https://doi.org/ 10.33472/AFJBS.6.10.2024.4983-5006

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Design, Synthesis and Pharmacological Evaluation Of 2-[3-(4-Nitro benzene) propionic acid-5-(Substituted phenyl)-1,3,4-Oxadiazole Derivatives

Avinash Kumar*[1], S. B. Tiwari[*2], Shiv Dev Singh[*3]

[*1,2,3,] Pharmaceutical Chemistry, Mahatma Jyotiba Phule Rohilkhand University, Bareilly

Corresponding author:

S. B. Tiwari[2]*

Professor, Mahatma Jyotiba Phule Rohilkhand University, Bareilly

E-mail: s.tiwari@mjpru.ac.in

Article History

Volume 6,Issue 10, 2024

Received:29 Apr 2024

Accepted : 27 May 2024

doi: 10.33472/AFJBS.6.10.2024.4983-5006

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 2-[3-(4-Nitro benzene) 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 i.e., 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 anxiolytic activity of synthesized novel oxadiazole derivatives were tested by Forced Swimming Test and Locomotor Activity models. In results, in all the models, novel derivatives of 1,3,4-oxadiazole (200mg/kg) significantly demonstrated anxiolytic potential at both the doses when compared to control. In both the doses, it significantly proved for its anxiolytic potential by facilitating the mood of animals. In conclusion, novel derivatives of 1,3,4-oxadiazole is significant anxiolytic synthetic drug. It can be effectively used in the treatment of anxiety, depression, mental agitation and other neurological disorders after successfully evaluating mechanism of action of the synthetic derivatives. It suggests to perform the structure elucidation of synthesized derivatives and develop after structural modification (SAR) in desired dosage form to determine the highest bioavailability, potency, and efficacy (intrinsic activity). It also suggests researchers to determine its mode of action for anxiolytic effect.

Keywords: 1,3,4-Oxadiazole, synthesis, Docking, FST, anxiolytic activity.

INTRODUCTION

Oxadiazoles are members of the heterocyclic ring-shaped category of compounds that consists of one oxygen and two nitrogen atoms. The pyridine type of nitrogen atoms replaces two carbon atoms in furan, the source of the oxadiazole molecule. Numerous features of oxadiazole compounds find use in several sectors [1]. These substances have a broad range of biological activity, which enables their use as active agents in pharmacology and medicine [2] e.g., antibacterial, antiviral, antifungal, anticancer, and blood pressure reducing effects.

The 1,2-diazole fragment of the molecule functions as an electron withdrawing group, which makes it extensively used in many kinds of conducting systems [3]. Thus, it is feasible to enhance the stability of the molecule and raise the quantum yield of fluorescence. Consequently, oxadiazole derivatives find application as organic light emitting diodes, laser dyes, optical brighteners, and scintillators [4]. Materials like thermal insulating polymers include these compounds as well [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 [6https://www.mdpi.com/2076-3417/12/8/3756][7][8].

Fig 1. Oxadiazoles: isomeric structures [6]

Anxiety is commonest mental illness with worldwide 7.3% of prevalence. Among these, specific phobias refer most common with 10.3% prevalence rate. Panic disorder has the prevalence rate of 6.0% that later develops social one (2.7%) and GAD (2.2%). Women are probably 1.5-2 times more prone to suffer from anxiety disorder than men [9]. Anxiety diseases resembles most prevalent type of mental disorder in children with 24.9% prevalence over a 12-month period. The most common disorders were certain phobias i.e., social anxiety [10]. Commonly, anxiety begins to propagate at 11 years (average age). While a mean onset age is 7 years but certain phobias and emotional states appear first followed by agoraphobia in absence of panic illness. The median onset age for GAD is considered as 31 years. German epidemiological study suggests that [11].

MATERIALS AND METHODS

Experimental Requirements

- Benzoic acid
- Salicylic acid
- Cinnamic acid
- Anthranilic acid
- Methanol
- Hydrazine hydrate
- nitrobenzene
- Succinic anhydride

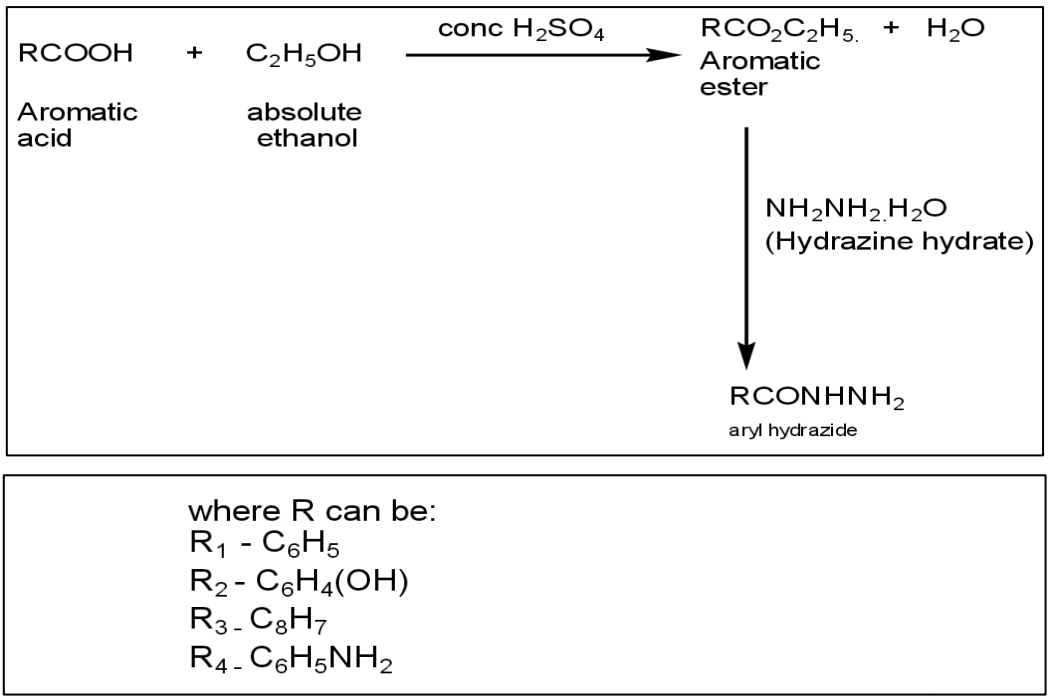
- Phosphorous oxychloride
- Anhydrous $AlCl_3$
- Concentrated sulphuric acid
- Sodium hydroxide
- Sodium bicarbonate
- Imipramine
- Ethanol
- Distilled water

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

The substituted aromatic acids were used as a versatile starting material for the synthesis of 1,3,4-oxadiazole derivatives involving the formation of corresponding esters and hydrazides. Ethyl esters were synthesized from substituted aromatic acids by means of Fischer esterification which were further reacted with hydrazine hydrate in the presence of ethanol to get the corresponding hydrazide derivative.

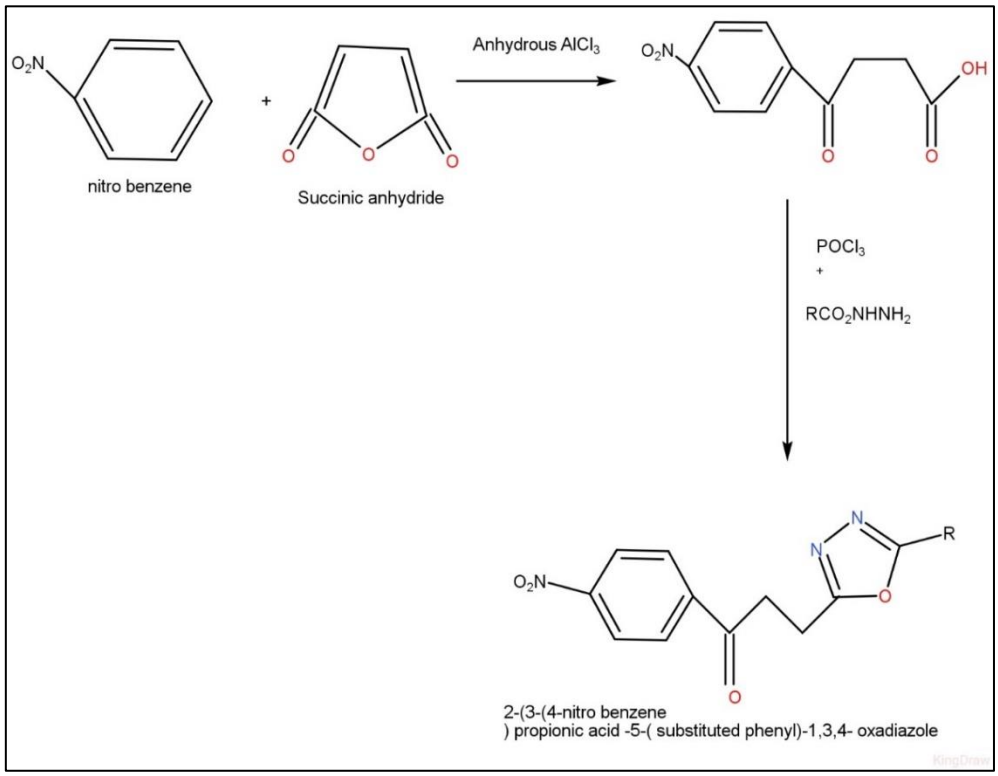


Step 2: Synthesis of derivative of 2- [3-(nitro benzene) propionic acid-5-(Substituted phenyl)-1,3,4-Oxadiazole Derivatives

3-(4-nitro benzene) propionic acid synthesis: to a solution of succinic anhydride (0.1 mol) in nitrobenzene (50ml), anhydrous aluminium chloride (0.11 mol) was added in small portions over a period of 2 hours under stirring. The reaction mixture was then refluxed for two hours and after completion of the reaction, excess benzoyl alcohol was removed by steam distillation. It was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. The solid so obtained was filtered, washed with cold water, dried and crystallized from methanol.

2-[3-(4-nitro benzene) propionic acid-5-(substituted phenyl)]1,3,4-oxadiazole: appropriate aryl acid hydrazide (1mmol) was dissolved in phosphorous oxychloride (5ml) and 3- [4- hydroxy methyl benzoyl)] propionic acid (1mmol) was added. The reaction

mixture, after refluxing for 5 hours, was cooled to room temperature and poured onto crushed ice. On neutralization of the contents with sodium bicarbonate solution (20%), a solid separated out and was filtered, washed with water and dried. It was crystallized from methanol to give the desired product.



Scheme 1. Synthesis of 1,3,4- oxadiazole derivatives

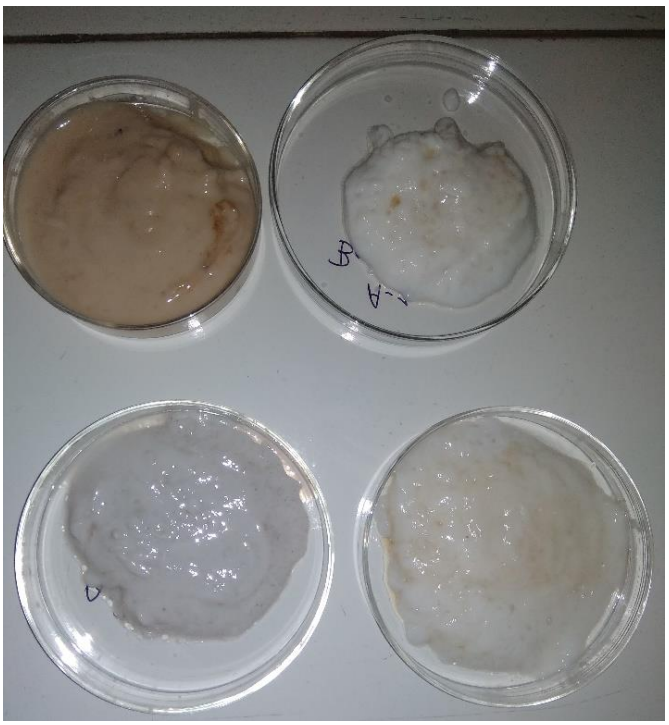
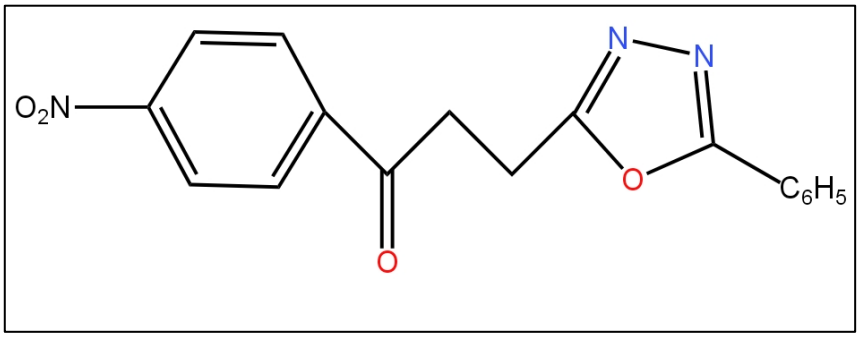


Fig 2. Synthesized derivatives

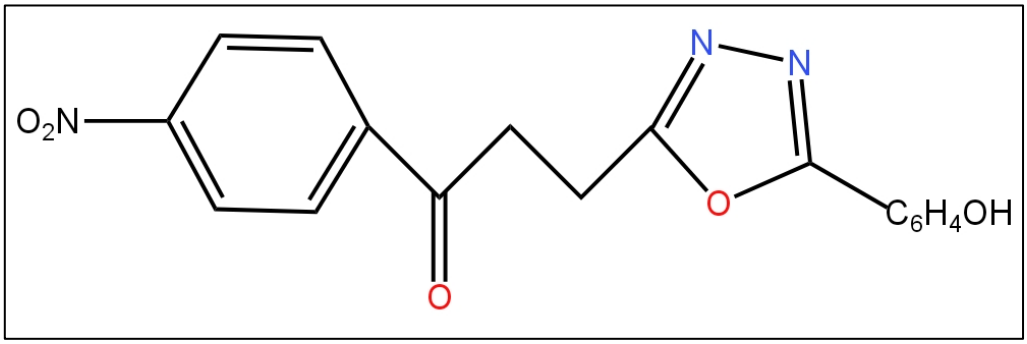
By using above scheme, 4 novel derivatives were synthesized as follows-

Compound 1 (A1):



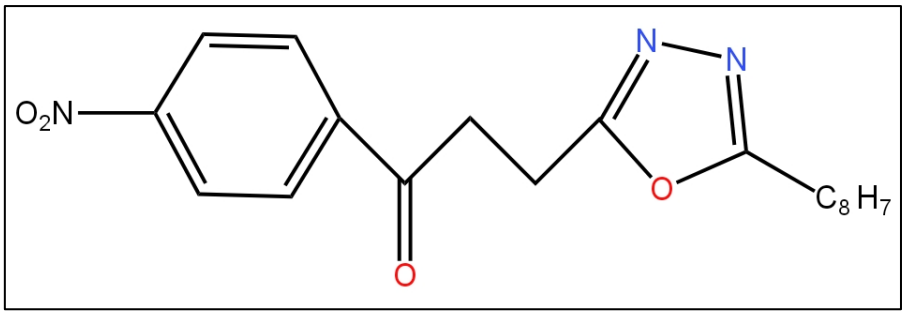
A1

Compound 2 (A2):



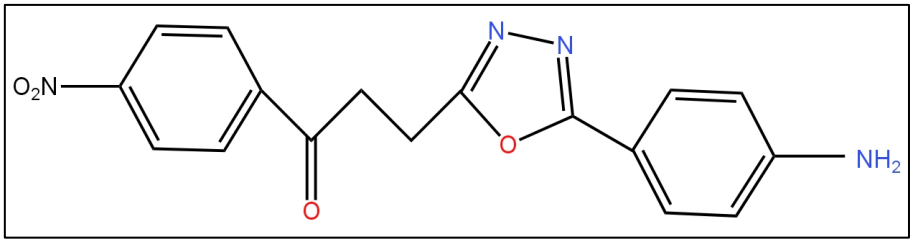
A2

Compound 3 (A3):



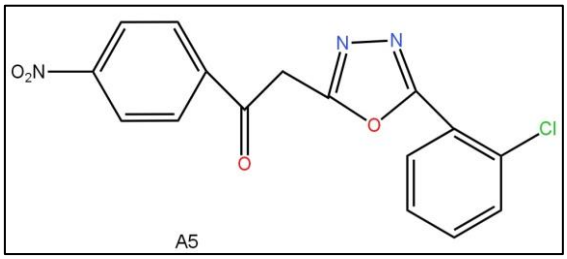
A3

Compound 4 (A4):



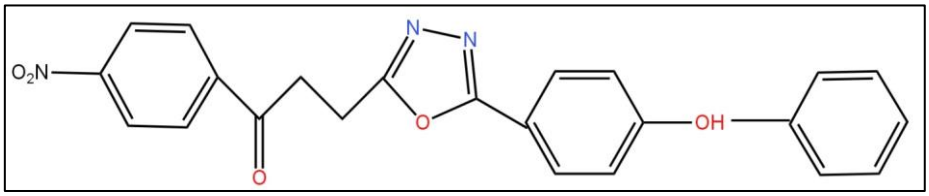
A4

Compound 5 (A5):



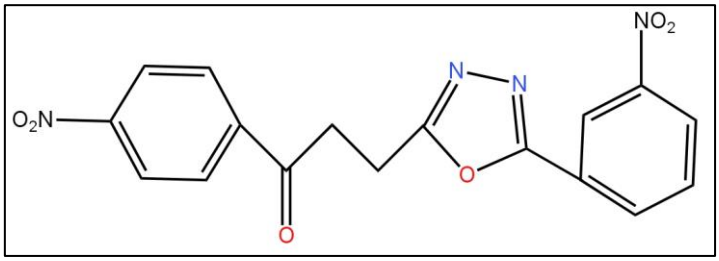
A5

Compound 6 (A6):



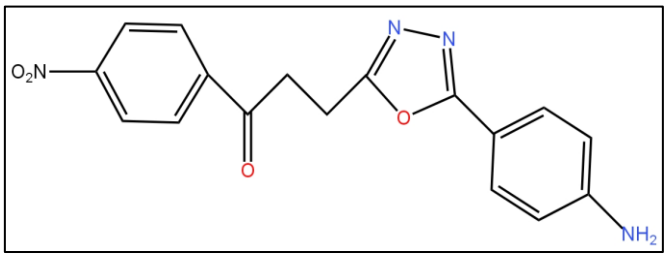
A6

Compound 7 (A7):



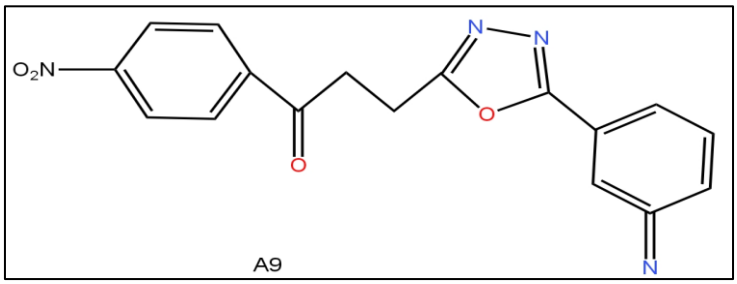
A7

Compound 8 (A8):

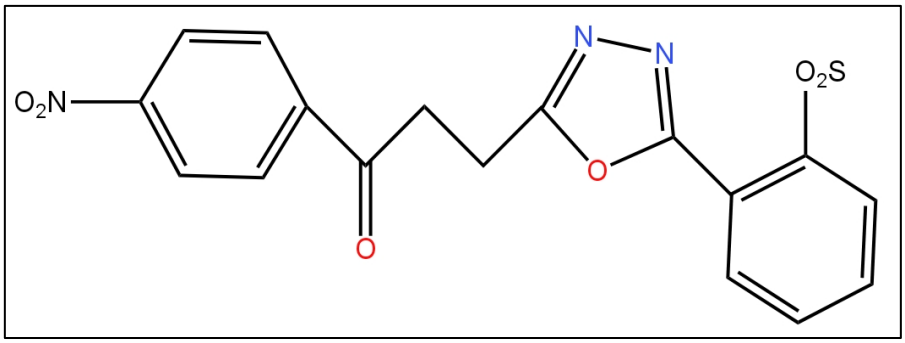


A8

Compound 9 (A9):



Compound 10 (A10):



A10

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].

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].

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 [15].

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 [16].

Molecular docking

Molecular Docking calculations of oxadiazole derivatives was done on the active site of $GABA_A$ receptors binding site (PDB ID: 6HUJ) using SwissDock (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 favorable 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].

Animal preparation

Animal House, Department of Pharmacy, MJP Rohilkhand University were provided rats (either sex) weighing 130-150g. 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].

Group design

All the rats were divided into 4 groups (n=6) as followings-

Group 1 were given only distilled water for 21 days.

Group 2 were given Imipramine (10mg/kg) for 21 days.

Group 3 were given novel derivatives of 1,3,4-oxadiazole (200mg/kg) for 21 days.

Group 4 were given novel derivatives of 1,3,4-oxadiazole (400mg/kg) for 21 days.

Pharmacological Evaluation Parameters

Forced Swimming Test

Rats are dropped into a glass (30x20cm) that is 15cm deep and kept at a temperature of about 30ºC. Rats are let to swim against their will for five minutes. Using a stopwatch, the total mobility time is recorded once every five minutes in seconds [19].

Locomotor Activity

Actophotometer is tuned on to check that all the photocells are working well for accurate readings. Rats are placed once at a time in activity cage for 10 min. Activity score is recorded in this due time. Thus, motor activity is observed and compared with standard drug-Imipramine [20].

RESULTS AND DISCUSSION

Synthesized derivatives

Novel derivatives of 1,3,4-oxadiazole (A1-A10) were developed using specified scheme. The procedure was followed as conventional tool for the 1,3,4-oxadiazole synthesis as mentioned in materials and methods section. After synthesis, all the derivatives were characterized through parameters i.e., % yield, Rf value and melting point.

Identification of physicochemical properties

Melting point determination

For 1,3,4-oxadiazole derivatives, the melting point was determined in the range of 164-168ºC, 172-176ºC, 174-178ºC, 203-206ºC, 128-132ºC, 156-160ºC, 152-156ºC, 134-138ºC, 140-144ºC and 142-146ºC for compounds A1, A2, A3, A4, A5, A6, A7, A8, A9 and A10 respectively.

Thin Layer Chromatography- Rf value

Thin layer chromatography is used in synthetic chemistry to confirm the production of derivatives based on their Rf value, which varies depending on the compound. Rf values were obtained as 0.62, 0.69, 0.67, 0.64, 0.66, 0.71, 0.68, 0.66, 0.67 and 0.69 of A1, A2, A3, A4, A5, A6, A7, A8, A9 and A10 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. A3 and A4 were demonstrated for its highest % yield as 69.21% and 68.52%. Lowest % yield was seen in A1 as 63.24%. The highest melting point was found in compound A3 as 148-152ºC. Highest melting point indicates about the strongest density of the compound. The following table summarized physical properties of all the compounds.

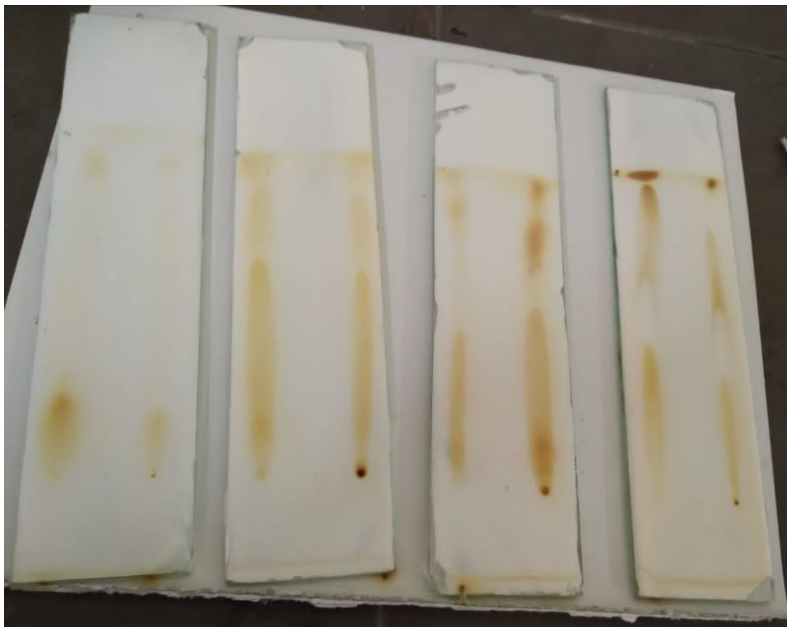


Fig 3. TLC of synthesized derivatives

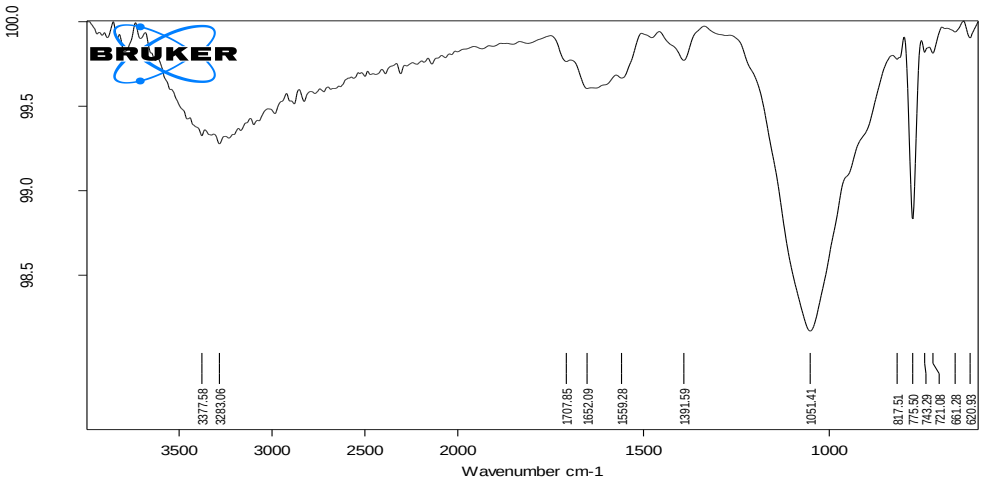
Table 1. Physicochemical properties of 1,3,4-oxadiazole derivatives

Compound	Yield (%)	Rf Value	Melting point
A1	63.24	0.62	140-144 ºC
A2	66.39	0.69	138-142 ºC

A3	69.21	0.67	148-152 ºC
A4	68.52	0.64	144-148 ºC
A5	64.35	0.66	128-132 ºC
A6	67.24	0.71	156-160 ºC
A7	69.46	0.68	152-156 ºC
A8	63.68	0.66	134-138 ºC
A9	66.74	0.67	140-144 ºC
A10	64.34	0.69	142-146 ºC

Infrared Spectroscopy

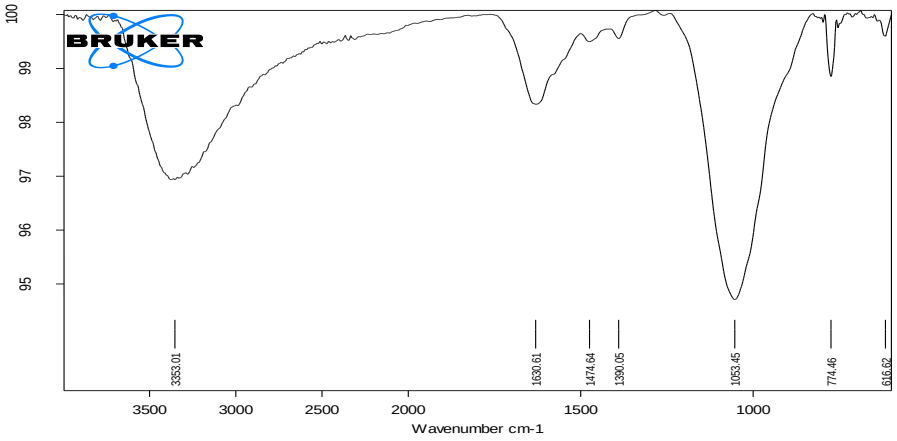
Compound A1-A4 were analyzed for infrared spectroscopy and these spectra were confirmed for the physicochemical characteristics of 1,3,4-oxadiazole derivatives.



FTIR Spectrum of A1

Table 2. FTIR Interpretation of A1

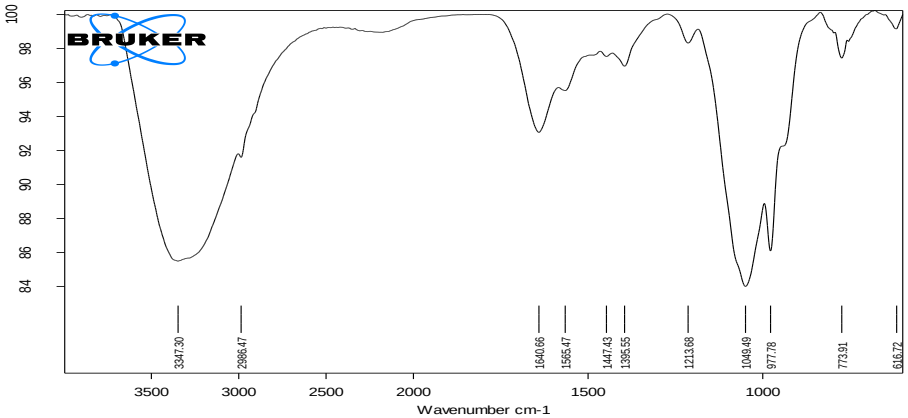
S. No.	Frequency (cm^{-1}) (observed)	Frequency (cm^{-1}) (theoretical)
1.	1061.4	1800-2000
3.	1061.4	1400-1600
4.	1392.6	900-1300
5.	3377.8	3000-3300



FTIR Spectrum of A2

Table 3. FTIR Interpretation of A1

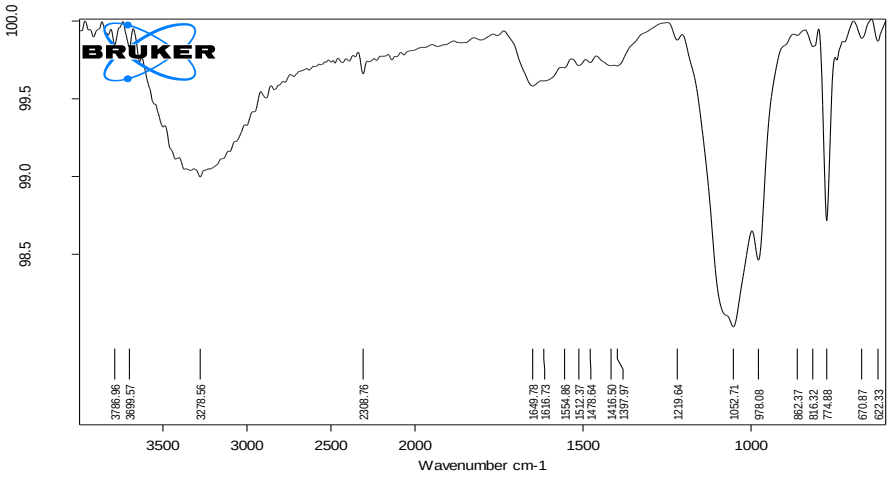
S. No.	Frequency (cm^{-1}) (observed)	Frequency (cm^{-1}) (theoretical)
1.	1053.4	1000-1300
3.	1300.5	1100-1400
4.	1474.5	1200-1500
5.	1630.6	3000-3300
6.	3353.1	3300-3500



FTIR Spectrum of A3

Table 4. FTIR Interpretation of A1

S. No.	Frequency (cm^{-1}) (observed)	Frequency (cm^{-1}) (theoretical)
1.	977.8	800-1000
3.	1049.5	9000-1100
4.	1640.6	1500-1700
5.	3347.5	3100-3400

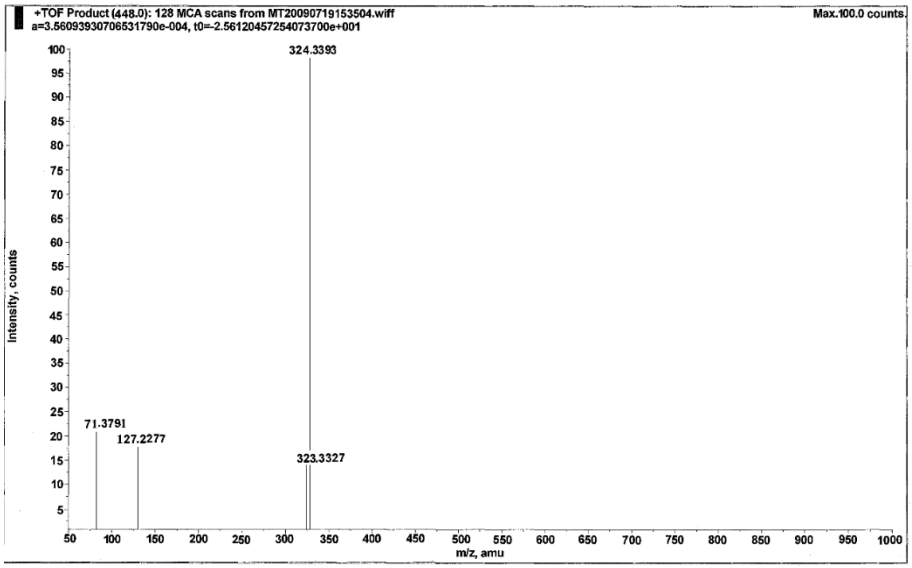


FTIR Spectrum of A4

Table 5. FTIR Interpretation of A1

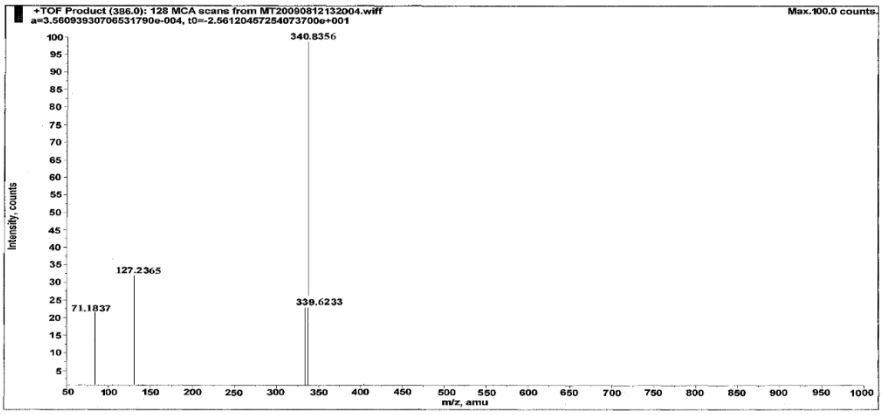
S. No.	Frequency (cm^{-1}) (observed)	Frequency (cm^{-1}) (theoretical)
1.	974.8	800-1000
3.	978.8	9000-1100
4.	1052.7	1000-1200
5.	3278.6	3000-3300

Mass spectroscopy



Interpretation: MS (m/z): 323 (100) $[M]^+$, 324 (15) $[M+1]^+$

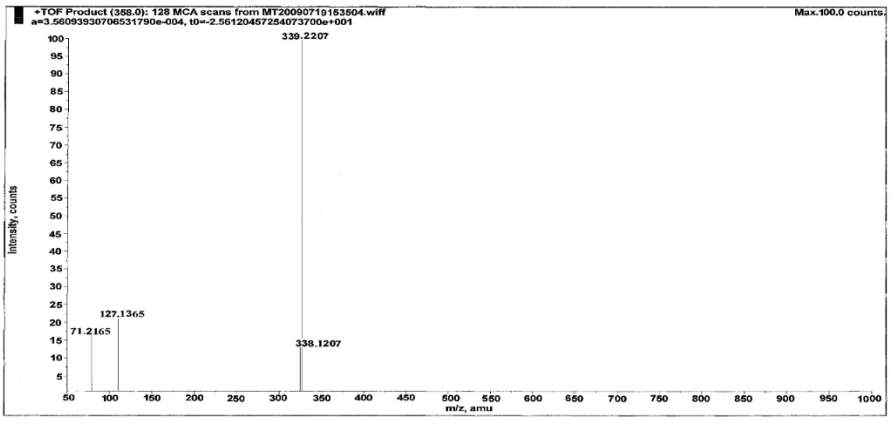
Fragments: 127 (18), 71 (23).



Mass Spectrum of A2

Interpretation: MS (m/z): 339 (100) [M]+, 340 (25) $[M+1]^+$

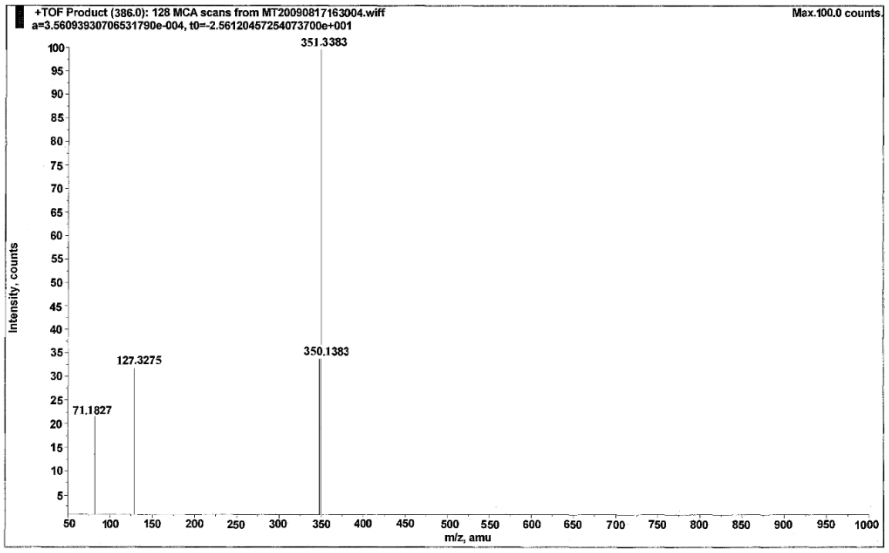
Fragments: 127 (33), 71 (24).



Mass Spectrum of A3

Interpretation: MS (m/z): 338 (100) $[M]^+$, 339 (15) $[M+1]^+$

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

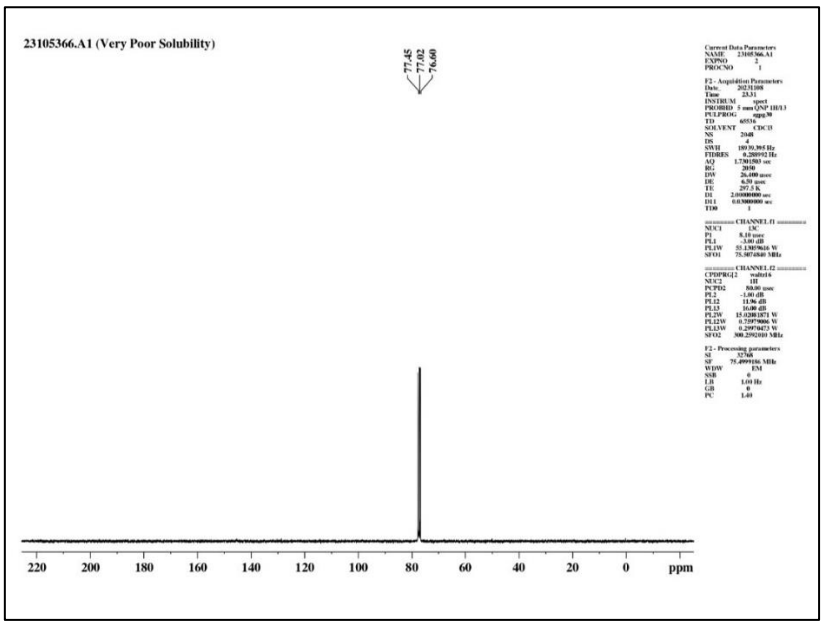


Mass Spectrum of A4

Interpretation: MS (m/z): 350 (100) $[M]^+$, 351 (35) $[M+1]^+$

Fragments: 127 (33), 71 (23).

NMR Spectroscopy

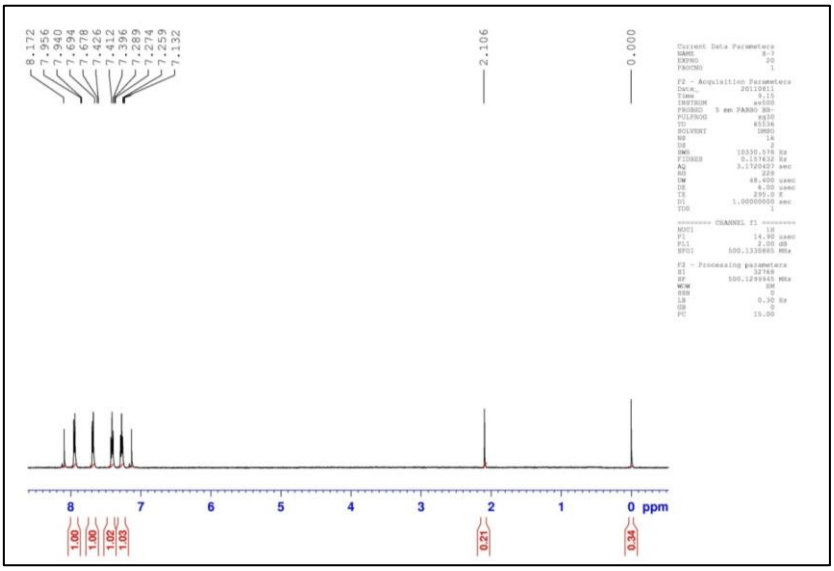


NMR Spectrum of A1

Table 6. NMR-Data of A1

S. No.	Chemical shift (ppm)	Proton
1.	2.22	2
2.	4.15-4.12	2

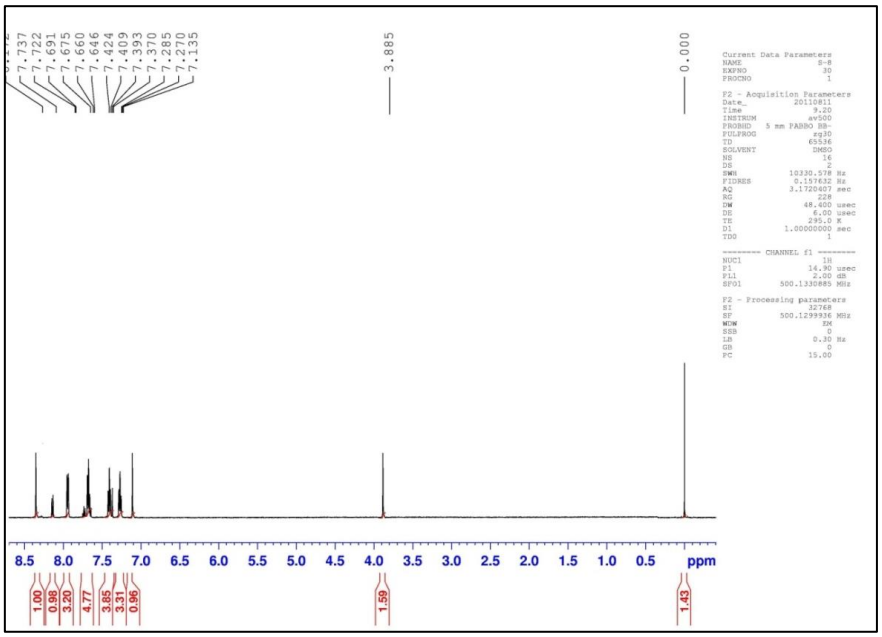
3.	7.08-7.75	4



NMR Spectrum of A2

Table 7. NMR-Data of A2

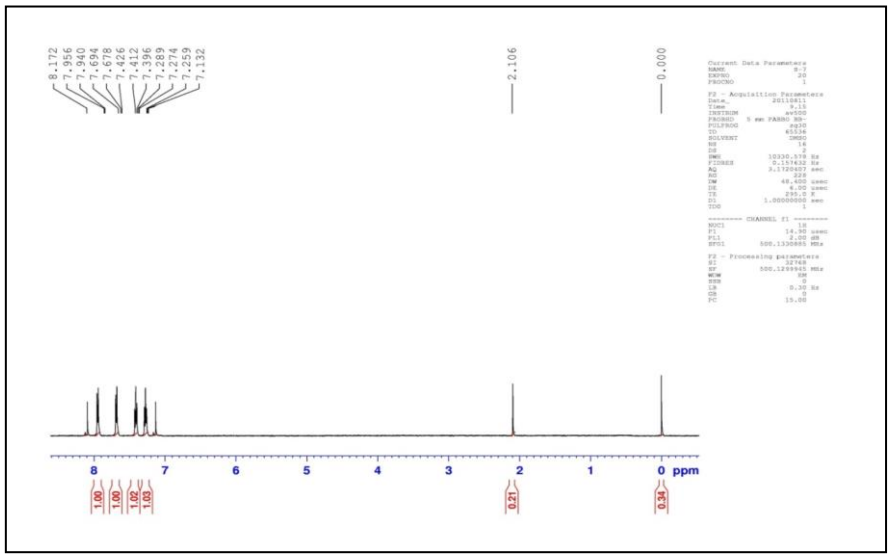
S. No.	Chemical shift (ppm)	Proton
1.	7.19-7.24	2
2.	7.36-8.17	13
3.	8.37	1



NMR Spectrum of A3

Table 8. NMR-Data of A3

S. No.	Chemical shift (ppm)	Proton
1.	3.96	3
2.	7.18	2
2.	7.27-8.16	13
3.	8.81	1



NMR Spectrum of A4

Table 9. NMR-Data of A4

S. No.	Chemical shift (ppm)	Proton
1.	7.14	2
2.	7.21-8.19	14
3.	8.35	1

Molecular Docking

We have performed the molecular docking studies for an oxadiazole derivative with the active binding site of $GABA_A$ receptors 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 $GABA_A$ receptors is extracted. All the compounds have shown the successful docking inside the active site of $GABA_A$ receptors with a binding energy of -6 to -7 Kcal/mol. We compared the predicted docking data with known $GABA_A$ receptors inhibitors.

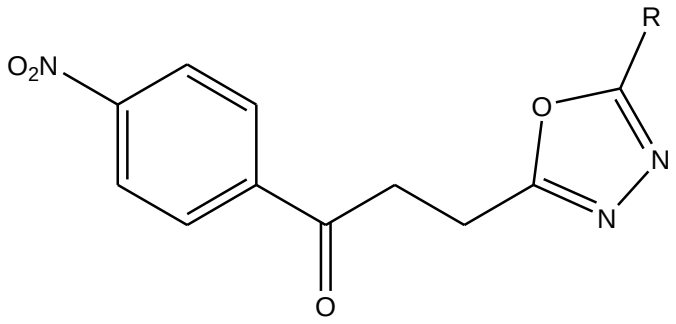
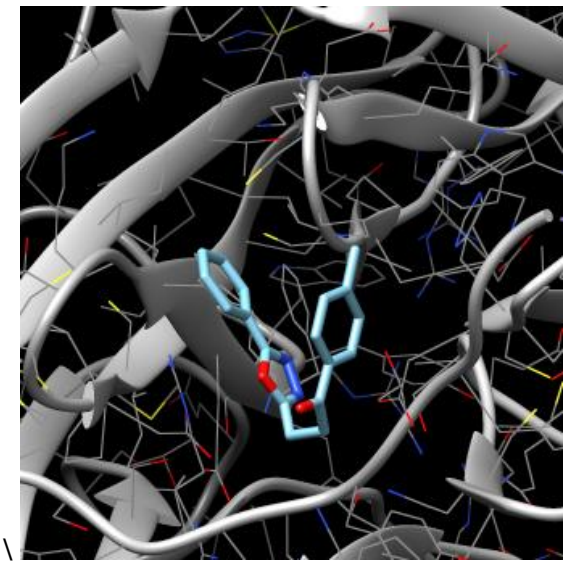
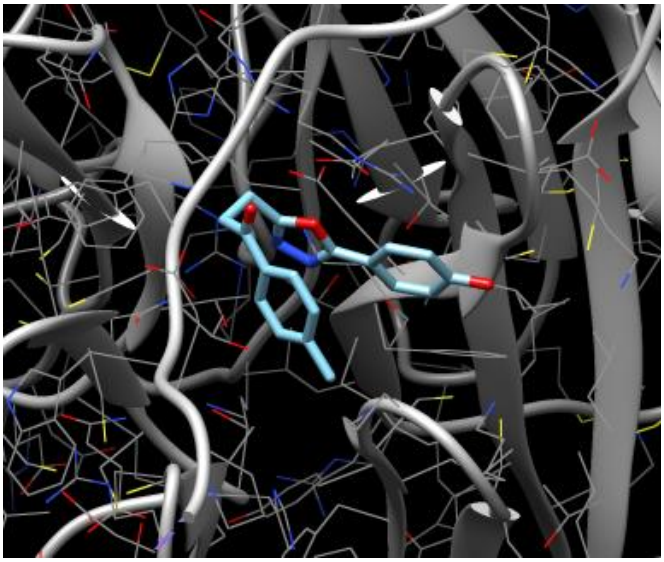


Table 10. Binding Energy in docking study

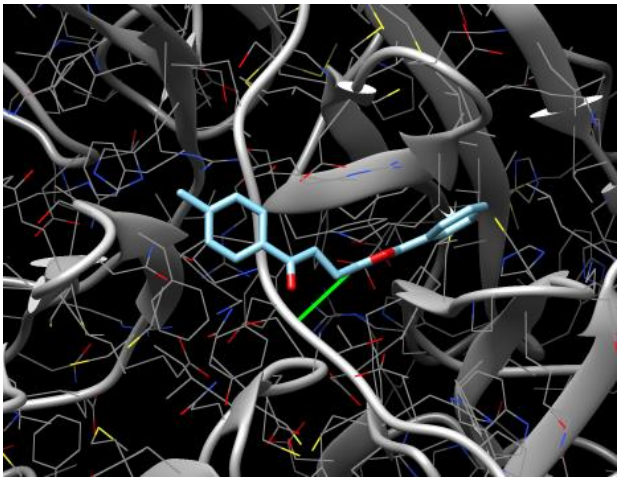
Compound No	R	Fullfitness (Kcal/mol)	Binding Energy (ΔG) (Kcal/mol)
A1	$-C_6H_5$	-2687.35	-7.35
A2	$-C_6H_4OH$	-2697.48	-7.60
A3	$-C_8H_7$	-2684.07	-6.94
A4	$-C_6H_4NH_2$	-2693.92	-7.17



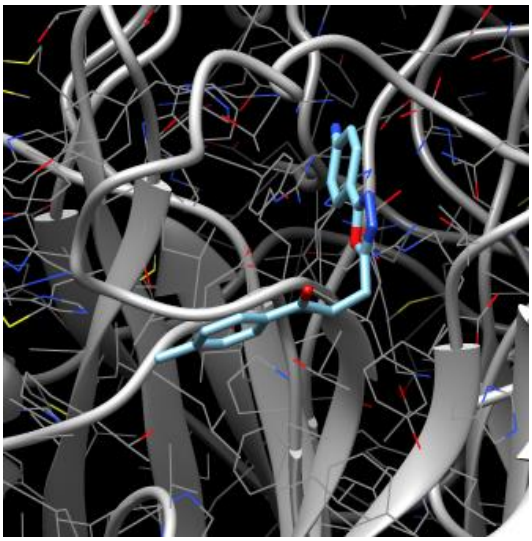
Molecular docking of A1



Molecular docking of A2



Molecular docking of A3



Molecular docking of A4

Evaluation of anxiolytic potential

Forced swimming test

In FST, mobility time was observed lowest in the case of control and highest in control which indicates for their anti-depressant accordingly. Novel derivatives of 1,3,4-oxadiazole (200mg/kg) and novel derivatives of 1,3,4-oxadiazole (400mg/kg) exhibited increase in mobility time as 242.36±0.23 sec and 262.11±0.25 sec, respectively. However, control group showed mobility time as 218.24±0.31sec. In both the doses, it significantly proved for its anxiolytic potential by facilitating the mood of animals. At higher dose, its effect was similar about same to standard group. It might be effective in relieving the anxiety and low mood in human too.

Table 11. Mobility time in FST of control, standard and novel derivatives of 1,3,4-oxadiazole treated rats

Treatment	Mobility time (sec) Mean± SEM
Normal saline	218.24±0.31
Imipramine (10mg/kg)	289.20±0.16
Novel derivatives of 1,3,4-oxadiazole (200mg/kg)	242.36±0.23
Novel derivatives of 1,3,4-oxadiazole (200mg/kg)	262.11±0.25

Significance Level= *

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

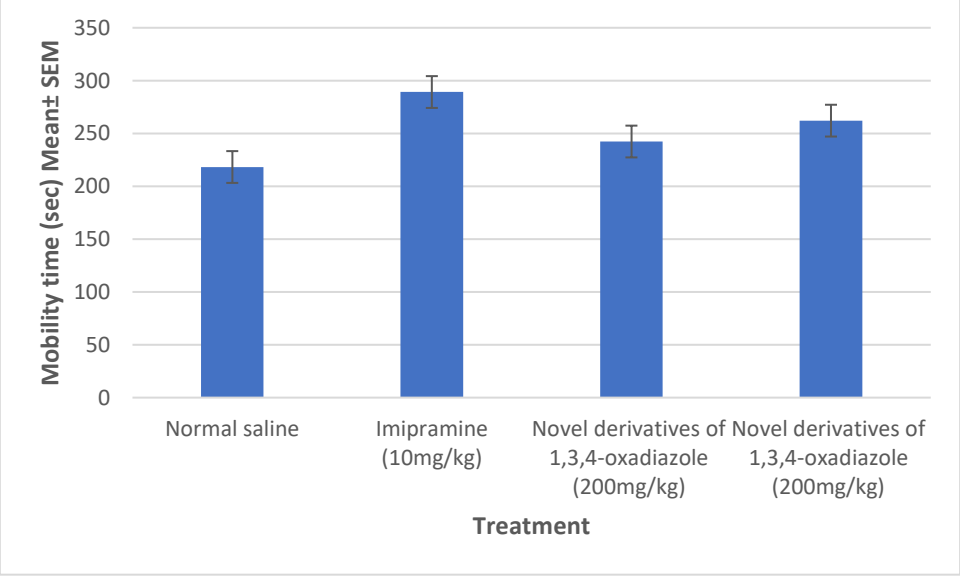


Fig 4. Mobility time in FST of control, standard and novel derivatives of 1,3,4-oxadiazole treated rats

Locomotor activity

In locomotor activity score test, highest locomotor activity was achieved in control as 149.24±0.11 sec whereas lowest activity score as found in imipramine treated rats as 98.27±0.24 sec. Novel derivatives of 1,3,4-oxadiazole (200mg/kg) and Novel derivatives of 1,3,4-oxadiazole (400mg/kg) exhibited the locomotor activity score as 134.33±0.29 sec and 105.19±0.26 sec, respectively. However, control group showed exhibited the locomotor activity score as 149.24±0.11 sec. Thus, it significantly decreased locomotion activity score at both the doses- proving itself a better anti- anxiolytic moiety.

Table 12. Locomotor test of control, standard and Novel derivatives of 1,3,4-oxadiazole treated groups

Treatment	Locomotor activity score (Sec ± SEM)
Normal saline	149.24±0.11
Imipramine (10mg/kg)	98.27±0.24
Novel derivatives of 1,3,4-oxadiazole (200mg/kg)	134.33±0.29
Novel derivatives of 1,3,4-oxadiazole (200mg/kg)	105.19±0.26

Significance Level= *

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

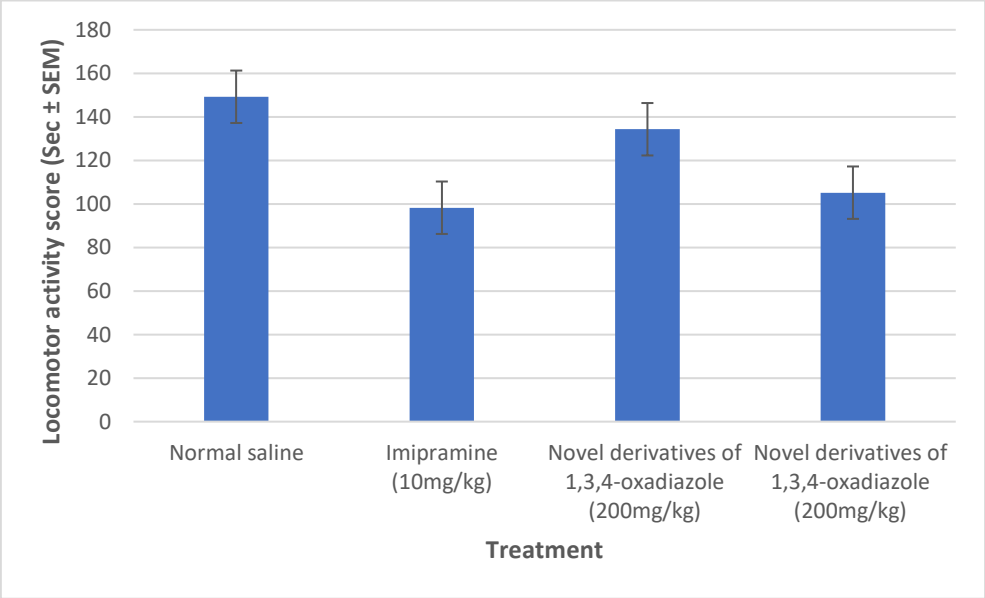


Fig 5. Locomotor test of control, standard and Novel derivatives of 1,3,4-oxadiazole treated groups

An effective anxiolytic agent should reduce anxiety and exert a calming effect. On the other hand, a hypnotic drug should produce drowsiness and encourage the onset and maintenance

of a state of sleep. Hypnotic effects involve more pronounced depression of the central nervous system than sedation and this can be achieved with many BZDs. Many of the common adverse effects of hypnotic agents result from dose-related depression of the central nervous system. Relatively low doses of BZDs may lead to drowsiness, impaired judgment and diminished motor skills. Aside from their quick onset of action and low toxicity, benzodiazepines have some undesirable effects such as sedation, negative effect on cognition, and development of tolerance to the desirable effects. Therefore, synthesis of novel agonists of benzodiazepine receptors with different chemical structure is still an important challenge. In this study, pharmacological evaluation of anxiolytic, sedative-hypnotic and memory impairment effects of the novel compounds and diazepam, as a reference, were tested using three well-known tests. Results of righting reflex test clearly indicated that the compounds with NH_2, SH, or SCH_3 groups on 2-position of 1,3,4-oxadiazole ring have a considerable hypnotic effect. However, their potencies were less than diazepam and there was no significant difference among those of the three compounds. It means the compounds with NH_2, SCH_3, or SH groups have similar hypnotic effects and compound with OH group on 2-position of the heterocyclic ring did not show hypnotic effect. The hypnotic activities of three compounds as well as diazepam were reduced by flumazenil; it concludes that these effects were mediated through benzodiazepine receptors. All the compounds show no significant effects on memory and anxiety in step-down passive avoidance and elevated-plus maze test respectively. Since the previously reported study showed that the compound with OH substituents on 2-position of 1,3,4- oxadiazole ring compound has a considerable anticonvulsant activity, Compound 2 might be a valuable lead compound to develop novel potent anticonvulsant agents with no impairment on learning and memory. The observed results in this study are completely compatible with our previous studies on other 1,3,4-oxadiazole and 1,2,4-triazole derivatives [21][22]. In all investigated heterocyclic derivatives, which were introduced as benzodiazepine receptor ligands, the amino substituent at the same position had the best effect on both hypnotic and anticonvulsant activities beside no effect on memory. The pharmacological relevance of the multitude of structurally diverse $GABA_A$ receptor subtypes determines that α_1 subunit of the $GABA_A$ receptors [23] is responsible for hypnotic activity of BZD agonists and also the effect on memory is mediated through the $GABA_A$ receptors with α_5 subunit. Since novel compounds had hypnotic activity with no effect on memory; it seems that these compounds may have higher affinity for α_1 than α_5 subunit. However, further studies are needed to prove this hypothesis [24].

In results, in all the models, novel derivatives of 1,3,4-oxadiazole (200mg/kg) significantly demonstrated anxiolytic potential at both the doses when compared to control.

Its effect was about similar and near to standard drug treated group. It indicates that actions might be similar to Imipramine, Nitrazepam etc. It exhibits antidepressant action probably by facilitating the release of neurotransmitters i.e., serotonin, dopamine. It also increases the release of GABA (Gamma Amino Butyric Acid) and chloride ions influx that leads to hyperpolarization. The effect was determined in dose-dependent manner. When compared to the control, the derivatives showed a considerable reduction in immobility period. The plant's successful antidepressant action prompted a futuristic attempt to bypass the blood-brain barrier by blocking P-gp. In contrast, this study confirmed anxiolytic and anti-depressant activity in both the doses without targeting the significant and selective constituent produced potential.

CONCLUSION

Novel derivatives of diphenyl 1, 3, 4-Oxadiazole as agonists of benzodiazepine receptors were investigated. Some of the novel synthesized compounds showed a better affinity for the

BZD site of action on the GABA-A receptor complex than Diazepam in radioligand receptor binding assay. All of the novel synthesized derivatives were evaluated for pharmacological assays. Surprisingly, a desirable correlation was observed between the ED_{50} values in the pharmacological evaluation and IC_{50} values in the radioligand receptor binding assay. All of the novel synthesized compounds showed no adverse effect on memory function. Memory deficit is an important unwanted effect of some BZDs. All of the novel derivatives had almost no significant negative effect on learning and memory in this study. Therefore, the novel derivatives could be the lead compounds in designing novel BZD ligands in future studies. Previous studies indicated that the α_1 subunit of the BZD receptor is the most important subunit in the sedative-hypnotic effects of BZD agonists. In addition, we know that the α_5 subunit is highly involved in the memory defect caused by BZDs. Therefore, However, this suggestion requires additional experiments to be confirmed.

In conclusion, novel derivatives of 1,3,4-oxadiazole is significant anxiolytic synthetic drug. It can be effectively used in the treatment of anxiety, depression, mental agitation and other neurological disorders after successfully evaluating mechanism of action of the synthetic derivatives. It suggests to perform the structure elucidation of synthesized derivatives and develop after structural modification (SAR) in desired dosage form to determine the highest bioavailability, potency, and efficacy (intrinsic activity). It also suggests researchers to determine its mode of action for anxiolytic effect.

FUNDING

Nil.

ACKNOWLEDGEMENT This work was supported by Dr. S.B Tiwari, Prashant Kumar, Pawan Kumar Gupta Vishal babu (lab assistant) of M.J.P Rohilkhand University Bareilly

CONFLICT OF INTEREST

Authors declared for none conflict of interest.

REFERENCES

1. Lelyukh, M.; Martynets, M.; Kalytovska, M.; Drapak, I.; Harkov, S.; Chaban, T.; Chaban, I.; Matiychuk, V. Approaches for synthesis and chemical modification of non-condensed heterocyclic systems based on 1,3,4-oxadiazole ring and their biological activity: A review. J. Appl. Pharm. Sci. 2020, 10, 151–165.
2. Glomb, T.; Świątek, P. Antimicrobial Activity of 1,3,4-Oxadiazole Derivatives. Int. J. Mol. Sci. 2021, 22, 6979.
3. Mandal S, Vishvakarma P. Nanoemulgel: A Smarter Topical Lipidic Emulsion-based Nanocarrier. Indian J of Pharmaceutical Education and Research. 2023;57(3s):s481-s498.
4. Mandal S, Jaiswal DV, Shiva K. A review on marketed Carica papaya leaf extract (CPLE) supplements for the treatment of dengue fever with thrombocytopenia and its drawback. International Journal of Pharmaceutical Research. 2020 Jul;12(3).
5. Bhandari S, Chauhan B, Gupta N, et al. Translational Implications of Neuronal Dopamine D3 Receptors for Preclinical Research and Cns Disorders. *African J Biol Sci (South Africa)*. 2024;6(8):128-140. doi:10.33472/AFJBS.6.8.2024.128-140
6. Tripathi A, Gupta N, Chauhan B, et al. Investigation of the structural and functional properties of starch-g-poly (acrylic acid) hydrogels reinforced with cellulose nanofibers for

cu2+ ion adsorption. *African J Biol Sci (South Africa)*. 2024;6(8): 144-153, doi:10.33472/AFJBS.6.8.2024.141-153

7. Sharma R, Kar NR, Ahmad M, et al. Exploring the molecular dynamics of ethyl alcohol: Development of a comprehensive model for understanding its behavior in various environments. Community Pract. 2024;21(05):1812-1826. doi:10.5281/zenodo.11399708
8. Mandal S, Kar NR, Jain AV, Yadav P. Natural Products As Sources of Drug Discovery: Exploration, Optimisation, and Translation Into Clinical Practice. African J Biol Sci (South Africa). 2024;6(9):2486-2504. doi:10.33472/AFJBS.6.9.2024.2486-2504
9. Kumar S, Mandal S, Priya N, et al. Modeling the synthesis and kinetics of Ferrous Sulfate production: Towards Sustainable Manufacturing Processes. African J Biol Sci (South Africa). 2024;6(9):2444-2458. doi:10.33472/AFJBS.6.9.2024.
10. Revadigar RV, Keshamma E, Ahmad M, et al. Antioxidant Potential of Pyrazolines Synthesized Via Green Chemistry Methods. African J Biol Sci (South Africa). 2024;6(10):112-125. doi:10.33472/AFJBS.6.10.2024.112-125
11. Sahoo S, Gupta S, Chakraborty S, et al. Designing, Synthesizing, and Assessing the Biological Activity of Innovative Thiazolidinedione Derivatives With Dual Functionality. African J Biol Sci (South Africa). 2024;6(10):97-111. doi:10.33472/AFJBS.6.10.2024.97-111
12. Mandal S, Bhumika K, Kumar M, Hak J, Vishvakarma P, Sharma UK. A Novel Approach on Micro Sponges Drug Delivery System: Method of Preparations, Application, and its Future Prospective. Indian J of Pharmaceutical Education and Research. 2024;58(1):45-63.
13. Mishra, N., Alagusundaram, M., Sinha, A., Jain, A. V., Kenia, H., Mandal, S., & Sharma, M. (2024). Analytical Method, Development and Validation for Evaluating Repaglinide Efficacy in Type Ii Diabetes Mellitus Management: a Pharmaceutical Perspective. Community Practitioner, 21(2), 29–37. https://doi.org/10.5281/zenodo.10642768
14. Singh, M., Aparna, T. N., Vasanthi, S., Mandal, S., Nemade, L. S., Bali, S., & Kar, N. R. (2024). Enhancement and Evaluation of Soursop (Annona Muricata L.) Leaf Extract in Nanoemulgel: a Comprehensive Study Investigating Its Optimized Formulation and Anti-Acne Potential Against Propionibacterium Acnes, Staphylococcus Aureus, and Staphylococcus Epidermidis Bacteria. Community Practitioner, 21(1), 102–115. https://doi.org/10.5281/zenodo.10570746
15. Khalilullah, H., Balan, P., Jain, A. V., & Mandal, S. (n.d.). Eupatorium Rebaudianum Bertoni (Stevia): Investigating Its Anti-Inflammatory Potential Via Cyclooxygenase and Lipooxygenase Enzyme Inhibition - A Comprehensive Molecular Docking And ADMET. Community Practitioner, 21(03), 118–128. https://doi.org/10.5281/zenodo.10811642
16. Mandal, S. Vishvakarma, P. Pande M.S., Gentamicin Sulphate Based Ophthalmic Nanoemulgel: Formulation and Evaluation, Unravelling A Paradigm Shift in Novel Pharmaceutical Delivery Systems. Community Practitioner, 21(03), 173-211. https://doi.org/10.5281/zenodo.10811540

17. Mandal, S., Tyagi, P., Jain, A. V., & Yadav, P. (n.d.). Advanced Formulation and Comprehensive Pharmacological Evaluation of a Novel Topical Drug Delivery System for the Management and Therapeutic Intervention of Tinea Cruris (Jock Itch). Journal of Nursing, 71(03). https://doi.org/10.5281/zenodo.10811676
18. Mishra, N., Alagusundaram, M., Sinha, A., Jain, A. V., Kenia, H., Mandal, S., & Sharma, M. (2024). Analytical Method, Development and Validation for Evaluating Repaglinide Efficacy in Type Ii Diabetes Mellitus Management: A Pharmaceutical Perspective. Community Practitioner, 21(2), 29–37. https://doi.org/10.5281/zenodo.10642768
19. Singh, M., Aparna, T. N., Vasanthi, S., Mandal, S., Nemade, L. S., Bali, S., & Kar, N. R. (2024). Enhancement and Evaluation of Soursop (Annona Muricata L.) Leaf Extract in Nanoemulgel: a Comprehensive Study Investigating Its Optimized Formulation and Anti-Acne Potential Against Propionibacterium Acnes, Staphylococcus Aureus, and Staphylococcus Epidermidis Bacteria. Community Practitioner, 21(1), 102–115. https://doi.org/10.5281/zenodo.10570746
20. Gupta, N., Negi, P., Joshi, N., Gadipelli, P., Bhumika, K., Aijaz, M., Singhal, P. K., Shami, M., Gupta, A., & Mandal, S. (2024). Assessment of Immunomodulatory Activity in Swiss Albino Rats Utilizing a Poly-Herbal Formulation: A Comprehensive Study on Immunological Response Modulation. Community Practitioner, 21(3), 553–571. https://doi.org/10.5281/zenodo.10963801
21. Mandal S, Vishvakarma P, Bhumika K. Developments in Emerging Topical Drug Delivery Systems for Ocular Disorders. Curr Drug Res Rev. 2023 Dec 29. doi: 10.2174/0125899775266634231213044704. Epub ahead of print. PMID: 38158868.
22. Abdul Rasheed. A. R, K. Sowmiya, S. N., & Suraj Mandal, Surya Pratap Singh, Habibullah Khallullah, N. P. and D. K. E. (2024). In Silico Docking Analysis of Phytochemical Constituents from Traditional Medicinal Plants: Unveiling Potential Anxiolytic Activity Against Gaba, Community Practitioner, 21(04), 1322–1337. https://doi.org/10.5281/zenodo.11076471
23. Foroumadi A, Sheibani V, Sakhteman A, Rameshk M, Abbasi M, Farazifard R, Tabatabai SA, Shafiee A. Synthesis and anticonvulsant activity of novel 2-amino-5-[4-chloro-2-(2-chlorophenoxy) phenyl]-1, 3, 4-thiadiazole derivatives. Daru J. Pharm. Sci. 2007;15:89–93.
24. Victor C, Loren M, Erin E, John K, Howard M, Franco T, John R, John M, Amit B, Neil C, Keith W, Beverley O. α5 GABAA receptors mediate the amnestic but not sedative-hypnotic effects of the general anesthetic etomidate. J. Neurosci. 2006;26:3713–3720.