Syntheses of Hitherto Unknown Thiazole, Ylidene and Pyridinethione Derivatives Having a Piperidin-1-yl Moiety and Their Use as Antimicrobial Agents

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The novel hydrazone derivatives **2a-c** were prepared by treatment of aldehydes **1a**,**b** with some hydrazines. Thiocarbamoyl functional group in compound **2a** was subjected to cyclization reactions with some α-halocarbonyl reagents and furnished the novel thiazoles **4**-**6**, **8** and **9**. Enaminonitrile **10** and pyridinone **13** derivatives were synthesized by interaction of active methylene compound **2b** with *N,N*-dimethylformamide-dimethylacetal and ketene dithioacetal **11**, respectively. Aliphatic, aromatic and heteroaromatic active methylene compounds were condensed with aldehydes **1a**,**b** to afford the new ylidenes **15a-d**, **19a**,**b**, **20** and **21**. Substituted pyridinethiones **22** and **23** were prepared in high yields by cyclocondensation of **15c** with malononitrile and ethyl cyanoacetate, respectively. Indeno[1,2-b]pyridines **26a**,**b** were obtained by the reaction of ylidenes **19a**,**b** with cyanothioacetamide in ethanol and in the presence of sodium ethoxide under reflux. The structures of the synthesized compounds were established from their analytical and spectral data. The prepared compounds were also screened for their antimicrobial activity.

Keywords: Thiazole; Ylidene; Pyridinethione; Piperidin-1-yl; Antimicrobial activity.

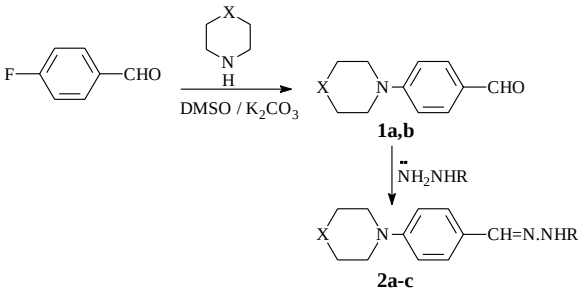
INTRODUCTION

Recently it was reported that a considerable number of piperidine derivatives are known to possess a wide range of pharmacological activities. For example, 4-arylpiperidines exhibited potent anticonvulsant effects[1] and various other derivatives act as acetylcholinesterase inhibitors,[2] matrix metalloproteinases (MMPs) inhibitors,[3] antagonists of leukocyte,[4] potent and selective β_3 agonists,[5] neuroprotective agents,[6] antidepressants,[7] antimicrobial agents[8] and in the management of pain.[9] This contribution represents a continuation of our studies of antimicrobial agents[10-15] and deals with the synthesis of heterocyclic compounds having in their structure the piperidin-1-yl moiety in order to investigate the antimicrobial activity.

RESULTS AND DISCUSSION

The starting materials, 4-piperidinobenzaldehyde **1a** and 4-morpholinobenzaldehyde **1b** were prepared by nucleophilic substitution of 4-fluorobenzaldehyde with cyclic secondary amines in dimethylsulfoxide and in the presence of potassium carbonate.[16] Treatment of aldehydes **1a**,**b** with hydrazines, namely thiosemicarbazide and cyanoacetic hydrazide, in refluxing ethanol gave the novel hydrazone derivatives **2a-c** (Scheme I).

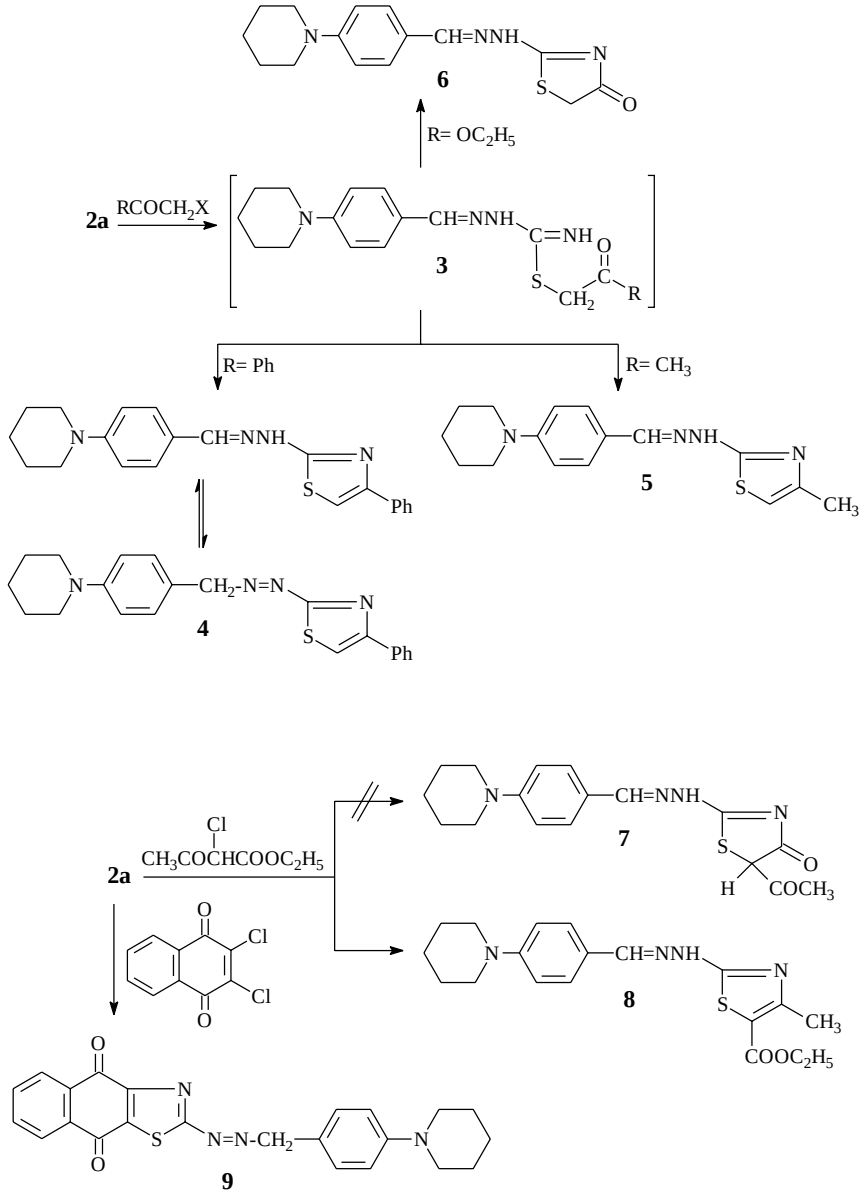
Scheme I



1a; X = CH_2 **2a**; X = CH_2 , R= $CSNH_2$
1b; X = O **2b**; X = CH_2, R = $COCH_2CN$
2c; X = O, R = $COCH_2CN$

The behaviour of thiocarbamoyl functional group in compound **2a** towards some α-halocarbonyl reagents was investigated. Thus, compound **2a** was reacted with phenacyl bromide in absolute ethanol in the presence of fused sodium acetate at room temperature to afford the corresponding *N*-(4-phenyl-thiazol-2-yl)-*N′*-(4-piperidin-1-yl-benzylidene) hydrazine **4** (Scheme II). Formation of thiazole derivative **4** was substantiated by its elemental analyses and spectral data. The infrared spectrum of compound **4** showed the CH-aliphatic at 2931 and 2815 cm^{-1} and the absence of NH band. The ^1H NMR spectrum of compound **4** in DMSO-d_6 revealed the presence of CH-thiazole, methine proton at 7.98 ppm in

Scheme II



addition to NH proton at 11.89 ppm besides other signals due to methylene and aromatic protons. In the mass spectrum a molecular ion peak at *m/z* 362 (11.3%) was observed. Formation of **4** is assumed to proceed via initial alkylation[17] to form intermediate **3** followed by intramolecular cyclization through elimination of water molecule. In the same manner, cycloalkylation of compound **2a** with chloroacetone and ethyl chloroacetate in refluxing ethanol and in the presence of sodium acetate yielded the novel thiazole derivatives **5** and **6**, respectively. Compound **6** showed an intense molecular ion peak at *m/z* 302 corresponding to the molecular formula $C_{15}H_{18}N_4OS$. The molecular ion peak was found to be the base peak in the spectrum. The ^{1}H NMR spectrum of compound **6** recorded in DMSO-d_6 showed a singlet of two protons at 3.91 ppm which is assigned to the methylene group of thiazolidinone. Reaction of compound **2a** with ethyl α-chloroacetoacetate in ethanol in the presence of fused sodium acetate at reflux temperature yielded the corresponding 5-ethoxycarbonyl-4-methyl-thiazol-2-yl derivative **8** instead of the expected product **7**. The absorption bands due to NH, CH-aliph, C=O and C=N functional groups in the infrared spectrum were observed. The ^{1}H NMR spectrum of **8** in DMSO-d_6 exhibited the presence of ethoxycarbonyl, methyl, five methylenes, NH and methine protons in addition to

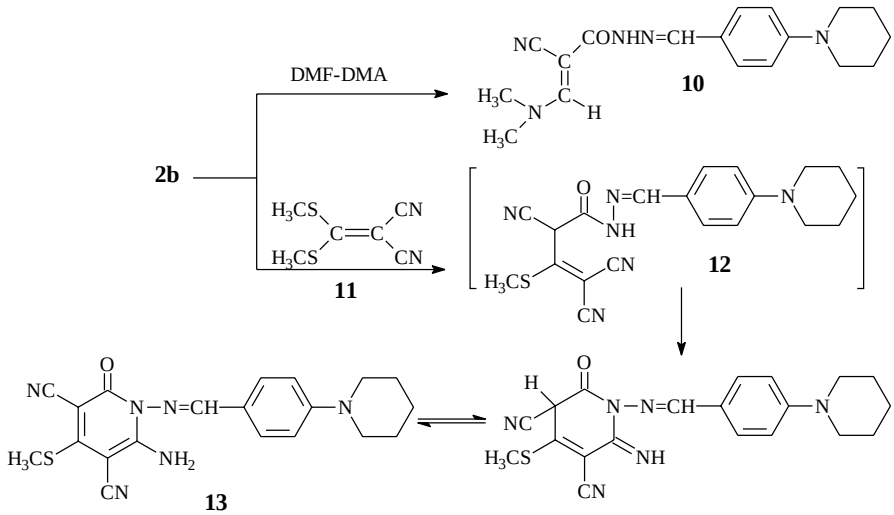
aromatic protons. Formation of **8** was assumed to proceed through initial alkylation followed by intramolecular cyclization via elimination of water. Naphtho[2,3-d]thiazole derivative **9** was synthesized by cyclocondensation of compound **2a** with 2,3-dichloronaphthoquinone in dimethylformamide in the presence of anhydrous potassium carbonate at reflux temperature.

Our investigation was extended to study the reactivity of compound **2b** towards some electrophilic reagents. Thus, condensation of compound **2b** with *N,N*-dimethylformamide-dimethylacetal in refluxing *m*-xylene furnished the novel enaminonitrile **10**. ^{1}H NMR spectrum of compound **10** recorded in DMSO-d_6 exhibited signal characteristic for *N,N*-dimethyl protons. The molecular ion peak of **10** was observed at *m/z* 325 (25%) corresponding to the molecular formula $C_{18}H_{23}N_5O$. Compound **2b** was reacted with ketene dithioacetal **11** as another electrophile in the presence of anhydrous potassium carbonate in dimethylformamide and gave pyridinone derivative **13**. The structure of **13** was inferred from their analytical and spectral data. The infrared spectrum of compound **13** showed absorption bands characteristic for NH_2, C≡N and C=O functional groups. ^{1}H NMR spectrum recorded in DMSO-d_6 displayed the thiomethyl group at 2.58 ppm, a broad band at 4.27 ppm assigned to amino function, a singlet at 8.01 ppm assigned to methine proton in addition to methylene and aromatic protons. Formation of **13** was assumed to proceed via Michael addition[18] of active methylene in **2b** to ketene **11** to form **12** followed by intramolecular cyclization and tautmerization to afford **13** (Scheme III).

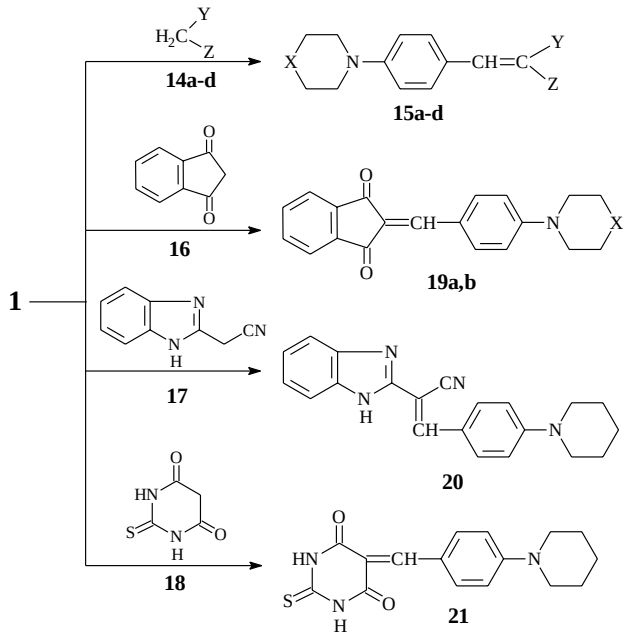
In this contribution, novel ylidenes were prepared by condensation of aldehydes **1** with aliphatic, aromatic and heteroaromatic active methylene compounds. Thus, compounds **1a**,**b** were reacted with malononitrile **14a** and cyanothioacetamide **14b** in ethanol in the presence of triethylamine at room temperature to produce the novel benzylidenes **15a-d**. (Scheme IV). Similarly, indan-1,3-dione **16**, benzimidazol-2-ylacetonitrile **17** and thiobarbituric acid **18** were condensed with aldehyde **1** at reflux temperature in dioxane in the presence of piperidine to furnish the corresponding ylidenes **19**, **20** and **21**, respectively.

Pyridinethione and its derivatives are known to possess various biological activities.[19,20] Substituted pyridinethiones are prepared by the reaction of benzylidene derivatives of cyanothioacetamide with active methylene compounds.[21] Thus, the pyridinethiones **22**, **23** and **24** were prepared in high yields by cyclocondensation of compunds **15c**,**d** with a variety of active methylene compounds as malononitrile **14a**, ethyl cyanoacetate **14c** and ethyl acetoacetate **14d** in ethanolic solution containing a catalytic amount of piperidine at reflux temperature. (Scheme V) A molecular ion peak of pyridinethione **22** was observed at *m/z* 335 (88.8%) corresponding to the molecular formula $C_{18}H_{17}N_5S$. The molecular ion of **22** underwent fragmentation to produce a peak at *m/z* 84 characteristic for the base peak and corresponding to the piperidinyl moiety. Also, the mass spectrum of compound **24** showed the molecular ion peak at *m/z* 383 which is the base peak in the spectrum. The reaction of 1,3-indanedione **16** with ylidenes **15c**,**d** in ethanol in the presence of piperidine as a catalyst under reflux for five hours did not produce indeno[1,2-b]pyridines **26a**,**b** but yielded instead the benzylidenes **19a**,**b**. The structure of **19** was established from their

Scheme III



Scheme IV



14a; Y = Z = CN
14b; Y = CN, Z = $CSNH_2$
14c; Y = CN, Z= $COOC_2H_5$
14d; Y = $COCH_3$, Z = $COOC_2H_5$
15a; X = CH_2, Y = Z = CN
15b; X = O, Y = Z = CN
15c X = CH_2, Y = CN, Z = $CSNH_2$
15d; X = O, Y = CN, Z = $CSNH_2$
19a; X = CH_2
19b; X = O

infrared spectra which exhibit a carbonyl functional group and lack of nitrile functional group. The formation of **19** is assumed to proceed via the addition of methylene moiety in **16** to benzylidene **15** to form a Michael adduct **25** which undergoes a retro-Michael elimination[22] to yield **19** (Scheme V). Indeno[1,2-b]pyridines **26a**,**b** were obtained by reaction of 2-arylidene-1,3-indanedione **19a**,**b** with cyanothioacetamide **14b** in the presence of sodium ethoxide at reflux temperature. The infrared spectra of **26a**,**b** revealed characteristic bands for NH, C≡N and C=O functional groups. Also, a molecular ion peak at *m/z* 399 was observed in the mass spectrum of compound **26b** which is the base peak in the spectrum. The formation of indenopyridines **26a**,**b** is assumed to proceed through the Michael adduct **25** followed by intramolecular cyclization to afford **26a**,**b**.

ANTIMICROBAL ACTIVITY

Twenty-three compounds were screened in vitro for their antimicrobal activities against four strains of bacteria: *Staphylococcus aureus* (NCTC-7447), *Bacillus cereus* (NCTC-14579), *Serratia marcesens* (IMRU-70) and *Proteus mirabilis* (NCTC-289) and two strains of the fungi: *Aspergillus ochraceus* Wilhelm (AUCC-230) and *Penicillium chrysogenum* Thom (AUCC-530) by the agar diffusion techniques.[23] The tested compounds were dissolved in *N,N*-dimethylformamide (DMF) to get a solution of 1000 μg mL^{-1} concentration. The bacteria and fungi cultures were maintained on nutrient agar and Czapek's-Dox agar media, respectively. DMF showed no inhibition zones. The agar media were incubated with different microorganisms culture tested. After 24 h. of incubation at 30 °C for bacteria and 48 h of incubation at 28 °C for fungi, the diameter of inhibition zone (mm) was measured (Table 1). Ampicillin in a concentration 25 μg mL^{-1} and Mycostatine in a concentration 30 μg mL^{-1} were used as references for antibacterial and antifungal activities, respectively. The minimal inhibitory concentration (MIC) of the active compounds was measured by a twofold serial dilution method.[24] The results are illustrated in Table 1. Compounds **4**, **5**, **6**, **8**, **20**, **21** and **22** were found to be the more active compounds against *Staphylococcus aureus* (NCTC-7447) (MIC values 40 μg mL^{-1}). On the other hand, compounds **2c**, **9** (MIC values 40 μg mL^{-1}) and **20** (MIC values 50 μg mL^{-1}) possess high activity against *Bacillus cereus* (NCTC-14579) while only compound **8** (MIC values 40 μg mL^{-1}) exhibited high activity against *Penicillium chrysogenum* Thom. However, none of the tested compounds showed superior activity over the reference.

EXPERIMENTAL

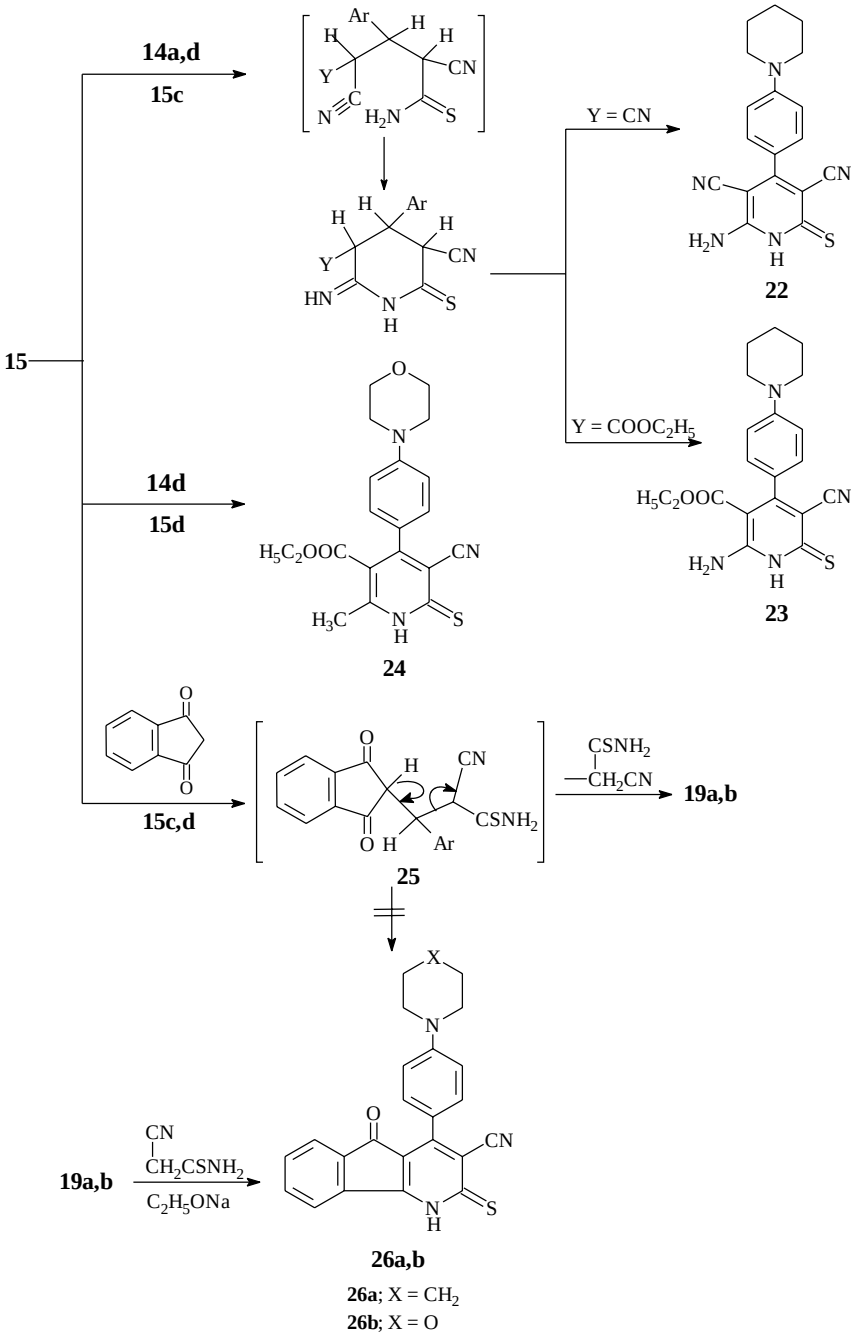
Melting points are uncorrected. IR spectra were recorded (KBr) on a Perkin Elmer 1650 spectrophotometer. ^1H NMR spectra were recorded on a Varian Gemini spectrometer 200 (200 MHz), using DMSO-d_6 as a solvent and TMS as internal standard. Chemical shifts are expressed as δ ppm units. Mass spectra were recorded on a gas chromatographic GC-MS qp 1000 Ex Shimadzu instrument at 70 eV. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University. Found: C, H, N for all compounds were within ± 4% from the theoretical value. Physical data for the synthesized compounds are given in Table 2. Also, the spectral data are collected in Table 3.

[4-(Piperidin-1-yl)benzylidenyl]thiosemicarbazide (2a) and cyanoacetic acid [4-(piperidin-1-yl)benzylidenyl/or 4-(morpholin-4-yl)benzylidenyl]hydrazide (2b,c)

General procedure

A mixture of aldehyde **1** (0.01 mole) and hydrazine deriv-

Scheme V



ative (0.012 mole) in ethanol (50 mL) was heated under reflux for 1 h, then allowed to cool. The solid product was collected and recrystallized from the proper solvent to give **2a-c**, Table 2.

***N*-(4-Phenyl-thiazol-2-yl)-*N′*-[4-(piperidin-1-yl)benzylidenyl]hydrazine (4)**

A mixture of **2a** (0.01 mole) and phenacyl bromide (0.01 mole) and fused sodium acetate (1 gm) in ethanol (50 mL) was stirred at room temperature for 5 min. The solid product was collected and recrystallized from the proper solvent to give **4**, Table 2.

MS: 362 (11.3%), 363 (M+1; 3.0%), 187 (13.7%), 186 (18.4%), 185 (19.0%), 176 (100%), 134 (23.7%), 104 (12%), 77 (14.2%).

Table 1. Antimicrobial Activity of the Synthesized Compounds and Inhibition Zones (mm)

Compd. No.	Gram positive bacteria		Gram negative bacteria		Fungi	
	Staphylococcus aureus (NCTC-7447)	*Bacillus cereus* (NCTC-14579)	*Serratia marcesens* (IMRU-70)	*Proteus mirabilis* (NCTC-289)	*Aspergillus ochraceus* Wilhelm (AUCC-230)	*Penicillium chrysogenum* Thom (AUCC-530)
2a	++	++	+	+	+	++
2b	++	+	++	++	+	+
2c	++	+++	++	+	+	++
4	+++	++	+	+	++	++
5	+++	++	+	+	++	+
6	+++	++	+	+	+	+
8	+++	+	+	+	+	+++
9	++	+++	+	+	+	+
10	+	++	+	+	+	+
13	+	+	+	+	+	++
15a	+	+	+	+	+	+
15b	+	++	++	+	+	+
15c	+	++	+	+	+	++
15d	++	++	++	++	++	+
19a	+	+	+	+	+	+
19b	+	++	+	+	+	+
20	+++	+++	+	+	++	+
21	+++	+	++	+	++	++
22	+++	+	+	++	+	+
23	++	++	+	+	+	+
24	++	++	+	+	++	+
26a	++	++	+	+	++	+
26b	++	+	+	+	++	+
Standard	++++	++++	++++	++++	++++	++++

+: Less active (2-5 mm).
++: Moderately active (6-14 mm).
+++: Highly active (15-20 mm).
++++: Very highly activity (> 20 mm).
Standard: For Gram positive and Gram negative bacteria: Ampicillin 25 μg mL^{-1}: for fungi: Mycostatine 30 μg mL^{-1}.

_N_-(4-Methyl-thiazol-2-yl)-_N′_-[4-(piperidin-1-yl)benzyl-idenyl]hydrazine (5) and 2-[N′-(4-piperidin-1-yl)benzyl-idenyl]hydrazino]-4,5-dihydro-thiazol-4-one (6)

A mixture of **2a** (0.01 mole) and chloroacetone or ethyl chloroacetate (0.01 mole) and sodium acetate (2 gm) in ethanol (40 mL) was heated under reflux for 2 h, then allowed to cool and poured into water (70 mL). The solid product was collected and recrystallized from the proper solvent to give **5** and **6**, respectively, Table 2.

MS (**5**): 300 (17.3%), 301 (M+1; 3.6%), 186 (38%), 185 (42%), 114 (100%), 104 (8.6%), 91 (6.1%), 77 (14.7%), 76 (6.0%).

MS (**6**): 302 (M^+; 100%), 301 (M-1; 18.8%), 187 (76%), 185 (31%), 159 (27%), 130 (21.6%), 104 (15.4%), 90 (21.9%), 77 (26%), 76 (13.4%).

_N_-(5-Ethoxycarbonyl-4-methyl-thiazol-2-yl)-_N′_-[4-(piperidin-1-yl)benzylidenyl]hydrazine (8)

A mixture of **2a** (0.01 mole) and ethyl α-chloroaceto-acetate (0.01 mole) and sodium acetate (2 gm) in ethanol (50 mL) was heated under reflux for 12 h, then allowed to cool and poured into cold water (60 mL). The solid product was collected and recrystallized from the proper solvent to give **8**, Table 2.

2-[_N′_-(4-(Piperidin-1-yl)benzylidenyl)hydrazino]naphtho-[2,3-d]thiazol-4,9-dione (9)

A mixture of **2a** (0.01 mole) and 2.3-dichloronaphtho-quinone (0.01 mole) and potassium carbonate (2 gm) in dimethylformamide (10 mL) was heated under reflux for 1 h, then allowed to cool and poured into cold water (40 mL). The

Table 2. Physical Data for the Synthesized Compounds

Compd No.	M.p. (°C)	Yield (%) (color)	Solvent cryst.	Molecular formula (Mol.wt)
2a	105-6	84 (yellow)	Ethanol	$C_{13}H_{18}N_4S$ (262.38)
2b	190-2	75 (orange)	Ethanol	$C_{15}H_{18}N_4O$ (270.34)
2c	145-7	67 (yellow)	Ethanol	$C_{14}H_{16}N_4O_2$ (272.31)
4	225-7	73 (yellow)	Dioxane	$C_{21}H_{22}N_4S$ (362.50)
5	200-1	64 (yellow)	Benzene	$C_{16}H_{20}N_4S$ (300.43)
6	270-2	65 (yellow)	Ethanol	$C_{15}H_{18}N_4OS$ (302.40)
8	308-10	70 (yellow)	Dioxane	$C_{19}H_{24}N_4O_2S$ (372.48)
9	> 300	63 (violet)	Dioxane	$C_{23}H_{20}N_4O_2S$ (416.51)
10	222-4	78 (orange)	Dioxane	$C_{18}H_{23}N_5O$ (325.42)
13	>300	57 (violet)	Ethanol	$C_{20}H_{20}N_6OS$ (392.49)
15a	120-1	83 (yellow)	Ethanol	$C_{15}H_{15}N_3$ (237.31)
15b	195-6	80 (orange)	Ethanol	$C_{14}H_{13}N_3O$ (239.28)
15c	225-7	87 (orange)	DMF	$C_{15}H_{17}N_3S$ (271.39)
15d	220-1	85 (orange)	DMF	$C_{14}H_{15}N_3OS$ (273.36)
19a	190-2	77 (violet)	Dioxane	$C_{21}H_{19}NO_2$ (317.39)
19b	240-2	76 (yellow)	Dioxane	$C_{20}H_{17}NO_3$ (319.36)
20	280-2	62 (orange)	Dioxane	$C_{21}H_{20}N_4$ (328.42)
21	235-6	54 (violet)	Dioxane	$C_{16}H_{17}N_3O_2S$ (315.40)
22	245-6	78 (orange)	Dioxane	$C_{18}H_{17}N_5S$ (335.43)
23	100-2	87 (orange)	Dioxane	$C_{20}H_{22}N_4O_2S$ (382.48)
24	280-2	82 (orange)	Dioxane	$C_{20}H_{21}N_3O_3S$ (383.47)
26a	282-4	69 (orange)	Dioxane	$C_{24}H_{19}N_3OS$ (397.50)
26b	260-1	65 (red)	Dioxane	$C_{23}H_{17}N_3O_2S$ (399.47)

solid product was collected and recrystallized from the proper solvent to give **9**, Table 2.

2-Cyano-3-dimethylamino-acrylic acid [4-(piperidin-1-yl)-benzylidenyl]hydrazide (10)

A mixture of compound **2b** (0.01 mole) and dimethylformamide-dimethylacetal (0.01 mole) in dry *m*-xylene (30 mL) was refluxed for 3 h, then cooled. The precipitated product was filtered off, washed with ether and recrystallized from the proper solvent to give **10**, Table 2.

MS: 325 (25%), 326 (M+1; 5.6%), 202 (14.8%), 187 (17.4%), 186 (63.7%), 185 (52.8%), 123 (100%), 104 (4.3%), 77 (7.7%), 76 (4.0%).

6-Amino-4-methylsulfanyl-2-oxo-1-[(4-(piperidin-1-yl)-benzylidenyl)amino]-1,2-dihydro-pyridine-3,5-dicarbonitrile (13)

A mixture of **2b** (0.01 mole) and ketene dithioacetal **11** (0.01 mole) and potassium carbonate (2 gm) in dimethylformamide (10 mL) was heated under reflux until the evolution of methyl mercaptan had stopped. After cooling, the reaction mixture was poured into cold water (100 mL) and acidified with HCl. The product was collected by filtration and recrystallization from the proper solvent to give **13**, Table 2.

2-[4-(Piperidin-1-yl)benzylidenyl/or 4-(morpholin-4-yl)-benzylidenyl]malononitriles (15a,b) and 2-cyano-3-[4-(piperidin-1-yl)phenyl/or 4-(morpholin-4-yl)phenyl]thioacrylamides (15c,d)

General procedure

A mixture of aldehyde **1** (0.01 mole) and active methylene compound (0.01 mole) and triethylamine (0.01 mole) in ethanol (50 mL) was stirred at room temperature for 15 min. The solid product was collected and recrystallized from the proper solvent to give **15a-d**, Table 2.

MS (**15d**): 273 (100%), 274 (M+1; 28%), 239 (45.9%), 214 (45.6%), 187 (55.9%), 181 (67.6%), 180 (23.9%), 153 (21.1%), 126 (19%), 104 (3.4%), 90 (8.2%), 76 (8.7%), 77 (27%).

2-[4-(Piperidin-1-yl)benzylidenyl/or 4-(morpholin-4-yl)-benzylidenyl]indan-1,3-diones (19a,b), 2-(1H-benzyimidazol-2-yl)-3-[4-(piperidin-1-yl)phenyl]acrylonitrile (20) and 5-[4-(piperidin-1-yl)benzylidenyl]-2-thioxo-dihydropyrimidine-4,6-dione (21)

General procedure

A mixture of **1** (0.01 mole) and active methylene compound (0.01 mole) and piperidine (0.01 mole) in dioxane (30 mL) was heated under reflux for 1 h. The solid product which was produced on heating was collected and recrystallized from the proper solvent to give **19-21**, Table 2.

Table 3. Spectral Data for the Synthesized Compounds

Compd. No.	IR/ν_{max} (cm^{-1})	^{1}H NMR (δ/ppm) (DMSO-d_6)
2a	3433, 3263, 3147 (NH, NH_2), 2931, 2823 (CH-aliph), 1610 (C=N).	1.59 (s, 6H, $3CH_2$), 3.25 (s, 4H, $N(CH_2)_2$), 6.89, 7.59 (2d, 4H, Ar-H), 7.80, 11.23 (2s, 2H, two NH), 7.96 (s, 1H, SH), 7.80 (s, 1H, CH=N).
2b	3394 (NH), 2923, 2839 (CH-aliph), 2268 (C≡N), 1705 (C=O), 1604 (C=N).	1.60 (s, 6H, $3CH_2$), 3.20 (s, 4H, $N(CH_2)_2$), 4.18 (s, 2H, CH_2CN), 6.95, 7.52 (2d, 4H, Ar-H), 7.90 (s, 1H, CH=N), 11.57 (s, 1H, NH).
2c	3209 (NH), 2962, 1854 (CH-aliph), 2206 (C≡N), 1685 (C=O), 1600 (C=N).	2.56 (s, 4H, $N(CH_2)_2$), 3.81 (s, 4H, $O(CH_2)_2$), 4.21 (s, 2H, CH_2CN), 7.00-7.66 (m, 4H, Ar-H), 7.95 (s, 1H, CH=N), 11.64 (s, 1H, NH).
4	2931, 2815 (CH-aliph), 1604 (N=N).	1.65 (s, 6H, $3CH_2$), 3.28 (s, 4H, $N(CH_2)_2$), 6.99, 7.89 (2d, 4H, Ar-H), 7.31-7.56 (m, 6H, Ar-H + thiazole-H), 7.98 (s, 1H, CH=N), 11.89 (s, 1H, NH).
5	3178 (NH), 2923, 2854 (CH-aliph), 1604 (C=N).	1.30 (s, 6H, $3CH_2$), 2.21 (s, 3H, CH_3), 3.29 (s, 4H, $N(CH_2)_2$), 6.35 (s, 1H, thiazole-H), 6.97, 7.42 (2d, 4H, Ar-H), 7.96 (s, 1H, CH=N), 11.45 (hump, 1H, NH).
6	2931, 2777 (CH-aliph), 1720 (C=O), 1635 (C=N), 1604 (N=N).	1.65 (s, 6H, $3CH_2$), 3.34 (s, 4H, $N(CH_2)_2$), 3.91 (s, 2H, SCH_2), 6.99, 7.65 (2d, 4H, Ar-H), 8.30 (s, 1H, CH=N), 11.87 (s, 1H, NH).
8	3192 (NH), 2931, 2854 (CH-aliph), 1717 (C=O), 1573 (C=N).	1.26 (t, 3H, CH_3), 1.57 (s, 6H, $3CH_2$), 1.78 (s, 3H, CH_3), 3.23 (s, 4H, $N(CH_2)_2$), 4.16 (q, 2H, OCH_2), 6.91, 7.51 (2d, 4H, Ar-H), 8.01 (s, 1H, CH=N), 8.10 (s, 1H, NH).
9	2931, 2815 (CH-aliph), 1651 (C=O), 1589 (N=N).	1.69 (s, 6H, $3CH_2$), 3.50 (s, 4H, $N(CH_2)_2$), 7.07-7.93 (m, 8H, Ar-H), 8.46 (Hump, 1H, NH), 8.75 (s, 1H, CH=N).
10	3355 (NH), 2931, 2854 (CH-aliph), 2191 (C≡N), 1666 (C=O), 1604 (C=N).	1.65 (s, 6H, $3CH_2$), 3.28 (s, 4H, $N(CH_2)_2$), 3.38 (s, 6H, $N(CH_3)_2$), 6.98, 7.51 (2d, 4H, Ar-H), 7.81, 8.30 (2s, 2H, two CH), 10.63 (s, 1H, NH).
13	3402, 3360 (NH_2), 2931, 2862 (CH-aliph), 2206 (C≡N), 1620 (C=O), 1542 (C=N).	1.69 (s, 6H, $3CH_2$), 2.58 (s, 3H, SCH_3), 3.51 (s, 4H, $N(CH_2)_2$), 4.27 (Hump, 2H, NH_2), 7.56, 8.20 (2d, 4H, Ar-H), 8.01 (s, 1H, CH=N).
15a	2928, 2956 (CH-aliph), 2210 (C≡N).	1.63 (s, 6H, $3CH_2$), 3.23, 3.29 (2s, 4H, $N(CH_2)_2$), 7.02, 7.81 (2d, 4H, Ar-H), 8.01 (d, 1H, CH).
15b	2954, 2854 (CH-aliph), 2214 (C≡N).	3.55 (s, 4H, $N(CH_2)_2$), 3.81 (s, 4H, $O(CH_2)_2$), 7.12, 7.89 (2d, 4H, Ar-H), 8.18 (s, 1H, CH).
15c	3348, 3283, 3163 (NH_2), 2933, 2851 (CH-aliph), 2215 (C≡N).	1.63 (s, 6H, $3CH_2$), 3.32 (s, 4H, $N(CH_2)_2$), 7.03, 7.87 (2d, 4H, Ar-H), 8.07 (s, 1H, CH), 9.17 (s, 1H, NH), 9.71 (s, 1H, SH).
15d	3381, 3302, 3190 (NH_2), 2960, 2877 (CH-aliph), 2197 (C≡N).	3.37 (s, 4H, $N(CH_2)_2$), 3.79 (s, 4H, $O(CH_2)_2$), 7.06, 7.91 (2d, 4H, Ar-H), 8.08 (s, 1H, CH), 9.22 (s, 1H, NH), 9.71 (s, 1H, SH).
19a	2950, 2854 (CH-aliph), 1666 (C=O).	1.69 (s, 6H, $3CH_2$), 3.62 (s, 4H, $N(CH_2)_2$), 7.07, 8.59 (2d, 4H, Ar-H), 7.91 (s, 4H, Ar-H), 7.70 (s, 1H, CH).
19b	2920, 2860 (CH-aliph), 1650 (C=O).	3.52 (s, 4H, $N(CH_2)_2$), 3.81 (s, 4H, $O(CH_2)_2$), 7.11, 8.57 (2d, 4H, Ar-H), 7.94 (s, 4H, Ar-H), 7.77 (s, 1H, CH).
20	3263 (NH), 2931, 2854 (CH-aliph), 2221 (C≡N).	1.60 (s, 6H, $3CH_2$), 3.41 (s, 4H, $N(CH_2)_2$), 7.02, 7.90 (2d, 4H, Ar-H), 7.22, 7.59 (2m, 4H, Ar-H), 8.16 (s, 1H, CH), 12.72 (Hump, 1H, NH).
21	3155 (NH), 2931, 2854 (CH-aliph), 1651 (C=O).	1.68 (s, 6H, $3CH_2$), 3.49 (s, 4H, $N(CH_2)_2$), 7.02, 8.45 (2d, 4H, Ar-H), 8.18 (s, 1H, CH), 11.93, 12.55 (2s, 2H, two NH).
22	3433, 3340, 3232 (NH, NH_2), 2931, 2831 (CH-aliph), 2198 (C≡N).	1.62 (s, 6H, $3CH_2$), 3.04 (s, 4H, $N(CH_2)_2$), 3.29 (s, 2H, NH_2), 3.60 (s, 1H, SH), 6.79, 7.30 (2d, 4H, Ar-H).
23	3300, 3210 (NH_2), 2931, 2854 (CH-aliph), 2206 (C≡N), 1705 (C=O).	1.28 (t, 3H, CH_3), 1.64 (s, 6H, $3CH_2$), 3.39 (s, 4H, $N(CH_2)_2$), 3.52 (s, 2H, NH_2), 4.24 (q, 2H, OCH_2), 7.03, 7.94 (2d, 4H, Ar-H), 8.12 (s, 1H, NH).
24	3433 (NH), 2923, 2854 (CH-aliph), 2225 (C≡N), 1708 (C=O).	0.92 (t, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.28 (s, 4H, $N(CH_2)_2$), 3.99 (s, 4H, $O(CH_2)_2$), 4.23 (q, 2H, OCH_2), 7.08, 7.31 (2d, 4H, Ar-H), 12.27 (s, 1H, NH).
26a	3100 (NH), 2950, 2880 (CH-aliph), 2221 (C≡N), 1681 (C=O).	1.67 (s, 6H, $3CH_2$), 3.31 (s, 4H, $N(CH_2)_2$), 6.99-7.73 (m, 8H, Ar-H), 8.25 (Hump, 1H, NH).
26b	3415 (NH), 2923, 2854 (CH-aliph), 2221 (C≡N), 1708 (C=O).	3.32 (s, 4H, $N(CH_2)_2$), 3.82 (s, 4H, $O(CH_2)_2$), 7.04, 7.46 (2d, 4H, Ar-H), 7.67-7.75 (m, 4H, Ar-H), 8.32 (s, 1H, NH).

MS (**19b**): 319 (100%), 320 (M+1; 23.1%), 261 (79.5%), 260 (74%), 233 (78%), 176 (32%), 151 (12.3%), 104 (26%), 77 (13.6%), 76 (42%), 75 (23.9%).

MS (**20**): 328 (M^+; 54%), 327 (M-1; 100%), 329 (M+1; 11.7%), 303 (4.5%), 271 (16.5%), 244 (8.7%), 164 (11.1%), 122 (12.0%), 104 (0.6%), 91 (3.6%), 77 (4.1%), 76 (2.7%).

6-Amino-4-[4-(piperidin-1-yl)phenyl]-2-thioxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (22) and 2-amino-4-[4-(piperidin-1-yl)phenyl]-3-ethoxycarbonyl-6-thioxo-1,6-dihydro-pyridine-5-carbonitrile (23)

General procedure

A mixture of **15** (0.01 mole) and active methylene compound (0.01 mole) and triethylamine (0.01 mole) in ethanol (50 mL) was heated under reflux for 8 h, then allowed to cool and poured into cold water (70 mL) and acidified with HCl. The solid product was collected and recrystallized from the proper solvent to give **22** and **23**, Table 2.

MS (**22**): 335 (M^+; 88%), 336 (M+1; 32%), 294 (13%), 251 (13%), 190 (12%), 139 (12%), 84 (100%), 77 (4.8%), 76 (5.1%).

5-Cyano-2-methyl-4-[4-(morpholin-4-yl)phenyl]-6-thioxo-1,6-dihydro-pyridine-3-carboxylic acid ethyl ester (24)

A mixture of **15d** (0.01 mole) and ethyl acetoacetate (0.01mole) and piperidine (0.5 mL) in dioxane (30 mL) was heated under reflux for 24 h, then allowed to cool and poured into cold water (70 mL) and acidified with HCl. The solid product was collected and recrystallized from the proper solvent to give **24**, Table 2.

MS: 383 (100%), 384 (M+1; 25.4%), 325 (45%), 296 (24.4%), 279 (15.5%), 280 (21.3%), 253 (13.2%), 224 (9.4%), 184 (3.7%), 152 (4.6%), 104 (5.1%), 91 (3.9%), 77 (7.4%), 76 (4.3%).

5-Oxo-4-[4-(piperidin-1-yl)phenyl/or 4-(morpholin-4-yl)-phenyl]-2-thioxo-2,5-dihydro-1H-indeno[1,2-b]pyridine-3-carbonitrile (26a,b)

A mixture of **19a** or **19b** (0.01 mole) and cyanothioacetamide **14b** (0.01 mole) and sodium ethoxide (0.01 mole) in ethanol (40 mL) was heated under reflux for 4 h, then allowed to cool and poured into cold water (40 mL) and acidified with HCl. The solid product was collected and recrystallized from the proper solvent to give **26a** and **26b**, respectively, Table 2.

MS (**26b**): 399 (100%), 400 (M+1; 29.7%), 341 (84%), 340 (30%), 313 (64%), 252 (10%), 214 (4%), 171 (39%), 157 (38%), 102 (17%), 77 (17.6%), 76 (9.2%).

ACKNOWLEDGEMENT

The author is grateful to Dr. M. M. Ghorab, Department of Drug Radiation Research, National Centre for Radiation Research and Technology, P.O. Box 29, Nasr City, Cairo, Egypt for antimicrobial activity tests.

Received March 5, 2003.

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