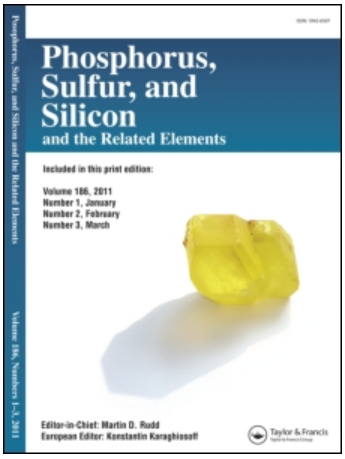


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND REACTIONS OF SOME NEW 5-CARBONYL(4-AMINO-3-CYANO-2-SUBSTITUTED THIOPHENE-5-YL)-8-HYDROXYQUINOLINE (PART II). SYNTHESIS OF THIAZOLE; ISOXAZOLE; PYRAZOLE, PYRIMIDINE AND PYRIDAZINE DERIVATIVES AS POSSIBLE ANTIMICROBIAL AGENTS

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 Schneider-berg, Hannover, Germany

To cite this Article Khalil, Z. H. , Yanni, A. S. , Gaber, A. M. and Abdel-Mohsen, SH. A.(2000) 'SYNTHESIS AND REACTIONS OF SOME NEW 5-CARBONYL(4-AMINO-3-CYANO-2-SUBSTITUTED THIOPHENE-5-YL)-8-HYDROXYQUINOLINE (PART II). SYNTHESIS OF THIAZOLE; ISOXAZOLE; PYRAZOLE, PYRIMIDINE AND PYRIDAZINE DERIVATIVES AS POSSIBLE ANTIMICROBIAL AGENTS', Phosphorus, Sulfur, and Silicon and the Related Elements, 166: 1, 57 — 69
To link to this Article: DOI: 10.1080/10426500008076531
URL: http://dx.doi.org/10.1080/10426500008076531

Phosphorus, Sulfur and Silicon, 2000, Vol. 166, pp. 57-69
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS AND REACTIONS OF SOME NEW 5-CARBONYL(4-AMINO-3-CYANO-2-SUBSTITUTED THIOPHENE-5-YL)-8-HYDROXYQUINOLINE (PART II). SYNTHESIS OF THIAZOLE; ISOXAZOLE; PYRAZOLE, PYRIMIDINE AND PYRIDAZINE DERIVATIVES AS POSSIBLE ANTIMICROBIAL AGENTS

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*

(Received April 4, 2000; In final form May 30, 2000)

5-Carbonyl-(3,4-diamino-2-ethylcarboxylatethieno[2,3-b]thiophene-5yl)-8-hydroxyquinoline (**1**) reacts with various reagents to afford thiazole, oxadiazole, pyrazole, isoxazole, pyrimidine and pyridazine derivatives (**2–13d**). 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

INTRODUCTION

The reactivity of heterocyclic amines towards carbon disulfide followed by cyclization with α-haloketones has been studied and found to yield thiazoles and their fused derivatives.[1–8] Thus, in continuation of our previous

* To whom correspondence should be addressed

work, we report herein the use of 5-carbonyl-(3,4-diamino-2-ethylcarboxylate thieno[2,3-b]thiophene-5-yl)-8-hydroxyquinoline[9] (**1**), for the synthesis of various azole, azine and azoloazine derivatives with anticipated antimicrobial activity.

RESULTS & DISCUSSION

The reaction of **1** with carbon disulfide in dimethylformamide, containing potassium hydroxide, afforded the potassium thiocarbamate intermediate **2**. The latter reacted, in situ with ω-bromoacetophenone to give the thiazole derivative **3**. In a similar manner, the reaction of **2** with ethyl bromoacetate provided the 4-hydroxythiazole derivative **4**. On the other hand, the condensation of the amino ester (**1**) with selected o-substituted aromatic amines such as o-aminothiophenol, o-aminophenol and o-phenylenediamine in the presence of poly phosphoric acid afforded 2-benzo(thiazolo, oxazolo, imidazolo) derivatives **5a-c**. A smooth reaction of **1** with aliphatic, aromatic and heterocyclic hydrazides such as acetic hydrazide, benzoic hydrazide and isonicotinic hydrazide in the presence of poly phosphoric acid gave the corresponding oxadiazoles derivatives **6a-c** (Scheme 1). Conversely, compound **1** was diazotized and coupled with ethyl cyanoacetate to yield the corresponding coupling product 5-carbonyl (4-amino-3-ethylcyano-hydrazono-2-ethyl carboxylate thieno[2,3-b]thiophene 5-yl) (**8**), in good yield. The reaction of **8** with hydrazine hydrate and phenyl hydrazine afforded the corresponding 5-carbonyl (4-amino-3-(3′-amino-5′-hydroxy-azo)pyrazole-4′-yl)-2-ethylcarboxylate thieno[2,3-b]thiophene-5-yl)-8-hydroxyquinoline derivatives **9a,b** respectively. By a similar way, the reaction of **8** with hydroxylamine hydrochloride in ethanolic sodium hydroxide solution, afforded the isoxazole derivative **10**. The reaction of **8** with equimolar amounts of urea or thiourea in refluxing sodium ethoxide solution provided the corresponding 4-amino-pyrimidine derivatives **11a,b** respectively (**Scheme 2**). Compound **8** also was caused to react with equimolar amounts of the malononitrile (**12a**), in refluxing sodium methoxide solution to yield 5-carbonyl (4-amino-3-(ethyl-4′-amino-5′-cyano-6′-imino-1′,6′-dihydropyridazine-3′-carboxylate-2′-yl)-2-ethylcarboxylate thieno[2,3,b]thiophene-5-y)-8-hydroxyquinoline derivative **13a**. Similarly, the reaction of **8** with ethyl cyanoacetate (**12b**), under the same experimental conditions, yielded the corresponding 5-carbonyl(4-amino-3-(ethyl-5′-cyano-6′-oxopyridazine-3′-c

arboxylate-2′-yl)-2-ethylcarboxylate thieno[2,3,b]thiophene-5-yl)-8-hydrox yquinoline **13b**. Conversely, **8** reacted with equimolar amount of ethyl acetoacetate (**12c**) to give the pyridazine derivative **13c**. Moreover, the reaction of **8** with cyanothioacetamide (**12d**) afforded the pyridazine derivative **13d** (Scheme 2). The newly synthesized compounds showed interesting antimicrobial activity; their structures were confirmed on the basis of analytical and spectral data.

ANTIMICROBIAL ACTIVITY

All the synthesized compounds (**3–13**) were screened for antibacterial and antifungal activities using bacteria *Escherichia coli, Staphylococcus aurius and fungi Aspergillus flavus, Fusarium axysporium* following the method of Bauer *et al*[10]. The concentration was 100 μg per disk. Streptomycin and Mycostatin were used as reference while testing antibacterial and antifungal activity, respectively. The results were listed in Table I.

TABLE I Antimicrobial activity of synthesized compounds, zone of growth inhibition (mm) (activity index)*

	Escherichia coli (8mm)	*Staphylococcus aurius (9mm)*	*Aspergillus flavus (10mm)*	*Fusarium axysporium (12mm)*
3	7.4 (0.92)	9.1 (1.01)	10.9 (1.09)	23.2 (1.93)
4	17.1 (2.13)	9.2 (1.02)	11.1 (1.11)	12.6 (1.05)
5a	7.8 (0.97)	10.4 (1.15)	10.3 (1.03)	13.6 (1.13)
5b	8.2 (1.02)	8.9 (0.98)	10.7 (1.07)	13.9 (1.15)
5c	8.4 (1.05)	9.4 (1.04)	11.5 (1.15)	19.7 (1.64)
6a	8.6 (1.07)	9.2 (1.02)	12.1 (1.12)	13.8 (1.15)
6b	8.0 (1.00)	9.5 (1.05)	11.4 (1.14)	12.9 (1.07)
6c	18.2 (2.27)	9.3 (1.03)	12.2 (1.22)	14.1 (1.17)

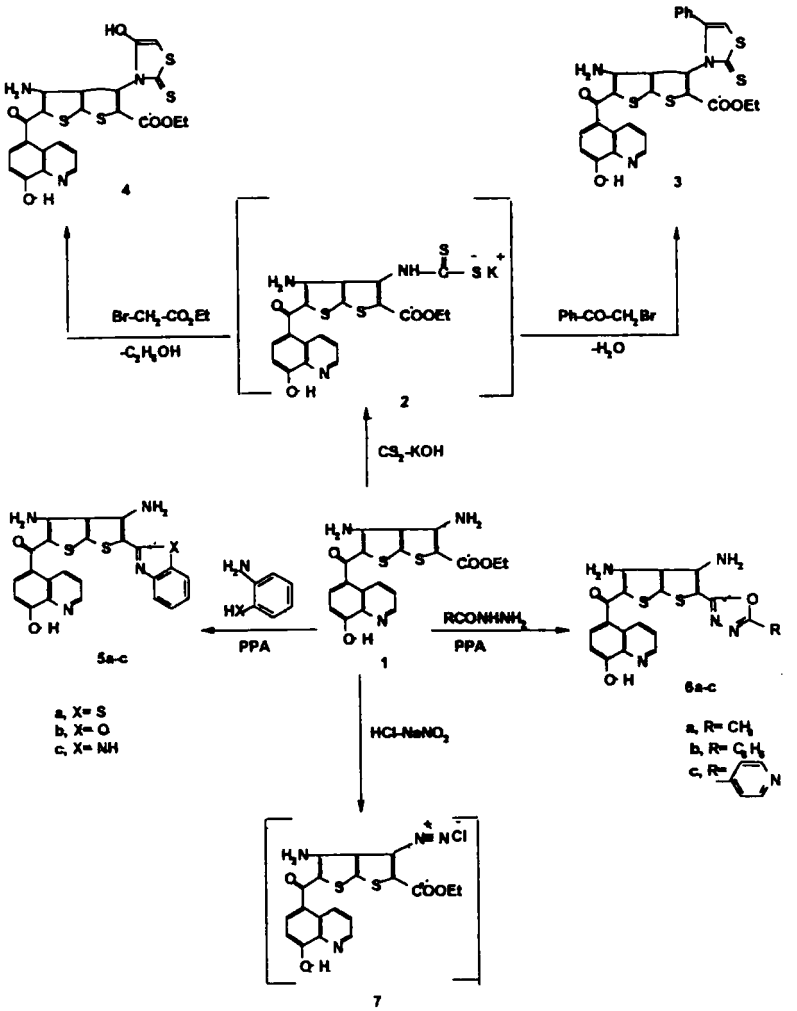
	Escherichia coli (8mm)	*Staphylococcus aurius* (9mm)	*Aspergillus flavus* (10mm)	*Fusarium axysporium* (12mm)
7	7.6 (0.95)	8.7 (0.96)	11.9 (1.19)	11.9 (0.99)
8	7.9 (0.98)	8.8 (0.97)	10.9 (1.09)	13.2 (1.10)
9a	8.1 (1.01)	9.2 (1.02)	11.1 (1.11)	12.6 (1.05)
9b	16.8 (2.10)	7.7 (0.85)	12.6 (1.26)	13.6 (1.13)
10	8.2 (1.02)	8.9 (0.98)	10.7 (1.07)	20.1 (1.67)
11a	9.8 (1.22)	10.5 (1.16)	11.5 (1.15)	13.7 (1.14)
11b	10.3 (1.28)	19.2 (2.13)	12.1 1.12)	14.2 (1.18)
13a	9.1 (1.00)	9.9 (1.05)	11.8 (1.14)	13.9 (1.07)
13b	9.7 (1.13)	11.0 (1.22)	12.2 (1.22)	12.8 (1.06)
13c	9.9 (1.23)	10.9 (1.21)	11.8 (1.18)	13.2 (1.10)
13d	10.4 (1.30)	11.3 (1.25)	9.9 (0.99)	13.7 (1.14)

Activity index = Inhibition area of the sample / Inhibition area of the standard.

ANTIBACTERIAL ACTIVITY

Among the five membered heterocyclic azolo derivatives **3–10**, the 4-hydroxythiazolo (**4**), the oxadiazolo **6c** (R=4-pyridyl) and the 4-hydroxypyrazolo **9b** (R=Ph) exihibited maximum activity against *Escherichia coli*, whereas rest of these compounds possessed no significant activity against both of the investigated bacteria. Among the six membered heterocyclic derivatives (pyrimidines and pyridazines) (**11a,b** and **13a-d**), only the pyrimidino derivative **11b** (X=S) exihibited maximum activity against

Staphylococcus aurius, whereas rest of these compounds possessed moderate activity against both of the investigated bacteria (Table I) .



SCHEME 1

ANTIFUNGAL ACTIVITY

It was observed from Table (I) that most of the synthesized compounds **3–13** showed moderate activity against the investigated fungi. Maximum activity among the different five and six embered heterocyclic rings are the 4-phenylthiazolo (**3**), the benzoimidazolo (**5c**, X=NH), the oxazolo(**10**) and the pyridazino derivative (**13d**, X=S, Y=CN) against *Fusarium oxysporium* (Table I)

EXPERIMENTAL

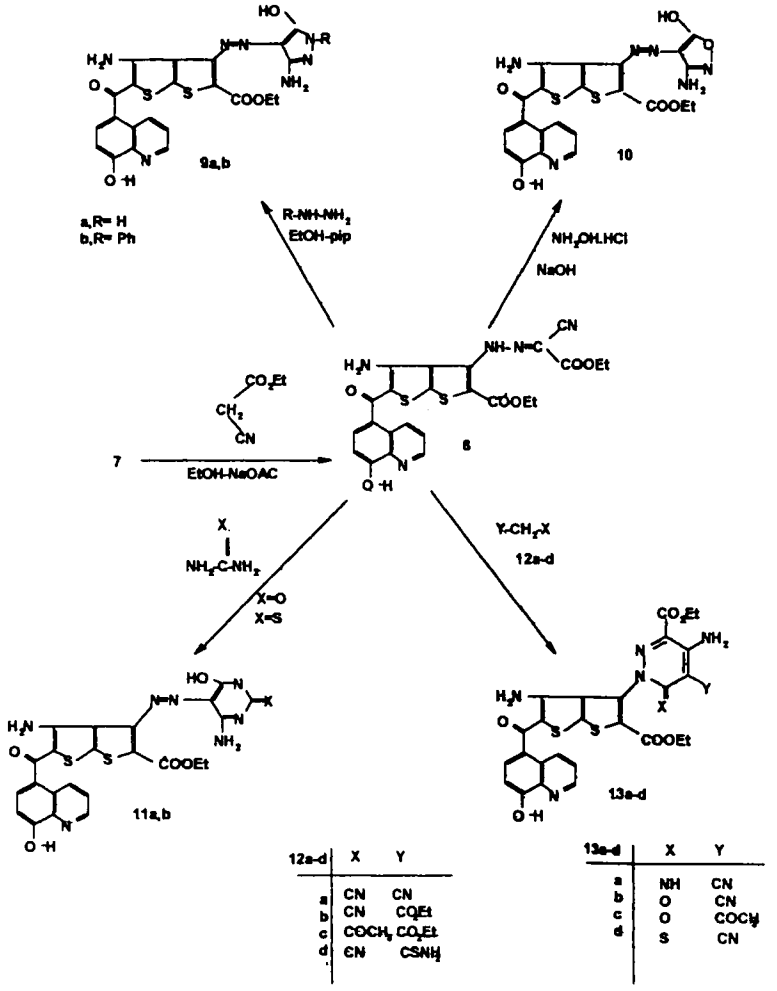
5-Carbonyl-(4-amino-3(4-phenyl(hydroxy)-2-thioxo-1,3-thiazole-3-yl)-2-ethylcarboxylate thieno[2,3,b]thiophene-5-yl)-8-hydroxyquinoline 3,4 respectively

General procedure

To a solution of the amino ester (**1**) (12.5 mmol) in DMF at 0°C was added successively dropwise: (i) aqueous KOH (10 M. 0.7 ml); ((ii) carbon disulfide (1.5 ml) and (iii) KOH (10 M. 0.5 ml). The mixture was stirred at 10–15°C for 30 min. ω-bromoacetophenone and \or bromoethylacetate (12.5 mmol) was added in one portion. The solution was stirred at room temperature for 2 hr and poured into water (150 ml). The resulting solid was filtered off, washed with water and recrystallized from DMF to give 3 and 4 respectively.

5-Carbonyl-(4-amino-3(4-phenyl-2-thioxo-1,3-thiazole-3-yl)-2-ethylcarboxylate thieno[2,3,b]thiophene-5-yl)-8-hydroxyquinoline 3

m.p. 205°C, yield 76 %. IR: 3400, 3300 (NH_2), 1730 (CO ester), 1660 (CO amidic) and 1170 (C=S) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.9–7.4 (m, 11H, aromatic), 7.2 (s, 2H, NH_2) 6.7 (s, 1H, CH thiazole ring), 4.2 (q, 2H, CH_2CH_3), 1.1 (t, 3H_CH_2CH_3,). MS, m/z (%):589 (M^+ 100). Anal.Calc.for $C_{28}H_{19}N_3O_4S_4$: C 57.03, H 3.25, N 7.13, S 21.75; found C 57.04, H 3.21, N 7.11, S 21.68 %.



SCHEME 2

5-Carbonyl-(4-amino-3(4-hydroxy-2-thioxo-1,3-thiazole-3-yl)-2-ethylcarboxylate thieno[2,3,b]thiophene-5-yl)-8-hydroxyquinoline 4

m.p. 315°C, yield 66 %. IR: 3400, 3300 (NH_2), 3290–3110 (br OH), 1735 (CO ester), 1660 (CO amidic) and 1170 (C=S) cm^{-1}. ^{1}H-NMR ($CDCl_3$)δ:

8.9–7.4 (m, 6H, aromatic), 7.2 (s, 2H, NH_2), 6.7 (s, 1H, CH thiazolering), 4.2 (q, 2H, CH_2CH_3), 1.1 (t, 3H_CH_2CH_3). MS, m/z (%):529 (M^+ 100). Anal. Calc. for $C_{22}H_{15}N_3O_5S_4$: C 54.81, H 3.47, N 7.24, S 22.09; found C 54.64, H 3.42, N 7.19, S 21.98 %.

5-Carbonyl-(3,4-diamino-2(benzothiazole;benzoxazole; bezoimidazole)-thieno[2,3,b]thiophene-5-yl)-8-hydroxyquinoline 5a-c

General procedure

A mixture of **1** (0.01mole) and the selected o-substitued aromatic amines such as o-aminothiophene, o-aminophenol, o-phenylenediamine (0.01mole) in the presence of poly phosphoric acid (10 ml) was stirred and heated at 160 °C for 3hr. The reaction mixture was cooled, slowly added to an ice -bath and neutralized with aqueous ammonia when the product precipitated. The product was filtered, washed with water, dried and recrystallized from ethanol to give the compounds **5a-c** respectively

Compound **5a** (X=S) m.p. 196–198°C, yield 80 %. IR: 3400, 3300 (NH_2), 1660 (CO amidic) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 10H, aromatic), 7.2- (s, 2H, NH_2) 6.9 (s, 2H, NH_2). MS, m/z (%):474 (M^+ 88). Anal.Calc.for $C_{23}H_{14}N_4O_2S_3$: C 55.80, H 3.33, N 8.56, S 21.56; found C 55.74, H 3.29, N 8.51, S 21.51 %.

Compound **5b** (X=O) m.p. >350°C yield 84 %. IR: 3400, 3300 (NH_2), 1660 (CO amidic) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 10H, aromatic), 7.2- (s, 2H, NH_2) 6.9 (s, 2H, NH_2). MS, m/z (%): 458(M^+ 88). Anal. Calc. for $C_{23}H_{14}N_4O_3S_2$: C 56.77, H 3.27, N 9.36, S 19.90; found C 56.70, H 3.22, N 9.31, S 19.83 %.

Compound **5c** (X=NH) m.p. 295°C. yield 75 %. IR: 3450, 3320, 3280 (NH_2, NH), 1660 (CO amidic) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 10H, aromatic), 7.2- (s, 2H, NH_2), 6.9 (s, 2H, NH_2). MS, m/z (%): 457 (M^+ 100). Anal.Calc.for $C_{23}H_{15}N_5O_2S_2$: C 60.38, H 3.30, N 15.31, S 14.02 found C 60.29 H 3.26, N 15.28, S 13.93 %.

5-Carbonyl-(3,4-diamino-2-(2-methyloxodiazole,2-phenyloxodiazole, 2(4′pyridyloxodiazole)-5-yl)thieno[2,3,b]thiophene-5-yl)-8-hydroxyquinolines 6a-c respectively

General procedure

A mixture of **1** (0.01mole) and the selected aliphatic, aromatic and heterocyclic hydrazides such as acetic, benzoic and isonicotinic hydrazide

(0.01mole) in the presence of polyphosphoric acid (10 ml) was stirred and heated at 180 °C for 3hr. The reaction mixture was cooled, slowly added to an ice -water and neutralized with aqueous ammonia. The precipitated product was filtered, washed with water, dried and recrystallized from DMF to give the compounds **6a-c** respectively.

Compound **6a** (R=CH_3) m.p. 235–237°C, yield 72 %. IR: 3400, 3300 (NH_2), 2990(CH aliphatic)1660 (CO amidic) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 6H, aromatic), 7.2 (s, 2H, NH_2), 6.9 (s, 2H, NH_2) and 2.9 (s, 3H, CH_3). MS, m/z (%):423 (M^+ 75). Anal.Calc.for $C_{19}H_{13}N_5O_3S_2$: C 57.26, H 3.20, N 15.90, S 14.56; found C 57.21, H 3.16, N 15.81, S 14.51 %. Compound **6b** (R=Ph) m.p. 294–296°C, yield 70 %. IR: 3400, 3300 (NH_2), 1660 (CO amidic) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 11H, aromatic), 7.2- (s, 2H, NH_2) and 6.9 (s, 2H, NH_2). MS, m/z (%): 485 (M^+ 100). Anal. Calc. for $C_{24}H_{15}N_5O_3S_2$: C 58.01, H 3.17, N 15.37, S 14.08; found C 57.96, H 3.16, N 15.30, S 13.93 %.

Compound **6c** (R=4-pyridyl) m.p. 355–356°C, yield 81 %. IR: 3510, 3350 (NH_2), 1650 (CO amidic) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 10H, aromatic), 7.2- (s, 2H, NH_2) and 6.9 (s, 2H, NH_2). MS, m /z (%): 486 (M^+ 100). Anal. Calc. for $C_{23}H_{14}N_6O_3S_2$: C 57.69, H 3.10, N 15.87, S 13.84; found C 57.66, H 3.09, N 15.80, S 13.79 %.

5-Carbonyl-(4-amino-3-diazonium chloride-2-ethyl carboxylate thieno[2,3,b]thiophene-5-yl)-8-hydroxyquinoline 7

A cold solution of **1** (0.01mole) in concentrated hydrochloric acid (1 ml) was treated with a cold saturated solution of sodium nitrite (0.015 mole), and the mixture was then stirred in an ice bath for 1–2 hr. The solid product obtained was filtered off, washed with water and recrystallized from ethanol to afforded compound **7**, m.p. 160°C yield 71 %. IR: 3450, 3350 (NH_2), 2980 (CH aliphatic) 1730 (CO ester), 1685 (CO amidic) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 6H, aromatic), 7.2 (s, 2H, NH_2). Anal. Calc. for $C_{19}H_{13}N_4O_4S_2Cl$: C 49.51, H 2.82, N 12.16, S 13.89; Cl 7.70; found C 49.47, H 2.75, N 12.11, S 13.81, Cl 7.68 %

5-Carbonyl-(4-amino-3-ethylcyano(2-yl-hydrazone)acetate-2-ethylcarboxylate thieno[2,3,b]thiophene-5-yl) –8-hydroxyquinoline 8

A solution of **7** (0.01 mole) in the presence of sodium acetate (1gm) was treated with ethylcyanoacetate (0.01 mole) and the whole mixture was

stirred in an ice bath for 1–2 hr. The solid obtained was filtered off, washed with water and crystallized form DMF to yield compound **8**, m.p. 272–274°C, yield 68 %. IR: 3510, 3350 (NH_2), 2980 (CH aliphatic), 2220 (CN), 1735,1725(2CO ester), 1650 (CO amidic) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 6H, aromatic), 7.2 (s, 2H, NH_2), 4.1–4.3(m, 4H, $2CH_2$-CH_3) and 1.1–0.95 (m, 6H, $2CH_2$-CH_3). MS, m /z (%): 537(M^+ 100). Anal. Calc. for $C_{24}H_{19}N_5O_6S_2$: C 53.62, H 3.56, N 13.03, S 11.93; found C 53.60, H 3.51, N 12.94, S 11.89 %.

5-Carbonyl(4-amino-3-(3′-amino-5′-hydroxy-azo(1′-N-phenyl)pyrazole-4′-yl)-2-ethyl carboxylate thieno[2,3-b] thiophene-5-yl)-8-hydroxyquinolines 9a,b respectively

General procedure

A mixture of **8** (0.01 mole), hydrazine hydrate and /or phenyl hydrazine (0.01 mole) in absolute ethanol (50 ml) containing 5 drops of piperidine was heated under reflux for 7hr. The reaction mixture was cooled, whereby the corresponding pyrazolo derivatives **9a** and **9b** were obtained, filtered off, washed with little ethanol and recrystallized from $CHCl_3$. Compound **9a** (R=H): m.p. 219°C, yield 79 %. IR: 3450, 3350, 3220 (NH_2, NH), 3208–3120 (br OH), 2980 (CH aliphatic), 1735 (CO ester), 1650 (CO amidic) and 1620 (N=N) cm^{-1}. ^{1}H-NMR (DMSO) δ: 12.1(S, 1H, OH), 8.9–7.4 (m, 6H, aromatic), 7.2- (s, 2H, NH_2), 6.8(s, 2H, NH_2 pyrazole ring), 4.1- 4.3 (q, 2H, CH_2-CH_3) and 1.1–0.95 (t, 3H, CH_2-CH_3). MS, m/z (%): 523 (M^+ 100). Anal. Calc. for $C_{22}H_{17}N_7O_5S_2$: C 52.07, H 3.42, N 15.84, S 12.09; found C 51.95, H 3.39, N 15.77, S 11.99 %.

Compound **9b** (R=Ph): m.p. 281°C, yield 73 %. IR: 3450, 3350 (NH_2), 3208–3120 (br OH), 2980 (CH aliphatic), 1735 (CO ester), 1650 (CO amidic) and 1620 (N=N) cm^{-1}. ^{1}H-NMR (DMSO) δ: 12.1(S, 1H, OH), 8.9–7.4 (m, 11H, aromatic), 7.2 (s, 2H, NH_2), 6.8 (s, 2H, NH_2 pyrazole ring), 4.1- 4.3 (q, 2H, CH_2-CH_3) and 1.1–0.95 (t, 3H, CH_2-CH_3). MS, m /z (%): 599 (M^+ 73.5). Anal. Calc. for $C_{28}H_{21}N_7O_5S_2$: C 53.52, H 3.46, N 16.02, S 11.58; found C 53.47, H 3.40, N 15.97, S 11.51 %.

5-Carbonyl(4-amino-3-(3′-amino-5′-hydroxy-azooxazole-4′-yl)-2-ethylcarboxylate thieno[2,3-b]thiophene-5-yl)-8-hydroxyquinolines 10

To a solution of **8** (0.01 mole) and hydroxylamine hydrochloride (0.01 mole) in absolute ethanol (30 ml), sodium hydroxide (0.015 mole) was

added and the reaction mixture was refluxed for 5hr. After completion of the reaction by TLC, it was concentrated to a small volume and neutralized with dilute hydrochloric acid, whereby the corresponding oxazolo derivatives **10** was obtained, filtered off, washed with ethanol and recrystallized from dioxane, m.p. 206°C, yield 87%. IR 3450, 3350 (NH_2), 3208–3120 (br OH), 2980 (CH aliphatic), 1735 (CO ester), 1650 (CO amidic) and 1620(N=N) cm^{-1}. ^{1}H-NMR (DMSO) δ: 12.1 (S, 1H, OH), 8.9–7.4 (m, 11H, aromatic), 7.2- (s, 2H, NH_2), 6.8(s, 2H, NH_2 oxazole ring), 4.1–4.3 (q, 2H, CH_2-CH_3) and 1.1–0.95 (t, 3H, CH_2-CH_3). MS, m /z (%): 524 (M^+85). Anal. Calc. for $C_{22}H_{16}N_6O_6S_2$: C 52.76, H 3.37, N 16.02, S 11.74; found C 52.71, H 3.31, N 15.94, S 11.69 %.

5-Carbonyl(4-amino-3-(4′-amino-6′-hydroxy-2′-oxo (thioxo) azo pyrimidine 5′-yl)-2-ethyl carboxylate thieno[2,3-b]thiophene-5-yl)-8-hydroxyquinolines 11a,b respectively

General procedure

A solution of **8** (0.01 mole), urea and / thiourea (0.015 mole) in sodium ethoxide solution (0.03 g Na in 20 ml absolute ethanol) was heated under reflux for 6hr. The reaction mixture was concentrated, neutralized with dilute hydrochloric acid, whereby the precipitated products **11a** and **11b** were obtained, filtered off, washed with little ethanol and recrystallized from dioxane. Compound **11a** (X=O): m.p. > 350°C, yield 82 %. IR: 3450, 3350 (NH_2), 3208–3120 (br OH), 2980 (CH aliphatic), 1735 (CO ester), 1650 (CO amidic) and 1620 (N=N) cm^{-1}. ^{1}H-NMR (DMSO) δ: 12.2 (S, 1H, OH), 8.9–7.4 (m, 6H, aromatic), 7.2- (s, 2H, NH_2), 6.8(s, 2H, NH_2 pyrimidine ring), 4.1–4.3 (q,2H,CH_2-CH_3) and 1.1–0.95 (t, 3H,CH_2-CH_3). m /z (%): 551(M^+ 100). Anal. Calc. for $C_{23}H_{17}N_7O_6S_2$: C 50.09, H 3.11, N 17.78, S 11.63; found C 49.99, H 3.09, N 17.74, S 11.59 %.

Compound **11b** (X=S): m.p. > 350°C, yield 62 %. IR: 3450, 3350 (NH_2), 3208–3120 (br OH), 2980 (CH aliphatic), 1735 (CO ester), 1650 (CO amidic) and 1620 (N=N) cm^{-1}. ^{1}H-NMR (DMSO) δ: 12.2 (S, 1H, OH), 8.9–7.4 (m, 6H, aromatic), 7.2- (s, 2H, NH_2), 6.8(s, 2H, NH_2 pyrimidine ring), 4.1–4.3(q, 2H, CH_2-CH_3) and 1.1–0.95(t, 3H, CH_2-CH_3). MS, m /z (%): 567 (M^+ 100). Anal. Calc. for $C_{23}H_{17}N_7O_5S_3$: C 49.37, H 3.06, N 17.52, S 14.32; found C 49.30, H 3.03, N 17.74, S 14.29 %.

5-Carbonyl-(4-amino-3-(ethyl-4′-amino-5′-cyano-6′-imino-1′,6′-dihydropyridazine-3′-carboxylate-2′-yl)-2-ethylcarboxylate thieno [2,3,b] thiophene-5-yl)-8-hydroxyquinoline; 5-carbonyl(4-amino-3-(ethyl-5′-cyano-6′-oxopyridazine-3′-carboxylate-2′-yl)-2-etyhylcarboxylate thieno[2,3,b]thiophene-5yl)-8-hydroxyquinoline; 5-carbonyl (4-amino-3-(ethyl-5′-acetyl-6′-oxo-pyridazine-3′-carboxylate-2′-yl)-2-ethylcarboxylate thieno[2,3,b]thiophene-5yl)-8-hydroxyquinoline and 5-carbonyl (4-amino-3-(ethyl-5′-cyano-6′-thioxopyridazine-3′-carboxylate-2′-yl)-2-ethylcarboxylate thieno[2,3,b]thiophene-5yl)-8-hydroxyquinoline derivatives 13a-d,respectively

General procedure

A solution of **8** (0.01 mole) in methanolic sodium ethoxide solution (0.01g Na in 100 ml methanol) was treated with each of the selected active methylene compounds such as malononitrile, cyanoethylacetate, ethylacetoacetate and cyanothioacetamide (**12a-d**) (0.01 mole). Each reaction was heated under reflux for 7 hr. The reaction mixture was cooled poured into ice-cooled water, and then acidified with dilute hydrochloric acid. The solid products obtained were filtered off, washed with water, and recrystallized from $CHCl_3$ to afforded compounds **13a-d**, respectively.

Compound **13a** (X=NH, Y=CN) m.p. 269°C, yield 74 %. IR: 3450, 3350 (NH_2), 2980 (CH aliphatic), 2200 (CN), 1740, 1735 (2 CO ester) and 1670 (CO amidic) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 6H, aromatic), 7.2-(s, 2H, NH_2), 6.8 (s, 2H, NH_2 pyridazine ring), 4.4–4.1 (m, 4H, 2 CH_2-CH_3) and 1.2–0.95 (m, 6H, 2 CH_2-CH_3). MS, m /z (%):603 (M^+ 100). Anal. Calc. for $C_{27}H_{21}N_7O_6S_2$: C 50.89, H 3.22, N 17.07, S 13.03; found C 50.69, H 3.19, N 16.94, S 12.99 %.

Compound **13b** (X=O, Y=CN) m.p. >340°C, yield 63%. IR: 3450, 3350 (NH_2), 2980 (CH aliphatic), 2220 (CN), 1740, 1735 (2 CO ester), 1700 (CO pyridazine) and 1670 (CO amidic) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 6H, aromatic), 7.2 (s, 2H, NH_2), 6.9(s, 2H, NH_2 pyridazine ring), 4.4–4.1 (m, 4H, 2 CH_2-CH_3) and 1.2–0.95 (m, 6H, 2 CH_2-CH_3). MS, m /z (%): 604 (M^+ 100). Anal. Calc. for $C_{27}H_{20}N_6O_7S_2$: C 51.61, H 3.25, N 16.25, S 12.40; found C 51.49, H 3.22, N 16.24, S 12.36 %.

Compound **13c** (X=O, Y=$CDCl_3$ $COCH_3$) m.p. > 340°C, yield 75%. IR: 3450, 3350 (NH_2), 2980 (CH aliphatic), 1740 1735 (2 CO ester), 1700 (CO pyridazine) and 1670 (CO amidic) cm^{-1}. H-NMR (DMSO) δ: 8.9–7.4 (m, 6H, aromatic), 7.2- (s, 2H, NH_2), 6.9(s, 2H, NH_2 pyridazine ring), 4.3–

4.1(m, 4H, 2 CH_2-CH_3), 3.8(s, 3H, COCH_3) and 1.2–0.95(m, 6H, 2 CH_2-CH_3). MS, m /z (%): 621(M^+ 97). Anal. Calc. for $C_{28}H_{23}N_5O_8S_2$: C 54.10, H 3.73, N 11.27, S 10.32; found C 54.99, H 3.72, N 11.24, S 10.28 %.

Compound 13d (X=S, Y=CN) m.p. 310°C, yield 71%. IR: 3450, 3350 (NH_2), 2980 (CH aliphatic), 2220 (CN), 1740, 1735 (2 CO ester), 1700 (CO pyridazine), 1670 (CO amidic) and 1170 (C=S) cm^{-1}. ^{1}H-NMR (DMSO) δ: 8.9–7.4 (m, 6H, aromatic), 7.2- (s, 2H, NH_2), 6.9 (s, 2H, NH_2 pyridazine ring), 4.3–4.1(m, 4H, 2 CH_2-CH_3) and 1.2–0.95 (m, 6H, 2 CH_2-CH_3). MS, m /z (%): 620 (M^+ 100). Anal. Calc. for $C_{27}H_{20}N_6O_6S_3$: C 53.17, H 3.49, N 12.40, S 12.90; found C 53.09, H 3.42, N 12.39, S 12.88 %.

References

[1] H. Graubaum, J. Prakt. Chem, **88**, 355, (1993).
[2] R. M. Mohareb, H.F. Zohdi and W. W. Wardakhan, *Monatsh. Chem.*, **126**, 1391, (1995).
[3] H.F. Zohdi, W.W. Wardakhan, S.H. Doss and R.M. Mohareb, *Monatsh. Chem.*, **126**, 440, (1996).
[4] O.S. Wolfbeis, *Monatsh. Chem.*, **112**, 875, (1981).
[5] K. Gewald, E. Schinke and H. Bottcher, *Chem. Ber.*, **99**, 94, (1966).
[6] R.W. Sabnis and D. W. Rangnekar, *J. Heterocycl. Chem.*, **29**, 1027, (1992).
[7] R. W. Sabnis and D. W. Rangnekar, *J. Heterocycl. Chem.*, **27**, 417, (1990).
[8] H. A. Elfahham, F.M. Abdel-Galil, Y. R. Ibrahim and M. H Elnagdi, *J. Heterocycl. Chem.*, **20**, 667, (1983).
[9] Z. H. Khalil, A. S. Yanni, A. M. Gaber and SH. A. Abdel-Mohsen, Phosphorus, *Sulfur and Silicon* (in press).
[10] N. Bauer, M.M. Kibby, J.C. Sheffins and M. Tuvck, Am J. Clin. Path., **45**, 493, (1966).