SYNTHESIS OF SOME DERIVATIVES OF 8-AMINOMETHYL- AND 8-AZOLYLMETHYL-2-PHENYL-3*H*-QUINAZOLINE-4-THIONES

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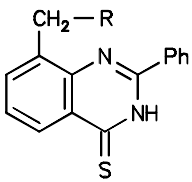
Derivatives of folic acid, the quinazoline-based antifolates, and their 4-thiosubstituted analogues are potent inhibitors of the enzyme thymidylate synthase and show promising antitumor activity[1,2]. This has motivated us to prepare a series of thio analogues of mentioned antifolate.

The starting 8-chloromethyl-2-phenyl-3*H*-quinazoline-4-thione (*I*) was prepared by intramolecular cyclization of *N*-(2-chloromethylphenyl)benzimidoyl isothiocyanate[3]. The title compounds *II* were prepared by the reaction of the thione *I* with the corresponding secondary amines and azoles.



I, *IIa* – *IIj*

In formulae *I*, *II* :

I,	R	= Cl
IIa,	R	= morpholinyl
IIb,	R	= 1-piperidyl
IIc,	R	= diethylamino
IId,	R	= 1-(2'-hydroxyethyl)piperazinyl
IIe,	R	= 1-(1,2,4-triazolyl)
IIf,	R	= 1-imidazolyl
IIg,	R	= 1-benztriazolyl
IIh,	R	= 1-benzimidazolyl
IIi,	R	= succinimido
IIj,	R	= phthalimido

EXPERIMENTAL

The IR spectra (ν, cm^{-1}) were measured with Philips PU 9800 FTIR spectrometer in KBr pellets. ^1H NMR spectra (δ, ppm) of hexadeuteriodimethyl sulfoxide solutions were recorded on Tesla BS 487C (80 MHz) spectrometer using tetramethylsilane as an internal standard. Preparation of the starting *N*-(2-chloromethylphenyl)benzimidoyl chloride was reported in the literature[3].

TABLE I
Characteristic data of prepared compounds

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found		
			% C	% H	% N
IIa	$C_{19}H_{19}N_3OS$	134 – 136	67.63	5.68	12.45
	(337.4)	42	67.57	5.61	12.32
IIb	$C_{20}H_{21}N_3S$	191– 193	71.61	6.31	12.53
	(335.5)	50	71.39	6.18	12.67
IIc	$C_{19}H_{21}N_3S$	121 – 123	70.55	6.54	12.99
	(323.5)	46	70.43	6.50	12.92
IId	$C_{21}H_{24}N_4OS$	217 – 219	66.29	6.36	14.72
	(380.5)	88	66.17	6.29	14.67
IIe	$C_{17}H_{13}N_5S$	232 – 235	63.93	4.10	21.93
	(319.4)	54	63.89	4.05	21.83
IIf	$C_{18}H_{14}N_4S$	169 – 170	67.90	4.43	17.60
	(318.4)	47	67.79	4.41	17.51
IIg	$C_{21}H_{15}N_5S$	210 – 212	68.27	4.09	18.96
	(369.4)	53	68.13	3.98	18.88
IIh	$C_{22}H_{16}N_4S$	170 – 172	71.71	4.38	15.21
	(368.5)	49	71.68	4.42	15.17
IIi	$C_{19}H_{15}N_3O_2S$	151 – 153	65.31	4.33	12.03
	(349.4)	64	65.23	4.30	11.91
IIj	$C_{23}H_{15}N_3O_2S$	133 – 135	69.51	3.80	10.57
	(397.5)	49	69.48	3.75	10.47

8-Chloromethyl-2-phenyl-3*H*-quinazoline-4-thione (*I*)

To *N*-(2-chloromethylphenyl)benzimidoyl chloride (5.28 g, 0.02 mol) in dry acetone (40 ml) potassium thiocyanate (1.94 g, 0.02 mol) dissolved in dry acetone (10 ml) was added dropwise under stirring and cooling to −10 °C. The reaction mixture was stirred for 1 h, the separated potassium chloride was filtered off and the solvent was evaporated almost to dryness. To the solid residue dry toluene (50 ml) was added and the resulting solution was refluxed for 8 h. After cooling the precipitate of the product *I* was collected by filtration and recrystallized from chloroform, yield 2.7 g, 48%, m.p. 253 – 255 °C. For $C_{15}H_{11}ClN_2S$ (286.8) calculated: 12.36% Cl, 11.18% S; found: 12.26% Cl, 11.46% S. IR spectrum: 3 200 ν(NH), 2 910 ν(CH_2), 1 608 ν(C=N), 1 568, 1 595 ν(C=$C_{arom.}$). ^{1}H NMR spectrum: 10.88 s, 1 H (NH), 8.66 – 7.63 m, 8 H (H-arom), 5.18 s, 2 H (CH_2). Mass spectrum (*m*/*z*): 286 (M^+), 288.

8-R-Methyl-2-phenyl-3*H*-quinazoline-4-thiones *IIa* – *IId*

To 0.003 mol of 8-chloromethyl-2-phenyl-3*H*-quinazoline-4-thione (*I*), 0.03 mol of the corresponding secondary amine was added. The reaction mixture was stirred for 24 h at room temperature. After addition of cold water (20 ml), the mixture was extracted with ether, dried and evaporated to dryness. The crude product was recrystallized from methanol. The yields and melting points are given in Table I, the IR and ^{1}H NMR spectral data in Table II.

TABLE II
Spectral data of compounds *II*

Compound	IR spectrum (ν, cm^{-1})			^{1}H NMR spectrum (δ, ppm)		
	ν(NH)	ν(CH_2)	ν(C=N)	CH_2	quinazoline	azole resp. amine
IIa	3 206	2 918	1 603	5.86 d, 2 H	7.58 – 7.38 m, 8 H	3.76 t, 4 H 2.74 t, 4 H
IIb	3 366	2 922	1 603	5.59 d, 2 H	8.75 – 7.59 m, 8 H	1.57 m, 6 H 2.9 – 2.57 m, 4 H
IIc	3 296	2 920	1 606	5.46 d, 2 H	8.69 – 7.50 m, 8 H	2.84 q, 4 H 1.23 t, 6 H
IId	3 331[a]	2 910	1 608	5.42 d, 2 H	8.50 – 7.44 m, 8 H	2.81 – 2.43 m, 12 H
IIe	3 167	2 918	1 608	5.49 d, 2 H	8.59 – 7.61 m, 8 H	8.70 s, 2 H
IIf	3 292	2 920	1 603	5.45 d, 2 H	8.64 – 7.47 m, 11 H	
IIg	3 155	2 918	1 608	5.32 d, 2 H	7.68 – 7.33 m, 8 H	8.51 – 8.19 m, 4 H
IIh	3 154	2 918	1 608	5.40 d, 2 H	7.94 – 7.34 m, 12 H	8.06 s, 1 H
IIi	3 333	2 918	1 610	5.49 d, 2 H	8.75 – 7.50 m, 8 H	2.88 – 2.81 m, 4 H
IIj	3 359	2 922	1 604	5.51 d, 2 H	8.27 – 7.81 m, 8 H	7.47 m, 4 H

[a] ν(OH) and ν(NH).

8-R-Methyl-2-phenyl-3*H*-quinazoline-4-thiones *IIe – IIj*

To 0.003 mol of 8-chloromethyl-2-phenyl-3*H*-quinazoline-4-thione (*I*) in acetonitrile (50 ml), 0.003 mol sodium salt of corresponding azole was added. The reaction mixture was stirred under reflux for 4 h, filtered and let to crystallize. The crude product was purified by recrystallization from ethanol. The yields and melting points are given in Table I, the IR and ^{1}H NMR spectral data in Table II.

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