Bioorganic & Medicinal Chemistry Letters, Vol.2, No.9, pp. 987-992, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

ANTINEOPLASTIC BICYCLICSULFONYLUREAS

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(*Received* 16 *April* 1992)

Abstract: This manuscript summarizes the antitumor properties of 23 bicyclicsulfonylureas against subcutaneously implanted 6C3HED lymphosarcoma in C3H mice.

As part of a program designed to discover antineoplastic sulfonylureas, the compounds described in this article were synthesized and tested for antitumor activity against 6C3HED lymphosarcoma implanted subcutaneously in mice.[1] Percent inhibition is expressed as a ratio of tumor weight (as estimated by the dimensions of the intact tumor when measured by calipers) of the treated animals (p.o., daily x 8) versus the untreated control mice.[2] Other forms of drug adminstration were precluded by the solubility of these molecules in the media used for dosing the mice.

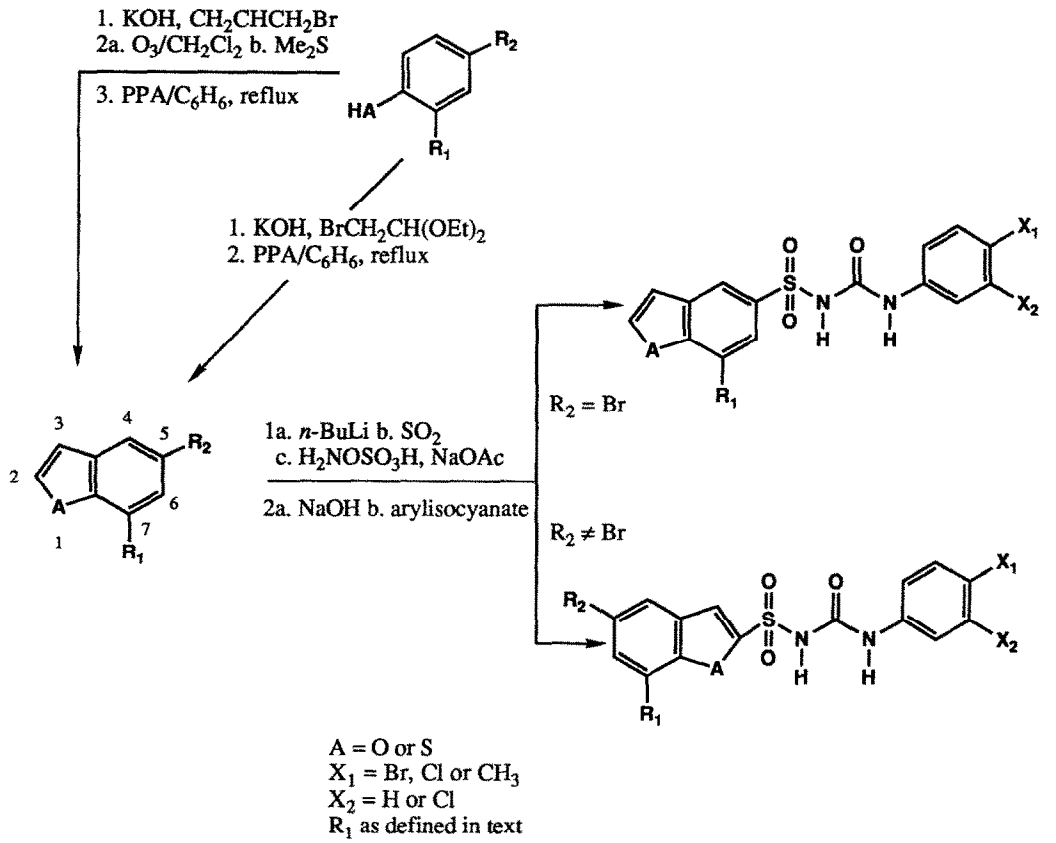
This protocol incorporates the oral bioavailability, the metabolic degradation, the pharmacokinetic properties, the phamacodynamic properties and the intrinsic activity of the molecule into a single parameter (i.e. percent inhibition of tumor growth). The advantages to this approach are obvious in that these variables are important attributes of a commercially useful anticancer drug. This strategy of drug discovery unfortunately does not allow the investigator to differentiate issues that impact the bioavailability of the drug versus the intrinsic activity of the molecule against the cell line being tested.

The heterogeneity of cancer as defined by the biochemical and morphological variability of the cell lines that are responsible for this disease made selection of the 6C3HED lymphosarcoma cell line as somewhat arbitrary with regard to discovery based on intrinsic activity of the molecule. This shortcoming will be compensated for by the evaluation of the antitumor properties of some of these molecules in a number of other cell lines (this class of antineoplastic compounds is not efficacious in the murine leukemia L1210 and P388 models).

The synthesis of compounds **1** - **4**, **7** and **12** - **22** is outlined in scheme I. The 2 position of the requisite halogenated benzofuran was deprotonated with lithium diisopropylamide instead of *n*-butyllithium for the synthesis of sulfonylureas **17** and **20**. Placement of a bromine atom at the 5 position of the aromatic ring results in a metallation versus deprotonation when this substrate is treated with *n*-butyllithium at -78 °C. In order to circumvent competitive deprotonation, the 2 position of 5-bromo-7-methoxybenzofuran was protected by a trimethylsilyl group that was removed with tetrabutylammonium fluoride after suitable functionalization of carbon 5 in the course of the synthesis of sulfonylurea **4**. The benzofuran required for the synthesis of **5** was obtained by PPA mediated cyclization of the alkylation product of chloroacetone and 4-bromophenol. The 2-methyl-5-bromobenzofuran required for the synthesis of sulfonylurea **6** was prepared by alkylation of 4-bromophenol with 2,3-dichloropropene, claisen rearrangement of the resulting allylphenylether followed by potassium hydroxide/*n*-butanol mediated ring closure. Compound **8** was prepared via benzothiophene-3-sulfonamide which was obtained

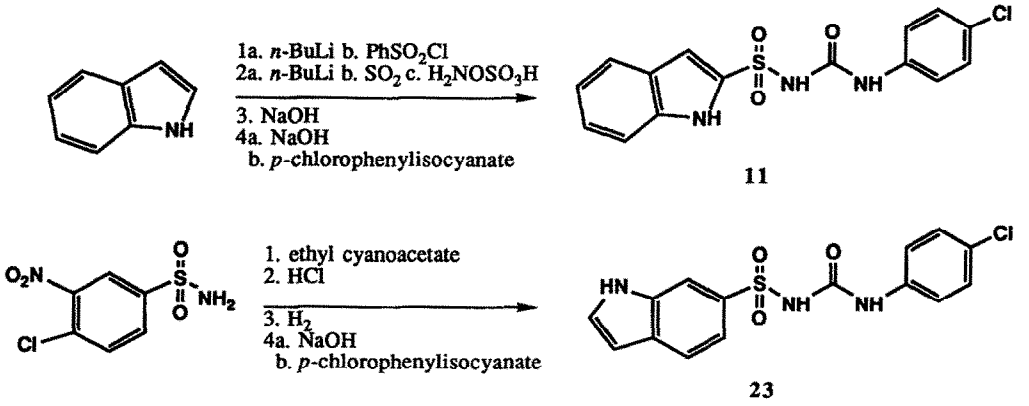
from chlorosulfonic acid mediated electrophilic aromatic substitution of benzothiophene after an ammonium hydroxide quench.

Scheme I

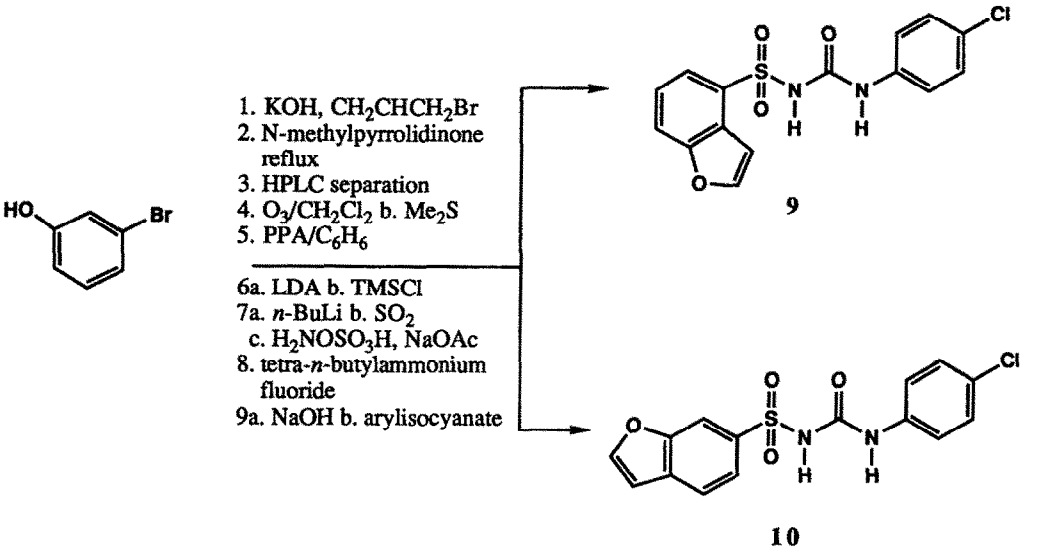


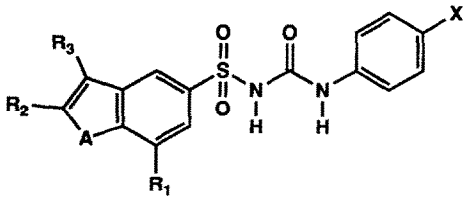
Scheme II outlines the synthesis of indolesulfonylureas **11** and **23.** As illustrated in scheme III benzofuransulfonylureas **9** and **10** are synthesized from 3-bromophenol. Unfortunately a preparative high pressure liquid chromatographic separation of the regioisomeric claisen rearrangement products (present in equimolar quantaties) is necessary.

Scheme II



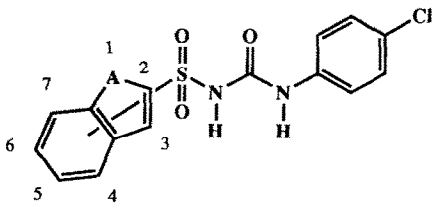
Scheme III





Entry	A	R_1	R_2	R_3	X	Percent[1] Inhibition	Number of Deaths / Number of Animals
1	O	H	H	H	Cl	100	5/8
2	O	H	H	H	CH_3	84	0/10
3	O	CH_3	H	H	Cl	89	1/10
4	O	OCH_3	H	H	Cl	51	0/10
5	O	H	H	CH_3	Cl	44	0/10
6	O	H	CH_3	H	Cl	57	0/10
7	S	H	H	H	Cl	44	0/8

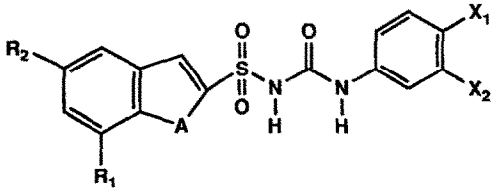
[1] Mice dosed p.o. daily x 8 at 150 mg/kg, except compound **7** where the mice were dosed p.o. daily x 8 at 80 mg/kg.



Entry	A	Substitution	Dose[1] (mg/kg)	Percent Inhibition	Number of Deaths / Number of Mice
8	S	3		43	0/10
9	O	4		84	1/10
10	O	6	160	100	1/10
11	NH	6		37	0/10

[1] Mice dosed p.o. daily x 8 at 150 mg/kg unless stated otherwise.

The antitumor activity of the benzofuransulfonylureas (**1-6, 9-10** and **12-20**) parallels the toxicity of the molecule in this murine model. The benzothiophene analogs (**7, 21** and **22**) of benzofuransulfonylureas **1, 19** and **12** were synthesized with the prospects of increasing the therapeutic window. A two fold decrease in potency was observed with the benzothiophene versus the benzofuransulfonylureas with a comparable therapeutic index. This prompted the synthesis of indolesulfonylureas **11** and **23**, which both showed disappointing levels of potency. A number of other naphthalene bioisoteres were also evaluated (e.g. thienothiophenes and thienopyridines) to address the toxicity problems. The thienopyridines synthesized were inactive, but the thienothiophenesulfonylureas were potent and even more toxic than the benzofuransulfonylureas. Determination of the variables contributing to the toxicity of this series of molecules such as metabolism/excretion of the cytotoxic agent and/or animal species dependency will provide additional insight into the pharmacology of these molecules.[3]



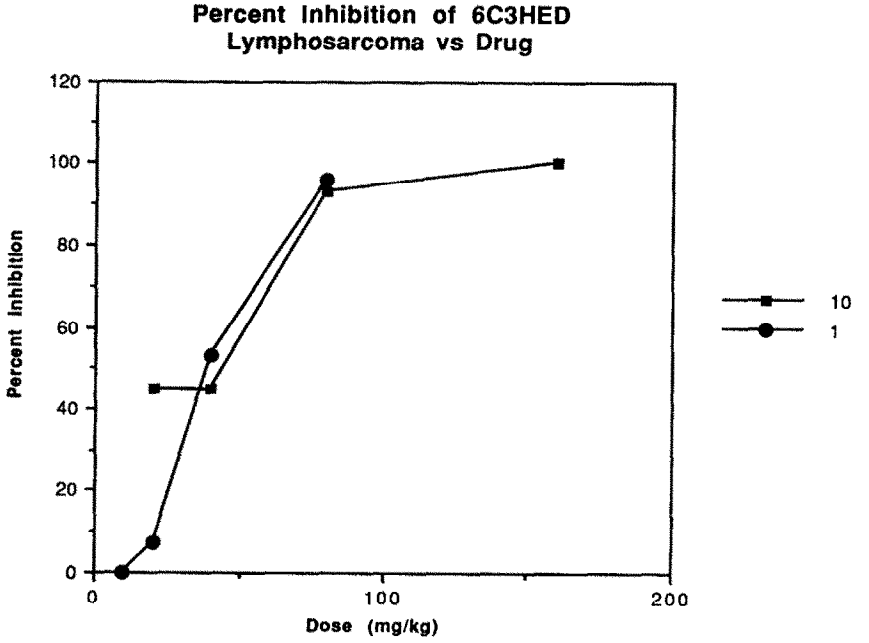
Entry	A	R_1	R_2	X_1	X_2	Percent[1] Inhibition	Number of Deaths / Number of Animals
12	O	H	H	Cl	H	84	4/10
13	O	H	H	CH_3	H	11	0/10
14	O	H	H	Cl	Cl	28	0/10
15	O	H	H	Br	H	48	1/10
16	O	CH_3	H	Cl	H	21	0/10
17	O	Br	H	Cl	H	18	0/10
18	O	H	OCH_3	Cl	H	25	1/10
19	O	H	CH_3	Cl	H	6	0/10
20[2]	O	H	Cl	Cl	H	40	0/8
21	S	H	CH_3	Cl	H	10	0/10
22	S	H	H	Cl	H	47	2/10
23	NH	H	H	Cl	H	26	0/10

[1] Mice dosed p.o. daily x 8 at 150 mg/kg unless stated otherwise.
[2] Compound tested as its sodium salt.

The plot below summarizes the dose response curve of the most potent antineoplastic agents described in this article, benzofuransulfonylureas **1** and **10**. Although in the 6C3HED lymphosarcoma model **1** and **10** are

approximately two fold more potent than N-(4-chlorophenyl)-N'-(5-indanesulfonyl)urea, both of these molecules have a narrow therapeutic index in this murine model.[4]

Elucidation of the mechanism of action of this class of novel antitumor agents will provide the option for determination of the intrinsic antineoplastic properties of the molecule being tested. Differentiation of this variable from the bioavailability issues will provide additional insight into the structure activity relationship of this class of molecules. A more important issue is the spectrum of activity of these molecule versus a variety of cell lines as discussed earlier and will play a critical role in the further development of these molecules as drug candidates.[5]



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