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Some New 2-Amino-4-(*N*-substituted-*1H*- indol -3-yl) thiophene-3-carbonitriles and their Antimicrobial Properties

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A NOVEL series of 2-amino-4-(*N*-substituted-*1H*-indol-3-yl) thiophene-3-carbonitriles (3a-f) were prepared *via* reaction of 2-(1-(*N*-substituted -*1H*-indol-3-yl) ethylidene) malononitriles (2a-f) with sulfur (Gewald reaction). Reaction of 3a-f with formic acid, formamide or malononitrile led to the formation of fused thieno [2,3-*d*] pyrimidin-4(3*H*)-ones (6a-f) thieno[2,3-*d*] pyrimidin-4-amines (7a-f) and thieno[2,3-*d*] pyridine-3-carbonitriles (8a-f), respectively. On the other hand, a series of 2-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)-4-(*N*-substituted-*1H*-indol-3-yl) thiophene-3-carbonitriles (10a-f) and *N*-3- [3-cyano-4-(*N*-substituted-*1H*-indol-3-yl)- (2-thienyl) -4-oxo-2- imino thiazolidinylidenes (12a-f), were prepared *via* reaction of Schiff bases 9a-f with thioglycollic acid or reaction of chloroacetamids 11a-f with potassium thiocyanate, respectively. Moreover, reaction of 3a-f with ethylenediamine yielded 3-(4,5-dihydro-1*H*-imidazol-2-yl)-4-(*N*-substituted-*1H*-indol-3yl) thiophen-2-amines (13a-f). The antimicrobial activity of the newly synthesized compounds revealed that, 2-(2-(naphthalene-1-yl)diazenyl)-4-(*N*-substituted-*1H*-indol-3-yl)thiophene-3-carbonitriles (4a-f) showed potent inhibition of 25-33 and 18-26mm at a dose of 20 and 10 µg per disc, respectively towards *Aspergillus fumigatus* compared to reference drug cycloheximide.

Keywords: Indole, 2-Aminothiophene-3-carbonitriles, Thieno [2,3-*d*] pyrimidine, Thieno [2,3-*d*] pyridine, Thiazolidine and Antimicrobial activity.

Highly substituted thiophenes are important heterocycles found in numerous biologically active and natural compounds [(1)]. Traditionally, polysubstituted 2-aminothiophenes with an electron-withdrawing group such as cyano, carbethoxy or carboxamide in the 3-position and alkyl, aryl or hetaryl groups in the 4- and 5-positions are prepared *via* the Gewald reaction [(2)]. There are two common variations on this synthesis: (a) one-pot procedure in which ketones or aldehydes react with an activated nitrile and elemental sulfur; and (b) two-step procedure in which alkene produced by the

Knoevenagel condensation is isolated prior to cyclization with sulfur and base, and the latter one is generally preferred and provides better yields [3]. Moreover, 2-aminothiophene has demonstrated a broad spectrum of uses including production of pharmaceuticals [4] and dyes [5] and starting materials for the synthesis of fused heterocyclic systems [6-8]. Also, indole being a potent basic pharmacodynamic nucleus, has been reported to possess a wide variety of biological properties *viz*, anti-inflammatory [9,10], anti-cancer [11,12] and antimicrobial activities [13]. Based on the above observation and as a part of our research on the preparation of new polyheterocycles of pharmaceutical value [9-14], herein, we synthesized some new series of 2-aminothiophenes *via* the second version of Gewald reaction using *N*-substituted-3-acetylindoles (1a-f) as starting materials.

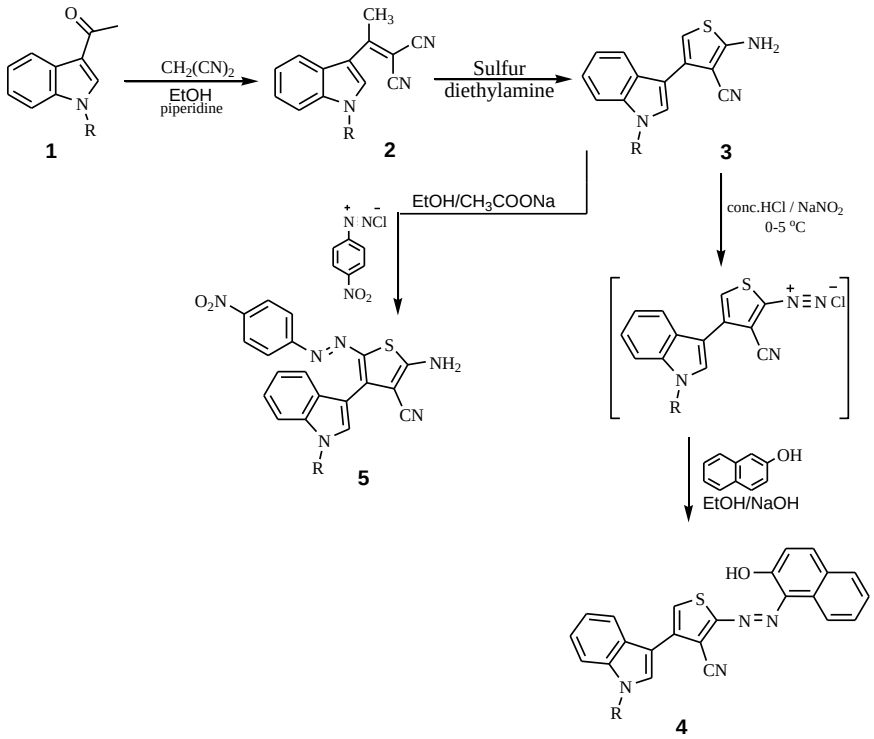
Results and Discussion

Chemistry

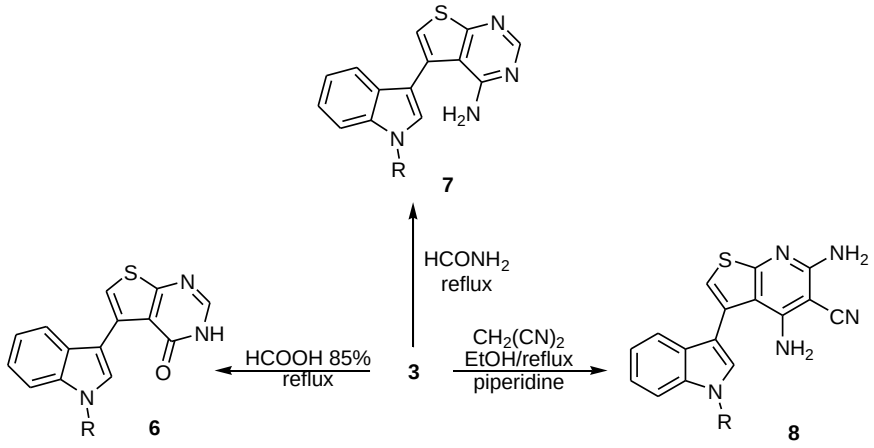
The reaction routes for the synthesis of title compounds were described in Schemes 1, 2 and 3. The first step of our strategy was the preparation of nitrile derivatives 2a-f. Compound 2a is obtained from reaction of 3-acetylindole (1a) with malononitrile in the presence of dimethylamine as a catalyst in 72% yield [15]. Herein we used piperidine as an alternative catalyst obtaining a high yield (95%, Scheme 1). Thus, reaction of these new starting compounds 1b-f with malononitrile in refluxing ethanolic piperidine led to the formation of a new series of 2-(1-(*N*-substituted-*1H*-indol-3-yl)ethylidene)malononitriles (2b-f) (Scheme 1). The structures of the new starting compounds were confirmed based on their correct elemental analyses (Table 1) and spectral data (Table 2).

Ring closure of compounds 2a-f *via* their reaction with sulfur in the presence of diethylamine in absolute ethanol (Gewald reaction) gave 2-amino -4-(*N*-substituted- *1H*-indol-3-yl) thiophene-3-carbonitriles (3a-f) (Scheme 1). The IR spectra of compounds 3a-f showed absorption bands at ~ 2191-2210 cm^{-1} (CN) and 3101-3404 cm^{-1} (NH_2). Their ^1H NMR (DMSO-d_6) spectra revealed singlet signals at ~ δ 8.19-8.31 ppm, attributed to thienyl 5-H besides the other aromatic protons.

For example, the IR spectrum of compound 3a showed characteristic absorption bands at 3404 (NH_2), 3159 (NH), 2204 (CN) & 1613 cm^{-1} (C=C). Its ^1H NMR (DMSO-d_6) spectrum revealed signals at 9.12 (s, 1H, NH, D_2O exchangeable), 8.31(s, 1H, indolyl 2-H), 8.19 (s, 1H, thienyl 5-H), 7.77 (d, 1H, indolyl 7-H), 7.48 (d, 1H, indolyl 4-H), 7.23-7.07 (m, 2H, indolyl 5-H & 6-H) 6.49 ppm (s, 2H, NH_2, D_2O exchangeable), and its ^{13}C NMR (DMSO-d_6) spectrum revealed signals at 138.86-111.55 (Ar-C) and 117.27 ppm (CN) (Table 2).



Scheme 1. Compounds 1-5; R, a = H; b = - CH_2CH_3; c= -CH_2Ph; d= COph;e= - SO_2CH_3; f=- SO_2ph .



Scheme 2. Compounds 3-8; R, a = H; b = - CH_2CH_3; c= -CH_2Ph; d= COph;e= - SO_2CH_3; f=- SO_2ph .

TABLE 1. Physical and analytical data of the synthesized compounds.

Compd. No.	M.F. (M. Wt.)	M. p. (°C)	Yield (%)	Analysis (calcd. /found) (%)		
				C	H	N
2b	$C_{15}H_{13}N_3$ (235.28)	66-8	88	76.57/76.39	5.57/5.41	17.86/17.67
2c	$C_{20}H_{15}N_3$ (297.35)	86-8	80	80.78/80.62	5.08/5.25	14.13/14.30
2d	$C_{20}H_{13}N_3O$ (311.34)	153-5	95	77.16/77.00	4.21/4.06	13.50/13.65
2e	$C_{14}H_{11}N_3O_2S$ (285.32)	126-8	73	58.93/59.11	3.89/3.75	14.73/14.62
2f	$C_{19}H_{13}N_3O_2S$ (347.39)	150-2	85	65.69/65.74	3.77/3.91	12.10/11.95
3a	$C_{13}H_9N_3S$ (239.30)	173-5	85	65.25/65.10	3.79/3.65	17.56/17.44
3b	$C_{15}H_{13}N_3S$ (267.35)	79-81	62	67.39/67.24	4.90/5.00	15.72/15.83
3c	$C_{20}H_{15}N_3S$ (329.42)	99-7	86	72.92/72.70	4.59/4.46	12.76/12.65
3d	$C_{20}H_{13}N_3OS$ (343.40)	167-9	82	69.95/70.00	3.82/4.04	12.24/12.00
3e	$C_{14}H_{11}N_3O_2S_2$ (317.39)	138-40	69	52.98/53.06	3.49/3.37	13.24/13.10
3f	$C_{19}H_{13}N_3O_2S_2$ (379.46)	133-5	75	60.14/60.26	3.45/3.30	11.07/11.00
4a	$C_{23}H_{14}N_4OS$ (394.45)	124-6	79	70.03/70.00	3.58/3.47	14.20/14.10
4b	$C_{25}H_{18}N_4OS$ (422.50)	65-7	45	71.07/71.00	4.29/4.13	13.26/13.10
4c	$C_{30}H_{20}N_4OS$ (484.57)	80-2	71	74.36/74.19	4.16/4.09	11.56/11.71
4d	$C_{30}H_{18}N_4O_2S$ (498.55)	62-4	75	72.27/72.34	3.64/3.51	11.24/11.17
4e	$C_{24}H_{16}N_4O_3S_2$ (472.54)	74-6	65	61.00/61.21	3.41/3.50	11.86/11.73
4f	$C_{29}H_{18}N_4O_3S_2$ (534.61)	57-9	69	65.15/65.00	3.39/3.20	10.48/10.59
5a	$C_{19}H_{12}N_6O_2S$ (388.40)	194-6	70	58.75/58.58	3.11/3.00	21.64/21.57
5b	$C_{21}H_{16}N_6O_2S$ (416.46)	248 dec.	50	60.56/60.41	3.87/4.00	20.18/20.01
5c	$C_{26}H_{18}N_6O_2S$ (478.53)	122-4	55	65.26/65.11	3.79/3.65	17.56/17.42
5d	$C_{26}H_{16}N_6O_3S$ (492.51)	172-4	69	63.41/63.50	3.27/3.16	17.06/17.00
5e	$C_{20}H_{14}N_6O_4S_2$ (466.49)	152-4	57	51.49/51.36	3.02/3.12	18.02/18.16
5f	$C_{25}H_{16}N_6O_4S_2$ (528.56)	171-3	59	56.81/56.66	3.05/3.22	15.90/16.00
6a	$C_{14}H_9N_3OS$ (267.31)	108-110	50	62.91/63.00	3.39/3.24	15.72/15.91
6b	$C_{16}H_{13}N_3OS$ (295.36)	110-2	25	65.06/65.20	4.44/4.34	14.23/14.09
6c	$C_{21}H_{15}N_3OS$ (357.43)	115-7	30	70.57/70.41	4.23/4.10	11.76/11.93
6d	$C_{21}H_{13}N_3O_2S$ (371.41)	105-7	45	67.91/67.75	3.53/3.47	11.31/11.25
6e	$C_{15}H_{11}N_3O_3S_2$ (345.40)	113-5	35	52.16/52.00	3.21/3.17	12.17/12.00
6f	$C_{20}H_{13}N_3O_3S_2$ (407.47)	106-8	51	58.95/59.00	3.22/3.13	10.31/10.24
7a	$C_{14}H_{10}N_4S$ (266.32)	280dec.	60	63.14/63.00	3.78/3.56	21.04/21.20
7b	$C_{16}H_{14}N_4S$ (294.37)	300dec.	42	65.28/65.21	4.79/4.77	19.03/19.11
7c	$C_{21}H_{16}N_4S$ (356.44)	199dec.	58	70.76/70.71	4.52/4.43	15.72/15.61
7d	$C_{21}H_{14}N_4OS$ (370.43)	320dec.	65	68.09/68.16	3.81/3.97	15.12/15.00
7e	$C_{15}H_{12}N_4O_2S_2$ (344.41)	366dec.	70	52.31/52.24	3.51/3.40	16.27/16.13
7f	$C_{20}H_{14}N_4O_2S_2$ (406.48)	>400dec.	65	59.10/59.00	3.47/3.56	13.78/13.85
8a	$C_{16}H_{11}N_5S$ (305.36)	84-6	70	62.93/63.00	3.63/3.51	22.93/23.00
8b	$C_{18}H_{15}N_5S$ (333.41)	58-60	50	64.84/64.75	4.53/4.60	21.01/21.17
8c	$C_{23}H_{17}N_5S$ (395.48)	63-5	63	69.85/70.00	4.33/4.21	17.71/17.64
8d	$C_{23}H_{15}N_5OS$ (409.46)	170-2	71	67.47/67.31	3.69/3.60	17.10/17.00
8e	$C_{17}H_{13}N_5O_2S_2$ (383.45)	102-4	69	53.25/53.10	3.42/3.35	18.26/18.09
8f	$C_{22}H_{15}N_5O_2S_2$ (445.52)	90-2	75	59.31/59.24	3.39/3.23	15.72/15.63
9a	$C_{20}H_{12}N_4O_2S$ (372.40)	88-90	85	64.50/64.41	3.25/3.12	15.04/15.12
9b	$C_{22}H_{16}N_4O_2S$ (400.45)	103-5	60	65.98/66.00	4.03/3.90	13.99/14.07
9c	$C_{27}H_{18}N_4O_2S$ (462.52)	52-4	75	70.11/70.01	3.92/4.00	12.11/12.33
9d	$C_{27}H_{16}N_4O_3S$ (476.51)	124-6	80	68.06/67.94	3.38/3.45	11.76/11.64
9e	$C_{21}H_{14}N_4O_4S_2$ (450.49)	152-4	75	55.99/55.85	3.13/3.10	12.44/12.32
9f	$C_{26}H_{16}N_4O_4S_2$ (512.56)	127-9	80	60.93/61.00	3.15/3.08	10.93/11.00
10a	$C_{22}H_{14}N_4O_3S_2$ (446.50)	149-51	40	59.18/59.04	3.16/3.00	12.55/12.43
10b	$C_{24}H_{18}N_4O_3S_2$ (474.55)	196-8	20	60.74/60.63	3.82/3.73	11.81/12.00
10c	$C_{29}H_{20}N_4O_3S_2$ (536.62)	116-8	32	64.91/65.00	3.76/3.86	10.44/10.31
10d	$C_{29}H_{18}N_4O_4S_2$ (550.61)	152-4	45	63.26/63.13	3.30/3.55	10.18/10.04

TABLE 1. Cont.

Compd. No.	M.F. (M. Wt.)	M. p. (°C)	Yield (%)	Analysis (calcd. /found) (%)		
				C	H	N
10e	$C_{23}H_{16}N_4O_5S_3$ (524.59)	121-3	30	52.66/52.44	3.07/3.16	10.68/10.56
10f	$C_{28}H_{18}N_4O_5S_3$ (586.66)	103-5	35	57.32/57.19	3.09/2.97	9.55/9.67
11a	$C_{15}H_{10}ClN_3OS$ (315.78)	160-2	80	57.05/56.92	3.19/3.10	13.31/13.24
11b	$C_{17}H_{14}ClN_3OS$ (343.83)	133-5	60	59.38/59.31	4.10/4.22	12.22/12.31
11c	$C_{22}H_{16}ClN_3OS$ (405.90)	67-9	68	65.10/65.25	3.97/4.07	10.35/10.26
11d	$C_{22}H_{14}ClN_3O_2S$ (419.88)	176-8	85	62.93/62.86	3.36/3.13	10.01/10.22
11e	$C_{16}H_{12}ClN_3O_3S_2$ (393.87)	112-4	70	48.79/48.64	3.07/3.14	10.67/10.51
11f	$C_{21}H_{14}ClN_3O_3S_2$ (455.94)	174-6	80	55.32/55.21	3.09/3.19	9.22/9.45
12a	$C_{16}H_{10}N_4OS_2$ (338.41)	175-7	45	56.79/56.63	2.98/3.15	16.56/16.43
12b	$C_{18}H_{14}N_4OS_2$ (366.46)	129-31	27	58.99/59.09	3.85/3.71	15.29/15.16
12c	$C_{23}H_{16}N_4OS_2$ (428.53)	221-3	30	64.46/64.31	3.76/3.59	13.07/13.15
12d	$C_{23}H_{14}N_4O_2S_2$ (442.51)	148-50	45	62.43/62.29	3.19/3.10	12.66/12.80
12e	$C_{17}H_{12}N_4O_3S_3$ (416.50)	90-2	35	49.02/48.91	2.90/3.00	13.45/13.51
12f	$C_{22}H_{14}N_4O_3S_3$ (478.57)	200-2	40	55.21/55.34	2.95/2.77	11.71/11.57
13a	$C_{15}H_{14}N_4S$ (282.36)	139-41	55	63.80/63.63	5.00/4.91	19.84/19.71
13b	$C_{17}H_{18}N_4S$ (310.42)	123-5	40	65.78/65.65	5.84/5.76	18.05/18.22
13c	$C_{22}H_{20}N_4S$ (372.49)	211-3	50	70.94/71.00	5.41/5.32	15.04/15.18
13d	$C_{22}H_{18}N_4OS$ (386.47)	223-5	60	68.37/68.24	4.69/4.51	14.50/14.32
13e	$C_{16}H_{16}N_4O_2S_2$ (360.45)	113-5	45	53.31/53.26	4.47/4.30	15.54/15.39
13f	$C_{21}H_{18}N_4O_2S_2$ (422.52)	221-3	50	59.69/59.50	4.29/4.17	13.26/13.10

Diazotization of 3a-f with concentrated hydrochloric acid and sodium nitrite at 0-5°C yielded the corresponding diazonium salts which, under coupling with β-naphthol in presence of sodium hydroxide gave 2-(2-(naphthalen-1-yl) diazenyl) -4-(*N*-substituted-*1H*-indol-3-yl) thiophene-3-carbonitriles (4a-f) (Scheme 1). Moreover, coupling reaction of 3a-f with diazotized 4-nitroaniline in presence of aqueous sodium acetate at 0-5°C led to the formation of 5-[2-(4-nitrophenyl) diazenyl] -2-amino-4-(*N*-substituted-*1H*-indol-3-yl) thiophene-3-carbonitriles (5a-f) (Scheme 1).

On the other hand, compounds 3a-f were used as starting materials for building up of the fused heterocyclic system by ring closure reaction of their α,β-bifunctional amino and cyano groups. Thus, reaction of compounds 3a-f with formic acid 85% under reflux led to the formation of fused 5-(*N*-substituted -*1H*-indol-3-yl) thieno [2,3-*d*] pyrimidin-4(3*H*)-ones (6a-f) (Scheme 2). Also, reaction of compounds 3a-f with formamide under reflux led to the formation of the corresponding 5-(*N*-substituted-*1H*-indol-3-yl)thieno[2,3-*d*]pyrimidin-4-amines (7a-f) (Scheme 2). While, condensation reaction of compounds 3a-f with malononitrile under reflux in ethanolic piperidine yielded the fused 2,4-diamino-5-(*N*-substituted-*1H*-indol-3-yl) thieno[2,3-*d*] pyridine-3-carbonitriles (8a-f) (Scheme 2).

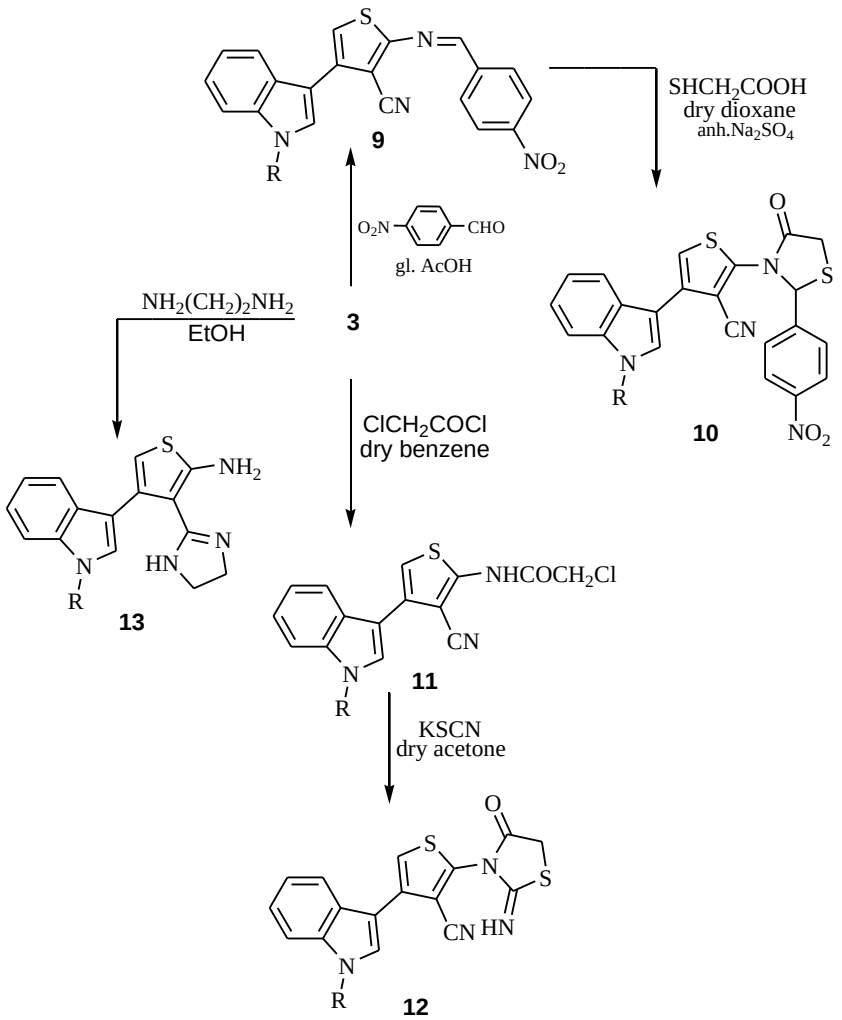
Acid catalyzed reaction of compounds 3a-f with 4-nitrobenzaldehyde in refluxing ethanol gave the corresponding Schiff bases, 2-(2-(4-nitrophenyl) methyleneamino)-4-(*N*-substituted-*1H*-indol-3-yl)thiophene-3-carbonitriles (9a-f) (Scheme 3). The ^{1}H NMR (DMSO-d_6) spectra of compounds 9a-f revealed singlet signals at ~ δ 10.12 ppm attributed to anil protons (CH=N) besides the other aromatic protons. For example, ^{1}H NMR (DMSO-d_6) spectrum of compound 9a revealed signals at 11.86 (s, 1H, NH, D_2O exchangeable), 10.15 (s, 1H, CH=N), 8.39 (s, 1H, indolyl 2-H), 8.26 (s, 1H, thienyl 5-H), 8.16-8.14 (m, 4H, Ar-H), 7.45-7.15 ppm (m, 4H, indolyl 4-H, 5-H, 6-H & 7-H) (Table 2).

Cyclocondensation of the latter Schiff bases 9a-f with thioglycollic acid in dry dioxane and in the presence of anhydrous sodium sulphate led to the formation of 2-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)-4-(*N*-substituted-*1H*-indol-3-yl)thiophene-3-carbonitriles (10a-f) (Scheme 3). The ^{1}H NMR (DMSO-d_6) spectra of 10a-f lack the presence of anil protons and revealed new signals at δ 3.64-4.42 and δ 5.15ppm attributed to thiazolidinyl 2-H and 5-H_2 , respectively. The ^{1}H NMR (DMSO-d_6) spectrum of compound 10a for example revealed signals at 11.88 (s, 1H, NH), 8.38 (s, 1H, indolyl 2-H), 8.26 (s, 1H, thienyl 5-H), 8.14 (d, 1H, indolyl 7-H), 7.73-7.13 (m, 8H, Ar-H), 5.15 (s, 1H, thiazolidinyl 2-H), 4.10 & 3.99 ppm (2s, 2H, thiazolidinyl 5-H_2) (Table 2).

Reaction of compounds 3a-f with chloroacetyl chloride in dry benzene led to the formation of *N*-[3-cyano-4- (*N*-substituted -*1H*-indol-3-yl) -2-thienyl] chloroacetamides (11a-f) (Scheme 3). Cyclization of the latter compounds *via* their reaction with potassium thiocyanate in dry acetone yielded 3-[3-cyano-4- (*N*-substituted -*1H*-indol-3-yl) -(2-thienyl) -4-oxo]-2-iminothiazolidinylidene (12a-f) (Scheme 3).

Moreover, reaction of 3a-f with ethylenediamine under reflux in ethanol 85% led to the formation of 3-(4,5-dihydro-1*H*-imidazol-2-yl)-4-(*N*-substituted-*1H*-indol-3-yl)thiophen-2-amines (13a-f) (Scheme 3). The reaction may be preceded through the attack of ethylenediamine with nitrile group to generate an amidine (–C(NH)-NH-(CH_2)-NH_2) which in turn undergoes ring closure and release of ammonia to give 13a-f. The structures of 13a-f were confirmed based on their elemental analyses and spectral data.

The IR spectrum of 13a for example showed absorption bands at 3360 (NH_2), 3160 & 3112 (NH), 1615 (C=N) and 1576 cm^{-1} (C=C). Its ^{1}H NMR (DMSO-d_6) spectrum revealed signals at 10.31 (s, 1H, indolyl NH), 8.28 (s, 1H, indolyl 2-H), 8.15 (s, 1H, thienyl 5-H), 7.70 (d,1H, indolyl 7-H), 7.44 (d, 1H, indolyl 4-H), 7.18-7.11 (m, 2H, indolyl 5-H & 6-H), 6.44 (s, 1H, imidazolinyl NH), 3.75 & 3.49 (m, 4H, imidazolinyl CH_2-CH_2), 2.46 ppm (s, 2H, NH_2) (Table 2).



Scheme 3. Compounds 3-13; R, a = H; b = - CH_2CH_3; c= -CH_2Ph; d = COph;e = - SO_2CH_3; f=- SO_2ph.

TABLE 2. Spectral characterization of the prepared compounds .

Compd.	IR (γ_{max} cm^{-1})	NMR (δ, ppm)	Mass (*m/z*, %)
2b	2211 (CN), 1636 (C=C)	^{1}H NMR: 8.22 (s, 1H, indolyl 2-H), 7.90-7.13 (m, 4H, Ar-H), 4.23 (q, 2H, CH_2), 2.73 (s, 3H, CH_3), 1.9 (t, 3H, CH_3)	235 (M^+, 1), 220 (1), 173(12), 172 (100), 144 (20), 130 (7), 116 (17)
2c	2216 (CN), 1615 (C=C)	^{1}H NMR: 8.12 (s, 1H, indolyl 2-H), 7.78-7.13 (m, 9H, Ar-H), 5.51 (s, 2H, CH_2), 2.73 (s, 3H, CH_3)	297 (M^+,1), 234 (36), 130 (5), 91 (100), 77 (20)
2d	2193 (CN), 1644 (C=O), 1614 (C=C)	^{1}H NMR: 8.25 (s, 1H, indolyl 2-H), 8.14 (d, 1H, indolyl 7-H), 7.90 (d, 1H, indolyl 4-H), 7.75-7.13 (m, 7H, Ar-H), 2.73 (s, 3H, CH_3)	311 (M^+, 1), 159(36), 144 (100), 117 (8), 89 (33)
2e	2190 (CN), 1617 (C=C), 1368 & 1168 (SO_2-N)		285 (M^+, 1), 222 (4), 145, (10), 144 (100), 130 (9), 89 (24)
2f	2190 (CN), 1617 (C=C), 1337 & 1173 (SO_2-N)		347 (M^+, 1), 145 (10), 144 (100), 130 (14), 116 (23), 89 (24)
3a	3404 (NH_2), 3159 (NH), 2204 (CN), 1613 (C=C)	^{1}H NMR: 9.12 (s, 1H, NH), 8.31(s, 1H, indolyl 2-H), 8.19 (s, 1H, thienyl 5-H), 7.77 (d, 1H, indolyl 7-H), 7.48 (d, 1H, indolyl 4-H), 7.23-7.07 (m, 2H, indolyl 5-H & 6-H) 6.49 (s, 2H, NH_2) ^{13}C NMR:138.86-111.55 (Ar-C), 117.27 (CN)	239 (M^+, 100), 237 (3), 180 (2), 165 (2), 115 (3), 89 (10)
3b	3167 & 3101 (NH_2), 2210 (CN), 1635 (C=C)	^{1}H NMR: 8.38 (s,1H, indolyl 2-H), 8.22 (s, 1H, thienyl 5-H), 7.58 (s, 2H, NH_2), 7.28-7.20 (m, 4H, Ar-H), 4.30 (q, 2H, CH_2), 1.44 (t, 3H, CH_3) ^{13}C NMR:137.72-103.05 (Ar-C), 117.86 (CN), 28.32 (CH_2-CH_3)	267 (M^+, 25), 265 (67), 250 (44), 172 (100), 145 (3), 116 (11)
3c	3102 & 3035 (NH_2), 2207 (CN), 1640 (C=C)	^{1}H NMR: 8.56 (s, 1H, indolyl 2-H), 8.23 (s, 1H, thienyl 5-H), 7.55 (s, 2H, NH_2), 7.35-7.19 (m, 9H, Ar-H), 5.51 (s, 2H, CH_2-N) ^{13}C NMR: 136.51-110.52 (Ar-C),115.80 (CN), 41.00 (CH_2)	329 (M^+, 45), 327 (10), 206 (2), 116 (1), 92 (9), 91 (100), 77 (20)
3d	3160 & 3044 (NH_2), 2205 (CN), 1644 (C=O), 1615 (C=C)	^{1}H NMR: 8.31 (s, 1H, indolyl 2-H), 8.20 (s, 1H, thienyl 5-H), 7.78-7.08 (m, 9H, Ar-H), 6.49 (s, 2H, NH_2) ^{13}C NMR:192.29 (C=O), 137.49-111.03 (Ar-C), 116.13 (CN)	343 (M^+, 1), 239 (3), 145 (10), 144 (100), 117 (5), 116 (24)
3e	3366 & 3224 (NH_2), 2191 (CN), 1653 (C=C), 1364 & 1162 (SO_2-N)	^{1}H NMR: 8.53 (s, 1H, indolyl 2-H), 8.31 (s, 1H, thienyl 5-H), 8.20 (d, 1H, indolyl 7-H), 7.92 (d, 1H, indolyl 4-H), 7.49 (m, 1H, indolyl 6-H), 7.23 (m, 1H, indolyl 5-H), 3.64 (s, 3H, CH_3-SO_2), 2.58 (s, 2H, NH_2) ^{13}C NMR:137.72-103.05 (Ar-C), 117.87 (CN), 28.32 (CH_3)	317 (M^+, 2), 292 (2), 260 (25), 245 (3), 141 (81), 115 (68), 91 (8), 77 (100)

TABLE 2. Cont.

Compd.	IR (γ_{max} cm^{-1})	NMR (δ, ppm)	Mass (*m/z*, %)
3f	3150 & 3116 (NH_2), 2195 (CN), 1617 (C=C), 1379 & 1137 (SO_2-N)	^{1}H NMR: 8.31 (s, 1H, indolyl 2-H), 8.28 (s, 1H, thienyl 5-H), 8.26-7.06 (m, 9H, Ar-H), 2.61 (s, 2H, NH_2), ^{13}C NMR: 136.62-112.04 (Ar-C), 116.76 (CN)	379 (M^+, 1), 145 (20), 144 (100), 116 (6), 115 (30), 77 (20)
4a	3430 (OH), 3155 (NH), 2224 (CN), 1610 (N=N), 1526 (C=C)	^{1}H NMR: 10.31 (s, 1H, OH), 9.51 (s, 1H, NH), 8.36 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.01-7.67 (m, 10H, Ar-H)	
4b	3291 (OH), 2208 (CN), 1628 (N=N), 1596 (C=C)	^{1}H NMR: 10.51 (s, 1H, OH), 8.36 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.01-7.67 (m,10H, Ar-H), 4.21 (q, 2H, CH_2), 1.91 (t, 3H, CH_3)	
4c	3427 (OH), 2190 (CN), 1629 (N=N), 1605 (C=C)	^{1}H NMR: 12.51 (s,1H, OH), 8.36 (s, 1H, thienyl 5-H), 8.21 (s,1H, indolyl 2-H), 7.01-7.67 (m, 15H, Ar-H), 5.51 (s, 2H, CH_2)	
4d	3408 (OH), 2208 (CN), 1676 (C=O), 1613 (N=N), 1523 (C=C)	^{1}H NMR: 11.41 (s, 1H, OH), 8.36 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.01-7.68 (m, 15H, Ar-H)	
4e	3370 (OH), 2203 (CN), 1620 (N=N), 1522 (C=C), 1345 & 1138 (SO_2-N)	^{1}H NMR: 12.51 (s, 1H, OH), 8.36 (s, 1H, thienyl 5-H), 8.11 (s, 1H, indolyl 2-H), 7.01-7.91 (m, 10H, Ar-H) , 3.13 (s, 3H, CH_3)	
4f	3420 (OH), 2196 (CN), 1626 (N=N), 1520 (C=C), 1375 & 1130 (SO_2-N)	^{1}H NMR: 12.51 (s,1H, OH), 8.36 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.01-7.68 (m, 15H, Ar-H)	
5a	3435 (br., NH_2 & NH), 2208 (CN), 1607 (N=N), 1549 (C=C)	^{1}H NMR: 9.51 (s, 1H, NH), 8.71 (s, 2H, NH_2), 8.21 (s, 1H, indolyl 2-H), 7.01-8.11 (m, 8H, Ar-H)	
5b	3423 (NH_2), 2207 (CN), 1617 (N=N), 1512 (C=C)	^{1}H NMR: 8.77 (s, 2H, NH_2), 8.21 (s, 1H, indolyl 2-H), 7.01-8.11 (m, 8H, Ar-H), 4.21 (q, 2H, CH_2), 1.91 (t, 3H, CH_3)	
5c	3421 (NH_2), 2205 (CN), 1605 (C=N), 1500 (C=C)	^{1}H NMR: 8.77 (s, 2H, NH_2), 8.21 (s, 1H, indolyl 2-H), 7.01-8.11 (m, 13H, Ar-H), 5.51 (s, 2H, CH_2)	
5d	3418 (NH_2), 2203 (CN), 1717 (C=O), 1616 (N=N), 1517 (C=C)	^{1}H NMR: 11.85 (s, 2H, NH_2), 8.22 (s, 1H, indolyl 2-H), 8.10 (d, 1H, indolyl 7-H), 7.40-7.12 (m, 12H, Ar-H)	
5e	3363 (NH_2), 2206 (CN), 1612 (N=N), 1590 (C=C), 1368 & 1168 (SO_2-N)	^{1}H NMR: 9.85 (s, 2H, NH_2), 8.22 (s, 1H, indolyl 2-H), 8.10-7.12 (m, 8H, Ar-H) , 3.13 (s, 3H, CH_3)	
5f	3405 (NH_2), 2205 (CN), 1676 (N=N), 1591 (C=C), 1377 & 1174 (SO_2-N)	^{1}H NMR: 8.85 (s, 2H, NH_2), 8.22 (s, 1H, indolyl 2-H), 8.11-7.12 (m,13H, Ar-H)	
6a	3440 (NH), 3180 (NH), 1654 (C=O), 1616 (C=N), 1512 (C=C)		267 (M^+, 1), 224 (5), 144 (100), 130 (7), 116 (34), 89 (25)

TABLE 2. Cont.

Compd.	IR (γ_{max} cm^{-1})	NMR (δ, ppm)	Mass (*m/z*, %)
6b	3443 (NH), 1717 (C=O), 1635 (C=N), 1517 (C=C)	^{1}H NMR: 8.72 (s, 1H, pyrimidinyl 2-H), 8.36 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.26-7.15 (m, 4H, Ar-H), 5.72 (s, 1H, NH), 4.42 (q, 2H, CH_2-N), 1.51 (t, 3H, CH_3)	
6c	3415 (NH), 1725 (C=O), 1634 (C=N), 1605 (C=C)	^{1}H NMR: 8.52 (s, 1H, pyrimidinyl 2-H), 8.38 (s, 1H, thienyl 5-H), 8.09 (s, 1H, indolyl 2-H), 7.26-7.15 (m, 9H, Ar-H), 5.72 (s, 1H, NH), 5.47 (s, 2H, CH_2-N).	
6d	3201 (NH), 1721 & 1657 (C=O), 1612 (C=N), 1526 (C=C)	^{1}H NMR: 8.56 (s, 1H, pyrimidinyl 2-H, 8.38 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.67-7.05 (m, 9H, Ar-H), 6.67 (s, 1H, NH)	
6e	3426 (NH), 1720 (C=O), 1619 (C=N), 1580 (C=C), 1366 & 1134 (SO_2-N)		345 (M^+,3), 317 (8), 302 (20), 195 (10), 144 (100), 116 (30)
6f	3430 (NH), 1657 (C=O), 1621 (C=N), 1528 (C=C), 1379 & 1176 (SO_2-N)	^{1}H NMR: 11.90 (s, 1H, NH), 8.78 (s, 1H, pyrimidinyl 2-H), 8.26 (s, 1H, thienyl 5-H), 8.13-7.16 (m, 10H, Ar-H)	407 (M^+, 1), 284 (15), 145 (7), 144 (5), 130 (13), 116 (6)
7a	3407 (NH_2), 3257 (NH ind.), 1656 (C=N), 1602 (C=C)	^{1}H NMR: 9.51 (s, 1H, NH), 8.77 (s, 2H, NH_2), 8.57 (s, 1H, pyrimidinyl 2-H), 8.51 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.76-7.13 (m, 4H, Ar-H)	
7b	3424 (NH_2), 1627 (C=N), 1542 (C=C)	^{1}H NMR: 8.98 (s, 2H, NH_2), 8.57 (s,1H, pyrimidinyl 2-H), 8.36 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.76-7.13 (m, 4H, Ar-H), 4.21 (q, 2H, CH_2), 1.61 (t, 3H, CH_3)	
7c	3381 & 3280 (NH_2), 1644 (C=N), 1589 (C=C)	^{1}H NMR: 9.09 (s, 2H, NH_2), 9.04 (s, 1H, pyrimidinyl 2-H), 8.87 (s, 1H, thienyl 5-H), 8.57 (s, 1H, indolyl 2-H), 8.46 (d, 1H, indolyl 7-H), 8.36 (d, 1H, indolyl 4-H), 8.13-7.13 (m, 7H, Ar-H), 4.40 (s, 2H, CH_2-N)	356 (M^+, 1), 266 (9), 194 (100), 167 (16), 134 (27), 116 (15), 89 (8)
7d	3399 & 3295 (NH_2), 1681 (C=O), 1649 (C=N), 1617 (C=C)		370 (M^+, 30), 327 (80), 288 (100), 144 (30), 116 (15)
7e	3420 & 3315 (NH_2), 1683 (C=N), 1615 (C=C), 1385 & 1160 (SO_2-N)	^{1}H NMR: 8.77 (s, 2H, NH_2), 8.57 (s, 1H, pyrimidinyl 2-H), 8.36 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.86-7.01 (m, 4H, Ar-H), 2.88 (s, 3H, CH_3)	
7f	3277 & 3190 (NH_2), 1683 (C=N), 1614 (C=C), 1348 & 1176 (SO_2-N)		406 (M^+, 10), 391 (8), 362 (30), 144 (100), 116 (13), 89 (32)
8a	3159 & 3112 (NH_2), 3064 (NH), 2191 (CN), 1615 (C=N), 1560 (C=C)	^{1}H NMR: 9.51 (s, 1H, NH), 8.52 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.51-7.16 (m, 4H, Ar-H), 6.56 (s, 2H, NH_2), 2.98 (s, 2H, NH_2)	

TABLE 2. Cont.

Compd.	IR (γ_{max} cm^{-1})	NMR (δ, ppm)	Mass (*m/z*, %)
8b	3320, 3256, 3192 & 3101 (NH_2), 2192 (CN), 1635 (C=N), 1564 (C=C)	^{1}H NMR: 8.51 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.51-7.16 (m, 4H, Ar-H), 6.56 (s, 2H, NH_2), 4.21 (q, 2H, CH_2), 2.98 (s, 2H, NH_2), 1.51 (t, 3H, CH_3)	333 (M^+, 90), 304 (20), 255 (100), 205 (60), 156 (50), 116 (46)
8c	3195 & 3107 (NH_2), 2192 (CN), 1641 (C=N), 1572 (C=C)	^{1}H NMR: 8.52 (s, 1H, thienyl 5-H), 8.17 (s, 1H, indolyl 2-H), 7.50 (d, 1H, indolyl 7-H), 7.56-7.01 (m, 8H, Ar-H), 6.66 (s, 2H, NH_2), 5.46 (s, 2H, CH_2), 2.98 (2H, s, NH_2)	
8d	3320 & 3157 (NH_2), 2240 (CN), 1660 (C=O), 1614 (C=N), 1576 (C=C)		409 (M^+, 100), 367 (20), 333 (100), 311 (30), 261 (40), 116 (30)
8e	3150 & 3112 (NH_2), 2190 (CN), 1617 (C=N), 1575 (C=C), 1364 & 1137 (SO_2-N)	^{1}H NMR: 8.76 (s,2H, NH_2), 8.51 (s, 1H, thienyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.51-7.01 (m, 4H, Ar-H), 2.98 (s, 2H, NH_2), 2.88 (s, 3H, CH_3)	
8f	3154 & 3128 (NH_2), 2190 (CN), 1615 (C=N), 1575 (C=C), 1380 & 1135 (SO_2-N)	^{1}H NMR:11.88 (s, 2H, NH_2), 8.80 (s, 1H, thienyl 5-H), 8.26 (s, 1H, indolyl 2-H), 8.15 (d, 1H, indolyl 7-H), 7.90 (d, 1H, indolyl 4-H), 7.43 (m, 1H, indolyl 6-H), 7.16-7.13 (m, 6H, Ar-H & indolyl 5-H), 2.96 (s, 2H, NH_2)	
9a	3155 (NH), 2224 (CN), 1616 (C=N), 1573 (C=C)	^{1}H NMR: 11.86 (s, 1H, NH), 10.15 (s, 1H, CH=N), 8.39 (s, 1H, indolyl 2-H), 8.26 (s, 1H, thienyl 5-H), 8.16-8.14 (m, 4H, Ar-H), 7.45-7.15 (m, 4H, indolyl 4-H, 5-H, 6-H &7-H)	
9b	2213 (CN), 1636 (C=N), 1601 (C=C)	^{1}H NMR: 10.12 (s, 1H, CH=N), 8.21 (s, 1H, indolyl 2-H), 8.07 (s, 1H, thienyl 5-H), 8.00-7.01 (m, 8H, Ar-H), 4.21 (q, 2H, CH_2), 1.91 (t, 3H, CH_3)	
9c	2216 (CN), 1638 (C=N), 1527 (C=C)	^{1}H NMR: 10.15 (s, 1H, CH=N), 8.36 (s, 1H, indolyl 2-H), 8.24 (s, 1H, thienyl 5-H), 7.87-7.01 (m, 13H, Ar-H), 5.51 (s, 2H, CH_2)	
9d	2217 (CN), 1710 (C=O), 1628 (C=N), 1599 (C=C)	^{1}H NMR:10.12 (s, 1H, CH=N), 8.51 (s, 1H, indolyl 2-H), 8.38-7.12 (m, 14H, Ar-H)	476 (M^+, 100), 459 (20), 150 (60), 145 (8), 116 (10), 89 (22)
9e	2213 (CN), 1623 (C=N), 1516 (C=C), 1386 & 1143 (SO_2-N)	^{1}H NMR: 10.15 (s, 1H, CH=N), 8.54 (s, 1H, indolyl 2-H), 8.36 (s, 1H, thienyl 5-H), 7.99-7.01 (m, 8H, Ar-H), 3.01 (s, 3H, CH_3-SO_2)	
9f	2202 (CN), 1617 (C=N), 1574 (C=C), 1381 & 1138 (SO_2-N)	^{1}H NMR: 10.15 (s, 1H, CH=N), 8.34 (s, 1H, indolyl 2-H), 8.26 (s, 1H, thienyl 5-H), 7.89-7.01 (m, 13H, Ar-H),	
10a	3156 (NH), 2250 (CN), 1704 (C=O), 1612 (C=C)	^{1}H NMR: 11.88 (s, 1H, indolyl-NH), 8.38 (s, 1H, indolyl 2-H), 8.26 (s, 1H, thienyl 5-H), 8.14 (d, 1H, indolyl 7-H), 7.73-7.13 (m, 7H, Ar-H), 5.15 (s, 1H, thiazolidinyl 2-H), 4.10 & 3.99 (2s, 2H, thiazolidinyl 5-H_2)	

TABLE 2. Cont.

Compd.	IR (γ_{max} cm^{-1})	NMR (δ, ppm)	Mass (*m/z*, %)
10b	2209 (CN), 1671 (C=O), 1599 (C=C)	^{1}H NMR: 8.21 (s, 1H, indolyl 2-H), 8.12 (s,1H, thienyl 5-H), 7.73-7.10 (m, 8H, Ar-H), 5.15 (s, 1H, thiazolidinyl 2-H), 4.21 (q, 2H, CH_2), 4.00 & 3.91 (2s, 2H, thiazolidinyl 5-H_2), 1.91 (t, 3H, CH_3)	
10c	2210 (CN), 1721 (C=O), 1610 (C=C)	^{1}H NMR: 8.21 (s, 1H, indolyl 2-H), 8.11 (s, 1H, thienyl 5-H), 7.73-7.10 (m, 13H, Ar-H), 5.55 (s, 2H, CH_2), 5.15 (s, 1H, thiazolidinyl 2-H), 4.00 & 3.91 (2s, 2H, thiazolidinyl 5-H_2)	
10d	2208 (CN), 1676 & 1692 (C=O), 1602 (C=C)	^{1}H NMR: 8.26 (s, 1H, indolyl 2-H), 8.17-7.13 (m, 14H, Ar-H), 4.32 (s, 1H, thiazolidinyl 2-H), 3.82 & 3.64 (2s, 2H, thiazolidinyl 5-H_2)	550 (M^+, 60), 504 (100), 432 (10), 330 (51), 145 (20), 116 (8)
10e	2207 (CN), 1712 (C=O), 1596 (C=C), 1353 & 1164 (SO_2-N)		524 (M^+, 1), 478 (1), 330 (2), 273 (2), 145 (7), 122 (3), 116 (14), 77 (72), 62 (100)
10f	2210 (CN), 1727 (C=O), 1607 (C=C), 1374 & 1133 (SO_2-N)	^{1}H NMR: 8.21 (s, 1H, indolyl 2-H), 8.01 (s, 1H, thienyl 5-H), 7.68-7.03 (m, 13H, Ar-H), 4.32 (s, 1H, thiazolidinyl 2-H), 4.12 & 3.84 (2s, 2H, thiazolidinyl 5-H_2)	
11a	3423 (br., NH), 2215 (CN), 1721 (C=O), 1617 (C=C), 748 (C-Cl)		315/317 (M^+/ M^++2, 70/20), 281 (8), 280 (30), 251 (20), 231 (22), 144 (16)
11b	3184 (NH), 2220 (CN), 1739 (C=O), 1672 (C=C), 747 (C-Cl)	^{1}H NMR: 8.39 (s, 1H, indolyl 2-H), 8.32 (s, 1H, thienyl 5-H), 8.21 (d, 1H, indolyl 7-H), 7.39-7.37 (m, 3H, Ar-H), 5.71 (s, 1H, NH), 5.23 (s, 2H, CH_2), 4.14 (q, 2H, CH_2), 1.13 (t, 3H, CH_3)	
11c	3103 (NH), 2214 (CN), 1733 (C=O), 1637 (C=C), 740 (C-Cl)	^{1}H NMR: 8.21 (s, 1H, indolyl 2-H), 8.12 (s, 1H, thienyl 5-H), 8.01-7.37 (m, 9H, Ar-H), 6.71 (s, 1H, NH), 5.55 (s, 2H, CH_2), 5.23 (s, 2H, CH_2)	
11d	3200 (NH), 2215 (CN), 1733 (C=O), 1655 (C=C), 756 (C-Cl)		419/421 (M^+/M^++2, 80/20), 388 (10), 333 (8), 252 (8)
11e	3127 (NH), 2208 (CN), 1733 (C=O), 1652 (C=C), 754 (C-Cl)		393/395 (M^+/M^++2, 7/2), 357 (20), 329 (10), 144 (100), 116 (70), 77 (20)
11f	3122 (NH), 2211 (CN), 1727 (C=O), 1612 (C=C), 752 (C-Cl)	^{1}H NMR: 8.78 (s, 1H, indolyl 2-H), 8.32 (s, 1H, thienyl 5-H), 8.21 (d, 1H, indolyl 7-H), 7.41-7.37 (m, 8H, Ar-H), 5.24 (s, 2H, CH_2), 2.47 (s, 1H, NH)	
12a	33091 (br., NH), 2190 (CN), 1711 (C=O), 1651 (C=N), 1540 (C=C)	^{1}H NMR: 11.86 (s, 1H, indolyl-NH), 8.48 (s, 1H, indolyl 2-H), 8.26 (s, 1H, thienyl 5-H), 8.13 (d, 1H, indolyl 7-H), 7.87 (d,1H, indolyl 4-H), 7.43 (m, 1H, indolyl 6-H), 7.16 (m, 1H, indolyl 5-H), 5.02 (s, 2H, CH_2), 1.20 (s, 1H, NH imino)	

TABLE 2. Cont.

Compd.	IR (γ_{max} cm^{-1})	NMR (δ, ppm)	Mass (*m/z*, %)
12b	3431 (NH), 2209 (CN), 1660 (C=O), 1610 (C=N), 1524 (C=C)		366 (M^+,1), 341 (8), 309 (100), 281 (3), 156 (7)
12c	3192 (NH), 2206 (CN), 1645 (C=O), 1602 (C=N), 1515 (C=C)		428 (M^+, 10), 403 (10), 371 (8), 356 (20), 220 (7), 115 (30), 91 (100)
12d	3113 (NH), 2215 (CN), 1707 (C=O), 1660 (C=N), 1546 (C=C)	^{1}H NMR: 8.86 (s, 2H, indolyl 2-H & thienyl 5-H), 8.32-8.21 (m, 4H, indolyl-H), 7.40-7.37 (m, 5H, Ar-H), 5.03 (s, 2H, CH_2), 2.46 (s, 1H, NH)	442 (M^+, 2), 413 (20), 369 (20), 342 (10), 207 (3), 145 (22), 116 (17)
12e	3113 (NH), 2220 (CN), 1709 (C=O), 1661 (C=N), 1614 (C=C), 1386 & 1149 (SO_2-N)	^{1}H NMR: 8.88 (s, 2H, indolyl 2-H& thienyl 5-H), 8.32 (d, 1H, indolyl 7-H), 8.21 (d, 1H, indolyl 4-H), 7.41-7.37 (m, 2H, indolyl 6-H & 5-H), 5.03 (s, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.05 (s, 1H, NH)	416 (M^+, 90), 387 (100), 369 (70), 330 (8), 240 (30), 159 (10), 116 (16)
12f	3373 (NH), 2232 (CN), 1645 (C=O), 1602 (C=N), 1545 (C=C), 1372 & 1175 (SO_2-N)		478 (M^+, 3), 414 (31), 389 (3), 325 (100), 116 (30), 89 (10)
13a	3360 (NH_2), 3160 & 3112 (NH), 1615 (C=N), 1576 (C=C)	^{1}H NMR: 10.31 (s, 1H, indolyl NH), 8.28 (s, 1H, indolyl 2-H), 8.15 (s, 1H, thienyl 5-H), 7.70 (d, 1H, indolyl 7-H), 7.44 (d, 1H, indolyl 4-H), 7.18-7.11 (m, 2H, indolyl 5-H & 6-H), 6.44 (s, 1H, NH), 3.75 & 3.49 (m, 4H, CH_2-CH_2), 2.46 (s, 2H, NH_2)	
13b	3416 (br., NH_2 & NH), 1602 (C=N), 1520 (C=C)	^{1}H NMR: 8.77 (s, 2H, NH_2), 8.22 (s, 1H, indolyl 2-H), 8.15 (s, 1H, thienyl 5-H), 7.98-7.04 (m, 4H, Ar-H), 4.42 (q, 2H, CH_2), 3.75-3.63 (m, 4H, CH_2-CH_2),2.69 (s, 1H, NH), 1.51 (t, 3H, CH_3)	310 (M^+, 70), 272 (100), 244 (95), 208 (30), 141 (30), 116 (16), 89 (17)
13c	3399 (br., NH_2 & NH), 1617 (C=N), 1588 (C=C)	^{1}H NMR: 8.76 (s, 2H, NH_2), 8.22 (s, 1H, indolyl 2-H), 8.11 (s, 1H, thienyl 5-H), 7.77-7.03 (m, 9H, Ar-H), 5.55 (s, 2H, CH_2), 3.75-3.63 (m, 4H, CH_2-CH_2),2.21(s, 1H, NH)	
13d	3414 (NH_2), 3208 (NH), 1741 (C=O), 1631 (C=N), 1530 (C=C)	^{1}H NMR: 8.21 (s, 1H, indolyl 2-H), 8.11 (s, 1H, thienyl 5-H), 7.98-7.03 (m, 9H, Ar-H), 6.76 (s, 2H, NH_2), 3.75-3.63 (m, 4H, CH_2-CH_2), 2.21(s, 1H, NH)	386 (M^+, 40), 371 (100), 314 (30), 193 (40), 115 (60)
13e	3368 (NH_2), 3112 (NH), 1618 (C=N), 1523 (C=C), 1384 & 1135 (SO_2-N)	^{1}H NMR: 8.71 (s, 2H, NH_2), 8.24 (s,1H, indolyl 2-H), 8.15 (s, 1H, thienyl 5-H), 7.88-7.01 (m, 4H, Ar-H), 3.75-3.63 (m, 4H, CH_2-CH_2), 2.61 (t, 3H, CH_3),2.21 (s,1H, NH)	
13f	3365 (NH_2), 3174 (NH), 1614 (C=N), 1527 (C=C), 1373 & 1132 (SO_2-N)	^{1}H NMR: 8.25 (s,1H, indolyl 2-H), 8.15 (s,1H, thienyl 5-H), 7.98-7.04 (m, 9H, Ar-H), 3.75-3.63 (m, 4H, CH_2-CH_2),2.69 (s,1H, NH), 2.46 (s, 2H, NH_2)	

Antimicrobial activity

The newly synthesized compounds were tested for their antimicrobial activity against a variety of pathogenic microorganisms using the disk diffusion method at two doses of 10 and 20 µg per disc (Table 3). 2-(2-(Naphthalene-1-yl)diazenyl)-4-(*N*-substituted-indol-3-yl)thiophene-3-carbonitriles (4a-f) were found to be highly active among all the new test compounds and showed potent inhibition ranging from 33 to 26 mm at a dose of 20 µg per disc and potent inhibition ranging from 26 to 18 mm at a dose of 10 µg per disc towards *A. fumigatus* compared to reference drug cycloheximide (39 and 28 mm) at 20 and 10 µg per disc, respectively (Table 3).

TABLE 3. Antimicrobial activity of some synthesized compounds (10 & 20 µg per disc) .

Compd No.	Inhibition zone (mm)											
	S. typhimurium		***P. fluorescens***		***S. aureus***		***B. subtilis***		***C. albicans***		***A. fumigatus***	
	20	10	20	10	20	10	20	10	20	10	20	10
3a	-	-	-	-	9	-	-	-	-	-	8	-
3b	-	-	-	-	-	-	-	-	8	-	10	-
3c	-	-	-	-	-	-	-	-	-	-	-	-
3d	-	-	-	-	8	-	-	-	-	-	-	-
3e	-	-	-	-	9	-	-	-	-	-	-	-
3f	-	-	-	-	-	-	-	-	-	-	-	-
4a	-	-	15	9	10	8	-	-	-	-	30	24
4b	-	-	8	-	22	16	-	-	8	-	25	18
4c	-	-	10	-	10	8	-	-	8	-	28	24
4d	9	-	6	-	10	8	8	-	14	8	26	20
4e	-	-	9	-	10	8	-	-	12	8	30	23
4f	8	-	8	-	10	8	-	-	15	9	33	26
7f	-	-	8	-	8	-	-	-	8	-	-	-
8a	-	-	8	-	10	8	-	-	-	-	-	-
8b	-	-	-	-	10	8	-	-	-	-	-	-
8c	-	-	-	-	8	-	-	-	-	-	-	-
10d	-	-	-	-	8	-	-	-	12	-	9	-
12e	-	-	-	-	-	-	-	-	-	-	24	18
12f	-	-	-	-	-	-	-	-	8	-	-	-
chloramphenecol	42	28	37	31	-	-	-	-	-	-	-	-
cephalothin	-	-	-	-	38	29	38	30	-	-	-	-
cycloheximide	-	-	-	-	-	-	-	-	39	28	40	31

Inhibition values. - 3-12mm-low activity; 13-21mm-moderate activity; > 22mm- high activity

Experimental

Melting points were determined in open capillary tubes on an Electrothermal 9100 digital melting point apparatus (Büchi, Switzerland) and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer (Perkin-Elmer, USA) and were found within ± 0.4 % of the theoretical values. IR spectra were recorded on a Perkin-Elmer 1600 FTIR (Perkin-Elmer, USA) in KBr discs. The NMR spectra were measured with a Bruker Avance spectrometer (300 and 125 MHz) (Bruker, Germany) in DMSO-d_6, and

chemical shifts were recorded in δ ppm relative to TMS as internal standard solvent. Mass spectra (EI) were run on Gas Chromatograph coupled to a Mass Spectrometer, single phase, 200V, 50/60 Hz, 30 A (Jeol Ltd. Japan). *N*-substituted-3-acetylindoles (1a-f) have been prepared as reported [16].

General synthetic procedures

2-(1-(N-substituted-1H-indol-3-yl)ethylidene)malononitriles (2a-f)

A mixture of *N*-substituted-3-acetylindoles (1a-e) (0.05 mol) and malononitrile (3.36 gm, 0.05 mol) in absolute ethanol (20 ml) containing few drops of piperidine was refluxed for 6-8hr. After cooling, the reaction mixture was poured onto ice-water (50 ml) and the solid that formed was filtered off, air dried and crystallized from absolute ethanol.

2-Amino-4-(N-substituted-1H-indol-3-yl)thiophene-3-carbonitriles (3a-f)

To a solution of compounds 2a-f (0.05 mol) and sulfur (1.6 g, 0.05 mol) in absolute ethanol (50 ml), diethylamine (3.65 gm, 0.05 mol) was added dropwise at 15°C, and then the reaction mixture was stirred for 2hr at 65°C. After evaporation of all solvent, the residue was dissolved in absolute ethanol (50 ml), followed by further stirring for 30min in an ice bath. The solid that formed was filtered off, washed with water, air dried and crystallized from methanol.

2-(2-(Naphthalen-1-yl)diazenyl)-4-(N-substituted-1H-indol-3-yl) thiophene-3-carbonitriles (4a –f)

To a solution of compounds 3a-f (0.01 mol) in a mixture of concentrated hydrochloric acid (10 ml) and ice-water (10 ml), cooled aqueous solution of sodium nitrite (0.96 g, 0.01 mol) in ice-water (10 ml) was added dropwise under stirring at 0-5°C. The diazoinum salt solutions thus prepared was added dropwise to a solution of β-naphthol (1.44 g, 0.01 mol) and sodium hydroxide (0.8 g, 0.02 mol) in ethanol and water (1:1) (50 ml) under stirring at 0-5°C. The solid that formed was filtered off, air dried and crystallized from absolute ethanol.

5- (2-(4- Nitrophenyl) diazenyl)-2-amino -4- (N-substituted -1H-indol -3-yl) thiophene -3- carbonitriles (5a-f)

To a solution of 4-nitroaniline (1.38 g, 0.01 mol) in a mixture of concentrated hydrochloric acid (10 ml) and ice-water (10 ml), cooled aqueous solution of sodium nitrite (0.96 g, 0.01 mol) in ice-water (10 ml) was added dropwise under stirring at 0-5°C. The diazoinum salt solutions thus prepared was added dropwise to a solution of compounds 3a-f (0.01 mol) and sodium acetate (1.38 g, 0.01 mol) in ethanol and water (1:1) (50 ml) under stirring at 0-5°C. The solid that formed was filtered off, air dried and crystallized from absolute ethanol.

5-(N-substituted-1H-indol-3-yl)thieno[2,3-d]pyrimidin-4(3H)-ones (6a-f)

A solution of compounds 3a-f (0.005 mol) in formic acid 85% (10 ml) was refluxed for 3hr. The solid that formed on hot, was filtered off, air dried and recrystallized from absolute ethanol.

5-(N-substituted-1H-indol-3-yl)thieno[2,3-d]pyrimidin-4-amines (7a-f)

A solution of compounds 3a-f (0.005 mol) in formamide (20 ml) was refluxed for 2-3hr. The solid that formed on hot was filtered off, air dried and crystallized from absolute ethanol.

2,4-Diamino -5- (N-substituted- 1H- indol -3- yl) thieno [2,3-d] pyridine -3 carbonitriles (8a-f)

A mixture of the compounds 3a-f (0.01 mol) and malononitrile (0.01 mol) in absolute ethanol (10 ml) containing few drops of piperidine was refluxed for 6-10hr. After cooling, the reaction mixture was poured onto ice-water (50 ml) and the solid that formed was filtered off, air dried and crystallized from absolute ethanol.

2- (2- (4-Nitropheny) methyleneamino) -4- (N-substituted -1H- indol -3-yl) thiophene -3-carbonitriles (9a-f)

A mixture of the compounds 3a-f (0.01 mol) and 4-nitrobenzaldehyde (0.93 g, 0.01 mol) in glacial acetic acid (20 ml) was refluxed for 4-6hr. After cooling, the reaction mixture was poured onto ice-water (50 ml). The solid that formed was filtered off, air dried and crystallized from benzene.

2-(2-(4-Nitrophenyl)-4-oxothiazolidin-3-yl)-4-(N-substituted-1H-indol-3-yl) thiophene-3-carbonitriles (10a-f)

To a stirred solution of compounds 9a-f (0.01 mol) in dry dioxane (25 ml), thioglycollic acid (1.39 g, 0.015 mol) was added. The reaction mixture was stirred for 4hr then, anhydrous sodium sulphate (30 g) was added and refluxed for 6hr, and then reaction filtered while hot. After cooling, the solid that formed was filtered off, air dried and crystallized from chloroform.

N-[3-cyano -4-(N-substituted-1H-indol-3-yl)-2-thienyl] chloroacetamides (11a-f)

To a solution of compounds 3a-f (0.02 mol) in dry benzene (60 ml), a solution of chloroacetyl chloride (5 ml, 0.04 mol) in dry benzene (20 ml) was added dropwise under vigorous stirring at 0-5°C. After complete addition, the reaction mixture was refluxed for 3hr. The solvent was evaporated under vacuum and the solid that formed was washed with 5% $NaHCO_3$ and then with water, air dried and crystallized from chloroform.

N-3-[3-cyano -4- (N-substituted -1H-indol-3-yl) -(2-thienyl) -4-oxo-2-imino-thiazolidinylidenes (12a-f)

A mixture of compounds 11a-f (0.03 mol) and potassium thiocyanate (5.82 g, 0.06 mol) in dry acetone (100 mL) was refluxed for 3hr. The solid that formed on hot was filtered off, air dried and crystallized from chloroform.

3-(4,5-Dihydro-1H-imidazol-2-yl)-4-(N-substituted-1H-indol-3-yl) thiophen-2-amines (13a-f)

A mixture of compounds 3a-f (0.01 mol), ethylenediamine (5 ml) in ethanol (85%, 10 ml) was refluxed for 4-6hr. The solid that formed on hot was filtered off, air dried and crystallized from chloroform to give the title compounds.

Antimicrobial evaluation

Antimicrobial activity of the synthesized compounds was determined *in vitro* by using the disc diffusion method [17] against a variety of pathogenic microorganisms: *S. typhimurium* (ATCC 14028), *P. fluorescens* (S 97) (Gram-positive bacteria), *S. aureus* (ATCC 25923), *B. subtilis* (ATCC 6635) (Gram-negative bacteria) and two strains of fungi, *C. albicans* (ATCC 10231) and *A. fumigatus* (identified microscopically according to Moubasher) [18]. The antimicrobial activities of the tested compounds were estimated by placing presterilized filter paper discs (6 mm in diameter) impregnated with two doses of the test compounds (10 and 20 µg per disc) on Nutrient and MacConky agar media for bacteria and on Sabouraud dextrose agar for fungus. Dimethyl formamide (DMF) was used as a solvent for impregnation. Inhibition zones (IZ) of the test compounds were measured after 24-48 hr incubation at 37°C for bacteria and after 5 days incubation at 28°C for fungi. Chloramphenicol and cephalothin were used as reference drugs for bacteria, whereas, cycloheximide (Sigma-Aldrich, USA) was used as reference drug for fungi.

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تشييد بعض المركبات الجديدة من 2-أمينو-4-(ن-مستبدل-1(H)-إندول-3-يل) ثايوفين-3-كاربونيتريل وفاعليتهم كمضادات للميكروبات

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من خلال العمل تم تحضير سلسلة جديدة من مشتقات 2-أمينو-4-(ن-مستبدل-1(H)-إندول-3-يل)ثايوفين-3-كاربونيتريل (3أ-و) و ذلك بتفاعل كلا من 2-(1-(ن-مستبدل-1(H)-إندول-3-يل)إيثيليدين)مالونونيتريل (2أ-و) مع عنصر الكبريت (تفاعل جيفلد). و من ثم بتفاعل المركبات (3أ-و) مع حمض الفورميك أو الفورماميد أو المالونونيتريل أعطت حلقات الثاينو(3,2-د) بريميدين - 4(3 H) أون (6أ-و) و الثاينو(3,2-د) بريميدين -4- أمين (7أ-و) و الثاينو(3,2-د)بريميدين-3-كاربونيتريل (8أ-و) على التوالى . من جهة أخرى تم تحضير سلسلة من 2-(2-(4-نيتروفينيل)-4-أوكسوثيازوليدين-3-يل)-4- (ن-مستبدل-1 (H) - إندول-3-يل)ثايوفين -3 - كاربونيتريل (10أ-و) و سلسلة من ن-3-(3-سيانو-4-(ن-مستبدل-1(H)-إندول-3-يل)-(2-ثاينيل)-4-اوكسو-ثيازوليدين)بنزاميد (12أ-و) من خلال تفاعل قواعد شيف (9أ-و) مع حمض الثايوجليكوليك أو بتفاعل مشتقات الكلورو اسيتاميد (11أ-و) مع البوتاسيوم ثايوسينات ، على التوالى. زيادة على ذلك تم تفاعل المركبات (3أ-و) مع الايثيلين ثنائى الامين ليعطى 3-(5,4-ثنائى الهيدرو-1 (H)-إيميدازول-2-يل)-4-(ن-مستبدل-1 (H)-إندول-3-يل) ثايوفين-2- أمين (13أ-و).

تم دراسة النشاط الميكروبى للمركبات التى تم تحضيرها و اوضحت النتائج أن المركبات 2-(2-نفثالين-1-يل)ثنائى أزينيل)-4-(ن-مستبدل-1 (H)-إندول-3-يل) ثايوفين-3-كاربونيتريل (4أ-و) لها فعالية عالية تجاه فطر الاسبيرجليس فيوميجاتيس مقارنة بالمركب المرجعى سيكلوهيكساميد عند الجرعتين 10 و 20 ميكروجرام لكل ديسك