Synthesis of Thiophenes, Azoles and Azines with Potential Biological Activity by Employing the Versatile Heterocyclic Precursor N-Benzoycyanoacetylhydrazine

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This research work is concerned with the use of N-benzoyl cyanoacetylhydrazine (**3**) in synthesizing several new heterocyclic compounds with potential biological activity, via its reaction with various chemical reagents. The synthesized derivatives have actually exhibited, upon screening, antibacterial and antifungal activities.

Keywords: N-Benzoylhydrazide; Thiophene; Thiazole; Coumarin.

INTRODUCTION

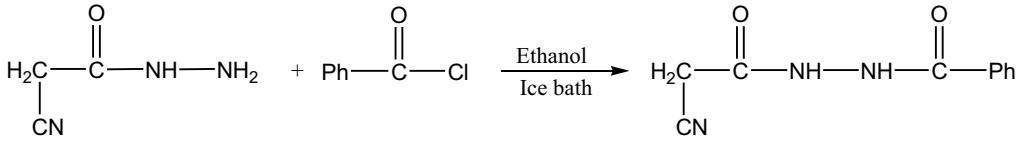
Our continuous interest in the chemistry of hydrazones and hydrazides[1-4] originates from our persistent trials to obtain pyridines, pyrimidines, pyridazines, thiophenes and their analogues. The importance of such compounds lies in their diverse pharmaceutical activities, namely antibacterial,[5,6] antidiabetic,[7] anti-HIV,[8] antiviral[9,10] and analgesic activities. To our knowledge, little work has been published on using N-benzoylcyanoacetyl hydrazine in heterocyclic synthesis. In this work we report the use of the title reagent in several heterocyclic transformations to obtain pyrazole, pyridine, pyridazine, thiophene and triazine derivatives of biological activity. N-benzoylcyanoacetyl hydrazine synthesis was previously reported in the literature;[11] however, we herein present a different and simple method of its preparation using cyanoacetylhydrazine (**1**) and benzoyl chloride (**2**).

RESULTS AND DISCUSSION

Benzoyl cyanoacetylhydrazine (**3**) was prepared via the reaction of an ethanol solution of cyanoacetyl hydrazine (**1**) with benzoyl chloride (**2**) in an ice bath with a temperature range of 0-5 °C.

Compound **3** reacts with benzaldehyde (**4a**), p-chlorobenzaldehyde (**4b**), or p-anisaldehyde (**4c**) in an ethanol solution in the presence of a catalytic amount of piperidine to give the benzal derivatives **5a**-**c**, respectively.

The reactivity of the benzal derivative **5a** towards some chemical reagents was studied aiming at the formation of polyfunctionally substituted heterocyclic compounds with potential biological activities. Thus, the reaction of **5a** with either malononitrile (**6a**) or ethyl cyanoacetate (**6b**) gave the pyridine derivatives **7a** and **7b**, respectively. The formation of compounds **7a** and **7b** is most likely to proceed *via* Michael addition followed by cyclization. Structures of the latter products were based on analytical and spectral data. Thus, the ^{13}C NMR spectrum of **7a** showed the presence of signals at δ 120.2, 123.4, 128.5, 130.2, 133.9, 138.1, 139.6, 140.0, and 156.6 corresponding to two C_6H_5 groups and the pyridine carbons, 115.6, 118.3 two CN groups and 160.2, 166.9 corresponding to two C=O groups. On the other hand, the reaction of **5a** with either hydrazine hydrate (**8a**) or phenylhydrazine (**8b**) gave the



1 **2** **3**

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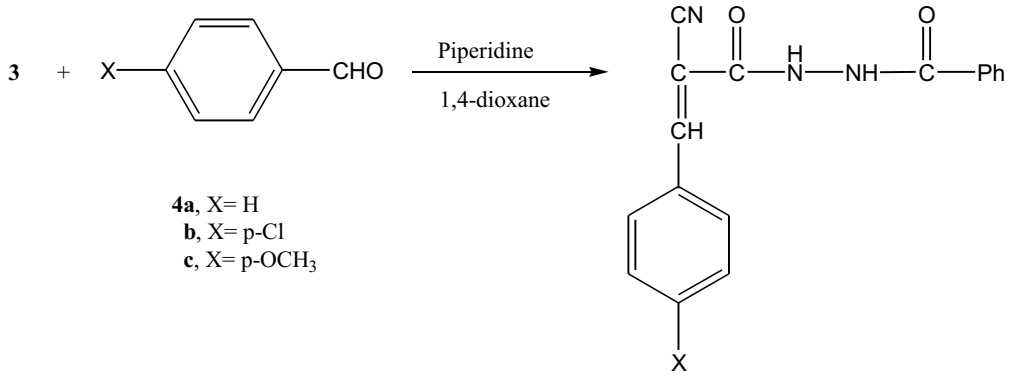


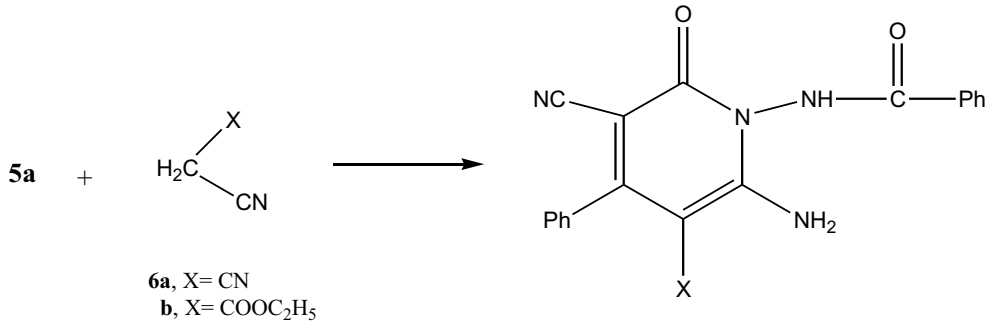
4a, X= H
b, X= p-Cl
c, X= p-OCH_3

5a, X= H
b, X= p-Cl
c, X= p-OCH_3

pyrazole derivatives **9a** and **9b**, respectively.

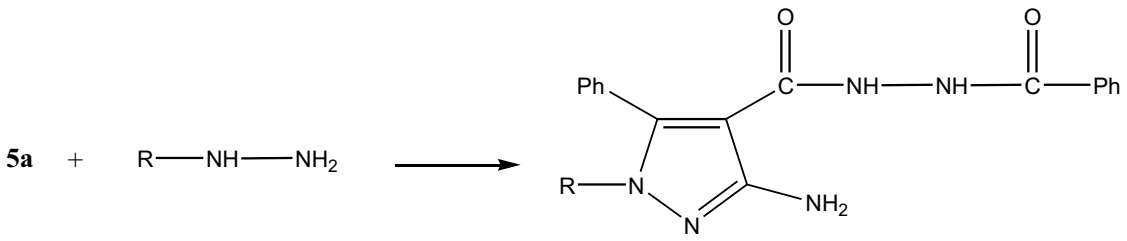
On the other hand, the reaction of **3** with salicaldehyde (**10**) gave the coumarin derivative **11**. Formation of similar coumarins through the reaction of cyanomethylene reagents with salicylaldehyde has been previously reported.[12]

The reaction of **3** with aromatic or heteroaromatic diazonium salts is studied aiming at the formation of hydrazones capable of heterocyclization. Thus the reaction of **3** with either benzenediazonium chloride (**12a**), p-chlorobenzenediazonium chloride (**12b**), p-tolyldiazonium chloride (**12c**), or the diazonium acetates of 2-diazo-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene (**12d**) and ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate



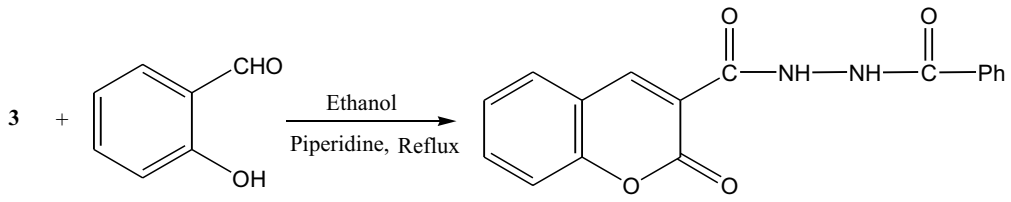
6a, X= CN
b, X= $COOC_2H_5$

7a, X= CN
b, X= $COOC_2H_5$



8a, R= H
b, R= Ph

9a, R= H
b, R= Ph



10 **11**

(**12e**), gave the corresponding hydrazone derivatives **13a-e**.

The ^{1}H NMR spectrum of **13a** (as an example) showed a multiplet at δ 7.21-7.57 ppm due to two phenyl groups and three singlets (D_2O exchangeable) at δ 8.22, 8.29 and 9.41 ppm due to the three NH groups. The reaction of **13a** with either hydrazine hydrate (**8a**) or phenylhydrazine (**8b**) gave the pyrazole derivatives **15a** and **15b**, respectively. Formation of the latter products takes place supposedly through the intermediate formation of the amidrazone derivatives **14a** and **14b**, followed by water elimination. Elemental and spectral analyses were consistent with the proposed structures (see experimental section).

Moreover, the reaction of **13a** with phenyl isothiocyanate **16** gave the 1,2,4-triazine derivative **18** which is presumably formed via the intermediate formation of **17**. Analytical and spectral data of the reaction product were in agreement with the proposed structure.

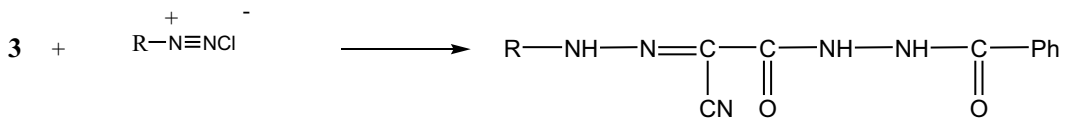
On the other hand, the reaction of **13a** with either malononitrile (**6a**) or ethyl cyanoacetate (**6b**) gave the pyridazine derivatives **20a** and **20b**, respectively. The reaction presumably took place via the intermediate formation of **19a** and **19b**, respectively.

Structures of the products were based on analytical and spectral data. Thus the ^{1}H NMR spectrum of **20a** showed a singlet at δ 5.36 ppm (D_2O exchangeable) due to the amino group, a multiplet at δ 7.30-7.38 ppm due to the two phenyl groups, and two singlets at δ 8.49 and 8.81 ppm (D_2O exchangeable) due to the two NH groups.

The scope and limitation of using N-benzoylcyanoacetyl hydrazine in forming condensed molecules were also studied. Thus the reaction of **3** with acetophenone (**21**) was carried out in the presence of ammonium acetate and gave the condensate **22**.

The ^{1}H NMR of **22** exhibited a singlet at δ 2.38 ppm for the methyl group, two multiplets at δ 7.31-7.38 ppm due to the two phenyl groups and two singlets (D_2O exchangeable) at δ 8.22 and 8.36 ppm for the two NH groups. Further confirmation for the structure of **22** was achieved through exploring its reactivity towards some chemical reagents. Thus, the reaction of compound **22** with sulfur in DMF containing triethylamine gave the thiophene derivative **23**. Analytical and spectral data were in agreement with the proposed structure (see experimental data).

Moreover, the reaction of **22** with benzaldehyde (**4a**)

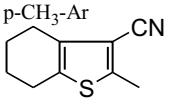


12a, R= Ph

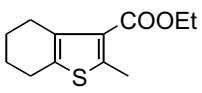
b, R= p-Cl-Ar

c, R= p-CH_3-Ar

d, R=



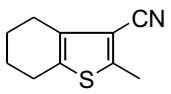
e, R=



13a, R= Ph

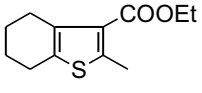
b, R= p-Cl-Ar

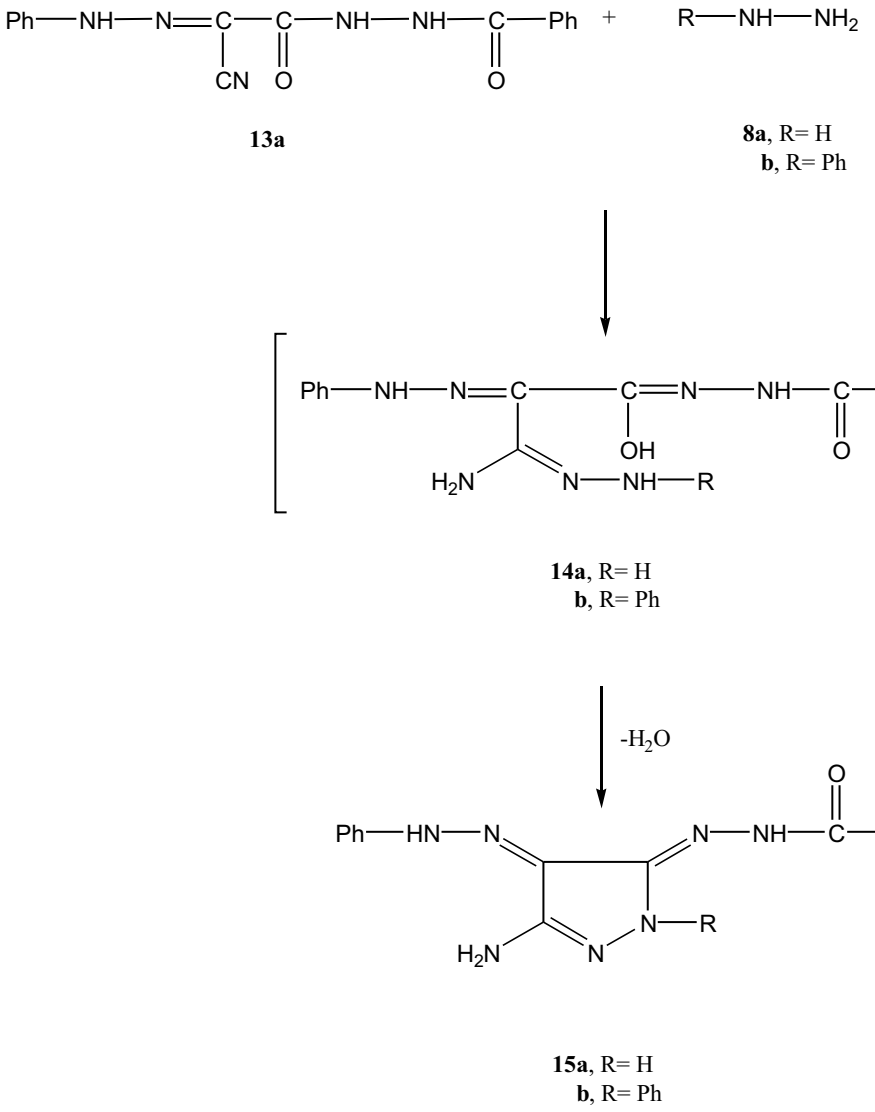
c, R= p-CH_3-Ar



d, R=

e, R=

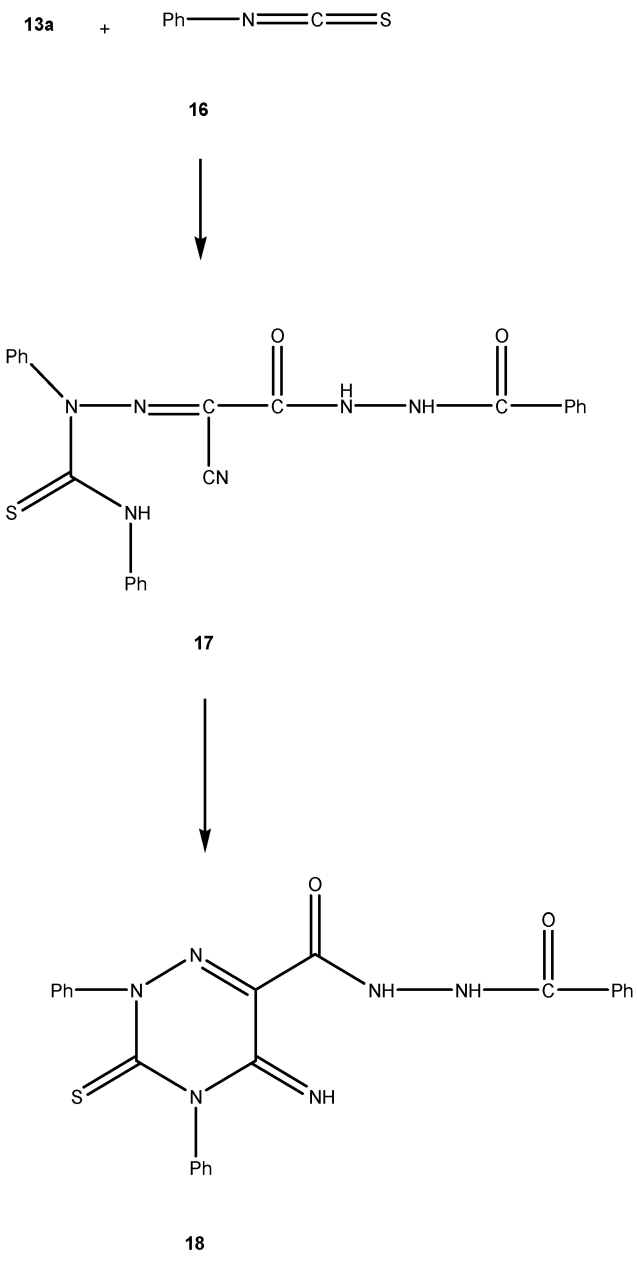




gave the benzal derivative **24**, and with benzenediazonium chloride (**12a**) gave the hydrazone derivative **25**.

In addition, the reaction of **22** with either malononitrile (**6a**) or ethyl cyanoacetate (**6b**) gave the polyfunctionally substituted benzene derivatives **27a** and **27b**, respectively. The proposed structures for the latter products were in agreement with their analytical and spectral data. Thus, the ^{1}H NMR spectrum of **27a** showed two singlets at δ 4.48 and 5.62 ppm (D_2O exchangeable) for the two amino groups, two singlets at δ 8.68 and 9.41 ppm (D_2O exchangeable) for the two NH groups, and a multiplet at δ 7.26-7.39 ppm due to eleven aromatic protons present in the two phenyl groups and in the parent benzene ring.

In recent years, our research group was involved in a comprehensive program dealing with the reaction of active methylene reagents with phenyl isothiocyanate in a basic dimethylformamide solution, followed by heterocyclization with α-halocarbonyl compounds.[13-18] The reaction leads to the formation of either thiophene or thiazole derivatives depending on the reaction conditions and the nature of the α-halocarbonyl compound. In continuation of this work, compound **3** has been subjected to the Hantzsch reaction, and it was found that it reacts with phenylisothiocyanate (**16**) in a solution of dimethylformamide and potassium hydroxide to give the non-isolable potassium sulfide salt **28**, which reacts with ethyl chloroacetate (**29a**) or methyl bromoacetate (**29b**) to give in each case a single product with a molecular formula $C_{21}H_{20}N_4SO_4$ and $C_{20}H_{18}N_4SO_4$, respectively. Two possible isomeric products were considered: either **30a,b** or **31a,b**.



The IR spectrum of the product was in favor of the thiophenes **31a,b** due to the absence of any cyano group stretching which is expected to appear in the range of 2210-2227 cm^{-1}, and the appearance of an amino group stretching in the range of 3480-3370 cm^{-1} instead. Moreover, the ^1H NMR spectrum showed in the case of **31b**, a singlet at δ 2.82 ppm for the methyl group, a multiplet at δ 7.28-7.35 ppm for the two phenyl groups and three singlets (D_2O exchangeable) at δ 8.30, 8.45 and 8.47 ppm for the three NH groups.

By following the same procedure, the non-isolable intermediate potassium salt **28** was also reacted with chloroacetone (**32**) and gave the thiophene derivative **33**.

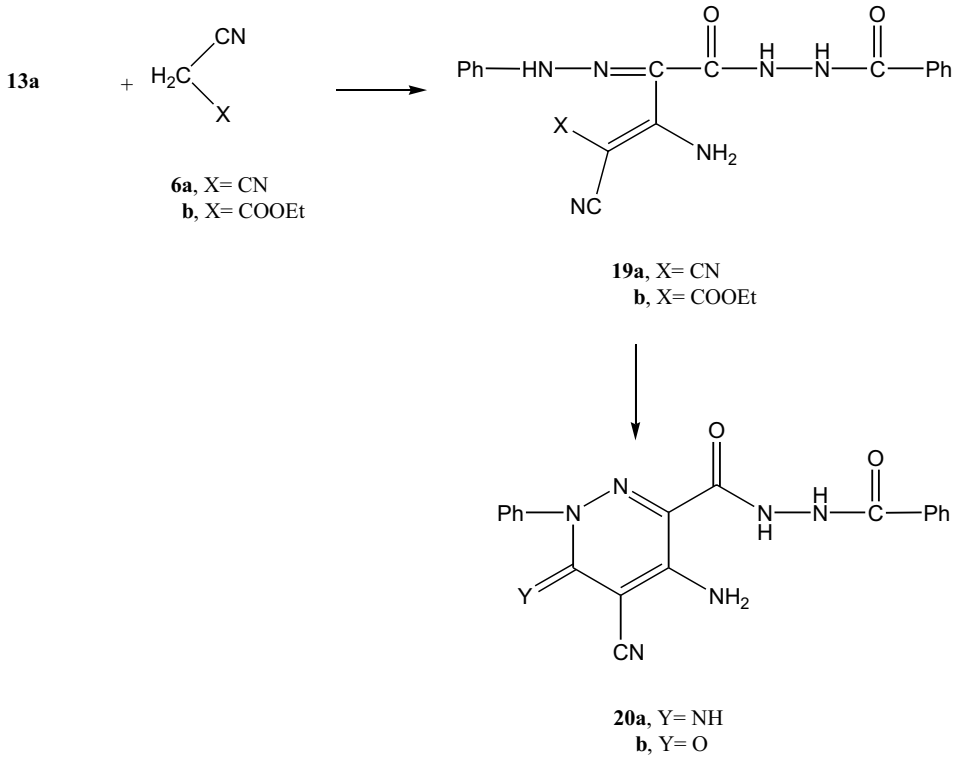
In a similar manner, **28** reacted with ω-bromoacetophenone **34** to yield the thiophene derivative **35**.

The reactivity of compound **3** towards cinnamonitrile derivatives was also studied. Thus **3** was reacted with the cinnamonitrile derivatives **36a-d** to give in each case a single product with a molecular formula $C_{20}H_{13}N_5O_2$, $C_{22}H_{18}N_4O_4$, $C_{21}H_{15}N_5O_3$ and $C_{23}H_{20}N_4O_5$, respectively.

Further confirmation for the latter structures was achieved through an alternative synthesis. Thus, the products **7a,b** were previously obtained via the reaction of **5a** with malononitrile (**6a**) and ethyl cyanoacetate (**6b**), respectively. Similarly, compounds **38a,b** were alternatively synthesized through reacting the benzal derivative **5c** with **6a** and **6b**, respectively.

SCREENING FOR ANTIMICROBIAL ACTIVITY

Twenty-one compounds were screened *in vitro* for their antimicrobial activity against two bacterial isolates, one saprophytic (*Escherichia coli*) and the other is parasitic (*Xanthomonas citi*) and 3 fungal isolates one saprophytic (*Aspergillus fumigatus*) and two phytopathogenic (*Rhizoctonia solani* and *Fusarium 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 7-day-old culture of 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 ºC 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 1. The results indicated that most of the prepared compounds are active against the test organisms. The most toxic compounds against bacterial and fungal isolates were **15a**, **15b**, **18**, **7a** and **38d**, followed by **5b**, **5c**, **11**, **13a-c**, **13e**, and **20a,b**. Compounds **13d**, **25** and **27a** and **27b** were less toxic to the test organisms. In general, bacterial isolates were more susceptible to the synthesized compounds than fungal isolate.

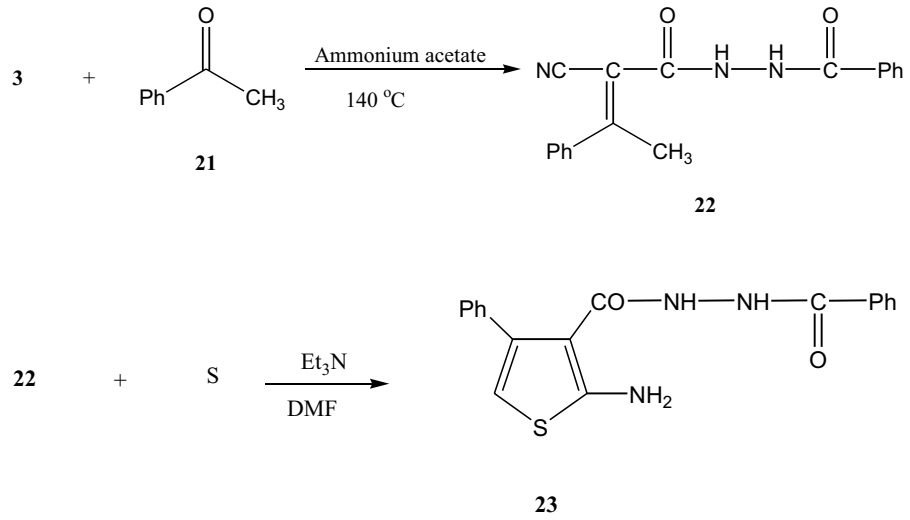


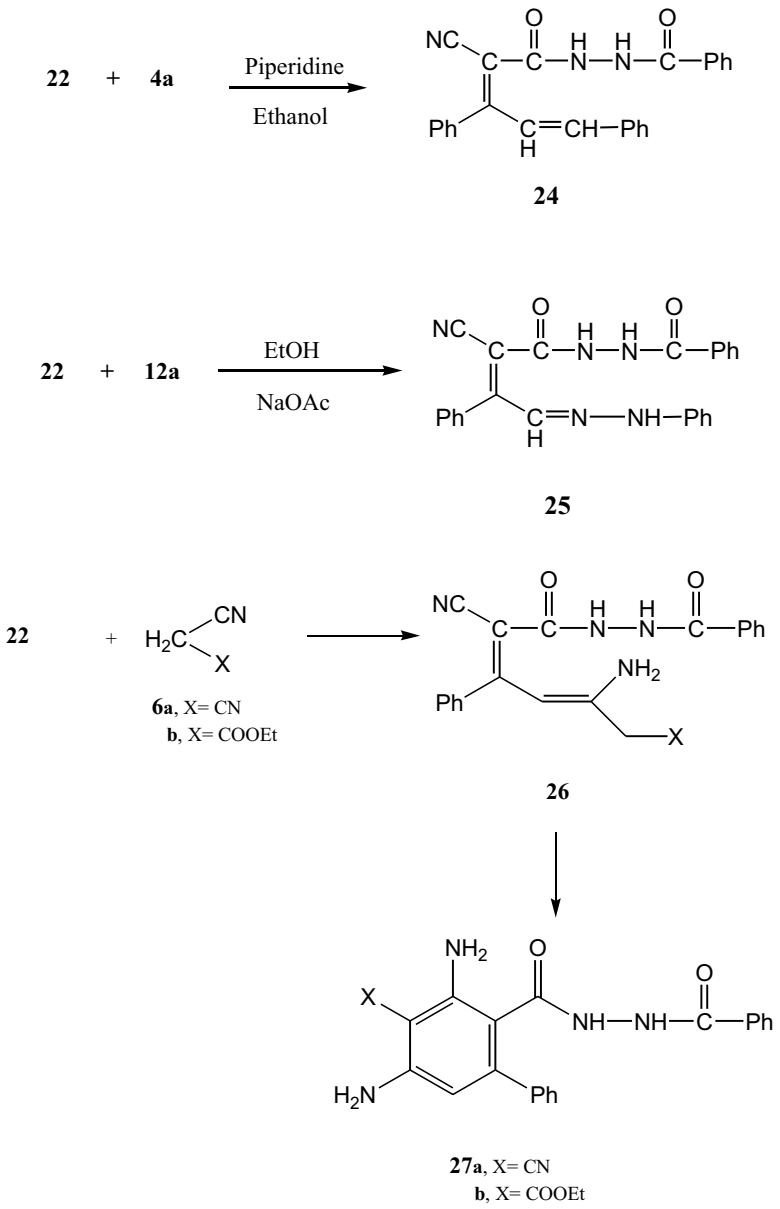
EXPERIMENTAL

All melting points were determined in open capillaries and are uncorrected. IR spectra were measured using KBr discs on a Pye Unicam SP-1000 spectrophotometer. ^{1}H-NMR spectra were measured on a Varian EM390-200 MHz instrument in CD_3SOCD_3 as solvent using TMS as internal standard, and chemical shifts are expressed as δ in units of ppm. Analytical data were obtained from the Micro Analytical Data Unit at Cairo University and UC Berkeley, California State University, USA.

N-Benzoylcyanoacetylhydrazine (3)

In an ice bath (0-5 °C), benzoyl chloride (11.6 g, 0.08 mol) is added dropwise to an ethanol solution of cyanoacetylhydrazine (8.20 g, 0.08 mol), with continuous stir-





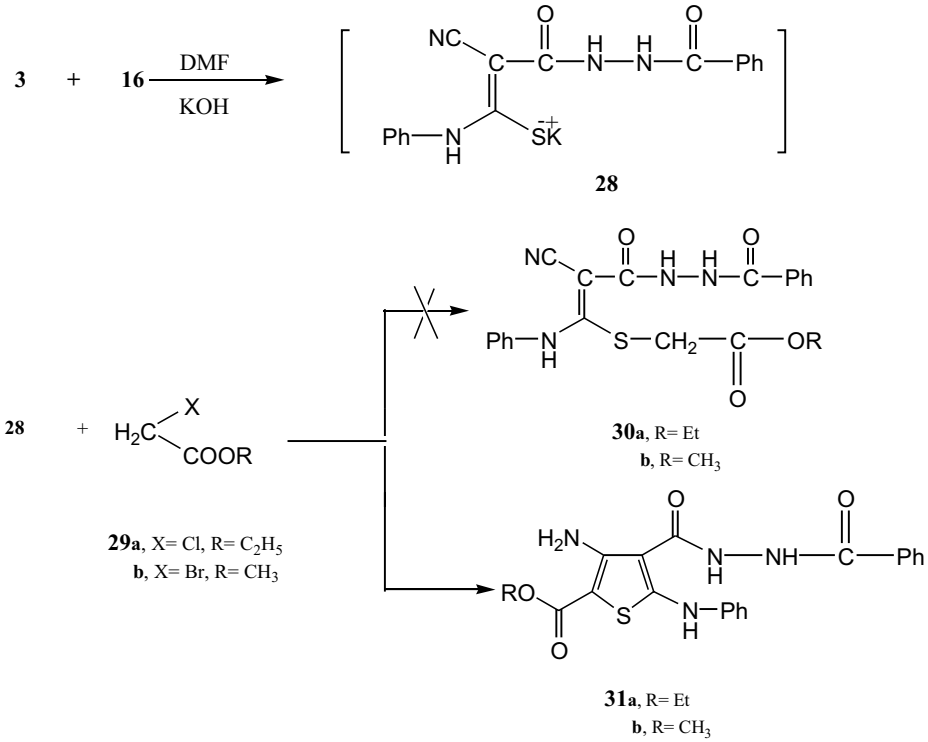
ring. The compound in question precipitates immediately and is collected by filtration. The analytical and spectral data of this compound are analogous with those reported in the literature. White crystals from ethanol, yield 80.05%, 13 g, m.p. 165 °C.

Synthesis of 5a-c (General Procedure)

Equimolar amounts (0.019 mol) of N-benzoylcyanoacetylhydrazine **3** and **4a**, **4b** or **4c**, in ethanol containing a catalytic amount of piperidine, were heated under reflux for 2 h. The reaction mixture was poured on an ice-water mixture and the solid product collected by filtration and recrystallized from the proper solvent.

N-Benzoyl-α-benzalcyanoacetylhydrazine (5a)

Yellowish white crystals from ethanol, yield 57.60%, 3.3 g, m.p. 110 °C. IR (KBr): υ/cm^{-1} = 3460-3310 (2 NH), 3062 (CH aromatic), 2225 (CN), 1700, 1680 (2 C=O), 1635 (C=C). ^{1}H NMR (DMSO) δ = 6.80 (CH=C), 7.21-7.38 (m, 10H, 2 C_6H_5), 8.32, 8.75 (2s, 2H, 2NH). $C_{17}H_{13}N_3O_2$ (291.31): Calcd: C, 70.09; H, 4.50; N, 14.43%; Found: C, 70.22; H, 4.77; N, 14.60%.



28

30a, R= Et
b, R= CH_3

29a, X= Cl, R= C_2H_5
b, X= Br, R= CH_3

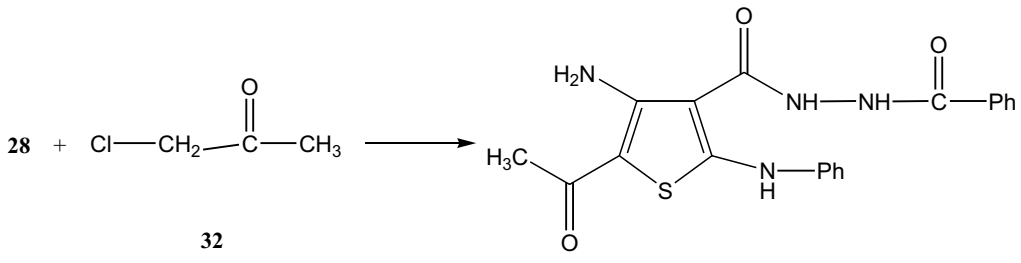
31a, R= Et
b, R= CH_3

N-Benzoyl-α-(4-chlorobenzal)cyanoacetylhydrazine (5b)

Yellow crystals from ethanol, yield 64.92%, 5.2 g, m.p. 145 ºC. IR (KBr): υ/cm^{-1} = 3444-3320 (2 NH), 3058 (CH aromatic), 2227 (CN), 1695, 1680 (2 C=O), 1638 (C=C). ^{1}H NMR (DMSO) δ = 6.75 (CH=C), 7.32-7.40 (m, 9H, C_6H_5, C_6H_4), 8.30, 8.69 (2 s, 2H, 2NH). $C_{17}H_{12}N_3O_2Cl$ (325.76): Calcd: C, 62.68; H, 3.71; N, 12.90%; Found: C, 62.70; H, 3.92; N, 12.65%.

N-Benzoyl-α-(4-methoxybenzal)cyanoacetylhydrazine (5c)

Pale yellow crystals from ethanol, yield 94.86%, 1.2 g, m.p. 130 ºC. IR (KBr): υ/cm^{-1} = 3435-3318 (2NH), 3050



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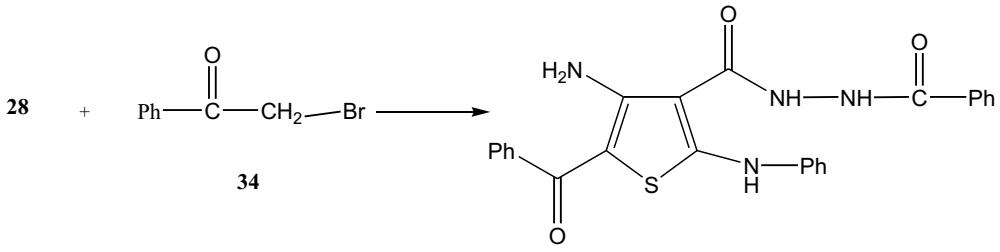

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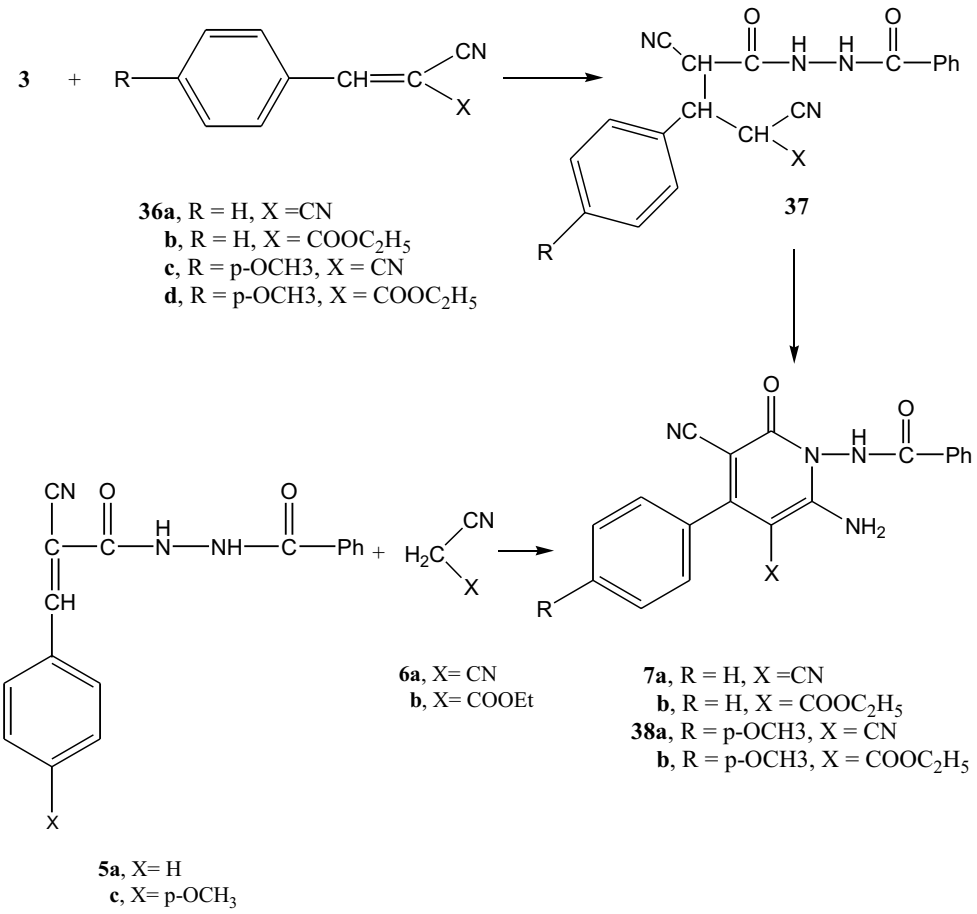

(CH aromatic), 2975 (CH_3), 2220 (CN), 1698, 1683 (2C=O), 1640 (C=C). ^{1}H NMR (DMSO) δ = 3.21 (s, 3H, CH_3), 6.80 (s, 1H, CH=C), 7.31-7.39 (m, 9H, C_6H_5, C_6H_4), 8.21, 8.30 (2s, 2H, 2NH). $C_{18}H_{15}N_3O_3$ (321.34): Calcd: C, 67.28; H, 4.71; N, 13.08%; Found: C, 67.50; H, 5.31; N, 13.50%.

Synthesis of 7a,b (General Procedure)

Equimolar amounts of N-benzoyl-α-benzalcyanoacetylhydrazine (**5a**) (1.72×10^{-3} mol) and either **6a** or **6b** in ethanol containing a catalytic amount of triethylamine (a few drops), were heated under reflux for 3 h. The reaction mixture was then poured over an ice-water mixture and treated with a few drops of HCl. The solid product was collected by filtration and recrystallized from ethanol.

2-Amino-1-benzamino-3,5-dicyano-6-oxo-5-phenylpyridine (7a)

Yellowish brown crystals from ethanol, yield 58.33%, 0.35 g, m.p. 170 ºC. IR (KBr): υ/cm^{-1} = 3565-3348 (NH_2, NH), 3054 (CH aromatic), 2222 (2CN), 1688, 1684 (2C=C), 1640 (C=C). ^{1}H NMR (DMSO) δ = 4.88 (s, 2H, NH_2), 7.29-7.36 (m, 10H, 2 C_6H_5), 8.43 (s, br, 1H, NH). ^{13}C NMR δ 120.2, 123.4, 128.5, 130.2, 133.9, 138.1, 139.6, 140.0, 156.6 (2C_6H_5), 115.6, 118.3 (2 CN), 160.2, 166.9 (2 CO). $C_{20}H_{13}N_5O_2$ (355.36): Calcd: C, 67.60; H, 3.69; N, 19.71%; Found: C, 67.90; H, 4.10; N, 19.95%.

Ethyl 2-amino-1-benzamino-5-cyano-6-oxo-4-phenylpyridine-3-carboxylate (7b)

Grey crystals from ethanol, yield 54.55%, 0.30 g, m.p. 130 ºC. IR (KBr): υ/cm^{-1} = 3495-3360 (NH_2, 3NH), 3050 (CH aromatic), 2975, 2870 (3C=O), 1640 (C=C). ^{1}H NMR (DMSO) δ = 1.15 (t, 3H, *J* = 7.05 Hz, CH_3), 4.24 (q, 2H, *J* = 7.05 Hz, CH_2), 5.21 (s, 2H, NH_2), 7.31-7.38 (m, 10H, 2 C_6H_5), 8.81 (s, 1H, NH). $C_{22}H_{18}N_4O_4$ (402.41): Calcd: C, 65.67; H, 4.51; N, 13.92%; Found: C, 66.15; H, 4.45; N, 14.40%.

Preparation of 9a,b (General Procedure)

To a solution of N-benzoyl-α-benzalcyanoacetylhy-

Table 1. Inhibition zones in mm for some of the synthesized compounds at a concentration level of 25 μg/mL

Compound	*E. coli*	*X. citri*	*A. fumigatus*	*R. solani*	*F. oxysporum*
5b	26	26	12	13	14
5c	22	18	10	14	18
7a	30	36	32	18	16
7b	32	15	12	4	0
11	14	10	8	9	8
13a	13	12	6	5	4
13b	24	18	16	13	17
13c	23	16	16	14	19
13d	10	10	6	8	0
13e	14	12	8	4	4
15a	34	30	18	14	18
15b	26	24	16	15	13
18	32	29	17	16	18
20a	28	26	19	17	13
20b	10	8	6	0	4
25	18	12	6	5	0
27a	22	16	5	3	0
27b	10	29	30	15	18
31a	18	22	18	6	4
33	26	33	28	16	17
38d	37	18	16	15	16

drazine (**5a**) (1.58×10^{-3} mol) in ethanol, an equimolar amount of **8a** or **8b** is added and the solution is heated under reflux for 3 h, after which the contents are poured on an ice-water mixture and the precipitated solid is then filtered out and recrystallized from ethanol.

5-Amino-4-N-benzoylhydrazido-3-phenyl-pyrazole (9a)

Pale brown crystals from ethanol, yield 54.90%, 0.28 g, m.p. 145 ºC. IR (KBr): υ/cm^{-1} = 3466-3312 (NH_2, 3 NH), 3060 (CH aromatic), 1690, 1685 (2 C=O), 1660 (C=N), 1640 (C=C). ^{1}H NMR (DMSO) δ = 5.42 (s, 2H, NH_2), 7.31-7.40 (m, 10H, $2C_6H_5$), 8.20, 9.23, 9.40 (3s, 3H, 3NH). ^{13}C NMR δ 124.5, 127.5, 127.5, 132.2, 134.2, 154.2 (two C_6H_5, pyrazole), 163.8, 168.4 (2 CO). $C_{17}H_{15}N_5O_2$ (321.34): Calcd: C, 63.54; H, 4.71; N, 21.80%; Found: C, 63.70; H, 4.90; N, 21.35%.

5-Amino-4-N-benzoylhydrazido-2,3-diphenylpyrazole (9b)

Yellowish brown crystals from ethanol, yield 70.59%, 0.48 g, m.p. 107 ºC. IR (KBr): υ/cm^{-1} = 3473-3318 (NH_2, 2 NH), 3063 (CH aromatic), 1688, 1685 (2 C=O), 1654 (C=N), 1638 (C=C). ^{1}H-NMR (DMSO) δ = 5.38 (s, 2H, NH_2), 7.26-7.36 (m, 15H, $3C_6H_5$), 8.22, 9.26 (2s, 2H, 2NH). $C_{23}H_{19}N_5O_2$ (397.44): Calcd: C, 69.51; H, 4.82; N, 17.62%; Found: C, 70.10; H, 4.35; N, 17.00%.

Synthesis of 11

To a solution of N-benzoylcyanoacetylhydrazine **3** (0.6 g, 2.96×10^{-3} mol) in ethanol, a few drops of piperidine are added, followed by the addition of salicylaldehyde (**10**) (0.36 g, 2.96×10^{-3} mol). The reaction mixture is then heated under reflux for 3 h, after which it is poured on an ice-water mixture. The precipitated crystals are then collected by filtration and recrystallized from ethanol.

3-(N-benzoylhydrazido)-coumarin (11)

Orange crystals from ethanol, yield 54.95%, 0.5 g, m.p. 60 ºC. IR (KBr): υ/cm^{-1} = 3420-3310 (2NH), 3054 (CH aromatic), 1690, 1682 (2C=O), 1640 (C=C). ^{1}H NMR (DMSO) δ = 6.82 (s, 1H, coumarin H-4), 7.33-7.41 (m, 9H, C_6H_5, C_6H_4), 8.22, 8.30 (2s, 2H, 2NH). $C_{17}H_{12}N_2O_4$ (308.30): Calcd: C, 66.23; H, 3.92; N, 9.09%; Found: C, 66.58; H, 4.23; N, 9.60%.

Synthesis of 13a-e (General Procedure)

To a cold (0-5 ºC) solution of compound **3** (4.25 g,

0.02 mol) in ethanol, containing a few sodium hydroxide pellets, an equimolar amount of any of compounds **12a-e** [prepared by adding an aqueous sodium nitrite solution (2.9 g, 0.04 mol) to a cold solution of either aniline, p-chloroaniline, p-toluidine, 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene or 2-amino-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophene, respectively, in the appropriate amount of conc. HCl at 0-5 ºC, with continuous stirring] was added with stirring. The reaction mixture was left at room temperature for an additional hour, then the formed solid product was filtered out and recrystallized from ethanol.

α-Phenylhydrazo-N-benzoyl cyanoacetylhydrazine (13a)

Reddish orange crystals from ethanol, yield 58.94%, 3.79 g, m.p. 195 ºC. IR (KBr): υ/cm^{-1} = 3480-3328 (3NH), 3062 (CH aromatic), 2228 (CN), 1688, 1680 (2C=O), 1660 (C=N), 1635 (C=C). ^{1}H NMR (DMSO) δ = 7.21-7.57 (m, 10H, $2C_6H_5$), 8.27, 8.29, 9.41 (3s, 3H, 3NH). $C_{16}H_{13}N_5O_2$ (307.32): Calcd: C, 62.54; H, 4.26; N, 22.79%. Found: C, 62.90; H, 4.40; N, 23.25%.

α-(4-Chloro-phenylhydrazo)-N-benzoylcyanoacetylhydrazine (13b)

Light brown crystals from ethanol, yield 41.67%, 0.35 g, m.p. 120 ºC. IR (KBr): υ/cm^{-1} = 3475-3340 (3NH), 3054 (CH aromatic), 2225 (CN), 1686, 1680 (2C=O), 1670 (C=N), 1634 (C=C). ^{1}H NMR (DMSO) δ = 7.26-7.34 (m, 9H, C_6H_5, C_6H_4), 8.29-8.34 (m, 3H, 3NH). $C_{16}H_{12}N_5O_2Cl$ (341.76): Calcd: C, 56.23; H, 3.54; N, 20.49%; Found: C, 56.09; H, 4.15; N, 19.88%.

α-(4-Methyl-phenyl hydrazo)-N-benzoylcyanoacetylhydrazine (13c)

Orange crystals from ethanol, yield 84.91%, 2.70 g, m.p. 125 ºC. IR (KBr): υ/cm^{-1} = 3478-3336 (3NH), 3058 (CH aromatic), 2980 (CH_3), 2228 (CN), 1690, 1683 (2C=O), 1665 (C=N), 1634 (C=C). ^{1}H NMR (DMSO) δ = 2.88 (s, 3H, CH_3), 7.32-7.39 (m, 9H, C_6H_5, C_6H_4), 8.30-8.34 (m, 3H, 3NH). $C_{17}H_{15}N_5O_2$ (321.34): Calcd: C, 63.54; H, 4.71; N, 21.80%; Found: C, 64.12; H, 4.55; N, 21.35%.

α-(3-Cyano-2-hydrazo-4,5,6,7-tetrahydrobenzo[b]-thieno)-N-benzoyl cyanoacetylhydrazine (13d)

Dark brown crystals from ethanol, yield 47.27%, 0.52 g, m.p. 140 ºC. IR (KBr): υ/cm^{-1} = 3468-3341 (3NH), 3060 (CH aromatic), 2225, 2220 (2 CN), 1684, 1680 (2C=O), 1663 (C=N), 1640 (C=C). ^{1}H NMR (DMSO) δ = 2.24-2.27 (m, 4H, $2CH_2$), 2.32-3.35 (m, 4H, $2CH_2$), 7.32-7.36 (m, 5H, C_6H_5), 8.30, 8.32-8.34 (3s, 3H, 3NH). $C_{19}H_{16}N_6O_2S$ (392.44): Calcd: C, 58.15; H, 4.11; N, 21.42; S, 8.17%; Found: C, 58.40; H, 4.24; N, 22.00; S, 8.65%.

α-(3-Ethoxycarbonyl-2-hydrazo-4,5,6,7-tetrahydrobenzo[b]thieno)-N-benzoylcyanoacetylhydrazine (13e)

Dark brown crystals from ethanol, yield 40.82%, 0.40 g, m.p. 180 ºC. IR (KBr): υ/cm^{-1} = 3465-3325 (3NH), 3054 (CH aromatic), 2985, 2875 (CH_3, CH_2), 2222 (CN), 1695, 1684 (3C=O), 1656 (C=N), 1633 (C=C). ^{1}H NMR (DMSO) δ = 1.16 (t, 3H, *J* = 7.45 Hz, CH_3), 2.24-2.26 (m, 4H, $2CH_2$), 2.33-2.36 (m, 4H, $2CH_2$), 4.24 (q, 2H, *J* = 7.45 Hz, CH_2), 7.32-7.38 (m, 5H, C_6H_5), 8.28, 8.32, 8.34 (3s, 3H, 3NH). $C_{21}H_{21}N_5O_4S$ (439.50): Calcd: C, 57.39; H, 4.82; N, 15.94; S, 7.30%; Found: C, 57.93; H, 4.33; N, 15.80; S, 7.02%.

Preparation of 15a,b (General Procedure)

To a solution of **13a** (1.30×10^{-3} mol) in ethanol, an equimolar amount of either **8a** or **8b** is added. The reaction mixture is then heated under reflux for 4 h, after which it is poured on an ice-water mixture and the resulting precipitate collected by filtration and recrystallized from ethanol.

5-Amino-3-benzoylhydrazono-4-phenylhydrazonopyrazole (15a)

Brick red crystals, yield 59.52%, 0.25 g, m.p. 105 ºC. IR (KBr): υ/cm^{-1} = 3492-3354 (NH_2, 3NH), 3060 (CH aromatic), 1670 (C=N), 1637 (C=C). ^{1}H NMR (DMSO) δ = 4.48 (s, 2H, NH_2), 7.32-7.41 (m, 10H, $2C_6H_5$), 8.09, 8.43, 8.98 (3s, 3H, 3NH). ^{13}C NMR δ 116.3, 118.6, 120.5, 128.9, 129.2, 130.1, 133.4 (2 C_6H_5), 153.3, 154.1, 154.5 (3 C=N), 164.0 (C=O). (321.35): Calcd: C, 59.80; H, 4.71; N, 30.51%. Found: C, 60.21; H, 4.58; N, 30.15%.

5-Amino-3-benzoylhydrazono-2-phenyl-4-phenylhydrazonopyrazole (15b)

Yellowish brown crystals, yield 58.82%, 0.3 g, m.p. 68 ºC. IR (KBr): υ/cm^{-1} = 3488-3305 (NH_2, 2NH), 3057 (CH aromatic), 1670 (C=N), 1640 (C=C). ^{1}H NMR (DMSO) δ = 4.91 (s, 2H, NH_2), 7.28-7.36 (m, 15H, $3C_6H_5$), 8.30, 8.78 (2s, 2H, 2NH). $C_{22}H_{19}N_7O$ (397.44): Calcd: C, 66.49;

H, 4.82; N, 24.67%. Found: C, 67.01; H, 4.69; N, 24.48%.

Synthesis of 18 and 20a,b (General Procedure)

To a solution of **13a** (0.5 g, 1.63×10^{-3} mol) in ethanol, a few drops of triethylamine are added, followed by the introduction of an equimolar amount of phenylisothiocyanate (**16**), malononitrile **6a** or ethyl cyanoacetate **6b**. The contents are then heated under reflux for 3 h, after which they are left to cool down at room temperature; a few drops of diethyl ether are added, and the solvents are evaporated under a vacuum. The precipitate is then air-dried.

6-N-benzoylhydrazido-5-imino-2,4-diphenyl-3-thioxo-1,2,4-triazine (18)

Reddish black crystals, yield 52.78%, 0.38 g, m.p. 45 ºC. IR (KBr): υ/cm^{-1} = 3460-3342 (3NH), 3063 (CH aromatic), 1660 (C=N), 1637 (C=C), 1205-1193 (C=S). ^{1}H NMR (DMSO) δ = 7.28-7.36 (m, 15H, $3C_6H_5$), 8.81-8.88 (m, 3H, 3NH). $C_{23}H_{18}N_6O_2S$ (442.50): Calcd: C, 62.43; H, 4.10; N, 19.00; S, 7.25%; Found: C, 62.85; H, 4.37; N, 19.20; S, 6.95%.

4-Amino-3-N-benzoylhydrazido-5-cyano-6-imino-1-phenylpyridazine (20a)

Orange brown crystals from ethanol, yield 57.38%, 0.35 g, m.p. 85 ºC. IR (KBr): υ/cm^{-1} = 3495-3309 (NH_2, 3NH), 3058 (CH aromatic), 2222 (CN), 1673 (C=N), 1634 (C=C). ^{1}H NMR (DMSO) δ = 5.36 (s, 2H, NH_2), 7.30-7.38 (m, 10H, $2C_6H_5$), 8.32, 8.49, 8.81 (3s, 3H, 3NH). $C_{19}H_{15}N_7O_2$ (373.38): Calcd: C, 61.12; H, 4.05; N, 26.26%; Found: C, 60.76; H, 4.23; N, 26.48%.

4-Amino-3-N-benzoylhydrazido-5-cyano-6-oxo-1-phenylpyridazine (20b)

Reddish crystals from ethanol, yield 51.02%, 0.25 g, m.p. 55 ºC. IR (KBr): υ/cm^{-1} = 3480-3312 (NH_2, 2NH), 3054 (CH aromatic), 2220 (CN), 1688-1680 (3C=O), 1658 (C=N), 1634 (C=C). ^{1}H NMR (DMSO) δ = 5.39 (s, 2H, NH_2), 7.26-7.34 (m, 10H, $2C_6H_5$), 8.40, 8.81 (2s, 2H, 2NH). $C_{19}H_{14}N_6O_3$ (374.36): Calcd: C, 60.96; H, 3.77; N, 22.45%; Found: C, 61.56; H, 4.20; N, 22.01%.

Synthesis of 22

Equimolar amounts of **3** (0.5 g, 2.46×10^{-3} mol), acetophenone **21** (0.3 g, 2.46×10^{-3} mol), and solid ammonium acetate (a few granules), are fused at 150 ºC in an oil bath for 1 h. The reactants are then left to cool down, treated with ethanol and subsequently with ice and water after which the formed solid is collected by filtration.

β-Phenyl-α-(N-benzoylhydrazido)-crotononitrile (22)

Pale yellow crystals from ethanol, yield 44%, 0.33 g, m.p. 80 ºC. IR (KBr): υ/cm^{-1} = 3460-3350 (2NH), 3050 (CH aromatic), 2220 (CN), 1688, 1679 (2C=O), 1640 (C=C). ^{1}H NMR (DMSO) δ = 2.38 (s, 3H, CH_3), 7.21-7.38 (m, 10H, $2C_6H_5$), 8.22, 8.36-8.38 (2s, 2H, 2NH). $C_{18}H_{15}N_3O_2$ (305.34): Calcd: C, 70.81; H, 4.95; N, 13.76%. Found: C, 71.23; H, 5.24; N, 14.14%.

2-Amino-3-N-benzoylhydrazido-4-phenylthiophene (23)

To a solution of **22** (0.5 g, 1.64×10^{-3} mol) in ethanol, an equimolar amount of sulfur and a few drops of triethylamine are added and the contents are heated under reflux for 3 h. The reaction mixture is then poured on an ice-water mixture and the precipitate filtered out.

Pale brown crystals from ethanol, yield 45.2%, 0.25 g, m.p. 85 ºC. IR (KBr): υ/cm^{-1} = 3474-3310 (NH_2, 3NH), 3055 (CH aromatic), 1693, 1686 (2C=O), 1665 (C=N), 1639 (C=C). ^{1}H NMR (DMSO) δ = 4.47 (s, 2H, NH_2), 6.77 (s, 1H, thiophene H-5), 7.30-7.37 (m, 10H, $2C_6H_5$), 8.27, 9.26 (2s, 2H, 2NH). $C_{18}H_{15}N_3O_2S$ (337.40): Calcd: C, 64.08; H, 4.48; N, 12.45; S, 9.50%. Found: C, 64.37; H, 4.13; N, 12.89; S, 10.02%.

β-Phenyl-γ-benzal-α-(N-benzoylhydrazido)-crotononitrile (24)

To a solution-containing a few drops of piperidine of **20** (0.12 g, 3.94×10^{-3} mol) in ethanol, benzaldehyde (**4a**) (0.07 g, 3.94×10^{-3} mol) is added, and the solution is then heated under reflux for 2.5 h, after which it is poured on an ice-water mixture. The formed solid is then collected by filtration.

Yellowish brown crystals from ethanol, yield 75%, 1.16 g, m.p. 42 ºC. IR (KBr): υ/cm^{-1} = 3445-3305 (2NH), 3052 (CH aromatic), 2218 (CN), 1686, 1680 (2C=O), 1637 (C=C). ^{1}H NMR (DMSO) δ = 6.36, 6.48 (2s, 2H, CH=CH), 7.28-7.36 (m, 15H, $3C_6H_5$), 8.40, 8.43 (2s, 2H, 2NH). $C_{25}H_{19}N_3O_2$ (393.45): Calcd: C, 76.32; H, 4.87; N, 10.68%. Found: C, 75.82; H, 4.29; N, 10.30%.

β-Phenyl-α-(N-benzoylhydrazido)-γ-phenylhydrazocrotononitrile (25)

To a cold (0-5 ºC) solution of **22** (1 g, 3.28×10^{-3} mol)

in ethanol, containing ammonium acetate, an equimolar quantity of benzenediazonium chloride (**12a**) (0.46 g, 3.28 × 10^{-3} mol) [prepared as previously described] is added, with stirring. The precipitated solid is then filtered out.

Golden brown crystals from ethanol, yield 67.17%, 0.9 g, m.p. 55 ºC. IR (KBr): υ/cm^{-1} = 3465, 3309 (3NH), 3065 (CH aromatic), 2218 (CN), 1686, 1675 (2C=O), 1655 (C=N), 1640 (C=C). ^{1}H NMR (DMSO) δ = 6.59 (s, 1H, CH=N), 7.26-7.36 (m, 15H, 3C_6H_5), 8.32, 8.84, 9.03 (3s, 3H, 3NH). $C_{24}H_{19}N_5O_2$ (397.44): Calcd: C, 70.40; H, 4.68; N, 17.10%. Found: C, 70.90; H, 5.00; N, 17.50%.

Preparation of 27a,b

(*General Procedure*): To a solution of **22** (0.46 g, 1.51 × 10^{-3} mol) in ethanol, containing a few drops of triethylamine, an equimolar amount of either malononitrile (**6a**) or ethyl cyanoacetate (**6b**) is added and all is heated under reflux for 4 h. The reaction mixture is then poured on an ice-water mixture and the formed solid is then collected by filtration.

1,3-Diamino-2-cyano-5-phenyl-6-(N-benzoylhydrazido)-benzene (27a)

Pale brown crystals from ethanol, yield 57.14%, 0.32 g, m.p. 70 ºC. IR (KBr): υ/cm^{-1} = 3475-3325 (2NH_2, 2NH), 3062 (CH aromatic), 2222 (CN), 1686 (C=O), 1640 (C=C). ^{1}H NMR (DMSO) δ = 4.48, 5.62 (2s, 4H, 2NH_2), 7.26-7.39 (m, 11H, 2C_6H_5, C_6H), 8.68, 9.41 (2s, 2H, 2NH). $C_{21}H_{17}N_5O_2$ (371.40): Calcd: C, 67.92; H, 4.61; N, 18.86%. Found: C, 67.57; H, 4.53; N, 18.66%.

Ethyl 1,3-diamino-5-phenyl-6-(N-benzoylhydrazido)-2-carboxylate (27b)

Pale brown crystals from ethanol, yield 52.81%, 0.47g, m.p. 80 ºC. IR (KBr): υ/cm^{-1} = 3510-3322 (2NH_2, 2NH), 3052 (CH aromatic), 1692-1678 (3C=O), 1638 (C=C). ^{1}H NMR (DMSO) δ = 1.15 (t, 3H, CH_3), 4.26 (q, 2H, CH_2), 4.52, 5.63 (2s, 4H, 2NH_2), 7.28-7.40 (m, 11H, 2C_6H_5, C_6H), 8.43, 9.21 (2s, 2H, 2NH). $C_{23}H_{22}N_4O_4$ (418.46): Calcd: C, 66.02; H, 5.30; N, 13.39%. Found: C, 66.33; H, 5.64; N, 13.83%.

Synthesis of 31a,b

(*General Procedure*): Compound **3** (0.5 g, 2.46 × 10^{-3} mol) is dissolved in dimethylformamide and a few sodium hydroxide pellets are added. Phenyl isothiocyanate (**16**) (0.33 g, 2.46 × 10^{-3} mol) is then stirred in and the solution is covered and left overnight. Equimolar amounts of either ethyl chloroacetate (**29a**) or methyl bromoacetate (**29b**) are stirred in (10 min) on the following day, and the solution is covered for another night, after which the reaction mixture is poured onto ice and the precipitated solid is filtered out.

Ethyl 2-phenylamino-3-N-benzoylhydrazido-4-amino-thiophene-5-carboxylate (31a)

Brown crystals from ethanol, yield 38.46%, 0.4 g, m.p. 125 ºC. IR (KBr): υ/cm^{-1} = 3480-3365 (NH_2, 3NH), 3058 (CH aromatic), 2975, 2890, (CH_3, CH_2), 1690-1680 (3C=O), 1642 (C=C). ^{1}H NMR (DMSO) δ = 1.16 (t, 3H, CH_3), 4.24 (q, 2H, CH_2), 5.02 (s, 2H, NH_2), 7.32-7.38 (m, 10H, 2 C_6H_5), 8.29, 8.39-8.45 (3s, 3H, 3NH). $C_{21}H_{20}N_4O_4S$ (424.48): Calcd: C, 59.42; H, 4.75; N, 13.20%. Found: C, 59.63; H, 4.89; N, 13.57%.

Methyl 2-phenylamino-3-N-benzoylhydrazido-4-amino-thiophene-5-carboxylate (31b)

Dark orange crystals from ethanol, yield 53%, 0.53 g, m.p. 130 ºC. IR (KBr): υ/cm^{-1} = 3475-3370 (NH_2, 3NH), 3060 (CH aromatic), 2970 (CH_3), 1694-1685 (3C=O), 1640 (C=C). ^{1}H NMR (DMSO) δ = 2.82 (s, 3H, CH_3), 4.82 (s, 2H, NH_2), 7.28-7.35 (m, 10H, 2C_6H_5), 8.30, 8.45-8.47 (3s, 3H, 3NH). $C_{20}H_{18}N_4O_4S$ (410.46): Calcd: C, 58.53; H, 4.42; N, 13.65%. Found: C, 58.24; H, 4.38; N, 13.50%.

Synthesis of 33 and 35

(*General Procedure*): Compound **3** (0.6 g, 2.96 × 10^{-3} mol) is dissolved in dimethylformamide, and a few sodium hydroxide pellets are added. Phenylisothiocyanate (**16**) (0.40 g, 2.96 × 10^{-3} mol) is then stirred in and the solution is covered and left overnight. An equimolar amount of either chloroacetone (**32**) or ω-bromoacetophenone (**34**) is then added and the solution is stirred for 10 minutes and left, covered, for another night. The reaction mixture is then poured onto an ice-water mixture and the formed solid is filtered out.

5-Acetyl-4-amino-3-N-benzoylhydrazido-2-phenyl-aminothiophene (33)

Dark brown crystals from ethanol, yield 30%, 0.35 g, m.p. 100 ºC. IR (KBr): υ/cm^{-1} = 3460-3335 (NH_2, 3NH), 3052 (CH aromatic), 2970 (CH_3), 1686-1678 (3C=O), 1640 (C=O). ^{1}H NMR (DMSO) δ = 3.26 (s, 3H, CH_3), 4.88

(s, 2H, NH_2), 7.32-7.38 (m, 10H, $2C_6H_5$), 8.32-8.36 (m, 3H, 3NH). $C_{20}H_{18}N_4O_3S$ (394.46): Calcd: C, 60.90; H, 4.60; N, 14.20; S, 8.13%. Found: C, 61.21; H, 4.75; N, 14.50; S, 8.45%.

4-Amino-5-benzoyl-3-N-benzoylhydrazido-2-phenyl-aminothiophene (35)

Brick yellow crystals from ethanol, yield 73.22%, 0.82 g, m.p. 80 ºC. IR (KBr): υ/cm^{-1} = 3489-3323 (NH_2, 3 NH), 3063 (CH aromatic), 1696, 1688-1680 (3C=O), 1643 (C=C). ^1H NMR (DMSO) δ = 4.57 (s, 2H, NH_2), 7.22-7.35 (m, 15H, $3C_6H_5$), 8.20, 9.23, 9.40 (3s, 3H, 3NH). $C_{25}H_{20}N_4O_3S$ (456.53): Calcd: C, 65.78; H, 4.42; N, 12.27; S, 7.02%. Found: C, 65.99; H, 4.74; N, 12.59; S, 7.35%.

Synthesis of 7a,b and 38a,b

(*General Procedure*): To a solution of **3** (0.37 g, 1.82 $\times 10^{-3}$ mol) in ethanol, an equimolar amount of either α-cyanocinnamonitrile (**36a**), ethyl α-cyanocinnamate (**36b**), 4-methoxy-α-cyanocinnamonitrile (**36c**) or ethyl 4-methoxy-α-cyanocinnamate (**36d**) is added and the resultant solution is heated under reflux for 2 h. The contents are then poured on an ice-water mixture and the precipitate is collected by filtration.

2-Amino-1-benzoamino-3,5-dicyano-6-oxo-4-(4-methoxy-phenyl)-pyridine (38a)

Yellow crystals from ethanol, yield 35.09%, 0.2 g, m.p. 115 ºC. IR (KBr): υ/cm^{-1} = 3460-3325 (NH_2, 2NH), 3055 (CH aromatic), 2225, 2220 (2CN), 1688, 1683 (2CO), 1638 (C=C). ^1H NMR (DMSO) δ = 3.22 (s, 3H, CH_3), 5.65 (s, 2H, NH_2), 7.24-7.36 (m, 9H, C_6H_5, C_6H_4), 8.34 (s, 1H, NH). $C_{21}H_{15}N_5O_3$ (385.39): Calcd: C, 65.45; H, 3.92; N, 18.17%. Found: C, 65.98; H, 4.30; N, 18.50%.

Ethyl 2-amino-1-benzoamino-5-cyano-4-(4-methoxy-phenyl)-6-oxo-pyridine-3-carboxylate (38b)

Yellowish white crystals from ethanol, yield 46.88%, 0.3 g, m.p. 55 ºC. IR (KBr): υ/cm^{-1} = 3468-3312 (NH_2, H), 3050 (CH aromatic), 2988, 2890 (CH_3, CH_2), 2222, 2220 (2CN), 1692, 1686 (2CO), 1636 (C=C). ^1H NMR (DMSO) δ = 1.16 (t, 3H, CH_3), 3.22 (s, 3H, CH_3), 4.26 (q, 2H, CH_2), 5.62 (s, 2H, NH_2), 7.26-7.34 (m, 9H, C_6H_5, C_6H_4), 8.30 (s, 1H, NH). $C_{23}H_{20}N_4O_5$ (432.44): Calcd: C, 63.88; H, 4.66; N, 12.96%. Found: C, 64.31; H, 5.01; N, 13.35%.

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