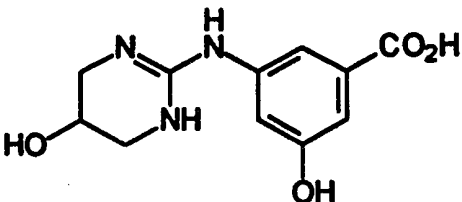




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US99/03279 (22) International Filing Date: 22 February 1999 (22.02.99) (30) Priority Data: 60/076,711 4 March 1998 (04.03.98) US (71) Applicant (for all designated States except US): G. S. SEARLE & CO. [US/US]; P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): RUMINSKI, Peter, G. [US/US]; 7687 Pierside Drive, Dardeene Prairie, MO (US). LU, Hwang-Fun [-/US]; 1723 Rosslare Court, Ballwin, MO (US). (74) Agents: KOVACEVIC, Cynthia, S. et al.; G.D. Searle & Co., P.O. Box 5110, Chicago, IL 60680-5110 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PROCESS FOR PREPARING 3- HYDROXY- 5-[(1, 4,5,6- TETRAHYDRO-5-HYDROXY- 2- PYRIMIDINYL)AMINO]BENZOIC ACID (57) Abstract The invention herein is directed to a process for preparing a compound of formula (I) and addition salts thereof.  (I)		

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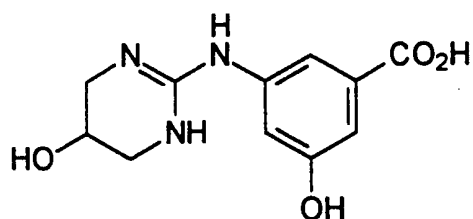
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PROCESS FOR PREPARING 3-HYDROXY-5-[(1,4,5,6-TETRAHYDRO-5-HYDROXY-2-PYRIMIDINYL)AMINO]BENZOIC ACID

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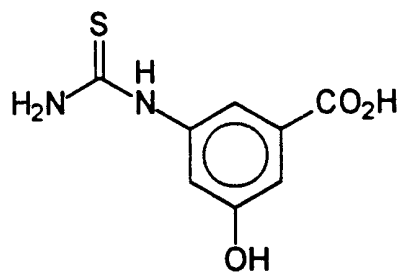
BACKGROUND OF THE INVENTION

The present invention is directed to a process for preparing a compound of the formula



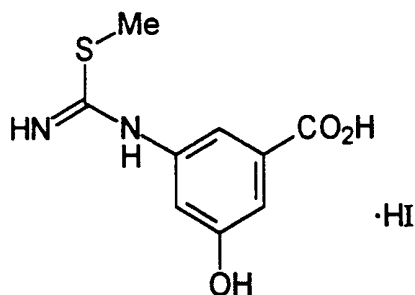
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which is useful as an intermediate for the synthesis of pharmaceutically active molecules. The process comprises reacting 3-amino-5-hydroxybenzoic acid with ammonium thiocyanate to produce a thiourea of the formula



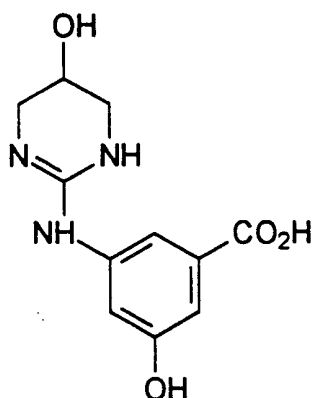
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reacting the thiourea with methyl iodide to produce:



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and reacting the compound so produced with 1,3-diamino-2-hydroxypropane in dimethylacetamide to yield a compound of the formula



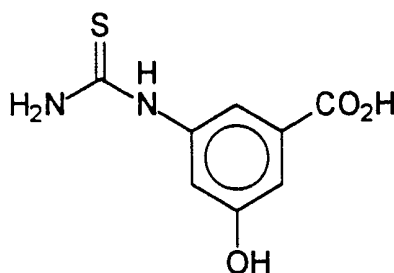
10 and isolating the resulting compound.

The compound produced by the present process is useful in preparing pharmaceutical agents, such as the $\alpha_v\beta_3$ integrin antagonists generally described in W097/08174.

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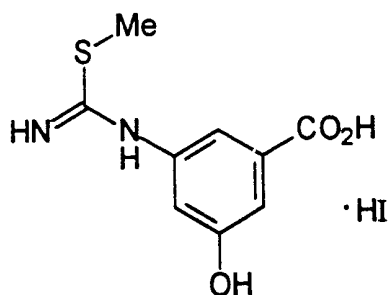
Summary of the Invention

The process of the present invention comprises reacting 3-amino-5-hydroxybenzoic acid with ammonium thiocyanate to produce a thiourea of the formula

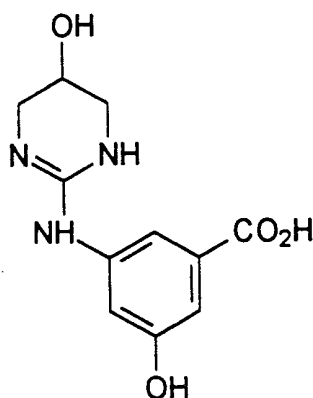


20

- 5 reacting the thiourea with methyl iodide to produce;



and reacting the compound so produced with 1,3-diamino-2-hydroxypropane in dimethylacetamide to yield a compound of the formula

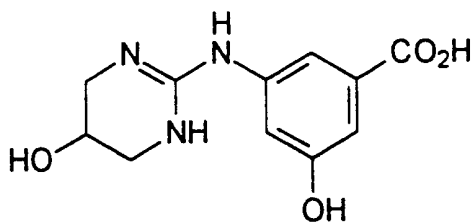


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and isolating the resulting compound.

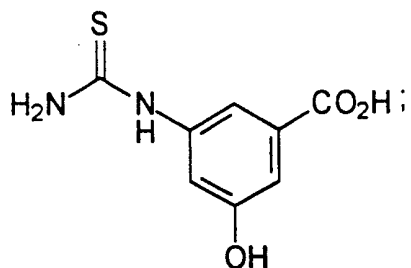
Detailed Description of the Invention

The invention herein is directed to a process for preparing



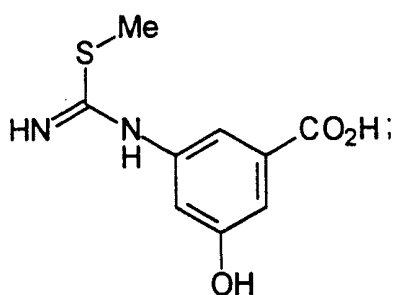
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and acid addition salts thereof comprising reacting 3-amino-5-hydroxy benzoic acid with a thiocyanate salt to produce a thiourea of the formula



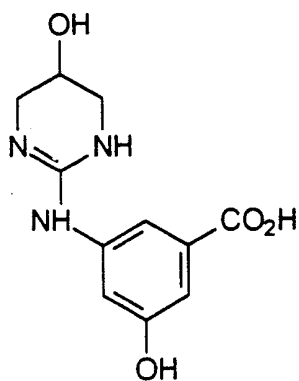
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reacting the thiourea compound with a methylating agent to produce a compound of the formula



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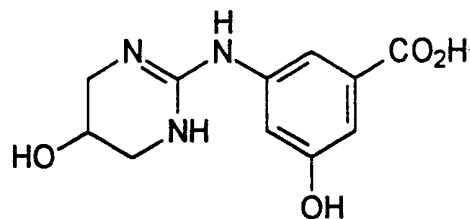
reacting the compound so produced with 1,3-diamino-2-hydroxy propane in a solvent to produce a compound of the formula



15

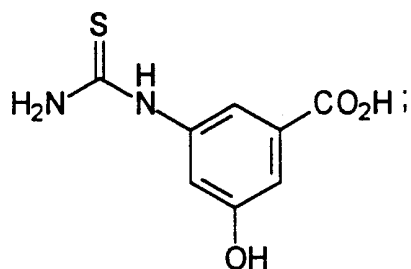
and isolating the resulting compound.

More preferably the invention is directed to a process for preparing a compound of the formula

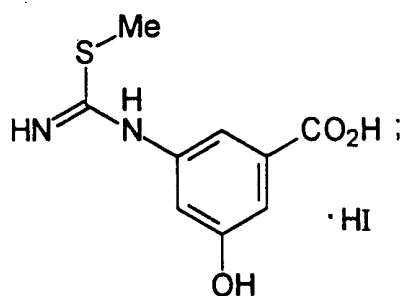


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and acid addition salts thereof comprising reacting 3-amino-5-hydroxybenzoic acid with ammonium thiocyanate in a solvent (most preferably in aqueous HCl) to produce a thiourea of the formula

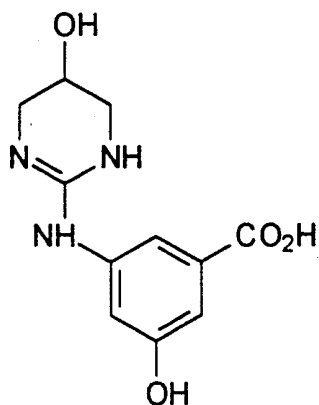


- 10 reacting the thiourea so produced with methyl iodide in a solvent (most preferably absolute ethanol) to produce a compound of the formula



reacting the compound so produced with 1,3-diamino-2-hydroxypropane in a solvent (most preferably dimethyl acetamide) to produce a compound of

- 15 the formula



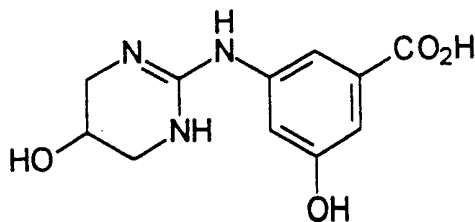
and isolating the resulting compound.

5 More generally the process can be varied by substituting various reactants and reagents which are known by those with skill in the art which are commercially available reactants or reagents, or reactants which can be prepared by conventional methodology. For example, but not limited to, in the first step ammonium thiocyanate can be replaced with sodium or
10 potassium thiocyanate, and aqueous HCl can be replaced with another aqueous acid. In the methylating step MeI can be replaced with dimethyl sulfate or other methylating agents known to those skilled in the art and ethanol can, for example, be replaced with tetrahydrofuran. In the last step DMA can, for example, be replaced with dimethylformamide and salts other
15 than HCl can be produced as would be readily apparent to those with skill in the art.

The following terms as used in this application have the definitions given below:

20	NH ₄ SCN	=	ammonium thiocyanate
	MeI	=	methyl iodide
	EtOH	=	ethanol
	Δ	=	heating the reaction
	DMA	=	dimethylacetamide
25	g	=	grams
	mL	=	milliliter
	MgSO ₄	=	magnesium sulfate
	¹ H-NMR	=	proton NMR
	MS	=	mass spectroscopy.

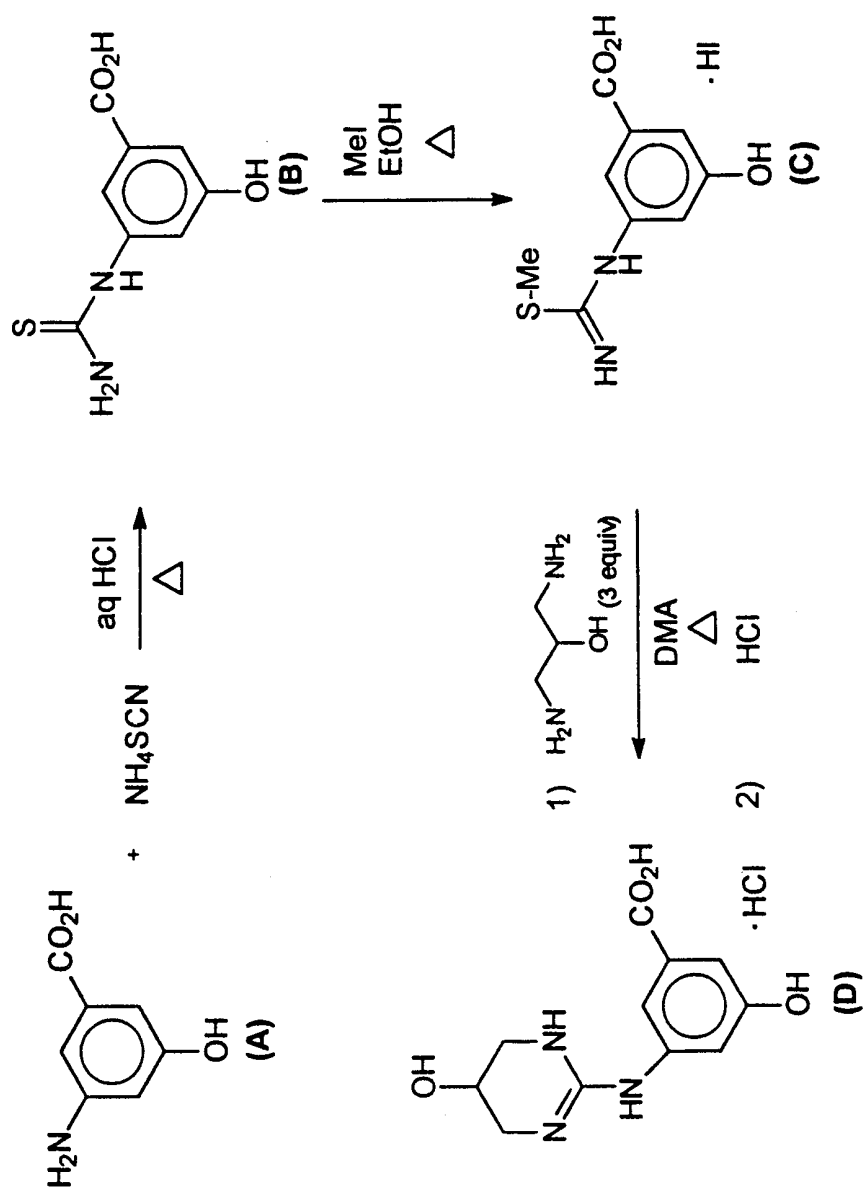
30 The present invention provides a method for preparing the novel compound



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which method is an improvement over the process described in co-filed, co-pending Attorney docket 2874/1 in that higher yields are obtained and greater purity is achieved. The presently claimed process requires fewer steps and has eliminated the need to use undesirable reagents such as carbon disulfide in the process.

A synthetic scheme for the most preferred method is outlined in Scheme I and the following descriptions thereof. The following Scheme and Examples are illustrative of the method for carrying out the process of the present invention. Both an explanation of, and the actual procedure for, the various aspects of the invention are described where appropriate. These Examples and Scheme are intended to be merely illustrative of the present invention and not limiting thereof in either scope or spirit. Those of skill in the art will readily understand that known variations of the conditions and processes described in these Examples and Scheme can be used to perform the process of the present invention. Unless otherwise indicated all starting materials and equipment employed were commercially available.

SCHEME I

5 Scheme I depicts the methodology for synthesizing 3-hydroxy-5-
[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoic acid, which is
useful as an intermediate in the preparation of pharmaceutically active
molecules.

 Hence, 3-amino-5-hydroxybenzoic acid **(A)** (Tetrahedron, Vol. 39,
10 No. 24, pp 4189-4192, 1983) is reacted with ammonium thiocyanate in
aqueous HCl at elevated temperatures to yield thiourea **(B)**. Other
thiocyanate salts or other solvents may be substituted for those
exemplified as would be apparent to those skilled in the art.

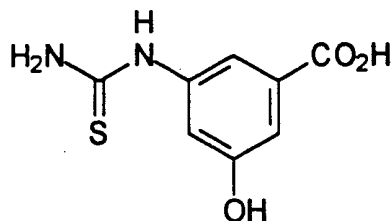
 Thiourea **(B)** is then reacted with methyl iodide in absolute ethanol
15 at elevated temperatures to produce **(C)**. Methylating agents other than
methyl iodide and solvents other than ethanol can be used to produce **(C)**
in an analogous manner.

(C) is then reacted with 1,3-diamino-2-hydroxy propane in
dimethylacetamide (DMA) at elevated temperatures to give the desired
20 product **(D)**. The HCl salt of **(D)** is formed after exposure to HCl. Solvents
other than DMA can be freely substituted and salts other than HCl can be
formed as would be apparent to those skilled in the art

5

Example 1

Preparation of



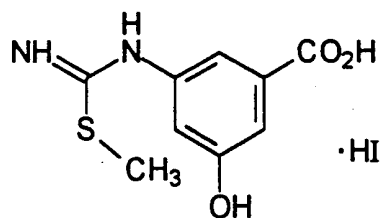
10 3-amino-5-hydroxybenzoic acid (5.0 g, 0.033 mole) [Tetrahedron, Vol. 39, No. 24, pp. 4189-4192, 1983], ammonium thiocyanate (7.4 g, 0.097 mole), distilled water (20 mL) and concentrated HCl (4.5 mL) were added together and heated at 100°C with stirring overnight. The reaction was cooled to room temperature and some solid particulates in suspension
15 were filtered off and discarded. The aqueous filtrate was extracted with ethyl acetate (3 x 80 mL). The combined ethyl acetate layers were washed with water (1 x 50 mL), brine (1 x 50 mL) and then dried over MgSO₄. The solvent was removed under vacuum to leave a crude yellow solid (6.3 g). Ethyl acetate (20 mL) was added to the yellow solid and the mixture was
20 stirred at room temperature for 10 minutes. The solid was filtered and washed with excess ethyl acetate. The solid was then dried under vacuum to give the desired product as a light yellow solid (5 g).

MS and ¹H-NMR were consistent with the desired product.

5

Example 2

Preparation of



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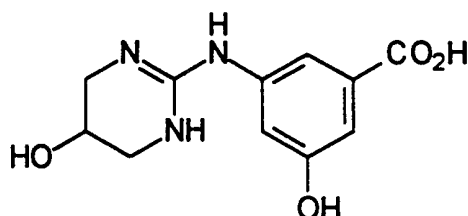
The product from Example 1 (4.25 g, 0.014 mole) and methyl iodide (2.85 g, 0.02 mole) in absolute ethanol (30 mL) were stirred at reflux for 2 hours. The solvent was removed under vacuum. The residue was slurried
15 with ethyl ether (2X, 1 hour each; then 1X overnight) and the ether was decanted off each time. The solid was then dried under vacuum to yield the desired product as a light yellow solid (5.09 g).

MS and ¹H-NMR were consistent with the desired product.

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Example 3

Preparation of



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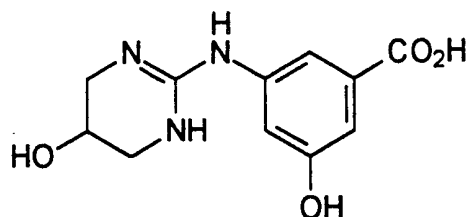
The product from Example 2 (4.85 g, 0.0137 mole), 1,3-diamino-2-hydroxypropane (3.7 g, 0.0411 mole) (Aldrich) and anhydrous DMA (7 mL) were heated to 95°C. Initially, the compound from Example 2 was an insoluble mass, but as the temperature was increased, it began to dissolve, followed by vigorous gas evolution. The reaction was stirred at 95°C for 2 hours, then at room temperature overnight. Methanol (15 mL) was added to the solution followed by CH₃CN (15 mL). A gummy precipitate formed. After stirring for 15 minutes, the solvent was decanted off. The residue was then slurried in CH₃CN (1x) and then methanol (2x) (solvent decanted off each time).

Methanol was added to the residue one final time, and after stirring 15 minutes, the resulting precipitate was filtered, washed with methanol, then ether and dried to give a white solid (2.17 g) as zwitterionic product. This solid was slurried in H₂O (10 mL) and acidified with concentrated HCl until solution. The solvent was removed under vacuum on a 90°C water bath. The residue was slurried with ether overnight, then with ether for 2 hours (ether decanted off each time) and the product was dried under vacuum on a 90°C water bath to yield the desired product as a white solid (2.4 g).

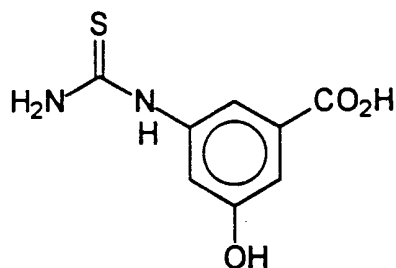
MS and ¹H-NMR were consistent with the desired product.

What is claimed is:

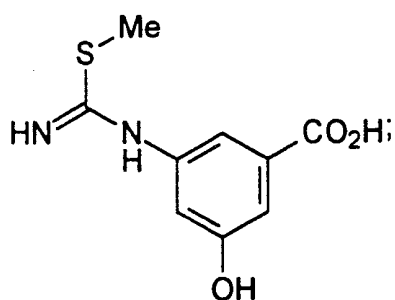
1. A process for preparing



and acid addition salts thereof comprising reacting 3-amino-5-hydroxy benzoic acid with a thiocyanate salt to produce a thiourea of the formula

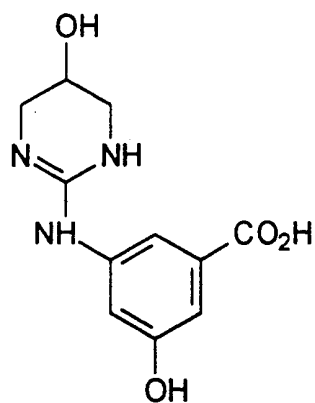


reacting the thiourea compound with a methylating agent to produce a compound of the formula



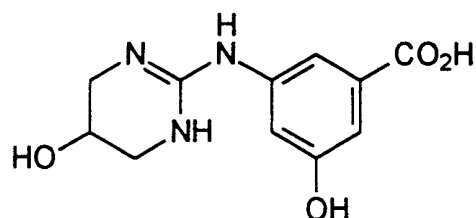
reacting the compound so produced with 1,3-diamino-2-hydroxy propane in a solvent to produce a compound of the formula

- 14 -

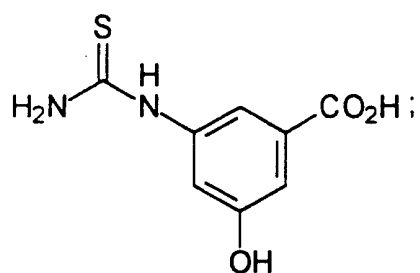


and isolating the resulting compound.

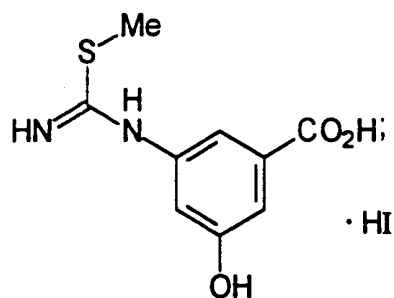
2. A process for preparing a compound of the formula



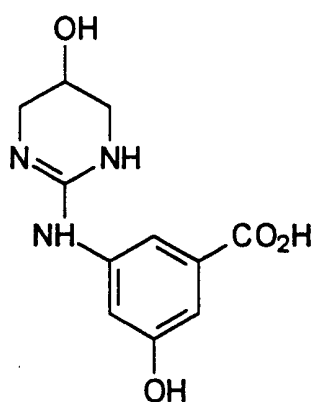
and acid addition salts thereof comprising reacting 3-amino-5-hydroxybenzoic acid with ammonium thiocyanate in a solvent to produce a thiourea of the formula



reacting the thiourea so produced with methyl iodide in a solvent to produce a compound of the formula



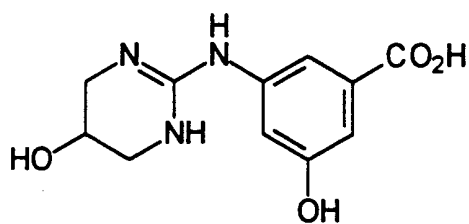
reacting the compound so produced with 1,3-diamino-2-hydroxypropane in a solvent to produce a compound of the formula



and isolating the resulting compound.

3. The process according to Claim 2 wherein the solvent used with the ammonium thiocyanate is aqueous HCl .
4. The process according to Claim 2 wherein the solvent used with the methyl iodide is ethanol.
5. The process according to Claim 2 wherein the solvent used with the 1,3-diamino-2-hydroxypropane is dimethylacetamide.

6. A compound of the formula



and addition salts thereof.

INTERNATIONAL SEARCH REPORT

Inter. .onal Application No

PCT/US 99/03279

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	S. S. G. SIRCAR, K. K. PATNAIK: "Preparation of antibacterials from organo-mercurials. Part II" J. INDIAN CHEM. SOC., vol. 27, 1950, pages 535-538, XP002106223 see table II	1-5
Y	A. P. T. EASSON, F. L. PYMAN: "CCCCXVI. - Amidines of Pharmacological Interest" J. CHEM. SOC., 1931, pages 2991-3001, XP002106224 see page 2996, line 10 - line 28 --- -/--	1-5



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents:

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

17 June 1999

Date of mailing of the international search report

06/07/1999

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Herz, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/03279

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	M. PROTIVA ET AL.: "1-Aryl- and 1-(arylmethyl)-4-guanylpiperazines and other heterocyclic and alicyclic guanidine derivatives" COLLECT. CZECH. CHEM. COMMUN., vol. 40, 1975, pages 3904-3923, XP000574972 * Compounds of formula XLVI and XLVII * ---	1-5
Y	H. FOKS ET AL.: "Studies on pyrazine derivatives. XXX. Synthesis of pyrazinylamino-1,3-diazacycloalkanes of potential circulatory activity" ACTA POL. PHARM., vol. 54, no. 1, 1997, pages 55-62, XP002106225 * Compounds of formula IV, V and VI * ---	1-5
Y	T. NAKAYAMA ET AL.: "Synthesis and Structure-Activity Study of Protease Inhibitors. V. Chemical Modification of 6-Amidino-2-naphthyl 4-Guanidinobenzoate" CHEM. PHARM. BULL., vol. 41, no. 1, 1993, pages 117-125, XP002106226 * Chart I; Compound 9 * ---	1-5
Y	K. WEINHARDT ET AL.: "Synthesis and Antidepressant Profiles of Phenyl-Substituted 2-Amino- and 2-(Alkoxy-carbonyl)amino-1,4,5,6-tetrahydropyrimidines" J. MED. CHEM., vol. 28, no. 6, 1985, pages 694-698, XP002058417 see table I ---	1-5
Y	L. S. HAFNER, R. EVANS: "Preparation of 2-Imino- and 2-Nitrimino-1,3-diazacycloalkanes" J. ORG. CHEM., vol. 24, 1959, pages 1157-1159, XP002106227 * entire document * -----	1-5