AMIDINOYL ISOTHIOCYANATES IN THE SYNTHESIS OF CONDENSED QUINAZOLINES. PREPARATION OF 3-ARYL-5,9-DISUBSTITUTED *s*-TRIAZOLO[4,3-*c*]QUINAZOLINES

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3-Aryl-5-((4-phenyl)piperazinyl)-9-chloro-*s*-triazolo[4,3-*c*]quinazolines were prepared by an oxidative cyclization of the corresponding arylhydrazones. The IR and ^{1}H NMR spectra of final products are presented.

The chemistry of quinazolines has been of great interest in the last 15 years namely for their biological effects. A great number of papers appearing in this field has described the preparation, biocidal and phytoeffectorial properties as reviewed in ref.[1]. Some derivatives showed also antimalaric and antimicrobial effects, other are known as CNS depressants, etc.[2,3].

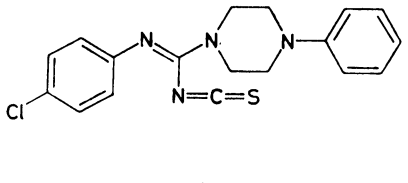
Of interest are also the condensed quinazoline derivatives because of the possibility to cumulate biological activities of quinazolines with those embodied in the newly condensed ring. Preparation and physicochemical properties of *s*-triazolo[4,3-*c*]-quinazolines without a substituent at the triazole skeleton and with a secondary amino group at the pyrimidine ring, as well as 3,5-diarylsubstituted derivatives have already been reported in our respective papers[4,5].

This contribution describes the synthesis of 3-arylsubstituted *s*-triazolo[4,3-*c*]-quinazolines with a secondary amino group in position 5. For the reason of potential biological activity we have chosen the quite frequented substituents – chlorine at the benzene ring, substituted piperazinyl grouping at the pyrimidine backbone and variously 4-substituted phenyl and 5-substituted 2-furyl groups at the triazole ring system.

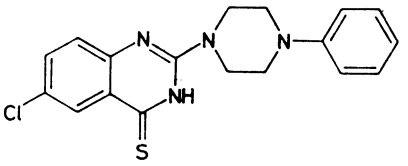
A procedure employing the easily available amidinoyl isothiocyanate (*I*) has been chosen; the latter underwent isomerization on heating to give 6-chloro-2-((4-phenyl)-piperazinyl)-3*H*-quinazoline-4-thione (*II*). An easy enolization of the thioamide grouping of the thione *II* facilitated the direct substitution of the thiol group by hydrazine to afford 6-chloro-2-((4-phenyl)piperazinyl)-4-hydrazinoquinazoline (*III*). The reaction of *III* with a series of 4-substituted benzaldehydes or 5-substituted 2-furancarbaldehydes yielded the corresponding arylhydrazones *IVa*–*IVh*. An oxidative

cyclization with bromine in acetic acid or alternatively with nitrobenzene furnished the title compounds *Va – Vh*.

It has been shown that the oxidative cyclization with bromine in acetic acid[7] is advantageous for obtaining high yields of compounds *V* except for hydrazones *IVc* and *IVg*, in other words for those where better yields afforded nitrobenzene as the oxidation reagent[8].



I



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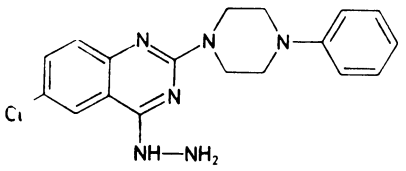
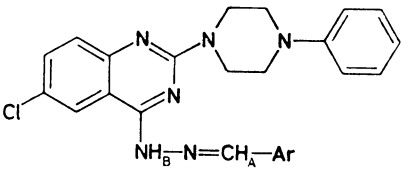
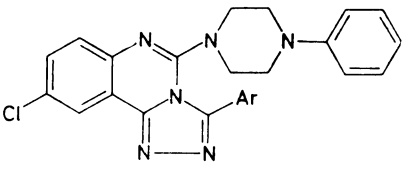


III



IVa – IVh



Va – Vh

In formulae *IV* and *V*: *a*, Ar = phenyl ; *b*, Ar = 4-chlorophenyl ; *c*, Ar = 4-nitrophenyl ; *d*, Ar = 4-dimethylaminophenyl ; *e*, Ar = furyl ; *f*, Ar = 5-chloro-2-furyl ; *g*, Ar = 5-nitro-2-furyl ; *h*, Ar = 5-bromo-2-furyl

The IR spectra of compounds *Va – Vh* revealed two well discernable absorption bands shifted to higher wavelengths when compared with those of the azomethine double bond of arylhydrazones *IVa – IVh*. An opposite trend was observed with 3,5-diaryl derivatives[5]. This phenomenon might be rationalized by a greater electron density of C=N bonds in compounds *V* due to the presence of two donors, i.e. the

aryl group at C-2 of the triazole ring and the secondary amine at C-5 of the pyrimidine ring system. The absorption band at lower wavelengths (1 630–1 609 cm^{-1}) is obviously associated with absorptions of the pyrimidine ring.

The ^1H NMR spectra of hydrazones *IVa–IVh* displayed a signal of the H_B proton as a well distinguished peak. Protons H-3, H-4 and H-5 of the furan ring in *IVe–IVh* as well as *Ve–Vh* could well be identified in the mutliplet of protons in the aromatic ring systems according to different coupling constants $J(3, 4) = 3{\cdot}5-3{\cdot}9$ Hz and $J(4, 5) = 1{\cdot}0-1{\cdot}1$ Hz.

EXPERIMENTAL

The IR spectra of compounds in KBr pellets were measured with a Philips PU 9800 FTIR and the ^1H NMR spectra of hexadeuteriodimethyl sulfoxide solutions containing tetramethylsilane as an internal standard with JEOL FX 100 (100 MHz) spectrometers. Preparation of the starting isothiocyanate *I* was reported in ref.[6].

TABLE I
Characteristic data for 6-chloro-2-((4-phenyl)piperazinyl)-4-quinazolylarylhydrazones *IV*

Compound	Formula (M.w.)	M.p., °C (Yield, %)	Calculated/Found		
			% C	% H	% N
IVa	$C_{25}H_{23}ClN_6$ (442·8)	194–196 (82)	67·80 67·55	5·23 5·26	18·96 19·19
IVb	$C_{25}H_{22}Cl_2N_6$ (477·4)	219–221 (88)	62·89 63·13	4·60 4·96	17·59 17·92
IVc	$C_{25}H_{22}ClN_7O_2$ (487·9)	225–227 (95)	61·53 61·23	4·50 4·57	20·08 19·84
IVd	$C_{27}H_{28}ClN_7$ (486·0)	244–247 (84)	66·66 66·27	5·76 5·73	20·16 19·89
IVe	$C_{23}H_{21}ClN_6O$ (432·9)	175–178 (74)	63·76 63·97	4·85 4·83	19·40 19·47
IVf	$C_{23}H_{20}N_6Cl_2O$ (467·3)	178–180 (72)	58·41 58·49	4·20 4·85	17·97 17·45
IVg	$C_{23}H_{20}ClN_7O_3$ (477·9)	225–227 (72)	57·12 57·92	4·18 4·40	20·50 19·64
IVh	$C_{23}H_{20}BrClN_6O$ (511·8)	177–180 (79)	53·34 54·07	3·90 3·87	16·41 16·57

6-Chloro-2-((4-phenyl)piperazinyl)-3*H*-quinazoline-4-thione (*II*)

Amidinoyl isothiocyanate *I* (35·6 g, 0·1 mol) in toluene (100 ml) was refluxed for 10 h, cooled, the precipitate was filtered off and crystallized from ethanol. Yield 89%, m.p. 204—206°C. For $C_{18}H_{17}ClN_4S$ (356·8) calculated: 9·94% Cl, 8·99% S; found: 9·87% Cl, 8·91% S. IR spectrum (cm^{-1}): 3 125 (NH).

6-Chloro-2-((4-phenyl)piperazinyl)-4-hydrazinoquinazoline (*III*)

The substituted quinazoline-4-thione *II* (3·5 g, 10 mmol) and hydrazine hydrate (80%, 5 ml) in ethanol (10 ml) were refluxed till the evolution of hydrogen sulfide ceased (5—10 h). The solution was then cooled, the crude product was filtered off and crystallized from ethanol. Yield 82%, m.p. 242—245°C. For $C_{18}H_{19}ClN_6$ (354·8) calculated: 60·93% C, 5·39% H, 23·68% N; found: 60·58% C, 5·33% H, 23·39% N. IR spectrum (cm^{-1}): 3 298 (NH), 1 608 (C=N).

TABLE II

Spectral properties of 6-chloro-2-((4-phenyl)piperazinyl)-4-quinazolylarylhydrazones *IV*

Compound	IR, cm^{-1}				^1H NMR (δ, ppm)			
	ν(NH)	ν(C=N)	ν(C—N)	Other	H_A	H_B	H_{Ar}[a]	H_{PP}[b]
IVa	3 300	1 640	1 360		8·57 s	10·81 s	8·39—7·03 m	4·08 m; 3·25 m
IVb	3 280	1 615	1 350		8·53 s	11·42 s	8·42—6·74 m	3·97 m; 3·16 m
IVc	3 260	1 610	1 330	1 570[c] 1 345[d]	8·52 s	11·67 s	8·26—7·03 m	4·03 m; 3·20 m
IVd	3 240	1 610	1 364		8·29 s	11·26 s	7·64—6·73 m	3·42 m
IVe	3 280	1 602	1 350		8·56 s	11·35 s	8·39—6·10 m	4·00 m; 3·19 m
IVf	3 320	1 640	1 380		8·60 s	10·72 s	8·22—6·64 m	4·0 m; 3·18 m
IVg	3 360	1 618	1 360	1 580[c] 1 350[d]	8·68 s	11·81 s	8·33—6·21 m	3·97 m; 3·23 m
IVh	3 370	1 630	1 350		8·60 s	10·74 s	8·22—6·72 m	4·02 m; 3·20 m

[a] *IVd*: 2·99 s (CH_3), *IVe*: 7·15 db (H-3), 6·66 db (H-4), 7·81 dd (H-5), *IVf*: 7·15 db (H-3), 6·65 db (H-4), *IVg*: 7·16 db (H-3), 6·83 db (H-4), *IVh*: 7·16 db (H-3), 6·72 db (H-4); [b] PP 4-phenylpiperazine; [c] $\nu_{as}(NO_2)$; [d] $\nu_s(NO_2)$.

6-Chloro-2-((4-phenyl)piperazinyl)-4-quinazolylarylhydrazones (*IVa—IVh*)

4-Hydrazinoquinazoline *III* (1·7 g, 5 mmol) and arylaldehyde (5 mmol) in ethanol (20 ml) were refluxed for 1 h. The solution was then moderately cooled; after addition of cold water (20 ml) the separated precipitate was filtered off and crystallized from dimethylformamide. Characteristic data for these compounds are presented in Tables I and II.

3-Aryl-5-((4-phenyl)piperazinyl)-9-chloro-*s*-triazolo[4,3-*c*]quinazolines (*Va— Vh*)

Method A: Sodium acetate (0·5 g) was added to the stirred solution of the substituted hydrazone *IV* (2 mmol) in acetic acid (20 ml) at room temperature to which bromine (0·32 g, 2 mmol) in acetic acid (10 ml) was introduced dropwise. The reaction went through during 1 h; the mixture was then poured on crushed ice (100 g), the separated precipitate was filtered off and crystallized from ethanol–dimethylformamide. This method was applied for preparation of compounds *Va*, *Vb*, *Vd— Vh*. Their characteristic data are listed in Tables III and IV.

Method B: Substituted hydrazone *IV* (2 mmol), nitrobenzene (7 ml), water (15 ml) and concentrated sulfuric acid (2 to 3 drops) were refluxed for 6—8 h. The excess of nitrobenzene was removed by distillation with steam and the crude product was crystallized from a suitable solvent.

TABLE III
Characteristic data for 3-aryl-5-((4-phenyl)piperazinyl-9-chloro-*s*-triazolo[4,3-*c*]quinazolines *V*

Compound	Formula (M.w.)	M.p., °C (Yield, %)	Calculated/Found		
			% C	% H	% N
Va	$C_{25}H_{21}ClN_6$ (440·9)	261—264 (86)	68·09 67·58	4·80 4·73	19·06 19·17
Vb	$C_{25}H_{20}Cl_2N_6$ (475·4)	239—241 (64)	63·16 62·82	4·24 4·19	17·67 17·02
Vc	$C_{25}H_{20}ClN_7O_2$ (485·9)	243—244 (82)	61·79 61·13	4·14 4·03	20·17 20·53
Vd	$C_{27}H_{26}ClN_7$ (484·0)	201—204 (80)	67·00 66·31	5·41 5·20	20·25 20·80
Ve	$C_{23}H_{19}ClN_6O$ (430·8)	242—245 (61)	62·95 62·43	4·40 4·13	19·49 19·87
Vf	$C_{23}H_{18}Cl_2N_6O$ (465·3)	239—242 (66)	59·31 58·97	3·86 3·46	18·05 17·51
Vg	$C_{23}H_{18}ClN_7O_3$ (475·9)	248—250 (50)	58·00 58·34	3·78 3·82	20·59 20·93
Vh	$C_{23}H_{18}BrClN_6O$ (509·8)	237—240 (60)	54·14 54·50	3·53 3·70	16·47 16·89

TABLE IV

Spectral properties of 3-aryl-5-((4-phenyl)piperazinyl)-9-chloro-*s*-triazolo[4,3-*c*]quinazolines *V*

Compound	IR, cm^{-1}				^1H NMR (δ, ppm)			
	ν(C=C)	ν(C=N)	ν(C—N)	Other	H_{Ar}[a,b]	H_{PP}[b,c]	H_3[d]	H_4[d]
Va	1 581	1 635 1 618	1 386		8·43—6·66	4·08; 3·27		
Vb	1 570	1 657 1 620	1 387		8·54—6·80	4·03; 3·34		
Vc	1 585 1 563	1 639 1 616	1 385	1 520[e] 1 340[f]	8·48—6·62	4·05; 3·24		
Vd	1 593 1 577	1 637 1 609	1 387		8·65—6·63	4·03; 3·22		
Ve	1 624 1 579	1 652 1 633	1 385		8·68—6·73	4·04; 3·25	7·16	6·83
Vf	1 591 1 572	1 639 1 613	1 385		8·83—6·65	4·08; 3·23	7·11	6·68
Vg	1 585 1 566	1 637 1 616	1 383	1 523[e] 1 350[f]	8·57—6·67	4·03; 3·23	7·05	6·71
Vh	1 591 1 574	1 643 1 622	1 383		8·76—6·76	4·09; 3·78	7·07	6·80

[a] *Vd*: 3·01 s (CH_3), *Ve*: 7·82 dd (H-5); [b] all signals are multiplets; [c] PP 4-phenylpiperazine; [d] all signals are doublets; [e] $\nu_{as}(NO_2)$; [f] $\nu_s(NO_2)$.

This method was applied for the synthesis of compounds *Vc* and *Vg*. Their characteristic data are given in Tables III and IV.

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