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SPRUSON & FERGUSON

AUSTRALIA

PATENTS ACT 1990

PATENT REQUEST: STANDARD PATENT

I/We, the Applicant(s)/Nominated Person(s) specified below, request I/We be granted a patent for the invention disclosed in the accompanying standard complete specification.

[70,71] Applicant(s)/Nominated Person(s):

Eli Lilly and Company, a corporation organised and existing under the laws of the State of Indiana, of Lilly Corporate Center, City of Indianapolis, State of Indiana, UNITED STATES OF AMERICA

[54] Invention Title:

Sulfonimidamides

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[33] Country:

US

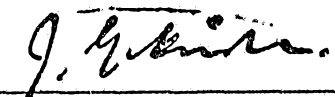
[32] Application Date:

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Eli Lilly and Company

By:


Registered Patent Attorney

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Our Case: X-8245

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NOTICE OF ENTITLEMENT

I, Leroy Whitaker, of Lilly Corporate Center, City of Indianapolis, State of Indiana, 46285, United States of America, being authorised by the Applicant/Nominated Person in respect of Application No. 30181/92 state the following:-

The Applicant/Nominated Person has entitlement from the actual inventors as follows:-

The Applicant/Nominated Person is the assignee of the actual inventors.

The Applicant/Nominated Person is entitled to rely on the basic application(s) listed on the Patent Request as follows:

The Applicant/Nominated Person is the assignee of the basic applicants.

The basic application(s) listed on the Patent Request is/are the application(s) first made in a Convention country in respect of the invention.

DATED this 9 day of NOVEMBER, 1992

ELI LILLY AND COMPANY



Leroy Whitaker
Deputy/General Counsel,
General Patent Counsel
and Assistant Secretary

INSTR CODE: 53710



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(54) Title
SULFONIMIDAMIDES

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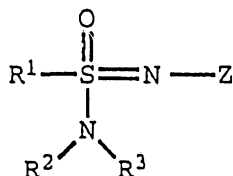
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(56) Prior Art Documents
US 5187189
US 5140926
EP 254577

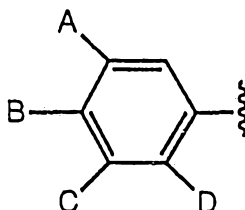
(57) This invention relates to certain novel
sulfonimidamides and their use as antineoplastic agents.

Claim

1. A compound of the formula



wherein R¹ is



wherein

A, B and C are independently:

(11) AU-B-30181/92
(10) 654069

-2-

(a) H with the proviso that at least one of A, B or C is other than H;

(b) chlorine, bromine or iodine;

(c) $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$;

(d) $-\text{C}(\text{O})\text{R}^a$, wherein R^a is H or C_1 - C_5 alkyl;

(e) $-(\text{CH}_2)_n\text{OR}^b$ wherein n is 1-4 and R^b is H or $-\text{C}(\text{O})\text{R}^c$ wherein R^c is C_1 - C_4 alkyl; or

(f) A and B or B and C together are

(i) $-(\text{CH}_2)_q-$ wherein q is 3 or 4,

(ii) $-(\text{CH}_2)_m\text{O}(\text{CH}_2)_b-$ wherein m is 0 or 1 and b is 1, 2 or 3 with the proviso that b is 2 or 3 when m is 0, or

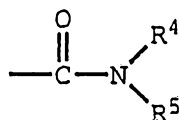
(iii) $-\text{O}-(\text{CH}_2)_n-\text{O}-$ wherein n is 1 or 2, and C or A respectively is H or CH_3 ; and

D is H, chlorine, bromine, iodine, $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$, and

R^2 is H, C_1 - C_8 alkyl with the proviso that except for the isopropyl group there is no branching in the alpha-position, C_3 - C_8 alkenyl, $-(\text{CH}_2)_n\text{OH}$ wherein n is 1-5, $-(\text{CH}_2)_p\text{C}_6\text{H}_5$ wherein p is 1-3, or $-\text{C}(\text{O})\text{R}^d$ wherein R^d is H or C_1 - C_4 alkyl;

R^3 is H or $-\text{CH}_3$;

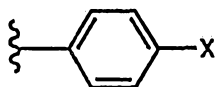
Z is



wherein

R^4 is hydrogen, methyl, or $-\text{C}(\text{O})\text{R}^a$ wherein R^a is hydrogen or C_1 - C_5 alkyl;

R^5 is



wherein X is chlorine, bromine, iodine or $-\text{CH}_3$;
or a tautomer or pharmaceutically acceptable salt thereof.

(11) AU-B-30181/92

-3-

(10) 654069

11. A method of treating a susceptible neoplasm in a mammal which comprises administering to that mammal a sulfonimidamide as claimed in any one of claims 1 to 2.

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COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

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Invention Title:

Sulfonimidamides

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

Sulfonimidamides

This invention relates to certain novel sulfonimidamides and their use as antineoplastic agents.

5 Cancer is one of the leading causes of death in the United States. The American Cancer Society reports that about 494,000 people died from cancer in the United States in 1988. A common method of treatment for cancer is the use of chemotherapy. The use of chemotherapy has
10 not been particularly successful in the treatment of solid tumors. Accordingly, there is a substantial need for new drugs which are effective in inhibiting the growth of such tumors.

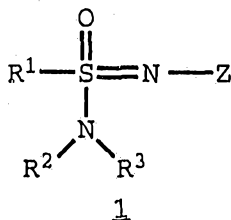
15 It has now been found that a new group of sulfonimidamides have been effective in inhibiting the growth of solid tumors.

Certain diarylsulfonylureas have been reported as being active antitumor agents. U.S. Patent 4,845,128 of Harper et al. (1989), U.S. Patent 5,116,874 of Foore (1992). These references are all directed to
20 sulfonylureas and there is no suggestion or disclosure of the sulfonimidamides of the instant invention.

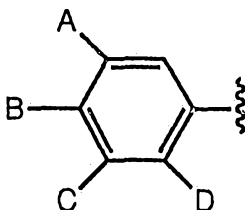
Certain sulfonimidamides have been reported. Johnson et al. Journal of Organic Chemistry, 44, 2055
25 (1979) discloses the preparation of certain of such compounds. One such compound, N-butyl-N'-(p-toluenesulfonimidoyl)urea (compound 16), is disclosed as being inactive in an antidiabetic screen. There is no disclosure of the instant compounds or their use in
30 inhibiting the growth of neoplasms.

U.S. Patent 4,666,506 of Hillemann (1987) discloses a large number of aryl and heteroaryl sulfonimidamides for use as herbicides and/or plant growth regulants. There is no suggestion or disclosure in this reference
35 of the compounds of the instant invention.

In one embodiment the present invention comprises compounds of formula 1



wherein R^1 is



wherein:

A, B and C are independently:

hydrogen, with the proviso that at least one of A, B or C is other than hydrogen;

chlorine, bromine or iodine; methyl or ethyl;

$-\text{C}(\text{O})\text{R}^a$, wherein R^a is hydrogen or C_1 - C_5

alkyl;

$-(\text{CH}_2)_n\text{OR}^b$ wherein n is 1-4 and R^b is

hydrogen or

$-\text{C}(\text{O})\text{R}^c$ wherein R^c is C_1 - C_4 alkyl;

or A and B or B and C together are

$-(\text{CH}_2)_q-$ wherein q is 3 or 4,

$-(\text{CH}_2)_m\text{O}(\text{CH}_2)_b-$ wherein m is 0 or 1 and b is

1, 2 or 3 with the proviso that b is 2 or 3 when m is 0,

or $-\text{O}-(\text{CH}_2)_n-\text{O}-$ wherein n is 1 or 2 and C or A

respectively is hydrogen or

$-\text{CH}_3$; and

D is hydrogen, chlorine, bromine, iodine, methyl, or ethyl; and

R^2 is hydrogen,

C₁-C₈ alkyl with the proviso that except for the isopropyl group there is no branching in the alpha-position,

C₃-C₈ alkenyl,

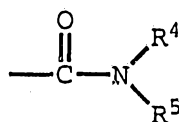
-(CH₂)_nOH wherein n is 1-5,

-(CH₂)_pC₆H₅ wherein p is 1-3, or

-C(O)R^d wherein R^d is hydrogen or C₁-C₄ alkyl;

R³ is hydrogen or methyl; and

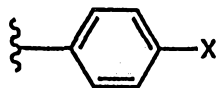
Z is



wherein

R⁴ is hydrogen, methyl, or -C(O)R^a wherein R^a is hydrogen or C₁-C₅ alkyl;

R⁵ is



wherein X is chlorine, bromine, iodine or methyl;

and tautomers

and pharmaceutically acceptable salts thereof.

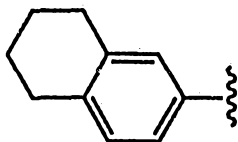
As used herein the following terms shall have the indicated meanings.

The term "C₁-C₈ alkyl" refers to straight and branched chain alkyl groups having from one to eight carbon atoms provided that except for the isopropyl group there is no branching at the alpha carbon, including without limitation methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 3-methylpentyl, n-heptyl, 3-ethylpentyl, and the like. The alpha carbon is the

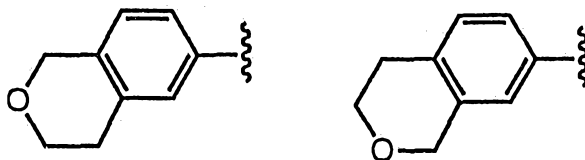
3-ethylpentyl, and the like. The alpha carbon is the first carbon in the alkyl chain, e.g., the methylene moiety in an ethyl group. The term "C₁-C₃ alkyl" refers to methyl, ethyl, n-propyl and isopropyl. The term "C₁-C₅ alkyl" refers to straight and branched chain alkyl groups having one to five carbon atoms.

The term "C₃-C₈ alkenyl" refers to straight and branched chain unsaturated alkyl groups having from three to eight carbon atoms provided there is a single bond between the alpha and beta carbons and further provided that except for 1-methylethene there is no branching at the alpha carbon. Such groups include 1-propenyl, 1-methyl-1-propenyl, 1-butenyl, 1-hexenyl, 2-methylpropenyl and the like.

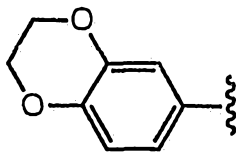
Compounds of the instant invention in which A and B together of R¹ are -(CH₂)_q- where q is 3 and C and D are each hydrogen have the following structure:



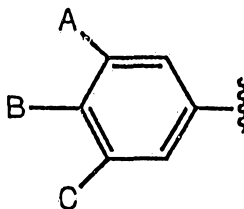
When B and C together are -(CH₂)_mO(CH₂)_b- in which m is 1, b is 2 and A and D are each hydrogen, the following structures are provided.



When A and B together are -O(CH₂)_n-O- and C and D are hydrogen, the following structure is provided when n is 2.



Preferred compounds of the instant invention are those of formula 1 in which R¹ is



wherein A and C are independently hydrogen or methyl; B is chlorine, bromine, methyl, -CH₂OH, -C(O)H, -CH₂OC(O)CH₃, or -CH₂CH₃; or A and B together are -(CH₂)₃- and C is hydrogen or methyl; R² is C₁-C₄ alkyl, hydrogen, or CH₃C(O); R³ is hydrogen; R⁴ is hydrogen or methyl; and R⁵ is parachlorophenyl, parabromophenyl or paramethylphenyl.

More preferred compounds of formula 1 include: N-[[[(4-chlorophenyl)amino]carbonyl]-4-methylbenzenesulfonimidamide, N-[[[(4-chlorophenyl)amino]carbonyl]-N'-4-dimethylbenzenesulfonimidamide, N-[[[(4-chlorophenyl)amino]carbonyl]-N'-ethyl-4-methylbenzenesulfonimidamide, N-[[[(4-chlorophenyl)amino]carbonyl]-N'-(1-methylethyl)-4-methylbenzenesulfonimidamide, N-[[[(4-chlorophenyl)amino]carbonyl]-N'-butyl-4-methylbenzenesulfonimidamide, N-[[[(4-chlorophenyl)amino]carbonyl]-N'-acetyl-N'-methyl-4-methylbenzenesulfonimidamide, N-methyl-N-[[[(4-chlorophenyl)amino]carbonyl]-4-methylbenzenesulfonimidamide, N-[[[(4-bromophenyl)amino]carbonyl]-4-methylbenzenesulfonimidamide, N-[[[(4-chlorophenyl)amino]carbonyl]-4-ethylbenzenesulfonimidamide, N-[[[(4-chlorophenyl)amino]carbonyl]-3,4-dimethylbenzenesulfonimidamide, N-[[[(4-

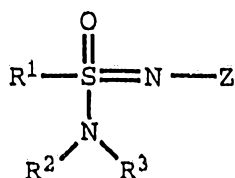
chlorophenyl)amino]carbonyl]-N'-butyl-4-methylbenzene-sulfonimidamide, N-[[[4-chlorophenyl)amino)carbonyl]-3,4,5-trimethylbenzenesulfonimidamide, N-[[[4-chlorophenyl)amino]-carbonyl]-4-

5 (acetoxymethyl)benzenesulfonimidamide, N-[[[4-chlorophenyl)]amino]carbonyl]-4-(hydroxymethyl)benzene-sulfonimidamide, N-[[[4-chlorophenyl)amino]carbonyl]-4-formylbenzenesulfonimidamide, N-[[[4-

10 chlorophenyl)amino]carbonyl-5-indanylsulfonimidamide, and N-[[[4-chloro-phenyl)amino]carbonyl]-N'-methyl-5-indanylsulfonimidamide.

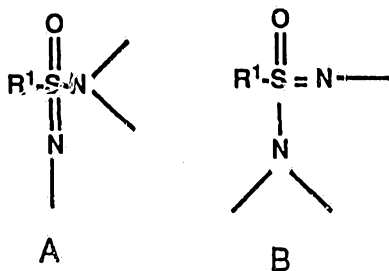
The instant compounds are named herein as sulfonimidamides. This refers to compounds having a sulfur atom which is covalently bonded to a carbon,

15 oxygen and two nitrogen atoms. This structure is represented in formula 1 as:

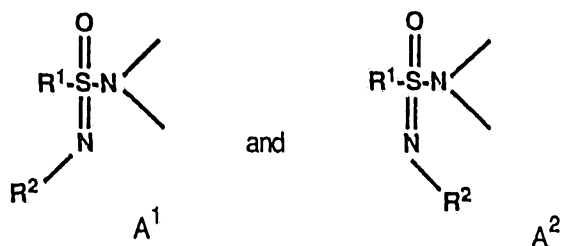


20 and expressly encompasses the tautomers thereof.

Formally, the bond between the sulfur and one of the nitrogens is a double bond while the other is single. The possible tautomers are represented as A and B below:



It has been reported by Johnson et al., J. Org. Chem., 44, at page 2056, that the tautomeric forms A and B may be in rapid equilibrium when there is a hydrogen on either of the two nitrogens. Each of these structures permits two racemic diastereoisomers based on the relative position of the moiety attached to the double-bonded nitrogen, e.g., A¹ and A².



All eight possible stereoisomers are contemplated as within the scope of the instant invention, including racemic mixtures and each substantially pure stereoisomer.

As provided in the Examples, nmr spectroscopy of the compounds of the instant invention indicates that they exist primarily in the form of tautomer B above.

The compounds of formula 1 in which R² is C(O)R^d and R³ is hydrogen are sufficiently acidic to form salts with strong and weak bases. This invention also includes the pharmaceutically acceptable salts of those compounds of formula 1 which can form salts. Other compounds of formula 1 are weakly acidic in nature and accordingly may form salts with only strongly basic materials. Examples of bases which may be useful in forming pharmaceutically acceptable salts, include amines, alkali metal and alkaline-earth metal bases or quaternary ammonium bases.

Preferred alkali metal and alkaline-earth metal hydroxides as salt formers are the hydroxides of

lithium, sodium, potassium, magnesium or calcium, in particular those of sodium and potassium.

Examples of amines suitable for forming salts are: primary, secondary and tertiary aliphatic and aromatic amines, such as methylamine, ethylamine, propylamine, isopropylamine, the four isomeric butylamines, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and i-quinoline, especially ethyl-, propyl-, diethyl- or triethylamine, but particularly isopropylamine and diethanolamine.

Examples of quaternary ammonium bases are in general the cations of haloammonium salts, for example the tetramethylammonium cation, the trimethylbenzylammonium cation, the triethylbenzylammonium cation, the tetraethylammonium cation or the trimethylethylammonium cation, but also the ammonium cation.

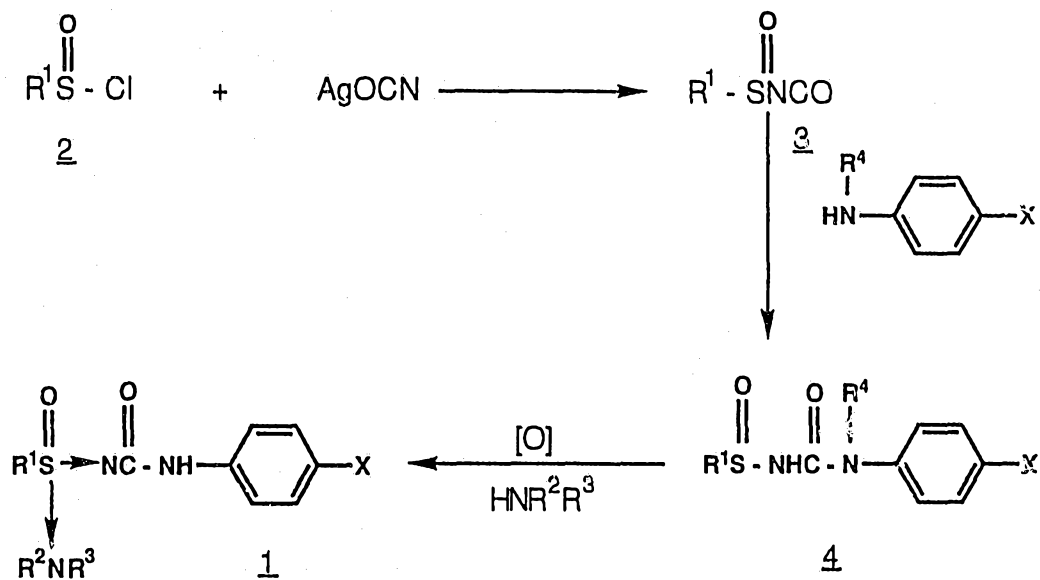
This invention also encompasses processes for preparing the compounds of formula 1. The compounds of the instant invention can be prepared using the reaction schemes disclosed in U.S. Patent No. 4,666,506 of Hillemann (1987) and the article of Johnson, et al., The Journal of Organic Chemistry, 44, 2055-2060, 1979, both of which are incorporated herein by reference in their entirety. Preferred reaction schemes are set forth in reaction Scheme 1 and Scheme 2 herein below. The sulfinyl chloride of formula 2 can be conveniently prepared according to the process provided in Organic Syntheses Collection, Vol. IV, 937 (1963) incorporated herein by reference in its entirety.

The sulfinyl chloride is preferably reacted with silver cyanate to provide the isocyanate 3 ($R^1S(O)NCO$) according to the procedure of Jähnchen et al., 39 Z.

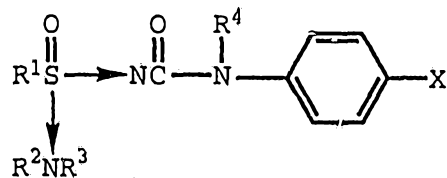
Chem., 2 (1969), p. 305, incorporated herein by reference in its entirety. This can be accomplished in a solvent such as diethylether, dioxane, tetrahydrofuran, etc., using about 1.0 to 1.5 equivalents of silver cyanate at a temperature of about 0°-25°C into which is added, normally dropwise, a solution of the sulfinyl chloride in a solvent such as diethyl ether or an alkane. After stirring at room temperature for about 1 to 24 hours, the solid silver chloride is removed by filtration to provide a solution of the isocyanate 3. This is then contacted with the arylamine to provide the intermediate product 4.

The symbol [O] refers to an oxidation reaction with preferred oxidants including chlorine, SO₂Cl₂, or N-chlorobenzotriazole as disclosed by Rees, et al., in Journal of the Chemical Society(C), 1474 (1969), or t-butyl hypochlorite (Johnson, et al. supra) both of which are incorporated herein by reference in their entirety.

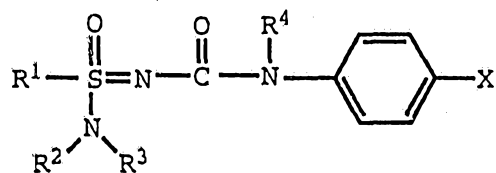
Intermediate 4 is contacted with a preferred oxidant, normally 1.0-1.2 equivalents, in a suitable solvent such as an ether or chlorinated hydrocarbon, preferably tetrahydrofuran. The resulting material is then added dropwise to excess amine to provide product 1. Intermediate 4 can also be prepared as shown in Scheme 2 using methods known in the art.

Scheme 1

wherein

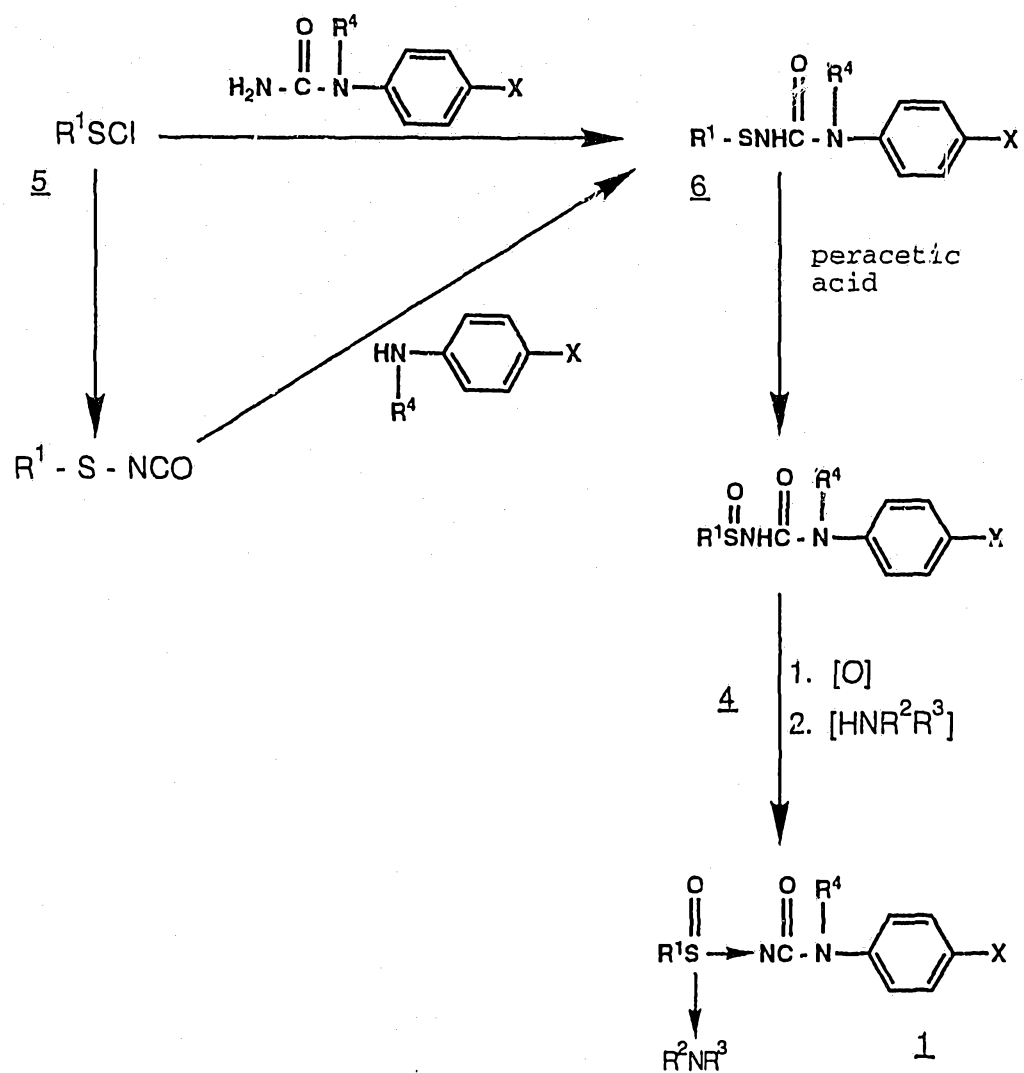


refers to compounds of the formula

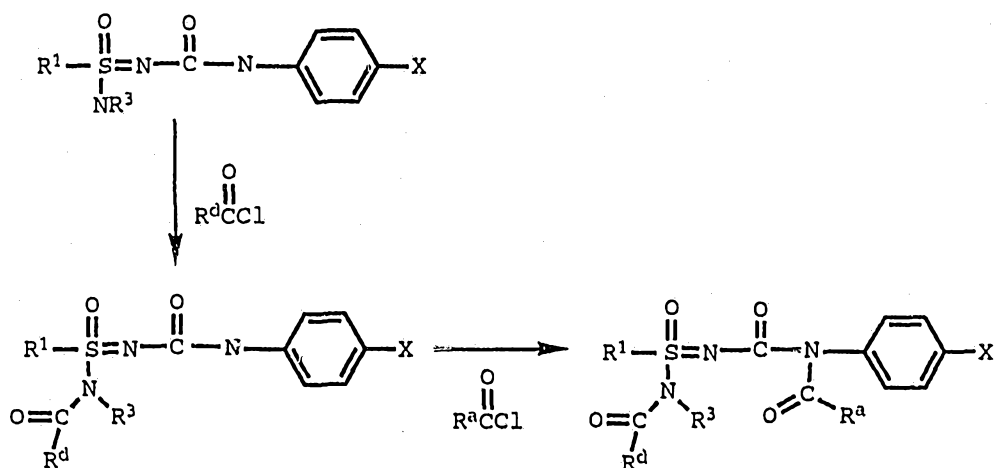


and the tautomers thereof.

Scheme 2



A preparation of compounds of formula 1 in which Z is $C(O)-N(R^5)C(O)R^a$ is exemplified in reaction Scheme 3. A compound of formula 1 of Scheme 1 or 2 is acylated to provide the desired product. This can be accomplished by contacting the substrate 1 with about 2.5 equivalents of a base such as triethylamine in a solvent such as dichloromethane in the presence of a catalytic amount of an acylation catalyst such as 4-dimethylaminopyridine. A typical acylating agent used in the art, for example an acid halide ($R^dC(O)Cl$ shown in Scheme 3) or an acid anhydride, is added normally in the amount of about 1.0-2.5 equivalents.

Scheme 3

The starting materials and intermediates for the preparation of the present compounds are commercially available or can be readily prepared by the above-described methods or other methods known in the literature. References to specific literature procedures are cited in the examples and listed following the example section hereinbelow.

The following examples further illustrate the preparation of the compounds of this invention. The examples are provided for purposes of illustration only and are not to be construed as limiting the scope of the instant invention in any way.

The terms and abbreviations used in the instant examples have their normal meaning unless otherwise designed, for example, "THF" means tetrahydrofuran; "EE" refers to diethyl ether; "°C" refers to degrees celsius; "N" refers to normal or normality; "mM" refers to millimole; "g" refers to gram; "mL" means milliliter; "M" refers to molar; "NMR" refers to nuclear magnetic resonance; "m.s." refers to mass spectrometry; "EtOAc" refers to ethyl acetate; "HOAc" refers to acetic acid; "DMSO" refers to dimethylsulfoxide; "MeOH" refers to methanol; "EtOH" refers to ethanol.

Table 1 provides structures of compounds prepared in the Examples. References to literature procedures given in the Examples and are provided at the end of the Examples. Unless otherwise indicated Z in formula 1 is $C(O)NR^4R^5$, R^4 is hydrogen, and R^5 is p-chlorophenyl.

Table 1*

Example No.	R ¹	R ²	R ³
2	p-tolyl	H	H
3	p-tolyl	CH ₃	H
4	p-tolyl	C ₂ H ₅	H
5	p-tolyl	n-C ₃ H ₇	H
6	p-tolyl	i-C ₃ H ₇	H
7	p-tolyl	n-C ₄ H ₉	H
8	p-tolyl	i-C ₄ H ₉	H
9	p-tolyl	n-C ₆ H ₁₂	H
10	p-tolyl	C ₂ H ₄ OH	H
11	p-tolyl	C ₃ H ₇ OH	H
12	p-tolyl	CH ₂ C ₆ H ₅	H
13	p-tolyl	(CH ₂) ₂ C ₆ H ₅	H
14	p-tolyl	C ₆ H ₅	H
15	p-tolyl	acetyl	H
16	p-tolyl	acetyl	CH ₃
17(a)	p-tolyl	acetyl	CH ₃
18	p-tolyl	CH ₃	CH ₃
20(b)	p-tolyl	H	H
22(c)	p-tolyl	H	H
24(d)	p-tolyl	H	H
27	p-Cl-phenyl	H	H

Example No.	R ¹	R ²	R ³
30	p-Br-phenyl	H	H
33	p-(C ₂ H ₅)phenyl	H	H
36	3,4-(CH ₃) ₂ -phenyl	H	H
39	3,5-(CH ₃) ₂ -phenyl	H	H
45	3,4,5-(CH ₃) ₃ -phenyl	H	H
49	p-(CH ₂ OAc)phenyl	H	H
50	p-(CH ₂ OH)phenyl	H	H
51	p-(CHO)phenyl	H	H
54	5-indanyl	H	H
55	5-indanyl	CH ₃	H
61	4-Cl-3,5-(CH ₃) ₂ -phenyl	H	H
62	3,4-(CH ₃) ₂ phenyl	CH ₃	H
63	3,4-(CH ₃) ₂ phenyl	acetyl	CH 3
64	p-tolyl	CH ₂ -CH=CH ₂	H
65(b)	p-tolyl	CH ₃	H

* Unless otherwise indicated R⁴ is hydrogen and R⁵ is p-chlorophenyl

(a) Z is -C(O)-N(R⁵)R^a where R^a is acetyl,

(b) R⁴ is methyl

(c) R⁵ is p-bromophenyl

(d) R⁵ is p-methylphenyl

EXAMPLE 1N-(4-Methylbenzenesulfinyl)-N'-(4-chlorophenyl)urea

5 A dry 250 mL 3-neck round-bottom flask fitted with a mechanical stirrer, addition funnel and nitrogen line was charged with silver cyanate (20.8 g, 138.6 mmol) and 70 mL of dry EE. This mixture was cooled to 0°C and the addition funnel charged with a solution of crude p-toluenesulfinyl chloride¹ (16.95 g, 97.05 mmol) in 70 mL
10 dry EE; the sulfinyl chloride solution was added dropwise to the cyanate mixture with vigorous stirring over 30 min, keeping the temperature at 0°C. After removing the cooling bath and stirring at room
15 temperature for 2 h, the suspended silver chloride was removed by filtration and the yellow sulfinyl isocyanate solution was transferred to a dry 1 L 3-neck flask. A solution of p-chloroaniline (11.2 g, 87.8 mmol) in 200 mL of dry EE was added dropwise to the ice-cold sulfinyl isocyanate solution over 15 min. The product
20 precipitated as a thick white solid during this time. After warming to room temperature and stirring overnight, the resulting solid was collected by filtration and rinsed with 1 L of EE. Vacuum drying at
25 40°C for 4 h gave 20.93 g (77%) of the product as a white to light purple solid: mp=163-164°C; R_f(10/1, EtOAc/HOAc)= 0.63; ¹H NMR (300 MHz, d₆-DMSO) δ 2.38 (s, 3H, CH₃), 7.33 (d, 2H, J=8.8 Hz, Ar-H), 7.41-7.46 (m, 4H, Ar-H), 7.63 (d, 2H, J=8.1 Hz, Ar-H), 8.83 (s, 1H, exchanges with D₂O, NH) and 9.56 (s, 1H, exchanges with D₂O, SONH); ¹³C NMR (75 MHz, d₆-DMSO) δ 21.3, 120.8, 125.2, 127.0, 129.2, 130.2, 137.9, 141.6, 142.0 and 153.2; IR(KBr) 3274, 3158, 1698, 1603, 1544, 1492, 1426, 1398, 1307, 1290, 1247, 1207, 1178, 1096, 1024, 1011, 901 and 824 cm⁻¹; FDMS(DMSO) m/e 308, 310

(M⁺). Anal Calcd for C₁₄H₁₃Cl₁N₂O₂S₁: C, 54.46; H, 4.24; N, 9.07. Found C, 54.34; H, 4.32; N, 8.91.

EXAMPLE 2

5 N-[[[4-Chlorophenyl)aminolcarbonyl]-4-
 methylbenzenesulfonimidamide
 [(p-CH₃C₆H₄)S(O)(NH₂)NC(O)NH(p-ClC₆H₄)]

10 The product of Example 1 (1.85 g, 6.0 mmol) was
suspended in 50 mL of dry THF under nitrogen and treated
with N-chlorobenzotriazole² (968 mg, 6.3 mmol) in one
portion. The mixture became homogeneous and yellow after
10 min and was stirred another 25 min. This solution was
added dropwise over 10 min to 25 mL of ammonia at -78°C.
After stirring 15 min the mixture was allowed to warm to
15 RT for 2 h. The volatiles were removed under vacuum and
the residue diluted with 50 mL of water. The resulting
slurry of white solid, after being stirred for 15 min,
was collected by filtration and rinsed with water (20
mL) and EE (50 mL). Vacuum drying overnight at 50°C
20 yielded 1.43 g (74%) of the product as a white solid:
mp=171-172°C; R_f(1/9, MeOH/CHCl₃)= 0.48; ¹H NMR (300
MHz, d₆-DMSO) δ 2.36 (s, 3H, CH₃), 7.18 (d, 2H, J=8.8
Hz, Ar-H), 7.37 (d, 2H, J=8.0 Hz, Ar-H), 7.45-7.48 (m,
4H, 2H exchanges with D₂O, 2Ar-H + NH₂), 7.76 (d, 2H,
25 J=8.2 Hz, Ar-H) and 9.24 (s, 1H, exchanges with D₂O,
NH); ¹³C NMR (75 MHz, d₆-DMSO) δ 21.4, 119.9, 125.2,
127.0, 128.6, 129.6, 140.2, 141.0, 142.8 and 157.2;
IR(KBr) 3429, 3401, 3279, 3056, 1651, 1618, 1591, 1521,
1494, 1400, 1312, 1273, 1222, 1175, 1114, 1093, 1011,
30 952, 910, 830, 815, 778, 701 and 686 cm⁻¹; UV(EtOH)
λ_{max}(e) 205.2(34293), 254.4(29327) nm; FDMS(DMSO) m/e
323, 325 (M⁺). Anal Calcd for C₁₄H₁₄Cl₁N₃O₂S₁: C, 51.93;
H, 4.36; N, 12.98. Found C, 51.67; H, 4.47; N, 12.68.

EXAMPLE 3

N-[[[4-Chlorophenyl)amino]carbonyl]-N',4-
dimethylbenzenesulfonimidamide

$[(p\text{-CH}_3\text{C}_6\text{H}_4)\text{S}(\text{O})(\text{NHCH}_3)\text{NC}(\text{O})\text{NH}(p\text{-ClC}_6\text{H}_4)]$

A flame-dried, 500 mL 3-neck round-bottom flask was charged with 200 mL of dry THF and the product of Example 1 (6.48 g, 21.0 mmol). N-chlorobenzotriazole² (3.39 g, 22.07 mmol) was added in one portion and stirring continued another 25 min. The resulting solution was added dropwise to 100 mL of methylamine at -78°C over 10 min. The cooling bath was removed and stirring continued at room temperature for 3 h. The reaction solution was concentrated in vacuo and the resulting residue dissolved in 350 mL of EtOAc and washed with 1N HCl solution (1x100 mL), water (1x100 mL) and brine (1x50 mL). After drying (Na₂SO₄), filtration and evaporation gave a foam (10 g). Trituration with warm toluene (120 mL) followed by cooling gave a white crystalline product which was collected by filtration, rinsed with chilled toluene (20 mL) and vacuum dried to yield 3.89 g (55%) of the product: mp=79-81°C; R_f(1/9, MeOH/CHCl₃)= 0.69; ¹H NMR (300 MHz, d₆-DMSO) δ 2.37 (s, 3H, CH₃), 2.40 (d, 3H, J=4.9 Hz, NCH₃), 7.20 (d, 2H, J=8.8 Hz, Ar-H), 7.40 (d, 2H, J=8.1 Hz, Ar-H), 7.47 (d obscuring NH, 3H, J=8.8 Hz, 1H exchanges with D₂O, Ar-H + NH), 7.72 (d, 2H, J=8.2 Hz, Ar-H) and 9.33 (s, 1H, exchanges with D₂O, NH); ¹³C NMR (75 MHz, d₆-DMSO) δ 21.4, 28.1, 120.0, 125.4, 127.7, 128.6, 130.0, 136.3, 140.0, 143.4 and 156.8; IR(KBr) 3357, 1630, 1592, 1526, 1399, 1278, 1232, 1121, 1090, 1082, 1011, 927, 829, 774 and 687 cm⁻¹; UV(EtOH) λ_{max}(ε) 204.6(37504), 254.6(27729) nm; FDMS (DMSO) m/e 337, 339 (M⁺). Anal Calcd for C₁₅H₁₆ClN₃O₂S₁: C, 53.33; H, 4.77; N, 12.44. Found C, 53.09; H, 4.72; N, 12.26.

EXAMPLE 4

$[(p\text{-CH}_3\text{C}_6\text{H}_4)\text{S}(\text{O})(\text{NHCH}_2\text{CH}_3)\text{NC}(\text{O})\text{NH}(p\text{-ClC}_6\text{H}_4)]$

The method of Example 3 was followed using the product of Example 1 (6.17 g, 20.0 mmol), N-chlorobenzotriazole² (3.23 g, 21.0 mmol) and ethylamine (13 mL) at 5-10°C. The crude product was chromatographed by Prep 500 (silica, toluene/EtOAc) and silica gel flash chromatography (toluene/EtOAc) to give 4.0 g of crude product. This was recrystallized from EE/hexane to yield 3.3 g (47%) of the product as a white solid.

Analysis of this product gave the following results: mp=134.5-136°C; R_f (EtOAc)= 0.64; ¹H NMR (300 MHz, d₆-DMSO) δ 0.98 (t, 3H, J = 7.2 Hz, CH₃CH₂), 2.37 (s, 3H, CH₃), 2.76-2.84 (m, 2H, CH₃CH₂), 7.21 (d, 2H, J=8.8 Hz, Ar-H), 7.39 (d, 2H, J=8.1 Hz, Ar-H), 7.48 (d, 2H, J=8.8 Hz, Ar-H), 7.59 (s, 1H, exchanges with D₂O, NH), 7.74 (d, 2H, J=0.2 Hz, Ar-H) and 9.29 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3282, 3242, 2979, 1644, 1593, 1530, 1400, 1275, 1227, 1134 and 1108 cm⁻¹; UV(EtOH) λ_{max}(ε) 204.4(38437) and 254.8(29281) nm; F₂MS (DMSO) m/e 351, 353 (M⁺). Anal Calcd for C₁₆H₁₈Cl₁N₃O₂S₁: C, 54.62; H, 5.16; N, 11.94. Found C, 54.39; H, 5.21; N, 11.65.

EXAMPLE 5

[(p-CH₃C₆H₄)S(O)(NHCH₂CH₂CH₃)NC(O)NH(p-ClC₆H₄)]

The method of Example 3 was followed using the product of Example 1 (12.4 g, 40.2 mmol), N-chlorobenzotriazole² (6.7 g, 44 mmol) and n-propylamine (9 mL, 110 mmol) at 0°C. The crude product (16.3 g) was purified by Prep 500 (toluene/EtOAc) chromatography and recrystallized from 50 mL EE/hexane (1:1) to yield 4.04 g (27%) of the product as a white solid.

Analysis of the product gave the following results: mp=118-119.5°C; R_f (1/1, EtOAc/hexane)= 0.62; ¹H NMR (300 MHz, d₆-DMSO) δ 0.7-0.8 (m, 3H, CH₂CH₂CH₃), 1.35-1.42 (m, 2H, CH₂CH₂CH₃), 2.37 (s, 3H, CH₃), 2.68-2.74 (m, 2H, CH₂CH₂CH₃), 7.20 (d, 2H, J=8.8 Hz, Ar-H), 7.38 (d, 2H,

J=8.1 Hz, Ar-H), 7.48 (d, 2H, J=8.8 Hz, Ar-H), 7.61 (m, 1H, exchanges with D₂O, NH) and 9.29 (bs, 1H, exchanges with D₂O, NH); IR(KBr) 3298, 3252, 2974, 1644, 1593, 1532, 1399, 1230, 1137, 1003, 836 and 681 cm⁻¹; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 206.0(33591) and 254.8 (29371) nm; FDMS (DMSO) m/e 365, 367(M⁺). Anal Calcd for C₁₇H₂₀Cl₁N₃O₂S₁: C, 55.81 H, 5.51; N, 11.49. Found C, 55.96; H, 5.64; N, 11.21.

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EXAMPLE 6

[(p-CH₃C₆H₄)S(O)(NHCH(CH₃)₂)NC(O)NH(p-ClC₆H₄)]

The method of Example 3 was followed, using the product of Example 1 (5.0 g, 16.2 mmol), t-butylhypochlorite (2.0 mL, 16.9 mmol) and 50 mL of 2-propylamine. Silica gel flash chromatography (EtOAc/hexane) yielded 4.87g (82%) of the product as a yellow foam.

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Analysis of the product gave the following results: mp =144-146°C; R_f(1/1, EtOAc/hexane)= 0.66; ¹H NMR (300 MHz, d₆-DMSO) δ 0.90 (d, 3H, J=6.5 Hz, CHCH₃), 1.03 (d, 3H, J=6.5 Hz, CHCH₃), 2.36 (s, 3H, CH₃), 3.20-3.40 (m, 1H, CHCH₃), 7.20 (d, 2H, J=8.9 Hz, Ar-H), 7.38 (d, 2H, J=8.2 Hz, Ar-H), 7.48 (d, 2H, J=8.9 Hz, Ar-H), 7.63 (d, 1H, J=7.7 Hz, exchanges with D₂O, CHNH), 7.77 (d, 2H, J=8.2 Hz, Ar-H) and 9.24 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3285, 2975, 1636, 1593, 1494, 1398, 1272, 1231, 1112, 1089, 1011 and 829 cm⁻¹; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 203.8(39333) and 254.4(28704) nm; FDMS (DMSO) m/e 365, 367 (M⁺). Anal Calcd for C₁₇H₂₀Cl₁N₃O₂S₁ : C, 55.81; H, 5.51; N, 11.48. Found C, 55.94; H, 5.54; N, 11.20.

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EXAMPLE 7

[(p-CH₃C₆H₄)S(O)(NHCH₂CH₂CH₂CH₃)NC(O)NH(p-ClC₆H₄)]

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The method of Example 3 was followed, using the product of Example 1 (5.0 g, 16.2 mmol), t-butylhypo-

chlorite (2.0 mL, 16.9 mmol) and 50 mL of n-butylamine. Silica gel flash chromatography (EtOAc/hexane) yielded 5.45 g (88%) of the product as a foam.

Analysis of the product gave the following results: mp=103-105°C; R_f (1/1, EtOAc/hexane)= 0.83; ^1H NMR (300 MHz, d_6 -DMSO) δ 0.76 (t, 3H, $J=7.3$ Hz, CH_2CH_3), 1.15-1.27 (m, 2H, CH_2CH_3), 1.27-1.40 (m, 2H, CH_2CH_2), 2.36 (s, 3H, CH_3), 2.60-2.80 (m, 2H, $\text{CH}_2\text{CH}_2\text{NH}$), 7.20 (d, 2H, $J=8.8$ Hz, Ar-H), 7.38 (d, 2H, $J=8.2$ Hz, Ar-H), 7.48 (d, 2H, $J=8.8$ Hz, Ar-H), 7.60 (t, 1H, $J=5.8$ Hz, exchanges with D_2O , CH_2NH), 7.74 (d, 2H, $J=8.2$ Hz, Ar-H) and 9.30 (s, 1H, exchanges with D_2O , NH); IR(KBr) 3283, 2959, 1637, 1593, 1526, 1399, 1232, 1090, 812 and 684 cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 204.6(37357) and 254.0(28514) nm; FDMS(DMSO) m/e 379, 381 (M^+). Anal Calcd for $\text{C}_{18}\text{H}_{22}\text{Cl}_1\text{N}_3\text{O}_2\text{S}_1$: C, 56.91; H, 5.84; N, 11.06. Found C, 56.87; H, 5.92; N, 10.98.

EXAMPLE 8

$[(p\text{-CH}_3\text{C}_6\text{H}_4)\text{S(O)}(\text{NHCH}_2\text{CH}(\text{CH}_3)_2)\text{NC(O)}\text{NH}(p\text{-ClC}_6\text{H}_4)]$

The method of Example 3 was followed, using the product of Example 1 (5.0 g, 16.2 mmol), t-butylhypochlorite (2.0 mL, 16.9 mmol) and 50 mL of isobutylamine. Silica gel flash chromatography (EtOAc/hexane) yielded 4.87 g (88%) of the product as a foam.

Analysis of the product gave the following results: mp=60-62°C; R_f (EtOAc)= 0.72; ^1H NMR (300 MHz, d_6 -DMSO) δ 0.77 (d, 3H, $J=6.5$ Hz, CHCH_3), 0.78 (d, 3H, $J=6.5$ Hz, CHCH_3), 1.52-1.70 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.36 (s, 3H, CH_3), 2.40-2.57 (m, 2H, CH_2NH), 7.20 (d, 2H, $J=8.8$ Hz, Ar-H), 7.38 (d, 2H, $J=8.2$ Hz, Ar-H), 7.48 (d, 2H, $J=8.8$ Hz, Ar-H), 7.66 (t, 1H, $J=6.1$ Hz, exchanges with D_2O , CH_2NH), 7.74 (d, 2H, $J=8.2$ Hz, Ar-H) and 9.30 (s, 1H, exchanges with D_2O , NH); IR(KBr) 3286, 2960, 2872, 1636, 1593, 1524, 1494, 1398, 1274, 1232 and 1122 cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 204.2(39301) and 254.4(28525) nm;

FDMS(DMSO) m/e 379, 381 (M^+). Anal Calcd for $C_{18}H_{22}Cl_1N_3O_2S_1$: C, 56.91; H, 5.84; N, 11.06. Found C, 56.96; H, 5.88; N, 10.85.

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EXAMPLE 9

$[(p-CH_3C_6H_4)S(O)[NH(CH_2)_5CH_3]NC(O)NH(p-ClC_6H_4)]$

The method of Example 3 was followed, using the product of Example 1 (5.0 g, 16.2 mmol), *t*-butylhypochlorite (2.4 mL, 20.3 mmol) and 40 mL of *n*-hexylamine. Silica gel flash chromatography (EtOAc/hexane) yielded 3.0 g (45%) of the product as colorless crystals.

Analysis of the product gave the following results: mp=92-93°C; R_f (2/3, EtOAc/hexane)= 0.76; ^1H NMR (300 MHz, d_6 -DMSO) δ 0.78 (t, 3H, $J=7.1$ Hz, CH_2CH_3), 1.03-1.25 (m, 6H, $(CH_2)_3CH_3$), 1.25-1.43 (m, 2H, $CH_2CH_2CH_2$), 2.36 (s, 3H, CH_3), 2.65-2.80 (m, 2H, CH_2CH_2NH), 7.20 (d, 2H, $J=8.6$ Hz, Ar-H), 7.38 (d, 2H, $J=8.0$ Hz, Ar-H), 7.48 (d, 2H, $J=8.6$ Hz, Ar-H), 7.60 (bs, 1H, exchanges with D_2O , CH_2NH), 7.74 (d, 2H, $J=8.0$ Hz, Ar-H) and 9.29 (s, 1H, exchanges with D_2O , NH); IR($CHCl_3$) 3420, 2932, 1634, 1590, 1510, 1395, 1302, 1277, 1122 and 1092 cm^{-1} ; UV(EtOH) $\lambda_{max}(e)$ 207.4(22570) and 254.4(24999) nm; FDMS(DMSO) m/e 407, 409 (M^+). Anal Calcd for $C_{26}H_{26}Cl_1N_3O_2S_1$: C, 58.88; H, 6.42; N, 10.30. Found C, 58.99; H, 6.58; N, 10.13.

EXAMPLE 10

$[(p-CH_3C_6H_4)S(O)(NHCH_2CH_2OH)NC(O)NH(p-ClC_6H_4)]$

The procedure of Example 3 was followed using the product of Example 1 (3.08 g, 10.0 mmol), *N*-chlorobenzotriazole² (1.54 g, 10.0 mmol) and ethanolamine (1.95 mL, 32.3 mmol) to give 6.0 g of a foam. Purification by silica gel flash chromatography (EtOAc/hexane) followed by recrystallization from toluene gave 1.48 g (40%) of the product.

Analysis of the product gave the following results:
mp=112.5-114°C; R_f (EtOAc)= 0.43; ^1H NMR (300 MHz, d_6 -DMSO) δ 2.79-2.88 (m, 2H, CH_2N), 3.32 (s, 3H, Ar- CH_3), 3.35-3.41 (m, 2H, CH_2OH), 4.70 (t, 1H, $J=5.5$ Hz, exchanges with D_2O , CH_2OH), 7.21 (d, 2H, $J=8.8$ Hz, Ar-H), 7.40 (d, 2H, $J=8.1$ Hz, Ar-H), 7.48 (d, 2H, $J=8.8$ Hz, Ar-H), 7.65 (t, 1H, $J=5.9$ Hz, exchanges with D_2O , CH_2NH), 7.75 (d, 2H, $J=8.1$ Hz, Ar-H) and 9.33 (s, 1H, exchanges with D_2O , NH); IR(CHCl_3) 1634, 1591, 1510, 1398, 1305, 1274, 1230, 1123, 1092, 1047 and 830 cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 204(38740), 223(16076), 255(28541), 311.8(629) nm; FDMS(DMSO) m/e 367, 369 (M^+). Anal Calcd for $\text{C}_{16}\text{H}_{17}\text{Cl}_1\text{N}_3\text{O}_3\text{S}_1$: C, 52.39; H, 4.67; N, 11.45. Found C, 52.19; H, 4.86; N, 11.43.

EXAMPLE 11

$[(p\text{-CH}_3\text{C}_6\text{H}_4)\text{S}(\text{O})(\text{NHCH}_2\text{CH}_2\text{CH}_2\text{OH})\text{NC}(\text{O})\text{NH}(p\text{-ClC}_6\text{H}_4)]$

The method of Example 3 was followed, using the product of Example 1 (5.0 g, 16.2 mmol), *t*-butylhypochlorite (2.4 mL, 20.3 mmol) and 20 mL of *n*-propanolamine. Silica gel flash chromatography (EtOAc/ CH_2Cl_2) yielded 1.8g (29%) of the product as a foam.

Analysis of the product gave the following results: mp =47-48°C; R_f (4/5/1, EtOAc/hexane/MeOH)= 0.48; ^1H NMR (300 MHz, d_6 -DMSO) δ 1.45-1.58 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.37 (s, 3H, CH_3), 2.70-2.83 (m, 2H, $\text{CH}_2\text{CH}_2\text{NH}$), 3.34-3.40 (m, 2H, $\text{CH}_2\text{CH}_2\text{OH}$), 4.43 (t, 1H, exchanges with D_2O , $J=5.1$ Hz, CH_2OH), 7.20 (d, 2H, $J=8.8$ Hz, Ar-H), 7.39 (d, 2H, $J=8.1$ Hz, Ar-H), 7.48 (d, 2H, $J=8.8$ Hz, Ar-H), 7.57 (bs, 1H, exchanges with D_2O , CH_2NH), 7.74 (d, 2H, $J=8.2$ Hz, Ar-H), and 9.30 (s, 1H, exchanges with D_2O , NH); IR(CHCl_3) 3420, 3020, 1636, 1591, 1509, 1397, 1303, 1275, 1123 and 1091 cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 204.0(38517) and 254.2(27947) nm; FDMS(DMSO) m/e 381, 383 (M^+). Anal Calcd for

C₁₇H₂₀Cl₁N₃O₃S₁: C, 53.47; H, 5.28; N, 11.00. Found C, 53.16; H, 5.33; N, 11.06.

EXAMPLE 12

5 [(p-CH₃C₆H₄)S(O)(NHCH₂C₆H₅)NC(O)NH(p-ClC₆H₄)]

The method of Example 3 was followed, using the product of Example 1 (5.0 g, 16.2 mmol), t-butylhypochlorite (2.4 mL, 20.3 mmol) and 40 mL of benzylamine. Silica gel flash chromatography (EtOAc/hexane and EtOAc/CH₂Cl₂) yielded 2.9 g (43%) of the product as a foam.

Analysis of the product gave the following results: mp = 49-51°C; R_f(2/3, EtOAc/hexane) = 0.65; ¹H NMR (300 MHz, d₆-DMSO) δ 2.37 (s, 3H, CH₃), 3.99 (s, 1H, ArCH₂NH), 4.02 (s, 1H, ArCH₂NH), 7.18-7.30 (m, 7H, Ar-H), 7.38 (d, 2H, J=8.2 Hz, Ar-H), 7.49 (d, 2H, J=8.8 Hz, Ar-H), 7.76 (d, 2H, J=8.2 Hz, Ar-H), 8.21 (t, 1H, J=5.0 Hz, exchanges with D₂O, CH₂NH), and 9.36 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3282, 1635, 1593, 1494, 1455, 1399, 1306, 1272, 1231 and 1122 cm⁻¹; UV(EtOH) λ_{max}(e) 208.2(28851) and 253.6(28726) nm; FDMS(DMSO) m/e 413, 415 (M⁺). Anal Calcd for C₂₁H₂₀Cl₁N₃O₂S₁: C, 60.94; H, 4.87; N, 10.15. Found C, 61.12; H, 4.80; N, 9.87.

EXAMPLE 13

25 [(p-CH₃C₆H₄)S(O)(NHCH₂CH₂C₆H₅)NC(O)NH(p-ClC₆H₄)]

The method of Example 3 was followed, using the product of Example 1 (5.0 g, 16.2 mmol), t-butylhypochlorite (2.4 mL, 20.3 mmol) and 45 mL of phenethylamine. Crystallization from EtOAc followed by vacuum drying at 40°C yielded 2.8 g (40%) of the product.

Analysis of the product gave the following results: mp=79-80°C; R_f(30/70, EtOAc/hexane) = 0.44; ¹H NMR (300 MHz, d₆-DMSO) δ 2.36 (s, 3H, CH₃), 2.67 (t, 2H, J=7.5 Hz, CH₂CH₂Ar), 2.90-3.05 (m, 2H, CH₂NH), 7.10-7.30

(m, 7H, Ar-H), 7.36 (d, 2H, J=8.1 Hz, Ar-H), 7.47 (d, 2H, J=8.8 Hz, Ar-H), 7.69 (d, 2H, J=8.1 Hz, Ar-H, obscuring 1H that exchanges with D₂O, NH), and 9.33 (s, 1H, exchanges with D₂O, NH); IR(CHCl₃) 3420, 3028, 3012, 1635, 1510, 1395, 1277, 1227, 1206 and 1092 cm⁻¹; UV(EtOH) λ_{max}(ε) 204.8(44173) and 254.4 (28180) nm; FDMS(DMSO) m/e 427, 429 (M⁺). Anal Calcd for C₂₂H₂₂Cl₁N₃O₂S₁: C, 61.75 H, 5.18; N, 9.82. Found C, 62.00; H, 5.33; N, 9.88.

EXAMPLE 14

[(p-CH₃C₆H₄)S(O)(NHC₆H₅)NC(O)NH(p-ClC₆H₄)]

The method of Example 3 was followed using the product of Example 1 (6.2 g, 20 mmol), N-chlorobenzotriazole² (3.2 g, 21 mmol) and aniline (2.0 g, 21 mmol) to give the crude product as a foam (10.6 g). Silica gel flash chromatography (1/9, MeOH/CHCl₃), followed by recrystallization from 75 mL of warm toluene gave 4.8 g (59%) of the product as a white solid.

Analysis of the product gave the following results: mp=160-161.5°C; R_f(1/9, MeOH/CHCl₃)= 0.77; ¹H NMR (300 MHz, d₆-DMSO) δ 2.32 (s, 3H, CH₃), 7.00-7.26 (m, 7H, Ar-H), 7.35 (d, 2H, J=8.2 Hz, Ar-H), 7.53 (d, 2H, J=8.8 Hz, Ar-H), 7.75 (d, 2H, J=8.2 Hz, Ar-H), 9.46 (bs, 1H, exchanges with D₂O, NH) and 10.30 (bs, 1H, exchanges with D₂O, NH); ¹³C NMR (75 MHz, d₆-DMSO) δ 21.3, 120.2, 121.1, 124.5, 125.7, 127.7, 128.8, 129.5, 130.0, 136.9, 137.9, 139.9, 143.8 and 156.2; IR(KBr) 3353, 3166, 1637, 1590, 1495, 1398, 1287, 1214, 1124 and 685 cm⁻¹; UV(EtOH) λ_{max}(ε) 205.8(44356), 255.2(34798) nm; FDMS(DMSO) m/e 399, 401 (M⁺). Anal Calcd for C₂₀H₁₈Cl₁N₃O₂S₁: C, 60.07 H, 4.54; N, 10.51. Found C, 60.13; H, 4.53; N, 10.26.

EXAMPLE 15

[(p-CH₃C₆H₄)S(O)(NHC(O)CH₃)NC(O)NH(p-ClC₆H₄)]

The method of Example 16 was followed, using the product of Example 2 (2.07 g 6.4 mmol), Et₃N (1.75 mL, 12.8 mmol), DMAP (5.0 mg) and acetic anhydride (0.70 mL, 7.5 mmol) in CH₂Cl₂ (50 mL). Recrystallization from EtOAc/hexane, followed by vacuum drying at 50°C yielded 2.0 g (85.5%) of the product.

Analysis of the product gave the following results: mp=168.5-170°C; R_f(19/1 CH₂Cl₂/MeOH)= 0.08; ¹H NMR (300 MHz, d₆-DMSO) δ 1.93 (s, 3H, COCH₃), 2.38 (s, 3H, Ar-CH₃), 7.26 (d, 2H, J=8.8 Hz, Ar-H), 7.42 (d, 2H, J=8.2 Hz, Ar-H), 7.54 (d, 2H, J=8.8 Hz, Ar-H), 7.89 (d, 2H, J=8.3 Hz, Ar-H), 9.53 (s, 1H, exchanges with D₂O, NH) and 12.06 (bs, 1H, exchanges with D₂O, NH); IR(KBr) 3321, 3053, 2851, 1590.5, 1706, 1638, 1594, 1534, 1283, 1138, 827 and 692 cm⁻¹; UV(EtOH) λ_{max}(ε) 204.2(37771) and 256.8(29683) nm; FDMS(DMSO) m/e 365, 367 (M⁺). Anal Calcd for C₁₆H₁₆Cl₁N₃O₃S₁: C, 52.53; H, 4.41; N, 11.49. Found C, 52.49; H, 4.49; N, 11.20.

EXAMPLE 16

[(p-CH₃C₆H₄)S(O)(N(CH₃)C(O)CH₃)NC(O)NH(p-ClC₆H₄)]

A slurry of the product of Example 3 (5.1 g, 15.1 mmol) in 120 mL CH₂Cl₂ was prepared; to this was added Et₃N (4.2 mL, 30 mmol) and DMAP (30 mg, 0.25 mmol), followed by acetic anhydride (1.62 mL, 16.7 mmol) dropwise, resulting in a solution. After stirring 1 hr, the mixture was washed with 1N aqueous HCl (1 x 50 mL), water (1 x 50 mL) and brine (1 x 50 mL); drying (Na₂SO₄), filtration and evaporation gave 5.4 g of a white solid. Silica gel flash chromatography (2/3, EtOAc/hexane) followed by recrystallization from EtOAc/hexane yielded 2.6 g (45%) of the product.

Analysis of the product gave the following results: mp=150-151°C; R_f(1/1 EtOAc/hexanes)= 0.40; ¹H NMR (300 MHz, d₆-DMSO) δ 2.21 (s, 3H, Ar-CH₃), 2.41 (s, 3H, OAc), 3.28 (s, 3H, N-CH₃), 7.28 (d, 2H, J=8.7 Hz,

Ar-H), 7. (d, 2H, J=8.1 Hz, Ar-H), 7.54 (d, 2H, J=8.7 Hz, Ar-H), 7.98 (d, 2H, J=8.1 Hz, Ar-H) and 9.74 (s, 1H, exchanges with D₂O, NH); IR(CHCl₃) 3450, 1702, 1664, 1590, 1510, 1399, 1268 and 1121 cm⁻¹; UV(EtOH) λ_{max}(e) 204.8(41076) and 259.0(24346) nm; FDMS(DMSO) m/e 379, 381 (M⁺). Anal Calcd for C₁₇H₁₈Cl₁N₃O₃S₁: C, 53.75; H, 4.78; N, 11.06. Found C, 53.84; H, 4.95; N, 11.05.

EXAMPLE 17

(p-CH₃C₆H₄)S(O)(N(CH₃)C(O)CH₃)NC(O)N[C(O)CH₃](p-ClC₆H₄)

The method of Example 16 was followed, using the product of Example 3 (3.38 g, 10 mmol), Et₃N (7 mL, 50 mmol), DMAP (100 mg, 0.8 mmol) and acetic anhydride (3.4 mL, 35 mmol) in 75 mL CH₂Cl₂. After stirring 48 hrs the reaction was worked up as in the example to give a yellow solid, 3.06 g. Recrystallization from 100 mL of EtOAc/hexane (3/7) yielded the product as a white solid, 2.33 g (55%).

Analysis of the product gave the following results: mp=138-139°C; R_f(1/1 EtOAc/hexane)= 0.27; ¹H NMR (300 MHz, CDCl₃) δ 2.30 (s, 3H, Ar-CH₃), 2.41 (s, 3H, OAc), 2.67 (s, 3H, OAc), 3.28 (s, 3H, N-CH₃), 7.17-7.22 (m, 4H, Ar-H), 7.34 (d, 2H, J=8.4 Hz, Ar-H) and 7.45 (d, 2H, J=8.6 Hz, Ar-H); IR(CHCl₃) 1702, 1492, 1371, 1256, 1149, 1093, 1015 and 926 cm⁻¹; UV(EtOH) λ_{max}(e) 203.4 (36566), 223.6(23490) and 238.6(20158) nm; FDMS(DMSO) m/e 421, 423 (M⁺). Anal Calcd for C₁₉H₂₀Cl₁N₃O₄S₁: C, 54.09; H, 4.78; N, 9.95. Found C, 54.31; H, 4.90; N, 9.91.

EXAMPLE 18

[(p-CH₃C₆H₄)S(O)(N(CH₃)₂)NC(O)NH(p-ClC₆H₄)]

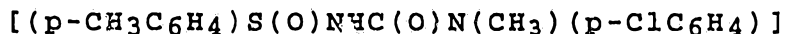
The method of Example 3 was followed using the product of Example 1 (6.2 g, 20 mmol), N-chlorobenzotriazole² (3.2 g, 21 mmol) and dimethylamine

(10 mL, 151 mmol) at -20°C. Recrystallization from 100 mL of warm toluene gave 4.2 g (59%) of the product.

Analysis of the product gave the following results: mp=183-184°C; $R_f(1/9, \text{MeOH}/\text{CHCl}_3) = 0.80$; $^1\text{H NMR}$ (300 MHz, d_6 -DMSO) δ 2.39 (s, 3H, CH_3), 2.66 (s, 6H, 2CH_3), 7.23 (d, 2H, $J=8.8$ Hz, Ar-H), 7.44 (d, 2H, $J=8.2$ Hz, Ar-H), 7.51 (d, 2H, $J=8.8$ Hz, Ar-H), 7.72 (d, 2H, $J=3.2$ Hz, Ar-H) and 9.50 (bs, 1H, exchanges with D_2O , NH); IR(KBr) 3285, 1630, 1536, 1284, 1127 and 958 cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 205.0(37973), 255.0(28328) nm; FDMS(DMSO) m/e 351, 353 (M^+). Anal Calcd for $\text{C}_{16}\text{H}_{18}\text{Cl}_1\text{N}_3\text{O}_2\text{S}_1$: C, 54.62; H, 5.16; N, 11.94. Found C, 54.40; H, 4.97; N, 11.77.

EXAMPLE 19

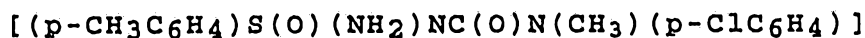
N-(4-Methylbenzenesulfinyl)-N'-methyl-N'-(4-chlorophenyl)urea



The method of Example 1 was followed using p-toluenesulfinyl chloride¹ (100 mmol), silver cyanate (18.7 g, 125 mmol) and N-methyl-p-chloroaniline (12.1 mL, 100 mmol) to yield after vacuum drying at 25°C, 18.9g (58%) of the product.

Analysis of the product gave the following results: mp=119-121°C; $^1\text{H NMR}$ (300 MHz, d_6 -DMSO) δ 2.34 (s, 3H, Ar- CH_3), 3.19 (s, 3H, N- CH_3), 7.28-7.45 (m, 6H, Ar-H), 7.52 (d, 2H, $J=8.1$ Hz, Ar-H) and 9.78 (s, 1H, N-H); IR(KBr) 3429, 2982, 2738, 1654, 1494, 1444, 1154, 1090, 1055, 1037 and 835 cm^{-1} ; FDMS(DMSO) m/e 322, 324 (M^+). Anal Calcd for $\text{C}_{15}\text{H}_{15}\text{Cl}_1\text{N}_2\text{O}_2\text{S}_1$: C, 55.81; H, 4.68; N, 8.68. Found C, 55.61; H, 4.86; N, 8.60.

EXAMPLE 20



The method of Example 3 was followed, using the product of Example 19 (5.0 g, 15.5 mmol), N-chlorobenzotriazole² (2.38 g, 15.5 mmol) and ammonia (10

mL). Silica gel flash chromatography (EtOAc/hexane) followed by recrystallization from CH₂Cl₂/hexane yielded 2.80 g (54%) of the product.

Analysis of the product gave the following results: mp=160-161.5°C; R_f (EtOAc)= 0.55; ¹H NMR (300 MHz, d₆-DMSO) δ 2.35 (s, 3H, CH₃), 3.17 (s, 3H, N-CH₃), 7.22-7.45 (m, 8 H, 2H exchanges with D₂O, Ar-H+NH₂) and 7.68 (d, 2H, J=8.2 Hz, Ar-H); IR(KBr) 3316, 3163, 3038, 1614, 1493, 1423, 1361, 1255, 1205, 1034 and 1014 cm⁻¹; UV(EtOH) λ_{max}(ε) 203.6(31100) and 233.6(16412) nm; FDMS(DMSO) m/e 337, 339 (M⁺). Anal Calcd for C₁₅H₁₆Cl₁N₃O₂S₁: C, 53.33; H, 4.79; N, 12.43. Found C, 53.04; H, 4.80; N, 12.41.

EXAMPLE 21

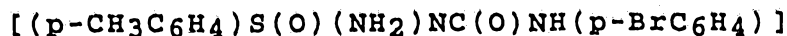
N-(4-Methylbenzenesulfinyl)-N'-(4-bromophenyl)urea



The method of Example 1 was followed using p-toluenesulfinyl chloride¹ (8.6 g, 49.2 mmol), silver cyanate (9.6 g, 64 mmol) and 4-bromoaniline (10.2 g, 59 mmol) to yield after drying, 15.8 g (91%) of white product.

Analysis of the product gave the following results: mp=142-143°C; R_f(10/10/2, EtOAc/EE/HOAc)= 0.75; ¹H NMR (300 MHz, d₆-DMSO) δ 2.35 (s, 3H, CH₃), 7.34-7.44 (m, 6H, Ar-H), 7.60 (d, 2H, J=7.8 Hz, Ar-H), 8.80 (s, 1H, exchanges with D₂O, NH) and 9.52 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3271, 3157, 3063, 1700, 1603, 1543, 1490, 1427, 1306, 1033, 902, 806 and 523 cm⁻¹; FDMS(DMSO) m/e 352, 354 (M⁺). Anal Calcd for C₁₄H₁₃Br₁N₂O₂S₁: C, 47.60 H, 3.71; N, 7.93. Found C, 47.85; H, 3.69; N, 7.94.

EXAMPLE 22



The method of Example 2 was followed using the product of Example 21 (7.0 g, 19.8 mmol), t-butylhypochlorite (2.6 mL, 22 mmol) and ammonia (100 mL). The isolated solid (6.9g) was recrystallized from 600 mL of toluene to give 4.05 g (55%) of the product.

Analysis of the product gave the following results: mp=171-173°C; R_f (1/9, MeOH/CHCl₃)= 0.43; ¹H NMR (300 MHz, d₆-DMSO) δ 2.35 (s, 3H, CH₃), 7.32-7.46 (m, 8H, 2H exchanges with D₂O, 6Ar-H + NH₂), 7.76 (d, 2H, J=8.3 Hz, Ar-H) and 9.25 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3397, 3242, 1650, 1522, 1393.8, 1270, 1236, 1125, 934, 815 and 533 cm⁻¹; UV(EtOH) λ_{max}(e) 256.8(29225), 204.8(34856) nm; FDMS(DMSO) m/e 367,369 (M⁺). Anal Calcd for C₁₄H₁₄BrN₃O₂S₁: C, 45.66; H, 3.83; N, 11.41. Found C, 45.69; H, 3.82; N, 11.50.

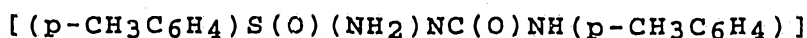
EXAMPLE 23

N-(4-Methylbenzenesulfinyl)-N'-(4-methylphenyl)urea

[*](c1ccc(C)cc1)S(=O)NHC(=O)NH(c2ccc(C)cc2)[*]

The method of Example 1 was followed using p-toluenesulfinyl chloride¹ (200 mmol), silver cyanate (35.9 g, 240 mmol) and p-anisidine (21.4 g, 200 mmol) to yield after recrystallization from MeOH and vacuum drying at 25°C, 11.0g (19%) of the product.

Analysis of the product gave the following results: mp 149-151°C; ¹H NMR(300 MHz, d₆-DMSO) δ 2.22 (s, 3H, Ar-CH₃), 2.36 (s, 3H, Ar-CH₃), 7.08 (d, 2H, J=8.2 Hz, Ar-H), 7.28 (d, 2H, J= 8.2 Hz, Ar-H), 7.42 (d, 2H, J= 8.0 Hz, Ar-H), 7.62 (d, 2H, J= 8.0 Hz, Ar-H), 8.57 (s, 1H, exchanges with D₂O, N-H) and 9.41 (s, 1H, exchanges with D₂O, N-H) ; IR(KBr) 3335, 3195, 1702, 1602, 1537, 1426, 1181, 1052, 1014, 910 and 807 cm⁻¹; FDMS(DMSO) m/e 288 (M⁺). Anal Calcd for C₁₅H₁₆N₂O₂S₁: C, 62.48; H, 5.59; N, 9.71. Found C, 62.47; H, 5.62; N, 9.45.

EXAMPLE 24

The method of Example 2 was followed, using the product of Example 23 (2.88 g, 10.0 mmol), N-chlorobenzotriazole² (1.53 g, 10.0 mmol) and ammonia (5 mL). Recrystallization from MeOH followed by vacuum drying at 45°C yielded 2.09 g (69%) of the product.

Analysis of the product gave the following results: mp=172-174°C; R_f (EtOAc)= 0.59; ¹H NMR (300 MHz, d₆-DMSO) δ 2.16 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 6.94 (d, 2H, J=8.3 Hz, Ar-H), 7.31 (d, 2H, J=8.3 Hz, Ar-H), 7.36 (d, 2H, J=8.2 Hz, Ar-H), 7.41 (s, 2H, exchanges with D₂O, NH₂), 7.77 (d, 2H, J=8.3 Hz, Ar-H) and 8.98 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3425, 3285, 3046, 1618, 1523, 1404, 1320, 1271, 1220, 1111, 951 and 821 cm⁻¹; UV(EtOH) λ_{max}(ε) 207.0 (28634) and 248.6(24243) nm; FDMS (DMSO) m/e 303 (M⁺). Anal Calcd for C₁₅H₁₇N₃O₂S₁: C, 59.39; H, 5.65; N, 13.85. Found C, 59.27; H, 5.63; N, 13.93.

EXAMPLE 25p-Chlorophenylsulfinyl chloride

This material was prepared quantitatively from 4-chlorothiophenol by the method of Herrmann³ using toluene as a solvent. The crude sulfinyl chloride had the following physical properties: ¹H NMR (300 MHz, CDCl₃) δ 7.36 (d, 2H, J=8 Hz, Ar-H) and 7.58 (d, 2H, J=8 Hz, Ar-H).

EXAMPLE 26N-(4-Chlorobenzenesulfinyl)-N'-(4-chlorophenyl)urea

The method of Example 1 was followed using the product of Example 25 (53.3 mmol), silver cyanate (12.33

g, 82.8 mmol) and p-chloroaniline (6.26g, 49.1 mmol) to yield after trituration with MeOH and drying, 2.46g (14%) of the product.

Analysis of the product gave the following results:
mp 145-146°C; ¹H NMR(300 MHz, d₆-DMSO) δ 7.34 (d, 2H, J=8.8 Hz, Ar-H), 7.45 (d, 2H, J= 8.8 Hz, Ar-H), 7.68 (d, 2H, J=8.5 Hz, Ar-H), 7.77 (d, 2H, J= 8.5 Hz, Ar-H), 8.91 (s, 1H, N-H), 9.79 (s, 1H, N-H); IR(CHCl₃) 3680, 3590, 2960, 1700, 1604, 1410, 1250 and 1034 cm⁻¹; FDMS(DMSO) m/e 328, 330, 332 (M⁺). Anal Calcd for C₁₃H₁₀Cl₂N₂O₂S₁: C, 47.43; H, 3.06; N, 8.51. Found C, 47.48; H, 3.13; N, 8.40.

EXAMPLE 27

[*](c1ccc(cc1)S(=O)(=O)NC(=O)NC2=CC=C(C=C2)Cl)Cl

The procedure of Example 2 was followed using the product of Example 26 (2.46 g, 7.4 mmol), t-butylhypochlorite (1.03 mL, 8.6 mmol), and ammonia (50 mL) to give 1.48 g (58%) of the product.

Analysis of the product gave the following results:
mp=164-165°C; R_f (1/1, EtOAc/hexane)= 0.47; ¹H NMR (300 MHz, d₆-DMSO) δ 7.19 (d, 2H, J= 8.5 Hz, Ar-H), 7.45 (d, 2H, J=7.8 Hz, Ar-H), 7.61 (s, 2H, exchanges with D₂O, NH₂), 7.66 (d, 2H, J=7.8 Hz, Ar-H), 7.88 (d, 2H, J=8.4 Hz, Ar-H) and 9.31 (s, 1H, exchanges with D₂O, N-H); IR(KBr) 3426, 3280, 3031, 1621, 1510, 1401, 1271, 1239, 1222, 1097 and 830 cm⁻¹; UV(EtOH) λ_{max}(e) 204.0(37404), 253.0(27588) nm; FDMS(DMSO) m/e 344, 346, 348 (M⁺). Anal Calcd for C₁₃H₁₁Cl₂N₃O₂S₁ : C, 45.36; H, 3.22; N, 12.21. Found C, 45.64; H, 3.43; N, 11.92.

EXAMPLE 28

p-Bromophenylsulfinyl chloride

[*](c1ccc(cc1)S(=O)Cl)Br

This material was prepared quantitatively from 4-bromothiophenol by the method of Example 25 using

toluene as a solvent. The crude sulfinyl chloride had the following physical properties: ^1H NMR (300 MHz, CDCl_3) δ 7.75 (s, 4H, Ar-H).

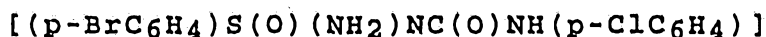
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EXAMPLE 29N-(4-Bromobenzenesulfinyl)-N'-(4-chlorophenyl)urea

10 The method of Example 1 was followed using the product of Example 28 (56 mmol), silver cyanate (9.25 g, 61.7 mmol) and p-chloroaniline (7.16g, 56.1 mmol) to yield 15.6 g (75%) of the product.

15 Analysis of a recrystallized portion (MeOH) of the product gave the following results: mp 176-178°C; ^1H NMR (300 MHz, d_6 -DMSO) δ 7.34 (d, 2H, J= 8 Hz, Ar-H), 7.46 (d, 2H, J=8 Hz, Ar-H), 7.69 (d, 2H, J=8 Hz, Ar-H), 7.82 (d, 2H, J=8 Hz, Ar-H), 8.90 (s, 1H, exchanges with D_2O , N-H) and 9.78 (s, 1H, exchanges with D_2O , N-H); IR(KBr) 3276, 3159, 1703, 1604, 1541, 1493, 1422, 1387, 20 1306, 1244, 1204, 1177, 1089, 1036, 1006 and 824 cm^{-1} ; FDMS(DMSO) m/e 374, 376, 378 (M^+). Anal Calcd for $\text{C}_{13}\text{H}_{10}\text{BrClN}_2\text{O}_2\text{S}$: C, 41.78; H, 2.70; N, 7.50. Found C, 41.82; H, 2.67; N, 7.33.

25

EXAMPLE 30

30 The procedure of Example 2 was followed using the product of Example 29 (5.0 g, 13.4 mmol), t-butylhypochlorite (2.0 mL, 14.7 mmol), and ammonia (50 mL) to give after recrystallization from ethanol, 2.47 g (48%) of the product;

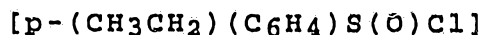
35 Analysis of the product gave the following results: mp=173-175°C; R_f (1/2, EtOAc/hexane)= 0.64; ^1H NMR (300 MHz, d_6 -DMSO) δ 7.18 (d, 2H, J= 8.9 Hz, Ar-H), 7.45 (d, 2H, J=8.9 Hz, Ar-H), 7.61 (s, 2H, exchanges with D_2O , NH_2), 7.80 (s, 4H, Ar-H) and 9.30 (s, 1H, exchanges with

40

D₂O, N-H); IR(KBr) 3401, 3242, 1649, 1592, 1574, 1522, 1399, 1267, 1235, 1009 and 833 cm⁻¹; UV(EtOH) λ_{max}(ε) 204.8(41062), 251.8(30480) nm; FDMS(DMSO) m/e 387, 389, 391 (M⁺). Anal Calcd for C₁₃H₁₁BrClN₃O₂S₁: C, 40.17; H, 2.85; N, 10.81. Found C, 40.34; H, 2.79; N, 10.60.

EXAMPLE 31

4-Ethylbenzenesulfinyl chloride

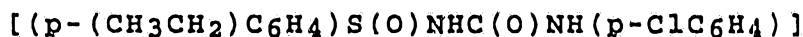


The method of Herrmann³ was followed using 8.0g (58 mmol) 4-ethylthiophenol.

Analysis of the product gave the following results: ¹H NMR (300 MHz, CDCl₃) δ 1.31 (t, 3H, J = 7.6 Hz, CH₃CH₂), 2.75 (q, 2H, J = 7.6 Hz, CH₃CH₂), 7.44 (d, 2H, J = 8.2 Hz, Ar-H) and 7.82 (d, 2H, J = 8.2 Hz, Ar-H).

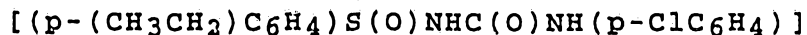
EXAMPLE 32

N-(4-Ethylbenzenesulfinyl)-N'-(4-chlorophenyl)urea



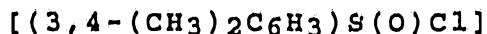
The method of Example 1 was followed, using the product of Example 31 (9.2 g, 54 mmol), silver cyanate (11 g, 73 mmol) and p-chloroaniline (8.2 g, 64 mmol) to provide 15.1 g (81%) of the product.

Analysis of the product gave the following results: mp=134-135°C; R_f(10/10/2, EtOAc/EE/AcOH)= 0.76; ¹H NMR (300 MHz, d₆-DMSO) δ 1.19 (t, 3H, J = 7.6 Hz, CH₃CH₂), 2.67 (q, 2H, J = 7.6 Hz, CH₃CH₂), 7.32 (d, 2H, J = 8.8 Hz, Ar-H), 7.43-7.47 (overlapping doublets, 4H, Ar-H), 7.66 (d, 2H, J= 8.2 Hz, Ar-H), 8.80 (bs, 1H, exchanges with D₂O, NH) and 9.55 (bs, 1H, exchanges with D₂O, NH); IR(KBr) 3260, 3193, 2969, 2934, 1669, 1608, 1551, 1495, 1430, 1308, 1094, 1029, 832 and 553 cm⁻¹; FDMS(DMSO) m/e 322, 324 (M⁺). Anal Calcd for C₁₅H₁₅ClN₂O₂S₁: C, 55.81; H, 4.68; N, 8.68. Found C, 56.02; H, 4.76; N, 8.74.

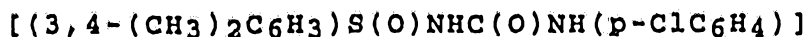
EXAMPLE 33

The method of Example 2 was followed using the product of Example 32 (9.7 g, 31 mmol), t-butylhypochlorite (4.7 mL, 39 mmol) and ammonia (50 mL) to yield after recrystallization from toluene (1250 mL) 5.88 g (58%) of the product.

Analysis of the product gave the following results: mp=168-169°C; $R_f(1/9, MeOH/CHCl_3)=0.41$; ^1H NMR (300 MHz, d_6 -DMSO) δ 1.16 (t, 3H, $J=7.6$ Hz, CH_3CH_2), 2.65 (q, 2H, $J=7.6$ Hz, CH_3CH_2), 7.18 (d, 2H, $J=8.8$ Hz, Ar-H), 7.39-7.48 (overlapping doublets obscuring bs, 6H, 2H exchanges with D_2O , Ar-H + NH_2), 7.80 (d, 2H, $J=8.8$ Hz, Ar-H) and 9.26 (s, 1H, exchanges with D_2O , NH); IR(KBr) 3389, 3258, 1647, 1591, 1524, 1493, 1399, 1234, 1124, 934 and 832 cm^{-1} ; UV(EtOH) $\lambda_{max}(e)$ 205.2(32135) and 254.6(28176) nm; FDMS (DMSO) m/e 337, 339 (M^+). Anal Calcd for $C_{15}H_{16}ClN_3O_2S$: C, 53.33; H, 4.77; N, 12.44. Found C, 53.47; H, 5.00; N, 12.43.

EXAMPLE 343,4-Dimethylbenzenesulfinyl chloride

This material was prepared quantitatively by the method of Example 25 from 3,4-dimethylthiophenol using toluene as a solvent. The crude orange product was analyzed as follows: ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 6H, 2 CH_3), 7.37 (d, 1H, $J=7.9$ Hz, Ar-H), 7.62 (d, 1H, $J=7.9$ Hz, Ar-H), 7.67 (s, 1H, Ar-H).

EXAMPLE 35N-(3,4-Dimethylbenzenesulfinyl)-N'-(4-chlorophenyl)urea

The method of Example 1 was followed, using the product of Example 34 (6.6 g, 34.7 mmol), silver cyanate (6.8g, 45 mmol) and p-chloroaniline (4.9 g, 38 mmol) to yield 9.14 g (82%) of the product.

Analysis of the product gave the following results: mp= 129-130°C; R_f (10/10/2, EtOAc/EE/AcOH) = 0.75; ^1H NMR (300 MHz, d_6 -DMSO) δ 2.29 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 7.32-7.51 (m, 7H, Ar-H), 8.81 (s, 1H, exchanges with D_2O , NH) and 9.52 (s, 1H, exchanges with D_2O , NH); IR(KBr) 3427, 3319, 3209, 1712, 1701, 1602, 1550, 1492, 1444, 1052, 832 and 661 cm^{-1} ; FDMS(DMSO) m/e 322, 324 (M^+). Anal Calcd for $\text{C}_{15}\text{H}_{15}\text{Cl}_1\text{N}_2\text{O}_2\text{S}_1$: C, 55.81; H, 4.68; N, 8.68. Found C, 55.53; H, 4.67; N, 8.52.

EXAMPLE 36

$[(3,4-(\text{CH}_3)_2\text{C}_6\text{H}_3)\text{S}(\text{O})(\text{NH}_2)\text{NC}(\text{O})\text{NH}(\text{p-ClC}_6\text{H}_4)]$

The method of Example 2 was followed, using the product of Example 35 (9.14 g, 28.3 mmol), t-butylhypochlorite (4.22 mL, 35.4 mmol) and ammonia (50 mL) to yield 8.02 g (84%) of 293348. Recrystallization from toluene (500 mL) gave 6.14 g (64%) of the product as a white fluffy solid.

Analysis of the product gave the following results: mp =150-151°C; R_f (1/9, MeOH/ CHCl_3)= 0.46; ^1H NMR (300 MHz, d_6 -DMSO) δ 2.27 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 7.18 (d, 2H, $J=8.8$ Hz, Ar-H), 7.32 (d, 2H, $J=8.0$ Hz, Ar-H), 7.42 (s, 2H, exchanges with D_2O , NH_2), 7.47 (d, 2H, $J=8.8$ Hz, Ar-H), 7.60 (d, 2H, $J=8.0$ Hz, Ar-H), 7.65 (s, 1H, Ar-H) and 9.22 (s, 1H, exchanges with D_2O , NH); IR(KBr) 3299, 3189, 1629, 1589, 1523, 1399, 1279, 1232, 1126, 953, 770 and 573 cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 207.0(34756) and 254.8(29008) nm; FDMS(DMSO) m/e 337, 339 (M^+). Anal Calcd for $\text{C}_{15}\text{H}_{16}\text{Cl}_1\text{N}_3\text{O}_2\text{S}_1$: C, 53.33; H, 4.77; N, 12.44. Found C, 53.58; H, 4.87; N, 12.22.

EXAMPLE 37

N-(3,5-Dimethylbenzenesulfonyl)-N'-(4-chlorophenyl)urea

$[(3,5-(\text{CH}_3)_2\text{C}_6\text{H}_3)\text{SNHC}(\text{O})\text{NH}(\text{p-ClC}_6\text{H}_5)]$

The method of Example 1 was followed using 3,5-dimethylsulfonyl chloride (13.9 g, 80.7 mmol) [(prepared from 3,5-dimethylthiophenol by the procedure of Harpp, Friedlander and Smith⁴, silver cyanate (16 g, 107 mmol)] and p-chloroaniline (12.4 g, 97.2 mmol) to give 10.8 g (46%) of crude product. Silica gel flash chromatography (EtOAc/hexane) afforded 1.92g (8%) of the product.

Analysis of the product gave the following results: mp=180-181°C; $R_f(1/9 \text{ MeOH/CHCl}_3) = 0.74$; $^1\text{H NMR}$ (300 MHz, $\text{d}_6\text{-DMSO}$) δ 2.22 (s, 6H, 2CH₃), 6.79 (s, 1H, Ar-H), 6.80 (s, 2H, Ar-H), 7.29 (d, 2H, J=8.8Hz, Ar-H), 7.48 (d, 2H, J=8.8Hz, Ar-H), 8.15 (s, 1H, exchanges with D₂O, NH) and 9.11 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3268, 1641, 1602, 1551, 1462, 1089, 834 and 681 cm^{-1} ; FDMS(DMSO) m/e 306, 308 (M^+). Anal Calcd for $\text{C}_{15}\text{H}_{15}\text{Cl}_1\text{N}_2\text{O}_1\text{S}_1$: C, 58.72; H, 4.93; N, 9.13. Found C, 58.45; H, 5.13; N, 9.19.

EXAMPLE 38

N-(3,5-Dimethylbenzenesulfonyl)-N'-(4-chlorophenyl)urea

$[(3,5-(\text{CH}_3)_2\text{C}_6\text{H}_3)\text{S}(\text{O})\text{NHC}(\text{O})\text{NH}(\text{p-ClC}_6\text{H}_4)]$

A solution of the product of Example 37 (2.53 g, 8.7 mmol) in 50 mL THF was cooled to 0°C. Peracetic acid (32%, 1.6 mL, 8.6 mmol) was added dropwise. Two hours later additional peracetic acid (0.2 mL, 1.07 mmol) was added to complete the oxidation. After diluting the mixture with 150 mL of water and stirring for 30 min, the solid was collected by filtration and rinsed with 100 mL of water to yield, after drying, 2.16 g (81%) of product.

Analysis of the product gave the following results: mp=114-115°C; $R_f(1/9 \text{ MeOH/CHCl}_3) = 0.65$; $^1\text{H NMR}$ (300

MHz, d₆-DMSO) δ 2.35 (s, 6H, 2CH₃), 7.23-7.46 (m, 7H, Ar-H), 8.83 (s, 1H, exchanges with D₂O, NH) and 9.58 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3427, 3313, 1654, 1609, 1550, 1492, 1402, 1136, 1041, 821 and 503 cm⁻¹; FDMS(DMSO) m/e 322, 324 (M⁺). Anal Calcd for C₁₅H₁₅Cl₁N₂O₂S₁: C, 55.81; H, 4.68; N, 8.68. Found C, 55.56; H, 4.65; N, 8.53.

EXAMPLE 39

$[(3,5-(CH_3)_2C_6H_3)S(O)(NH_2)NC(O)NH(p-ClC_6H_4)]$

The method of Example 2 was followed using the product of Example 38 (2.16g, 7.04 mmol), t-butylhypochlorite (1.1 mL, 9.22 mmol) and ammonia (50 mL) to yield 1.82 g (76%) of the product.

Analysis of the product gave the following results: mp=176-177°C; R_f(1/9 MeOH/CHCl₃)= 0.3; ¹H NMR (300 MHz, d₆-DMSO) δ 2.33 (s, 6H, 2CH₃), 7.18-7.23 (m, 3H, Ar-H), 7.40-7.55 (overlapping m, 6H, 2H exchanges with D₂O, 4Ar-H + NH₂) and 9.23 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3303, 3197, 1624, 1519, 1398, 1279, 1232, 1130, 761 and 679 cm⁻¹; UV(EtOH) $\lambda_{max}(e)$ 254.4(23141.2) and 206.4(33094.0) nm; FDMS(DMSO) m/e 337, 339 (M⁺). Anal Calcd for C₁₅H₁₆Cl₁N₃O₂S₁: C, 53.33 ; H, 4.77 ; N, 12.43 . Found C, 53.06 ; H, 4.67 ; N, 12.23 .

EXAMPLE 40

O-(3,4,5-Trimethylphenyl)-N,N-
dimethylthiocarbamate

$[(3,4,5-(CH_3)_3C_6H_2)OC(S)N(CH_3)_2]$

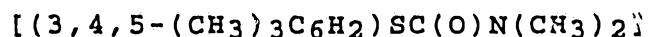
A 3-neck 1000mL round-bottom flask, fitted with a mechanical stirrer, thermometer, addition funnel and nitrogen purge, was charged with 3,4,5-trimethylphenol (35.80 g, 0.26 mol) and 200 mL of DMF. Sodium hydride (60% dispersion in mineral oil, 11.60 g, ~0.29 mol) was cautiously added in portions with vigorous stirring over 20 min. The resulting mixture was stirred 30 min under

nitrogen. N,N-dimethylthiocarbamoyl chloride (39.0 g, 0.3 mol), dissolved in 30 mL of DMF, was added dropwise to the sodium trimethylphenolate mixture, maintaining an internal temperature of $<60^{\circ}\text{C}$. After the addition was complete, the reaction mixture was heated at 90°C for 40 min, then cooled to room temperature. Following dilution with 300 mL of cold water, the solution was poured into 350 mL of aqueous KOH, stirred briefly, and placed in the refrigerator for 2 h. The resulting solid was isolated by filtration, rinsed with 200 mL of water and dissolved in EE (500 mL). The organic phase was washed with water (1x100 mL), brine (1x100 mL) and dried (MgSO_4). Filtration and evaporation gave 62 g of crude product. Recrystallization from 100 mL of MeOH gave 35.8 g of the product as a light yellow solid (61%).

Analysis of the product gave the following results: mp= $90-91^{\circ}\text{C}$; R_f (3/7, EtOAc/hexane)= 0.45; ^1H NMR (300 MHz, CDCl_3) δ 2.16 (s, 3H, CH_3), 2.30 (s, 6H, 2CH_3), 3.33 and 3.46 (s, 6H, NCH_3) and 6.74 (s, 2H, Ar-H); IR(CHCl_3) 2983, 2871, 1535, 1479, 1398, 1304, 1276, 1217, 1179, 1121, 1026, 924 and 867 cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 205.4(25402) and 250.8(14013) nm; FDMS(DMSO) m/e 223 (M^+). Anal Calcd for $\text{C}_{12}\text{H}_{17}\text{N}_1\text{O}_1\text{S}_1$: C, 64.54; H, 7.67; N, 6.27. Found C, 64.77; H, 7.87; N, 6.33.

EXAMPLE 41

S-(3,4,5-Trimethylphenyl)-N,N-dimethylthiocarbamate

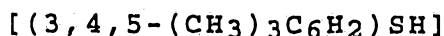


The product of Example 40 (27.40 g, 0.12 mol) was heated neat under nitrogen to a temperature of 290°C ; rearrangement to product was conveniently monitored by TLC (30% EtOAc/hexane) and was complete after 4 h. A small sample was purified by silica gel flash chromatography (3/7, EtOAc/hexane) and recrystallized from EE/hexane to provide an analytical sample.

Analysis of the product gave the following results:
mp=80-81°C; R_f (3/7, EtOAc/hexane)= 0.25; ¹H NMR (300
MHz, CDCl₃) δ 2.18 (s, 3H, CH₃), 2.29 (s, 6H, 2CH₃),
3.07 (bs, 6H, NCH₃) and 7.16 (s, 2H, Ar-H); IR(CHCl₃)
3011, 2932, 1655, 1474, 1367, 1261 and 1099 cm⁻¹;
UV(EtOH) λ_{max}(e) 212.4(23432) nm; FDMS(MeOH) m/e 223
(M⁺) Anal Calcd for C₁₂H₁₇N₁O₁S₁: C, 64.54; H, 7.67; N,
6.27. Found C, 64.79; H, 7.71; N, 6.10.

EXAMPLE 42

3,4,5-Trimethylthiophenol

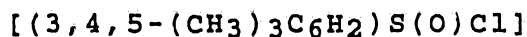


The crude product of Example 41 (30 g, 0.13 mol)
was dissolved in 350 mL of MeOH and 30 mL of water.
Potassium hydroxide (35 g, 0.6 mol) was added and the
mixture was heated at reflux for 3 h. After cooling and
removing the MeOH in vacuo, the residue was diluted with
water (500 mL) and washed with EE (3 x 100 mL). The
aqueous layer was acidified with conc. HCl and extracted
with CH₂Cl₂ (3 x 100 mL); the combined organic extract
was dried (Na₂SO₄) and evaporated to yield 16.4 g of an
orange oil. Vacuum distillation provided the product as
a clear oil.

Analysis of the product gave the following results:
bp=68-70°C (0.25 mm Hg); R_f (3/7, EtOAc/hexane)= 0.63;
¹H NMR (300 MHz, CDCl₃) δ 2.13 (s, 3H, CH₃), 2.25 (s,
6H, 2CH₃), 3.33 (s, 1H, exchanges with D₂O, SH) and 6.97
(s, 2H, Ar-H); IR(CHCl₃) 3010, 2978, 1589, 1475, 1444,
1379, 1196, 886 and 853 cm⁻¹; UV(EtOH) λ_{max}(e)
212.0(23084) and 240.8(7803) nm; EIMS(MeOH) m/e
152(M⁺), 137, 119, 91. Anal Calcd for C₉H₁₂S₁: C, 70.99;
H, 7.94. Found C, 70.89; H, 8.08.

EXAMPLE 43

3,4,5-Trimethylbenzenesulfinyl chloride



The method of Hermann³ was followed using 3,4,5-trimethylthio-phenol (10 g, 66 mmol).

Analysis of the product gave the following results:
¹H NMR (300 MHz, CDCl₃) δ 2.28 (s, 3H, CH₃), 2.40 (s, 6H, 2CH₃) and 7.52 (s, 2H, Ar-H).

EXAMPLE 44

N-(3,4,5-Trimethylbenzenesulfinyl)-N'-(4-chlorophenyl)urea

Cc1cc(C)c(C)cc1S(=O)NC(=O)NC1=CC=C(Cl)C=C1

The method of Example 1 was followed, using the product of Example 43 (13.3 g, 65.7 mmol), silver cyanate (12.8 g, 85.4 mmol) and p-chloroaniline (9.2 g, 72 mmol) to provide 9.01 g (41%) of the product.

Analysis of the product gave the following results: mp=140-145°C; R_f(1/9, MeOH/CHCl₃)= 0.66; ¹H NMR (300 MHz, d₆-DMSO) δ 2.18 (s, 3H, CH₃), 2.31 (s, 6H, 2CH₃), 7.33 (d, 2H, J=8.8 Hz, Ar-H), 7.36 (s, 2H, Ar-H), 7.43 (d, 2H, J=8.8 Hz, Ar-H), 8.81 (bs, 1H, exchanges with D₂O, NH) and 9.50 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3427, 3314, 1655, 1586, 1492, 1470, 1133, 821 and 618 cm⁻¹; FDMS(DMSO) m/e 336, 338 (M⁺). Anal Calcd for C₁₆H₁₇ClN₂O₂S: C, 57.05; H, 5.09; N, 8.31. Found C, 56.75; H, 5.20; N, 8.65.

EXAMPLE 45

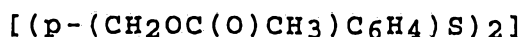
Cc1cc(C)c(C)cc1S(=O)(NC(=O)NC1=CC=C(Cl)C=C1)N

The method of Example 2 was followed, using the product of Example 44 (8.8 g, 26 mmol), t-butylhypochlorite (4.1 mL, 34 mmol) and ammonia (50 mL) to provide, after recrystallization from toluene (1200 mL), 5.5 g (60%) of the product as a white solid.

Analysis of the product gave the following results: mp=173-174°C; R_f(1/9, MeOH/CHCl₃)= 0.52; ¹H NMR (300 MHz, d₆-DMSO) δ 2.17 (s, 3H, CH₃), 2.29 (s, 6H,

2CH₃), 7.18 (d, 2H, J=8.8Hz, Ar-H), 7.37 (s, 2H, exchanges with D₂O, NH₂), 7.46 (d, 2H, J=8.8Hz, Ar-H), 7.51 (s, 2H, Ar-H) and 9.21 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3309, 3205, 1626, 1595, 1495, 1398, 1232, 1127, 821 and 576 cm⁻¹; UV(EtOH) λ_{max}(ε) 206.8(43619) and 254.6(29602) nm; FDMS(DMSO) m/e 351, 353 (M⁺). Anal Calcd for C₁₆H₁₈Cl₁N₃O₂S₁: C, 54.62; H, 5.16; N, 11.94. Found C, 54.83; H, 5.22; N, 11.70.

EXAMPLE 46

4-(Acetoxymethyl)phenyl disulfide

A solution of the 4-(hydroxymethyl)phenyl disulfide⁵ (2.65 g, 9.52 mmol) in CH₂Cl₂ (75mL) was treated with catalytic DMAP under nitrogen followed by Et₃N (4.0 mL, 28.6 mmol) and acetic anhydride (2.24 mL, 23.8 mmol). One h later, the reaction mixture was washed with 1N HCl solution, water, brine and dried (Na₂SO₄); filtration followed by evaporation yielded the crude product, which was combined with a similarly prepared lot of crude product (from 1.27 g, 4.56 mmole of 4-(hydroxymethyl)phenyl disulfide) and purified by silica gel flash chromatography (EE/hexane) to provide 4.45 g (87%) of the product.

Analysis of the product gave the following results: mp=52-54°C; R_f(EtOAc)= 0.69 ; ¹H NMR (300 MHz, CDCl₃) δ 2.11 (s, 3H, COCH₃), 5.08 (s, 2H, ArCH₂-OAc), 7.31 (d, 2H, J=8.2 Hz, Ar-H) and 7.50 (d, 2H, J=8.3 Hz, Ar-H); IR(CHCl₃) 3028, 3013, 1735, 1494, 1380, 1362, 1231, 1210, 1028 and 1015 cm⁻¹; FDMS(DMSO) 362 (M⁺). Anal Calcd for C₁₈H₁₈O₄S₂: C, 59.65; H, 5.01. Found C, 59.90; H, 5.08.

EXAMPLE 47



This material was prepared from the product of Example 46 by the method of Herrmann⁶. The crude sulfinyl chloride had the following physical properties: IR(film) 1750 and 1160 cm^{-1} ; ^1H NMR(300 MHz, CDCl_3) δ 2.16 (s, 3H, COCH_3), 5.21 (s, 2H, $\text{ArCH}_2\text{-OAc}$), 7.60 (d, 2H, $J=8.2$ Hz, Ar-H) and 7.89 (d, 2H, $J=8.3$ Hz, Ar-H).

EXAMPLE 48

$[(\text{p}-(\text{CH}_2\text{OC(O)CH}_3)\text{C}_6\text{H}_4)\text{S(O)NHC(O)NH}(\text{p-ClC}_6\text{H}_4)]$

The method of Example 1 was followed using the product of Example 47 (22.9 mmol), silver cyanate (5.46 g, 36.4 mmol) and p-chloroaniline (2.92 g, 22.9 mmol) to yield after vacuum drying at 25°C , 6.15g (73.4%) of the product.

Analysis of the product gave the following results: mp= $131-133^\circ\text{C}$; ^1H NMR(300 MHz, $d_6\text{-DMSO}$) δ 2.07 (s, 3H, CO-CH_3), 5.16 (s, 2H, $\text{ArCH}_2\text{-OAc}$), 7.34 (d, 2H, $J=8.8$ Hz, Ar-H), 7.44 (d, 2H, $J=8.8$ Hz, Ar-H), 7.59 (d, 2H, $J=8.1$ Hz, Ar-H), 7.75 (d, 2H, $J=8.1$ Hz, Ar-H), 8.84 (s, 1H, exchanges with D_2O , N-H) and 9.67 (s, 1H, exchanges with D_2O , N-H); IR(KBr) 3264, 3195, 3130, 1746, 1689, 1668, 1609, 1551, 1495, 1481, 1245, 1225, 1094, 1067, 1028 and 1010 cm^{-1} ; FDMS(DMSO) m/e 366, 368(M^+). Anal Calcd for $\text{C}_{16}\text{H}_{15}\text{Cl}_2\text{N}_2\text{O}_4\text{S}$: C, 52.39; H, 4.12; N, 7.64. Found C, 50.29; H, 4.17; N, 7.79.

EXAMPLE 49

$[(\text{p}-(\text{CH}_2\text{OC(O)CH}_3)\text{C}_6\text{H}_4)\text{S(O)(NH}_2\text{)NC(O)NH}(\text{p-ClC}_6\text{H}_4)]$

The procedure of Example 2 was followed using the product of Example 48 (2.90 g, 7.92 mmol), N-chlorobenzo-triazole² (1.22 g, 7.92 mmol), and ammonia (excess) to give 2.84 g (94%) of the product; recrystallization from EtOAc and vacuum drying at 50°C for 65 h returned 1.6g of the product.

Analysis of the product gave the following results: mp= $170-172^\circ\text{C}$; R_f (30/19/1, Toluene/THF/HOAc,) = 0.50; ^1H

NMR (300 MHz, d_6 -DMSO) δ 2.08 (s, 3H, CO-CH₃), 5.14 (s, 2H, Ar-CH₂OAc), 7.19 (d, 2H, J= 8.8 Hz, Ar-H), 7.47 (d, 2H, J=8.8 Hz, Ar-H), 7.53-7.56 (s overlapping d, 3H, 2H exchanges with D₂O, Ar-H and NH₂), 7.87 (d, 2H, J=8.4 Hz, Ar-H) and 9.28 (s, 1H, exchanges with D₂O, N-H); IR(KBr) 3429, 3347, 3139, 3062, 1740, 1618, 1590, 1530, 1401, 1315, 1272, 1225, 1105 and 834 cm⁻¹; UV(EtOH) $\lambda_{max}(e)$ 204.8(33680), 253.6(28027) nm; F₂₅₄MS(DMSO) m/e 382,384 (M⁺). Anal Calcd for C₁₆H₁₆Cl₁N₃O₄S₁: C, 50.33; H, 4.22; N, 11.00. Found C, 50.40; H, 4.18; N, 10.70.

EXAMPLE 50

[(p-(CH₂OH)C₆H₄)S(O)(NH₂)NC(O)NH(p-ClC₆H₄)]

A suspension of the product of Example 49 (2.95 g, 7.74 mmol) in aqueous methanol was treated with solid K₂CO₃ (1.06 g, 7.7 mmol), warmed briefly to solubilize the reactants, and stirred at room temperature for 19 h. The resulting solution was evaporated to the aqueous, diluted with brine and extracted with EtOAc (3x100 mL). The combined extract was washed with brine, dried(Na₂SO₄) and evaporated to give 1.52 g of crude product. The original aqueous layer was saturated with solid NaCl and extracted with THF/EtOAc (1/2, 3x150 mL). After drying (Na₂SO₄), evaporation gave an additional 1.15g of the product. The combined crude product (2.67g) was recrystallized from THF/hexane to give 2.19 g (83%) of product after vacuum oven drying at 60°C for 20 h.

Analysis of the product gave the following results: mp=165-167°C; R_f(30/19/1, Toluene/THF/HOAc,)= 0.26; ¹H NMR (300 MHz, d_6 -DMSO) δ 4.56 (d, 2H, J=5.3 Hz, Ar-CH₂-OH), 5.37 (t, 1H, J=5.6 Hz, exchanges with D₂O, CH₂-OH), 7.19 (d, 2H, 8.8 Hz, Ar-H), 7.45-7.50 (overlapping m, 6H, 2H exchanges with D₂O, Ar-H +NH₂), 7.85 (d, 2H, 8.2 Hz, Ar-H) and 9.25 (s, 1H, exchanges with D₂O, N-H); IR(KBr) 3327, 1625, 1593, 1531, 1494, 1400, 1311, 1266, 1224, 1110, 1011, 959, 828 and 782 cm⁻¹; UV(EtOH)

$\lambda_{\max}(\text{e})$ 204.6(34167), 253.6(28365) nm; FDMS(DMSO) m/e 340,342 (M^+). Anal Calcd for $C_{14}H_{14}Cl_1N_3O_3S_1$: C, 49.49; H, 4.15; N, 12.37. Found C, 49.24; H, 4.01; N, 12.07.

5

EXAMPLE 51

$[(p-(C(O)H)C_6H_4)S(O)(NH_2)NC(O)NH(p-ClC_6H_4)]$

A solution of the product of Example 50 (2.88 g, 8.5 mmol) in THF (100 mL) was treated with MnO_2 (7.4 g, 84.8 mmol) under nitrogen at room temperature for 18 h. Additional MnO_2 (5.4 g, 62 mmol) was added and stirring continued for 48.8 h. The reaction mixture was filtered through a pad of flash silica gel (THF) and the filtrate residue, upon evaporation, purified by silica gel flash chromatography (EtOAc/hexane) to provide, after vacuum drying at 45°C, 1.40 g (49%) of the product.

Analysis of the product gave the following results: mp=137-140°C; $R_f(30/19/1, \text{Toluene/THF/HOAc},) = 0.48$; ^1H NMR (300 MHz, d_6 -DMSO) δ 7.19 (d, 2H, 8.3 Hz, Ar-H), 7.45 (d, 2H, Ar-H), 7.72 (s, 2H, exchanges with D_2O , NH_2), 8.09 (s, 4H, Ar-H), 9.35 (s, 1H, exchanges with D_2O , N-H) and 10.07 (s, 1H, CHO); IR(KBr) 3428, 3284, 3118, 3038, 1709, 1616, 1591, 1522, 1400, 1271, 1241, 1223, 1106, 958, 823 and 774 cm^{-1} ; UV(EtOH) $\lambda_{\max}(\text{e})$ 208.0(20473), 252.4(29659) nm; FDMS(DMSO) m/e 337,339 (M^+). Anal Calcd for $C_{14}H_{12}Cl_1N_3O_3S_1$: C, 49.78; H, 3.58; N, 12.44. Found C, 50.07; H, 3.67; N, 12.16.

EXAMPLE 52Indanesulfinic acid, sodium salt

$[(5\text{-indanyl})S(O)O^-Na^+]$

Indanesulfonyl chloride⁷ (10.8 g, 50 mmol) in 75 mL of acetone was treated over 10 min with a solution consisting of $NaHSO_3$ (12.6 g, 100 mmol) and $NaHCO_3$ (8.4 g, 100 mmol) in 150 mL of water. This mixture was heated at reflux (60°C) for 1 h, during which time it became homogeneous. The cooled reaction mixture was washed with

CH₂Cl₂ (1x100 mL). Evaporation of the aqueous to dryness under vacuum gave a solid residue which was extracted with CH₃OH (1x300 mL). This extract was filtered and evaporated to a volume of about 50 mL. The product was precipitated by the addition of 200 mL EE. Filtration and vacuum drying yielded 10.1 g (99%) of product.

Analysis of the product gave the following results: ¹H NMR (300 MHz, D₂O) δ 2.05 (m, 2H, CH₂), 2.88 (m, 4H, 2CH₂), 7.4 (m, 2H, 2Ar-H) and 7.5 (s, 1H, Ar-H); FABMS (D₂O) m/e 227(M⁺), 205(M+H-Na)⁺.

EXAMPLE 53

N-(Indanesulfinyl)-N'-(4-chlorophenyl)urea
[(5-indanyl)S(O)NHC(O)NH(p-ClC₆H₄)]

The method of Example 1 was followed using indanesulfinyl chloride (4.2 g, 21.1 mmol) [prepared from the product of Example 52 (6.1 g, 29.9 mmol) and thionyl chloride (15 mL, 206 mmol)]¹, silver cyanate (4.4 g, 29.6 mmol) and p-chloroaniline (3.5 g, 27.5 mmol) to provide 4.48 g (45%) of the product.

Analysis of the product gave the following results: mp =140-142°C; R_f(1/9, MeOH/CHCl₃)= 0.68; ¹H NMR (300 MHz, d₆-DMSO) δ 2.02-2.1 (m, 2H, CH₂), 2.89-2.94 (m, 4H, 2CH₂), 7.32-7.49 (m, 6H, Ar-H), 7.60 (s, 1H, Ar-H), 8.82 (s, 1H, exchanges with D₂O, NH) and 9.53 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3425, 3313, 1655, 1547, 1492, 1401, 1089, 820 and 589 cm⁻¹; FDMS (DMSO) m/e 334, 336(M⁺). Anal Calcd for C₁₆H₁₅ClN₂O₂S: C, 57.40 H, 4.52; N, 8.37. Found C, 57.27; H, 4.62; N, 8.10.

EXAMPLE 54

[(5-indanyl)S(O)(NH₂)NC(O)NH(p-ClC₆H₄)]

The method of Example 2 was followed using the product of Example 53 (6.7 g, 20mmol), N-chlorobenzotriazole² (3.3 g, 21.5 mmol) and ammonia (100 mL) to give 5.89 g of the product as a tan solid. After washing with 125 mL absolute EtOH and vacuum drying, there remained 5.0 g (71%) of the product.

Analysis of the product gave the following results: mp=175-176°C; R_F(1/9, MeOH/CHCl₃)= 0.66; ¹H NMR (300 MHz, d₆-DMSO) δ 1.95-2.1 (m, 2H, CH₂), 2.87-2.93 (m, 4H, 2CH₂), 7.18 (d, 2H, J=8.8 Hz, Ar-H), 7.37-7.49 (m, 5H, 2H exchanges with D₂O, 3Ar-H +NH₂), 7.65 (d, 1H, J=7.9 Hz, Ar-H), 7.73 (s, 1H, Ar-H) and 9.23 (bs, 1H, exchanges with D₂O, NH); IR(KBr) 3292, 3182, 2962, 1622, 1589, 1520, 1310, 1281, 1233, 1127, 956, 829 and 775 cm⁻¹; UV(EtOH) λ_{max}(ε) 206.2(38823), 255.0(25277) nm; FDMS(DMSO) m/e 349, 351 (M⁺). Anal Calcd for C₁₆H₁₆ClN₃O₂S₁: C, 54.93 H, 4.61; N, 12.01. Found C, 55.13; H, 4.59; N, 12.09.

EXAMPLE 55

[(5-indanyl)S(O)(NHCH₃)NC(O)NH(p-ClC₆H₄)]

The method of Example 3 was followed using the product of Example 53 (3.3 g, 10 mmol), N-chlorobenzotriazole² (1.6 g, 10.5 mmol) and methylamine (30 mL) to give 4.2 g of foam. Silica gel flash chromatography (1/19, MeOH/CHCl₃) followed by recrystallization from 20 mL of toluene gave 1.6 g (44%) of the product.

Analysis of the product gave the following results: mp=131-133°C; R_F(1/9, MeOH/CHCl₃)= 0.74; ¹H NMR (300 MHz, d₆-DMSO) δ 1.95-2.1 (m, 2H, CH₂), 2.42 (s, 3H, CH₃), 2.87-2.93 (m, 4H, 2CH₂), 7.18 (d, 2H, J=8.8 Hz, Ar-H), 7.37-7.49 (m, 4H, 1H exchanges with D₂O, 3Ar-H + NH), 7.65 (d, 1H, J=7.9 Hz, Ar-H), 7.73 (s, 1H, Ar-H) and 9.31 (bs, 1H, exchanges with D₂O, NH); IR(KBr) 3332, 3185, 1621, 1516, 1399, 1307, 1229, 1092, 1050, 935, 816

and 774 cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 206.0(45381),
254.2(29481) nm; FABMS(DMSO) m/e 364, 366 (M^+). Anal
Calcd for $C_{17}H_{18}Cl_1N_3O_2S_1$: C, 56.12 H, 4.98; N, 11.55.
Found C, 56.03; H, 5.01; N, 11.32.

5

EXAMPLE 56O-(4-Chloro-3,5-dimethylphenyl)-N,N-
dimethylthiocarbamate

10 This material was prepared in 83% yield from 15.7g
(100 mmol) 4-chloro-3,5-dimethylphenol using the
procedure of Goralski and Burk⁸. Recrystallization from
EE/hexane gave an analytical sample.

15 Analysis of the product gave the following results:
mp=125-126°C; R_f (3/7 EtOAc/hexane)= 0.42; $^1\text{H NMR}$ (300
MHz, CDCl_3) δ 2.39 (s, 6H, 2 CH_3), 3.33 (s, 3H, NCH_3),
3.46 (s, 3H, NCH_3), 6.82 (s, 2H, Ar-H); IR(KBr) 2987,
1538, 1468, 1399, 1311, 1277, 1213, 1155, 1054 and 868
 cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 251.2 (13933) and 204.2 (30099)
20 nm; FDMS(DMSO) m/e 243, 245 (M^+). Anal Calcd for
 $C_{11}H_{14}Cl_1N_1O_1S_1$: C, 54.20; H, 5.79; N, 5.75. Found C,
54.45; H, 6.00; N, 5.86.

EXAMPLE 57S-(4-Chloro-3,5-dimethylphenyl)-N,N-
dimethylthiocarbamate

25 The method of Example 41 was followed, using O-(4-
chloro-3,5-dimethyl-phenyl)-N,N-dimethylthiocarbamate
30 (18g, 74 mmol) and heating at 210°C for 7 h. A small
sample was purified by silica gel chromatography (3/7,
EtOAc/hexane) to provide an analytical sample as a
yellow solid.

35 Analysis of the product gave the following results:
mp=99-100°C; R_f (3/7 EtOAc/hexanes)= 0.28; $^1\text{H NMR}$ (300
MHz, CDCl_3) δ 2.39 (s, 6H, 2 CH_3), 3.07 (bs, 6H, 2 NCH_3),

7.23 (s, 2H, Ar-H); IR(CHCl₃) 3012, 1657, 1465, 1368, 1262, 1101 and 1052 cm⁻¹; UV(EtOH) λ_{max}(e) 248.0 (8002) and 207.8 (30759) nm; FDMS(DMSO) m/e 243, 245 (M⁺).
Anal Calcd for C₁₁H₁₄Cl₁N₁O₁S₁: C, 54.20; H, 5.79; N, 5.75. Found C, 54.47; H, 5.86; N, 6.02.

EXAMPLE 58

4-Chloro-3,5-dimethylthiophenol

[(4-Cl-3,5-(CH₃)₂C₆H₂)SH]

The method of Example 42 was followed using crude S-(4-chloro-3,5-dimethylphenyl)-N,N-dimethylthiocarbamate to give a brown oil which was vacuum distilled to yield 8.9g (72%) of the product as a light yellow oil.

Analysis of the product gave the following results: bp=70-72°C (0.25mm Hg); R_f(1/9 EtOAc/hexane)= 0.44; ¹H NMR (300 MHz, CDCl₃) δ 2.34 (s, 6H, 2CH₃), 3.38 (s, 1H, SH), 7.02 (s, 2H, Ar-H); IR(CHCl₃) 3010, 2985, 2928 1577, 1465, 1210, 1138, 1049 and 854 cm⁻¹; UV(EtOH) λ_{max}(e) 247.4 (7613) and 208.2 (15887) nm; FDMS(DMSO) m/e 342, 344 (2M⁺). Anal Calcd for C₈H₉Cl₁S₁: C, 55.65; H, 5.25; Found C, 55.49; H, 5.32.

EXAMPLE 59

4-Chloro-3,5-Dimethylbenzenesulfinyl chloride

[(4-Cl-3,5-(CH₃)₂C₆H₂)S(O)Cl]

This material was prepared quantitatively as a bright yellow oil from the product of Example 58, following the method of Example 34.

Analysis of the crude product gave the following results: ¹H NMR (300 MHz, CDCl₃) δ 2.51 (s, 6H, 2CH₃), 7.61 (s, 2H, Ar-H).

EXAMPLE 60

N-(4-Chloro-3,5-dimethylbenzenesulfinyl)-N'-(4-chlorophenyl)urea

CC(C)c1ccc(cc1)S(=O)(=O)NC(=O)Nc2ccc(Cl)cc2

The method of Example 1 was followed, using the product of Example 59 (9.4g, 42 mmol), silver cyanate (7.9g, 53 mmol) and p-chloroaniline (5.8g, 45 mmol) to provide 9.5g (63%) of the product.

Analysis of the product gave the following results: mp 151-152°C; R_f (10/10/2 EtOAc/EE/AcOH) = 0.82; ^1H NMR(300 MHz, d_6 -DMSO) δ 2.42 (s, 6H, 2CH₃), 7.33 (d, 2H, J=8.9 Hz, Ar-H), 7.45 (d, 2H, J=8.9 Hz, Ar-H), 7.59 (s, 2H, Ar-H), 8.88 (s, 1H, exchanges with D₂O, N-H) and 9.72 (s, 1H, exchanges with D₂O, N-H); IR(KBr) 3366, 3056, 2812, 1674, 1527 and 1049 cm⁻¹; FDMS(DMSO) m/e 356, 357, 358 (M⁺). Anal Calcd for C₁₅H₁₄Cl₂N₂O₂S₁: C, 50.43; H, 3.95; N, 7.84. Found C, 50.66; H, 4.21; N, 7.61.

EXAMPLE 61

CC(C)c1ccc(cc1)S(=O)(=O)NC(=O)Nc2ccc(Cl)cc2

The method of Example 2 was followed, using the product of Example 60 (8.9g, 25 mmol), t-butylhypochlorite (3.7mL, 31 mmol) and ammonia (50 mL) to provide, after recrystallization from 1000 mL of toluene, 5.24 g (56%) of the product as a white solid.

Analysis of the product gave the following results: mp 177-178°C; R_f (9/1 CHCl₃/MeOH) = 0.52; ^1H NMR(300 MHz, d_6 -DMSO) δ 2.39 (s, 6H, 2CH₃), 7.18 (d, 2H, J=8.9 Hz, Ar-H), 7.45 (d, 2H, J=8.9 Hz, Ar-H), 7.52 (s, 2H, Ar-H), 7.70 (s, 2H, exchanges with D₂O, NH₂) and 9.23 (s, 1H, exchanges with D₂O, NH); IR(KBr) 3307, 3201, 1630, 1592, 1525, 1401, 1275, 1232, 1125, 1048, 950 and 875 cm⁻¹; UV(EtOH) $\lambda_{max}(e)$ 253.0 (28581) and 206.4 (49071) nm; FDMS(DMSO) m/e 371, 373 (M⁺). Anal Calcd for C₁₅H₁₅Cl₂N₃O₂S₁: C, 48.4; H, 4.06; N, 11.29. Found C, 48.61; H, 4.19; N, 11.34.

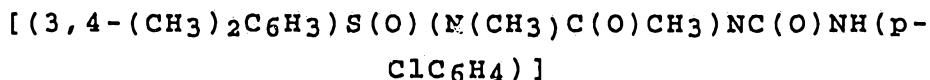
EXAMPLE 62



The method of Example 3 was followed, using the product of Example 35 (11.3g, 35 mmol), t-butylhypochlorite (5.22mL, 43.7 mmol) and methylamine (40mL) to provide 11.3g (92%) of product.

Analysis of the product gave the following results: mp 76-79°C; R_f (9/1 $\text{CHCl}_3/\text{MeOH}$) = 0.64; ^1H NMR(300 MHz, d_6 -DMSO) δ 2.29 (s, 6H, 2 CH_3), 2.40 (d, 3H, J = 5 Hz, NCH_3), 3.58 (m, 1 H, exchanges with D_2O , HNCH_3), 7.20 (d, 2H, J =8.9 Hz, Ar-H), 7.36 (d, 1H, J = 8 Hz, Ar-H), 7.42-7.58 (m, 4H, Ar-H), 7.61 (s, 1H, Ar-H) and 9.30 (s, 1H, exchanges with D_2O , N-H); IR(KBr) 3250, 1631, 1591, 1493, 1397, 1271, 1236, 1009 and 830cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 254.2 (27145) and 205.4 (38773) nm; FDMS(DMSO) m/e 351, 353 (M^+). Anal Calcd for $\text{C}_{16}\text{H}_{18}\text{Cl}_1\text{N}_3\text{O}_2\text{S}_1$: C, 54.62; H, 5.16; N, 11.94. Found C, 54.64; H, 5.37; N, 11.72.

EXAMPLE 63



The method of Example 16 was followed, using the product of Example 62 (5.3g, 15 mmol), Et_3N (4.2 mL, 30 mmol), DMAP (20 mg, 0.2 mmol) and Ac_2O (1.8 mL, 18 mmol) to give, after trituration with EE, 3.3g (55%) of product as a white solid.

Analysis of the product gave the following results: mp 147-149°C; R_f (1/1 $\text{EtOAc}/\text{hexane}$) = 0.33; ^1H NMR(300 MHz, d_6 -DMSO) δ 2.22 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 7.20 (d, 2H, J =8.9 Hz, Ar-H), 7.36 (d, 1H, J = 8 Hz, Ar-H), 7.42-7.58 (m, 4H, Ar-H), 7.61 (s, 1H, Ar-H) and 9.27 (s, 1H, exchanges with D_2O , NH); IR(KBr) 3304, 1709, 1643, 1537, 1399, 1239, 1088 and 850cm^{-1} ; UV(EtOH) $\lambda_{\text{max}}(\epsilon)$ 244.6 (21307) and 205.4 (43504) nm; FDMS(DMSO) m/e 393,

395 (M⁺). Anal Calcd for C₁₈H₂₀Cl₁N₃O₃S₁: C, 54.89; H, 5.12; N, 10.67. Found C, 54.88; H, 5.16; N, 10.38.

EXAMPLE 64

5 [(p-CH₃C₆H₄)S(O)(NHCH₂CH=CH₂)NC(O)NH(p-ClC₆H₄)]

The method of Example 3 was followed, using the product of Example 1 (9.3 g, 30 mmol), t-butylhypochlorite (4.5 mL, 37.5 mmol) and 50 mL of allylamine. Recrystallization from 100 mL of EE gave
10 4.6g (42%) product as a white solid.

Analysis of the product gave the following results:
mp 115-116°C; R_f (9/1 CHCl₃/MeOH) = 0.75; ¹H NMR (300
MHz, d₆-DMSO) δ 2.37 (s, 3H, CH₃), 3.44 (m, 2H,
CH₂CH=CH₂), 5.03 (dd, 1 H, J=1, 10 Hz, -CH₂CH=CH₂), 5.15
15 (dd, 1 H, J=1, 17 Hz, -CH₂CH=CH₂), 5.68 (m, 1 H,
-CH₂CH=CH₂), 7.20 (d, 2H, J=8.9 Hz, Ar-H), 7.38 (d, 1H,
J= 8 Hz, Ar-H), 7.48 (d, 1H, J= 8.9 Hz, Ar-H), 7.75 (d,
1H, J= 8 Hz, Ar-H), 7.85 (m, 1H, exchanges with D₂O, NH)
and 9.33 (s, 1H, exchanges with D₂O, NH); IR (KBr) 3356,
20 3206, 1641, 1591, 1524, 1398, 1299, 1234, 925 and 815
cm⁻¹; UV (EtOH) λ_{max}(ε) 254.2 (28961) and 204.6 (36847)
nm; FDMS (MeOH) m/e 363, 365 (M⁺). Anal Calcd for
C₁₇H₁₈Cl₁N₃O₂S₁: C, 56.12; H, 4.99; N, 11.55. Found C,
56.01; H, 5.00; N, 11.47.

EXAMPLE 65

[(p-CH₃C₆H₄)S(O)(NHCH₃)NC(O)N(CH₃)(p-ClC₆H₄)]

The method of Example 3 was followed, using the product of Example 19 (6.45 g, 20.0 mmol), t-butylhypochlorite (2.4 mL, 20 mmol) and 30 mL of methylamine. Recrystallization from toluene gave 4.56g (65%) product as a white solid.

Analysis of the product gave the following results: mp=119-120°C; R_f (EtOAc)= 0.53; ¹H NMR (300
MHz, d₆-DMSO) δ 2.31 (d, 3H, J=4.7 Hz, N-CH₃), 2.36 (s,
35 3H, CH₃), 3.18 (s, 3H, N-CH₃), 7.29-7.38 (m, 7 H, 1H

exchanges with D₂O, Ar-H+NH) and 7.61 (d, 2H, J=8.2 Hz, Ar-H); IR(KBr) 3151, 1589, 1494, 1435, 1360, 1314, 1295, 1252, 1198, 1071 and 1010 cm⁻¹; UV(EtOH) λ_{max}(ε) 203.8(32668) and 235.4(17590) nm; FDMS(DMSO) m/e 351, 353 (M⁺). Anal Calcd for C₁₆H₁₈Cl₁N₃O₂S₁: C, 54.62; H, 5.16; N, 11.94. Found C, 54.41; H, 5.09; N, 11.90.

References

- 1) Kurzer, F., Org. Syn., Coll. Vol. IV, 1963, 937.
- 2) Rees, C. W., Storr, R. C., J. Chem. Soc. (C), 1969, 1474.
- 3) Herrmann, R., Youn, J-H, Synthesis, 1987, 72.
- 4) Harpp, D. N., Friedlander, B. T., Smith, R. A., Synth. Comm., 1979, 181.
- 5) Young, R. N., Gauthier, J. Y., Coombs, W., Tetrahedron Letters, 1984, 25, 1753; Grieco, R., Owen, L. N., J. Chem. Soc., 1963, 1947.
- 6) Herrmann, R., Youn, J-H., Tetrahedron Lett., 1986, 27(13), 1493.
- 7) Tao, E. V., Aikens, J., Eur. Pat. Appl., EP 254,577.
- 8) Goralski, Christian T. and Burk, George A., J. Chem. Eng. Data., 1975, 20(4), 443.

In a further embodiment the present invention comprises a method for treating a susceptible neoplasm in a mammal which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula 1 or a pharmaceutically acceptable salt thereof.

The compounds of formula 1 have been shown to be active against transplanted mouse tumors in vivo. The compounds were tested in C3H mice bearing a 6C3HED lymphosarcoma, also known as the Gardner lymphosarcoma (GLS), and in a variety of human tumor xenografts in CD1

nu/nu mice, including CX-1, LX-1, HXGC3, and VRC5. The 6C3HED lymphosarcoma was obtained from the Division of Cancer Treatment, National Cancer Institute, Tumor Bank, maintained at E. G. and G. Mason Research (Worcester, Massachusetts). The CX-1 human colon carcinoma and the LX-1 human lung carcinoma xenografts were obtained from the National Cancer Institute. The HXGC3 and VRC5 human colon xenografts were obtained from Dr. P. J. Houghton, St. Jude Children's Hospital in Memphis (see Br. J. Cancer, 37, 213 (1978)). First passage tumor was stored in liquid nitrogen using standard techniques. The transplanted tumor was reestablished from the Tumor Bank every six months or as needed. The tumor was maintained by serial passage twice weekly in C3H mice.

In the procedure the tumor was removed from passage animals and minced into 1- to 3-mm square fragments using sterile techniques. Tumor pieces were checked for sterility using both Antibiotic Medium 1 and Brain Heart Infusion (Difco, Detroit, Michigan). Recipient mice were shaved and tumor pieces were implanted subcutaneously in the auxiliary region by trocar. Drug therapy on the appropriate schedule was initiated on the day after tumor implant for 6C3HED and after a seven (7) day delay for xenografts (or other delay as noted in Table 2). The compound being tested was mixed with 2.5% Emulphor EL620 from GAF Corporation (1:40 dilution in saline). Food and water were provided ad libitum. The drug was administered orally in 0.5 mL of 2.5% Emulphor (unless otherwise indicated). The tumor was measured the day after treatment ended with two dimensional measurements (width and length) of the tumor taken using automated digital calipers interfaced to a microcomputer. Approximate weight for the tumor was calculated using the following formula [Worzalla, J. F., et al., Invest. New Drugs, 8, 241 (1990), (tumor weight in mg) = (width in mm)² x (length in mm)/2.

At least one control group of an equal number of mice was treated with the same volume of 2.5% Emulphor only. The percent inhibition was determined by subtracting the ratio of the mean tumor size of the test group relative to the control group from one and multiplying the result times 100.

The results of several experiments in mice bearing a 6C3HED lymphosarcoma (or other tumor where indicated) when the indicated compounds were administered are provided in Table 2. In Table 2, column 1 gives the Example number of the compound used, column 2 lists the dose level in mg/kg, column 3 provides the percent inhibition of tumor growth, column 4 gives the number of mice which died relative to the total number of animals in the group, column 5 gives the method of administration of the compound, and column 6 gives the dosage schedule. The protocol used with other tumors was the same as with the 6C3HED lymphosarcoma.

TABLE 2

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (a)	Dose (b) Sched.
2	300.00	98	6/10	IP	D X 8
	150.00	92	1/10	IP	
	25.00	52	1/10	IV	
	12.50	36	0/10	IV	
	800.00	99	1/10		BID X 8
	400.00	99	0/10		
	200.00	98	0/10		
	100.00	96	0/10		
	50.00	95	0/10		
	300.00	82	0/10		D X 8
	150.00	74	0/10		
	1200.00	100	0/10		
	600.00	99	0/10		
	300.00	95	0/10		
	150.00	93	0/10		
	75.00	76	0/10		
	(c) 500.00	TOX	9/9		BID X 14; (b-1)
	(c) 250.00	68	2/9		
	(d) 300.00	66	5/10		BID X 14; (b-2)
	(d) 100.00	51	0/10		
	(d) 30.00	28	0/10		
	(d) 10.00	18	0/10		
	(d) 3.00	24	0/10		

2 (con't)

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (n)	Dose (b) Sched.
3	200.00	100	0/10		BID X 8
	100.00	99	0/10		
	50.00	91	0/10		
	25.00	82	0/10		
	12.50	58	0/10		
	300.00	99	0/10		D X 8
	150.00	93	1/10		
	1200.00	TOX	10/10		
	600.00	100	4/10		
	300.00	99	0/10		
	150.00	96	1/10		
	75.00	81	0/10		
	(d) 300.00	TOX	8/8		BID X 10
	(d) 150.00	TOX	8/8		
4	300.00	18	0/10	IP	D X 8
	150.00	10	0/10	IP	
	300.00	96	0/10		BID X 8
	150.00	87	0/10		
5	300.00	44	0/10	IP	D X 8
	150.00	34	0/10	IP	
	300.00	69	0/10		
	150.00	64	0/10		
6	150.00	93	0/10		BID X 8
	75.00	86	0/10		
	37.50	60	0/10		
	18.75	18	0/10		
	300.00	99	2/10		
	150.00	99	2/10		

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (n)	Dose (b) Sched.
7	150.00	88	0/10		BID X 10
	75.00	69	0/10		
	37.50	45	0/10		
	18.75	21	0/10		
	(e) 50.00	0	0/10		BID X 10
8	150.00	97	0/9		BID X 8
	75.00	85	0/10		
	37.50	60	0/10		
	18.75	29	0/10		
	300.00	TOX	10/10		D X 8
	150.00	98	4/10		
	100.00	51	0/10		
	50.00	31	0/10		
	25.00	28	0/10		
9	300.00	79	2/10		BID X 8
	150.00	65	0/10		
10	300.00	60	0/10		D X 8
	150.00	40	0/10		
11	300.00	89	2/10		BID X 8
	150.00	65	0/10		
12	300.00	87	1/10		BID X 8
	150.00	73	0/9		
13	300.00	48	0/10		BID X 8
	150.00	39	0/10		
14	300.00	38	3/10	IP	D X 8
	150.00	1	2/10	IP	
	300.00	5	0/10		
	150.00	0	0/10		

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (a)	Dose (b) Sched.
15	300.00	TOX	10/10	IP	D X 8
	150.00	0	0/10	IP	
	300.00	84	0/10		BID X 8
	150.00	0	0/10		
	300.00	44	0/10		D X 8
	150.00	23	0/10		
16	300.00	99	1/10		BID X 8
	150.00	98	1/10		
17	300.00	96	0/10		BID X 8
	150.00	83	0/10		
18	600.00	99	6/8	IP	D X 8
	300.00	93	4/8	IP	
	300.00	63	0/10		
	150.00	45	0/10		
20	300.00	93	0/10		BID X 8
	150.00	83	0/10		
22	300.00	100	3/10		BID X 8
	150.00	100	0/10		
24	300.00	52	0/10	IP	D X 8
	150.00	31	0/10	IP	
	300.00	40	0/10		
	150.00	10	0/10		
27	200.00	TOX	10/10		BID X 8
	100.00	100	9/10		
	100.00	94	0/10		
	50.00	80	0/10		
	25.00	39	0/10		

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (a)	Dose (b) Sched.
30	300.00	TOX	10/10		BID X 8
	150.00	99	3/10		
	150.00	89	1/10		
	75.00	67	0/10		
	37.50	42	1/10		
	18.75	19	1/10		
	9.00	4	0/10		
	50.00	55	0/10		
	300.00	100	8/10		
	150.00	100	8/10		
33	100.00	99	0/10		BID X 8
	50.00	98	1/10		
	25.00	91	2/10		
	12.50	60	0/9		
	6.25	36	0/10		
	100.00	100	3/10		
	50.00	99	0/10		
	25.00	99	0/10		
	12.50	88	0/10		
	4.00	97	0/10		
36	2.00	75	0/10		BID X 8
	1.00	43	0/10		
	0.50	29	0/10		
	0.25	16	0/10		
	50.00	100	6/10		
	25.00	100	2/10		
	12.50	98	1/10		
	6.25	93	0/10		
	3.125	74	0/10		
	50.00	100	6/10		
	25.00	100	2/10		DX 8
	12.50	98	1/10		
	6.25	93	0/10		
	3.125	74	0/10		
	50.00	100	6/10		
	25.00	100	2/10		
	12.50	98	1/10		
	6.25	93	0/10		
	3.125	74	0/10		
	50.00	100	6/10		

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (a)	Dose (b) Sched.
36 (con't)	300.00	TOX	10/10		BID X 8
	150.00	99	6/10		
	100.00	TOX	8/8		
	50.00	100	7/8		
	25.00	100	2/8		
	12.50	100	5/8		
	6.25	100	2/8		
	(f) 30.00	9	0/10	IP	D X 10
	(f) 15.00	0	0/10	IP	
	(f) 7.50	0	0/10	IP	
	(f) 3.75	0	0/10	IP	
	(g) 30.00	TOX	10/10	IP	
	(g) 15.00	74	6/10	IP	
	(g) 7.50	69	0/10	IP	
	(g) 3.75	38	1/10	IP	
	(h) 30.00	72	0/10	IP	
	(h) 15.00	42	0/10	IP	
	(h) 7.50	1	0/10	IP	
	(h) 3.75	26	0/10	IP	
	(i) 30.00	26	0/10	IP	
	(i) 15.00	6	0/10	IP	
	(i) 7.50	14	0/10	IP	
	(i) 3.75	5	0/10	IP	

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (a)	Dose (b) Sched.
36 (con't)	(j) 30.00	23	4/10	IP	D X 10, (b-2)
	(j) 15.00	32	1/10	IP	
	(j) 7.50	10	0/10	IP	
	(j) 3.75	4	0/10	IP	
	(k) 30.00	TOX	10/10	IP	D X 10
	(k) 15.00	3	0/10	IP	
	(k) 7.50	0	0/10	IP	
	(k) 3.75	0	0/10	IP	
	(l) 30.00	12	9/10	IP	
	(l) 15.00	13	1/10	IP	
	(l) 7.50	17	0/10	IP	
	(l) 3.75	6	0/10	IP	
	(c) 60.00	TOX	10/10	IP	
	(c) 30.00	46	6/10	IP	
	(c) 15.00	24	0/10	IP	
	(c) 7.50	1	0/10	IP	
	(m) 30.00	34	0/10	IP	
	(m) 15.00	32	0/10	IP	
	(m) 7.50	6	0/10	IP	

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (a)	Dose (b) Sched.
36 (con't)	(d) 30.00	TCX	10/10	IP	D X 10; (b-2)
	(d) 15.00	18	1/10	IP	
	(d) 7.50	1	0/10	IP	
	(d) 3.75	16	0/10	IP	
	(n) 30.00	38	1/10	IP	D X 10; (b-3)
	(n) 15.00	47	0/10	IP	
	(n) 7.50	19	0/10	IP	
	(n) 3.75	10	0/10	IP	
	(o) 30.00	12	4/10	IP	D X 10
	(o) 15.00	0	0/10	IP	
	(o) 7.50	0	0/10	IP	
	(o) 3.75	5	0/10	IP	
	(e) 60.00	TOX	10/10	IP	D X 10; (b-2)
	(e) 30.00	44	4/10	IP	
	(e) 15.00	0	0/10	IP	
	(e) 7.50	0	1/10	IP	
	(e) 20.00	45	2/9		D X 10
	(e) 10.00	10	0/10		
	(e) 5.00	0	0/10		
	(p) 30.00	97	3/10	IP	
	(p) 15.00	88	4/10	IP	
	(p) 7.50	63	1/10	IP	
	(p) 3.75	35	0/10	IP	
39	200.00	77	0/10		BID X 8
	100.00	44	0/10		

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (a)	Dose (b) Sched.
45	300.00	100	3/10		DAYS 1,3,5,7
	150.00	100	2/10		
	150.00	99	2/10		
	75.00	99	1/10		
	37.50	99	2/10		
	18.75	95	0/10		
	9.37	78	0/10		
	(d) 300.00	31	0/10		DAYS 1,4,7,10; (b-2)
	(d) 150.00	40	0/9		
49	300.00	TOX	10/10	IP	D X 8
	150.00	99	8/10	IP	
	50.00	63	1/10	IP	
	25.00	36	0/10	IP	
	12.50	29	0/10	IP	BID X 8
	300.00	100	3/10		
	150.00	99	0/10		
	75.00	96	0/10		
	50.00	87	0/10		
	25.00	64	0/10		

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (a)	Dose (b) Sched.
50	40.00	86	1/10	IP	BID X 8
	20.00	72	0/10	IP	
	10.00	49	0/10	IP	
	5.00	34	0/10	IP	
	300.00	100	9/10	IP	D X 8
	150.00	99	0/10	IP	
	75.00	96	0/10	IP	
	300.00	99	1/10	IP	
	150.00	93	0/10	IP	BID X 8
	300.00	100	9/10		
	150.00	100	2/10		
	75.00	99	2/10		
	(c) 150.00	23	2/9		BID X 10
	(c) 75.00	46	0/9		
	(c) 40.00	71	1/10	IP 0.6ML	BID X 14
	(c) 20.00	33	0/10	IP 0.6ML	
	(c) 10.00	31	0/10	IP 0.6ML	
	(c) 5.00	6	0/10	IP 0.6ML	
				IP 0.6ML	
	(d) 300.00	34	0/10		D X 10; (b-2)
	(d) 150.00	32	0/10		
	(e) 300.00	59	0/10		D X 10
	(e) 150.00	27	0/10		

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (a)	Dose (b) Sched.
51	300.00	99	9/10	IP	D X 8
	150.00	80	0/10	IP	
54	100.00	70	0/10	IP	BID X 8
	50.00	44	0/10	IP	
	25.00	30	0/10	IP	
	12.50	6	0/10	IP	
	300.00	94	3/10	IP	D X 8
	150.00	86	1/10	IP	
	25.00	19	0/10	IV	BID X 8
	12.50	3	0/10	IV	
	300.00	33	0/10		
	150.00	22	0/10		
61	300.00	39	0/10		D X 8
	150.00	39	0/10		
	600.00	34	0/10		BID X 8
	300.00	12	0/10		
	150.00	16	0/10		
	150.00	75	1/10		
	75.00	70	0/10		D X 8
	300.00	TOX	10/10	IP	
	150.00	72	2/10	IP	BID X 8
	300.00	0	0/10		
62	50.00	99	2/10		D X 8
	25.00	98	0/10		
63	50.00	95	0/10		D X 8
	25.00	79	0/10		

Ex. No.	Dose mg/kg	% Inhib.	Tox/Tot	Admin (a)	Dose (b) Sched.
64	300.00	43	0/10	IP	D X 8
	150.00	22	0/10	IP	
	300.00	45	0/10		BID X 8
	150.00	22	0/10		
65	300.00	97	0/10		BID X 8
	150.00	91	0/10		

(a) Route of Administration unless otherwise indicated compound was administered orally by gavage

IP = intraperitoneal, 0.5 mL (diluted as with oral dose).

5 IV = intravenous, 0.25 mL (diluted with 10% DMSO, 20% Emulphor EL-620, 70% of 0.9% aqueous NaCl).

(b) Dosage Schedule

DX = daily for indicated number of days

BIDX = twice daily 8 hours apart for the indicated number of days

Days + day number indicates administration of drug occurred on indicated day(s) after implanting of neoplasm

(b-1) Dosage initiated 14 days after implanting neoplasm

(b-2) Dosage initiated 7 days after implanting neoplasm

(b-3) Dosage initiated 5 days after implanting neoplasm

(c) Tumor type HC-1

(d) Tumor type LX1

(e) Tumor type VRC5

(f) Tumor type B-16

(g) Tumor type C3H mammary adenocarcin

(h) Tumor type CA-755 adenocarcinoma

(i) Tumor type colon carcinoma-26

(j) Tumor type CX-1

(k) Tumor type ELC2

(l) Tumor type GC3

(m) Tumor type Lewis Lung Carcinoma

(n) Tumor type M-5 Ovarian Carcinoma

(o) Tumor type MX-1

(p) Tumor type X5563 Plasma Cell Myeloma

The compounds of formula 1 are antineoplastic agents and the invention provides a method of treating susceptible neoplasms. In particular the present
5 compounds are useful in treating solid tumors including carcinomas such as ovarian, non-small cell lung, gastric pancreatic, prostate, renal cell, breast, colorectal, small cell lung, melanoma and head and neck; and sarcomas such as Kaposi's sarcoma and rhabdomyosarcoma.

10 The instant compounds can be administered individually or in combination, preferably orally, and usually in the form of a pharmaceutical composition. The instant compounds can also be used in combination with other chemotherapeutic agents. The pharmaceutical
15 compositions of the instant compounds are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

Accordingly, the present invention also includes pharmaceutical compositions comprising as active
20 ingredient certain compounds of formula 1 associated with a pharmaceutically acceptable carrier, diluent or excipient. The invention further comprises the method of treating susceptible neoplasms using these pharmaceutical compositions containing as an active
25 ingredient a compound of formula 1.

In making the compositions of the present invention, as well as compositions containing other
30 compounds of formula 1, the active ingredients are usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid or liquid material which acts as a vehicle, carrier or medium for the active ingredient.
35 Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs,

suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

In preparing a formulation it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than about 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyland propylhydroxybenzoates, sweetening agents or flavoring agents.

The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. The compositions are preferably formulated in a unit dosage form, each dosage normally containing from about 5 to about 500 mg, more usually about 25 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic

effect, in association with a suitable pharmaceutical excipient.

The active compounds are effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.5 to about 1200 mg/kg of body weight. In the treatment of adult humans, the range of about 1 to about 50 mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, the chosen route of administration, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way.

The following formulation examples can employ as active compounds any of the compound of formula 1. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	<u>Quantity (mg/capsule)</u>
Example 2	250
Starch	305
Magnesium stearate	5

The above ingredients are mixed and filled into hard gelatin capsules in 560 mg quantities.

Formulation 2

A tablet formula is prepared using the ingredients below:

	<u>Quantity (mg/tablet)</u>
Example 3	250

Cellulose, microcrystalline	400
Colloidal Silicon dioxide	10
Stearic acid	5

- 5 The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

- 10 A dry powder inhaler formulation is prepared containing the following components:

	<u>Weight %</u>
Example 4	5
Lactose	95

- 15 The active compound is mixed with the lactose and the mixture added to a dry powder inhaling appliance.

Formulation 4

Tablets each containing 60 mg of active ingredient are made up as follows:

Example 6	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	
(as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 4 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a No.

16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules each containing 80 mg of medicament are made as follows:

Example 17	80 mg
Starch	109 mg
Magnesium stearate	1 mg
Total	190 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 190 mg quantities.

Formulation 6

Suppositories each containing 225 mg of active ingredient are made as follows:

Example 16	225 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid.

Formulation 7

Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

Example 20	50 mg
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	Xanthan Gum	4 mg
	Sodium carboxymethyl cellulose (11%)	50 mg
	Microcrystalline Cellulose (89%)	
	Sucrose	1.75 g
5	Sodium Benzoate	
	Flavor	q.v.
	Color	q.v.
	Purified water to	5 mL

10 The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl-cellulose in water. The sodium benzoate, flavor and) color are diluted with some of the water and added with

15 stirring. Sufficient water is then added to produce the required volume.

Formulation 8

20 Capsules each containing 150 mg of medicament are made as follows:

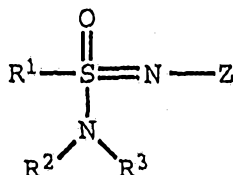
Example 33	150 mg
Starch	407 mg
Magnesium stearate	3 mg
25 Total	560 mg

30 The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 560 mg quantities.

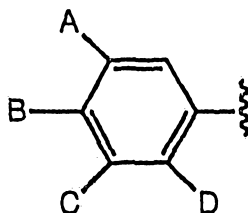
~~We claim:~~

The claims defining the invention are as follows:

1. A compound of the formula



wherein R^1 is



wherein

A, B and C are independently:

(a) H with the proviso that at least one of A, B or C is other than H;

(b) chlorine, bromine or iodine;

(c) $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$;

(d) $-\text{C}(\text{O})\text{R}^a$, wherein R^a is H or C_1 - C_5 alkyl;

(e) $-(\text{CH}_2)_n\text{OR}^b$ wherein n is 1-4 and R^b is H or $-\text{C}(\text{O})\text{R}^c$ wherein R^c is C_1 - C_4 alkyl; or

(f) A and B or B and C together are

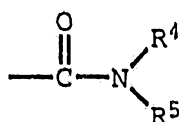
(i) $-(\text{CH}_2)_q-$ wherein q is 3 or 4,

(ii) $-(\text{CH}_2)_m\text{O}(\text{CH}_2)_b-$ wherein m is 0 or 1 and b is 1, 2 or 3 with the proviso that b is 2 or 3 when m is 0, or

(iii) $-\text{O}-(\text{CH}_2)_n-\text{O}-$ wherein n is 1 or 2, and C or A respectively is H or CH_3 ; and

D is H, chlorine, bromine, iodine, $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$, and

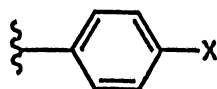
5



10

R^4 is hydrogen, methyl, or $-C(O)R^a$ wherein R^a is hydrogen or C_1 - C_5 alkyl;

15



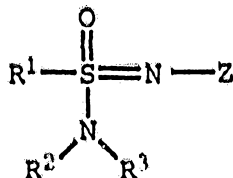
or a tautomer or pharmaceutically acceptable salt thereof.

2. A compound selected from the group consisting of N-[[(4-chlorophenyl) amino] carbonyl]-4-methylbenzene-sulfonimidamide; N-[[(4-chlorophenyl) amino] carbonyl]-N'-4-dimethylbenzenesulfonimidamide; N-[[(4-chlorophenyl) - amino] carbonyl]-N'-ethyl-4-methylbenzenesulfonimidamide; N-[[(4-chlorophenyl) amino] carbonyl]-N'-(1-methylethyl)-4-methyl-benzenesulfonimidamide; N-[[(4-chlorophenyl) - amino] -carbonyl]-N'-butyl-4-methylbenzene-sulfonimidamide; N-[[(4-chlorophenyl) amino] carbonyl]-N'-acetyl-N-methyl-4-methyl-benzenesulfonimidamide; N-methyl-N-[[(4-chlorophenyl) amino] carbonyl]-4-methyl-benzenesulfonimidamide; N-[[(4-bromophenyl) - amino] carbonyl]-4-methylbenzene-sulfonimidamide; N-[[(4-

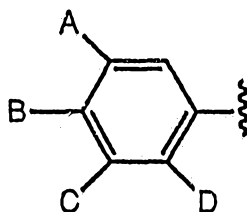
chlorophenyl)amino]carbonyl]-4-ethylbenzene-sulfonimidamide; N-[[[(4-chlorophenyl)amino]carbonyl]-N'-(2-methyl)propyl(4-methyl)benzenesulfonimidamide; N-[[[(4-chlorophenyl)amino]carbonyl]-4-chlorobenzene-sulfonimidamide; N-[[[(4-chlorophenyl)amino]carbonyl]-3,4-dimethylbenzenesulfonimidamide; N-[[[(4-chlorophenyl)amino]carbonyl]-3,4,5-trimethylbenzenesulfonimidamide; N-[[[(4-chlorophenyl)amino]carbonyl]-4-(acetoxymethyl)benzenesulfonimidamide; N-[[[(4-chlorophenyl)amino]carbonyl]-4-(hydroxymethyl)benzenesulfonimidamide; N-[[[(4-chlorophenyl)amino]carbonyl]-4-formylbenzenesulfonimidamide; N-[[[(4-chlorophenyl)amino]carbonyl]-5-indanylsulfonimidamide; N-[[[(4-chlorophenyl)amino]carbonyl]-N'-methyl-5-indanylsulfonimidamide; and N-[[[(4-chlorophenyl)amino]carbonyl]-N'-methyl-3,4-dimethylbenzenesulfonimidamide; or a tautomer or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical formulation comprising as an active ingredient a sulfonimidamide as claimed in any one of Claims 1 to 2, associated with one or more pharmaceutically acceptable carriers, excipients, or diluents therefor.

4. A process for preparing a sulfonimidamide of the formula



wherein R¹ is



wherein

A, B and C are independently:

- 5 (a) H with the proviso that at least one of A, B or C is other than H;
 (b) chlorine, bromine or iodine;
 (c) $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$;
 (d) $-\text{C}(\text{O})\text{R}^a$, wherein R^a is H or C_1 - C_5 alkyl;
 10 (e) $-(\text{CH}_2)_n\text{OR}^b$ wherein n is 1-4 and R^b is H or $\text{C}(\text{O})\text{R}^c$ wherein R^c is C_1 - C_4 alkyl; or

(f) A and B or B and C together are

(i) $-(\text{CH}_2)_q-$ wherein q is 3 or 4,

(ii) $-(\text{CH}_2)_m\text{O}(\text{CH}_2)_b-$ wherein m is 0 or 1

15 and b is 1, 2 or 3 with the proviso that b is 2 or 3 when m is 0, or

(iii) $-\text{O}-(\text{CH}_2)_n-\text{O}-$ wherein n is 1 or 2,

and C or A respectively is H or CH_3 ; and

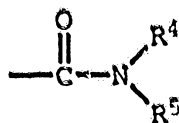
D is H, chlorine, bromine, iodine, $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$,

20 and

R^2 is H, C_1 - C_8 alkyl with the proviso that except for the isopropyl group there is no branching in the alpha-position, C_3 - C_8 alkenyl, $-(\text{CH}_2)_n\text{OH}$ wherein n is 1-5, $-(\text{CH}_2)_p\text{C}_6\text{H}_5$ wherein p is 1-3, or $-\text{C}(\text{O})\text{R}^d$ wherein R^d is H or C_1 - C_4 alkyl;

R^3 is H or $-\text{CH}_3$;

Z is

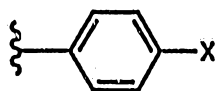


wherein

R^4 is hydrogen, methyl, or $-C(O)R^a$ wherein R^a is hydrogen or C_1 - C_5 alkyl;

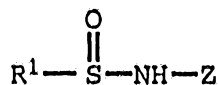
R^5 is

5



wherein X is chlorine, bromine, iodine or $-CH_3$;

10 which comprises reacting a compound of the formula



with a compound of the formula

15

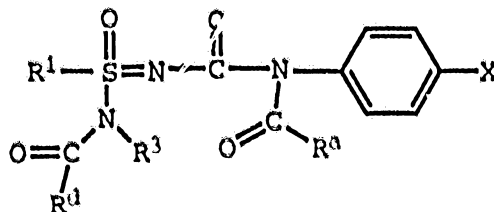


in the presence of an oxidant.

5. A process as claimed in Claim 4 wherein the oxidant is selected from the group consisting of chlorine, N-chlorobenzotriazole, t-butyl hypochlorite and sulfonyl chloride.

6. A process for preparing a sulfonimidamide of the formula

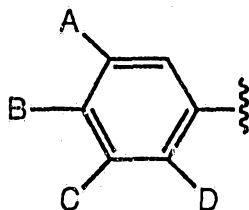
25



wherein:

R^1 is

30



wherein

A, B and C are independently:

- 5 (a) H with the proviso that at least one of A, B or C is other than H;
 (b) chlorine, bromine or iodine;
 (c) $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$;
 (d) $-\text{C}(\text{O})\text{R}^a$;
 10 (e) $-(\text{CH}_2)_n\text{OR}^b$ wherein n is 1-4 and R^b is H or $\text{C}(\text{O})\text{R}^c$ wherein R^c is $\text{C}_1\text{-C}_4$ alkyl; or
 (f) A and B or B and C together are

(i) $-(\text{CH}_2)_q-$ wherein q is 3 or 4,

(ii) $-(\text{CH}_2)_m\text{O}(\text{CH}_2)_b-$ wherein m is 0 or 1

15 and b is 1, 2 or 3 with the proviso that b is 2 or 3 when m is 0, or

(iii) $-\text{O}-(\text{CH}_2)_n-\text{O}-$ wherein n is 1 or 2,

and C or A respectively is H or $-\text{CH}_3$; and

D is H, chlorine, bromine, iodine, $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$,

20 and

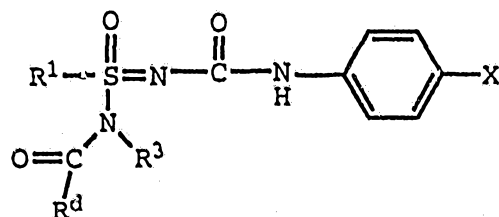
R^a is H or $\text{C}_1\text{-C}_5$ alkyl;

R^c is H or $\text{C}_1\text{-C}_4$ alkyl;

R^3 is H or $-\text{CH}_3$; and

X is chlorine, bromine, iodine or $-\text{CH}_3$;

25 which comprises reacting a compound of the formula



with an acid halide of the formula



5 in the presence of catalytic amount of an acylation catalyst.

7. A process as claimed in any one of Claims 4 to 6 that further comprises a subsequent salification step.

8. A sulfonimidamide whenever prepared by a process
10 according to any one of Claims 4 to 6.

9. A process for preparing a sulfonimidamide substantially as hereinbefore described with reference to any one of the examples.

10. A sulfonimidamide substantially as hereinbefore
15 described with reference to any of the examples.

11. A method of treating a susceptible neoplasm in a mammal which comprises administering to that mammal a sulfonimidamide as claimed in any one of claims 1 to 2.

DATED this FIRST day of DECEMBER 1992

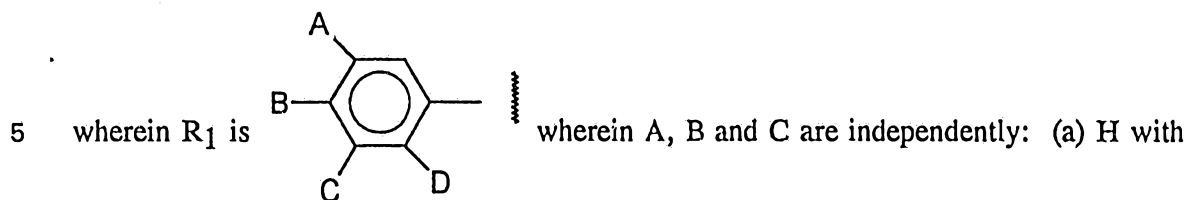
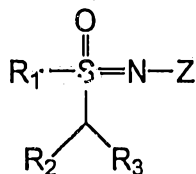
Eli Lilly and Company

Patent Attorneys for the Applicant
SPRUSON & FERGUSON

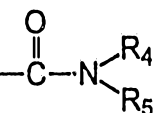
Sulfonimidamides

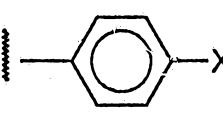
Abstract

The invention relates to antineoplastic sulfonimidamides of the formula



the proviso that at least one of A, B or C is other than H; (b) chlorine, bromine or iodine; (c) $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$; (d) $-\text{C}(\text{O})\text{R}^a$, wherein R^a is H or alkyl; (e) $-(\text{CH}_2)_n\text{OR}^b$ wherein n is 1-4 and R^b is H or $-\text{C}(\text{O})\text{R}^c$ wherein R^c is alkyl; or (f) A and B or B and C together are (i) $-(\text{CH}_2)_q-$ wherein q is 3 or 4, (ii) $-(\text{CH}_2)_m\text{O}(\text{CH}_2)_b-$ wherein m is 0 or 1 and b is 1, 2 or 3 with the proviso that b is 2 or 3 when m is 0, or (iii) $-\text{O}-(\text{CH}_2)_n-\text{O}-$ wherein n is 1 or 2, and C or A respectively is H or CH_3 ; and D is H, chlorine, bromine, iodine, $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$, and R_2 is H, alkyl with the proviso that except for the isopropyl group there is no branching in the α -position, alkenyl, $-(\text{CH}_2)_n\text{OH}$ wherein n is 1-5, $-(\text{CH}_2)_p\text{C}_6\text{H}_5$ wherein p is 1-3, or $-\text{C}(\text{O})\text{R}^d$ wherein R^d is H or alkyl; R_3 is H

15 or $-\text{CH}_3$; Z is  wherein R_4 is hydrogen, $-\text{CH}_3$, or $-\text{C}(\text{O})\text{R}^a$ wherein R^a is

hydrogen or alkyl; R_5 is  wherein X is chlorine, bromine, iodine or $-\text{CH}_3$; or a tautomer or pharmaceutically acceptable salt thereof.