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SYNTHESIS AND BIOLOGICAL SCREENING OF (E)-3-{[(3′-DIFLUOROMETHOXY)-5′-(3″-METHYL)-4″-(2‴, 2‴, 2‴-TRIFLUOROETHOXY)PYRIDIN-2″-YL]METHOXYPHENYL}-1-ARYL-PROP-2-ENE-1-ONES

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ABSTRACT

Chalcones are intermediate compounds to synthesis of many heterocyclic compounds. They are especially interesting for their biological and industrial application. (E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridine-2″-yl]methoxyphenyl}-1-aryl-prop-2-ene-1-ones (4a-4k) have been synthesized by the condensation of 3-Difluoromethoxy-4-{[(3′-methyl)-4′-(2″,2″,2″-trifluoro ethoxy)pyridin-2′-yl]methoxyphenyl}-1-carboxaldehyde with aromatic ketones in presence of aqueous NaOH. All synthesized compounds characterized with IR, ^{1}H NMR, Mass spectra, TLC and physical constants. All the synthesized compounds evaluated for their antimicrobial activity against Gram +ve bacteria *(B.mega, B.Subtillis)* Gram -ve bacteria *(E.coli, P.fluorescens)* and fungi *(A.awamori).*

KEYWORD: Chalcones, Anti-microbial activity; (Heterocyclic Compounds).

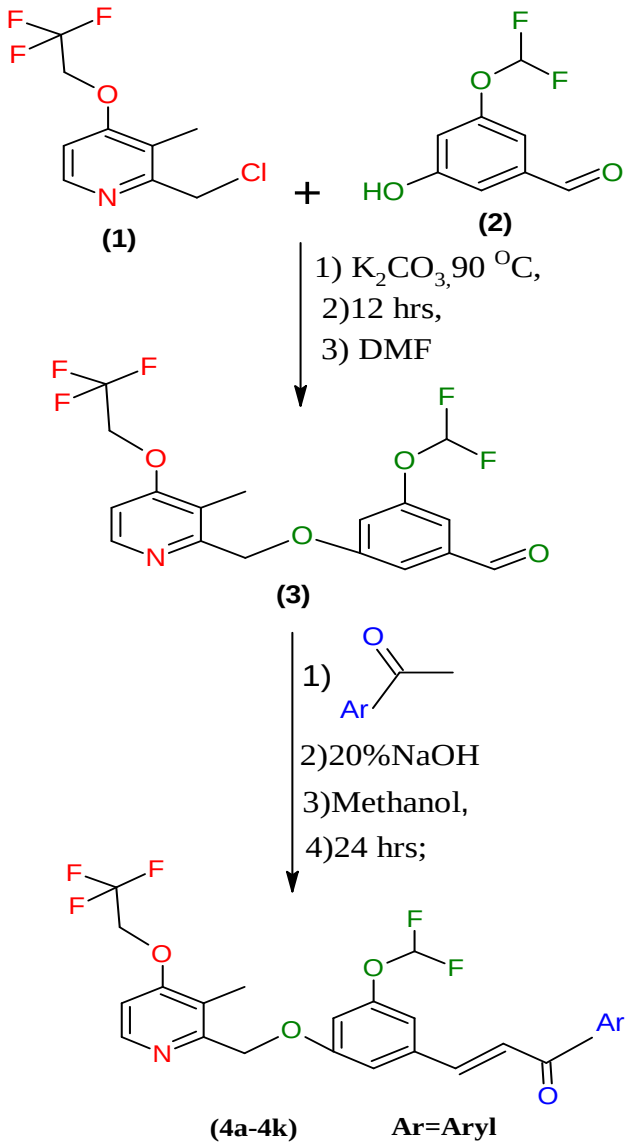
INTRODUCTION

Chalcones has popularized demanding scientific studies throughout the world, especially interesting for their biological and industrial applications. Chalcones are coloured compounds because of the presence of the chromophor and auxochromes. Chalcones are also known as benzalaceto phenones or bezylidene acetophenones, Kostanecki and Tambor[1,2] gave the name of “Chalcones”. Chalcones are β-phenyl styryl ketones containing reactive keto-ethylenic group -CO-CH=CH-. Chalcones possess conjugated double bonds and a

completely delocalized Π electron system on both benzene rings. The chemistry of chalcone has been recognized as a significant field of study.An interesting feature of chalcone is that it serves as starting materials for the synthesis of various heterocyclic compounds such as pyrimidines, isoxazoles, pyrans, pyrazolines, pyrazoles, triazoles etc.

A large number of substituted chalcone derivatives are showed their biological activity such as Anti-inflammatory[3,4] Antiallergic,[5] Antitumor[6,7] Anti pasmodic,[8] Antiulcer,[9,10] Anthelmintic,[11,12] Antiviral and Anticancer[13,14] Antitubercular,[15] Anti HIV[16] and Bactericidal[17,18] etc.

REACTION SCHEME



(E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridine-2″-yl] methoxyphenyl}-1-aryl-prop-2-ene-1-ones (4a-4k) have been prepared by the condensation

of 3-difluoromethoxy-4-{[(3′-methyl)-4′-(2″,2″,2″-trifluoroethoxy) pyridin-2′-yl]methoxyphenyl}-1- carboxaldehyde with aromatic ketones in presence of aqueous NaOH. The products (4a-4k) were assigned the IR, ^{1}HNMR, Mass spectral data, TLC and elemental analysis. The physical data and antimicrobial activities are represented in TABLE-I.

ANTIMICROBIAL ACTIVITY

(E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy) pyridine-2″-yl] methoxyphenyl}-1-aryl-prop-2-ene-1-ones.(4a-4k) 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 *Awamori* using DMF as solvent at 50µg/ml. Concentration by cup-plat method [19].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.

All synthesized compounds (4a-4k) showed moderate to good and remarkable activities with compare to known standard drugs at the same concentration, which represent in TABLE-I. The comparable antimicrobial activity, are represented in TABLE-II. **[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 hydrochlo ride (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 , IR (KBr, cm^{-1}): 2958(C-H str.,asym); 2839(C-Hstr. ,Sym); 1739 (C=Ostr., ketone);1043(C-Fstr.,Halide);1250(C-O-Cstr., ether); ^{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); MS: (m/z) 391.2 (M^+); 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%). **[B] Synthesis of (E) -3 -{[(3′-Difluoro methoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-**

trifluoroethoxy)pyridin-2-yl]methoxy phenyl}-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}-1carboxaldehde (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.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(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,δppm,);3.7(s,2H-CH^{2});7.8-7.9 (s,2H-Ar-H);7.2-7.6(s,4H-Ar-H); (s,3H-O-CH_3).m/z;41,78,191, 344,418,524.

Similarly, other compounds (E)-3-{[(3′-Difluoromethoxy)-5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridine-2″-yl]methoxyphenyl} -1- aryl- prop- 2- ene- 1- ones. (4a-4k) were synthesized. The physical data are record in TABLE NO.-I.

Table -I: The physical data and antimicrobial activities of compounds. (4a-4k).

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
4a	4-OCH_3.C_6H_4-	$C_{26}H_{22}F_5NO_5$	148	15	17	17	18	16	85.75	2.68	2.62
4b	2-OH. C_6H_4-	$C_{25}H_{20}F_5NO_5$	101	16	15	17	18	18	78.02	2.75	2.70
4c	3-OH. C_6H_4-	$C_{25}H_{20}F_5NO_5$	112	18	19	17	19	20	77.30	2.75	2.69
4d	4-OH. C_6H_4-	$C_{25}H_{20}F_5NO_5$	135	**20**	**18**	**19**	**20**	**22**	80.10	2.75	2.69
4e	3-NO_2. C_6H_4-	$C_{25}H_{19}F_5N_2O_6$	137	17	16	18	18	17	79.50	5.20	5.14
4f	4-NO_2. C_6H_4-	$C_{25}H_{19}F_5N_2O_6$	100	**21**	**18**	**20**	**21**	**21**	78.25	5.20	5.14
4g	2-Cl. C_6H_4-	$C_{25}H_{19}ClF_5NO_4$	97	**20**	17	17	18	**23**	86.75	2.65	2.58
4h	4-Cl. C_6H_4-	$C_{25}H_{19}ClF_5NO_4$	102	19	15	15	**21**	**22**	79.02	2.65	2.58
4i	4-Br. C_6H_4-	$C_{25}H_{19}BrF_5NO_4$	98	**21**	**18**	**21**	18	17	80.25	2.45	2.40
4j	4-CH_3. C_6H_4-	$C_{26}H_{22}F_5NO_4$	139	15	16	17	17	18	82.15	2.76	2.71
4k	3-NH_2. C_6H_4-	$C_{25}H_{21}F_5N_2O_4$	86	14	16	16	18	17	78.15	5.51	5.45

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*
	(4a-4k)	4d	4d	4d	4d	4d
		4f	4f	4f	4f	4f
		4g	4i	4i	4h	4g
		4i	-	-	-	4h
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

(E)-3-{[(3′-Difluoromethoxy) -5′-(3″-methyl)-4″-(2‴,2‴,2‴-trifluoroethoxy)pyridin-2″-yl] methoxyphenyl}-1-aryl-prop-2-ene-1-ones.(4a-4k) have been synthesized. The compounds 4d,4f,4g,4i showed good remarkable antibacterial and antifungal activity with compared to known standard drugs e.g. Ampicillin, Chloramphenicol, Norfloxacin and Griseofulvin at same concentration 50 µg/ml.

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