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Synthesis and Antimicrobial Screening of 3-aryl-5′-{[(3′-Difluoromethoxy)-5′-(3″-Methyl)-4″-(2‴, 2‴, 2‴-Trifluoroethoxy) Pyridin-2″-Yl] Methoxyphenyl}-4,5-Dihydroisoxazoles.

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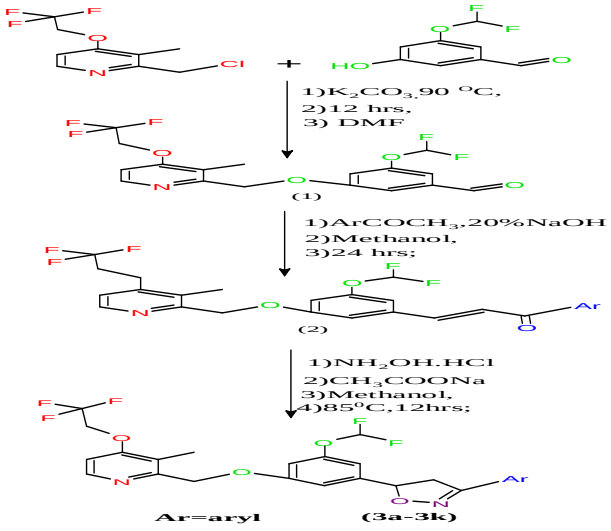
Abstract: ***Isoxazole derivatives showed good therapeutic and biological activities. In view of getting to synthesized 3-aryl-5-{[(3'-difluoromethoxy)-5'-(3''-methyl)-4''-(2‴,2‴, 2‴-trifluoroethoxy)pyridin-2''-yl]methoxy phenyl}-4,5-dihydroisoxazoles (3a-3k) by the cyclo condensation of (E)-3-{[(3'-difluoromethoxy)-5'-(3''-methyl)-4''-(2‴,2‴, 2‴-trifluoroethoxy)pyridine-2''-yl]methoxy phenyl}-1-aryl- prop- 2- ene- 1- ones with hydroxylamine hydrochloride. All Synthesized compounds characterized by TLC, IR, [1]HNMR, Mass spectra and elemental analysis. All the synthesized compounds screened for their antimicrobial activity against Gram +ve bacteria (B.mega, B.Subtillis) Gram –Ve bacteria (E.coli, P.fluorescens) and fungi (A.awamori).***

Keywords: Isoxazoles, Anti-microbial activity; (Heterocyclic Compounds)

I. INTRODUCTION

Five-membered ring systems containing one oxygen and one nitrogen atom adjacently are isoxazole. The parent ring system (unsaturated), Isoxazole is historically old and an isolated compound, but not identified until 1888. Claisen was the first to identify isoxazole and named as “monazole” in 1888. Hantszch modified the name “monazole” to “isoxazole”. The partially saturated systems isoxazolines are known in the literature since 1898. Studies on isoxazole systems are extensive, due to their versatility in chemical synthesis of a variety of compounds as well as in their usefulness in several fields such as agriculture, medicine and industry. Claisen was the first reported the product from the reaction of 1,3-diketone with hydroxylamine.[1] The next important contribution to the chemistry of Isoxazoles was made by A. Quelico [2] in 1945, when he began to study the formation of isoxazoles from nitrile N-oxide and unsaturated compounds. A large number of substituted isoxazoles derivatives shows tested variety of biological activity such as , Antibacterial [3,4], Anticonvulsant [5,6] Anticholestermic [7], Anticancer [8] , Anthelmintics [9] , Anti inflammatory [10-14] , Adenosine antagonist [15],Fungicidal [16,17], Hypoglycemic1[18] etc. In view of getting to synthesized isoxazole derivatives

II. REACTION SCHEME



3-aryl-5-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridin-2″-yl] methoxyphenyl}-4,5-dihydro isoxazoles.(3a-3k) have been synthesized by the condensation of (E)-3-{[(3′-Difluoro methoxy)-5′-(3″-methyl) -4″-(2‴,2‴,2‴-tri fluoroethoxy) pyridine-2″-yl] methoxy phenyl}-1-aryl-prop-2-ene-1-ones with hydroxyl amine hydrochloride in presence of sodium acetate. The products (3a-3k) were assigned the IR,[1]HNMR, Mass spectral data, TLC and elemental analysis and evaluated their antimicrobial activities. The physical data and antimicrobial activities are represented in TABLE-I.

III. ANTIMICROBIAL ACTIVITY

3-Aryl-5-{[(3′-difluoromethoxy) -5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoro ethoxy)pyridin-2″-yl]methoxyphenyl}-4,5-di hydroisoxazoles (3a-3k) have been synthesized. Products were evaluated in vitro for their antimicrobial activity against Gram +ve bacteria like B.Mega, B.Subtilis Gram –ve bacteria like E.coli, P.fluorescens. Fungi as A.awamori using DMF as solvent at 50µg/ml. concentration by cup-plat method [19]. After 24 hrs. of incubation at 37 °C, The zones of inhibition were measured in mm. The activity was compared with the known standard drugs, viz, Ampicilin, Chloram phenicol , Norfloxacin and Gresiofulvin at same concentration.

All synthesized compounds (3a-3k) showed moderate to good and remarkable activities with compare to known standard drugs at the same concentration, which represent in TABLE-I. The comparable antimicrobial activity are represented in TABLE-II.

A. Synthesis of 3-Difluoromethoxy-5-{[(3 "-methyl)-4'-(2",2",2"-trifluoroethoxy)py ridin-2"- yl]methoxyphenyl}carbaldehyde.

A mixture of 2-(chloromethyl)-3-methyl-4-(2′,2′,2′-trifluoroethoxy)pyridine hydrochloride(11.67g, 32.8 mol), potassium carbonate(13.61g,98.6mol) and 3-(difluoro methoxy)-5-hydroxybenzaldehyde (5.0g, 32.8 mol) in DMF (50 ml) was stirred for 12 hrs at 90 °C. After completion of the reaction, the reaction mixture was poured in to ice cold water (500 ml). The precipitates obtained were filtered to get required product. Yield 75.25% (off white solid); m.p 128 °C, Anal. Calcd. for ($C_{17}H_{14}F_5NO_4$: required; C: 52.18, H: 3.61, N: 3.58 Found: C: 52.12, H: 3.57, N: 3.51%).IR (KBr,cm^{-1}): 2958(C-Hstr.,asym) ; 2839 (C-Hstr.,Sym); 3033(C-Hstr.,Aromatic);1739(C=Ostr., ketone); 1043(C-Fstr.,Halide) ^{1}H-NMR (DMSO-d_6,δ ppm): 9.83 (s, 1H, -CHO), 8.33-8.34 (d, 1H, *J* = 5.6 Hz, aromatic), 7.50-7.52 (d, 1H, *J* = 8.4 Hz, aromatic), 7.39 (s, 1H, aromatic), 7.29-7.31 (d, 1H, *J* = 8.4 Hz, aromatic), 7.13-7.15 (d, 1H, *J* = 5.6 Hz, aromatic), 5.28 (s, 2H, -O-CH_2-), 4.86-4.93 (q, 2H, -O-CH_2-CF_3), 2.19 (s, 3H, -CH_3); MS : (m/z) 391.2 (M^+);

B. Synthesis of (E)-3-{[(3′-Difluorometho xy)-5′-(3"-methyl)-4"-(2‴,2‴,2‴-trifluoro ethoxypyridine-2"-yl]methoxyphenyl}-1-(4''''-methoxyphenyl)-prop-2-ene-1-one.

To a solution of 3-Difluoromethoxy-5-{[(3″-methyl)-4′-(2‴,2‴,2‴-trifluoro ethoxy)pyridin-2″-yl]methoxyphenyl}-1-carboxaldehyde (3.91gm, 0.01m) in methanol was added 4-methoxy aceto phenone (1.50gm, 0.01m) followed by catalytic amount of 20% aqueous NaOH solution and the reaction mixture was stirred for 24 hrs. at room temperature. Completion of reaction checked with TLC. The reaction mixture was poured into crushed ice, filtered and dried. Yield 85.75 % (light yellow solid); m.p 148OC Anal.Calcd for C26H22F5NO5; Required: C, 59.66; H, 4.24; N, 2.68; found : C, 59.60; H, 4.17; N, 2.62%), IR (KBr, cm-1): 2958(C-H str., asym);1456,(C-H def.,asym);2839(C-H str.,Sym);3079(C-Hstr.,Aromatic);1577 (C=Cstr.,Aromatic);1656(C=Ostr.,ketone); 3046(CH=CH str .,Vinayl);1220 (C-N.,str); 1253(C-O-C str., ether); 1043 (C-F str., Halide), 1HNMR (DMSO-d6);3.7(s,2H-CH2);7.8-7.9(s,2H-Ar-H);7.2-7.6(s,4H-Ar-H);(s,3H-O-CH3). MS; m/z; 41, 78, 191, 344, 418, 524. Similarly other chalcones have been synthesized.

C. Synthesis of 3-(4''''-methoxyphenyl)- 5-{[(3′-difluoromethoxy)-5′-(3"-methyl)-4"-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2"-yl]methoxyphenyl}-4,5-dihydroisoxazoles.

A mixture of (E)-3-{[(3′-difluoro methoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-tri fluoroethoxy)pyridin-2″-yl]methoxyphenyl} -1-(4''''-methoxyphenyl)prop-2-ene-1-one. (0.5gm, 1.09 mol) and hydroxylamine hydrochloride(0.15gm, 2.18 mol) in methanol (50 ml) were added. The reaction mixture was refluxed at 85°C for 12 hrs. The product was isolated and crystallised from MeOH. Yield 76.15 %, m.p. 162 °C. Anal.Calcd for $C_{26}H_{23}F_5N_2O_5$; Required: C, 57.99; H, 4.31; N, 5.20%; found: C, 57.93; H, 4.25; N, 5.15%) IR(KBr):2962(C-Hstr.,asym);1456,(C-H def.,asym);2866(C-Hstr.,Sym);3062 (C-Hstr.,Aromatic) ; 1579 (C=C.,str) ;1650 (C=N str.,Isoxazole) ; 817
(N-Ostr.,isoxazole) ; 2738 (CH2-CH2-str., isoxazole);1220(C-N str.,arom-amine); 1255(C-O-Cstr.,ether) ;1028(C-F str ., Halide), ^{1}HNMR(DMSO-d6);3.7(s,2H.,-CH_2);3.8(s,2H.,-CH2);7.8-7.9(s,2H.,Ar-H);7.2-7.6(s,4H.,Ar-H);6.8-7.5(s,3H.,Ar-H);3.3(s,3H.,O-CH_3) m/z; 41, 78, 191, 221, 319,377,422,436,539.

Similarly other 3-aryl-5-{[(3′-difluoro methoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-tri fluoroethoxy)pyridin-2″-yl]methoxyphenyl} -4,5-

dihydroisoxazoles (3a-3k),compounds were synthesized. The physical data and antimicrobial activity represented in TABLE NO.-01 and TABLE NO.-02.

TABLE-01 : The Physical data and antimicrobial activities of compounds. (3a-3k)

Sr No.	Ar	Moleculer Formula	M.P. °C	Antibacterial activity				Antifungal activity	% Yield	% of Nitrogen	
				B.mega.	B.subtillis	E.coli.	P.fluorescens	A.awamori		Cald.	Found
3a	4-$OCH_3.C_6H_4$-	$C_{26}H_{23}F_5N_2O_5$	162	18	17	18	18	19	76.15	5.20	5.15
3b	2-$OH.C_6H_4$-	$C_{25}H_{21}F_5N_2O_5$	136	17	16	17	21	18	82.15	5.34	5.29
3c	3-$OH.C_6H_4$-	$C_{25}H_{21}F_5N_2O_5$	167	19	19	20	19	18	80.45	5.34	5.28
3d	4-$OH.C_6H_4$-	$C_{25}H_{21}F_5N_2O_5$	107	21	20	21	22	21	79.75	5.34	5.30
3e	3-$NO_2.C_6H_4$-	$C_{25}H_{20}F_5N_3O_6$	132	16	16	18	16	17	78.45	7.59	7.53
3f	4-$NO_2.C_6H_4$-	$C_{25}H_{20}F_5N_3O_6$	126	18	21	21	23	20	75.95	7.59	7.54
3g	2-Cl. C_6H_4-	$C_{25}H_{20}ClF_5N_2O_4$	141	22	16	17	16	17	83.00	5.16	5.12
3h	4-Cl. C_6H_4-	$C_{25}H_{20}ClF_5N_2O_4$	159	23	17	17	18	20	78.50	5.16	5.12
3i	4-Br. C_6H_4-	$C_{25}H_{20}BrF_5N_2O_4$	136	22	19	18	17	22	79.50	4.77	4.72
3j	4-$CH_3.C_6H_4$-	$C_{26}H_{23}F_5N_2O_4$	185	19	15	17	19	17	78.75	5.36	5.30
3k	3-$NH_2.C_6H_4$-	$C_{25}H_{22}F_5N_3O_3$	143	17	18	21	18	19	76.75	8.03	7.98

TABLE 2: Compound showing comparable antimicrobial activity with known standard drugs:-

	Compounds	Antibacterial activity Zone of inhibition in mm.				Antifungal activity Zone of inhibition in mm.
		B. mega.	B. subtillis	E. coli.	P. fluorescens	A. awamori
	(3a-3k)	3d	3c	3c	3d	3d
		3g	3d	3d	3b	3f
		3h	3f	3f	3f	3h
		3i	3i	3k	-	3i

Activity of Standard drugs

		B. mega.	B. subtillis	E. coli.	P. fluorescens	A. awamori
1	Ampicilin (50 µg)	24	19	18	27	-
2	Chloramphenicol (50 µg)	23	18	23	23	-
3	Norfloxacin (50 µg)	23	20	24	25	-
4	Griseofulvin (50 µg)	-	-	-	-	23

IV. SUMMARY

3-aryl-5-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-4,5-dihydro isoxazoles (3a-3k) have been synthesized. The compounds 3d,3f,3i show good remarkable antibacterial and antifungal activity with compare to known standard drugs e.g. Ampicilin, Chloramphenicol, Norfloxacin and Griseofulvin at same concentration 50 µg/ml.

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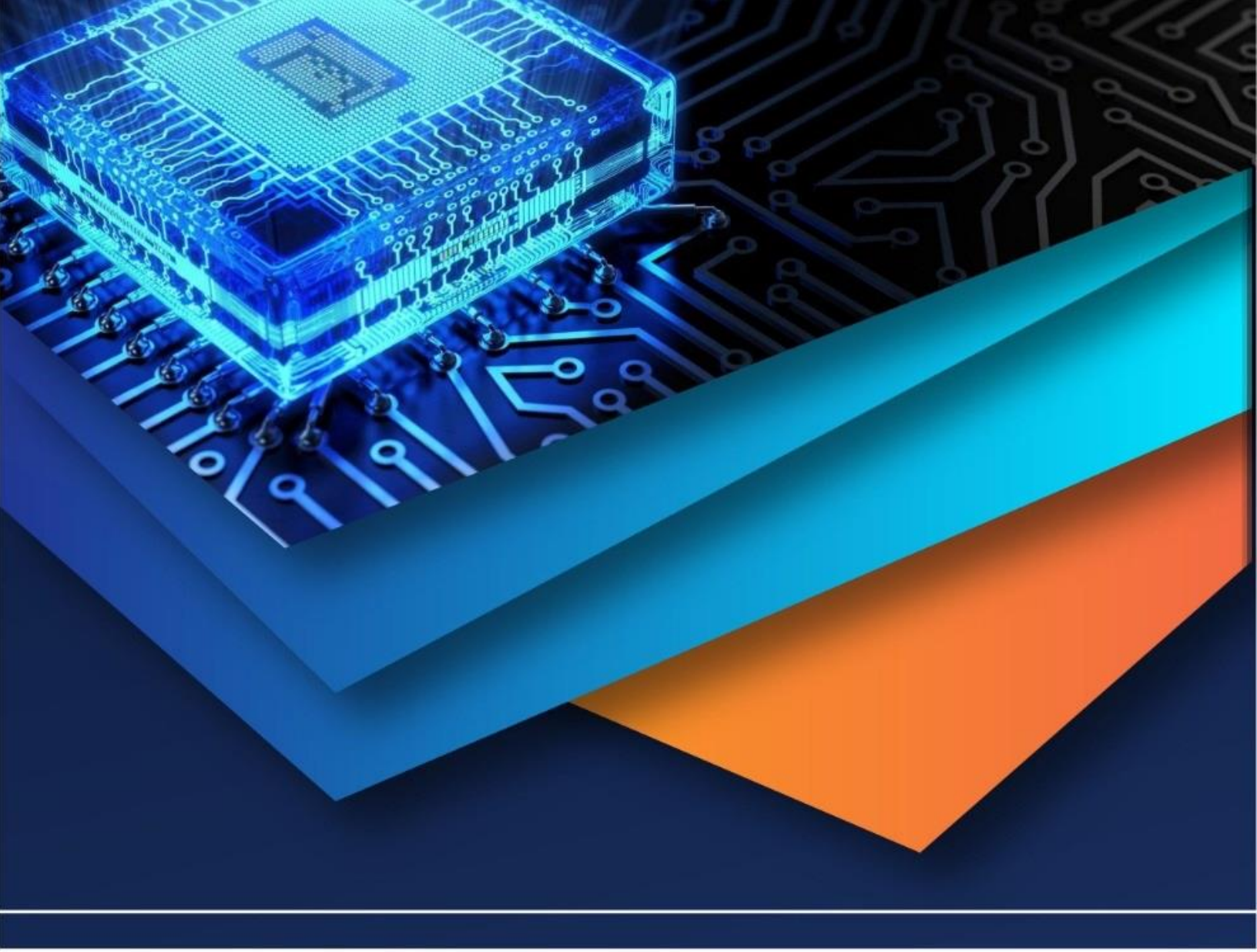

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