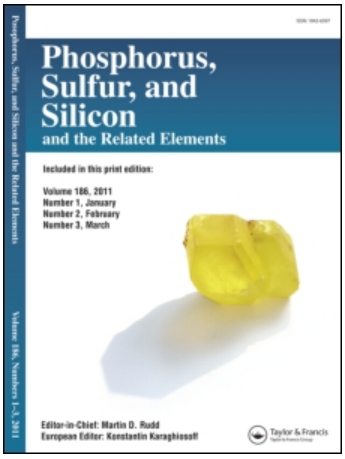

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Synthesis, Structure Elucidation, and Biological Evaluation of Some Fused and/or Pendant Thiophene, Pyrazole, Imidazole, Thiazole, Triazole, Triazine, and Coumarin Systems Based on Cyanoacetic 2-[(Benzoylamino)thioxomethyl] Hydrazide

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Synthesis, Structure Elucidation, and Biological Evaluation of Some Fused and/or Pendant Thiophene, Pyrazole, Imidazole, Thiazole, Triazole, Triazine, and Coumarin Systems Based on Cyanoacetic 2-[(Benzoylamino)thioxomethyl] Hydrazide

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Aiming to produce cyclized systems with potential bioactivity, a variety of fused and/or pendant thiophene, pyrazole, imidazole, thiazole, triazole, triazine, and coumarin systems were synthesized based on a cyanoacetic 2-[(benzoylamino)thioxomethyl] hydrazide precursor. The structure of the synthesized compounds was established based on elemental analysis and spectral data. The antibacterial and antifungal activities of the compounds are discussed and evaluated.

Keywords Antimicrobial; imidazoles; pyrazoles; thiazoles; thiophenes; triazoles

INTRODUCTION

Substituted aminothioxomethyl hydrazides are important building blocks in synthetic heterocyclic chemistry. The S/N regioselective nucleophilic competition in the synthesis of heterocyclic systems by intermolecular and intramolecular cyclization, as well as the change in reaction conditions, which might favor an N-attack, S-attack, or even an attack on the substituted terminals, are important factors for

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the diversity of produced heterocyclic systems from the title reaction precursor.

On the other hand, the synthetic potential and biological activity of several heterocyclics related to the named hydrazides have been explored to their maximum extent. Among the pharmacological profiles are their antimicrobial,[1,2] antitubercular,[3,4] anticonvulsant,[5,6] anti-inflammatory,[7,8] antidepressant[9] and antitumor[10] activities.

Continuing our interest in developing new heterocyclic systems based on phenylthiosemicarbazide[11,12] as well as the design and synthesis of heterocyclics with promising biological activities,[13–16] we focused our work on developing novel polyfunctionalized heterocyclic compounds with potential bioactivity.

RESULTS AND DISCUSSION

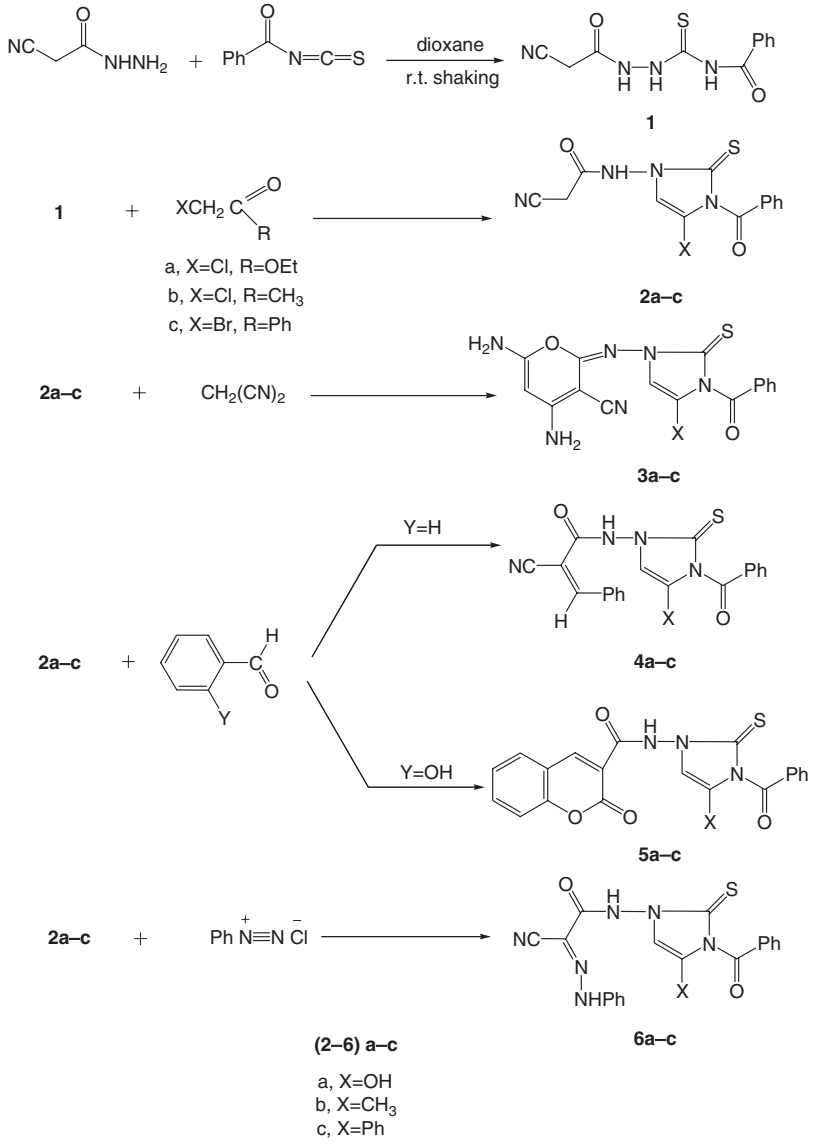
Chemistry

The synthetic strategies adopted to obtain the target systems are outlined in Schemes 1–6. CHNS elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and MS spectral data are recorded in the Experimental section.

The key precursor for the synthesis of the title systems is the hydrazide **1**. According to previously reported articles,[17,18] compound **1** was prepared by the treatment of cyanoacetic hydrazide with benzoyl isothiocyanate in acetone and heating under reflux for 2–3 h. Erian et al.[19] reported that using acetone as a solvent afforded almost exclusively the corresponding 1,3,4-thiadiazole condensate, and that using dioxane as a solvent and heating it under reflux for 2 h afforded the 1,3,4-thiadiazole via dehydrative cyclization of the initially formed thiosemicarbazide.

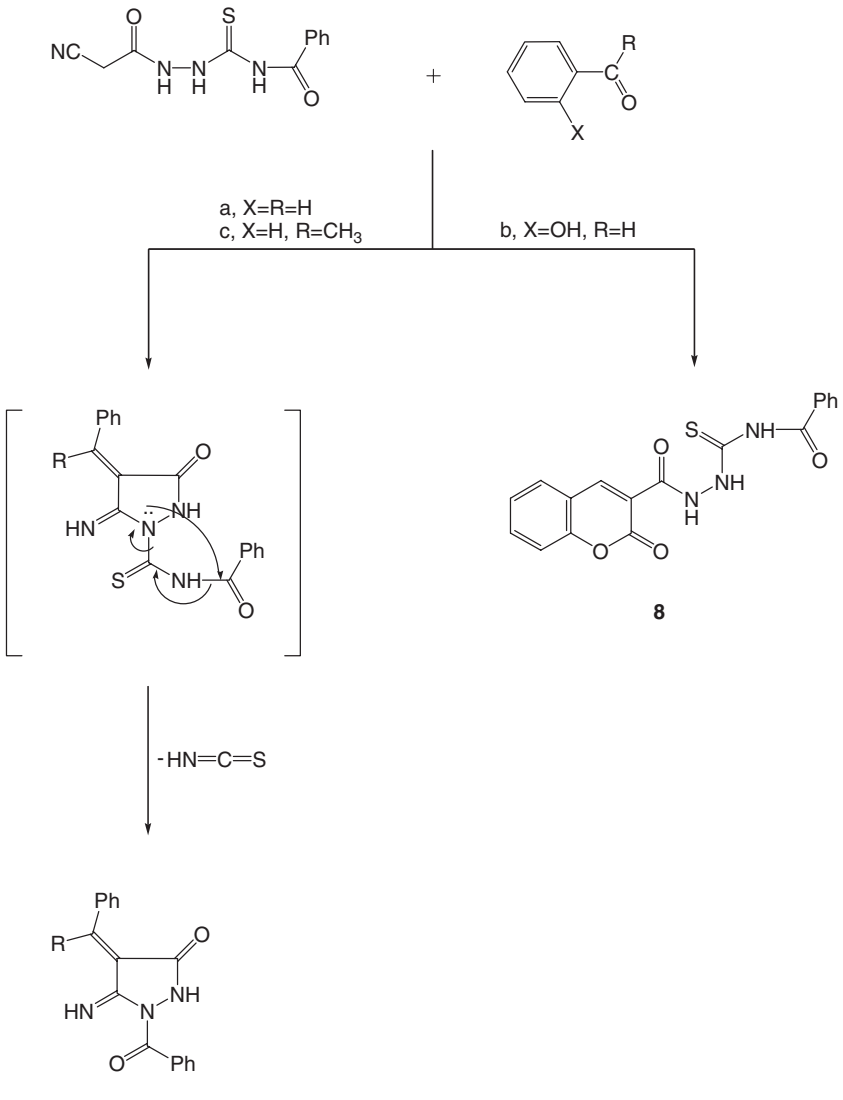
In the present work we herein report the formation of **1** in a high yield by simply shaking equimolar amounts of cyanoacetic hydrazide and benzoyl isothiocyanate in dioxane at r.t. Compound **1** revealed analytical and spectral data in accordance to its molecular structure. Mass spectral data for compound **1** revealed the molecular formula $C_{11}H_{10}N_4O_2S$ (m/z 262). Two important common fragments were detected at m/z 105 (base peak) and m/z 77 indicating $[phenyl{-}C{=}O]^+$ and $[phenyl]^+$ fragment ions, respectively. The reactive moieties in **1** allowed valuable organic functionalizations, which permitted the synthesis of various systems containing different heterocyclic cores.

Treating **1** with α-haloketons ($XCH_2C(=O)R$; X=Cl, R=OEt; X=Cl, R=CH_3; X=Br, R=Ph) afforded the respective imidazolethione



SCHEME 1

derivatives **2a–c**. Compounds **2a–c** revealed two absorption bands at 1300 and 1256 cm^{-1} (IR) characteristic of an imidazole thioxo function as well as δ-^{1}H singlet at 6.24–7.01 ppm (^{1}H NMR) assigned to an imidazole C_5 H proton. Other protons were seen at the expected chemical shifts and integral values.

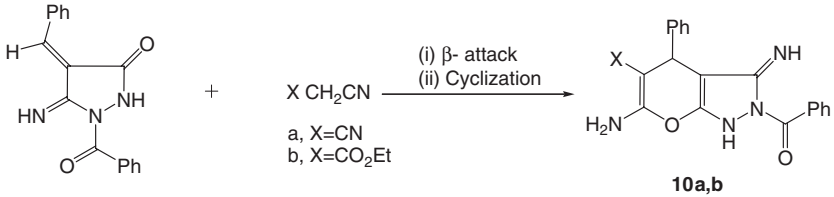


8

7, 9

7, R= H
9, R= CH_3

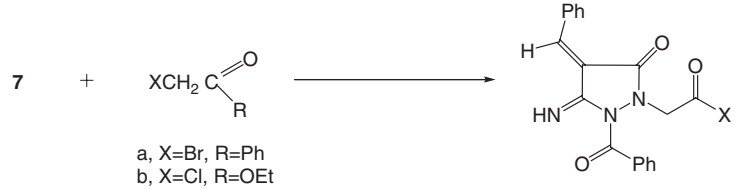
SCHEME 2



7

10a,b

a, X=CN
b, X=CO_2Et

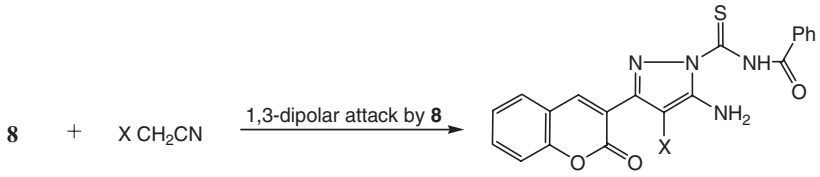


a, X=Br, R=Ph
b, X=Cl, R=OEt

11a,b

a, X=Ph
b, X=OEt

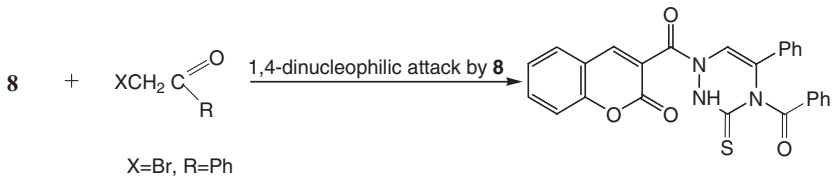
SCHEME 3



a, X=CN
b, X=CO_2Et

12 a,b

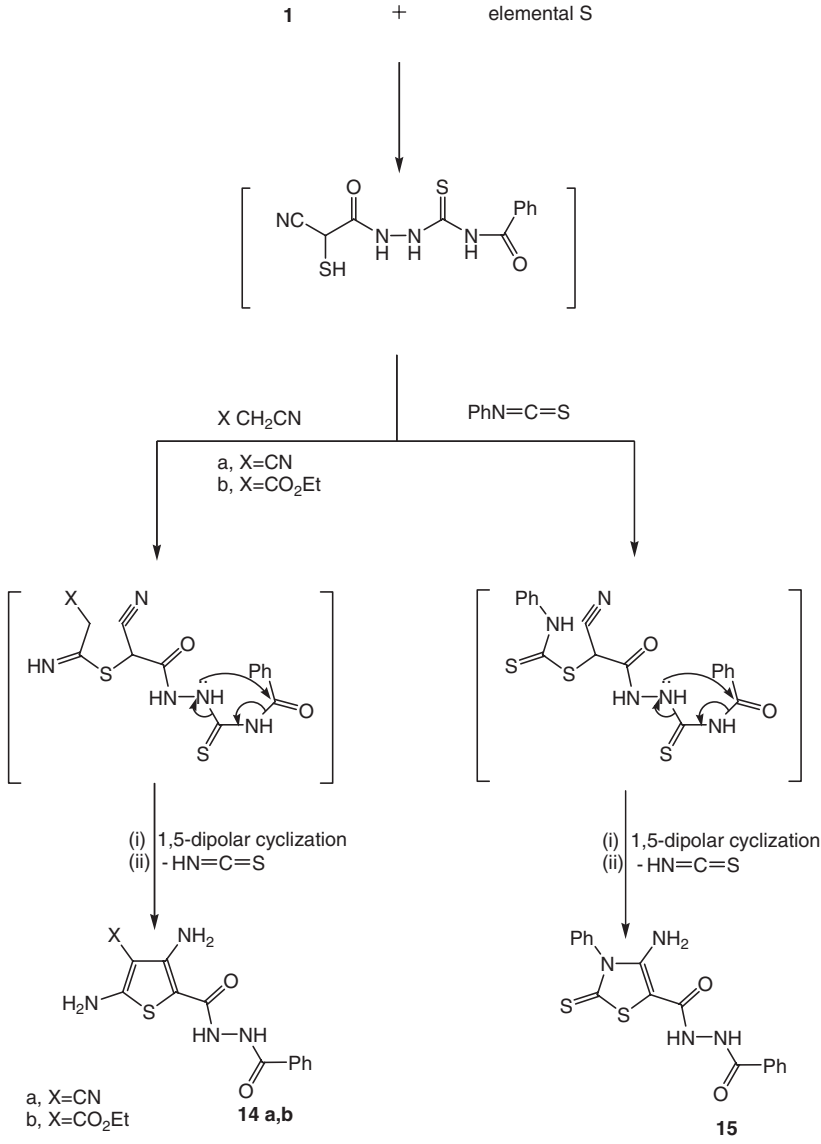
a, X=CN
b, X=CO_2Et



X=Br, R=Ph

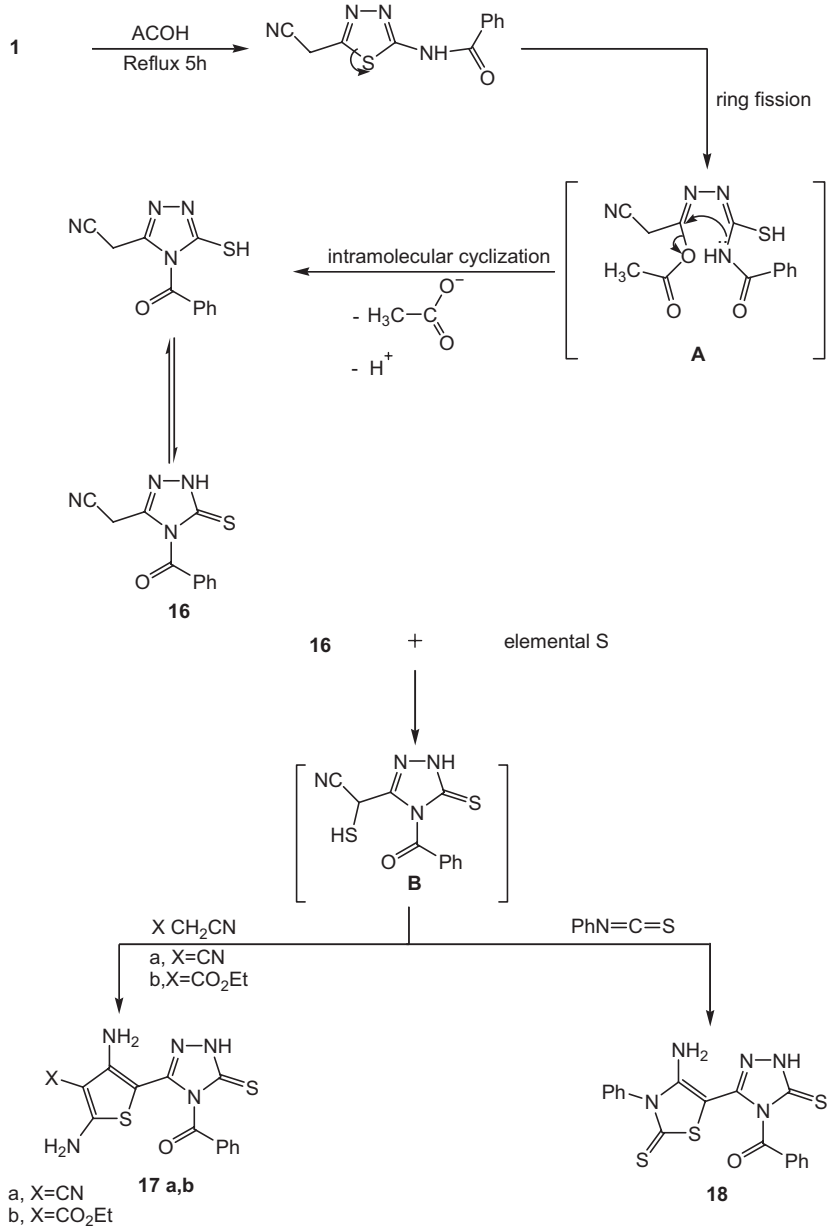
13

SCHEME 4



SCHEME 5

The reactivity of **2a–c** with malononitrile, aromatic aldehydes, and diazotized aniline was studied. Thus, treating **2a–c** with malononitrile afforded the pyran systems **3a–c** via a anucleophilic attack on the carbonitrile reagent followed by 1,6-dipolar intramolecular cyclization. As expected, as a consequence of cyclization, the acetyl C=O stretching



SCHEME 6

observed for **2a–c** at about 1740 cm^{-1} (IR) was not observed in the IR spectra of **3a–c**. ^1H NMR of **3a–c** displayed two NH_2 singlets resonating at δ 3.31–4.63 ppm. The signal of methylene CH_2 protons was not observed due to removal of these protons through an attack on the carbonitrile reagent.

The reaction of **2a–c** with aromatic aldehydes, namely benzaldehyde and salicylaldehyde, afforded benzal derivatives **4a–c** and coumarin derivatives **5a–c**, respectively. All data were consistent with the proposed structure. The absence of a CN absorption band and the appearance of a high-frequency C=O stretching about the 1719–1722 cm^{-1} region cited for a coumarin oxo function in the IR spectra of **5a–c** and the observation of a benzylidene =CH proton at about δ 4.62 ppm in the ^1H NMR spectra of **4a–c** have proven the proposed structure.

The liability of a methylene function in **2a–c** for coupling was studied through a reaction with diazotized aniline to produce the respective azo systems **6a–c**. ^1H NMR of **6a–c** revealed the absence of a CH_2 signal observed for **2a–c** at about δ 4.62 ppm and the presence of a downfield δ-^1H at 12.80–12.90 ppm for hydrazone NH, which confirmed the assigned structure (Scheme 1).

The reactivity of hydrazide **1** toward condensation was studied through treatment with aromatic carbonyl reagents. Treating **1** with benzaldehyde was previously reported to afford the respective condensation adduct[20] by subjecting an ethanolic solution of the reactants containing a catalytic amount of piperidine to reflux for 3 h.

We used dimethylformamide as a solvent to which a slight excess of piperidine was added, and the reaction mixture was heated under reflux for 5 h. The reaction product, thus produced, was found to be the pyrazole derivative **7**. It seems likely that **7** was formed via 1,5-dipolar cyclization of the initially formed adduct followed by rearrangement via elimination of HN=C=S. The absence of CN absorption at about the 2200–2250 cm^{-1} region, the disappearance of a C=S stretching band expected at about 1300 cm^{-1} (IR), and the absence of a SH singlet expected around δ 13 ppm for a resonating —N=C—SH proton (^1H NMR) confirmed the assignment for pyrazole structure **7**. Mass spectrum of **7** exhibited molecular ion m/z 291 corresponding to molecular formula $C_{17}H_{13}N_3O_2$. Main fragmentation was revealed by a base peak m/z 105 and a fragment ion m/z 77 corresponding to $[phenyl—C=O]^+$ and $[phenyl]^+$, respectively. Fragmentation of $[phenyl—C=O]^+$ from $[M^+ + 1]$ was observed as a fragment ion peak at m/z 187.

Treating **1** with salicyldehyde afforded the coumarin derivative **8**. Compound **8** revealed the absence of C≡N absorption at about 2250 cm^{-1} (IR) and of methylene CH_2 protons observed with **1**

(^{1}H NMR). δ-^{1}H signals of NH, coumarin C_4 H, and aromatic protons were observed at their respective chemical shifts and integral values.

When **1** was condensed with acetophenone through fusion in ammonium acetate, pyrazole derivative **9** was obtained. The reaction followed a similar mechanistic pathway adopted for the pyrazole derivative **7**. Microanalysis, IR, and ^{1}H NMR of **9** were fully consistent with the proposed structure. The mass spectrum of **9** exhibited a molecular ion m/z 305 corresponding to the molecular formula $C_{18}H_{15}N_3O_2$. The base peak was observed at m/z 51 corresponding to the [HN=C=C=C] fragment. Fragment ions corresponding to [phenyl–C=O]$^+$ and [phenyl]$^+$ were also indicated at m/z 105 and m/z 77, respectively (Scheme 2).

Aiming to produce cyclized systems with potential biological activity, compounds **7** and **8** were subjected to a reaction with different carbonitrile and carbonyl methylene reagents.

Subjecting **7** to a reaction with methylene carbonitrile reagents (XCH_2CN; X=CN; X=CO_2Et) afforded the respective pyranopyrazole derivatives **10a** and **10b** via a β-attack on the benzylidene moiety followed by cyclization through the pyrazole oxo function.

The IR spectrum of **10a** revealed a characteristic band at 2184 cm^{-1} attributed to C≡N stretching. ^{1}H NMR spectra of **10a** and **10b** exhibited signals due to a pyran C_4 H proton at δ 5.17 and 5.14 ppm and due to NH_2 at δ 3.50 and 3.61 ppm, respectively. δ-^{1}H signals integrated for ester CH_3 and CH_2 protons were observed at 1.15–1.32 and 4.04–4.36 ppm, respectively, in the ^{1}H NMR of **10b**. In the mass spectrum of **10a** the existing [M$^+$] ion (m/z = 357) confirmed the molecular weight of this compound. The peak at m/z 251 represents the fragmentation of [phenyl–C=O]$^+$(m/z = 105) as a base peak from the [M$^+$-1] of **10a**. A peak observed at m/z 203 indicated the fragmentation of [Ph CH=C(CN)$_2$] (m/z =154) from the [M$^+$] ion.

The treatment of **7** with α-haloketones ($XCH_2C(=O)R$; X=Br, R=Ph; X=Cl, R=OEt) afforded the functionalized pyrazole derivatives **11a** and **11b**. IR spectra of **11a,b** revealed three carbonyl stretching modes at about 1658, 1622 and 1598 cm^{-1}. Compound **11b** exhibited δ-^{1}H ester signals integrated for a triplet at 1.15–1.25 and a quartet at 4.17–4.66 ppm (^{1}H NMR). The disappearance of a ring NH singlet at about δ 10 ppm and the presence of a CH_2 singlet at δ 5.22 ppm in the ^{1}H NMR of **10b** confirmed a nucleophilic displacement mechanism. The mass spectrum of **11a** displayed the [M$^+$] ion at m/z 409 corresponding to the molecular formula $C_{25}H_{19}N_3O_3$. The base peak observed at m/z 105 indicated the fragment ion [phenyl–C=O]$^+$, and the most abundant peak recorded at m/z 77 indicated [phenyl]$^+$. The peak observed at

m/z 304 resulted from the fragmentation of [phenyl–C=O]$^+$ from [M$^+$], and that observed at m/z 293 indicated the fragmentation of [phenyl–C(=O)–CH$_2$]$^+$ from [M$^+$+3] (Scheme 3).

When the coumarin derivative **8** was reacted with methylene carbonitrile reagents (XCH$_2$CN; X=CN; X=CO$_2$Et), the respective pyrazole derivatives **12a** and **12b** were produced. The reaction followed a 1,3-dipolar attack by the hydrazinocarbonyl moiety of **8** on the methylene carbonitrile dipole. Compound **12a** revealed two C=O stretching modes at 1712 and 1607 cm^{-1} and a C≡N absorption band at 2201 cm^{-1} (IR), whereas the IR spectrum of **12b** exhibited three C=O absorption bands at 1719, 1665, and 1608 cm^{-1}. ^{1}H NMR of **12a** and **12b** revealed signals due to NH$_2$ and NH at about δ 3.58 and δ 9.18 ppm, respectively. Signals integrated for ester protons in compound **12b** were also observed in the respective field. The mass spectrum of **12b** exhibited molecular ion peak [M$^+$] at m/z 462 corresponding to the formula $C_{23}H_{18}N_4O_5S$. Main fragmentation of **12b** appeared by the fragments [phenyl–C=O]$^+$ m/z 105 as the base peak, [phenyl]$^+$m/z 77, and [coumarin]$^{+\cdot}$m/z 146. A peak observed at m/z 289 revealed the fragmentation of [coumarin –CH=NH]$^{+\cdot}$m/z 173 from [M$^+$].

Treatment of **8** with phenacyl bromide afforded 1,2,4-triazine-3-thione derivative **13**. The reaction is assumed to follow a 1,4-dinucleophilic attack by the aminothioxomethylhydrazine moiety on the α-haloketone. ^{1}H NMR of **13** exhibited singlets due to triazine C$_6$ H and NH at δ 8.14 and 11.74 ppm, respectively (Scheme 4).

At the other extreme, when **1** was affected with elemental sulfur and methylene carbonitrile reagents or phenyl isothiocyanate, the mode of attack was directed toward the cyanomethylene terminal of **1**. The synthetic pathway used in these reactions are outlined in Scheme 5. A stepwise pathway is suggested to take place via a Gewald reaction of **1** with elemental sulfur followed by a nucleophilic attack by the resulting thiol intermediate on the named reagents to afford the respective acyclic intermediates. The latter then suffered 1,5-dipolar cyclization followed by an elimination-rearrangement step via the loss of HN=C=S to afford the respective thiophenes **14a** and **14b** or thiazole **15**. Compounds **14a**, **14b,** and **15** revealed the absence of δ-^{1}H CH$_2$ and –N=C–SH singlets observed for compound **1** at 3.89 and 12.54 ppm (^{1}H NMR), respectively, thus confirming the assigned structure.

The mass spectrum of **14b** showed molecular ion peak [M$^+$] = 348 corresponding to its molecular formula $C_{15}H_{16}N_4O_4S$. Main fragmentation of **14b** appeared by the cleavage of [phenyl–C=O]$^+$ m/z 105 as

the base peak and $[phenyl]^+$ fragment ion m/z 77. A peak at m/z = 203 resulting from the fragmentation of $[H_2N–C(S^+)=C^––CO_2Et]$ m/z 145 from the molecular ion peak was also observed (Scheme 5).

As a continuation of our work aiming to synthesize heterocyclic systems with expected biological activities, compound **1** was subjected to cyclization under acidic conditions. Thus, when **1** was heated under reflux in acetic acid for 5 h, we observed that the reaction product was almost exclusively 1,2,4-triazole thione **16**. A possible mechanism is that the reaction proceeded via an initial formation of the 1,3,4-thiadiazole derivative. The latter undergoes ring opening, under the reaction conditions, to yield the intermediate **A,** which then cyclizes to afford the triazole thione **16**. It is noteworthy that acid cyclization of acylthiosemicarbazides in concentrated sulfuric acid produces 1,3,4-thiadiazole derivatives[9,21,22]. Cyclization in acetic acid was also reported to afford 1,3,4-thiadiazole.[19]

The structure of **16** was confirmed based on analytical and spectral data. Thus, the IR spectrum revealed absorption bands at 1302 and 1257 cm^{-1}corresponding to C=S. ^1H NMR showed a downfield singlet at δ 13.19 ppm attributed to the –N=C–SH proton indicating the facile thione-thiol tautomerism. The mass spectrum of **16** exhibited a molecular ion peak $[M^+]$ at m/z = 244 corresponding to the molecular formula $C_{11}H_8N_4OS$. The base peak was observed at m/z 105, which corresponds to $[phenyl–C=O]^+$. The fragment ion detected at m/z 216 indicated a direct loss of N_2 from the molecular ion. The ^{13}C NMR spectrum of **16** showed the thiocarbonyl carbon at δ 164.81. The signal at δ 160.10 was assigned to the carbonyl carbon.

Treatment of **16** with elemental sulfur and each of malononitrile, ethyl cyanoacetate, or phenacyl bromide afforded the respective systems **17a**, **17b,** and **18** via the intermediacy of the thiol **B**. IR spectra of compounds **17a**, **17b,** and **18** revealed stretching modes in the 1300 and 1244–1254 cm^{-1} regions assigned to the thione C=S. Mass spectra of compounds **17a** and **18** revealed molecular ion peaks at m/z 342 and 411, respectively, corresponding to respective molecular formulas $C_{14}H_{10}N_6OS_2$ and $C_{18}H_{13}N_5OS_3$. Main fragmentation of **17a** appeared by the fragments $[phenyl–C=O]^+$ m/z 105 and $[phenyl]^+$ m/z 77. A peak at m/z 244 indicated the fragmentation of $[NH_2–C(S^+)=C^––CN]$ m/z 98 from the molecular ion peak. Loss of $[N=C=S]^+$ from the fragment ion m/z 244 resulted in the base peak at m/z 186. The mass spectrum of **18** revealed a fragment ion at m/z 249 as a result of fragmentation of benzoyl isothiocyanate from $[M^+ + 1]$. A peak observed at m/z 135 revealed a phenyl isothiocyanate fragment (Scheme 6).

Microbiology

In vitro Evaluation of Antibacterial and Antifungal Activities

The synthesized compounds were screened in vitro for their antimicrobial activity against a variety of bacterial and fungal isolates.[23] The recorded inhibition zones are summarized in Table I.

The results indicated that most of the synthesized systems exhibited noticeable antimicrobial activity and that the bacterial isolates were more susceptible to the synthesized compounds than the fungal isolates.

TABLE I Antimicrobial Activity Data of the Synthesized Compounds in Terms of Inhibition Zones in mm (Concentration Level = 25 μg mL^{-1})

Compound	*E. coli*	*X. citri*	*A. fumigatus*	*R. solani*	*F. oxysporum*
F	26	26	12	10	12
2a	13	12	6	5	4
2b	26	20	16	13	17
2c	26	26	16	18	19
3a	32	34	32	20	17
3b	12	10	8	8	8
3c	11	9	6	6	0
4a	34	14	12	6	0
4b	11	11	4	5	4
4c	12	12	6	5	4
5a	38	28	18	16	16
5b	26	20	14	16	17
5c	36	32	16	12	12
6a	26	28	15	18	16
6b	26	18	14	13	18
6c	22	20	14	12	11
7	34	30	18	14	18
8	16	12	8	0	4
10a	20	18	4	2	0
10b	19	28	32	16	19
11a	18	26	17	4	4
11b	28	36	29	18	17
12a	26	26	18	16	14
12b	12	6	4	2	4
13	16	16	4	4	0
14a	18	10	6	5	0
14b	21	16	5	3	0
15	18	20	16	4	4
16	28	29	30	15	18
17a	16	14	6	8	8
17b	14	10	8	4	2
18	23	19	18	12	18

As summarized in Table I, antimicrobial activity of the test compounds against each microbial isolate may be arranged in descending order according to measured inhibition zones (in mm) following the sequence "*Microbial isolate*" (inhibition zone in mm) (test compound number) as follows.

"Escherichia coli" [38] **(5a)**, [36] **(5c)**, [34] **(4a, 7)**, [32] **(3a)**, [28] **(11b, 16)**, [26] **(1, 2b, 2c**, **5b, 6a, 6b, 12a)**, [23] **(18)**, [22] **(6c)**, [21] **(14b)**, [20] **(10a)**, [19] **(10b)**, [18] **(11a, 14a, 15)**, [16] **(8, 13, 17a)**, [14] **(17b)**, [13] **(2a)**, [12] **(3b, 4c, 12b)**, [11] **(3c, 4b)**.

"Xanthomonas citri" [36] **(11b)**, [34] **(3a)**, [32] **(5c)**, [30] **(7)**, [29] **(16)**, [28] **(5a, 6a, 10b)**, [26] **(1, 2c, 11a, 12a)**, [20] **(2b, 5b, 6c, 15)**, [19] (18), [18] **(6b, 10a)**, [16] **(13, 14b)**, [14] **(4a, 17a)**, [12] **(2a, 4c, 8)**, [11] **(4b)**, [10] **(3b, 14a, 17b)**, [9] **(3c)**, [6] **(12b)**.

"Aspergillus fumigatus" [32] **(3a, 10b)**, [30] **(16)**, [29] **(11b)**, [18] **(5a, 7, 12a, 18)**, [17] **(11a)**, [16] **(2b, 2c, 5c, 15)**, [15] **(6a)**, [14] **(5b, 6b, 6c)**, [12] **(1, 4a)**, [**8**] **(3b, 8, 17b)**, [6] **(2a, 3c, 4c, 14a, 17a)**, [5] **(14b)**, [4] **(4b, 10a, 12b, 13)**.

"Rhizoctonia solani" [20] **(3a)**, [18] **(2c, 6a, 11b)**, [16] **(5a, 5b, 10b, 12a)**, [15] **(16)**, [14] **(7)**, [13] **(2b, 6b)**, [12] **(18, 5c, 6c)**, [10] **(1)**, [8] **(3b,17a)**, [6] **(3c, 4a)**, [5] **(2a, 4b, 4c, 14a)**, [4] **(11a, 13, 15, 17b)**, [3] **(14b)**, [2] **(10a, 12b)**, [0] **(8)**.

"Fusarium oxysporum" [19] **(2c, 10b)**, [18] **(6b, 7, 16, 18)**, [17] **(2b, 3a, 5b, 11b)**, [16] **(5a, 6a)**, [14] **(12a)**, [12] **(1, 5c)**, [11] **(6c)**, [8] **(3b, 17a)**, [4] **(2a, 4b, 4c, 8, 11a, 12b, 15)**, [2] **(17b)**, [0] **(3c, 4a, 10a, 13, 14a, 14b)**.

Analysis and evaluation of the antimicrobial spectra of the synthesized systems revealed that compounds **5a**, **3a**, **5c**, **16**, and **11b** demonstrated the broadest spectrum inhibitory activity against most of the test microorganisms. Compound **5a** exhibited the highest inhibitory activity against *Escherichia coli* and compound **11b** was highly active against *Xanthomonas citri,* while compounds **3a** and**10b** demonstrated the highest inhibitory activity against *Aspergillus fumigatus*.

On the other hand, compound **8**, while slightly active against most of the tested bacterial strains, did not exhibit any activity against *Rhizoctonia solani*. Also, compounds **3c**, **4a**, **10a**, **13**, **14a,** and **14b** ware inactive against *Fusarium oxysporum*. It was also observed that while compound **4a** was totally inactive against *F. oxysporum*, it exhibited a high anti–*E. coli* effect.

EXPERIMENTAL

All melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. IR spectra were recorded (KBr

disks) on FTIR plus 460 or Pay Unicam SP-1000 spectrophotometers. ^{1}H and ^{13}C NMR spectra were recorded with Varian Gemini-200 (200 MHz) and Varian EM-300 (300 MHz) instruments with TMS as an internal standard (chemical shifts in δ ppm). Mass spectra were recorded with a Hewlett Packard 5988 A GC/MS system and GCMS-QP 1000 Ex Shimaduz instruments. Analytical data, obtained from the Microanalytical Data Centre at Cairo University, were performed on a Vario EL III Elemental CHNS analyzer.

Synthesis of Cyanoacetic 2-[(Benzoylamino)thioxomethyl]hydrazide (1)

A suspension of equimolar amounts of ammonium thiocyanate (0.76 g, 0.01 mol) and benzoyl chloride (1.16 g, 0.01 mol) in dioxane (20 mL) was heated under reflux for 20 min and then left to cool. A cold solution of cyanoacetic hydrazide (0.99 g, 0.01 mol) in dioxane (15 mL) was then added while shaking, and the reaction mixture was left at r. t. for 10 min. The solid product formed upon pouring onto an ice-water mixture was collected by filtration and recrystallized from ethanol.

(1) $C_{11}H_{10}N_4O_2S$, m.wt. 262, white crystals, 80% yield, m.p. 189–190°C. Elemental analysis (% calcd./found): 50.38/50.31 (C), 3.82/3.67 (H), 21.37/21.35 (N), 12.21/12.32 (S). IR (ν, cm^{-1}): 3270–3215 (3NH); 3051 (CH aromatic); 2970–2925 (CH_2); 2650 (SH); 2260 (CN); 1682, 1599 (2C=O); 1532, 1491 (C=C); 1333 (C=S). ^{1}H NMR (δ, ppm): 3.89 (s, 2H, CH_2), 7.50–7.99 (m, 5H, C_6H_5), 11.25 (s, 1H, NH), 11.79 (s, 1H, NH), 12.54 (s, 1H, NH). MS m/z (%): 262 [M^+] (7.9) , 105 [phenyl–C=O]$^+$ (100), 77 [phenyl]$^+$ (46.5).

Reaction of Cyanoacetic Hydrazide 1 with α-Haloketones

General Procedure for the Synthesis of 3-Benzoyl-1-(2-cyanoacetamido)-4-substituted-1,3-dihydro-2H-imidazole-2-thiones (2a–c)

To a solution of **1** (2.62 g, 0.01 mol) in ethanol (25 mL), ethyl chloroacetate (1.225 g, 0.01 mol), chloroacetone (0.925 g, 0.01 mol), or phenacyl bromide (1.99 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 h. The solid products formed upon pouring onto an ice-water mixture containing few drops of diluted solution of NaOH were collected by filtration and recrystallized from dioxane.

3-Benzoyl-1-(2-cyanoacetamido)-4-hydroxy-1,3-dihydro-2H-imidazole-2-thione(2a). $C_{13}H_{10}N_4O_3S$, m.wt. 302, white crystals, 75% yield, m.p. 244°C. Elemental analysis (% calcd./found): 51.65/51.90 (C),

3.31/3.50 (H), 18.54/18.91 (N), 10.60/10.93 (S). IR (ν, cm^{-1}): 3300–3155 (OH, NH); 3067–3011 (CH aromatic); 2940–2915 (CH_2); 2250 (CN); 1743, 1650 (2C=O); 1598, 1488(C=C); 1300, 1256 (C=S). ^1H NMR (δ, ppm): 4.62 (s, 2H, CH_2), 7.54–8.15 (m, 6H, C_6H_5, imidazole C_5 H), 13.14–13.15 (s, 2H, NH, OH).

3-Benzoyl-1-(2-cyanoacetamido)-4-methyl-1,3-dihydro-2H-imidazole-2-thi-one (2b). $C_{14}H_{12}N_4O_2S$, m.wt. 300, white crystals, 88% yield, m.p. 243°C. Elemental analysis (% calcd./found): 56.00/55.86 (C), 4.00/3.74 (H). IR (ν, cm^{-1}): 3200–3155 (NH); 3067–3011 (CH aromatic); 2940–2914 (CH_2, CH_3); 2250 (CN); 1743, 1650 (2 C=O); 1598, 1488 (C=C); 1300, 1256 (C=S). ^1H NMR (δ, ppm): 3.36 (s, 3H, CH_3), 4.62–4.63 (s, 2H, CH_2), 7.54–8.16 (m, 6H, C_6H_5, imidazole C_5 H), 13.17 (s, 1H, NH).

3-Benzoyl-1-(2-cyanoacetamido)-4-phenyl-1,3-dihydro-2H-imidazole-2-thi-one (2c). $C_{19}H_{14}N_4O_2S$, m.wt. 362, pale brownish-yellow crystals, 70% yield, m.p. 225°C. Elemental analysis (% calcd./found): 62.98/62.63 (C), 3.87/3.80 (H),15.47/15.75 (N), 8.84/9.05 (S). IR (ν, cm^{-1}): 3200–3156 (NH); 3067–3011 (CH aromatic); 2940–2915 (CH_2); 2250 (CN); 1742, 1651 (2C=O); 1598, 1488 (C=C); 1300, 1256 (C=S). ^1H NMR (δ, ppm): 4.61 (s, 2H, CH_2), 6.24 (s, 1H, imidazole C_5 H), 7.55–8.16 (m, 10H, $2C_6H_5$), 13.20 (s, 1H, NH).

Reaction of Imidazole Thione Derivatives 2a–c with Malononitrile

General Procedure for the Synthesis of 3-Benzoyl-1-(3-cyano-4,6-diamino-2H-2-pyranylideneamino)-4-substituted-1,3-dihydro-2H-imidazole-2-thiones (3a–c)

Equimolar amounts of **2a** (3.02 g, 0.01 mol), **2b** (3.00 g, 0.01 mol), or **2c** (3.62 g, 0.01mol) and malononitrile (0.66 g, 0.01 mol) in dioxane containing a catalytic amount of triethylamine were heated under reflux for 4 h. The solid products formed upon pouring onto an acidified ice-water mixture were collected by filtration and recrystallized from dioxane.

3-Benzoyl-1-(3-cyano-4,6-diamino-2H-pyranylideneamino)-4-hydroxy-1,3-dihydro-2H-imidazole-2-thione (3a). $C_{16}H_{12}N_6O_3S$, m.wt. 368, brown crystals, 82% yield, m.p. 220°C. Elemental analysis (% calcd./found): 52.17/52.38 (C), 3.26/3.31 (H), 22.83/22.80 (N), 8.69/8.98 (S). IR (ν, cm^{-1}): 3428 (OH); 3300–3160 ($2NH_2$); 3067–3014 (CH aromatic); 2941–2918 (CH_2); 2209 (CN); 1652 (C=O); 1599, 1490 (C=C); 1301, 1258 (C=S).^1H NMR (δ, ppm): 3.58, 4.62 (2s, 2H each,

$2NH_2$), 7.54–8.16 (m, 7H, C_6H_5, imidazole C_5 H, pyran C_5 H), 13.17 (s, 1H, resonating OH).

3-Benzoyl-1-(3-cyano-4,6-diamino-2H-pyranylideneamino)-4-methyl-1,3-dihydro-2H-imidazole-2-thione (3b). $C_{17}H_{14}N_6O_2S$, m.wt. 366, dark brown crystals, 82% yield, m.p. 235°C. Elemental analysis (% calcd./found): 55.74/55.67 (C), 3.82/3.69 (H), 22.95/22.71 (N), 8.74/9.00 (S). IR (ν, cm^{-1}): 3200–3158 (2 NH_2); 3011 (CH aromatic); 2939–2853 (CH, CH_3); 2210 (CN); 1652 (C=O); 1599, 1489 (C=C); 1301, 1256 (C=S). ^{1}H NMR (δ, ppm): 2.52 (s, 3H, CH_3), 3.58, 4.63 (2s, 2H each, $2NH_2$), 7.54–8.16 (m, 7H, C_6H_5, imidazole C_4H, pyran C_5 H).

3-Benzoyl-1-(3-cyano-4,6-diamino-2H-pyranylideneamino)-4-phenyl-1,3-dihydro-2H-imidazole-2-thione (3c). $C_{22}H_{16}N_6O_2S$, m.wt. 428, brown crystals, 88% yield, m.p. 110°C. Elemental analysis (% calcd./found): 61.68/61.59 (C), 3.74/3.90 (H), 19.63/19.40 (N), 7.48/7.19 (S). IR (ν, cm^{-1}): 3322–3217 ($2NH_2$); 3060 (CH aromatic); 2921–2853 (CH aliphatic); 2198 (CN); 1722 (C=O); 1604, 1475 (C=C); 1315, 1283 (C=S). ^{1}H NMR (δ, ppm): 3.31, 3.56 (2s, 2H each, $2NH_2$), 7.53–8.13 (m, 12H, $2C_6H_5$, imidazole C_4 H, pyran C_5 H).

Reaction of Imidazole Thione Derivatives 2a–c with Aromatic Aldehydes

General Procedure for the Synthesis of 3-Benzoyl-1-(2-cyano-3-phenylacrylamido)-4-substituted-1,3-dihydro-2H-imidazole-2-thiones (4a–c) and 3-benzoyl-1-(coumarincarbonylamino)-4-substituted-1,3-dihydro-2H-imidazole-2-thiones (5a–c)

To a solution of **2a** (3.02 g, 0.01 mol), **2b** (3.00 g, 0.01 mol), or **2c** (3.62 g, 0.01 mol) in dioxane (20 mL) containing a catalytic amount of pipyridine, each of benzaldehyde (1.06 g, 0.01 mol) or salicylaldehyde (1.22 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 h. The solid products obtained upon pouring onto an acidified ice-water mixture were recrystallized from dioxane.

3-Benzoyl-1-(2-cyano-3-phenylacrylamido)-4-hydroxy-1,3-dihydro-2H-imidazole-2-thione (4a). $C_{20}H_{14}N_4O_3S$, m.wt. 390, yellow crystals, 90% yield, m.p. 217°C. Elemental analysis (% calcd./found): 61.54/61.60 (C), 3.59/3.82 (H), 14.36/14.10 (N), 8.20/8.55 (S). IR (ν, cm^{-1}): 3420–3157 (resonating OH, NH); 3062–3021 (CH aromatic); 2922–2853 (CH aliphatic); 2223 (CN); 1669, 1600 (2C=O); 1525, 1496 (C=C); 1302, 1252 (C=S). ^{1}H NMR (δ, ppm): 4.62 (s, 1H, =CH), 7.54–8.18 (m, 6H, C_6H_5, imidazole C_5 H), 8.28 (s, 1H, NH) 13.24 (s, 1H, resonating OH).

3-Benzoyl-1-(2-cyano-3-phenylacrylamido)-4-methyl-1,3-dihydro-2H-imidzole-2-thione (4b). $C_{21}H_{16}N_4O_2S$, m.wt. 388, yellow crystals, 92% yield, m.p. 225°C. Elemental analysis (% calcd./found): 64.95/64.71 (C), 4.12/4.40 (H), 14.43/14.55 (N), 8.25/8.49 (S). IR (ν, cm^{-1}): 3401–3158 (NH); 3062–3014 (CH aromatic); 2926–2855 (CH, CH_3); 2224 (CN); 1669, 1599 (2C=O); 1525, 1496 (C=C), 1302, 1253 (C=S). ^{1}H NMR (δ, ppm): 2.52 (s, 3H, CH_3), 4.63 (s, 1H, =CH), 7.55–8.19 (m, 11H, $2C_6H_5$, imidazole C_5 H), 8.29 (s, 1H, NH).

3-Benzoyl-1-(2-cyano-3-phenylacrylamido)-4-phenyl-1,3-dihydro-2H-imidazole-2-thione (4c). $C_{26}H_{18}N_4O_2S$, m.wt. 450, greenish brown crystals, 93% yield, m.p. 220°C. Elemental analysis for $C_{26}H_{18}N_4O_2S.H_2O$ (% calcd./found): 66.67/66.92 (C), 4.27/4.52 (H), 11.96/11.62 (N), 6.84/6.94 (S). IR (ν, cm^{-1}): 3394 (NH); 3137–3013 (CH aromatic); 2926–2855 (CH aliphatic); 2225 (CN); 1664, 1598 (2C=O); 1527, 1450 (C=C); 1305, 1254 (C=S). ^{1}H NMR (δ, ppm): 6.21 (s, 1H, =CH), 7.57–8.17 (m, 16H, $3C_6H_5$, imidazole C_5 H), 8.25 (s, 1H, NH).

3-Benzoyl-1-(3-coumarincarbonylamino)-4-hydroxy-1,3-dihydro-2H-imidazole-2-thione (5a). $C_{20}H_{13}N_3O_5S$, m.wt. 407, bright yellow crystals, 98% yield, m.p. 275°C. Elemental analysis (% calcd./found): 58.97/58.69 (C), 3.19/3.43 (H), 10.32/10.55 (N), 7.86/7.98 (S). IR(ν, cm^{-1}): 3447–3274 (OH, NH); 3158–3065 (CH aromatic); 2977–2849 (CH, CH_2); 1721, 1661, 1601 (3C=O); 1568, 1491 (C=C), 1298, 1264 (C=S).^{1}H NMR (δ, ppm): 7.23–8.64 (m, 11H, C_6H_5, C_6H_4, imidazole C_5 H, coumarin, C_4 H), 9.08 (s, 1H, NH), 12.91 (s, 1H, resonating OH).

3-Benzoyl-1-(2H-3-coumarincarbonylamino)-4-methyl-1,3-dihydro-2H-imidazole-2-thione (5b). $C_{21}H_{15}N_3O_4S$, m.wt. 405, bright yellow crystals, 98% yield, m.p. 273°C. Elemental analysis (% calcd./found): 62.22/62.38 (C), 3.70/3.84 (H), 10.37/10.69 (N), 7.90/7.69 (S). IR (ν, cm^{-1}): 3448–3157 (NH); 3060 (CH aromatic); 3001–2850 (CH, CH_3); 1722, 1661, 1601 (3 C=O); 1569, 1490 (C=C), 1299, 1265 (C=S). ^{1}H NMR (δ, ppm): 3.58 (s, 3H, CH_3), 7.24–8.66 (m, 11H, C_6H_5, C_6H_4, imidazole C_5 H, coumarin, C_4 H), 9.11 (s, 1H, NH).

3-Benzoyl-1-(2H-3-coumarincarbonylamino)-4-phenyl-1,3-dihydro-2H-imidazole-2-thione (5c). $C_{26}H_{17}N_3O_4S$, m.wt. 467, pale brown crystals, 90% yield, m.p. 200°C. Elemental analysis (% calcd./found): 66.81/66.68 (C), 3.64/3.95 (H), 8.99/9.24 (N), 6.85/6.95 (S). IR (ν, cm^{-1}): 3397–3152 (NH); 3058 (CH aromatic); 2929–2853 (CH aliphatic); 1720, 1669, 1602 (3C=O); 1532, 1492 (C=C), 1306, 1250 (C=S). ^{1}H NMR

(δ, ppm): 6.76 (s, 1H, imidazole C_5 H), 7.24–8.12 (m, 15H, $2C_6H_5$, C_6H_4, coumarin C_4H), 9.07 (s, 1H, NH).

Reaction of Imidazole Thione Derivatives 2a–c with Diazotized Aniline

General Procedure for the Synthesis of 3-benzoyl-1-[2-cyano-2-(phenylhydrazono) acetamido]-4-substituted-1,3-dihydro-2H-imidazole-2-thiones (6a–c)

To a cold solution (0–5°C) of **2a** (3.02 g, 0.01 mol), **2b** (3.00 g, 0.01 mol), or **2c** (3.62 g, 0.01 mol) in ethanol (20 mL) containing sodium hydroxide (1.00 g) an equimolar amount of diazotized aniline was gradually added while stirring. The solid product formed upon cooling in an ice bath was collected by filtration, washed with water, and recrystallized from dioxane.

3-Benzoyl-1-[2-cyano-2-(phenylhydrazono)acetamido]-4-hydroxy-1,3-dihydro-2H-imidazole-2-thione (6a). $C_{19}H_{14}N_6O_3S$, m.wt. 406, yellowish-green crystals, 81% yield, m.p. 225°C. Elemental analysis (% calcd./found): 56.16/56.32 (C), 3.45/3.77 (H), 20.69/20.35 (N), 7.88/7.95 (S). IR (ν, cm^{-1}): 3397 (OH); 3210–3151 (2NH); 3060–3009 (CH aromatic); 2934 (CH aliphatic); 2212 (CN); 1672, 1601 (2C=O); 1530, 1490 (C=C); 1302, 1258 (C=S). ^{1}H NMR (δ, ppm): 7.42–7.65 (m, 11H, $2C_6H_5$, imidazole C_5H), 8.12–8.16 (2s, 2H, 2NH), 13.50 (s, 1H, resonating OH).

3-Benzoyl-1-[2-cyano-2-(phenylhydrazono)acetamido]-4-methyl-1,3-di-hydro-2H-imidazole-2-thione (6b). $C_{20}H_{16}N_6O_2S$, m.wt. 404, greenish-yellow crystals, 76% yield, m.p. 155°C. Elemental analysis (% calcd./found): 59.40/59.09 (C), 3.96/3.59 (H), 20.79/20.51 (N), 7.92/7.99 (S). IR (ν, cm^{-1}): 3423–3156 (2NH); 3060 (CH aromatic); 2982–2930 (CH, CH_3); 2215 (CN); 1670, 1628 (2C=O); 1601, 1492 (C=C); 1303, 1261 (C=S).^{1}H NMR (δ, ppm): 2.58 (s, 3H, CH_3), 7.09–7.66 (m, 11H, $2C_6H_5$, imidazole C_5H), 8.12, 8.18 (2s, 2H, 2NH).

3-Benzoyl-1-[2-cyano-2-(phenylhydrazono)acetamido]-4-phenyl-1,3-di-hydro-2H-imidazole-2-thione (6c). $C_{25}H_{18}N_6O_2S$, m.wt. 466, creamy crystals, 76% yield, m.p. 134°C. Elemental analysis (% calcd./found): 64.38/64.12 (C), 3.86/3.87 (H), 18.02/18.10 (N), 6.87/7.12 (S). IR (ν, cm^{-1}): 3419–3162 (2NH); 3060 (CH aromatic); 2930 (CH aliphatic); 2215 (CN); 1673, 1601 (2 C=O); 1531, 1492 (C=C); 1304, 1261 (C=S). ^{1}H NMR (δ, ppm): 6.58 (s, 1H, imidazole C_5 H), 7.14–7.58 (m, 15H, $3C_6H_5$), 8.13, 8.16 (2s, 2H, 2NH).

Reaction of Cyanoacetic Hydrazide Derivative 1 with Aromatic Carbonyl Reagents

Reaction of 1 with Benzaldehyde

Equimolar amounts of **1** (2.62 g, 0.01 mol), and benzaldehyde (1.06 g, 0.01 mol) were refluxed for 5 h in dimethylformamide containing a slight excess of piperidine (2 mL). After cooling, the solution was acidified by hydrochloric acid. The crude product was precipitated, filtered, washed with water, and recrystallized from dimethylformamide.

1-Benzoyl-4-benzylidine-5-iminopyrazolidin-3-one(7). $C_{17}H_{13}N_3O_2$, m.wt. 291, pale creamy crystals, 75% yield, m.p. 225°C. Elemental analysis for $C_{17}H_{13}N_3O_2.H_2O$ (% calcd./found): 66.02/65.96 (C), 4.85/4.66 (H), 13.59/13.95 (N), IR (ν, cm^{-1}): 3375–3245 (2NH); 3061 (CH aromatic); 3030–2928 (CH aliphatic); 1659, 1620 (2C=O); 1601, 1495 (C=C). ^1H NMR (δ, ppm): 6.70 (s, 1H, =CH), 7.11–7.96 (m, 10H, $2C_6H_5$), 8.46–8.48 (s, 1H, NH), 10.03 (s, 1H, NH). MS m/z (%): 291 $[M^+]$ (17.1), 187 $[(M^+ + 1)\text{-}105]$ (12.6), 105 [phenyl–C=O]$^+$ (100), 77 [phenyl]$^+$ (63.5).

Reaction of 1 with Salicylaldehyde

Equimolar amounts of **1** (2.62 g, 0.01 mol) and salicylaldehyde (1.22 g, 0.01 mol) were heated under reflux in ethanol and a catalytic amount of piperidine for 1 h. The precipitate obtained by cooling was recrystallized from ethanol.

N-[2-(3-Coumarincarbonyl) Hydrazinothioxomethyl] Benzamide (8)

$C_{18}H_{13}N_3O_4S$, m.wt. 367, yellow crystals, 72% yield, m.p. 275°C. Elemental analysis (% calcd./found): 58.85/59.01 (C), 3.54/3.57 (H), 11.44/11.69 (N), 8.72/9.01 (S). IR (ν, cm^{-1}): 3307–3161 (3NH); 3100–3059 (CH aromatic); 3002–2922 (CH); 1719, 1660, 1603 (3C=O); 1567, 1490 (C=C); 1298 (C=S). ^1H NMR (δ, ppm): 7.19–8.15 (m, 10H, C_6H_5, C_6H_4, coumarin C_4 H), 8.57 (s, 1H, NH), 9.02, 9.07 (2s, 2H, 2NH).

Reaction of 1 with Acetophenone

To a mixture of equimolar amounts of **1** (2.62 g, 0.01 mol) and acetophenone (1.20 g, 0.01 mol), 0.5 g of ammonium acetate was added, and the reaction mixture was heated to fusion for 45 min. The mixture was then boiled in ethanol for a few minutes and poured onto an ice-water mixture, and the product was recrystallized from ethanol.

1-Benzoyl-5-imino-4-(1-phenylethylidene)-pyrazolidin-3-one (9)

$C_{18}H_{15}N_3O_2$, m.wt. 305, brown crystals, 60% yield, m.p. 120°C. Elemental analysis for $C_{18}H_{15}N_3O_2.H_2O$ (% calcd./found): 66.87/66.67 (C), 5.26/4.99 (H), 13.00/12.98 (N), IR (ν, cm^{-1}): 3397–3189 (2NH); 3100–3062 (CH aromatic); 2924–2854 (CH_3); 1654, 1603 (2C=O); 1570, 1494 (C=C). ^1H NMR (δ, ppm): 2.29 (s, 3H, CH_3), 7.24–8.12 (m, 10H, $2C_6H_5$), 8.13 (s, 1H, NH), 10.12 (s, 1H, NH). MS m/z (%): 308 [M^++3] (33.3), 305 [M^+] (17.5), 304 [M^+-1] (24.6), 303 [M^+-2] (57.0), 288 [(M^+-1)-16] (56.1), 204 [(M^++4)-105] (27.2), 128 [Ph C(CH_3)=C=C] (29.8), 105 [phenyl–C=O]$^+$ (71.9), 77 [phenyl]$^+$ (57.0), 51 [HN=C=C=C] (100).

Reaction of Pyrazolidine Derivative 7 with Methylene Carbonitrile Reagents

General Procedure for the Synthesis of 6-Amino-2-benzoyl-5-substituted-3-imino-4-phenyl-1,2-dihydro-3H-,4H-pyrano [2,3-c] Pyrazoles (10a, 10b)

To a solution of **7** (3.09 g, 0.01 mol) in ethanol (25 mL) and dimethylformamide (5 mL) containing a catalytic amount of triethylamine, malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 h, cooled, and then neutralized by pouring it onto an acidified ice-water mixture. The solid product formed in each case was filtered off and recrystallized from an ethanol/dimethylformamide mixture.

6-Amino-2-benzoyl-5-cyano-3-imino-4-phenyl-1,2-dihydro-3H-,4H-pyrano [2, 3-c] pyrazole (10a). $C_{20}H_{15}N_5O_2$, m.wt. 357, pale grey crystals, 70% yield, m.p. 196°C. Elemental analysis for $C_{20}H_{15}N_5O_2.H_2O$ (% calcd./found): 64.00/63.88 (C), 4.53/4.57 (H), 18.67/18.58 (N). IR (ν, cm^{-1}): 3310–3207 (2NH, NH_2); 3061 (CH aromatic); 2922–2852 (CH); 2184 (CN); 1670 (C=O); 1598, 1493 (C=C). ^1H NMR (δ, ppm): 3.35 (s, 2H, NH_2), 5.17 (s, 1H, pyran C_4 H), 7.09–7.88 (m, 10H, $2C_6H_5$), 7.98 (s, 1H, NH), 10.50 (s, 1H, NH). MS m/z (%): 357 [M^+] (4.5), 291 [M^+-66] (8.5), 251 [(M^+-1)-105] (11.0), 203 [M^+-154] (8.0), 154 [Ph CH=C$(CN)_2$]$^{+\cdot}$ (7.5), 105 [phenyl–C=O]$^+$ (100), 77 [phenyl]$^+$ (57.0).

6-Amino-2-benzoyl-5-ethoxycarbonyl-3-imino-4-phenyl-1,2-dihydro-3H-,4H-pyrano[2, 3-c] pyrazole (10b). $C_{22}H_{20}N_4O_4$, m.wt. 404, pale creamy crystals, 65% yield, m.p. 200°C. Elemental analysis for

$C_{22}H_{20}N_4O_4.H_2O$ (% calcd./found): 62.56/62.90 (C), 5.21/4.89 (H), 13.27/13.10 (N). IR (ν, cm^{-1}): 3218 (2NH, NH_2); 3061 (CH aromatic); 2924–2851 (CH_2, CH_3); 1720, 1661 (2C=O); 1598, 1473 (C=C). ^1H NMR(δ, ppm): 1.15–1.32 (t, 3H, CH_3), 4.04 (s, 2H, NH_2), 4.32–4.36 (q, 2H, CH_2), 5.14 (s, 1H, pyran C_4 H), 7.19–7.87 (m, 10H, $2C_6H_5$), 8.41 (s, 1H, NH), 10.42 (s, 1H, NH).

Reaction of Pyrazolidine Derivative 7 with α-Haloketones

General Procedure for the Synthesis of 1-Benzoyl-4-benzylidene-2-substituted-5-imino-3-pyrazolidinones (11a,11b)

To a solution of **7** (3.09 g, 0.01 mol) in ethanol (30 mL) and dimethylformamide (10 mL), phenacyl bromide (1.99 g, 0.01 mol) or ethyl chloroacetone (1.225 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 h. The solid products formed upon pouring onto an ice-water mixture containing potassium carbonate were collected by filtration and recrystallized from an ethanol/dimethylformamide mixture.

1-Benzoyl-2-(benzoylmethyl)-4-benzylidene-5-imino-3-pyrazolidinone (11a). $C_{25}H_{19}N_3O_3$, m.wt. 409, reddish brown crystals, 63% yield, m.p. 240°C. Elemental analysis for $C_{25}H_{19}N_3O_3.H_2O$ (% calcd./found): 70.26/69.92 (C), 4.92/4.65 (H), 9.84/9.53 (N). IR (ν, cm^{-1}): 3285 (NH); 3060 (CH aromatic); 2923–2853 (CH aliphatic); 1720, 1660, 1620 (3C=O), 1598, 1495 (C=C). MS m/z (%): 411 [M^++2] (1.52), 410 [M^++1] (1.59), 409 [M^+] (2.42), 304 [M^+-105] (2.41), 293 [(M^++3)-119] (12.15), 188 [293-(phenyl–C^+ =O)] (1.60), 119 [phenyl–C(=O)CH_2]$^+$ (6.4), 105 [phenyl–C=O]$^+$ (100), 77 [phenyl]$^+$ (66.98).

1-Benzoyl-4-benzylidene-2-(ethoxycarbonylmethyl)-5-imino-3-pyrazolidinone (11b). $C_{21}H_{19}N_3O_4$, m.wt. 377, pale brown crystals, 60% yield, m.p. >300°C. Elemental analysis for $C_{21}H_{19}N_3O_4.H_2O$ (% calcd./found): 63.80/63.49 (C), 5.32/5.34 (H), 10.63/10.34 (N). IR (ν, cm^{-1}): 3295 (NH); 3060 (CH aromatic); 2923–2853 (CH_2, CH_3), 1745, 1658, 1622 (3C=O), 1562, 1496 (C=C). ^1H NMR (δ, ppm): 1.16–1.25 (t, 3H, CH_3), 4.17–4.66 (q, 2H, CH_2), 5.22 (s, 2H, CH_2), 5.84 (s, 1H, CH), 7.25–7.51 (m, 10H, $2C_6H_5$), 7.97 (s, 1H, NH).

Reaction of Coumarin Derivative 8 with Methylenecarbonitrile Reagents

General Procedure for the Synthesis of N-[5-Amino-4-substituted-3-(3-coumarinyl)pyrazole-1-thioxomethyl]benzamides (12a, 12b)

To a solution of **8** (3.67 g, 0.01 mol) in ethanol (20 mL) and dimethylformamide (10 mL) containing a catalytic amount of triethylamine, malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 h. The solid products formed upon pouring an onto an acidified ice-water mixture were collected by filtration and recrystallized from an ethanol/dimethylformamide mixture.

N-[5-Amino-4-cyano-3-(3-coumarinyl)pyrazole-1-thioxomethyl]-benzamide (12a). $C_{21}H_{13}N_5O_3S$, m.wt. 415, greenish brown crystals, 80% yield, m.p. 185°C. Elemental analysis (% calcd./found): 60.72/59.57 (C), 3.13/2.91 (H), 16.87/16.83 (N), 7.71/7.40 (S). IR (ν, cm^{-1}): 3341–3207 (NH, NH_2); 3050 (CH aromatic); 2925–2854 (CH); 2201 (CN); 1721, 1680 (2C=O); 1607, 1488 (C=C); 1285 (C=S). ^1H NMR (δ, ppm): 3.58 (s, 2H, NH_2), 7.02–8.20 (m, 10H, C_6H_5, C_6H_4, coumarin C_4 H), 8.96 (s, 1H, NH).

N-[5-Amino-3-(3-coumarinyl)-4-ethoxycarbonylpyrazole-1-thioxomethyl] benzamide (12b). $C_{23}H_{18}N_4O_5S$, m.wt. 462, pale brown crystals, 72% yield, m.p. 180°C. Elemental analysis (% calcd./found): 59.74/59.89 (C), 3.90/4.01 (H), 12.12/11.88 (N), 6.93/6.63 (S). IR (ν, cm^{-1}): 3185 (NH, NH_2); 3064 (CH aromatic); 2922–2851 (CH, CH_2, CH_3); 1750, 1719, 1665 (3C=O); 1608, 1496 (C=C); 1289 (C=S). ^1H NMR (δ, ppm): 1.18–1.22 (t, 3H, CH_3), 3.57 (s, 2H, NH_2), 4.03–4.19 (q, 2H, CH_2), 7.01–8.20 (m, 10H, C_6H_5, C_6H_4, coumarin C_4 H), 9.18 (s, 1H, NH). MS m/z (%): 462 [M^+] (2.0), 350 [(M^++1)-113] (2.5), 305 [462-(coumarin—C^+)] (18.0), 289 [M^+-173] (13.0), 204 [C^+ =N–N^-—C=(S)–NHCOPh]$^+$(17.0), 173 [coumarin—CH=NH]$^{+\cdot}$(36.5), 146 [cou-marin]$^{+\cdot}$(18.0), 113 [N≡C—CH_2—CO_2Et]$^{+\cdot}$, 105 [phenyl—C=O]$^+$ (100), 77 [phenyl]$^+$ (68.0), 58 [N=C=S]$^+$ (25.2).

Reaction of Coumarin Derivative 8 with Phenacyl Bromide

Equimolar amounts of **8** (3.67 g, 0.01 mol) and phenacyl bromide (1.99 g, 0.01 mol) in ethanol (20 mL) and dimethylformamide (10 mL) were heated under reflux for 5 h. The solid product formed upon pouring onto-an ice-water mixture containing a few drops of diluted solution of

sodium hydroxide was collected by filtration and recrystallized from an ethanol/dimethylformamide mixture.

3-(4-Benzoyl-5-phenyl-3-thioxo-3H-1,2,4-triazine-1-(carbonyl)-coumarin (13)

$C_{26}H_{17}N_3O_4S$, m.wt. 467, yellowish brown crystals, 70% yield, m.p. 120°C. Elemental analysis (% calcd./found): 66.81/66.45 (C), 3.64/4.00 (H), 8.99/9.28 (N), 6.85/6.56 (S). IR (ν, cm^{-1}): 3256 (NH); 3061 (CH aromatic); 2924–2854 (CH); 1719, 1650, 1608 (3C=O); 1567, 1471 (C=C); 1285, 1254 (C=S). ^1H NMR (δ, ppm): 7.17–8.18 (m, 15H, $2C_6H_5$, C_6H_4, triazine C_6 H, coumarin C_4 H), 8.91 (s, 1H, NH).

Reaction of Cyanoacetic Hydrazide Derivative 1 with Elemental Sulfur and Methylene Carbonitrile Reagents

General Procedure for Synthesis of Benzoic 2-(3,5-Diamino-4-substituted-2-thiophenecarbonyl) Hydrazides (14a, 14b)

To a solution of **1** (2.62 g, 0.01 mol) in ethanol (25 mL) containing a catalytic amount of triethylamine, malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added followed by the addition of an equimolar amount of elemental sulfur. The reaction mixture was heated under reflux for 3 h and then cooled and neutralized by pouring it onto an acidified ice-water mixture. The solid product formed in each case was filtered off and recrystallized from dimethylformamide.

Benzoic 2-(3,5-diamino-4-cyano-2-thiophenecarbonyl) hydrazide (14a). $C_{13}H_{11}N_5O_2S$, m.wt. 301, brown crystals, 60% yield, m.p. 210°C. Elemental analysis (% calcd./found): 51.83/51.68 (C), 3.65/3.88 (H), 23.25/22.97 (N), 10.63/10.96 (S). IR (ν, cm^{-1}): 3317–3206 (2NH, $2NH_2$); 3060 (CH aromatic); 2211 (CN); 1650, 1576 (2C=O); 1530, 1460 (C=C). ^1H NMR (δ, ppm): 3.58 (broad s, 4H, $2NH_2$), 7.43–7.97 (m, 5H, C_6H_5), 10.40, 10.58 (2s, 2H, 2NH).

Benzoic 2-(3,5-diamino-4-ethoxycarbonyl-2-thiophenecarbonyl) hydrazide (14b). $C_{15}H_{16}N_4O_4S$, m.wt. 348, pale yellow crystals, 60% yield, m.p. >300°C. Elemental analysis (% calcd./found): 51.72/51.90 (C), 4.60/4.43 (H), 16.09/16.33 (N), 9.19/8.88 (S). IR (ν, cm^{-1}): 3315–3106 (2NH, $2NH_2$); 3066–3031 (CH aromatic); 3001–2823 (CH_2, CH_3); 1750, 1664, 1577 (3C=O); 1537, 1451 (C=C). ^1H NMR (δ, ppm): 1.14–1.32 (t, 3H, CH_3), 3.32 (broad s, 4H, $2NH_2$), 4.15 (q, 2H, CH_2), 7.42–7.98 (m, 5H, C_6 H_5), 10.26, 10.53 (2s, 2H, 2NH). MS m/z (%): 348 [M^+] (0.4), 203 [M^+-145] (16.0), 173 [NH_2–$C(S^+)$ =$C(CO_2Et)$–C^-–NH_2]$^+$ (12.0), 145 [NH_2–$C(S^+)$=C^- (CO_2Et)] (4.0), 121 [phenyl–C(=O)–NH_2]$^{+\cdot}$ (23.0),

105 [phenyl–C=O]$^+$ (100), 84 [N≡C–CH_2–C(=O)–NH_2]$^{+\cdot}$ (8.0), 77 [phenyl]$^+$ (63.5).

Reaction of Cyanoacetic Hydrazide Derivative 1 with Elemental Sulfur and Phenyl Isothiocyanate

To equimolar amounts of **1** (2.62 g, 0.01 mol) and phenyl isothiocyanate (13.51 g, 0.01 mol) in ethanol (20 mL) containing a catalytic amount of triethylamine, an equimolar amount (0.32 g, 0.01 mol) of elemental sulfur was added. The reaction mixture was heated under reflux for 4 h. The solid product formed upon pouring onto an acidified ice-water mixture was collected by filtration and recrystallized from dioxane.

Benzoic 2-(4-Amino-3-phenyl-2-thioxo-2H-5-thiazolecarbonyl) Hydrazide (15)

$C_{17}H_{14}N_4O_2S_2$, m.wt. 370, brown crystals, 71% yield, m.p. 110°C. Elemental analysis (% calcd./found): 55.13/54.86 (C), 3.78/4.02 (H), 15.13/15.43 (N), 17.30/16.95 (S). IR (ν, cm^{-1}): 3325–3214 (2NH, NH_2); 3100–2981 (CH aromatic); 1650, 1595 (2C=O); 1544, 1498 (C=C); 1331, 1280 (C=S). ^{1}H NMR (δ, ppm): 4.50 (s, 2H, NH_2), 7.00–7.99 (m, 10H, $2C_6H_5$), 9.80 (s, 1H, NH), 11.06 (s, 1H, NH).

Cyclization Reaction of Cyanoacetic Hydrazide Derivative 1 with Acetic Acid

A solution of **1** (2.62 g, 0.01 mol) in glacial acetic acid (30 mL) was heated under reflux for 5 h. The solid product formed upon pouring onto an ice-water mixture was collected by filtration and recrystallized from dimethylformamide.

4-Benzoyl-3-cyanomethyl-1,4-dihydro-5H-1,2,4-triazole-5-thione (16)

$C_{11}H_8N_4OS$, m.wt. 244, white crystals, 86% yield, m.p. 232°C. Elemental analysis (% calcd./found): 54.10/53.91 (C), 3.28/3.59 (H), 22.95/22.81 (N), 13.11/13.42 (S). IR (ν, cm^{-1}): 3425–3158 (NH); 3067–3012 (CH aromatic); 2941–2916 (CH_2); 2252 (CN); 1651 (C=O); 1599, 1489 (C=C); 1302, 1257 (C=S). ^{1}H NMR (δ, ppm): 4.62 (s, 2H, CH_2), 7.54–8.15 (m, 5H, C_6H_5), 13.20 (s, 1H, resonating N=C–SH). MS m/z (%): 244 [M^+] (3.0), 216 [M^+-N_2] (3.7), 105 [phenyl–C=O]$^+$ (100), 77 [phenyl]$^+$ (59.2), 51 [CN–CH=C] (28.9).^{13}C NMR (δ, ppm): 17.78 (CH_2), 115.94 (C≡N), 127.87, 128.13, 128.53, 132.55 (phenyl carbons), 153.62 (triazole C_5), 160.10 (C=O), 164.81 (C=S).

Reaction of Triazole Thione Derivative 16 with Elemental Sulfur and Methylene Carbonitrile Reagents

General Procedure for the Synthesis of 4-Benzoyl-3-(2,4-diamino-3-substituted-5-thenyl)-1,4-dihydro-5H-1,2,4-triazole-5-thiones (17a, 17b)

To a solution of **16** (2.44 g, 0.01 mol) in ethanol (20 mL) and dimethylformamide (10 mL) containing a catalytic amount of triethylamine, malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added followed by the addition of an equimolar amount (0.32 g, 0.01 mol) of elemental sulfur. The reaction mixture was heated under reflux for 5 h, cooled, and then neutralized by it pouring onto an acidified ice-water mixture. The solid products formed in each case were filtered off and recrystallized from dimethylformamide

4-Benzoyl-3-(2,4-diamino-3-cyano-5-thenyl)-1,4-dihydro-5H-1,2,4-triazole-5-thione (17a). $C_{14}H_{10}N_6OS_2$, m.wt. 342, dark brown crystals, 86% yield, m.p. >300°C. Elemental analysis (% calcd./found): 49.12/49.25 (C), 2.92/3.11 (H), 24.56/24.20 (N), 18.71/18.41 (S), IR (ν, cm^{-1}): 3380–3300 (NH, $2NH_2$); 3157–3050 (CH aromatic); 2193 (CN), 1663 (C=O); 1602, 1491 (C=C); 1299, 1248 (C=S). ^1H NMR (δ, ppm): 3.54–3.55 (2s, 4H, $2NH_2$), 7.59–7.96 (m, 5H, C_6H_5), 8.10 (s, 1H, NH). MS m/z (%): 342 [M^+] (trace), 341 [M^+-1] (0.47), 300 [M^+-(H_2N–C≡N)] (1.96), 244 [M^+-(NH_2–$C(S^+)$ =C^-–CN)] (79.15), 212 [244-S](3.43), 186 [244-(N=C=S)$^+$] (100), 105 [phenyl–C=O]$^+$ (26.52), 77 [phenyl]$^+$ (21.63), 59 [HN=C=S]$^{+\cdot}$ (3.31).

4-Benzoyl-3-(2,4-diamino-3-ethoxycarbonyl-5-thenyl)-1,4-dihydro-5H-1,2,4-triazole 5-thione (17b). $C_{16}H_{15}N_5O_3S_2$, m.wt. 389, dark brown crystals, 65% yield, m.p. 185°C. Elemental analysis (% calcd./found): 49.36 /49.70 (C), 3.86 /4.22 (H), 17.99/18.10 (N), 16.45/16.64 (S), IR (ν, cm^{-1}): 3420–3163 (NH, $2NH_2$); 3062 (CH aromatic); 2922–2850 (CH_2, CH_3), 1725, 1672 (2C=O); 1600, 1494 (C=C); 1302, 1257 (C=S). ^1H NMR (δ, ppm): 1.19–1.23 (t, 3H, CH_3), 4.25–4.31 (q, 2H, CH_2), 4.62 (s, 2H, NH_2), 7.55–8.15 (m, 5H, C_6H_5), 13.00 (s, 1H, NH).

Reaction of Triazole Thione Derivative 16 with Elemental Sulfur and Phenyl Isothiocyanate

To an equimolar amount of **16** (2.44 g, 0.01 mol) and phenyl isothiocyanate (1.35 g, 0.01 mol) in ethanol (20 mL) and dimethylformamide (10 mL) containing a catalytic amount of triethylamine, elemental sulfur (0.32 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 h. The solid product formed upon pouring onto an acidified

ice-water mixture was collected by filtration and recrystallized from dimethylformamide.

4-Benzoyl-3-(4-amino-3-phenyl-2H-2-thioxo-5-thiazolyl)-1,4-dihydro-5H-1,2,4-triazole-5-thione (18)

$C_{18}H_{13}N_5OS_3$, m.wt. 411, deep green crystals, 72% yield, m.p. 200°C. Elemental analysis (% calcd./found): 52.55/52.23 (C), 3.16/3.49 (H), 17.03/16.83 (N), 23.36/22.98 (S). IR (ν, cm^{-1}): 3398–3163 (NH, NH_2); 3058 (CH aromatic); 1671 (C=O); 1599, 1470 (C=C); 1300, 1244 (C=S). ^1H NMR (δ, ppm): 3.51 (s, 2H, NH_2), 7.16–8.15 (m, 10H, $2C_6H_5$), 13.06 (s, 1H, NH). MS m/z (%): 412 [M^++1] (1.91), 411 [M^+] (6.42), 332 [411- (phenyl)$^+$] (1.51), 249 [412- (Ph C(=O)–N=C=S)]$^{+\cdot}$ (7.26), 204 [$C_9H_6N_3OS$]$^{+\cdot}$ (2.49), 135 [phenyl–N=C=S]$^{+\cdot}$ (46.05), 105 [phenyl–C=O]$^+$ (100), 77 [phenyl]$^+$ (24.99).

Microbiology: Biological Screening of the Synthesized Compounds for Antimicrobial Activity

Thirty-two compounds were screened in vitro for their antimicrobial activity against two bacterial isolates (Saprophytic, *E. coli,* Parasitic, *X. citri*) and 3 fungal isolates (Saprophytic, *A. fumigatus;* Phytopathogenic, *R. solani; F. oxysporum*). The culture medium was the nutrient agar for bacteria and Czapek's Dox agar medium for fungi. The sterile medium was inoculated with the test organism so that each 100 mL of the medium received 1 mL of a 24-hour culture of the bacterium or a 7-day-old culture of the spore suspension of the fungus. The solutions of the tested compounds at 25 μg/mL in dimethylformamide (DMF) were placed separately in the cup (8 mm diameter). The plates were incubated at 28°C, and the resulting inhibition zones were measured. DMF as a blank exhibited no antimicrobial activity against any of the tested organisms used. The recorded inhibition zones are summarized in Table I.

CONCLUSION

We have reported a convenient synthesis of a variety of fused and pendant hetero-cyclic systems from cyanoacetic 2-[(benzoylamino) thioxomethyl]hydrazide. The S/N regioselective nucleophilic competition, as well as the selectivity for terminal attack at the cyanoacetic moiety, led to the diversity of the produced heterocyclic systems. Most of the synthesized systems were found to be promising antibacterial agents and hence deserve further pharmacological investigation. Currently, we are investigating the potential antitumor activity of the synthesized

systems and related derivatives. The results of these investigation will be published in due time.

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