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RESEARCH ARTICLE

Reactions with hydrazonoyl halides 46 [1]: Synthesis of some new 2,3-dihydro-1,3,4-thiadiazoles and triazolino[4,3-*a*]pyrimidines as antimicrobial agents

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2,3-Dihydro-1,3,4-thiadiazoles and triazolino[4,3-*a*]pyrimidines were synthesized in a good yields from reactions of hydrazonoyl halides with alkyl carbodithioate and pyrimidine-2-thione, respectively. All structures of the newly synthesized compounds were elucidated by elemental analysis, spectral data and alternative synthesis methods. Some of the new compounds were tested against bacteria and some fungi.

Keywords: 1,3,4-Thiadiazolines; Hydrazonoyl halides; Triazolino[4,3-*a*]pyrimidines; 1,3-Dipolar cycloaddition

1. Introduction

It has been reported that heterocyclic compounds containing the naphthalene nucleus are useful as antibacterial [2, 3], antimalarial [4], and anticancer agents [5]. Also, 1,3,4-thiadiazole derivatives have become very useful compounds in medicine, agriculture, and many fields of technology [6]. In continuation of an interest in the chemistry of thiadiazole systems we would like to report on some new heterocyclic systems containing a naphthalene nucleus, a combination that is expected to possess high biological activity.

2. Results and discussion

Treatment of 1-naphthalenecarbaldehyde **1a** with the appropriate methyl hydrazinecarbodithioate **2a** or benzyl hydrazinecarbodithioate **2b** in propan-2-ol gave methyl *N′*-(naphthalen-1-yl)ethylenehydrazinecarbodithioate **3a** and benzyl *N′*-(naphthalen-1-yl)ethylenehydrazinecarbodithioate **4a**. Structures **3a** and **4a** were confirmed by elemental

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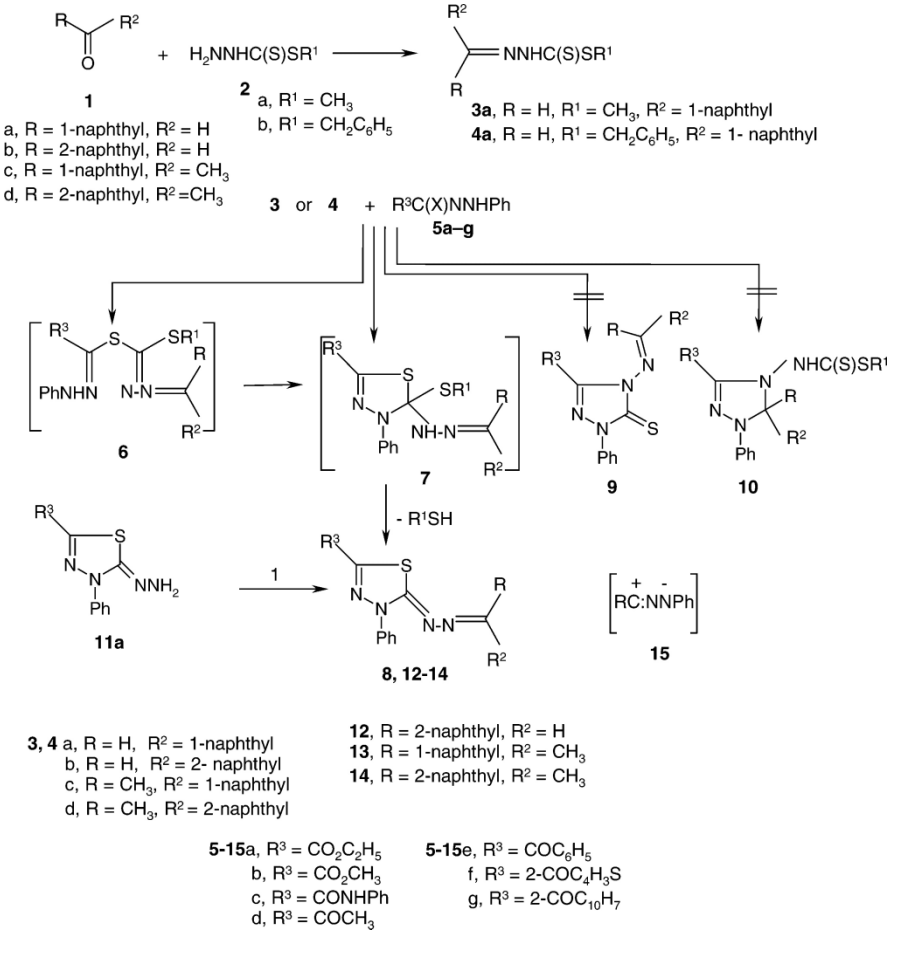
analysis, spectral data, and chemical transformation. The ^{1}H NMR spectrum of **3a** showed signals at $\delta = 2.00$ (s, 3H), 7.32–7.96 (m, 7H), 8.21 (s, 1H), and 11.20 (s, br, 1H). Treatment of *C*-ethoxycarbonyl-*N*-phenylformohydrazonoyl chloride **5a** with **3a** in ethanolic triethylamine solution furnished exclusively one product (as evidenced by TLC) whose structure could be assigned as any of **8a**, **9a** or **10a** (Scheme 1).



SCHEME 1

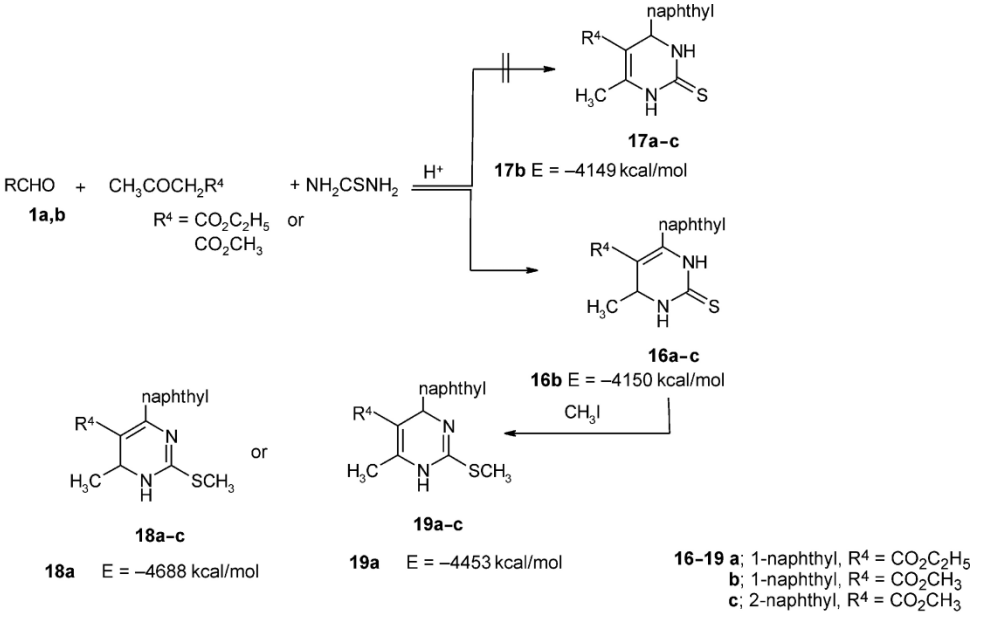
Elemental analyses, spectral data, and alternative synthesis are in agreement with the formation of ethyl 2-[(2*E*)-3-(1-naphthyl)-1,2-diazaprop-2-enylidene]-3-phenyl-2,3-dihydro-1,3,4-thiadiazole-5-carboxylate **8a**. The IR spectrum of the product revealed bands at 1710 (CO), 1618 (C=N), and 1583 (C=C). Its ^{1}H NMR showed signals at $\delta = 1.44$ (t, 3H), 4.46 (q, 2H), 7.25–8.05 (m, 12H), and 9.05 (s, 1H). Also, treatment of **4a** with **5a** in ethanolic triethylamine afforded products identical in all respects (mp, mixed mp, and spectra) with **8a**. Unequivocal support for the structure of product **8a** was obtained by reaction of the 2-hydrazino-1,3,4-thiadiazoline **11a** [7] with **1a**, which gave a product identical with **8a** (Scheme 1). From the foregoing results, structures **9** and **10** for the product were excluded.

Two possible pathways can account for the formation of product **8** : i) 1,3-addition of the thiol tautomer **3** to the nitrilium imide **15a**, prepared *in situ* by treatment of hydrazonoyl chloride **5a**

with triethylamine, can give the thiohydrazonate ester **6a**, which in turn undergoes nucleophilic cyclization to yield **7a** and then **8a** by loss of R^1SH; ii) alternatively, 1,3-cycloaddition of the nitrilium imide **15a** to the C=S double bond of **3a** (or **4a**) can give **7a** directly (Scheme 1). Similarly, the appropriate hydrazonoyl halides **5b–g** react with each of the alkyl carbodithioates **3a** and **4a** to afford 2,3-dihydro-1,3,4-thiadiazole derivatives **8b–g**, respectively.

By analogy, treatment of the appropriate hydrazonoyl halides **5a–g** with methyl carbodithioates **3b–d** (or benzyl carbodithioates **4b–d**), prepared from naphthalene-2-carbaldehyde, 1-(1-naphthyl)ethanone, or 1-(2-naphthyl)ethanone **1b–d** with either methyl hydrazinecarbodithioate **2a** or benzyl hydrazinecarbodithioate **2b**, afforded 2,3-dihydro-1,3,4-thiadiazoles **13a–g**, **14a–g**, respectively (Scheme 1).

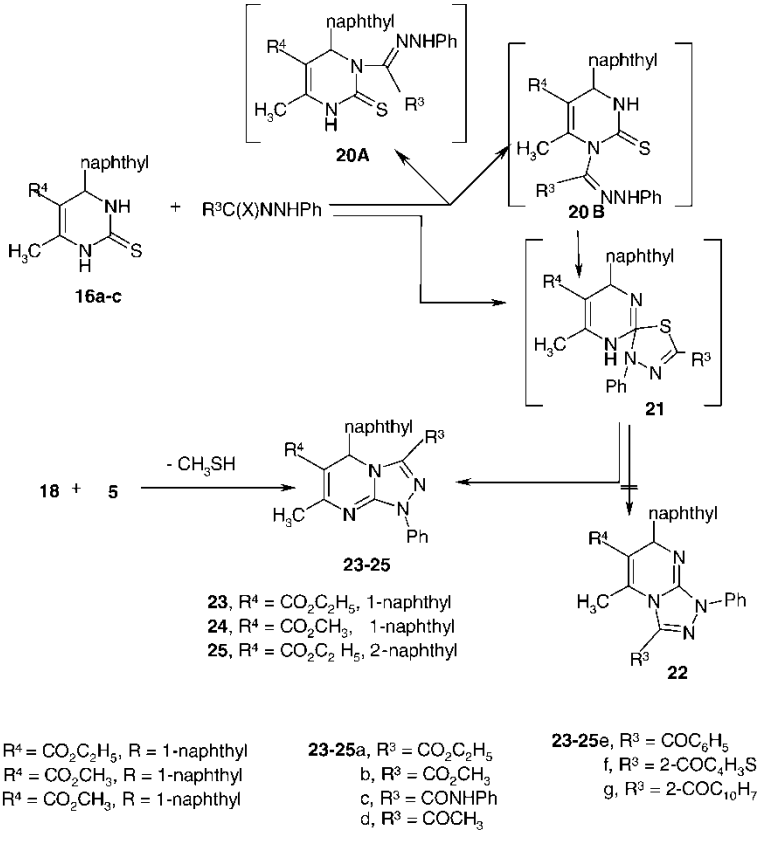
Treatment of the naphthalenecarbaldehydes **1a, 1b** with ethyl (or methyl) 3-oxobutanoate, thiourea, and a catalytic amount of hydrochloric acid in boiling ethanol gave a 3,4-dihydropyrimidine-2(1*H*)-thione derivative **16a–c** or the isomeric **17a–c** (Scheme 2). The structure of the product was assigned as **16** by ^{1}H NMR analysis and molecular orbital calculations. Thus, the ^{1}H NMR spectrum of **16a** showed signals at $\delta = 1.43$ (t, 3H), 2.61 (s, 3H), 3.49 (s, 1H), 4.12 (q, 2H), 7.22–7.94 (m, 7H), 8.01 (s, 1H) and 9.00 (s, br., 1H). According to molecular orbital calculations, using the HyperChem AM1 semiempirical method, the total energy showed structure **16** to be the most stable isomer (Scheme 2).



SCHEME 2

Methylation of **16a** with methyl iodide in the presence of sodium ethoxide led to the formation of either **18a** or its isomeric structure **19a**. The structural assignment could again be established for these possible products based on their ^{1}H NMR analysis and molecular orbital calculations (Scheme 2). Thus, the ^{1}H NMR spectrum of the product showed signals at $\delta = 1.43$ (t, 3H), 2.32 (s, 3H), 2.50 (s, 3H), 3.36 (s, 1H), 4.12 (q, 2H), 7.22–7.91 (m, 7H), and 8.71 (s, 1H). According to molecular orbital calculations, again using the HyperChem AM1 semiempirical method, the total energy showed that structure **18** is most stable isomer.

Finally, treatment of hydrazonoyl chloride **5a** with **16a** in boiling chloroform under reflux gave either triazolino[4,3-*a*]pyrimidine **22a** or its isomer **23a** (Scheme 3).



SCHEME 3

In Scheme 3, it is suggested that the reaction of **16** starts with nucleophilic attack on N-1 or N-3 to give substitution products **20A** and **20B**. Cyclization of the latter intermediates and elimination of hydrogen sulfide would give the end products **22** or **23**, respectively. The formation of **23** is similar to the reaction of 3,4-dihydropyrimidine-2-thione derivatives with halogeno ketones [8] and hydrazonoyl halides [9]. The structure of the product as **23** was elucidated on the basis of elemental analysis, spectral data, and an alternative synthesis. Thus, the ^{1}H NMR spectrum of **23a** showed signals at $\delta = 1.01$ (t, 3H), 1.23 (t, 3H), 2.53 (s, 3H), 3.95 (q, 2H), 4.15 (q, 2H), 7.25–7.72 (m, 12H), and 8.024 (s, 1H). Its IR spectrum revealed bands at 1753 (CO ester), 1689 (CO conjugated), and 1608 (C=N). Finally, hydrazonoyl chloride **5a** reacted with **18a** in boiling ethanolic sodium ethoxide gave a product identical with **23a**.

By analogy, ethyl 6-methyl-2-methylthio-4-(1-naphthyl)-3,4-dihydropyrimidine-5-carboxylate **18a** reacted with the appropriate hydrazonoyl halides **5b–g** in ethanolic sodium hydroxide solution (or the pyrimidine-2-thione **18a** in boiling chloroform containing triethylamine solution), to give triazolino[4,3-*a*]pyrimidines **23b–g**, respectively (Scheme 3). Similarly, treatment of methyl 6-methyl-2-methylthio-4-(1-naphthyl)-3,4-dihydropyrimidine-5-carboxylate **18b**, and methyl 6-methyl-2-methylthio-4-(2-naphthyl)-3,4-dihydropyrimidine-5-carboxylate **18c** with the appropriate hydrazonoyl halides **5a–g** afforded triazolino[4,3-*a*]pyrimidines **24a–g** and **25a–g**, respectively (Scheme 3).

2.1 *Antimicrobial activity*

The tested microorganisms were gram +ve bacteria [*Staphylococcus aureus (ATCC25923)* and *Streptococcus pyrogenes (ATCC19615)*] and gram −ve bacteria (*Pseudomonas syrinage PV phasealicola*). In addition, some fungal pathogens (*Aspergillus niger* and *Fusarium oxysporum*) were also tested. Sensitivity of the selected microorganisms to some synthesized compounds was determined *in vitro* at two concentrations (100, 400 μg/mL) in $CHCl_3$. The tests were carried out using the filter paper and hole plate method [10].

Studies on the biological activity of compounds **8f**, **8g**, **13g**, and **25b** led to the fact that these compounds have moderate biological activity against the tested bacteria, and only weak activity against fungi. Also, it can be observed (Table 1) that compounds **13d,g, 14f,g**, and **25e** have only a weak effect on bacteria. Compounds **8a**, **8f**, **8g**, **13d**, **14d,f,g**, and **18g** showed weak antifungal activity, but compounds **18b**, **23e,g**, and **25e,g** showed moderate antifungal activity.

3. Experimental

All melting points were determined on an Electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer, and chemical shifts are expressed in δ units using TMS as internal reference. Mass spectra were recorded on a GC-MS QO 1000 EX (Shimadzu). Elemental analyses were carried out at the Microanalytical Center of Cairo University. Hydrazonoyl halides **5** [11–17] were prepared as previously reported.

3.1 *Synthesis of alkyl hydrazinecarbodithioates 3a–d and 4a–d. General method*

Equimolar amounts of the appropriate naphthalene derivative **1a,b** and the appropriate alkyl hydrazinecarbodithioate **2a,b** [18] (5 mmol each) in propan-2-ol (10 mL) were stirred for 2 h at room temperature. The resulting solid was collected, and crystallized from ethanol to give yellow crystals **3a–d** and **4a–d**, respectively (Tables 2 and 3).

Table 1. Response of various microorganisms to some synthesized compounds in *in vitro* culture.

Compound	S.a.	S.p.	P.s.	A.n.	F.o
8a					W
8f	M	M		W	W
8g		M		W	W
13d		W		W	
13g	W	W			
14f	W	W		W	
14g		W		W	
18b					M
18f	W	W			
18g	W	W	M		W
23b		M			
23e		W			M
23g					M
25b		M			
25e		W			M
25g					M

Diameter of the zone of inhibition: W: low activity (3–5 mm) (+), M: moderate activity (6–15 mm) (++).

Table 2. Characterization data of the newly synthesized compounds.

Compound	Mp/°C (Solvent)	Color Yield (%)	Mol. Formula (Mol. Wt.)	Elemental analysis [Calcd./Found (%)]			
				C	H	N	S
3a	158–161	Pale yellow	$C_{13}H_{12}N_2S_2$	59.69	4.64	10.75	24.63
	EtOH	90	(260.38)	59.30	4.22	10.45	24.23
3b	197–198	Yellow	$C_{13}H_{12}N_2S_2$	59.69	4.64	10.75	24.63
	EtOH	90	(260.38)	59.30	4.22	10.45	24.23
3c	110–111	Yellow	$C_{14}H_{14}N_2S_2$	61.20	5.14	10.20	23.37
	EtOH	90	(274.41)	61.00	5.04	10.00	23.11
3d	167–169	Pale yellow	$C_{14}H_{14}N_2S_2$	61.20	5.14	10.20	23.37
	EtOH	90	(274.41)	61.00	5.04	10.00	23.11
4a	179–181	Yellow	$C_{19}H_{16}N_2S_2$	67.82	4.79	8.32	10.05
	AcOH	70	(336.48)	67.50	4.55	8.22	10.00
4b	169–171	White	$C_{19}H_{16}N_2S_2$	67.82	4.79	8.32	10.05
	AcOH	70	(336.48)	67.50	4.55	8.22	10.00
4c	110–112	Yellow	$C_{20}H_{18}N_2S_2$	68.53	5.17	7.99	18.29
	AcOH	60	(350.51)	68.30	5.00	7.63	18.00
4d	136–138	Yellow	$C_{20}H_{18}N_2S_2$	68.53	5.17	7.99	18.29
	AcOH	90	(350.51)	68.30	5.00	7.63	18.00
8a	129–131	Yellow	$C_{22}H_{18}N_4O_2S$	65.65	4.50	13.92	7.96
	EtOH	90	(402.46)	65.40	4.30	13.60	7.66
8b	149–151	Yellow	$C_{21}H_{16}N_4O_2S$	64.93	4.15	14.42	8.25
	AcOH	90	(388.43)	64.60	4.00	14.12	8.00
8c	233–235	Yellow	$C_{26}H_{19}N_5OS$	69.47	4.26	15.57	7.13
	AcOH	90	(449.52)	69.17	4.00	15.20	7.00
8d	145–147	Yellow	$C_{21}H_{16}N_4OS$	67.72	4.33	15.04	8.60
	EtOH	90	(372.44)	67.50	4.00	15.00	8.30
8e	170–172	Red	$C_{26}H_{18}N_4OS$	72.03	4.18	12.92	7.39
	EtOH	70	(433.51)	72.00	4.11	12.75	7.31
8f	205–207	Orange	$C_{24}H_{16}N_4OS_2$	65.43	3.66	12.71	14.55
	AcOH	65	(440.54)	65.23	3.40	12.53	14.30
8g	185–187	Red	$C_{30}H_{20}N_4OS$	74.36	4.16	11.56	6.61
	AcOH	60	(484.57)	74.30	4.00	11.26	6.45
12a	113–115	Yellow	$C_{22}H_{18}N_4O_2S$	65.65	4.50	13.92	7.96
	AcOH	90	(402.46)	65.40	4.30	13.60	7.66
12b	140–142	Yellow	$C_{21}H_{16}N_4O_2S$	64.93	4.15	14.42	8.25
	AcOH	90	(388.43)	64.60	4.00	14.12	8.00
12c	204–205	Yellow	$C_{26}H_{19}N_5OS$	69.47	4.26	15.57	7.13
	AcOH	90	(449.52)	69.40	4.12	15.35	7.00
12d	124–126	Orange	$C_{21}H_{16}N_4OS$	67.72	4.33	15.04	8.60
	AcOH	60	(372.44)	67.52	4.15	15.00	8.50
12e	145–147	Orange	$C_{26}H_{18}N_4OS$	72.03	4.18	12.92	7.39
	AcOH	70	(433.51)	72.00	4.00	12.80	7.31
12f	192–194	Orange	$C_{24}H_{16}N_4OS_2$	65.43	3.66	12.71	14.55
	AcOH	65	(440.54)	65.21	3.40	12.50	14.30
12g	175–176	Orange	$C_{30}H_{20}N_4OS$	74.36	4.16	11.56	6.61
	AcOH	65	(484.57)	74.00	4.00	11.28	6.45
13a	116–117	Yellow	$C_{23}H_{20}N_4O_2S$	66.33	4.84	13.45	7.69
	AcOH	60	(416.48)	66.20	4.70	13.30	7.60
13b	170–172	Yellow	$C_{22}H_{18}N_4O_2S$	65.65	4.50	13.92	7.96
	AcOH	65	(402.46)	65.65	4.40	13.80	7.90
13c	213–215	Yellow	$C_{27}H_{21}N_5OS$	69.95	4.56	15.10	6.91
	AcOH	65	(463.55)	69.80	4.40	15.00	6.81
13d	128–130	Orange	$C_{22}H_{18}N_4OS$	68.37	4.69	14.49	8.29
	EtOH	70	(386.47)	68.30	4.60	14.40	8.20
13e	117–119	Orange	$C_{27}H_{20}N_4OS$	72.30	7.49	12.49	7.14
	EtOH	75	(448.54)	72.20	7.40	12.40	7.00
13f	136–138	Orange	$C_{25}H_{18}N_4OS_2$	66.05	3.99	12.33	14.10
	EtOH	70	(454.56)	65.90	3.90	12.23	14.00
13g	196–198	Orange	$C_{31}H_{22}N_4OS$	74.67	4.44	11.23	6.43
	AcOH	55	(498.60)	74.60	4.30	11.10	6.30

(*continued*)

Table 2. Continued.

Compound	Mp/°C (Solvent)	Color Yield (%)	Mol. Formula (Mol. Wt.)	Elemental analysis [Calcd./Found (%)] C	H	N	S
14a	221–222	Yellow	$C_{23}H_{20}N_4O_2S$	66.33	4.84	13.45	7.69
	AcOH	80	(416.48)	66.20	4.70	13.30	7.60
14b	147–148	Yellow	$C_{22}H_{18}N_4O_2S$	65.65	4.50	13.92	7.96
	AcOH	70	(402.46)	65.60	4.40	13.80	7.75
	218–220	Yellow	$C_{27}H_{21}N_5OS$	69.95	4.56	15.10	6.91
14c	AcOH	70	(463.55)	69.80	4.40	15.00	6.70
14d	192–194	Yellow	$C_{22}H_{18}N_4OS$	68.37	4.69	14.49	8.29
	EtOH	70	(386.47)	68.20	4.60	14.40	8.00
14e	159–160	Red	$C_{27}H_{20}N_4OS$	72.30	7.49	12.49	7.14
	AcOH	80	(448.54)	72.20	7.30	12.40	7.00
14f	187–189	Orange	$C_{25}H_{18}N_4OS_2$	66.05	3.99	12.33	14.10
	AcOH	80	(454.56)	65.90	3.80	12.23	14.00
14g	178–180	Red	$C_{31}H_{22}N_4OS$	74.67	4.44	11.23	6.43
	AcOH	80	(498.60)	74.60	4.30	11.10	6.30
16a	224–226	White	$C_{18}H_{18}N_2O_2S$	66.23	5.56	8.58	9.81
	EtOH	70	(326.16)	66.10	5.40	8.50	9.70
16b	252–253	White	$C_{17}H_{16}N_2O_2S$	65.36	5.16	8.96	10.26
	EtOH	70	(312.37)	65.20	5.00	8.90	10.10
16c	255–256	White	$C_{17}H_{16}N_2O_2S$	65.36	5.16	8.96	10.26
	EtOH	80	(312.37)	65.30	5.00	8.90	10.10
18a	212–214	White	$C_{19}H_{20}N_2O_2S$	67.25	5.92	8.23	9.40
	AcOH	70	(340.18)	67.10	5.80	8.10	9.30
18b	240–241	White	$C_{18}H_{18}N_2O_2S$	66.23	5.56	8.58	9.81
	AcOH	70	(326.16)	66.10	5.40	8.50	9.70
18c	250–252	White	$C_{18}H_{18}N_2O_2S$	66.23	5.56	8.58	9.81
	AcOH	75	(326.16)	66.10	5.40	8.50	9.70
23a	137–139	Yellow	$C_{28}H_{26}N_4O_4$	69.69	5.42	11.61	
	EtOH	70	(482.52)	69.22	5.15	11.95	
23b	166–168	Yellow	$C_{27}H_{24}N_4O_4$	69.50	5.30	11.50	
	EtOH	70	(468.50)	69.00	5.00	11.90	
23c	180–182	Brown	$C_{32}H_{27}N_5O_3$	72.57	5.13	13.22	
	EtOH	75	(529.56)	72.40	5.00	13.10	
23d	202–204	Yellow	$C_{27}H_{24}N_4O_3$	71.66	5.34	12.38	
	EtOH	60	(452.50)	71.50	5.20	12.30	
23e	169–170	Brown	$C_{32}H_{26}N_4O_3$	74.69	5.09	10.88	
	AcOH	75	(514.55)	74.60	4.90	10.80	
23f	145–147	Brown	$C_{30}H_{24}N_4O_3S$	69.21	4.64	10.76	6.15
	EtOH	70	(520.57)	69.10	4.50	10.70	6.10
23g	83–85	Black	$C_{36}H_{28}N_4O_3$	76.57	4.99	9.92	
	EtOH	65	(564.67)	76.50	4.90	9.80	
24a	154–156	Yellow	$C_{27}H_{24}N_4O_4$	69.22	5.16	11.95	
	EtOH	60	(468.50)	69.00	5.00	11.90	
23b	146–148	Yellow	$C_{26}H_{22}N_4O_4$	68.71	4.67	12.32	
	EtOH	70	(454.48)	68.60	4.50	12.30	
24c	177–178	Yellow	$C_{31}H_{25}N_5O_3$	72.22	4.88	10.86	
	EtOH	60	(515.54)	72.10	4.80	10.80	
24d	289–291	Brown	$C_{26}H_{22}N_4O_3$	71.22	5.05	12.77	
	EtOH	50	(438.48)	71.00	4.90	12.70	
24e	187–189	Yellow	$C_{31}H_{24}N_4O_3$	74.38	4.83	11.19	
	EtOH	55	(500.55)	74.20	4.70	11.00	
24f	260–262	Brown	$C_{29}H_{22}N_4O_3S$	68.76	4.37	11.06	6.33
	EtOH	65	(506.55)	68.60	4.20	11.00	6.20
24g	157–159	Orange	$C_{35}H_{26}N_4O_3$	76.35	4.75	10.17	
	EtOH	60	(550.59)	76.20	4.60	10.00	
25a	123–124	Yellow	$C_{27}H_{24}N_4O_4$	69.22	5.16	11.95	
	EtOH	70	(468.50)	69.00	5.00	11.90	
23b	130–131	Yellow	$C_{26}H_{22}N_4O_4$	68.71	4.67	12.32	
	EtOH	70	(454.48)	68.50	4.70	12.20	

(*continued*)

Table 2. Continued.

Compound	Mp/°C (Solvent)	Color Yield (%)	Mol. Formula (Mol. Wt.)	Elemental analysis [Calcd./Found (%)] C	H	N	S
25c	178–180	Yellow	$C_{31}H_{25}N_5O_3$	72.22	4.88	10.86	
	EtOH	60	(515.54)	72.00	4.70	10.80	
25d	168–169	Yellow	$C_{26}H_{22}N_4O_3$	71.22	5.05	12.77	
	EtOH	65	(438.48)	71.00	4.90	12.70	
25e	158–159	Orange	$C_{31}H_{24}N_4O_3$	74.38	4.83	11.19	
	EtOH	65	(500.55)	74.20	4.70	11.00	
25f	230–232	Orange	$C_{29}H_{22}N_4O_3S$	68.76	4.37	11.06	6.33
	EtOH	65	(506.55)	68.60	4.30	11.00	6.20
25g	144–146	Orange	$C_{35}H_{26}N_4O_3$	76.35	4.75	10.17	
	EtOH	66	(550.59)	76.20	4.60	10.00	

Table 3. Spectra of some selected synthesized compounds.

Compound	Spectra
3a	^{1}H NMR: 2.00 (s, 3H), 7.32–7.96 (m, 7H), 8.21 (s, 1H), and 11.20 (s, br, 1H) IR: 3163 (NH), 2916 (CH), 1596 (C=N), and 1269 (CS)
3b	^{1}H NMR: 2.00 (s, 3H), 7.32–7.96 (m, 7H), 8.21 (s, 1H), and 11.20 (s, br, 1H) IR: 3163 (NH), 2923 (CH), 1604 (C=N), and 1269 (CS)
3c	^{1}H NMR: 2.39 (s, 2H), 2.70 (s, 3H), 7.50–8.15 (m, 7H), and 10.06 (s, 1H) IR: 3163 (NH), 2923 (CH), 1604 (C=N), and 1269 (CS)
3d	^{1}H NMR: 2.39 (s, 2H), 2.70 (s, 3H), 7.50–8.15 (m, 7H), and 10.06 (s, 1H) IR: 3163 (NH), 2923 (CH), 1604 (C=N), and 1269 (CS)
4a	^{1}H NMR: 4.63 (s, 2H), 7.26–7.95 (m, 12H), 8.48 (s, 1H), and 15.58 (s, br, 1H) IR: 3109 (NH), 2974 (CH), 1596 (C=N), and 1238 (CS)
4b	^{1}H NMR: 4.63 (s, 2H), 7.26–7.95 (m, 12H), 8.48 (s, 1H), and 15.58 (s, br, 1H) IR: 3109 (NH), 2974 (CH), 1596 (C=N), and 1238 (CS)
4c	^{1}H NMR: 2.39 (s, 3H), 4.60 (s, 3H), 7.26–8.09 (m, 12H), and 10.05 (s, br, 1H) IR: 3163 (NH), 2904 (CH), 1596 (C=N), and 1238 (CS)
4d	^{1}H NMR: 2.39 (s, 3H), 4.60 (s, 3H), 7.26–8.09 (m, 11H), and 10.05 (s, br, 1H) IR: 3163 (NH), 2904 (CH), 1596 (C=N), and 1238 (CS)
8a	^{1}H NMR: 1.44 (t, 3H), 4.46 (q, 2H), 7.25–8.05 (m, 11H), and 9.05 (s, 1H) IR: 1710 (CO), 1618 (C=N), and 1583 (C=C)
8b	^{1}H NMR: 3.67 (s, 3H), 6.46–7.96 (m, 12H), and 8.19 (s, 1H) IR: 1710 (CO), 1618 (C=N), and 1583 (C=C)
8c	^{1}H NMR: 7.20–7.69 (m, 10H), 7.88–8.05 (m, 6H), 8.46 (s, 1H), 8.87–8.91 (d, 1H), and 9.06 (s, 1H) IR: 3359 (NH), 1666 (CO; amide), 1593 (C=N), and 1531 (C=C)
8d	^{1}H NMR: 2.64 (s 3H), 7.25–8.07 (m, 12H), and 9.04 (s, 1H) IR: 1681 (CO), 1589 (C=N), and 1527 (C=C)
8e	^{1}H NMR: 7.20–7.69 (m, 10H), 7.88–8.05 (m, 6H), 8.46 (s, 1H), and 8.87–8.91 (d, 1H) IR: 1739 (CO), 1589 (C=N), and 1535 (C=C)
8f	^{1}H NMR: 7.25 (m, 3H), 7.44–8.84 (m, 12H), and 9.04 (s, 1H) IR: 1700 (CO), 1585 (C=N), and 1535 (C=C)
8g	^{1}H NMR: 7.01–6.96 (m, 19H), and 8.09 (s, 1H) IR: 1620 (CO), 1585 (C=N), and 1546 (C=C)
12a	^{1}H NMR: 1.44 (t, 3H), 4.46 (q, 2H), 7.25–8.05 (m, 12H), and 9.05 (s, 1H) IR: 1710 (CO), 1608 (C=N), and 1546 (C=C)
12b	^{1}H NMR: 4.01 (s, 3H), 7.25–8.16 (m, 12H), and 8.86 (s, 1H) IR: 1710 (CO), 1608 (C=N), and 1577 (C=C)
12c	^{1}H NMR: 6.91 (s, NH), 7.25–8.05 (m, 17H), and 8.95 (s, 1H) IR: 3285 (NH), 1689 (C=O), 1604 (C=N), and 1527 (C=C)
12d	^{1}H NMR: 2.62 (s, 3H), 7.24–8.06 (m, 12H), and 8.54 (s, 1H) IR: 1681 (CO), 1589 (C=N), and 1527 (C=C)
12e	^{1}H NMR: 7.24–8.01 (m, 17H) and 8.21 (s, 1H) IR: 1631 (CO), 1612 (C=N), and 1550 (C=C)
12f	^{1}H NMR: 7.21–8.12 (m, 15H) and 8.34 (s, 1H) IR: 1650 (CO), 1585 (C=N), and 1535 (C=C)

(*continued*)

Table 3. Continued.

Compd.	Spectra
12g	^{1}H NMR: 7.12–8.51 (m, 19H) and 9.01 (s, 1H) IR: 1650 (CO), 1585 (C=N), and 1535 (C=C)
13a	^{1}H NMR: 1.60 (t, 3H), 2.64 (s, 3H), 4.64 (q, 2H), and 7.1–8.4 (m, 12H) IR: 1712 (CO), 1598 (C=N), and 1573 (C=C)
13b	^{1}H NMR: 2.54 (s, 3H), 4.31 (s, 3H), and 7.20–8.19 (m, 12H) IR: 1712 (CO), 1598 (C=N), and 1573 (C=C)
13c	^{1}H NMR: 2.59 (s, 3H), 7.19–8.26 (m, 17H), and 8.46 (s, br, 1H) IR: 3359 (NH), 1666 (CO), and 1593 (C=N)
13d	^{1}H NMR: 2.59 (s, 3H), 2.67 (s, 3H), and 7.21–8.25 (m, 12H) IR: 1670 (CO), 1608 (C=N), and 1550 (C=C)
13e	^{1}H NMR: 2.60 (s, 3H) and 6.84–8.30 (m, 17H) IR: 1670 (CO), 1608 (C=N), and 1550 (C=C)
13f	^{1}H NMR: 2.45 (s, 3H) and 7.06–7.96 (m, 15H) IR: 1604 (CO) and 1550 (C=N)
13g	^{1}H NMR: 2.67 (s, 3H), 7.26–8.30 (m, 19H) and 9.02 (s, 1H) IR: 1660 (CO), 1600 (C=N), and 1530 (C=C)
14a	^{1}H NMR: 1.46 (t, 3H), 2.64 (s, 3H), 4.51 (q, 2H), and 7.15–8.22 (m, 12H) IR: 1712 (CO), 1598 (C=N), and 1573 (C=C)
14b	^{1}H NMR: 2.64 (s, 3H), 4.1 (s, 3H), and 7.15–8.20 (m, 12H) IR: 1712 (CO), 1598 (C=N), and 1573 (C=C)
14c	^{1}H NMR: 2.59 (s, 3H), 7.19–8.26 (m, 17H), and 8.46 (s, br, 1H) IR: 3200 (NH), 1712 (CO), 1598 (C=N), and 1573 (C=C)
14d	^{1}H NMR: 2.60 (s, 3H), 2.65 (s, 3H), and 7.26–8.41 (m, 12H) Mass: 386 (17.02), 153 (100), 127 (35), 77 (23), and 305 (11.35) IR: 1712 (CO), 1598 (C=N), and 1573 (C=C)
14e	^{1}H NMR: 2.60 (s, 3H) and 6.84–8.30 (m, 17H) IR: 1631 (CO), 1577 (C=N), and 1550 (C=C)
14f	^{1}H NMR: 2.45 (s, 3H) and 7.06–7.96 (m, 15H) IR: 1681 (CO), 1593 (C=N), and 1546 (C=C)
14g	^{1}H NMR: 2.64 (s, 3H) and 7.26–8.41 (m, 19H) IR: 1681 (CO), 1593 (C=N), and 1546 (C=C)
16a	^{1}H NMR: 1.43 (t, 3H), 2.61 (s, 3H), 4.12 (q, 2H), 6.41 (s, 1H), 7.23–7.94 (m, 7H), 8.01 (s, 1H), and 9.00 (s, br, 1H) IR: 3300 (NH), 1700 (CO), and 1593 (C=C)
16b	^{1}H NMR: 2.56 (s, 3H), 3.61 (s, 3H), 6.42 (s, 1H), 7.26–7.94 (m, 7H), 8.05 (s, 1H), and 8.50 (s, br, 1H) IR: 3220 (NH), 1704 (CO), and 1595 (C=C)
16c	^{1}H NMR: 2.61(s, 3H), 3.55 (s, 3H), 5.35 (s, 1H), 7.31–8.02 (m, 7H), 8.04 (s, 1H), and 8.55 (s, br, 1H) IR: 3280 (NH), 1706 (CO), and 1598 (C=C)
18a	^{1}H NMR: 1.43 (t, 3H), 2.32 (s, 3H), 2.50 (s, 3H), 4.12 (q, 2H), 5.38 (s, 1H), 7.26–7.91 (m, 7H), and 8.71 (s, 1H) IR: 3300 (NH), 1700 (CO), and 1593 (C=C)
18b	^{1}H NMR: 2.32 (s, 3H), 2.50 (s, 3H), 3.78 (s, 3H), 5.38 (s, 1H), 7.26–7.91 (m, 7H), and 8.71 (s, 1H) IR: 3300 (NH), 1700 (CO), and 1593 (C=C)
18c	^{1}H NMR: 2.13 (s, 3H), 2.45 (s, 3H), 3.73 (s, 3H), 5.38 (s, 1H), 7.26–7.91 (m, 7H), and 8.71 (s, 1H) IR: 3300 (NH), 1700 (CO), and 1593 (C=C)
23a	^{1}H NMR: 1.01 (t, 3H), 1.23 (t, 3H), 2.53 (s, 3H), 3.95 (q, 2H), 4.15 (q, 2H), 7.25–7.72 (m, 12H), and 8.24 (s, br, 1H) IR: 1735(CO), 1689 (CO conjugated), and 1608 (C=N)
23b	^{1}H NMR: 1.23 (t, 3H), 2.56 (s, 3H), 4.09 (q, 2H), 3.68 (s, 3H), 7.33–7.78 (m, 12H), and 8.02 (s, br, 1H) IR: 1702 (CO), 1697 (CO conjugated), and 1612 (C=N)
23c	^{1}H NMR: 1.24 (t, 3H), 2.56 (s, 3H), 4.12 (q, 2H), 7.23–8.02 (m, 17H), 8.22 (s, 1H), and 8.46 (s, br, 1H) IR: 3394 (NH), 1693 (CO), and 1600 (C=N).
23d	^{1}H NMR: 1.23 (t, 3H), 2.58 (s, 3H), 2.65 (s, 3H), 4.12 (q, 2H), 7.32–7.91 (m, 12H), and 8.21 (s, 1H) IR: 1697 (CO), 1635 (C=N), and 1535 (C=C)
23e	^{1}H NMR: 1.24 (t, 3H), 2.56 (s, 3H), 4.14 (q, 2H), 7.23–8.11 (m, 17 H), and 8.41 (s, 1H) IR: 1666 (CO), 1608 (C=N), and 1535 (C=C)
23f	^{1}H NMR: 1.25 (t, 3H), 2.61 (s, 3H), 4.21 (q, 2H), 7.12–8.21 (m, 15 H), and 8.31 (s, 1H) IR: 1697 (CO), 1635 (C=N), and 1535 (C=C)
23g	^{1}H NMR: 1.22 (t, 3H), 2.65 (s, 3H), 4.05 (q, 2H), 7.23–8.02 (m, 19H), and 8.42 (s, 1H) IR: 1685 (CO), 1631 (C=N), and 1519 (C=C)

(*continued*)

Table 3. Continued.

Compd.	Spectra
24a	^{1}H NMR: 1.01 (t, 3H), 1.23 (t, 3H), 2.52 (s, 3H), 3.95 (q, 2H), 4.15 (q, 2H), 7.18–7.92 (m, 12H), and 8.24 (s, br., 1H) IR: 1751 (CO), 1685 (CO-conjugated), and 1608 (C=N)
24b	^{1}H NMR: 1.12 (t, 3H), 2.54 (s, 3H), 3.51 (s, 3H), 4.18 (q, 2H), 7.16–7.81 (m, 12H), and 8.02 (s, br., 1H) IR: 1712 (CO), 1697 (CO-conjugated), 1604 (C=N), and 1539 (C=C)
24c	^{1}H NMR: 2.53 (s, 3H), 3.60 (s, 3H), and 7.01–8.21 (m, 19H) IR: 3386 (NH), 1689 (CO), 1608 (C=N), and 1542 (C=C)
24d	^{1}H NMR: 2.34 (s, 3H), 2.65 (s, 3H), 3.61 (s, 3H), 7.18–8.0 (m, 12H), and 8.23 (s, 1H) IR: 1689 (CO), 1608 (C=N), and 1542 (C=C)
24e	^{1}H NMR: 2.53 (s, 3H), 3.95 (s, 3H), 7.15 (m, 5H), 7.44–7.89 (m, 12H), and 8.24 (s, 1H) IR: 1678 (CO), 1654 (C=N), and 1542 (C=C)
24f	IR: 1678 (CO), 1631 (C=N), and 1608 (C=C)
24g	^{1}H NMR: 2.65 (s, 3H), 3.52 (s, 3H), 7.41 (m, 7H), 7.6–8.07 (m, 12H), and 8.19 (s, 1H) IR: 1697 (CO), 1654 (C=N), and 1608 (C=C)
25a	^{1}H NMR: 1.25 (t, 3H), 2.54 (s, 3H), 3.63 (s, 3H), 4.36 (q, 2H), 7.04 (s, 1H), and 7.25–8.19 (m, 12H) IR: 1735 (CO), 1697 (CO conjugated), and 1612 (C=N)
25b	^{1}H NMR: 2.54 (s, 3H), 3.51 (s, 3H), 4.10 (s, 3H), 7.12 (s, 1H), and 7.31–8.21 (m, 12H) IR: 1735 (CO-ester), 1697 (CO-conjugated), and 1612 (C=N)
25c	^{1}H NMR: 2.54 (s, 3H), 3.70 (s, 3H), 7.01 (s, 1H), 7.21–8.22 (m, 17H), and 8.31 (s, 1H)
25d	^{1}H NMR: 2.56 (s, 3H), 2.72 (s, 3H), 3.61 (s, 3H), 7.12 (s, 1H), and 7.31–8.22 (m, 12H)
25e	IR: 1660 (CO), 1608 (C=N), and 1542 (C=C)
25f	^{1}H NMR: 2.63 (s, 3H), 3.62 (s, 3H), 7.22 (m, 3H), 7.34–8.11 (m, 12H), and 8.23 (s, 1H) IR: 1678 (CO), 1654 (C=N), and 1542 (C=C)
25g	^{1}H NMR: 2.65 (s, 3H), 3.50 (s, 3H), and 7.24–8.52 (m, 20 H) IR: 1689 (CO), 1608 (C=N), and 1542 (C=C)

3.2 *Synthesis of 2,3-dihydro-1,3,4-thiadiazoles 8, 12–14a–g*

A mixture of the appropriate alkyl carbodithioate **3a–d** or **4a–d** (5 mmol), the appropriate hydrazonoyl halide **5a–g** (5 mmol), and triethylamine (0.75 mL, 0.005 mol) in ethanol (20 mL) was stirred for 2 h at room temperature. The resulting solid was collected and crystallized to give the corresponding 2,3-dihydro-1,3,4-thiadiazole **8**, **12–14a–g**, respectively (Tables 2 and 3).

3.3 *Synthesis of ethyl and methyl 6-methyl-2-methylthio-4-(1- or 2-naphthyl)-1,6-dihydropyrimidine-5-carboxylates 18a–c. General method*

Methyl iodide (0.71 g, 5 mmol) was added dropwise to a solution of the appropriate pyrimidine-2-thione derivative **16a–c** in ethanolic sodium ethoxide (5 mmol; 20 mL) and stirring was continued at room temperature for 3 h. The resulting solid was collected and crystallized to give the corresponding sulfide **18a–c**, respectively (Tables 2 and 3).

3.4 *Synthesis of triazolo[4,3-a]pyrimidines derivatives 23–25a–g*

3.4.1 Method A. Equimolar amounts of the appropriate hydrazonoyl halide **5a–g** and the appropriate pyrimidine-2-thione derivative **16a–c**, together with triethylamine (5 mmol each) in chloroform (20 mL), were boiled under reflux for 10 h. The chloroform was evaporated off under reduced pressure and the resulting solid was collected and crystallized to give the corresponding triazolo[4,3-*a*]pyrimidine derivative **23–25a–g**, respectively (Tables 2 and 3).

3.4.2 Method B. A mixture of the appropriate hydrazonoyl halide **5a–g**, the appropriate derivative **18a–c**, and triethylamine (5 mmol each) in ethanol (20 mL) was boiled under reflux for 3 h. The resulting solid was collected, and crystallized from ethanol to give the corresponding triazolo[4,3-*a*]pyrimidine derivative **23–25a–g**, respectively (Tables 2 and 3).

3.5 *Synthesis of ethyl or methyl 4-methyl-6-(1- or 2-naphthyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 16a–c. General method*

A mixture of the appropriate naphthalene-1-carbaldehyde **1a** or naphthalene-2-carbaldehyde **1b**, the appropriate ethyl acetoacetate (or methyl acetoacetate), and thiourea (5 mmol each) was refluxed in ethanol (40 mL) containing hydrochloric acid (1 mL; 12M) for 6 h. The reaction mixture was left overnight and the resulting solid was collected, and crystallized from ethanol to give the corresponding thione **16a–c**, respectively (Tables 2 and 3).

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