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SYNTHESIS OF REMARKABLE SUBSTITUTED ARYL 1,3,4-OXADIAZOLE DERIVATIVES AND THEIR POTENT ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES.

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ABSTRACT: ***The key objective of the current research is to synthesize and analgesic action 5-(2-(2,3-dimethylphenylamino)phenyl)-2-(aryl)- 1,3,4-oxadiazole and to test this activity (VT1-VT8). During this investigation, the condensed methanone {2-[(2,3-dimethylphenyl)amino]phenyl}(hydrazinyloxide), and various aryl-acids in presence of phosphorous oxychloride were synthesized in the present investigations by a sequence of 5-(2-(2,3-dimethylphenylamino)phenyl]-2,3,4-oxadiazols (VT1-VT8). Both synthesized compounds have been tested with 50 mg/kg and 10 mg/kg po respectively for their in vivo anti-inflammatory and analgesic activities. Carrageen's mediated acute rat paw oedema model and Eddy's hot plate system were used to analyze the anti-inflammatory and analgesic function of the synthesized compounds. Any substances have been effective at their anti-inflammatory and analgesic activities, according to biological results. Elemental research (C, H, N) and spectral analysis also verified the composition of both substances (IR, 1H NMR and mass spectrometry).***

KEYWORDS: ***Mefenamic acid, 1,3,4-oxadiazole derivatives,Anti-inflammatory activity, Analgesic activity and Spectroscopy.***

1. INTRODUCTION

A heterocyclic compound forms a cyclic form in the ring of two or the same hetero-atom varieties. The most popular heteroatoms are nitrogen, oxygen and sulphur. Heterocyclic compounds are ubiquitous and essential for life in several respects. Extra heteroatom's induction effect means oxadiazole is a very thin base. The displacement of the two -CH = furan groups by two pyridine-type nitrogen groups (-N=) decreases oxadiazole ring aromaticity such that the oxadiazole ring has a conjugated diene characteristic. Electrophilic alternations in the carbon atom's oxadiazole ring are quite difficult due to the comparatively low electron density in the carbon atom attributed to the electron's pyridine-type nitrogen withdrawal impact. Literature

surveys disclosed the number of reactions to 1,3,4 oxadiazole such as electrophilic, electrical, thermal and photochemical replacements. This was used in preparation for multiple 1,3,4-oxadiazole therapeutic molecules. 1,3,4-oxadiazole derivatives form an essential heterocyclic compound family. Since many of them demonstrate amazing biological behaviour and experience large applications, they have gained longer attention as colours, polymer precursors, photosensitive electricians and transformations. Inflammatory [1,2], antibacterial [5,6], antibacterial [7,8], anti-cancer [9,10], tuberculostatic [11,12] and anthelmintic [13,14] behaviours display innumerable biological activities.

2. MATERIAL AND METHODS

Experimental

Open capillary melting points were identified and uncorrected.1H NMR spectra were recorded using the internal standard of TMS on Perkin-Elmer EM-390 (300 MHz) and Bruker-WH-200 (400 MHz). On a Shimadzu FT-IR 157 spectrophotometer, the IR spectra (in KBr pellets) were recorded. On a Jeol JMS-D 300 mass spectrometer (FAB) with 70 eV the mass spectra were recorded. TLC checked the cleanliness of the compounds on the pre-coated sheets of silica gel 60 F254 using hexane and ethyl acetate 4: 1, starting material was obtained and used without any further purification from Aldrich Chemical Company or Spectrochemical Company. All solvents were analytically classified and freshly distilled before use.

General Method for the synthesis of ethyl 2-(2,3-dimethyphenylamino)benzoate (2) from Mefenamic acid (1)

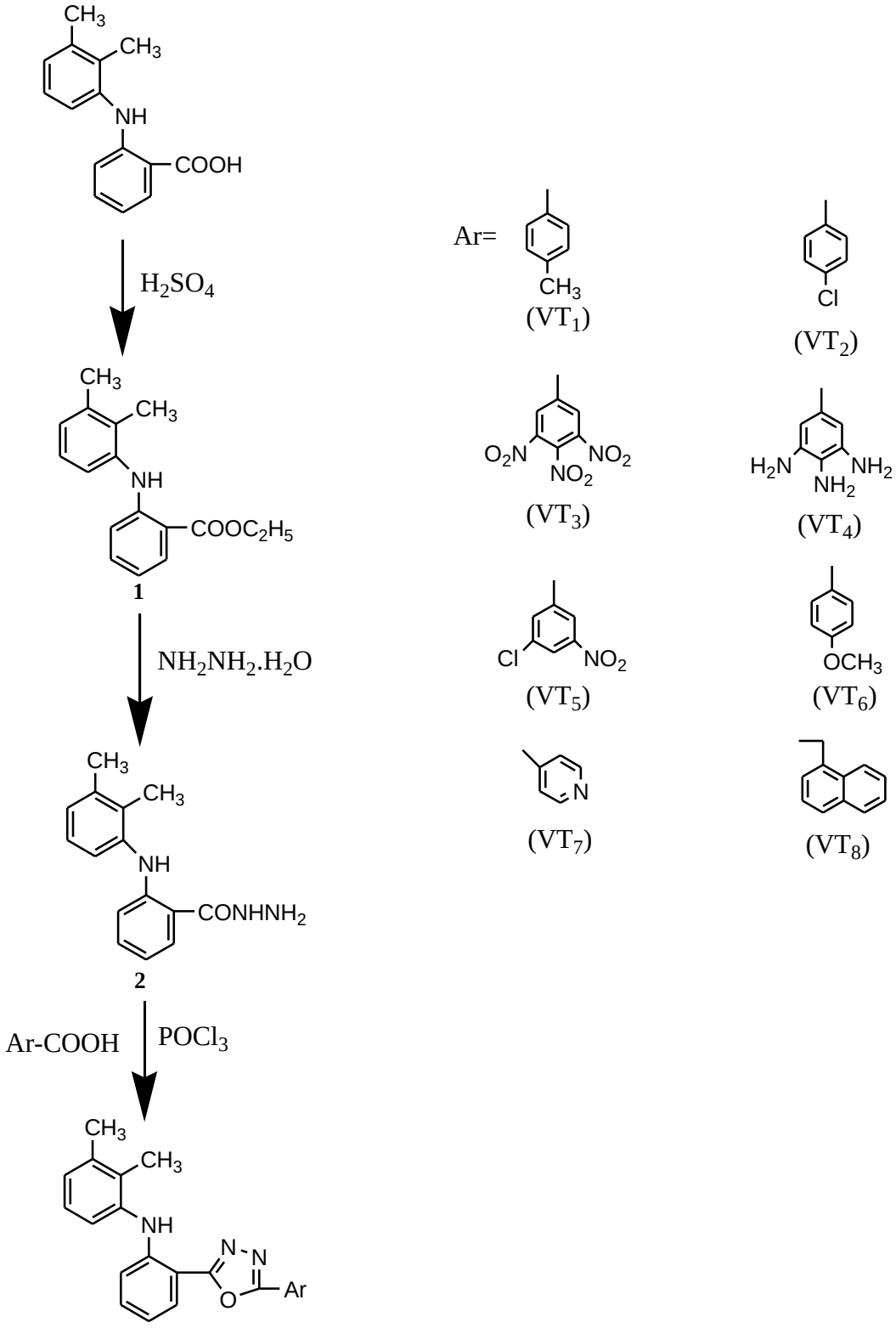
A blend of benzoic acid 2-(2,3-dimethylphenyl), i.e. Mefenamic acid, 100ml of absolute ethanol (0.206mol, 43.67gm), and 2.7ml of concentrates. For 18-20 hrs. on the water bath, sulphuric acid was refluxed. The excess of ethanol was distilled and the viscous material obtained was tested by TLC for its purity after completion of the reaction, which was compared to the initial material, with a different TLC design. Benzene: acetone was a solvent system for the TLC, in the 8:2 ratio. The hydrazide preparation has been used as such.

General Method for the synthesis of {2-[(2,3-dimethylphenyl)amino]phenyl}(hydrazinyloxy)methanone (3) fromethyl 2-(2,3-dimethylphenyl)amino benzoate (2)

For 12-15 hours ethanol was refluxed into the blend of ethyl 2- (22.3-dimethylphenyl)aminobenzoate (0.1 mol, 30.80 gm) and hydrazine hydrate (0.5mol, 24.3 mL). Excess ethanol was distilled until small volumes were left after the reaction was completed. The hydrazide crystal was filtered out and recrystallized from ethanol to give the pure compound during cooling. TLC was able to check the purity of the compound using Benzene: Acetone solvent system (8:2).

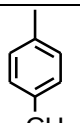
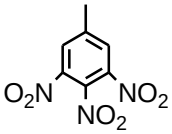
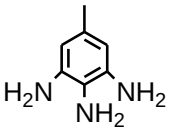
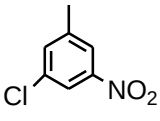
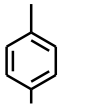
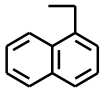
General Method for the synthesis of of5-(2-(2,3-dimethylphenylamino)phenyl)-2-(aryl)-1,3,4-oxadiazole from {2-[(2,3-dimethylphenyl)amino]phenyl}(hydrazinyloxy)methanone

Methanone (3)(0.002 mol), suitable aromatic acid (0.002 mol), phosphorylated chloride(5 mL), and {2-(2,3-dimethylphenyl)amino]phenyl} (hydrazine) were replanted in an 8 - 10-hours steam bath. It was added to the crushed ice by continuous agitation when it stood at room temperature. The solid crystals were collected, filtered, washed with water to obtain final compounds and recrystalled from ethanol (VT1-VT8). Table 1 presents the physical and chemical parameters of those compounds and scheme I gives the synthesis pathway.



Scheme 1- Synthesis pathway of all resultant compounds (VT_1-$VT_{8)}$

Table 1. Characterization of the synthesized compounds (VT_1-VT_8)

Compound	R	Mol. Formula	Mol. Weight	Melting Point ^{0}C	Yield,%
(VT_1)		$C_{23}H_{21}N_3O$	355	252-256	69
(VT_2)		$C_{22}H_{18}ClN_3O$	375	204-208	66
(VT_3)		$C_{22}H_{16}N_6O_7$	476	188-192	76
(VT_4)		$C_{22}H_{22}N_6O$	386	242-246	70
(VT_5)		$C_{22}H_{17}ClN_4O_3$	420	180--184	65
(VT_6)		$C_{23}H_{21}N_3O_2$	371	190-194	69
(VT_7)		$C_{21}H_{18}IN_4O$	342	179-183	72
(VT_1)		$C_{27}H_{23}N_3O$	343	109-113	54

Spectral Data

VT_1: ^{1}H NMR (DMSO): δ 1.18-1.90 (m, 9H, 3×CH_3) 6.18-7.89 (m, 11H, Ar-H), 9.96 (s, 1H, NH). **VT_1***m/z*: Molecular ion peak at 355. **VT_2:** ^{1}H NMR (DMSO): δ 1.49-1.64 (m, 6H, 2×CH_3), 6.21-6.94 (m, 11H, Ar-CH), 8.23(s,1H, NH). **VT_2***m/z*: Molecular ion peak at 375. **VT_6:**^{1}H NMR (DMSO): δ1.28-1.92 (m, 9H, 3×CH_3), 6.06-6.89 (m, 11H, Ar-H), 8.26 (s, 1H, NH) .**VT_6***m/z*: Molecular ion peak at 371. **VT_7:** ^{1}H NMR (DMSO): δ 1.04-1.83 (m, 6H, 2×CH_3), 6.23-7.74 (m, 11H, Ar-H), 9.37 (s, 1H, NH). **VT_7:** *m/z*: Molecular ion peak at 342.

Pharmacology

The animals used in these experiments were housed in compliance with the guidelines and requirements provided by the Animal Control and Management Commission (CPCSEA), Ministry of Social Justice and Empowerment, Government of India, and Vivek Technical Education Unit. The animals were sheltered. The experiments were performed with prior

approval by the Committee on Institutional Animal Ethics (IAEC), and the animals were treated in the most gentle and satisfactory manner. Wistar Rats and Albino mouses were each 150-200 gm and 20-25 gm (Vivek College of Technical Education, India). Eliminating pregnant mothers.

Anti-inflammatory Activity

The caused rat paw edoemamethod[15] used carrageenan anti-inflammatory compound action. Experiments were performed with 150-200 gm Wistar albino rats, either sex. Housed in clean polypropylene cages, the natural dark light cycle was kept under RT (25 ±2oC) relative humidity 60-70%. Animals had defined regular lab water and food. Food was removed 12 hours before and after experimental hours.

The animals had six animal groups. The control group was suspended orally from 0,2 ml of 5% gum acacia, while the other groups received multiple treatments as described below. A 0.1 ml of 1 percent Carrageenan suspension with 5 percent gum acacia in regular saline in the right hind paw of rats caused an intense inflammation hour after oral drug therapy. To encourage subsequent readings, a marker was mounted on the molecules' leg. Mercury displacement techniques were used to calculate paw volume fully[16]. The new bound formula was used to calculate an oedema volume and the percentage of anti-inflammatory activity[17]. Table 2 presents anti-inflammatory findings.

Analgesic Activity

Animals: For analgesic test, male albino mouse (20-25 gm) were used. The animals were fed into a laboratory maintained under standard conditions at a constant temperature of 22^{o}C (12:12 h light-dark cycle, standard diet, tap water).

Hot plate test

The well-acting compounds (>50 percent) are protected against inflammation. For analgesic activity[18], the Eddy hot plate method was used. Six albino mice groups consisting of four 20-25 gm animals had been deprived of water and food for 18 hours before the experiment. For a basic reaction time of less than 8 seconds, the animal was considered. The heat platform has been fixed to 55±10C and the animals have been arranged on a hot platform. The time required for a stopwatch to record how long it took to leave or jump with the animals as a last point. The reaction time of 0, 20, 40, 60, 80, 100, and 120 minutes was recorded, followed by oral or subcutaneous use of Standard or Test Compound. The results of antiviral studies are presented in Table 3.

Statistical analysis

The experimental animal data were determined to be medium ±SEM. A one-way ANOVA study carried out by Dunnett's multiple comparison test approved statistical characteristics between treatments and the Standard.

Table 2: Anti-inflammatory activity of newly synthesized oxadiazole derivatives (VT_1-VT_8) in Carrageenan induced acute rat paw oedema model

Animals: Albino rat Route: P.O

Group	Treatment	Dose mg/kg	Paw oedema volume							
			After 1st hr		After 2nd hr		After 3rd hr		After 4th hr	
			Mean	% ROV	Mean	% ROV	Mean	% ROV	Mean	% ROV
1	Control	1.5 ml	0.64 ±0.021	-	0.68 ±0.015	-	0.65 ±0.026	-	0.76 ±0.015	-
2	Standard	50	0.30 ±0.023	70.30	0.26 ±0.018	75.66	0.22 ±0.009	79.60	0.20 ±0.010	84.80
3	VT_1	200	0.31 ±0.018	61.44	0.25 ±0.015	63.12	0.21 ±0.009	65.22	0.20 ±0.009	68.20
4	VT_2	200	0.30 ±0.002	50.11	0.25 ±0.023	55.12	0.17 ±0.014	58.55	0.15 ±0.018	62.10
5	VT_3	200	0.31 ±0.033	40.16	0.29 ±0.025	43.18	0.25 ±0.018	46.10	0.23 ±0.014	48.30
6	VT_4	200	0.30 ±0.014	42.10	0.25 ±0.023	44.08	0.20 ±0.007	49.22	0.16 ±0.014	55.66
7	VT_5	200	0.33 ±0.009	62.44	0.28 ±0.018	66.80	0.22 ±0.009	70.18	0.17 ±0.014	75.50
8	VT_6	200	0.30 ±0.020	40.00	0.25 ±0.015	42.10	0.20 ±0.012	46.28	0.16 ±0.007	50.12
9	VT_7	200	0.31 ±0.012	55.50	0.28 ±0.011	59.44	0.23 ±0.009	62.66	0.21 ±0.009	68.10
10	VT_8	200	0.30 ±0.021	40.50	0.25 ±0.012	45.18	0.16 ±0.014	50.43	0.15 ±0.009	58.66

Animals: Albino rat, Route: P.O, Dose: 20, 25 mg/kg for anti-inflammatory activity. Mean ± SEM, n=4

TABLE 3: Analgesic activity of newly synthesized oxadiazole derivatives

Treatment	No. of animals	Average weight of animals (grams)	Average Dose (mg)	Basal reaction time (sec.) after						
				0 min	20 min	40 min	60 min	80 min	100 min	120 min
Control (gum acacia)	4	22	-	4.00 ±0.416	4.16 ±0.498	4.18 ±0.396	4.28 ±1.106	4.29 ±0.345	3.98 ±0.475	5.22 ±0.357
Standard (Pentazocin) (10 mg/kg)	4	24.8	0.248	7.45 ±0.214	12.80 ±1.004	12.90 ±0.426	13.92 ±0.345	13.80 ±1.175	11.90 ±0.621	12.60 ±0.771
Compound (VT_1)	4	24.12	2.412	3.56 ±0.328	4.80 ±0.487	10.70 ±0.580	9.90 ±0.498	12.68 ±0.484	11.48 ±0.560	11.50 ±0.978
Compound (VT_2)	4	22.20	2.220	3.655 ±0.301	13.498 ±0.886	13.176 ±0.642	11.988 ±0.866	14.550 ±0.373	13.80 ±0.540	10.96 ±0.653
Compound (VT_3)	4	24	2.4	4.186 ±0.484	4.50 ±0.288	12.998 ±0.999	12.432 ±1.239	11.345 ±0.391	10.234 ±0.672	9.662 ±0.484
Compound (VT_4)	4	25	2.5	4.355 ±0.342	12.88 ±0.377	11.998 ±0.359	13.19 ±0.866	12.222 ±0.706	10.779 ±0.388	11.213 ±0.489
Compound (VT_5)	4	22.45	2.045	5.876 ±0.478	7.842 ±0.381	12.098 ±0.633	14.022 ±0.252	12.123 ±0.547	13.020 ±0.952	12.010 ±0.996
Compound (VT_6)	4	24.22	2.422	3.120 ±0.122	6.132 ±0.639	7.654 ±0.301	10.70 ±0.452	11.80 ±0.59	11.030 ±0.402	12.10 ±0.514

								0		
Compound (VT_7)	4	23.12	2.312	4.045 ±0.341	5.098 ±0.315	10.120 ±0.736	13.250 ±0.535	13.350 ±0.547	13.444 ±0.392	12.128 ±0.767
Compound (VT_8)	4	24.20	2.420	3.80 ±0.586	6.350 ±0.358	10.208 ±0.481	9.866 ±0.172	12.098 ±0.642	11.122 ±0.524	11.550 ±0.470

Dose: 20, 25 mg/kg for analgesic activity. Mean± SEM, n=4

3. RESULT AND DISCUSSION

In compliance with representative scheme, title compounds were synthesized 1. Synthetic compounds for analogues of oxadiazole (VT1 – VT8) were composed of ethyl 2-(2,3-dimethohenyl)aminobenzoate (2) synthesized. Hydrazine hydrate, which has been liquefied in ethanol, was added by drop with continuous agitation and the contents refluxed at room temperature for 8 hours. The solid was separated from {2-[(2,3-dimethylphenyl)amino]phenyl}(hydrazine)methanone (3). The addition of aromatic acid and phosphoryl chloride (10 mL) in a steam bath for 5-6 hours is advisable. It was added to the crushed ice by continuous agitation when it stood at room temperature. The obtained solid crystals were filtered, water washed and ethanol recrystallized in order to produce the final compounds (VT1 – VT8).

The new compounds were structured on basis of their elementary and spectral analyses (IR, NMR and Mass). The final compounds' IR spectral peak was decided to between 3375-3200 cm-1 for N-H stretching, for C-Haliphatic and aromatic 3075-2800 cm-1, for -OH 3200-3325 cm-1 and for the NO2 1300-1400 cm-1 respectively Table-1. Aliphatic and aromatic C-H signals were found in 1HNMR spectra, around 2.36-3.68, 8.06-6.30 т ppm. Exact molecular ion peaks were seen in mass spectrums. All finishing compounds were genuine and well balanced.

Carrageen-induced paw edema method was used to evaluate anti-inflammatory activity of compounds (VT1–VT8). The compounds were tested for 200 mg/kg and comparison was made with the reference drug Diclofenac Sodium. Table 2 summarizes the results. Few of the compounds have demonstrated good edema inhibition in rats against carrageenan. The anti-inflammatory screenings revealed an activity of 84.80% after 4hr of VT1, VT2, VT5 and VT7 compounds. The findings indicate high anti-inflammatory activity, compared with the normal medication Diclofenac Sodium.

The resulting analgesic compound activity (VT1–VT8) results were detected by hot plate technique, with results shown in Table 3. The standard Pentazocin drug in all compounds was a 10 mg/kg dose. Examination of the outputs revealed excellent analgesic activity for the compound (Flufenamic Hydrazide) with replacement of the 5th oxadiazole ring. The VT1, VT4, VT5, VT6, VT7 and VT8 compounds were well analgesic relative to regular compounds.

The literature survey found that novel oxadiazole was reported excellently or well for a variety of pharmacological activities. It synthesized and tested for their anti-inflammatory and analgesic activities some novel oxadiazole analogues.

4. CONCLUSION

The research shows successful synthesis by Carrageenan-induced paw edema process and the hot plate method of the corresponding unknown title compounds in good yields and assessment of the anti-inflammatory and analgesic activities.

With this result it was determined that a sequence of 8 compounds have been produced to generate 5-(2-(2,3-dimethylphenyl)phenyl)-2-(aryl)-1,3,4-oxadiazazolial derivatives by simple and helpful method, characterized by a TLC, M.P., elementary and spectral method, and a series of eight compounds have been producing replaced ethyl-2,3-dimethylphenyl), aminobenzoate and {2-(2,3-dimmethylphenyl)phenyl}(hydrazinyl)methanone. In vivo anti-inflammatory and analgesic function, synthesized compounds have been screened. Methyl and methoxy compounds display good standards anti-inflammatory and analgesic efficacy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to reveal.

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