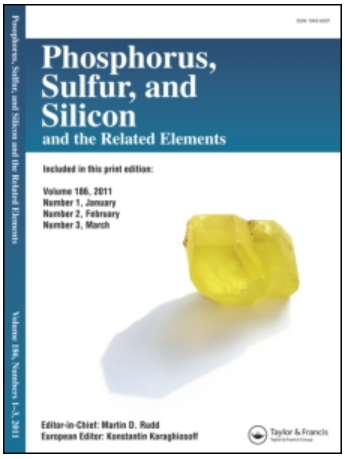

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SYNTHESIS OF SOME BIOLOGICALLY ACTIVE HETEROCYCLES. REACTIONS OF THE HYDRAZIDE OF 2'-THIENOYL ANTHRANILIC ACID AND ITS 3,5-DIBROMO DERIVATIVE

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SYNTHESIS OF SOME BIOLOGICALLY ACTIVE HETEROCYCLES. REACTIONS OF THE HYDRAZIDE OF 2′-THIENOYL ANTHRANILIC ACID AND ITS 3,5-DIBROMO DERIVATIVE

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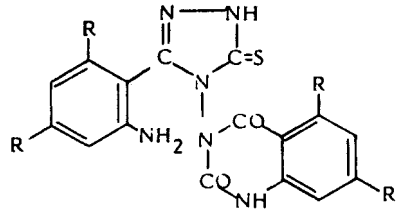
The hydrazide of 2′-thienoyl anthranilic acid and its 3,5-dibromo derivative (**1a** and **b**) were condensed with carbon disulphide to give 1-3′-quinazolin-2-thione 5-2″-aminophenyl-1,3,4-triazoles (**2a, b**). When treated with acetyl chloride 3-*N*-acetamidoquinazolin-4-ones (**3a, b**), with aromatic aldehydes the schiff bases **4** and **5(a, b)**. Potassium thiocyanate and phenyl isothiocyanate gave the semicarbazide derivatives (**6a, b**) while ammonium thiocyanate afforded the triazol-thiones (**7a, b**). Reaction with ethyl aceto-acetate and acetylacetone gave the pyrazole derivatives **8** and **9** respectively; Biological activities of some of these compounds are tested.

The wide range of pharmacological properties exhibited by cyclic compounds such as pyrazoles,[1] oxadiazoles,[2–4] triazoles[5] and quinazolines[6] made them worthy to be synthesized. Furthermore, this gave a basis for the synthesis of these heterocycles attached to thienyl as well as dibromophenyl groups hoping to obtain promising biologically active compounds.

2′-Thienoylanthranilic acid hydrazide[7] (**1a**) or 3,5-dibromo-2′-thienoylanthranilic acid hydrazide[8] (**1b**) were condensed with carbon disulphide in an alkaline solution, the product was found to be 1-3′-quinazolin-2-thione-5,2″-aminophenyl-1,3,4-triazole (**2a**) or its tetrabromo derivative (**2b**)

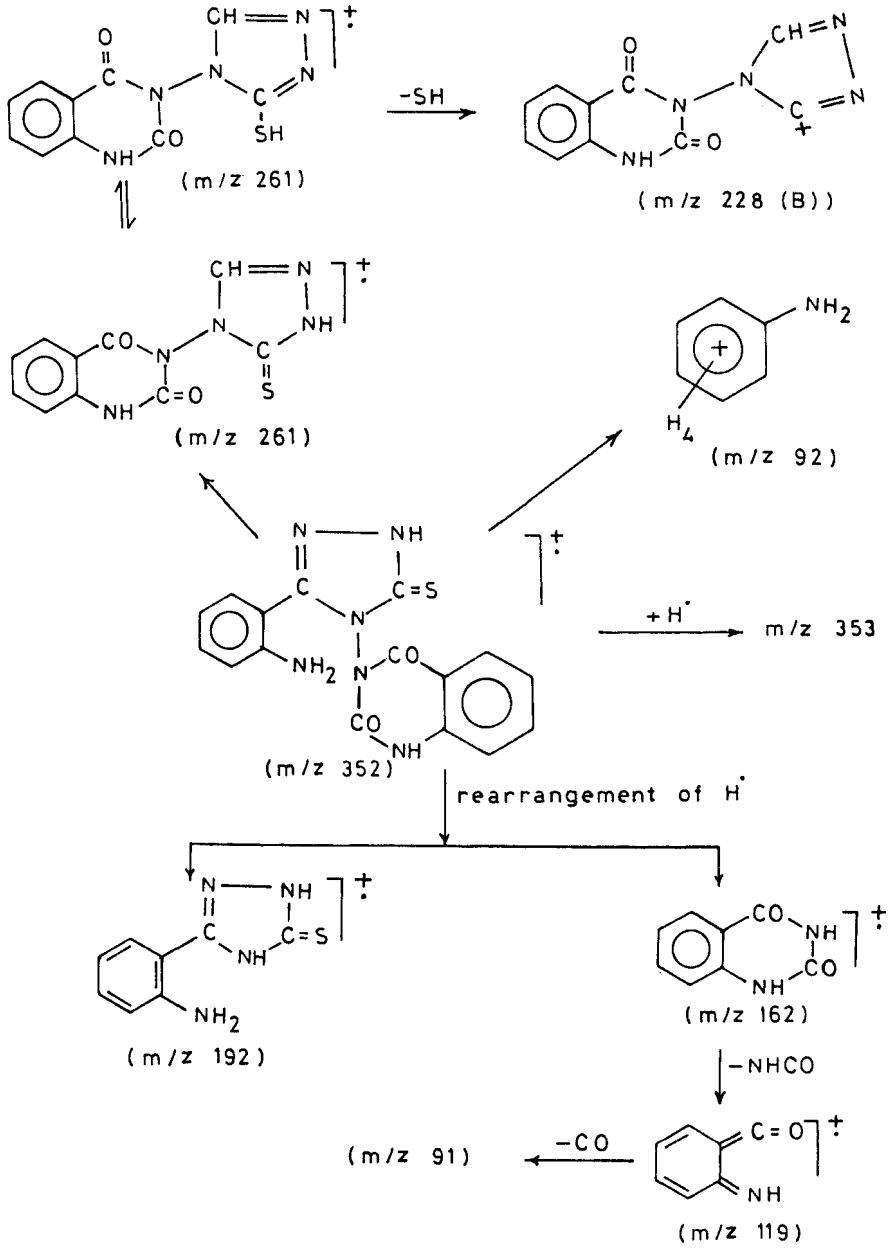


(2a,b)

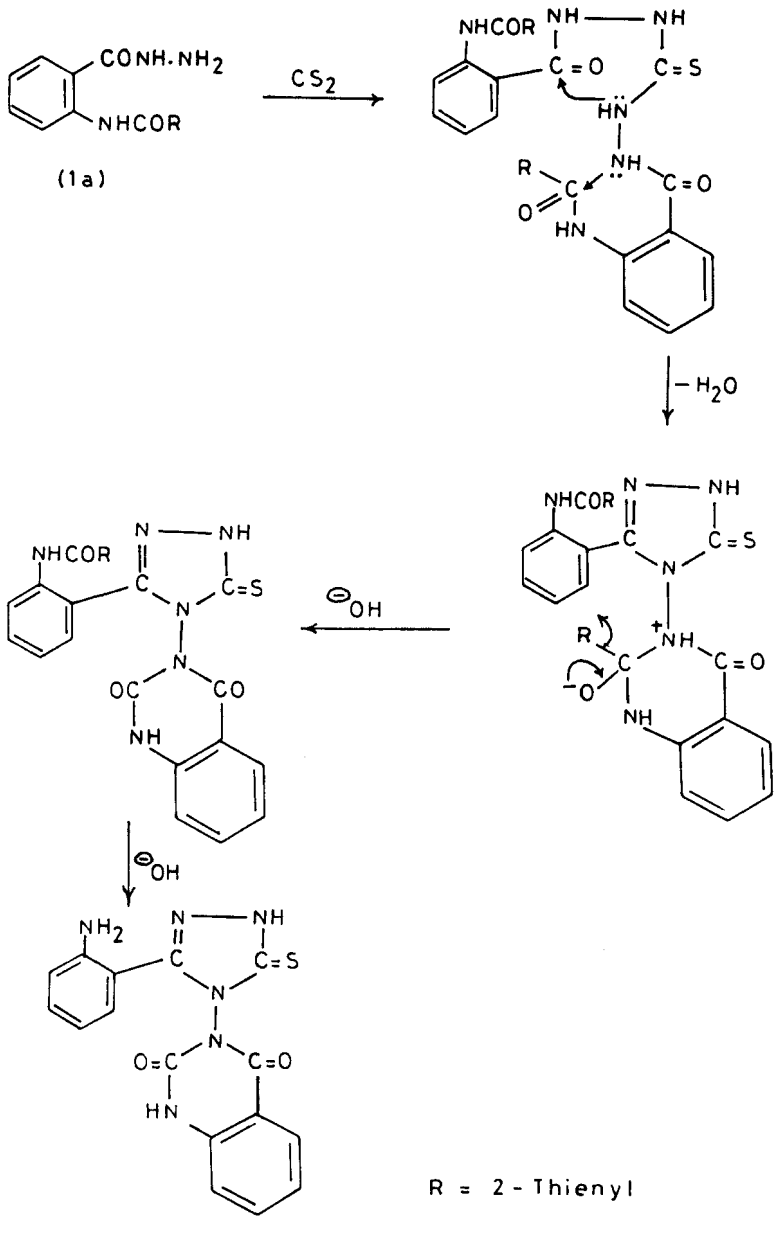
a, R = H b, R = Br

The structure assigned to (**2a**) is based on its mass spectrum which shows $[M + H]^+$ at m/z 353 (arising from protonation in the ionisation process indicating a molecular formula $C_{16}H_{12}N_6O_2S$ (Chart 1).

The fragmentation of (**2a**) takes place either by route (A) to give the ions at m/z 192 and 162, m/z 119 [162—NHCO (**43**)] m/z 91 (119—CO)] or according to route



(Chart 1)



(Chart 2)

(B) to give the azepinium cation (m/z 92) together with the ion at m/z 261 which loses SH (261–33) to give the ion m/z 228 (B).

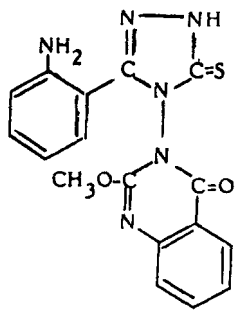
A further support for the structure of (**2a, b**) is given by their IR spectra which show a broad absorption at 3400–3300, 3250–3150 and 3100–2900 cm^{-1} for NH and OH; $\nu C{=}O$ at 1680 cm^{-1} and 1650 cm^{-1} for the carbonyl of quinazolinone, $\nu C{=}N$ at 1580 cm^{-1}, C—H, o.p. 750 cm^{-1}, i.p.d. 1290 cm^{-1}, and C—H, 860 cm^{-1} for **2a** and **2b** respectively.

The ^{1}H-NMR spectrum of **2a** shows 2 singlets at δ 12.0 and 11.6 for SH and OH of enol, δ centered at 8.4 (d.d 2H for NH_2) δ centered at 7.5 (m, 8H, aromatic protons).

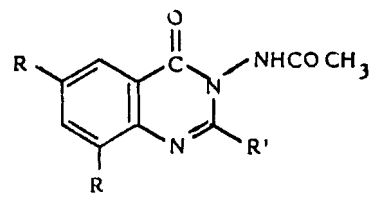
The formation of (**2a**) is believed to take place by initial condensation of the hydrazide (2 molecules) with CS_2 followed by cyclisation to the triazole ring and to dearylation cyclisation to the quinazoline, the formed anilide is hydrolysed under the reaction conditions to the amino derivative, dearylation during cyclisation have been previously reported (Chart 2).[9]

Methylation of **2a** gave its OCH_3 derivative **2c** by methylation of the enol form of **2a**. The structure of **2c** is confirmed beside elemental analysis by its IR spectrum which shows: νNH at 3190 and 3215 cm^{-1}, $\nu C{=}O$ at 1660 cm^{-1}.

The ^{1}H-NMR spectrum of **2c** gave δ at 3.1 (s, 3H, OCH_3) which was absent in **2a** and in the downfield region only one signal at δ 12.2 (s, 1H for SH proton) beside the aromatic multiplet, centered at δ 7.8 for 8 aromatic H and 2 singlets at δ 8.7 and 8.85 for the 2H of NH_2.



(2c)



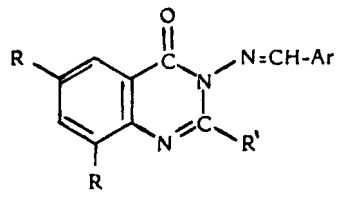
(3)

a; R = H R' = 2-thienyl

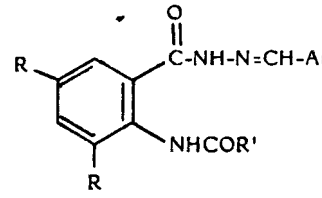
b; R = Br R' = 2-thienyl

When (**1a, b**) were treated with acetyl chloride, 3-*N*-acetamido-2-thienylquinazolin-4-one (**3a, b**) were isolated. The structure assigned to (**3a, b**) is based on elemental analysis (cf. Table II) as well as on their IR spectra which exhibits νNH at 3200, 3100 and 3250, 3050 cm^{-1}, $\nu C{=}O$ for quinazolinone at 1705 and 1710 cm^{-1}, $\nu C{=}O$ of amide at 1660 and 1680 cm^{-1} and $\nu C{=}N$ at 1600 cm^{-1} for (**3a** and **b**) respectively.

When the hydrazides (**1a, b**) were condensed with aromatic aldehydes, a mixture of the schiff bases corresponding to N-amino-quinazolin-4-one (**4a–h**) and their open chain isomers (**5a–h**) were obtained.



(4)



(5)

a; R = H; Ar = C_6H_5

b; R = H, Ar = p-$OCH_3C_6H_4$

c; R = H, Ar = p-ClC_6H_4

d; R = H, Ar = p-NO_2-C_6H_4

e; R = Br, Ar = C_6H_5

f; R = Br, Ar = p-$OCH_3C_6H_4$

g; R = Br, Ar = p-Cl-Cl-C_6H_4

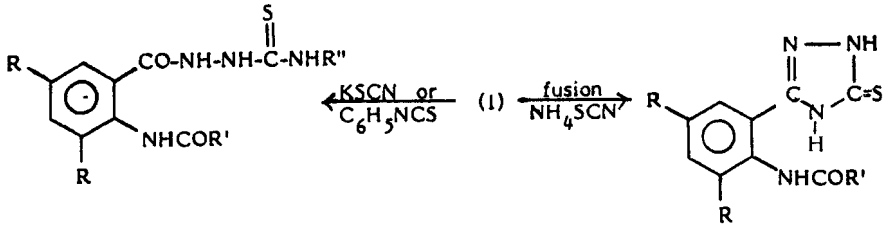
h; R = Br, Ar = p-$NO_2C_6H_4$

R' = 2-Thienyl

The structure of (**4e–h**) and (**5a–d**) was proved by their preparation euthentically according to El-Khamry *et al.*[8–10] The structure of (**4b–d**) was based on their elemental analysis (Table II). Their IR spectra which show $\nu C{=}O$ at *ca* 1710 cm^{-1} for quinazolinone.

The structure of (**5e–h**) is substantiated from their elemental analysis (Table II) as well as their IR spectra which shows $\nu C{=}O$ at *ca* 1660 cm^{-1} corresponding to acid amides.

The hydrazides (**1a, b**) were converted to the thiosemicarbazide derivatives (**6a–d**) by refluxing with potassium thiocyanate or phenyl isothiocyanate in ethanol.



(6)

a; R = R" = H

b; R = Br, R" = H

c, R = H, R" = C_6H_5

d, R = Br, R" = C_6H_5

R' = 2-thienyl

(7)

a; R = H

b; R = Br

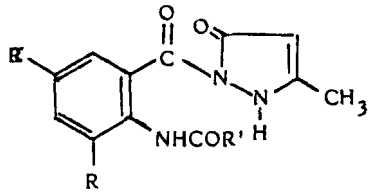
The structure of (**6a–d**) was deduced from their elemental analysis, their IR spectra which displayed an absorption at 3200 cm^{-1}, a strong absorption at 1690–1640 cm^{-1} for $\nu C{=}O$ of amides, 1430, 1410 for $\nu C{=}S$ attached to NH.[11]

The ^{1}H-NMR data of **6a** and **6d** are given in (Table III).

When the hydrazides (**1a, b**) were fused with ammonium thiocyanate the product was found to be 2-(2′-thien-2″-oylaminophen-1′-yl)-1,3,4-triazole-5-thiols (**7a, b**).

The structure of (**7a, b**) is deduced from their elemental analysis (Table II), from their IR absorption spectra which shows broad absorption in the 3 μ region at 3500–3400 and 3050–2090 cm^{-1} for νOH, NH, νC=O at *ca* 1655 for amides and νC=N at 1590 cm^{-1}.

The ^{1}H-NMR data of (**7a**) are given in (Table III). When the hydrazides (**1a, b**) were condensed with ethyl acetoacetate,[12,13] the pyrazolone derivatives (**8a, b**) were obtained. This pyrazolone structure is based, beside elemental analysis on

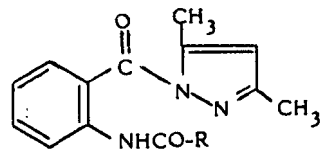


(8)

a; R = H b; R = Br R' =2-Thienyl

their IR spectra which displayed strong absorption at 3200 and 3100 cm^{-1} for νNH, νC=O at 1680 and 1660 cm^{-1}. The ^{1}H-NMR data (**8a**) are given in (Table III).

When condensed with acetylacetone, the hydrazide (**1a**) afforded the dimethyl pyrazole derivative (**9**).



(9)

R = 2-Thienyl

The structure of (**9**) was supported by both, analytical data (Table II), their IR spectra which showed broad absorption in the 3 μ region νNH, OH, νC=O at 1640 cm^{-1} for carbonyl of amides, νC=N at 1600, 1590 cm^{-1}. The ^{1}H-NMR data of (**9a**) are given in (Table III).

Biological Activity

Eleven organic compounds were screened for their possible antibacterial activity against two representative strains belonging to Gram-positive and Gram-negative species (one of each). From the results presented in Table I, it could be concluded that, among these compounds, only five were shown to be active biologically. Two of them (compounds No. **2b**, **5c**) possess an antibacterial activity against both

TABLE I

Antibacterial activity of investigated compounds

Compound	Gram-positive Bacillus subtilis -B-4378	Gram-negative Escherichia coli -B-4375
2b	+	+
3b	-	-
4b	-	-
4c	++	-
5a	-	-
5b	-	-
5c	++	++
5d	-	-
6a	-	-
7a	+	-
7b	+++	-

-inactive ++; MIC 500 +++; MIC 250

TABLE II

Characterization data of compounds prepared

Compd (yield %)	Solvent m.p.°C	Molecular formula (M. Wt.)	Analysis % Found / Calcd C	H	Br	N	S
2a	B/E	$C_{16}H_{12}N_6O_2S$	55.00	3.10		23.50	
(85)	245-46	(352)	54.54	3.40		23.86	
2b	Bu	$C_{16}H_8Br_4N_6O_2S$	28.49	1.03		12.34	
(92)	345	(668)	28.74	1.20		12.27	
2c	L.P.	$C_{17}H_{14}SN_6O_2$	55.16	3.42		23.40	
(95)	155-56	(366)	55.73	3.84		22.95	
3a	T	$C_{14}H_{11}SN_3O_2$	59.21	3.63		14.87	11.56
(84)	215-16	(285)	58.95	3.86		14.74	11.23
3b	B/E	$C_{14}H_9Br_2N_3O_2S$	38.00	2.20	36.41	9.70	7.55
(89)	303-4	(443)	37.92	2.03	36.12	9.48	7.22

Table II (*Continued*)

Compd (yield %)	Solvent m.p.°C	Molecular formula (M. Wt.)	Analysis % Found / Calcd				
			C	H	Br	N	S
4b	B/E	$C_{20}H_{15}SN_3O_2$	66.72	4.23		11.33	8.71
(76)	227-29	(361)	66.48	4.16		11.63	8.86
4c	T	$C_{19}H_{12}SClN_3O$	62.07	3.31		11.21	8.53
(71)	233-35	(365.5)	62.38	3.28		11.49	8.76
4d	T	$C_{19}H_{12}SN_4O_3$	60.99	2.89		15.03	8.41
(73)	247-49	(376)	60.64	3.19		14.89	8.51
5e	B	$C_{19}H_{13}SBr_2N_3O_2$	45.01	2.61	31.42	8.51	6.10
(62)	235-36	(507)	44.97	2.56	31.56	8.28	6.31
5f	X	$C_{20}H_{15}SBr_2N_3O_3$	44.23	2.99	29.50	7.93	6.01
(73)	247-48	(537)	44.69	2.79	29.80	7.82	5.96
5g	E	$C_{19}H_{12}SBr_2ClN_3O_2$	42.10	2.19	29.26	7.81	5.82
(58)	215-17	(541.5)	42.11	2.22	29.55	7.77	5.91
5h	T	$C_{19}H_{12}SBr_2N_4O_4$	41.12	2.07	28.67	9.87	6.02
(54)	242-44	(552)	41.30	2.17	28.99	10.15	5.80
6a	B/E	$C_{13}H_{12}S_2N_4O_2$	48.51	3.62		17.50	19.82
(60)	215-16	(320)	48.75	3.75		17.50	20.00
6b	B/E	$C_{13}H_{10}S_2Br_2N_4O_2$	32.61	2.12	33.12	11.95	14.01
(50)	201-3	(478)	32.64	2.09	33.47	11.72	13.90
6c	B/E	$C_{19}H_{16}S_2N_4O_2$	57.29	3.92		14.20	15.90
(39)	236	(396)	57.58	4.04		14.14	16.16
6d	B/E	$C_{19}H_{14}S_2Br_2N_4O_2$	41.29	2.51	29.12	10.32	11.44
(42)	246-48	(554)	41.16	2.53	28.88	10.11	11.55
7a	B/E	$C_{13}H_{10}S_2N_4O$	51.51	3.28		18.42	21.02
(88)	292-94	(302)	51.65	3.31		18.54	21.19
7b	X	$C_{13}H_8S_2Br_2N_4O$	34.02	1.92	34.51	12.30	14.20
(92)	337-38	(460)	33.91	1.74	34.78	12.17	13.91

Table II (*Continued*)

Compd (yield %)	Solvent m.p.°C	Molecular formula (M. Wt.)	Analysis % Found / Calcd				
			C	H	Br	N	S
8a	B/E	$C_{16}H_{13}SN_3O_3$	59.09	4.12		12.72	9.81
(62)	215-17	(327)	58.72	3.98		12.84	9.79
8b	B/E	$C_{16}H_{11}SBr_2N_3O_3$	39.22	2.20	33.01	9.00	6.72
(65)	238	(485)	39.59	2.27	32.99	8.66	6.66
9	T	$C_{17}H_{15}SN_3O_2$	62.39	4.60		13.05	10.01
(90)	191-92	(325)	62.77	4.62		12.92	9.85

B = Benzene; Bu = n-Butanol; E = Ethanol; L.P. = Light petrol (b.p. 80-100°); T = Toluene; X = Xylene.

TABLE III

^{1}H-NMR data of prepared compounds

Compd. No.	^{1}H-NMR signals in δ
6a	12 (s, 1H, OH), 11.6 (s, 1H, OH) disappeared by D_2O, δ centered at 7.8 (m, 10 H, aromatic protons and 3 NH), integration decreases by 3H on addition of D_2O.
6d	12 (s, 1H, OH); 11.5 (s, 1H, OH) disappeared by D_2O. δ centered at 8.2 (m, 11H, aromatic protons and one NH), δ 6.1 (s, 1H, SH), δ 3.2 (s, 1H for NH - C_6H_5).
7a	12.5 (s, 1H, OH) disappeared by D_2O. Centered 7.7 (m, 8H, aromatic protons and 1NH), D_2O integration decreases by 1; δ 3.4 (s, 1H, NH).
8a	8.8 (s, 1H, NH), δ ccntered at δ 7.7 (m, 5H, aromatic protons), δ 6.8 (s, 1H, C_4-H of pyrazole) δ 3.4 (s, 1H, NH), δ 2.2 (s, 3 H, CH_3 protons).

Table III (*Continued*)

Compd. No.	^{1}H-NMR signals in δ
9a	12.0 (s, 1H, OH), δ centered at δ 7.8 (m, 7H, aromatic protons), δ 6.2 (s, 1H, C_4-H of pyrazole), δ 2.4 (s, 3H, CH_3), δ 2.2 (s, 3H, CH_3)

species, whereas the other display antibacterial activity against *B. subtilis*. The most potent compounds are those having minimum inhibitory concentration (MIC) ≥ 250 μg/ml (compound No. (**7b**) against Gram-positive bacterium, while the MIC values for the other compounds are equal to 500 μg/ml. All the investigated compounds were assayed by using standardized disk assay procedure of Bauer *et al.*[14]

EXPERIMENTAL

All m.p.'s are uncorrected. IR spectra were measured on a Pye Unicam SP 200 G with KBr wafer technique. ^{1}H-NMR spectra were taken on a Varian EM-360 instrument operating at 60 MHz using TMS as an internal standard with chemical shift (δ) expressed in ppm.

1-3'-Quinazolin-2-thione-5-2"-aminophenyl-1,3,4-triazole and its tetrabromo derivative (**2a** *and* **b**). To a solution of the hydrazide 1 (0.01 mol) in ethanol (50 ml) containing KOH (1 gm) was added by shaking CS_2 (10 ml). The reaction mixture was refluxed on a water bath for 4 h. The solvent was concentrated and the residue was diluted with cold water, then neutralized with concentrated HCl, and the precipitated product was filtered off and crystallised from a suitable solvent to give (**2a, b**) as colourless crystals.

Methylation of **2a** *to* **2c**. A solution of CH_3I (0.015 mol) or $(CH_3)_2SO_4$ (0.015 mol) was added dropwise to a solution of **2a** (0.01 mol) in the least amount of 10% NaOH and the reaction mixture was refluxed for one hour on a water-bath. The precipitated product was filtered off and crystallised from light petrol (b.p. 80–100°C) to give **2c** as colorless crystals.

3-N-Acetamido-2-(thien-2-yl)-3H-quinazolin-4-ones (**3a, b**). A mixture of **1a** (or **1b**) (0.01 mol) and acetyl chloride (20 ml) was refluxed on a water-bath for 3 h. The solvent was removed and the separated solid washed with light petrol (40–60°C) and recrystallised from a suitable solvent to give (**3a, b**) as colorless crystals (cf. Table II).

The Schiff bases (**4** *and* **5**). A mixture of hydrazides **1a** (or **1b**) (0.01 mol), aromatic aldehydes such as benzaldehyde, *p*-anisaldehyde, *p*-chlorobenzaldehyde and/or *p*-nitrobenzaldehyde (0.01 mol) in ethanol (50 ml) and few drops of piperidine was refluxed for 4 h. The solid separated after concentration was crystallised from a suitable solvent to give **4** and **5** as colorless crystals (cf. Table II).

Thiosemicarbazide derivatives (**6a–d**). A mixture of hydrazide **1a** (or **1b**) (0.01 mol), potassium thiocyanate and/or phenylisothiocyanate (0.01 mol) and HCl (1 ml) in ethanol (50 ml) was refluxed for 12 h. The solid separated after concentration of the solvent was crystallised from benzene-ethanol mixture to give **6a–d** as colorless crystals.

2-(2'-Thien-2"-oylaminophen-1'-yl)-1,3,4-triazol-5-thiones (**7a, b**). A mixture of hydrazide **1a** (or **1b**) (0.01 mol) and ammonium thiocyanate (2 gm) was fused at 210°C for one hour. The solid mass was then acidified with HCl. The isolated precipitate was recrystallised from a proper solvent to give **7a** (or **7b**) as colorless crystals.

2-(2'-Thien-2"-oylaminobenzoyl)-5-methylpyrazol-3-ones (**8a, b**). A mixture of hydrazide **1a** (or **1b**) (0.01 mol), ethyl acetoacetate (0.01 mol), and few drops of piperidine in ethanol (50 ml) was refluxed for 8 h. The solid separated after concentration was recrystallised from benzene-ethanol mixture to give **8a** (or **8b**) as colorless crystals.

2-(2"-Thien-2"-oylaminobenzoyl)-3,5-dimethylpyrazole (**9**). A mixture of hydrazide **1a** (0.01 mol), acetylacetone (0.01 mol) and few drops of piperidine was fused at 170°C for 3 h. The solid mass was triturated with ethanol to give (**9**) as colorless crystals.

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