Cyanothioacetamide and its Derivatives in Heterocyclic Synthesis: A New Route for the Synthesis of Several Pyridine and Thieno[2,3-b]pyridine Derivatives and their Biological Evaluation

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Several new pyridine and thieno[2,3-b]pyridine derivatives were synthesized *via* the reactions of some pyridinethiones, obtained by the action of acetylacetone on some thiocarboxamidocinnamonitriles, with halogenated esters and ketones. Structures were established based on elemental and spectral data. All the synthesized compounds were tested for their biological activity.

Introduction

Thiazole and its derivatives are long known for their antibacterial [1] activity and their use as hypoglycemic agents [2]. Fungicidal [3], herbicidal [4], insecticidal [5] and plant-growth regulating [6] properties have been reported for this group of heterocyclics. In addition, pyridines are also reported to exhibit diverse biological activities as antimycotic [7], antidepressant [8], antiarrhythmic [9], and antilipemic [10] agents. The fusion of the thiazole and the pyridine ring might combine the biological activities of both moieties. The reactions of cyanothioacetamide (**1**) and its derivatives (**2**) with different halogenated esters and ketones and active methylene-containing reagents constituted an easy and logic route for the synthesis of these heterocyclic derivatives. These reactions could be considered to be of interest in the chemistry of **1** and **2** [11–18].

Results and Discussion

The reaction of α-thiocarboxamidocinnamonitriles (**2**) with acetylacetone (**3**) has been leading to contradictory results. Thus, whereas Litvinov *et al.* [19], Ghozlan [20] and Elnagdi *et al.* [21] reported that the reaction products were dihydropyridine-2-thiones (**4**), Krauze *et al.* [22, 23] reported that tetrahydropyridine-2-thiones (**5**) were the only isolated reaction products. Therefore, we re-investigated this reaction. As we found α-thiocarboxamido-*p*-methoxyphenylacrylonitrile (**2a**) reacted, base catalyzed, with acetylacetone (**3**) to yield a reaction product of the molecular formula $C_{16}H_{14}N_2SO_2$ which corresponds to the addition of **2a** to **3** with the loss of H_2O and two hydrogens. The IR spectrum of this product showed the presence of NH, CN, CH_3CO and C=S groups. The ^1H NMR spectrum revealed the absence of any signals in the range of 4–6.8 ppm which, if present, might be due to pyridine protons. Based on the above data, the reaction product could be formulated as the dihydropyridine-2-thione derivative **4a**. Concentration and cooling of the mother liquor afforded another product of the molecular formula $C_{16}H_{18}N_2SO_2$, corresponding to the addition of **2a** to **3** followed by loss of H_2O. The ^1H NMR spectrum of this product revealed signals of pyridine H-3 and H-4 at 6.4 and 6.8 δ ppm, respectively. Accordingly this reaction product could be formulated as the tetrahydropyridine-2-thione derivative **5a**.

Analogously, **2b** reacted with **3** to yield the dihydropyridine-2-thione (**4b**) and the tetrahydropyridine-2-thione (**5b**). In all cases, the dihydro derivative constituted the major product. On the other hand, compounds **5a,b** could be converted into the corresponding **4a,b** by boiling their solutions in pyridine for 5 h. Compounds **4a,b** and **5a,b** were taken as starting materials for the present study. Thus, it has been found that **4a** condensed with

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chloroacetone (**6**) in methanolic sodium methoxide to give a reaction product of the molecular formula $C_{19}H_{18}N_2SO_3$. The IR spectrum of this product showed the presence of bands of CN (2220 cm^{-1}) and two carbonyl groups at 1720 and 1708 cm^{-1}. ^1H NMR revealed the absence of any signals that might be attributed to the presence of pyridine protons. Consequently, this product could be formulated as 5-acetyl-3-cyano-6-methyl-4-(4′-methoxyphenyl)-2-S-acetonylpyridine **7a**. Similarly, **4b** reacted with **6** to afford the corresponding 2-S-acetonylpyridine derivative **7b** whose structure was also established based on analytical and spectral data.

Compounds **7a,b** could be cyclized by the action of boiling 10% ethanolic KOH to give the 2-acetylthieno[2,3-b]pyridine derivatives **8a,b**. The structure of **8a,b** was established *via* elemental analysis and spectral data. A solid evidence for the structure of **8a,b** came from their authentication *via* different routes as follows:

a) Carrying out the reaction of **4a,b** with **7** in glacial acetic acid instead of methanolic sodium methoxide.

b) The reaction of **4a,b** (or **5a,b**) with α-chloroacetylacetone (**9**) yielded the 2-S-diacetylmethylpyridine derivatives **10a,b** which cyclized in ethanolic KOH to afford **8a,b**. The structure of **10a,b** was also confirmed by elemental analysis and spectral data.

c) Carrying out the reaction between **4a,b** (or **5a,b**) and **9** in boiling glacial acetic acid led to direct formation of **8a,b**.

Moreover, the mass spectrum of **8a** gave *m/e* = 354 (100%) which corresponds exactly to the formula weight of $C_{19}H_{18}N_2SO_2$ of **8a**. In addition, the activity of enaminoacetyl moiety in **8a,b** was demonstrated by treatment with nitrous acid to yield the thienopyridopyrizazinones **11a,b**. The IR spectra of **11a,b** showed the presence of pyridazinone-CO (1722 cm^{-1}) and CH_3CO (1695 cm^{-1}) groups while their ^1H NMR spectra revealed the absence of NH_2 signals.

Work was further extended to study the behaviour of **4a,b** and **5a,b** towards the action of ethyl α-chloroacetoacetate (**12**). Thus, **4a** and **12** reacted in methanolic sodium methoxide to give a product with the molecular formula $C_{22}H_{22}N_2SO_5$. The IR spectrum of this product showed absorption bands of CN (2222 cm^{-1}), ester-CO (1745 cm^{-1}) and two CH_3CO groups at 1721 and 1700 cm^{-1}. Also, its ^1H NMR spectrum revealed signals of $COOCH_2CH_3$,

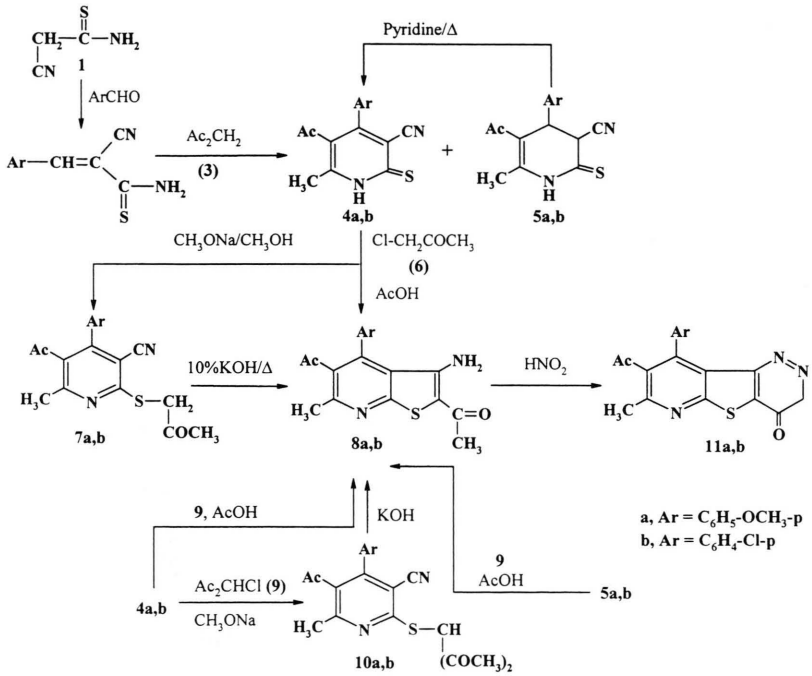

Chart 1

CH_3, two $COCH_3$ and saturated CH groups in addition to aromatic protons in their proper positions. Accordingly, this product could be formulated as 5-acetyl-3-cyano-6-methyl-4-(4′-methoxyphenyl)-2-S-(acetylethoxycarbonylmethyl)pyridine (**13a**) formed *via* dehydrochlorination. Analogously, **4b** yielded **13b** on its reaction with **12**.

13a,b, cyclized by the action of ethanolic KOH yielded products that showed IR absorption bands of NH_2, ester-CO and one CH_3CO group in each case. CN function bands were entirely absent in each case. ^{1}H NMR spectra revealed signals of only one CH_3CO group. Based on the above data, these compounds could be formulated as enaminoethoxycarbonylthieno[2,3-b]pyridines **15a,b**. The formation of **15a,b** in this reaction involves first, addition to the CN function to yield the iminothieno[2,3-b]pyridine **14a,b**; to which one molecule of water is added and then one molecule of acetic acid liberated yielding the isolated **15a,b** rather than **8a,b** (cf. Chart 2).

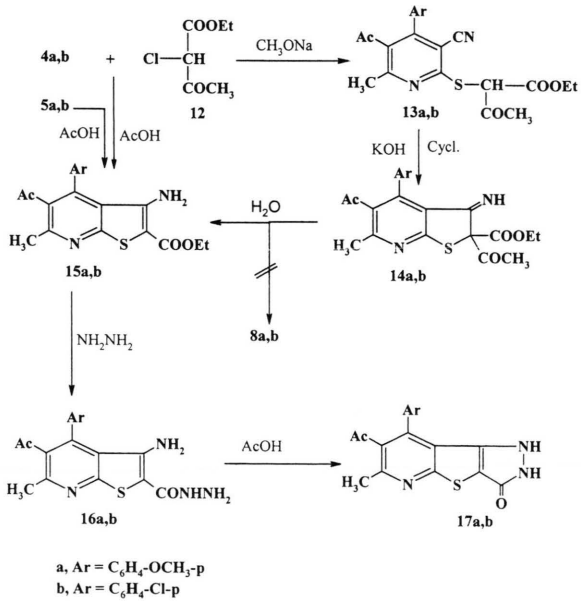

Chart 2

Compounds **15a,b** could also be confirmed *via* two other routes:

a) Carrying out the reaction of **4a,b** with **12** in glacial acetic acid instead of CH_3ONa, and

b) of **5a,b** with **12** in boiling glacial acetic acid.

Compounds **15a,b** reacted with hydrazine hydrate *via* ethanol elimination to yield the acid hydrazides of the thieno[2,3-b]pyridines **16a,b**. No ester-CO band was detected in the IR spectra of **16a,b**. Moreover, their ^{1}H NMR did not reveal the doublet and quartet of the ester-CH_2CH_3 group in each case.

Compounds **16a,b** could be cyclized by the action of boiling glacial acetic acid *via* ammonia elimination to produce the pyrazolino-[3′,4′:4,5]-thieno[2,3-b]pyridines **17a,b** whose ^{1}H NMR spectra revealed the presence of only two D_2O-exchangeable NH protons. It is remarkable to report that trials to dehydrogenate the pyrazoline moiety to yield the corresponding pyrazolone were unsuccessful under a variety of reaction conditions.

Biological Activity

The synthesized comounds were tested *in vitro* against some gram negative bacteria such as *Neisseria polysacchareae, Listeria monocytogenes* and *Escherichia coli* and some gram postive bacteria such as *Bacillus subtilis* and *Micrococcus roseus*. Nutrient agar medium has been utilized for growing test organisms. The diameters of clearing zones have been used as a parameter to express the antimicrobial activity where all the compounds were tested at a unique concentration of 75 μg/ml. All the synthesized compounds were biologically evaluated and results are reported in Table I.

Experimental

All melting points are uncorrected. IR spectra in KBr discs were recorded on Pye Unicam SP-1100 and Perkin-Elmer FT-IR type 4 spectrophotometers. ^{1}H NMR were recorded on Gemini 200 MHz spectrometer using TMS as an internal standard in DMSO-d_6 and chemical shifts are expressed as δ ppm units. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 series A using DIP technique at 15 and 70 eV. Microanalyses were performed by the Microanalytical Center of Cairo University.

Compounds **2a,b** were prepared according to a literature procedure [24].

Preparation of the starting materials **4a,b** *and* **5a,b**

General procedure

A solution of acetylacetone (**4**, 0.01 mol) and each of **2a,b** (0.01 mol) in absolute ethanol (30 ml) containing triethylamine (0.5 ml) was heated

Table I. Biological activity of the tested new comounds.

Comp. No.	*Neisseria polysacchareae*	*Listeria monocytogenes*	*Escherichia coli*	*Bacillus subtilis*	*Micrococcus roseus*
4a	+	−	−	+	−
4b	−	+	+	+	−
5a	−	−	+	−	−
5b	+	−	+	−	+
7a	−	+	−	−	−
7b	+	+	++	+	+
8a	−	−	++	+	−
8b	++	+	−	++	+
10a	−	−	+	−	−
10b	−	++	−	+	+++
11a	++	+	+	−	−
11b	++	−	−	−	−
13a	−	+	++	−	−
13b	+	−	+++	+	+
15a	+	−	++	−	−
15b	−	++	−	−	−
16a	−	++	++	+	+
16b	−	+	+++	+	+
17a	−	−	++	+	−
17b	−	++	+	+	−

Highly active: +++; large clearing zone. Slightly active: +; small clearing. Moderately active: ++; medium clearing. Inactive: −; no clearing zone

under reflux for 5 h. The solids obtained were filtered off and crystallized from ethanol to give yellow crystals of **4a** [19–21] and **4b** [19–21], respectively.

Concentration and cooling of the mother liquor gave pale yellow solid products which were filtered off and crystallized from ethanol to give **5a** and **5b** [22, 23], respectively.

Conversion of **5a,b** *into* **4a,b**

A solution of each of **5a,b** (1 g) in pyridine (20 ml) was heated under reflux for 5 h and then poured onto ice-cold water. Addition of conc. HCl (1 ml) yielded yellow solid products that were filtered off, washed with water, then crystallized from ethanol to give **4a,b**, respectively with m.p. showing no depression when admixed with authentic samples obtained as described above.

Reactions of **4a,b** *and* **5a,b** *with chloro-ketones and esters in methanolic sodium methoxide*

General procedure

A solution of each of **4a,b** (0.01 mol) and **5a,b**, respectively, and chloroacetone (**6**), α-chloroacetylacetone (**9**) or ethyl-α-chloroacetoacetate (**12**) (0.01 mol) was heated under reflux with methanolic sodium methoxide (prepared from 0.01 atom of sodium metal in 30 ml of methanol) for 2–5 h (TLC). The products obtained after cooling were filtered off and crystallized from the proper solvent to yield **7a,b**, **10a,b** and **13a,b** respectively (*cf.* Tables II and III).

Reactions of **4a,b** *and* **5a,b** *with chloro-ketones and esters in glacial acetic acid*

General procedure

The repetition of the experiments described above in glacial acetic acid and boiling for 5 h resulted in the formation of **8a,b** and **15a,b**, respectively (*cf.* Tables II and III).

Cyclization reactions in ethanolic KOH

General procedure

A solution of each of **7a,b**, **10a,b** and **13a,b** (0.01 mol) in ethanol (30 ml) was heated under reflux with KOH (10%) for 3–5 h. The reaction mixture was then cooled and acidified with dil. HCl and the solids precipitated were filtered off, washed with water and then crystallized from the proper solvent to give **8a,b** and **15a,b**, respectively (*cf.* Tables II and III).

Cyclization of **16a,b**

A solution of each of **16a,b** (0.01 mol) in glacial acetic acid (30 ml) was heated under reflux for 5 h. The solid obtained after cooling were filtered off and crystallized from ethanol to give **17a,b**, respectively (*cf.* Tables II and III).

Table II. Characterization data of the newly synthesized compounds.

Comp.*	Solvent of Cryst.	M. p. [°C]	Yield [%]	Molecular formula	Analysis Calcd/Found [%] C	H	N	S	Cl
7a	EtOH	86	81	$C_{19}H_{18}N_2SO_3$	64.40	5.08	7.90	9.03	–
					64.1	5.3	7.7	9.2	–
7b	EtOH	164	83	$C_{18}H_{15}N_2SO_2Cl$	60.25	4.18	7.81	8.92	9.90
					60.0	4.0	7.6	8.6	9.7
8a	EtOH	162	75	$C_{19}H_{18}N_2SO_3$	64.40	5.08	7.90	9.03	–
					64.1	5.2	7.6	9.1	–
8b	EtOH	236–8	69	$C_{18}H_{15}N_2SO_2Cl$	60.25	4.18	7.81	8.92	9.90
					60.1	4.4	7.7	8.7	9.6
10a	EtOH	120	79	$C_{21}H_{20}N_2SO_4$	63.63	5.05	7.07	8.08	–
					63.4	5.3	7.2	7.8	–
10b	EtOH	176	81	$C_{20}H_{17}N_2SO_3Cl$	59.92	4.24	6.99	7.99	8.86
					59.7	4.1	7.1	7.8	8.6
11a	Toluene Pet. ether	102	60	$C_{19}H_{15}N_3SO_3$	62.46	4.10	11.50	8.76	–
					62.7	4.3	11.7	8.9	–
11b	EtOH	196–8	62	$C_{18}H_{12}N_3SO_2Cl$	58.45	3.24	11.36	8.66	9.60
					58.2	3.1	11.1	8.9	9.4
13a	EtOH	158–9	63	$C_{22}H_{22}N_2SO_5$	61.97	5.16	6.57	7.51	–
					61.8	5.3	6.3	7.4	–
13b	EtOH	120–2	59	$C_{21}H_{19}N_2SO_4Cl$	58.53	4.41	6.50	7.43	8.24
					58.3	4.2	6.7	7.6	8.0
15a	AcOH	220–1	68	$C_{20}H_{20}N_2SO_4$	62.50	5.20	7.29	8.33	–
					62.8	5.0	7.5	8.6	–
15b	EtOH	206–7	70	$C_{19}H_{17}N_2SO_3Cl$	58.68	4.37	7.20	8.23	9.13
					58.4	4.1	7.0	8.1	9.4
16a	EtOH	188–9	66	$C_{18}H_{18}N_4SO_3$	58.37	4.86	15.13	8.64	–
					58.1	4.6	15.4	8.4	–
16b	EtOH	248–9	64	$C_{17}H_{15}N_4SO_2Cl$	54.47	4.00	14.95	8.54	9.47
					54.2	4.2	14.7	8.3	9.2
17a	EtOH	295–7	62	$C_{17}H_{15}N_3SO_3$	61.18	4.24	11.89	9.06	–
					61.4	4.0	11.6	9.3	–
17b	EtOH	320–2	60	$C_{17}H_{12}N_3SO_2Cl$	57.06	3.35	11.74	8.92	9.93
					56.8	3.2	11.5	8.8	9.7

* All compounds are yellow in color except **15a**, orange and **17a,b**; colourless.

Reaction of **8a,b** *with* HNO_2

A cold solution of each of **8a,b** (0.01 mol) in conc. HCl (1 ml) was treated with a cold saturated solution of $NaNO_2$ (0.015 mol) and then stirred in the ice-chest for 1 h. The solid product obtained was filtered off, washed with water and crystallized from the proper solvent to give **11a,b**, respectively (*cf.* Tables II and III).

Reaction of **15a,b** *with hydrazine hydrate*

A solution of each of **15a,b** (0.01 mol) in ethanol (30 ml) was treated with hydrazine hydrate (10 ml) and then heated under reflux for 6 h. The solid products obtained after cooling were filtered off and crystallized from the proper solvents to give **16a,b**, respectively (Tables II and III).

Acknowledgement

Thanks are due to Prof. Dr. Y. E. Saleh, Department of Botany, Faculty of Science, Cairo University for carrying out the biological activity of the newly synthesized compounds.

Table III. IR and ^{1}H NMR spectral data.

Compd. No.	IR [cm^{-1}]	^{1}H NMR [ppm]
7a	2220 (CN); 1720 (acetonyl-CO); 1708 (acetyl-CO) and 1618 (C=N).	1.2 (s, 3H, pyridine-CH_3); 2.1 (s, 6H, two $COCH_3$); 3.1 (s, 2H, CH_2); 3.8 (s, 3H, $COCH_3$) and 6.9–7.5 (m, 4H, ArH's).
7b	2222 (CN); 1720 (acetonyl-CO); 1708 (acetyl-CO) and 1620 (C=N).	1.3 (s, 3H, pyridine-CH_3); 2.3 (s, 6H, two $COCH_3$); 3.3 (s, 2H, CH_2) and 7–7.5 (m, 4H, ArH's)
8a	3500, 3340 (NH_2); 1700 (pyridine-$COCH_3$); 1630 (thiophene-$COCH_3$ with H-bonding) and 1620 (C=N).	1.3 (s, 3H, pyridine-CH_3); 2.6 (s, 6H, two $COCH_3$); 3.5 (s, 3H, OCH_3); 4.5* (s, br, 2H, NH_2) and 6.8–7.4 (m, 4H, ArH's).
8b	3480, 3350 (NH_2); 1695 (pyridine-$COCH_3$); 1635 (thiophene-$COCH_3$ with H-bonding) and 1625 (C=N).	1.4 (s, 3H, pyridine-CH_3); 2.5 (s, 6H, two $COCH_3$); 4.7* (s, br, 2H, NH_2) and 7.0–7.6 (m, 4H, ArH's).
10a	2220 (CN); 1697 (acetyl-CO) and 1611 (C=N)	1.2 (s, 3H, pyridine-CH_3); 2.1 (s, 3H, pyridine-$COCH_3$); 2.4 (s, 6H, $-CH\ (COCH_3)_2$); 3.1 (s, 1H, $-CH\ (COCH_3)_2$); 3.6 (s, 3H, $-OCH_3$); and 6.6–7.0 (m, 4H, ArH's).
10b	2223 (CN); 1691 (acetyl-CO) and 1620 (C=N)	1.2 (s, 3H, pyridine-CH_3); 2.2 (s, 3H, pyridine-$COCH_3$); 2.3 (s, 6H, two $-CH\ (COCH_3)_2$; 3.2 (s, 1H, $-CH\ (COCH_3)_2$) and 6.8–7.2 (m, 4H, ArH's).
11a	1715 (pyridazinone-CO); 1701 (pyridine-$COCH_3$); 1625 (N=N) and 1620 (C=N).	1.3 (s, 3H, pyridine-CH_3); 2.2 (s, 3H, pyridine-$COCH_3$); 3.1 (s, 2H, pyridazinone-CH_2); 3.5 (s, 3H, OCH_3); and 6.9–7.3 (m, 4H, ArH's).
11b	1722 (pyridazinone-CO); 1695 (pyridine-$COCH_3$); 1626 (N=N) and 1615 (C=N).	1.3 (s, 3H, pyridine-CH_3); 2.3 (s, 3H, pyridine-$COCH_3$); 3.2 (s, 2H, pyridazinone-CH_2) and 7.0–7.4 (m, 4H, ArH's).
13a	2222 (CN); 1745 (ester-CO); 1721 ($COCH_3$); 1700 (pyridine-$COCH_3$) and 1628 (C=N).	1.2 (s, 3H, pyridine-CH_3); 1.8 (t, 3H, CH_2CH_3); 2.1 (s, 3H, pyridine $-COCH_3$); 2.4 (s, 1H, S–CH); 3.4 (s, 3H, OCH_3); 3.6 (q, 2H, CH_2CH_3) and 7.0–7.3 (m, 4H, ArH's).
13b	2219 (CN); 1747 (ester-CO); 1737 ($COCH_3$); 1695 (pyridine-$COCH_3$) and 1625 (C=N).	1.3 (s, 3H, pyridine-CH_3); 1.5 (t, 3H, CH_2CH_3); 2.1 (s, 3H, pyridine $-COCH_3$); 2.4 (s, 3H, $COCH_3$); 3.2 (s, 1H, S–CH); 3.5 (q, 2H, CH_2CH_3) and 6.9–7.2 (m, 4H, ArH's).
15a	1695 (pyridine-$COCH_3$); 1675 (ester-CO with H-bonding) and 1620 (C=N).	1.2 (s, 3H, pyridine-CH_3); 1.4 (t, 3H, CH_2CH_3); 2.1 (s, 3H, pyridine $-COCH_3$); 3.5 (s, 3H, OCH_3); 4.2 (q, 2H, CH_2CH_3); 5.8* (s, br, 2H, NH_2) and 6.9–7.3 (m, 4H, ArH's).
15b	1700 (pyridine-$COCH_3$); 1673 (ester-CO with H-bonding) and 1615 (C=N).	1.1 (s, 3H, pyridine-CH_3); 1.5 (t, 3H, CH_2CH_3); 2.1 (s, 3H, pyridine $-COCH_3$); 4.3 (q, 2H,CH_2CH_3); 5.7* (s, br, 2H, NH_2) and 7.0–7.4 (m, 4H, ArH's).
16a	3465, 3355, 3297, 3221 (two NH_2 and NH); 1696 (pyridine-$COCH_3$); 1630 (hydrazide-CO with H-bonding) and 1620 (C=N).	1.2 (s, 3H, pyridine-CH_3); 2.1 (s, 3H, pyridine $-COCH_3$); 3.7 (s, 3H, OCH_3); 5.2* (s, br, 2H, thiophene-NH_2); 6.3* (s, 2H, $CONHNH_2$); 6.7–7.1 (m, 4H, ArH's) and 9.0* (s, br, 1H, $CONHNH_2$).
16b	3467, 3312, 3235 (two NH_2 and NH); 1692 (pyridine-$COCH_3$); 1618 (hydrazide-CO with H-bonding) and 1620 (C=N).	1.2 (s, 3H, pyridine-CH_3); 2.2 (s, 3H, pyridine-$COCH_3$); 5.2* (s, br, 2H, thiophene-NH_2); 6.3* (s, 2H, $CONHNH_2$); 6.9–7.1 (m, 4H, ArH's) and 9.1* (s, br, 1H, $CONHNH_2$).
17a	3221 (NH); 1720 (pyrazolone-CO); 1682 (pyridine-$COCH_3$); and 1625 (C=N).	1.3 (s, 3H, pyridine-CH_3); 2.1 (s, 3H, pyridine-$COCH_3$); 3.8 (s, 3H, pyridine $-COCH_3$); 3.8 (s, 3H, OCH_3); 6.9–7.1 (m, 4H, ArH's); 7.8* (s, br, 1H, pyrazolone, NH) and 8.3* (s, br, 1H, pyrazolone-CONH).
17b	3222 (NH); 1722 (pyrazolone-CO); 1685 (pyridine-$COCH_3$); and 1615 (C=N).	1.1 (s, 3H, pyridine-CH_3); 2.2 (s, 3H, pyridine-$COCH_3$); 7.0–7.3 (m, 4H, ArH's); 7.9* (s, br, 1H, pyrazolone, NH) and 8.5* (s, br, 1H, pyrazolone-CONH).

* Lost after D_2O-exchange.

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