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Original Article

Synthesis, Molecular Docking, and Anticonvulsant Activity of 1,3,4-Oxadiazole Derivatives

Anagha Balachandra[1] Shridhar Narayan Deshpande[1] Anjana Raj[1] Bistuvalli C. Revanasiddappa[1]

[1] Department of Pharmaceutical Chemistry, Nitte Gulabi Shetty Memorial Institute of Pharmaceutical Sciences (NGSMIPS), Nitte (Deemed to be University), Mangalore, Karnataka, India

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Address for correspondence B. C. Revanasiddappa, PhD, Department of Pharmaceutical Chemistry, Nitte Gulabi Shetty Memorial Institute of Pharmaceutical Sciences (NGSMIPS), Nitte (Deemed to be university), Mangalore 575018, Karnataka, India (e-mail: revan@nitte.edu.in).

Abstract

A novel series of 1,3,4-oxadiazoles (O1–4) were synthesized and physical characterization was done by spectroscopic data (infrared, mass, proton nuclear magnetic resonance). To ascertain the synthesized compound's likely binding mechanism and affinity toward the protein target (Protein Data Bank ID: 3R7X), molecular docking was performed. The synthesized compounds were subjected to in silico analysis using Schrodinger suite 2020–4 and absorption, distribution, metabolism, and excretion screening. Some of the synthesized compounds were subjected to in vivo evaluation of anticonvulsant activity by maximal electroshock seizure and pentylenetetrazol model. The synthesized 1,3,4-oxadiazole analogs may be developed as lead compounds and effective anticonvulsant agents for the pharmaceutical industry based on computational and in vivo data.

Keywords

- 1,3,4-oxadiazoles
- molecular docking
- anticonvulsant activity
- MES method
- diazepam

Introduction

A widespread nervous system disorder called epilepsy, which affects 1% of world's population, is characterized by recurring seizures brought on by aberrant electrical discharge from brain neurons. However, we are still unable to pinpoint the cellular basis of epilepsy's pathogenesis.[1] According to the International League Against Epilepsy, the identification of epilepsy can be established through the occurrence of one unprovoked (or reflex) seizure, or at least two unprovoked (or reflex) seizures that take place more than 24 hours apart.[2] Additionally, the diagnosis of an epilepsy syndrome and a risk of subsequent seizures equivalent to the general recurrence risk (which is at least 60%) after two unprovoked seizures within the next 10 years are also indicative of epilepsy. The elderly are more prone to epilepsy, revealing this age group's higher prevalence of stroke, neurological conditions, and tumors. The occurrence of epilepsy is most common in men when compared with women.[3]

Epilepsy therapies are still insufficient despite the creation of numerous new anticonvulsants. Even the most effective treatments for epilepsy cannot control seizures in more than 30% of patients.[1] When used to treat epilepsy, several medications, including diazepam, carbamazepine, phenobarbital, sodium valproate, and phenytoin, have failed to stop seizures in roughly 30% of patients. Antiepileptic medications are chosen for the treatment based on their effectiveness in treating a particular type of seizure as well as their tolerance and safety.

Antiepileptic medications like barbiturates and benzodiazepines are frequently used, however, they are ineffective at reducing seizures.[4] Other commercially available antiepileptic drugs (AEDs) include gabapentin, pregabalin, vigabatrin, lacosamide, lamotrigine, levetiracetam, etc. Three novel AEDs—brivaracetam, cannabidiol, and stiripentol—were recently approved by the United States Food and Drug Administration.[5] Nevertheless, there is always a need to look for new chemical substances that are more effective and have fewer side effects to use as AEDs.[6]

The presence of diverse pharmacological activities makes heterocyclic compounds highly valuable in the development of new pharmaceuticals. 1,3,4-oxadiazole is a heterocyclic

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compound that contains one oxygen and two nitrogen atoms in a five-carbon ring. Heterocyclic derivatives play an important role in pharmaceutical chemistry.[7] It serves as a bioisostere for carbonyl-containing compounds like esters, amides, and carbamates in certain instances, while also serving as a planar aromatic linker to achieve the desired molecular geometry.[8] The derivatives of oxadiazoles play a very significant role in medicinal chemistry as they have the properties like analgesic,[9] anticancer,[10] antiproliferative,[11] cytotoxic,[12] sedative,[13] etc., 1,3,4-oxadiazoles are commonly prepared through the utilization of carbohydrazides, Schiff bases, and diacylhydrazines. Numerous oxidizing agents and cyclizing agents can be employed for their synthesis, such as those that are readily accessible, namely, phosphorus oxy chloride,[14] iodobenzene diacetate,[15] and $FeCl_3$.[16]

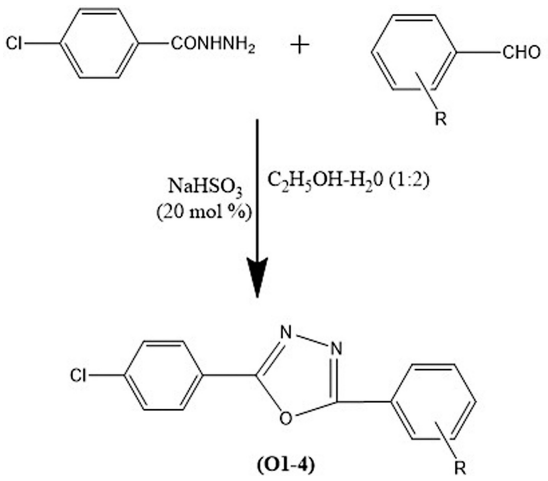
These findings and our interest in pharmaceutical chemistry of heterocyclic compounds led us to synthesize different derivatives of 1,3,4-oxadiazole with different substitution at 2,5 position.

Materials and Methods

The determination of melting points was conducted using the Equiptronics digital melting point apparatus (Model EQ-730, India). For Fourier-transform infrared (FT-IR) spectral analysis, KBr discs were utilized on the Alpha Bruker FT-IR spectrophotometer (Germany) (cm^{-1}). The Agilent 400MR DD2 spectrometer (United States) was utilized to record proton nuclear magnetic resonance (^{1}H-NMR) spectra at 400 MHz with d_6-DMSO/$CDCl_3$ as a solvent, where tetramethylsilane was used as an internal standard. The recording of mass spectra was performed using the Waters liquid chromatography-tandem mass spectrometry (United States). Thin-layer chromatography was used to examine the reaction progress and purity of the synthesized compounds, using silica gel G plates (stationary phase) and ethyl acetate: methanol (95:5) in various proportions (mobile phase). Analytical grade solvents were procured from Sigma Aldrich and HiMedia (India).

General Procedure for Synthesis of 1,3,4-oxadiazole Derivatives (O1–4)

In a round bottom flask, carbohydrazide (0.01 M) was dissolved in ethanol (25 mL). To this, solution of aromatic aldehydes (0.01 M) in ethanol was added. The contents were refluxed for 10 to 12 hours using 20 mol% $NaHSO_3$ and ethanol-water system (1:2, v/v) solvent. After completion of the reaction, the contents were poured into the crushed ice, filtered, and washed with water and recrystallized from alcohol[7] (►**Scheme 1**).



Scheme 1 Describes the reaction sequence followed. The spectroscopic data will confirm the formation of the new compounds.

O1: 2-(4-chlorophenyl)-5-phenyl-1,3,4-oxadiazole: MP-102–04°C IR (KBr, cm^{-1}) ν_{max}: 1012 (C-O-C), 1561 (C=C), 1605 (C=N), 3020 (C-H), ^{1}H-NMR (400 MH_Z, DMSO-d_6) (δ, ppm): 7.47–7.98 (m, Ar-H, 9H). MS (m/z): 256.70 (M+).

O2: 2-(4-chlorophenyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole: MP-118–20°C IR (KBr, cm^{-1}) ν_{max}: 1011 (C-O-C), 1566 (C=C), 1603 (C=N), 3043 (C-H), ^{1}H-NMR (400 MH_Z, DMSO-d_6) (δ, ppm): 7.30–7.97 (m, Ar-H, 8H). MS(m/z): 316.74 (M+).

O3: 2-(4-chlorophenyl)-5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole: MP-132–34°C IR (KBr, cm^{-1}) ν_{max}: 1014 (C-O-C), 1554 (C=C), 1596 (C=N), 3035 (C-H), ^{1}H-NMR (400 MH_Z, DMSO-d_6) (δ, ppm): 3.83 (s, 2× OCH_3, 6H), 7.04–7.96 (m, Ar-H, 7H). MS(m/z): 274.68 (M+).

O4: 2-(4-bromophenyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole: MP-114–46°C IR (KBr, cm^{-1}) ν_{max}: 1006 (C-O-C), 1554 (C=C), 1588 (C=N), 3028 (C-H), ^{1}H-NMR (400 MH_Z, DMSO-d_6) (δ, ppm): 7.58–7.93 (m, Ar-H, 9H). MS(m/z): 335.59 (M+).

In Silico Analysis

Protein Preparation

The protein (Protein Data Bank: 3R7X) (https://www.rcsb.org) was prepared using the protein preparation wizard module of Schrodinger suite 2020–4. Water atoms that exceed 5 A^0 and have no hydrogen bonds are evacuated. The primary module is used to fill in missing chain Iotas. All possible ionization states for the heteroatoms of the protein were formed. The state with the highest stability was selected. The OPLS3 force field was then used to perform a controlled energy reduction on the protein structure to shift the hydroxyl groups of the side chain and minimize the risk of steric clashes.[17]

Ligand Preparation

Using CHEMDRAW (http://www.cambridgesoft.com), the structures of all the newly synthesized compounds (O1–4) were drawn. The LigPrep module of Schrodinger suite 2020–4 was used to prepare the smile strings for each compounds after they were imported into the Maestro utility workspace. The force field used is OPLS_2005 minimized energy. With the proper state of ionization, tautomer, ring confirmations, and stereochemistry, two-dimensional molecular structures can be transformed into three-dimensional structures.[17]

Receptor Grid Generation

The conjugated ligand was stored in the protein's crystal structure. The protein preparation wizard was used to generate the grid box for the dynamic site centroid to be used for docking. The grid box is $14A^o \times 14A^o/14A^o$. The glide grid generation wizard was also used to generate this grid box.[17]

Receptor Ligand Docking

Finding the optimal ligand binding modes with the target protein's active residue is facilitated by in silico docking studies (https://www.schrodinger.com). The Schrodinger suite 2020–4's GLIDE module, which uses the standard protocol, was used to carry out the investigation. An extra-precision approach was used after a standard precision algorithm to dock the synthesized compounds into the protein target's (3R7X) pocket. In the assessment of the docking data, consideration was given to the binding energy. The optimal confirmation is indicated by the lowest binding energy or a highly negative value of the binding affinity.[18]

Absorption, Distribution, Metabolism, and Excretion Prediction

Absorption, distribution, metabolism, and excretion (ADME) calculations were performed for all the synthesized compounds by using the QikProp module of the Schrödinger suite 2020–4 (https://www.schrodinger.com/products/qikprop). The pharmacokinetic behavior of the compounds is determined by their physicochemical properties.[18]

In Vivo Anticonvulsant Screening

Selection of Animals

Swiss albino mice of both sexes weighing 20 to 25 g were used in this study. The animals were procured from the animal house of Nitte Gulabi Shetty Memorial Institute of Pharmaceutical Sciences, Mangalore, Karnataka, India, 1 week prior to experimentation and were subsequently acclimatized in the laboratory (Reg. No: NGSM/IAEC/2022–23/301). The mice were housed and maintained in polypropylene cages under 12-hour dark/light cycles at a temperature of 27 ± 2°C. They were provided with standard pellet food and water, except during experimental procedures. Pregnant females were excluded from the study. The ethical considerations were taken into account during the course of the study.

Acute Toxicity Studies

The acute toxicity studies of 1,3,4-oxadiazoles (OECD 425) on female albino mice weighing in between 20 and 25 g are conducted under standard husbandry conditions. Prior to experimentation, the animals will be subjected to an overnight fast. A single dose of 1,3,4-oxadiazole derivatives will be administered to the animals, and they will be monitored for a period of 48 hours for any instances of mortality. The subsequent doses will be determined in accordance with OECD guidelines no.425, based on the short-term toxicity profile.[19]

Maximal Electroshock Seizure

In the study, six groups of Swiss albino mice, consisting of six animals each, were selected. The mice were of either gender and had a body weight of between 20 and 25 g. The first group was administered with 1% aqueous solution of Tween 80 as a control, while the second group was given phenytoin (25 mg/kg orally) and served as a standard. The third to six groups were orally administered with respective 1,3,4-oxadiazole derivatives at low and high doses, respectively. The experiment commenced 45 minutes subsequent to the administration of either the vehicle or the test compounds, and 30 minutes following the standard drug. To initiate the session, a 60-Hz alternate current was administered to the animals via corneal electrodes for a duration of 0.2 seconds. The various stages of convulsion, including flexion, hindlimb extension, and stupor, as well as the total duration of the convulsion and the recovery period were recorded. A reduction in the duration of hindlimb extension was deemed to be a protective action, indicative of anticonvulsant activity.[19] The results of maximal electroshock seizure (MES) study are shown in ►**Table 1**.

Pentylenetetrazol-Induced Convulsions

A total of six groups, each containing six Swiss albino mice weighing between 20 and 25 g and of any gender, were selected. The control group received 1% aqueous solution of Tween 80. The second group, considered as the standard, was given diazepam (5mg/kg intraperitoneally). The third to six groups were orally administered with 1,3,4-oxadiazole derivatives at a dose of low and high doses, respectively. After 45 minutes of administering the vehicle or test compounds, and 30 minutes after the standard drug, pentylenetetrazol (PTZ) was administered. The mice were subsequently placed in separate cages and their latency to clonic convulsions and mortality were observed for a duration of 30 minutes.[19] The results of MES study are shown in ►**Table 2**.

Statistical Analysis

The results are displayed as mean ± standard error of the mean, with a group of six individuals. Statistical evidence was obtained using a one-way analysis of variance, and Dunnett's multiple comparison test was conducted. Results with a *p*-value below 0.05 were considered significant.

Results and Discussion

Chemistry

In the present work, a new series of 1,3,4-oxadiazole derivatives (O1–4) were synthesized in good yields by refluxing 4-chloro benzhydrazide with substituted aromatic aldehydes and a catalytic amount of $NaHSO_3$ with water as solvent. The hydrazide reaction with aromatic aldehydes is made easier by NaHSO3, leading to the removal of a water molecule and then cyclization to form substituted 1,3,4-oxadiazole. The desired compounds were obtained by heating the respective hydrazide compounds and aromatic aldehydes at 100°C in a mixture of ethanol and water (1:2) with 20 mol% $NaHSO_3$. Environmentally benign solvents such as water play an

Table 1 Data of anticonvulsant activity study by MES method

Groups	Treatment	Dose	Duration of flexion phase	Duration of extensor phase	Duration of colonus phase	Duration of stupor phase	% Protection
I	Control	–	13.3 ± 0.89	22.09 ± 2.1	35.16 ± 58	10.26 ± 1.25	0
II	STD (diazepam)	5.0 mg/kg (p.o.)	0.9 ± 0.26**	9.36 ± 0.89**	14.25 ± 3.25**	3.58 ± 1.35**	100
III	Low (O1)	2.88 mg/kg (p.o.)	6.1 ± 0.25**	15.25 ± 2.35**	23.56 ± 1.29^{ns}	5.25 ± 2.58**	66.6
IV	High (O1)	11.7 mg/kg (p.o.)	3.69 ± 0.98**	11.25 ± 3.5*	19.56 ± 2.56**	4.58 ± 1.28**	83.3
V	Low (O4)	2.88 mg/kg (p.o.)	4.2.9 ± 1.2**	16.58 ± 1.31**	20.58 ± 1.25**	6.58 ± 1.14**	66.6
VI	High (O4)	11.7 mg/kg (p.o.)	3.2.08 ± 1.28**	12.52.25 ± 1.25**	16.16 ± 1.2**	2.32 ± 3.25**	83.3

Abbreviations: MES, maximal electroshock seizure; p.o., orally; SEM, standard error of the mean; STD, standard.
Note: The above data are presented as mean ± SEM, $n = 6$.

important role in "green chemistry." In the field of green chemistry, the importance of utilizing environmentally friendly solvents such as water has increased substantially. The experiment was performed with water that had 20 mol% $NaHSO_3$. Nevertheless, the reaction progressed slowly, potentially because of the restricted solubility of the reactants. To address this problem, a solvent blend of ethanol and water (1:2, v/v) was employed, demonstrating to be a successful remedy for the synthesis. To investigate this, the reaction for the synthesis of title compounds was performed using 20 mol% $NaHSO_3$ in water with corresponding substrates.

The mass spectrum of compound O2 showed a molecular ion peak at M/z = 274.68 (M +), which is in agreement with the assigned molecular formula. The IR spectra of the compound O2 depicted the absorption bands at 3043 for aromatic (C-H) and 1603 (C = N), respectively. In the ^{1}H-NMR spectra of the compound, O2 aromatic protons were observed as multiplets in the region δ 7.30 to 7.97.

Lipinski's Rule of Five

The physicochemical properties of the compounds showed (►**Table 3**) no deviations from the standard ranges. All the synthesized compounds obey the Lipinski's rule of 5.

Molecular Docking Studies

The affinity of the compounds with receptor 3R7X is given in ►**Table 3** in terms of dock score. The binding free energy of the synthesized compounds ranges from –2.03 to –0.63 kcal/mol. The active residues in 3R7X are Asp48, Met49, Val50, Ser51, Glu52, Val53, Tyr143, Leu183, and Pro184. The highest affinity is demonstrated by compound O4 having a binding energy of –2.03 kcal/mol, followed by compound O1, with a binding energy of –1.85 kcal/mol. However, the standard diazepam showed the binding energy of –2.82 kcal/mol. The docking conformations of all the synthesized compounds with respect to 3R7X are depicted in ►**Fig. 1**. All the compounds fit into the binding cleft and participate in hydrogen bond interactions with GLN 185. The hydrophobic interaction between the ligand and the receptor also represents good interaction.

ADME Prediction

The ADME properties of the compounds are shown in ►**Table 4**. All the compounds demonstrated very high percentages of human oral bioavailability. Since the human oral absorption of all compounds was > 80%, the bioavailability would not be affected. Water solubility plays a major role in the absorption and distribution properties of a compound. All the compounds' log *p*-values were found within the acceptable range and are expected to exhibit good absorption and distribution.

Caco-2 cells are a great model to depict gut-blood barrier and nonactive transport. QPPCaco-2 predicts the apparent Caco-2 cell permeability in nm/sec. A value above 500 indicates great intestinal permeability whereas a value below 25 indicates very poor permeability. The predicted values of QPPCaco-2 indicated that all the synthesized compounds have good intestinal permeability. Another property that Qikprop can

Table 2 Data of anticonvulsant activity study by PTZ-induced convulsion method

Groups	Treatment	Dose (mg/kg)	Latency of tonic clonic seizures (s)	Duration of tonic clonic seizure (s)	Status of animal after 0.5 h	
					No. of animals alive	% protection
I	Control	–	51.26 ± 2.37	100.08 ± 2.31	0/6	0
II	STD (diazepam)	Diazepam 5 mg/kg	156.96 ± 3.58**	196.38 ± 1.86**	1/6	16.66
III	Low (O1)	2.88 mg/kg (p.o.)	59.56 ± 2.39**	139.25 ± 1.35**	5/6	83.33
IV	High (O1)	11.7 mg/kg (p.o.)	83.12 ± 1.35**	149.25 ± 1.37**	6/6	100
V	Low (O4)	2.88 mg/kg (p.o.)	99.28 ± 3.31**	110.25 ± 2.36**	5/6	83.33
VI	High (O4)	11.7 mg/kg (p.o.)	120.25 ± 2.23**	121.25 ± 2.17**	5/6	83.33

Abbreviations: p.o., orally; PTZ, pentylenetetrazol; SEM, standard error of the mean; STD, standard.
Note: The above data are presented as mean ± SEM, $n = 6$.

Table 3 Lipinski's rule of 5 and dock scores of compounds (O1–4)

Comp	MW	Log p	Donor HB	Accept HB	Rule of 5	Glide score
Acceptable range	≤ 500	> 5	≤ 5	≤ 10	< 5	–
O1	256.69	1.13	0	2.5	0	**–1.85**
O2	274.68	1.27	0	2.5	0	–0.63
O3	316.74	1.32	0	4.0	0	–0.88
O4	335.58	1.30	1	2.5	0	**–2.03**
Diazepam	284.74	1.67	0	4.0	0	–2.82

Abbreviations: Accept HB, estimated number of hydrogen bonds; donor HB, Estimated number of hydrogen bonds; Log p, lipophilicity; MW, molecular weight.

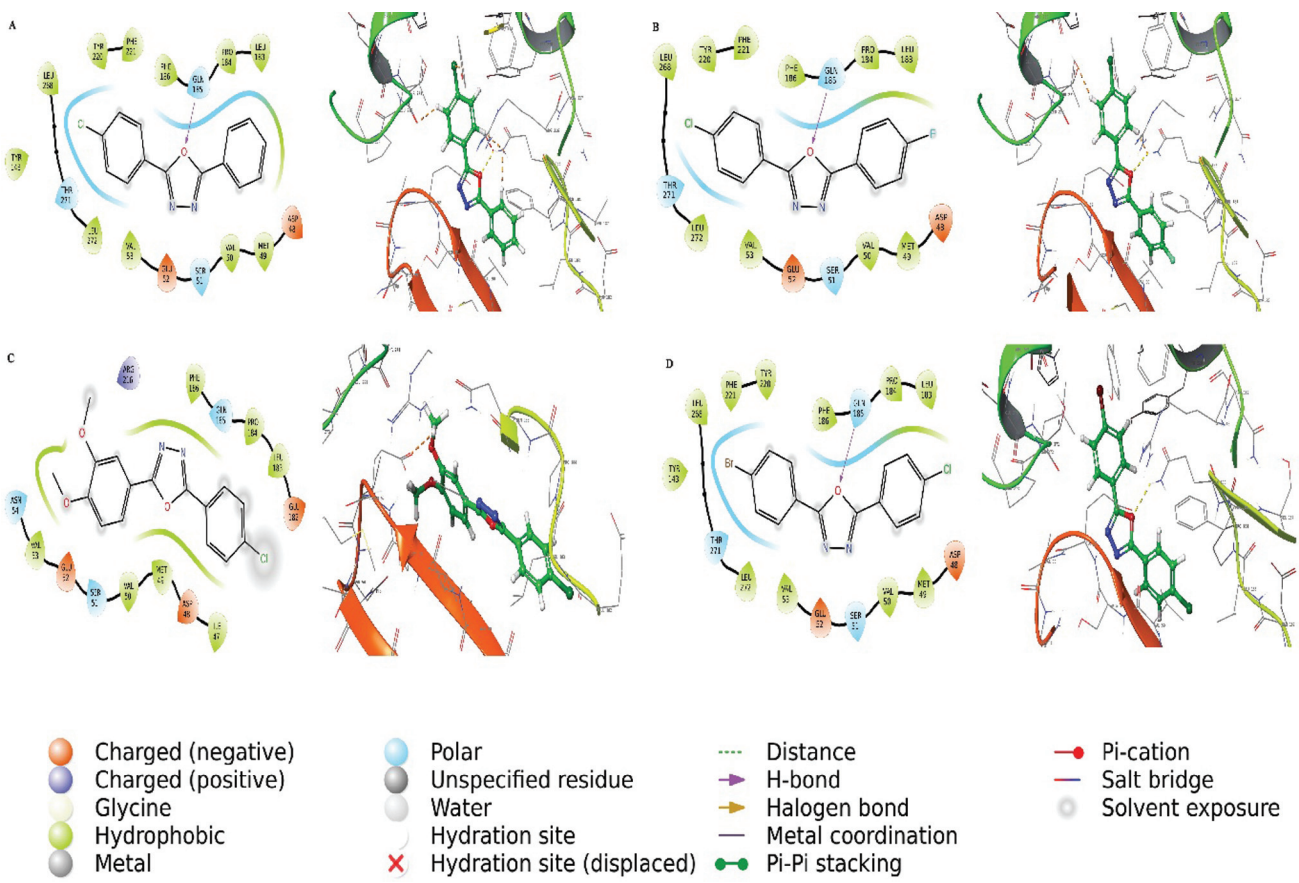


Fig. 1 Two-dimensional (2D) and three-dimensional (3D) interaction of compounds (**A**) O1, (**B**) 02, (**C**) O3, and (**D**) O4 with (Protein Data Bank [PDB]: 3R7X).

Table 4 Pharmacokinetic properties of compounds by Qikprop

Comp	% Human oral absorption	QPlog S	QPPCaco	# Metab	QplogBB	QPPMDCK	QPlogKHSA	SASA	FOSA	FISA
Acceptable range	> 80% high, < 25% low	(−6.5 to 0.5)	< 25 poor, > 500 great	(1–8)	(−3 to 1.2)	< 25 poor, > 500 great	(−1.5 to 1.5)	(300.0–1000)	(0.0–750)	(7.0–330)
O1	100.00	−3.82	2684.72	1	0.199	3548.517	0.149	523.093	121.519	59.791
O2	100.00	−4.58	3292.22	2	0.208	4428.290	0.305	531.872	92.697	50.449
O3	100.00	−5.48	3292.83	1	0.457	10000.000	0.485	523.964	0.000	50.441
O4	100.00	−4.85	3293.50	3	0.132	4429.779	0.273	569.253	183.798	50.431
Diazepam	100.00	−4.61	994.27	3	−0.386	1213.959	0.270	548.012	92.697	105.282

Abbreviations: FISA, hydrophilic component of SASA; FOSA, hydrophobic component of SASA; SASA, total solvent accessible surface area.

predict is the #metab which is the number of metabolic reactions that a drug can undergo. It predicts how easy it is for the drug to reach the site of target. All the synthetic derivatives are in the recommended range from 1 to 8.

The QlogBB (probable blood barrier partition) indicates how well the drug penetrates the central nervous system. All synthesized compounds have QlogBB values between –3 and 1.2 and fall within the recommended range. Madin-Darby canine kidney (MDCK) is a good mimic of the blood–brain barrier (BBB). This additional information helps predict BBB penetration. MDCK values indicate that all synthesized compounds have excellent BBB penetration capability. QPlogKhsa score predicts how well the compounds bind to the human serum albumin. The higher the QPlogKhsa value, the more strongly the compound binds to the serum albumin and the less likely it is to be active. All the compounds fall in the recommended range. This means that the compounds are not highly bound to the human serum albumin, therefore they are not active.

From the surface area components, total solvent accessible surface area (SASA), FOSA (a hydrophobic component of SASA), and FISA (a hydrophilic component of SASA) were predicted. Most of the values were found in the acceptable range as mentioned by the Qikprop manual of Schrodinger.

Anticonvulsant Activity

Based on the best docking scores, two compounds (O1, O4) were selected for screening by two in vivo models: MES-induced and PTZ-induced convulsions (►**Tables 1** and **2**). Latency and duration are the important parameters to evaluate anticonvulsant properties in both models.

When compared with the control group in the MES model, compounds O1 and O2, at both high and low doses, demonstrated a significant ($p < 0.01$) reduction in the duration of flexion, extensor, colonus, and stupor phases of epileptic episodes. As indicated in ►**Tables 1**, the percentage of protection for both the low and high concentrations of compound O1 and O2 was 66.6 and 83.3%, respectively. Diazepam was determined to have 100% protection (►**Table 1**).

The PTZ-induced tonic convulsion and its duration were both dose-dependently delayed by compounds O1 and O2 (low and high dose), but the compounds' effects on the control group were statistically significant ($p < 0.01$) in terms of the delayed onset and duration of the tonic convulsion. When compared with the control, compounds O1 and O2 (low and high dose) demonstrated 83.3% protection against mortality and were statistically significant ($p < 0.01$), while diazepam (5 mg/kg, intraperitoneally) only exhibited 16% protection (►**Table 2**).

Conclusion

In conclusion, a convenient synthesis method was employed to produce a novel series of 1,3,4-oxadiazole derivatives. These derivatives were obtained by reacting 4-chloro benzhydrazide with various substituted aromatic aldehydes, resulting in high yields by using sodium bisulfate and water solvent system. The reported methodology offers many

advantages such as simplicity of procedure, clean, and fast reaction, with good yields. Some of the tested compounds O1 and O2 showed moderate anticonvulsant activity.

Conflict of Interest

None declared.

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