International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.7, pp 112-115, 2017

Synthesis of fluorinated pyrazolines as an anti-inflammatory agents containing pyrazole moiety

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Abstract : In the present work, seven novel 2-(5-(3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenol 2(a-g) were synthesized by cyclization between substituted chalcones and hydrazine hydrate in the presence of glacial acetic acid under reflux condition. The structures of the synthesized compounds were characterized on the basis of IR, ^{1}HNMR and Mass spectral data. All the synthesized compounds are screened for their anti-inflammatory activity by paw oedema method. Diclofenac employed as a reference standard. From the results it is concluded that, compounds 2b-2f exhibited moderate anti-inflammatory activity.
Keywords : Pyrazolines,antimicrobial activity,ulcerogenic activity.

Introduction

Nitrogen-linked heterocyclic compounds received considerable attention in recent times because of their medicinal and pesticidal importance. It is well known that the study of pyrazole derivatives is significant in pesticide chemistry, and some of the pyrazole derivatives were widely used because of theiranti-inflammatory[1], antitumor[2], antimicrobial[3], analgesic[4], antagonist[5], antidepressant andanticonvulsant[6], hypoglycemic[7], antioxidant[8],antidepressant properties[9], immunosuppressive[10],ulcerogenic and lipid peroxidation activities[11]. In addition, many biological compounds contain a fluoro moiety, which indicates that this moiety may be important for biological activity[12].

Experimental

A General procedure for the synthesis of4-chloro-2-(5-(3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)-5-ethylphenol(2c):

Compound 1**c** (0.01mol) was dissolved in 15ml ethanol. To this reaction mixture, 0.02 mol of hydrazine hydrate was added. Contents were heated under mild reflux for 4 hr and then to the reaction mixture 4-5 drops of glacial acetic acid was added and heating was continued further for 3hr and then cooled to room temperature. Cold water (50ml) was slowly added to the flask and separated product was filtered, washed with cold water for several times and crystallized from ethanol. The compounds **2(a-g)**were prepared by following the general procedure. Physical data are recorded in **Table 1**. Their structures have been confirmed by IR, ^{1}HNMR and Mass spectra.

IR (2c) (cm^{-1}): 964(C-Cl), 1062(Ar-F), 1266(C-O), 1514(Ar C=C), 1595(C=N),

3084(O-H), 3341(N-H).

^{1}H NMR (2c)(DMSO)δ ppm: 3.0637-3.1254 (dd, 1H, -CH_2-,*J*=8.48Hz & 8.28 Hz),3.4480-3.5147 (dd, 1H, -CH_2-,*J*=10.48Hz & 10.72 Hz), 4.8287-4.8740 (t,1H,-CH-,*J*=9Hz &9.12Hz), 6.0463(s, 1H, Pyrazoline N-H), 6.5917-6.9933 (m, 3H, Ar-H), 7.0147-7.2131 (m, 4H, Ar-H), 7.3221-7.6842(m, 3H, Ar-H), 8.0925 (s, 1H,Pyrazole-H), 10.9231 (s, 1H, Ar-OH).

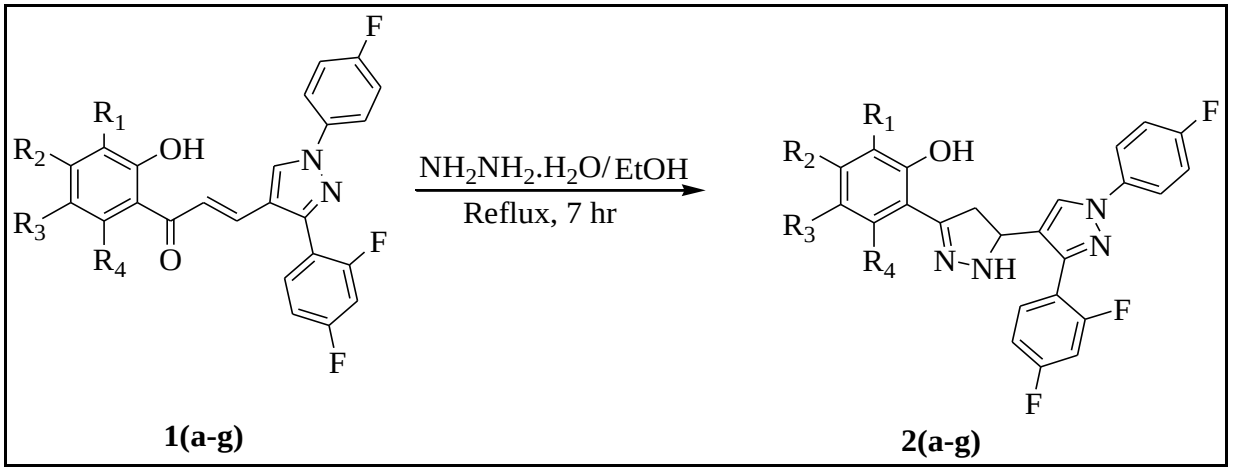
ES-MS (2c) (m/z):469.43(M+1), 471.43(M+3).

IR (2f) (cm^{-1}): 964(C-Cl), 1063(Ar-F), 1267(C-O), 1514(Ar C=C), 1595(C=N),

3084(O-H), 3128(N-H).

^{1}H NMR (2f) (DMSO)δ ppm: 2.3160 (s, 3H, CH_3), 3.047-3.1096 (dd, 1H, -CH_2-,*J*=8.28Hz & 8.44 Hz),3.4240-3.4955 (dd, 1H, -CH_2-,*J*=12.24Hz & 10.16 Hz), 4.8040-4.8497 (t,1H,-CH-,*J*=9.44Hz & 8.84Hz), 6.0132(s, 1H, Pyrazoline N-H), 6.7853 (s, 1H, Ar-H), 6.8816-6.9554(m, 1H, Ar-H), 6.9764-6.9818(m, 1H, Ar-H),7.1076-7.1235 (m, 1H, Ar-H), 7.1445-7.1659(m, 1H, Ar-H) ,7.2041-7.2111(m, 1H, Ar-H), 7.5421-7.5652(m, 1H, Ar-H), 7.6459-7.6574(m, 1H, Ar-H), 7.6681-7.6794(m, 1H, Ar-H), 7.9449 (s, 1H,Pyrazole-H), 10.8053 (s, 1H, Ar-OH).

ES-MS (2f) (m/z): 481.21(M-1), 483.19(M+2).



Scheme1- Synthesis of various substituted 2-(5-(3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenol

Table 1: Physical data of compounds (2a-g)

Comp.	R_1	R_2	R_3	M.P. (^{o}C)	Yield (%)
2a	H	H	H	96-98	69
2b	H	H	CH_3	120-122	73
2c	H	H	Cl	108-110	68
2d	Cl	H	Cl	126-128	80
2e	H	H	F	130-132	71
2f	H	CH_3	Cl	90-92	67
2g	H	H	Br	110-112	81

Results and Discussion

Antimicrobial activity:

Compounds **2(a-g)** were screened for their in vitro antimicrobial activity against *Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853), Staphylococcus aureus (ATCC 25923)* using Gentamycin as a reference standard drug by paper disc diffusion method. Antifungal activity was evaluated against *Candida sp.* using Nystatin as standard drug. All the tests were evaluated at 100 µg/ml concentration.

The culture media was Muller Hinton agar. The zone of inhibition was measured in mm after 24 hr of incubation at 37^{o}C.Microbial data for corresponding compounds is summarized in **Table 2.**

Table 2: Antimicrobial Analysis Data

Sr. No.	**Comp. No.**	***Escherichia coli (ATCC 25922)***	***Pseudomonas aeruginosa (ATCC 27853)***	***Staphylococcus aureus (ATCC 25923)***	***Candida sp.***
1	2a	No Zone	No Zone	No Zone	No Zone
2	2b	No Zone	No Zone	No Zone	No Zone
3	2c	No Zone	No Zone	No Zone	No Zone
4	2d	No Zone	No Zone	No Zone	No Zone
5	2e	No Zone	No Zone	No Zone	No Zone
6	2f	No Zone	No Zone	No Zone	No Zone
7	2g	No Zone	No Zone	No Zone	No Zone
8	Gentamycin	28 mm	23 mm	32 mm	--
9	Nystatin	--	--	--	23 mm

Anti-Inflammatory Activity:

Compounds **2(b-f)** were screened for their anti-inflammatory activity. All analysis was performed using graph pad prism for Windows. All statistical analysis is expressed as mean ± standard error of the mean (SEM). Data were analyzed by one way ANOVA, where applicable $p<0.05$ was considered statistically significant, compared with vehicle followed by Dunnett's test.

Table 3.Effect of different Compounds 2b-2fon paw oedema induced by carrageenan in rat

	Treatment	**Mean Difference in Paw volume (ml)**	**Percentage Inhibition (%)**
Control	**0.1 ml of 1% (w/v)**	**1.6±0.02**	**----**
Diclofenac	30	1.5±0.02	93.75
2b	10	1.0±0.01	62.50
	20	1.1±0.03*	68.75
2c	10	0.9±0.01	56.25
	20	1.1±0.01*	68.75
2d	10	1.1±0.01*	68.75
	20	1.2±0.01**	75.00
2e	10	1.0±0.01	62.50
	20	1.2±0.02*	68.75
2f	10	1.0±0.01	62.50
	20	1.2±0.02**	75.00

Each data suggests Mean ± SEM (n=6). One-way ANOVA using Dunnett's test is applied for statistical analysis, Treatment groups compared with Control group.

Significant at* $p < 0.01$, compared to control group.

Conclusion

The novel synthesized compounds were tested againstGram positive and Gram negative bacterial strains. As well asthey were tested against Candida species. The other compounds have shown no activity compared to standard drug.The synthesized compounds were screened for their anti-inflammatory activity bypaw oedema method. Diclofenacemployed as a reference standard. From the results it is concludedthat, compounds 2b-2f exhibited moderate anti-inflammatoryactivity.

Acknowledgements

The authors are thankful to UGC, WRO, Pune for financial support and Principal Dr. B. B. Sonwane for providing laboratory facilities.The authors are grateful to Director, SAIF/CIL, Panjab University, Chandigarh for providing spectral data. The authors are thankful to Uday Khedkar, Director, BAC-TEST Laboratory, Nashik for antimicrobial analysis. The authors are grateful to Prabhat Jain, Director, Scan Research Laboratory, Bhopal for anti-inflammatory activity.

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