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Synthesis and Biological Screening of 3-Aryl-5-[(4′-difluoromethoxy)(3′-hydroxy)phenyl]-4,5-dihydro isoxazole

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ABSTRACT

Isoxazoline derivatives shows various types of therapeutic activities like antimicrobial[1], anti-inflammatory[2], anticonvulsant[3], Hypoglycemic[4] etc. getting to synthesized in view of 3-Aryl-5-[(4′-difluoromethoxy)(3′-hydroxy)phenyl]-4,5-dihydro isoxazole (4a-4i) have been synthesized. All the newly synthesized compounds were screened for their antibacterial activity against *S. aureus, M. luteus* (Gram-positive bacteria), *E. coli, S. thyphi* (Gram-negative bacteria) and antifungal activity against Candida albicans (Fungi). The biological activities (MIC) of the synthesized compounds were compared with known standard drugs.

Keywords: Isoxazole; antibacterial activity; antifungal activity

1. INTRODUCTION

The designing of new types of heterocyclic compounds along with the refining of procedures for synthesis is as target of the modern heterocyclic chemistry. Amongst the five-member heterocyclic compounds, much interest has been focused on the isoxazole nucleus which is known to possess a broad spectrum of biological properties such as anti-inflammatory [5-7], anticonvulsant [8], antiviral [9], herbicidal [10,11] etc. 3-Aryl-5-[(4′-difluoromethoxy)(3′-hydroxy)phenyl]-4,5-dihydro isoxazole have been synthesized and evaluated their antibacterial activity against *S. aureus*, *M. luteus*, *E. coli*, *S. thyphi* and antifungal activity against *Candida albicans (Fungi).*

2. EXPERIMENTAL SECTION

2.1. Method section

All the melting points were taken in open glass capillaries and are uncorrected. IR absorption spectra were recorded on a SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm-1(KBr disc) and ^{1}H NMR spectra on a BRUKER

spectrometer (400 MHz) using DMSO as solvent and TMS as internal standard. Purity of the compounds were routinely checked by TLC using silica gel G .

2.1.1. Spectral section

(E)-3-[(4′-difluoromethoxy)-3-hydroxyphenyl]-1-(2′′-methoxy phenyl)-lprop-2- en-1-one (3d)

A mixture of 3-hydroxyl-4-difluoromethoxy phenyl carboxaldehyde (1.88 gm, 0.01 mol), 40% sodium hydroxide solution in ethanol and 2-methoxy acetophenone (1.5 gm, 0.01 mol) was stirred for 24 hrs at room temperature. After completion of the reaction, the reaction mixture was poured into ice cold water and acidified with diluted HCl. The precipitates obtained were filtered to get required product. Than purified in chilled methanol / diethyl ether. Yield 88%, m.p. 192^{o}C, Ana. cal. for ($C_{17}H_{14}F_2O_4$) Required C, 63.75; H, 4.41 %. Found: C, 63.81; H, 4.18%. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.02 (1H, s, -OH), 7.55-7.58 (1H, dd, Ar-CH), 7.50-7.54 (1H, dd, Ar-CH), 7.40-7 .44 (1H, s, -CH), 7.31-7.32 (1H, d, Ar-CH), 7.26-7.27 (1H, t, Ar-CH), 7.21-7.22 (1H, t, -CH), 7.19-7.20 (1H, m, Ar-CH), 7.13-7.16 (1H, d, Ar-CH), 7.04-7.08 (1H, m, Ar-CH), 6.94 (1H, s, -CHF_2), 3.88 (1H, s, -OCH_3) . IR (cm^{-1}) : 2955 (C-H str. asym), 2868 (C-H str. sym), 1496 (C=C str.), 1658 (C=O str.), 3088 (CH=CH), 1265 (C-O-C), 3263 (-OH), 1132 (C-F). MASS : m/z ; 77, 91, 119, 207, 237, 253,269,287,320 .

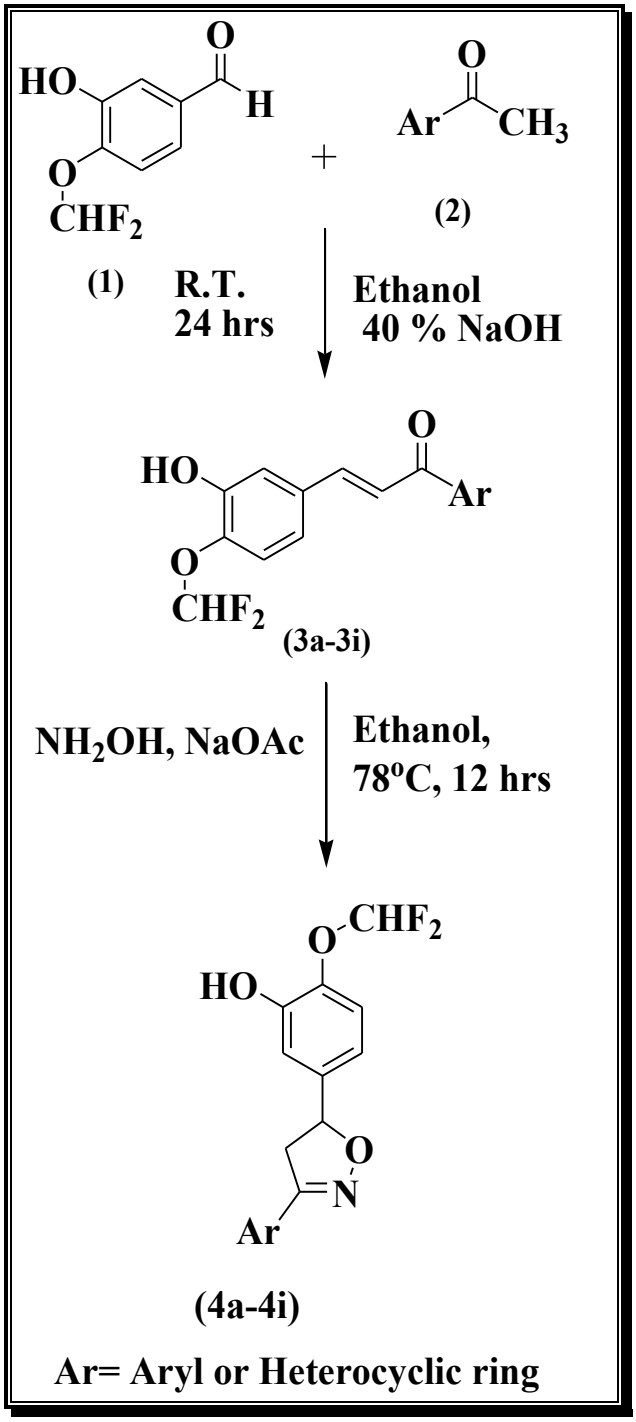
Similarly, other chalcones (3a–3i) where prepared and their physical data and antimicrobial activities data already publised.

3-(4′′-fluoro phenyl)-5-[(4′-difluoromethoxy)(3′-hydroxy)phenyl]-4,5-dihydro isoxazole (4f)

To a solution of (E)-1-(4′′-fluoro phenyl) -3-[(4′-difluoromethoxy) (3′-hydroxy) phenyl] prop-2-en-1-one (3.09 gm, 0.01 mol) in ethanol (5 ml) was added hydroxyl amine hydrochloride (0.89 gm, 0.015 mol) and sodium acetate (2.46 gm, 0.03 mol) is added in catalytically amount. The reaction mixture was reflux at 78^{O}C for 12 hrs. After completion of the reaction, the reaction mixture was poured into crushed ice water and product was extracted with ethyl acetate (20 ml). The organic layer was washed with brine, dry over sodium sulphate and evaporated under reduced pressure. The crude residue was washed with diethyl ether to a give a pure product as a solid. Yield 64%, m.p. 178^{O}C. Ana. cal. for ($C_{16}H_{12}F_3NO_3$) Required C, 59.45; H, 3.74; N, 4.12. Found: C, 59.36; H, 3.68; F, N, 4.08 %. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.12 (1H, s, -OH), 7.71-7.76 (2H, d, Ar-CH_2), 7.53-7.69 (2H, m, Ar-CH_2), 7.33-7.48 (1H, m, Ar-CH), 7.13-7.28 (1H, m, Ar-CH), 6.91 (1H, s, -CHF_2), 6.70-6.77 (1H, t, Ar-CH), 5.79-5.86 (1H, q, -CH), 3.61-3.67 (1H, q, -CH), 3.02-3.1 (1H, q, -CH). IR (cm^{-1}): 3336 (-OH), 3036 (C-H str.), 3034 (C=N str.), 1599, 1502 (C=C str.), 1315 (N-O str.), 1228 (C-O-C), 1228 (C-F). MASS m/z: 77, 120, 166, 222, 270, 290, 305,323.

Similarly, other Isoxazoles (4a – 4i) where prepared and their physical data and antimicrobial activities data are describe in Table no. I and Table no. II respectively.

2.2. Reaction Scheme



2.3. Antimicrobial Activity

The newly synthesized compounds were screened for their antibacterial activity against two Gram-positive bacteria (*S. aureus* ATCC 6538, *M. luteus* ATCC 9345) and two Gram-negative bacteria (*E. coli* ATCC 4230, *S. thphi* ATCC 14028) and antifungal activities one yeast strain (*C. albicans* ATCC 14053) as described by the guidelines in NCCLS-approved

standard document M7-A4, using the micro dilution broth procedure [12,13] Ampicillin trihydrate and Fluconazole were used as the reference antibacterial and antifungal agent respectively. Solutions of the compounds and reference drug were dissolved in DMSO at a concentration of 2560 μg/ml. The two-fold dilutions of the compounds and the reference drug were prepared (1280, 640, 320, 160, 80, 40, 20, 10, 5 μg/ml). The minimum inhibitory concentration (MIC) of each chemical compound was recorded as the lowest concentration of each chemical compound in the tubes with no growth (i.e., no turbidity) of inoculated bacteria and yeast.

3. RESULTS AND DISCUSSIONS

In this study, a series of nine new compounds were synthesized. Scheme illustrates the synthetic route for the preparation of target compounds. Chalcones are synthesized by Claisen–Schmidt condensation. In Claisen– Schmidt condensation, an aromatic aldehyde react with an aryl methyl ketones in the presence of a base to form an α,β -unsaturated ketone (enone). In the initial step, chalcones were synthesized by condensing 3-hydroxyl-4-difluoromethoxy phenyl carboxaldehyde with aromatic ketones in the presence of ethanolic sodium hydroxide solution at room temperature (3a–3i). Isoxazoles (4a–4i) were synthesized via cyclocondensation with hydroxylamine hydrochloride. The purity of the compounds was checked via TLC. And aslo checked via spectral analysis 1H NMR, IR and Mass Spectroscopy.
Physical data of compounds (4a-4i) are represented in Table no. 1

Table 1.

Sr. No.	Ar	Molecular Formula	M.W.	M.P. ^{O}C	Yield %	% of Nitrogen	
						Calculated	Found
4a	C_6H_5 -	$C_{16}H_{13}F_2NO_3$	306	212	77	4.59	4.53
4b	4- CH_3-C_6H_4 -	$C_{17}H_{15}F_2NO_3$	320	186	87	4.39	4.31
4c	4- OCH_3-C_6H_4-	$C_{17}H_{15}F_2NO_4$	336	171	78	4.18	4.16
4d	2- OCH_3-C_6H_4-	$C_{17}H_{15}F_2NO_4$	336	150	72	4.18	4.11
4e	4-Cl-C_6H_4 -	$C_{16}H_{13}ClF_2NO_3$	340	134	69	4.33	4.15
4f	4-F-C_6H_4 -	$C_{16}H_{12}F_3NO_3$	324	178	64	4.12	4.08
4g	4-Br-C_6H_4 -	$C_{16}H_{12}BrF_2NO_3$	385	144	73	3.65	3.59
4h	C_4H_3S- 2-Thiophenyl	$C_{14}H_{11}F_2NO_3S$	312	164	55	4.50	4.48
4i	C_5H_4N- 3-Pyridinyl	$C_{15}H_{12}F_2N_2O_3$	307	149	61	9.15	9.03

Antimicrobial screening activities of synthesized compounds (4a-4i) in MIC (µg/mL) are represented in Table no. 2.

Table 2.

Compounds Id	Antibacterial Activity				Antifungal Activity
	Gram-positive bacteria		Gram-negative bacteria		
	S. aureus	*M. luteus*	*E. coli*	*S. aureus*	*M. luteus*
4a	80	80	160	160	160
4b	80	80	160	80	160
4c	160	80	80	40	40
4d	40	80	40	40	40
4e	40	80	40	40	40
4f	160	80	80	160	160
4g	80	40	80	40	80
4j	80	160	160	160	160
4i	40	80	80	40	40
Ampicillin	20	20	40	20	-
Fluconazole	-	-	-	-	10

4. CONCLUSION

From the result of biological evaluation, it has been observed that the compounds exhibited interesting biological activity, however with a degree of variation. Most of the compounds tested were found to have comparable antibacterial and exhibit low antifungal activity. From the Table 4, it can be observed that compounds 4c, 4g and 4i were moderate active against *S. aureus* A, *S. aureus, M. luteus, Escherichia coli* , *S. thyphi., C. albicans*. Compound 4d and 4e were give promising activity against *S. aureus* A, *S. aureus, M. luteus, Escherichia coli* , *S. thyphi., C. albicans*.

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