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Synthesis of Substituted Pyrimidine Derivatives and Evaluation of their Antimicrobial Activity

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ABSTRACT

Keto group of cyano pyridine moiety have been treated with various aromatic aldehydes to give corresponding chalcones. The Chalcones have been reacted with urea and thiourea to get corresponding novel oxopyrimidines and thiopyrimidines, the structure of all newly synthesized compounds were confirmed by spectral analysis. The synthesized compounds were evaluated for their antimicrobial activity. All the synthesized pyrimidine compounds have show good to moderate antimicrobial activity.

Keywords: 2-chloro 3-cyanopyridine, pyrimidine, microwave, chalcones, antimicrobial acitivity.

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INTRODUCTION

Many naturally occurring and synthetic compounds contain cyanopyridine as a basic moiety, which posses interesting pharmacological properties, Cyanopyridine and its derivative are well known for their versatile biological activities like antimicrobial [1], antitubercular [2], antifungal [3], antiviral [4] etc. Oxopyrimidines & Thiopyrimidines and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activities. Pyrimidine derivatives which occurs in natural products like nucleic acid, vitamin-B and having remarkable pharmaceutical importance because of their broad spectrum of biological activities, It is revealed from the literature survey that pyrimidine derivatives have been found to possessing biological activities like Anti HIV [5, 6] Antimicrobial [7] Antitumor [8] Antimalarial [9]. Looking to this multifold property exhibited by cyanopyridine and pyrimidine, we are reporting here the synthesis and antimicrobial activity of some cyanopyridine derivative. In the present study, this strategy is used for the synthesis of these compounds in the hope that they may possess potent biological activities.

Chemistry:

The reaction of 2-chloro 3-cyno pyridine with p-amino acetophenone gives corresponding 2-(4-Acetylphenylamino) pyridine-3-carbonitrile (1). Further treated with different aromatic aldehydes to give corresponding chalcones then on treating it with Urea and Thiourea give oxopyrimidine and thiopyrimidine respectively.

Biology:

Antimicrobial activity:

The antimicrobial activity was assayed by cup-plate agar diffusion method [10], by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activity against verity of bacterial stains such as gram-positive bacteria and gram-negative bacteria. The antimicrobial activity is listed in table.

Experimental Section:

All the melting points were determined in open capillary tube and are uncorrected, The purity of the compounds were checked by TLC, Microwave irradiation was carried out in the domestic microwave oven by LG.

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Antibacterial Data of Compounds 3(a-f) & 4(a-f):

S No	Compounds	Antibacterial Activity			
		B.subtilis	*S.aureus*	*P.aeruginosa*	*E.coli*
1	3a	8	10	9	5
2	3b	18	13	9	16
3	3c	**19**	14	18	14
4	3d	16	12	**19**	15
5	3e	12	9	16	12
6	3f	**20**	16	12	17
7	3g	11	9	13	6
8	3h	14	10	9	13
9	4a	9	10	11	8
10	4b	13	15	11	10
11	4c	**18**	16	12	16
12	4d	16	14	12	**19**
13	4e	9	10	13	10
14	4f	**19**	14	16	12
15	4g	**20**	17	16	**19**
16	4h	16	12	18	10
Std Drug	Sparfloxacin	25	24	25	22
	Benzyl Penicillin	17	18	16	16

Method:

2-(4-Acetylphenylamino)pyridine-3-carbonitrile (1)

Take 0.01 mole of 2-chloro-3-cyano pyridine and 0.01 mole of p-amino acetophenone taken in RBF with 25 ml ethanol and 3-4 drops of Con HCl, The mixture was refluxed for 12-14 hours or irradiated for 15 minutes, neutralized and poured it into cold water with stirring, separated precipitates were dried and re-crystallized by ethanol. Yield 80%, m.p. 163°C. ($C_{14}H_{13}N_3O$; required: C 70.87%, H 4.46%, N 17.71%, found: C 70.63%, H 4.31%, N 17.65%).

2- (4- (3-PHENYLACRYLOYL) PHENYLAMINO) PYRIDINE-3-CARBONITRILE (2).

A Solution of Benzaldehyde (0.01 M) in minimum quantity of DMF (5 ml) was added to the mixture of 2-(4-acetylphenylamino)pyridine-3-carbonitrile in 15ml DMF and 40% KOH was added to make mixture alkaline, the reaction mixture was then stirred for 24 hours at room temperature (Irradiated for 10 minutes). The product was isolated by adding mixture in cold water and crystallized it from DMF. Yield 77%, m.p. 254°C. ($C_{21}H_{15}N_3O$; required: C 77.52%, H 4.65%, N 12.91%; found: C 77.39%, H 4.53%, N 12.86%).

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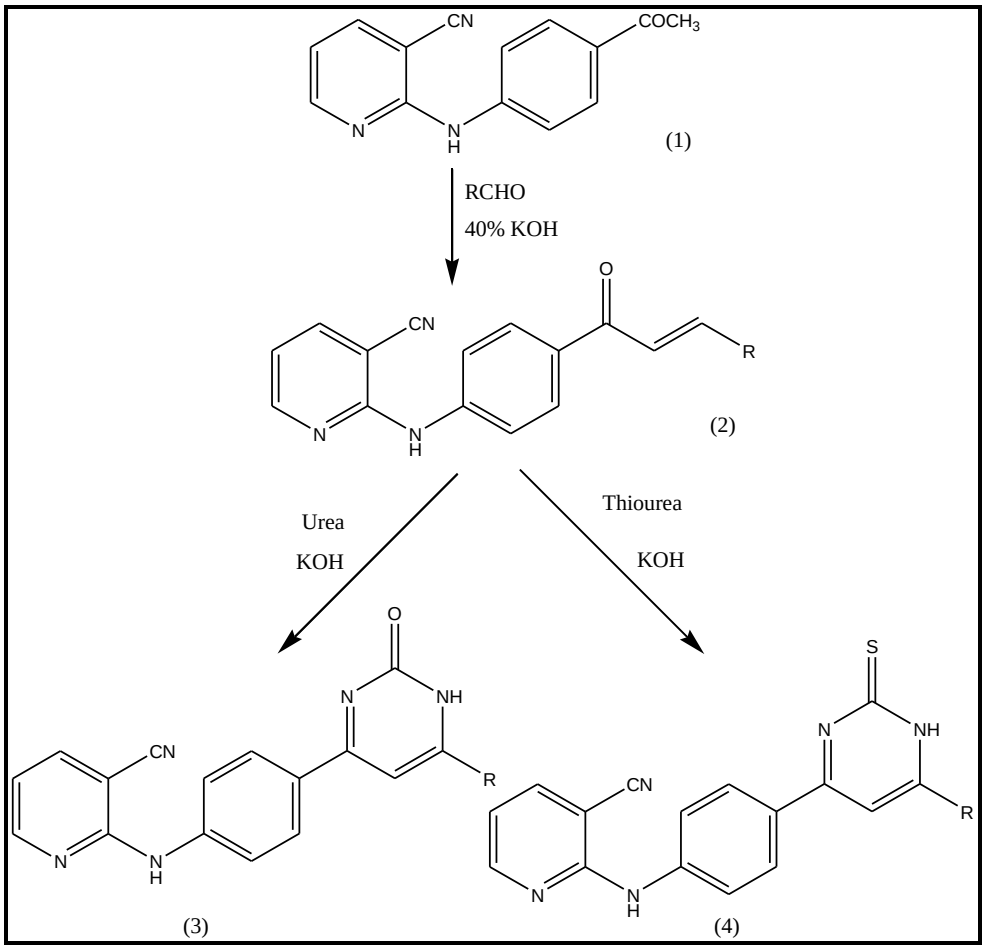
2-(4-(1,2-dihydro-2-oxo-6-phenylpyrimidin-4-yl)phenylamino)pyridine-3-carbonitrile (3).

A mixture of 2-(4-(3-phenylacryloyl)phenylamino)pyridine-3-carbonitrile (0.01 mol) and urea (0.01 mol) in ethanol (20 ml) was refluxed on water bath in presence of alcoholic KOH for 12 hrs (irradiated for 8 min). The residue was neutralized with 10% HCl, the separated solid was filtered out and crystallized from methanol. Yield 71 %, m.p. 219^{0}C.

Similarly, other 2-(4-(1,2-dihydro-2-oxo-6-Arylpyrimidin-4-yl)phenylamino)pyridine-3-carbonitrile were prepared. The physical data are recorded in Table.

Reaction Scheme



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Physical and Analytical Data of Compounds 3(a-f) & 4(a-f):

Sr No	R	Mol Formula	M.P	Yield %		Reaction Time		N %
				Conv	M.W	Conv(hrs)	M.W(min)	
(3a)	C_6H_5-	$C_{22}H_{15}N_5O$(365)	219-221	71	85	9.3	5.4	19.13
(3b)	4-NMe_2-C_6H_4-	$C_{24}H_{20}N_6O$(408)	154-156	68	76	9	5.3	20.52
(3c)	4-OCH_3-C_6H_4-	$C_{23}H_{17}N_5O_2$(395)	143-145	68	82	8.4	4.5	17.67
(3d)	4-Cl-C_6H_4-	$C_{22}H_{14}ClN_5O$(399)	274-276	70	81	8.3	5	17.48
(3e)	4-OH-C_6H_4-	$C_{22}H_{15}N_5O_2$(381)	293-295	69	81	8.3	4	18.29
(3f)	3-NO_2-C_6H_4-	$C_{22}H_{14}N_6O_3$(410)	294-296	66	78	8	4.5	20.43
(3g)	2-OH-C_6H_4-	$C_{22}H_{15}N_5O_2$(381)	281-283	66	79	8.5	5	18.36
(3h)	2-Cl- C_6H_4-	$C_{22}H_{14}ClN_5O$(399)	245-247	66	78	9.3	5.5	17.48
(4a)	C_6H_5-	$C_{22}H_{15}N_5S$(381)	268-270	70	82	8.3	5.2	18.30
(4b)	4-NMe_2-C_6H_4-	$C_{24}H_{20}N_6S$(424)	251-252	73	85	8	4.3	19.76
(4c)	4-OCH_3-C_6H_4-	$C_{23}H_{17}N_6OS$(411)	262-264	70	82	8.5	5.2	17.00
(4d)	4-Cl-C_6H_4-	$C_{22}H_{14}ClN_5S$(415)	222-224	71	83	8.2	5	16.80
(4e)	4-OH-C_6H_4-	$C_{22}H_{15}N_5OS$(397)	262-264	70	82	8.5	5.2	17.57
(4f)	3-NO_2-C_6H_4-	$C_{22}H_{14}N_6O_2S$(426)	248-250	68	79	9	4.5	19.67
(4g)	2-OH-C_6H_4-	$C_{22}H_{15}N_5OS$(397)	248-250	68	79	9	4.5	17.58
(4h)	2-Cl- C_6H_4-	$C_{22}H_{14}ClN_5S$(416)	284-286	65	77	9	5.5	16.79

2-(4-(1,2-dihydro-6-phenyl-2-thioxopyrimidin-4-yl)phenylamino)pyridine-3-carbonitrile(4).

A mixture of 2-(4-(3-phenylacryloyl)phenylamino)pyridine-3-carbonitrile (0.01 mol) and Thiourea (0.01 mol) in ethanol (20 ml) was refluxed on waterbath in presence of alcoholic KOH for 10 hrs (irradiated for 8 min). The residue was neutralized with 10% HCl, the separated solid was filtered out and crystallized from ethanol. Yield 70 %, m.p. 268^{O}C.

Similarly, other 2-(4-(1,2-dihydro-6-phenyl-2-thioxopyrimidin-4-yl)phenylamino)pyridine-3-carbonitrile were prepared. The physical data are recorded in Table.

CONCLUSION

All the transformation were carried out using conventional and microwave irradiation method which lead to considerable time saving, better yields and environmentally profitable procedure. The less solvent condition diminishes the problem of waste disposal and is eco friendly. Some of synthesized compounds have shown significant antimicrobial activity. It is there for important to anticipate that appropriate molecular manipulation of these compounds, may result in the compounds with potent antimicrobial action. However, certain structural

alterations did not increase antimicrobial activity and working ahead in that direction may give quite promising results.

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