Synthesis, Reactions and Antimicrobial activity of Some Substituted 4, 6-Diphenyl Pyridine 2-Thione Derivatives

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Abstract: Some substituted 4, 6-diaryl-3-cayno-2-thioxopyridine derivatives were synthesized from appropriate substituted 1, 3-diphenyl prop-2-en-1-one (Chalcone) reaction with cyanothioacetamide. The final compounds were structurally elucidated on the basis of IR, ^{1}H-,^{13}C-NMR and EIMS data and microanalyses as well as chemical evidence via reactions with some nucleophilic and electrophilic reactants.
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1. Introduction:

Multi-component reactions are theoretically useful organic reactions involving three or more starting materials which react to give a product [Soliman et al. 1991; Comins et al. 2001]. They are one of the most important protocols in organic synthesis and medicinal chemistry [Dong et al. 2005]. They constitute a major part in the present day namely organic synthesis with the advantage ranging from lower reaction times, increased reaction rates to higher yields and reproducibility. The diversity, efficiency and rapid access to small and highly functionalized organic molecules make this approach of central current interest in the construction of combinatorial libraries and optimization in drug discovery process [Weber et al. 2002]. Pyridones are important intermediates for the synthesis of natural products and they have been extensively investigated as valuable building blocks for many fused systems [Johns et al. 2003] with a wide range of biological and pharmacological activities. On the other hand they exhibit antiproliferative and antitubolin activities, [Magedov et al. 2008], potent antimalarial activity, [Yeats et al. 2008] and good anticonvulsant activity against acutely elicited seizures [Revas et al. 2009] as well. On the other hand, pyrido[2,3-d]primidines have manifold implications, such as antifungal and antibacterial [Singh et al. 2000; Yadav et al. 2001; Singh et al. 2002]. For this compounds have attracted the attention due to their wide range of biological activities associated with this scaffold.

The present investigation deals with the development synthetic strategy to polyfunctionalized heterocycles prompted by the chemotherapeutic importance of pyridine derivatives and in view to synthesize bioactive molecules [Soliman et al.1992; Soliman et al. 1993], it was contemplated to synthesize a series of novel pyridine derivatives possessing sulfur moiety at position 2 and study their reactivity towards some nucleophiles and their biological properties as well.

Chemistry

Various 4, 6-diaryl-2-thioxo-1, 2-dihydropyridine-3-carbonitrile has been synthesized in reasonable yields by the one-pot reaction of substituted acetophenones namely, 4-methoxyacetophenone and/or 2,4-dimethoxyacetophenone with α-arylidene-cyanothioacetamide in boiling ethanol containing excess ammonium acetate.

2. Experimental

All melting points are in degree centigrade and were determined on Gallenkamp electric melting point apparatus. The IR spectra were measure (KBr) on a Perkin – Elmer 1430 spectrometer. The ^{1}H-NMR and ^{13}C-NMR spectra (8, ppm) were recorded on JEOL-JNM1.A400 FTNMR spectrometer (Cairo University), using DMSO-d_6 as a solvent and TMS as internal standard. Mass spectra were recorded on GCMSQ 1000 EX Shimadzu Japan (Gas Chromatography-Mass spectrometer). Micro analytical data were obtained at the micro analytical center at Cairo University.

General procedure

Synthesis of 4-(substituted phenyl)-6-(substituted phenyl)-2-oxo-1, 2-dihydropyridin-2-carbonitrile.
It was prepared according to the procedure in literature [Soliman et al.1991]. Synthesis of 4-(substituted phenyl)-6-(substituted phenyl)-2- thioxo-1, 2-dihydropyridin-2-carbonitrile (**1a-g**).

It was prepared according to the procedure in literature [Waksman et al.1945]

Synthesis of 4-(substituted phenyl)-2-hydrazinyl- or/2-(2-phenyl hydrazinyl)-6-(substituted phenyl) nicotinonitrile (2a-d) and (2e).

To a solution of **1a-c, e** and **g** (0.01 mol) in 30 mL of absolute ethanol was added hydrazine hydrate (0.01 mol) or phenyl hydrazine (0.01 mol) and the reaction was refluxed for 6h (or till the evaluation of H_2S was stopped); the solids separated after concentration and cooling were collected, washed with petroleum ether and recrystallised from the proper solvents as (**2a-e)** (c.f. Table 1).

Synthesis of 7-(substituted phenyl) -5- (substituted phenyl) -3-methyl- and 3-phenyl[1, 2, 4]triazolo[4, 3-a]pyridine-8-carbonitrile (3a, b).

To a solution of **1b** (0.01 ml) in 30 mL of n-butanol acetyl hydrazine (0.01 mol) (prepared from the reaction of 0.01 mol of hydrazine hydrate and 0.01 mol of acetic anhydride) /or benzoyl hydrazine (0.01 mol) (prepared from the reaction of 0.01 mol of hydrazine hydrate and 0.01 mol of benzoyl chloride) was added and the reaction mixtures were refluxed for 12h. The product separated after concentration was collected, washed well with dilute ethanol and recrystallised from the proper solvents as (**3a, b)** (c.f. Table 1).

Synthesis of 5-(4-chlorophenyl) -7- (4-methoxyphenyl)-3-methylpyrido [2, 3-c] pyridazine-4(1H) imine (4).

To a solution of **1b** (0.01 mol) in 30 mL of n-butanol phenyl acetyl hydrazine (prepared from the reaction of hydrazine hydrate (0.01 mol) and phenyl acetic anhydride (0.01 mol) was added and the mixture was refluxed for 12h. After concentration and cooling the produced precipitate was filtered off washed well with dilute ethanol and recrystallized from the proper solvent to give (**4)** (c.f. Table 1).

Reaction of the hydrazine derivatives with carbonyl compounds Synthesis of 4-(substituted phenyl)-6-(substituted phenyl)-2-(N-arylidene) hydrazonyl-3-nicotinonitrile (5a-d).

A mixture of **2a, c, d** (0.01 mol) and carbonyl compounds namely, benzaldehyde, o-nitrobenzaldehyde, and acetone (0.01 mol) in 30 mL of absolute ethanol containing sodium ethoxide was well stirred for 6h, and left to cool overnight. Then it was diluted with water and the product was filtered off and recrystallised from the proper solvents as (**5a-d)** (c.f.Table 1).

Synthesis of 2-(substitutedaryl) imino-4-(substituted phenyl)-6-(substituted phenyl)-1, 2-dihydropyridine-3-carbonitrile (6a-h).

A mixture of **1a-e** and **g** (0.01 mol) and primary amines namely, benzylamine, 2-aminothiazole, 4-bromoaniline, and 2-amino-3-hydroxypridine (0.01 mol) in 30 mL of dry xylene was refluxed for 18-24h. After concentration (reduced pressure) the products that separated were collected, washed with ether then recrystallised from the proper solvent to give (**6a-h)** (c.f. Table 1).

Synthesis of 2-chloro-4-(4-chlorophenyl)-6-(4-methoxyphenyl)-3-nicotinonitrile (7)

A mixture of **1b** (0.01 mol) and thionylchloride (0.04 mol) was well stirred in an ice-bath for 3h, then heated on a steam-bath for 2h. After cooling, it was diluted with cold water and the organic layer was extracted with ether. The product obtained after evaporation of the etherial layer was recrystallised from the proper solvent as **(7)** (c.f. Table 1).

Synthesis of 2-benzyl amino - 4-(4-chlorophenyl)-6-(4-methoxyphenyl) nicotinonitrile (8)

A mixture of compound **(7)** (0.01 mol) and benzyl amine (0.0l mol) in 30 ml of absolute ethanol was refluxed for 6h. After concentration and cooling, the solid product was recrystallised from the proper solvent to give **(8)** (c.f. Table 1).

Synthesis of 2-methoxy- 4-(4-chlorophenyl)-6-(4-methoxyphenyl) nicotinonitrile (9)

A solution of **7** (0.01 mol) dissolved in 30 mL of methanol containing (0.01 mol) of sodium methoxide was refluxed for 6h. After concentration and cooling the reaction mixture was diluted with water/and the separated product was collected and recrystallised from the proper solvent as **(9)** (c.f. Table 1).

Synthesis of 4-(4-fluorophenyl)-6-(4-methoxyphenyl)-2-thioxo pyridine-1-yl-propanenitrile (10)

A mixture of compound **1a** (3.39, 0.10 mol) and acyrylonitrile (6 mL, 0.06 mol) in 30 mL of dry pyridine was refluxed for 6h. After cooling it was poured into water – HCl (150 mL 2:1 by volume), the product was collected washed well and recystallised from ethyl acetate as **(10)** (c.f. Table 1).

Synthesis of 8-(4-fluorophenyl)-6-(4-methyoxyphenyl)-2-oxo2,3,4,9a-tetrahydropyrido[2,1-b] [1,3-]thiazine-9-carboxamide (11).

In glacial acetic acid - hydrochloric acid mixture (30 + 10 mL) compound **10** (4.1g, 0.01 mol) was refluxed for 4h. After concentration (reduced pressure), the solid separated was collected, washed well with dilute ethanol and recrystallised from acetic acid as **(11)** (c.f. Table 1).

3. Results and Discussion

One mole of 4-methoxyacetophenone or 2,4-dimethoxy acetophenone and one mole of each of 4-flurobenzylidene-, 4-chlorobenzylidene, 3,4,5-trimethoxybenzylidene, 4-methoxybenzylidne and/or 4-hydroxybenzylidene-cyanothioacetamide with 4 moles of ammonium acetate in absolute, ethanol under reflux

gave the corresponding 4,6-diaryl-2-thioxo-1,2-dihydropyridine-3- carbonitrile (**1a-g**). Compounds **1** possess active sites, viz-CN, NH, C=S groups which play a great role in the synthesis of heterocyclic derivatives most of which are interesting from both the chemical and biological point of view. Compounds (**1a-g**) were prepared authentically from the condensation of the corresponding 1,3-diaryl-2-propen-1-ones with ethylcyanoacetate in boiling ethanol containing excess ammonium acetate followed by reaction of the product with P_2S_5 in boiling xylene (Soliman et al.1991) (scheme 1). The structures of the compounds (**1a-g**) were supported by elemental analysis, IR, ^{1}H-NMR and EIMS spectral studies. The infrared spectra of 1 showed characteristic absorption bands in the region 3382-3319 cm^{-1} for stretching frequencies of NH group and stretching bands in the region 1237-1253cm^{-1} for the stretching frequencies of $>C=S$. ^{1}H–NMR spectrum of **1a** (DMSO-d_6) clearly showed a singlet for the methine proton δ 6.6 ppm and the multiplet of the aromatic protons **(8)** at δ 6.72-7.28ppm. The mass spectrum of **1d** showed molecular ion peak at m/z 378 (21.7%). On the basis of the IR data of compounds **(1a-g)** (Table 2), it may formulated as 2-thioxo-1, 2-dihydropyridine -3-carbonitrile [**A**]/or 2-mercapto nicotinonitrile [**B**]. Compounds (**1a, c, d, g**) reacted with hydrazines namely, hydrazaine hydrate, phenyl hydrazine in boiling ethanol, and with acetyl /or benzoyl hydrazine in boiling butanol and gave the corresponding 4,6-diaryl-2-hydrazinyl-/or-phenylhydrazinyl nicotinonitrile (**2a-d**), (**2e**), triazolo[4,3-a]pyridine-8-carbonitrile derivatives **(3a,b),** respectively,. 4, 6-diaryl-2-thioxo-1,2-dihydropyridine -3-carbonitrile **(1b)** underwent cyclocondensation by refluxing with phenylacetic hydrazide in butanol for long time afforded 5-(4-chlorophenyl)-7-(4-methoxyphenyl)-3-methylpyrido[2,3-c]pyridazine-4(1H)imine- **(4)**. The IR spectra of **3a, b** showed absorption, bands for C≡N, C=N as well as the other expected bands corresponding to that structure. The IR spectrum of compound **4** revealed the absence of the cyano group beside the presence of the NH group and the (C=N) absorption as well as other expected absorption bands (Table 2).

Treatment of the hydrazinyl derivatives **2a-c** with carbonyl compounds namely, benzaldehyde, 2-nitrobenzaldehyde and/or acetone in the presence of sodium ethoxide yielded the corresponding N-arylidene hydrazinyl derivatives **(5a-d)** respectively. The ^{1}H-NMR spectrum of **5d** agreed well with the proposed structure. The mass spectrum of **5d** showed the molecular ion peaks at m/z 421 (30.2%), 422 (11.1%) for (M^++1). The reaction of 2-thioxo-1, 2-dihydropyridine-3-carbonitrile (**1a-d and g**) with primary amines namely, benzyl amine, 2-aminothiazole, 4-romoaniline and/or 2-amino-3-hydroxy pyridine in boiling xylene yielded the corresponding 2-substituted imino-4, 6-diaryl-1, 2-dihydropyridine-3-carbonitrile derivatives (**6a-h).** The IR spectra of compounds 6 revealed the absence of the thioxo/or the mercapto bands besides the presence of the nitrile and NH as well as the other expected absorption bands. The reaction of **1b** with thionylchloride affected desulphurization with the formation of the corresponding 2-chloronicotinonitrile derivative **(7)**. The IR spectrum of compound **7** displayed nitrile absorption band besides the absence of absorption representing NH, C=S and SH which indicates the involvement of the NH, C=S groups in **1b** in the formation of the 2-chloro derivatives. The ^{1}H-,^{13}C-NMR spectra supported the structure. Compound **7** reacted with benzylamine in boiling ethanol and gave the corresponding 2-(benzyl amino)-4, 6-diarylnicotinonitrile (**8).** The IR spectrum of **8** displayed absorption band in the amino region at 3336cm^{-1}. Furthermore, the reaction of (**7)** with methanolic sodium methoxide yielded the corresponding 2-methoxy-4, 6-diaryl nicotinonitrile **(9)**. The structure of **9** was supported by the IR, ^{1}H- and ^{13}C-NMR spectral data (Table 2).

Cyanoethylation of compound (**1a)** with an equimolecular amount of acrylonitrile in boiling dry pyridine gave 4-(4-flurophenyl)-6-(4-methoxyphenyl)-3-carbonitrile-2-thioxopyridin-1-yl propionitrile **(10).** The IR spectrum of **10** revealed the presence of the 3-nitrile, 2-thioxo at 2224 and 1241cm^{-1} respectively, with the absence of stretching absorption of NH (Table 2). The reaction of the N-ethyl cyanopyridinyl-3-carbonitrile derivatives **(10)** with glacial acetic acid-hydrochloric acid mixture (3:1) affected cyclization to the corresponding 8-(4-fluorophenyl)-6-(4-methoxyphenyl)-2-oxo-2,3,4,9a-tetrahydropyrido[2,1-b][1,3-]thiazine-9-carboxamide **(11)**. The IR spectrum of **11** showed the presence of two C=O groups and the absence of the stretching absorption of the nitrile groups. Also the ^{1}H and ^{13}C- NMR spectrum agreed well with the proposed structure (Table 2).

Table. 1: Physical data of the cyanopyridine derivatives (1-11):

Compd. No.	Empirical formula (Mol. Wt)	M. P. °c. Solvent of crystallization	Colour of crystals yield %	Analysis calcd/found % X						
				C	H	N	S	F	Cl	Br
1a	$C_{19}H_{13}N_2OSF$	198	Yellow	67.85	3.86	8.33	9.52	5.65	—	—
	(336)	EtOH	68	67.9	3.9	8.3	9.5	5.7	—	—
1b	$C_{19}H_{13}N_2OSCl$	144	Orange	64.68	3.68	7.94	9.07	—	10.07	—
	(352.5)	P.E.	78	64.7	3.7	7.9	9.1	—	10.1	—
1c	$C_{22}H_{20}N_2O_4S$	148	Yellow	64.705	4.901	6.86	7.84	—	—	—
	(408)	EtOH	85	67.7	4.9	6.9	7.8	—	—	—
1d	$C_{21}H_{18}N_2O_3S$	218	Yellow	66.66	4.76	7.407	8.46	—	—	—
	(378)	AcOH	70	66.7	4.8	7.4	8.5	—	—	—
1e	$C_{20}H_{16}N_2O_3S$	258	Orange	65.93	4.39	7.69	8.79	—	—	—
	(364)	AcOH	75	65.9	4.4	7.7	8.8	—	—	—
1f	$C_{23}H_{22}N_2O_5S$	217	Yellow	63.01	5.02	6.39	7.305	—	—	—
	(438)	AcOH	83	63.1	5.1	6.4	7.3	—	—	—
1g	$C_{20}H_{15}N_2O_2SCl$	237	Orange	62.74	3.92	7.32	8.36	—	9.28	—
	(382.5)	AcOH	79	62.7	3.9	7.3	8.4	—	9.3	—
2a	$C_{19}H_{15}N_4O.F$	237	Orange	68.25	4.52	16.76	—	5.68	—	—
	(334)	EtOH	50	68.2	4.5	16.7	—	5.7	—	—
2b	$C_{22}H_{22}N_4O_4$	155	Yellow	65.01	5.46	13.18	—	—	—	—
	(406)	P.E.		65.1	5.5	13.8	—	—	—	—
2c	$C_{20}H_{18}N_4O_3$	192	Orange	66.29	5.01	15.46	—	—	—	—
	(362)	EtOH	72	66.2	5.0	15.5	—	—	—	—
2d	$C_{20}H_{17}N_4O_2Cl$	160	Orange	63.08	4.50	14.71	—	—	9.31	—
		P.E.	60	64.2	4.6	14.7	—	—	9.3	—
2e	$C_{25}H_{19}N_4OCl$	178	Red break	70.34	4.49	13.12	—	—	8.30	—
		ETOH	62	70.4	4.5	13.2	—	—	8.4	—
3a	$C_{21}H_{15}N_4OCl$	87	Pale Yellow	67.28	4.00	14.95	—	—	9.47	—
	(374.5)	P.E.	65	67.3	4.1	15.0	—	—	9.5	—
3b	$C_{26}H_{17}N_4OCl$	165	Brown	71.48	3.92	12.82	—	—	8.11	—
	(436.5)	P.E.	75	71.4	4.0	12.8	—	—	8.0	—
4	$C_{21}H_{17}N_4OCl$	207	Brown	66.93	4.55	14.87	—	—	9.41	—
	(376.5)	EtOH	75	67.1	4.6	15.1	—	—	9.4	—
5a	$C_{26}H_{19}N_4OF$	252	Light Orange	73.92	4.53	13.26	—	4.50	—	—
	(422)	EtOH	70	74.2	4.6	13.2	—	4.6	—	—
5b	$C_{27}H_{22}N_4O_3$	244	Brown	71.99	4.92	12.44	—	—	—	—
	(450)	EtOH	71	72.02	4.9	12.4	—	—	—	—
5c	$C_{27}H_{20}N_5O_4Cl$	236	Pale Brown	63.10	3.92	13.63	—	—	6.90	—
	(513.5)	EtOH	65	63.2	4.1	13.6	—	—	7.1	—
5d	$C_{23}H_{21}N_4O_2Cl$	187	Dark Orange	65.63	5.03	13.31	—	—	8.42	—
	(420.5)	EtOH	85	65.7	5.1	13.3	—	—	8.5	—
6a	$C_{26}H_{20}N_3OF$	104	Yellow	76.27	4.92	10.26	—	—	4.64	—
	(409)	P.E.	85	76.2	4.9	10.2	—	—	4.7	—
6b	$C_{22}H_{15}N_4OSF$	170	Orange	65.66	3.76	13.92	7.97	4.72	—	—
	(402)	EtOH	77	65.7	3.8	13.9	8.1	4.7	—	—
6c	$C_{25}H_{17}N_3OClBr$	107	Pale Yellow	61.18	3.49	8.56	—	—	7.22	16.28
	(490.5)	P.E.	84	61.2	3.5	8.6	—	—	7.2	16.3
6d	$C_{24}H_{17}N_4O_2Cl$	179	Pale Yellow	67.21	4.00	13.06	—	—	8.27	—
	(428.5)	EtOH	75	67.2	4.1	13.0	—	—	8.3	—
6e	$C_{27}H_{22}N_3O_2Cl$	192	Light Orange	71.13	4.86	9.22	—	—	7.78	—
	(455.5)	EtOH	82	71.1	4.9	9.2	—	—	7.8	—
6f	$C_{28}H_{25}N_3O_3$	116	Yellowish Brown	74.48	5.58	9.31	—	—	—	—
	(451)	P.E.	75	74.5	5.6	9.3	—	—	—	—
6g	$C_{23}H_{19}N_5O_3S$	153	Brown	60.01	4.30	15.72	7.20	—	—	—
	(445)	P.E.	79	60.2	4.4	15.7	7.3	—	—	—
6h	$C_29H_{27}N_3O_4$	144	Orange	72.33	5.65	8.73	—	—	—	—
	(481)	EtOH	81	72.4	5.7	8.8	—	—	—	—
7	$C_{19}H_{12}N_2OCl_2$	244	Brown	64.24	3.41	7.89	—	—	19.96	
	(354)	EtOH	88	64.3	3.4	7.9	—	—	20.0	
8	$C_{26}H_{20}N_3OCl$	149	Dark Yellow	73.32	4.73	9.87	—	—	8.32	—
	(425.5)	P.E.	58	73.3	4.8	9.9	—	—	8.3	—
9	$C_{20}H_{15}N_2O_2Cl$	132	Yellow	68.48	4.31	7.99	—	—	10.11	—
	(350.5)	P.E.	65	68.5	4.3	8.0	—	—	10.1	—
10	$C_{22}H_{16}N_3OSF$	234	Beige	67.86	4.1	10.79	8.22	4.88	—	—
	(389)	EtcOH	68	67.9	4.1	10.8	8.2	4.9	—	—
11	$C_{22}H_{19}N_2O_3SF$	257	Yellowish Brown	64.38	4.67	6.82	7.81	4.63	—	—
	(410)	EtcOH	62	64.4	4.7	6.8	7.8	4.6	—	—

Where EtOH = absolute ethanol; P. E. = Petroleum ether (b.p. 80-110°); and AcOH = Acetic acid.

Table. 2: Spectnal data of the prepared compounds:

Compd. No.	IR, KBr, υCm^{-1}	^{1}H-NMR, DMSO-d$_6$, δ-ppm	^{13}C–NMR	EIMS m/z (%)
1a	3382 (υ NH), 3071. 2824 (υ CH), 2652. (υ SH), 2220 (C≡N), 1606 (υ C=N), 1237 (υ C=S).	3.41 (s, 3H, Ar–OCH_3), 4.65 (s, 1H, cyclic NH), 6.6 (s, 1H, methine proton), 6.72-7.28 (m, 8H, Ar–H).	56.1 (CH_3), 103.1 (CH), 106.1 (C–CN), 114.9 (2CH), 115.9 (2CH), 116.1 (C≡N) 127.4 (C), 127.9 (2CH), 128.0 (2CH), 128.9 (C), 159.9 (C–O), 162.3 (C–F) 162.9 (CS), 168.1 (C), 169.8 (C).	
1b	3380 (υ NH), 3005-2837 (υ CH), 2650 (υ SH), 2219 (υ C≡N), 1602 (υ C=N), 1249 (υ C=S)	3.01 (s, 1H, SH), 3.47 (s, 3H, Ar–OCH_3), 6.68 (s, 1H, methine proton), 6.91-7.97 (m, 8H, Ar-H).		
1c	3380.7 (υ NH), 3020–2837 (υ CH), 2651 (υ SH), 2218 (υ C≡N), 1601 (υ C=N), 1245 (υ C=S)	3.01 (s, 1H, SH), 3.49, 3.50, 3.52 (3xs, 3x3H, 3xAr–OCH_3), 6.47 (s, 1H, methine proton), 6.86-7.97 (m, 6H, Ar-H).	56.1 (CH_3), 99.79 (C–CN), 114.9 (CH), 117.11 (C≡N) 119.9 (CH), 128.7 (C), 128.9 (2CH), 129.7 (2CH), 134.9 (C), 162.7 (C) 156.6 (C), 159.7 (2C), 184.9 (CS).	
1d	3381 (υ NH), 3010–2950 (υ CH), 2640 (υ SH), 2218 (υ C≡N), 1609 (υ C=N), 1253 (υ C=S)			M 378 (21.7), M+1  379 (19.1), 360 (39.4), 317 (11.4), 316 (2.1), 271 (7.9), 243 (16.3), 137 (4.4), 107 (1.7), 97 for C_4H_3NS (100).
1e	3340 (υ NH), 3060–2818 (υ CH), 2627 (υ SH), 2221 (υ C≡N), 1619 (υ C=N), 1242(υ C=S)	3.31, 3.33 (2xS, 2x3H, 2xAr–OCH_3), 4.95 (S, 1H, methine proton), 6.91-7.93 (m, 7H, Ar-H), 10.06 (s, 1H, OH).		
1f	3319 (υ NH), 3006–2835 (υ CH), 2623 (υ SH), 2218 (υ C≡N), 1606 (υ C=N), 1244 (υ C=S)			
1g	3320 (υ NH), 3010–2837 (υ C–H), 2612 (υ SH), 2212 (υ C≡N), 1602 (υ C=N), 1241 (υ C=S)	3.01 (S, 1H, SH), 3.31, 3.33 (2xS, 2x3H, 2xAr–OCH_3), 6.49 (s, 1H methine proton), 6.79-7.79 (m, 7H, Ar-H).		
2a	3350, 3291 (NH_2NH), 2221 (C≡N), 1605 (C=N)	3.37 (s, 3H, Ar–OCH_3), 4.95 (d, 2H, NH_2), 5.17 (1, 1H, NH), 6.09 (s, 1H, methine proton), 6.86-7.88 (m, 8H, Ar–H).	55.4 (CH_3), 83.7 (C–CN), 114.8 (2CH), 116.3 (2CH), 116.6 (CH), 117.1 (C≡N), 128.6 (2C H), 129.1 (2CH), 133.8 (C), 156.6 (C–C), 156.8 (C–N), 159.9 (N=C–N), 161.1 (C–O), 163.4 (C–F).	
2b	3320, 3130 (NH_2, NH), 2217 (C≡N), 1602 (C=N).	3.37, 3.38, 3.58 (3xs, 3x3H, 3xAr–OCH_3), 3.61 (s, 3H, Ar–OCH_3) 4.99 (d, 2H, NH_2) 5.09 (t, 1H, NH), 6.09 (s, 1H, methine proton), 6.95-7.88 (m, 6H, Ar–H).	56.3 (CH_3), 81.9 (C–CN), 114.8 (2CH), 116.1 (2CH), 116.7 (CH), 117 (c), 128.9 (2C), 129.3 (CH), 129.9 (2CH), 133.9 (C), 156.7 (C) 156.9 (c), 159.1 (C), 161.3 (C).	
2c	3402, 3320, 3150 (OH, NH_2, NH), 2225 (C≡N), 1601 (C=N).			

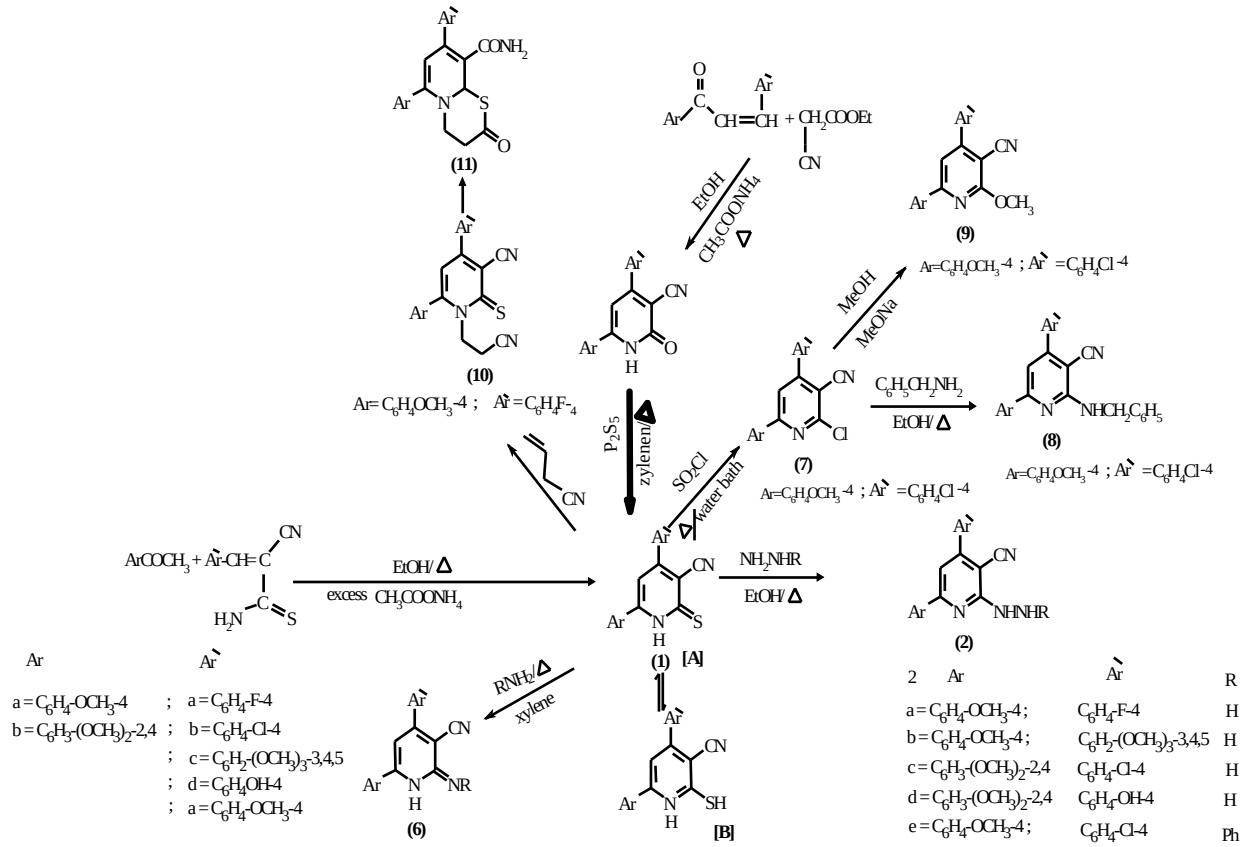
2d	3350, 3210 (NH_2, NH), 2225 (C≡N), 1599 (C=N).			
2e	3320.3105 (NH_2NH), 2218 (C≡N), 1601 (C=N).	3.34 (s,3H, $ArOCH_3$), 4.66 (d, 1H, NH), 5.01 (d, 1H, NH), 6.45 (s, 1H, methine proton), 6.66-7.89 (m, 13H, Ar–H).	54.3 (CH_3), 84.1 (C–CN), 113.1 (2CH), 114.9 (2CH), 116.3 (CH), 117.7 (C≡N), 119.7 (CH), 128.9 (2CH), 129.1 (2CH), 129.4 (2CH), 130.1 (2CH), 130.3 (C–C–N), 137.3 (C), 138.3 (C–NH), 161.1 (O–C).	
3a	3007,2929,2828 (CH) 2214 (C≡N), 1605 (C=N).	1.93 (s, 3H, CH_3), 3.41 (s, 3H, Ar–OCH_3), 6.74 (s, 1H, methine proton), 6.89-7.88 (m, 8H, Ar–H).	20.6 (CH_3), 54.9 (CH_3), 102.3(C-CN),114.9(2CH),119.9(C≡N),129.9(2CH),130.9(2CH), 134.9(2CH),136.6(C-Cl),138.9(C),144.5(C-N),149.9(C=N),155.3(C),161.1(C-O),163.7(C).	
3b	3050,2988,2828 (CH), 2221 (C≡N), 1606 (C=N).	3.47 (s, 3H, Ar–OCH_3), 6.86 (s, 1H, methine proton), 6.99-7.82 (m, 13H, Ar–H).		
4	3212. 3175 (NH), 3007, 2918, 2828 (CH), 1599 (C=N).	1.1 (s, 3H, CH_3), 3.43 (s, 3H, Ar–OCH_3), 5.82 (s, 1H, cyclic NH), 6.69 (s, 1H, methine proton), 6.99-7.88 (m, 8H, Ar–H), 10.18 (s, 1H, NH exchangeable).	19.9 (CH_3), 56.1 (CH_3), 105.1 (C), 112.9 (CH), 116.9 (2CH), 129.1 (2CH), 129.4 (3CH), 131.1 (2CH) 134.8 (C), 136.8 (C), 153.9 (C), 156.9 (C), 159.3 (C), 162.9 (C), 165.1 (C).	
5a	3350 (NH), 3009, 2928, 2818 (CH), 2225 (C≡N), 1610 (C=N)	3.41 (s, 3H, Ar–OCH_3), 4.65 (s, 1H, NH), 6.12 (s, 1H methane proton), 6.79-7.95 (m, 13H, Ar–H), 8.1 (s, 1H, N=CH).		
5b	3422,3363 (OH, NH), 3050, 2918,2888 (CH), 2221 (C≡N), 1606 (C=N).	3.47,3.48 (2xs, 2x3 H, 2x$ArOCH_3$), 4.68 (s, 1H, NH), 6.43 (s, 1H, methine proton), 6.78-7.89 (m, 12H, Ar–H), 8.09 (s, 1H, N=CH), 10.15 (s, 1H, OH).	55.6 (CH_3), 56.9 (CH_3), 86.7 (C–CN), 101.7 (CH), 109.3 (CH), 112.2 (CH), 116.5 (C), 117.2 (2C), 118.1 (C), 128.8 (2CH), 129.1 (2CH), 129.4 (2CH), 129.9 (CH), 131.4 (C), 131.9 (CH), 134.1 (CH), 144.1 (CH), 159.1 (C–O), 159.9 (C–OH), 160.1 (C–O), 161.4 (C), 166.7 (C–NH).	
5c	3356 (NH), 3052, 2990, 2818 (C0H), 2223 (C≡N), 1614 (C=N).			
5d	3293 (NH), 3002, 2928, 2819 (CH), 2214 (C≡N),1599(C=N), 1257 (HN–N=C).	1.24, 1.25 (2xS, 2x3H, 2x$ArOCH_3$), 5.09 (S, 1H, NH), 6.37 (S, 1H, methine proton), 6.81-7.76 (m, 7H, ArH).		M $^{+}$ 421 (30.2), M+2 $^{+4}$ (11.1), 395 (100), 406 (61), 385 (11.6), 370 (36.1), 349 (8.3), 320 (159), 137 (3.8), 112 (1.4), 101 (4.8) 75 (6.1), 71 (5.3), 63 (7.2).

Compd. No	IR υ Cm^{-1}	1H-NMR δ ppm	13c NMR δ ppm	Ms m/z (%)
6a	3235 (NH), 2988, 2828 (CH), 2214 (C≡N), 1605 (C=N).	2.81 (S, 2H, CH_2Ph), 3.45 (S, 3H, Ar–OCH_3), 5.49 (S, 1H, cyclic NH, D_2O exchangeable, 6.54 (S, 1H, methine proton), 6.89-7.79 (m, 13H, Ar–H).	50.1 (CH_2), 56.1 (CH_3), 99.6 (C–CN), 105.1 (CH), 115.8 (2CH), 116.7 (2CH), 119.1 (CN), 128.3 (C), 129.2 (2CH) 129.9 (3CH), 130.1 (C), 130.3 (CH), 130.6 (2CH), 137.1 (C), 137.3 (C), 156.4 (C), 160.1 (C–O), 163.1 (C–F).	
6b	3328 (NH), 3030, 2919, 2828 (CH), 2221 (C≡N), 1617 (C=N).	3.41 (S, 3H, Ar–OCH_3), 5.50 (S, 1H, cyclic NH, D_2O exchangeable), 6.51 (S, 1H, methine proton), 6.92-8.91 (m, 10H, Ar–H).	56.2 (CH_3), 103.3 (CH), 115.3 (2CH), 116.9 (2CH), 117.1 (C), 118.9 (C–CN), 126.1 (C), 126.9 (C), 127.9 (2CH) 128.4 (2CH), 128.5 (C), 128.9 (2CH), 130.1 (2CH), 139.4 (C), 160.1 (C–O), 162.3 (C), 163.3 (C), 169.9 (C).	
6c	3330 (NH), 3010, 2918, 2828 (CH), 2217 (C≡N), 1619 (C=N).	3.45 (S, 3H, Ar–OCH_3), 5.61 (S, 1H, cyclic NH, D_2O exchangeable), 6.60	56.9 (CH_3), 103.7 (CH), 115.3 (2CH), 116.3 (2CH), 118.1 (CN), 119.4 (C–CN), 121.7 (C), 122.1 ©, 127.1 (C), 127.9 (2CH), 128.1 (2CH), 128.4 (C),	

		(S, 1H, methine proton), 6.72-7.91 (m, 12H, Ar–H).	131.1 (2CH), 136 (2CH), 143.7 (C), 154.9 (CH), 159.9 (C–O), 162.4 (C=C), 162.9 (C–CL), 164.7 (C=N), 169.8 (C–NH), 170.1 (C).	
6d	34, 22 (OH), 3299 br (NH), 3010, 2988 2828 (CH), 2223 (C≡N), 1623 (C=N).	3.34 (S, 3H, Ar–OCH_3), 5.21 (S, 1H, cyclic NH, S_2O exchangeable), 6.81 (S, 1H, methine proton), 6.91-7.84 (m, 11H, Ar–H), 8.95 (S, 1H, OH).		
6e	3328 (NH), 3010, 2988, 2828 (CH), 2221 (C≡N), 1608 (C=N).		56.4 (CH_3), 103.1 (CH), 115.1 (2CH0, 115.9 (CH), 118.6 (C–CN), 121.9 (C), 124.9 (2CH), 127.1 (C), 128.1 (2CH), 128.9 (2CH), 129.3 (2CH), 133.9 (C–N), 134.1 (2CH), 135.1 (C), 160.1 (C–O), 161.7 (C), 164.3 (C=N), 169.3 (C–NH).	
6f	3317 (NH), 3010, 2928, 2828 (CH), 2217 (C≡N), 1605 (C=N).			
6g	3325 (NH), 3005, 2988, 2818 (CH), 2224 (C≡N), 1609 (C=N).	3.14, 3.29, 3.34 (3xS, 3x3H, 3xOCH_3), 5.23 (S, 1H, cyclic NH, D_2O exchangeable), 6.72 (S, 1H, methine proton), 6.92-8.19 (m, 9H, Ar–H).	56.6 (CH_3), 103.4 (CH), 115.3 (2CH), 115.9 (CN), 118.6 (C–CN), 123.9 (CH), 124.9 (CH), 126.9 (C), 127.9 (2CH), 128.3 (2CH), 129.1 (2CH), 131.1 (C), 134.1 (C), 142.3 (CH), 149.1 (C), 160.3 (C–O), 161.4 (C), 165.3 (C), 171.1 (C–NH).	
6h	3235 (NH), 3003, 2918, 2828 (CH), 2221 (C≡N), 1605 (C=N).			
7	3030, 2928, 2818 (CH), 2224 (C≡N), 1623 (C=N).	3.31 (S, 3H, Ar–OCH_3), 6.80 (S, 1H, methine [roton), 6.99-8.19 (m, 8H, Ar–H).	59.3 (CH_3), 104.1 (CH), 116.1 (2 CH), 116.4 (CN), 119.3 (C–CN), 119.9 (2CH), 120.3 (C), 121.3 (C), 123.9 (C), 124.7 (2CH), 151.3 (C), 154.9 (C), 161.9 (C–O), 163.3 (C), 169.8 (C–N).	
8	3236 (NH), 2960, 2935, 2837 (CH), 2214 (C≡N), 1605 (C=N).		51.2 (CH_2–Ph), 56.3 (CH_3), 90.1 (C–CN), 109.1 (CH), 115.1 (2CH), 118.3 (CN), 129.1 (2CH), 129.9 (2CH), 131.3 (2CH), 136.4 (C), 139.4 (C–CL), 156.9 (C), 161.2 (C–N), 162.3 (C–O), 165.9 (C–NH).	
9	3030, 2988, 2818 (CH), 2221 (C≡N), 1621 (C=N).	3.34, 3.47 (2xS, 2xCH_3, 2OCH_3), 6.19 (S, 1H, methine proton), 6.86-7.89 (m, 8H, Ar–H).	56.1 (CH_3), 59.3 (CH_3), 106.1 (C–CN), 114.9 (2CH), 118.3 (C), 121.9 (C), 129.1 (3CH), 129.9 (2CH), 131.1 (2CH), 135 (C), 137.1 (C–Cl), 153.2) (C–O), 158.3 (C), 160.1 (C), 162.1 (C–N).	
10	3005, 2918, 2828 (CH), 2224 (C≡N), 1241 (C=S).			
11	3433 (NH_2), 1676, 1645 (C=O amide, C=O thiazine, 1559 (C=C).	2.55, 2.58 (T, 2HCH_2–CO), 2.85, 2.94 (T, 2H,N–CH_2), 3.48 (S, 3H, OCH_3), 4.75 (S, 1H, N–CH–S), 6.74 (S, 1H, methine proton), 6.92–7.82 (m, 8H, Ar–H), 10.01 (S, 2H, NH_2, D_2O exchanpeable.	46.5 (N–CH_2), 47.9 (CH_2–O), 56.3 (CH_3), 58.8 (N–CH–S), 99.7 (CH), 114.9 (CH), 116.6 (2CH), 125.9 (C), 127.9 (C), 129.1 (2CH), 131.1 (2CH), 132.2 (C), 139.1 (C), 146.9 (C), 160.3 (C–O), 164.1 (C–F), 171.1 ($CONH_2$), 193.4 (S–$COCH_2$).	

Table 3. Antimicrobial activity of some synthesized compounds (2-11)

Compd. No.	*E.coli*	*P.species*	*B.Subtilis*	*S.aureus*	*C.Albicans*
2a	-	-	-	++++	-
2b	++	-	-	-	-
2d	+++	+	-	-	-
2e	+++	++	-	-	-
3b	-	-	-	++++	-
4	+++	+	-	++++	-
5a	-	-	-	+++	++
5d	-	-	++	-	++
6a	+++	+	-	++++	-
6b	+++	++	+	+++++	-
6d	++	+	+	+++	-
6g	+++	+	+	+++++	++
8	++	+	-	++++	-
10	-	-	++	++++	+
11	-	-	++	++++	-



Ar

a = C_6H_4-OCH_3-4 ; b = C_6H_3-$(OCH_3)_2$-2,4

Ar`

a = C_6H_4-F-4 ; b = C_6H_4-Cl-4 ; c = C_6H_2-$(OCH_3)_3$-3,4,5 ; d = C_6H_4OH-4 ; a = C_6H_4-OCH_3-4

2

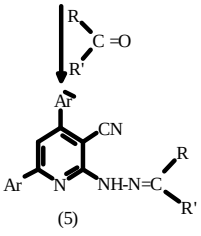
Ar	Ar`	R
a = C_6H_4-OCH_3-4 ;	C_6H_4-F-4	H
b = C_6H_4-OCH_3-4 ;	C_6H_2-$(OCH_3)_3$-3,4,5	H
c = C_6H_3-$(OCH_3)_2$-2,4	C_6H_4-Cl-4	H
d = C_6H_3-$(OCH_3)_2$-2,4	C_6H_4-OH-4	H
e = C_6H_4-OCH_3-4 ;	C_6H_4-Cl-4	Ph

6

Ar	Ar`	R
a = C_6H_4-OCH_3-4 ;	C_6H_4-F-4	$CH_2C_6H_5$
b = C_6H_4-OCH_3-4 ;	C_6H_4-F-4	
c = C_6H_4-OCH_3-4 ;	C_6H_4-Cl-4	C_6H_4-Br-4
d = C_6H_4-OCH_3-4 ;	C_6H_4-Cl-4	
e = C_6H_3-$(OCH_3)_2$-2,4	C_6H_4-Cl-4	CH_2-C_6H_5
f = C_6H_3-$(OCH_3)_2$-2,4	$C_6H_4OCH_3$-4	CH_2-C_6H_5
g = C_6H_3-$(OCH_3)_2$-2,4	$C_6H_4OCH_3$-4	
h = C_6H_4-(OCH_3)-4	C_6H_2-$(OCH_3)_3$-3,4,5	CH_2-C_6H_5

1

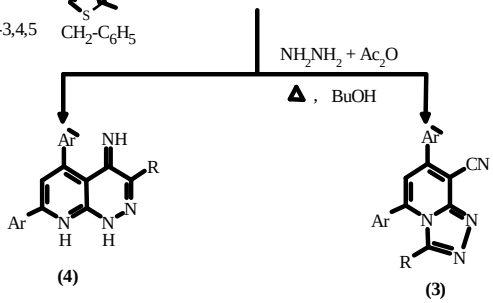
Ar	Ar`
a = C_6H_4-OCH_3-4 ;	C_6H_4-F-4
b = C_6H_4-OCH_3-4 ;	C_6H_4-Cl-4
c = C_6H_4-OCH_3-4 ;	C_6H_2-$(OCH_3)_3$-3,4,5
d = C_6H_3-$(OCH_3)_2$-2,4;	C_6H_4-OCH_3-4
e = C_6H_3-$(OCH_3)_2$-3,4 ;	C_6H_4-OH-4
f = C_6H_3-$(OCH_3)_2$-2,4 ;	C_6H_2-$(OCH_3)_3$-2,4,5
g = C_6H_3-$(OCH_3)_2$-2,4 ;	C_6H_4-Cl-4



(5)

5

Ar	Ar`	R	R'
a = C_6H_4-OCH_3-4 ;	C_6H_4-F-4	H	C_6H_5
b = C_6H_3-$(OCH_3)_2$-2,4 ;	C_6H_4-OH-4	H	C_6H_5
e = C_6H_3-$(OCH_3)_2$-3,4 ;	C_6H_4-Cl-4	H	$C_6H_4NO_2$-2
d = C_6H_3-$(OCH_3)_2$-2,4 ;	C_6H_4-Cl-4	CH_3	CH_3



4

Ar	Ar`	R
a = C_6H_4-OCH_3-4 ;	C_6H_4-Cl-4 ;	CH_2Ph

3

Ar	Ar`	R
a = C_6H_4-OCH_3-4 ;	C_6H_4-Cl-4	CH_3
b = C_6H_4-OCH_3-4 ;	C_6H_4-Cl-4	C_6H_5

Conclusion

A series of 2-thioxo -4, 6-diaryl-1, 2-dihydropyridine-3-carbonitrile, 4, 6-diaryl-2-hydrazinylnicotinonitrile, 2-(substituted aryl) imino-4, 6-diaryl-1, 2-dihydropyridine-3-carbonitrile, fused triazine, fused pyridazine and fused thiazine derivatives containing = NH,  functional groups. The antibacterial and antifungal activity data of the prepared compounds showed that compounds **2a,b,d,e** and the fused triazine (**3b**), the fused pyridazine **(4)**, compounds **(5a,5d m 6a, 6b,6g, 8, 10)** and the fused thiazine (**11**) showed very good antimicrobial activity. It is also clear that the introduction of a strong electron withdrawing atom (Cl, F) at the aromatic moiety at position 4 of the pyridine nucleus **(2a, 2d, 2e, 3b , 4, 5a, 5d, 6a, 6b, 6d, 8, 10 and 11),** Seemed to enhance their activity towards the tested organisms. Also, the presence of N-N-C-R at position 2 of the pyridine nucleus as in **5a, 5d, 6g** made the derivatives more active towards the tested fungi, further incorporation of N and moieties in the nucleus as in **6b, 6g and 11** increased lipophilicity as well as biological activity.

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