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Reactions with hydrazonoyl halides: Part XVIII[1]—Synthesis of pyrrolidino[3,4-*c*] pyrazole, pyrazolo[3,4-*d*]pyridazine, imidazo-[1,2-*a*]pyridine, pyrazolo[3,4-*d*]pyrimidine and other heterocyclic derivatives

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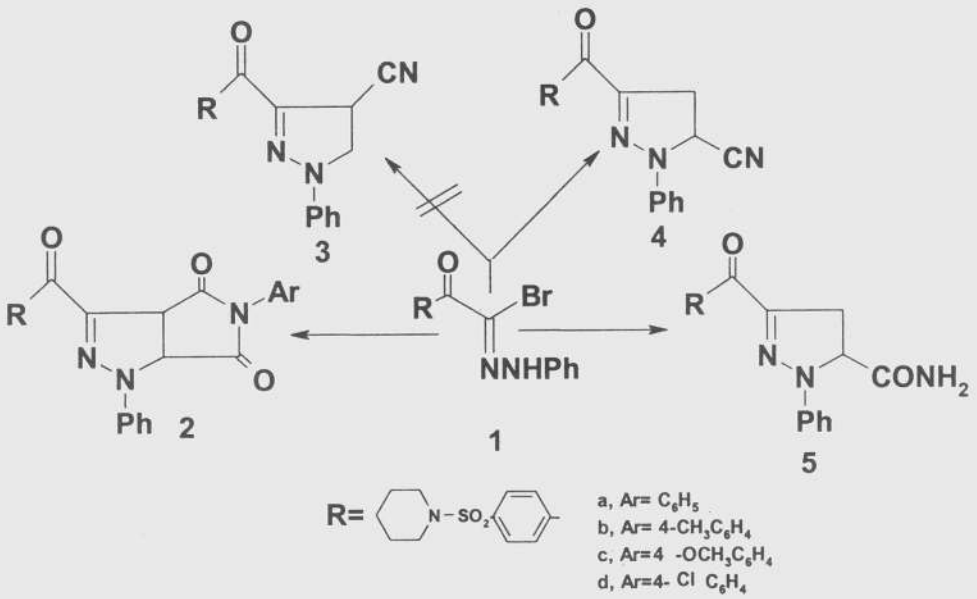
A synthesis of 1,4-benzothiazine, 1,4-benzoxazine, 1,4-dihydroquinoxaline, imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine and pyrazole derivatives has been accomplished from the reaction of hydrazonoyl bromide **1** with 2-aminothiophenol, 2-aminophenol, 1,2-phenylenediamine, 2-aminopyridine, 2-aminopyrimidine and some active methylene compounds. Also, compound **1** reacts with some dipolarophiles to give pyrazolines and pyrrolidino[3,4-*c*]pyrazolines. All structures have been elucidated on the basis of elemental analyses and spectral data.

During the last few years we have been highly interested in the chemistry of heterocyclic derivatives of potential biological activities and reported their synthesis[2-8]. Pyrazole and annelated derivatives are long known to exhibit diverse biological activities. They inhibit CAMP Phosphodiesterases[9,10] in addition to their antipyretic[11], antitumor[12], tranquilizing and herbicidal[13] activities. Hydrazonoyl halides are one of the most important starting materials for the synthesis of these pyrazoles. Recently we have reported[1] the synthesis of 1-bromo-2- [4-(N-piperidinosulfonyl)-phenyl]ethanedione-1-phenylhydrazone **1**, which was involved in the synthesis of a vast number of heterocyclic derivatives.

Results and Discussion:

It has been found that compound **1**, reacted with N-arylmaleimide to give **2a-d,**. which were assigned the structure 3a,6a-dihydro-1*H*-pyrrolidino-[3,4-*c*]pyrazole-2,6-dione based on both elemental analyses and spectral data. IR spectra of **2** revealed absorption bands at 1790-1720 and 1710-1690 cm^{-1} attributed to –CO-NR–CO– group[14]. ^1H NMR spectrum of **2b** showed signals at 1.61(m, 6H, piperidine H-3, H-4 and H-5), 2.41(s, 3H, 4-$CH_3C_6H_4$0, 3.01 (t, 4H, *j*=6.7 H, piperidine H-2, H-6); 5.30-5.50 (d, 1*h*, *J*=10 H, pyraoline H-4), 6.05-6.15 (d, 1H, *J*=10.5 Hz, pyrazoline H-5) and 7.25-8.76 (m, 13H, ArH). Also, compund **1** on treatment with acrylonitrile in the presence of triethylamine afforded a single product (TLC). ^1H NMR spectrum of the product showed signals at 1.62(m, 6H, piperidine H-3, H-4 and H-5); 3.10 (t, 4H, *J*=6.7 Hz, piperidine H-2, H-60; 4.8 (d, 2H, *J*=10.5 Hz, pyrazoline H-4); 5.12 (t, 1H, *J*=10.5 Hz, pyrazoline H-5) and 7.15-8.21 (m, 9H, ArH). Its IR spectrum revealed absorption band at 1650 (CO) and no CN absorption at 2200-2300 in support of 5-cyano structure[15]. The product was readily hydrolyzed by sulfuric acid to give the corresponding amide (IR spectral bands at 1681 with 3436 and 3313 due to $CONH_2$). Hence, the product has structure as 3-[4-N-piperidinosulfonyl)benzoyl]-5-cyano-1-phenylpyrazoline **4** and structure **3** was eliminated (cf. Scheme I). Further, treatment of **1** with acrylamide produced the same product which was found to be identical in all respects (m.p., mixed m.p., and spectral data) with amide structure **5**.

Hydrazonoyl bromide **1** reacted with 2-oxosulfone, benzoylacetonitrile, 2,4-pentanedione/or malononitrile in ethanolic sodium ethoxide solution to afford pyrazole derivatives **6-9**, respectively (cf. Scheme II). Structures **6-9** were confirmed on the basis of elemental analyses and spectral data. 4-Acetyl-3-[4-(piperidinosulfonyl)benzoyl]-5-methyl-1-



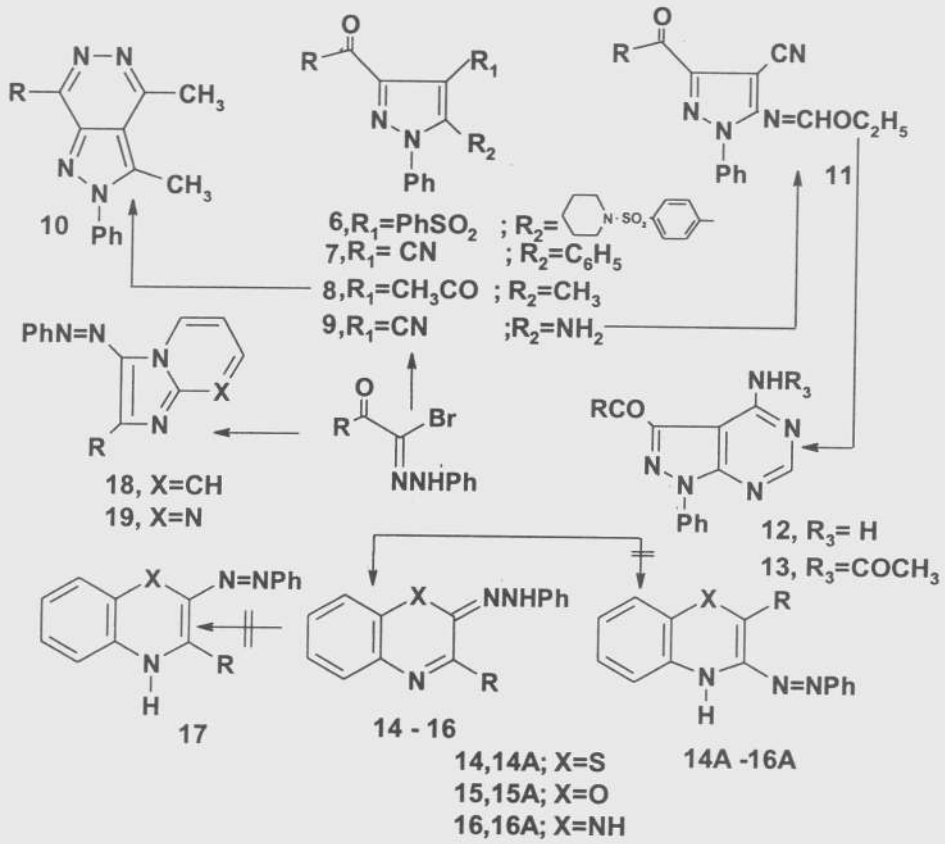
Scheme I

phenylpyrazole **8** was converted to 3,4-dimethyl-7-[4-(piperidinosulfonyl)phenyl]-2-phenylpyrazolo-[3,4-*d*]pyridazine **10** on refluxing with hydrazine hydrate. The structure of **10** was established on the basis of spectral data and elemental analysis. Its IR spectrum revealed no CO absorption at 1650-1800 cm^{-1}. Its ^1H NMR showed signals at 1.61 (m, 6H, piperidine H-3, H-4 and H-5), 2.50 (s, 3H, CH_3; 2.90 (s, 3H, CH_3); 3.10 (t, J=6.7 Hz, 4H, piperidine H-2, H-6) and 7.15-8.10 (m, 9H, ArH). Also, structure of **9** as 5-amino-3-[4-(N-piperidinosulfonyl)benzoyl]-4-cyano-1-phenylpyrazole was confirmed by elemental analysis, spectral data and its reaction with triethyl orthoformate. IR spectrum of **9** revealed bands at 3454, 3367(NH_2), 2219.9 (CN) and 1664.5 cm^{-1} (CO). ^1H NMR spectrum of **9** showed signals at 1.62 (m, 6H, piperidine H-3, H-4 and H-5), 3.10 (t, 4H, piperidine H-2, H-6), 4.21 (s, br, 2H, NH_2) and 7.21-8.25 (m, 9H, ArH's Compound **9** reacted with triethyl orthoformate in acetic anhydride to give **11**, which was easily converted into 4-aminopyraolo[3,4-*d*]pyrimidine **12**. The structures **11** and **12** were confirmed via both elemental analyses and spectral data. Compound **12** reacted with acetic anhydride to afford acetyl derivative **13**.

2-Aminothiophenol condensed easily with **1** in the presence of triethylamine as a HBr acceptor, to afford a single product (TLC). The IR spectrum of the product showed a band at 3310(NH) and no absorption band due to CO group. ^1H NMR showed signals at 1.60 (m, 6H, piperidine H-3, H-4 and H-5), 3.01(t, 4H, J=6.7 Hz, piperidine H-2, H-6), 7.21-8.20 (m, 13H, ArH) and 9.53(s, br, 1H, NH). UV-vis spectrum indicate λ_{max}=412 nm (log ε >4). ^1H NMR spectrum of the product was assigned the structure 2-phenyhydrazono-3-[4-(N-piperidinosulfonyl)phenyl]-1,4-benzothiazine **14**. The tautomeric structure **17** was ruled out on the basis of UV spectral data[16]. Structure **14A** was excluded on the basis of reaction of α-keto hydrazonoyl halides with 2-aminothiophenol which gave 2-hydrazono-3-substituted-1,4-benzothiazine[16].

Compound **1** behaves similarly toward *o*-aminophenol and 1,2-phenylenediamine to give the corresponding 2-phenylhydrazono-3-[4-(N-piperidinosulfonyl)-phenyl]-1,4-benzoxazine **15** and 2-phenylhydrazono-3-[4-(N-piperidinosulfonyl)-phenyl]-1(*H*)-quinoxaline **16**, respectively in a good yields. IR of each **15** and **16** revealed no CO absorption band but a weak NH absorption near 3240 cm^{-1}.

Treatment of **1** with 1.2 equivalent of 2-aminopyridine or 2-aminopyrimidine in ethanol at reflux condenser, yielded a single product (TLC) in each case. On the basis of elemental analyses and spectral data, the products were assigned the structures 2-[4-(piperidinosulfonyl)phenyl]-3-phenylaoimidao[1,2-*a*]pyridine **18** and 2-[4-piperidinosulfonyl)phenyl]-3-phenylazoimidao[1,2-*a*]pyri-



Scheme II

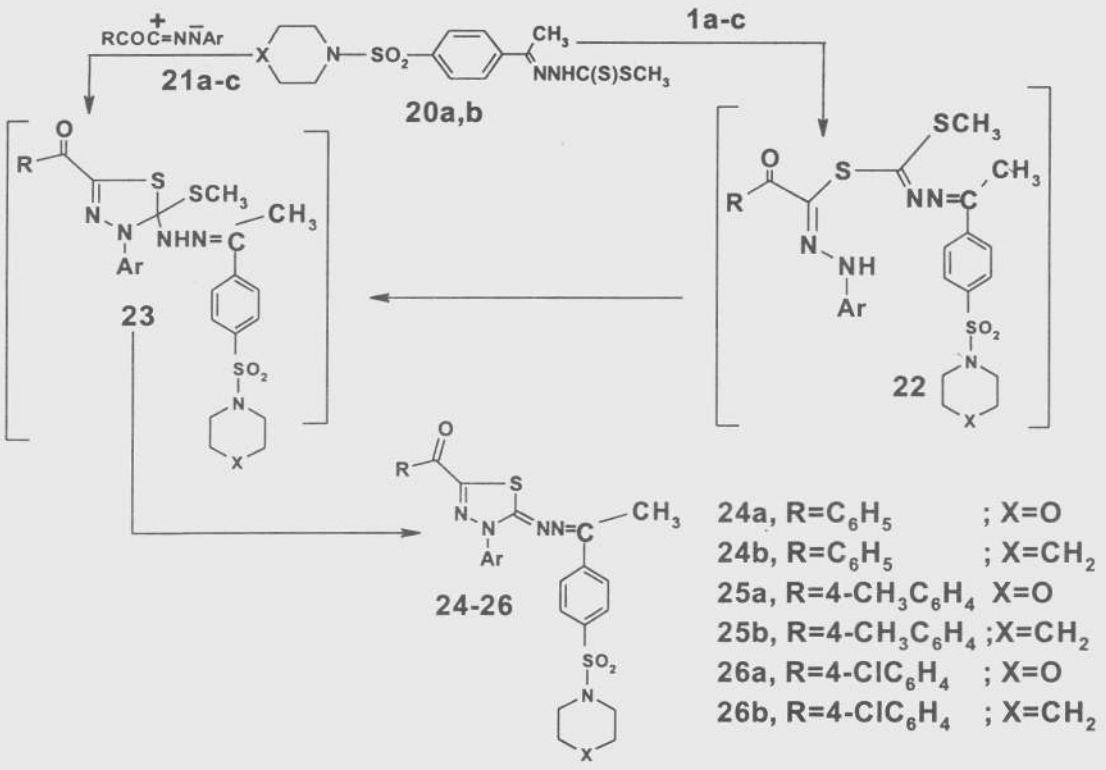
midine **19**, respectively. The absence of CO and NH absorption bands in the IR spectra indicated cyclization of **1** into **18** or **19** via reaction with 2-aminopyridine or 2-aminopyrimidine. This was supported by the absence of NH signal in the ^{1}H NMR spectra of **18** or **19**.

Compounds **1a-c** reacted with the appropriate dithioesters[17] **20a,b** in the presence of triethylamine to give 2,3-dihydro-1,3,4-thiadiazoles **24a,b-26a,b** (cf. Scheme III). On the basis of both elemental analyses and spectral data, structures **24-26** were established. The products **24a,b-26a,b** are assumed to be formed via elimination of methyl mercaptan from the corresponding cycloadduct **23**, formed from 1,3-dipolar cycloaddition of nitrilimine to C=S of methyl dithioester (cf Scheme III). The formation of **24-26** can also explained by the stepwise path involving substitution to give acyclic hydrazone **22**, which was readily cyclized to give an intermediate **23**, which losses methanethiol to give the final products **24a,b-26a,b**. Scheme IV shows the mass specrometric fragmentation of compounds **24a,b-26a,b**.

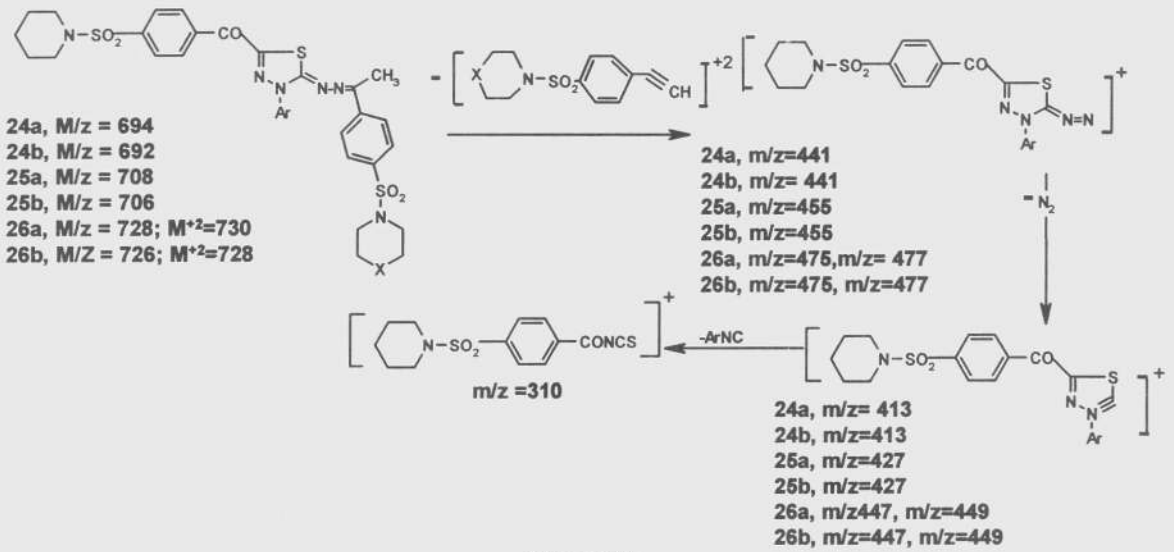
Experimental Section

All melting points were determined on Electrothermal melting point apparatus and are uncorrected. IR (KBr) spectra were recorded on FT-IR 8201 PC Schimadzu spectrophotometer; ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer and (chemical shifts in δ, ppm) using TMS as internal reference; Electronic absoptrion spectra in ethanol on a Perkin-Elmer Lambda 4 spectrophotometer, and mass spectra on a GCMS-QP 1000 EX Shimadzu. Elemental analyses were performed by Microanalytical Center, Cairo University, Giza, Egypt.

Synthesis of pyrrolidino[3,4-*c*]pyrazoles 2a-d and pyrazolines 4,5. To a mixture of hydrazonyl bromide **1** (2.25 g, 5 mmoles) and the appropriate N-arylmaleimide, acrylonitrile and acrylamide (5 mmoles) in benzene (20 mL), triethylamine (0.7 mL, 5 mmoles) was added dropwise. The mixture was refluxed for 3 hr and the triethylamine hydrobromide was collected. The filtrate was evaporated under reduced pressure. The solid thus separated was crystallized from acetic acid to give



Scheme III



Scheme IV

2a-d, **4** and **5**, respectively in 78-82% yields (cf. Table I).

Hydrolysis of 4. Pyrazoline **4** (1g) was stirred with conc. sulfuric acid (10 mL) at room temperature ffor 1 hr and poured into ice-cold water (50 mL). The solid was collected, washed with water and recystallized from ethanol to give a product **5**.

Synthesis of pyrazoles 6-9. Hydrazonoyl bromide **1** (2.25 g, 5 mmoles) was added to a solution of the appropriate 2-oxosulfone/benzoylacetonitrile/2,4-pentanedione/or malononitrile (5 mmoles) in ethanolic sodium ethoxide (prepared by dissolving 0.11 g-atom of sodium metal in 20 ml ethanol). The reaction mixture was kept overnight

at room temperature. The solid obtained was collected, washed with water and crystallized from ethanol to give pyrazoles **6-9**, respectively in a good yields (cf. Table I).

Synthesis of pyrazolo[3,4-*d*]pyridazine 10. A mixture of **8** (2.26 g, 5 mmoles) and hydrazine hydrate (1 mL, 10 mmoles) in ethanol (10 mL) was refluxed for 2hr. The solid that separated after cool-

Table I—Characterization data of the newly synthesized compounds.

Compd.	m.p. °C	Mol. Formula (Mol. Wt.)	% Calcd Found C	H	N	S
2a	252-3	$C_{29}H_{26}N_4O_5S$	64.19	4.83	10.33	5.91
		(542.62)	(64.20	4.90	10.40	6.00)
2b	248-50	$C_{30}H_{28}N_4O_5S$	64.73	5.07	10.07	5.76
		(556.64)	(64.90	5.10	10.10	5.90)
2c	239-40	$C_{30}H_{28}N_4O_6S$	62.92	4.93	9.87	5.60
		(572.64)	(63.00	4.90	9.80	5.60)
2d	258-60	$C_{29}H_{25}ClN_4O_5S$	60.36	4.37	9.71	5.56
		(577.06)	(60.40	4.40	9.80	5.60)
4	92-94	$C_{22}H_{22}N_4O_3S$	62.54	5.25	13.26	7.59
		(422.51)	(62.50	5.30	13.30	7.60)
5	235-37	$C_{22}H_{24}N_4O_4S$	59.98	5.49	12.72	7.28
		(440.52)	(60.00	5.50	12.80	7.30)
6	230-32	$C_{38}H_{38}N_4O_7S_3$	60.14	5.05	7.38	12.67
		(758.94)	(60.20	5.10	7.40	12.70)
7	245-46	$C_{28}H_{24}N_4O_3S$	67.72	4.87	11.28	6.46
		(496.59)	(67.80	4.90	11.30	6.50)
8	133-34	$C_{24}H_{25}N_3O_4S$	63.84	5.58	9.31	7.10
		(451.55)	(63.90	5.70	9.30	7.10)
9	234-35	$C_{22}H_{21}N_5O_3S$	60.67	4.86	16.08	7.36
		(435.51)	(60.70	4.90	16.10	7.40)
10	234-36	$C_{24}H_{25}N_5O_2S$	64.41	5.63	15.65	7.16
		(447.56)	(64.50	5.70	15.80	7.20)
11	185-87	$C_{25}H_{25}N_5O_4S$	61.08	5.13	14.25	6.52
		(491.57)	(61.10	5.20	14.30	6.50)
12	245-47	$C_{23}H_{22}N_6O_3S$	59.73	4.79	18.17	6.93
		(462.53)	(59.80	4.80	18.20	7.00)
13	223-25	$C_{25}H_{24}N_6O_4S$	59.51	4.79	16.66	6.35
		(504.57)	(59.50	4.80	16.70	6.40)
14	212-14	$C_{25}H_{24}N_4O_2S_2$	63.00	5.08	11.76	13.45
		(476.62)	(63.00	5.10	11.80	13.50)
15	184-86	$C_{25}H_{24}N_4O_3S$	65.20	5.25	12.17	6.96
		(460.56)	(65.20	5.30	12.20	7.00)
16	196-98	$C_{25}H_{25}N_5O_2S$	65.34	5.48	15.24	6.98
		(459.57)	(65.40	5.50	15.30	7.00)
18	209-10	$C_{24}H_{23}N_5O_2S$	64.70	5.20	15.72	7.20
		(445.55)	(64.80	5.20	15.80	7.20)
19	221-23	$C_{23}H_{22}N_6O_2S$	61.87	4.97	18.82	7.18
		(446.53)	(61.90	5.00	18.80	7.20)
24a	212-13	$C_{32}H_{34}N_6O_6S_3$	55.31	4.93	12.09	13.84
		(694.86)	(55.30	5.00	12.10	13.80)
24b	219-20	$C_{33}H_{36}N_6O_5S_3$	57.20	5.24	12.13	13.88
		(692.88)	(57.20	5.30	12.20	13.90)
25a	260-62	$C_{33}H_{36}N_6O_6S_3$	55.91	5.12	11.86	13.57
		(708.88)	(56.00	5.10	11.90	13.60)
25b	255-57	$C_{34}H_{38}N_6O_5S_3$	57.77	5.42	11.89	13.61
		(706.91)	(57.80	5.40	11.90	13.70)
26a	233-35	$C_{32}H_{33}ClN_6O_6S_3$	52.70	4.56	11.52	13.19
		(729.30)	(52.70	4.60	11.60	13.30)
26b	263-65	$C_{33}H_{35}ClN_6O_5S_3$	54.50	4.85	11.55	13.23
		(727.33)	(54.50	4.90	11.60	13.30)

ing was collected, washed with water and crystallized from ethanol to give **10** in 81% yield (cf. Table I).

Synthesis of 4-Aminopyrazolo[3,4-*d*]pyrimidine 12. Equimolar amounts of 5-amino-4-cyanopyrazole **9** and ethyl orthoformate (5 mmoles each) in acetic anhydride (20 mL) was refluxed for 5 hr. The excess acetic anhydride was removed, the solid formed was collected and crystallized from ethanol to give **11** in 72% yield. Compound **11** (1 g) was stirred with methanolic ammonia (20 mL) at room temperature for 1hr. The solid was collected and crystallized from acetic acid to give 4-aminopyrazolo[3,4-*d*]pyrimidine **12** in 78% yield (cf. Table I).

Acylation of 12. A solution of **12** (1 g) in acetic acid-acetic anhydride mixture (20 mL; 1:1 v/v) was refluxed for 30 min. and poured into ice-cold water (50 mL). The precipitate was collected and crystallized from acetic acid to afford the acetyl derivative **13** in almost quantitative yield (cf. Table I).

Synthesis of 14-16,18 and 19. Equimolar amounts of hydrazonoyl bromide **1** and the appropriate 2-aminothiophenol/2-aminophenol/1,2-phenylenediamine/2-aminopyridine/ or 2-aminopyrimidine (5 mmoles each) in ethanol (20 ml) containing triethylamine (0.7 ml, 5 mmoles) were refluxed for 2hr. The solid formed was collected and crystallized from acetic acid to afford products **14-16**, **18** and **19**, respectively in quantitative yields (cf. Table I). ^{1}H NMR spectra of **15** showed signals at 1.60 (m, 6H, piperidine H-3, H-4 and H-5), 3.10 (t, 4H, piperidine H-2, H-6), 7.15-8.20 (m, 9H, ArH) and 9.53(s, *br.*, 1H, N*H*), ^{1}H NMR spectra of **16** showed signals at 1.61 (m, 6H, piperidine H-3, H-4 and H-5). 3.08 (t, 4H, piperidine H-2, H-6); 7.22-8.21 (m, 13H, ArH); 9.50 (s, br., 1H, NH) and 12.12 (s, br., 1H, NH), ^{1}H NMR spectra of **18** showed signals at 1.60 (m, 6H, piperidine H-3, H-4 and H-5); 3.00 (t, 4H, piperidine H-2, H-6) and 7.15-8.11 (m, 13H, aromatic and pyridine protons) and ^{1}H NMR spectra of **19** showed signals at 1.60 (m, 6H, piperidine H-3, H-4 and H-5), 3.10 (t, 4H, piperidine H-2, H-6) and 7.13-8.21(m, 12H, aromatic and pyrimidine protons).

Synthesis of 24a,b-26a,b. To a mixture of the appropriate **20a,b** and the appropriate hydraonoyl bromide **1a-c** (5 mmoles each) in ethanol (20 mL), triethylamine (0.7 mL, 5 mmoles) was added dropwise while stirring. The reaction mixture was stirred for 1hr, the solid was collected and crystallized from acetic acid to give 2,3-dihydro-1,3,4-thiadiazoles **24a,b-26a,b** in almost quantitative yields (cf. Table I).

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