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SYNTHESIS AND BIOLOGICAL SCREENING OF 2-AMINO-6-ARYL-4-{[(3′-DIFLUOROMETHOXY)-5′-(3″-METHYL)-4″-(2‴,2‴,2‴-TRIFLUOROETHOXY)PYRIDIN-2″-YL]METHOXYPHENYL}-4H-PYRAN-3-CARBONITRILES

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ABSTRACT: Cyanopyran derivatives shows good biological and therapeutic activities, With a view of getting to synthesized 2-amino-6-aryl-4-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-4H-pyran-3-carbonitriles(3a-3k) 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 with malononitrile in pyridine. 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-6-aryl-4-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-4H-pyran-3-carbonitriles,(E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1-aryl-prop-2-ene-1-ones,Malononitrile,Pyridine.(Heterocyclic Compounds)

INTRODUCTION: Heterocyclic compounds such as pyran derivatives continue to be a rich source of innovative chemistry because a number of versatile applications in various fields viz. pharmaceuticals, dyes, agrochemicals and sweet smelling substances.insecticide possess this ring system. Pyran ring system is also present in large number of naturally occurring colored compounds, in vitamin-E, hemorrhagic compounds in cloves, in certain alkaloids and other substances. Pyran is a doubly unsaturated six membered ring system with single oxygen as

hetero atom.The two double bonds may be conjugated as α, β or 1,2-pyran or isolated as in α, δor 1,4-pyran.

A large number of substituted pyran derivatives showed pharmaceutical and biological activity such as Anti HIV[i,ii], Antifungal[iii-v], Antiallergic[vi], Analgesic[vii] ,Antagonist[viii,ix], Antitumor[x], CNS active agent[xi], Cytotoxic[xii], Inhibitors of cell proliferation[xiii], Gastric acid secretion inhibitor[xiv], Antimicrobial[xv] and Hypolipidemic[xvi]etc. In view of getting to synthesized cyanopyran derivatives.

EXPERIMENTAL: Purity of all the synthesised 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)[xvii,xviii], ^{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 Instrument. 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 ^{o}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 ^{o}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^{O}C

[C] Synthesis of 2-amino-6-(4⁗-methoxyphenyl)-4-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-4H-pyran-3-carbonitriles.(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 (0.5 gm, 1.09 mol) and malononitrile (0.086gm, 1.31 mol) in pyridine (10 ml), was heated under reflux for 16 hrs on oil bath. The reaction mixture was cooled and concentrated on rotavap. Residue was poured on to crushed ice. The product was neutralized with 20% HCl, product was filtered dried and crystallized from ethanol. Yield 78.35%, m.p.194^{o}C

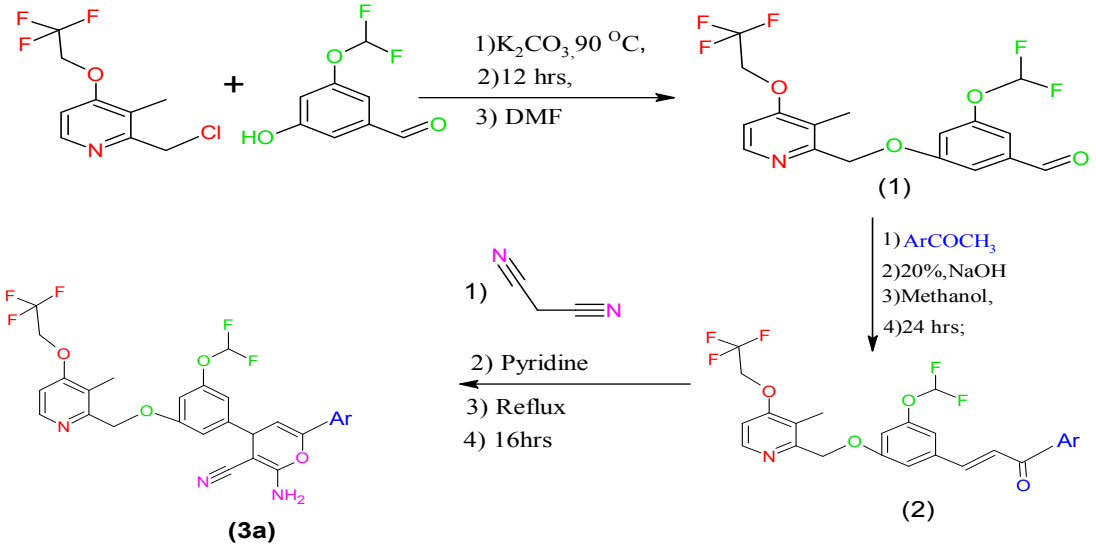
RESULTS AND DISCUSSION:-

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=Ostr., 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);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 of2-amino-6-(4‴-methoxyphenyl)--4-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-4H-pyran-3-carbonitriles.(3a)IR(KBrcm^{-1}):2945(C-Hstr.,asym);1454(C-Hdef.,asym);2837(C-Hstr.,Sym);3066(C-Hstr.,aromatic) ;1598(C=Cstr.,Aromatic);3343(N-Hstr.,Amine);1539(N-Hbending.,Amine);3283(N=Nstr.,PyranNitrile);1226(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);6.9-7.2(broad s,2H.,Ar-NH_2);7.2-7.6(m,4H.,Ar-H);3.3(s,3H.,O-CH_3); 4.8((s,1H.,O-CH-F_2);6.9.7.1(m,2H.,Ar-CH), In MS m/z;43, 78, 41, 78, 102, 193, 253, 295, 327, 472,506,590(M^+) was observed.

REACTION SCHEME:-



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

ANTIMICROBIAL ACTIVITY:-

2-amino-6-aryl-4-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-4H-pyran-3-carbonitriles.(3a-3k) 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 [xix].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, 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	Molecular Formula	M.P. ^{o}C	Antibacterial activity				Antifungal activity	% Yield	% of Nitrogen	
				B.mega.	*B.subtillis*	*E.coli.*	*P.fluorescens*	*A.awamori*		Cald.	Found
3a	4-$OCH_3.C_6H_4$-	$C_{29}H_{24}F_5N_3O_5$	194	11	14	**19**	18	18	78.35	7.13	7.08
3b	2-OH.C_6H_4-	$C_{28}H_{22}F_5N_3O_5$	190	17	14	15	**21**	18	75.50	7.30	7.24
3c	3-OH.C_6H_4-	$C_{28}H_{22}F_5N_3O_5$	203	**18**	17	**19**	**22**	19	82.50	7.30	7.23
3d	4-OH.C_6H_4-	$C_{28}H_{22}F_5N_3O_5$	266	**19**	**18**	**20**	**23**	**21**	80.75	7.30	7.24
3e	3-$NO_2.C_6H_4$-	$C_{28}H_{21}F_5N_4O_6$	259	16	**18**	18	17	16	76.75	9.27	9.21
3f	4-$NO_2.C_6H_4$-	$C_{28}H_{21}F_5N_4O_6$	248	**21**	**20**	**21**	19	16	78.50	9.27	9.22
3g	2-Cl. C_6H_4-	$C_{28}H_{21}ClF_5N_3O_4$	202	16	15	**21**	18	**21**	79.25	7.07	7.02
3h	4-Cl. C_6H_4-	$C_{28}H_{21}ClF_5N_3O_4$	188	17	**18**	16	20	**22**	81.15	7.07	7.01
3i	4-Br. C_6H_4-	$C_{28}H_{21}BrF_5N_3O_4$	163	15	15	18	**22**	**22**	82.85	6.58	6.52
3j	4-$CH_3.$ C_6H_4-	$C_{29}H_{24}F_5N_3O_4$	258	14	15	17	**23**	18	80.50	7.33	7.27
3k	3-$NH_2.$ C_6H_4-	$C_{28}H_{23}F_5N_4O_4$	214	16	15	18	18	17	77.90	9.75	9.69

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	3a	3b	3d
		3d	3e	3c	3c	3g
		3f	3f	3d	3d	3h
			3h	3f	3i	3i
		-	-	3g	3j	-
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-6-aryl-4-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-4H-pyran-3-carbonitriles(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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