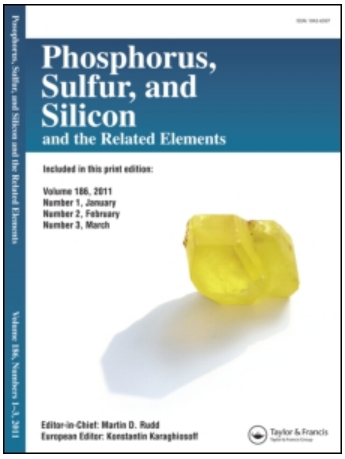

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME NOVEL THIOUREA, NAPHTHO[2,3-d]THIAZOLE, QUINAZOLINE AND THIENO[2,3-d]PYRIMIDINE DERIVATIVES CONTAINING SULFONAMIDO MOIETIES

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME NOVEL THIOUREA, NAPHTHO[2,3-d]THIAZOLE, QUINAZOLINE AND THIENO[2,3-d]PYRIMIDINE DERIVATIVES CONTAINING SULFONAMIDO MOIETIES

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p-Substituted sulfamoylphenyl isothiocyanates **1a-d** were prepared using reported procedures. The reactivity of **1a-d** towards some nitrogen nucleophiles was investigated. Thus, interaction of **1** with aromatic amines and anthranilic acids furnished N^1,N^3-disubstituted thioureas **2a-c** and 3-[4-N-substituted sulphonamido]phenyl-2-thioxo-4-(3H)-quinazolin-4-ones **4a-f**, respectively. Alkylation of **4c** with ethyl chloroacetate in acetone containing anhydrous potassium carbonate to yield quinazoline **5**. Hydrazinolysis of **5** using ethanolic hydrazine hydrate afforded the corresponding acid hydrazide **6**. Finally, treatment of **1a,b,d** with 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene yielded thieno[2,3-d]pyrimidines **10a-c** bearing sulphonamido moieties. Structures of the new compounds were established by their elemental analyses and spectral data. Also, the most of these compounds were tested in vitro for their antimicrobial activity against some Gram positive and Gram negative bacteria.

Keywords: Thioureas; Naphtho[2,3-d]thiazoles; Quinazolines; Thieno[2,3-d]pyrimidines and Antimicrobial activity

INTRODUCTION

Quinazoline derivatives have found to be biologically active compounds having antimicrobial[1], antimalarial[2], anticovulsive[3], antidepressant[4], antihistamines[5], stimulant[6], biocidal[5], plant-growth regulating[7],

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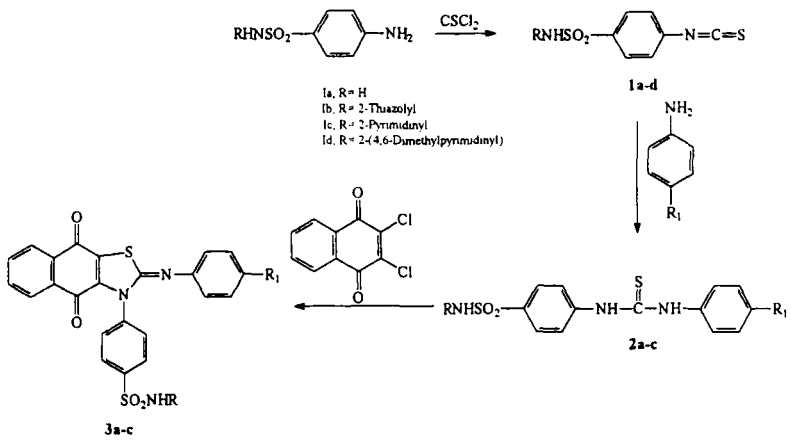
anticancer[8], antiinflammatory properties[9]. Many thieno[2,3-d]pyrimidines exhibiting interesting biological as well as medicinal applications[10–18]. Also, sulphonamides are drugs of therapeutic importance and have a wide spectrum of antibacterial activities[19,20]. Some active sulphonamides as antibacterials are also known for their immunomodifying effects[21]. These observation encouraged us to synthesize new series of thiourea, naphtho[2,3-d]thiazole, quinazoline and thieno[2,3-d]pyrimidine derivatives containing sulphonamido moieties to evaluate the antibacterial activity of them.

DISCUSSION

The starting materials **1a-d**[22] were prepared via the reaction of sulfanilamides and thiophosgene in dilute HCl at room temperature (Scheme 1). The reactivity of isothiocyanates **1a-d** towards some nitrogen nucleophiles was investigated. Thus, interaction of **1a,b,d** with aromatic amines in the presence of triethylamine led to the direct formation of N^1,N^3-disubstituted thioureas **2a-c**. The structures of compounds **2a-c** were deduced from elemental analyses and spectral data. IR spectra of **2a-c** showed the presence of NH, CH-aliphatic, CH-aromatic, C=S and S=O functional groups. The mass spectrum of **2b** exhibited a molecular ion peak at m/z 420 (1%), and the base peak at m/z 108, the fragmentation pattern is illustrated in Scheme 2. Compounds **2a-c** react with 2,3-dichloro-1,4-naphthoquinone to yield 2-[4-N-substituted sulphonamido]phenylimino-3-aryl-4,9-dioxo-naphtho[2,3-d]thiazole derivatives **3a-c**. Elemental analyses and spectral data are in agreement with the proposed structures **3a-c**, (Scheme 1).

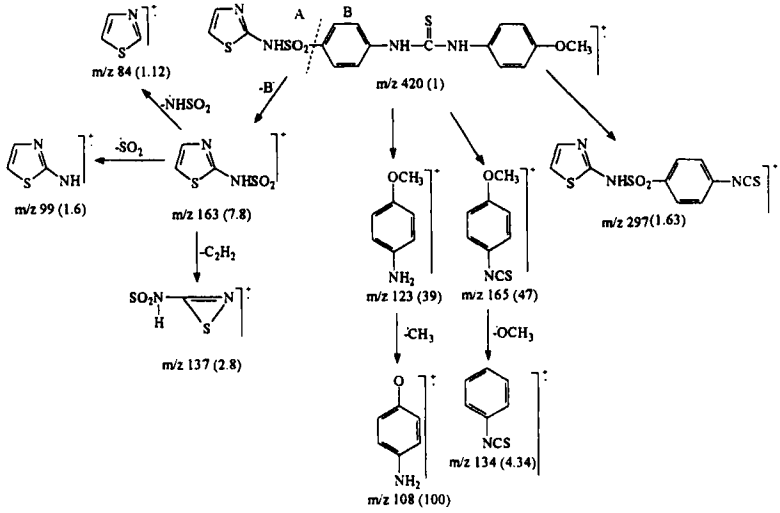
In course of the investigation, it was planned to synthesize some new quinazolines bearing a sulphonamido moieties. Thus, refluxing equimolar amounts of anthranilic acids with appropriate **1a-d** in dioxane containing triethylamine as catalyst afforded the corresponding 3-[4-N-substituted sulphonamido]phenyl-2-thioxo-4(3H)-quinazolin-4-ones **4a-f**, (Scheme 3). The structures of the compounds **4a-f** were identified by elemental analyses, UV, IR and for a representative examples **4b,f** by ^{1}H NMR, mass spectrum for compound **4d** and analogy with previous work [23]. Alkylation of **4c** was achieved through the interaction with ethyl chloroacetate in



SCHEME I

acetone in the presence of potassium carbonate to give ethyl 2{4-oxo-3-[4-(1,3-thiazol-2-yl)sulfamoyl phenyl]-3,4-dihydro-2-quinazolinyl sulfanyl}acetate **5**. The structure of compound **5** was established by elemental analyses and spectral studies. The IR spectrum of compound **5** howed absorption bands in the region 3379, 3087, 2981 and 1743 cm^{-1} characteristic for NH, CH-aromatic, CH-aliphatic and C=O (ester) groups, respectively along with bands at 1685 and 1330, 1135 cm-1 due to C=O (quinazoline) and S=O, respectively. Also, the structure was confirmed from ^1H NMR spectrum, which exhibited signals in the range 1.17, 3.88, 4.2, 6.91–8.04 and 8.14 ppm due to the CH_3, SCH_2, OCH_2, aromatic and NH, respectively. The structure of **5** was also supported from mass spectrum which gave a molecular ion peak at m/z 502 (2.29%) which underwent fragmentation to give a well established fragment at m/z 148 (100%; base peak), (Scheme 4). Hydrazinolysis of **5** using ethanolic hydrazine hydrate afforded the 3,4-dihydro-3-{4-(1,3-thiazol-2-yl) sulphonamido}phenyl-4-oxo-2-quinazolinylthioacetic acid hydrazide **6**. Refluxing of **4a,b,d** with hydrazine hydrate in ethanol furnished 2-hydrazino-3,4-dihydro-3-[4-N-substituted sulphonamido]phenyl-4-oxo-quinazolines **7a-c**, (Scheme 3).

In continuation of this investigation, interaction of **1a,d** with 2-amino-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophene[24] in dioxane/TEA, the corresponding N^1,N^3-disubstituted thioureas **8a,b** were obtained. On the other hand, treatment of **1a,b,d** with



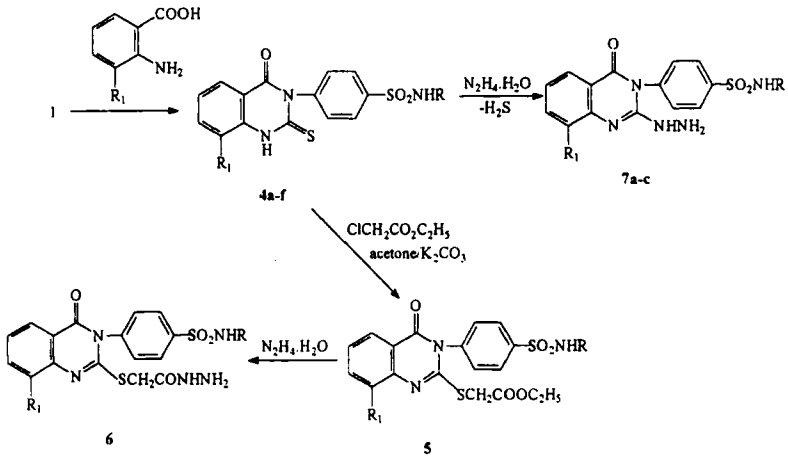
SCHEME 2

2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene[24] gave thieno [2,3-d]pyrimidines **10a-c** in high yield. The structure of compounds **10a-c** are supported by their elemental analyses and spectral data. The formation of **10** from **1** and 2-amino-3-cyano-4,5,6,7-tetrahydro-benzo[b]thiophene is assumed to proceed through *Dimorth rearrangement*[25] of the initial cyclization products **9** under the reaction conditions to yield **10**, (Scheme 5).

ANTIMICROBIAL ACTIVITY

Compounds **2b,c, 4a-f, 5, 6, 8a** and **10a-c** were tested for their antimicrobial activity using the gram positive bacteria: *Staphylococcus aureus* (NCTC 7447), *Bacillus subtilis* (NCTC 10400) and *Sarcina sp.* (NCTC 1117); gram negative bacteria: *Escherichia coli* (NCTC 10416) and *Klebsiella pneumonia* (NCIMB 9111), by the filter paper disc method[26]. The results of the antimicrobial activity tests are summarized in Table (IV).

Most of the synthesized compounds were found to possess various antimicrobial activity towards all the microorganisms used with minimal inhibitory concentration (MIC). Compound **2c** which containing pyrimidine moiety possesses a high antimicrobial activity towards *Staphylococ-*



SCHEME 3

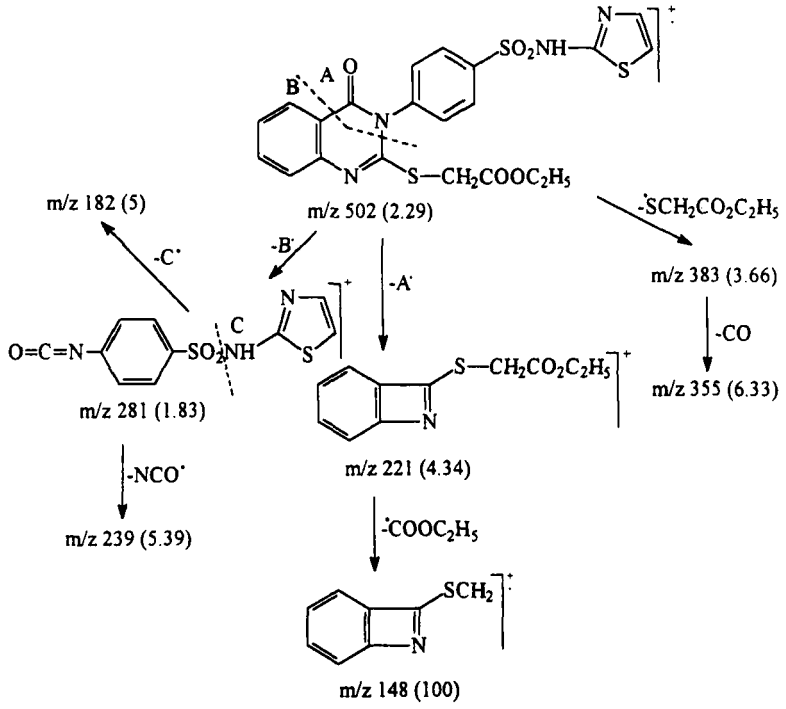
cus aureus (NCTC 7447), *Sarcina sp.* (NCTC 1117) and *Escherichia coli* (NCTC 10416). Also, compound **4c**, which contains thiazole moiety, was found to possess the highest antimicrobial activity towards *Staphylococcus aureus* (NCTC 7447) and *Sarcina sp.* (NCTC 1117) as compared to the remaining compounds. On the other hand compounds **4e, 4f, 10a** and **10c** were possesses antimicrobial activity against *sarcina sp.* (NCTC 1117).

EXPERIMENTAL

M.p.'s reported were uncorrected. IR spectra (KBr) were recorded on Pye Unicam (UK) SP 1000 instrument. UV spectra were run on UV-160 A, UV-VIS recording spectrophotometer (Shimaduz), ^{1}H NMR spectra were recorded on a Varian Gemini 200 instrument, 200 MHz, using DMSO-d_6 as a solvent and TMS as internal standard. Chemical shifts are expressed as δ ppm units. Mass spectra were recorded on a gas chromatographic GC-MSq p1000 (Shimadzu, Japan) instrument. Microanalytical data were obtained from the microanalytical data unit at the Cairo University.

N^1-[4-N-substituted sulphonamido]phenyl-N^3-(4-substituted phenyl)-thioureas (2a-c)

To a suspension of **1a,b,d** (0.01 mol) and aromatic amines (0.01 mol) in 1,4-dioxane (20 ml), triethylamine (0.01 mol) was added. The reaction



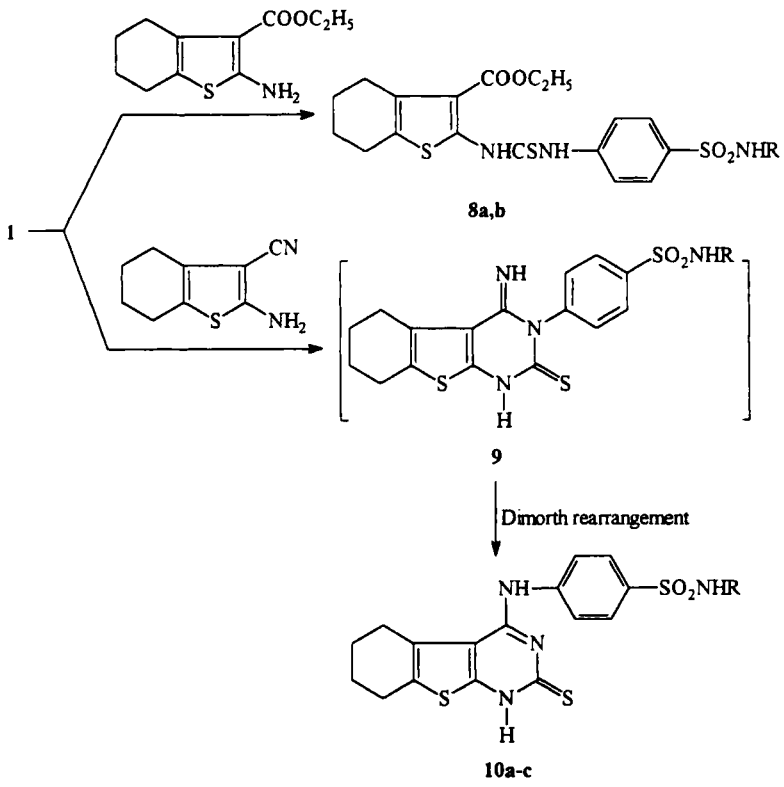
SCHEME 4

mixture was heated at reflux temperature until the clear solution was obtained. The solid residue was collected by filteration, washed with cold water and recrystallized from proper solvent to give **2a-c**, (Table I).

m/z (**2b**): 420 (M^+; 1%), 389 (1.43%), 297 (1.63%), 254 (5.74%), 239 (39.13%), 165 (47%), 163(7.8%) and 108 (100%; base peak), (Scheme 2).

2-[4-N-substituted sulphonamido]phenylimino-3-(4-substituted phenyl)-4,9-dioxonaphtho[2,3-d]thiazoles (3a-c)

A mixture of **2a-c** (0.01 mol) and the required 2,3-dichloro-1,4-naphthoquinone (0.01 mol) in absolute ethanol was heated under reflux for 10 min. The precipitate formed after cooling was collected by filteration and recrystallized from proper solvent to give **3a-c**, (Table I).



SCHEME 5

3-[4-N-substituted sulphonamido]phenyl-2-thioxo-4(3H)-quinazolin-4-ones (4a-f)

To a stirred suspension of **1a-d** (0.01 mol) and anthranilic acids (0.01 mol) in a 1,4-dioxane (20 ml), triethylamine (0.01 mol) was added. The reaction mixture was heated under reflux for 30 min., filtered while hot and then cooled. The solid obtained was collected by filtration and recrydtallized from proper solvent to give **4a-f**, (Table I).

m/z (**4d**): 411 (M^+; 1%), 374 (2.75%), 357 (3.38%), 273(76.37%), 227(100%; base peak), 185 (86.04%), 108 (24.61%) and 92(42.23%).

TABLE I Characteristics of the synthesized compounds

R	R_1	*M.P.* [°C]	*Solvent cryst.*	*Yield (%)*	*Mol.Formula (Mol.wt)*	*Elemental Analyses Required/F*			
						%C	*%H*	*%N*	
H	CH_3	180–81	Ethanol	67	$C_{14}H_{15}N_3O_2S_2$	52.34	4.67	13.08	19
					(321)	52.20	4.70	13.10	20
2-Thiazolyl	OCH_3	165–66	Ethanol	60	$C_{17}H_{16}N_4O_3S_3$	48.57	3.80	13.34	22
					(420)	48.40	3.80	13.30	22
2-(4,6-Dimethyl)-pyrimidinyl	CH_3	174–75	Ethanol	70	$C_{20}H_{21}N_5O_2S_2$	56.20	4.91	16.39	14
					(427)	56.10	4.80	16.40	15
H	CH_3	200–1	Ethanol	80	$C_{24}H_{17}N_3O_4S_2$	60.63	3.58	8.84	13
					(475)	60.70	3.40	8.90	13
2-Thiazolyl	OCH_3	185–86	Ethanol	90	$C_{27}H_{18}N_4O_5S_3$	56.45	3.14	9.76	16
					(574)	56.30	3.00	9.80	16
2-(4,6-Dimethyl)-pyrimidinyl	CH_3	180–81	Ethanol	82	$C_{30}H_{23}N_5O_4S_2$	61.96	3.96	12.05	11
					(581)	62.00	4.00	12.10	11
H	H	>300	DMF/H_2O	92	$C_{14}H_{11}N_3O_3S_2$	50.45	3.31	12.61	19
			(3:1)		(333)	50.50	3.20	12.70	19
H	OCH_3	>300	DMF/H_2O	95	$C_{15}H_{13}N_3O_4S_2$	49.59	3.58	11.57	17

R	R_1	M.P. [°C]	Solvent cryst.	Yield (%)	Mol.Formula (Mol.wt)	Elemental Analyses Required/Fo			
						%C	%H	%N	
			(3:1)		(363)	49.60	3.40	11.60	17
2-Thiazolyl	H	250–251	DMF/H_2O	93	$C_{17}H_{12}N_4O_3S_3$	49.04	2.89	13.46	23
			(3:1)		(416)	49.00	2.90	13.50	23
2-Pyrimidinyl	H	> 300	Dioxane	80	$C_{18}H_{13}N_5O_3S_2$	52.56	3.16	17.03	15
					(411)	52.60	3.20	17.10	15
2-(4,6-Dimethyl)-pyrimidinyl	H	>300	Dioxane	70	$C_{20}H_{17}N_5O_3S_2$	54.67	3.87	15.95	14
					(439)	54.70	3.90	16.00	14
2-(4,6-Dimethyl)-pyrimidinyl	OCH_3	>300	Dioxane	85	$C_{21}H_{19}N_5O_4S_2$	53.73	4.05	14.93	13
					(469)	53.60	4.10	14.80	13
2-Thiazolyl	H	80–81	Ethanol	30	$C_{21}H_{18}N_4O_5S_3$	50.20	3.59	11.16	19
					(502)	50.10	3.60	11.20	19
2-Thiazolyl	H	180–82	Ethanol	50	$C_{19}H_{16}N_6O_4S_3$	46.72	3.28	17.21	19
					(488)	46.70	3.10	17.10	19
H	H	260–61	Ethanol	82	$C_{14}H_{13}N_5O_3S$	50.76	3.93	21.15	9.(
					(331)	50.60	4.00	21.00	9..
H	OCH_3	250–51	Ethanol	85	$C_{15}H_{15}N_5O_4S$	49.86	4.16	19.39	8..

R	R_1	M.P. [°C]	Solvent cryst.	Yield (%)	Mol.Formula (Mol.wt)	Elemental Analyses Required/Fo			
						%C	%H	%N	
					(361)	49.70	4.20	19.20	8.9
2-(4,6-Dimethyl)-	OCH_3	245–46	Ethanol	78	$C_{21}H_{21}N_7O_4S$	53.96	4.50	20.99	6.8
pyrimidinyl					(467)	53.80	4.60	21.00	6.9
H	-----	210–21	Dioxane	55	$C_{18}H_{21}N_3O_4S_3$	49.20	4.79	9.57	21
					(439)	49.10	4.80	9.40	21
2-(4,6-Dimethyl)	-----	200–1	Ethanol	67	$C_{24}H_{27}N_5O_4S_3$	52.85	4.96	12.85	17
pyrimidinyl					(545)	52.90	5.00	12.70	17
H	-----	195–96	Dioxane	60	$C_{16}H_{16}N_4O_2S_3$	48.98	4.08	14.29	24
					(392)	48.80	4.00	14.10	24
2-Thiazolyl		180–81	Dioxane	63	$C_{19}H_{17}N_5O_2S_4$	48.00	3.58	14.74	26
					(475)	48.10	3.60	14.60	26
2-(4,6-Dimethyl)-	-----	> 300	Dioxane	67	$C_{22}H_{22}N_6O_2S_3$	53.01	4.42	16.87	19
pyrimidinyl					(498)	53.00	4.50	16.90	19

Ethyl 2-{4-oxo-3-[4-(1,3-thiazol-2-yl)sulfamoylphenyl]-3,4-dihydro-2-quinazolinylsulphanyl}acetate (5)

A mixture of **4c** (0.01 mol), ethyl chloroacetate (0.01 mol) anhydrous K_2CO_3 (2gm) in dry acetone (50 ml) was refluxed for 24 h. The reaction mixture was filtered while hot and the product obtained after concentration of the filterate was recrystallized from proper solvent to give **5**, (Table I).

m/z: 502 (M^+;2.29%), 383(3.66%), 366(6.33%), 281(1.83%), 239(5.39%), 221(4.34%) and 148 (100%; base peak), (Scheme 3).

3,4-Dihydro-3-{4-(1,3-thiazol-2-yl)sulphonamido}phenyl-4-oxo-2-quinazolinylthioacetic acid hydrazide (6)

Hydrazine hydrate (0.02 mol) was added to a solution of **5** (0.01 mol) in ethanol (50 ml) and the reaction mixture was heated under reflux for 3h. The reaction mixture was cooled and poured on crushed ice. The product was filtered, washed with water and recrystallized from proper solvent to give **6**, (Table I).

2-Hydrazino-3-[4-N-substituted sulphonamido]phenyl-4(3H)-quinazolin-4-ones (7a-c)

Hydrazine hydrate (0.02 mol) was added to a solution of **4a,b,f** (0.01 mol) in ethanol (50 ml) the reaction mixture was heated under reflux for 3h. The reaction mixture was cooled and poured on crushed ice/HCl. The product was filtered, washed with water and recrystallized from proper solvent to give **7a-c**, (Table I).

m/z (**7c**): 467(M^+; 10.23%), 457(5.68%), 444(13.31), 413(20%), 301(35.06%), 241(46%), 186(22%) and 57(100%).

N^1-[3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo(b)thienyl-2-yl]-N^3-[4-N-substituted sulphonamido]phenyl thioureas (8a,b)

A mixture of **1a,c** (0.01 mol) and 2-amino-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophene (0.01 mol), triethylamine (0.01 mol) in ethanol (50 ml) was heated under reflux for 3h. The solid obtained was collected by filteration and recrystallized from proper solvent to give **8a,b**, (Table I).

TABLE II IR and UV spectra of the synthesized compounds

...O.	IR, cm^{-1}					UV^a
	$\nu NH\ (NH_2)$	$\nu C{=}O$	νSO_2 Asym.	νSO_2 Sym.	$\nu C{=}S$	λ_{max} (nm
	3224, 3100	-----	1320	1150	1552, 1230	308
	3455, 3155	-----	1341	1131	1549, 1236	308
	3180	1675,1615	1315	1127	-----	500, 352
	3380, 3322, 3100	1713	1338	1107	1533, 1218	288
	3384, 3273, 3136	1689	1350	1124	1533, 1226	296
	3258, 3140	1658	1312	1131	1527, 1221	284
	3425, 3250	1661	1340	1152	1529, 1235	288
	3460, 3250	1699	1330	1151	1531, 1226	288
	3450, 3255	1668	1340	1153	1526, 1251	296
	3379	1743 1668, 1685	1320	1153	-----	304
	3327, 3211	1685	1332	1140	-----	308
	3450, 3323, 3211	1662	1335	1146	-----	308
	3328, 3240, 3103	1656	1334	1150	-----	309
	3420, 3200	1723	1336	1152	-----	344, 260
	3415, 3195	1730	1334	1140	-----	408
	3330, 3244, 3157	-----	1340	1130	1530, 1280	260
	3435, 3190, 3100	-----	1321	1129	1523, 1260	412, 296
	3470, 3330, 3163	-----	1314	1163	1520, 1290	408, 372

...tra of the synthesized compounds were measured in N,N-dimethylformamide as solvent (concentration 4×10^{-5}M)

TABLE III ^{1}H-NMR data of synthesized compounds

	(DMSO-d_6) δ (ppm)
	3.98(s,OCH_3), 6.68(s,NH; exchangeable), 6.80(s,NH; exchangeable), 6.85–6.93(m,thiazole ring), 7.3-7.5(m,aromatic), 8.38(s,SO_2N exchangeable).
	3.85 (s,OCH_3), 6.90–6.93 (m,thiazole ring), 7.1–8.01 (m,aromatic), 8.12 (s,SO_2NH; exchangeable).
	3.96 (s, OCH_3), 7.33 (s, SO_2NH_2; exchangeable), 7.43–7.96 (m, aromatic), 11.91 (s, NH; exchangeable).
	2.1 (s,$2CH_3$), 3.8 (s,OCH_3), 6.5–7.4 (m, aromatic), 7.8 (s,SO_2NH; exchangeable), 8.2(s,pyrimididine-H), 11.0 (s,NH;exchangeable
	1.17 (t, CH_3), 3.88 (s, SCH_2), 4.21 (q, OCH_2), 6.54–6.90 (m, thiazole ring), 6.91–8.04 (m, aromatic), 8.14 (s, SO_2NH; exchangeab
	3.8 (s,SCH_2), 5.8 (s,NH_2; exchangeable), 6.70–6.82 (m, thiazole ring), 7.20–7.80 (m, aromatic), 8.06 (s,SO_2NH; exchangeable), 10.6 (s,CONH; exchangeable).
	3.4 (s, NH_2; exchangeable), 5.71 (s, NH; exchangeable), 7.13 (s,SO_2NH_2; exchangeable), 7.16–8.21 (m, aromatic).
	3.91 (s,OCH_3), 5.76 (s, NH_2; exchangeable), 7.23 (s,SO_2NH_2; exchangeable), 7.27- 8.37 (m, aromatic), 9.75 (s,NH; exchangeable)
	2.12 (s,CH_3), 2.26(s,CH_3), 2.50 (s, NH_2; exchangeable), 3.94 (s,OCH_3),6.4(s,NH; exchangeable), 6.73 (s,pyrimidine) 7.26–7.52(m,aromatic), 8.06(s,SO_2NH; exchangeable).
	1.2 (t,CH_3), 1.68(s,$4CH_2$), 2.27 (s, CH_3), 2.51 (s,CH_3), 4.1(q, OCH_2), 8.56 (s, pyrimidine-H), 7.54 (q, AB-system), 8.01(s, SO_2NH exchangeable), 11.38 (s, NH; exchangeable), 11.99 (s, NH; exchangeable).
	1.61 (s,$4CH_2$), 3.8(s, NH; exhangeable), 7.27 (s,SO_2NH_2; exchangeable), 7.44 (q,AB-system), 9.45 (s,NH; exchangeable).
	1.7 (s,$4CH_2$), 2.15 (s,CH_3), 2.30 (s,CH_3), 7.25–7.86 (m,aromatic), 8.29 (s,SO_2NH; exchangeable), 10.20 (s,NH;exchangeable), 12.0(s,NH; exchangeable).

TABLE IV Antimicrobial* screen of the syntheized compounds

Compd. NO.	Gram positive			Gram negative	
	Staphyloccus aureus (NCTC 7447)	*Bacillus aubtilis (NCTC 10400)*	*Sarcina sp. (NCTC 1117)*	*Escherichia coli (NCTC 10416)*	*Klebsiella pneumonia (NCIMB 9111)*
2b	++	-----	-----	++	++
2c	+++	+	+++	+++	++
4a	++	-----	-----	++	+
4b	-----	++	+	+	++
4c	++++	+	++ +	++	++
4d	+	+	++	-----	+
4e	-----	++	+++	+++	+
4f	++	++	+++	++	-----
5	++	+ +	+	+	++
6	++	-----	++	+	+
8a	+	++	++	+	++
10a	-----	-----	+++	++	++
10b	+	++	++	+++	-----
10c	-----	-----	+++	++	++
DMF	-----	-----	-----	-----	-----

* Inhibition zones are measured in mm. The concentration used is 4×10^{-5}M. Control discs were performed with DMF (dimethylformamide) and no zones of inhibition were observed. (---) Resistant, (+) moderately sensitive giving a zone of inhibition 11 mm, (++) sensitive giving a zone of inhibition 12 mm, (+++) very sensitive giving a zone of inhibition 13 mm, (++++) very sensitive giving a zone of inhibition 14 mm.

4-(2-Thioxo-1,2,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d] pyrimidin-4-yl)-1-benzene sulphonamides (10a-c)

A mixture of **1a,b,d** (0.01 mol), 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo-[b]thiophene (0.01 mol) and triethylamine (0.01 mol) in ethanol (50 ml) was refluxed 3h. The solid obtained was recrystallized from proper solvent to give **10a-c**, (Table I).

m/z (**10c**): 457 (M^+-CH_3CN; 0.75%), 398 (100%; base peak), 366 (26.28%), 340 (10%), 233 (2.9%), 77 (11.7%) and 76 (4.63).

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