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SYNTHESIS AND BIOLOGICAL SCREENING OF 3-ARYL-5-{[(3′-DIFLUOROMETHOXY)-5′-(3′′-METHYL)-4′′-(2′′′,2′′′,2′′′-TRIFLUOROETHOXY)PYRIDIN-2′′-YL] METHOXYPHENYL}-3,4-DIHYDROPYRAZOLES

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ABSTRACT:-

Pyrazoles derivatives shows good biological and therapeutic activities, With a view of getting to synthesized 3-Aryl-5-{[(3′-difluoromethoxy)-5′-(3′′-methyl)-4′′-(2′′′,2′′′,2′′′-trifluoro ethoxy)pyridin-2′′-yl]methoxyphenyl}-3,4-dihydropyrazoles(5a-5k) by the condensation of (E)-3-{[(3′-difluoromethoxy)-5′-(3′′-methyl)-4′′-(2′′′,2′′′,2′′′-trifluoroethoxy)pyridine-2-yl]methoxyphenyl}-1-aryl-prop-2-ene-1-ones (4a-4k) with hydrazine hydrate in methanol .All synthesized compounds characterized by TLC, IR, ^{1}HNMR, Mass spectra and physical constants. 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:-

3-Aryl-5-{[(3′-difluoromethoxy)-5′-(3′′-methyl)-4′′-(2′′′,2′′′,2′′′-trifluoro ethoxy)pyridin-2′′-yl]methoxyphenyl}-3,4-dihydropyrazoles,(E)-3-{[(3′-Difluoromethoxy)-5′-(3′′-methyl)-4′′-(2′′′, 2′′′, 2′′′-trifluoroethoxy) pyridin-2′′-yl]methoxy phenyl}-1-aryl-prop-2-ene-1-ones, Methanol hydrazine hydrate, (Heterocyclic Compounds)

INTRODUCTION:-

Nitrogen containing five member heterocycles, pyrazolines have proved to be the most useful frame work for biological activities. The chemistry of pyrazoline was reviewed by Jarobe in 1967. The chemistry of pyrazolines[i], which have been studied extensively for their biodynamic behavior. A large number of substituted 2-Pyrazole derivatives showed pharmaceutical and biological activity such as Antimicrobial[ii], Antiinflammatory[iii,iv], Antiallergic[v],Anticonvulsant and Antidepressant[vi], Antidiabetic[vii], Antiimplantation[viii],Antitumor[ix],Antineoplastic[x],Analgesic[xi,xii],Fungicidal[xiii,xiv],Bactericidal[xv,xv i],Herbicidal[xvii],Cardiovascular[xviii], Antiamoebic[xix], Tranquilizer[xx]. In view of getting to synthesized pyrazole derivatives.

EXPERIMENTAL: Purity of all the compounds was checked on silica gel G plates using iodine vapour as the detecting agent. Melting points were determined in open capillary tubes using Royal Scientific melting point apparatus. IR spectra were recorded Instrument: SHIMADZU-FT-IR-8400, Spectrophotometer, frequency range: 4000-400cm^{-1} (KBr disc)[xxi,xxii], ^{1}HNMR spectra were recorded on Instrument: 400 MHz BrukerAvance- III, using TMS, Solvent DMSO-d6, (chemical shifts are recorded in δ ppm).The mass spectra were recorded on Water mass spectrometer. Physical data of the compounds are recorded in Table NO-I

[A] Synthesis of 3-Difluoromethoxy-5-{[(3″-methyl)-4′-(2″,2″,2″-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}carbaldehyde.(3)

A mixture of 2-(chloromethyl)-3-methyl-4-(2′,2′,2′-trifluoroethoxy)pyridine hydro chloride(11.67g, 32.8 mol), potassium carbonate (13.61g, 98.6 mol) and 3-(difluoromethoxy)-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,

[B] Synthesis of (E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridin-2″-ylmethoxyphenyl}-1-(4⁗-methoxyphenyl)-prop-2-ene-1-one.(4a)

To a solution of 3-Difluoro methoxy-5-{[(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridin-2″-yl]methoxyphenyl}-1-carboxaldehyde(3.91gm, 0.01m) in methanol was added 4-methoxy acetophenone (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 148°C

[C] Synthesis of 3-(4⁗-methoxyphenyl)-5-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-3,4-dihydropyrazole.(5a)

A solution of (E)-3-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1-(4⁗-methoxyphenyl)-prop-2-ene-1-one,Chalcone(0.5gm, 1.09 mol) in methanol (5 ml) was added hydrazine hydrate (0.11 ml, 2.18 mol) and heated to reflux at 78°C for 8 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 toagiveapureproduct asasolid. Yield 75.85%, m.p. 138°C.($C_{26}H_{24}F_5N_3O_4$Required: C, 58.10; H, 4.50; N, 7.82; Found : C,58.04, H,4.35, N.7.77%)

RESULTS AND DISCUSSION:-

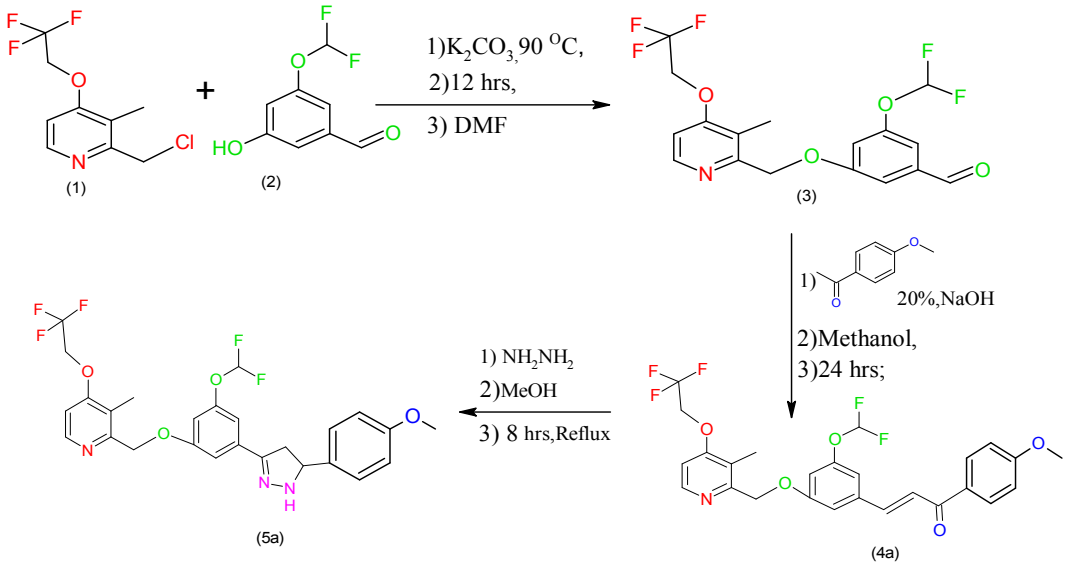
IR spectra 3-Difluoromethoxy-5-{[(3″-methyl)-4′-(2″,2″,2″-trifluoroethoxy)pyridin-2″-yl] methoxyphenyl}carbaldehyde.(KBr,cm^{-1}):2958(C-Hstr.,asym);,2839(C-Hstr.,Sym);1739(C=O str., ketone), 3033(C-Hstr.,Aromatic); 1043(C-Fstr., Halide),; ^{1}H-NMR (DMSO-d_6,δ ppm): 9.83 (s, 1H, -CHO), 8.33-8.34 (d, 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); In MS : (m/z) 391.2 (M^+) was observed; 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 spectra of(E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridin-2″-ylmethoxyphenyl}-1-(4‴′-methoxyphenyl)-prop-2-ene-1-one. IR(KBr cm^{-1}); 2958(C-Hstr.,asym);1456,(C-Hdef.,asym);2839(C-Hstr.,Sym);3079(C-Hstr.,Aromatic);1577(C=Cstr., Aromatic);1656(C=Ostr.,ketone); 3046 (CH=CHstr .,Vinayl);1220 (C-N.,str) ;1253 (C-O-Cstr., ether); 1043 (C-Fstr., Halide) ,^{1}HNMR (DMSO-d6);3.7(q,2H,O-CH_2-CF_3);7.8-7.9(d,2H,Ar-H);7.2-7.6(m,4H,Ar-H);2.5(s,3H,Ar-CH_3);3.3(s,3H,-O-CH_3).In MS: m/z; 41,78,191,344,418, 524(M^+) was observed.. Anal.Calcd for $C_{26}H_{22}F_5NO_5$; Required: C, 59.66; H, 4.24; N, 2.68; found : C, 59.60; H, 4.17; N, 2.62%),

IR spectra of3-(4‴′-methoxyphenyl)-5-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-3,4-dihydropyrazole.(3a) IR(KBrcm^{-1}):2935(C-Hstr.,asym);1456(C-Hdef.,asym);2845(C-Hstr.,Sym);3069(C-Hstr.,Aromatic);1579(C=Cstr.,aromatic);3304(N-Hstr.,Pyrazoline);1512(C=Nstr.,Pyrazoline);1188(C-O-Cstr.,ether);1107(C-Fstr.,Halide)^{1}HNMR(DMSO-d6);3.7(q,2H.,O-CH_2-CF_3);3.8(s,2H.,O-CH_2);7.8-7.9(d,2H.,Ar-H);7.6(s,3H.,Ar-H);2.5(s,3H.,Ar-CH_3);7.2-7.6(m,4H.,Ar-H);3.3(s,3H.,O-CH_3) ;2.7-2.8(d,2H.,CH-CH_2); 4.8((s,1H.,O-CH-F_2);6.5-7.0(s,1H.,Ar-NH), In MS m/z; 42, 78,108,123,144, 205,313,363,377,405,431,507,523,538(M^+) was observed.

REACTION SCHEME:-



Similarly other 3-Aryl-5-{[(3′-difluoromethoxy)-4′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-3,4-dihydropyrazoles(5a-5k), Compounds have been synthesized and the reaction scheme below shows in Graphical abstract. The physical data and antimicrobial activity represented in TABLE-NO.-I.

ANTIMICROBIAL ACTIVITY:-

3-Aryl-5-{[(3′-difluoromethoxy)-4′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-

yl]methoxyphenyl}-3,4-dihydropyrazoles(5a-5k), 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 [xxiii]. After 24 hrs.of incubation at 37 ^{o}C, the zones of inhibition were measured in mm. The activity was compared with the known standard drugs, viz, Ampicilin, Norfloxacin Chloramphenicol and Gresiofulvin at same concentration.
The comparable antimicrobial activity are represented in TABLE-II.

TABLE-I : The Physical data and antimicrobial activities of compounds. (5a-5k)

Sr No.	Ar	Moleculer Formula	M.P. ^{o}C	Antibacterial activity				Antifungal activity	% Yield	% of Nitrogen	
				B.mega.	*B.subtilis*	*E.coli.*	*P.fluorescens*	*A.awamori*		Cald.	Found
3a	4-$OCH_3.C_6H_4$-	$C_{26}H_{24}F_5N_3O_4$	138	18	16	17	18	**21**	75.85	7.82	7.77
3b	2-OH. C_6H_4-	$C_{25}H_{22}F_5N_3O_4$	129	**21**	15	19	**21**	19	79.30	8.03	7.96
3c	3-OH. C_6H_4-	$C_{25}H_{22}F_5N_3O_4$	254	20	**18**	18	19	**22**	76.50	8.03	7.97
3d	4-OH. C_6H_4-	$C_{25}H_{22}F_5N_3O_4$	165	**22**	**19**	**20**	**22**	**20**	78.75	8.03	7.98
3e	3-NO_2. C_6H_4-	$C_{25}H_{21}F_5N_4O_5$	138	20	15	17	19	17	81.85	10.14	10.08
3f	4-NO_2. C_6H_4-	$C_{25}H_{21}F_5N_4O_5$	148	18	16	**19**	18	19	77.50	10.14	10.09
3g	2-Cl. C_6H_4-	$C_{25}H_{21}ClF_5N_3O_3$	170	20	**18**	18	**21**	**20**	76.25	7.75	7.70
3h	4-Cl. C_6H_4-	$C_{25}H_{21}ClF_5N_3O_3$	243	19	17	16	17	18	76.25	7.75	7.71
3i	4-Br. C_6H_4-	$C_{25}H_{22}BrF_5N_3O_3$	98	**22**	**20**	**23**	**22**	**21**	79.85	7.17	7.12
3j	4-CH_3. C_6H_4-	$C_{26}H_{24}F_5N_3O_3$	183	16	18	15	17	19	82.50	8.06	8.00
3k	3-NH_2. C_6H_4-	$C_{25}H_{23}F_5N_4O_3$	149	**22**	**19**	**19**	**20**	17	76.50	10.72	10.67

TABLE II: Compounds 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*
	(5a-5k)	5b	5c	5d	5b	5a
		5d	5d	5f	5d	5c
		5i	5g	5i	5g	5d
		5k	5i	5k	5i	5g
			5k	-	5k	5i
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	26	-
4	Griseofulvin (50 µg)	-	-	-	-	23

SUMMARY:-

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

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