(CONVENTION. By one or more persons and/or a Company) Form 4

624092

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

~~I~~/We[1] HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED of Route 202-206 North, Somerville, New Jersey 08876, United States of America

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled:[2] 3-[4(1-SUBSTITUTED-4-PIPERAZINYL)BUTYL]-4-THIAZOLIDINONES A PROCESS FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS

(3) Here insert number(s) of basic application(s)

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered[3] 123,622

(4) Here insert Name of basic Country or Countries, and basic date or dates

for a patent or similar protection made in[4] United States of America on 20th November 1987

~~My~~/Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys, 50 Queen Street, Melbourne, Victoria, Australia.

DATED this 17th day of November 19 88

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

(5) HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED

By D. B. Mischlewski

Registered Patent Attorney

To:

Form 7 57/5026

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION UNDER PART XVI. FOR A PATENT.

In support of the Convention application made under Part XVI. of the Patents Act 1952 by HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED, Route 202-206 North, Somerville, New Jersey 08876, United States of America for a patent for an invention entitled:

3-[4(1-Substituted-4-piperazinyl)butyl]-4-thiazolidinones a process for their preparation and their use as medicaments

I, Donald R. Thorsen, Route 202-206 North, Somerville, NJ, United States of America

do solemnly and sincerely declare as follows:

1. I am authorized by HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in the United States of America under No. 123,622 on November 20, 1987

by Nicholas J. Hrib and John Gerard Jurcak

3. a) Nicholas J. Hrib, 356 Gemini Drive, Apt. 4, Somerville, N.J. 08876
b) John Gerard Jurcak, 70 JFK Boulevard, Apt. 315, Somerset, N.J. 08873
a) and b) United States of America

~~is~~/are the actual inventor(s) of the invention and the facts upon which HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED is entitled to make the application are as follows:

The said HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED is the assignee of the said Nicholas J. Hrib and John Gerard Jurcak

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Somerville, New Jersey, United States of America this 9th day of September, 1988

HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED

Donald R. Thorsen

Donald R. Thorsen - Secretary

To the Commissioner of Patents

(12) PATENT ABRIDGMENT (11) Document No. AU-B-25694/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 624092

(54) Title
3-(4(1-SUBSTITUTED-4-PIPERAZINYL)BUTYL)-4-THIAZOLIDINONES A PROCESS FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS

(51)[4] International Patent Classification(s)
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A61K 031/495

(21) Application No. : **25694/88** (22) Application Date : **18.11.88**

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123622	20.11.87	US UNITED STATES OF AMERICA

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(44) Publication Date of Accepted Application : **04.06.92**

(71) Applicant(s)
HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED

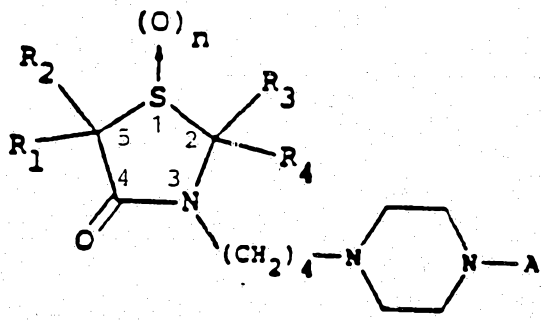
(72) Inventor(s)
NICHOLAS J. HRIB; JOHN GERARD JURCAK

(74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122

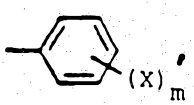
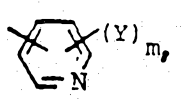
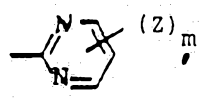
(56) Prior Art Documents
AU 591473 52294/86 C07D 417/12 413/12 413/14 401/12
AU 593247 57276/86 C07D 277/14 277/34 417/06 417/12
JP 51-125389

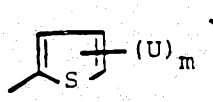
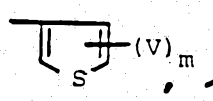
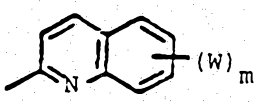
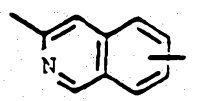
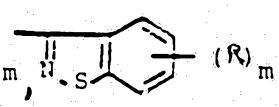
(57) Claim

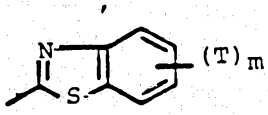
1. A compound of the formula I



I

where n is ϕ or 1; A is   

or  where X, Y, Z, U, V, W, Q, R and T are each hydrogen, halogen, loweralkyl, hydroxy, nitro, loweralkoxy, amino, cyano or trifluoromethyl; m is 1 or 2; R_1 and R_2 are independently hydrogen, loweralkyl or aryl,

.../2

or alternatively R_1 + R_2 taken together with the carbon atom to which they are attached form a cyclopentane, cyclohexane, cycloheptane, pyran, thiopyran, pyrrolidine or piperidine ring; R_3 and R_4 are independently hydrogen or loweralkyl, or alternatively R_3 + R_4 taken together with the carbon atom to which they are attached form a cyclopentane, cyclohexane, cycloheptane, pyran, thiopyran, pyrrolidine or piperidine ring, the term aryl signifying an unsubstituted phenyl group or a phenyl group substituted with 1, 2 or 3 substituents each of which being independently loweralkyl, loweralkoxy, hydroxy, halogen, loweralkylthio, cyano, amino or trifluormethyl, or a pharmaceutically acceptable acid addition salt thereof.

11. A method of preparation of a medicament having antipsychotic, analgesic preparation of a medicament having antipsychotic, analgesic and/or anticonvulsant activity comprising combining in pharmacologically effective amounts of compound as claimed in claim 1 and as pharmaceutically acceptable carrier or excipient.

624092

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

Name of Applicant : HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED

Address of Applicant : Route 202-206 North, Somerville, New Jersey 08876, United States of America

Actual Inventor: NICHOLAS J. HRIB and JOHN GERARD JURCAK

Address for Service : EDWD. WATERS & SONS,
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

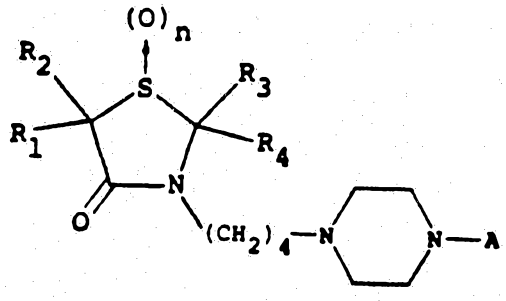
3-[4(1-SUBSTITUTED-4-PIPERAZINYL)BUTYL]-4-THIAZOLIDINONES A PROCESS FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS

The following statement is a full description of this invention, including the best method of performing it known to :- us

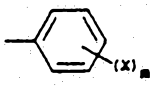
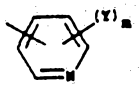
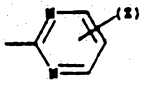
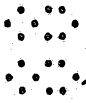
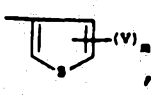
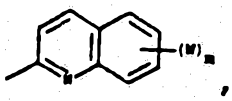
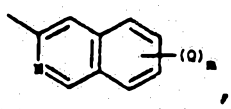
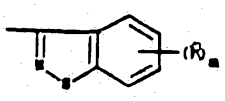
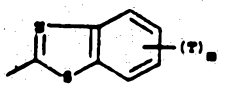
HOECHST-ROUSSEL PHARMACEUTICALS INC. HOE 87/S 026

3-[4(1-Substituted-4-piperazinyl)butyl]-4-thiazolidinones a process for their preparation and their use as medicaments.

The present invention relates to compounds of the formula I



I

where n is 0 or 1; A is  ,  ,  ,  ,  ,  ,  ,  , or  where X, Y, Z, U, V, W, Q, R and T are each hydrogen, halogen, loweralkyl, hydroxy, nitro, loweralkoxy, amino, cyano or trifluoromethyl; m is 1 or 2; R_1 and R_2 are independently hydrogen, loweralkyl or aryl, or alternatively $R_1 + R_2$ taken together with the carbon atom to which they are attached form a cyclopentane, cyclohexane, cycloheptane, pyran, thiopyran, pyrrolidine or piperidine ring; R_3 and R_4

are independently hydrogen or loweralkyl, or alternatively $R_3 + R_4$ taken together with the carbon atom to which they are attached form a cyclopentane, cyclohexane, cycloheptane, pyran, thiopyran, pyrrolidine or piperidine ring, the term aryl signifying an unsubstituted phenyl group or a phenyl group substituted with 1, 2 or 3 substituents each of which being independently loweralkyl, loweralkoxy, hydroxy, halogen, loweralkylthio, cyano, amino or trifluormethyl, which are useful as antipsychotic, analgesic, anticonvulsant and anxiolytic agents.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo, optical, and geometrical isomers thereof where such isomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof such as for instance hydrates.

The following general rules of terminology shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term loweralkyl denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said loweralkyl group include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

Unless otherwise stated or indicated, the term loweralkoxy denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms. Examples of said

loweralkoxy include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and straight- and branched-chain pentoxy and hexoxy.

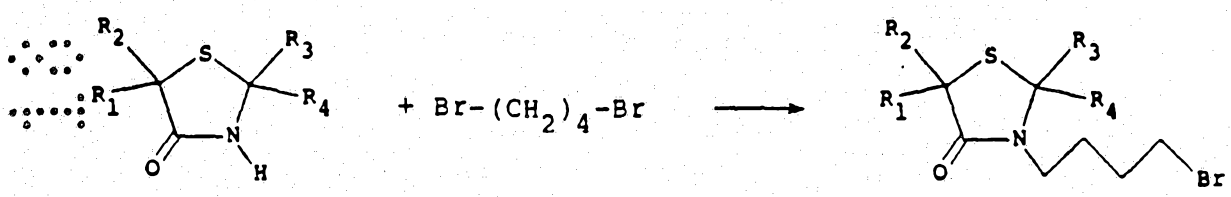
Unless otherwise stated or indicated, the term halogen shall mean fluorine, chlorine, bromine or iodine.

Unless otherwise stated or indicated, the term aryl shall mean a phenyl group having Ø, 1, 2 or 3 substituents each of which being independently loweralkyl, loweralkoxy, hydroxy, halogen, loweralkylthio, cyano, amino or CF_3.

The compounds of this invention are prepared by following one or more of the steps described below. Throughout the description of the synthetic steps, the definitions of n, m, A, X, Y, Z, U, V, W, Q, S and T; R_1 through R_4 are as given above unless otherwise stated or indicated.

STEP A

A compound of formula II is reacted with 1,4-dibromobutane to afford a compound of formula III.

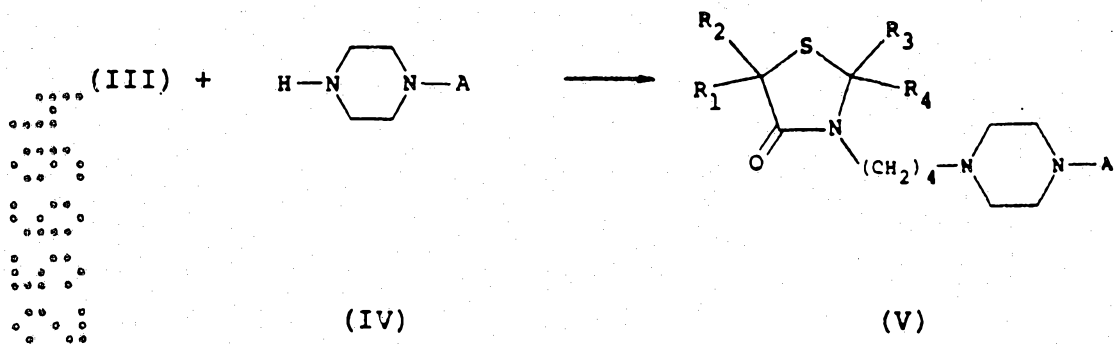


(II) (III)

The above reaction is typically conducted in the presence of a suitable medium such as dimethylformamide or THF and a base such as potassium hydroxide, sodium hydroxide or sodium hydride at a temperature of about 23 to 70°C.

STEP B

Compound III is reacted with a compound of formula IV to afford a compound of formula V.

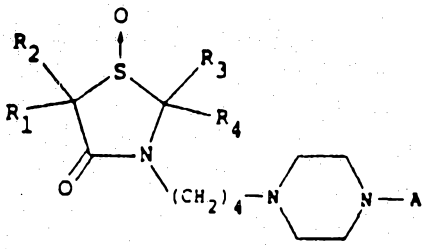


(III) (IV) (V)

The above reaction is typically conducted in the presence of a suitable medium such as anhydrous acetonitrile, an acid scavenger such as potassium carbonate or sodium carbonate and a small amount of potassium iodide or sodium iodide at a temperature of about 20 to 100°C.

STEP C

Compound V is oxidized with a suitable oxidizing agent such as $NaIO_4$ to afford a compound of formula VI.

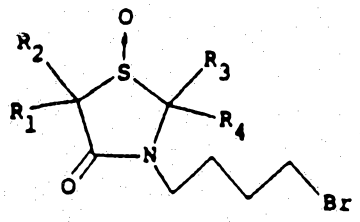
(V) + $NaIO_4$ ⟶ 

(VI)

The above reaction is typically conducted in the presence of a suitable medium such as tetrahydrofuran at a temperature of about -10 to 23°c.

STEP D

Compound III is oxidized in substantially the same manner as in STEP C to afford a compound of formula VII.

(III) + $NaIO_4$ ⟶ 

(VII)

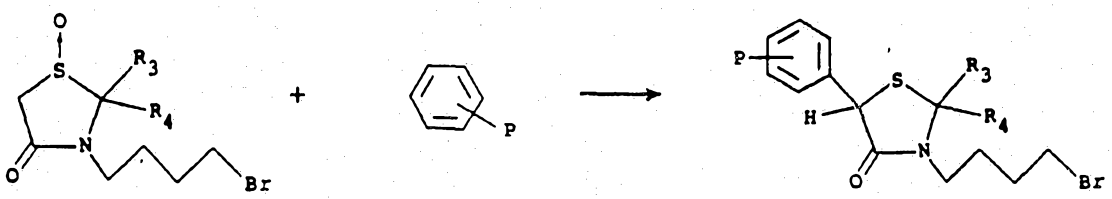
STEP E

Compound VII is reacted with compound IV in substantially the same manner as in STEP B to afford a compound of formula VI.

(VII) + (IV) ⟶ (VI)

STEP F

As an alternative to the foregoing scheme, one can obtain a compound of formula VIII where P is independently hydrogen, loweralkyl, loweralkoxy, hydroxy, loweralkylthio or amino by reacting a compound of formula IX with an aromatic compound of formula X.



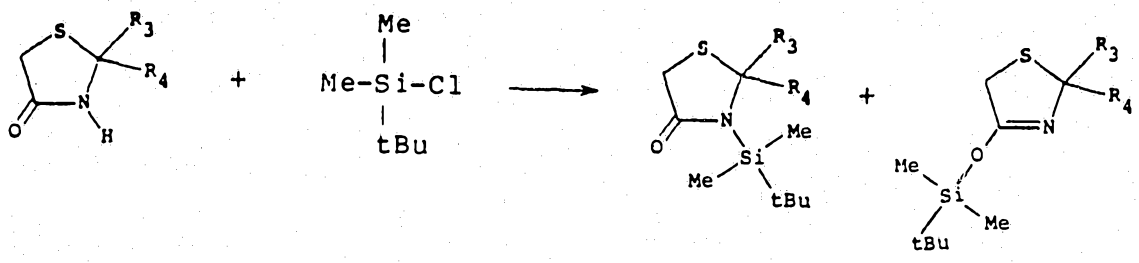
(IX) (X) (VIII)

The above reaction is typically conducted in the presence of H_2SO_4 or p-toluenesulfonic acid at a temperature of about -10 to about 23°C.

STEP G

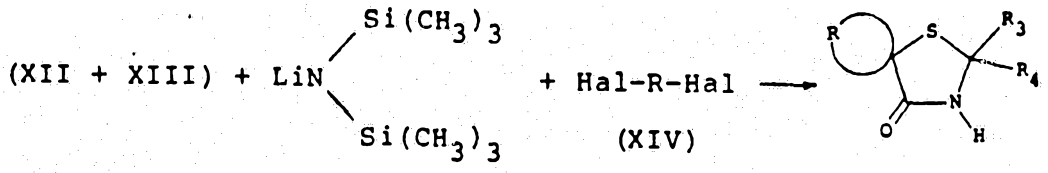
As an alternative to the foregoing scheme, one can obtain a compound of formula XI where the divalent group -R- plus the spiro carbon as combined constitutes a cyclopentane, cyclohexane, cycloheptane, pyran, thiopyran, pyrrolidine or piperidine ring, in the following manner.

First, 4-thiazolidinone is reacted with t-butyldimethylsilyl chloride in a suitable solvent such as dichloromethane at a suitable temperature such as about 20-30°C to afford a mixture of compounds of formulas XII and XIII. Typically the molar ratio between compound XII and compound XIII is about 70:30.



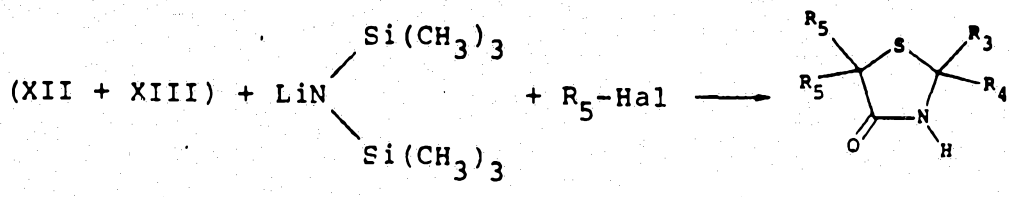
(IIa) (XII) (XIII)

The above-mentioned mixture is reacted with lithium bis(trimethylsilyl)amide and a compound of formula XIV where R is as defined above and Hal is Br or I in a suitable medium such as tetrahydrofuran and at a low temperature such as -75°C to -50°C to afford compound XI.



(XIV) (XI)

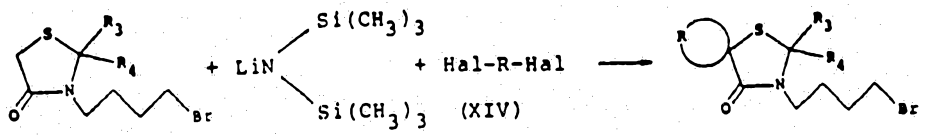
Similarly, if one uses a mono-bromide or mono-iodide of the formula R_5-Hal where R_5 is loweralkyl in the place of Hal-R-Hal, one can obtain a compound of formula XV.



(XV)

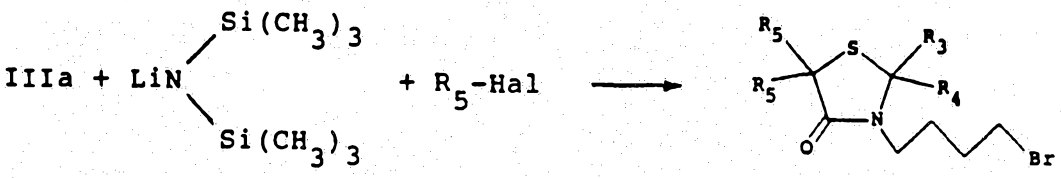
STEP H

As an alternative to STEP G, one can react compound IIIa (R_1=R_2=H) with lithium bis(trimethylsilyl)amide and compound XIV in substantially the same manner as in STEP G to afford a compound of formula XVI.



(IIIa) (XIV) (XVI)

Similarly, if one uses R_5-Hal instead of Hal-R-Hal, one can obtain a compound of formula XVII.



(XVII)

The compounds of the present invention having formula I are useful as antipsychotic agents.

Antipsychotic activity is determined in the climbing mice assay by methods similar to those described by P. Protais, et al., Psychopharmacol., 50, 1 (1976) and B. Costall, Eur. J. Pharmacol., 50, 39, (1978).

The subject CK-1 male mice (23-27 grams) are group-housed under standard laboratory conditions. The mice are individually placed in wire mesh stick cages (4" x 4" by 10") and are allowed one hour for adaptation and exploration of the new environment. Then apomorphine is injected subcutaneously at 1.5 mg/kg, a dose causing climbing in all subjects for 30 minutes. Compounds to be tested for antipsychotic activity are injected intraperitoneally 30 minutes prior to the apomorphine challenge at a screening dose of 10 mg/kg.

For evaluation of climbing, 3 readings are taken at 10, 20 and 30 minutes after apomorphine administration according to the following scale:

Climbing Behavior Mice with:	Score
4 paws on bottom (no climbing)	0
2 paws on the wall (rearing)	1
4 paws on the wall (full climb)	2

Mice consistently climbing before the injection of apomorphine are discarded.

With full-developed apomporphine climbing, the animals are hanging onto the cage walls, rather motionless, over longer periods of time. By constrast, climbs due to mere motor stimulation usually last only a few seconds.

The climbing scores are individually totaled (maximum score: 6 per mouse over 3 readings) and the total score of the control group (vehicle intraperitoneally-apomorphine subcutaneously) is set to 100%. ED_{50} values with 95% confidence limits, calculated by a linear regression analysis of some of the compounds of this invention are presented in Table 1.

TABLE 1

Compound	Antipsychotic Activity (Climbing Mice Assay) ED_{50} mg/kg ip
3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone	12.7
2,2-dimethyl-3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride hydrate	21.9
3-[4-[1-(3-trifluoromethylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride hemihydrate	19.3
3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]-butyl]-5-methyl-4-thiazolidinone oxalate	12.0

3-[4-[1-(2-methylphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone hydrochloride	13.Ø
2,2-dimethyl-3-[4-[1-(3-methylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone dihydrochloride	16.7
3-[4-[1-(1,2-benzisothiazol-3-yl)-4-piperazinyl]butyl]-5,5-dimethyl-4-thiazolidinone hydrochloride	1.4
(reference compound)	
Clozapine	8.1
Sulpiride	14.5

Antipsychotic response is achieved when the compounds of this invention are administered to a subject requiring such treatment as an effective oral, parenteral or intraveneous dose of from Ø.Ø1 to 5Ø mg/kg of body weight per day. A particularly preferred effective amount is about 25 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need and the professional judgement of the person administering or supervising the administration of the aforesaid compound. It is to be further understood that the dosages set forth herein are exemplary only and they do not to any extent, limit the scope or practice of the invention.

The compounds of the present invention having formula I are also useful as analgesic agents due to their ability to alleviate pain in mammals. The activity of the compounds is demonstrated in the 2-phenyl-1,4-benzoquinone-induced

writhing test in mice, a standard assay for analgesia, [Proc. Soc. Exptl. Biol. Med., 95, 729 (1957)]. Table 2 shows a result of the test of the analgesic activities of some of the compounds of this invention.

TABLE 2

Compound	Analgesia Activity (Phenylquinone Writhing) ED_{50} (mg/kg sc)
2-methyl-3-[4-[1-(4-fluorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride	1.2
3-[4-[1-(4-chlorophenyl)-4-piperazinyl]-butyl]-4-thiazolidinone hydrochloride	2.2
3-[4-[1-(3-methoxyphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone hydrochloride	4.3
3-[4-[1-(2,3-dimethylphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone hydrochloride	2.1
3-[4-[1-(4-fluorophenyl)-4-piperazinyl]-butyl]-4-thiazolidinone	2.9
3-[4-[1-(3-methylphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone hydrochloride	1.0
3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]-butyl]-1,4-dioxothiazolidine	13.2
(reference compound)	
Pentazocine	1.3

Compounds of the present invention are also useful as anticonvulsant agents. The activity of the compounds is demonstrated in supramaximal electroshock assay. Groups of male mice (18-30 grams) are used. Drugs are prepared using distilled water and if insoluble, a surfactant is added. Control animals receive vehicle. Drugs are routinely administered intraperitoneally. The dosage volume is 10 ml/kg.

The animal's eyes are placed across the output terminals of an A.C. shocker that delivers 206 volts rms for 300 milliseconds. Electrode paste coats the animals's eyes at the point of contact with the terminals.

A compound is considered to give protection if the mouse does not exhibit extensor tonus. Protection is expressed as normalized percent inhibition relative to vehicle control.

$$\text{Normalized \% inhibition} = \frac{\frac{\#\text{ Rx protected}}{\#\text{ Rx tested}} - \frac{\#\text{ Control protected}}{\#\text{ Control tested}}}{1 - \frac{\#\text{ Control protected}}{\#\text{ Control tested}}} \times 100$$

A time response is carried out using 6 animals per group. Animals are tested at 30, 60, and 120 minutes postdrug. Additional time periods are tested if indicated by previous tests.

When the peak activity time has been determined, a dose response is initiated, using 10 animals per group at that time period. The ED_{50} and 95% confidence interval are calculated by computerized probit analysis.

Results of the anticonvulsant activities of some of the compounds of this invention are shown in Table 3.

TABLE 3

ANTICONVULSANT ACTIVITY

Compound	Supramaximal Electroshock ED_{50}, mg/kg, ip
5-phenyl-3-[4-[1-(3-trifluoromethylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone oxalate	14.4
5,5-dimethyl-3-[4-[1-(3-trifluoromethylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride	37.3
(reference compound)	
Chlorodiazepoxide	8.0

Compounds of the present invention are also useful as anxiolytic agents. The activity of the compounds is demonstrated in Fixed-Ratio (FR) Conflict Paradigm in Rats.

This testing paradigm is used to reveal possible "antianxiety" effects of compounds. The fixed-ratio (FR) conflict paradigm directly tests drug-induced reduction in anxiety. The method is described below.

METHOD:

The FR conflict paradigm is as described by Davidson and Cook, "Effects of combined treatment with trifluoroperazine HCl and amobarbital on punished behavior in rats", Psychopharmacologia, Volume 15, 159-168 (1969). Male rats are used as test subjects. They are housed individually and food and water are available ad libitum until they are 300 to 400 g prior to the start of training. Subsequently, they are food deprived until their body weight is reduced to approximately 80% of original and it is maintained at this level by a restricted food diet.

The programming and test equipment consists of Coulbourn Instrument shockers and BRS/LVE cages within sound-attenuated environmental enclosures. The data are recorded by a computer which also controls the food and shock presentation. The cages are equipped with a house light, a single lever, que lights, a liquid dipper, a speaker and a grid-floor connected to a shocker. Sweetened condensed milk delivered by the liquid dipper serves as the positive reinforcement for all subjects.

The subjects are trained to lever press for the milk reward in two distinct response-reward sections. In the anxiety or "conflict" segment (signaled by onset of both tone and que lights), a dipper of milk is delivered in response to each fifth lever press (FR-5 schedule of reinforcement). However, each fifth lever press during this period is also accompanied by a 40-msec pulse of aversive

footshock through the grid floor. This creates a "conflict" between 1) easy access to milk reward and 2) the simultaneous presentation of a painful footshock. This conflict period is three minutes in duration.

During the other segment of this paradigm, the lever presses produce a dipper of milk only at variable intervals of time from 8 to 60 seconds with an average reward of once/30 seconds (VI-30 sec.). No shocks are ever administered during this VI phase of testing which is 4 minutes in duration.

The test procedure consists of six (nonshock) VI segments where reinforcement is available on a limited basis. Each VI period is followed by a three-minute FR-conflict phase when reinforcement is constantly available but always accompanied by an aversive footshock.

The shock level is titrated for each subject to reduce the FR responding to a total of more than 10 and less than 40 lever presses during the entire test. The rats are tested two to three days a week. Drugs are administered on the day following a control day at criteria level. After treatment, the performance is compared to the previous day's control trial. The VI responses are used to evaluate any general debilitating drug effects while the FR responses are used to evaluate any antianxiety effects as indicated by increased responding during the FR conflict period.

All test compounds are administered by i.p. injection or oral intubation in volumes of 1.0 cc/kg and the pretreat

interval is usually one-half hour after i.p. administration and 60 minutes after oral administration.

An antianxiety drug will increase the FR conflict responding. It should be observed that the VI responding may also be increased.

The animals have different control VI and FR response rates and respond to antianxiety compounds at different doses. This individuality of response prevents use of group averages and does not allow meaningful ED_{50} calculation. In the standard screening procedure, at least three rats that have previously shown positive anxiolytic effects with standard compounds are doses with an experimental compound and tested. If no increase in FR responding is observed and the VI responding is not sufficiently suppressed to indicate general debilitation, then the animals are retested the following week with a greater dose. At least one subject must show a significant increase in FR responding to indicate a positive drug effect. Drug's effects are expressed as FR conflict ratios (drug/control).

The results of this test for some of the compounds of this invention are shown in Table 4.

TABLE 4

ANXIOLYTIC ACTIVITY

Compound	dose (mg/kg i.p.)	FR conflict ratios (drug/control) responses	rewards
2,2-dimethyl-3-[4-[1-(3-methylmercaptophenyl)-4-piperazinyl]-butyl]-4-thiazolidinone dihydrochloride	10	2.7	3.6
5,5-dimethyl-3-[4-[1-(3-trifluoromethylphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone hydrochloride	20	1.8	2.2
(reference compound)			
diazepam	15	4.5	6.5

Effective quantities of the compounds of the invention may be administered to a patient by any of the various methods, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The free base final products, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition

salts for purposes of stablity, convenience of crystallization, increased solubility and the like.

Acids useful for preparing the pharmaceutically acceptable acid addition salts of the invention include inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids, as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric and oxalic acids.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated wth excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum and the like. These preparations should contain at least 0.5% of active compound, but may be varied depending upon the particular form and may conveniently be between 5% to about 70% of the weight of the unit. The amount of active compound in such composition is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0- 300 milligrams of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such

as micro-crystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes, coloring and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of active compound, but may be varied between 0.5 and 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according

to the present invention are prepared so that a parenteral dosage unit contains between 0.5 and 100 milligrams of active compound.

The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraactic acid; buffers such as acetates; citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral multiple dose vials made of glass or plastic.

Examples of the compounds of this invention include:

3-[4-[1-(2-methylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(3-methylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(2,3-dimethylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(3-methoxyphenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(4-fluorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(2-chlorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(3-chlorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(4-chlorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(3-trifluoromethylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]butyl]-1,4-dioxo-thiazolidine;

3-[4-[1-(4-fluorophenyl)-4-piperazinyl]butyl]-1,4-dioxo-thiazolidine;

3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]butyl]-2-methyl-4-thiazolidinone;

3-[4-[1-(4-fluorophenyl)-4-piperazinyl]butyl]-2-methyl-4-thiazolidinone;

3-[4-[1-(3-chlorophenyl)-4-piperazinyl]butyl]-2-methyl-4-thiazolidinone;

3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]butyl]-5-methyl-4-thiazolidinone;

2,2-dimethyl 3-[4-[1-(3-methylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

2,2-dimethyl-3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

2,2-dimethyl-3-[4-[1-(3-chlorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

2,2-dimethyl-3-[4-[1-(3-trifluoromethylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

2,2-dimethyl-3-[4-[1-(3-methylmercaptophenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

5,5-dimethyl-3-[4-[1-(2-methoxyphenyl]-4-piperazinyl]butyl]-4-thiazolidinone;

5,5-dimethyl-3-[4-[1-(3-trifluoromethylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone;

5-phenyl-3-[4-[1-(3-trifluoromethylphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone;

2-methyl-3-[4-[1-(2-pyrimidinyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(1,2-benzisothiazol-3-yl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(1,2-benzisothiazol-3-yl)-4-piperazinyl]butyl]-5,5-dimethyl-4-thiazolidinone;

3-[4-[1-(2-benzothiazolyl)-4-piperazinyl]butyl]-5,5-dimethyl-4-thiazolidinone;

3-[4-[1-(2-quinolinyl)-4-piperazinyl]butyl]-4-thiazolidinone;

5,5-dimethyl-3-[4-[1-(2-quinolinyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(3-isoquinolinyl)-4-piperazinyl]butyl]-5-phenyl-4-thiazolidinone;

3-[4-[1-(3-isoquinolinyl)-4-piperazinyl]butyl]-5-(4-methoxyphenyl)-4-thiazolidinone;

3-[4-[1-(3-isoquinolinyl)-4-piperazinyl]butyl]-1-thia-3-azaspiro[4.4]nonan-4-one;

3-[4-[1-(5-fluoro-2-pyrimidinyl)-4-piperazinyl]butyl]-5,5-dimethyl-4-thiazolidinone;

3-[4-[1-(5-fluoro-2-pyrimidinyl)-4-piperazinyl]butyl]-1-thia-3-azaspiro[4.4]nonan-4-one;

3-[4-[1-(5-fluoro-2-pyrimidinyl)-4-piperazinyl]butyl]-4-thiazolidinone;

3-[4-[1-(1,2-benzisothiazol-3-yl)-4-piperazinyl]butyl]-1-thia-3-azaspiro[4.4]nonan-4-one;

3-[4-[1-(1,2-benzisothiazol-3-yl)-4-piperazinyl]butyl]-5-phenyl-4-thiazolidinone;

3-[4-[1-(1,2-benzisothiazol-3-yl)-4-piperazinyl]butyl]-5-(4-methoxyphenyl)-4-thiazolidinone;

3-[4-[1-(1,2-benzisothiazol-3-yl)-4-piperazinyl]butyl]-1-thia-3-azaspiro[4.5]decan-4-one;

3-[4-[1-(3-isoquinolinyl)-4-piperazinyl]butyl]-5,5-dimethyl-4-thiazolidinone; and

3-[4-[1-(3-isoquinolinyl)-4-piperazinyl]butyl]-1-thia-3-azaspiro[4.5]decan-4-one.

The following examples are presented in order to illustrate this invention.

EXAMPLE 1

5,5-Dimethyl-4-thiazolidinone

A solution of 4-thiazolidinone (10.0 g), t-butyldimethylsilyl chloride (16.40 g), triethylamine (20.3 mL) and CH_2Cl_2 (250 mL) was stirred at room temperature under nitrogen. After 15 min. the reaction mixture became cloudy. After 27 h, Et_2O (200 mL) was added, the mixture was filtered through Al_2O_3 and the triethylammonium chloride cake washed with Et_2O (350 mL). The combined filtrate was concentrated in vacuo to a cloudy oil (26.1 g). Distillation of the cloudy oil gave 19.63 g of a clear liquid, bp. 73-75°C at 0.30 mmHg. Spectral data showed oil to be a 70:30 mixture of N- and O- silylated material, namely, 3-t-butyldimethylsilyl-4-thiazolidinone and 4-t-butyldimethylsilyloxy-3-thiazoline.

To a -45°C solution of lithium bis(trimethylsilyl)amide (80.0 mmol) and tetrahydrofuran (80 mL) under N_2 was added a 0°C solution prepared from 7.91 g of the above-mentioned 70:30 mixture between 3-t-butyldimethylsilyl-4-thiazolidinone and 4-t-butyldimethylsilyloxy-3-thiazoline, iodomethane (11.36 g) and THF (30 mL). The reaction mixture was stirred at -40°C to -50°C for 70 min. TLC analysis (silica gel, 7% ethyl acetate/hexane) showed a trace of starting material, R_f=0.31, and a major product, R_f=0.50, along with material at the origin. The reaction mixture was removed from the cold bath and quenched with 2N HCl (120 mL). The aqueous

mixture was stirred rapidly for 1.5 h. TLC analysis (silica gel, ethyl acetate) showed a major product, R_f=Ø.45, and 4-thiazolidinone, R_f=Ø.31, after visualization with iodine. The aqueous mixture was evaporated in vacuo to remove tetrahydrofuran and the resultant aqueous mixture was extracted with dichloromethane (5 x 7Ø mL). The combined extracts were washed with brine (15Ø mL), dried over Na_2SO_4 and concentrated in vacuo to 3.88 g of a dark solid. The crude product was flash chromatographed (18Ø g silica gel, 1Ø% hexane/ethyl acetate) to give 2.28 g of an off-white solid. It was recrystallized from diethyl ether (25 ml) to yield 1.12 g of crystals, mp 1Ø5-1Ø7°C.

ANALYSIS:

Calculated for C_5H_9NOS:	45.77%C	6.92%H	1Ø.68%N
Found:	45.74%C	6.88%H	1Ø.67%N

EXAMPLE 2

1-Thia-3-azaspiro[4.4]nonane-4-one

To a -75°C (CO_2/isopropanol bath) mixture of lithium bis(trimethylsilyl)amine (Ø.151 mol) and THF (151 mL) under nitrogen was added a Ø°C solution prepared from 14.95 g of a 7Ø:3Ø mixture between 3-t-butyldimethylsilyl-4-oxothiazolidine and 4-t-butyldimethylsilyloxy-3-thiazoline (prepared as in Example 1) and 1,4-dibromobutane (14.85 g) in THF (5Ø mL) over a period of Ø.5 h. The resultant homogeneous solution

was stirred at -75°C for 70 min. TLC analysis (silica gel, 10% EtOAc/hexane) showed a major product, (R_f=0.48) and a minor product (R_f=0.31). The reaction mixture was removed from the cold bath and acidified with 2N HCl (200 mL). The aqueous mixture was stirred rapidly for 3.5 h at room temperature, placed in vacuo to remove the tetrahydrofuran, and extracted with dichloromethane (5 x 75 mL). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo to yield 14.2 g of an oily solid. The crude oily product was chromatographed (Waters Prep 500, 2 silica gel columns, 20% hexane/ethyl acetate) to give 2.75 g of a white solid (R_f=0.45). Recrystallization from diethylether/hexane yielded 1.37 g of a crystalline solid, mp 92-94°C.

ANALYSIS:

Calculated for $C_7H_{11}NOS$:	53.47%C	7.05%H	8.91%N
Found:	53.41%C	7.01%H	8.88%N

EXAMPLE 3

3-(4-Bromobutyl)-4-thiazolidinone

A mixture of 4-thiazolidinone (25 g), dimethylformamide (DMF hereafter, 500 ml) and KOH (27.16 g) was stirred under N_2 at room temperature for 1.5 h. To the resulting mixture was added 1,4-dibromobutane (101 ml), which rapidly caused the reaction mixture to turn milky white. Stirring was continued at room temperature for 44 h. The reaction mixture was poured into H_2O (1000 ml) and the aqueous mixture was extracted with ethyl acetate (EtOAc

hereafter, 3 x 300 ml). The combined extracts were washed successively with H_2O (300 ml) and brine (300 ml), dried over Na_2SO_4, and concentrated in vacuo to an amber oil. HPLC (high performance liquid chromatography) of a 44.95 g aliquot yielded 7.15 g of an oil which upon distillation yielded a clear liquid, b.p. 134-137°C/0.12 mm Hg.

ANALYSIS:

Calculated for $C_7H_{12}BrNOS$:	35.30%C	5.08%H	5.88%N
Found:	35.24%C	5.09%H	5.83%N

EXAMPLE 4

3-(4-Bromobutyl)-5,5-dimethyl-4-thiazolidinone

To a -75°C (CO_2/isopropanol bath) mixture of lithium bis(trimethylsilyl)amide and tetrahydrofuran (102 mL) under nitrogen was added a 0°C solution consisting of 3-(4-bromobutyl)-4-thiazolidinone (11.65 g), iodomethane (20.8 g) and tetrahydrofuran (20 mL) over a period of 20 min. The resultant solution was stirred at -75°C for 25 min. TLC analysis (silica gel, 32% EtOAc/hexane) of a small aliquot acidified with 1N HCl showed the absence of a starting bromide and the presence of a major product, R_f=0.41. The reaction mixture was removed from the cold bath and acidified with 1N HCl (200 mL). The aqueous mixture was extracted with diethyl ether (3 x 175 mL). The combined extracts were washed with brine (200 ml), dried over Na_2SO_4 and concentrated in vacuo to an oil. The crude oil was chromatographed (Waters Prep 500, 2 silica gel

columns, 30% EtOAc/hexane) to give 11.02 g of an oil as the major product, R_f=0.41. A sample (2.80 g) of this was distilled using a short path head yielding 2.68 g of a faint yellow oil (bath temperature 90-100°C/0.05 mm Hg).

ANALYSIS:

Calculated for $C_9H_{16}BrNOS$:	40.60%C	6.06%H	5.26%N
Found:	40.64%C	6.12%H	5.20%N

EXAMPLE 5

2-Methyl-3-(4-bromobutyl)-4-thiazolidinone

To a stirred suspension of 2-methyl-4-thiazolidinone (20 g) in 500 ml of anhydrous DMF under N_2 was added in one portion potassium hydroxide (19.1 g). Stirring was continued for 1/2 h resulting in a yellow solution. At this time 1,4-dibromobutane (61 ml) was added in one portion.

After 1 hour, no starting material remained as judged by TLC [silica, EtOAc]. The mixture was quenched in 600 ml of H_2O and extracted exhaustively with EtOAc. The organic fractions were washed twice with H_2O, dried over $MgSO_4$ and concentrated in vacuo. HPLC of the residue, using a 3:1 hexane/EtOAc eluent, provided 16.02 g of product as an oil which was homogeneous by TLC [silica 2:1 hexane/EtOAc].

ANALYSIS:

Calculated for $C_8H_{14}BrNOS$:	38.10%C	5.60%H	5.55%N
Found:	37.81%C	5.78%H	5.39%N

EXAMPLE 6

3-(4-Bromobutyl)-2,2-dimethyl-4-thiazolidinone

A solution of 2,2-dimethyl-4-thiazolidinone (5.00 g) in DMF (30 ml) was added dropwise to a suspension of NaH (0.0419 mole, previously washed with hexane) in DMF (30 ml) under N_2. The resultant mixture was stirred for 1 h, transferred to an addition funnel and added dropwise to a solution of 1,4-dibromobutane (18.10 g) in DMF (50 ml) over a period of 40 min. The resultant solution was heated at 70°C under N_2 for 120 hr. TLC analysis (silica gel, 10% EtOAc/CH_2Cl_2) showed the presence of one major product and starting thiazolidinone. The reaction mixture was cooled to room temperature and poured into H_2O (400 ml), and the aqueous mixture extracted with EtOAc (3 x 175 ml). The combined extracts were washed with H_2O (200 ml) and brine (200 ml), dried over Na_2SO_4, and concentrated in vacuo to an oily residue (20.44 g). The crude product was purified by HPLC (4% EtOAc/CH_2Cl_2) to yield 5.91 g of oil. Distillation in vacuo afforded 4.61 g of a faint yellowish oil, bp 133-136°C/0.70 mm Hg.

ANALYSIS:

Calculated for $C_9H_{16}BrNOS$:	40.60%C	6.06%H	5.26%N
Found:	40.63%C	6.03%H	5.17%N

EXAMPLE 7

3-(4-Bromobucyl)-5-methyl-4-thiazolidinone

To 12.35 g of 5-methyl-4-thiazolidinone placed in a

500 ml round bottom flask was added 210 ml of DMF and the mixture stirred for 3.5 h. An additional 30 ml of DMF was added and the mixture stirred for 10 minutes and thereafter 11.8 g of KOH was added all at once. The resultant solution was stirred for 0.5 h at room temperature and thereafter 38 ml of 1,4-dibromobutane was added rapidly. The mixture was stirred at room temperature overnight. After 24 hours of stirring at room temperature, the reaction mixture was poured into 600 ml of water and the resultant mixture extracted with EtOAc (2 x 175 ml). The combined EtOAc layers were washed successively with water (200 ml) and brine (150 ml), dried over $MgSO_4$ and concentrated in vacuo to 49.68 g of oil. After removal of DMF by vacuum distillation, the residual oil was purified by flash chromotography (silica gel column) to obtain the desired product.

EXAMPLE 8

3-(4-Bromobutyl)-5-phenyl-4-thiazolidinone

To a rapidly stirred mixture of H_2SO_4 (73 ml) and benzene (30 ml) was added a mixture of 3-(4-bromobutyl)-1,4-dioxothiazolidine (13.66 g, prepared from 3-(4-bromobutyl)-4-thiazolidinone by oxidation with $NaIO_4$ conducted in substantially the same manner as in Example 17 described later), benzene (120 ml) and CH_2Cl_2 (10 ml). The exothermic reaction was cooled with an ice/water bath and stirring was continued for 50 minutes, during which the

mixture was gradually warmed to room temperature. The mixture was poured onto 750 g of ice and extracted with CH_2Cl_2 (4 x 150 ml). The combined extracts were washed with 5% $NaHCO_3$ (300 ml), H_2O (300 ml) and brine (300 ml), dried over Na_2SO_4, and concentrated in vacuo to yield 15.00 g of an oil. TLC analysis (silica gel, 40% EtOAc/hexane) showed a major product with Rf=0.37. The crude oil was purified by HPLC chromatography, whereupon the product solidified. It (6.17 g) was recrystallized from Et_2O to yield 2.7 g of a crystalline solid, mp 48-50°C.

ANALYSIS:

Calculated for $C_{13}H_{16}BrNOS$:	49.68%C	5.13%H	4.46%N
Found:	49.73%C	5.26%H	4.78%N

EXAMPLE 9

3-(4-Bromobutyl)-5-(4-methoxyphenyl)-4-thiazolidinone

A mixture of p-toluenesulfonic acid monohydrate (6.56 g) and 1,2-dichloroethane (100 mL) was heated to reflux using an apparatus equipped with a water separator. Approximately 70 mL of distillate was removed and the reddish solution was cooled to room temperature. To this solution was added anisole (9.30 g), followed by a solution of 3-(4-bromobutyl)-1,4-dioxothiazolidine (4.38 g) and 1,2-dichloroethane (60 mL) and the resultant mixture was heated to reflux (bath temperature = 120°C). Approximately 60 mL of distillate was removed, another 30 mL of 1,2-dichloroethane was added, and the reaction allowed to

reflux. Another 30 mL of distillate was removed, the reaction mixture was cooled to ambient temperature and poured into H_2O (60 mL). The aqueous mixture was extracted with Et_2O (4 x 40 mL) and the combined extracts were washed with brine (70 mL), dried (Na_2SO_4) and concentrated in vacuo to a yellow liquid. TLC analysis (silica gel, 2% EtOAc/CH_2Cl_2) of the liquid showed an elongated spot, R_f=0.33. The yellow liquid was chromatographed to afford 3.70 g of oil, a mixture of o- and p- isomers as determined by proton NMR and 1.55 g of the pure p-isomer (R_f=0.48, silica gel, 3% EtOAc/CH_2Cl_2). The latter was dried at room temperature/0.1 mmHg for 100 h.

ANALYSIS:

Calculated for $C_{14}H_{18}BrNO_2S$:	48.84%C	5.27%H	4.07%N
Found:	48.61%C	5.40%H	3.97%N

EXAMPLE 10

3-[4-[1-(2-Methylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride

A mixture of 3-(4-bromobutyl)-4-thiazolidinone (4.10 g), 1-(2-methylphenyl)piperazine (5.6 g), K_2CO_3 (7.13 g), NaI (300 mg) and CH_3CN (200 ml) was refluxed (oil bath temperature 95°C) under N_2 for 20 h. TLC analysis (silica gel, 20% MeOH/EtOAc) showed one major product at Rf=0.37, and a trace of starting bromide at Rf=0.67. The mixture was cooled to room temperature, EtOAc(100 ml) was added and the mixture was filtered. The filtrate was

concentrated in vacuo to an oil which was triturated with EtOAc to precipitate a solid. The mixture was filtered and the filtrate concentrated in vacuo to an oil. The oil was chromatographed by HPLC over silica gel and the purified oil (5.42 g) was dissolved in Et_2O (600 ml). The salt of this amine was precipitated by the addition of an HCl/Et_2O solution until pH=1, yielding 5.50 g of crystals. The crude salt (4.00 g) was recrystallized from EtOH/EtOAc to yield 3.13 g of a crystal solid, mp 207-209°C.

ANALYSIS:

Calculated for

$C_{18}H_{27}N_3OS \cdot HCl$:	58.44%C	7.63%H	11.36%N	9.58%Cl
Found:	58.35%C	7.56%H	11.35%N	9.69%Cl

EXAMPLE 11

3-[4-[1-(3-Methylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride

A mixture of 3-(4-bromobutyl)-4-thiazolidinone (4.00 g), 1-(3-tolyl)piperazine dihydrochloride (4.23 g), K_2CO_3 (9.40 g), NaI (200 mg) and CH_3CN (150 ml) was heated at reflux (bath temperature 90°c) under N_2 for 52 h. TLC analysis (silica gel, 7.5% EtOH/CH_2Cl_2) showed some starting bromide at Rf=0.57 and a major product at Rf=0.41. The reaction mixture was cooled to room temperature, filtered, and the filtrate concentrated in vacuo to an oil. The crude product was flash chromatographed (silica gel) to yield 3.40 g of a heavy oil. TLC analysis (silica gel) of this showed

the presence of starting bromide. The oil solidified on cooling and the resultant solid was triturated with Et_2O/hexane yielding 2.48 g of solid, mp 69-73°C. Flash chromatography (silica gel) of the crude product afforded 2.10 g of a purified solid, mp 70-72°C. The salt of this amine was prepared in ether by the addition of an HCl/Et_2O solution. It was recrystallized from EtOH/EtOAc to provide 1.55 g of white crystals, mp 201-203°C.

ANALYSIS:

Calculated For $C_{18}H_{27}N_3OS \cdot HCl$:	58.44%C	7.63%H	11.36%N
Found:	58.44%C	7.73%H	11.31%N

EXAMPLE 12

3-[4-[1-(2,3-Dimethylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride

To a solution of 3-(4-bromobutyl)-4-thiazolidinone (4.0 g) and 1-(2,3-dimethylphenyl)piperazine hydrochloride (3.8 g) in 100 ml of anhydrous CH_3CN were added K_2CO_3 (9.3 g) and NaI (200 mg). The mixture was heated to 80° with stirring under N_2.

After 18 hours the mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, taken up in EtOAc and filtered again. The solvent was removed in vacuo and the residue chromatographed on silica using 98:2 EtOAc/CH_3OH as an eluent. Fractions containing the pure product were combined and concentrated to give 3.36 g of free amine.

The HCl salt of this amine was precipitated from Et_2O to provide 3.118 g of product, mp 228-230°C.

ANALYSIS:

Calculated for $C_{19}H_{29}N_3OS \cdot HCl$:	59.43%C	7.87%H	10.94%N
Found:	59.34%C	8.07%H	10.93%N

EXAMPLE 13

3-[4-[1-(2-Methoxyphenyl)-4-piperazinyl]butyl]-4-thiazolidinone

A suspension of 3-(4-bromobutyl)-4-thiazolidinone (3.0 g), 1-(2-methoxyphenyl)piperazine (2.43 g), anhydrous K_2CO_3 (3 g) and NaI (200 mg) in 100 ml of anhydrous CH_3CN was heated to reflux under N_2. After 18 hours the mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, and the residue taken up and chromatographed (silica, EtOAc eluent) to provide 3.49 g of product as a white solid,

mp 80-81°C.

ANALYSIS:

Calculated for $C_{18}H_{27}N_3O_2S$:	61.86%C	7.79%H	12.02%N
Found:	62.07%C	7.89%H	11.95%N

EXAMPLE 14

3-[4-[1-(3-Methoxyphenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride

To a solution of 3-(4-bromobutyl)-4-thiazolidinone (3.0 g) and 1-(3-methoxyphenyl)piperazine dihydrochloride

(3.34 g) in 100 ml of anhydrous CH_3CN were added K_2CO_3 (8.7 g) and NaI (200 mg). The mixture was heated to 80° with stirring under N_2.

After 18 hours the mixture was cooled to room temperature and filtered. The CH_3CN was removed in vacuo and the residue was chromatographed on silica using 98:2 EtOAc/CH_3OH as the eluent. The fractions containing the desired product were combined, concentrated in vacuo and taken up in anhydrous Et_2O.

The HCl salt of the free amine was precipitated from Et_2O, collected and dried to provide 2.850 g of product, mp 161-162°C.

ANALYSIS:

Calculated for $C_{18}H_{27}N_3O_2S \cdot HCl$:	56.02%C	7.31%H	10.89%N
Found:	55.66%C	7.37%H	10.83%N

EXAMPLE 15

3-[4-[1-(4-Fluorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone

A mixture of 3-(4-bromobutyl)-4-thiazolidinone (4.01 g), 1-(4-fluorophenyl)piperazine (3.35 g), K_2CO_3 (4.64 g), NaI (150 mg) and CH_3CN (150 ml) was heated at 100°C (bath temperature) under N_2 for 18 h. TLC analysis (silica gel, 8% MeOH/$CHCl_3$) showed one major product at R_f=0.36, and the absence of starting bromide. The reaction mixture was cooled to room temperature and concentrated in vacuo to an oil which was taken up in EtOAc. The mixture

was filtered to remove the precipitate and the filtrate concentrated in vacuo to an amber oil which solidified under vacuum. The solid (5.86 g) was dissolved in $CHCl_3$ and flash chromatographed (silica gel) and thereafter recrystallized from hexane/CH_2Cl_2 to yield in two crops 3.93 g of white crystals, mp 83-85°C. TLC analysis showed a trace of slower moving impurity. Recrystallization from hexane/CH_2Cl_2 afforded 3.1 g of white needles which were still slightly impure by TLC. The material was again flash chromatographed (silica gel) and recrystallized from hexane/CH_2Cl_2 to give 2.67 g of pure product, mp 84-85°C.

ANALYSIS:

Calculated for $C_{17}H_{24}N_3OSF$:	60.50%C	7.17%H	12.45%N
Found:	60.55%C	7.19%H	12.43%N

EXAMPLE 16

3-[4-[1-(2-Chlorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride

A mixture of 3-(4-bromobutyl)-4-thiazolidinone (4.02 g), 1-(2-chlorophenyl)piperazine (3.94 g), K_2CO_3 (7.01 g), NaI (250 mg) and CH_3CN (130 ml) was heated at 100°C (bath temperature) for 20 hours under N_2. The mixture was cooled to room temperature, filtered and concentrated in vacuo to an amber oil. The oil was triturated with EtOAc and the mixture was filtered. The filtrate was concentrated in vacuo to 6.07 g of an oil residue which was flash chromatographed (silica gel) to yield 4.47 g of an oily

product. The HCl salt of this amine was prepared in ether with ethereal HCl to give 3.77 g of a white solid, mp 182-185°C. The solid was recrystallized from EtOAc (130 ml)/CH_2Cl_2 (30 ml) yielding 3.01 g of white needles, mp 185-187°C.

ANALYSIS:

Calculated for $C_{17}H_{24}N_3ClOS \cdot HCl$:	52.30%C	6.46%H	10.76%N
Found:	52.28%C	6.51%H	10.64%N

EXAMPLE 17

3-[4-[1-(3-Chlorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride

To a solution of 3-(4-bromobutyl)-4-thiazolidinone (3.0 g) and 1-(2-chlorophenyl)piperazine dihydrochloride (3.4 g) in 100 ml of anhydrous CH_3CN were added K_2CO_3 (8.7 g) and NaI (200 mg). The mixture was heated at 80° with stirring under N_2.

After 18 hours the mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, taken up in EtOAc and chromatographed on silica using EtOAc/CH_3OH (95:5) as the eluent. The fractions containing the product were combined and concentrated in vacuo.

The HCl salt of the amine was precipitated from Et_2O, dried and collected to provide 2.7 g of product, mp 157-159°C.

ANALYSIS:

Calculated for $C_{17}H_{24}ClN_3OS \cdot HCl$:	52.30%C	6.45%H	10.76%N
Found:	51.93%C	6.80%H	10.81%N

EXAMPLE 18

3-[4-[1-(4-Chlorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride

To a solution of 3-(4-bromobutyl)-4-thiazolidinone (3.0 g) and 1-(4-chlorophenyl)piperazine dihydrochloride (3.4 g) in 100 ml of anhydrous CH_3CN were added K_2CO_3 (8.7 g) and KI (200 mg). The mixture was heated to 80° with stirring under N_2.

After 18 hours the mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, taken up in EtOAc and chromatographed on silica using EtOAc/CH_3OH (95:5) as the eluent. The fractions containing the product were combined and concentrated in vacuo.

The HCl salt of the amine was precipitated from Et_2O, dried and collected to provide 2.33 g of product, mp 186-188°C (dec).

ANALYSIS:

Calculated for $C_{17}H_{24}ClN_3OS \cdot HCl$:	52.30%C	6.45%H	10.76%N
Found:	52.17%C	6.51%H	10.85%N

EXAMPLE 19

3-[4-[1-(3-Trifluoromethylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride hemihydrate

To a solution of 3-(4-bromobutyl)-4-thiazolidinone (3.0 g) and 1-(3-trifluoromethylphenyl)piperazine (2.91 g) in 100 ml of anhydrous CH_3CN were added K_2CO_3 (3.5 g) and KI

(200 mg). The mixture was heated to 80° with stirring under N_2.

After 18 hours the mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, taken up in EtOAc, filtered and concentrated. The residue was chromatographed on silica using EtOAc as the eluent, and fractions containing the product were combined and concentrated in vacuo.

The HCl salt of this amine was precipitated from Et_2O, dried and collected to provide 3.7458 g of product as a hemihydrate, mp 138-140°.

ANALYSIS

Calculated for			
$C_{18}H_{24}N_3F_3OS \cdot HCl \cdot 1/2H_2O$:	49.94%C	6.05%H	9.70%N
Found:	49.85%C	6.07%H	9.77%N

EXAMPLE 20

3-[4-[1-(2-Methoxyphenyl)-4-piperazinyl]butyl]-1,4-dioxothiazolidine

A mixture of 3-(4-bromobutyl)-1,4-dioxothiazolidine (3.37 g), 1-(2-methoxyphenyl)piperazine (2.80 g), K_2CO_3 (4.60 g), NaI (190 mg) and CH_3CN (150 ml) was heated at reflux (bath temperature 95°C) for 24 h. TLC analysis (silica gel, 20% MeOH/CH_2Cl_2) showed the consumption of the starting sulfoxide and the presence of the major product with R_f=0.43. The mixture was cooled to room temperature, EtOAc (100 m) was added and the mixture was filtered. The

filtrate was concentrated in vacuo to an oil which was filtered through silica gel using 20% MeOH/CH_2Cl_2 as the eluent. The fractions containing the material with R_f=0.43 were concentrated in vacuo to yield 4.83 g of a foam, which was dissolved in MeOH/CH_2Cl_2 and flash chromatographed (silica gel) to yield 3.28 g of a crude product. Rechromatography over silica gel using 50% MeOH/toluene as eluent yielded 2.98 g of an oil which solidified on standing. The solid was dissolved in 50% MeOH/EtOAc and filtered through silica gel. The filtrate containing the product was concentrated to approximately 5 ml and the oily liquid was seeded and left standing, yielding 0.91 g of a white solid, mp, 111-113°C. The mother liquor was concentrated in vacuo to a solid which was recrystallized from CH_2Cl_2/Et_2O, yielding an additional 0.79 g of fine needles, mp, 111-113°C.

ANALYSIS:

Calculated for $C_{18}H_{27}N_3O_3S$:	59.15%C	7.48%H	11.50%N
Found:	59.02%C	7.06%H	11.49%N

EXAMPLE 21

3-[4-[1-(4-Fluorophenyl)-4-piperazinyl]butyl]-1,4-dioxothiazolidine

To a solution of $NaIO_4$ (710 mg) in H_2O (12 ml) was added a solution of 3-[4-[1-(4-fluorophenyl)-4-piperazinyl]-butyl]-4-thiazolidinone 1, (1.02 g) in tetrahydrofuran (THF, 12 ml). The resultant mixture was stirred at room

temprature for 18 h. TLC analysis (silica gel, 30% MeOH/$CHCl_3$) showed a major product with R_f=0.33 along with a material having the same R_f as 1, namely 0.79. The mixture was filtered to remove the $NaIO_3$. The filtrate was concentrated in vacuo, poured onto H_2O (35 ml) and extracted with CH_2Cl_2 (4 x 20 ml). The combined extracts were washed with brine (50 ml), dried through Na_2SO_4 and concentrated to an oil. Flash chromatography over silica gel afforded 185 mg of material with R_f identical to 1 and 0.520 g of an oil which solidified on standing.

A second run using $NaIO_4$ (1.41 g), H_2O (13 ml), 1 (2.02 g) and THF (20 ml) was conducted in a similar manner yielding 0.910 g of product.

The combined products, 1.43 g, were dissolved in 50% MeOH/EtOAC and filtered through silica gel using 50% MeOH/EtOAc as eluent. The fractions containing the product were concentrated to approximately 8 ml, seeded, and left to deposit 1.02 g of a white crystalline material, mp, 118-119.5°c.

ANALYSIS:

Calculated for $C_{17}H_{24}N_3O_2FS$:	57.77%C	6.84%H	11.89%N
Found:	57.61%C	6.83%H	11.83%N

EXAMPLE 22

3-[4-[1-(2-Methoxyphenyl)-4-piperazinyl]butyl]-2-Methyl-4-thiazolidinone

A suspension of 2-methyl-3-(4-bromobutyl)-4-

thiazolidinone (3.0 g), 1-(2-methoxyphenyl)piperazine (2.3 g), anhydrous K_2CO_3 (3.5 g) and NaI (200 mg) in 100 ml of anhydrous CH_3CN was heated to 80° under N_2. After 4 hours no starting material remained as judged by TLC. The mixture was cooled to room temperature, filtered and concentrated in vauco. The residue was chromatographed on silica, using EtOAc as the eluent. This provided 2.18 g of product as a clear oil which solidified in vacuo (0.1 mmHg) overnight.

ANALYSIS:

Calculated for $C_{19}H_{29}N_3O_2S$:	62.78%C	8.04%H	11.56%N
Found:	62.55%C	7.94%H	11.17%N

EXAMPLE 23

3-[4-[1-(4-Fluorophenyl)-4-piperazinyl]butyl]-2-Methyl-4-thiazolidinone hydrochloride

To a solution of 2-methyl-3-(4-bromobutyl)-4-thiazolidinone (3.0 g) and 1-(4-fluorophenyl)piperazine (2.15 g) in 100 ml of anhydrous CH_3CN were added K_2CO_3 (3.5 g) and NaI (200 mg).

The mixture was heated to 80° with stirring under N_2. After 18 hours the mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, and the residue was taken up in EtOAc and chromatographed (silica, EtOAc eluent). The fractions containing the desired product were combined and concentrated.

The HCl salt was precipitated from Et_2O, collected and dried to provide 3.273 g of product as a white solid, mp 178-182° (dec).

ANALYSIS:

Calculated for $C_{18}H_{24}FN_3OS \cdot HCl$:	55.73%C	7.01%H	10.83%N
Found:	55.45%C	6.90%H	10.86%N

EXAMPLE 24

3-[4-[1-(3-Chlorophenyl)-4-piperazinyl]butyl]-2-Methyl-4-thiazolidinone hydrochloride

To a solution of 2-methyl-3-(4-bromobutyl)-4-thiazolidinone (4.0 g) and 1-(3-chlorophenyl)piperazine hydrochloride (3.69 g) in 100 ml of dry CH_3CN were added K_2CO_3 (8.8 g) and NaI (200 mg). The mixture was heated to reflux with stirring under N_2.

After 18 hours the mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, taken up in EtOAc and chromatographed (silica, EtOAc as the eluent). The fractions containing the desired product were combined and concentrated. The HCl salt of the free amine was precipitated from Et_2O and the excess HCl and Et_2O were removed in vacuo to leave 5.176 g of product as a white solid, mp 180-183° (dec.)

ANALYSIS:

Calculated for $C_{18}H_{26}ClN_3OS \cdot HCl$:	53.46%C	6.73%H	10.39%N
Found:	53.27%C	6.88%H	10.27%N

EXAMPLE 25

3-[4-[1-(2-Methoxyphenyl)-4-piperazinyl]butyl]-5-methyl-4-thiazolidinone oxalate

A mixture of 3-(4-bromobutyl)-5-methyl-4-thiazolidinone (5.03 g), 1-(2-methoxyphenyl)piperazine (4.06 g), K_2CO_3 (7.28 g), NaI (190 mg) and CH_3CN (100 mL) was refluxed (bath temperature 99°C) for 48 h. TLC analysis (10% EtOH/CH_2Cl_2) showed the absence of starting bromide and formation of one major product, R_f=0.48. The reaction mixture was cooled to room temperature and filtered, the filtrate was concentrated in vacuo and passed through silica gel to yield 6.06 g of an amber oil. Chromatography of the crude product, followed by treatment with ethereal HCl yielded 5.45 g of a salt. Attempts to recrystallize the crude salt failed, so it was freebased utilizing 5% $NaHCO_3$ yielding, after an EtOAc extraction, 3.82 g of an oil. The oil was chromatographed (silica gel, 10% EtOH/CH_2Cl_2) yielding 2.2 g of an oil which solidified on standing. The solid was rechromatographed (silica gel, 10% EtOH/CH_2Cl_2) and dissolved in Et_2O (200 ml), and its oxalate salt was precipitated by the addition of a saturated solution of oxalic acid in Et_2O. The oxalate was dried in vacuo and recrystallized from EtOAc to yield fine white needles, mp 129-131°C.

ANALYSIS:

Calculated for $C_{19}H_{29}N_3O_2S \cdot C_2H_2O_4$:	55.61%C	6.89%H	9.26%N
Found:	55.56%C	6.86%H	9.33%N

EXAMPLE 26

2,2-Dimethyl-3-[4-[1-(3-methylphenyl)-4-piperazinyl]butyl]-4-thiazolidinone dihydrochloride

A mixture of 2,2-dimethyl-3-(4-bromobutyl)-4-thiazolidinone (4.01 g), 1-(3-methylphenyl)piperazine (3.17 g), K_2CO_3 (5.30 g), NaI (230 mg) and CH_3CN (180 mL) was heated at reflux (oil bath temperature; 100°C) for 20 h. TLC analysis (silica gel, 7.5% EtOH/CH_2Cl_2 showed one major product, R_f=0.53, and a trace of starting bromide, R_f=0.70. The reaction mixture was cooled to room temperature, EtOAc (100 mL) was added and the mixture filtered. The filtrate was concentrated in vacuo to an oil which was triturated with EtOAc (150 mL). The mixture was filtered and the filtrate concentrated in vacuo to an oil. HPLC of the crude oil (Waters Prep 500 silica gel, 8% MeOH/EtOAc) yielded 5.42 g of an oil, R_f=0.53. The hydrochloride salt of this amine was precipitated by the addition of HCl/Et_2O to a solution of the base in 600 ml of ether until pH=2 to give 5.30 g of a white powder. Recrystallization from EtOH yielded 2.91 g of white crystals, mp 204°C (dec).

ANALYSIS:

Calculated for				
$C_{20}H_{31}N_3OS \cdot 2HCl$:	55.29%C	7.66%H	9.67%N	16.32%Cl
Found:	55.41%C	8.07%C	9.78%N	16.65%Cl

EXAMPLE 27

2,2-Dimethyl-3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride hydrate

To a solution of 2,2-dimethyl-3-(4-chlorobutyl)-4-thiazolidinone (3.26 g) and 1-(2-methoxyphenyl)piperazine (2.8 g) in 100 ml of anhydrous CH_3CN were added anhydrous K_2CO_3 (4.5 g) and NaI (200 mg). The mixture was heated with stirring to 80° under N_2.

After 18 hours the mixture was cooled to room temperature and filtered, concentrated in vacuo, taken up in EtOAc and again filtered. The EtOAc was removed in vacuo and the residue chromatographed on silica using EtOAc as the eluent to provide 4.2 g of amine.

The HCl salt was precipitated from Et_2O and dried in vacuo to provide a monohydrate, homogeneous by TLC, mp 189-192°C. The yield was 4.465 g.

ANALYSIS:

Calculated for $C_{20}H_{31}N_3O_2S \cdot HCl \cdot H_2O$:	55.60%C	7.93%H	9.72%N
Found:	55.28%C	7.61%H	9.53%N

Karl Fisher Titration:

Calculated: 4.17%

Found: 4.36%

EXAMPLE 28

2,2-Dimethyl-3-[4-[1-(3-chlorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone dihydrochloride

A mixture of 2,2-dimethyl-3-(4-bromobutyl)-4-thiazolidinone (4.02 g), 1-(3-chlorophenyl)piperazine hydrochloride (3.85 g), K_2CO_3 (6.84 g), NaI (200 mg) and CH_3CN (160 mL) was refluxed (bath temperature 95°C) under N_2 for 48 h. TLC analysis (silica gel, 7.5% EtOH/CH_2Cl_2) showed one major product, R_f=0.33 and the absence of starting thiazolidinone. The mixture was cooled to room temperature, EtOAc(100 ml) was added, and the mixture filtered. The filtrate was concentrated in vacuo to an oil which was redissolved in EtOAc causing a white solid to precipitate. The mixture was filtered and the filtrate concentrated in vacuo to an oil. Purification of the crude product by HPLC (Waters Prep 500 A, 5% EtOH/EtOAc) afforded 4.3 g of oil. The oil was dissolved in Et_2O (600 mL) and the solution acidified to pH=2 (hydrion paper) with an HCl/Et_2O solution, and the precipitated salt (3.7 g) was recrystallized from EtOH to yield 2.10 g of a crystalline solid, mp 205-207°C.

ANALYSIS:

Calculated for $C_{19}H_{28}N_3ClOS \cdot 2HCl$:	50.16%C	6.65%H	9.24%N
Found:	50.23%C	6.57%H	9.19%N

EXAMPLE 29

2,2-Dimethyl-3-[4-[1-(3-trifluoromethyl)-4-piperazinyl]-butyl]-4-thiazolidinone dihydrochloride

A mixture of 2,2-dimethyl-3-(4-bromobutyl)-4-thiazolidinone (4.06 g), 1-(3-trifluoromethylphenyl)-piperazine (4.07 g), K_2CO_3 (5.11 g), NaI (200 mg) and CH_3CN (160 mL) under N_2 was heated at reflux for 24 h. The reaction mixture was cooled to room temperature and filtered, and the filtrate concentrated in vacuo to an amber oil. The oil was triturated with EtOAc and the mixture was filtered. The filtrate was concentrated in vacuo to an oily residue which was chromatographed by HPLC (silica gel, 5% EtOH/EtOAc) to give 4.85 g of product which solidified on cooling. The solid was dissolved in Et_2O (500 mL) and its HCl salt precipitated by addition of HCl/Et_2O. It was dried in vacuo and recrystallized from isopropanol to yield white crystals, mp 184°C (dec).

ANALYSIS:

Calculated for			
$C_{20}H_{30}F_3Cl_2N_3OS \cdot 2HCl$:	49.18%C	6.19%H	8.60%N
Found:	49.24%C	6.52%H	8.84%N

EXAMPLE 30

2,2-Dimethyl-3-[4-[1-(3-methylmercaptophenyl)-4-piperazinyl]butyl]-4-thiazolidinone dihydrochloride

A mixture of 2,2-dimethyl-3-(4-bromobutyl)-4-thiazolidinone (4.17 g), 1-(3-methylmercaptophenyl)-

piperazine (3.92 g), K_2CO_3 (5.42 g), NaI (240 mg) and CH_3CN (180 mL) was heated to reflux (bath temperature 100°C) under N_2 for 24 h. TLC analysis (silica gel, 5% EtOH/EtOAc) showed the absence of starting bromide and the presence of one major product with R_f=0.23. The reaction mixture was cooled to room temperature, EtOAc (100 mL) was added, and the mixture filtered. The filtrate was concentrated in vacuo to an oil which was chromatographed by HPLC (silica gel, 8% MeOH/EtOAc) to give 5.60 g of a yellow oil. The oil was dissolved in Et_2O (450 mL) and the HCl salt of this amine was precipitated by the addition of an HCl/Et_2O solution, yielding 6.26 g of a white solid. Recrystallization of the crude product from EtOH (250 mL) and HCl/Et_2O solution (2 mL) afforded 3.79 g of fine crystals, mp 202°C (dec).

ANALYSIS:

Calculated for $C_{20}H_{31}N_3OS_2 \cdot 2HCl$:	51.49%C	7.13%H	9.01%N
Found:	51.32%C	7.42%H	8.86%N

EXAMPLE 31

5,5-Dimethyl-3-[4-[1-(2-methoxyphenyl)-4-piperazinyl]butyl]-4-thiazolidinone dihydrochloride

A mixture of 5,5-dimethyl-3-(4-bromobutyl)-4-thiazolidinone (4.25 g), 1-(2-methoxyphenyl)piperazine hydrochloride (4.38 g), K_2CO_3 (8.8 g), NaI (300 mg) and acetonitrile (200 mL) was heated at 110°C (bath temperature) under nitrogen. After 25 hours,

TLC analysis (silica gel, 10% methanol/ethyl acetate) showed the absence of starting bromide and a major product, R_f=0.20. The reaction mixture was cooled to room temperature, ethyl acetate (150 mL) was added, and the mixture filtered. The filtrate was concentrated in vacuo to an oil which was redissolved in ethyl acetate causing a solid to precipitate. The mixture was filtered and the filtrate concentrated to 6.01 g of an oily residue which was chromatographed (Waters Prep 500, one silica gel column, 10% methanol/ethyl acetate) to give 3.02 g of an oil. Trituration of the oil with diethyl ether (300 mL) deposited a fluffy white solid which was removed by filtration. The filtrate was acidified with an HCl/diethyl ether solution to pH=1 and the resulting salt (3.25 g) was collected as a white solid. After one recrystallization from EtOH/ethyl acetate the salt was freebased to give 2.45 g of an oil which was dissolved in diethyl ether. The solution was filtered and the filtrate acidified with an HCl/diethyl ether solution again to yield 2.60 g of a salt. Recrystallization from EtOH/ether yielded 2.29 g of a white solid, mp 213-218° (dec.).

ANALYSIS:

Calculated for

$C_{20}H_{31}N_3O_2S \cdot 2HCl$: 53.32%C 7.38%H 9.33%H 15.74%Cl

Found: 53.40%C 7.46%H 9.34%H 15.76%Cl

EXAMPLE 32

5,5-Dimethyl-3-[4-[1-(3-trifluoromethylphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone hydrochloride

A mixture of 5,5-dimethyl-3-(4-bromobutyl)-4-thiazolidinone (4.00 g), 1-(3-trifluoromethylphenyl)-piperazine (4.15 g), K_2CO_3 (6.22 g), NaI (220 mg) and CH_3CN (120 mL) was refluxed (oil bath temperature =97°C) under N_2 for 20 h. TLC analysis (silica gel, 10% MeOH/EtOAc) of the reaction mixture showed one major product, R_f=0.49, and the absence of starting bromide. The mixture was cooled to room temperature, EtOAc (150 mL) was added, and the mixture filtered. The filtrate was concentrated in vacuo to a yellow oil. The oil was triturated with EtOAc (200 mL) and filtered, and the filtrate concentrated in vacuo to an oil. The crude oily product was chromatographed (Waters Prep 500, 2 silica gel columns, 5% MeOH/EtOAc) to give 4.2 g of a clear oil. The HCl salt of this amine was precipitated by the addition of a diethyl ether/HCl solution until pH=2 (hydrion paper). The resultant salt was collected, dried and recrystallized from ethanol/ethyl acetete to afford 2.85 g of crystals, mp 169-171°C.

ANALYSIS:

Calculated for

$C_{20}H_{28}F_3N_3OS \cdot HCl$: 53.15%C 6.47%H 7.84%N 9.30%Cl

Found: 53.10%C 6.61%H 8.09%N 9.29%Cl

EXAMPLE 33

5-Phenyl-3-[4-[1-(3-trifluoromethylphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone oxalate

A mixture of 3-(4-bromobutyl)-5-phenyl-4-thiazolidinone (4.67 g), 1-(3-trifluoromethylphenyl)-piperazine (3.76 g), K_2CO_3 (5.15 g), NaI (300 mg) and CH_3CN (150 mL) was heated at reflux (bath temperature 95°C) under N_2. After 17 hours, TLC analysis (silica gel, 5% MeOH/EtOAc) showed the absence of starting bromide and presence of one major product with an R_f=0.33. The mixture was cooled to room temperature, EtOAc (100 mL) was added, and the mixture filtered. The filtrate was concentrated in vacuo to an oil which was triturated with EtOAc. The mixture was filtered and the filtrate concentrated again in vacuo to 7.59 g of an oil. The crude product was chromatographed (Waters Prep 500, 2 columns, silica gel, 5% MeOH/EtOAc) to give 6.42 g of an oil, and from this 4.47 g of the oxalate salt of this amine was prepared. The solid was recrystallized from EtOH/EtOAc giving 3.65 g of fine white crystals, mp 140-142°C.

ANALYSIS:

Calculated for $C_{24}H_{28}F_3N_3OS \cdot C_2H_2O_4$:	56.41%C	5.46%H	7.59%N
Found:	56.31%C	5.56%H	7.53%N

EXAMPLE 34

2-Methyl-3-[4-[1-(2-pyrimidyl)-4-piperazinyl]butyl]-4-thiazolidinone maleate

To a stirred solution of 3-(4-bromobutyl)-2-methyl-4-thiazolidinone (3.0 g) and 1-(2-pyrimidinyl)piperazine dihydrochloride (2.83 g) in 100 ml of dry CH_3CN were added K_2CO_3 (6.6 g) and NaI (200 mg). The mixture was heated to reflux under N_2.

After 18 hours, the mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, taken up in EtOAc and chromatographed (silica, 10:90 CH_3OH/EtOAc). The fractions containing the desired product were combined and concentrated.

The maleate salt was precipitated from Et_2O, collected and dried to provide 3.18 g of product as a white solid, mp 155-157°C, homogeneous by TLC (silica, 10:88:2 CH_2OH/EtOAc/Et_3N, R_f=0.26).

ANALYSIS:

Calculated for $C_{16}H_{25}N_5OS \cdot C_4H_4O_4$:	53.20%C	6.47%H	15.51%N
Found:	53.00%C	6.65%H	15.43%N

EXAMPLE 35

3-[4-[1-(1,2-Benzisothiazol-3-yl)-4-piperazinyl]butyl]-4-thiazolidinone hydrochloride

A mixture of 3-(4-bromobutyl)-4-thiazolidinone (3.50 g), 1-(1,2-benzisothiazol-3-yl)piperazine (3.87 g), K_2CO_3 (6.09 g), NaI (200 mg) and acetonitrile (130 mL) was heated

at reflux (bath temperature 95°C) under nitrogen. After 30 hours, TLC analysis (silica gel, 10% MeOH/EtOAc) showed the absence of the starting bromide and the presence of a major product (R_f~=0.21) and a minor product (R_f~=0.30). The reaction mixture was cooled to room temperature, ethyl acetate (150 mL) was added and the mixture was filtered. The filtrate was concentrated in vacuo to a brown oil which was triturated with EtOAc. The mixture was filtered and the filtrate, after concentration in vacuo, was chromatographed (Waters Prep 500, silica gel, 15% MeOH/EtOAc) to give 2.75 g of a yellowish oil.

The chromatographed free base (3.88 g) was dissolved in ethyl acetate/diethyl ether, the resulting mixture was filtered in order to remove a fluffy insoluble material, and the filtrate was acidified with an HCl/diethyl ether solution until pH=1 (hydrion paper). The resultant solid was collected and dried at 55°C/3.0 mmHg yielding 3.1 g of a beige solid, mp 219-222°C. Recrystallization from EtOH (165 mL) yielded after drying (78°C/0.30 mmHg) 2.65 g of amber crystals, mp 220-225°C.

ANALYSIS:

Calculated for

$C_{18}H_{24}N_4OS_2 \cdot HCl$:	52.35%C	6.10%H	13.57%N	8.58%Cl
Found:	52.10%C	6.03%H	13.41%N	8.85%Cl

EXAMPLE 36

3-[4-[1-(1,2-Benzisothiazol-3-yl)-4-piperazinyl]butyl]-5,5-dimethyl-4-thiazolidinone hydrochloride

A mixture of 3-(4-bromobutyl)-5,5-dimethyl-4-thiazolidinone (3.50 g), 1-(1,2-benzisothiazol-3-yl)-piperazine hydrochloride (3.70 g), K_2CO_3 (6.34 g), NaI (330 mg) and acetonitrile (175 mL) was heated at 95°C (bath temperature) under nitrogen. After 21 hours, TLC analysis (silica gel, 5% MeOH/CH_2Cl_2) showed the absence of starting bromide and the presence of a major product, R_f=0.33. The reaction mixture was cooled to room temperature, ethyl acetate (150 mL) was added, and the mixture filtered. The filtrate was concentrated in vacuo to an oil which was triturated with ethyl acetate. The mixture was filtered again and the filtrate, after concentration, was chromatographed (Waters Prep 500, one silica gel column, 3% MeOH/CH_2CL_2) to give 3.48 g of a viscous oil. The oil was dissolved in diethyl ether (500 mL), the solution filtered to remove a fluffy solid, and the filtrate acidified to pH=1 (hydrion paper) with an HCl/diethyl ether solution. The resultant salt (3.23 g) was recrystallized from ethanol/ethyl acetate yielding 2.29 g of white needles, mp 222-227°C.

ANALYSIS:

Calculated for				
$C_{20}H_{28}N_4OS_2 \cdot HCl$:	54.46%C	6.63%H	12.70%N	8.04%Cl
Found:	53.93%C	6.73%H	12.58%N	8.57%Cl

EXAMPLE 37

3-[4-[1-(2-Benzothiazolyl)-4-piperazinyl]butyl]-5,5-dimethyl-4-thiazolidinone

A mixture of 3-(4-bromobutyl)-5,5-dimethyl-4-thiazolidinone (3.42 g), 1-(2-benzothiazolyl)piperazine (3.10 g), K_2CO_3 (6.19 g), NaI (250 mg) and acetonitrile was heated at 65°C (bath temperature) under nitrogen. After 19 hours, TLC analysis (5% methanol/methylene chloride) showed the absence of starting bromide and the presence of a major product, R_f=0.29. The reaction mixture was cooled to room temperature, ethyl acetate (100 ml) was added and the mixture filtered. The filtrate was concentrated in vacuo to a solid which was redissolved in hot ethyl acetate causing a solid to precipitate. The mixture was filtered and the filtrate concentrated in vacuo to an off-white solid. Chromatography of the crude product by HPLC (Waters Prep 500, one silica gel column, 5% methanol/methylene chloride) yielded 4.05 g of a solid, mp 99.5-100.5°C. It was recrystallized from methylene chloride/hexane to give 2.83 g of fine needles, mp 101-102°C.

ANALYSIS:

Calculated for $C_{20}H_{28}N_4OS_2$:	59.37%C	6.98%H	13.85%N
Found:	59.29%C	7.06%H	14.01%N

EXAMPLE 38

3-[4-[1-(2-Quinolinyl)-4-piperazinyl]butyl]-4-thiazolidinone

A mixture of 3-(4-bromobutyl)-4-thiazolidinone (4.00 g), 1-(2-quinolinyl)piperazine (3.94 g), K_2CO_3 (6.97 g), NaI (230 mg) and acetonitrile (150 mL) was heated at 80°C (bath temperature) under nitrogen. After 19 hours, TLC analysis (silica gel, 13% MeOH/EtOAc) showed the absence of starting bromide and the presence of one major product, R_f=0.19. The reaction mixture was cooled to room temperature, ethyl acetate (100 mL) was added, and the mixture was filtered. The filtrate was concentrated in vacuo to a solid and triturated with EtOAc. The mixture was filtered again to remove insoluble materials and the filtrate concentrated in vacuo to 6.32 g of beige solid. Chromatography of the crude product by HPLC (Waters Prep 500, one silica gel column 8% MeOH/CH_2Cl_2) yielded 5.67 g of a solid, mp 105-107°C. It was recrystallized from ethyl acetate/cyclohexane to give 3.62 g of off-white crystals, mp 106-107.5°C.

ANALYSIS:

Calculated for $C_{20}H_{26}N_4OS$:	64.83%C	7.07%H	15.12%N
Found:	64.78%C	7.07%H	15.18%N

EXAMPLE 39

5,5-Dimethyl-3-[4-[1-(2-quinolinyl)-4-piperaiznyl]butyl]-4-thiazolidinone

A mixture of 5,5-dimethyl-3-(4-bromobutyl)-4-

thiazolidinone (4.20 g), 1-(2-quinolinyl)piperazine (3.70 g), K_2CO_3 (6.55 g), NaI (200 mg) and acetonitrile (150 mL) was heated at reflux (bath temperature 95°C) under N_2 for 20 h. TLC analysis (silica gel, 10% MeOH/EtOAc) showed the absence of starting bromide and the formation of a major product, R_f=0.31. The reaction mixture was cooled to room temperature and left standing for 44 h. To this was added ethyl acetate (100 ml) and the resultant mixture was filtered. The filtrate was concentrated in vacuo to an oily solid which was redissolved in ethyl acetate (200 mL) causing a white solid to precipitate. The mixture was gravity filtered and the filtrate concentrated to an off-white solid (6.86 g). Chromatography of the crude product (Waters Prep 500, 1 silica gel column, 10% MeOH/EtOAc) yielded 4.22 g of a white solid (R_f=0.26), mp 107-111°c. It was recrystallized from ethyl acetate/hexane (1:2) to yield 2.83 g of white crystals, mp 110.5-111.5°C.

ANALYSIS:

Calculated for $C_{22}H_{30}N_4OS$:	66.29%C	7.59%H	14.06%N
Found:	66.26%C	7.61%H	13.95%N

EXAMPLE 40

3-[4-[1-(1,2-Benzisothiazol-3-yl)-4-piperazinyl]butyl]-2,2-dimethyl-4-thiazolidinone hydrochloride

A mixture of 3-(4-bromobutyl)-4-thiazolidinone (4.00 g), 1-(1,2-benzisothiazol-3-yl)piperazine (3.62 g), K_2CO_3 (7.25 g), NaI (400 mg) and CH_3CN (180 mL) was heated

at 80°C under nitrogen. After 20 h, TLC analysis (silica gel, 5% MeOH/CH_2Cl_2) showed the absence of starting bromide and the presence of a major product, R_f=0.40. The mixture was cooled to room temperature, EtOAc (100 mL) was added, and the mixture filtered. The filtrate was concentrated in vacuo to an oil which was dissolved in EtOAc (150 mL) causing a small amount of solid to precipitate. The mixture was filtered again and the filtrate concentrated to a yellowish brown oil. The oil was chromatographed (Waters Prep 500, 1 silica gel column, 4% MeOH/CH_2Cl_2) to yield 5.10 g of a yellowish solid.

The solid (5.00 g) was dissolved in EtOAc (100 mL)/Et_2O (500 mL) and the resultant cloudy solution was filtered to remove a small amount of brown solid. The filtrate was acidified with an HCl/Et_2O solution until pH=2. The resultant salt was collected and dried to give 5.15 g of an off-white powder, mp 211-214°C. A 4.00 g sample of the salt was recrystallized from EtOH/ethyl acetate to yield 2.92 g of white needles, mp 213-216°C.

ANALYSIS:

Calculated for

$C_{20}H_{28}N_4OS_2 \cdot HCl$: 54.46%C 6.63%H 12.70%N 8.04%Cl

Found: 54.16%C 6.66%H 12.58%N 8.10%Cl

EXAMPLE 41

3-[4-[1-(2-Benzothiazolyl)-4-piperazinyl]butyl]-4-thiazolidinone

A mixture of 3-(4-bromobutyl)-4-thiazolidinone (4.00 g), 1-(2-benzothiazolyl)piperazine (4.05 g), K_2CO_3 (7.01 g), NaI (250 mg) and acetonitrile (160 mL) was heated at 93° (bath temperature) under nitrogen. After 19 h, TLC analysis (silica gel, 5% methanol/methylene chloride) showed the absence of starting bromide and the presence of a major product, R_f=0.26. The reaction mixture was cooled to room temperature, ethyl acetate (100 mL) was added, and the mixture filtered. The filtrate was concentrated in vacuo to a solid which was redissolved in ethyl acetate causing a white solid to precipitate. The mixture was filtered again and the filtrate concentrated in vacuo to 6.43 g of an off-white solid. Chromatography of the crude product by HPLC (Waters Prep 500, 1 silica gel column, 5% methanol/methylene chloride) yielded 5.44 g of an off-white solid. A sample of the solid (3.08 g) was recrystallized from methylene chloride (15 mL)/hexanes (85 mL) yielding 2.28 g of a crystalline solid, mp 111-112°C.

ANALYSIS:

Calculated for $C_{18}H_{24}N_4OS_2$:	57.42%C	6.42%H	14.88%N
Found:	57.36%C	6.38%H	14.83%N

EXAMPLE 42

3-[4-[1-(3-Isoquinolinyl)-4-piperazinyl]butyl]-5,5-dimethyl-4-thiazolidinone

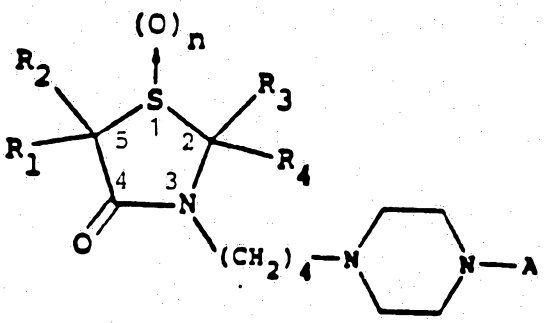
A mixture of 3-(4-bromobutyl)-4-thiazolidinone (4.00 g), 1-(3-isoquinolinyl)piperazine (3.53 g), K_2CO_3 (6.22 g), NaI (300 mg) and acetonitrile (190 mL) was heated at 75°C (bath temperature) under N_2. After 16 h, TLC analysis (silica gel, 40% EtOAc/hexane) showed the absence of starting bromide and a major product at R_f=0.22 (silica gel, 5% MeOH/CH_2Cl_2). The reaction mixture was cooled to ambient temperature and filtered, the inorganic solid was washed with hot ethyl acetate, and the wash was combined with the above filtrate and concentrated in vacuo to a green solid. The solid was triturated with hot ethyl acetate (300 mL) and the mixture filtered. The filtrate was concentrated in vacuo to a solid which was chromatographed (Waters Prep 500, 1 silica gel column, 5% MeOH/CH_2Cl_2) to yield 5.10 g of a green solid. The solid was recrystallized from methylene chloride/hexanes to give 2.99 g of light green crystals, mp 145-146.5°C.

ANALYSIS:

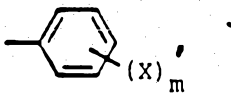
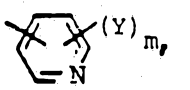
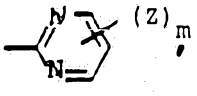
Calculated for $C_{22}H_{30}N_4OS$:	66.29%C	7.59%H	14.06%N
Found:	66.45%C	7.60%H	14.00%N

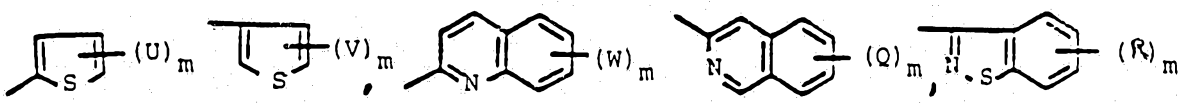
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:
XXXXXXXXX
Claims:

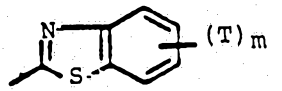
1. A compound of the formula I



I

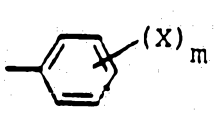
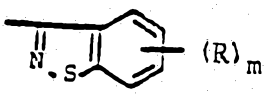
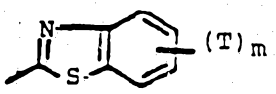
where n is ∅ or 1; A is   



or  where X, Y, Z, U, V, W, Q, R and T are each hydrogen, halogen, loweralkyl, hydroxy, nitro, loweralkoxy, amino, cyano or trifluoromethyl; m is 1 or 2; R_1 and R_2 are independently hydrogen, loweralkyl or aryl, or alternatively R_1 + R_2 taken together with the carbon atom to which they are attached form a cyclopentane, cyclohexane, cycloheptane, pyran, thiopyran, pyrrolidine or piperidine ring; R_3 and R_4 are independently hydrogen or loweralkyl, or alternatively R_3 + R_4 taken together with the carbon atom to which they are attached form a cyclopentane, cyclohexane, cycloheptane, pyran, thiopyran, pyrrolidine or piperidine ring, the term aryl signifying an unsubstituted phenyl group or a phenyl group substituted with 1, 2 or 3 substituents each of which being independently loweralkyl, loweralkoxy, hydroxy, halogen, loweralkylthio, cyano, amino or trifluormethyl, or a pharmaceutically acceptable acid addition salt thereof.

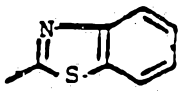
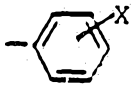
2. A compound according to claim 1, where n is O.

3. A compound according to claim 2, where R_1 and R_2 are independently hydrogen, loweralkyl or aryl, R_3 and R_4 are independently hydrogen or loweralkyl and A is the radical

where X, R and T are as defined.

4. A compound according to claim 3, where R_1 and R_2 are independently hydrogen, methyl or phenyl, R_3 and R_4 are independently hydrogen or methyl and A is the radical


or

where X is

methyl, methoxy, Cl, F or CF_3.

5. The compound according to claim 1, which is 2-methyl-3-[4-[1-(4-fluorphenyl)-4-piperazinyl]butyl]-4-thiazolidinone or a pharmaceutically acceptable acid addition salt thereof.

6. The compound according to claim 1, which is 3-[4-[1-(3-methylphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone or a pharmaceutically acceptable acid addition salt thereof.

7. The compound according to claim 1, which is 3-[4-[1-(2,3-dimethylphenyl)-4-piperazinyl]-butyl]-4-thiazolidinone or a pharmaceutically acceptable acid addition salt thereof.

8. The compound according to claim 1, which is 3-[4-[1-(4-chlorophenyl)-4-piperazinyl]butyl]-4-thiazolidinone or a pharmaceutically acceptable acid addition salt thereof.

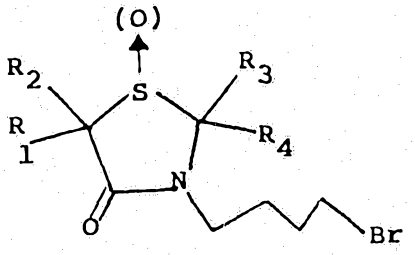
9. The compound according to claim 1, which is 3-[4[1-(1,2-benzisothiazol-3-yl)-4-piperazinyl]butyl]-5,5-dimethyl-4-thiazolidinone or a pharmaceutically acceptable acid addition salt thereof.

10. A pharmaceutical composition comprising as the active ingredient a compound as defined in claim 1 and a suitable carrier therefor.

11. A method of preparation of a medicament having antipsychotic, analgesic preparation of a medicament having antipsychotic, analgesic and/or anticonvulsant activity comprising combining in pharmacologically effective amounts of compound as claimed in claim 1 and as pharmaceutically acceptable carrier or excipient.

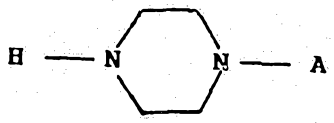
12. A process for the preparation of a compound as defined in claim 1, which comprises

a) reacting a compound of the formula III



III

where n, R_1, R_2, R_3 and R_4 are as defined, with a compound of the formula IV



IV

where A is as defined, or

b) optionally reacting a compound of the formula I where n is 0 and R_1, R_2, R_3 and R_4 are as defined hereinabove with an oxidizing agent to afford a compound of the formula I where n is 1.

DATED this 8th day of March, 1991.

HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED

WATERMARK PATENT &
TRADE MARK ATTORNEYS
"THE ATRIUM", 2ND FLOOR
290 BURWOOD ROAD
HAWTHORN VIC. 3122.