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AN EFFICIENT AND FACILE SYNTHESIS OF 2-AMINO-4-ARYL-6-{[(3′-DIFLUOROMETHOXY)-5′-(3″-METHYL) -4″-(2‴,2‴,2‴-TRIFLUOROETHOXY)PYRIDIN-2″-YL]METHOXYPHENYL}-1-6-DIHYDROPYRIMIDINES AND ITS ANTIMICROBIAL EVALUATION

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ABSTRACT: Pyrimidine derivatives gave good biological activity and therapeutic activities, With a view of getting to synthesized 2-Amino-4-aryl-6-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1-6-dihydropyrimidines(3a-3k) by the condensation of (E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1-aryl-prop-2-ene-1-ones with guanidine hydro chloride in presence of alcoholic KOH. 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:
2-Amino-4-aryl-6-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1-6-dihydropyrimidines,(E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1-aryl-prop-2-ene-1-ones.

INTRODUCTION: Pyrimidine derivatives shows good biological and therapeutic activities such as Antitubercular[i],Antidiabetic[ii],Anticonvulsant[iii],Fungicidal[iv],Insecticidal[v], Analgestic[vi], Tranquilizing[vii],Antibacterial[viii],Diuretic[ix]andAntihypertensive[x]etc.Pyrimidine and their derivatives like **uracil**, **thymine** and **cytosine** occur widely in nature showing remarkable pharmaceutical importance because of their diverse pharmacological activities. Pyrimidine derivatives which occurs in natural products[xi]. Like nucleic acid, vitamin-B and having remarkablepharmaceutical importance because of their broad spectrum of biological activitiesSeveral analogues of nucleic acid have been used as a compound that interferes with the synthesis and function of nucleic acids, an example is fluorouracil which has been usedin cancer treatment. Pyrimidine's are among those molecules that make like possible as being some of the building blockers of DNA and RNA.Pyrimidine is considered to be a resonance

hybrid of the charged anduncharged canonical structures, its resonance energy has been found to be less than benzene or pyridine.

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)[xiii,xiv], ^{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.

A mixture of 2-(chloromethyl)-3-methyl-4-(2′,2′,2′-trifluoroethoxy)pyridine hydrochloride(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.

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 2-Amino-4-(4⁗′-methoxyphenyl)-6-{[(3′-difluoromethoxy) -5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1,6-dihydro pyrimidine.(3a)

A mixture 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.(0.5gm, 1.09 mol) and guanidine hydrochloride(0.166gm, 2.18 mol) in methanol (15 ml) wasrefluxed in presence of alcoholic KOH for 16 hrs.The excess of solvent was distilled out and the product was poured into crushed ice, the separated solid was filtered out and crystallized from ethanol.Yield 78.15 %, m.p. 158°C

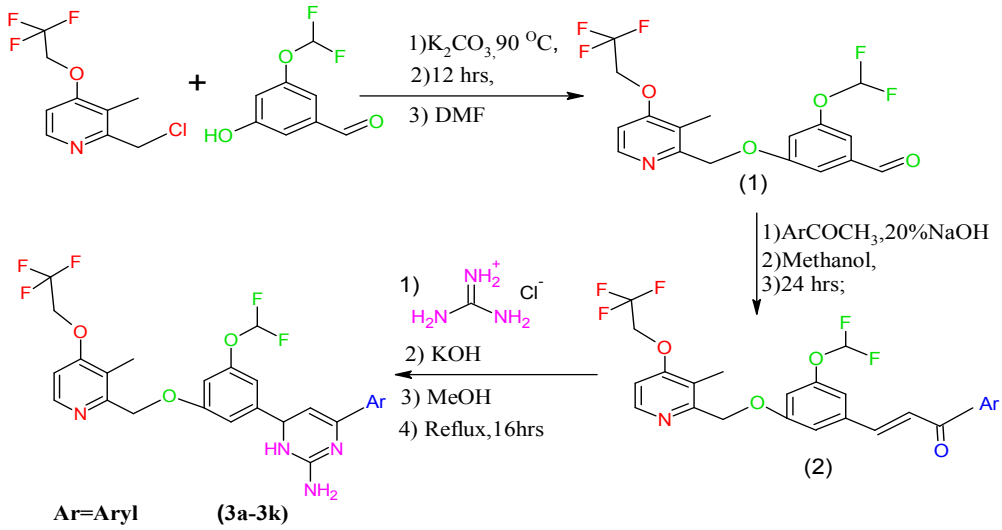
RESULTS AND DISCUSSION:-

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(KBrcm^{-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);(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 of2-Amino-4-(4‴′-methoxyphenyl)-6-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1,6-dihydropyrimidine.(3a) IR(KBRcm^{-1}):2935(C-Hstr.,asym);1458(C-Hdef.,asym);2866(C-Hstr.,Sym);3030(C-Hstr., Aromatic);1581,(C=Cstr.,aromatic);3448(N-Hstr.,pyrimidine);1581(C=Nstr.,pyrimidine);817 (C-Nstr.,pyrimidine);3262(N-H-str.,arom.amine);1255(C-O-Cstr.,ether);1028(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);6.9-7.2 (m,4H.,Ar-H);7.2-7.6(m,4H.,Ar-H);3.3(s,3H.,O-CH_3);6.7(s,2H.,-NH_2),In MS :m/z;41,78,191, 221 ,319,377,422,436,564(M+) was observed.

Reaction scheme:-



Similarly other 2-Amino-4-Aryl-6-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1,6-dihydropyrimidines.(3a-3k),Compounds have been synthesized.The physical data and antimicrobial activity represented in TABLE-NO.-I.

ANTIMICROBIAL ACTIVITY:-

2-Amino-4-aryl-6-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1,6-dihydropyrimidines.(3a-3k)

Productswereevaluated 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 [xii].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, Chloramphenicol, Norfloxacin and Gresiofulvin at same concentration.

The comparable antimicrobial activity are represented in TABLE-II.

TABLE-I : 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-$OCH_3.C_6H_4$-	$C_{27}H_{25}F_5N_4O_4$	158	19	15	18	20	17	78.15	9.92	9.85
3b	2-$OH.C_6H_4$-	$C_{26}H_{23}F_5N_4O_4$	103	19	13	18	19	18	76.25	10.18	10.12
3c	3-$OH.C_6H_4$-	$C_{26}H_{23}F_5N_4O_4$	118	**22**	18	**20**	**23**	**22**	77.35	10.18	10.14
3d	4-$OH.C_6H_4$-	$C_{26}H_{23}F_5N_4O_4$	108	**23**	**19**	**23**	**23**	**20**	78.64	10.18	10.15
3e	3-$NO_2.C_6H_4$-	$C_{26}H_{22}F_5N_5O_5$	98	**24**	16	18	19	18	80.15	12.09	12.02
3f	4-$NO_2.C_6H_4$-	$C_{26}H_{22}F_5N_5O_5$	94	20	18	**20**	20	**22**	75.67	12.09	12.03
3g	2-Cl. C_6H_4-	$C_{26}H_{22}ClF_5N_4O_3$	116	18	16	17	19	19	78.54	9.85	9.80
3h	4-Cl. C_6H_4-	$C_{26}H_{22}ClF_5N_4O_3$	90	19	15	17	**21**	18	81.24	9.85	9.81
3i	4-Br. C_6H_4-	$C_{26}H_{22}BrF_5N_4O_3$	91	**22**	**20**	**22**	**22**	**20**	83.02	9.13	9.08
3j	4-CH_3. C_6H_4-	$C_{27}H_{25}F_5N_4O_3$	99	19	**20**	18	16	17	75.75	10.21	10.17
3k	3-NH_2. C_6H_4-	$C_{26}H_{24}F_5N_5O_3$	112	20	18	**20**	19	**24**	79.15	12.75	12.70

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***
	(3a-3k)	3c	3d	3c	3c	3c
		3d	3i	3d	3d	3d
		3e	3j	3f	3h	3f
		3i	-	3i	3i	3i
		-	-	3k		3k
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

SUMMARY:-
2-Amino-4-Aryl-6-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoro ethoxy)pyridin-2″-yl]methoxyphenyl}-1,6-dihydropyrimidines(3a-3k) have been synthesized. The compounds 3c, 3d, 3f, 3i show good remarkable antibacterial and antifungal activity with compared to known standard drugs e.g.Ampicilin, Chloramphenicol, Norfloxacin and Griseofulvin at same concentration 50 μg/ml.

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