reaction was
 15 stirred at room temperature overnight. The reaction mixture was evaporated, taken up in 3 ml methanol, and purified over an SCX column (elution with 2 M ammonia in methanol) to afford 0.067 g (99%) of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide.

¹H NMR(CDCl₃) δ 8.08(d, 2H, J=9), 7.90(d, 2H, J=9), 7.26(m, 2H), 7.01(m, 1H),
 25 6.94(t, 1H, J=8), 6.88(d, 2H, J=9), 4.22(t, 2H, J=6), 4.07(s, 2H), 3.57(q, 2H, J=6), 3.06(t, 2H, J=6), 2.74(t, 2H, J=6), 2.60(m, 4H), 1.80(m, 4H). MS (ES) m/e, 452.19 (C₂₄H₂₈N₄O₃S).

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Example 35

Preparation of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N-(3-aminopropyl)pyrrolidine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N-(3-aminopropyl) pyrrolidine to afford 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide.

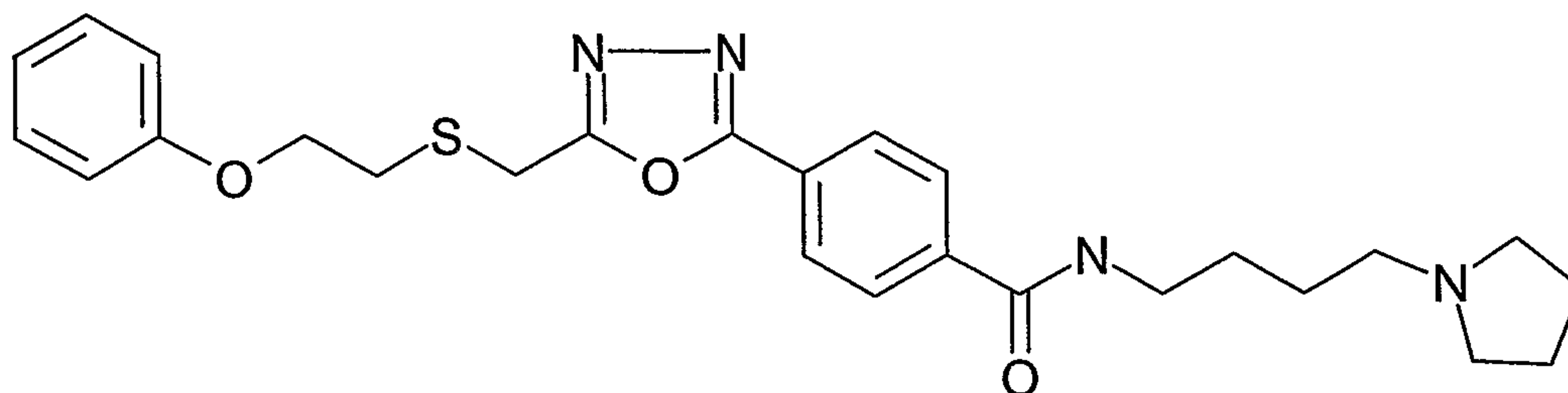
^1H NMR(CDCl₃) δ 9.29(m, 1H), 8.08(d, 2H, J=9), 7.99(d, 2H, J=9), 7.27(m, 2H), 6.98(t, 1H, J=8), 6.89(d, 2H, J=7), 4.21(t, 2H, J=7), 4.07(s, 2H), 3.62(q, 2H, J=6), 3.06(t, 2H, J=6), 2.74(t, 2H, J=6), 2.59(m, 4H), 1.83(m, 6H).

MS (ES) m/e, 466.20. Anal. Calcd for C₂₅H₃₀N₄O₃S·0.5H₂O: C, 63.13; H, 6.75; N, 11.78.

Found C, 63.33; H, 6.26; N, 11.95.

Example 36

Preparation 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(4-pyrrolidin-1-yl-butyl)-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N-(4-aminobutyl)pyrrolidine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-

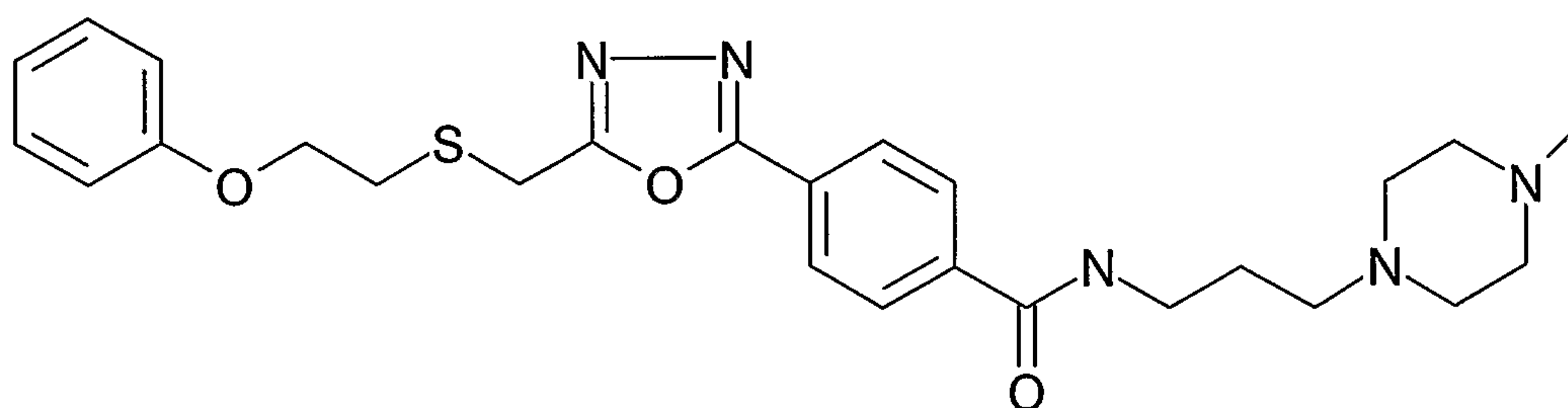
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yl]benzoic acid and N-(4-aminobutyl) pyrrolidine to afford 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(4-pyrrolidin-1-yl-butyl)-benzamide.

^1H NMR(CDCl_3) δ 8.25(m, 1H), 8.09(d, 2H, J=8), 7.88(d, 2H, J=8), 7.28(m, 2H), 6.95(t, 1H, J=7), 6.89(d, 2H, J=8), 4.22(t, 2H, J=7), 4.07(s, 2H), 3.47(q, 2H, J=7), 3.06(t, 2H, J=6), 2.48(m, 6H), 1.71(m, 8H). MS (ES) m/e, 480.22. Anal. Calcd for $\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_3\text{S}\cdot 0.33\text{H}_2\text{O}$: C, 64.17; H, 6.77; N, 11.51. Found C, 64.16; N, 6.58; H, 11.59.

Example 37

Preparation N-[3-(4-Methyl-piperazin-1-yl)-propyl]-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-(4-Methyl-piperazin-1-yl)-propylamine



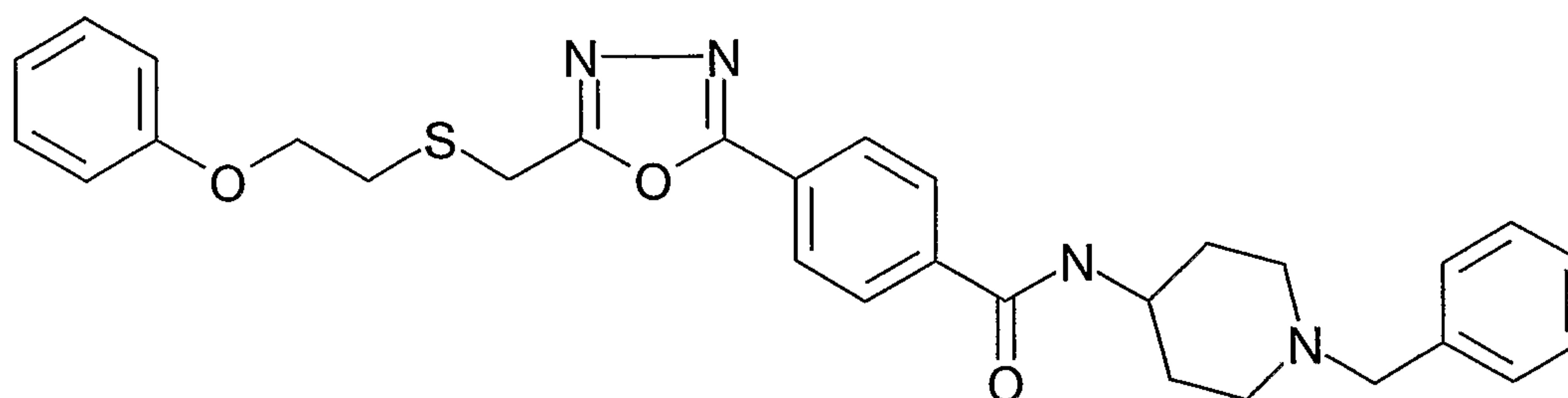
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-(4-Methyl-piperazin-1-yl)-propylamine to afford N-[3-(4-Methyl-piperazin-1-yl)-propyl]-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

^1H NMR(CDCl_3) δ 8.09(m, 4H), 7.26(m, 2H), 6.95(t, 1H, J=8), 6.89(d, 2H, J=9), 4.22(t, 2H, J=8), 4.07(s, 2H), 4.00(m, 1H), 3.82(m, 1H), 3.64(q, 2H, J=7), 3.40(m, 1H), 3.06(t, 2H, J=6), 2.97(m, 6H), 2.51(m, 2H), 2.12(m, 1H), 1.77(m, 5H). MS (ES) m/e, 495.23. Anal. Calcd for $\text{C}_{26}\text{H}_{33}\text{N}_5\text{O}_3\text{S}\cdot \text{HCl}\cdot \text{H}_2\text{O}$: C, 56.77; H, 6.60; N, 12.73. Found C, 56.71; H, 6.82; N, 13.57.

Example 38

Preparation N-(1-Benzyl-piperidin-4-yl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 1-Benzyl-piperidin-4-ylamine

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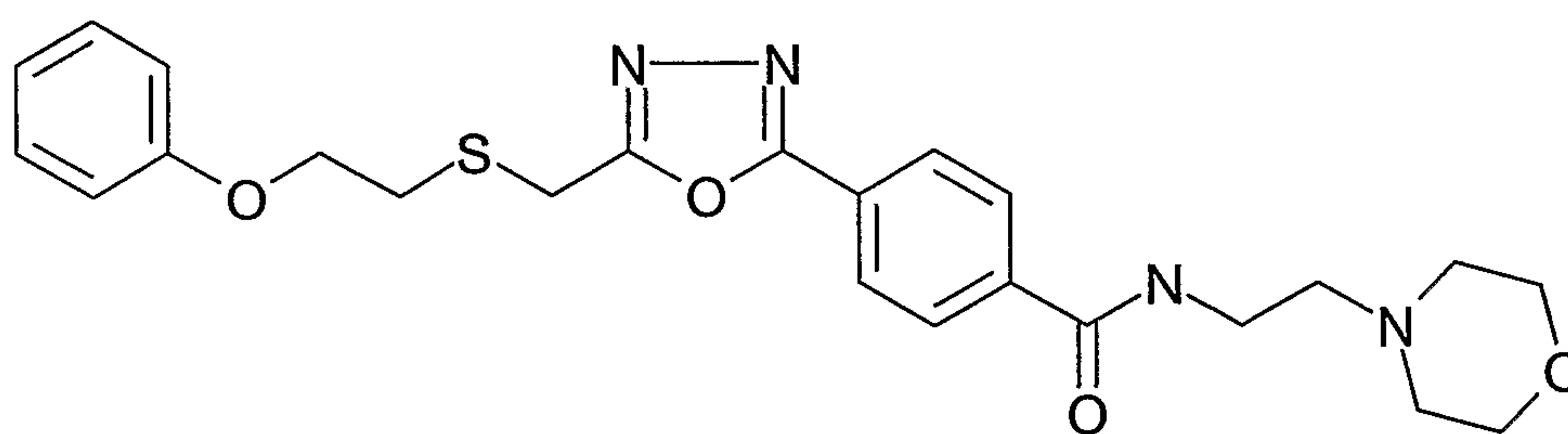
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 1-Benzyl-piperidin-4-ylamine to afford N-(1-Benzyl-piperidin-4-yl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4] oxadiazol-2-yl]-benzamide.

^1H NMR(CDCl_3) δ 8.09(d, 2H, J=9), 7.86(d, 2H, J=9), 7.31(m, 2H), 7.24(m, 5H), 6.95(t, 1H, J=8), 6.89(d, 2H, J=9), 4.21(d, 1H, J=7), 4.07(s, 2H), 4.03(m, 1H), 3.52(s, 2H), 3.06(t, 2H, J=7), 2.88(d, 2H, J=11), 2.14(t, 2H, J=10), 2.04(d, 2H, J=13), 1.58(m, 2H). MS (ES) m/e, 528.22. Anal. Calcd for $\text{C}_{30}\text{H}_{32}\text{N}_4\text{O}_3\text{S}$: C, 68.16; H, 6.10; N, 10.60.

Found C, 67.78; H, 6.11; N, 10.53.

Example 39

Preparation N-(2-Morpholin-4-yl-ethyl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 2-Morpholin-4-yl-ethylamine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 2-morpholin-4-yl-ethylamine to afford N-(2-Morpholin-4-yl-ethyl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

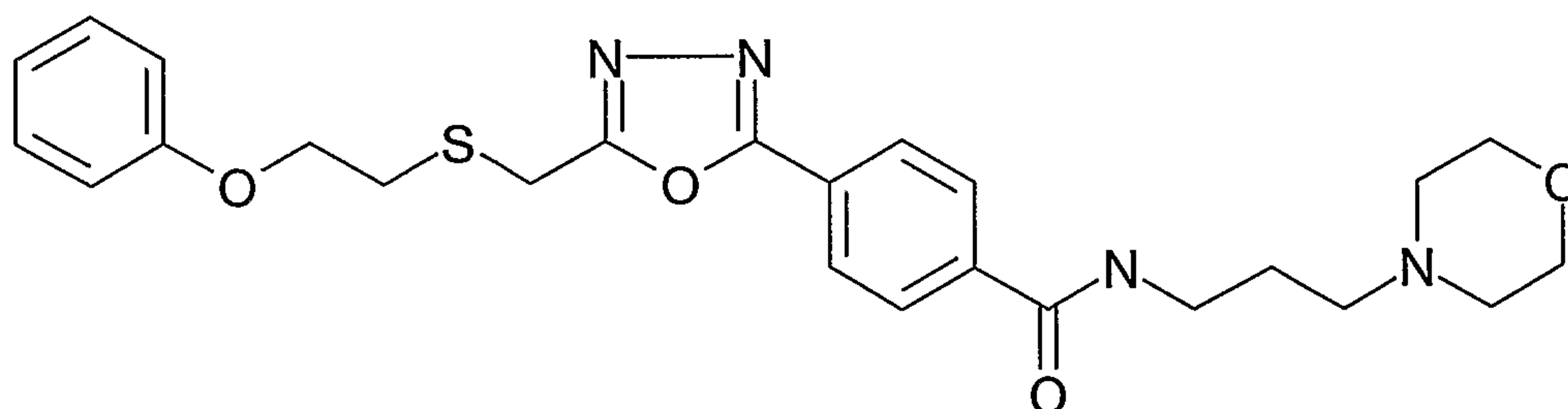
^1H NMR(CDCl_3) δ 8.11(d, 2H, J=9), 7.90(d, 2H, J=9), 7.28(m, 2H), 6.94(t, 1H, J=9), 6.89(d, 2H, J=8), 6.85(m, 1H), 4.21(t, 2H, J=7), 4.08(s, 2H), 3.75(t, 4H, J=2), 3.58(q, 2H, J=6), 3.06(t, 2H, J=6), 2.63(t, 2H, J=3), 2.52(m, 4H). MS (ES) m/e, 468.18.

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Anal. Calcd for $C_{24}H_{28}N_4O_4S$: C, 61.52; H, 6.02; N, 11.96. Found C, 61.36; H, 5.94; N, 11.95.

Example 40

- 5 Preparation N-(3-Morpholin-4-yl-propyl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-Morpholin-4-yl-propylamine

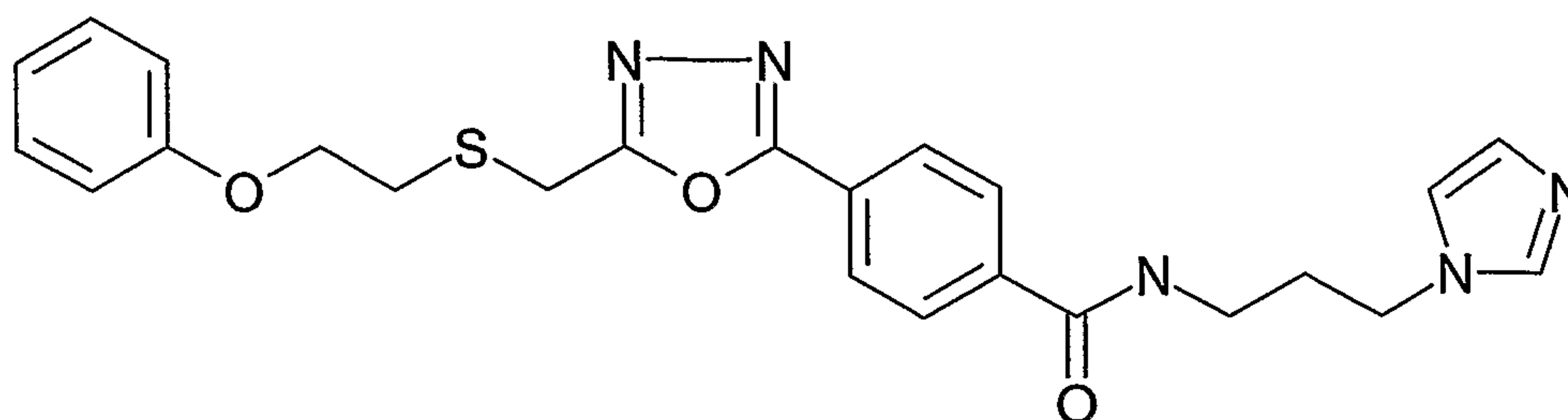


- 10 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-morpholin-4-yl-propylamine to afford N-(3-Morpholin-4-yl-propyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

- 15 ^1H NMR(CDCl_3) δ 8.29(m, 1H), 8.12(d, 2H, J=9), 7.95(d, 2H, J=9), 7.25(m, 2H), 6.95(t, 1H, J=8), 6.89(d, 2H, J=9), 4.22(t, 2H, J=6), 4.08(s, 2H), 3.70(t, 4H, J=6), 3.61(q, 2H, J=5), 3.06(t, 2H, J=8), 2.58(t, 2H, J=7), 2.51(m, 4H), 1.81(m, 2H, J=6). MS (ES) m/e, 482.20. Anal. Calcd for $C_{25}H_{30}N_4O_4S \cdot 2.33\text{H}_2\text{O}$: C, 57.23; H, 6.66; N, 10.68. Found C, 57.12; H, 5.69; N, 10.74.

Example 41

- 20 Preparation N-(3-Imidazol-1-yl-propyl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-Imidazol-1-yl-propylamine



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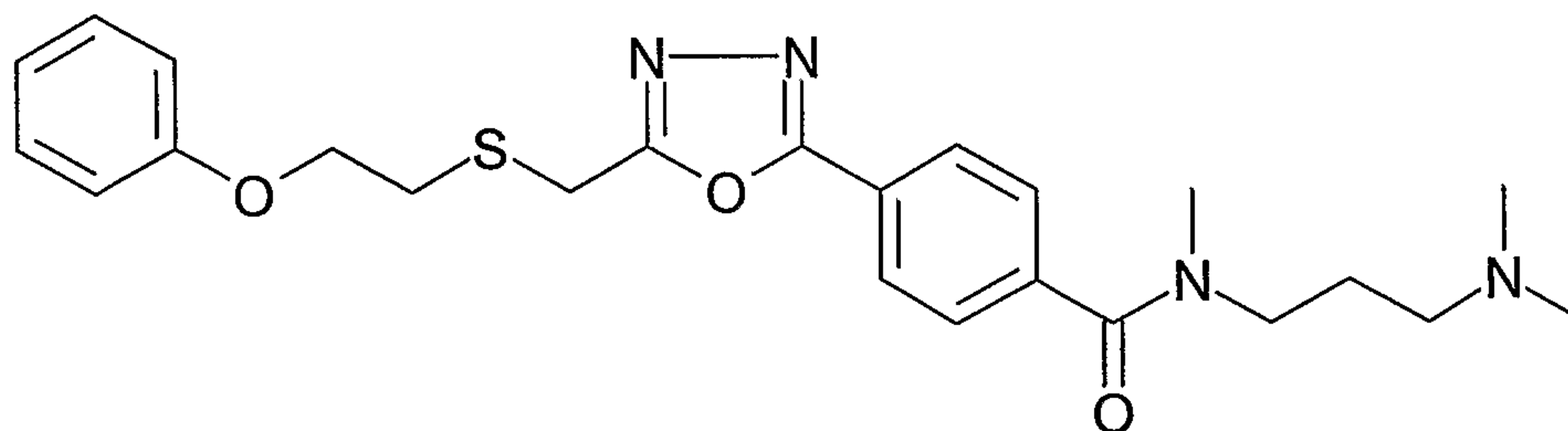
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-Imidazol-1-yl-propylamine to afford N-(3-Imidazol-1-yl-propyl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

¹H NMR(CDCl₃) δ 8.08(d, 2H, J=9), 7.85(d, 2H, J=9), 7.56(s, 1H), 7.26(m, 2H), 7.07(s, 1H), 6.98(s, 1H), 6.95(t, 1H, J=8), 6.89(d, 2H, J=9), 6.43(t, 1H, J=6), 4.21(t, 2H, J=7), 4.07(t, 4H, J=7), 3.51(q, 2H, J=7), 3.05(t, 2H, J=7), 2.18(m, 2H, J=7). MS (ES) m/e, 463.17.

10

Example 42

Preparation N-(3-Dimethylamino-propyl)-N-methyl-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N,N,N'-Trimethyl-propane-1,3-diamine



15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N,N,N'-Trimethyl-propane-1,3-diamine to afford N-(3-Dimethylamino-propyl)-N-methyl-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

20

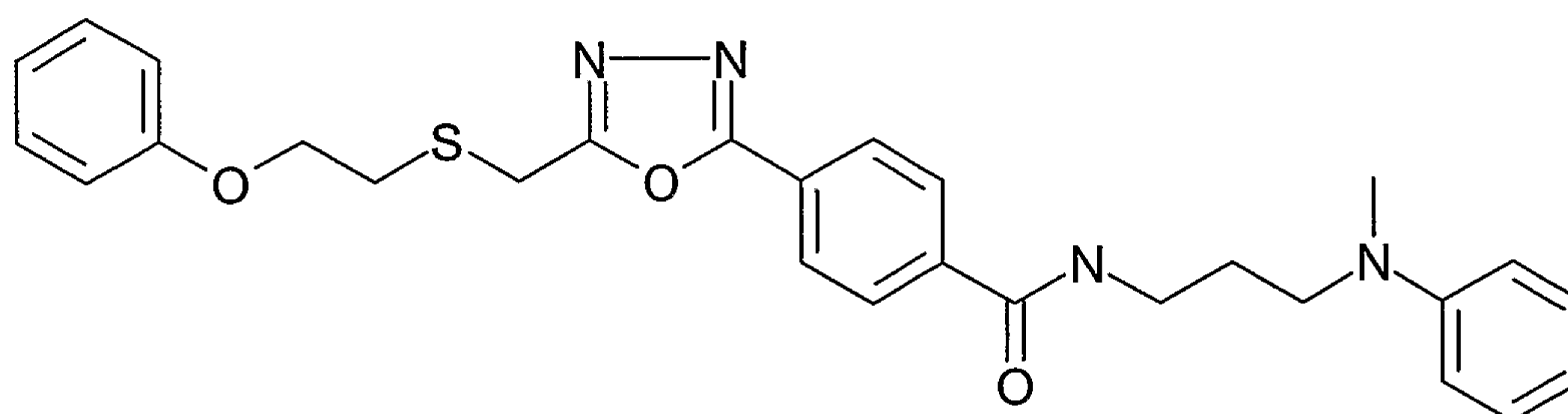
¹H NMR(CDCl₃) δ 8.06(d, 2H, J=9), 7.52(d, 2H, J=9), 7.25(m, 2H), 6.94(t, 1H, J=9), 6.89(d, 2H, J=9), 4.21(t, 2H, J=7), 4.07(s, 2H), 3.59(t, 1H, J=7), 3.28(t, 1H, J=8), 3.08(q, 2H, J=7), 3.06(s, 1.5H), 2.96(s, 1.5H), 2.36(t, 1H, J=9), 2.26(s, 3H), 2.10(m, 1H), 2.09(s, 3H), 1.85(m, 1H), 1.69(m, 1H). MS (ES) m/e, 454.20. Anal. Calcd for C₂₄H₃₀N₄O₃S·0.33H₂O: C, 62.59; H, 6.71; N, 12.16. Found C, 62.44; H, 6.54; N, 12.48.

25

Example 43

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Preparation N-[3-(Methyl-phenyl-amino)-propyl]-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N1-Methyl-N1-phenyl-propane-1,3-diamine



5 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N1-Methyl-N1-phenyl-propane-1,3-diamine to afford N-[3-(Methyl-phenyl-amino)-propyl]-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

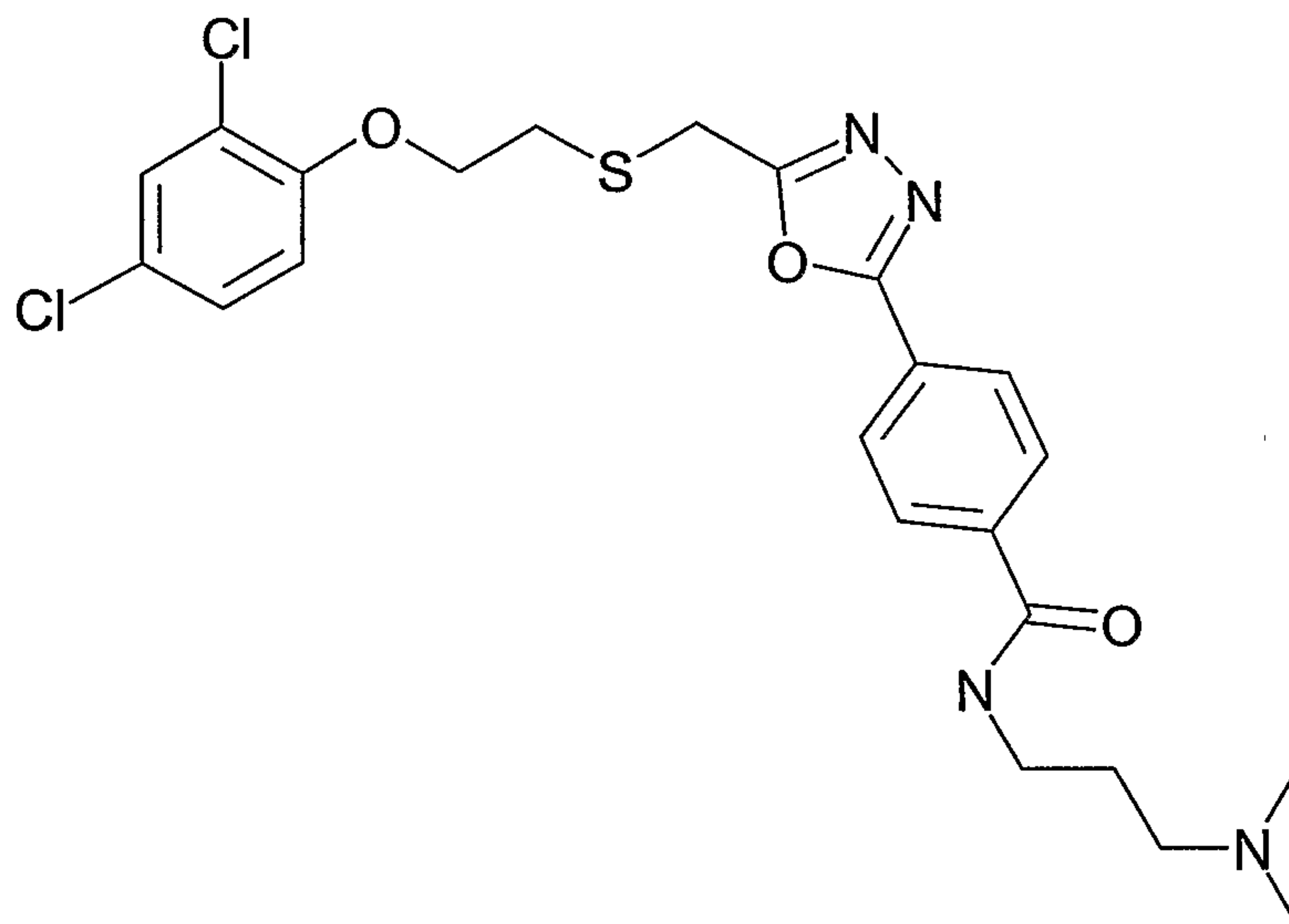
10 ^1H NMR(CDCl_3) δ 8.04(d, 2H, J=9), 7.84(d, 2H, J=9), 7.26(m, 4H), 6.95(t, 1H, J=8), 6.87(d, 2H, J=9), 6.77(m, 3H), 6.53(t, 1H, J=7), 4.21(t, 2H, J=6), 4.07(s, 2H), 3.57(q, 2H, J=7), 3.47(t, 2H, J=7), 3.06(t, 2H, J=6), 2.93(s, 3H), 1.95(m, 2H, J=7). MS (ES) m/e, 502.20. Anal. Calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_3\text{S}\cdot 0.33\text{H}_2\text{O}$: C, 66.12; H, 6.08; N, 11.01. Found C, 66.91; H, 5.71; N, 11.03.

15

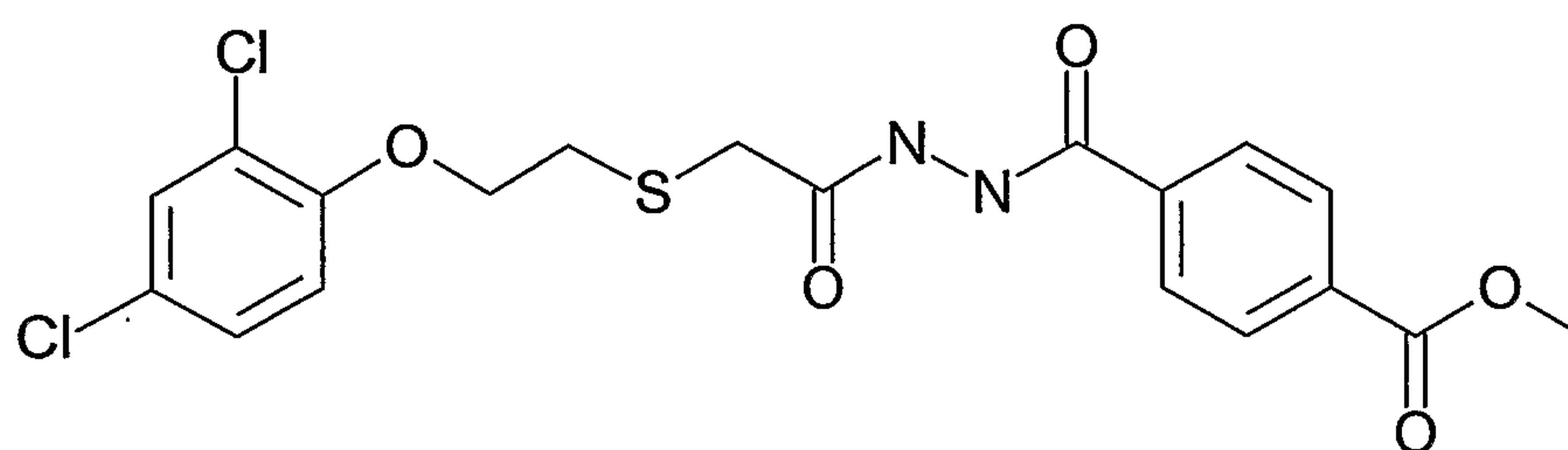
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Example 44

Preparation of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]-oxadiazol-2-yl}-N-(3-dimethylaminopropyl)-benzamide



- 5 a) 4-(N'-{2-[2-(2,4-dichlorophenoxy)-ethylsulfanyl]-acetyl}-hydrazinocarbonyl)-benzoic acid methyl ester



- 10 A solution of 2-[[2-(2,4-dichlorophenoxy)ethyl]-[thio]acetic acid hydrazide (1.48 g, 5.0 mmol), terephthalic acid, monomethyl ester chloride (0.993 g, 5.0 mmol), and triethylamine (0.836 mL, 6.0 mmol) in 35 mL THF was stirred at room temperature for 6 h. The resultant precipitate was collected by filtration, washed with THF, and the filtrate was concentrated in vacuo to afford an off-white solid, which was crystallized from
- 15 ethanol to afford 1.94 g (85%) of 4-(N'-{2-[2-(2,4-dichlorophenoxy)-ethylsulfanyl]-acetyl}-hydrazinocarbonyl)-benzoic acid methyl ester as a white solid (MP 156-157 °C, MW 456.03).

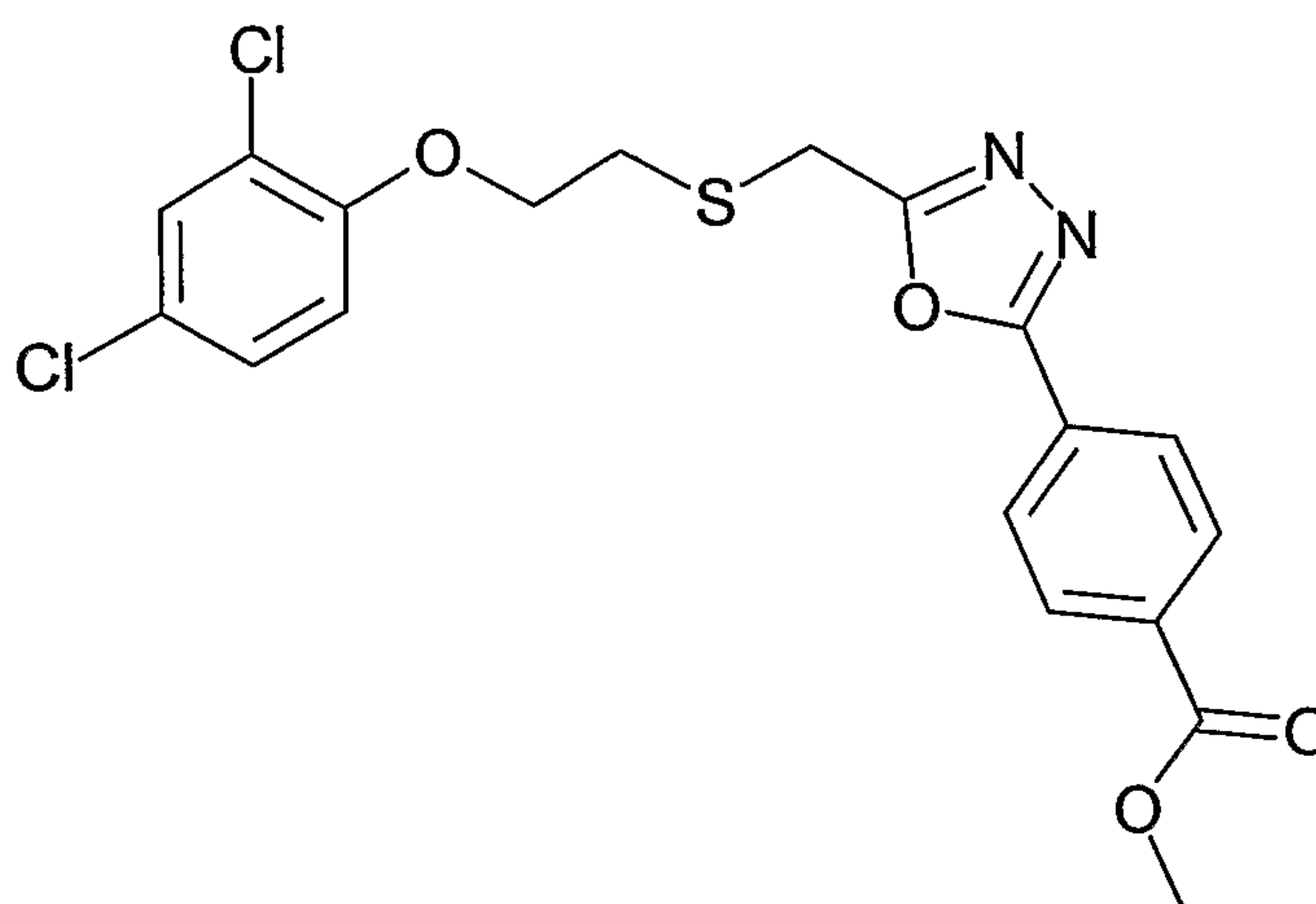
¹H NMR (CDCl₃) δ 9.30 (d, 1H, J=6 Hz), 8.82 (d, 1H, J=6 Hz), 8.11 (d, 2H, J=8 Hz), 7.84 (d, 2H, J=8 Hz), 7.36 (d, 1H, J=2 Hz), 7.17 (dd, 1H, J=2 and 9 Hz), 6.87 (d, 1H,

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J=9 Hz), 4.30 (t, 2H, J=6 Hz), 3.95 (s, 3H), 3.59 (s, 2H), and 3.16 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 3193, 1714, 1604, 1568, 1481, 1465, 1295, 1105, and 869. MS (ESI) m/e 455, 457, 459, 461. Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_5\text{S}$: C, 49.90; H, 3.97; Cl, 15.50; N, 6.13; S, 7.01. Found C, 49.99; H, 3.98; Cl, 15.79; N, 6.15; S, 7.37.

5

b) 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid methyl ester

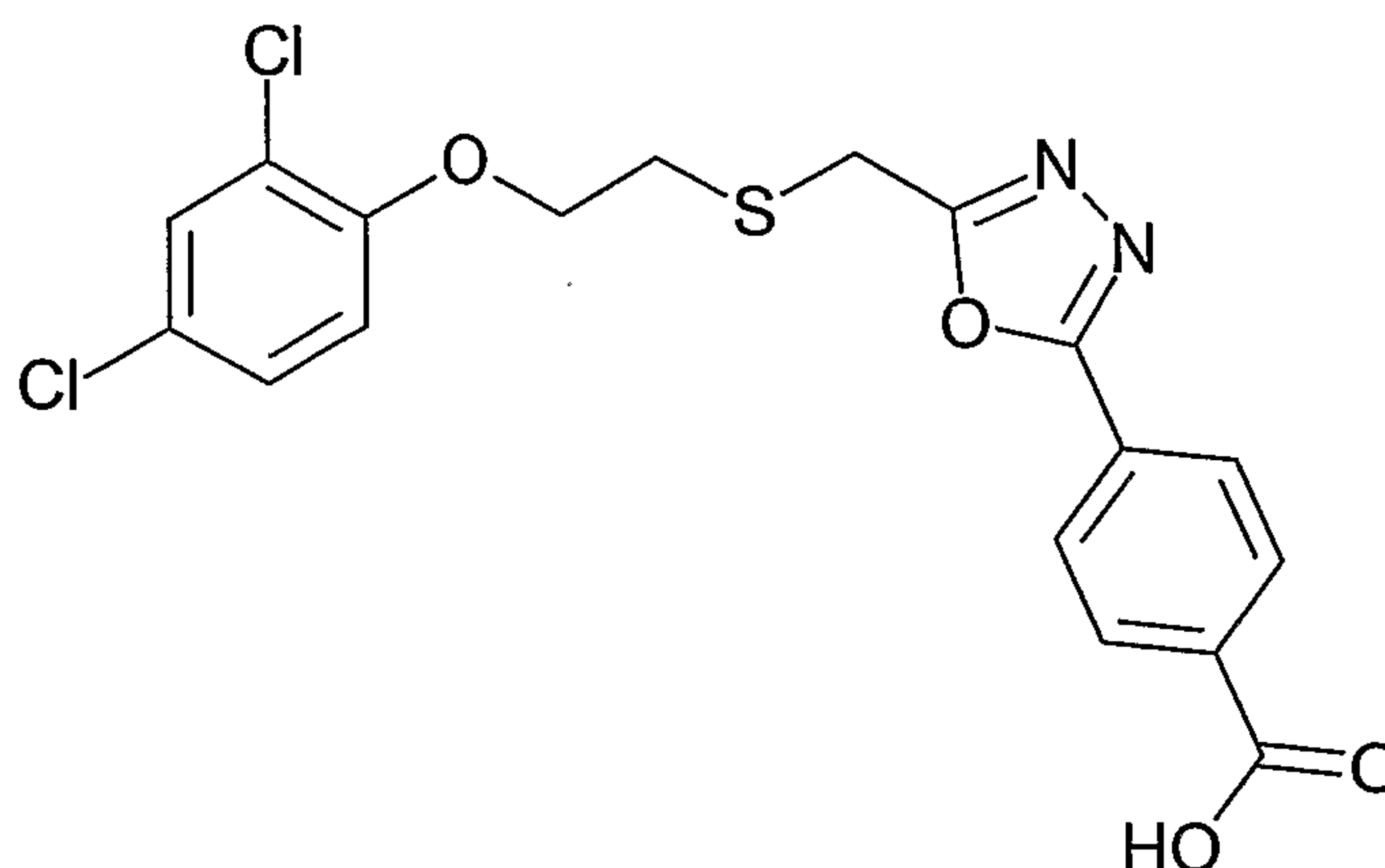


10 A heterogeneous mixture of 4-(N'-{2-[2-(2,4-dichlorophenoxy)-ethylsulfanyl]-acetyl}-hydrazinocarbonyl)-benzoic acid methyl ester (0.228 g, 0.5 mmol), triphenylphosphine (0.265 g, 1.0 mmol), triethylamine (0.251 mL, 1.8 mmol) and carbon tetrachloride (0.202 mL, 2.06 mmol) in 4 mL acetonitrile was stirred at room temperature for 4 h. The resultant precipitate was collected by filtration, washed with acetonitrile and diethyl ether,
15 and the solid was dried in vacuo at 40 °C for 2 h to afford 0.153 g (70%) of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid methyl ester as a white solid (MP 148-152 °C, MW 438.02).

^1H NMR (CDCl_3) δ 8.17 (d, 2H, J=8 Hz), 8.10 (d, 2H, J=8 Hz), 7.34 (d, 1H, J=2 Hz), 7.17 (dd, 1H, J=2 and 9 Hz), 6.84 (d, 1H, J=9 Hz), 4.26 (t, 2H, J=6 Hz), 4.18 (s, 2H),
20 3.97 (s, 3H), and 3.12 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 2940, 1717, 1485, 1470, 1437, 1432, 1287, 1252, 1236, 1114, 1062, 1010, 776, 719, and 715. MS (ESI) m/e 437, 439, 441, 443. Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_4\text{S}$: C, 51.95; H, 3.67; Cl, 16.14; N, 6.38; S, 7.30. Found C, 52.32; H, 3.69; Cl, 15.86; N, 6.38; S, 7.33.

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c) 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid

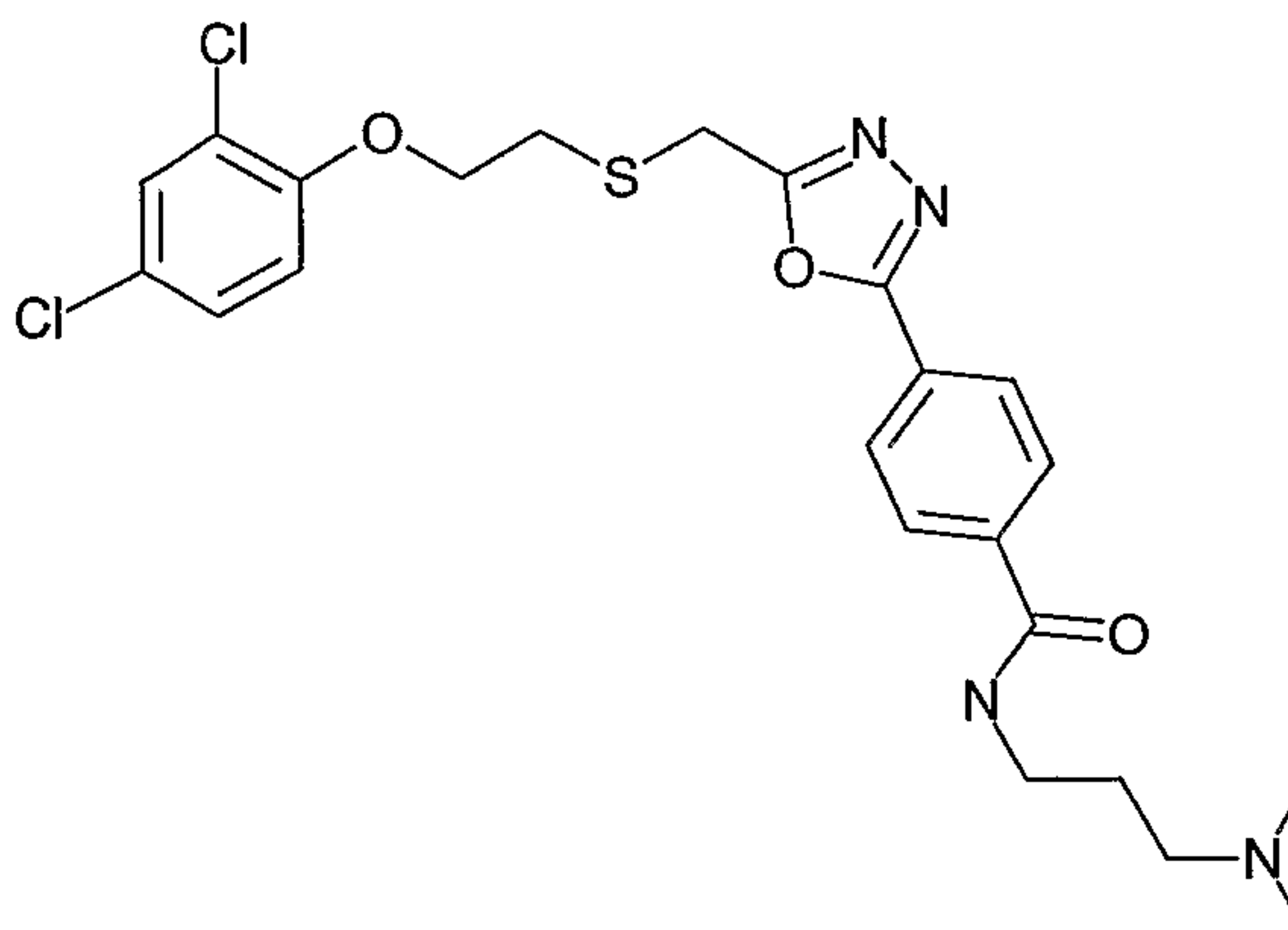


A suspension of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-
 5 [1,3,4]oxadiazol-2-yl}-benzoic acid methyl ester (0.22 g, 0.5 mmol), and lithium
 hydroxide (0.036 g, 1.5 mmol) in 3.5 mL THF and 1.5 mL H₂O was stirred at room
 temperature for 5 h. The THF was removed in vacuo, and the remaining aqueous solution
 adjusted to pH 1.7 with concentrated HCl. The resultant precipitate was collected by
 filtration, washed with H₂O, and dried in vacuo at 40 °C to afford 0.134 g (63%) of 4-{5-
 10 [2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid as a
 white solid (MP 161-163 °C, MW 424.01).

¹H NMR (DMSO-d₆) δ 13.30 (bs, 1H), 8.11 (d, 2H, J=9 Hz), 8.04 (d, 2H, J=9 Hz),
 7.52 (d, 1H, J=2 Hz), 7.33 (dd, 1H, J=2 and 9 Hz), 7.17 (d, 1H, J=9 Hz), 4.28 (t, 2H, J=6
 Hz), 4.27 (s, 2H), and 3.05 (t, 2H, J=6 Hz). IR (KBr, cm⁻¹) 2910, 2670, 2550, 1704, 1686,
 1551, 1485, 1433, 1291, 1262, 1072, 871, and 714. MS (ESI) m/e 423, 425, 427, 429.
 15 Anal. Calcd for C₁₈H₁₄Cl₂N₂O₄S: C, 50.84; H, 3.32; Cl, 16.67; N, 6.59; S, 7.54. Found C,
 50.78; H, 3.40; Cl, 16.83; N, 6.55; S, 7.74.

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d) 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]-oxadiazol-2-yl}-N-(3-dimethylaminopropyl)-benzamide



A solution of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-
 5 [1,3,4]oxadiazol-2-yl}-benzoic acid (0.361 g, 0.85 mmol), and 1,1'-carbonyldiimidazole (0.139 g, 0.86 mmol) in 10.0 mL THF was stirred at 60 °C for 0.5 h. The reaction solution was allowed to cool to ambient temperature followed by addition of 3-(dimethylamino)propylamine (0.129 mL, 1.02 mmol), then stirred at room temperature for 3 h. The THF was concentrated in vacuo and the resultant precipitate was collected by
 10 filtration, washed with ethyl acetate and diethyl ether, and dried in vacuo at 40 °C to afford 0.25 g (57%) of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]-oxadiazol-2-yl}-N-(3-dimethylaminopropyl)-benzamide as a white solid (MP 140-141 °C, MW 508.11).

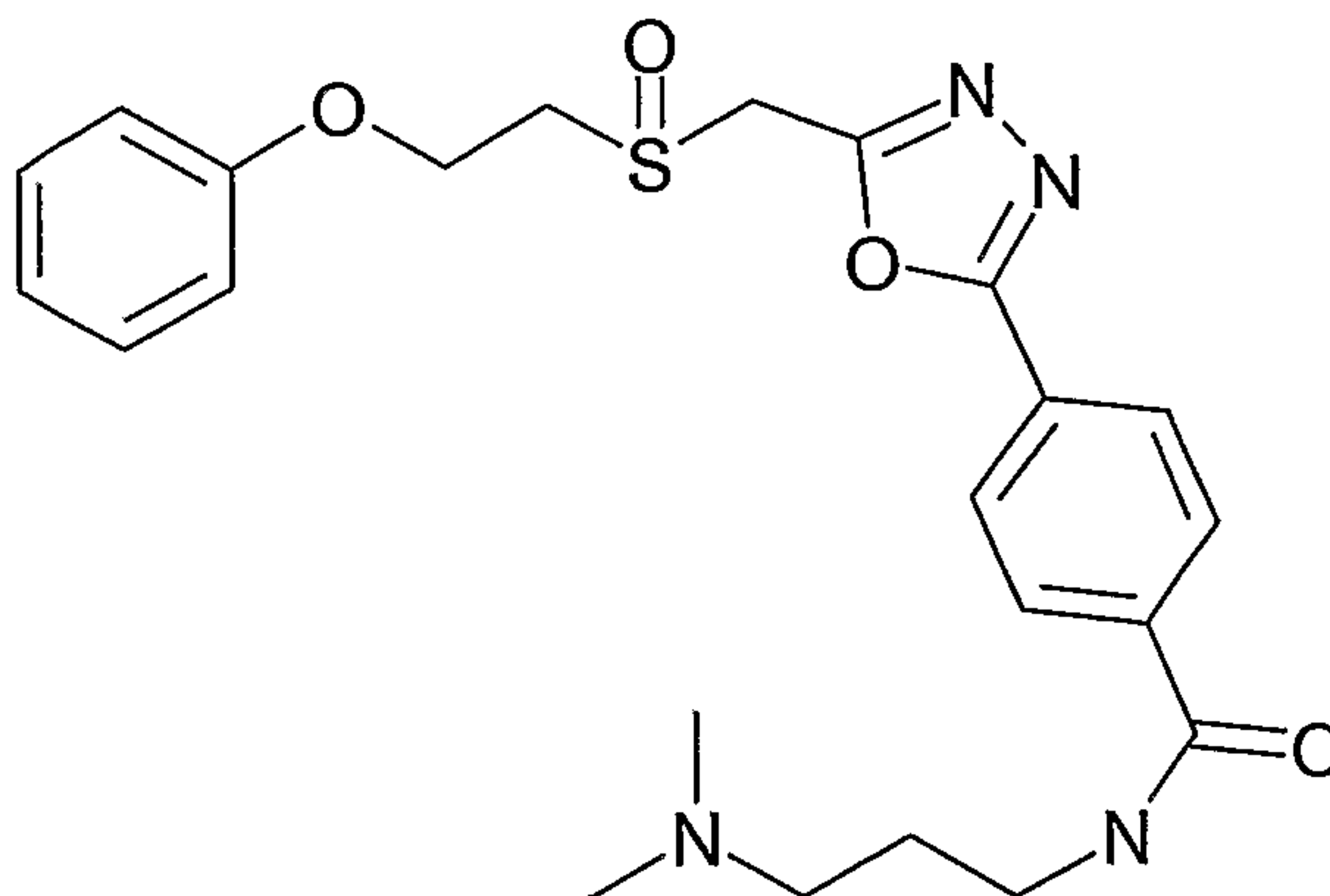
¹H NMR (CDCl₃) δ 8.86 (bs, 1H), 8.09 (d, 2H, J=9 Hz), 7.92 (d, 2H, J=9 Hz),
 15 7.34 (d, 1H, J=2 Hz), 7.17 (dd, 1H, J=2 and 9 Hz), 6.84 (d, 1H, J=9 Hz), 4.26 (t, 2H, J=6 Hz), 4.17 (s, 2H), 3.61 (m, 2H), 3.11 (t, 2H, J=6 Hz), 2.61 (m, 2H), 2.38 (bs, 6H), 1.83 (m, 2H). IR (KBr, cm⁻¹) 3335, 2942, 2761, 2722, 1635, 1555, 1484, 1105, and 803. MS (ESI) m/e 507, 509, 511, 513. Anal. Calcd for C₂₃H₂₆Cl₂N₄O₃S: C, 54.23; H, 5.14; Cl, 13.92; N, 11.00; S, 6.29. Found C, 54.03; H, 5.15; Cl, 13.98; N, 10.98; S, 6.25.

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Example 45

Preparation of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfinylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

-161-



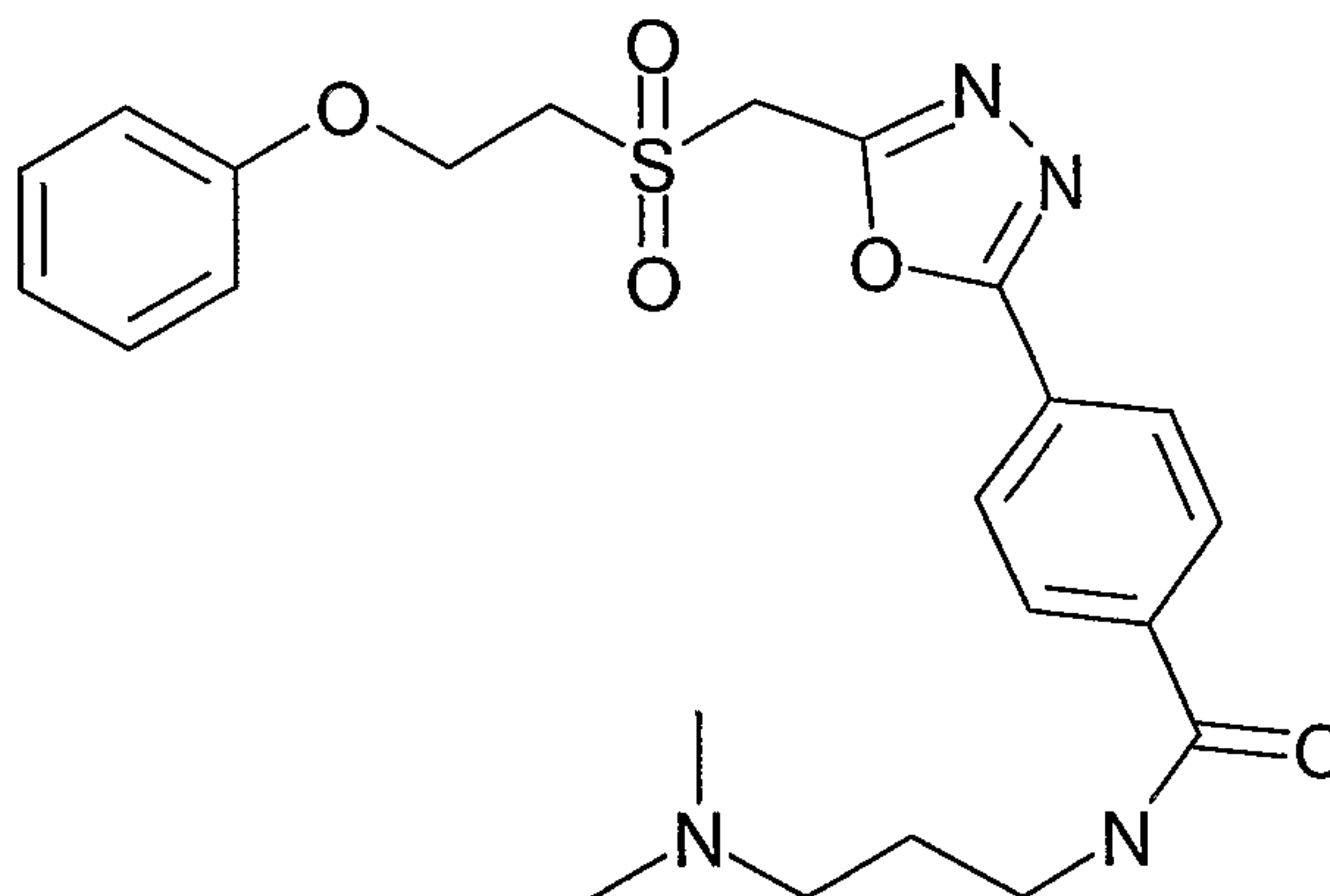
A solution of the N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide (0.044 g, 0.1 mmol) prepared in Example 32, glacial acetic acid (1.14 mL, 20.0 mmol), and 3-chloroperoxybenzoic acid (0.022 g, 0.1 mmol) in 1 mL of dichloromethane was stirred at room temperature for 1 h. The mixture was quenched with 3 mL saturated sodium sulfite followed by addition of 6 mL H₂O and 1 mL dichloromethane. The resultant biphasic solution was adjusted to pH 10.3 with 1N NaOH, the solvent layers separated, and the aqueous phase back extracted with 6x10 mL dichloromethane. The combined dichloromethane extracts were washed with H₂O and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 0.043 g (95%) of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as a white solid (MP 112-114 °C, MW 456.57). Analytical HPLC: 93% purity.

¹H NMR (CDCl₃) δ 8.88 (bs, 1H), 8.12 (d, 2H, J=8 Hz), 7.95 (d, 2H, J=8 Hz), 7.30 (t, 2H, J=8 Hz), 7.01 (t, 1H, J=7 Hz), 6.93 (d, 2H, J=8 Hz), 4.62 (d, 1H, J=14 Hz), 4.48 (m, 2H), 4.36 (d, 1H, J=14 Hz), 3.61 (m, 2H), 3.40 (m, 2H), 2.65 (m, 2H), 2.41 (bs, 6H), and 1.86 (m, 2H). IR (KBr, cm⁻¹) 3344, 2922, 2761, 1636, 1549, 1497, 1251, and 1044. MS (ESI) m/e 457, 455. Anal. Calcd for C₂₃H₂₈N₄O₄S: C, 60.51; H, 6.18; N, 12.27; S, 7.02. Found C, 59.91; H, 6.16; N, 11.61; S, 6.50.

Example 46

Preparation of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

-162-



A solution of the N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide (0.022 g, 0.05 mmol) prepared in Example 32, glacial acetic acid (0.58 mL, 10.0 mmol), and 3-chloroperoxybenzoic acid (0.022 g, 0.1 mmol) in 1 mL of dichloromethane was stirred at room temperature for 19 h. The mixture was quenched with 3 mL saturated sodium sulfite followed by addition of 2 mL H₂O and 4 mL dichloromethane. The resultant biphasic solution was adjusted to pH 10.3 with 1N NaOH, the solvent layers separated, and the aqueous phase back extracted with 3x15 mL dichloromethane. The combined dichloromethane extracts were washed with H₂O and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 0.017 g (73%) of a mixture composed primarily of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide and a minor amount of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfinylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as a white solid. A solution of the preceding mixture (0.015 g, ~0.03 mmol), osmium tetroxide (2.5 weight percent solution in 2-methyl-2-propanol, 0.003 mL, 0.25 μ M), and 4-methylmorpholine N-oxide (0.003 g, 0.025 mmol) in 1 mL of THF and 0.5 mL dichloromethane was stirred at room temperature for 1 h. The THF was removed in vacuo, the resultant gum redissolved in dichloromethane, washed with H₂O and brine, dried over anhydrous sodium sulfate, filtered, and and concentrated in vacuo to afford 0.008 g of a black solid. Purification by column chromatography on silica gel (isocratic elution with 8:2 CHCl₃/2.0 M ammonia in methanol) afforded 0.003 g (13%) of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white solid (MW 472.57).

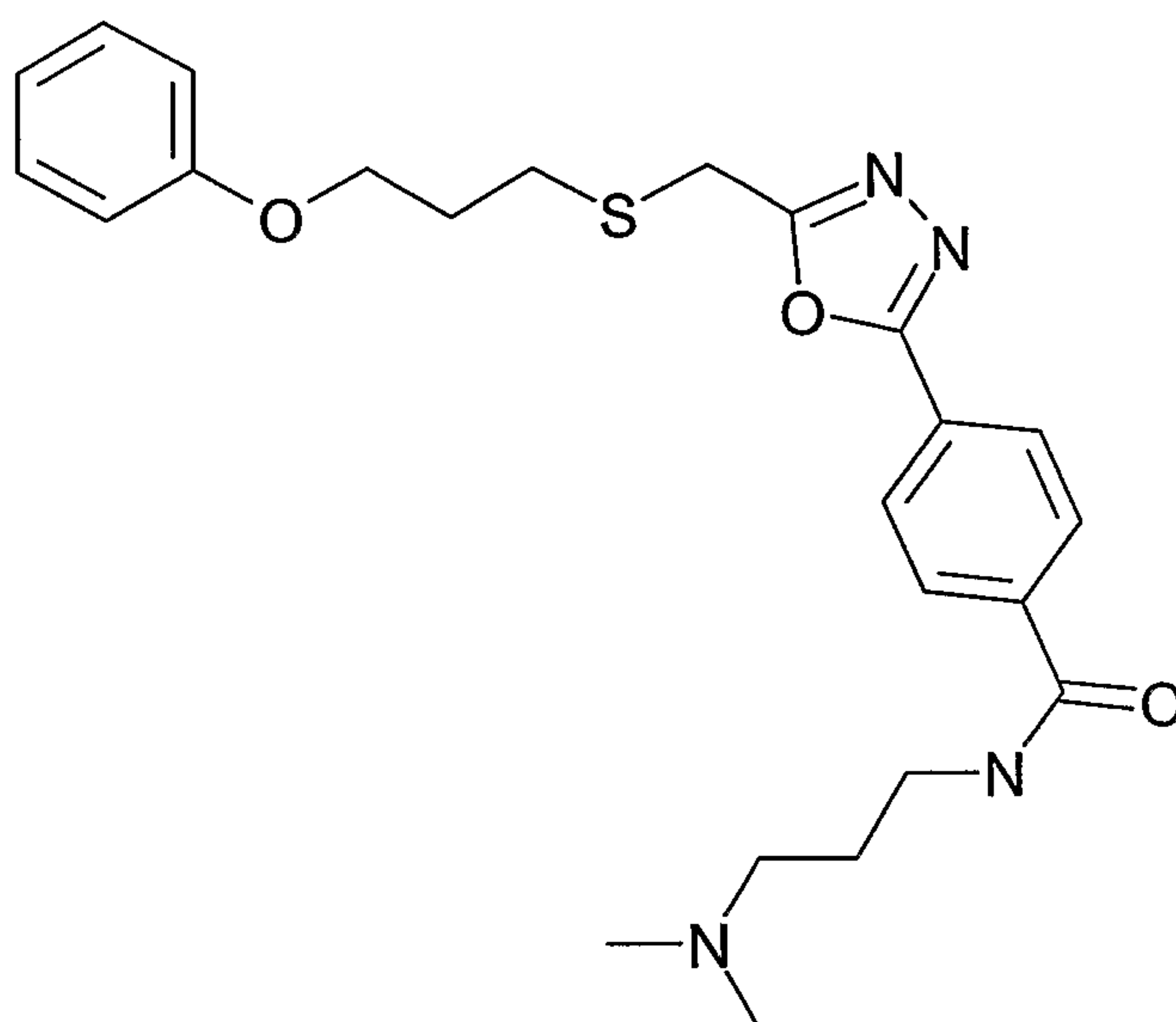
-163-

^1H NMR (CDCl_3) δ 8.88 (bs, 1H), 8.11 (d, 2H, $J=8$ Hz), 7.95 (d, 2H, $J=8$ Hz), 7.33 (t, 2H, $J=8$ Hz), 7.04 (t, 1H, $J=7$ Hz), 6.97 (d, 2H, $J=8$ Hz), 4.86 (s, 2H), 4.53 (t, 2H, $J=5$ Hz), 3.71 (t, 2H, $J=5$ Hz), 3.61 (m, 2H), 2.65 (m, 2H), 2.41 (bs, 6H), and 1.87 (m, 2H). MS (ESI) m/e 471, 473.

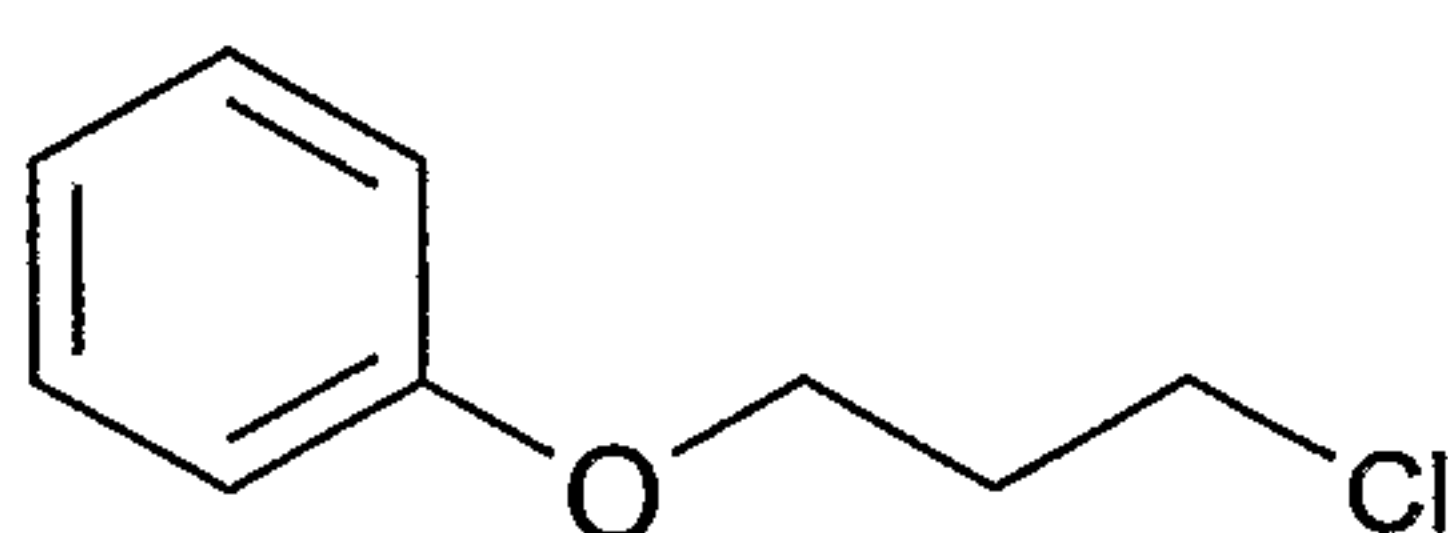
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Example 47

Preparation of N-(3-dimethylaminopropyl)-4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



10 a) 3-chloropropoxy benzene



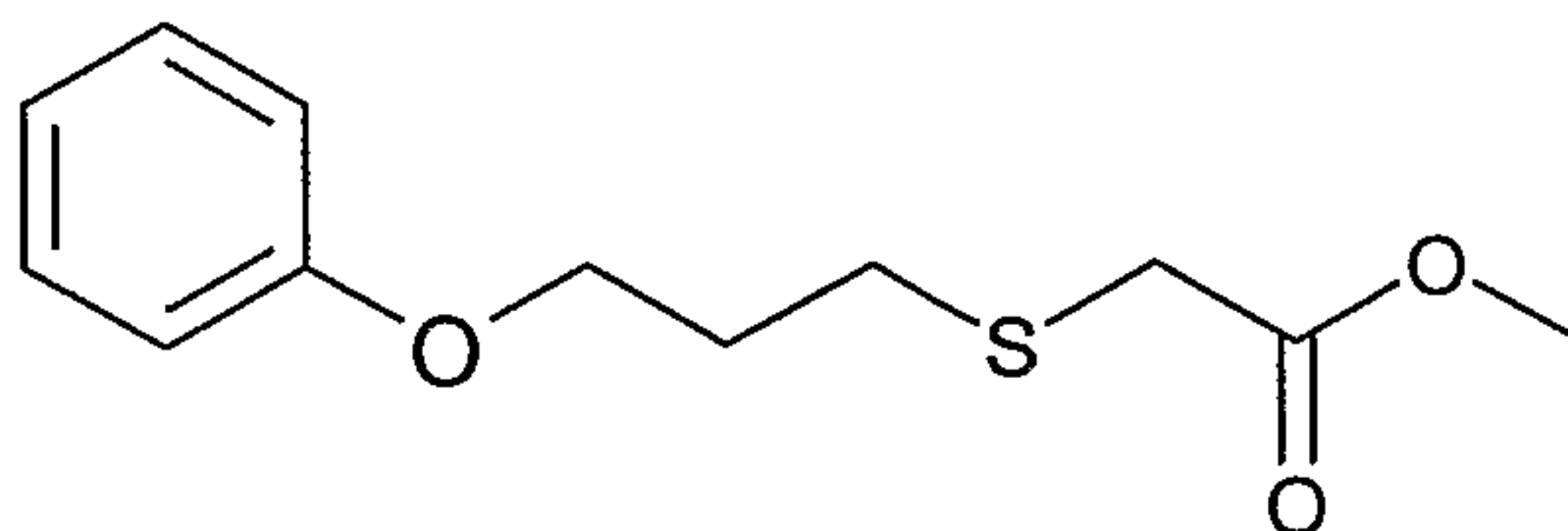
A solution of phenol (9.41 g, 0.1 M), 1-bromo-3-chloropropane (15.74 g, 0.1 M) and potassium carbonate (13.8 g, 0.1 M) in 150 mL of DMF was stirred at room temperature for 48 h, then sonicated at 50-60 °C for 12 h. The DMF was removed in vacuo, the residue diluted with EtOAc, washed with water, 5 N NaOH, and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 14.4 g (84%) of 3-chloropropoxy benzene as a clear oil.

^1H NMR ($\text{DMSO}-d_6$) δ 7.3 (m, 2H), 6.9 (m, 3H), 4.1 (t, 2H, $J=6$ Hz), 3.6 (t, 2H, $J=6$ Hz), and 2.1 (quintet, 2H, $J=6$ Hz). IR (CHCl_3 , cm^{-1}) 1600, 1587, 1498, 1470, 1244,

-164-

1226, 1172, and 1039. MS (EI) m/e 170. Anal. Calcd for C₉H₁₁ClO: C, 63.35; H, 6.50; Cl, 20.78. Found C, 65.60; H, 6.57; Cl, 17.41.

b) (3-phenoxypropylsulfanyl)-acetic acid methyl ester

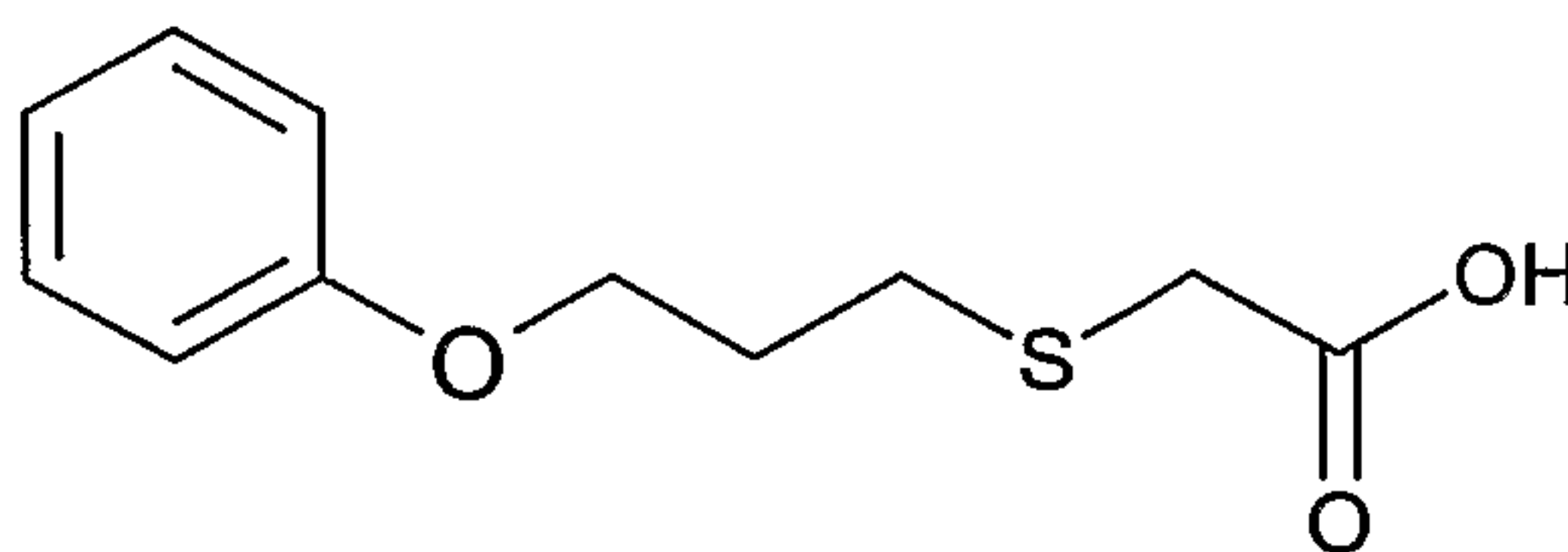


5

A solution of 3-chloropropoxy benzene (1.00 g, 5.86 mmol), thioglycolate methyl ester (0.622 g, 5.86 mmol) and potassium carbonate (1.00 g, 7.25 mmol) in 5 mL of DMF was stirred at room temperature for 48 h, then sonicated at 50-60 °C for 8 h, then stirred at room temperature for an additional 64 h. The mixture was diluted with EtOAc, washed
10 with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1.29 g (92%) of (3-phenoxypropylsulfanyl)-acetic acid methyl ester as a clear oil.

¹H NMR (DMSO-d₆) δ 7.3 (m, 2H), 6.9 (m, 3H), 4.0 (t, 2H, J=6 Hz), 3.65 (s, 3H), 3.4 (s, 2H), 2.7 (t, 2H, J=7 Hz), and 1.9 (m, 2H). IR (CHCl₃, cm⁻¹) 2954, 1734, 1600,
1587, 1497, 1469, 1437, 1289, and 1244. MS (FD) m/e 241. Anal. Calcd for C₁₂H₁₆O₃S:
15 C, 59.98; H, 6.71. Found C, 58.81; H, 6.24.

c) (3-phenoxypropylsulfanyl)-acetic acid

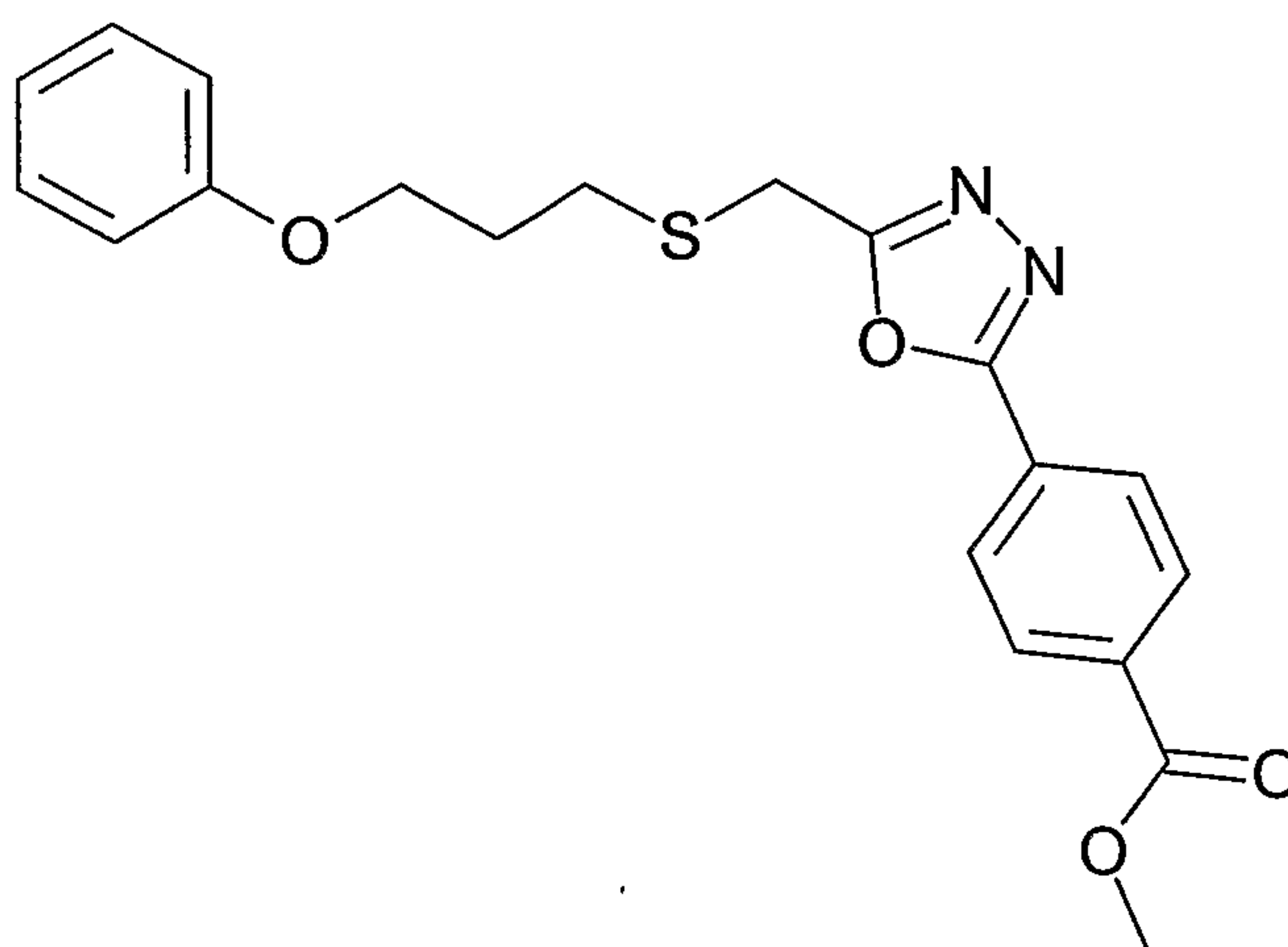


A solution of (3-phenoxypropylsulfanyl)-acetic acid methyl ester (1.20 g, 5.0 mmol) and 1 N NaOH (15.0 mL, 15 mmol) in 15 mL of methanol was stirred at room temperature for 48 h. The solvent was removed in vacuo, the residue triturated with EtOAc, then dissolved in 1 N HCl and EtOAc. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford
20 0.853 g (75%) of 3-phenoxypropylsulfanyl)-acetic acid as a clear oil.
25

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^1H NMR (DMSO- d_6) δ 12.5 (br s, 1H), 7.3 (m, 2H), 6.9 (m, 3H), 4.0 (t, 2H, $J=6$ Hz), 3.3 (s, 2H), 2.7 (t, 2H, $J=7$ Hz), and 2.0 (quintet, 2H, $J=6$ Hz). IR (CHCl_3 , cm^{-1}) 3010, 2944, 1711, 1601, 1497, 1301, 1290, 1244, and 1172. MS (ESI) m/e 227, 225. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3\text{S}$: C, 58.38; H, 6.23; S, 14.17. Found C, 58.16; H, 6.20; S, 13.78.

d) 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester

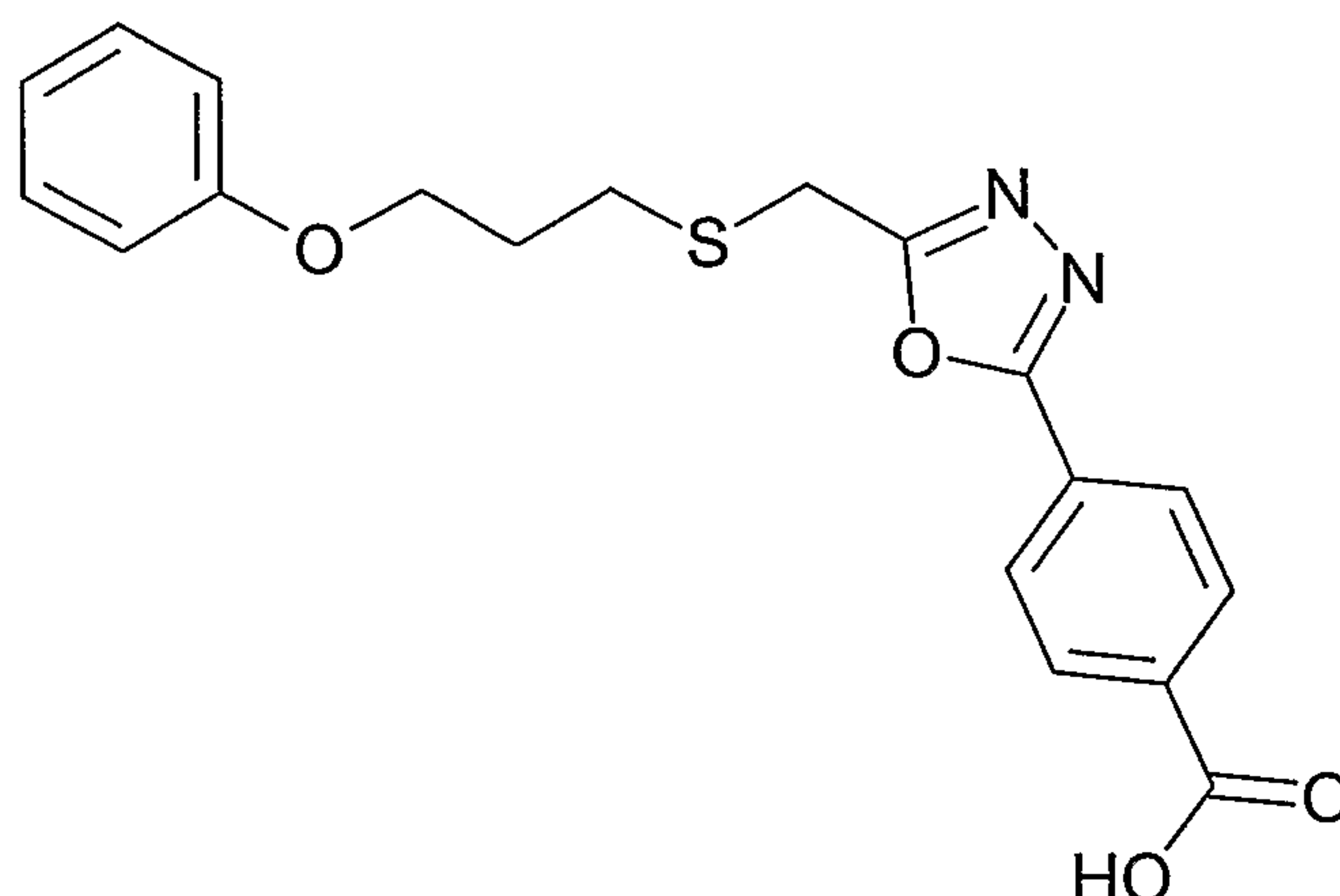


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 4-(1H-tetrazol-5-yl)-benzoic acid methyl ester (0.714 g, 3.5 mmol) and (3-phenoxypropylsulfanyl)-acetic acid (0.8 g, 3.54 mmol). Purification by column chromatography on silica gel (elution with linear gradient of 15-100% ethyl acetate/hexane) afforded 0.985 g (73%) of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester as a tan solid (MP 97-100 °C, MW 384.46).

^1H NMR (CDCl_3) δ 8.17 (d, 2H, $J=9$ Hz), 8.12 (d, 2H, $J=9$ Hz), 7.26 (t, 2H, $J=8$ Hz), 6.94 (t, 1H, $J=8$ Hz), 6.87 (d, 2H, $J=8$ Hz), 4.06 (t, 2H, $J=6$ Hz), 3.97 (s, 3H), 3.96 (s, 2H), 2.86 (t, 2H, $J=7$ Hz), and 2.11 (m, 2H). IR (KBr, cm^{-1}) 2920, 1718, 1604, 1439, 1280, 1254, 1109, 755, and 709. MS (ESI) m/e 385, 383. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: C, 62.48; H, 5.24; N, 7.29; S, 8.34. Found C, 62.90; H, 5.77; N, 7.30; S, 8.81.

e) 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid

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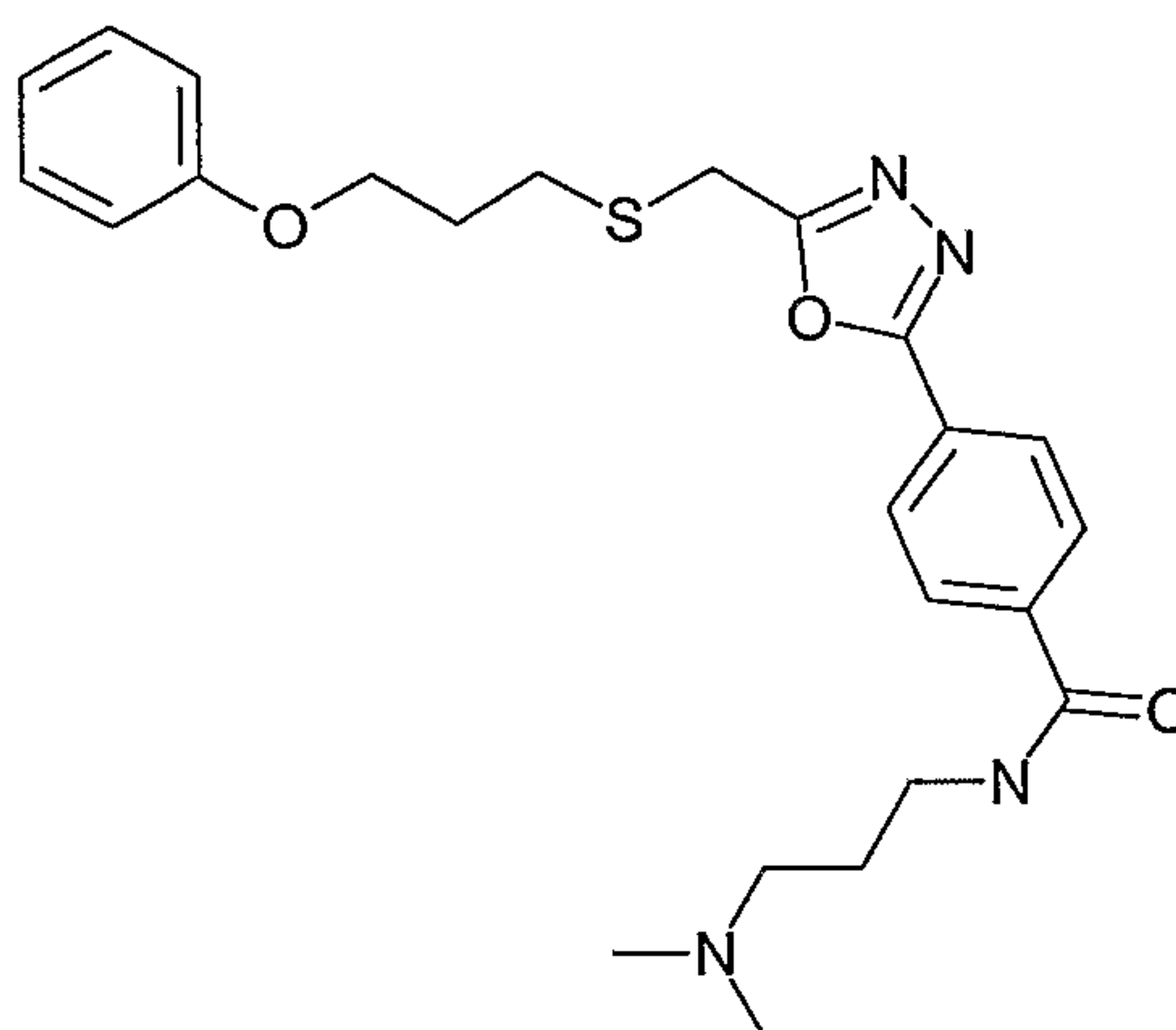


A suspension of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester (0.961 g, 2.5 mmol), and lithium hydroxide (0.183 g, 7.5 mmol) in 9 mL THF and 4 mL H₂O was stirred at room temperature for 4 h. The THF was removed in vacuo, an additional 10 mL of H₂O was added, and the heterogeneous aqueous mixture was adjusted to pH 1.8 with concentrated HCl. The resultant precipitate was collected by filtration, washed with H₂O, and dried in vacuo at 40 °C to afford 0.917 g (99%) of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid as an off-white solid (MP 180-185 °C, MW 370.43).

¹H NMR (DMSO-d₆) δ 13.30 (bs, 1H), 8.11 (d, 2H, J=9 Hz), 8.07 (d, 2H, J=9 Hz), 7.23 (t, 2H, J=8 Hz), 6.88 (m, 3H), 4.15 (s, 2H), 4.01 (t, 2H, J=6 Hz), 2.78 (t, 2H, J=7 Hz), and 1.99 (m, 2H). IR (KBr, cm⁻¹) 2997, 2643, 2522, 1709, 1471, 1267, 1242, 753, and 714. MS (ESI) m/e 371, 369. Anal. Calcd for C₁₉H₁₈N₂O₄S: C, 61.61; H, 4.90; N, 7.56; S, 8.66. Found C, 62.26; H, 5.52; N, 7.54; S, 8.29.

f) N-(3-dimethylaminopropyl)-4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

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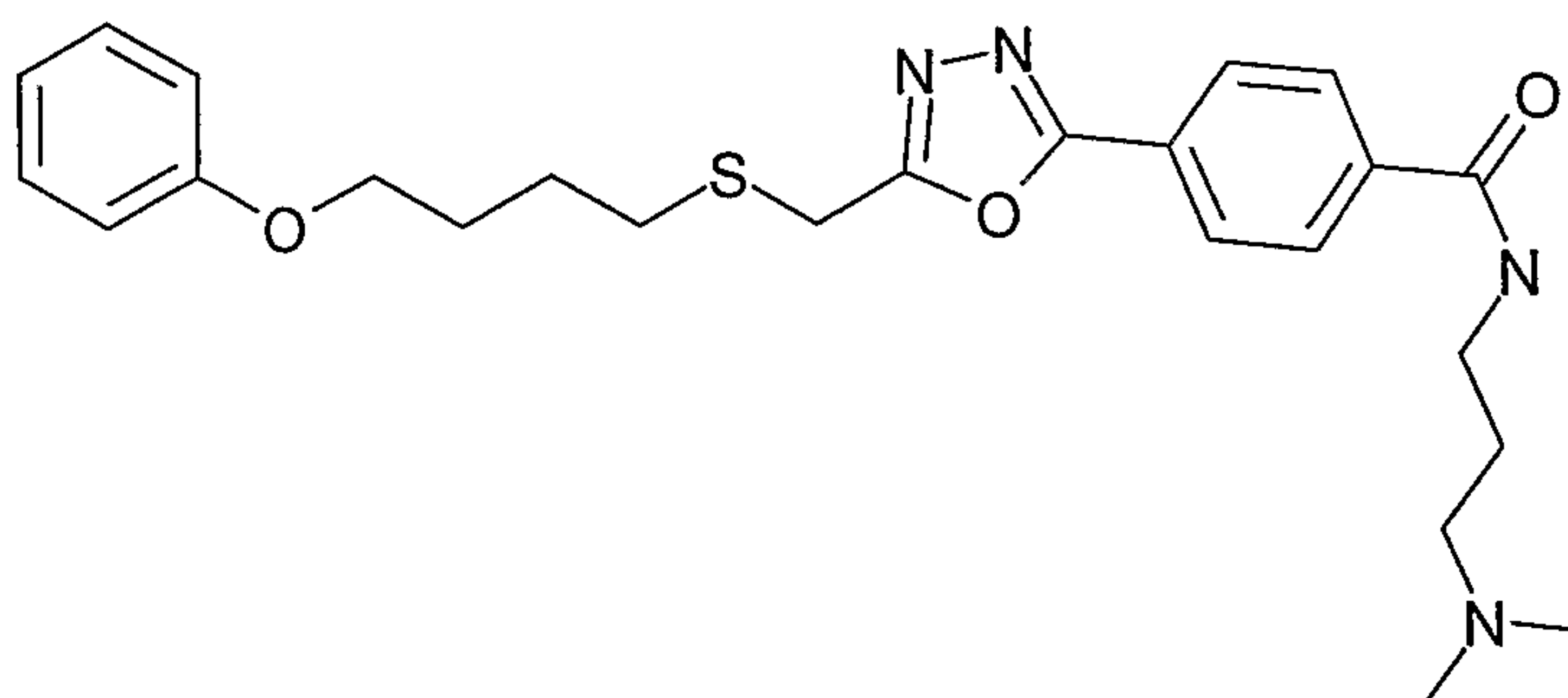
A solution of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.37 g, 1.0 mmol), and 1,1'-carbonyldiimidazole (0.164 g, 1.01 mmol) in 10.0 mL THF was stirred at 60 °C for 0.5 h. The reaction solution was allowed to cool to ambient temperature followed by addition of 3-(dimethylamino)propylamine (0.152 mL, 1.2 mmol), then stirred at room temperature for 6 h. The THF was concentrated in vacuo, and the oily residue redissolved in ethyl acetate/H₂O. The solvent layers were separated, and the ethyl acetate layer was washed with H₂O and brine, dried over anhydrous sodium sulfate, filtered, concentrated in vacuo to afford 0.342 g of a tan solid. Purification by column chromatography on silica gel (isocratic elution with 1:1 toluene/ethyl acetate followed by 9:1 CHCl₃/2.0 M ammonia in methanol) afforded 0.256 g (56%) of N-(3-dimethylaminopropyl)-4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white solid (MP 77-80 °C, MW 454.60).

¹H NMR (CDCl₃) δ 8.79 (bs, 1H), 8.12 (d, 2H, J=8 Hz), 8.01 (d, 2H, J=8 Hz), 7.26 (t, 2H, J=8 Hz), 6.92 (t, 1H, J=7 Hz), 6.88 (d, 2H, J=8 Hz), 4.06 (t, 2H, J=6 Hz), 3.95 (s, 2H), 3.64 (m, 2H), 2.86 (t, 2H, J=7 Hz), 2.77 (m, 2H), 2.52 (bs, 6H), 2.11 (m, 2H), and 1.96 (m, 2H). IR (KBr, cm⁻¹) 3304, 3063, 2937, 2814, 2762, 1633, 1586, 1561, 1554, 1541, 1499, 1469, 1245, 1183, 853, and 751. MS (ESI) m/e 455, 453. Anal. Calcd for C₂₄H₃₀N₄O₃S: C, 63.41; H, 6.65; N, 12.32; S, 7.05. Found C, 63.29; H, 6.67; N, 12.34; S, 7.03.

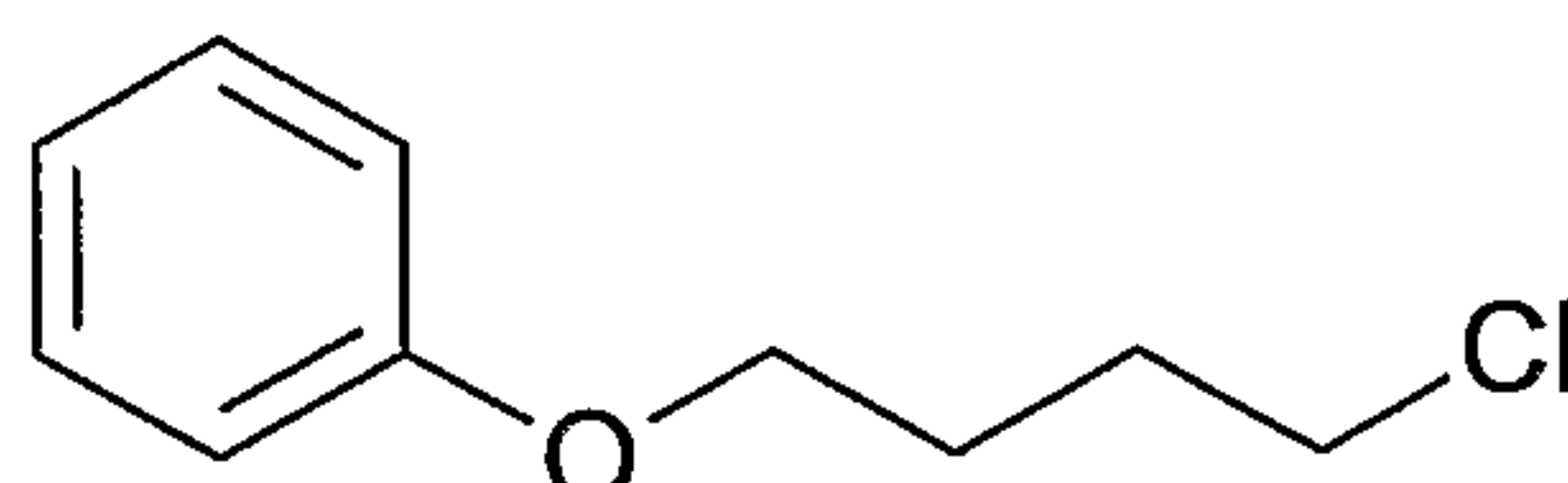
Example 48

Preparation of N-(3-dimethylaminopropyl)-4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

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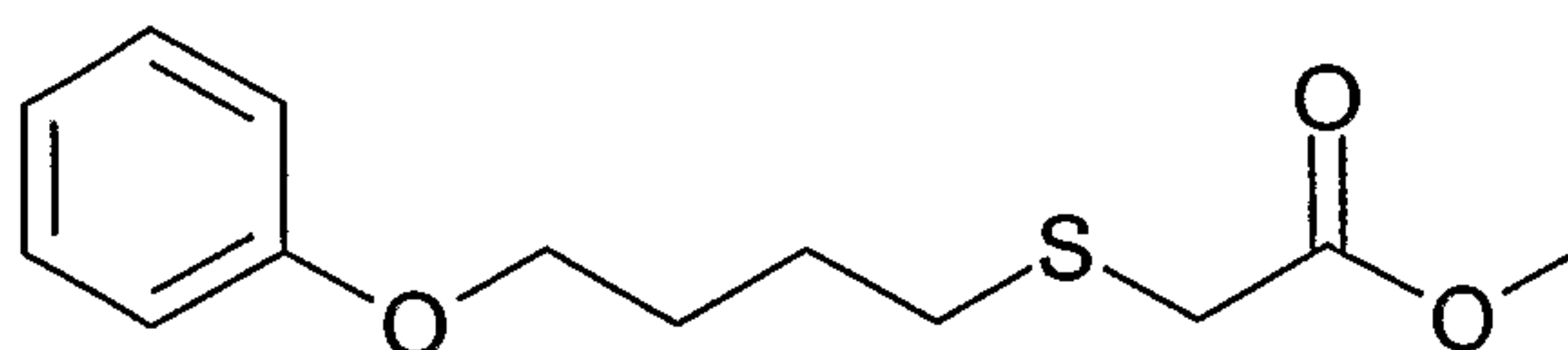
a) 4-chlorobutoxy benzene



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47a, from phenol (4.75 g, 50.0 mmol) and 1-bromo-4-chlorobutane (5.82 mL, 50.0 mmol) to afford 9.5 g (quantitative) of 4-chlorobutoxy benzene as a colorless oil (MW 184.67).

^1H NMR (CDCl_3) δ 7.28 (t, 2H, $J=8$ Hz), 6.94 (t, 1H, $J=8$ Hz), 6.89 (d, 2H, $J=8$ Hz), 4.00 (t, 2H, $J=6$ Hz), 3.62 (t, 2H, $J=6$ Hz), and 1.97 (m, 4H). IR (CHCl_3 , cm^{-1}) 3012, 2960, 2875, 1599, 1587, 1498, 1471, 1244, and 1172. MS (EI) m/e 184. Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{ClO}$: C, 65.04; H, 7.10; Cl, 19.20. Found C, 64.96; H, 7.03; Cl, 18.91.

b) (4-phenoxybutylsulfanyl)-acetic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47b, from 4-chlorobutoxy benzene (1.85 g, 10.0 mmol) and methyl thioglycolate (1.03 mL, 11.0 mmol) to afford 2.46g (96%) of (4-phenoxybutylsulfanyl)-acetic acid methyl ester as a colorless oil (MW 254.35).

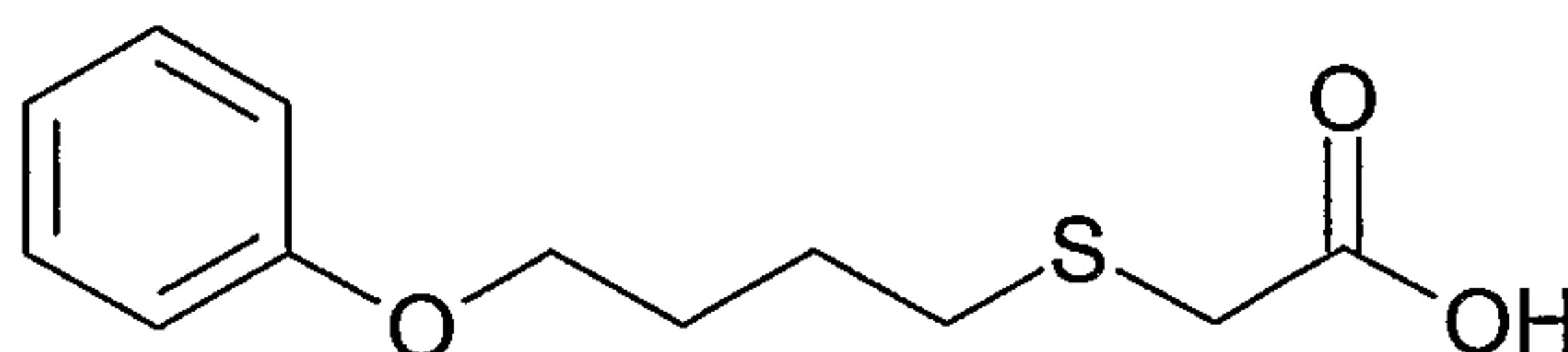
^1H NMR (CDCl_3) δ 7.28 (t, 2H, $J=8$ Hz), 6.93 (t, 1H, $J=8$ Hz), 6.89 (d, 2H, $J=8$ Hz), 3.98 (t, 2H, $J=6$ Hz), 3.73 (s, 3H), 3.24 (s, 2H), 2.72 (t, 2H, $J=7$ Hz), and 1.86 (m, 4H). IR (CHCl_3 , cm^{-1}) 3012, 2930, 1733, 1600, 1497, 1287, and 1244. MS (FD) m/e 254.

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Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13; S, 12.61. Found C, 60.43; H, 7.06; S, 10.84.

c) (4-phenoxybutylsulfanyl)-acetic acid

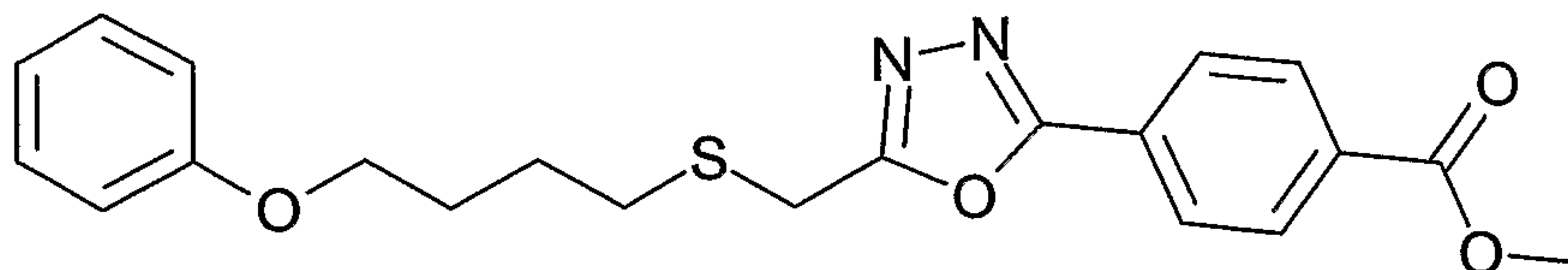
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The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47c, from 4-phenoxybutylsulfanyl)-acetic acid methyl ester (2.29 g, 9.0 mmol) and 2N NaOH (13.5 mL, 27.0 mmol) to afford 2.04g (94%) of 4-phenoxybutylsulfanyl)-acetic acid as a pale yellow solid (MP 48-50 °C, MW 240.32).

^1H NMR ($CDCl_3$) δ 7.28 (t, 2H, J=8 Hz), 6.94 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 3.98 (t, 2H, J=6 Hz), 3.28 (s, 2H), 2.74 (t, 2H, J=7 Hz), and 1.86 (m, 4H). IR ($CHCl_3$, cm^{-1}) 3010, 2944, 1710, 1600, 1497, 1300, 1291, 1244, and 1172. MS (ESI) m/e 241, 239. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71; S, 13.34. Found C, 58.55; H, 6.66; S, 16.01.

d) 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester



20

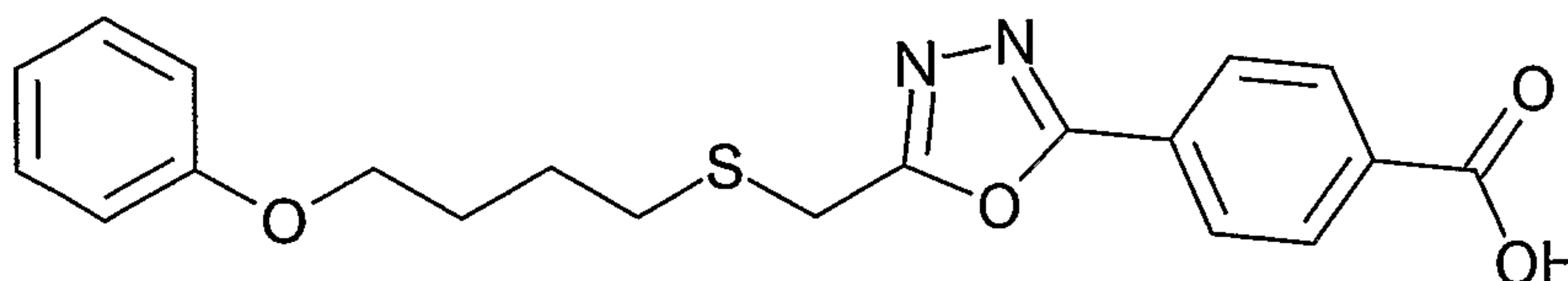
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47d, from 4-(1H-tetrazol-5-yl)-benzoic acid methyl ester (0.817 g, 4.0 mmol) and (4-phenoxybutylsulfanyl)-acetic acid (0.971 g, 4.04 mmol). Purification by column chromatography on silica gel (elution with linear gradient of 10-100% ethyl acetate/hexane) afforded 1.08 g (68%) of 4-[5-(4-phenoxybutylsulfanylmethyl) - [1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester as an off-white solid (MP 98-105 °C, MW 398.48).

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^1H NMR (CDCl_3) δ 8.17 (d, 2H, $J=9$ Hz), 8.13 (d, 2H, $J=9$ Hz), 7.26 (t, 2H, $J=8$ Hz), 6.92 (t, 1H, $J=8$ Hz), 6.86 (d, 2H, $J=8$ Hz), 3.96 (m, 7H), 2.73 (t, 2H, $J=7$ Hz), and 1.87 (m, 4H). IR (KBr, cm^{-1}) 2930, 1713, 1554, 1498, 1426, 1289, 1283, 1241, 1119, 1112, 754, and 713. MS (ESI) m/e 399, 397. Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$: C, 63.30; H, 5.56; N, 7.03; S, 8.05. Found C, 63.41; H, 6.04; N, 6.82; S, 7.97.

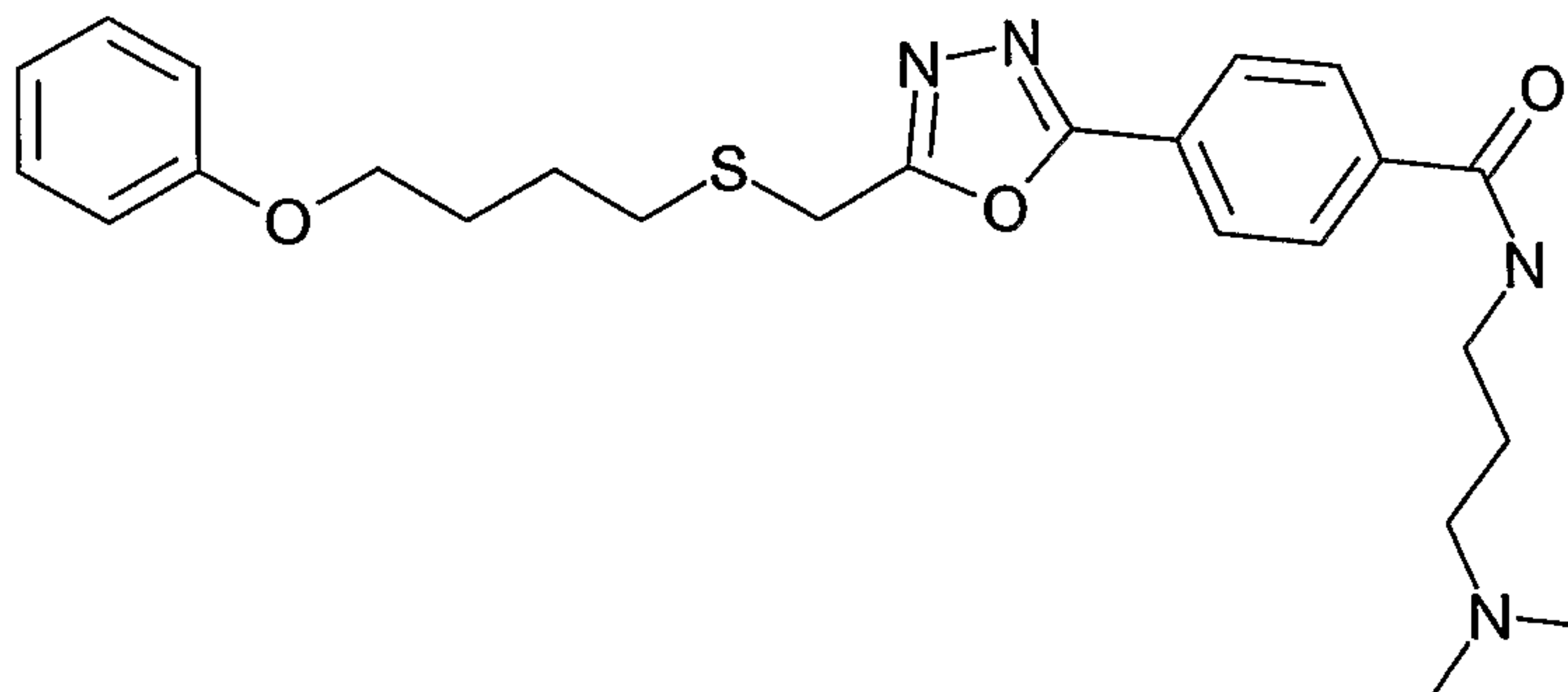
e) 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47e, from 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester (1.04 g, 2.6 mmol), and lithium hydroxide (0.191 g, 7.8 mmol) to afford 1.0 g (quantitative) of 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid as an off-white solid (MP 153-160 °C, MW 384.46).

^1H NMR ($\text{DMSO}-d_6$) δ 13.25 (bs, 1H), 8.11 (d, 2H, $J=9$ Hz), 8.08 (d, 2H, $J=9$ Hz), 7.22 (t, 2H, $J=8$ Hz), 6.87 (m, 3H), 4.12 (s, 2H), 3.93 (t, 2H, $J=6$ Hz), 2.69 (t, 2H, $J=7$ Hz), and 1.73 (m, 4H). IR (KBr, cm^{-1}) 3314, 2925, 2851, 1705, 1684, 1498, 1293, 1247, 748, and 715. MS (ESI) m/e 385, 383. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: C, 62.48; H, 5.24; N, 7.29; S, 8.34. Found C, 63.19; H, 5.99; N, 7.13; S, 8.37.

f) N-(3-dimethylaminopropyl)-4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



A solution of 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.384 g, 1.0 mmol), and 1,1'-carbonyldiimidazole (0.164 g, 1.01 mmol) in 8.0 mL

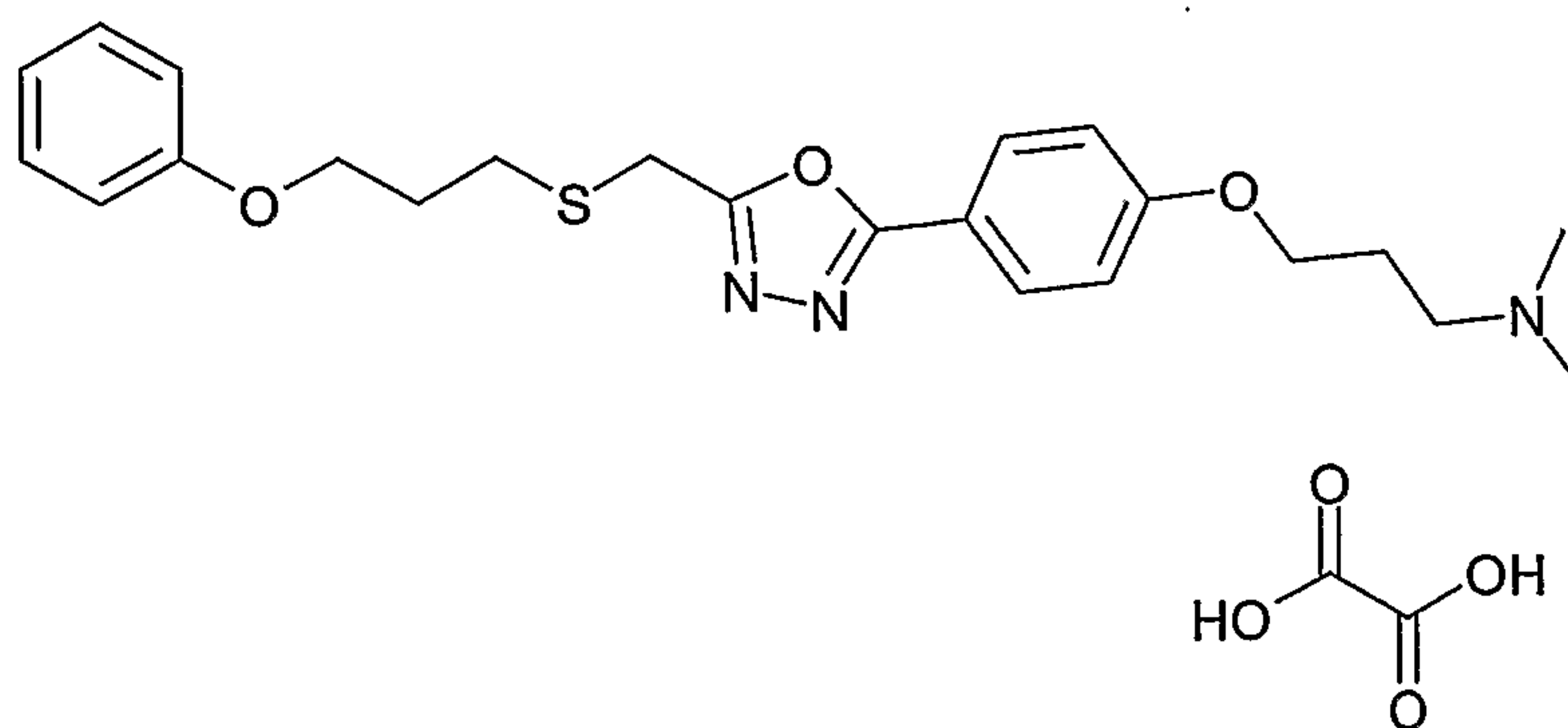
-171-

THF was stirred at 65 °C for 0.5 h. The reaction solution was allowed to cool to ambient temperature followed by addition of 3-(dimethylamino)propylamine (0.152 mL, 1.2 mmol), then stirred at room temperature for 4.5 h. The THF was concentrated in vacuo, and the oily residue redissolved in 5-10% THF/ethyl acetate and H₂O. The solvent layers were separated, and the ethyl acetate/THF layer was washed with H₂O, saturated aqueous NaHCO₃ solution, and brine, dried over anhydrous sodium sulfate, filtered, concentrated in vacuo to afford 0.334 g of a tan solid. Crystallization from EtOH/diethyl ether afforded 0.182 g (39%) of N-(3-dimethylaminopropyl)-4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white solid (MP 87-93 °C, MW 468.62).

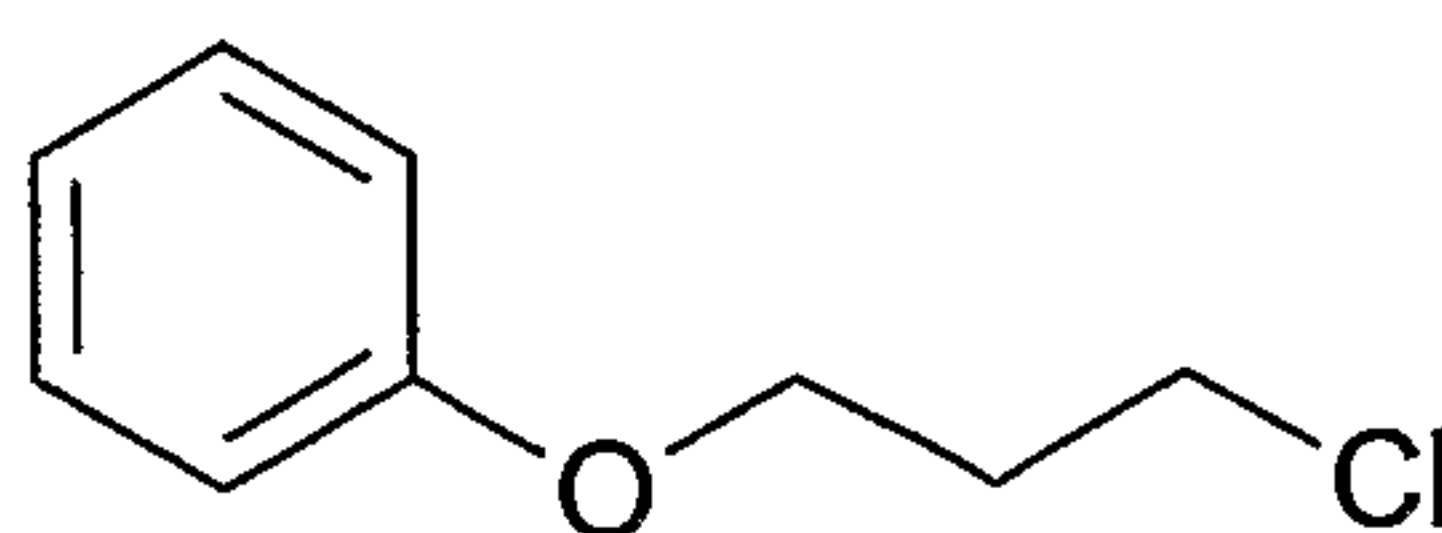
¹H NMR (CDCl₃) δ 8.75 (bs, 1H), 8.12 (d, 2H, J=8 Hz), 8.03 (d, 2H, J=8 Hz), 7.26 (t, 2H, J=8 Hz), 6.92 (t, 1H, J=7 Hz), 6.86 (d, 2H, J=8 Hz), 3.96 (t, 2H, J=6 Hz), 3.94 (s, 2H), 3.64 (m, 2H), 2.83 (m, 2H), 2.73 (t, 2H, J=7 Hz), 2.56 (bs, 6H), 1.99 (m, 2H), and 1.86 (m, 4H). IR (KBr, cm⁻¹) 3341, 2941, 2764, 1640, 1552, 1536, and 1244. MS (ESI) m/e 467, 469. Anal. Calcd for C₂₅H₃₂N₄O₃S: C, 64.08; H, 6.88; N, 11.96; S, 6.84. Found C, 63.76; H, 6.97; N, 11.56; S, 6.72.

Example 49

Preparation of dimethyl-(3-{4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt



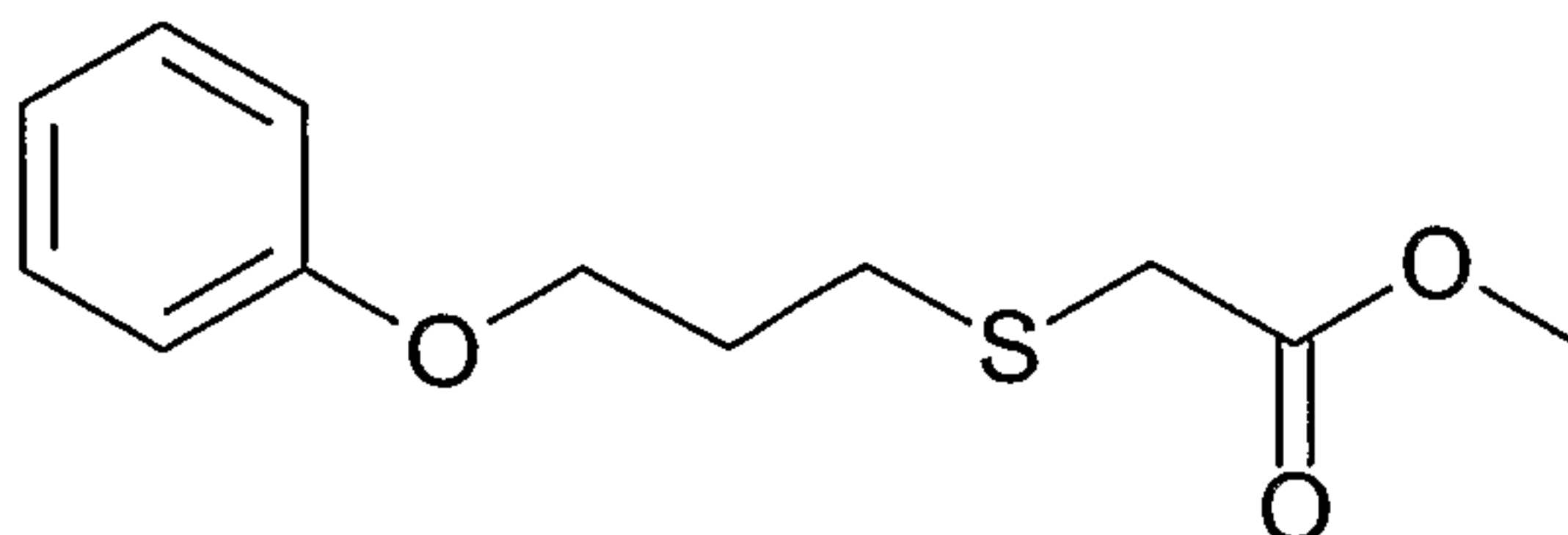
a) 3-chloropropoxy benzene



The above compound was prepared as exemplified in Example 47a.

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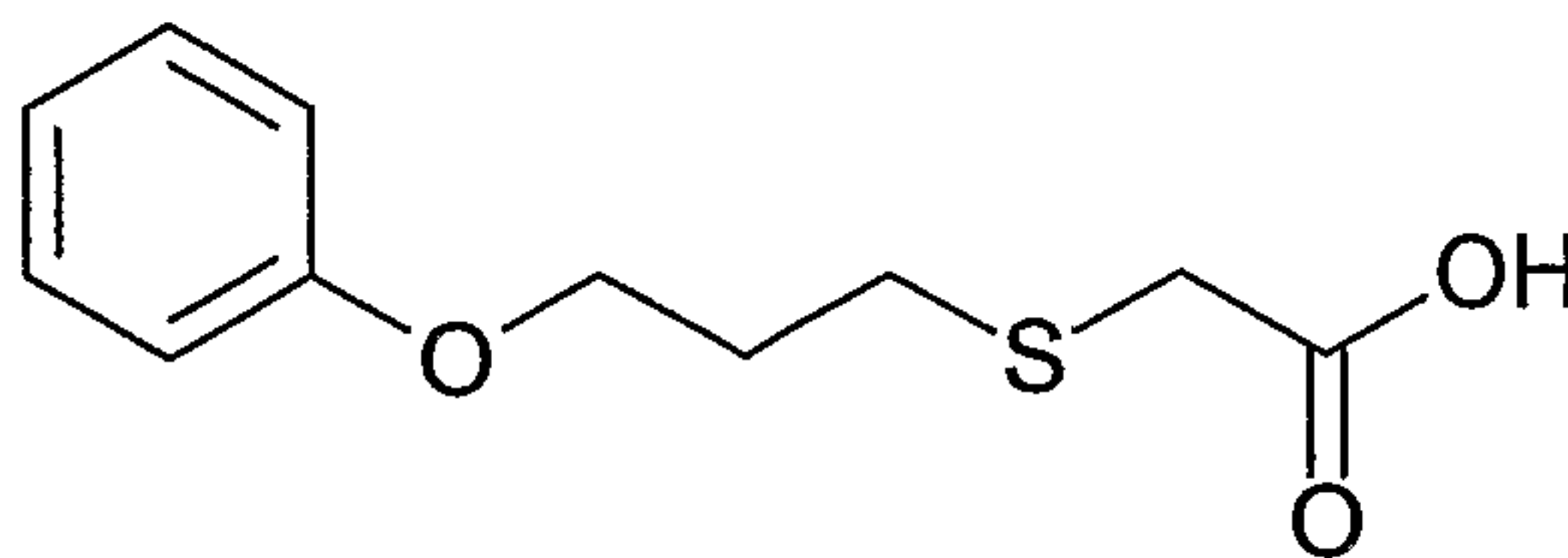
b) (3-phenoxypropylsulfanyl)-acetic acid methyl ester



The above compound was prepared as exemplified in Example 47b from 3-chloropropoxy benzene (3.41 g, 20.0 mmol) and methyl thioglycolate (2.07 mL, 22.0 mmol). Purification by column chromatography on silica gel (isocratic elution with 10% ethyl acetate/toluene) afforded 2.95g (61%) of (3-phenoxypropylsulfanyl)-acetic acid methyl ester as a colorless oil (MW 240.32).

^1H NMR (CDCl_3) δ 7.28 (t, 2H, $J=8$ Hz), 6.93 (t, 1H, $J=8$ Hz), 6.89 (d, 2H, $J=8$ Hz), 4.06 (t, 2H, $J=6$ Hz), 3.73 (s, 3H), 3.25 (s, 2H), 2.84 (t, 2H, $J=7$ Hz), and 2.08 (m, 2H). IR (CHCl_3 , cm^{-1}) 3010, 2954, 1734, 1601, 1497, 1437, 1288, 1244, and 1225. MS (ESI) m/e 241. Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3\text{S}$: C, 59.97; H, 6.71; S, 13.34. Found C, 59.22; H, 6.71; S, 18.00.

c) (3-phenoxypropylsulfanyl)-acetic acid

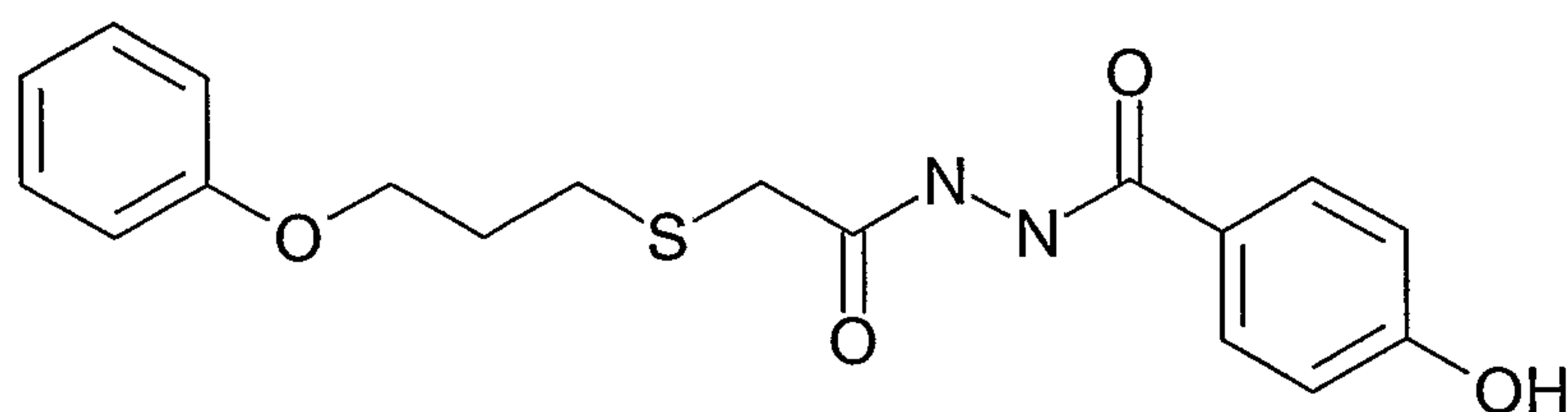


The above compound was prepared as exemplified in Example 47c from (3-phenoxypropylsulfanyl)-acetic acid methyl ester (2.64 g, 11.0 mmol) and 2N NaOH (16.5 mL, 33.0 mmol) to afford 2.33g (94%) of (3-phenoxypropylsulfanyl)-acetic acid as a white crystalline solid (MP 35-37 °C, MW 226.30).

^1H NMR (CDCl_3) δ 7.28 (t, 2H, $J=8$ Hz), 6.94 (t, 1H, $J=8$ Hz), 6.89 (d, 2H, $J=8$ Hz), 4.06 (t, 2H, $J=6$ Hz), 3.28 (s, 2H), 2.87 (t, 2H, $J=7$ Hz), and 2.11 (m, 2H). IR (CHCl_3 , cm^{-1}) 3041, 2927, 2674, 2565, 1710, 1601, 1498, 1244, 1172 and 1040. MS (ESI) m/e 227, 225. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3\text{S}$: C, 58.38; H, 6.24; S, 14.17. Found C, 57.95; H, 6.08; S, 14.11.

d) 4-hydroxy-benzoic acid N'-[2-(3-phenoxypropylsulfanyl)-acetyl]-hydrazide

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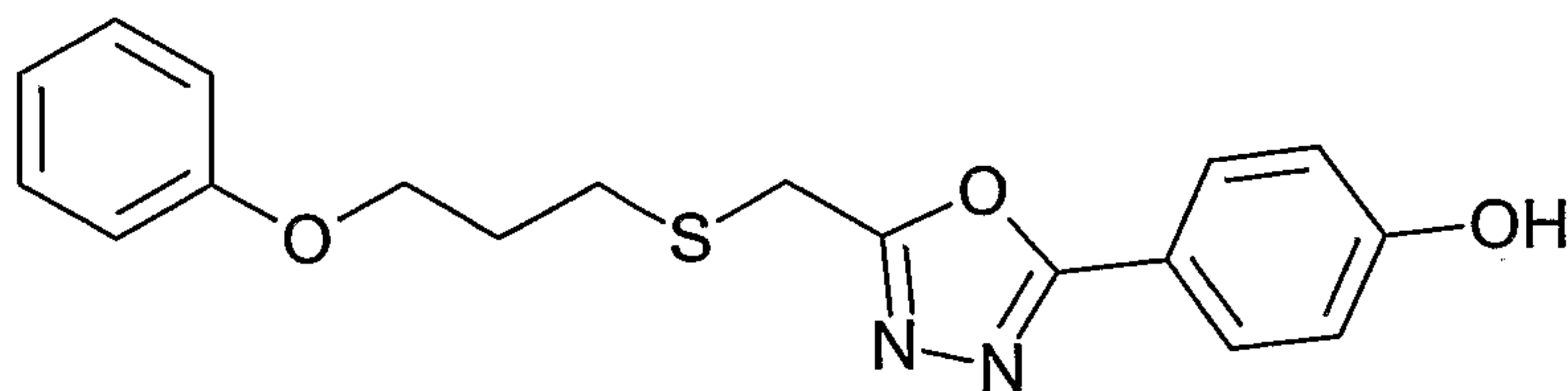


A solution of (3-phenoxypropylsulfanyl)-acetic acid (1.13 g, 5.0 mmol), and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (1.25 g, 5.0 mmol) in 5.0 mL THF and 20.0 mL acetonitrile was stirred at ambient temperature for 1.0 h followed by
 5 addition of 4-hydroxybenzoic hydrazide (0.776 g, 5.0 mmol), then stirred at room temperature for 66 h. The THF/acetonitrile were concentrated in vacuo and the resultant off-white solid redissolved in 20% THF/ethyl acetate. The ethyl acetate/THF solution was washed with 1N HCl, H₂O, saturated aqueous NaHCO₃ solution, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford an off-
 10 white solid. The solid was triturated with a mixture of CH₂Cl₂/diethyl ether/n-hexane, filtered, and the collected solid washed with diethyl ether and n-hexane to afford 1.53 g (85%) of 4-hydroxy-benzoic acid N'-[2-(3-phenoxypropylsulfanyl)-acetyl]-hydrazide as an amorphous white solid (MP 146-151 °C, MW 360.44).

¹H NMR (DMSO-d₆) δ 10.14 (s, 1H), 10.07 (s, 1H), 9.96 (s, 1H), 7.73 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.91 (m, 3H), 6.79 (d, 2H, J=8 Hz), 4.02 (t, 2H, J=6 Hz), 3.22 (s, 2H), 2.78 (t, 2H, J=7 Hz), and 2.00 (m, 2H). IR (KBr, cm⁻¹) 3304, 3228, 1667, 1607, 1575, 1514, 1498, 1468, 1277, 1250, 1235, and 755. MS (ESI) m/e 361, 359. Anal. Calcd for C₁₈H₂₀N₂O₄S: C, 59.98; H, 5.59; N, 7.77; S, 8.90. Found C, 59.94; H, 5.62; N, 7.73; S, 8.92.

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e) 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol



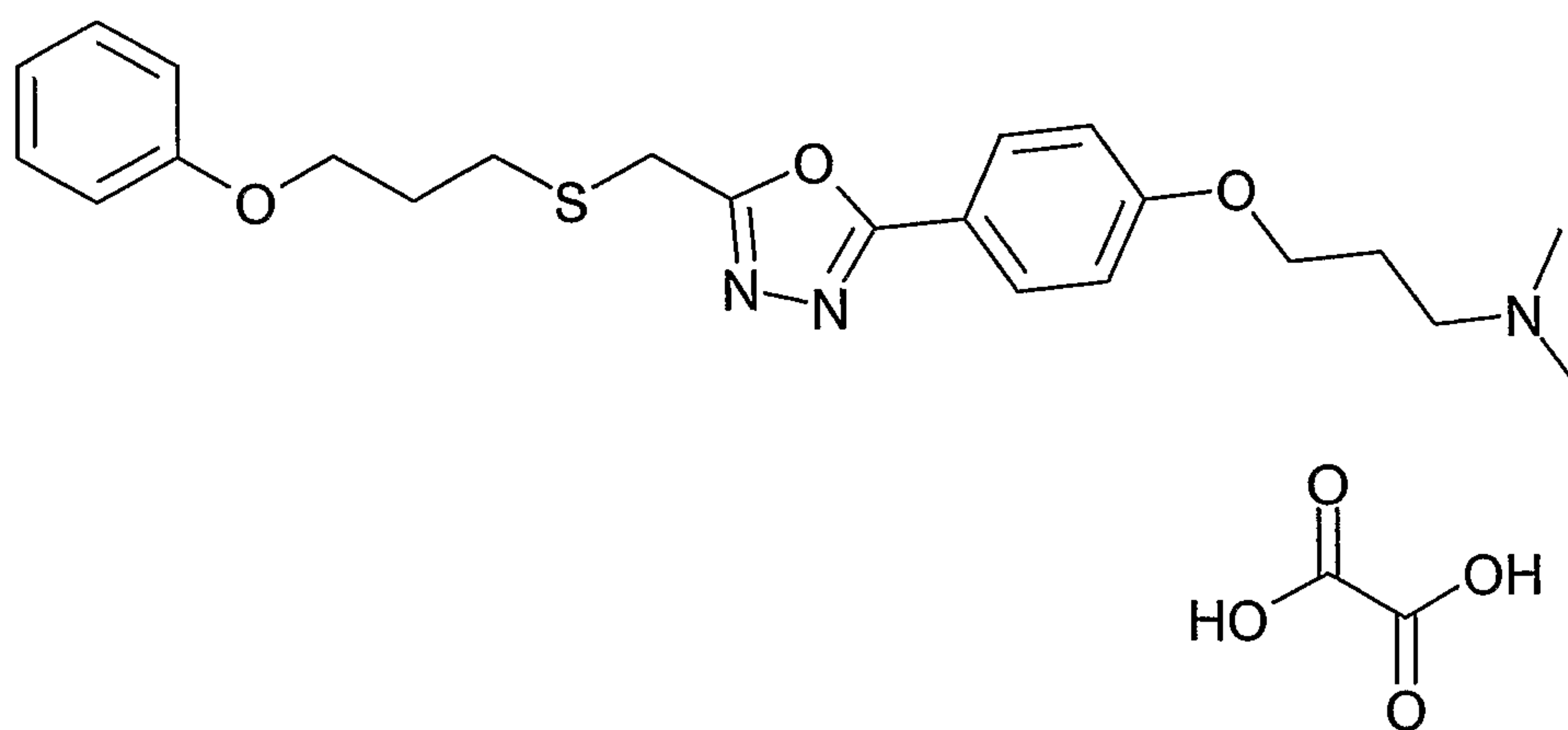
A heterogeneous mixture of 4-hydroxy-benzoic acid N'-[2-(3-phenoxypropylsulfanyl)-acetyl]-hydrazide (1.44 g, 4.0 mmol), triphenylphosphine (2.12 g, 8.0 mmol), triethylamine (2.0 mL, 14.4 mmol) and carbon tetrachloride (1.61 mL, 16.5
 25

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mmol) in 20 mL acetonitrile was stirred at room temperature for 2.5 h. The resultant precipitate was collected by filtration, washed with acetonitrile and discarded. The filtrate was concentrated in vacuo and the resultant solid redissolved in 10% THF/ethyl acetate. The ethyl acetate/THF solution was washed with 1N HCl, H₂O, saturated aqueous NaHCO₃ solution, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 3.92 g of a yellow oil. Purification by column chromatography on silica gel (elution with linear gradient of 0-100% ethyl acetate/toluene) afforded 1.15 g (83%) of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 122-127 °C, MW 342.42).

¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.96 (d, 2H, J=9 Hz), 6.93 (t, 1H, J=8 Hz), 6.87 (d, 2H, J=8 Hz), 4.05 (t, 2H, J=6 Hz), 3.92 (s, 2H), 2.85 (t, 2H, J=7 Hz), and 2.10 (m, 2H). IR (KBr, cm⁻¹) 3442, 3127, 2944, 1609, 1599, 1586, 1497, 1472, 1246, 1229, 1174, and 756. MS (ESI) m/e 343, 341. Anal. Calcd for C₁₈H₁₈N₂O₃S: C, 63.14; H, 5.30; N, 8.18; S, 9.36. Found C, 63.31; H, 5.32; N, 8.14; S, 9.17.

f) Dimethyl-(3-{4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt



A heterogeneous mixture of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.342 g, 1.0 mmol), 3-chloro-N,N-dimethylpropylamine hydrochloride (0.174 g, 1.1 mmol), and sodium hydride (0.092 g, 2.3 mmol) in 10 mL DMF was stirred at 100 °C for 2.5 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate/H₂O. The solvent layers were separated, the aqueous layer back extracted with ethyl acetate, the combined organic extracts washed

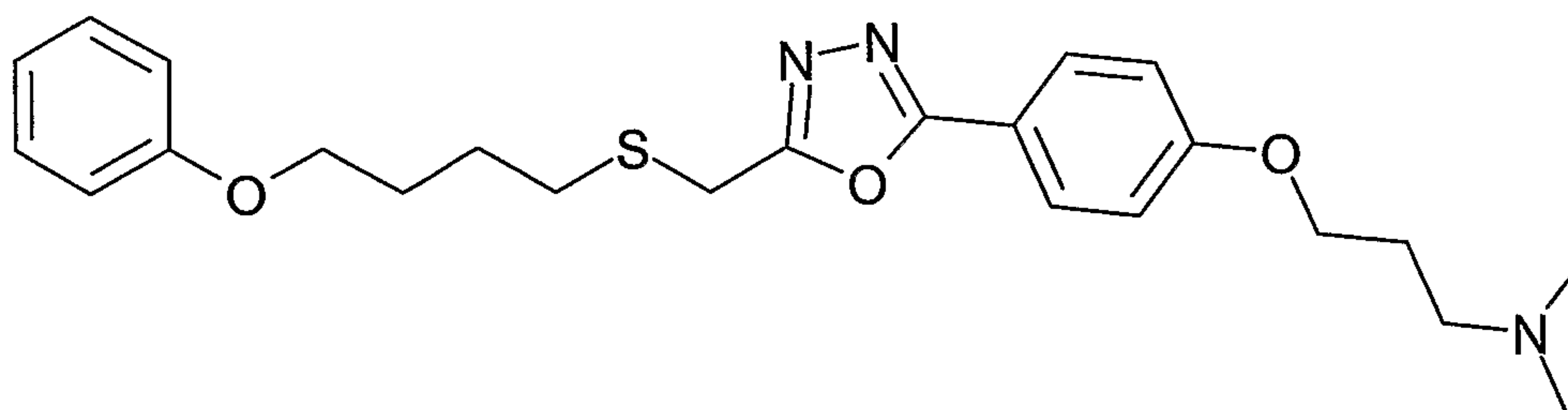
-175-

with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 0.332 g of a yellow oil. Purification by column chromatography on silica gel (isocratic elution with 1:1 toluene/ethyl acetate followed by 9:1 CHCl₃/2.0 M ammonia in methanol) afforded 0.188 g (44%) of dimethyl-(3-{4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as an oily gum. The gum (0.182 g, 0.426 mmol) was dissolved in 2 mL acetone, and oxalic acid (0.042 g, 0.468 mmol), dissolved in 1 mL acetone, was added with rapid stirring at room temperature. Filtered the resultant thick precipitate, washed the collected solid with acetone and diethyl ether, and dried in vacuo at 40 °C to afford 0.205 g (93%) of dimethyl-(3-{4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt as a white solid (MP 131-133 °C, MW oxalate salt 517.61, MW free amine 427.57).

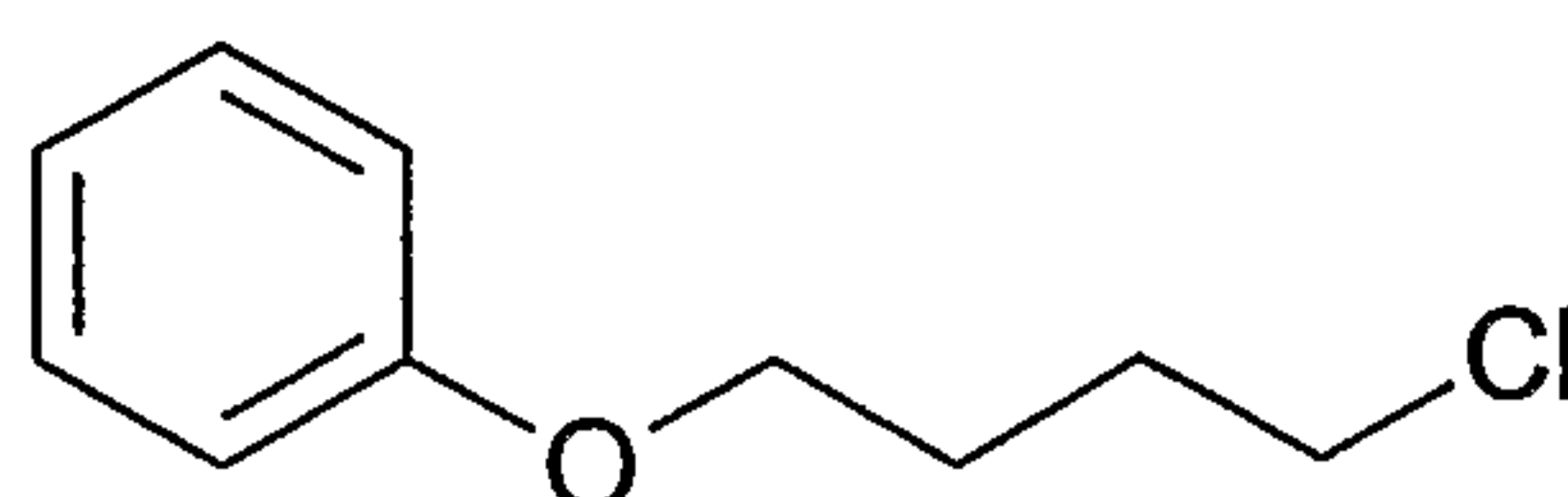
¹H NMR (DMSO-d₆) δ 7.91 (d, 2H, J=9 Hz), 7.24 (t, 2H, J=8 Hz), 7.12 (d, 2H, J=9 Hz), 6.89 (m, 3H), 4.12 (t, 2H, J=6 Hz), 4.09 (s, 2H), 4.01 (t, 2H, J=6 Hz), 3.13 (m, 2H), 2.76 (t, 2H, J=7 Hz), 2.74 (s, 6H), 2.10 (m, 2H), and 1.99 (t, 2H, J=7 Hz). IR (KBr, cm⁻¹) 3042, 2928, 1723, 1611, 1499, 1472, 1259, 1248, 1177, 756, and 696. MS (ESI) m/e 428. Anal. Calcd for C₂₃H₂₉N₃O₃S·C₂H₂O₄: C, 58.01; H, 6.04; N, 8.12; S, 6.19. Found C, 57.72; H, 6.01; N, 7.78; S, 6.55.

Example 50

Preparation of dimethyl-(3-{4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



a) 4-chlorobutoxy benzene

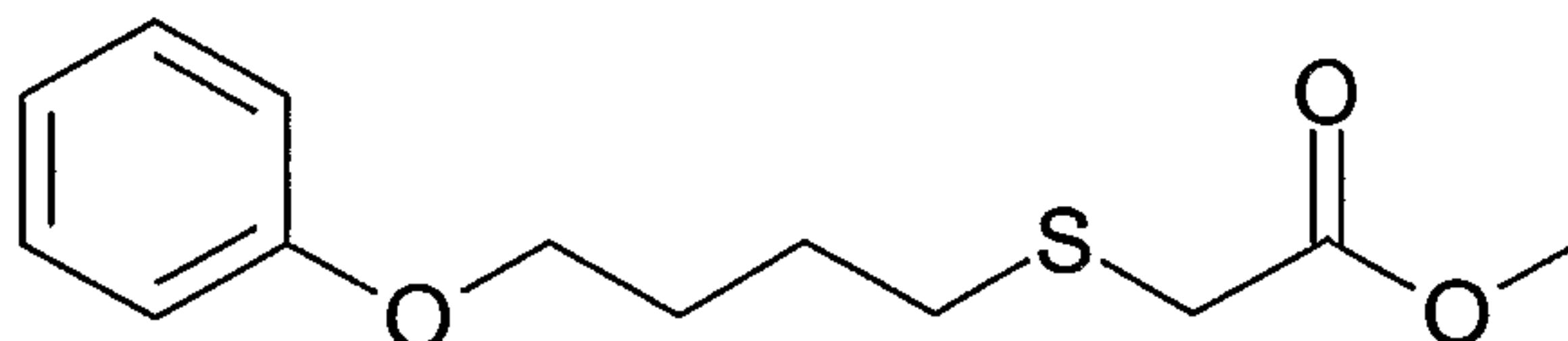


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The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47a, from phenol (4.75 g, 50.0 mmol) and 1-bromo-4-chlorobutane (5.82 mL, 50.0 mmol) to afford 9.5 g (quantitative) of 4-chlorobutoxy benzene as a colorless oil (MW 184.67).

¹H NMR (CDCl₃) δ 7.28 (t, 2H, J=8 Hz), 6.94 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 4.00 (t, 2H, J=6 Hz), 3.62 (t, 2H, J=6 Hz), and 1.97 (m, 4H). IR (CHCl₃, cm⁻¹) 3012, 2960, 2875, 1599, 1587, 1498, 1471, 1244, and 1172. MS (EI) m/e 184. Anal. Calcd for C₁₀H₁₃ClO: C, 65.04; H, 7.10; Cl, 19.20. Found C, 64.96; H, 7.03; Cl, 18.91.

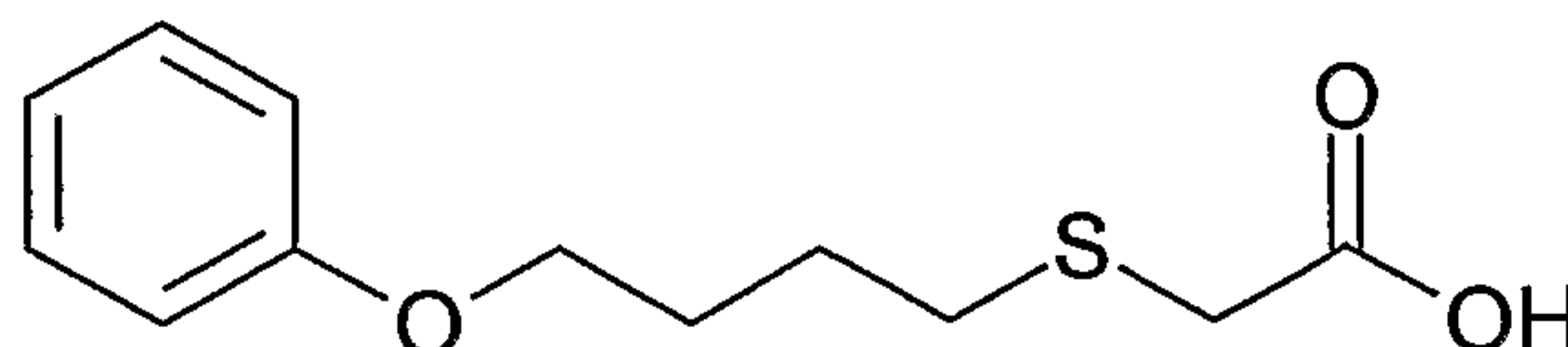
b) (4-phenoxybutylsulfanyl)-acetic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47b, from 4-chlorobutoxy benzene (1.85 g, 10.0 mmol) and methyl thioglycolate (1.03 mL, 11.0 mmol) to afford 2.46g (96%) of (4-phenoxybutylsulfanyl)-acetic acid methyl ester as a colorless oil (MW 254.35).

¹H NMR (CDCl₃) δ 7.28 (t, 2H, J=8 Hz), 6.93 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 3.98 (t, 2H, J=6 Hz), 3.73 (s, 3H), 3.24 (s, 2H), 2.72 (t, 2H, J=7 Hz), and 1.86 (m, 4H). IR (CHCl₃, cm⁻¹) 3012, 2930, 1733, 1600, 1497, 1287, and 1244. MS (FD) m/e 254. Anal. Calcd for C₁₃H₁₈O₃S: C, 61.39; H, 7.13; S, 12.61. Found C, 60.43; H, 7.06; S, 10.84.

c) (4-phenoxybutylsulfanyl)-acetic acid

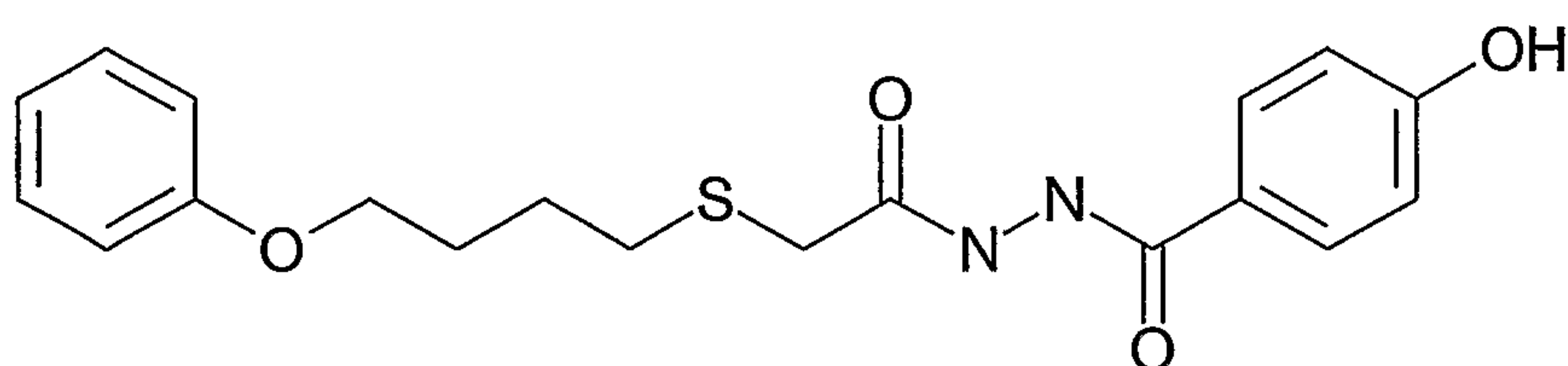


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47c, from (4-phenoxybutylsulfanyl)-acetic acid methyl ester (2.29 g, 9.0 mmol) and 2N NaOH (13.5 mL, 27.0 mmol) to afford 2.04g (94%) of (4-phenoxybutylsulfanyl)-acetic acid as a pale yellow solid (MP 48-50 °C, MW 240.32).

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^1H NMR (CDCl_3) δ 7.28 (t, 2H, $J=8$ Hz), 6.94 (t, 1H, $J=8$ Hz), 6.89 (d, 2H, $J=8$ Hz), 3.98 (t, 2H, $J=6$ Hz), 3.28 (s, 2H), 2.74 (t, 2H, $J=7$ Hz), and 1.86 (m, 4H). IR (CHCl_3 , cm^{-1}) 3010, 2944, 1710, 1600, 1497, 1300, 1291, 1244, and 1172. MS (ESI) m/e 241, 239. Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3\text{S}$: C, 59.97; H, 6.71; S, 13.34. Found C, 58.55; H, 6.66; S, 16.01.

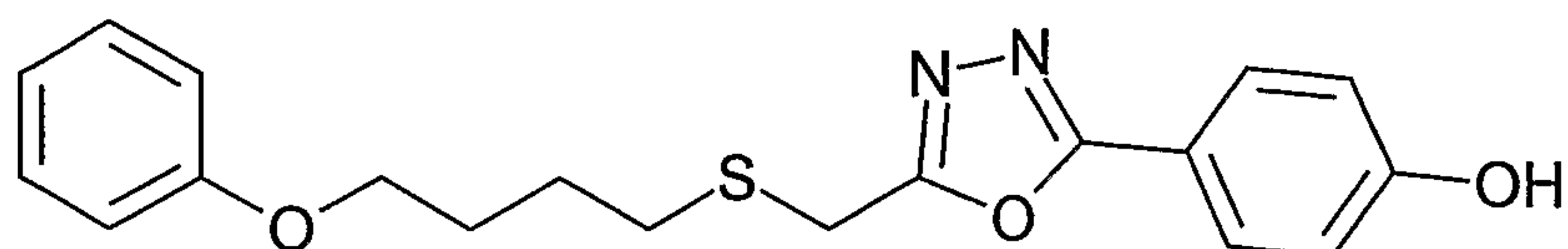
d) 4-hydroxy-benzoic acid N' -[2-(4-phenoxybutylsulfanyl)-acetyl]-hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49d, from (4-phenoxybutylsulfanyl)-acetic acid (0.961 g, 4.0 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (0.999 g, 4.0 mmol), and 4-hydroxybenzoic hydrazide (0.621 g, 4.0 mmol) to afford 1.14 g (76%) of 4-hydroxy-benzoic acid N' -[2-(4-phenoxybutylsulfanyl)-acetyl]-hydrazide as an amorphous white solid (MP 113-115 $^{\circ}\text{C}$, MW 374.46).

^1H NMR ($\text{DMSO}-d_6$) δ 10.13 (s, 1H), 10.07 (s, 1H), 9.94 (s, 1H), 7.73 (d, 2H, $J=9$ Hz), 7.25 (t, 2H, $J=8$ Hz), 6.89 (m, 3H), 6.79 (d, 2H, $J=8$ Hz), 3.96 (t, 2H, $J=6$ Hz), 3.19 (s, 2H), 2.70 (t, 2H, $J=7$ Hz), and 1.74 (m, 4H). IR (CHCl_3 , cm^{-1}) 3281, 3003, 2940, 1631, 1609, 1587, 1497, 1470, 1387, 1279, 1244, and 1171. MS (ESI) m/e 375, 373. Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$: C, 60.94; H, 5.92; N, 7.48; S, 8.56. Found C, 60.24; H, 5.92; N, 7.50; S, 9.12.

e) 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol



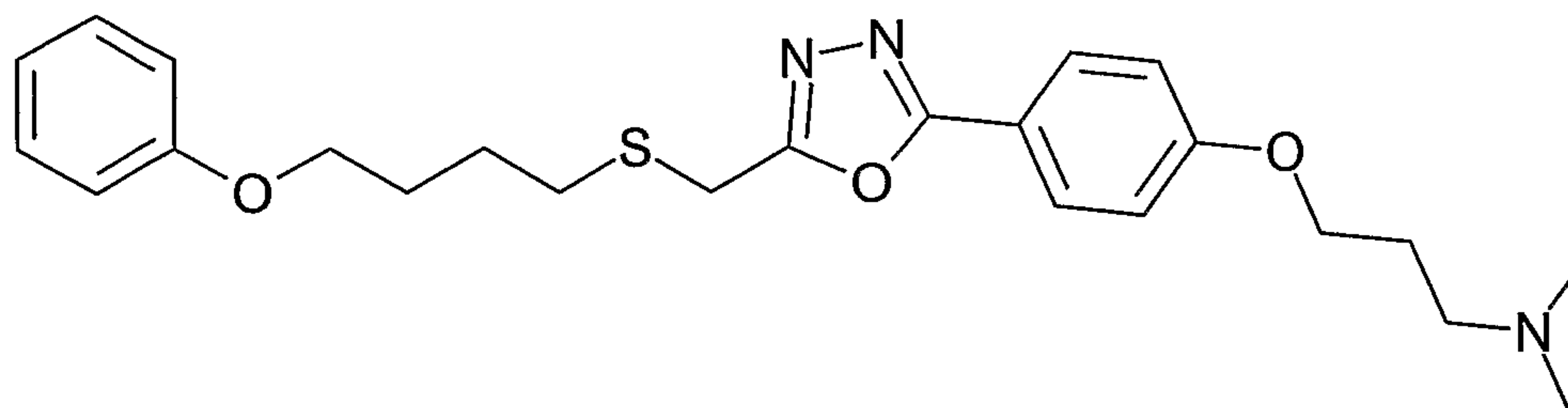
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, using 4-hydroxybenzoic acid N' -[2-(4-phenoxybutylsulfanyl)-acetyl]-hydrazide (1.09 g, 2.9 mmol), triphenylphosphine (1.54 g,

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5.8 mmol), and triethylamine (1.46 mL, 10.44 mmol) to afford 0.831 g (80%) of 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 129-130 °C, MW 356.45).

¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.95 (d, 2H, J=9 Hz), 6.93 (t, 1H, J=8 Hz), 6.86 (d, 2H, J=8 Hz), 3.96 (t, 2H, J=6 Hz), 3.91 (s, 2H), 2.71 (t, 2H, J=7 Hz), and 1.85 (m, 4H). IR (KBr, cm⁻¹) 3096, 2935, 1610, 1600, 1567, 1498, 1475, 1456, 1284, 1275, 1237, 1178, 757, and 691. MS (ESI) m/e 357, 355. Anal. Calcd for C₁₉H₂₀N₂O₃S: C, 64.02; H, 5.66; N, 7.86; S, 9.00. Found C, 63.81; H, 5.68; N, 7.84; S, 9.09.

f) [Dimethyl-(3-{4-[5-(4-phenoxybutylsulfanylmethyl)-1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



A heterogeneous mixture of 4-[5-(4-phenoxybutylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.178 g, 0.5 mmol), 3-chloro-N,N-dimethylpropylamine hydrochloride (0.087 g, 0.55 mmol), and sodium hydride (0.046 g, 1.15 mmol) in 5 mL DMF was stirred at 100 °C for 2.5 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate/H₂O. The solvent layers were separated, the aqueous layer back extracted with ethyl acetate, the combined organic extracts washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 0.223 g of a tan solid. Purification by column chromatography on silica gel (isocratic elution with 1:1 toluene/ethyl acetate followed by 9:1 CHCl₃/2.0 M ammonia in methanol) afforded 0.15 g (68%) of dimethyl-(3-{4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as a white solid (MP 69-73 °C, MW 441.60).

¹H NMR (CDCl₃) δ 7.98 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.97 (d, 2H, J=9 Hz), 6.92 (t, 1H, J=7 Hz), 6.87 (d, 2H, J=8 Hz), 4.13 (t, 2H, J=6 Hz), 3.96 (t, 2H, J=6 Hz), 3.91 (s, 2H), 2.92 (m, 2H), 2.72 (t, 2H, J=7 Hz), 2.60 (bs, 6H), 2.25 (m, 2H), and 1.84 (m,

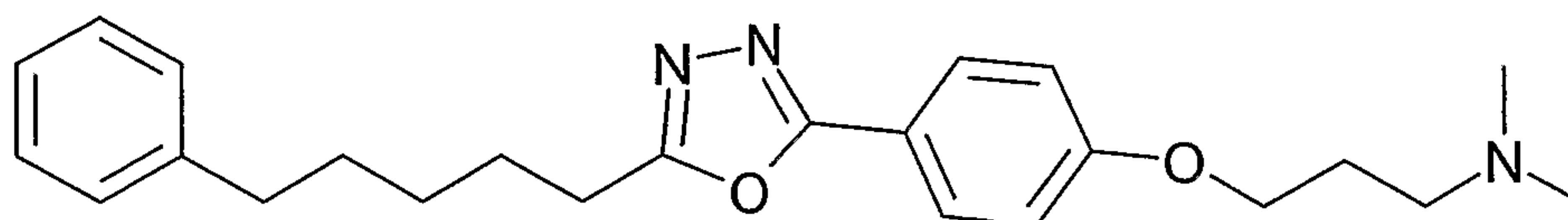
-179-

4H). IR (KBr, cm^{-1}) 2947, 1612, 1501, 1468, 1258, and 749. MS (ESI) m/e 442, 440.
 Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3\text{S}$: C, 65.28; H, 7.08; N, 9.52; S, 7.26. Found C, 65.36; H, 7.12; N, 9.38; S, 7.39.

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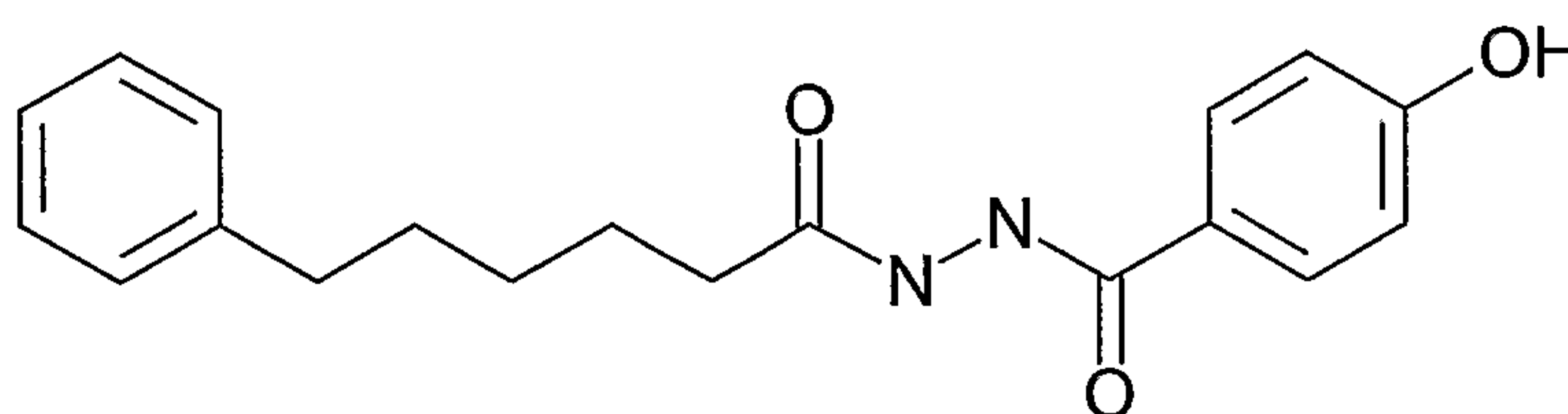
Example 51

Preparation of dimethyl-(3-{4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



a) 4-hydroxybenzoic acid N' -(6-phenylhexanoyl)-hydrazide

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A solution of 6-phenylhexanoic acid (0.961 g, 5.0 mmol), and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (1.25 g, 5.0 mmol) in 5.0 mL THF and 20.0 mL acetonitrile was stirred at ambient temperature for 1.0 h followed by addition of
 15 4-hydroxy-benzoic hydrazide (0.776 g, 5.0 mmol), then stirred at room temperature for 18 h followed by heating at 65 °C for 1.5 h. The reaction mixture was allowed to cool to room temperature, the THF/acetonitrile were concentrated in vacuo, and the resultant gold oil redissolved in ethyl acetate. The ethyl acetate solution was washed with 1N HCl, H_2O , saturated aqueous NaHCO_3 solution, and brine, dried over anhydrous magnesium sulfate,
 20 filtered, and concentrated in vacuo to afford an off-white solid. The solid was triturated with a mixture of CH_2Cl_2 /diethyl ether/n-hexane, filtered, and the collected solid washed with diethyl ether and n-hexane to afford 1.16 g (71%) of 4-hydroxy-benzoic acid N' -(6-phenylhexanoyl)-hydrazide as an amorphous white solid (MP 155-160 °C, MW 326.40).

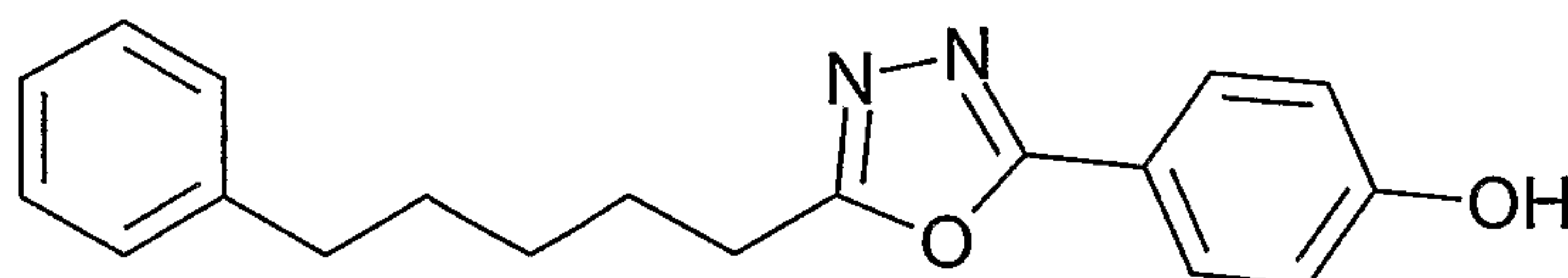
^1H NMR ($\text{DMSO}-d_6$) δ 10.04 (s, 1H), 9.98 (s, 1H), 9.69 (s, 1H), 7.72 (d, 2H, $J=9$ Hz), 7.25 (t, 2H, $J=8$ Hz), 7.16 (m, 3H), 6.79 (d, 2H, $J=8$ Hz), 2.55 (t, 2H, $J=8$ Hz), 2.14 (t, 2H, $J=7$ Hz), 1.56 (m, 4H) and 1.32 (m, 2H). IR (KBr, cm^{-1}) 3314, 3222, 3023, 2930, 2856, 1699, 1626, 1609, 1584, 1517, 1492, 1287, 1237, and 697. MS (ESI) m/e 327, 325.

25

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Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found C, 69.83; H, 6.66; N, 8.43.

b) 4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenol



5

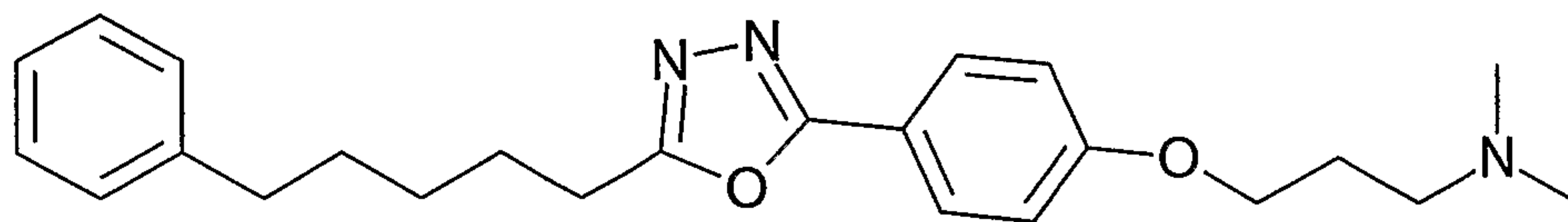
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-hydroxy-benzoic acid N'-(6-phenylhexanoyl)-hydrazide (1.1 g, 3.4 mmol), triphenylphosphine (1.8 g, 6.8 mmol), and triethylamine (1.71 mL, 12.24 mmol) to afford 0.841 g (80%) of 4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 118-123 °C, MW 308.38).

10

^1H NMR ($CDCl_3$) δ 7.94 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=8 Hz), 7.17 (m, 3H), 6.98 (d, 2H, J=8 Hz), 2.91 (t, 2H, J=7 Hz), 2.63 (t, 2H, J=8 Hz), 1.86 (m, 2H), 1.68 (m, 2H), and 1.48 (m, 2H). IR (KBr, cm^{-1}) 2921, 1610, 1600, 1496, 1283, and 1231. MS (ESI) m/e 309, 307. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found C, 73.52; H, 6.40; N, 8.66.

15

c) Dimethyl-(3-{4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



20

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, from 4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.154 g, 0.5 mmol) to afford 0.119 g (60%) of dimethyl-(3-{4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as a white solid (MP 49-50 °C, MW 393.53).

25

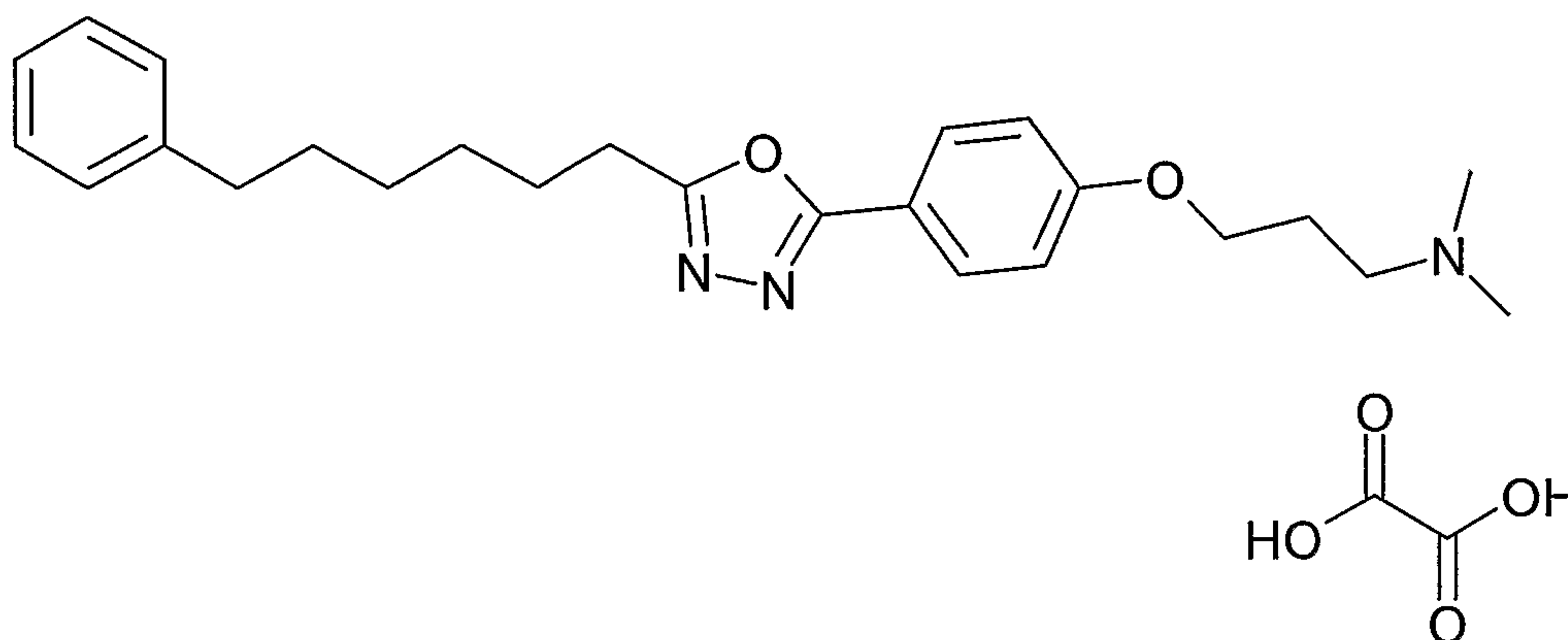
^1H NMR ($CDCl_3$) δ 7.95 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=7 Hz), 7.18 (m, 3H), 6.98 (d, 2H, J=9 Hz), 4.13 (t, 2H, J=6 Hz), 2.91 (t, 2H, J=7 Hz), 2.88 (m, 2H), 2.63 (t, 2H, J=8 Hz), 2.56 (bs, 6H), 2.23 (m, 2H), 1.87 (m, 2H), 1.68 (m, 2H), and 1.49 (m, 2H). IR (KBr, cm^{-1}) 3083, 3026, 2938, 2859, 2764, 1612, 1574, 1502, 1466, 1259, 1176, and 999. MS

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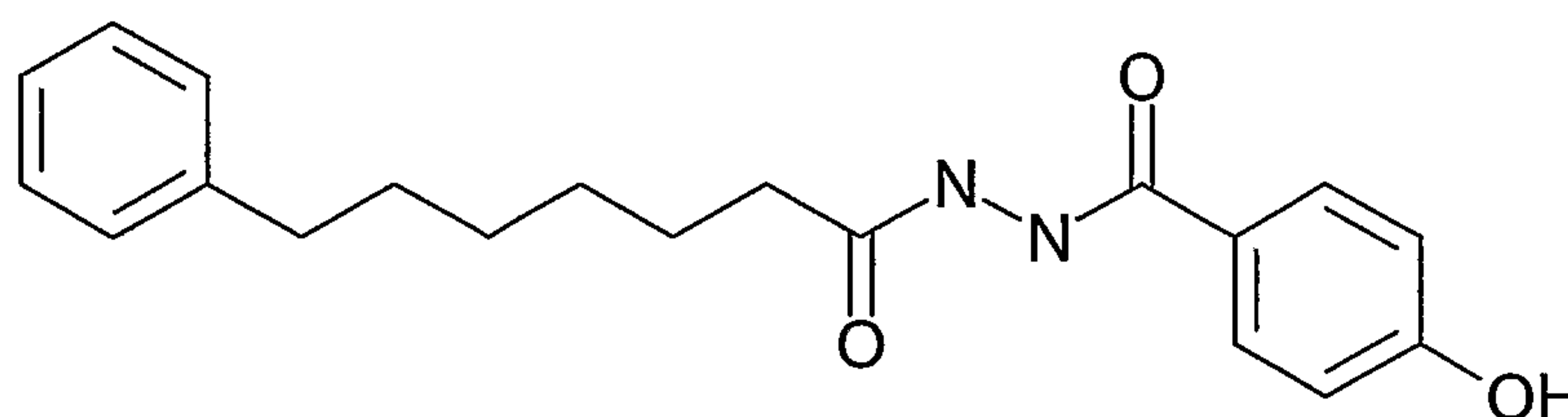
(ESI) m/e 394, 392. Anal. Calcd for $C_{24}H_{31}N_3O_2$: C, 73.25; H, 7.94; N, 10.68. Found C, 72.94; H, 7.99; N, 10.52.

Example 52

- 5 Preparation of dimethyl-(3-{4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt



- a) 4-hydroxy-benzoic acid N'-(7-phenylheptanoyl)-hydrazide



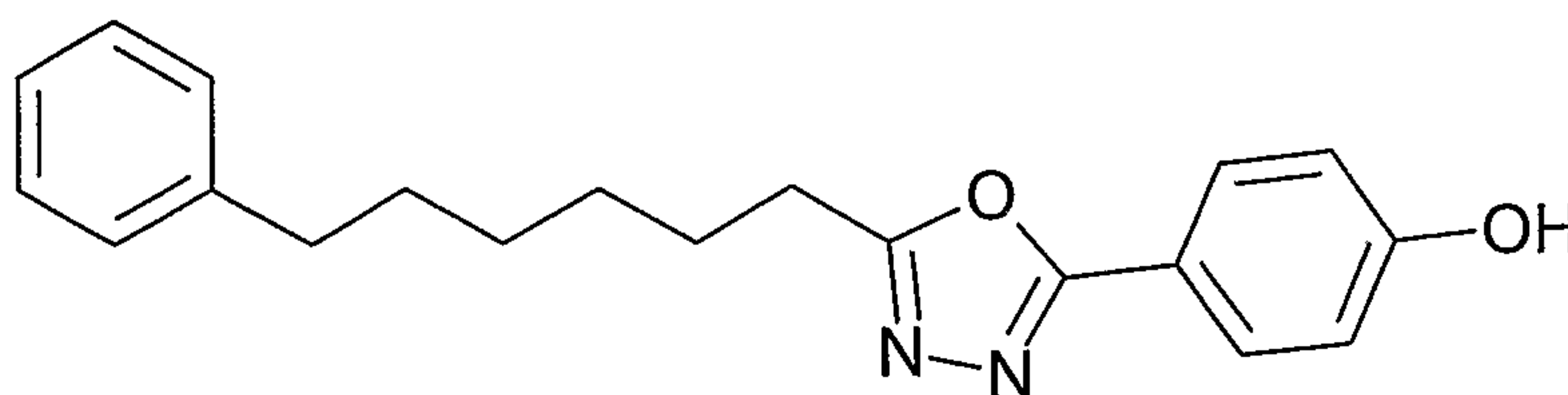
- 10 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 51a, from 7-phenylheptanoic acid (1.06 g, 5.0 mmol) to afford 1.39 g (81%) of 4-hydroxy-benzoic acid N'-(7-phenylheptanoyl)-hydrazide as a white solid (MP 154-158 °C, MW 340.43).

- 15 ^1H NMR (DMSO- d_6) δ 10.04 (s, 1H), 9.97 (s, 1H), 9.68 (s, 1H), 7.72 (d, 2H, J=9 Hz), 7.25 (t, 2H, J=7 Hz), 7.15 (m, 3H), 6.79 (d, 2H, J=9 Hz), 2.55 (t, 2H, J=8 Hz), 2.13 (t, 2H, J=8 Hz), 1.53 (m, 4H) and 1.29 (m, 4H). IR (KBr, cm^{-1}) 3213, 3024, 2931, 2855, 1765, 1684, 1670, 1646, 1610, 1583, 1506, 1492, 1464, 1453, 1308, 1279, 1254, 1225, 1174, and 699. MS (ESI) m/e 341, 339. Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found C, 69.87; H, 7.05; N, 8.00.

20

- b) 4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenol

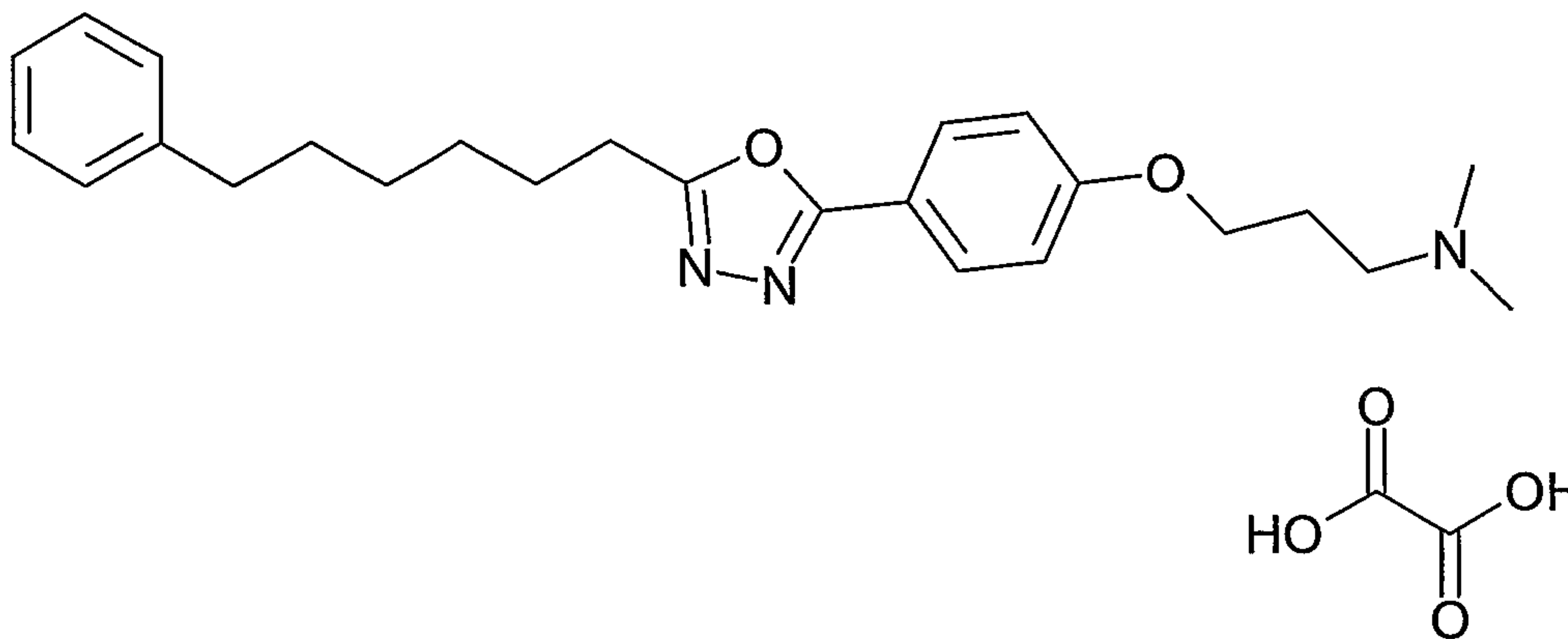
-182-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-hydroxy-benzoic acid N'-(7-phenylheptanoyl)-hydrazide (1.3 g, 3.82 mmol), triphenylphosphine (2.02 g, 7.64 mmol), and triethylamine (1.92 mL, 13.75 mmol) to afford 0.883 g (71%) of 4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 125-129 °C, MW 322.41).

¹H NMR (CDCl₃) δ 7.94 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=8 Hz), 7.17 (m, 3H), 6.98 (d, 2H, J=8 Hz), 2.90 (t, 2H, J=7 Hz), 2.60 (t, 2H, J=8 Hz), 1.84 (m, 2H), 1.64 (m, 2H), and 1.43 (m, 4H). IR (KBr, cm⁻¹) 3061, 3020, 2925, 2852, 2809, 2686, 2608, 2481, 1612, 1600, 1577, 1498, 1466, 1375, 1286, 1239, and 1174. MS (ESI) m/e 323, 321. Anal. Calcd for C₂₀H₂₂N₂O₂: C, 74.51; H, 6.88; N, 8.69. Found C, 74.27; H, 6.76; N, 8.61.

c) Dimethyl-(3-{4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt



15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, from 4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.161 g, 0.5 mmol) to afford 0.153 g (75%) of dimethyl-(3-{4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as an oily gum. The gum (0.151 g, 0.37 mmol) was dissolved in 2 mL acetone, and oxalic acid (0.037 g, 0.41 mmol), dissolved in 1 mL acetone, was added with rapid stirring at room temperature. Filtered the resultant thick precipitate, washed the collected solid with acetone and diethyl ether, and dried in

20

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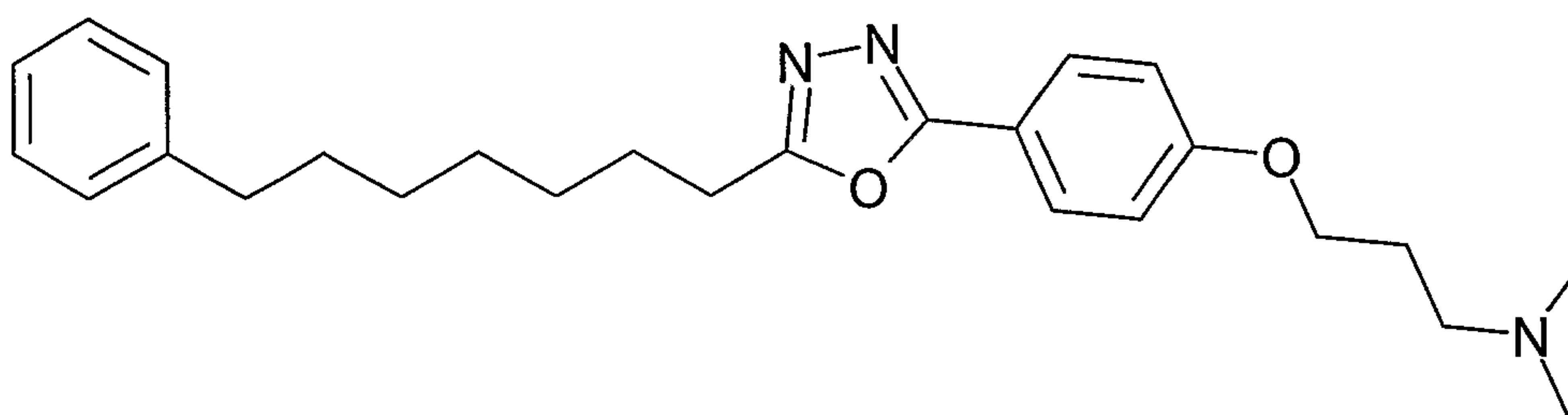
vacuo at 40 °C to afford 0.18 g (97%) of dimethyl-(3-{4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt as a white solid (MP 147-152 °C, MW oxalate salt 497.60, MW free amine 407.56).

¹H NMR (DMSO-d₆) δ 7.90 (d, 2H, J=9 Hz), 7.24 (t, 2H, J=7 Hz), 7.15 (m, 3H),
 5 7.11 (d, 2H, J=9 Hz), 4.12 (t, 2H, J=6 Hz), 3.13 (t, 2H, J=7 Hz), 2.87 (t, 2H, J=7 Hz),
 2.74 (s, 6H), 2.54 (t, 2H, J=8 Hz), 2.08 (m, 2H), 1.72 (m, 2H), 1.55 (m, 2H), and 1.34 (m,
 4H). IR (KBr, cm⁻¹) 2970, 2925, 2854, 2676, 1721, 1612, 1590, 1496, 1311, 1232, 1177,
 1040, and 842. MS (ESI) m/e 408, 408.5. Anal. Calcd for C₂₅H₃₃N₃O₂·C₂H₂O₄: C, 65.17;
 H, 7.09; N, 8.44. Found C, 64.95; H, 6.94; N, 8.39.

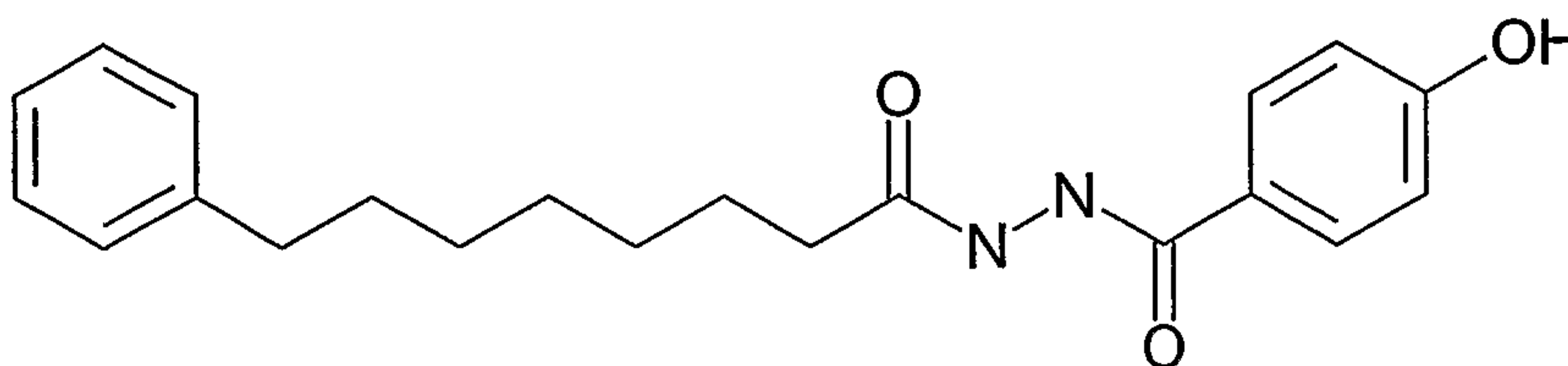
10

Example 53

Preparation of dimethyl-(3-{4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



15 a) 4-hydroxy-benzoic acid N'-(8-phenyloctanoyl)-hydrazide



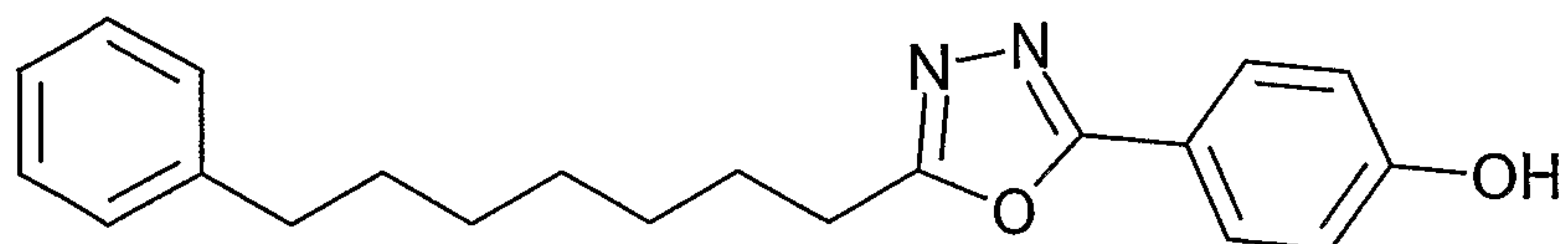
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 51aa, from 8-phenyloctanoic acid (1.14 g, 5.0 mmol) to afford 1.27 g (71%) of 4-hydroxy-benzoic acid N'-(8-phenyloctanoyl)-hydrazide as a white solid
 20 (MP 150-152 °C, MW 354.45).

¹H NMR (DMSO-d₆) δ 10.04 (s, 1H), 9.97 (s, 1H), 9.68 (s, 1H), 7.72 (d, 2H, J=9 Hz), 7.24 (t, 2H, J=7 Hz), 7.15 (m, 3H), 6.79 (d, 2H, J=9 Hz), 2.55 (t, 2H, J=8 Hz), 2.13 (t, 2H, J=8 Hz), 1.53 (m, 4H) and 1.28 (bs, 6H). IR (KBr, cm⁻¹) 3280, 3023, 2927, 2852, 1759, 1659, 1607, 1575, 1515, 1494, 1277, 1237, 1181, 845, and 698. MS (ESI) m/e 355,

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353. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found C, 70.45; H, 7.34; N, 7.69.

b) 4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenol



5

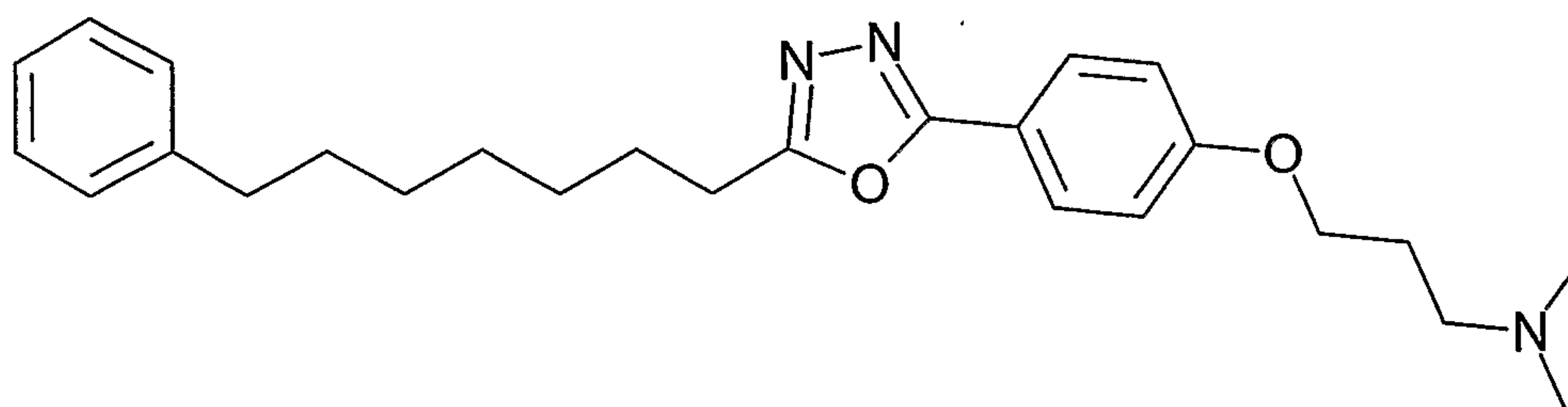
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-hydroxy-benzoic acid N'-(8-phenyloctanoyl)-hydrazide (1.2 g, 3.4 mmol), triphenylphosphine (1.8 g, 6.8 mmol), and triethylamine (1.71 mL, 12.24 mmol) to afford 0.935 g (82%) of 4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 138-140 °C, MW 336.44).

10

^1H NMR ($CDCl_3$) δ 7.95 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=8 Hz), 7.17 (m, 3H), 6.99 (d, 2H, J=9 Hz), 2.90 (t, 2H, J=8 Hz), 2.59 (t, 2H, J=8 Hz), 1.82 (m, 2H), 1.61 (m, 2H), and 1.37 (m, 6H). IR (KBr, cm^{-1}) 3083, 3063, 3024, 2925, 2852, 1611, 1599, 1576, 1497, 1467, 1454, 1287, 1234, 1174, 862, 819, 739, and 695. MS (ESI) m/e 337, 335. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found C, 74.90; H, 7.05; N, 8.36.

15

c) Dimethyl-(3-{4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



20

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, using 4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.168 g, 0.5 mmol) to afford 0.198 g (94%) of dimethyl-(3-{4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as an off-white solid (MP 36-39 °C, MW 421.59).

25

^1H NMR ($CDCl_3$) δ 7.95 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=7 Hz), 7.17 (m, 3H), 6.98 (d, 2H, J=9 Hz), 4.12 (t, 2H, J=6 Hz), 2.89 (t, 2H, J=8 Hz), 2.74 (m, 2H), 2.59 (t, 2H, J=8

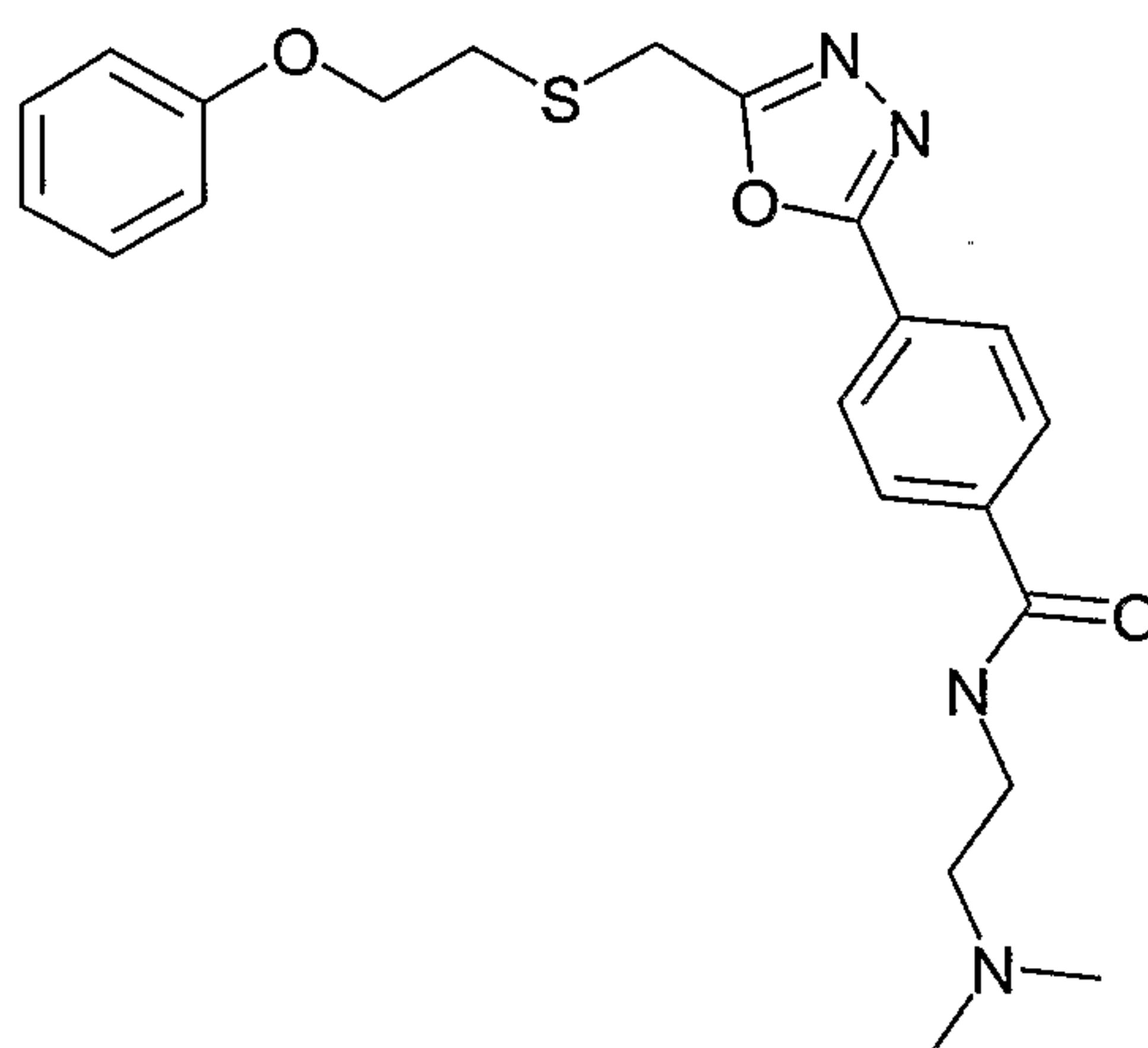
-185-

Hz), 2.48 (bs, 6H), 2.16 (m, 2H), 1.81 (m, 2H), 1.62 (m, 2H), and 1.37 (m, 6H). IR (KBr, cm^{-1}) 2925, 2853, 2765, 1613, 1500, 1468, 1254, 1174, and 836. MS (ESI) m/e 420, 422. Anal. Calcd for $\text{C}_{26}\text{H}_{35}\text{N}_3\text{O}_2$: C, 74.07; H, 8.37; N, 9.97. Found C, 73.88; H, 8.44; N, 9.90.

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Example 54

Preparation of N-(2-dimethylaminoethyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



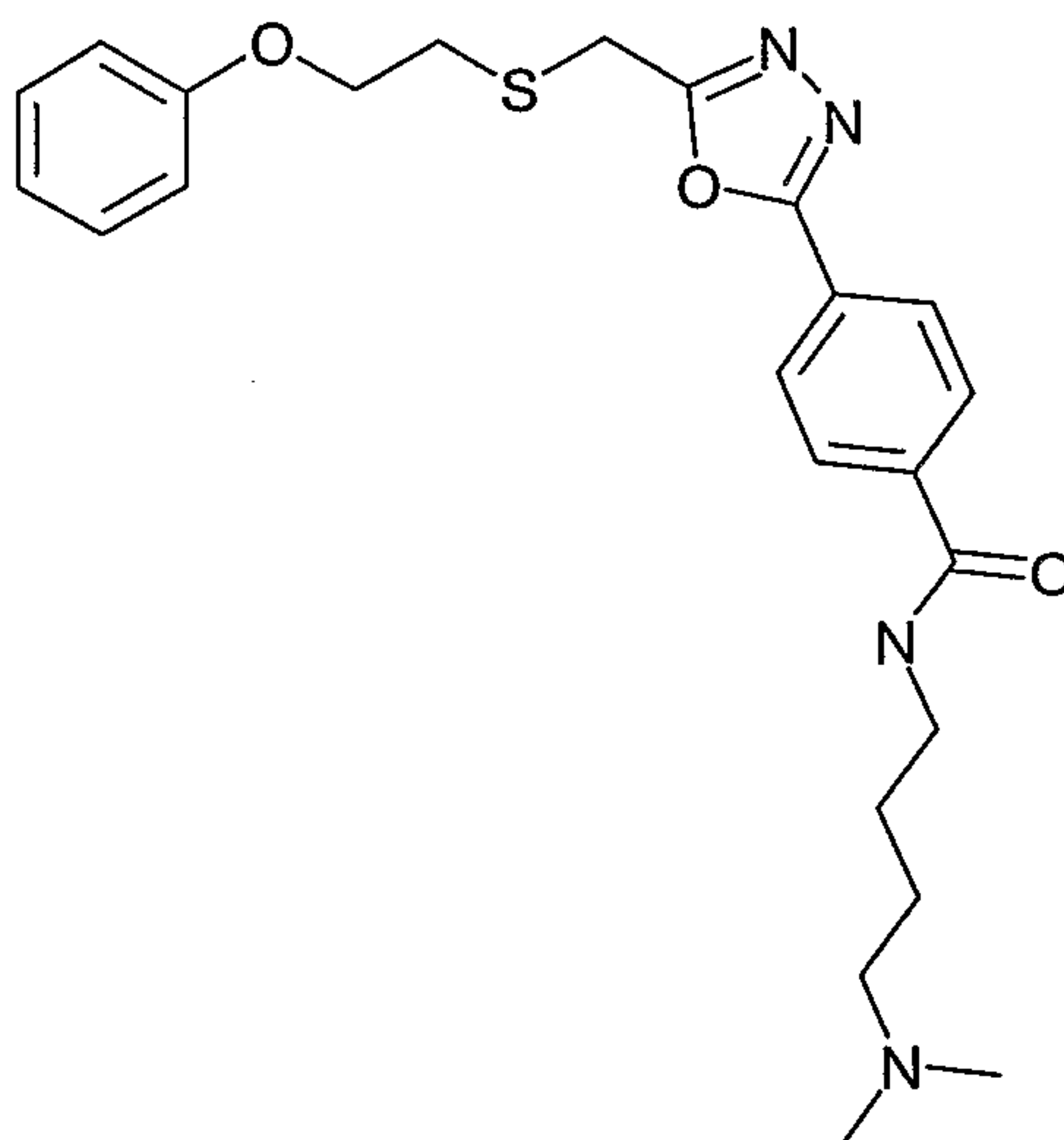
10 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47f, from 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.178 g, 0.5 mmol), 1,1'-carbonyldiimidazole (0.082 g, 0.505 mmol), and 2-(dimethylamino)ethylamine (0.069 mL, 0.6 mmol) to afford 0.128 g (60%) of N-(2-dimethylaminoethyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as a white solid (MP 94-100 °C, MW 426.54).

15 ^1H NMR (CDCl_3) δ 8.15 (t, 1H, $J=7$ Hz), 8.12 (s, 4H), 7.27 (t, 2H, $J=8$ Hz), 6.95 (t, 1H, $J=7$ Hz), 6.89 (d, 2H, $J=8$ Hz), 4.22 (t, 2H, $J=6$ Hz), 4.08 (s, 2H), 3.79 (m, 2H), 3.07 (t, 2H, $J=6$ Hz), 2.99 (m, 2H), and 2.67 (bs, 6H). IR (KBr, cm^{-1}) 3350, 2943, 2819, 2766, 1643, 1554, 1538, 1494, 1245, 1033, 863, and 750. MS (ESI) m/e 427, 425. Anal. 20 Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_3\text{S}$: C, 61.95; H, 6.14; N, 13.14; S, 7.52. Found C, 61.40; H, 5.90; N, 13.00; S, 7.59. Analytical HPLC: 97% purity.

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Example 55

Preparation of N-(4-dimethylaminobutyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



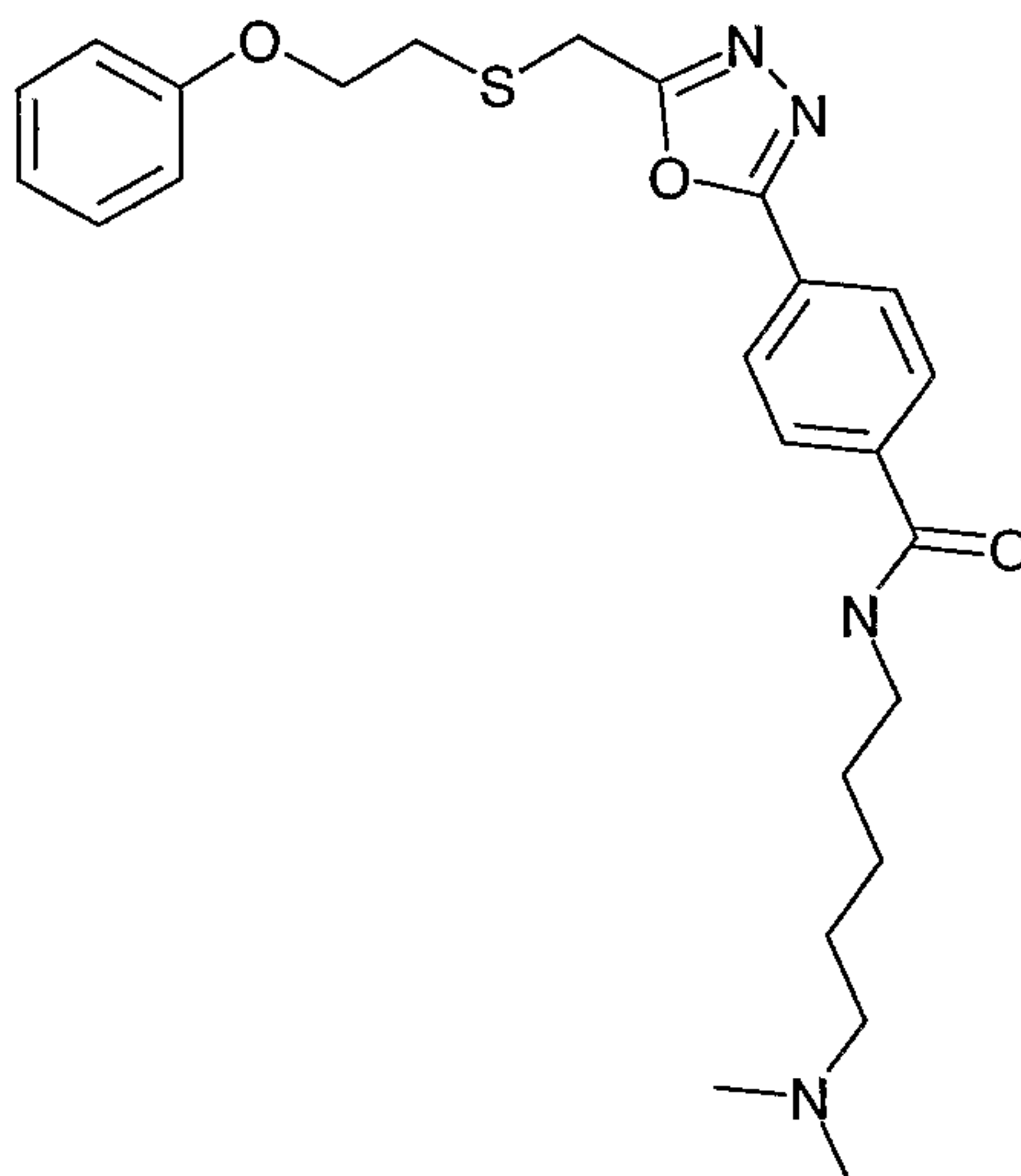
5 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47f, from 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.178 g, 0.5 mmol), 1,1'-carbonyldiimidazole (0.082 g, 0.505 mmol), and 4-(dimethylamino)butylamine (0.07 g, 0.6 mmol) to afford 0.136 g (60%) of N-(4-dimethylaminobutyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white waxy solid (MP 71-78 °C, MW 454.60).

10 ¹H NMR (CDCl₃) δ 8.11 (bs, 1H), 8.09 (d, 2H, J=9 Hz), 8.05 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=8 Hz), 6.95 (t, 1H, J=7 Hz), 6.89 (d, 2H, J=8 Hz), 4.22 (t, 2H, J=6 Hz), 4.07 (s, 2H), 3.53 (m, 2H), 3.06 (t, 2H, J=6 Hz), 2.78 (m, 2H), 2.56 (bs, 6H), and 1.83 (m, 4H). IR (KBr, cm⁻¹) 3338, 2943, 1643, 1602, 1554, 1533, 1494, 1468, 1289, 1246, 749, and 691. MS (ESI) m/e 453, 455. Anal. Calcd for C₂₄H₃₀N₄O₃S: C, 63.41; H, 6.65; N, 12.32; S, 7.05. Found C, 62.75; H, 6.77; N, 12.53; S, 6.93. Analytical HPLC: 97% purity.

Example 56

20 Preparation of N-(5-dimethylaminopentyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

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The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47f, from 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.178 g, 0.5 mmol), 1,1'-carbonyldiimidazole (0.082 g, 0.505 mmol), and 5-(dimethylamino)pentylamine (0.078 g, 0.6 mmol) to afford 0.126 g (53%) of N-(5-dimethylaminopentyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white waxy solid (MP 83-89 °C, MW 468.62).

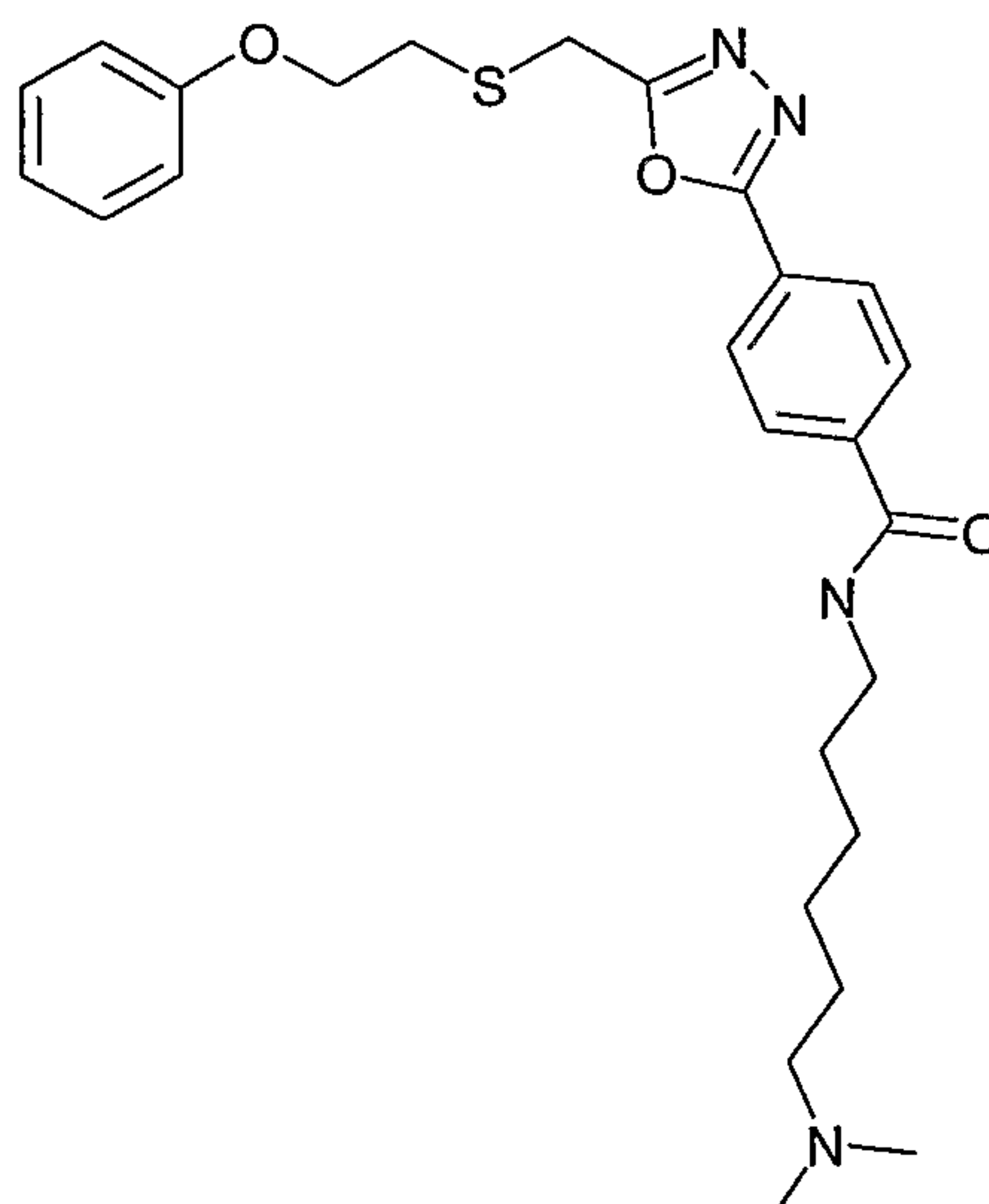
¹H NMR (CDCl₃) δ 8.11 (bs, 1H), 8.09 (d, 2H, J=8 Hz), 7.98 (d, 2H, J=8 Hz), 7.27 (m, 2H), 6.93 (t, 1H, J=7 Hz), 6.89 (d, 2H, J=8 Hz), 4.22 (t, 2H, J=6 Hz), 4.07 (s, 2H), 3.52 (m, 2H), 3.06 (t, 2H, J=6 Hz), 2.62 (m, 2H), 2.48 (bs, 6H), 1.71 (m, 4H), and 1.54 (m, 2H). IR (KBr, cm⁻¹) 3346, 2942, 2761, 1717, 1644, 1554, 1533, and 1246. MS (ESI) m/e 467, 469. Anal. Calcd for C₂₅H₃₂N₄O₃S: C, 64.08; H, 6.88; N, 11.96; S, 6.84. Found C, 63.05; H, 6.78; N, 11.71; S, 6.47. Analytical HPLC: 96% purity.

15

Example 57

Preparation of N-(6-dimethylaminohexyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

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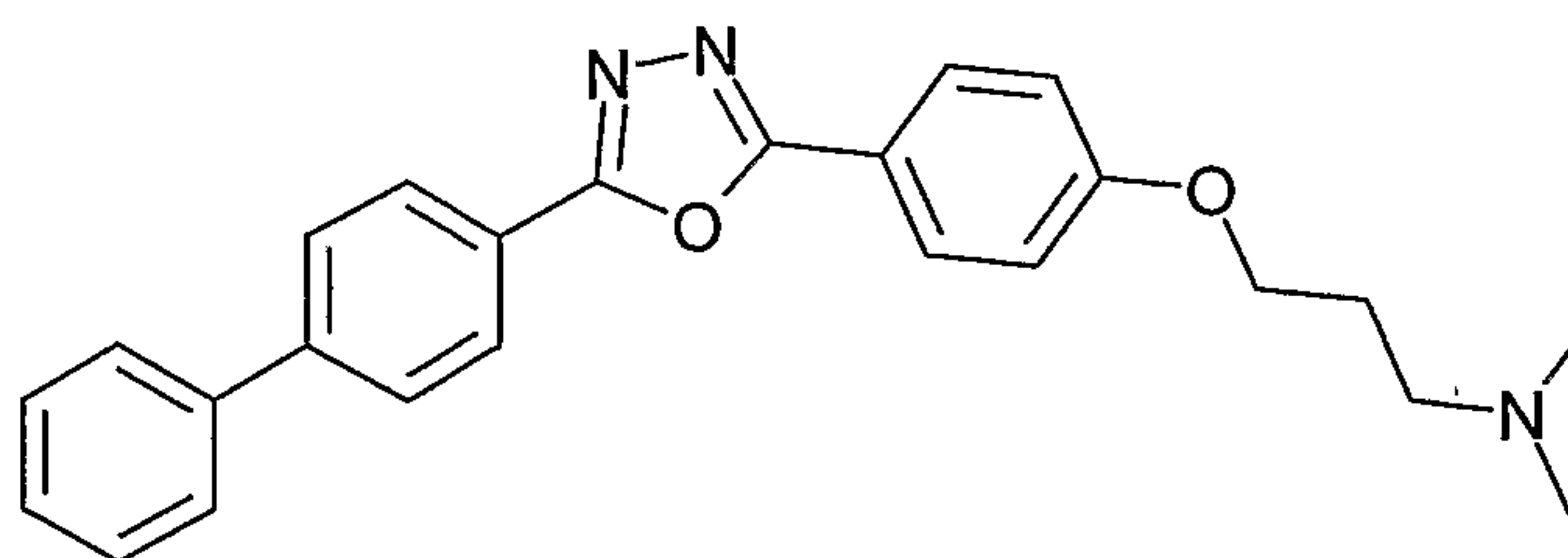


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47f, from 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.178 g, 0.5 mmol), 1,1'-carbonyldiimidazole (0.082 g, 0.505 mmol), and 6-(dimethylamino)hexylamine (0.087 g, 0.6 mmol) to afford 0.148 g (61%) of N-(6-dimethylaminohexyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white solid (MP 86-93 °C, MW 482.65).

¹H NMR (CDCl₃) δ 8.13 (bs, 1H), 8.10 (d, 2H, J=9 Hz), 8.02 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=8 Hz), 6.95 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 4.22 (t, 2H, J=6 Hz), 4.07 (s, 2H), 3.51 (m, 2H), 3.06 (t, 2H, J=6 Hz), 2.87 (m, 2H), 2.70 (bs, 6H), 1.83 (m, 2H), 1.71 (m, 2H) and 1.47 (m, 4H). IR (KBr, cm⁻¹) 3339, 2929, 2854, 2815, 2776, 1642, 1602, 1580, 1554, 1532, 1492, 1468, 1247, 1017, 749, and 691. MS (ESI) m/e 481, 483. Anal. Calcd for C₂₆H₃₄N₄O₃S: C, 64.70; H, 7.10; N, 11.61; S, 6.64. Found C, 63.86; H, 7.13; N, 12.19; S, 6.76. Analytical HPLC: 97% purity.

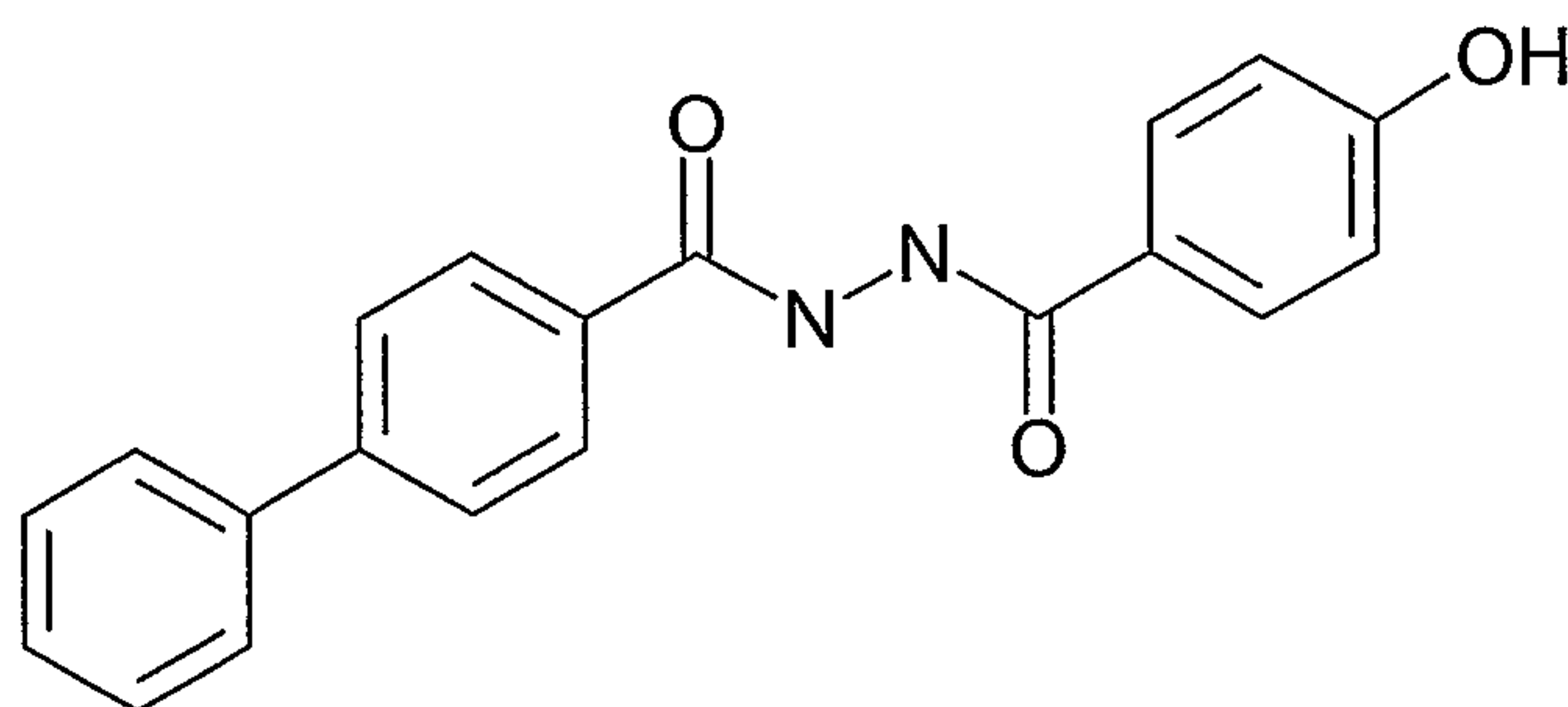
Example 58

Preparation of {3-[4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-dimethylamine



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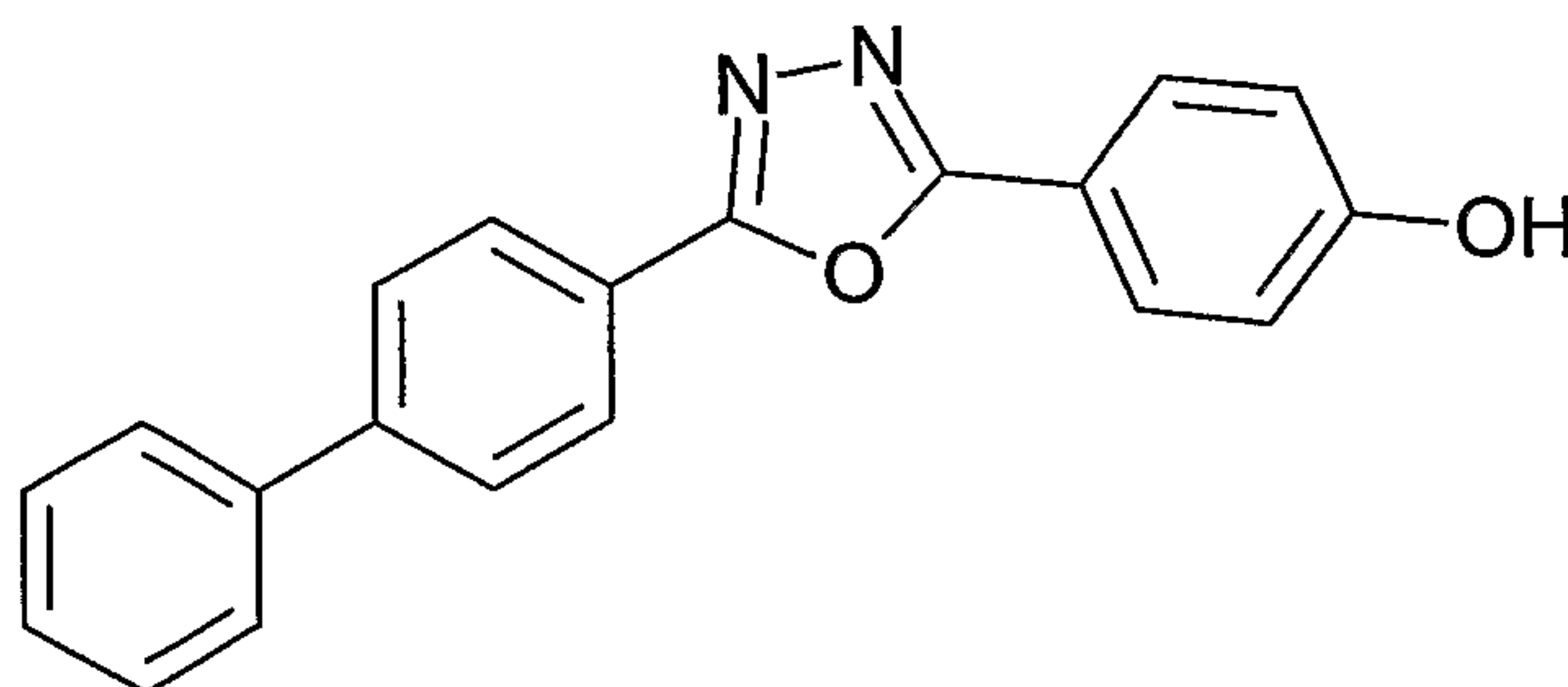
a) 4-hydroxy-benzoic acid N'-(biphenyl-4-carbonyl)-hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 51a, from 4-biphenylcarboxylic acid (1.04 g, 5.0 mmol) to afford 1.52 g (91%) of 4-hydroxy-benzoic acid N'-(biphenyl-4-carbonyl)-hydrazide as an off-white solid (MP 279-281 °C, MW 332.36).

¹H NMR (DMSO-d₆) δ 10.44 (s, 1H), 10.24 (s, 1H), 10.09 (s, 1H), 8.00 (d, 2H, J=9 Hz), 7.81 (d, 2H, J=8 Hz), 7.79 (d, 2H, J=9 Hz), 7.74 (d, 2H, J=8 Hz), 7.49 (t, 2H, J=8 Hz), 7.40 (t, 1H, J=7 Hz), and 6.84 (d, 2H, J=9 Hz). IR (KBr, cm⁻¹) 3272, 1674, 1622, 1608, 1582, 1513, 1492, 1484, 1284, 1277, 1236, 847, and 745. MS (ESI) m/e 331, 333. Anal. Calcd for C₂₀H₁₆N₂O₃: C, 72.28; H, 4.85; N, 8.43. Found C, 72.52; H, 4.99; N, 8.27.

b) 4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenol



15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-hydroxy-benzoic acid N'-(biphenyl-4-carbonyl)-hydrazide (1.33 g, 4.0 mmol), triphenylphosphine (2.12 g, 8.0 mmol), and triethylamine (2.0 mL, 14.4 mmol) to afford 0.343 g (27%) of 4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenol as an off-white solid (MP 256-260 °C, MW 314.35).

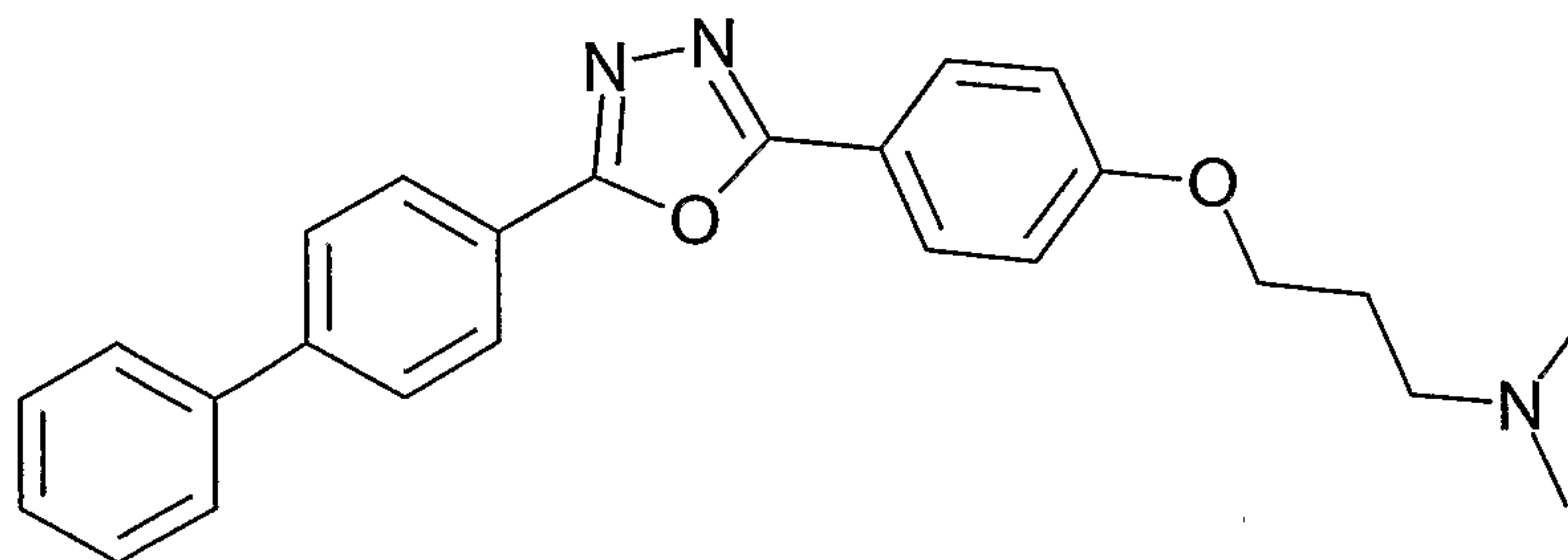
20

¹H NMR (DMSO-d₆) δ 10.34 (s, 1H), 8.17 (d, 2H, J=8 Hz), 7.97 (d, 2H, J=8 Hz), 7.92 (d, 2H, J=8 Hz), 7.77 (d, 2H, J=8 Hz), 7.51 (t, 2H, J=8 Hz), 7.42 (t, 1H, J=8 Hz), and 6.97 (d, 2H, J=8 Hz). IR (KBr, cm⁻¹) 3110, 1613, 1498, 1483, 1293, 1176, 1074, 838, and

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739. MS (ESI) m/e 313, 315. Anal. Calcd for C₂₀H₁₄N₂O₂: C, 76.42; H, 4.49; N, 8.91. Found C, 76.34; H, 4.75; N, 8.35.

c) {3-[4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-dimethylamine



5

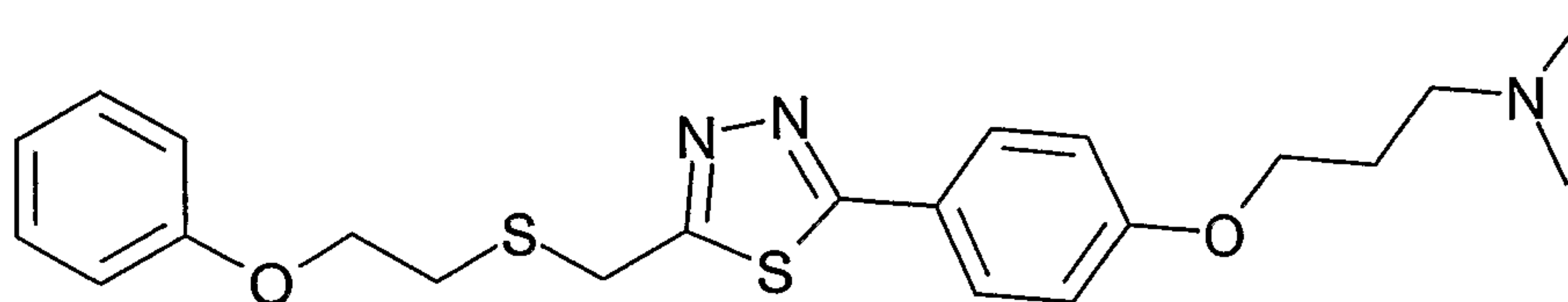
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, from 4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenol (0.157 g, 0.5 mmol) to afford 0.162 g (81%) of {3-[4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-dimethylamine as a white solid (MP 130-132 °C, MW 399.50).

¹H NMR (CDCl₃) δ 8.19 (d, 2H, J=9 Hz), 8.09 (d, 2H, J=9 Hz), 7.76 (d, 2H, J=9 Hz), 7.66 (d, 2H, J=8 Hz), 7.49 (t, 2H, J=7 Hz), 7.41 (t, 1H, J=7 Hz), 7.03 (d, 2H, J=8 Hz), 4.18 (t, 2H, J=6 Hz), 3.07 (m, 2H), 2.72 (bs, 6H), and 2.36 (m, 2H). IR (KBr, cm⁻¹) 2940, 2752, 1613, 1473, 1464, 1257, 1006, 842, and 740. MS (ESI) m/e 400. Anal. Calcd for C₂₅H₂₅N₃O₂: C, 75.16; H, 6.31; N, 10.52. Found C, 73.89; H, 6.33; N, 10.35.

15 Analytical HPLC: 95% purity.

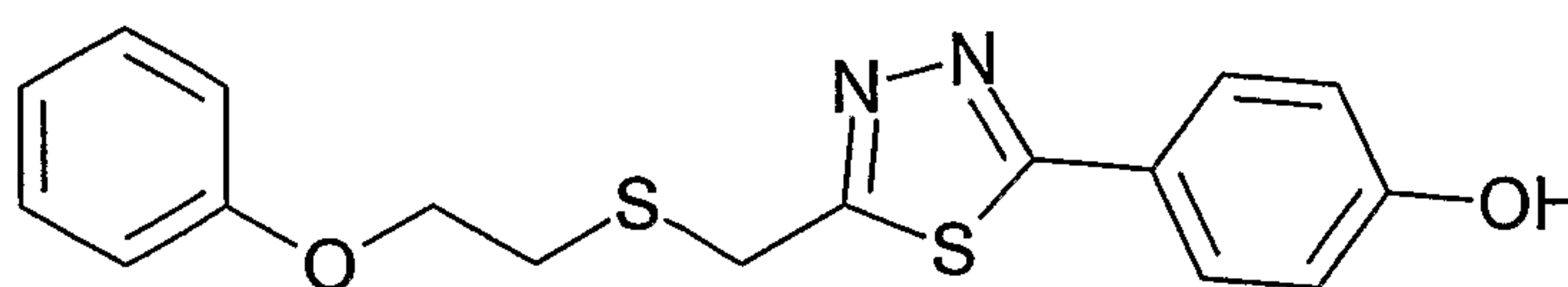
Example 59

Preparation of Dimethyl-(3-{4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenoxy}-propyl)-amine



20

a) 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenol

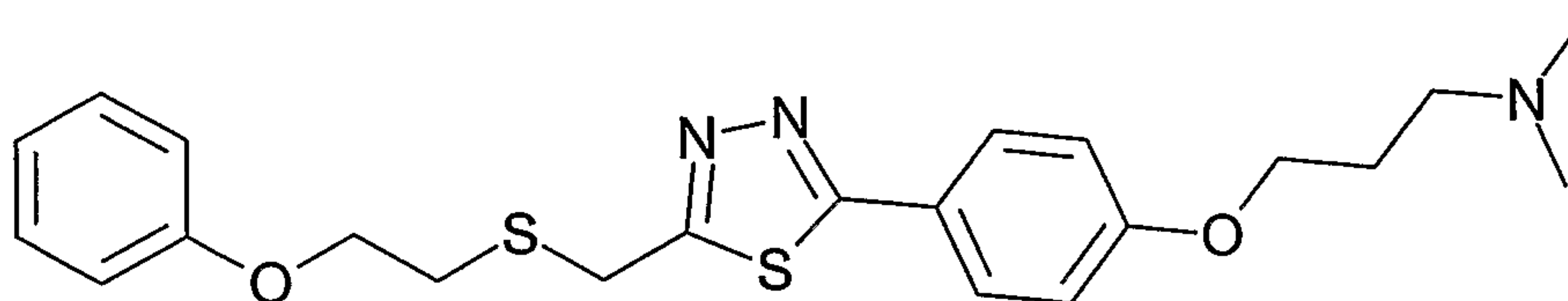


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A heterogeneous mixture of 4-hydroxy-benzoic acid N'-[2-(2-phenoxyethylsulfanyl)-acetyl]-hydrazide (1.04 g, 3.0 mmol), and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's Reagent) (1.25 g, 3.0 mmol) in 30 mL toluene was stirred at reflux temperature (111 °C) for 1.5 h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo to afford 2.37 g of a yellow solid. Purification by column chromatography on silica gel (elution with linear gradient of 0-100% ethyl acetate/hexane followed by isocratic elution with 5% methanol/ethyl acetate) afforded 0.144 g (14%) of 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenol as a white solid (MP 127-128 °C, MW 344.46).

¹H NMR (DMSO-d₆) δ 10.17 (s, 1H), 7.76 (d, 2H, J=9 Hz), 7.25 (t, 2H, J=8 Hz), 6.90 (m, 5H), 4.32 (s, 2H), 4.14 (t, 2H, J=6 Hz), and 2.93 (t, 2H, J=6 Hz). IR (KBr, cm⁻¹) 3415, 3125, 2920, 1600, 1586, 1496, 1243, 1177, 1032, 754, and 690. MS (ESI) m/e 345, 343. Anal. Calcd for C₁₇H₁₆N₂O₂S₂: C, 59.28; H, 4.68; N, 8.13; S, 18.62. Found C, 59.24; H, 4.71; N, 8.20; S, 18.36.

b) Dimethyl-(3-{4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenoxy}-propyl)-amine



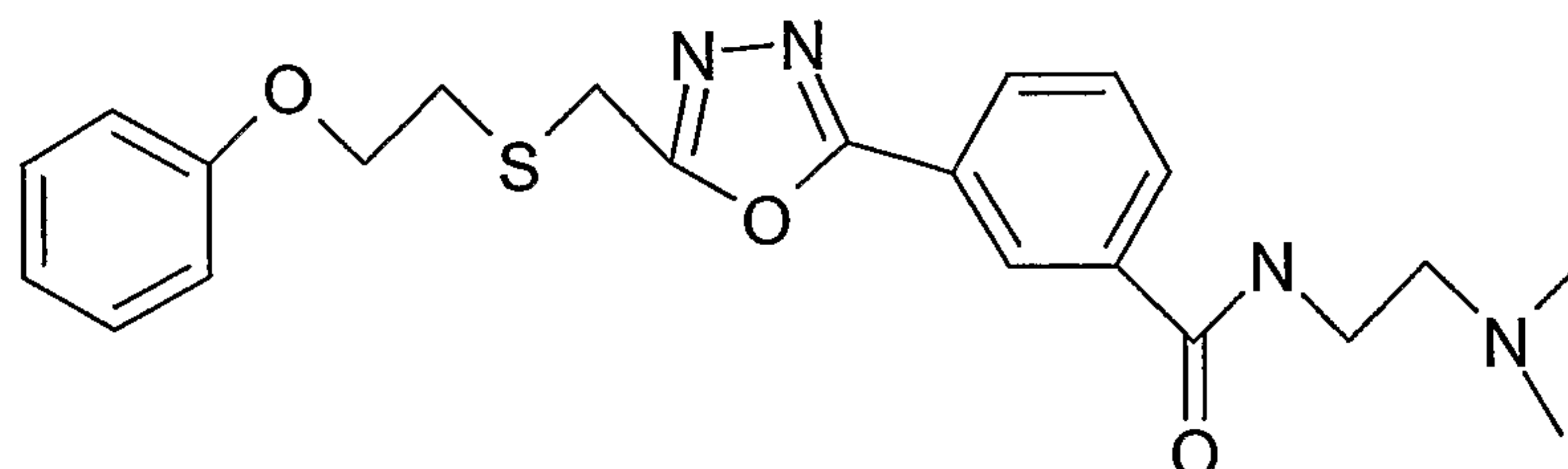
The above compound was prepared as exemplified in Example 50f, using 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenol (0.12 g, 0.35 mmol) to afford 0.038 g (25%) of dimethyl-(3-{4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenoxy}-propyl)-amine as a white solid (MP 72-73 °C, MW 429.61).

¹H NMR (CDCl₃) δ 7.87 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.95 (d, 2H, J=9 Hz), 6.91 (t, 1H, J=8 Hz), 6.88 (d, 2H, J=8 Hz), 4.22 (s, 2H), 4.18 (m, 4H), 3.25 (m, 2H), 2.99 (t, 2H, J=6 Hz), 2.87 (s, 3H), 2.86 (s, 3H), and 2.47 (m, 2H). IR (KBr, cm⁻¹) 2948, 2923, 2873, 2825, 2779, 1602, 1499, 1465, 1452, 1253, 1178, 1057, 955, 842, and 757. MS (ESI) m/e 428, 430. Anal. Calcd for C₂₂H₂₇N₃O₂S₂: C, 61.51; H, 6.33; N, 9.78; S, 14.93. Found C, 61.89; H, 6.68; N, 9.19; S, 13.88. Analytical HPLC: 91% purity.

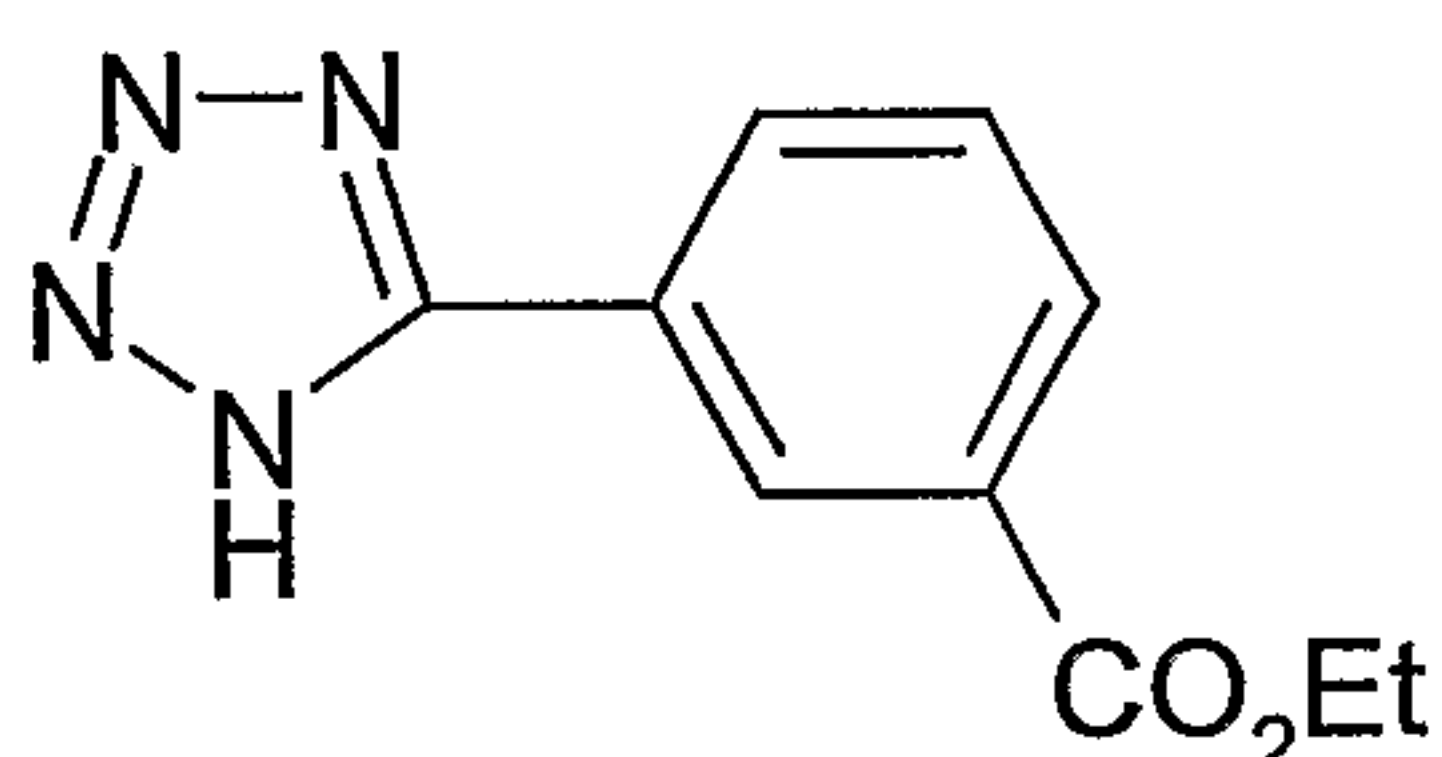
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Example 60

Preparation of *N*-(2-Dimethylamino-ethyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



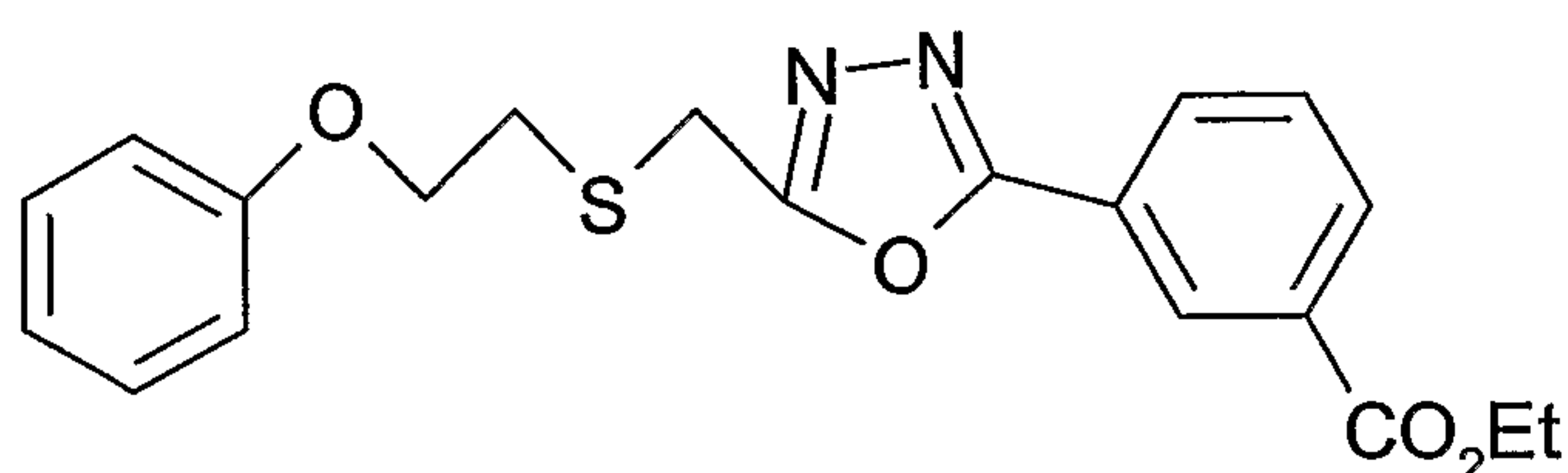
5 a) 3-(1*H*-Tetrazol-5-yl)-benzoic acid ethyl ester



A solution of 3-cyano-benzoic acid ethyl ester (2.00 g, 11.4 mmol), sodium azide (2.22 g, 34.2 mmol), and triethylamine hydrochloride (4.71 g, 34.2 mmol) in 40 mL toluene was heated to 100°C for 4.5 h. The mixture was cooled to room temperature and
 10 150 mL of H₂O was added. The suspension was stirred for 10 min. and transferred to a separatory funnel and separated. The aqueous layer was transferred to a round-bottom flask with H₂O (50 mL), cooled to 0°C and acidified with HCl (conc). The resultant precipitate was collected by filtration, washed with H₂O, and dried in vacuo to afford 2.36 g (95%) of 3-(1*H*-Tetrazol-5-yl)-benzoic acid ethyl ester as a white solid.

15 ¹H NMR (DMSO-d₆) δ 8.62 (s, 1H), 8.30 (d, 1H, J= 8 Hz), 8.13 (d, 1H, J=8 Hz), 7.76 (t, 1H, J=8 Hz), 4.36 (q, 2H, J=7 Hz) and 1.3 (t, 3H, J=7 Hz). IR (KBr, cm⁻¹) 3153, 3102, 2924, 1690, 1295, 1277, and 733. MS (ESI) m/e 217. Anal. Calcd for C₁₀H₁₀N₄O₂Cl: C, 55.04; H, 4.62; N, 25.67. Found C, 55.09; H, 4.64; N, 25.39.

b) 3-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid ethyl
 20 ester



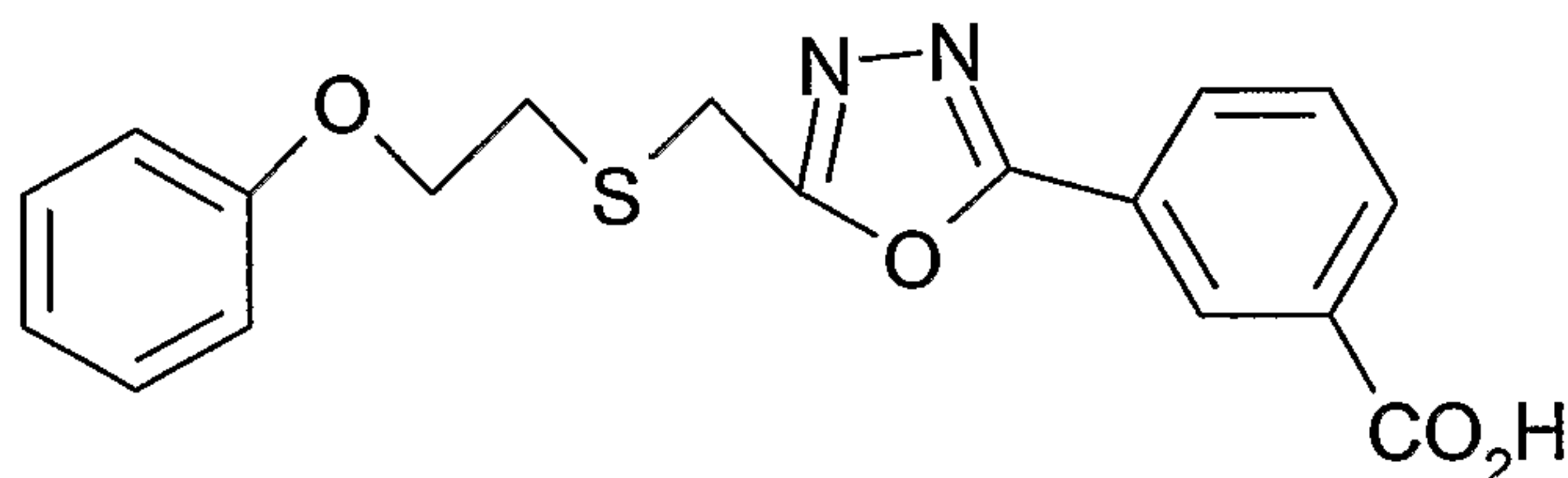
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To a solution of thiolacetic acid (0.65 g, 3.1 mmol) and 1,3-dicyclohexylcarbodiimide (0.64 g, 3.1 mmol) in 5 mL of toluene was added 3-(1*H*-Tetrazol-5-yl)-benzoic acid ethyl ester (0.67 g, 3.1 mmol). The reaction mixture was heated to 111°C for 20 min., concentrated *in vacuo* and titrated with CH₂Cl₂ (5 mL).

5 The resultant precipitate was collected by filtration and the filtrate concentrated *in vacuo*. The filtrate was purified directly by column chromatography on silica gel (elution with 1/1 ethyl acetate and toluene) to afford 0.880 g (75%) of 3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid ethyl ester.

¹H NMR (CDCl₃) δ 8.7 (s, 1H), 8.2 (m, 2H), 7.6 (t, 1H, J=8 Hz), 7.3 (m, 3H), 6.9 (m, 2H), 4.4 (q, 2H, J=7 Hz), 4.2 (t, 2H, 6 Hz), 4.086 (s, 2H), 3.1 (t, 2H, J=6 Hz), and 1.4 (t, 3H, J=7Hz). IR (KBr, cm⁻¹) 2935, 1719, 1601, 1498, 1303, 1244. MS (ESI) m/e 385. Anal. Calcd for C₂₀H₂₀N₂O₄S: C, 62.48; H, 5.24; N, 7.29. Found C, 61.7; H, 5.34; N, 6.83.

15 c) 3-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



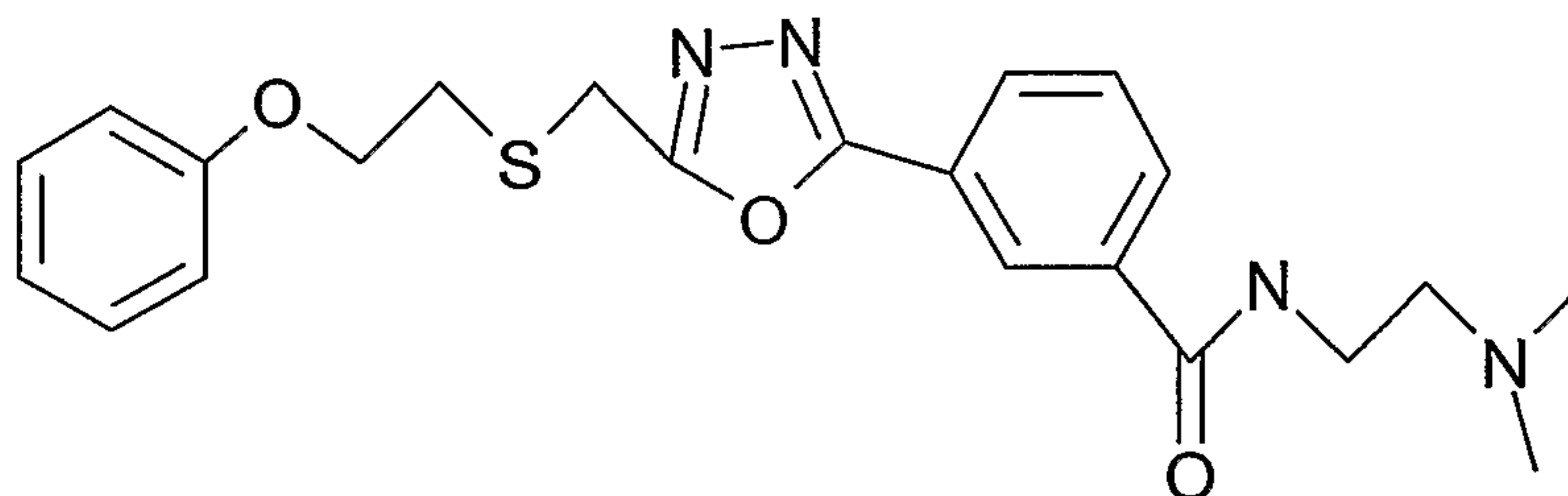
A solution of 3-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid ethyl ester (0.880 g, 2.29 mmol) and lithium hydroxide (0.164 g, 6.87 mmol) in water (3 mL) and THF (7 mL) was stirred at room temperature overnight.

20 Concentrated HCl (0.59 mL) was added and the resulting precipitate was collected by filtration and dried *in vacuo* to afford 0.694 g (85%) of 3-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid as a gold solid.

¹H NMR (DMSO-d₆) δ 8.5 (s, 1H), 8.1 (m, 2H), 7.7 (t, 1H, J=7.7 Hz), 7.25 (m, 2H), 6.9 (m, 3H), 4.2 (s, 2H), 4.2 (t, 2H, J=6.2 Hz), and 3.0 (t, 2H, J=6.3 Hz). IR (KBr, cm⁻¹) 3419, 3295, 2928, 2852, 1717, 1600, 1498, 1246, 757, 714, and 690. MS (ESI) m/e 357, 355. Anal. Calcd for C₁₈H₁₆N₂O₄S: C, 60.66; H, 4.53; N, 7.86. Found C, 58.25; H, 5.16; N, 6.99.

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d) N-(2-Dimethylamino-ethyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



3-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid was added to a nitrogen flushed vessel with CH₂Cl₂ (5 mL) followed by the addition of oxalyl chloride (0.397 g, 3.13 mmol) and DMF (2 drops). The mixture was stirred at room temperature for 35 min., concentrated in *vacuo* and azeotroped with CH₂Cl₂ (3 X 5 mL) to give 3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoyl chloride. N1,N1-Dimethyl-ethane-1,2-diamine was dissolved in CH₂Cl₂ (1 mL) and added to a nitrogen flushed vessel. 3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoyl chloride was dissolved in CH₂Cl₂ (3 mL) and added dropwise. The reaction was stirred at room temperature overnight and diluted with water, CH₂Cl₂, and NaOH (1N). The aqueous layer was extracted 2 times with CH₂Cl₂. The combined organic extracts were washed with saturated brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with 95 CHCl₃/5 NH₃ (2.0M in MeOH) to afford 0.167 g (63%) of N-(2-dimethylamino-ethyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide. Recrystallization from Et₂O and EtOAc gave 0.079 g (30%) of the title compound.

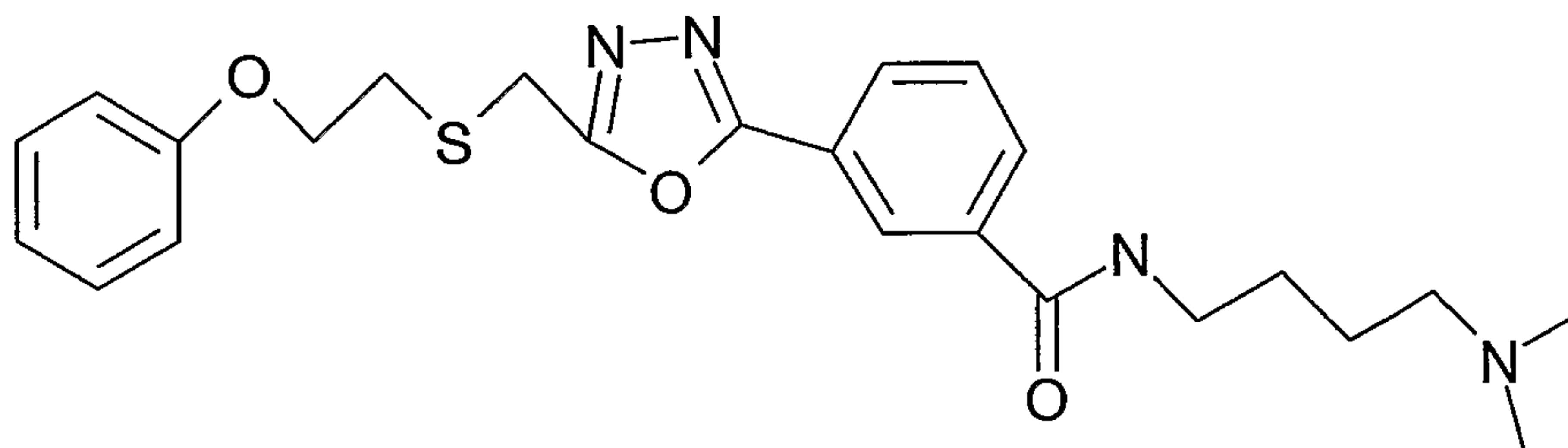
¹H NMR (DMSO-d₆) δ 8.7 (t, 1H, J=5 Hz), 8.4 (s, 1H), 8.1 (m, 2H), 7.7 (t, 1H, J=8), 7.2 (m, 2H), 6.9 (m, 3H), 4.2 (s, 2H), 4.2 (t, 2H, J=6 Hz), 3.4 (m, 2H), 3.0 (t, 2H, J=6 Hz), 2.4 (t, 2H, J=7 Hz), 2.1 (s, 6H). IR (KBr, cm⁻¹) 2952, 2864, 2827, 2785, 1658, 1601, 1498, 1243. MS (ESI) m/e 428, 429, 425. Anal. Calcd for C₂₂H₂₆N₄O₃S: C, 61.95; H, 6.14; N, 13.14. Found C, 61.80; H, 6.23; N, 12.92. MP=64°C.

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Example 61

Preparation of N-(4-dimethylamino-butyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

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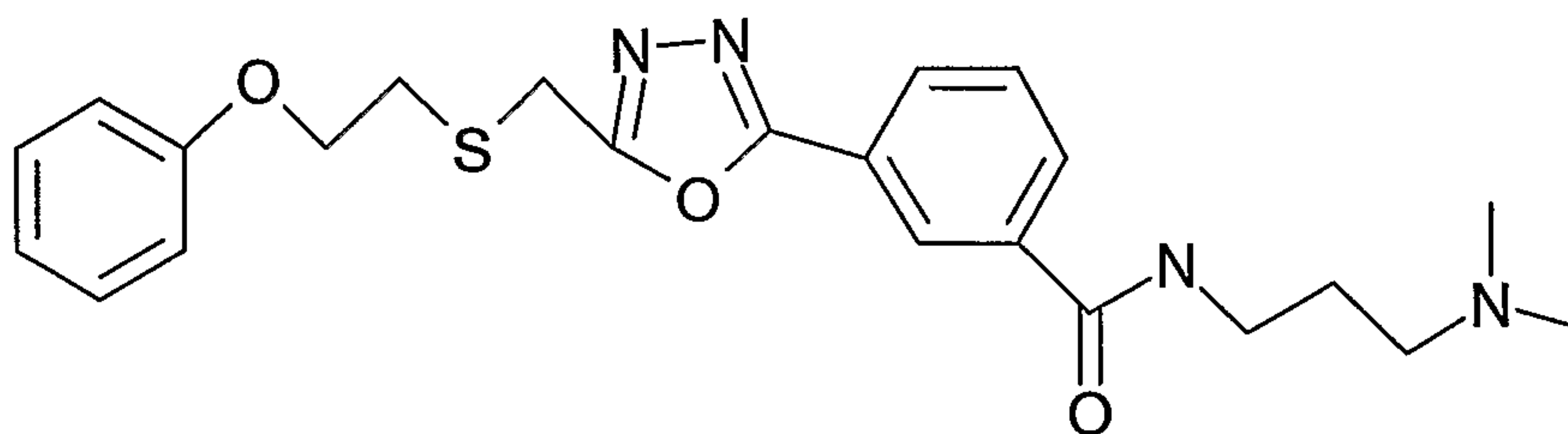


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60, from 3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.353 g, 1.0 mmol) and N1,N1-dimethyl-butane-1,4-diamine (0.230 g, 1.98 mmol) to give 0.346 g (77%) of the title compound.

^1H NMR (CDCl_3) δ 8.4 (s, 1H), 8.1, (d, 1H, $J=8$ Hz), 8.0 (d, 1H, $J=8$ Hz), 7.6, (t, 1H, $J=8$ Hz), 7.2 (m, 3H), 6.9 (m, 2H), 4.2 (t, 2H, $J=6$ Hz), 4.1 (s, 2H), 3.5 (q, 2H, $J=5$ Hz), 3.1 (t, 2H, $J=6$ Hz), 2.4 (t, 2H, $J=6$ Hz), 2.2 (s, 6H), 1.8 (m, 2H), 1.7 (m, 2H). IR (KBr, cm^{-1}) 2940, 2864, 2826, 2784, 1659, 1601, 1549, 1498, 1243. MS (ESI) m/e 455, 453. Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_3\text{S}$: C, 63.41; H, 6.65; N, 12.32. Found C, 63.52; H, 7.17; N, 12.07. MP=38-42°C.

Example 62

Preparation of N-(3-dimethylamino-propyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60, from 3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.387 g, 1.1 mmol) and N1,N1-dimethyl-propane-1,3-diamine (221 mg, 2.16 mmol) to give 0.046 g (10%) of N-(3-dimethylamino-propyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

^1H NMR (CDCl_3) δ 9.1 (s, br, 1H), 8.4, (s, 1H), 8.14 (d, 1H, $J=8$ Hz), 8.1 (d, 1H, $J=8$ Hz), 7.3 (m, 2H), 6.94 (t, 1H, $J=7$ Hz), 6.9 (d, 2H, $J=8$ Hz), 4.2 (t, 2H, $J=6$ Hz), 4.1 (s, 2H), 3.6 (m, 2H), 3.1 (t, 2H, $J=6$ Hz), 2.6 (m, 2H), 2.4 (s, 6H), 1.8 (q, 2H, $J=6$ Hz). IR

10)

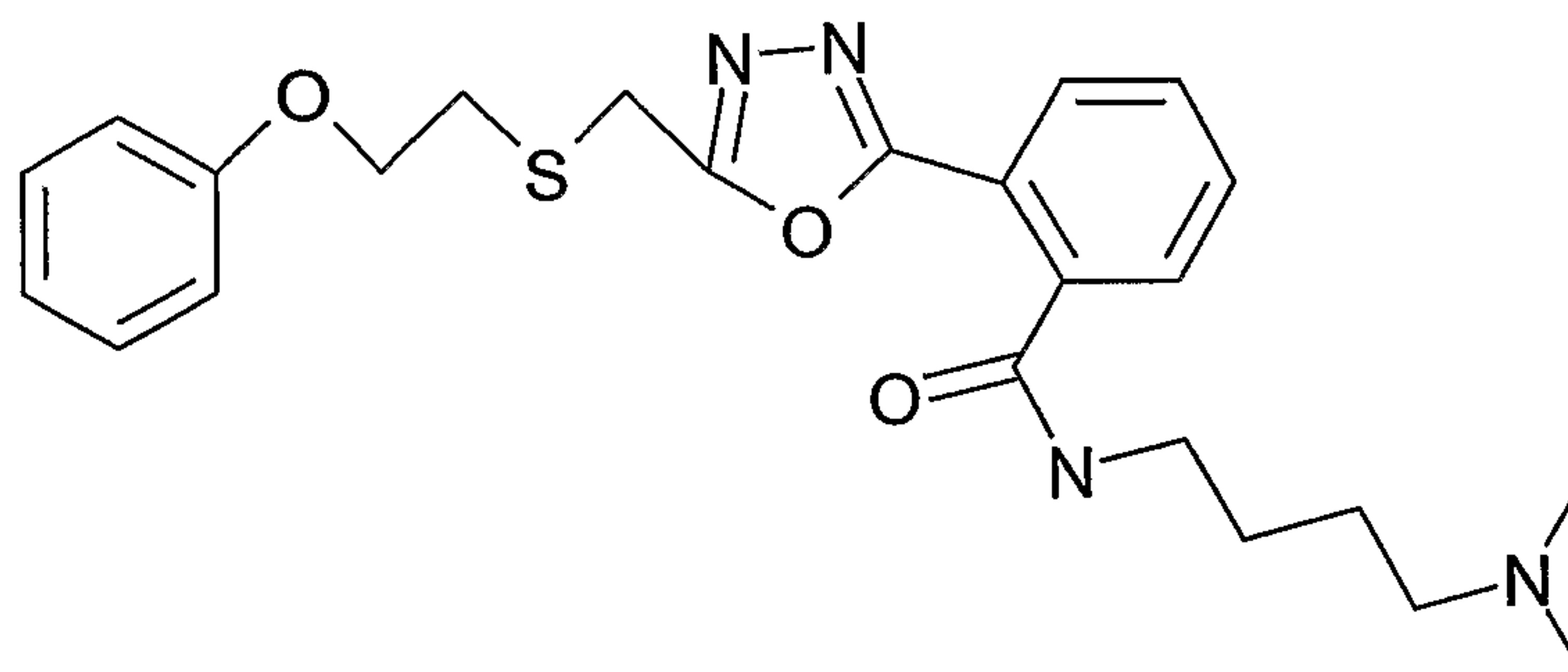
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(KBr, cm^{-1}) 3018, 1653, 1548, 1498, 1243. MS (ESI) m/e 441, 439. HPLC 100%. Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_3\text{S}$: C, 62.70; H, 6.41; N, 12.72. Found C, 61.60; H, 6.19; N, 12.22. MP=88-90°C.

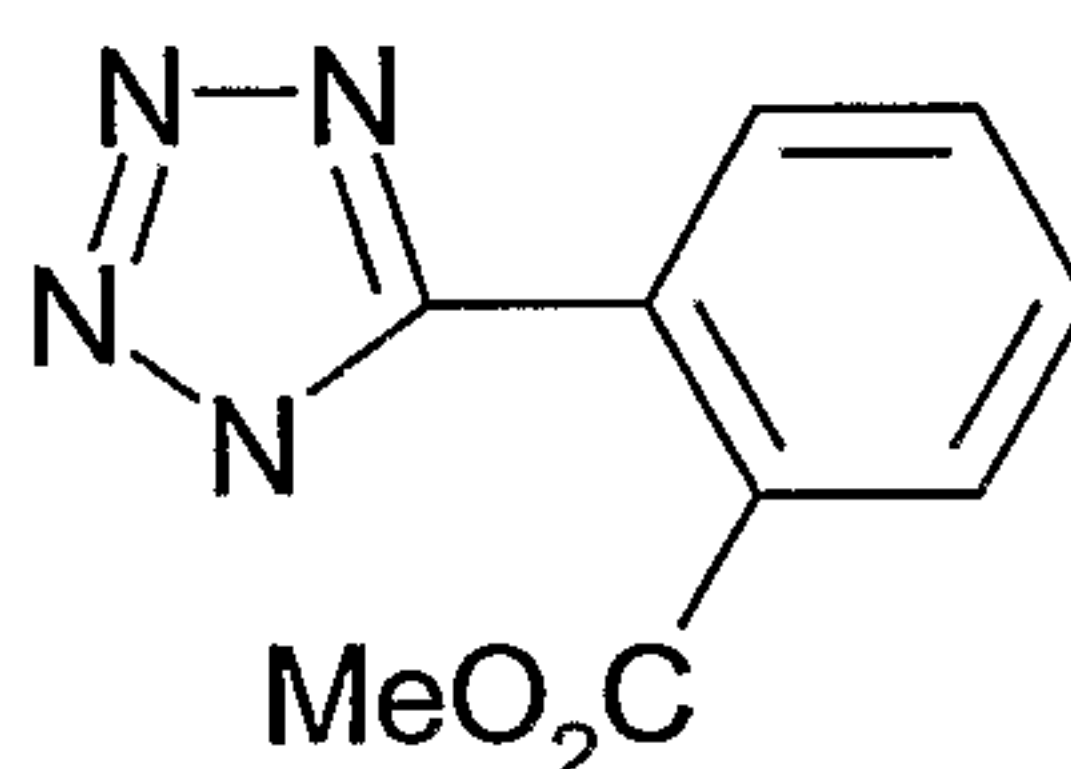
5

Example 63

Preparation of N-(4-dimethylamino-butyl)-2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



a) 2-(1H-Tetrazol-5-yl)-benzoic acid methyl ester



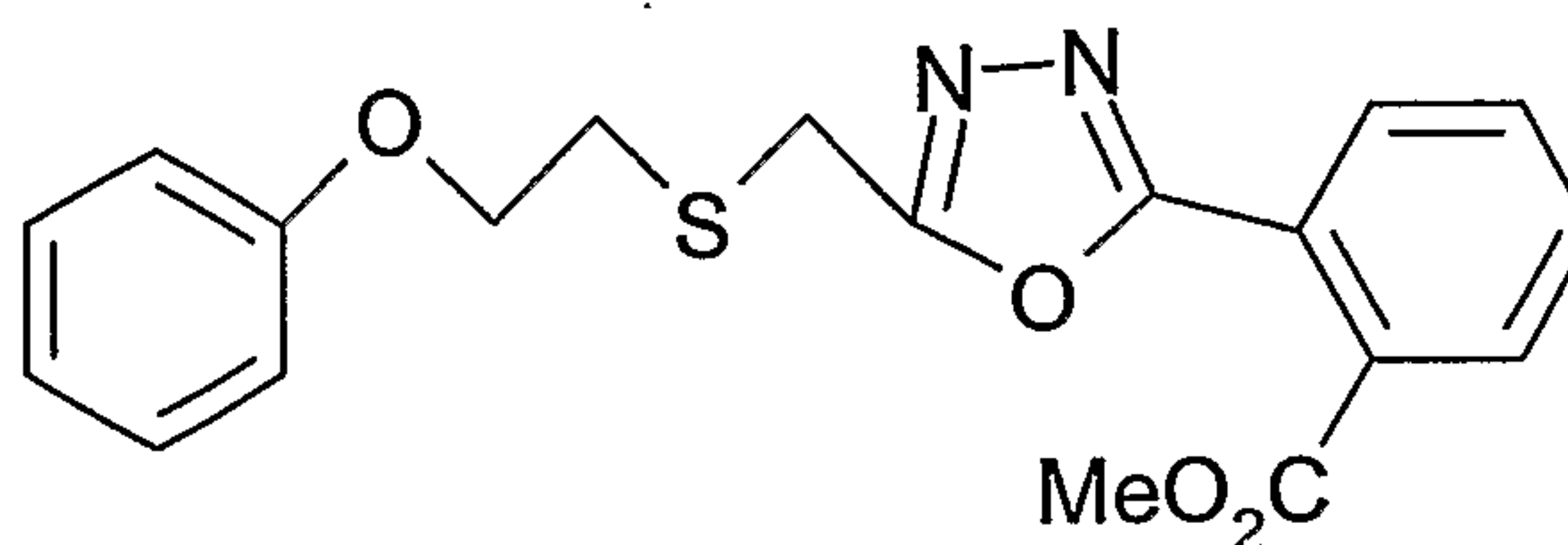
10

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60a, from 2-cyano-benzoic acid methyl ester (2.031g, 12.6 mmol) to give 1.87g (73%) of 2-(1H-tetrazol-5-yl)-benzoic acid methyl ester.

^1H NMR (DMSO- d_6) δ 7.9 (m, 1H), 7.7 (m, 3H), 3.7 (s, 3H). IR (KBr, cm^{-1}) 1715, 1273. MS (ESI) m/e 203. Anal. Calcd for $\text{C}_9\text{H}_8\text{N}_4\text{O}_2$: C, 55.04; H, 4.62; N, 25.67. Found C, 53.68; H, 3.89; N, 28.61.

15

b) 2-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester



20

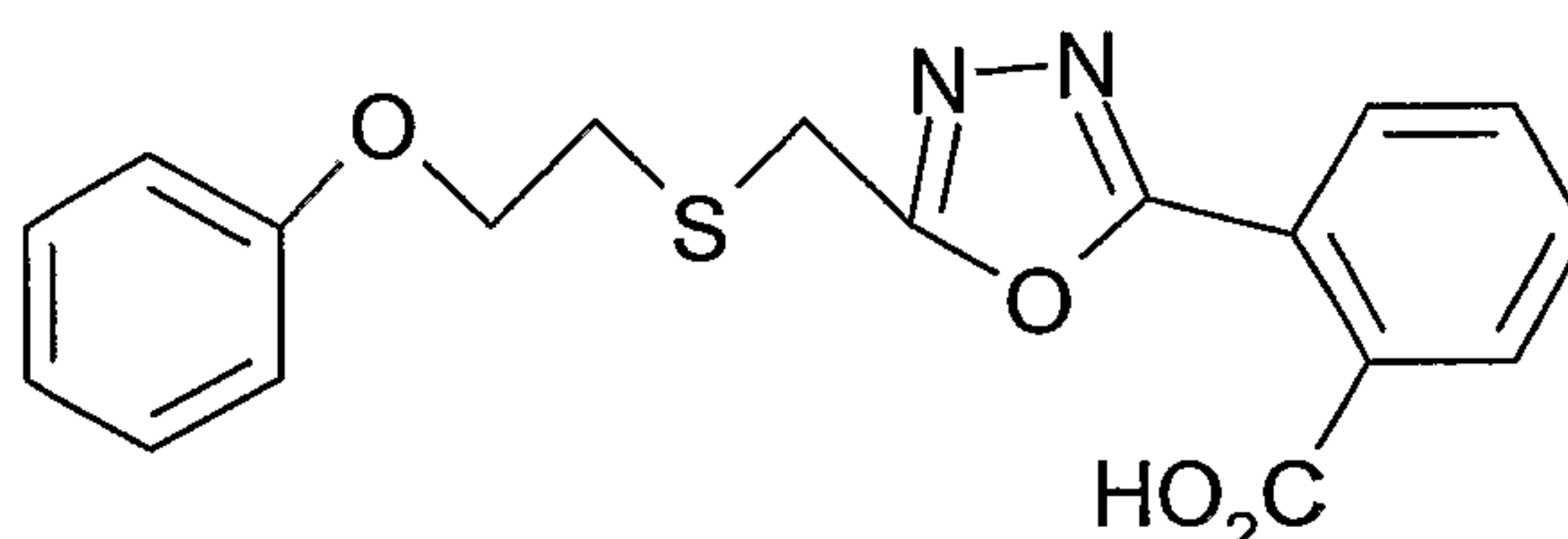
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60b, from 2-(1H-Tetrazol-5-yl)-benzoic acid methyl ester (0.705

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g, 3.45 mmol) to give 0.985 g (73%) of 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester.

¹H NMR (CDCl₃) δ 7.9 (m, 1H), 7.8 (m, 1H), 7.6 (m, 1H), 7.2 (m, 2H), 6.95 (t, 1H, J=7 Hz), 6.9 (d, 2H, J=9 Hz), 4.2 (t, 2H, J=6 Hz), 4.0 (s, 2H), 3.8 (s, 3H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm⁻¹) 1728, 1601, 1498, 1299, 1276, 1243. MS (ESI) m/e 371. Anal. Calcd for C₁₉H₁₈N₂O₄S: C, 61.61; H, 4.90; N, 7.56. Found C, 61.41; H, 4.94; N, 7.46.

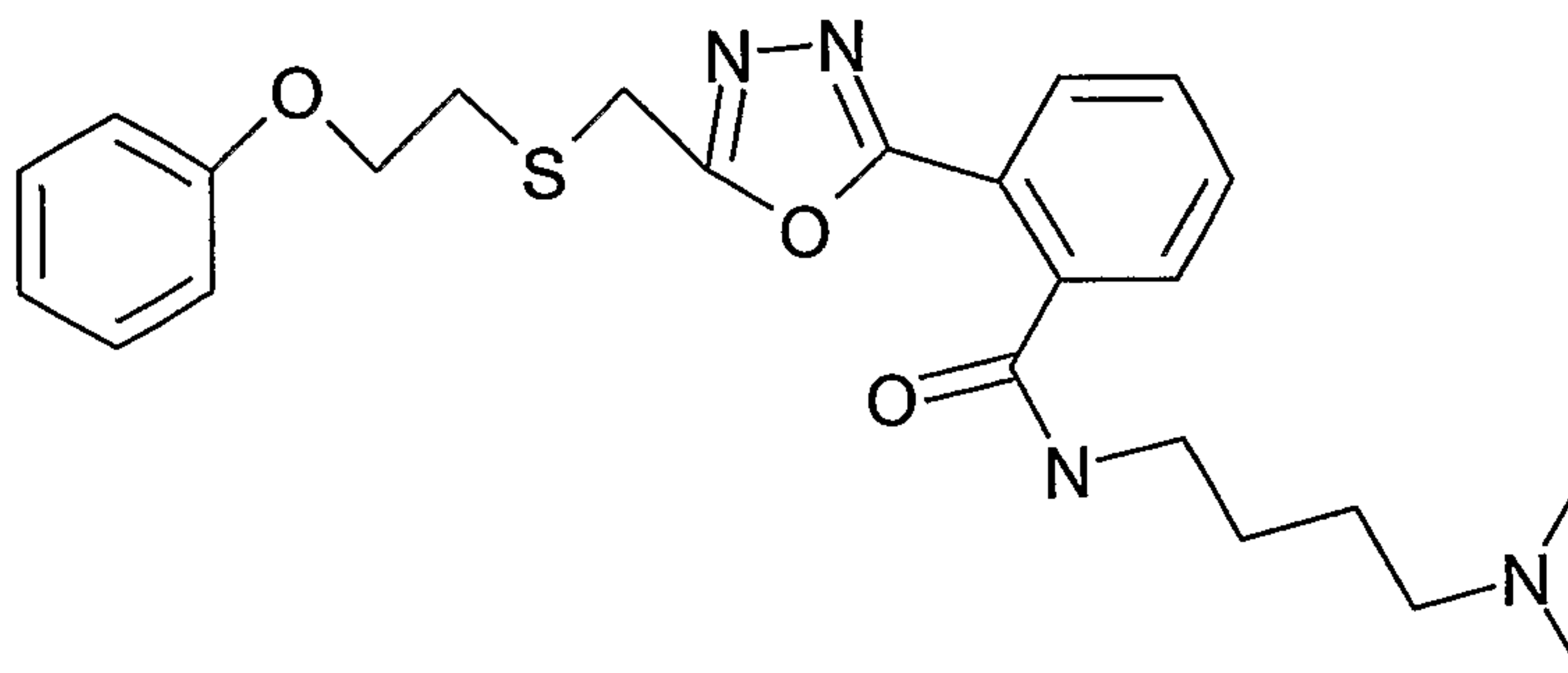
c) 2-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60c, from 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester (0.929 g, 2.51 mmol) with the exception that a gold oil formed upon treatment with conc. HCl. This material was titrated with H₂O and concentrated to dryness in vacuo to give 0.808 g (90%) of 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid.

¹H NMR (CD₃OD) δ 8.1 (m, 1H), 7.7 (m, 3H), 7.2 (m, 2H), 6.9 (m, 3H), 4.2 (t, 2H, J=6 Hz) 4.16 (s, 2H), 3.1 (t, 2H, J=6 Hz). IR (KBr, cm⁻¹) 3430, 1723, 1635, 1601, 1241. MS (ESI) m/e 357, 355. Anal. Calcd for C₁₈H₁₆N₂O₄S: C, 60.66; H, 4.53; N, 7.86. Found C, 55.74; H, 4.48; N, 7.28.

d) N-(4-Dimethylamino-butyl)-2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



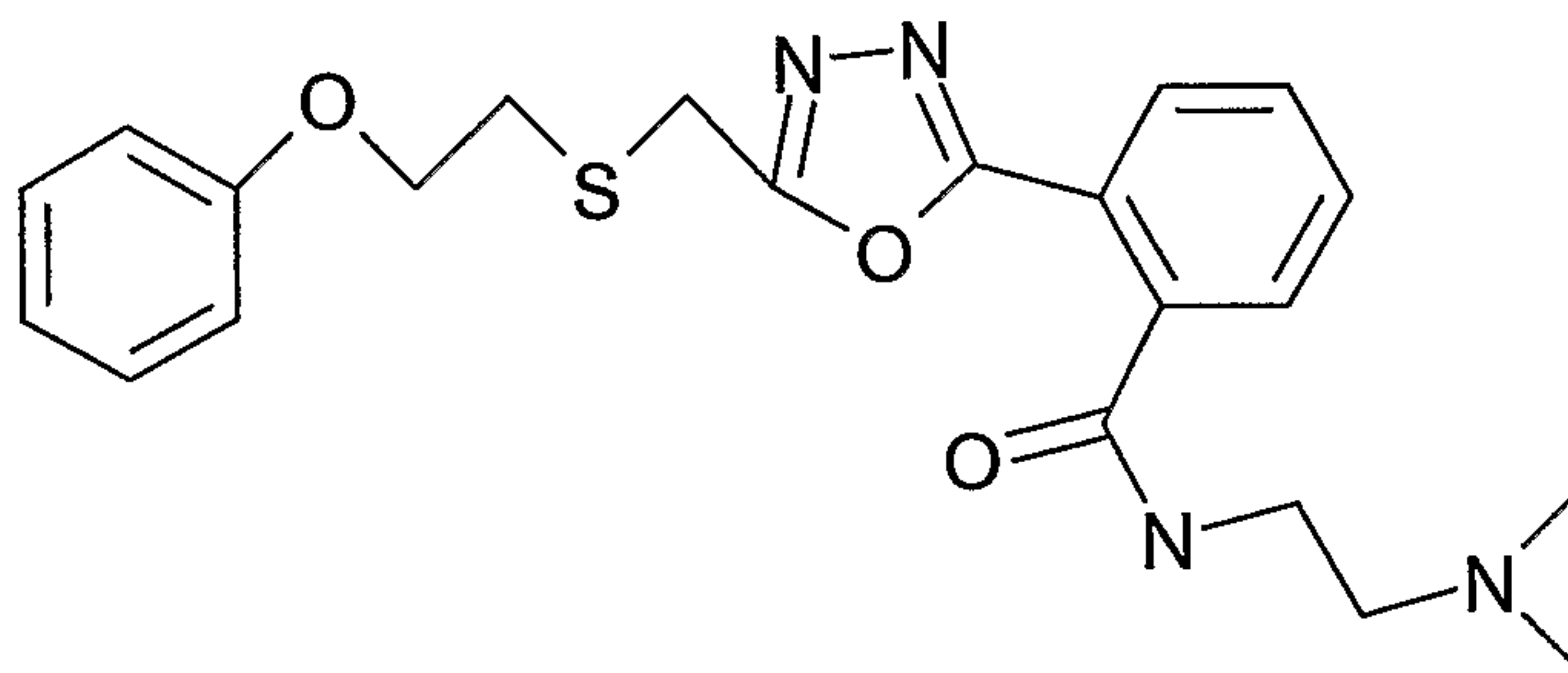
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The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60d, from 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.434 g, 1.22 mmol) and N1,N1-dimethyl-butane-1,4-diamine (0.283 g, 2.44 mmol) to give 0.334 g (60%) of the title compound.

¹H NMR (CDCl₃) δ 8.1 (s (br), 1H), 7.9 (d, 1H, J=7 Hz), 7.5 (m, 3H), 7.3 (m, 2H), 6.95 (t, 1H, J=6 Hz), 6.9 (d, 2H, J=8 Hz), 4.2 (t, 2H, J=6 Hz), 4.0 (s, 2H), 3.4 (q, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.3 (t, 2H, J=6 Hz), 2.0 (s, 6H), 1.66 (m, 2H), 1.6 (m, 2H). IR (KBr, cm⁻¹) 3008, 2941, 2864, 2824, 2782, 1721, 1662, 1601, 1588, 1498, 1469, 1243. MS (ESI) m/e 455, 453. Anal. Calcd for C₂₄H₃₀N₄O₃S: C, 63.41; H, 6.65; N, 12.32. Found C, 63.38; H, 7.01; N, 11.73. MP = 62-65°C.

Example 64

Preparation of N-(2-dimethylamino-ethyl)-2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60d, from 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.169g, 0.474 mmol) and N1,N1-dimethyl-ethane-1,2-diamine (0.084 g, 0.948 mmol) to give 0.082 g (41%) of the title compound.

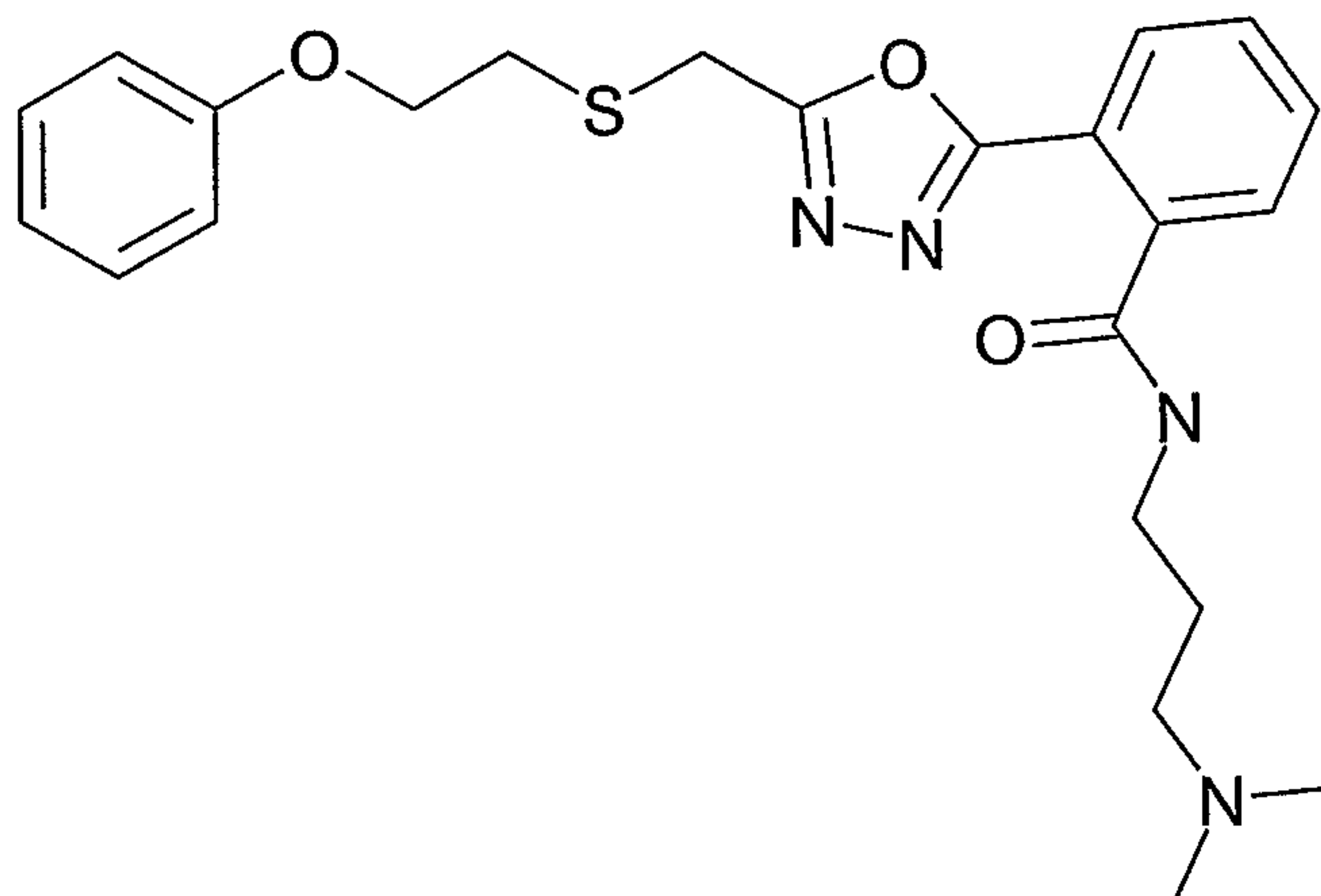
¹H NMR (CDCl₃) δ 7.8 (d, 1H, J=7 Hz), 7.5 (m, 3H), 7.2 (m, 2H), 6.9 (t, 1H, J=7 Hz), 6.8 (d, 2H, J=8 Hz), 4.1 (t, 2H, J=6 Hz), 3.9 (s, 2H), 3.5 (m, 2H), 3.0 (t, J=6 Hz) 2.5 (s, br, 1H), 2.2 (s, 6H). IR (KBr, cm⁻¹) 3009, 1722, 1665, 1601, 1498, 1470, 1402, 1242. MS (ESI) m/e 427, 425. Anal. Calcd for C₂₂H₂₆N₄O₃S: C, 61.95; H, 6.14; N, 13.13. Found C, 59.49; H, 5.91; N, 12.18. MP=80-85°C.

25

Example 65

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Preparation of N-(3-dimethylamino-propyl)-2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



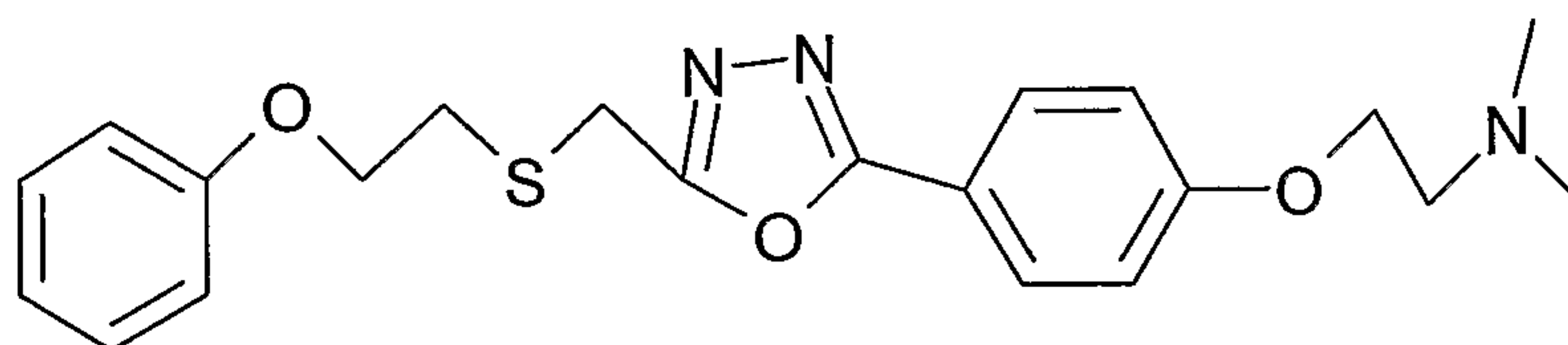
To a solution of 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.159 g, 0.45 mmol) in 3 mL THF was added 1,1'-carbonyldiimidazole (0.073 g, 0.45mM) and 0.044 mL DMF. The mixture was heated to 60°C for 30 min followed by stirring at room temperature for 5 min. N1,N1-Dimethyl-propane-1,3-diamine (0.091 g, 0.89 mmol) was added to the mixture and stirring was continued at room temperature for 2 hours. The mixture was extracted with ethyl acetate and washed
10 with water, brine, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography on silica gel (elution with chloroform and 2M ammonia in methanol gave 0.072 g (37%) of the title compound.

¹H NMR (CDCl₃) δ 7.9 (d, 1H, J=7 Hz), 7.5 (m, 3H), 7.3 (m, 2H), 7.1 (s, 1H), 6.96 (t, 1H, J=7 Hz), 6.9 (d, 3H, J=9 Hz), 4.2 (7, 2H, J=6 Hz), 4.0 (s, 2H), 3.5 (m, 2H),
15 3.0 (t, 2H, J=6 Hz), 2.5 (t, 2H, J=6 Hz), 2.2 (s, 6H), 1.7 (m, 2H, J=6 Hz). IR (KBr, cm⁻¹) 2928, 2864, 1722, 1684, 1498, 1242. MS (ESI) m/e 441. Anal. Calcd for C₂₃H₂₈N₄O₃S: C, 62.70; H, 6.41; N, 12.72. Found C, 58.41; H, 6.16; N, 11.47. MP=60-65°C.

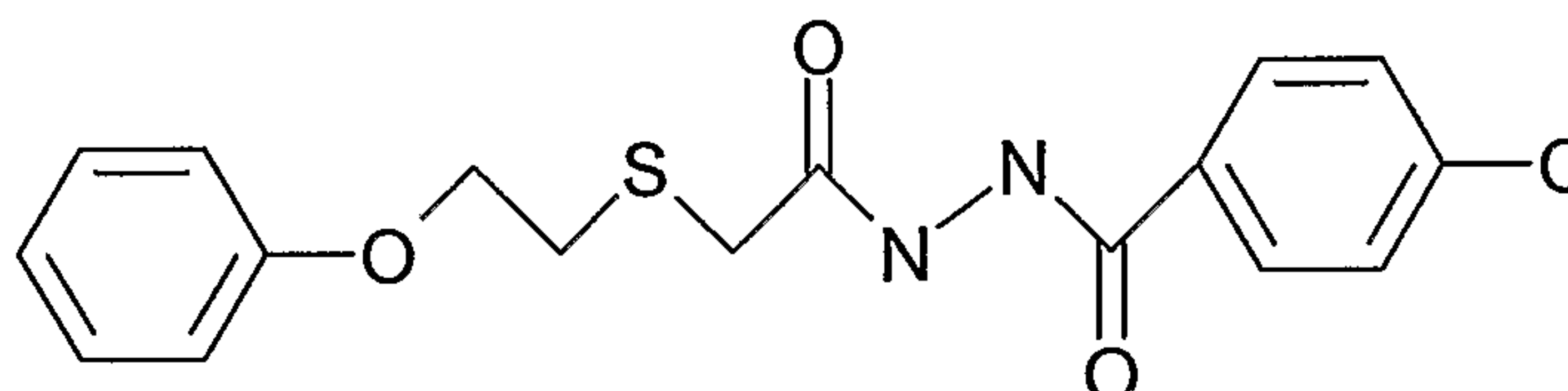
Example 66

20 Preparation of dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine

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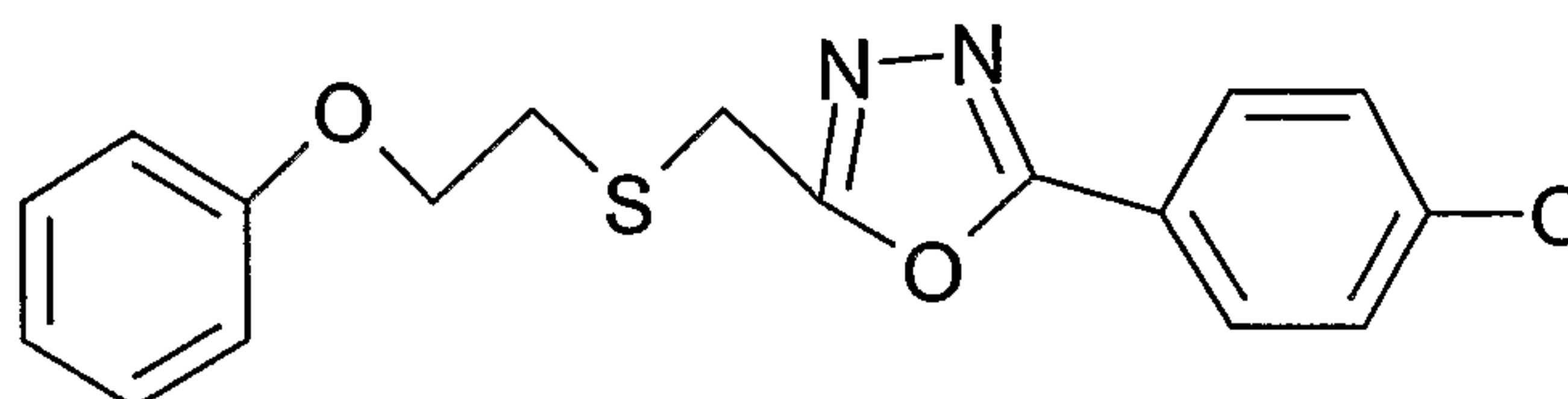
a) 4-Hydroxy-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide



A solution of (2-phenoxy-ethylsulfanyl)-acetic acid (0.848 g, 4.0 mmol) and (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, ethyl 1,2-dihydro-2-ethoxy-1-quinolinecarboxylate), (EEDQ), (0.989 g, 4.0 mmol) in 20 mL acetonitrile and 5 mL THF were stirred together at room temperature for 1 hr. 4-Hydroxy-benzoic acid hydrazide (0.608 g, 4.0 mmol) was added and the mixture was sonicated for 2 hrs and stirred at room temperature for 16 hrs. The mixture was concentrated to low volume and extracted with ethyl acetate. The organic extract was washed with 1N HCl, H₂O, NaHCO₃, brine, dried over magnesium sulfate, filtered, and concentrated to dryness to give 1.28 g (92%) of 4-hydroxy-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide.

¹H NMR (DMSO-d₆) δ 10.2 (s, 1H), 10.1 (s, 1H), 10.0 (s, 1H), 7.7 (d, 2H, J=9 Hz), 7.3 (m, 2H), 6.9 (m, 3H), 6.8 (d, 2H, J=9 Hz), 4.2 (t, 2H, J=6 Hz), 3.3 (m, 2H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm⁻¹) 3305, 3201, 3003, 2918, 2867, 1696, 1623, 1609, 1584, 1517, 1287, 1242, 1229. MS (ESI) m/e 347, 345. Anal. Calcd for C₁₇H₁₈N₂O₄S: C, 58.95; H, 5.24; N, 8.09. Found C, 58.37; H, 5.51; N, 7.19.

b) 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol



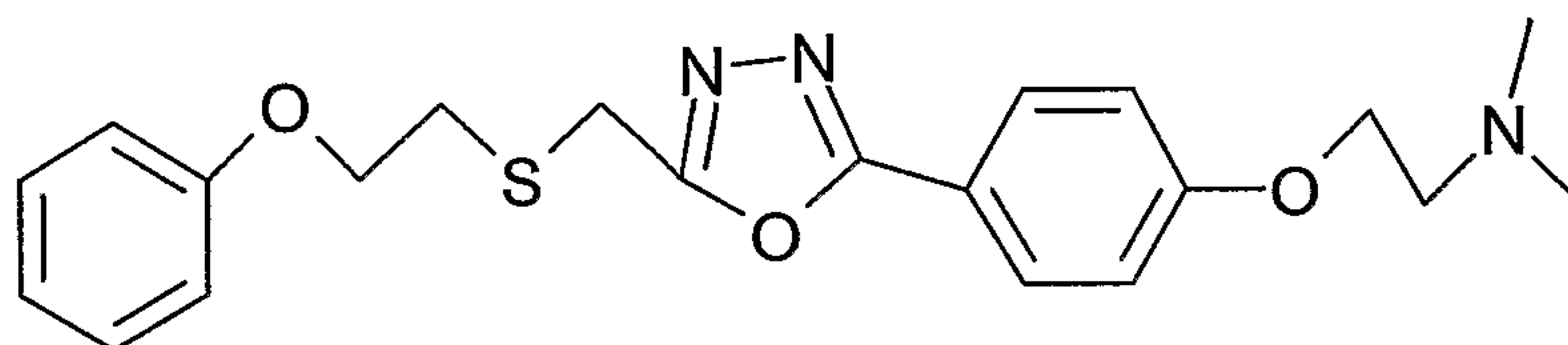
A solution of 4-hydroxy-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide (4.87 g, 14.1 mmol), triphenyl phosphine (7.38 g, 28.1 mmol), and

-201-

triethylamine (5.14 g, 50.7 mmol) were stirred together in acetonitrile (15 mL). Carbon tetrachloride (9.17 g, 57.9 mmol) was added and the mixture was stirred at room temperature for 3 hrs. The material was concentrated to low volume and diluted with hexane (100 mL), ethyl acetate (6 mL), and ethanol (25 mL). The mixture was sonicated for 5 minutes and a precipitate formed. The solid was collected and dried in vacuo (30°C). The solid was slurried with 1N HCl, collected and dried to give 3.149 g (68%) of the title compound.

¹H NMR (DMSO-d₆) δ 7.8 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 6.9 (m, 5H), 4.2 (m, 4H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm⁻¹) 3410, 1762, 1611, 1601, 1498, 1242, 1226, 1174, 752. MS (ESI) m/e 329, 327. Anal. Calcd for C₁₇H₁₆N₂O₃S: C, 62.18; H, 4.91; N, 8.53. Found C, 61.99; H, 5.00; N, 7.92. M.P.=172-175°C.

c) Preparation of dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine



15

A solution of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.214 g, 0.652 mmol) and 60% NaH (0.075 g, 1.95 mmol) was stirred at 5°C in 10 mL DMF for 2 min. at which time (2-chloro-ethyl)-dimethyl-amine, hydrochloride (0.140 g, 0.978 mmol) was added and the mixture was stirred at 100°C for 2.5 hours. The resultant mixture was extracted 2 times with ethyl acetate and washed with water, brine, dried over sodium sulfate and concentrated to give 0.243 g of crude product. This was purified directly by column chromatography on silica gel (elution with 1/1 ethyl acetate, toluene followed by chloroform/2M ammonia in methanol) to give a yellow oil which was recrystallized from ethyl ether and ethyl acetate to give 0.098 g (38%) of the title compound.

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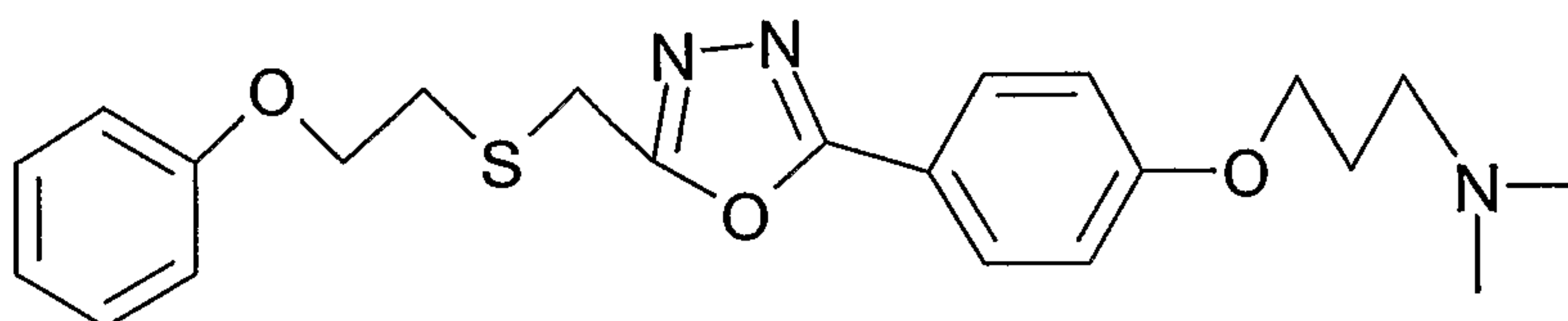
¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.1 (m, 6H), 3.0 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=5 Hz), 2.2 (s, 6H). IR (KBr, cm⁻¹) 1616, 1499, 1466, 1253, 1242, 1177, 756. MS (ESI) m/e 400.9. Anal. Calcd for

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$C_{21}H_{25}N_3O_3S$: C, 63.14; H, 6.31; N, 10.52. Found C, 62.92; H, 6.09; N, 10.38. MP=62-64°C.

Example 67

- 5 Preparation of dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



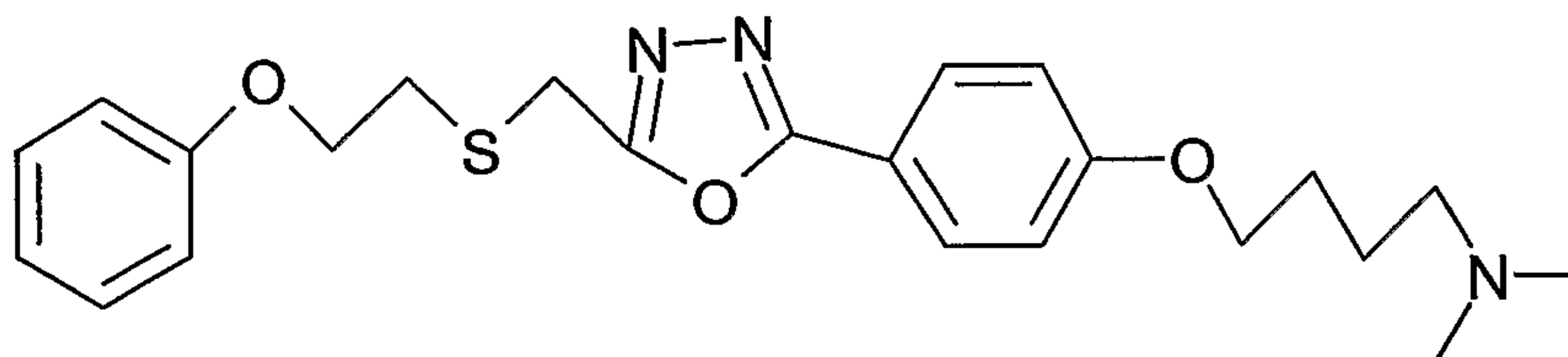
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-

- 10 [1,3,4]oxadiazol-2-yl]-phenol (0.548 g, 1.67 mmol) and (3-chloro-propyl)-dimethyl-amine, hydrochloride (396 mg, 2.5 mmol) to give 0.288 g (42%) of the title compound.

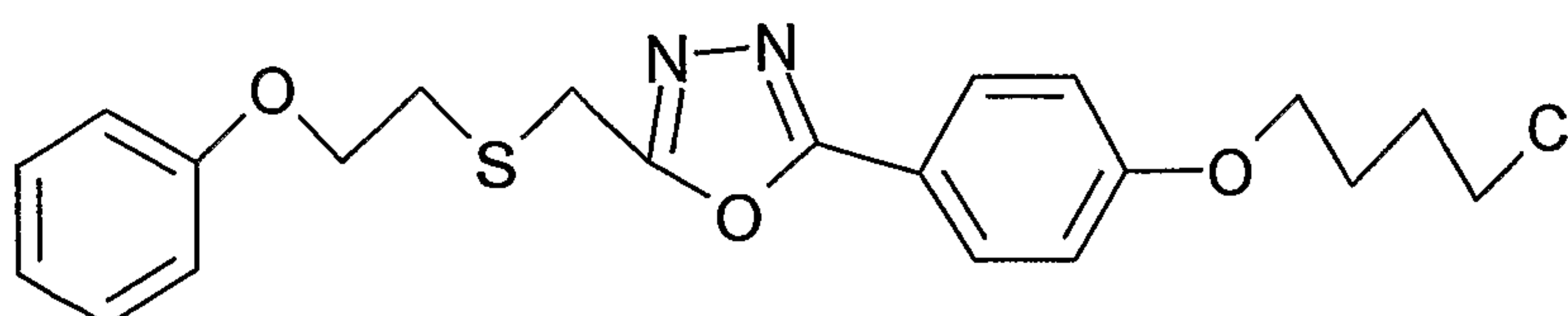
- ^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, J=9 Hz), 7.3 (t, 2H, J=7 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.4 (t, 2H, J=7 Hz), 2.1 (s, 6H), 1.9 (m, 2H). IR (KBr, cm^{-1}) 2934, 1612, 1601, 1503, 1491, 1466, 1253, 1243, 1178, 762. MS (ESI) m/e 414. Anal. Calcd for $C_{22}H_{27}N_3O_3S$: C, 63.90; H, 6.58; N, 10.16. Found C, 63.55; H, 6.50; N, 10.04. MP=70°C.

Example 68

- 20 Preparation of dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine



- a) 2-[4-(4-Chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole

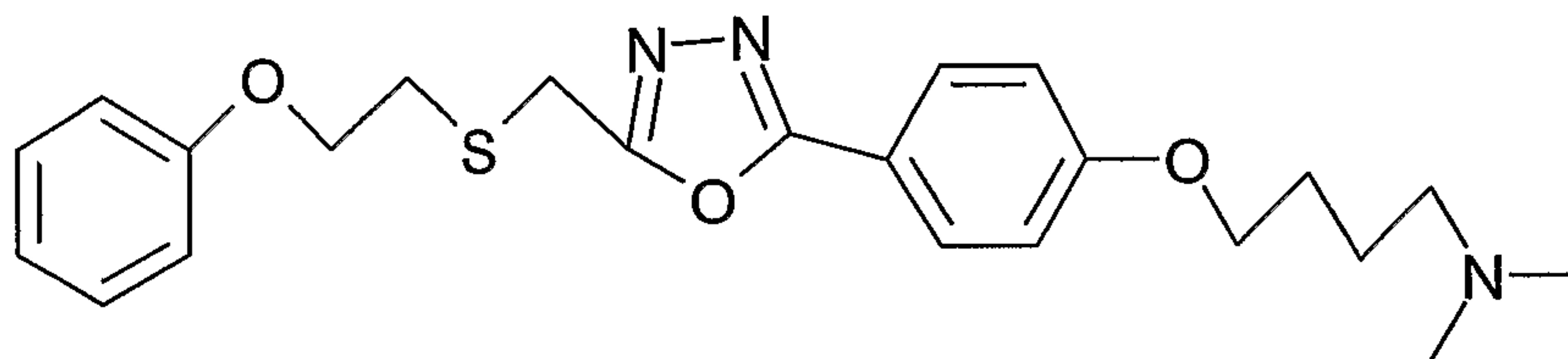


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A solution of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.202 g, 0.615 mmol), 1-bromo-4-chloro-butane (0.158 g, 0.922 mmol), and potassium carbonate (0.195 g, 1.41 mM) was refluxed in 5 mL acetone overnight. The solid was removed by filtration and the filtrate concentrated to dryness. Recrystallization of the filtrate from ether and ethyl acetate gave 0.127 g (49%) of 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole.

^1H NMR (DMSO- d_6) δ 7.8 (d, 2H, $J=9$ Hz), 7.2 (m, 2H), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.7 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 1.9 (m, 4H). IR (KBr, cm^{-1}) 1614, 1604, 1586, 1499, 1253, 1242, 1176. MS (ESI) m/e 419, 417. Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{ClN}_2\text{O}_3\text{S}$: C, 61.80; H, 6.09; N, 6.26. Found C, 59.82; H, 5.67; N, 6.41.

b) Dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine



15

A solution of 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.127 g, 0.303 mmol), dimethyl amine (2M THF, 3.8 mL, 7.58 mmol), NaI (0.004 g, 0.0236 mmol), and NaHCO_3 (0.071 g, 0.84 mmol) in 4 mL DMF was heated to 80°C overnight in a sealed tube. The mixture was extracted with ethyl acetate followed by washing with water, brine, dried over sodium sulfate and concentrated to dryness. The residue was purified directly by column chromatography on silica gel (elution with ethyl acetate/ toluene followed by 90% chloroform/10% 2M ammonia in methanol) to give 0.090 g (70%) of the title compound.

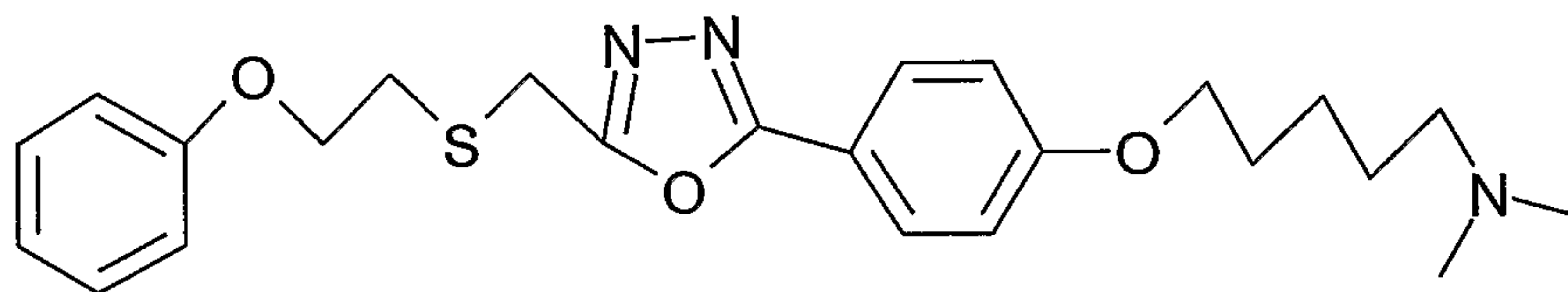
^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (m, 2H), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.2 (t, 2H, $J=7$ Hz), 2.1 (s, 6H), 1.7 (m, 2H), 1.5 (m, 2H). IR (KBr, cm^{-1}) 2763, 1612, 1501, 1259, 1246, 1177, 999, 841. MS (ESI) m/e 428. Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3\text{S}$: C, 64.61; H, 6.84; N, 9.83. Found C, 64.60; H, 6.85; N, 9.69. MP= $62-63^\circ\text{C}$.

25

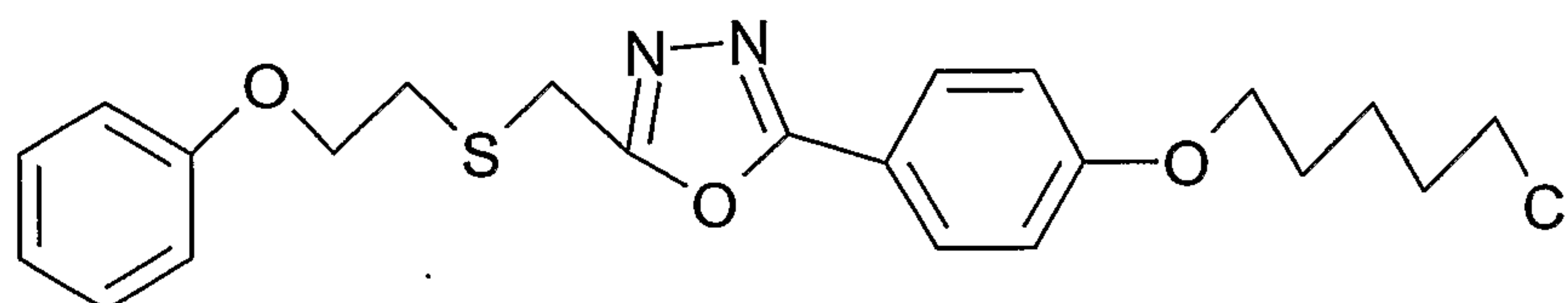
-204-

Example 69

Preparation of dimethyl-(5-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-pentyl)-amine



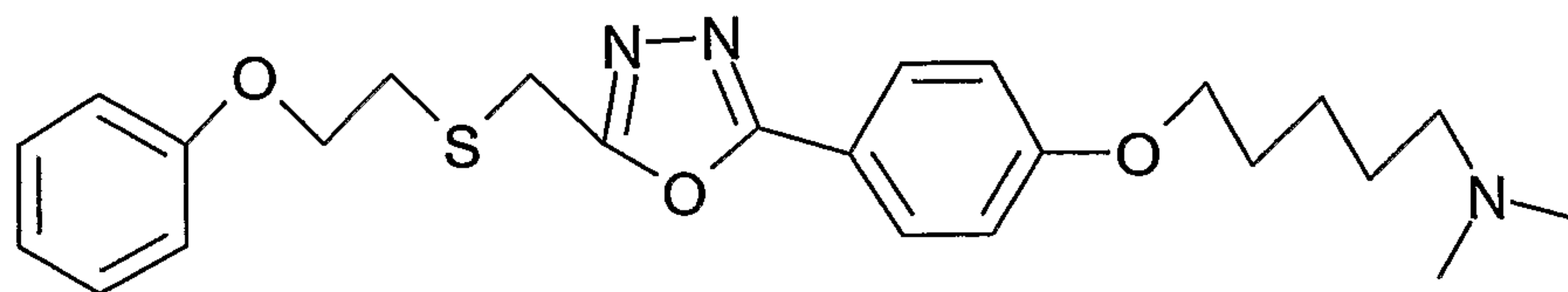
- 5 a) 2-[4-(5-Chloro-pentyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-
10 [1,3,4]oxadiazol-2-yl]-phenol (0.304 g, 0.926 mmol), and 1-bromo-5-chloro-pentane (0.250 g, 1.38 mmol) to give 0.260 g (65%) of 2-[4-(5-chloro-pentyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz) 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m 4H), 4.0 (t, 2H, J=6 Hz), 3.6 (t, 2H, J=7 Hz), 3.0 (t, 2H, J=6 Hz), 1.8 (m,
15 4H), 1.5 (m, 2H). IR (KBr, cm⁻¹) 1611, 1503, 1490, 1258, 1244, 1178, 1005, 844, 765. MS (ESI) m/e 433. Anal. Calcd for C₂₂H₂₅N₂ClO₃S: C, 61.03; H, 5.82; N, 6.47. Found C, 59.71; H, 5.75; N, 6.34.

- 20 b) Dimethyl-(5-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-pentyl)-amine



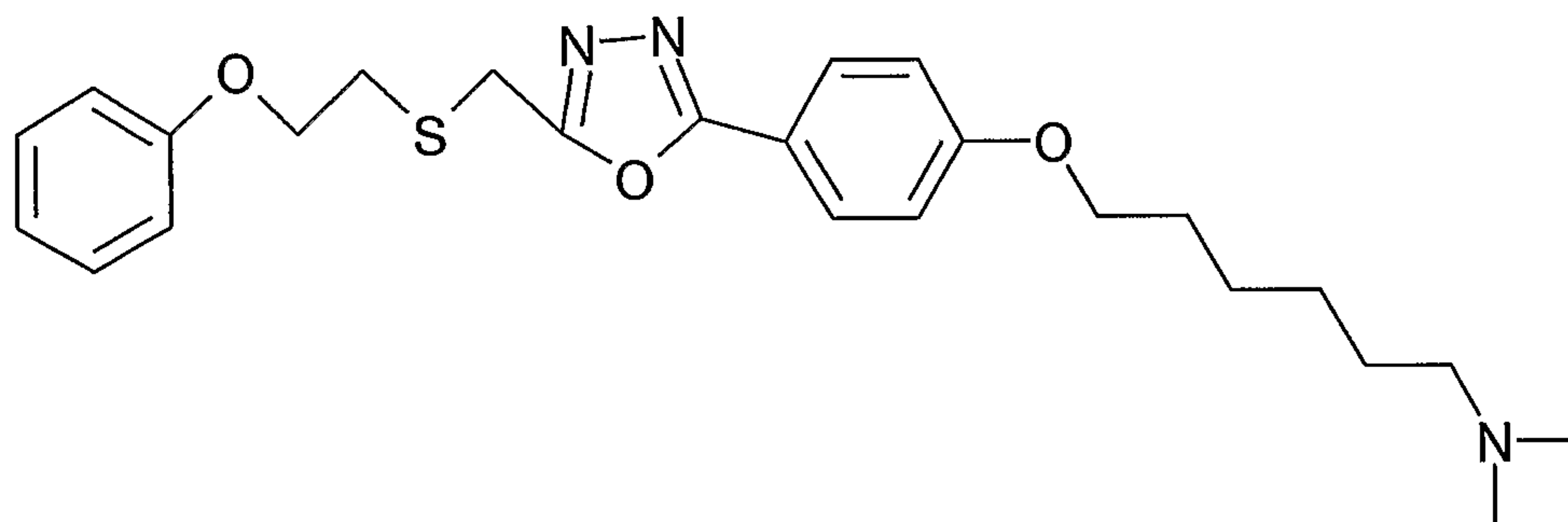
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(5-chloro-pentyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.210 g, 0.487 mmol) to give 0.111 g (52%) of
25 the title compound.

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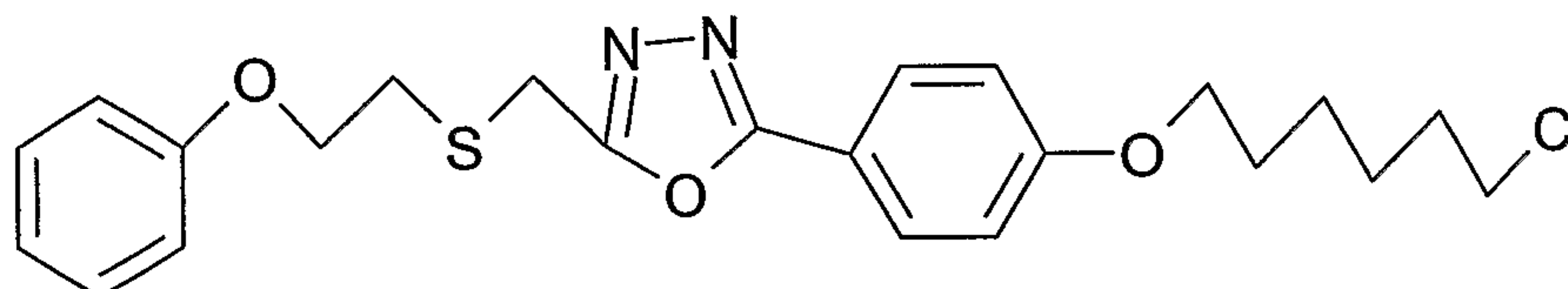
¹H NMR (DMSO-d₆) δ 7.8 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.1 (m, 4H), 4.0 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.2 (t, 2H, J=7 Hz), 2.1 (s, 6H), 1.7 (m, 2H), 1.4 (m, 4H). IR (KBr, cm⁻¹) 2941, 1602, 1610, 1500, 1466, 1253, 1175, 1032, 835, 751. MS (ESI) m/e 442. Anal. Calcd for C₂₄H₃₁N₃O₃S: C, 65.28; H, 7.08; N, 9.51. Found C, 65.47; H, 7.03; N, 9.35. MP 51-54°C.

Example 70

Preparation of dimethyl-(6-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-hexyl)-amine



a) 2-[4-(6-Chloro-hexyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole

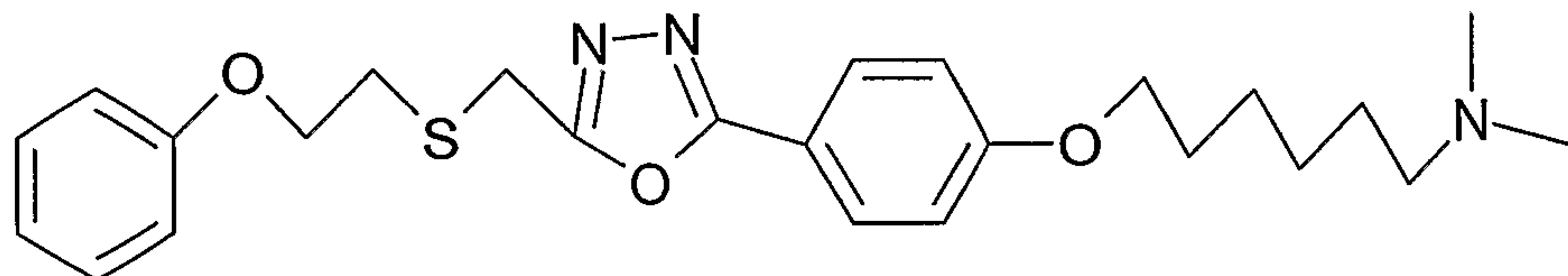


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.243 g, 0.739 mmol) and 1-bromo-6-chloro-hexane (0.221 g, 1.11 mmol) to give 0.266 g (81%) of 2-[4-(6-chloro-hexyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, 2H, J=6 Hz), 3.6 (t, 2H, J=7 Hz), 3.0 (t, 2H, J=6 Hz), 1.7 (m, 4H), 1.4 (m, 4H). IR (KBr, cm⁻¹) 3456, 2936, 2866, 1615, 1586, 1503, 1466, 1258, 1239, 1176, 1007, 843, 764. MS (ESI) m/e 447. Anal. Calcd for C₂₃H₂₇N₂ClO₃S: C, 61.80; H, 6.09; N, 6.27. Found C, 61.62; H, 5.55; N, 6.21.

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b) Dimethyl-(6-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-hexyl)-amine

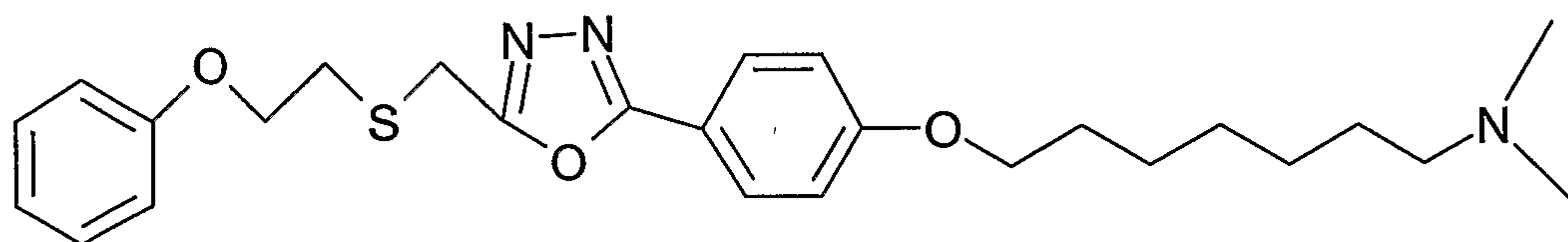


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(6-chloro-hexyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.266g, 0.595 mmol) to give 0.116 g (43%) of the title compound.

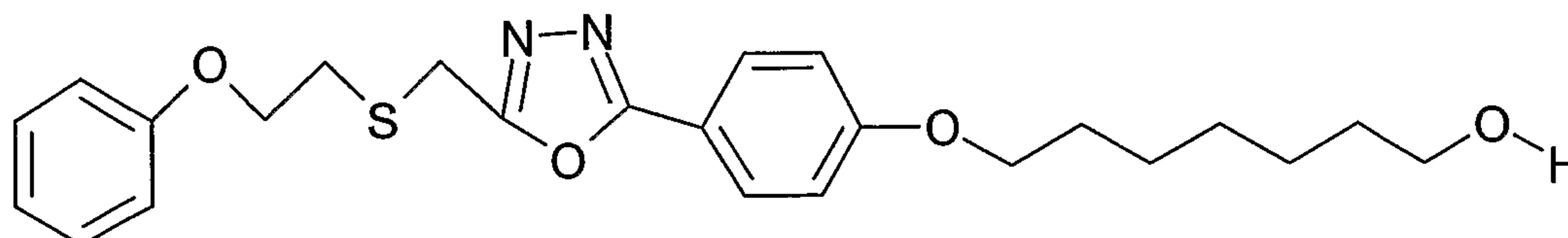
^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (m, 2H), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.2 (t, 2H, $J=7$ Hz), 2.1 (s, 6H), 1.7 (m, 2H), 1.4 (m, 4H), 1.3 (m, 2H). IR (KBr, cm^{-1}) 1611, 1602, 1587, 1500, 1466, 1249, 1175, 1024, 756. MS (ESI) m/e 456. Anal. Calcd for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3\text{S}$: C, 65.90; H, 7.30; N, 9.22. Found C, 65.37; H, 7.16; N, 9.08.

Example 71

Preparation of dimethyl-(7-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-heptyl)-amine



a) 7-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-heptan-1-ol



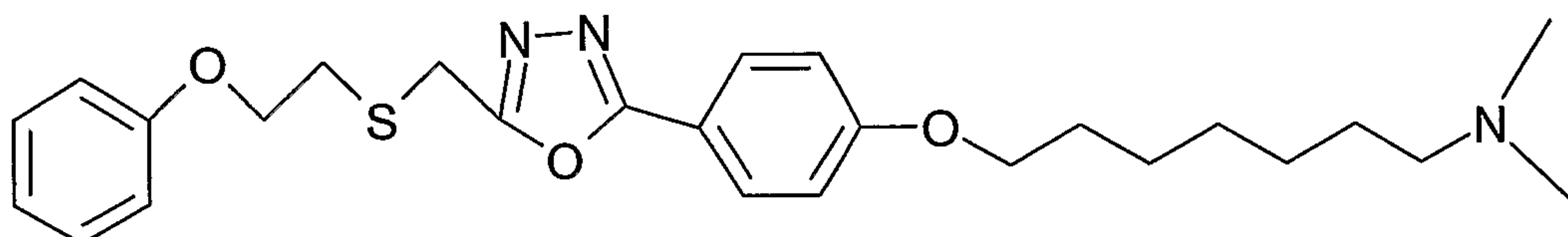
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.260 g, 0.792 mmol) and 7-bromo-heptan-1-ol (0.232 g,

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1.19 mmol) to give 0.164 g (47%) of 7-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-heptan-1-ol.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, 9 Hz), 6.9 (m, 3H), 4.3 (s, 1H) 4.2 (m, 4H), 4.0 t, 2H, J=6 Hz), 3.3 (m, 2H), 3.0 (t, 2H, J=6 Hz), 1.7 (m, 2H), 1.2-1.4 (m, 8H). IR (KBr, cm⁻¹) 3622, 3011, 2936, 2861, 1613, 1602, 1499, 1469, 1256, 1224, 1174, 1034. MS (ESI) m/e 443. Anal. Calcd for C₂₄H₃₀N₂O₄S: C, 65.13; H, 6.83; N, 6.33. Found C, 63.3; H, 6.72; N, 5.91.

b) Dimethyl-(7-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-heptyl)-amine



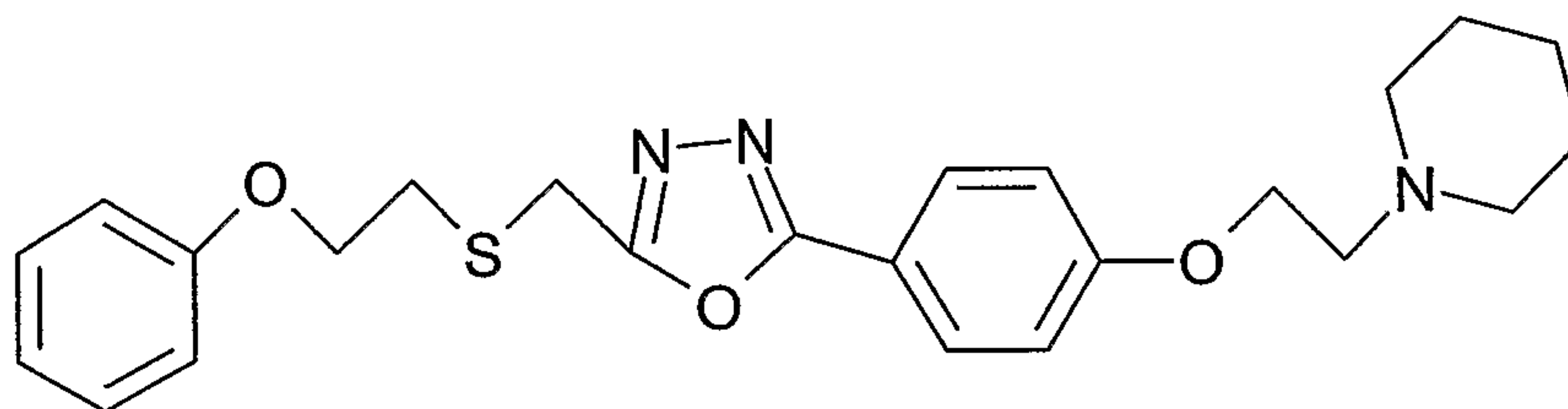
Methanesulfonyl chloride (0.046 g, 0.407 mmol) was added dropwise to a solution of 7-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-heptan-1-ol (0.164 g, 0.374 mmol) and triethylamine (0.045 g, 0.444 mmol) in dichloromethane (20 mL). The mixture was stirred at room temperature for 5 min and concentrated to dryness to give the crude mesylate. The crude solid was dissolved in methanol (10 mL) in a sealed tube and dimethylamine was added (5 mL). The mixture was heated to 80° overnight and concentrated to dryness. The crude solid was dissolved in ethyl acetate and washed with water, brine, dried over sodium sulfate, filtered and concentrated to dryness. The solid was purified directly by column chromatography on silica gel (elution with 1/1 ethyl acetate followed by 90% CHCl₃ and 10% 2M NH₃ in methanol to give 0.063 g (36%) of the title compound.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.2 (t, 2H, J=7 Hz), 2.1 (s, 6H), 1.7 (m, 2H), 1.2-1.4 (m, 8H). IR (KBr, cm⁻¹) 2925, 2854, 2762, 1611, 1500, 1254, 1175, 750. MS (ESI) m/e 470. Anal. Calcd for C₂₆H₃₅N₃O₃S: C, 66.49; H, 7.51; N, 8.95. Found C, 64.78; H, 7.57; N, 8.44. HPLC 90%. MP=39-40°C.

Example 72

-208-

Preparation of 1-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-piperidine

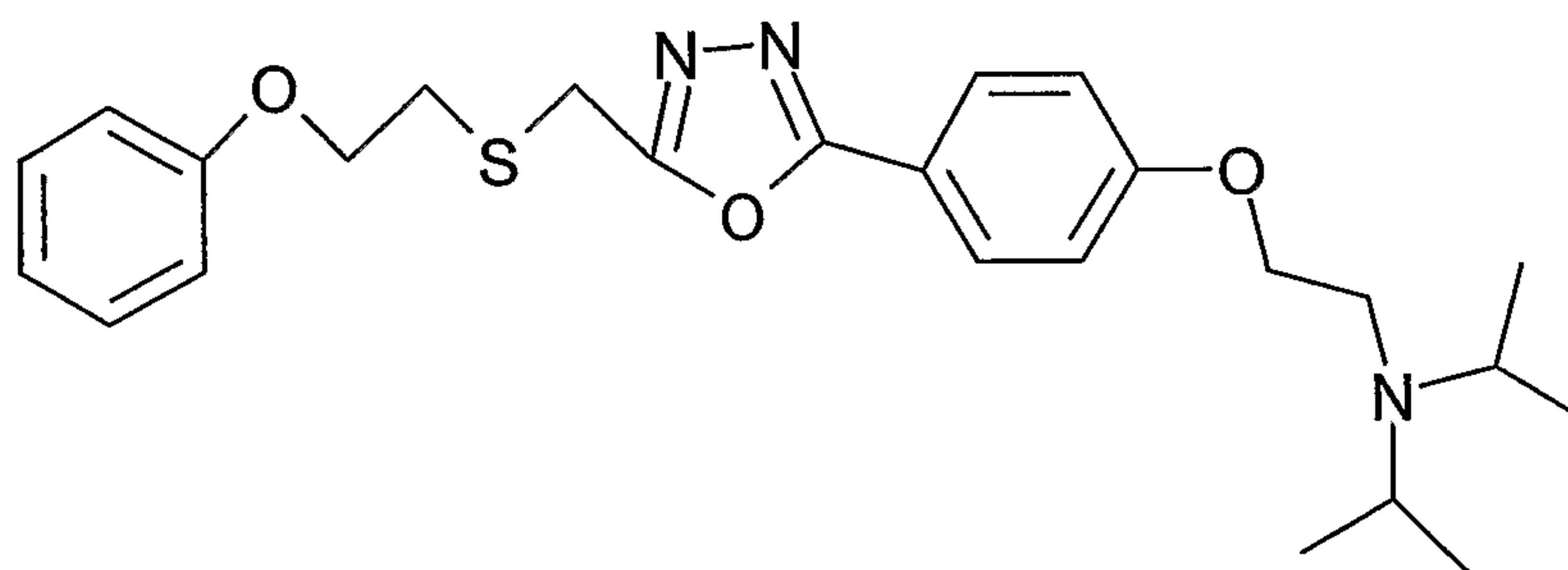


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.202 g, 0.615 mmol) and 1-(2-chloroethyl)piperidine monohydrochloride (0.17 g, 0.922 mmol) to give 0.059 g (22%) of the title compound.

^1H NMR (DMSO- d_6) δ 7.8 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.0 (t, 2H, $J=6$ Hz), 2.6 (m, 2H), 2.4 (m, 4H), 1.5 (m, 4H), 1.4 (m, 2H). IR (KBr, cm^{-1}) 2940, 1613, 1499, 1255, 1245, 1175. MS (ESI) m/e 440. Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_3\text{S}$: C, 65.58; H, 6.65; N, 9.56. Found C, 64.56; H, 6.61; N, 9.42. HPLC 100%. MP = 70°C.

Example 73

Preparation of diisopropyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.223 g, 0.679 mmol) and (2-chloro-ethyl)-diisopropylamine, monohydrochloride (0.204 g, 1.02 mmol) to give 0.178 g (58%) of the title compound.

^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, 2H, $J=7$ Hz), 3.0 (m, 4H), 2.8 (t, 2H, $J=7$ Hz), 1.0 (d,

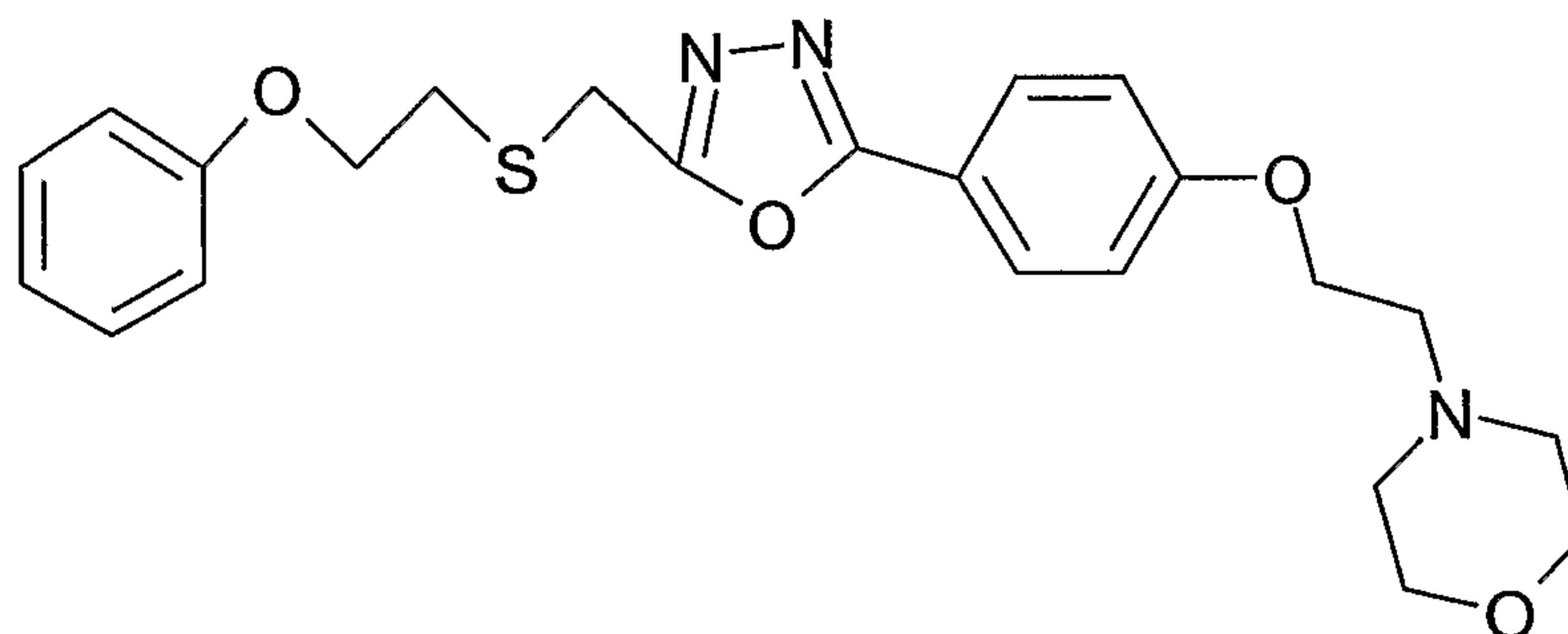
-209-

12H, J=6 Hz). IR (KBr, cm^{-1}) 3632, 3432, 3013, 2945, 2838, 1602, 1464, 1333, 1242. MS (ESI) m/e 456. Anal. Calcd for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3\text{S}$: C, 65.90; H, 7.30; N, 9.22. Found C, 65.68; H, 7.16; N, 9.17. MP=42-45°C.

5

Example 74

Preparation of 4-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-morpholine

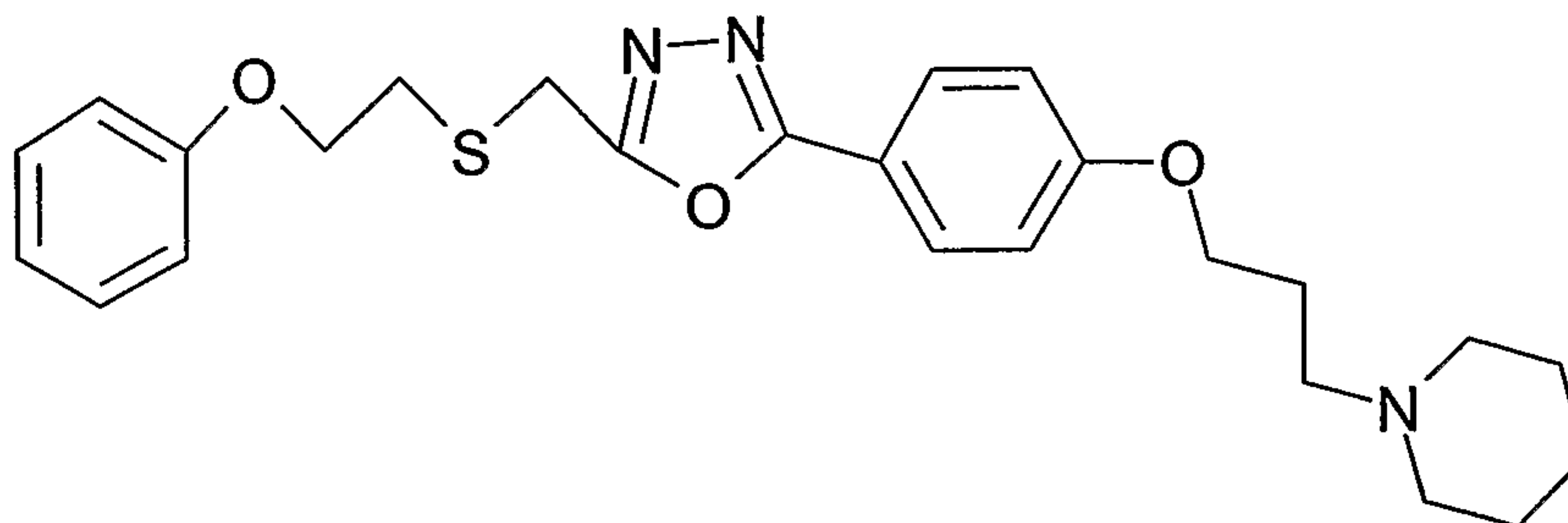


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.266 g, 0.81mM) and 4-(2-chloro-ethyl)-morpholine monohydrochloride (0.226.g, 1.22 mmol) to give 0.225 g (63%) of the title compound.

^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, J=8 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.6 (t, 4H, J=4 Hz), 3.0 (t, 2H, J=6 Hz), 2.7 (t, 2H, J=6 Hz), 2.5 (m, 4H). IR (KBr, cm^{-1}) 1613, 1601, 1588, 1499, 1302, 1253, 1175, 1117. MS (ESI) m/e 442, 440.5. Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_4\text{S}$: C, 62.56; H, 6.16; N, 9.51. Found C, 62.20; H, 6.02; N, 9.39. MP=70-72°C.

Example 75

Preparation of 1-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidine



-210-

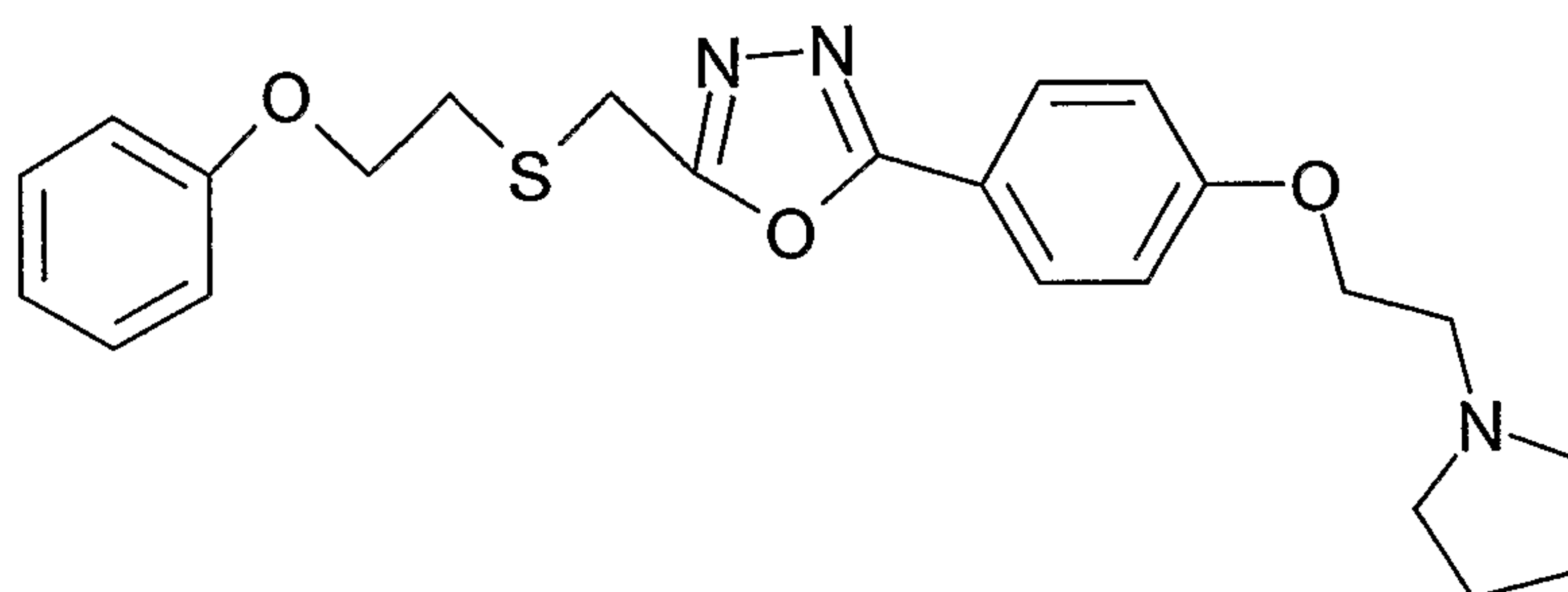
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.218 g, 0.664 mmol) and 1-(3-chloro-propyl)-piperidine, monohydrochloride (0.197 g, 0.996 mmol) to give 0.055 g (18%) of the title compound.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=8 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=7 Hz), 3.0 (t, 2H, J=6 Hz), 2.4-2.3 (m, 6H), 1.9 (t, 2H, J=7 Hz), 1.5 (m, 4H), 1.4 (m, 2H). IR (KBr, cm⁻¹) 3008, 2939, 1614, 1601, 1499, 1303, 1256, 1245, 1175, 839. MS (ESI) m/e 454. Anal. Calcd for C₂₅H₃₁N₃O₄S: C, 65.58; H, 6.65; N, 9.55. Found C, 65.34; H, 6.65; N, 8.95. MP=65°C.

10

Example 76

Preparation of 2-(2-phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,3,4]oxadiazole



15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.216 g, 0.658 mmol) and 1-(2-chloro-ethyl)-pyrrolidine, monohydrochloride (0.168 g, 0.987 mmol) to give 0.052 g (18%) of the title compound.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=8 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=8 Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.0 (t, 2H, J=6 Hz), 2.8 (m, 2H), 2.5 (m, 4H), 1.6 (m, 4H). IR (KBr, cm⁻¹) 1614, 1500, 1246, 1175. MS (ESI) m/e 426. Anal. Calcd for C₂₃H₂₇N₃O₃S: C, 64.92; H, 6.40; N, 9.87. Found C, 64.92; H, 6.44; N, 9.76. MP=65°C.

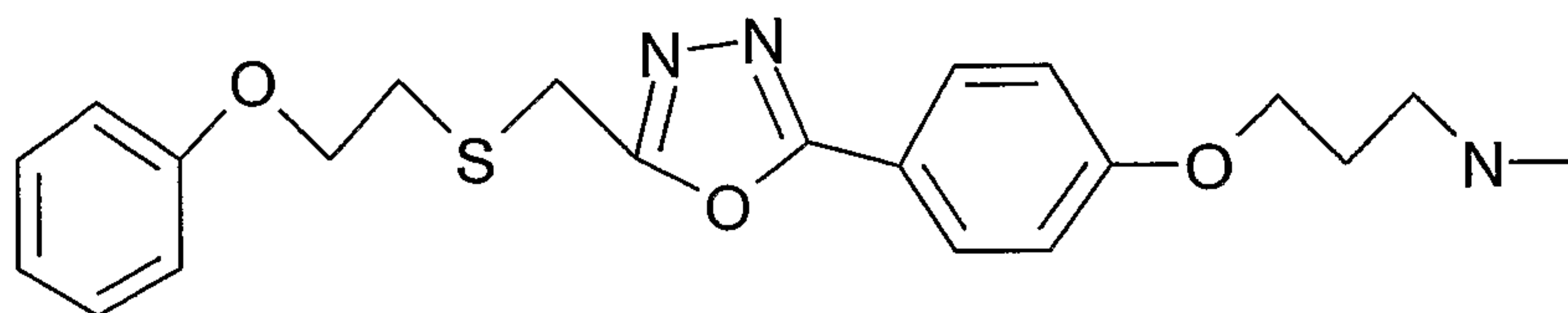
20

Example 77

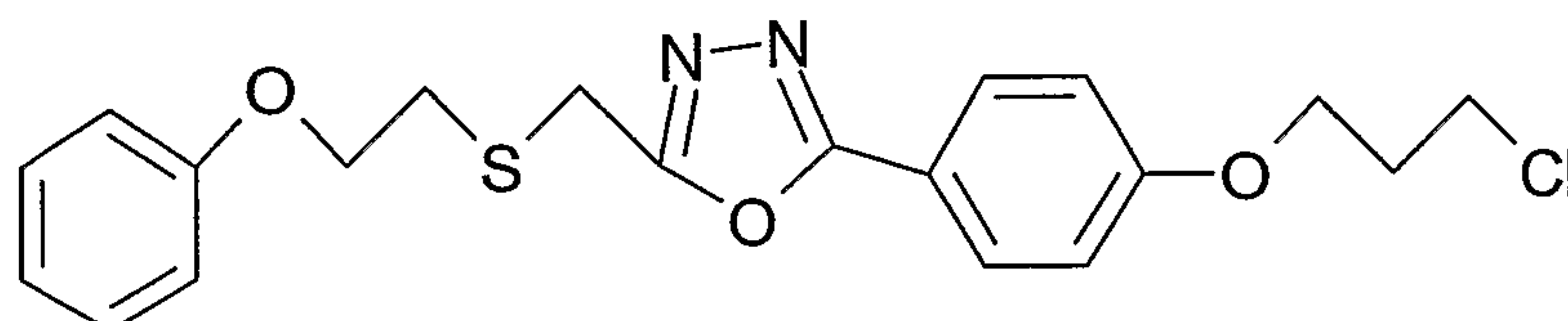
25

Preparation of methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine

-211-



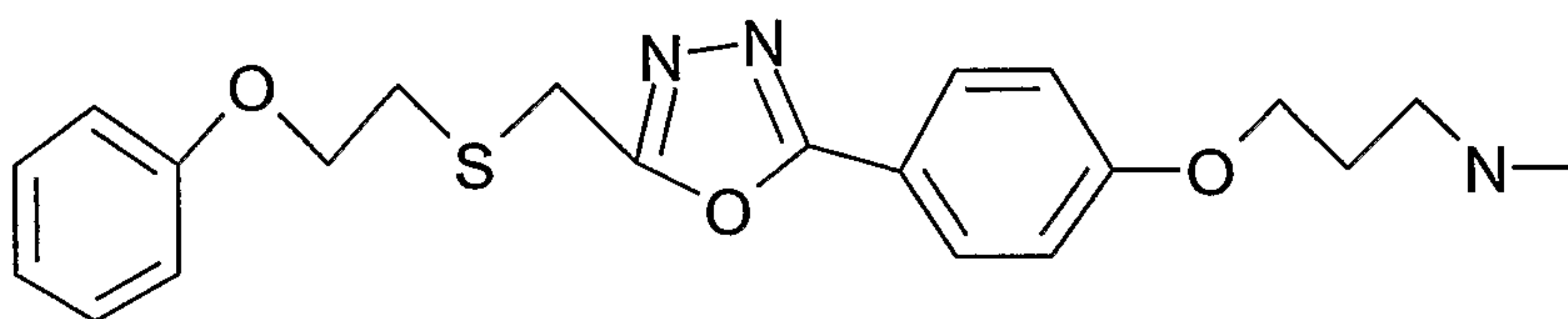
a) 2-[4-(3-Chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole



5 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (2.396 g, 7.30 mmol) and 1-bromo-3-chloro-propane (1.72 g, 10.9 mmol) to give 1.60 g (54%) of 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole.

10 ^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.8 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.2 (m, 2H). MS (ESI) m/e 405.

15 b) Methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



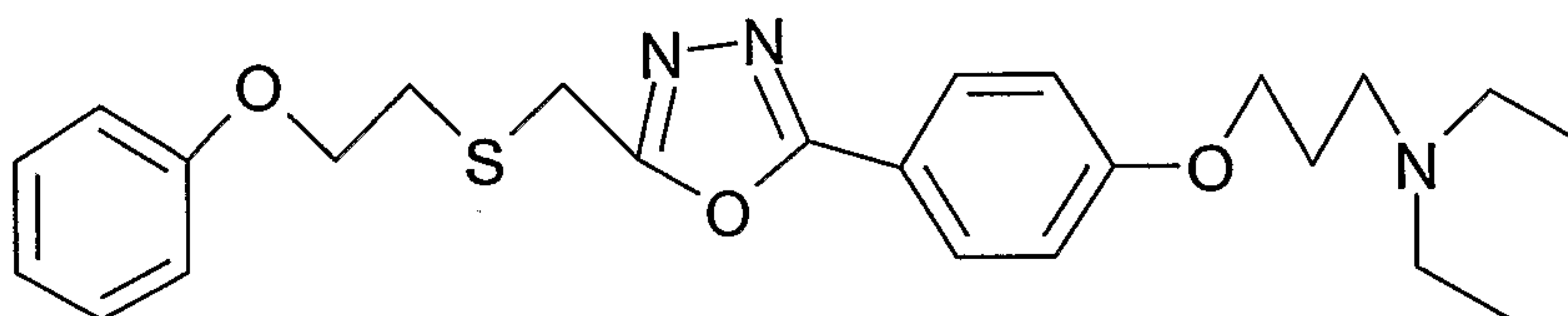
20 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.247 g, 0.61 mmol) and methylamine (40% weight in water, 2 mL, 26 mmol). HPLC chromatography on the material previously purified by silica chromatography and combination of various lots gave 190 mg of material as the TFA salt which was desalted to the free amine by washing with 1N NaOH, dried over sodium sulfate, filtered and concentrated to dryness to give 0.088 g (14%) of the title compound.

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^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.6 (t, 2H, $J=7$ Hz), 2.3 (s, 3H), 1.8 (m, 2H). IR (KBr, cm^{-1}) 1677, 1611, 1500, 1254, 1205, 1176, 1131, 835, 754, 722. MS (ESI) m/e 400, 398. Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$: C, 63.14; H, 6.31; N, 10.52. Found C, 61.78; H, 5.92; N, 9.91. MP=40-44°C. HPLC 100%.

Example 78

Preparation of diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine

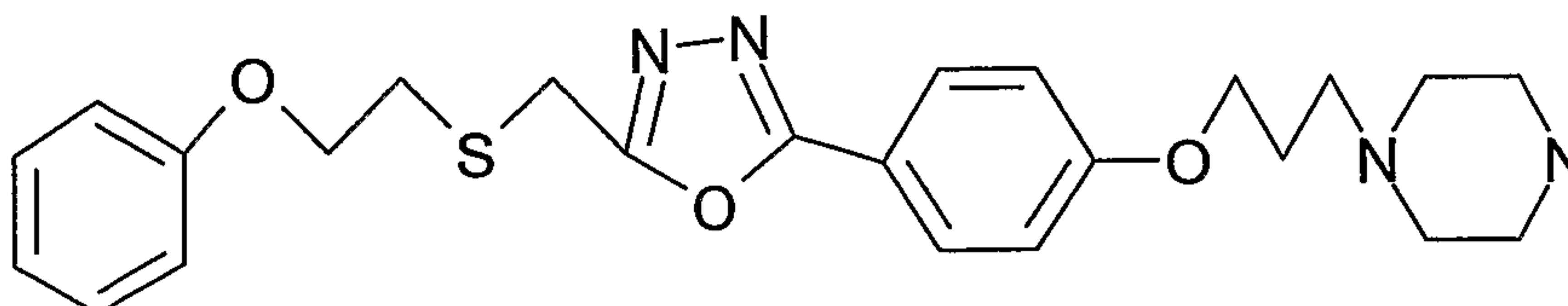


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.230 g, 0.568 mmol) and diethylamine (1.04 g, 14.2 mmol) to give 0.127 g (50%) of the title compound.

^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.5 (m, 4H), 1.8 (t, 2H, $J=6$ Hz), 0.9 (t, 6H, $J=7$ Hz). IR (KBr, cm^{-1}) 2973, 1613, 1602, 1499, 1256, 1245, 1174. MS (ESI) m/e 442. Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3\text{S}$: C, 65.28; H, 7.08; N, 9.52. Found C, 65.19; H, 7.17; N, 9.41. MP=27-31°C.

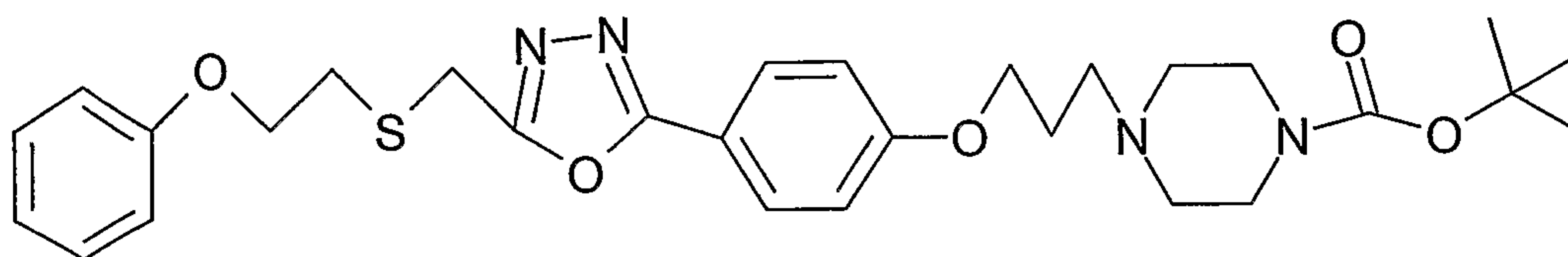
Example 79

Preparation of 1-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperazine



a) 4-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperazine-1-carboxylic acid tert-butyl ester

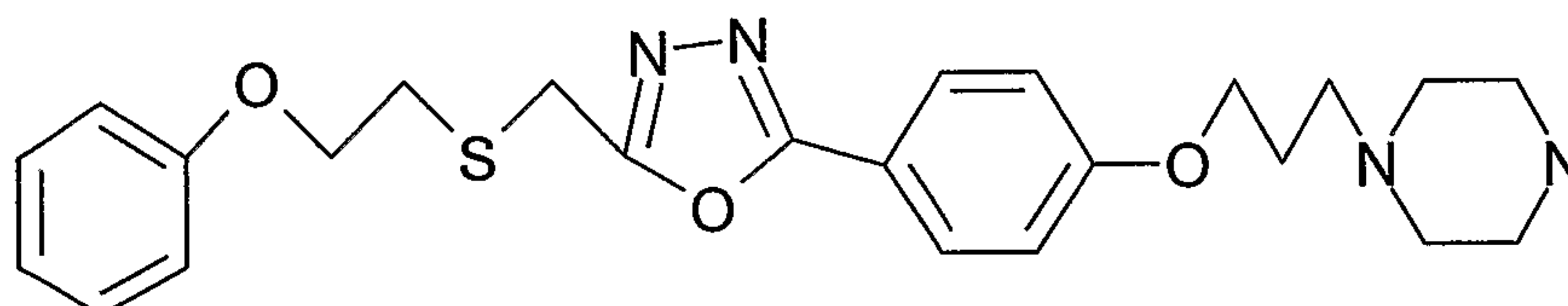
-213-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.241 g, 0.595 mmol) and piperazine-1-carboxylic acid tert-butyl ester (0.111 g, 0.595 mmol) to give 0.096 g (29%) of 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperazine-1-carboxylic acid tert-butyl ester.

^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (m, 2H), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=5$ Hz), 3.3 (m, 4H), 3.0 (t, 2H, $J=6$ Hz), 2.4 (m, 2H), 2.3 (m, 4H), 1.9 (m, 2H), 1.4 (s, 9H). MS (ESI) m/e 555. Anal. Calcd for $\text{C}_{29}\text{H}_{38}\text{N}_4\text{O}_5\text{S}$: C, 62.79; H, 6.90; N, 10.10. Found C, 61.53; H, 6.70; N, 9.73. HPLC 100%.

b) 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperazine



15

A solution of 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperazine-1-carboxylic acid tert-butyl ester (20a) (0.115 g, 0.20 mmol) and trifluoroacetic acid (5 mL) in 5 mL CH_2Cl_2 was stirred at 5°C for 1 hr. The reaction mixture was concentrated to dryness and extracted into ethyl acetate. The organic extract was washed with NaHCO_3 , brine, dried over sodium sulfate, filtered and concentrated to give 0.065 g which was purified directly by column chromatography on silica gel (elution with ethyl acetate and toluene followed by 90 chloroform/10 ammonia (2M methanol) to give 0.044 g (47%) of the title product.

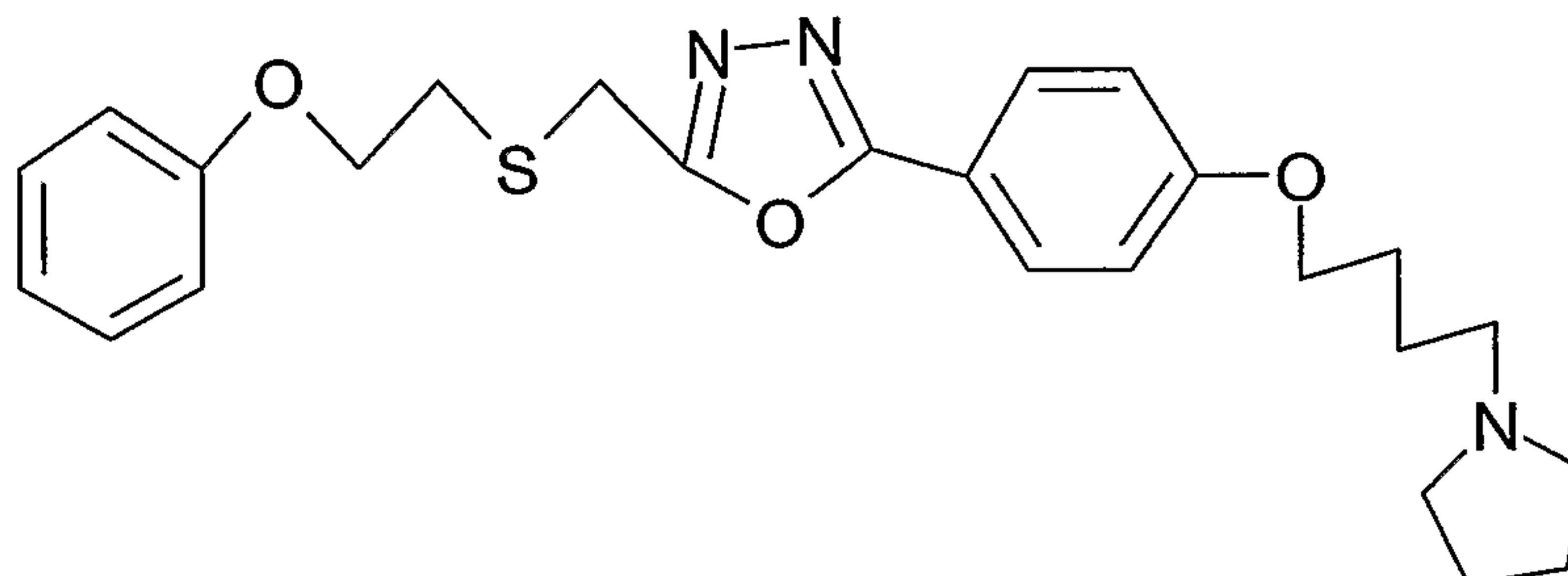
^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.6 (m, 4H), 2.4 (t, 2H, $J=7$ Hz), 2.3 (m, 4H), 1.8 (m, 2H). MS (ESI) m/e 455. HPLC 100%.

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Example 80

Preparation of 2-(2-phenoxy-ethylsulfanylmethyl)-5-[4-(4-pyrrolidin-1-yl-butoxy)-phenyl]-[1,3,4]oxadiazole

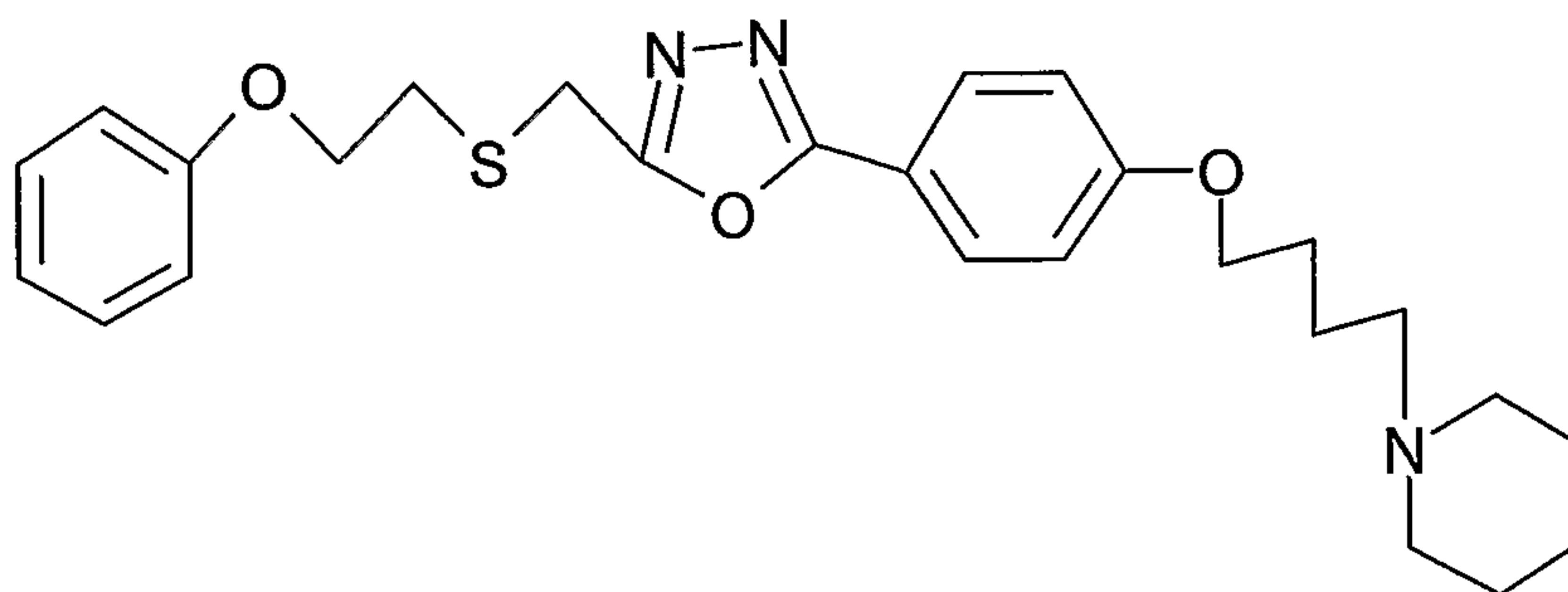


5 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.235 g, 0.561 mmol) and pyrrolidine (0.099 g, 1.4 mmol) to give 0.145 g (57%) of the title compound.

10 ^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.4 (m, 6H), 1.8 (m, 2H), 1.7 (m, 4H), 1.6 (m, 2H). IR (KBr, cm^{-1}) 2932, 2563, 2467, 1617, 1500, 1257, 1248. MS (ESI) m/e 454. Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_3\text{S}$: C, 66.20; H, 6.89; N, 9.26. Found C, 65.98; H, 6.90; N, 9.13. M.P.=45°.

15 Example 81

Preparation of 1-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-piperidine



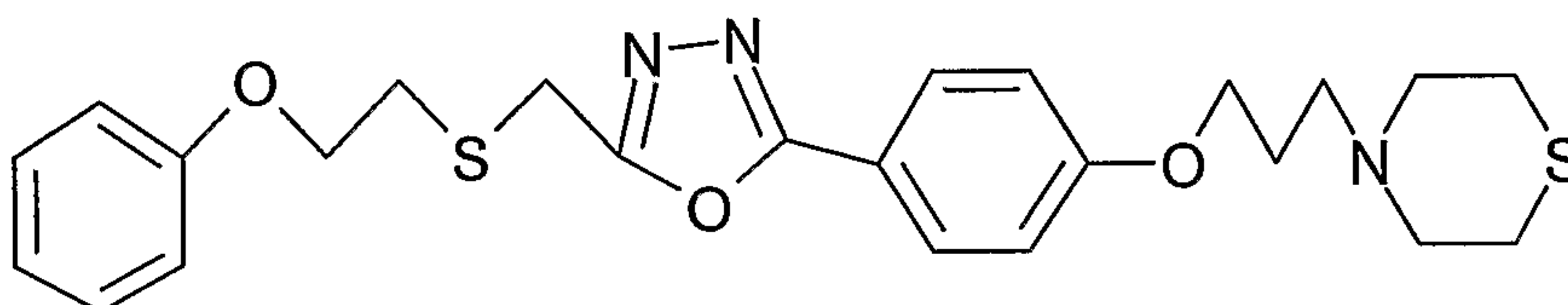
20 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.232 g, 0.554 mmol) and piperidine (0.118 g, 1.38 mmol) to give 0.041 g (16%) of the title compound.

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^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.3 (m, 6H), 1.7 (m, 2H), 1.6 (m, 2H), 1.5 (m, 4H), 1.4 (m, 2H). IR (KBr, cm^{-1}) 2923, 1610, 1601, 1586, 1500, 1467, 1304, 1256, 1248, 1174, 1031. MS (ESI) m/e 470. Anal. Calcd for $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_3\text{S}$: C, 66.78; H, 7.11; N, 8.99. Found C, 66.16; H, 6.91; N, 8.80. M.P.=57-62°C.

Example 82

Preparation of 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-thiomorpholine

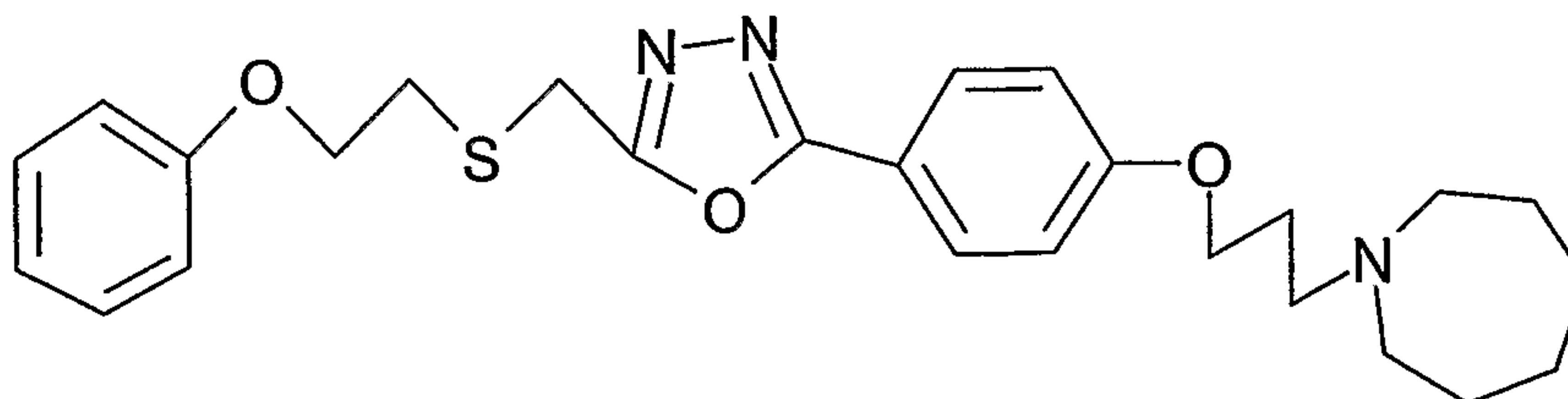


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.248 g, 0.612 mmol) and thiomorpholine (0.157 g, 1.53mM) to give 0.136 g (47%) of the title compound.

^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.6 (m, 8H), 2.4 (t, 2H, $J=7$ Hz), 1.9 (m, 2H). IR (KBr, cm^{-1}) 2922, 2810, 2775, 1611, 1601, 1590, 1502, 1491, 1468, 1256, 1244, 1176, 837, 766. MS (ESI) m/e 472, 470. Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_3\text{S}_2$: C, 61.12; H, 6.20; N, 8.91. Found C, 60.85; H, 6.26; N, 8.75. M.P.=85°C.

Example 83

Preparation of 1-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-azepane



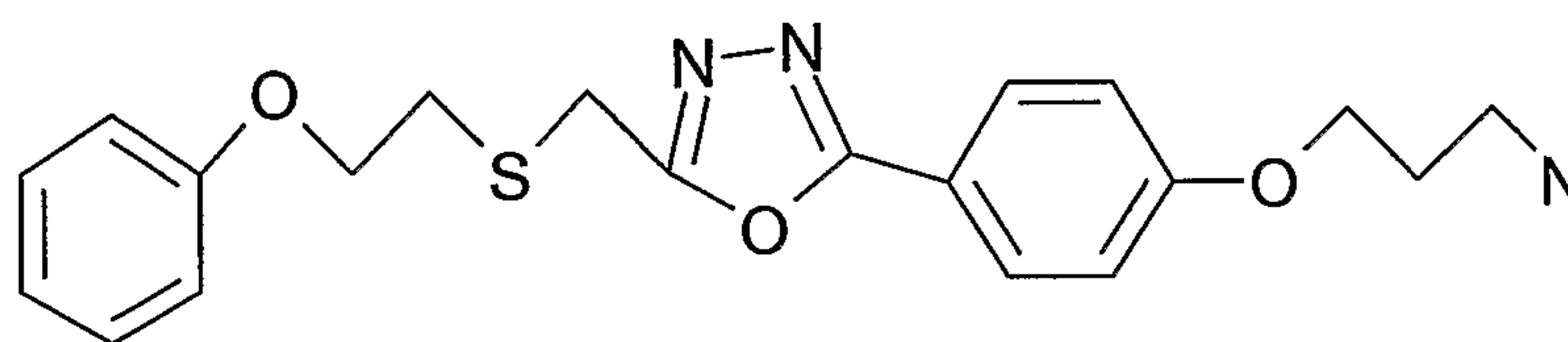
-216-

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.213 g, 0.526 mmol) and azepane (1.30 g, 13.1 mmol) to give 0.103 g (42%) of the title compound.

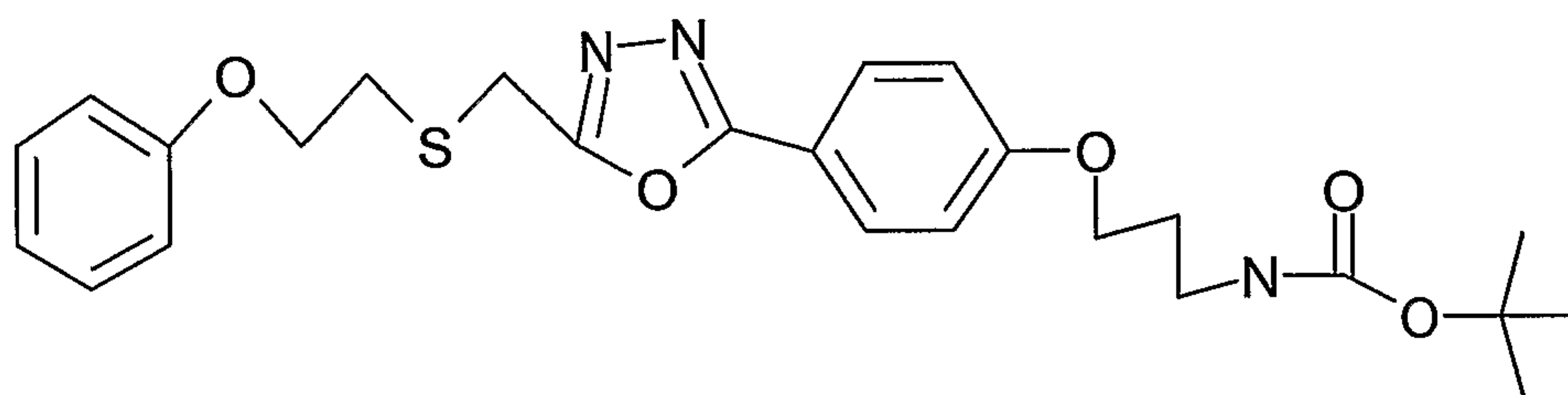
¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.6 (m, 6H), 1.8 (m, 2H), 1.5 (m, 8H). IR (KBr, cm⁻¹) 2927, 2905, 1614, 1497, 1468, 1251, 1181, 1171, 1036, 1029, 747, 689. MS (ESI) m/e 468. Anal. Calcd for C₂₆H₃₃N₃O₃S: C, 66.78; H, 7.11; N, 8.98. Found C, 66.48; H, 6.94; N, 8.91. M.P.=50°C.

Example 84

Preparation of 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propylamine



a) (3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-carbamic acid tert-butyl ester



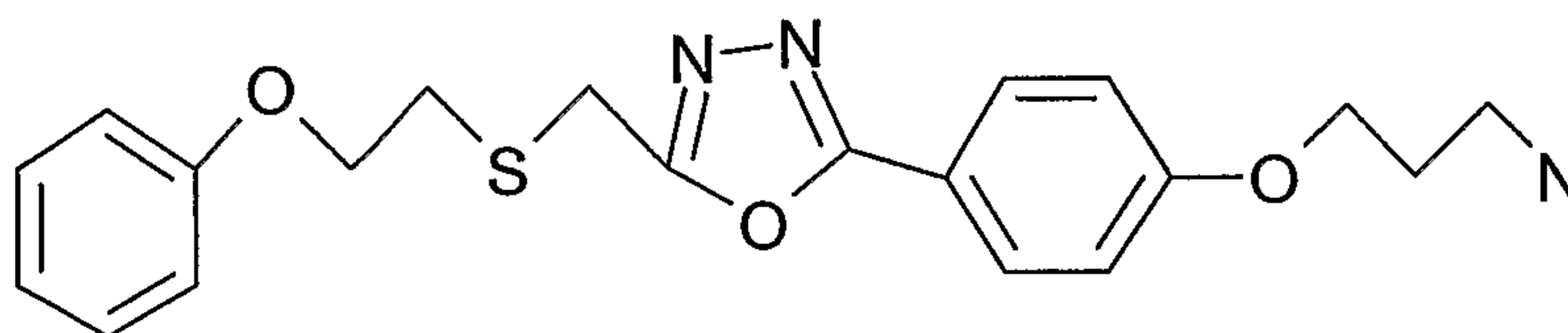
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.501 g, 1.52 mmol) and (3-bromo-propyl)-carbamic acid tert-butyl ester (0.545 g, 2.28 mmol) to give the BOC protected product which was purified by column chromatography on silica gel (elution with ethyl acetate/toluene) to give 0.617 g (84%) of the (3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-carbamic acid tert-butyl ester.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, 2H, J=6 Hz), 3.1 (q, 2H, J=6 Hz), 3.0 (t, 2H, J=6

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Hz), 1.8 (m, 2H), 1.4 (s, 9H). IR (KBr, cm^{-1}) 3400, 1692, 1609, 1524, 1501, 1248, 1242, 1176, 844, 764. MS (ESI) m/e 486. Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_5\text{S}$: C, 70.12; H, 5.23; N, 9.08. Found C, 69.86; H, 5.19; N, 8.92.

- 5 b) 3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propylamine

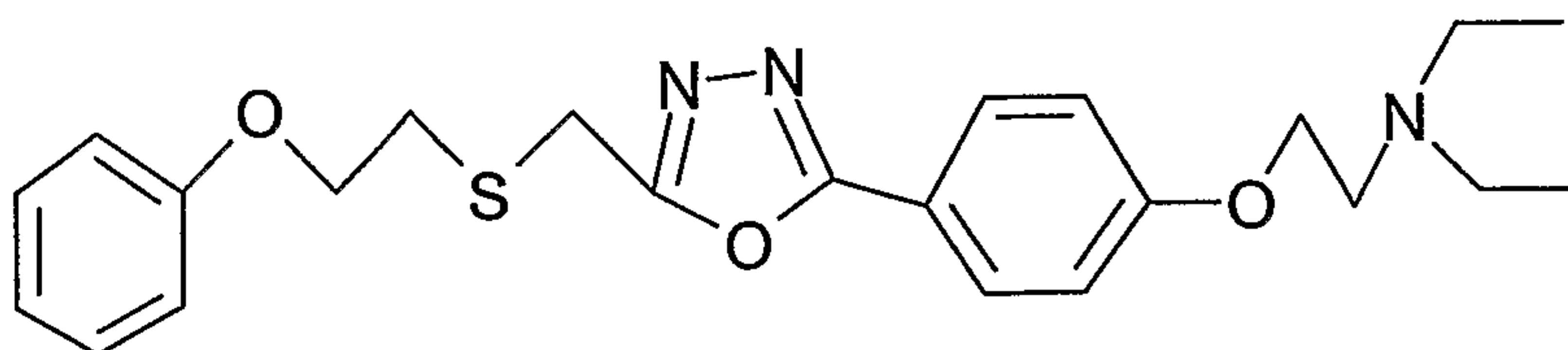


- A solution of (3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-carbamic acid tert-butyl ester (0.600 mg, 1.23 mmol) in TFA (7 mL) and CH_2Cl_2 , (5 mL) was stirred at 5°C for 1 hr. The reaction mixture was concentrated to dryness and extracted into ethyl acetate. The organic extract was washed with NaHCO_3 , brine, dried over Na_2SO_4 , filtered and concentrated to give 0.300 g. Elemental analysis indicated the presence of fluorine. The material was dissolved in water, ethyl acetate and a minimum amount of methanol to solubilize the material. The mixture was washed with 1N NaOH, dried over sodium sulfate, and concentrated to give 0.183 g, (38%) of the 3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propylamine.

- ^1H NMR ($\text{DMSO}-d_6$) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.7 (t, 2H, $J=7$ Hz), 1.8 (m, 2H). IR (KBr, cm^{-1}) 3004, 2972, 2928, 2902, 1616, 1504, 1474, 1252, 1175, 833. MS (ESI) m/e 386. Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$: C, 62.31; H, 6.01; N, 10.90. Found C, 61.08; H, 5.99; N, 10.49. HPLC 100%. M.P.= $30-35^\circ$.

Example 85

- Preparation of diethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine



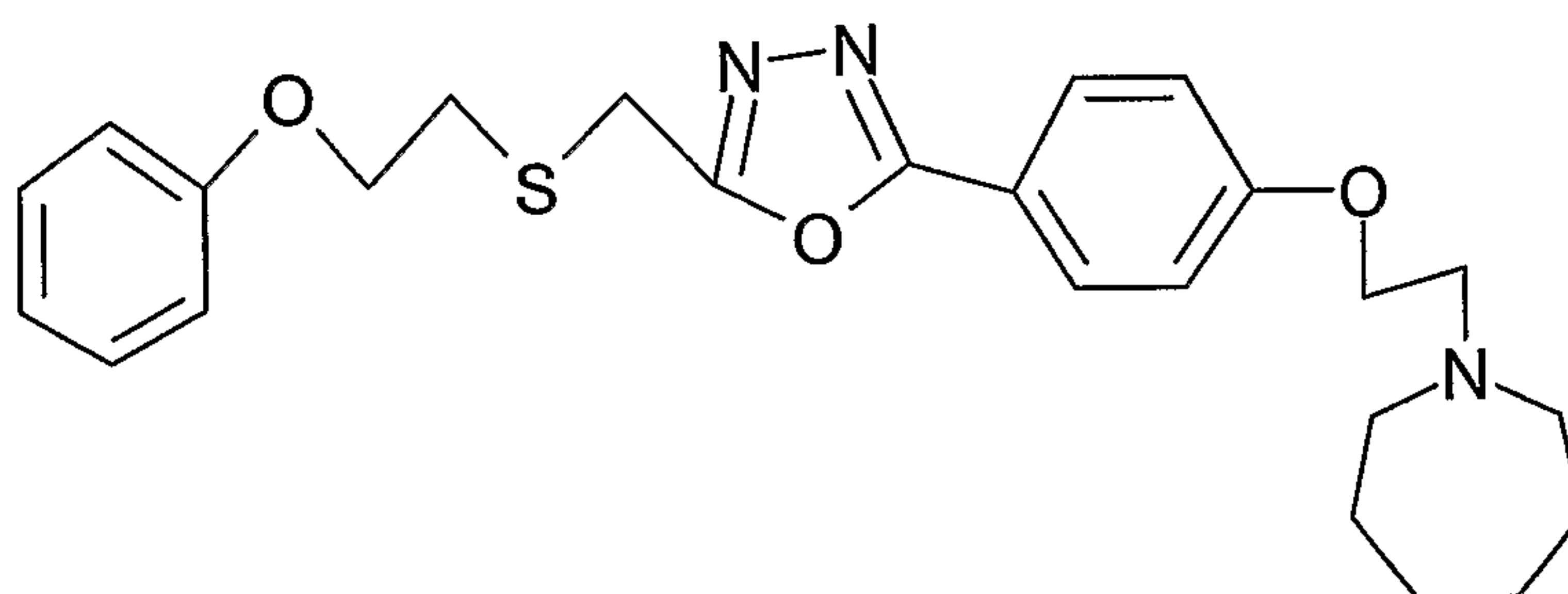
-218-

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.206 g, 0.627 mmol) and (2-bromo-ethyl)-diethyl-amine hydrobromide to give 0.041 g (15%) of the title compound.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.8 (m, 2H), 2.6 (m, 4H), 1.0 (t, 6H, J=7 Hz). IR (KBr, cm⁻¹) 1614, 1498, 1258, 1176, 1172, 752. MS (ESI) m/e 429. Anal. Calcd for C₂₃H₂₉N₃O₃S: C, 64.61; H, 6.84; N, 9.83. Found C, 64.37; H, 6.85; N, 9.77. M.P.=32-35°C.

Example 86

Preparation of 1-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-azepane



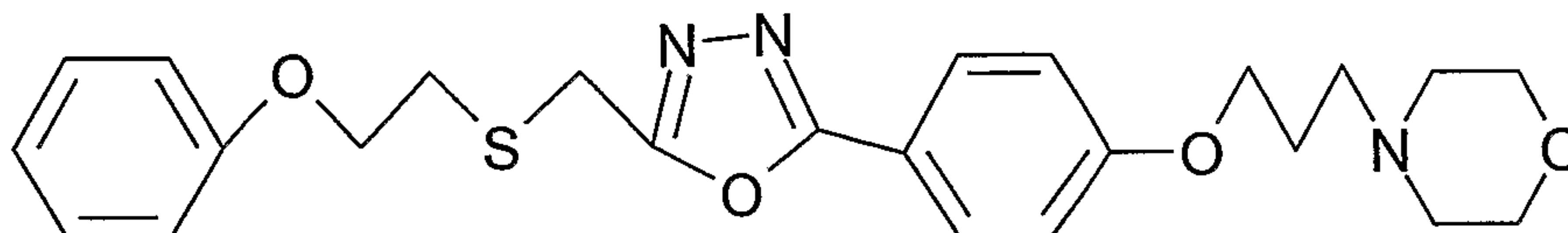
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.197 g, 0.599 mmol) and 1-(2-chloro-ethyl)-azepane hydrochloride (0.178 g, 0.899 mmol) to give crude material that was purified directly by column chromatography on silica gel (elution with ethyl acetate/toluene followed by 90% chloroform/10% 2M NH₃ in methanol to give 0.216 g (79%) of the title compound.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.9 (m, 2H), 2.7 (m, 4H), 1.5 (m, 8H). IR (KBr, cm⁻¹) 2917, 1613, 1604, 1500, 1261, 1247, 1176, 749. MS (ESI) m/e 454. Anal. Calcd for C₂₅H₃₁N₃O₃S: C, 66.20; H, 6.89; N, 9.26. Found C, 66.17; H, 6.96; N, 9.16. M.P.=40°C.

Example 87

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Preparation of 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-morpholine



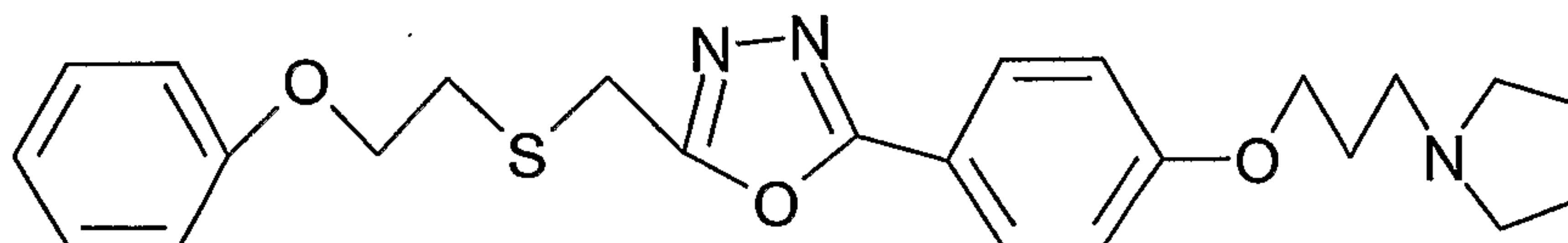
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.222 g, 0.548 mmol) and morpholine (0.119 g, 1.37 mmol) to give 0.078 g (31%) of the title compound.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.6 (t, 4H, J=4 Hz) 3.0 (t, 2H, J=6 Hz), 2.4 (t, 2H, J=7 Hz), 2.3 (m, 4H), 1.9 (m, 2H). IR (KBr, cm⁻¹) 3436, 2965, 2943, 2926, 2863, 2810, 1609, 1500, 1468, 1297, 1256, 1242, 1174, 1115, 838, 764. MS (ESI) m/e 456, 454. Anal. Calcd for C₂₄H₂₉N₃O₄S: C, 63.27; H, 6.41; N, 9.22. Found C, 63.06; H, 6.60; N, 9.04. M.P.=65°C.

15

Example 88

Preparation of 2-(2-phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-[1,3,4]oxadiazole



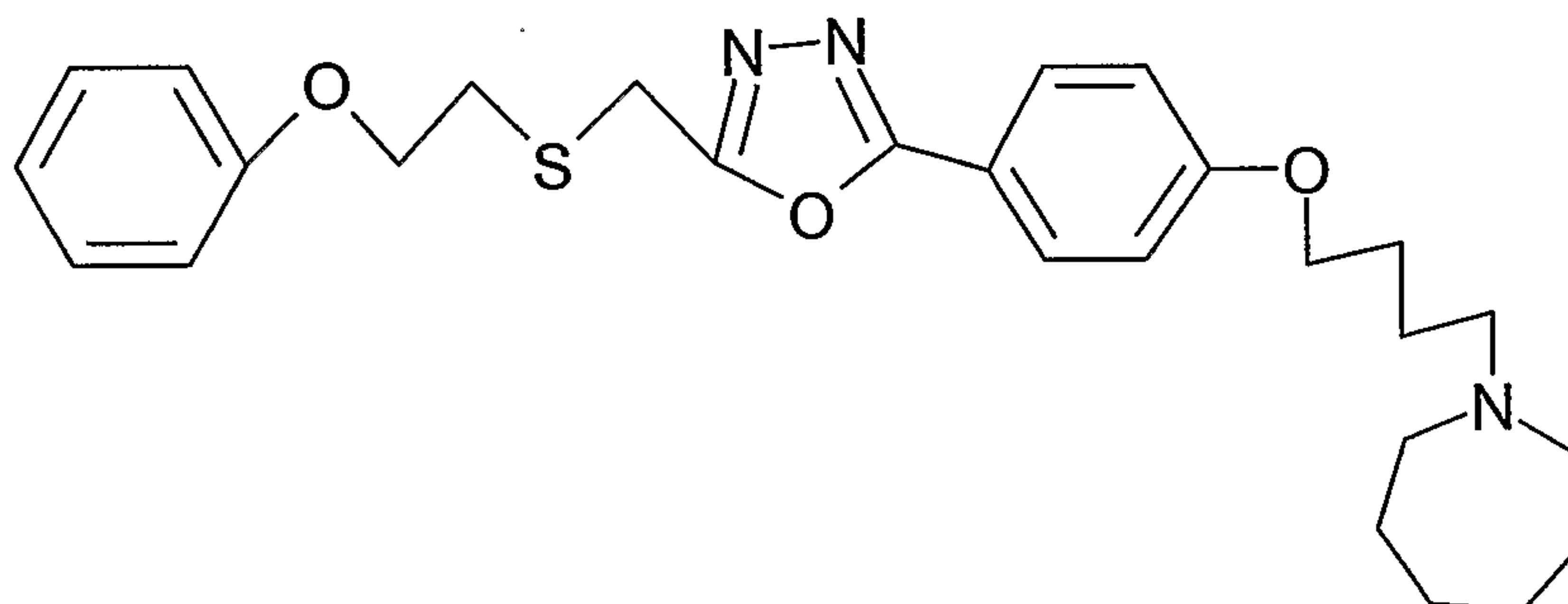
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.222 g, 0.548 mmol) and pyrrolidine (0.097 g, 1.37 mmol) to give 0.131 g (54%) of the title compound.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=7 Hz), 2.5 (m, 4H), 1.9 (m, 2H), 1.7 (m, 4H). IR (KBr, cm⁻¹) 2972, 2944, 2928, 2865, 2792, 1613, 1584, 1500, 1478, 1466, 1402, 1253, 1183, 1152, 1006, 849, 757. MS (ESI) m/e 440, 439. Anal. Calcd for C₂₄H₂₉N₃O₃S: C, 65.58; H, 6.65; N, 9.56. Found C, 65.28; H, 6.70; N, 9.45. M.P.=70°C.

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Example 89

Preparation of 1-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-azepane



5

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.227 g, 0.542 mmol) and azepane (0.56 g, 5.64 mmol) to give 0.091 g (35%) of the title compound.

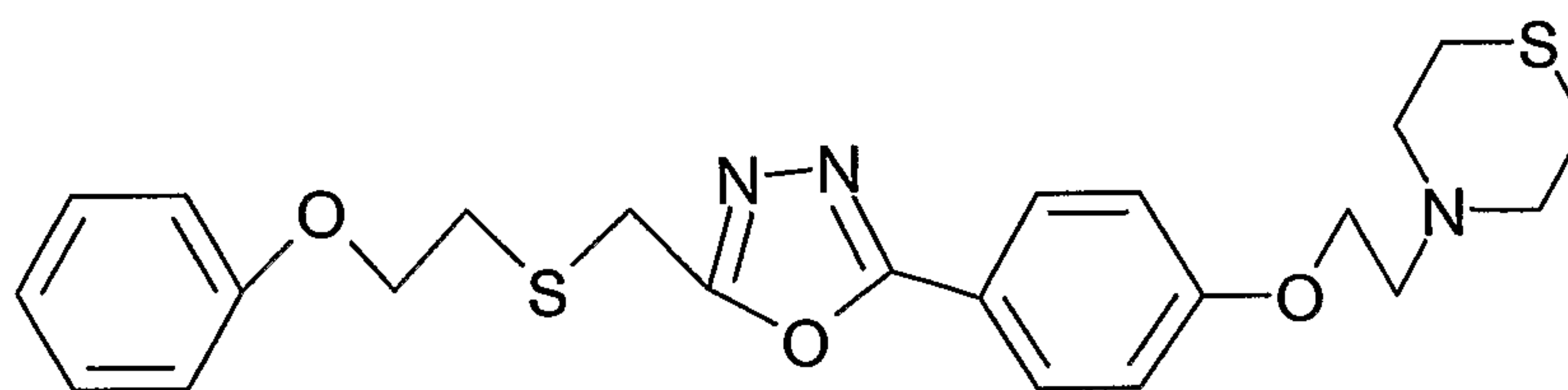
10

^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.5 (m, 6H), 1.7 (m, 2H), 1.5 (m, 10H). IR (KBr, cm^{-1}) 2930, 1610, 1493, 1248, 1175, 837. MS (ESI) m/e 482, 480. Anal. Calcd for $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_3\text{S}$: C, 67.33; H, 7.32; N, 8.72. Found C, 67.35; H, 7.25; N, 8.91. M.P.=35-38°C.

15

Example 90

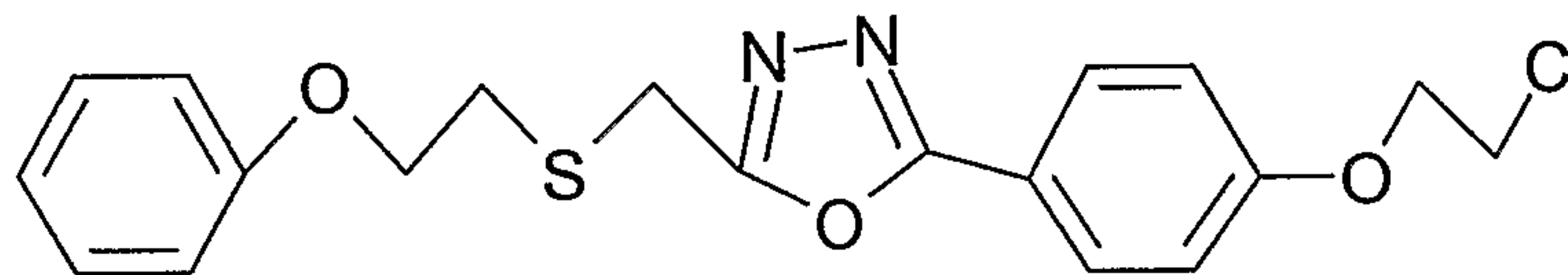
Preparation of 4-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-thiomorpholine



20

a) 2-[4-(2-Chloro-ethoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole

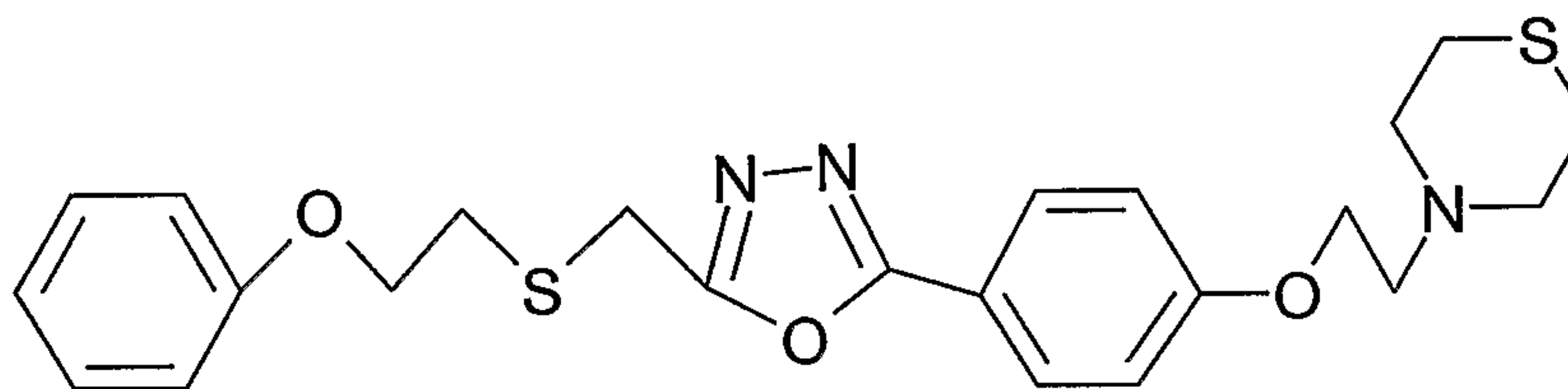
-221-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (1.491 g, (4.54 mmol) and 1-bromo-2-chloro-ethane (0.98 g, 6.81 mmol) to give 1.216 g (68%) of 2-[4-(2-chloro-ethoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole.

^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.3 (t, 2H, $J=5$ Hz), 4.2 (m, 4H), 4.0 (t, 2H, $J=5$ Hz), 3.0 (t, 2H, $J=6$ Hz). IR (KBr, cm^{-1}) 3439, 2965, 2929, 2916, 1619, 1603, 1586, 1499, 1465, 1249, 1177, 1088, 1023, 1008, 756. MS (ESI) m/e 391. Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_3\text{S}$: C, 58.38; H, 4.90; N, 7.17. Found C, 58.27; H, 5.01; N, 7.07.

b) 4-(2-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-thiomorpholine



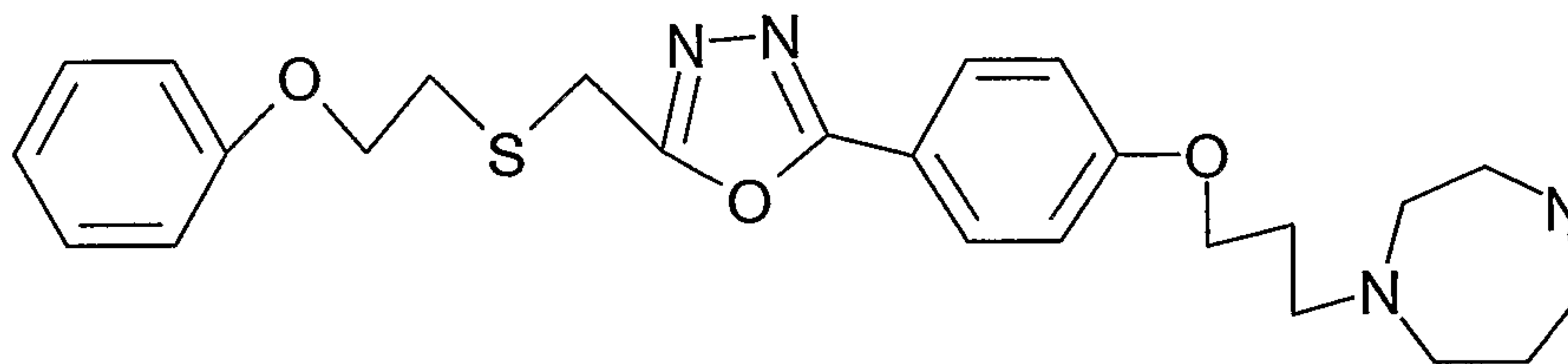
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(2-chloro-ethoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.215 g, 0.55 mmol) and thiomorpholine (0.141 g, 1.37 mmol) to give 0.066 g (26%) of the title product.

^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.0 (t, 2H, $J=6$ Hz) 2.8 (m, 6H), 2.6 (m, 4H). IR (KBr, cm^{-1}) 2926, 2807, 1614, 1503, 1459, 1297, 1253, 1173, 834, 754. MS (ESI) m/e 458, 456. Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_3\text{S}_2$: C, 60.37; H, 5.95; N, 9.18. Found C, 59.64; H, 5.61; N, 8.94. M.P.=60°C. HPLC 100%.

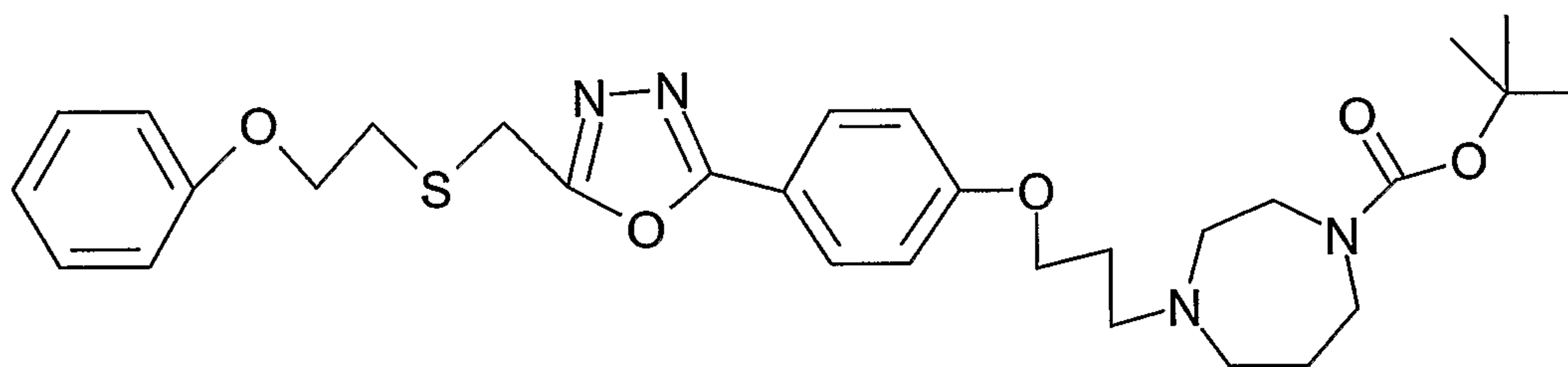
Example 91

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Preparation of 1-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-[1,4]diazepane



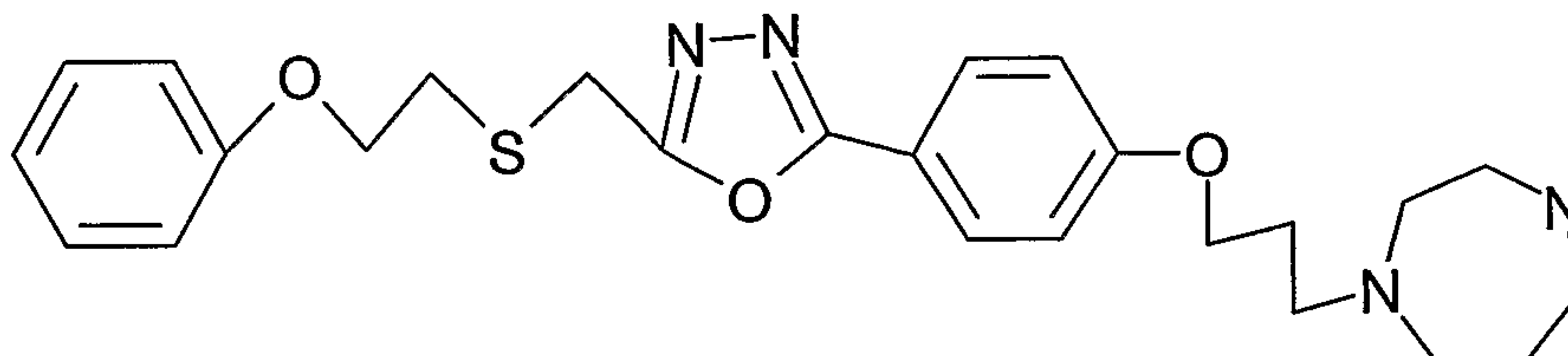
a) 4-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.223 g, 0.679 mmol) and 4-(3-chloro-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester (0.376 g, 1.36 mmol) to give crude material that was purified directly by column chromatography on silica gel (elution with ethyl acetate/toluene followed by 90% chloroform/10% 2M NH₃ in methanol) to give 0.49 g (100%) of 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=7 Hz), 3.6 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz) 2.6 (m, 4H), 1.8 (m, 4H), 1.6 (m, 4H), 1.4 (s, 9H). MS (ESI) m/e 569.

b) 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-[1,4]diazepane



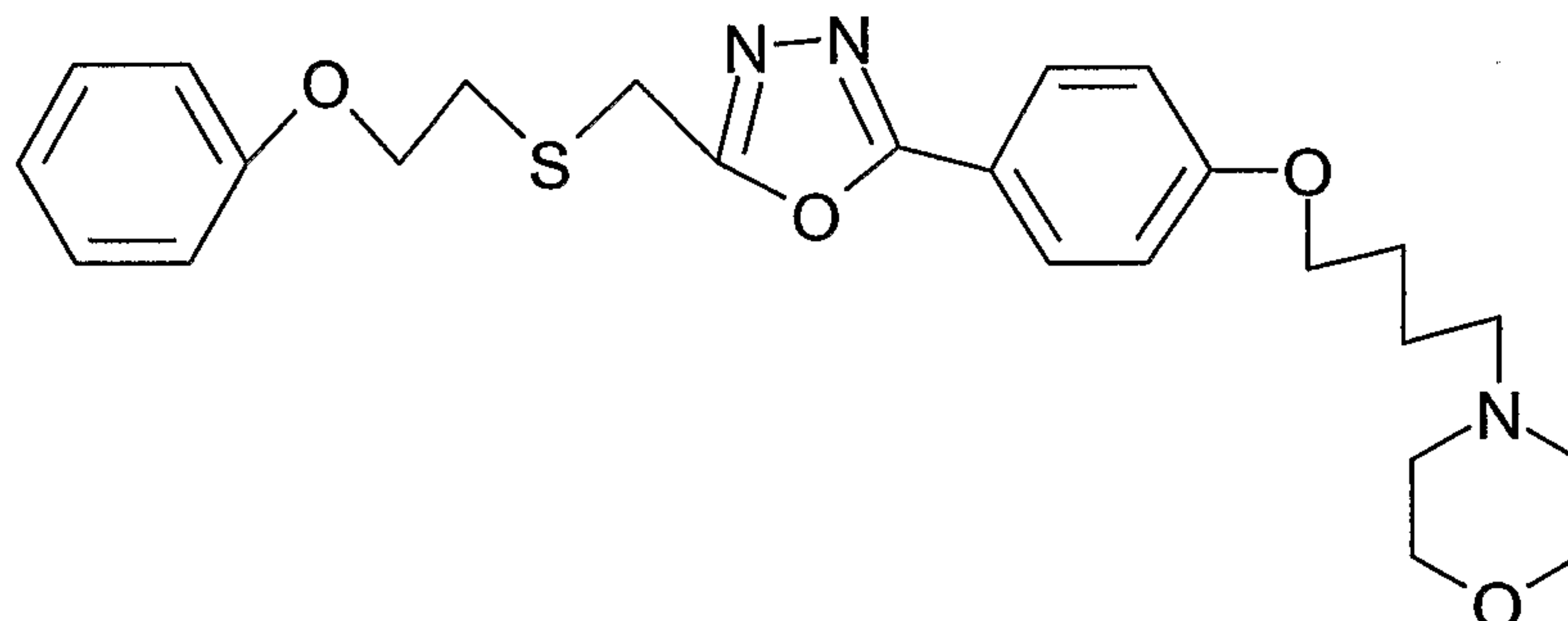
-223-

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 79b, from 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester (0.49 g, 0.862 mmol) and trifluoroacetic acid (5 mL) to give 0.136 g (34%) of the title product.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.3 (m, 2H), 3.0 (t, 2H, J=6 Hz) 2.8 (m, 3H), 2.6 (m, 6H), 1.8 (m, 2H), 1.6 (m, 2H). IR (KBr, cm⁻¹) 2337, 1671, 1613, 1499, 1256, 1245, 1175. MS (ESI) m/e 469. Anal. Calcd for C₂₅H₃₂N₄O₃S: C, 64.08; H, 6.88; N, 11.95. Found C, 58.41; H, 6.35; N, 10.64. HPLC 100%.

Example 92

Preparation of 4-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-morpholine



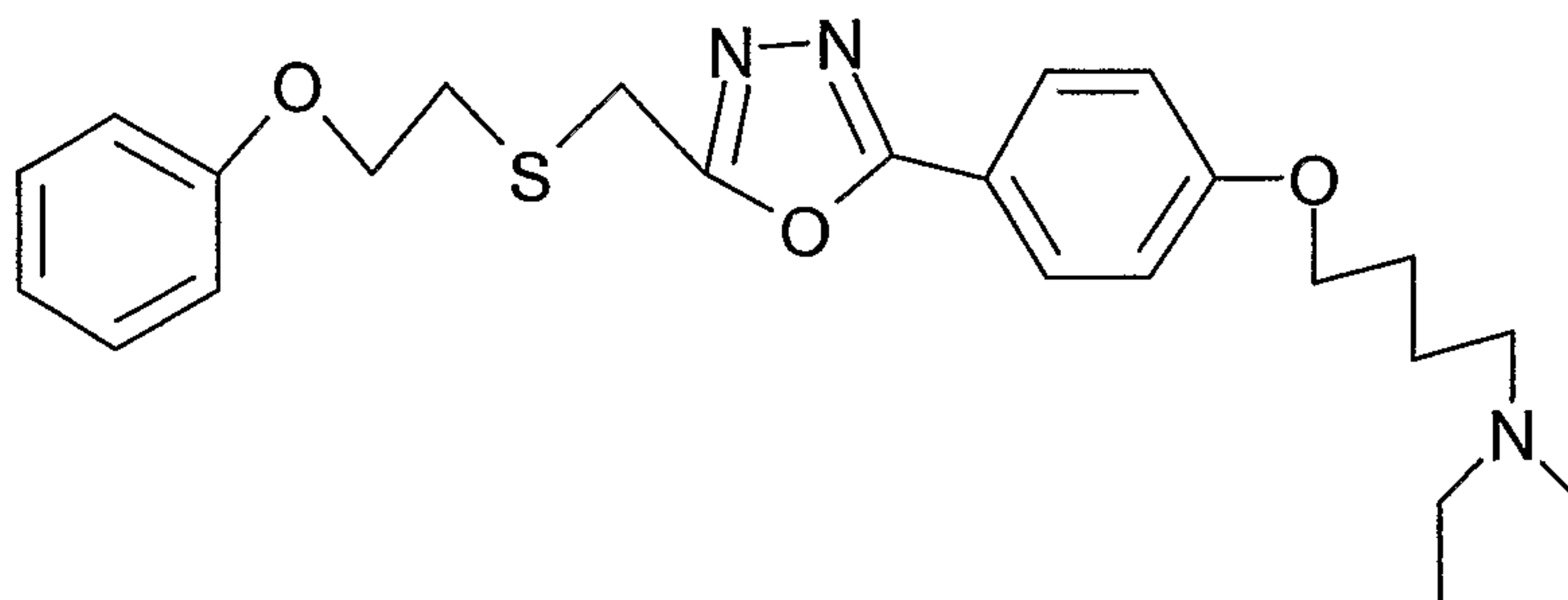
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.225 g, 0.537 mmol) and morpholine (0.117 g, 1.34 mmol) to give 0.144 g (57%) of the title compound.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.5 (m, 4H), 3.0 (t, 2H, J=6 Hz) 2.3 (m, 6H), 1.8 (m, 2H), 1.6 (m, 2H). IR (KBr, cm⁻¹) 2935, 2852, 2811, 1611, 1499, 1303, 1249, 1174, 1118, 836. MS (ESI) m/e 470, 468. Anal. Calcd for C₂₅H₃₁N₃O₄S: C, 63.94; H, 6.65; N, 8.95. Found C, 63.83; H, 6.72; N, 8.93. M.P.=64-67°C.

Example 93

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Preparation of diethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine

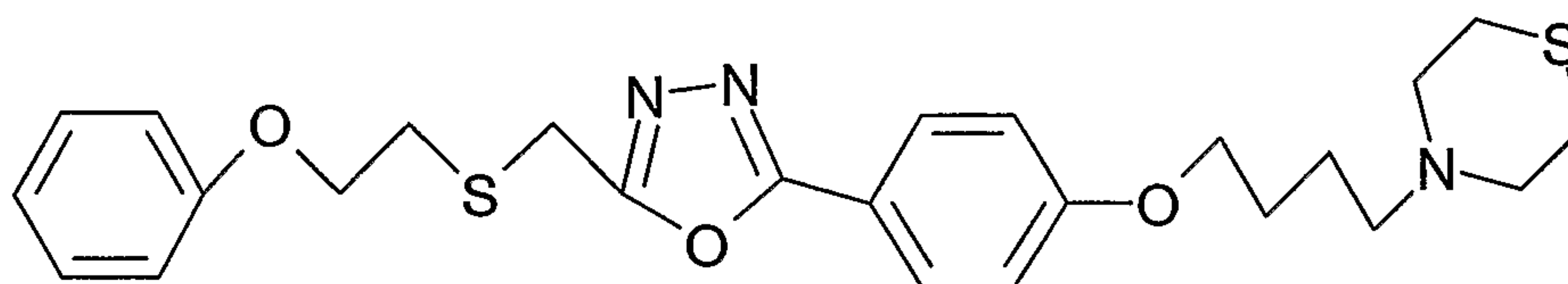


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.225 g, 0.537 mmol) and diethyl amine (0.989 g, 13.4 mmol) to give 0.090 g (37%) of the title compound.

^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz) 2.4 (m, 6H), 1.7 (m, 2H), 1.6 (m, 2H), 1.0 (t, 6H, $J=7$ Hz). IR (KBr, cm^{-1}) 2929, 2799, 1610, 1500, 1248, 1174, 1005, 837. MS (ESI) m/e 456. Anal. Calcd for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3\text{S}$: C, 65.90; H, 7.30; N, 9.22. Found C, 63.98; H, 7.08; N, 9.72. M.P.=35-38°C. HPLC 99%.

Example 94

Preparation of 4-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-thiomorpholine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.313 g, 0.747 mmol) and thiomorpholine (0.154 g, 1.49 mmol) to give 0.219 g (60%) of the title compound.

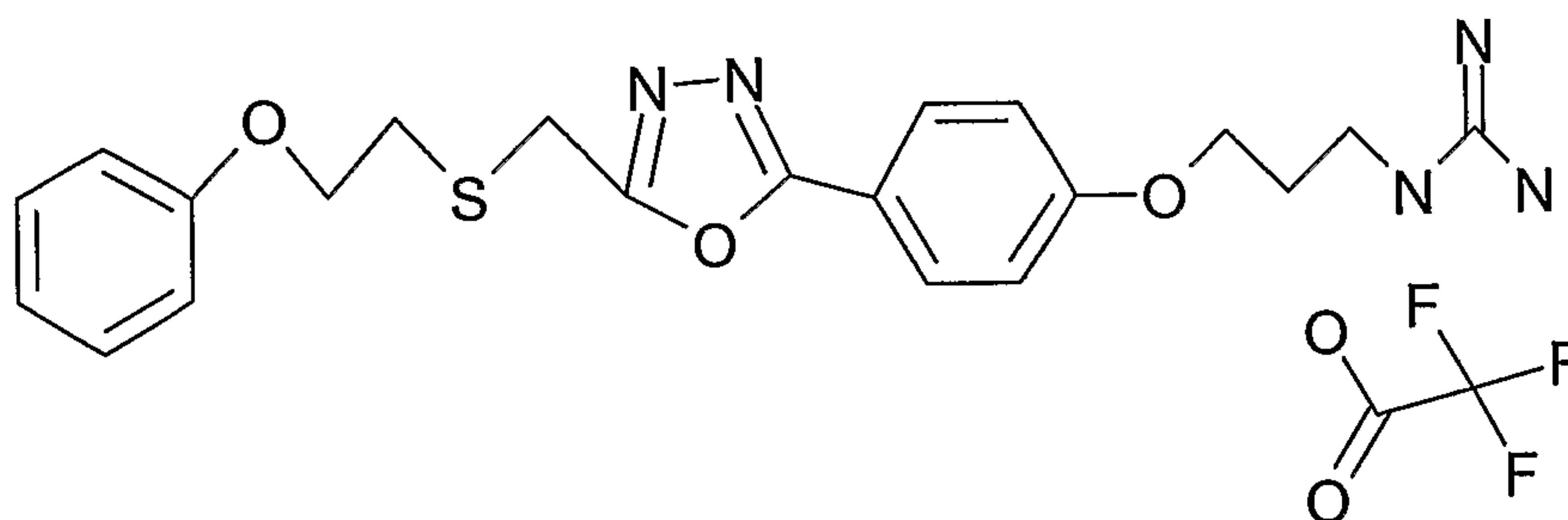
^1H NMR (DMSO- d_6) δ 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.0 (t, 2H, $J=6$ Hz), 2.6 (m, 8H), 2.3 (m, 2H), 1.8 (m, 2H), 1.6 (m, 2H). IR (KBr, cm^{-1}) 3000, 2873, 2816, 1613, 1588, 1499,

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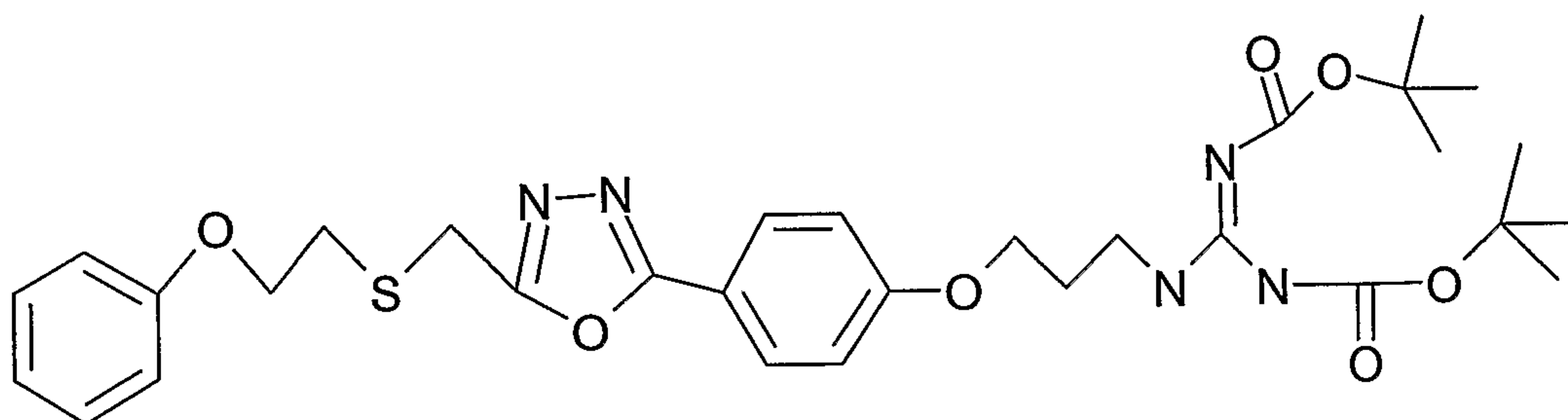
1256, 1245, 1174, 1006, 839. MS (ESI) m/e 486, 484. Anal. Calcd for $C_{25}H_{31}N_3O_3S_2$: C, 61.83; H, 6.43; N, 8.65. Found C, 61.66; H, 6.44; N, 8.59. M.P.=58°C.

Example 95

- 5 Preparation of N-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-methanetriamine, trifluoroacetic acid salt



- a) N-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-methanetriamine, di-carboxylic acid tert-butyl ester



10

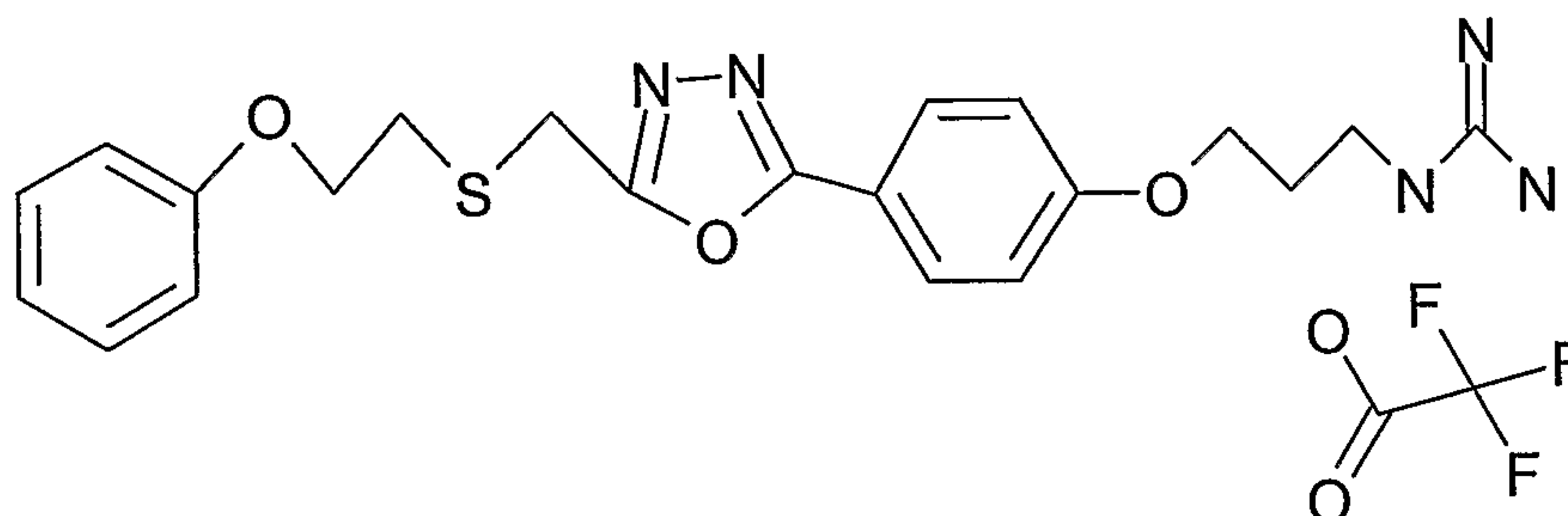
A solution of 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propylamine (Example 85b) (0.142 g, 0.368 mmol) and 1,3-bis(*t*-butoxycarbonyl)-2-methyl-2-thiopseudourea (0.112 g, 0.387 mmol) in acetonitrile (7 mL) was stirred at room temperature overnight. The mixture was diluted with ethyl acetate and washed with saturated NaHCO_3 . The aqueous layer was extracted once with ethyl acetate. The combined organics were washed with water, brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate/toluene) to give 0.119 g (52%) of N-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-methanetriamine, di-carboxylic acid tert-butyl ester (40a).

20

^1H NMR (DMSO-d_6) δ 8.5 (m, 1H), 7.9 (d, 2H, $J=9$ Hz), 7.2 (t, 2H, $J=8$ Hz), 7.1 (d, 2H, $J=9$ Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, $J=6$ Hz), 3.5 (m, 2H), 3.0 (t, 2H, $J=6$ Hz) 2.0 (m, 2H), 1.5 (s, 9H), 1.4 (s, 9H). MS (ESI) m/e 628.

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b) N-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-methanetriamine, trifluoroacetic acid salt



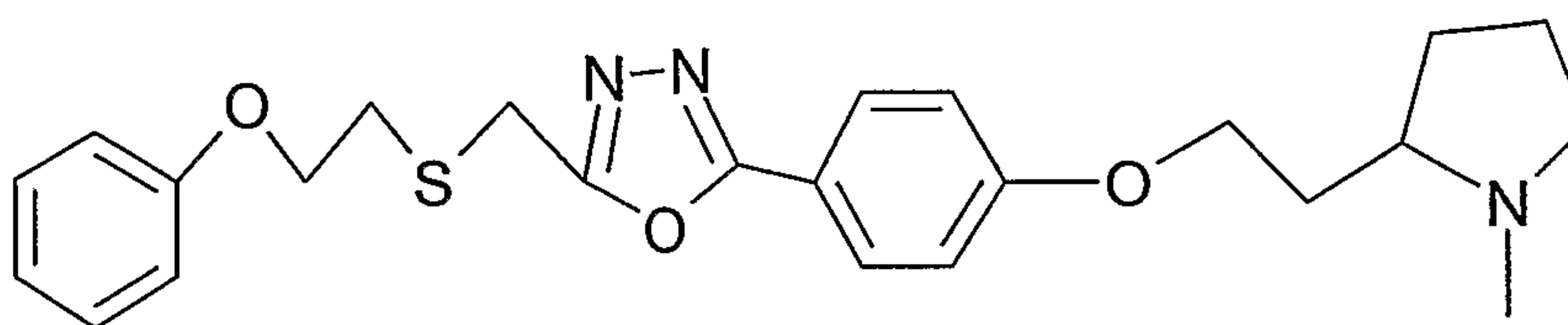
5 N-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-methanetriamine, di-carboxylic acid tert-butyl ester (0.253 g, 0.403 mmol) was dissolved in CH₂Cl₂ (5 mL) and cooled to 5°C. Trifluoroacetic acid (5 mL) was added and the mixture was stirred at 5°C for 1 hr and at room temperature for 1 hr. The mixture was concentrated to dryness, diluted with ethyl acetate and washed with 1N NaOH. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with water, brine, dried over sodium sulfate, filtered, and concentrated to 0.073 g. Due to low recovery, the aqueous layer was extracted 4 times with CH₂Cl₂ and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated to 0.186 g. The combined residues were purified by column chromatography on silica gel (elution with ethyl acetate/toluene followed by 90% chloroform/10% 2M NH₃ in methanol) to give 0.106 g that was recrystallized from 1 mL ethyl acetate and 5 mL ethyl ether to give 0.075 g (34%) of the title compound.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.6 (m, 1H), 7.2 (m, 3H), 7.1 (m, 3H), 7.0 (s, 1H), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.3 (m, 2H), 3.0 (t, 2H, J=6 Hz), 2.0 (m, 2H). IR (KBr, cm⁻¹) 3400, 3110, 1674, 1636, 1612, 1500, 1252, 1205, 1176, 1136. MS (ESI) m/e 428. Anal. Calcd for C₂₃H₂₆N₅F₃O₅S: C, 51.01; H, 4.84; N, 12.93; F, 10.52. Found C, 45.58; H, 4.91; N, 13.21; F, 11.96. M.P.=100°C. HPLC 100%.

Example 96

25 Preparation of 2-{4-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole

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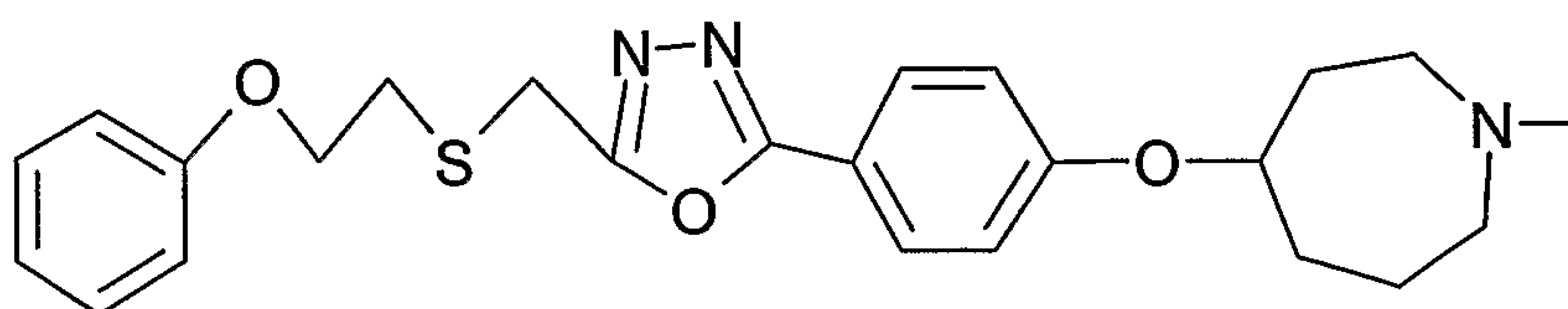
A mixture of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.346 g, 1.05 mmol) and 60% NaH (0.121 g, 3.15 mmol) was stirred at 5°C for 2 minutes in DMF (5 mL). Added 2-(2-chloro-ethyl)-1-methyl-pyrrolidine (0.291 g, 1.58 mmol) and heated the mixture to 100°C for 10 hrs. Diluted with ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed 3 X water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate/toluene followed by 90% chloroform/10% 2M NH₃ in methanol) to give 0.054 g, (12%) of the title compound and material that was a mixture of 2 products, one being the title compound and a second product of the reaction (Example 97), see procedure for Example 97.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (m, 2H), 3.0 (m, 3H), 2.3 (s, 3H), 2.2 (m, 1H), 2.1 (m, 2H), 2.0 (m, 1H), 1.7 (m, 3H), 1.5 (m, 1H). IR (KBr, cm⁻¹) 3410, 3000, 2910, 2800, 1610, 1500, 1468, 1257, 1241, 1173, 764. MS (ESI) m/e 440. Anal. Calcd for C₂₄H₂₉N₃O₃S: C, 65.58; H, 6.65; N, 9.56. Found C, 63.09; H, 6.22; N, 8.96. M.P.=46-50°C. HPLC 94%.

20

Example 97

Preparation of 1-methyl-4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-azepane



Prepared in the same manner as exemplified in Example 96 and isolated as a by-product of the reaction mixture. The mixture isolated via chromatography from procedure 96 was purified a second time using a Waters Preparatory 2000 with a Kromasil silica column (5 X 25 cm) (elution with 50/50 ethyl acetate/dichloromethane/1%

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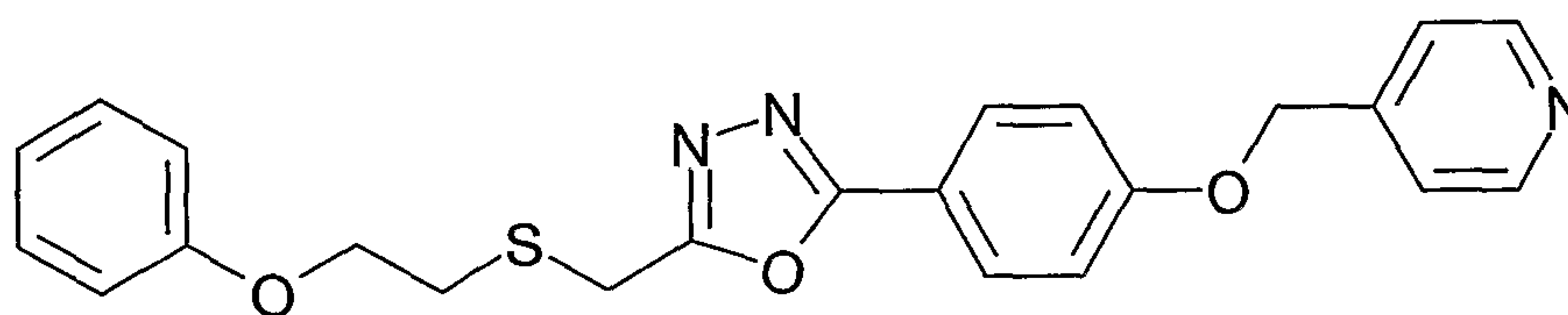
dimethylethylamine to give 0.209 g (12%) of the title compound and 0.200 g (12%) of the compound of Example 96.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.7 (m, 1H), 4.2 (m, 4H), 3.0 (m, 2H), 2.65 (m, 1H), 2.6 (m, 2H), 2.5 (m, 1H), 2.3 (s, 3H), 2.1 (m, 2H), 1.9 (m, 1H), 1.8 (2H), 1.6 (m, 1H). IR (KBr, cm⁻¹) 2923, 1612, 1602, 1587, 1499, 1465, 1295, 1237, 1174, 1002. MS (ESI) m/e 440. Anal. Calcd for C₂₄H₂₉N₃O₃S: C, 65.58; H, 6.65; N, 9.56. Found C, 66.35; H, 6.83; N, 9.05. M.P.=60-61°C. HPLC 100%.

10

Example 98

Preparation of 4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy-methyl}-pyridine



15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 96, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.303 g, 0.923 mmol) and 4-bromomethyl-pyridine hydrobromide salt (0.350 g, 1.38 mmol) to give a crude solid which was purified directly by column chromatography on silica gel (elution with ethyl acetate/toluene followed by 90% chloroform/10% 2M NH₃ in methanol to give material which was recrystallized from ethyl acetate, methanol, and ethyl ether to give 0.233 g (59%) of the title compound.

20

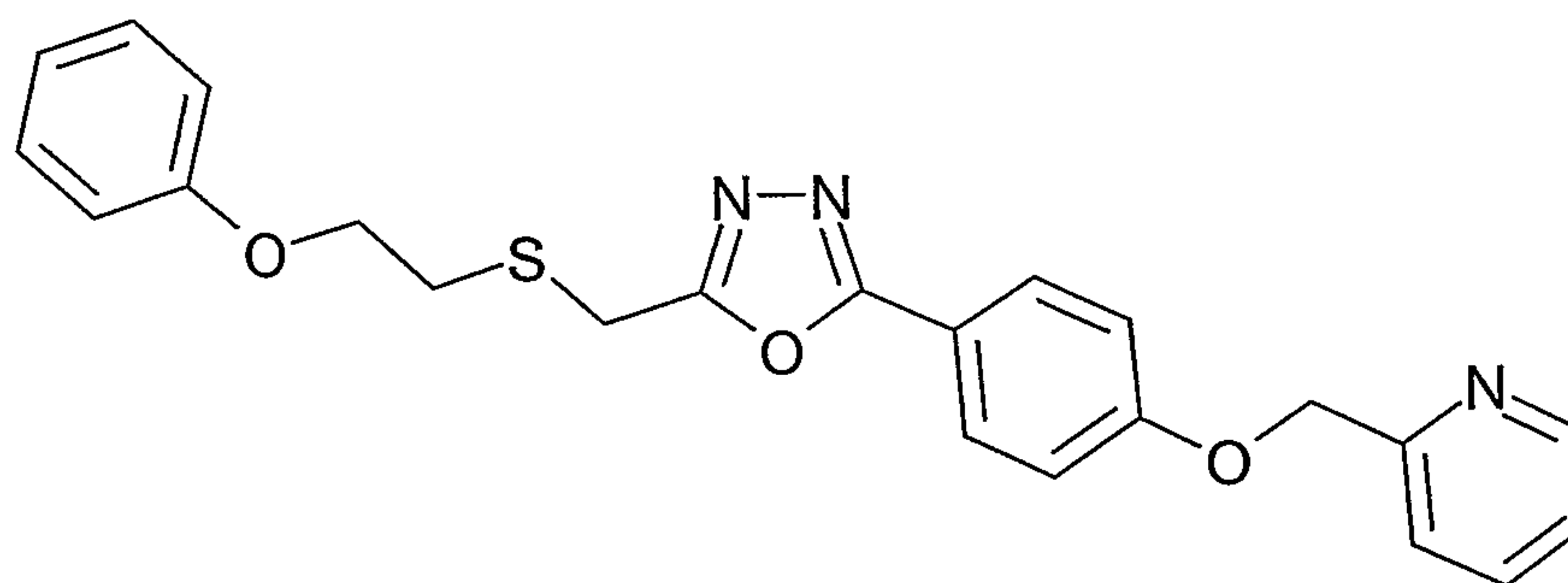
¹H NMR (DMSO-d₆) δ 8.6 (d, 2H, J=5 Hz), 7.9 (d, 2H, J=9 Hz), 7.4 (d, 2H, J=5 Hz), 7.2 (m, 4H), 6.9 (m, 3H), 5.3 (s, 2H), 4.2 (m, 4H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm⁻¹) 1603, 1501, 1264, 1249, 1172, 1005, 755. MS (ESI) m/e 420. Anal. Calcd for C₂₃H₂₁N₃O₃S: C, 65.85; H, 5.04; N, 10.02. Found C, 65.82; H, 5.11; N, 10.34. M.P.=80-90°C.

25

Example 99

Preparation of 2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy-methyl}-pyridine

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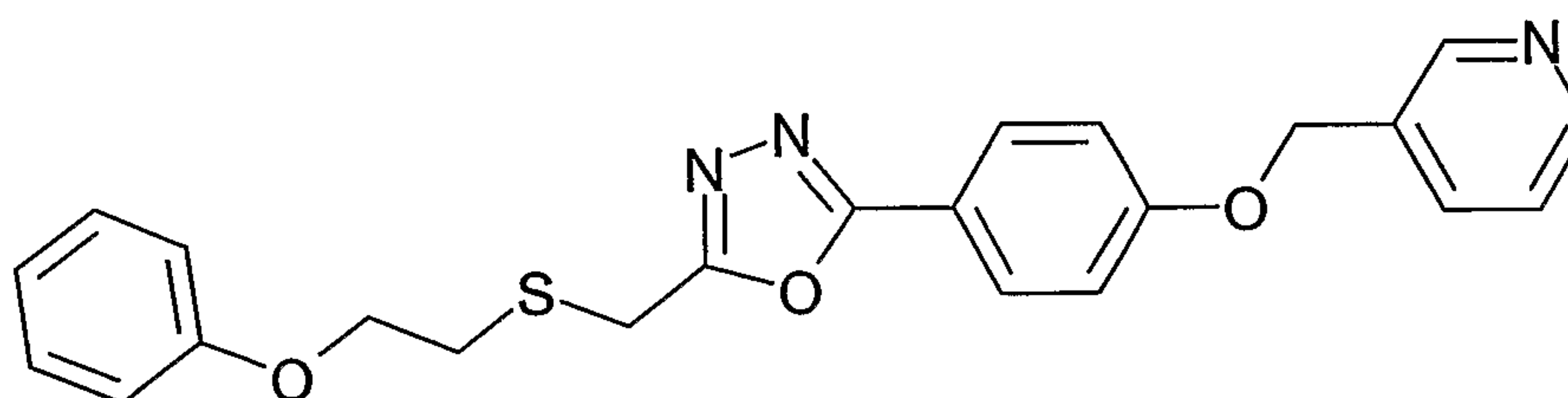
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 96, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.269 g, 0.819 mmol) and 2-bromomethyl-pyridine hydrobromide salt
 5 (0.311 g, 1.23 mmol) to give 0.146 g (42%) of the title compound.

^1H NMR (DMSO- d_6) δ 8.6 (m, 1H), 7.9 (m, 3H), 7.5 (d, 1H, $J=8$ Hz), 7.4 (m, 1H), 7.2 (m, 4H), 6.9 (m, 3H), 5.3 (s, 2H), 4.2 (m, 4H), 3.0 (t, 2H, $J=6$ Hz). IR (KBr, cm^{-1}) 1617, 1589, 1498, 1269, 1249, 1172, 1039, 753. MS (ESI) m/e 420. Anal. Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$: C, 65.85; H, 5.04; N, 10.02. Found C, 65.55; H, 4.88; N, 9.88.

10 M.P.=115°C.

Example 100

Preparation of 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy-methyl}-pyridine



15 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 96, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.274 g, 0.834 mmol) and 3-bromomethyl-pyridine hydrobromide salt (0.316 g, 1.25 mmol) to give 0.177 g (50 %) of the title compound.

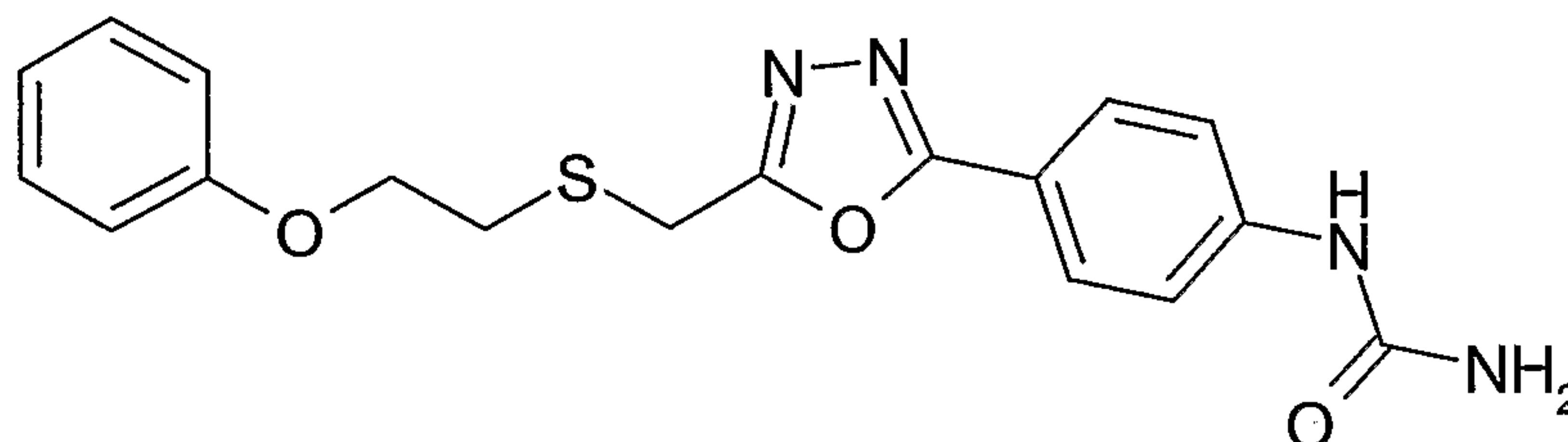
20 ^1H NMR (DMSO- d_6) δ 8.7 (d, 1H, $J=2$ Hz), 8.6 (m, 1H), 7.9 (m, 3H), 7.4 (m, 1H), 7.2 (m, 4H), 6.9 (m, 3H), 5.3 (s, 2H), 4.2 (m, 4H), 3.0 (t, 2H, $J=6$ Hz). IR (KBr, cm^{-1}) 1610, 1588, 1498, 1464, 1421, 1299, 1249, 1173, 1006, 758. MS (ESI) m/e 420. Anal.

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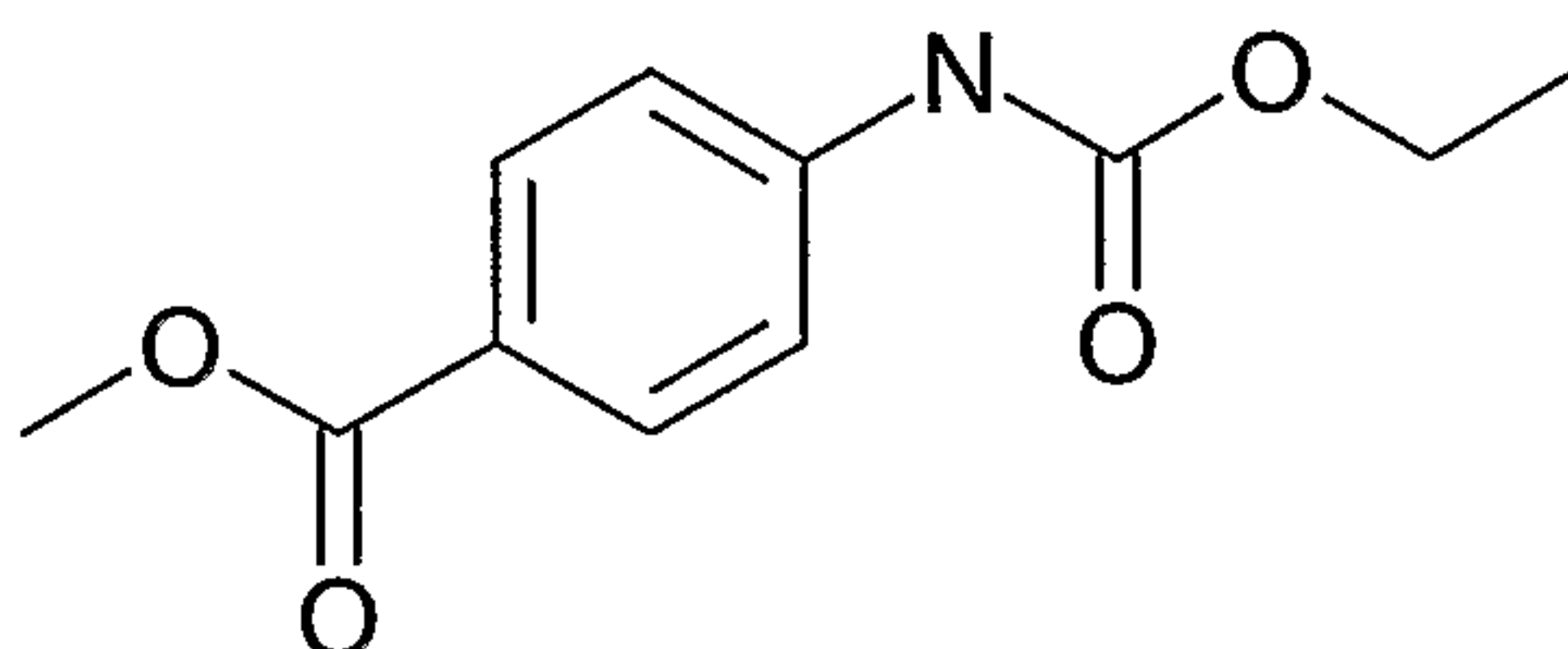
Calcd for $C_{23}H_{21}N_3O_3S$: C, 65.85; H, 5.04; N, 10.02. Found C, 65.83; H, 5.02; N, 10.04.
M.P.=111-112°C.

Example 101

- 5 Preparation of {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea



- a) 4-Ethoxycarbonylamino-benzoic acid methyl ester



10

Ethyl chloroformate (16.15 g, 148.85 mmol, 1.5 eq.) was added dropwise via syringe to a solution of methyl 4-aminobenzoate (15.0 g, 99.23 mmol, 1 eq.) in pyridine (400 mL) at 0 °C. After addition was complete, the reaction was allowed to stir and gradually warm to room temperature. After 4 hours, the pyridine was removed *in vacuo* and the residue suspended in water. The aqueous mixture was extracted with 50% Et₂O in EtOAc. The combined organic layers were washed with aqueous 1M HCl, saturated sodium bicarbonate, and then brine, dried over MgSO₄, filtered, and the solvent removed *in vacuo* to afford 21.79 g (98%) of 4-ethoxycarbonylamino-benzoic acid methyl ester as a yellow solid.

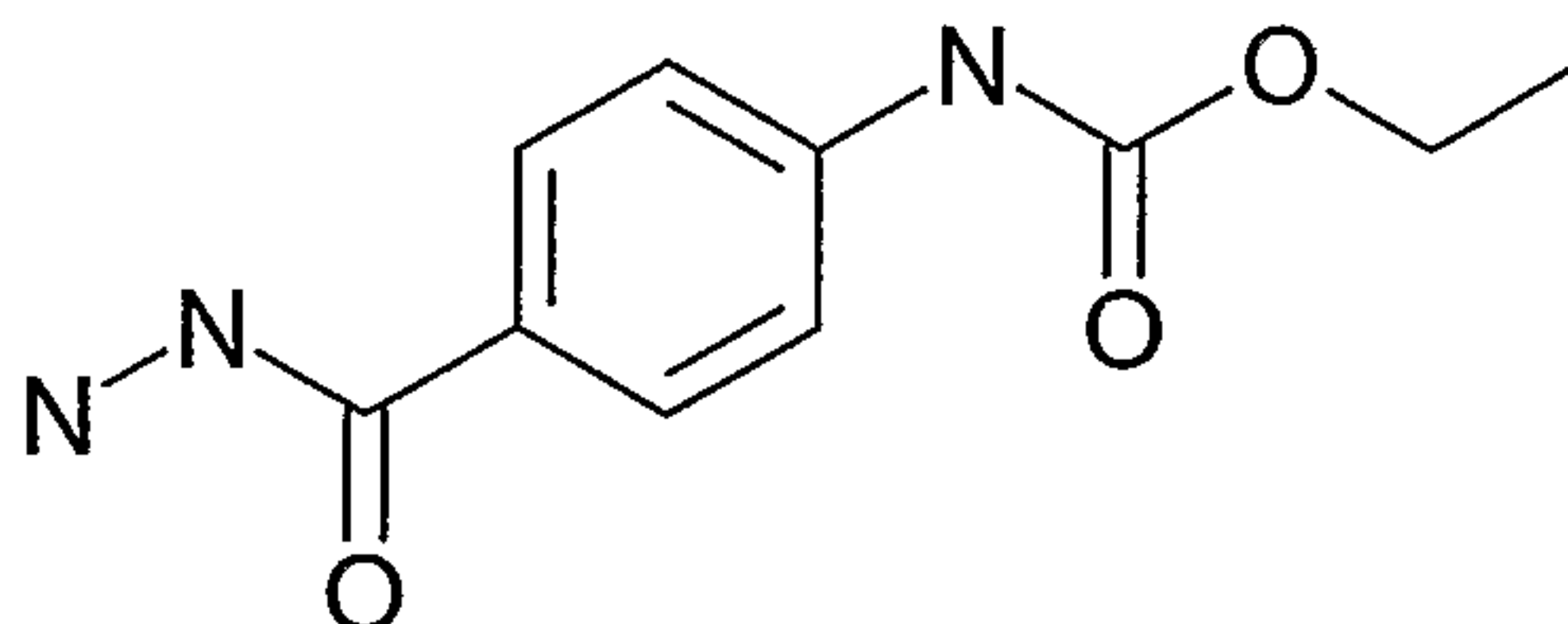
20

¹H NMR (DMSO-d₆) δ 10.04 (s, 1H), 7.88 (d, 2H, J=9 Hz), 7.59 (d, 2H, J=9 Hz), 4.15 (q, 2H, J=7 Hz), 3.81 (s, 3H), 1.26 (t, 3H, J=7 Hz). IR (KBr, cm⁻¹) 3318, 1730, 1692, 1596, 1538, 1415, 1298, 1224, 1180, 1057. MS (ES⁺) m/e 224. MS (ES⁻) m/e 222. Anal. Calcd for C₁₁H₁₃NO₄ C, 59.19; H, 5.87; N, 6.27. Found C, 59.33; H, 5.92; N, 6.30. MP 159-162°C.

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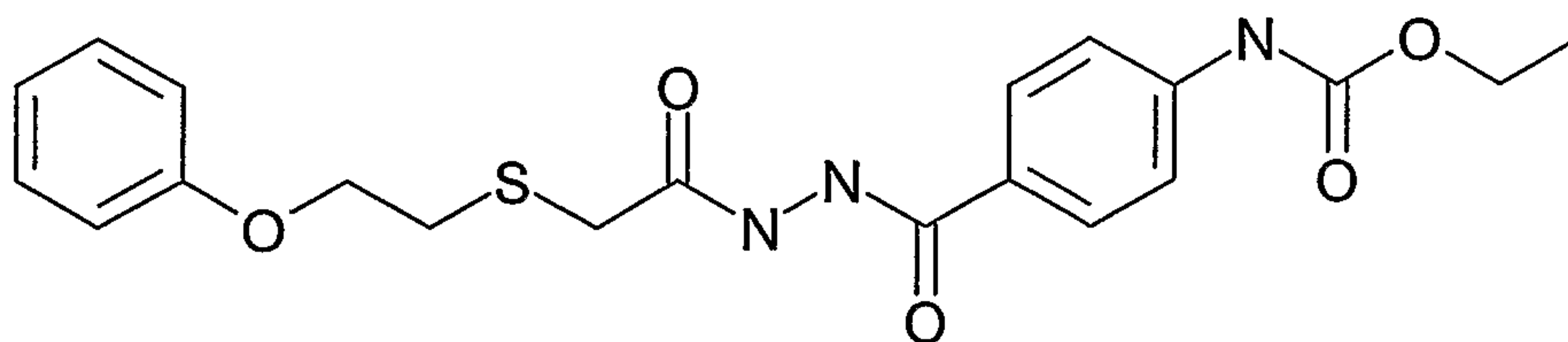
b) (4-Hydrazinocarbonyl-phenyl)-carbamic acid ethyl ester



Hydrazine hydrate (3.59 g, 112.0 mmol, 5 eq.) was added to a solution of 4-ethoxycarbonylamino-benzoic acid methyl ester (5.0 g, 22.40 mmol, 1 eq.) in ethanol. The mixture was heated at 76 °C for 16 h. The solvent was removed in vacuo. The resultant white solid was suspended in EtOAc (150 mL) and heated on a hot plate until ~100 mL remained, then allowed to cool. The resultant precipitate was collected by filtration to give 4.25 g (85%) of (4-hydrazinocarbonyl-phenyl)-carbamic acid ethyl ester as a white solid.

¹H NMR (DMSO-d₆) δ 9.85 (s, 1H), 9.56 (s, 1H), 7.74 (d, 2H, J=9 Hz), 7.50 (d, 2H, J=9 Hz), 4.52 (br s, 2H), 4.13 (q, 2H, J=7 Hz), 1.25 (t, 3H, J=7 Hz). IR (KBr, cm⁻¹) 3303, 3278, 1715, 1631, 1593, 1525, 1503, 1328, 1228, 1067. MS (ES⁺) m/e 224. Anal. Calcd for C₁₀H₁₃N₃O₃ C, 53.81; H, 5.87; N, 18.82. Found C, 53.52; H, 5.86; N, 19.20. MP softening at 186°C then 193-195°C.

c) (4-{N'-[2-(2-Phenoxy-ethylsulfanyl)-acetyl]-hydrazinocarbonyl}-phenyl)-carbamic acid ethyl ester



EEDQ (8.30 g, 33.55 mmol, 1.1 eq.) was added as a solid to a solution of (2-Phenoxyethylthio)acetic acid (6.47 g, 30.50 mmol, 1 eq.) in anhydrous 450 mL acetonitrile and 150 mL THF at room temperature. The reaction was stirred at room temperature for 1 h, then (4-hydrazinocarbonyl-phenyl)-carbamic acid ethyl ester (7.49 g, 33.55 mmol, 1.1 eq.) was added as a solid. The mixture was stirred at room temperature for an additional 16 h. The solvent was removed *in vacuo* to afford a tan solid. The solid was suspended in aqueous 1 M HCl and extracted with EtOAc. The organic extract was

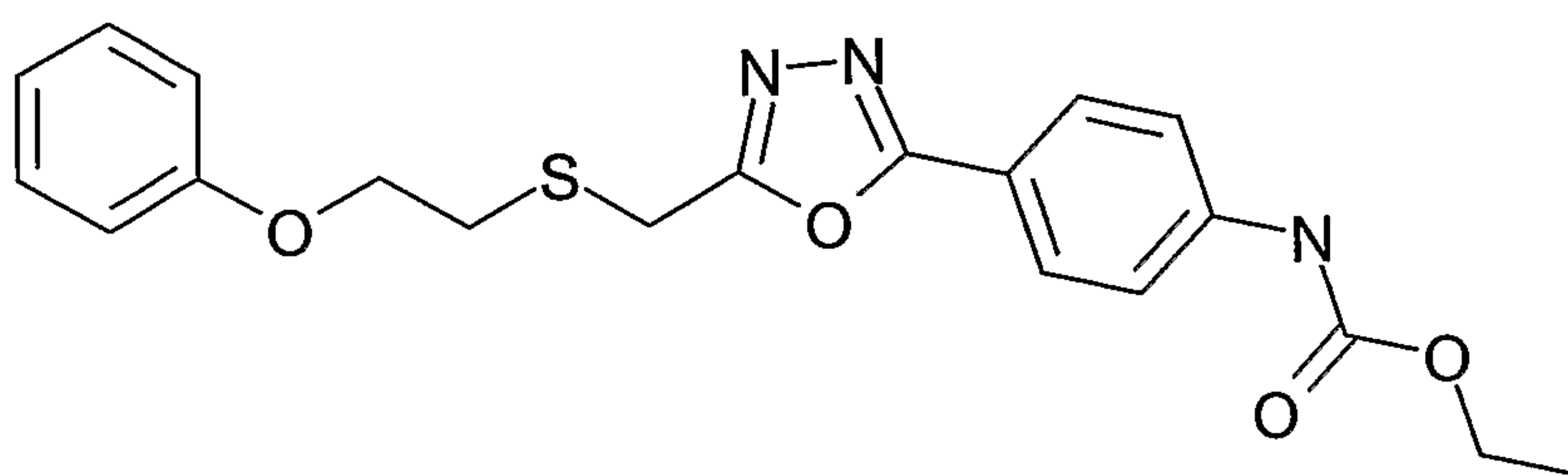
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washed with water, saturated aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, filtered and concentrated to afford an off-white solid.

The resulting solid was recrystallized from EtOAc and collected by filtration to afford 10.01 g (79%) of (4-{N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazinocarbonyl}-phenyl)-carbamic acid ethyl ester as an off-white solid.

¹H NMR (DMSO-d₆) δ 10.28 (s, 1H), 10.05 (s, 1H), 9.94 (s, 1H), 7.82 (d, 2H, J=9 Hz), 7.55 (d, 2H, J=9 Hz), 7.29 (m, 2H), 6.95 (m, 3H), 4.16 (m, 4H), 3.32 (s, 2H), 3.04 (t, 2H, J=7 Hz), 1.26 (t, 3H, J=7 Hz). IR (CHCl₃, cm⁻¹) 1737, 1525, 1508, 1498, 1215. MS (ES⁺) m/e 418. MS (ES⁻) m/e 416. Anal. Calcd for C₂₀H₂₃N₃O₅S C, 57.54; H, 5.55; N, 10.06. Found C, 57.18; H, 5.59; N, 10.10.

d) {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester



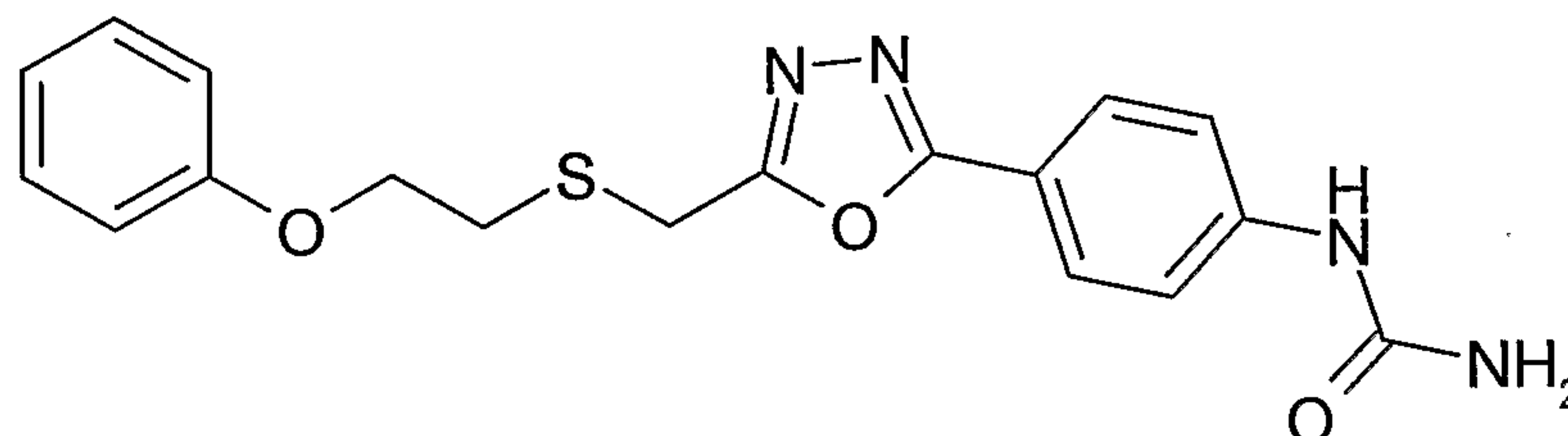
Triphenylphosphine (2.76 g, 10.54 mmol, 1.1 eq.) was added to a suspension of (4-{N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazinocarbonyl}-phenyl)-carbamic acid ethyl ester (4.0 g, 9.58 mmol, 1 eq.) in anhydrous THF (250 mL) at room temperature. Triethylamine (3.49 g, 34.49 mmol, 3.6 eq.) was then added to the mixture via syringe. After stirring for 5 minutes, carbon tetrabromide (3.50 g, 10.54 mmol, 1.1 eq.) was added as a solid with vigorous stirring. The reaction was allowed to stir at room temperature for 16 h. The solvent was removed *in vacuo* leaving a dark brown solid. The solid was purified via silica gel flash chromatography using a step gradient of EtOAc in hexane as the mobile phase to afford 1.93 g (50%) of {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester as a yellow solid.

¹H NMR (DMSO-d₆) δ 10.06 (s, 1H), 7.88 (d, 2H, J=9 Hz), 7.67 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.18 (m, 6H), 3.02 (t, 2H, J=7 Hz), 1.26 (t, 3H, J=7 Hz). IR (CHCl₃, cm⁻¹) 3432, 3009, 1737, 1522, 1504, 1242, 1226, 1224, 1216, 1210, 1206, 1182.

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MS (ES⁺) m/e 400. MS (ES⁻) m/e 398. Anal. Calcd for C₂₀H₂₁N₃O₄S C, 60.14; H, 5.30; N, 10.52. Found C, 59.78; H, 5.34; N, 10.41.

e) Preparation of {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea



Triethylamine (0.30 g, 3.0 mmol, 1.2 eq.) was added via syringe to a suspension of {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (1.0 g, 2.5 mmol, 1 eq.) in anhydrous toluene (10 mL). The mixture was heated to reflux, after 5 minutes, *B*-chlorocatecholborane (0.46 g, 3.0 mmol, 1.2 eq.) was added as a solid and the reaction allowed to stir at reflux for 15 minutes. The reaction was allowed to cool to about 40°C and then ammonia in methanol (1.07 mL of 7M NH₃ in MeOH) was added via syringe with vigorous stirring (turning the dark brown solution to a yellow suspension). The suspension was allowed to stir at room temperature for 1.5 h. The resultant suspension was filtered to obtain 1.19 g of a yellow solid, which was purified by recrystallization from ethanol to afford 0.67 g (72%) {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a light yellow solid.

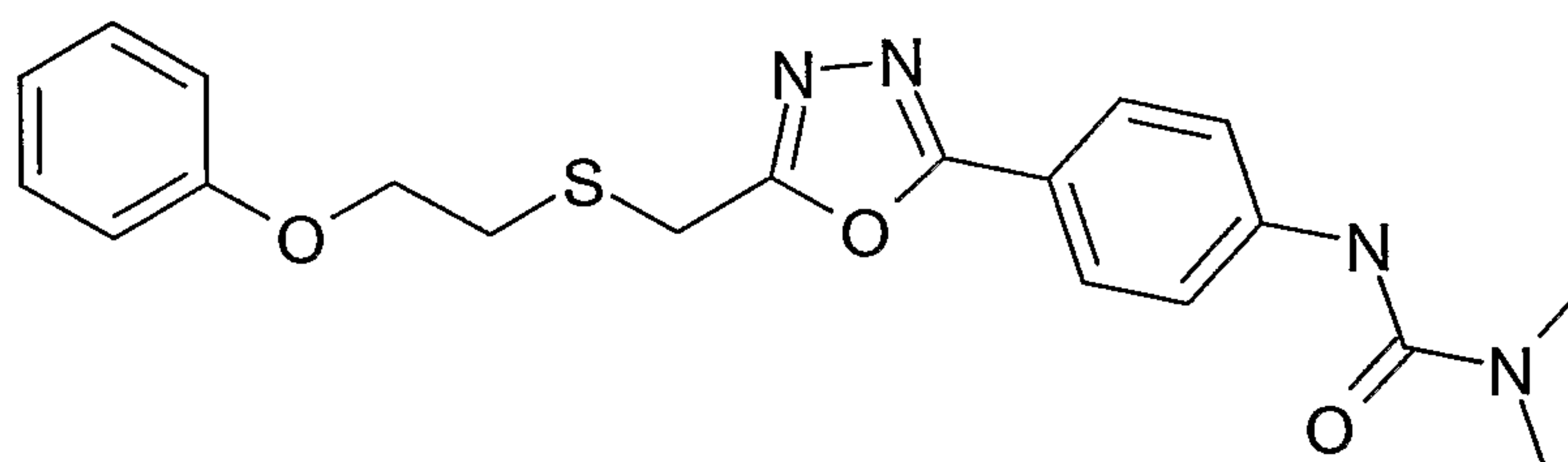
¹H NMR (DMSO-d₆) δ 8.97 (s, 1H), 7.82 (d, 2H, J=9 Hz), 7.61 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.94 (m, 3H), 6.05 (s, 2H), 4.20 (m, 4H), 3.02 (t, 2H, J=7 Hz). IR (KBr, cm⁻¹) 3343, 3175, 1699, 1599, 1530, 1497, 1418, 1242, 843. MS (ES⁺) m/e 371. MS (ES⁻) m/e 369. Anal. Calcd for C₁₈H₁₈N₄O₃S C, 58.36; H, 4.90; N, 15.12. Found C, 58.21; H, 4.95; N, 14.96. MP >220°C.

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Example 102

Preparation of 1,1-dimethyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea

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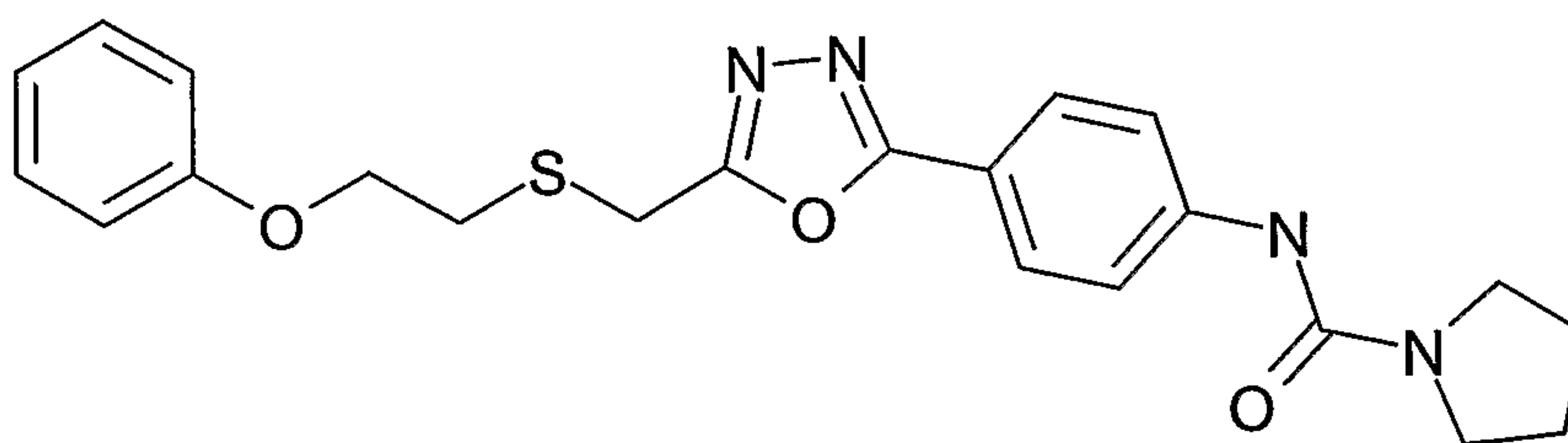


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and dimethylamine (2M in THF, 1.2 mL, 2.4 mmol, 1.2 eq.) to produce 0.53 g (67%) of 1,1-dimethyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as an off-white solid.

^1H NMR (DMSO- d_6) δ 8.68 (s, 1H), 7.83 (d, 2H, $J=9$ Hz), 7.71 (d, 2H, $J=9$ Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.02 (t, 2H, $J=7$ Hz), 2.95 (s, 6H). IR (CHCl_3 , cm^{-1}) 3009, 1674, 1598, 1519, 1498, 1415, 1244, 1173. MS (ES^+) m/e 399. MS (ES^-) m/e 397. Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_3\text{S}$ C, 60.28; H, 5.56; N, 14.06. Found C, 60.26; H, 5.47; N, 13.80. Analytical HPLC 97.3% purity. MP softening at 163°C then 167 - 169°C .

Example 103

Preparation of pyrrolidine-1-carboxylic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide



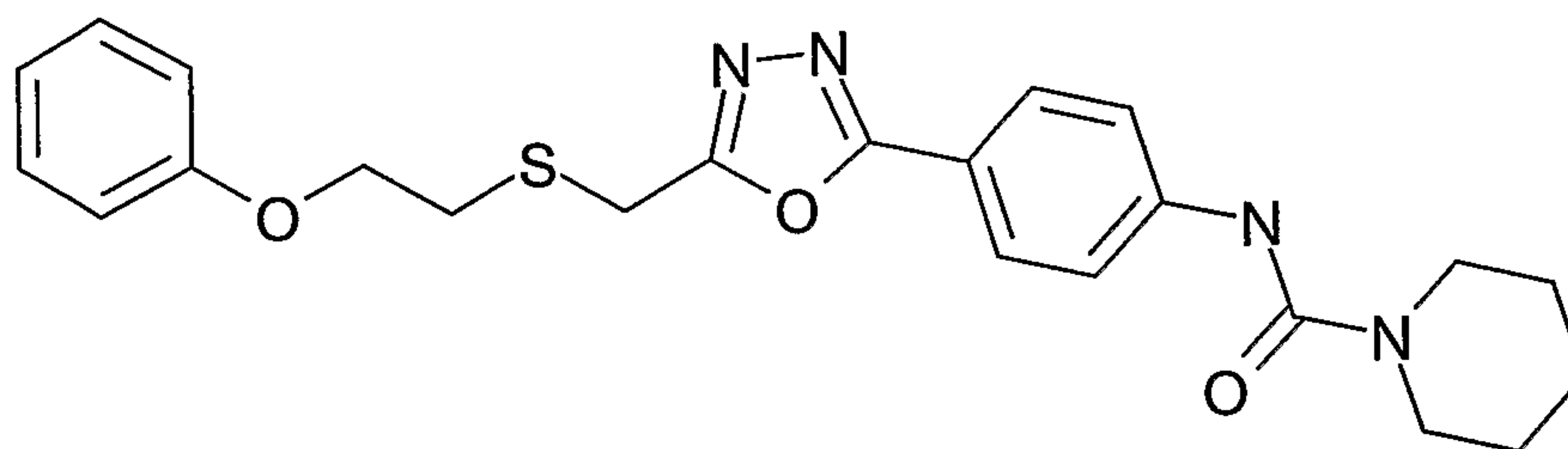
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and pyrrolidine (0.17 g, 2.4 mmol, 1.2 eq.) to produce 0.50 g (59%) of pyrrolidine-1-carboxylic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide as an orange/brown solid.

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¹H NMR (DMSO-d₆) δ 8.51 (s, 1H), 7.83 (d, 2H, J=9 Hz), 7.76 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.40 (m, 4H), 3.02 (t, 2H, J=7 Hz), 1.86 (m, 4H). IR (KBr, cm⁻¹) 3394, 1660, 1595, 1524, 1497, 1252, 835, 759. MS (ES⁺) m/e 425. MS (ES⁻) m/e 423. Anal. Calcd for C₂₂H₂₄N₄O₃S C, 62.24; H, 5.70; N, 13.20. Found C, 61.85; H, 5.81; N, 12.93. Analytical HPLC >99% purity. MP 184-185°C.

Example 104

Preparation of piperidine-1-carboxylic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide



10

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and piperidine (0.20 g, 2.4 mmol, 1.2 eq.) to produce 0.33 g (38%) of piperidine-1-carboxylic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide as a light yellow solid.

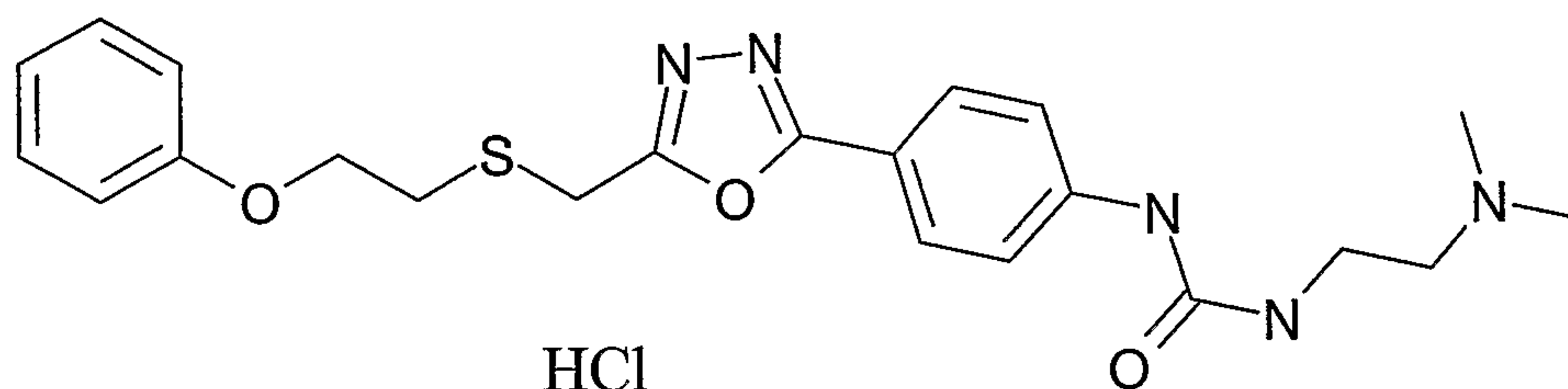
¹H NMR (DMSO-d₆) δ 8.84 (s, 1H), 7.82 (d, 2H, J=9 Hz), 7.69 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.44 (m, 4H), 3.02 (t, 2H, J=7 Hz), 1.54 (m, 6H). IR (CHCl₃, cm⁻¹) 3005, 2944, 2860, 1662, 1599, 1515, 1497, 1420, 1312, 1241, 1181. MS (ES⁺) m/e 439. MS (ES⁻) m/e 437. Anal. Calcd for C₂₃H₂₆N₄O₃S C, 62.99; H, 5.98; N, 12.78. Found C, 62.59; H, 5.87; N, 12.48. Analytical HPLC 99% purity. MP softening at 128°C then 132-134°C.

Example 105

Preparation of 1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea hydrochloride

25

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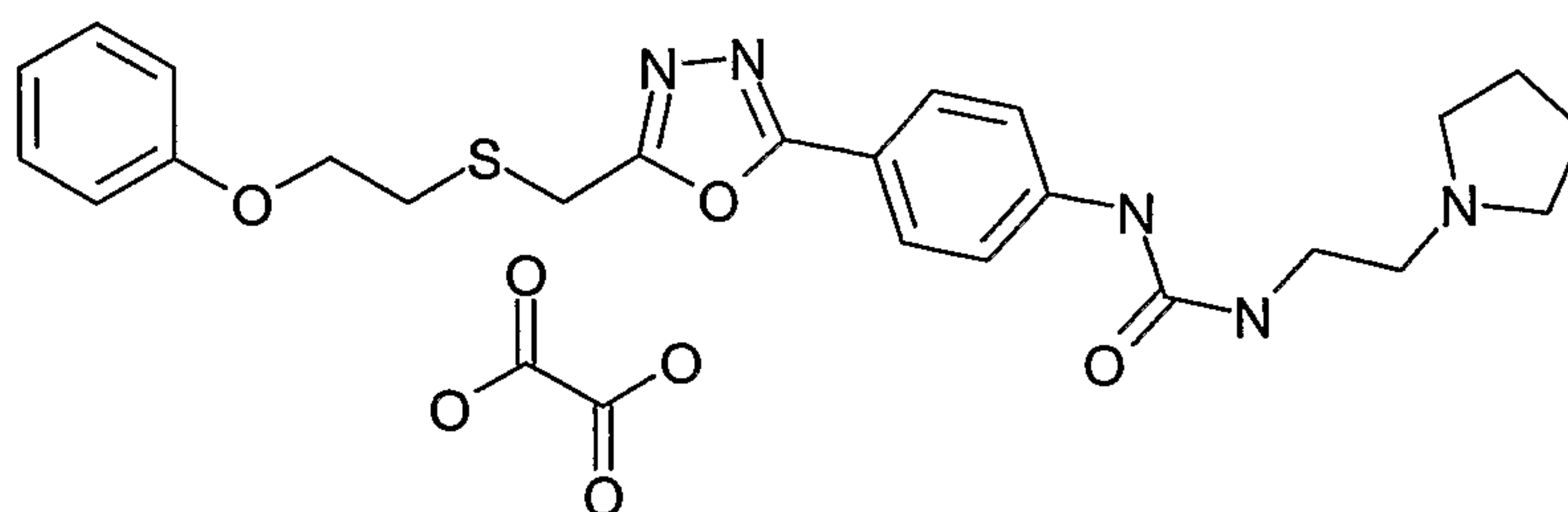


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (1.00 g, 2.5 mmol, 1 eq.) and *N,N*-dimethylethylenediamine (0.26 g, 3.0 mmol, 1.2 eq.) to afford 0.93 g (85%) of 1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as an orange oil following purification via silica gel flash chromatography using 10% 2M NH₃ in methanol in chloroform as the mobile phase. The free base was converted to the hydrochloride salt by adding 1.2 eq. of 4M HCl in 1,4-dioxane (0.33 mL) dropwise to an EtOAc solution of the free base (0.48 g). The resulting white solid was quickly collected by filtration and dried to give 0.26 g of 1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea hydrochloride as a white solid.

¹H NMR (DMSO-d₆) δ 10.06 (s, 1H), 9.70 (s, 1H), 7.84 (d, 2H, J=9 Hz), 7.64 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.94 (m, 4H), 4.19 (m, 4H), 3.48 (m, 2H), 3.18 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.82 (s, 6H). IR (CHCl₃, cm⁻¹) 3302, 3000, 1695, 1602, 1545, 1499, 1318, 1233, 1181. MS (ES⁺) m/e 442. MS (ES⁻) m/e 440. Anal. Calcd for C₂₂H₂₈ClN₅O₃S C, 55.28; H, 5.90; N, 14.65. Found C, 53.48; H, 5.62; N, 14.60. Analytical HPLC >99% purity.

Example 106

Preparation of 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea oxalate



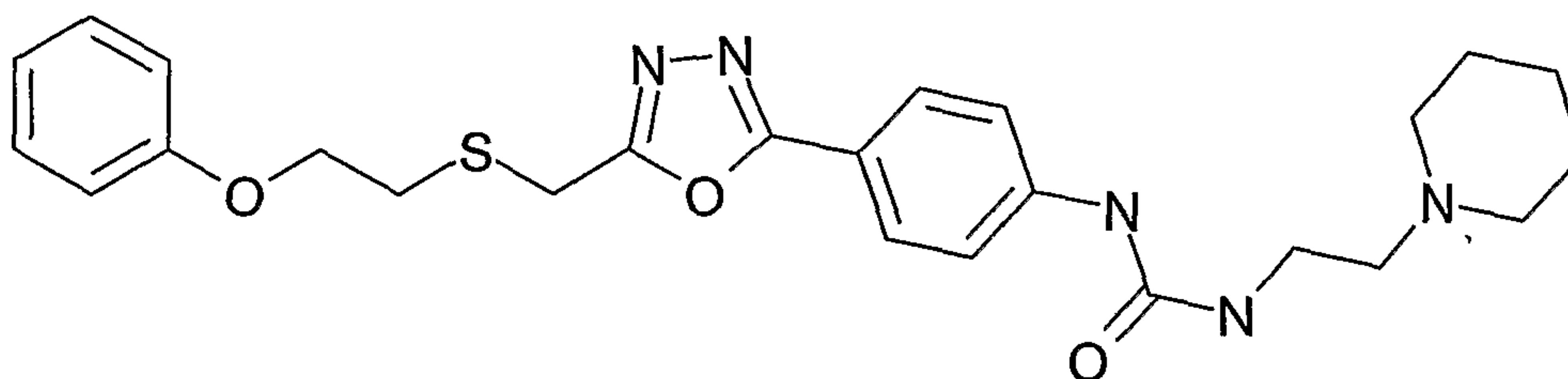
-237-

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and 1-(2-aminoethyl)pyrrolidine (0.27 g, 2.4 mmol, 1.2 eq.) to afford 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea as a light brown oil following purification via silica gel flash chromatography using 10% 2M NH₃ in methanol in diethyl ether as the mobile phase. The free base was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.20 g) in acetone to a warm acetone solution of the amine. After several minutes, a tan solid formed which was collected by filtration leaving 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea oxalate as an off-white solid.

¹H NMR (DMSO-d₆) δ 9.63 (s, 1H), 7.83 (d, 2H, J=9 Hz), 7.65 (d, 2H, J=9 Hz), 7.27 (m, 2H), 7.15 (m, 1H), 6.93 (m, 3H), 4.20 (m, 4H), 3.42 (m, 2H), 3.23 (m, 6H), 3.01 (t, 2H, J=7 Hz), 1.92 (m, 4H). IR (CHCl₃, cm⁻¹) 3345, 3230, 1689, 1599, 1541, 1498, 1243, 1224. MS (ES⁺) m/e 468. MS (ES⁻) m/e 466. Anal. Calcd for C₂₆H₃₁N₅O₇S C, 56.00; H, 5.60; N, 12.56. Found C, 55.52; H, 5.65; N, 12.09. Analytical HPLC 100% purity. MP 111-115°C.

Example 107

Preparation of 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.70 g, 1.75 mmol, 1 eq.) and 1-(2-aminoethyl)piperidine (0.27 g, 2.1 mmol, 1.2 eq.) to afford 0.79 g (94%) of 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea as a yellow oil following purification via silica gel flash chromatography using 10%

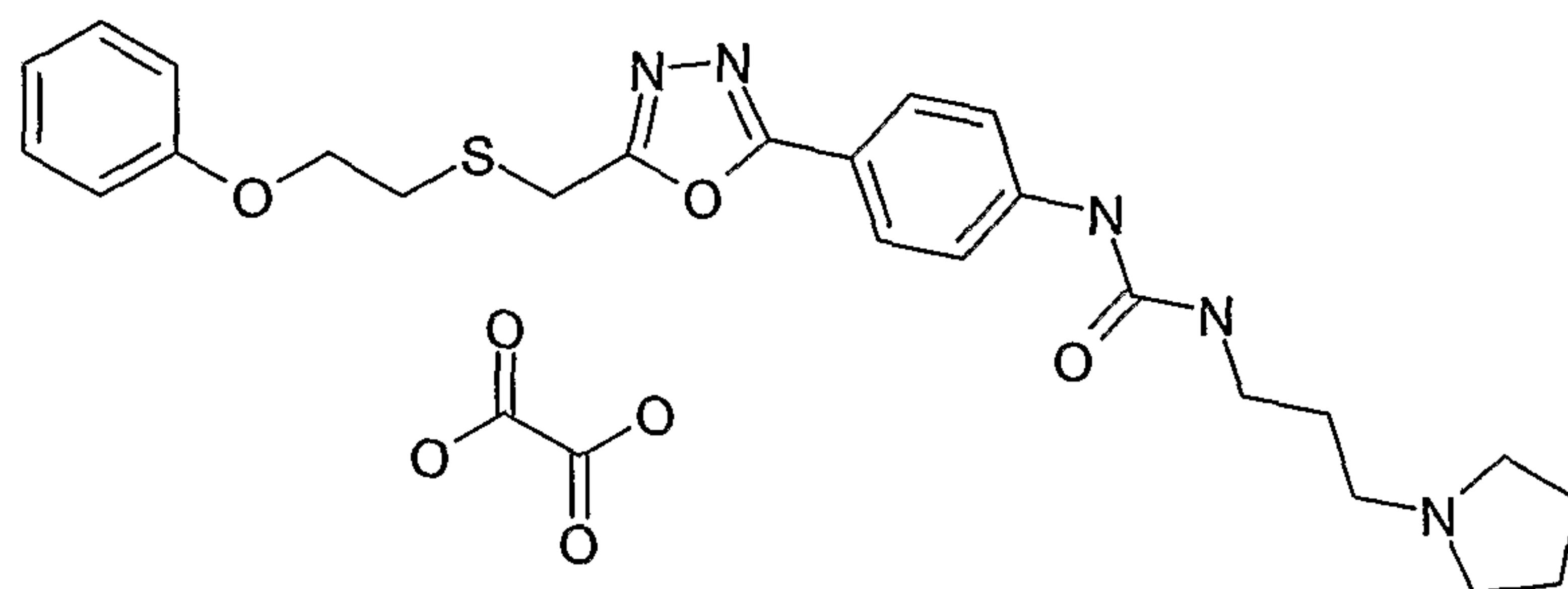
-238-

2M NH₃ in methanol in diethyl ether as the mobile phase. The oil was triturated with diethyl ether/ethyl acetate and the resulting solid collected by filtration leaving 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea (0.50 g) as a yellow solid.

5 ¹H NMR (DMSO-d₆) δ 9.09 (s, 1H), 7.82 (d, 2H, J=9 Hz), 7.59 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 6.20 (br m, 1H), 4.20 (m, 4H), 3.20 (m, 2H), 3.01 (t, 2H, J=7 Hz), 2.35 (m, 6H), 1.51 (m, 4H), 1.38 (m, 2H). IR (CHCl₃, cm⁻¹) 3418, 3358, 3008, 2942, 1690, 1602, 1499, 1244, 1180. MS (ES⁺) m/e 482. MS (ES⁻) m/e 480. Anal. Calcd for C₂₅H₃₁N₅O₃S C, 62.35; H, 6.49; N, 14.54. Found C, 62.07; H, 6.39; N, 14.33. Analytical
10 HPLC 100% purity. MP 126-128°C.

Example 108

Preparation of 1-{4-[5-(4-Phenoxy-butyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea oxalate



15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and 1-(3-aminopropyl)pyrrolidine (0.31 g, 2.4 mmol, 1.2 eq.) to afford 0.64 g (67%) of 1-{4-[5-(4-phenoxy-butyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea as a tan foam following purification via silica gel flash chromatography using 10% 2M NH₃ in methanol in diethyl ether as the mobile phase. The free base was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.13 g) in acetone to an acetone solution of the free base. The resultant solid was collected by filtration and crystallized from
20
25 methanol to afford 0.39 g of 1-{4-[5-(4-phenoxy-butyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea oxalate as an off-white solid.

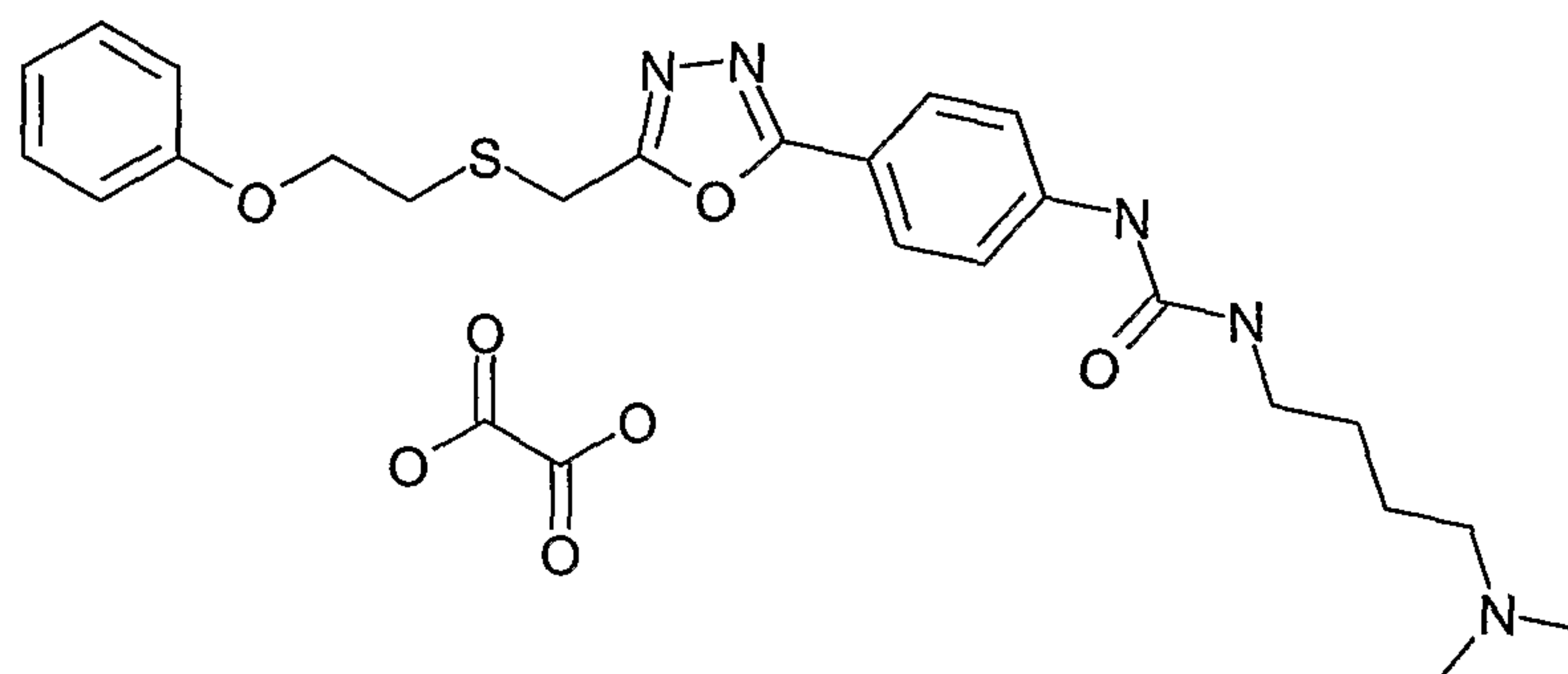
-239-

¹H NMR (DMSO-d₆) δ 9.44 (s, 1H), 7.82 (d, 2H, J=9 Hz), 7.63 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 4H), 4.20 (m, 4H), 3.17 (m, 8H), 3.01 (t, 2H, J=7 Hz), 1.92 (m, 4H), 1.81 (m, 2H). IR (KBr, cm⁻¹) 3364, 3293, 3041, 2932, 2877, 1691, 1600, 1541, 1497, 1417, 1316, 1236, 1179, 843, 757. MS (ES⁺) m/e 482. MS (ES⁻) m/e 480. Anal.

5 Calcd for C₂₇H₃₃N₅O₇S C, 56.73; H, 5.82; N, 12.25. Found C, 56.24; H, 6.08; N, 12.11. Analytical HPLC 97.8% purity. MP softening at 122°C then 126-128°C.

Example 109

Preparation of 1-(4-dimethylamino-butyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-
 10 [1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-
 [1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.87 g, 2.18 mmol, 1 eq.) with
 15 4-dimethylaminobutylamine (0.30g, 2.62 mmol, 1.2 eq.) to afford 1.0 g (98%) of 1-(4-dimethylamino-butyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as an orange oil following purification via silica gel flash chromatography using 10% 2M NH₃ in methanol in diethyl ether as the mobile phase. The free base was converted to the oxalate salt by adding 1.1 eq of oxalic acid in acetone to an acetone
 20 solution of the free base. The 1-(4-dimethylamino-butyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate (0.74 g) was collected by filtration leaving a yellow solid.

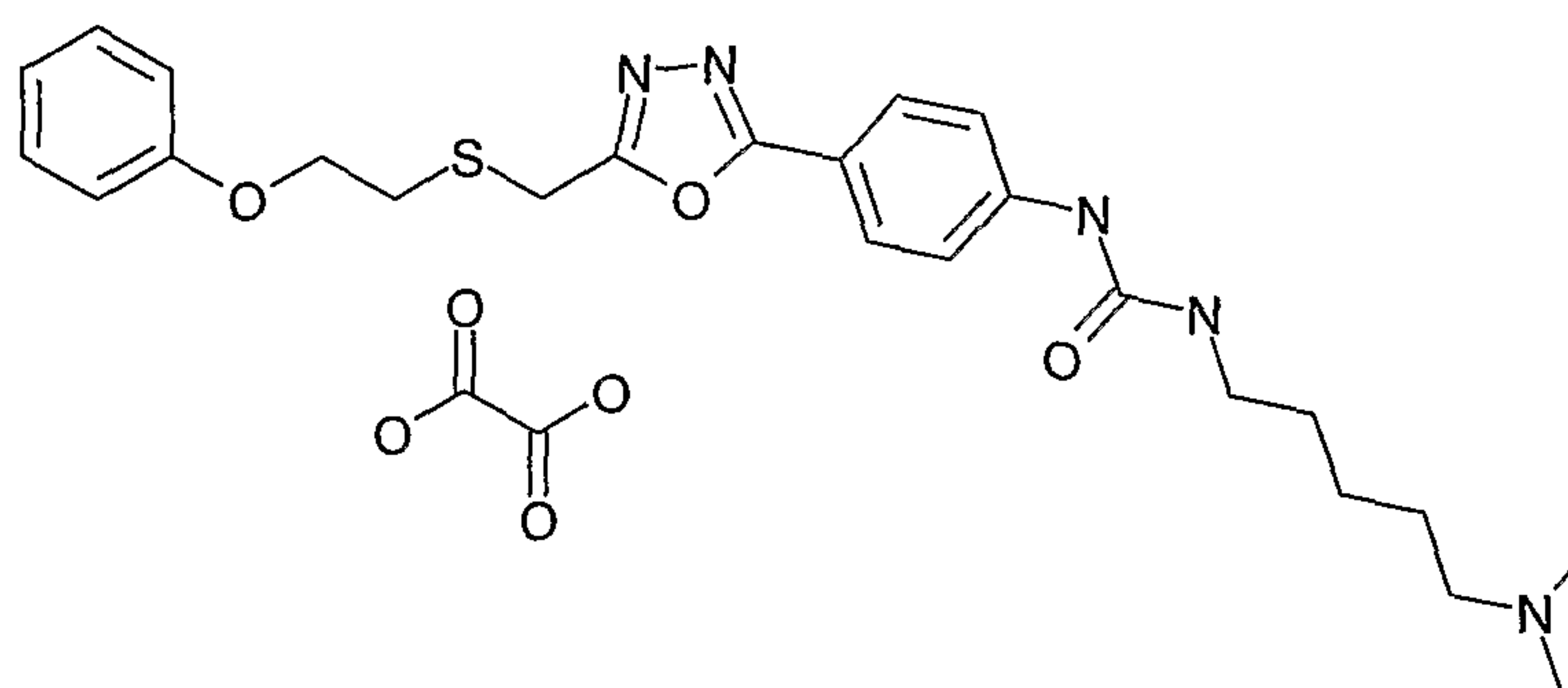
¹H NMR (DMSO-d₆) δ 9.54 (s, 1H), 7.81 (d, 2H, J=9 Hz), 7.64 (d, 2H, J=9 Hz), 7.27 (m, 2H), 7.11 (br t, 1H), 6.93 (m, 3H), 4.20 (m, 4H), 3.13 (m, 2H), 3.02 (m, 4H),
 25 2.74 (s, 6H), 1.65 (m, 2H), 1.47 (m, 2H). IR (CHCl₃, cm⁻¹) 3311, 3010, 1778, 1693, 1656, 1601, 1499, 1417, 1318, 1241, 1224, 1180. MS (ES⁺) m/e 470. MS(ES⁻) m/e 468.

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Anal. Calcd for $C_{26}H_{33}N_5O_7S$ C, 55.80; H, 5.94; N, 12.51. Found C, 54.87; H, 5.63; N, 12.30. Analytical HPLC 100% purity. MP softening at 60°C then 75-78°C.

EXAMPLE 110

- 5 Preparation of 1-(5-dimethylamino-pentyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate

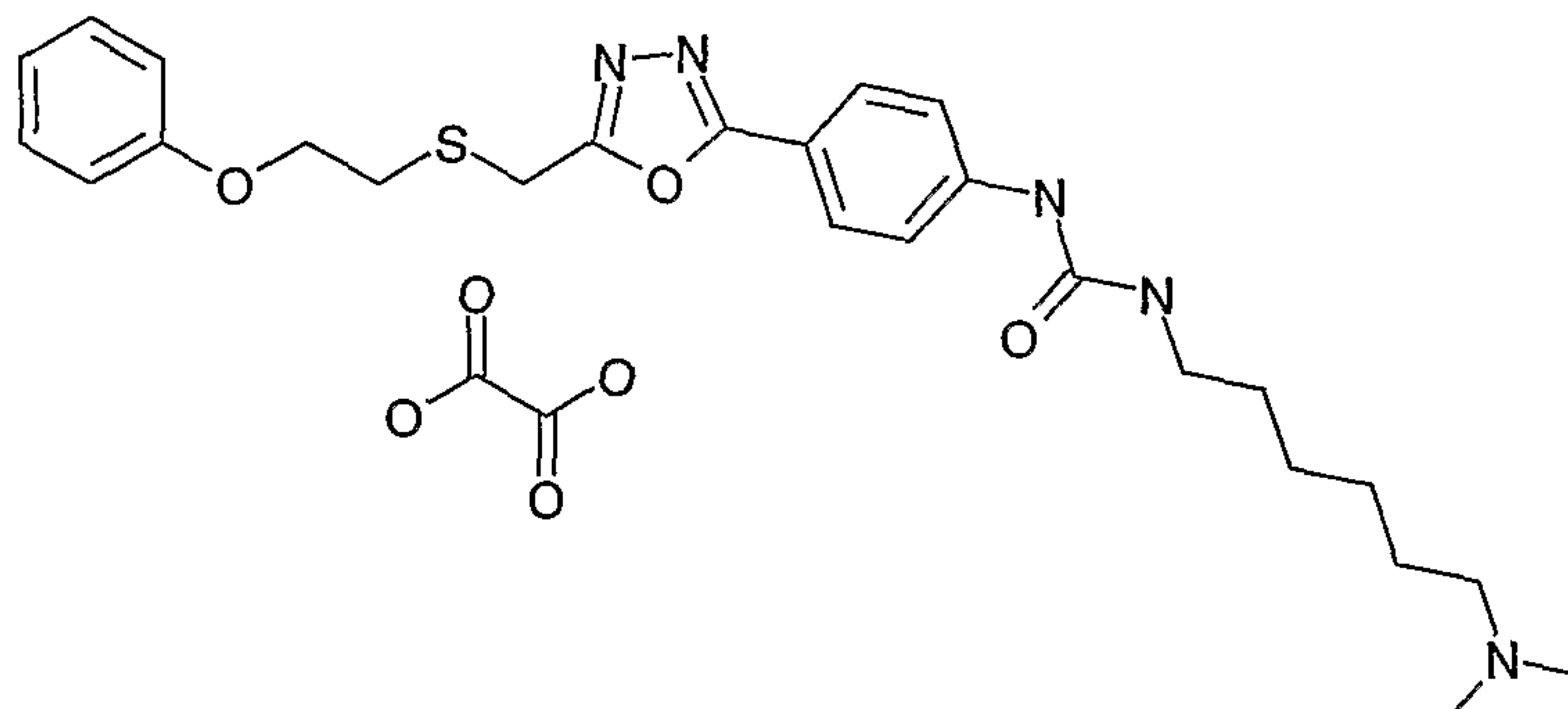


- The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) with 5-(dimethylamino)pentylamine (0.31 g, 2.4 mmol, 1.2 eq.) to afford 0.92 g (95%) of 1-(5-dimethylamino-pentyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a dark yellow oil following purification via silica gel flash chromatography using 7.5% 2M NH_3 in methanol in diethyl ether as the mobile phase.
- 15 The oil was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.19 g) in acetone to an acetone solution of the free base. The solid that formed was collected by filtration to afford 0.73 g of 1-(5-dimethylamino-pentyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate as an off-white solid.

- ^1H NMR ($DMSO-d_6$) δ 9.33 (s, 1H), 7.81 (d, 2H, $J=9$ Hz), 7.62 (d, 2H, $J=9$ Hz), 7.27 (m, 2H), 6.93 (m, 3H), 6.79 (br t, 1H), 4.19 (m, 4H), 3.10 (m, 2H), 3.01 (m, 4H), 2.73 (s, 6H), 1.63 (m, 2H), 1.47 (m, 2H), 1.31 (m, 2H). IR (KBr, cm^{-1}) 3394, 2937, 1696, 1600, 1541, 1499, 1416, 1405, 1318, 1233, 1179, 1083, 1032, 721. MS (ES^+) m/e 484. MS (ES^-) m/e 482. Anal. Calcd for $C_{27}H_{35}N_5O_7S$ C, 56.53; H, 6.15; N, 12.21. Found C, 56.47; H, 6.21; N, 11.98. MP softening at 77°C then 82-85°C.

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Preparation of 1-(6-dimethylamino-hexyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) with 6-(dimethylamino)hexylamine (0.35 g, 2.4 mmol, 1.2 eq.) to afford 0.97 g (98%) of 1-(6-dimethylamino-hexyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a dark yellow oil following purification via silica gel flash

chromatography using 7.5% 2M NH₃ in methanol in diethyl ether as the mobile phase. The oil was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.21 g) in acetone to an acetone solution of the free base. The solid that formed was collected by filtration to afford 0.94 g of 1-(6-dimethylamino-hexyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate as an off-white solid.

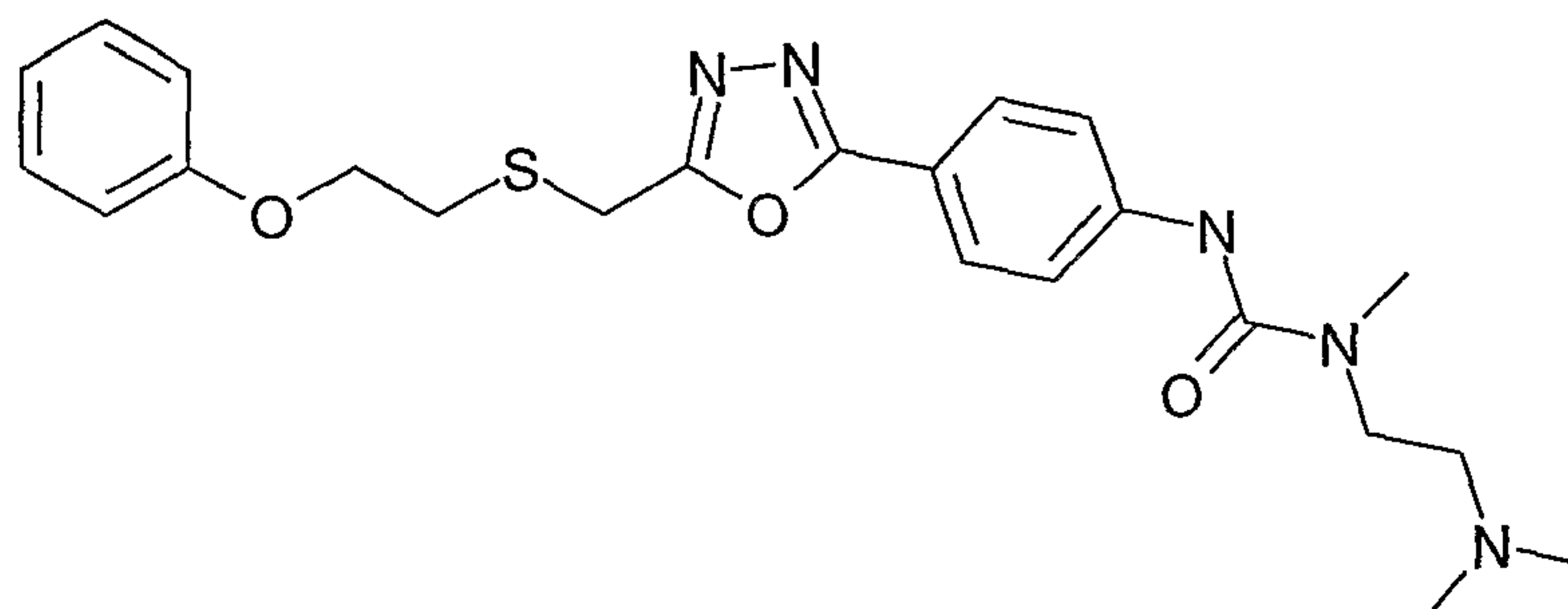
The solid was recrystallized from methanol/acetone to give an off-white crystalline solid.

¹H NMR (DMSO-d₆) δ 9.32 (s, 1H), 7.80 (d, 2H, J=9 Hz), 7.62 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 6.78 (br t, 1H), 4.20 (m, 4H), 3.09 (m, 2H), 2.99 (m, 4H), 2.72 (s, 6H), 1.59 (m, 2H), 1.44 (m, 2H), 1.31 (m, 4H). IR (KBr, cm⁻¹) 3334, 3041, 2931, 2859, 1690, 1600, 1543, 1498, 1244, 1179. MS (ES⁺) m/e 498. MS (ES⁻) m/e 496. Anal. Calcd for C₂₈H₃₇N₅O₇S C, 57.23; H, 6.35; N, 11.92. Found C, 56.55; H, 6.21; N, 11.69. Analytical HPLC 95% purity. MP softening at 100°C then 105-108°C.

Example 112

Preparation of 1-(2-dimethylamino-ethyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea

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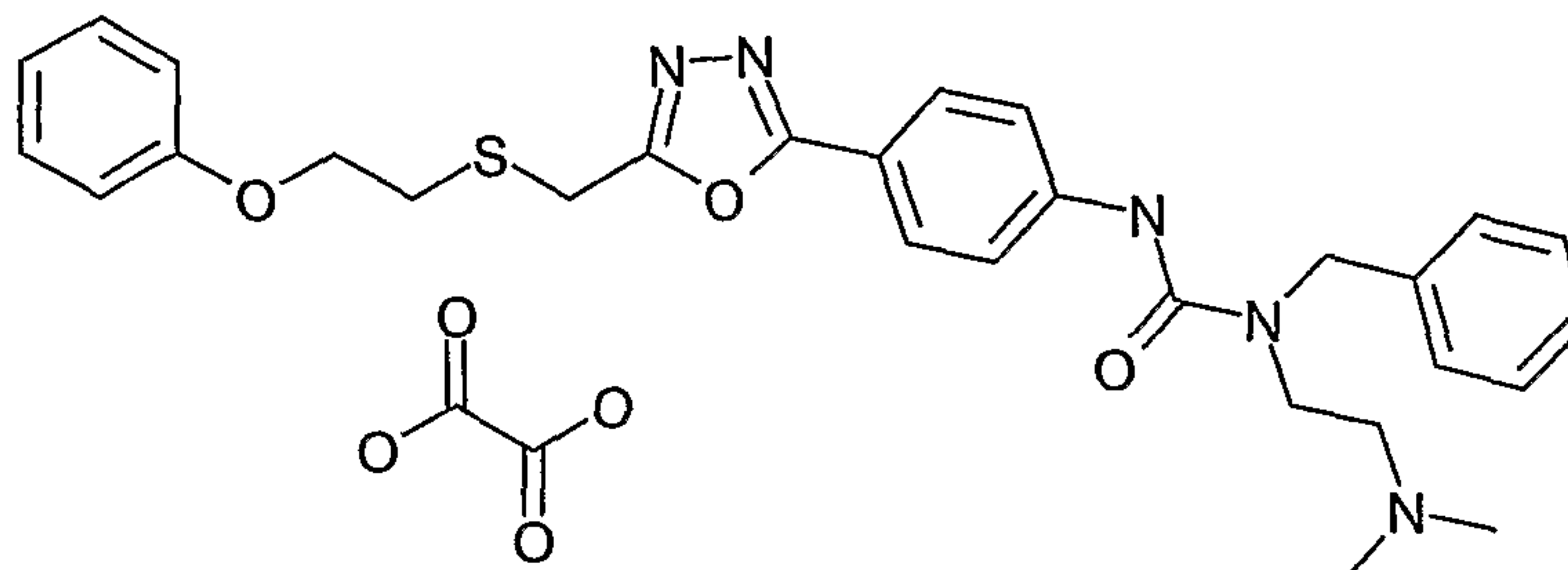


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and
 5 *N,N,N'*-trimethylethylenediamine (0.25 g, 2.4 mmol, 1.2 eq.) to afford 0.73 g (80%) of 1-(2-dimethylamino-ethyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a light yellow solid following purification via silica gel flash chromatography using 10% 2M NH₃ in methanol in diethyl ether as the mobile phase.

10 ¹H NMR (DMSO-d₆) δ 9.63 (s, 1H), 7.83 (d, 2H, J=9 Hz), 7.62 (m, 2H), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.40 (t, 2H, J=7 Hz), 3.02 (t, 2H, J=7 Hz), 2.95 (s, 3H), 2.45 (m, 2H), 2.24 (s, 6H). IR (CHCl₃, cm⁻¹) 3008, 2953, 2862, 2791, 1674, 1603, 1542, 1499, 1470, 1390, 1317, 1243, 1180. MS (ES⁺) m/e 456. MS (ES⁻) m/e 454. Anal. Calcd for C₂₃H₂₉N₅O₃S C, 60.64; H, 6.42; N, 15.37. Found C, 60.34; H, 6.29; N, 15.17.
 15 Analytical HPLC 99% purity. MP softening at 121°C then 134-135°C.

Example 113

Preparation of 1-benzyl-1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate



20 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-

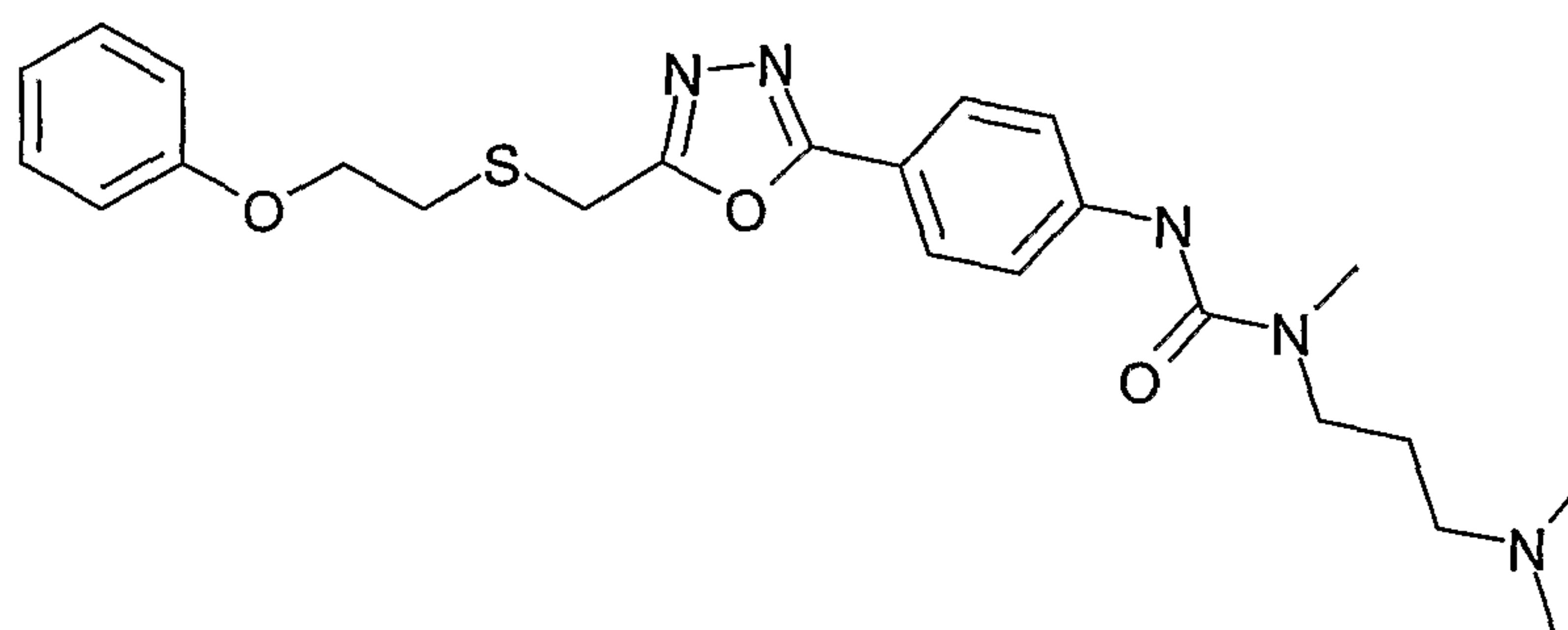
-243-

[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and *N*-benzyl-*N,N*-dimethylethylenediamine (0.43 g, 2.4 mmol, 1.2 eq.) to afford 0.89 g (84%) 1-benzyl-1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a yellow oil following purification via silica gel
 5 flash chromatography using 5% 2M NH₃ in methanol in diethyl ether as the mobile phase. The free base was converted to the oxalate salt by adding 1.2 eq. of oxalic acid (0.18 g) in acetone to an acetone solution of the free base. Addition of diethyl ether to the cloud point and cooling produced 0.98 g of 1-benzyl-1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate as an off-
 10 white solid.

¹H NMR (DMSO-d₆) δ 9.43 (s, 1H), 7.86 (d, 2H J=9 Hz), 7.73 (d, 2H, J=9 Hz), 7.38 (m, 2H), 7.28 (m, 5H), 6.93 (m, 3H), 4.69 (m, 2H), 4.19 (m, 4H), 3.58 (m, 2H), 3.09 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.69 (s, 6H). IR (CHCl₃, cm⁻¹) 3306, 3009, 1777, 1661, 1601, 1499, 1316, 1242, 1224. MS (ES⁺) m/e 532. MS(ES⁻) m/e 530. Anal. Calcd for
 15 C₃₁H₃₅N₅O₇S C, 59.89; H, 5.67; N, 11.26. Found C, 58.66; H, 5.32; N, 11.23. Analytical HPLC 98% purity. MP softening at 70°C then 72-76°C.

Example 114

Preparation of 1-(3-dimethylamino-propyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea
 20



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and
 25 *N,N,N'*-trimethyl-1,3-propanediamine (0.24 g, 2.1 mmol, 1.2 eq.). to afford 0.51 g (62%) of 1-(3-dimethylamino-propyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a crystalline orange solid following purification by

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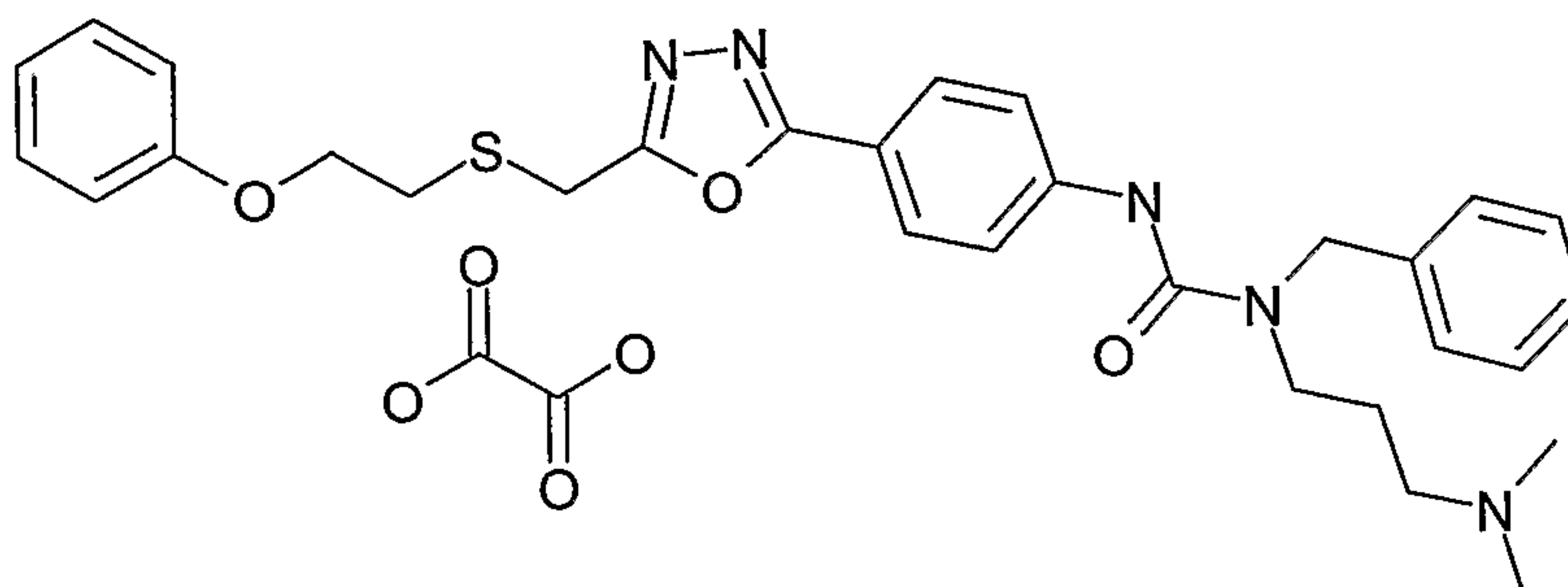
silica gel flash chromatography using 10% 2M NH₃ in methanol in chloroform as the mobile phase and recrystallization from EtOAc/Et₂O.

¹H NMR (DMSO-d₆) δ 9.66 (s, 1H), 7.83 (d, 2H, J=9 Hz), 7.62 (m, 2H), 7.27 (M, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.32 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.89 (s, 3H), 2.29 (m, 2H), 2.23 (s, 6H), 1.70 (m, 2H). IR (CHCl₃, cm⁻¹) 3008, 2950, 2827, 2787, 1665, 1604, 1498, 1229, 1179. MS (ES⁺) m/e 470. MS (ES⁻) m/e 468. Anal. Calcd for C₂₄H₃₁N₅O₃S C, 61.38; H, 6.65; N, 14.91. Found C, 60.75; H, 6.49; N, 14.43. Analytical HPLC 99% yield. MP softening at 114°C then transition at 116-118°C then melting at 136-139°C.

10

Example 115

Preparation of 1-benzyl-1-(3-dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate



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The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and *N*-Benzyl-*N,N*-dimethyl-propane-1,3-diamine (0.46 g, 2.4 mmol, 1.2 eq.) to afford 0.80 g (73%) of 1-benzyl-1-(3-dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as an orange oil following purification by silica gel flash chromatography using 5% 2M NH₃ in methanol in chloroform as the mobile phase. The free base was converted to the oxalate salt by adding 1.2 eq. of oxalic acid (0.14 g) in acetone to an acetone solution of the free base. Addition of diethyl ether to the resulting yellow solution and cooling produced 0.62 g of 1-benzyl-1-(3-dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate as a tan solid.

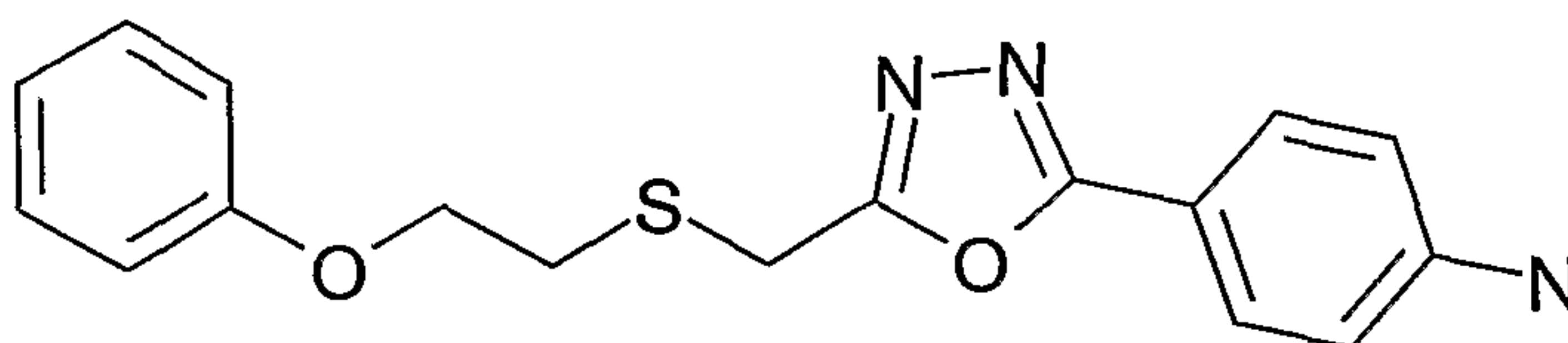
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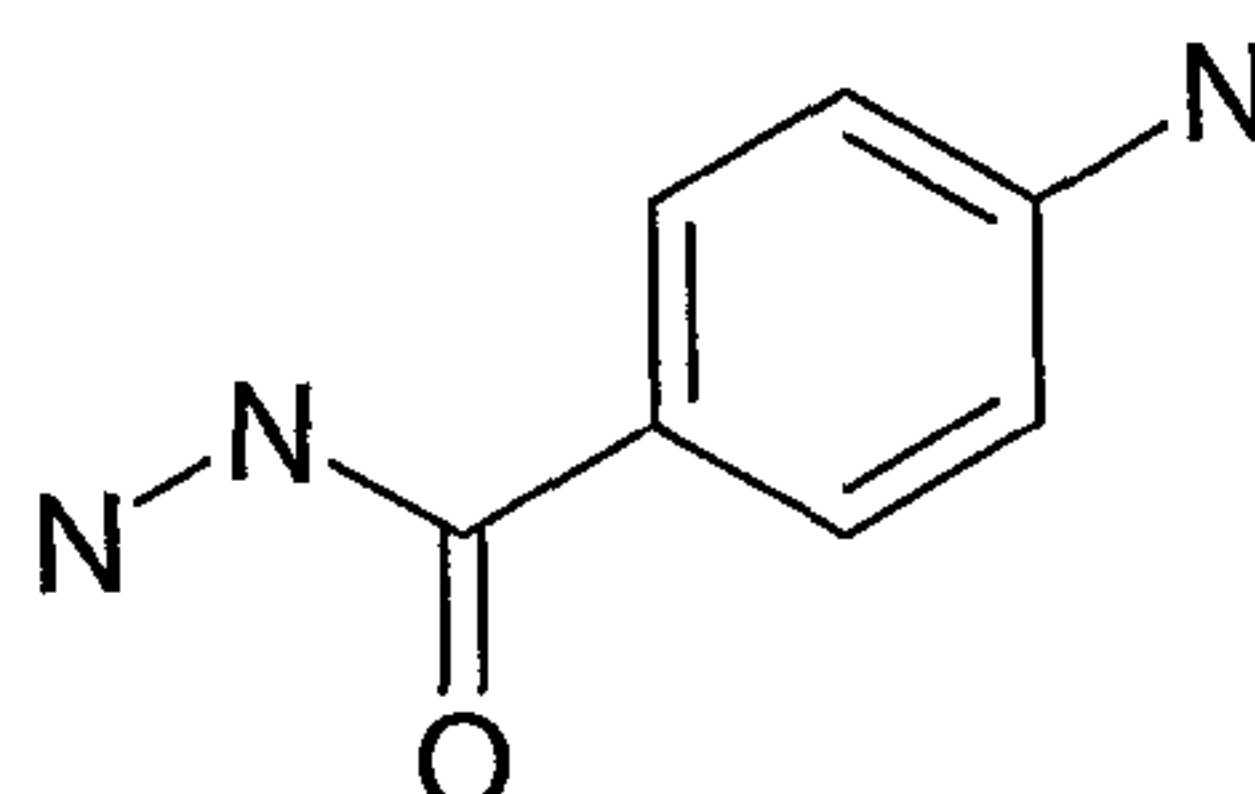
¹H NMR (DMSO-d₆) δ 9.03 (s, 1H), 7.85 (d, 2H, J=9 Hz), 7.75 (d, 2H, J=9 Hz), 7.37 (m, 2H), 7.27 (m, 5H), 6.93 (m, 3H), 4.66 (m, 2H), 4.19 (m, 4H), 3.37 (m, 2H), 3.00 (m, 4H), 2.69 (s, 6H), 1.88 (m, 2H). IR (KBr, cm⁻¹) 3435, 1723, 1653, 1599, 1524, 1498, 1234, 838, 703. MS (ES⁺) 546. MS (ES⁻) m/e 544. Anal. Calcd for C₃₂H₃₇N₅O₇S C, 60.46; H, 5.87; N, 11.02. Found C, 60.14; H, 5.60; N, 10.60. Analytical HPLC 99% purity. MP softening at 117°C then 159-164°C.

Example 116

Preparation of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine



a) 4-Amino-benzoic acid hydrazide

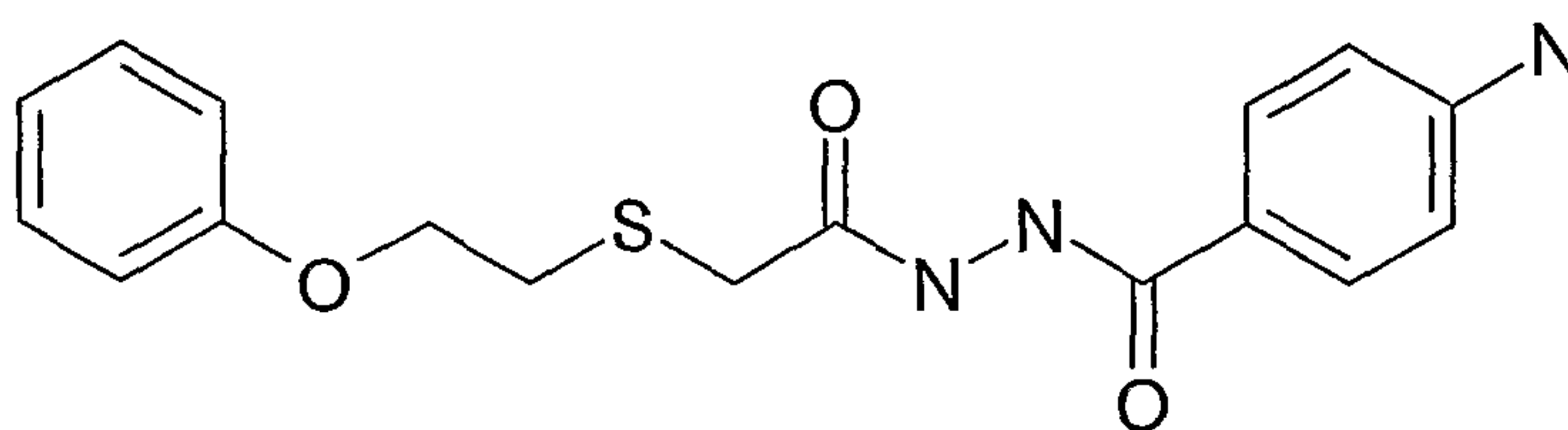


A solution of methyl 4-aminobenzoate (10 g, 66.15 mmol, 1 eq.) and hydrazine hydrate (40 mL) in absolute ethanol (120 mL) was allowed to reflux for 16 h. The solvent was removed in vacuo and the resulting off-white solid was triturated with hot ethyl acetate. The solid was collected by filtration to afford 9.1 g (91%) of 4-amino-benzoic acid hydrazide as an off-white solid.

¹H NMR (DMSO-d₆) δ 9.25 (s, 1H), 7.53 (d, 2H, J=9 Hz), 6.52 (d, 2H, J=9 Hz), 5.56 (s, 2H), 4.32 (s, 2H). IR (KBr, cm⁻¹) 3428, 3348, 3308, 3233, 1630, 1604, 1504, 1321, 1306, 958, 842. MS (ES⁺) m/e 152. MS (ES⁻) m/e 150. Anal. Calcd for C₇H₉N₃O C, 55.62; H, 6.00; N, 27.80. Found C, 55.93; H, 6.21; N, 27.53.

b) 4-Amino-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide

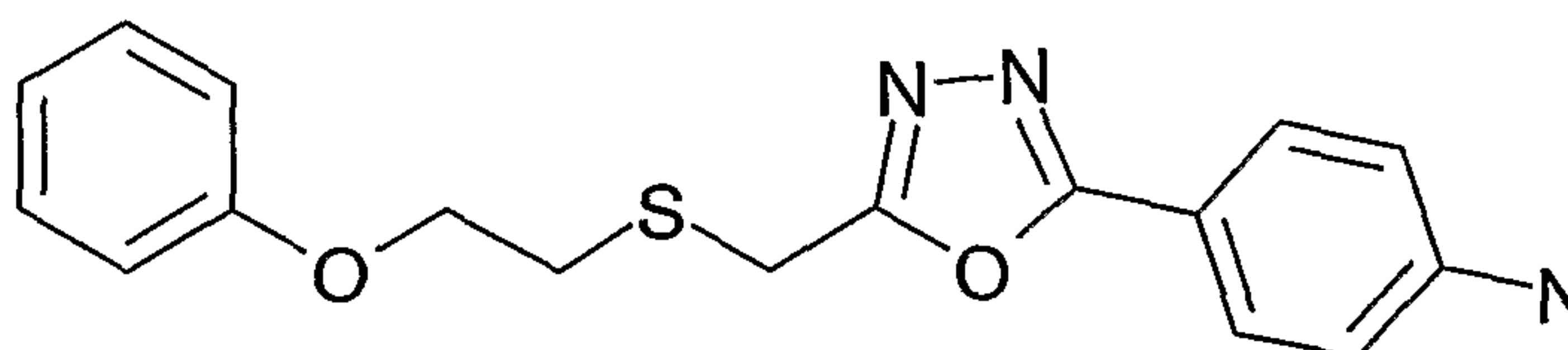
-246-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101c, from (2-phenoxyethylthio)acetic acid (4.25 g, 20.0 mmol, 1 eq.) and 4-amino-benzoic acid hydrazide (3.33 g, 22.0 mmol, 1.1 eq.) to afford 5.85 g (85%) of 4-amino-benzoic acid *N'*-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide as a yellow foam following purification by silica gel flash chromatography using a step gradient of acetone in hexane as the mobile phase.

¹H NMR (DMSO-d₆) δ 9.91 (s, 2H), 7.60 (d, 2H, J=9 Hz), 7.28 (m, 2H), 6.95 (m, 3H), 6.55 (d, 2H, J=9 Hz), 4.19 (t, 2H, J=7 Hz), 3.31 (s, 2H), 3.03 (t, 2H, J=9 Hz). IR (KBr, cm⁻¹) 3450, 3357, 3268, 3214, 1696, 1627, 1611, 1592, 1562, 1482, 1291, 1242, 1173, 837. MS (ES⁺) m/e 346. MS (ES⁻) m/e 344. Anal. Calcd for C₁₇H₁₉N₃O₃S C, 59.11; H, 5.54; N, 12.16. Found C, 59.13; H, 5.79; N, 12.09.

c) 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine



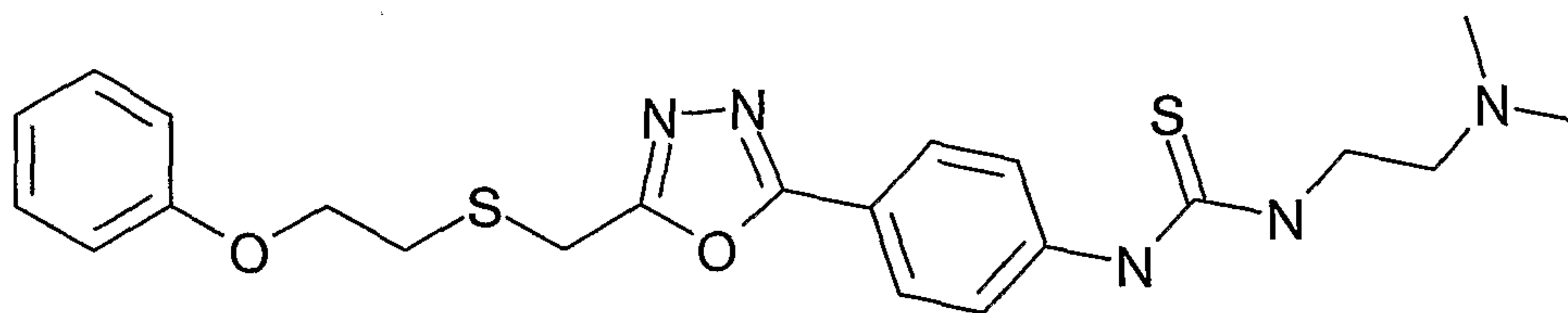
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101d, from 4-amino-benzoic acid *N'*-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide (11.42 g, 33.06 mmol) to afford 10.77 g (99%) of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine as a yellow solid following purification by silica gel flash chromatography using a step gradient of ethyl acetate in hexane as the mobile phase.

¹H NMR (DMSO-d₆) δ 7.60 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 6.66 (d, 2H, J=9 Hz), 5.93 (m, 2H), 4.18 (m, 4H), 3.00 (t, 2H, J=7 Hz). IR (CHCl₃, cm⁻¹) 3011, 1624, 1610, 1501, 1243, 1180. MS (ES⁺) m/e 328. Anal. Calcd for C₁₇H₁₇N₃O₂S C, 62.37; H, 5.23; N, 12.83. Found C, 61.61; H, 5.12; N, 12.50. Analytical HPLC 97.8% purity. MP 126-130°C.

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Example 117

Preparation of 1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-thiourea



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A solution of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine (5.21 g, 15.92 mmol, 1 eq., prepared in Example 119) in anhydrous acetonitrile was treated with 1,1'-thiocarbonyldiimidazole (3.15 g, 15.92 mmol, 1 eq.) as a solid and stirred at room temperature for 16 h. The solvent was removed *in vacuo* leaving imidazole-1-carbothioic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide as a brown oil. A portion of one-half of this material (7.96 mmol) was dissolved in anhydrous DMF and treated with *N,N*-dimethylethylenediamine (0.84 g, 9.55 mmol, 1.2 eq.). The resulting mixture was heated at 100°C for 1.5 h, cooled, then diluted with EtOAc and washed with 50% brine. The organic layer was collected, dried over MgSO₄, filtered, and the solvent removed *in vacuo* leaving a yellow oil. The residue was purified by preparative HPLC to afford 2.33 g (64%) of 1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-thiourea as a yellow oil which later crystallized. A portion of material was recrystallized from ethyl acetate to afford an off-white solid.

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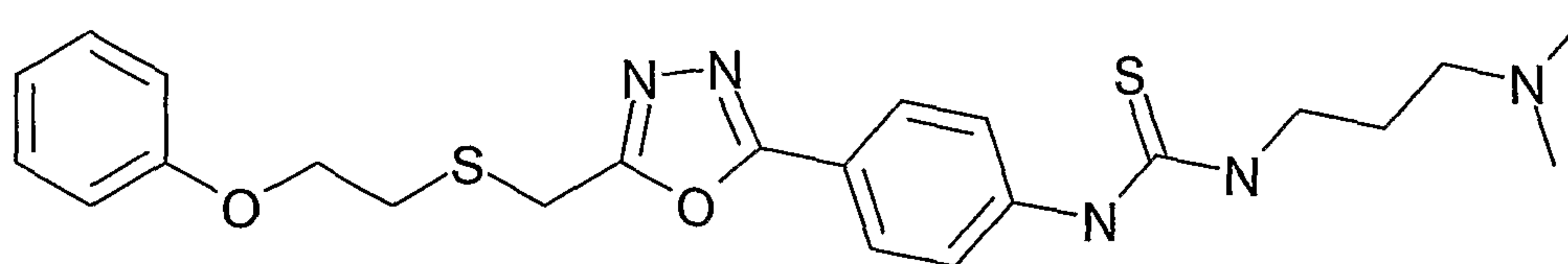
¹H NMR (DMSO-d₆) δ 10.06 (s, 1H), 7.84 (m, 5H), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.56 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.45 (m, 2H), 2.20 (s, 6H). IR (CHCl₃, cm⁻¹) 3429, 3407, 3007, 2982, 2956, 2829, 2781, 1731, 1614, 1601, 1497, 1337, 1243, 1173. MS (ES⁺) m/e 458. MS (ES⁻) m/e 456 Anal. Calcd for C₂₂H₂₇N₅O₂S₂ C, 57.74; H, 5.95; N, 15.30. Found C, 57.60; H, 5.88; N, 14.89. Analytical HPLC 96.9% purity. MP 155-158°C.

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Example 118

Preparation of 1-(3-dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-thiourea

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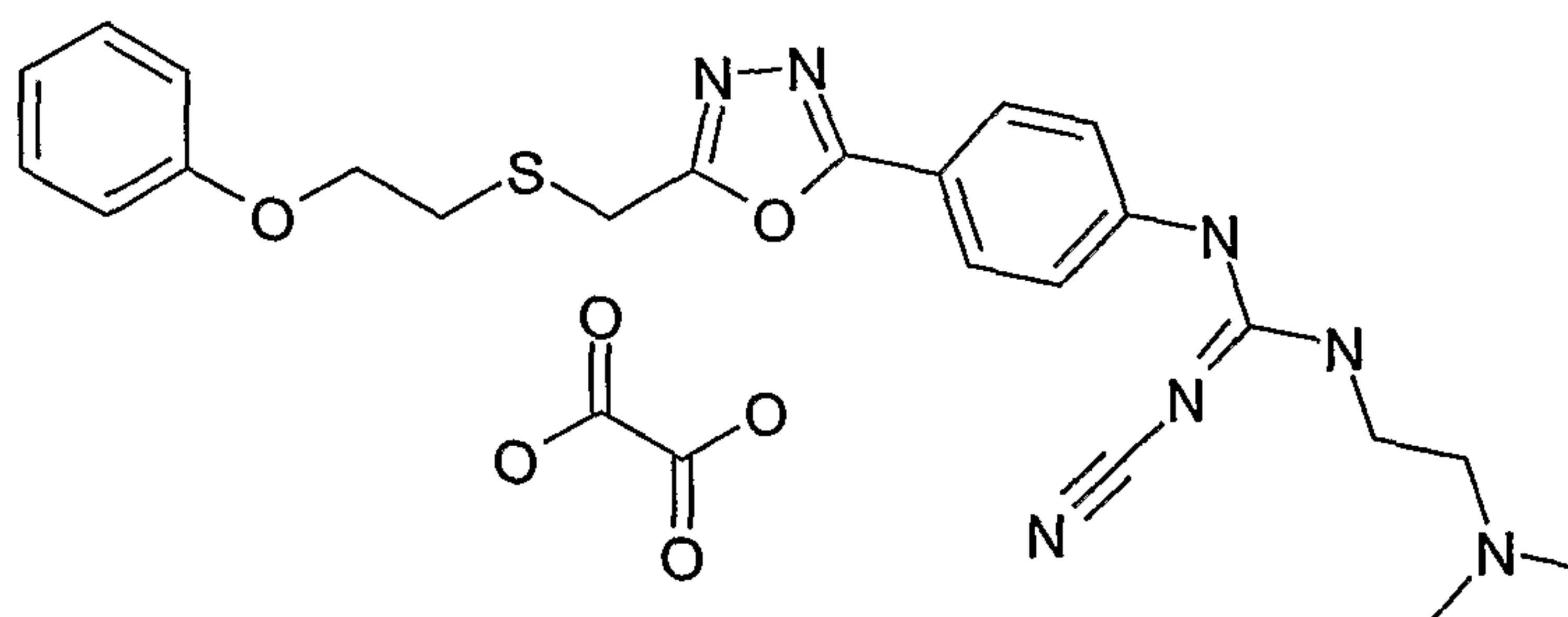
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 117, from {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide (7.96 mmol, 1 eq) and 3-

5 dimethylaminopropylamine (0.98 g, 9.55 mmol, 1.2 eq.) to afford 2.87 g (77%) of 1-(3-dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-thiourea as a yellow oil which started to crystallize following purification by preparative HPLC. A small portion was recrystallized from ethyl acetate giving an off-white solid.

10 ^1H NMR (DMSO- d_6) δ 9.86 (s, 1H), 8.25 (s, 1H), 7.89 (d, 2H, $J=9$ Hz), 7.70 (d, 2H, $J=9$ Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.50 (m, 2H), 3.02 (t, 2H, $J=7$ Hz), 2.21 (t, 2H, $J=7$ Hz), 2.10 (s, 6H), 1.68 (m, 2H). IR (CHCl_3 , cm^{-1}) 3411, 2980, 2952, 2862, 2827, 2787, 1615, 1601, 1588, 1532, 1499, 1469, 1307, 1242. MS (ES^+) m/e 472. MS (ES^-) m/e 470. Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{N}_5\text{O}_2\text{S}_2$ C, 58.57; H, 6.20; N, 14.85. Found C, 59.11; H, 6.49; N, 14.85. Analytical HPLC 97.9% purity. MP 136-139°C.

Example 119

Preparation of *N*-(2-dimethylamino-ethyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine oxalate



20 Diphenyl cyanocarbonimidate (1.53 g, 6.42 mmol, 1.05 eq.) was added to a yellow solution of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine (2.0 g, 6.11 mmol, 1 eq., prepared in Example 116) in 50 mL of anhydrous acetonitrile. The resultant solution heated at reflux for 16 h. The solvent was removed in vacuo to

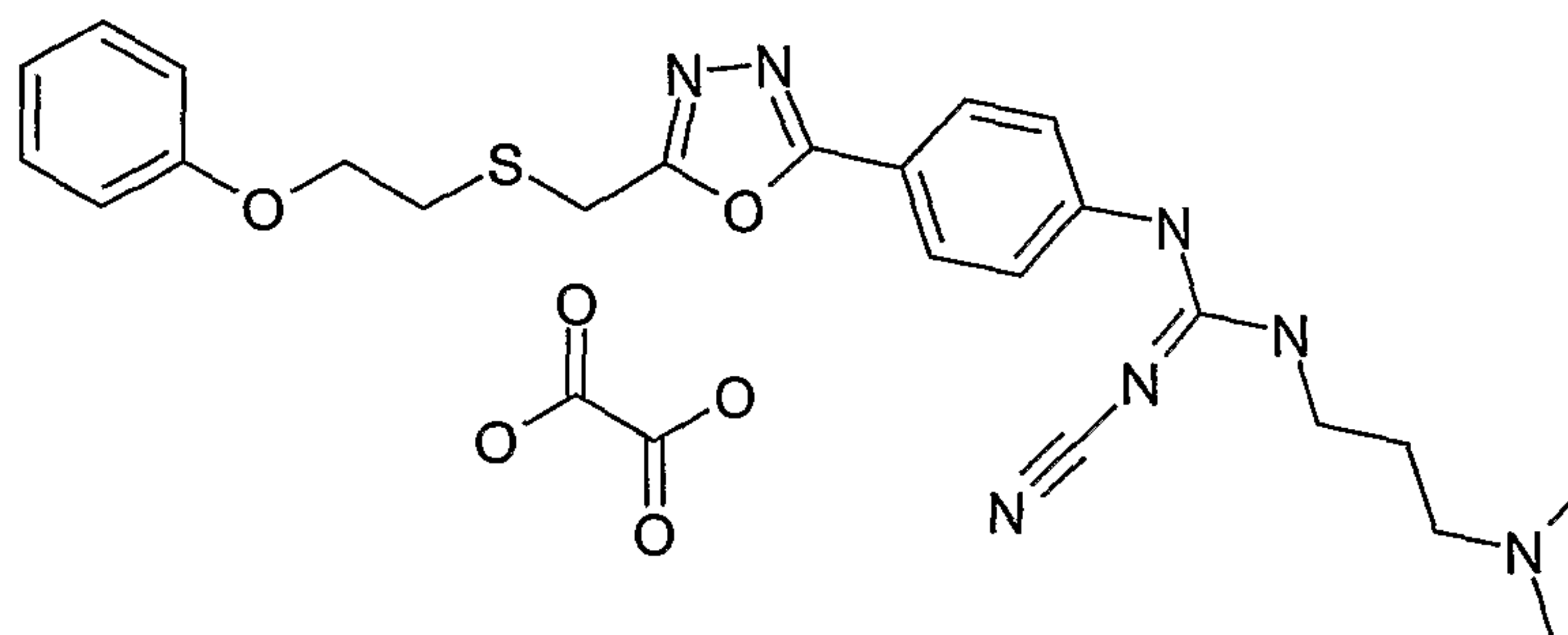
-249-

afford a yellow oil that solidified on standing. The solid was triturated with diethyl ether to afford the corresponding carbamimidic acid phenyl ester (1.78 g, 62% yield) as a yellow solid (MS for carbamimidic acid phenyl ester (ES⁻) m/e 470). *N,N*-dimethylethylenediamine (1.87 g, 21.2 mmol, 20 eq.) was added to a solution of this carbamimidic acid phenyl ester (0.50 g, 1.06 mmol, 1 eq.) in isopropanol, then heated to reflux. After 5 h, the reaction was cooled, diluted with ethyl acetate, and washed with aqueous sodium bicarbonate. The organic layer was collected, dried over MgSO₄, filtered, and the solvent removed *in vacuo* to afford an orange oil. The oil was purified by silica gel flash chromatography using 10% 2M NH₃ in methanol in diethyl ether as the mobile phase to afford 0.14 g (29%) of *N*-(2-dimethylamino-ethyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine as an off-white solid. The free base was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.03 g) in acetone to an acetone solution of the base to afford 0.13 g of *N*-(2-dimethylamino-ethyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine oxalate as a tan solid.

¹H NMR (DMSO-d₆) δ 10.04 (s, 1H), 7.93 (m, 3H), 7.48 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.19 (m, 4H), 3.02 (m, 4H), 2.81 (t, 2H, J=7 Hz), 2.73 (s, 6H). IR (KBr, cm⁻¹) 3404, 3302, 3040, 2174, 1720, 1618, 1598, 1562, 1500, 1461, 1243, 1010. MS (ES⁺) m/e 466. MS (ES⁻) m/e 464. Anal. Calcd for C₂₅H₂₉N₇O₆S C, 54.04; H, 5.26; N, 17.65. Found C, 51.71; H, 5.70; N, 14.23. Analytical HPLC 95.7% purity. MP softening at 138°C then decomposition at 145-147°C.

Example 120

Preparation of *N*-(3-dimethylamino-propyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine oxalate



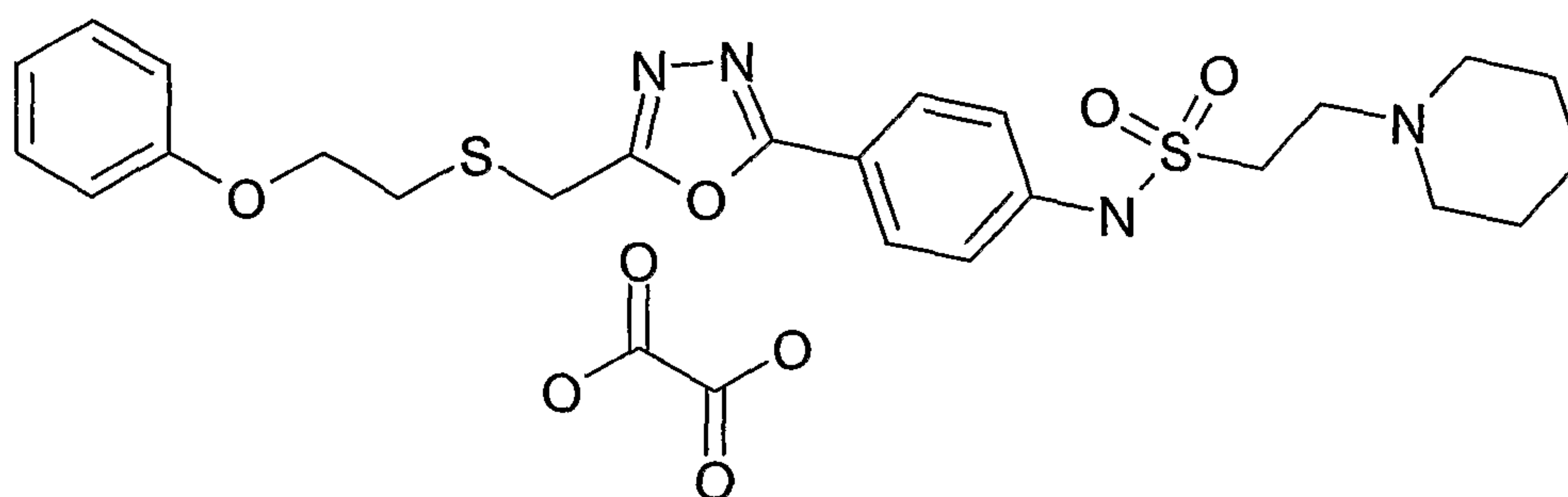
-250-

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 119, from the carbamimidic acid phenyl ester (1.2 g, 2.54 mmol, 1 eq.) and 3-dimethylaminopropylamine (5.19 g, 50.8 mmol, 20 eq.) to afford 0.22 g (18%) of *N*-(3-dimethylamino-propyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine as an off-white solid. The free base was converted to the oxalate salt as described to afford 0.20 g of *N*-(3-dimethylamino-propyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine oxalate as a white solid.

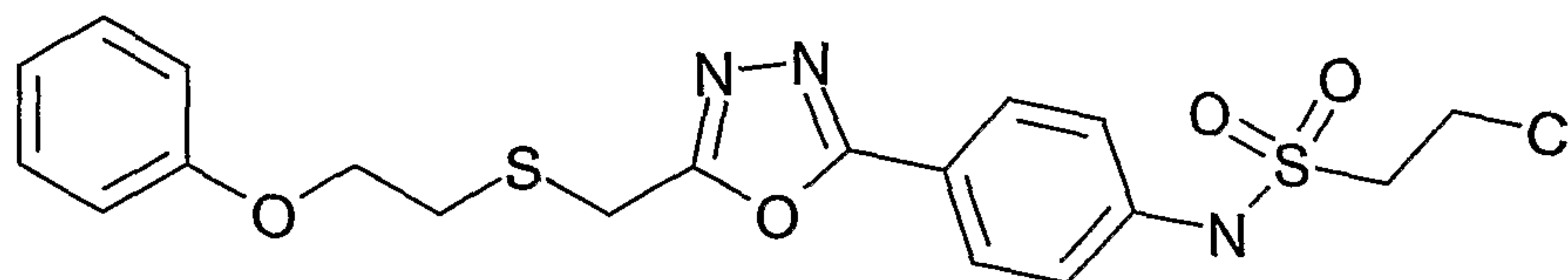
¹H NMR (DMSO-d₆) δ 9.78 (s, 1H), 7.92 (m, 3H), 7.47 (d, 2H, J=9 Hz), 7.28 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.33 (m, 2H), 3.02 (m, 4H), 2.73 (s, 6H), 1.88 (m, 2H). IR (KBr, cm⁻¹) 3316, 3255, 2171, 1720, 1600, 1500, 1237, 755, 720. MS (ES⁺) m/e 480. MS (ES⁻) m/e 478. Anal. Calcd for C₂₆H₃₁N₇O₆S C, 54.82; H, 5.49; N, 17.21. Found C, 53.91; H, 5.43; N, 16.76. Analytical HPLC 100% purity. MP softening at 110°C then decomposition from 130-134°C.

Example 121

Preparation of 2-piperidin-1-yl-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide oxalate



a) Preparation of 2-chloro-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide



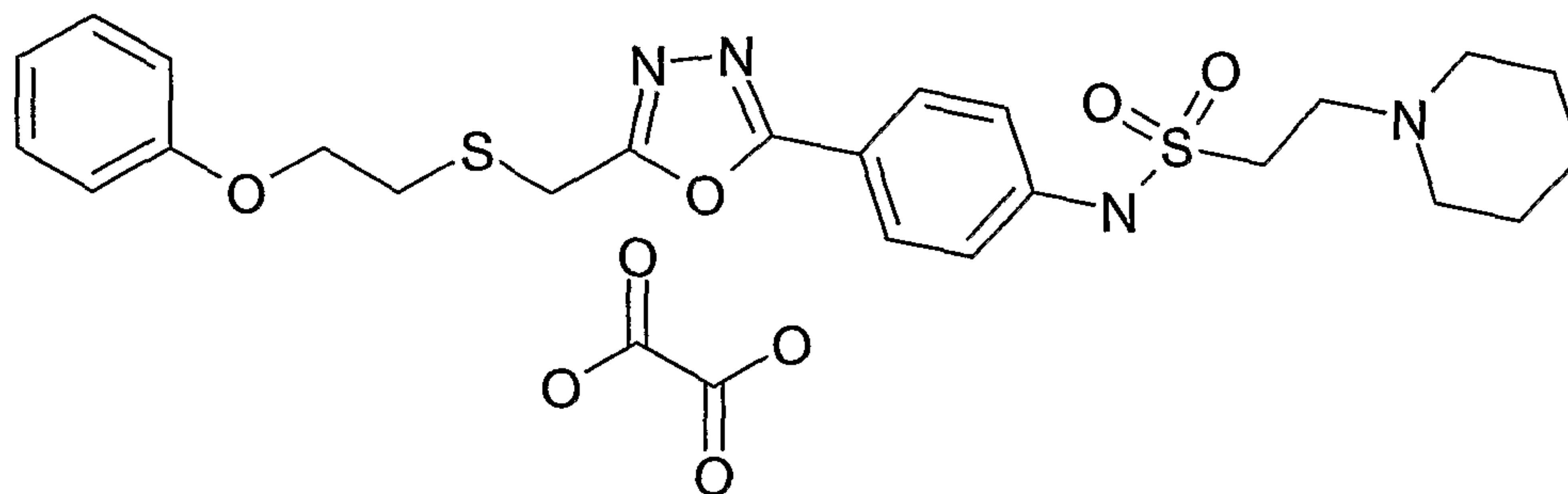
A solution of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine (3.0 g, 9.16 mmol, 1 eq.) in anhydrous CH₂Cl₂ was treated with

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triethylamine (1.39 g, 13.74 mmol, 1.5 eq.) and 2-chloro-1-ethanesulfonyl chloride (1.79 g, 10.99 mmol, 1.2 eq.). The reaction was allowed to stir at room temperature for 16 h, then was quenched with water and the organic layer removed. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over
 5 MgSO₄, filtered, and concentrated to afford an orange oil. The oil was purified by silica gel flash chromatography using a step gradient of ethyl acetate in hexane as the mobile phase to afford 0.97 g (23%) of 2-chloro-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide as an off-white solid.

¹H NMR (DMSO-d₆) δ 8.06 (d, 2H, J=8 Hz), 7.57 (d, 2H, J=9 Hz), 7.28 (m, 3H),
 10 6.91 (m, 3H), 6.44 and 6.41 (m, 2H total), 6.32 and 6.27 (m, 2H total), 4.25 (s, 2H), 4.18 (t, 2H, J=7 Hz), 3.03 (t, 2H, J=7 Hz). IR (CHCl₃, cm⁻¹) 1602, 1491, 1384, 1217, 1163, 916. MS (ES⁻) m/e 416 [M-Cl]⁻. Anal. Calcd for C₁₉H₂₀ClN₃O₄S C, 50.27; H, 4.44; N, 9.26. Found C, 49.71; H, 4.15; N, 8.27.

15 b) Preparation of 2-piperidin-1-yl-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide oxalate



2-Chloro-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-
 [1,3,4]oxadiazol-2-yl]-phenyl}-amide (0.91 g, 2.0 mmol, 1 eq.) in anhydrous DMF was
 20 treated with sodium bicarbonate (0.50 g, 6.0 mmol, 3 eq.) and sodium iodide (0.03 g, 0.2 mmol, 0.1 eq.) followed by piperidine (0.51 g, 6.0 mmol, 3 eq.). The reaction was then heated to 90°C and allowed to stir at that temperature for 16 h. The reaction was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over MgSO₄, filtered, and the solvent removed in vacuo
 25 leaving an orange oil which was purified by silica gel flash chromatography using 10% 2M NH₃ in methanol in diethyl ether as the mobile phase to afford 0.95 g (94%) of 2-piperidin-1-yl-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-

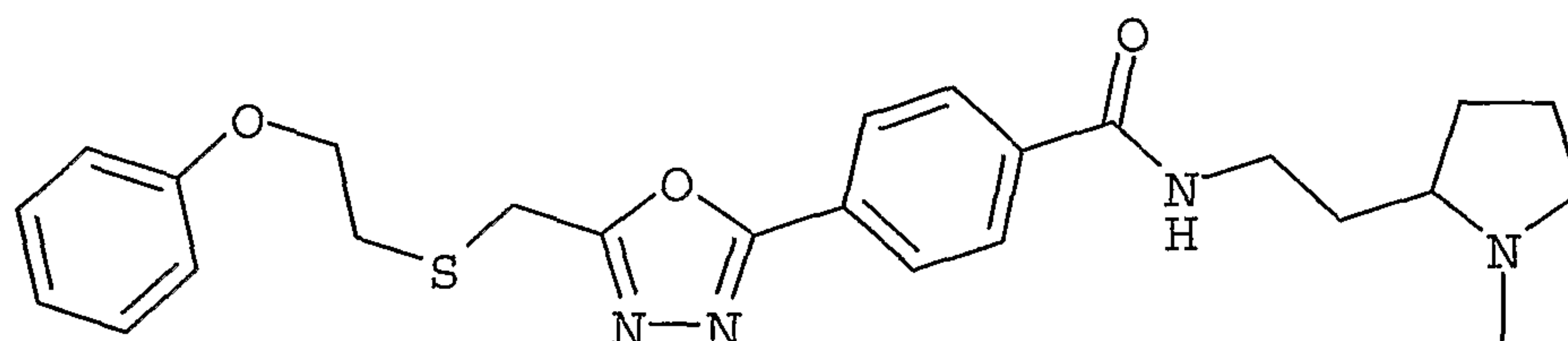
-252-

[1,3,4]oxadiazol-2-yl]-phenyl}-amide as a yellow oil. The free base was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.19 g) in acetone dropwise to an acetone solution of the free base. The resulting white precipitate was collected by filtration and crystallized from methanol to afford 0.48 g of 2-piperidin-1-yl-ethanesulfonic acid {4-[5-
 5 (2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide oxalate as a crystalline white solid.

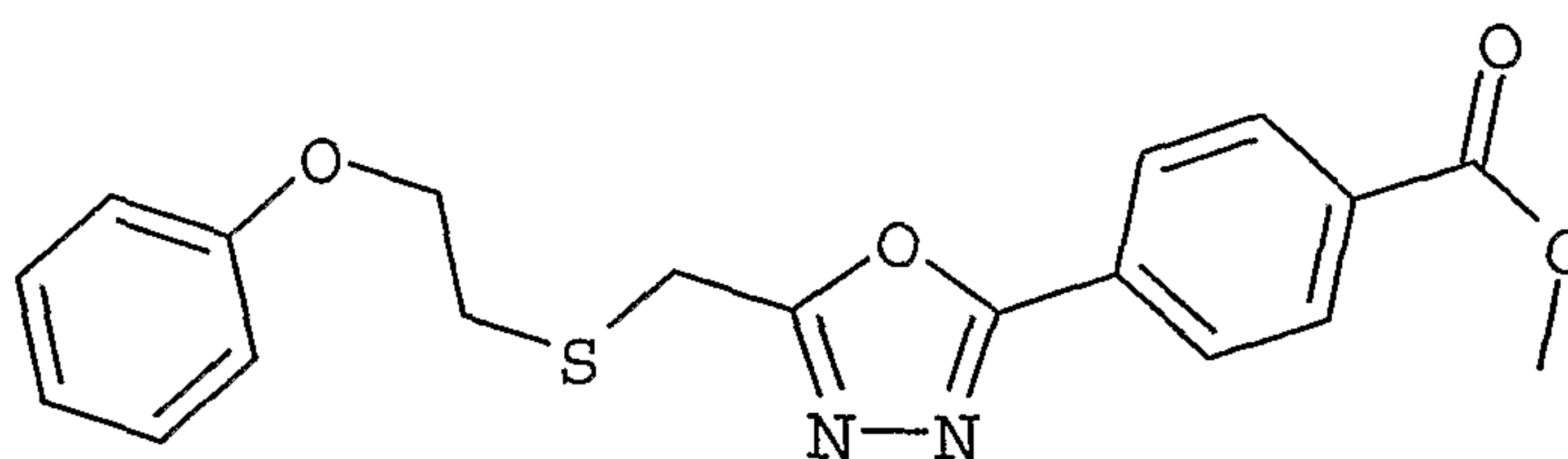
¹H NMR (DMSO-d₆) δ 7.93 (d, 2H, J=9 Hz), 7.39 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.19 (m, 4H), 3.62 (m, 2H), 3.14 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.82 (m, 4H), 1.57 (m, 4H), 1.41 (m, 2H). IR (KBr, cm⁻¹) 3409, 1617, 1344, 1243, 1159, 916,
 10 759, 705. MS (ES⁺) m/e 503. MS (ES⁻) m/e 501. Anal. Calcd for C₂₆H₃₂N₄O₈S₂ C, 52.69; H, 5.44; N, 9.45. Found C, 52.44; H, 5.46; N, 9.37. Analytical HPLC 99.6% purity. MP softening at 159°C then 162-166 °C.

Example 122

15 Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[(2-(N-methylpyrrolidin-2-yl)ethyl)amino)carbonyl]phenyl}-1,3,4-oxadiazole



a) 2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(methoxycarbonyl)phenyl]-1,3,4-oxadiazole



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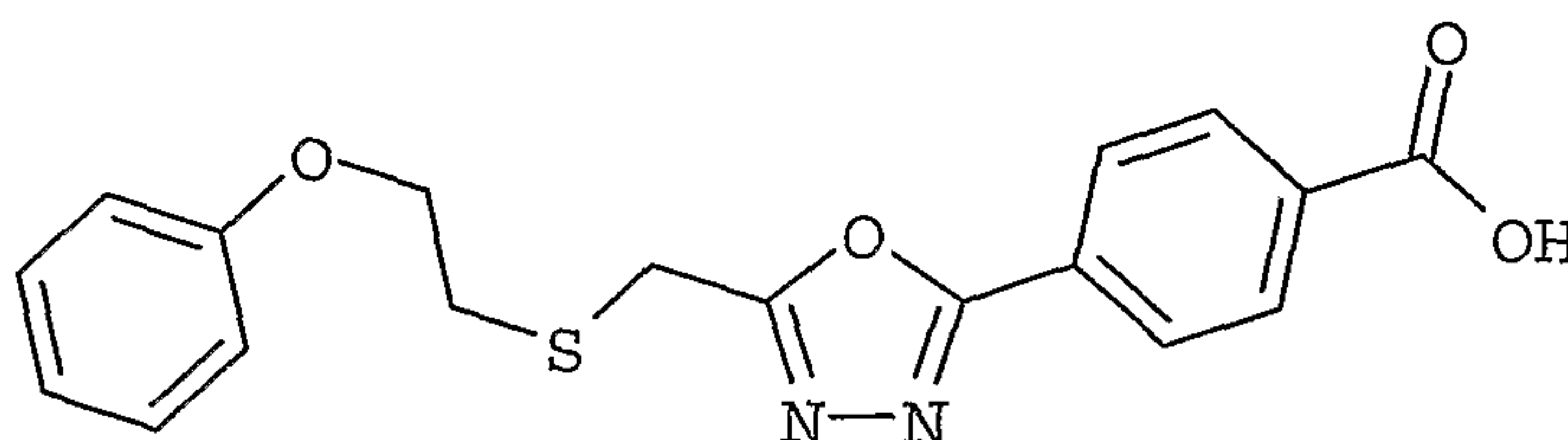
A solution of 2-[(2-phenoxyethyl)thio]acetic acid hydrazide hydrochloride (3.15 g, 12 mmol), triethylamine (4.2 mL, 30 mmol) and terephthalic acid monomethyl ester chloride (1.99 g, 10 mmol) in methylene chloride (100 mL) was stirred at room temperature for 3 h. After filtering the solids, the filtrate was concentrated. The residue
 25 was recrystallized from ethanol to yield a pale yellow solid (1.31 g, 3.37 mmol). This solid, 4-(dimethylamino)phenyldiphenylphosphine (2.06 g, 6.74 mmol), triethylamine (1.4

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mL, 10 mmol) and carbon tetrachloride (1.6 mL, 16.6 mmol) were stirred in acetonitrile (75 mL) at room temperature for 18 h. The product was filtered from the reaction mixture, washed with acetonitrile (50 mL) and dried to yield 1.13 g (30%) of a pale yellow solid, which was used without further purification.

5 ^1H NMR (CDCl_3) δ 8.14 (d, 2H, $J=9$ Hz), 8.06 (d, 2H, $J=9$ Hz), 7.23 (m, 2H), 6.92 (dd, 1H, $J=7$ and 8 Hz), 6.86 (d, 2H, $J=8$ Hz), 4.19 (t, 2H, $J=12$ Hz), 4.05 (s, 2H), 3.93 (s, 3H), 3.03 (t, 2H, $J=12$ Hz). MS (ES+) m/e 371 ($M+1$).

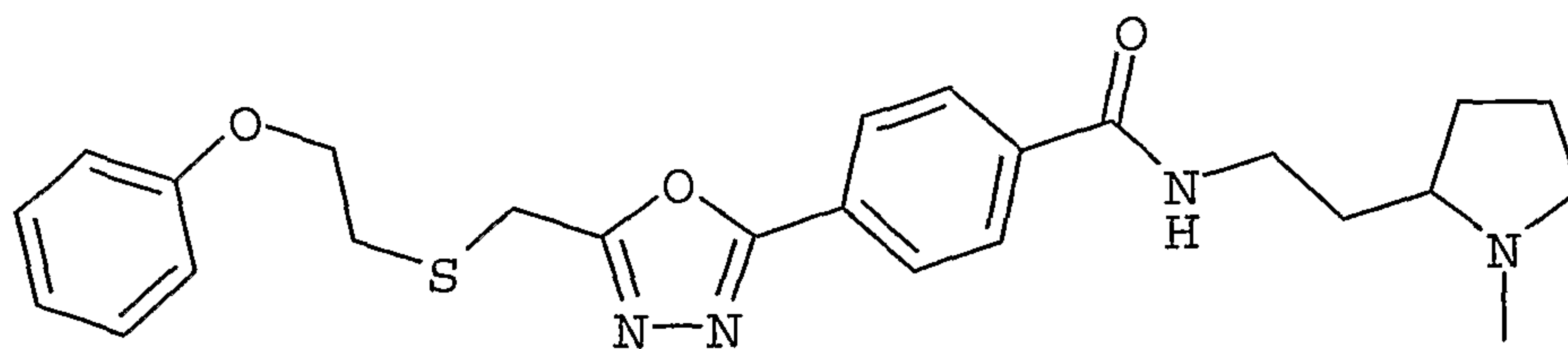
b) 2-[[2-Phenoxyethylthio]methyl]-5-[4-(hydroxycarbonyl)phenyl]-1,3,4-oxadiazole



A mixture of 2-[[2-phenoxyethylthio]methyl]-5-[4-(methoxycarbonyl)phenyl]-1,3,4-oxadiazole (1.13 g, 3.0 mmol) and 2N aqueous NaOH (4.5 mL, 9.0 mmol) in THF (20 mL) was stirred at room temperature for 16 h. The mixture was diluted with water (30 mL) and extracted with ethyl ether (50 mL). The aqueous material was acidified with 2N HCl to a pH of 5, then extracted with ethyl ether (3x30 mL). The organic material was dried (MgSO_4), filtered and concentrated to yield 803 mg (74%) of a pale yellow solid.

20 ^1H NMR (CDCl_3) δ 8.20 (d, 2H, $J=8$ Hz), 8.12 (d, 2H, $J=8$ Hz), 7.25 (m, 2H), 6.93 (dd, 1H, $J=7$ and 8 Hz), 6.87 (d, 2H, $J=8$ Hz), 4.20 (t, 2H, $J=12$ Hz), 4.08 (s, 2H), 3.05 (t, 2H, $J=12$ Hz). MS (ES-) m/e 355 ($M-1$).

c) 2-[[2-Phenoxyethylthio]methyl]-5-{4-[[2-(N-methyl pyrrolidin-2-yl)ethyl]amino]carbonyl]phenyl}-1,3,4-oxadiazole



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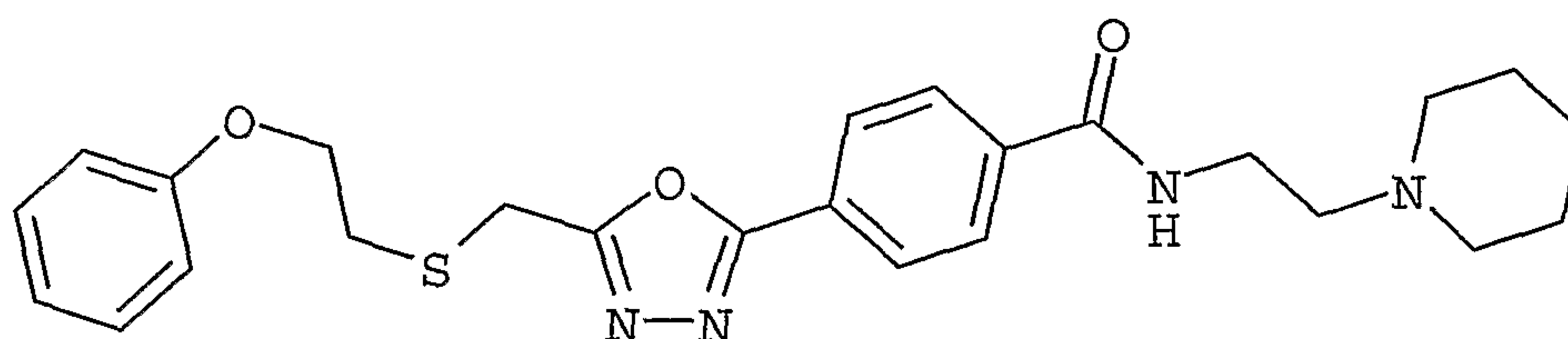
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A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(hydroxycarbonyl)phenyl]-1,3,4-oxadiazole (300 mg, 0.84 mmol), 2-(2-aminoethyl)-1-methylpyrrolidine (0.18 mL, 1.24 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (242 mg, 1.26 mmol) and 1-hydroxybenzo-triazole (171 mg, 1.26 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 16 h. The mixture was diluted with ethyl acetate (50 mL) and extracted with saturated aqueous lithium chloride (2x25 mL), dried (MgSO₄), filtered and concentrated to yield 700 mg of a yellow oil. This oil was purified by preparative TLC [90% methylened chloride-5% methanol-5%(2.0 N ammonia in methanol)] to yield 146 mg (37%) of a white solid.

¹H NMR (CDCl₃) δ 8.75 (br s, 1H), 8.07 (d, 2H, J=8 Hz), 7.88 (d, 2H, J=8 Hz), 7.24 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.05 (s, 2H), 3.77 (m, 1H), 3.47 (m, 1H), 3.15 (m, 1H), 3.04 (t, 2H, J=12 Hz), 2.57 (m, 1H), 2.40 (s, 3H), 2.31 (m, 1H), 1.90 (m, 2H), 1.75 (m, 4H). IR (film, cm⁻¹) 3432, 3335, 2943, 2868, 2778, 2359, 1641, 1584, 1547, 1493, 1456, 1302, 1244, 1082, 1021, 863, 753, 694, 654. MS (ES⁺) m/e 467 (M+1). Anal. Calcd for C₃₁H₃₃N₃O₂S: C, 64.35; H, 6.48; N, 12.01; S, 6.87. Found C, 64.42; H, 6.19; N, 12.45; S, 6.80.

Example 123

Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[(2-piperidinoethyl)amino)carbonyl]phenyl}-1,3,4-oxadiazole



This compound was synthesized similarly to 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[(2-(N-methyl pyrrolidin-2-yl)ethyl)amino)carbonyl]phenyl}-1,3,4-oxadiazole using 1-(2-aminoethyl)piperidine (0.12 mL).

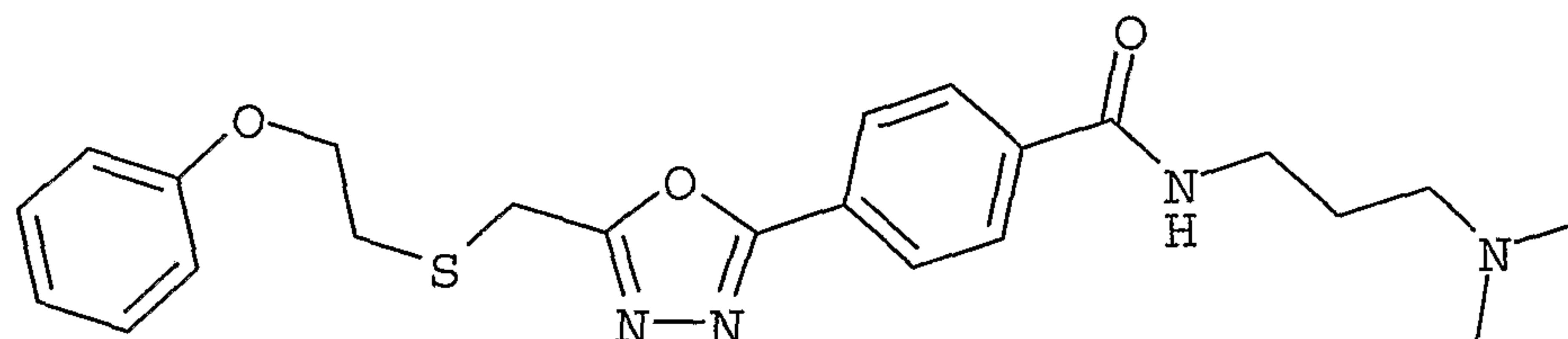
¹H NMR (CDCl₃) δ 8.08 (d, 2H, J=9 Hz), 7.89 (d, 2H, J=9 Hz), 7.24 (m, 2H), 7.15 (br s, 1H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=9 Hz), 4.20 (t, 2H, J=12 Hz), 4.06 (s, 2H), 3.53 (dd, 2H, J=6 and 11 Hz), 3.04 (t, 2H, J=12 Hz), 2.57 (dd, 2H, J=6 and 11 Hz), 2.44 (m, 4H), 1.60 (m, 4H), 1.47 (m, 2H). IR (film, cm⁻¹) 3313, 2938, 2885, 2851, 2778, 1635, 1552, 1493, 1296, 1239, 1024, 747. MS (ES⁺) m/e 467 (M+1). Anal. Calcd

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for C₂₅H₃₀N₄O₃S: C, 64.35; H, 6.48; N, 12.01; S, 6.87. Found C, 64.02; H, 6.41; N, 12.00; S, 7.02.

Example 124

- 5 Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[(N',N'-dimethyl-1,3-propanediamino)carbonyl]phenyl}-1,3,4-oxadiazole



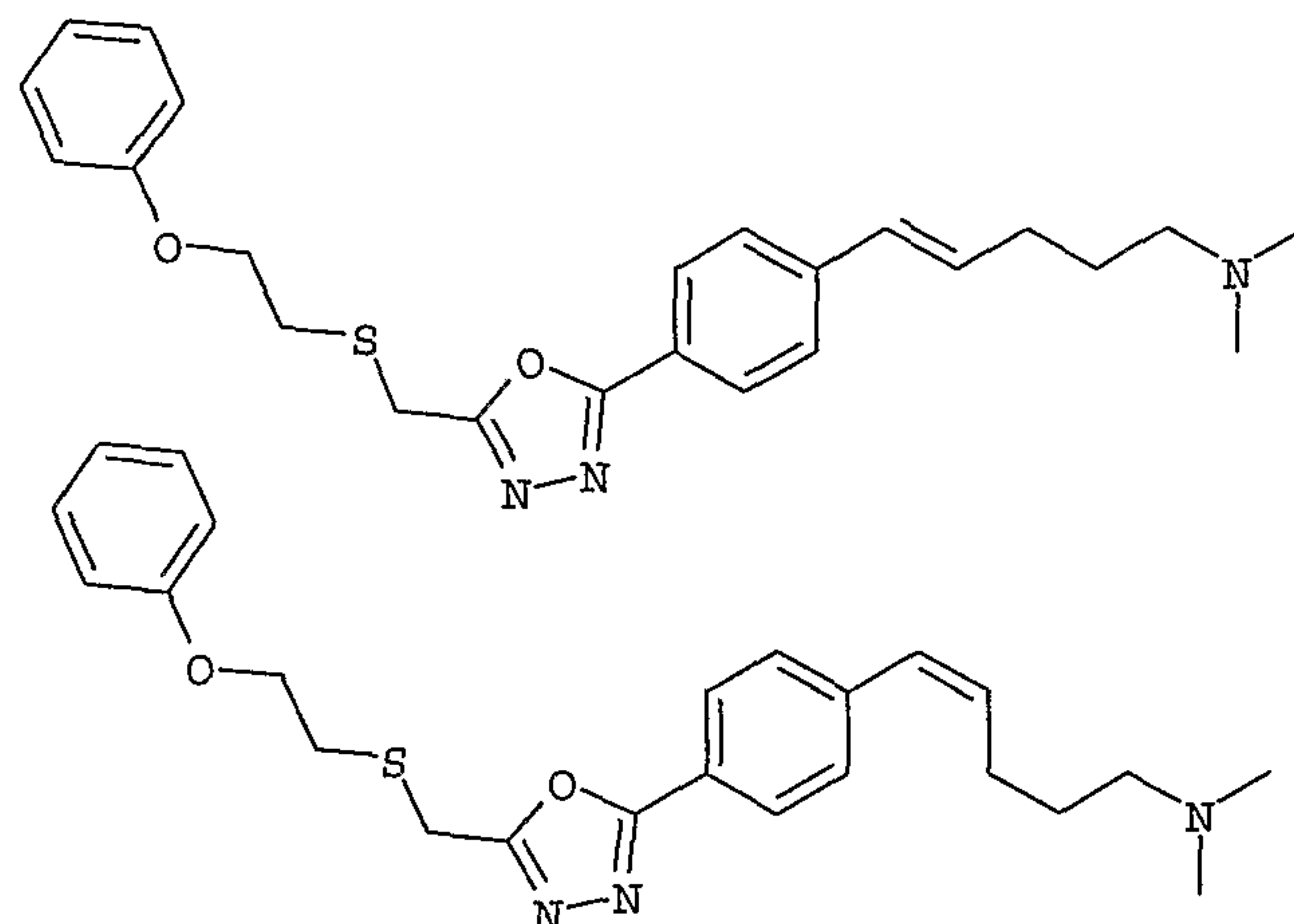
- This compound was synthesized similarly to 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[[2-(N-methyl pyrrolidin-2-yl)ethyl]amino]carbonyl]phenyl}-1,3,4-oxadiazole using
10 3-(dimethylamino)propylamine (0.11 mL).

- ¹H NMR (CDCl₃) δ 8.81 (br s, 1H), 8.07 (d, 2H, J=8 Hz), 7.87 (d, 2H, J=8 Hz), 7.24 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 4.20 (t, 2H, J=12 Hz), 4.05 (s, 2H), 3.58 (dd, 2H, J=6 and 11 Hz), 3.04 (t, 2H, J=12 Hz), 2.54 (dd, 2H, J=6 and 11 Hz), 2.30 (s, 6H), 1.77 (m, 2H). IR (film, cm⁻¹) 3431, 3345, 2943, 2867, 2810, 2762,
15 1641, 1581, 1542, 1494, 1466, 1300, 1246, 1178, 1082, 1026, 750, 693, 651. MS (ES+) m/e 441 (M+1). Anal. Calcd for C₂₃H₂₈N₄O₃S: C, 62.70; H, 6.41; N, 12.72; S, 7.28. Found C, 62.13; H, 6.32; N, 12.63; S, 6.99.

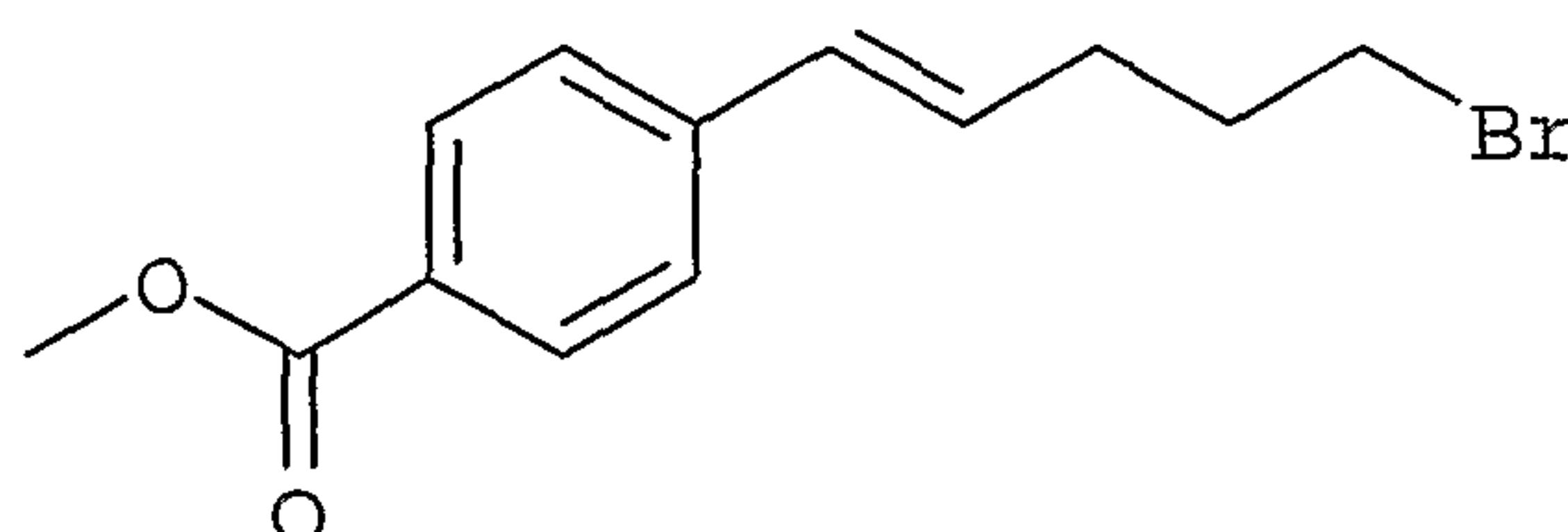
Example 125

- 20 Preparation of 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[5-(N,N-dimethylamino)penten-1-yl]phenyl}-1,3,4-oxadiazole, (E)- and (Z)-isomers

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a) Methyl 4-(5-bromopenten-1-yl)benzoate



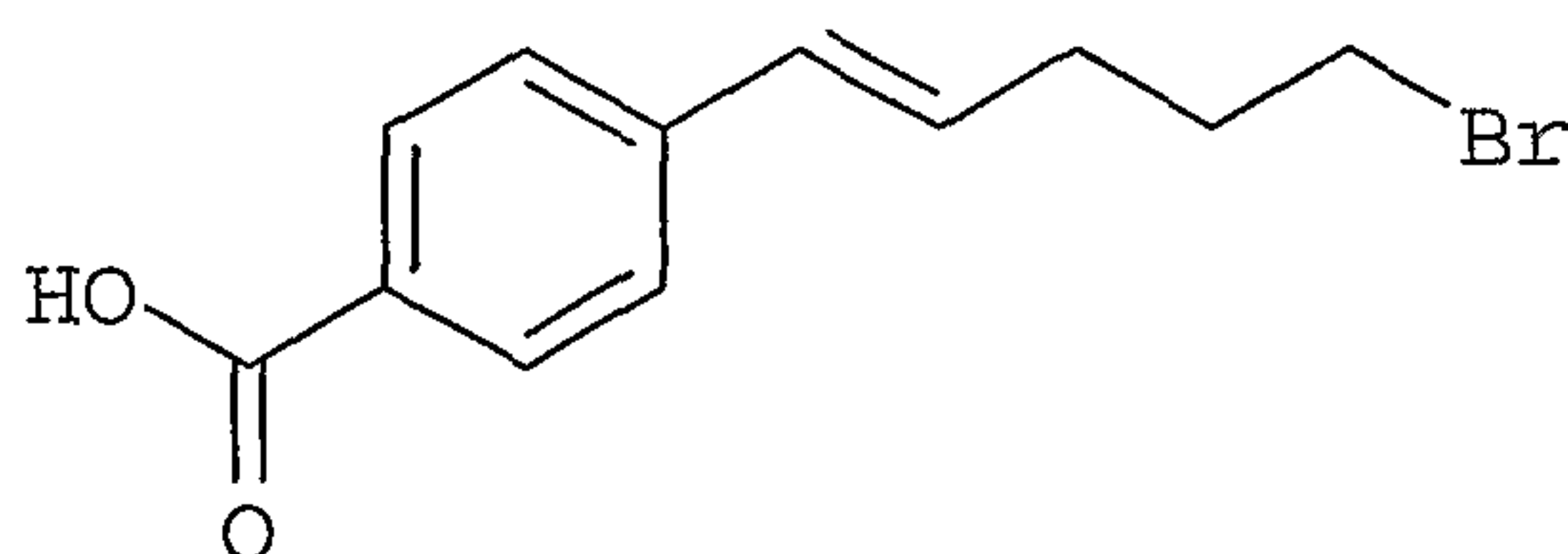
A mixture of methyl 4-formylbenzoate (9.85 g, 60 mmol), 4-
 5 bromobutyltriphenylphosphonium bromide (31.56 g, 66 mmol), powdered NaOH (3 g, 75
 mmol), and 12 drops of water in methylene chloride (150 mL) was stirred under reflux for
 4 h. The mixture was allowed to cool to room temperature and filtered. The filtrate was
 concentrated and chromatographed on a silica gel column, eluted with ethyl
 acetate/hexanes 1:50 to 1:30, to give the Z-isomer (colorless oil, 3.68 g, 22%), a mixture
 10 of Z- and E-isomers (colorless oil, 2.69 g, 16%), and the E-isomer (white solid, 2.97 g,
 17%).

E-isomer: ^1H NMR (CDCl_3) δ 7.94 (d, 2H, $J=8.5$ Hz), 7.37 (d, 2H, $J=8.4$ Hz), 6.46
 (d, 1H, $J=15.8$ Hz), 6.28 (dt, 1H, $J=15.8, 7.0$ Hz), 3.88 (s, 3H), 3.44 (t, 2H, $J=6.6$ Hz),
 2.39 (q, 2H, $J=7.0$ Hz), 2.03 (quint, 2H, 6.6 Hz). MS (ES+) m/e 284 ($M+1$).

15 Z-isomer: ^1H NMR (CDCl_3) δ 7.98 (d, 2H, $J=8.1$ Hz), 7.31 (d, 2H, $J=8.4$ Hz), 6.48 (d,
 1H, $J=11.7$ Hz), 5.70 (dt, 1H, $J=11.7, 7.3$ Hz), 3.89 (s, 3H), 3.39 (t, 2H, $J=6.8$ Hz), 2.47
 (q, 2H, $J=7.3$ Hz), 1.99 (quint, 2H, 6.9 Hz). MS (ES+) m/e 284 ($M+1$).

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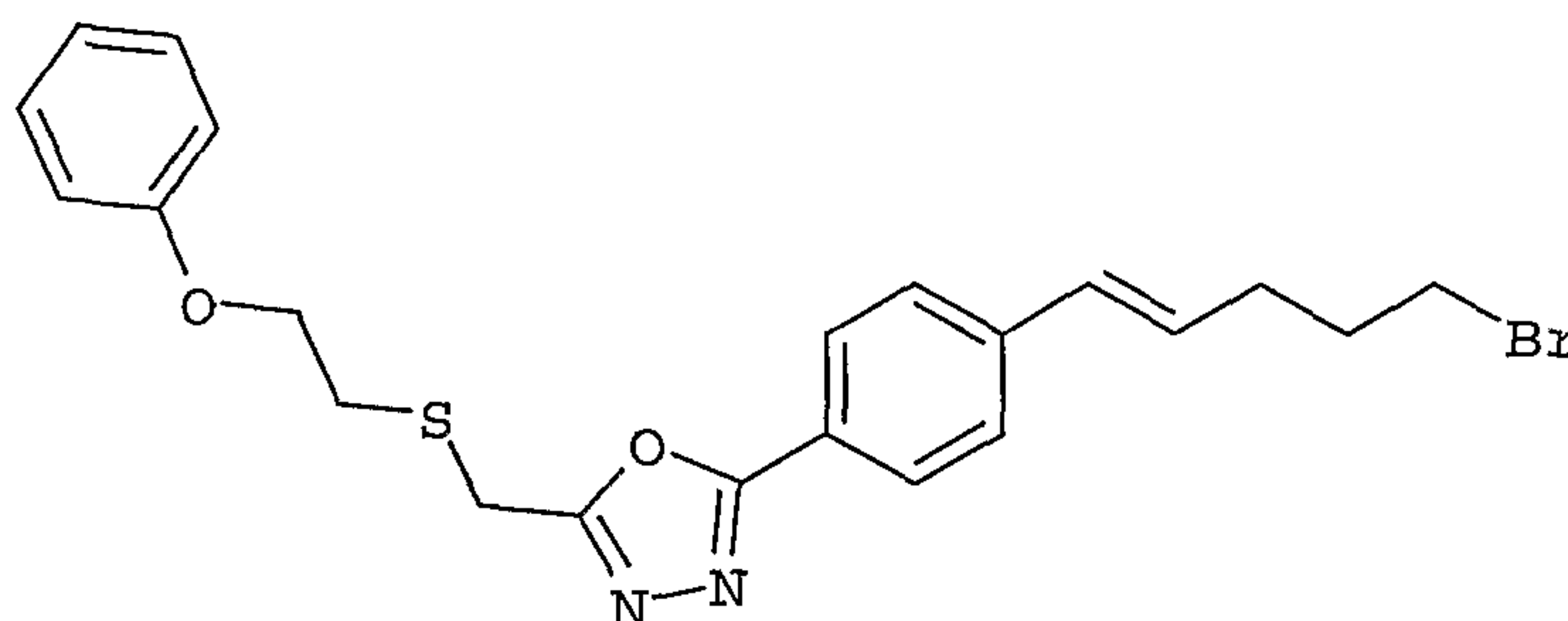
b) 4-(5-bromopenten-1-yl)benzoic acid



Methyl 4-(5-bromopenten-1-yl)benzoate (1.415 g, 5 mmol) was dissolved in 1,4-dioxane (25 mL) and 2 N NaOH (25 mL, 50 mmol) was added. The mixture was stirred at room temperature for 5 h, cooled in an ice bath, acidified with conc. HCl, and extracted with ether (3 x 25 mL). The combined ether extracts were dried (MgSO₄) and concentrated to give a white solid (1.264 g, 94%).

E-isomer: ¹H NMR (CDCl₃) δ 8.05 (d, 2H, J=7.7 Hz), 7.43 (d, 2H, J=8.5 Hz), 6.51 (d, 1H, J=16.3 Hz), 6.34 (dt, 1H, J=16.3, 6.9 Hz), 3.47 (t, 2H, J=6.9 Hz), 2.43 (q, 2H, J=6.9 Hz), 2.07 (quint, 2H, 6.8 Hz). MS (ES-) m/e 268 (M-1).

c) 2-[[2-(Phenoxyethyl)thio]methyl]-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole



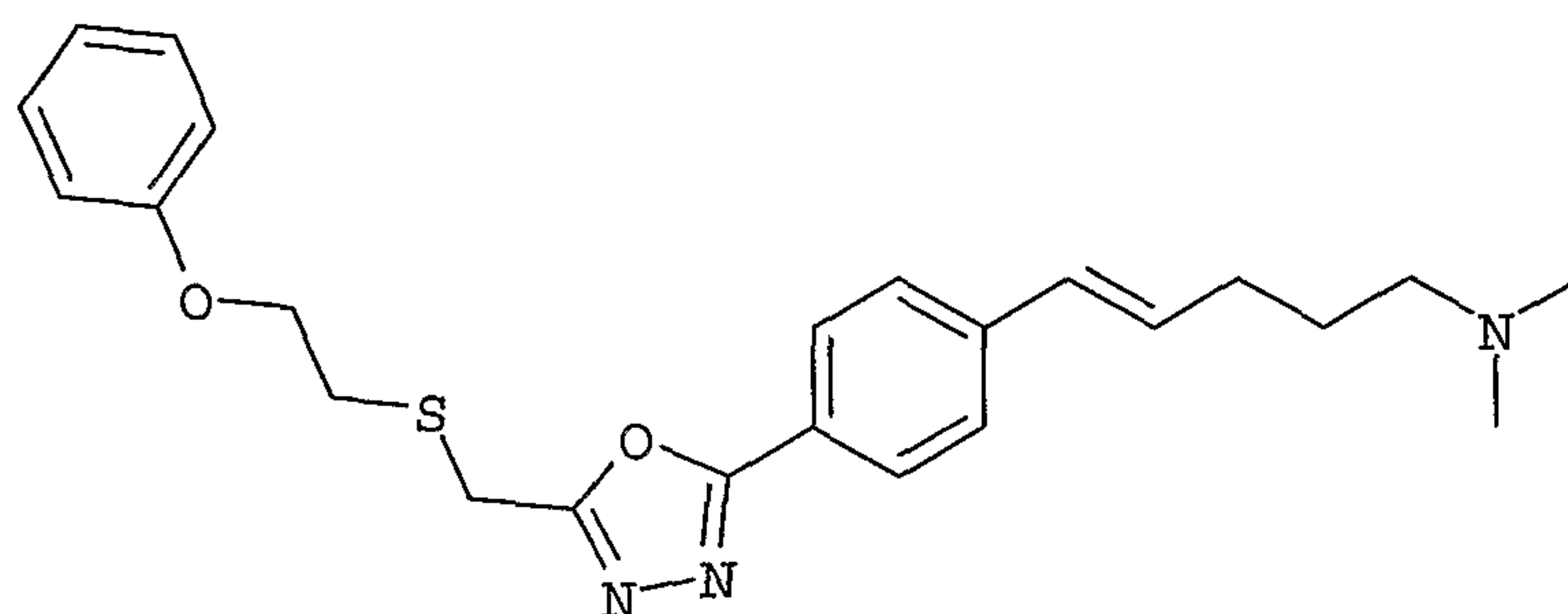
A stirred mixture of 4-(5-bromopenten-1-yl)benzoic acid (1.264 g, 4.7 mmol), 2-(2-phenoxyethyl)thioacetylhydrazide hydrochloride (1.314 g, 5 mmol), and 4-(N,N-dimethylamino)phenyldiphenylphosphine (4.58 g, 15 mmol) in acetonitrile (50 mL) was cooled in ice bath and triethylamine (3.04 g, 30 mmol) in carbon tetrachloride (3.85 g, 25 mmol) was added dropwise. The cooling bath was removed after 10 min and stirring was continued for 5 h. The mixture was concentrated to approximately half the original volume and partitioned between ether (150 mL) and 2 N HCl (150 mL). The ether layer was washed with 2 N HCl (4 x 50 mL), dried (MgSO₄), and concentrated. The residue was purified by chromatography (SiO₂, ethyl acetate/hexanes 1:5) to give a white solid (1.43 g, 66%).

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E-isomer: ^1H NMR (CDCl_3) δ 7.96 (d, 2H, $J=8.5$ Hz), 7.45 (d, 2H, $J=8.5$ Hz), 7.27 (m, 2H), 6.96 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=8.5$ Hz), 6.50 (d, 1H, $J=16.2$ Hz), 6.32 (dt, 1H, $J=16.2, 6.9$ Hz), 4.22 (t, 2H, $J=6.0$ Hz), 4.06 (s, 2H), 3.47 (t, 2H, $J=6.9$ Hz), 3.06 (t, 2H, $J=6.0$ Hz), 2.43 (q, 2H, $J=6.9$ Hz), 2.07 (quint, 2H, 6.9 Hz). MS (ES+) m/e 460 (M+1).

Z-isomer: ^1H NMR (CDCl_3) δ 7.97 (d, 2H, $J=8.5$ Hz), 7.37 (d, 2H, $J=8.5$ Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=7.7$ Hz), 6.48 (d, 1H, $J=11.8$ Hz), 5.72 (dt, 1H, $J=11.7, 7.3$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.04 (s, 2H), 3.41 (t, 2H, $J=6.6$ Hz), 3.04 (t, 2H, $J=6.2$ Hz), 2.49 (q, 2H, $J=7.3$ Hz), 2.01 (quint, 2H, 7.0 Hz). MS (ES+) m/e 460 (M+1).

d) 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[5-(N,N-dimethylamino)penten-1-yl]phenyl}-1,3,4-oxadiazole



A mixture of 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole (300 mg, 0.65 mmol), 2 N dimethylamine in tetrahydrofuran (1.7 mL, 3.4 mmol), and potassium carbonate (903 mg, 6.5 mmol) in acetonitrile (5 mL) was stirred at room temperature for 24 h, diluted with methylene chloride (25 mL) and filtered. The filtrate was concentrated and purified by chromatography (silica gel, methanol/methylene chloride 2% to 10%) to give a white solid (263 mg, 96%).

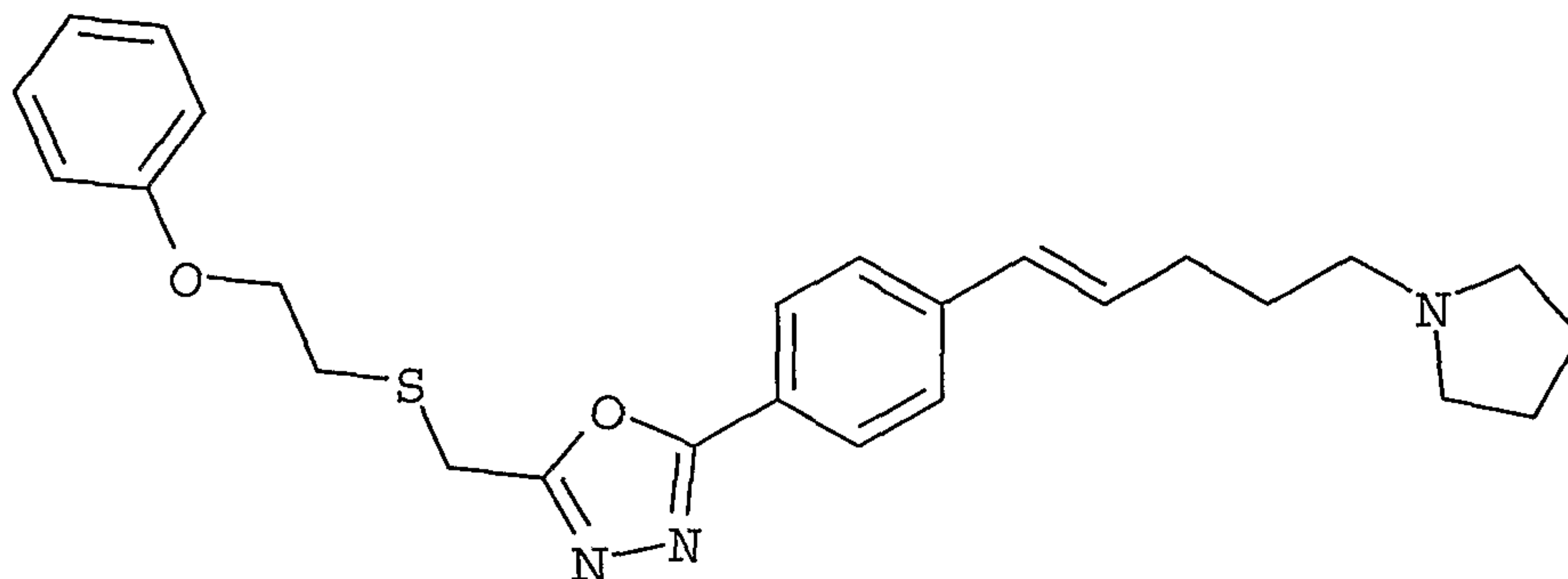
E-isomer: ^1H NMR (CDCl_3) δ 7.93 (d, 2H, $J=8.5$ Hz), 7.42 (d, 2H, $J=8.4$ Hz), 7.22~7.27 (m, 2H), 6.93 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=7.7$ Hz), 6.42 (d, 1H, $J=16.1$ Hz), 6.34 (dt, 1H, $J=15.7, 6.4$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz), 2.40 (m, 2H), 2.30 (s, 6H), 2.27 (m, 2H), 1.71 (quint, 2H, 7.3 Hz). IR (KBr, cm^{-1}) 3074, 3056, 3038, 2955, 2924, 2856, 1602, 1495, 1237, 1168, 751. MS (ES+) m/e 424 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_2\text{S}$: C, 68.05; H, 6.90; N, 9.92; S, 7.57. Found C, 68.16; H, 6.99; N, 10.23; S, 7.66.

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Z-isomer: ^1H NMR (CDCl_3) δ 7.96 (d, 2H, $J=8.4$ Hz), 7.37 (d, 2H, $J=8.4$ Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=8.0$ Hz), 6.44 (d, 1H, $J=11.8$ Hz), 5.75 (dt, 1H, $J=11.4, 7.3$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.04 (t, 2H, $J=6.2$ Hz), 2.32~2.39 (m, 4H), 2.29 (s, 6H), 1.69 (quint, 2H, 7.3 Hz). IR (KBr, cm^{-1}) 3029, 2940, 2863, 2844, 2649, 1598, 1505, 1246, 1174, 752. MS (ES+) m/e 424 ($M+1$). Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_2\text{S}$: C, 68.05; H, 6.90; N, 9.92; S, 7.57. Found C, 68.45; H, 6.44; N, 10.37; S, 7.41.

Example 126

10 Preparation of 2-[[2-(Phenoxyethyl)thio]methyl]-5-[4-(5-pyrrolidinopenten-1-yl)phenyl]-1,3,4-oxadiazole



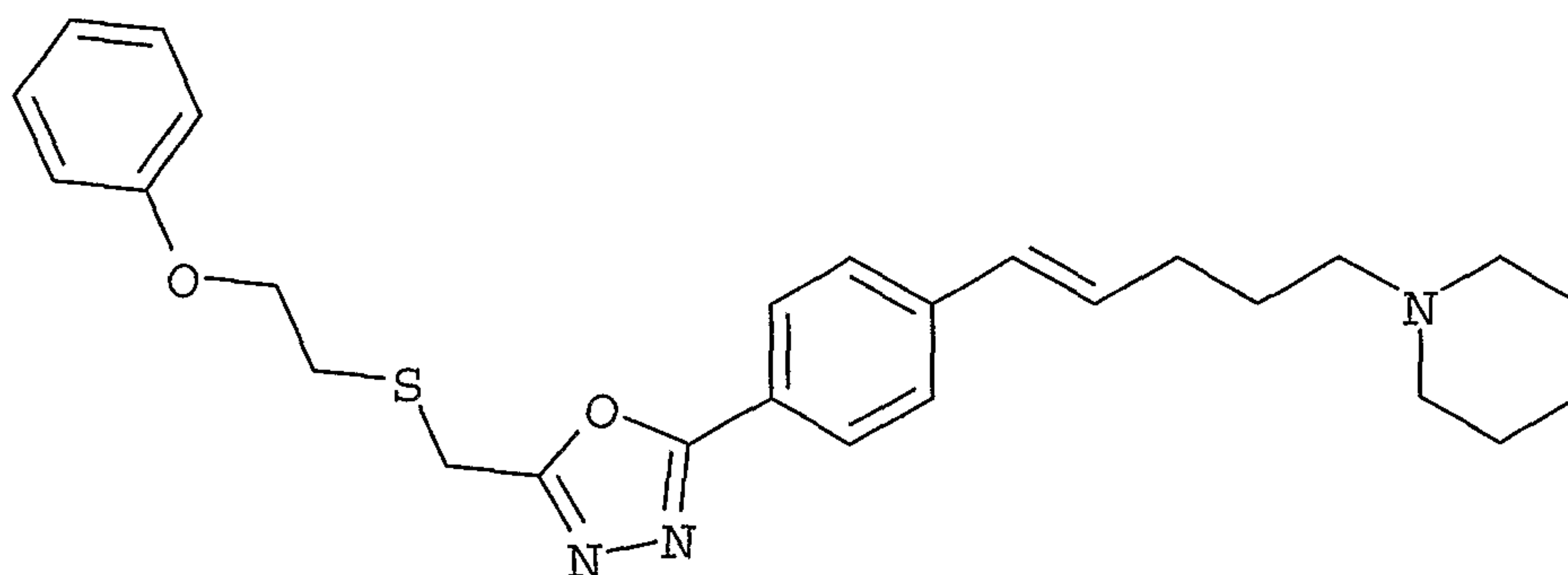
A mixture of 2-[[2-(phenoxyethyl)thio]methyl]-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole (150 mg, 0.33 mmol), pyrrolidine (118 mg, 1.65 mmol), and potassium carbonate (457 mg, 3.3 mmol) in acetonitrile (3.5 mL) was stirred at room temperature for 24 h, diluted with methylene chloride (15 mL), filtered, dried (MgSO_4), and concentrated. The residue was purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a yellow oil (129 mg, 87%).

^1H NMR (CDCl_3) δ 7.92 (d, 2H, $J=8.4$ Hz), 7.42 (d, 2H, $J=8.4$ Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, $J=7.7$ Hz), 6.87 (d, 2H, $J=7.7$ Hz), 6.41 (d, 1H, $J=15.7$ Hz), 6.36 (dt, 1H, $J=15.7, 6.5$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz), 2.46~2.50 (m, 6H), 2.27 (q, 2H, $J=6.9$ Hz), 1.67~1.80 (m, 6H). IR (film, cm^{-1}) 3070, 3024, 2968, 2841, 2793, 1598, 1506, 1337, 1306, 1229, 1020, 736. MS (ES+) m/e 450 ($M+1$). Anal. Calcd for $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_2\text{S}$: C, 69.46; H, 6.95; N, 9.35; S, 7.13. Found C, 68.98; H, 7.01; N, 9.73; S, 7.19.

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Example 127

Preparation of 2-[[2-(Phenoxyethyl)thio]methyl]-5-[4-(5-piperidinopenten-1-yl)phenyl]-1,3,4-oxadiazole

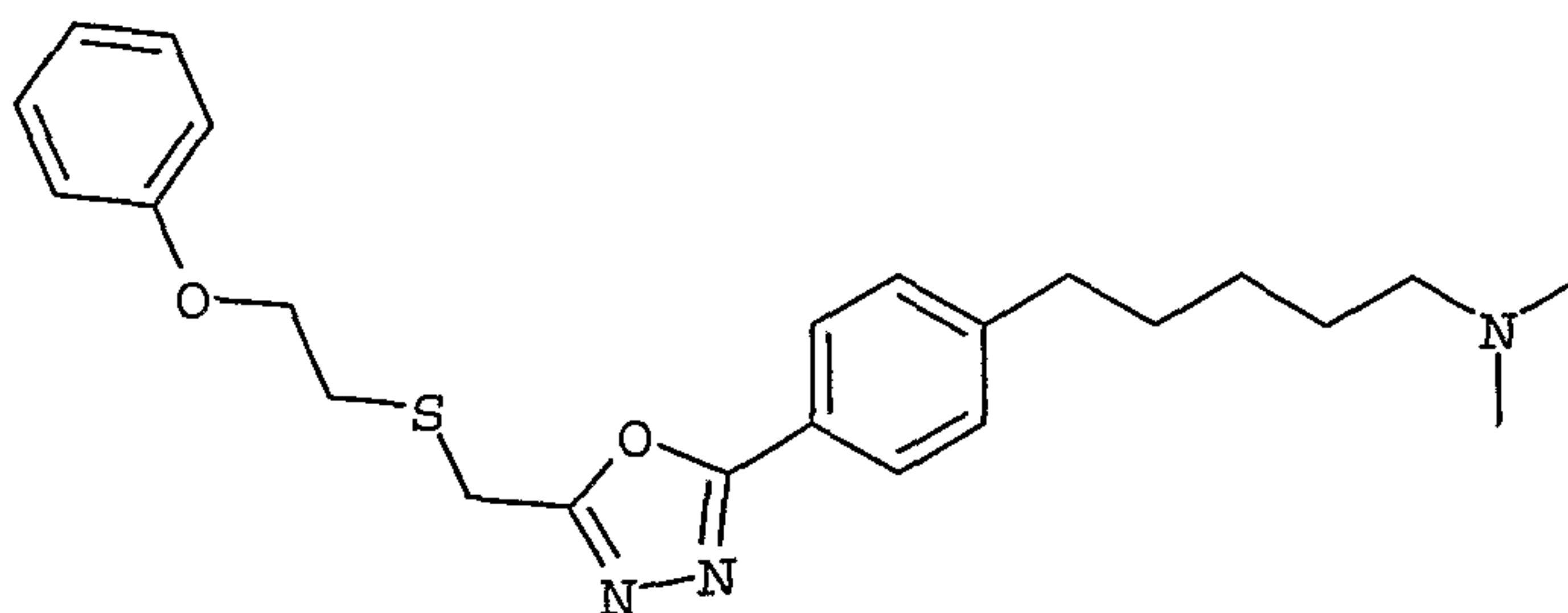


5 A mixture of 2-[[2-(phenoxyethyl)thio]methyl]-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole (150 mg, 0.33 mmol), piperidine (140 mg, 1.65 mmol), and potassium carbonate (458 mg, 3.3 mmol) in acetonitrile (3.5 mL) was stirred at room temperature for 18 h, diluted with methylene chloride (15 mL), filtered, dried (MgSO₄), and concentrated. The residue was purified by preparative TLC (silica gel, 10%
10 methanol/methylene chloride) to give yellow oil (136 mg, 89%).

¹H NMR (CDCl₃) δ 7.92 (d, 2H, J=8.5 Hz), 7.42 (d, 2H, J=8.4 Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=8.4 Hz), 6.41 (d, 1H, J=16.1 Hz), 6.34 (dt, 1H, J=16.1, 6.9 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.03 (t, 2H, J=6.2 Hz), 2.38~2.43 (m, 6H), 2.25 (q, 2H, J=6.9 Hz), 1.43~1.74 (m, 8H). IR (film, cm⁻¹) 3072, 3027, 2945,
15 2936, 2691, 1600, 1533, 1274, 1196, 1020, 764. MS (ES⁺) m/e 464 (M+1). Anal. Calcd for C₂₇H₃₃N₃O₂S: C, 69.95; H, 7.17; N, 9.06; S, 6.92. Found C, 69.24; H, 7.12; N, 9.68; S, 7.11.

Example 128

Preparation of 2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[5-(N,N-dimethylamino)pentan-1-yl]phenyl}-1,3,4-oxadiazole
20



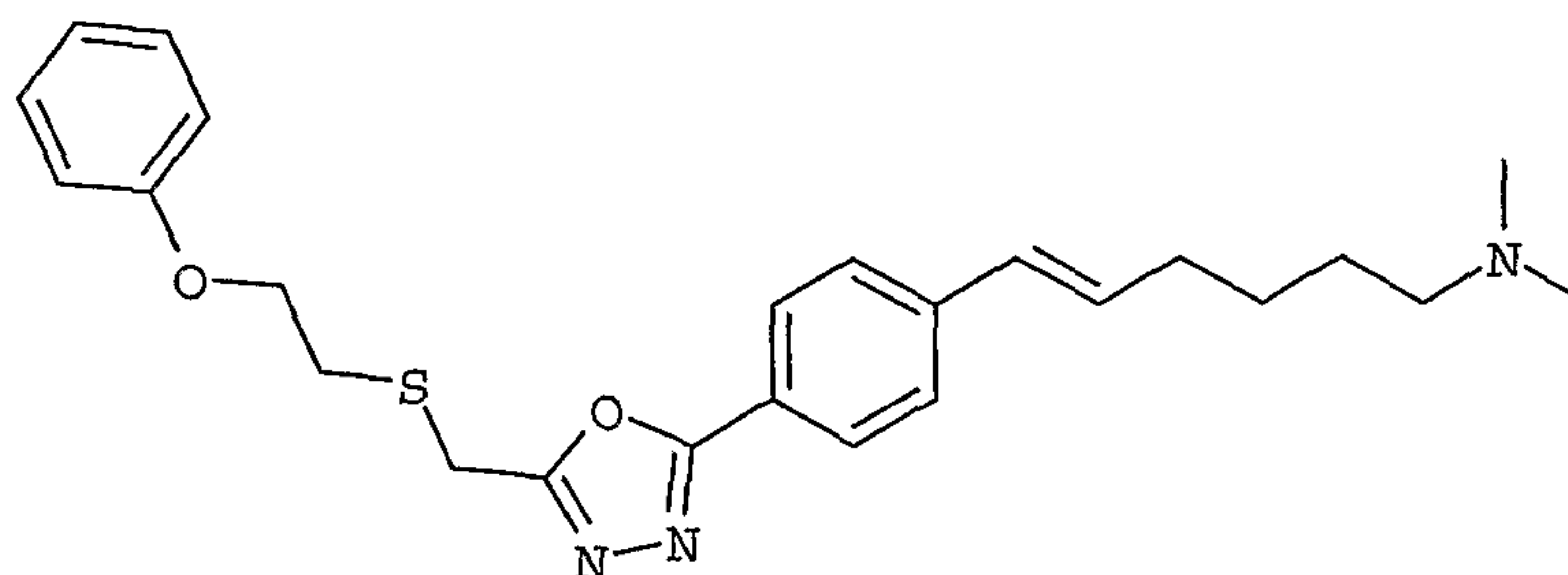
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A mixture of (E)- and (Z)-2-[[2-phenoxyethylthio]methyl]-5-{4-[5-(N,N-dimethylamino)penten-1-yl]phenyl}-1,3,4-oxadiazole was made according to the above procedure from 460 mg (1 mmol) of a mixture of (E)- and (Z)-2-[[2-phenoxyethylthio]methyl]-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole. Without purification this material was stirred with p-toluenesulfonylhydrazide (2.25 g, 12 mmol) and sodium acetate trihydrate (1.02 g, 7.5 mmol) in tetrahydrofuran (12 mL) and water (12 mL) under reflux for 6 h. 2 N NaOH (20 mL) was added and the mixture was extracted with methylene chloride (2 x 20 mL). The combined methylene chloride extracts were dried (MgSO₄), and concentrated. The residue was purified by column chromatography (silica gel, methanol/methylene chloride 2% to 5% to 10%) to give a colorless oil (333 mg, 78% over two steps).

¹H NMR (CDCl₃) δ 7.91 (d, 2H, J=8.1 Hz), 7.27 (d, 2H, J=8.4 Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=8.5 Hz), 4.18 (t, 2H, J=6.2 Hz), 4.02 (s, 2H), 3.03 (t, 2H, J=6.2 Hz), 2.66 (t, 2H, J=7.7 Hz), 2.24 (t, 2H, J=7.5 Hz), 2.20 (s, 6H), 1.65 (quint, 2H, 7.7 Hz), 1.49 (q, 2H, J=7.5 Hz), 1.34 (q, 2H, J=7.5 Hz). IR (film, cm⁻¹) 3034, 3017, 2954, 2883, 2820, 1515, 1357, 1344, 1235, 1137, 1002. MS (ES⁺) m/e 426 (M+1). Anal. Calcd for C₂₄H₃₁N₃O₂S: C, 67.73; H, 7.34; N, 9.87; S, 7.53. Found C, 67.37; H, 7.42; N, 10.06; S, 7.27.

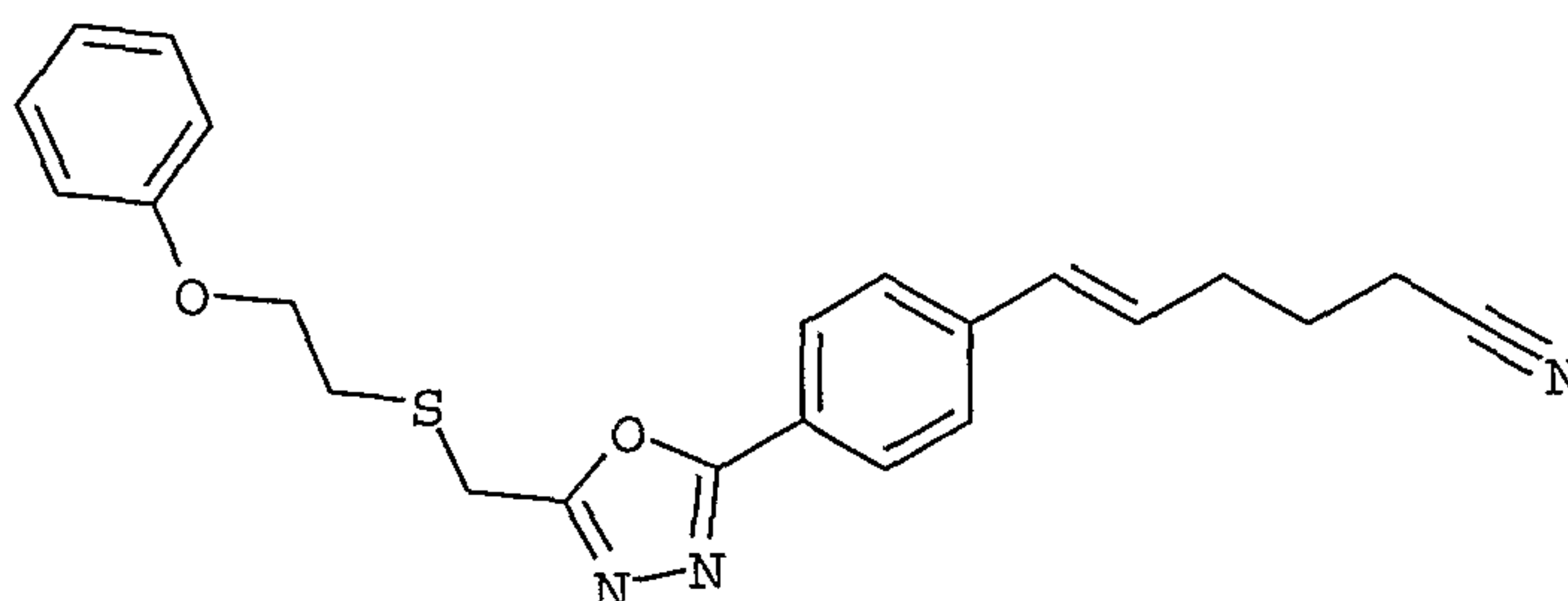
Example 129

Preparation of 2-[[2-Phenoxyethylthio]methyl]-5-{4-[6-(N,N-dimethylamino)hexen-1-yl]phenyl}-1,3,4-oxadiazole



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a) 2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(5-cyanopenten-1-yl)phenyl]-1,3,4-oxadiazole

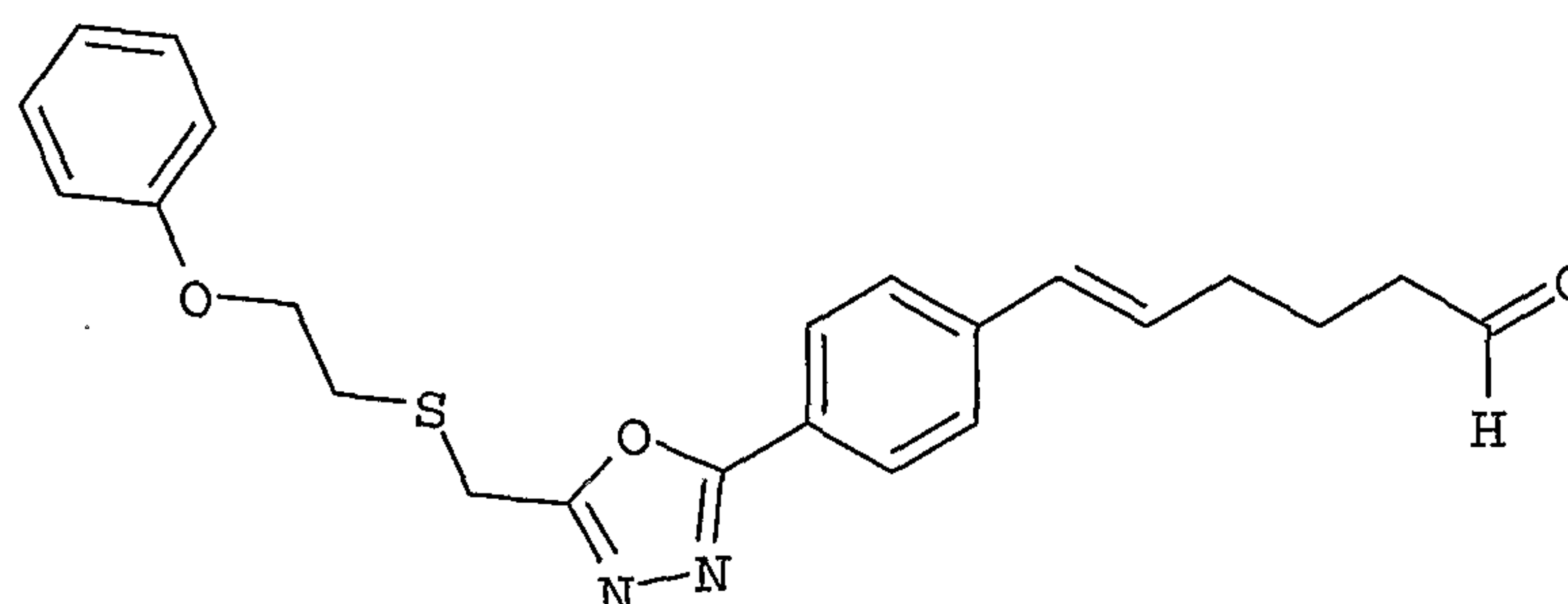


A mixture of 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole (460 mg, 1 mmol) and potassium cyanide (195 mg, 3 mmol) in dimethylsulfoxide (6 mL) was stirred at room temperature for 4 h. Water (25 mL) was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined ethyl acetate extracts were washed with water (3 x 15 mL) and brine (15 mL), dried (MgSO₄), and concentrated to give a pale yellow solid (403 mg, 100%).

10 E-isomer: ¹H NMR (CDCl₃) δ 7.97 (d, 2H, J=7.7 Hz), 7.46 (d, 2H, J=7.7 Hz), 7.28 (m, 2H), 6.96 (t, 1H, J=7.3 Hz), 6.90 (d, 2H, J=7.3 Hz), 6.51 (d, 1H, J=15.4 Hz), 6.29 (dt, 1H, J=15.4, 7.7 Hz), 4.22 (t, 2H, J=6.0 Hz), 4.06 (s, 2H), 3.06 (t, 2H, J=6.0 Hz), 2.41~2.46 (m, 4H), 1.89 (quint, 2H, 6.9 Hz). MS (ES+) m/e 406 (M+1).

15 Z-isomer: ¹H NMR (CDCl₃) δ 8.01 (d, 2H, J=7.7 Hz), 7.37 (d, 2H, J=8.5 Hz), 7.28 (m, 2H), 6.95 (t, 1H, J=7.7 Hz), 6.90 (d, 2H, J=7.7 Hz), 6.56 (d, 1H, J=11.1 Hz), 5.72 (dt, 1H, J=11.1, 6.8 Hz), 4.22 (t, 2H, J=6.0 Hz), 4.07 (s, 2H), 3.06 (t, 2H, J=6.0 Hz), 2.51 (m, 2H), 2.37 (t, 2H, J=6.8 Hz), 1.85 (m, 2H). MS (ES+) m/e 406 (M+1).

b) 2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(6-oxohexen-1-yl)phenyl]-1,3,4-oxadiazole



20 A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(5-cyanopenten-1-yl)phenyl]-1,3,4-oxadiazole (400 mg, 1 mmol) in methylene chloride (10 mL) was cooled to -78 °C and 1 M DIBAL-H in hexane (2 mL, 2 mmol) was added dropwise. The

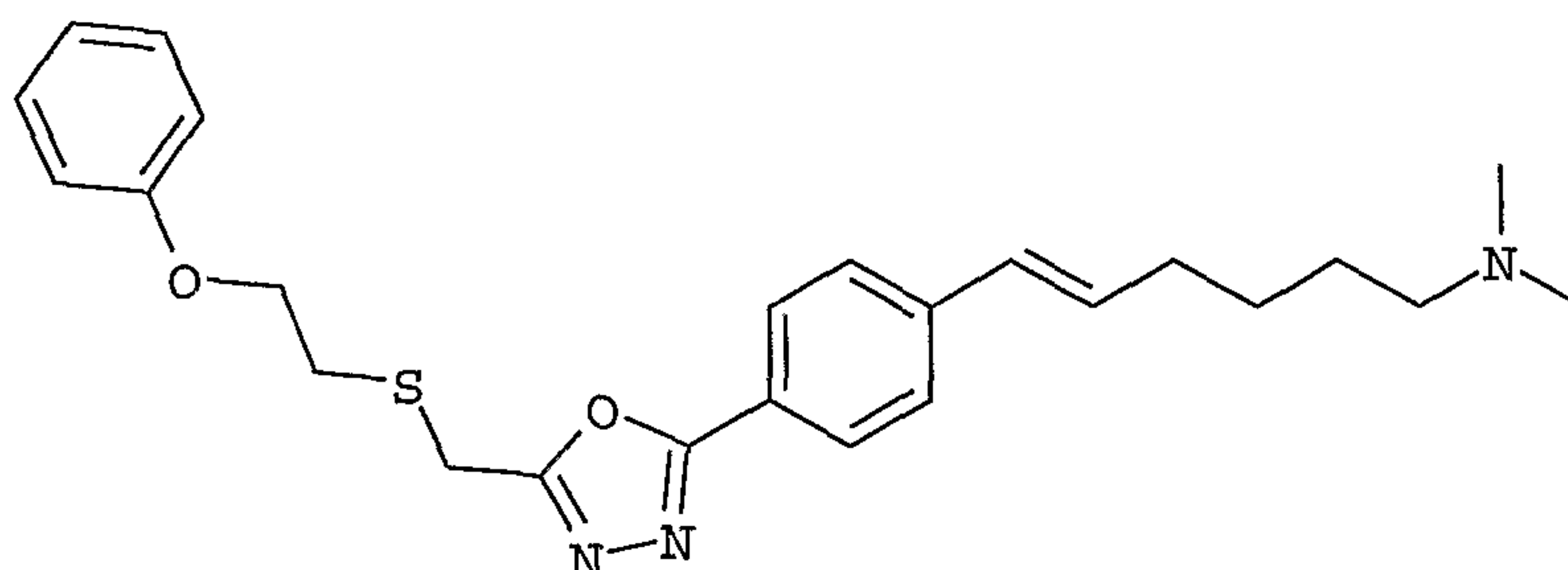
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mixture was stirred at -78°C for 2 h, 1 N HCl (20 mL) was added, and the mixture was allowed to warm to room temperature. The mixture was extracted with methylene chloride (3 x 10 mL). The combined methylene chloride extracts were dried (MgSO_4), concentrated, and purified by chromatography (silica gel, ethyl acetate/hexanes 1:4) to give a white solid (146 mg, 36%).

E-isomer: ^1H NMR (CDCl_3) δ 9.81 (s, 1H), 7.96 (d, 2H, $J=7.7$ Hz), 7.45 (d, 2H, $J=8.6$ Hz), 7.28 (m, 2H), 6.96 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=7.7$ Hz), 6.45 (d, 1H, $J=16.3$ Hz), 6.33 (dt, 1H, $J=16.3, 6.8$ Hz), 4.22 (t, 2H, $J=6.0$ Hz), 4.06 (s, 2H), 3.06 (t, 2H, $J=6.0$ Hz), 2.53 (t, 2H, $J=6.0$ Hz), 2.31 (dd, 2H, $J=10.8, 7.7$ Hz), 1.86 (quint, 2H, 7.7 Hz). MS (ES+) m/e 412 ($M+1$).

Z-isomer: ^1H NMR (CDCl_3) δ 9.78 (s, 1H), 7.99 (d, 2H, $J=8.5$ Hz), 7.38 (d, 2H, $J=8.6$ Hz), 7.26~7.29 (m, 2H), 6.95 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=7.7$ Hz), 6.49 (d, 1H, $J=11.1$ Hz), 5.75 (dt, 1H, $J=11.1, 6.8$ Hz), 4.22 (t, 2H, $J=6.4$ Hz), 4.06 (s, 2H), 3.06 (t, 2H, $J=6.0$ Hz), 2.48 (t, 2H, $J=6.8$ Hz), 2.39 (m, 2H), 1.81 (m, 2H). MS (ES+) m/e 412 ($M+1$).

c) 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[6-(N,N-dimethylamino)hexen-1-yl]phenyl}-1,3,4-oxadiazole



To a stirred mixture of 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(6-oxohexen-1-yl)phenyl]-1,3,4-oxadiazole (103 mg, 0.25 mmol), 2 M dimethylamine in tetrahydrofuran (0.25 mL, 0.5 mmol), and acetic acid (15 mg, 0.25 mmol) in 1,2-dichloroethane (2 mL) was added sodium triacetoxyborohydride (106 mg, 0.5 mmol) and stirring was continued at room temperature for 2 h. 2N NaOH (10 mL) was added and the mixture was extracted with methylene chloride (3 x 10 mL). The combined methylene chloride extracts were dried (MgSO_4), concentrated, and purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a white solid (87 mg, 80%).

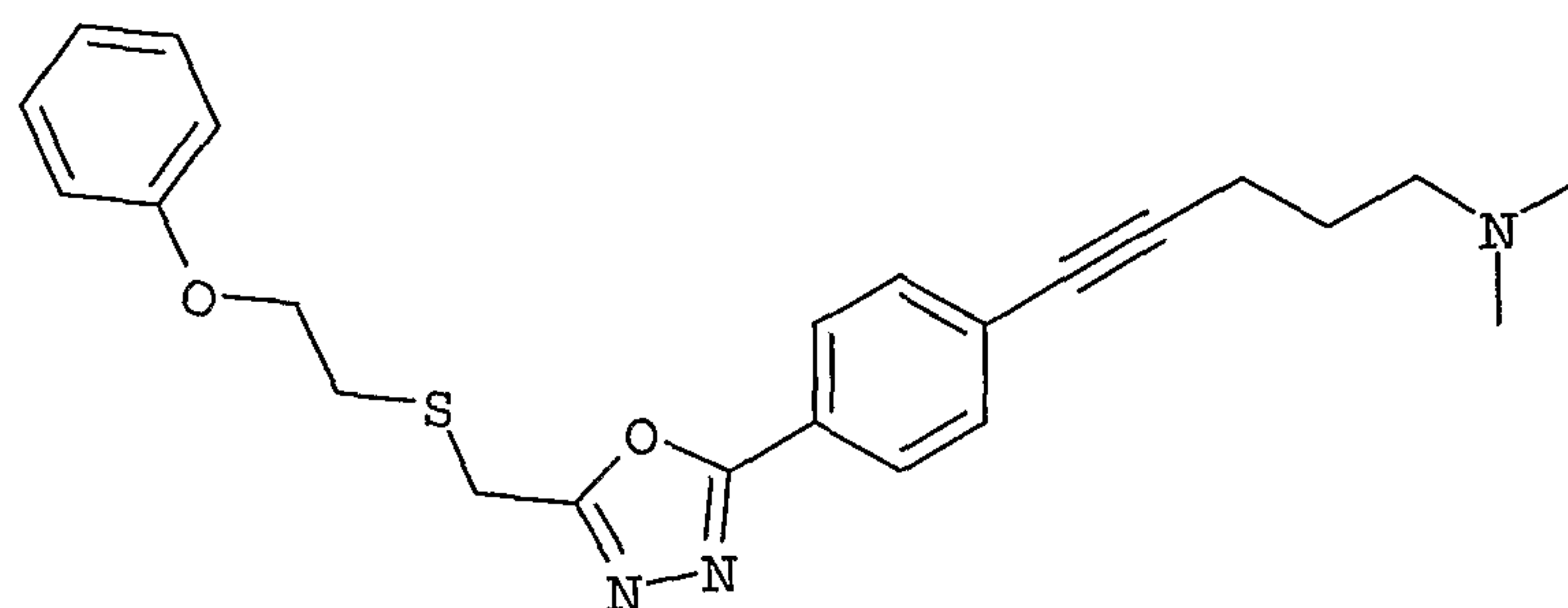
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E-isomer: ^1H NMR (CDCl_3) δ 7.95 (d, 2H, $J=8.6$ Hz), 7.44 (d, 2H, $J=8.6$ Hz), 7.28 (m, 2H), 6.95 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=7.7$ Hz), 6.43 (d, 1H, $J=15.4$ Hz), 6.36 (dt, 1H, $J=15.4, 6.8$ Hz), 4.21 (t, 2H, $J=6.4$ Hz), 4.05 (s, 2H), 3.06 (t, 2H, $J=6.0$ Hz), 2.34 (t, 4H, $J=6.8$ Hz), 2.29 (s, 6H), 2.28 (m, 2H), 1.50~1.59 (m, 4H). IR (KBr, cm^{-1}) 3070, 3035, 2954, 2879, 2684, 1599, 1566, 1475, 1339, 1254, 1057, 921, 748. MS (ES+) m/e 438 (M+1). Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_2\text{S}$: C, 68.62; H, 7.14; N, 9.60; S, 7.33. Found C, 68.33; H, 7.21; N, 9.47; S, 7.28.

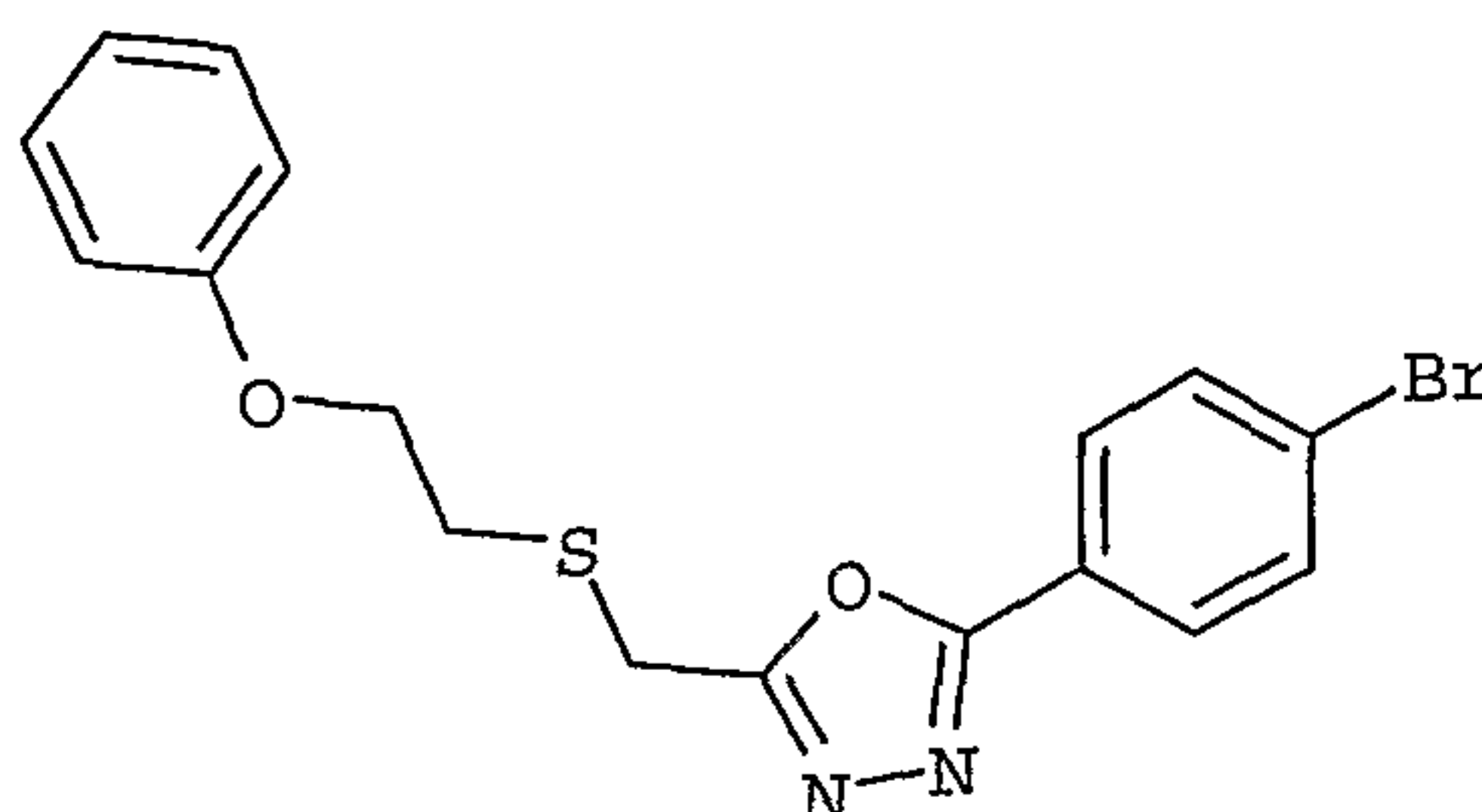
Z-isomer: ^1H NMR (CDCl_3) δ 7.99 (d, 2H, $J=7.7$ Hz), 7.39 (d, 2H, $J=8.6$ Hz), 7.28 (m, 2H), 6.95 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=7.7$ Hz), 6.45 (d, 1H, $J=11.1$ Hz), 5.78 (dt, 1H, $J=11.1, 7.7$ Hz), 4.22 (t, 2H, $J=6.4$ Hz), 4.06 (s, 2H), 3.06 (t, 2H, $J=6.4$ Hz), 2.37 (m, 2H), 2.29 (m, 2H), 2.24 (s, 6H), 1.50~1.56 (m, 4H). IR (film, cm^{-1}) 3061, 3029, 2943, 2856, 2816, 1600, 1508, 1458, 1248, 1061, 913, 743. MS (ES+) m/e 438 (M+1). Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_2\text{S}$: C, 68.62; H, 7.14; N, 9.60; S, 7.33. Found C, 68.56; H, 7.20; N, 9.81; S, 7.24.

Example 130

Preparation of 2-[[2-Phenoxyethylthio]methyl]-5-{4-[5-(N,N-dimethylamino)pentyn-1-yl]phenyl}-1,3,4-oxadiazole



a) 2-[[2-Phenoxyethylthio]methyl]-5-(4-bromophenyl)-1,3,4-oxadiazole



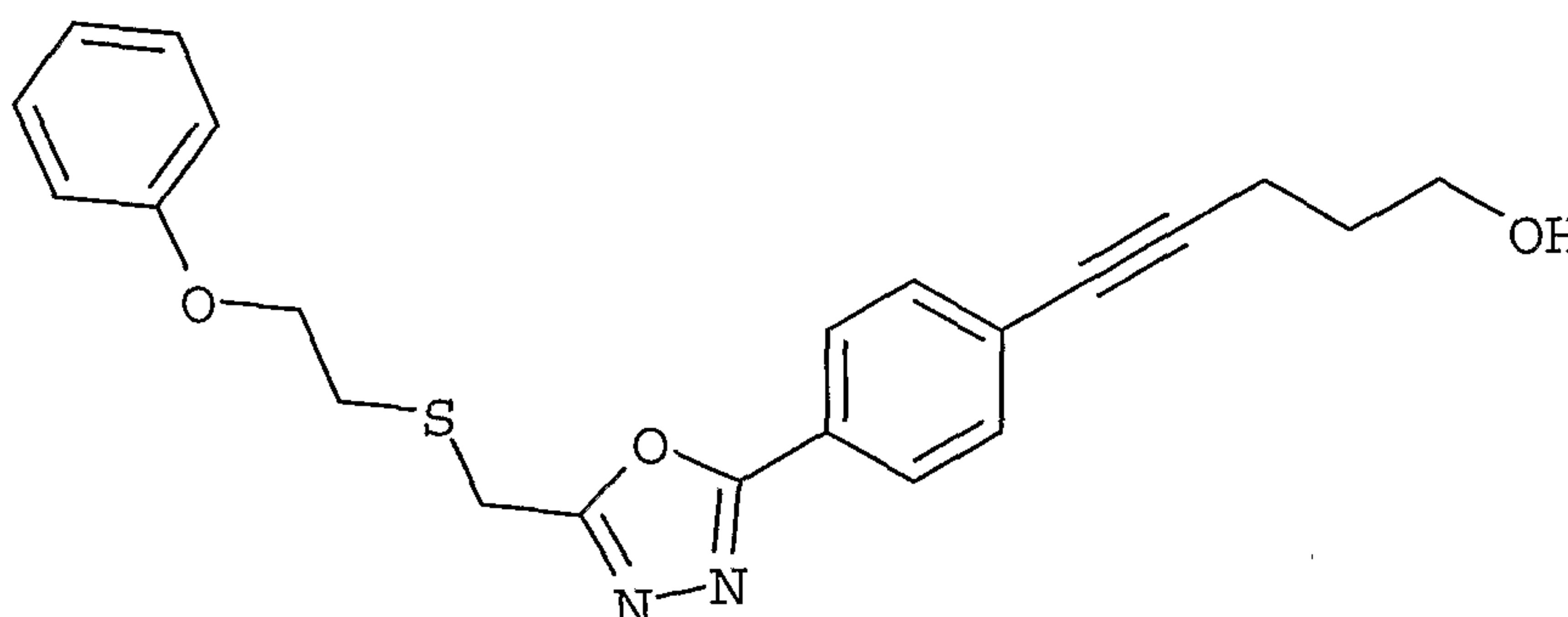
To a mixture of 4-bromobenzoic hydrazide (2.58 g, 12 mmol), 2-[[2-phenoxyethylthio]methyl]acetic acid (2.12 g, 10 mmol), and 4-(N,N-

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dimethylamino)phenyldiphenylphosphine (9.16 g, 30 mmol) in acetonitrile (100 mL) at 0 °C was added triethylamine (5.06 g, 50 mmol) in carbon tetrachloride (7.69 g, 50 mmol). After 15 min the cooling bath was removed and the mixture was stirred at room temperature overnight. The mixture was concentrated to approximately half the original volume and partitioned between ether (150 mL) and 2 M HCl (100 mL). The ether layer was washed with 2 M HCl (4 x 30 mL), dried (MgSO₄), and concentrated. The residue was triturated from methylene chloride and hexanes to give white powder (2.80 g, 72%)

¹H NMR (CDCl₃) δ 7.87 (d, 2H, J=8.8 Hz), 7.62 (d, 2H, J=8.8 Hz), 7.23~7.27 (m, 2H), 6.93 (t, 1H, J=7.5 Hz), 6.87 (d, 2H, J=7.7 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.04 (s, 2H), 3.03 (t, 2H, J=6.2 Hz). MS (ES+) m/e 392 (M+1).

b) 2-[(2-Phenoxyethyl)thio]methyl}-5-[4-(5-hydroxypentyn-1-yl)phenyl]-1,3,4-oxadiazole

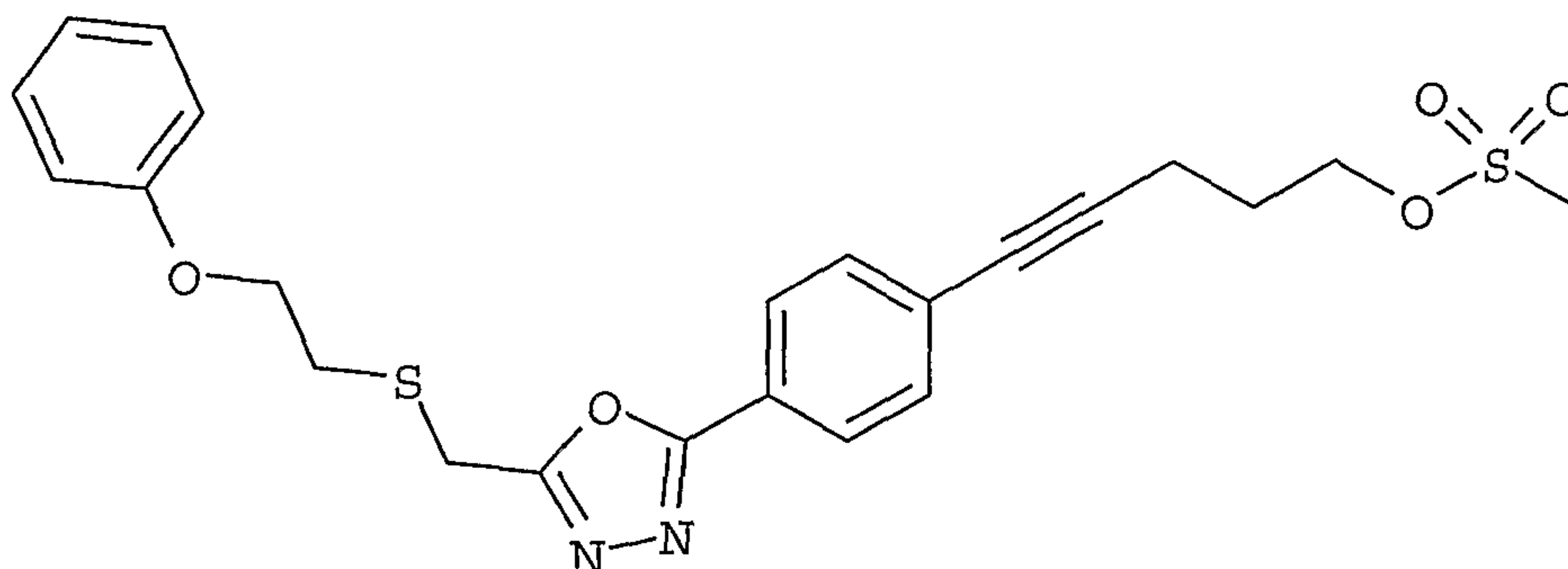


Palladium (II) acetate (30 mg, 0.13 mmol) and copper (I) iodide (30 mg, 0.16 mmol) were added to a solution of 2-[(2-phenoxyethyl)thio]methyl}-5-(4-bromophenyl)-1,3,4-oxadiazole (782 mg, 2 mmol), 4-pentyn-1-ol (186 mg, 2.2 mmol), triphenylphosphine (104 mg, 0.4 mmol), and diethylamine (438 mg, 6 mmol) in dimethylsulfoxide (15 mL). The mixture was stirred at 90 °C for 5 h, diluted with water (20 mL), and extracted with ethyl acetate (3 x 15 mL). The combined ethyl acetate extracts were washed with water (2 x 20 mL) and brine (20 mL), dried (MgSO₄), and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexanes 1:2) to give a yellow oil (704 mg, 89%).

¹H NMR (CDCl₃) δ 7.92 (d, 2H, J=8.5 Hz), 7.47 (d, 2H, J=8.5 Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=7.7 Hz), 4.19 (t, 2H, J=6.0 Hz), 4.03 (s, 2H), 3.81 (t, 2H, J=6.2 Hz), 3.03 (t, 2H, J=6.0 Hz), 2.56 (t, 2H, J=6.9 Hz), 1.86 (quint, 2H, J=6.9 Hz). MS (ES+) m/e 395 (M+1).

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c) 2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[5-(methylsulfonyloxy)pentyn-1-yl]phenyl}-1,3,4-oxadiazole

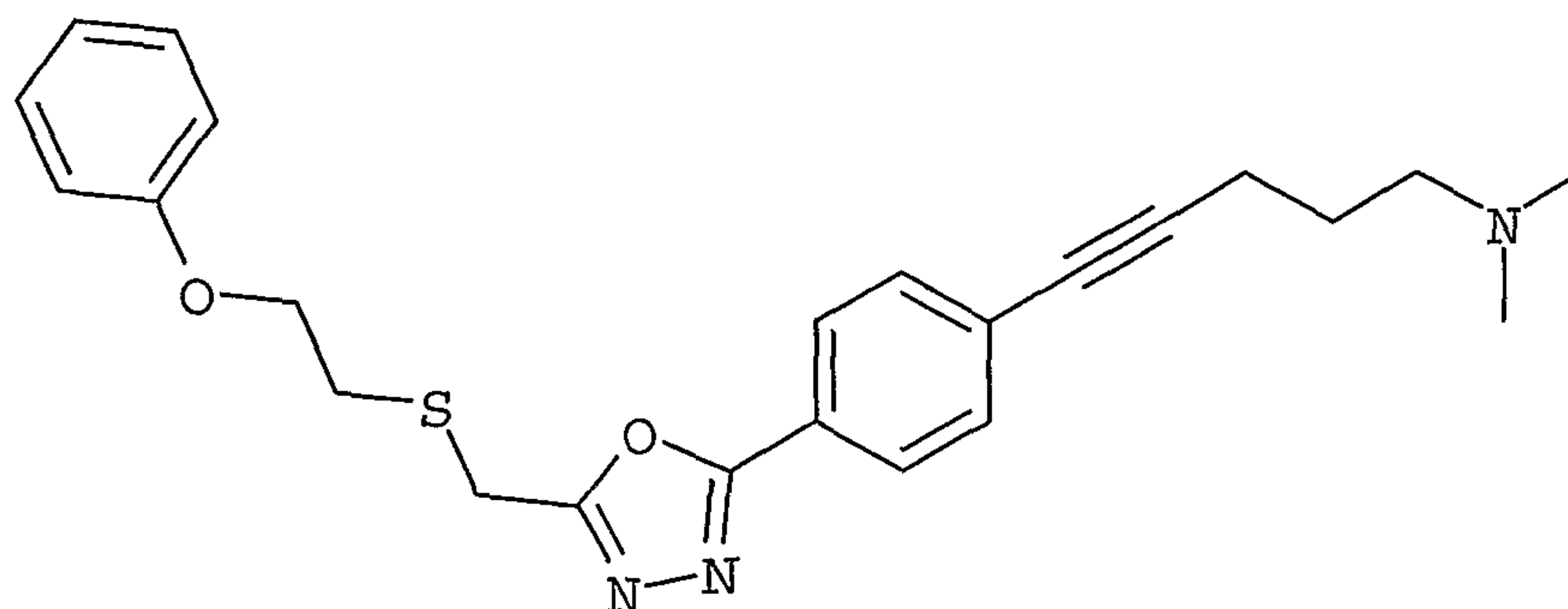


5 To a solution of 2-[[2-(phenoxyethyl)thio]methyl]-5-[4-(5-hydroxypentyn-1-yl)phenyl]-1,3,4-oxadiazole (205 mg, 0.5 mmol) and triethylamine (250 mg, 2.5 mmol) in methylene chloride (5 mL) was added methanesulfonyl chloride (115 mg, 1 mmol). The mixture was stirred at room temperature overnight, diluted with methylen chloride (10 mL), washed with 2 M NaOH (3 x 10 mL), dried (MgSO₄), and concentrated to give a
10 yellow oil (235, 100%).

¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8.4 Hz), 7.48 (d, 2H, J=8.4 Hz), 7.23~7.27 (m, 2H), 6.93 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=7.7 Hz), 4.40 (t, 2H, J=6.1 Hz), 4.19 (d, 2H, J=6.0 Hz), 4.04 (s, 2H), 3.03 (t, 2H, J=6.0 Hz), 3.02 (s, 3H), 2.61 (t, 2H, J=6.8 Hz), 2.05 (quint, 2H, J=6.9 Hz). MS (ES+) m/e 473 (M+1).

15

d) 2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[5-(N,N-dimethylamino)pentyn-1-yl]phenyl}-1,3,4-oxadiazole



A mixture of 2-[[2-(phenoxyethyl)thio]methyl]-5-{4-[5-(methylsulfonyloxy)pentyn-1-yl]phenyl}-1,3,4-oxadiazole (220 mg, 0.5 mmol), 2 M
20 dimethylamine in tetrahydrofuran (1 mL, 2 mmol), and potassium carbonate (690 mg, 5

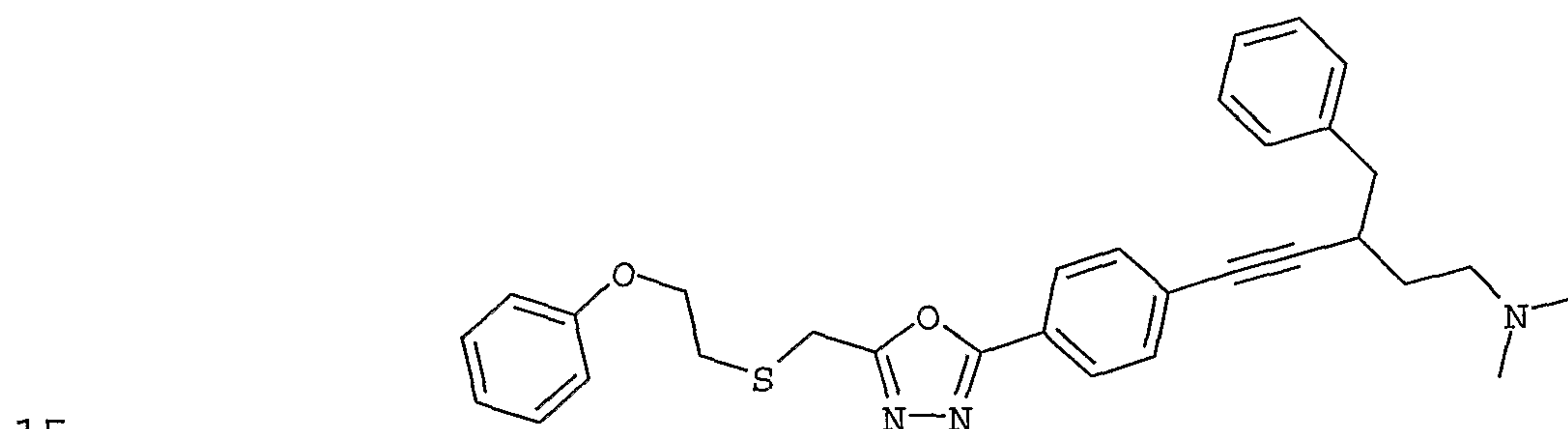
-267-

mmol) in acetonitrile (5 mL) was stirred under reflux overnight. The mixture was cooled to room temperature and filtered. The filtrate was concentrated and purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a yellow oil (101 mg, 50%).

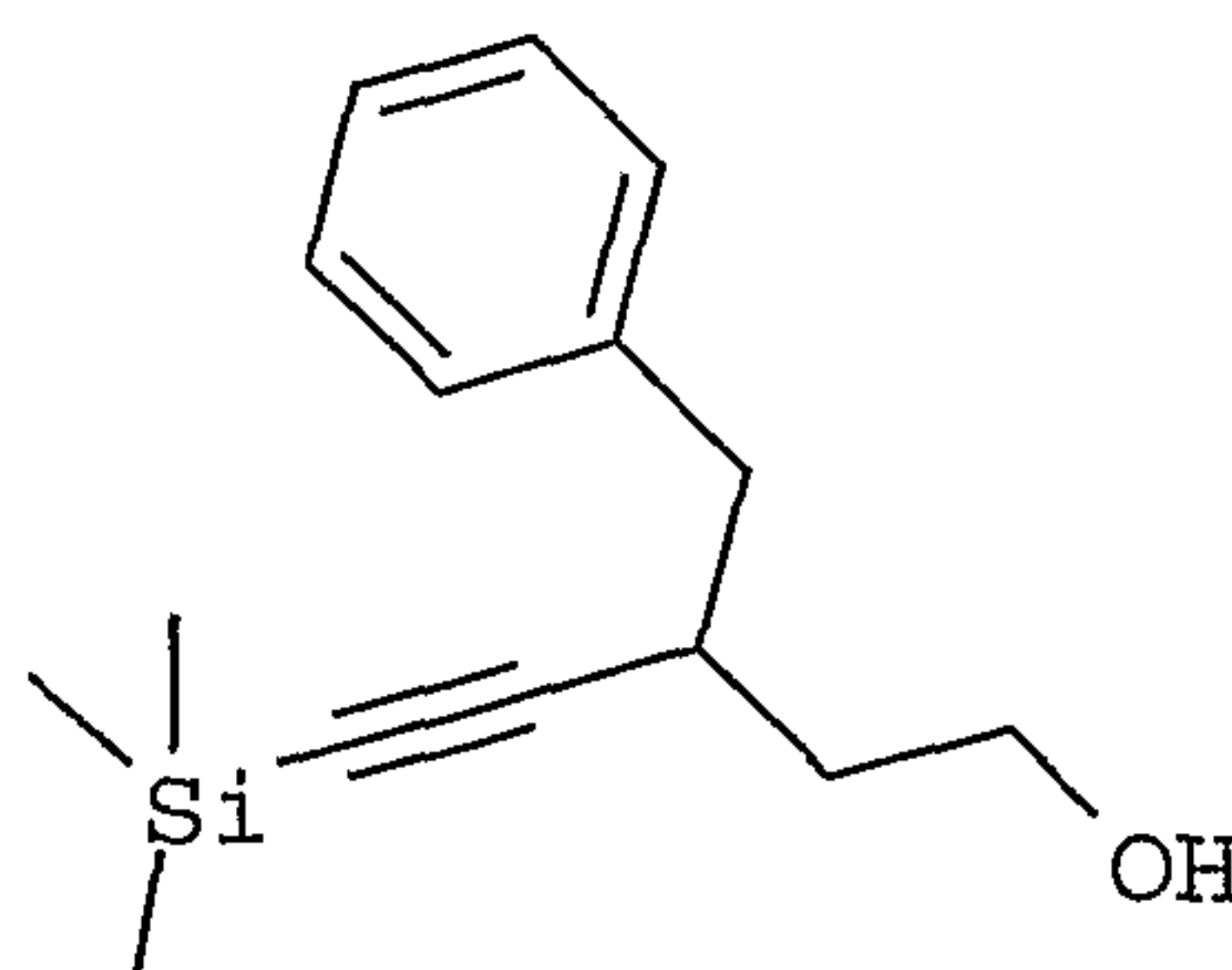
5 ^1H NMR (CDCl_3) δ 7.92 (d, 2H, $J=8.4$ Hz), 7.47 (d, 2H, $J=8.4$ Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=8.1$ Hz), 4.19 (d, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz), 2.47 (t, 2H, $J=7.3$ Hz), 2.41 (t, 2H, $J=7.3$ Hz), 1.81 (s, 6H), 1.77 (quint, 2H, $J=7.3$ Hz). IR (film, cm^{-1}) 3020, 2997, 2946, 2885, 2212, 1406, 1347, 1225, 1120, 1088. MS (ES+) m/e 422 ($M+1$). Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_2\text{S}$: C, 68.38; H, 6.46; N, 9.97; S, 7.61. Found C, 68.26; H, 6.59; N, 9.64; S, 7.69.

Example 131

Preparation of (+)-2-[(2-Phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-5-(N,N-dimethylamino)pentyn-1-yl]phenyl}-1,3,4-oxadiazole



a) (+)-3-Benzyl-5-hydroxy-1-trimethylsilyl-1-pentyne



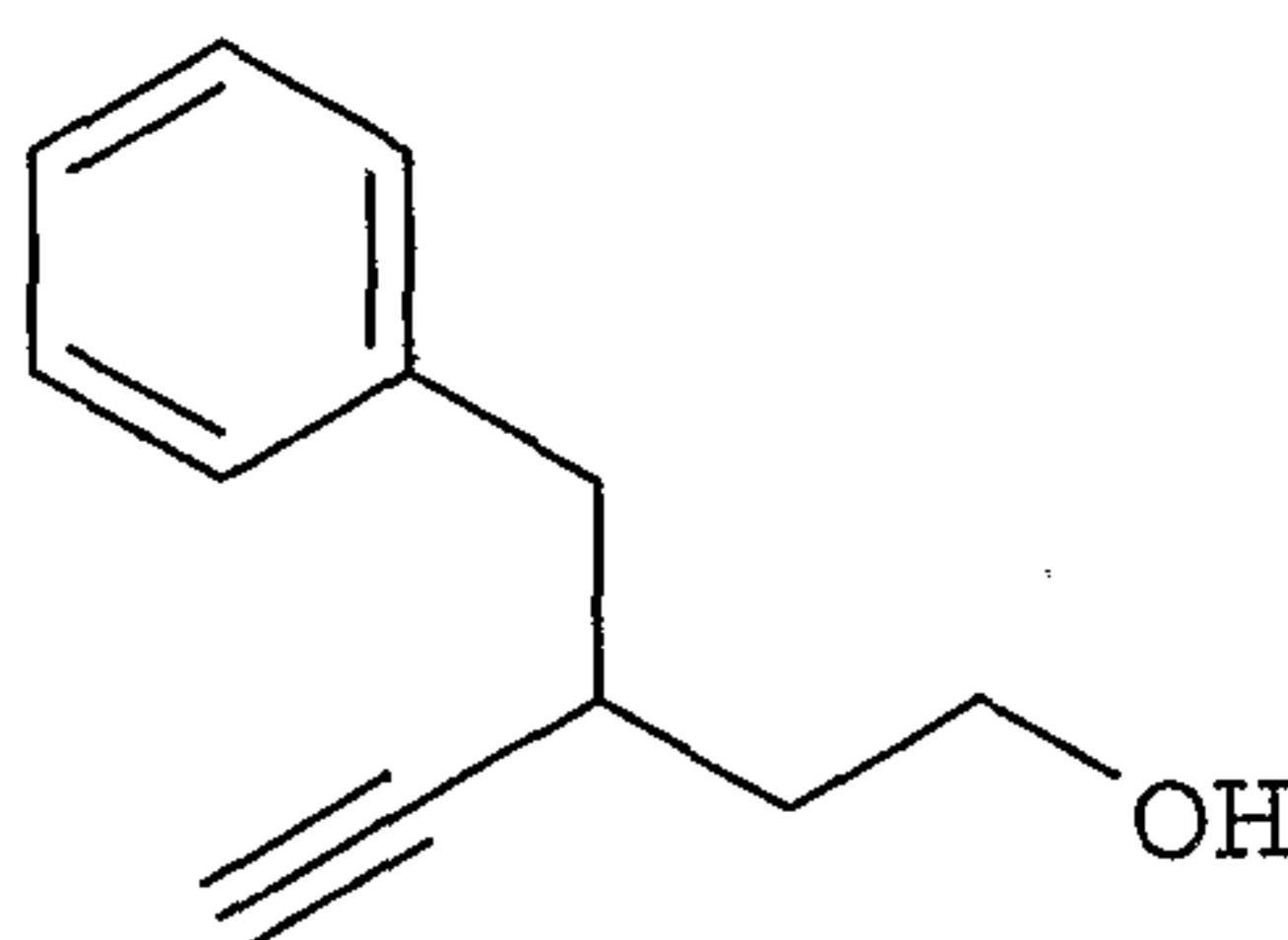
20 A solution of 5-(trimethylsilyl)-4-pentyn-1-ol (20 g, 128 mmol) and N,N,N',N'-tetramethylethylenediamine (42.5 mL, 282 mmol) in anhydrous THF (650 mL) was stirred under nitrogen and cooled to -30°C (dry ice/methylene chloride). n-Butyllithium (2.0 M in cyclohexane, 70.5 mL, 141 mmol) and t-butyllithium (1.7 M in pentanes, 82.8 mL, 141 mmol) were sequentially added slowly, while the temperature was maintained

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between -25° and -35° C. After complete addition, the mixture was stirred for 2 h, within this temperature range. The mixture was then cooled to -78° C (dry ice/acetone) and benzyl bromide (16 mL, 134 mmol) in tetrahydrofuran (400 mL) was added dropwise while temperature was maintained below -60° C. The reaction was then allowed to warm
5 to room temperature over 3 h. The reaction was quenched with saturated aqueous ammonium chloride (400 mL) and extracted with ethyl ether (2x300 mL). The organic material was dried (Na₂SO₄), filtered and concentrated to yield 35 g of a yellow liquid. This was purified on silica gel (20% ethyl acetate/hexanes) to yield 23.9 g (76%) of a yellow liquid.

10 ¹H NMR (CDCl₃) δ 7.28 (m, 3H), 7.22 (d, 2H, J=7 Hz), 3.79 (dd, 2H, J=5 and 6 Hz), 2.74-2.85 (m, 3H), 2.36 (t, 1H, J=14 Hz), 1.64-1.77 (m, 2H). MS (ES+) m/e 247 (M+1).

b) (+)-3-Benzyl-5-hydroxy-1-pentyne

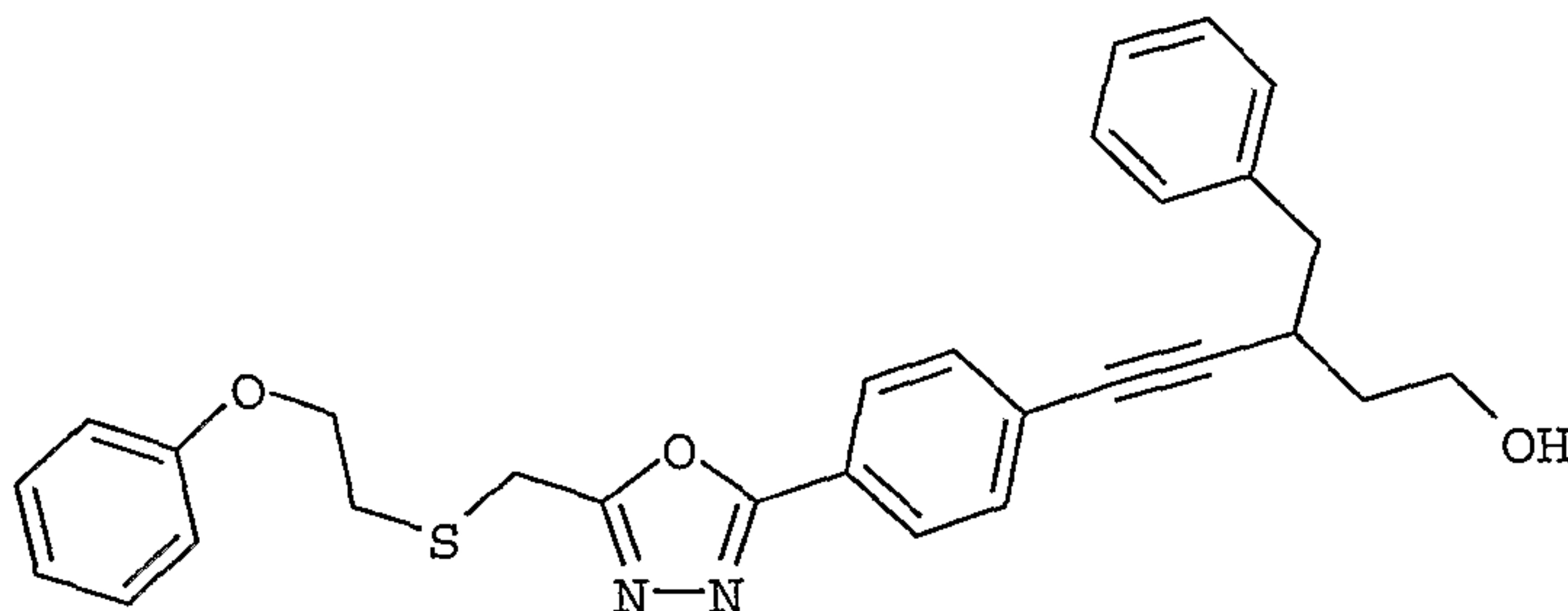


15 A solution (+)-3-benzyl-5-hydroxy-1-trimethylsilyl-1-pentyne (12.5 g, 50.8 mmol) in methanol (300 mL) saturated with potassium fluoride was refluxed for 1 h. The reaction was cooled to room temperature, diluted with brine (100 mL) and extracted with ethyl ether (3x100 mL). The organic material was washed with brine (2x50 mL), dried
20 (MgSO₄), filtered and concentrated to yield a colorless liquid. This was purified by silica gel (33% ethyl acetate/hexanes) to yield 3.68 g (42%) of a colorless liquid.

¹H NMR (CDCl₃) δ 7.30 (m, 5H), 3.83 (d, 2H, J=4 Hz), 2.77-2.88 (m, 3H), 2.12 (s, 1H), 1.78 (m, 1H), 1.66 (m, 1H), 1.53 (br s, 1H). MS (ES+) m/e 175 (M+1).

25 c) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(1-(3-benzyl-5-hydroxypentyn-1-yl)phenyl)-1,3,4-oxadiazole

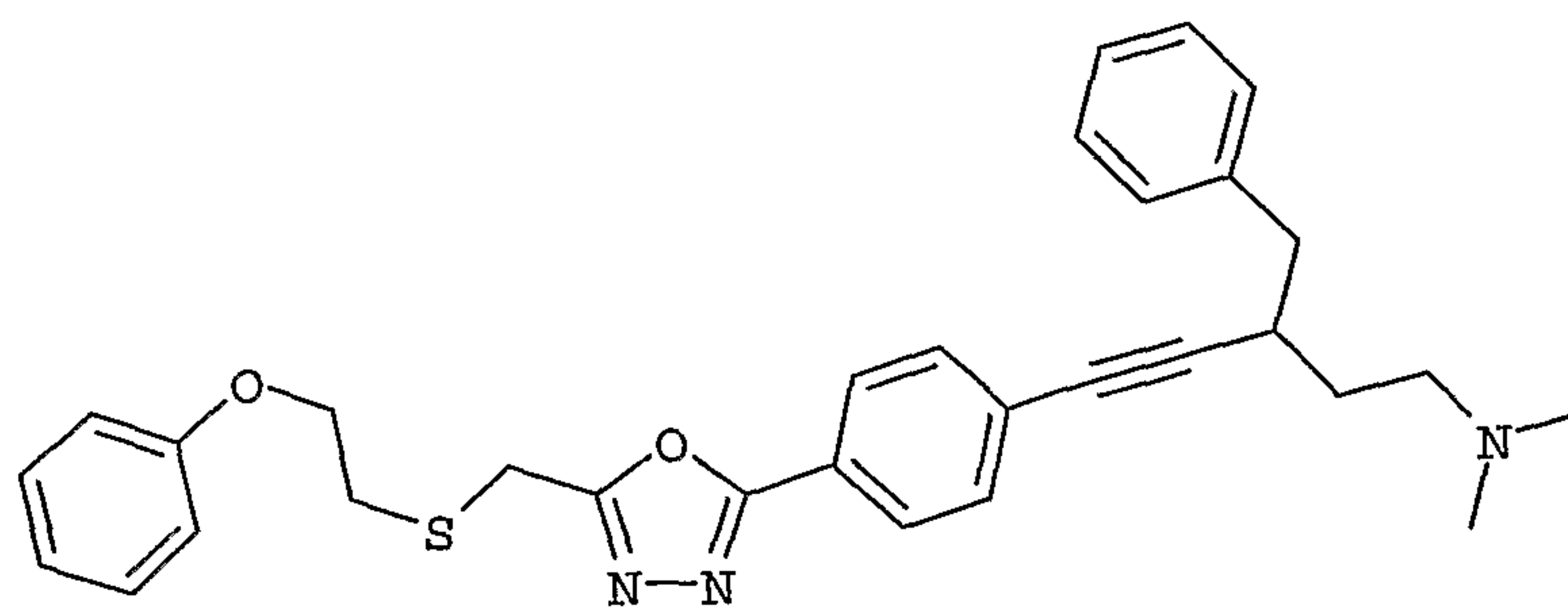
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A mixture containing 2-[[2-(2-phenoxyethyl)thio]methyl]-5-(4-bromophenyl)-1,3,4-oxadiazole (980 mg, 2.5 mmol), triphenyl-phosphine (131 mg, 0.5 mmol) and palladium (II) acetate (56 mg, 0.25 mmol) was stirred in anhydrous DMSO (10 mL) at room temperature under nitrogen. Solutions of (+)-3-benzyl-5-hydroxy-1-pentyne (480 mg, 2.75 mmol) in methyl sulfoxide (2 mL) and diethylamine (0.78 mL, 7.5 mmol) in methyl sulfoxide (5 mL) were subsequently added, followed by copper (I) iodide (5 mg, 0.025 mmol). This mixture was heated to 90° C for 4h. The reaction was cooled to room temperature, quenched with water (15 mL) and extracted with methylene chloride (3x40 mL). The organic material was washed with water (20 mL), dried (MgSO₄), filtered and concentrated to yield 1.67 g of a brown oil. This oil was purified by silica gel (33% ethyl acetate-hexanes) to yield 856 mg (71%) of a colorless oil.

¹H NMR (CDCl₃) δ 7.94 (d, 2H, J=9 Hz), 7.44 (d, 2H, J=9 Hz), 7.28 (m, 7H), 6.96 (dd, 1H, J=8 and 9 Hz), 6.89 (d, 2H, J=9 Hz), 4.21 (t, 2H, J=12 Hz), 4.06 (s, 2H), 3.89 (d, 2H, J=4 Hz), 3.09 (m, 1H), 3.06 (t, 2H, J=12 Hz), 2.92 (m, 2H), 1.90 (m, 1H), 1.78 (m, 1H), 1.52 (br s, 1H). MS (ES+) m/e 485 (M+1).

d) (+)-2-[[2-(2-Phenoxyethyl)thio]methyl]-5-{4-[3-benzyl-5-(N,N-dimethylamino)pentyn-1-yl]phenyl}-1,3,4-oxadiazole



A solution of (+)-2-[[2-(2-Phenoxyethyl)thio]methyl]-5-[4-(1-(3-benzyl-5-hydroxypentyn-1-yl)phenyl)-1,3,4-oxadiazole (250 mg, 0.52 mmol), triethylamine (0.36 mL, 2.58 mmol) and methanesulfonyl chloride (0.08 mL, 1.04 mmol) were stirred in

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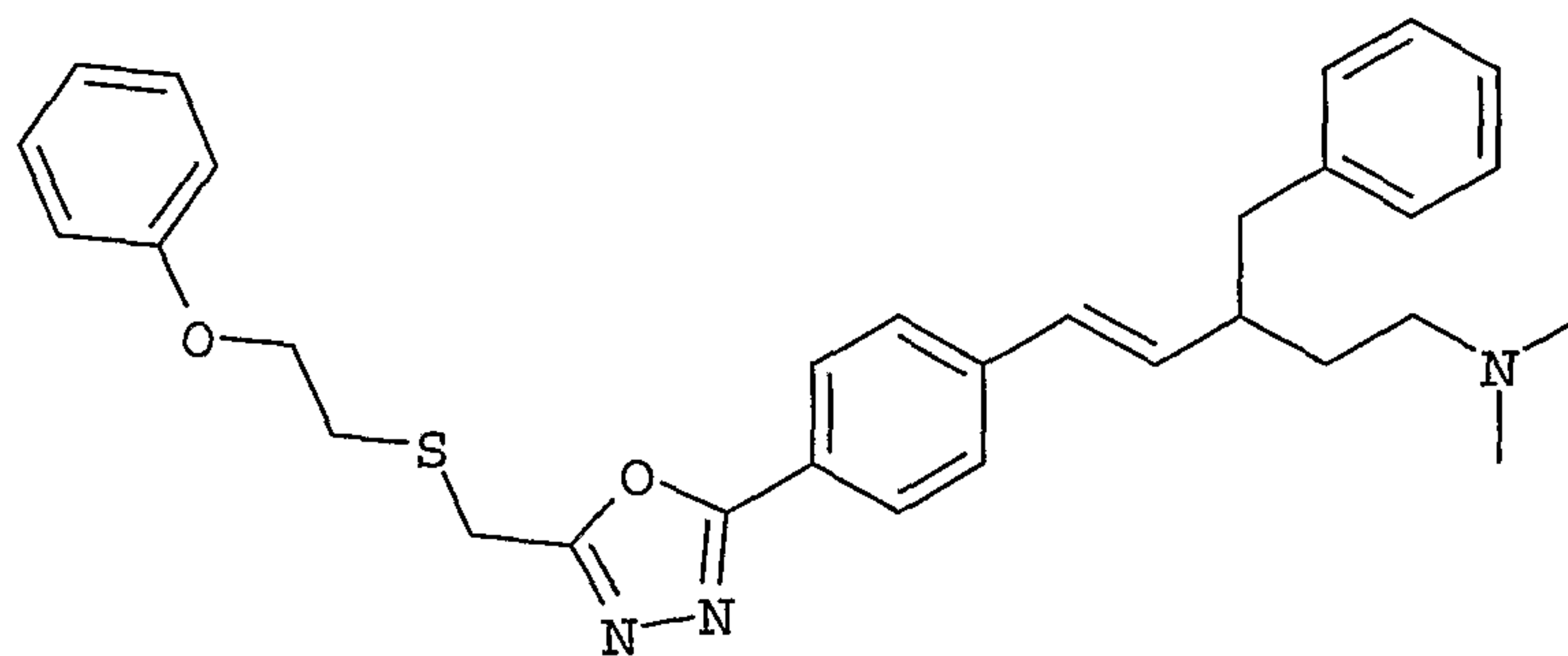
methylene chloride (5 mL) at room temperature for 16 h. The mixture was diluted with methylene chloride (20 mL), extracted with 2N NaOH (20 mL), dried (MgSO₄), filtered and concentrated to yield a quantitative amount of the corresponding mesylate.

The mesylate was combined with dimethylamine (2.0 M in THF, 1.03 mL, 2.06 mmol) and potassium carbonate (720 mg, 5.2 mmol) in acetonitrile (10 mL) and refluxed for 6 h. Since the reaction was not complete after 6 h., it was allowed to react at room temperature for an additional 16 h. After filtering the solids, the filtrate was concentrated to yield 231 mg of a brown oil. This was purified by preparative TLC (10% methanol/methylene chloride) to yield 73 mg (27%) of a colorless oil.

¹H NMR (CDCl₃) δ 7.91 (d, 2H, J=8 Hz), 7.41 (d, 2H, J=8 Hz), 7.26 (m, 7H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=9 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.03 (t, 2H, J=12 Hz), 2.93 (m, 1H), 2.85 (m, 2H), 2.47 (m, 2H), 2.21 (s, 6H), 1.74 (m, 1H), 1.65 (m, 1H). MS (ES+) m/e 512 (M+1). IR (film, cm⁻¹) 3410, 2936, 1601, 1493, 1462, 1239, 752, 698. Anal. Calcd for C₃₁H₃₃N₃O₂S: C, 72.77; H, 6.50; N, 8.21; S, 6.27. Found C, 72.45; H, 6.33; N, 8.16; S, 6.18.

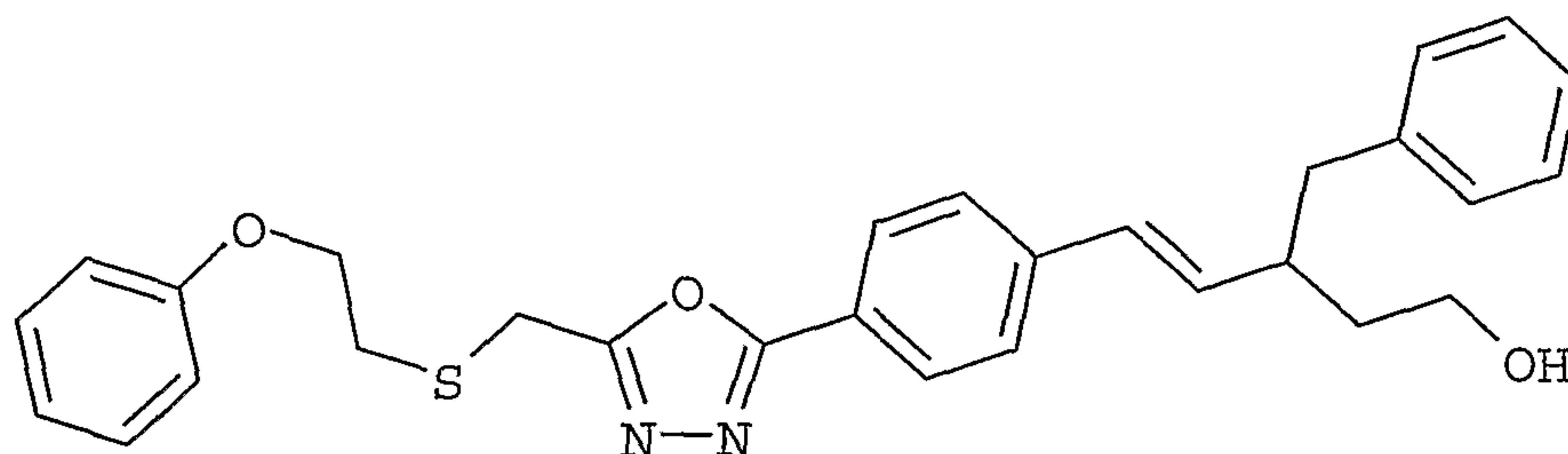
Example 132

Preparation of (E)-(+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-5-(N,N-dimethylamino)penten-1-yl]phenyl}-1,3,4-oxadiazole



a) (E)-(+)-2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(3-benzyl-5-hydroxypenten-1-yl)phenyl]-1,3,4-oxadiazole

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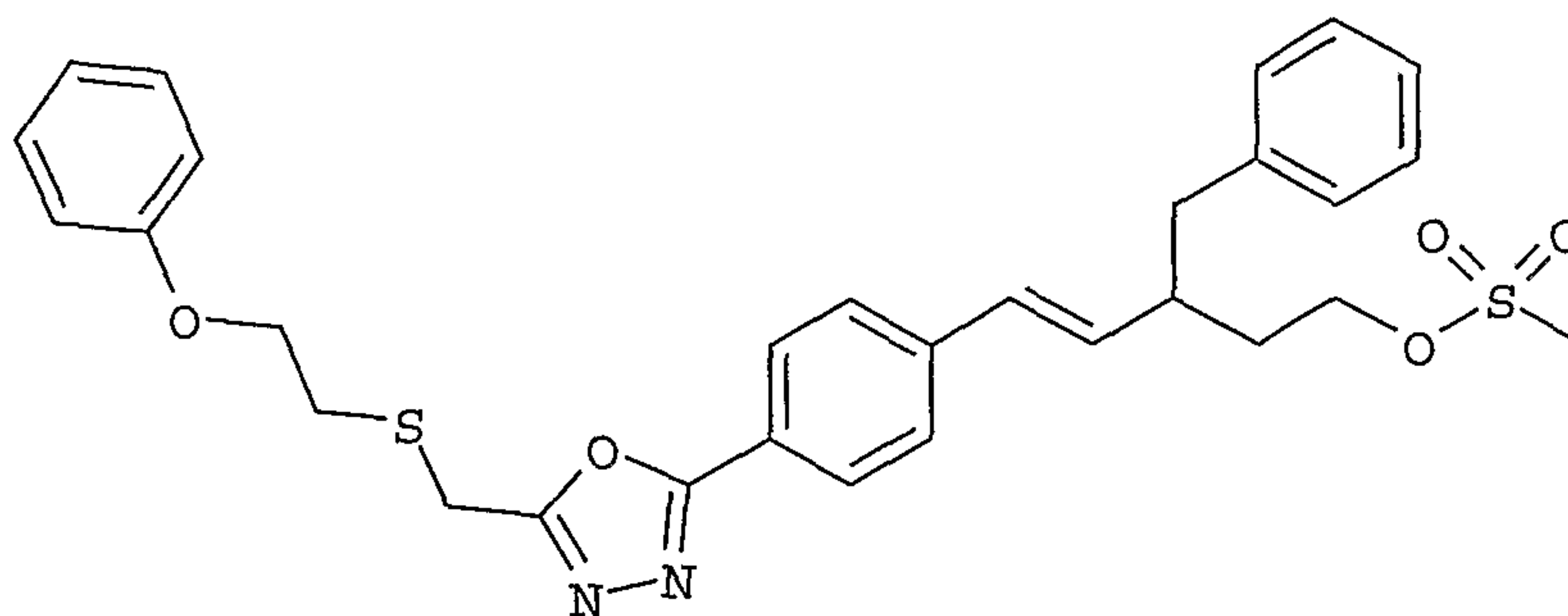


A solution containing Red-Al (65 wt% in toluene, 0.2 mL, 0.67 mmol) in anhydrous tetrahydrofuran (5.5 mL) was stirred in an ice-water bath under nitrogen. A solution of (+)-2-[[[2-(phenoxyethyl)thio]methyl]-5-[4-(1-(3-benzyl-5-hydroxypentyn-1-yl)phenyl]-1,3,4-oxadiazole (0.27 g, 0.56 mmol) in anhydrous tetrahydrofuran (10 mL) was added and stirring was continued in the cooling bath until the bubbling due to hydrogen evolution had ceased. The bath was then removed and the reaction was refluxed for 2 h. Since the reaction had not completed, the mixture was again cooled in an ice-water bath and more Red-Al (0.1 mL, 0.33 mmol) was added. The reaction was refluxed for another 1.5 h until starting material was gone. The mixture was then cooled in an ice-water bath and quenched with water (3 mL). The mixture was then extracted with ethyl acetate (2x10 mL). The combined organic material was extracted with brine (2x10 mL), dried (MgSO₄), filtered and concentrated to yield 257 mg of a yellow oil. This material was purified by chromatography (50% ethyl acetate/hexanes) to yield 34 mg (12%) of a white solid. This procedure was repeated twice to generate enough material to continue.

¹H NMR (CDCl₃) δ 7.92 (d, 2H, J=9 Hz), 7.38 (d, 2H, J=9 Hz), 7.25 (m, 4H), 7.16 (m, 3H), 6.93 (dd, 1H, J=7 and 7 Hz), 6.87 (d, 2H, J=8 Hz), 6.32 (d, 1H, J=6 Hz), 6.16 (dd, 1H, J=6 and 9 Hz), 4.18 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.68 (m, 2H), 3.03 (t, 2H, J=12 Hz), 2.75 (d, 2H, J=7 Hz), 2.52 (m, 1H), 1.81 (m, 1H), 1.63 (m, 1H), 1.20 (m, 1H). MS (ES⁺) m/e 487 (M+1).

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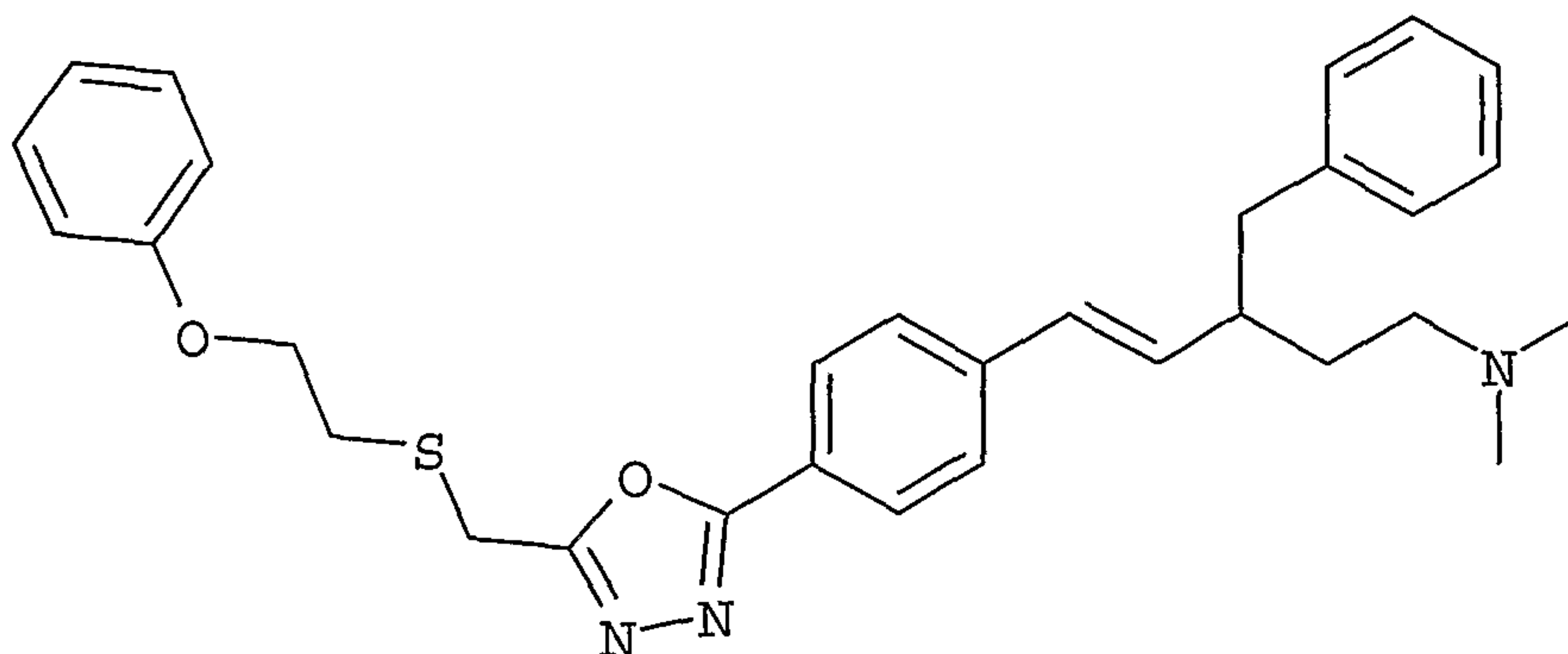
b) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-5-(methylsulfonyloxy)penten-1-yl]phenyl}-1,3,4-oxadiazole



To a solution of (E)-(+)-2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(3-benzyl-5-hydroxypenten-1-yl)phenyl]-1,3,4-oxadiazole (60 mg, 0.12 mmol) and triethylamine (50 mg, 0.5 mmol) in methylene chloride (2 mL) at 0 °C was added methanesulfonyl chloride (29 mg, 0.25 mmol). The resultant mixture was stirred at room temperature overnight, diluted with methylene chloride (20 mL), washed with 2 M HCl (5 mL) and 2 M NaOH (5 mL), dried (MgSO₄), and concentrated to give a yellow oil (61 mg, 90%).

¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8.6 Hz), 7.38 (d, 2H, J=8.6 Hz), 7.20~7.31 (m, 4H), 7.18 (t, 1H, J=7.0 Hz), 7.14 (d, 2H, J=7.0 Hz), 6.93 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.35 (d, 1H, J=15.6 Hz), 6.10 (dd, 1H, J=15.6, 8.9 Hz), 4.20~4.26 (m, 2H), 4.19 (d, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.03 (t, 2H, J=6.2 Hz), 2.91 (s, 3H), 2.76 (d, 2H, J=6.3 Hz), 2.03 (m, 1H), 1.75 (m, 1H), 1.38 (m, 1H). MS (ES⁺) m/e 565 (M+1).

c) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-5-(N,N-dimethylamino)penten-1-yl]phenyl}-1,3,4-oxadiazole



A mixture of (+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-5-(methylsulfonyloxy)penten-1-yl]phenyl}-1,3,4-oxadiazole (61 mg, 0.11 mmol), 2 M dimethylamine in tetrahydrofuran (0.6 mL, 1.2 mmol), and potassium carbonate (166 mg,

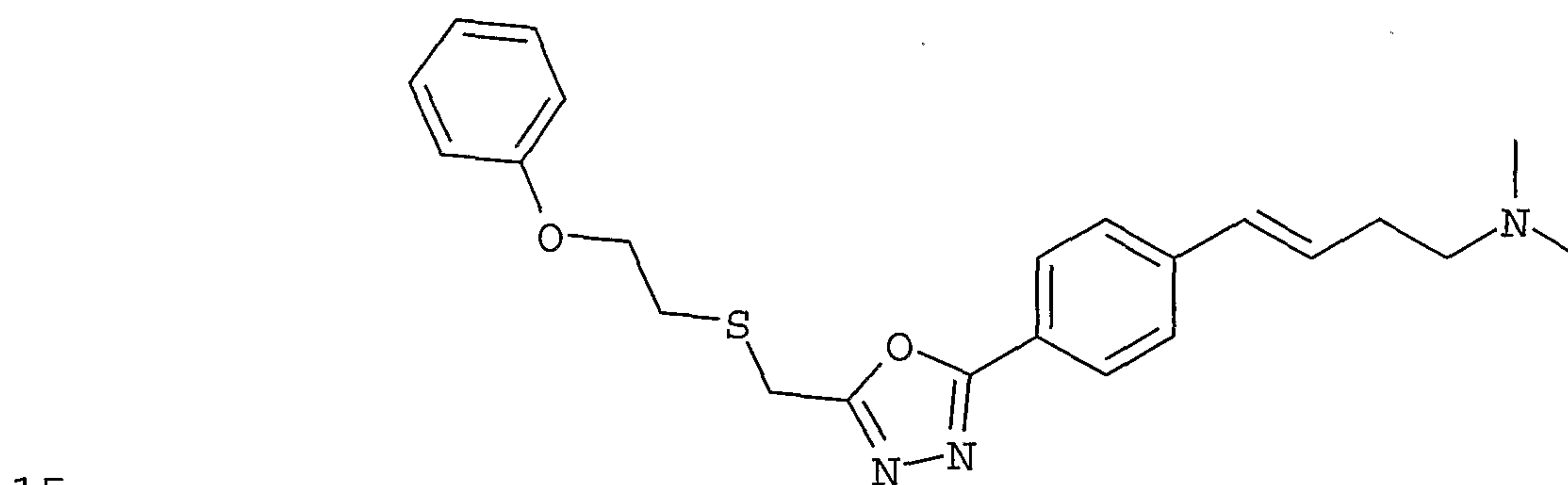
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1.2 mmol) in acetonitrile (10 mL) was stirred under reflux for 20 h and filtered. The filtrate was concentrated and purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a white solid (32 mg, 57%).

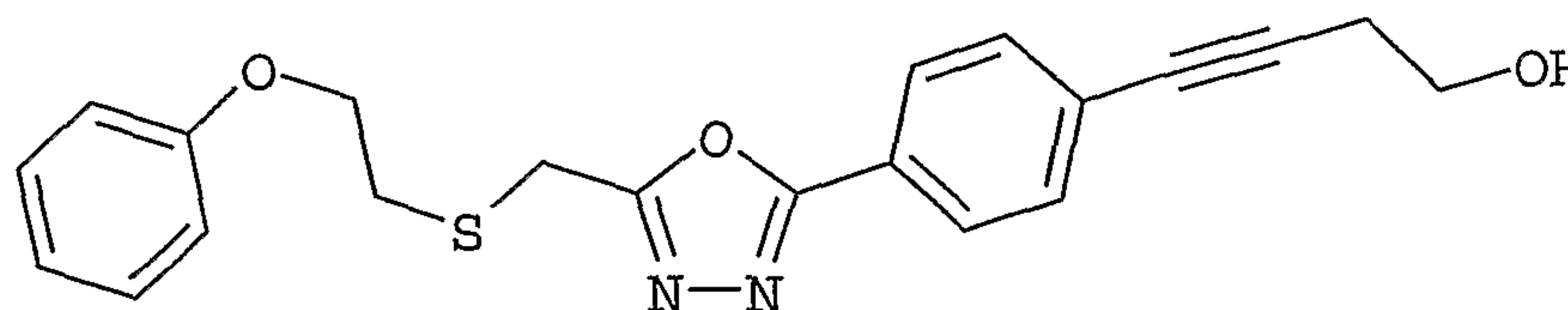
¹H NMR (CDCl₃) δ 7.92 (d, 2H, J=8.6 Hz), 7.38 (d, 2H, J=8.6 Hz), 7.13~7.26 (m, 7H), 6.93 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.28 (d, 1H, J=16.4 Hz), 6.13 (dd, 1H, J=16.3, 8.5 Hz), 4.18 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.03 (t, 2H, J=6.2 Hz), 2.74 (d, 2H, J=7.0 Hz), 2.55 (m, 1H), 2.32 (t, 2H, J=7.8 Hz), 2.21 (s, 6H), 1.74 (m, 1H), 1.55 (m, 1H). IR (KBr, cm⁻¹) 3032, 2955, 2906, 1600, 1557, 1476, 1348, 1179, 1126, 747. MS (ES+) m/e 514 (M+1). Anal. Calcd for C₃₁H₃₅N₃O₂S: C, 72.48; H, 6.87; N, 8.18; S, 6.24. Found C, 71.91; H, 6.81; N, 8.23; S, 6.34.

Example 133

Preparation of 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[4-(N,N-dimethylamino)buten-1-yl]phenyl}-1,3,4-oxadiazole



a) 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(4-hydroxybutyn-1-yl)phenyl]-1,3,4-oxadiazole



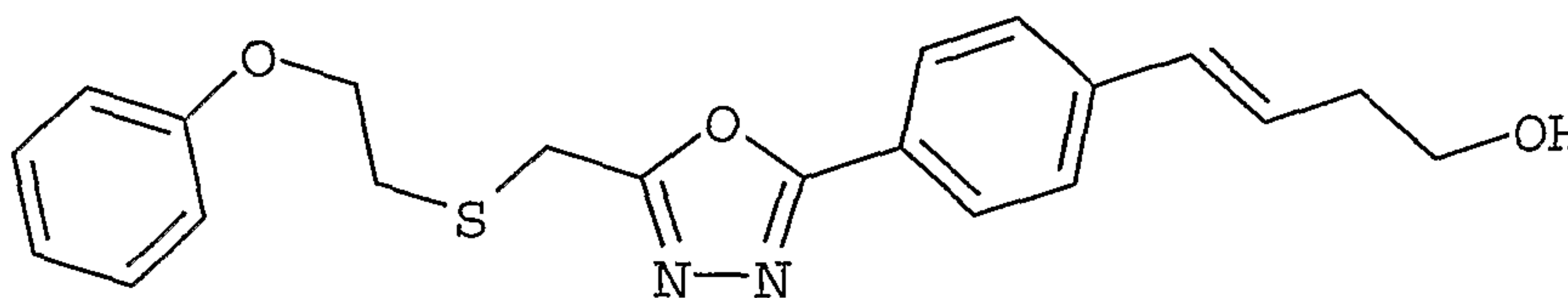
A mixture containing 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-bromophenyl)-1,3,4-oxadiazole (5g, 12.8 mmol), triphenyl-phosphine (0.67 g, 2.56 mmol) and palladium (II) acetate (287 mg, 1.28 mmol) was stirred in anhydrous dimethylsulfoxide (50 mL) at room temperature under nitrogen. Solutions of 3-butyn-1-ol (1.07 mL, 14.1 mmol) in dimethylsulfoxide (10 mL) and diethylamine (4 mL, 38.4 mmol) in dimethylsulfoxide (10 mL) were subsequently added, followed by copper (I) iodide (25 mg, 0.128 mmol). This

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mixture was heated to 90° C for 3 h. The reaction was cooled to room temperature, quenched with water (75 mL) and extracted with ethyl acetate (3x100 mL). The organic material was washed with brine (3x50 mL), dried (MgSO₄), filtered and concentrated to yield 5.92 g of a brown oil. This oil was purified by silica gel (50% ethyl acetate/hexanes) to yield 1.91 g (39%) of a colorless oil.

¹H NMR (CDCl₃) δ 7.94 (d, 2H, J=8 Hz), 7.50 (d, 2H, J=8 Hz), 7.28 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.83 (dd, 2H, J=6 and 12 Hz), 3.09 (m, 1H), 3.04 (t, 2H, J=12 Hz), 2.71 (t, 2H, J=12 Hz), 1.76 (t, 1H, J=12 Hz). MS (ES+) m/e 381 (M+1).

b) (E)-2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(4-hydroxybuten-1-yl)phenyl]-1,3,4-oxadiazole



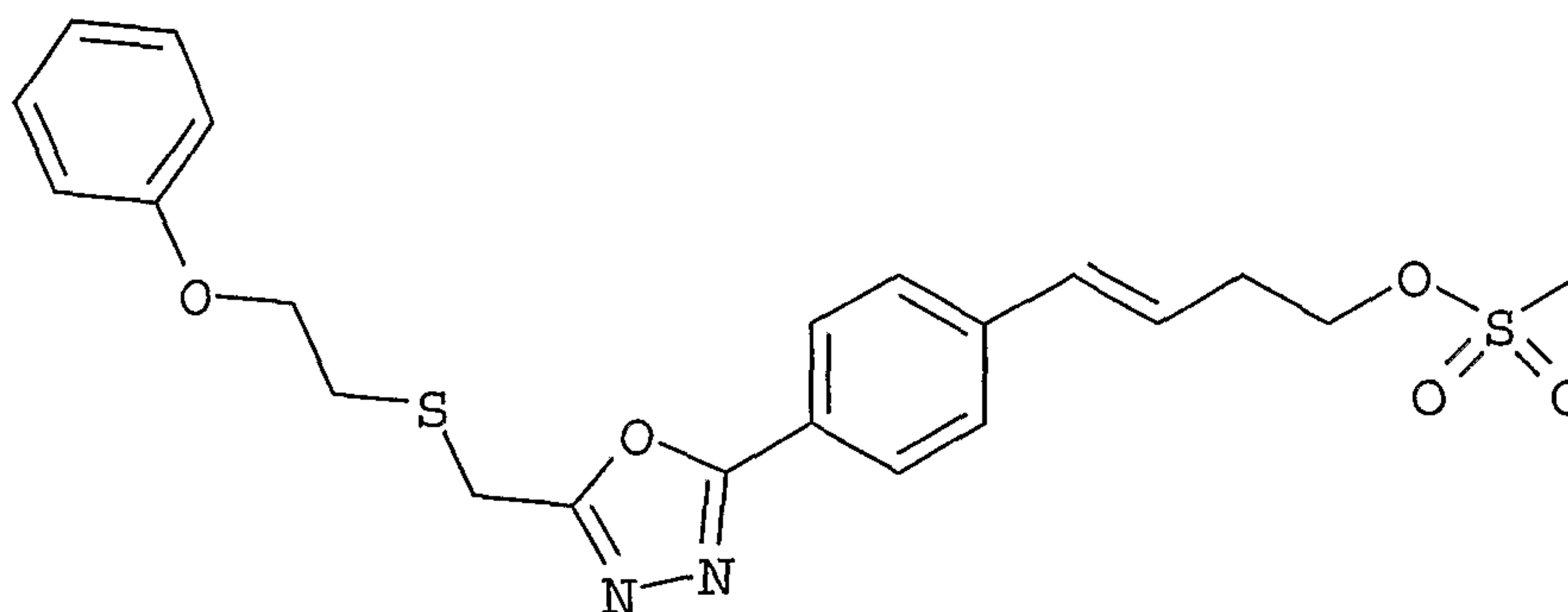
A solution containing Red-Al (0.73 mL, 2.4 mmol) in anhydrous tetrahydrofuran (12 mL) was stirred in an ice-water bath under nitrogen. A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(4-hydroxybutyn-1-yl)phenyl]-1,3,4-oxadiazole (0.76 g, 2.0 mmol) in anhydrous tetrahydrofuran (10 mL) was added and stirring was continued in the cooling bath until the bubbling due to hydrogen evolution had ceased. The bath was then removed and the reaction was refluxed for 1 h. Even though some of the alkyne starting material was present, the reaction was stopped here because TLC indicated that the product was decomposing. The mixture was then cooled in an ice-water bath and quenched with water (5 mL). The mixture was diluted with more water (10 mL) and then extracted with ethyl acetate (3x30 mL). The combined organic material was extracted with brine (2x20 mL), dried (MgSO₄), filtered and concentrated to yield 890 mg of a yellow oil which contained products and the alkyne starting material. This material was purified by preparative TLC (50% ethyl acetate/hexanes) to yield 128 mg (22%, based on converted starting material) of a white solid and 187 mg of alkyne starting material.

¹H NMR (CDCl₃) δ 7.94 (d, 2H, J=8 Hz), 7.45 (d, 2H, J=8 Hz), 7.25 (m, 4H), 7.25 (m, 2H), 6.94 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 6.52 (d, 1H, J=15 Hz), 6.36

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(m, 1H), 4.18 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.78 (m, 2H), 3.03 (t, 2H, J=12 Hz), 2.75 (d, 2H, J=7 Hz), 2.52 (m, 2H), 1.43 (m, 1H). MS (ES+) m/e 383 (M+1).

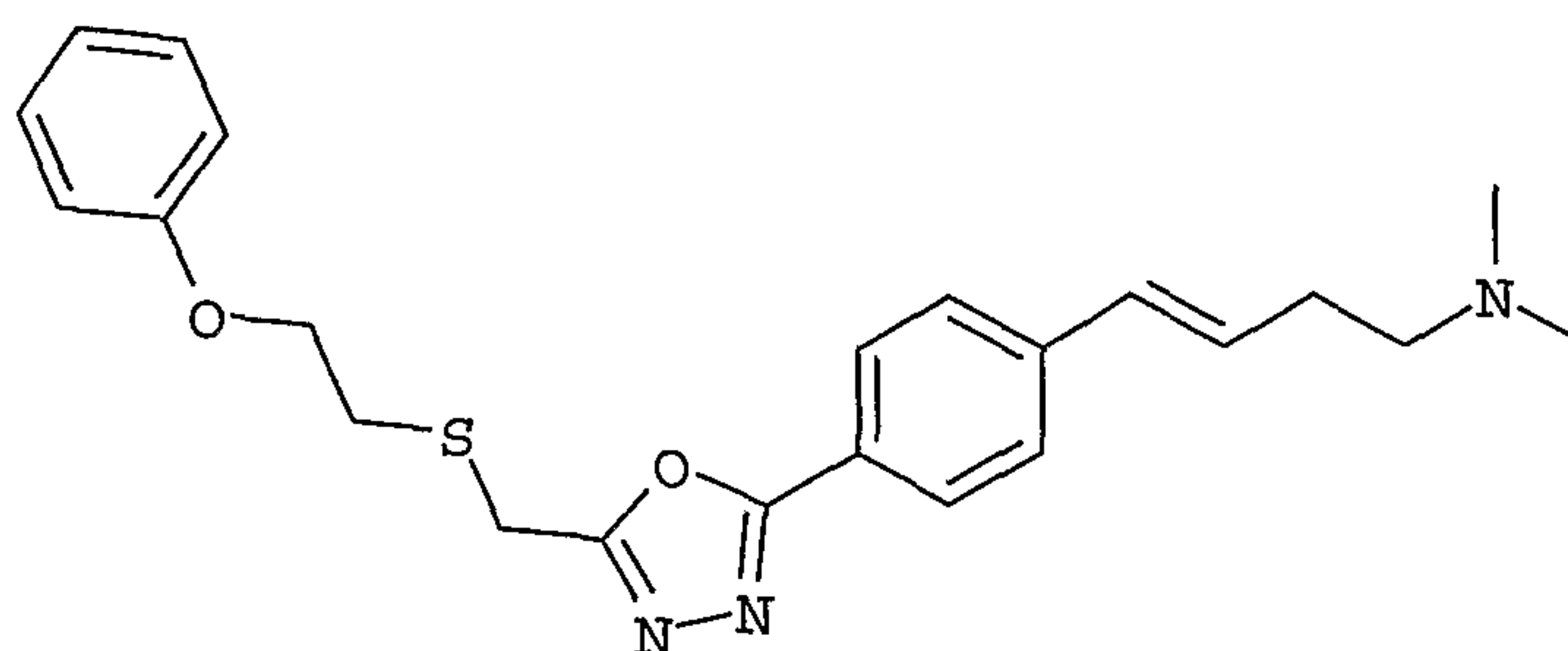
c) (E)-2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[4-(methylsulfonyloxy)buten-1-yl]phenyl}-1,3,4-oxadiazole



To a solution of (E)-2-[[2-(phenoxyethyl)thio]methyl]-5-[4-(4-hydroxybuten-1-yl)phenyl]-1,3,4-oxadiazole (120 mg, 0.31 mmol) and triethylamine (121 mg, 1.2 mmol) in methylen chloride (3 mL) at 0 °C was added methanesulfonyl chloride (69 mg, 0.6 mmol). The resultant mixture was stirred at room temperature overnight, diluted with methylene chloride (20 mL), washed with 2 M HCl (5 mL) and 2 M NaOH (5 mL), dried (MgSO₄), and concentrated to give yellow oil (138 mg, 97%).

¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8.6 Hz), 7.44 (d, 2H, J=8.6 Hz), 7.22~7.27 (m, 2H), 6.93 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.54 (d, 1H, J=16.4 Hz), 6.28 (dt, 1H, J=16.4, 7.0 Hz), 4.34 (t, 2H, J=6.2 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.04 (t, 2H, J=6.2 Hz), 3.01 (s, 3H), 2.68 (m, 2H). MS (ES+) m/e 461 (M+1).

d) (E)-2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[4-(N,N-dimethylamino)buten-1-yl]phenyl}-1,3,4-oxadiazole



A mixture of (E)-2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[4-(methylsulfonyloxy)buten-1-yl]phenyl}-1,3,4-oxadiazole (120 mg, 0.29 mmol), 2 M

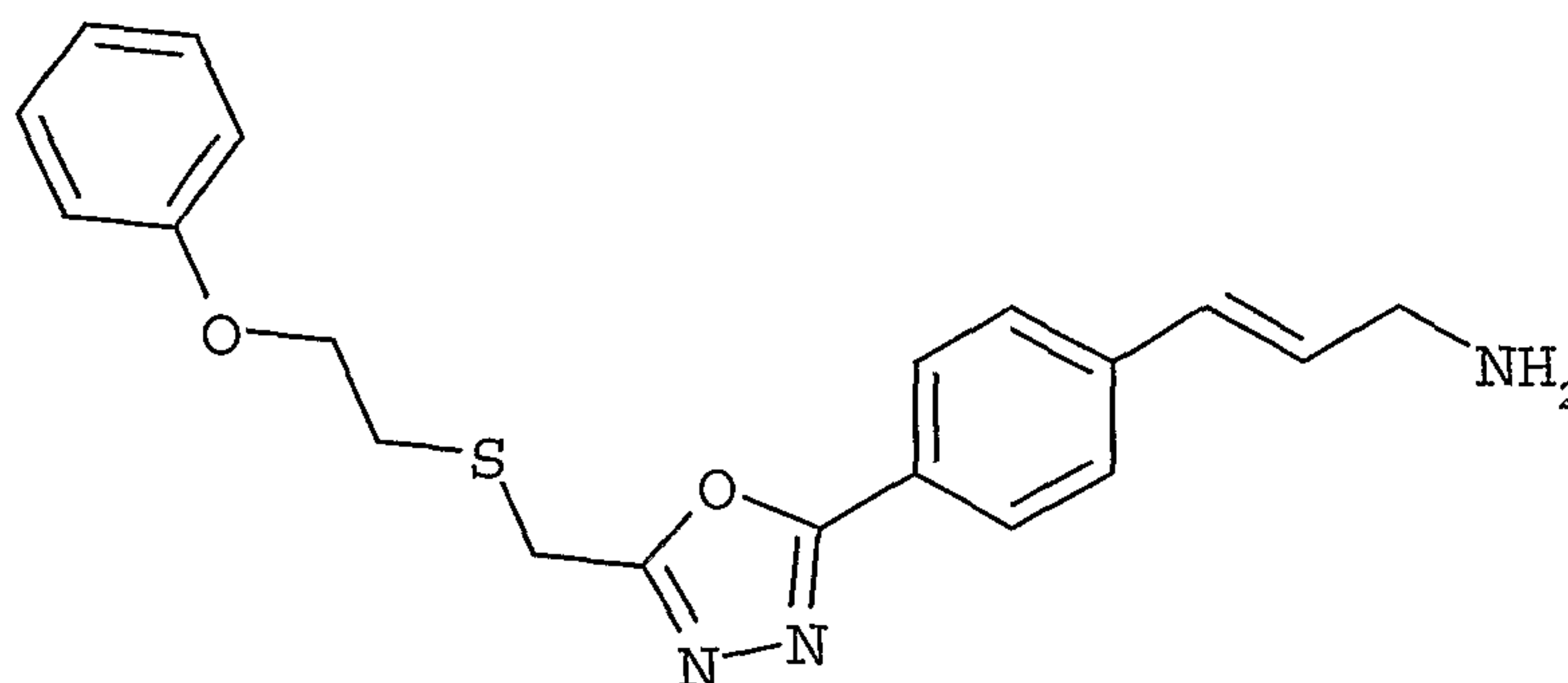
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dimethylamine in tetrahydrofuran (1.5 mL, 3 mmol), and potassium carbonate (400 mg, 2.9 mmol) in acetonitrile (15 mL) was stirred under reflux for 20 h and filtered. The filtrate was concentrated and purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a white solid (111 mg, 93%).

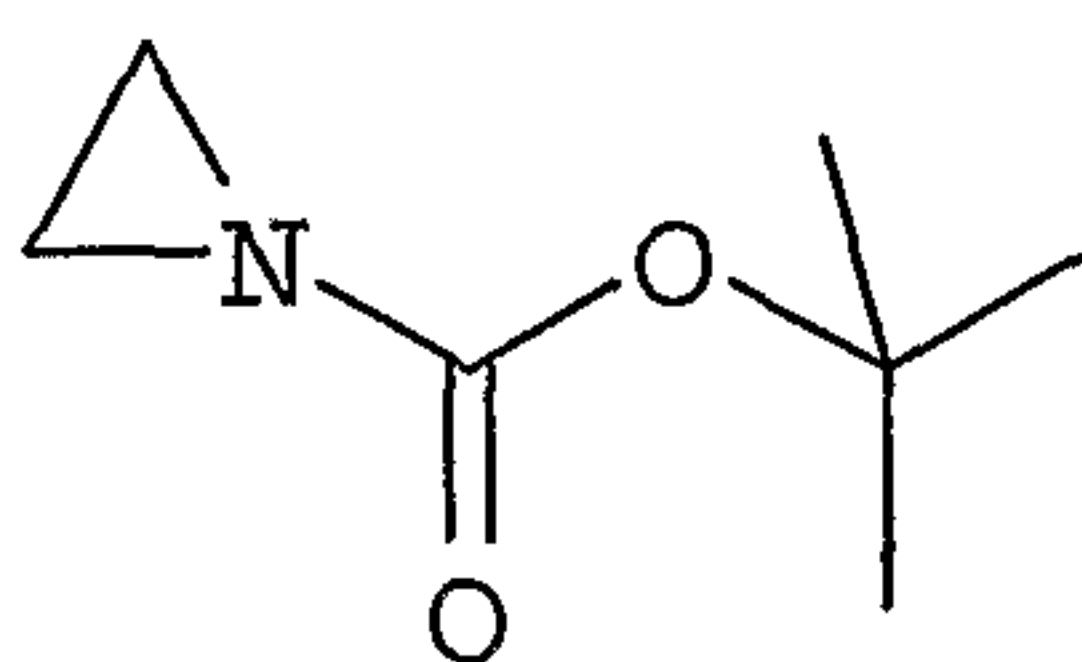
5 ^1H NMR (CDCl_3) δ 7.92 (d, 2H, $J=7.8$ Hz), 7.43 (d, 2H, $J=8.6$ Hz), 7.22~7.27 (m, 2H), 6.93 (t, 1H, $J=7.4$ Hz), 6.87 (d, 2H, $J=7.6$ Hz), 6.46 (d, 1H, $J=15.6$ Hz), 6.35 (dt, 1H, $J=15.6, 6.2$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz), 2.40-2.49 (m, 4H), 2.28 (s, 6H). IR (KBr, cm^{-1}) 3032, 2960, 2931, 2880, 1589, 1553, 1499, 1239, 1094, 1042, 746. MS (ES+) m/e 410 ($M+1$). Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_2\text{S}$: C, 67.45; H, 6.65; N, 10.26; S, 7.83. Found C, 67.32; H, 6.68; N, 10.50; S, 7.88.

Example 134

Preparation of (E)-2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(3-aminopropen-1-yl)phenyl]-1,3,4-oxadiazole



15 a) 1-tert-Butoxycarbonylaziridine.



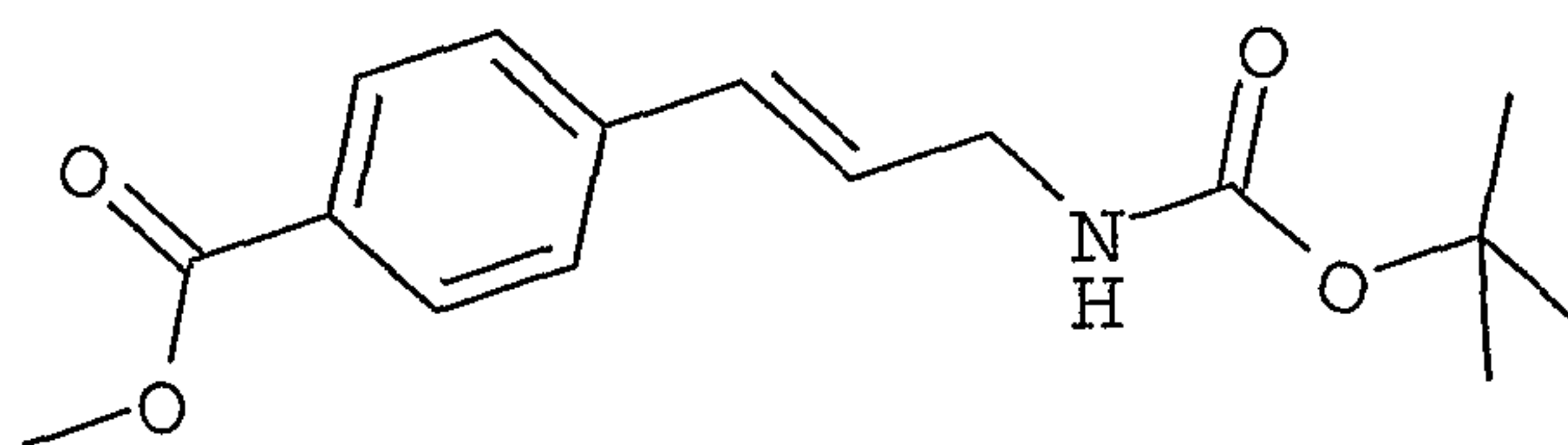
20 A solution containing ethanolamine (6 g, 98.2 mmol) and di-tert-butyl dicarbonate (23.6 g, 108 mmol) in isopropyl alcohol (40 mL) and dioxane (80 mL) was stirred at room temperature for 3 hr. The mixture was concentrated and dried under vacuum overnight. This material was then combined with p-toluenesulfonyl chloride (22.5 g, 117.8 mmol) and powdered KOH (22.0 g, 392.8 mmol) in ethyl ether (800 mL). The mixture was refluxed for 1.5 days, but only 50% was converted. More KOH (11 g, 146 mmol) was added, the heat was removed and the reaction stirred 2 days at room temperature. The

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mixture was poured over ice-water (600 mL) and the organic material was separated. The aqueous layer was extracted with ethyl ether (200 mL) and the combined organic extracts were dried (MgSO_4), filtered and concentrated at 1 atm to remove most of the ether. The flask was left open in the hood overnight to allow complete evaporation of ether to yield
 5 14 g (99%) of a colorless oil.

^1H NMR (CDCl_3) δ 2.11 (s, 4H), 1.43 (s, 9H).

b) Methyl 4-{3-[(tert-butoxycarbonyl)amino]propen-1-yl}benzoate

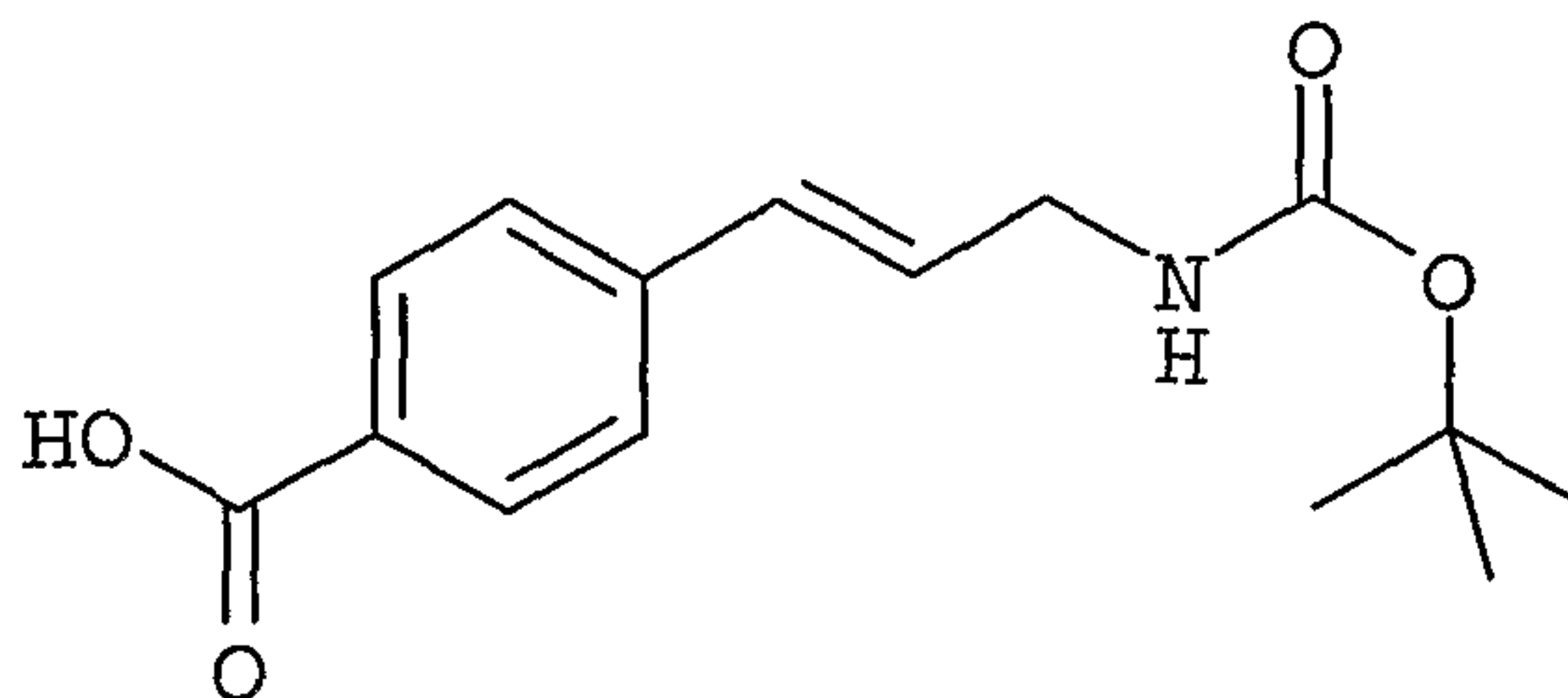


10 A solution containing methyl 4-formylbenzoate (2.7 g, 16.45 mmol), 1-(tert-butoxycarbonyl)aziridine (7.07 g, 49.4 mmol), and triphenylphosphine (12.9 g, 49.4 mmol) in isopropyl alcohol (150 mL) was refluxed for 3h. The reaction was concentrated to yield 4.63 g of a colorless oil which contained an approximately 1:3 ratio of Z-olefin (top spot on TLC) to E-olefin (bottom spot). This material was purified on silica gel
 15 (20% ethyl acetate/hexanes) to yield 1.24 g (26%) of a white solid (E-isomer). Another 2.2 g (46%) of E/Z mixture was isolated, too.

E-isomer: ^1H NMR (CDCl_3) δ 7.95 (d, 2H, $J=8$ Hz), 7.38 (d, 2H, $J=8$ Hz), 6.51 (d, 1H, $J=16$ Hz), 6.29 (m, 1H), 4.68 (br s, 1H), 3.91 (m, 2H), 3.88 (s, 3H), 1.44 (s, 9H). MS (ES+) m/e 292 ($M+1$).

20

c) 4-{3-[(tert-butoxycarbonyl)amino]propen-1-yl}benzoic acid, (E)- and (Z)-isomers



To a solution of methyl 4-{3-[(tert-butoxycarbonyl)amino]propen-1-yl}benzoate (1.46 g, 5 mmol) in 1,4-dioxane (25 mL) was added 2 M NaOH (25 mL, 50 mmol) and
 25 the reaction was stirred at room temperature for 3 h. Ice (30 g) was added and the mixture

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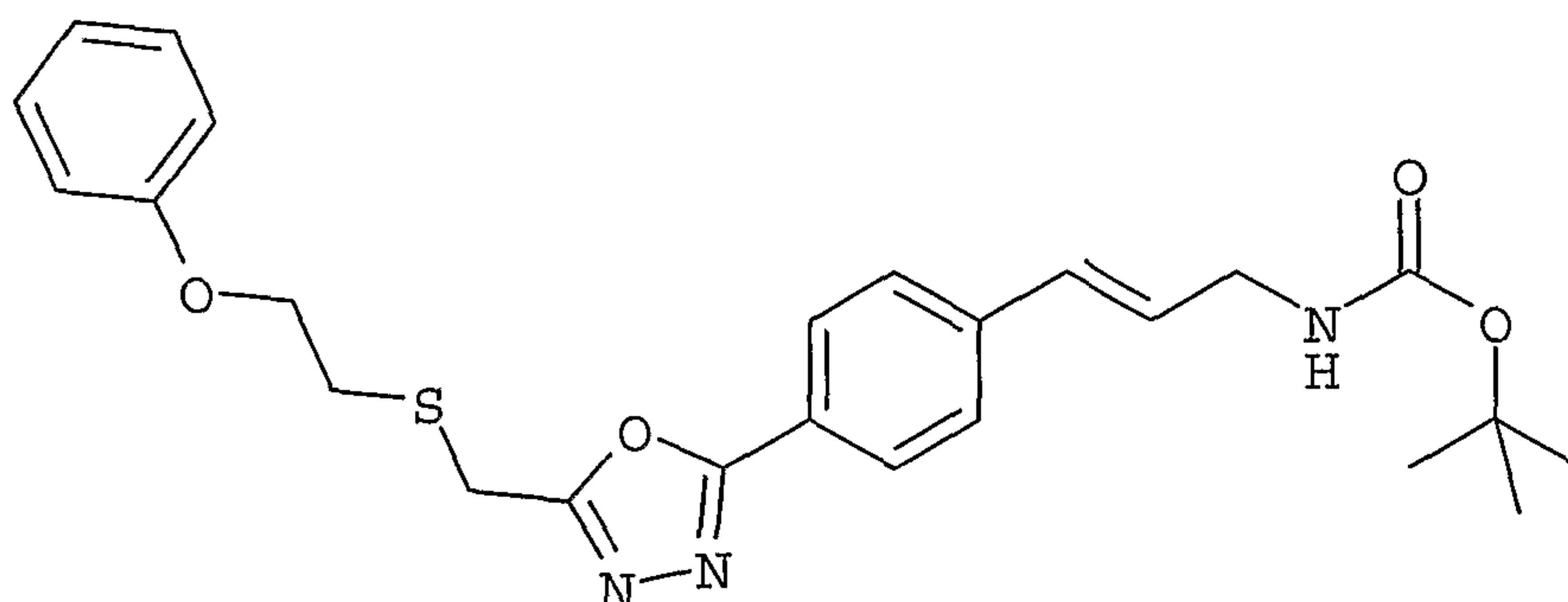
was acidified with 2 M HCl (26 mL) and extracted with methylene chloride (3 x 30 mL). The combined methylene chloride extracts were washed with water (2 x 50 mL), dried (MgSO₄), and concentrated to give a white solid (1.20 g, 86%).

E-isomer: ¹H NMR (CDCl₃) δ 7.96 (d, 2H, J=8.6 Hz), 7.52 (d, 2H, J=8.8 Hz), 6.59 (d, 1H, J=15.6 Hz), 6.43 (dt, 1H, J=15.6, 5.5 Hz), 6.19 (br s, 1H), 3.87 (m, 2H), 1.41 (s, 9H). MS (ES-) m/e 276 (M-1).

Z-isomer: ¹H NMR (CDCl₃) δ 8.04 (d, 2H, J=7.8 Hz), 7.29 (d, 2H, J=8.6 Hz), 6.55 (d, 1H, J=11.7 Hz), 5.77 (dt, 1H, J=11.7, 6.0 Hz), 4.64 (br s, 1H), 4.03 (m, 2H), 1.43 (s, 9H). MS (ES-) m/e 276 (M-1).

10

d) 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[3-((tert-butoxycarbonyl)amino)propen-1-yl]phenyl}-1,3,4-oxadiazole, (E)- and (Z)-isomers



To a stirred mixture of 4-{3-[(tert-butoxycarbonyl)amino]propen-1-yl}benzoic acid (1.11 g, 4mmol), 2-(2-phenoxyethyl)thioacetic hydrazide hydrochloride (1.16 g, 4.4 mmol), and *p*-(N,N-dimethylamino)phenyldiphenylphosphine (3.66 g, 12 mmol) in acetonitrile (40 mL) at 0 °C was added a solution of triethylamine (2.43 g, 24 mmol) in carbon tetrachloride (3.08 g, 20 mmol). After 10 min the cooling bath was removed and stirring was continued at room temperature overnight. The mixture was concentrated to approximately half the original volume and partitioned between ether (100 mL) and 2 M HCl (100 mL). The ether layer was washed with 2 M HCl (4 x 50 mL) and water (50 mL), dried (MgSO₄) and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexanes 1:2) to give a colorless oil (1.23 g, 66%).

E-isomer: ¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8.6 Hz), 7.44 (d, 2H, J=7.9 Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.52 (d, 1H, J=16.4

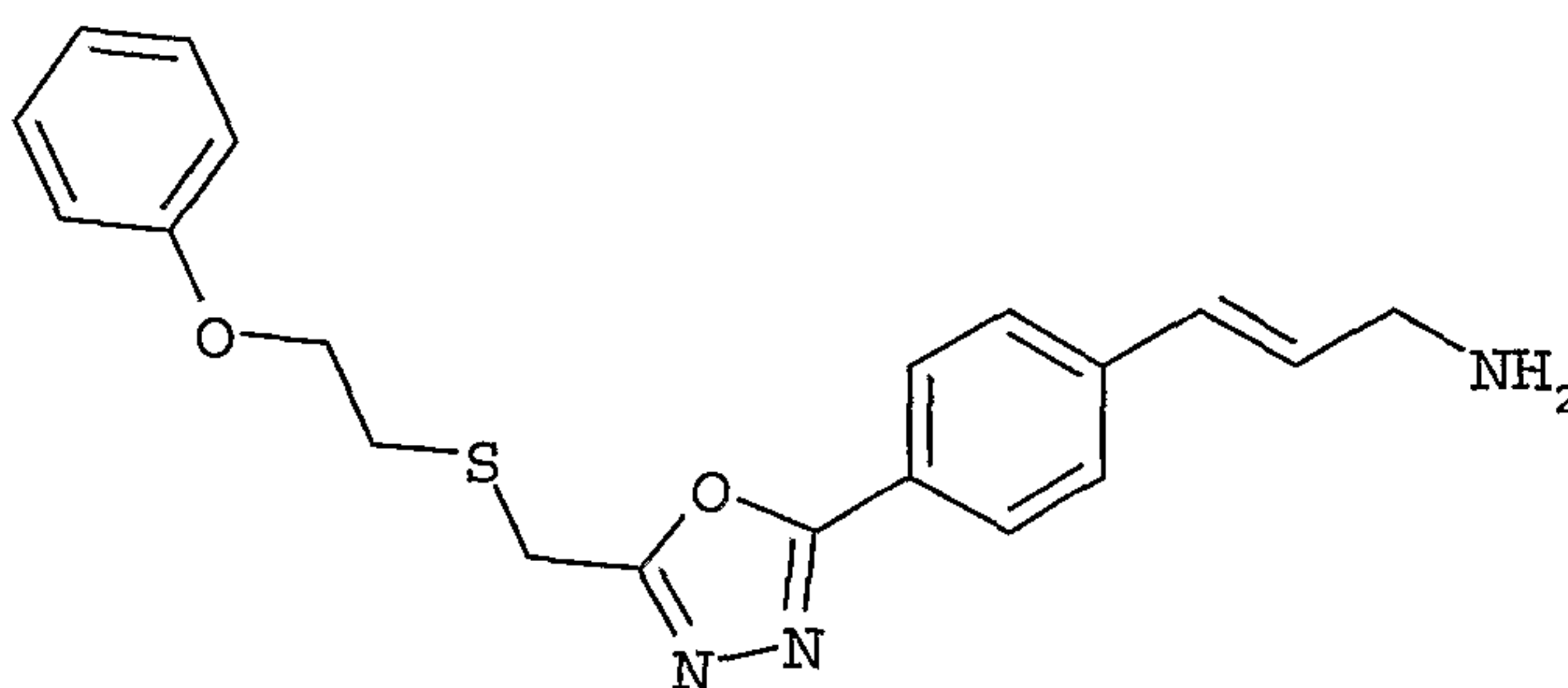
25

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Hz), 6.31 (dt, 1H, J=16.6, 6.3 Hz), 4.67 (br s, 1H), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.93 (m, 2H), 3.03 (t, 2H, J=6.2 Hz), 1.45 (s, 9H). MS (ES+) m/e 468 (M+1).

Z-isomer: ^1H NMR (CDCl_3) δ 7.98 (d, 2H, J=8.6 Hz), 7.32 (d, 2H, J=8.5 Hz), 7.23~7.27 (m, 2H), 6.93 (t, 1H, J=7.8 Hz), 6.86 (d, 2H, J=7.8 Hz), 6.54 (d, 1H, J=11.7 Hz), 5.76 (dt, 1H, J=11.7, 6.3 Hz), 4.62 (br s, 1H), 4.18 (t, 2H, J=6.2 Hz), 4.06 (m, 2H), 4.04 (s, 2H), 3.04 (t, 2H, J=6.2 Hz), 1.43 (s, 9H). MS (ES+) m/e 468 (M+1).

e) 2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(3-aminopropen-1-yl)phenyl]-1,3,4-oxadiazole, (E)- and (Z)-isomers



Trifluoroacetic acid (2 mL) was added slowly to a solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[3-((tert-butoxycarbonyl)amino)propen-1-yl]phenyl}-1,3,4-oxadiazole (467 mg, 1 mmol) in methylene chloride (8 mL). The mixture was stirred at room temperature for 1 h and concentrated. The residue was partitioned between 2 M NaOH (10 mL) and methylene chloride (20 mL), and the aqueous layer was extracted with methylene chloride (15 mL). The combined methylene chloride extracts were dried (MgSO_4) and concentrated. The residue was triturated from methylene and hexanes to give a white powder (323 mg, 88%).

E-isomer: ^1H NMR (CDCl_3) δ 7.95 (d, 2H, J=8.6 Hz), 7.46 (d, 2H, J=8.6 Hz), 7.23~7.26 (m, 2H), 6.93 (t, 1H, J=7.1 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.54 (d, 1H, J=16.3 Hz), 6.44 (dt, 1H, J=15.6, 5.5 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.51 (d, 2H, J=5.5 Hz), 3.04 (t, 2H, J=6.2 Hz). IR (KBr, cm^{-1}) 3430, 3029, 2952, 2945, 2858, 1600, 1563, 1504, 1461, 1244, 1175, 752. MS (ES+) m/e 368 (M+1). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$: C, 65.37; H, 5.76; N, 11.43; S, 8.73. Found C, 65.58; H, 6.01; N, 11.20; S, 8.61.

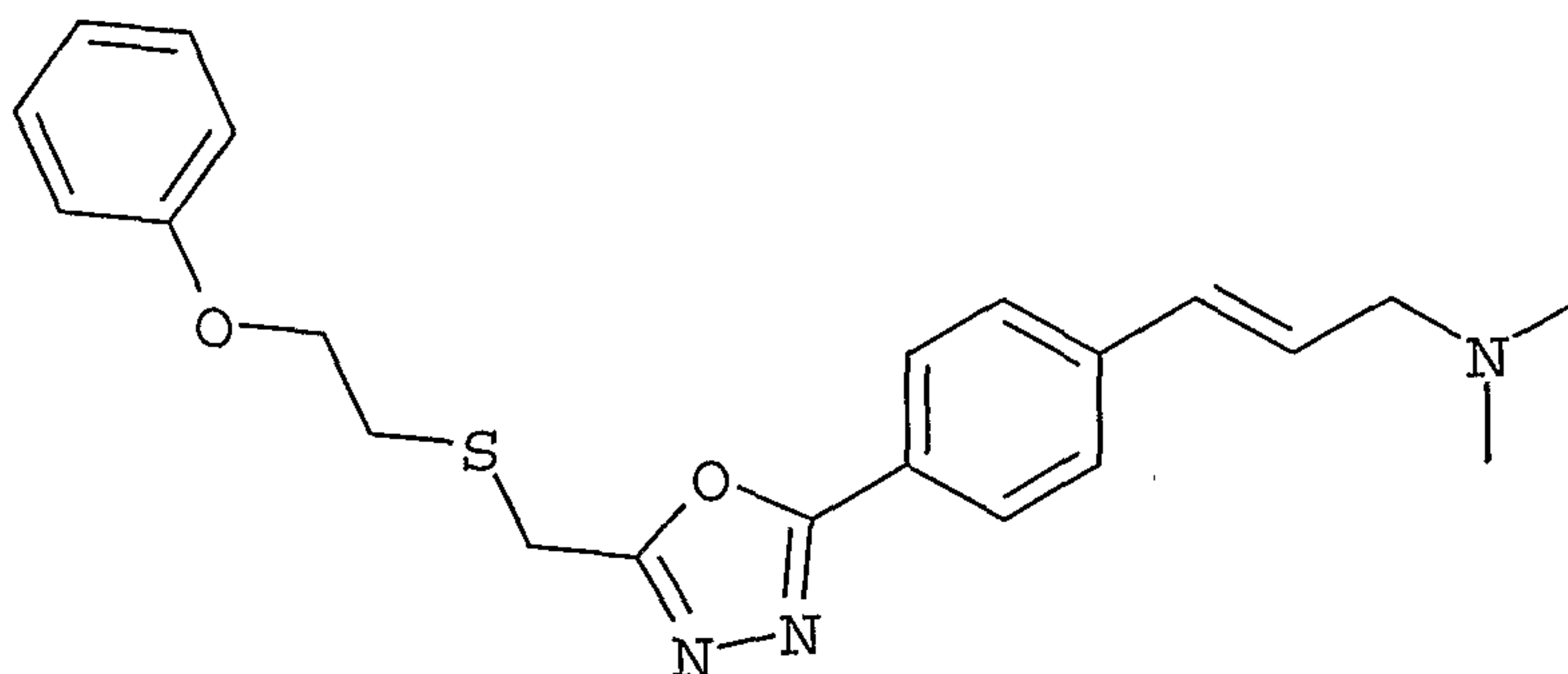
Z-isomer: ^1H NMR (CDCl_3) δ 7.97 (d, 2H, J=8.6 Hz), 7.32 (d, 2H, J=8.7 Hz), 7.22~7.27 (m, 2H), 6.93 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.47 (d, 1H, J=11.7 Hz), 5.84 (dt, 1H, J=11.7, 5.8 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.04 (s, 2H), 3.60 (d, 2H, J=6.2

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Hz), 3.04 (t, 2H, J=6.3 Hz). IR (KBr, cm^{-1}) 3430, 3031, 2950, 2945, 2841, 1599, 1550, 1486, 1410, 1235, 1147, 755. MS (ES+) m/e 368 (M+1). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$: C, 65.37; H, 5.76; N, 11.43; S, 8.73. Found C, 64.97; H, 5.94; N, 11.26; S, 8.83.

Example 135

- 5 Preparation of 2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[3-(N,N-dimethylamino)propen-1-yl]phenyl}-1,3,4-oxadiazole, (E)- and (Z)-isomers



A mixture of 2-[[2-(Phenoxyethyl)thio]methyl]-5-[4-(3-aminopropen-1-yl)phenyl]-1,3,4-oxadiazole (229 mg, 0.62 mmol) and paraformaldehyde (187 mg, 6.2 mmol) in methanol (6 mL) was stirred under reflux for 3 h and then cooled to room temperature. Sodium cyanoborohydride (117 mg, 1.86 mmol) was added in three portions and the resultant mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of water (0.5 mL) and most of the methanol was evaporated. The residue was diluted with saturated sodium bicarbonate (10 mL) and extracted with methylene chloride (3 x 10 mL). The combined methylene chloride extracts were dried (MgSO₄) and concentrated. The residue was purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a pale yellow solid (176 mg, 72%).

E-isomer: ¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8.6 Hz), 7.46 (d, 2H, J=8.6 Hz), 7.22~7.27 (m, 2H), 6.93 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.54 (d, 1H, J=15.6 Hz), 6.38 (dt, 1H, J=16.4, 6.3 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.11 (d, 2H, J=6.3 Hz), 3.04 (t, 2H, J=6.2 Hz), 2.28 (s, 6H). IR (film, cm^{-1}) 3030, 2952, 2928, 2884, 1598, 1552, 1481, 1293, 1065, 739. MS (ES+) m/e 396 (M+1). Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_2\text{S}$: C, 66.81; H, 6.37; N, 10.62; S, 8.11. Found C, 67.05; H, 6.28; N, 10.79; S, 8.04.

Z-isomer: ¹H NMR (CDCl₃) δ 7.98 (d, 2H, J=7.8 Hz), 7.35 (d, 2H, J=7.8 Hz), 7.23~7.27 (m, 2H), 6.93 (t, 1H, J=7.4 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.58 (d, 1H, J=11.7 Hz), 5.90 (dt, 1H, J=12.5, 6.2 Hz), 4.18 (t, 2H, J=6.2 Hz), 4.04 (s, 2H), 3.20 (d, 2H, J=6.2

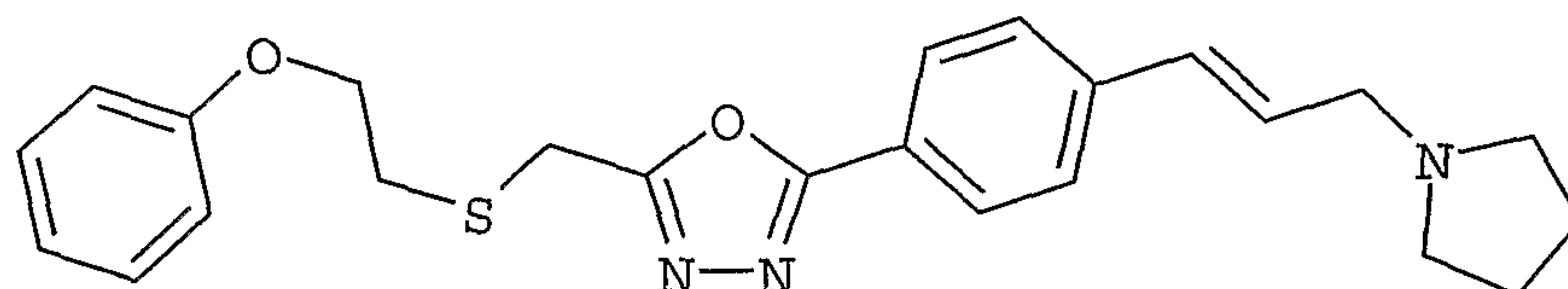
-281-

Hz), 3.04 (t, 2H, J=6.2 Hz), 2.25 (s, 6H). IR (film, cm^{-1}) 3031, 2980, 2963, 1600, 1552, 1481, 1295, 1055, 983, 750. MS (ES+) m/e 396 (M+1). Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_2\text{S}$: C, 66.81; H, 6.37; N, 10.62; S, 8.11. Found C, 67.37; H, 6.50; N, 10.43; S, 8.03.

5

Example 136

Preparation of (E)-2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(3-pyrrolidinopropen-1-yl)phenyl]-1,3,4-oxadiazole



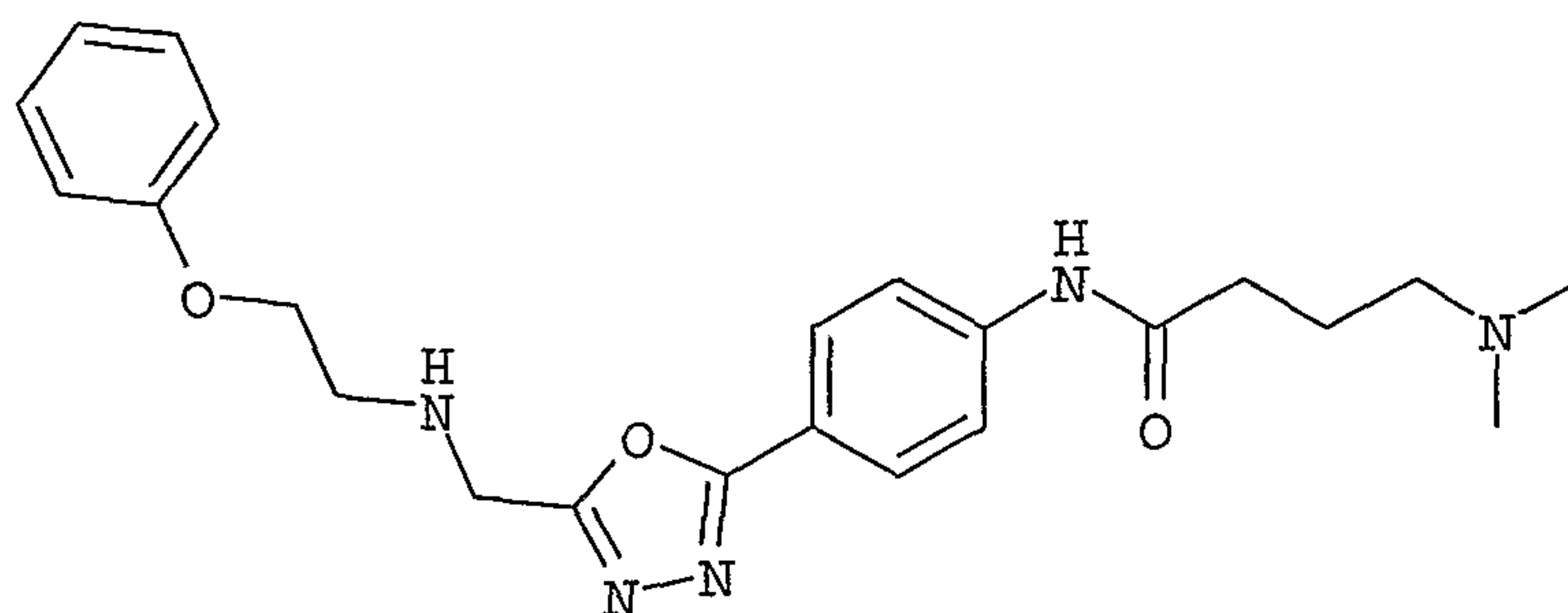
A suspension containing (E)-2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(3-aminopropen-1-yl)phenyl]-1,3,4-oxadiazole (135 mg, 0.367 mmol) and 1,4-butanedial bisulfite adduct (121 mg, 0.367 mmol) was stirred in methanol (4 mL). Sodium cyanoborohydride (46.1 mg, 0.734 mmol) was added and the reaction stirred for 72 h. The reaction was quenched with 2N aqueous NaOH (2 mL), extracted with methylene chloride (3x5 mL), dried (MgSO_4) and filtered to yield 147 mg of a yellow oil. This material was purified by preparative TLC (10% methanol/methylene chloride) to yield 55 mg (36%) of a yellow solid.

^1H NMR (CDCl_3) δ 7.95 (d, 2H, J=8 Hz), 7.46 (d, 2H, J=8 Hz), 7.24 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 6.57 (d, 1H, J=16 Hz), 6.45 (dd, 1H, J=7 and 16 Hz), 4.18 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.31 (d, 2H, J=6 Hz), 3.03 (t, 2H, J=12 Hz), 2.60 (m, 4H), 1.81 (m, 4H). IR (film, cm^{-1}) 3428, 2952, 2930, 2787, 1596, 1493, 1241, 755. MS (ES+) m/e 422 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_2\text{S}$: C, 68.38; H, 6.46; N, 9.97; S, 7.61. Found C, 68.52; H, 6.38; N, 9.89; S, 7.70.

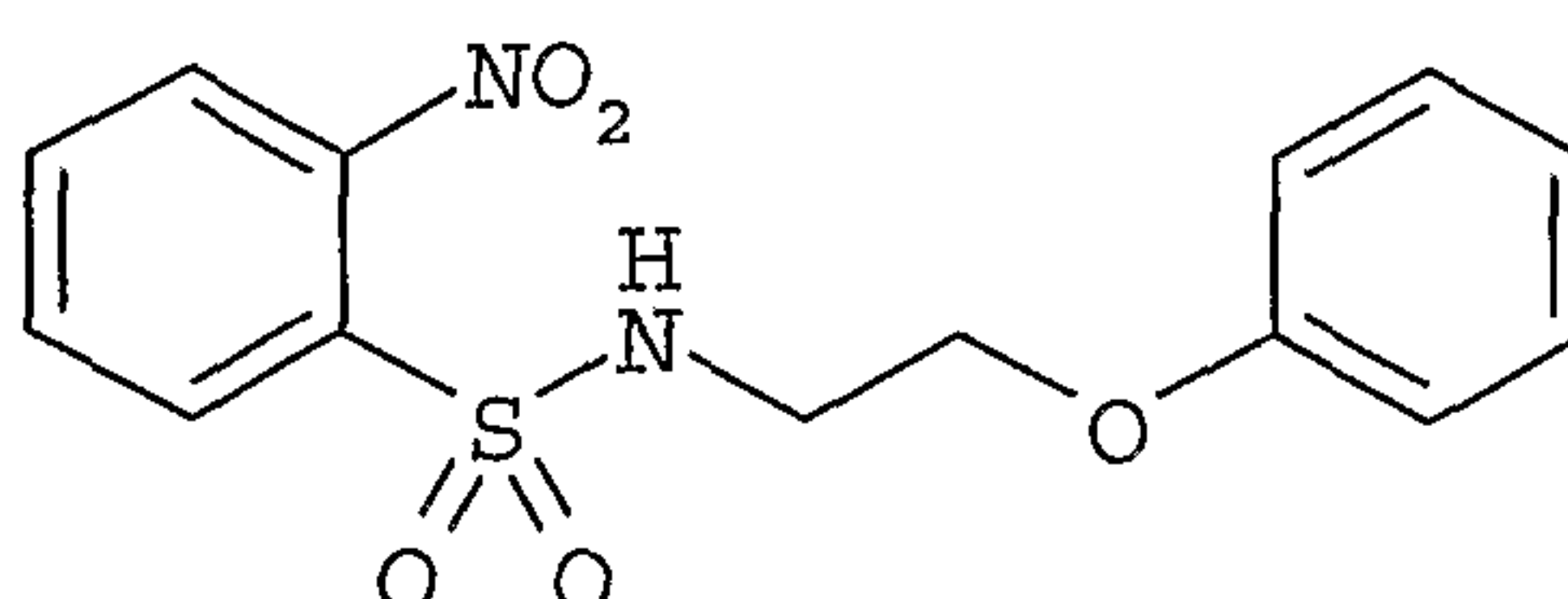
Example 137

Preparation of 2-{[(2-phenoxyethyl)amino]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole

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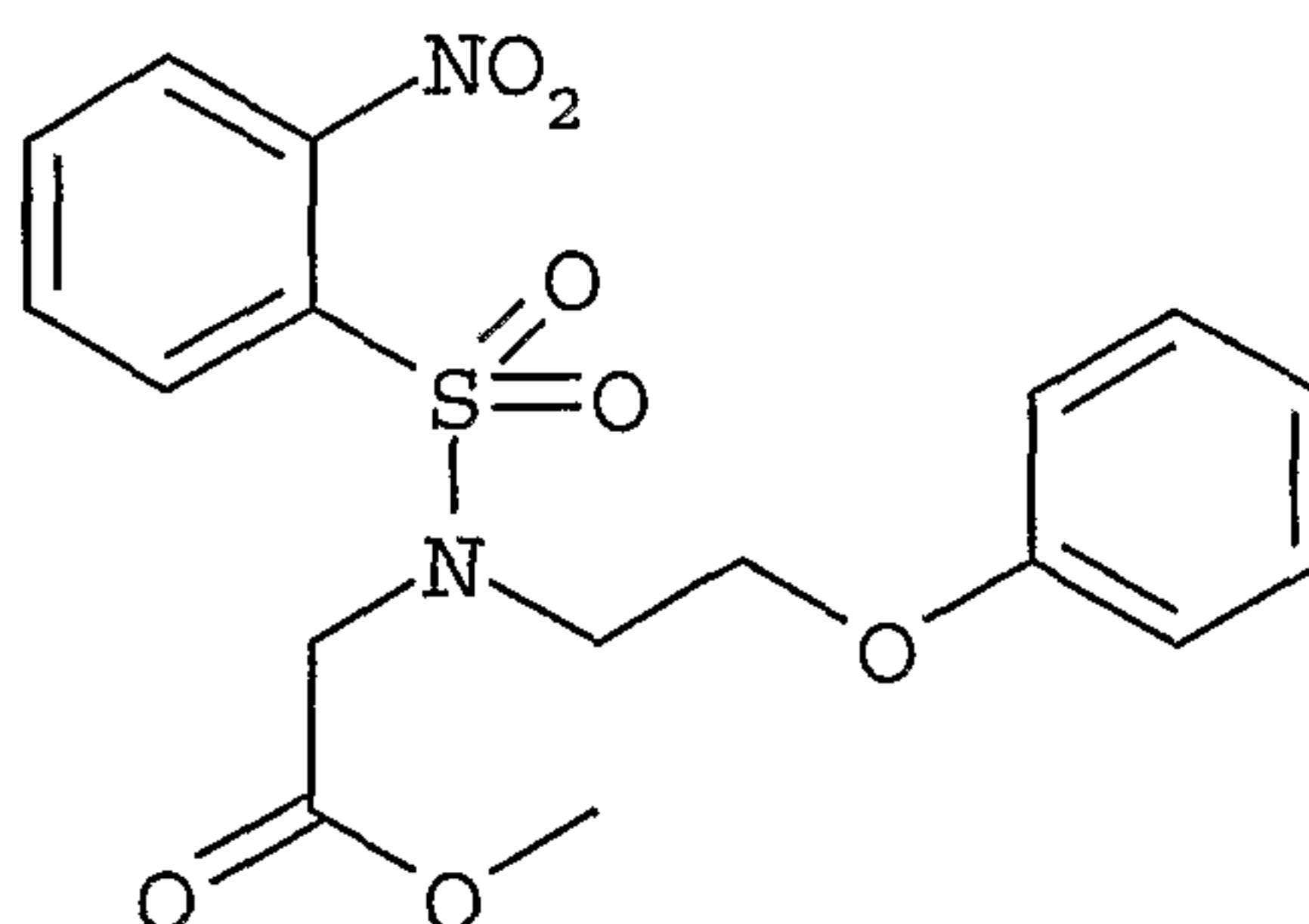
a) 2-(2-Nitrobenzensulfonamido)ethyl phenyl ether



To a stirred mixture of 2-phenoxyethylamine (3.29 g, 24 mmol) and potassium
 5 bicarbonate (10 g, 100 mmol) in methylene chloride (200 mL) was added 2-
 nitrobenzenesulfonyl chloride (4.43 g, 20 mmol) in several portions. The resultant
 mixture was stirred at room temperature overnight and filtered. The filtrate was washed
 with 2 M HCl (3 x 30 mL), dried (MgSO₄), and concentrated. The residue was triturated
 from methylene chloride/hexanes to give a white solid (5.7 g, 88%).

10 ¹H NMR (CDCl₃) δ 8.13 (d, 1H, J=7.7 Hz), 7.80 (d, 1H, J=7.7 Hz), 7.63~7.71 (m,
 2H), 7.18~7.24 (m, 2H), 6.92 (t, 1H, J=7.3 Hz), 6.71 (d, 2H, J=8.0 Hz), 5.90 (br t, 1H,
 J=5.5 Hz), 4.0 (t, 2H, J=5.1 Hz), 3.52 (t, 2H, 5.5 Hz). MS (ES+) m/e 323 (M+1).

b) N-[(Methoxycarbonyl)methyl]-N-(2-phenoxyethyl)-2-nitrobenzenesulfonamide



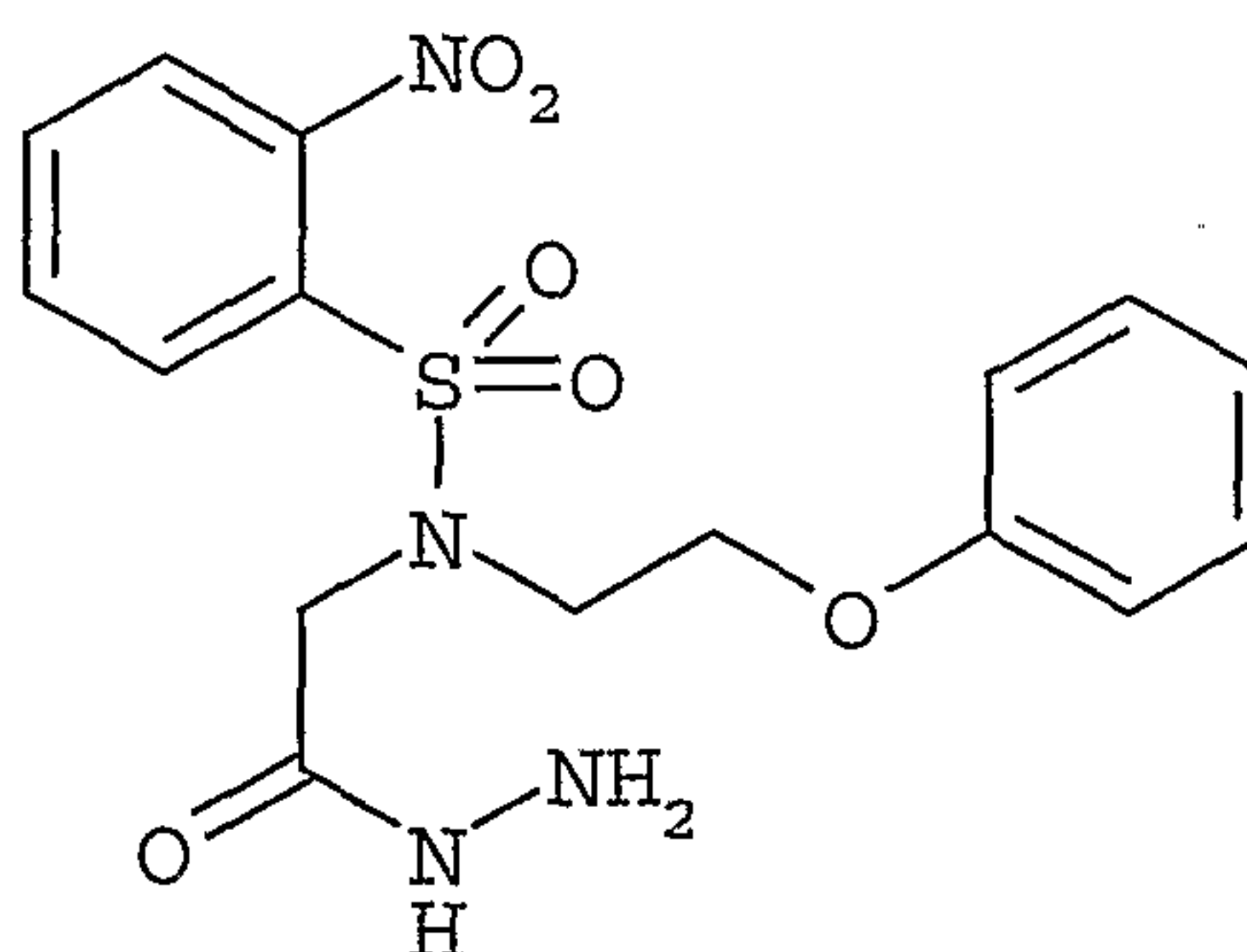
15 To a stirred mixture of 2-(2-nitrobenzensulfonamido)ethyl phenyl ether (1.61 g, 5
 mmol) and potassium carbonate (6.91 g, 50 mmol) in tetrahydrofuran (50 mL) was added
 sodium iodide (300 mg, 2 mmol) and methyl bromoacetate (1.53 g, 10 mmol) and stirring
 was continued at room temperature overnight. The mixture was diluted with ethyl acetate

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(25 mL), washed with water (2 x 30 mL) and brine (25 mL), dried (MgSO₄), and concentrated to give yellow oil (1.99 g, 100%).

¹H NMR (CDCl₃) δ 8.08 (d, 1H, J=8.8 Hz), 7.60~7.68 (m, 3H), 7.24 (m, 2H), 6.93 (t, 1H, J=7.3 Hz), 6.77 (d, 2H, J=8.8 Hz), 4.37 (s, 2H), 4.15 (t, 2H, J=4.8 Hz), 3.80 (t, 2H, J=4.8 Hz), 3.56 (s, 3H). MS (ES+) m/e 395 (M+1).

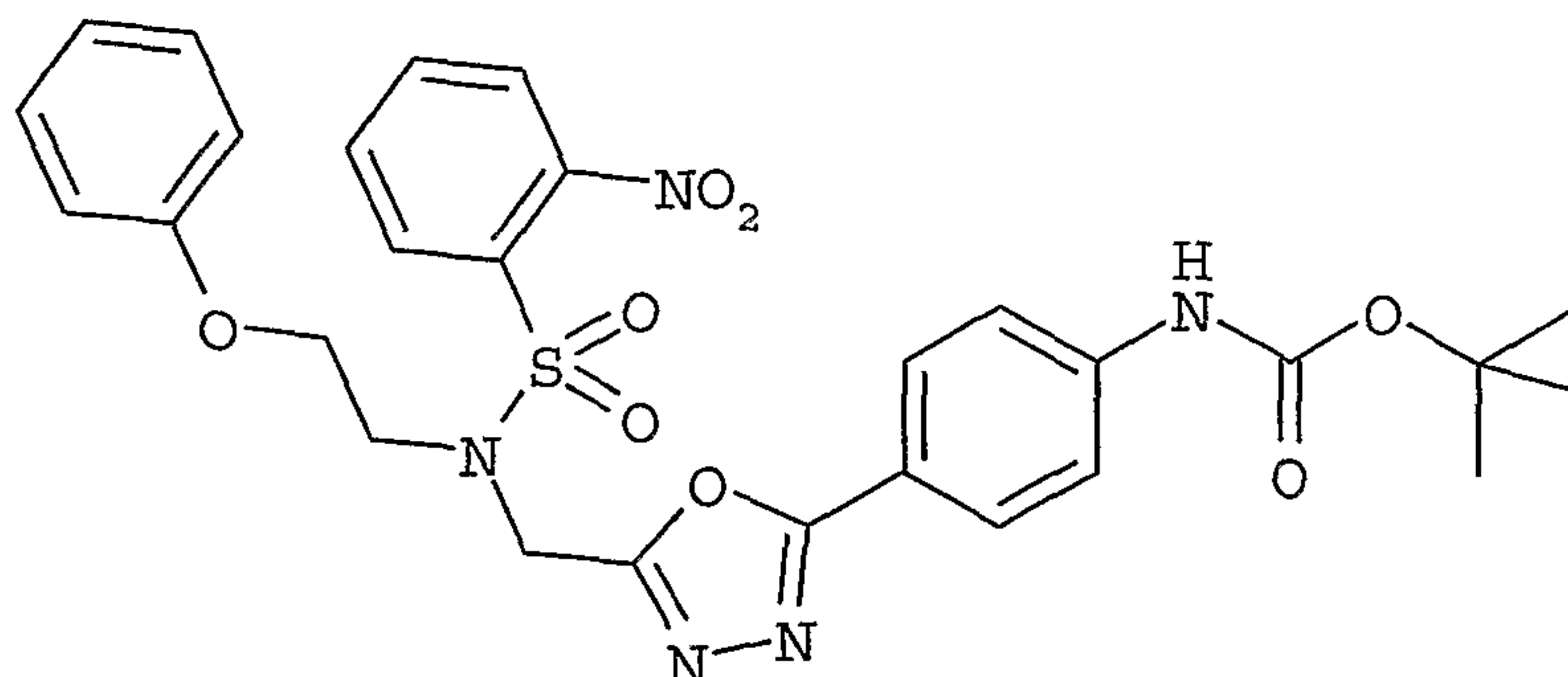
c) 2-[N-(2-phenoxyethyl)-2-nitrobenzenesulfonylamido]acetic hydrazide



A mixture of methyl N-[(methoxycarbonyl)methyl]-N-(2-phenoxyethyl)-2-nitrobenzenesulfonamide (1.97 g, 5 mmol) and hydrazine monohydrate (2.5 g, 50 mmol) in ethanol was stirred at room temperature overnight and concentrated. Excess hydrazine was also removed under vacuum. The residue was taken up in ethyl acetate (75 mL) and washed with water (2 x 50 mL), dried (MgSO₄), and concentrated to give a yellow oil (1.73 g, 88%).

¹H NMR (CDCl₃) δ 8.06 (d, 1H, J=7.7 Hz), 7.65~7.74 (m, 3H), 7.23~7.27 (m, 2H), 6.95 (t, 1H, J=7.3 Hz), 6.80 (d, 2H, J=8.4 Hz), 4.15 (t, 2H, J=5.0 Hz), 4.12 (s, 2H), 3.81 (t, 2H, J=5.0 Hz), 3.56 (s, 3H). MS (ES+) m/e 395 (M+1).

d) 2-[[N-(2-nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl]-5-{4-[(tert-butoxycarbonyl)amino]phenyl}-1,3,4-oxadiazole

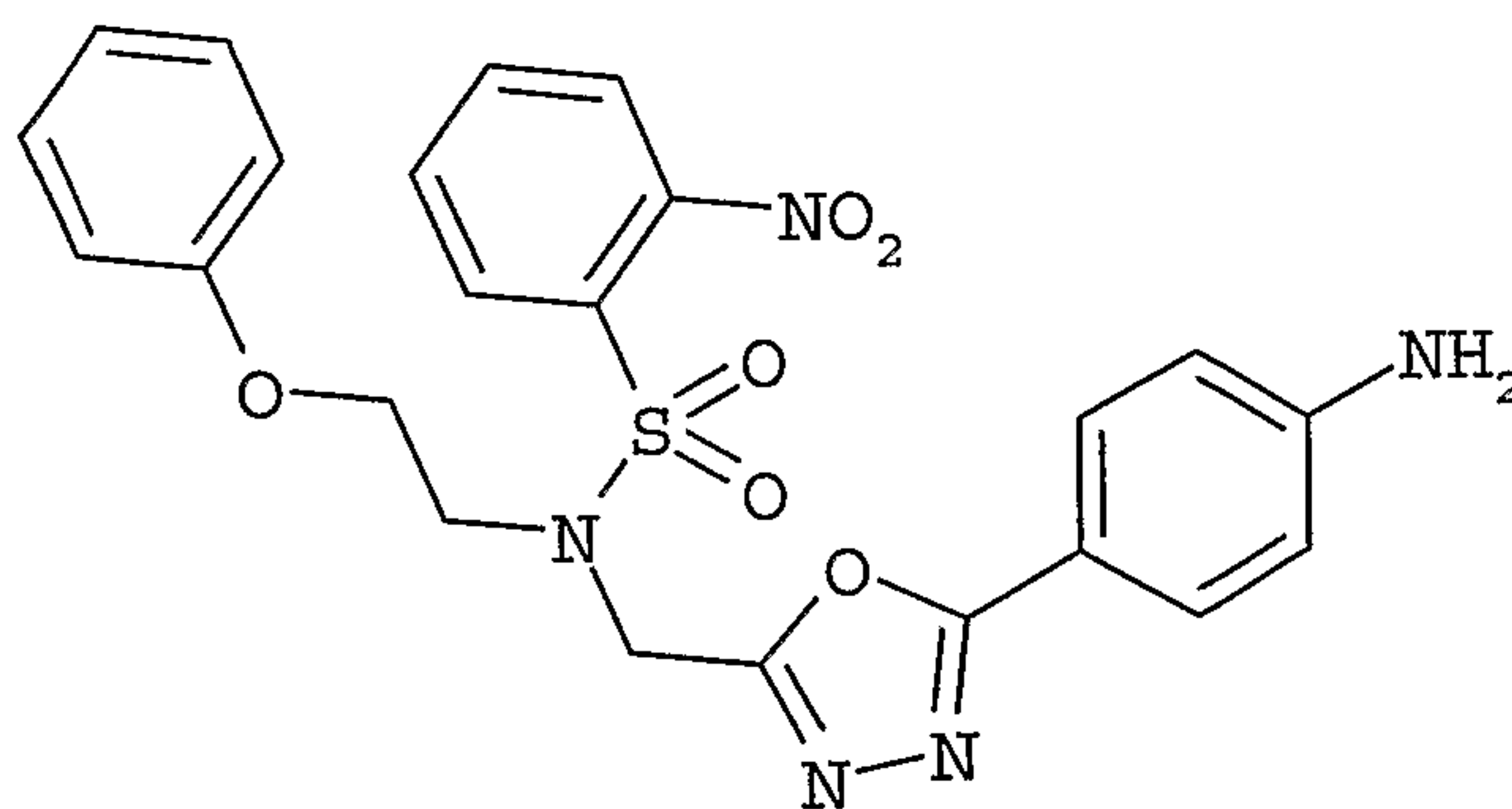


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To a stirred mixture of 2-[N-(2-phenoxyethyl)-2-nitrobenzenesulfonylamido]acetic hydrazide (1.58 g, 4 mmol), 4-(tert-butyloxycarbonyl)benzoic acid (1.19 g, 5 mmol), and 4-(N,N-dimethylamino)phenyldiphenylphosphine (4.58 g, 15 mmol) in acetonitrile (50 mmol), at 0 °C, was added a solution of triethylamine (2.56 g, 25 mmol) in carbon tetrachloride (3.85 g, 25 mmol). After 10 min the cooling bath was removed and stirring was continued at room temperature overnight. The resultant mixture was concentrated to approximately half the original volume and partitioned between ether (150 mL) and 2 M HCl (100 mL). The organic layer was washed with 2 M HCl (3 x 150 mL) and 2 M NaOH (3 x 50 mL), dried (MgSO₄), and concentrated to give a brown oil (1.81 g, 76%).

¹H NMR (CDCl₃) δ 8.04 (d, 1H, J=8.8 Hz), 7.77 (d, 2H, J=8.8 Hz), 7.43~7.67 (m, 5H), 7.19 (t, 2H, J=8.0 Hz), 6.90 (t, 1H, J=7.3 Hz), 6.71 (d, 2H, J=7.7 Hz), 5.04 (s, 2H), 4.19 (t, 2H, J=5.1 Hz), 3.90 (t, 2H, J=5.1 Hz), 1.51 (s, 9H). MS (ES+) m/e 596 (M+1).

e) 2-[[N-(2-nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl]-5-(4-aminophenyl)-1,3,4-oxadiazole

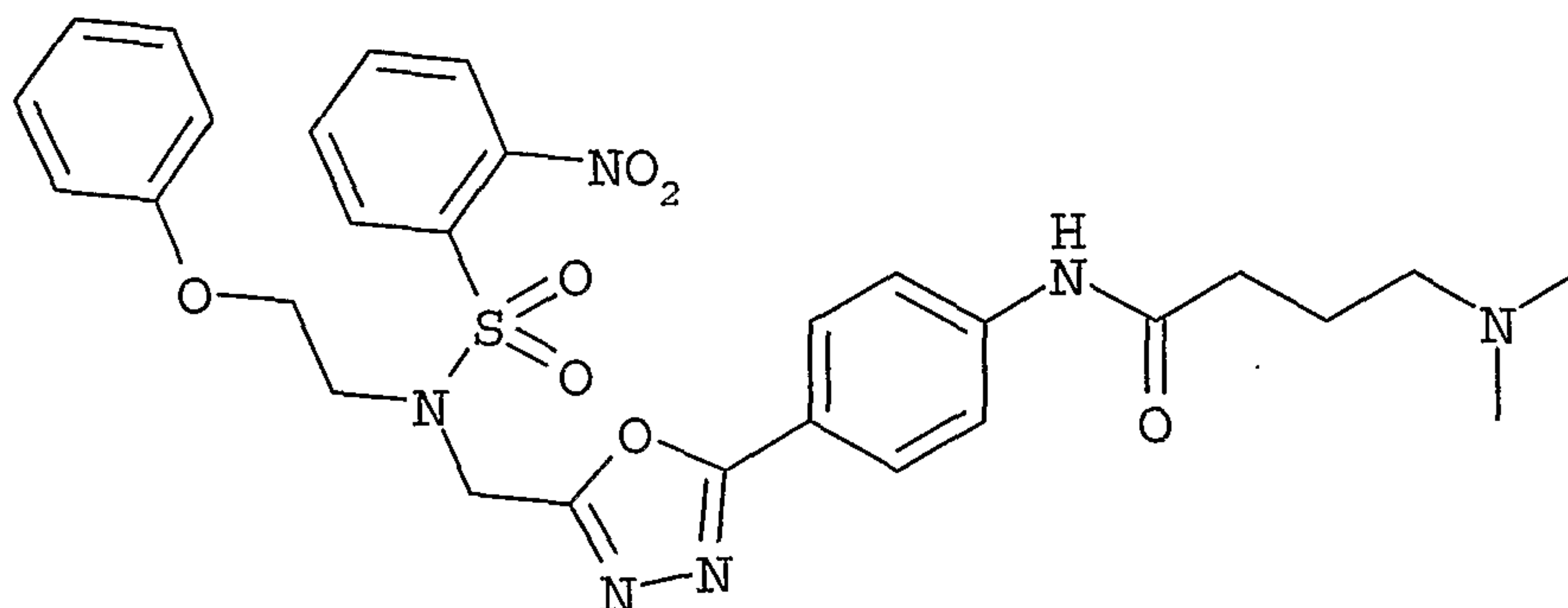


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Trifluoroacetic acid (2.5 mL) was added to a solution of 2- $\{[N-(2$ -
 nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl}-5- $\{4-[(tert$ -
 butoxycarbonyl)amino]phenyl}-1,3,4-oxadiazole (1.19 g, 2 mmol) in methylene chloride
 (7.5 mL). The mixture was stirred at room temperature for 3 h and concentrated. The
 5 residue was dissolved in methylene chloride (15 mL) and washed with 2 M NaOH (15
 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column
 chromatography (silica gel, ethyl acetate/hexanes) to give a pale yellow oil (400 mg,
 40%).

^1H NMR ($CDCl_3$) δ 8.09 (d, 1H, $J=7.4$ Hz), 7.57~7.66 (m, 5H), 7.22 (m, 2H), 6.90
 10 (t, 1H, $J=7.3$ Hz), 6.71 (d, 2H, $J=8.0$ Hz), 6.65 (d, 2H, $J=8.8$ Hz), 5.01 (s, 2H), 4.18 (t,
 2H, $J=5.0$ Hz), 3.90 (t, 2H, $J=5.0$ Hz). MS (ES+) m/e 496 ($M+1$).

f) 2- $\{[N-(2$ -nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl}-5- $\{4-[(4$ -(N,N -
 dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole



15

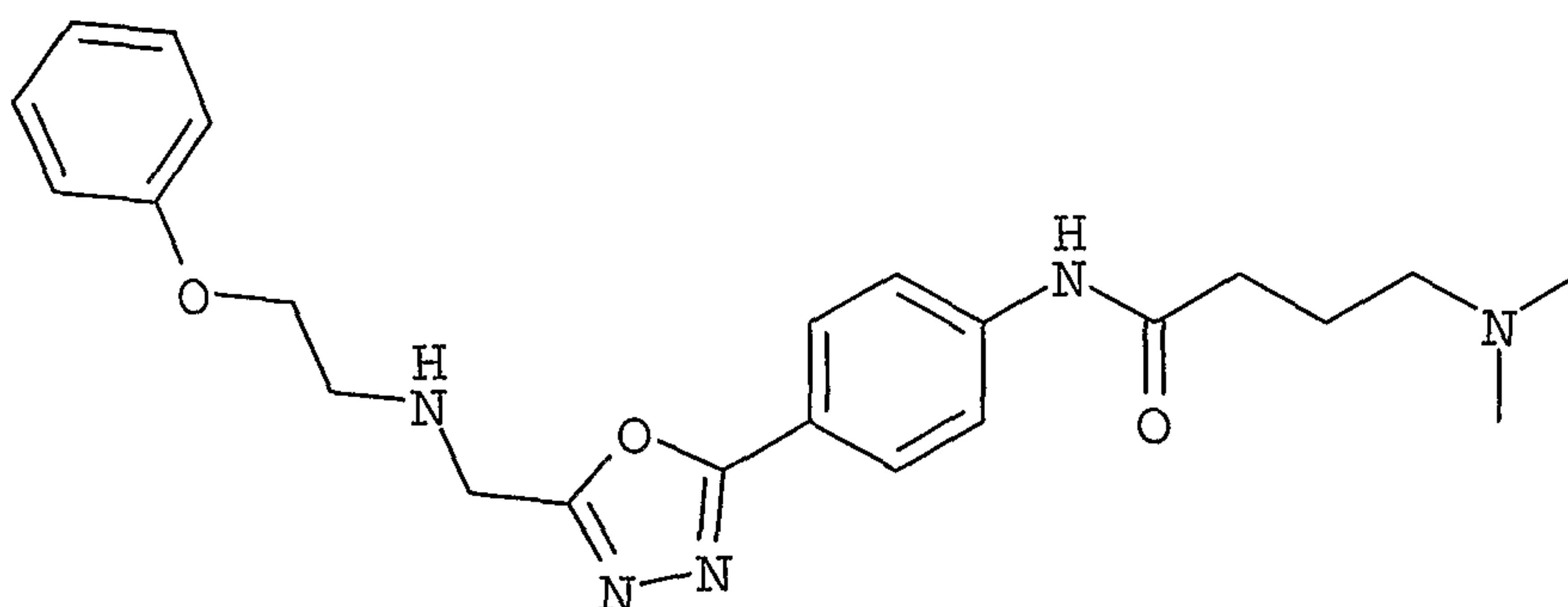
To a stirred mixture of 2- $\{[N-(2$ -nitrobenzenesulfonyl)-(2-
 phenoxyethyl)amino]methyl}-5-(4-aminophenyl)-1,3,4-oxadiazole (248 mg, 0.5 mmol),
 4-(N,N -dimethylamino)butanoic acid hydrochloride (168 mg, 1 mmol), and 1-
 hydroxybenzotriazole (135 mg, 1 mmol) in N,N -dimethylformamide (5 mL) was added
 20 diisopropylcarbodiimide (126 mg, 1 mmol) and stirring was continued at room
 temperature overnight. The mixture was diluted with ethyl acetate (25 mL), washed with
 2 M NaOH (3 x 10 mL), water (2 x 10 mL), and brine (10 mL), dried ($MgSO_4$), and
 concentrated. The residue was purified by chromatography (silica gel, 20%
 methanol/methylene chloride) to give a pale yellow oil (228 mg, 75%).

^1H NMR ($CDCl_3$) δ 10.68 (s, 1H), 8.10 (d, 1H, $J=9.1$ Hz), 7.77 (d, 2H, $J=8.8$ Hz),
 25 7.58~7.65 (m, 5H), 7.19 (m, 2H), 6.90 (t, 1H, $J=7.3$ Hz), 6.71 (d, 2H, $J=7.7$ Hz), 5.04 (s,

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2H), 4.19 (t, 2H, J=4.9 Hz), 3.90 (t, 2H, J=4.9 Hz), 2.49~2.56 (m, 4H), 2.36 (s, 6H), 1.86 (m, 2H). MS (ES+) m/e 609 (M+1).

g) 2-{[(2-phenoxyethyl)amino]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole

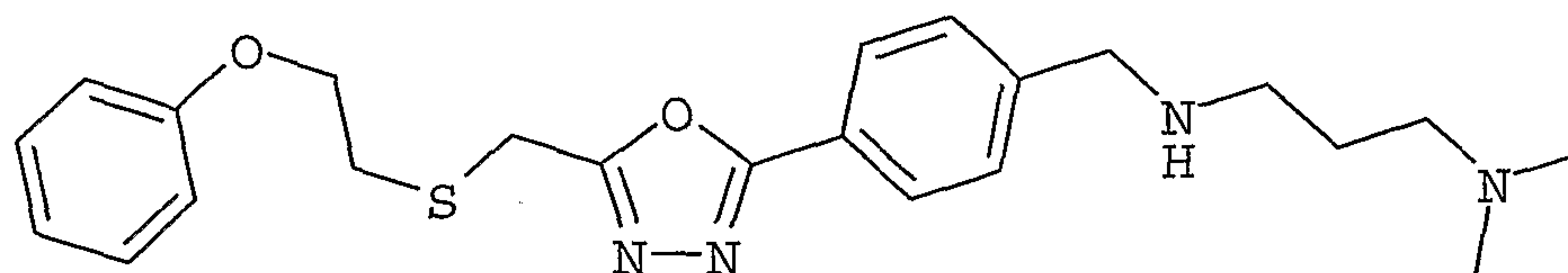


A mixture of 2-{[N-(2-nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole (152 mg, 0.25 mmol) and potassium carbonate (104 mg, 0.75 mmol) in N,N-dimethylformamide (1.5 mL) was stirred at room temperature and benzenethiol (33 mg, 0.3 mmol) was added. Stirring was continued for 3 h and the mixture was diluted with water (5 mL) and extracted with ethyl acetate (8 mL). The ethyl acetate extract was loaded to a cation exchange column (Bio-Rad 50W-x2 resin) and eluted with methanol. The basic material was recovered by flushing the column with 2 M ammonia in methanol and further purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a pale yellow oil (71 mg, 67%).

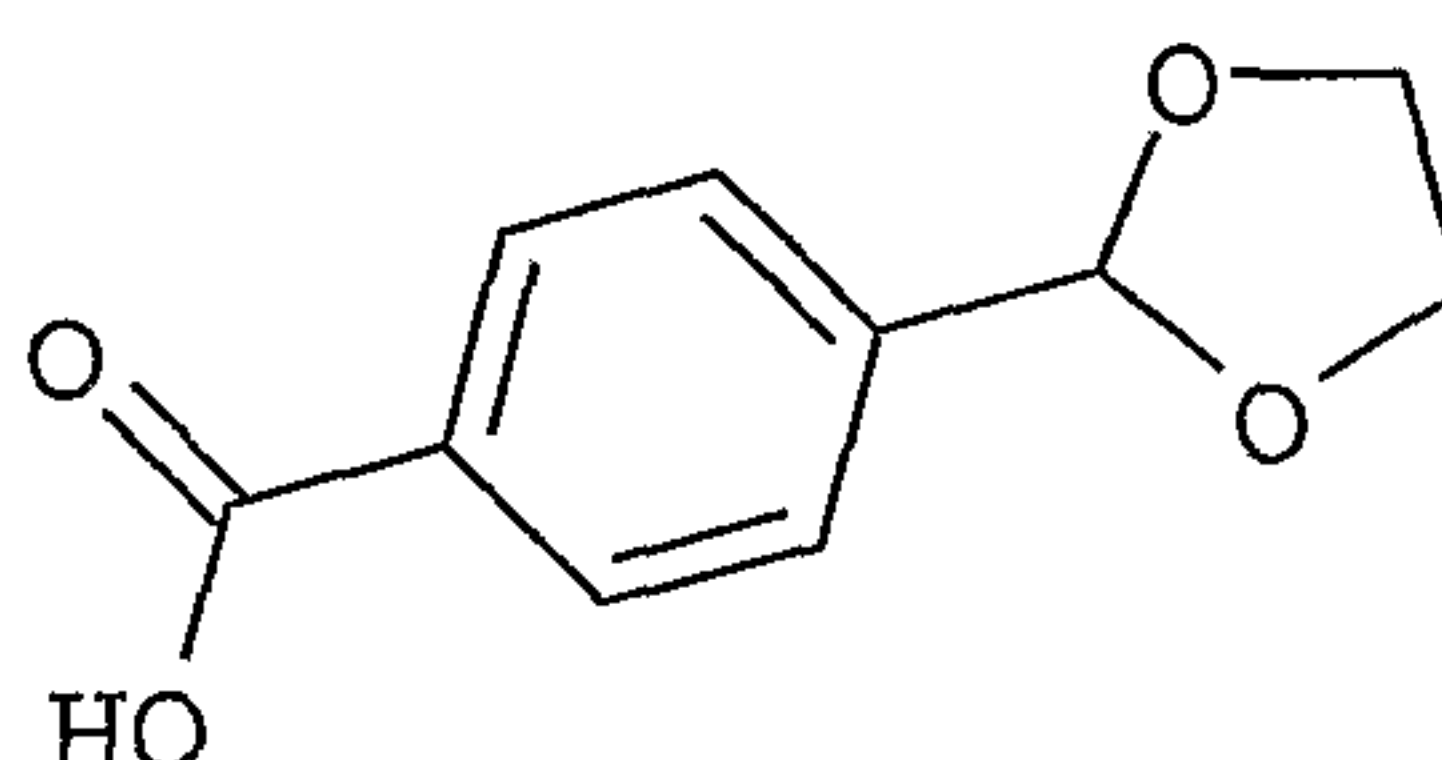
¹H NMR (CDCl₃) δ 10.59 (s, 1H), 7.95 (d, 1H, J=8.8 Hz), 7.65 (d, 2H, J=8.8 Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=8.1 Hz), 4.16 (s, 2H), 4.08 (t, 2H, J=5.0 Hz), 3.11 (t, 2H, J=5.0 Hz), 2.49~2.56 (m, 4H), 2.36 (s, 6H), 1.88 (m, 2H). IR (film, cm⁻¹) 3483, 3340, 2948, 2925, 1661, 1605, 1500, 1428, 1182, 1067, 1027, 756. MS (ES+) m/e 424 (M+1). Anal. Calcd for C₂₃H₂₉N₅O₃: C, 65.23; H, 6.90; N, 16.54. Found C, 65.01; H, 6.96; N, 16.77.

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Preparation of 2-[[[2-(phenoxyethyl)thio]methyl]-5-{4-[(N',N'-dimethyl-1,3-propanediamino)methyl]phenyl}-1,3,4-oxadiazole



a) 2-[4-(hydroxycarbonyl)phenyl]-1,3-dioxolane

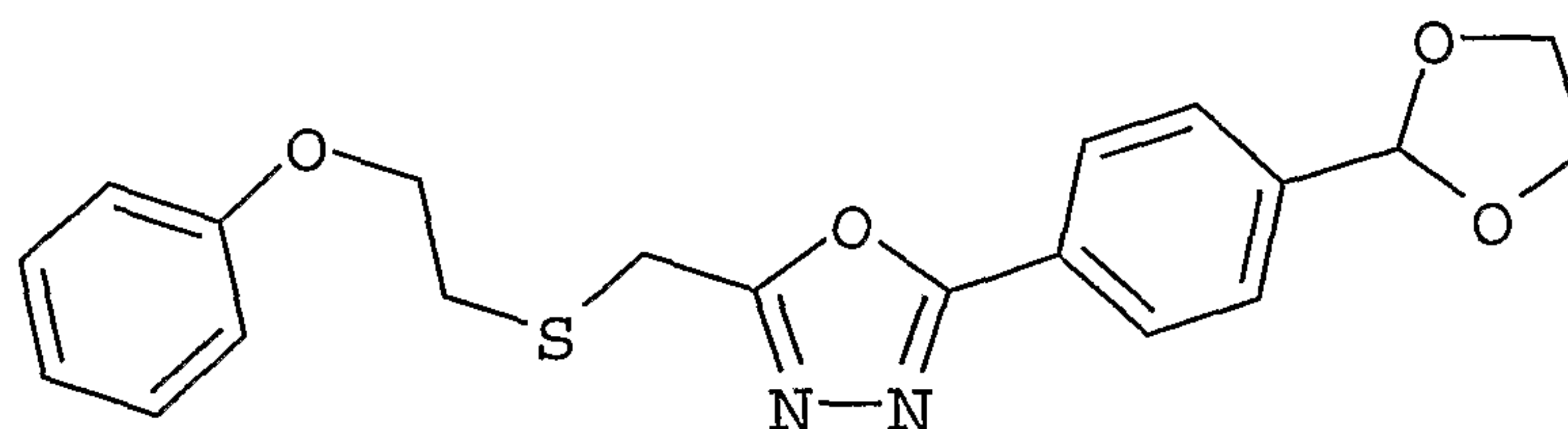


5

Aluminum oxide (Brockmann I, basic, 150 mesh, 34 g, 0.33 mol) was added to a solution of 4-carboxybenzaldehyde (20 g, 0.13 mol) and ethylene glycol (83 g, 1.3 mol) in toluene (700 mL). The resulting suspension was refluxed for 24 h. After cooling, the solids were filtered and washed with ethyl acetate (300 mL). The filtrate was extracted with water (10x100 mL), dried (MgSO₄), filtered and concentrated to yield 15.9 g (61%) of a white solid that required no further purification.

¹H NMR (CDCl₃) δ 8.09 (d, 2H, J=8 Hz), 7.57 (d, 2H, J=8 Hz), 5.86 (s, 1H), 4.07 (m, 4H). MS (ES-) m/e 193 (M-1).

15 b) 2-[[[2-(Phenoxyethyl)thio]methyl]-5-[4-(1,3-dioxolan-2-yl)phenyl]-1,3,4-oxadiazole



A suspension containing 2-[4-(hydroxycarbonyl)phenyl]-1,3-dioxolane (6.55 g, 33.7 mmol), 2-[(2-phenoxyethyl)thio]acetic acid hydrazide, hydrochloride salt (10.63 g, 40.4 mmol) and 4-(dimethylamino)phenyldiphenylphosphine (30.9 g, 101.1 mmol) was cooled in an ice/water bath. Triethylamine (28.2 mL, 202.3 mmol) and carbon tetrachloride (16.3 mL, 168.6 mmol) were combined and added dropwise over 5 min. The reaction stirred in the bath for 10 min, then stirred at room temperature for 16 h. The

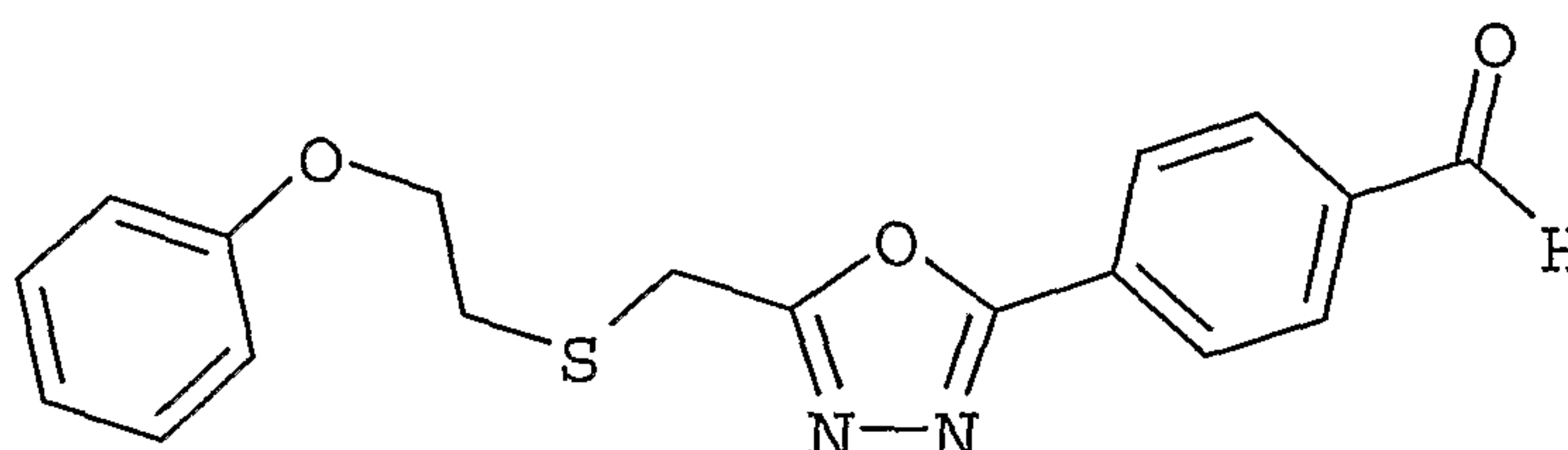
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solution was concentrated to about 10% of its original volume and diluted with ethyl ether (300 mL) and 2 N HCl (200 mL). The organic phase was further extracted with 2 N HCl (6x100 mL), dried (MgSO₄), filtered and concentrated to yield 8 g (62%) of a yellow solid that was not further purified.

5 ¹H NMR (CDCl₃) δ 8.03 (d, 2H, J=7 Hz), 7.59 (d, 2H, J=7 Hz), 7.24 (m, 2H), 6.88 (m, 3H), 5.85 (s, 1H), 4.20 (m, 2H), 4.12 (m, 2H), 4.07 (m, 2H), 4.04 (m, 2H), 3.04 (m, 2H). MS (ES+) m/e 385 (M+1).

c) 2-{[(2-Phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole



10

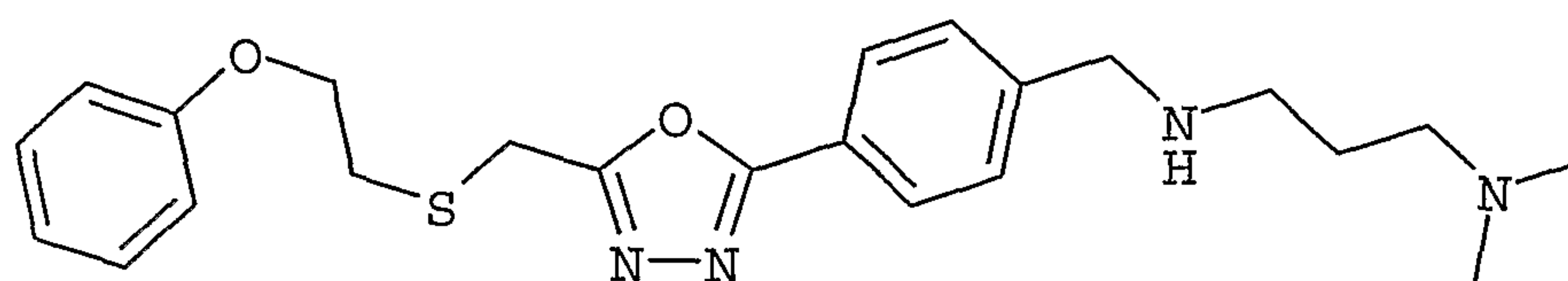
A solution 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(1,3-dioxolan-2-yl)phenyl]-1,3,4-oxadiazole (8.0 g, 20.8 mmol) and pyridinium p-toluenesulfonate (1.0 g, 4.0 mmol) and water (5 mL) in acetone (200 mL) was refluxed for 6 h, cooled and concentrated. The residue was diluted with ethyl acetate (250 mL) and washed with saturated aqueous sodium bicarbonate (3x60 mL), dried (MgSO₄), filtered and concentrated. This residue was purified over silica gel (25% ethyl acetate/hexanes) to yield 2.22 g (31%) of a white solid.

15

¹H NMR (CDCl₃) δ 10.08 (s, 1H), 8.18 (d, 2H, J=7 Hz), 7.99 (d, 2H, J=7 Hz), 7.26 (m, 2H), 6.93 (m, 1H), 6.87 (d, 2H, J=8 Hz), 4.20 (t, 2H, J=11 Hz), 4.07 (s, 2H), 3.05 (t, 2H, J=11 Hz). MS (ES+) m/e 341 (M+1).

20

d) 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[(N',N'-dimethyl-1,3-propanediamino)methyl]phenyl}-1,3,4-oxadiazole



25

A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (200 mg, 0.59 mmol), 3-(N,N-dimethylamino)propylamine (0.08 mL, 0.64

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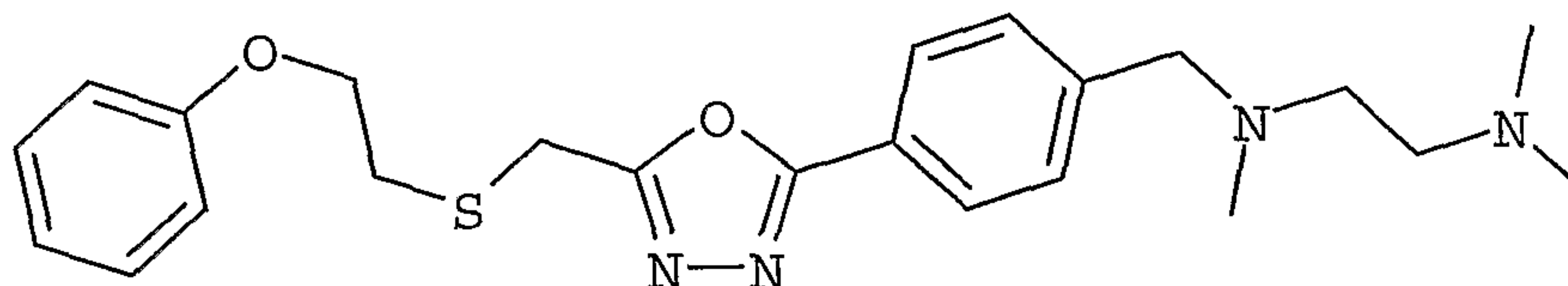
mmol) and glacial acetic acid (0.03 mL, 0.59 mmol) in 1,2-dichloroethane (3.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (190 mg, 0.88 mmol) was added and the reaction stirred for 5 h. The mixture was then diluted with methylene chloride (5 mL), washed with 2 N NaOH (10 mL), dried (MgSO₄), filtered and concentrated to yield 0.29 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 164 mg (66%) of a colorless oil.

¹H NMR (CDCl₃) δ 7.97 (d, 2H, J=8 Hz), 7.44 (d, 2H, J=8 Hz), 7.25 (m, 2H), 6.93 (m, 1H), 6.87 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.84 (s, 2H), 3.04 (t, 2H, J=12 Hz), 2.68 (t, 2H, J=14 Hz), 2.34 (t, 2H, J=14 Hz), 2.22 (s, 6H), 1.72 (m, 2H). MS (ES⁺) m/e 427 (M+1). IR (film, cm⁻¹) 3458, 3425, 3397, 1640, 1591, 1491, 1241. Anal. Calcd for C₂₃H₃₀N₄O₂S: C, 64.76; H, 7.09; N, 13.13; S, 7.52. Found C, 64.40; H, 6.98; N, 13.29; S, 7.80.

15

Example 138

Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-{[4-[(N,N',N'-trimethyl-1,2-ethanediamino)methyl]phenyl]-1,3,4-oxadiazole



A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (200 mg, 0.59 mmol), N,N,N'-trimethylethylenediamine (0.15 mL, 1.18 mmol) and glacial acetic acid (0.03 mL, 0.59 mmol) in 1,2-dichloroethane (3.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (190 mg, 0.88 mmol) was added and the reaction stirred for 3 h. The mixture was then diluted with methylene chloride (5 mL), washed with 2 N NaOH (10 mL), dried (MgSO₄), filtered and concentrated to yield 0.31 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 172 mg (69%) of a white solid.

¹H NMR (CDCl₃) δ 7.96 (d, 2H, J=6 Hz), 7.44 (d, 2H, J=6 Hz), 7.25 (m, 2H), 6.93 (m, 1H), 6.87 (d, 2H, J=7 Hz), 4.19 (m, 2H), 4.03 (s, 2H), 3.56 (s, 2H), 3.04 (m, 2H), 2.48

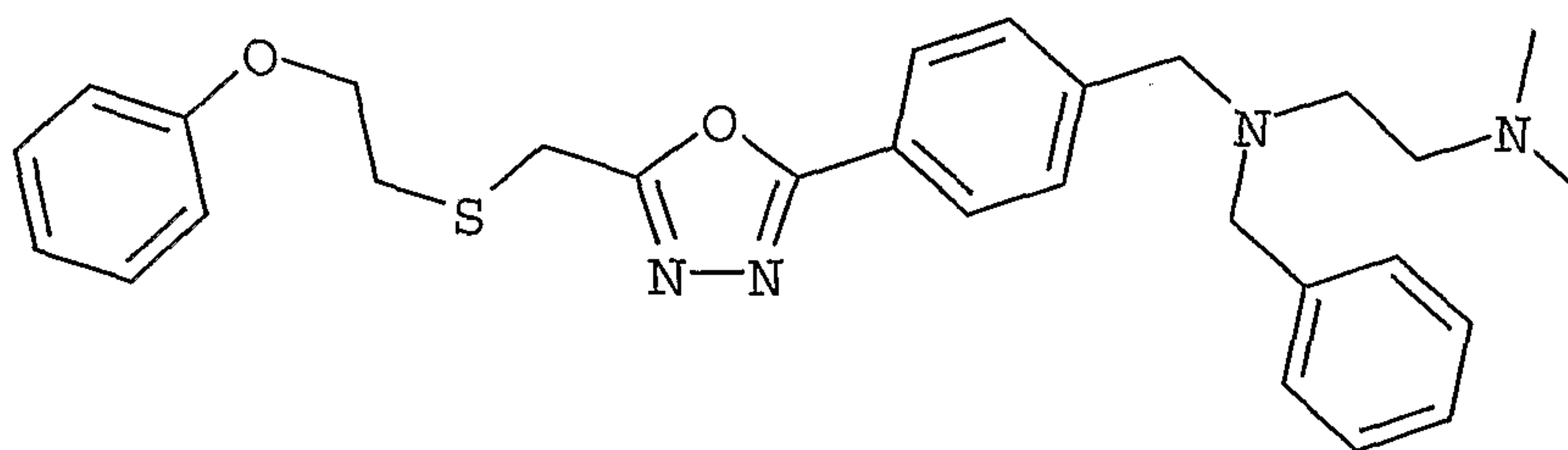
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(m, 4H), 2.24 (s, 3H), 2.22 (s, 6H). IR (KBr, cm^{-1}) 3419, 2945, 2802, 2763, 1594, 1559, 1493, 1460, 1416, 1310, 1237, 1180, 1136, 1083, 1029, 851, 752, 693. MS (ES+) m/e 427 (M+1). Anal. Calcd for $\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$: C, 64.76; H, 7.09; N, 13.13; S, 7.52. Found C, 64.96; H, 7.01; N, 13.47; S, 7.38.

5

Example 139

Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[(N-benzyl-N',N'-dimethyl-1,2-ethanediamino)methyl]phenyl}-1,3,4-oxadiazole



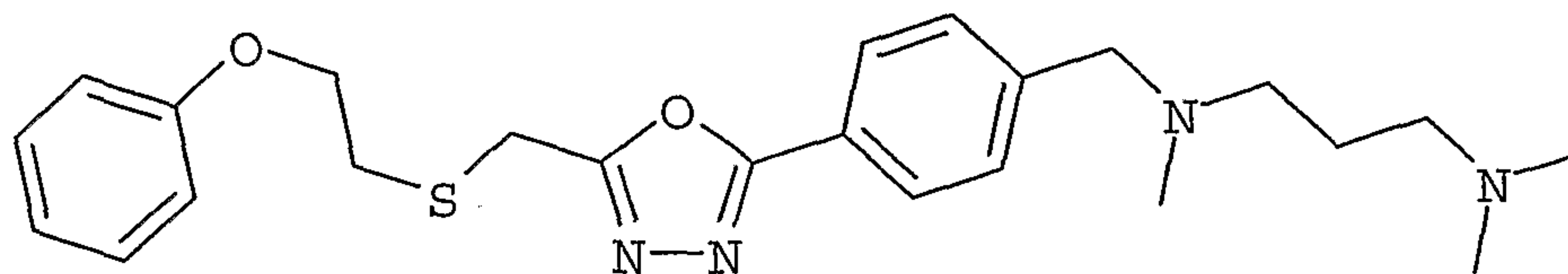
10 A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (144 mg, 0.42 mmol), N'-benzyl-N,N-dimethylethylenediamine (0.16 mL, 0.85 mmol) and glacial acetic acid (0.025 mL, 0.44 mmol) in 1,2-dichloroethane (3.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (135 mg, 0.64 mmol) was added and the reaction stirred for 4 h. The mixture was then diluted with
15 methylene chloride (5 mL), washed with 2 N NaOH (10 mL), dried (MgSO_4), filtered and concentrated to yield 0.31 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 101 mg (47%) of a white solid.

^1H NMR (CDCl_3) δ 7.95 (d, 2H, J=8 Hz), 7.48 (d, 2H, J=8 Hz), 7.32 (m, 5H), 7.27
20 (m, 2H), 6.92 (m, 1H), 6.87 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.64 (s, 2H), 3.60 (s, 2H), 3.03 (t, 2H, J=12 Hz), 2.58 (dd, 2H, J=7 and 8 Hz), 2.45 (dd, 2H, J=7 and 8 Hz), 2.22 (s, 6H). IR (KBr, cm^{-1}) 3435, 3028, 2970, 2931, 2877, 2793, 1597, 1557, 1496, 1458, 1418, 1364, 1295, 1239, 1170, 1119, 1077, 1018, 971, 836, 746, 694. MS (ES+) m/e 503 (M+1). Anal. Calcd for $\text{C}_{29}\text{H}_{34}\text{N}_4\text{O}_2\text{S}$: C, 69.29; H, 6.82; N, 11.15; S, 6.38. Found C, 68.96; H, 6.90; N, 11.15; S, 6.27.
25

Example 140

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Preparation of 2-[[2-(phenoxyethyl)thio]methyl]-5-{4-[(N,N',N'-trimethyl-1,2-propanediamino)methyl]phenyl}-1,3,4-oxadiazole



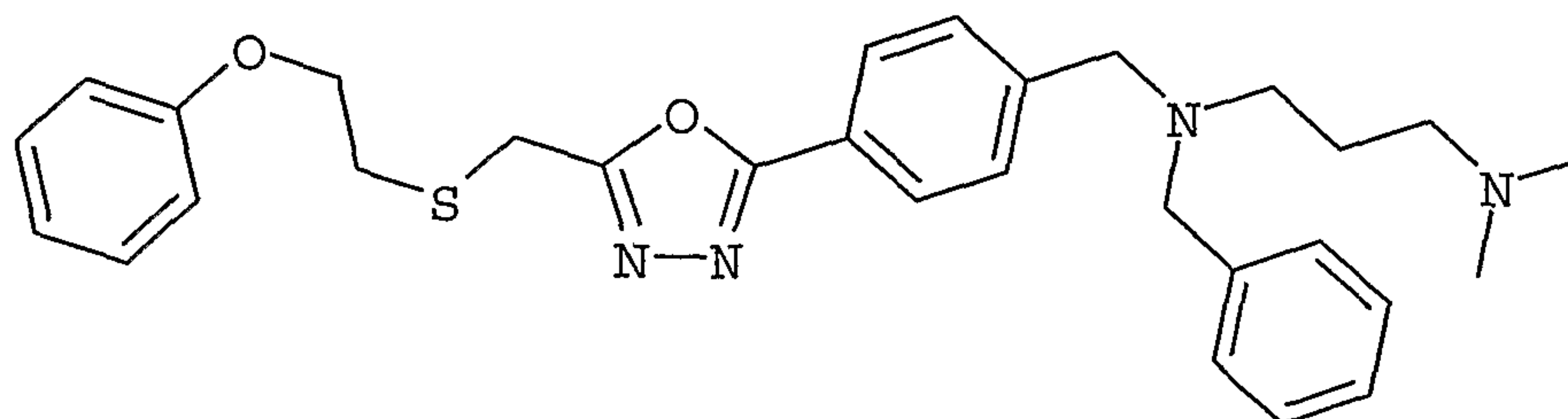
A solution of 2-[[2-(phenoxyethyl)thio]methyl]-5-(4-formylphenyl)-1,3,4-oxadiazole (144 mg, 0.42 mmol), N,N,N'-trimethyl-1,3-propanediamine (0.125 mL, 0.85 mmol) and glacial acetic acid (0.025 mL, 0.44 mmol) in 1,2-dichloro-ethane (3.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (135 mg, 0.64 mmol) was added and the reaction stirred for 3 h. The mixture was then diluted with methylene chloride (5 mL), washed with 2 N NaOH (10 mL), dried (MgSO₄), filtered and concentrated to yield 0.24 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 87 mg (47%) of a colorless oil.

¹H NMR (CDCl₃) δ 7.96 (d, 2H, J=8 Hz), 7.43 (d, 2H, J=8 Hz), 7.25 (m, 2H), 6.92 (m, 1H), 6.87 (d, 2H, J=9 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.52 (s, 2H), 3.03 (t, 2H, J=12 Hz), 2.40 (dd, 2H, J=7 and 8 Hz), 2.31 (dd, 2H, J=7 and 8 Hz), 2.23 (s, 6H), 2.18 (s, 3H), 1.71 (m, 2H). IR (film, cm⁻¹) 3402, 1595, 1491, 1239, 755, 730. MS (ES+) m/e 442 (M+1). Anal. Calcd for C₂₄H₃₂N₄O₂S: C, 65.42; H, 7.32; N, 12.72; S, 7.28. Found C, 65.68; H, 7.58; N, 12.61; S, 7.23.

20

Example 141

Preparation of 2-[[2-(phenoxyethyl)thio]methyl]-5-[4-(N-benzyl-N',N'-dimethyl-1,3-propanediamino)methyl]phenyl]-1,3,4-oxadiazole



A solution of 2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[(N',N'-dimethyl-1,3-propanediamino)methyl]phenyl}-1,3,4-oxadiazole (110 mg, 0.26 mmol), benzaldehyde

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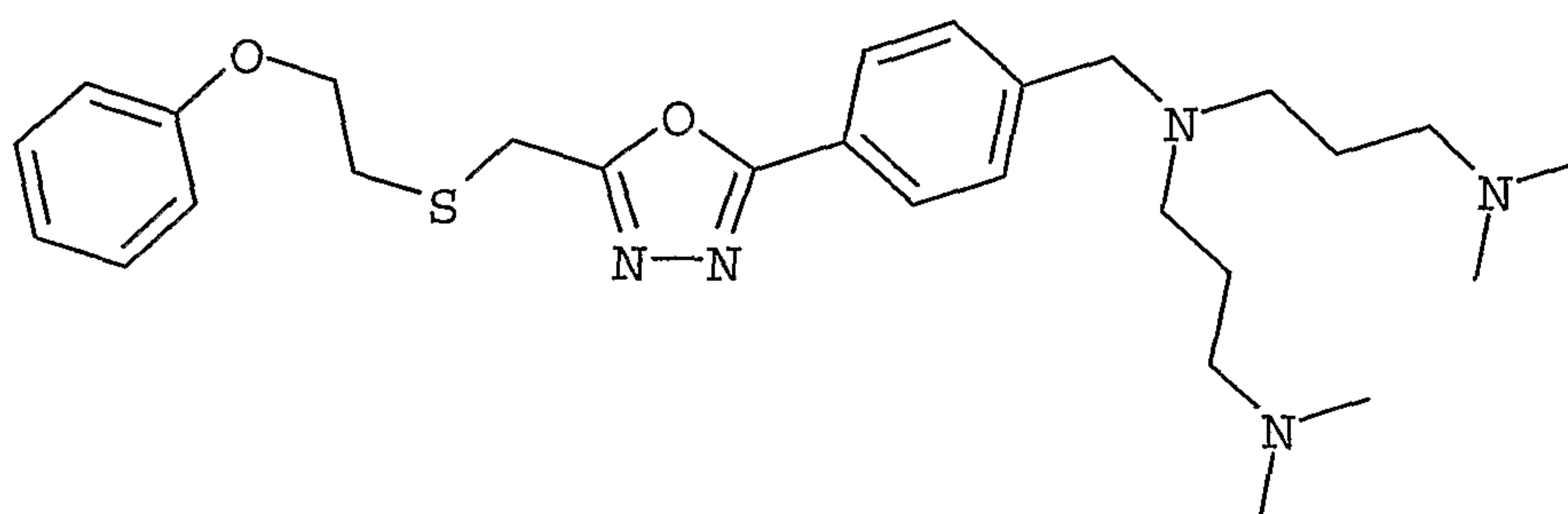
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(0.03 mL, 0.28 mmol) and glacial acetic acid (0.015 mL, 0.26 mmol) in 1,2-dichloroethane (3.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxymethylborohydride (82 mg, 0.39 mmol) was added and the reaction stirred for 8 h. The mixture was then diluted with methylene chloride (5 mL), washed with 2 N NaOH (10 mL), dried (MgSO₄), filtered and concentrated to yield 0.15 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 52 mg (39%) of a white solid.

¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8 Hz), 7.47 (d, 2H, J=8 Hz), 7.32 (m, 5H), 7.28 (m, 2H), 6.92 (m, 1H), 6.87 (d, 2H, J=8 Hz), 4.18 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.59 (s, 2H), 3.56 (s, 2H), 3.03 (t, 2H, J=12 Hz), 2.45 (dd, 2H, J=7 and 8 Hz), 2.24 (m, 2H), 2.17 (s, 6H), 1.68 (m, 2H). IR (KBr, cm⁻¹) 3434, 3026, 2934, 2874, 2785, 2357, 1597, 1558, 1495, 1456, 1419, 1369, 1297, 1239, 1173, 1118, 1075, 1020, 967, 830, 745, 693. MS (ES⁺) m/e 518 (M+1). Anal. Calcd for C₃₀H₃₆N₄O₂S: C, 69.74; H, 7.02; N, 10.84; S, 6.21. Found C, 69.65; H, 6.96; N, 10.67; S, 6.39.

Example 142

Preparation of 2-[[2-(phenoxyethyl)thio]methyl]-5-{4-[(N,N-bis-(3-(N',N'-dimethyl)propyl)amino)methyl]phenyl}-1,3,4-oxadiazole



A solution of 2-[[2-(phenoxyethyl)thio]methyl]-5-(4-formylphenyl)-1,3,4-oxadiazole (163 mg, 0.48 mmol), 3,3'-iminobis-(N,N-dimethylpropylamine) (0.22 mL, 0.99 mmol) and glacial acetic acid (0.03 mL, 0.52 mmol) in 1,2-dichloroethane (4.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxymethylborohydride (153 mg, 0.72 mmol) was added and the reaction stirred for 16 h. The mixture was then diluted with methylene chloride (10 mL), washed with 2 N NaOH (10 mL), dried (MgSO₄), filtered and concentrated to yield 0.35 g of a pale yellow oil. Half of this material was

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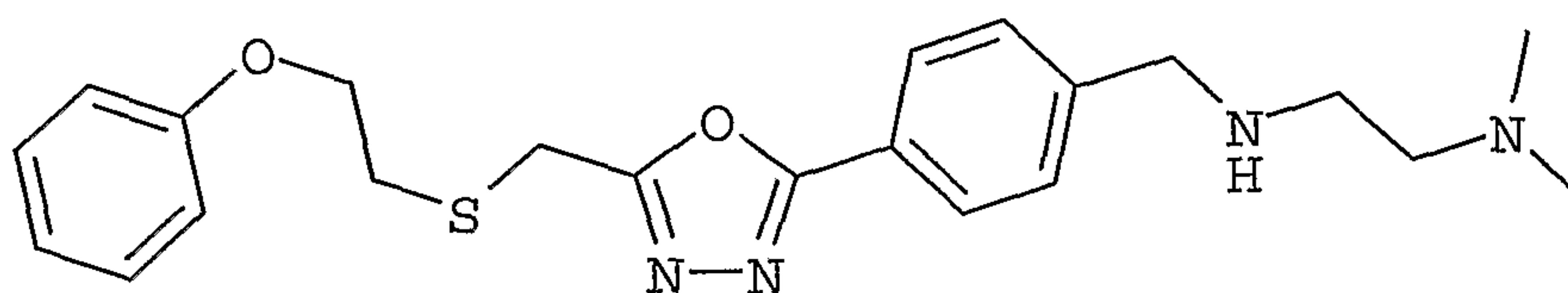
purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia-methanol)] to yield 84 mg (34%) of a white solid.

¹H NMR (CDCl₃) δ 7.94 (d, 2H, J=8 Hz), 7.43 (d, 2H, J=8 Hz), 7.25 (m, 2H), 6.90 (m, 1H), 6.88 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.59 (s, 2H), 3.04 (t, 2H, J=12 Hz), 2.44 (t, 4H, J=15 Hz), 2.26 (t, 4H, J=15 Hz), 2.20 (s, 12H), 1.63 (m, 4H). IR (KBr, cm⁻¹) 3430, 2939, 2889, 2863, 2812, 2770, 2720, 1599, 1562, 1497, 1461, 1380, 1297, 1242, 1173, 1082, 1027, 826, 751, 691. MS (ES+) m/e 513 (M+1). Anal. Calcd for C₂₈H₄₁N₅O₂S: C, 65.72; H, 8.08; N, 13.68; S, 6.26. Found C, 65.19; H, 8.10; N, 13.39; S, 6.28.

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Example 143

Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[(N',N'-dimethyl-1,2-ethanediamino)methyl]phenyl}-1,3,4-oxadiazole



A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (340 mg, 1.0 mmol), N,N-dimethyl-1,2-ethylenediamine (0.22 mL, 2.0 mmol) and glacial acetic acid (0.06 mL, 1.0 mmol) in 1,2-dichloroethane (6.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (320 mg, 1.5 mmol) was added and the reaction stirred for 16 h. The mixture was then diluted with methylene chloride (10 mL), washed with 2 N NaOH (10 mL), dried (MgSO₄), filtered and concentrated to yield 0.43 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 154 mg (37%) of a white solid.

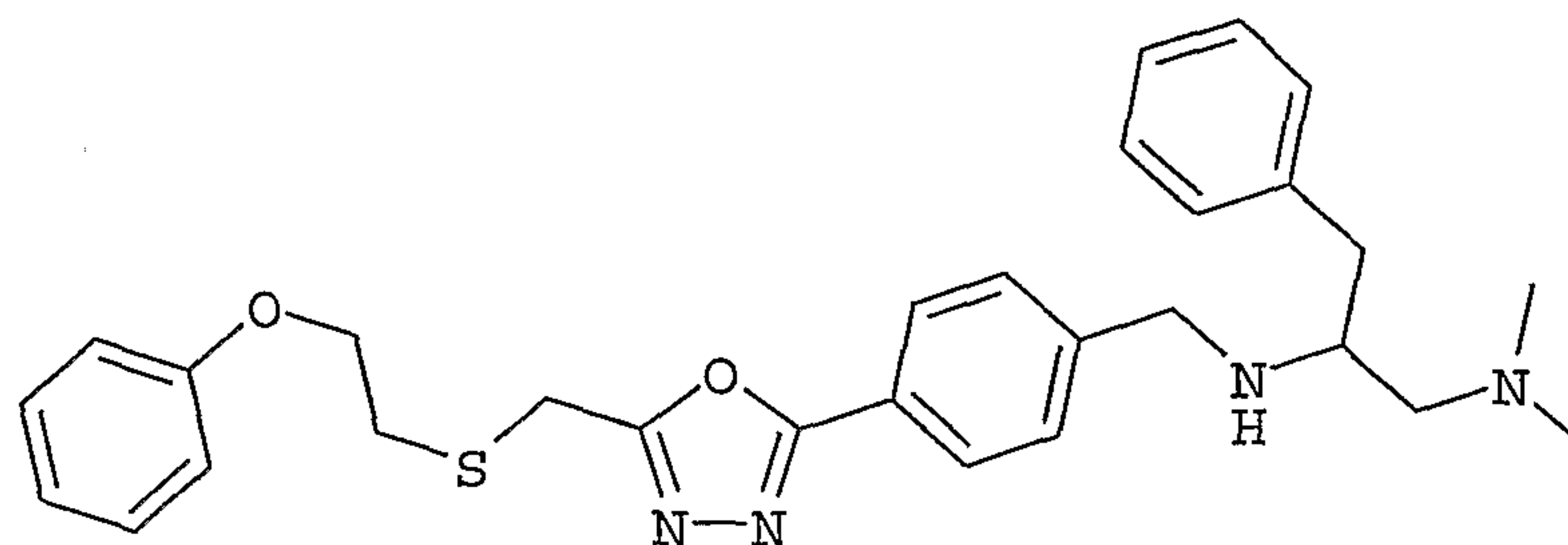
¹H NMR (CDCl₃) δ 7.97 (d, 2H, J=8 Hz), 7.45 (d, 2H, J=8 Hz), 7.25 (m, 2H), 6.93 (m, 1H), 6.87 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.86 (s, 2H), 3.04 (t, 2H, J=12 Hz), 2.67 (t, 2H, J=12 Hz), 2.43 (t, 2H, J=12 Hz), 2.20 (s, 6H). IR (KBr, cm⁻¹) 3423, 3318, 2970, 2928, 2856, 2812, 2781, 1595, 1560, 1492, 1461, 1418, 1237, 1079, 1019, 818, 757, 697. MS (ES+) m/e 414 (M+1). Anal. Calcd for C₂₂H₂₈N₄O₂S: C, 64.05; H, 6.84; N, 13.58; S, 7.77. Found C, 64.32; H, 6.24; N, 13.52; S, 7.60.

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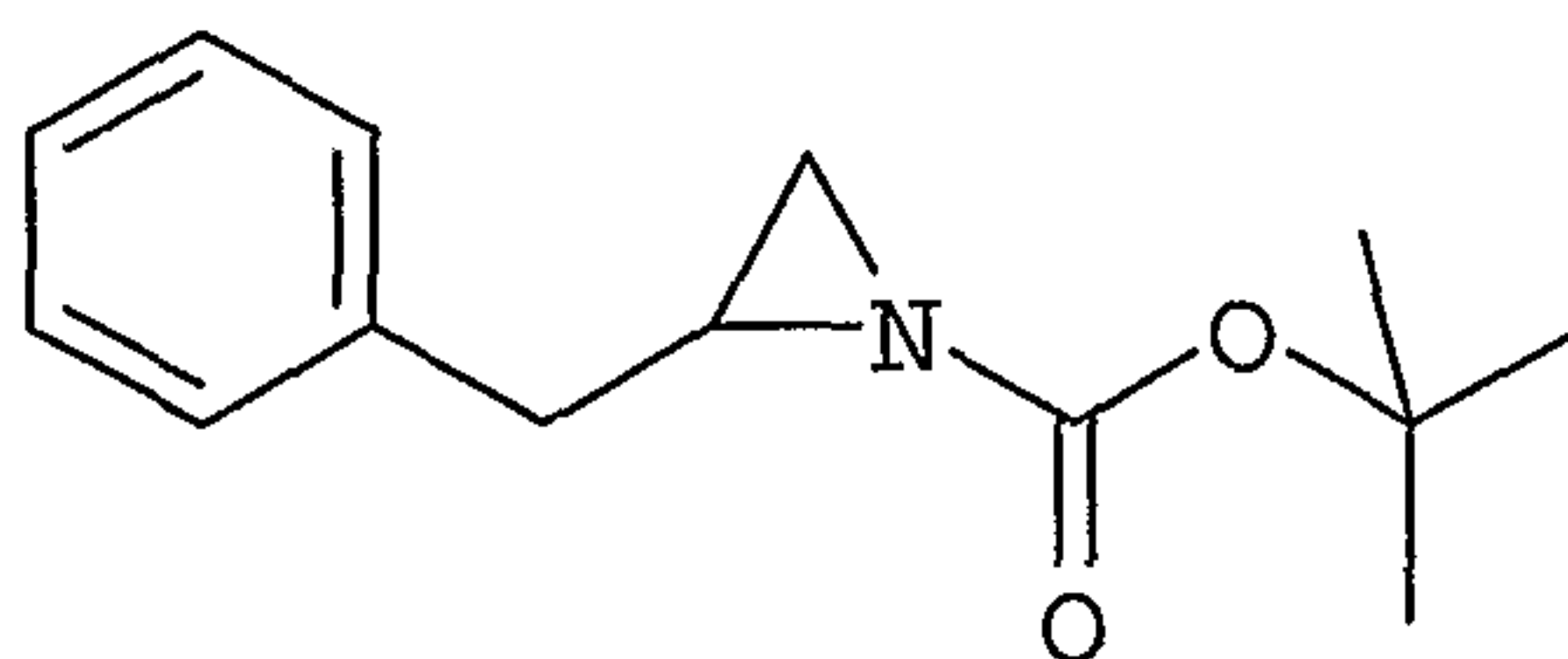
Example 144

Preparation of (+)-2-[[[(2-phenoxyethyl)thio]methyl]-5-{4-[[[(1-benzyl-2-(N,N-dimethylamino)ethyl)amino)methyl]phenyl]-1,3,4-oxadiazole



5

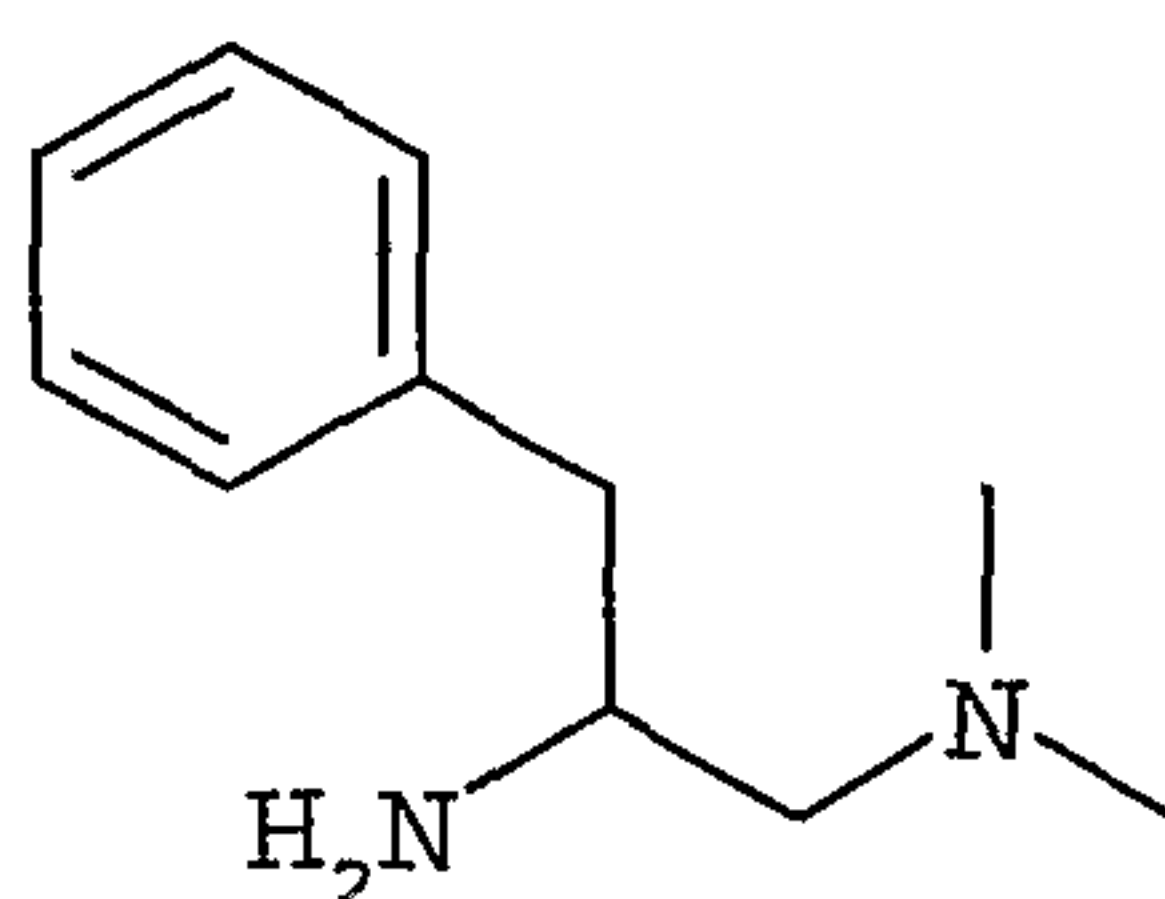
a) (+)-N-(tert-Butyloxycarbonyl)-2-benzylaziridine



A solution of (+)-2-amino-3-phenylpropanol (6g, 40 mmol) and di-t-butyl dicarbonate (9.53 g, 44 mmol) in isopropyl alcohol (20 mL) and 1,4-dioxane (40 mL) was stirred at room temperature for 4 h. The reaction was concentrated and vacuum dried. This material, p-toluenesulfonyl chloride (9.2 g, 48 mmol) and potassium hydroxide (9.0g, 160 mmol) were stirred in ethyl ether (400 mL) at room temperature for 20 h. The mixture was then poured into ice water (400 mL). The aqueous material was extracted with ethyl ether (300 mL) and the combined organic fractions were dried (MgSO₄), filtered and concentrated to yield 9.0 g (97%) of a colorless oil.

¹H NMR (CDCl₃) δ 7.25 (m, 5H), 2.95 (m, 1H), 2.60 (m, 2H), 2.33 (m, 1H), 2.00 (m, 1H), 1.42 (s, 9H). MS (ES+) m/e 134 (M+1-Boc).

b) (+)-N,N-Dimethyl-2-amino-3-phenylpropylamine



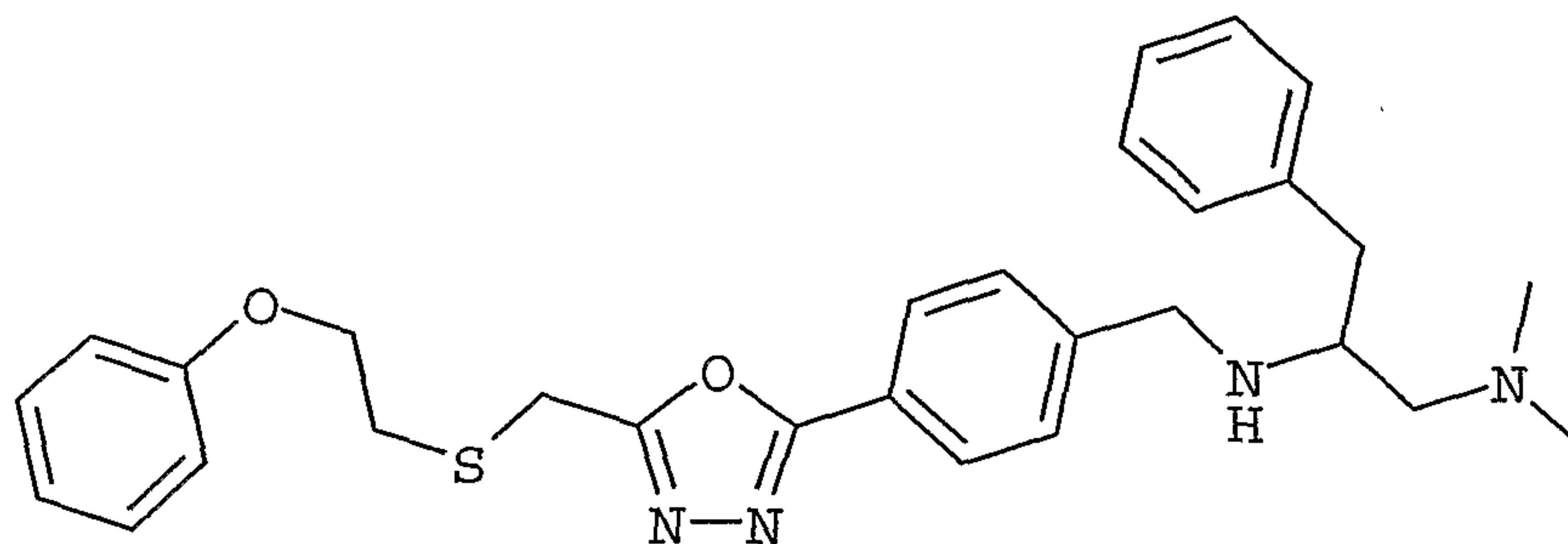
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A solution of (+)-N-boc-2-benzylaziridine (3.0 g, 12.9 mmol) and dimethylamine (2.0 M in THF, 50 mL, 100 mmol) in anhydrous acetonitrile (20 mL) was split among three sealed tubes and refluxed for 20 h. The mixture was concentrated to yield 4.0 g of an orange oil. This material was dissolved in methanol (20 mL) and loaded onto a column containing Bio-Rad 50W-X2 cationic exchange resin (60 g, pre-washed with 800 mL of methanol). The column was washed with methanol (800 mL) and methylene chloride (200 mL). The product was eluted with 2.0 N ammonia/methanol (400 mL) and concentrated to yield 3.2 g (89%) of an orange oil. This product was dissolved in 25% trifluoroacetic acid/methylene chloride (40 mL) and stirred at room temperature for 16 h. The reaction was concentrated, dissolved in methanol (5 mL) and added dropwise to 2N HCl in ethyl ether to generate a solid hydrochloride salt, but the result was a thick oil which would not crystallize. This mixture was then concentrated, dissolved in methanol (20 mL) and loaded onto another column of 50W-X2 resin (50 g), described above. The product was isolated (1.86 g, 91% yield) as a yellow oil.

¹H NMR (CDCl₃) δ 7.17-7.30 (m, 5H), 3.12 (m, 1H), 2.72 (dd, 1H, J=5 and 9 Hz), 2.45 (dd, 1H, J=5 and 9 Hz), 2.21 (s, 6H), 2.14 (m, 2H). MS (ES+) m/e 179 (M+1).

c) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[(1-benzyl-2-(N,N-dimethylamino)ethyl)amino)methyl]phenyl}-1,3,4-oxadiazole



A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (205 mg, 0.6 mmol), (+)-N,N-dimethyl-2-amino-3-phenylpropylamine hydrochloride salt (430 mg, 2.0 mmol) and glacial acetic acid (0.06 mL, 1 mmol) in 1,2-dichloroethane (8 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (191 mg, 0.9 mmol) was added and the reaction stirred for 2 h. The mixture was diluted with methylene chloride (10 mL), extracted with 2 N NaOH (10 mL), dried (MgSO₄), filtered and concentrated to yield 483 mg of an orange oil. This oil

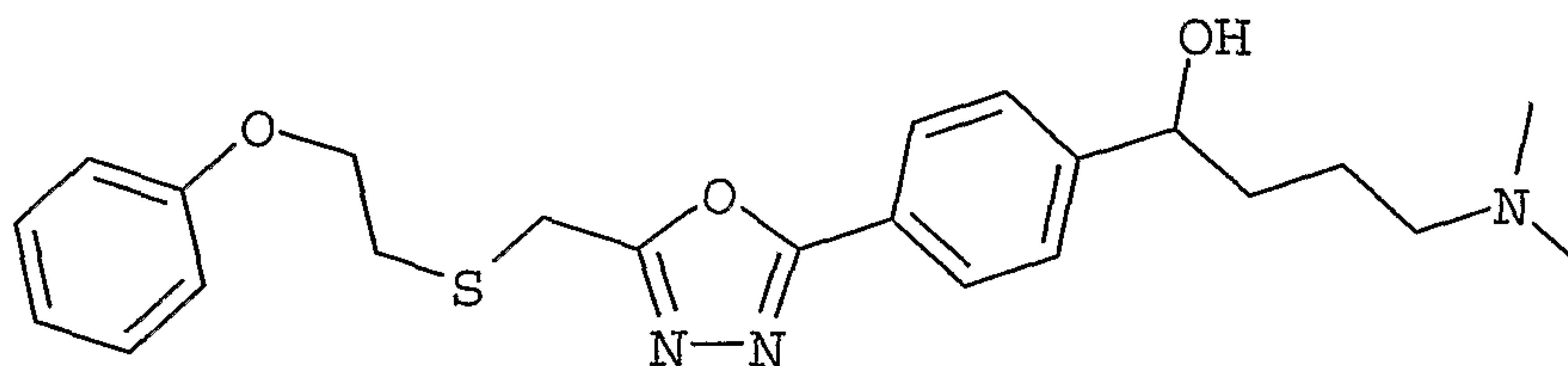
-296-

was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 N ammonia in methanol)] to yield 98 mg (32%) of a solid.

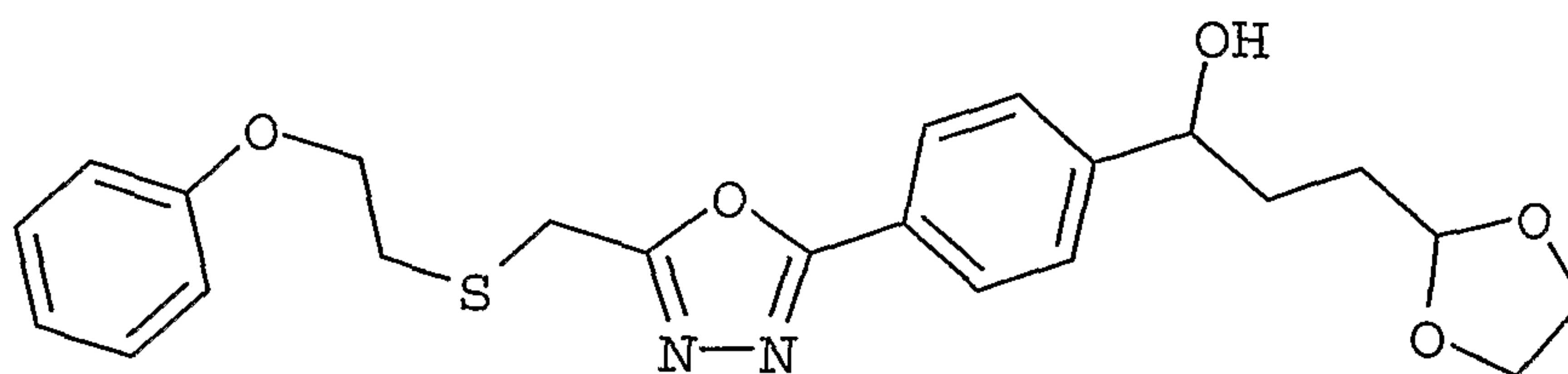
¹H NMR (CDCl₃) δ 7.94 (d, 2H, J=8 Hz), 7.36 (d, 2H, J=8 Hz), 7.25 (m, 5H), 7.18 (m, 1H), 7.14 (d, 2H, J=8 Hz), 6.93 (dd, 1H, J=7 and 8 Hz), 6.88 (d, 2H, J=9 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.78 (dd, 2H, J=14 and 14 Hz), 3.04 (t, 2H, J=12 Hz), 2.82 (m, 1H), 2.61 (m, 1H), 2.29 (m, 1H), 2.08 (s, 6H), 2.05 (m, 1H). IR (KBr, cm⁻¹) 3027, 2978, 2933, 2885, 2853, 2816, 2777, 1599, 1562, 1495, 1454, 1359, 1289, 1244, 1167, 1121, 1078, 1025, 976, 835, 803, 749, 696, 512. MS (ES⁺) m/e 503 (M+1). Anal. Calcd for C₂₉H₃₄N₄O₂S: C, 69.29; H, 6.82; N, 11.15; S, 6.38. Found C, 69.65; H, 6.84; N, 10.90; S, 6.22.

Example 145

Preparation of (+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[4-(N,N-dimethylamino)-1-hydroxybutyl]phenyl}-1,3,4-oxadiazole



a) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[3-(1,3-dioxolan-2-yl)-1-hydroxypropyl]phenyl}-1,3,4-oxadiazole



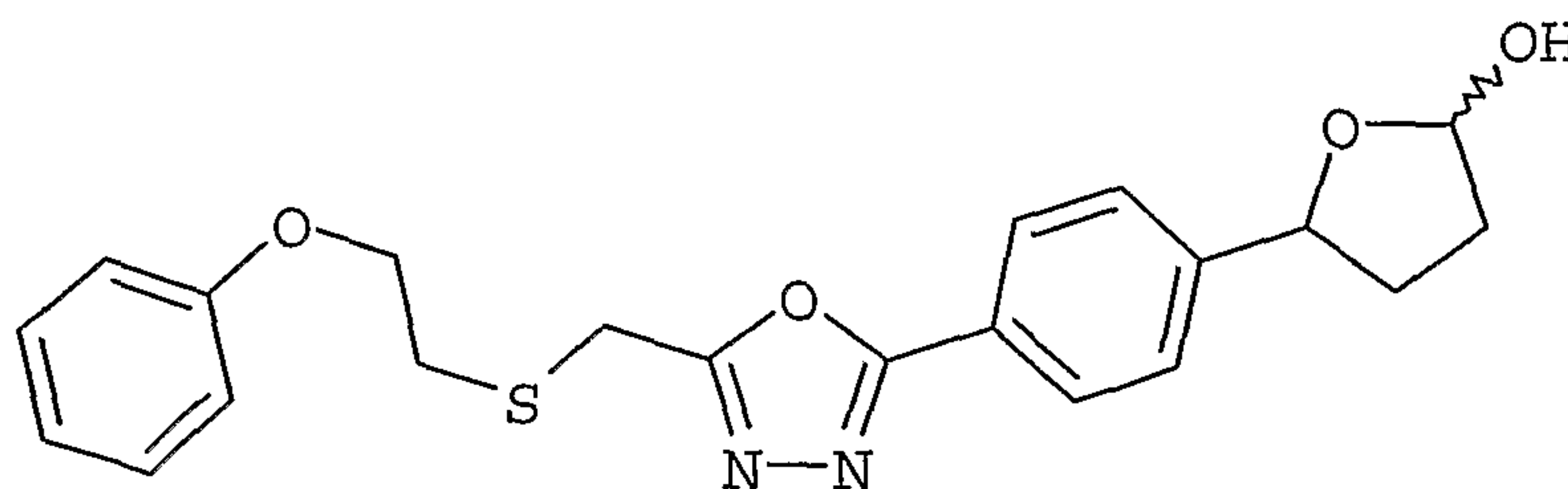
A mixture of 1,2-dibromoethane (0.09 mL, 1 mmol) and magnesium turnings (243 mg, 10 mmol) in anhydrous tetrahydrofuran (5 mL) was cooled in an ice water bath under nitrogen. A solution of 2-(2-bromoethyl)-1,3-dioxolane (1.5 mL, 12.5 mmol) in tetrahydrofuran (1 mL) was added dropwise and the mixture stirred in the cooling bath for 10 min. The mixture was then stirred at room temperature until the magnesium had gone into solution (50 min). After cooling in a dry ice/isopropanol bath, a solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole in tetrahydrofuran (5 mL) was added dropwise and stirred for 2 h in the cooling bath. The reaction was

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quenched with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (3x20 mL). The organic material was extracted with brine (25 mL), dried (MgSO₄), filtered and concentrated to yield 1.56 g of a pale yellow oil. This oil was purified by silica gel (50% ethyl acetate/hexanes) to yield 781 mg (88%) of an oil.

¹H NMR (CDCl₃) δ 7.98 (d, 2H, J=8 Hz), 7.47 (d, 2H, J=8 Hz), 7.24 (m, 1H), 6.93 (dd, 1H, J=6 and 7 Hz), 6.87 (d, 2H, J=7 Hz), 4.91 (t, 1H, J=8 Hz), 4.81 (m, 1H), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.95 (m, 2H), 3.86 (m, 2H), 3.03 (t, 2H, J=12 Hz), 2.85 (d, 1H, J=4 Hz), 1.89 (m, 2H), 1.82 (m, 2H). MS (ES+) m/e 443 (M+1).

b) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(5-hydroxy-2,3,4,5-tetrahydrofuran-2-yl)phenyl]-1,3,4-oxadiazole, mixture of cis- and trans-isomers

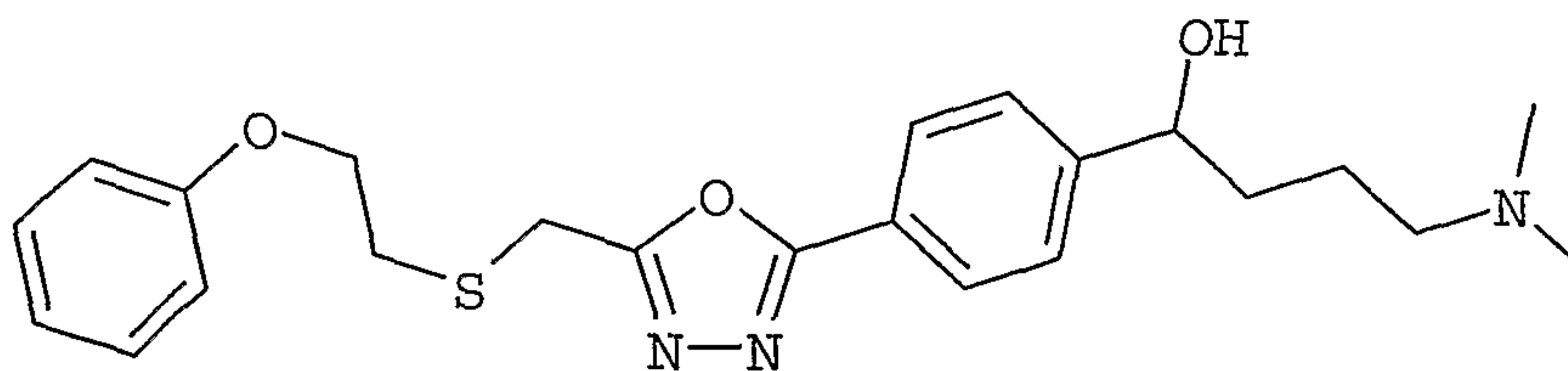


A mixture of (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[3-(1,3-dioxolan-2-yl)-1-hydroxypropyl]phenyl}-1,3,4-oxadiazole (658 mg, 1.49 mmol) and iron (III) chloride hexahydrate (1.41 g, 5.21 mmol) in methylene chloride (30 mL) was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous sodium bicarbonate (25 mL) and extracted with methylene chloride (3x25 mL). The organic material was washed with brine (4x20 mL), dried (MgSO₄), filtered and concentrated to yield 498 mg of an orange oil. This oil was purified by preparative TLC (50% ethyl acetate/hexanes) to yield 103 mg (17%) of a colorless oil.

¹H NMR (CDCl₃) δ 7.99 (d, 2H, J=8 Hz), 7.52 (d, 1H, J=8 Hz), 7.42 (d, 1H, J=8 Hz), 7.24 (m, 1H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=7 Hz), [cis/trans protons: 5.79 (m, 0.5H), 5.66 (m, 0.5H), 5.29 (m, 0.5H), 5.06 (m, 0.5H)], 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.04 (t, 2H, J=12 Hz), 2.73 (br s, 0.5H), 2.56 (br s, 0.5H), 2.33-2.54 (m, 1H), 1.96-2.18 (m, 2H), 1.76 (m, 1H). MS (ES+) m/e 399 (M+1).

c) (+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[4-(N,N-dimethylamino)-1-hydroxybutyl]phenyl}-1,3,4-oxadiazole

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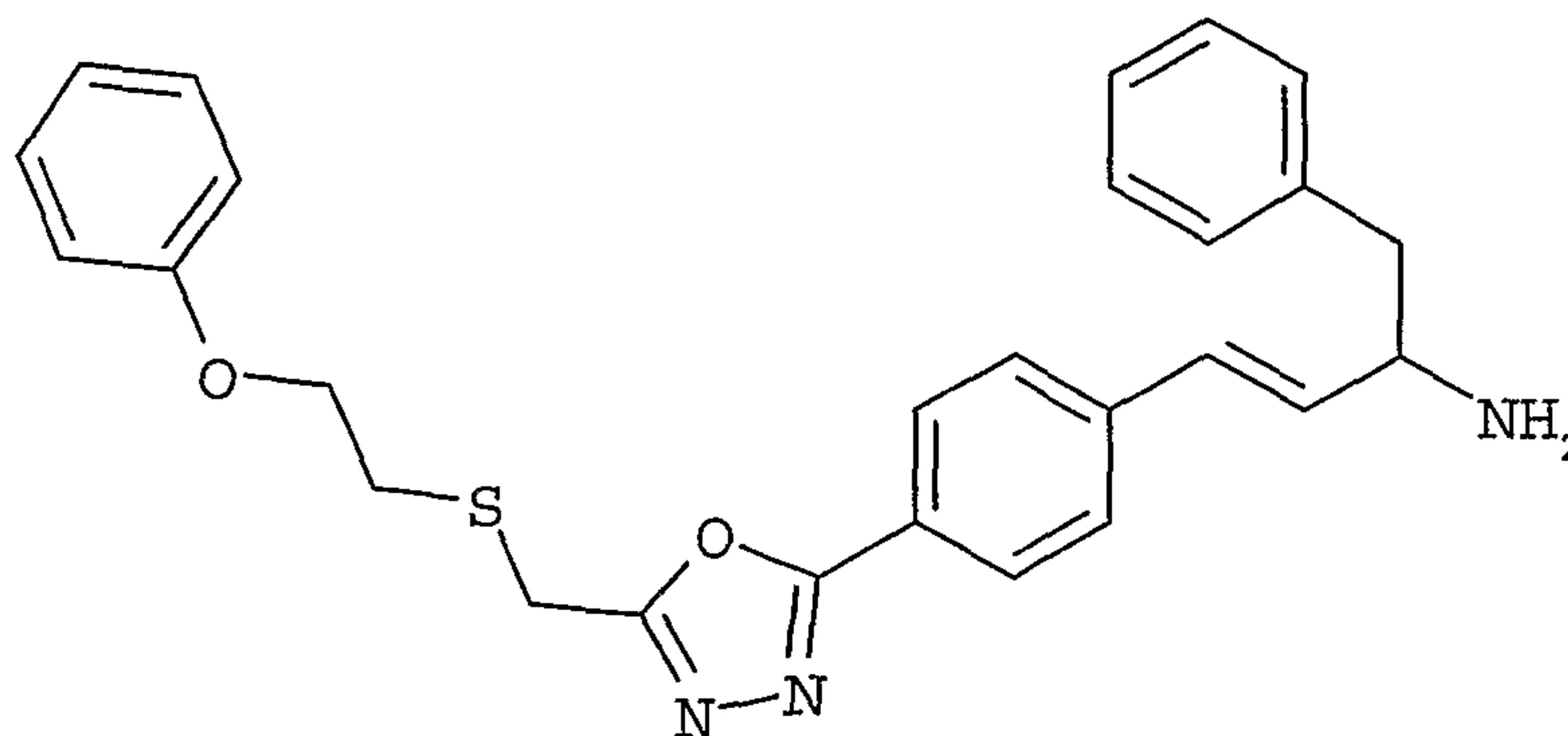


A solution of cis- and trans-(+)-2-[[[2-(2-phenoxyethyl)thio]methyl]-5-[4-(5-hydroxy-2,3,4,5-tetrahydrofuran-2-yl)phenyl]-1,3,4-oxadiazole (100 mg, 0.25 mmol), dimethylamine (2.0 M in THF, 2 mL, 4 mmol) and glacial acetic acid (0.02 mL, 0.35 mmol) in 1,2-dichloroethane was stirred under nitrogen. Sodium triacetoxyborohydride (160mg, 0.76 mmol) was added and the reaction stirred at room temperature for 16 h. The mixture was diluted with methylene chloride (10 mL) and extracted with 2N NaOH (10 mL), dried (MgSO₄), filtered and concentrated to yield 210 mg of an orange oil. This oil was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 N ammonia in methanol)] to yield 35 mg (33%) of a white solid.

¹H NMR (CDCl₃) δ 7.97 (d, 2H, J=8 Hz), 7.51 (d, 2H, J=8 Hz), 7.24 (m, 2H), 6.92 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 4.72 (d, 1H, J=6 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.47 (s, 1H), 3.03 (t, 2H, J=12 Hz), 2.42 (m, 2H), 2.32 (s, 6H), 1.99 (m, 2H), 1.75-1.86 (m, 2H). IR (KBr, cm⁻¹) 3407, 3167, 3093, 3058, 2916, 2868, 2794, 2734, 1594, 1562, 1493, 1464, 1414, 1293, 1236, 1171, 1078, 1013, 838, 755, 696. MS (ES⁺) m/e 428 (M+1). Anal. Calcd for C₂₃H₂₉N₃O₃S: C, 64.61; H, 6.84; N, 9.83; S, 7.50. Found C, 64.66; H, 6.41; N, 9.31; S, 7.30.

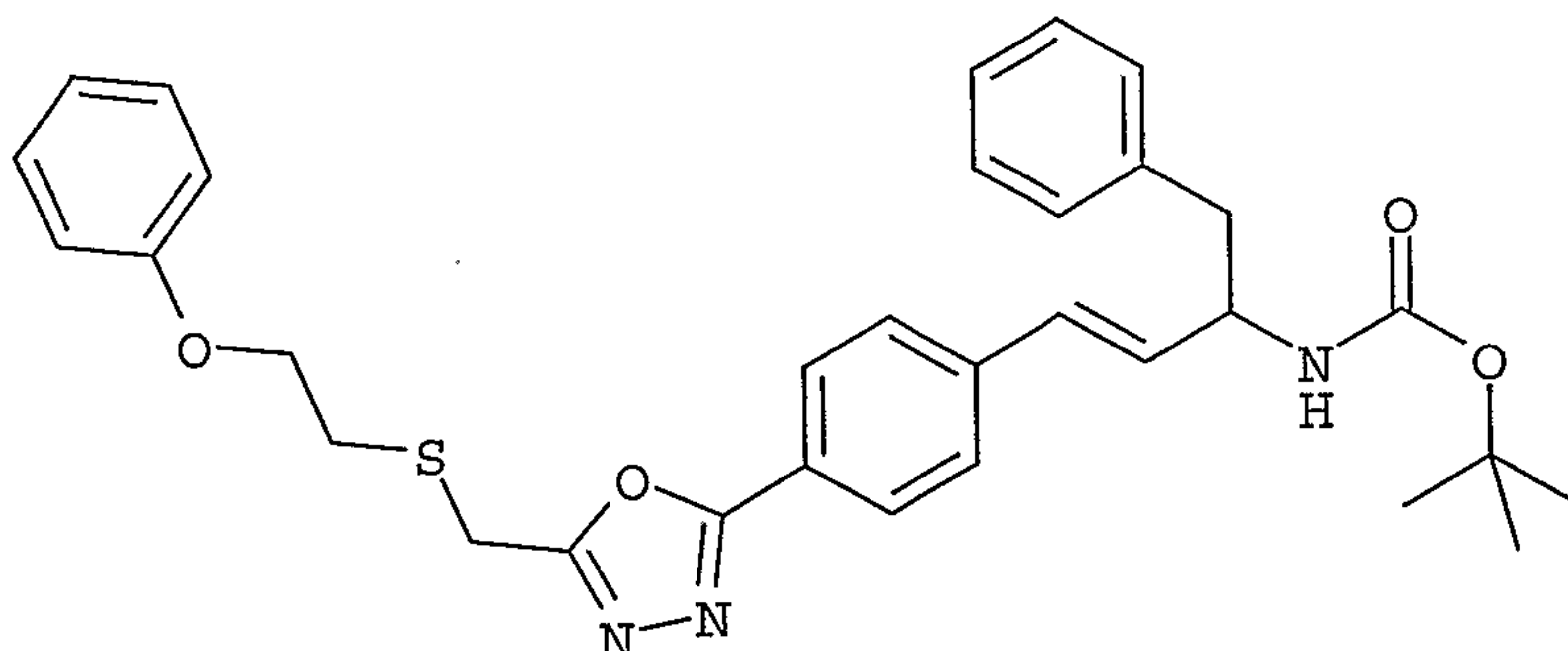
Example 146

Preparation of (E)-2-[[[2-(2-Phenoxyethyl)thio]methyl]-5-[4-(3-amino-3-benzylpropen-1-yl)phenyl]-1,3,4-oxadiazole



-299-

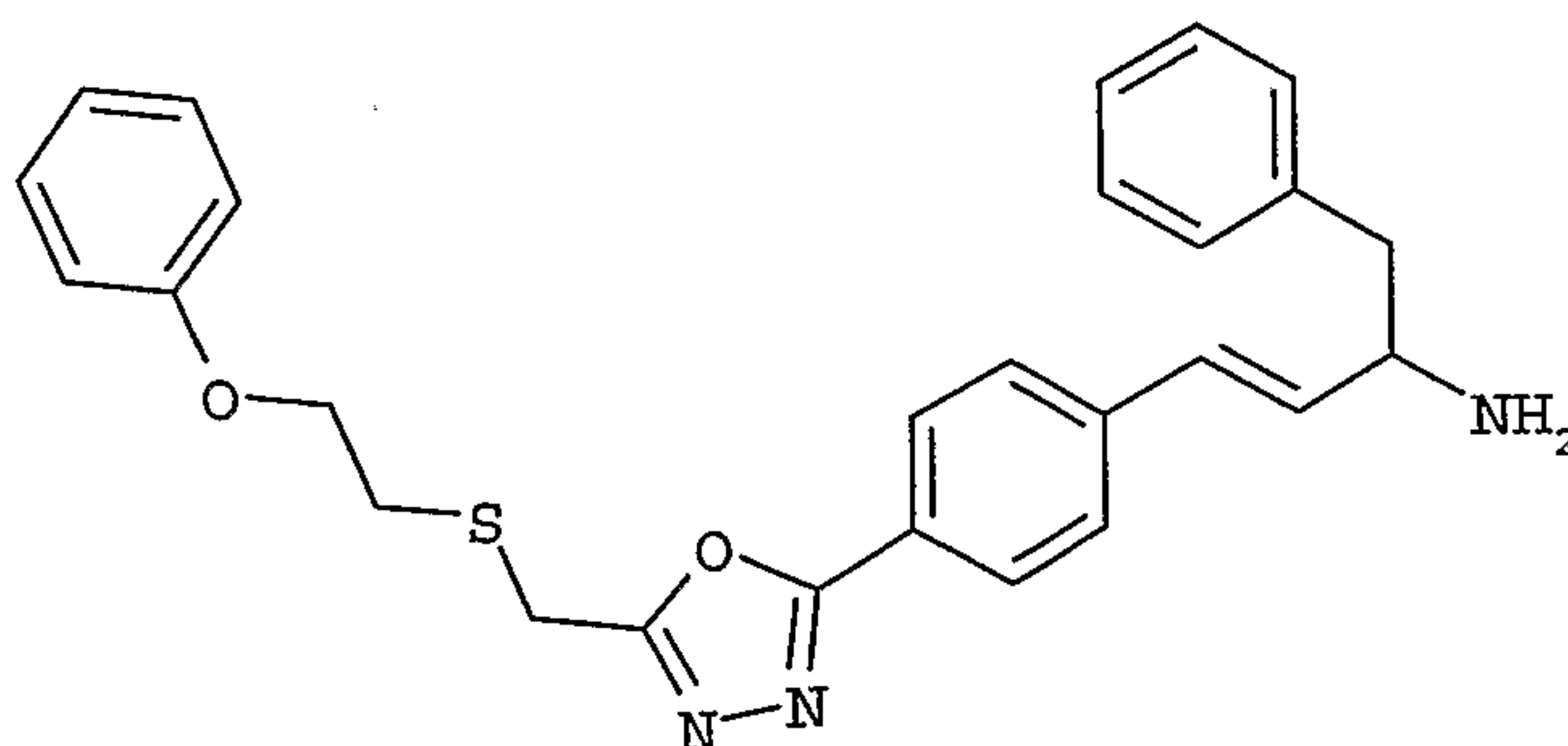
a) 2-[[[(2-Phenoxyethyl)thio]methyl]-5-{4-[3-benzyl-3-(tert-butoxycarbonylamino)propen-1-yl]phenyl}-1,3,4-oxadiazole



A mixture of 2-[[[(2-phenoxyethyl)thio]methyl]-5-(4-formylphenyl)-1,3,4-oxadiazole (510 mg, 1.5 mmol), 1-(ter-butoxycarbonyl)-2-benzylaziridine (R- or S-isomer, 933 mg, 4 mmol), and triphenylphosphine (1.05 g, 4 mmol) in 2-propanol (2 mL) was stirred in a sealed tube at 95~100 °C (bath temperature) for 3 days. The reaction mixture was concentrated and purified by chromatography (silica gel, EtOAc/hexanes 1:5). The isolated product was triturated from methylene chloride and hexanes to give pure E-olefines: R-isomer (210 mg, 25%), S-isomer (241 mg, 29%).

¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8.4 Hz), 7.40 (d, 2H, J=8.1 Hz), 7.18~7.31 (m, 7H), 6.93 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=7.6 Hz), 6.46 (d, 1H, J=16.1 Hz), 6.25 (dd, 1H, J=16.1, 5.6 Hz), 4.52~4.65 (m, 2H), 4.19 (t, 2H, J=6.1 Hz), 4.03 (s, 2H), 3.04 (t, 2H, J=6.1 Hz), 2.93 (d, 2H, J=6.3 Hz), 1.40 (s, 9H). IR (KBr, cm⁻¹) 3014, 2949, 2796, 2251, 1688, 1598, 1553, 1326, 1243, 926, 744, 651. MS (ES⁺) m/e 558 (M+1). Anal. Calcd for C₃₂H₃₅N₃O₄S: C, 68.92; H, 6.33; N, 7.53; S, 5.75. Found R-isomer, C, 68.84; H, 6.35; N, 7.44; S, 5.82; S-isomer, C, 68.88; H, 6.27; N, 7.36; S, 5.79.

b) 2-[[[(2-Phenoxyethyl)thio]methyl]-5-[4-(3-amino-3-benzylpropen-1-yl)phenyl]-1,3,4-oxadiazole



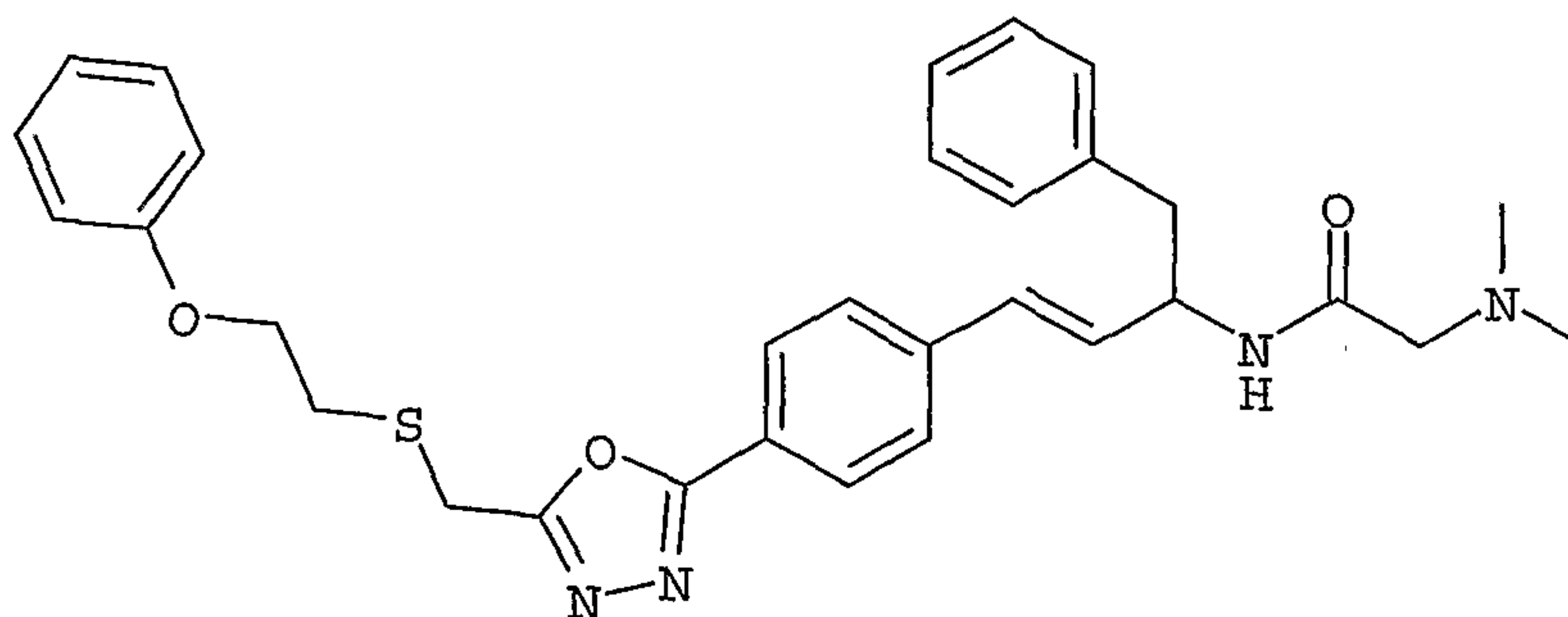
-300-

Trifluoroacetic acid (0.5 mL) was added to a solution of 2-[[2-Phenoxyethyl)thio]methyl]-5-{4-[3-benzyl-3-(tert-butoxycarbonylamino)propen-1-yl]phenyl}-1,3,4-oxadiazole (139 mg, 0.25 mmol) in methylene chloride (2 mL). The resultant mixture was stirred at room temperature overnight, concentrated, and partitioned
 5 between methylene chloride (20 mL) and 2 M NaOH (5 mL). The organic layer was dried (MgSO₄), concentrated and purified by chromatography (silica gel, 5% methanol/methylene chloride) to give a pale yellow solid: R-isomer, 87 mg, 76%; S-isomer, 80 mg, 70%.

¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8.5 Hz), 7.44 (d, 2H, J=8.4 Hz), 7.21~7.32 (m, 7H), 6.93 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=7.7 Hz) 6.53 (d, 1H, J=16.1 Hz), 6.36 (dd, 1H, J=15.8, 6.6 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.81 (m, 1H), 3.04 (t, 2H, J=6.2 Hz), 2.93 (dd, 2H, J=13.3, 5.3 Hz), 2.73 (dd, 1H, J=13.3, 8.2 Hz). IR (KBr, cm⁻¹) 3028, 2935, 2866, 2830, 1601, 1560, 1494, 1464, 1221, 1050, 915, 733, 700. MS (ES⁺) m/e 458 (M+1). Anal. Calcd for C₂₇H₂₇N₃O₂S: C, 70.87; H, 5.95; N, 9.18; S, 7.01. Found R-isomer, C, 70.52; H, 5.93; N, 9.03; S, 7.28; S-isomer, C, 70.94; H, 5.88; N, 9.12; S, 7.00.
 15

Example 147

Preparation of (E)-2-[[2-(2-Phenoxyethyl)thio]methyl]-5-{4-[3-benzyl-3-(2-(N,N-dimethylamino)acetamido)propen-1-yl]phenyl}-1,3,4-oxadiazole



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A mixture of 2-[[2-(2-Phenoxyethyl)thio]methyl]-5-[4-(3-amino-3-benzylpropen-1-yl)phenyl]-1,3,4-oxadiazole (46 mg, 0.1 mmol) and N,N-dimethylglycine (20 mg, 0.2 mmol) in pyridine (1 mL), under nitrogen, was cooled to -10~-5 °C (ice-salt bath) and phosphorus oxychloride (0.05 mL, 0.5 mmol) was added. The mixture was stirred at -
 25 10~-5 °C for 90 min and water (2 mL), followed by ethyl acetate (25 mL), was added. The mixture was washed with 2 M NaOH (2 x 5 mL), water (3 x 10 mL), and brine (10 mL), dried (MgSO₄), and concentrated. The residue was co-evaporated with toluene (20

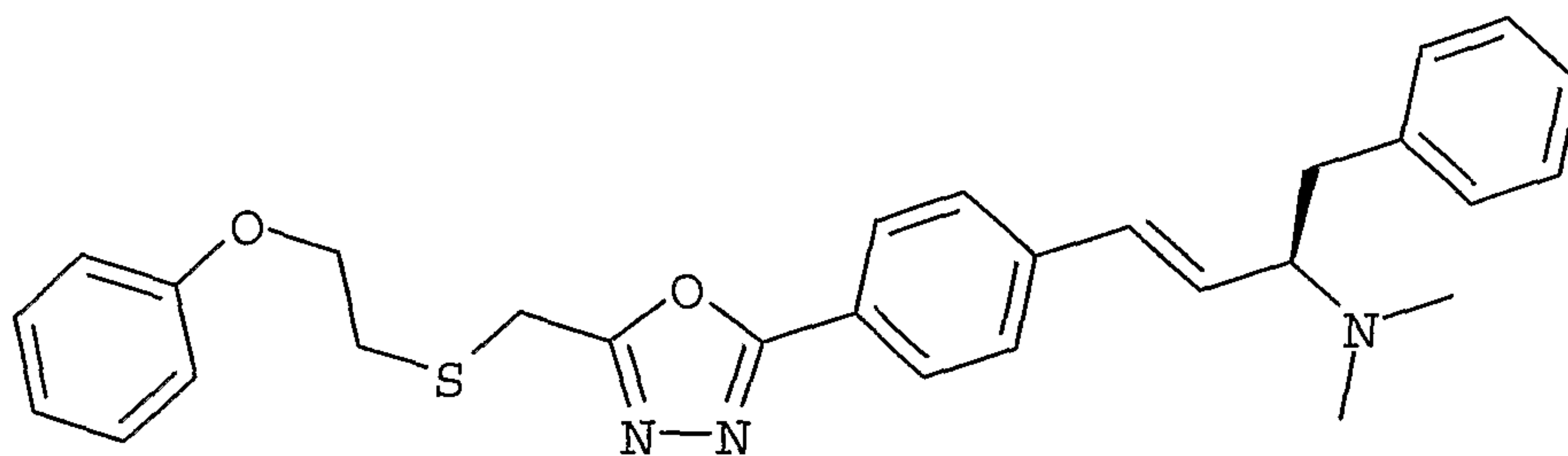
-301-

mL) under reduced pressure and purified by preparative TLC (silica gel, 5% methanol/methylene chloride) to give a white solid: R-isomer, 34 mg, 62%; S-isomer, 35 mg, 65%.

¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8.5 Hz), 7.41 (d, 2H, J=8.5 Hz), 7.19~7.30 (m, 7H), 6.93 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=7.7 Hz) 6.49 (d, 1H, J=16.1 Hz), 6.29 (dd, 1H, J=16.1, 6.2 Hz), 4.95 (m, 1H), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.04 (t, 2H, J=6.2 Hz), 2.82~3.06 (m, 4H), 2.18 (s, 6H). IR (KBr, cm⁻¹) 3402, 3025, 2958, 2855, 2799, 2776, 1688, 1597, 1550, 1494, 1481, 1239, 1058, 980, 751. MS (ES+) m/e 543 (M+1). Anal. Calcd for C₃₁H₃₄N₄O₃S: C, 68.61; H, 6.31; N, 10.32; S, 5.91. Found R-isomer C, 68.88; H, 6.27; N, 10.25; S, 5.74; S-isomer C, 68.78; H, 6.22; N, 10.24; S, 5.92.

Example 148

Preparation of (R)-(E)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-3-(N,N-dimethylamino)propen-1-yl]phenyl}-1,3,4-oxadiazole



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A solution containing (R)-(E)-2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(3-benzyl-3-aminopropen-1-yl)phenyl]-1,3,4-oxadiazole (258 mg, 0.56 mmol) and paraformaldehyde (170 mg, 5.6 mmol) in methanol (6.0 mL) was refluxed for 3h. The mixture was cooled and sodium cyanoborohydride (107 mg, 1.70 mmol) was added; the reaction stirred at room temperature for 2 h. The mixture was diluted with water (10 mL) and the methanol was removed in vacuo. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was extracted with methylene chloride (3x15 mL). The organic material was dried (MgSO₄), filtered and concentrated to yield 355 mg of an orange oil. This oil was purified by preparative TLC (10% methanol/methylene chloride) to yield 163 mg (59%) of a pale yellow oil.

25

¹H NMR (CDCl₃) δ 7.91 (d, 2H, J=9 Hz), 7.35 (d, 2H, J=8 Hz), 7.24 (m, 5H), 7.13 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 4.18 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.20 (m, 1H), 3.11 (dd, 2H, J=4 and 9 Hz), 3.03 (t, 2H, J=12 Hz), 2.75 (dd, 2H,

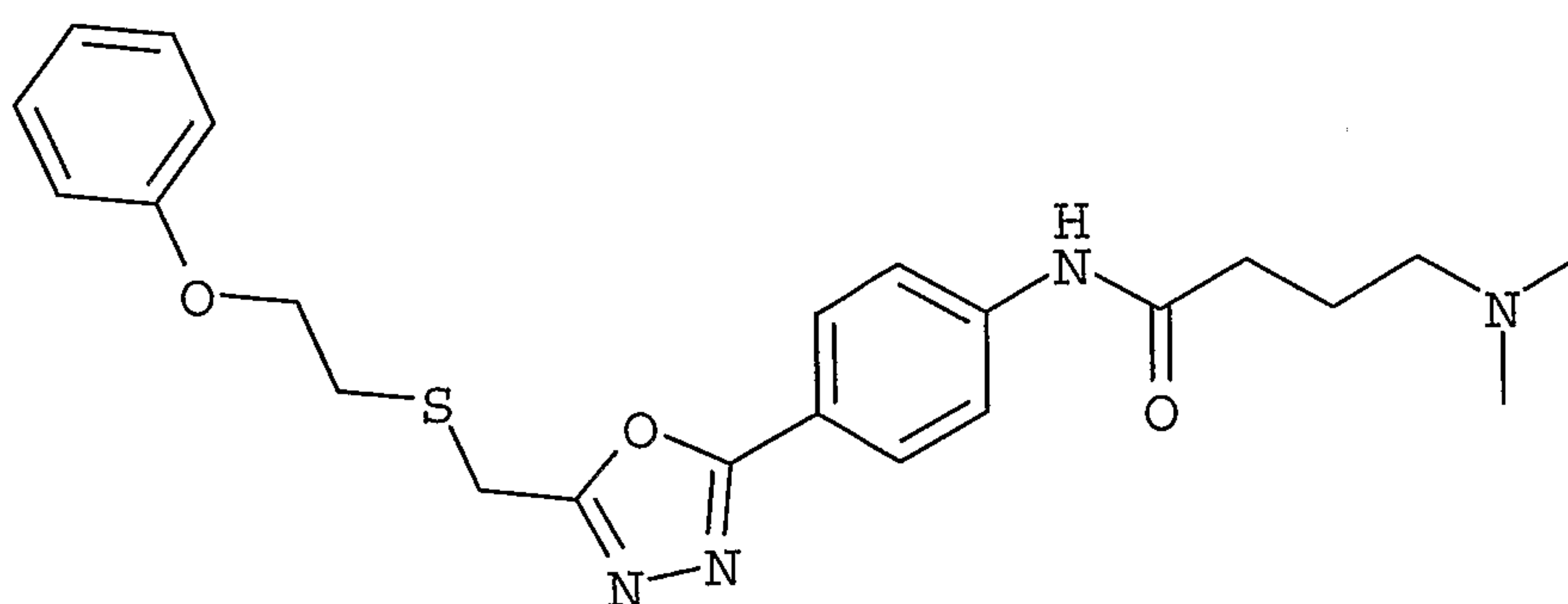
-302-

J=4 and 9 Hz), 2.37 (s, 6H). IR (film, cm^{-1}) 3030, 2935, 2865, 2823, 2779, 1599, 1557, 1494, 1462, 1239, 1078, 1031, 910, 733, 699. MS (ES+) m/e 486 (M+1). Anal. Calcd for $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_2\text{S}$: C, 71.72; H, 6.43; N, 8.65; S, 6.60. Found C, 71.26; H, 6.21; N, 8.54; S, 6.53.

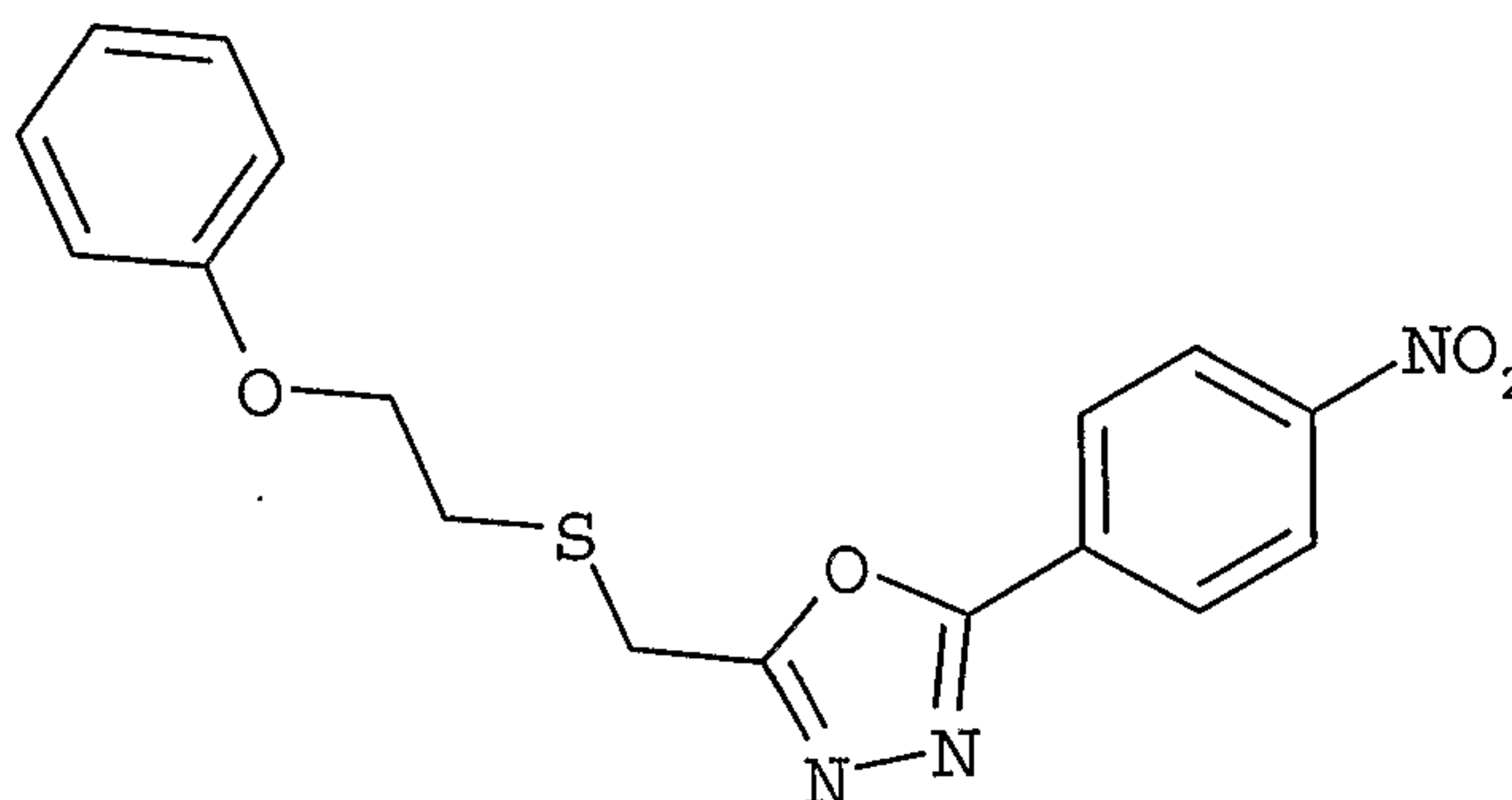
5

Example 149

Preparation of 2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole



10 a) 2-[[2-(Phenoxyethyl)thio]methyl]-5-(4-nitrophenyl)-1,3,4-oxadiazole



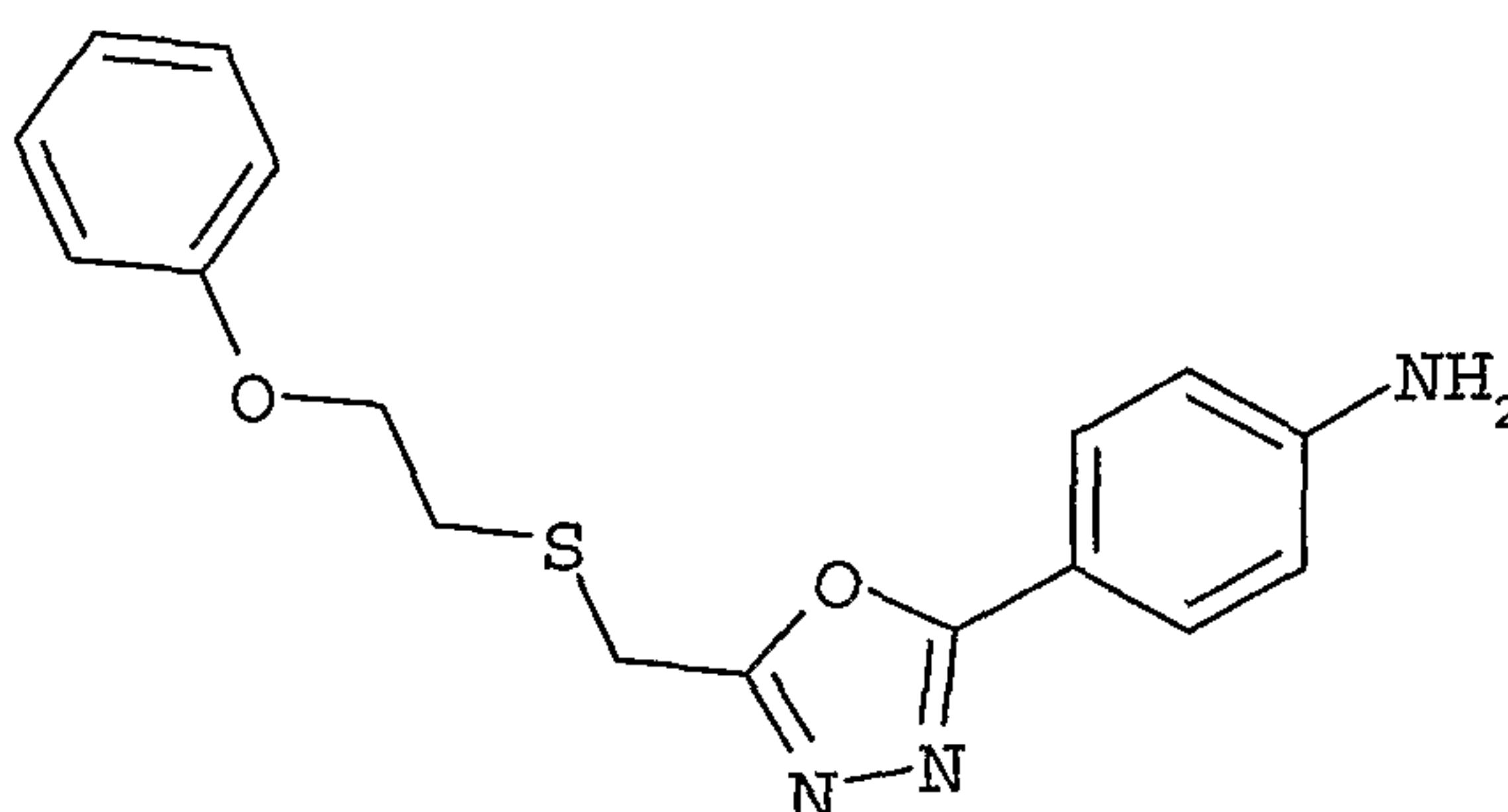
A mixture of 4-nitrobenzoic hydrazide (4.35 g, 24 mmol), 2-(2-phenoxyethylthio)acetic acid (4.25 g, 20 mmol), and (4-N,N-dimethylaminophenyl)diphenylphosphine (18.32 g, 60 mmol) in acetonitrile (200 mL) was stirred and cooled with an ice bath. A mixture of triethylamine (10.12 g, 100 mmol) and carbon tetrachloride (15.38 g, 100 mmol) was added dropwise over 5 min. The cooling was maintained for additional 10 min and removed, and the mixture was allowed to stir overnight. The resultant mixture was concentrated to approximately half the original volume. Diethyl ether (50 mL) and 2 N HCl (300 mL) were added and the mixture was swirled until all solid was dispersed. The solid was collected by filtration and transferred to a beaker. 2 M HCl (300 mL) was added and the mixture was stirred

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until finely dispersed. The solid was collected by filtration and similarly washed again with 2M HCl (300 mL), followed by water (300 mL). The solid was air-dried to give a light tan powder (5.01 g, 70%).

¹H NMR (CDCl₃) δ 8.33 (d, 2H, J=9.2 Hz), 8.18 (d, 2H, J=9.2 Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, J=7.3 Hz), 6.86 (d, 2H, J=7.7 Hz), 4.20 (t, 2H, J=6.1 Hz), 4.08 (s, 2H), 3.05 (t, 2H, J=6.0 Hz). MS (ES+) m/e 358 (M+1).

b) 2-{[(2-Phenoxyethyl)thio]methyl}-5-(4-aminophenyl)-1,3,4-oxadiazole

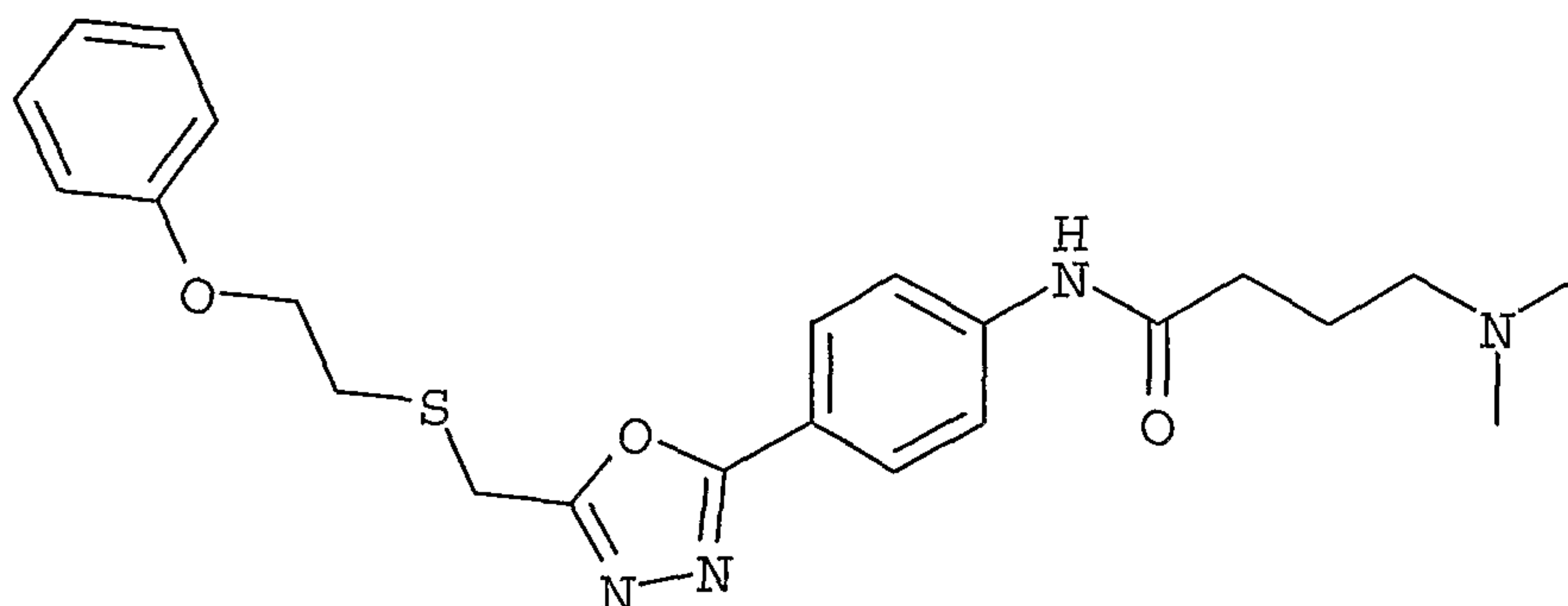


A mixture of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-nitrophenyl)-1,3,4-oxadiazole (3.57 g, 10 mmol), indium powder (8.03 g, 70 mmol), ethanol (40 mL), and sat. aqueous ammonium chloride (12 mL), added in that order, was stirred under reflux for 2 h. 2 M NaOH (50 mL) was added and the mixture was filtered over Celite. The reaction flask and Celite pad were washed with methylene chloride (50 mL). The combined filtrates were evaporated to remove dichloromethane and most ethanol. The precipitate was collected by filtration, washed with water (15 mL) and ethanol (3 mL), and air-dried to give the desired product (yellow to orange solid, 75 –80% yield).

¹H NMR (CDCl₃) δ 7.79 (d, 2H, J=8.4 Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=8.1 Hz), 6.69 (d, 2H, J=8.8 Hz), 4.17 (t, 2H, J=6.2 Hz), 3.99 (s, 2H), 3.02 (t, 2H, J=6.2 Hz). MS (ES+) m/e 328 (M+1).

c) 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole

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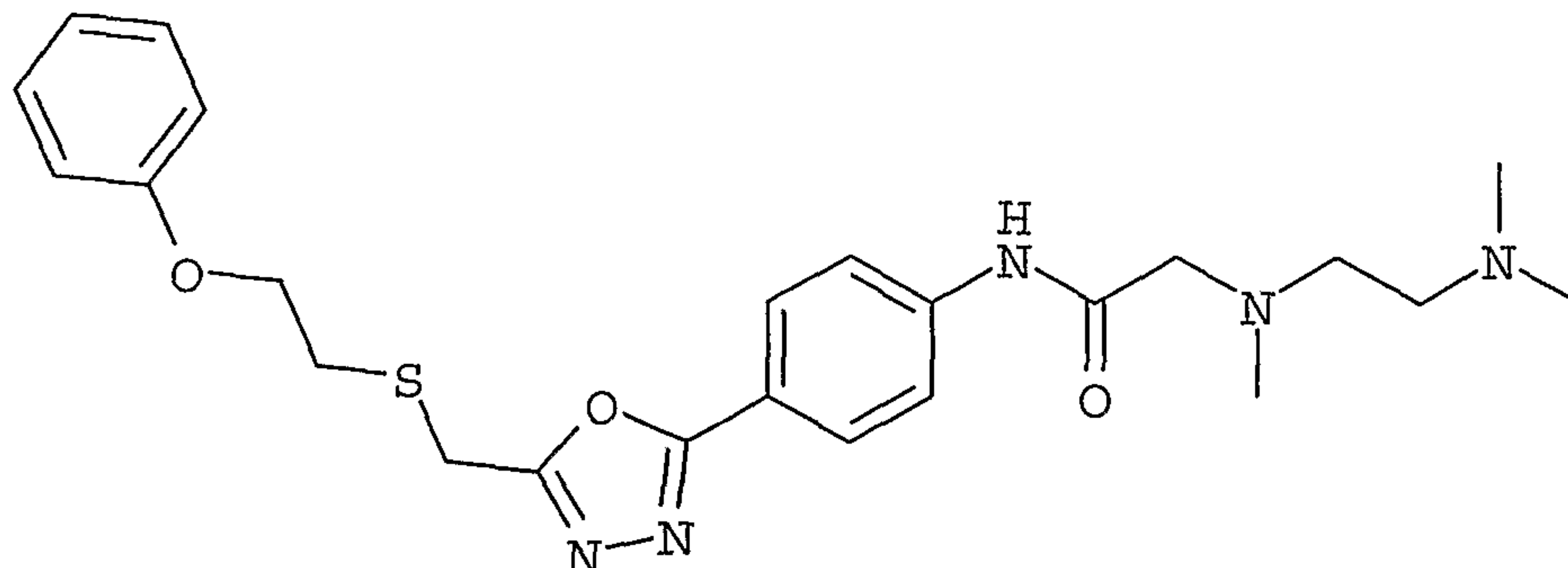
To a suspension of 4-(N,N-dimethylamino)butyric acid hydrochloride (1.67 g, 10 mmol) in N,N-dimethylformamide (0.5 mL) and methylene chloride (50 mL) was added oxalyl chloride (1.48 mL, 17 mmol) dropwise over a period of 10 min. The mixture was stirred at room temperature for 2 h and evaporated under reduced pressure to remove methylene chloride and excess oxalyl chloride. The resultant white solid was dissolved in methylene chloride (5 mL) and added dropwise over 2 min to a solution of 2-[(2-phenoxyethyl)thio]methyl-5-(4-aminophenyl)-1,3,4-oxadiazole (982 mg, 3 mmol), 4-(N,N-dimethylamino)pyridine (183 mg, 1.5 mmol), and triethylamine (1.01 g, 10 mmol) in methylene chloride (25 mL) at 0 °C. After 20 min the cooling bath was removed, and the mixture was allowed to stir overnight, washed with 2 M NaOH (4 x 15 mL), dried (MgSO₄), and concentrated. The residue was dissolved in methanol (30 mL), diluted with water (5 mL), and concentrated under reduced pressure to remove most methanol. The precipitate was collected by filtration, washed with water (5 mL), redissolved in methylene chloride (30 mL), washed with water (15 mL), dried (MgSO₄), and concentrated. The residue was triturated from methylene chloride and hexanes to give an off-white solid (839 mg, 64%).

¹H NMR (CDCl₃) δ 10.60 (s, 1H), 7.94 (d, 2H, J=8.4 Hz), 7.65 (d, 2H, J=8.8 Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=7.7 Hz), 4.18 (t, 2H, J=6.2 Hz), 4.02 (s, 2H), 3.03 (t, 2H, J=6.0 Hz), 2.49~2.57 (m, 4H), 2.36 (s, 6H), 1.87~1.91 (m, 2H). IR (KBr, cm⁻¹) 3494, 3456, 3313, 2939, 1666, 1605, 1499, 1465, 1243, 1177, 1035, 760. MS (ES⁺) m/e 441 (M+1). Anal. Calcd for C₂₃H₂₈N₄O₃S: C, 62.70; H, 6.41; N, 12.72; S, 7.28. Found C, 62.59; H, 6.51; N, 12.69; S, 7.23.

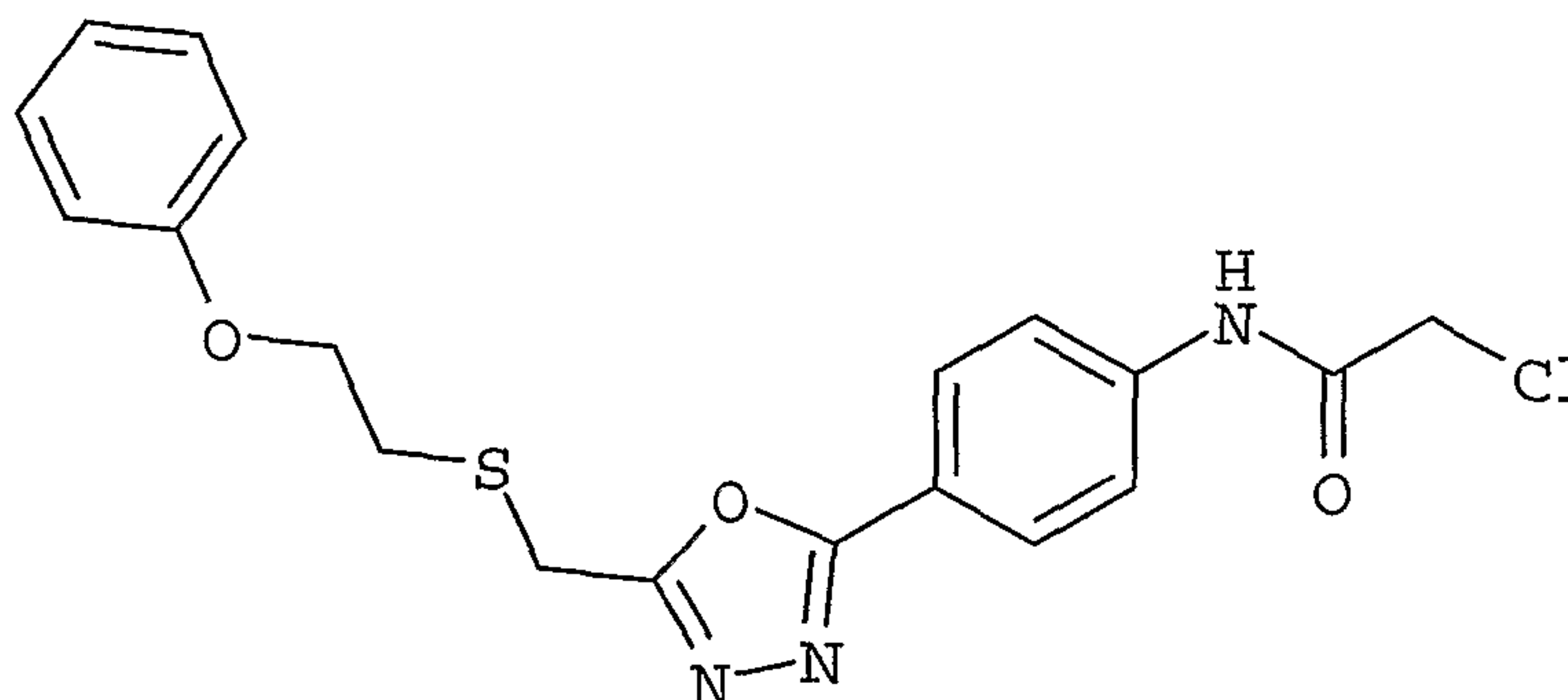
Example 150

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Preparation of 2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[2-(N,N',N'-trimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



a) 2-[[2-(Phenoxyethyl)thio]methyl]-5-[4-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole

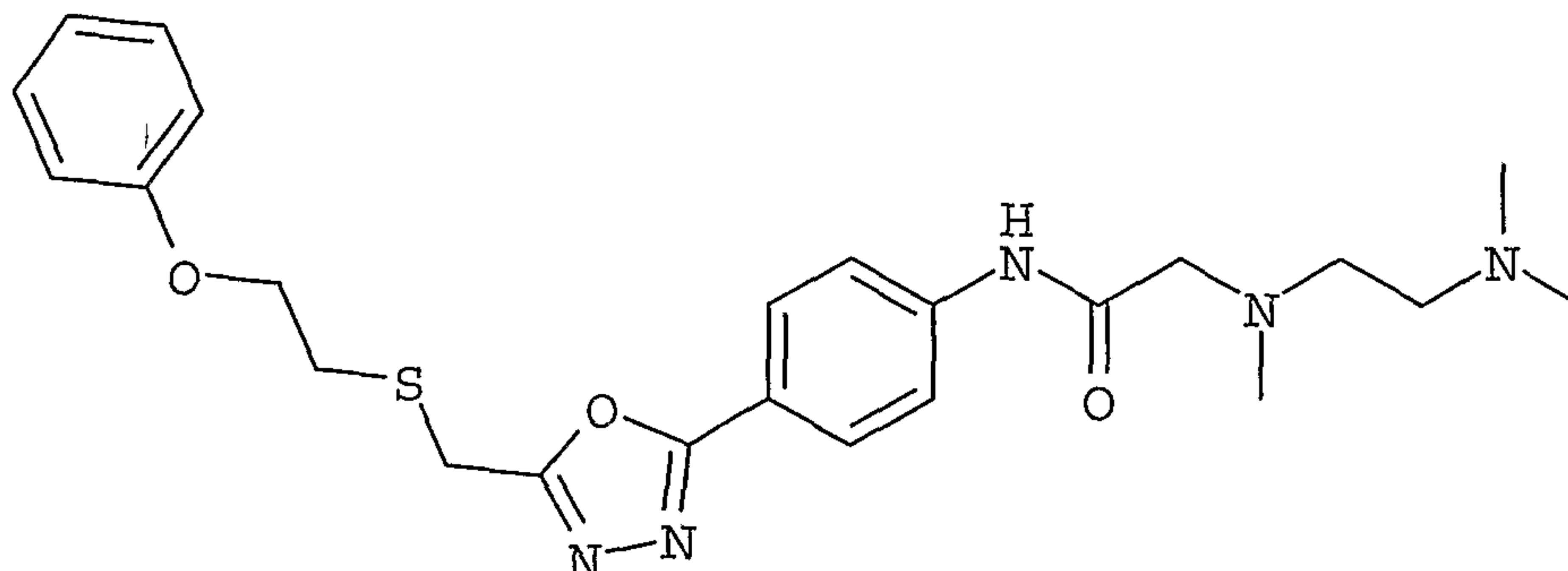


A suspension of 2-[[2-(phenoxyethyl)thio]methyl]-5-(4-aminophenyl)-1,3,4-oxadiazole (1.636 g, 5 mmol) in toluene (30 mL) was heated to approximately 50 °C and chloroacetic chloride (1.6 mL, 20 mmol) was added. The mixture was stirred under reflux for 4 h and allowed to cool to room temperature. The solid was collected by filtration, washed with hexanes and air-dried to give the desired product (1.61 g, 80%).

¹H NMR (CDCl₃) δ 8.8 (s, 1H), 8.01 (d, 2H, J=8.6 Hz), 7.70 (d, 2H, J=8.6 Hz), 7.23~7.27 (m, 2H), 6.93 (t, 1H, J=7.4 Hz), 6.87 (d, 2H, J=7.8 Hz), 4.21 (s, 2H), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.04 (t, 2H, J=6.2 Hz). MS (ES⁺) m/e 404 (M+1).

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b) 2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[2-(N,N',N'-trimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole

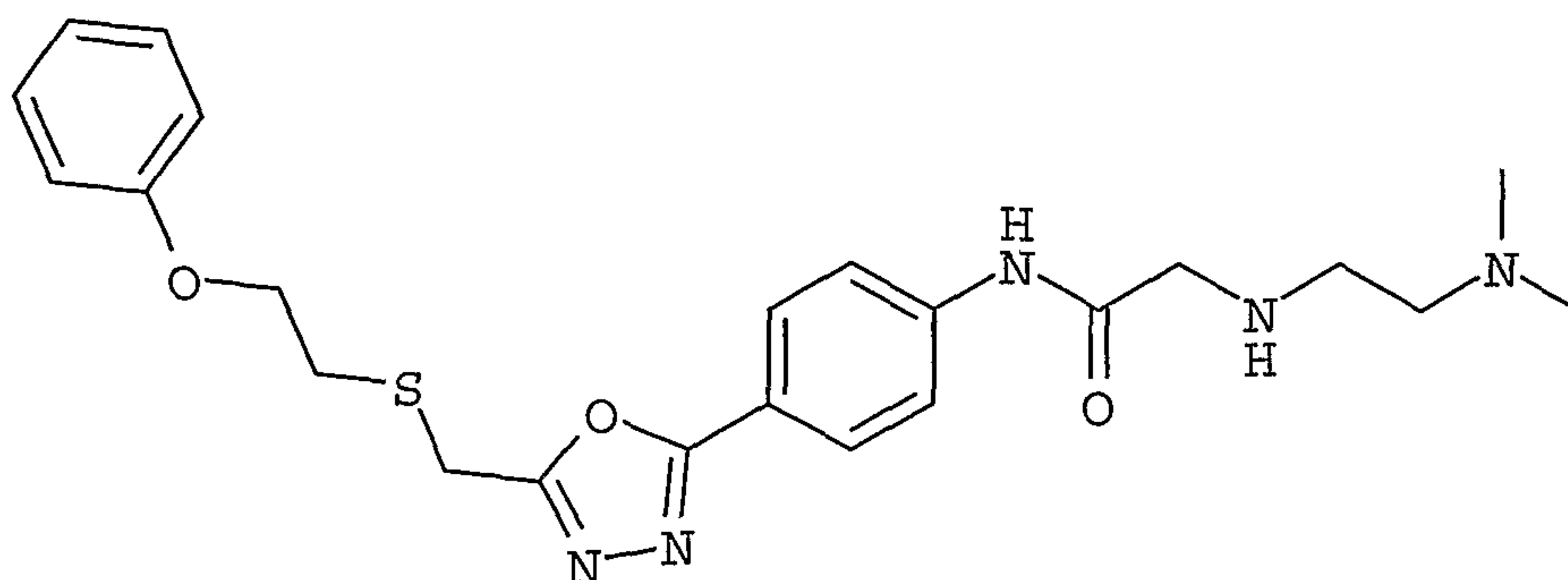


A mixture of 2-[[2-(phenoxyethyl)thio]methyl]-5-[4-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole (100 mg, 0.25 mmol) and N,N,N'-trimethylethylenediamine (1.5 mL) was stirred at room temperature overnight and excess N,N,N'-trimethylethylenediamine was evaporated under vacuum. The residue was purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a pale yellow oil (100 mg, 85%).

¹H NMR (CDCl₃) δ 10.41 (s, 1H), 7.96 (d, 2H, J=8.5 Hz), 7.79 (m, 2H), 7.23~7.27 (m, 2H), 6.93 (t, 1H, J=7.3 Hz), 6.88 (d, 2H, J=7.6 Hz), 4.19 (t, 2H, J=6.0 Hz), 4.02 (s, 2H), 3.20 (s, 2H), 3.03 (t, 2H, J=6.0 Hz), 2.60 (m, 2H), 2.44 (s, 6H), 2.27 (m, 5H). IR (film, cm⁻¹) 3458, 3321, 2940, 1669, 1602, 1501, 1411, 1257, 1181, 753. MS (ES⁺) m/e 468 (M+1). Anal. Calcd for C₂₅H₃₃N₅O₂S: C, 64.21; H, 7.11; N, 14.98; S, 6.86. Found C, 64.10; H, 7.06; N, 14.79; S, 6.88.

Example 151

Preparation of 2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



A mixture of 2-[[2-(phenoxyethyl)thio]methyl]-5-[4-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole (50 mg, 0.12 mmol) and N,N-dimethylethylenediamine (1 mL) was

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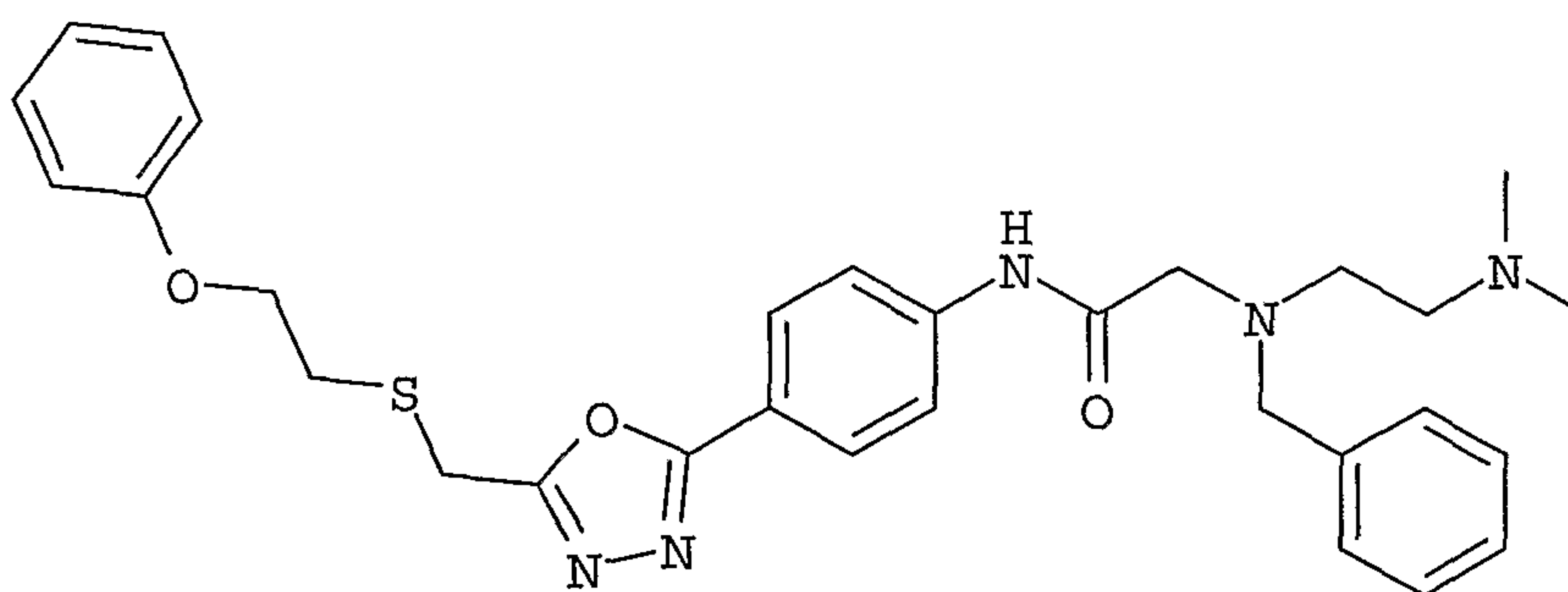
stirred at room temperature overnight and excess N,N-dimethylethylenediamine was evaporated under vacuum. The residue was purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a pale yellow oil (28 mg, 51%).

¹H NMR (CDCl₃) δ 7.96 (d, 2H, J=8.7 Hz), 7.79 (d, 2H, J=8.8 Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, J=7.7 Hz), 6.87 (d, 2H, J=7.7 Hz), 4.18 (t, 2H, J=6.2 Hz), 4.02 (s, 2H), 3.41 (s, 2H), 3.04 (s, 1H), 3.03 (t, 2H, J=5.9 Hz), 2.79 (t, 2H, J=5.6 Hz), 2.50 (t, 2H, J=5.6 Hz), 2.31 (s, 6H). IR (film, cm⁻¹) 3464, 3327, 2959, 1669, 1604, 1521, 1260, 1134, 757. MS (ES+) m/e 454 (M+1). Anal. Calcd for C₂₄H₃₁N₅O₂S: C, 63.55; H, 6.89; N, 15.44; S, 7.07. Found C, 63.75; H, 6.91; N, 15.28; S, 7.26.

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Example 152

Preparation of 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[2-(N-benzyl-N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



A mixture of 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole (202 mg, 0.5 mmol) and N,N-dimethyl-N'-benzylethylenediamine (1.34 g, 7.5 mmol) was stirred at 80~90 °C overnight and excess N,N-dimethyl-N'-benzylethylenediamine was evaporated under vacuum. The residue was purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a pale yellow oil (168 mg, 62%).

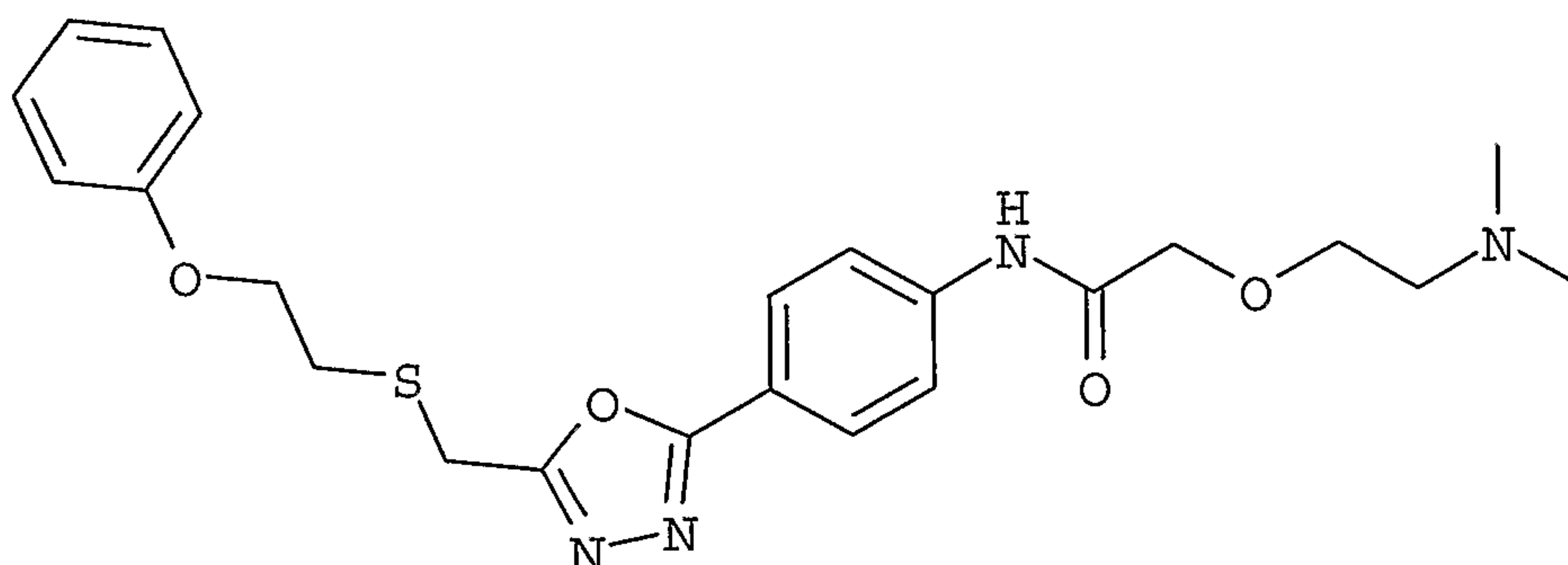
¹H NMR (CDCl₃) δ 10.75 (s, 1H), 7.96 (d, 2H, J=8.4 Hz), 7.72 (d, 2H, J=8.3 Hz), 7.24~7.31 (m, 7H), 6.93 (t, 1H, J=7.5 Hz), 6.88 (d, 2H, J=8.0 Hz), 4.19 (t, 2H, J=6.0 Hz), 4.03 (s, 2H), 3.75 (s, 2H), 3.28 (s, 2H), 3.04 (t, 2H, J=6.0 Hz), 2.70 (t, 2H, J=5.4 Hz), 2.33~2.42 (m, 2H), 2.17 (s, 6H). IR (film, cm⁻¹) 3455, 3330, 2946, 1670, 1606, 1500, 1420, 1301, 1256, 1177, 758. MS (ES+) m/e 544 (M+1). Anal. Calcd for C₃₁H₃₇N₅O₂S: C, 68.48; H, 6.86; N, 12.88; S, 5.90. Found C, 68.53; H, 6.63; N, 12.71; S, 5.82.

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Example 153

Preparation of 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[2-((N,N-dimethylamino)ethoxy)acetamido]phenyl}-1,3,4-oxadiazole



5 Sodium hydride (60% suspension in oil, 64 mg, 1.6 mmol) was washed with tetrahydrofuran (10 mL), suspended in N,N-dimethylformamide (15 mL) and cooled to 0 °C. N,N-dimethylethanolamine (171 mg, 1.92 mmol) was added dropwise over 2 min with stirring, and the mixture was allowed to warm to room temperature and stir for 30 min. 2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(2-chloroacetamido)phenyl]-1,3,4-

10 oxadiazole (130 mg, 0.32 mmol) was added and stirring was continued for 18 h. The reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (4 x 15 mL). The combined ethyl acetate extracts were washed with water (2 x 15 mL) and brine (20 mL), dried (MgSO₄), and concentrated. The residue was purified by chromatography (silica gel, 10% methanol/methylene chloride) to give a colorless oil (77 mg, 53%).

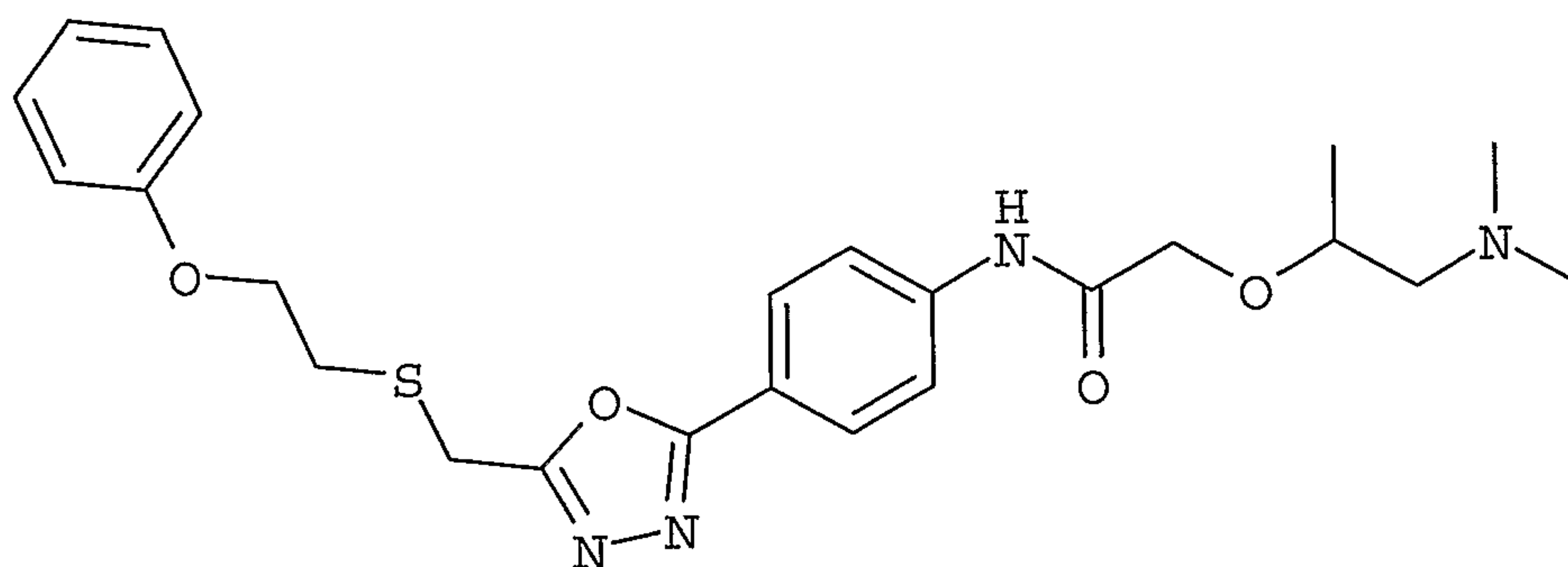
15 ¹H NMR (CDCl₃) δ 10.25 (s, 1H), 7.97 (d, 2H, J=8.8 Hz), 7.78 (d, 2H, J=8.4 Hz), 7.22~7.27 (m, 7H), 6.93 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=7.6 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.11 (s, 2H), 4.02 (s, 2H), 3.69 (t, 2H, J=5.0 Hz), 3.03 (t, 2H, J=6.0 Hz), 2.60 (m, 2H), 2.36 (s, 6H). IR (film, cm⁻¹) 3470, 3334, 2934, 1669, 1599, 1498, 1412, 1248, 1182, 1036, 756. MS (ES⁺) m/e 457 (M+1). Anal. Calcd for C₂₃H₂₈N₄O₄S: C, 60.51; H, 6.18; N, 12.27; S, 7.02. Found C, 60.37; H, 6.10; N, 12.17; S, 6.94.

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Example 154

Preparation of (+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[2-(2-(N,N-dimethylamino)-1-methylethoxy)acetamido]phenyl}-1,3,4-oxadiazole

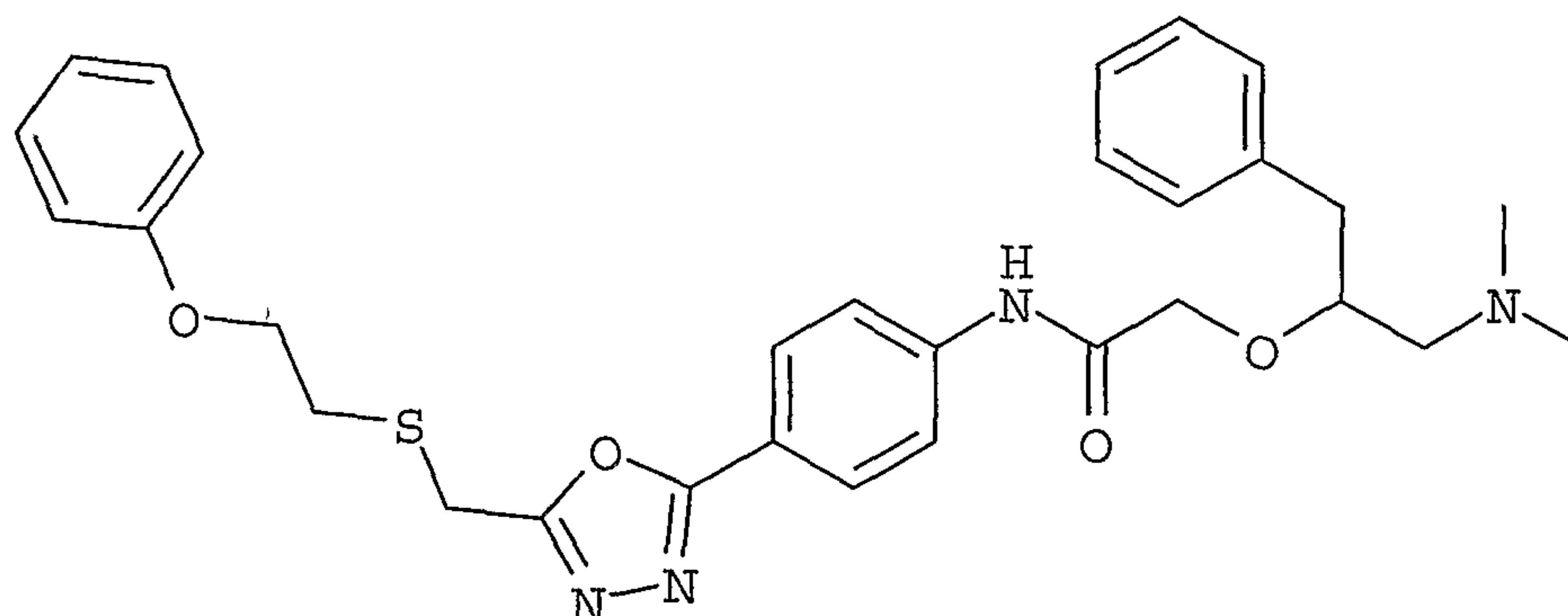


- 5 Sodium hydride (60% suspension in oil, 200 mg, 5 mmol) was washed with tetrahydrofuran (10 mL), suspended in N,N-dimethylformamide (5 mL) and cooled to 0 °C with stirring. 1-(N,N-dimethylamino)-2-propanol (1.03 g, 10 mmol) in N,N-dimethylformamide (2 mL) was added dropwise, and stirring was continued for 10 min at 0 °C and 30 min at room temperature. 2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole (202 mg, 0.5 mmol) was added and the resultant mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with ethyl acetate (40 mL), washed with water (5 x 15 mL) and brine (15 mL), dried (MgSO₄), and concentrated. The residue was purified by chromatography (silica gel, 5% methanol/methylene chloride) to give a colorless oil (120 mg, 51%).
- 10 ¹H NMR (CDCl₃) δ 10.83 (s, 1H), 7.97 (d, 2H, J=8.8 Hz), 7.73 (d, 2H, J=8.5 Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, J=7.7 Hz), 6.87 (d, 2H, J=7.6 Hz), 4.23 (d, 1H, J=16.9 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.95 (d, 1H, J=16.9 Hz), 3.55 (m, 1H), 3.03 (t, 2H, J=6.2 Hz), 2.61 (t, 1H, J=11.5 Hz), 2.31 (s, 6H), 2.15 (m, 1H), 1.13 (d, 3H, J=5.8 Hz). IR (film, cm⁻¹) 3456, 3344, 2931, 1668, 1602, 1503, 1412, 1248, 1172, 1037, 756.
- 15 MS (ES+) m/e 471 (M+1). Anal. Calcd for C₂₄H₃₀N₄O₄S: C, 61.26; H, 6.43; N, 11.91; S, 6.81. Found C, 61.23; H, 6.27; N, 11.79; S, 6.88.
- 20

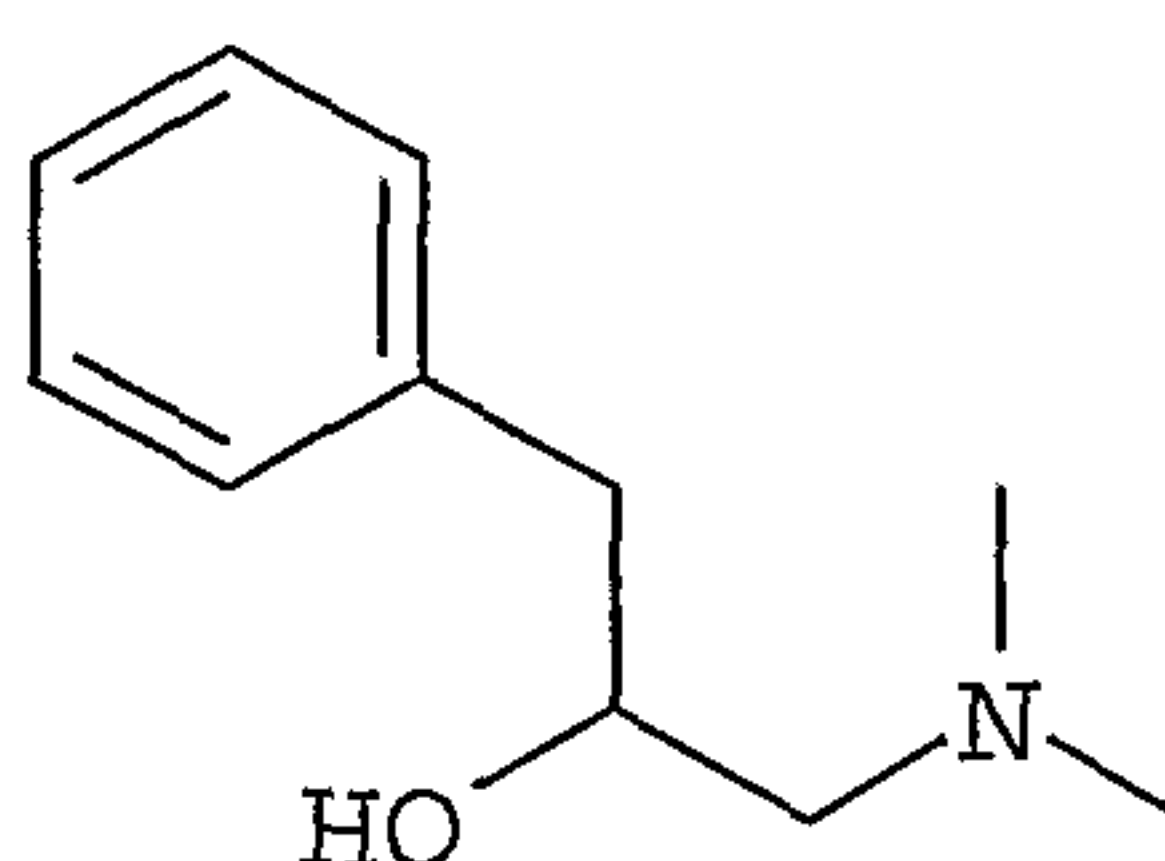
Example 155

- Preparation of (+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[2-(1-benzyl-2-(N,N-dimethylamino)ethoxy)acetamido]phenyl}-1,3,4-oxadiazole
- 25

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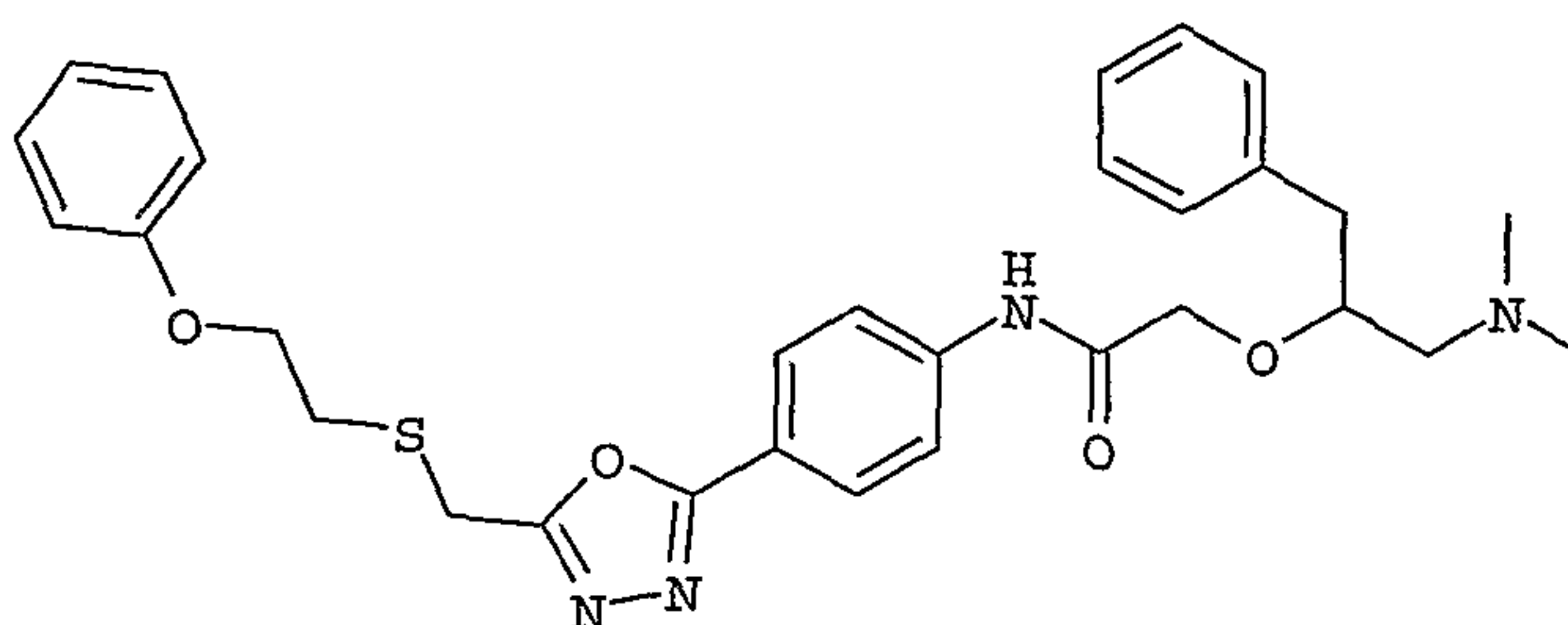
a) (+)-1-Benzyl-2-(N,N-dimethylamino)ethanol



To a solution of 2,3-epoxypropylbenzene (1.34 g, 10 mmol) and lithium perchlorate (1.17 g, 11 mmol) in acetonitrile (10 mL) was added 2 M dimethylamine in tetrahydrofuran (5 mL 10 mmol). The resultant mixture was stirred at room temperature overnight, diluted with ether (20 mL), washed with water (3 x 10 mL), dried (MgSO₄), and concentrated to give a yellow oil (1.61 g, 90%). This material was used in the next step without further purification.

¹H NMR (CDCl₃) δ 7.16-7.28 (m, 5H), 3.84 (m, 1H), 2.78 (dd, 1H, J=13.5, 7.1 Hz), 2.63 (dd, 1H, J=13.5, 5.6 Hz), 2.30 (dd, 1H, J=11.8, 10.4 Hz), 2.22 (s, 6H), 2.15 (dd, 1H, J=12.1, 3.3 Hz). MS (ES+) m/e 181 (M+1).

b) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[2-(1-benzyl-2-(N,N-dimethylamino)ethoxy)acetamido]phenyl}-1,3,4-oxadiazole



Sodium hydride (60% suspension in oil, 80 mg, 2 mmol) was washed with tetrahydrofuran (10 mL), suspended in N,N-dimethylformamide (4 mL) and cooled to 0

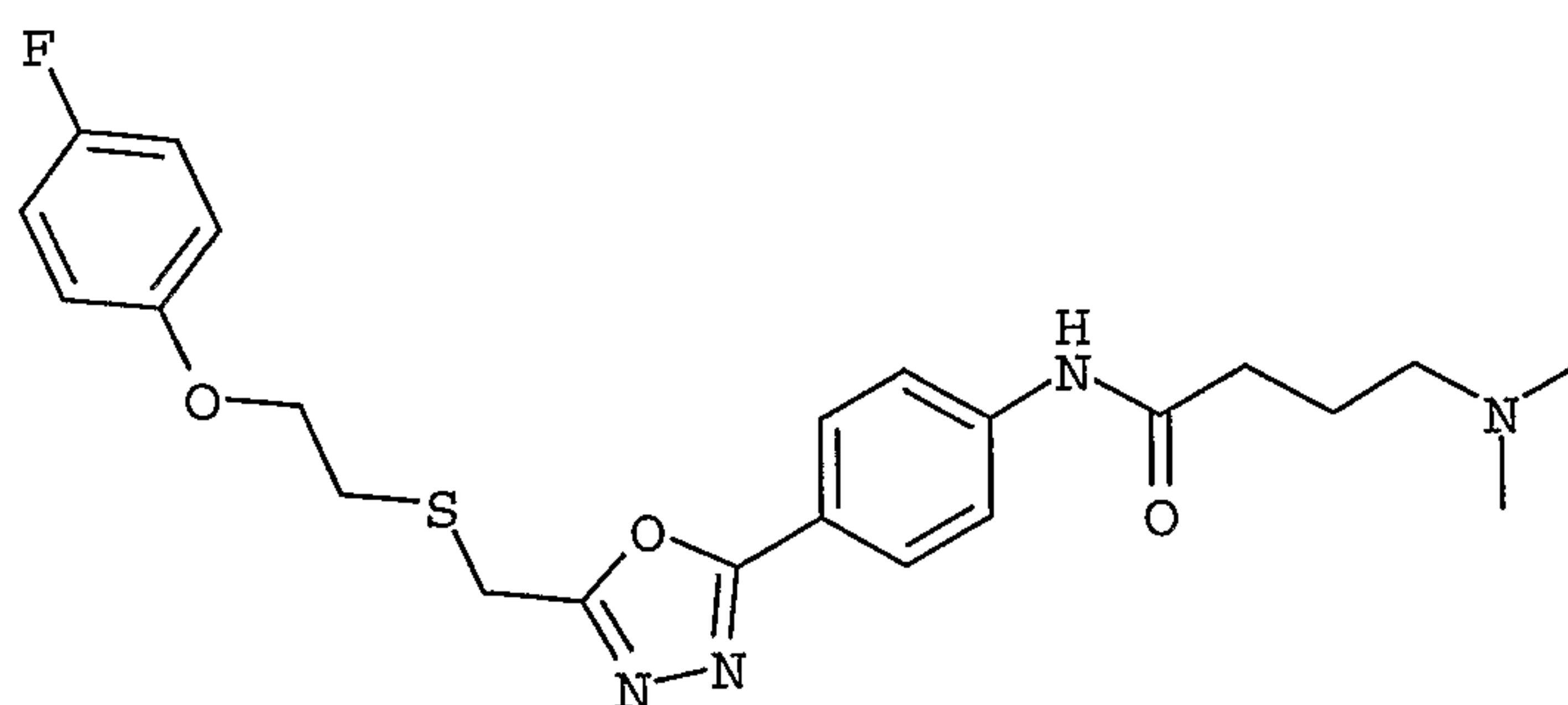
-311-

°C with stirring. (+)-1-benzyl-2-(N,N-dimethylamino)ethanol (358 mg, 2 mmol) in N,N-dimethylformamide (3 mL) was added dropwise, and stirring was continued for 10 min at 0 °C and 20 min at room temperature. 2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole (202 mg, 0.5 mmol), followed by sodium iodide (149 mg, 1 mmol) was added and the resultant mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (4 x 25 mL) and brine (25 mL), dried (MgSO₄), and concentrated. The residue was purified by chromatography (silica gel, 5% methanol/methylene chloride) to give a colorless oil (114 mg, 42%).

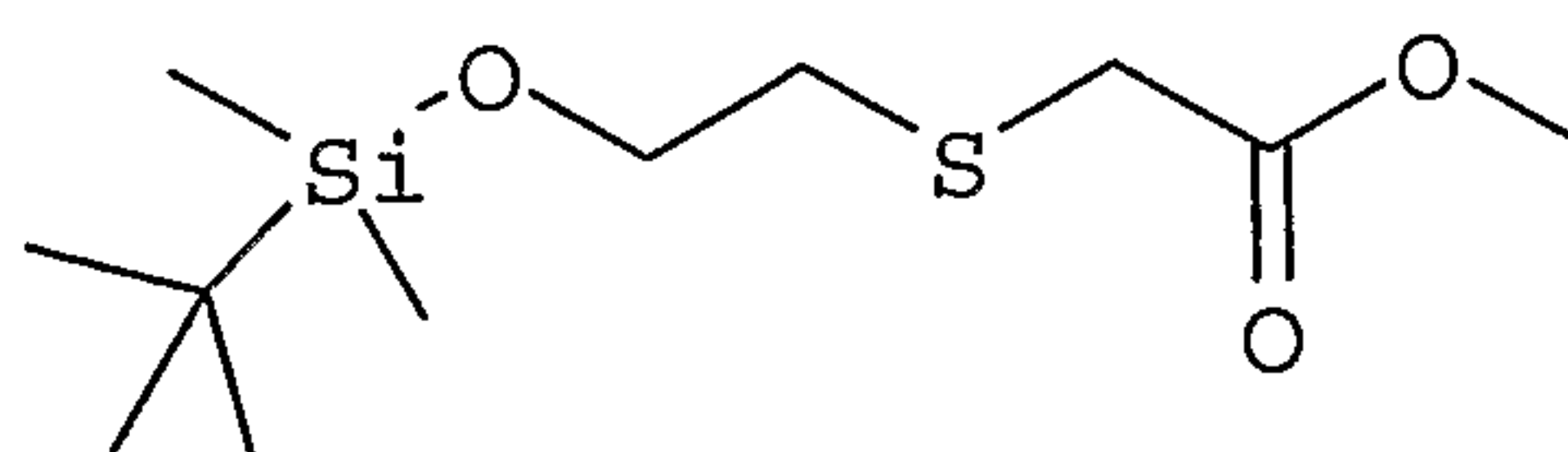
¹H NMR (CDCl₃) δ 10.87 (s, 1H), 7.98 (d, 2H, J=8.8 Hz), 7.67 (d, 2H, J=8.8 Hz), 7.17~7.32 (m, 7H), 6.92 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=8.0 Hz), 4.18 (t, 2H, J=6.2 Hz), 4.11 (d, 1H, J=17.2 Hz), 4.02 (s, 2H), 3.75 (d, 1H, J=17.2 Hz), 3.66 (m, 1H), 3.03 (t, 2H, J=6.2 Hz), 2.76 (m, 2H), 2.62 (dd, 1H, J=13.0, 10.4 Hz), 2.28 (m, 1H), 2.27 (s, 6H). IR (film, cm⁻¹) 3460, 3334, 2934, 1658, 1600, 1501, 1426, 1280, 1175, 1053, 761. MS (ES+) m/e 547 (M+1). Anal. Calcd for C₃₀H₃₄N₄O₄S: C, 65.91; H, 6.27; N, 10.25; S, 5.87. Found C, 66.04; H, 6.25; N, 10.31; S, 5.49.

Example 156

Preparation of 2-{[(2-(4-Fluorophenoxy)ethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole



a) Methyl 2-{[2-(tert-butyldimethylsilyloxy)ethyl]thio}acetate



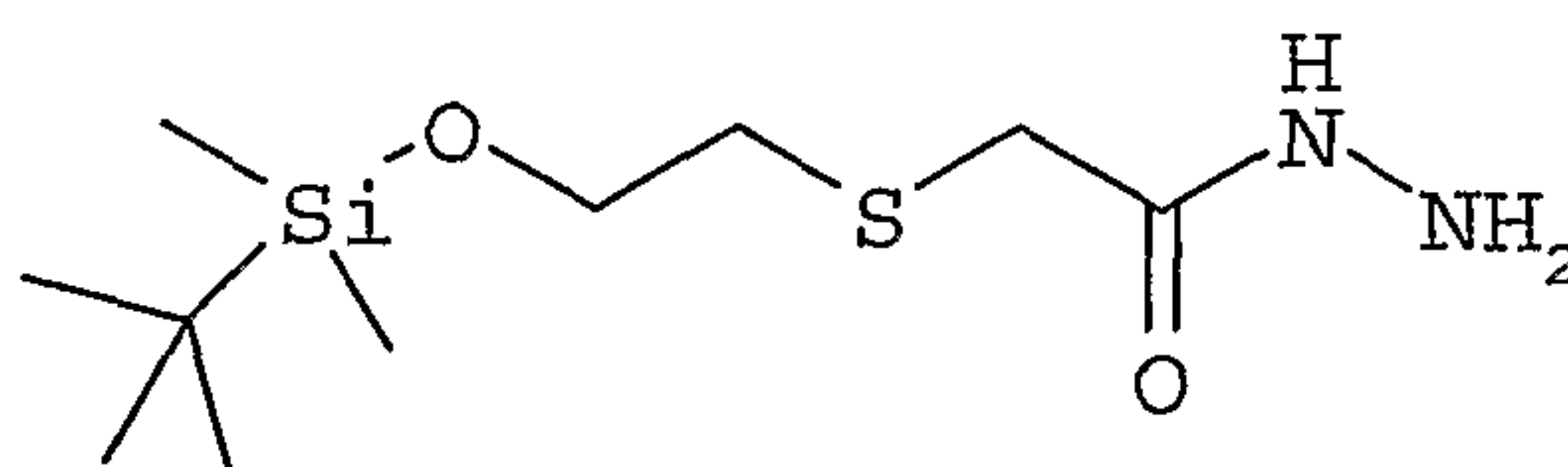
A mixture of methyl thioglycolate (4.78 g, 45 mmol), 2-bromoethoxy-tert-butyldimethylsilane (7.18 g, 30 mmol), and potassium carbonate (10.37 g, 75 mmol) in

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tetrahydrofuran (150 mL) was stirred under reflux overnight. The resultant mixture was cooled to room temperature, diluted with ether (100 mL), washed with water (3 x 100 mL) and brine (100 mL), dried (MgSO₄), and concentrated to give a colorless oil (7.85 g, 99%).

5 ¹H NMR (CDCl₃) δ 3.78 (t, 2H, J=6.6 Hz), 3.71 (s, 3H), 3.27 (s, 2H), 2.74 (t, 2H, J=6.6 Hz), 0.87 (s, 9H), 0.04 (s, 6H). MS (ES+) m/e 265 (M+1).

b) 2-[[2-(tert-butyldimethylsilyloxy)ethyl]thio}acetic hydrazide

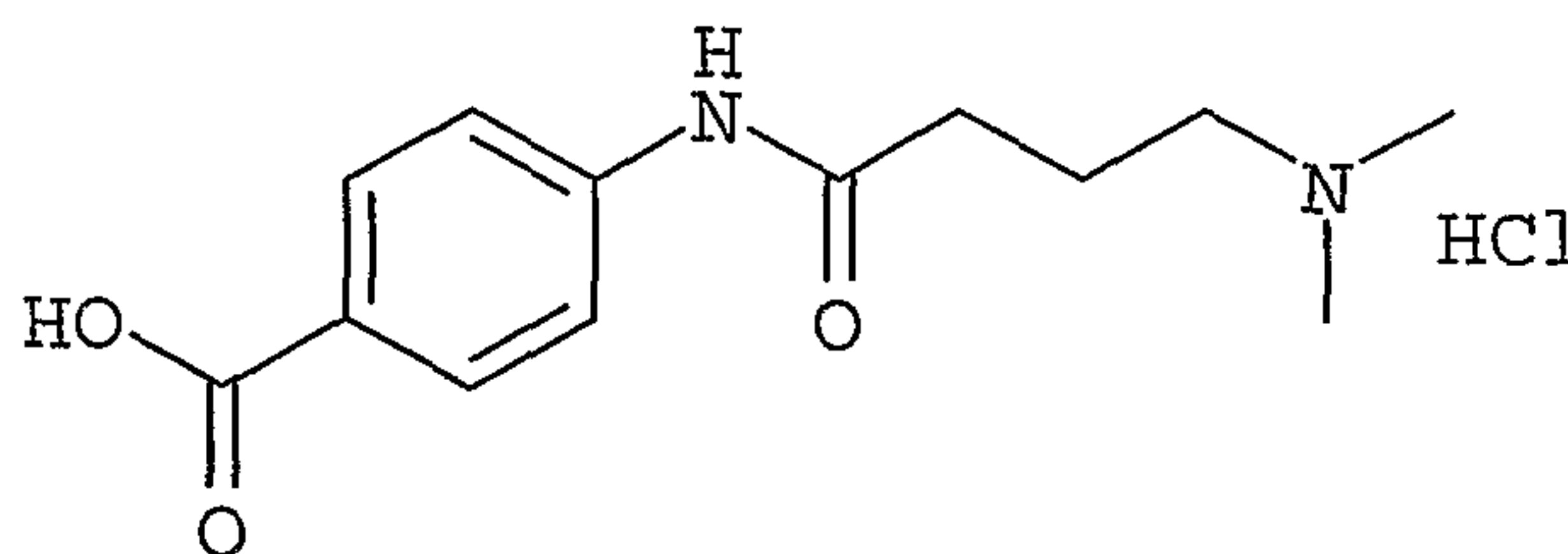


10

A mixture of methyl 2-[[2-(tert-butyldimethylsilyloxy)ethyl]thio}acetate (2.65 g, 10 mmol) and hydrazine monohydrate (5 g, 100 mmol) in ethanol was stirred at room temperature for 2 h and concentrated. The residue was taken up in ethyl acetate (50 mL), washed with water (5 x 20 mL), dried (MgSO₄), and concentrated to give a colorless oil
15 (2.53 g, 96%).

¹H NMR (CDCl₃) δ 7.99 (br s, 1H), 3.85 (br s, 2H), 3.79 (t, 2H, J=6.0 Hz), 3.29 (s, 2H), 2.68 (t, 2H, J=6.2 Hz), 0.88 (s, 9H), 0.06 (s, 6H). MS (ES+) m/e 265 (M+1).

c) 4-[[4-(N,N-Dimethylamino)butanoyl]amino}benzoic acid hydrochloride



20

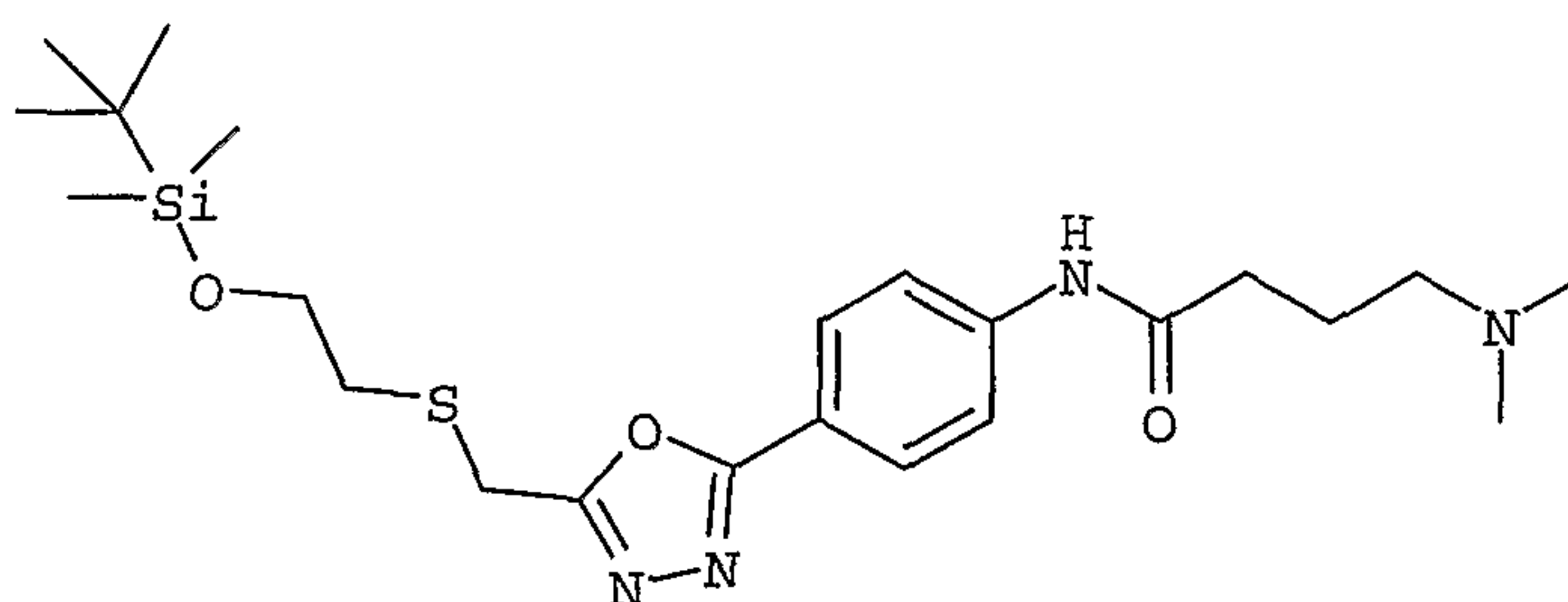
A mixture of methyl 4-aminobenzoate (4.53 g, 30 mmol), 4-(N,N-dimethylamino)butyric acid hydrochloride (6.71 g, 40 mmol), diisopropylcarbodiimide (5.05 g, 40 mmol), and 1-hydroxybenzotriazole (5.41 g, 40 mmol) in N,N-dimethylformamide (200 mL) was stirred at room temperature over the weekend. The
25 reaction mixture was poured into water (600 mL), made basic with 2 M NaOH to pH ~10, and extracted with ethyl acetate (5 x 150 mL). The combined ethyl acetate extracts were

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washed with 2 M NaOH (2 x 150 mL), dried (MgSO₄), and concentrated. The residue was purified on a cation exchange column (Bio-Rad 50W-X2 resin) to give colorless oil (6.18 g, 78%). This material (5.28 g, 20 mmol) was dissolved in tetrahydrofuran (30 mL) and stirred with 2 M NaOH (50 mL, 100 mmol) at room temperature overnight. Ether (30 mL) was added and the phases were separated. The aqueous layer was loaded to an anion exchange column (Bio-Rad AG1-X2 resin). The column was eluted with water until the eluent became neutral, followed by 4 M HCl in dioxane to recover the product. Dioxane was evaporated. The resultant solid was washed with dioxane (250 mL) and methylene chloride (200 mL) to give the final product (3.68, 64%).

¹H NMR (DMSO-d₆) δ 10.40 (s, 1H), 10.0 (br s, 1H), 7.84 (d, 2H, J=8.8 Hz), 7.68 (d, 2H, J=8.8 Hz), 3.03 (m, 2H), 2.72 (s, 6H), 2.45 (m, 2H), 1.92 (m, 2H). MS (ES-) m/e 249 (M-1).

d) 2-{[(2-(tert-Butyldimethylsilyloxy)ethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole



To a stirred mixture of 2-{[(2-(tert-butyldimethylsilyloxy)ethyl)thio]acetic hydrazide (2.65 g, 10 mmol), 4-{[4-(N,N-Dimethylamino)butanoyl]amino}benzoic acid hydrochloride (2.86 g, 10 mmol), and 4-(N,N-dimethylaminophenyl)diphenylphosphine (9.16 g, 30 mmol) in acetonitrile (100 mL) at 0 °C was added slowly a solution of triethylamine (6.07 g, 60 mmol) in carbon tetrachloride (7.69 g, 50 mmol). The resultant mixture was stirred at room temperature overnight and concentrated. The residue was taken up in methylene chloride (150 mL), washed with 2 M NaOH (2 x 50 mL), dried (MgSO₄), and concentrated. The residue was purified by chromatography (silica gel, 10% methanol/methylene chloride to 5% methanol and 5% 7 M methanolic ammonia/methylene chloride) to give a pale yellow oil (1.79 g, 38%).

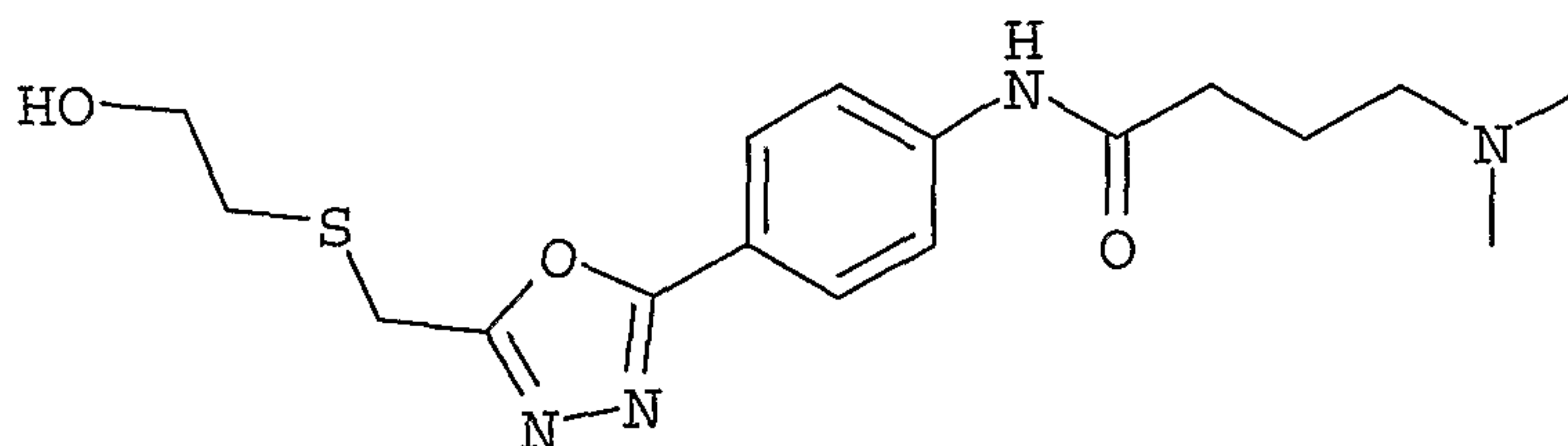
¹H NMR (CDCl₃) δ 10.16 (s, 1H), 7.97 (d, 2H, J=8.8 Hz), 7.87 (d, 2H, J=8.8 Hz), 3.96 (s, 2H), 3.81 (t, 2H, J=6.4 Hz), 3.0 (t, 2H, J=5.6 Hz), 2.75~2.85 (m, 4H), 2.76 (s,

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6H), 2.15~2.19 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H). IR (film, cm^{-1}) 3473, 3327, 2963, 1659, 1598, 1496, 1245, 1181, 1088, 750. MS (ES+) m/e 479 (M+1). Anal. Calcd for $\text{C}_{23}\text{H}_{38}\text{N}_4\text{O}_3\text{SSi}$: C, 57.71; H, 8.00; N, 11.70; S, 6.70. Found C, 57.57; H, 8.12; N, 11.52; S, 6.91.

5

e) 2-{[(2-hydroxyethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole

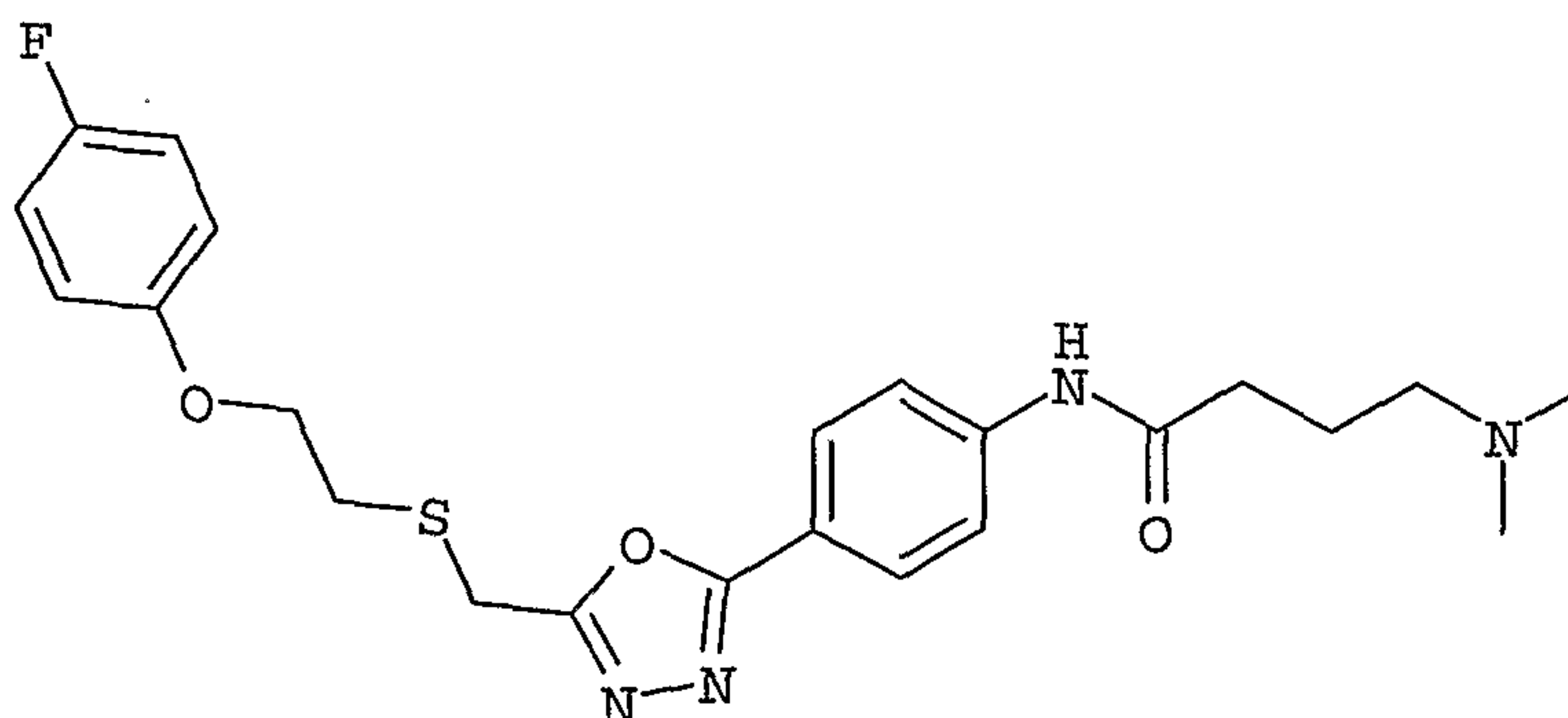


2-{[(2-(tert-Butyldimethylsilyloxy)ethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole (1.47 g, 3 mmol) was stirred in 2 M HCl (15 mL) until it appeared completely dissolved (~30 min). The solution was washed with methylene chloride (3 x 10 mL), treated with 2 M NaOH to pH ~11, and extracted with methylene chloride (3 x 10 mL). The combined methylene chloride extracts were dried (MgSO_4) and concentrated to give a pale yellow solid (430 mg, 39%).

^1H NMR (CDCl_3) δ 10.66 (s, 1H), 7.96 (d, 2H, $J=7.8$ Hz), 7.66 (d, 2H, $J=7.8$ Hz), 3.94 (s, 2H), 3.81 (t, 2H, $J=5.9$ Hz), 2.83 (t, 2H, $J=5.6$ Hz), 2.49~2.56 (m, 4H), 2.36 (s, 6H), 1.88 (m, 2H). IR (KBr, cm^{-1}) 3482, 3330, 2957, 1661, 1603, 1501, 1411, 1168, 756. MS (ES+) m/e 365 (M+1). Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_4\text{O}_3\text{S}$: C, 56.02; H, 6.64; N, 15.37; S, 8.80. Found C, 56.16; H, 6.74; N, 15.38; S, 8.94.

20

f) 2-{[(2-(4-Fluorophenoxy)ethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole



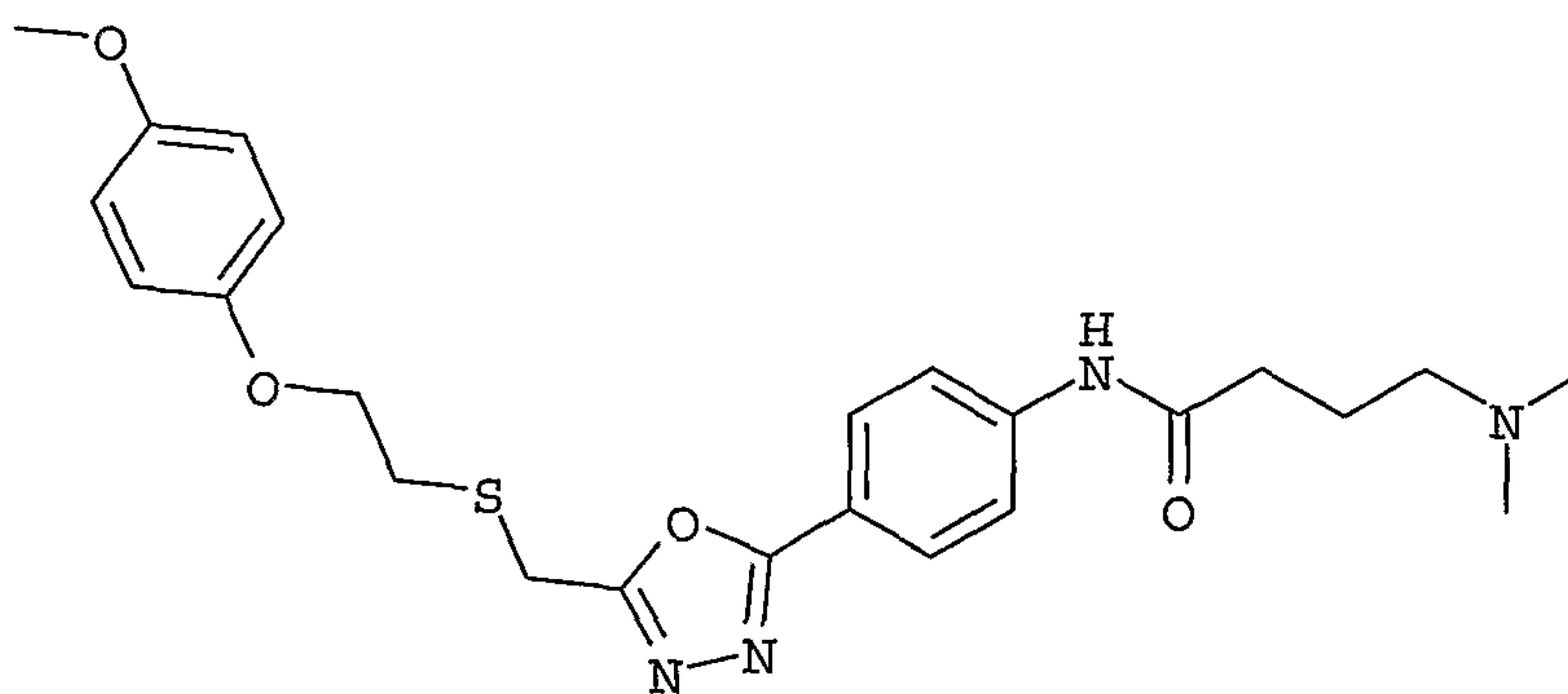
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A solution of 2-{[(2-hydroxyethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole (130 mg, 0.36 mmol), 4-fluorophenol (161 mg, 1.44 mmol), and triphenylphosphine (184 mg, 0.7 mmol) in tetrahydrofuran (6 mL) was cooled with an ice bath and diisopropyl azodicarboxylate (142 mg, 0.7 mmol) in tetrahydrofuran (1 mL) was added dropwise. After 5 min the cooling bath was removed and the mixture was stirred at room temperature overnight. The resultant mixture was diluted with ethyl acetate (10 mL), washed with 2 M NaOH (3 x 10 mL), dried (MgSO₄), and concentrated. The residue was purified by preparative TLC (silica gel, 5% methanol and 5% 7 M methanolic ammonia in methylene chloride, twice developed) to give a colorless oil (151 mg, 92%).

¹H NMR (CDCl₃) δ 10.67 (s, 1H), 7.94 (d, 2H, J=8.8 Hz), 7.65 (d, 2H, J=8.4 Hz), 6.92 (t, 2H, J=8.6 Hz), 6.79~6.82 (m, 2H), 4.13 (t, 2H, J=6.2 Hz), 4.01 (s, 2H), 3.01 (t, 2H, J=6.2 Hz), 2.54 (t, 2H, J=6.4 Hz), 2.49 (t, 2H, J=5.8 Hz), 2.35 (s, 6H), 1.84~1.88 (m, 2H). IR (film, cm⁻¹) 3456, 3322, 2957, 1657, 1600, 1446, 1382, 1215, 1177, 755. MS (ES+) m/e 459 (M+1). Anal. Calcd for C₂₃H₂₇FN₄O₃S: C, 60.24; H, 5.93; N, 12.22; S, 6.99. Found C, 60.13; H, 5.86; N, 12.36; S, 6.94.

Example 157

Preparation of 2-{[(2-(4-Methoxyphenoxy)ethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole



A solution of 2-{[(2-hydroxyethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole (80 mg, 0.22 mmol), 4-methoxyphenol (109 mg, 0.88 mmol), and triphenylphosphine (115 mg, 0.44 mmol) in tetrahydrofuran (8 mL) was cooled with an ice bath and diisopropyl azodicarboxylate (89 mg, 0.44 mmol) in tetrahydrofuran (0.5 mL) was added dropwise. After 5 minutes the

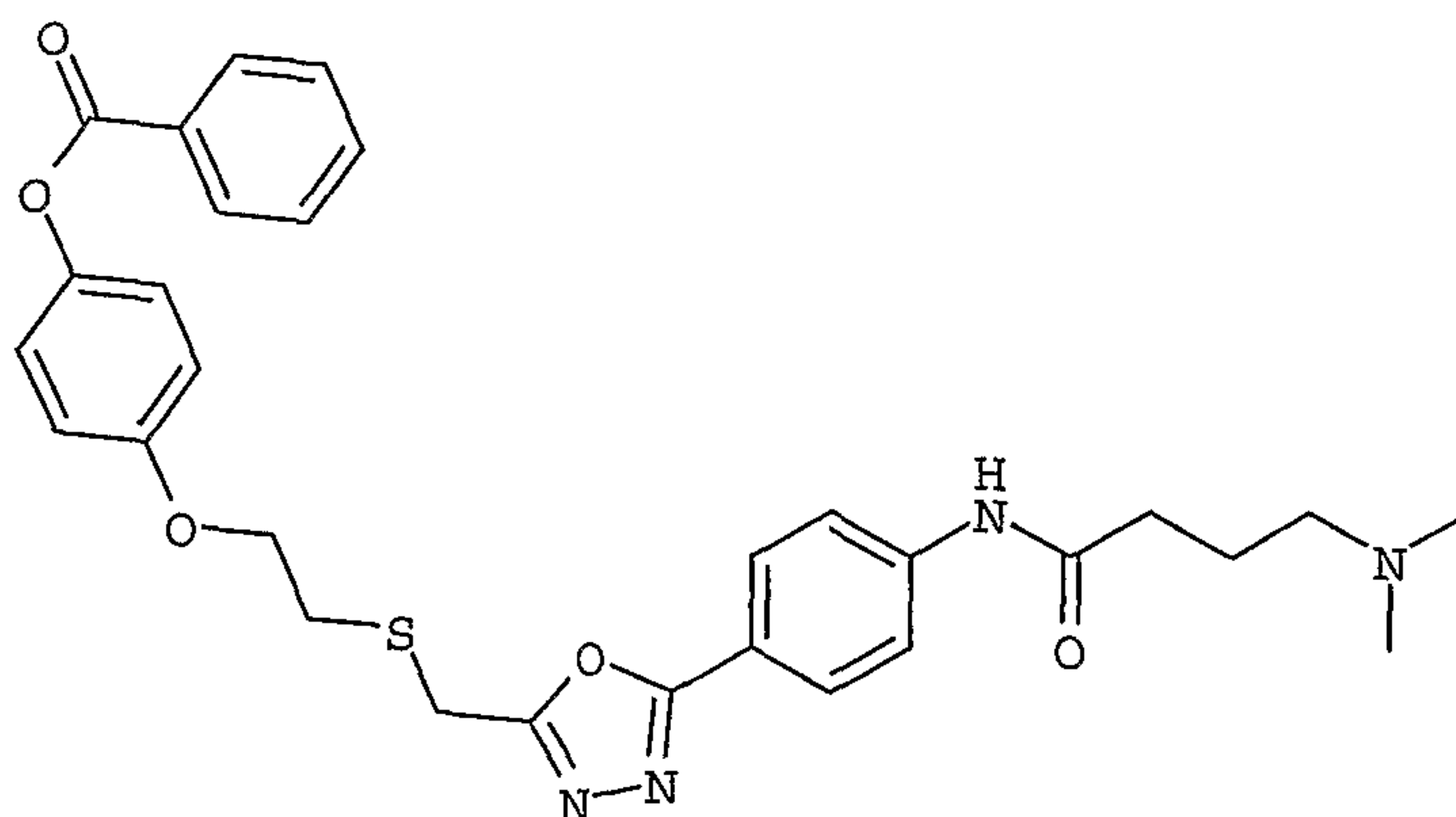
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cooling bath was removed and the mixture was stirred at room temperature overnight. The resultant mixture was diluted with ethyl acetate (10 mL), washed with 2 M NaOH (3 x 5 mL), dried (MgSO₄), and concentrated. The residue was purified by preparative TLC (silica gel, 5% methanol and 5% 7 M methanolic ammonia in methylene chloride, twice
5 developed) to give a colorless oil (53 mg, 50%).

¹H NMR (CDCl₃) δ 10.63 (s, 1H), 7.94 (d, 2H, J=8.8 Hz), 7.66 (d, 2H, J=8.7 Hz), 6.81 (d, 2H, J=9.5 Hz), 6.78 (d, 2H, J=9.2 Hz), 4.13 (t, 2H, J=6.2 Hz), 4.01 (s, 2H), 3.73 (s, 3H), 3.0 (t, 2H, J=6.2 Hz), 2.49~2.57 (m, 4H), 2.36 (s, 6H), 1.83~1.91 (m, 2H). IR (film, cm⁻¹) 3470, 3341, 2955, 1661, 1606, 1500, 1438, 1388, 1237, 1176, 764. MS
10 (ES⁺) m/e 471 (M+1). Anal. Calcd for C₂₄H₃₀N₄O₄S: C, 61.26; H, 6.43; N, 11.91; S, 6.81. Found C, 61.29; H, 6.45; N, 11.74; S, 6.73.

Example 158

Preparation of 2-{[(2-(4-Benzoyloxyphenoxy)ethyl)thio]methyl-5-{4-[(4-(N,N-
15 dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole



A solution of 2-{[(2-hydroxyethyl)thio]methyl}-5-{4-[(4-(N,N-
dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole (80 mg, 0.22 mmol), 4-
hydroxyphenyl benzoate (189 mg, 0.88 mmol), and triphenylphosphine (116 mg, 0.44
20 mmol) in tetrahydrofuran (8 mL) was cooled with an ice bath and diisopropyl
azodicarboxylate (89 mg, 0.44 mmol) in tetrahydrofuran (0.5 mL) was added dropwise.
After 5 min the cooling bath was removed and the mixture was stirred at room
temperature overnight. The resultant mixture was diluted with ethyl acetate (10 mL),
washed with 2 M NaOH (3 x 5 mL), dried (MgSO₄), and concentrated. The residue was

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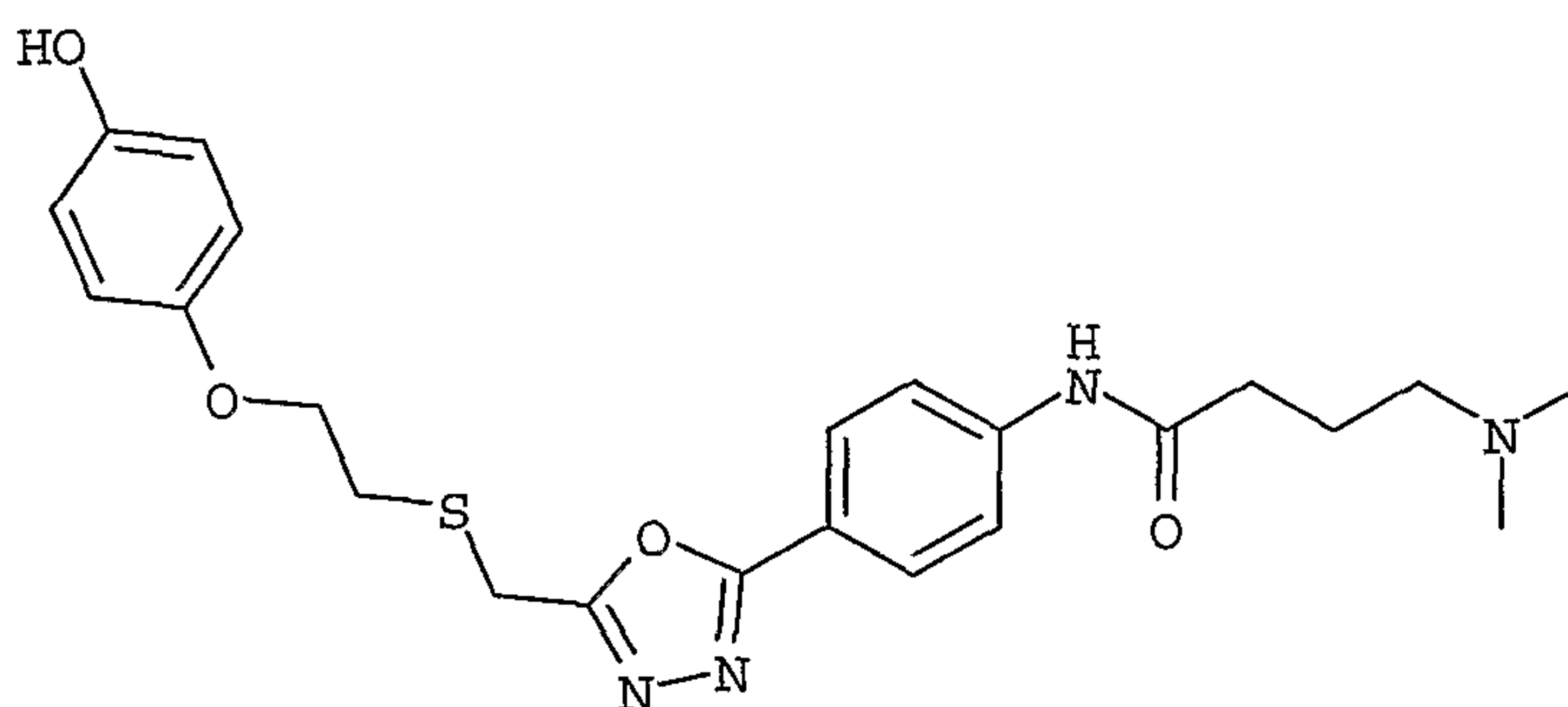
purified by preparative TLC (silica gel, 5% methanol and 5% 7 M methanolic ammonia in methylene chloride, twice developed) to give colorless oil (72 mg, 58%).

¹H NMR (CDCl₃) δ 10.55 (s, 1H), 8.17 (d, 2H, J=7.7 Hz), 7.95 (d, 2H, J=8.4 Hz), 7.67 (d, 2H, J=8.4 Hz), 7.61 (t, 1H, J=7.3 Hz), 7.48 (t, 2H, J=7.6 Hz), 7.09 (d, 2H, J=9.2 Hz), 6.91 (d, 2H, J=8.8 Hz), 4.19 (t, 2H, J=6.0 Hz), 4.02 (s, 2H), 3.05 (t, 2H, J=6.2 Hz), 2.46~2.57 (m, 4H), 2.37 (s, 6H), 1.86~1.90 (m, 2H). IR (film, cm⁻¹) 3420, 3035, 2957, 2771, 1763, 1660, 1601, 1499, 1423, 1215, 1170, 755. MS (ES+) m/e 561 (M+1). Anal. Calcd for C₃₀H₃₂N₄O₅S: C, 64.27; H, 5.75; N, 9.99; S, 5.72. Found C, 64.40; H, 5.62; N, 10.03; S, 5.74.

10

Example 159

Preparation of 2-{[(2-(4-Hydroxyphenoxy)ethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole



To a solution of 2-{[(2-(4-benzoyloxyphenoxy)ethyl)thio]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole (50 mg, 0.1 mmol) in MeOH (1 mL) and tetrahydrofuran (0.5 mL) was added 2M NaOH (1 mL, 2 mmol). The mixture was stirred at room temperature overnight and extracted with methylene chloride (3 x 5 mL). The combined methylene chloride extracts were washed with water (1 mL), dried (MgSO₄), and concentrated to give a colorless oil (30 mg, 66%).

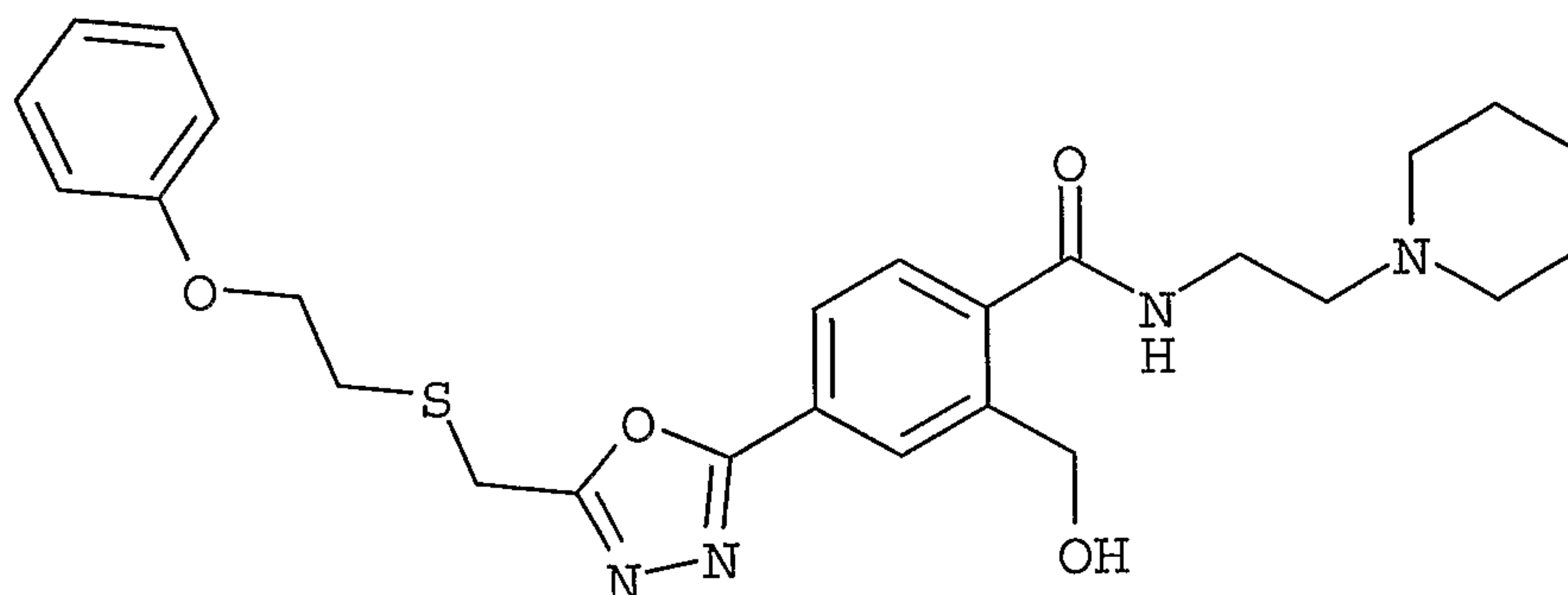
¹H NMR (CDCl₃) δ 10.60 (s, 1H), 7.86 (d, 2H, J=8.4 Hz), 7.58 (d, 2H, J=8.4 Hz), 6.72 (d, 2H, J=8.8 Hz), 6.67 (d, 1H, J=9.2 Hz), 4.07 (t, 2H, J=6.2 Hz), 4.0 (s, 2H), 3.01 (t, 2H, J=6.2 Hz), 2.44~2.56 (m, 4H), 2.34 (s, 6H), 1.83~1.92 (m, 2H). IR (film, cm⁻¹) 3458, 3333, 2965, 1660, 1597, 1500, 1410, 1395, 1264, 1163, 757. MS (ES+) m/e 457 (M+1). Anal. Calcd for C₂₃H₂₈N₄O₄S: C, 60.51; H, 6.18; N, 12.27; S, 7.02. Found C, 61.02; H, 6.26; N, 12.09; S, 7.08.

25

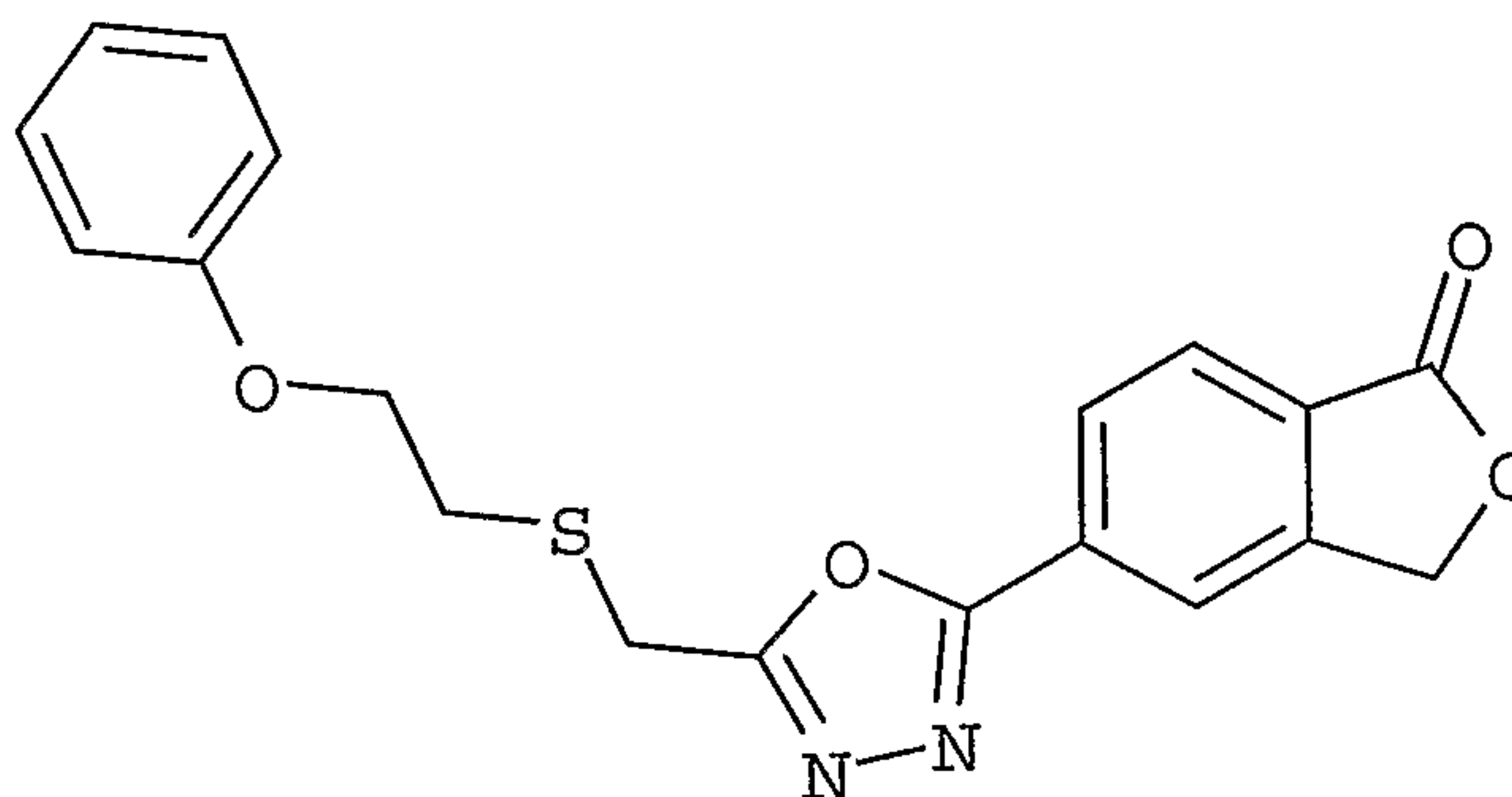
-318-

Example 160

Preparation of 2-[[[(2-Phenoxyethyl)thio]methyl]-5-{3-hydroxymethyl-4-[[[(2-piperidinoethyl)amino]carbonyl]phenyl]-1,3,4-oxadiazole



5 a) 5-{2-[[[(2-Phenoxyethyl)thio]methyl]-1,3,4-oxadiazol-5-yl}phthalide



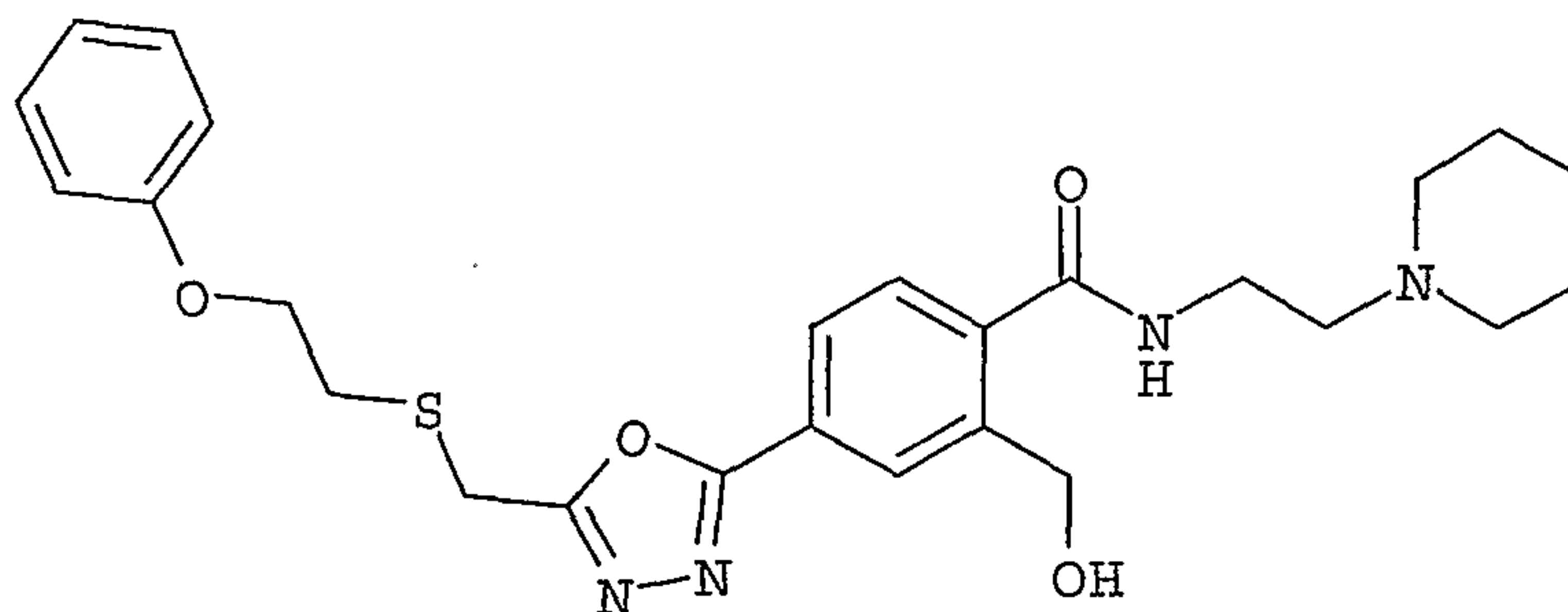
To a mixture of 4-carboxyphthalide (178 mg, 1 mmol), 2-phenoxythioacetic hydrazide hydrochloride (316 mg, 1.2 mmol), 4-(N,N-dimethylamino)phenyldiphenylphosphine (917 mg, 3 mmol), and triethylamine (607 mg, 6 mmol) in acetonitrile (10 mmol) was added carbon tetrachloride (770 mg, 5 mmol). The resultant mixture was stirred at room temperature overnight and concentrated. The residue was partitioned between ether (50 mL) and 2 M HCl (30 mL). The organic layer was washed with 2 M HCl (5 x 20 mL), dried (MgSO₄), and concentrated. The residue was triturated from methylene chloride and hexanes to give a white solid (186 mg, 51%).

15 The reaction was repeated on 3 mmol scale to give the same product (652 mg, 59%).

¹H NMR (CDCl₃) δ 8.16 (d, 1H, J=8.1 Hz), 8.13 (s, 1H), 8.02 (d, 1H, J=7.8 Hz), 7.22-7.26 (m, 2H), 6.93 (t, 1H, J=7.3 Hz), 6.86 (d, 2H, J=8.0 Hz), 5.37 (s, 2H), 4.20 (t, 2H, J=5.8 Hz), 4.09 (s, 2H), 3.05 (t, 2H, J=5.9 Hz). MS (ES⁺) m/e 369 (M+1).

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b) 2-[[[(2-Phenoxyethyl)thio]methyl]-5-{3-hydroxymethyl-4-[[[(2-piperidinoethyl)amino)carbonyl]phenyl]-1,3,4-oxadiazolo



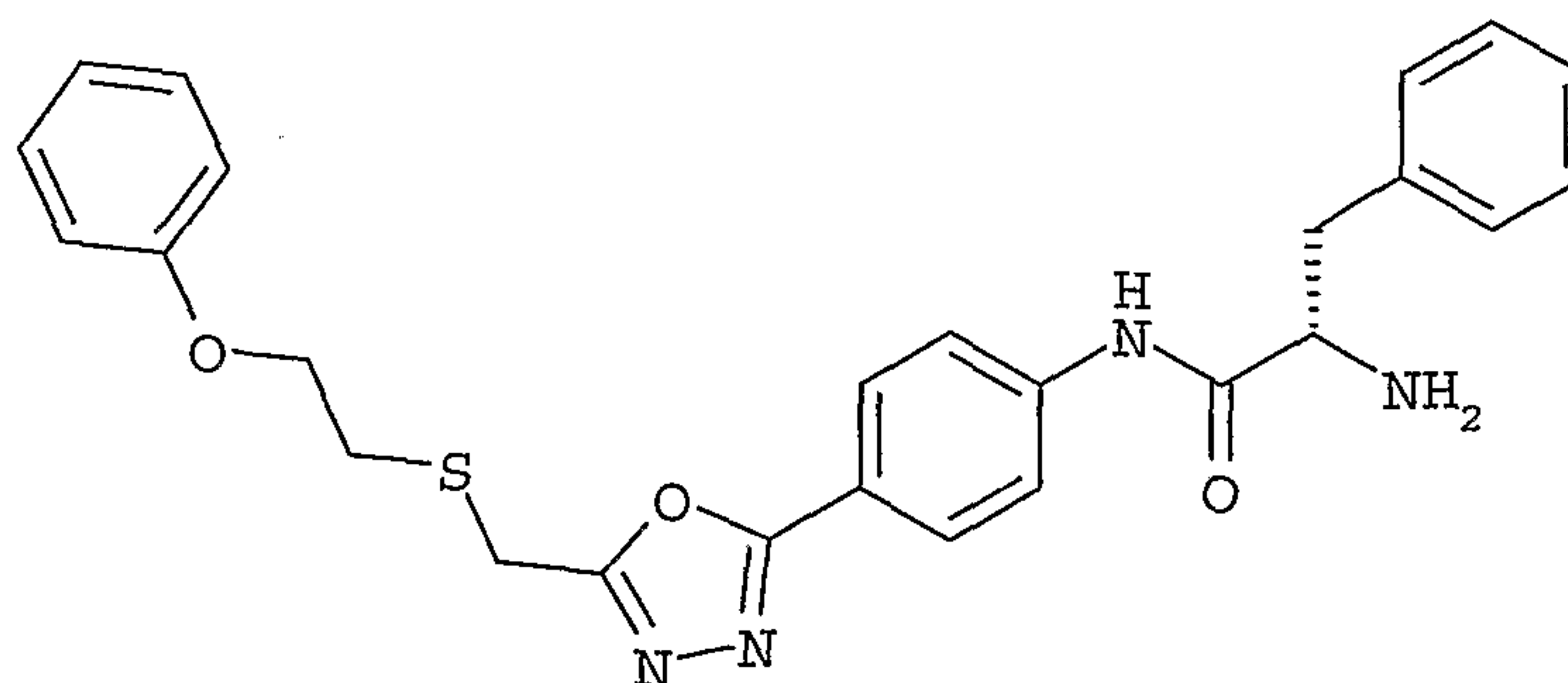
Lithium aluminum hydride (1 M in ether, 1 mL, 1 mmol) was diluted with
 5 tetrahydrofuran (1 mL) and N-(2-aminoethyl)piperidine (641 mg, 5 mmol) in
 tetrahydrofuran (1 mL) was added dropwise over 3 min. The resultant mixture was stirred
 at room temperature for 2 hr, diluted with tetrahydrofuran (4 mL), and 5-{2-[[[(2-
 phenoxyethyl)thio]methyl]-1,3,4-oxadiazol-5-yl]phthalide (368 mg, 1 mmol) was added.
 Stirring was continued at room temperature overnight and tetrahydrofuran (5 mL),
 10 followed by 2 M NaOH (5 mL) was added. The mixture was stirred for 30 min, diluted
 with water (15 mL), and extracted with ethyl acetate (3 x 15 mL). The combined ethyl
 acetate extracts were washed with brine (15 mL), dried (MgSO₄), and concentrated. The
 residue was recrystallized from methylene chloride and hexanes (1:1) to give a white solid
 (280 mg, 56%).

15 ¹H NMR (CDCl₃) δ 8.02 (s, 1H), 8.0 (d, 1H, J=8.0 Hz), 7.64 (d, 1H, J=7.7 Hz),
 7.22-7.26 (m, 2H), 7.10 (br s, 1H), 6.92 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=8.4 Hz), 4.64 (s,
 2H), 4.19 (t, 2H, J=6.0 Hz), 4.05 (s, 2H), 3.59 (dd, 2H, J=8.2, 5.5 Hz), 3.04 (t, 2H, J=5.9
 Hz), 2.60 (t, 2H, J=5.7 Hz), 2.4-2.52 (m, 4H), 1.60-1.66 (m, 4H), 1.47-1.50 (m, 2H). IR
 (KBr, cm⁻¹) 3465, 3310, 2940, 2888, 2854, 1638, 1556, 1496, 1420, 1297, 1020, 750. MS
 20 (ES⁺) m/e 497 (M+1). Anal. Calcd for C₂₆H₃₂N₄O₄S: C, 62.88; H, 6.49; N, 11.28; S,
 6.46. Found C, 63.27; H, 6.46; N, 11.14; S, 6.28.

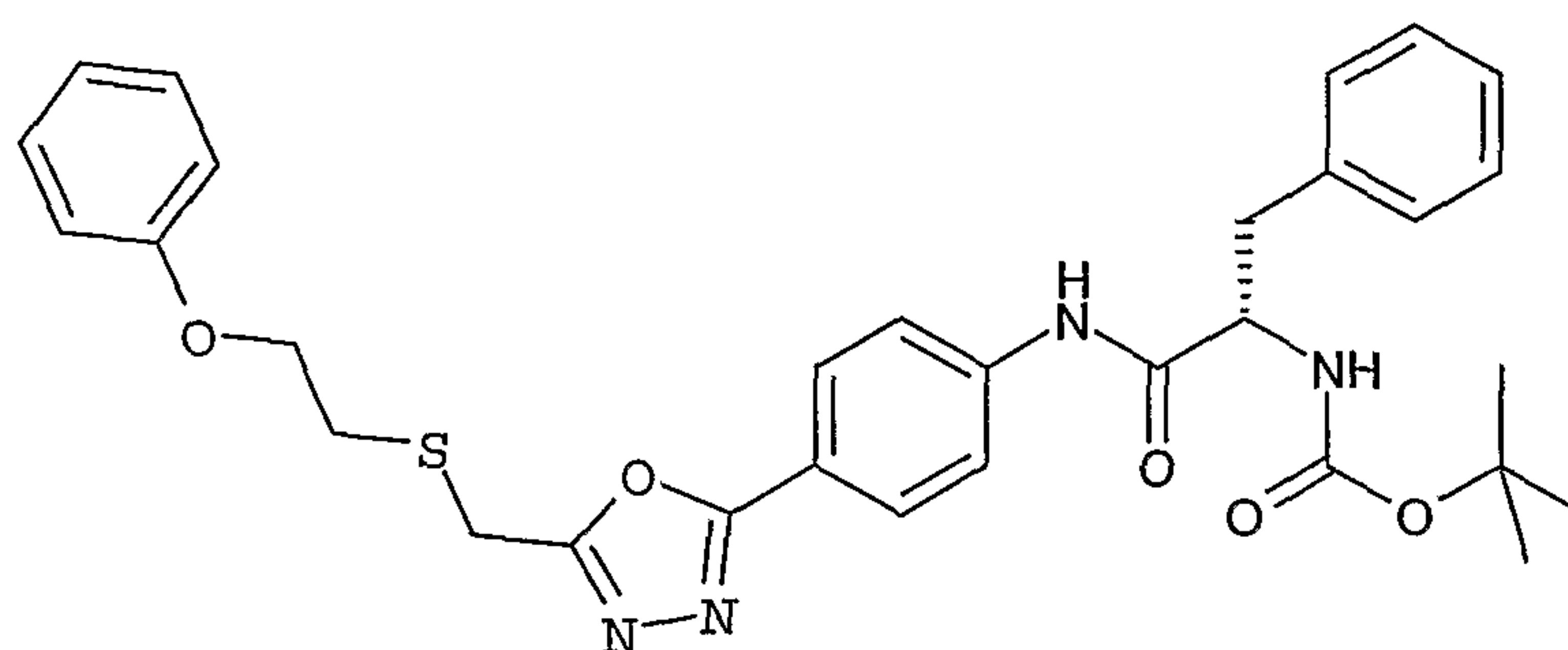
-320-

Example 161

Preparation of 2-[[2-(Phenoxyethyl)thio]methyl]-5-[4-(2-benzyl-2-aminoacetamido)phenyl]-1,3,4-oxadiazole



- 5 a) 2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[2-benzyl-2-((tert-butoxycarbonyl)amino)acetamido]phenyl}-1,3,4-oxadiazole

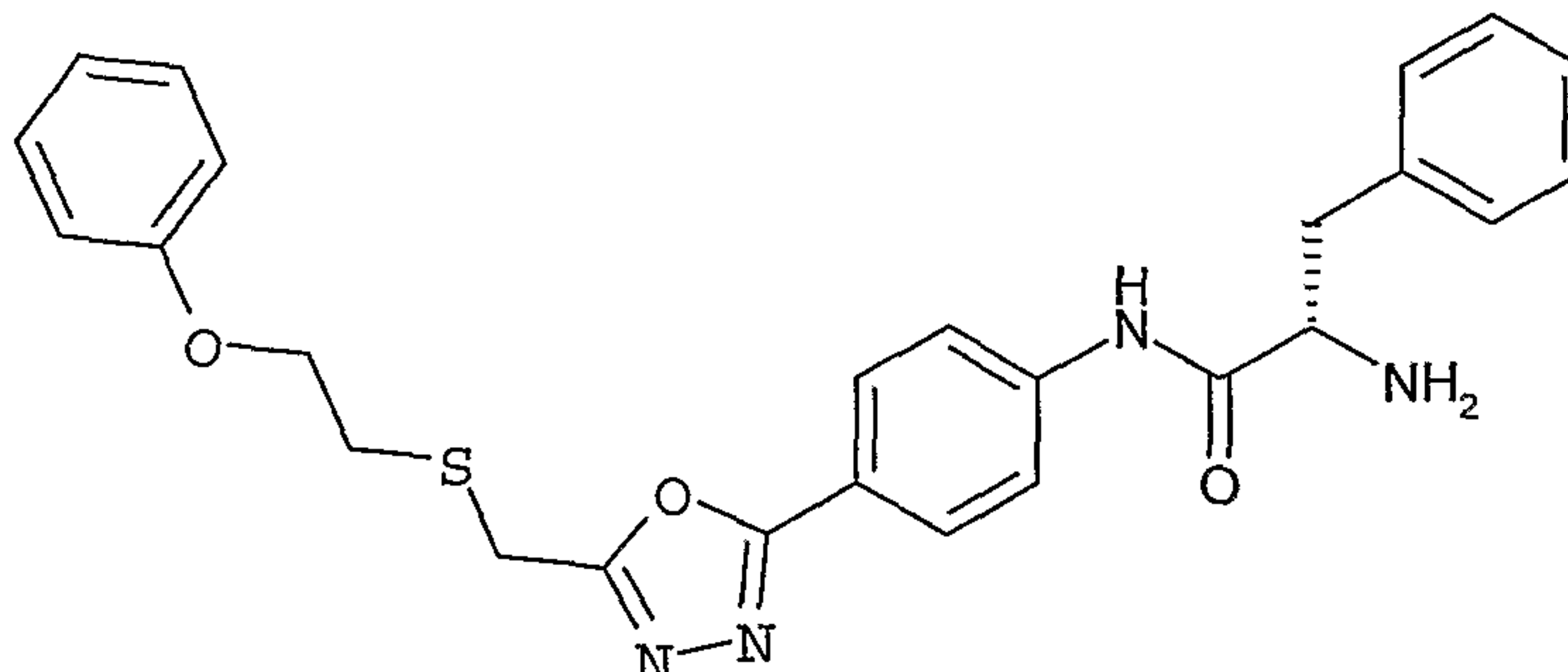


To a mixture of 2-[[2-(phenoxyethyl)thio]methyl]-5-(4-aminophenyl)-1,3,4-oxadiazole (327 mg, 1 mmol), Boc-L-phenylalanine (796 mg, 3 mmol), and 1-hydroxybenzotriazole (405 mg, 3 mmol) in tetrahydrofuran (25 mL) was added diisopropylcarbodiimide (379 mg, 3 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 mL), washed with 2 M NaOH (3 x 10 mL) and brine (25 mL), dried (MgSO₄), and concentrated. The residue was purified by chromatography (silica gel) to give a yellow solid (167 mg, 29%).

¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8.4 Hz), 7.80 (d, 2H, J=8.4 Hz), 7.22-7.32 (m, 7H), 6.93 (t, 1H, J=7.5 Hz), 6.87 (d, 2H, J=7.7 Hz), 5.08 (br s, 1H), 4.18 (t, 2H, J=6.2 Hz), 4.02 (s, 2H), 3.78 (t, 1H, J=6.4 Hz), 3.14 (d, 2H, J=6.9 Hz), 3.03 (t, 2H, J=6.2 Hz), 1.12 (s, 9H). MS (ES⁺) m/e 575 (M+1).

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b) 2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(2-benzyl-2-aminoacetamido)phenyl]-1,3,4-oxadiazole



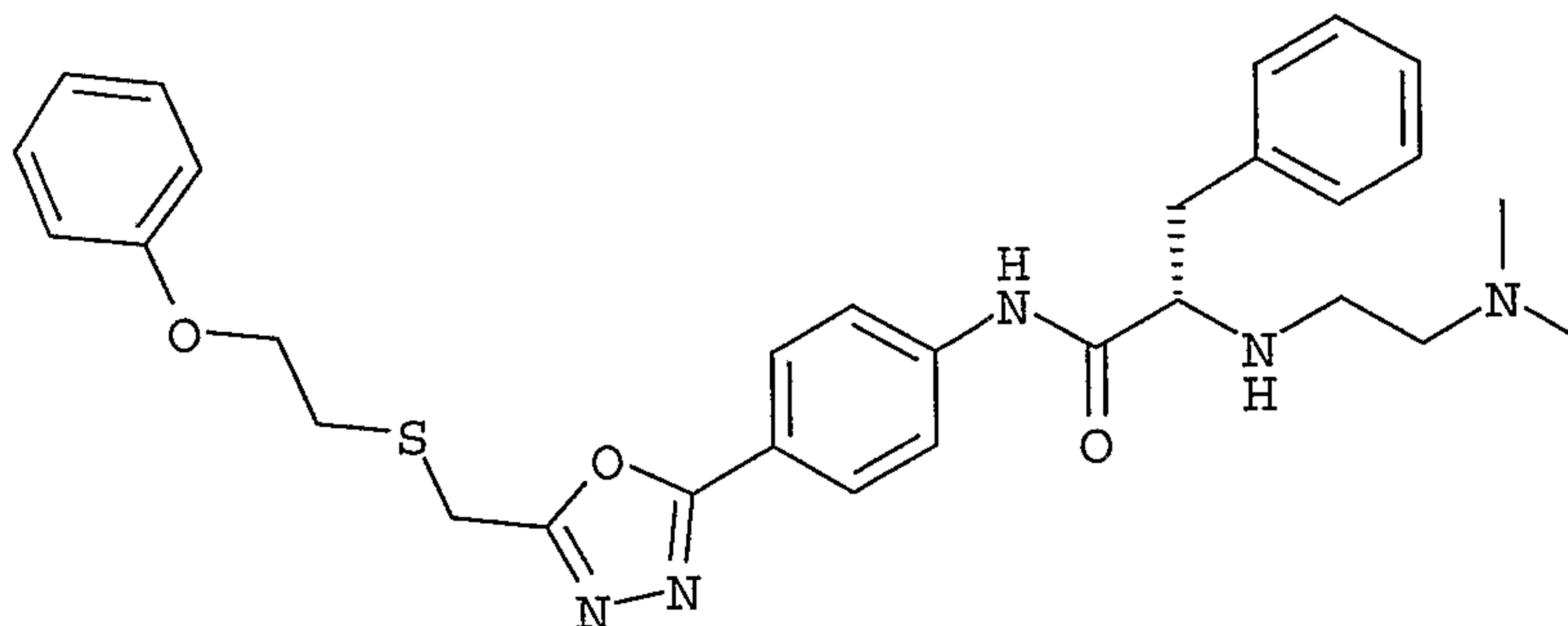
A mixture of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[2-benzyl-2-((tert-butoxycarbonyl)amino)acetamido]phenyl}-1,3,4-oxadiazole (144 mg, 0.25 mmol) and 25% trifluoroacetic acid in methylene chloride (2.5 mL) was stirred at room temperature overnight and concentrated. The residue was taken up in methylene chloride (15 mL), washed with 2 M NaOH (2 x 10 mL), dried (MgSO₄), and concentrated. The residue was purified by chromatography (silica gel, 10% methanol/methylene chloride) to give a white solid (74 mg, 60%).

¹H NMR (CDCl₃) δ 9.69 (s, 1H), 7.98 (d, 2H, J=8.8 Hz), 7.74 (d, 2H, J=8.7 Hz), 7.23-7.34 (m, 7H), 6.93 (t, 1H, J=7.3 Hz), 6.89 (d, 2H, J=8.8 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.75 (dd, 1H, J=9.5, 4.0 Hz), 3.37 (dd, 2H, J=13.9, 3.7 Hz), 3.04 (t, 2H, J=6.2 Hz), 2.80 (dd, 1H, J=13.9, 9.5 Hz). IR (KBr, cm⁻¹) 3430, 3060, 2981, 2926, 1681, 1599, 1501, 1426, 1386, 1238, 1094, 744. MS (ES⁺) m/e 475 (M+1). Anal. Calcd for C₂₆H₂₆N₄O₃S: C, 65.80; H, 5.52; N, 11.81; S, 6.76. Found C, 65.70; H, 5.56; N, 11.68; S, 6.61.

Example 162

20 Preparation of (S)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[2-benzyl-2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole

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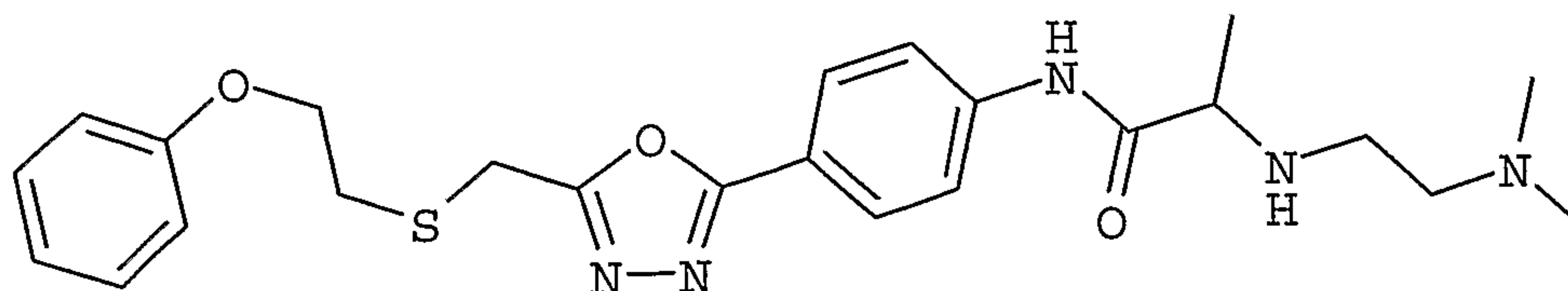


A mixture of 2-[[2-(2-phenoxyethyl)thio]methyl]-5-[4-(2-benzyl-2-aminoacetamido)phenyl]-1,3,4-oxadiazole (61 mg, 0.125 mmol), 2-(N,N-dimethylamino)ethylchloride hydrochloride (72 mg, 0.5 mmol), sodium carbonate (211 mg, 2 mmol), and sodium iodide (75 mg, 0.5 mmol) in ethanol (5 mL) was stirred under reflux overnight. The reaction mixture was poured into water (20 mL) and extracted with methylene chloride (3 x 10 mL). The combined methylene chloride extracts were dried (MgSO₄) and concentrated. The residue was purified by chromatography (silica gel, 10% methanol/methylene chloride) to give the desired product (30 mg, 44%) and recovered starting amine (13 mg, 21%).

¹H NMR (CDCl₃) δ 10.06 (s, 1H), 7.98 (d, 2H, J=8.5 Hz), 7.78 (d, 2H, J=8.8 Hz), 7.23-7.33 (m, 7H), 6.93 (t, 1H, J=7.3 Hz), 6.88 (d, 2H, J=8.4 Hz), 4.20 (t, 2H, J=6.0 Hz), 4.03 (s, 2H), 3.32-3.42 (m, 2H), 3.04 (t, 2H, J=6.2 Hz), 2.74 (dd, 1H, J=13.9, 10.2 Hz), 2.54-2.58 (m, 2H), 2.38 (m, 1H), 2.24 (m, 1H), 2.09 (s, 6H). MS (ES⁺) m/e 546 (M+1).
 Anal. Calcd for C₃₀H₃₅N₅O₃S: C, 66.03; H, 6.46; N, 12.83; S, 5.88. Found C, 66.18; H, 6.37; N, 12.71; S, 6.01.

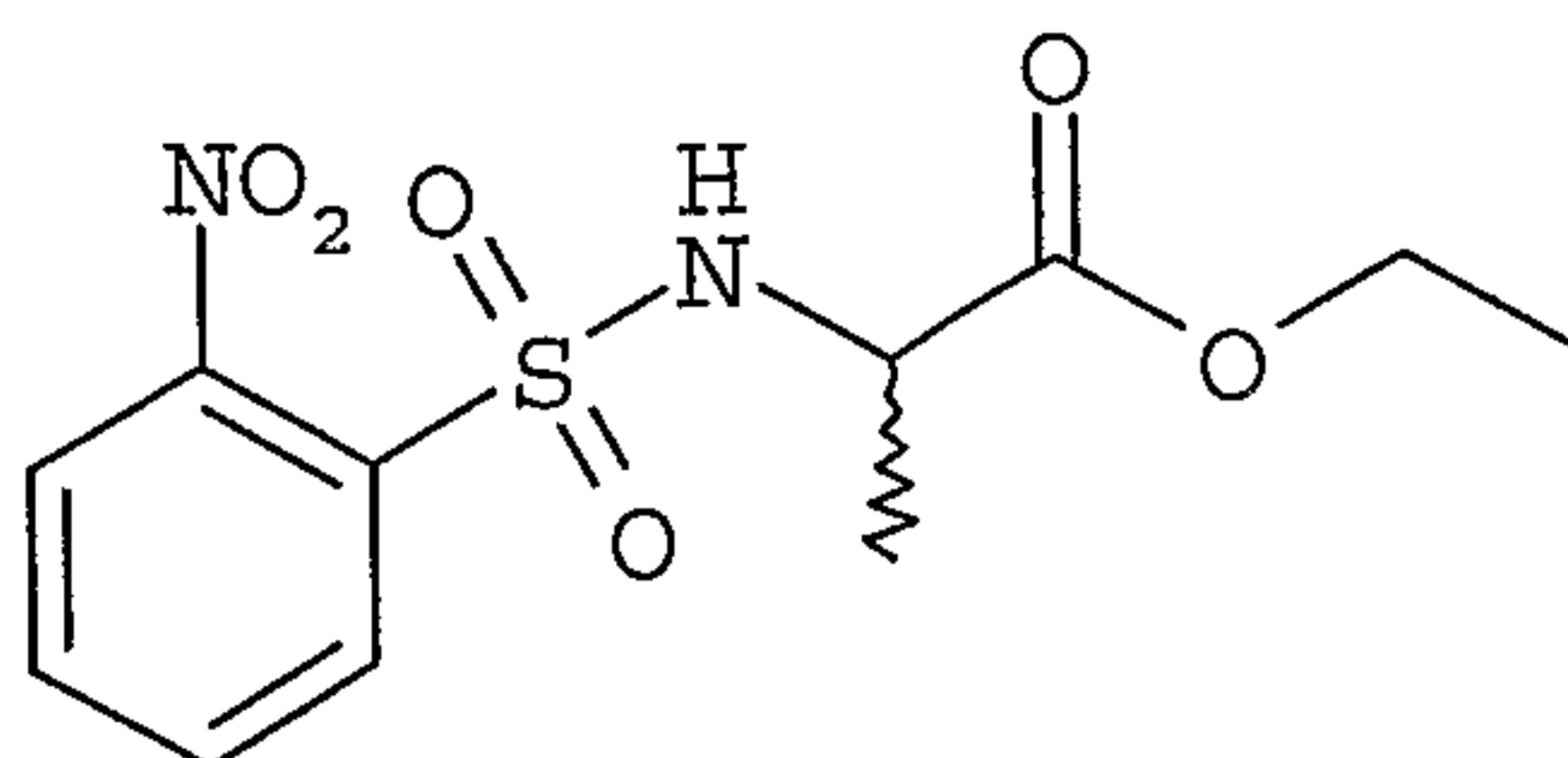
Example 163

Preparation of (+)-2-[[2-(2-Phenoxyethyl)thio]methyl]-5-{4-[2-methyl-2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



a) (+)-Ethyl 2-[(2-nitrobenzenesulfonyl)amino]propionate

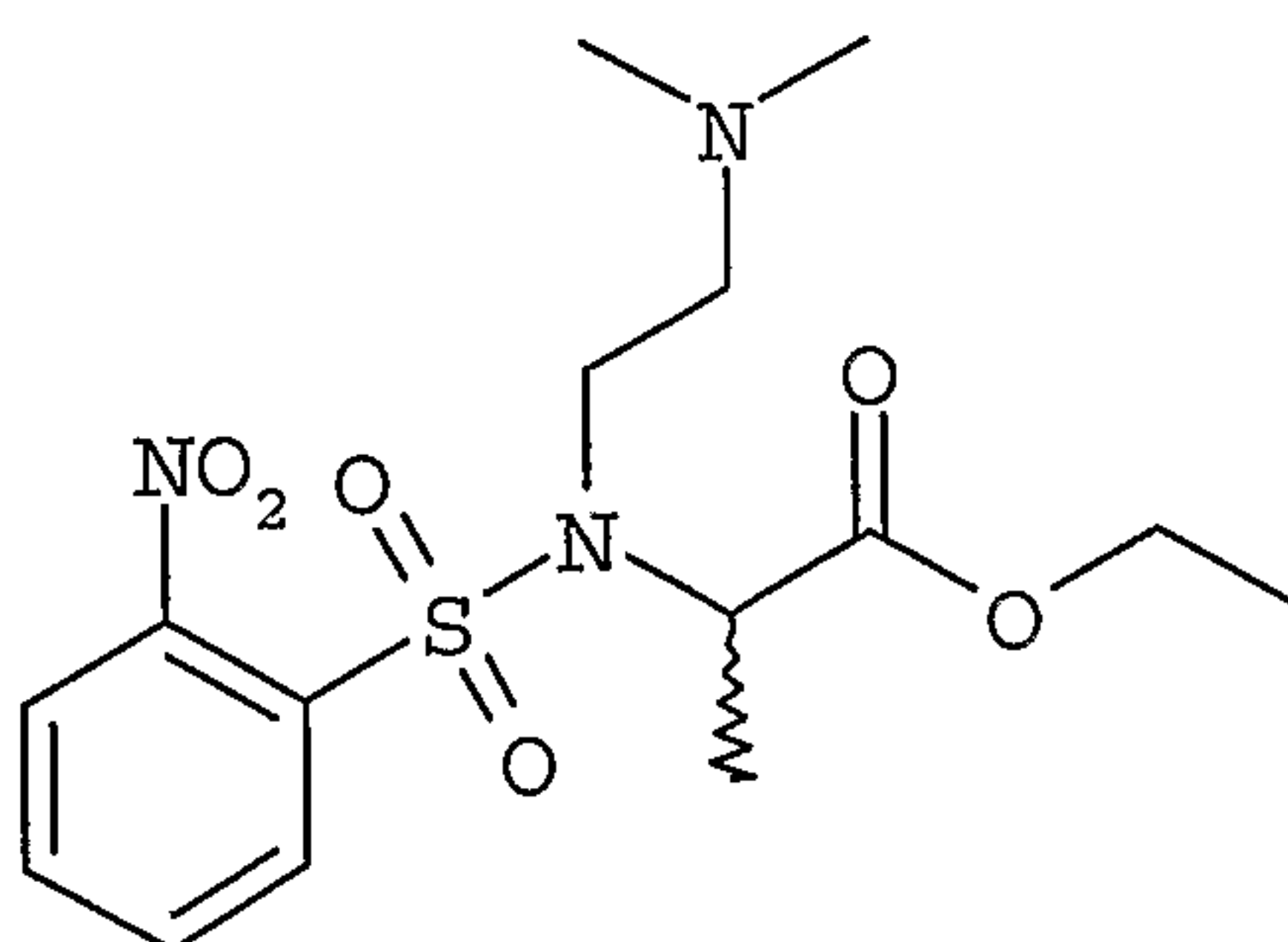
-323-



A solution of 2-nitrobenzenesulfonyl chloride (6.0 g, 27.1 mmol) and DL-alanine ethyl ester hydrochloride (5.0 g, 32.5 mmol) in methylene chloride (250 mL) was cooled in an ice/water bath. Triethylamine (9.5 mL, 67.8 mmol) was added dropwise over 3 min. The reaction was stirred for 10 min in the ice/water bath, then at room temperature for 3 h. The mixture was extracted with 2N HCl (3x100 mL), dried (MgSO₄), filtered and concentrated to yield 8.1 g (98%) of a yellow solid.

¹H NMR (CDCl₃) δ 8.05 (m, 1H), 7.89 (m, 1H), 7.69 (m, 2H), 6.07 (d, 1H, J=8 Hz), 4.19 (m, 1H), 3.93 (dd, 2H, J=14 and 14 Hz), 1.45 (dd, 3H, J=3 and 6 Hz), 1.07 (dt, 3H, J=14 and 14 Hz). MS (ES+) m/e 303 (M+1).

b) (+)-Ethyl 2-[N-(2-nitrobenzenesulfonyl)-N-(N',N'-dimethylamino)-1,2-ethanediamino]propionate



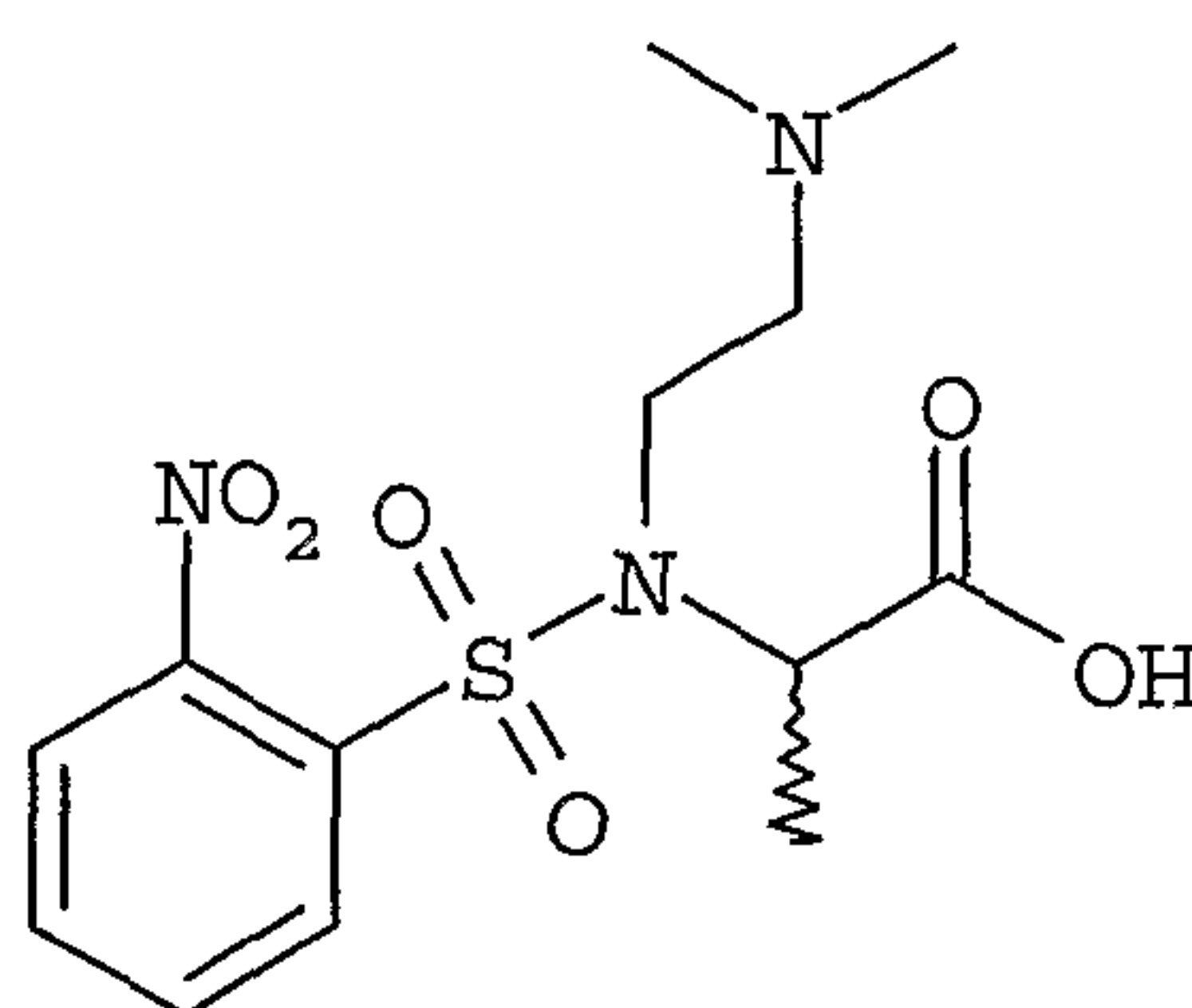
A solution of ethyl (+)-ethyl 2-[(2-nitrobenzenesulfonyl)amino]propionate (3.0 g, 10 mmol), N,N-dimethylethanolamine (2.0 mL, 20 mmol) and triphenylphosphine (6.56 g, 25 mmol) in THF (100 mL) were cooled in an ice/water bath. Diethyl azodicarboxylate (4.0 mL, 25 mmol) was added dropwise over 3 min, stirred another 10 min, then stirred at room temperature for 16 h. The mixture was concentrated, diluted with methanol (20 mL) and loaded onto a column containing Bio-Rad 50W-X2 cation exchange resin (50 g, pre-washed 800 mL of methanol). The column was washed with methanol (800 mL) and methylene chloride (200 mL). The product was then eluted with 2N ammonia/methanol (500 mL) and concentrated to yield 3.34 g of a yellow oil. This material was diluted with

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ethyl acetate (50 mL), extracted with water (3x50 mL), dried (MgSO₄), filtered and concentrated to yield 2.92 g (78%) of a yellow oil.

¹H NMR (CDCl₃) δ 8.07 (m, 1H), 7.65 (m, 2H), 7.57 (m, 1H), 4.75 (m, 1H), 4.03 (m, 2H), 3.56 (m, 1H), 3.17 (m, 1H), 2.63 (m, 1H), 2.46 (m, 1H), 2.20 (s, 6H), 1.51 (d, 3H, J=7 Hz), 1.12 (t, 3H, J=14 Hz). MS (ES+) m/e 375 (M+1).

c) (+)-2-[N-(2-Nitrobenzenesulfonyl)-N-(N',N'-dimethylamino)-1,2-ethanediamino]propionic acid

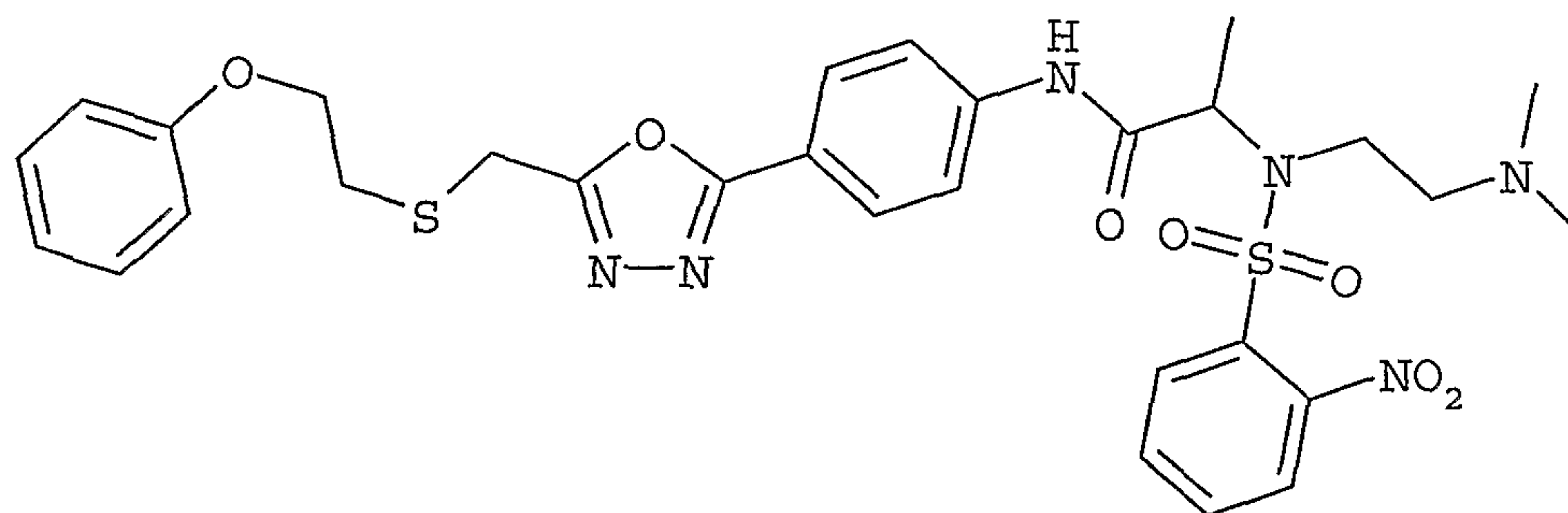


A solution of (+)-ethyl 2-[N-(2-nitrobenzenesulfonyl)-N-(N',N'-dimethylamino)-1,2-ethanediamino]propionate (2.92 g, 7.8 mmol) and aqueous 2 N NaOH (20 mL, 40 mmol) in tetrahydrofuran (14 mL) was stirred at room temperature for 2 h. The mixture was loaded onto a column of Bio-Rad AG1-X2 anionic exchange resin (40 g, pre-washed with 800 mL of water) and allowed to settle for 20 min before it was passed through the column. The column was washed with water (800 mL) and 1,4-dioxane (600 mL). The product was then eluted with 4 N HCl in 1,4-dioxane and concentrated to yield 2.06 g (76%) of a yellow oil.

¹H NMR (DMSO-D₆) δ 10.00 (br s, 1H), 8.17 (m, 1H), 7.80-7.92 (m, 3H), 4.55 (m, 1H), 4.15 (m, 1H), 3.80 (m, 1H), 3.75 (m, 2H), 2.75 (s, 6H), 1.45 (d, 2H, J=7 Hz). MS (ES-) m/e 344 (M-1).

d) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[(2-(N',N'-dimethyl-N-(2-nitrobenzenesulfonyl)-1,2-ethanediamino)propionyl)amino]phenyl}-1,3,4-oxadiazole

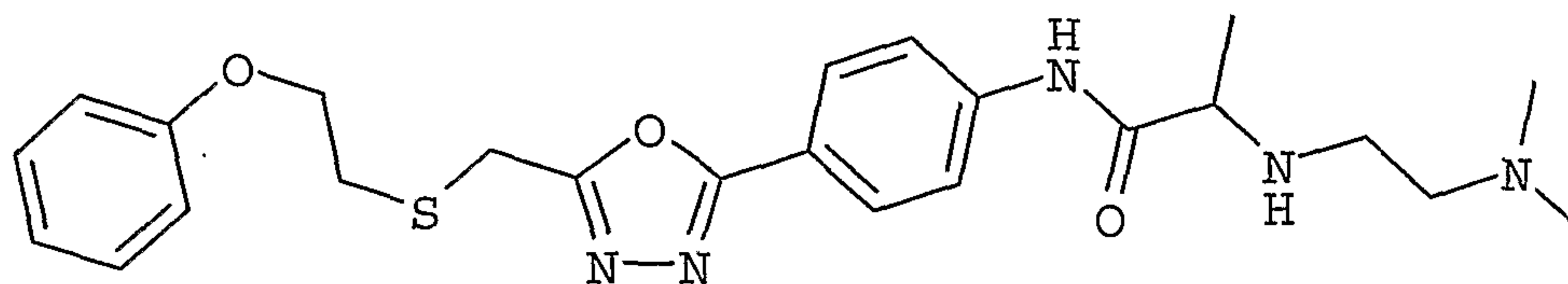
-325-



A solution of (+)-2-[N-(2-nitrobenzenesulfonyl)-N-(N',N'-dimethylamino)-1,2-ethanediamino]propionic acid (345 mg, 1 mmol) and 2-[[2-(phenoxyethyl)thio]methyl]-5-(4-aminophenyl)-1,3,4-oxadiazole (327 mg, 1 mmol) in anhydrous pyridine (3.0 mL) was cooled in an ice-salt water bath under nitrogen. Phosphorus oxychloride (0.15 mL, 1.6 mmol) was added dropwise and the cooled reaction stirred for 3 h. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (3x10 mL). The combined organic phase was extracted with saturated aqueous sodium bicarbonate (3x10 mL), water (3x10 mL) and brine (3x10 mL), dried (MgSO₄), filtered and concentrated. The residue was co-evaporated with toluene (3x5 mL) to remove any lingering pyridine. This material was purified by preparative TLC (5% methanol/methylene chloride) to yield 147 mg (22%) of a brown oil.

¹H NMR (CDCl₃) δ 8.59 (br s, 1H), 8.16 (d, 1H, J=9 Hz), 7.97 (d, 2H, J=9 Hz), 7.63-7.75 (m, 5H), 7.25 (m, 2H), 6.93 (m, 1H), 6.87 (d, 2H, J=8 Hz), 4.18 (m, 3H), 4.02 (s, 2H), 3.91 (m, 1H), 3.42 (m, 1H), 3.02 (m, 2H), 2.55 (m, 1H), 2.43 (m, 1H), 2.24 (s, 6H), 1.40 (t, 3H, J=14 Hz). MS (ES⁺) m/e 655 (M+1).

e) (+)-2-[[2-(Phenoxyethyl)thio]methyl]-5-{4-[2-methyl-2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



A mixture of (+)-2-[[2-(phenoxyethyl)thio]methyl]-5-{4-[(2-(N',N'-dimethyl-N-(2-nitrobenzenesulfonyl)-1,2-ethanediamino)propionyl)amino]phenyl}-1,3,4-oxadiazole (147 mg, 0.22 mmol), benzenethiol (0.04 mL, 0.39 mmol) and potassium carbonate (93 mg, 0.67 mmol) was stirred in N,N-dimethylformamide (2.0 mL) at room temperature for

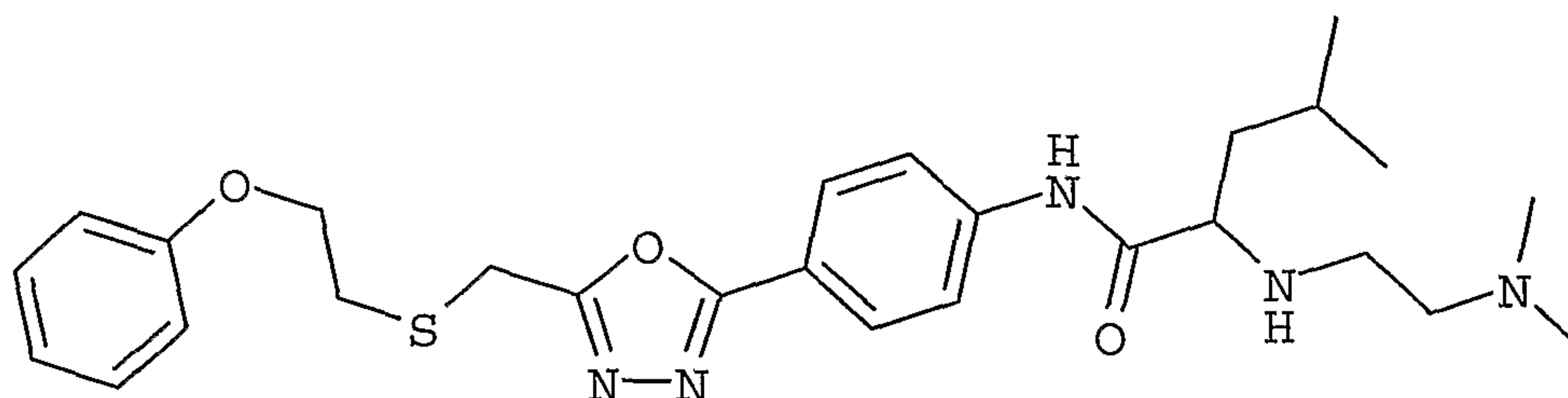
-326-

1 h. The mixture was diluted with ethyl acetate (40 mL), extracted with water (5x10 mL), dried (MgSO₄), filtered and concentrated to yield 182 mg of a brown oil. This residue was purified by preparative TLC (10% methanol/methylene chloride) to yield 35 mg (33%) of a colorless oil.

5 ¹H NMR (CDCl₃) δ 9.97 (s, 1H), 7.97 (d, 2H, J=8 Hz), 7.76 (d, 2H, J=8 Hz), 7.26 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.88 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.02 (s, 2H), 3.26 (m, 1H), 3.04 (t, 2H, J=12 Hz), 2.81 (m, 1H), 2.64 (m, 1H), 2.47 (m, 1H), 2.37 (m, 1H), 2.24 (s, 6H), 1.40 (d, 2H, J=7). IR (film, cm⁻¹) 3421, 3071, 2977, 2938, 1683, 1603, 1499, 1413, 1242, 732. MS (ES+) m/e 470 (M+1). Anal. Calcd for
10 C₂₄H₃₁N₅O₃S: C, 61.38; H, 6.65; N, 14.91; S, 6.83. Found C, 61.86; H, 6.62; N, 15.06; S, 6.41.

Example 164

Preparation of (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[2-isobutyl-2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



15

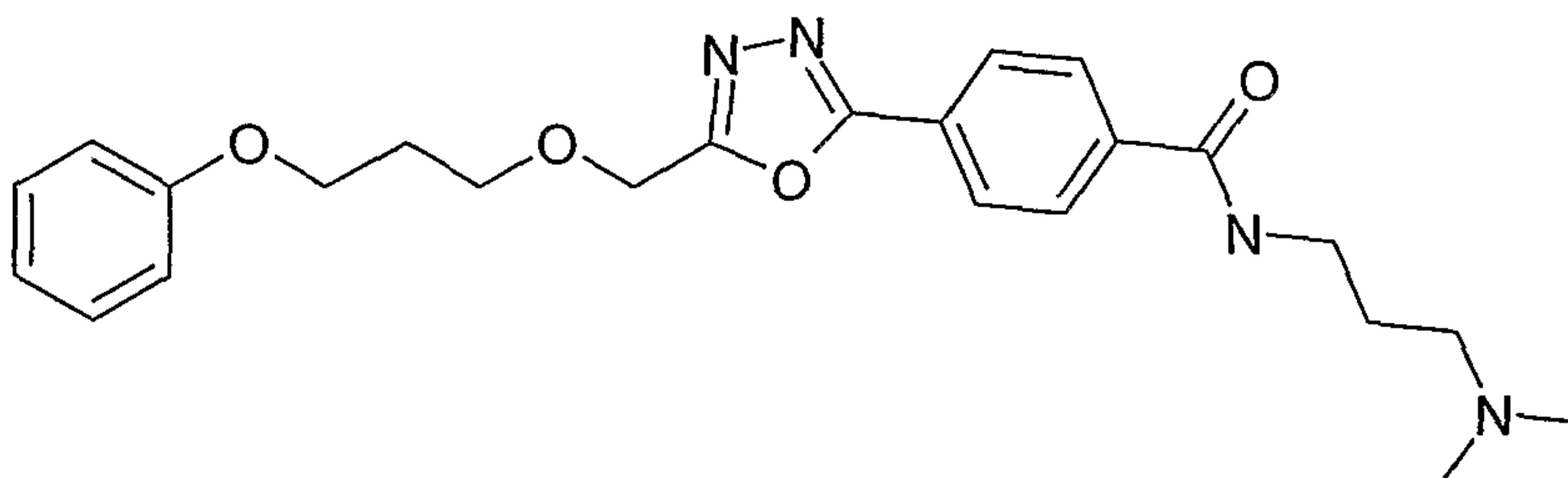
This compound was prepared similarly to (+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[2-methyl-2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole from DL-alanine ethyl ester hydrochloride.

20 ¹H NMR (CDCl₃) □ 9.98 (s, 1H), 7.96 (d, 2H, J=9 Hz), 7.76 (d, 2H, J=9 Hz), 7.25 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.02 (s, 2H), 3.18 (m, 1H), 3.04 (t, 2H, J=12 Hz), 2.76 (m, 1H), 2.65 (m, 1H), 2.47 (m, 1H), 2.39 (m, 1H), 2.24 (s, 6H), 1.65-1.78 (m, 2H), 1.48 (m, 1H), 0.96 (dd, 6H, J=2 and 9 Hz). IR (film, cm⁻¹) 2958, 2867, 2250, 1684, 1601, 1505, 1240, 909, 734, 650. MS (ES+) m/e 512 (M+1). Anal. Calcd for C₂₇H₃₇N₅O₃S: C, 63.38; H, 7.29; N, 13.69; S, 6.27. Found C,
25 63.70; H, 6.73; N, 13.79; S, 5.93.

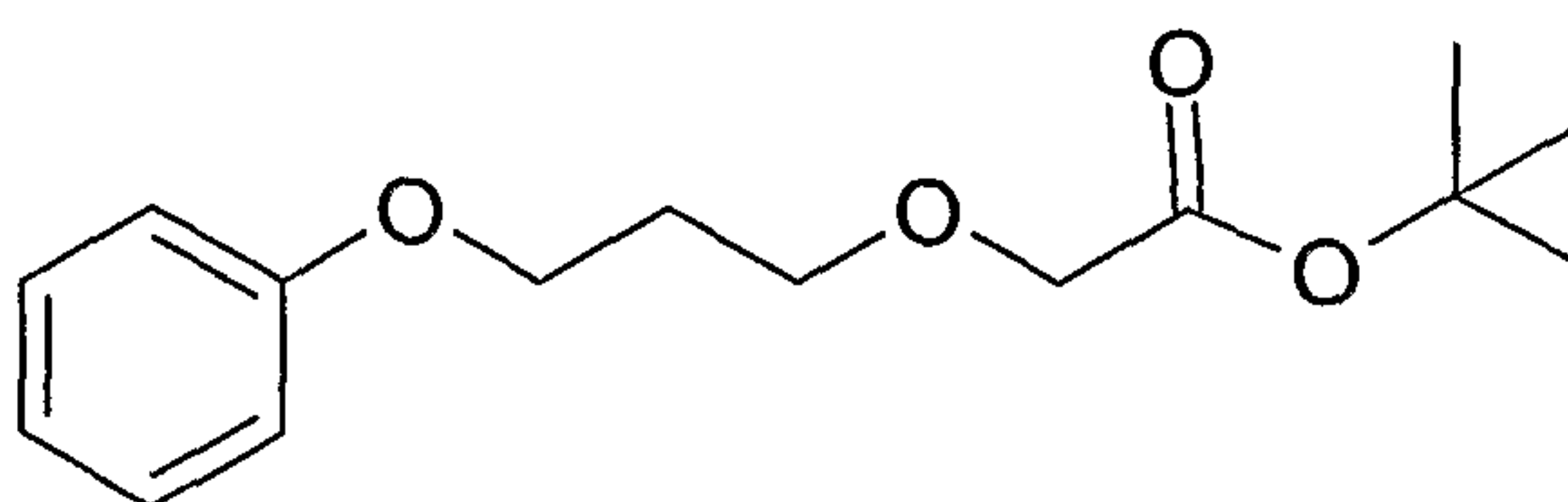
Example 165

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Preparation of N-(3-Dimethylamino-propyl)-4-[5-(3-phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



a) (3-Phenoxy-propoxy)-acetic acid tert-butyl ester



5

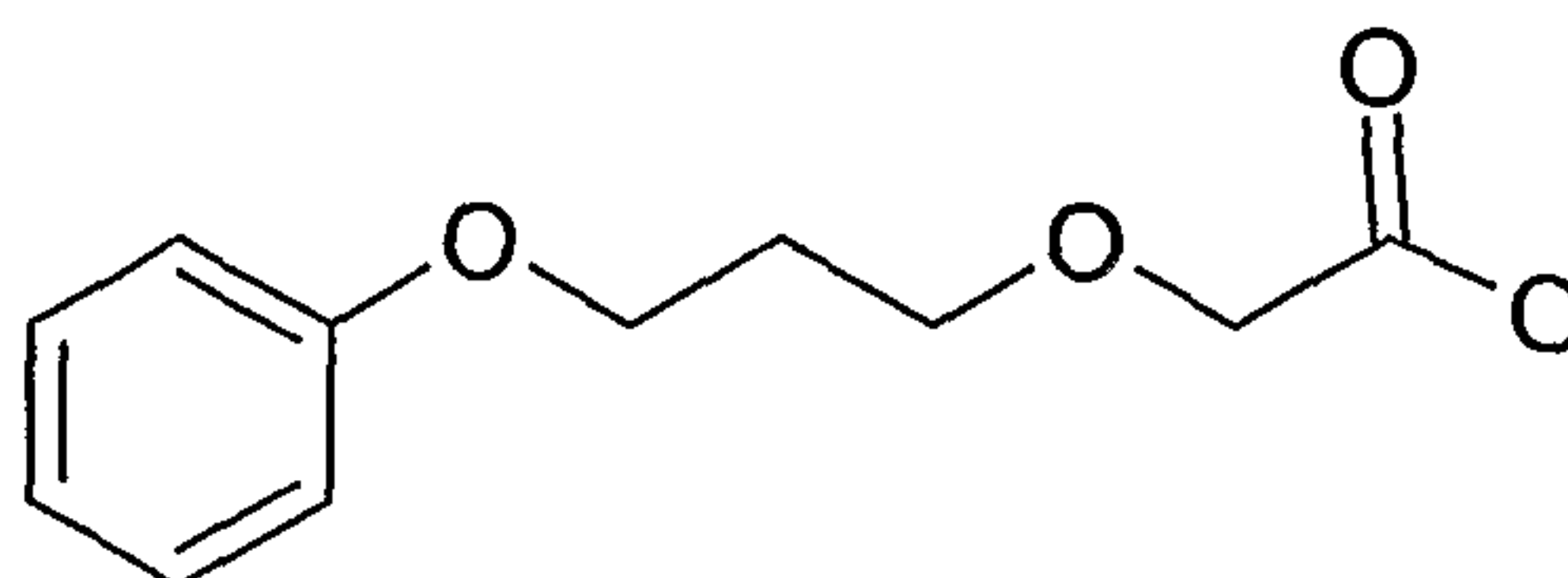
To a solution of 3-phenoxypropanol (5 g, 32.8 mmol) in 30 mL toluene was added tert-butylbromoacetate (19.2 g, 99 mmol) and tetrabutylammonium hydrogen sulfate (2.8 g, 8.2 mmol). The mixture was cooled to 0°C and treated with 25 mL 50% aqueous NaOH. After stirring for 10 minutes at 0°C the cooling bath was removed and the reaction was stirred at ambient temperature for 2 hours. It was diluted with 50 mL toluene and the layers were separated. The aqueous layer was extracted with 50 mL toluene and the combined organic layer was dried over MgSO₄ before concentrating to dryness. The resulting colorless oil was purified by chromatography using EtOAc in hexanes to recover 6.1 g (23 mmol, 69%) of the desired product as an oil. MS (ES) m/e 378

10

15

¹H NMR (CDCl₃) δ 7.29-7.25 (m, 2H), 6.95-6.89 (m, 3H), 4.11-4.07 (m, 2H), 3.97 (s, 2H), 3.72-3.69 (m, 2H), 2.11-2.08 (m, 2H,) and 1.47 (s, 9H).

b) (3-Phenoxy-propoxy)-acetic acid



20

(3-Phenoxy-propoxy)-acetic acid tert-butyl ester (7.6 g, 29 mmol) was mixed with 18 g anisole and 50 mL CH₂Cl₂ then treated with 25 mL TFA. The mixture was stirred at ambient temp overnight, concentrated to dryness under vacuum and purified by

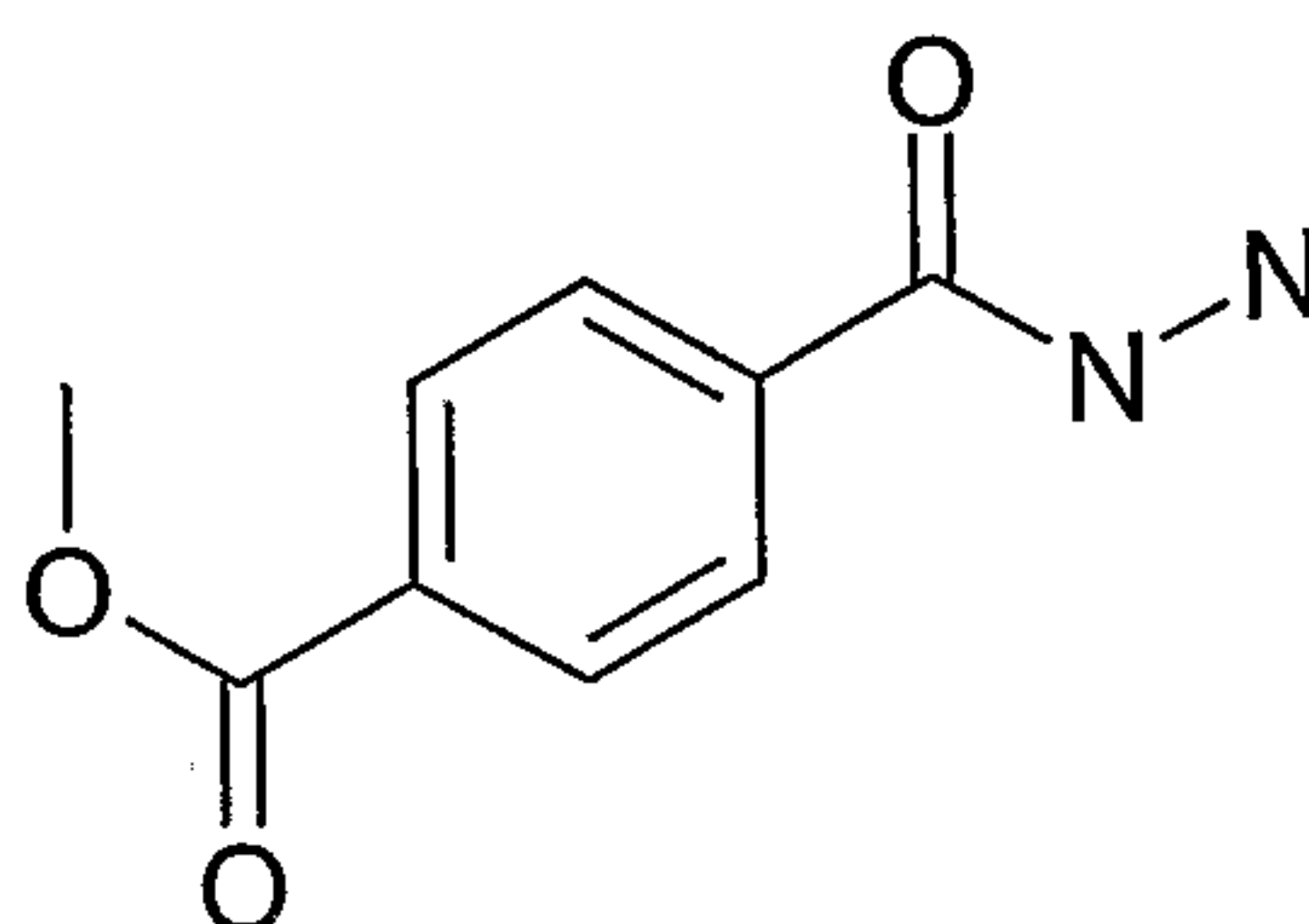
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chromatography using MeOH in CHCl₃ to recover 5.5 (26 mmol, 90%) of the desired product as an oil. MS (ES) m/e 211

¹H NMR (CDCl₃) δ 10.55 (bs, 1H), 7.3-7.6 (m, 2H), 6.97-6.90 (m, 3H), 4.15 (s, 2H), 4.14-4.10 (m, 2H), 3.78-3.75 (m, 2H), 2.14-2.08 (m, 2H).

5

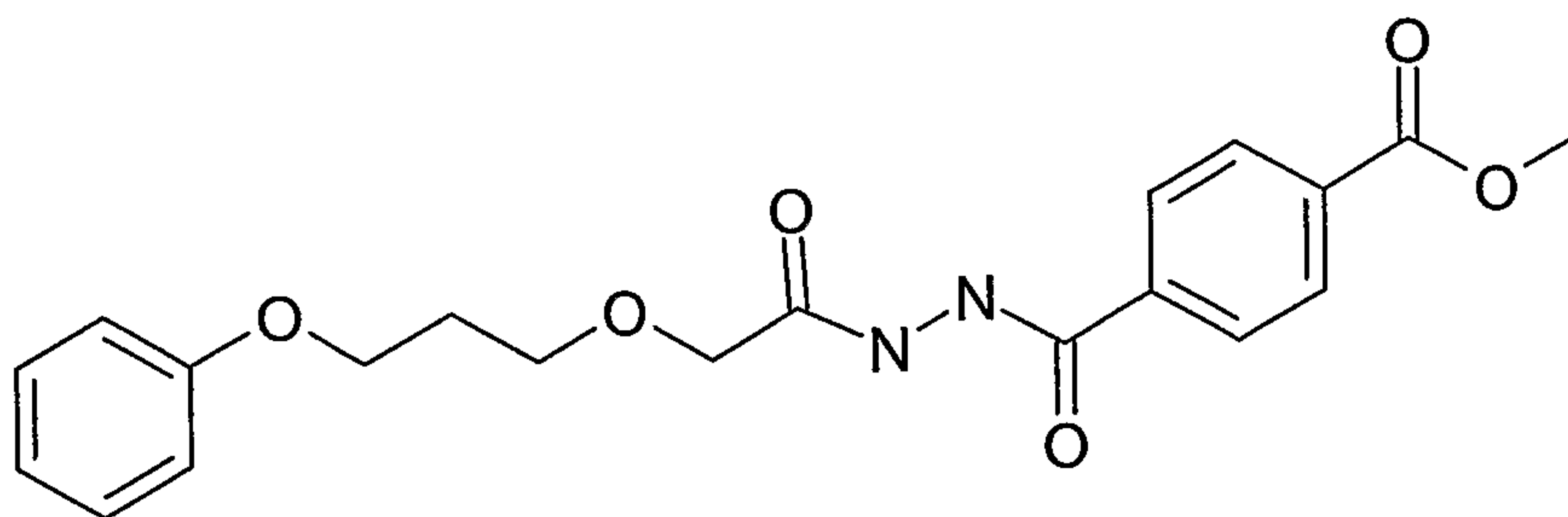
c) 4-Hydrazinocarbonyl-benzoic acid methyl ester



A mixture of dimethyl terephthalate (11 g, 57 mmol) and 350 mL MeOH was treated with 2 mL (62 mmol) of anhydrous hydrazine. The mixture was refluxed for 4 hours, cooled to room temp and filtered. The filtrate was allowed to stand at room temp for several hours then refiltered. The second filtrate was concentrated to dryness, mixed with 200 mL THF, refluxed for several minutes then allowed to stand at room temperature for several hours. The solid was filtered to recover 3.9 g (20 mmol, 35%) product as white crystals. MS (ES) m/e 211

¹H NMR (DMSO-d₆) δ 9.95 (s, 1H), 8.0-7.98 (m, 2H), 7.92-7.90 (m, 2H), 4.56 (s, 2H), and 3.30 (s, 3H).

d) 4-{N'-[2-(3-Phenoxy-propoxy)-acetyl]-hydrazino}-benzoic acid methyl ester



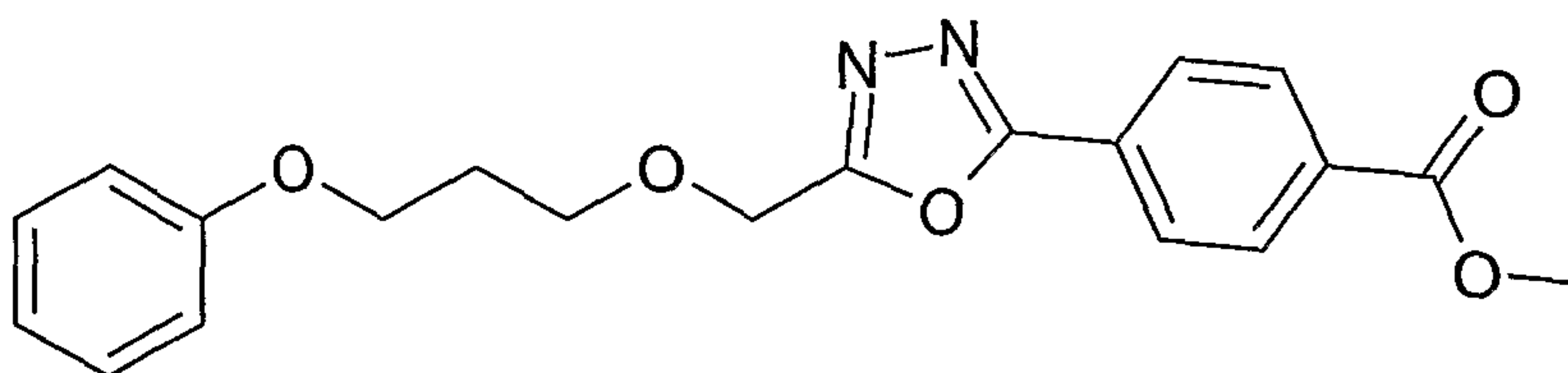
A mixture of (3-phenoxy-propoxy)-acetic acid (3 g, 14.3 mmol) in 25 mL CH₂Cl₂ was treated with an excess (1 mL) oxalyl chloride and 1 drop of DMF then stirred overnight. After concentration to dryness under vacuum, the residue was dissolved in 10 mL CH₂Cl₂ and added to a cold (0°C) mixture of 125 mL pyridine and the 4-

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hydrazinocarbonyl-benzoic acid methyl ester. The reaction was stirred overnight at ambient temperature, concentrated to dryness under vacuum and purified by chromatography using EtOAc in hexanes to recover 2.7 g of oil which crystallized.

¹H NMR (CDCl₃) δ 9.36-9.35 (m, 1H), 9.11-9.09 (m, 1H), 8.07-8.03 (m, 2H),
 5 7.82-7.80 (m, 2H), 7.28-7.22 (m, 2H), 6.94-6.86 (m, 3H), 4.12-4.06 (m, 4H), 3.94 (s, 3H),
 3.79-3.76 (m, 2H), and 2.15-2.07 (m, 2H).

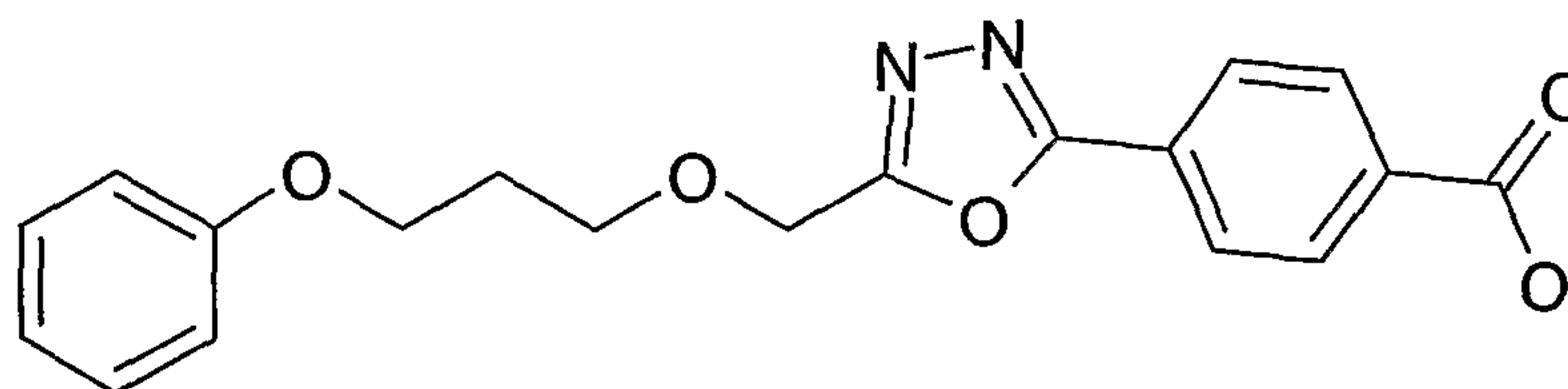
e) 4-[5-(3-Phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester



10 A mixture of 4-{N'-[2-(3-Phenoxy-propoxy)-acetyl]-hydrazino}-benzoic acid
 methyl ester (2.3 g, 6 mmol) and 25 mL SOCl₂ was refluxed overnight and concentrated
 to dryness under vacuum. Residual SOCl₂ was removed by mixing with toluene and
 reconcentrating to an oil. After dissolving in 16 mL CH₂Cl₂ and 4 mL MeOH, it was
 treated with 3 mL 2 M trimethylsilyldiazomethane in hexanes, reconcentrated to dryness
 15 and purified by silica gel chromatography using EtOAc in hexanes to recover 0.8 g of
 product.

¹H NMR (CDCl₃) δ 8.15-8.08 (m, 4H), 7.24-7.21 (m, 2H), 6.91-6.84 (m, 3H),
 4.79 (s, 2H), 4.08-4.06 (m, 2H), 3.96 (s, 3H), 3.82-3.79 (m, 2H), 2.13-2.07 (m, 2H).

20 f) 4-[5-(3-Phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



4-[5-(3-Phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester
 (0.8 g, 2.3 mmol) was dissolved in 50 mL THF, treated with 3.5 mL 1 M aqueous LiOH,
 and stirred overnight at ambient temperature. The reaction was neutralized with 3.5 mL 1
 25 N HCl, mixed with 20 mL brine and extracted twice with 20 mL EtOAc. The extracts

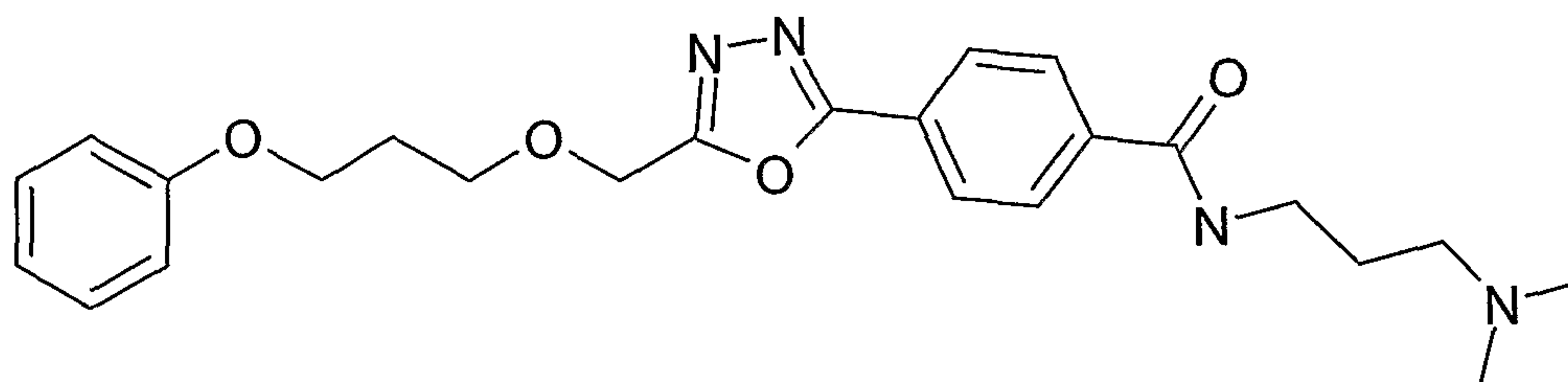
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were dried over MgSO₄ and concentrated to 550 mg (1.6 mmol, 68%) of a white solid which was used as isolated in the next procedure.

¹H NMR (DMSO-d₆) δ 8.15-8.08 (m, 4H), 7.24-7.21 (m, 2H), 6.91-6.84 (m, 3H), 4.08-4.06 (m, 2H), 3.96 (s, 3H), 3.82-3.79 (m, 2H), 2.13-2.07 (m, 2H).

5

g) N-(3-Dimethylamino-propyl)-4-[5-(3-phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



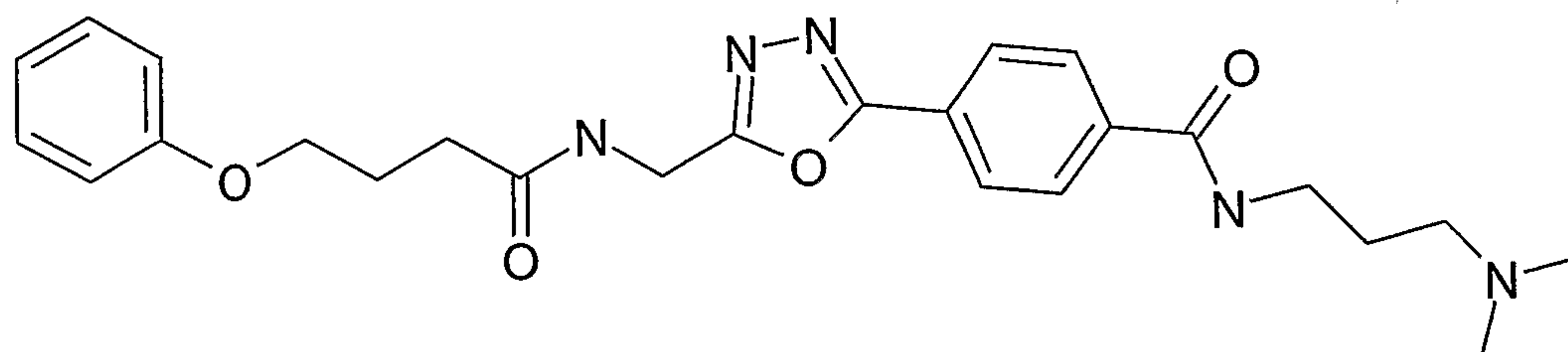
4-[5-(3-Phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (500 mg, 1.4 mmol) was converted to its acid chloride by mixing with 50 mL CH₂Cl₂, 2 mL oxalyl chloride and 2 drops of DMF and stirring for 1 hour. After concentration to dryness it was re-dissolved in 10 mL CH₂Cl₂ and added to a cold mixture of 3-dimethylaminopropylamine (317 mg, 3.1 mmol) in 30 mL CH₂Cl₂. The reaction was stirred at 0°C for 1 hour, concentrated to dryness then purified by silica gel chromatography using MeOH in CHCl₃ to recover 250 mg white solid.

¹H NMR (CDCl₃) δ 8.81 (s, 1H), 8.10-8.07 (m, 2H), 7.88-7.86 (m, 2H), 7.25-7.22 (m, 2H), 6.92-6.85 (m, 3H), 4.78 (s, 2H), 4.09-4.06 (m, 2H), 3.82-3.79 (m, 2H), 3.62-3.58 (m, 2H), 2.55-2.52 (m, 2H), 2.3 (s, 6H), 2.13-2.07 (m, 2H), 1.81-1.75 (m, 2H).
Anal. Calcd for C₂₄H₃₀N₄O₄·0.2C₄H₁₀O·0.1H₂O: C, 65.19; H, 7.15; N, 12.26. Found C, 65.33; H, 6.86; N, 12.60.

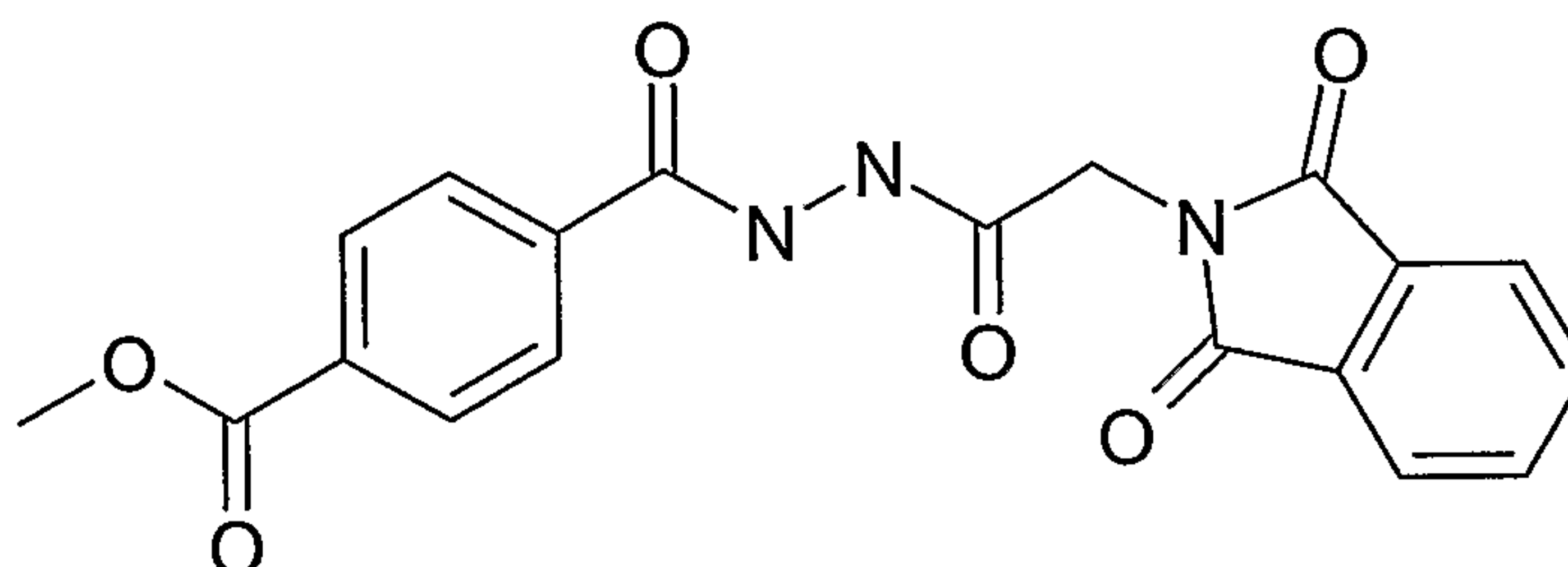
Example 166

Preparation of N-(3-Dimethylamino-propyl)-4-{5-[(4-phenoxy-butyrylamino)-methyl]-[1,3,4]oxadiazol-2-yl}-benzamide

-331-



a) 4-{N'-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetyl]-hydrazinocarbonyl}-benzoic acid methyl ester

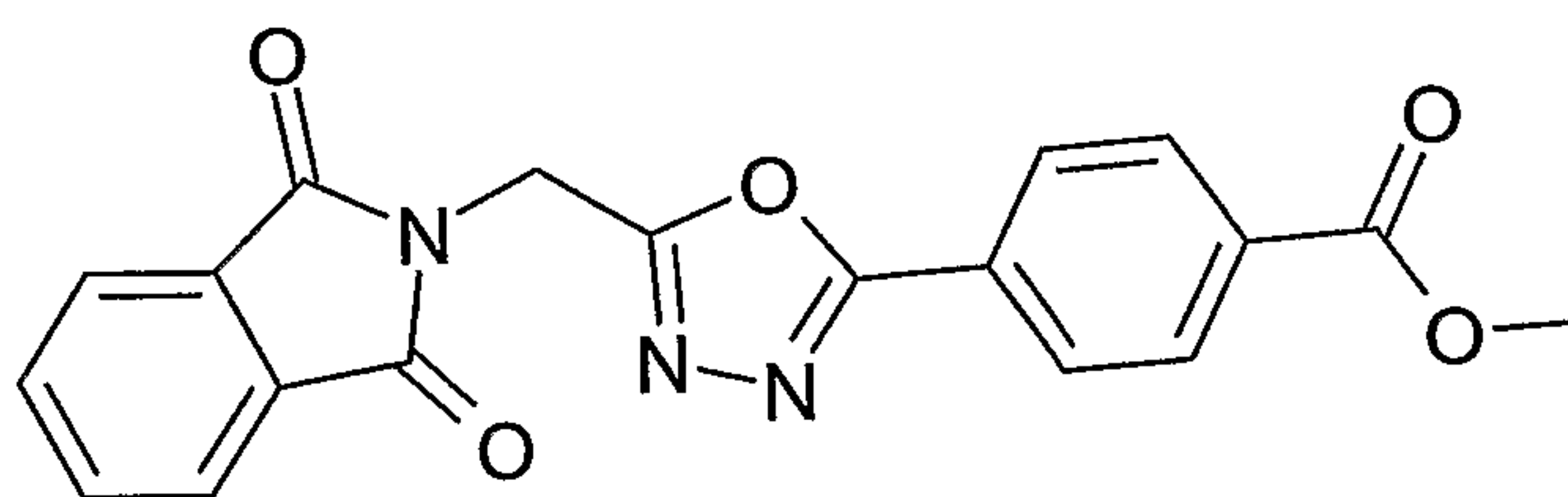


5 Starting from 4-hydrazinocarbonyl-benzoic acid methyl ester and N-phthaloylglycine, this compound was prepared in 69% yield in a similar manner as exemplified in example 165 d.

¹H NMR (DMSO-d₆) δ 10.66(s, 1H), 10.45 (s, 1H), 8.05-8.03 (m, 2H), 7.96-7.91 (m, 4H), 7.88-7.85 (m, 2H), 4.34 (s, 2H), 3.86 (s, 3H) MS (ES) m/e 382.

10

b) 4-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester



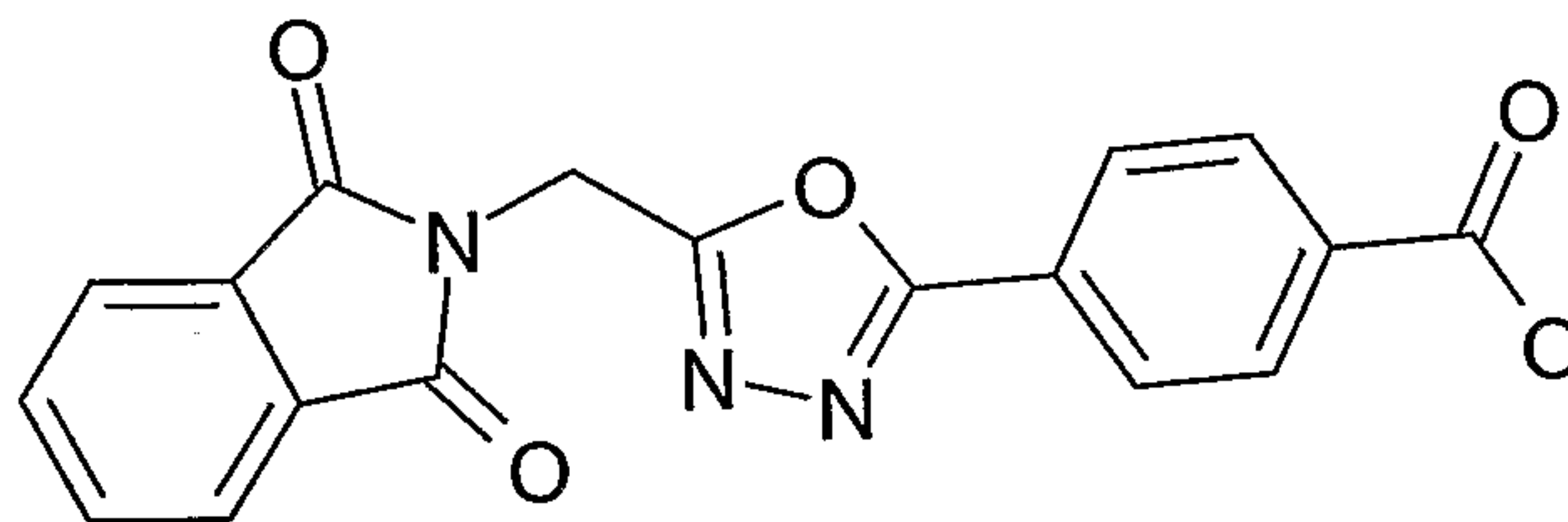
15 4-{N'-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetyl]-hydrazinocarbonyl}-benzoic acid methyl ester (5 g, 13.11 mmol) was mixed with 100 mL SOCl₂ and refluxed over night. Concentration under vacuum gave a solid which was triturated with MeOH to recover 3 g (8.3 mmol, 63%) of the product as a white solid.

¹H NMR (DMSO-d₆) δ 8.14-8.07 (m, 4H), 7.96-7.94 (m, 2H), 7.93-7.87 (m, 2H), 5.15 (s, 2H), 3.87 (s, 3H).

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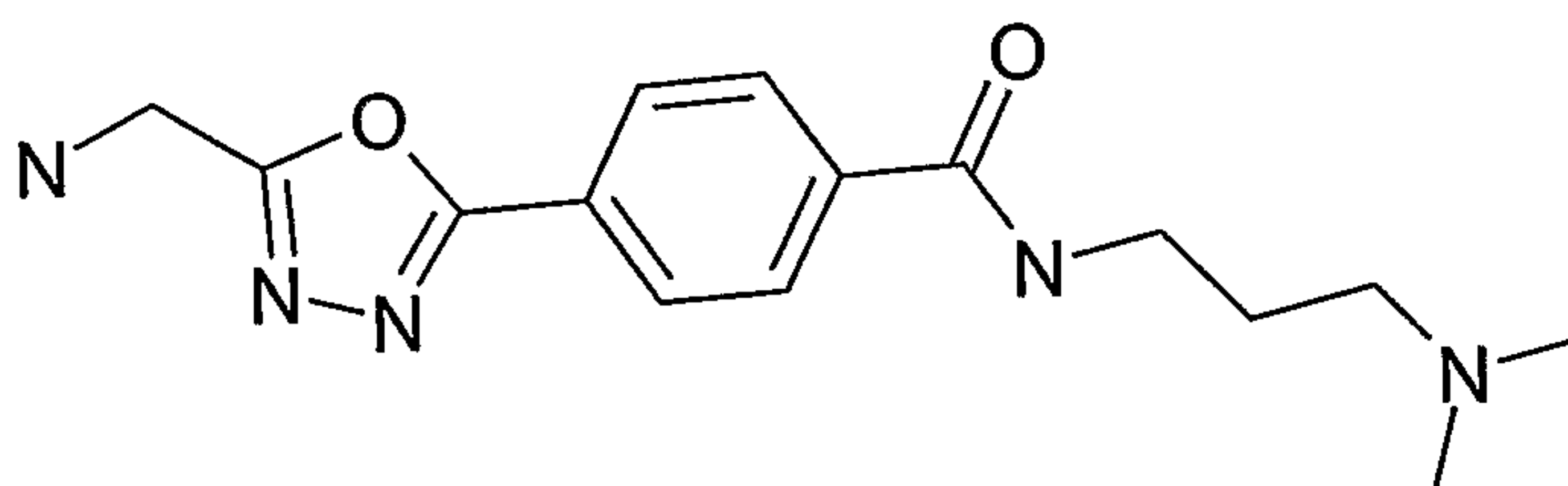
- c) 4-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



A mixture of 4-[5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,3,4]oxadiazol-
 5 2-yl]-benzoic acid methyl ester (6 g, 16.5 mmol), thiophenol (3.6 g, 33 mmol), Potassium
 fluoride (1.9 g, 33 mmol) and N-methylpyrrolidinone (60 mL) was heated in a sealed tube
 at 180°C for 60 hours. The reaction was poured into 200 mL brine, diluted with 40 mL
 5N HCl and extracted 3 times with 200 mL EtOAc. The combined extracts was dried over
 MgSO₄ and concentrated to dryness under vacuum. The residue was mixed with 50 mL
 10 CHCl₃ and filtered to recover 3.5 g solid.

¹H NMR (DMSO-d₆) δ 12.0 (t, 1H), 8.1-8.0 (m, 2H), 7.95-7.85 (m, 2H), 7.8-7.7
 (m, 1H), 7.6-7.5 (m, 1H), 7.4-7.3 (m, 2H), 7.7-7.8 (m, 2H). MS (ES) m/e 350.

- d) 4-(5-Aminomethyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylamino-propyl)-
 15 benzamide



A mixture of 4-[5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,3,4]oxadiazol-
 2-yl]-benzoic acid (4 g, 11.45 mmol), 3-dimethylaminopropyl amine (1.4 g, 13.7 mmol)
 and triethylamine (2.3 g, 22.9 mmol) in 100 mL dry DMF was cooled to 0°C and treated
 20 with dicyclohexylcarbodiimide (2.8 g, 13.7 mmol) and hydroxy benzotriazole (1.86 g,
 13.7 mmol). The cooling bath was removed and the reaction was stirred for 2 hours before
 adding an additional 1 g (4.8 mmol) of dicyclohexylcarbodiimide. After stirring an
 additional 18 hours it was concentrated to dryness under vacuum, mixed with 250 mL
 CHCl₃ and filtered. The filtrate was purified by 2 chromatographies on silica using

-333-

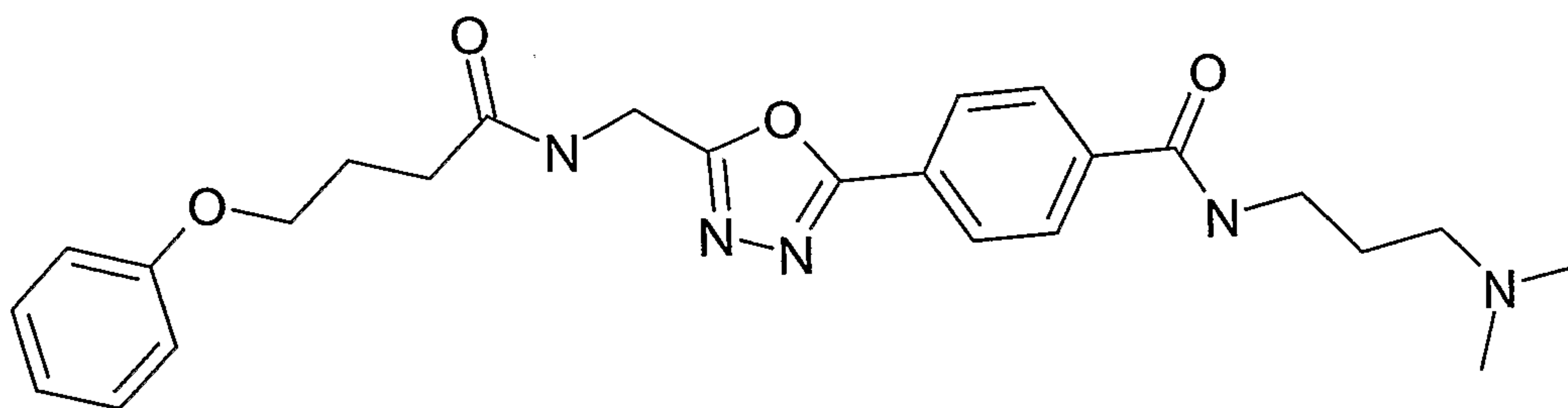
CHCl₃ and MeOH then THF, Hexanes and triethylamine to give 2 g of a solid. This was further purified using an ion exchange column to recover 1.7 g of an oil.

The above oil was dissolved in 50 mL EtOH and treated with 1 mL hydrazine monohydrate. After refluxing for 15 minutes, the reaction was concentrated to dryness, mixed with 30 mL MeOH and filtered. The filtrate was purified by ion exchange chromatography to recover 1.2 g of a solid.

¹H NMR (CDCl₃) δ 8.75-8.65 (m, 1H), 8.10-8.0 (m, 4H), 3.95 (s, 2H), 3.3-3.25 (m, 4H), 2.3-2.25 (m, 2H), 2.15 (s, 6H), 1.7-1.6 (m, 2H).

Anal. Calcd for C₁₅H₂₁N₅O₂: C, 59.39; H, 6.98; N, 23.01. Found C, 59.11; H, 7.04; N, 22.78. MS (ES) m/e 304

e) N-(3-Dimethylamino-propyl)-4-{5-[(4-phenoxy-butyrylamino)-methyl]-[1,3,4]oxadiazol-2-yl}-benzamide



A mixture of the 4-(5-aminomethyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylamino-propyl)-benzamide (150 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (147 mg, 0.74 mmol), 3-phenoxybutyric acid (133 mg, 0.74 mmol) and triethylamine (200 mg, 2 mmol) in 20 mL dry DMF was stirred for 4 hours. Concentrated to an oil under vacuum, mixed with CHCl₃ and purified by chromatography on silica using a mixture of CHCl₃, MeOH and ammonium hydroxide to recover 78 mg (.17 mmol, 33%) of a white solid. MS (ES) m/e 304

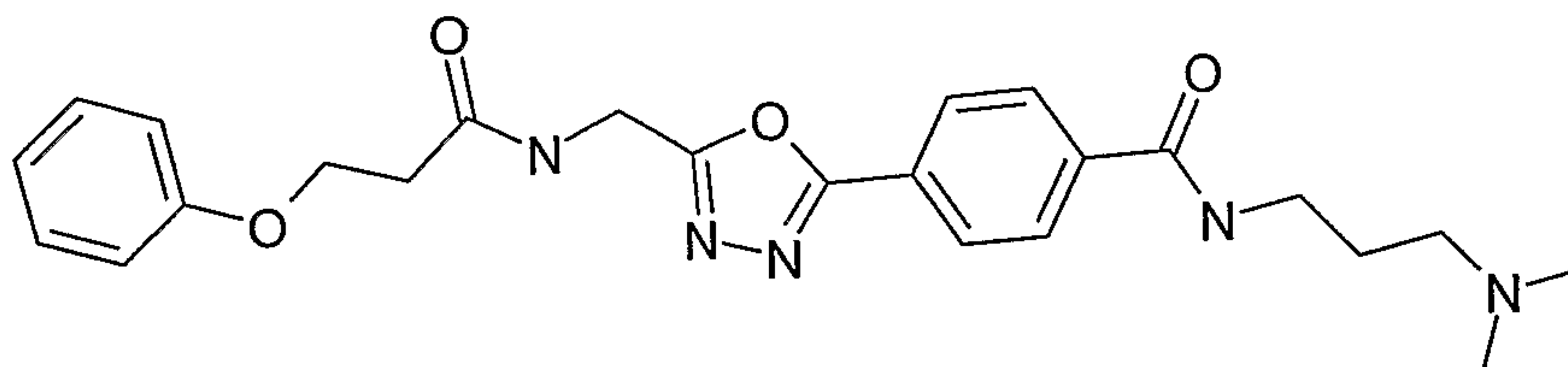
¹H NMR (CDCl₃) δ 8.92 (s, 1H), 8.03-8.01 (m, 2H), 7.84-7.82 (m, 2H), 7.27-7.23 (m, 2H), 6.94-6.86 (m, 3H), 6.63-6.60 (m, 1H), 4.77-4.75 (m, 2H), 4.05-4.02 (m, 2H), 3.60-3.56 (m, 2H), 2.56-2.51 (m, 4H), 2.30 (s, 6H), 2.22-2.15 (m, 2H), 1.8-1.74 (m, 2H).

Anal. Calcd for C₂₅H₃₁N₅O₄: C, 64.50; H, 6.73; N, 15.22. Found C, 64.50; H, 6.71; N, 15.04.

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Example 167

Preparation of N-(3-Dimethylamino-propyl)-4-{5-[(3-phenoxy-propionylamino)-methyl]-[1,3,4]oxadiazol-2-yl}-benzamide



5 Starting from 3-phenoxy propionic acid and 4-(5-aminomethyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylamino-propyl)-benzamide this compound was prepared in 13% yield using the procedure exemplified in Example 166 e.

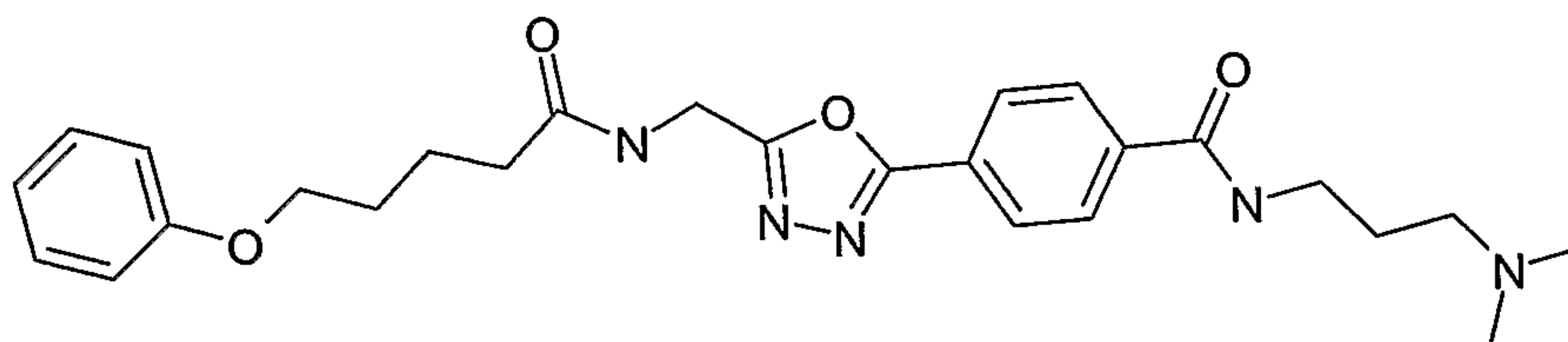
MS (ES) m/e 452

10 ^1H NMR (CDCl_3) δ 8.92 (s, 1H), 8.03-8.01 (m, 2H), 7.84-7.82 (m, 2H), 7.29-7.25 (m, 2H), 6.98-6.90 (m, 4H), 4.81-4.79 (m, 2H), 4.32-4.30 (m, 2H), 3.59-3.48 (m, 2H), 2.82-2.79 (m, 2H), 2.54-2.51 (m, 2H), 2.31 (s, 6H), 1.80-1.74 (m, 2H). Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_4 \cdot 0.2\text{C}_4\text{H}_{10}\text{O} \cdot 0.5\text{H}_2\text{O}$: C, 62.59; H, 6.57; N, 15.21. Found C, 62.93; H, 6.27; N, 15.23.

15

Example 168

Preparation of N-(3-Dimethylamino-propyl)-4-{5-[(5-phenoxy-pentanoylamino)-methyl]-[1,3,4]oxadiazol-2-yl}-benzamide



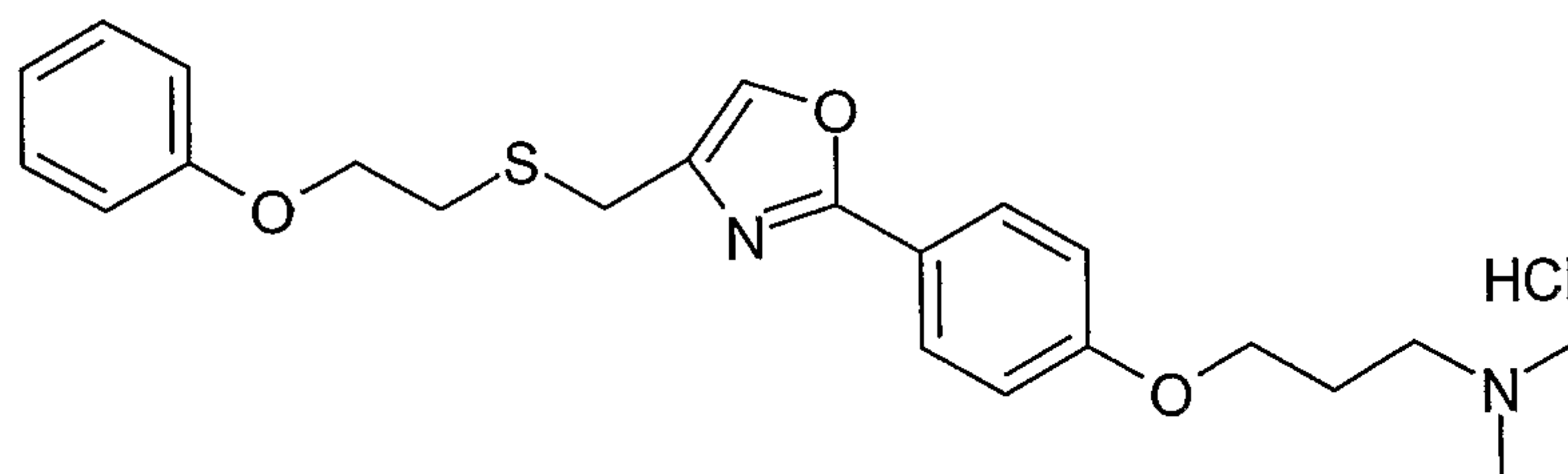
20 Starting from 3-phenoxy butyric acid and 4-(5-aminomethyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylamino-propyl)-benzamide this compound was prepared in 22 % yield using the procedure procedure exemplified in Example 166 e.

MS (ES) m/e 480. ^1H NMR (CDCl_3) δ 8.92 (s, 1H), 8.04-8.02 (m, 2H), 7.84-7.82 (m, 2H), 7.28-7.23 (m, 2H), 6.94-6.85 (m, 3H), 6.57 (s, 1H), 4.76-4.75 (m, 2H), 4.00-3.97 (m, 2H), 3.60-3.56 (m, 2H), 2.54-2.51 (m, 2H), 2.43-2.40 (m, 2H), 2.30 (s, 6H), 1.92-1.84 (m, 4H), 1.80-1.74 (m, 2H). Anal. Calcd for $\text{C}_{26}\text{H}_{33}\text{N}_5\text{O}_4 \cdot 0.2\text{H}_2\text{O}$: C, 64.63; H, 6.96; N, 14.50. Found C, 64.37; H, 6.76; N, 14.41.

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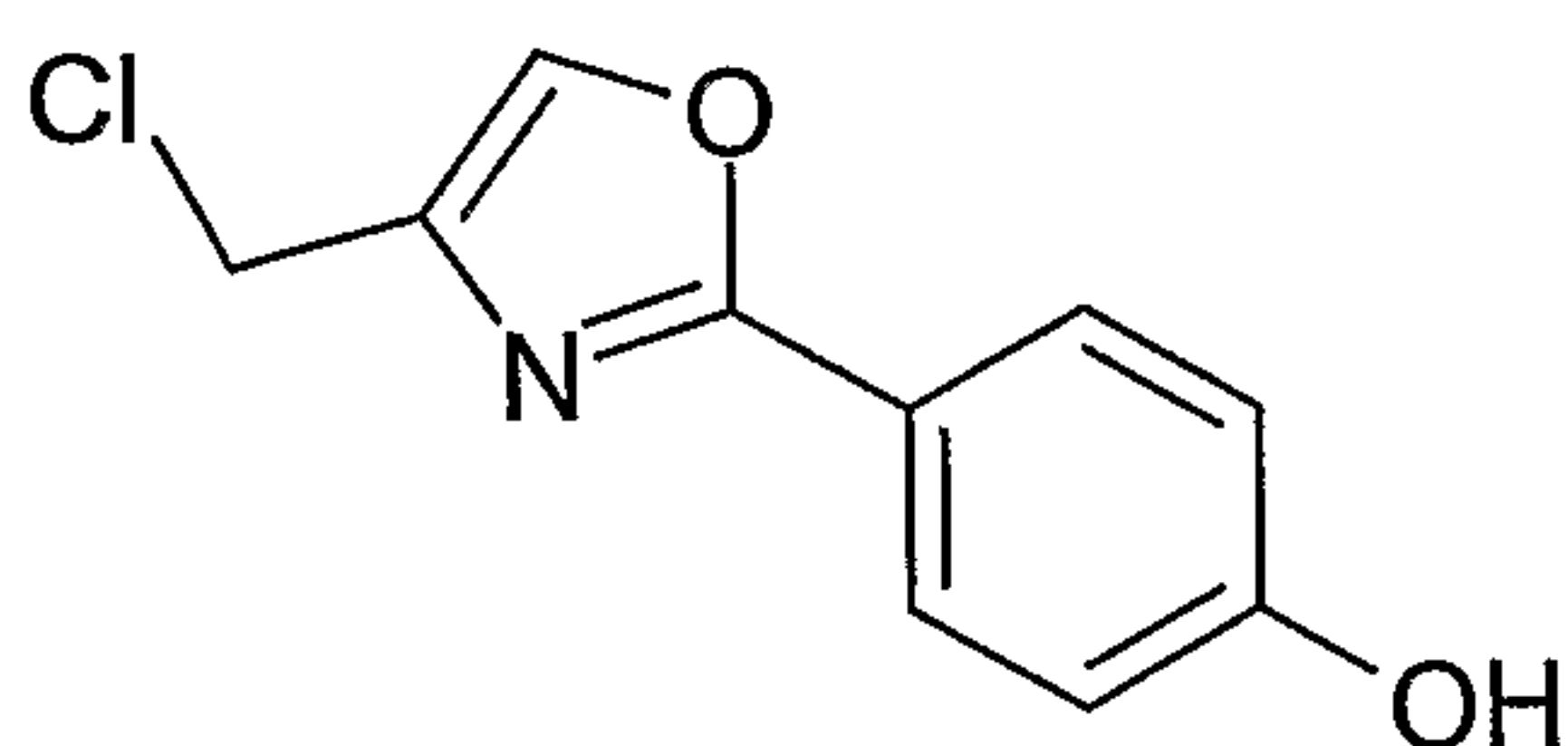
EXAMPLE 169

Preparation of Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenoxy}-propyl)-amine Hydrochloride



5

a) 4-(4-Chloromethyl-oxazol-2-yl)-phenol



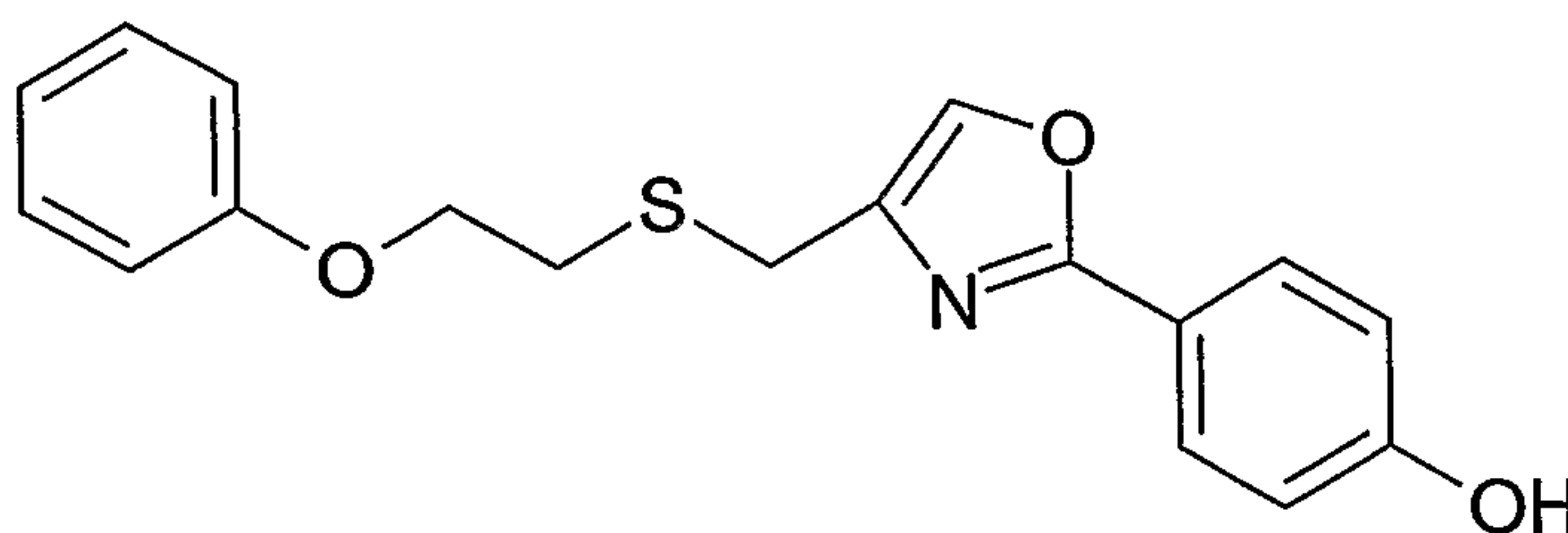
A solution of 4-hydroxy-benzamide (3.20 g, 23.33 mmol) and 1,3-dichloro acetone (5.93 g, 46.66 mmol) in 40 mL dimethylformamide was warmed to 120°C for 4 h. The reaction mixture was allowed to cool to room temperature and poured into 50 g of ice/water. The resulting precipitate was filtered and dried in vacuo to afford 3.98 g (82%) 2-(4-hydroxyphenyl)-4-chloromethyl-oxazole as a white solid.

10

^1H NMR (DMSO- D_6 , 300 MHz): δ 10.12 (s, 1H), 8.15 (s, 1H), 7.81 (d, 2H, $J=9$ Hz), 6.89 (d, 2H, $J=9$ Hz), 4.70 (s, 2H). MS (MH^+) 210.

15

b) 4-[4-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenol



A solution of sodium hydride (200 mg, 8.34 mmol) in ethanol (47 mL) was treated with 2-phenoxy-ethanethiol (1.17 g, 7.59 mmol) in 5 mL ethanol at room temperature and stirred for 10 minutes. 4-(4-Chloromethyl-oxazol-2-yl)-phenol (1.99 g, 9.48 mmol) was added and stirring was continued for 16 hours. The solvent was evaporated in vacuo and

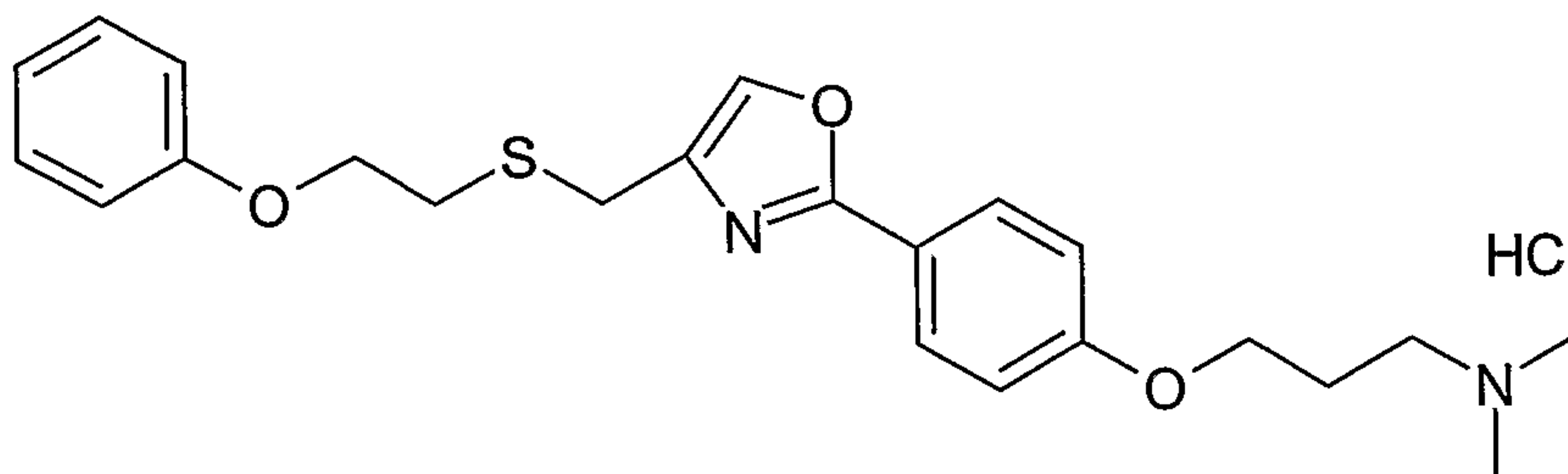
20

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the remains were poured into 50 mL water. The precipitate was filtered and dried in vacuo. The solid was stirred in 8 mL solvent mixture of hexane and tert.-butyl methylether (10 : 1), and dried again in vacuo to afford 2.13 g (86%) 4-[4-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenol as a white solid.

5 ^1H NMR (DMSO- D_6 , 300 MHz): δ 10.18 (br s, 1H), 7.95 (s, 1H), 7.78 (d, 2H, $J=9$ Hz), 7.27 (d, 2H, $J=12$ Hz), 6.96 - 6.85 (m, 5H), 4.17 (t, 2H, $J=7$ Hz), 3.76 (s, 2H), 2.92 (t, 2H, $J=7$ Hz). MS (MH^+) 328.

c) Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenoxy}-
10 propyl)-amine Hydrochloride



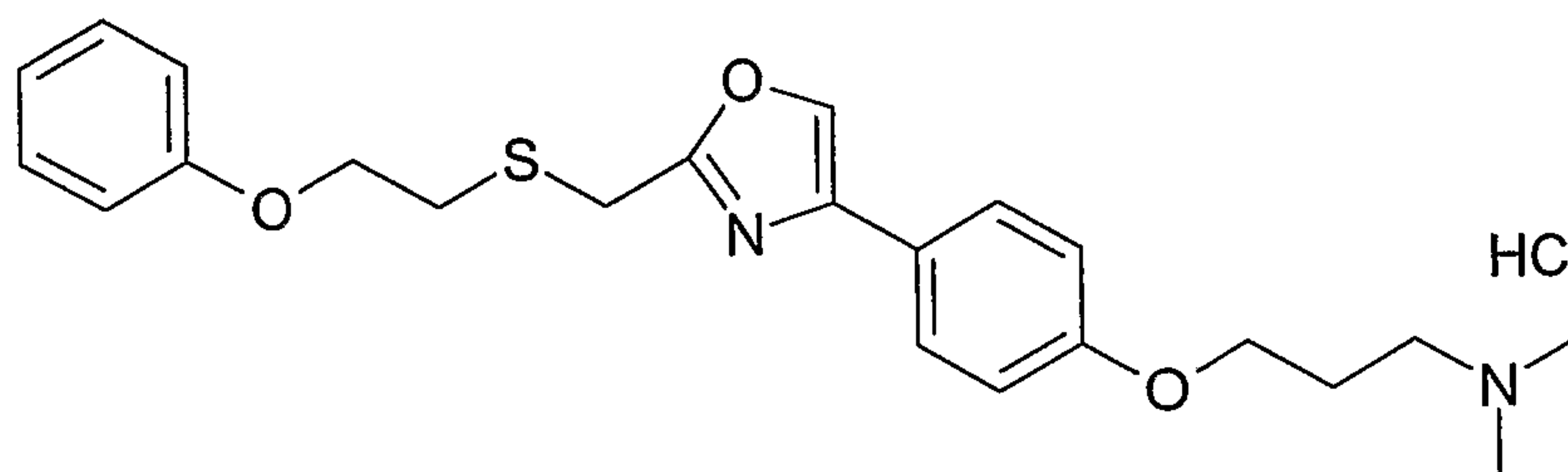
A suspension of 4-[4-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenol (524 mg, 1.60 mmol), dimethyl 3-chloro-propyl-amine hydrochloride (304 mg, 1.92 mmol), and potassium carbonate (531 mg, 3.84 mmol) in dimethylformamide (20 mL) was heated
15 at 80°C for 14 hours. The solvent was removed in vacuo and the remains partitioned between water and methylene chloride. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride/ethanol containing 10% ammonia) to afford a white solid. The solid was dissolved in 10 mL dioxane and treated with 0.1 mL 4M HCl in
20 dioxane and stirred for 10 minutes. Ether was added and the precipitation filtered and dried in vacuo to afford 204 mg (28%) of dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenoxy}-propyl)-amine as a white solid.

^1H NMR (DMSO- D_6 , 300 MHz): δ 10.42 (br s, 1H), 8.01 (s, 1H), 7.90 (d, 2H, $J=9$ Hz), 7.28 (t, 2H, $J=8$ Hz), 7.09 (d, 2H, $J=9$ Hz), 6.99 - 6.88 (m, 3H), 4.22 - 4.10 (m, 4H), 3.78 (s, 2H), 3.26 - 3.17 (m, 2H), 2.93 (t, 2H, $J=7$ Hz), 2.79 (s, 3H), 2.78 (s, 3H),
25 2.23 - 2.12 (m, 2H). MS (MH^+) 413.

-337-

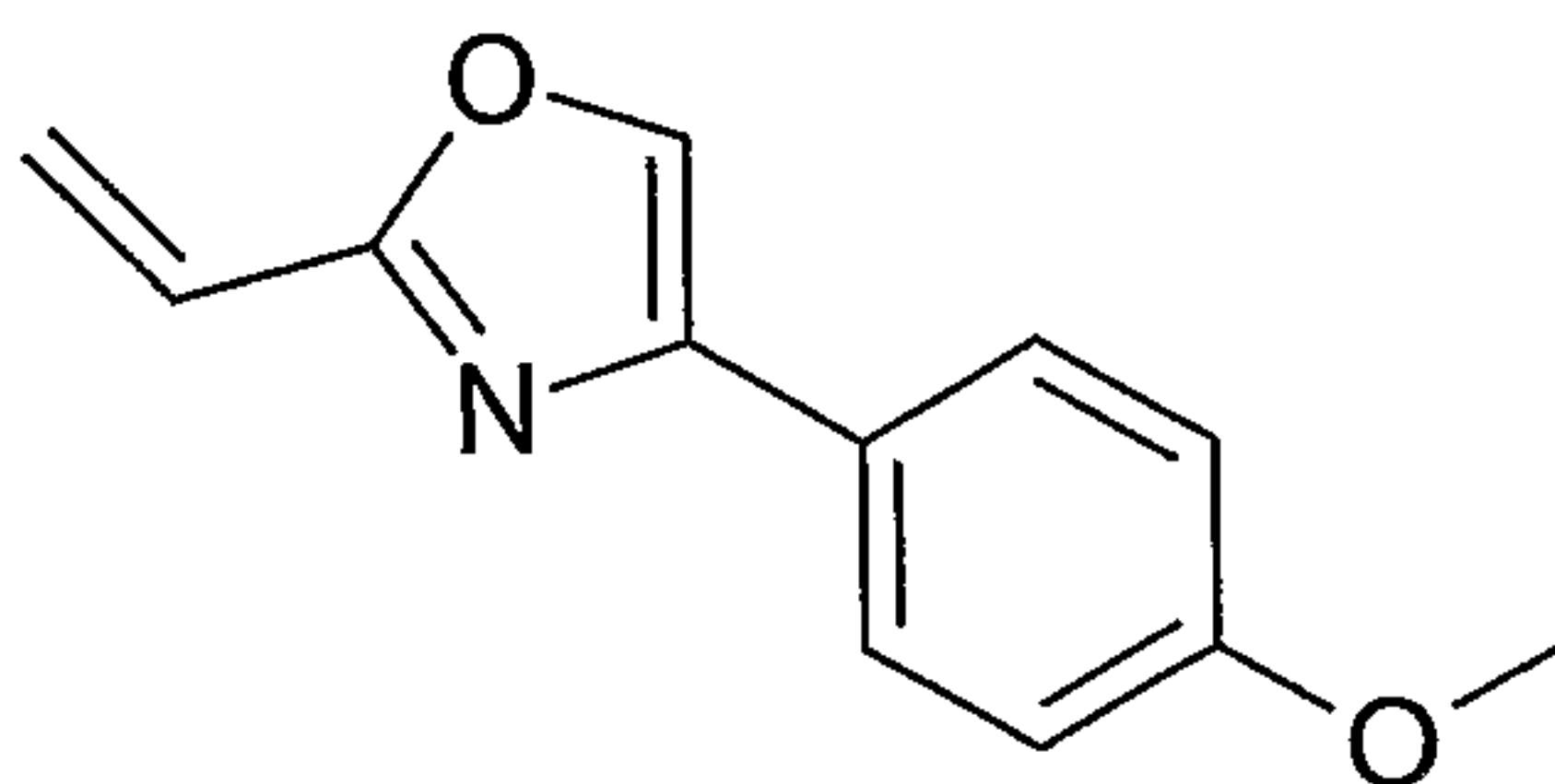
EXAMPLE 170

Preparation of Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-4-yl]-phenoxy}-propyl)-amine



5

a) 4-(4-Methoxy-phenyl)-2-vinyl-oxazole



10

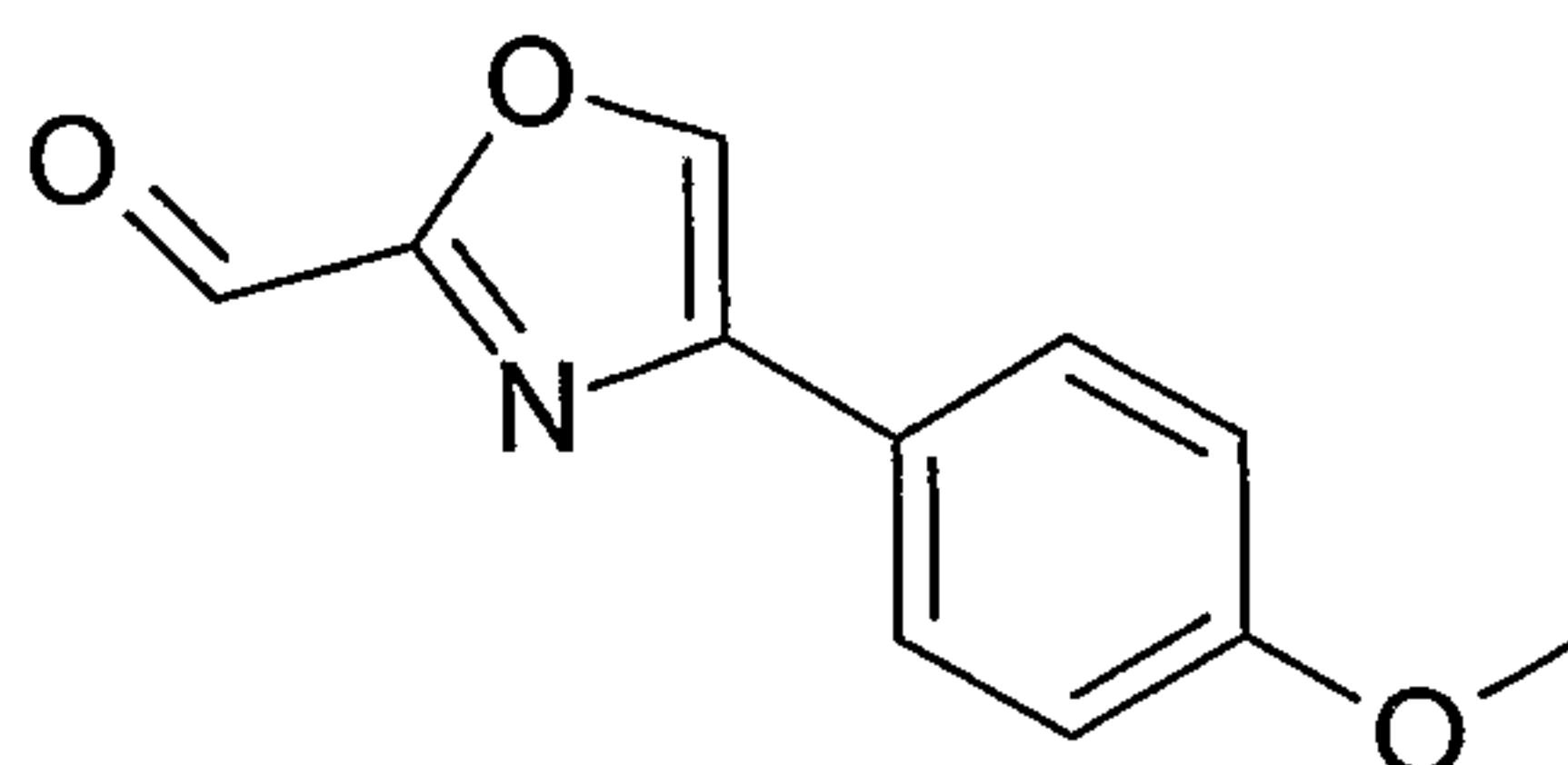
A solution of ω -bromo acetophenone (11.93 g, 52.08 mmol), 2,6 di-tert.-butyl-4-methyl-phenol as a stabilizer (1.15 g, 5.21 mmol), and acryl amide (7.40 g, 104.16 mmol) were dissolved in 360 mL dimethylformamide and heated at 150°C for 4 hours. The solvent was evaporated and the remaining oil dissolved in 200 mL ethyl acetate and washed with 150 mL water. The organic layer was dried over sodium sulfate and evaporated and the remaining oil purified by chromatography on silica gel (elution with gradient hexane/ethyl acetate) to afford 5.59 g (53%) of 4-(4-methoxy-phenyl)-2-vinyl-oxazole as a white solid.

15

^1H NMR (CDCl_3 , 300 MHz): δ 7.76 (s, 1H), 7.67 (d, 2H, $J=9$ Hz), 6.94 (d, 2H, $J=9$ Hz), 6.65 (dd, 1H, $J=18$ Hz, $J=11$ Hz), 6.22 (d, 1H, $J=18$ Hz), 5.65 (d, 1H, $J=11$ Hz), 3.34 (s, 3H). MS (MH^+) 202.

20

b) 4-(4-Methoxy-phenyl)-oxazole-2-carbaldehyde

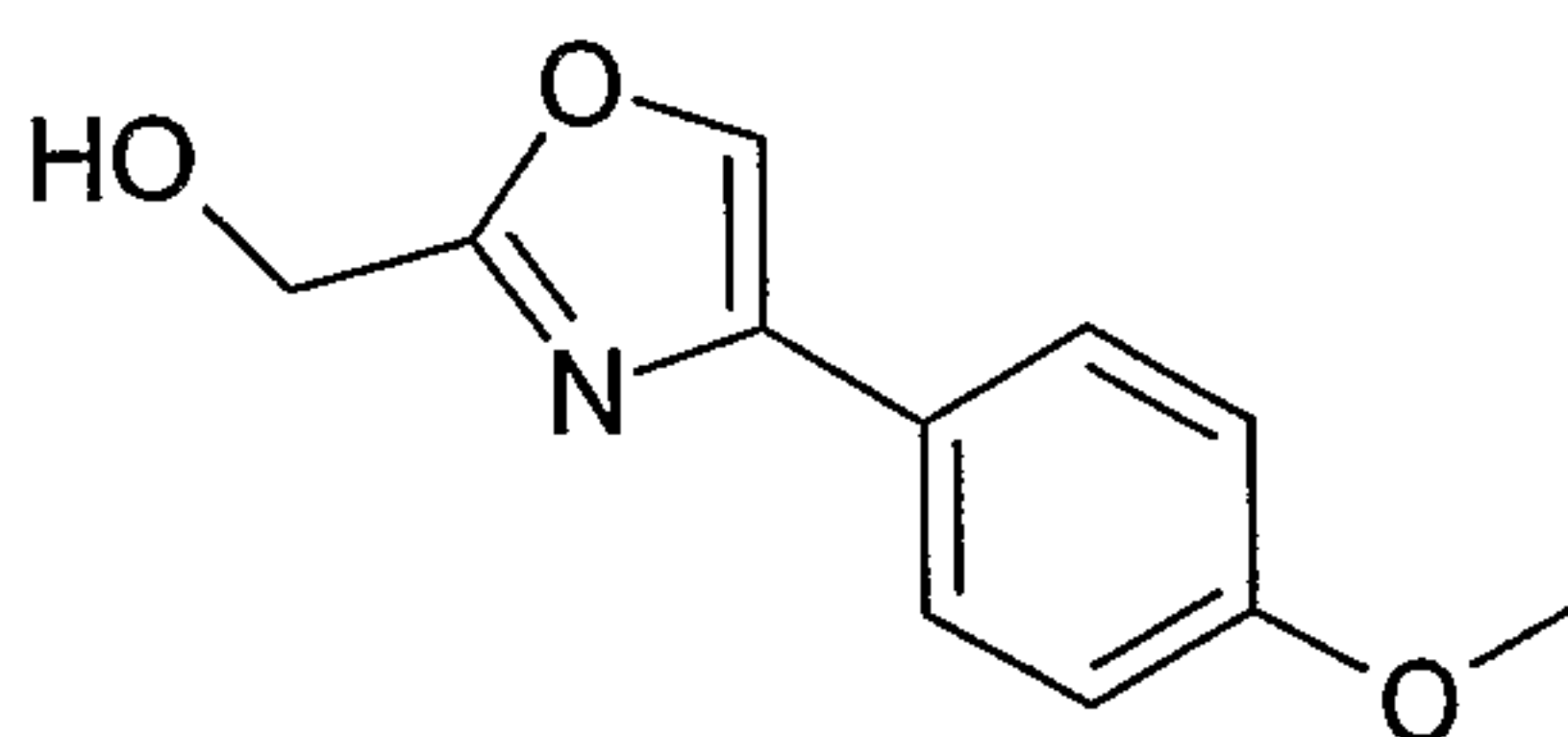


-338-

A solution of 4-(4-methoxy-phenyl)-2-vinyl-oxazole (3.06 g, 15.21 mmol), N-methyl-morpholine N-oxide (2.16 g, 15.97 mmol), hydroquinidine-(1,4-phthalazindiyl-diether) (116 mg, 1.49 mmol) in 70 mL acetone : water (4 : 1) was treated with 4 mL of 0.079 M aqueous osmium tetroxide solution and was stirred at room temperature for 4 hours. The solvent was evaporated in vacuo and remaining oil was dissolved in 150 mL methylene chloride and washed with 50 mL 10 % aqueous sodium sulfite solution. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was dissolved in 50 mL tert.-butyl methylether and 50 mL water and treated with sodium metaperiodate and stirred for 4 hours. The organic layer was then separated, dried over sodium sulfate and evaporated to afford 1.5 g (49%) of 4-(4-methoxy-phenyl)-oxazole-2-carbaldehyde as a colourless oil.

^1H NMR (CDCl_3 , 300 MHz): δ 9.82 (s, 1H), 8.04 (s, 1H), 7.73 (d, 2H, $J=9$ Hz), 6.98 (d, 2H, $J=9$ Hz), 3.87 (s, 3H). MS (MH^+) 204.

c) [4-(4-Methoxy-phenyl)-oxazol-2-yl]-methanol



15

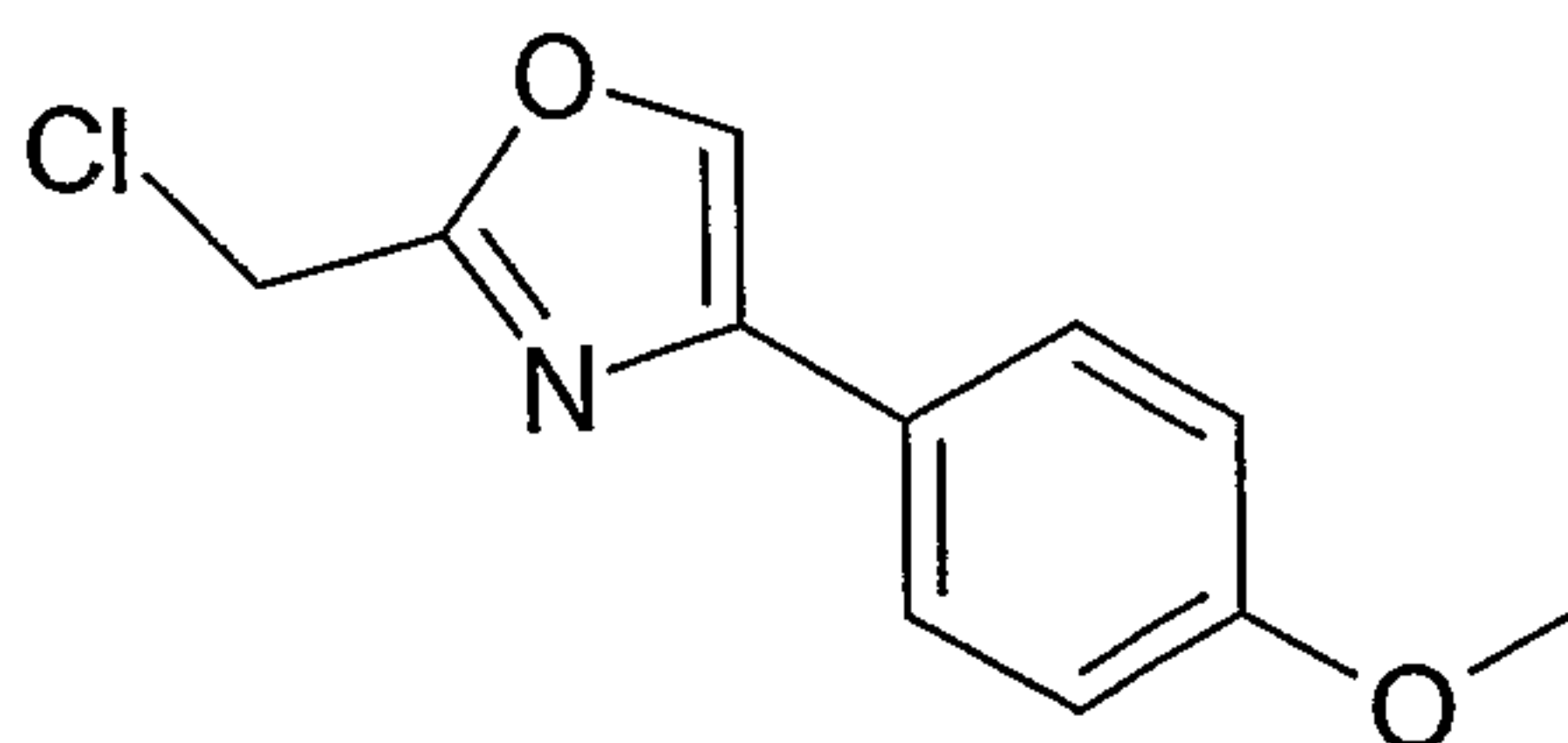
A solution of 4-(4-methoxy-phenyl)-oxazole-2-carbaldehyde (1.27 g, 6.23 mmol) in 50 mL ethanol: water (4 : 1) was treated with sodium borohydride (236 mg, 6.23 mmol) and stirred at room temperature for 30 minutes. The reaction was quenched with 2 mL acetone and evaporated. The remaining oil was dissolved in 75 mL methylene chloride and washed with 50 mL water. The organic layer was dried over sodium sulfate and evaporated and the remaining oil purified by chromatography on silica gel (elution with gradient hexane/ethyl acetate) to afford 1.17 g (92%) [4-(4-methoxy-phenyl)-oxazol-2-yl]-methanol as white crystals.

^1H NMR (CDCl_3 , 300 MHz): δ 7.78 (s, 1H), 7.63 (d, 2H, $J=9$ Hz), 6.93 (d, 2H, $J=9$ Hz), 4.77 (s, 2H), 3.83 (s, 3H). MS (MH^+) 206.

25

d) 2-Chloromethyl-4-(4-methoxy-phenyl)-oxazole

-339-

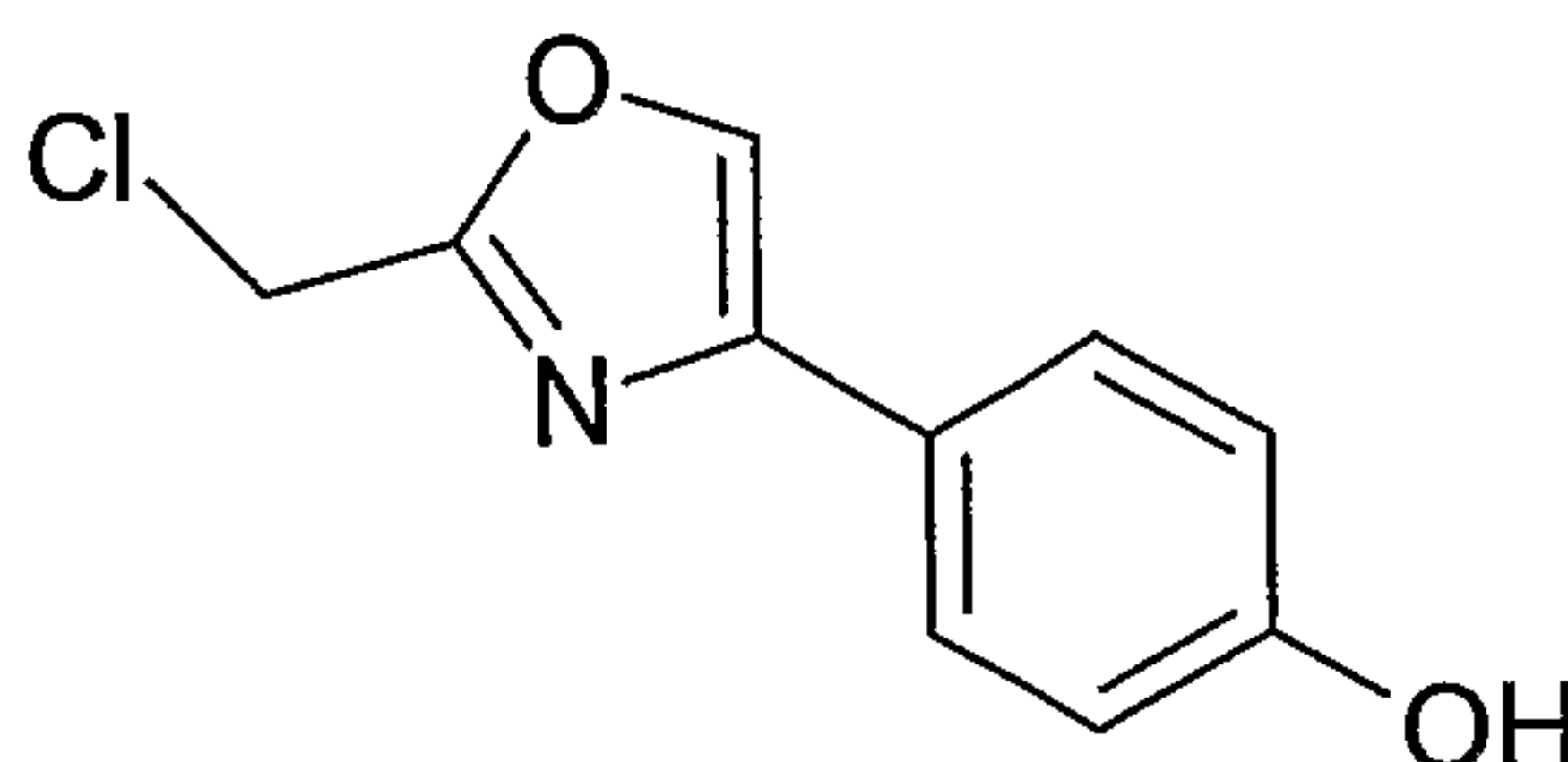


A solution of [4-(4-methoxy-phenyl)-oxazol-2-yl]-methanol (861 mg, 4.2 mmol) in 10 mL carbon tetrachloride was treated with triphenylphosphine (1.18 g, 4.49 mmol) and heated at 80°C for 7 hours. The solvent was evaporated and the remaining yellow solid purified by chromatography on silica gel (elution with gradient methylene chloride /ethanol) to afford 769 mg (82%) 2-chloromethyl-4-(4-methoxy-phenyl)-oxazole as yellow crystals.

¹H NMR (CDCl₃, 300 MHz): δ 7.83 (s, 1H), 7.65 (d, 2H, J=9 Hz), 6.94 (d, 2H, J=9 Hz), 4.65 (s, 2H), 3.85 (s, 3H). MS (MH⁺) 224.

10

e) 4-(2-Chloromethyl-oxazol-4-yl)-phenol



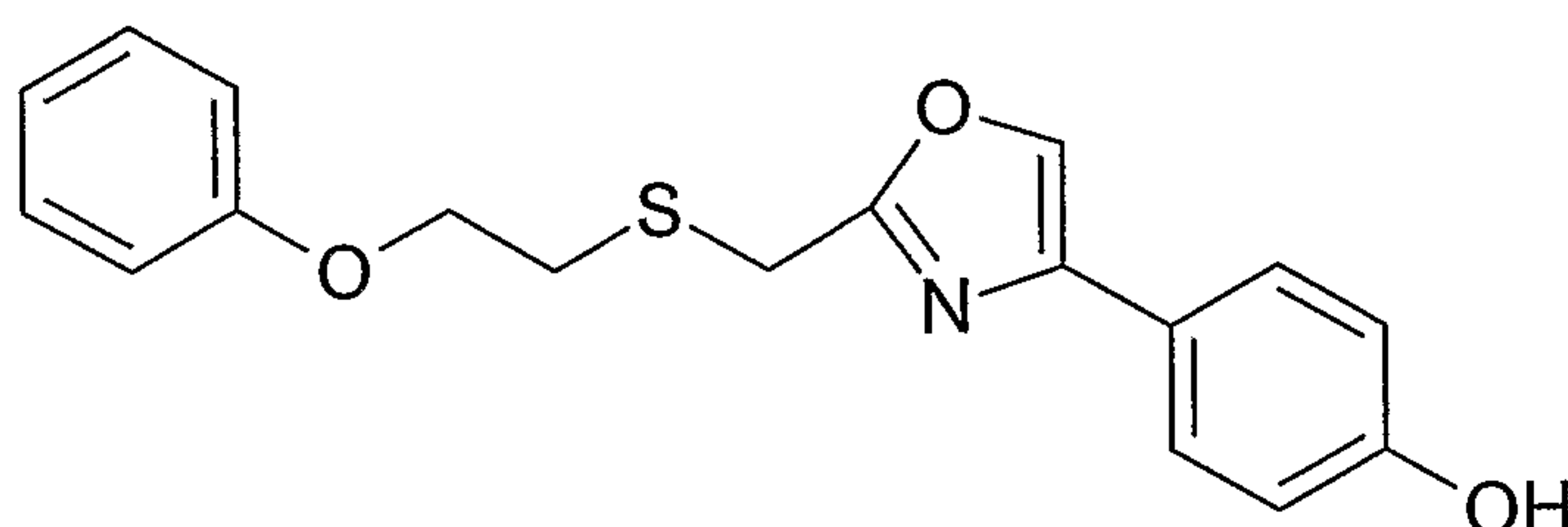
2-Chloromethyl-4-(4-methoxy-phenyl)-oxazole (753 mg, 3.37 mmol) was dissolved in 20 mL methylene chloride, cooled to -70°C and treated with 6.74 ml 1M boron tribromide solution in methylene chloride. Within 2 hours the reaction mixture was allowed to warm to room temperature and quenched with 15 mL saturated aqueous sodium bicarbonate solution. The organic layer was washed with 10 mL 2M hydrochloric acid, dried over sodium sulfate and evaporated to afford 682 mg (97%) 4-(2-chloromethyl-oxazol-4-yl)-phenol as a white solid.

¹H NMR (CDCl₃) δ 7.83 (s, 1H), 7.59 (d, 2H, J=9 Hz), 6.87 (d, 2H, J=9 Hz), 5.42 (br S, 1H), 4.65 (s, 2H). MS (MH⁺) 210.

20

f) 4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-4-yl]-phenol

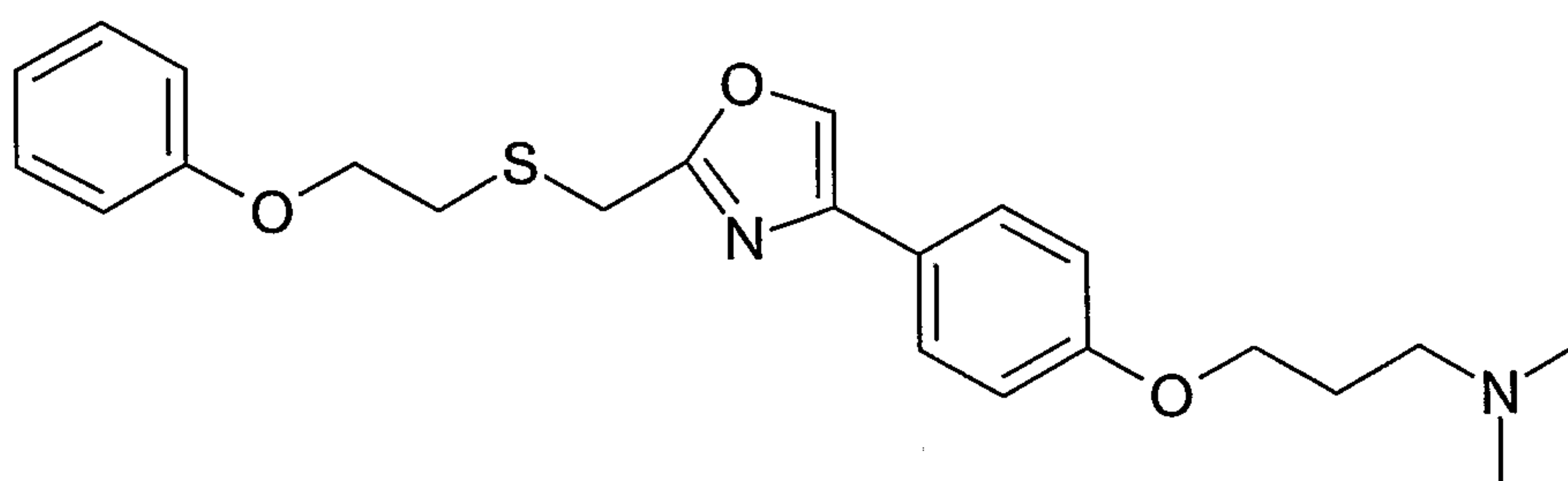
-340-



A solution of sodium hydride (82 mg, 3.42 mmol) in 3 mL ethanol was treated with 2-phenoxy-ethanethiol (502 mg, 3.25 mmol) in 2 mL ethanol at room temperature and stirred for 10 minutes. 4-(2-Chloromethyl-oxazol-4-yl)-phenol (682 mg, 3.25 mmol) was added and stirring was continued for 72 hours. The solvent was evaporated in vacuo and the remains were poured into 50 mL water. The precipitate was filtered, dried in vacuo to afford 1.02 g (96%) 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-4-yl]-phenol as a white solid.

¹H NMR (CDCl₃, 300 MHz): δ 7.77 (s, 1H), 7.75 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=7 Hz), 6.98 – 6.82 (m, 5H), 4.16 (t, 2H, J=6 Hz), 3.93 (s, 2H), 3.03 (t, 2H, J=6 Hz). MS (MH⁺) 328.

g) Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-4-yl]-phenoxy}-propyl)-amine

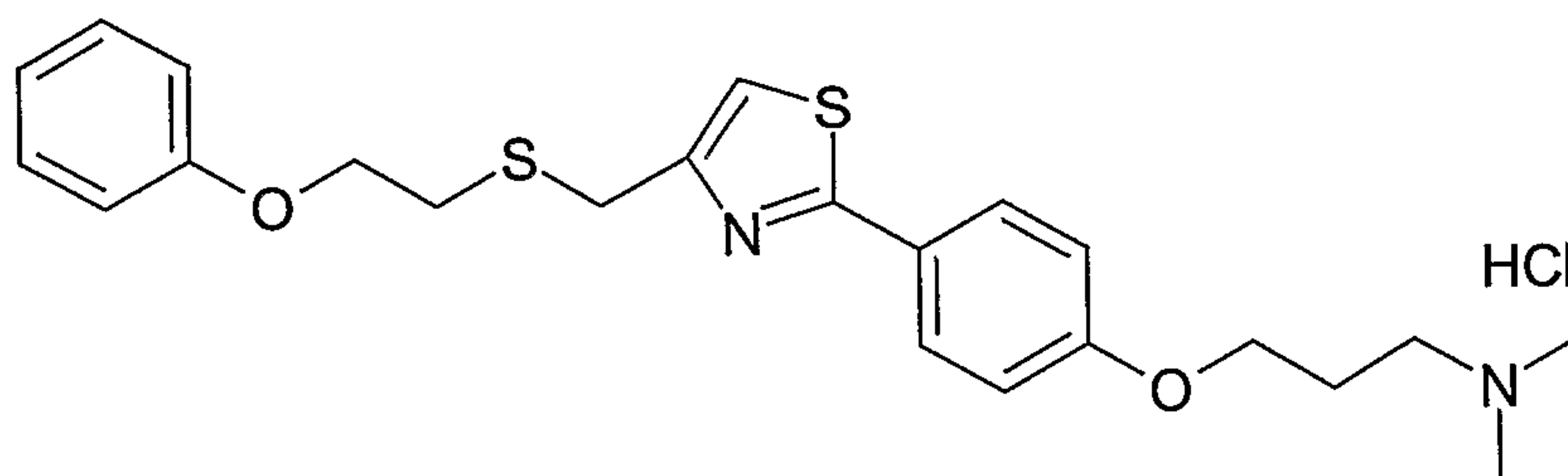


A suspension of 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-4-yl]-phenol (1.00 g, 3.05 mmol), dimethyl 3-chloro-propyl-amine hydrochloride (507 mg, 3.21 mmol), and potassium carbonate (929 mg, 6.72 mmol) in dimethylformamide (20 mL) was heated at 80°C for 24 hours. The solvent was removed in vacuo and the remains partitioned between water and methylene chloride. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride/ethanol containing 10% ammonia) to afford 765 mg (61

%) of dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-4-yl]-phenoxy}-propyl)-amine as white solid.

¹H NMR (CDCl₃, 300 MHz): δ 7.77 (s, 1H), 7.62 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=7 Hz), 6.97 – 6.86 (m, 5H), 4.17 (t, 2H, J=7 Hz), 4.04 (t, 2H, J=7 Hz), 3.93 (s, 2H), 3.04 (t, 2H, J=7 Hz), 2.46 (t, 2H, J=7 Hz), 2.27 (s, 6H), 2.02 – 1.92 (m, 2H). MS (MH⁺) 413.

Preparation of Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenoxy}-propyl)-amine Hydrochloride

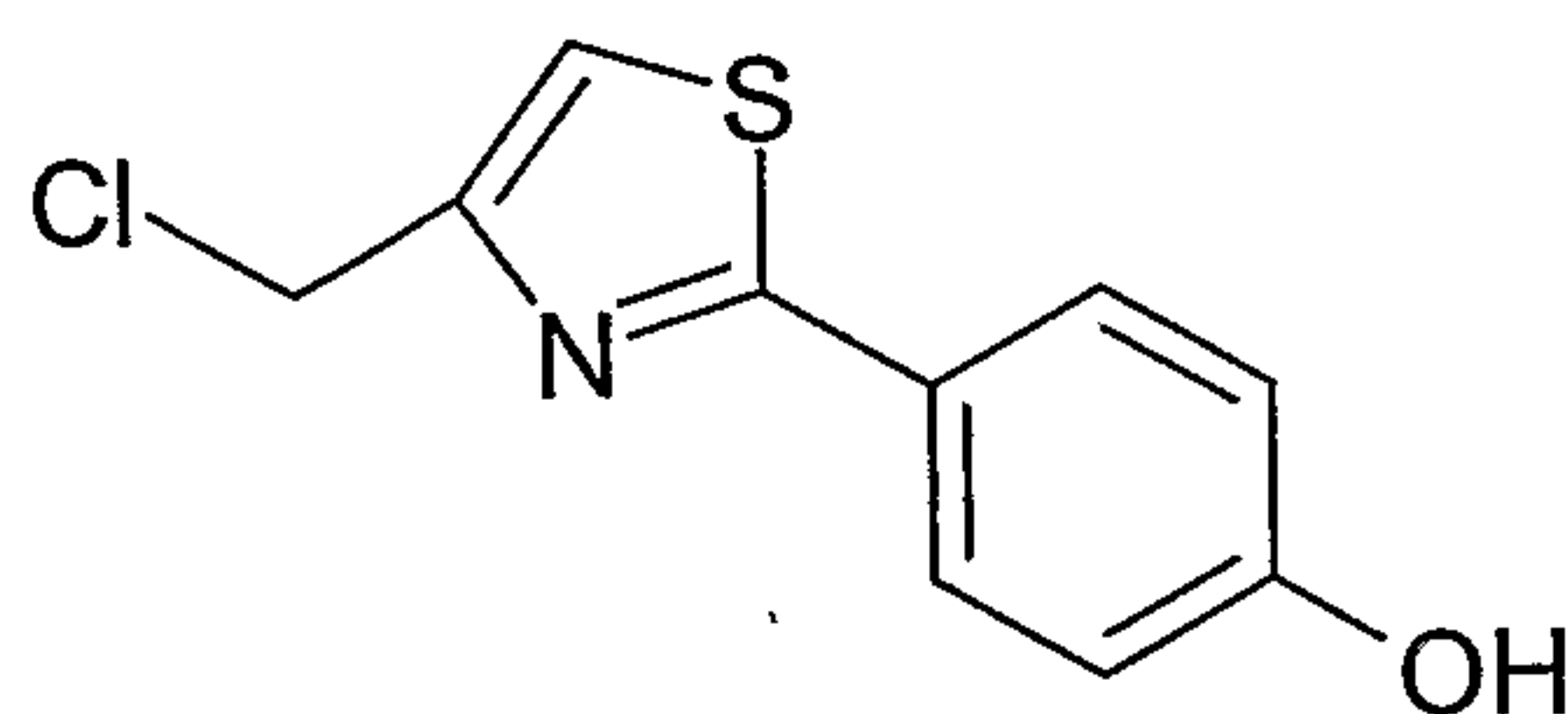
COc1ccc(cc1)c2nc(cc2)CCl

A solution of 4-methoxy-thiobenzamide (1.90 g, 11.33 mmol) and 1,3-dichloroacetone (2.8 g, 22.6 mmol) in 20 mL dimethylformamide was warmed to 100°C for 2 h. The reaction mixture was allowed to cool to room temperature and poured into 30 g of ice/water. The resulting precipitate was filtered and dried in vacuo to afford 1.60 g (59%) 4-chloromethyl-2-(4-methoxy-phenyl)-thiazole as a white solid.

¹H NMR (CDCl₃, 300 MHz): δ 7.88 (d, 2H, J=9 Hz), 7.23 (s, 1H), 6.95 (d, 2H, J=9 Hz), 4.72 (s, 2H), 3.83 (s, 3H). MS (MH⁺) 240.

b) 4-(4-Chloromethyl-thiazol-2-yl)-phenol

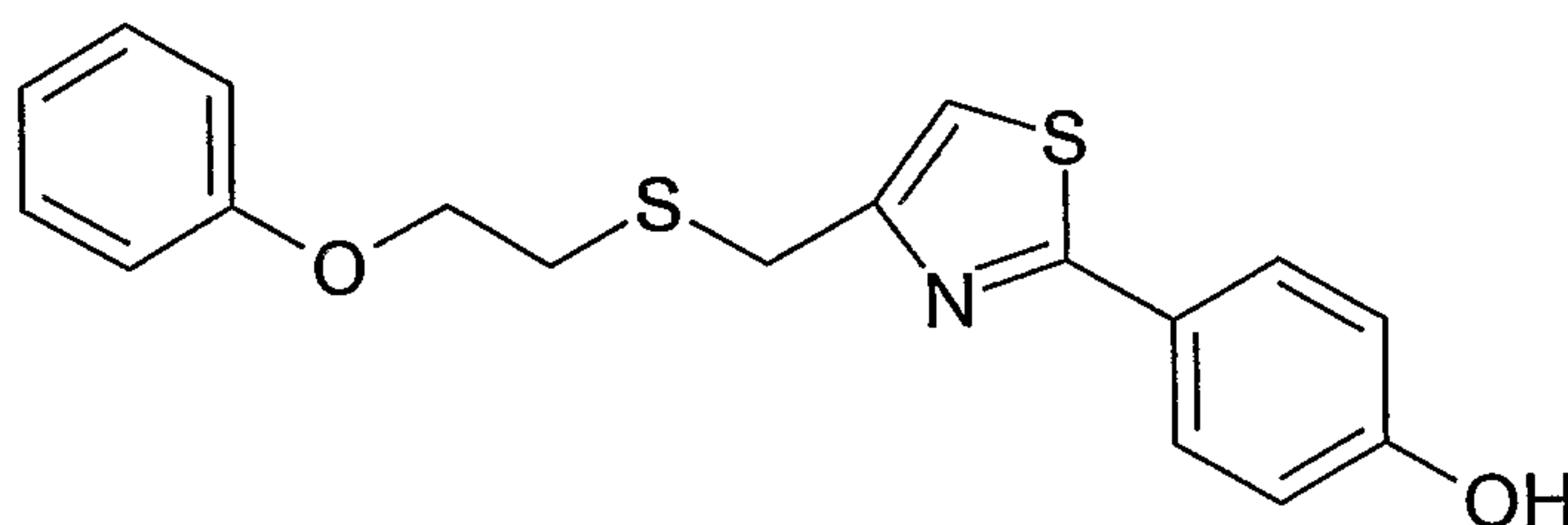
-342-



4-Chloromethyl-2-(4-methoxy-phenyl)-thiazole (1.0 g, 4.17 mmol) was dissolved in 20 mL methylene chloride, cooled to -70°C and treated with 8.34 ml 1M boron tribromide solution in methylene chloride. Within 2 hours the reaction mixture was
5 allowed to warm to room temperature and quenched with 15 mL saturated aqueous sodium bicarbonate solution. The organic layer was washed with 10 mL 2M hydrochloric acid, dried over sodium sulfate and evaporated. The solid was stirred with 5 mL methylene chloride. The remaining solid was dried in vacuo to afford 795 mg (85%) 4-(4-chloromethyl-thiazol-2-yl)-phenol as a white solid.

10 ¹H NMR (DMSO-D₆, 300 MHz): δ 9.80 (br s, 1H), 7.77 (d, 2H, J=9 Hz), 7.67 (s, 1H), 6.87 (d, 2H, J=9 Hz), 4.83 (s, 2H). MS (MH⁺) 226.

c) 4-[4-(2-Phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenol



15

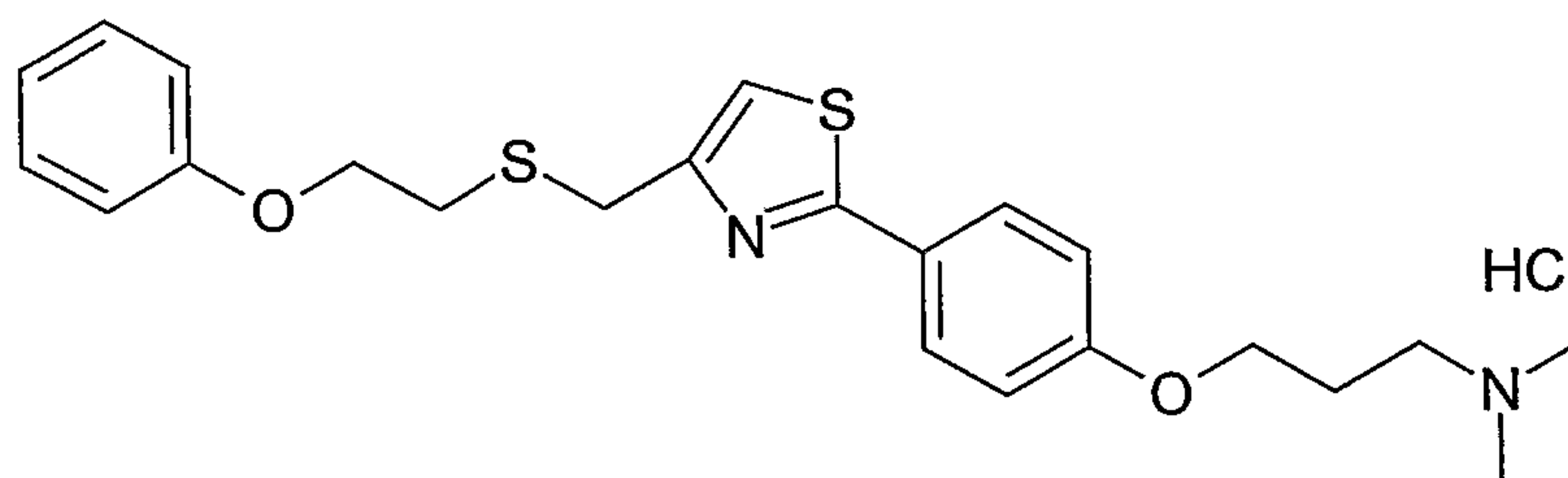
-343-

A solution of sodium hydride (80 mg, 3.34 mmol) in 5 mL ethanol was treated with 2-phenoxy-ethanethiol (490 mg, 3.18 mmol) in 2 mL ethanol at room temperature and stirred for 10 minutes. 4-(4-chloromethyl-thiazol-2-yl)-phenol (790 mg, 3.18 mmol) was added and stirring was continued for 16 hours. The solvent was evaporated in vacuo and the remains were poured into 50 mL water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride/ethanol containing 10% ammonia) to afford 767 mg (70%) 4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenol as a white solid.

¹H NMR (CDCl₃, 300 MHz): δ 7.80 (d, 2H, J=8 Hz), 7.26 (t, 2H, J=9 Hz), 7.07 (s, 1H), 6.98 – 6.80 (m, 5H), 5.69 (s, 1H), 4.18 (t, 2H, J=7 Hz), 3.99 (s, 2H), 2.96 (t, 2H, J=7 Hz).

MS (MH⁺) 344.

d) Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenoxy}-propyl)-amine Hydrochloride



A suspension of 4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenol (751 mg, 2.19 mmol), dimethyl 3-chloro-propyl-amine hydrochloride (363 mg, 2.30 mmol), and potassium carbonate (665 mg, 4.81 mmol) in dimethylformamide (15 mL) was heated at 80°C for 14 hours. The solvent was removed in vacuo and the remains partitioned between water and methylene chloride. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride/ethanol containing 10% ammonia) to afford a white solid. The solid was dissolved in 10 mL dioxane and treated with 0.5 mL 4M HCl in dioxane and stirred for 10 minutes. Ether was added and the precipitation filtered and dried in vacuo to afford 546 mg (54%) of dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenoxy}-propyl)-amine as a white solid.

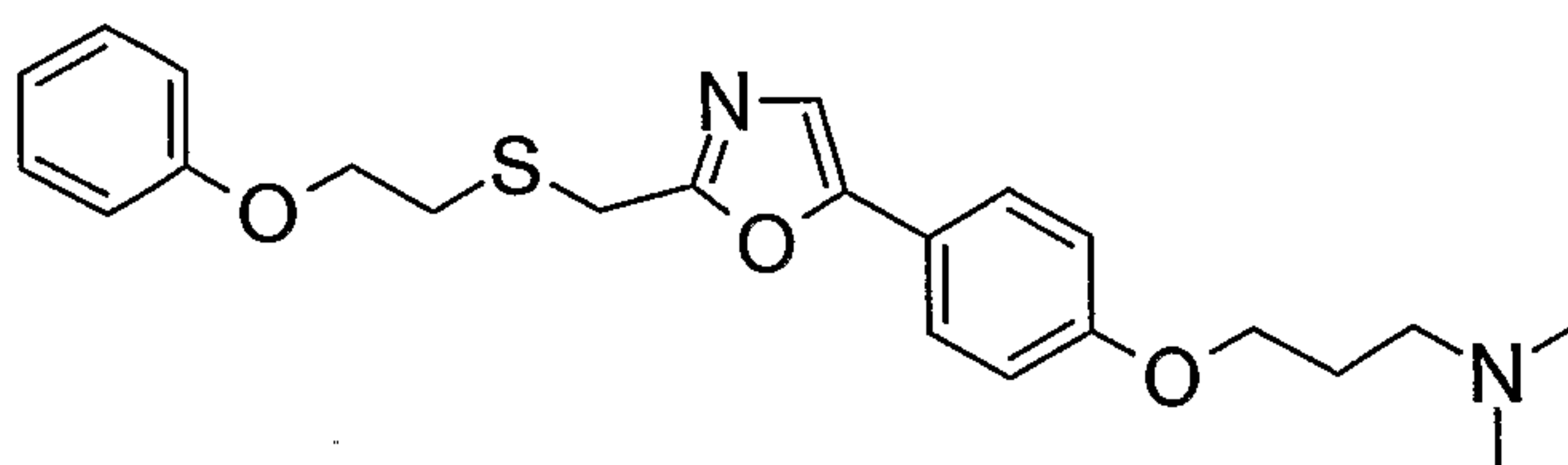
-344-

^1H NMR (DMSO- D_6 , 300 MHz): δ 10.49 (br s, 1H), 7.86 (d, 2H, $J=9$ Hz), 7.46 (s, 1H), 7.27 (t, 2H, $J=8$ Hz), 7.04 (d, 2H, $J=9$ Hz), 6.97 – 6.89 (m, 3H), 4.22 – 3.98 (m, 6H), 3.97 (s, 2H), 3.26 – 3.17 (m, 2H), 2.94 (t, 2H, $J=7$ Hz), 2.79 (s, 3H), 2.77 (s, 3H), 2.23 – 2.11 (m, 2H). MS (MH^+) 429.

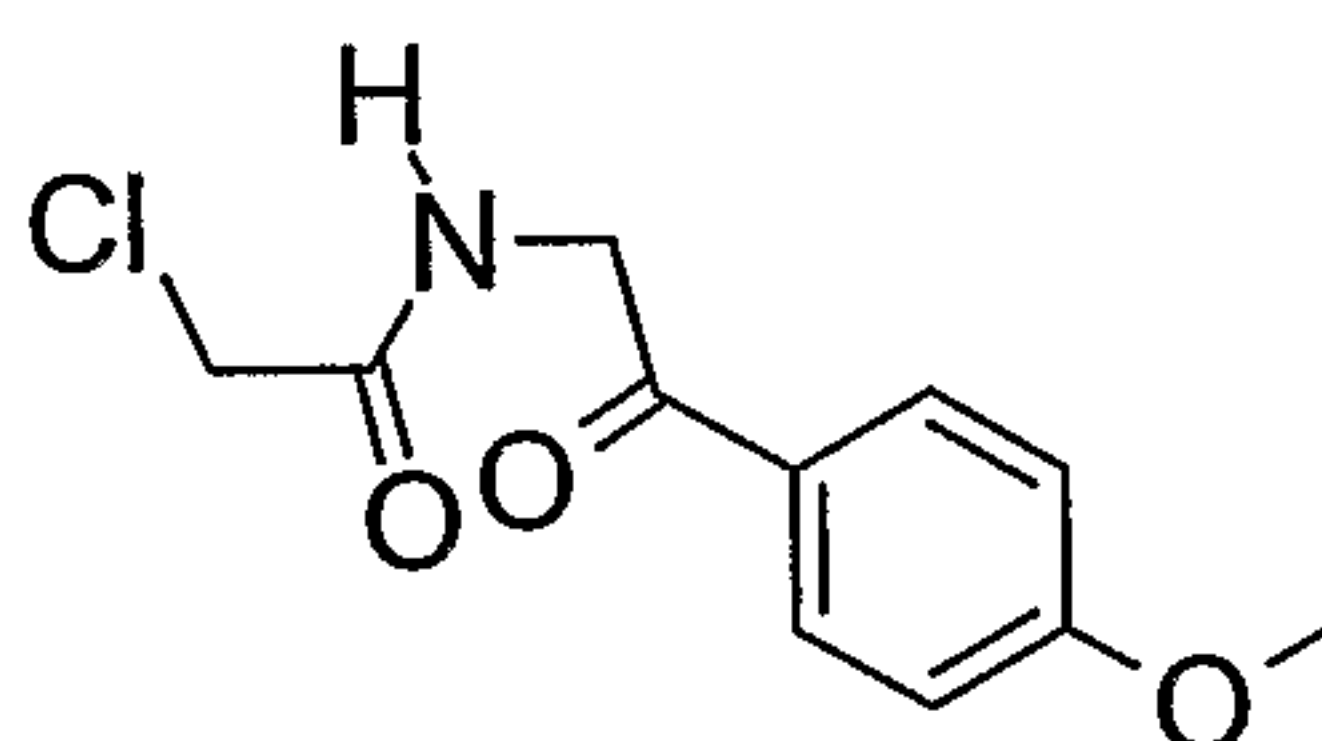
5

EXAMPLE 172

Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-amine



10 a) 2-Chloro-N-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-acetamide



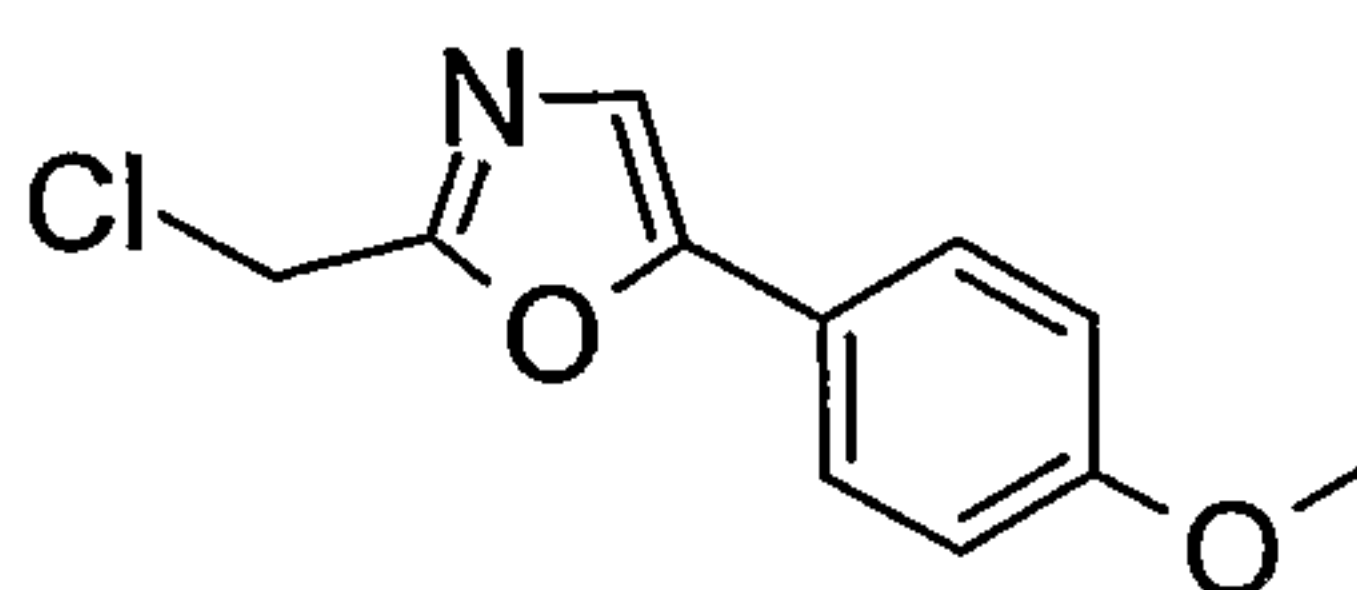
6.30 g (31 mmol) ω -amino-4-methoxy acetophenon hydrochloride was suspended in 70 mL methylene chloride and treated with 8.6 mL (62 mmol) triethylamine.

2.46 ml (31 mmol) of chloro acetylchloride was added drop wise under slight cooling

15 (~10°C). After complete addition the reaction mixture was stirred at room temperature for 24h. The reaction was quenched with water (100 mL) and the organic layer was dried over sodium sulfate and evaporated to yield 7.45 g (100%) 2-chloro-N-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-acetamide.

20 ^1H NMR (CDCl_3 , 300 MHz): δ 7.96 (d, 2H, $J=7$ Hz), 7.68 (br s, 1H), 6.98 (d, 2H, $J=7$ Hz), 4.73 (d, 2H, $J=4$ Hz), 4.13 (s, 2H), 3.89 (s, 3H).

b) 2-Chloromethyl-5-(4-methoxy-phenyl)-oxazole

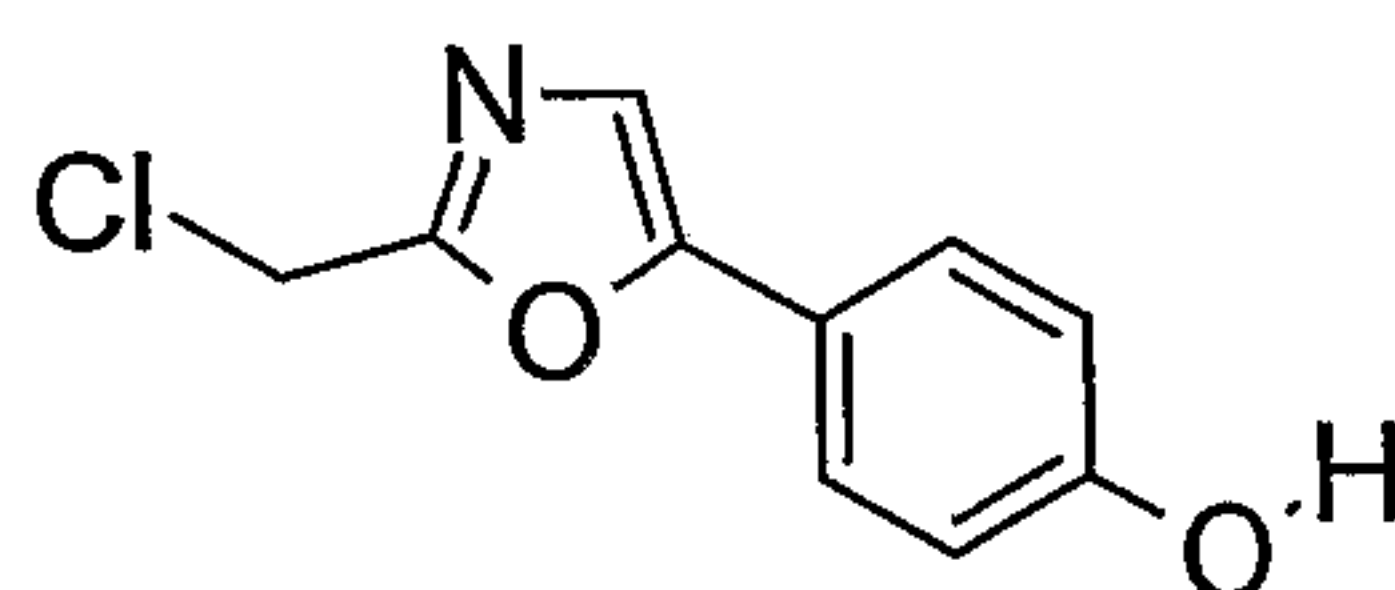


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1.7 g (7 mmol) of 2-chloro-N-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-acetamide was treated with 20 ml of phosphorous oxychloride and stirred for 2h at 100°C. The dark mixture was poured into water cautiously in portions. The temperature was held below 40°C by addition of ice. After being basification with conc. aqueous ammonia the mixture was extracted with tert.-butyl methylether. The organic layer was dried over sodium sulfate and evaporated to yield 1.5 g (96%) of 2-chloromethyl-5-(4-methoxy-phenyl)-oxazole.

¹H NMR (CDCl₃, 300 MHz): δ 7.58 (d, 2H, J=9 Hz), 7.19 (s, 1H), 6.95 (d, 2H, J=9 Hz), 4.66 (s, 2H), 3.85 (s, 3H).

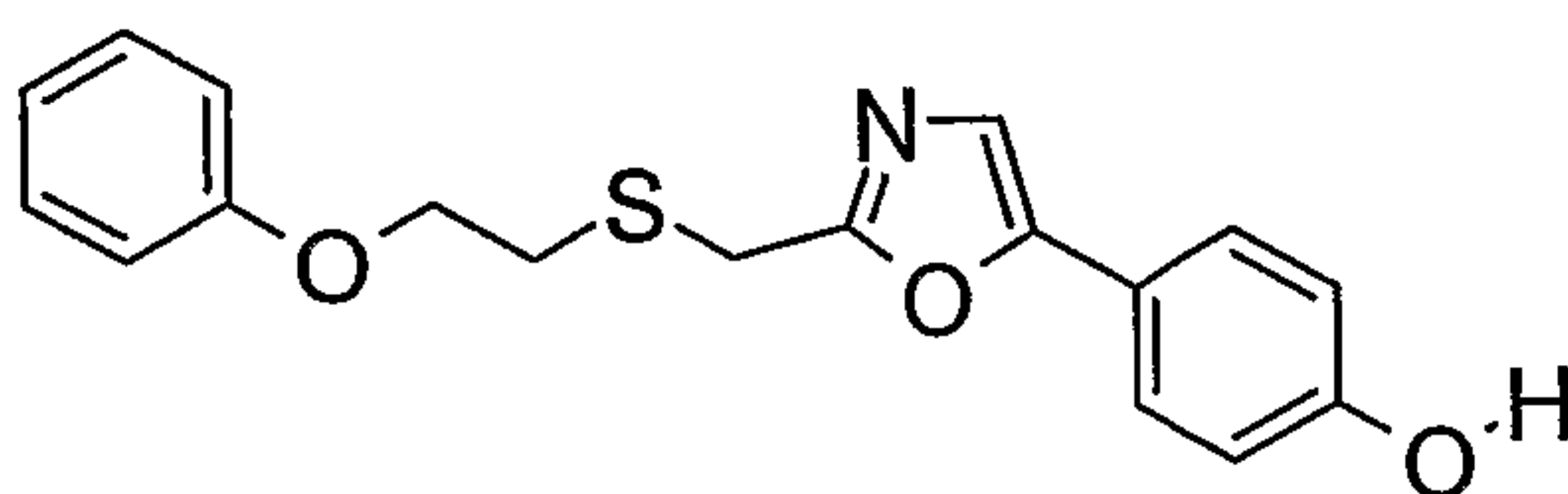
c) 4-(2-Chloromethyl-oxazol-5-yl)-phenol



1.4 g (6.2 mmol) of 2-chloromethyl-5-(4-methoxy-phenyl)-oxazole were dissolved in 25 mL methylene chloride, cooled to -70°C, and treated dropwise with 12.4 mL of a borane tribromide solution (1M in methylene chloride). After complete addition the reaction mixture was allowed to warm to room temperature. The mixture was poured into ice/water, basified with saturated aqueous sodium carbonate and acidified with aqueous 2M HCl solution. After extraction with methylene chloride, drying over sodium sulfate and evaporation, the crude product was dissolved in 5mL chloroform filtered and dried to yield 0.79 g (61%) 4-(2-chloromethyl-oxazol-5-yl)-phenol.

¹H NMR (DMSO-d₆, 300 MHz): δ 9.86 (br s, 1H), 7.54 (d, 2H, J=9 Hz), 7.47 (s, 1H), 6.86 (d, 2H, J=9 Hz), 4.91 (s, 2H).

d) 4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol



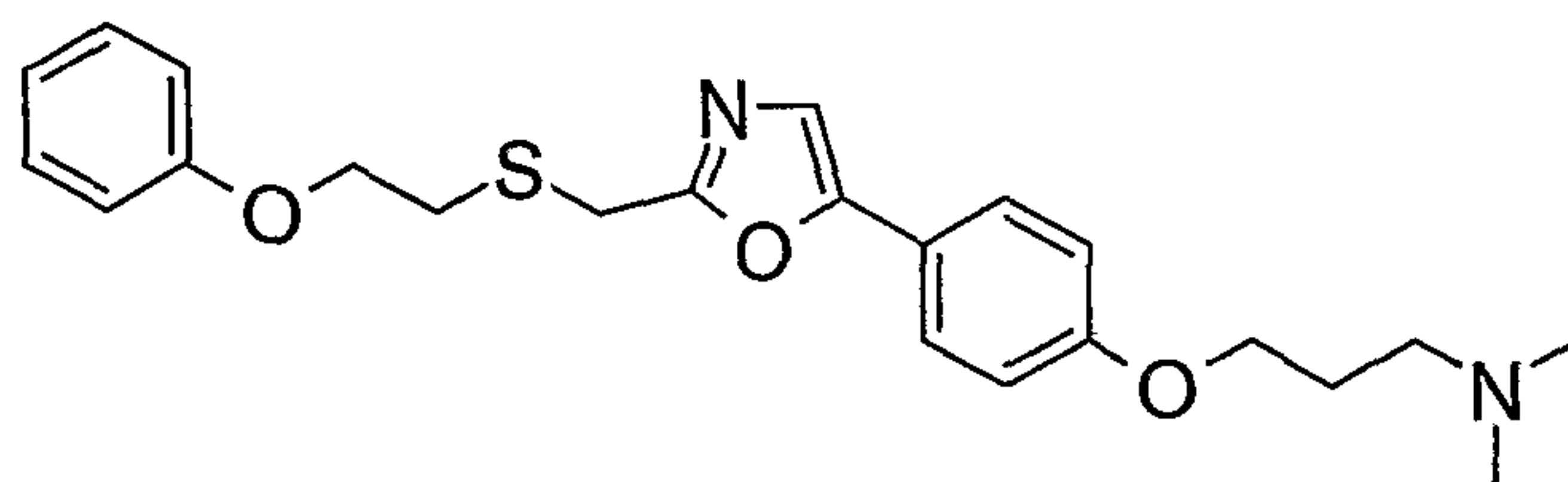
0.54 g (3.5 mmol) of 2-phenoxy-ethanethiol was dissolved in 8 ml of ethanol and treated with 1.75 mL (3.5 mmol) of 2M ethanolic sodium ethoxide solution. After stirring

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at room temperature for 10 minutes 0.78 g (3.7 mmol) of 4-(2-chloromethyl-oxazol-5-yl)-phenol was added. Stirring at room temperature was continued for 20 hours. The solvent was evaporated and the residue was treated with 100 mL water and 100 mL ethyl acetate. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was
 5 purified by chromatography on silica gel (elution with gradient methylene chloride/ethanol) to afford 0.4 g (35%) 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol.

¹H NMR (DMSO-d₆, 300 MHz): δ 9.78 (s, 1H), 7.48 (d, 2H, J=8 Hz), 7.36 (s, 1H), 7.27 (t, 3H, J=8 Hz), 6.97 – 6.90 (m, 3H), 6.83 (d, 2H, J=8 Hz), 4.16 (t, 2H, J=6 Hz),
 10 4.02 (s, 2H), 2.99 (t, 2H, J=6 Hz). MS (MH⁺) 328.

e) Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-amine



15

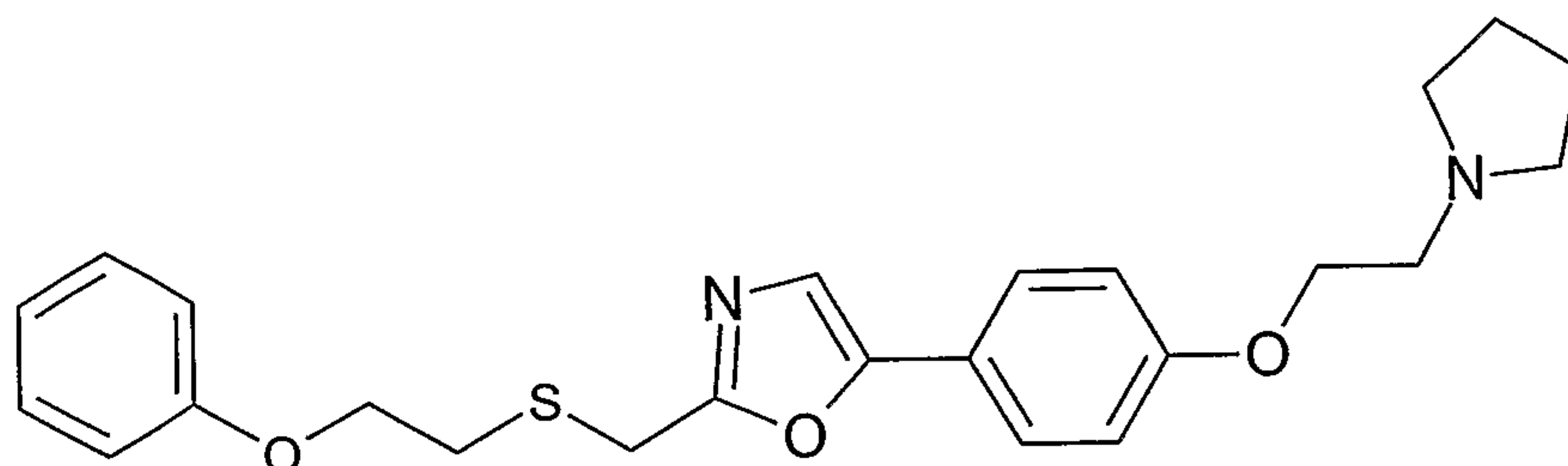
0.39 g (1.2 mmol) of 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol, 0.28 g (1.8 mmol) of 3-dimethylaminopropyl chloride hydrochloride, and 0.5 g (3.6 mmol) of potassium carbonate were dissolved in 10 mL dimethylformamide and heated to 80°C for 65 hours. The reaction mixture was poured into 100 mL water and was extracted
 20 with tertiarybutyl methylether. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by HPLC to afford 70 mg (14 %) dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-amine.

¹H NMR (CDCl₃, 300 MHz): δ 7.53 (d, 2H, J=9 Hz), 7.30 – 7.22 (m, 2H), 7.12 (s, 1H), 6.98 – 6.85 (m, 5H), 4.17 (t, 2H, J=7 Hz), 4.05 (t, 2H, J=7 Hz), 3.94 (s, 2H), 3.04 (t,
 25 2H, J=7 Hz), 2.47 (t, 2H, J=7 Hz), 2.27 (s, 6H), 2.03 – 1.92 (m, 2H). MS (MH⁺) 413.

Example 173

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazole

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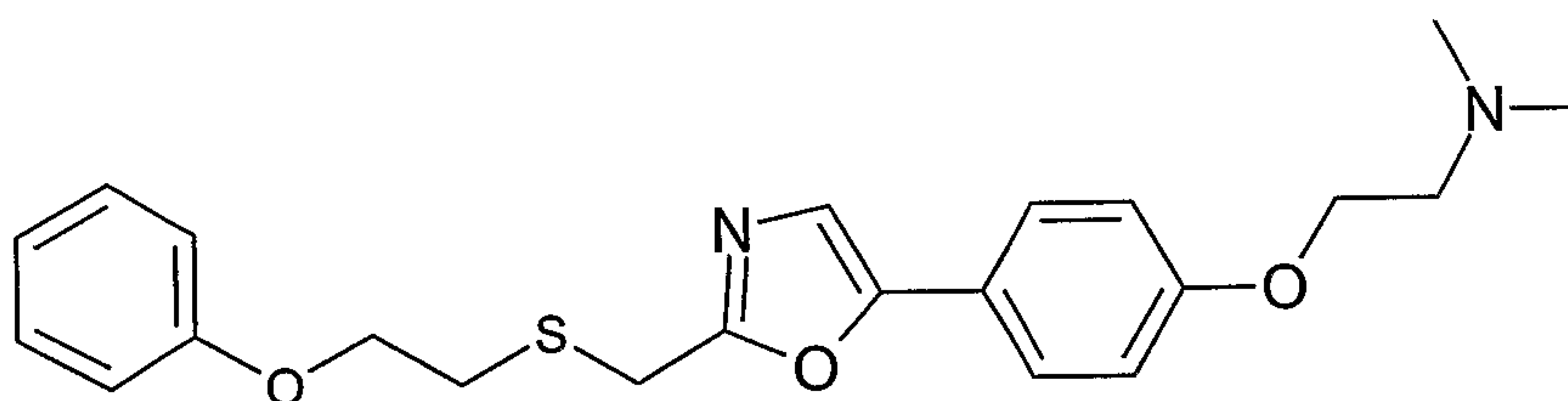


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 172 e, from 300 mg (0.92 mmol) 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol, 164 mg (0.962 mmol) N-(2-chloro-ethyl)-pyrrolidine hydrochloride, and 278 mg (2.015 mmol) potassium carbonate in 6 mL DMF. Yield: 209 mg (53%).

^1H NMR (CDCl_3 , 300 MHz): δ 7.53 (d, 2H, $J=9$ Hz), 7.30 – 7.22 (m, 2H), 7.12 (s, 1H), 6.98 – 6.87 (m, 5H), 4.17 (t, 2H, $J=7$ Hz), 4.14 (t, 2H, $J=7$ Hz), 3.94 (s, 2H), 3.04 (t, 2H, $J=7$ Hz), 2.96 – 2.88 (m, 2H), 2.68 – 2.61 (m, 4H), 1.86 – 1.78 (m, 4H). MS (MH^+) 425.

Example 174

Dimethyl-(2-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazo-5-yl]-phenoxy}-ethyl)-amine



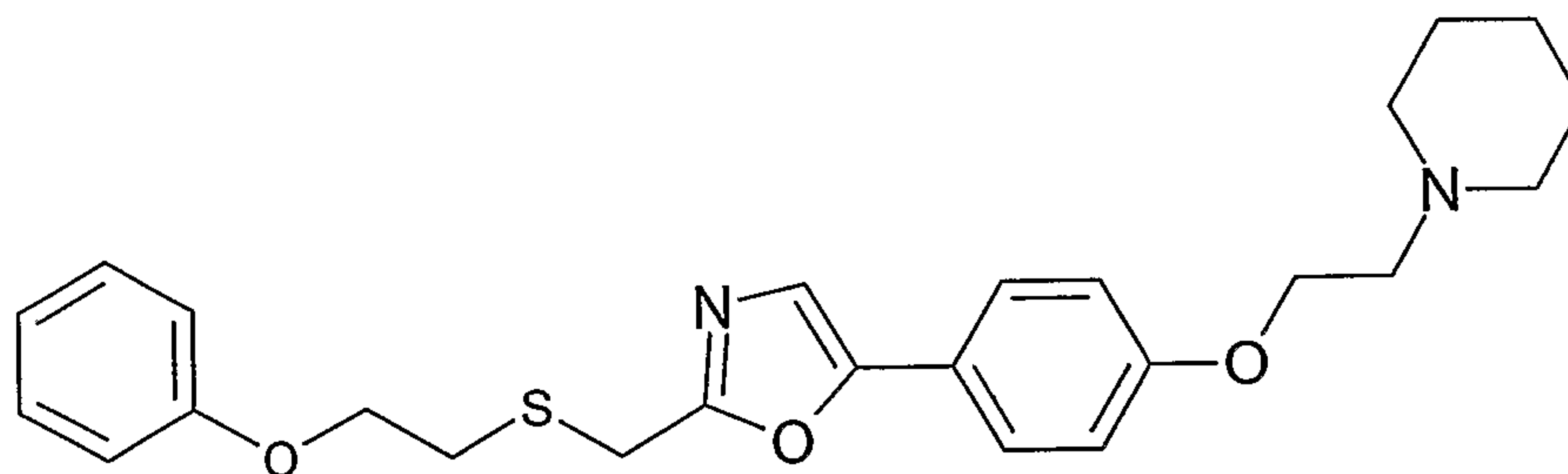
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 172 e, from 455 mg (1.39 mmol) of 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol, 210 mg (1.46 mmol) (2-chloro-ethyl)-dimethylamine hydrochloride, and 423 mg (3.06 mmol) of potassium carbonate in 9 mL DMF. Yield: 304 mg (55%).

^1H NMR (CDCl_3 , 300 MHz): δ 7.53 (d, 2H, $J=9$ Hz), 7.29 – 7.23 (m, 2H), 7.12 (s, 1H), 6.98 – 6.87 (m, 5H), 4.17 (t, 2H, $J=6$ Hz), 4.10 (t, 2H, $J=6$ Hz), 3.94 (s, 2H), 3.04 (t, 2H, $J=6$ Hz), 2.75 (t, 2H, $J=6$ Hz), 2.35 (s, 6H). MS (MH^+) 399.

Example 175

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1-(2-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-piperidine

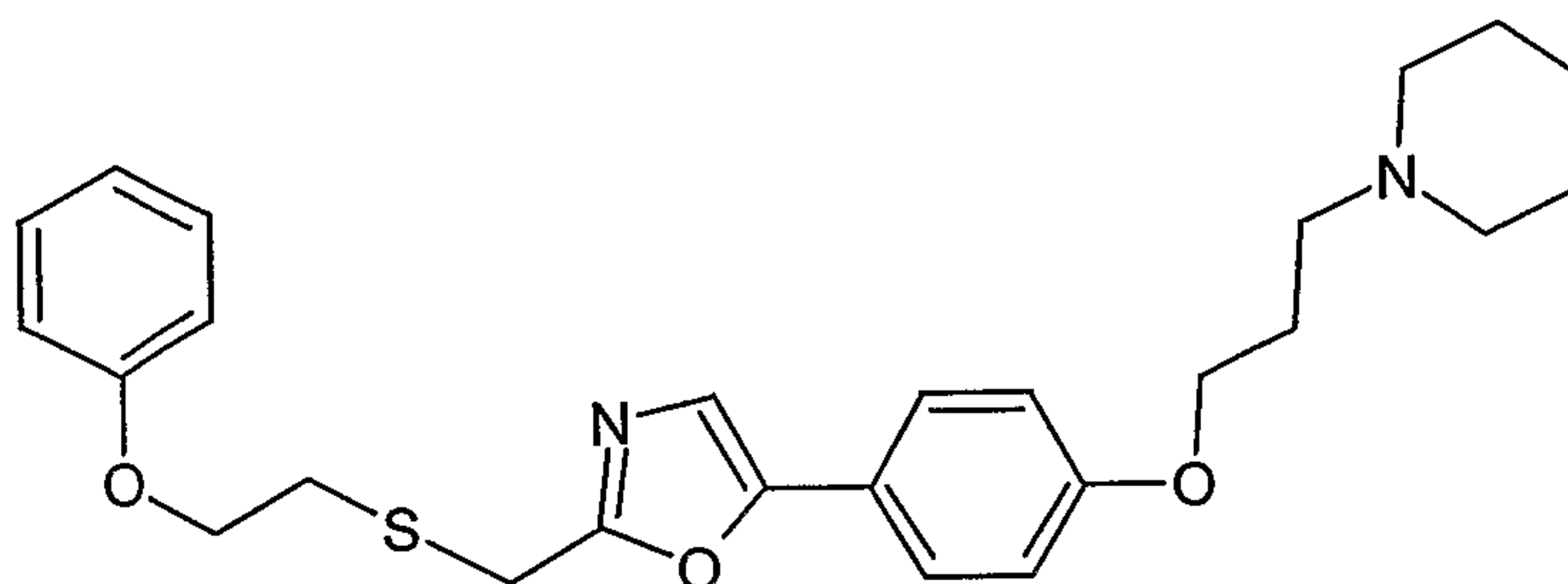


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 172 e, from 455 mg (1.39 mmol) 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol, 269 mg (1.46 mmol), N-(2-chloro-ethyl)-piperidine hydrochloride, and 423 mg (3.06 mmol) of potassium carbonate in 9 mL DMF. Yield: 414 mg (68%).

¹H NMR (CDCl₃, 300 MHz): δ 7.53 (d, 2H, J=9 Hz), 7.30 – 7.22 (m, 2H), 7.12 (s, 1H), 6.98 – 6.87 (m, 5H), 4.17 (t, 2H, J=7 Hz), 4.14 (t, 2H, J=7 Hz), 3.94 (s, 2H), 3.04 (t, 2H, J=6 Hz), 2.79 (t, 2H, J=6 Hz), 2.56 – 2.48 (m, 4H), 1.67 – 1.57 (m, 4H), 1.50 – 1.41 (m, 2H). MS (MH⁺) 439.

Example 176

1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-piperidine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 172 e, from 455 mg (1.39 mmol) 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol, 289 mg (1.46 mmol) N-(3-chloro-propyl)-piperidine hydrochloride, and 423 mg (3.06 mmol) potassium carbonate in 9 mL DMF. Yield: 525 mg (83%).

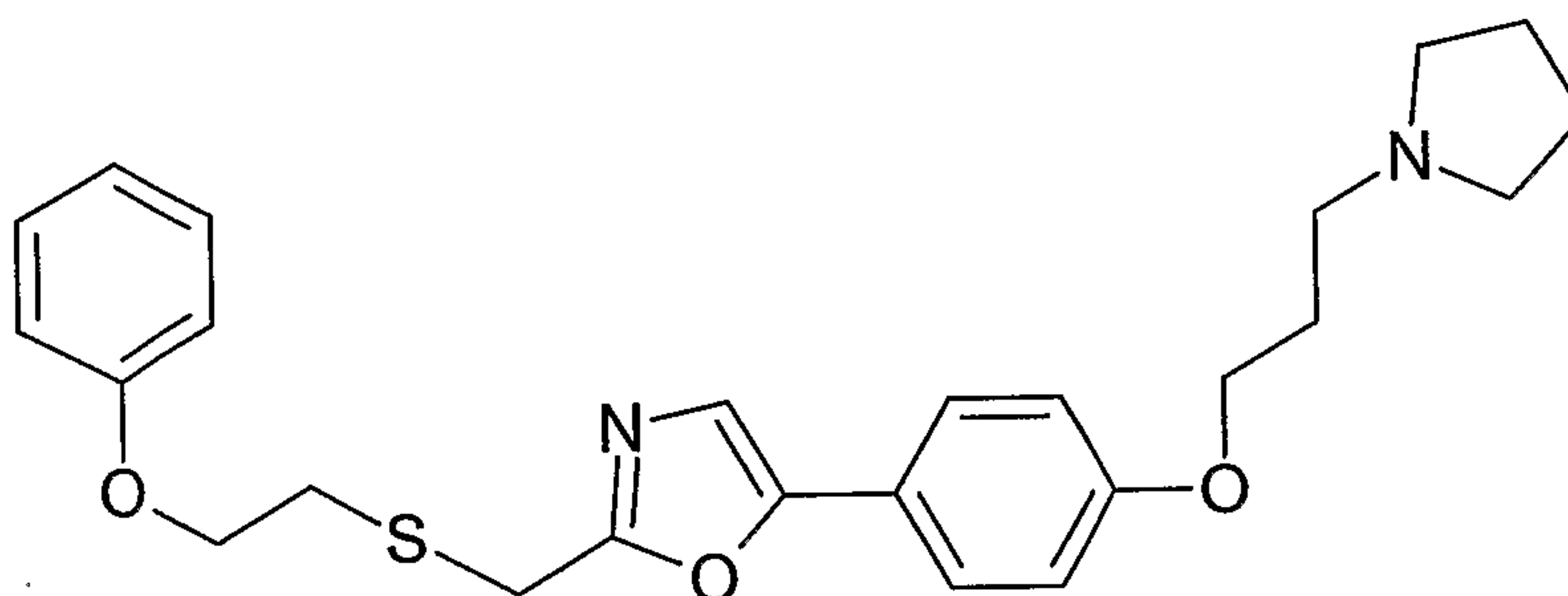
¹H NMR (CDCl₃, 300 MHz): δ 7.52 (d, 2H, J=9 Hz), 7.30 – 7.22 (m, 2H), 7.12 (s, 1H), 6.98 – 6.87 (m, 5H), 4.17 (t, 2H, J=6 Hz), 4.04 (t, 2H, J=6 Hz), 3.94 (s, 2H), 3.04 (t,

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2H, J=6 Hz), 2.52 – 2.37 (m, 6H), 2.05 – 1.93 (m, 2H), 1.66 – 1.55 (m, 4H), 1.50 – 1.40 (m, 2H). MS (MH⁺) 453.

Example 177

5 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-oxazole

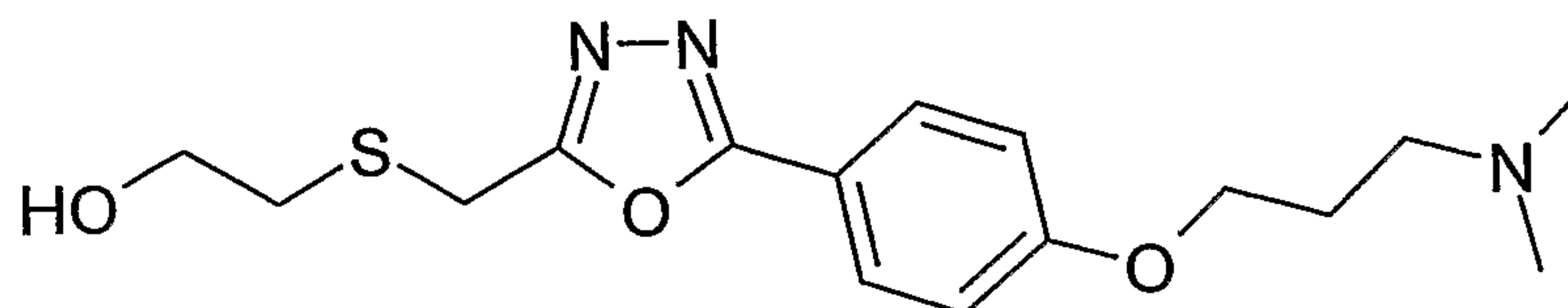


The above compound was prepared in a manner similar to that exemplified for the
 10 preparation of Example 172 e, from 455 mg (1.39 mmol) 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol, 269 mg (1.46 mmol) N-(3-chloro-propyl)-pyrrolidine hydrochloride, and 423 mg (3.06 mmol) potassium carbonate in 9 mL DMF. Yield : 470 mg (77%).

¹H NMR (CDCl₃, 300 MHz): δ 7.53 (d, 2H, J=9 Hz), 7.30 – 7.22 (m, 2H), 7.12 (s, 1H), 6.98 – 6.87 (m, 5H), 4.17 (t, 2H, J=6 Hz), 4.14 (t, 2H, J=6 Hz), 3.94 (s, 2H), 3.04 (t, 2H, J=7 Hz), 2.78 (t, 2H, J=7 Hz), 2.56 – 2.49 (m, 4H), 1.67 – 1.58 (m, 4H), 1.50 – 1.41 (m, 2H). MS (MH⁺) 439.

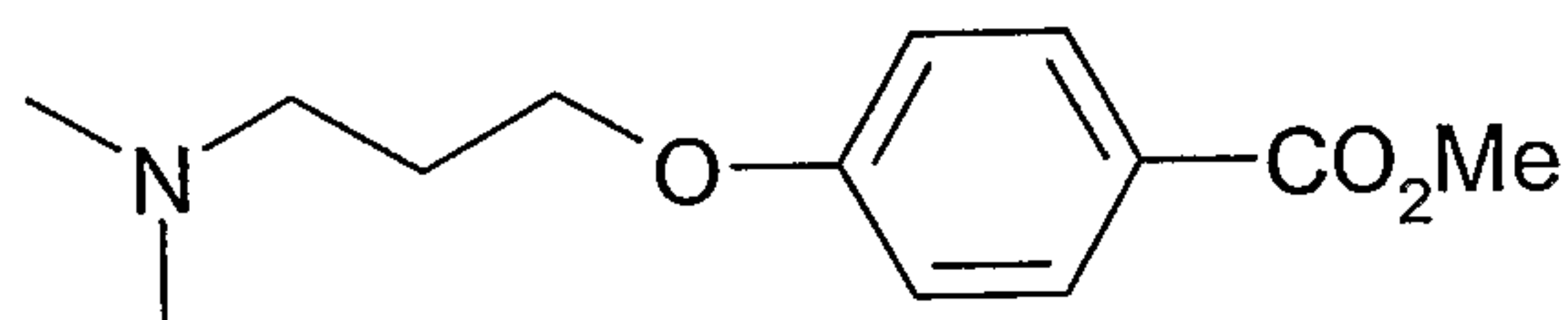
Example 178

20 Preparation of 2-(2-hydroxyethylthio)methyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole hydrochloride from methyl 4-hydroxy-benzoate



a) Methyl 4-[3-(dimethylamino)propoxy]-benzoate

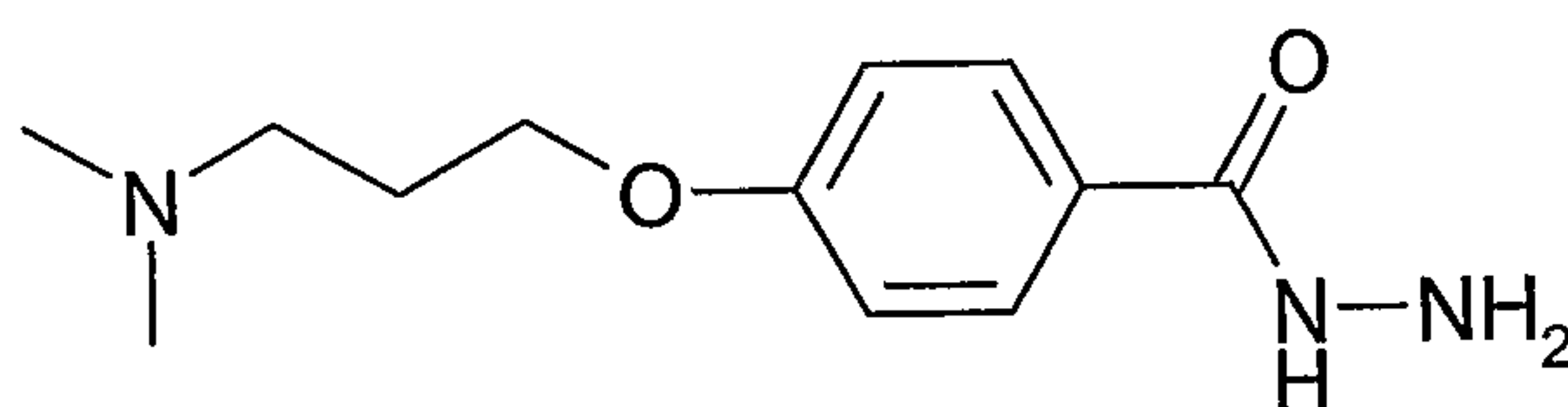
-350-



To a solution of 4-hydroxy benzoic acid methyl ester (50.0 g, 328.6 mmol), triphenyl phosphine (130.0 g, 493.5 mmol), and 3-dimethylamino-1-propanol (50.5 g, 57 ml, 493.5 mmol) in 1000 mL of dry THF was added dropwise isopropyl azo dicarboxylate at 0 °C. After completed addition the temperature was brought to ambient temperature and the mixture was stirred for 16 h. The mixture was evaporated. It was then dissolved in ethyl acetate and extracted with 2N aqueous HCl. The aqueous phase was made alkaline with solid sodium hydroxide pellets and extracted with ethyl acetate (3 times). The collected organic phases were dried with sodium sulphate and evaporated. The crude material (75 g, 96%) was used directly in the next step.

¹H NMR (DMSO-d₆) δ 7.95 (d, 2H, J=8 Hz), 7.00 (d, 2H, J=8 Hz), 4.13 (t, 2H, J=6 Hz), 3.83 (s, 3H), 2.32(t, 2H, J=6 Hz), 2.13 (s 6H), and 1.88 (quint., 2H, J=6 Hz), MS (FD) m/e 238.

b) 4-[3-(dimethylamino)propoxy]-benzoic acid hydrazide

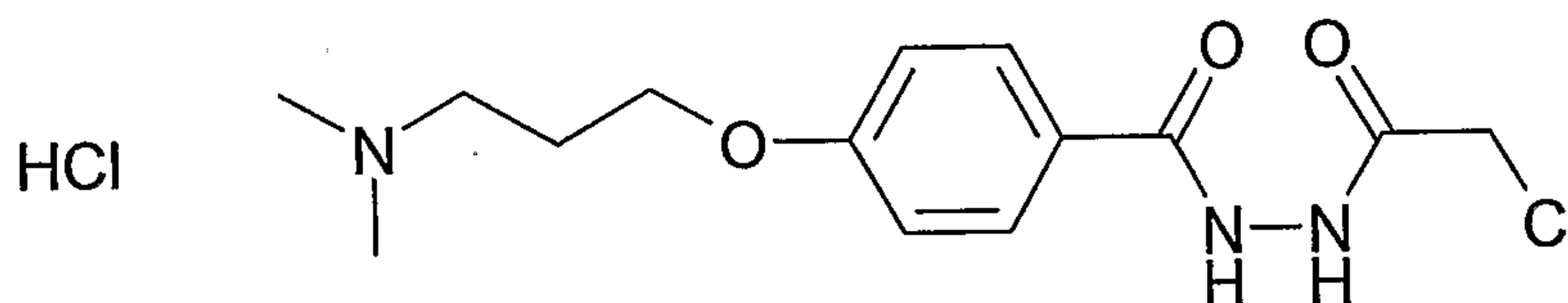


A solution of methyl 4-[3-(dimethylamino)propoxy]-benzoate (108.0 g, 457.0 mmol), in 443 ml (458 g, 9.14 M) of neat hydrazine hydrate was subdivided into ten aliquots and each aliquot was heated in a Teflon bomb in a microwave oven ETHOS 1600 for 1 h to 120 °C. After TLC indicated complete conversion the reaction mixture was poured in water and extracted with DCM. The collected organic phases were dried over sodium sulphate, filtered and evaporated. The residue was purified via column chromatography using a DCM/DCM-MeOH/ DCM-MeOH-ammonia gradient (100% to 90:10). Yield 32.7 g (42%)

¹H NMR (DMSO-d₆) δ 9.58 (s, 1H, exch.), 7.80 (d, 2H, J=8 Hz), 6.98 (d, 2H, J=8 Hz), 4.40 (s, 2H, br., exch.), 4.05 (t, 2H, J=6 Hz), 2.35(t, 2H, J=6 Hz), 2.15 (s 6H), and 1.88 (quint., 2H, J=6 Hz), MS (FD) m/e 238.

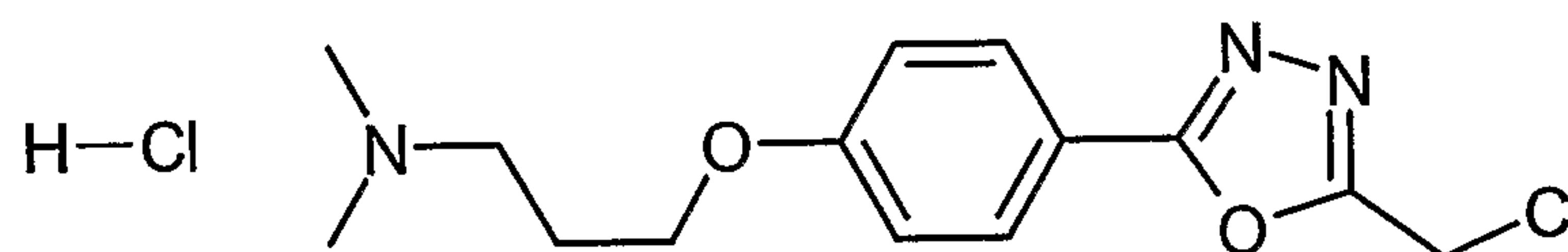
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c) 4-[3-(dimethylamino)propoxy]-benzoic acid 2-(chloroacetyl)hydrazide hydrochloride



5 Chloro acetylchloride (2.40 g, 1.68 ml, 21.07 mmol) was slowly added to a solution of 4-[3-(dimethylamino)propoxy]-benzoic acid hydrazide (5.0 g, 21.07 mmol) in 50 ml DCM. After stirring overnight at ambient temperature TLC showed incomplete conversion. After successive addition of chloro acetyl chloride (0.17 ml, additional stirring for 2h, 0.5 ml additional stirring for 1 h) TLC showed almost complete
10 conversion. The mixture was diluted with 50 ml MTBE and the colorless precipitate thus formed was filtered off and dried in a vacuum oven at 40 °C for 1 h. 6.7 g (91 %) of colorless crystals. The material was used in the next step without purification.

d) 2-Chloromethyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole hydrochloride
15



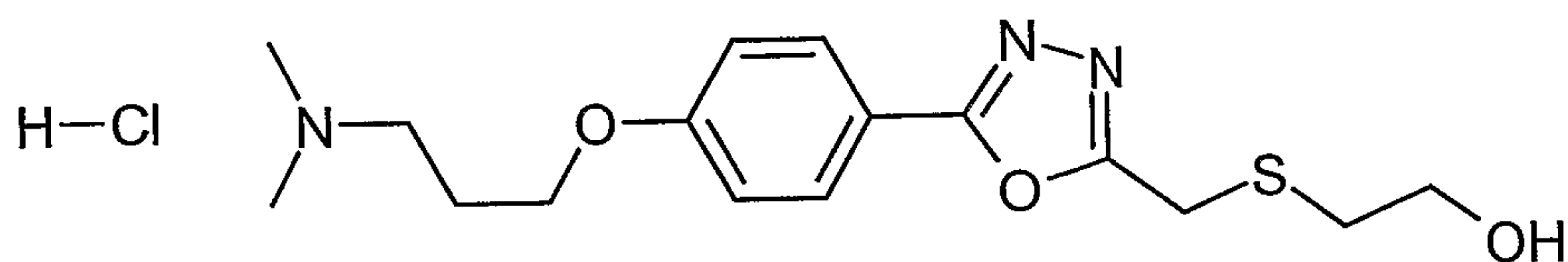
4-[3-(dimethylamino)propoxy]-benzoic acid 2-(chloroacetyl)hydrazide (6.7 g, 19.13 mmol) was added to 34 ml of phosphoryl chloride POCl₃ and the mixture was stirred at 95 °C overnight. The mixture was diluted with DCM and evaporated to dryness.
20 The residue was repeatedly triturated with toluene and evaporated to remove remaining traces of POCl₃ and HCl. The colorless residue was sufficiently pure for the next step.

¹H NMR (DMSO-d₆) δ 10.58 (s, 1H, exch.), 7.98 (d, 2H, J=8 Hz), 7.20 (d, 2H, J=8 Hz), 5.12 (s, 2H), 4.18 (t, 2H, J=6 Hz), 3.20 (t, 2H, J=6 Hz), 2.80 (d 6H, J=4 Hz), and 2.20 (quint., 2H, J=6 Hz),.MS (FD) m/e 296.1.

25

e) 2-(2-hydroxyethylthio)methyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole hydrochloride

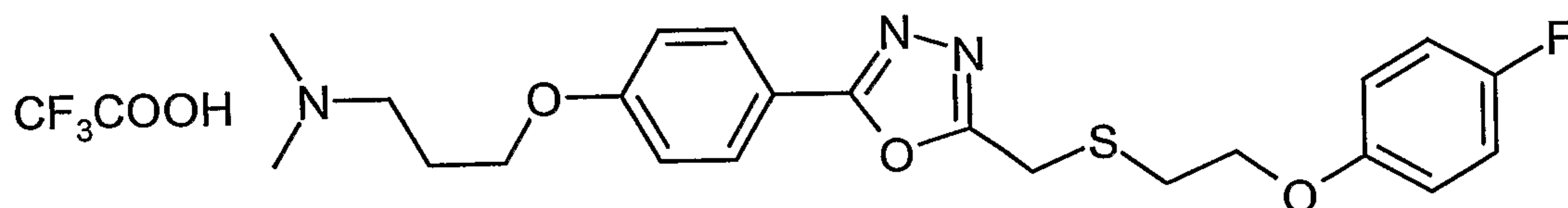
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To a solution of sodium ethylate in ethanol, prepared by adding sodium hydride (60% dispersion, 2.1 g, 51.96 mmol) to 90 ml of absolute ethanol was added 2-mercaptoethanol (4.1 g, 51.96 mmol, 3.7 ml). The mixture was stirred at room temperature for 30 min. Then 2-chloromethyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole hydrochloride (8.6 g, 25.98 mmol) was added as a solid. After 2 h stirring at ambient temperature the mixture was evaporated. The residue was suspended in DCM (dichloromethane) and extracted with aqueous sodium bicarbonate. The organic phase was dried over sodium sulphate and evaporated the residue was purified via flash chromatography on silica gel using DCM-DCM/ethanolic ammonia gradient (100% to 90% DCM) yielding 4.8 g (49%) of pure compound.

^1H NMR (DMSO- d_6) δ 7.90 (d, 2H, $J=8$ Hz), 7.12 (d, 2H, $J=8$ Hz), 4.88 (t, 1H, exch.), 4.10 (m, 2H), 4.10 (s, 2H), 3.57 (q, 2H), 2.72 (t 2H, $J=4$ Hz), 2.36 (t, 2H, $J=4$ Hz), 2.18 (s, 6H) and 1.88 (quint. 2H, $J=4$ Hz). MS (FD) m/e 338.1.

f) Dimethyl-(3-{4-[5-(2-(4-fluorophenoxy-ethylsulfanylmethyl)-1,3,4-oxadiazol-2-yl]-phenoxy}-propyl)-amine.



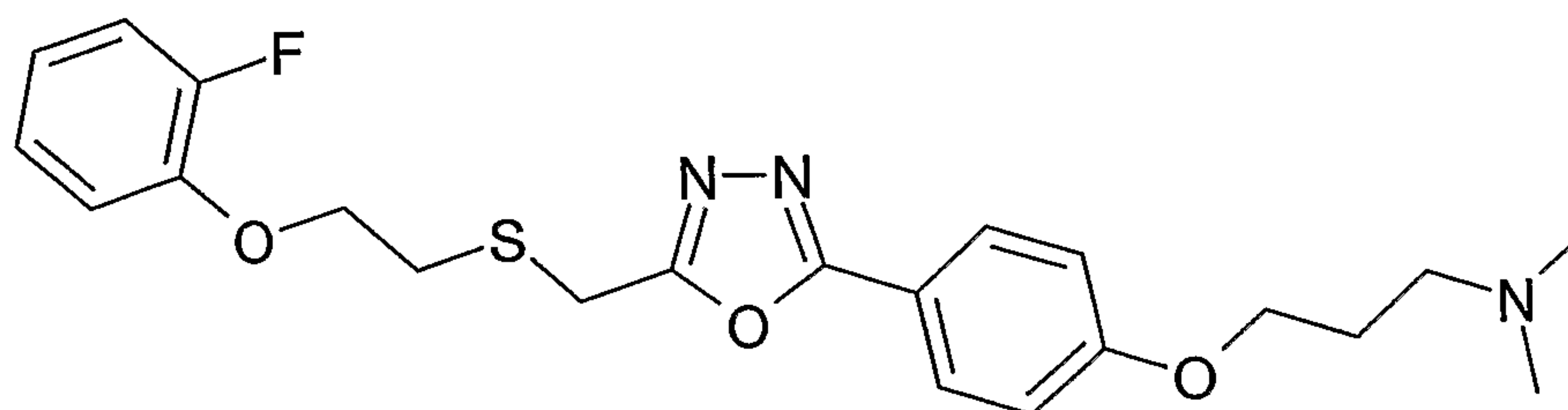
To a mixture of 2-(2-hydroxyethylthio)methyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole hydrochloride (0.200 g, 0.592 mmol), 4-fluorophenol (0.100 mg, 0.888 mmol) triphenyl phosphine polystyrene resin (0.888 g, 0.888 mmol, 1meq./g) in 6 ml DCM was added diisopropyl azodicarboxylate (0.180 g, 176 μl , 0.888 mmol) and stirred at ambient temperature for 12 h. The mixture was evaporated and redissolved in methanol. The solution was purified via a SCX-cartridge using 20 ml methanol to remove impurities. The compound was eluted with methanolic ammonia. The residue (206 mg) was finally purified via prep. HPLC (RP-18) using acetonitrile/water/0.1% TFA gradient yielding 44 mg (17%) of the desired compound

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^1H NMR (DMSO- d_6) δ 9.50 (s, br, exch) 7.89 (m, 2H), 7.05 (m, 6H), 4.25 (s, 2H), 4.10 (m, 2H), 3.90 (m, br 2H), 3.23 (m, 2H), 3.05 (q, 2H), 2.80 (2s, 6H), and 2.12 (m, 2H). MS (FD) m/e 432.1.

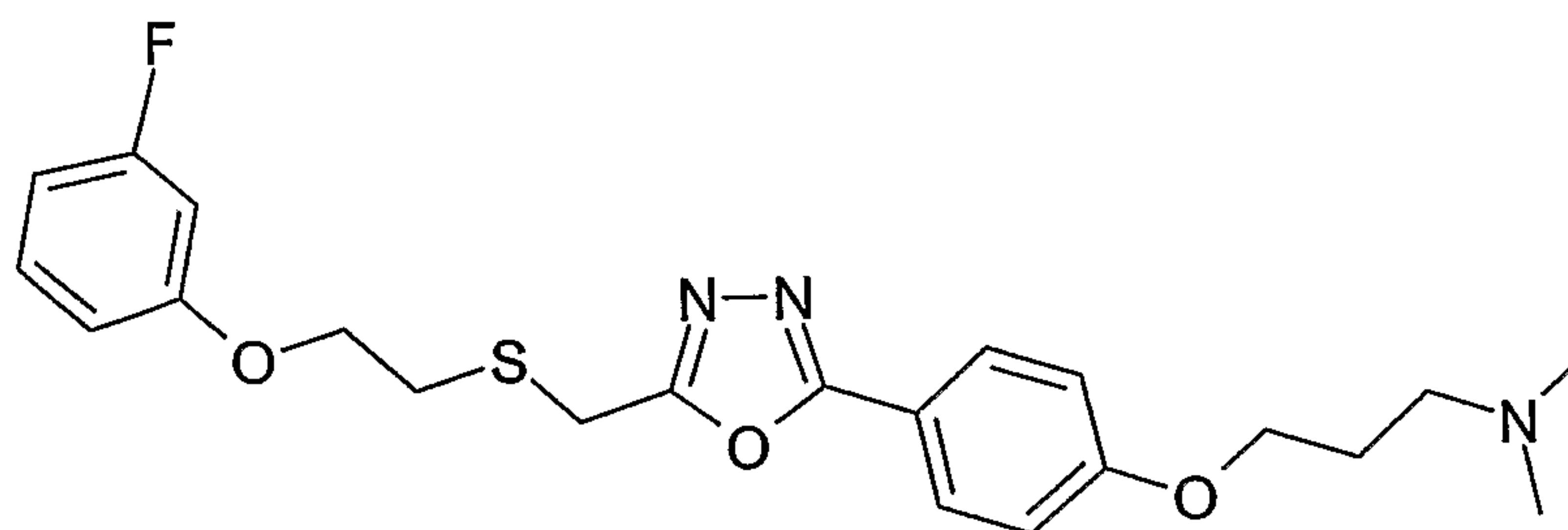
5 The following compounds were prepared using the protocol described above, using 2-(2-hydroxyethylthio)methyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole and the appropriate substituted phenol. After prep. HPLC the appropriate fractions were collected, evaporated and redissolved in methanol. Filtration of the methanolic solution of the trifluoroacetate salts of the desired compounds through SCX
10 cartridges yielded the free bases of the desired compounds:

Example 179



^1H NMR (CDCl_3) δ 7.97 (d, 2H, J=8 Hz), 7.00 (m, 4H), 6.98 (d, 2H, J=8 Hz), 6.65 (m, 3H), 4.28 (t, 2H), 4.11 (s, 2H), 4.10 (t, 2H), 3.10 (t, 2H), 2.40 (t, 2H), 2.30 (s, 6H), and 2.00 (quint., 2H). MS (FD) m/e 432.1.

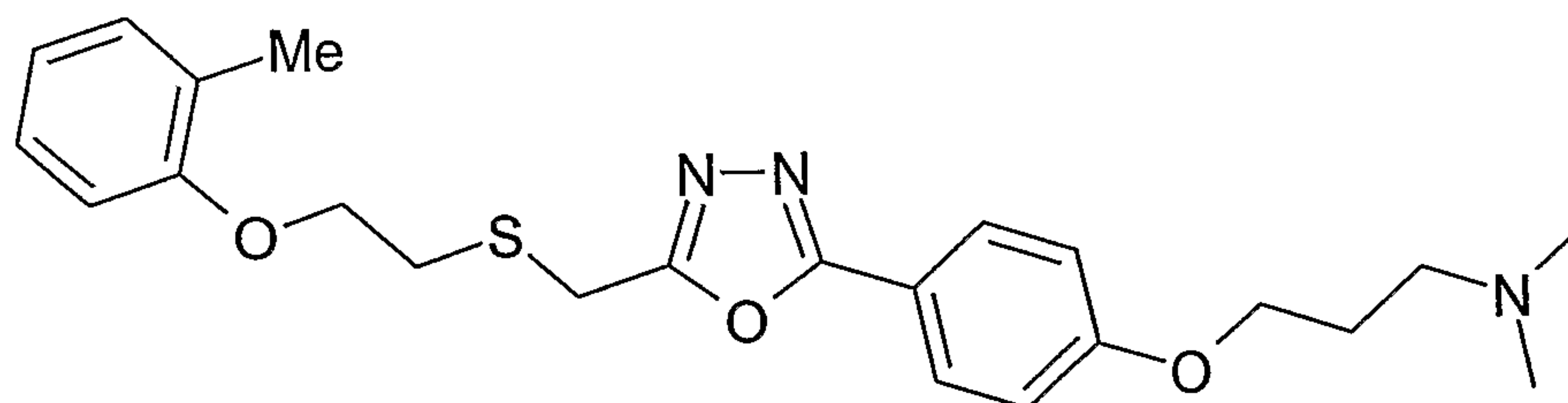
Example 180



20 ^1H NMR (CDCl_3) δ 7.95 (d, 2H, J=8 Hz), 7.20 (m, 1H), 6.98 (d, 2H, J=8 Hz), 6.65 (m, 3H), 4.20 (t, 2H), 4.12 (t, 2H), 4.03 (s, 2H), 3.05 (t, 2H), 2.45 (t, 2H), 2.25 (s, 6H), and 2.00 (quint., 2H). MS (FD) m/e 432.1.

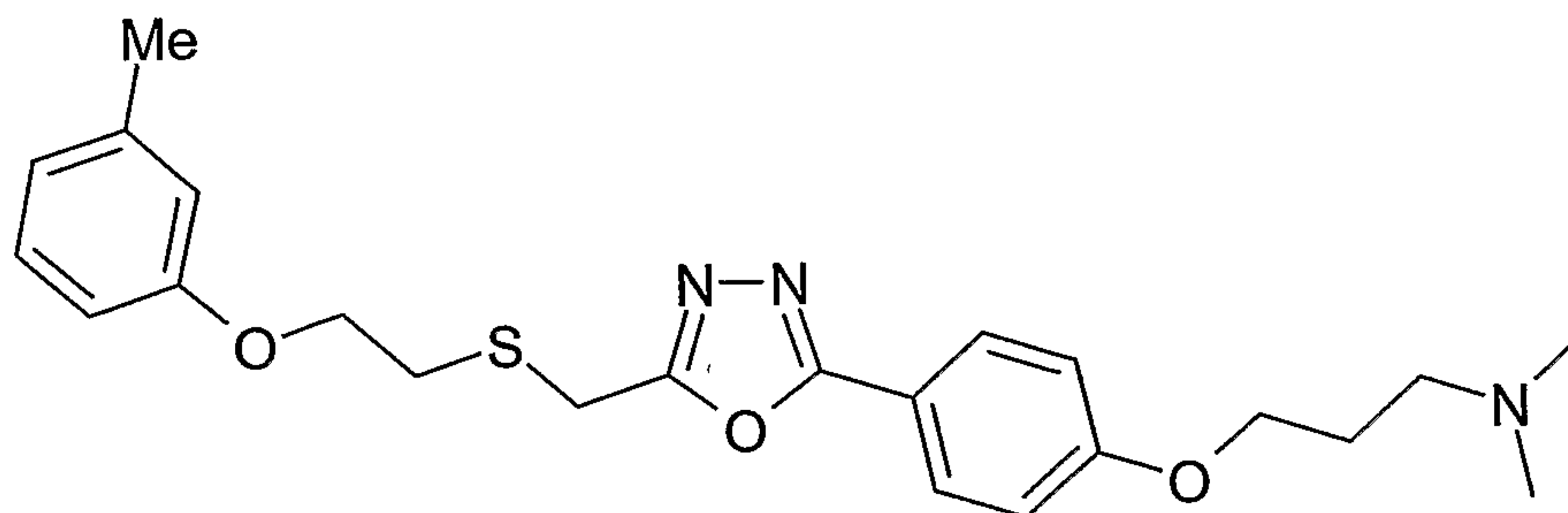
-354-

Example 181



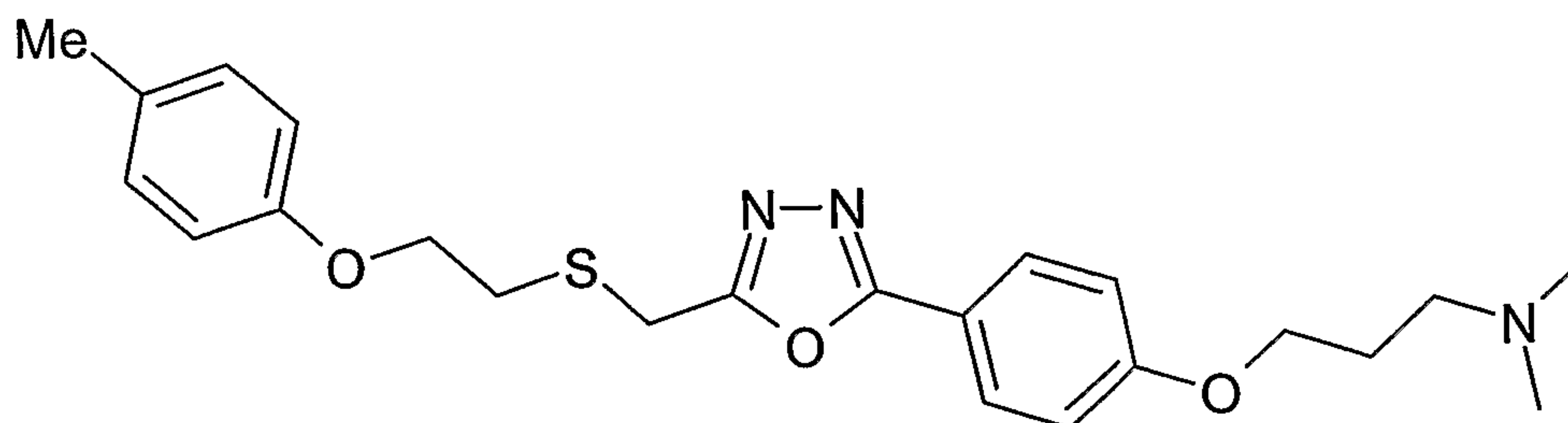
^1H NMR (CDCl_3) δ 7.95 (d, 2H, $J=8$ Hz), 7.12 (d, 2H, $J=8$ Hz), 7.00 (d, 2H, $J=8$ Hz), 6.85 (m, 2H), 4.25 (t, 2H), 4.13 (t, 2H), 4.08 (s, 2H), 3.10 (t, 2H), 2.50 (t, 2H), 2.28 (s, 6H), 2.23 (s, 3H), and 1.98 (quint., 2H). MS (FD) m/e 428.1.

Example 182



^1H NMR (CDCl_3) δ 7.95 (d, 2H, $J=8$ Hz), 7.15 (t, 1H, $J=8$ Hz), 7.00 (d, 2H, $J=8$ Hz), 6.75 (m, 2H), 4.20 (t, 2H), 4.10 (t, 2H), 4.05 (s, 2H), 3.05 (t, 2H), 2.45 (t, 2H), 2.33 (s, 3H), 2.30 (s, 6H), and 1.98 (quint., 2H). MS (FD) m/e 428.1.

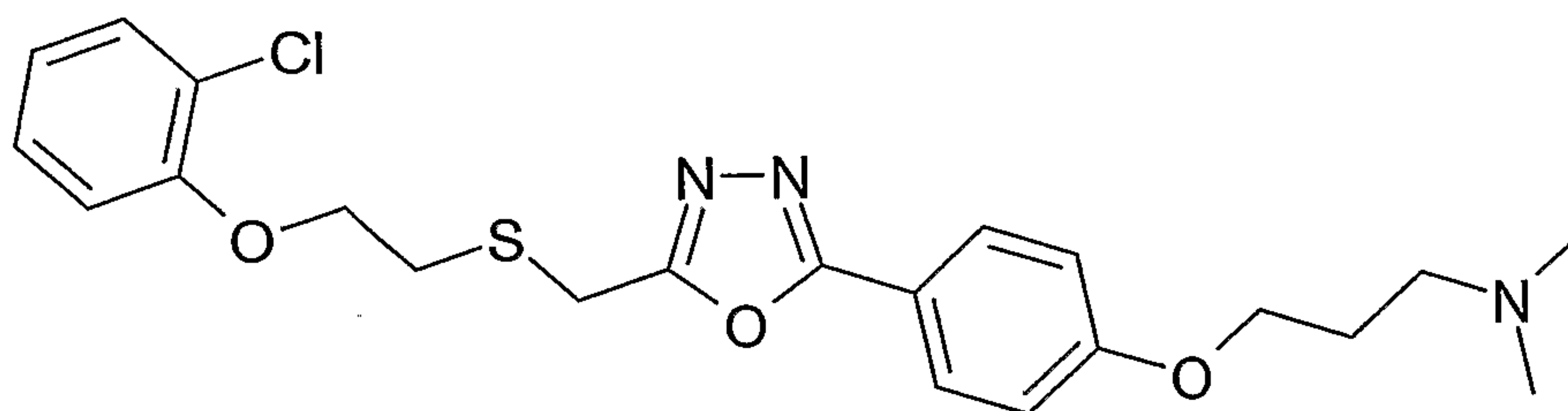
Example 183



^1H NMR (CDCl_3) δ 7.93 (d, 2H, $J=8$ Hz), 7.08 (d, 1H, $J=8$ Hz), 7.20 (t, 1H), 7.00 (d, 2H, $J=8$ Hz), 6.80 (d, 2H, $J=8$ Hz), 4.18 (t, 2H), 4.10 (t, 2H), 4.05 (s, 2H), 3.07 (t, 2H), 2.50 (t, 2H), 2.27 (s, 6H), 2.26 (s, 3H), and 2.00 (quint., 2H). MS (FD) m/e 428.2.

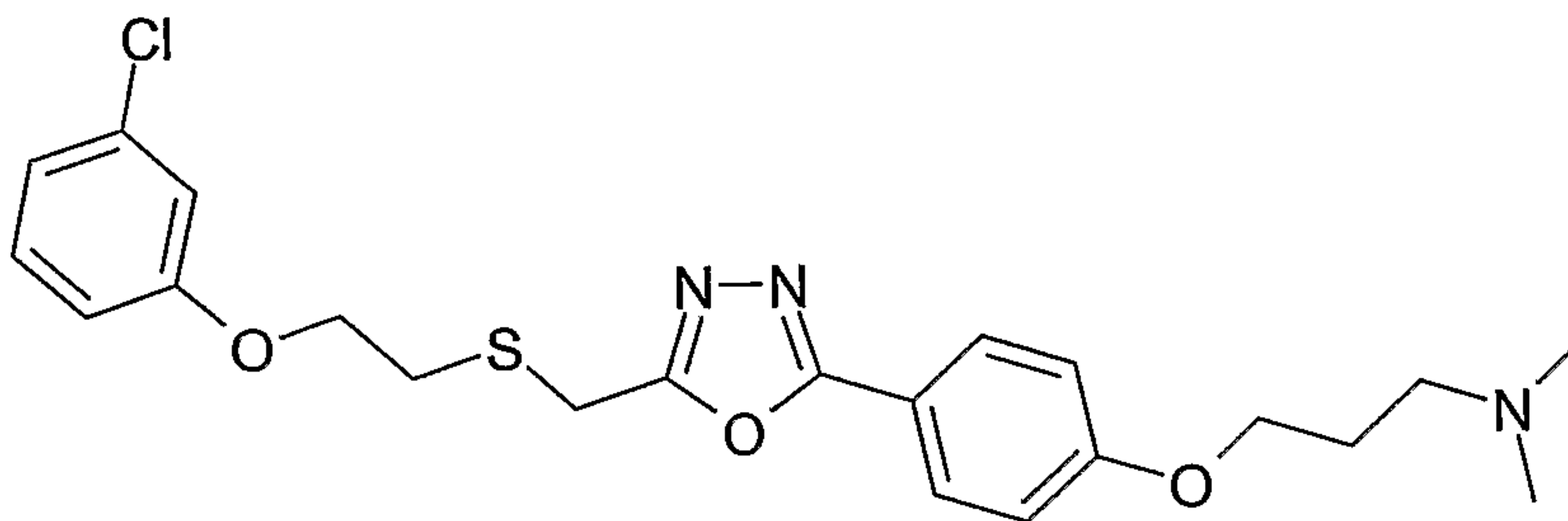
-355-

Example 184



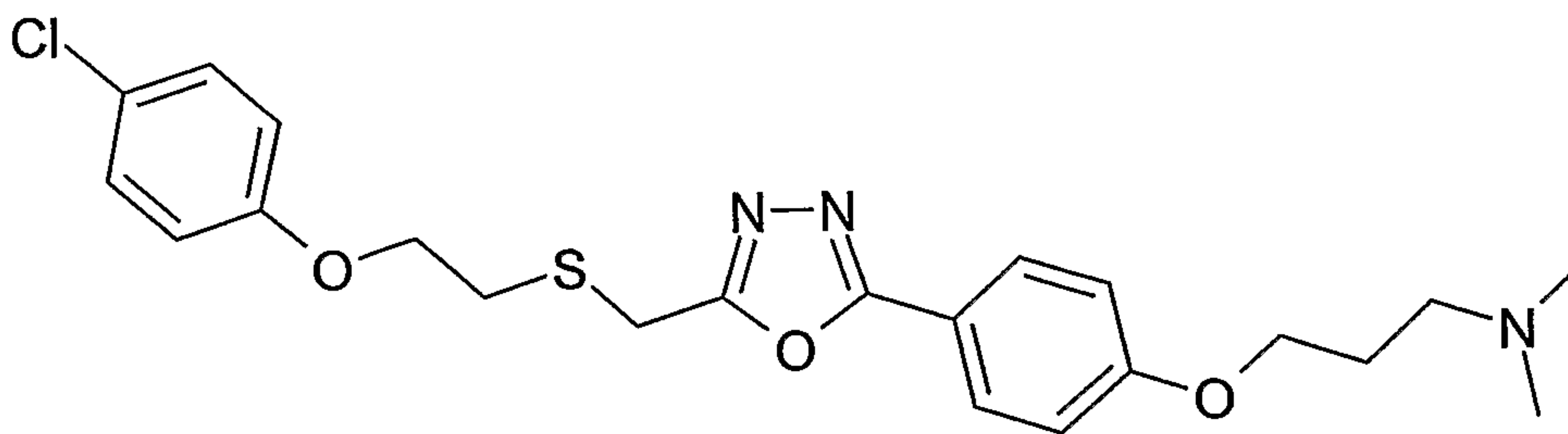
¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8 Hz), 7.33 (d, 1H, J=8 Hz), 7.20 (t, 1H), 7.00 (d, 2H, J=8 Hz), 6.90 (d, 2H, J=8 Hz), 6.70 (d, 1H), 4.30 (t, 2H), 4.15 (s, 2H), 4.10 (t, 2H), 3.10 (t, 2H), 2.50 (t, 2H), 2.27 (s, 6H), and 2.00 (quint., 2H). MS (FD) m/e 448.1.

Example 185



¹H NMR (CDCl₃) δ 7.88 (d, 2H, J=8 Hz), 7.11 (t, 1H, J=8 Hz), 6.90 (d, 2H, J=8 Hz), 6.75 (m, 2H), 6.70 (d, 1H), 4.10 (t, 2H), 4.02 (t, 2H), 3.98 (s, 2H), 3.01 (t, 2H), 2.40 (t, 2H), 2.21 (s, 6H), and 1.90 (quint., 2H). MS (FD) m/e 448.0.

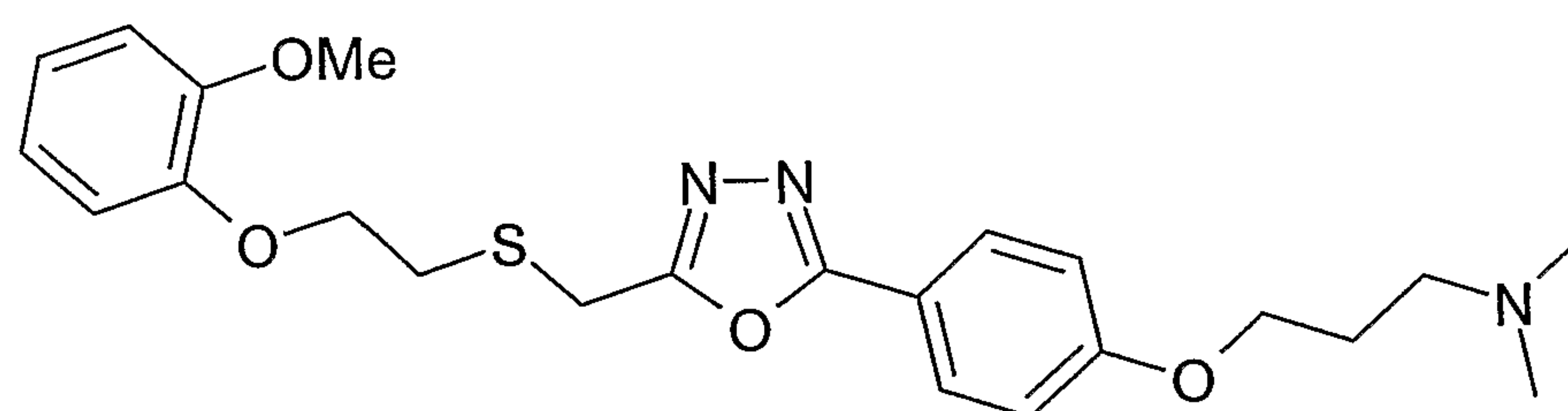
Example 186



¹H NMR (MeOD) δ 7.39 (d, 2H, J=8 Hz), 7.20 (d, 2H, J=9 Hz), 7.02 (d, 2H, J=8 Hz), 6.83 (d, 2H, J=9 Hz), 4.20 (t, 2H), 4.10 (t, 2H), 4.08 (s, 2H), 3.07 (t, 2H), 2.55 (t, 2H), 2.35 (s, 6H), and 2.05 (quint., 2H). MS (FD) m/e 448.1.

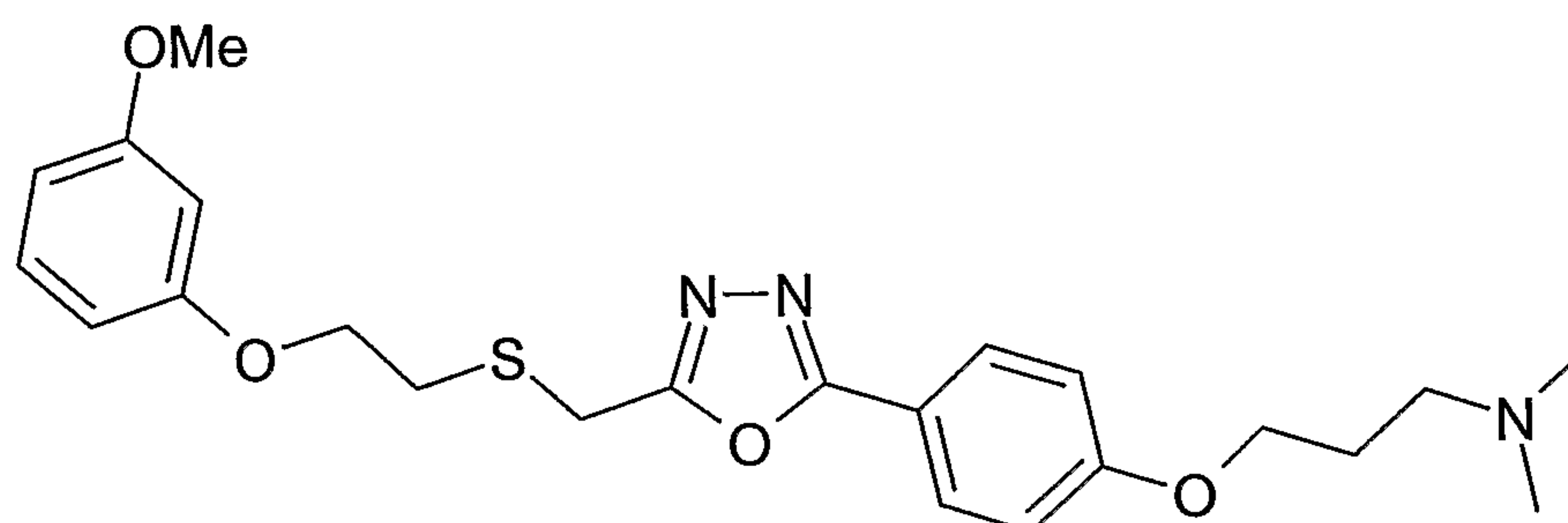
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Example 187



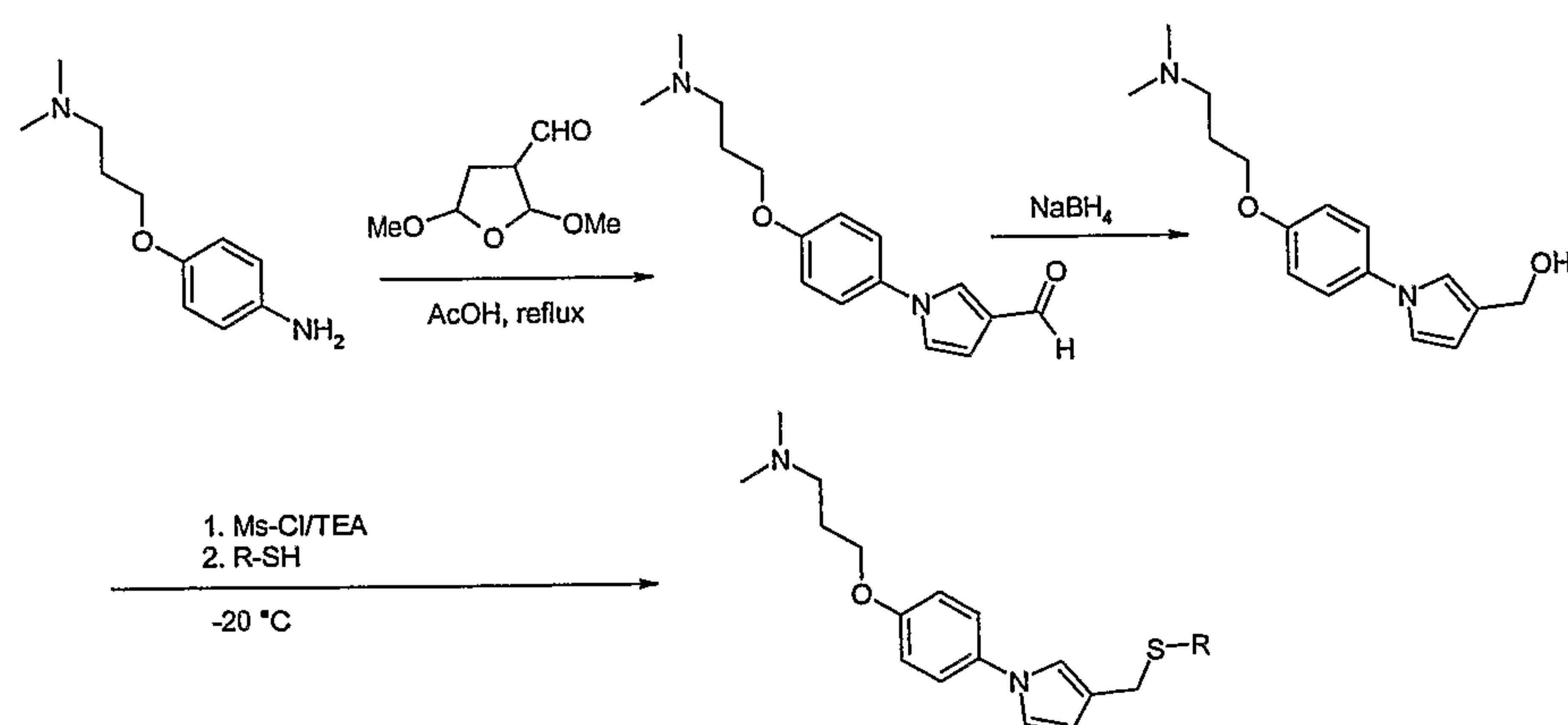
^1H NMR (CDCl_3) δ 7.95 (d, 2H, $J=8\text{Hz}$), 7.00 (d, 2H, $J=8\text{Hz}$), 6.90 (m, 4H), 4.20 (t, 2H), 4.10 (t, 2H), 4.05 (s, 2H) 3.78 (s, 3H), 3.07 (t, 2H), 2.45 (t, 2H), 2.25 (s, 6H), and 1.98 (m, 2H). MS (FD) m/e 444.2.

Example 188



^1H NMR (CDCl_3) 7.95 (m, 2H), 7.15 (t, 1H, $J=8\text{Hz}$), 7.00 (m, 2H), 6.42 (m, 3H), 4.20 (t, 2H), 4.05 (t, 2H), 4.05 (s, 2H) 3.78 (s, 3H), 3.05 (t, 2H), 2.45 (t, 2H), 2.25 (s, 6H), and 1.98 (m, 2H). MS (FD) m/e 444.2

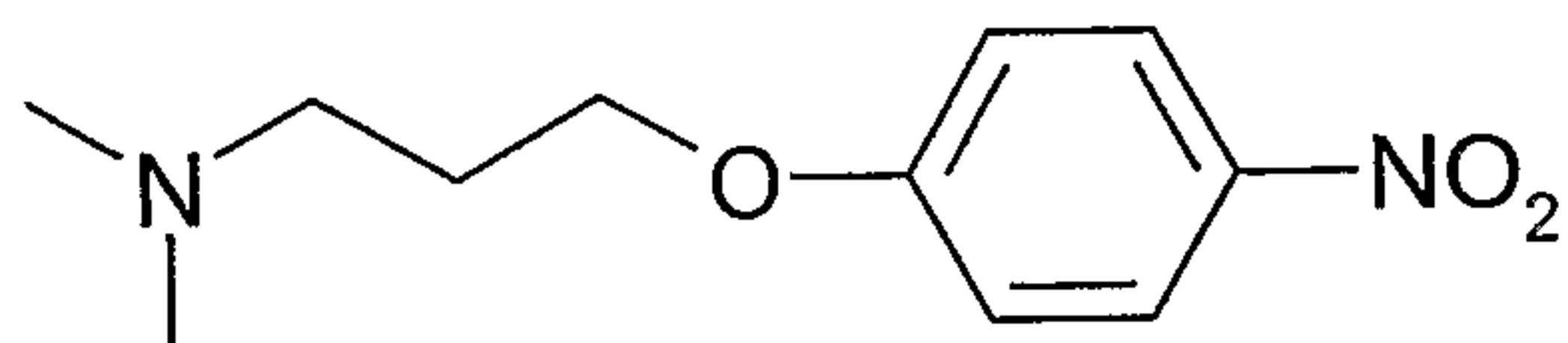
Example 189



15

a) 4-[3-(dimethylamino)propoxy]-nitro benzene

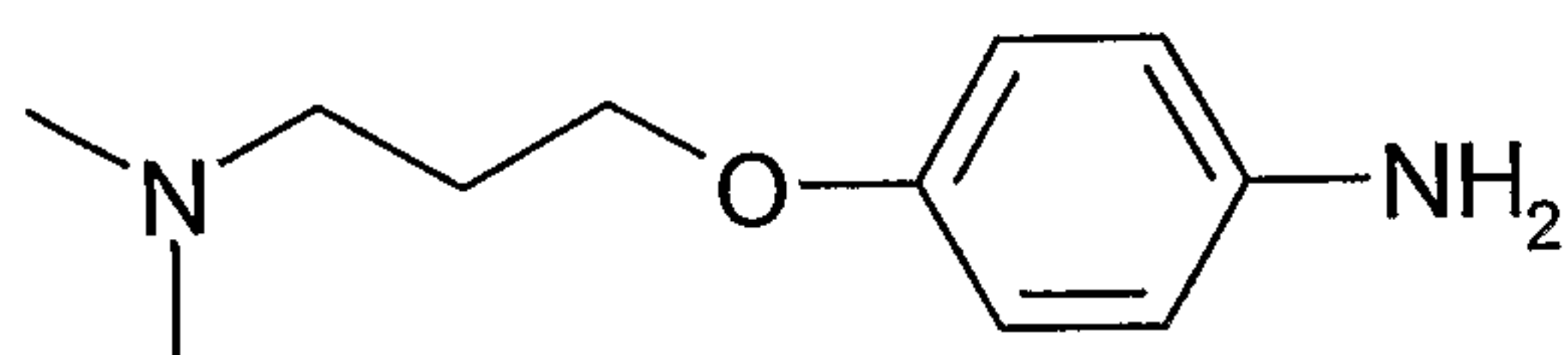
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To a suspension of 4-nitro phenol (30.0 g, 216 mmol), anhydrous potassium carbonate (86.7 g, 627 mmol), and potassium iodide (5.5 g, 33 mmol) in 360 ml of dry DMF was added finely ground 3-dimethylamino-1-propyl chloride hydrochloride (51.7 g, 327 mmol). The mixture was stirred at 80 °C for 4 days. Successively another portion of 3-dimethylamino-1-propyl chloride hydrochloride (15.81 g, 100 mmol) and anhydrous potassium carbonate (25.2 g, 200 mmol) was added and stirring at 80 °C was continued for 16 h. After cooling the mixture was diluted with 1.5 l water and extracted with MTBE (2 times 600 ml). The collected organic phases were dried with sodium sulphate and evaporated. The crude yellow oil (31.7 g, 65.6%) was sufficiently pure and used directly in the next step.

^1H NMR (CDCl_3) δ 8.19 (d, 2H, $J=8$ Hz), 6.96 (d, 2H, $J=8$ Hz), 4.13 (t, 2H, $J=6$ Hz), 2.48 (t, 2H, $J=6$ Hz), 2.28 (s 6H), and 2.00 (quint., 2H, $J=6$ Hz), MS (FD) m/e 225.1.

b) 4-[3-(dimethylamino)propoxy]-aniline



To a solution of 4-[3-(dimethylamino)propoxy]-nitro benzene (12 g, 54 mmol) in 65 ml of absolute ethanol was added 200 mg of $\text{Pd}(\text{OH})_2$ on carbon (Pearlman's catalyst). The mixture was hydrogenated at atmospheric hydrogen pressure for 16 h. The mixture was filtered over diatomaceous earth and the filter cake rinsed with ethanol. The collected ethanolic filtrates were evaporated. The crude orange oil (10.38g, 99%) was sufficiently pure and used directly in the next step.

^1H NMR (CDCl_3) δ 6.83 (d, 2H, $J=8$ Hz), 6.72 (d, 2H, $J=8$ Hz), 3.83 (t, 2H, $J=6$ Hz), 3.40 (s, br, exch. 2H), 2.42 (t, 2H, $J=6$ Hz), 2.25 (s 6H), and 1.91 (quint., 2H, $J=6$ Hz), MS (FD) m/e 195.0.

c) 1-[4-(3-dimethylaminopropoxy)-phenyl]-1H-pyrrole-3-carboxaldehyde

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 357

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 357

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

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WE CLAIM:

1. A compound of formula I:



(I)

- 5 or a pharmaceutically acceptable salt, solvate, enantiomer, diastereomer or mixture of diastereomers or prodrug thereof wherein:

Ar¹ is a cyclic group optionally substituted with one to five groups selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, hydroxy, C₁-C₈ alkoxy, C₁-C₈ alkylaryl, phenyl, -O-aryl, heteroaryl, cycloalkyl, C₁-C₈ alkylcycloalkyl, cyano, -(CH₂)_nNR⁶R⁶, C₁-C₈ haloalkyl, C₁-C₈ haloalkoxy, halo, (CH₂)_nCOR⁶, (CH₂)_nNR⁵SO₂R⁶, -(CH₂)_nC(O)NR⁶R⁶, heterocyclic, and C₁-C₈ alkylheterocyclic; wherein the cycloalkyl, phenyl, aryl, and heterocyclic substituents are each optionally substituted with one to three groups selected from hydroxy, C₁-C₈ alkoxyalkyl, C₁-C₈ haloalkoxy, C₁-C₈ alkyl, halo, C₁-C₈ haloalkyl, nitro, cyano, amino, carboxamido, phenyl, aryl, alkylheterocyclic, heterocyclic, and oxo;

L¹ is a bond or a divalent linker having a main chain of 1 to 10 atoms; or represented by the formula X₂-(CR³R⁴)_m-X₃ where X₂ is attached to Ar¹ and X₃ is attached to Ar² wherein R³ and R⁴ are independently selected from a bond, hydrogen, C₁-C₈ alkyl, C₂-C₈ alkylene, C₂-C₈ alkynyl, phenyl, aryl, C₁-C₈ alkylaryl; wherein the alkyl, alkenyl, phenyl, and aryl groups are optionally substituted with one to five substituents independently selected from oxo, nitro, cyano, C₁-C₈ alkyl, aryl, halo, hydroxy, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, (CH₂)_nC(O)R⁶, and (CH₂)_nCONR⁶R⁶;

X₂ is independently oxygen, -CH, -CONH(CR³R⁴)_m, -NHCO(CR³R⁴)_m, -(CR³R⁴)_m, -CHR⁶, -NR⁵, S, SO, SO₂, -O(CR³R⁴)_m, or -S(CR³R⁴)_m;

25 X₃ is independently oxygen, -C, -CH, -CHR⁶, -(CR³R⁴)_m, -CONH(CR³R⁴)_m, -NHCO(CR³R⁴)_m, -NR⁵, -NR⁵(CR³R⁴)_m, S, SO(CR³R⁴)_m, SO₂(CR³R⁴)_m, S(CR³R⁴)_m, SO, or SO₂; -O(CR³R⁴)_m, or -S(CR³R⁴)_m;

Ar² is a 5-member monocyclic heterocyclic aromatic group or positional isomer thereof, having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; and optionally substituted with one to three substituents selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, hydroxy, C₁-C₈ alkoxy, C₁-C₈ alkylaryl, phenyl, aryl, C₃-C₈

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cycloalkyl, C₁-C₈ alkylcycloalkyl, cyano, C₁-C₈ haloalkyl, halo, (CH₂)_nC(O)R⁶, (CH₂)_nC(O)OR⁶, (CH₂)_nNR⁵SO₂R⁶, (CH₂)_nC(O)NR⁶R⁶, and C₁-C₈ alkylheterocyclic; Ar³ is a 6-member monocyclic, aromatic, carbocyclic or heterocyclic ring having 0, 1, 2, or 3 heteroatoms selected from nitrogen, oxygen and sulfur and which is optionally substituted with one to three substituents independently selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, halo, -NHR⁵, C₁-C₈ haloalkyl, C₃-C₈ cycloalkyl, hydroxy, alkoxy, (CH₂)_nC(O)R⁶, (CH₂)_nC(O)OR⁶, (CH₂)_nNR⁵SO₂R⁶, (CH₂)_nC(O)NR⁶R⁶, phenyl, C₁-C₈ alkylaryl, and aryl;

L² is a divalent linker having a chain length of between 1 and 10 atoms in the main chain or is represented by the formula:



wherein X₄ is attached to Ar³ and is selected from the group consisting of C, -CH, CHR⁶, -CO, O, -NR⁵, -NC(O)-, -NC(S), -C(O)NR⁵-, -NR⁶C(O)NR⁶, -NR⁶C(S)NR⁶, -SO₂NR⁷, -NRSO₂R⁷, and -NR⁶C(NR⁵)NR⁶;

X₅ is selected from the group consisting of -CH₂, -CH, -O(CR³R⁴)_m, NR³(CR³R⁴)_m, SO, SO₂, S, and SCH₂; wherein the group X₄-(CR³R⁴)_m-X₅ imparts stability to the compound of formula (1) and may be a saturated or unsaturated chain or divalent linker.

Q is a basic group or a group represented by -NR¹R²; wherein

R¹ and R² are independently hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₈ cycloalkane, C₁-C₈ alkylaryl, -C(O)C₁-C₈ alkyl, -C(O)OC₁-C₈ alkyl, C₁-C₈ alkylcycloalkane, (CH₂)_nC(O)OR⁵, (CH₂)_nC(O)R⁵, (CH₂)_nC(O)NR⁶R⁶, and (CH₂)_nNSO₂R⁵; wherein each of the alkyl, alkenyl, aryl are each optionally substituted with one to five groups

independently selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, phenyl, and alkylaryl; and

wherein R¹ and R² may combine together, and with the nitrogen atom to which they are

attached or with 0, 1, 2 or 3 atoms adjacent to the nitrogen atom to form a nitrogen containing heterocycle which may have 1, or 2 substituents independently selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₈ cycloalkane, C₁-C₈ alkylaryl, -C(O)C₁-C₈ alkyl, -C(O)OC₁-C₈ alkyl, C₁-C₈ alkylcycloalkane, oxo, halo amino, and (CH₂)_nC(O)NR⁶R⁶;

provided that L²-Q is not CONH₂; wherein R¹ and R² may combine with the nitrogen

atom to which they are attached to form an imine; and provided that Q is not a substituent on an amide;

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R^5 is hydrogen, CN, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_5 - C_8 alkylaryl, $(CH_2)_nNSO_2C_1$ - C_8 alkyl, $(CH_2)_nNSO_2$ phenyl, $(CH_2)_nNSO_2$ aryl, $-C(O)C_1$ - C_8 alkyl, or $-C(O)OC_1$ - C_8 alkyl; and R^6 and $R^{6'}$ are each independently hydrogen, C_1 - C_8 alkyl, phenyl, aryl, C_1 - C_8 alkylaryl, or C_3 - C_8 cycloalkyl;

5 R^7 is hydrogen, C_1 - C_8 alkyl, phenyl, aryl, C_1 - C_8 alkylaryl, or C_3 - C_8 cycloalkyl, and wherein m is an integer from 1 to 8; and n is an integer from 0 to 8.

2. A compound according to Claim 1 wherein the Ar^1 is selected from the group consisting of cycloheptane, cyclohexane, cyclopentane, phenyl, naphthyl,
10 benzofuranyl and benzothienyl.

3. A compound according to Claim 1 wherein the Ar^1 is selected from the group consisting of phenyl, naphthyl, benzofuranyl and benzothienyl.

15 4. A compound according to Claim 1 wherein the group L^1 is a divalent linker selected from the group consisting of: $-CH_2CH_2CH_2-$, $-SCH_2-$, $-OCH_2-$, $-CH_2SCH_2-$, $-CH_2OCH_2-$, $-OCH_2CH_2SCH_2-$, $-O(CH_2)_3SCH_2-$, $-OCH_2CH_2OCH_2-$, $-O(CH_2)_3OCH_2-$, $-O(CH_2)_3CH_2O-$, $-(CH_2)_3SCH_2-$, and $-(CH_2)_4SCH_2-$.

20 5. A compound according to Claim 3 wherein the group L^1 is a divalent linker selected from the group consisting of: $-CH_2SCH_2-$, $-CH_2OCH_2-$, $-OCH_2CH_2OCH_2-$, and $-OCH_2CH_2SCH_2-$.

6. A compound according to Claim 1 wherein Ar^2 is a 5-member aromatic group selected from the group consisting of: furan, thiophene, pyrrole, thiazole,
25 oxazole, isoxazole, isothiazole, thiadiazole and oxadiazole.

7. A compound according to Claim 5 wherein Ar^2 is a 5-member aromatic group selected from the group consisting of: furan, thiophene, pyrrole, thiazole,
30 oxazole, isoxazole, isothiazole, thiadiazole and oxadiazole.

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8. A compound according to Claim 5 wherein Ar² is 5-member aromatic group selected from the group consisting of: furan, oxazole, and oxadiazole.

9. A compound of Claim 1 wherein Ar³ is a 6-member aromatic group
5 selected from the group consisting of phenyl, and pyridine.

10. A compound of Claim 1 wherein Ar³ is 1,4 -phenylene.

11. A compound of Claim 7 wherein Ar³ is 1,4 -phenylene.

10

12. A compound according to Claim 7 wherein Ar³ is pyridine.

13. A compound according to Claim 1 wherein the linker L² is: —
OCH₂CH₂-, -O(CH₂)₃-, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH=CHCH₂-, -
15 CH=CHCH₂CH₂-, - CH=CHCH₂CH₂CH₂-, -CONHCH₂CH₂CH₂-, -CONHCH₂CH₂-, -
NHCONHCH₂CH₂-, -NHCON(CH₃)CH₂CH₂-, - NHCON(CH₃)CH₂CH₂CH₂-, -
NHCONHCH₂CH₂CH₂-, -NHCSNHCH₂CH₂-, -NHCSNHCH₂CH₂CH₂-, -
NHC(CN)NHCH₂CH₂-, -NHC(CN)NHCH₂CH₂CH₂-, -NHCOCH₂CH₂-, and -
NHCOCH₂CH₂CH₂-.

20

14. A compound according to Claim 5 wherein the linker L² is: —
OCH₂CH₂-, -O(CH₂)₃-, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH=CHCH₂-, -
CH=CHCH₂CH₂-, - CH=CHCH₂CH₂CH₂-, -CONHCH₂CH₂CH₂-, -CONHCH₂CH₂-, -
NHCONHCH₂CH₂-, -NHCON(CH₃)CH₂CH₂-, - NHCON(CH₃)CH₂CH₂CH₂-, -
25 NHCONHCH₂CH₂CH₂-, -NHCSNHCH₂CH₂-, -NHCSNHCH₂CH₂CH₂-, -
NHC(CN)NHCH₂CH₂-, -NHC(CN)NHCH₂CH₂CH₂-, -NHCOCH₂CH₂-, and -
NHCOCH₂CH₂CH₂-.

15. A compound according to Claim 7 wherein the linker L² is: —
30 OCH₂CH₂-, -O(CH₂)₃-, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH=CHCH₂-, -
CH=CHCH₂CH₂-, - CH=CHCH₂CH₂CH₂-, -CONHCH₂CH₂CH₂-, -CONHCH₂CH₂-, -
NHCONHCH₂CH₂-, -NHCON(CH₃)CH₂CH₂-, - NHCON(CH₃)CH₂CH₂CH₂-, -

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NHCONHCH₂CH₂CH₂-, -NHCSNHCH₂CH₂-, -NHCSNHCH₂CH₂CH₂-, -
 NHC(CN)NHCH₂CH₂-, -NHC(CN)NHCH₂CH₂CH₂-, -NHCOCH₂CH₂-, and -
 NHCOCH₂CH₂CH₂-.

- 5 16. A compound according to Claim 11 wherein the linker L² is: -
 OCH₂CH₂-, -O(CH₂)₃-, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH=CHCH₂-, -
 CH=CHCH₂CH₂-, -CH=CHCH₂CH₂CH₂-, -CONHCH₂CH₂CH₂-, -CONHCH₂CH₂-, -
 NHCONHCH₂CH₂-, -NHCON(CH₃)CH₂CH₂-, -NHCON(CH₃)CH₂CH₂CH₂-, -
 NHCONHCH₂CH₂CH₂-, -NHCSNHCH₂CH₂-, -NHCSNHCH₂CH₂CH₂-, -
 10 NHC(CN)NHCH₂CH₂-, -NHC(CN)NHCH₂CH₂CH₂-, -NHCOCH₂CH₂-, and -
 NHCOCH₂CH₂CH₂-.

17. A compound according to Claim 11 wherein the linker L² is: -
 OCH₂CH₂-, or -O(CH₂)₃-.

15

18. A compound according to Claim 11 wherein the linker L² is: -
 CH=CHCH₂-, -CH=CHCH₂CH₂-, and -CH=CHCH₂CH₂CH₂-.

19. A compound according to Claim 11 wherein the linker L² is: -
 20 NHCONHCH₂CH₂-, -NHCON(CH₃)CH₂CH₂-, -NHCON(CH₃)CH₂CH₂CH₂-, and -
 NHCONHCH₂CH₂CH₂-.

20. A compound according to Claim 1 wherein R¹ and R² combine
 with the nitrogen atom to form piperidinyl, pyrrolidinyl, azepine, or azetidyl.

25

21. A compound according to Claim 1 wherein R¹ and R² are
 independently selected from the group consisting of hydrogen, methyl, ethyl, propyl,
 isopropyl, methylcyclopentane, methylcyclohexane, phenyl, benzyl, cyclopentyl,
 cyclohexyl, methylcyclopropane and methylcyclobutane.

30

22. A compound according to Claim 1 wherein the group Ar² is
 oxadiazole.

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23. A compound according to Claim 1 wherein the group Ar² is oxazole.

5 24. A compound according to Claim 9 wherein the group Ar³ is phenyl or pyridyl substituted with 1 to 3 substituents selected from chloro, fluoro, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₈ alkenyl, substituted or unsubstituted phenyl, aryl, C₁-C₈ alkylaryl, (CH₂)_nC(O)R⁶, (CH₂)_nCONR⁶R⁶, and (CH₂)_nOR⁶.

10 25. A compound according to Claim 1 wherein at least one of L¹ and L² has a chain length of between 3 to 8 atoms.

26. A compound according to Claim 1 wherein L² has a chain length of between 3 to 8 atoms.

15 27. A compound selected from the group consisting of:
 1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-dimethylamino-ethyl)-urea,
 1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,
 20 1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,
 1-(3-{4-[5-(Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidine,
 25 Cyclohexyl-ethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
 4-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-morpholine,
 1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azepane,
 30 Diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,

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- 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-piperidine,
- (3-{2-Chloro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,
- 5 1-Methyl-4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-piperazine,
- (3-{2-Fluoro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,
- Ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
- 10 Cyclopentyl-methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
- 1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azocane,
- Diethyl-(2-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-amine,
- 15 Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
- Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-4-yl]-phenoxy}-propyl)-amine,
- 2-{4-[2-(1-Methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole,
- 20 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propenyl)-phenyl]-[1,3,4]oxadiazole,
- Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-furan-2-yl]-phenoxy}-propyl)-amine,
- 4-Dimethylamino-N-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-butyramide,
- 25 1-(2-Dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- 1-(3-Dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- 30 Dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine,

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- 1-(2-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-piperidine,
- Dimethyl-(5-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-pent-4-enyl)-amine,
- 5 2-(2-Dimethylamino-ethoxy)-N-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-acetamide,
- Dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine,
- 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidine,
- 10 Diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,
- 1-(4-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-piperidine,
- 15 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(4-pyrrolidin-1-yl-butoxy)-phenyl]-[1,3,4]oxadiazole,
- 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-azepane,
- 1-(2-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-azepane,
- 20 Methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,
- Diethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine,
- 25 1-(2-Dimethylamino-ethyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-[1,3,4]oxadiazole,
- 1-(5-Dimethylamino-pentyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- 30 1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,

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- 1-(4-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-azepane,
- Diethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine,
- 5 1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,
- 1-(2-Dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- (3-{4-[5-(Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,
- 10 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(5-pyrrolidin-1-yl-pent-1-enyl)-phenyl]-[1,3,4]oxadiazole,
- 1-(5-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-pent-4-enyl)-piperidine,
- 15 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidin-4-one,
- 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazole,
- Dimethyl-(2-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-amine,
- 1-(2-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-piperidine,
- 20 1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-piperidine,
- 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-oxazole,
- Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-amine,
- Dimethyl-(6-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-hex-
- 25 5-enyl)-amine,
- Dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-but-3-enyl)-amine,
- Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenoxy}-propyl)-amine,
- 30 (3-{4-[5-(Benzo[b]thiophen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,

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Dimethyl-(3-{4-[5-(naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,

Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,

5 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,3,4]oxadiazole,

2-[4-(3-Azetidin-1-yl-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole,

10 1-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,

1-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,

1-(2-Dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-urea,

15 1-(2-Dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-urea,

1-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea,

20 1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea,

N,N-dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-ethane-1,2-diamine,

N,N-Dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-propane-1,3-diamine,

25 1-Methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy-methyl}-piperidine,

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propenyl)-phenyl]-oxazole,

1-(2-Diethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

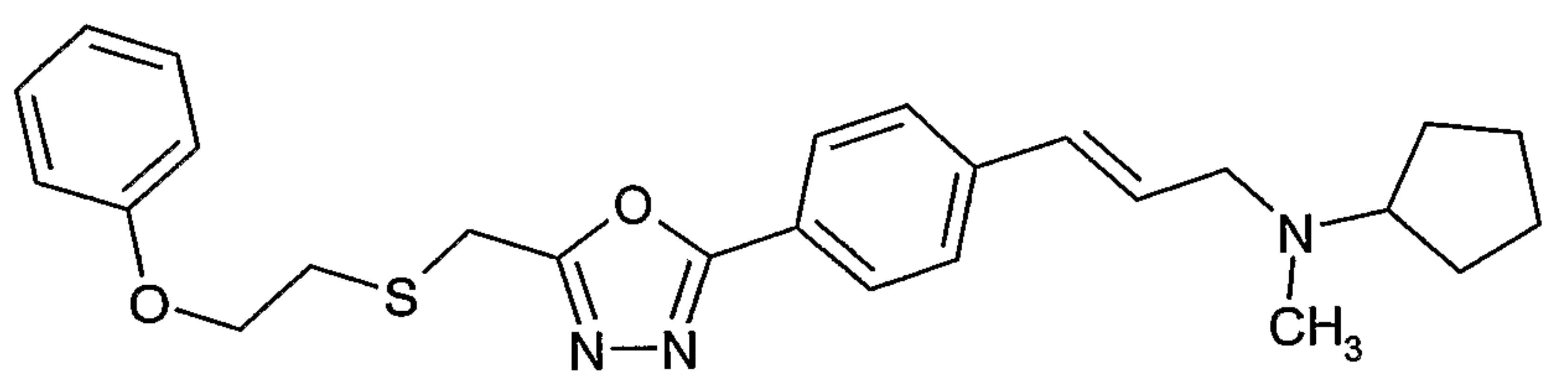
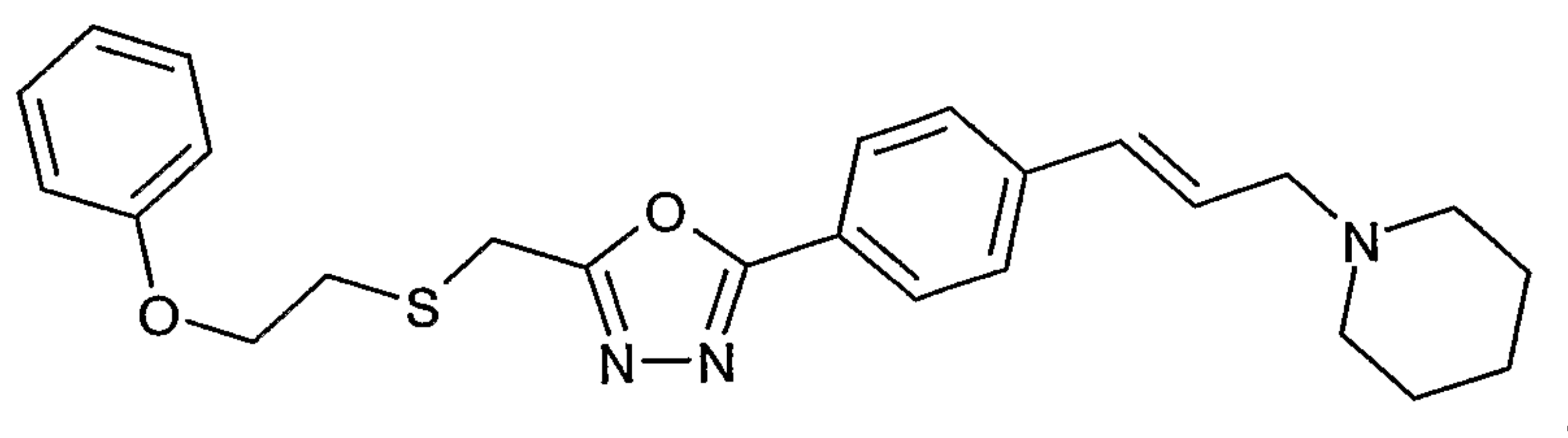
30 5-(2-Phenoxy-ethylsulfanylmethyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,2,4]oxadiazole,

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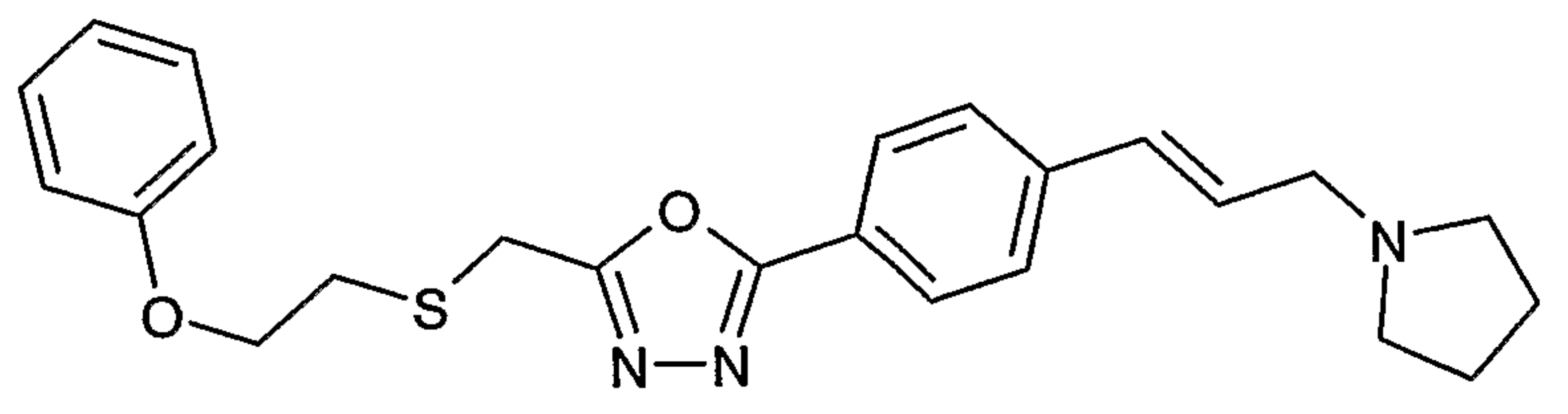
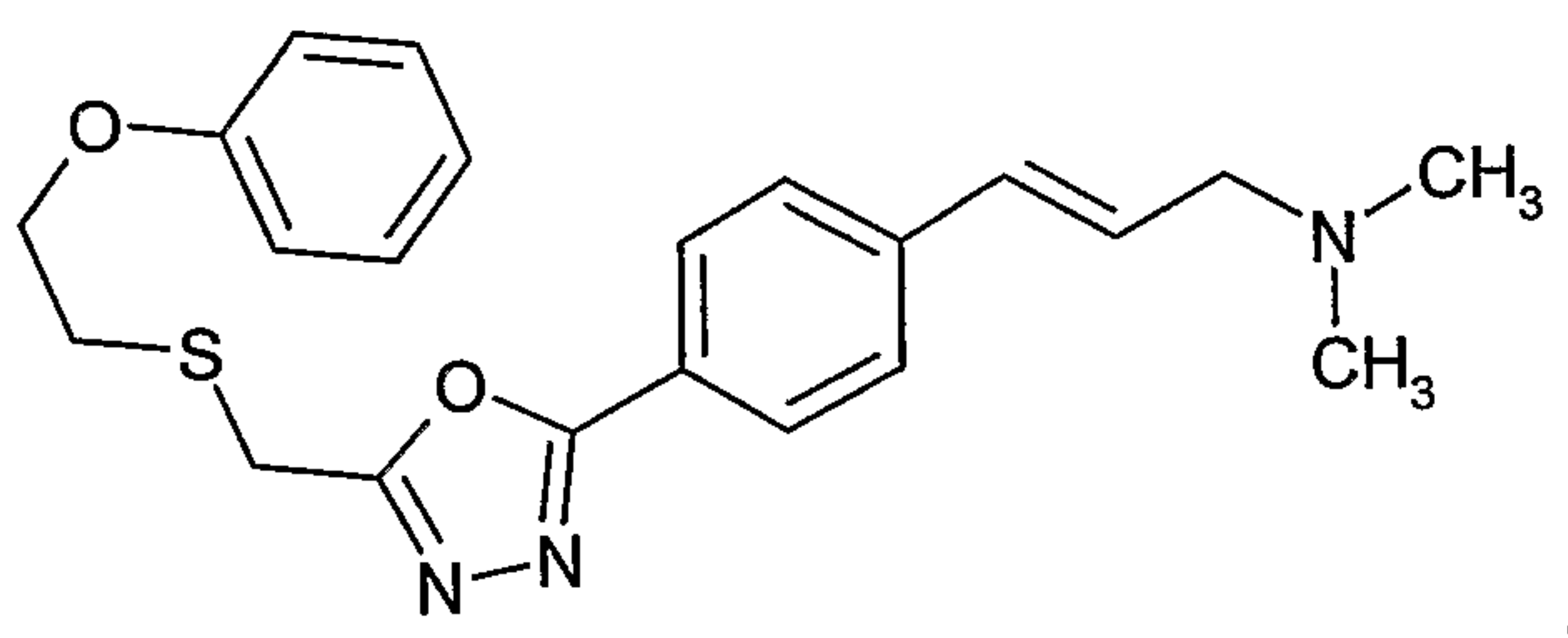
Dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenoxy}-ethyl)-amine, and pharmaceutically acceptable salts, solvates, enantiomers, diastereomers and mixture of diastereomers thereof.

5

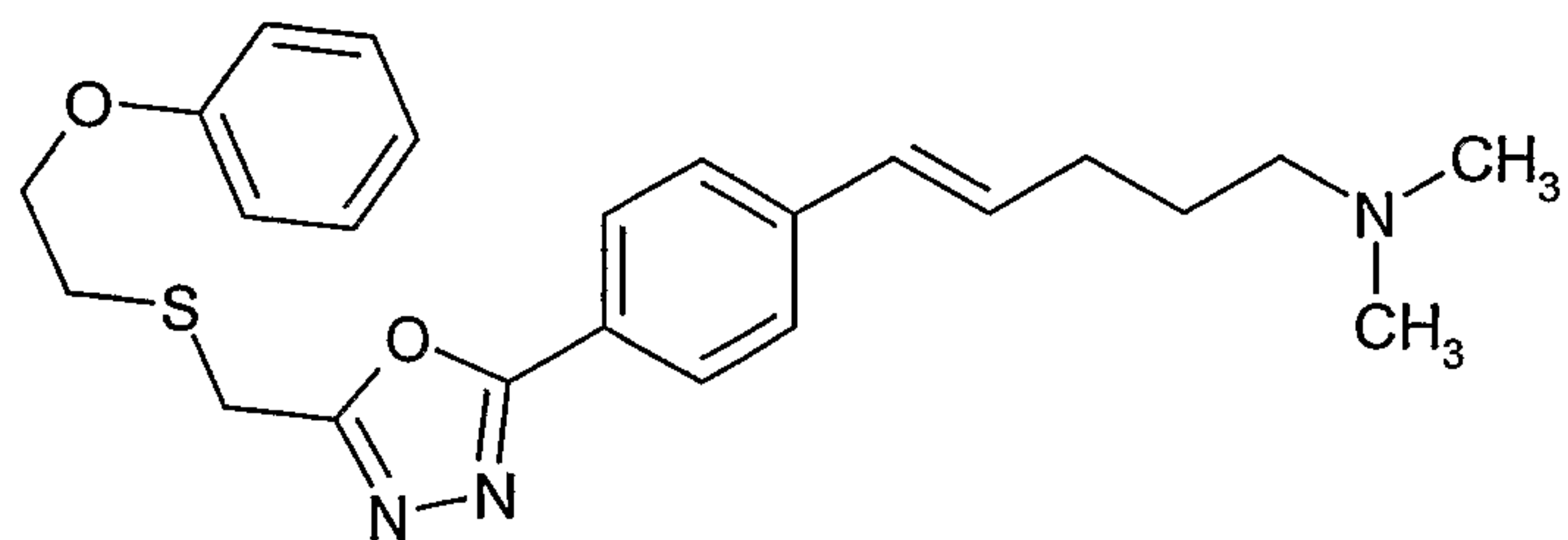
28. A compound represented by the formulae.



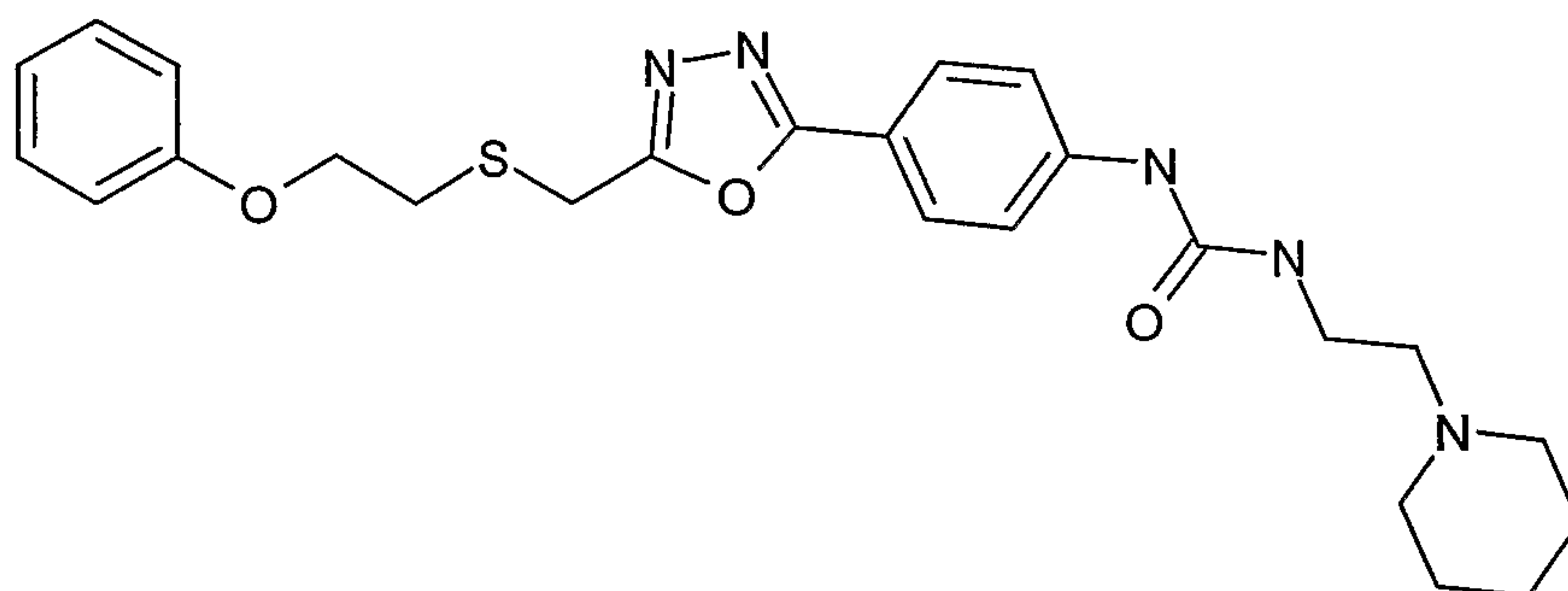
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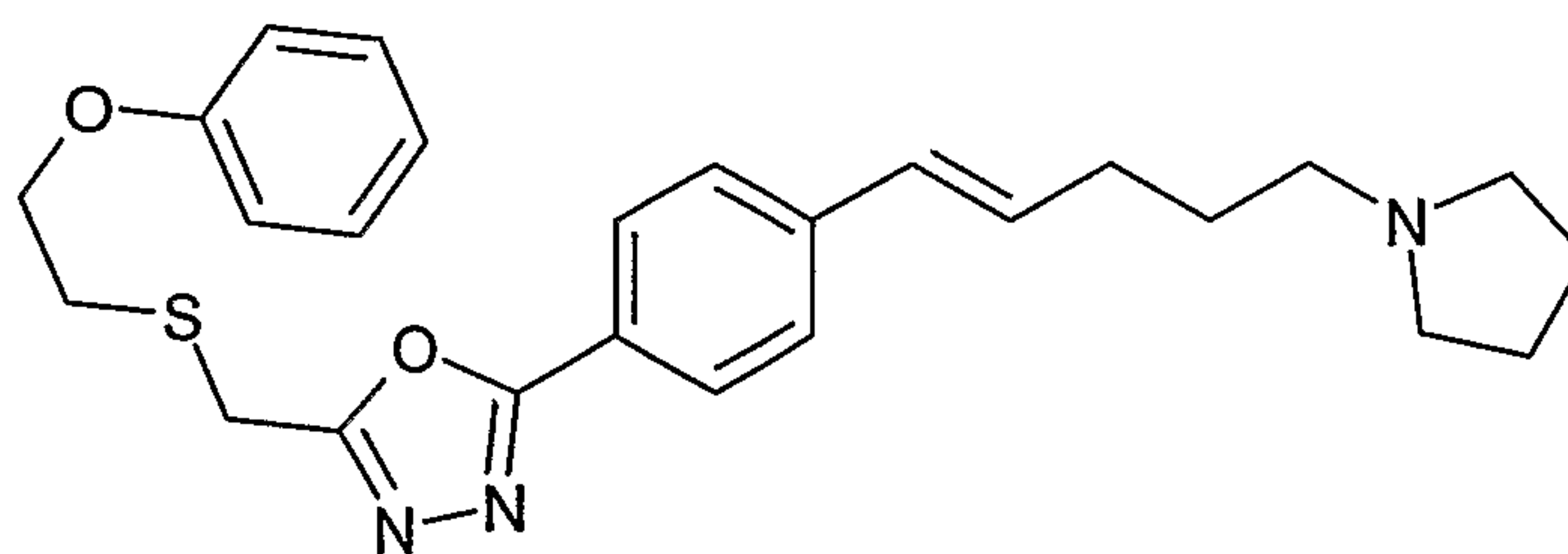
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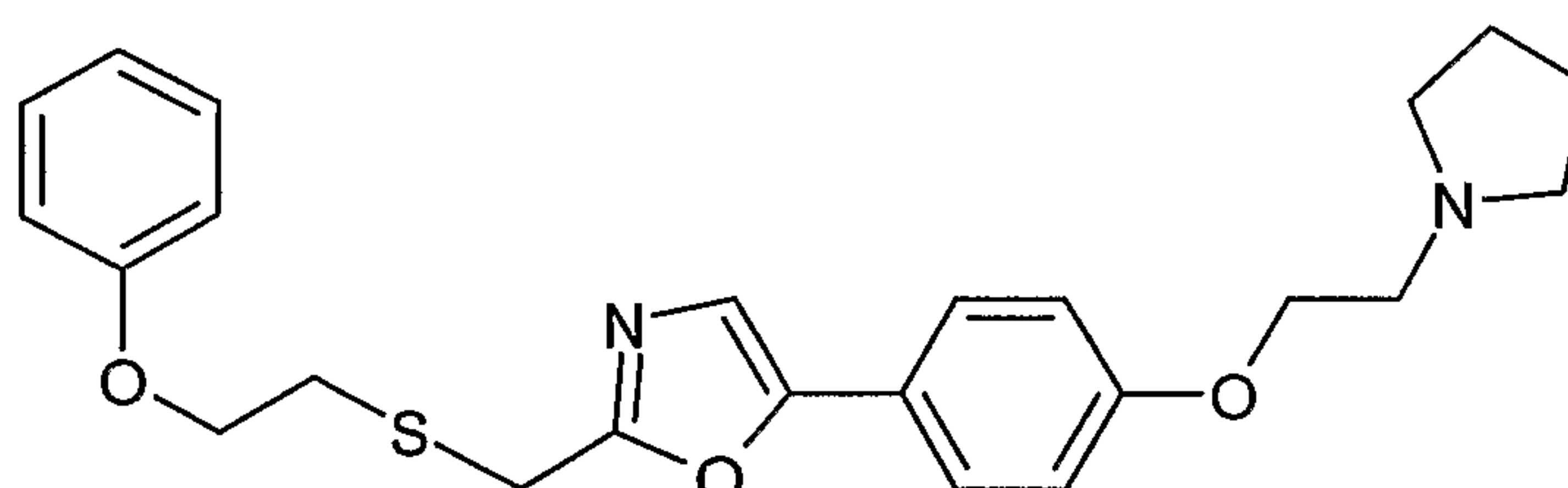
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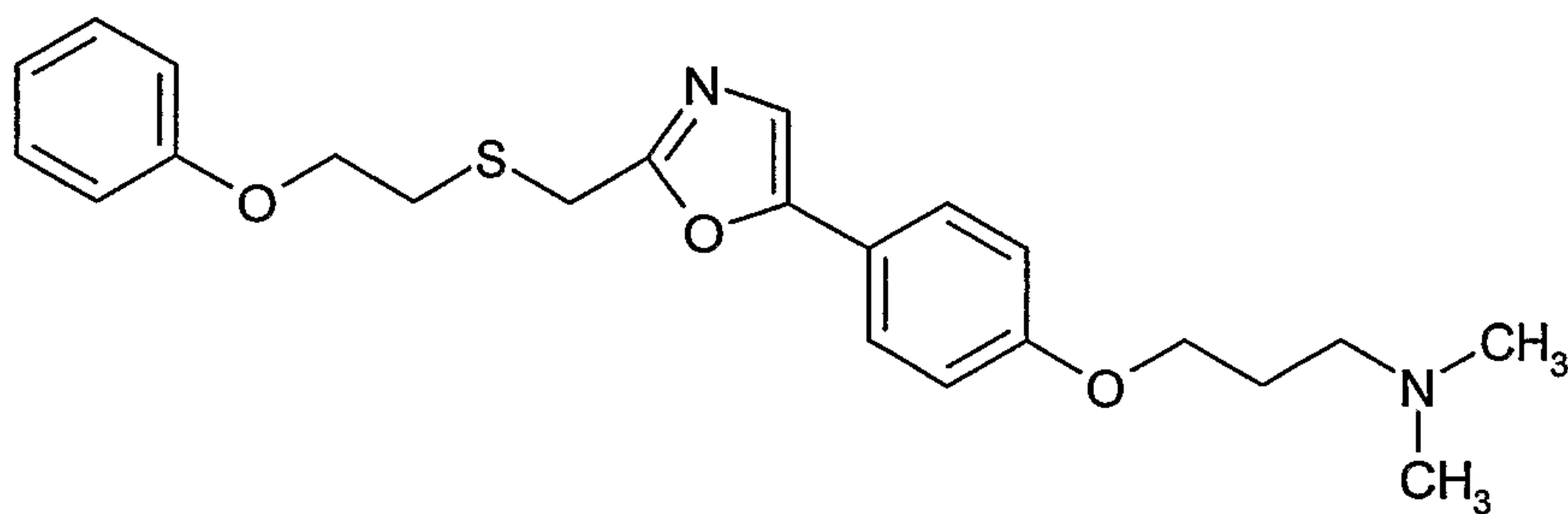
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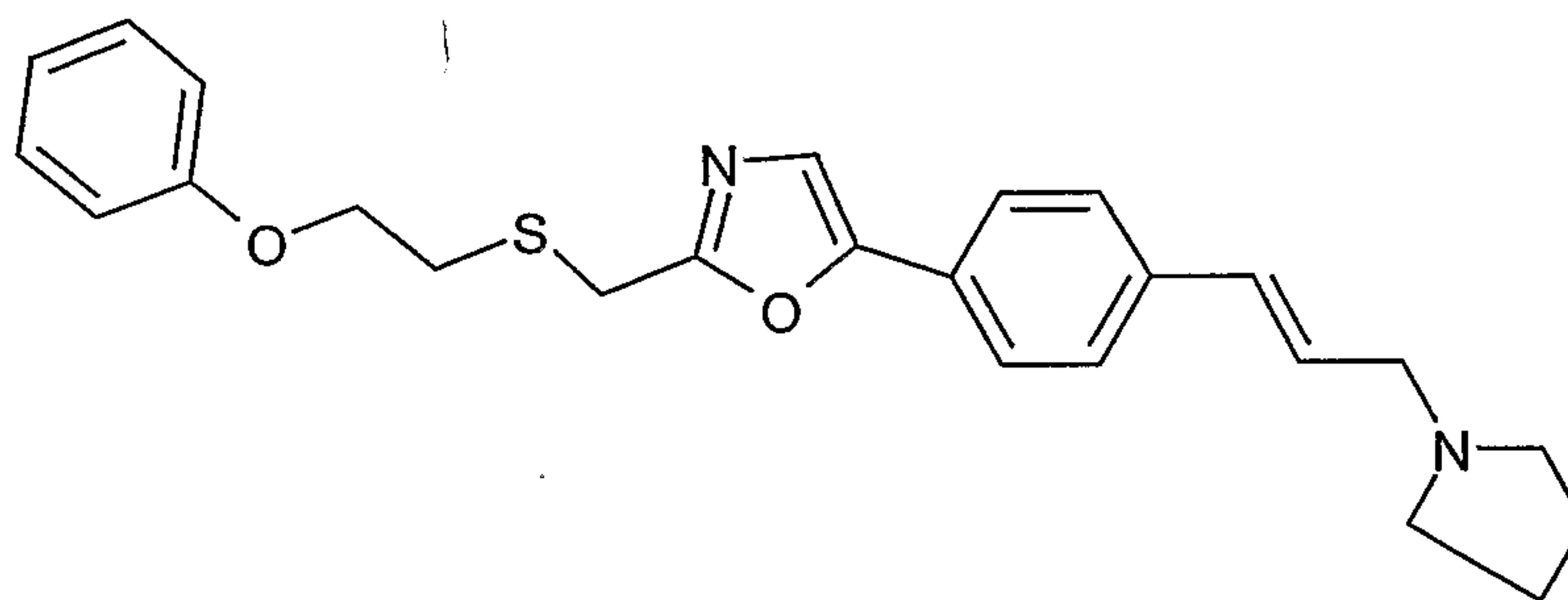


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or a pharmaceutically acceptable salt, solvate, prodrug, enantiomer, diastereomer or mixture of diastereomers thereof.

5 29. The compound of any one of Claims 1-28 which is the hydrochloride salt or the bisulfate salt.

 30. A method of treating obesity comprising administering to a patient in need thereof a compound of any one of Claims 1-28.

10 31. A method of preventing Type II Diabetes comprising administering to a patient in need thereof a compound of any one of Claims 1-28.

 32. A method of inhibiting release of the melanocortin concentrating hormone comprising administering to a patient in need thereof a compound of any one of
15 Claims 1-28.

 33. A method of treating, preventing or ameliorating the symptoms of obesity and Related Diseases comprising administering to a patient in need thereof, a pharmaceutically effective amount of a compound of formula I.

20 34. A pharmaceutical formulation comprising a compound of any one of Claims 1-28 and a pharmaceutical carrier for the treatment of obesity and related diseases.

25 35. Use of a compound of formula I as an appetite suppressant.

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36. Use of a compound of formula I for the treatment, prevention or amelioration of the symptoms of eating disorders (bulima, anorexia nervosa, etc.), diabetes, diabetic complications, diabetic retinopathy, sexual/reproductive disorders, depression, anxiety, social withdrawal, urge incontinence, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleeping disorders, atherosclerosis, rheumatoid arthritis, stroke, hyperlipidemia, hypertriglycemia, hyperglycemia, and hyperlipoproteinenamia, comprising administering an effective amount of a compound of formula I to a patient in need thereof.

37. Use of a compound of formula I in the manufacture of a medicament for the treatment of obesity and Related Diseases including diabetes mellitus, hyperglycemia, obesity, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, atherosclerosis of coronary, cerebrovascular and peripheral arteries, gastrointestinal disorders including peptid ulcer, esophagitis, gastritis and duodenitis, (including that induced by H. pylori), intestinal ulcerations (including inflammatory bowel disease, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal ulcerations, neurogenic inflammation of airways, including cough, asthma, depression, prostate diseases such as benign prostate hyperplasia, irritable bowel syndrome and other disorders needing decreased gut motility, diabetic retinopathy, neuropathic bladder dysfunction, elevated intraocular pressure and glaucoma and non-specific diarrhea dumping syndrome.

38. The combination of a compound of formula I, its salt, enantiomer or prodrug thereof, with other approved therapeutic agents for the treatment and/or prevention of obesity and related diseases.