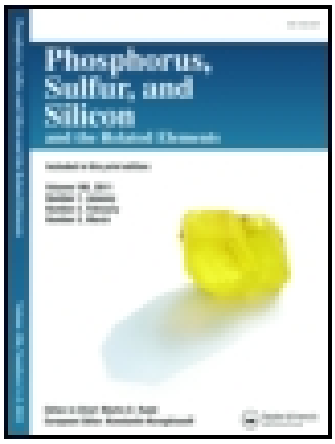

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Studies on Quinazolines. Part I. Annelation to the Quinazoline Ring Utilizing Amino Acid Esters

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STUDIES ON QUINAZOLINES. PART I. ANNELATION TO THE QUINAZOLINE RING UTILIZING AMINO ACID ESTERS

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The reaction of quinazoline-4(3H)-thiones ***2a–d*** *with amino acid ester hydrochlorides in boiling solvents, under the basic catalysis, afforded the corresponding substitution products* ***(3–6)a–e*** *in low yield. The reaction could be improved by carrying it without a solvent yielding imidazo[1,2-c]- and pyrimido[1,2-c]quinazolines* ***(7–10)a–e****. The antibacterial and antifungal activities of the prepared compounds were tested.*

Keywords: Annelated quinazoline derivatives; antimicrobial activities; quinazoline-4(3H)-thione derivatives

The recent literature contains much information concerning the synthesis and pharmacological activity of the quinazolines.[1–4] Particular interest is focused on condensed quinazolines, where a synergistic effect resulting from the combination with other pharmacophores or new types of activity is expected.[2,5]

Various tricyclic annelated derivatives of quinazoline have recently received significant importance because of their diverse biological properties; many of them such as imidazo[1,2-c]- and pyrimido[1,2-c] quinazolines show marked adrenomimetic, psychoanaleptic, broncholytic, and antidepressant properties.[6–8] The most common route for preparation of the annelated quinazolines involves reaction of 4-chloro- or 2,4-dichloroquinazolines with aziridine, ethylenediamine, or amino alcohol followed by cyclization in the presence of a suitable condensation

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agent.[8,9] In continuation of our investigation on biologically active derivatives among six-membered heterocycles,[10,11] it was considered worthwhile to extend our previous studies[12,13] to synthesize some new annelated quinazoline derivatives.

2-Methyl-4(3H)-quinazolinethione **1** is a convenient precursor to the target 2-[2-(4-methoxy- or 4-nitro-phenyl)ethenyl]-, 2-(2-phenyl-1-propenyl)-, 2-(1,3-dioxoindan-2-yl)-4(3H)-quinazolinethiones **2a–d**. Direct thionation of 2-methyl-4(3H)-quinazolinone[14] with P_2S_5 in boiling xylene afforded the corresponding 2-methyl-4(3H)-quinazolinethione **1** in low yield.[15]

Thus, we preferred to synthesize the starting thione **1** by reaction of 2-methyl-4(3H)-quinazolinone[14] with phosphorus pentachloride and phosphorus oxychloride to give 4-chloro-2-methylquinazoline,[16] which upon subsequent reaction with thiourea in boiling ethanol furnished the corresponding thione **1** in good yield.[17] The target thiones **2a–d** were prepared by condensing thione **1** with appropriate aromatic aldehydes, namely, p-anisaldehyde or p-nitrobenzaldehyde, acetophenone, and phthalic anhydride under different reaction conditions to yield 2-[2-(4-methoxy- or 4-nitro-phenyl)ethenyl]-4(3H)-quinazolinethiones **2a**,**b**, 2-(2-phenyl-1-propenyl)-4(3H)-quinazolinethione **2c** and 2-(1,3-dioxoindan-2-yl)-4(3H)-quinazolinethione **2d** respectively.

Unlike their oxy analogues, the enhanced leaving group ability of sulfur in the thione **2** allows direct substitution of the thiol group with an amino group of the corresponding amino acids. Thus, the reaction of thiones **2a–d** with the methyl ester hydrochloride of glycine, L-serine, L-valine, L-leucine and β-alanine in boiling solvents under basic catalysis, furnished the corresponding substitution products methyl N-{2-[2-(4-methoxy- or 4-nitro-phenyl)ethenyl]-, 2-(2-phenyl-1-propenyl)- or 2-(1,3-dioxoindan-2-yl)-quinazolin-4-yl}amino-acetate, -3-hydroxypropionate, -3-methylbutanoate, -4-methylpentanoate, or -propanoate **(3–6)$_{a-e}$** in low yield. Variation of reaction condition led us to the conclusion that esters of amino acids reacted very reluctantly and that this approach is of little preparative value. The procedure could be improved significantly by carrying it out without a solvent. At the melting temperature, when the reaction mixture becomes homogenous not only nucleophilic substitution was facilitated but thermal cyclization also occurred to give directly 5-[2-(4-methoxy- or 4-nitro-phenyl)ethenyl]-, 5-(2-phenyl-1-propenyl)- or 5-(1,3-dioxoindan-2-yl)-3-oxo-2H-imidazo[1,2-c]quinazolines **(7–10)$_a$**; 5-[2-(4-methoxy- or 4-nitro-phenyl)ethenyl]-, 5-(2-phenyl-1-propenyl)- or 5-(1,3-dioxoindan-2-yl)-2-hydroxymethyl-, 2-(2-propyl)- or 2-(2-methylpropyl)-3-oxo-2H-imidazo[1,2-c]quinazolines **(7–10)$_{b-d}$** and 6-[2-(4-methoxy- or 4-nitro-phenyl)ethenyl]-, 6-(2-phenyl-1-propenyl)- or

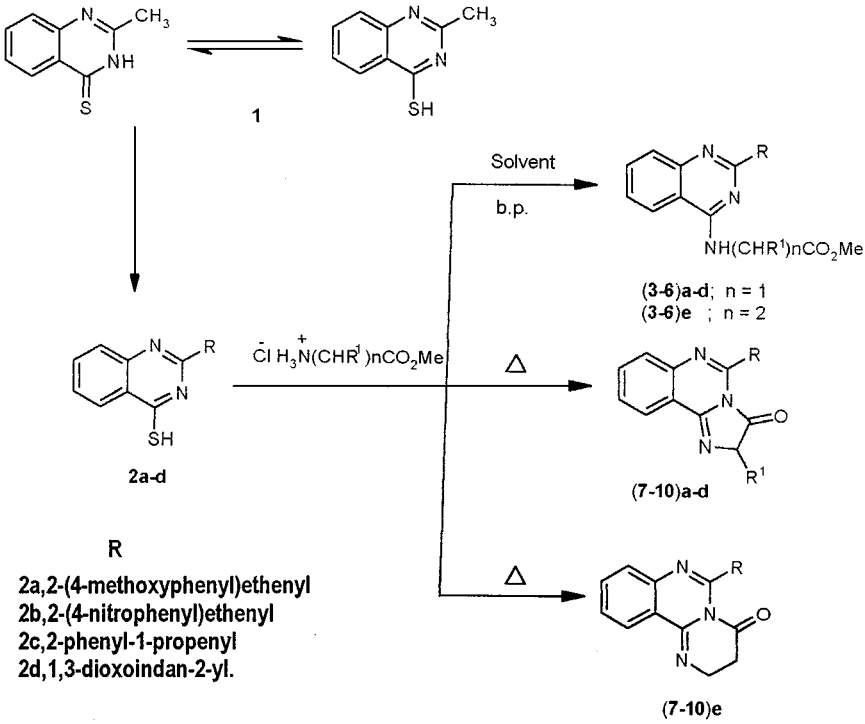

FIGURE 1

6-(1,3-dioxoindan-2-yl)-4-oxo-2H, 3H-pyrimido[1,2-c]quinazolines **(7–10)$_e$**. The structures of all prepared compounds (Figure 1) were confirmed from their physical and spectral data (Table I and II).

SCREENING FOR AN ANTIMICROBIAL ACTIVITY

The performed antimicrobial activities of the synthesised derivatives were determined in vitro by the filter paper disc method.[18] All compounds were tested for activity against gram-positive, gram-negative bacteria, and selected fungi using methaqualone as a reference standard. The culture medium was normal nutrient agar (NA) supplemented with 1 g of yeast per mililiter. According to the solubility of the tested compounds different polar and nonpolar solvents were used, and a good solubility was found in 10% acetone (V/V) for all test compounds. Based on the previous preliminary test, closely spaced test concentrations (500, 250, 125 μg/ml) were selected. Methaqualone was dissolved

TABLE I Analytical Data of Compounds (**3–10**)$_{\mathbf{a–e}}$

Compd. no.	R [a]*	R^1	MP [b] θm/°C	Yield [c] i	ii	iii	Mol. formula	Calcd. (found) (%) C	H	N
3a	A	H	166[a]	37	40	—	$C_{20}H_{19}N_3O_3$	68.8 (68.9)	5.4 5.6	12.0 12.3)
3b	A	CH_2OH	202[e]	34	35	—	$C_{21}H_{21}N_3O_4$	66.5 (66.7)	5.5 5.7	11.1 11.3)
3c	A	$CH(CH_3)_2$	192[d]	41	42	—	$C_{23}H_{25}N_3O_3$	70.6 (70.8)	6.4 6.6	10.7 10.9)
3d	A	$CH_2CH(CH_3)_2$	175[d]	33	34	—	$C_{24}H_{27}N_3O_3$	71.1 (71.4)	6.7 6.9	10.4 10.6)
3e	A	H	190[d]	40	43	—	$C_{21}H_{21}N_3O_3$	69.4 (69.6)	5.8 5.4	11.6 11.8)
4a	B	H	200[e]	45	45	—	$C_{19}H_{16}N_4O_4$	62.6 (62.8)	4.4 4.8	15.4 15.8)
4b	B	CH_2OH	164[b]	37	38	—	$C_{20}H_{18}N_4O_5$	60.9 (60.6)	4.6 4.8	14.2 14.4)
4c	B	$CH(CH_3)_2$	177[b]	47	46	—	$C_{22}H_{22}N_4O_4$	65.0 (65.3)	5.4 5.6	13.8 13.5)
4d	B	$CH_2CH(CH_3)_2$	190[d]	38	38	—	$C_{23}H_{24}N_4O_4$	65.7 (65.9)	5.7 5.9	13.3 13.6)
4e	B	H	180[d]	47	47	—	$C_{20}H_{18}N_4O_4$	63.5 (63.8)	4.8 5.0	14.8 14.4)
5a	C	H	160[b]	45	44	—	$C_{20}H_{19}N_3O_2$	72.1 (72.4)	5.7 5.9	12.6 12.9)
5b	C	CH_2OH	188[d]	36	38	—	$C_{21}H_{21}N_3O_3$	69.4 (69.8)	5.8 5.7	11.6 11.7)
5c	C	$CH(CH_3)_2$	178[d]	40	42	—	$C_{23}H_{25}N_3O_2$	73.6 (73.8)	6.7 6.8	11.2 11.4)
5d	C	$CH_2CH(CH_3)_2$	167[c]	40	40	—	$C_{24}H_{27}N_3O_2$	74.0 (74.1)	6.9 6.6	10.8 10.5)
5e	C	H	147[a]	44	45	—	$C_{21}H_{21}N_3O_2$	72.6 (72.8)	6.1 6.4	12.1 12.3)
6a	D	H	156[a]	48	47	—	$C_{20}H_{15}N_3O_4$	66.5 (66.7)	4.2 4.4	11.6 11.8)
6b	D	CH_2OH	168[c]	37	38	—	$C_{21}H_{17}N_3O_5$	64.5 (64.6)	4.3 4.6	10.7 10.8)
6c	D	$CH(CH_3)_2$	195[e]	41	43	—	$C_{23}H_{21}N_3O_4$	68.5 (68.6)	5.2 5.3	10.4 10.7)
6d	D	$CH_2CH(CH_3)_2$	182[e]	32	34	—	$C_{24}H_{23}N_3O_4$	69.1 (69.3)	5.5 5.8	10.1 10.5)
6e	D	H	172[d]	47	47	—	$C_{21}H_{17}N_3O_4$	67.2 (67.4)	4.5 4.7	11.2 11.4)
7a	A	H	247[g]	—	—	84	$C_{19}H_{15}N_3O_2$	71.9 (71.7)	4.7 4.9	13.2 13.4)
7b	A	CH_2OH	254[h]	—	—	81	$C_{20}H_{17}N_3O_3$	69.2 (69.3)	4.9 5.1	12.1 12.3)
7c	A	$CH(CH_3)_2$	239[h]	—	—	85	$C_{22}H_{21}N_3O_2$	73.5 (73.6)	5.8 5.4	11.7 11.8)

TABLE I Analytical Data of compounds (**3–10**)$_{\mathbf{a–e}}$ *(Continued)*

Compd. no.	R [a]*	R^1	MP [b] θm/°C	Yield [c] i	ii	iii	Mol. formula	Calcd. (found) (%) C	H	N
7d	A	$CH_2CH(CH_3)_2$	277[g]	—	—	80	$C_{23}H_{23}N_3O_2$	73.9 (73.8)	6.1 6.3	11.3 11.5)
7e	A	—	214[f]	—	—	86	$C_{20}H_{17}N_3O_2$	72.5 (72.7)	5.1 5.4	12.7 12.9)
8a	B	H	272[d]	—	—	79	$C_{18}H_{12}N_4O_3$	65.1 (65.3)	3.6 3.9	16.9 16.7)
8b	B	CH_2OH	262[d]	—	—	74	$C_{19}H_{14}N_4O_4$	62.9 (63.1)	3.9 4.1	15.5 15.7)
8c	B	$CH(CH_3)_2$	256[d]	—	—	76	$C_{21}H_{18}N_4O_3$	67.4 (67.6)	4.8 4.6	15.0 14.8)
8d	B	$CH_2CH(CH_3)_2$	224[d]	—	—	73	$C_{22}H_{20}N_4O_3$	68.0 (68.1)	5.2 5.4	14.4 14.8)
8e	B	—	205[d]	—	—	79	$C_{19}H_{14}N_4O_3$	65.9 (65.8)	4.0 4.2	16.2 16.4)
9a	C	H	220[e]	—	—	85	$C_{19}H_{15}N_3O$	75.7 (75.8)	5.0 5.2	14.0 14.2)
9b	C	CH_2OH	243[f]	—	—	80	$C_{20}H_{17}N_3O_2$	72.5 (72.8)	5.1 5.3	12.7 12.9)
9c	C	$CH(CH_3)_2$	232[f]	—	—	82	$C_{22}H_{21}N_3O$	76.9 (76.8)	6.1 6.3	12.2 12.4)
9d	C	$CH_2CH(CH_3)_2$	263[g]	—	—	80	$C_{23}H_{23}N_3O$	77.3 (77.4)	6.4 6.6	11.8 11.9)
9e	C	—	186[d]	—	—	87	$C_{20}H_{17}N_3O$	76.2 (76.4)	5.4 5.8	13.3 13.5)
10a	D	H	227[h]	—	—	90	$C_{19}H_{11}N_3O_3$	69.3 (69.4)	3.3 3.5	12.8 12.7)
10b	D	CH_2OH	233[h]	—	—	83	$C_{20}H_{13}N_3O_4$	66.9 (66.8)	3.6 3.8	17.8 17.7)
10c	D	$CH(CH_3)_2$	243[g]	—	—	81	$C_{22}H_{17}N_3O_3$	71.2 (71.4)	4.6 4.8	11.3 11.5)
10d	D	$CH_2CH(CH_3)_2$	214[f]	—	—	78	$C_{23}H_{19}N_3O_3$	71.7 (71.8)	4.9 5.2	10.9 10.8)
10e	D	—	252[g]	—	—	85	$C_{20}H_{13}N_3O_3$	60.0 (60.2)	3.8 4.1	12.2 12.5)

[a] A = 2-(4-methoxyphenyl)ethenyl; B = 2-(4-nitrophenyl)ethenyl; C = 2-phenyl-1-propenyl; D = 1,3-dioxoindan-2-yl.

[b] solvent for crystallisation.

[a]Benzene-pet. ether (p.b. 40–60°).

[b]Benzene.

[c]Dioxane.

[d]Ethanol.

[e]Methanol.

[f]Acetic acid.

[g](Methanol + benzene).

[h](Ethanol + dimethyl formamide).

[c] Yield was determined in different boiling solvent: i) tetrahydrofuran, ii) dioxane, iii) without solvent (fusion).

TABLE II Spectral Data of Compounds (**3a–10c**)

Compd. no.	IR (KBr)cm^{-1}	^{1}H NMR (DMSO) δ/ppm [a]
3a	3340–3225 (NH); 1743–1720 (CO); 1610 (CN)	3.5 (s, 3H, OCH_3); 3.9 (s, 3H, $ArOCH_3$); 4.3 (s, 2H, NCH_2O); 6.6 (d, 1H, J = 14 Hz, =CHAr); 6.9 (d, 1H, J = 14 Hz, =CH-heteryl); 7.3–8.8 (m, 8H, Ar—H); 12.5 (s, br, 1H, NH)
3c	3270–3200 (NH); 2935–2915 (alkyl-H); 1735–1715 (CO); 1603 (CN)	0.9 (d, 6 H, J = 7 Hz, 2 x CH_3); 1.6 (m, 1H, —CH); 3.4 (s, 3 H, OCH_3); 3.85 (s, 3H, $ArOCH_3$); 4.5 (d, 1H, J = 7 Hz, NCHCO); 6.7 (d, 1H, J = 14 Hz, =CH—Ar); 6.95 (d, 1H, J = 14 Hz, =CH-heteryl); 7.4–8.8 (m, 8H, Ar—H); 12.1 (s, br, 1H, NH)
3e	3285–3160 (NH); 2975–2925 (alkyl-H); 1740–1725 (CO); 1608 (CN)	2.6 (t, 2H, J = 7 Hz, CH_2N); 3.3 (t, 2H, J = 7 Hz, CH_2CO); 3.5 (s, 3H, OCH_3); 3.85 (s, 3H, $ArOCH_3$); 6.6 (d, 1H, J = 14 Hz, =CHAr); 6.9 (d, 1H, J = 14 Hz, =CH-heteryl); 7.4–8.7 (m, 8H, Ar—H); 11.9 (s, br, 1H, NH)
4b	3500–3390 (OH); 3285–3170 (NH); 1745–1728 (CO); 1615 (CN)	2.1 (d, 2H, CH_2); 3.4 (s, 3H, OCH_3); 4.2 (t, 1H, NCHCO); 4.6 (t, 1H, CH_2OH); 6.8 (d, 1H, J = 14 Hz, =CHAr); 6.95 (d, 1H, J = 14 Hz, =CH-heteryl); 7.4–8.8 (m, 8H, Ar—H); 12.8 (s, br, 1H, NH)
4c	3280–3100 (NH); 2930–2840 (alkyl-H); 1738–1725 (CO); 1606 (CN)	1.1 (d, 6H, J = 7 Hz, 2x CH_3); 1.5 (m, 1H, —CH); 3.5 (s, 3H, OCH_3), 4.3 (d, 1H, J = 7 Hz, NHCO); 6.7 (d, 1H, J = 14 Hz, =CHAr); 6.9 (d, 1H, J = 14 Hz, =CH-heteryl); 7.3–8.7 (m, 8H, Ar—H); 12.6 (s, br, 1H, NH)
4e	3290–3200 (NH); 2900–2860 (alkyl-H); 1735–1720 (CO); 1608 (CN)	2.5 (t, 2H, J = 7 Hz, CH_2N); 3.4 (t, 2H, J = 7 Hz, CH_2CO); 3.6 (s, 3H, OCH_3); 6.7 (d, 1H, J = 14 Hz, =CHAr); 6.9 (d, 1H, J = 14 Hz, =CH-heteryl); 7.5–8.8 (m, 8H, Ar—H); 12.7 (s, br, 1H, NH)
7a	1668–1660 (CO); 1610 (CN)	3.9 (s, 3H, $ArOCH_3$); 4.5 (s, 2H, cyclic NCH_2CO); 6.7 (d, 1H, J = 14 Hz, =CHAr); 6.9 (d, 1H, J = 14 Hz, =CH-heteryl); 7.2–8.8 (m, 8H, Ar—H)
8c	2920–2870 (alkyl-H); 1670–1650 (CO); 1605 (CN)	1.1 (d, 6H, J = 7 Hz, 2x CH_3); 1.6 (m, 1H, —CH); 4.8 (d, 1H, J = 7 Hz, cyclic NCHCO); 6.7 (d, 1H, J = 14 Hz, =CHAr); 6.85 (d, 1H, J = 14 Hz, =CH-heteryl); 7.2–8.7 (m, 8H, Ar—H)
8e	2930–2880 (alkyl-H); 1665–1655 (CO); 1610 (CN)	2.9 (t, 2H, J = 7 Hz, cyclic CH_2N); 3.7 (t, 2H, J = 7 Hz, cyclic CH_2CO); 6.7 (d, 1H, J = 14 Hz, =CHAr); 6.9 (d, 1H, J = 14 Hz, =CH-heteryl); 7.3–8.8 (m, 8H, Ar—H)
9a	2850–2820 (alkyl-H); 1669–1660 (CO); 1602 (CN)	2.1 (d, 3H, CH_3 due to long range coupling); 4.5 (s, 2H, cyclic NCH_2CO); 6.5 (s, 1H, =CH); 7.2–8.8 (m, 9H, Ar—H)
10c	2905–2840 (alkyl-H); 1778–1740 (CO); 1690–1670 (CO); 1610 (CN)	1.1 (d, 6H, J = 7 Hz, 2x CH_3); 1.6 (m, 1H, —CH); 4.8 (d, 1H, J = 7 Hz, cyclic NCHCO); 5.0 (s, 1H, cyclic COCHCO), 7.3–8.8 (m, 8H, Ar—H)

[a] All NH signals were exchangeable with deuterium oxide.

TABLE III Activity (A) and Minimum Inhibitory Concentration (MIC) Calculated as mmol/ml for Compounds (**3b–10e**)

Compd.	Bacillus cereus		Bacillus subtilis		Escherichia coli		Aspergillus niger	
no.	A	MIC	A	MIC	A	MIC	A	MIC
3b	++	0.13×10^{-2}	++	0.13×10^{-2}	+	0.65×10^{-3}	++	0.65×10^{-3}
3d	++	0.12×10^{-2}	++	0.61×10^{-3}	+	0.61×10^{-3}	++	0.12×10^{-2}
4b	++	0.63×10^{-3}	++	0.31×10^{-3}	++	0.63×10^{-3}	++	0.63×10^{-3}
4c	++	0.61×10^{-3}	++	0.30×10^{-3}	++	0.30×10^{-3}	++	0.30×10^{-3}
4d	+	0.29×10^{-3}	++	0.59×10^{-3}	++	0.59×10^{-3}	+	0.29×10^{-3}
5b	+	0.69×10^{-3}	+	0.69×10^{-3}	++	0.14×10^{-2}	+	0.69×10^{-3}
5d	+	0.64×10^{-3}	+	0.64×10^{-3}	+	0.12×10^{-2}	+	0.64×10^{-3}
7d	++	0.67×10^{-3}	++	0.67×10^{-3}	++	0.13×10^{-2}	+	0.13×10^{-2}
7e	++	0.75×10^{-3}	++	0.15×10^{-2}	++	0.15×10^{-2}	+	0.75×10^{-3}
8b	+++	0.69×10^{-3}	++	0.69×10^{-3}	+++	0.69×10^{-3}	++	0.34×10^{-3}
8c	++	0.33×10^{-3}	++	0.33×10^{-3}	+++	0.66×10^{-3}	+++	0.66×10^{-3}
8d	++	0.64×10^{-3}	++	0.32×10^{-3}	++	0.64×10^{-3}	++	0.32×10^{-3}
8e	++	0.36×10^{-3}	+++	0.72×10^{-3}	+++	0.36×10^{-3}	++	0.36×10^{-3}
9d	+	0.70×10^{-3}	+	0.70×10^{-3}	++	0.14×10^{-2}	+	0.14×10^{-2}
9e	+	0.79×10^{-3}	+	0.15×10^{-2}	++	0.15×10^{-2}	++	0.79×10^{-3}
10d	+	0.12×10^{-2}	+	0.12×10^{-2}	++	0.12×10^{-2}	++	0.64×10^{-3}
10e	+	0.14×10^{-2}	+	0.14×10^{-2}	+	0.14×10^{-2}	+	0.72×10^{-3}
M[a]	+++	0.5×10^{-3}	++	0.5×10^{-3}	+++	0.1×10^{-2}	+++	0.1×10^{-2}

The width of the zone of inhibition indicates the potency of antimicrobial activity. (−) no antimicrobial activity; (+) weak activity with the diameter of the zone equal to 0.7 cm.; (++) moderate activity with the diameter of the zone equal to 1.3 cm.; (+++) marked activity with the diameter of the zone equal to 1.7 cm.

Origin of cultures: Botany Department, Faculty of Science, Benha University, Egypt.

The results of control samples were not included in the table; they show negative response.

[a]Methaqualone.

in filter sterilized 10 mL of 10% acetone (V/V) and employed in similar concentration as control. A qualitative screen was performed on all compounds while quantitative assays were done on active compounds only. The results are summarized in Table III. Other biological studies are still in progress.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr were recorded on a Shimadzu 470 spectrophotometer and ^{1}H NMR spectra in DMSO on a JOEL Fx 90 Q 9 MHz (Fourier transform NMR spectrometer) using TMS as internal reference (chemical shifts are expressed as δ, ppm).

The starting compounds 2-methyl-4(3H)-quinazolinone[14] and 4-chloro-2-methylquinazoline[16] were prepared as described in the literature. Also, the amino acid methyl ester hydrochlorides were prepared according to the published procedure.

Glycine methyl ester hydrochloride (81%), m.p. 173–175°C, lit.,[19] m.p. 175°C; L-serine methyl ester hydrochloride (88%), m.p. 176–177°C, lit.,[20] m.p. 175°C, $[\alpha]_D^{20}$ + 0.96; L-valine methyl ester hydrochloride (86%), m.p. 167–168°C, lit.,[20] m.p. 165–167°C $[\alpha]_D^{20}$ + 15.8; L-leucine methyl ester hydrochloride (85%), m.p. 148–150°C, lit.,[21] m.p. 150–151°C, $[\alpha]_D^{20}$ − 13.5; β-alanine methyl ester hydrochloride (79%), m.p. 95–96°C, lit.,[22] m.p. 95°C.

2-Methyl-4(3H)-quinazolinethione (1)

A mixture of 4-chloro-2-methylquinazoline (32.1 g, 180 mmol) and thiourea (35.7 g, 470 mmol) in anhydrous ethanol (200 mL) were refluxed for 4 h. The product which separated on cooling was collected, washed with ethanol and diethyl ether, and dried, 24.1 g (76%), m.p. 217–219°C; IR; 3250–3150 (NH), 2250 (SH), 1625 (C=N), 1270 cm^{-1} (C=S), NMR, δ = 2.1 (s, 3H, CH_3), 7.9–8.8 (m, 4H, quinazoline ring), 9.2 (s br, 1H, NHC=S ratio 55.7), 11.3 (s br, 1H, SH ratio 44.3).

2-[2-(4-Methoxy- or 4-Nitro-phenyl)ethenyl]-4(3H)-quinazolinethiones (2a,b)

A mixture of 2-methyl-4(3H)-quinazolinethione **1** (13.2 g, 75 mmol) and an aromatic aldehydes, namely, p-anisaldehyde (10.2 g, 76 mmol) or p-nitrobenzaldehyde (11.5 g, 76 mmol) were heated for 3 h at 180–185°C. The mixture liquified after one-half hour of heating and at the end of 3 h was semisolid. When cold, it was pulverized and boiled with ethyl alcohol (160 mL) to remove unchanged starting material and crystallized from glacial acetic acid to yield the corresponding quinazolinethione derivatives **2a**,**b** respectively.

2a: yield 18 g (82%), m.p. 265–267°C; IR; 3310–3220 (NH), 2570 (SH), 1640 (C=C), 1615 (C=N), 1265 cm^{-1} (C=S), NMR, δ = 3.9 (s, 3H, OCH_3), 6.6 (d, 1H, J = 14 Hz, olefinic H), 6.9 (d, 1H, J = 14 Hz, olefinic-H), 7.2–8.8 (m, 8H, Ar–H), 9.3 (s, 1H, NHC=S, ratio 55.4), 11.1 (s, 1H, SH, ratio 44.6). Found: C, 69.6; H, 5.0; N, 9.8%. Calcd for $C_{17}H_{14}N_2OS$: C, 69.4; H, 4.8; N, 9.5%.

2b: yield 18 g (78%), m.p. 238–240°C; IR; 3270–3220 (NH), 2560 (SH), 1630 (C=C), 1595 (C=N), 1260 cm^{-1} (C=S). Found: C,

62.4; H, 4.0; N, 13.8%. Calcd for $C_{16}H_{11}N_3O_2S$: C, 62.1; H, 3.6; N, 13.6%.

2-(2-Phenyl-1-propenyl)-4(3H)-quinazolinethione (2c)

A mixture of compound **1** (14.8 g, 84 mmol) and acetophenone (10.2 g, 85 mmol) was refluxed in acetic acid/acetic anhydride mixture for 5 h. The resulting solid was filtered off, washed with cold water, dried, and recrystallized from aqueous alcohol to afford **2c**, 18.6 g (80%), m.p. 278–280°C, IR, 3200 (NH), 2986–2937 (alkyl-H), 2250 (SH), 1622 (C=C), 1605 (C=N), 1150 cm^{-1} (C=S), NMR, $\delta = 2.1$ (d, 3H, CH_3 due to long range coupling), 6.5 (q, 1H, =CH), 7.1 (m, 9H, Ar–H), 9.7 (s br, 1H, NHC=S ratio 53.8), 11.5 (s br, 1H, SH ratio 46.2). Found: C, 73.5; H, 5.2; N, 10.3%. Calcd for $C_{17}H_{14}N_2S$: C, 73.4; H, 5.0; N, 10.1%.

2-(1,3-Dioxoindan-2-yl)-4(3H)-quinazolinethione (2d)

A mixture of compound **1** (15.5 g, 88 mmol) and phthalic anhydride (13.2 g, 89 mmol) was heated rapidly to about 200°C. The mass soon solidified at this temperature, but the heating was continued for about 3 h to complete the reaction. The crystalline yellow cake thus obtained was pulverized and extracted repeatedly with small amounts of boiling alcohol, to remove unchanged starting materials, and crystallized twice from glacial acetic acid to furnish **2d**, 18.8 g (70%), m.p. 290–292°C; IR, 3330–3280 (NH), 2535 (SH), 1780–1740 (cyclic dione system), 1610 (C=N), 1350 cm^{-1} (C=S); NMR, $\delta = 4.5$ (s, 1H, cyclic CH), 7.1–8.6 (m, 8H, Ar–H), 9.4 (s br, 1H, NHC=S ratio 56.3), 11.5 (s br, 1H, SH ratio 43.7). Found: C, 66.8; H, 5.1; N, 9.4%. Calcd for $C_{17}H_{10}N_2O_2S$: C, 66.7; H, 4.9; N, 9.2%.

Methyl N-{2-[2-(4-methoxy- or 4-Nitro-phenyl)ethenyl]-, 2-(2-Phenyl-1-propenyl)- or 2-(1,3-Dioxoindan-2-yl)-quinazolin-4-yl}amino-acetate, -3-Hydroxypropionate, -3-Methylbutanoate, -4-Methylpentanoate, or -Propanoate (3–6)$_{a-e}$

Thiones **2a–d** (2.1 mmol) were dissolved in THF or dioxane (15 mL), amino acid methyl ester hydrochlorides (2.2 mmol) in (15 mL) THF or dioxane were added with stirring followed by Et_3N (10 mmol). The reaction mixture was refluxed for 6 h, cooled, concentrated, and partitioned between ether and water, the ether extract was worked up as usual. The residue crystallized from a suitable solvent affording **(3–6)$_{a-e}$**.

3-Oxo-2H-imidazo[1,2-c]- and 4-Oxo-2H,3H-pyrimido-[1,2-c]-quinazolines Derivatives (7–10)$_{a-e}$

A mixture of thiones **2a–d** (2 mmol), amino acid methyl ester hydrochlorides (2.1 mmol) and Et_3N (10 mmol) was heated at its melting temperature for 3 h. After cooling, water (100 mL) was added and the residue and then extracted with ether; the ether extract was worked up as usual. The remaining residue was crystallized from a suitable solvent affording (**7–10**)$_{a-e}$.

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