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ANTITUMOR COMPOSITIONS AND METHODS OF TREATMENT

5 This invention relates to a novel sulfonylurea
useful in the treatment of cancer. This invention further
describes the preparation of this compound and formulations
employing this sulfonylurea.

10 In recent years fundamental advances have been
made in the development of chemical agents and regimens of
therapy to combat neoplastic diseases. Despite these
continuing advances, cancers continue to exact intolerable
levels of human pain and suffering. The need for new and
better methods of treating neoplasms and leukemias
15 continues to fuel efforts to create new classes of
compounds, especially in the area of inoperable or
metastatic solid tumors, such as the various forms of lung
cancer. Of the one million new cases of cancer diagnosed
in the United States each year, more than 90% represent
20 non-hematopoietic tumors, where improvements in five-year
survival rates have been modest, at best. B.E. Henderson,
et al., Science, 254:1131-1137 (1991).

25 The recent avalanche of information regarding
the basic biological processes involved in neoplasms has
led to a deeper understanding of the heterogeneity of
tumors. Ongoing work has led to the realization that
individual tumors may contain many subpopulations of
neoplastic cells that differ in crucial characteristics
such as karyotype, morphology, immunogenicity, growth rate,
30 capacity to metastasize, and response to antineoplastic
agents.

35 It is because of this extreme heterogeneity
among populations of neoplastic cells that new
chemotherapeutic agents should have a wide spectrum of
activity and a large therapeutic index. In addition, such
agents must be chemically stable and compatible with other

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agents. It is also important that any chemotherapeutic regimen be as convenient and painless as possible to the patient.

5 This invention reports a sulfonylurea which is useful in the treatment of solid tumors. This compound is orally active -- which, of course, results in less trauma to the patient -- and is relatively non-toxic. This compound also has an excellent therapeutic index and limited adverse reaction profile. The compound and its
10 formulation are novel.

Many sulfonylureas are known in the art. Certain of these compounds are known to have hypoglycemic activities, and have been used medicinally as such agents. In addition, sulfonylureas have been taught to have
15 herbicidal and antimycotic activities. General reviews of compounds of this structural type are taught by Kurzer, Chemical Reviews, 50:1 (1952). Some diarylsulfonylureas have been reported as being active antitumor agents. e.g., U.S. Patent 4,845,128 of Harper, et al. (1989) and European
20 Patent Publication 0222475 (published May 20, 1987).

Ongoing trials with the broad spectrum anti-neoplastic agent sulofenur [N-(indan-5-sulfonyl)-N'-(4-chlorophenyl)urea] have shown varying metabolic processes resulting in several major species and many minor species
25 of metabolites. Initial preclinical pharmacokinetic and disposition studies have been performed in mice, rats, dogs, and monkeys. These studies showed good adsorption and extensive metabolism of sulofenur in all species. The metabolic breakdown products of interest are as follows:

30 N-(1-hydroxyindan-5-sulfonyl)-N'-(4-chlorophenyl)urea;

N-(1-ketoindan-5-sulfonyl)-N'-(4-chlorophenyl)urea;

35 N-(3-hydroxyindan-5-sulfonyl)-N'-(4-chlorophenyl)urea;



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N-(3-ketoindan-5-sulfonyl)-N'-(4-chlorophenyl)urea;

N-(1,2-dihydroxyindan-5-sulfonyl)-N'-(4-chlorophenyl)urea;

5 Dihydroxyindanyl metabolite;

p-Chloroaniline;

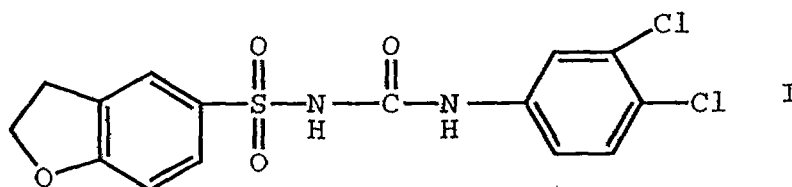
2-Amino-5-chlorophenyl sulfate;

p-Chloro-oxanilic acid;

W.J. Ehlhardt, Drug Metabolism and Disposition, 19:370-375
10 (1991).

The main urinary metabolites of sulofenur in animal trials were identified as the mono-hydroxy- and mono-keto- indanyl metabolites. The 1-hydroxy- and 1-ketoindansulfonylureas were also found to be the major
15 metabolites in patients receiving the drug in phase I clinical studies. P.H. Dhahir, et al., Proceedings of the 36th ASMS Conference on Mass Spectroscopy and Allied Topics, pp. 972-973 (1988); W.J. Ehlhardt, supra at 372..

This invention provides the novel compound of
20 Formula I



as well as the pharmaceutically acceptable salts thereof.
25 These compounds are especially preferred in the treatment of susceptible neoplasms in mammals, having fewer adverse effects than other sulfonylureas.

The compound of Formula I is generally referred to as N-[[5-(2,3-dihydrobenzofuran-5-yl)sulfonyl]-N'-(3,4-dichlorophenyl)]urea. Alternatively the
30 compound may be referred to as N-[5-(2,3-dihydrobenzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea or



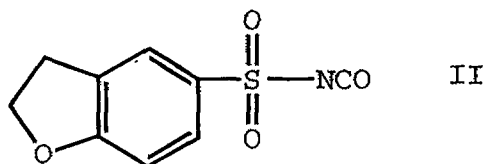
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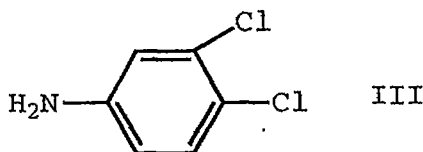
1 (3,4-dichlorophenyl) 3 [5-(2,3-dihydrobenzofuran)sulfonyl]urea.

This invention further encompasses processes for synthesizing the compound of Formula I. The compound of Formula I may be prepared by variations of any number of methods known in the literature. These methods are generally summarized by Kurzer, Chemical Reviews, 50:1 (1952), especially pages 4-19. See also, R.W. Harper, et al., European Patent Publication 291,269, published November 17, 1988.

A preferred method of preparing the compound of Formula I is that of the reaction of a sulfonylisocyanate of Formula II



with the 3,4-dichloroaniline of Formula III



The reaction between compounds II and III is usually performed using equimolar amounts of the two reactants, although other ratios are operative. The reaction is best carried out in an aprotic non-reactive solvent such as benzene, toluene, acetonitrile, diethyl ether, tetrahydrofuran, dioxane, methylene chloride, or preferably acetone.

The reaction can be carried out at temperatures from about 0°C up to about 100°C. At the preferred temperature range of about 20°C to about 30°C, the reaction produces an exotherm and the reaction is usually complete

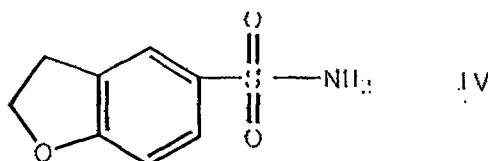


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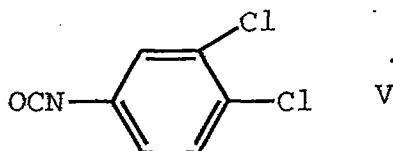
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within one hour. The product thus obtained is recovered by neutralization followed by filtration, and can be purified, if desired, by any number of methods known to those skilled in the art, such as chromatography or crystallization.

In another preferred method, the sulfonamide of Formula IV



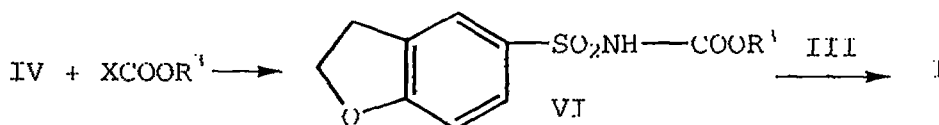
may be reacted with the isocyanate of Formula V



to provide the compound of Formula I. This reaction is generally conducted in a water miscible, non-reactive solvent such as tetrahydrofuran or acetone, in the presence of an acid scavenger such as sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium methoxide, sodium hydride and the like. Generally, an equimolar amount or slight molar excess of the compound of Formula V is employed, although other ratios are operative.

The reaction may be performed at temperatures ranging from about 0°C to about 100°C, although the preferred temperature range is from about 20°C to about 30°C. At this preferred temperature the reaction is usually complete within about three hours.

Another method of preparing the compound of Formula I involves the reaction of the sulfonamide of Formula IV with an alkyl haloformate to provide carbamate VI which is then reacted with the substituted aniline of Formula III to provide the product of Formula I



where X is bromo or chloro and R^3 is C_1 - C_3 alkyl. The transformation of IV into VI is usually accomplished in a non-reactive solvent, such as acetone or methyl ethyl ketone, in the presence of an acid scavenger, such as an alkali metal carbonate, for example potassium carbonate. A molar excess of the haloformate is usually added, although other ratios are operative. This reaction is generally performed at a temperature from about 30°C up to about 100°C for a period of 1-6 hours to provide the desired intermediate of Formula VI. The intermediate of Formula VI and the substituted aniline of Formula III are then heated together in an inert high-boiling solvent, such as dioxane, toluene, or diglyme, at temperatures from about 50°C up to the reflux temperature of the mixture to provide the desired product I.

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.

This invention includes the pharmaceutically acceptable salts of the compound of Formula I. The compound of this invention can react with basic materials such as alkali metal- or alkaline earth metal hydroxides, carbonates, and bicarbonates including, without limitation, sodium hydroxide, sodium carbonate, potassium hydroxide, calcium hydroxide, lithium hydroxide, etc. to form pharmaceutically acceptable salts such as the corresponding sodium, potassium, lithium, or calcium salt. Nontoxic organic bases can also be used, including primary, secondary, and tertiary alkyl amines, such as methylamine, triethylamine, and the like.



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The terms and abbreviations used in the instant example have their normal meanings unless otherwise designated. For example, "°C" refers to degrees Celsius; "N" refers to normal or normality; "mmole" means millimole; "g" refers to gram; "ml" means milliliter; "M" refers to molar or molarity; and "NMR" refers to nuclear magnetic resonance.

The following examples further illustrate the preparation of the compound of Formula I. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

Example 1

2,3-Dihydrobenzofuran-5-sulfonamide

This compound was prepared essentially according to the teachings of J.A. Aikins, et al., European Patent Publication 254,577, published January 27, 1988. N,N-dimethylformamide (23.0 ml, 297 mmol) was cooled in an ice-salt bath and treated dropwise with sulfuryl chloride (20.0 g, 148 mmol) at such a rate that the reaction temperature was maintained below 15°C. To this was added 2,3-dihydrobenzofuran (17.0 g, 142 mmol), and after warming to room temperature, the reaction mixture was rapidly heated to 130°C over ten minutes, and then allowed to cool to room temperature. The reaction mixture was poured into water/ice/dichloromethane, 1/5/1 (700 ml), and the organic layer collected. The aqueous layer was diluted with water (100 ml) and extracted with dichloromethane. The combined organic phase was dripped into an ammonium hydroxide solution (3N, 250 ml), and allowed to stir overnight. Residual dichloromethane was removed by distillation and the resulting solid collected on a filter, washed with a small amount of water, followed by ether and then dried by aspiration to provide 12.8 g (45%) of the product.

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Analysis of the product gave the following results: mp = 163-164.5°C; ^1H NMR (300 MHz, d_6 -DMSO) δ 3.21 (t, 2H, J=8.8 Hz, CH_2), 4.60 (t, 2H, J=8.8 Hz, CH_2), 6.86 (d, 1H, J=8.4 Hz, Ar-H), 7.12 (bs, 2H, exchanges with D_2O , SO_2NH_2), 7.56 (d, 1H, J=8.4 Hz, Ar-H), 7.64 (s, 1H, Ar-H); IR(KBr) 3356, 3255, 1606, 1590, 1557, 1407, 1442, 1314, 1249, 1149, 1116, 1070, 982, 923 and 836 cm^{-1} ; FDMS (MeOH) m/e 200 (M^+).

Analysis for $\text{C}_8\text{H}_9\text{NO}_3\text{S}$:

10 Theory: C, 48.23; H, 4.55; N, 7.03; S, 16.09.
Found: C, 48.01; H, 4.71; N, 7.00; S, 16.36.

Example 2

15 N-[5-(2,3-dihydrobenzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea

A solution of the product of Example 1 (29.6 g, 148.6 mmol) in acetone (75 ml) and 1N aqueous NaOH (150 ml, 150 mmol) was treated dropwise with a solution of 3,4-dichlorophenylisocyanate (30.0 g, 154.8 mmol) in 75 ml of acetone over 20 minutes. After stirring two hours, the insoluble bis(3,4-dichlorophenyl)urea was removed by filtration and the resulting clear solution neutralized by the addition of 1N aqueous HCl (150 ml, 150 mmol). The slurry was stirred 30 minutes, filtered and washed with water (500 ml), ether (200 ml), ether/hexane (1/1, 100 ml) and hexane (200 ml). Vacuum drying gave 50.1 g of crude product which was slurried in ethanol (300 ml) for one hour, collected on a filter and washed with ether. This ethanol reslurry was repeated and provided 42.7 g (74%) of the title compound after vacuum drying (50°C).

35 Analysis of the product gave the following results: mp = 188-189°C; ^1H NMR (300 MHz, d_6 -DMSO) δ 3.25 (t, 2H, J=8.8 Hz, CH_2), 4.63 (t, 2H, J=8.8 Hz, CH_2), 6.92 (d, 1H, J=8.6 Hz, Ar-H), 7.25 (dd, 1H, J=2.5, 8.8 Hz, Ar-H),



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7.48 (d, 1H, J=8.8 Hz, Ar-H), 7.68 (d, 1H, J=2.5 Hz, Ar-H),
7.71 (d, 1H, J=8.5 Hz, Ar-H), 7.77 (s, 1H, Ar-H), 9.08 (s,
1H, exchanges with D₂O, ArNH), 10.85, (bs, 1H, exchanges
with D₂O, SO₂NH); IR(KBr) 3275, 1701, 1580, 1511, 1452,
1380, 12444, 1202, 1142, 1115, 1045, 896, 708 and 585 cm⁻¹;
FDMS (MeOH) m/e 386, 388, 390 (M⁺).

Analysis for C₁₅H₁₂Cl₂N₂O₄S:

Theory: C, 46.53; H, 3.12; N, 7.23.

Found: C, 46.77; H, 3.24; N, 7.26.

The compound of Formula I has been shown to be
active against transplanted human tumors in vivo.
Accordingly, this invention provides a method of treating a
susceptible neoplasm in a mammal which comprises
administering to a mammal in need of said treatment an
effective amount of a compound of the Formula I.

To demonstrate the anti-tumor activity of the
compound of Formula I, the compound was tested in mice
bearing different xenograft tumors. Two of the tumor
models used for showing the anti-neoplastic activity of the
sulfonylurea of this invention were the human colon
xenografts, HXGC3 and VRC5. J.A. Houghton and D.M. Taylor,
British Journal of Cancer, 37:213-223 (1978). These tumors
were obtained from St. Jude's Children's Research Hospital
and have been widely used as human tumor models.

First passage tumors were 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 nude mice.

In the procedures utilized here, the tumor was
removed from passage animals and minced into 1- to 3-mm
cubic fragments using sterile techniques. Tumor pieces
were checked for sterility using both Antibiotic Medium 1
and Brain Heart Infusion (Difco, Detroit, Michigan). The



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tumor pieces were implanted into the recipient CD1 Nu/Nu mice subcutaneously in an axillary site by trochar.

Drug therapy on the appropriate schedule was initiated seven days after tumor implantation. The compound being tested was mixed with 2.5% Emulphor EL620 from GAF Corporation (1:40 dilution in 0.9% saline). The total dosage volume for each administration was 0.5 ml. All animals were weighed at the beginning and end of administration of the subject compounds. Food and water were provided ad libitum.

Each control group and each dosage level of the treated groups consisted of 10 mice selected at random from the pool of implanted animals. The formulations were administered orally by gavage with the use of an 18-gauge needle. Compounds were dosed daily for 10 days.

The tumor was measured five days after treatment ended with two dimensional measurements (width and length) of the tumor taken using digital electronic calipers interfaced to a microcomputer. J.F. Worzalla, et al., Investigational New Drugs, 8:241-251 (1990). Tumor weights were calculated from these measurements using the following formula:

$$\text{Tumor weight (mg)} = \frac{\text{tumor length (mm)} \times [\text{tumor width (mm)}]^2}{2}$$

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 is 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 by 100.



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The results of several experiments in mice bearing the HXGC3 and VRC5 human colon adenocarcinomas when the instant compounds were administered orally are provided in Table I. In the Table, column 1 describes the particular human tumor xenograft being studied; column 2 gives the dosage level of the compound of Formula I in milligrams per kilogram of body weight; column 3 describes the percent inhibition of tumor growth; and column 4 tallies the number of mice which died during the course of the experiment relative to the total number of animals in the group.

TABLE 1

	<u>Tumor</u>	<u>Dosage</u>	<u>Percent Inhibition</u>	<u>Toxic/Total</u>
	HXGC3	1200	99	0/10
		600	98	0/10
		300	98	0/10
		150	81	0/10
	VRC5	1200	100	0/10
		600	100	0/10
		300	98	0/10
		150	97	0/10

As a result of the high therapeutic index of the compound of Formula I, toxicological studies were performed to determine whether the compound of the current invention possessed the same adverse reaction profile of sulofenur. For these experiments thirty male Fischer 344 rats were administered varying dosages of a formulation containing the compound of Formula I. These formulations contained between 65 and 1000 mg of the active ingredient per kilogram of body weight of the rat, in combination with a suitable excipient, usually containing 10% acacia. The compounds were administered orally by gavage. The compounds were dosed daily for 14 days. All animals were



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weighed at the beginning and end of administration of the subject compounds. Food and water were provided ad libitum.

Upon completion of the testing regimen,
5 morphological and hematological studies were performed. These studies indicated an absence of hemolytic anemia, which is the dose-limiting toxicity of sulofenur. Pathological studies performed indicate effectiveness
10 against tissues with a high mitotic index, including lymph nodes, thymus, gut, testis, and bone marrow, these changes being consistent with the tissue effects produced by other efficacious anticancer drugs. Unexpected tissue changes were not observed, demonstrating a more limited adverse reaction profile than other compounds of its class.

15 The compound of Formula I is an antineoplastic agent and the invention provides a method of treating susceptible neoplasms. In particular, the present compound is useful in treating solid tumors including carcinomas
20 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.

The instant compound is usually administered in the form of a pharmaceutical composition, preferably
25 orally. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Accordingly, the present invention also encompasses pharmaceutical compositions which contain, as the active ingredient, the compound of Formula I associated
30 with a pharmaceutically acceptable carrier, diluent, or excipient. These formulations are useful in the treatment of mammals suffering from susceptible neoplasms.. The invention further comprises a method of treating susceptible neoplasms using compositions containing as an
35 active ingredient the compound of Formula I.



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In making the compositions of the present invention the active ingredient is 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. 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 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, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, 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 methyl- and propylhydroxybenzoates; sweetening agents; and 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 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 compound is 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 dose, 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 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.

Formulation Example 1

Hard gelatin capsules are prepared using the following ingredients:

5

	<u>Quantity (mg/capsule)</u>
N-[[(3,4-dichlorophenyl) amino] carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide	250.0
10 Starch	305.0
Magnesium stearate	5.0

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

Formulation Example 2

20 A tablet formula is prepared using the ingredients below:

	<u>Quantity (mg/tablet)</u>
N-[[(3,4-dichlorophenyl) amino] carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide	250.0
25 Cellulose, microcrystalline	400.0
Colloidal silicon dioxide	10.0
30 Stearic acid	5.0

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



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Formulation Example 3

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

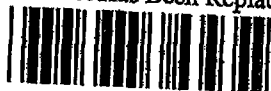
	<u>Weight %</u>
N-[[(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide	5
10 Lactose	95

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

15 Formulation Example 4

Tablets, each containing 60 mg of active ingredient, are prepared as follows:

20	N-[[(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide	60.0 mg
	Starch	45.0 mg
25	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
30	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1.0 mg</u>
35	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 16 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a 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 Example 5

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

N-[[(3,4-dichlorophenyl) amino] carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide	80.0 mg
Starch	109.0 mg
Magnesium stearate	<u>1.0 mg</u>
Total	190.0 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.



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Formulation Example 6

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

N-[(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide 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 glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

N-[(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide 50.0 mg

Xanthan gum 4.0 mg

Sodium carboxymethyl cellulose (11%)
Microcrystalline cellulose (89%) 50.0 mg

Sucrose 1.75 g

Sodium benzoate 10.0 mg

Flavor and Color q.v.

Purified water to 5.0 ml



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

Formulation Example 8

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

N-[[(3,4-dichlorophenyl) amino] carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide	150.0 mg
Starch	407.0 mg
Magnesium stearate	<u>3.0 mg</u>
Total	560.0 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 560 mg quantities.



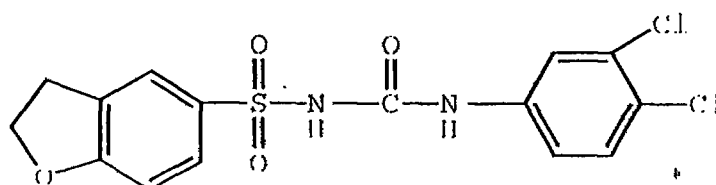
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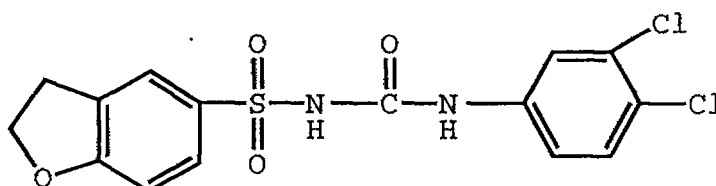
We claim:

1. A compound of the formula



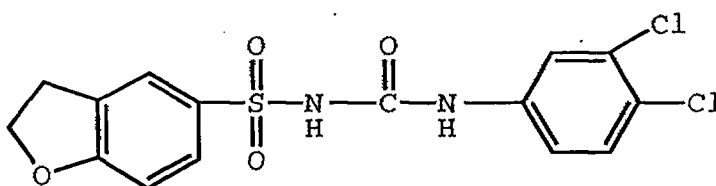
or a pharmaceutically acceptable salt thereof.

2. A compound of the formula



or a pharmaceutically acceptable salt thereof, for use as an antineoplastic agent.

3. A pharmaceutical formulation comprising, as an active ingredient, a compound of the formula



or a pharmaceutically acceptable salt thereof, associated with one or more suitable pharmaceutically acceptable carriers, excipients or diluents therefor.

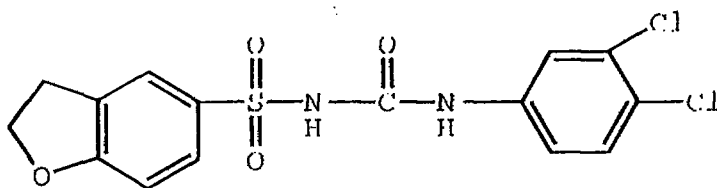
4. A process for preparing a compound of the formula

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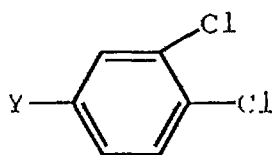


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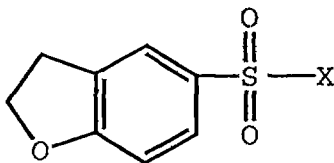


which comprises reacting with a compound of the formula



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in which Y is $-NH_2$ or $-NCO$, a sulfonyl compound of the formula



10

in which X is $-NCO$, $-NH_2$, or $-NH-COOR$ in which R is C_1-C_3 alkyl, provided that if X is $-NCO$ or $-NH-COOR$, then Y is $-NH_2$ and if X is $-NH_2$ then Y is $-NCO$.

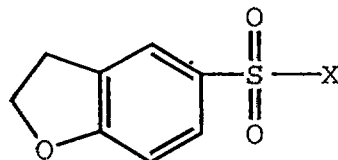
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X-8802 (IN)

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in which Y is $-NH_2$ or $-NCO$, a sulfonyl compound of the formula



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in which X is $-NCO$, $-NH_2$, or $-NH-COOR$ in which R is C_1-C_3 alkyl, provided that if X is $-NCO$ or $-NH-COOR$, then Y is $-NH_2$ and if X is $-NH_2$ then Y is $-NCO$.

4. A N-[[(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide whenever prepared by a process according to Claim 3.

5. A process for preparing an N-[[(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide substantially as hereinbefore described with reference to any one of the examples.

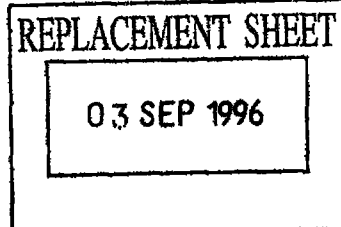
6. An N-[[(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide substantially as hereinbefore described with reference to any one of the examples.

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Abstract

5 This invention provides the use of N-[[(3,4-
dichlorophenyl) amino] carbonyl]-2,3-dihydrobenzofuran-5-
sulfonamide, and pharmaceutically acceptable salts
thereof, in the treatment of susceptible neoplasms in
mammals. This invention further provides the novel
aforementioned compound and its pharmaceutical
10 formulations.



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ANTITUMOR COMPOSITIONS AND METHODS OF TREATMENT

5 This invention relates to a novel sulfonylurea
useful in the treatment of cancer. This invention further
describes the preparation of this compound and formulations
employing this sulfonylurea.

10 In recent years fundamental advances have been
made in the development of chemical agents and regimens of
therapy to combat neoplastic diseases. Despite these
continuing advances, cancers continue to exact intolerable
levels of human pain and suffering. The need for new and
15 better methods of treating neoplasms and leukemias
continues to fuel efforts to create new classes of
compounds, especially in the area of inoperable or
metastatic solid tumors, such as the various forms of lung
cancer. Of the one million new cases of cancer diagnosed
20 in the United States each year, more than 90% represent
non-hematopoietic tumors, where improvements in five-year
survival rates have been modest, at best. B.E. Henderson,
et al., Science, 254:1131-1137 (1991).

25 The recent avalanche of information regarding
the basic biological processes involved in neoplasms has
led to a deeper understanding of the heterogeneity of
tumors. Ongoing work has led to the realization that
individual tumors may contain many subpopulations of
neoplastic cells that differ in crucial characteristics
such as karyotype, morphology, immunogenicity, growth rate,
30 capacity to metastasize, and response to antineoplastic
agents.

35 It is because of this extreme heterogeneity
among populations of neoplastic cells that new
chemotherapeutic agents should have a wide spectrum of
activity and a large therapeutic index. In addition, such
agents must be chemically stable and compatible with other

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agents. It is also important that any chemotherapeutic regimen be as convenient and painless as possible to the patient.

5 This invention reports a sulfonylurea which is useful in the treatment of solid tumors. This compound is orally active -- which, of course, results in less trauma to the patient -- and is relatively non-toxic. This compound also has an excellent therapeutic index and limited adverse reaction profile. The compound and its
10 formulation are novel.

Many sulfonylureas are known in the art. Certain of these compounds are known to have hypoglycemic activities; and have been used medicinally as such agents. In addition, sulfonylureas have been taught to have
15 herbicidal and antimycotic activities. General reviews of compounds of this structural type are taught by Kurzer, Chemical Reviews, 50:1 (1952). Some diarylsulfonylureas have been reported as being active antitumor agents. e.g., U.S. Patent 4,845,128 of Harper, et al. (1989) and European
20 Patent Publication 0222475 (published May 20, 1987).

Ongoing trials with the broad spectrum anti-neoplastic agent sulofenur [N-(indan-5-sulfonyl)-N'-(4-chlorophenyl)urea] have shown varying metabolic processes resulting in several major species and many minor species
25 of metabolites. Initial preclinical pharmacokinetic and disposition studies have been performed in mice, rats, dogs, and monkeys. These studies showed good adsorption and extensive metabolism of sulofenur in all species. The metabolic breakdown products of interest are as follows:

30 N-(1-hydroxyindan-5-sulfonyl)-N'-(4-chlorophenyl)urea;

N-(1-ketoindan-5-sulfonyl)-N'-(4-chlorophenyl)urea;

35 N-(3-hydroxyindan-5-sulfonyl)-N'-(4-chlorophenyl)urea;

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N-(3-ketoindan-5-sulfonyl)-N'-(4-chlorophenyl)urea;

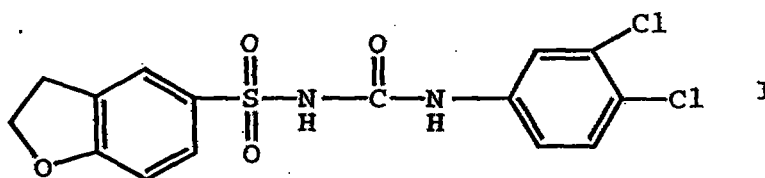
N-(1,2-dihydroxyindan-5-sulfonyl)-N'-(4-chlorophenyl)urea;

- 5 Dihydroxyindanyl metabolite;
p-Chloroaniline;
2-Amino-5-chlorophenyl sulfate;
p-Chloro-oxanilic acid;

10 W.J. Ehlhardt, Drug Metabolism and Disposition, 19:370-375 (1991).

The main urinary metabolites of sulofenur in animal trials were identified as the mono-hydroxy- and mono-keto- indanyl metabolites. The 1-hydroxy- and 1-ketoindansulfonylureas were also found to be the major metabolites in patients receiving the drug in phase I clinical studies. P.H. Dhahir, et al., Proceedings of the 36th ASMS Conference on Mass Spectroscopy and Allied Topics, pp. 972-973 (1988); W.J. Ehlhardt, supra at 372..

20 This invention provides the novel compound of Formula I



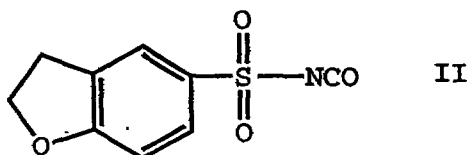
25 as well as the pharmaceutically acceptable salts thereof. These compounds are especially preferred in the treatment of susceptible neoplasms in mammals, having fewer adverse effects than other sulfonylureas.

30 The compound of Formula I is generally referred to as N-[[5-(2,3-dihydrobenzofuran-5-sulfonyl)]amino]carbonyl]-2,3-dichlorophenyl]urea. Alternatively the compound may be referred to as N-[5-(2,3-dihydrobenzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea or

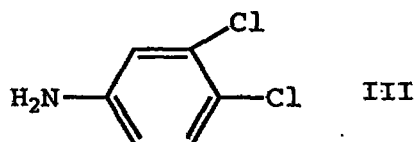
1-(3,4-dichlorophenyl)-3-[5-(2,3-dihydrobenzofuran)sulfonyl]urea.

This invention further encompasses processes for synthesizing the compound of Formula I. The compound of Formula I may be prepared by variations of any number of methods known in the literature. These methods are generally summarized by Kurzer, Chemical Reviews, 50:1 (1952), especially pages 4-19. See also, R.W. Harper, et al., European Patent Publication 291,269, published November 17, 1988.

A preferred method of preparing the compound of Formula I is that of the reaction of a sulfonylisocyanate of Formula II



with the 3,4-dichloroaniline of Formula III



The reaction between compounds II and III is usually performed using equimolar amounts of the two reactants, although other ratios are operative. The reaction is best carried out in an aprotic non-reactive solvent such as benzene, toluene, acetonitrile, diethyl ether, tetrahydrofuran, dioxane, methylene chloride, or preferably acetone.

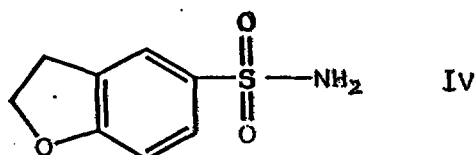
The reaction can be carried out at temperatures from about 0°C up to about 100°C. At the preferred temperature range of about 20°C to about 30°C, the reaction produces an exotherm and the reaction is usually complete

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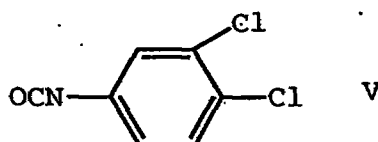
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within one hour. The product thus obtained is recovered by neutralization followed by filtration, and can be purified, if desired, by any number of methods known to those skilled in the art, such as chromatography or crystallization.

5 In another preferred method, the sulfonamide of Formula IV



10 may be reacted with the isocyanate of Formula V



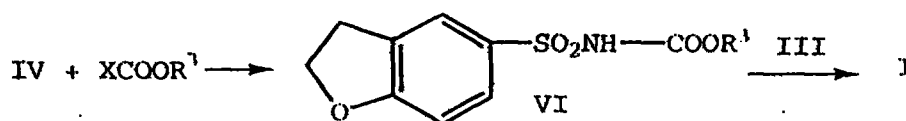
15 to provide the compound of Formula I. This reaction is generally conducted in a water miscible, non-reactive solvent such as tetrahydrofuran or acetone, in the presence of an acid scavenger such as sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium methoxide, sodium hydride and the like. Generally, an equimolar amount or
20 slight molar excess of the compound of Formula V is employed, although other ratios are operative.

The reaction may be performed at temperatures ranging from about 0°C to about 100°C, although the preferred temperature range is from about 20°C to about
25 30°C. At this preferred temperature the reaction is usually complete within about three hours.

Another method of preparing the compound of Formula I involves the reaction of the sulfonamide of Formula IV with an alkyl haloformate to provide carbamate
30 VI which is then reacted with the substituted aniline of Formula III to provide the product of Formula I

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where X is bromo or chloro and R³ is C₁-C₃ alkyl. The transformation of IV into VI is usually accomplished in a non-reactive solvent, such as acetone or methyl ethyl ketone, in the presence of an acid scavenger, such as an alkali metal carbonate, for example potassium carbonate. A molar excess of the haloformate is usually added, although other ratios are operative. This reaction is generally performed at a temperature from about 30°C up to about 100°C for a period of 1-6 hours to provide the desired intermediate of Formula VI. The intermediate of Formula VI and the substituted aniline of Formula III are then heated together in an inert high-boiling solvent, such as dioxane, toluene, or diglyme, at temperatures from about 50°C up to the reflux temperature of the mixture to provide the desired product I.

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.

This invention includes the pharmaceutically acceptable salts of the compound of Formula I. The compound of this invention can react with basic materials such as alkali metal- or alkaline earth metal hydroxides, carbonates, and bicarbonates including, without limitation, sodium hydroxide, sodium carbonate, potassium hydroxide, calcium hydroxide, lithium hydroxide, etc. to form pharmaceutically acceptable salts such as the corresponding sodium, potassium, lithium, or calcium salt. Nontoxic organic bases can also be used, including primary, secondary, and tertiary alkyl amines, such as methylamine, triethylamine, and the like.

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The terms and abbreviations used in the instant example have their normal meanings unless otherwise designated. For example, "°C" refers to degrees Celsius; "N" refers to normal or normality; "mmole" means millimole; "g" refers to gram; "ml" means milliliter; "M" refers to molar or molarity; and "NMR" refers to nuclear magnetic resonance.

The following examples further illustrate the preparation of the compound of Formula I. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

Example 1

2,3-Dihydrobenzofuran-5-sulfonamide

This compound was prepared essentially according to the teachings of J.A. Aikins, et al., European Patent Publication 254,577, published January 27, 1988. N,N-dimethylformamide (23.0 ml, 297 mmol) was cooled in an ice-salt bath and treated dropwise with sulfuryl chloride (20.0 g, 148 mmol) at such a rate that the reaction temperature was maintained below 15°C. To this was added 2,3-dihydrobenzofuran (17.0 g, 142 mmol), and after warming to room temperature, the reaction mixture was rapidly heated to 130°C over ten minutes, and then allowed to cool to room temperature. The reaction mixture was poured into water/ice/dichloromethane, 1/5/1 (700 ml), and the organic layer collected. The aqueous layer was diluted with water (100 ml) and extracted with dichloromethane. The combined organic phase was dripped into an ammonium hydroxide solution (3N, 250 ml), and allowed to stir overnight. Residual dichloromethane was removed by distillation and the resulting solid collected on a filter, washed with a small amount of water, followed by ether and then dried by aspiration to provide 12.8 g (45%) of the product.

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Analysis of the product gave the following results: mp = 163-164.5°C; ^1H NMR (300 MHz, d_6 -DMSO) δ 3.21 (t, 2H, $J=8.8$ Hz, CH_2), 4.60 (t, 2H, $J=8.8$ Hz, CH_2), 6.86 (d, 1H, $J=8.4$ Hz, Ar-H), 7.12 (bs, 2H, exchanges with D_2O , SO_2NH_2), 7.56 (d, 1H, $J=8.4$ Hz, Ar-H), 7.64 (s, 1H, Ar-H); IR(KBr) 3356, 3255, 1606, 1590, 1557, 1407, 1442, 1314, 1249, 1149, 1116, 1070, 982, 923 and 836 cm^{-1} ; FDMS (MeOH) m/e 200 (M^+).

Analysis for $\text{C}_8\text{H}_9\text{NO}_3\text{S}$:

10 Theory: C, 48.23; H, 4.55; N, 7.03; S, 16.09.
Found: C, 48.01; H, 4.71; N, 7.00; S, 16.36.

Example 2

15 N-[5-(2,3-dihydrobenzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea

A solution of the product of Example 1 (29.6 g, 148.6 mmol) in acetone (75 ml) and 1N aqueous NaOH (150 ml, 150 mmol) was treated dropwise with a solution of 3,4-dichlorophenylisocyanate (30.0 g, 154.8 mmol) in 75 ml of acetone over 20 minutes. After stirring two hours, the insoluble bis(3,4-dichlorophenyl)urea was removed by filtration and the resulting clear solution neutralized by the addition of 1N aqueous HCl (150 ml, 150 mmol). The slurry was stirred 30 minutes, filtered and washed with water (500 ml), ether (200 ml), ether/hexane (1/1, 100 ml) and hexane (200 ml). Vacuum drying gave 50.1 g of crude product which was slurried in ethanol (300 ml) for one hour, collected on a filter and washed with ether. This ethanol reslurry was repeated and provided 42.7 g (74%) of the title compound after vacuum drying (50°C).

35 Analysis of the product gave the following results: mp= 188-189°C; ^1H NMR (300 MHz, d_6 -DMSO) δ 3.25 (t, 2H, $J=8.8$ Hz, CH_2), 4.63 (t, 2H, $J=8.8$ Hz, CH_2), 6.92 (d, 1H, $J=8.6$ Hz, Ar-H), 7.25 (dd, 1H, $J=2.5, 8.8$ Hz, Ar-H).

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7.48 (d, 1H, J=8.8 Hz, Ar-H), 7.68 (d, 1H, J=2.5 Hz, Ar-H),
7.71 (d, 1H, J=8.5 Hz, Ar-H), 7.77 (s, 1H, Ar-H), 9.08 (s,
1H, exchanges with D₂O, ArNH), 10.85, (bs, 1H, exchanges
with D₂O, SO₂NH); IR(KBr) 3275, 1701, 1580, 1511, 1452,
5 1380, 12444, 1202, 1142, 1115, 1045, 896, 708 and 585 cm⁻¹;
FDMS (MeOH) m/e 386, 388, 390 (M⁺).

Analysis for C₁₅H₁₂Cl₂N₂O₄S:

Theory: C, 46.53; H, 3.12; N, 7.23.

Found: C, 46.77; H, 3.24; N, 7.26.

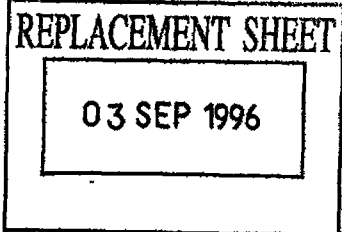
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The compound of Formula I has been shown to be
active against transplanted human tumors in vivo.
Accordingly, this invention provides a method of treating a
susceptible neoplasm in a mammal which comprises
15 administering to a mammal in need of said treatment an
effective amount of a compound of the Formula I.

To demonstrate the anti-tumor activity of the
compound of Formula I, the compound was tested in mice
bearing different xenograft tumors. Two of the tumor
20 models used for showing the anti-neoplastic activity of the
sulfonylurea of this invention were the human colon
xenografts, HXGC3 and VRC5. J.A. Houghton and D.M. Taylor,
British Journal of Cancer, 37:213-223 (1978). These tumors
were obtained from St. Jude's Children's Research Hospital
25 and have been widely used as human tumor models.

First passage tumors were 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
30 passage twice weekly in nude mice.

In the procedures utilized here, the tumor was
removed from passage animals and minced into 1- to 3-mm
cubic fragments using sterile techniques. Tumor pieces
were checked for sterility using both Antibiotic Medium 1
35 and Brain Heart Infusion (Difco, Detroit, Michigan). The



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tumor pieces were implanted into the recipient CD1 Nu/Nu mice subcutaneously in an axillary site by trochar.

Drug therapy on the appropriate schedule was initiated seven days after tumor implantation. The compound being tested was mixed with 2.5% Emulphor EL620 from GAF Corporation (1:40 dilution in 0.9% saline). The total dosage volume for each administration was 0.5 ml. All animals were weighed at the beginning and end of administration of the subject compounds. Food and water were provided ad libitum.

Each control group and each dosage level of the treated groups consisted of 10 mice selected at random from the pool of implanted animals. The formulations were administered orally by gavage with the use of an 18-gauge needle. Compounds were dosed daily for 10 days.

The tumor was measured five days after treatment ended with two dimensional measurements (width and length) of the tumor taken using digital electronic calipers interfaced to a microcomputer. J.F. Worzalla, et al., Investigational New Drugs, 8:241-251 (1990). Tumor weights were calculated from these measurements using the following formula:

$$\text{Tumor weight (mg)} = \frac{\text{tumor length (mm)} \times [\text{tumor width (mm)}]^2}{2}$$

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 is 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 by 100.

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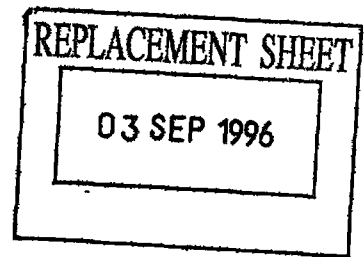
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The results of several experiments in mice bearing the HXGC3 and VRC5 human colon adenocarcinomas when the instant compounds were administered orally are provided in Table I. In the Table, column 1 describes the particular human tumor xenograft being studied; column 2 gives the dosage level of the compound of Formula I in milligrams per kilogram of body weight; column 3 describes the percent inhibition of tumor growth; and column 4 tallies the number of mice which died during the course of the experiment relative to the total number of animals in the group.

TABLE 1

	<u>Tumor</u>	<u>Dosage</u>	<u>Percent Inhibition</u>	<u>Toxic/Total</u>
15	HXGC3	1200	99	0/10
		600	98	0/10
		300	98	0/10
		150	81	0/10
20	VRC5	1200	100	0/10
		600	100	0/10
		300	98	0/10
		150	97	0/10

As a result of the high therapeutic index of the compound of Formula I, toxicological studies were performed to determine whether the compound of the current invention possessed the same adverse reaction profile of sulofenur. For these experiments thirty male Fischer 344 rats were administered varying dosages of a formulation containing the compound of Formula I. These formulations contained between 65 and 1000 mg of the active ingredient per kilogram of body weight of the rat, in combination with a suitable excipient, usually containing 10% acacia. The compounds were administered orally by gavage. The compounds were dosed daily for 14 days. All animals were



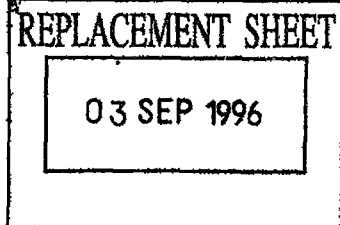
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weighed at the beginning and end of administration of the subject compounds. Food and water were provided ad libitum.

5 Upon completion of the testing regimen, morphological and hematological studies were performed. These studies indicated an absence of hemolytic anemia, which is the dose-limiting toxicity of sulofenur. Pathological studies performed indicate effectiveness against tissues with a high mitotic index, including lymph
10 nodes, thymus, gut, testis, and bone marrow, these changes being consistent with the tissue effects produced by other efficacious anticancer drugs. Unexpected tissue changes were not observed, demonstrating a more limited adverse reaction profile than other compounds of its class.

15 The compound of Formula I is an antineoplastic agent and the invention provides a method of treating susceptible neoplasms. In particular, the present compound is useful in treating solid tumors including carcinomas
20 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.

 The instant compound is usually administered in the form of a pharmaceutical composition, preferably
25 orally. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Accordingly, the present invention also encompasses pharmaceutical compositions which contain, as the active ingredient, the compound of Formula I associated
30 with a pharmaceutically acceptable carrier, diluent, or excipient. These formulations are useful in the treatment of mammals suffering from susceptible neoplasms.. The invention further comprises a method of treating susceptible neoplasms using compositions containing as an
35 active ingredient the compound of Formula I.



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5 In making the compositions of the present invention the active ingredient is 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. 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.

10 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 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.

15 Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, 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 methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed

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release of the active ingredient after administration to the patient by employing procedures well known in the art.

5 The compositions are preferably formulated in a unit dosage form, each dosage 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
10 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 compound is 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
15 weight. In the treatment of adult humans, the range of about 1 to about 50 mg/kg, in single or divided dose, 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,
20 including the condition to be treated, 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.

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Formulation Example 1

Hard gelatin capsules are prepared using the following ingredients:

5		<u>Quantity (mg/capsule)</u>
	N-[[(3,4-dichlorophenyl) amino] carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide	250.0
10	Starch	305.0
	Magnesium stearate	5.0

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

Formulation Example 2

A tablet formula is prepared using the ingredients below:

		<u>Quantity (mg/tablet)</u>
	N-[[(3,4-dichlorophenyl) amino] carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide	250.0
25	Cellulose, microcrystalline	400.0
	Colloidal silicon dioxide	10.0
30	Stearic acid	5.0

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

Formulation Example 3

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

5

Weight %

N-[[(3,4-dichlorophenyl) amino] carbonyl] 2,3-dihydrobenzofuran 5-sulfonamide 5

10 Lactose 95

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

15

Formulation Example 4

Tablets, each containing 60 mg of active ingredient, are prepared as follows:

20 N-[[(3,4-dichlorophenyl) amino] carbonyl] -2,3-dihydrobenzofuran-5-sulfonamide 60.0 mg

Starch 45.0 mg

25 Microcrystalline cellulose 35.0 mg

Polyvinylpyrrolidone (as 10% solution in water) 4.0 mg

30 Sodium carboxymethyl starch 4.5 mg

Magnesium stearate 0.5 mg

Talc 1.0 mg

35

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
5 with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are
10 then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

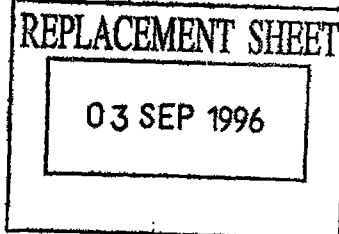
Formulation Example 5

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

20	N-[[{(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide	80.0 mg
	Starch	109.0 mg
	Magnesium stearate	<u>1.0 mg</u>
25	Total	190.0 mg

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



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Formulation Example 6

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

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N-[[(3,4-dichlorophenyl) amino] carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide 225 mg

Saturated fatty acid glycerides to 2,000 mg

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The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

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Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

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N-[[(3,4-dichlorophenyl) amino] carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide 50.0 mg

25 Xanthan gum 4.0 mg

Sodium carboxymethyl cellulose (11%)
Microcrystalline cellulose (89%) 50.0 mg

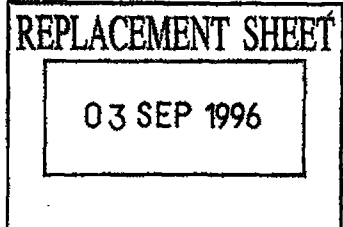
30 Sucrose 1.75 g

Sodium benzoate 10.0 mg

Flavor and Color q.v.

35

Purified water to 5.0 ml



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

Formulation Example 8

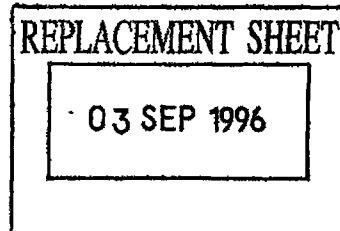
Capsules, each containing 150 mg of medicament, are made as follows:

N-[[[(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydrobenzofuran-5-sulfonamide	150.0 mg
Starch	407.0 mg
Magnesium stearate	<u>3.0 mg</u>
Total	560.0 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 560 mg quantities.



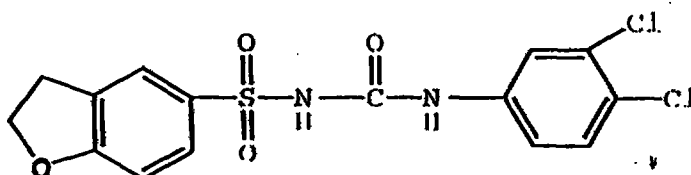
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We Claim:

1. A compound of the formula

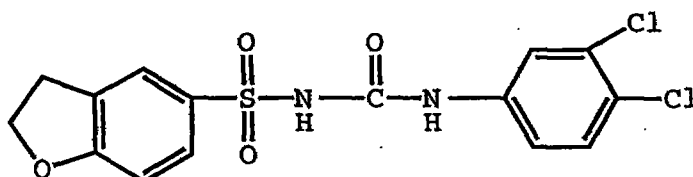
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or a pharmaceutically acceptable salt thereof.

2. A compound of the formula

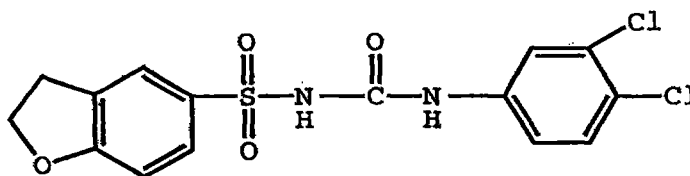
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or a pharmaceutically acceptable salt thereof, for use as an antineoplastic agent.

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3. A pharmaceutical formulation comprising, as an active ingredient, a compound of the formula



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or a pharmaceutically acceptable salt thereof, associated with one or more suitable pharmaceutically acceptable carriers, excipients or diluents therefor.

4. A process for preparing a compound of the formula

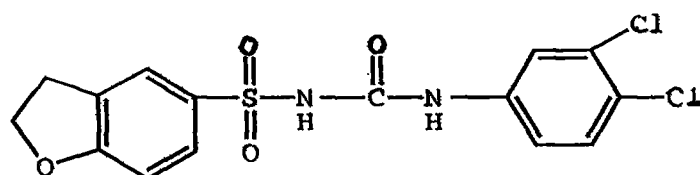
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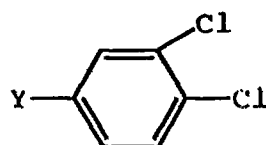
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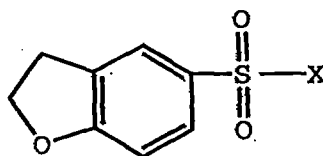


which comprises reacting with a compound of the formula



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in which Y is -NH_2 or -NCO , a sulfonyl compound of the formula



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in which X is -NCO , -NH_2 , or -NH-COOR in which R is $\text{C}_1\text{-C}_3$ alkyl, provided that if X is -NCO or -NH-COOR , then Y is -NH_2 and if X is -NH_2 then Y is -NCO .

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ANTITUMOR COMPOSITIONS AND METHODS OF TREATMENT

Abstract

5 This invention provides the use of N-[[[(3,4-
dichlorophenyl)amino]carbonyl]-2,3-dihydrobenzofuran-5-
sulfonamide, and pharmaceutically acceptable salts
thereof, in the treatment of susceptible neoplasms in
mammals. This invention further provides the novel
10 aforementioned compound and its pharmaceutical
formulations.