International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN: 0974-4290
Vol.7, No.4, pp 2108-2111, 2014-2015

Synthesis, Characterization and biological evaluation of some novel Schiff bases containing trifluoromethyl pyridine moiety

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Abstract : 4-Hydroxymethylbenzoate and 2-fluoro-6-(trifluoromethyl) pyridine were treated in DMF at given condition to get pyridine moiety having ether linkage. Which was further treated with hydrazine to get benzohydrazide, which on reaction with different substituted aldehydes givesSchiff bases containing trifluoromethyl pyridine.The compounds were evaluated for microbial screening against Gram positive & Gram negative bacteria and fungal strain. Most of the compounds show significant activity against all the spices of bacteria and fungi.
Keywords: Pyridine, hydrazine, ester, Schiff base, ether.

Introduction

The pyridine system has shown many interesting biological and pharmacological properties such as such as anti-tubercular activity[1,2], activity against gram positive and negative bacteria[3]. Interest in the synthesis of substituted pyridines has recently revived because of the wide variety of their biological properties[4-6]. Although the pyridine ring system has proved to be an interesting class in heterocyclic chemistry, it has received little attention in the literature. Some of its derivatives are important as anticancer agents with low toxicity[7,8], as anti-inflammatories[9],as blood platelet aggregation inhibitors[9],as bone metabolism improvers[10] as adenosine antagonists[11,12]and as controlling herbicides[13]. They also show antifungal and anti-parasitic activities[14,15].

There is always need for the safer antibacterial agents and research efforts are going on for developing safer antibacterial agents. Schiff base approach is one of the most promising amongst these[16]. In recent years, there has been an increasing interest in the design and development of Schiff base derivatives. Schiff base are associated with antibacterial, antifungal andanti-tubercular activities and have diverse biologicalactivities[17]. Besides, several Schiff bases have been reported to possess remarkableantibacterial[18], anti -fungal[19], anticancer[20], anti HIV[21], anti-inflammatory[22], antiparasitic[23,24] and diuretic[25] activities.

The constitution of the synthesized products have been supported by using IR, NMR and Mass spectral analysis.

Experimentals

Materials and Methods

All the melting points are uncorrected. TLC method was used tocheck reaction progress.

1} preparation of *methyl 4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}benzoate:*

Take *methyl 4-hydroxybenzoate*(5g, 1eq) and *2-fluoro-6-(trifluoromethyl)pyridine*(1eq) in DMF (25 ml) add K_2CO_3 (2eq) at room temperature.Then reaction mass heated at 90 ^{0}C for 6h.Cool the reaction mass, add water extract with ethyl acetate.Wash organic layer with cold water to remove DMF.

Organic layer was concentrated to yield desired compound as off white solid.Compound was purified by column chromatography.

2} Preparation of *4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}benzohydrazide*:

Take *methyl 4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}benzoate*(5 g) in ethanol (25 ml) add hydrazine hydrate ($NH_2NH_2H_2O$, 10 ml) to the reaction mass.Then after reaction mass heated at reflux temperature for 8h.Cool the reaction mass to yield white crystalline solid filter the reaction mass to yield desired compound.

3} preparation of *N*'-[(*Z*)-phenylmethylidene]-4-{[6-(trifluoromethyl)pyridin-2-yl]

oxy}benzohydrazide:

Take *4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}benzohydrazide* (2 g, 1eq) in methanol (20 ml).Add aromatic aldehyde (1 eq) to this reaction mass and add 2-3 drops acetic acid.Reaction mass was stirred at room temperature for 1-3 hr. so solid material was precipitate.Filter the solid residue to yield desired compound.

Physical data of all synthesized products are given in (**Table-1).**

4} Antimicrobial activity of the synthesized compounds:

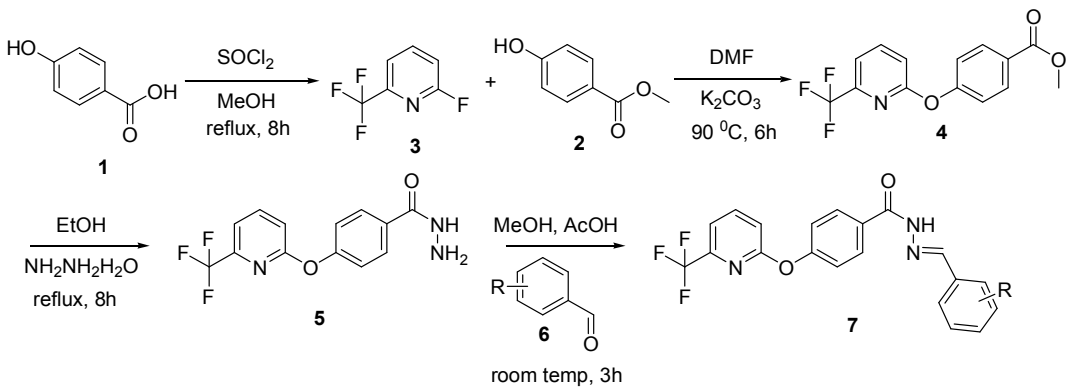
Antimicrobial activity was carried out by cup-plate agar diffusion method which has been described as under.

The purified products were screened for their antibacterial activity. The nutrient agarbroth prepared by the usual method, was inoculated aseptically with 0.5mL of 24 hrs. old subcultures of *B.subtillis, S.aureus, P.aerougenosa, E.coli* in separate conical flasks at 40-50 ^{o}C and mixed well by gentle shaking. About 25mL content of the flask were poured and evenly spreaded in a Petridis (13 cm in diameter) and allowed to set for 2 hr.

The cup (8mm in diameter) were formed by the help of borer in agar medium and filled with 0.04mL(40mg) solution of sample in DMSO. The plates were incubated at 37^{o}C for 24 hrs. The control was also maintained with 0.04mL of DMF in a similar manner and the zones of inhibition of the bacterial growth were measured in millimeter and are recorded in **(Table-2).**

The antibacterial activity data of the synthesized compounds have been compared with standard antibiotics like Benzylpenicilline, Ciprofloxacine, Sparfloxacine, and Ampicilin.

Results and Discussion



Reaction Scheme:

Discussion

It has been observed from the experimental data that all the compounds were moderately active against Gram positive and Gram negative bacterial strains.In case of Gram positive bacterial strain maximum activity was observed in compounds bearing R=3-trifluorometyl and 4-methoxy have fairly inhibit the growth of *B.subtillis*. Almost all the compounds have least active against *S.aureus*, while the compounds having R= 4-Fluoro displayed significant activity.

In case of Gram negative bacterial strain compounds bearing R=2-chloroand 2-Bromo have shown maximum activity against *E.coli* and R= 2-Chloro has shown maximum activity against *P.aerougenosa*.

Table-1 Physical data.

Sr. No.	R	Molecular Formula	M. Mass	M.P. °C	R_f# value	Yield %	Nitrogen %
1	4-F	$C_{20}H_{13}F_4N_3O_2$	403	182	0.61	22	10.42
2	3,4-dimethoxy	$C_{22}H_{18}F_3N_3O_4$	445	192	0.79	40	09.43
3	-H	$C_{20}H_{14}F_3N_3O_2$	385	204	0.84	54	10.90
4	4-OCH_3	$C_{21}H_{16}F_3N_3O_3$	415	201	0.13	32	10.12
5	2-OH	$C_{20}H_{14}F_3N_3O_3$	401	225	0.77	41	10.47
6	2-Cl	$C_{20}H_{13}ClF_3N_3O_2$	419	187	0.54	39	10.01
7	3-OH	$C_{20}H_{14}F_3N_3O_3$	401	255	0.45	72	10.47
8	3-Cl	$C_{20}H_{13}ClF_3N_3O_2$		232	0.23	62	10.01
9	2-Br	$C_{20}H_{13}BrF_3N_3O_2$	464	114	0.66	33	09.05
10	3-OCH_3	$C_{21}H_{16}F_3N_3O_3$	415	198	0.21	52	10.12
11	3-OCF_3	$C_{21}H_{13}F_6N_3O_3$	469	168	0.68	41	08.95
12	3-F	$C_{20}H_{13}F_4N_3O_2$	403	112	0.31	49	10.42

 # TLC SYSTEM : Ethyl acetate:Hexane (6:4)

Table-2 Antimicrobial activity

Sr. No.	Compound	*B.subtillis*	*S.aureus*	*E.coli*	*P.aerougenosa*
1	4-F	16	18	10	15
2	3,4-dimethoxy	10	19	13	08
3	-H	09	21	14	09
4	4-OCH_3	11	26	12	09
5	2-OH	14	09	18	16
6	2-Cl	13	11	22	28
7	3-OH	16	14	12	24
8	3-Cl	18	13	16	16
9	2-Br	20	16	18	13
10	3-OCH_3	21	18	20	12
11	3-OCF_3	28	15	21	16
12	3-F	12	08	28	18
	Benzylpenicillin	17	18	16	16
	Ciprofloxacin	35	34	12	12
	Sparfloxacine	30	30	10	36
	Ampicilline	22	16	10	18

Acknowledgements

The authors are thankful to Principal, M.D.Sciencecollege, porbandar, for providing research facility. Authors arealso thankful to RSIC-Chandigarh, CDRI-Lucknow for spectral analyses.

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