Dipartimento di Chimica e Tecnologie Farmaceutiche, Università degli Studi di Palermo, Italy

Synthesis of new 3-(3-phenyl-isoxazol-5-yl) or 3-[(3-phenyl-isoxazol-5-yl)-amino] substituted 4(3*H*)-quinazolinone derivatives with antineoplastic activity

D. Raffa, G. Daidone, D. Schillaci, B. Maggio and F. Plescia

A novel series of 3-(3-phenyl-isoxazol-5-yl) or 3-[(3-phenyl-isoxazol-5-yl)amino] substituted 4(3*H*)-quinazolinone derivatives was synthesized. The compounds were tested for their antineoplastic activity *in vitro* against Raji (human Burkitt limphoma), K-562 (human chronic myelogeneous leukemia) and U937 (human histiocytic limphoma) cell lines. The most active quinazolinones showed IC_{50} values in the range 16–30 μM.

1. Introduction

4(3*H*)-Quinazolinones bearing a pyrazole or isoxazole nucleus at N-3 have drawn our attention for a long time due to their interesting antiinflammatory, analgesic and antipyretic properties [1, 2] as well as their antimicrobial activity [3]. Moreover, compounds including the 3-heterocycle-substituted quinazolinone nucleus are known to posses antitumor activity.

The (1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinones and the 3-[(1,2-dihydro-1-R_1-2-oxo-3*H*-indol-3-yilidene)amino]-4(3*H*)-quinazolinones, taken as examples, are compounds with potential anticancer activity [4, 5]. It was also described that some quinazolonymercaptotriazoles were synthesized and tested for their potential antitumor activity [6]. For these reasons, with the aim to ascertain if the 3-(3-methyl-isoxazol-5-yl)-quinazolin-4(3*H*)-ones **1a**–**n**, previously synthesized for their antiinflammatory activity in our laboratories [2], were antitumor agents too, we tested them for their antiproliferative activity *in vitro* against Raji cells, a human leukemic cell line. In the set of compounds tested, only the quinazolinones **1g** and **1m** showed a moderate antiproliferative activity at 10^{-4} M (54.4 and 42.7% of growth inhibition, respectively) [7]. Thus, in order to improve the pharmacological activity, we performed the synthesis of new derivatives **2a**–**n**, whose isoxazole nucleus is substituted at C-3 position by a phenyl group.

This substitution seemed of to be of interest, keeping in mind that one of the mechanisms of antitumor drugs is intercalation in the DNA strains of the tumoral cells. The presence of the phenyl group at the C-3 position of the isoxazole nucleus therefore could improve the capability of compounds **2** to intercalate in DNA strains in view of more extension of the aromatic substituent.

Moreover, literature reports some 4(3*H*)-quinazolinones with potential antineoplastic activity bearing at N-3 an heterocyclic nucleus not directly bound but separated by a C or N atom [5, 8]. So we also synthesized the *N*(3)-[(3-phenyl-isoxazol-5-yl)amino]-quinazolin-4(3*H*)-ones **3b**, **c**, **f**, **l**, **m** to ascertain if the introduction of a NH bridge between the 4(3*H*)-quinazolinone and isoxazole nuclei could strengthen the antineoplastic activity of the corresponding compounds **2**.

2. Investigations, results and discussion

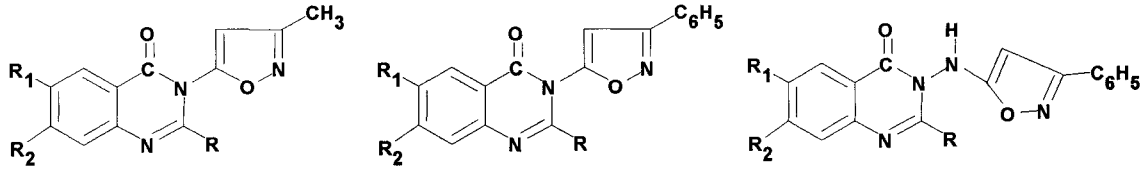
2.1. Synthesis

Compounds **1a**–**n** were known [2], the new derivatives **2a**–**n** and **3b**, **c**, **f**, **l**, **m** were obtained by different routes.

Compounds **2a**–**n** were synthesized by a previously described method (Scheme 1) [2]. The appropriate *N*-(3-phenyl-isoxazol-5-yl)-2-nitrobenzamides **6a**, **e**, **i** were thus synthesized starting from the opportune 2-nitroaroyl chloride [9] **4a**, **e**, **i** and 5-amino-3-phenylisoxazole [10] **5** in anhydrous chloroform. When compounds **6** were treated with stannous chloride in aqueous hydrochloric acid the corresponding *N*-(3-phenyl-isoxazol-5-yl)-2-aminobenzamides **7a**, **e**, **i** were obtained. By refluxing products **7** with the appropriate orthoester, the isoxazolylquinazolinones **2a**–**n** were obtained in very good yields.

Attempts to synthesize compounds **3** by the same route (Scheme 1) starting from the chlorides **4** and 1-(3-phenyl-isoxazol-5-yl)hydrazine **9** failed. However, the reaction of 3,1-benzoxazin-4-ones **8b**, **c** [11], **8f** [12], **8l** [13], **8m** [14], with **9** [15] gave a complex mixture: chromathographic and crystallization procedures afforded compounds **3b**, **c**, **f**, **l**, **m** in very poor yields (Scheme 2). The structures of the new compounds **2a**–**n** and **3b**, **c**, **f**, **l**, **m** were assigned on the basis of analytical as well as spectroscopic data.

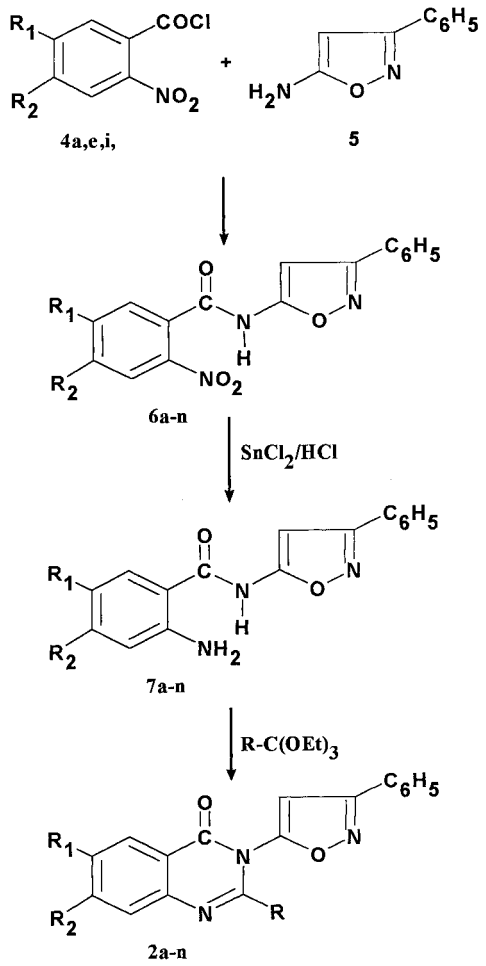
^{1}H NMR spectra of products **1a**–**n** and **2a**–**n** show the H-4 isoxazole proton resonance signal hardly affected by



1a-n **2a-n** **3b,c,f,l,m**

	a	b	c	d	e	f	g	h	i	l	m	n
R	H	CH_3	C_2H_5	C_6H_5	H	CH_3	C_2H_5	C_6H_5	H	CH_3	C_2H_5	C_6H_5
R_1	H	H	H	H	H	H	H	H	Cl	Cl	Cl	Cl
R_2	H	H	H	H	Cl	Cl	Cl	Cl	H	H	H	H

Scheme 1



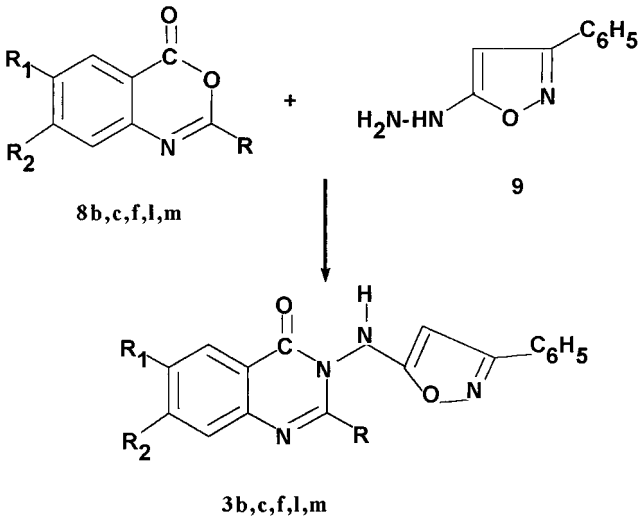
	a	b	c	d	e	f	g	h	i	l	m	n
R	H	CH_3	C_2H_5	C_6H_5	H	CH_3	C_2H_5	C_6H_5	H	CH_3	C_2H_5	C_6H_5
R_1	H	H	H	H	H	H	H	H	Cl	Cl	Cl	Cl
R_2	H	H	H	H	Cl	Cl	Cl	Cl	H	H	H	H

the C-2 substituent in the quinazolinone ring, being this signal progressively shielded when the C-2 substituent is H, CH_3 or C_2H_5 and C_6H_5, respectively (see Table 1). Probably this is due to the steric hindrance of the C-2 substituents which influence the dihedral angle between the two heterocyclic moieties. As a consequence, the H-4 isoxazole proton changes its position in respect of the deshielding zone of the carbonyl double bound. Moreover, in the case of the 2-phenyl substituent the relative upfield absorption of the H-4 proton resonance signal could be also due to the diamagnetic anisotropic effect of this substituent.

Table 1: H-4 isoxazole proton resonance signals [2, 15]

C-2 Quinazolinone substituent							
H		CH_3		C_2H_5		C_6H_5	
Compd.	δ	Compd.	δ	Compd.	δ	Compd.	δ
1a	6.83	**1b**	6.42	**1c**	6.40	**1d**	6.12
1e	6.73	**1f**	6.33	**1g**	6.33	**1h**	6.03
1i	6.76	**1l**	6.33	**1m**	6.30	**1n**	6.05
2a	7.27	**2b**	6.79	**2c**	6.78	**2d**	6.51
2e	7.26	**2f**	6.80	**2g**	6.78	**2h**	6.52
2i	7.26	**2l**	6.79	**2m**	6.78	**2n**	6.52

Scheme 2



	b	c	f	l	m
R	CH_3	C_2H_5	CH_3	CH_3	C_2H_5
R_1	H	H	H	Cl	Cl
R_2	H	H	Cl	H	H

2.2. Biological results and discussion

Compounds **2a**–**n** and **3b**, **c**, **f**, **l**, **m** were tested for their *in vitro* antineoplastic activity against Raji (human Burkitt lymphoma), K-562 (human chronic myelogenous leuke-

Table 2: Percent growth inhibition recorded on Raji, K-562 and U937 cell lines at 50 µM concentration of quinazolinone compounds

Compd.	RAJI	K-562	U937
2a	46.1	28.0	38.7
2b	44.0	ns	38.6
2c	71.6	36.9	59.9
2d	54.8	ns	30.0
2e	18.4	ns	22.7
2f	76.1	72.5	91.6
2g	85.9	64.5	92.4
2h	71.6	ns	ns
2i	16.0	20.9	43.8
2l	70.1	63.2	90.3
2m	66.9	68.1	87.7
2n	25.8	ns	20.9
3b	73.6	26.6	60.2
3c	91.0	37.4	69.3
3f	83.7	76.4	84.9
3l	76.6	55.3	73.5
3m	93.6	78.9	89.5
MTX*	72.0	84.8	73.6

MTX* = Metotrexate tested at 0.2 µM; values are the mean of at least three independent determinations; variation was less than 15%; ns = not significant

Table 3: IC_{50} (µM) recorded on Raji, K-562 and U937 cell lines of the most active quinazolinones.

Compd.	IC_{50} (µM)		
	Raji	K-562	U937
2f	22.9	23.0	22.4
2m	16.2	23.4	23.4
3f	24.5	30.0	25.7
3m	22.9	23.9	23.9

mia) and U937 (human histiocytic lymphoma) cell lines. The percent of growth inhibition of the compounds tested at 50 μM, compared to that of methotrexate at 0.2 μM, are reported in Table 2. The antiproliferative activity of compounds **2a**–**n** and **3b**, **c**, **f**, **l**, **m** was somewhat influenced by their substitution pattern. However, a coherent trend for all the cell lines was not observed. The prevalent trend of the activity of the tested compounds is that the 2-substituted compounds are more active than the unsubstituted ones; moreover, 3-phenyl-isoxazol-5-yl-substituted **2g** and **2m** showed against Raji cell lines a percentage growth inhibition (see introduction) greater than that of the 3-methyl isoxazol-5-yl-substituted compounds **1g** and **1m**, respectively.

For compounds **2f**, **2m**, **3f** and **3m**, which were overall the most active compounds, the IC_{50} values are reported in Table 3.

3. Experimental

All melting points were determined on a Büchi 530 capillary apparatus and are uncorrected; IR spectra were recorded with a Jasco IR-810 spectrophotometer as nujol mull supported on NaCl disks; ^{1}H NMR spectra were obtained using a Bruker AC-E 250 MHz spectrometer (tetramethylsilane as internal standard). Microanalyses (C, H, N) performed in the laboratories of the Institut de Chimie Pharmaceutique, Université de Genève, Switzerland, were within ±0.41% of the theoretical values.

3.1. Synthesis of the compounds

3.1.1. General procedure for 2-nitrobenzoyl chlorides **4e**, **i**

Crude 2-nitrobenzoyl chlorides **4e**, **i** were obtained by refluxing the opportunely substituted 2-nitrobenzoic acid (10 mmol) with thionyl chloride (8 ml) for 5 h [9]. After evaporation under reduced pressure, the crude liquid residue was used for the reaction with the aminoisoxazole **5**.

3.1.2. N-(3-Phenyl-isoxazol-5-yl)-2-nitrobenzamides **6a**, **e**, **i**

To a solution of 10 mmol (1.6 g) of 3-phenyl-5-aminoisoxazole **5**, absolute benzene (40 ml), 10 mmol (1.85 g) of the chloride **4a**, commercially available, **4e**, **i**, were added. The mixture was refluxed for 2 h. After cooling, the solid which separated out was filtered, washed first with benzene then with diluted HCl, aqueous dilute $NaHCO_3$ solution and water. The obtained product **6a**, **e**, **i** (Table 4) were crystallized from ethanol; yield 42–58%.

3.1.3. N-(3-Phenyl-isoxazol-5-yl)-2-aminobenzamides **7a**, **e**, **i**

Compounds **6a**, **e**, **i** (5.8 mmol) were added to a cold (0–5 °C) magnetically stirred suspension of stannous chloride (17 mmol) in concentrated HCl (7 ml) at such a rate that the temperature of the slurry was maintained below 10 °C. After complete addition, the mixture was left under a magnetic stirrer overnight. The white slurry thus obtained was diluted with cold water (80 ml). The solution was extracted with ethyl acetate (3 × 100 ml), the extract was dried (sodium sulfate) and evaporated under reduced pressure. The obtained solid (**7a**, **e**, **i**, Table 4) was crystallized from methanol; yields 27–44%.

Table 5: Physical and spectroscopical data of 3-(3-phenyl-isoxazol-5-yl)-4(3*H*)-quinazolinones 2a–n

Compd.	Yield	Mp (°C)	Crystallization solvent	Formula	IR cm^{-1}
					ν (CO)
2a	50	164–166	ethanol	$C_{17}H_{11}N_3O_2$	1710
2b	50	124	ethanol	$C_{18}H_{13}N_3O_2$	1705
2c	50	104	ethanol	$C_{19}H_{15}N_3O_2$	1705
2d	73	200	ethanol	$C_{23}H_{15}N_3O_2$	1710
2e	40	209	benzene	$C_{17}H_{10}ClN_3O_2$	1700
2f	40	135–140	benzene	$C_{18}H_{12}ClN_3O_2$	1700
2g	40	140	ethanol	$C_{19}H_{14}ClN_3O_2$	1700
2h	44	213	benzene	$C_{23}H_{14}ClN_3O_2$	1700
2i	30	190–195	benzene	$C_{17}H_{10}ClN_3O_2$	1700
2l	63	180–186	ethanol	$C_{18}H_{12}ClN_3O_2$	1700
2m	75	145	ethanol	$C_{19}H_{14}ClN_3O_2$	1700
2n	36	210	benzene	$C_{23}H_{14}ClN_3O_2$	1718

^{1}H NMR ($CDCl_3$) (δ): **2a** 7.27 (s, 1H, isoxazole H-4), 7.49–8.41 (m, 9H, C_6H_5 and C_6H_4), 8.72 (s, 1H, quinazolinone H-2). **2b** 2.43 (s, 3H, CH_3), 6.79 (s, 1H, isoxazole H-4), 7.48–8.29 (m, 9H, C_6H_5 and C_6H_4). **2c** 1.32 (t, 3H, CH_3), 2.60 (q, 2H, CH_2) 6.78 (s, 1H, isoxazole H-4), 7.48–8.29 (m, 9H, C_6H_5 and C_6H_4). **2d** 6.51 (s, 1H, isoxazole H-4), 7.34–8.34 (m, 14H, 2 × C_6H_5 and C_6H_4). **2e** 7.25 (s, 1H, isoxazole H-4), 7.49–8.34 (m, 8H, C_6H_5 and C_6H_3), 8.72 (s, 1H, quinazolinone H-2). **2f** 2.41 (s, 3H, CH_3), 6.80 (s, 1H, isoxazole H-4), 7.42–8.19 (m, 8H, C_6H_3 and C_6H_4). **2g** 1.32 (t, 3H, CH_3), 2.58 (q, 2H, CH_2) 6.78 (s, 1H, isoxazole H-4), 7.42–8.19 (m, 9H, C_6H_5 and C_6H_4). **2h** 6.52 (s, 1H, isoxazole H-4), 7.34–8.26 (m, 13H, 2× C_6H_5 and C_6H_3). **2i** 7.23 (s, 1H, isoxazole H-4), 7.47–8.32 (m, 8H, C_6H_5 and C_6H_3), 8.68 (s, 1H, quinazolinone H-2). **2l** 2.41 (s, 3H, CH_3), 6.79 (s, 1H, isoxazole H-4), 7.49–8.22 (m, 8H, C_6H_3 and C_6H_4). **2m** 1.31 (t, 3H, CH_3), 2.60 (q, 2H, CH_2) 6.78 (s, 1H, isoxazole H-4), 7.48–8.22 (m, 9H, C_6H_5 and C_6H_4). **2n** 6.52 (s, 1H, isoxazole H-4), 7.37–8.30 (m, 13H, 2 × C_6H_5 and C_6H_3).

3.1.4. 3-(3-Phenyl-isoxazol-5-yl)-4(3H)-quinazolinones **2a**–**n**

Aminobenzamides **7a**, **e**, **i** (10 mmol) and triethyl orthoester (20 ml) were heated under reflux for 5 h. After cooling, the crystalline solid (**2a**–**n**) which separated out was recrystallized from the opportune solvent (Table 5); yields 30–75%.

3.1.5. General procedure for 3,1-benzoxazinones **8b**, **c**, **f**, **l**, **m**

Benzoxazinones **8** were synthesized by the methods previously described in literature [11–14]. The opportune anhydride (0.4 mol) and the appropriate anthranilic acid (0.05 mol) were heated under reflux for 1 h. The benzoxazinones **8c**, **f**, **l**, **m** were obtained, after cooling, as crude solids which separated out from the solution, while, for compound **8b**, it was needful to evaporate the excess of acetic anhydride under reduced pressure. All compounds **8** were used for the following reaction without any purification procedure.

3.1.6. N(3) [(3-phenyl-isoxazol-5-yl)amino]quinazolin-4(3H)-ones **3b**, **c**, **f**, **l**, **m**

Equimolar amounts (12 mmol) of 1-(3-phenyl-isozaxol-5-yl)hydrazine **9** [15] and benzoxazinone **8b**, **c**, **f**, **l**, **m** were heated under reflux for 3 h in acetic acid (40 ml). After this time, the solution was poured into 400 ml of cold water, and the solid which separated out was collected and dried; if a gummy residue was formed, it was solidified by adding a few millilitres of ethanol.

The obtained solid from the reaction was a complex mixture by which quinazolinones **3** were isolated by flash chromatography [17]: diameter of

Table 4: Physical and spectroscopic data of benzamides 6e,i and 7a,e,i

Compd.	Yield	Mp (°C)	Crystallization solvent	Formula	IR (Nujiol, cm^{-1})	
					ν (CO)	ν (NH)
6e	43	215–230	ethanol	$C_{16}H_{10}ClN_3O_4$	1700	3400–3000
6i	42	196–200	ethanol	$C_{16}H_{10}ClN_3O_4$	1670	3300–3020
					ν (CO)	ν (NH and NH_2)
7a	27	202–204	methanol	$C_{16}H_{13}N_3O_2$	1675	3520–3100
7e	27	205–207	methanol	$C_{16}H_{12}ClN_3O_2$	1670	3520–3120
7i	44	190–192	methanol	$C_{16}H_{12}ClN_3O_2$	1660	3520–3040

^{1}H NMR (DMSO-d_6) (δ): **6e** 6.94 (s, 1H. isoxazole H-4), 7.53–8.33 (m, 8H, C_6H_5 and C_6H_3), 12.63 (br s, 1H, NH, exchangeable with D_2O). **6i** 6.93 (s, 1H, isoxazole H-4), 7.53–8.26 (m, 8H, C_6H_3), 12.60 (br s, 1H, NH, exchangeable with D_2O). **7a** 6.59–7.89 (m, 9H, C_6H_5, C_6H_4 and isoxazole H-4). **7e** 6.61–7.91 (m, 8H, C_6H_5, C_6H_3 and isoxazole H-4). **7i** 6.81–7.88 (m, 9H, C_6H_5, C_6H_3 and isoxazole H-4).

Table 6: Physical and spectroscopic data of N(3)[(3-phenyl-isoxazol-5-yl)amino]-quinazolin-4(3H)-ones 3b, c, f, l, m

Compd.	Yield	Mp (°C)	Crystallization solvent	Formula	IR (Nujiol, cm^{-1})	
					ν (CO)	ν (NH)
3b	24	199–201	ethanol	$C_{18}H_{14}N_4O_2$	1700	3220–3080
3c	24	147–148	ethanol	$C_{19}H_{16}N_4O_2$	1710	3240–3080
3f	23	204–205	ethanol	$C_{18}H_{13}ClN_4O_2$	1710	3220–3080
3l	25	184–185	ethanol	$C_{18}H_{13}ClN_4O_2$	1710	3240–3000
3m	24	186–187	ethanol	$C_{19}H_{15}ClN_4O_2$	1695	3220–3000

^{1}H NMR (DMSO-d_6) (δ): **3b** 2.73 (s, 3H, CH_3), 4.32 (s, 1H, isoxazole H-4), 7.34–8.22 (m, 9H, C_6H_5 and C_6H_4), 8.50 (s, 1H, NH, exchangeable with D_2O), **3c**: 1.38 (t, 3H, CH_3), 3.03 (br s, 2H, CH_2), 5.64 (s, 1H, isoxazole H-4), 7.31–8.22 (m, 9H, C_6H_5 and C_6H_4), 8.43 (s, 1H, NH exchangeable with D_2O). **3f** 2.73 (s, 3H, CH_3), 5.70 (s, 1H, isoxazole H-4), 7.38–7.70 (m, 9H, C_6H_5, C_6H_3 and exchangeable NH). **3l**: 2.73 (s, 3H, CH_3), 5.71 (s, 1H, isoxazole H-4), 7.37–7.66 (m, 9H, C_6H_5, C_6H_3 and exchangeable NH). **3m**: 1.38 (t, 3H, CH_3), 3.04 (br s, 2H, CH_2), 5.66 (s, 1H, isoxazole H-4), 7.33–8.16 (m, 9H, C_6H_5, C_6H_3 and exchangeable NH).

column 5 cm, silica gel (32–63 μm) (200 g), eluant chloroform-ethyl acetate 7:3, each fraction 50 ml. The fractions 22–35 were collected and evaporated under reduced pressure to give compounds **3** (Table 6) which were crystallized from ethanol.

3.2 Cytotoxicity studies in vitro

Compounds **2a**–**n** and **3b**, **c**, **f**, **l**, **m** were tested *in vitro* for antiproliferative activity against Raji (human Burkitt lymphoma), K-562 (human chronic myelogenous leukemia) and U937 (human histiocytic lymphoma) cell lines. These cell lines were grown at 37 °C in a humidified atmosphere containing 5% CO_2, in RPMI-1640 medium (Biochrom KG) supplemented with 10% fetal calf serum and antibiotics. Methotrexate (MTX), whose activity as antileukemic is well known, was used as reference compound.

Raji, K-562 and U937 cells were suspended at a density of 1×10^5 cells per ml in growth medium, transferred to 24-well plate (1 ml per well), cultured with or without screening concentration of compounds and incubated at 37 °C for 72 h or 48 h in the case of K-562 [18].

Numbers of viable cells were determined by counting in a hematocymeter after dye esclusion with trypan blue. The antiproliferative effects of the compounds were estimated in terms of percent growth inhibition, the activity of those compounds which showed a value of percent growth inhibition greater than 15%, at screening concentration of 50 μM, was reported. We determined the IC_{50} values (test agent concentration at which the cell proliferation was inhibited to 50% of the untreated growth control) for compounds **2f**, **2m**, **3f**, **3m** which exhibited the best activities at screening concentration.

References

1 Daidone, G.; Maggio, B.; Raffa, D.; Plescia, S.; Bajardi, M. L.; Caruso, A.; Cutuli, V. M. C.; Amico-Roxas, M.: Eur. J. Med. Chem. **29**, 707 (1994)

2 Plescia, S.; Daidone, G.; Raffa, D.; Bajardi, M. L.; Caruso, A.; Cutuli, V. M. L.; Amico-Roxas M.: Il Farmaco **47** (4), 465 (1992)

3 Raffa, D.; Daidone, G.; Plescia, S.; Schillaci, D.: Pharmazie **46**, 667 (1991)

4 Parkanyl, C.; Liang Tuan, H.; Strömberg, D. H. F.; Eienzahav, A.: J. Heterocycl. Chem. **29**, 749 (1992)

5 Labouta, J. M.; Salama, H. M.; Eshba, N. H.; El-Chrbini, E.: Acta Pharm. Jugosl. **38**, 189 (1988)

6 Joshi, P. C.; Sah, M. M.; Pant, C. K.: J. Indian Chem. Soc. **68** (7), 416 (1991)

7 Not published data

8 Samia, M. R.; Farid, S.; Soliman, G.; El-Sayed, A. M. B.: Pharmazie **41**, 563 (1986)

9 Palmer, M. H., McVie, G. J.: J. Chem. Soc. (B), 745 (1968)

10 Shaw, G.; Sugowbz, G.: J. Chem. Soc. 665 (1954) and references cited therein

11 Zentmeyer, D. T.; Wagner, E. C.: J. Org. Chem. **14**, 967 (1949)

12 Desai, D. R.; Patel, V. S.; Patel, S. R.: J. Indian Chem. Soc. **43**(5), 351 (1966)

13 Tomisek, A. J.; Christensen, B. E.: J. Am. Chem. Soc. **70**, 2423 (1948)

14 Marchetti, E.; Bergesi, G; Mattalia, G.: Ann. Chim. **52**, 836 (1962)

15 Adembri, G.; Ponticelli, F.; Tedeschi, P.: J. Heterocycl. Chem. **6** (6), 783 (1969)

16 Plescia, S.; Bajardi, M. L.; Daidone, G.: Boll. Chim. Farm. **121**, 563 (1982)

17 Still, W. C.; Khan, H.; Mitra, A.: J. Org. Chem. **43**, 2923 (1978)

18 Manfredini, S.; Bazzanini, R.; Baraldi, P. G.; Guarneri, M. Simoni, D.; Marongiu, M. E.; Pani, A.; Tramontano, E.; La Colla, P.: J. Med. Chem. **35**, 917 (1992)

Received April 4, 1998
Accepted July 7, 1998

Prof. Giuseppe Daidone
via Archirafi, 32
90123 Palermo
Italy