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Synthesis and Biological Screening of New Cyanopyridine Scaffold for Medicinal Interest

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ABSTRACT

Pyridine nucleus is extensively released for their application in the field of biologically active compund, agriculture and industrial place. Cyanopyridine have huge attention as they seen of interest to consist antifungal,antimicrobial, antidiabetic and antihypertensive properties. We have done the synthesis in chalcones on a synthetically affordable route with 2-amino/methoxy-6-aryl-4-[(3'-methoxy)-4'-[(3"-methyl)-4"-(2"', 2"', 2"'-trifluroethoxy) pyridine-2"-yl]-methoxyphenyl}-nicotinonitrile as a starting material.This work contains with the synthesis of Cyanopyridine derivatives were they prepared with condensation of numerous substituted chalcones (4a-f) derivatives reacts withmalanonitrile and ammonium acetate using methanol as a solvent. Our finding of this development by synthetic medicinal chemistry to optimize drugs of new generation. The structural conformation of synthesized molecules has been made by spectroscopy like Mass, IR and ^{1}H NMR. All the synthesized molecules were placed for *in-vitro*with properties likeantifungal andantibacterial.

KEYWORDS: Chalcones, malanonitrile,Cyanopyridine, antifungal and antibacterial activities.

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INTRODUCTION

Cyanopyridine, nucleus have been explored for their focus in the field of drug, medicine, agriculture and industrial field. Types of isomeric materials as cyanopyridine like 2-cyanopyridine (2-CNP), 3-cyanopyridine (3-CNP) and 4-cyanopyridine (4-CNP) these are called as picolinonitrile, nicotinonitrile and isonicotinonitrile too, as usual contain Cyano group (CN) substituted at ortho, meta, para place of ring. These Cyanopyridine have positive activity in pharma, corrosion inhibition, catalytic, reaction of organic substance and organometallic complexes[1]. Cyanopyridine are widely used as a starting material and intermediates for the reaction of higher valued acids and amides. For example, 3-CNP is as an intermediate in the reaction of nicotinic acid (vitamin B3, niacin) and nicotinamide (bimolecular). Since nitrogen of both Cyano group and the pyridine ring of Cyanopyridine are used to coordinating with metal ions, these substances are used in the preparation of organo-metallic complexes [1] too.The molecule containing Cyanopyridine moiety are used as nonlinear optical substance, electrical materials and chelating agents as a metal ligand chemistry. Among them Cyanopyridine are called as IKK-β-inhibitors [2]. Besides, they are applicable and useful intermediates in synthesizing types of heterocyclic materials.

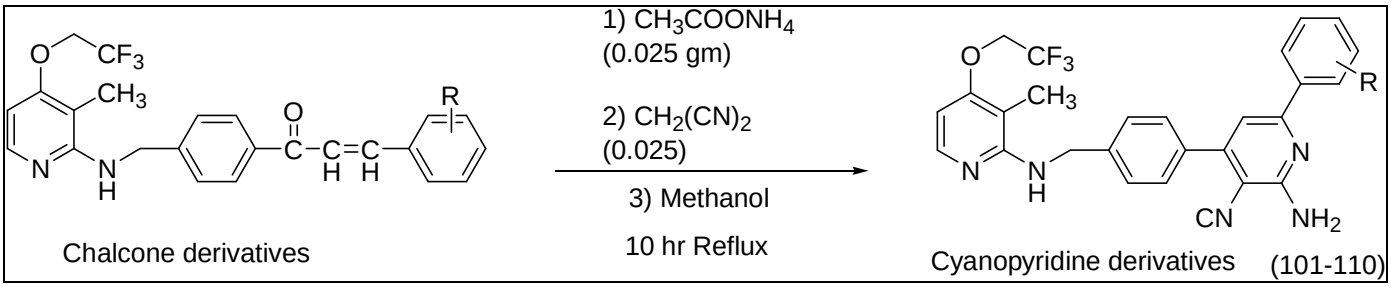
A report of the literature review gives that the huge synthetic approaches that are used to prepare different types of Cyanopyridine derivatives as starting material, chalcones on react with ammonium acetate via the condensation method, as well as with a one pot four components reaction in like conventional heating or under microwave irradiation, andcan use some other methods [2]. Although diverse substituted of Cyanopyridine derivatives are made by various method. The Cyanopyridine derivatives are synthesized by the cyclisation of aliphatic or aromatic raw material. The applicability of 3-Cyanopyridine, nicotinamide and nicotinic acid make possibilities their use as preparing intermediates. However the simple pyridine substances are organized by the cyclization aliphatic substrate. In our continuation work as the chemistry of pyridine nucleus, we have taken the process of 2-amino/methoxy-6-aryl-4-[(3'-methoxy)-4'-[(3"-methyl)-4"-(2"', 2"', 2"'-trifluroethoxy) pyridine-2"-yl]-methoxyphenyl}-nicotinonitrile via chalcones.

MATERIAL AND METHOD

Experiment

General procedure to synthesized substituted Cyanopyridine derivatives

In a RBF take an similar molar mixture of 1-(4-{[3-Methyl-4-(2, 2, 2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-amino}-phenyl)- propenone derivatives and malanonitrile (0.025 gm) and ammonium acetate (0.025 gm) in methanol. The synthesis mixture was refluxed with 10 hrs. Now take 40gm crushed ice and chill the reaction mass and poured in ice. The progress of the synthesis was seen by TLC. After end of the preparation, The reaction mass was filtered and completion with hot methanol and dried with vacuum at 50 °C. And the product was derivatives of 3-Isocyano-4-(4-{[3-methyl-4-(2, 2, 2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-amino}-phenyl)-6-(phenyl)-pyridin-2-ylamine as Cyanopyridine.



RESULT AND DISCUSSION

Biological aspects

Compound and cells

A list of newly synthesized compounds weretake in DMSO at a starting concentration at 1280 µg/ml and then diluted in culture base medium. Bacterial strains were gaveby the Culture Collection like American Type culture.

Antifungal assay

The antifungal reporting of the generated chemical substanceswere tried against yeast strain (*C. albicans* ATCC 14053) according to NCCLS- guidelines approved standard data M27A2, using the micro-dilution broth way[4]. Fluconazole was used as like antifungal agent. The MIC of each and every synthesized chemical active compound was noted as the lowest concentration of each latestprepared

materials in the tubes with no growth of yeast (inoculated). The MIC values of the compound shows in below table.

Antibacterial assay

Gram's positive (*S. aureus* ATCC 6538, *M. luteus* ATCC 9345) and Gram's negative (*E. coli* ATCC 4230, *S. thphi* ATCC 14028) bacterial isolates killed by this types of chemically synthesized compounds were evaluated for their antibacterial properties, as placed according to NCCLS notes, permitted standard document M7-A4, using the micro dilution broth culture way[3]. As a reference control of antibacterial compound shown by using Ampicillin trihydrate. The lowest concentration of each and every chemical compound in the tubes with no growth of inoculated bacteria indicates the minimal inhibitory concentration (MIC) of synthesized compound.

Table No 1. Antibacterial assay compound

Antibacterial assay compound (µg/ml)											
Microbes	101	102	103	104	105	106	107	108	109	110	Amp
Escherichia coli ATCC 4230	160	640	20	80	20	40	40	40	40	80	20
Micrococcus luteus ATCC 9345	320	640	40	40	80	40	10	320	320	160	10
Salmonella typhi ATCC 14028	160	160	10	160	10	80	10	80	160	160	10
Staphylococcus aureus ATCC 6538	320	160	20	40	10	40	20	640	320	320	10
Microbes	101	102	103	104	105	106	107	108	109	110	Fluconazole
Candida albicans ATCC 14053	160	320	160	160	640	160	40	80	640	10	5

The antimicrobial screening test report exhibited a lower activity compared to other standard drugs.Compared to a standard fluconazole, compound 110 and exhibited excellent activity, From activity data it is crystal clear that compounds 4c and 4g exhibited moderate activity against *Micrococcus* and *Staphylococcus* respectively but good activity against *Escherichia coli* and *Salmonella typhi* respectively in comparison to standard antibiotic Ampicillin. On the other Hand antifungal study shows excellent activity against *P. Candida albicans*.

Spectral data of respective compound

1) *3-Isocyano-4-(4-{[3-methyl-4-(2,2,2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-amino}-phenyl)-6-(3,4,5-trimethoxy-phenyl)-pyridin-2-ylamine*

IR (cm^{-1}): 2972 (C-H stretching alkane), 2870 (C-H stretching alkane), 1437 (C-H alkane), 1372 (C-H alkane), 3036 (C-H stretching aromatic), 1568 (C=H stretching aromatic), 1148 (C-H aromatic), 2237 (C=N stretching nitrile), 3457 (N-H stretching amine), 1257 (C-O-C ether), 3402 (C-N (-NH_2) stretching pyridine nitrile), 2225 (-CN stretching pyridine nitrile), 1163 (-C-N stretching pyridine nitrile); ^{1}H NMR (400 MHz, DMSO-d6) δppm: 3.88 (s, 6H), 7.60 (d, 2H), 8.11 (m, 2H), 7.10 (d, 2H), 7.11 (d, 2H), 3.33 (s, 1H), 4.91 (s, 2H), 7.02 (d, 1H), 2.50 (s, 3H), 6.65 (q, 2H), 4.09 (s, 2H), 3.73 (s, 3H); EI-MS: m/z 405.0, 576 (M^+).

2) *3-Isocyano-4-(4-{[3-methyl-4-(2, 2, 2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-amino}-phenyl)-6-pyridin-2-ylamine*

IR (cm^{-1}): 2972 (C-H stretching alkane), 2870 (C-H stretching alkane), 2870 (C-H stretching alkane), 1437 (C-H alkane), 1372 (C-H alkane), 3036 (C-H stretching aromatic), 1568 (C=H stretching aromatic), 1148 (C-H aromatic), 2237 (C=N stretching nitrile), 3457 (N-H stretching amine), 1257 (C-O-C ether), 3402 (C-N (NH_2) stretching pyridine nitrile), 2225 (-CN stretching pyridine nitrile), 1163 (-C-N stretching pyridine nitrile); ^{1}H NMR (400 MHz, DMSO-d6) δppm: 4.10 (s 2H)4.90 (q, 2H),2.50 (s, 3H),6.92 (d, 1H),4.91 (s, 2H),3.33 (s, 1H),7.65 (d, 2H),7.71 (d, 2H),8.11 (m, 2H),7.98 (d, 2H),7.42 (m, 3H); EI-MS: m/z486,404.9 (M^+).

Table No 2. Analytical data table and physical parameter of synthesized Cyanopyridine derivatives

Sr. No.	Compound	M.F	R	M.W (gm/mol)	M.P	Yield (%)
1	101	$C_{27}H_{21}O_3N_6F_3$	-NO_2	531	125	75 %
2	102	$C_{30}H_{28}O_4N_5F_3$	-OCH_3	576	123	76 %
3	103	$C_{27}H_{22}O_2N_5F_3$	-OH	502	122	66 %
4	104	$C_{27}H_{22}O_2N_5F_3$	-OH	502	122	66 %
5	105	$C_{27}H_{21}O_2N_5F_3Cl$	-Cl	519	127	70 %
6	106	$C_{27}H_{21}O_3N_6F_3$	-NO2	531	125	75 %
7	107	$C_{27}H_{21}O_3N_6F_3$	-NO2	531	125	75 %
8	108	$C_{29}H_{26}O_3N_5F3$	-OCH_3	546	124	74 %
9	119	$C_{28}H_{29}O_2N_5F_3$	-OCH_3	514	123	75 %
10	110	$C_{27}H_{22}O_1N_5F_3$	-H	486	120	66 %

CONCLUSION

In the light of the observation projected in above description, we have successfully Synthesized new structural variants of 2-cloromethyl-3-methyl-4-(2, 2, 2-trifloroethoxy) pyridine. In the course of this research we have sharply observed that some of Cyanopyridine derivatives (101, 102, 103, 104, 105, 106, 107, 108, 109, 110) exhibited antimicrobial activity similar to the marketed drug (ampicillin, fluconazole) our observation can be summarized as *E. coli* bacteria 103 are highly active and 107,108 & 109 are moderate active. *M. luteus* are 107 are highly active. *S. typhi* are 103&107 are highly active. *S. aureus*105 are highly active and 103&107 are moderate active. *Candida* are 107 are moderate active and 110 are highly active. The derivatives of chalcones, substituted, 2-amino-3cynopyridine commonly found effective it shows the rational of this study was 107 compound are highly broad spectrum they meticulous and carefully expected. The motto of finding this development is synthetic and medicinal chemistry to optimize drugs of new generation.

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