Synthesis and biological evaluation of oxadiazole derivatives of valproic acid

Rimsha Rasheed[1], Muhammad Suleman[1], Freeha Hafeez[1*], Komal Sana[1], Saba Parveen[1]
[1]Department of Chemistry, Riphah International University Faisalabad Campus, Pakistan

Abstract: In the search for novel inhibitors, we examined two oxadiazole derivatives of valproic acid (VPA) synthesized using the StigIich method. The novel compounds' structures were confirmed by spectroscopic tests and strong in vitro biological activity. Compounds 112b and 112c inhibited Bacillus subtilis and E. coli well. Compound 157 showed no significant hemolytic profile in the cytotoxic studies, as compounds 150 and 155 were likely to be more toxic. Compound 153 showed potent thrombolytic activity, and that of the compound exceeded the standard control. With this discovery, the links explaining how valproic acid derivatives not only stop seizures but may also clamp down on bacteria-and perhaps cancer-were ready all along. The study establishes the pharmacological scope of activity associated with these derivatives, lays a perfect foundation for future investigations to optimize them chemically, and explores their precise mechanisms in detail. This work establishes potential novel therapeutic agents that are valproic acid-derived multi-biodegradable (VAMD) technologies.

Keywords: Thiophene derivatives, S-heterocyclic compounds, hemolysis, thrombolysis, cytotoxic evaluation

INTRODUCTION

Valproic acid (VPA) is a classic pharmaceutical that, besides being an antiepileptic drug widely used in the treatment of neuropathic pain and bipolar disorder (Imran et al.; Noor et al.), has recently promoted as redifferentiation agent for cancer therapy with differentiation potential on different types of solid tumors (Adewole et al., 2023; Safdar & Ismail, 2023). VPA has also been identified as having several biological characteristics in addition to its primary clinical uses (Singh et al., 2021), it shows antibacterial (F Hafeez et al., 2022; Hafeez, Zahoor, et al., 2021) and antimicrobial properties, besides a relevant anti-inflammatory one (Taleb et al., 2016). Recent data also indicate that reactivation can influence cancer therapy (Kumari et al., 2022), by behaving as a histone deacetylase inhibitor and then changing gene expression producing apoptosis (Zhang & Zhong, 2014).

Even though several chemical modifications have been done in VPA to make it more attractive from a therapeutic index perspective (Lipska et al., 2020), nitrogen based derivatives, which divide subpopulations of acting cells better, such as N-methyl-2-pyrrolidone and 1-N-benzylamine may be superior formulations for dividing the populations of the neurotoxic subsets (Mazzaro et al., 2019; Usula et al., 2014). StigIich ester derivatives were tested by the method of StigIich (Ayoub et al., 2021) for bactericidal activity. We recently demonstrated the synthesis of a series of oxadiazole derivatives from VPA that exhibited in vivo biological activity characteristics (Mishra et al., 2021). Beyond their ability to kill bacteria like Bacillus subtilis and Escherichia coli, these derivatives have also been found in preliminary studies to have potency against cancer by inhibiting (Castillo-Juárez et al., 2022) some key enzymes responsible for the proliferation of tumor cells (Lincet & Icard, 2015) (Schiliro & Firestein, 2021).

This research focuses on the inhibition of enzymes by these novel compounds, bridging this wide gap between VPA and oxadiazole derivatives with promising characteristics (Dalkara & Karakurt, 2012). Although the therapeutic applications of VPA are known, the mechanisms by which its oxadiazole derivatives bind to enzymes or how they inhibit enzyme activity have yet to be defined in detail (AyeshaTariq et al.). This knowledge gap restricts utilizing these molecules for selective therapeutic strategies (Kumar et al., 2023).

In this investigation, we describe the successful synthesis and enzyme inhibition study of new oxadiazole derivatives (Freeha Hafeez et al., 2022; Iftikhar et al., 2023) of valproic acid. We report the successful synthesis of a range of VPA nitrogen-based derivatives employing the StigIich method using (aniline) as an intermediate to attain new lead compounds with more potent activities (Kumar et al., 2023). Next, the confirmatory analyses of these derivatives were carried out using mass, FT-IR & NMR spectroscopy for their chemical structures (Dixon et al., 2022).

The synthesized oxadiazole derivatives showed good enzyme inhibition activity and anticancer and antibacterial properties. Compounds 112b & c had the maximum antibacterial activity, while compounds 157, with minimum cytotoxicity, indicated they could be safely used as effective therapeutic agents. Ethanol was the most effective solvent (under reflux) for obtaining high yields of desired ethoxylated products and proving its synthetic advantage.

The enzyme inhibition characteristics of the VPA derivatives containing the oxadiazole ring not only help us understand their mode of action but also underscore their potential as multi-targeting therapeutic agents. These results suggest that future work should explore the development of VPA

derivatives with improved efficacies to target a wider diversity of diseases, such as bacterial infections and cancer. This study significantly contributes to filling the knowledge gaps on enzyme inhibition, thereby helping to develop new and improved therapeutic strategies using valproic acid derivatives.

MATERIALS AND METHOD

GP 01: Synthesis of Hydrazide Analogue:

equiv) 2-propylpentanoic acid 1.0 equiv., 2-nitrobenzaldehyde treated with 5 equiv. of monohydrated hydrazine under reflux for 4 hours. TLC monitoring of reaction progress. A Filtered, dried and crystallized product (Yılmaz et al., 2012) (Alvi et al.; Hafeez, Mansha, et al., 2021).

GP 02: Synthesis of Oxadiazole Compound

2-Propylpentanehydrazide (1.0 equiv.) Closed in with KOH (1.5 equiv.) in ethanol. Carbon disulfide (1.2 equiv.) suspended, and refluxed for 10 hr (Shahzadi et al., 2020).

GP 03: Synthesis of Oxadiazole Derivatives

Compound 5-(oxadiazole-2-thiol)-1,3,4 heptan-4-yl (1.0 equiv.) N-bromo-N-phenylhydroxylamine (1.0 equiv.) was reacted with the starting material under reflux for a duration of 4 hours. After filtering, drying, and crystallizing, the product (Popiołek et al., 2020).

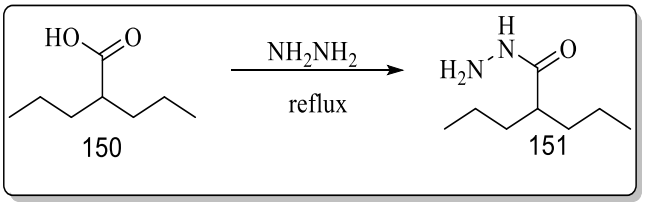
GP 04: Synthesis of Oxadiazole Metal Derivatives

Aryl-5-(heptan-4-yl)-1,3,4-thiadiazolonyloxy (1.0 equiv.) treated with metal salt (1.0 equiv.) under reflux for 4 hours. Obtained after filtration of the product followed by drying and crystallization (Matore et al., 2022).

Synthesis of Compounds

Synthesis of 2-propylpentanehydrazide 151

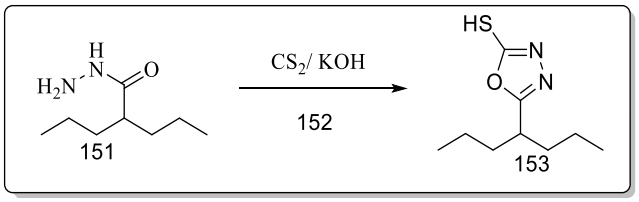
Using GP 01, 2-propylpentanehydrazide 151 was produced by refluxing 0.1g of 2-propylpentanoic acid150 (0.0006mol.) with 0.15g of monohydrated hydrazine (0.003mol.) for 20-30 minutes. The product was filtered after the reaction. Recrystallization with ethanol purified the raw product (El-Faham et al., 2015).



Scheme 1: Synthesis of 2-propylpentanehydrazide

Synthesis of 5-(heptan-4-yl)-1, 3, 4-oxadiazole -2- thiol 153

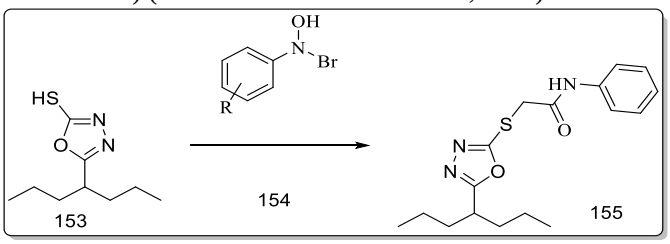
To synthesize 5-(heptan-4-yl)-1, 3, 4-oxadiazole -2-thiol, dissolve 2-propylpentanehydrazide 151 (0.05g, 0.0003mol.) in potassium hydroxide (0.01g, 0.00017mol.) in ethanol (20mL) according to GP 02. After adding in 0.02 g (0.0002 mol) of carbon disulfide, the liquid was reflux-heated for ten hours. After the solution was cooled and acidified with hydrochloric acid to a pH of 5–6, ethanol precipitated out of it (Patel et al., 2014).



Scheme 2: Synthesis of 5-(heptan-4-yl)-1, 3, 4-oxadiazole -2-thiol

Synthesis of aryl-1-((5-(heptan-4-yl)-1,3,4-oxadiazole-2-yl)thiol)-3-phenylpropan-2-one 155

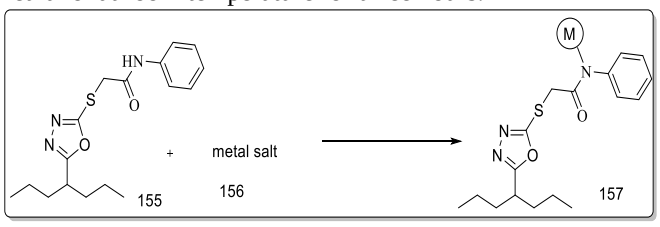
Compound GP 3,aryl-1-((5-(heptan-4-yl)-1,3,4-oxadiazole-2-yl)thiol)3-(heptan-4-yl)-phenylpropan-2-one 155 from equimolar 5-N-bromo-N-phenylhydroxylamine compound 154 (0.007g, 0.0008mol.) and 1, 3, 4-oxadiazole -2-thiol 153 (0.05g, 0.0002mol.) were agitated at room temperature for two hours using DCM (20mL) and pyridine (0.015g, 0.0001mol.) (Salah El-Din Mohamed et al., 2014).



Scheme 3: Synthesis of aryl-1-((5-(heptan-4-yl)-1,3,4-oxadiazol-2-yl)thiol)-N-phenylacetamide

Synthesis of oxadiazole derivatives 157

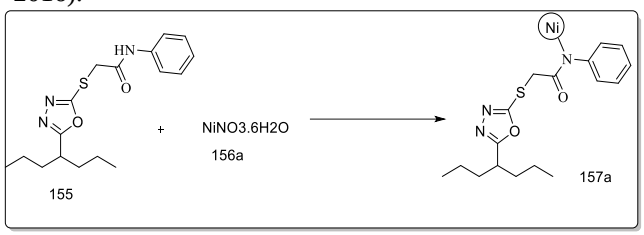
As per GP-04, equimolar quantities of metal salts (0.08g, 0.00027mol.) were reacted with compound (0.007g, 0.0008mol.) aryl-1-((5-(heptan-4-yl)-1,3,4-oxadiazol-2-yl) thiol) to create oxadiazole metal derivarities 157.-N-phenylacetamide 155 (0.1g, 0.00028mol.) in 20 milliliters of ethanol at room temperature for three hours.



Scheme 4: Aryl-1-((5-(heptan-4-yl)-1,3,4-oxadiazol-2-yl)thiol)-N-phenylacetamide metal salt

Synthesis of metal complex 157a

Equimolar quantities of different $NiNO_3.6H2O$ 156a (0.08g, 0.00027mol.) and aryl-1-((5-(heptan-4-yl)-1,3,4-oxadiazol-2-yl) thiol)-N-phenylacetamide 155 (0.1g, 0.00028mol.) in ethanol (20mL) at room temperature for three hours were used to create oxadiazole metal derivarities (Vaidya et al., 2016).



Scheme 5: Synthesis of (((5-(2-((2-chlorophenyl)amino)benzyl)-1,3,4-oxadiazole-2-yl)tho)oxy)nickel salt

Synthesis of metal complex 2 157b

Equimolar quantities of $ZnCl_2$ 156b (0.07g, 0.00028mol.) and aryl-1-((5-(heptan-4-yl)-1,3,4-oxadiazol-2-yl) thiol)-N-phenylacetamide 155 (0.1g, 0.00028mol.) in ethanol (20mL) at room temperature for three hours were used to create oxadiazole metal derivarities (Reddy et al., 2011).

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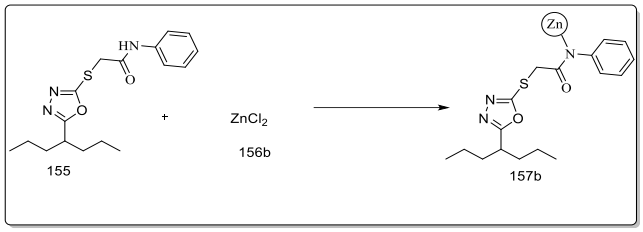
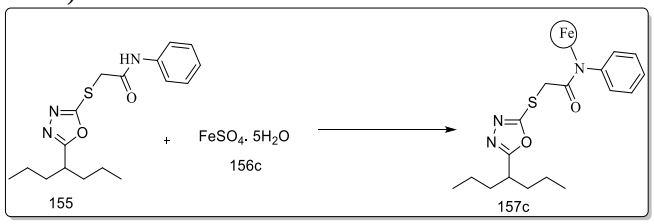


Scheme 6: Synthesis of (((5-(2-((2-chlorophenyl)amino)benzyl)-1,3,4-oxadiazole-2-yl)tho)oxy) zinc salt

Synthesis of metal complex 3 157c

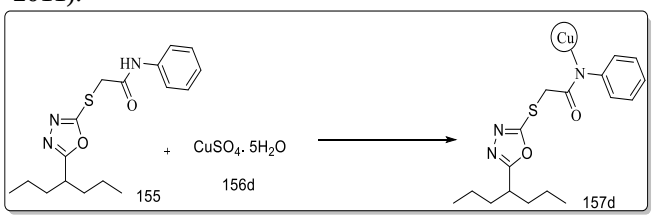
Equimolar quantities of $FeSO_4.5H_2O$ 156c (0.06g, 0.00024mol.) and aryl-1-((5-(heptan-4-yl)-1,3,4-oxadiazol-2-yl) thiol)-N-phenylacetamide 155 (0.1g, 0.00028mol.) in ethanol (20mL) at room temperature for three hours were used to create oxadiazole metal derivarities (Terenzi et al., 2011).



Scheme 7: Synthesis of (((5-(2-((2-chlorophenyl)amino)benzyl)-1,3,4-oxadiazole-2-yl)tho)oxy)iron salt

Synthesis of metal complex 4 157d

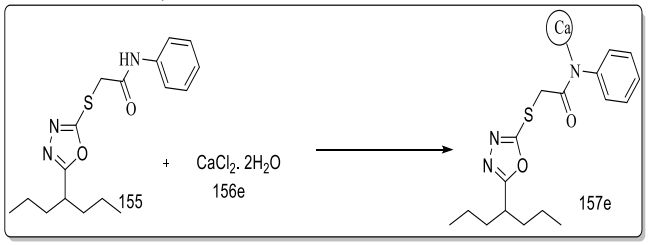
Equimolar quantities of $CuSO_4.\ 5H_2O$ 156d (0.07g, 0.00028mol.) and aryl-1-((5-(heptan-4-yl)-1,3,4-oxadiazol-2-yl) thiol)-N-phenylacetamide 155 (0.1g, 0.00028mol.) in ethanol (20mL) at room temperature for three hours were used to create oxadiazole metal derivarities (Khedr et al., 2011).



Scheme 8: Synthesis of (((5-(2-((2-chlorophenyl)amino)benzyl)-1,3,4-oxadiazole-2-yl)tho)oxy)cuppor salt

Synthesis of metal complex 5 157e

Equimolar volumes of different $CaCl_2.2\ H_2O$ 156e (0.05g, 0.00033mol.) and aryl-1-((5-(heptan-4-yl)-1,3,4-oxadiazol-2-yl) thiol)-N-phenylacetamide 155 (0.1g, 0.00039mol.) in ethanol (20mL) at room temperature for three hours were used to create oxadiazole metal derivarities (Salassa & Terenzi, 2019).



Scheme 9: Synthesis of (((5-(2-((2-chlorophenyl)amino)benzyl)-1,3,4-oxadiazole-2-yl)tho)oxy)calcium salt

Cytotoxic Evaluation

Thrombolysis

Blood was taken from the human donor and, for each sample (Shoaib et al.), 500 µL of this blood aliquoted into Eppendorf tubes that had been pre-cleaned using HNO_3 cleaning solution. The tubes were then incubated at 37°C for one hour to allow clot formation. The supernatant was collected postincubation and clots weighed. Then each clot was incubated with 40 µL volume buffer solution containing material dissolved in DMSO (Iftikhar et al., 2023; Khushnood et al.). After 3 hours the tubes were again placed in an incubator at 37°C on its side for reading of clot lysis (Domínguez et al., 2010; Hafeez, Mansha, et al., 2021). The same method was carried out three times, the direction of lysis is justified with a formula.

$$\text{Clot lysis} = \frac{(\text{weight of clot lysis})}{\text{weight of clot before lysis}} \times 100$$

Hemolysis

EDTA tube with 50 mL of blood withdrawn from a single healthy volunteer. The whole fresh sheep RBCs were centrifuged in microcentrifuge tubes at the speed of 1000 rpm for 5 min to collect red blood cells (RBCs) (Noureen et al.; Siddique et al.). After that, the supernatant was aspirated and RBC pellet washed with PBS for a total of 3 times. One hour of incubation at 37°C ensued after which the pellet was resuspended in DMSO (20 uL). Then Tubes were centrifuged (13000 rpm for 05 min) supernatant discarded, and cold PBS was added (Dong & Liu, 2016) (Hafeez, Mansha, et al., 2021).

Characterization

Characterization techniques comprised Fourier transform infrared spectroscopy (FT-IR) for solid, liquid and gaseous samples to study absorption or emission spectra as well NMR nuclear magnetic resonance measurements on 1H-NMR [13C]-NMR with AV-400, -500 model spectrometer operating at frequencies located at 100 and set up at founded over the last few years in application levels MHz~ initial stages (Mao et al., 2008).

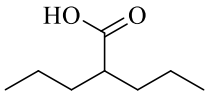
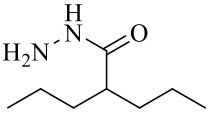
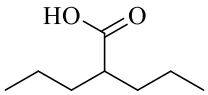
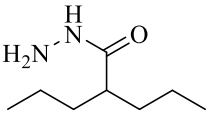
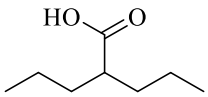
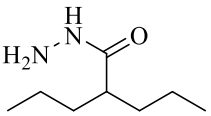
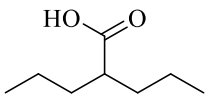
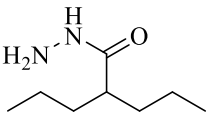
Statistical analysis was performed in Excel 2010 spreadsheet program and each experiment repeated three times. Results were reported as mean ± standard deviation and data presented here are based on cell viability assays (Mélard, 2014).

RESULTS

Analysis of hydrazide analogue

Entry 1- No Product (2% PPA) Hydrazine monohydrate was added for reaction with 150 mmol of 24 hours without stirring brothanol at a constant temperature. The reaction in ethanol solvent and reflux for 6 h yielded a product of 60% (Table 1, entry2). With constant stirring in ethanol for 20 hours, the reaction gave no product (Table 1, entry 3). 2-propylpentanehydrazide has been isolated in high yield (84%) under reflux-conditions using methanol solvent for 4 hours (Table 1, entry 4)

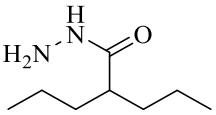
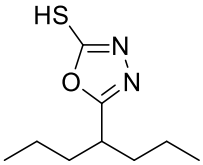
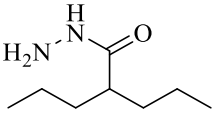
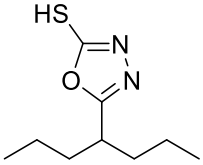
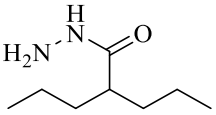
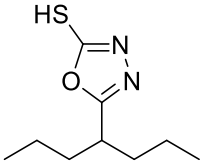
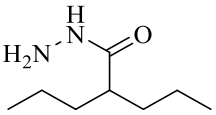
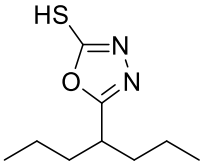
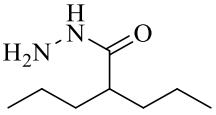
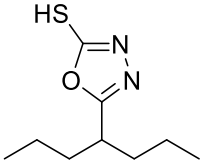
Table 1: Synthesis of hydrazide analogue

Entry.#	Compound	Condition	Solvent	Time (hr)	Product	Yield %
1		Stirring	EtOH	24		Failed
2		Reflux	EtOH	6		60
3		Stirring	MeOH	20		Failed
4		Reflux	MeOH	10		84

Analysis of oxadiazole

An attempted reaction between 2-propylpentanehydrazide and carbon disulfide in DCM for 2 hr did not produce the desired compound (Table 2, entry 1). The refluxing for 4 hours gave a yield of only about 10% (Table 2 entry no:2). The 20 hours reaction between 2-propylpentanoic acid and hydrazine monohydrate in ethanol did not afford any product (Table 1, entry 3). Hydrazide 10 was obtained by using methanol and reflux for 4 h with a yield of ~30% (Table 1, entry 4). Optimal yield was obtained when the 2-propylpentanehydrazide and carbon disulfide were reacted in ethanol at reflux for 10 hours, providing a total volume of 65% (Table 2: entry5).

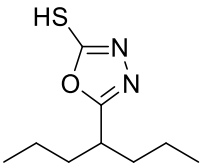
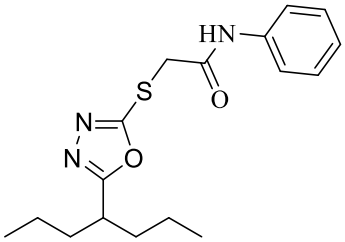
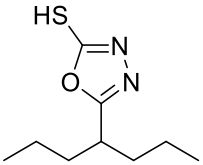
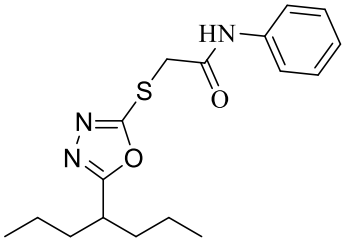
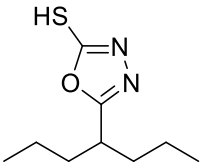
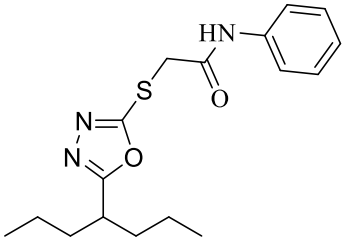
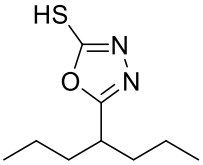
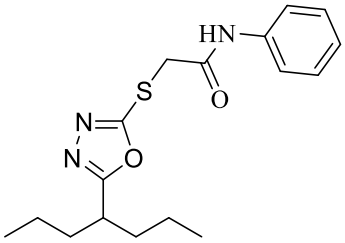
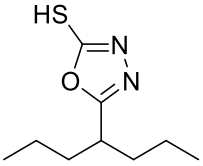
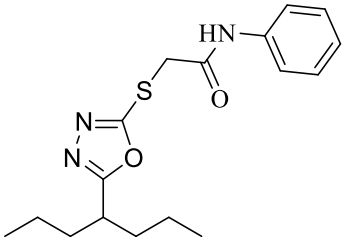
Table 2: Analysis of oxadiazole synthesis

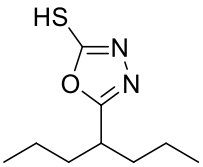
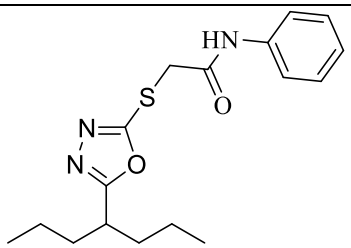
Entry. #	Compound	Condition	Solvent	Time (hr)	Product	Yield %
1		Stirring	DCM	2		Failed
2		Reflux	EtOH	4		10
3		Reflux	MeOH	6		22
4		Reflux	DMF	5		30
5		Reflux	EtOH	10		65%

Analysis of oxadiazole metal derivatives

However, the same reaction between 5-(heptan-4-yl)-1,3,4-oxadiazole2-thiol and N-bromo-Nphenylinderivata in DMF at reflux for 5 h proved unsuccessful (Table 3). The reaction was performed with ethanol using magnetic stirring for 10 h resulting in a product isolated yield of only an average of 15% (Table Tables3,3, entry b). Table 3, entry 3: Repeating of the reaction in DCM by stirring for additional on weekend causing a yield =30 % However, the 15 h response in methanol resulted no product (Table 3). However, this yielded only 20% (Table 3, entry5) in DCM at reflux for 2 h. In the end, with ethanol under reflux for 4 h favoured as much as a yield of 90% (Table 3; entry nro6) was obtained in accordance other reports and among others.

Table 3: Oxadiazole metal derivatives

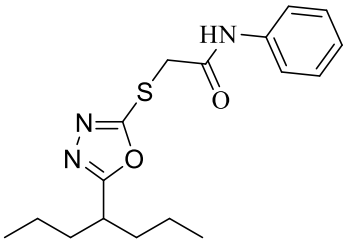
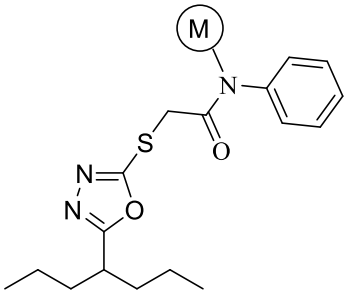
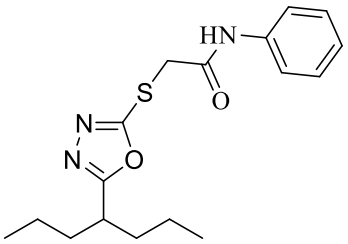
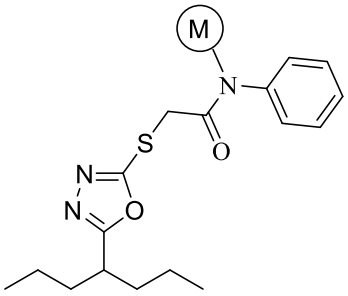
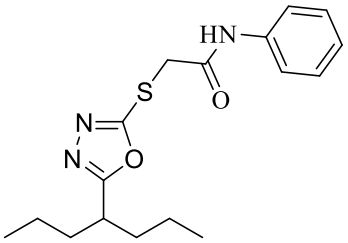
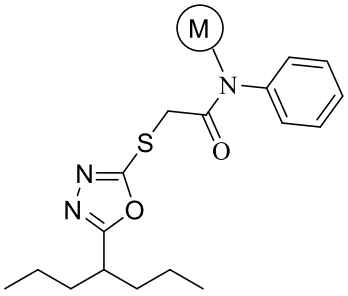
Entry.#	Compound	Condition	Solvent	Time hours	Product	Yield (%)
1		Reflux	DMF	5		Failed
2		Stirring	EtOH	10		15
3		Stirring	DCM	20		30
4		Stirring	MeOH	15		Negligible
5		Reflux	DCM	3		20%

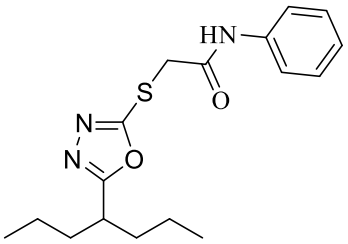
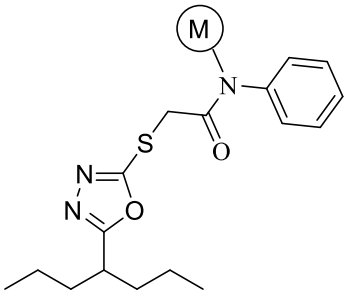
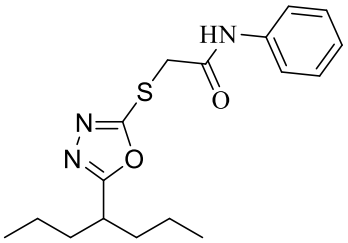
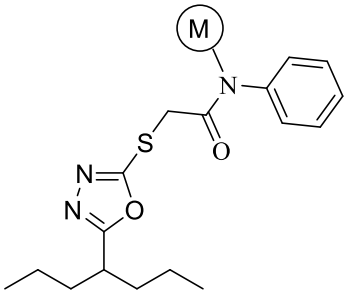
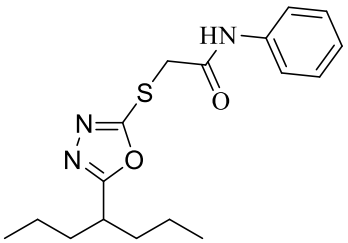
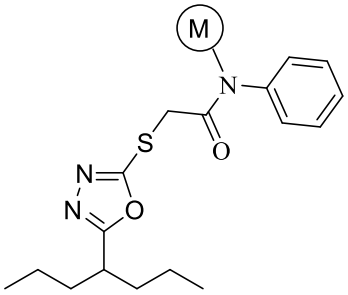
6		Reflux	EtOH	4		90%

Analysis of oxadiazole compound

First, the reaction of aryl-5-(heptan-4-yl)-1,3,4-thiadiazole with a metal salt (Table 2) was performed in DCM and stirring continuously for 20 h but no target product could be obtained(Table 4 Entry. Analogous attempt of using MeOH as the solvent for 24 h under magnetic stirring also brought no improvement (Table 3, Entry 2). Table 4 showed the effect of switching to ethanol and then refluxing for 6 hours, affording product at a meagre yield (10%, Entry-3). A yield increase to 20% was observed upon employing DMF as the solvent at room temperature for 5 hours (Table S3, Entry 4). A further 24 h MeOH attempt (Table 4, Entry pro-eb) Gave no product. Where the yield using ethanol and refluxing for 4 hours gave an overall sufficient result of 85% (Table 4, Entry-6) .

Table 4: Analysis of oxadiazole compound

Sr.#	Reacting compound	Condition	Solvent	Time hours	Product	Yield
1		Stirring	DCM	20		Failed
2		Stirring	MeOH	24		Failed
3		Reflux	EtOH	6		10%

4		Reflux	DMF	5		20%
5		Stirring	MeOH	24		Failed
6		Reflux	EtOH	4		84%

Thrombolysis Analysis

We obtained complete data for all synthezized compounds with very poor thrombolytic properties. Nevertheless, 153d and/or 150 was/were more effective than the standard control ABTS. The maximum lysis rate was 60.2% for compound 153, a level also higher than ABTS. This is opposed to compound 157 which exhibited the poorest lysis ratio of only 30.5% (Table 5) The current research is intended to further assess the effects of beneficial (Domínguez et al., 2010) functional groups upon thrombolyisis (Nazeer et al., 2023; Noreen et al., 2022).

Hemolysis Analysis

According to this tested series, Compound 157 exhibited only limited cytotoxicity (0.6%); Compounds 150 and 155 showed much higher toxicity m i n vitro Compound 153 had the strongest RBC lysis rate at 5.7%, higher than ABTS, a reference control (Table 5). Moreover, in this case at 1.49%, as Compound 153 with high hemolyzed tumour cytotoxicity a hemolysis was found to be very significant (3.90%). These data point towards the substantial variations in the hemolytic activities of these compounds depending on their structural diversity (type and location of functional groups) which ranges from mild to very severe, thereby offering them as potential anticancer agents (Dong & Liu, 2016) (Shoaib et al.).

Table 5: Thrombolytic and hemolytic activities of newly synthesized derivatives

Sr. #	Derivatives	% of Hemolysis ± SD	% of Thrombolysis ± SD
1	150	3.05 ± 0.13	57.20 ± 0.09
2	151	1.49 ± 0.01	55.10 ± 0.09
3	153	3.90 ± 0.01	60.20 ± 0.06
4	155	7.70 ± 0.06	54.20 ± 0.03
5	157	0.60 ± 0.01	30.50 ± 0.04
Standards	ABTS	95.90	89.00

FTIR analysis

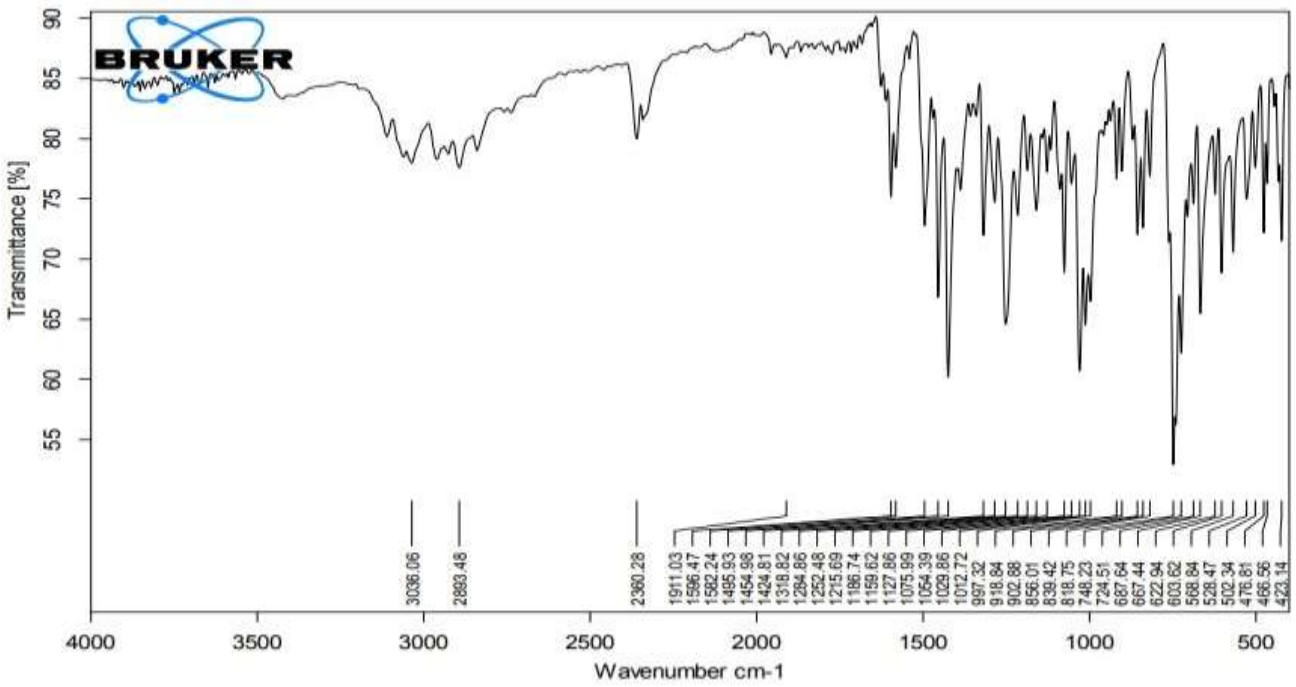


Figure 1: FTIR analysis of compound 155

Observing the FT-IR spectrum of Compound 155 in Figure 1, one can notice the sharp peaks at 3500.6 cm^{-1} which could be associated with –OH stretching and the presence of Hydroxy; 3228.3 cm^{-1} which could be related to the –N-H stretching and the amines or amides group; 1913.9 cm^{-1} which might originate from the C≡C or C≡N stretching and the presence of Alkynes or nitriles; 1549.3 cm^{-1} which also might possible be –N-O stretching or C=C stretching leading to the conclusion of Aromatic nitro group or double bonds; and lastly, 1037.1 cm^{-1} peak which might be C-O stretching and the presence of Alcohols, ethers, esters, or Carboxylic acids. These functional groups together form Compound 155 which is a mixture of structurally diverse substances. FT-IR spectrum of compound 157 shows in Figure 2 major peaks at around (cm^{-1}) for: N-H stretching (3291.81, amines or amides), C-H stretching (2922.78, alkanes), C=O group (Carbonyl groups) (1703.21), alkene Functional Group Stretching-C=C-(1604.87 aromatics and C-O functional group is shown by 1030. These peaks account for the variety of functional groups in this compound.

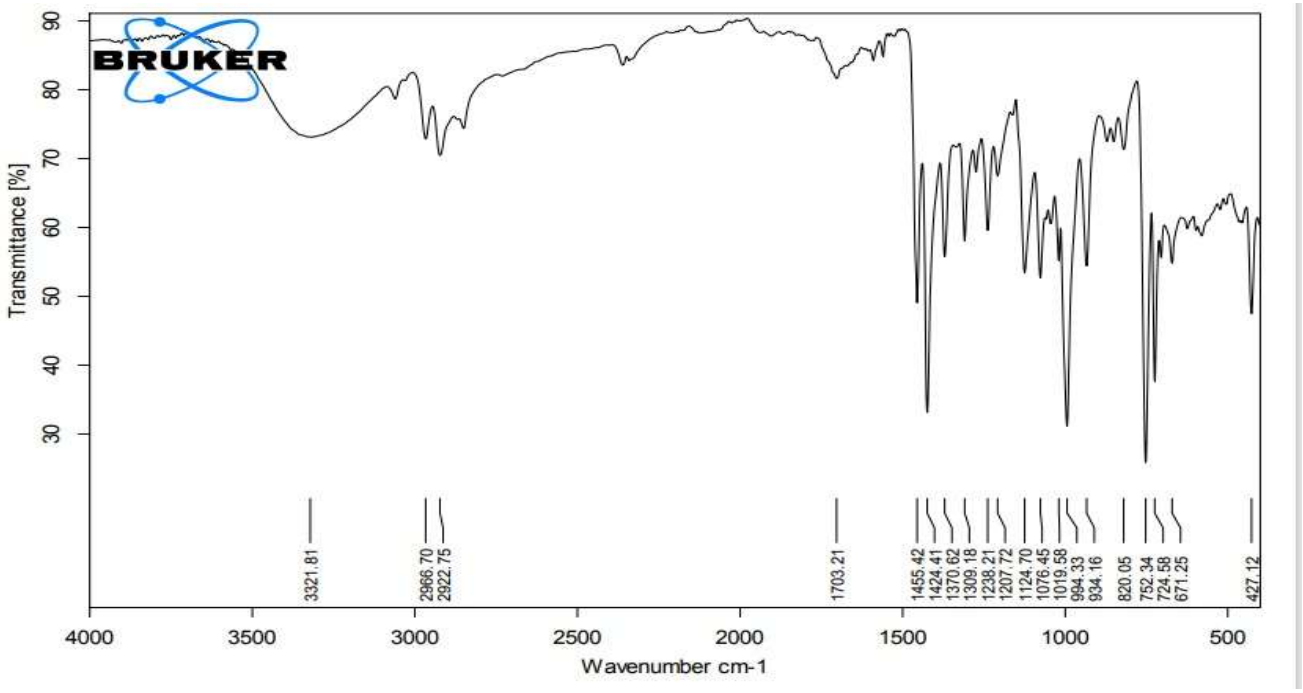


Figure 2: FTIR analysis of compound 157

NMR analysis

The NMR spectral values for compounds 150, 151, 153, 155, and 157 are presented in Table 6. The color of all of the compounds is off-white, and they also appear amorphous. The NMR data has similar peaks for CH_3, CH_2, and CH methylene and methene groups as compared here. The different analyzed peaks for each compound are the NH2 and NH of compound 150 at 4.22 ppm and 9.08 ppm and at the SH peaks of compound 151 at 13.28 ppm. For compounds 153, 155, and 157, specifically the other peaks of aryl proton are presented, and the NH of compound 153 is also at 10.27 ppm. There are structural similarities and slight differences between the synthesized derivatives, which are shown in the table.

Table 6: NMR analysis of Compounds

Compounds	NMR Values
150	Off-white amorphous; 0.89 (CH_3, t, 6H), 1.30 (CH_2, tq, 4H), 1.49 (CH_2, dt, 4H), 2.27 (CH, tt, 1H), 4.22 (NH_2, d, 2H), 9.08 (NH, t, 1H)
151	Off-white amorphous; 0.89 (CH_3, t, 6H), 1.30 (CH_2, tq, 4H), 1.54 (CH_2, dt, 4H), 2.58 (CH, tt, 1H), 13.28 (SH, s, 1H)
153	Off-white amorphous; 0.89 (CH_3, t, 6H), 1.30 (CH_2, tq, 4H), 1.54 (CH_2, dt, 4H), 2.58 (CH, tt, 1H), 4.05 (CH_2, s, 2H), 7.07 (aryl, dd, 1H), 7.30 (aryl, dd, 2H), 7.58 (aryl, d, 2H), 10.27 (NH, s, 1H)
155	Off-white amorphous; 0.89 (CH_3, t, 6H), 1.30 (CH_2, tq, 4H), 1.54 (CH_2, dt, 4H), 2.58 (CH, tt, 1H), 4.05 (CH_2, s, 2H), 7.07 (aryl, dd, 1H), 7.30 (aryl, dd, 2H), 7.58 (aryl, d, 2H)
157	Off-white amorphous; 0.89 (CH_3, t, 6H), 1.30 (CH_2, tq, 4H), 1.54 (CH_2, dt, 4H), 2.58 (CH, tt, 1H), 4.05 (CH_2, s, 2H), 7.07 (aryl, dd, 1H), 7.30 (aryl, dd, 2H), 7.58 (aryl, d, 2H)

CONCLUSION

To sum up, research on oxadiazole derivatives of valproic acid has shown good outcomes in terms of enzyme inhibition. The synthesis of these new nitrogen-based derivatives using the StigIich method showed compounds with remarkable biological activities in this study.

Spectroscopic analyses established the structures of the derivatives, and they were tested extensively for their enzyme inhibition activities. Compound 112b and compound 112c displayed good antibacterial activity against Bacillus subtilis and Escherichia coli, indicating dual-targeting was effective for combination treatment to kill bacteria, compromising the best potential of using them as antibacterial. Moreover, cytotoxicity investigations revealed that some derivatives were more toxic, but compound 157 is minimally active while significantly inhibiting enzymes. Conclusions these results fill a void in the knowledge of the enzyme inhibition properties of VPA derivatives and also indicate possibilities for these compounds that still need to be considered to deal with selected antibacterial and anticancer. So, future research must concentrate on refining these compounds for the clinic and better understanding their modes of action.

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