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Synthesis of Some Novel Five and Six Membered Hetrocyclic Derivative From 6-Chloro Nicotinamide

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ABSTRACT

A series of new Pyrazolines, Oxazine & Thiazine bearing 6-Chloronicotinamide moiety have been synthesized by the condensation of 6-Chloro-{4-[(2E)-3-(Aryl) prop-2-enoyl] phenyl} pyridine-3-carboxamide with Hydrazine Hydrate, Phenyl Hydrazine, Methyl acetate, urea and thiourea a using appropriate catalyst and solvent respectively. The structure of the newly synthesized compounds were confirmed by analytical and IR, 1H NMR, MASS spectral data.

Keywords : IR, 1H NMR, MASS Spectra, Nicotinamide derivatives, Urea, Chalcone, Thiourea.

I. INTRODUCTION

5-membered heterocyclic compound i.e. Pyrazoline with two adjacent nitrogen at 1-2 positions and three carbon atoms are well known and have been synthesized using various methods. The three partially reduced forms of the pyrazole are 1-Pyrazoline, 2-pyrazoline and 3-pyrazoline, all are having different positions of the double bonds. Pyrazoline derivatives are having one endocyclic double bond.

Sucinate dehydrogenase inhibitors have been developed for nearly 50 years since Carboxin was launched commercially in 1966; They are the first commercial fungicides that contain amide groups[1]. At present, 18 fungicides belonging to a novel fungicide class have been commercialized by the Fungicidal Resistance Action Committee [2,3]. The mode of action of these fungicides is based on disruption of the mitochondrial tricarboxylic acid cycle and respiratory chain [4,5]. Nicotinamide derivatives [6] have attracted great attention since the first pyridine carboxamide boscalid was commercialized by the BASF Company because of their broad fungicidal spectrum.

Wu et al.[7] reported a series of nicotinamide derivatives containing a 1,3,4-oxadiazole group. Compound A shows good fungicidal activities against Fusarium oxysporum at 50 mg/L. Li et al.[8] described compound B, which exhibits excellent fungicidal activities against Rhizoctonia solani and Botrytis cinerea in vitro. Du et al.[9] studied compound C which shows 75% inhibition against R. solani at 50 mg/L in vitro. Ye et al.[10] demonstrated that compound D has good inhibitory effects against six fungi.

II. MATERIAL AND METHOD

Chalcone derivatives occupy a unique place in the field of medicinal chemistry due to wide range of biological activities, exhibited by them. Prompted by these facts, the preparation of chalcones of type (I) have been under taken by condensation of N-(4-

acetylphenyl)-6-chloropyridine-3-carboxamide with various aromatic ketones.

Synthesis of 6-Chloropyridine-3-Carbonyl Chloride
6-chloropyridine-3-carboxylic acid (1.56gm, 0.01 mole) added in 20ml thionyl chloride in presence of DMF (0.5ml) as a catalyst and then reaction mixture was refluxed for 4hr. at 98°C and then thionyl chloride was distilled off and reaction mixture was poured in to ice and separated product was collected and crystallized from DMF Yield-84%, m.p. 50-52°C.

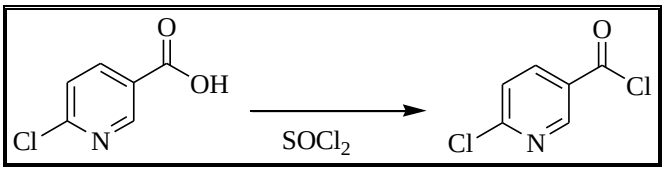

Figure-1 Synthesis of 6-Chloropyridine-3-Carbonyl Chloride

Synthesis of N-(4-Acetylphenyl)-6- Chloropyridine-3-Carboxamide
A solution of 6-chloropyridine-3-carbonyl chloride (1.76gm, 0.01mole) in 20ml toluene was added to p-amino aceto phenone (1.35gm, 0.01mole) with pyridine (0.05ml) as a catalyst. The mixture was refluxed for 3hr. at 110°C. The toluene was distilled off and mixture was poured into ice and the product was crystallized from DMF Yield 78%, m.p.80-82°C.

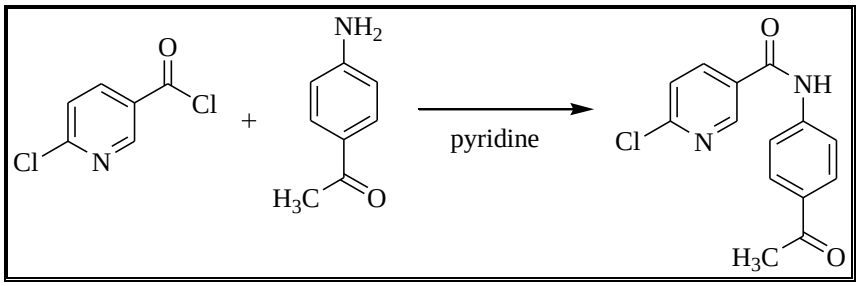

Figure-2 Synthesis of N-(4-Acetylphenyl)-6- Chloropyridine-3-Carboxamide

Synthesis of 6-Chloro-N-{(2e)-3-(4-Methoxyphenyl) Prop-2-Enoyl] Phenyl} Pyridine-3- Carboxamide
A solution of N-(4-acetylphenyl)-6-chloropyridine-3-carboxamide (2.74gm, 0.01mole) in ethanol (10ml) was added to a 4-methoxybenzaldehyde(1.36gm, 0.01mole) in ethanol. To this, 40% NaOH (1ml) as a catalyst was added to make it alkaline. The reaction mixture was then stirred for 24 hr. at room temperature. The separated product was isolated and crystallized from DMF Yield-74%, m.p.-40'C.

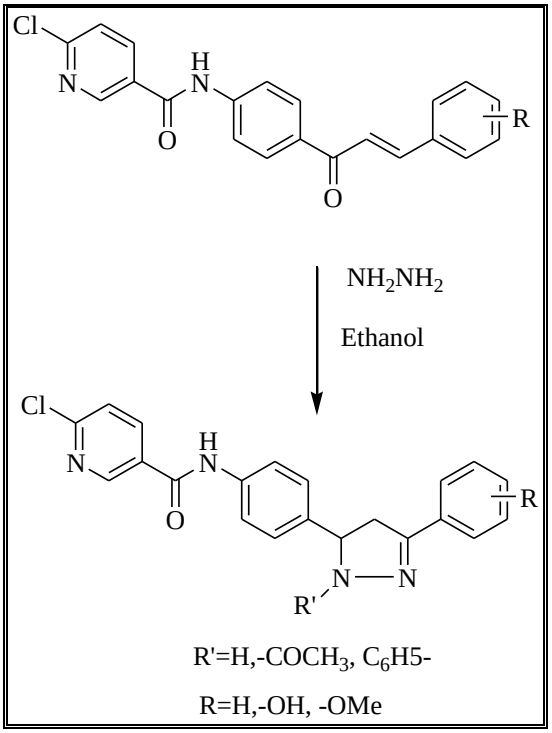

Figure-3 Synthesis of 6-Chloro-N-{(2e)-3-(4-Methoxyphenyl) Prop-2-Enoyl] Phenyl} Pyridine-3- Carboxamide Synthesis of N-[4-(2-Amino-4-(4-Chlorophenyl)-6h-1, 3-Oxazin-6-Yl) Phenyl] - 6-Chloro Pyridine-3-Carboxamide

A mixture of 6-chloro-N-{4-[(2E)-3-phenylprop-2-enoyl] phenyl} pyridine-3-carboxamide (4.20gm, 0.01mole) and urea (0.01mole) were dissolved in ethanolic sodium hydroxide (10ml) was stirred about 2-3 hr. with a magnetic stirrer. This was then poured into 400ml 0f cold water with continuous stirring for an hour and then kept in refrigerator for 24 hr. The precipitate obtained was filtered, washed and crystallized from DMF.Yield-63%, m.p.-196°C.

Synthesis of N-[4-(2-Amino-4-(4-Chlorophenyl)-6h-1, 3-Thiazin-6-Yl) Phenyl] - 6-Chloro Pyridine-3-Carboxamide

Amixture of 6-chloro-N-{4-[(2E)-3-phenylprop-2-enoyl] phenyl} pyridine-3-carboxamide (4.20gm, 0.01mole) and thiourea(0.01mole))(part-1, section-1) were dissolved in ethanolic sodium hydroxide (10ml) was stirred about 2-3 hr. with a magnetic stirrer. This was then poured into 400ml 0f cold water with continuous stirring for an hour and then kept in refrigerator for 24 hr. The precipitate obtained was filtered, washed and crystallised from DMF. Yield-73%, m.p.-156°C.

Remaining derivatives of Chalcone, Oxazine and Thiazine have been prepared by using above General Procedures.

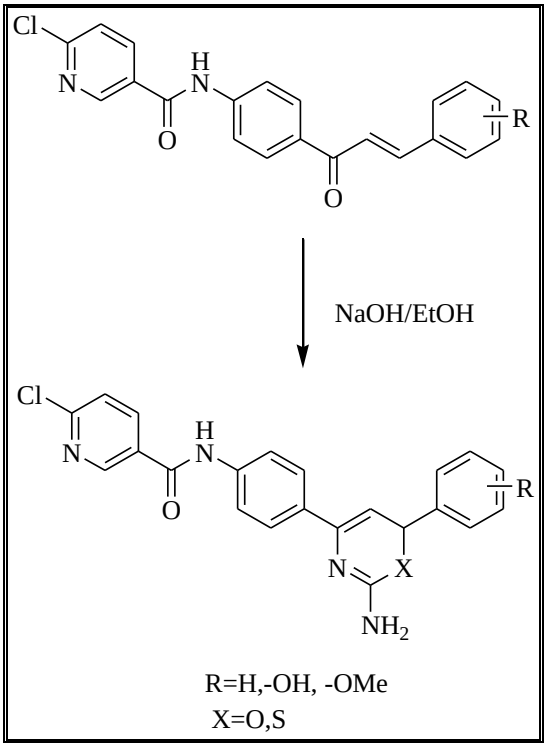

Figure-4 Synthesis of N-[4-(2-Amino-4-(4-Chlorophenyl)-6h-1, 3-Thiazin/Oxazine-6-Yl) Phenyl] - 6-Chloro Pyridine-3-Carboxamide

III. RESULT & DISCUSSION

Molecular weight & Formula, Melting Point & CHN ratio of synthesized molecule

Table-1 Molecular weight & CHN ratio of synthesized molecule

SR.NO	COMP.	R	R'	M.F. & Mol. Wt.	M. P. °C	Yield %	% Calc. / Found		
							C	H	N
1	1a	-H	_	$C_{21}H_{15}ClN_2O_2$ 362.81	82	65	65.52 65.50	4.17 4.21	7.72 7.70
2	1b	-OH	_	$C_{21}H_{15}ClN_2O_3$ 378.80	38	62	66.58 66.60	3.99 3.97	7.40 7.42
3	1c	-OMe	_	$C_{22}H_{17}ClN_2O_3$ 392.83	40	74	67.26 67.24	4.36 4.40	7.13 7.10
4	1d	-Cl	_	$C_{21}H_{14}Cl_2N_2O_2$ 397.25	39	78	63.49 63.50	3.25 3.22	7.05 7.06
5	2a	-H	-H	$C_{21}H_{17}ClN_4O$ 376.83	112	48	66.93 66.88	4.55 4.58	14.8 14.6
6	2b	-OH	-H	$C_{21}H_{17}ClN_4O_2$ 392.83	125	59	64.21 64.17	4.36 4.33	14.2 14.3
7	2c	-OMe	-H	$C_{22}H_{19}ClN_4O_2$ 406.86	100	67	64.94 64.90	4.71 4.66	13.7 13.6

8	2d	-Cl	-H	$C_{21}H_{16}Cl_2N_4O$ 411.28	117	72	61.33 61.30	3.92 3.88	13.6 13.5
9	3a	-H	-C6H5	$C_{27}H_{21}ClN_4O$ 452.93	128	42	71.60 71.54	4.67 4.63	12.3 12.3
10	3b	-OH	-C6H5	$C_{27}H_{21}ClN_4O_2$ 468.93	208	63	69.15 69.12	4.51 4.48	11.9 11.8
11	3c	-OMe	-C6H5	$C_{28}H_{23}ClN_4O_2$ 482.96	122	66	69.53 69.50	4.80 4.74	11.6 11.7
12	3d	-Cl	-C6H5	$C_{27}H_{20}Cl_2N_4O$ 487.37	190	78	66.54 66.50	4.14 4.13	11.5 11.4
13	4a	-H	-COCH3	$C_{23}H_{19}ClN_4O_2$ 418.87	168	52	65.95 65.89	4.57 4.53	13.3 13.2
14	4b	-OH	-COCH3	$C_{23}H_{19}ClN_4O_3$ 434.87	194	61	63.52 63.49	4.40 4.37	12.8 12.6
15	4c	-OMe	-COCH3	$C_{24}H_{21}ClN_4O_3$ 448.90	165	66	64.21 64.19	4.72 4.70	12.4 12.3
16	4d	-Cl	-COCH3	$C_{23}H_{18}Cl_2N_4O2$ 448.90	180	72	60.94 60.91	4.00 4.02	12.3 12.4

IV. SPECTRAL STUDY

IR Spectra of N-(4-Acetylphenyl)-6- Chloropyridine-3- Carboxamide

N-(4-Acetylphenyl)-6- Chloropyridine-3- Carboxamide IR (Kbr): 3272, 3061, 2991, 2852, 1673, 1592, 1540, 1358, 755 Cm-1 Pmr 400 Mhz (Δ Ppm: Dmso – D6): 2.1 (3h, S), 6.8 – 7.9 (7h, M), 8.9 (1h, S), Ms M/Z = 274 (M+), 275 (M+1).

Table-2 IR Spectrum Correlation Table of N-(4-Acetylphenyl)-6- Chloropyridine-3- Carboxamide

Type	Vibration Mode	Frequency in cm^{-1}	
		Observed	Reported
Alkane	C-H str.(asym)	2991	2975-2950
	C-H str.(sym)	2852	2880-2860
	C-H in.p.def.(asym)	1358	1471-1435
Aromatic	C-H str.	3061	3080-3030
	C=C str.	1540	1580-1480
	C-H inb.	1019	1070-1000
	C-H o.o.p.	828	835-810
Amide	C=O str.	1673	1680-1630
	NH str.	3272	3500-3400
	NH bend.	1592	1550-1510
Halide	C-Cl str.	755	800-600
Ketone	C=O str.	1695	1700-1680

IR Spectra of 6-Chloro-N-{(2e)-3-(4-Chloro-Phenyl) Prop-2-Enoyl] Phenyl} Pyridine-3- Carboxamide
6-Chloro-N-{(2e)-3-(4-Chloro-Phenyl)Prop-2-Enoyl]Phenyl} Pyridine-3- Carboxamide Ir (Kbr): 3048, 2924, 2851, 1680, 1650, 1527, 1463, 1362, 823 Cm-1 Pmr 400 Mhz (Δ Ppm:Dmso – D6): 2.58 (1h, D), 3.26 (1h, D), 7.3 – 8.07 (11h, M), 9.04 (1h, S), Ms M/Z = 392 (M+), 393 (M+1).

Table-3 IR Spectrum Correlation Table of 6-Chloro-N-{(2e)-3-(4-Chloro-Phenyl) Prop-2-Enoyl] Phenyl} Pyridine-3- Carboxamide

Type	Vibration Mode	Frequency in cm^{-1}	
		Observed	Reported
Aromatic	C-H str.	3049	3080-3030
	C=C str.	1546	1520-1480
	C-H inb.	1020	1070-1000
	C-H o.o.p.	818	780-830
Amide	C=O str.	1620	1680-1630
	NH str.	3461	3500-3400
	NH bend.	1493	1550-1510
Halide	C-Cl str.	653	800-600
Chalcone	C=O str.	1640	1685-1645

IR Spectra of N-[4-(2-Amino-4-(4-Chlorophenyl)-6h-1, 3-Oxazin-6-Yl) Phenyl] - 6-Chloro Pyridine-3-Carboxamide
N-[4-(2-Amino-4-(4-Chlorophenyl)-6h-1,3-Oxazin-6-Yl)Phenyl]-6-Chloropyridine-3-Carboxamide Ir (Kbr): 3048, 1673,1528,1523,1274,1112,1024, 825, 643, Pmr 400 Mhz (Δ Ppm:Dmso – D6): 7.7 – 7.9 (11h, M), 7.52 (1h, S), 7.50 (2h, S) 9.02 (1h, S), (Ms M/Z = 420 (M+), 421 (M+1).
Table-4 IR Spectrum Correlation Table of N-[4-(2-Amino-4-(4-Chlorophenyl)-6h-1, 3-Oxazin-6-Yl) Phenyl] - 6-Chloro Pyridine-3-Carboxamide

Type	Vibration Mode	Frequency in cm^{-1}	
		Observed	Reported
Aromatic	C-H str.	3048	3080-3030
	C=C str.	1523	1580-1480
	C-H inb.	1024	1070-1000
	C-H o.o.p.	825	835-810
Amide	C=O str.	1673	1680-1630
	NH str.	3324	3500-3400
	NH bend.	1518	1550-1510
Halide	C-Cl str.	643	800-600
Oxazine	C-O-C str.	1116	1280-1070
	C-N str.	1274	1280-1180

V. CONCLUSION

We have synthesized some different novel possible hit molecules. The present synthetic methodology offers very attractive features such as short reaction time, mild reaction condition and good to excellent yield.

VI. ACKNOWLEDGEMENT

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