

## Synthesis, Characterization, and Antitumor Activity of Four Novel Sulphonamide compounds

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**Abstract:** A selected series of substituted sulphonamides were synthesized. These compounds were tested for potential antitumor activity against three of human tumor cell lines, Liver carcinoma cell line [HEPG2], Brain tumor cell line [U251] and Colon carcinoma cell line [HCT116]. Cytotoxic activity was assessed by SRB assay. The structures of the resulting compounds have been investigated by elemental microanalysis,  $^1\text{H}$  NMR and FT-IR analyses. These results indicate that the sulphonamide derivatives merit further investigation as potential antitumor drugs. The results indicated that the title compounds exhibit their highest cytotoxic effect on the Liver carcinoma cell line [HEPG2]. The thermodynamic parameters, the micellization free energy,  $\Delta_{\text{mic}}G^\circ$  and the standard free energy of solubilization,  $\Delta G_s^\circ$ , and the physical properties as surface tension, critical micelle concentration, cmc, and octanol/water partition coefficients,  $P_{\text{ow}}$ , for the prepared compounds were measured. In parallel studies,  $P_{\text{ow}}$  and cmc of the investigated compounds could be used as indication of the biological activities. Thus, the title compounds exhibit biological activities with the lowest Log  $P_{\text{ow}}$  values. In addition, the micellar solubilization is an important tool that finds numerous applications for dissolving hydrophobic drugs in organic and aqueous environments. In this work, we provide an insight into this subject in order to increase drug bioavailability

**Key words:** Antitumor activity, Cancer cell lines, Sulphonamide, Surface tension, Critical micelle concentration and Octanol/Water partition coefficients.

### INTRODUCTION

Sulpha drugs are a group of compounds used for eliminating a wide range of infections in human and other animal systems. Many chemotherapeutically important sulpha drugs, like sulphadiazine, sulphathiazole, sulphamerazine, and sulphonamides, possess  $\text{SO}_2\text{NH}$  moiety which is an important toxophoric function (Franklin A. Davis, 2006).

Drug absorption is influenced by many biological and physicochemical factors. The two most important physicochemical factors that affect both the extent and the rate of absorption are lipophilicity and solubility (Xue-Qing Chen, *et al.*, 2006). Similarly, Daniel *et al.*, have shown that the absorption rates of a series of cationic drugs in rat small intestine correlated well with their lipophilicity (Daniel, Y. Hung, *et al.*, 2001).

The membrane of the gastrointestinal epithelial cells is composed of tightly packed phospholipids interspersed with proteins. Thus, the transcellular passage of drugs depends on their permeability characteristics to penetrate the lipid bilayer of the epithelial cell membrane, which is in turn dependent on the lipophilicity of the drugs. The effect of lipophilicity on the absorption rates is best exemplified by the classical study of barbiturates conducted by Zhong (Zhong-Yue Sun, *et al.*, 2000).

The effects of lipophilicity on membrane permeability and first-pass metabolism appear to have opposing effects on the bioavailability. Thus, it is important to balance the effects of lipophilicity on membrane permeability and first-pass metabolism to improve bioavailability (Jiunn H. Lin, and Anthony Y.H. Lu, 1997).

In studies with structure related sulfonamides, Yuan *et al.* have shown that there was a strong correlation between plasma protein binding of the drugs and their lipophilicity (Yuan Wan Sun, *et al.*, 2006). Monish *et al.*, found that the volume of distribution increased with increasing lipophilicity when administering a series of sulfonyl drugs to selected tumor cell lines (Monish, Jain, *et al.*, 2004).

The influence of lipophilicity on the metabolic clearance of drugs is attributed mainly to the increased affinity of drugs for the enzymes (Monish Jain and Chul-Hoon Kwon, 2003).

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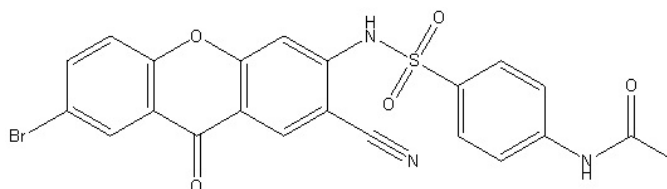
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Also, it should be pointed out that there are many factors, in addition to lipophilicity, that can influence first-pass metabolism. Solubility is an important determinant in drug absorption; a drug must be reasonably soluble in the aqueous environment to be absorbed properly, i.e. highly lipophilic and poorly soluble, resulting in poor bioavailability. Consequently, the drug Solubility will depend on its polarity: nonpolar molecules will be solubilized in the micellar core, and substances with intermediate polarity will be distributed. Micellar systems of drugs can increase their bioavailability, they can stay in the body (blood) long enough to provide gradual accumulation in the required area, and their sizes permit them to accumulate in areas with leaky vasculature (Kun-Ming Chen, *et al.*, 2004).

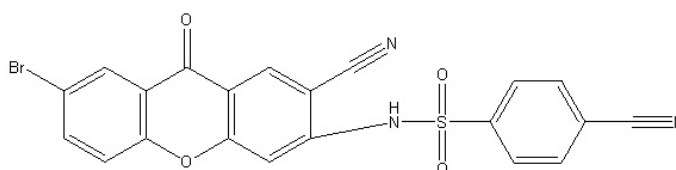
In general, micellization, CMC, plays an important role in contemporary pharmaceutical biotechnology, since it can control wetting, stability, bioavailability, among other properties (Carlota *et al.*, 2005).

In this study, the absorption of sulpha compounds ( $\Gamma_{\max}$ ) increased with decreasing lipophilicity ( $\log P_{ow}$ ) as a result of increased membrane permeability. Physical properties,  $\gamma_{cmc}$ ,  $cmc$ ,  $A_{\min}$ ,  $\Delta_{mic}G^{\circ}$ , and  $\Delta G_s^{\circ}$ , are useful tools for studying drug absorption and the relationships between drug intestinal permeability and lipophilicity to increase drug bioavailability. These physical properties have been used to explain the influence and main effects of surface activity on drug absorption. The study of the changes in absorption-partition relationships,  $P_{ow}$ , of the investigated compounds with decreasing lipophilicity may constitute a useful approach in the interpretation of their influences and the underlying mechanisms (Rege, R.D., 2002).

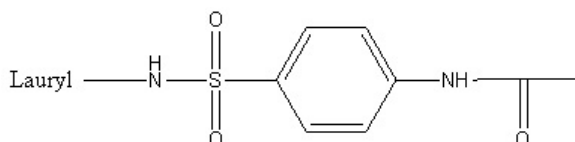
**Scheme 1 Structure of Tested Drugs:**



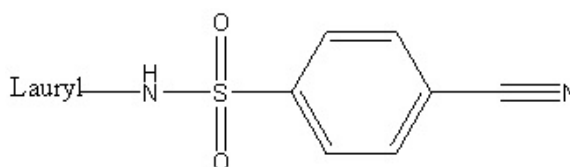
N-(7-bromo-2-cyano-9-oxo-9H-xanthene-3-yl)amino]sulfonyl}phenyl) acetamide [A]



N-(4-{(7-bromo-2-cyano-9-oxo-9H-xanthene-3-yl)-1-cyanobenzene-4-sulfonamide [B]



N-{4-[(laurylamino) sulfonyl] phenyl} acetamide [C]



N-lauryl [4-cyano-benzene] sulfonamide [D]

**MATERIALS AND METHODS**

**Materials:**

All reagents and solvents were of high purity and used as purchased without any further purification. N-acetyl sulfanilyl chloride, 4-cyanobenzene-sulfonyl chloride, 3-amino-7-bromo-9-oxo-9H-xanthene-2-carbonitrile

and dodecyl amine were supplied by Aldrich Co. All compounds studied, A, B, C and D, were synthesized according to published methods (A. Badawi *et al.*, 1983 and O.A. Fathalla *et al.*, 2005). Elemental analyses were performed using a Varian Elemental. FT-IR spectra were recorded on a Perkin Elmer-spectrum one spectrophotometer in the 4,000-400  $\text{cm}^{-1}$  range using KBr discs.  $^1\text{H-NMR}$  spectra was recorded on Varian Gemini 200 MHz instrument in  $\text{CDCl}_3$  solution. Surface tension measurements were performed using 8451 process tensiometer (Krüss) employing the Du-Nouy ring method. The cmc was determined by plotting the surface tension values versus concentrations. The antitumor screenings of the investigated compounds were carried out by the Pharmacology Unit, National Cancer Institute (NCI, Cairo University).

#### **Synthesis:**

##### ***N*-(4-[(7-bromo-2-cyano-9-oxo-9H-xanthene-3-yl)amino]sulfonyl)phenyl) acetamide (A):**

A mixture of N-Acetyl sulfanilyl chloride (0.01 mol), 3-Amino-7-bromo-9-oxo-9H-xanthene-2-carbonitrile (0.02 mol) and Pyridine (0.01 mol) in diethylether (50 ml) was heated under reflux for 4h. The solvent was then evaporated under reduced pressure and some cold water (20 ml) was added. The solution was extracted with ethyl alcohol (100 ml) to remove the excess of hydrochloric acid.

##### ***N*-(7-bromo-2-cyano-9-oxo-9H-xanthene-3-yl)-1-cyanobenzene-4-sulfon- amide (B):**

A mixture of 4-Cyanobenzene-sulfonyl chloride (0.01 mol), 3-Amino-7-bromo-9-oxo-9H-xanthene-2-carbonitrile (0.02 mol) and Pyridine (0.01 mol) in diethylether (50 ml) was heated under reflux for 4h. The solvent was then evaporated under reduced pressure and some cold water (20 ml) was added. The solution was extracted with ethyl alcohol (100 ml) to remove the excess of hydrochloric acid.

##### ***N*-(4-[(laurylamino) sulfonyl] phenyl) acetamide (C):**

A mixture of N-Acetyl sulfanilyl chloride (0.01 mol), lauryl amine (0.02 mol) and Pyridine (0.01 mol) in diethylether (50 ml) was heated under reflux for 4h. The solvent was then evaporated under reduced pressure and some cold water (20 ml) was added. The solution was extracted with ethyl alcohol (100 ml) to remove the excess of hydrochloric acid.

##### ***N*-lauryl [4-cyano-benzene] sulfonamide (D):**

A mixture of 4-Cyanobenzene-sulfonyl chloride (0.01 mol), lauryl amine (0.02 mol) and Pyridine (0.01 mol) in diethylether (50 ml) was heated under reflux for 4h. The solvent was then evaporated under reduced pressure and some cold water (20 ml) was added. The solution was extracted with ethyl alcohol (100 ml) to remove the excess of hydrochloric acid.

#### **Human Cell Lines:**

The antitumor screenings were carried out on three human tumor cell lines namely, Liver carcinoma cell line [HEPG2], Brain tumor cell line [U251] and Colon carcinoma cell line [HCT116].

#### **Sulforhodamine B (SRB) assay:**

NCI protocol for the 48h continuous drug exposure method, utilizing high initial inoculums of tumor cells, was used to assess the antitumor activity of the title drugs. The cells were inoculated into a series of standard 96-well micro-titer plates (10 000 cells/well) and pre-incubated for 24h. The test compounds were added after the pre-incubated period in four dilutions (0, 1, 2.5, 5, 10  $\mu\text{g/ml}$ ). The cells were incubated for 48h, then fixed with 10% trichloroacetic acid and washed several times with de-ionized water. The sulforhodamine B (SRB) was added and the cells were washed and dried. Cell viability was determined by solubilizing the bound dye and determining the concentration spectrophotometrically at 540 nm. Data were used for construction of concentration response curves and the determination of  $\text{IC}_{50}$  values (Zhong-You Sun, *et al.*, 2000).

#### **Physical Measurements:**

##### **Surface Tension and Critical Micelle Concentration:**

Surface tension values of the synthesized compounds solutions (A, B, C and D) were obtained at 30°C using Du-Nouy Tensiometer (Krüss K6 Type 4851) with a platinum ring. Apparent surface tensions were measured about five times for the sample within 2 min interval between each reading. The averages of five determinations were plotted against  $-\log C$  without any correction. The cmc values were determined from the plot of surface tension versus concentration (Hanan El-Sharkawy Ali, 2007).

**Methodology of Octanol/water partition coefficients ( $P_{ow}$ ) and Solubility:**

The volume ratio of octanol and water mixture is adjusted according to the expected value of  $P_{ow}$  ( $< 3$ ) (Carlota O. Rangel-Yagui, *et al.*, 2005).

- The concentration of the solute in the system should be less than 0.001 mol /litter in any single phase.
- Very pure octanol and water must be used.
- The system, usually in a separator funnel or similar device, is shaken gently until equilibrium is achieved. The system is then centrifuged to separate the two phases and break any emulsions.
- The two phases are then analyzed by an appropriate technique, UV-Vis, to determine solute concentrations. If possible, both phases are analyzed to achieve mass balance.
- To evaluate the concentration of solute in two phases, different moles of solute were used in the range of 0.01-0.03 mM, holding constant the value of the wavelength ( $\lambda$  of that sample), the corresponding absorbance were investigated.
- The partition coefficient,  $P_{ow}$ , of solute in two phases is described as

$$P_{ow} = \frac{\text{Concentration of solute in octanol phase}}{\text{Concentration of solute in aqueous phase}} \quad (1)$$

**RESULTS AND DISCUSSIONS**

Structure of the synthesized compounds was confirmed by elemental analysis which was satisfactorily for C, H, O, N, S and Br (Table 1). Also their IR measurements (Table 2) showed the characteristic N-H stretching vibrations around 3317-3445  $\text{cm}^{-1}$  regions, together with the symmetric and asymmetric vibrations of the  $\text{SO}_2$  group at 1021-1133  $\text{cm}^{-1}$ , and also at 2220  $\text{cm}^{-1}$  characteristic for the  $\text{C}\equiv\text{N}$ . Table 3 showed  $^1\text{H-NMR}$  measurements of the investigated compounds. All compounds exhibited the following signals: multiplet at 7.8-7.9 ppm (4H) characteristic for aromatic protons and the NH amide group appeared as singlet at 4 ppm for A and B whereas this group appeared as singlet at 2 ppm for C and D.

**Table 1:** Elemental analyses data for the title compounds.

Abbreviation	Yield(%) M.P( $^{\circ}\text{C}$ )	MF	MW	Analysis data calc / found%					
				C	H	O	N	S	Br
A	72 315	$\text{C}_{22}\text{H}_{14}\text{O}_3\text{N}_3\text{SBr}$	512	51.6	2.7	15.6	8.2	6.3	15.6
B	70 310	$\text{C}_{21}\text{H}_{10}\text{O}_4\text{N}_3\text{SBr}$	480	52.5	2.1	13.3	8.8	6.7	16.7
C	78 365	$\text{C}_{20}\text{H}_{34}\text{O}_3\text{N}_2\text{S}$	382	62.8	8.9	12.6	7.3	8.4	----
D	74 361	$\text{C}_{19}\text{H}_{30}\text{O}_2\text{N}_2\text{S}$	350	65	8.6	9.0	8	9	----

**Table 2:** Selected IR frequencies ( $\text{cm}^{-1}$ )

Cpd	$\nu(\text{CH}_2\text{-stret.})$	$\nu(\text{N-stret.})$	$\nu(\text{CH}_2\text{-stret.})$	$\nu(\text{C}\equiv\text{N})$	$\nu(\text{C}=\text{C})$	$\nu(\text{S}=\text{O})$	$\nu(\text{S-N})$
A	2960	3219-3330	3062	2220	1608	1021-1133	2394
B		3217-3327	3062	2221	1608	1021-1133	2403
C	2852	3445	2920	2045	1633	1032-1121	2369
D	2848	3437	2901	2059	1640	1110-1127	2364

**Table 3:**  $^1\text{H-NMR}$  data ( $\delta$ , ppm)

cpd	m,Ph (4H)	m,Ph (3H)	m,Ph (2H)	s,NH amide	s,NH- acetyl	s,CH <sub>3</sub> - acetyl	t,CH <sub>3</sub> - lauryl	m,CH <sub>3</sub> - CH <sub>2</sub>	m, CH <sub>2</sub> -N	m, CH <sub>2</sub> - CH <sub>2</sub> -N	m, (CH <sub>2</sub> ) <sub>n</sub>
A	7.9	7-7.8	6.4-7.7	4	8	2					
B	7.8-8.1	7-7.8	6.4-7.7	4							
C	7.9			2	8	2	0.96	1.33	3	1.6	1.29
D	7.8-8			2			0.96	1.33	3	1.6	1.29

**Adsorption Isotherms:**

As reported previously (Carlota O. Rangel-Yogui, *et al.*, 2005), surface activity can increase solubility of drugs in the aqueous media because of the micelle formation. Surface-active compounds can also disrupt membranes and can thus lead to toxicity.

The surface tension ( $\gamma_{cmc}$ ) as a function of log of the molar concentration of drug in aqueous solution at 30° C was measured. The adsorption amount of drugs was calculated according to the Gibb's model of 2:1 electrolytes:

$$\Gamma_{max} = -d\gamma/3 \times 2.303RT \, d\log C \tag{2}$$

Here  $\gamma_{cmc}$  is the surface tension in  $Nm^{-1}$ , and C (mol/l) is the total concentration of the corresponding surfactant in a system.  $\Gamma_{max}$  is the maximum adsorption rate in  $mol \, m^{-2}$ .  $\{d\gamma\}/\{d\log C\}$  is the maximal slope in each case. T is absolute temperature.  $R = 8.314 \, J \, mol^{-1} \, K^{-1}$  (Torehilin, V.P., 2001). The minimum surface area per adsorbed drug molecule,  $A_{min}$  ( $nm^2$ ) is obtained from the maximum adsorption rate by:

$$A_{min} = 10^{18} / N_A \Gamma_{max} \tag{3}$$

Here  $N_A$  is the Avogadro constant.

The values of the free energy of micellization,  $\Delta_{mic}G^\circ$ , give additional information on the thermodynamics of micellization of drug solutions. These values can be obtained from the following equations:

$$\Delta_{mic}G^\circ = -2.303 \, RT \log (cmc) \tag{4}$$

The thermodynamic parameters were calculated at each temperature according to Rosen (Rosen, M.J., 1978). Table 4 lists the values of the log  $P_{ow}$ , cmc, surface tension at cmc ( $\gamma_{cmc}$ ),  $\Gamma_{max}$  and  $A_{min}$  of drugs, as well as micellization free energy ( $\Delta_{mic}G^\circ$ ), and free energy of solubilization ( $\Delta G_s^\circ$ ).

**Correlation Between Surface Parameters and Solubility:**

Knowledge of the thermodynamic parameters controlling solubilization is helpful to a better understanding of the mechanisms involved in this process (C. Gambo, and A.F. Olea, 2006). In order to correlate between surface parameters and solubility, the micellization free energy was calculated and was presented in Table 4. For all compounds studied  $\Delta_{mic}G^\circ$  was negative indicating spontaneous solubilization. The lowest values were observed for C and D compounds, confirming that the solubilization process of these drugs is energetically more favorable than that of A and B drugs, due to the low cmc,  $\gamma_{cmc}$  values. However, because of the stronger tendency of the nonionic surfactant in forming micelles in solution, at the same surfactant concentration, the closed values nearly were obtained.

**Table 4:** log  $P_{ow}$ ,  $\gamma$ , cmc,  $\Gamma_{max}$ ,  $A_{min}$ ,  $\Delta_{mic}G^\circ$  and  $\Delta G_s^\circ$  values of synthesized drugs

Comp	Log $P_{ow}$	$\gamma$ ( $mN \, m^{-1}$ )	cmc (mol/l)	$\Gamma_{max}$ ( $mol \, m^{-2}$ )	$A_{min}(nm^2)$	$-\Delta_{mic}G^\circ$ (KJ/mol)	$-\Delta G_s^\circ$ (KJ/mol)
A	4.21	52	0.06	$6.9 \times 10^{-6}$	0.242	7.09	4
B	4.55	52.5	0.08	$8.3 \times 10^{-6}$	0.201	6.36	3.8
C	6.38	48	0.02	$4.88 \times 10^{-6}$	0.342	9.86	4.6
D	6.72	49	0.05	$5.86 \times 10^{-6}$	0.284	7.55	3.36

$P_{ow}$ : Octanol/water partition coefficient,

$\gamma_{cmc}$ : Surface tension of the drug solutions,

cmc: Critical micelle concentration of the drug solutions,

$\Gamma_{max}$ : The maximum adsorption rate,

$A_{min}$ : The minimum surface area per adsorbed drug molecule,

$\Delta_{mic}G^\circ$ : Micellization free energy, and  $\Delta G_s^\circ$ : Free energy of solubilization.

For series of compounds, the partition coefficient can provide an empiric handle in screening for some biological properties. For drug delivery, the lipophilic/hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption. Since biological membranes are lipoidal in nature, the rate of drug transfer for passively absorbed drugs is directly related to the lipophilicity of the molecule.

The partition coefficient is commonly determined using an oil phase of octanol or chloroform and water. Drugs having values of  $P_{ow}$  much greater than 1 are classified as lipophilic, whereas those with partition coefficients much less than 1 are indicative of a hydrophilic drug. Although it appears that the partition coefficient may be the best predictor of absorption rate, the effect of dissolution rate, pKa, and solubility on absorption must not be neglected (Carlota O. Rangel-Yagui, *et al.*, 2005).

Partition coefficient (oil/water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes. It is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium.

$$P_{o/w} = (C_{oil}/C_{water})_{\text{equilibrium}}$$

On the other hand, from the thermodynamic point of view, the solubilization can be considered as a normal partitioning of the drug between two phases, micelle and aqueous, and the standard free energy of solubilization ( $\Delta G_s^\circ$ ) can be represented by the following expression (Torchilin V.P., 2001):

$$\Delta G_s^\circ = -2.303 RT \log P \quad (1)$$

where  $R$  is the universal constant of the gases,  $T$  is the absolute temperature, and  $P$  is the partition coefficient between the micelle and the aqueous phase.

**Cytotoxicities of Target Compounds:**

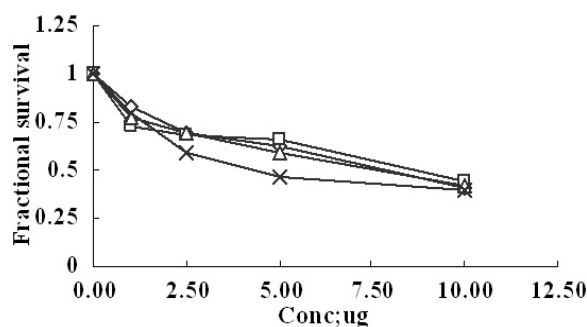
The comparative cytotoxicities of compounds A, B, C, and D were determined by SRB assay against Liver carcinoma cell line [HEPG2], Brain tumor cell line [U251] and Colon carcinoma cell line [HCT116] as shown in Table 5 & 6 and Figures 1-3.

**Table 5:** Cytotoxic activity of the drugs.

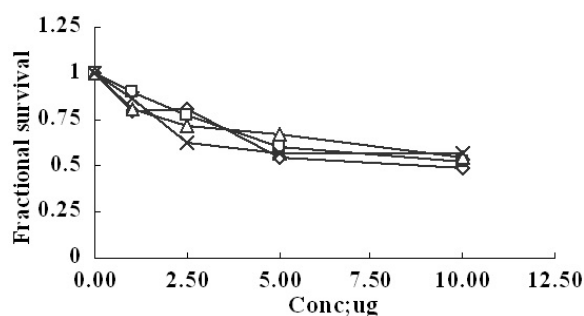
Cell line	HEPG2								
Cpd	A		B		C		D		
Conc	Y	SEM	Y	SEM	Y	SEM	Y	SEM	
0	1	0.037	1	0.037	10.037	1		0.037	
1	0.831	0.032	0.724	0.013	0.778	0.022	0.801	0.007	
2.5	0.692	0.036	0.681	0.01	0.695	0.014	0.591	0.027	
5	0.625	0.01	0.661	0.008	0.594	0.021	0.469	0.008	
10	0.41	0.032	0.447	0.008	0.424	0.003	0.399	0.007	
	U251								
0	1	0.167	1	0.167	1	0.167	1	0.167	
1	0.797	0.018	0.893	0.023	0.81	0.04	0.864	0.042	
2.5	0.81	0.039	0.769	0.026	0.715	0.017	0.626	0.011	
5	0.543	0.006	0.597	0.021	0.666	0.009	0.573	0.02	
10	0.492	0.003	0.528	0.006	0.544	0.018	0.566	0.017	
	Hct116								
0	1	0.036	1	0.036	1	0.167	1	0.036	
1	0.864	0.038	0.871	0.014	0.864	0.044	0.868	0.02	
2.5	0.837	0.02	0.828	0.009	0.593	0.036	0.745	0.01	
5	0.673	0.031	0.821	0.003	0.523	0.008	0.679	0.012	
10	0.579	0.018	0.807	0.006	0.466	0.017	0.641	0.009	

**Table 6:** Inhibitory effect of title compounds on tumor cells

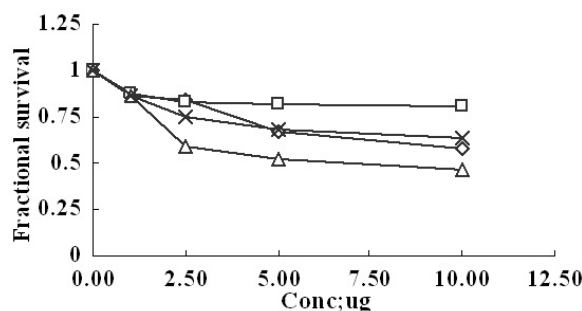
Compd	IC50 (Um)		
	HEPG2	U251	HCT116
A	7.73	8.52	----
B	8.79	----	----
C	7.6	----	5.64
D	7.65	----	----



**Fig. 1:** Cytotoxicity of A, B, C & D against Liver tumor cell line: ◇[A] □[B] △[C] \*[D].



**Fig. 2:** Cytotoxicity of A, B, C & D against Brain tumor cell line: ◇[A] □[B] △[C] \*[D].



**Fig. 3:** Cytotoxicity of A, B, C & D against Colon tumor cell line: ◇[A] □[B] △[C] \*[D].

**Liver Carcinoma Cell Line [HEPG2]:**

This work is concerned with investigation of the structure-lipophobicity relationships for sulphonamide drugs in Liver carcinoma cell line [HEPG2]. The liver is the main organ in the body for the conversion of drugs, toxins, and body products into more water-soluble forms so as to facilitate excretion by the kidney and biliary system (Deniel Y. Hung, *et al.*, 2001).

Compound C was slightly more cytotoxic against [HEPG2] than A,B and D. From Figure 4, the order of antitumor activity is: B < A < D < C. This order is as the same as that for their lipophilicity, a fact which shows that the lipophilicity influences the antitumor activity. The higher the lipophilicity, the higher antitumor activity is. It is interesting to note that B is considerably more cytotoxic than D. This result may suggest the importance of the aryl group for the cytotoxicity of the series. The diaryl sulphonamides were found to be better substrates compared to alkyl aryl sulphonamides in the presence of 4-cyanobenzene. The lipophilicity of a drug not only affects the membrane permeability, but the metabolic activity as well. In general, the lower the lipophilicity of a drug, the higher its permeability and the greater its metabolic clearance and thereby its first-pass metabolism. Differences in partition behavior of B and A compared to D and C may also contribute to the overall uptake and hence intracellular drug availability for cell damage. Moreover compound C showed a lower cmc (0.02mol/l) than the other compounds which appears probable to facilitate its combination with the tumor cell lipids and interferes with its enzyme balance (Akash Jain *et al.*, 2004).

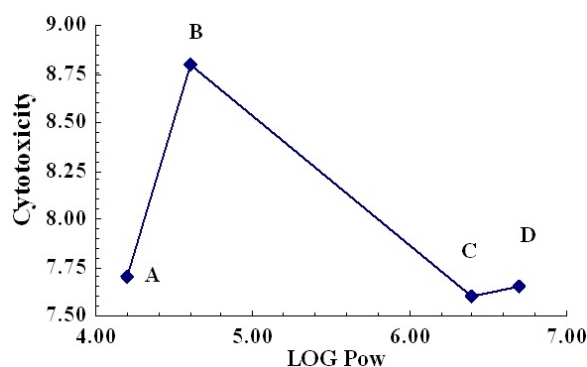


Fig. 4: Correlation between lipophilicity and cytotoxicity of A, B, C & D

All of the sulphonamides were quite potent and their cytotoxicities were nearly similar. This indicates that the sulphonamide group may also contribute to their cytotoxicities.

#### **Brain Tumor Cell Line [U251]:**

The brain is different from other organs in several aspects. One of the most important features is that the brain is completely separated from the blood by the blood-brain barrier (BBB). All organs are perfused by capillaries lined with endothelial cells that have small pores to allow for the rapid movement of drugs into the organ interstitial fluid from the circulation. However, the capillary endothelium of the brain lacks these pores and, therefore, drugs must cross the BBB and enter the brain by simple diffusion. Because most drugs cross the BBB by passive diffusion, lipophilicity is an important determinant of brain penetration. Lin and Lu found that the rate of brain uptake of drugs was dependent on their lipophilicity (Jiunn H. Lin, and Anthony Y.H. Lu, 1997). Many reports show a correlation between lipophilicity and brain penetration of drugs (Ward, S. and Back D.J., 1993).

The anticancer screening test showed that compound A was highly effective against Brain tumor cell line [U251]. The mechanism of antitumor activity of compound A might be similar to that of the antitumor drug E7820 chemically named N-(3-Cyano-4-methyl-1H-indol-7-yl)-3-cyanobenzene-sulfonamide. This sulfonamide derivative, E7820, is a unique inhibitor of tumor induced angiogenesis in mouse dorsal air sac model (Yasuhiro Funahashi *et al.*, 2002).

#### **Colon Carcinoma Cell Line [HCT116]:**

Colorectal cancer, also called colon cancer or bowel cancer, includes cancerous growths in the colon, rectum and appendix. It is the third most common form of cancer ([www.medicinenet.com/colon\\_cancer](http://www.medicinenet.com/colon_cancer)).

The anticancer screening test showed that compound C was highly effective against Colon carcinoma cell line [HCT116]. The higher lipophilicity of compound C affects its absorption, metabolism, its binding and distribution (Akash Jain *et al.*, 2004).

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