SYNTHESIS AND ANTIMICROBIAL SCREENING OF SOME CHROMONES AND THIAZEPINES BY CONVENTIONAL AND MICROWAVE IRRADIATION.

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Abstract: Base catalyzed condensation of **1** with substituted o-hydroxy acetophenone gives 3-(1-4-(pyridin-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroaryl)prop-2-en-1-one **2** on oxidative cyclization with DMSO-I_2 gives 2-(1-(4-(pyridine-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-substituted-4*H*-chromon-4-one **3.** Compound **2** on condensation with 2-aminothiophenol gives 2-(-2-(1-(4-(pyridine-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[1,4]thiazepin-4-yl)substituted phenol **4.** Compounds **3** and **4** are prepared by conventional and microwave irradiation and characterized by IR and ^{1}H NMR. These compounds were tested for their antimicrobial activities.

Introduction:

The chemistry of pyridine and its derivatives have been studied since past century due to their close association with diverse bioactivities and found in a number of natural and synthetic pharmaceutical agents[1]. Several bi and tri substituted pyridines like Etoricoxib[2], Milrinone and Amrinone[3] have been reported as COX-2 inhibitors and cardiotonic agents for the treatment of congestive heart failure. Many of them are also reported to posses antitumour[4] and antibacterial activities[5].

Benzothiazepines have been shown to exhibit various kinds of biological and pharmaceutical activities as antagonist[6], antitumour agents[7], antipsychotic agent[8,9], antidepressant[10], anticonvulsant[11] and neuroleptic[12].

Last few decades the chemistry of chromones and its derivatives have been studied by chemist due to important bioactivity[13-15]. Various bioactivities associated with the chromones nucleus such as antioxidant[16], antibacterial[17,18], antitumor[19,20] and antiplatelet activity[21].

Our past decades, the many significant advantages in the practical aspects of organic chemistry have included novel strategies and methods as well as the advent of a vast array of analytical techniques[22]. It was first reported that organic reactions could be accelerated in domestic microwave ovens[23,24].

The use of unaltered domestic microwave oven as a convenient source of energy in organic synthesis is now well establishes procedure[25,26]. Using microwave rapid heating of the reactants can be achieved, owing to substantial reduction in the reaction period. Many of the reactions have been carried out in open vessels using polar solvents such as alcohol, water, DMF etc. as the energy transfer media, which absorbs microwave energy through dipole rotation.

Activities associated with these nuclei and advantages of microwaves in organic synthesis prompted use to synthesis new chromones and benzothiazepines by conventional microwave methods.

In the present investigation 1-(4-(pyridine-2-yl)benzyl)-3--phenyl-1*H*-pyrazole-4-carbaldehyde **1** were condensed with substituted o-hydroxy acetophenones to get 3-(1-4-(pyridin-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroaryl)prop-2-en-1-ones **2.** Different chalcones **2** are treated with DMSO / I_2 to get 2-(1-(4-(pyridine-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-substituted-4*H*-chromon-4-ones **3.** Similarly chalcones **2** on treatment with o-aminothiophenol gives 2-(-2-(1-(4-(pyridine-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[1,4]thiazepin-4-yl)substituted phenol **4.** Compounds **3** and **4** are prepared by conventional and microwave methods. The required 1-(4-(pyridine-2-yl)benzyl)-3--phenyl-1*H*-pyrazole-4-carbaldehyde **1** were obtained by Vilsmeier Haack reaction on hydrazone of acetophenone[27].

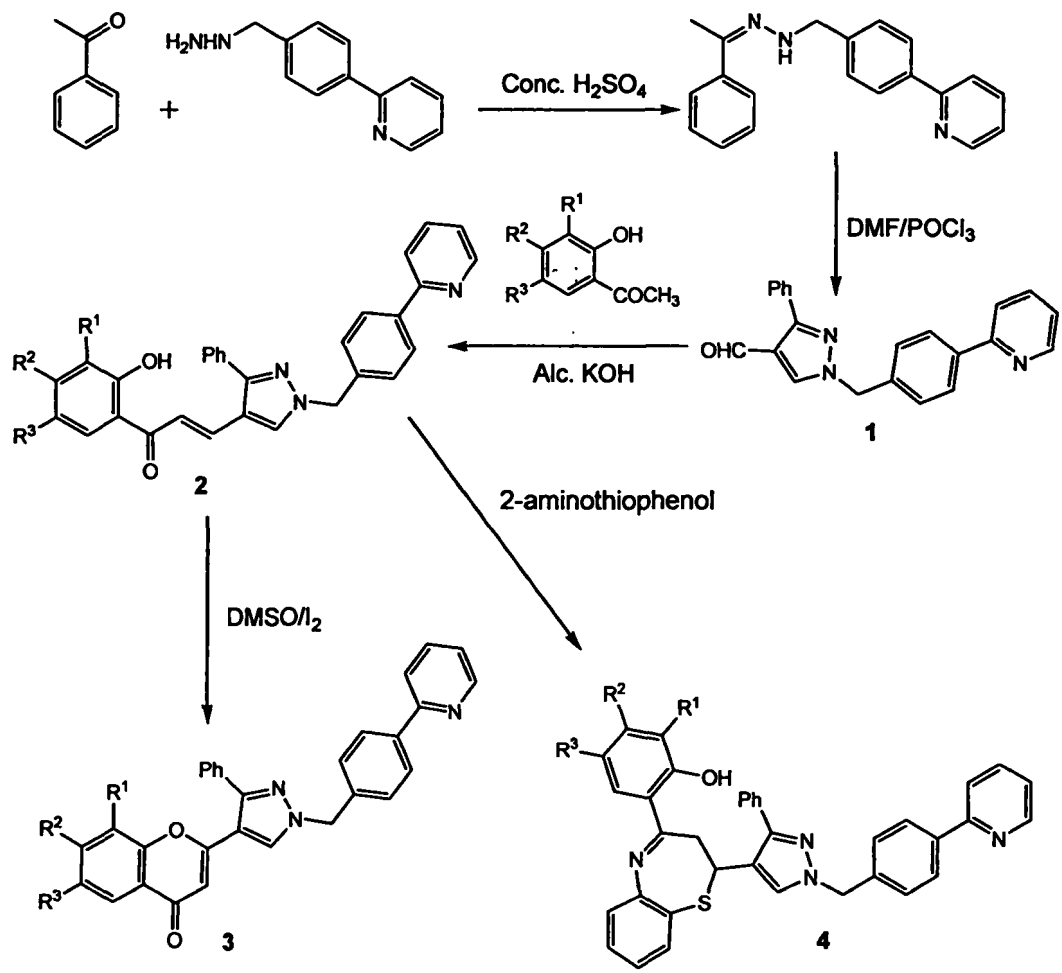
Antimicrobial Screening

The *invitro* antimicrobial activity of the test compounds were assessed against 24 hrs cultures of several selected bacteria and fungi. The bacteria used were Escherichia coli, *staphylococcus aureus* and *staphylococcus faecium*; the fungi used were *Candida albicans*, *Candida krusei* and *Aspergillus fumigatus*.

The antimicrobial activity was performed by agar diffusion method at 1 mg/ml conc. in DMSO. Nutrient agar and potato dextrose agar were used to culture the bacteria and fungi respectively.

Fluconazole, Amphotericin, Vancomycin and linezolid were prepared in DMSO and used as standards for comparison of antibacterial and antifungal activities respectively. The activity is reported by measuring the diameter of the inhibition zone in mm. All the compounds are showing activity against some of the test organisms. Antimicrobila screening data is given in **Table-II.**

Scheme:



Experimental:

All experiments under microwave irradiation were carried out in unmodified domestic microwave oven model 800T manufactured by BPL Appliances and Utilities Ltd, Bangalore, India having maximum power output of 800W and 2450 MHz frequency.

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr disc on a FT-IR spectrometer. ^{1}H NMR spectra were recorded on 300 MHz instrument with DMSO-d_6 or $CDCl_3$ as solvent using TMS as internal standard, while mass spectra were recorded on Finnigan mass spectrometer.

The structures of all compounds were assigned on the basis of IR and NMR. Purity of the compounds was checked by TLC on silica gel glass plates.

General procedure

3-(1-4-(Pyridin-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroaryl)prop-2-en-1-ones 2

A 100 ml RBF was charged with 1-(4-(pyridine-2-yl)benzyl)-3--phenyl-1*H*-pyrazole-4-carbaldehyde **1** (0.01 mol), substituted o-hydroxy acetophenone and ethanol (25 mL). To this 2 gm of KOH was added and the resulting mixture was stirred for 24 h at r. t. Progress of the reaction was monitored by TLC. After completion of the reaction, the solution was poured into crushed ice and acidified by dropwise addition of AcOH. The solid thus obtained was separated by filtration and crystallized from alcohol to give 3-(1-4-(Pyridin-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroaryl)prop-2-en-1-ones **2**. This experimental procedure was followed to prepare the compounds **2a-e**. The characterization data is summarized in **Table I**.

(2a): ^{1}H NMR, δ ppm: 5.45 (s, 2H), 7.16 to 8.14 (m, 19H), 13.50 (s, 1H) exchangeable with D_2O; IR (KBr, cm^{-1}): 3408, 1635, 1565, 1441, 1056.

(2b): ^{1}H NMR, δ ppm: 5.47 (s, 2H), 7.18 to 8.13 (m, 18H), 13.52 (s, 1H) exchangeable with D_2O; IR (KBr, cm^{-1}): 3408, 1634, 1568, 1440, 1053.

(2c): ^{1}H NMR, δ ppm: 5.48 (s, 2H), 7.15 to 8.12 (m, 19H), 13.48 (s, 1H) exchangeable with D_2O; IR (KBr, cm^{-1}): 3414, 1651, 1570, 1444, 1170.

(2d): ^{1}H NMR, δ ppm: 2.52 (s, 3H), 5.38 (s, 2H), 7.20 to 8.10 (m, 18H), 13.55 (s, 1H) exchangeable with D_2O; IR (KBr, cm^{-1}): 3416, 1648, 1568, 1440, 1051.

2-(1-(4-(pyridine-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-substituted-4*H*-chromon-4-ones 3

Method (A) Conventional Method:

In 100 mL of RBF, a mixture of 3-(1-4-(Pyridin-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroaryl)prop-2-en-1-ones (0.003 mol) **2** and iodine crystal (0.2 gms) were dissolved in 5 mL of DMSO. The reaction mixture was refluxed for 3 h. Progress of the reaction was monitored with the help of TLC. After completion of the reaction, the resulting solution was allowed to cool to r. t. and the solid thus obtained was separated by filtration and washed with 20 % sodium thiosulphate solution. The dried product was crystallized from alcohol to give 2-(1-(4-(pyridine-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-substituted-4*H*-chromon-4-one **3**.This experimental procedure was followed to prepare the compounds **3a-e**. The characterization data is summarized in **Table-I**.

Method (B) Microwave:

A 25 mL beaker covered with a glass lid charged with a mixture of 3-(1-4-(pyridin-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroaryl)prop-2-en-1-ones (0.003 mol) **2** and iodine crystal (0.2 gms) were dissolved in 5 mL of DMSO. The mixture was irradiated for 2-3 minutes under 450 watts of microwave. Completion of the reaction was checked by TLC. After completion of the reaction the beaker was allowed to cool to r. t. Product was collected by filtration and

crystallized from alcohol. This experimental procedure was followed to prepare the compounds **3a-e**. The characterization data is summarized in **Table-I**.

(3a): ^{1}H NMR, δ ppm: 5.45 (s, 2H), 6.30 (s, 1H), 7.17 to 7.80 (m, 17H); IR (KBr, cm^{-1}): 3054, 1648, 1602, 1565, 1530, 1455, 1017.

(3b): ^{1}H NMR, δ ppm: 5.48 (s, 2H), 6.35 (s, 1H), 7.26 to 7.76 (m, 16H); IR (KBr, cm^{-1}): 3058, 1647, 1600, 1562, 1532, 1456, 1015.

(3c): ^{1}H NMR, δ ppm: 5.38 (s, 2H), 6.32 (s, 1H), 7.20 to 7.75 (m, 17H); IR (KBr, cm^{-1}): 3055, 1644, 1605, 1560, 1531, 1458, 1170.

(3d): ^{1}H NMR, δ ppm: 2.48 (s, 3H), 5.35 (s, 2H), 6.35 (s, 1H), 7.19 to 7.81 (m, 16H); IR (KBr, cm^{-1}): 3050, 1647, 1603, 1563, 1530, 1460, 1014.

2-(2-(1-(4-(pyridine-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[1,4]thiazepine-4-yl)substituted phenols 4

Method (A) Conventional Method:

To a 100 mL RBF, solution of 3-(1-4-(pyridin-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroaryl)prop-2-en-1-ones (0.003 mol) **2** in ethanol (15 mL) was added with *o*-amino thiophenol (0.003 mol) and the reaction mixture was refluxed for 4 h. To this reaction mixture 1 mL of gl. acetic acid was added, and was further refluxed for 3 h. Progress of reaction was checked by TLC. It was then cooled to r. t. and poured into crushed ice. The solid product was separated by filtration, dried and crystallized from alcohol to give compound **4**. This experimental procedure was followed to prepare the compounds **4a-e**. The characterization data is summarized in **Table-I**.

Method (B) Microwave:

A mixture of 3-(1-4-(pyridin-2-yl)benzyl)-3-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroaryl)prop-2-en-1-ones (0.003 mol) **2** and *o*-amino thiophenol (0.003 mol) was added with 5 mL AcOH in to 25 mL beaker and covered with a glass lid. The content was irradiated in microwave for 2-3 minutes under 450 watts. Completion of the reaction was checked by TLC. After completion of reaction, the flask was allowed to cool to r. t. Product was collected by filtration and crystallized from alcohol. This experimental procedure was followed to prepare the compounds **4a-e**. The characterization data is summarized in **Table-I**.

(4a): ^{1}H NMR, δ ppm: 2.84 (dd, 1H), 3.16 (dd, 1H), 5.34 (s, 2H), 5.41 (dd, 1H), 7.09 to 8.73 (m, 21H), 15.76 (s, 1H) exchangeable with D_2O; IR (KBr, cm^{-1}): 3389, 3052, 1659, 1598, 1553, 1463, 1012.

(4b): ^{1}H NMR, δ ppm: 2.85 (dd, 1H), 3.15 (dd, 1H), 5.35 (s, 2H), 5.45 (dd, 1H), 7.09 to 8.72 (m, 20H), 15.76 (s, 1H) exchangeable with D_2O; IR (KBr, cm^{-1}): 3388, 3050, 1660, 1600, 1552, 1465, 1010.

(4c): ^{1}H NMR, δ ppm: 2.85 (dd, 1H), 3.18 (dd, 1H), 5.38 (s, 2H), 5.44 (dd, 1H), 7.11 to 8.76 (m, 21H), 15.75 (s, 1H) exchangeable with D_2O; IR (KBr, cm^{-1}): 3385, 3048, 1658, 1605, 1555, 1460, 1170.

Table I — Characterization data of synthesized compounds **2, 3 and 4**

Compd. No.	R_1	R_2	R_3	M.P (°C)	Conventional method		Microwave method	
					Time	Yield (%)	Time	Yield (%)
2a	H	H	Cl	125	24 h	61	--	--
2b	Cl	H	Cl	149	24 h	65	--	--
2c	H	H	F	151	24 h	59	--	--
2d	H	CH_3	Cl	164	24 h	63	--	--
2e	CH_3	H	H	150	24 h	57	--	--
3a	H	H	Cl	215	180 min	51	2 min	70
3b	Cl	H	Cl	227	180 min	54	3 min	73
3c	H	H	F	210	180 min	49	2.5 min	68
3d	H	CH_3	Cl	208	180 min	55	3 min	74
3e	CH_3	H	H	182	180 min	48	2 min	47
4a	H	H	Cl	147	420 min	56	3 min	75
4b	Cl	H	Cl	194	420 min	59	2 min	80
4c	H	H	F	137	420 min	55	3 min	69
4d	H	CH_3	Cl	170	420 min	62	2.5 min	82
4e	CH_3	H	H	191	420 min	57	2 min	79

Table II — Antibacterial and antifungal activity of compounds **2, 3 and 4**

	Average zone of inhibition in mm					
	Fungal modes			Bacterial modes		
Compd. No.	C. albicans	A. fumigatus	C. krusei	S. aureus	E. coli	S. faecium
2a	16	10	12	10	12	14h
2b	12	10	nil	12	10	12
2c	16	12	10	14	12	10
2d	12h	10h	08	14hv	10	10
2e	14	10	12	12	14h	12
3a	12	10	10	12h	12	14
3b	14	12	08	10	14h	12
3c	12h	10	12	14	14	10
3d	10	12	08	10	14h	12
3e	10h	08	12	12	08	14
4a	12	10h	08	10	14	12h
4b	08h	12	12	12h	12	14
4c	10	16	12	10	08	10
4d	12	10	nil	12	10	10h
4e	10	14	08	12h	14	10
Fluconazole	24h	20h	18	NA	NA	NA
Vancomycin	NA	NA	NA	15	15	15

Note: h=hazzy, vh=vary hazzy and NA= Not applicable

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