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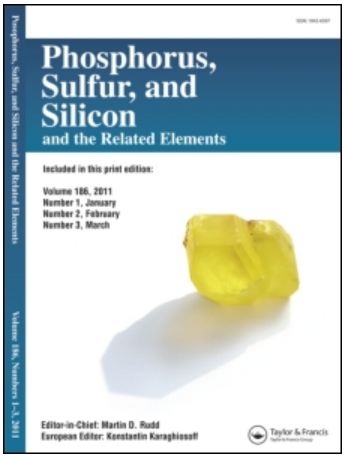

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SYNTHESIS AND REACTIONS OF SOME NEW 5-CARBONYL(4-AMINO-3-CYANO-2-SUBSTITUTED THIOPHENE-5-YL)-8-HYDROXY QUINOLINE AS POSSIBLE ANTIMICROBIAL AGENTS (PART I)

Z. H. Khalil[a]; A. S. Yanni[a]; A. M. Gaber[a]; Sh. A. Abdel-Mohsen[b]
[a] Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt [b] Department of Organic Chemistry, University of Hannover, Hannover, Germany

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SYNTHESIS AND REACTIONS OF SOME NEW 5-CARBONYL(4-AMINO-3-CYANO-2-SUBSTITUTED THIOPHENE-5-YL)-8-HYDROXYQUINOLINE AS POSSIBLE ANTIMICROBIAL AGENTS (PART I)

Z.H. KHALIL[a], A.S. YANNI[a], A.M. GABER[a] and SH. A. ABDEL-MOHSEN[b*]

[a]Chemistry Department, Faculty of Science, Assiut University, Assiut, 71516 Egypt and [b]Department of Organic Chemistry, University of Hannover, Schneiderberg 1B D-30167 Hannover, Germany

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S-Alkylation of 5-carbonyl-(4-amino-3-cyanothiophene-2-thiol-5-yl)-8-hydroxyquinoline (4) with several halogen- containing compounds afforded the alkylthio derivatives (5a-f). Treatment of 4 with chloramine gave isothiazolothiophene (7), which was allowed to react with diethylmalonate and/or ethylacetoacetate to give the corresponding pyrimidinoisothiazolothiophenes (8) and (9). Ring closure of 5d-f with ethanolic sodium ethoxide gave thieno[2,3-b]thiophene derivatives (6a-c). Acetic anhydride, ammonium acetate, phenylisothiocyanate, nitrous acid, acetylacetone, phosphorus oxychloride, phosphorus pentachloride, hydrazine hydrate and benzoyl chloride gave further cyclization to construct an additional ring. The structure of the compounds has been established by elemental analysis, IR, NMR and mass spectra. The compounds thus synthesized were screened for their antimicrobial activity.

Keywords: Synthesis of some new 5-carbonyl-(substituted thieno[2,3,b]thiophene)-8-hydroxyquinoline derivatives; antimicrobial activity

* To whom correspondence should be addressed

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INTRODUCTION

8-Quinolinol is widely used as a precursor for the synthesis of different heterocycles of biological interest[1–3]. Several nitrogen, oxygen and sulfur containing heterocyclic compounds incorporating thiophene residues have been said to possess interesting biological properties[4–12]. Thiophenes with new patterns of substitution are of interest as potentials to pharmaceuticals[13] and dyestaff[14]. A number of highly substituted thiophenes can be obtained by the "Gewald synthesis", which has wide spread application[15]. In view of this, we planned to synthesize 5-carbonyl-(4-amino-3-cyanothiophene-2-potassium thiolate-5-yl)-8-hydroxyquinoline (4) as a starting material for the synthesis of other linear and angular tetra, penta, and hexaheterocyclic ring systems based on the 5-carbonyl-8- hydroxyquinoline moiety.

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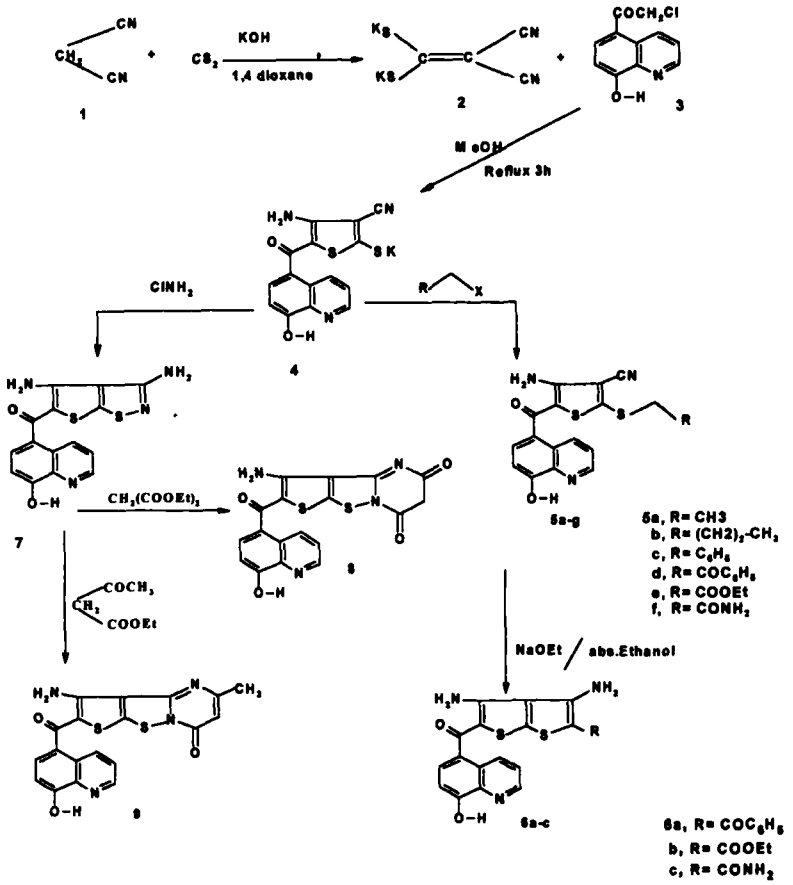
RESULTS & DISCUSSION

Malononitrile (**1**) was reacted with potassium hydroxide and carbon disulphide in the presence of dioxane to yield potassium 1,1-thiolate (**2**), which was converted to 5-carbonyl- (4-amino-3-cyanothiophene-2-potassium thiolate-5-yl)-8-hydroxyquinoline (**4**) on treatment with 5-chloroacetyl-8-hydroxyquinoline (**3**) in methanol under reflux. Treatment of **4** with alkyl (benzyl) halides, α-halo ketones, ester and (or) acylamides gave the corresponding 2-substituted thio compounds (**5a-f**). Cyclocondensation of **5d-f** in boiling ethanol in presence of sodium ethoxide gave a new series of 5-carbonyl-(3,4-diamino-2-substituted thieno[2,3-b]-thiophene-5-yl)-8-hydroxyquinolines (**6a-c**). The interaction of **4** with chloroamine fumished 5-carbonyl-(3,4-diamino-isothiazolo[5,4-b]thiophene-5-yl)-8-hydroxyquinoline (**7**), which was caused to reacted with diethylmalonate and/or ethylacetoacetate to give **8** and **9** respectively. (Scheme 1). Alkaline hydrolysis of the ethyl ester **6b** gave the corresponding 2-carboxylic acid derivative **10**, which afforded the 5-carbonyl-(8-amino-2-methyl-thieno[3′,2′:4,5]thieno[3,2-d]-3,1-oxazine-4(3H)-one-7-yl)-8-hydroxyquinoline (**11**) upon heating under reflux in acetic anhydride. Reaction of **11** with ammonium acetate in boiling acetic acid led to the formation of 5-carbonyl-(8-amino-2-methylthieno[3′,2′:4,5]



SCHEME 1

thieno[3,2-d]pyrimidino-4(3H)-7-yl)-8-hydroxyquinoline (**12**). The same product **12** was obtained also when **6c** was treated under reflux with acetic anhydride. Interaction of **6c** with phenyl isothiocyanate in dry pyridine for 20 h gave 5-carbonyl-(8-amino-2-thioxo-3-phenyl-thieno[3′,2′:4,5]thieno [3,2-d]-pyrimidino-4-(3H)-one-7-yl)-8-hydroxyquinoline (**13**). The synthon **6c** reacted with acetylacetone to give 5-carbonyl-(3,4-diamino-2-[3,5-dimethylpyrazol-1-yl]-carbonyl-thieno[2,3-b]thiophene-5-yl)-8-hydroxyquinoline (**14**). Furthermore, the synthon **6c** reacted with concentrated hydrochloric acid and sodium nitrite in the presence of acetic

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acid at −5 °C and furnished 5-carbonyl-(8-amino-thieno[3′,2′:4,5]thieno [3,2-d]-1,2,3-triazine-4-(3H)-one-7-yl)-8-hydroxyquinoline (**15**). Treatment of the triazino compound **15** with phosphorus pentasulphide in dry pyridine gave the corresponding 5-carbonyl-(8-amino-7-thieno[3′,2′:4,5] thieno[3,2-d]-1,2,3-triazine-4(3H)-thione-7-yl)-8-hydroxyquinoline (**16**). Refluxing of **15** in phosphorus oxychloride gave the chlorotriazino derivative **17**, which on further reaction with hydrazine hydrate in ethanol gave 5-carbonyl-(8-amino-thieno[3′,2′:4,5]thieno[3,2-d]-4-hydrazino-1,2,3-triazino-7- yl)-8-hydroxyquinoline (**18**). This compound was alternatively produced by refluxing of **16** with hydrazine hydrate. Reaction of **18** with acetylacetone gave 5-carbonyl-(8-amino-thieno[3′,2′:4,5]-thieno[3,2-d]-5-(3,4-dimethylpyrazol-1-yl)-1,2,3-triazine-7-yl)-8-hydroxyquinoline (**19**). Compound **18** underwent also cyclization reaction, for example, boiling of **18** With benzoyl chloride gave 5-carbonyl-(8-amino-thieno[3′,2′:4,5]-thieno [3,2-d]-3-phenyl-s-triazolo[4″,3″:1′, 6′]-1,2,3-triazine-7-yl)-8-hydroxyquinoline (**20**) (Scheme 2).

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ANTIMICROBIAL ACTIVITY

All the synthesized compounds were screened for antibacterial and antifungal activities using bacteria *Escherichia coli, Staphylococcus aurius and fungi Aspergillus flavus, Fusarium oxysporium*, following the method of Bauer *et al*[16]. The concentration was 100 μg per disk. Streptomycin and Mycostatin were used as reference while testing antibacterial and antifungal activity, respectively. The results were summerized in Table I.

Antibacterial Activity

Among the 5-carbonyl-(4-amino-3-cyanothiophene-2-alkyl (aralkyl)-thiol-5-yl)-8-hydroxyquinolines (**5a-f**), compounds **5c** and 5e were highly active against *E. coli*, whereas the rest of these compounds were moderately active against *S. aurius*. Among the cyclocondensation products (**6a-c**), compounds **6a** and **6c** exihibited weak activity against *E. coli*, whereas compound **6b** showed moderate activity against *S. aurius*. Among the different heterocycles (oxazino-, triazino-, and triazolotriazino-)-derivatives (**7–20**), the chlorotriazino and s-triazolotriazino (**17**) and (**20**),

respectively showed the maximum activity against both the organisms, whereas all other compounds showed moderate activity against *S. aurius*. (Table I).

TABLE I Antimicrobial activity of the synthesized compounds, zone of growth inhibition (mm)(activity index)[a]

	Escherichia coli (8mm)	*Staphylococcus aurius (9mm)*	*Aspergillus flavus (10mm)*	*Fusarium axysporium (12mm)*
4	6.2	8.2	12.0	13.4
	(0.77)	(0.91)	(1.20)	(1.11)
5a	8.8	9.6	8.8	12.6
	(1.11)	(1.06)	(0.88)	(1.05)
5b	7.9	10.6	9.6	13.0
	(0.98)	(1.17)	(0.96)	(1.08)
5c	13.9	11.1	11.0	11.9
	(1.73)	(1.23)	(1.10)	(0.99)
5d	8.1	10.7	10.9	12.7
	(1.01)	(1.18)	(1.09)	(1.05)
5e	15	9.5	7.8	13.6
	(1.87)	(1.05)	(0.78)	(1.13)
5f	8.8	9.7	6.6	13.3
	(1.10)	(1.07)	(0.66)	(1.11)
6a	7.8	5.9	11.1	14.0
	(0.97)	(0.65)	(1.11)	(1.16)
6b	6.0	12.6	10.7	12.0
	(0.75)	(1.40)	(1.07)	(1.00)
6c	8.4	4.8	11.9	12.9
	(1.05)	(0.53)	(1.19)	(1.07)
7	5.7	12.0	10.8	13.2
	(0.71)	(1.33)	(1.08)	(1.10)
8	7.8	10.3	6.5	12.7
	(0.97)	(1.14)	(0.65)	(1.05)

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	Escherichia coli (8mm)	*Staphylococcus aurius (9mm)*	*Aspergillus flavus (10mm)*	*Fusarium axysporium (12mm)*
9	6.7	9.8	12.1	10.8
	(0.83)	(1.08)	(1.21)	(0.90)
10	8.0	9.7	13.1	13.8
	(1.00)	(1.07)	(1.31)	(1.15)
11	6.9	11.5	11.8	12.9
	(0.86)	(1.27)	(1.18)	(1.07)
12	6.1	10.0	10.5	12.0
	(0.76)	(1.11)	(1.05)	(1.00)
13	5.2	11.2	11.2	11.9
	(0.65)	(1.24)	(1.12)	(0.99)
14	5.8	9.0	10.7	12.7
	(0.72)	(1.00)	(1.07)	(1.05)
15	3.4	10.7	9.9	12.8
	(0.42)	(1.18)	(0.99)	(1.06)
16	7.3	10.3	12.1	13.6
	(0.91)	(1.14)	(1.21)	(1.13)
17	16.6	18.1	10.6	13.8
	(2.07)	(2.01)	(1.06)	(1.15)
18	8.0	11.0	12.5	12.9
	(1.00)	(1.22)	(1.25)	(1.07)
19	7.9	10.8	13.1	13.3
	(0.98)	(1.20)	(1.31)	(1.10)
20	15.9	17.2	10.4	13.1
	(1.98)	(1.91)	(1.04)	(1.09)

[a] Activity index = Inhibition area of the sample / Inhibition area of the standard.

Antifungal Activity

It was observed from the data listed in Table I, that most of the synthesized compounds exihibited moderate activity against both the fungi species (Table I).

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EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin- Elmer 1710 infrared spectrometer. ^{1}H- NMR spectra were recorded on a Bruker AM 400 spectrometer in deuterated chloroform or dimethyl sulfoxide with tetramethylsilane as internal standard. Mass spectra were recorded on a Finnigan MAT 312 (70 ev) or a VG Autospectrometer. Microanalyses were performed in the Department of Organic Chemistry of the University of Hannover.

5-Carbonyl-(4-amino-3-cyanothiophene-2-potassiumthiolate-5-yl)-8-hydroxyquinoline 4

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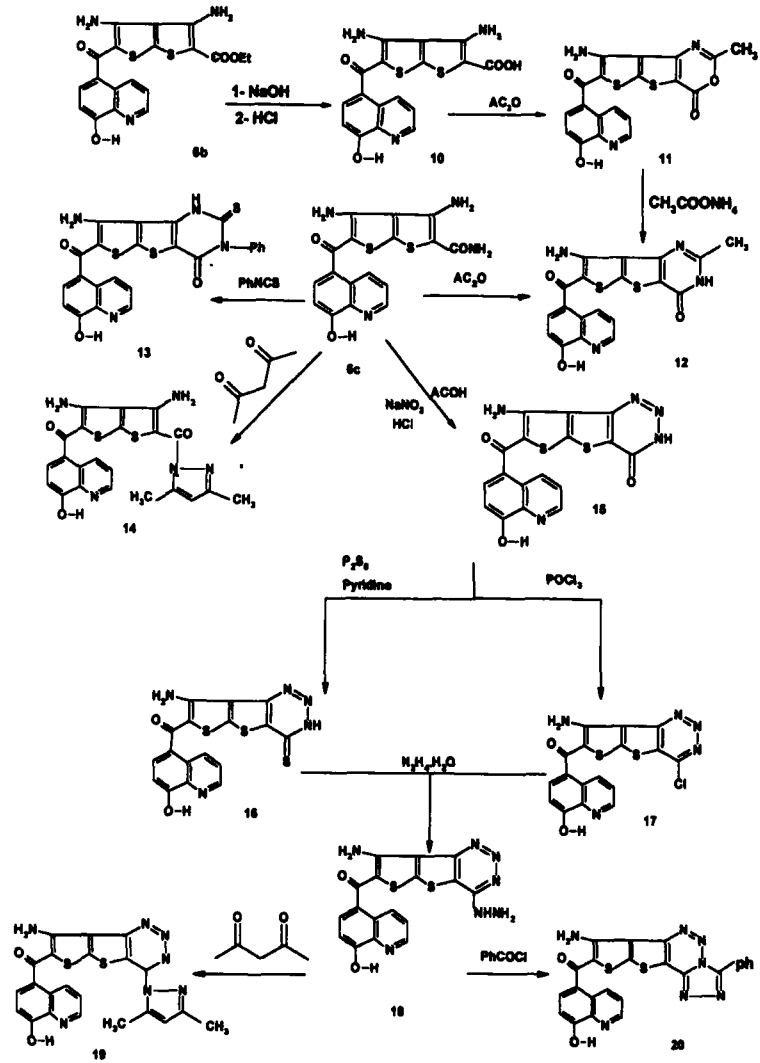
Sodium hydroxide (11mmol) was suspended in dioxane (15ml) and a solution of malononitrile (5.5mmol) and carbon disulfide (5.5mmol) in dioxane (5ml) was added at 15–20°C. The mixture was stirred for 30 min and diluted with diethyl ether (40ml). The resulting precipitate was filtered and was washed with dioxane-ether (1:1v/v). The above prepared potassium 1,1-dithiolate was then dissolved in methanol (20 ml) and 5-chloroacetyl-8-hydroxyquinoline **3** in methanol (10ml) was added over 3h. After that the whole mixture was refluxed for 1h. The reaction mixture was then concentrated and the solid product was collected to give a yellowish preciptate, mp>250°C, Yield 74.5 %. IR: 3353, 3250 (NH_2), 2207 (CN), 1650 (CO) cm^{-1}. ^{1}H-NMR (DMSO) δ: 7.12 (s, 2H, NH_2) and 7.45–8.9 (m, 6H, ArH). MS, m/z (%): 365 (M^+ 78.91). Anal. Calc. for; $C_{15}H_8N_3O_2S_2$ C 49.31, H 2.19, N 11.50, S 17.53; found: C 49.22, H 2.15, N 11.44, S 17.23%.

5-Carbonyl-(4-amino-3-cyanothiophene-2-alkyl(aralkyl)-thiol-5-yl)-8-hydroxyquinolines 5a-f

General procedure

A mixture of **4** (0.01 mol) and alkyl (or aralkyl) halide (0.01 mol) was refluxed in ethanol (30 ml) for 2h. The reaction mixture was poured into cold water and the solid product was collected and recrystallized from ethanol to yield **5a-f**



SCHEME 2

5-Carbonyl-(4-amino-3-cyanothiophene-2-methylthio-5-yl)-8-hydroxyquinoline 5a

Yield 83 %, m.p. 168 °C. IR: 3300, 3200 (NH_2), 2980, 2870 (CH-aliphatic), 2240 (CN) and 1650 (CO) cm^{-1}. ^{1}H-NMR (DMSO) δ:

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8.9- 7.2 (m, 6H, ArH), 7.12 (s, 2H, NH_2), 2.9- 3.2 (q, 2H, CH_2) and 1.4-1.2 (t, 3H, CH_3). MS, m/z (%): 355 (M^+ 100). Anal. Calc. for $C_{17}H_{13}N_3O_2S_2$: C 57.45, H 3.69, N 11.82, S 18.04; found: C 57.22, H 3.58, N 11.78, S 17.92%.

5-Carbonyl-(4-amino-3-cyanothiophene-2-n-butylthio-5-yl)-8-hydroxyquinoline 5b

Yield 86 %, m.p. 127°C. IR: 3300, 3200 (NH_2), 2980, 2870 (CH aliphatic), 2230 (CN) and 1650 (CO) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9- 7.2 (m, 6H, ArH), 7.12 (s, 2H, NH_2), 3.2- 3.0 (t, 2H, S-CH_2), 1.8- 1.2 (m, 4H, $(CH_2)_2$), and 1.1- 0.9 (t, 3H, CH_3). MS, m/z (%): 382 (M^+-1 88.36). Anal. Calc. for $C_{19}H_{17}N_3O_2S_2$: C 59.51, H 4.47, N 10.96, S 16.72; found: C 59.28, H 4.32, N 10.89, S 16.68%.

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5-Carbonyl-(4-amino-3-cyanothiophene-2-benzylthio 5-yl)-8-hydroxyquinoline 5c

Yield 77 %, m.p. 195 °C. IR: 3300, 3200 (NH_2), 2990 (CH aliphatic), 2210 (CN) and 1660 (CO) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9- 7.2 (m, 11H, ArH), 7.10 (s, 2H, NH_2), 4.3(s, 2H, CH_2). MS, m/z (%): 417 (M^+ 100). Anal. Calc. for $C_{22}H_{15}N_3O_2S_2$: C 63.29, H 3.62, N 10.06, S 15.36; found: C 63.11, H 3.54, N 10.45, S 15.33%.

5-Carbonyl-(4-amino-3-cyanothiophene-2-benzylthio 5-yl)-8-hydroxyquinoline 5d

Yield 81 %, m.p. 220°C. IR: 3300, 3200 (NH_2), 2990 (CH aliphatic), 2190 (CN) and 1695 (CO) and 1650 (CO) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.2 (m, 11H, ArH), 7.10 (s, 2H, NH_2), 5.1(s, 2H, CH_2). MS, m/z (%): 445 (M^+ 87.82). Anal. Calc. for $C_{23}H_{15}N_3O_3S_2$: C 62.01, H 3.39, N 9.43, S 14.39; found C 61.98, H 3.21, N 9.22, S 14.19%.

5-Carbonyl-(4-amino-3-cyanothiophene-2-benzylthio-5-yl)-8-hydroxyquinoline 5e

Yield 89 %, m.p 132°C. IR: 3400, 3300 (NH_2), 2980 (CH aliphatic), 2200 (CN) and 1754(CO) and 1650 (CO) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.2

(m, 6H, ArH), 7.12 (s, 2H, NH_2), 5.2 (s, 2H, S- CH_2), 4.3–4.1 (q, 2H, CH_2) and 1.3–1.1 (t, 3H, CH_3). MS, m/z (%): 413 (M^+ 100). Anal. Calc. for $C_{19}H_{15}N_3O_4S_2$: C 55.19, H 3.66, N 10.16, S 15.51; found: C 55.03, H 3.65, N 9.99, S 15.47 %.

5-Carbonyl-(4-amino-3-cyanothiophene-2-benzylthio-5-yl)-8-hydroxyquinoline 5f

Yield 75 %, m.p 218°C. IR: 3300, 3200 (NH_2), 2980 (CH aliphatic), 2190 (CN), 1685 (CO) and 1645 (CO) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9- 7.2 (m, 6H, ArH), 7.12 (s, 2H, NH_2), 6.9 (s, 2H, NH_2) and 3.9 (s, 2H,CH_2) MS, m/z (%): 384 (M^+ 100). Anal. Calc. for $C_{17}H_{12}N_4O_3S_2$: C 53.11, H 3.15, N 14.57, S 16.68; found C 52.92, H 3.11, N 14.50, S 16.59 %.

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5-Carbonyl-(3,4-diamino-2-substitutedthieno[2,3-b]-thiophene-5-yl)-8-hydroxyquinoline 6a-c

A mixture of each of the mercapto derivatives **(5d-g)** (0.01 mol) in ethanol (30 ml) and five drops of ethanolic sodium ethoxide was refluxed for 1h. After cooling, the product was collected and recrystallized from ethanol to give **6a-c**

5-Carbonyl-(3,4-diamino-2-benzoyl-thieno[2,3-b]-thiophene-5-yl)-8-hydroxyquinoline 6a

Yield 79 %, m.p 280°C. IR: 3300, 3200 (NH_2), 1690 (CO) and 1660(CO) cm^{-1}. ^{1}H-NMR (DMSO) δ 8.9- 7.3 (m, 11H, ArH), 7.00- 7.15 (2 s, 4H, $2NH_2$). MS, m/z (%): 445 (M^+ 100). Anal. Calc. for $C_{23}H_{15}N_3O_3S_2$: C 62.01, H 3.39, N 9.43, S 14.39; found: C 61.90, H 3.30, N 9.41, S 14.30 %.

5-Carbonyl-(3,4-diamino-2-ethylcarboxylate-thieno[2,3-b]-thiophene-5-yl)-8-hydroxyquinoline 6b

Yield 82 %, m.p 259°C. IR: 3450, 3350 (NH_2), 2900, 2850 (CH, aliphatic) 1737 (CO) and 1660 (CO) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9- 7.3 (m, 6H,

ArH), 7.15- 7.0 (2 s, 4H, $2NH_2$), 4.3- 4.1(q, 2H, CH_2) and 1.3- 1.2 (t, 3H, CH_3). MS, m/z (%): 413 (M^+ 100). Anal. Calc. for $C_{19}H_{15}N_3O_4S_2$: C 55.19, H 3.66, N 10.16, S 15.51; found: C 55.10, H 3.49, N 10.12, S 15.46 %.

5-Carbonyl-(3,4-diamino-2-carboxamide-thieno[2,3-b]-thiophene-5-yl)-8-hydroxyquinoline 6c

Yield 77 %, m.p 298 °C. IR: 3300, 3200 (NH_2), 1680 (CO) and 1645 (CO) cm^{-1}. ^{1}H-NMR (DMSO) δ 8.9–7.3 (m, 6H, ArH) and 7.12–7.0 (2s, 4H, $2NH_2$). MS, m/z (%): 384 (M^+ 77.78). Anal. Calc. for $C_{17}H_{12}N_4O_3S_2$: C 53.11, H 3.15, N 14.57, S 16.68; found: C 52.89, H 2.99, N 14.49, S 16.61 %.

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5-Carbonyl-(3, 4-diamino-isothiazolo[5,4-b]thiophene-5-yl)-8-hydroxyquinoline 7

An aqueous chloramine solution [made by mixing 14 % w/w sodium hypochlorite (150 g) and aqueous ammonia (d 0.88, 12 g) at 0°C Was added in one portion to a stirred solution of compound **4** (0.05 mol) at 70°C. The mixture was allowed to cool, the yellow precipitate was collected, washed well with water and recrystallized from ethanol to give yellow crystalls mp 256 °C, yield 81%. IR: 3420, 3300 (NH_2), 1630 (C=N) cm^{-1}. ^{1}H-NMR (DMSO) δ: 7.12 (s, 2H, NH_2), 7.2 (s, 2H, NH_2 isothiozole), 7.5–8.9 (m, 6H, ArH). MS, m/z (%): 342 (M^+50.1). Anal. Calc. for; C 52.62, H 2.94, N 16.36, S 18.73; found: C 52.59, H 2.88, N 16.33, S 18.69 %.

5-Carbonyl-(8-amino-thieno[3′,2′-4,5]isothiazolo[3,2-c]-1,5-pyrimidino-2,4-dione-3-dihydro-7-yl)-8-hydroxyquionline 8

A mixture of **7** (0.01 mol) and (0.01 mol) of diethylmalonate in o-dichlorobenzene (20 ml) was heated under reflux for 3h. When the solution was cooled, a white solid crystallized cotich was purified from o-dichlorobenzene, mp. 243°C, yield 68%. IR: 3400,3350 (NH_2), 2990 (CH aliphatic), 1700,1650 (2CO), 1630 (C=N)cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.9 (s, 2H, 2CO), 7.3 (s, 2H, NH_2), 7.7–8.9 (m,6H,ArH). MS, m/z (%) 409 (M+ 1

83),410 (M^+ 100). Anal. Calc. for $C_{18}H_{10}N_4O_4S_2$: C 52.68, H 2.46, N 13.65, S 15.62; found: C 52.59, H 2.44, N 13.62, S 15.58 %.

5-Carbonyl-(8-amino-thieno[3',2'-4,5]isothiazolo[3,2-c]-1,5-pyrimidino-4(3H)-one-2-methyl-7-yl)-8-hydroxyquionline 9

A mixture of **7** (0.01 mol), ethylacetoacetate (0.01 mol) and 20 ml of ethanol was refluxed for 3h. When cooled, a solid product precipitated which was recrystallized from methanol, mp. 286°C, yield 71%. IR: 3400, 3350 (NH_2), 3010 (CH, olefinic), 2990 (CH aliphatic), 1650 (CO), 1630 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.5 (s, 3H, CH_3), 7.3 (s, 2H, NH_2), 7.7–8.9 (m, 6H, ArH). MS, m/z (%): 408 (M^+ 85). Anal. Calc for $C_{19}H_{12}N_4O_3S_2$: C 55.87, H 2.96, N 13.72, S 15.70; found: C 55.81, H 2.95, N 13.69, S 15.66 %.

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5-Carbonyl-(3,4-diamino-2-carboxylic acid thieno[2,3-b]-thiophene-5-yl)-8-hydroxyquinoline 10

A mixture of **6b** (0.01 mol) and alcoholic sodium ethoxide (30 ml, 25%) was refluxed for 5h. The solid product obtained after cooling was filtered and acidified with diluted HCl. The solid free was collected and recrystallized from dioxane, mp. 330°C, yield 82%. IR: 3400, 3300 (NH_2), 1730, 1650 (2CO)cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6,90 (s, 2H, NH_2), 7.2 (s, 2H,NH_2), 7.7–8.9 (m, 6H, ArH), 10.50 (s, 1H, OH). Anal. Calc for $C_{17}H_{11}N_3O_4S_2$: C 52.98, H 2.88, N 10.90, S 16.64; found: C 52.82, H 2.88, N 10.84, S 16.59 %.

5-Carbonyl-(8-amino-2-methyl-thieno[3,2':4,5]thieno[3,2-d]-3,1-oxazine-4(3H)-one-7-yl)-8-hydroxyquinoline 11

The amino acid **10** (0.01 mol) and acetic anhydride (20 ml) was refluxed for 4h. The solid obtained on cooling was filtered and recrystallized from dioxane to give as yellow crystals, mp >350°C, yield 77%. IR:3400, 3300 (NH_2), 1754 (CO oxazine), 1650 (CO) cm^{-1}. ^{1}H-NMR (DMSO) δ: 2.70 (s,3H,CH_3), 7.2 (s, 2H, NH_2), 7.7–8.9 (m, 6H, ArH). MS, m/z (%):409 (M^+ 100). Anal. Calc for $C_{19}H_{11}N_3O_4S_2$: C 55.74, H 2.71, N 10.26, S 15.66; found C 55.71, H 2.70, N10.23, S 15.65 %.

5-Carbonyl-(8-amino-2-methyl-thieno[3′,2′:4,5]thieno[3,2-d] pyrimidino-4(3H)-7-yl)-8-hydroxyquinoline 12

Method A

A mixture of **11** (0.01 mol), and ammonium acetate (0.02 mol) was heated under reflux in acetic acid (20 ml) for 4h. The solid product obtained after concentration and cooling was filtered and recrystallized from acetic acid to give yellow crystals, mp 310 °C, yield 80 %. IR: 3550 br (NH), 3400,3300 (NH_2),1650 (CO) cm^{-1}. ^{1}H-NMR (TFA-d) δ: 3.1 (s, 3H, CH_3), 7.7–8.9 (m, 6H, ArH). Anal. Calc for $C_{19}H_{12}N_4O_3S_2$:C 55.87, H 2.96, N 13.72, S15.70; found C55.78, H 2.93, N 13.69, S 15.66%.

Method B

A solution of **6c** (0.01 mol) in acetic anhydride (5ml) was heated under reflux for 18 h. After cooling a solid formed which was collected and crystallized from ethanol to give yellow crystals, identical with the sample obtained above.

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5-Carbonyl-(8-amino-2-thioxo-3-phenyl-thieno[3′,2′:4,5]thieno[3,2-d]-pyrimidino-4-(3H)-one 13–7-yl)-8ydroxyquinoline 13

A mixture of **6c** (0.01 mol) and phenyl isothiocyanate (0.01 mol), was heated under reflux in pyridine (15 ml) in an oil bath for 9 hrs. The reaction mixture was cooled and triturated with aqueous ethanol. The resuling solid was filtered, dried and recrystallized from dimethylformamide mp. >340°C, yield 85 %. IR: 3400, 3300 (NH, NH_2), 1700 (CO), 1600 (C=N), 1280(C=S) cm^{-1}. ^{1}H-NMR (DMSO) δ: 7.2 (s, 2H, NH_2), 7.7-.9 (m, 11H, ArH), 10.7 (s, 1H, NH). MS, m/z (%):502 (M^+ 15.30). Anal. Calc. for $C_{24}H_{14}N_4O_3S_3$: 57.36, H 2.81, N 11.15, S 19.14; found C 57.28, H 2.79, N 11.11, S 19.09 %.

5-Carbonyl-(3,4-diamino-2-[3,5-dimethylpyrazol-1-yl]carbonylthieno [2,3-b]thiophene-5-yl)-8-hydroxyquinoline 14

A mixture of **6c** (0.01 mol) and acetylacetone (0.01 mol) was heated under reflux in (20 ml) ethanol for 7 h and was then concentrated and allowed to cool. The precipitated solid was filtered and recrystallized from ethanol.

mp. 297°C, yield 65 %. IR: 3400, 3300 (NH_2), 1710 (CO), 1620(C=N) cm^{-1}. ^{1}H-NMR (DMSO) δ: 3.4 (s, 6H, $2CH_3$), 7.2 (s, 2H, NH_2), 7.7–8.9 (m, 7H, ArH). MS, m/z (%): 463 (M^+ 100). Anal. Calc. for $C_{22}H_{17}N_5O_3S_2$: C 57.01, H 3.70, N 15.11, S 13.83; found C 56.96, H 3.68, N 15.07, S 13.79 %.

5-Carbonyl-(8-amino-thieno[3′,2′:4,5]thieno[3,2-d]-1,2,3-triazine-4-(3H)-one 15–7-yl)-8-hydroxyquinoline 15

A mixture of **6c** (0.01 mol) and hydrochloric acid was cooled to −5°C, while adding dropwise a sodium nitrite solution (15 ml) in the presence of acetic acid (10 ml) and stirred for 2 hr. The separated solid was recrystallized from chloroform as buff crystals mp. 301°C, yield 67% IR: 3300, 3200 (NH, NH_2) 1600 (CO traizine) cm^{-1}. ^{1}H-NMR (DMSO) δ: 7.2 (s, 2H, NH_2), 7.7–8.9 (m, 6H, ArH), 9.3 (s, 1H, NH). Anal. Calc. for $C_{17}H_9N_5O_3S_2$: C 51.64, H 2.29, N 17.71, S 16.22; found C 51.55, H 2.26, N 17.68, S 16.20 %.

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5-Carbonyl-(8-amino-7-thieno[3′,2′:4,5]thieno[3,2-d]-1,2,3-triazine-4 (3H)-thione-7-yl)-8-hydroxyquinoline 16

A mixture of **15** (0.01 mol) and phosphorus pentasulphide (0.05 mol) in dry pyridine was refluxed for 6hr. The reaction mixture was poured onto cold water and the separated solid was filtered and recrystallized from dimethylformamide mp. 289°C, yield 73 %. IR: 3300, 3200, (NH, NH_2), 1220 (C=S)cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.2 (s, 2H, NH_2), 7.7–8.9 (m, 6H, ArH), 9.2 (s, 1H, NH). MS, m/z (%) 411(M^+ 100). Anal. Calc. for $C_{17}H_9N_5O_3S_3$: C 49.62, H 2.20, N 17.02, S 23.38; found C 49.59, H 2.17, N 16.97, S 23.31 %.

5-Carbonyl-(8-amino-thieno[3′,2′:4,5]thieno[3,2-d]-4chloro-1,2,3-triazine-7-yl)-8-hydroxyquinoline 17

A mixture of **15** (0.01 mol) in phosphorus oxychloride (30 ml) was refluxed for 3 hr and allowed to cool. The reaction mixture was poured into ice-cold water. The separated solid was then filtered off and recrystallized from ethanol, mp. 215°C, yield 67%. IR: 3400, 3300 (NH_2), 1650

(CO), 1620 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.2 (s, 2H, NH_2). MS, m/z (%) 409(M^+ 100). Anal. Calc. for $C_{17}H_8ClN_5O_2S_2$: C49.34, H 1.95, Cl 8.57, N 16.92, S 15.49; found C 49.29, H 1.93, Cl 8.50, S 15.44 %.

5-Carbonyl-(8-amino-thieno[3′,2′:4,5]thieno[3,2-d]-4-hydrazino-1,2,3-triazine-7-yl)-8-hydroxyquinoline 18

Hydrazine hydrate (10 ml) was refluxed with either **16** or **17** (0.01 mol) in absolute ethanol (40 ml) for 4 hr. The separated solid was washed with ethanol and recrystallized from ethanol, m.p. 312°C, yield 79 %. IR: 3400, 3330, 3210 (NH, NH_2), 1650 (CO), 1630 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 11.2–11 (s, 1H, NH), 7.7–8.9 (m, 6H, ArH).), 6.9, 7.2 (2s, 4H, $2NH_2$). Anal. Calc. for $C_{17}H_{11}N_7O_2S_2$. C 49.87, H 2.71, N 23.95, O 7.82, S 15.66.

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5-Carbonyl-(8-amino-thieno[3′,2′:4,5]-thieno[3,2-d]-5-(3,4-dimethylpyrazol-1-yl)-1,2,3-triazine-7-yl)-8-hydroxyquinoline 19

A mixture of **18** (0.01 mol) and acetylacetone (0.02 mol) in ethanol (50 ml) was refluxed for 5 hr. The separated solid was recrystallized from ethanol, mp. 305°C, yield 78% IR: 3400, 3300 (NH_2), 1650 (CO), 1620 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.7 (s, 3H, CH_3), 3.3 (s, 3H, CH_3) both of pyrazole ring, 6.7 (s, 1H, CH), 7.2 (s, 2H, NH_2), 7.7–8.9 (m, 6H, ArH). MS, m/z (%): 473 (M^+ 75). Anal. Calc. for $C_{22}H_{15}N_7O_2S_2$: C 55.80, H 3.19, N 20.71, S 13.54; found C 55.74, H 3.18, N 20.68, S 13.52 %.

5-Carbonyl-(8-amino-thieno[3′,2′:4,5]-thieno[3,2-d]-3-phenyl-s-triazolo[4″,3″:1′,6′]-1,2,3-triazine-7-yl)-8-hydroxyquinoline 20

Refluxing of **18** (0.01 mol) in benzoyl chloride (10ml) for 4 hr gave after cooling a solid product which was filtered and washed with pet-ether (40–60°C) and recrystallized from dioxane, mp. 299 °C, yield 66%, IR: 3400, 3300 (NH_2), 1650 (CO), 1620 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.2 (s, 2H, NH_2), 7.6–8.9 (m, 11H, ArH). Anal. Calc. for $C_{24}H_{13}N_7O_2S_2$: C 58.17, H 2.64, N 19.79, S 12.94; found C 58.12, H 2.63, N 19.75, S 12.90 %.

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