International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor:6.887
Volume 5 Issue X, October 2017- Available at www.ijraset.com

An Efficient and Facile Synthesis of 4-Aryl-2-Hydroxy-6-{[(3′-Difluoromethoxy)-5′-(3″-Methyl)-4″-(2‴, 2‴, 2‴-Trifluoroethoxy) Pyridin-2″-Yl] Methoxyphenyl}-1-6-Dihy Dropyrimidines.

Sandip P. Kakadiya[1], Heta D. Purohit[2], Nutan B. Vekariya[3], Piyush A. Patel[4], Asha K. Joshi[5], Dipak M. Purohit[6]
[1, 2, 3, 4, 5, 6] *Shree M.& N. Virani Science College, Chemistry Department, Kalawad Road,Rajkot-5,Gujarat,(INDIA)*

Abstract: ***Pyrimidine (1:3 Diazine) derivatives showed good biological and therapeutic activities, with a view of getting to synthesized 4-aryl-2-hydroxy-6-{[(3'-Difluoromethoxy)-5'-(3"-methyl)-4"-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2"-yl]methoxyphenyl}-1-6-dihydropyrimidines (3a-3k) by the cyclo 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 urea 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: 4-Aryl-2-hydroxy-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,Aromatic Ketone,Urea(Heterocyclic Compounds)

I. INTRODUCTION

A large number of substituted pyrimidine derivatives showed of biological and pharmacological activities such as, Antitubercular[1], Antidiabetic[2], Anticonvulsant[3] ,Fungicidal [4,] Insecticidal[5], Analgestic[6], Tranquilizing [7],Antibacterial [8],Diuretic[9]and Antihypertensive[10] etc. In view of getting to synthesized (3a-3k) pyrimidine derivatives.

Pyrimidine derivatives which occurs in natural products[11]. Like nucleic acid,vitamin-B and having remarkable pharmaceutical importance because of their broad spectrum of biological activities. Several 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 used in cancer treatment. Pyrimidine's are among those molecules that make like possible as being some of the building blockers of DNA and RNA.

II. 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)[13,14], ^{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 ^{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 4-(4‴-methoxyphenyl)-2- hydroxy-6-{[(3′-Difluoromethoxy)-5′- (3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1-6-dihydro pyrimidines.(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.(0.6gm,1.09mol) Urea(0.104gm,1.09mol) in Methanol (15 ml).The reaction mixture was refluxed 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 product was filtered out and crystallized from ethanol.Yield 71%, m.p.165^{o}C

III. 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 of 4-(4‴-methoxyphenyl)-2-hydroxy-6-{[(3′-Difluoromethoxy)-5′-(3″ -methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-1-6-dihydropyrimidines .(3a)IR(KBRcm-1):2945(C-Hstr.,asym);1454(C-Hdef.,asym);2852(C-Hstr.,Sym);3053(C-Hstr., Aromatic);1539(C=Cstr.,aromatic);3550(N-Hstr.,pyrimidine);1581(C=Nstr.,pyrimidine);3552 (O-Hstr.,Hydroxy);1168(C-O-Cstr.,ether);1028(C-Fstr.,Halide)1HNMR(DMSO-d6);3.7(q,2H.,O-CH2-CF3);3.8(s,2H.,O-CH2);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-CH3);4.9-5.0((s,1H.,Ar-OH);6.7(s,1H.,Ar-NH), In MS m/z;43, 78, 98,109,147,204, 283, 346, 362, 447, 498, 535,566(M+) was observed.

Similarly other 4-Aryl-2-hydroxy-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.

A. Antimicrobial Activity

4-Aryl-2-hydroxy-6-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoro ethoxy) pyridin-2″-yl]methoxyphenyl}-1,6-dihydropyrimidines(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.awamoriusing 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, 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. ^{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-	$C_{27}H_{24}F_5N_3O_5$	165	19	21	16	20	18	71.00	7.43	7.38
3b	2-OH.C_6H_4-	$C_{26}H_{21}F_5N_3O_5$	123	17	16	18	15	19	80.12	7.62	7.56

3c	3-OH.C_6H_4-	$C_{26}H_{21}F_5N_3O_5$	93	21	18	19	22	17	83.50	7.62	7.55
3d	4-OH.C_6H_4-	$C_{26}H_{21}F_5N_3O_5$	87	23	20	21	22	21	76.47	7.62	7.56
3e	3-NO_2.C_6H_4-	$C_{26}H_{21}F_5N_4O_6$	101	18	17	22	20	18	75.95	9.65	9.60
3f	4-NO_2.C_6H_4-	$C_{26}H_{21}F_5N_4O_6$	91	23	18	20	23	20	82.15	9.65	9.61
3g	2-Cl. C_6H_4-	$C_{26}H_{21}ClF_5N_3O_4$	104	16	19	17	18	17	79.55	7.37	7.33
3h	4-Cl. C_6H_4-	$C_{26}H_{21}ClF_5N_3O_4$	108	17	21	19	18	22	80.15	7.37	7.33
3i	4-Br. C_6H_4-	$C_{26}H_{21}BrF_5N_3O_4$	121	22	15	20	21	21	76.85	6.84	6.78
3j	4-CH_3. C_6H_4-	$C_{27}H_{24}F_5N_3O_4$	132	17	15	14	20	18	77.85	7.65	7.60
3k	3-NH_2. C_6H_4-	$C_{26}H_{23}F_5N_4O_4$	135	19	20	17	16	16	76.27	10.18	10.12

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	3a	3d	3c	3d
		3d	3d	3e	3d	3f
		3f	3h	3f	3f	3h
		3i	3k	3i	3i	3i

B. 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

C. Summary

4-Aryl-2-hydroxy-6-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) 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.

IV. 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.

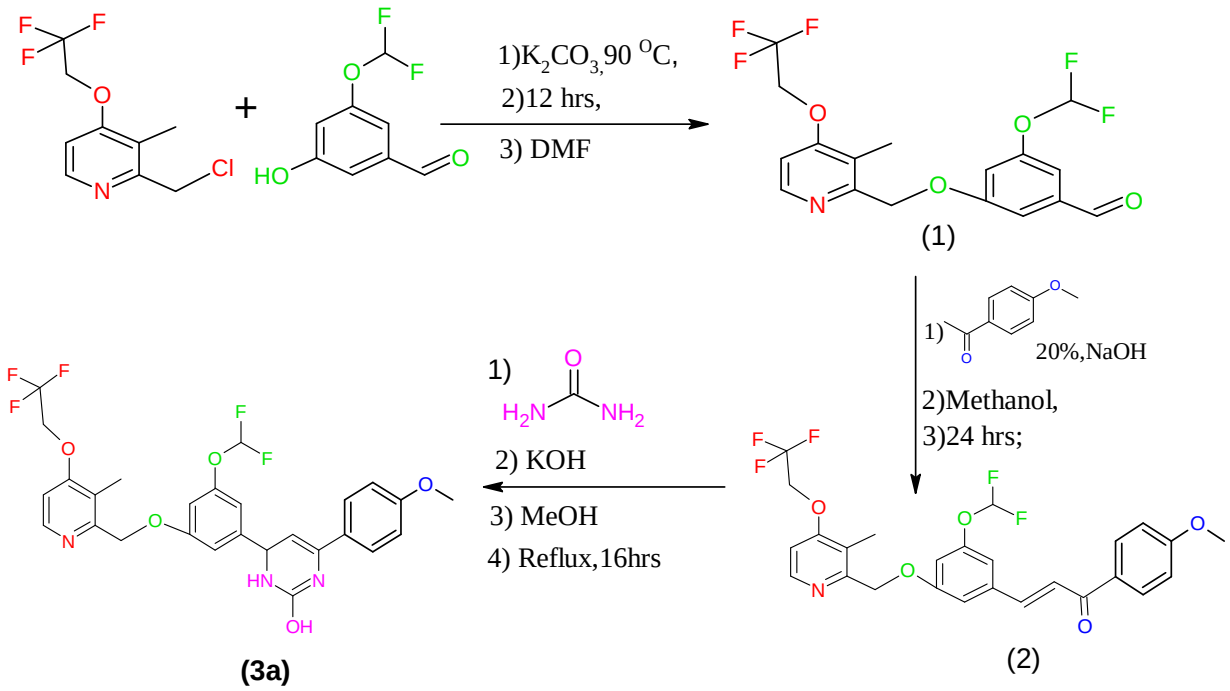
REFERENCES

[1] AmitR.Trivedi, Arif B. Siddiqui, and Viresh H. Shah,;ARKIVOC (ii) 210-217 (2008).
[2] A. S. Noranyan, A. Sr. Oranisyan, G. O. Grigoryan, S. Vartanyanet. al.;ChemAbstr., 126, 70176f (1997).
[3] Mochida Pharmaceutical Co. Ltd.;JP, 81,127,383 (1981).
[4] N.Henrie Robert, J Peake Clinton., G.Cullen Thomas et. al.;PCTInt Appl., WO 98,20,878, Appl. 96/08,17748 (1996).
[5] M. M. Ghorob and S. G. Abdel-Hamid ,;Indian J. Het. Chem., 4, 103-06 (1994).
[6] ObatokioFujii, KatsuToshi, Narita Isamiet. al.;Jpn. KokaiTpkkyoKoho JP, 08,269,021 (1995).
[7] R. K. Russell, J. B. Press, R. A. Rampulla, J. J. McNally et. al.;J. Med. Chem., 31, 1786 (1988).
[8] Ranise Angelo, Bruno Olga, Schenone Silvia, BondalalliFrancesoet. al.;Farmaco,52(8-9), 547-552 (1997); Chem. Abstr., 128, 238986n (1986).
[9] Y. S. Sadanandan, N. M. Shetty and P. V. Diwan,;Chem.Abstr., 117, 7885k (1990).
[10] A. K. Khalafallah, F. M. Abd-El Latifand M. A. Salim,;Asian J. Chem., 5, 988-94 (1993).
[11] R. R. Williams and J. K. Cline.;J. Amer. Chem. Soc., 58, 1504 (1936).
[12] A. L. Barry; "The Antimicrobial Suceptibility test, principle and practices(ELBS-4th Edition)180-193 (1976).

[13] V. M. Parikh,;"Absorption spectroscopy of organic molecules", Addition-Wesley Pub. Co.London243, 258 (1978). A. Hand book of spectroscopic data by B. D.Mishtry; 1st ed. ABD Press, Jaipur 11-36 (2000).
[14] A. R. Kartizky and R. AlansJones,;J. Chem. Soc., 2942 (1960). Introduction of Infra redand Raman spectroscopy by Norman,B. Colthup, Lowrence H. Daly and Stephan E. Wiberluy. Academic Press (1975).

Graphical Abstract

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



4-Aryl-2-hydroxy-6-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridin-2″-yl]methoxyphenyl}-1,6-dihydropyrimidines(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 guanidine hydrochloride in alkali medium.The products (3a-3k) were assigned by IR, ^{1}HNMR, Mass spectral data, TLC and element analysis.

Sandip P. Kakadiya, DipakM.Purohit*
Shree M.& N. Virani Science College,Chemistry Department
Kalawad Road,Rajkot-5,Gujarat,(INDIA)
E-mail: sandip.k.msc@gmail.com