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A GREEN SYNTHESIS OF SCHIFF'S BASES WITH MULTIFLUORINATED CORE AND THEIR ANTIFUNGAL STUDY

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ABSTRACT- The present work explains an eco-friendly synthesis of Schiff's bases derived from the reaction of 2-(3,5-bis(trifluromethyl)phenoxy)acetohydrazide with different aromatic aldehydes. They were synthesized by environmentally benign methods like grinding, stirring and ultrasonication irradiation. The chemical structures of these new compounds were established by spectral analysis like IR, PMR and LCMS. The synthesized compounds were checked for their antifungal potential using C. Albicans and A.Niger Strains.
Keywords – Multifluorinated, Schiff's base, antifungal, grinding, stirring, ultrasound irradiation.

INTRODUCTION

Schiff's bases are subclass of imines which consists of –C=N- group. They are synthesized by condensation of carbonyl compounds like aldehydes or ketones with primary amines. Schiff's bases are the compounds with pharmaceutical importance like antiproliferative [1], anticonvulsant [2], antitubercular [3], antibacterial [4], anti-inflammatory [5] and acetylcholinesterase [6]. The schiffs bases of isonicotinoylhydrazide and their cobalt, copper, nickel and zinc complexes have shown antibacterial, antifungal and cytotoxic activity [7]. The carvone Schiff bases derived from isoniazid were studied for pharmacokinetic potential [8].

The Schiffs bases are not only biologically potent but are have many applications in dyes, pigments, electrical conductivity, agrochemical and analytical chemistry [9].

The schiffs base of pyridine-3-carbohydrazide were synthesized in basic medium [10]. Various green synthetic methods for the preparation of Schiffs bases have also reported in literature. Synthesis of Schiffs bases in aqueous medium with good yield was reported [11]. The green methods also include the use of nature derived catalyst like lemon juice [12], calcined egg shell [13], PEG-400 [14] and heteropolyacid PTA [15].

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EXPERIMENTAL

The required chemicals like 3,5-bis(trifluoromethyl)phenol, ethyl-2-bromoacetate and different aromatic aldehydes were purchased from Merck and utilized as it is. The melting points of the products were determined with the help of open capillary tubes in liquid paraffin bath. Shimadzu IR spectrophotometer was used to obtain IR spectra. PMR spectra were recorded on Varian NMR 400 MHz instrument using DMSO-d6 solvent and TMS as an internal standard. The instrument used to obtain LCMS was Water's Acquity Ultra Performance TQ Detector Mass Spectrometer.

GENERAL PROCEDURE

Grinding: In a mortar, equimolar amount (1mmol) of 2-(3,5-bis(trifluromethyl)phenoxy)acetohydrazide (1) and aromatic aldehyde (2) were mixed with excess of citric acid (1g) and ground at room temperature. The progress of reaction was checked by TLC using petroleum ether and ethyl acetate in 8:2 proportion. When the reaction was completed, the quenching was carried out by addition of crushed ice. The separated solid product was filtered, dried and purified by recrystallization in ethanol to obtain the targeted compounds 3a-g. The physical data of synthesized compounds is given in Table-1.

Stirring: In a round bottom flask, 2-(3,5-bis(trifluromethyl)phenoxy)acetohydrazide (1mmol) was dissolved in 5 mL glacial acetic acid. An equimolar amount of aromatic aldehyde (2) was added in it and the reaction mixture was stirred at room temperature. The progress of reaction was checked by TLC using petroleum ether and ethyl acetate in 8:2 proportion. After completion of reaction, the quenching was carried out by adding crushed ice. The separated solid product was filtered, dried and purified by recrystallization in ethanol to obtain the targeted compounds 3a-g. The physical data of synthesized compounds is given in Table-1.

(*E*)-N'-benzylidene-2-(3,5-bis(trifluoromethyl)phenoxy)acetohydrazide (3a): IR (cm^{-1}): 3100 (NH), 1680 (C=O),
1180 (C-F); ^{1}H NMR (δ, ppm): 5.26 (s, CH2), 7.28-7.65(m, Ar-H, 9H), 14.12 (s, NH); Mass: M^+ ion: 390.

(*E*)-2-(3,5-bis(trifluoromethyl)phenoxy)-N'-(4-(trifluoromethoxy)benzylidene)acetohydrazide (3b):): IR (cm^{-1}):
3120 (NH), 1685 (C=O), 1184 (C-F);^{1}H NMR (δ, ppm): 5.45 (s, CH2), 7.43-8.04 (m, Ar-H, 8H), 11.76 (s, NH);
Mass: M^+ ion: 474.

(*E*)-2-(3,5-bis(trifluoromethyl)phenoxy)-N'-(4-fluorobenzylidene)acetohydrazide (3c): IR (cm^{-1}): 3128 (NH),
1689 (C=O), 1183 (C-F); ^{1}H NMR (δ, ppm): 5.23 (s, CH2), 7.25-7.56 (m, Ar-H, 8H), 14.00 (s, NH); Mass: M^+ ion:
408.

ANTIFUNGAL ASSAY

All the synthesized compounds were screened for their antifungal activity against C. Albicans and A.Niger by National Committee for Clinical Laboratory Standards (NCCLS) protocol. Amphotericin B was used as a standard drug for this study. The stock solutions of all the title compounds and standard were prepared in dimethyl sulphoxide solvent. The % cell inhibition results were listed in Table-2 and Table-3. The results of these activities showed that the newly synthesized compounds show positive control in case of C. Albicans whereas negative control on A. Niger.

RESULTS AND DISCUSSION

The 2-(3,5-bis(trifluromethyl)phenoxy)acetohydrazide was prepared from 3,5-bis(trifluoromethyl)phenol. Phenol on reaction with ethyl bromoacetate get converted into ethyl 2-(3,5-bis(trifluoromethyl)phenoxy)acetate which on treatment with hydrazine hydrate forms 2-(3,5-bis(trifluromethyl)phenoxy)acetohydrazide 1. Compund 1 was treated with different aromatic aldehydes to get target compounds 3. The infrared spectrum of compound 3b shows presence of amide carbonyl peak at 1685cm-1. The PMR and other spectral techniques confirm the formation of products. The synthesized compounds were tested for their antifungal potential.

CONCLUSION

A series of new Schiff's bases were synthesized in good yields by simple and an eco-friendly method.

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Table 1: 2-(3,5-Bis(trifluromethyl)phenoxy)acetohydrazide derivatives

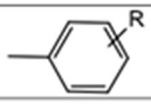
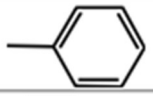
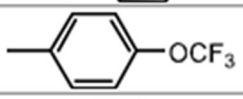
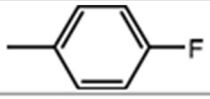
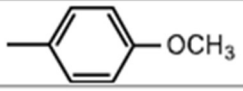
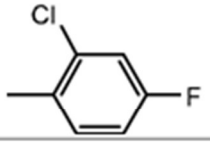
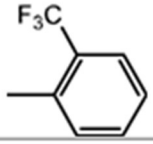
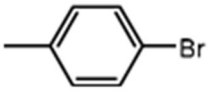
Compd		M. P. (^{0}C)	Yield (%) (Grinding)	Yield (%) (Stirring)
3a		135-137	80	68
3b		198-200	83	70
3c		207-208	86	62
3d		158-160	85	73
3e		104-106	88	75
3f		152-153	81	65
3g		225-227	89	76

Table-2: Antifungal activity against *C. Albicans*

Conc.	% Cell Inhibition						
	Amphotericin B	Sample A	Sample B	Sample C	Sample D	Sample E	Sample F
0.20	27.15	8.76	27.25	8.43	13.39	18.52	22.38
0.39	37.59	-2.53	-9.11	-6.70	8.46	6.39	7.69
0.78	28.52	-24.64	5.35	16.58	3.19	16.28	-3.27
1.56	13.89	-14.03	-10.79	-8.10	10.62	1.99	-7.48
3.13	17.14	-4.77	1.81	-5.49	-6.06	12.94	-12.72
6.25	22.20	-27.56	3.39	3.13	3.71	21.82	1.66
12.50	26.27	-5.89	8.60	13.40	17.19	42.21	20.15
25.00	36.22	26.43	35.71	31.71	41.39	54.71	34.38
50.00	42.60	33.90	38.82	26.51	41.62	52.39	32.87
100.00	37.09	29.58	13.76	22.56	42.14	50.03	14.12

Table-3: Antifungal activity against *A. Niger*

Conc.	% Cell Inhibition

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	Amphotericin B	Sample A	Sample B	Sample C	Sample D	Sample E	Sample F
0.20	38.27	-16.84	2.89	30.25	-43.63	-27.78	17.91
0.39	16.14	-120.09	-41.45	3.07	-34.39	-25.82	-34.96
0.78	11.32	-25.67	-40.14	-10.08	-46.35	-30.88	25.54
1.56	-10.38	-40.17	-43.46	-19.23	-48.91	-24.28	-69.28
3.13	25.23	-34.56	-94.53	-30.57	-71.42	-48.80	-35.60
6.25	22.41	-20.63	-73.81	-24.74	-31.67	-71.45	-34.18
12.50	34.09	7.22	-17.40	5.14	0.91	-20.04	13.63
25.00	28.11	29.38	2.10	9.96	2.72	6.52	42.74
50.00	44.32	12.83	-5.25	6.33	8.99	25.82	27.19
100.00	35.96	-19.91	-37.08	-6.83	6.19	33.65	-27.33