WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 7, Issue 1, 1156-1162. Research Article ISSN 2277– 7105

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

Sandip P. Kakadiya, Heta D. Purohit, Asha K. Joshi, Pankaj M. Akbari and Dipak M. Purohit*

*Shree M. & N. Virani Science College, Chemistry Department, Kalawad Road, Rajkot-5, Gujarat, (India).

Article Received on
15 Nov. 2017,

Revised on 05 Dec. 2017,
Accepted on 25 Dec. 2017

DOI: 10.20959/wjpr20181-10576

***Corresponding Author**
Dr. Dipak M. Purohit
Shree M. & N. Virani Science College, Chemistry Department, Kalawad Road, Rajkot-5, Gujarat, (India).

ABSTRACT

Cyanopyridine 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}-nicotinonitriles (3a-3k) by the 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 malononitrile in presence of ammonium acetate. 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: Chacones, Cyanopyridines, Malononitrile, Ammonium acetate (Heterocyclic Compounds).

INTRODUCTION

Pyridine, nucleus has been extensively explored for their applications in the field of medicine, agriculture and industrial field. Although many substituted pyridine derivatives are synthesized by different routes. The pyridine derivatives are prepared by the cyclization of aliphatic raw material. The availability of 3-cyanopyridines, Nicotinamide and nicotinic acid make possible their use as synthetic intermediates.

Most of pyridine derivatives are synthesized by manipulation of pyridine and its simple homologues in a manner similar to chemistry of the benzenoid chemistry. However the simple pyridine compounds are prepared by the cyclization of aliphatic raw materials. In our continuation work in the chemistry of pyridine nucleus, we have undertaken the synthesis of 2-Amino-6-aryl-4-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridin-2″-yl]-methoxyphenyl}-nicotinonitriles via chlacones.

A large number of substituted cyanopyridine derivatives showed pharmaceutical and biological activity such as Antifungal[1], Antiepileptic[2], Antibacterial[3], Anticonvulsant[4], Antitubercular.[5] Analgesic.[6], Insecticidal.[7], Antisoriasis[8] and Antihypertensivix.[9] In view of getting to synthesized cyanopyridine 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)[10,11], ^{1}HNMR spectra were recorded on Instrument: 400 MHz Bruker Avance- 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 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^{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)-4′-(3′′-methyl)-4′′-(2′′′,2′′′,2′′′- trifluoroethoxy)pyridin-2′′-yl]methoxyphenyl}-nicotinonitriles.

A mixture of (E)-3-{[(3′-difluoromethoxy)-5-′(3′′-methyl)-4′′-(2′′′,2′′′,2′′′-trifluoro ethoxy)pyridin-2′′-yl]methoxyphenyl}-1-(4′′′-methoxyphenyl)-prop-2-ene-1-one. (0.5gm, 1.09 mol), Malononitrile (0.086g, 1.31 mol) and ammonium acetate (0.25g, 3.28 mol) in methanol (10 ml) was refluxed for 16 hrs., The content was poured in to crushed ice. The solid was obtained filtered, washed with water and crystallized from dioxane. Yield 78.35%, m.p. 216^{o}C.

($C_{29}H_{23}F_5N_4O_4$; Required : C, 59.39; H, 3.95; N, 9.55; found : C, 59.20; H, 3.25;N, 9.50%)

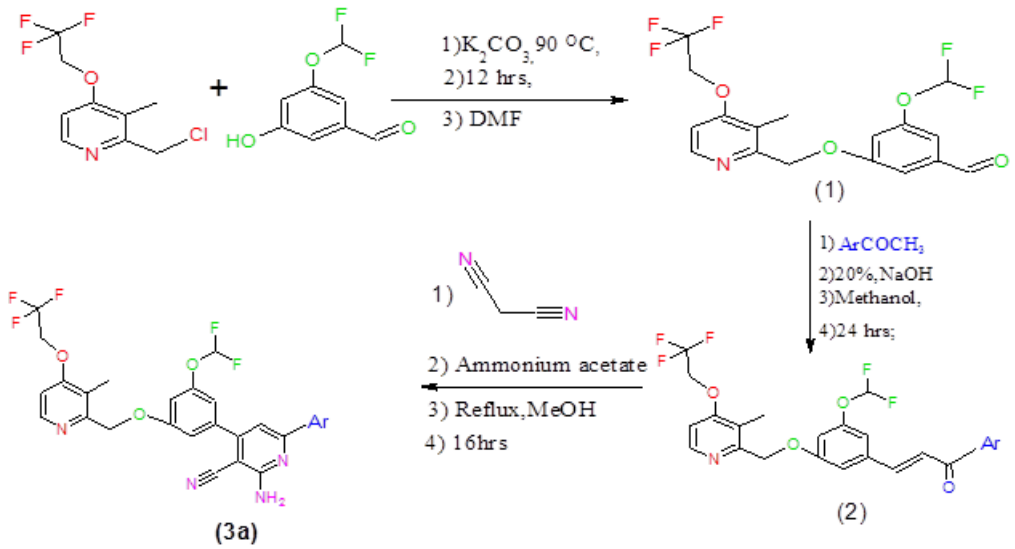
RESULTS AND DISCUSSION

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 of 2-Amino-6--(4′′′-methoxyphenyl**)**-4-{[(3′-difluoromethoxy)-5′-(3′′-methyl)-4′′-(2′′′,2′′′,2′′′-trifluoroethoxy) pyridin-2′′-yl]methoxyphenyl}-nicotinonitriles.(3a) IR(KBrcm^{-1}):2960(C-Hstr.,asym); 1481(C-Hdef.,asym); 2868(C-Hstr.,Sym); 3057(C-Hstr., Aromatic); 1516(C=Cstr.,aromatic); 3357(N-Hstr., Amine);1616(N-Hbending., Amine); 3427(C-Nstr., Pyridinenitrile-NH_2); 1136(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); 6.8-7.2(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);7.5-7.8(s,1H.,Ar-CH), In MS m/z; 42, 78,108, 151, 187,202,348,364,426,480,527,587(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}-nicotinonitriles(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}-nicotinonitriles.(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.[12] 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. (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-$OCH_3.C_6H_4$-	$C_{29}H_{23}F_5N_4O_4$	216	19	17	16	17	19	78.35	9.55	9.50
3b	2-$OH.C_6H_4$-	$C_{28}H_{21}F_5N_4O_4$	172	14	16	15	19	18	75.50	9.79	9.74
3c	3-$OH.C_6H_4$-	$C_{28}H_{21}F_5N_4O_4$	112	17	**18**	18	**20**	19	82.50	9.79	9.73
3d	4-$OH.C_6H_4$-	$C_{28}H_{20}F_5N_4O_4$	174	**20**	**19**	**21**	**20**	**22**	80.75	9.79	9.74
3e	3-$NO_2.C_6H_4$-	$C_{28}H_{20}F_5N_5O_5$	170	**20**	**19**	18	18	**21**	78.85	11.64	11.59
3f	4-$NO_2.C_6H_4$-	$C_{28}H_{20}F_5N_5O_5$	183	**21**	17	**22**	**21**	17	80.50	11.64	11.58
3g	2-Cl. C_6H_4-	$C_{28}H_{20}ClF_5N_4O_3$	199	19	17	**20**	16	15	76.25	9.48	9.43
3h	4-Cl. C_6H_4-	$C_{28}H_{20}ClF_5N_4O_3$	248	**20**	**19**	18	**21**	17	77.25	9.48	9.42
3i	4-Br. C_6H_4-	$C_{28}H_{20}BrF_5N_4O_3$	201	**22**	17	**20**	15	13	80.85	8.82	8.77
3j	4-$CH_3.C_6H_4$-	$C_{29}H_{23}F_5N_4O_3$	149	16	**19**	17	19	18	81.50	9.82	9.77
3k	3-$NH_2.C_6H_4$-	$C_{28}H_{22}F_5N_5O_3$	141	18	14	16	19	**21**	77.50	12.25	12.20

Table II: Compounds showing comparable antimicrobial activity with known standard drugs.

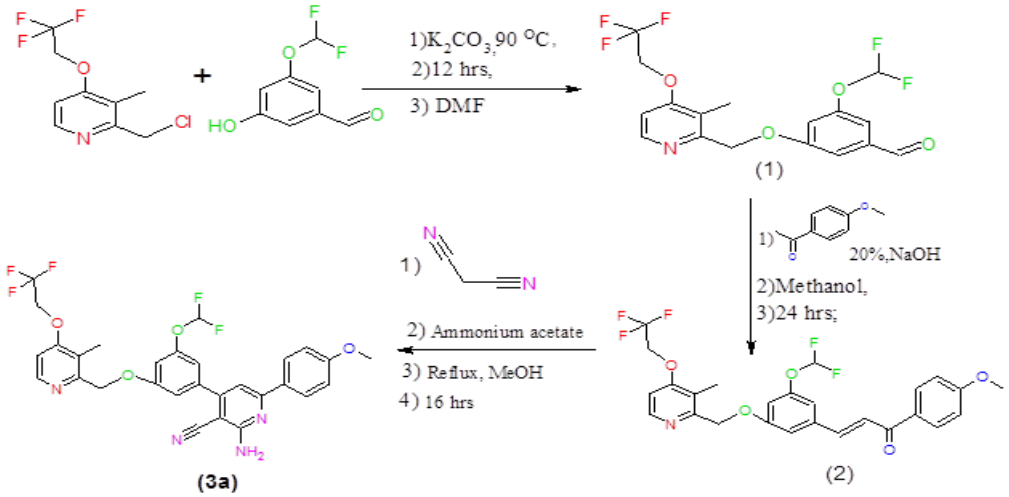
Compounds	Antibacterial activity Zone of inhibition in mm.				Antifungal activity Zone of inhibition in mm.
	B. mega.	*B. subtillis*	*E. coli.*	*P. fluorescens*	*A. awamori*
(3a-3k)	3d	3d	3d	3c	3d
	3e	3e	3f	3d	3e
	3f	3h	3g	3f	3k
	3h	3j	3i	3h	-
	3i	-	-	-	-

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	26	-
4	Griseofulvin (50 µg)	-	-	-	-	23

Graphical Abstract

2-Amino-6-(4′′′′-methoxyphenyl)-4-{[(3′- difluoromethoxy)-5′-(3′′-methyl)-4′′-(2′′′,2′′′,2′′′-trifluoroethoxy) pyridin-2′′- yl] methoxyphenyl}-nicotnonitrile.(3a)



2-Amino-6-aryl-4-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridin-2″-yl] methoxyphenyl}-nicotinonitriles (3a-3k) have been synthesized by the condensation (E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridin-2″-yl] methoxy phenyl}-1-aryl-prop-2-ene-1-ones with malanonitrile and ammonium acetate in MeOH. The products (3a-3k) were assigned by IR, ^{1}HNMR, Mass spectral data, TLC and element analysis.

SUMMARY

2-Amino-6-aryl-4-{[(3′-difluoromethoxy)-5′-(3″-methyl) -4″-(2‴,2‴,2‴-trifluoroethoxy) pyridin-2″-yl] methoxyphenyl}-nicotinonitriles (3a-3k) have been synthesized. The compounds 3d, 3e, 3f, 3h,3i shows 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.

ACKNOWLEDGEMENT

I am thankful to Principal and Management of Shree M. & N. Virani Science College, Rajkot for their kind support and providing chemicals, research facilities and glassware's etc. Also thanks full to Department of chemistry, Saurashtra University, Rajkot for providing spectral analysis.

REFERENCES

1. N. Latif, N. Mishrky and N. S. Girgis,; Indian *J. Chem., 1981; 20B: 147-149.*
2. W. von Behenburg, J. Engel, J. Heese and K. Thiele,; *Ger. Often., D.E.,* 1984; 3: 337,593 *Chem. Abstr.,* 1984; 101: 130595n.
3. L. Castedo, J. M. Quintela and R. Riguers,; *Eur. J. Med. Chem.,* 1984; 19(6): 555.
4. M. R. Pavia, C. P. Taylor, F. M. Hershenson and S. J. Lobbestael,; *J. Med. Chem.,* 1987; 30(5): 1210.
5. W. L. Hoefling, D. Elhaner and E. Reckling,; *VEB Leund-Werke "Walter Ulbricht" Ger.,* 1965; 1(193): 506.
6. Thiele Kurt, Von Be Benburg and Walter E.;*S. African,* 1970; 6: 905,06.
7. B. John E.D., F. M. Peter and Freeman,; *Ger. Often.,* 1971; 2: 029,079 (Cl. A 01 N007d).
8. V. Scott and Joseph,; *Jap. Pat.,* 1979; 2: 803,592; *Chem. Abstr.,* 1980; 92: 47216.
9. J. Baldwin, A. Scrialrine, G.Ponticeello, E. Engelhardt and C. Sweeti,; *J. Het. Chem.,* 1980; 17(3): 425.

10. V. M. Parikh,; "Absorption spectroscopy of organic molecules", Addition-Wesley Pub. Co.London, 1978; 243, 258. A. Hand book of spectroscopic data by B. D.Mishtry; 1st ed. ABD Press, Jaipur 11-36 (2000).
11. A. R. Kartizky and R. Alans Jones,; J. Chem. Soc., 2942 (1960). Introduction of Infra-red and Raman spectroscopy by Norman, B. Colthup, Lowrence H. Daly and Stephan E. Wiberluy. Academic Press (1975).
12. A. L. Barry; *"The Antimicrobial Suceptibility test, principle and practices (ELBS-4th Edition), 1976; 180-193.*