Original Research Paper

Volume-8 | Issue-2 | February-2018 | PRINT ISSN No 2249-555X

Pharma

IN-VIVO ANALGESIC ACTIVITY OF NOVEL DERIVATIVES OF 2, 5 DISUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES.

Somashekhar M* Department of Pharmaceutical Chemistry, BLDEA's SSM College of Pharmacy and Research Centre Vijaypur-586101, Karnataka. *Corresponding Author

R B Kotnal Department of Pharmaceutical Chemistry, BLDEA's SSM College of Pharmacy and Research Centre Vijaypur-586101, Karnataka.

ABSTRACT Oxadiazole types of five membered heterocyclic compounds contain oxygen and two nitrogen atoms at position 1, 3 and 4 positions respectively. These derivatives are synthesized by both conventional as well as microwave assisted. As with the azoles, this 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. 1,3,4- oxadiazoles also display a wide spectrum of activities such as antibacterial, antimalarial, anti- inflammatory, antifungal and anticonvulsant, antihistaminic, anticancerous, and antihypertensive activities. Hence, some new 1,3,4 – oxadiazoles are synthesized and biologically evaluated as analgesic activity according to reaction sequence outlined in scheme. From these 1,3,4-oxadiazoles act as starting material for the synthesis of various derivatives of 1,3,4-oxadiazoles. With the aim of obtaining the new broad spectrum various 1, 3, 4-oxadiazole derivatives, which will devoid of side effects associated with current therapy.

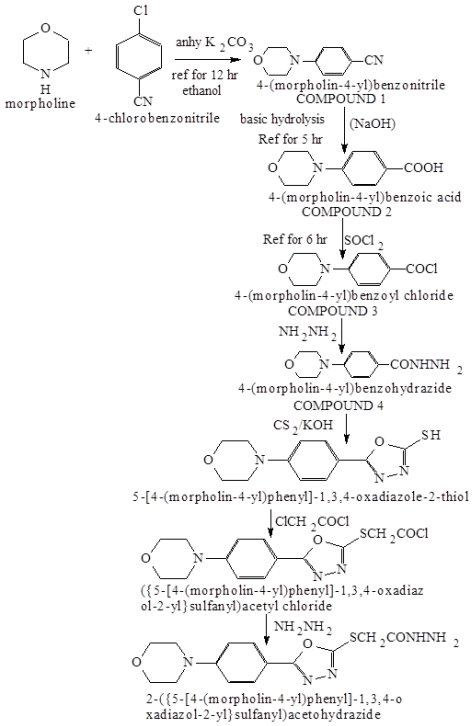
KEYWORDS : 1,3,4-oxadiazole, Morpholine and Analgesic activity.

INTRODUCTION[1-3]

Oxadiazole is a five membered heterocyclic compound containing oxygen and two nitrogen atoms 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.

1,3,4-Oxadiazoles also display a wide spectrum of activities such as antibacterial, antimalarial, anti- inflammatory, antioxidant, antipyretic, antiproliferative, antifungal and anticonvulsant, antihistaminic, anticancerous, and antihypertensive activities. The novel morpholine and 1,3,4 -oxadiazole derivatives are obtained staring from morpholine and Para chlorobenzonitrile and cyclisation by carbon di sulphide and potassium hydroxide.

EXPERIMEMTAL MATERIALAND METHODS[4-9]



Method of preparation of 4-Morpholin-4-yl-benzonitrile (SMRB1-1)

To a mixture of morpholine (4gm, 0.14 mol) in ethanol (25ml) and 4-chloro-benzonitrile (3.2gm, 0.05 mol) in 250ml round bottom flask, added anhydrous potassium carbonate (3gm). Then the reaction mixture was heated at 120°C for 12 h. Water (25ml) was added onto the reaction mixture. The precipitate was filtered off, washed with water and dried under vacuum (30° C) to obtain title compound. The crude product was recrystalized from 50% aqueous ethanol, Physical data presented in table No.1.

Method of preparation of Synthesis of 4-morpholin-4-yl-benzoicacid (SMRB1-2)

To a solution of sodium hydroxide (6gm, 0.3mol) in water (120ml), 4-morpholin–4ylbenzonitrile (SMRB1-1) (3gm, 0.01mol) was added. Small amount of methanol was added to increase the rate of the reaction. The reaction mixture was refluxed on water bath for 5 hrs. It was cooled to room temperature and make acidic by the addition of HCl (10%) with efficient stirring. The precipitate was filtered off, washed with water and dried under vacuum (60° C) to obtain the title compound. Crude product was recrystallized from ethanol, Physical data presented in table No.1.

Method of Preparation of Synthesis of 4-Morpholin-4-yl-Benzoylchloride (SMRB1-3)

A mixture of 4-morpholin– 4yl-benzoic acid (SMRB1-2) (6gm, 1 mol) in ethanol (25ml) and thionyl chloride (SOCl2) (3.3ml, 0.5 mol) was refluxed on water bath for 6 hrs. Excess of thionyl chloride was removed by distillation under reduced pressure or by adding formic acid dropwise as required and the residue so collected was used for the next step, Physical data presented in table No.1.

Method of Preparation of Synthesis of (4-morpholin-4-yl) benzohydrazide (SMRB1-4)

To the solution of 4-morpholin– 4ylbenzoyl chloride (SMRB1-3) (6gm, 0.01 mol) in 15ml of methanol, 99% hydrazine hydrate (1.94ml, 0.03 mol) was added and the mixture was refluxed with on water bath for 4hrs. After cooling the precipitate was filtered off, washed with water and dried under vacuum (60°C) to obtain title compound. The crude product was recrystalized from 50% aqueous ethanol, Physical data presented in table No.1.

Method of Preparation of Synthesis of 5[4-Morpholin-4-yl-Phenyl)-1,3,4-oxadiazole 2-thiol. (SMRB1-5)

A mixture of (4-morpholin-4-yl) benzohydrazide (SMRB1-4) (0.01mmol) 10ml and carbon di sulphide 0.6ml added a solution of KOH 0.56gm in 50ml water and 50ml ethanol was refluxed on water bath for about 3hrs then the reaction mixture was acidified with conc HCl. The solid product was filtered and washed with water and dried

under vacuum (50°C) to obtain title compound. The crude product was recrystalized from 50% aqueous ethanol, Physical data presented in table No.2.

Method of Preparation of Synthesis of {5[4-Morpholin-4-yl-Phenyl)]-1,3,4-oxadiazole-2yl} Sulfonyl acetyl chloride. (SMRB1-6)

The suspension of 5[4-Morpholin-4-yl-Phenyl)1,3,4 oxadiazole 2 thiol (SMRB1-5) in glacial acetic acid 30 ml and chloroacetyl chloride was added dropwise with constant stirring the reaction mixture was refluxed gentaly at 120° C for 5 hours and poured on crushed ice and filtered off, washed with water and dried under vacuum (60° C) to obtain title compound. The crude product was recrystalized from 50% aqueous ethanol, Physical data presented in table No.2.

Method of Preparation of Synthesis of 2{5[4-Morpholin-4-yl-Phenyl)]-1,3,4-oxadiazole-2yl} Sulfonyl acetohydrazide. (SMRB1-7)

To the solution of {5[4-Morpholin-4-yl-Phenyl)] 1,3,4 oxadiazole-2yl} Sulfonyl acetyl chloride. (SMRB1-6) (6gm, 0.01 mol) in 15ml of methanol, 99% hydrazine hydrate (1.94ml, 0.03 mol) was added and the mixture was refluxed with on water bath for 4hrs. After cooling the precipitate was collected, washed with distilled water, and dried under vacuum (50° C) to obtain title compound. The crude product was recrystalized from 70% aqueous ethanol, Physical data presented in table No.2.

RESULT AND DSISCUSSION

Table no.1: Physicochemical properties of compound SMRB1-1, SMRB1-2 and SMRB1-3 and SMRB1-4.

Sl.no	Parameter	SMRB1-1	SMRB1-2	SMRB1-3	SMRB1-4
1	Molecular Formula	$C_{11}H_{12}N_2O$	$C_{11}H_{13}NO_3$	$C_{11}H_{12}ClNO_2$	$C_{11}H_{15}N_3O_2$
2	Molecular weight	188.22	207.25	225.6	221.6
3	Theoretical yield	8.64gm	3.30gm	6.5gm	5.86gm
4	Practical yield	6.23gm	2.90gm	5.9gm	2.90gm
5	% yield	72.10%	87.87%	90.76 %	49.48%
6	Melting point	118-120° C	208-210°C	210-212° C	223-225°C
7	Recrystallization Solvent	Ethanol	Ethanol	Ethanol	Ethanol
8	TLC	Benzene: Ethanol	Benzene: Ethanol	Benzene:Methanol	Benzene:Methanol
9	RF Value	0.7	0.74	0.52	0.68

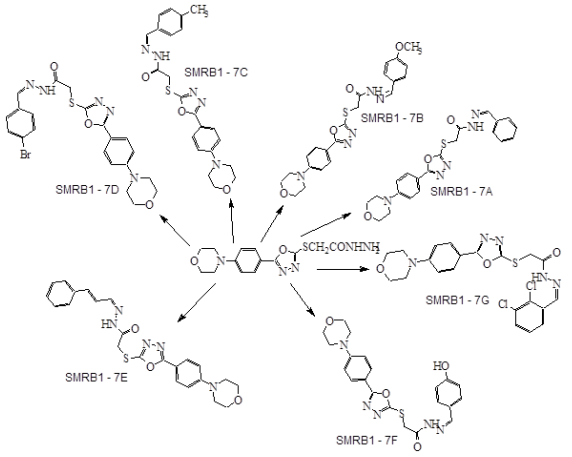
Table no.2: Physicochemical properties of compound SMRB1-5, SMRB1-6 and SMRB1-7.

Sl.no	Parameter	SMRB1-5	SMRB1-6	SMRB1-7
1	Molecular Formula	$C_{12}H_{13}N_3O_2S$	$C_{14}H_{14}ClN_3O_2S$	$C_{14}H_{17}N_5O_3S$
2	Molecular weight	263.3	339.8	335.38
3	Theoretical yield	11.90gm	10.31gm	5.92gm
4	Practical yield	8.62gm	6.48gm	3.27gm
5	% yield	72.43%	62.85 %	55.23%
6	Melting point	192-195°C	214-216° C	205-206°C
7	Recrystallization Solvent	Ethanol	Ethanol	Ethanol
8	TLC	Benzene:Methanol	Benzene:Methanol	Benzene:Methanol
9	RF Value	0.80	0.65	0.55

Derivatives of 2{5[4-Morpholin-4-yl-Phenyl)]-1,3,4-oxadiazole-2yl} Sulfonyl acetohydrazide10-17 (SMRB1-7).

Method of Preparation of Derivatives of 2{5[4-Morpholin-4-yl-Phenyl)]-1,3,4-oxadiazole-2yl} Sulfonyl acetohydrazide. (SMRB1-7A-7G)

A Mixture of 2{5[4-Morpholin-4-yl-Phenyl)] 1,3,4 oxadiazole-2yl} Sulfonyl acetohydrazide 0.01mole and Aromatic aldehyde and few drops of glacial acetic acid in ethanol 30 ml refluxed for 5 hours the residue was stirred with ice cold water 50 ml and filtered off, and dried under vacuum to obtain title compound. The crude product was recrystalized from aqueous ethanol, Physical data presented in table No.4 and 5



Sl.No	Product Code	Name of Ar-CHO	Name of Derivatives of SMRB1-7
1	SMRB1-7A	Benzaldehyde	N'-(benzylidene)-2-((5-(4-Morpholino -phenyl)-1,3,4-oxadiazol-2-yl)thio) acetohydrazide
2	SMRB1-7B	4-Methoxy benzaldehyde	N'-(4-methoxybenzylidene)-2-((5-(4-Morpholino -phenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide
3	SMRB1-7C	4-Methyl benzaldehyde	N'-(4-methylbenzylidene)-2-((5-(4-Morpholinophenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide
4	SMRB1-7D	4-Bromo benzaldehyde	N'-(4-bromobenzylidene)-2-((5-(4-Morpholinophenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide
5	SMRB1-7E	Cinnamaldehyde	(2-((5-(4-Morpholinophenyl)-1,3,4-oxadiazol-2-yl)thio)-N-3-phenylallylidene) acetohydrazide
6	SMRB1-7F	4-Hydroxy benzaldehyde	N'-(4-hydroxybenzylidene)-2-((5-(4-Morpholino-phenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide
7	SMRB1-7G	2,3 dichloro benzaldehyde	N'-(4-(2,3-dichlorobenzylidene)-2-((5-(4-Morpholino-phenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide

Table No 3: list of 1,3,4-oxadiazole Novel Derivatives

Table no.4: Physical properties of compound SMRB1-7A, SMRB1-7B, SMRB1-7C and SMRB1-7D.

Sl. No	Parameter	SMRB1-7A	SMRB1-7B	SMRB1-7C	SMRB1-7D
1	Molecular Formula	$C_{21}H_{21}N_5O_3S$	$C_{22}H_{23}N_5O_4S$	$C_{22}H_{23}N_5O_3S$	$C_{21}H_{20}N_5O_3SBr$
2	Molecular weight	423.49	453.51	437.51	502.38
3	Theoretical yield	1.26gm	1.35gm	1.30gm	1.49gm
4	Practical yield	1.20gm	1.10gm	0.83gm	1.12gm
5	% yield	95.23 %	81.48 %	63.84 %	75.16 %
6	Melting point	192-194° C	226-228° C	219-221° C	208-210° C
7	Recrystallization Solvent	Ethanol	Ethanol	Ethanol	Ethanol
8	TLC	Benzene: Methanol	Benzene: Methanol	Benzene: Methanol	Benzene: Methanol
9	RF Value	0.76	0.52	0.77	0.80

Table no.5: Physicochemical properties of compound SMRB1-7E, SMRB1-7F and SMRB1-7G.

Sl.No	Parameter	SMRB1-7E	SMRB1-7F	SMRB1-7G
1	Molecular Formula	$C_{23}H_{23}N_5O_3S$	$C_{21}H_{21}N_5O_4S$	$C_{21}H_{19}N_5O_3SCl_2$
2	Molecular weight	449.53	439.49	492.38
3	Theoretical yield	1.34gm	1.31gm	1.46gm
4	Practical yield	1.31gm	1.22gm	1.15gm
5	% yield	97.76 %	93.12 %	78.76 %
6	Melting point	217-218^{0}C	182-183^{0}C	204-206^{0}C
7	Recrystallization Solvent	Ethanol	Ethanol	Ethanol
8	TLC	Benzene:Methanol	Benzene:Methanol	Benzene:Methanol
9	RF Value	0.79	0.72	0.53

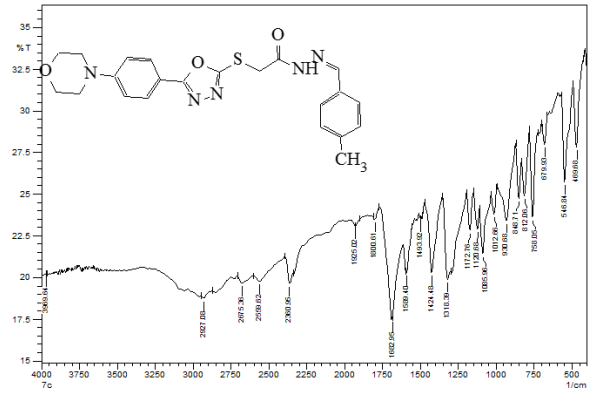


Fig 1: FTIR spectrum data of compound N'-(4-methylbenzylidene)-2-((5-(4-Morpholinophenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide (SMRB1-7C)

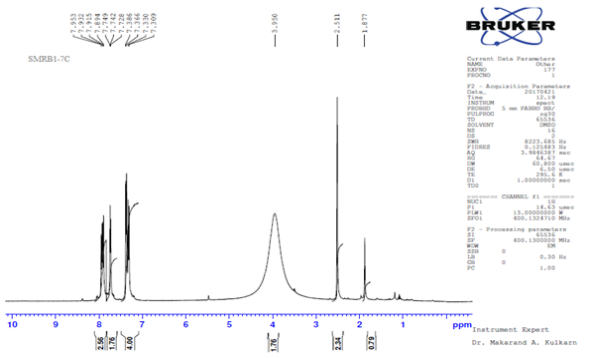


Fig 2: H^1 NMR spectrum of compound N'-(4-methylybenzylidene)-2-((5-(4-Morpholinophenyl)-1,3,4-oxadiazol-2 yl)thio) aceto- hydrazide (SMRB1-7C).

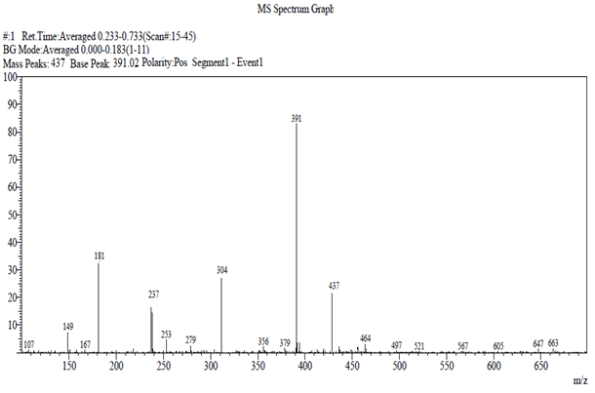


Fig No 3: **- Mass spectrum of compound** N'-(4-methylbenzylidene)-2-((5-(4-Morpholinophenyl)-1,3,4-oxadiazol-2 yl)thio) aceto-hydrazide (SMRB1-7C).

- **M$^+$Peaks (Mass Peak)at m/z 437 and Base Peak is 391**
- Molecular weight of compound N'-(4-methylbenzylidene)-2-((5-(4-Morpholinophenyl)-1,3,4-oxadiazol-2 yl)thio) aceto-hydrazide (SMRB1-7C) is 437.

DISCUSSION

Compounds reported were intermediates of reaction scheme-SMRB1; they were obtained in high purity with good yield. The FTIR studies shows following peeks corresponding to structure character. Infrared spectrum of compound SMRB1-1 shows a peak at 3181cm-1 corresponding to aromatic C-H stretch, 2924 cm-1 corresponding to aliphatic C-H stretch, 1620 cm-1 for aromatic C=C stretch, 1220 cm-1 for C-N stretch (nitrile). The Infrared spectrum of compound SMRB1-2 shows a peaks at 2925cm^{-1} corresponding aromatic C-H stretch, peak at 2850 cm-1 for aliphatic C-H stretch, 1593 cm-1 for aromatic C=C stretch, 1321 cm-1 C-N stretch (morpholine), disappearance of peak at 1220 cm-1 of nitrile and appearance peak at 1683 cm-1 C=O stretch proves formation of carboxylic acid. Infrared spectrum of compound SMRB1-3 shows a peak at 2926 cm^{-1} corresponding to aromatic C-H stretch, 2675 cm^{-1} corresponding to aliphatic C-H stretch, 1424 cm^{-1} for aromatic C=C stretch, 1246 cm^{-1} for C-N stretch (morpholine), 1683 cm^{-1} C=O Stretch (carbonyl), 1014 cm^{-1} C-O aromatic Stretch, appearance peak at 1088 cm^{-1} C-Cl Stretch proves formation of chloride on aromatic ring. The Infrared spectrum of compound SMRB1-4 shows a peaks at 3150 cm^{-1} N-H Stretch of 1^o amine, peak at 2851 cm^{-1} corresponding aromatic C-H stretch, peak at 2676 cm^{-1} for aliphatic C-H stretch, peak at 1683 cm^{-1} C=O Stretch (carbonyl), peak at 1424 cm^{-1} for aromatic C=C stretch, peak at 1130 cm^{-1} C-N stretch (morpholine), appearance peak at 852 cm^{-1} N-H Bend proves formation of hydrazine hydrate. The Infrared spectrum of compound SMRB1-5 shows a peaks at 2843 cm^{-1} N-H Stretch of 1^o amine, peak at 2634 cm^{-1} corresponding aromatic C-H stretch, peak at 2557 cm^{-1} for aliphatic C-H stretch, peak at 1681 cm^{-1} C=O Stretch (carbonyl), peak at 1416 cm^{-1} for aromatic C=C stretch, peak at 1134 cm^{-1} is of C-N stretch (morpholine), appearance of peak at 680 cm^{-1} C-S Stretch proves formation of 1,3,4-oxadiazole by cyclisation. The Infrared spectrum of compound SMRB1-6 shows a peaks at 3320 cm^{-1} N-H Stretch of 1^o amine, peak at 2846 cm^{-1} corresponding aromatic C-H stretch, peak at 2635 cm^{-1} for aliphatic C-H stretch, peak at 1683 cm^{-1} C=O Stretch (carbonyl), peak at 1533 cm^{-1} for aromatic C=C stretch, peak at 1134 cm^{-1} C-N stretch (morpholine), peak at 670 cm^{-1} C-S Stretch(thiol), appearance peak at 1089 cm^{-1} C-Cl Stretch proves formation of chloride. The Infrared spectrum of compound SMRB1-7 shows a peaks at 2845 cm^{-1} N-H Stretch of 1^o amine, peak at 2676 cm^{-1} corresponding aromatic C-H stretch, peak at 2559 cm^{-1} for aliphatic C-H stretch, peak at 1686 cm^{-1} C=O Stretch (carbonyl), peak at 1586 cm^{-1} for aromatic C=C stretch, peak at 1133 cm^{-1} C-N stretch (morpholine), peak at 670 cm^{-1} C-S Stretch(thiol), appearance peak at 813 cm^{-1} N-H Bend proves formation of hydrazine hydrate.

These intermediates converted into corresponding derivatives and they were obtained in high purity with good yield. The FTIR studies show peeks at 1422-1425 cm^{-1} C=N stretch proves formation of derivatives of corresponding structure SMRB1-7A-G and 1H-NMR spectrum: 1H-NMR (DMSO-d6, 300 MHz), δ (ppm): 1.0-2.30 (s, 1H, -NH), 2.9-4.1 (-N (CH2)2 Morpholine Moiety), 2.0-2.79 (–CH_3), 6.8-7.5 (m, 8H, Ar-H), 7.7-8.3 (-CONH), 3.6-4.2 (-CH_2). Element analysis is C-55.32, H-4.93, N-12.10, O-18.42, and S-9.23. LC-MS (m/z): 437 and Base Peak is 391 (M+ 1). These derivatives will be tested for their biological activities.

PHARMACOLOGY[18-25]

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 20-25 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 SMRB1-7A to SMRB1-7G 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 SMRB1-7A to SMRB1-7G were determined as per the reported method.

IN VIVO ANALGESIC EVALUATION

The compounds that display good anti-inflammatory active (>50%) were protected for analgesic activity. Analgesic activity was carried out by Eddy's hot plate method. Six groups of albino mice of either sex each comprising of four animals, weighing between 20-25 gms were deprived of food and water for 12hrs prior to the experiment. The animal with a basal reaction time of less than 8 seconds were considered for the study. The hot plate was stabilized at 55±1°C, the animals are placed on the hot plate and the time until either licking or jumping response with the animals is recorded by a stopwatch, the time taken as the end point. The reaction time was recorded at prefixed time interval i.e., 0, 20, 40, 60, 80, 100 and 120 minutes following oral or subcutaneous administration of the standard or the test compound. The animal experimental data were indicated as mean±SEM. Statistical characteristic between the treatments and the standard were approved by one-way ANOVA pursue by Dunnett's multiple comparison test shown in table no 8.

Table No 6: Data showing analgesic activity of 1,3,4-oxadiazole derivatives (SMRB1-7A SMRB1-7G).

Sl. No	Compound	Basal reaction time(Sec.)after						
		0min	20min	40min	60min	80min	100min	120min
1	Control (Gum Acacia)	4.27±0.60	4.32±0.65	4.6±0.53	4.22±0.25	4.14±0.70	4.50±0.81	5.03±0.47
2	Standard (Pentazocin 10mg/kg)	7.45±1.02	16.23±0.22	16.45±1.13	17.48±0.67	17.47±1.56	15.22±0.78	16.73±0.89
3	SMRB1-7A	5.20±0.32	11.23±1.12	12.26±0.35	11.65±0.70	12.56±1.11	14.37±0.34	14.22±0.19
4	SMRB1-7B	4.21±1.10	5.28±0.19	13.44±0.45	12.57±0.82	10.25±1.09	11.66±0.79	11.47±1.25
5	SMRB1-7C	6.44±0.56	11.23±0.22	12.45±1.13	12.48±0.67	14.48±1.06	14.22±0.18	15.73±0.89
6	SMRB1-7D	5.85±0.66	9.03±0.94	13.21±0.85	13.71±0.70	14.58±1.56	15.74±0.78	14.23±0.56
7	SMRB1-7E	4.89±1.74	6.13±0.62	6.45±1.05	11.45±0.97	12.44±1.33	11.27±0.19	13.52±0.67
8	SMRB1-7F	6.78±1.62	10.03±0.22	13.54±1.54	15.27±0.67	15.87±0.45	16.01±0.70	16.73±0.13
9	SMRB1-7G	3.45±1.02	6.32±0.22	6.45±1.63	7.88±0.98	9.47±1.86	10.22±1.08	11.03±0.09

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

STATICALANALYSIS

The synthesized compounds have shown a significant Analgesic activity. Results are tabulated in table No 6. The compounds SMRB1-7C and SMRB1-7F have shown potent Analgesic activity. The compounds SMRB1-7A and SMRB1-7D showed a moderate analgesic activity. The other compound SMRB1-7B, SMRB1-7E and SMRB1-7G also showed a significant analgesic activity till 120 minutes.

CONCLUSION

From the above result it has been concluded that a series of seven compounds Derivatives of 2{5[4-Morpholin-4-yl-Phenyl)]-1,3,4-oxadiazole-2yl} Sulfonyl acetohydrazide. (SMRB1-7A-7G). Characterized by TLC, M.P and spectral analysis like NMR, IR and Mass Spectroscopy. Synthesized compounds were screened for their In-vivo Analgesic activity. The synthesized compounds have shown a significant Analgesic activity. Results are tabulated in Table No 6. The compounds SMRB1-7C and SMRB1-7F have shown potent Analgesic activity. The compounds SMRB1-7A and SMRB1-7D showed a moderate analgesic activity. The other compound SMRB1-7B, SMRB1-7E and SMRB1-7G also showed a significant analgesic activity till 120 minutes.

ACKNOWLEDGEMENT

The authors wish to thank Dr. N V Kalyane. Principal, BLDEA'S SSM College of Pharmacy and Research Centre Vijaypur, Dr. B Shivkumar HOD, Pharmaceutical Chemistry Department and the Management of BLDEA's SSM College of Pharmacy for providing facilities to carry out the research work.

REFERENCES

1. Huda SK, Nurdiana N, Thorsten H, Azlina AA, Azhar A. Conjugated Oligo-Aromatic Compounds Bearing a 3,4,5-Trimethoxy Moiety: Investigation of Their Antioxidant Activity Correlated with a DFT Study. Molecules, 2016; 21(224): 1-19.
2. Wang P, Chen L, Zhou J, Fang H, Wua Z, Song B, Yang S. Synthesis and bioactivities of 1-aryl-4-hydroxy-1H-pyrrol-2(5H)-one derivatives bearing 1,3,4-oxadiazole moiety. Journal of Saudi Chemical Society, 2016; 20: S121-S130.
3. Shridhar A, Keshavayya J, Peethambar S, Hoskeri H. Synthesis and biological activities of Bis alkyl 1,3,4-oxadiazole incorporated azo dye derivatives. Arabian Journal of Chemistry, 2016; 9: S1643–S1648.
4. Khalid H, Rehman A, Abbasi MA, Malik A, Rasool S, Nafeesa K, Ahmad I, Afzal S. Synthesis, spectral analysis and anti-bacterial study of N-substituted derivatives of 2-(5-(1- (phenylsulfonyl) piperidin-4-yl)-1,3,4-oxadiazol- 2-ylthio)acetamide. Journal of Saudi Chemical Society, 2016; 20: S615–S623.
5. Desai N, Dodiya A. Conventional and microwave techniques for the synthesis and antimicrobial studies of novel 1-[2-(2-chloro-6-methyl (3-quinolyl))-5-(4- nitrophenyl) -(1,3,4-oxadiazolin-3-yl)]-3-(aryl)prop-2-en-1-ones. Arabian Journal of Chemistry, 2016; 9: S379–S387.
6. Selvaraj K, Kulanthai K, Sadhasivam G. Synthesis, characterization and biological evaluation of novel 2,5 substituted-1,3,4 oxadiazole derivatives. Saudi Pharmaceutical Journal, 2016: 1-9.
7. Khalilullah H, Khan S, Nomani Md, Ahmed B. Synthesis, characterization and antimicrobial activity of benzodioxane ring containing 1,3,4-oxadiazole derivatives. Arabian Journal of Chemistry, 2016; 9: S1029–S1035.
8. Pagare A, Kankate RS, Shaikh AR. Synthesis and Antimicrobial Evaluation of newer 1,3,4- Oxadiazole Derivatives containing R-phenyl moiety under Conventional conditions. Res J. Chem. Environ. Sci., 2016; 4(2):45-50.
9. Roohi S, Ashvini V, Farooqui SM, Durrani A. Synthesis of Some Novel 1,3,4-Oxadiazole. Journal of Medicinal Chemistry and Drug Discovery, 2016; 2(1): 354-360.
10. Rubab K, Abbasi1 MA, Rehman A, Siddiqui SZ, Akhtar MN. S-Alkylated/aralkylated 2-(1H-indol-3-yl-methyl)-1,3,4-oxadiazole-5-thiol derivatives. 1. Synthesis and characterization. Tropical Journal of Pharmaceutical Research, 2016; 15(7): 1515-1524.
11. Altıntop Md, ODevrim C, Ozkay UD, Kaplancıkl ZA. Synthesis and Evaluation of New 1,3,4-Thiadiazole Derivatives as Antinociceptive Agents. Molecules, 2016; 21(1004): 1-10.
12. Mohammad I, Roshan DN, Naqui JS. Synthesis of 2,3,5-Trisubstituted 1,3,4-Oxadiazole Via Cyclization of 5-Fused Heteryl Pyrazole-3-Carbohydrazone having Quinolin-3-yl Moiety and their Antibacterial Activity. Am. J. PharmTech Res., 2016; 6(5): 535-547.
13. Masoud K. Investigation of the Stability of Oxadiasole and Their Analogs Using Quantum Mechanics Computation. Computational Chemistry, 2016; 4: 11-16.
14. Entesar, Obeed AT, Khalida, Ali T. Synthesi s, Characterization and Polymerization of 1,3,4- Oxadiazole Derivatives of Amoxicillin and Evaluation Antibacterial Activities. Int.J.Curr.Microbiol.App.Sci., 2016; 5(2): 511-522.
15. Huda AB, Maysoon SA, Layla AO. Synthesis of Some New Oxadiazole and Tetrazole Derived from Naproxen Drugs. Swift Journal of Pharmacy and Pharmacology, 2016; 1(1): 011-015.
16. Aruna SM, Yadav DB, Kenchappa R, Sandeep T, Belenahalli MV. Conventional and Microwave Assisted Synthesis of 5-phenyl-2-substituted-1,3,4-oxadiazole Derivatives and Evaluation of their Biological Studies. Ind. J. of Advances in Chem. Sci., 2016; 4(3): 257-268.
17. Yousif E, Abdalla M, Ahmed A, Salimon J, Salih N. Photochemical stability and photostabilizing efficiency of poly (methyl methacrylate) based on 2-thioacetic acid-5-phenyl-1,3,4-oxadiazole Complexes. Arabian Journal of Chemistry, 2016; 9: S595–S601.
18. Vishwanathan B, Gurupadayya BM. In vitro antioxidant and in vivo anti-inflammatory activity of 1,3,4-Oxadiazole derivatives. Int. J. Pharma. Pharmaceutical Res., Human, 2015; 2(2): 41-51.
19. Anu M Y, Nand L S, Vihangesh D, Shashi A, Nitika G. In-vitro evaluation of anticonvulsant activity of raphanus sativus. Int. J. Pharm, 2015; 2(10): 514-18.
20. Mayank K, Shashi A, Sanjay K J, Amita V. In-vitro study of anticonvulsant activity on the fruits extracts of coccinia indica (wight &arn.) induced maximal electroshock seizure (MES) model in rats. Int. J. Pharm. Sci. Res, 2013; 4(11): 4319-324.
21. Debasis M, Goutam G, Sudhir K, Prasanna K P. An experimental study of analgesic activity of selective cox-2 inhibitor with Conventional NSAIDs. Asian J. of Pharma. Clinical Res., 2011; 4(1): 78-82.
22. Mohammad S Y, Mohammad W A. Synthesis and anticonvulsant activity of substituted Oxadiazole and thiadiazole derivatives. Acta Poloniae Pharmaceutica and Drug Research, 2009; 66(4): 393-97.
23. Babeet S T, Soniya C, Rekha V. In vitro anti-inflammatory, analgesic and acute toxicity studies of ethanol extracts of Andrographis paniculata Nees and Spilanthus acemella Murr. Der Pharmacia Sinica, 2012; 3(5): 590-93
24. Radhika B, Nasreen B, Srisailam K. In-Vitro and In-Vivo Anti-Inflammatory and Analgesic Activity of Bixa orellana Linn Leaf Extracts. Int J Pharm Pharmacol, 2017; 1(2): 108; 1-10.
25. Parle M, Yadav M. Laboratory models for screening analgesics. Int. Res. J. Pharm., 2013; 4(1): 15-19.