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

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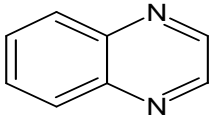
ABSTRACT:-
Quinoxalinederivatives shows good biological and therapeutic activities, With a view of getting to synthesized 2-Aryl-{[(3-methylene)-(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridine-2″-yl]methoxyphenyl-quinoxalines(5a-5k) by the condensation of (E)-3-{[(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridin-2″-yl]methoxyphenyl}-1-aryl-prop-2-ene-1-one(4a-4k)with bromine in glacial acetic acid and o-phenylenediamine.AllSynthesized 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 -vebacteria*(E.coli, P.fluorescens)* and fungi *(A.awamori).*

KEYWORDS:-
2-Aryl-{[(3-methylene)-(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridine-2″-yl]methoxyphenyl-quinoxalines,(E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴, 2‴, 2‴-trifluoroethoxy) pyridin-2″-yl]methoxy phenyl}-1-aryl-prop-2-ene-1-ones,Bromine in glacial acetic acid(Heterocyclic Compounds)

INTRODUCTION:-

The quinoxaline or benzopyrazine (I) are the product formed by spontaneous condensation of o-phenylenediamine with 1, 2-dicarbonyl compounds.



(I)

This reaction was discovered by Korner and by Hinsberg[i] independently. Since quinoxalino are also obtained when $\alpha-\beta$-dihalo ketones condensed with o-phenylienediamine. The structure of these cyclic base are obvious from the mode of formatiora and analytical data. The ring structure was further confirmed by Gabriel. who demonstrated experimentally the relationship between the quinoxaline and the pyrazines by oxidizing quinoxaline to pyrazine-2, 3-dicarboxylic acid.

A large number of substituted Quinoxaline derivatives showed pharmaceutical and biological activity such asInhibition of Candida albicans[ii,iii],CNS depressant[iv,v],Antitubercular[vi], Antiulcer[vii,viii],Analgesic[ix],Anxiolytic[x],Antihypertensive[xi],Antitumor[xii],Cardiovascular[xiii]Herbi cidal[xiv].In view of getting to synthesized Quinoxalinederivatives.

EXPERIMENTAL: Purity of all the synthesized compounds were 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)[xv,xvi], ^{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.(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 ^{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‴-trifluoro ethoxy)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^{O}C

[C] Synthesis and biological Screening of 2-(4‴′-methoxyphenyl)-3-{[(methylene) (3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″yl] methoxyphenyl}-quinoxaline.(5a)

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(6.8 gm, 0.01 mol) and O-phenyl diamine (1.08gm, 0.01 mol) in methanol (25 ml), A few drop of bromine in glacial acetic acid.The reaction mixture was heated at 90^{o}C for six hour in water bath. The reaction mixture was poured on to crushed ice. The product was filtered dried and crystallized from dioxaneYield 69%, m.p. 193 ^{o}C.($C_{32}H_{26}F_5N_3O_4$; Required : C, 62.85; H, 4.29; N, 6.87; found C, 62.78; H, 4.23; N,6.82%)

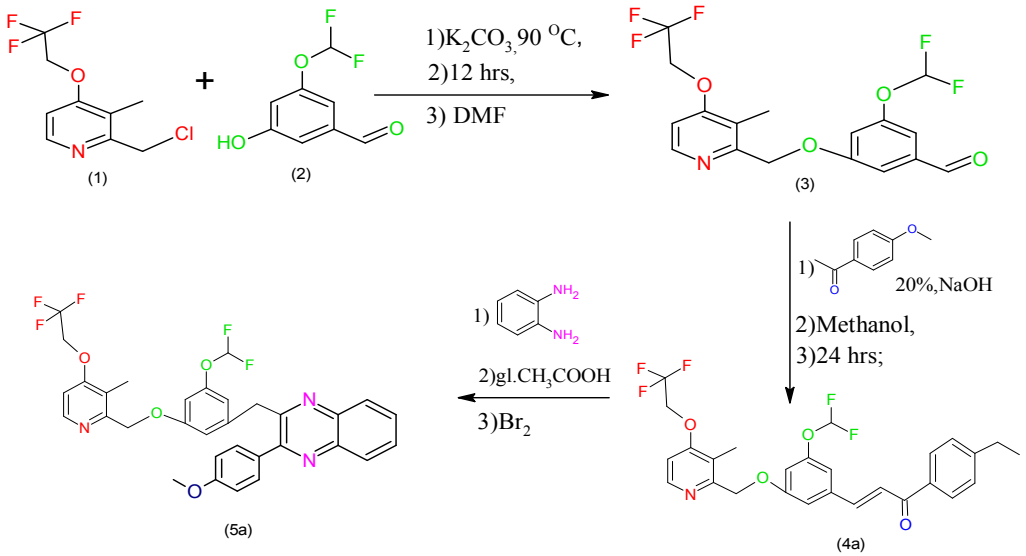
RESULTS AND DISCUSSION:-

IR spectra of3-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-(4‴′-methoxyphenyl)-3-{[(methylene) (3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl]methoxyphenyl}-quinoxalines.IR(KBr cm^{-1}):2978(C-Hstr.,asym);1456(C-Hdef.,asym);2860(C-Hstr.,Sym);3030(C-Hstr.,Aromatic);1514(C=Cstr.,aromatic);1612(C=Nstr.,Quinoxazoline);1029(C-Nstr.,Quinoxazoline);1257(C-O-Cstr.,ether);975(C-Fstr.,Halide)^{1}HNMR(DMSO-d6);3.7(q,2H.,O-CH_2-CF_3);3.8(s,2H.,O-CH_3);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.,Ar-CH_2); 4.6-6.5((s,1H.,Ar-OH);7.2-7.6(m,4H.,Ar-H), In MS m/z; 42, 78,109,123,131, 205,313,363,377,418,433,505,557,597,612(M^+) was observed.

REACTION SCHEME:-



Similarly other 2-Aryl-{[(3-methylene)-(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoro ethoxy)pyridine-2″-yl]methoxyphenyl-quinoxalines(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:-

2-Aryl-{[(3-methylene)-(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoro ethoxy)pyridine-2″-yl]methoxyphenyl-quinoxalines(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 [xvii].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, 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**	**Molecular Formula**	**M.P. °C**	**Antibacterial activity**				**Antifungal activity**	**% Yield**	**% of Nitrogen**	
				B.mega.	***B.subtillis***	***E.coli.***	***P.fluorescens***	***A.awamori***		**Cald.**	**Found**
5a	4-OCH_3. C_6H_4-	$C_{32}H_{26}F_5N_3O_4$	193	14	15	17	**22**	18	69.00	6.87	6.82
5b	2-OH. C_6H_4-	$C_{31}H_{23}F_5N_3O_4$	137	**23**	**18**	17	19	17	76.30	7.03	6.98
5c	3-OH. C_6H_4-	$C_{31}H_{23}F_5N_3O_4$	108	20	17	**20**	18	16	78.30	7.03	6.96

5d	4-OH. C_6H_4-	$C_{31}H_{23}F_5N_3O_4$	119	**22**	**20**	17	**21**	17	81.30	7.03	7.01
5e	3-NO_2. C_6H_4-	$C_{31}H_{23}F_5N_4O_5$	240	15	**19**	18	19	18	79.85	8.94	8.88
5f	4-NO_2. C_6H_4-	$C_{31}H_{23}F_5N_4O_5$	101	**21**	**21**	19	**21**	**21**	76.15	8.94	8.80
5g	2-Cl. C_6H_4-	$C_{31}H_{23}ClF_5N_3O_3$	113	17	15	16	18	17	77.75	6.82	6.77
5h	4-Cl. C_6H_4-	$C_{31}H_{23}ClF_5N_3O_3$	104	**21**	17	**22**	15	18	79.25	6.82	6.76
5i	4-Br. C_6H_4-	$C_{31}H_{23}BrF_5N_3O_3$	240	16	14	**20**	17	**20**	75.85	6.36	6.30
5j	4-CH_3. C_6H_4-	$C_{32}H_{26}F_5N_3O_3$	132	17	15	16	18	17	80.50	7.06	7.01
5k	3-NH_2. C_6H_4-	$C_{31}H_{25}F_5N_4O_3$	109	19	17	**21**	15	18	77.50	9.39	9.34

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	5b	5c	5a	5f
		5d	5d	5h	5d	5i
		5f	5e	5i	5f	-
		5h	5f	5k	-	-
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:-

2-Aryl-{[(3-methylene)-(3′-difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridine-2″-yl]methoxyphenyl-quinoxalines.(5a-5k) have been synthesized. The compounds 3d, 5e, 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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REFRENCES:-

i. Korner :Ber.,**17.** *ref.* 593. (1884).Hinsberg; Ber. **40,** 4830. (1907.)
ii. J. Metzner; E. Lippmann, F. G. Weber*; Pharmazie*1981. **36(5)**. 368-70 *(Ger.) : Chem. Abstr.,* **95,** 55520m (1981).
iii. M. C. Almanni; G. Pirisino; F. Savelli; F. Sparator; P. Mana *et al.; Farmaco Ed. Sci.,* 1981. **36(5),** 1450-*3.(Russ) : Chem. Abstr.,* **108,** 146999e (1988).
iv. HansanHolger; Euf. Pat. Appl. *EP.* 344. 94*3; Chem. Abstr,* **112,** 216962 (1990).
v. T. V. Kartseva; O. N. Oleahko; L. I. Lazareva and co-workers; Khim-Farm. *Zh*1987.21 **(2),** 1450-*3 (Russ); Chem. Abstr.,* **108,** 1469996e (1988).
vi. Takahashi Tashihiro. HagiharaKochiro *et al., Eur. Pat. Appl. EP.* 334-346*; Chem. Abstr.,* **112,** 216958x (1990).
vii. TokohashiTashihiro. HagiharaKoichiro *et al.,Eur. Pat. Appl. EP.* 338, 346 *: Chem. Abstr.,* **112,** 216958X (1990).
viii. M. Satto; A. Peana; M. C. Alamanni M. C. et al*., Farmaco Ed. Set.* **41(1)**, 54-8 (1986); *Chem. Abstr.,* **104,** 10960J (1986).
ix. Hansen Holger Claus, Watjen Fran*k; Eur. Pat. Appl. EP.* 347. 094*; Chem. Abstr.,* **87,** 682862(1977).
x. Sparotor Ann. BiodoCanu, CatennaBoido, Vito SparatoreFbio*; Farmaco***44 (10),** 945-50 (1989); *Chem. Abstr.,***112,** 15126w (1990)
xi. Yaso Masao, Suzuki Yukio. Shibala Kensuke, Hayashi Elichi*: Japan. KokaiTokkyoKohoJp. 62, 186, 671; Chem. Abstr,* **108,** 1675012 (1988).
xii. Foery Werner. Nyffeler Andreas, Gerber Hans-Rudolf, Martin Henry*; Eur. Pat. Appl. Ep.* 190. 105*; Chem. Abstr.* **105,** 166904j (1986)
xiii. Enomato-Masayuki, NagahoHideyashi, SakakiMasuharu, Sato Makato; Jpn. KokaiTokkyoKohoJ. 04. 193. 876*; Chem. Abstr.* **117,** 228449y (1992).
xiv. A. Carter Geoffrey . Clark Terence, James Carolyn S., R. S.Loeffler; Thomas Pestic *Sci.* **14(2)**, 135-44 (198*3); Chem. Abstr.***99**, 100826m (1983),
xv. V. M. Parikh,;"Absorption spectroscopy of organic molecules", Addition-Wesley Pub.Co.London**243**, 258 (1978). *A. Hand book of spectroscopic data by* B. D.Mishtry; *1st ed. ABD Press, Jaipur***11**-36 (2000).
xvi. A. R. Kartizky and R. AlansJones,;*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).
xvii. A. L. Barry; *"The Antimicrobial Suceptibility test, principle and practices (ELBS-4th Edition) 180-193 (1976).*

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