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Original article

Synthesis and antimicrobial evaluation of some new thiazole, thiazolidinone and thiazoline derivatives starting from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde

Samir Bondock*, Wesam Khalifa, Ahmed A. Fadda

Department of Chemistry, Faculty of Science, Mansoura University, El-gomhuria street, El-Dakhlia, ET-35516 Mansoura, Egypt

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Abstract

The thiosemicarbazones (**3** and **6**) and *N*-arylidene cyanoacetohydrazide (**12**) were prepared and used as key intermediates for the synthesis of 4-thiazolidinones (**4**, **5**, **7**–**9**), thiazoles (**10a**,**b** and **11a**–**d**) and thiazoline (**13**) derivatives. Treatment of **13** with a mixture of triethylorthoformate and acetic anhydride afforded thiazolo[5,4-*d*]pyrimidinone derivative (**14**). The newly synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral studies. Representative compounds of the synthesized products were tested and evaluated as antimicrobial agents.

Keywords: Thiazoles; Thiazolines; Thiazolidinones; 1-Chloro-3,4-dihydronaphthalene-2-carboxaldehyde; Thiosemicarbazone; Antimicrobial activity

1. Introduction

Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities [1,2], recently found application in drug development for the treatment of allergies [3], hypertension [4], inflammation [5], schizophrenia [6], bacterial [7], HIV infections [8], hypnotics [9] and more recently for the treatment of pain [10], as fibrinogen receptor antagonists with antithrombotic activity [11] and as new inhibitors of bacterial DNA gyrase B [12]. In view of the above mentioned findings and as continuation of our effort [13–15] to identify new candidates that may be value in designing new, potent, selective and less toxic antimicrobial agents, we report in the present work the synthesis of some new thiazole, thiazolidinone, and thiazoline derivatives starting from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde [16] in order to investigate their antimicrobial activity.

2. Results and discussion

2.1. Chemistry

The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1–3. The key intermediate **3** was prepared in an excellent yield in two consequence steps by condensing 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde (**1**) with hydrazine hydrate to afford Schiff's base **2**, which was added to phenyl isothiocyanate in boiling dioxane. To investigate the structure–activity relationship with respect to antimicrobial properties we cyclized the thiosemicarbazide functionality into thiazolidinone. Thus, refluxing **3** in glacial acetic acid with chloroacetic acid and in the presence of anhydrous sodium acetate revealed formation of 2-(2-((4-chloro-1,2-dihydronaphthalen-3-yl)methylene)hydrazono)-3-phenylthiazolidin-4-one (**4**). Compound **4** was characterized by the presence of a strong band at 1722 cm^{-1} in the IR spectrum. This is considered to be a strong confirmation for the thiazolidinone nucleus formation. Another piece of evidence for cyclization is the appearance of a singlet signal, equivalent to two protons in the ^{1}H NMR spectrum at 4.05 ppm which represents the C-5 protons

* Corresponding author. Tel.: +20 502369267; fax: +20 502246781.
E-mail address: Bondock@mans.edu.eg (S. Bondock).

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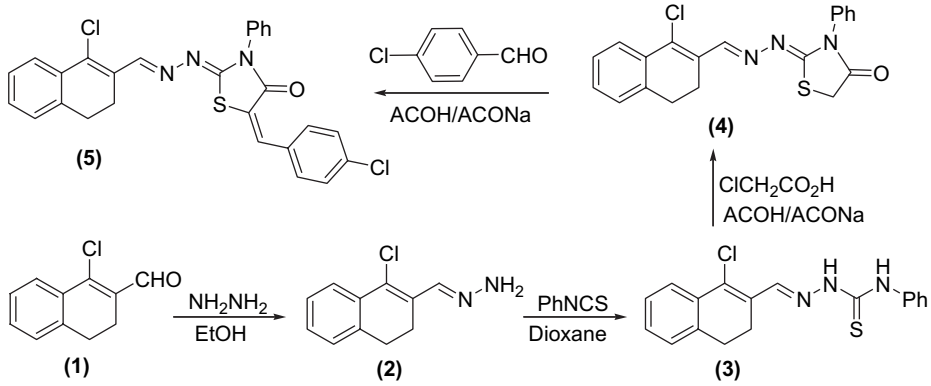
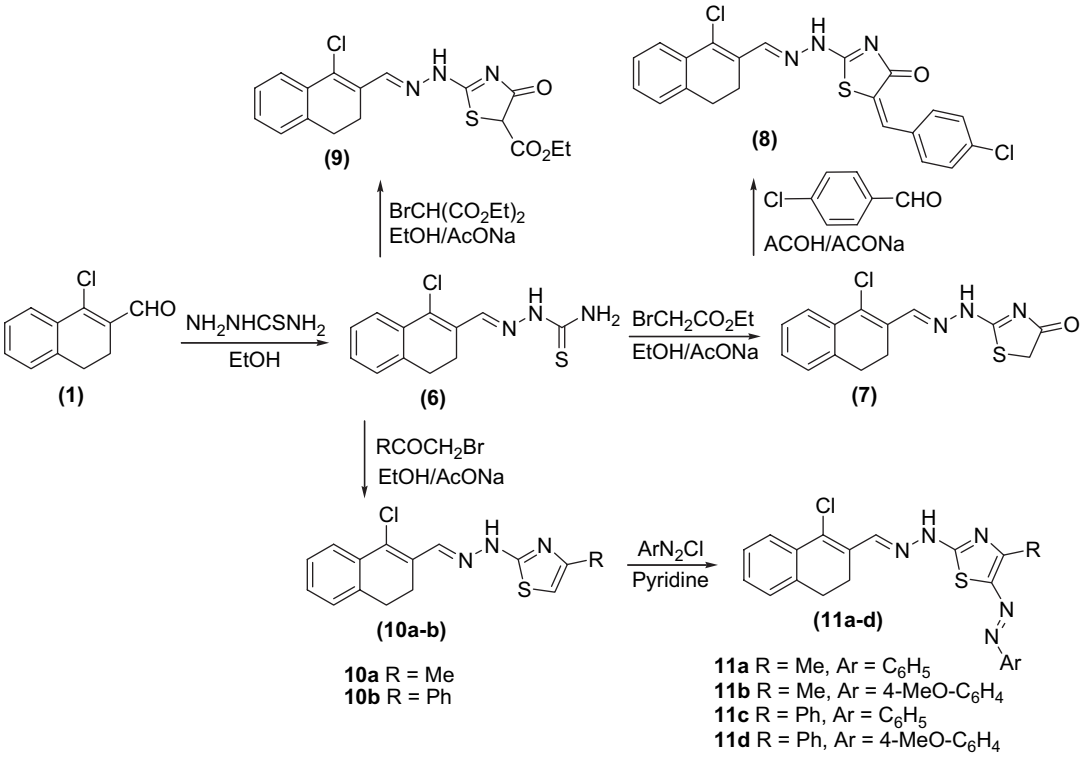


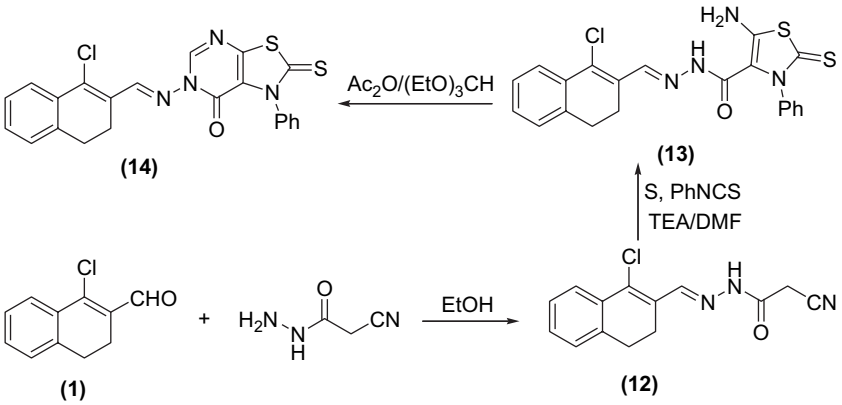
Scheme 1.

of the thiazolidine nucleus. Condensation of compound **4** with 4-chlorobenzaldehyde in the presence of fused sodium acetate in boiling acetic acid yielded the target 2-(2-((4-chloro-1,2-dihydronaphthalen-3-yl)methylene)hydrazono)-5-(4-chlorobenzylidene)-3-phenylthiazolidin-4-one (**5**).

Furthermore, the intermediate **6** represent a versatile building block for the synthesis of new heterocycles incorporating thiazole nucleus, was synthesized by heating **1** with thiosemicarbazide in ethanol. Thus, treatment of thiosemicarbazone derivative **6** with ethyl bromoacetate and/or diethyl 2-bromomalonate in refluxing ethanol containing a catalytic amount of freshly fused sodium acetate afforded a single product which analysed correctly for **7** ($C_{14}H_{12}ClN_3OS$) and **9** ($C_{17}H_{16}ClN_3O_3S$), respectively. The structure of compound **7** was identified as 2-(2-((4-chloro-1,2-dihydronaphthalen-3-yl)-methylene)hydrazinyl)thiazol-4(5*H*)-one on the basis of its spectral data as well as its chemical transformation, where it is condensed with 4-chlorobenzaldehyde (Aldol type condensation) by refluxing in acetic acid containing freshly fused sodium acetate as basic catalyst to give the corresponding arylidene derivative **8**. The mass spectrum of **8** showed a molecular ion peak at *m/z* 393 (M^+). In addition, the thiazole derivatives **10a** and **10b** were synthesized in good yields by the treatment of thiosemicarbazone derivative **6** with bromoacetone and/or phenacyl bromide in boiling ethanol in the presence of anhydrous sodium acetate following Hantzsch thiazole synthesis [17]. The mass spectra of compounds **10a** and **10b** showed their molecular ion peak at *m/z* 303 (M^+)



Scheme 2.



Scheme 3.

and 365 (M^+), respectively. The obtained thiazoles **10a** and **10b** seemed to be also a good precursor. The free 5-position was found to be active toward the diazotized aromatic amines and couples readily with them to afford the azo derivatives **11a–d**, as highly colored solid compounds with relatively high melting point on the basis of their elemental analyses and spectral data. However, the appearance of N=N band at 1570–1550 cm^{-1} region in the IR spectra of the isolated products and the lack of signals due to C-5 proton of thiazole ring in their ^1H NMR spectra provided a firm support for compounds **11a–d**. The mass spectra of compounds **11b** and **11c** showed their molecular ion peak at *m/z* 438 ($M^+ + 1$) and 469 (M^+), respectively. The azo derivatives of similar thiazoles have found wide applications in the dyeing of synthetic fibers [18,19] and the azo derivatives described in the present work may find similar applications.

In view of the growing biological importance of fused thiazoles, and particularly of the thiazolo[4,5-*d*]pyrimidines, it was considered of interest to synthesize novel 6-{[(1-chloro-3,4-dihydronaphthalene-2-yl)methylene]amino}-1-phenyl-2-thioxo-1,6-dihydro[1,3]thiazolo[5,4-*d*]pyrimidin-7(2*H*)-one (**14**). This bicyclic system is considered as a 7-thia analogue of the natural purine bases, adenine and guanine. The key intermediate **12** was prepared in an excellent yield by condensing **1** with cyanoacetic acid hydrazide [20]. Taking advantage of the Gewald reaction [21] and using the Schiff's base of cyanoacetic acid hydrazide **12**, as the nitrile containing active methylene moiety, 5-amino-*N*′-[1-chloro-3,4-dihydronaphthalen-2-yl)methylene]-3-phenyl-2-thioxo-2,3-dihydro-1,3-thiazole-4-carbohydrazide (**13**) was prepared by the reaction of **12** with sulfur and phenyl isothiocyanate in the presence of triethylamine as a basic catalyst. The thiazolo[5,4-*d*]pyrimidinone derivative **14** was prepared by heating **13** with a mixture of triethylorthoformate and acetic anhydride (1:1). The structure of the prepared compounds was elucidated on the basis of elemental analysis and spectral data. The IR spectrum of compound **13** showed three strong absorption bands in the NH region at 3300, 3265 and 3145 cm^{-1} and a strong hydrazide C=O at 1665 cm^{-1}. The ^1H NMR spectrum of compound **14** was characterized by the existence of the thiazolopyrimidine C-5-H at 9.24 ppm. Its IR spectrum showed an absorption band due to C=O at 1675 cm^{-1} due to C-7-pyrimidone.

3. Pharmacology

3.1. Antimicrobial evaluation

Thirteen compounds were screened *in vitro* for their antimicrobial activities against three strains of bacteria *Bacillus subtilis*, *Bacillus megaterium*, *Escherichia coli*, and two strains of fungi *Aspergillus niger* and *Aspergillus oryzae* by the agar diffusion technique [23]. A 1 mg/mL solution in dimethylformamide was used. The bacteria and fungi were maintained on nutrient agar and Czapek's-Dox agar media, respectively. DMF showed no inhibition zones. The agar media were incubated with different microorganisms culture tested. After 24 h of incubation at 30 °C for bacteria and 48 h of incubation at 28 °C for fungi, the diameter of inhibition zone (mm) was measured (Table 1). Ampicillin, chloramphenicol, and fluconazole were purchased from Egyptian market and used in a concentration of 25 μg/mL as references for antibacterial and antifungal activities. The results depicted in Table 1 revealed that while most of the prepared thiazolidinones **4**, **5**, and **7–9** showed comparable activity, the thiazole **11b** and **11d**, thiazoline **13** and thiazolo[5,4-*d*]pyrimidine **14** derivatives revealed very high activity with respect to the used references. On the other hand, nearly all of the prepared compounds exhibited an interesting high antifungal activity against the reference chemotherapeutics.

In conclusion, we reported herein a convenient route for the synthesis of some new thiazole derivatives for antimicrobial evaluation *via* the reaction of thiosemicarbazone derivatives with α-halocarbonyl compounds and/or the Gewald reaction of *N*-arylidene cyanoacetic acid hydrazide starting from 1-chloro-3,4-dihydronaphthalene-2-carbaldehyde.

4. Experimental

All melting points were determined with a Büchi melting point apparatus (type Nr. 535) and are uncorrected. IR spectra were recorded for KBr disc on a Mattson 5000 FTIR spectrophotometer. ^1H NMR spectra were measured on a Bruker AC 300 (300 MHz) in $CDCl_3$ or DMSO-d_6 as solvent, using TMS as an internal standard, and chemical shifts are expressed as δ_{ppm}. Mass spectra were determined on Finnigan Incos 500

Table 1
Inhibition zone (mean diameter of inhibition in mm) as a criterion of antibacterial and antifungal activities of the newly synthesized thiazole, thiazolidinone and thiazoline derivatives

Compound	Inhibition zone in mm				
	Bacteria			Fungi	
	Gram positive bacteria		Gram negative bacteria	*A. niger*	*A. oryzae*
	B. subtilis	*B. megaterium*	*E. coli*		
4	66	55	–	63	71
5	42	43	–	58	69
7	35	40	30	66	78
8	34	34	25	75	74
9	42	35	–	69	73
10a	55	60	40	72	75
10b	65	68	56	77	79
11a	81	86	60	84	89
11b	87	85	50	80	86
11c	85	79	49	79	82
11d	90	84	55	75	86
13	89	82	60	64	75
14	95	92	85	78	86
Reference drugs					
Ampicillin	40	29	26	33	–
Chloramphenicol	30	55	48	35	–
Fluconazole	–	–	–	22	16

(70 ev). Elemental analyses were carried out in the Microanalytical Unit of the Faculty of Science, Cairo University. 1-Chloro-3,4-dihydronaphthalene-2-carboxaldehyde (**1**) [16] and 1-((4-chloro-1,2-dihydronaphthalen-3-yl)methylene)hydrazine (**2**) [22] were prepared by a previously reported procedure.

*4.1. 1-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)-4-phenylthiosemicarbazide (**3**)*

To a boiling solution of compound **2** (2 g, 0.01 mol) in dioxane (10 mL), phenyl isothiocyanate (1.3 mL, 0.01 mol) was added. The reaction mixture was heated under reflux for 1 h. The reaction mixture was left to stand at room temperature overnight; the solid product which separated was filtered off, washed with ether, dried, and recrystallized from dioxane to give compound **3**.

Yellow crystals; yield 77%; mp 190–192 °C; IR (KBr): $\nu/cm^{-1} = 3215–3180$ (NH), 1640 (C=C), 1595 (C=N), 1288 (C=S). ^1H NMR ($CDCl_3$): $\delta_{ppm} = 2.90$ (t, $J = 2.4$ Hz, 2H, CH_{2ring}), 3.22 (t, $J = 2.4$ Hz, 2H, CH_{2ring}), 7.18–7.63 (m, 9H, Ar-H), 8.21 (s, 1H, CH=N), 9.0 (s, 1H, NH-exchangeable), 9.91 (s, 1H, NH-exchangeable). Anal. Calcd. for $C_{18}H_{16}ClN_3S$ (341.86): C 63.24; H 4.72; N 12.29%. Found: C 63.52; H 4.61; N 12.42%.

*4.2. 2-(2-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)hydrazono)-3-phenylthiazolidin-4-one (**4**)*

A mixture of compound **3** (3.2 g, 0.01 mol), chloroacetic acid (1 g, 0.01 mol) and anhydrous sodium acetate (0.82 g, 0.01 mol) in glacial acetic acid (15 mL) was heated under reflux for 8 h. The reaction mixture was left to cool, poured into ice cold water, and the separated solid was filtered off, washed with water and recrystallized from a mixture of EtOH–DMF (2:1) to give compound **4**.

Red crystals; yield 67%; mp 250–252 °C; IR (KBr): $\nu/cm^{-1} = 1722$ (C=O), 1645 (C=C), 1596 (C=N). ^1H NMR (DMSO-d_6): $\delta_{ppm} = 2.92$ (t, $J = 2.4$ Hz, 2H, CH_{2ring}), 3.25 (t, $J = 2.4$ Hz, 2H, CH_{2ring}), 4.05 (s, 2H, S–CH_2), 7.28–7.83 (m, 9H, Ar-H), 8.35 (s, 1H, CH=N). MS: m/z (%) = 381 (M^+, 30), 346 (85), 193 (26), 119 (100), 91 (26). Anal. Calcd. for $C_{20}H_{16}ClN_3OS$ (381.88): C 62.90; H 4.22; N 11.00%. Found: C 62.71; H 4.28; N 11.12%.

*4.3. 2-(2-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)hydrazono)-5-(4-chlorobenzylidene)-3-phenylthiazolidin-4-one (**5**)*

To a solution of compound **4** (0.38 g, 0.001 mol) and anhydrous sodium acetate (0.12 g, 0.0015 mol) in glacial acetic acid (10 mL), was added 4-chlorobenzaldehyde (0.15 g, 0.001 mol). The mixture was heated under reflux for 6 h, where upon the solid product partially crystallized out. The reaction mixture was left to cool and the separated solid product was filtered off, washed with water, dried, and recrystallized from acetic acid to give compound **5**.

Yellow crystals; yield 65%; mp 286–288 °C; IR (KBr): $\nu/cm^{-1} = 1715$ (CO), 1620 (C=C), 1603 (C=N). ^1H NMR (DMSO-d_6): $\delta_{ppm} = 2.91$ (t, $J = 2.5$ Hz, 2H, CH_{2ring}), 3.26 (t, $J = 2.5$ Hz, 2H, CH_{2ring}), 7.3, 7.8 (two d, $J = 7.5$ Hz, each 2H, C_6H_4–Cl), 7.4–7.7 (m, 9H, Ar-H), 7.84 (s, 1H, olefinic CH=), 8.37 (s, 1H, CH=N). Anal. Calcd. for $C_{27}H_{19}Cl_2N_3OS$ (503.43): C 64.29; H 3.80; N 8.33%. Found: C 64.32; H 3.74; N 8.51%.

*4.4. 1-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)thiosemicarbazide (**6**)*

To a solution of compound **1** (1.92 g, 0.01 mol) in ethanol (20 mL) was added an equimolar amount of thiosemicarbazide (0.91 g, 0.01 mol). The reaction mixture was heated under reflux for 3 h, partially concentrated and cooled. The separated solid product was filtered off, dried, and recrystallized from ethanol to give compound **6**.

Yellow crystals; yield 85%; mp 236 °C; IR (KBr): $\nu/cm^{-1} = 3375–3262$ (NH_2), 3221(NH), 1620 (C=C), 1605 (C=N), 1360 (C=S). ^1H NMR ($CDCl_3$): $\delta_{ppm} = 2.93$ (t, $J = 2.4$ Hz, 2H, CH_{2ring}), 3.20 (t, $J = 2.4$ Hz, 2H, CH_{2ring}), 7.25–7.58 (m, 4H, Ar-H), 8.25 (s, 1H, CH=N), 9.2 (s, 1H, NH-exchangeable), 9.91 (s, 2H, NH_2-exchangeable). MS: m/z (%) = 265 (M^+, 55), 189 (60), 170 (53), 154 (100), 127 (75), 71 (84), 60 (83). Anal. Calcd. for $C_{12}H_{12}ClN_3S$ (265.76): C 54.23; H 4.55; N 15.81%. Found: C 54.39; H 4.48; N 15.92%.

*4.5. 2-(2-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)hydrazinyl)thiazol-4(5H)-one (**7**)*

A mixture of compound **6** (1.3 g, 0.005 mol), ethyl bromoacetate (0.83 g, 0.005 mol), anhydrous sodium acetate (1.64 g,

0.02 mol), and absolute ethanol (30 mL) was refluxed for 8 h. The product obtained upon cooling was collected by filtration, washed with water, dried, and recrystallized from a mixture of EtOH–DMF (1:1) to give compound **7**.

Yellow crystals; yield 70%; mp 255–257 °C; IR (KBr): ν/cm^{-1} = 3240 (NH), 1716 (C=O), 1600 (C=N), 767 (C–Cl). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.90 (t, J = 2.4 Hz, 2H, CH_{2ring}), 3.18 (t, J = 2.4 Hz, 2H, CH_{2ring}), 4.01 (s, 2H, S–CH_2), 7.18–7.42 (m, 4H, Ar-H), 8.35 (s, 1H, CH=N), 9.11 (s, 1H, NH-exchangeable). MS: m/z (%) = 306 ($M^+ + 1$, 25), 270 (41), 171 (70), 115 (65), 77 (100), 63 (52). Anal. Calcd. for $C_{14}H_{12}ClN_3OS$ (305.78): C 54.99; H 3.96; N 13.74%. Found: C 54.91; H 3.93; N 13.80%.

*4.6. 2-(2-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)hydrazinyl)-5-(4-chlorobenzyliden)thiazol-4 (5H)-one (**8**)*

A mixture of compound **7** (0.3 g, 0.001 mol), 4-chlorobenzaldehyde (0.15 g, 0.001 mol) and anhydrous sodium acetate (0.32 g, 0.004 mol) in glacial acetic acid (20 mL) was refluxed for 6 h. After cooling the mixture, the precipitated solid was filtered off, washed with water and recrystallized from acetic acid to give compound **8**.

Yellow crystals; yield 68%; mp 279–281 °C; IR (KBr): ν/cm^{-1} = 3245 (NH), 1695 (CO), 1612 (C=C), 1595 (C=N). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.96 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.32 (t, J = 2.5 Hz, 2H, CH_{2ring}), 7.2, 7.7 (two d, J = 7.5 Hz, each 2H, C_6H_4–Cl), 7.35–7.65 (m, 4H, Ar-H), 7.94 (s, 1H, olefinic CH=), 8.42 (s, 1H, CH=N), 9.15 (s, 1H, NH-exchangeable). Anal. Calcd. for $C_{21}H_{15}C1_2N_3OS$ (427.03): C 58.89; H 3.53; N 9.81%. Found: C 58.81; H 3.50; N 9.78%.

*4.7. Ethyl 2-(2-((4-chloro-1,2-dihydronaphthalen-3-yl)-methylene)hydrazinyl)-4,5-dihydro-4-oxothiazol-5-carboxylate (**9**)*

A mixture of compound **6** (1.3 g, 0.005 mol), diethyl 2-bromomalonate (1.2 g, 0.005 mol), anhydrous sodium acetate (1.64 g, 0.02 mol), and absolute ethanol (30 mL) was refluxed for 8 h. The product obtained upon cooling was collected by filtration, washed with water, dried, and recrystallized from a mixture of EtOH–DMF (1:1) to give compound **9**.

Orange crystals; yield 78%; mp 280–282 °C; IR (KBr): ν/cm^{-1} = 3290 (NH), 1740 (CO), 1710 (ring CO), 1635 (C=C), 1600 (C=N). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.05 (t, J = 7.5 Hz, 3H, CH_3–CH_2), 2.89 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.26 (t, J = 2.5 Hz, 2H, CH_{2ring}), 4.21 (q, J = 7.5 Hz, 2H, OCH_2–CH_3), 4.81 (s, 1H, S–CH), 7.23–7.45 (m, 4H, Ar-H), 8.31 (s, 1H, CH=N), 8.98 (s, 1H, NH-exchangeable). Anal. Calcd. for $C_{17}H_{16}ClN_3O_3S$ (377.85): C 54.04; H 4.27; N 11.12%. Found: C 54.08, H 4.30; N 11.13%.

*4.8. General procedure for the synthesis of thiazole derivatives (**10a–b**)*

To a solution of thiosemicarbazone **6** (1.3 g, 0.005 mol) in absolute ethanol (10 mL) were added equimolar amounts (0.005 mol) of the appropriate α-haloketone (bromoacetone or phenacyl bromide) and anhydrous sodium acetate (1.6 g, 0.02 mol). The reaction mixture was heated under reflux for 6 h, concentrated and left to cool. The separated solid product was filtered off, dried, and recrystallized from a mixture of EtOH–$CHCl_3$ (1:1).

*4.8.1. N-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)-N′-(4-methylthiazol-2-yl)hydrazine (**10a**)*

Orange powder; yield 77%; mp 202–204 °C; IR (KBr): ν/cm^{-1} = 3310 (NH), 1625 (C=C), 1594 (C=N), 760 (C–Cl). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.11 (s, 3H, CH_3), 2.94 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.22 (t, J = 2.5 Hz, 2H, CH_{2ring}), 7.18–7.38 (m, 4H, Ar-H), 7.71 (s, 1H, Thiazole-H5), 8.42 (s, 1H, CH=N), 9.48 (s, 1H, NH-exchangeable). MS: m/z (%) = 303 (M^+, 30), 268 (21), 239 (16), 190 (25), 162 (41), 128 (55), 114 (100), 69 (62). Anal. Calcd. for $C_{15}H_{14}C1N_3S$ (303.81): C 59.30; H 4.64; N 13.83%. Found: C 59.38; H 4.59; N 13.80%.

*4.8.2. N-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)-N′-(4-phenylthiazol-2-yl)hydrazine (**10b**)*

Yellow crystal; yield 78%; mp 260–262 °C; IR (KBr): ν/cm^{-1} = 3285 (NH), 1630 (C=C), 1598 (C=N), 765 (C–Cl). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.90 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.26 (t, J = 2.5 Hz, 2H, CH_{2ring}), 7.22–7.46 (m, 9H, Ar-H), 7.62 (s, 1H, Thiazole-H5), 8.38 (s, 1H, CH=N), 9.32 (s, 1H, NH-exchangeable). MS: m/z (%) = 365 (M^+, 29), 329 (18), 207 (12), 176 (100), 134 (82), 128 (62), 77 (40). Anal. Calcd. for $C_{20}H_{16}C1N_3S$ (362.88): C 65.65; H 4.41; N 11.48%. Found: C 65.69; H 4.46; N 11.46%.

*4.9. General procedure for the synthesis of 5-arylazothiazole derivatives (**11a–d**)*

Preparation of the diazonium salt: A solution of sodium nitrite (0.7 g in 10 mL water) was gradually added to a well-cooled (0 °C) solution of the aromatic amine (0.01 mol) in conc. HCl (3.0 mL). The diazonium salt solution was added with continuous stirring to a cold (0 °C) solution of the thiazole derivatives (**10a**,**b**) in pyridine (30 mL). The reaction mixture was allowed to stand in the cold for 3 h and then filtered. The 5-arylazothiazoles (**11a–d**) thus obtained, were dried and recrystallized from a mixture of EtOH–DMF (1:1).

*4.9.1. N-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)-N′-(5-phenylazo-4-methylthiazol-2-yl)hydrazine (**11a**)*

Red powder; yield 77%; mp 239–241 °C; IR (KBr): ν/cm^{-1} = 3220 (NH), 1628 (C=C), 1597 (C=N), 1570 (N=N), 765 (C–Cl). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.05 (s, 3H, CH_3), 2.90 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.26 (t, J = 2.5 Hz, 2H, CH_{2ring}), 7.15–7.49 (m, 9H, Ar-H), 7.65 (s, 1H, Thiazole-H5), 8.37 (s, 1H, CH=N), 9.36 (s, 1H, NH-exchangeable). Anal. Calcd. for $C_{22}H_{18}C1N_5S$ (407.92): C 61.83; H 4.45; N 17.17%. Found: C 61.79; H 4.43; N 17.20%.

*4.9.2. N-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)-N′-(5-(4-methoxyphenylazo)-4-methylthiazol-2-yl)hydrazine (**11b**)*

Brown crystals; yield 78%; mp 260–262 °C; IR (KBr): ν/cm^{-1} = 3300 (NH), 1620 (C=C), 1600 (C=N), 1560 (N=N), 768 (C–Cl). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.03 (s, 3H, CH_3), 2.94 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.19 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.95 (s, 3H, OCH_3), 7.10, 7.58 (two d, J = 8.0 Hz, each 2H, C_6H_4–OCH_3), 7.15–7.45 (m, 4H, Ar-H), 7.61 (s, 1H, Thiazole-H5), 8.45 (s, 1H, CH=N), 9.62 (s, 1H, NH-exchangeable). MS: *m/z* (%) = 438 (M^+ + 1, 26), 394 (34), 322 (20), 249 (62), 219 (71), 149 (54), 106 (100), 63 (36). Anal. Calcd. for $C_{22}H_{20}C1N_5OS$ (437.95): C 60.34; H 4.60; N 15.99%. Found: C 60.29; H 4.55; N 15.96%.

*4.9.3. N-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)-N′-(5-phenylazo-4-phenylthiazol-2-yl)-hydrazine (**11c**)*

Brown crystals; yield 75%; mp 200–202 °C; IR (KBr): ν/cm^{-1} = 3290 (NH), 1619 (C=C), 1605 (C=N), 1560 (N=N), 770 (C–Cl). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.90 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.26 (t, J = 2.5 Hz, 2H, CH_{2ring}), 7.19–7.48 (m, 14H, Ar-H), 7.60 (s, 1H, Thiazole-H5), 8.33 (s, 1H, CH=N), 9.41 (s, 1H, NH-exchangeable). MS: *m/z* (%) = 469.5 (M^+), Anal. Calcd. for $C_{26}H_{20}C1N_5S$ (469.99): C 61.44; H 4.29; N 14.90%. Found: C 66.50; H 4.28; N 14.85%.

*4.9.4. N-((4-Chloro-1,2-dihydronaphthalen-3-yl)-methylene)-N′-(5-(4-methoxyphenylazo)-4-phenylthiazol-2-yl)hydrazine (**11d**)*

Red crystal; yield 77%; mp 240–242 °C; IR (KBr): ν/cm^{-1} = 3310 (NH), 1620 (C=C), 1598 (C=N), 1550 (N=N), 769 (C–Cl). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.94 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.32 (t, J = 2.5 Hz, 2H, CH_{2ring}), 7.12, 7.60 (two d, J = 8.0 Hz, each 2H, C_6H_4–OCH_3), 7.15–7.55 (m, 9H, Ar-H), 7.62 (s, 1H, Thiazole-H5), 8.36 (s, 1H, CH=N), 9.35 (s, 1H, NH-exchangeable). Anal. Calcd. for $C_{27}H_{22}C1N_5OS$ (500.01): C 64.86; H 4.43; N 14.01%. Found: C 64.79; H 4.40; N 14.06%.

*4.10. N′-[(1-Chloro-3,4-dihydronaphthalen-2-yl)-methylene]-2-cyanoacetohydrazide (**12**)*

An equimolar mixture of **1** (3.84 g, 0.02 mol) and cyanoacetic acid hydrazide (2 g, 0.02 mol) in absolute ethanol (30 mL) was heated under reflux for 2 h. The precipitate formed after cooling was filtered off, washed with cold ethanol, dried, and recrystallized from ethanol.

Orange crystals; yield 80%; mp 185–187 °C; IR (KBr): ν/cm^{-1} = 3194 (NH), 2224 (CN), 1692 (CO). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.90 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.22 (t, J = 2.5 Hz, 2H, CH_{2ring}), 4.0 (s, 2H, CH_2CN), 7.21–7.64 (m, 4H, Ar-H), 8.31 (s, 1H, CH=N), 9.61 (s, 1H, NH-exchangeable). Anal. Calcd. for $C_{14}H_{12}ClN_3O$ (273.72): C 61.43; H 4.42; N 15.35%. Found: C 61.56; H 4.38; N 15.42%.

*4.11. 5-Amino-N′-[(1-chloro-3,4-dihydronaphthalen-2-yl)methylene]-3-phenyl-2-thioxo-2,3-dihydro-1,3-thiazole-4-carbohydrazide (**13**)*

To a stirred solution of **12** (5.46 g, 0.02 mol), finely divided sulfur (0.65 g, 0.02 mol) and triethylamine (2.5 mL) in ethanol (20 mL), phenyl isothiocyanate (2.5 mL, 0.02 mol) was added. The reaction mixture was heated under reflux for 4 h during which the product was crystallized out. The reaction mixture was cooled to room temperature and the formed product was filtered off, washed with ethanol, dried, and recrystallized from a mixture of EtOH–DMF (1:1) to give compound **13**.

Brown crystals; yield 65%; mp 262–264 °C; IR (KBr): ν/cm^{-1} = 3420–3340 (NH_2), 3230 (NH), 1665 (CO). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.95 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.27 (t, J = 2.5 Hz, 2H, CH_{2ring}), 6.29 (s, 2H, NH_2-exchangeable), 7.25–7.68 (m, 9H, Ar-H), 7.91 (s, 1H, CH=N), 8.84 (s, 1H, NH-exchangeable). Anal. Calcd. for $C_{21}H_{17}ClN_4OS_2$ (440.97): C 57.20; H 3.89; N 12.71%. Found: C 57.27; H 3.92; N 12.66%.

*4.12. 6-{[(1-Chloro-3,4-dihydronaphthalene-2-yl)-methylene]amino}-1-phenyl-2-thioxo-1,6-dihydro[1,3]thiazolo[5,4-d]pyrimidin-7(2H)-one (**14**)*

A solution of **13** (0.88 g, 0.002 mol) in a mixture of triethylorthoformate (2.5 mL) and acetic anhydride (2.5 mL) was heated under reflux for 3 h during which the product partially crystallized out. The reaction mixture was allowed to cool to room temperature and the separated product was filtered off, washed with ethanol, dried, and recrystallized from acetic acid.

Yellow crystals; yield 60%; mp 300–302 °C; IR (KBr): ν/cm^{-1} = 1675 cm^{-1} (CO), 1645 (C=N), 1600 (C=C), 1238 (C=S). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.90 (t, J = 2.5 Hz, 2H, CH_{2ring}), 3.26 (t, J = 2.5 Hz, 2H, CH_{2ring}), 7.23–7.74 (m, 9H, Ar-H), 8.21 (s, 1H, CH=N), 9.24 (s, 1H, Pyrimidine C_5-H). Anal. Calcd. for $C_{22}H_{15}ClN_4OS_2$ (450.04): C 58.59; H 3.35; N 12.42%. Found: C 58.57; H 3.32; N 12.37%.

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