

**SYNTHESIS AND ANTIPROLIFERATIVE ACTIVITY OF ACRIDINE-SULFONAMIDE CONJUGATES**Feby Awad-Allah Ibrahim<sup>1</sup> and Ibrahim El Tantawy El Sayed<sup>2\*</sup><sup>1</sup>Menoufia University Hospital, Clinical Pathology Department, Shebin El Koom, Menoufia, Egypt.<sup>2</sup>Chemistry Department, Faculty of Science, Menoufia University, Shebin El-Koam, Menoufia, Egypt.**\*Corresponding Author: Prof. Dr. Ibrahim El Tantawy El Sayed**

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**ABSTRACT**

The present study describes the synthesis and antiproliferative evaluation of several acridine analogues carrying sulfonamide and thiouredoside chain at C-9 position. The key intermediate aminoacridines 5 were prepared by nucleophilic aromatic substitution ( $S_{NAr}$ ) of 9-chloroacridine 4 with 4,4'-diaminodiphenylmethane or p-phenylenediamine. The 9-amino derivatives 5 were further reacted with phenylisothiocyanate or arylsulfonfylchloride to afford the corresponding thiourea-, or acridine sulfonamide analogues 6 and 7 respectively. Some of the prepared derivatives showed a strong antiproliferative activity against the breast, colon and hepatocellular carcinoma cell lines. Among them, compounds 5b and 8b were the most potent with  $IC_{50}$  values 5.88, 8.30, 8.93 and 8.83, 14.51, 9.39 against breast, hepatocellular and colon carcinoma cell lines respectively.

**KEYWORDS:** 9-Chloroacridin, Sulfonamide, Synthesis, Antiproliferative Activity.**INTRODUCTION**

Acridine derivatives form an important class of heterocycles containing nitrogen compounds due to their broad range of pharmaceutical applications<sup>[1-5]</sup> Acridine derivatives are characterized by unique physical, chemical and biological activities, as well as industrial applications. It was reported that acridine derivatives have exhibited bioactivities such as anti-inflammatory,<sup>[6,7]</sup> anticancer,<sup>[8]</sup> antimicrobial,<sup>[9]</sup> antitubercular,<sup>[10,11]</sup> antiparasitic,<sup>[12]</sup> antimalarial,<sup>[13-15]</sup> antiviral,<sup>[16-17]</sup> and fungicidal activities.<sup>[18]</sup> Acridine derivatives have been shown to be effective as inhibitors of acetylcholinesterase.<sup>[19]</sup> Furthermore, acridines are used as dyes, fluorescent materials for visualization of biomolecules, and in laser technologies.<sup>[20]</sup> These properties of acridines are attributed to their semi-planar heterocyclic structure, which appreciably interacts with different biomolecular targets. Acridine derivatives are found in natural plants and various marine organisms.<sup>[21,22]</sup> Notably, the anticancer activity of acridine derivatives has attracted increasing interest. To date, many derivatives of acridine have been synthesized

and tested for anti-tumour activity. The unique planar structure allows acridine derivatives to act as DNA intercalators<sup>[23,24]</sup> and to inhibit topoisomerase or telomerase enzymes.<sup>[25-28]</sup> A variety of acridine derivatives have been synthesized; such as N-(2-(dimethylamino)ethyl)acridine-4-carboxamide (DACA) (1),<sup>[29-31]</sup> triazoloacridone (C-1305) (2)<sup>[32]</sup> and amsacrine (m-AMSA) (3)<sup>[33]</sup> (Fig.1) have entered clinical studies. Among them, m-AMSA (3) was the first synthetic drug exhibiting clinical efficacy as a topoisomerase inhibitor. Many m-AMSA derivatives (AHMA (4), D3CLP (5) (Fig.1) have been developed for stronger anti-cancer properties and removal of many harmful side effects.<sup>[31,34]</sup> Intermolecular interactions in acridine and acridinium derivatives determine their biological and physical properties including their chemiluminogenic abilities. Therefore, hydrogen bonding and  $\pi-\pi$  interactions within the Hirshfeld surface have been studied. Recently, Wera and co-workers reported the synthesis and structural investigations of some new acridine and acridinium derivatives.<sup>[35]</sup>



2H, NH<sub>2</sub>), 6.54 – 6.98 (m, 5H, 4Ar-H + NH-Ar), 7.47 – 7.54 (m, 8H, Ar-H). EIMS, m/z (C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>) calcd, 285.34 [M]<sup>+</sup>; found, 285.07.

**general procedure for synthesis of compounds (6a-b):**

Compound 5a (0.1 gm, 0.27 mmol) or 5b (0.1 gm, 0.35 mmol) and phenylisothiocyanate (1:1eq) were dissolved in 3-4mL chloroform and left them on stirring at room temp until the starting materials were consumed as monitored by TLC (2-8 day). The solvent was removed and diethylether was added to the remaining residue to give pure ppt, which was filtered and dried.

**1-(4-(4-(Acridin-9-ylamino)benzyl)phenyl)-3-**

**phenylthiourea(6a):** yield (0.107gm, 78.5%), as a red solid, m.p. 198°C, IR (KBr) cm<sup>-1</sup>: 3427 (NH), 3024 (CH-Ar), 2918 (CH-Alkane), 1633 (C=N), 1585(C=C -Ar), 1311(C-N, Aromatic amine), 1245(=C-N), 1110 (C=S). <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 300MHZ), δ(ppm): 3.53 (br.s, 2H, CH<sub>2</sub>), 7.08– 7.20 (m, 8H, Ar-H), 7.31– 7.44 (m, 5H, 5Ar-H), 7.76 – 7.85 (br.s, 1H, NH-Ar), 8.01– 8.04 (m, 8H, Ar-H), 10.76– 10.84 (br.s, 1H, -CS-HN-C<sub>6</sub>H<sub>5</sub>), 12.05 – 12.25 (br.s, 1H, -C<sub>6</sub>H<sub>4</sub>-HN-CS-). EIMS, m/z (C<sub>33</sub>H<sub>26</sub>N<sub>4</sub>S) calcd, 510.65 [M]<sup>+</sup>; found, 510.43.

**1-(4-(4-(Acridin-9-ylamino)phenyl)-3-**

**phenylthiourea(6b):** yield (0.093gm, 63.33%), as a brownish red solid, m.p. >250°C. IR (KBr) cm<sup>-1</sup>: 3427 (NH), 3030 (CH-Ar), 1630 (C=N), 1588(C=C-Ar), 1315(C-N, Aramine), 1243(=C-N), 1161(C=S). <sup>1</sup>H – NMR (DMSO-d<sub>6</sub>, 400MHZ), δ(ppm): 6.53 – 7.17 (m, 4H, Ar-H), 7.21 – 7.68 (m, 5H, Ar-H), 7.87 – 8.30 (m, 8H, Ar-H), 9.257 (br.s, 1H, NH-Ar), 10.06 (s, 1H, -CS-NH-C<sub>6</sub>H<sub>5</sub>), 10.10 (s, 1H, -C<sub>6</sub>H<sub>4</sub>-NH-CS-). EIMS, m/z (C<sub>26</sub>H<sub>20</sub>N<sub>4</sub>S) calcd, 420.53 [M]<sup>+</sup>; found, 419.14.

**general procedure for synthesis (7a-e) and (8a-d):**

Compound 5a (0.1 gm, 0.27 mmol) or 5b (0.1 gm, 0.35 mmol), arylsulfonyl chloride (1:1.2 eq) for 7 (a,b,c), 8(a,b,d), and (1:2.4 eq) for 7(d, e), 8(c) and 3 excess from triethylamine were dissolved in DMF. 7a was left on stirring at room temp for 5 day. 7b – 5e were refluxed until the starting materials were consumed as monitored by TLC (13-26h).

8a[at room temp., 8d], 8b [at room temp., 3d], 8c[reflux, 3d], 8d[at room temp, 20d]

After the completion of the reaction, the mix. was poured into ice to afford a solid product which was filtered and dried.

**N-(4-(4-(Acridin-9-ylamino)benzyl)phenyl)-2-**

**nitrobenzenesulfonamide (7a):** Yield (0.072gm, 48%) as a light orange solid, m.p. 172°C, IR (KBr) cm<sup>-1</sup>: 3431 (NH), 3038 (CH – Ar), 2924 (CH – Alkane), 1623 (C=N), 1511(C=C -Ar), 1258 (C-N Aromatic amine), 1160 (=C-N), 1509, 1346(N-O, asym, sym). <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 300MHZ), δ(ppm): 2.90 (s, 2H, CH<sub>2</sub>), 6.75 – 7.11 (m, 9H, 8Ar-H+NH-Ar), 7.56 – 8.03 (m, 12H, Ar-

H), 8.20 – 8.38 (m, 1H, HN-SO<sub>2</sub>). EIMS, m/z (C<sub>32</sub>H<sub>24</sub>N<sub>4</sub>SO<sub>4</sub>) calcd, 560.62[M]<sup>+</sup>; found, 560.07.

**N-(4-(4-(Acridin-9-ylamino)benzyl)phenyl)-4-**

**methylbenzenesulfonamide(7b):** Yield (0.08gm, 57%) as a yellow solid, m.p. >250°C. IR (KBr) cm<sup>-1</sup>: 3426 (NH), 3028 (CH-Ar), 2923 (CH-Alkane), 1620 (C=N), 1592 (C=C-Ar), 1418 (C-N-Ar amine), 1334, 1092(S=O, asym, sym), 1157(=C-N). <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 300MHZ), δ(ppm): 2.39 (br.s, 3H, CH<sub>3</sub>), 2.89 (br.s, 2H, CH<sub>2</sub>), 6.26 – 6.40 (br.s, 1H, NH-Ar), 6.96 – 7.24 (m, 8H, Ar-H), 7.62 – 7.64 (m, 12H, Ar-H), 7.98 – 8.05 (br.s, 1H, HN-SO<sub>2</sub>). EIMS, m/z (C<sub>33</sub>H<sub>27</sub>N<sub>3</sub>SO<sub>2</sub>) calcd, 529.65 [M]<sup>+</sup>; found, 529.34.

**N-(4-(N-(4-(4-(Acridin-9-**

**ylamino)benzyl)phenyl)sulfamoyl)phenyl)acetamide(7c):** yield (0.043gm, 28.67%) as a dark yellow solid, m.p. >250°C. IR (KBr) cm<sup>-1</sup>: 3434 (NH), 3037 (CH-Ar), 2922 (CH-Alkane), 1623 (C=N), 1511 (C=O), 1473(C=C-Ar), 1420, 1157(S=O asym, sym), 1260 (C-N, Ar amine), 1157(=C-N). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHZ), δ(ppm): 2.89 (m, 2H, CH<sub>2</sub>), 3.60 (br.s, H, NH), 3.84 (s, 3H, CH<sub>3</sub>), 6.61 – 6.65 (m, 4H, Ar-H), 6.81 – 6.85 (m, 4H, Ar-H), 6.95 – 7.11 (m, 4H, 4Ar-H), 7.63– 7.68 (m, 8H, Ar-H), 8.00 – 8.03 (m, 2H, HN-SO<sub>2</sub> +HN-CO). EIMS, m/z (C<sub>34</sub>H<sub>28</sub>N<sub>4</sub>SO<sub>3</sub>) calcd, 572.68[M]<sup>+</sup>; found, 572.39.

**N-(4-(4-(Acridine-9-ylamino)benzyl)phenyl)-4-(phenyldiazanyl)benzenesulfonamide(7d):**

yield (0.125gm, 75%), as an orange solid, m.p. >250°C. IR (KBr) cm<sup>-1</sup>: 3433 (NH), 3040 (CH-Ar), 2925 (CH-Alk), 1631 (C=N), 1590 (C=C-Ar), 1512 (N=N), 1439, 1119 (S=O, asym, sym), 1342 (C-N, Ar amine), 1165 (=C-N). <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 300MHZ), δ(ppm): 2.89(s, 2H, CH<sub>2</sub>), 6.58 – 6.65 (br.s, 1H, NH-Ar), 7.00 – 7.07 (m, 8H, Ar-H), 7.27 – 7.55 (m, 4H, Ar-H), 7.74 – 8.05 (m, 8H, Ar-H), 8.25 – 8.49(m, 5H, Ar-H), 10.80 – 10.90 (br.s, 1H, HN-SO<sub>2</sub>). EIMS, m/z (C<sub>38</sub>H<sub>29</sub>N<sub>5</sub>SO<sub>2</sub>) calcd, 619.73[M]<sup>+</sup>; found, 619.34.

**N-(4-(4-(Acridine-9-ylamino)benzyl)phenyl)-2,4,6-**

**triisopropylbenzenesulfonamide(7e):** yield (0.07gm, 78.5%), as an olive solid, m.p. 168°C. IR (KBr) cm<sup>-1</sup>: 3418 (NH), 3033 (CH-Ar), 2958 (CH-Alkane), 1672 (C=N), 1628 (C=C), 1472, 1158 (S=O, asym, sym), 1339 (C-N, Ar amine), 1262 (=C-N). <sup>1</sup>H – NMR (CDCl<sub>3</sub>, 300MHZ), δ(ppm): 1.25 – 1.35(br.s, 18H, 6CH<sub>3</sub>), 2.89 (m, 2H, CH<sub>2</sub>), 3.86-3.92 (m, 3H, CH), 6.65 – 7.23 (m, 11H, 10Ar-H + NH-Ar), 7.35 – 8.42 (m, 8H, Ar-H), 9.70 – 9.80 (br.s, 1H, HN-SO<sub>2</sub>). EIMS, m/z (C<sub>41</sub>H<sub>43</sub>N<sub>3</sub>SO<sub>2</sub>) calcd, 641.86[M]<sup>+</sup>; found, 641.71.

**N-(4-(Acridin-9-ylamino)phenyl)-2-**

**nitrobenzenesulfonamide(8a):** yield (0.078gm, 47%), as a brownish solid, m.p. >250°C. IR (KBr) cm<sup>-1</sup>: 3423 (NH), 3112 (CH-Ar), 1628 (C=N), 1584 (C=C-Ar), 1505, 1288 (N-O asym, sym), 1366, 1104 (S=O, asym, sym), 1254 (C-N). <sup>1</sup>H – NMR (DMSO-d<sub>6</sub>, 400MHZ), δ(ppm): 6.54 – 6.72 (m, 4H, Ar-H), 7.01 – 7.43 (m, 8H, Ar-H), 7.81 – 7.96 (m, 4H, Ar-H), 10.22 (br.s, 1H, NH-Ar),

10.84 (br.s, 1H, NH-SO<sub>2</sub>). EIMS, m/z (C<sub>25</sub>H<sub>18</sub>N<sub>4</sub>SO<sub>4</sub>) calcd,470.50[M]<sup>+</sup>; found, 470.05.

#### N-(4-(Acridin-9-ylamino)phenyl)-4-

**methylbenzenesulfonamide(8b):** yield (0.096gm, 62%), as a light brown solid, m.p. >250°C. IR (KBr)cm<sup>-1</sup>: 3324(NH), 3089 (CH-Ar), 1619 (C=N), 1589 (C=C-Ar), 1328, 1154 (S=O, asym, sym), 1258 (C-N). <sup>1</sup>H – NMR (DMSO-d<sub>6</sub>, 400MHZ),δ(ppm): 2.35 (s, 3H, CH<sub>3</sub>), 6.57 – 6.99 (m, 8H, Ar-H), 7.25 – 7.60 (m, 8H, Ar-H), 8.03(br.s, 1H, NH-Ar), 9.80 (br.s, 1H, NH-SO<sub>2</sub>). EIMS, m/z (C<sub>26</sub>H<sub>21</sub>N<sub>3</sub>SO<sub>2</sub>) calcd,439.53 [M]<sup>+</sup>; found,439.19.

#### N-(4-(Acridin-9-ylamino)phenyl)-4-

**(phenyldiazenyl)benzenesulfonamide(8c):** yield (0.158gm, 84.98%), as a brown solid, m.p. >250°C. IR (KBr)cm<sup>-1</sup>: 3420(NH), 3250 (CH-Ar), 1626 (C=N), 1510(C=C-Ar), 1470 (N=N), 1335, 1035 (S=O, asym, sym), 1158(C-N). <sup>1</sup>H – NMR (DMSO-d<sub>6</sub>, 400MHZ),δ(ppm): 6.37 – 6.94 (m, 4H, Ar-H), 7.00 – 8.22 (m, 17H, Ar-H), 10.16 (br.s, H, NH-Ar), 10.41(br.s, H, NH-SO<sub>2</sub>). EIMS, m/z (C<sub>31</sub>H<sub>23</sub>N<sub>5</sub>SO<sub>2</sub>) calcd,529.61[M]<sup>+</sup>; found,529.21.

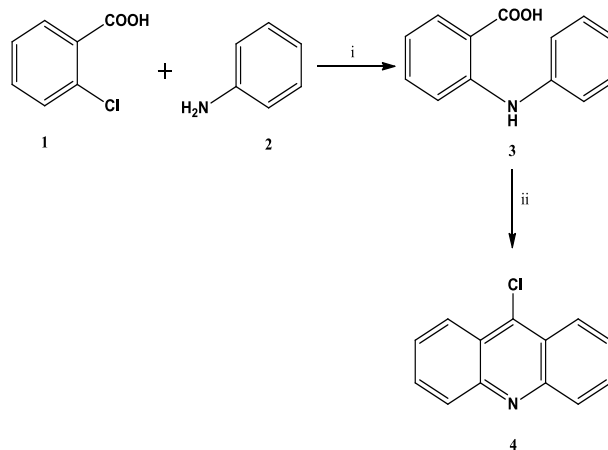
#### N-(4-(Acridin-9-ylamino)phenyl)-2,4,6-

**triisopropylbenzenesulfonamide(8d):** yield (0.078gm, 40%), as a light brown solid, m.p. >250°C. IR (KBr)cm<sup>-1</sup>: 3425 (NH), 3250 (CH-Ar),2958(CH-Alkane), 1619 (C=N), 1563(C=C), 1369, 1152 (S=O, asym, sym), 1259 (C-N). <sup>1</sup>H – NMR (DMSO-d<sub>6</sub>, 400MHZ ),δ(ppm): 2.43 (s, 18H, 6CH<sub>3</sub>), 2.87 – 2.91 (m, 3H, 3CH), 6.59 – 6.98 (m, 4H, Ar-H), 7.20 – 7.26 (m, 2H, Ar-H), 7.41 – 8.01 (m, 8H,Ar-H), 8.30(br.s, 1H, NH-Ar), 9.82 (br.s, 1H, NH-SO<sub>2</sub>). EIMS, m/z (C<sub>43</sub>H<sub>37</sub>N<sub>3</sub>SO<sub>2</sub>) calcd,551.74[M]<sup>+</sup>; found,551.42.

## RESULTS AND DISCUSSION

The synthesis of 9-chloroacridine was synthesized according to the literature procedure following scheme 1.<sup>[36]</sup> The synthesis included the reaction of o-

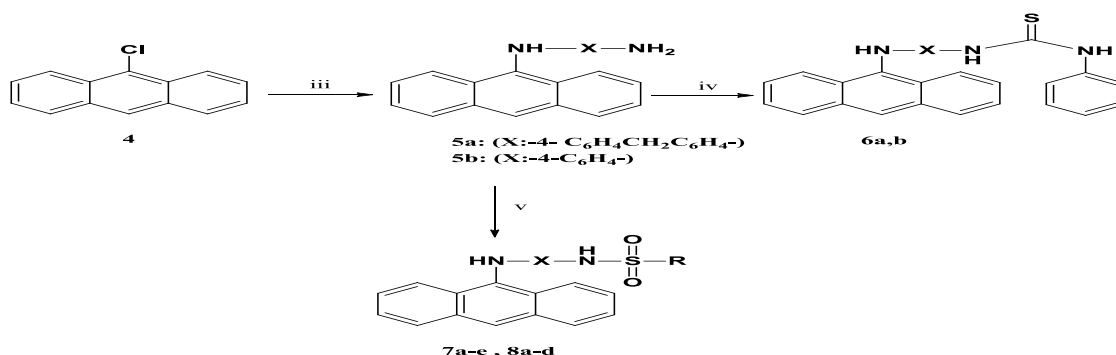
chlorobenzoic acid **1** with aniline **2** in DMF in presence of potassium carbonate anhydrous and copper metal as catalyst. After workup and crystallization in chloroform afforded the intermediate **3** with good yields as a pale yellow color. Compound **3** was then cyclized and dehydroxy chlorinated by phosphorus oxychloride under heating condition to give the key intermediate 9-chloroacridine **4** as a pale green powder in good yield.



**Scheme. (1): Synthesis of 9-chloroacridine.**

(i).K<sub>2</sub>CO<sub>3</sub>, Cu, and DMF, 130°C, 4-8h. (ii).POCl<sub>3</sub>,90-110°C, (reflux), 2-3h.

The key intermediate 9-chloroacridine was further diversified by nucleophilic aromatic substitution (S<sub>N</sub>Ar) reaction. Therefore, compound **4** was reacted with diamines such as p-phenylenediamine and bis (4-aminophenyl) methane in ethanol with presence of triethylamine as a base catalyst to afford the diaminosubstituted acridine derivatives in excellent yields as shown in Scheme 2.



Compound No.	R	Compound No.	R
7a	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -	7e	2,4,6-[(CH <sub>3</sub> ) <sub>2</sub> CH] <sub>3</sub> C <sub>6</sub> H <sub>3</sub> -
7b	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	8a	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -
7c	4-(CH <sub>3</sub> CO-NH)-C <sub>6</sub> H <sub>4</sub> -	8b	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -
7d	-C <sub>6</sub> H <sub>4</sub> -N=N-C <sub>6</sub> H <sub>5</sub>	8c	-C <sub>6</sub> H <sub>4</sub> -N=N-C <sub>6</sub> H <sub>5</sub>

**Scheme. 2:** (iii). H<sub>2</sub>N-R-NH<sub>2</sub>,EtOH,Et<sub>3</sub>N,Reflux(80°C),2.5-7h. (iv). Chloroform, Ph-N=C=S, stirring at room temp. (2-8 day). (v).DMF, Et<sub>3</sub>N, RSO<sub>2</sub>Cl (rt. or reflux).

The synthesis of 9-chloroacridine was shown in scheme 1, the reaction of *o*-Chloro benzoic acid with the anilines in DMF produced compound **3** which was refluxed in POCl<sub>3</sub> to give 9- Chloroacridine in Reaction of Chloroacridine and diamine in excess from Triethylamine which were refluxed in ethanol to give compounds **6a,b** as shown in Scheme 2.

Moreover, the compounds **5a,b** were reacted with phenyl isothiocyanate in chloroform at room temperature to give the thiourea derivatives **6a**, and **6b** in good yields. Furthermore, the reaction of aminoacridines **5** with arylsulfonyl chlorides in DMF in presence of excess triethylamine either on stirring at room temp. or under refluxed afforded the sulfonamide **7a-e**, and **8a-d** in good yields.

**Structures characterization:** The structure elucidation for all end products and their intermediates were performed using IR, <sup>1</sup>HNMR and mass spectroscopy. The IR showed a characteristic peaks at 3438, 3380 and 3392, 3240 cm<sup>-1</sup> which are characteristic for NH<sub>2</sub> and NH absorption in compounds **5a** and **5b** respectively. On the other hand, compounds **6a**, **6b** showed in characteristic peaks corresponds to NH absorption

respectively. Compounds **7a-7e** show a characteristic peak for NH absorption ranging from 3418 for **7e** and 3434 for **7c** respectively. Compounds **8a-8d** show a characteristic peak for NH absorption ranging from 3324 for **8b** and 3425 for **8d** respectively.

**Antiproliferative Activity:** In this investigation all compounds were examined *in vitro* for their anticancer activity against human hepatic (HepG2), colon (HCT-8) and breast (MCF-7) carcinoma cell lines. Screening for *in vitro* anticancer activity included measurement of inhibitory concentration IC<sub>50</sub> by using MTT colorimetric assay at 100 μM concentration.<sup>37</sup> The results shown in Table (1) indicated that compounds **5b**, **8b**, **6b** and **8a** exhibited significant anticancer activity against all three cancer cell lines. It is worth to note that **5b** and **8b** are the most active against HepG2. HCT-116, MCF-7 with IC<sub>50</sub> 8.30, 8.93, 5.88 and 14.51, 9.39, 8.83 μM respectively when compared with reference drug DOX used in the same assay. The obtained results also indicated that the incorporation of basic side-chains with para-phenylenediamine into acridines scaffold at C-9 position significantly increased the anticancer activity *in vitro* against human HepG2, colon (HCT-8) and breast (MCF-7) carcinoma.

**Table. 1: Antiproliferative activity induced by acridine analogues in human hepatic ((HepG<sub>2</sub>)), colon (HCT-8), and breast (MCF-7) carcinoma cell lines after 72 hs.**

Compounds	In vitro Cytotoxicity IC <sub>50</sub> (μM)•		
	HePG2	HCT-116	MCF-7
DOX	4.50±0.2	5.23±0.3	4.17±0.2
5a	45.34±3.6	51.44±4.1	64.43±4.5
5b	8.30±0.7	8.93±0.8	5.88±0.4
6a	36.71±3.5	47.21±3.9	40.93±3.8
6b	17.98±1.7	13.07±1.2	16.47±1.5
7a	62.32±4.4	72.16±4.7	88.36±5.1
7b	93.60±5.3	88.53±4.8	73.81±4.5
7c	31.07±3.1	40.61±3.7	29.08±2.7
7d	45.49±3.9	57.96±4.3	33.65±3.3
7e	55.35±4.2	66.67±4.5	50.76±4.0
8a	20.63±1.8	15.18±1.6	10.54±1.0
8b	14.51±1.4	9.39±0.9	8.83±0.9
8c	22.38±2.0	35.69±3.4	25.47±2.4
8d	23.13±2.2	29.85±2.8	19.69±1.7

•IC<sub>50</sub> (μM): 1 – 10 (very strong). 11 – 20 (strong). 21 – 50 (moderate). 51 – 100 (weak) and above 100 (non-cytotoxic), • DOX: Doxorubicin.

## CONCLUSION

In conclusion, a series of novel acridine bearing sulfonyl and thiourea moieties have been synthesized. The *in vitro* anticancer activity was evaluated *in vitro* in three cancer cell lines. The obtained data revealed that, among the tested compounds, four of them showed a strong activity.

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