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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF SOME NOVEL 1,3,5 TRISUBSTITUTED 2-PYRAZOLINES

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ABSTRACT

Certain pyrazolines of Nicotinic acid derivatives were synthesized. Nicotinic acid was converted to Nicotinic acid hydrazide. 10 different Chalcones were synthesized by reacting different aromatic aldehydes with paracetamol. These Chalcones on reaction with Nicotinic acid hydrazide yielded 10 different 2-Pyrazolines. The structure of synthesized compounds was confirmed by spectral data. They were screened for anti-microbial activities.

Keywords: Nicotinic acid hydrazide; 2- pyrazolines; anti-microbial.

INTRODUCTION

Pyrazolines were reported with analgesic, anti-inflammatory activities[1], anti-convulsant[2], anti-microbial[3], anti-tubercular activities[4]. Nicotinic acid is a water soluble vitamin. Nicotinic acid was converted to Nicotinyl chloride which on reaction with hydrazide yielded Nicotinic acid hydrazide. The nicotinic acid hydrazide underwent Claisen- Schmidt condensation reaction with Chalcones to form Pyrazolines.

EXPERIMENTAL

Procedure for Preparation of Nicotinic Acid Hydrazide

A mixture of nicotinic acid (0.03mol) (4.1 gms) and Phosphorous penta chloride (0.05mol) (10.3gms) in anhydrous Carbon tetra chloride (20ml) were refluxed for 2 hour at 100^{o}C. Solvent was distilled off and the solid acid chloride thus obtained was used for further reaction without any purification. To the nicotinoyl chloride (0.03mol) was added hydrazine hydrate (0.1mol) drop wise below 5^{o}C and the resultant mixture was stirred for 5 hour at room temperature. A solid that separated out was washed with aqueous sodium bicarbonate ($NaHCO_3$) (10%) and dried in vaccuo. It was recrystallised from methanol to obtain pure crystalline solid.

M.P - 146-152^{o}C
R_F - 0.3672
% YIELD - 76.24%

Procedure for Synthesis of Pyrazolines

10 different chalcones were prepared as per literature[3]. Chalcone (4.62 m mole) and Nicotinyl hydrazide (9.25 mmole) were refluxed in an oil bath at 120-130˚C for 16-18 hours. After cooling mixture was diluted with ice- cold water and solid separated was filtered. It was recrystallised from DMF.

RESULTS AND DISCUSSION

PHARMACOLOGICAL EVALUATION

Anti-Microbial Activity[5]

All the synthesized compounds were been screened for their anti-bacterial and anti-fungal activities. For preliminary screening, the anti- microbial testing was carried out by the disc diffusion method, using Mueller-Hinton agar (MHA) medium and Sabouraud's dextrose agar (SDA) medium, for bacteria and fungi respectively. The discs (6mm in diameter), impregnated with the test compounds (25µ g/ml/disc) and Clotrimazole (1000 µ g/disc) were used as positive reference standards to determine the sensitivity of each microbial species tested. The inoculated plates were incubated at 37˚C for 24 hours and 27˚ C for 72 hours for bacterial and fungal strains respectively. Anti-microbial activity was evaluated by measuring the diameter of the zone of inhibition against test organisms.

Based on the results (Table 2) it is referred that 1,3,5-trisubstituted 2-pyrazolines derivatives have significant inhibition effect on the growth of bacteria like *Staphylococcus aureus(SA), Staphylococcus epidermidis(SE), Klebsiella pneumonia(KP), Escherichia coli(EC) and fungi like Candida albicans(CA), Aspergillus niger(AN).*

Compounds **b, d, e, h** and **j** showed more significant activity against Gram positive organisms, whereas compounds **d, h** and **j** showed significant activity for Gram negative organisms. Compounds **b, c, f** and **i** showed significant anti-fungal activity.

CONCLUSION

In summary, pyrazolines with Chloro phenyl, methoxy phenyl and hydroxyl phenyl substitution showed more anti-bacterial activity. Hydroxy and methoxy phenyl substituted Pyrazolines showed good anti-fungal activity.

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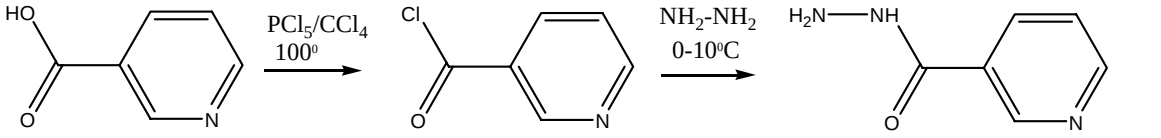


NICOTINIC ACID — NICOTINYL CHLORIDE — NICOTINIC ACID HYDRAZIDE

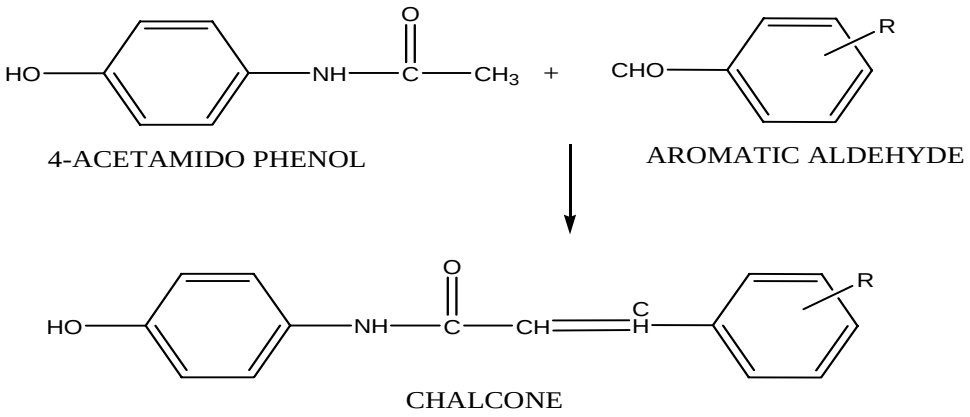
Scheme-1

Table-1: Physical and Spectral data of the synthesized Pyrazolines

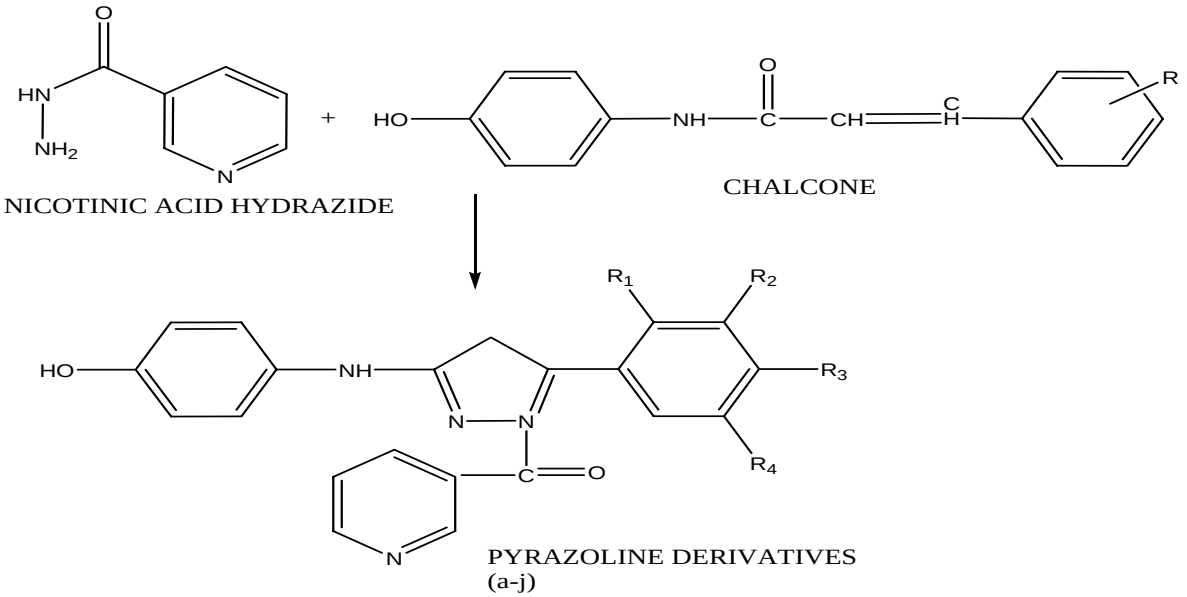
Compd	R	Mol.Formula	M.W	M.P(˚C)	Yield (%)	I.R	NMR	Mass
a	H	$C_{21}H_{18}N_4O_2$	358. 39	205-210	54	1491,3585, 3377,1731	6.21-7.27, 5.02,4.01	359
b	2-OH	$C_{21}H_{18}N_4O_3$	374. 39	215-218	82	1490,3580, 3418,1730	6.51-7.26, 5.01,4.01	375
c	4-OH	$C_{21}H_{18}N_4O_3$	374. 39	210-213	70	1493,3529, 3466,1727	6.51-7.24, 5.02,4.01	375
d	4-Cl	$C_{21}H_{17}N_4O_2Cl$	392. 84	235-240	66	1493,3582,836, 3379,1727	6.26-7.25, 5.01,4.02	393
e	4-OCH_3	$C_{22}H_{18}N_4O_3$	389. 43	205-208	54	1490,3578,1099, 3418,1742	6.27-7.14, 5.00,4.02,3.73	390
f	3,4-$(OCH_3)_2$	$C_{23}H_{22}N_4O_4$	418. 45	230-232	68	1491,3581,1098, 3378,1741	6.66-7.27, 5.02,4.00,3.72	419
g	3,4,5-$(OCH_3)_3$	$C_{24}H_{24}N_4O_5$	448. 47	232-234	65	1490,3571,1009, 3442,1728	6.21-7.24, 5.00,4.01,3.73	449
h	3-OCH_3, 4-OH	$C_{22}H_{22}N_4O_4$	406. 44	236-240	75	1488,3582,1078, 3377,1745	6.51-7.27 5.00,4.02,3.74	407
i	3,5-$(OCH_3)_2$ 4-OH	$C_{23}H_{22}N_4O_5$	434. 35	235-238	70	1489,3523,1073, 3323,1734	6.16-7.27 5.00,4.00,3.73	435
j	4-$N(CH_3)_2$	$C_{23}H_{24}N_5O_2$	402. 47	256-258	55	1492,3572,1098, 3335,1742	6.72-7.26 5.00,4.02,2.85	403

Table-2: Anti-microbial activity

Compd	Anti-bacterial (25µg/disc)				Anti-fungal (25µg/disc)	
	Zone of inhibition in mm				Zone of inhibition in mm	
	SA	SE	KP	EC	CA	AN
a	12	11	14	13	17	15
b	18	17	15	17	18	14
c	14	19	17	14	21	14
d	19	18	22	21	12	17
e	19	13	16	14	15	16
f	16	15	15	14	18	16
g	11	13	18	17	20	18
h	20	20	23	18	21	19
i	15	13	14	16	21	21
j	17	18	19	20	18	15
STD	24	22	28	27	26	22



Scheme-2



Scheme-3

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If an elderly but distinguished scientist says that something is possible, he is almost certainly right; but if he says that it is impossible, he is very probably wrong.

-Arthur C. Clarke