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Analysis of synthesis and insecticidal activity of 1, 2, 4-triazole dirivatives

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Abstract
The objective of the present study was to synthesize new pyrimidine substituted 1,3,4-oxadiazole derivatives and evaluate them for antimicrobial and anti-inflammatory activities. Novel pyrimidine substituted 1,3,4-oxadiazole derivatives (11a-k) were synthesized from the condensation of different substituted aromatic carboxylic acids with substituted pyrimidine carboxy hydrazide using $POCl_3$ as condensing agent. Their structures were characterized by physical and spectral studies. The synthesized compounds were evaluated for their in vitro antimicrobial and anti-inflammatory activity. Some of the newly synthesized compounds showed good antimicrobial and anti-inflammatory activities.

Keywords: antimicrobial, anti-inflammatory and triazole dirivatives

Introduction
Heterocyclic compounds containing the five-membered oxadiazole nucleus possess a diversity of useful biological effects. Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical interest. For instance, 2-amino-1,3,4-oxadiazoles act as muscle relaxants [1] and show antimitotic activity. Anti-inflammatory [2], antihepatitis B [3] and antidiarrheal activity [2] of some new 1,3,4- oxadiazole derivatives was also reported. Recently several 1,3,4-oxadiazole derivatives were identified as potentially active antimycobacterial [5-6], antitubercular [7], anticonvulsant [8], anticancer [9] activities and also reported as enzyme tyrosinase inhibitors [10].
Data analysis was carried out using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison tests. $P < 0.05$ was considered statistically significant.
The results of carrageenan induced rat paw oedema model indicated that all the synthesized compounds showed moderate to good anti-inflammatory activity. Out of all the synthesized compounds 11b, 11d, 11f and 11h showed highly significant good anti-inflammatory activity, whereas the compounds 11a, 11e and 11j showed moderate activity when compared with that of standard ibuprofen.

Results and Discussion
Novel pyrimidine substituted-1,3,4-oxadiazole derivatives were synthesized in a seven step process. The core intermediate for the synthesis of new pyrimidine-oxadiazole derivatives is compound 9 which was prepared by the known literature as shown in Scheme 1.

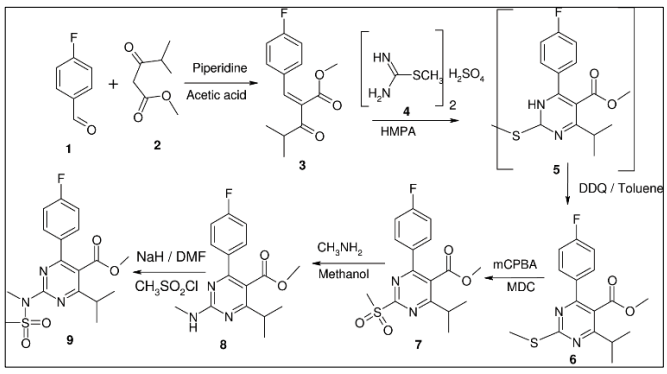

Fig 1: Synthetic method for the preparation of intermediate compound 9

The compound 3 was synthesized from 4-flouro benzaldehyde (1) and methyl isobutyl acetate (2) by Knoevenagel condensation. The compound 3 was reacted with S-methyl thiourea hydrogen sulfate (4) in the presence of hexamethyl phosphoramide (HMPA) forms an intermediate 5, which was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in toluene to furnish the compound 6. The obtained S-methyl pyrimidine (6) compound was oxidized to sulfonyl methyl pyrimidine (7) using m-chloro perbenzoicacid. The N-methyl derivative (8) of the pyrimidine was synthesized by treating the compound 7 with methyl amine in methanolic medium. The compound 8 was further treated with methane sulfonyl chloride in the presence of NaH in anhydrous DMF to form compound 9. The pyrimidine hydrazide (10) was synthesized from the compound 9 upon refluxing with hydrazine hydrate solution for 6 hours.

Cyclization of the hydrazide compound (10) with different aromatic acids in presence of phosphorous oxychloride gave the titled compounds 11a-k (Scheme 2).

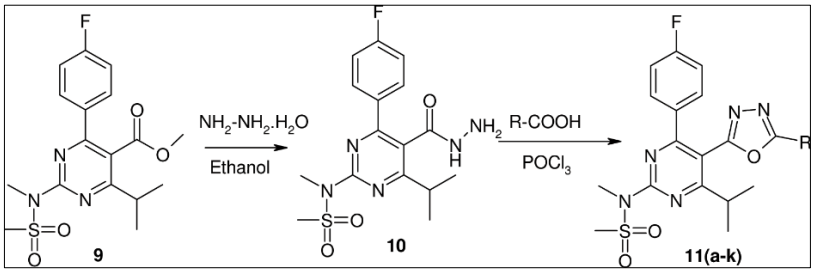

Fig 2: Synthetic method for the preparation of pyrimidine oxadiazoles 11(a-k)

The final compounds were obtained in good yields in the range of 64-85%. The completion of the reaction was monitored by TLC and the product was isolated by column chromatography in pure form.

The structure of the newly synthesized compounds was elucidated by their Mass, IR, NMR and melting points. In the IR spectra, the band due to –C=C- and C=N group, which was present in all studies, the peaks were observed at about 1400 cm^{-1} and 1550 cm^{-1}, respectively. The bands at about 1300 cm^{-1} and 990 cm^{-1} were characteristic for the S=O (sulfonyl group) and C-F groups respectively. About 1100 cm^{-1} was characteristic for the C-O group. The molecular ion peaks in the mass spectra were in accordance with their molecular formulae. In ^{1}HNMR spectra, the pyrimidine attached isopropyl protons were appeared as, doublet at about δ 1.3 and septet at about δ 3.2 to 3.3, two singlets at about δ 3.7 and δ 3.5 in all derivatives. The other aromatic protons were observed as two double doublets at δ 7.65 – 7.45 and δ 6.95 – 7.05 with respective ortho and meta fluorine couplings, in all the synthesized compounds with four protons. Similarly in ^{13}CNMR spectra of all synthesized compounds, aromatic carbon peaks were observed at about δ 165 – 162, 133, 130, 115 with respective fluorine couplings and the aliphatic carbons corresponding to N-CH_3, SO_2CH_3, isopropyl peaks at about δ 42, 33, 32 and 21 respectively. The physical characteristic of the newly synthesized compounds were represented in Table 1.

Table 1: Physical characterization data of compounds 11(a-k)

Comp Code	R	Molecular formula	Mol. Wt.	M.P (^{0}C)	Yield (%)
11a		$C_{23}H_{22}FN_5O_3S$	467	194	73
11b		$C_{23}H_{21}FN_5O_3SBr$	546	155	70
11c		$C_{23}H_{21}FN_5O_3SBr$	546	177	75
11d		$C_{23}H_{21}FN_5O_3SCl$	501	182	80
11e		$C_{23}H_{21}FN_5O_3SCl$	501	165	72
11f		$C_{23}H_{21}F_2N_5O_3S$	485	265	65
11g		$C_{23}H_{21}F_2N_5O_3S$	485	186	72
11h		$C_{23}H_{21}FN_6O_5S$	512	155	70
11i		$C_{23}H_{21}FN_6O_5S$	512	205	85
11j		$C_{23}H_{23}FN_6O_4S$	498	199	64
11k		$C_{23}H_{23}FN_6O_4S$	498	242	85

The minimum inhibitory concentration at which no growth was observed was taken as the MIC values. The comparison of the MICs (in µg/mL) of potent compounds and standard drugs against tested strains are presented in Table 2. Similarly the MIC for antifungal activity was determined using 72 h old broth culture. The results were compared with Clotrimazole and summarized in Table 2.

Table 2: The results were compared with Clotrimazole and summarized

Compounds	Minimum Inhibitory concentration (MIC) in µg / mL						
	Antibacterial activity				Antifungal activity		
	B.subtilis	*B.pumilus*	*E.coli*	*P.aeruginosa*	*A.niger*	*C.arachidis*	*F.verticilloides*
11a	200	100	100	400	200	12.5	12.5
11b	50	25	25	400	50	200	200
11c	12.5	50	25	25	50	100	100
11d	12.5	25	25	12.5	12.5	400	400
11e	12.5	12.5	12.5	12.5	50	100	50
11f	100	50	50	50	12.5	12.5	12.5
11g	400	400	200	200	12.5	50	25
11h	12.5	12.5	50	12.5	25	25	25
11i	25	12.5	25	12.5	200	200	100
11j	25	50	12.5	50	12.5	25	25
11k	25	50	12.5	50	50	25	25
Ciprofloxacin	6.25	6.25	6.25	6.25	-	-	-
Clotrimazole	-	-	-	-	6.25	6.25	6.25
DMSO	-	-	-	-	-	-	-

Minimum inhibitory concentration (MIC) of all compounds was determined, which is defined as the lowest concentration of inhibitor at which bacterial growth was not visually apparent. Investigation on antibacterial screening data (Table 2) showed some of the compounds were active against four human pathogenic bacteria. The results of antimicrobial activity of newly synthesized compounds 11(a-k) reveals that out of eleven compounds, seven compounds were found to have good antibacterial activity and only five compounds showed good antifungal activity. Among these compounds the 11c, 11d, 11e, 11h, 11i, 11j and 11k were active against the bacterial strains and only the compound 11e active against the all four bacterial strains where as the 11h was found to be active against the Bacillus subtilis, Bacillus pumilus and Pseudomonas aeruginosa. The compound 11d showed good activity against two organisms Bacillus subtilis and Pseudomonas aeruginosa. From the antifungal activity data it was clear that among the thirteen tested compounds only four compounds 11f, 11g, 11h and 11j, showed good antifungal activity, the compound 11f was the only compound to show good activity against all three fungal strains.

Conclusion

Among the newly synthesized compounds, 11c, 11d, 11e, 11h, 11i, 11j and 11k showed the most promising antibacterial activity and the compounds 11f, 11g, 11h and 11j showed promising antifungal activity. Whereas the anti inflammatory activity data suggest that the newly synthesized compounds showed moderate to equipotent anti inflammatory activity when compared to standard employed for the study. The compounds 11b, 11d, 11f and 11h showed good activity, whereas the compounds 11a, 11e and 11j showed moderate activity. Hence the fact that the compounds prepared in this study are chemically unrelated to the current medication, suggests that further work with similar analogues is clearly warranted.

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