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DESIGN AND SYNTHESIS OF SOME SUBSTITUTED ACRIDINE DERIVATIVES OF ANTICIPATED ANTITUMOR ACTIVITY

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في ظل البحث عن مركبات جديدة ذات فعالية بيولوجية ضد السرطان وفي ظل الفعالية المعروفة لمركبات الاكريدين كان من الاهمية ان يتم تشييد واختبار الفعالية البيولوجية ضد السرطان لمشتقات جديدة من نواة الاكريدين. وقد تم في هذا البحث تشييد ٤ سلاسل جديدة مشتقة من نواة الاكريدين كمشتقات الأكريدون ذات الإحلال فى الموقع الرابع **10a-h** ومشتقات الأكريدين ذات الإحلال فى الموقعين الرابع والتاسع **12a-k** ، **15a-k** ، **17a-j** كمركبات محتمل أن يكون لها فعالية ضد السرطان. تتضمن المجموعة الأولى ٤-مشتقات فينيل هيدرازينو كربونيل ميثيل ٩-اوكسو-١٠,٩- ثنائي هيدرواكريدين-٤-كربوكسيلات **10a-h**. تشمل المجموعة الثانية فينيل هيدرازينو كربونيل ميثيل ٩-(٤-مشتقات فينيل)امينواكريدين-٤-كربوكسيلات **12a-k**. بينما تشمل المجموعة الثالثة ٤-مشتقات فينيل كرباموبل ميثيل ٩-(٤-مشتقات فينيل)امينواكريدين-٤-كربوكسيلات **15a-k**. وتشمل المجموعة الرابعة فينيل كرباموبل ميثيل ٩-(٤-مشتقات فينيل)امينواكريدين-٤-كربوكسيلات **17a-j**. وقد تم إثبات التركيب البنائى للمركبات المشيدة من خلال التحليل الدقي للعناصر المكونة والتحاليل الطيفية المختلفة كالإشعة تحت الحمراء وأشعة الرنين النووى المغناطيسى وأشعة مطياف الكتلة. والمركبات المشيدة مشابهة لأخرى معروف لها فعالية ضد الأورام السرطانية وسبق تحضيرها من قبل و قد تم اختبار سبعة عشر مركب (**10a**، **10g** ، **10h** ، **12a** ، **12d** ، **12g** ، **12h** ، **12k** ، **15a** ، **15c** ، **15g**، **15h** ، **15k** ، **17a** ، **17f** ، **17g** ، **17j**) ضد سرطان الثدى و وجد لثمانية مركبات (**12g** ، **12h** ، **12k** ، **15g** ، **15h** ، **17f** ، **17g** ، **17j**) فعاليه ضد السرطان فى الإختبارات التى اجريت بمعهد الأورام جامعة القاهرة.

*Four series of new acridine derivatives of anticipated antitumor activity have been designed and synthesized. The first series belongs to 4-substituted phenylhydrazinocarbonylmethyl 9-oxo-9,10-dihydroacridine-4-carboxylate **10a-h**. The second series*

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*consists of phenylhydrazinocarbonylmethyl 9-(4-substituted phenyl)aminoacridine-4-carboxylate **12a-k**, while the third series comprises 4-substituted phenylcarbamoylmethyl 9-(4-substituted phenyl)aminoacridine-4-carboxylate **15a-k**. The fourth one belongs to phenylcarbamoylmethyl 9-(4-substituted phenyl)aminoacridine-4- carboxylate **17a-j**. The chemical structure of synthesized compounds was elucidated by spectral data and elemental analysis. Seventeen selected compounds (**10a**, **10g**, **10h**, **12a**, **12d**, **12g**, **12h**, **12k**, **15a, 15c, 15g, 15h, 15k, 17a, 17f, 17g** and **17j**) were tested against breast cancer cell line (MCF7) and eight compounds (**12g**, **12h**, **12k**, **15g**, **15h**, **17f**, **17g**, **17j**) were found to exhibit significant antitumor activity.*

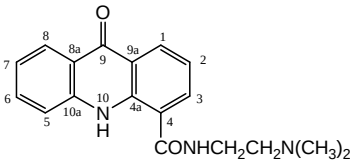
INTRODUCTION

The most important class of antitumor drugs is the DNA intercalating agents. The majority of DNA intercalating antitumor drugs has a common general structure, comprising a tri or tetracyclic chromophore to which is attached one or two flexible side chains bearing cationic charges[1]. Acridines represent one of the early and most thoroughly investigated compounds.

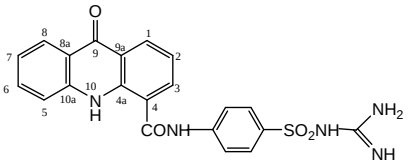
Recently, series of N-mustard derivatives of 9-anilinoacridine was synthesized and evaluated for cytotoxicity against human lymphoplastic leukemic cells (CCRF-CEM) in culture. The results showed that, all of the new N-mustard derivatives exhibited significant cytotoxic activity[2&3.] Furthermore, several mono and dinuclear isoquinolino[4,5-bc]acridine derivatives were designed and synthesized. Their DNA binding properties and antitumor activities were investigated and some of these compounds were found to be cytotoxic against P388 and A549[4&5].

Moreover, a series of N-substituted triamine linked acridine dimers was synthesized and tested for cytotoxic activity. Most acridine dimer derivatives revealed high potent *in vitro* cytotoxicity properties and DNA binding activity[6]. Telomere and telomerase are attractive targets for anticancer therapeutic[7]. Replacement of aniline substituent in BRACO-19, a potent G-quadreplex binding molecule and telomerase inhibitor, by benzylamino- groups resulted in enhanced quadreplex interaction[8].

The carbonyl containing chromophore **I**, although it is planar, it binds significantly less tightly, but appears to intercalate DNA. Results of *in vitro* cytotoxicity revealed that compound **I** showed potential interesting levels of cytotoxicity[9.] Furthermore, in our laboratories compound **II** was prepared in analogy to compound **I** substituting alkyl side chain amide by an aromatic one and was found to show antitumor activity[10].

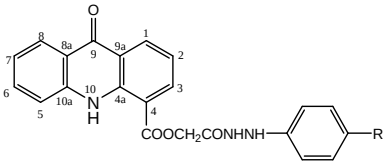


I



II

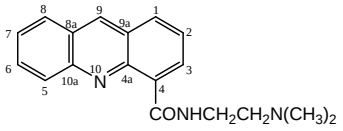
In our work, substitution of the carboxamide moiety of the acridone **II** by phenylhydrazinocarbonylmethyl carboxylate afforded **10**.



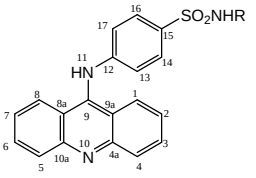
10

R=H, CH_3, Br, OCH_3, Cl, COOH, NO_2 and SO_2NH_2

Also, it was documented that N-[2-(dimethylamino)ethyl]acridine-4-carboxamide, DACA **III** showed a broad spectrum of *in vivo* activity against leukemia and solid tumors[9]. DACA **III** is known to be mixed topoisomerase I / II inhibitor[11]. In addition, compounds **IV** that were prepared in our laboratories, showed an interesting level of antitumor activity[12].



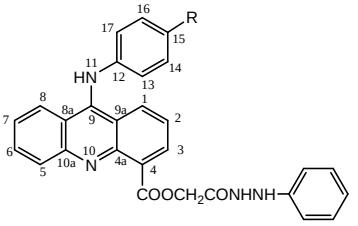
III



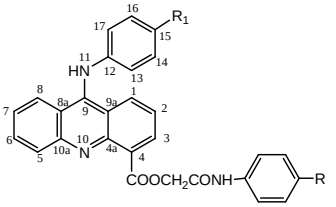
IV

R=H, amidino and different heterocycles

Accordingly, in the present work, compounds **12**, **15** and **17** are prepared as a structure hybrid of compounds **III** and **IV** by combining the characteristic feature of compound **III** having carbonyl function at position 4 of the acridine structure and the alignment of 9-anilino moiety in compound **IV** which is important in insertion into the minor groove.



12 R= H,CH_3,OCH_3,Cl,COOH,NO_2 and SO_2NH_2, $SO_2NHC(NH)NH_2$, SO_2NHR'(R′=different heterocycles)



15 R=R_1=H,CH_3,OCH_3,Cl,COOH,NO_2 and SO_2NH_2, $SO_2NHC(NH)NH_2$ SO_2NHR'(R′=different heterocycles)

17 R=H, R_1=CH_3,OCH_3,Cl,COOH,NO_2 and SO_2NH_2, $SO_2NHC(NH)NH_2$, SO_2NHR'(R′=different heterocycles)

EXPERIMENTAL

Torsion angle

A comparative measurement of torsion angles (10, 4a, 4, CO) and torsion angle (10a, 8a, 9, 9a) of the known active compounds **I, II** and that of the prepared compounds **10h** (Table 1), and torsion angles (10, 4a, 4, CO), torsion angle (9, 11, 12, 13) and torsion angle (9a, 9, 11, 12) of the well known active compounds **III** and **IV** and that of the prepared compounds **12g**, **15g** and **17f** (Table 2) revealed certain 3D structural similarities. A comparison of the electrostatic potentials of these compounds have been constructed and presented, where certain similarities of these maps of the active compounds and the corresponding designed and prepared compounds were shown. For sake of torsion angle study HyperChem software[13] had been used.

Table 1: Torsion angle results of compounds **I, II** and **10h**.

	compounds **I**	compounds **II**	compounds **10h**
Torsion angle 10a,8a,9,9a	11.2047^o	18.7147^o	14.5483^o
Torsion angle 10,4a,4,CO	1.91655^o	3.97261^o	1.59358^o

Table 2: Torsion angle results of compounds **III, IV, 12g, 15g** and **17f**.

	compounds **III**	Compounds **IV**	compounds **12g**	compounds **15g**	compounds **17f**
Torsion angle 10,4a,4,CO	2.77241^o	-	5.20834^o	3.96954^o	2.9716^o
Torsion angle 9, 11, 12, 13	-	18.0039^o	25.4523^o	22.1519^o	22.7416^o
Torsion angle 9a, 9, 11, 12	-	85.0268^o	72.5832^o	78.2066^o	77.7536^o

Procedure

First the structure models were generated, then fully minimized to obtain the optimum structures using RMS gradient of 0.1 and Fletcher-Reeves algorism. The electrostatic potential maps were constructed first by calculating the charges by Modified Neglect of Differential Overlap (MNDO) method. The potential maps were calculated, derived from a single point charge models at horizontal grid points = 100 and vertical grid points = 100 and

contour level of 50 and an increment of 0.1. The obtained isopotential surfaces were moved in space together with the underlying molecules in order to obtain maximum overlap.

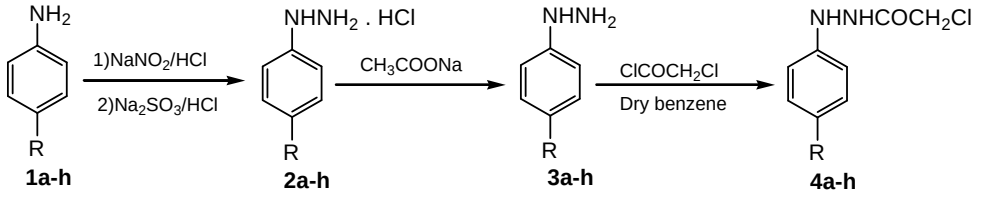
Chemistry

Melting points were determined by open capillary tube using IA 9100 MK/ Digital Melting Point Apparatus and were uncorrected. IR Spectra were recorded as KBr pellets on Bruker Vector 22. ^{1}H NMR spectra were recorded on Jeol FT 90Q, 300 MHz using DMSO-d_6 as solvent and were reported as δ values in ppm relative to tetramethylsilane (TMS) as internal standard. Electron Impact at 70 ev were performed with Finnegan MAT, SSQ 7000, Mass Spectrometers. Elemental analyses were carried out at the Microanalyical Center, Faculty of Science, Cairo University and National Research Center.

Syntheses of intermediate compounds **3b-h**[14-17], **4a-c**[18], **7**[19], **8**[19&20], and **9**[19] were according to the literature.

Chloroacetic acid, 2-(substituted phenyl)hydrazide 4d-h (Scheme 1, Table 3)

4-Substituted phenylhydrazine **3d-h** (12 mmol) was dissolved in the least amount of dry benzene, followed by dropwise addition of chloroacetyl chloride (2.5 ml, 15 mmol) under stirring at room temperature. The reaction mixture was stirred for further 10 min then ice-cold water (50 ml) was added while stirring. The obtained precipitate was filtered and crystallized from ethanol.



a R=H
b R=CH_3
c R=Br
d R= OCH_3
e R= Cl,
f R= COOH
g R= NO_2
h R=SO_2NH_2

Scheme 1

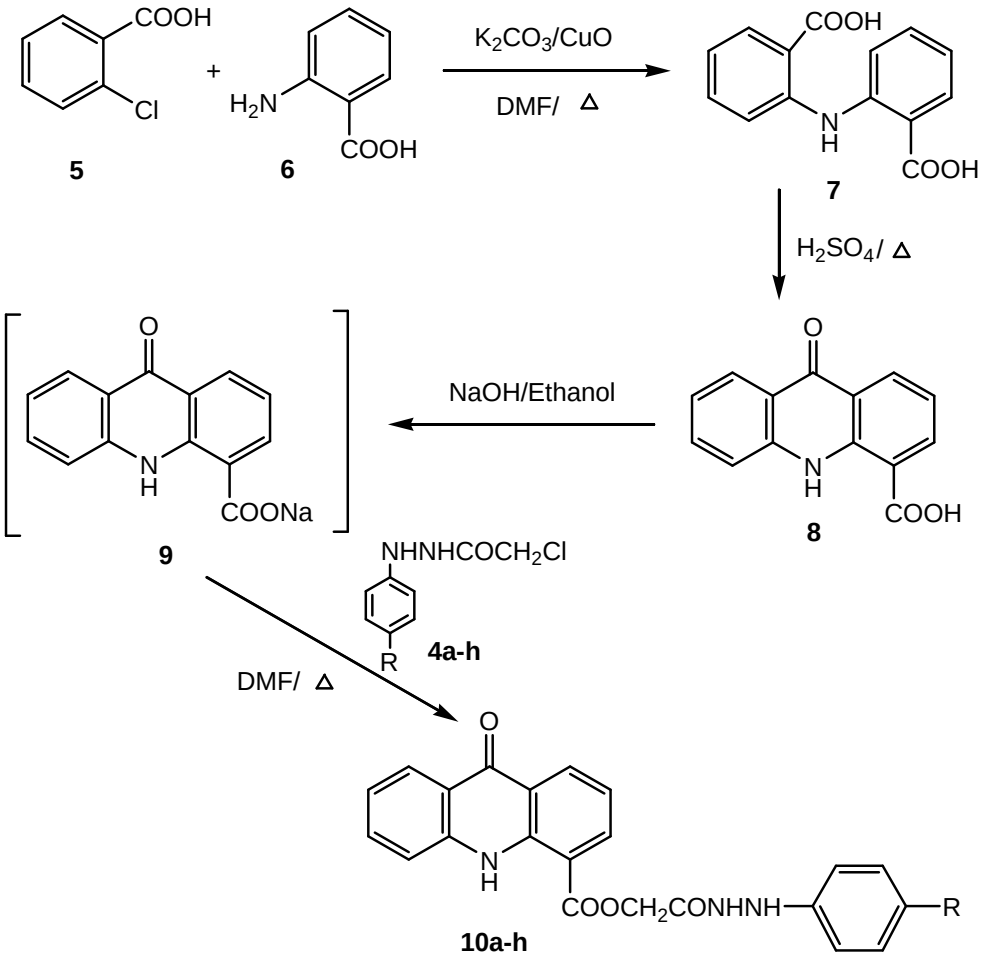
Table 3: Physical, analytical and IR spectral data for compounds **4d-h**.

Cpd. No.	R	Mol. Formula Mol. Wt.	m.p° Yield %	Micro analysis		IR cm^{-1}
				Calc.	Found	
4d	OCH_3	$C_9H_{11}ClN_2O_2$ 214.65	221-3 54	C 50.36 H 5.17 N 13.05	C 50.74 H 5.60 N 13.09	3446br (2NH), 3068 (CH arom.), 2964,2840(CH_3,CH_2),1652(CO), 1604, 1541, 1511 (NH, C=C).
4e	Cl	$C_8H_8Cl_2N_2O$ 219.07	192-3 68	C 43.86 H 3.68 N 12.79	C 43.70 H 3.90 N 12.81	3422,3206(2NH),2986,2929(CH_2), 1681(CO),1652, 1584, 1494 (NH, C=C).
4f	COOH	$C_9H_9ClN_2O_3$ 228.64	196-8 81	C 47.28 H 3.97 N 12.25	C 47.32 H 3.50 N 11.98	3353,3253(2NH),3023(CHarom.), 2668,2551(OHacid),1672(2CO), 1605, 1538, 1514 (NH, C=C).
4g	NO_2	$C_8H_8ClN_3O_3$ 229.62	170-2 77	C 41.85 H 3.51 N 18.3	C 41.76 H 3.63 N 18.13	3292(2NH),2958,2925(CH_2), 1662 (CO),1596,1507 (NH, C=C).
4h	SO_2NH_2	$C_8H_{10}ClN_3O_3S$ 263.71	203-5 82	C 36.44 H 3.82 N 15.93	C 36.76 H 3.96 N 15.69	3349,3292,3186(NH_2,2NH), 3093 (CHarom.),2960(CH_2),1653 (CO), 1605,1551(NH, C=C), 1294, 1157 (SO_2).

4-Substituted phenylhydrazinocarbonylmethyl 9-oxo-9,10-dihydroacridine-4-carboxylate 10a-h (Scheme 2, Table 4)

Acridone-4-carboxylic acid **8** (0.57 g, 2.4 mmol) was dissolved in 2 % NaOH solution (5 ml), followed by addition of ethanol (40 ml). The resulting solution was evaporated to dryness and the yellow residue of sodium 9-oxo-9,10-dihydroacridine-4-carboxylate **9** obtained was dried, then dissolved in DMF (10 ml) and treated with an equimolar amount of **4a-h** dissolved in DMF (10 ml). The reaction mixture was refluxed for 2 hrs, where NaCl was separated and filtered. The filtrate was poured onto ice-water (150 ml). The precipitate formed was filtered, washed with water, dried and crystallized from DMF/water.

10a ^{1}H NMR**:** δ = 5.11 (s, 2H, C<u>H</u>$_2$), 7.08-8.59 (m, 13H, arom. <u>H</u>, N<u>H</u>), 10.36 (s, 1H, N<u>H</u>), 11.6 (s, 1H, N<u>H</u>). **10f** ^{1}H NMR**:** δ = 5.13 (s, 2H, C<u>H</u>$_2$), 7.31-8.54 (m, 12H, arom. <u>H</u>, N<u>H</u>), 10.4 (s, 1H, N<u>H</u>), 11.6 (s, 1H, N<u>H</u>), 11.97(s, 1H, COO<u>H</u>). **10a** MS**:** m/z **(**%) M^+, 387, (0.36) and 221, (100). **10g** MS**:** m/z (%) M^+, 432 (0.23) and 221, (100).



R = H, CH_3, Br, OCH_3, Cl, NO_2, COOH, SO_2NH_2

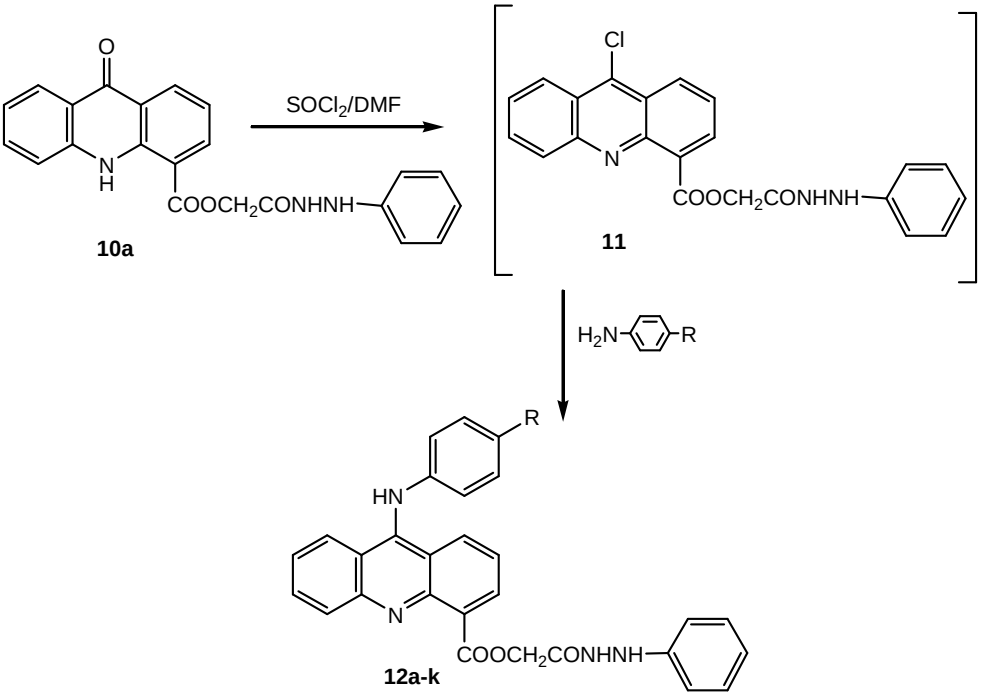
Scheme 2

Table 4: Physical, analytical and IR spectral data for compounds **10a-h**.

Cpd. No.	R	Mol. Formula Mol. Wt.	m.p° Yield %	Micro analysis		IR cm^{-1}
				Calc.	Found	
10a	H	$C_{22}H_{17}N_3O_4$ 387.4	259-61 92	C 68.21 H 4.42 N 10.85	C 68.27 H 4.50 N 10.45	3420, 3277 (3NH), 3064 (CH arom.), 2950, 2854 (CH_2), 1697br, 1619 (3CO),1594,1522(NH,C=C).
10b	CH_3	$C_{23}H_{19}N_3O_4$ 401.42	220- 1 41	C 68.82 H 4.77 N 10.47	C 68.53 H 4.51 N 10.44	3252,3193,3133(3NH),3082(CH arom),2928,2857(CH_3,CH_2),1738, 1689,1620 (3CO),1594,1565,1520 (NH, C=C).
10c	Br	$C_{22}H_{16}BrN_3O_4$ 466.29	141-3 45	C 56.67 H 3.46 N 9.01	C 56.75 H 3.64 N 9.25	3192br (3NH), 2926 (CH_2), 1685br, 1621(3CO),1595,1522 (NH,C=C).
10d	OCH_3	$C_{23}H_{19}N_3O_5$ 417.42	198- 9 43	C 66.18 H 4.59 N 10.07	C 66.40 H 4.63 N 10.42	3251, 3193, 3133 (3NH), 3081 (CH arom.),2963,2839(CH_3,CH_2), 1737, 1690, 1621(3CO),1594, 1565,1513(NH, C=C).
10e	Cl	$C_{22}H_{16}ClN_3O_4$ 421.84	165- 7 55	C 62.64 H 3.82 N 9.96	C 62.84 H 4.09 N 10.15	3251,3192,3132 (3NH),3082(CH arom),2931,2854(CH_2),1737,1689 ,1619 (3CO),1594,1565,1523(NH, C=C).
10f	COOH	$C_{23}H_{17}N_3O_6$ 431.41	265-7 74	C 64.04 H 3.97 N 9.74	C 64.23 H 4.35 N 9.92	3422,3226br (3NH),2924(CH_2), 2600br (OH acid),1687br,1622 (4CO),1595,1522(NH, C=C).
10g	NO_2	$C_{22}H_{16}N_4O_6$ 432.39	231-3 56	C 61.11 H 3.73 N 12.96	C 61.62 H 3.52 N 12.66	3228br (3NH), 2925 (CH_2), 1689br, 1621 (3CO),1593,1521 (NH,C=C).
10h	SO_2NH_2	$C_{22}H_{18}N_4O_6S$ 466.48	285-7 61	C 56.65 H 3.89 N 12.01	C 56.86 H 3.92 N 11.90	3351, 3288, 3220br (NH_2, 3NH), 3076 (CH arom.),1683br,1621 (3CO), 1596,1573, 1522(NH, C=C), 1324, 1147 (SO_2).

Phenylhydrazinocarbonylmethyl 9-chloroacridine-4-carboxylate 11 (Scheme 3)

A suspension of **10a** (1 g, 2.58 mmol) in thionyl chloride (5 ml) containing 2 drops dry DMF was heated gently under reflux until a homogenous solution was obtained, then for further 30 min. The solution was evaporated to dryness under vacuum on a water bath to remove excess thionyl chloride. The residue was azeotroped three times with dry benzene (5 ml each) where the last traces of thionyl chloride were removed. The residue was used directly for preparation of **12a-k**.



R = H, CH_3, OCH_3,Cl, NO_2, COOH, SO_2NH_2 , $SO_2NHC(NH)NH_2$, SO_2NHR'(R'=different heterocycles)

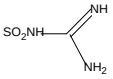
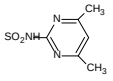
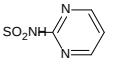
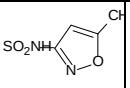
Scheme 3

Phenylhydrazinocarbonylmethyl 9-(4-substituted phenyl)amino-acridine-4-carboxylate 12a-k (Scheme 3, Table 5)

A suspension of the freshly prepared **11** in dry DMF (10 ml) was added to a stirred solution of equimolar amount of substituted amines (2.58 mmol) in dry DMF (10 ml) acidified with few drops of dilute HCl and stirring was continued for 30 min at room temperature. The resulting solution diluted with ice-water and neutralized by dropwise addition of dilute NH_4OH solution. The precipitate was filtered, washed with water, dried and crystallized from DMF/water.

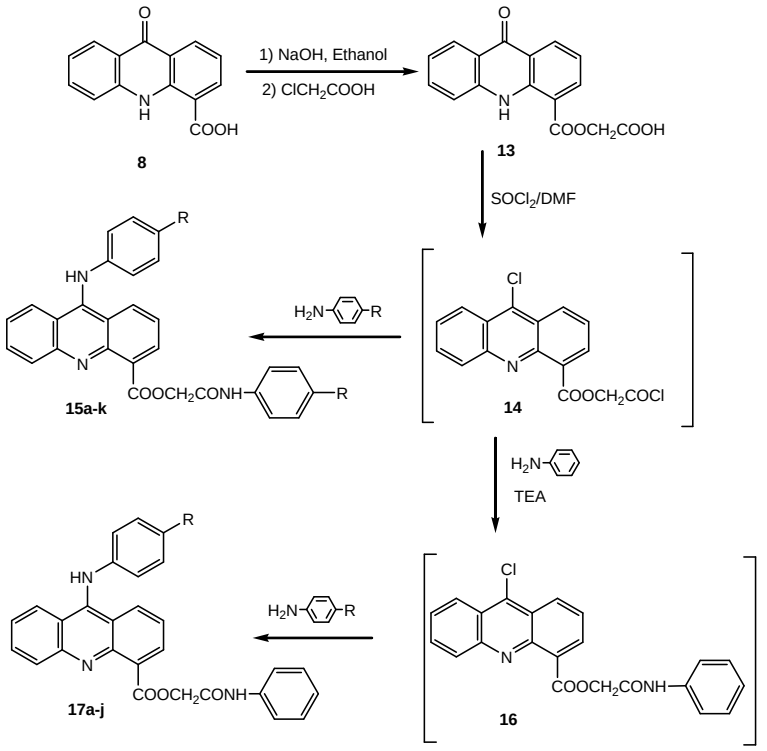
12a ^{1}H NMR**:** δ = 5.14 (s, 2H, C<u>H</u>$_2$), 7.09-8.62 (m, 18H, arom. <u>H</u>, N<u>H</u>), 10.30 (s, 1H, N<u>H</u>), 11.6 (s, 1H, N<u>H</u>). **12k** ^{1}H NMR**:** δ = 2.28 (s, 3H, C<u>H</u>$_3$), 5.14 (s, 2H, C<u>H</u>$_2$), 6.04-8.62 (m, 17H, arom. <u>H</u>), 10.38 (s, 1H, N<u>H</u>), 10.87 (s, 2H, 2N<u>H</u>), 11.63 (s, 1H, N<u>H</u>). **12a** MS**:** m/z (%) M^+**,** 462 **(**0.51**)** and 256, (100). **12b** MS**:** m/z (%) M^+**,** 476 **(**14.2**)** and 221, (100).

Table 5: Physical, analytical and IR spectral data for compounds **12a-k**.

Cpd. No.	R	Mol. Formula Mol. Wt.	m.p° Yield %	Micro analysis		IR cm^{-1}
				Calc.	Found	
12a	H	$C_{28}H_{22}N_4O_3$ 462.51	231-3 79	C 72.71 H 4.79 N 12.11	C 72.96 H 4.62 N 12.43	3318 (3NH),3051(CH arom.),2927 (CH_2),1645br (2CO),1618,1593, 1554,1522 (NH,C=C,C=N)
12b	CH_3	$C_{29}H_{24}N_4O_3$ 476.54	218-20 42	C 73.09 H 5.08 N 11.76	C 73.11 H 5.20 N 11.73	3310, 3257, 3123 (3NH),3052(CH arom.),2917,2860(CH_3,CH_2),1692, 1668 (2CO),1620,1594,1542,1518 (NH,C=C,C=N).
12c	OCH_3	$C_{29}H_{24}N_4O_4$ 492.54	197-9 54	C 70.72 H 4.91 N 11.38	C 70.22 H 4.54 N 11.50	3308,3258,3123 (3NH),3051(CH arom.),2953,2916 (CH_3,CH_2),1693, 1668 (2CO),1619,1594,1541,1518 (NH,C=C,C=N).
12d	Cl	$C_{28}H_{21}ClN_4O_3$ 496.95	161-3 57	C 67.67 H 4.26 N 11.27	C 68.19 H 4.29 N 11.59	3420br,3142 (3NH), 3055(CH arom.), 2929 (CH_2),1670br(2CO),1626, 1586,1557,1516 (NH,C=C,C=N).
12e	COOH	$C_{29}H_{22}N_4O_5$ 506.52	211-3 61	C 68.77 H 4.38 N 11.06	C 69.00 H 4.59 N 11.42	3255,3194,3133 (3NH),3082(CH arom.),2985,2946(CH_2),2646br, 2528br(OHacid),1737,1687(3CO), 1618,1593,1570,1522(NH,C=C,C=N)
12f	NO_2	$C_{28}H_{21}N_5O_5$ 507.51	203-5	C 66.27 H 4.17 N 13.8	C 66.45 H 4.33 N 13.89	3192br (3NH),2926(CH_2),1687br (2CO),1622,1596,1568,1522(NH, C=C,C=N).
12g	SO_2NH_2	$C_{28}H_{23}N_5O_5S$ 541.59	231-3 62	C 62.10 H 4.28 N 12.93	C 62.25 H 4.30 N 12.63	3284br (NH_2,3NH),3063(CH arom.), 2926(CH_2),1660br (2CO),1617,1578, 1520 (NH,C=C,C=N)1329,1151 (SO_2).
12h		$C_{29}H_{25}N_7O_5S$ 583.63	235-7 49	C 59.68 H 4.32 N 16.80	C 59.38 H 4.73 N 16.67	3424,3325,3209(NH_2,5NH),2926 (CH_2),1663br(2CO),1618,1581,1542 (NH,C=C,C=N), 1315,1132 (SO_2).
12i		$C_{34}H_{29}N_7O_5S$ 647.72	225-7 42	C 63.05 H 4.51 N 15.14	C 63.01 H 4.80 N 15.31	3423,3355,3259(4NH),3037(CH arom),2936,2870(CH_3,CH_2),1694, 1651(2CO),1622,1583,1494(NH, C=C,C=N),1324,1154 (SO_2).
12j		$C_{32}H_{25}N_7O_5S$ 619.66	241-2 52	C 62.03 H 4.07 N 15.82	C 61.93 H 3.82 N 15.61	3426,3365,3291,3249(4NH),3061 (CHarom.),2924(CH_2),1695br(2CO), 1625,1596,1575,1525 (NH,C=C, C=N),1342,1141(SO_2).
12k		$C_{32}H_{26}N_6O_6S$ 622.66	184-6 67	C 61.73 H 4.21 N 13.50	C 61.90 H 4.40 N 13.15	3423,3219br (4NH),3061(CH arom.), 2926(CH_3,CH_2),1655 br(2CO),1620, 1594,1520(NH,C=C,C=N),1326, 1157(SO_2).

9-Oxo-9,10-dihydroacridine-4-carbonyloxyacetic acid 13 (Scheme 4)

Acridone-4-caboxylic acid **8** (1.14 g, 4.8 mmol) was dissolved in 2 % NaOH solution (5 ml) followed by addition of ethanol (40 ml), the resulting solution was evaporated to dryness. The yellow residue of sodium 9-oxo-9,10-dihydroacridine-4-carboxylate **9** obtained was dried then dissolved in dry DMF (20 ml) and treated with equimolar amount of mono chloroacetic acid (0.45 g, 4.8 mmol) in dry DMF (10 ml). The reaction mixture was refluxed for 3 hrs, where NaCl separated out, then filtered and the filtrate was poured onto ice-water (150 ml). The yellow precipitate was collected, washed with water and dried to give (0.65 g, 91 %). The solid was crystallized from DMF/water. m.p. 315-7˚. IR (KBr): 3222br (NH), 2926 (CH_2), 2600 br (OH acid), 1722, 1688, 1622 (3CO), 1594, 1522 cm^{-1} (NH, C=C). ^{1}H NMR: δ = 4.93 (s, 2H, C<u>H</u>$_2$), 7.19-8.42 (m, 8H, arom.<u>H</u>, N<u>H</u>), 11.8 (s, 1H, COO<u>H</u>). MS: m/z (%) M^+, 297, (3.9) and 221, (100). Calculated $C_{16}H_{11}NO_5$ (297.27), calculated C 64.65, H 3.73, N 4.71. Found C 64.81, H 3.91, N 4.42.



R = H, CH_3, OCH_3,Cl, NO_2, COOH, SO_2NH_2, $SO_2NHC(NH)NH_2$, SO_2NHR'(R'=different heterocycles)

Scheme 4

2-Chloro-2-oxoethyl 9-chloroacridine-4-carboxylate 14 (Scheme 4)

A suspension of **13** (1 g, 3.36 mmol) in thionyl chloride (5 ml) containing drops of dry DMF was heated gently under reflux until a homogenous solution was obtained, then for further one hr. The solution was evaporated to dryness to remove excess thionyl chloride. The residue was azeotroped three times with dry benzene (5 ml each) where the last traces of thionyl chloride were removed. The residue was used directly for preparation of **15a-k** and **17a-j**.

4-Substituted phenylcarbamoylmethyl 9-(4-substituted phenyl) aminoacridine-4-carboxylate 15a-k (Scheme 4, Table 6)

A freshly prepared solution of **14** (3.36 mmol) dissolved in dry DMF (10 ml) was added to stirred solution of substituted amines (6.72 mmol) dissolved in dry DMF (10 ml) and stirring was continued for 30 min at room temperature. The reaction mixture was diluted with ice-water and neutralized by dropwise addition of dilute NH_4OH solution till complete precipitation. The precipitate was filtered, washed with water, dried and crystallized from DMF/water.

15a ^{1}H NMR**:** δ = 4.95 (s, 2H, C<u>H</u>$_2$), 7.28-8.59 (m, 17 H, arom.<u>H</u>), 11.44 (s, 1H, N<u>H</u>), 11.48 (s, 1H, N<u>H</u>). **15d** ^{1}H NMR**:** δ = 5.17 (s, 2H, C<u>H</u>$_2$), 7.34-8.58 (m, 16 H, arom.<u>H</u>, N<u>H</u>), 11.43 (s, 1H, N<u>H</u>). **15a** MS**:** m/z (%) M^+**,** 447, **(**17.24**)** and 295, (100). **15b** MS**:** m/z (%) M^+**,** 475, **(**51.44**)** and 221, (100).

Phenylcarbamoylmethyl 9-(4-substituted phenyl)aminoacridine-4- carboxylate 17a-j (Scheme 4, Table 7)

To the freshly prepared solution of **14** (2.17 mmol) dissolved in dry DMF (10 ml), a solution of aniline (0.2 g, 2.17 mmol) in dry DMF (10 ml) buffered with few drops of triethylamine was added and stirred for 10 min at room temperature. The resulting solution was then added to a solution of substituted amine (2.17 mmol) dissolved in DMF (10 ml) acidified with drops of dilute HCl and stirring was continued for further 30 min. The resulting solution was diluted with ice-water and neutralized by dropwise addition of dilute NH_4OH solution. The precipitate was filtered, washed with water, dried and crystallized from DMF/water.

17a ^{1}H NMR**:** δ = 2.12 (s, 3H, C<u>H</u>$_3$), 4.74 (s, 2H, C<u>H</u>$_2$), 6.46-8.60 (m, 16 H, arom.<u>H</u>), 10.39 (s, 1H, N<u>H</u>), 11.64 (s, 1H, N<u>H</u>). **17f** ^{1}H NMR**:** δ = 4.99 (s, 2H, C<u>H</u>$_2$), 7.29-8.53 (m, 18 H, arom.<u>H</u>, N<u>H</u>$_2$), 10.95 (s, 1H, N<u>H</u>), 11.97 (s, 1H, N<u>H</u>,). **17a** MS**:** m/z (%) M^+**,** 461, **(**0.87**)** and 221, (100). **17b** MS**:** m/z (%) M^+**,** 477, **(**4.19**)** and 221, (100).

Table 6: Physical, analytical and IR spectral data for compounds **15a-k**.

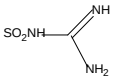
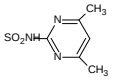
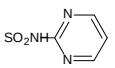
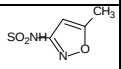
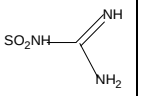
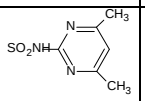
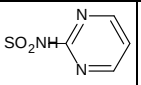
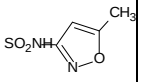
Cpd. No.	R	Mol. Formula Mol. Wt.	m.p° Yield %	Micro analysis		IR cm^{-1}
				Calc.	Found	
15a	H	$C_{28}H_{21}N_3O_3$ 447.5	240-2 81	C 75.15 H 4.73 N 9.39	C 75.34 H 4.40 N 9.26	3278br (2NH),3057(CH arom.), 2965,2924 (CH_2),1730,1691 (2CO),1653,1600,1555,1519(NH, C=C,C=N)
15b	CH_3	$C_{30}H_{25}N_3O_3$ 475.55	243-5 68	C 75.77 H 5.30 N 8.84	C 76.15 H 4.99 N 8.81	3423, 3303 (2NH), 3032(CH arom.), 2921, 2857(CH_3,CH_2), 1742, 1662 (2CO), 1619, 1586, 1559, 1514 (NH, C=C,C=N).
15c	OCH_3	$C_{30}H_{25}N_3O_5$ 507.55	208-9 71	C 70.99 H 4.96 N 8.28	C 70.66 H 5.21 N 8.42	3249 (2NH), 3061 (CH arom.), 2930, 2836 (CH_3,CH_2), 1742, 1667 (2CO), 1619, 1593, 1558, 1510 (NH, C=C,C=N).
15d	Cl	$C_{28}H_{19}Cl_2N_3O_3$ 516.39	181-2 63	C 65.13 H 3.71 N 8.14	C 64.98 H 3.55 N 7.83	3254br(2NH),3061(CH arom.), 2926(CH_2),1655br(2CO),1615, 1583,1557,1513(NH,C=C,C=N).
15e	COOH	$C_{30}H_{21}N_3O_7$ 535.51	226-8 79	C 67.29 H 3.95 N 7.85	C 67.59 H 3.94 N 7.85	3253,3133(2NH),3081(CHarom), 2670br (OH acid), 1736, 1688 (4CO),1615,1523(NH,C=C,C=N)
15f	NO_2	$C_{28}H_{19}N_5O_7$ 537.49	221-3 55	C 62.57 H 3.56 N 13.03	C 62.59 H 3.59 N 13.04	3252,3194(2NH),3082(CHarom), 2930(CH_2),1737,1689(2CO), 1621,1596,1567,1524(NH,C=C, C=N).
15g	SO_2NH_2	$C_{28}H_{23}N_5O_7S_2$ 605.65	245-7 76	C 55.53 H 3.83 N 11.56	C 55.40 H 3.70 N 11.46	3255br (2NH_2,2NH),3055(CH arom),2928(CH_2),1627br(2CO), 1587,1552,1518(NH,C=C,C=N), 1333,1155(SO_2).
15h		$C_{30}H_{27}N_9O_7S_2$ 689.73	251-3 69	C 52.24 H 3.95 N 18.28	C 52.31 H 4.21 N 18.01	3424,3197(2NH_2,6NH),1696br (2CO),1623,1591,1525 (NH, C=C,C=N),1271,1138 (SO_2).
15i		$C_{40}H_{35}N_9O_7S_2$ 817.91	220-2 61	C 58.74 H 4.31 N 15.41	C 58.71 H 4.20 N 15.01	3423,3355,3255,3194(4NH), 3075(CH arom.),2936,2870(CH_3, CH_2),1689,1651(2CO),1620, 1586, 1494 (NH,C=C,C=N), 1324, 1153(SO_2).
15j		$C_{36}H_{27}N_9O_7S_2$ 761.8	238-9 59	C 56.76 H 3.57 N 16.55	C 57.02 H 4.00 N 16.32	3425,3364,3248,3134(4NH), 3059 (CH arom.),2925(CH_2), 1688, 1636 (2CO),1573,1501 (NH,C=C,C=N),1341,1142(SO_2).
15k		$C_{36}H_{29}N_7O_9S_2$ 767.80	215-7 66	C 56.32 H 3.81 N 12.77	C 56.42 H 3.76 N 12.55	3259br(4NH),1691br(2CO), 1620,1594,1525(NH,C=C,C=N), 1326,1163 (SO_2).

Table 7: Physical, analytical and IR spectral data for compounds **17a-j**.

Cpd. No.	R	Mol. Formula Mol. Wt.	m.p° Yield %	Micro analysis		IR cm^{-1}
				Calc.	Found	
17a	CH_3	$C_{29}H_{23}N_3O_3$ 461.52	247-9 51	C 75.47 H 5.02 N 9.10	C 75.18 H 4.83 N 9.08	3423,3254 (2NH),3060(CHarom.), 2923(CH_3,CH_2),1742,1687(2CO), 1620, 1593, 1557, 1518 (NH,C=C, C=N)
17b	OCH_3	$C_{29}H_{23}N_3O_4$ 477.52	230-2 54	C 72.94 H 4.85 N 8.80	C 73.21 H 4.81 N 8.42	3446,3249(2NH),3062 (CHarom.), 2930 (CH_3,CH_2),1741,1667(2CO), 1619,1593,1557,1512(NH, C=C, C=N).
17c	Cl	$C_{28}H_{20}ClN_3O_3$ 481.94	190-2 41	C 69.78 H 4.18 N 8.72	C 69.36 H 4.61 N 8.72	3396,3276(2NH),3063(CHarom.), 2925(CH_2),1656br(2CO),1614, 1583,1558,1512 (NH, C=C,C=N).
17d	COOH	$C_{29}H_{21}N_3O_5$ 491.50	251-3 60	C 70.87 H 4.31 N 8.55	C 70.45 H 4.48 N 8.22	3352,3252(2NH),3023(CHarom), 2668br(OHacid),1735,1685(3CO), 1605,1543,1521 (NH,C=C,C=N).
17e	NO_2	$C_{28}H_{20}N_4O_5$ 492.49	236-8 45	C 68.29 H 4.09 N 11.38	C 68.24 H 4.00 N 11.58	3251,3194(2NH),3081(CH arom.), 1736,1689(2CO),1621,1595,1567, 1523 (NH, C=C,C=N).
17f	SO_2NH_2	$C_{28}H_{22}N_4O_5S$ 526.57	253-5 79	C 63.87 H 4.21 N 10.64	C 63.91 H 4.18 N 10.48	3285,3186(NH_2,2NH),3055(CH arom.),2927(CH_2),1657br(2CO), 1612,1556,1518(NH,C=C,C=N), 1330, 1149 (SO_2).
17g		$C_{29}H_{24}N_6O_5S$ 568.61	261-2 49	C 61.26 H 4.25 N 14.78	C 61.20 H 4.50 N 14.65	3422,3337,3204(NH_2,4NH),3062 (CHarom.),2926(CH_2),1742,1656 (2CO),1621,1593,1543(NH,C=C, C=N), 1336, 1135 (SO_2).
17h		$C_{34}H_{28}N_6O_5S$ 632.7	223-5 42	C 64.55 H 4.46 N 13.28	C 64.73 H 4.34 N 12.97	3423,3355,3255(3NH),3076(CH arom.),2936,2870(CH_3,CH_2),1737, 1689(2CO),1653,1621,1586,1494 (NH,C=C,C=N),1324,1154 (SO_2).
17i		$C_{32}H_{24}N_6O_5S$ 604.65	250-2 43	C 63.57 H 4.00 N 13.90	C 63.47 H 3.81 N 13.63	3425,3361,3251(3NH),3082 (CH arom.),1737,1690 (2CO),1621, 1594,1571,1527(NH,C=C,C=N), 1326,1142 (SO_2).
17j		$C_{32}H_{25}N_5O_6S$ 607.65	216-8 53	C 63.25 H 4.15 N 11.53	C 63.35 H 4.25 N 11.48	3422br(3NH),3061(CHarom.), 2925(CH_3,CH_2),1741,1657(2CO), 1619,1582,1515(NH,C=C,C=N), 1332,1161(SO_2).

Antitumor Screening

Seventeen selected compounds **10a, 10g, 10h, 12a, 12d, 12g, 12h, 12k, 15a, 15c, 15g, 15h, 15k, 17a, 17f, 17g** and **17j,** were tested against the tumor cell line MCF7 (Breast carcinoma cell line) using the method of Skehan et al[21] at National Cancer Institute, Cairo University.

Procedure

Cells were plated in 96-multiwell plate (10^4 cells/well) for 24 hrs before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentration of the compounds under test (0, 1, 2.5, 5 and 10 µg/ml) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 hr at 37º and in atmosphere of 5% CO_2. After 48 hrs, cells were fixed, washed and stained with sulforhodamine B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tri EDTA buffer. Color intensity was measured in an ELISA reader. The relation between the surviving fraction and drug concentration was plotted to get the survival curve of each tumor cell line after the specified compound Fig. 1-17.

IC_{50} of the tested compounds were illustrated in Table 8.

Table 8: IC_{50} of tested compounds for antitumor screening.

Fig.	Cell line MCF7	
	Compound	IC_{50}
1	**10a**	-ve
2	**10g**	-ve
3	**10h**	-ve
4	**12a**	-ve
5	**12d**	-ve
6	**12g**	9.67
7	**12h**	10
8	**12k**	4.85
9	**15a**	-ve
10	**15c**	-ve
11	**15g**	9.53
12	**15h**	7.46
13	**15k**	-ve
14	**17a**	-ve
15	**17f**	4.75
16	**17g**	9.50
17	**17j**	7.72

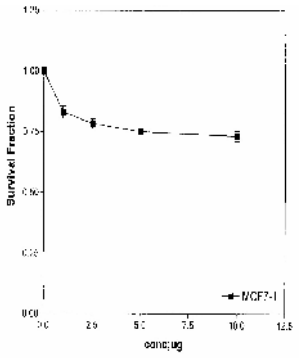


Fig. 1: Cytotoxic activity of compound **10a**.

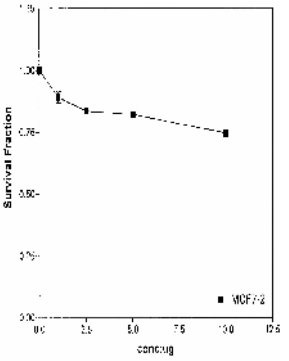


Fig. 2: Cytotoxic activity of compound **10g**.

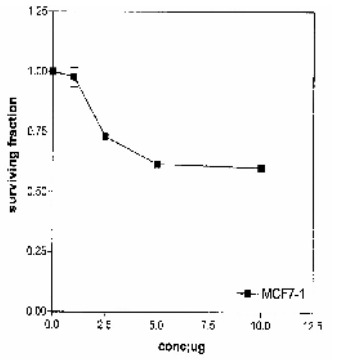


Fig. 3: Cytotoxic activity of compound **10h**.

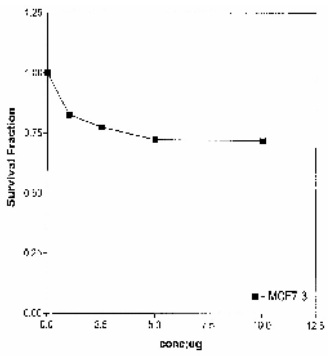


Fig. 4: Cytotoxic activity of compound **12a**.

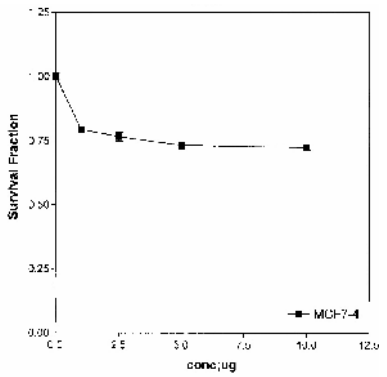


Fig. 5: Cytotoxic activity of compound **12d**.

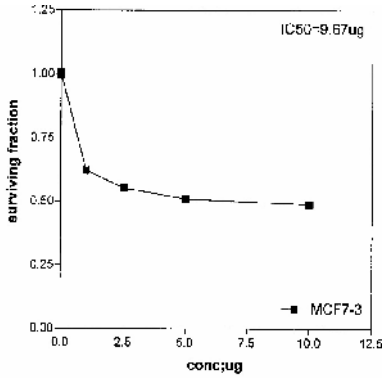


Fig. 6: Cytotoxic activity of compound **12g**.

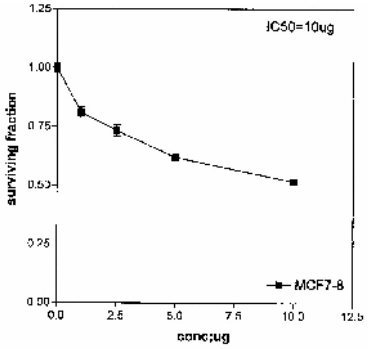


Fig. 7: Cytotoxic activity of compound **12h**.

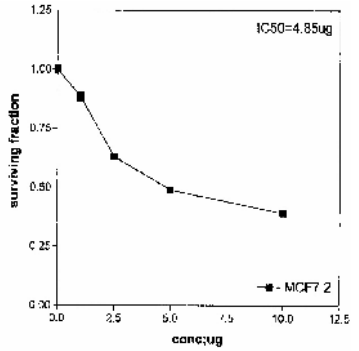


Fig. 8: Cytotoxic activity of compound **12k**.

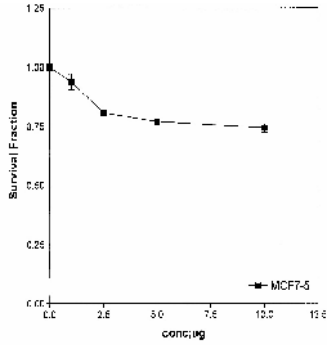


Fig. 9: Cytotoxic activity of compound **15a**.

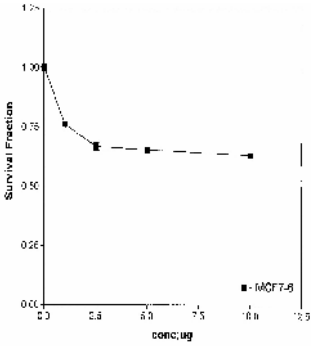


Fig. 10: Cytotoxic activity of compound **15c**.

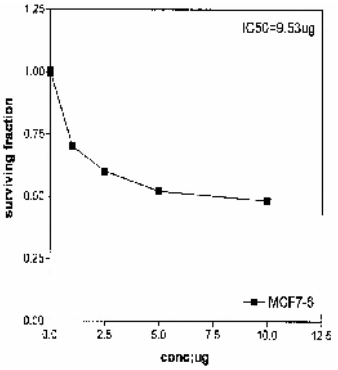


Fig. 11: Cytotoxic activity of compound **15g**.

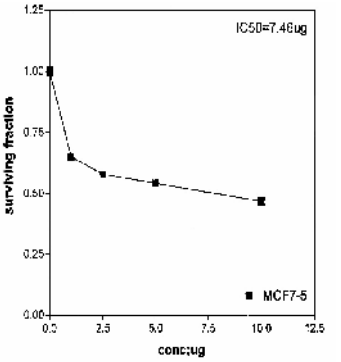


Fig. 12: Cytotoxic activity of compound **15h**.

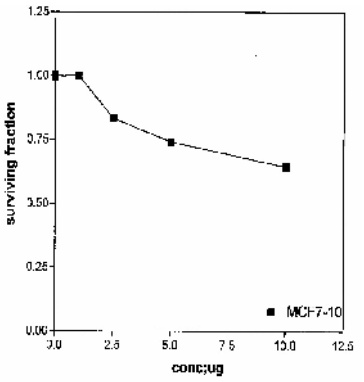


Fig. 13: Cytotoxic activity of compound **15k**.

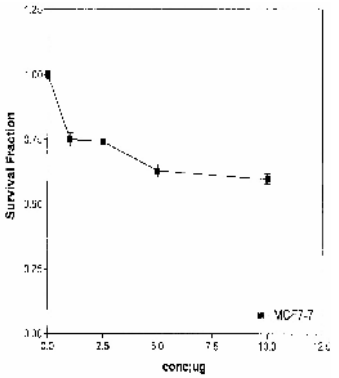


Fig. 14: Cytotoxic activity of compound **17a**.

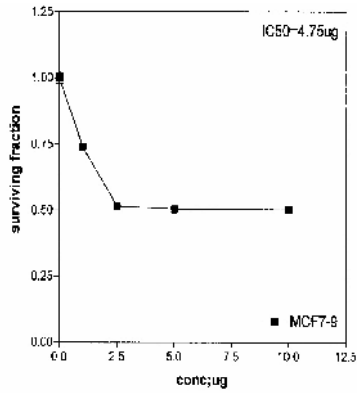


Fig. 15: Cytotoxic activity of compound **17f**.

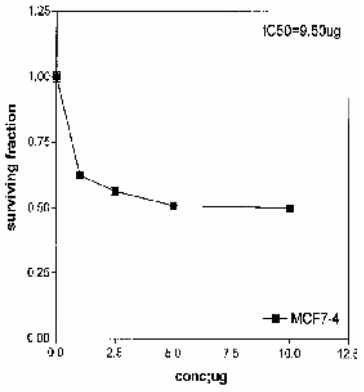


Fig. 16: Cytotoxic activity of compound **17g**.

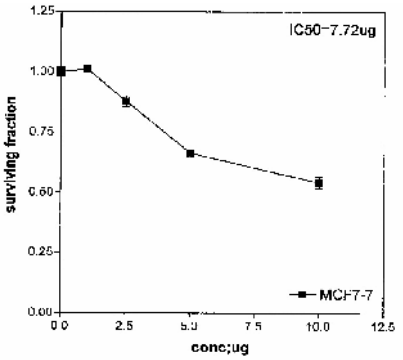


Fig. 17: Cytotoxic activity of compound **17j**.

RESULTS AND DISCUSSION

Torsion angle

Torsion angle comparative study results of compounds **I, II** and the prepared target compounds **10h** revealed that a comparable torsion angle (10, 4a, 4, CO) and torsion angle (10a, 8a, 9, 9a) of compounds **I, II** and **10h** indicating similar alignment of the carbonyl function in all compounds.

Torsion angle comparative study results of compounds **III, IV** and the prepared target compounds **12g, 15g** and **17f** showed that comparable torsion angle (10, 4a, 4, CO) in compounds **12g**, **15g** and **17f** with that of compound **III** indicating similar alignment of carbonyl function. Also torsion angle (9, 11, 12, 13) and torsion angle (9a, 9, 11, 12) of compounds **12g**, **15g** and **17f** are comparable with that of

compound **IV** indicating similar alignment of 9-anilino moiety.

Chemistry

The synthetic pathway utilized to obtain the target compounds **10a-h**, **12a-k**, **15a-k** and **17a-j** is illustrated in Schemes 1-4.

The substituted phenylhydrazines **3b-h** were prepared via diazotization of different aromatic amines or sulfonamides **1b-h** with sodium nitrite and hydrochloric acid followed by reduction with sodium sulfite in acidic medium to give substituted phenylhydrazine hydrochloride salts **2b-h**. The free bases **3b-h** were obtained using sodium acetate[14-17].

Chloroacetic acid, 2-(substituted phenyl)hydrazide **4a-h** were obtained by dropwise addition of chloroacetyl chloride into a solution of the corresponding phenylhydrazine **3a-h** in dry benzene at room temperature. IR spectra revealed aliphatic CH_2 stretching at about 2964, 2840 cm^{-1} and carbonyl stretching at 1681-1653 cm^{-1}.

Sodium salt of acridone-4-caboxylic acid **9** was prepared by cyclodehydration of N-(2-caboxyphenyl)anthranilic acid **7**[19] obtained through Jordan-Ullmann copper catalyzed condensation between 2-chlorobenzoic acid **5** and anthranilic acid **6** to give acridone-4-carboxylic acid **8**[19&20] which was dissolved in sodium hydroxide solution to give sodium 9-oxo-9,10-dihydroacridine-4-carboxylate **9**[19]. Refluxing **4a-h** with **9** in dry DMF yielded compounds **10a-h**. IR spectra showed aliphatic CH_2 stretching at about 2928, 2857 cm^{-1} and carbonyl stretching at about 1738, 1689, 1620 corresponding to ester, hydrazide and acridone C=O respectively. ^{1}H NMR revealed a singlet at δ = 5.11 ppm attributed to CH_2 protons in addition to multiplet at δ = 7.08-8.59 ppm corresponding to 12 aromatic protons and NH proton and singlet at δ =10.36 ppm and 11.6 ppm corresponding to NH protons for compound **10a**.

Chlorination of **10a** using thionyl chloride and few drops of DMF (as catalyst)[22-26] gave phenylhydrazino-carbonylmethyl 9-chloroacridine-4-carboxylate **11** which was added to an equimolar amount of aromatic amines or sulfonamides dissolved in DMF acidified with hydrochloric acid and stirred to give compound **12a-k**. IR spectra showed stretching of aliphatic CH_2 and carbonyl function group at about 2917, 2860 and 1692, 1668 cm^{-1} respectively. ^{1}H NMR exhibited the appearance of a singlet at δ = 5.14 ppm corresponding to CH_2 protons for compounds **12a** and **12k**.

Furthermore, reaction of sodium 9-oxo-9,10-dihydroacridine-4-carboxylate **9** and mono chloroacetic acid afforded **13**. IR spectra showed stretching of aliphatic CH_2 at 2926 and 2850 cm^{-1} in addition to carbonyl stretching at 1722, 1688 and 1622 cm^{-1} of the acid, ester and acridone. ^{1}H NMR revealed a singlet at δ = 4.93 ppm for CH_2 protons.

Chlorination of 9-Oxo-9,10-dihydroacridine-4-carbonyloxyacetic acid **13** using thionyl chloride and

few drops of DMF (as catalyst)[10,20&27] provided 2-chloro-2-oxoethyl 9-chloroacridine-4-carboxylate **14.** The newly introduced chlorine atoms were either substituted simultaneously in one step with 2 moles of appropriate aromatic amines or sulfonamides[27] to give compounds **15** or the acid chloride was preferentially substituted with equimolar amount of amine at low temperature under mild basic anhydrous conditions to yield intermediate phenylcarbamoylmethyl 9-chloroacridine-4-carboxylate **16** which was further reacted with equimolar amount of different aromatic amines or sulfonamides under mild acidic conditions[20&27] to give compound **17**.

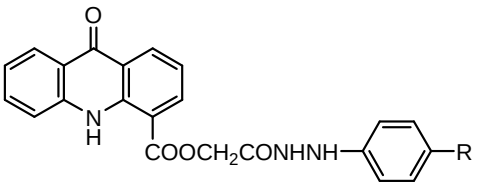
IR spectra showed CH_2 stretching at about 2930, 2836 cm^{-1} and carbonyl stretching at about 1742, 1667 cm^{-1}. ^1H NMR spectra revealed a singlet at δ = 4.95 ppm for CH_2 protons in addition to multiplet at δ =7.28-8.59 ppm assigned to 17 aromatic protons and singlet at δ =11.44 ppm and 11.48 ppm corresponding to NH protons for compound **15a**.

IR spectra showed CH_2 stretching at about 2936, 2870 cm^{-1} and carbonyl stretching at about 1737, 1689 cm^{-1}. ^1H NMR spectra showed a singlet at δ = 4.99 ppm for CH_2 protons in addition to multiplet at δ = 7.29-8.53 ppm attributed to 16 aromatic protons and NH_2 protons and singlet at δ =10.95 ppm and 11.97 ppm corresponding to NH protons for compound **17f**.

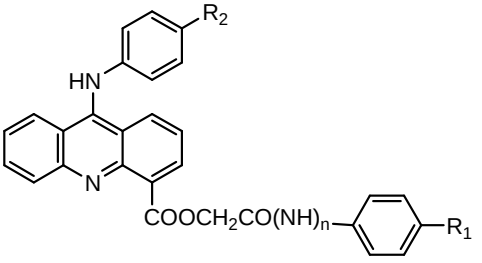
Mass spectra of some representative compounds **10a, 10g, 12a, 12b, 15a, 15b, 17a** and **17b** were in compliance with their molecular weights.

Antitumor screening

The results showed that eight acridine derivatives **12g**, **12h**, **12k**, **15g**, **15h**, **17f**, **17g**, **17j** exhibited good level of antitumor activity. The relationship between different substituents and activity is described as follow:



A



B n = 1, 2

1- Compounds **A** showed no activity.
2- Compounds **B** showed good activity when R_1 and R_2 are sulfamoyl moiety or when only R_2 was sulfamoyl moiety. But, no activity when R_1 and R_2 were unsubstituted or when substitution was other than sulfamoyl moiety.

Conclusion

Acridone derivatives **10** bearing 4-substituted phenylhydrazinocarbonyl methyl 4-caboxylate at position 4 showed no antitumor activity although compound **10h** revealed comparable torsion angle (10, 4a, 4, CO) and torsion angle (10a, 8a, 9, 9a) compared to **I** and **II** which were reported to possess marked antitumor activity.

Introduction of sulfonamido or anilino or substituted anilino moiety to 4-substituted phenylhydrazino-carbonylmethyl acridine-4-caboxylate or 4-substituted phenylcarbamoyl-methyl acridine-4-carboxylate at position 9 showed antitumor activity in case of compounds having sulfonamide substitution as shown by comparable torsion angle (9, 11, 12, 13) and torsion angle (9a, 9, 11, 12) of compounds **12g**, **15g** and **17f** with that of compound **IV** indicating similar alignment of 9-anilino moiety. Therefore, we concluded that substitution with 9-anilino moiety carrying sulfamoyl group exhibits good antitumor activity.

REFERENCES

1- L. P. G. Wakelin, G. J. Atwell, G. W. Rewcastle and W. A. Denny, J. Med. Chem., 30, 855 (1987).

2- V. A. Bacherikov, T.-C. Chou, H.-J. Dong, X. Zhang, C.-H. Chen, Y.-W. Lin, T.-J. Tasi, R.-Z. Lee, L. F. Liu and T.-L. Su, Bioorg. Med. Chem., 13, 3993 (2005).

3- V. A. Bacherikov, T.-C. Chou, H.-J. Dong, C.-H. Chen, Y.-W. Lin, T.-J. Tasi and T.-L. Su, Bioorg. Med. Chem. Lett., 14, 4719 (2004).

4- P. Yang, Q. Yang and X. Qian, Tetrahedron, 61, 11895 (2005).

5- P. Yang, Q. Yang, X. Qian, L. Tong and X. Li, J. Photochem. Photobiol. B: Biol., 84, 221 (2006).

6- S.-S. Wang, Y.-J. Lee, S.-C. Hsu, H.-O. Chang, W.-K. Yin, L.-S. Chang and S.-Y. Chou, Bioorg. Med. Chem., 15, 735 (2007).

7- K. A. Olaussen, K. Dubrana, J. Domont, J. P. Spano, L. Sabatier, and J. C. Soria,, Crit. Rev. Oncol. Hematol., 57, 191 (2006).

8- C. Martins, M. Gunaratnam, J. Stuart, V. Makwana, O. Greciano, A. P. Reszka, L. R. Kelland and S. Neidle, Bioorg. Med. Chem. Lett., 17, 2293 (2007).

9- B. D. Palmer, G. W. Rewcastle, G. J. Atwell, B. C. Baguley and W. A. Denny, J. Med. Chem., 31, 707 (1988).

10- M. Y. Ebeid, S. M. El-Moghazy Aly, A. N. Mikhael and A. A. H. Eissa, Egypt. J. Pharm. Sci., 33, 293 (1992).

11- A. K. Todd, A. Adams, J. H. Thorpe, W. A. Denny, L. P. G. Wakelin and C. J. Gardin, J. Med. Chem., 42**,** 536 (1999).

12- H. A. Abu-Shady, H. Safwat and S. El-Moghazy, Egypt. J. Pharm. Sci., 19, 85 (1978).

13- HyperChem Release 4 for windows, molecular modeling software, Serial No. 519-10007596 (1994).
14- H. Seefried, Chem. Ber., 55, 1827 (1922).
15- J. B. Muenzen, L. P. Cerecedo and C. P. Sherwin, J. Biol. Chem., 67, 469 (1926). Through Chem. Abstr., 20, 1837, (1926).
16- B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell "Vogel's Text Book of Practical Organic Chemistry", 5th Ed., Longman Scientific and Technical, Longman Group UK Ltd, 1989, p. 960.
17- K. Itano, J. Pharm. Soc. Japan, 75, 441 (1955). Through Chem. Abstr., 50**,** 22552d, (1956).
18- T. Hidaka, T. Kawakami (Nippon Soda Co., Ltd., Japan). Jpn. Kokai Tokkyo Koho JP 2002 249,481 (Cl.C07C323/60) 6 sep, 2002, JP Appl. 2000/389,703, 22 Dec 2000. Through Chem. Abstr., 137, 224142h, (2002).
19- S. M. El-Moghazy Aly, Egypt. J. Pharm. Sci., 33, 527 (1992).
20- G. J. Atwell, B. F. Cain, B. C. Baguley, G. J. Finlay and W. A. Denny, J. Med. Chem., 27, 1481 (1984).
21- P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J. T. Warren, H. Bokesch, S. Kenney and M. R. Boyd, J. Natl. Cancer Inst., 82, 1107 (1990).
22- H. I. El-Subbagh, A. H. Abadi and H. A. Al-Khamees, Arch. Pharm. Pharm. Med. Chem.,330, 277 (1997).
23- B. F. Cain, R. N. Seelye and G. J. Atwell, J. Med. Chem., 17, 922 (1974).
24- G. J. Atwell, B. C. Baguley, G. J. Finlay, G. W. Rewcastle and W. A. Denny, ibid., 29, 1769 (1986).
25- W. A. Denny, G. J. Atwell and B. F. Cain, ibid., 22, 1453 (1979).
26- G. W. Rewcastle, G. J. Atwell, B. C. Baguley and W. A. Denny, ibid., 27, 1053 (1984).
27- S. M. El-Moghazy Aly, A. N. Mikhael, A. A. H. Eissa and M. Y. Ebeid, Egypt. J. Pharm. Sci., 34, 401 (1992).