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1,3,4-Oxadiazole Derivatives: Synthesis, Characterization and Anti-Inflammatory Studies

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Abstract : In the present study, a series of 2-({5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-2-yl}amino) acetohydrazide derivatives have been synthesized by multistep reaction scheme. Morpholine and p-cholorobenzonitrile was used as the starting material. The structures of all synthesized compounds are characterized and confirmed by FT-IR, proton NMR and mass spectral studies with the intention of developing the novel biologically active compounds. All title synthetic compounds were screened for their invitro and invivo anti-inflammatory.
Keywords : 1,3,4-oxadiazole, Morpholine and anti-inflammatory.

Introduction

Oxadiazoles are the heterocyclic compounds containing one oxygen and two nitrogen atoms in a five membered ring containing at C-1, C-3 and C-4 positions respectively. These derivatives are synthesized by both conventional as well as microwave assisted. It is also an electronegative ring system with weak basic characteristics due to the inductive effects of the extra hetero atoms. Oxadiazoles are susceptible to nucleophilic attack as because it readily undergoes ring cleavage with aqueous acid or base hence both carbon positions are substituted [1]. Morpholine is an organic chemical compound having the chemical formula $O(CH2\text{-}CH_2)_2NH$. This heterocyclic structure features both amine and ether functional groups. Morpholine derivative plays an important role in the treatment of several diseases. Nitrogen containing hetero cyclic compounds plays a major role in pharmaceutical applications. 1,3,4-oxadiazole is widely being shows different biological activities like antibacterial, antifungal, antitubercular[2], vasodilatory, analgesic, antiinflammatory, anticonvulsant, cytotoxic, anaesthetic, hypolipidimic, anticancer[3], antioxidant, and ulcerogenic activities. 1,3,4-oxadiazole derivatives were reported to possess anti-inflammatory activity[4].

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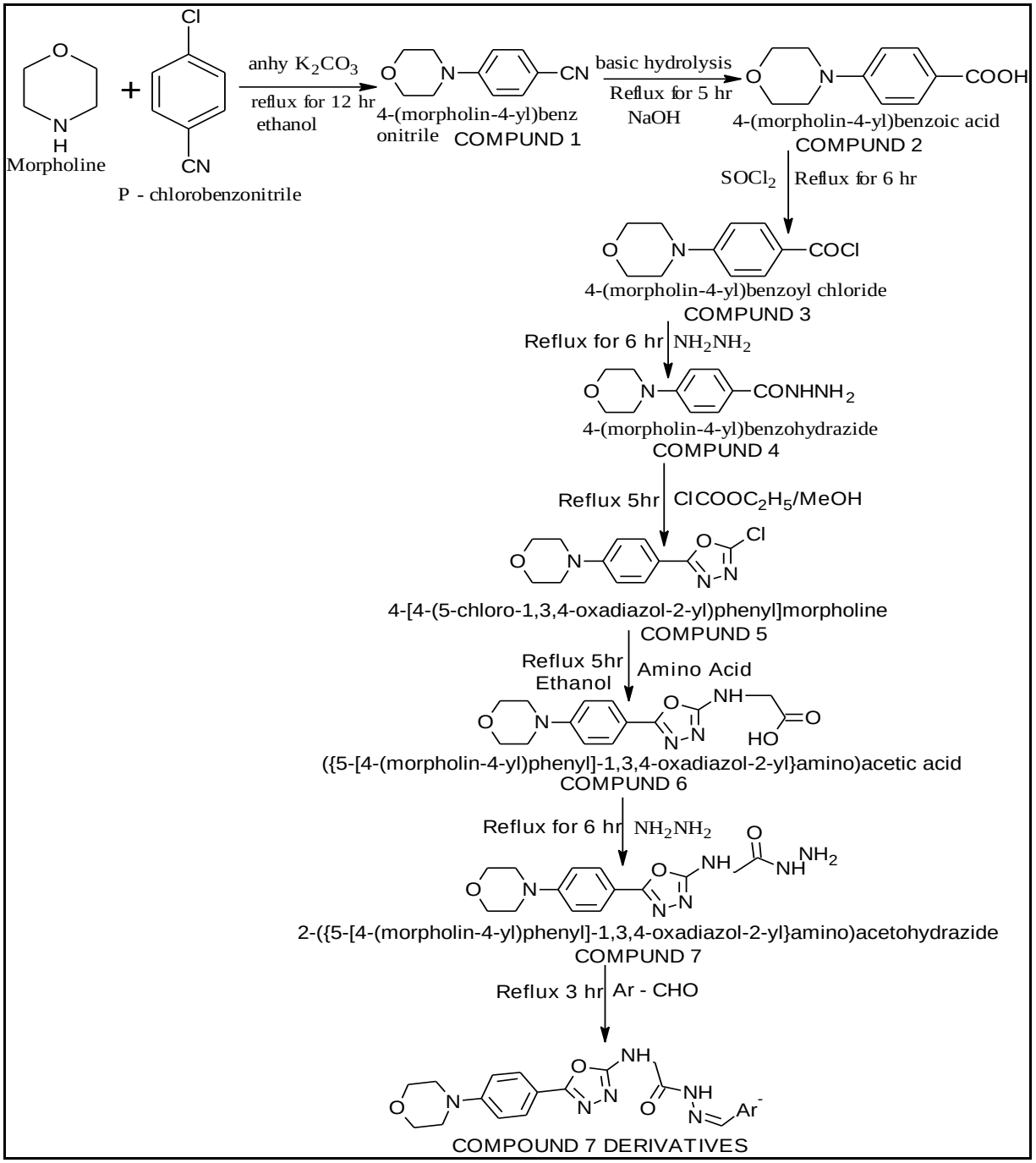
Scheme: SMRB4.



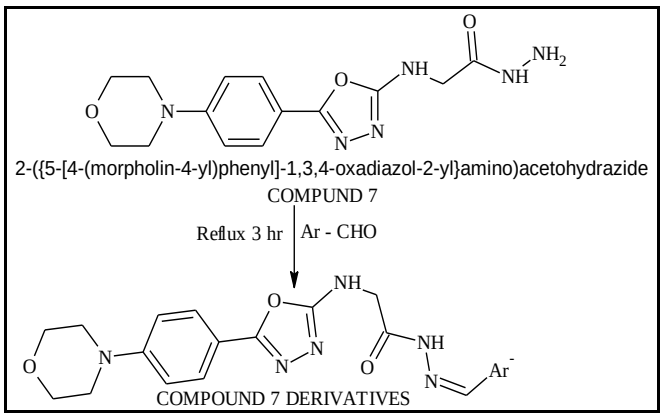
Scheme: 2-({5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-2-yl}amino) acetohydrazide (SMRB4-7).

Material and Methods

Method of Preparation of Derivatives of 2-({5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-2-yl}amino)acetohydrazide. (SMRB4-7A-7N)

A mixture of substituted benzaldehydes (1 mmol), 2-({5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-2-yl}amino)acetohydrazide. (SMRB4-7) (1 mmol) in ethanol were refluxed for 3-4 h. As the reaction progresses, the Derivatives of 2-({5-[4-(morpholin-4-yl) phenyl]-1,3,4 oxadiazol-2-yl}amino)acetohydrazide (SMRB4-7) separates out as a solid product in the reaction mixture and was collected by simple filtration. The product obtained so was dried and purified by recrystallisation from hot ethyl acetate/hexane. The purity of the product **(SMRB4-7A-7N)** was confirmed by a single spot on TLC plate using methanol: carbon tetrachloride

(8:2, v/v) as solvent system. Physical data presented in table No 2, 3, 4 and 5.



Scheme: Derivatives of 2-({5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-2-yl}amino)acetohydrazide (SMRB4-7).

Table No.1: Derivatives of 2-({5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-2-yl}amino)acetohydrazide (SMRB4-7)

Sl. No	Product Code	Name of -ArCHO	Name of Derivatives of SMRB4-7
1	SMRB4-7A	Benzaldehyde	(E)-N'-Benzylidene-2-(5-(4-morpholinophenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
2	SMRB4-7B	4- Fluorobenzaldehyde	(E)-N'(4-Flurobenzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
3	SMRB4-7C	3- Methoxy Benzaldehyde	(E)-N'(3-Methoxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
4	SMRB4-7D	2- Chlorobenzaldehyde	(E)-N'(2-Chlorobenzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
5	SMRB4-7E	4- Methoxy Benzaldehyde	(E)-N'(4-Methoxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
6	SMRB4-7F	3- Nitrobenzaldehyde	(E)-N'(3-Nitro benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
7	SMRB4-7G	4- Chlorobenzaldehyde	(E)-N'(4-Chlorobenzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
8	SMRB4-7H	3-Methoxy 4-Hydoxy Benzaldehyde	(E)-N'(3-Methoxy, 4-hydroxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
9	SMRB4-7I	4- Hydroxy Benzaldehyde	(E)-N'(4-Hydroxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
10	SMRB4-7J	3-Hydroxy 4-Methoxy Benzaldehyde	(E)-N'(3-Hydroxy, 4-methoxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
11	SMRB4-7K	4- Bromobenzaldehyde	(E)-N'(4-Bromobenzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
12	SMRB4-7L	2- Hydroxy Benzaldehyde	(E)-N'(2-Hydroxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
13	SMRB4-7M	4- Nitrobenzaldehyde	(E)-N'(4-Nitro benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide
14	SMRB4-7N	2-Nitrobenzaldehyde	(E)-N'(2-Nitro benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide

Table No.2: Physicochemical properties of compounds SMRB4-7A, SMRB4-7B, SMRB4-7C, SMRB4-7D and SMRB4-7E

Sl. No	Parameter	SMRB4-7A	SMRB4-7B	SMRB4-7C	SMRB4-7D	SMRB4-7E
1	Molecular Formula	$C_{21}H_{22}N_6O_3$	$C_{21}H_{21}FN_6O_3$	$C_{22}H_{24}N_6O_4$	$C_{21}H_{21}ClN_6O_3$	$C_{22}H_{24}N_6O_4$
2	Molecular weight	406.18	424.17	436.19	440.14	436.19
3	**T**heoretical yield	1.27 gm	1.33 gm	1.37 gm	1.38 gm	1.37 gm
4	Practical yield	1.19 gm	1.22 gm	1.34 gm	1.19 gm	1.23 gm
5	**%** yield	93.70%	91.72%	97.81%	86.23%	89.78%
6	Melting point	110-112º C	109-111º C	110-112º C	104 -106º C	118-120º C
7	Recrystallization Solvent	Hexane	Hexane	Hexane	Hexane	Hexane
8	Solvent for TLC	$CH_3OH:CCl_4$ 8:2	$CH_3OH:CCl_4$ 8:2	$CH_3OH:CCl_4$ 8:2	$CH_3OH:CCl_4$ 8:2	$CH_3OH:CCl_4$ 8:2
9	R_f Value	0.80	0.96	0.90	0.98	0.96

Table No.3: Physicochemical properties of compounds SMRB4-7F, SMRB4-7G, SMRB4-7H and SMRB4-7I

Sl. No	Parameter	SMRB4-7F	SMRB4-7G	SMRB4-7H	SMRB4-7I
1	Molecular Formula	$C_{21}H_{21}N_7O_5$	$C_{21}H_{21}ClN_6O_3$	$C_{22}H_{24}N_6O_5$	$C_{21}H_{22}N_6O_4$
2	Molecular weight	451.16	440.14	452.18	422.17
3	**T**heoretical yield	1.41 gm	1.38 gm	1.42 gm	1.32 gm
4	Practical yield	1.01 gm	1.20 gm	1.06 gm	1.25 gm
5	**%** yield	71.63%	86.95%	74.64%	94.69%
6	Melting point	106 -108º C	112-114º C	106-108º C	112 -114º C
7	Recrystallization Solvent	Hexane	Hexane	Hexane	Hexane
8	TLC	$CH_3OH:CCl_4$ 8:2	$CH_3OH:CCl_4$ 8:2	$CH_3OH:CCl_4$ 8:2	$CH_3OH:CCl_4$ 8:2
9	RF Value	0.94	0.88	0.87	0.90

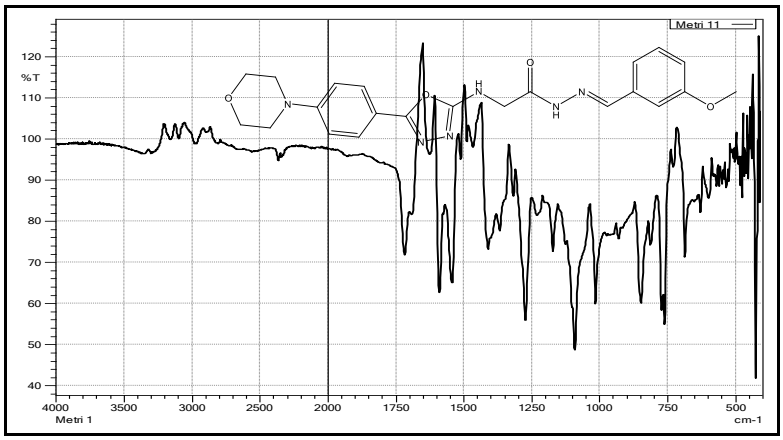
Table No.4: Physicochemical properties of compounds SMRB4-7J, SMRB4-7K, and SMRB4-7L

Sl. No	Parameter	SMRB4-7J	SMRB4-7K	SMRB4-7L
1	Molecular Formula	$C_{22}H_{24}N_6O_5$	$C_{21}H_{21}BrN_6O_3$	$C_{21}H_{22}N_6O_4$
2	Molecular weight	452.18	484.09	422.17
3	**T**heoretical yield	1.42 gm	1.52 gm	1.32 gm
4	Practical yield	1.34 gm	1.23 gm	1.10 gm
5	**%** yield	94.36%	80.92%	83.33%
6	Melting point	112 -114º C	110-112º C	122–124º C
7	Recrystallization Solvent	Hexane	Hexane	Hexane
8	TLC	$CH_3OH:CCl_4$ 8:2	$CH_3OH:CCl_4$ 8:2	$CH_3OH:CCl_4$ 8:2
9	RF Value	0.96	0.86	0.84

Table No.5: Physicochemical properties of compounds SMRB4-7M and SMRB4-7N

Sl. No	Parameter	SMRB4-7M	SMRB4-7N
1	Molecular Formula	$C_{21}H_{21}N_7O_5$	$C_{21}H_{21}N_7O_5$
2	Molecular weight	451.16	451.16
3	**T**heoretical yield	1.41 gm	1.41 gm
4	Practical yield	1.34 gm	1.30 gm
5	**%** yield	95.03%	92.19%
6	Melting point	112 -114º C	110-112º C
7	Recrystallization Solvent	Hexane	Hexane
8	TLC	CH_3OH:CCl_4 8:2	CH_3OH:CCl_4 8:2
9	RF Value	0.80	0.88

Fig No 1: FTIR spectrum of compound (E)-N' (3-Methoxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide (SMRB4-7C): 3280 cm^{-1} N-H stretch of 2^o amine, 3100 cm^{-1} aromatic C-H stretch, 2960 cm^{-1} aliphatic C-H stretch, 2890 cm^{-1} -OCH_3 stretch, 1680 cm^{-1} C = O stretch, 1630 cm^{-1} C = N stretch. Infrared spectra's (v-cm-1) was recorded on a Shimadzu IRAffinity-1(Miracle-10) auto sampler.



H^1 NMR spectrum of (E)-N' (3-Methoxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide (SMRB4-7C)

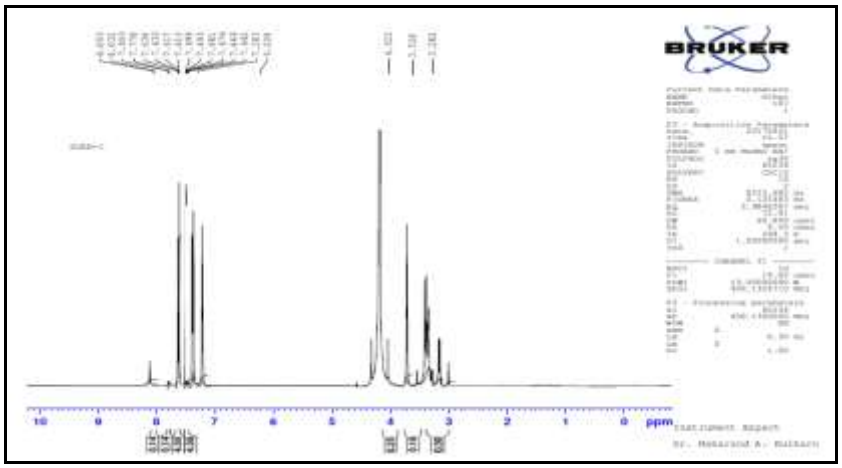


Fig No 2: H^1 NMR spectrum of compound (E)-N' (3-Methoxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide (SMRB4-7C)

Table No 6: H^1 NMR spectrum data of (E)-N' (3-Methoxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide (SMRB4-7C)

Sl. No	δ Value (ppm)	Observed δ Value (ppm)	Peak assigned
1	3.3-2.70	3.262	3H, -OCH_3 (s)
2	4.1-3.1	3.528	8H, -$N(CH_2)_2$ Morpholine(d)
3	4.5-4.1	4.022	2H, -CH_2 (s) 1H, -NH (s)
4	7.9-6.6	7.44-7.90	8H, Ar-H (m)
5	8.2-7.9	8.032	1H, -NH (s) hydrazide
6	8.2-7.9	8.053	1H, -N=CH (s)

Mass spectrum of (E)-N' (3-Methoxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide (SMRB4-7C)

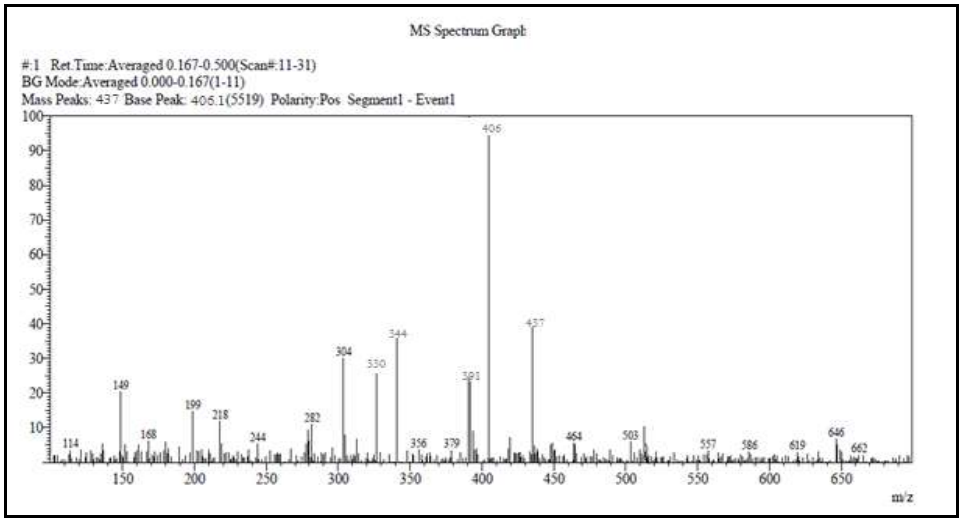


Fig No 3: - Mass spectrum of compound (E)-N'(3-Methoxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide (SMRB4-7C)

- M^+ Peaks (Mass Peak)at m/z 437 and Base Peak is 406
- Molecular weight of compound (E)-N'(3-Methoxy benzylidene)-2-(5-(4-morpholino -phenyl)-1,3,4-oxadiazol-2-ylamino) acetohydrazide (SMRB4-7C) is 437.

Pharmacology[14-18]

The animals used in the examination were sheltered in analogy of the BLDEU B M Patil Medical College animal house, which follows the guidelines and regulation set by the committee for the control and administration of experiments on animals (CPCSEA), Ministry of social justice and empowerment, Government of India. The studies were attempted with previous approval from the Institutional Animal Ethics committee (IAEC) and ultimate care was taken to establish that the animals were handling in the most kind and satisfactory manner. Wister rats and albino mice of eithersex (BLDEU B M Patil Medical College animal house Vijaypur), weighing 150-200 gm and 22-25 gm, respectively, were used. Pregnant females were eliminated.

Acute Toxicity Studies

Acute toxicity studies were performed to estimate the median lethal dose (LD50) value of the Synthesized compounds SMRB4-7A to SMRB4-7N as per the OECD (Organization for Economic Cooperation and Development) guidelines (TG 420) and the testing dose for the newly synthesized compounds on the animal model for the *in vivo* anti inflammatory activity was fixed. The LD50 of the 1,3,4-oxadizoles SMRB4-7A to SMRB4-7N were determined as per the reported method.

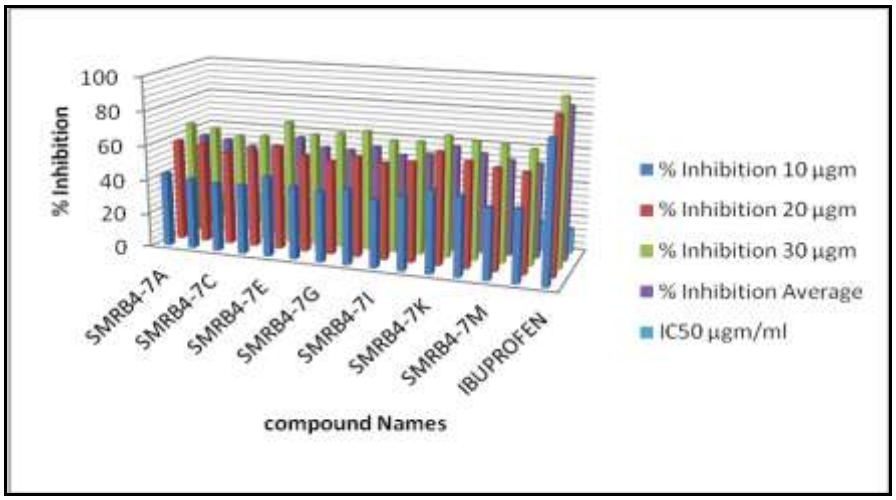
In-Vitro Anti-Inflammatory

In-vitro Anti-inflammatory activity the synthesized compounds were screened for in-vitro anti-inflammatory activity by inhibition of bovine serum albumin denaturation method. The test compounds were dissolved in minimum amount of dimethyl sulphoxide (DMSO) and diluted with phosphate buffer (0.2M, pH 7.4). Final concentration of DMF in all solution was less than 2.5%. Test solution (1 ml) containing different concentrations of drug was mixed with 1 ml of 1mM albumin solution in phosphate buffer and incubated at 270 ±10 C for 15 min. Denaturation was induced by keeping the reaction mixture at 600 ± 10 C in a water bath for 10 min. After cooling the turbidity was measured at 660 nm. (Shimadzu Spectrometer). Percentage inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and the average was taken. The percentage of inhibition is calculated from the following formula. The standard solution was also prepared as similar to that of the test solution. Ibuprofen was used as a standard. % Inhibition = 100(1 - Vt/Vc)

Where, Vt = Drug absorbance of triplicate average, Vc = Control absorbance of triplicate average

Table No 7: In-vitro anti-inflammatory Activity

Comp code	% Inhibition				IC_{50} µgm/ml
	10 µgm	20 µgm	30 µgm	Average	
SMRB4-7A	43.13	59.18	66.14	56.15	15.34
SMRB4-7B	41.15	58.43	64.38	54.65	17.38
SMRB4-7C	39.65	54.22	61.32	51.73	18.89
SMRB4-7D	40.23	56.28	62.32	52.94	17.50
SMRB4-7E	46.45	60.32	71.34	59.37	15.09
SMRB4-7F	42.16	56.43	65.32	54.63	16.76
SMRB4-7G	40.67	54.56	67.12	54.11	17.50
SMRB4-7H	43.56	58.34	69.62	57.17	15.43
SMRB4-7I	38.89	55.89	65.30	53.36	17.90
SMRB4-7J	42.56	57.80	65.87	55.41	16.80
SMRB4-7K	47.78	64.66	70.32	60.92	15.00
SMRB4-7L	45.30	60.56	68.40	58.08	15.18
SMRB4-7M	40.67	58.34	67.44	55.48	16.67
SMRB4-7N	41.44	57.12	66.30	54.95	16.45
IBUPROFEN	80.28	89.26	96.32	88.62	14.13



Graph 1: In-vitro anti-inflammatory Activity

In-vitro Anti-inflammatory activity was carried out using Bovine Serum albumin denaturation method. All the title compounds (SMRB4-7A-N) were screened for anti-inflammatory activity. The results of the anti-inflammatory activity of the compounds are shown in the table no 7 and graph 1. SMRB4-7E, SMRB4-7K and SMRB4-7L showed good activity. Whereas compounds SMRB4-7A and SMRB4-7H showed mild activity and remaining compounds showed poor anti-inflammatory activity.

In vivo Anti-Inflammatory Evaluation

Anti-inflammatory activity was evaluated by carrageenan-induced paw edema test using groups of albino rats weighing 100-120 gm each and 6 rats per group, the animals were injected with 0.1 mL of carrageenan (1% solution in normal saline) in the plantar tissue of the right hind paw. The first group received only 0.5% carboxymethylcellulose (CMC) orally and served as untreated control. The test groups received compounds suspended in 0.5% CMC orally at a dose of 25 mg/kg one hour prior to carrageenan injection. While the positive control group received 25 mg/kg Indomethacin suspended in 0.5% CMC, orally one hour before carrageenan injection. Four hours after carrageenan administration, the paw volumes (mL) were measured using the mercury displacement technique with the help of a plethysmograph. The percent inhibition of paw edema was calculated by using the following formula.

$$\%\text{Inhibition} = \left(\frac{a-x}{b-y}\right) \times 100$$

Where, **x** is the mean paw volume of rats in the test group before the administration of carrageenan and/or test compounds or reference drug, a is the mean paw volume of rats after the administration of carrageenan in the test group (reference drug/ test compound treated), b is the mean paw volume of rats after the administration of carrageenan in the control group, **y** is the mean paw volume of rats before the administration of carrageenan in the control group. The mean percent inhibition of Indomethacin and tested compounds at 25 mg/kg concentrations was compared with control using the repeated measures ANOVA with Dunnett's test.

Statical Analysis

The compounds SMRB4-7A to SMRB4-7N at a dose of 25 mg/kg were evaluated for in vivo anti-inflammatory activity by carrageenan induced paw edema method. Indomethacin at 25 mg/kg was used as reference standard and CMC as control. The result of the anti-inflammatory screening at the end of four hours after the administration of carrageenan showed that compounds SMRB4-7A to SMRB4-7N exhibited edema reduction of 35.2 to 59.43%, in comparison to standard Indomethacin, which showed an edema reduction of about 60.3%. Interestingly, compounds with aromatic aldehydes substitution at position C2 of the oxadiazole moiety (SMRB4-7E, SMRB4-7K and SMRB4-7L) in the present series exhibited significant anti-inflammatory efficacy ranging from 35.2 to 59.43% edema reduction. The anti-inflammatory results highlight the importance of aromatic aldehydes as substituent at position 2 and 5 of the oxadiazole moiety as possible reason for the anti-inflammatory efficacy. The statistical analysis of the anti-inflammatory data by Dunnett's test revealed that compounds SMRB4-7E and SMRB4-7L exhibited significant anti-inflammatory activity compared to control. The percentage inhibition of inflammation by the test compounds at dose of 25mg/kg at the end of four hours time intervals are expressed as m ± SEM. in below Table no 8.

Table No 8: In vivo anti-inflammatory activity of the test compounds at 25 mg/kg by carrageenan induced paw edema method.

Sl. No	Compound	% Protection
1	SMRB4-7A	56.02±1.90***
2	SMRB4-7B	51.29±1.76***
3	SMRB4-7C	51.45±1.02***
4	SMRB4-7D	55.09±1.15***
5	SMRB4-7E	59.29±1.12***
6	SMRB4-7F	48.13±1.80***
7	SMRB4-7G	50.19±1.06***
8	SMRB4-7H	57.62±0.43***
9	SMRB4-7I	44.20±0.34***

10	SMRB4-7J	35.29±1.69***
11	SMRB4-7K	58.12±0.65***
12	SMRB4-7L	59.43±1.66***
13	SMRB4-7M	50.12±2.30***
14	SMRB4-7N	46.27±1.16***
15	Indomethacin	60.30±1.46***

Results are expressed as the mean values from three independent experiments ± SEM.

Data was analysed by Dunnett's test n=3: (***) equals P≤0.0001

Conclusion

Compounds reported were derivatives of reaction scheme-SMRB4; they were obtained in high purity with good yield. The FTIR studies show peeks at 1490-1690 cm^{-1} C=N stretch proves formation of derivatives of corresponding structure (SMRB4-7) and these derivatives will be tested for their biological activities. H^1 NMR spectrum data and mass spectra of synthesized derivatives compounds of Scheme SMRB4-6 analysis proves that resultant compound and The statistical analysis of the anti-inflammatory data by in vivo and in-vitro method compounds SMRB4-7E and SMRB4-7L exhibited significant anti-inflammatory activity compared to control.

Conflict of Interest:

Author is not having conflict of interest

Acknowledgments

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