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DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NOVEL 2-[3-(4-HYDROXY METHYL BENZOYL) PROPIONIC ACID-5-(SUBSTITUTED PHENYL)-1,3,4-OXADIAZOLE DERIVATIVES

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ABSTRACT

Oxadiazoles belong to the group of heterocyclic compounds which contains one oxygen and two nitrogen atoms, forming a five-membered heterocyclic ring. The current research was based on the design, synthesis and pharmacological evaluation of novel 2-[3-(4-Hydroxy methyl benzoyl) propionic acid-5-(Substituted phenyl)-1,3,4-Oxadiazole Derivatives.The novel derivatives of oxadiazole were synthesized by utilizing specific conditions and process and evaluated their physical properties including melting point, RF value, FTIR, NMR, Mass, and Docking studies.The animals were obtained from animal house, Department of Pharmacy, MJPRU Bareilly for in-vivo study.The anti-inflammatory activity of synthesized novel oxadiazole derivatives were tested by carrageenan-induced paw edema. In results, when compared anti-inflammatory activity among all compounds, D3 and D4 were found excellent moiety in terms of maximum % inhibition comparable to standard group. Novel oxadiazole derivatives synthesized successfully and exhibited significant anti-inflammatory activity at both the doses used. The response was noted as dose-dependent. Maximum inhibition was recorded in the dose of 200mg/kg of oxadiazole. In conclusion, novel oxadiazole derivatives might be much significant in reducing the inflammation and counter it. Maximum percentage inhibition was obtained in D3 and D4, respectively.It suggests to perform the structure elucidation of synthesized derivatives and develop after structural modification (SAR) in desired dosage form to avail the highest potency and efficacy (intrinsic activity). It also needed to further researchers to determine its mode of action for anti-inflammatory response.

Keywords: 1,3,4-Oxadiazole, synthesis, FTIR, Docking, anti-inflammatory activity.

INTRODUCTION

Oxadiazoles belong to the group of heterocyclic compounds which contains one oxygen and two nitrogen atoms, forming a five-membered heterocyclic ring [1]. The oxadiazole molecule is derived from furan, where two carbon atoms are replaced by nitrogen atoms of the pyridine type [2]. Oxadiazole compounds exhibit a wide spectrum of biological activity, which makes it possible to apply them in medicine and pharmacology as active agents, e.g., with anti-inflammatory and analgesic, antimicrobial, antiviral, antifungal, antitumor and blood pressure lowering properties [3][4][5]. These compounds are composed of a five-membered heterocyclic ring containing two nitrogen atoms and one oxygen atom. Due to the different arrangement of the het-ero-atoms, oxadiazoles exist in different isomeric forms, e.g., 1,3,4-oxadiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole and 1,2,5-oxadiazole. Aromatic systems are so-called azoxins, while five-membered cyclic molecules with the same number of nitrogen and oxygen atoms that have been partially reduced are known as furoxanes [6].

Fig1. Isomeric structures of oxadiazoles [6]

In contrast to 1,2,3-oxadiazoles, other isomers, namely 1,2,4-oxadiazoles, are thermodynamically stable. Their reactivity is mainly influenced by their aromaticity [7]. The high reactivity to ring rearrangement reactions is attributed to the relatively low aromaticity of 1,2,4-oxadiazoles [8]. On the basis of the performed calculations, it was found that the aromaticity index for 1,2,4-oxadiazole was lower than for the furan molecule [9]. In recent years, many 1,2,4-oxadiazole derivate structures have been detected using X-ray structure spectroscopy [10]. The structures that can be used in energetic materials [28] and complex compounds based on 1,2,4-oxadiazole derivatives that can bind copper or cobalt cations, and have biological activity, have been determined [11]. The current research was based on the design, synthesis and pharmacological evaluation of novel 2-[3-(4-Hydroxy methyl benzoyl) propionic acid-5-(Substituted phenyl)-1,3,4-Oxadiazole Derivatives.

MATERIALS AND METHODS

Experimental Requirements

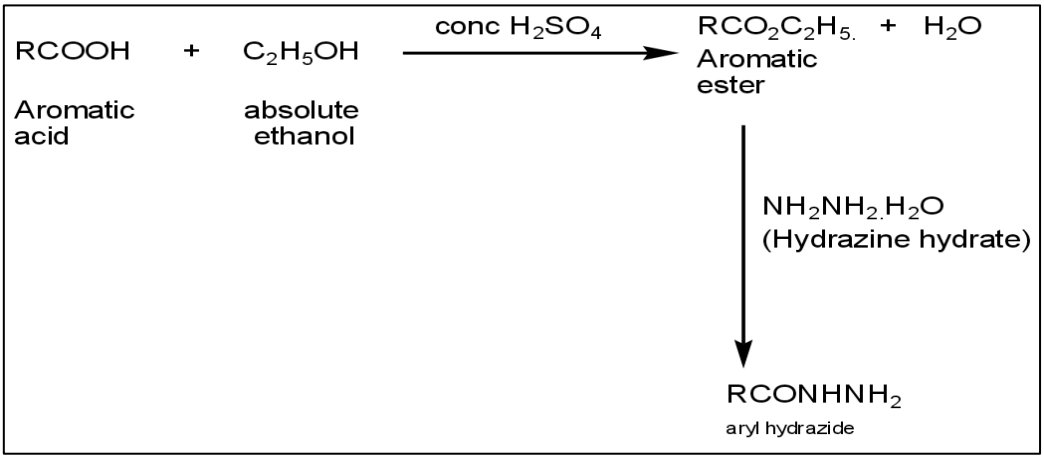
- Benzoic acid
- Salicylic acid
- Cinnamic acid
- Anthranilic acid
- Methanol
- Hydrazine hydrate
- Benzyl alcohol
- Succinic anhydride
- Phosphorous oxychloride
- Anhydrous $AlCl_3$
- Concentrated sulphuric acid
- Sodium hydroxide

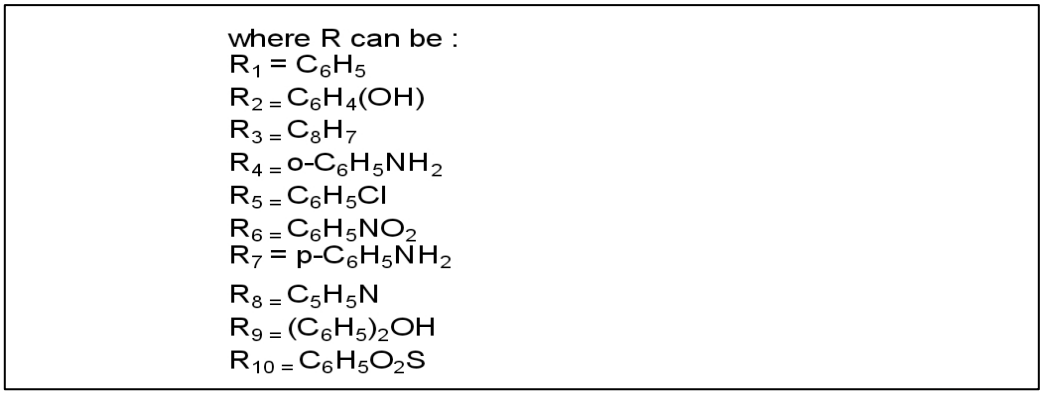
- Sodium bicarbonate
- Ethanol
- 4-Chloro benzoic acid
- 4-nitro benzoic acid
- 4-amino benzoic acid
- Nicotinic acid
- Benzylic acid
- P-toluene sulfonic acid
- Distilled water
- Diclofenac

Digital weighing balance, hot plate, beaker, laboratory thermometer and Digital pH meter.

Synthesis of novel derivatives of 1,3,4- oxadiazole

Step 1: Synthesis of aryl acid hydrazide





In this strategy, substituted-aromatic acids were used as the starting reactant in the synthesis of 1,3,4-Oxadiazole derivatives, resulting in the creation of the appropriate esters and hydrazides. Fischer esterification was used to create ethyl esters from aromatic acids, which were then combined with hydrazine hydrate in the presence of ethanol to create the appropriate hydrazide derivative.

Step 2: Synthesis of derivative of 2-[3-(4-Hydroxy methyl benzoyl) propionic acid-5-(Substituted phenyl)-1,3,4-Oxadiazole Derivatives

3-(4-Hydroxy methyl benzoyl) propionic acid synthesis: Anhydrous aluminium chloride (0.11 mol) was gradually added over a 2-hour period while stirring to a succinic anhydride (0.1 mol) in benzoyl alcohol (50 ml) solution. Following a two-hour period of refluxing the reaction

mixture, surplus benzoyl alcohol was removed by steam distillation. By dissolving in sodium hydroxide solution, filtering, and then adding hydrochloric acid, it was made purer. The filtered, cold-water-washed, dried, and crystallized solid from the methanol was produced.

Fig2. Synthesis procedure for derivatives

2-[3-(4-Hydroxy methyl benzoyl) propionic acid-5-(substituted phenyl)]1,3,4-oxadiazole: In phosphorous oxychloride (5ml), suitable aryl acid hydrazide (1mmol) was dissolved, and 1mmol of 3-[4-hydroxymethyl benzoyl) propionic acid was added. The reaction liquid was

cooled to room temperature and then poured onto crushed ice after 5 hours of refluxing. A solid separated after the contents were neutralized (20%) with sodium bicarbonate solution, then it was filtered, water washed, and dried. To produce the desired product, methanol was crystallized**.**

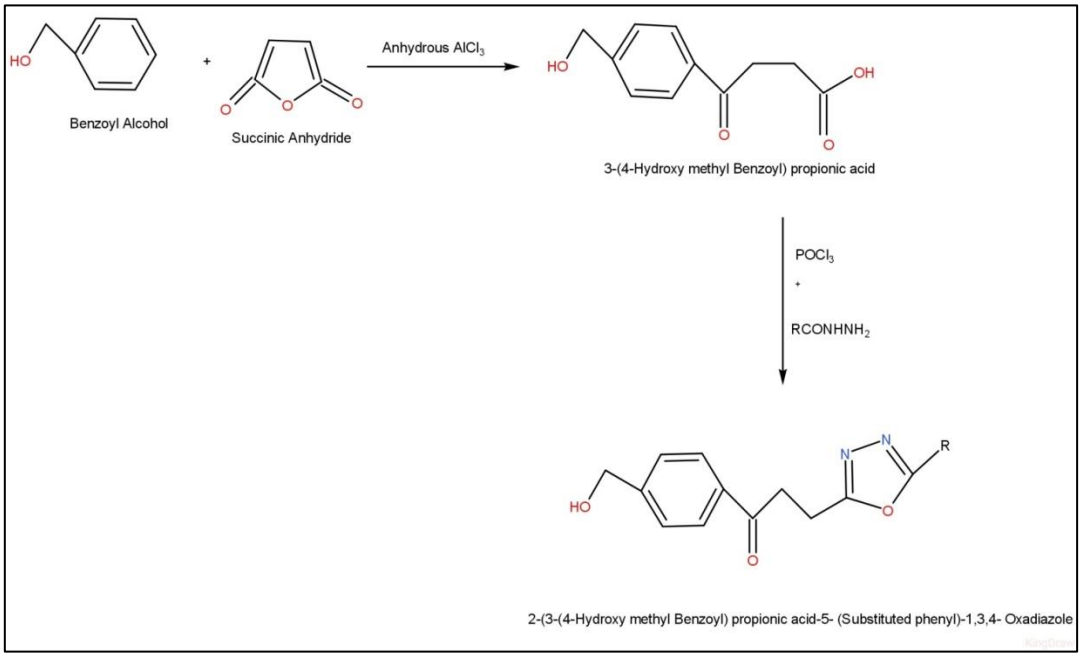


Fig 3.Schemefor the synthesis of 1,3,4- oxadiazolederivatives

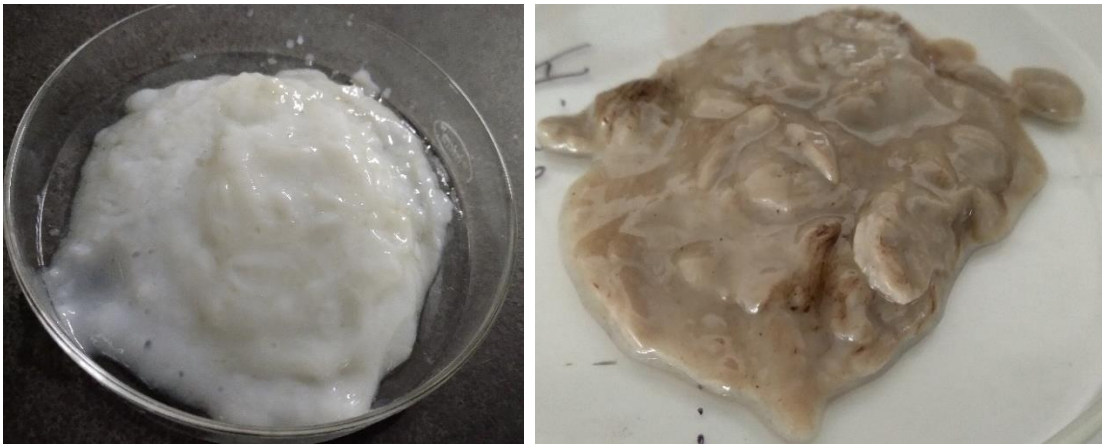


Fig 4. Synthesized derivatives

4.3 Characterization parameters

Melting point determination

Thiel's melting point tube was used to determine the melting point of an organic compound (capillary tube method). The most important and straightforward means of distinguishing one compound from another is to determine its melting point [12].

Thin Layer Chromatography (Rf value)

TLC stands for thin layer chromatography and is used in synthetic chemistry to infer the production of a molecule based on its Rf value, which varies depending on the compound. It also aids in confirming the reaction's progress [13].

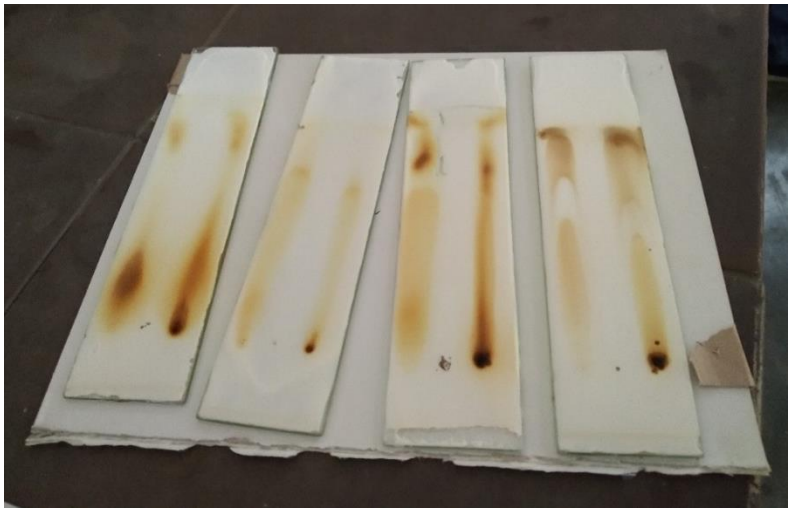


Fig5. TLC of synthesized derivatives

Infrared Spectroscopy

Infrared spectroscopy is one of the most essential methods for determining different functional groups and probable chemical structures. The main benefit of IR over other techniques is that it easily produces fingerprints (1300-650/cm) of molecules' structure (functional group, associating with one other). There are no two compounds with the same fingerprint region. This method is based on the molecular vibration of the chemical, which causes each bond to vibrate at a particular frequency, which corresponds to the IR frequency. As a result, IR spectra of each bond was created. On a Jasco V410, FTIR spectra were obtained in KBr powder [14].

NMR Spectroscopy

By exposing a substance to two magnetic forces, one fixed and the other fluctuating at a radio frequency, the interaction between matter and electromagnetic forces can be seen. The sample detects energy at a certain combination of fields, and absorption is detected as a change in single developed by a radio frequency detector and amplifier. The magnetic dipolar character of a spinning nucleus can be linked to this absorption energy. Nuclear Magnetic Resonance is the name for this technology. This method is beneficial for determining the molecule's structure. A Bruker Ultraspec 500MHz/AMX400MHz spectrometer was used to measure 1H-NMR spectra in CDCl3 and d6-DMSO [15].

Mass Spectroscopy

In this method, a beam of powerful electrons is used to repeatedly strike individual molecules. After being ionized, the molecules disintegrate into a plethora of pieces, some of which are positive ions. The mass-to-charge ratio, or m/e, is unique for each ion type. Most ions have a single charge, making their m/e ratio equal to their molecular mass. Mass spectra are obtained by detecting and recording signals from moving ions as they go through a system of magnetic and electric fields to a detector [16].

Molecular docking

Molecular Docking calculations of oxadiazole derivatives was done on the active site of enzyme COX-2 binding site (PDB ID: 3LN1) using Swiss Dock (http://swissdock.vital-it.ch/) web service based on the docking software EADock DSS. This web-based service was selected because it has user friendly interface with the facility to input desired protein and ligand structures directly from databases, modify docking parameters, and visualize most favourable clusters online. The structure of compounds was drawn in Chemsketch and subject to energy

minimization. Binding modes were scored using their FullFitness and clustered. Clusters were then ranked according to the average FullFitness of their elements. Results of the SwissDock were visualized by UCSF Chimera package [17].

4.4 Animal preparation

Animal House, Department of Pharmacy, MJP Rohilkhand University were provided rats (either sex) weighing 120-150g. The rats are kept in good health, with room temp. of 25°C and 12hr light & dark cycle. The relative humidity was kept at 50±2% percent, and provided a regular rodent diet and free access to water. The rodents were continuing to fast but have free access to water until 1 hour before the study [18].

4.5 Experimental protocols

All the rats were divided into 5 groups (n=6) as followings-

Group 1: rats are given only normal saline daily for 21 days.

Group 2: rats are given carrageenan (2%) intradermally for 21 days.

Group 3: rats are given carrageenan (2%) + indomethacin (10mg/kg, p.o.) for 21 days.

Group 4: rats are given carrageenan (2%) + all the novel 1,3,4 Oxadiazole derivatives (100mg/kg, p.o.) for 21 days.

Group 5: rats are given carrageenan (2%) + all the novel 1,3,4 Oxadiazole derivatives derivatives (200mg/kg, p.o.) for 21 days.

4.6 Evaluation of anti-inflammatory potential

4.6.1 Carrageenan- induced paw edema

The rats were divided into 5 groups, each weighing 120-150g. The synthesized derivatives (D1-D4) suspended in the water and administered in the doses of 200mg/kg and 400mg/kg. The right foot pad received 0.1 ml of carrageenan (2%) intradermally, with the left paw served as a control. Simultaneously with the phlogistic agent, indomethacin (the reference medication) was given intraperitoneally. Both hind paws are diagnosed, just above the ankle joint and recorded for the volume of inflammation. The medication treatments are repeated at 5, 10, 15, and 21 days [19].

RESULTS AND DISCUSSION

Novel derivatives of 1,3,4-oxadiazole (D1-D10) were synthesized by adopting the above mentioned scheme. After synthesis, all the derivatives were characterized through parameters i.e., % yield, melting point, and molecular weight.

Identification of physicochemical properties

Melting point determination

For 1,3,4-oxadiazole derivatives, the melting point was determined in the range of164-168ºC, 172-176ºCºC, 174-178ºC, and 203-206ºC for compounds D1, D2, D3, and D4, respectively.

Thin Layer Chromatography- Rf value

Thin layer chromatography is used in synthetic chemistry to confirm the production of a molecule based on its Rf value, which varies depending on the compound. Rf value was obtained as 0.69, 0.77, 0.74, and 0.76 of D1, D2, D3, and D4 respectively.

All the synthesized 1,3,4-oxadiazole derivatives were tested for their physical properties i.e., % yield, melting point, and functional groups attached with were tested. D1 and D2 were demonstrated for its highest % yield as 71.42% and 68.26%. Lowest % yield was seen in D4 as 64.29%. The highest melting point was found in compound D4 as 203-206ºC. Highest

melting point indicates about the strongest density of the compound. The following table summarized physical properties of all the compounds.

Table 1. Physicochemical properties of synthesized 1,3,4-oxadiazole derivatives

Compound	Yield (%)	Rf Value	Melting point
D1	71.42	0.69	164-168ºC
D2	68.26	0.77	172-176ºC
D3	66.17	0.74	174-178ºC
D4	64.29	0.76	203-206ºC
D5	67.18	0.73	182-186ºC
D6	72.20	0.72	201-204ºC
D7	62.19	0.76	168-172ºC
D8	69.12	0.72	184-188ºC
D9	68.28	0.68	168-172ºC
D10	69.14	0.73	202-206ºC

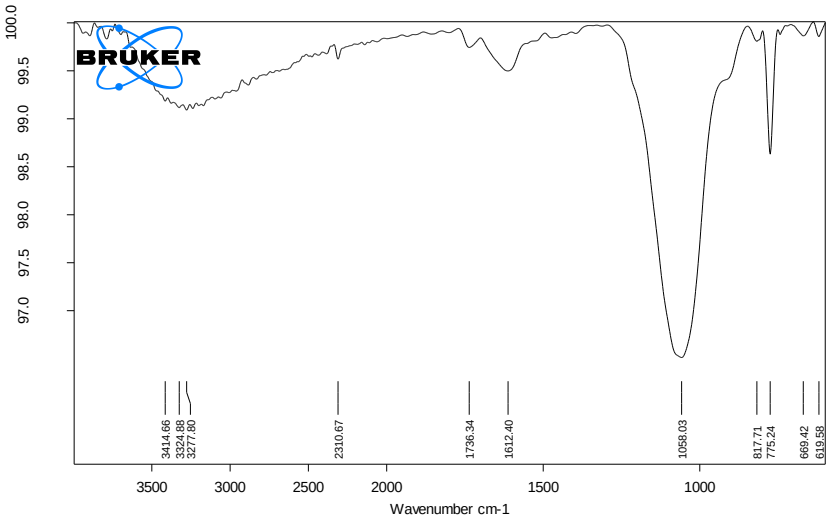
Infrared Spectroscopy

The IR spectra of the compounds D1-D4 is represented below:

FTIR Spectrum of D1

Table 2. FTIR Interpretation of D1

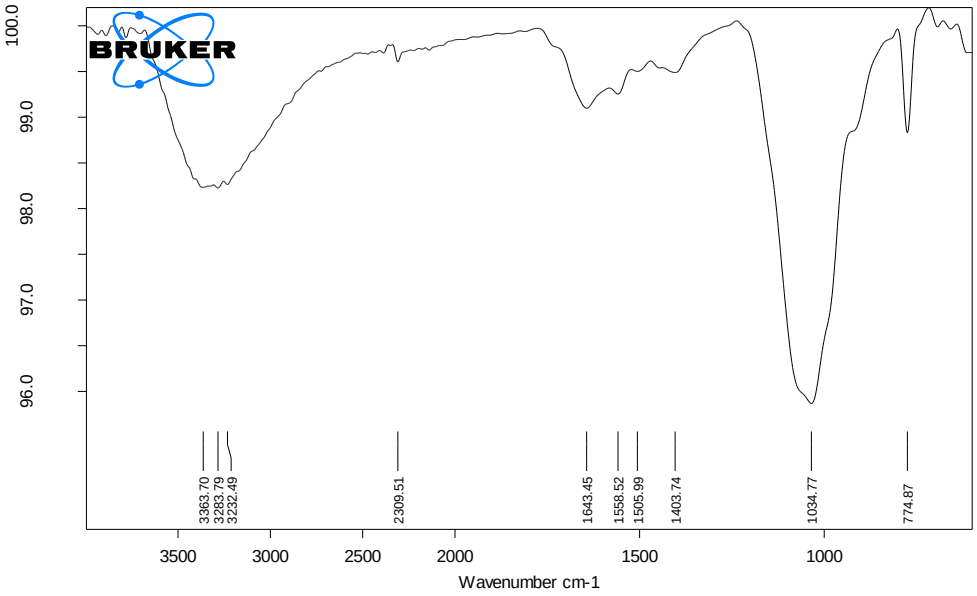
S. No.	Frequency (cm^{-1}) (observed)	Frequency (cm^{-1}) (theoretical)
1.	1720.2	1600-1900
3.	1599.2	1500-1700
4.	3137.4	3200-3300
5.	759.2	600-700



FTIR Spectrum of D2

Table 3. FTIR Interpretation of D2

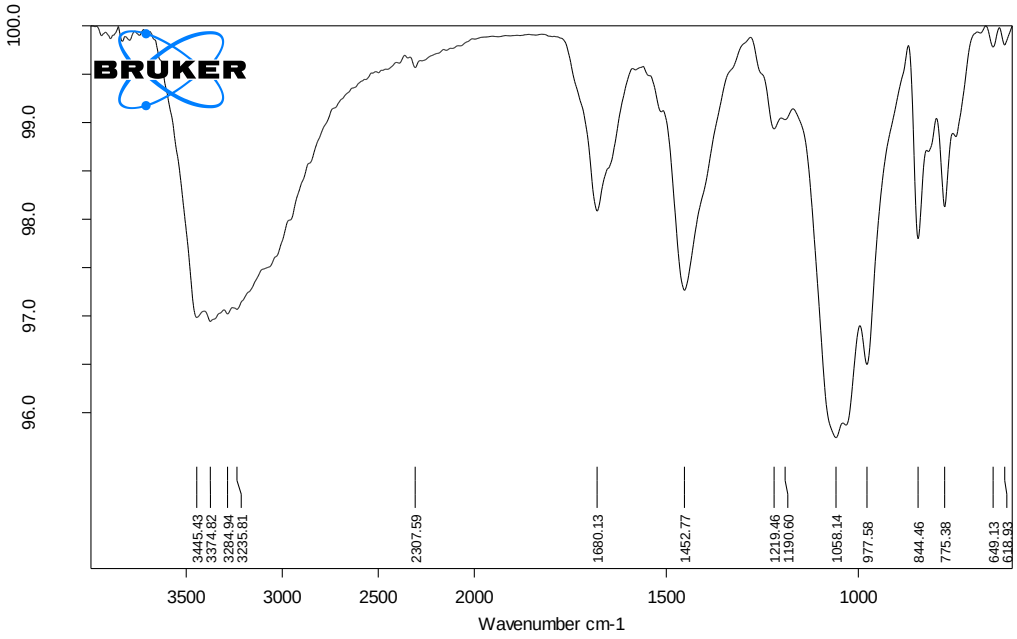
S. No.	Frequency (cm^{-1}) (observed)	Frequency (cm_{-1}) (theoretical)
3.	1599.5	1500-1700
4.	3141.4	3100-3300
5.	691.8	600-700
6.	1607.8	1640-1667



FTIR Spectrum of D3

Table 4. FTIR Interpretation of D3

S. No.	Frequency (cm^{-1}) (observed)	Frequency (cm^{-1}) (theoretical)
1.	1720.6	1600-1900
3.	1557.8	1500-1700
4.	3133.2	3100-3300
5.	690.8	600-700
6.	1605.1	1640-1667
7.	1012.4	900-1300



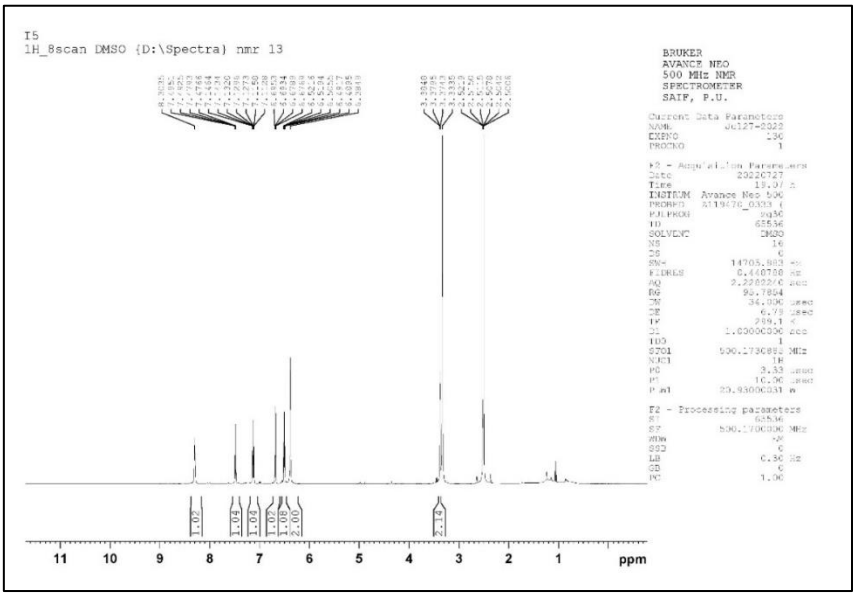
FTIR Spectrum of D4

Table 5. FTIR Interpretation of D4

S. No.	Frequency (cm^{-1}) (observed)	Frequency (cm^{-1}) (theoretical)
1.	1720.2	1600-1900
3.	1560.6	1500-1700
5.	695.4	600-700
6.	1649.2	1640-1667
7.	1096.2	1096-1089

NMR Spectroscopy

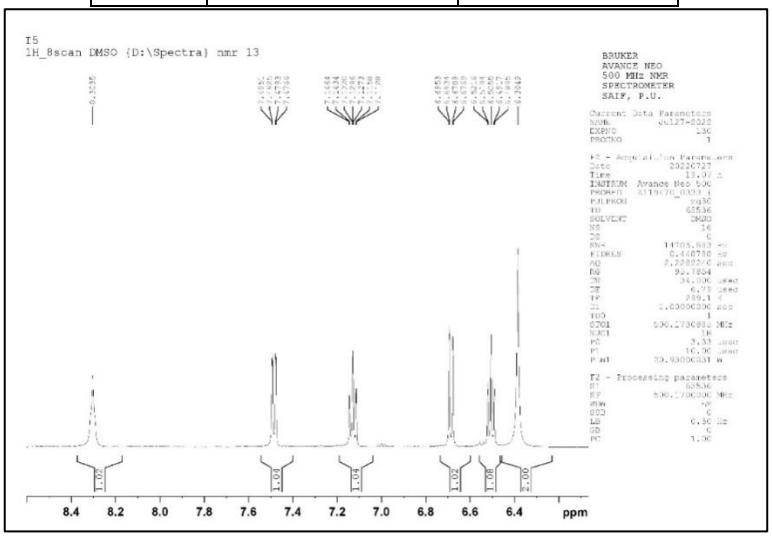
The NMR spectra of the compounds D1-D4 are as follows:



NMR Spectrum of D1

Table 6. NMR Interpretation of D1

S. No.	Chemical shift (ppm)	Proton
1.	7.132	2
2.	7.297-8.186	14
3.	8.346	1

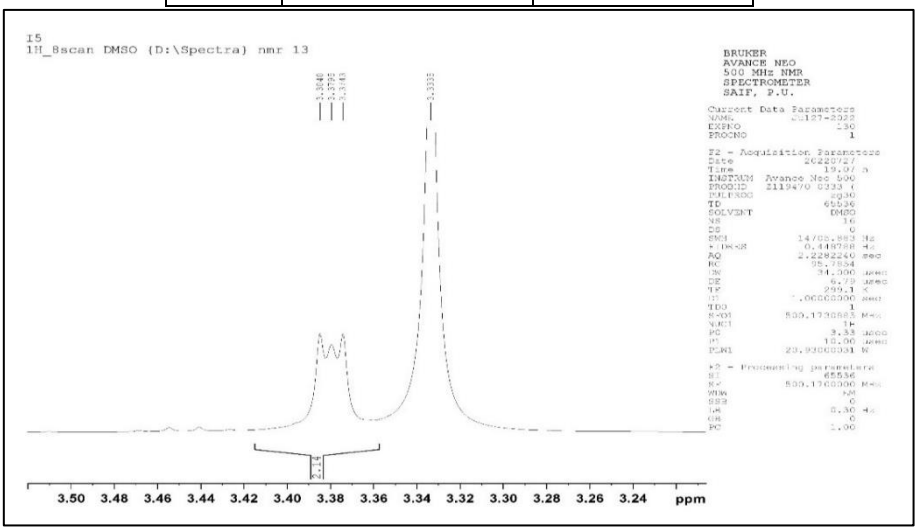


NMR Spectrum of D2

Table 7. NMR Interpretation of D2

S. No.	Chemical shift (ppm)	Proton
1.	3.95	3

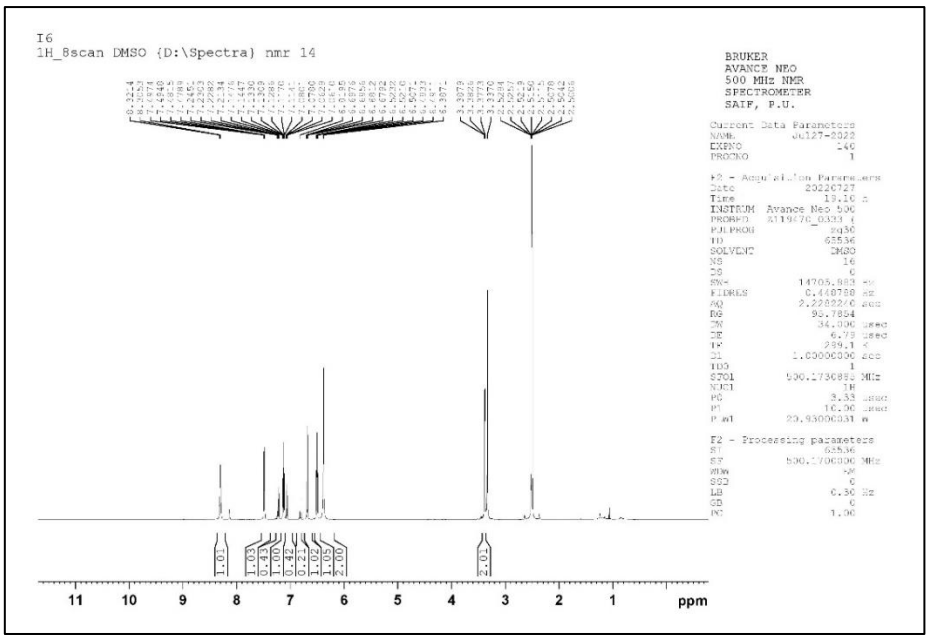
2.	7.17	2
2.	7.26-8.16	13
3.	8.80	1



NMR Spectrum of D3

Table 8. NMR Interpretation of D3

S. No.	Chemical shift (ppm)	Proton
1.	7.20-7.23	2
2.	7.35-8.16	13
3.	8.36	1



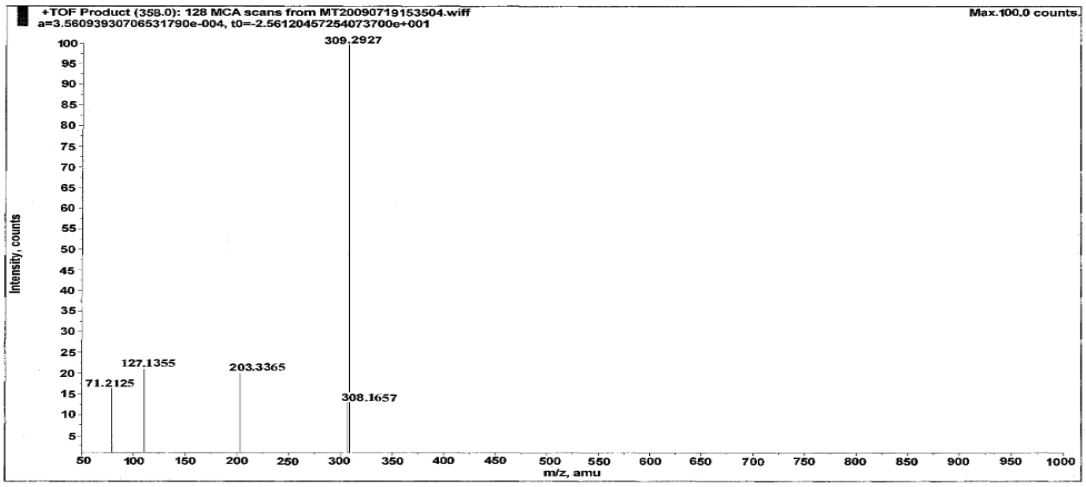
NMR Spectrum of D4

Table 9. NMR Interpretation of D4

S. No.	Chemical shift (ppm)	Proton
1.	7.20	2
2.	7.22-8.16	13
3.	8.18	1

Mass Spectroscopy

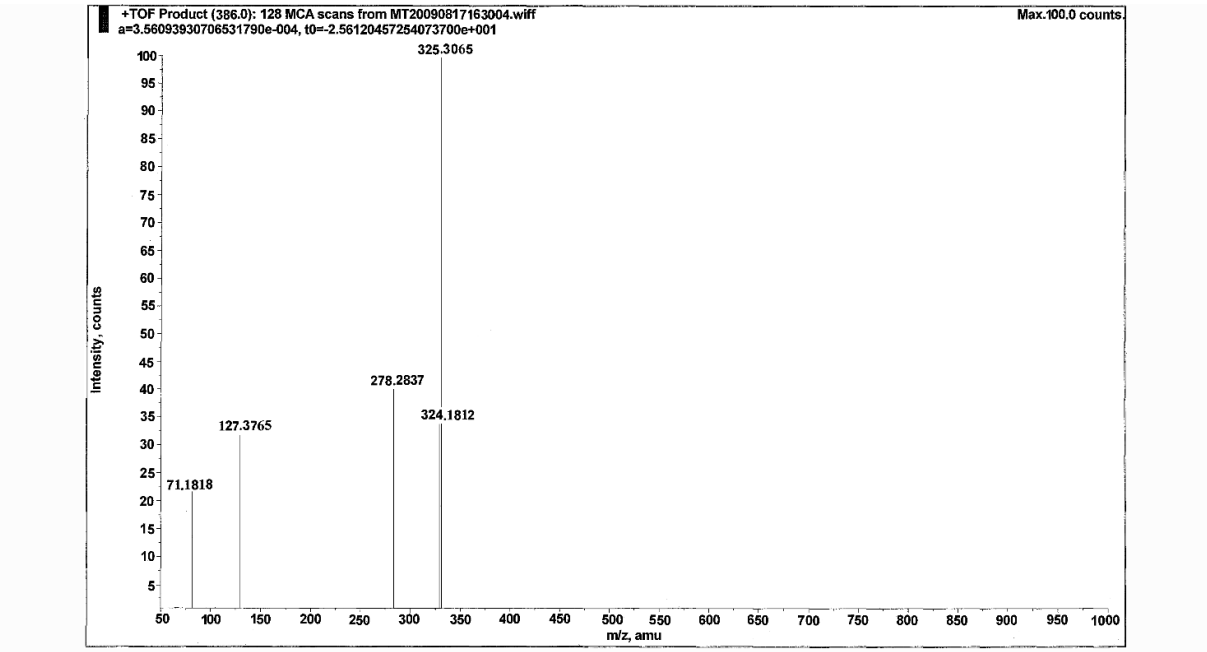
The mass spectra of the compounds D1-D4 are as follows:



Mass Spectrum of D1

Interpretation: MS (m/z): 308 (100) $[M]^+$, 309 (15) $[M+1]^+$

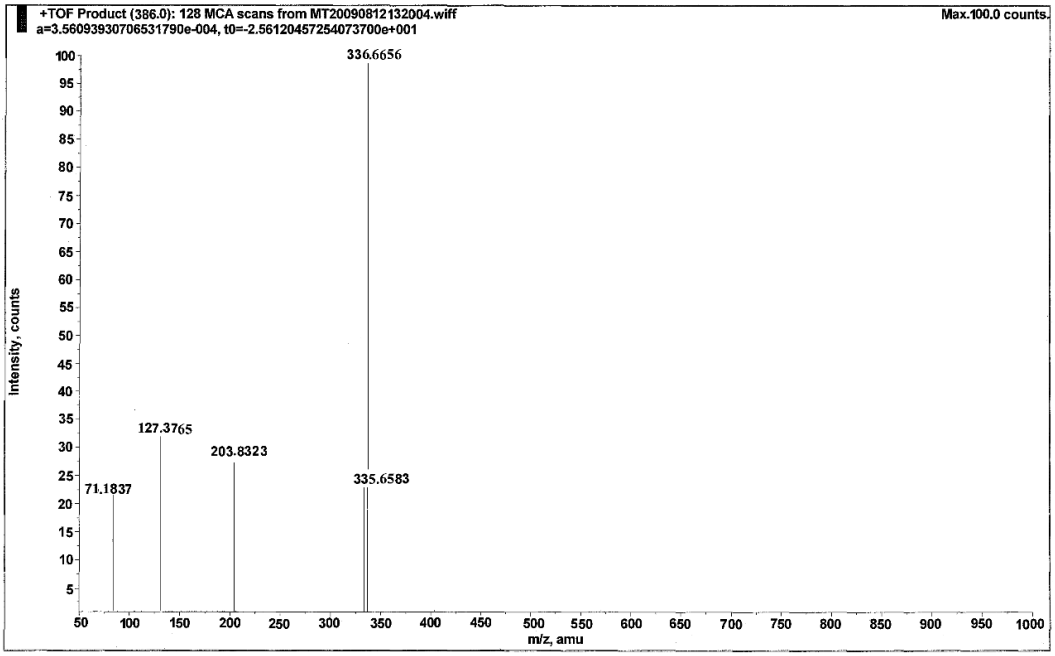
Fragments: 203 (22), 127 (23), 71 (18).



Mass Spectrum of D2

Interpretation: MS (m/z): 324 (100) [M]+, 325 (35) [M+1]+

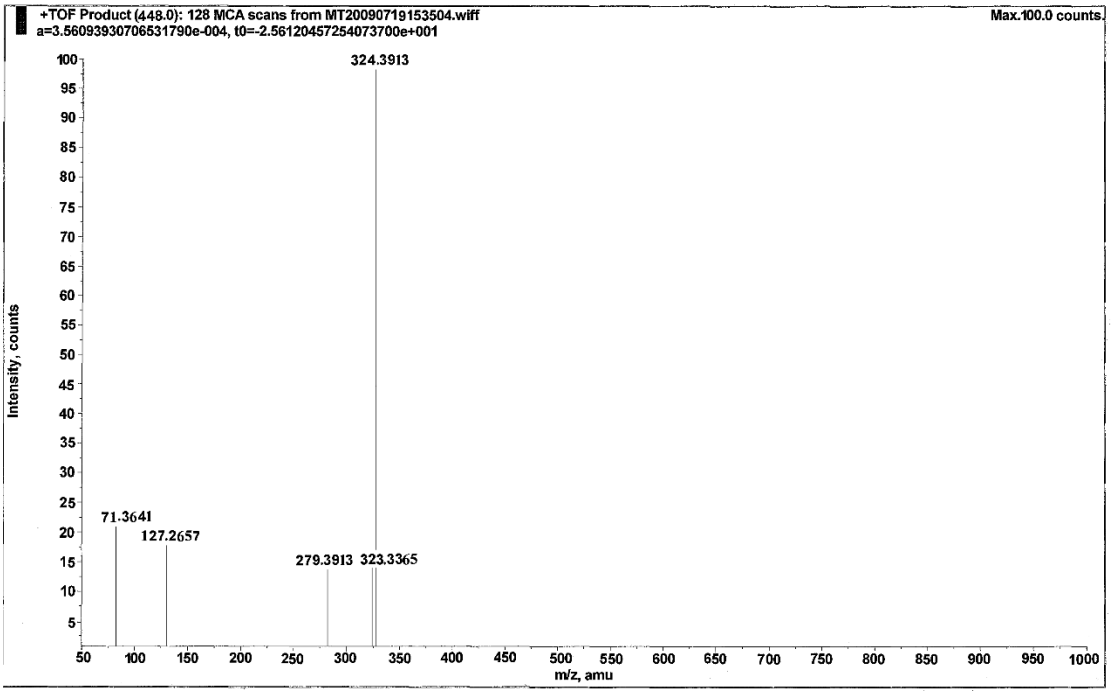
Fragments: 278 (42), 127 (33), 71 (22).



Mass Spectrum of D3

Interpretation: MS (m/z): 335 (100) [M]+ , 336 (25) [M+1]+

Fragments: 203 (28), 127 (34), 71 (23)



Mass Spectrum of D4

Interpretation: MS (m/z): 323 (100) [M]+, 324 (17) [M+1]+

Fragments: 279 (15), 127 (19), 71 (22)

Molecular docking

We have performed the molecular docking studies for an oxadiazole derivative with the active binding site of enzyme COX-2 target is completed. The binding energy involved in the enzyme ligand complex formation is determined. The molecular atomic level of interactions responsible for the target specific binding affinity of the compounds towards enzymeCOX-2 is

extracted (Table). All the compounds have shown the successful docking inside the active site of enzymeCOX-2 with a binding energy of -6 to -9 Kcal/mol. We compared the predicted docking data with known COX-2 inhibitors.

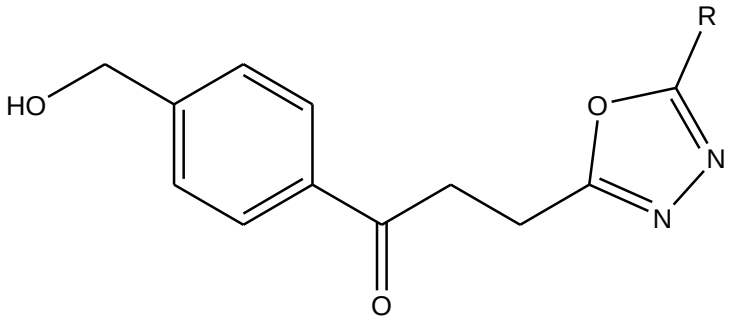
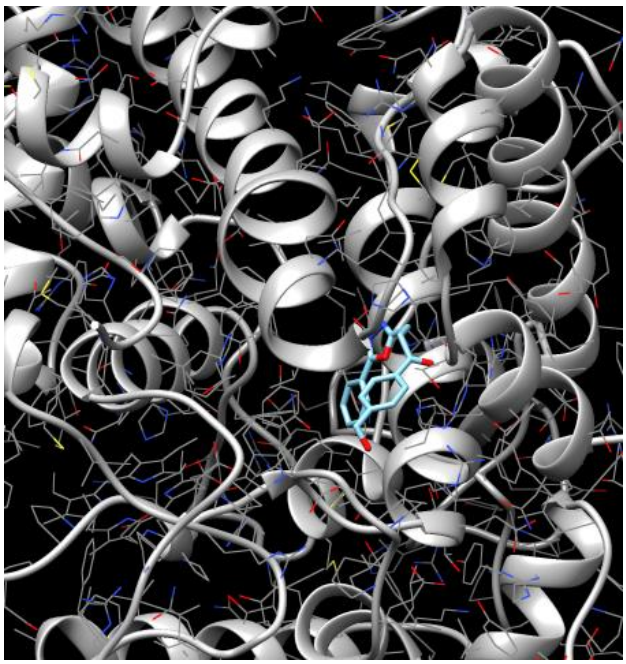
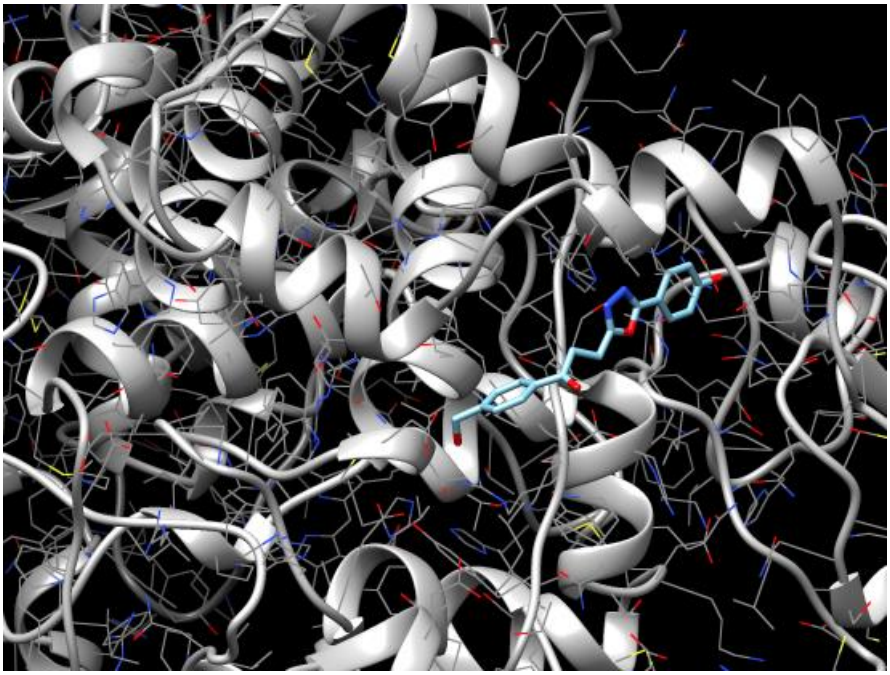


Table 10. Binding energy in docking profile

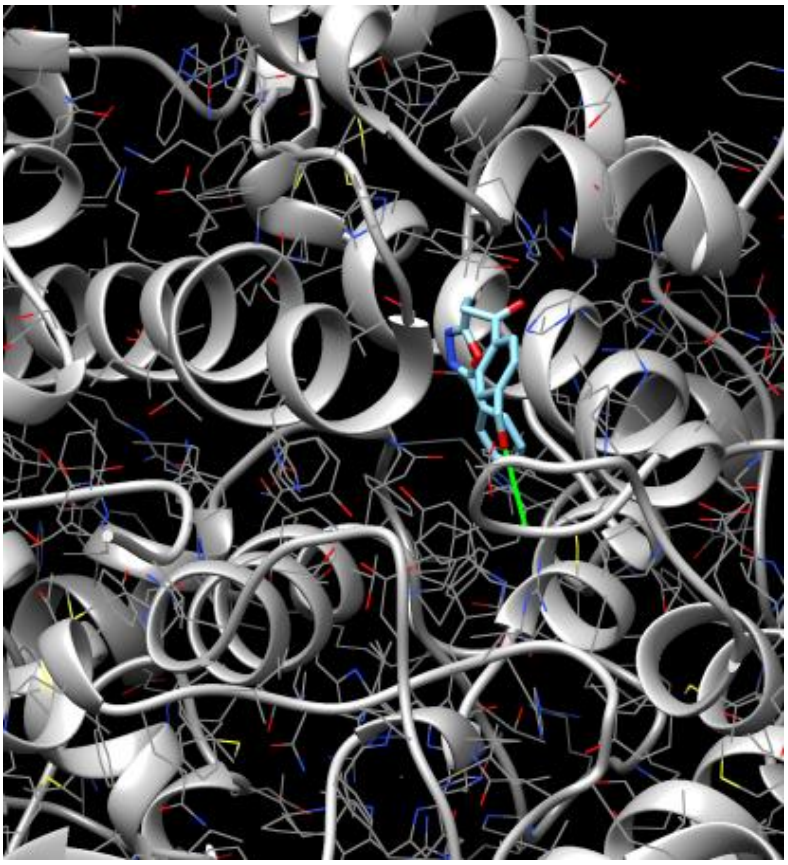
Compound No	R	Fulfillness(Kcal/mol)	Binding Energy (ΔG)(Kcal/mol)
D1	$-C_6H_5$	-2262.29	-8.50
D2	$-C_6H_4OH$	-2267.48	-8.12
D3	$-C_8H_7$	-2259.07	-8.26
D4	$-C_6H_4NH_2$	-2261.45	-8.51



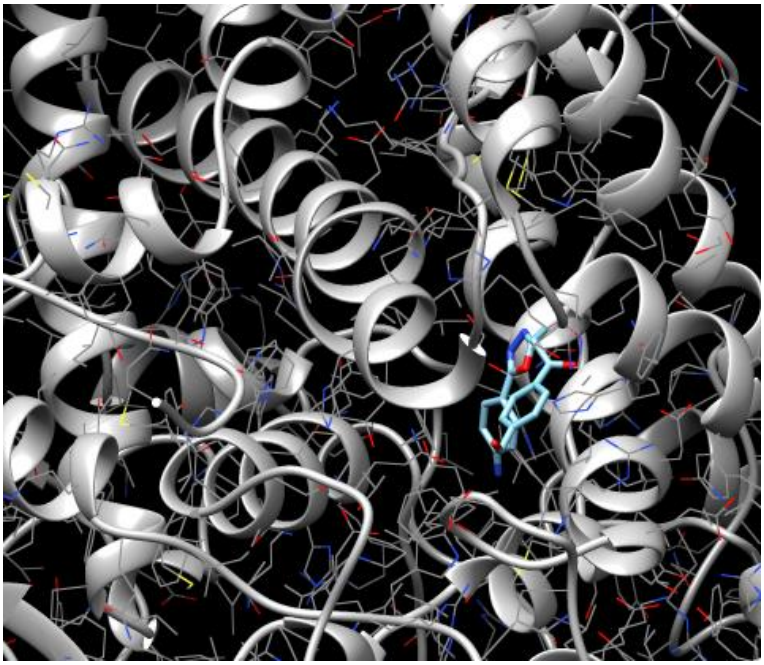
Docking of compound D1



Docking of compound D2



Docking of compound D3



Docking of compound D4

Evaluation of anti-inflammatory potential

- **Carrageenan-induced paw edema**

The oxadiazole derivatives (D1-D4) were evaluated for anti-inflammatory effect by using carrageenan induced paw edema model. In this method, carrageenan (2%) was given to group 1 in the dose of 0.1ml for 21 days on daily basis. After completion of treatment time, they all were evaluated after 30, 60, 120 and 180 minutes for reduction in paw edema. The activity was estimated at 100mg/kg and 200mg/kg separately. Indomethacin was given in the dose of 10mg/kg b. w. of rats.

After 180min, compound D1, D2, D3, and D4 showed the volume of left hind paw as 3.58±0.27**, 3.61±0.13**, 3.63±0.18**, and 3.54±0.25**, respectively when observed at the dose of 100mg/kg, whereas indomethacin treated group showed 3.11±0.18** and disease control group 4.68±0.10**, after 180min of treatment. It showed that all the synthesized compounds exhibited significantly anti-inflammatory potential when compared with control group.

Table 11.Estimation of volume of left hind paw in control (1ml), standard (10mg/kg) and oxadiazole derivatives (100mg/kg)

Treatment	**Dose (mg/kg)**	**Volume of left hind paw (Mean± SEM)**			
		30min	**60min**	**120min**	**180min**
Carrageenan (2%)	0.1 ml	2.71±0.27*	3.48±0.11**	4.18±0.20**	4.68±0.10**

Indo. + Carrageenan	10	2.29±0.14**	2.37±0.12**	2.69±0.31**	3.11±0.18**
D1 + Carrageenan	100	2.49±0.29**	2.64±0.14**	3.82±0.13**	3.58±0.27**
D2 + Carrageenan	100	2.46±0.34**	2.52±0.19**	3.78±0.26**	3.61±0.13**
D3 + Carrageenan	100	2.43±0.41**	2.47±0.27**	3.81±0.12**	3.63±0.18**
D4 + Carrageenan	100	2.47±0.21**	2.43±0.16**	3.76±0.27**	3.54±0.25**

Indo. = Indomethacin; Significance Level= *

Values were given in Mean ± S.E.M. and found statistically significant at P<0.05, compared to control (n=6).

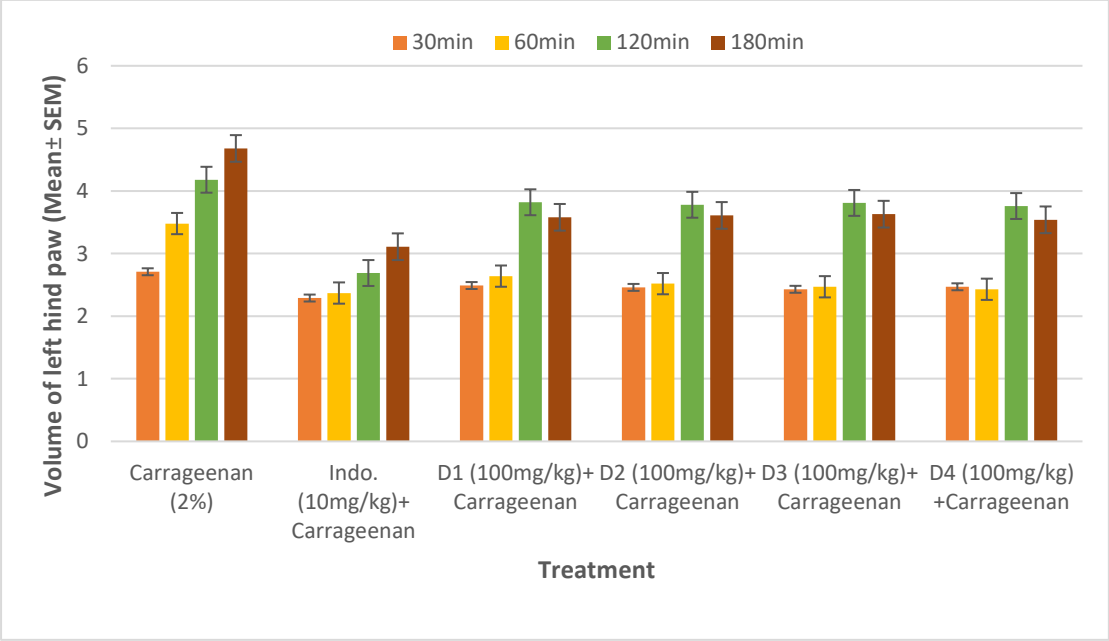


Fig 6. Estimation of volume of left hind paw in control (1ml), standard (10mg/kg) and oxadiazole derivatives (100mg/kg)

Compound D1, D2, D3, and D6 showed the volume of left hind paw as 3.47±0.35**, 3.34±0.15**, 3.23±0.12*, and 3.26±0.21**, respectively when observed at the dose of 200mg/kg, whereas indomethacin treated group showed 3.11±0.180* and control group 4.68±0.10**, after 180min of treatment. It showed that all the synthesized derivatives exhibited significant anti-inflammatory potential when compared with control group.

Table 12.Estimation of volume of left hind paw in control (1ml), standard (10mg/kg) and oxadiazole derivatives (200mg/kg)

Compounds	Dose (mg/ kg)	Volume of left hind paw (Mean± SEM)			
		30 min	60 min	120 min	180min
Carrageenan (2%)	0.1 ml	2.71±0.27*	3.48±0.11**	4.18±0.20**	4.68±0.10**
Indo. + Carrageenan	10	2.29±0.14**	2.37±0.14**	2.69±0.31**	3.11±0.180*
D1 + Carrageenan	200	2.41±0.32**	2.43±0.19**	3.27±0.17**	3.47±0.35**
D2 + Carrageenan	200	2.39±0.27**	2.46±0.24**	3.21±0.29**	3.34±0.15**
D3 + Carrageenan	200	2.34±0.31**	2.39±0.22**	2.82±0.16**	3.23±0.12*
D4 + Carrageenan	200	2.38±0.32**	2.42±0.14**	2.87±0.31**	3.26±0.21**

Indo. = Indomethacin; Significance Level= *

Values were given in Mean ± S.E.M. and found statistically significant at P<0.05, compared to control (n=6).

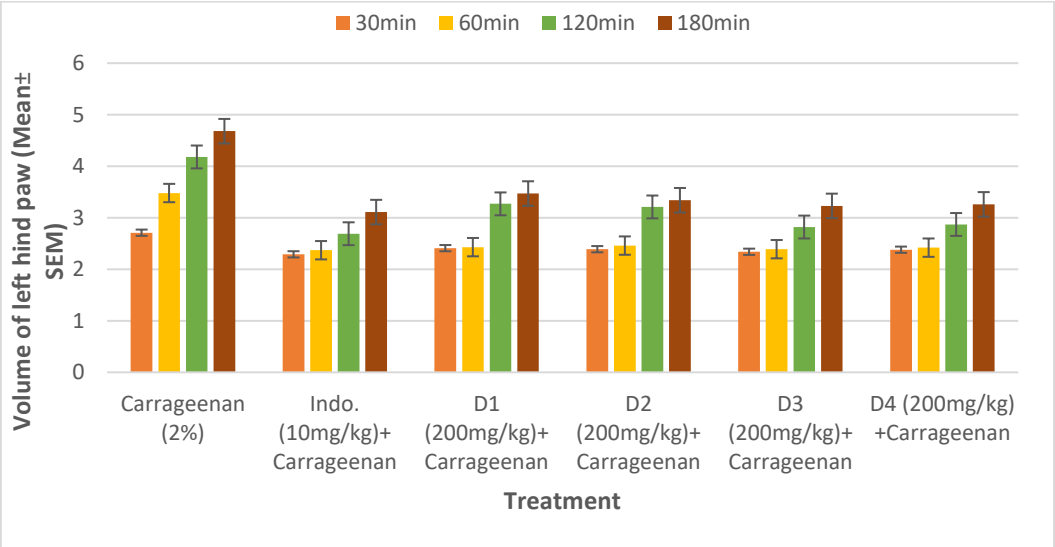


Fig 7. Estimation of volume of left hind paw in control (1ml), standard (10mg/kg) and oxadiazole derivatives (200mg/kg)

5.4 Percentage inhibition of Inflammation

The oxadiazole derivatives (D1-D4) were evaluated for anti-inflammatory effect by percentage inhibition. In this method, carrageenan (2%) was given to group 1 in the dose of 0.1ml for 21 days on daily basis. After completion of treatment time, they all were evaluated after 30, 60, 120 and 180 minutes for reduction in paw edema. The activity was estimated at 100mg/kg and 200mg/kg separately. Indomethacin was given in the dose of 10mg/kg b. w. of rats.

The % inhibition was recorded in all the treated animals. It was found maximum in the indomethacin treated group as a sign of potent COX (cyclooxygenase) inhibitor. All the synthesized compounds (D1-D4) also demonstrated better % inhibition. Indomethacin itself showed % inhibition as 72.13±0.29%. Compound D1, D2, D3, and D4, showed % inhibition as 63.12±0.24%, 64.15±0.11%, 68.12±0.25%, and 66.19±0.16%, respectively.

Table 13. Percentage inhibition of Indomethacin and synthesized derivatives

Treatment	% Inhibition (Mean ± SEM)
Indomethacin	72.13±0.29
D1	63.12±0.24
D2	64.15±0.11
D3	68.12±0.25
D4	66.19±0.16

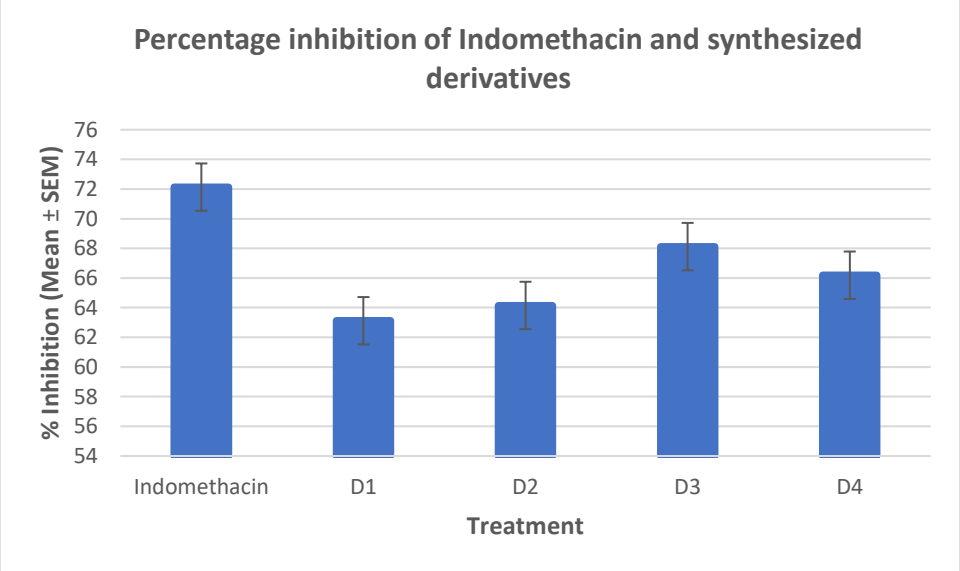


Fig 1.20 Percentage inhibition of Indomethacin and synthesized derivatives

When compared anti-inflammatory activity among all compounds, D3 and D4 were found excellent moiety in terms of maximum % inhibition comparable to standard group. Novel oxadiazole derivatives synthesized successfully and exhibited significant anti-inflammatory activity at both the doses used. The response was noted as dose-dependent. Maximum inhibition was recorded in the dose of 200mg/kg of oxadiazole.

This action might be due to involvement in suppression of prostaglandins, cytokines responsible for edema and inflammation, in fact. It may be assumed that these derivatives blocked COX and LOX enzymes. It declares, that D3 and D4 had demonstrated highest anti-inflammatory potential when compared with control.

The results indicate that synthesized oxadiazole derivatives exhibited significant anti-inflammatory activity at both the doses. The response was noted as dose-dependent (100mg/kg & 200mg/kg). Maximum inhibition was recorded in the dose of 200mg/kg of oxadiazole derivatives when given with carrageenan.

CONCLUSION

Inflammation has become one common symptoms among the various pathological states; therefore, it is required to counter it with reliable medicines.It would be a great change towards ayurvedic medicines to counter the gastric problems and heal the life of millions. It may also be refined that its production would be reasonable in terms of cost with relatively strong usefulness. It would be great deal for stability of formulation that would be done further. It will be much effective with minimized chances of side-effects related to allopathic medicines.This action might be produced through involvement in suppression of prostaglandins, cytokines responsible for edema and inflammation, in fact. It may be assumed that these derivatives blocked non-selectively COX and LOX enzymes and thus subside the production of inflammatory mediators & inflammation.

In conclusion, novel oxadiazole derivatives might be much significant in reducing the inflammation and counter it. Maximum percentage inhibition was obtained in D3 and D4, respectively.

It suggests to perform the structure elucidationof synthesized derivatives and develop after structural modification (SAR) in desired dosage form to avail the highest potency and efficacy(intrinsic activity). It also needed to further researchers to determine its mode of action for anti-inflammatory response.

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CONFLICT OF INTEREST

'None' declared by the authors.

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