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Synthesis, Pharmacological Evaluation And Molecular Docking Studies Of 1,3,4-Oxadiazole Containing Dopamine D_3 Receptor Ligands

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Abstract: This paper includes the synthesis of new 1,3,4-Oxadiazole derived from 4-(2,4-di chlorophenoxy) butyric acid (**1**) by multistep reaction, the first step synthesis ester (**2**) by the esterification reaction of 4-(2,4-di chlorophenoxy) butyric acid. These esters were converted to the corresponding 4-(2,4-dichloro phenoxy)butane hydrazide (**3**) by reaction with hydrazine hydrate, after that 1,3,4-oxadiazole (4a-e) derivatives were obtained by the reaction carboxylic acid hydrazide (**3**) with various substituted benzoic acid, The molecular docking study was carried out with essential Dopamine D3 receptor (PDB ID 3pbl) which suggests that (**4b**) are the most active derivatives of the series. All newly synthesized compounds in this study were confirmed by physical and spectral (FT-IR, and ^{1}H NMR analysis.

Keywords. Hydrazide, hydrazone, 1,3,4-oxadiazole, Dopamine, D3 Receptor, molecular docking.

التشييد والتقييم الدوائي ودراسات الالتحام الجزيئي لـ 1 ، 3 ، 4- اوكسادايازول المحتوي على روابط مستقبلات الدوبامين د 3

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الملخص:

يتضمن البحث تحضير 1 ، 3 ، 4- اوكسادايازول جديدة مشتقة من 4- (2 ، 4- ثنائي كلورو فينوكسي) حامض البيوتيريك (1) عن طريق تفاعل متعدد الخطوات ،الخطوة الأولى تحضير الاستر (2) عن طريق تفاعل الأسترة 4- (2 ، 4- ثنائي كلورو فينوكسي) حامض البيوتيريك. تم تحويل هذه الاسترات إلى 4- (2 ، 4- ثنائي كلورو فينوكسي) هيدرازايد البيوتان (3) عن طريق التفاعل مع الهيدرازين المائي ، بعد أن تم الحصول على مشتقات 1 ، 3 ، 4- اوكسادايازول (4 أ- ه) عن طريق التفاعل حامض الكاربوكسيل هيدرازايد (3) مع مختلف معوضات حامض البنزويك ، أجريت دراسة الالتحام الجزيئي مع مستقبلات الدوبامين الأساسية د 3 (PDB ID 3pbl) مما يشير إلى أن (4 ب) هي المشتقات الأكثر نشاطا من السلسلة. تم تأكيد جميع المركبات المحضرة حديثا في هذه الدراسة من خلال التحليل الفيزيائي والطيفي (طيف الاشعة تحت الحمراء وطيف الرنين النووي المغناطيس).

الكلمات الدالة. هيدرازيد، هيدرازون، 1،3،4-أوكساديازول، دوبامين، مستقبلD3 ، الالتحام الجزيئي.

Introduction

Dopamine is one of the most important neurotransmitters in the central nervous system (CNS). In humans, dopamine is involved in regulation of learning, memory, feeling of reward and affection, and control of movement [1]. exerts its actions through five types of receptors which belong to two major subfamilies such as D1-like (i.e., D1 and D5 receptors) and D2-like (i.e., D2, D3 and D4) receptors. Dopamine D3 receptor (D3R) was cloned 30 years ago, and its distribution in the CNS and in the periphery, molecular structure, cellular signaling mechanisms have been largely explored [2].The dopamine D3 receptor (D3R) is found within a key neuronal network involved in motivation and cognition and does not appear to regulate movements. Compared with other dopamine receptor subtypes, the D3R exhibits restricted distribution in the mesolimbic system and has the highest affinity for endogenous dopamine. Therefore, the D3R subtype is considered an important target for treating various nervous system diseases such as schizophrenia, Parkinson's disease, and abuse [3].

Oxadiazole compounds are one of the most important heterocyclic compounds containing one oxygen, two nitrogen and two carbon atoms, usually the oxadiazoles have four isomeric structures depending on the position of hetero atoms 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole, 1,3,4-Oxadiazoles ., among the isomers, the greatest interest is involved with 1,3,4-oxadiazole.there have verity use in a large number of applications in various scientific areas, in particular pharmaceutical industry, drug discovery, as well as dyestuff industry [4].

Heterocyclic chemistry is an important and unique class among the applied branches of organic chemistry [5] 1,3,4-oxadiazole compounds have activity on various fields, including industrial an agricultural, as well as biological and pharmaceutical uses such as treatment of many cancer diseases [6], Paın analgesic [7] it has been used Compounds 1,3,4-oxadiazole as an antibacterial [8], anti-inflammatory [9], Biologically Antifungal [10], In the agricultural field, derivatives have been used 1,3,4-oxadiazole as an effective insecticide [8], anti-tubercular [11], treatment of depression status [12], treatment of brain cell Dystrophy Disease (Alzheimer's disease) [13], antimicrobial activity [14], antitumor activity [15], treatment of chronic inflammatory pain [7], against the main coronavirus protease [16], antihypertensive [17], anti-diabetes [18].

2. Materials and Methods

2.1. Materials.

All the chemicals used were purchased from Fluka Chemical Co. (Switzerland), Aldrich-Sigma Chemical Co. (Milwaukee, WI, USA), and used without further

purification. Melting points were determined on Stuard-SMP30 device and were not corrected. The FTIR spectra were listed on FT-IR (400-4000 cm^{-1}) bruker .tech engineering magement spectrophotometer using KBr disc. The ^{1}H-NMR spectra were recorded on a Bruker (400 MHz), by using TMS as internal standard and DMSO-d6 as a solvent.

Synthesis of ethyl 4-(2,4-dichlorophenoxy) butanoate (2).

A mixture of compound (**1**) (2g, 0.008 mole), in absolute ethanol (30 ml) and (1 ml) sulfuric acid then was based on Ultrasound Techniques for 1 hr. The completion of reaction was monitored by TLC and the solvent was evaporated. The residual poured into crushed ice with stirring, then neutralized with 10% sodium bicarbonate to give compound **(2)** as an oil.

Synthesis of 4-(2,4-dichlorophenoxy)butane hydrazide (3)

A mixture of compound (**2**) (0.001 mole) and hydrazine hydrate 80% (15ml) in ethanol (25ml) was based on Ultrasound Techniques for 1 to 1.5 hrs. The completion of reaction was monitored by TLC technique and the reaction mixture was concentrated and cooled. The solid was filtered, washed with water, dried, and recrystallized from ethanol to give solid as white .[19]

Synthesis of 1,3,4-oxadiazoles (4a-e).

An equimolar mixture of (0.001 mole) compound (**L3**), (0.001 mole) different aromatic carboxylic acid and (5 ml) phosphorous oxychloride was refluxed for (5hrs.) on water bath. The mixture was concentrated through evaporator, the residue was poured on ice water and the solid separated was filtered off, washed with water and further purified by recrystallization with ethanol to give compounds solid [20], Physical data are listed in table (1) as below

Table 1: Physical data for compounds (4a-e)

Comp. No.	R	Color	Molecular Formula	M.P ^{0}C	Yield%
4a	H	brown	$C_{17}H_{14}Cl_2N_2O_2$	120-122	68
4b	3-CH_3	brown	$C_{18}H_{16}Cl_2N_2O_2$	146-148	48
4c	4-Cl	light brown	$C_{17}H_{13}Cl_3N_2O_2$	173-175	51
4d	4-OCH_3	brown	$C_{18}H_{16}Cl_2N_2O_3$	148-150	40
4e	4-NO_2	light brown	$C_{17}H_{13}Cl_2N_3O_4$	185-187	65

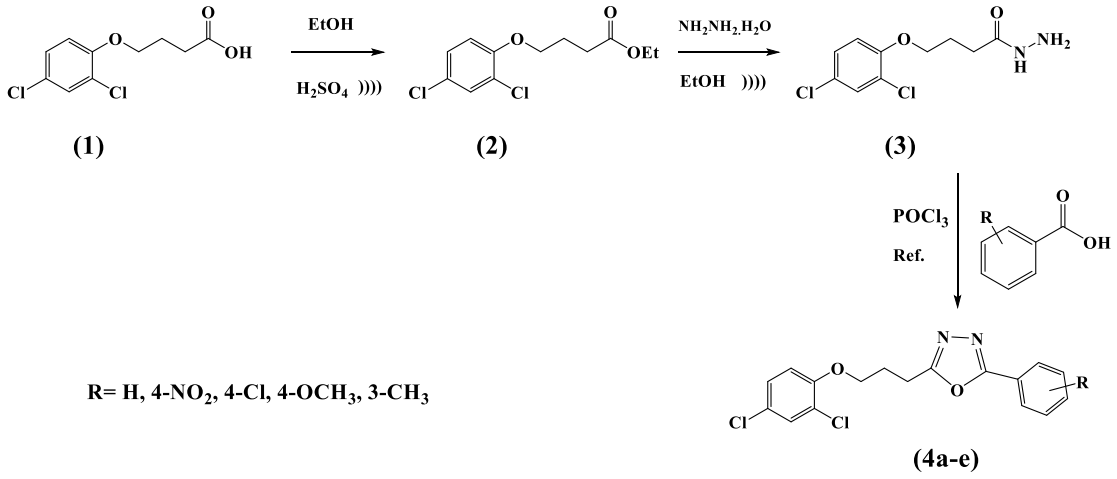
2.2. Molecular docking analysis.

The binding orientations and interactions of the potent compounds derivatives (**4a-e**) with Dopamine namely D_3 receptor, were simulated using MCULE docking and BIOVIA discovery studio (2021) software. 'The three-dimensional structure (3D) of the selected proteins was downloaded from the PDB website. proteins were added with ligand in the Mcule docking [21]. The Mcule docking specializes in the analysis and evaluation of biological activity by using the novel chemical compound of interest and selecting the enzymes for studying their interaction [22]. These enzymes are chosen from the available enzyme database (PDB) [23]. Mcule assesses the binding strength between the chemical compound and the selected enzymes by calculating the ΔG value (free energy of the interaction). The ΔG value helps estimate the interaction strength and its potential impact on the enzyme [24]. Additionally, Mcule docking can provide 2D and 3D images of the binding that occurred between the prepared chemical compound and the enzyme as part of the result reports [25],[26]

Results and Discussion.

Because of the potential medical and biological activity, In the present work, the synthesis of some substituted 1,3,4-oxadiazole (**4a-e**) derivatives are achieved. The reaction sequence leading to the formation of the desired heterocyclic compounds are listed in Scheme (1).

Scheme (1): Synthesis of new intermediates and final compounds.



(1) (2) (3) (4a-e)

The starting material of carboxylic acid hydrazide (**3**)**,** which was made by reacting of 4-(2,4-dichlorophenoxy) butyric acid (**1**) with ethanol in an sulfuric acid to produce 4-(2,4-dichlorophenoxy) butanoate (2).which, when combined with hydrazine hydrate in ethanol, yielded the corresponding hydrazide (**3**).When substituted benzoic acid is reacted with carboxylic acid hydrazide (**3**) in the presence of phosphorus oxychloride as cyclic reagent leading to formation of substituted 1,3,4-oxadiazoles (**4a-e**).

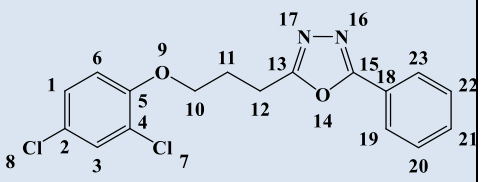
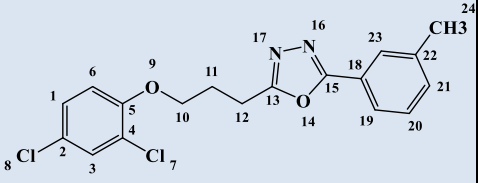
The structures of compounds (**4a-e**) have been identified based on their FT-IR and ^{1}H-NMR**.** The FT- IR spectra for compounds (**4a-e**) shows absoption band at the range (1591-1608 cm^{-}1) due to (C=N) group, at range (3029-3077 cm^{-1}) for (CH-Ar) , at range (2942-2969 cm^{-1}) for (CH-aliphtic) and other absoption band as shown in the table (**2**) below

Table 2: FT-IR data for compounds (4a-e).

Comp. No.	FTIR(KBr) γcm^{-1}				
	C-H Ar	C-H Aliph	C=N	C-O-C sym&asym	Others
4a	3066	2945	1600	1176 ,1351	--------
4c	3070	2969	1606	1174,1389	CH_3 sym&asym 2934, 2969
4b	3029	2942	1591	1153,1344	C-Cl 828
4d	3065	2957	1595	1152,1345	$OCH_3$1040
4e	3077	2944	1608	1162,1390	NO_2 sym&asym 1162, 1265

The ^{1}H-NMR spectra studies of compounds (4a and b) showed doublet signal at (7.17-7.50 ppm) due to Ar_1-H, while the Ar_2-H protons appeared as a (multiplet and dd) at (7.35–8.40 ppm) in addition the other signal for protons in this compound as shown in table (3) below

Table 3: ^{1}H-NMR data of compounds (4a and b).

Comp .No.	Structure of Comp.	^{1}H-NMR δ (ppm) DMSO-d_6
4a		^{1}H NMR (400 MHz, DMSO) δ 8.51 – 8.37 (m, 2H, 19, 23), 7.50 (d, J = 2.6 Hz, 1H, 3), 7.35 (dd, J = 8.9, 2.6 Hz, 3H, 20, 21, 22), 7.17 (d, J = 8.9 Hz, 2H, 1, 6), 4.22 (t, J = 5.9 Hz, 2H, 10), 3.18 (t, J = 7.1 Hz, 2H, 12), 2.30 (p, J = 6.5 Hz, 2H, 11)
4b		^{1}H NMR (400 MHz, DMSO) δ 7.85 (ddd, *J* = 9.9, 2.2, 1.2 Hz, 1H, 19), 7.67 – 7.63 (m, 1H, 23), 7.45 (dd, *J* = 9.9, 7.7 Hz, 1H, 20), 7.32 (d, *J* = 2.1 Hz, 1H, 3), 7.24 – 7.18 (m, 1H, 21), 7.16

		(dd, *J* = 9.0, 2.0 Hz, 1H, 1), 6.82 (d, *J* = 9.0 Hz, 1H, 6), 4.13 (t, *J* = 6.4 Hz, 2H, 10), 2.98 (t, *J* = 8.2 Hz, 2H, 12), 2.39 (d, *J* = 0.8 Hz, 3H, 24), 2.28 (tt, *J* = 8.1, 6.4 Hz, 2H, 11).

As previously mentioned in the practical part, the effectiveness of the compounds prepared in the research was evaluated (**4a-e**) on Dopamine D_3 receptor.

The binding strength between the chemical compounds and the selected enzymes by calculating the ΔG value (free energy of the interaction). The ΔG value helps estimate the interaction strength and its potential impact on the enzyme. Additionally, Mcule docking can provide 2D and 3D images of the binding that occurred between the prepared chemical compound and the enzyme as part of the result reports as shown in table 3 and Figures (**1,2,3,4 and 5**).

Table 4. Binding energies of the compounds (4a-e) with Dopamine D_3 receptor.

The ligand	Insulin [Kcal/mol]
4a	**-8.4**
4b	**-8.8**
4c	**-8.6**
4d	**-8.6**
4e	**-8.7**

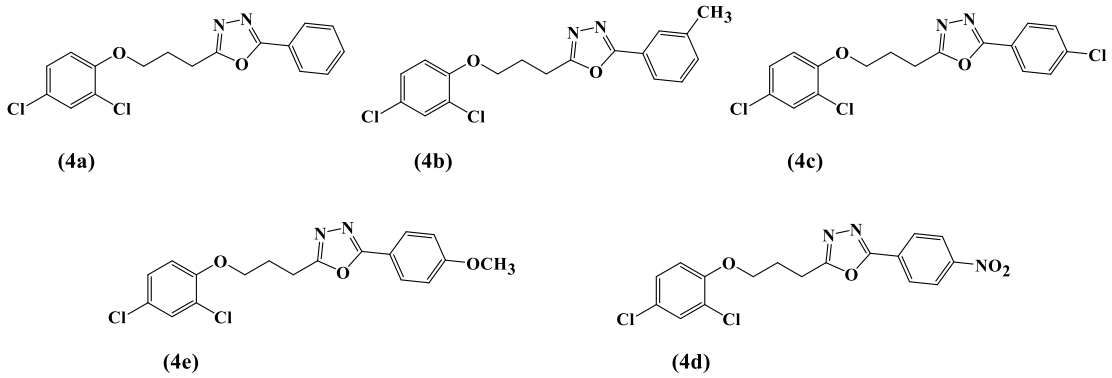


Figure 1- 3D&2D illustration of possible interactions of compound 4a with the Dopamine (PDB ID 3pbl).

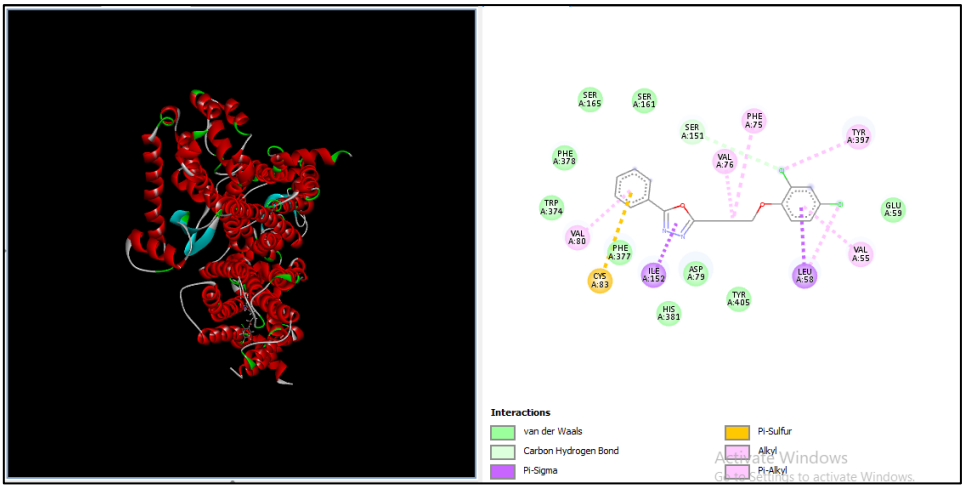


Figure 2- 3D&2D illustration of possible interactions of compound 4b with the Dopamine (PDB ID 3pbl).

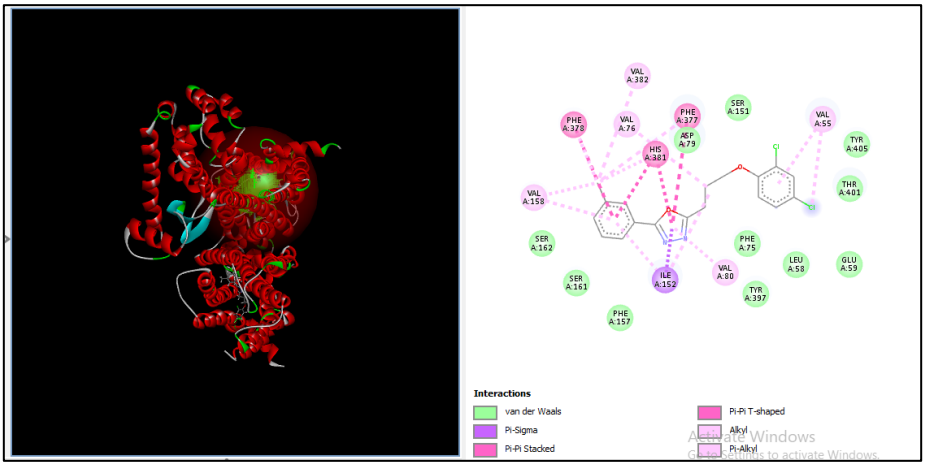


Figure 3- 3D&2D illustration of possible interactions of compound 4c with the Dopamine (PDB ID 3pbl).

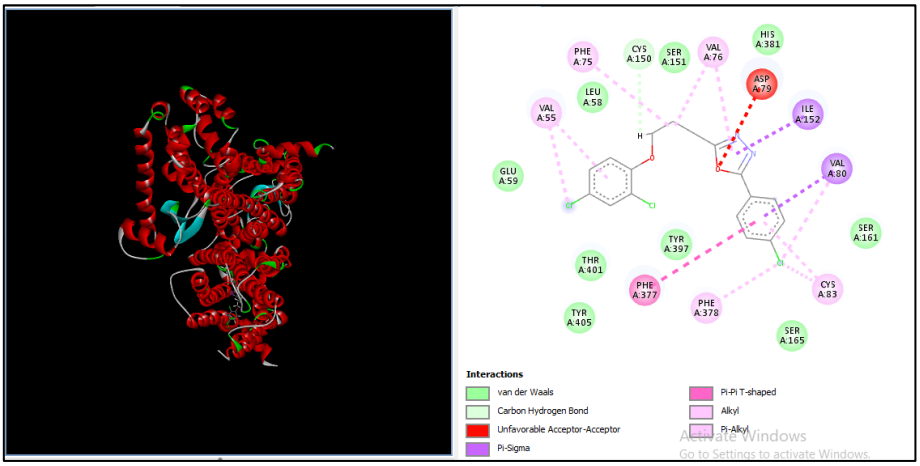


Figure 4- 3D&2D illustration of possible interactions of compound 4d with the Dopamine (PDB ID 3pbl).

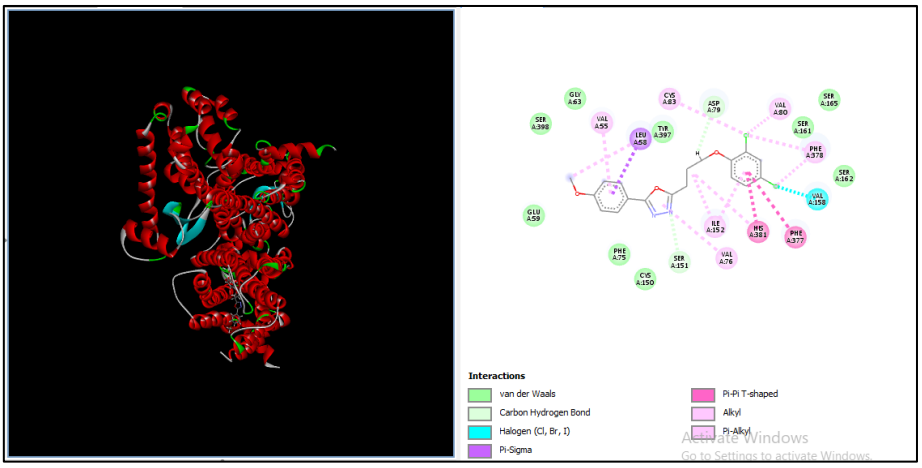
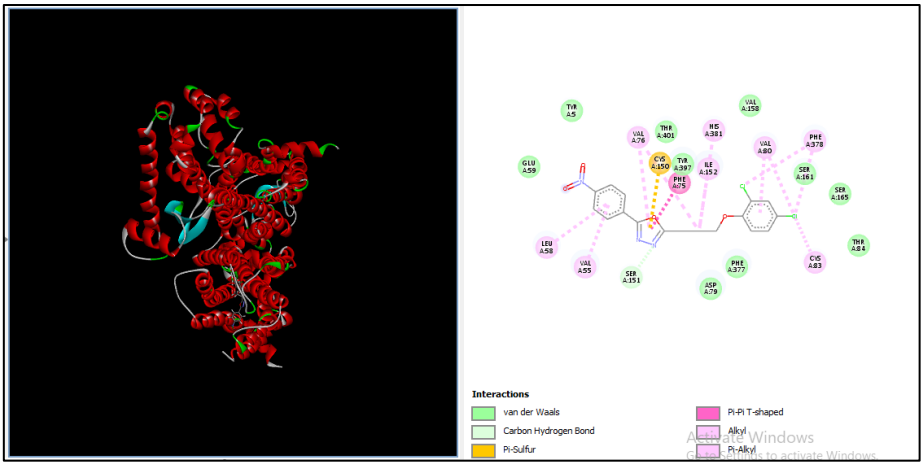


Figure 5- 3D&2D illustration of possible interactions of compound 4e with the Dopamine (PDB ID 3pbl).



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