Zagazig J. Pharm. Sci., June 2009
Vol. 18 , No. 1, pp. 40-50.

ISSN 1110-5089

SYNTHESIS OF SOME SUBSTITUTED ACRIDINE DERIVATIVES OF ANTICIPATED ANTICANCER ACTIVITY

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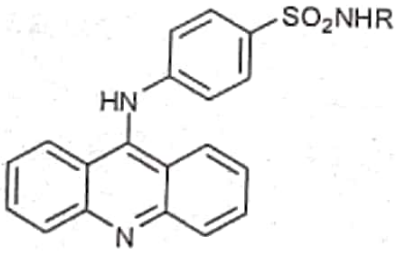
ABSTRACT

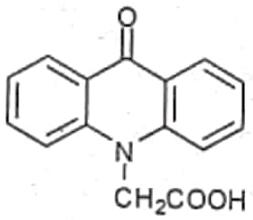
In the present investigation four series of new acridine derivatives of anticipated antitumor activity have been synthesized. The first series belongs to 9-phenylimino-acridine-10-acetate derivatives. The second and third series comprise 9-phenylimino-acridine-10-carboxamide derivatives, while the last one includes 9-oxo-acridine-10-carboxamide derivatives of different substitution pattern.

INTRODUCTION

The search for novel antitumor agents is the main target of many scientists. Screening the literature revealed that 9-anilinoacridines (A) and acridone acetic acid (cycloferon) (B) have been found to possess antitumor activities.[1-3]



(A)



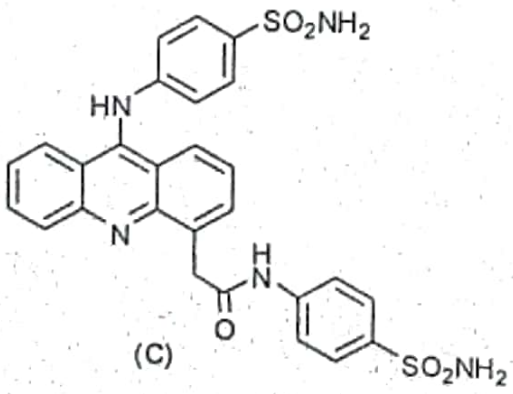
(B)

In view of the preceding facts, it was of interest to synthesize a hybridized molecule of the general formula ethyl (9-substituted acridin-10-yl) acetate (1) motivated by the hope that these derivatives might possess marked antitumor activity.

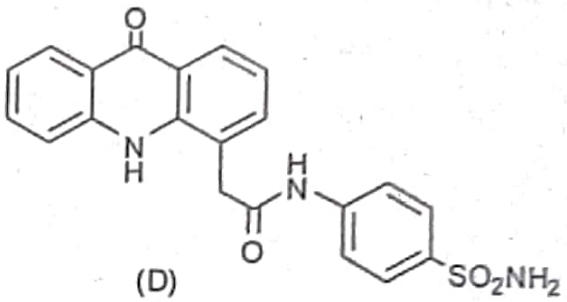
In addition, N-(4-sulfamoylphenyl)-2-(9-(4-sulfamoylphenylamino)acridin-4-yl)acetamide (C) has been reported to exhibit significant activity in human mammary carcinoma cell line (MCF7).[4]

Therefore, the present work described the synthesis of several 9, 10- disubstituted acridine derivatives (2aand 3a) in analogy to compound (C).

Also, 2-(9-oxo-9, 10-dihydroacridin-4-yl)-N-(sulfamoylphenyl) acetamide (D) has been reported to show marked activity in human mammary carcinoma cell line.[4]



(C)



(D)

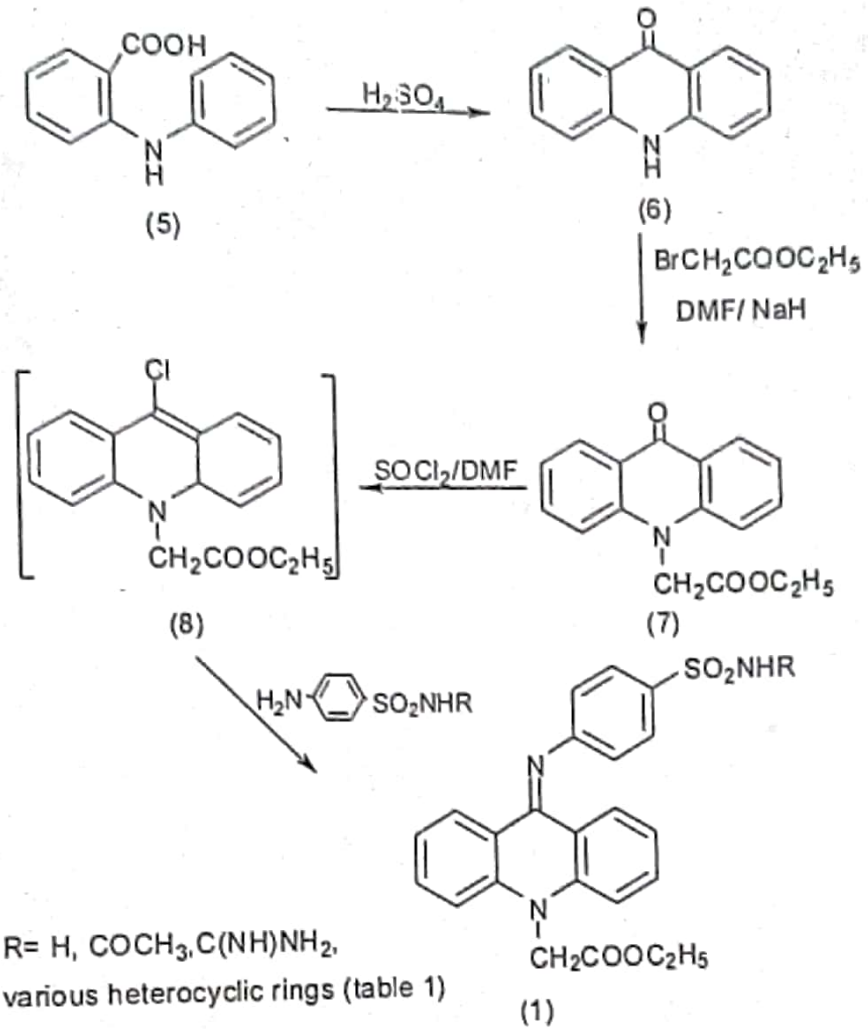
Accordingly, a series of 10-substituted acridones having the general formula (4) was synthesized aiming to obtain new derivatives with significant antitumor activity.

CHEMISTRY

The rational of the synthesis of the target compounds (1), (2), (3), and (4) is presented in schemes 1 and 2.

The synthesis of acridone (6) was achieved by cyclization of diphenylamine-2-carboxylic acid (5) with concentrated sulphuric acid.[5] N-alkylation of acridone was carried out by reaction of ethyl bromoacetate in presence of NaH to afford ethyl (9-oxo-9H- acridin-10-yl) acetate (7)[6], which was verified by IR and ^{1}H NMR. 9-Chloroacridine derivative (8) was obtained by treating the acetate ester (7) with thionyl chloride in presence of catalytic amount of DMF.[2,7-12] Ethyl [9-(4-substituted sulfamoyl-phenylimino)-9H-acridin-10-yl] acetates (1) were prepared by coupling of the 9-chloroacridines (8) with the appropriate sulfonamide following the reported method[13]. IR spectrum showed the reappearance of the NHs bands at 3400-3200 cm^{-1} and the presence of SO_2 bands at 1300 and 1100 cm^{-1}. ^{1}H-NMR spectra of compounds (1a), (1b) and (1d) showed increase in the integration of aromatic portions. The mass spectrum of compound (1a) showed the molecular ion peak at m/z (%) = 435 (100), while that of (1b) revealed M^+ at 478 (20.75%) and a base peak at 180.

Scheme I



Compounds (2,3 and 4) were prepared via the intermediate (9-oxo-9H-acridin-10-yl) acetic acid (9) which was obtained by hydrolysis of the corresponding acetate ester (7) using methanolic potassium hydroxide to produce the corresponding acetate salt [14,15] followed by acidification with HCl to liberate the desired (9-oxo-9H-acridin-10-yl) acetic acid (9). (9-Chloroacridin-10-yl) acetyl chloride (10) was obtained by refluxing 9-acridinon-10-acetic acid (9) with thionyl chloride in presence of catalytic amount of DMF.[16-21] Two series of compounds (4-substituted sulfamoyl-phenyl-2-[9-(4-substituted sulfamoylphenylimino)-9H-acridin-10-yl] acetamide (2and3) were synthesized. The first series included the same sulfonamide substitution at both 9- and 10- positions which was obtained by direct reaction of 2-(9-chloroacridin-10-yl) acetyl chloride (10) with two equimolar amounts of sulfonamides in dry acetone. The second one, bearing different sulfonamides at positions 9 and 10, this was achieved by adding the appropriate sulfonamide under anhydrous basic conditions.[21]

The more reactive acid chloride was first substituted selectively followed by reaction with different sulfonamide under acidic condition in dry DMF to give the target product (3).[16,21, 25] IR spectra revealed the presence of NHs bands together with the SO_2 bands. ^1H NMR spectra of compound (2a), (2b), (2e), (3a), (3e) and (3r) revealed an increase in the integration of aromatic protons, the disappearance of the triplet and quartet bands of the ethyl group and shifting of the singlet band of the CH_2 of acetamide to δ 6.20. Also compound (2e) showed the introduction of a singlet at δ 2.35 representing the six protons of the two methylisoxazole moieties, compound (3e) showed the introduction of a singlet at δ 2.35 representing the three protons of the methylisoxazole moiety. Mass spectra of compound (2a) revealed M^++4 at 566 (4.21%) and a base peak at 69, Mass spectrum of (2b) showed M^+ at 646 (11.11%) and a base peak at 195, Mass spectrum of (2e) gave M^+ at 724 (13.04%) and a base peak at 64, Mass spectrum of (2a) showed M^+ at 603 (0.13%) and a base peak at 195 and Mass spectrum of (2m) revealed M^++2 at 645 (0.96%) and a base peak at 194.

Compounds 2-(9-oxo-9H-acridin-10-yl)-N-(4-substituted sulfamoylphenyl) acetamide (4) were obtained by reaction of the appropriate sulfonamide with 2-(9-oxo-acridin-10-yl) acetyl chloride (12) which in turn was prepared by chlorination of 2-(9-oxo-

ISSN 1110-5089

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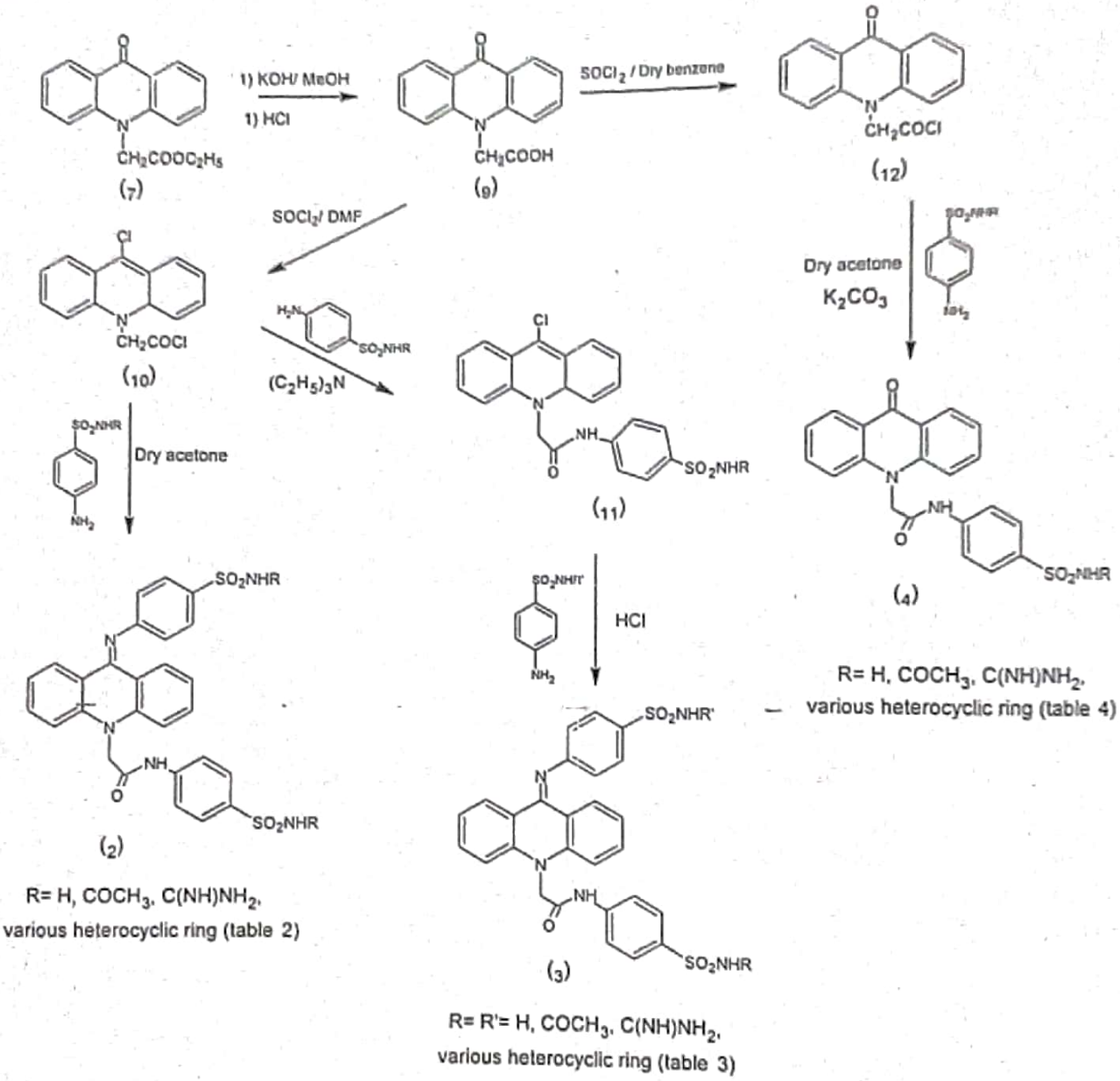
acridin-10-yl) acetic acid (9) using thionyl chloride in absence of DMF which is necessary for chlorination of the 9 position.[16,26] IR spectra showed also the presence of NH band and SO_2 bands. ^1H NMR of compounds (4a), (4b) and (4c) showed the presence of a singlet at δ 6.2 of the $\underline{CH_2}CONH$ moiety protons, compound (4c) showed in addition a singlet at δ 2.32 due to the three protons of the methylisoxazole. Mass spectrum of compound (4a) showed M^+ at 407 (2.91%) and a base peak at 64, Mass spectrum of (4b) revealed M^+-1 at 448 (0.57%) and MS of (4c) gave M^++3 at 492 (1.35%) and a base peak at 166.

Scheme 2



EXPERIMENTAL

Melting points were uncorrected and were determined by open capillary tube method using Electrothermal 9100 digital melting point apparatus. Elemental microanalyses were carried out at the microanalytical centre, Faculty of Science, Cairo University. Infrared spectra were recorded on JASCO FT/IR-460 plus spectrophotometer Vector 22 as potassium bromide discs or neat. The proton nuclear magnetic resonance (^1H- NMR) spectra were recorded on Varian Mercury spectrophotometer at 300 MHZ (chemical shifts are related to that of the solvent). Chemical shifts values (δ) are given in parts per million (ppm). Mass spectra were performed on Schimadzu GCMS- QP1000EX mass spectrophotometer, Hewlett.Packard 5988A GC/MS mass spectrophotometer, and Fennigan MAT, SSQ 7000 GC/MS mass spectrophotometer at 70 ev. Reaction time was monitored by Thin Layer Chromatography, using Macherey-Nagel Alugram Sil G/UV_{254} silica gel plates with fluorescent detector system, chloroform/methanol was used in elution, and the spots were visualized using Vilber Lourmet ultraviolet lamp at λ= 254 nm.

Ethyl [9-(4-sulfamoyl-phenylimino)-9H-acridin-10-yl]-acetate (1a):

Ethyl (9-chloroacridin-10(9H)-yl) acetate (8) (1.4 g, 5 mmol) was dissolved in water (25 mL). The resulted solution was then treated with sulfanilamide (0.86g, 5 mmol) previously dissolved in dilute HCl (20 mL), an intermediate orange to red color was formed. After 10 minutes the reaction mixture was basified with NH_4OH and the yellowish orange precipitate formed was collected, dried and recrystallized from DMF/H_2O to afford orange crystals, yield (65%), m.p: 245°C.[13]

IR (cm^{-1}): 3327, 3291 (NH); 3129 (Ar- CH); 2994, 2924 (aliph- CH); 1740 (CO); 1603, 1580, 1557 (NH, C=C, C=N); 1329 and 1153 cm $^{-1}$ (SO_2). ^{1}H NMR(DMSO-d_6): δ = 1.28(t , 3H , $\underline{CH_3}CH_2$) , 4.25 (q , 2H , $CH_3\underline{CH_2}$) , 5.19 (s, 2H, $\underline{CH_2}COOCH_2CH_3$) , 6.93-7.78 (m , 14H , aromatic H and $SO_2\underline{NH_2}$) MS: m/z (%) = M^+ 435 (100%) Calculated for $C_{23}H_{21}N_3O_4S$ (435.50): C 63.43 H 4.86 N: 9.65. Found: C 63.75 H 5.00 N: 9.61.

Compounds (1b-f) were similarly prepared from ethyl (9-chloro-acridin-10-yl)-acetate (8) with the appropriate sulfonamide and recrystallized from DMF/ H_2O (table1).

^{1}H NMR (DMSO-d_6) of compound (1b): δ = 1.28(t, 3H, $\underline{CH_3}CH_2$), 4.27 (q, 2H, $CH_3\underline{CH_2}$), 5.20 (s, 2H, $CH_2COOCH_2CH_3$), 6.72-7.71 (m, 16H, aromatic H and N=C ($N\underline{H_2}$)$_2$)

(1b) MS: m/z (%) = M^+ 478 (20.75), 180 (100)

^{1}H-NMR (DMSO-d_6) of compound (1d): δ= 1.27(t, 3H, $\underline{CH_3}CH_2$), 4.25 (q, 2H, $CH_3\underline{CH_2}$), 5.19 (s, 2H, $\underline{CH_2}COOCH_2CH_3$), 6.85-8.11 (m, 17H, aromatic H and $SO_2N\underline{H_2}$).

N-(4-Sulfamoyl-phenyl-2-[9-(4-sulfamoyl-phenylimino)-9H-acridin-10-yl] acetamide (2a) :

A solution of the freshly prepared (9-chloroacridin-10-yl)- acetyl chloride (10) in dry acetone (30 mL) was added to a stirred solution of sulfanilamide (1.4g, 8.4 mmol) in dry acetone (10 mL) and dilute HCl (few drops). The immediately resulting red solution was stirred for 30 minutes, where an orange precipitate was formed. The suspension was diluted with ice-water and neutralized with dilute ammonium hydroxide for complete precipitation. The product was filtered, washed with water and dried to give 1.2 g (54%). The product was recrystallized from DMF/H_2O, m.p: 230-2°C. IR (cm^{-1}): 3446, 3294 (NHs), 3050 (Ar-CH), 2095 (aliph-CH), 1702(CO), 1633, 1580, 1558 (NH, C=C, C=N), 1325, 1159 (SO_2) .^{1}H NMR (DMSO-d_6): δ = 6.97(s, 2H, $C\underline{H_2}CONH$), 7.08-9.03 (m, 20H, aromatic H and $2SO_2\underline{NH_2}$), 10.64(s, 1H, $CON\underline{H}$). MS: m/z (%) = 566M^++4 (4.21), 69 (100). Calculated for $C_{29}H_{23}N_7O_5S_2$ (561.63): C: 57.74 H: 4.13 N: 12.47. Found: C: 57.94 H: 4.19 N: 12.67.

Compounds (2b-f) were similarly prepared from (9-Chloro-acridin-10-yl)-acetyl chloride (10) with the appropriate sulfonamide and recrystallized from DMF/H_2O (table 2).

^{1}H NMR (DMSO-d_6) of compound (2b): δ= 6.16 (s, 2H, $C\underline{H_2}CONH$), 6.86-8.38 (m, 24H, aromatic H and 2 N=C ($N\underline{H_2}$)$_2$), 11.60 (s, 1H, $CON\underline{H}$). Compound (2b) MS: m/z (%) =M^+ 646 (11.11), 195 (100)

^{1}H NMR (DMSO-d_6) of compound (2d): δ= 6.89(s, 2H, $C\underline{H_2}CONH$), 6.92-8.25(m, 26H, aromatic H and $2SO_2\underline{NH}$), 10.5(s, 1H, $CON\underline{H}$). ^{1}H NMR (DMSO-d_6) of compound (2e): δ= 2.28(s, 6H, 2x $C\underline{H_3}$ of sulfamethoxazole), 6.78(s, 2H, $C\underline{H_2}CONH$), 6.83-8.4(m, 20H, aromatic H and $2SO_2\underline{NH}$), 11.1(s, 1H, $CON\underline{H}$). Compound (2e) MS: m/z (%) = M^+ 724(13.04), 64(100).

N-(4-Sulfamoyl-phenyl-2-[9-(4-amidinosulfamoyl-phenylimino)-9H-acridin-10-yl] acetamide (3a) :

A solution of sulfanilamide (0.72g, 4.2 mmol) in dry DMF containing 3- 4 drops of triethylamine was added to equimolar solution of freshly prepared (9-chloroacridin-10-yl) acetyl chloride (10) in dry DMF. The mixture was set aside for 10 minutes, the resulting red solution was then added to a solution of an equimolar amount of sulfaguanidine (0.97g, 4.2 mmol) in DMF (10 mL); acidified with dil. HCl. The resulting reaction mixture was set aside for 30 minutes then diluted with ice-water. The orange precipitate formed was completely precipitated by dropwise addition of dilute ammonium hydroxide. The solid was filtered, washed with water and dried to give 1.35g (58%). The product was crystallized from DMF/H_2O, m.p: 185-190°C. IR (Cm^{-1}): 3425 (NHs), 3055 (Ar-CH), 2924 (aliph-CH), 1703 (CO), 1628, 1544, 1520 (NH, C=C,C=N), 1344 and 1158 (SO_2). ^{1}H NMR (DMSO-d_6): δ= 6.85(s, 2H, $C\underline{H_2}CONH$), 7.26-8.37(m, 22H, aromatic H and $SO_2N\underline{H_2}$and N=C ($N\underline{H_2}$)$_2$), 10.60(s, 1H, $CON\underline{H}$). MS: m/z (%) = M^+ 603 (0.13), 195(100). Calculated for $C_{28}H_{25}N_7O_5S_2$ (603.67): C: 55.71 H: 4.17 N: 16.24. Found: C: 56.05 H: 4.05 N: 16.65

Compounds (3b-f) were similarly prepared from (9-chloro-acridin-10-yl) acetyl chloride (10) with the appropriate sulfonamide and recrystalized from DMF/H_2O (table 3).

^{1}H NMR (DMSO-d_6) of compound (3e): δ= 2.34(s, 3H, $C\underline{H_3}$ of sulfamethoxazole), 6.18(s, 2H, CH_2CONH), 7.10-8.26 (m, 20H, aromatic H and $SO_2N\underline{H_2}$and $SO_2\underline{NH}$), 11.40 (s, 1H, CONH). ^{1}H NMR (DMSO-d_6) of compound (3r): δ= 6.91(s, 2H, $C\underline{H_2}CONH$), 7.22-8.85 (m, 23H, aromatic H and 2 $SO_2\underline{NH}$), 11.9(s, 1H, CONH). Compound (3l) MS: m/z (%) = M^++2 645 (0.96), 194 (100).

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(9-Oxo-9H-acridin-10-yl)- acetyl chloride (12) :

A suspension of (9- oxo- 9H- acridin-10- yl)- acetic acid (9) (1.06g, 4.2 mmol) in thionyl chloride (7mL) containing dry benzene (2- 3 drops) was heated gently under reflux till a homogenous solution was obtained then for further one hour, excess thionyl chloride was removed under vacuum. The yellow residue was azeotroped with dry benzene to remove the last traces of thionyl chloride and used directly for the next step.

2-(9-Oxo-9H- acridin-10-yl)-N-(4-sulfamoyl-phenyl)-acetamide (4a):

A solution of the freshly prepared (9- oxo- 9H- acridin-10- yl) - acetyl chloride (12) in dry acetone (30 mL) was added to a stirred solution of sulfanilamide (0.7g , 4.2 mmol) in dry acetone (10 mL) and triethylamine (few drops). The immediately resulting orange- red solution was stirred for 30 minutes, where an orange precipitate was formed. The suspension was diluted with ice-water and neutralized with dilute ammonium hydroxide for complete precipitation. The product was filtered, washed with water and dried to give 1.25 g (77%) The product was recrystallized from DMF/H_2O, m.p 320-5 °C

IR (cm^{-1}): 3294, 3152 (NHs), 1703,1634 (CO_s), 1580,1516 (NH,C=C), 1324 and 1159 (SO_2).^{1}H NMR (DMSO-d_6): δ = 6.14 (s, 2H, $C\underline{H}_2CONH$), 6.65-8.28(m, 14H, aromatic H and SO_2NH_2), 13.34(s, 1H, $CONH$). MS: m/z (%) = M^+ 407(2.91), 64(100). Calculated for $C_{21}H_{17}N_3O_4S.H_2O$ (425.47): C: 59.28, H: 4.50, N: 9.88. Found: C: 59.20, H: 4.40, N: 9.89.

Compounds (4b-f) were prepared similarly from (9-oxo-9H-acridin-10-yl) - acetyl chloride (12) with the appropriate sulfonamide and recrystallized from DMF/H_2O (table 4).

^{1}H NMR (DMSO-d_6) of compound (4b): δ= 6.56 (s, 2H, $C\underline{H}_2CONH$), 6.59- 8.32 (m, 16H, aromatic H and SO_2NH and N=C (NH_2)$_2$), 10.50 (s, 1H, CONH).

Compound (4b): m/z (%) = M^+-1 448 (0.57), 212 (100).

^{1}H NMR (DMSO-d_6) of compound (4d): δ= 6.50 (s, 2H, CH_2CONH), 7.09-8.56 (m, 16H, aromatic H and SO_2NH), 9.50 (s, 1H, CONH).

^{1}H NMR (DMSO-d_6) of compound (4e): δ= 2.34 (s, 3H, CH_3 of sulfamethoxazole) 6.19 (s, 2H, $C\underline{H}_2CONH$), 7.13-8.39 (m, 14H, aromatic H and $SO_2N\underline{H}$) 9.47 (s, 1H, $CONH$).

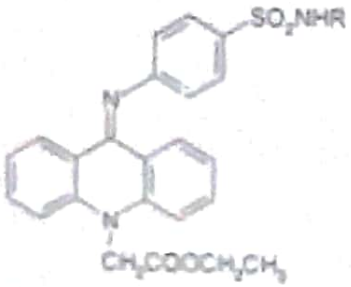


Table 1 : Experimental data of compound 1 (b-f)

Cpd. No.	R	Molecular Formula M-wt	m.p. °C Yield %	Microanalysis Calc.	Microanalysis Found	IR (cm^{-1})
1b		$C_{28}H_{23}N_5O_4S$ 477.54	230-1 80	C 60.36 H 4.85 N 14.67	60.03 4.88 14.38	3435, 3227 (NHs), 3015 (Ar-CH), 2979, 2928 (Aliph-CH), 1742(CO), 1623, 1602,1579(NH, C=C, C=N), 1376, 1120 (SO_2)
c		$C_{28}H_{23}N_3O_5S$ 477.51	218-220 75	C 62.88 H 4.85 N 8.80	62.59 4.78 8.40	3234(NH), 3088(Ar-CH), 2979, 2881(Aliph-CH), 1736,1710(CO_s), 1684,1601,1578(NH,C=, C=N), 1377, 1158(SO_2)
d		$C_{30}H_{24}N_4O_4S$ 512.58	225-6 85	C 65.61 H 4.72 N 10.93	65.56 4.72 10.88	3231(NH), 3055(Ar-CH), 2981, 2928,2813 (Aliph-CH), 1744(CO), 1623, 1600,1578 (NH,C=C, C=N), 1385, 1146(SO_2)
e		$C_{30}H_{25}N_5O_4S$ 513.57	220-2 87	C 63.15 H 4.51 N 13.64	62.91 4.63 13.88	3300(NH), 3100(Ar-CH), 2950, 2900 (Aliph-CH), 1720(CO),1620,1600, 1580(NH,C=C, C=N), 1310, 1110 (SO_2)
f		$C_{32}H_{31}N_5O_4S$ 541.62	215-6 90	C 64.31 H 5.02 N 12.93	64.03 4.66 12.73	3290(NH), 3033(Ar-CH), 2979 (Aliph-CH), 1734 (CO),1622,1596, 1500(NH,C=C,C=N), 1372, 1158 (SO_2)

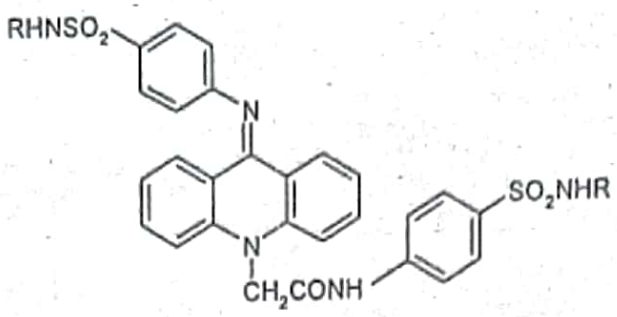
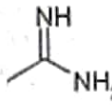
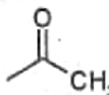
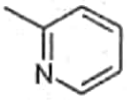
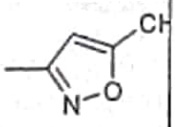
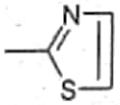


Table 2 : Experimental data of compound 2 (b-f)

Cpd	R	Molecular Formula M-wt	M.P. °C Yield %	Microanalysis		IR (cm^{-1})
				Calc.	Found	
2b		$C_{29}H_{27}N_9O_5S_2$ 645.71	201-3 55	C 53.94 H 4.21 N 19.52	53.70 4.39 19.48	3418,3315,3192(NHs), 3031(Ar-CH), 2923 (Aliph-CH),1685(CO), 1634,1580, 1545(NH, C=C,C=N), 1330 and 1166 (SO_2)
c		$C_{31}H_{27}N_5O_7S_2$.$2H_2O$ 681.73	195-2 52	C 54.62 H 4.58 N 10.27	54.15 4.38 10.02	3422(NHs), 3050(Ar-CH), 2924 (Aliph-CH), 1710 (COs), 1602, 1500, 1490 (NH,C=C, C=N), 1346 and 1159 (SO_2)
d		$C_{37}H_{29}N_7O_5S_2$ 715.80	200-5 49	C 62.09 H 4.08 N 13.70	61.80 4.24 13.42	3366,3264(NHs), 3031(Ar-CH), 2919 (Aliph-CH), 1704 (CO), 1635,1579,1550 (NH, C=C,C=N), 1367 and 1140(SO_2)
e		$C_{35}H_{29}N_7O_7S_2$ 723.78	210-13 60	C 58.08 H 4.04 N 13.55	57.81 4.21 13.74	3237(NHs), 3067(Ar-CH), 2923 (Aliph-CH), 1705(CO), 1627,1598,1551(NH,C=C,C=N), 1348 and 1157 (SO_2)
f		$C_{33}H_{25}N_7O_5S_4$.$4H_2O$ 799.91	198-9 57	C 49.55 H 4.16 N 12.26	49.70 4.29 12.50	3450(NHs), 3100(Ar-CH), 2960 (Aliph-CH), 1700(CO), 1640,1620, 1580(NH,C=C, C=N), 1330 and 1140 (SO_2)

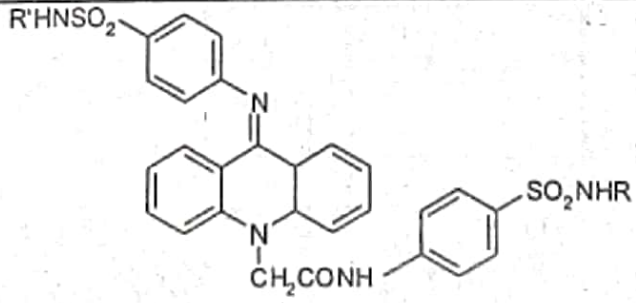


Table 3 : Experimental data of compound 3 (b-t)

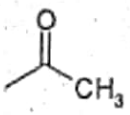
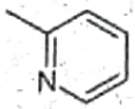
Cpd No.	R	R'	Molecular Formula M-wt	M.P. °C Yield %	Microanalysis		IR (cm^{-1})
					Calc.	Found	
3b	H		$C_{29}H_{25}N_5O_6S_2$ 603.67	180-2 69	C 57.70 H 4.17 N 11.60	57.69 4.14 12.01	3245(NHs), 3095(Ar-CH), 2950(Aliph-CH), 1704, 1630 (COs), 1598, 1520, 1510 (NH, C=C, C=N), 1341 and 1158 (SO_2)
c	H		$C_{32}H_{26}N_6O_5S_2$ 638.72	195-8 55	C 60.18 H 4.10 N 13.16	60.85 3.62 13.14	3366,3264(NHs), 3031(Ar-CH), 2919 (Aliph-CH), 1704 (CO), 1635,1579, 1550(NH, C=C,C=N), 1367 and 1140 (SO_2)

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Table3 : continue

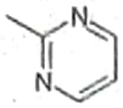
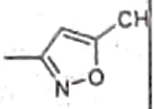
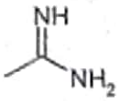
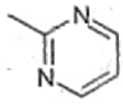
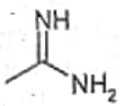
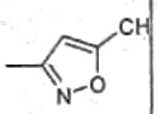
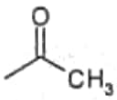
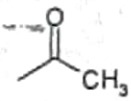
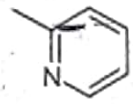
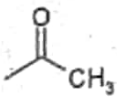
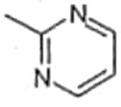
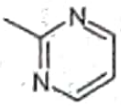
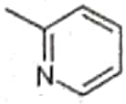
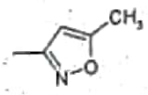
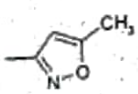
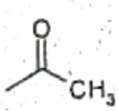
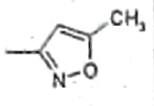
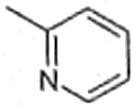
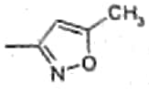
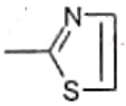
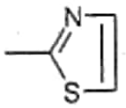
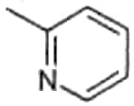
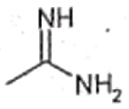
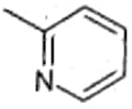
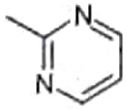
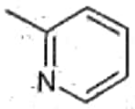
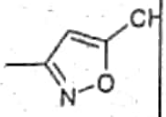
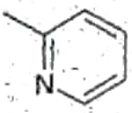
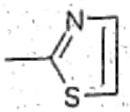
Cpd No.	R	R'	Molecular Formula M-wt	M.P. °C Yield %	Microanalysis Calc.	Microanalysis Found	IR (cm^{-1})
d	H		$C_{31}H_{25}N_7O_5S_2$ 639.70	160-170 63	C 58.21 H 3.94 N 15.33	58.29 4.10 15.00	3445(NHs), 3099(Ar-CH), 2925(Aliph-CH), 1702(CO), 1629, 1600, 1580(NH,C=C, C=N), 1342 and 1159 (SO_2)
e	H		$C_{31}H_{26}N_6O_6S_2$ 642.70	165-170 69	C 57.93 H 4.08 N 13.08	57.88 4.05 13.23	3423(NHs), 3096(Ar-CH), 2928 (Aliph-CH), 1719(CO), 1627,1600, 1508(NH,C=C, C=N), 1340 and 1165 (SO_2)
f			$C_{32}H_{27}N_9O_5S_2$ 681.74	180-3 43	C 56.38 H 3.99 N 18.49	56.26 3.83 18.59	3434, 3335, 3229 (NHs), 3100 (Ar-CH), 2923 (Aliph-CH), 1690(CO),1627, 1597, 1580(NH ,C=C, C=N), 1343 and 1133 (SO_2)
g			$C_{32}H_{28}N_8O_6S_2$ 684.74	201-3 57	C 56.13 H 4.12 N 16.36	56.20 4.25 16.37	3422(NHs), 3065(Ar-CH), 2922(Aliph-CH),1723 (CO), 1620, 1602, (NH,C=C,C=N), 1336 and 1162 (SO_2)
h		H	$C_{29}H_{25}N_5O_6S_2$ 603.67	>350 58	C 57.70 H 4.17 N 11.60	57.80 4.02 11.52	3251(NHs), 3058(Ar-CH), 2921(Aliph-CH), 1715, 1699 (COs), 1651, 1579,1509(NH, C=C,C=N), 1321 and 1156 (SO2)
i			$C_{34}H_{28}N_6O_6S_2$ 680.75	165-170 56	C 59.99 H 4.15 N 12.35	59.74 3.78 12.52	3430(NHs), 3050(Ar-CH), 2910(Aliphatic CH),1705, 1650(COs), 1640, 1630, 1600 (NH, C=C,C=N), 1360 and 1160 (SO2)
j			$C_{33}H_{27}N_7O_6S_2$ 681.74	180-3 57	C 58.14 H 3.99 N 14.35	58.39 4.15 13.95	3440(NHs), 3025(Ar-CH), 2970(Aliph-CH),1700,1650 (COs), 1640, 1620, 1605 (NH,C=C,C=N), 1315 and 1125 (SO2)
k			$C_{36}H_{28}N_8O_5S_2$ 716.79	160-3 62	C 60.32 H 3.94 N 15.63	59.90 4.08 15.91	3450(NHs), 3010(Ar-CH), 2900(Aliphatic CH),1710 (CO), 1680, 1660, 1640 (NH, C=C,C=N), 1320 and 1120 (SO_2)
l		H	$C_{31}H_{26}N_6O_6S_2$ 642.70	185-7 58	C 57.93 H 4.08 N 13.08	57.79 4.09 13.25	3449, 3292 (NHs), 3061 (Ar-CH), 2925 (AliphCH), 1704(CO), 1626, 1580, 1525(NH, C=C,C=N), 1326 and 1153 (SO_2)
m			$C_{33}H_{28}N_6O_7S_2$ 684.74	173-5 63	C 57.89 H 4.12 N 12.27	57.83 3.91 12.72	3250,3156 (NHs), 3077 (Ar-CH), 2950 (Aliph-CH), 1705,1648 (COs), 1619, 1600,1580 (NH,C=C, C=N), 1384and1159 (SO_2)

Table3 : continue

Cpd No.	R	R'	Molecular Formula M-wt	M.P. °C Yield %	Microanalysis		IR (cm^{-1})
					Calc.	Found	
n			$C_{36}H_{29}N_7O_6S_2$ 719.79	195-7 68	C 60.07 H 4.06 N 13.62	60.30 4.20 13.66	3420(NHs), 3100(Ar-CH), 2900(Aliph-CH),1690 (CO), 1660, 1640, 1625(NH, C=C, C=N), 1315 and 1160 (SO_2)
o			$C_{34}H_{27}N_7O_5S_3$ 725.81	178-80 70	C 56.26 H 3.75 N 13.51	56.51 3.92 14.01	3410(NHs), 3080(Ar-CH), 2910(Aliph-CH),1715 (CO), 1685, 1680,1660 (NH,C=C, C=N), 1330 and 1130 (SO2)
p		H	$C_{30}H_{24}N_7O_6S_3$ 644.74	163-5 55	C 55.89 H 3.75 N 13.03	55.69 4.02 13.21	3471(NHs), 3050(Ar-CH), 2960(Aliph-CH),1685(CO), 1654, 1637, 1618 (NH,C=C, C=N), 1322 and 1149 (SO2)
q			$C_{33}H_{28}N_8O_5S_2$ 680.76	190-3 69	C 58.22 H 4.15 N 16.46	57.99 4.03 16.22	3410(NHs), 3100(Ar-CH), 2900(Aliph-CH), 1720 (CO), 1685, 1650, 1620(NH, C=C, C=N), 1340 and 1140 (SO2)
r			$C_{36}H_{28}N_8O_5S_2$ 716.79	200-3 54	C 60.32 H 3.94 N 15.63	60.43 4.19 15.1	3300 (NHs), 3100 (Ar-CH), 2923 (Aliph-CH), 1689 (CO),1629, 1615, 1580 (NH,C=C,C=N), 1384,1160 (SO2)
s			$C_{36}H_{29}N_7O_5S_2$ 719.79	203-5 56	C 60.07 H 4.06 N 13.62	60.09 4.10 14.01	3420(NHs), 3050(Ar-CH), 2910(Aliph-CH),1720 (CO), 1630, 1600, 1580 (NH,C=C, C=N), 1350 and 1150 (SO2)
t			$C_{35}H_{27}N_7O_5S_3$ 721.82	185-7 63	C 58.24 H 3.77 N 13.58	58.23 4.42 13.20	3400(NHs), 3050(Ar-CH), 2960(Aliph-CH),1720(CO), 1625, 1615, 1610(NH,C=C, C=N), 1310 and 1110 (SO2)

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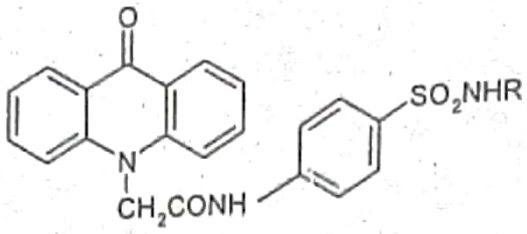
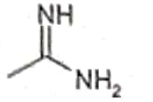
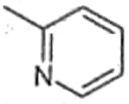
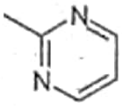
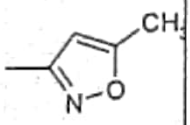


Table 4 : Experimental data of compound 4 (b-e)

Cpd No.	R	Molecular Formula M-wt	M.P. °C Yield %	Microanalysis		IR (cm^{-1})
				Calc.	Found	
4b		$C_{22}H_{19}N_5O_4S$ 449.48	325-8 39	C 58.79 H 4.26 N 15.58	59.01 4.19 15.60	3423,3237 (NHs), 3033 (Ar-CH), 2924 (Aliph-CH), 1704, 1631 (Cos), 1595,1524 (NH,C=C), 1384and1137 (SO_2)
c		$C_{26}H_{20}N_4O_4S.H_2O$ 502.54	305-8 40	C 62.14 H 4.41 N 11.15	61.69 4.11 11.15	3420, 3328 (NHs), 3063(Ar-CH),2991(Aliph-CH), 1680, 1629 (COs), 1560,1545(NH, C=C), 1344, 1138(SO_2)
d		$C_{25}H_{19}N_5O_4S$ 485.52	316-7 43	C 61.85 H 3.94 N 14.42	61.89 3.99 15.01	3250, 3100 (NHs), 3036(Ar-CH),2923(Aliph-CH), 1705, 1626 (COs), 1578,1500(NH, C=C), 1339, 1158(SO_2)
e		$C_{25}H_{20}N_4O_4S$ 488.52	322-5 65	C 61.47 H 4.13 N 11.47	61.70 4.29 11.79	3384 (NHs), 3066 (Ar-CH), 2926 (Aliph-CH), 1705,1627 (Cos), 1599,1540 (NH,C=C), 1337and1162 (SO_2)

Antitumor screening:

Twelve compounds (1a), (1b), (2a), (2b), (2e), (3a), (3e), (3g), (3m), (4a), (4b) and (4e) were selected and screened for antitumor activity in the National Cancer Institute, Cairo University using breast cell line. The antitumor screening was done following Skehan et al method.[27]

Cells were plated in 96-multiwell plate (10^4 cells/ well) for 24 hours before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentrations of the compound 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 hours at 37°C and in atmosphere of 5% CO_2. After 48 hours, cells were fixed, washed and stained with Sulforhodamine B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tris EDTA buffer. Color intensity was measured in an ELISA reader.

Table 5 : Probit (p) of the tested compounds that give probit regression 0.9

Compound No.	Concentration µg/ mL
1a	28.23
1b	28.73
2a	22.04
2b	29.97
2e	25.10
3a	29.36
3e	24.26
3g	19.34
3m	23.60
4a	28.72
4b	25.81
4e	32.07

CONCLUSION

The antitumor screening for compounds (1a), (1b), (2a), (2b), (2e), (3a), (3e), (3g), (3m), (4a), (4b) and (4e) revealed that monosubstitution by sulfaguanidine at position 9 of ethyl acridine 10-yl acetate (1a) or 5-methylisoxazol-3-yl as in compounds (1b, 4b, 4e) showed moderate activity. Also, compound (3a) bearing different sulfonamides at positions 9 and 10 had moderate activity. Disubstitution by similar

sulfonamide at positions 9 and 10 bearing 5-methylisoxazol-3-yl moiety (2e) possessed moderate activity. The other tested compounds exhibited no antitumor activity.

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Received: April. 02, 2009
Accepted: May, 28, 2009

Zagazig J. Pharm. Sci., June 2009
Vol. 18 , No. 1, pp. 40-50.

ISSN 1110-5089

تشييد بعض مشتقات الأكريدين المستبدلة من المتوقع أن يكون لها فاعلية مضادة للأورام

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تم في هذا البحث تشييد أربع مجموعات جديدة من مشتقات الأكريدين المتميزة بتركيب بنائي يزيد من احتمال فعاليتها كمضادات للأمراض السرطانية. تتضمن المجموعة الأولي مشتقات 9-فينيل إمينو أكريدين و تشمل المجموعة الثانية و الثالثة مشتقات 9- فينيل إمينو أكريدين-10-كربوكساميد، أما المجموعة الرابعة فهي مشتقات 9-أوكسوأكريدين-10-كربوكساميد . إن التركيب البنائي لجميع المركبات المشيدة يجعلها مشابهة لمركبات سبق تشييدها و ثبت فعالية بعض منها كمضادات للسرطان. ولقد تم اختبار اثنتي عشر مركبا في المعهد القومي للأورام و دراسة تاثيرها كمضادات لسرطان الثدي و ثبت أن لخمس منها فعالية متوسطة.