Reactivity of pyridin-2-thione derivatives towards some nucleophilic and electrophilic reagents

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Abstract: The bifunctional 3-cyano-2-thioxo (1H) pyridine derivatives **(1)** were prepared by the reaction of cyanothioacetamide with α,β, unsaturated carbonyl compounds. Compound **(1)** reacted with thiourea to give the corresponding thiouredo derivatives **(2)**. Compound **(2)** was used as the key intermediate to prepare the pyrido pyrimidine thione derivatives **(3,6,7,8)** through its reaction with malonic acid , diethyl malonate , acetylacetone and acetoacetic ester. Reaction of **(3)** with aromatic aldehydes and/or primary amines and formaldehyde (Mannich reaction conditions) were also investigated. The reaction of **(Ib)** with ethylchloroacetate followed by hydrazinolysis gave the hydrazide derivative **(lla)** which on treatment with phenyl isothiocyanate followed by cyclyization with conc. Sulfuric acid , mercuric oxide or sodium hydroxide to give **(13,14, and 15).** Reaction of compound **(l1d)** with sulfuric acid affected cyclization to give **(16).** Alkaline hydrolysis of the mercapto ester **(10)** gave the acid derivative **(17).**

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1. Introduction

In continuation of the previous studies**(Mahmoud et al. 2011 .; Mohamed et al. 2007 .; El-Soghier et al. 2008 .; Al-Omar et al. 2005) ,**we report here synthesis of some new azines**(El-Gaby et al. 2011)** and study their reactivity towards some nucleophilic and electrophilic reagents**(Cesur et al. 2002 .; Pitucha et al. 2010 .; Davidkov et al. 1995)**This study was also directed towards the development of simple new procedure for the synthesis of biologically active heterocyclic compounds**(Madkour et al. 2007 .; Hamouda et al. 2011 .; El-Essawy et al. 2005)** Thus, it has been found that 4,6-diaryl-cyanopyridin-2-thiones**(1a,b)**reacted in the presence of base catalysed or in ethanol-acetic acid mixture with thiourea to afford products formulated as 3-cyano-2-thioureido pyridine derivatives**(2a,b)** respectively**(Abdel-Ghaffar et al. 2002)**

2. Experimental:

All melting points are uncorrected. The infrared spectra (KBr) were carried out on a Pye unican SP 3-200 Spectrophotometer. The ^{1}H-NMR spectra were measured on varian EM 60 and JEOL-90 MHz spectrometers with TMS as internal reference, chemical shifts were expressed in 5 ppm. The mass spectra were determined on a FINNI-Gas 3300 mass spectrometer by direct inlet (Source temperature 90-300 C°, beam energy 70 ev).

All elemental analysis, spectral data and biological effects are listed in tables 1,2 and 3 respectively.

Compounds 4,6-diaryl-3-cyanopyridin-2-thiiones **(la,b)** were prepared according to **(Jones et al.2000)** the solids were crystallized from the proper solvent to give **(la,b)** .

l-(3-cyano-4-(4-halophenyl)-6-(4-methoxyphenyl)pyridin-2-yl) thiourea (2a,b).

To a solution of **la** and/or **lb** (0.01 mol)in base catalysed or in ethanol-acetic acid mixture (20:15 ml),thiourea (0.0l mol) was added. The reaction mixture was refluxed for 6 hours. The solid separated after concentration and cooling was recrystallized from the proper solvent to give **(2a,b)** respectively .

Reaction of (2b) with malonic acid and acetyl chloride: Formation of 2-(3-acetyl-4,6-dioxo-tetrahydro-pyrimidin-l(2H)-yl)-4-(4-chlorophenyl)-6-(4-methoxy phenyl) nicotinonitrile (3).

A mixture of **2b** (0.01 mol) and malonic acid (0.01 mol) in acetyl chloride (7.9 ml) was refluxed on a steam bath for 12 hours. After cooling the reaction mixture was poured onto ice while stirring. The solid separated was recrystallized from the proper solvent to give **(3)**.

Reaction of (3)with aromatic aldehydes :Formation of 3-cyano-4,6-diaryl-2-[3-N(lN-acetyl-5-arylidene)-2-thiono)pyrimidinyl-4,6-dione]pyridine derivatives(4a-c)respectively.

A mixture **of 3** (0.01 mol) in (40 ml) acetic acid containing 3 gm fused sodium acetate, (0.01 mol) of aromatic aldehydes namely; 4-nitrobenzaldehyde,N,N-dim-ethylaminobezaldehyde and/or 3,4,5-trimethoxybenzaldehyde (0.01 mol)

was refluxed for 6hrs.After cooling it was poured onto cold water and the solid that separated was recrystallized from the proper solvent to give **(4a-c)** respectively .

Reaction of (3) with aromatic amines :Formation of 3 – cyano - 4,6 – diaryl – 2 - [3N(1N-acetyl-5-methylamino-2-thiono) pyrimidinyl-4,6-dione]pyridine derivatives (5a,b)

To a solution of 3 (0.01 mol) in (l0 ml) of formaline solution we added (0.01 mol) of p-anisidine and/or 4-bromo aniline, the reaction mixture was refluxed for 6 hours. The solid separated on cooling was crystallized from the proper solvent to give the Mannich bases **(5a,b)** respectively .

Reaction of (2b) with diethylmalonate, acetylacetone and/or ethyl-acetoacetate: Formation of 4-(4-chlorophenyl)-2-(4,6-dioxo-2-thioxo-tetrahydropyrimidin-l(2H)-yl)-6-(4-methoxyphenyl) nicotinonitrile;4-(4-chlorophenyl)-2-(4,6-dimethyl-2- hioxopyrimidin-1(2H)-yl)-6-(4-methoxyphenyl) nicotinonitrile and 4-(4-chlorophenyl)-6-(4-methoxyphenyl)-2-(6-methyl-4-oxo-2-thioxotetrahydropyrimidin-1 (2H)yl)nicotinonitrile(6,7,8)

A mixture of **2b** (0.01 mol) and (0.01 mol) of diethyl malonate, acetyl acetone and/or ethylacetoacetate in (50 ml)sodium methoxide were refluxed for 6 hours. After concentration and cooling, the reaction mixtures were poured onto cold water. The solids separated were collected and recrystallized from the proper solvent to give **(6,7,8)** respectively .

Reaction of (2b) with ethylchloroacetate: Formation of ethyl-4-(4-chlorophenyl)-3-cyano-6-(4-methoxyphenyl)pyridin-2-yl)thiocarbamoyl carbamate (9)

A mixture of **2b**(0.01 mol)and ethyl chloroacetate(0. 01 mol) in (30 ml) Pyridine was refluxed for 8 hours. After concentration and cooling, the reaction mixture was poured onto ice/HCl mixture the formed solid was collected and recrystallized from the proper solvent to give **(9)**.

Reaction of (1b) with ethyl chloro acetate: Formation of 3-cyano-2-mercaptoethyl-[6(-4-methoxyphenyl)-4-(4-chlorophenyl-2 -thio)-pyridin-2yl] acetate (10)

A mixture of **lb** (0.01 mol) and ethylchloroacetate (0.015 mol) in (50 ml) dry acetone containing (0.03 mol) anhydrous potassium carbonate was refluxed for 24 hours. The reaction mixture was filtered on hot, then concentrated and cool. The separated solid was collected, washed well with water and recrystallized from the proper solvent to give **(10)**

Reaction of (10) with hydrazines and carbazide derivatives to give(11a-d)

To a solution of **10** (0.01 mol) in (30 ml)absolute ethanol (0.01mol) of hydrazine hydrate, phenyl hydrazine, semicarbazide and/or thiosemicarbazide were added. The reaction mixture was refluxed for 6 hours. After concentration and cooling the obtained product was crystallized from the proper solvent to give **(11a-d)**

Reaction of (11a) with phenylisothiocyante: Formation of 1-(2-(3-cyano-6(4-methoxyphenyl)-4-(4-chlorophenyl)pyridin-2-yl-thio)acetyl)-4-phenylthiosemicarbazide(12)

A mixture of **11a** (0.01 mol) phenyl isothiocyanate (0.013 mol) in (20 ml) pyridine was refluxed for 6 hours. After cooling the reaction mixture was poured onto ice/HCI mixture the formed solid was filtered off washed well with water and recrystallized from the proper solvent to give **(12)** .

Reaction of (12) with mercuric Oxide: Formation of 6-(4-methoxyphenyl)-4-(4-chlorophenyl)-2-(5-(phenylamino)-l,3,4-oxodiazol-2-yl)methylthio) nicotinonitrile(13)

To a solution of **12** (0.01 mol) in (30 ml) ethanol (0.01mol) of mercuric oxide was added. The reaction mixture was refluxed for 36 hours until all H_2S gas was extruded then filtered on hot. After concentration and cooling the separated solid was recrystallized from the proper solvent to give **(13).**

Reaction of(13)with concentrated sulphuric acid :Formation of 6-(4-methoxyphenyl)-4-(4-chlorophenyl)-2-(5-(phenylamino)-l,3,4-thiadiazol-2-yl)methylthio)nicotinonitrile (14).

A suspension of **12** (0.01 mol) in (15ml) concentrated sulphuric acid was stirred well for 2 hours at room temp. the reaction mixture was left overnight then poured onto cold water. The separated solid was recrystallized from the proper solvent to give **(14)**

Reaction of(12) with sodium hydroxide solution(8%):Formation of 6-(4-methoxyphenyl)-4-(4-chlorophenyl)-2-(4-phenyl-5-thioxo-4,5-dihydro-1H-l,2,4-triazol-3-yl)methylthio)nicotinonitrile(15)

A suspension of **(12)** (0.01mol) in 10 ml of absolute ethanol and sodium hydroxide solution (8%; 30 ml)was refluxed for 2 hours. After concentration and cooling the reaction mixture was acidified with

HCl. The solid that formed was collected and recrystallized from the proper solvent **(15**)

Reaction of (11d) with sulphuric acid 50%: Formation of 2-((5-amino-1,3,4-thiodiazole-2-yl)methylthio-6-(4-methoxyphenyl)-4-(4-chlorophenyl) nicotinonitrile(l6)

A suspension of **11d** (0.01 mol) in (20 ml) sulphuric acid (50%) was stirred well at room temperature for 3 hours, then the reaction mixture was left over night, then poured onto water. The separated solid was recrystallized from the proper solvent to give **(16)**.

Reaction of (10) with ethanolic sodium hydroxide: Formation of 2- (3-cyano-6- (4-methoxyphenyl) -4-(4-chlorophenyl) pyridin-2-yl) thio acetic acid (17)

A mixture of **10** (0.01 mol) and sodium hydroxide (0.032 mol dissolved in 5ml water) in (20 ml) of absolute ethanol was refluxed for 6 hours. After concentration and cooling, the reaction mixture was acidified with dilute HCI/the formed solid was filtered off and washed well with water then recystallized from the proper solvent to give **(17)** .

3. Results and discussion

The new compound **(2b)** prepared from 4,6-diaryl-3-cyano pyridin-2-thione**(lb)**by its reaction with thiourea was taken as starting material for the present investigation of the study owing to the presence of more than one active site, thus interaction of equimolecular amount of **(2b)**, malonic acid and acetyl chloride on a steam bath for 12 hrs.yielded the corresponding 2-(3-acetyl-4,6-dioxo-2-thioxo-tetrahydropyrimidin-l(2H)-yl)-4-(4-chlorophenyl)-6-(4-methoxyphenyl) nicotinonitrile**(3).**

A further proof of **(3)** was achieved via the reaction with a variety of electrophiles such as carbonyl compounds with the carbonyl objective of synthesis of other new heterocyclic derivatives. Thus **(3)** reacted with aromatic aldehydes namely,4-nitrobenzaldehyde ,4-N,N-dimethylaminobenzaldehyde and 3,4,5-trimethoxybenzaldehyde in boiling acetic acid containing a pinch of fused sodium acetate to give the corresponding 3-cyano-4,6-diaryl-2-[3-N-(lN-acetyl-5-arylidene-2-thiono)prymidinyl-4,6-dione] pyridine**(4a-c)** respectively. A further proof of the structure of **(3)** was obtained via its conversion into the corresponding 4-methyl amino pyrimidinyl derivatives **(5a,b)** by boiling with primary aromatic amines in the presence of formaldehyde, (Mannich reaction conditions). Thus, refluxing of**(3)**with each of p-anisidine or 4-bromoaniline in formaline solution afforded products which were formulated as 2-(3-acetyl-5-((4-methoxy/or bromo phenyl amino)methyl)-4,6-dioxo-2-thioxo-tetrahydropyri-midin-l(2H)-yl)-4-(4-chlorophenyl)-6-(4-methoxyphenyl)nicotinonitrile**(5a,b)**is assumed to proceed via the attack of the intermediate methyloyl amine which under the inductive effect of the two carbonyl carbons of **(3)**is converted to methylene moiety(at position 4) of **(3)**activated by the neighbouring keto groups to give rise to a water molecule with the formation of Mannich bases **(5a,b).**

The condensation of l-(4-(4-chlorophenyl)-3-cyano-6-(4-methoxyphenyl) pyridin-2-yl)thiourea**(2b)**with active methylene compounds namely diethylmalonate, acetylacetone and ethylacetoacetate in boiling sodium methoxide solution afforded the corresponding 4-(4-chlorophenyl)-2-(4,6-dioxotetrahydropyrimidin-l(2H)-yl)-6-(4-methoxyphenyl)nicotinonitrile**(6)**,4-(4-chlorophenyl)-2-(4,6-dimethyl-2-thioxopyrimidin-l(2H)-yl)-6-(4-methoxyphenyl) nicotinonitrile **(7)**and 4-(4-chlorophenyl)-6-(4-methoxyphenyl)-2-(6-methyl-4-oxo-2-thioxo-tetrahydropyrimidin-l(2H)-yl) nicotinonitrile **(8).**

On the other hand the reaction of **(2b)** with ethylchloroacetate in boiling pyridine afforded ethyl -4-(4-chlorophenyl)-3-cyano-6-(4-methoxyphenyl) pyridin-2-yl)carbamothioyl carbamate **(9).**

It has been found that the alkylation of 3-cyano-4,6-diarylpyridin-2-thione**(lb)**with ethylchloroacetate in boiling dry acetone containing anhydrous potassium carbonate afforded the corresponding ethyl-2-(3-cyano-6-(4-methoxyphenyl)-4-(4-chlorophenyl) pyridin-2yl)thioacetate**(10)**.

The structure**(10)**was further established via its reaction with hydrazinehydrate, phenylhydrazine , semicarbazide and/or thio -semicarbazide in boiling ethanol to give 2-(3-cyano-6-(4-methoxyphenyl)-4-(4-chlorophenyl) pyridin-2-yl- thio) acetohydrazide **(IIa),** 2-(3-cyano-6-(4-methoxyphenyl)-4-(4-chlorophenyl)pyridin-2-yl-thio)-N-phenylacetohydrazide **(llb),**l-(2-(3-cyano-6-(4-methoxyphenyl)-4-(4-chlorophenyl)pyridin-2-yl-thio)acetyl) semicarbazide **(11c)** and l-(2-(3-cyano-6-(4-methoxyphenyl)-4-(4-chlorophenyl) pyridin-2-yl-thio) acetyl)thiosemicarbazide**(11d).**

The reaction of **(11b)** with phenyl isothiocyanate in boiling pyridine afforded l-(2-(3- cyano-6- (4-methoxyphenyl)-4-(4-chlorophenyl)pyridin-2-yl-thio) acetyl)-4-phenylthiosemicarbazide**(12).**

As a point of interest the present investigation includes a study of the behavior of **(12)**

towards different reagents such as mercuric oxide, concentrated sulphuric acid and sodium hydroxide (8% solution)with the aim of preparing some new heterocycles of expected antimicrobial activity. Thus, interaction of **(12)** with mercuric oxide in boiling ethanol afforded the corresponding 6-(4-methoxyphenyl) 4- (4-chlorophenyl)-2-(5-phenylamino)-1,3,4-oxadiazol-2yl) methylthio) nicotinonitrile**(13)**

Similarly the interaction of **(12)** with concentrated sulphuric acid afforded the corresponding 6-(4-methoxyphenyl) -4-(4-chlorophenyl)-2-((5-(phenylamino)-l,3,4-thiadiazol-2-yl)methylthio)nicotinonitrile**(15).**

On the other hand the interaction of compound **(13)** with sodium hydroxide solution (8%) yielded the corresponding 6-(4-methoxyphenyl) -4-(4-chlorophenyl)-2-(4-phenyl-5-thioxo-4,5-dihyd ro-lH-l,2,4-triazol-3-yl) methylthio) nicotinonitrile **(15)**.

In the present investigation it was found that in the study of the behaviour of **(11d)** towards sulphuric acid(50%)on cold for long time about 24 hours afforded 2 ((5-amino-l,3,4-thiadiazol-2-yl) methylthio) - 6 - (4-methoxyphenyl) - 4 - (4-chlorophenyl) nicotinonitrile**(16).**

It was found that the alkaline hydrolysis of the mercapto derivative **(10)** using ethanolic sodium hydroxide solution afforded the corresponding 2-(3-cyano-6-(4-methoxyphenyl)-4-(4-chlorophenyl) pyridin-2-yl-thio)acetic acid**(17).** This was in agreement with the previous findings **(Soliman et al. 2007)**

Biological Evaluation:

Antimicrobial activity: The antimicrobial activity was evaluated by filter paper disc agar diffusion method **(Marruzella et al. 1958)**. For antibacterial studies Hi-media bacteriological nutrient broth **(National committee.; 1997)** and bacteriological nutrient agar were used against Gram-positive *Bacillus subtilis, Staphylococcus aureus* and Gram-negative *Salmonella typhi* and *Escherichia coli.* Antifungal studies were carried out using *Sabouraud´s dextrose* broth and dextrose agar against *Aspergillus fumigates, Aspergillus niger, Alternaria alternate* and *penicillum chrysogenum.* Dimethyl formamide was used as solvent and also for control studies. The concentration of the compounds taken was 1 mg m L^{-1}. Norfloxaxin (1 mg m L^{-1}) and clotrimazole (1 mg m L^{-1})were used as standards for bacterial and fungal studies respectively. The sensitivity of microorganisms to the compounds is identified in Table (3).

Electron-rich nitrogen heterocycles play an important role in diverse biological activities. Introducing oxadiazole, thiadiazole and triazine rings(compounds 13,14 and 15)**(Junghein et al 1987)** influence the antibacterial or pharmacokinetic properties**(Boyd. 1982 .; Jungheim et al. 1988 .; Ternamskym et al. 1990 .; Ilango et al. 2010)**

The antimicrobial activity of some newly synthesized compounds **(2a,b; 4a,b; 5a,b; 11a-d ; 13; 14; 15)** were tested and the results are shown in Table 3.

Evaluation of the new compounds **11a,11d,13 and 15** have shown the highest inhibitory activity against Gram-positive bacterium *"B, subtilis*", while compounds **5b,11a,11d,13,14,15** have shown the same highest inhibitory activity against Gram-positive bacterium "*S. aureus*". It was also noticed that compounds **5b,11b,11c** and compounds **4b,5a,11b,11c** as well demonstrated antibacterial activity less effective towards Gram-positive bacterium *"B.subtilis"* and *"S.aureus"* respectively. Compounds **2a, 4a,b ,5a** were slightly active against the same bacterium, while compound **2b** was inactive.

For the Gram-negative bacterium. *"S.typhi"* and *"E. coli"*, compounds **2a,11a-d, 13** revealed the highest inhibitort activity, while compounds **2b,4a,b,5a,b,11d,14,15** were moderately sensitive against those two organisms, and compound **11a,**demonstrated no sensitivity against *E.coli* for the fungi used, *A.fumigates, A.nigen, A. alternate* and *P. chynsogenum* compounds **2a,b,4a,b,11b** revealed no activity towards all of them while compound **15** was more effective than other tested compounds . Compounds **11a,c,13** were slightly active against the tested fungi (c.f. Table 3).

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Table 1: Physical data of synthesized compounds from (1—17).

Comp No.	M.P. °C solvent	Yield %	Colour and shap	Mol. Formula/ (Mol. Wt)	Analysis Calcd/found					
					C	H	N	S	Cl	F
Ia	198 EtOH	60	Yellow Crystals	$C_{19}H_{13}N_2OSF$ (336.38)	67.84 67.80	3.90 3.87	8.33 8.30	9.53 9.50	— —	5.65 5.60
Ib	144 EtOH	75	Orange Crystals	$C_{19}H_{13}N_2OSCl$ (352.84)	64.68 64.65	3.71 3.70	7.94 7.90	9.09 9.05	10.05 10.02	— —
2a	205 EtOH	68	White Crystals	$C_{20}H_{15}N_4OSF$ (378.42)	63.48 63.60	4.00 4.02	14.81 14.60	8.47 8.40	— —	5.02 5.10
2b	134 EtOH	65	Yellow Crystals	$C_{20}H_{15}N_4OSCl$ (394.88)	60.83 60.90	3.83 3.60	14.19 14.30	8.12 8.90	8.98 8.90	— —
3	294 Bennzene	59	Dark Brown Crystals	$C_{25}H_{17}N_4O_4SCl$ (504.94)	59.47 59.50	3.39 3.50	11.10 11.20	6.35 6.30	7.02 7.10	— —
4a	118 EtOH	55	Brown Crystals	$C_{32}H_{20}N_5O_6SCl$ (637.5)	60.23 60.50	3.13 3.30	10.98 10.70	5.01 5.10	5.56 5.50	— —
4b	180 EtOH	50	Brown Crystals	$C_{34}H_{26}N_5O_4SCl$ (636.07)	64.20 64.40	4.09 4.10	11.01 11.01	5.03 5.00	5.58 5.60	— —
4c	267 EtOH	46	Dark Brown Crystals	$C_{35}H_{27}N_4O_7SCl$ (683.13)	61.53 61.70	3.95 3.80	8.20 8.30	4.68 4.60	5.20 5.18	— —
5a	339 EtOH	70	Black Crystals	$C_{33}H_{26}N_5O_5SCl$ (640.11)	61.92 61.90	4.09 4.30	10.94 10.90	5.01 5.30	5.54 5.50	— —
5b	160 EtOH	63	Brown Crystals	$C_{32}H_{23}N_5O_4SClBr$ (688.98)	55.77 55.80	3.34 3.30	10.16 10.30	4.64 4.60	5.15 5.30	Br 11.61 11.50
6	210 EtOH	75	Red Crystals	$C_{23}H_{15}N_4O_3SCl$ (462.91)	59.68 59.90	3.27 3.30	12.10 12.01	6.93 6.70	7.66 7.70	— —
7	116 EtOH	80	Orange Crystals	$C_{25}H_{19}N_4OSCl$ (458.96)	65.42 65.30	4.17 4.20	12.21 12.30	6.99 6.80	7.72 7.60	— —
8	220 EtOH	65	Orange Crystals	$C_{24}H_{19}N_4O_2SCl$ (462.95)	62.27 62.30	4.14 4.20	12.12 12.30	6.93 6.80	7.66 7.60	— —
9	133 EtOH	65	Brown Crystals	$C_{24}H_{21}N_4O_3SCl$ (480.5)	59.93 59.90	4.37 4.40	11.65 11.70	6.65 6.70	7.38 7.40	— —
10	131 EtOH	80	Yellow Crystals	$C_{23}H_{19}N_2O_3SCl$ (438.5)	62.94 63.00	4.33 4.30	6.39 6.40	7.29 7.30	8.09 8.10	— —
11a	207 EtOH	70	White Crystals	$C_{21}H_{17}N_4O_2SCl$ (424.5)	59.36 59.40	4.02 4.00	13.19 13.20	7.53 7.50	8.36 8.2	— —
11b	118 EtOH	75	Brown Crystals	$C_{27}H_{21}N_4O_2SCl$ (500.5)	64.73 64.70	4.19 4.20	11.18 11.20	6.39 6.40	7.09 7.10	— —
11c	167 EtOH	65	Brown Crystals	$C_{22}H_{18}N_5O_3SCl$ (467.5)	56.47 56.50	3.85 3.90	14.97 15.00	6.84 6.80	7.59 7.60	— —
11d	174 EtOH	59	Brown Crystals	$C_{22}H_{18}N_5O_2S_2Cl$ (483.5)	54.60 54.58	3.72 3.70	14.47 14.50	13.23 13.20	7.34 7.30	— —
12	101 EtOH	78	Yellow Crystals	$C_{28}H_{22}N_5O_2S_2Cl$ (559.5)	60.05 60.10	3.93 3.90	12.51 12.49	11.43 11.40	6.34 6.30	— —
13	210 EtOH	40	Yellow Crystals	$C_{28}H_{20}N_5O_2SCl$ (525.5)	63.93 63.95	3.80 3.85	13.32 13.30	6.08 6.10	6.75 6.80	— —
14	207 EtOH	60	Yellowish Crystals	$C_{28}H_{20}N_5OS_2Cl$ (541.5)	62.05 62.10	3.69 3.70	12.92 12.90	11.82 11.80	6.55 6.60	— —
15	210 EtOH	50	Brown Crystals	$C_{28}H_{20}N_5OS_2Cl$ (541.5)	62.05 62.10	3.69 3.70	12.92 12.90	11.82 11.80	6.55 6.60	— —
16	98 EtOH	50	Yellow Crystals	$C_{22}H_{16}N_5OS_2Cl$ (465.5)	56.71 56.70	3.43 3.40	15.03 15.00	13.74 13.70	7.62 7.60	— —
17	250 EtOH	55	Brown Crystals	$C_{21}H_{15}N_2O_3SCl$ (410.5)	61.38 61.40	3.65 3.70	6.82 6.80	7.79 7.80	8.64 8.65	— —

Table 2: Spectral data of the synthesized compounds from (1—17)

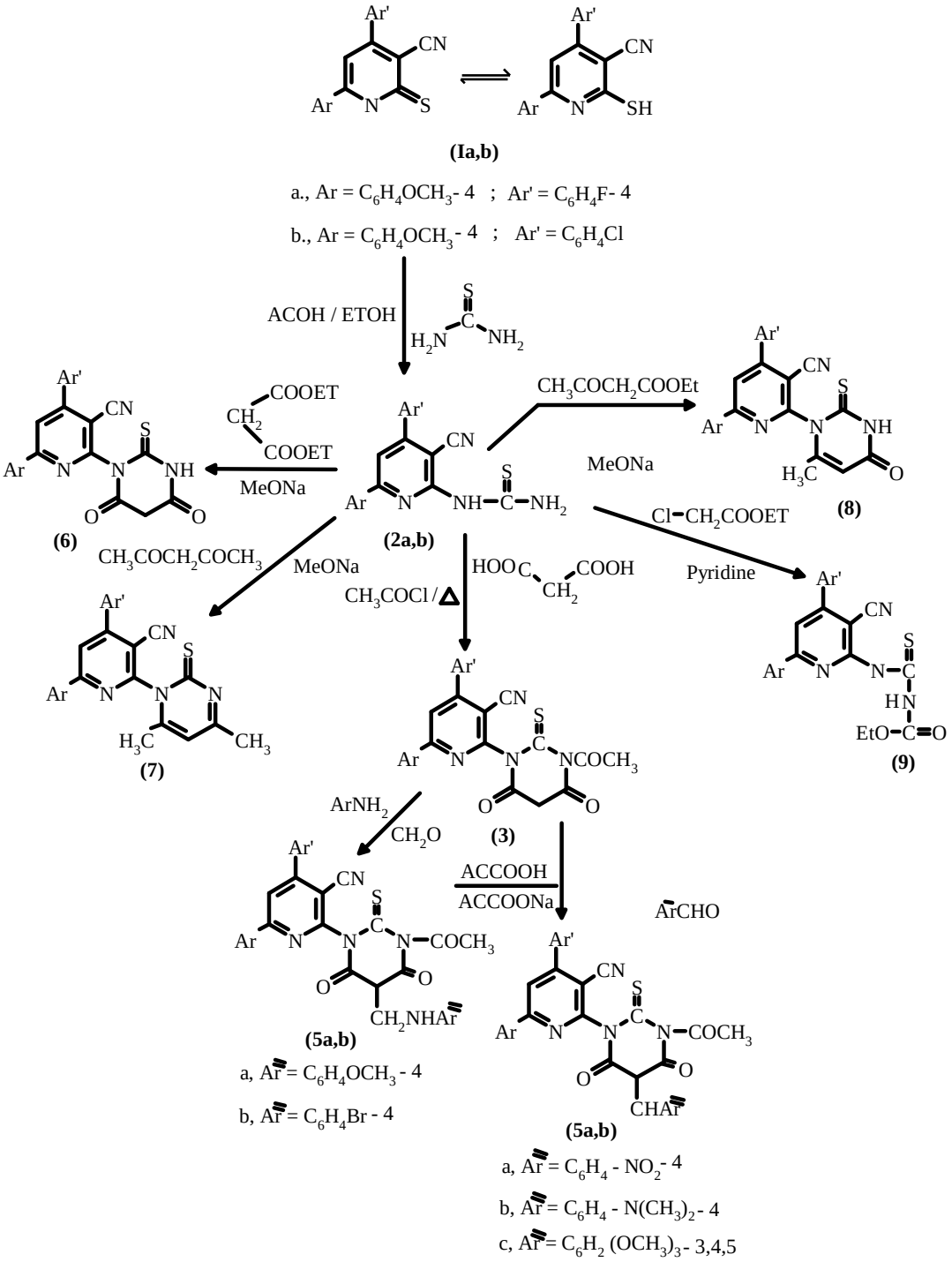
Com. No	IR (υ Cm^{-1})	^{1}H–NMR δ-ppm	Mass. Spectra m/e (%)
Ia	3382 (NH), 3071-2804(CH), 2562 (SHweak), 2217 (C≡N), 1606 (C=N), 1227 (C=S).	10 (1H, s, NH), 6.091-8.091 (9H, m, Ar–H)	336.07 (100%)
Ib	3380 (NH), 3000-2837 (CH), 2500 (SHweak), 2212 (C≡N), 1602 (C=N), 1249 (C=S).	10 (1H, s, NH), 6.070-8.10 (9H, m, Ar–H)	352.04 (100%)
2a	3350 (NH_2), 3190 (NH), 2927 (CH), 2216 (C≡N), 1606.6 (C≡N), 1232.4 (C=S).	6.03-7.41 (9H, m, Ar–H), 3.73 (3H, s,OCH_3), 10.1 (2H, s, NH_2).	378.10 (100%)
2b	3356 (NH_2), 3190 (NH), 2930 (CH), 2215 (C≡N), 1230 (C=S),1606.7(C=N)	6.02–7.60 (9H, m, Ar–H), 3.72 (3H, s,O CH_3), 10.3 (2H, s, $NH_{2)}$.	394.07 (100%)
3	2923.9, 2854.5 (CH), 2213.6 (C≡N), 1604.7 (C=N), 1704, 1698 (C=O).	6.03-7.91 (9H, m, Ar–H), 3.4 (3H, s, $COCH_3$),2.7(2H,s,CH_2)	504.07 (100%)
4a	2216 (C≡N), 1606 (C=N), 1227 (C=S), 1705, 1696 (C=O), 3070-2805 (CH).	3.40 (3H, s, $COCH_3$), 6.05-7.62 (13H, m, Ar–H), 3.42 (3H, s, OCH_3),2.1(1H,s,CH)	637.5 (100%)
4b	1706, 1695 (C=O), 2217 (C=N), 1607 (C=N), 1227 (C=S), 3072-2803 (CH).	3.4 (3H, s, $COCH_3$), 6.05-7.60 (13H, m, Ar-H), 3.44 (3H, s, OCH_3,1.9,1.92(2Xs,2X3H,2CH_3)	636.07(100%)
4c	2215 (C≡N), 1608 (C=N), 1226 (C=S), 3070-2804 (CH),1678,1716(C=O)	2.515 (1H, s, CH), 3.446 (3H, s, OCH_3), 3.452(3H,s,OCH_3),3.463(3H,s,OCH_3), 6.09-7.69 (11H, m, Ar–H), 2.4 (3H, s, $COCH_3$).	682.13 100%)
5a	3417.6 (NH), 2931.6 (CH), 1604.7 (C=N), 1249.8 (C=S),1701(C=O)	10.2 (1H, t, NH), 6.05-7.7a (13H, m, Ar–H), 3.4 (3H,s, $COCH_3$), 3.46 (3H, s, OCH_3),2.44(2H,d,CH_2)	639.13 100%)
5b	3379 (NH), 2931.6 (CH), 2214 (C≡N), 1686, 1706.9 (C=O) , 1249.8 (C=S).	10.1 (1H, t, NH), 6.03-7.72 (13H, m, Ar–H), 3.32 (3H, s, $COCH_3$), 3.4 (3H, s, OCH_3)2.46(2H,d,CH_2)	689.03 100%)
6	3425 (NH), 2924 (CH), 2214 (C≡N), 1680 (C=O), 1249.8 (C=S)	3.733 (3H, s, OCH_3), 6.082-7.904 (9H, m, Ar–H), 3.62 (2H, s, CH_2), 10.7 (1H, s, NH) .	462.04 100%)
7	2924 (υCH), 2214 (C≡N), 1581 (C=N), 1249.8 (C=S).	1.16-1.23 (2X3H, 2Xs, 2xCH_3), 3.87 (3H, s, OCH_3) and 6.07-8.26 (9H, m, Ar–H),5.6(1H,s,CH)	458.1 (10%)
8	3209 (NH), 3032 (CH), 2214 (C≡N), 1678 (C=O), 1596.9 (C=N), 1249.8 (C=S).	1.17-1.20 (3H, s, CH_3), 3.78 (3H, s, OCH_3) and 6.01-8.23 (9H, m, Ar–H),2.87(1H,s,CH)	462.09 100%)
9	3448 (NH), 2931 (CH), 2214 (C≡N), 1735.8 (C=O ester), 1590 (C=N) and 1249.8 (C=S).	6.012-7.692 (9H, m, Ar–H), 4.293 (2H, t, CH_2-CH_3),3.1(3H,q,CH_3),11.01(1H,s,NH).	480.5(100%)
10	2902.7-2933.5 (CH), 1743.5-1740 (C=O ester) 1608.5 (C=N), 1406 (C-S-C).	6.012-7.620 (9H, m, Ar-H,), 3.1(2H, s, CH_2), 3.887 (3H, s, OCH_3), 2.3(3H, t, CH_2-CH_3),3.4(2H,q,CH_2-CH_3)	438.5(100%)
11a	3321.2 (NH_2), 3155.3 (NH), 2933.5-2835.2 (CH), 2214.1 (C≡N), 1657.1 (C=O amide), 1458.1 (C-S-C).	6.0632-7.730(9H,m,Ar-H),4.092(2H,s,CH_2),3.740(3H,s,OCH_3), 9.6(1H,s,NH),10.9(2H,d ,NH_2)	424.5(100%)
11b	3230 (NH), 2923.9-2854.9 (CH), 2234.4 (C≡N), 1670.2 (C=O), 1463.9 (C–S–C).	9.7(1H,s,NH),3.643(3H,s,OCH_3),10.01(1H,q,NH) 3.643(3H,s,OCH_3),6.023-7.812(14H,m,Ar-H), 4.280(2H,s,CH_2)	500.5(100%)
11c	3423.4 (NH_2), 3261.4 (NH) 2214 (C≡N), 1685.7 (C=O), 1473.5 (C–S–C).	6.302-7.894 (9H, m, Ar–H), 5.60 (1H, d, NH), 5.79(1H, d, NH), 10.1(2H, s,NH2), 3.726 (3H, s, OCH_3), 2.817 (2H, s, S–CH_2–C).	467.5(100%)
11d	3371.3 (NH_2), 3263.3 (NH), 2214.1 (C≡N), 1658(C=O), 1451 (C–S–C),1241(C=S)	10.2(2H,s,NH_2),6.0423-7.832(9H,m,Ar-H),2.423(2H,s,CH_2),8.9 (1H,d,NH),9.8(1H,d,NH)	483.5(100%)
12	3209.7 (NH), 3031.9, 2839 (CH), 2214 C≡N), 1650 (C=O), 1596.9 (C=N), 1220.7 (C=S), 1450 (C–S–C).	8.3 (1H,d ,NH),3.702(3H,s,OCH_3),6.0 83-7.830(14H,m,Ar-H),2.530(2H,s,S-CH_2-C),9.8(1H,d,NH),10.1(1H,s,NH)	559.5(100%)
13	3286.5 (NH), 3055-2854.4 (CH), 2214 (C≡N), 1651-1596 (C=N),	6.0678-7.942 (14H, m, Ar–H), 3.850 (3H, s, OCH_3) 2.517 (2H, s, CH_2) and9.759 (1H, s, NH).	525.5(100%)

Com. No	IR (υ Cm^{-1})	^{1}H–NMR δ-ppm	Mass. Spectra m/e (%)
	1442.7 (C–S–C).		
14	3280 (NH), 2936-2839 (CH), 2214.1 (C≡N), 1581.5 (C=N), 1458 (C–S–C).	6.03-7.60 (14H, m, Ar–H, CH) 3.87 (3H, s, OCH_3), 2.517 (2H, s, CH_2) and9.759 (1H, s, NH)	
15	3332.8 (NH), 2931.6-2846.7 (CH), 2214 (C≡N), 1604.7 (C=N), 1450 (C–S–C), 1249.8 (C=S).	6.05-7.80 (14H, m, Ar–H, CH), 3.76 (3H, s, OCH_3), 2.61 (2H, s, CH_2) and9.74 (1H, s, NH).	541.5(100%)
16	3370 (NH_2) 2931-2839 (CH), 2214 (C≡N), 1604 (C=N), 1504 (C–S–C).	6.08-7.82 (9H, m, Ar–H, CH) 3.6 (3H, s, OCH_3), 2.8 (2H, s, CH_2), 9.752 (1H, s, NH_2).	465.5(100%)
17	3440.8 (OH), 939.3-2831.3 (CH), 2214 (C≡N), 1720 (C=O), 1590 (C=N), 1458 (C–S–C).	6.032-7.820(9H,m,Ar-),3.4(3H,s,OCH_3), 2.7(2H,s,CH_2),12.3(1H,s,OH)	410.5(100%)

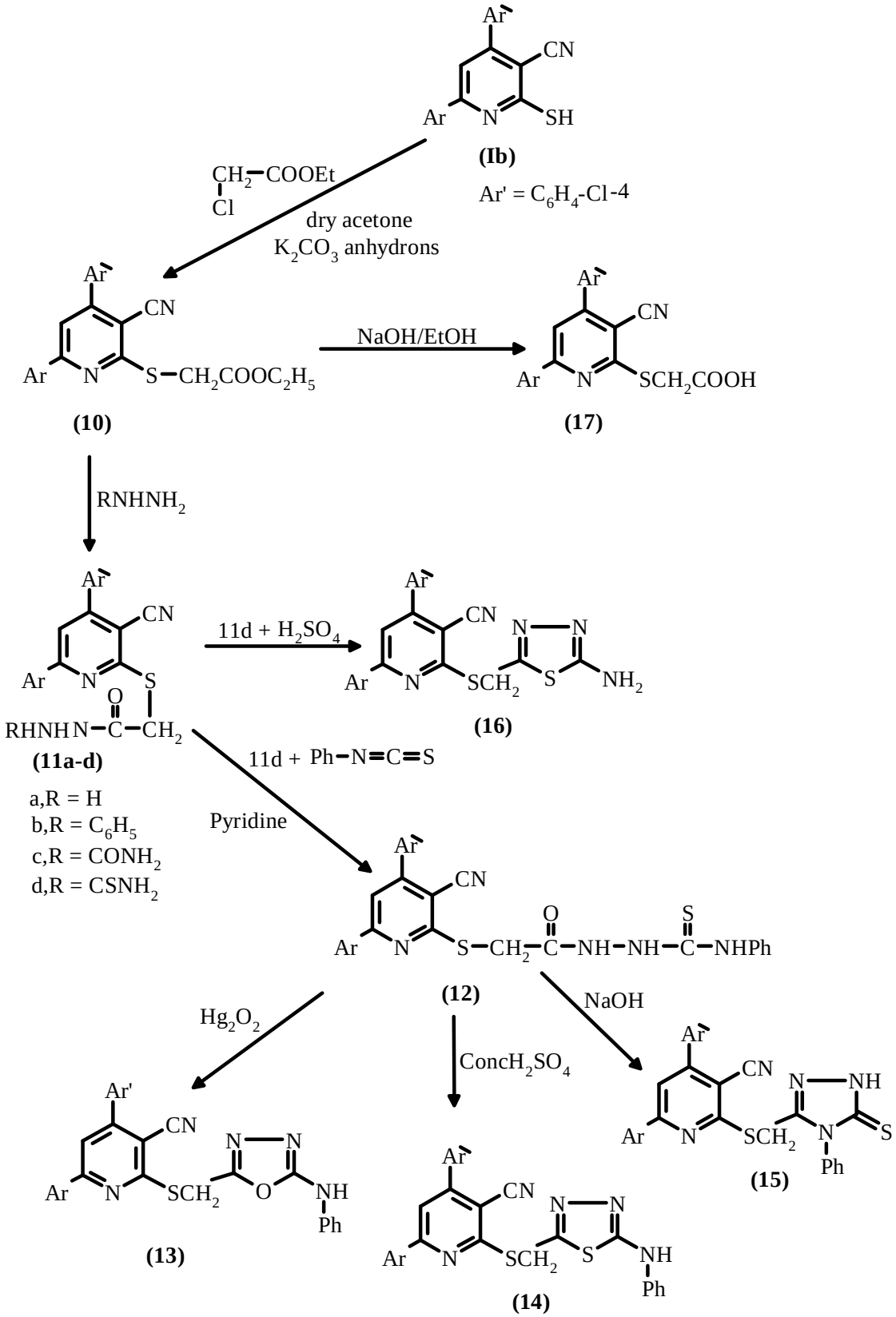
Table 3. *In vitro* antimicrobial activity of some newly synthesized heterocyclic compounds

Compd	Gram-positive		Gram-negative		Fungi			
	Bacillus subtilis	*Staphylococcus aureus*	*Salmonella typhi*	*Escherichia. coli*	*Aspergillu s fumigates*	*Aspergillus niger*	*Alternaria alternate*	*Penicillium chrysogenum*
2a	**5**	**5**	**16**	**16**	**0**	**0**	**0**	**0**
2b	**0**	**0**	**14**	**12**	**0**	**0**	**0**	**0**
4a	**5**	**5**	**10**	**10**	**0**	**0**	**0**	**0**
4b	**10**	**10**	**14**	**12**	**0**	**0**	**0**	**0**
5a	**10**	**10**	**10**	**10**	**0**	**5**	**5**	**5**
5b	**14**	**15**	**14**	**12**	**5**	**5**	**12**	**12**
11a	**18**	**15**	**18**	**0**	**0**	**12**	**12**	**12**
11b	**12**	**13**	**16**	**16**	**0**	**0**	**0**	**0**
11c	**14**	**12**	**18**	**16**	**12**	**12**	**13**	**12**
11d	**18**	**18**	**16**	**12**	**12**	**0**	**0**	**12**
13	**18**	**15**	**16**	**16**	**12**	**10**	**12**	**10**
14	**15**	**18**	**10**	**10**	**12**	**10**	**10**	**10**
15	**17**	**17**	**13**	**12**	**18**	**18**	**17**	**10**

Where : highly sensitive = 15-20; moderately sensitive = 10-15mm; slightly sensitive = 15-15mm; slightly sensitive = 5-10 and not sensitive = 0 mm


(Ia,b)
a., Ar = C6H4OCH3- 4 ; Ar' = C6H4F- 4
b., Ar = C6H4OCH3- 4 ; Ar' = C6H4Cl
ACOH / ETOH
MeONa
CH3COCH2COEt
MeONa
Cl-CH2COOET
Pyridine
CH3COCH2COCH3
MeONa
CH3COCl / Δ
HOOC-CH2-COOH
ArNH2
CH2O
ACCOOH
ACCOONa
ArCHO
(6)
(2a,b)
(8)
(7)
(3)
(9)
(5a,b)
a, Ar = C6H4OCH3 - 4
b, Ar = C6H4Br - 4
(5a,b)
a, Ar = C6H4 - NO2- 4
b, Ar = C6H4 - N(CH3)2- 4
c, Ar = C6H2 (OCH3)3- 3,4,5

(Schem 1)


Ar
CN
Ar N SH
(Ib)
Ar' = C6H4-Cl-4
CH2-COOEt
Cl
dry acetone
K2CO3 anhydrons
Ar
CN
Ar N S-CH2COOC2H5
(10)
NaOH/EtOH
Ar
CN
Ar N SCH2COOH
(17)
RNHNH2
Ar
CN
Ar N S
O
RHNH N-C-CH2
(11a-d)
a,R = H
b,R = C6H5
c,R = CONH2
d,R = CSNH2
11d + H2SO4
Ar
CN
N N
Ar N SCH2 S NH2
(16)
11d + Ph-N=C=S
Pyridine
Ar
CN
Ar N S-CH2-C-NH-NH-C-NHPh
O S
(12)
Hg2O2
ConcH2SO4
NaOH
Ar'
CN
N N
Ar N SCH2 O NH
Ph
(13)
Ar
CN
N N
Ar N SCH2 S NH
Ph
(14)
Ar
CN
N NH
Ar N SCH2 N S
Ph
(15)

(Schem 2)

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