Interaction of dihydrofuran-2-one and its derivatives with either MAO-B or COMT enzymes using a theoretical model

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Abstract

There are several drugs for treating Parkinson's such as L-Dopa, carbidopa, benserazide, entacapone, bromocriptine, safinamide, rasagiline, and others. However, some of these drugs can produce some secondary effects such as hypotension, insomnia, dizziness, nausea, and constipation. In the search for a new therapeutic alternative for treating Parkinson´s, this study aimed to evaluate the theoretical interaction of Dehydrofuran-2-one (1) and their derivatives (2-31) with both MAO-B and COMT enzymes. To evaluate the interaction of Dehydrofuran-2-one (1) and their derivatives (2-31) with both MAO-B and COMT enzymes, the 1gos and 1vid proteins as theoretical tools. Besides, some drugs, such as selegiline, rasagiline, safinamide, entacapone, and tolcapone, were used as controls in the DockingServer program. The results showed differences in the interaction of compounds 1-31 with either 1gos or 1vid proteins surface compared to the controls. Other data showed that inhibition constants (Ki) for 2, 3, 12, and 26 were lower compared to selegeline, rosagiline, and sofinamide, respectively. In addition, the Ki for 1-3, 7, 9, 10, 13, 21, and 25 were lower than entacapone and tolcapone. These data suggest that 1-3, 12, and 26 could act as MAO-B inhibitors and compounds 1-3, 7, 9, 10, 13, 21, and 26 as COMT antagonists. In conclusion, these compounds may be a good therapeutic alternative for treating Parkinson´s disease.

Keywords: Parkinson´s, MAO-B, COMT, dihydrofuran-2-one, derivative, tolcapone.

Interação da Diidrofuran-2-ona e seus derivados com enzimas MAO-B ou COMT usando um modelo teórico

Resumo

Existem vários medicamentos para o tratamento do Parkinson como L-Dopa, carbidopa, benserazida, entacapona, bromocriptina, safinamida, rasagilina e outros. No entanto, alguns desses medicamentos podem produzir alguns efeitos secundários, como hipotensão, insônia, tontura, náusea e prisão de ventre. Na busca de novas alternativas terapêuticas para o tratamento do Parkinson, o objetivo deste estudo foi avaliar a interação teórica do Deidrofurano-2-ona (1) e seus derivados (2-31) com as enzimas MAO-B e COMT. Para avaliar a interação da Deidrofuran-2-ona (1) e seus derivados (2-31) com as enzimas MAO-B e COMT foram utilizadas as proteínas 1gos e 1vid como ferramentas teóricas. Além disso, alguns medicamentos, como selegelina, rasagilina, safinamida, entacapone e tolcapone, foram utilizados como controles no programa DockingServer. Os resultados mostraram diferenças na interação dos compostos 1-31 com a superfície das proteínas 1gos ou 1vid em comparação com os controles. Outros dados mostraram que as constantes de inibição (Ki) para 2, 3, 12 e 26 foram

menores em comparação com selegelina, rosagilina e sofinamida, respectivamente. Além disso, o Ki para 1-3, 7, 9, 10, 13, 21 e 25 foi inferior ao do entacapone e do tolcapone. Estes dados sugerem que 1-3, 12 e 26 poderiam actuar como inibidores da MAO-B e os compostos 1-3, 7, 9, 10, 13, 21 e 26 como antagonistas da COMT. Em conclusão, estes compostos podem ser uma boa alternativa terapêutica para o tratamento da doença de Parkinson.

Palavras-chave: Parkinson, MAO-B, COMT, diidrofurano-2-ona, derivado, tolcapone.

1. Introduction

Parkinson's disease is a progressive neurodegenerative disorder that leads to a decrease in motor functions such as bradykinesia, tremors, rigidity, and postural instability (Alexander, 2004; Willis et al., 2022; Blesa et al., 2022). Several factors are involved in the development of Parkinson's disease, such as genetic (Billingsley et al., 2018; Dulski et al., 2022), age (Pagano; Ferrara, 2016; Wang et al., 2024), air pollution (Palacios, 2017; Kasdagli et al., 2019; Murata et al., 2022), ischemic stroke (Song et al., 2022; Lohmann et al., 2022; Choi et al., 2023) and others.

It is important to mention that there are different drugs to treat Parkinson's, such as levodopa [precursor to dopamine] (Fahn, 2018), carbidopa, and benzerazide [aromatic L-amino acid decarboxylase inhibitor] (Burkhard et al., 2001; Montioli et al., 2016), entacapone and tolcapone [catechol-O-methyltransferase (COMT) antagonist] (Fabbri et al., 2022), amantadine (presynaptic dopamine release activator and postsynaptic dopamine reuptake inhibitor] (Gianulsos et al., 1985; Peeters et al., 2003), selegiline [monoamine oxidase B inhibitor; MAO-B] (Marconi et al., 1992), pramipexole [D2/D3 dopamine receptor agonist] (Kaltenboeck et al., 2022), and benztropine [muscarinic acetylcholine receptor inhibitor] (Kang et al., 2022).

However, some of these drugs can produce secondary effects such as hypotension (Dowell; Lee, 1970), hepatotoxicity (Olanow, 2000), arrhythmia (Churchyard et al., 1997), somnolence and dizziness (Shen; Kong, 2018). In the search for new drugs for the treatment of Parkinson's disease, several compounds have been developed; for example, one study showed that some indazolyl-spiro[2.3]hexane-carbonitrile derivatives act as LRRK2 kinase inhibitors which can be used to treat Parkinson's disease (Abdel-Magid, 2019). Furthermore, a study showed the preparation of compound VU0155041 to treat Parkinson's disease through metabotropic glutamate receptor 4 activation using Chinese hamster ovary cells (Niswender et al., 2008).

Other studies have shown that compound VU2957 [Valiglurax] can be an antiparkinsonian agent through metabotropic glutamate 4 receptor activation (Panarese et al., 2018). Another report described the synthesis of three coumarin derivatives to treat Parkinson's disease using a Caenorhabditis elegans transgenic model (Sashidhara et al., 2014). Furthermore, other data indicated that a purine derivative may exert effects on Parkinson's disease using a haloperidol-induced catalepsy model (Basu et al., 2014).

On the other hand, a 1,2,4-oxadiazole analog was prepared to treat Parkinson's disease with inhibitory activity on the COMT enzyme using rat liver homogenates (Kiss et al., 2010). Besides, other data use a propanone derivative's preparation as a COMT inhibitor to treat Parkinson's disease using a theoretical model (Learmonth et al., 2004). In addition, some reports have shown that some thiazole-derivatives [34], oxazolopyridines, thiazolopyridines, and different pyrrolidine analogs could act as monoamine oxidase-B enzymes using various theoretical models (Park et al., 2013; Wang et al., 2021). Finally, a study suggests that a furanone derivative (-{[(E)-3-(5,5-dimethyl-4-oxo-4,5-dihydro-2-furanyl)-2-propenyl]oxy}-2H-chromen-2-one) could produce biological activity against MAO-B enzyme using a spectrophotometric method (Carotti et al., 2002). All these data indicate that several compounds and furanone derivatives may act as antiparkinsonian agents through different molecular mechanisms; however, the interaction with either COMT or MAO-B enzymes is not clear. Analyzing these data, the aim of this study was to evaluate the interaction between dihydro-furan-2-one and their derivatives using a theoretical model.

2. Materials and Methods

2.1 Dihydro-furan-2-one and derivatives

Dihydro-furan-2-one and its derivatives (Figure 1) were used to evaluate their possible interaction with both catechol O-methyltransferase and monoamine oxidase-B enzymes surface as follows:

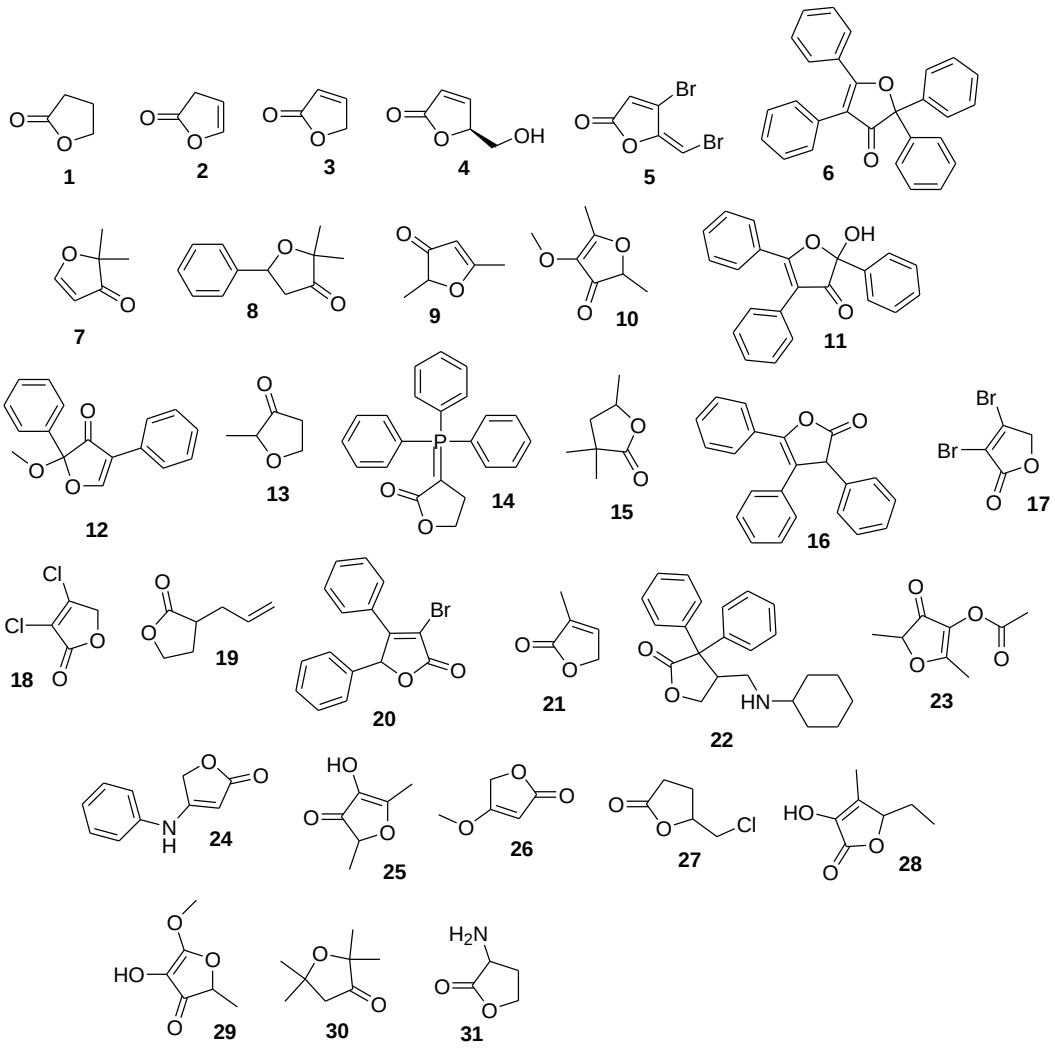

Figure 1. Chemical structure of Dihydrofuran-2-one (1) and their derivatives (2-31). Source: https://pubchem.ncbi.nlm.nih.gov/.

1 = Dihydrofuran-2-one
2 = 3H-Furan-2-one
3 =5H-Furan-2-one
4 = (S)-(-)-5-Hydroxymethyl-2(5H)-furanone
5 = 4-Bromo-5-bromomethylene-5H-furan-2-one
6 = 2,2,4,5-tetraphenyl-3(2H)-furanone
7 = 2,2-Dimethyl-3(2H)-furanone
8 = 2,2-dimethyl-5-phenyldihydro-3(2H)-furanone
9 = 2,5-Dimethyl-3(2H)-furanone
10 = 2,5-Dimethyl-4-methoxy-3(2H)-furanone
11 = 2-Hydroxy-2,4,5-triphenyl-3(2H)-furanone
12 = 2-Methoxy-2,4-diphenyl-3(2H)-furanone
13 = 2-Methyltetrahydro-3-furanone
14 = 3-(Triphenylphosphoranylidene)dihydro-2(3H)-furanone
15 = 3,3,5-trimethyldihydro-2(3H)-furanone
16 = 3,4,5-Triphenyl-2(3H)-furanone
17 = 3,4-Dibromo-2(5H)-furanone
18 = 3,4-Dichloro-2(5H)-furanone
19 = 3-allyldihydro-2(3H)-furanone
20 = 3-Bromo-4,5-diphenyl-5H-furan-2-one
21 = 3-Methyl-2(5H)-furanone
22 = 4-[(Cyclohexylamino)methyl]-3,3-diphenyldihydro-2(3H)-furanone
23 = 4-Acetoxy-2,5-dimethyl-3(2H)furanone
24 = 4-anilino-2(5H)-furanone
25 = 4-Hydroxy-2,5-dimethyl-3(2H)-furanone
26 = 4-Methoxy-2(5H)-furanone
27 = 5-(chloromethyl)dihydro-2(3H)-furanone
28 = 5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone
29 = 4-Hydroxy-5-methoxy-2-methyl-furan-3-one
30 = 2,2,5,5-tetramethyl-dihydro-furan-3-one
31= 3-amino-dihydro-furan-2-one

2.2 Pharmacophore model

The pharmacophore model for dihydro-furan-2-one (1) and its derivatives (2-30) was determined using LigandScout 4.08 software (Wolbe; Langer, 2005).

2.3 Protein-ligand

The interaction of Dihydro-furan-2-one (1) derivatives (2-30) with both COMT and MAO-B enzymes was determined using 1gos (https://doi.org/10.2210/pdb1GOS/pdb) and 1vid (https://doi.org/10.2210/pdb1VID/pdb) proteins as theoretical tools. Besides, selegiline, rasagiline, safinamide [monoamine oxidase-B inhibitors] (Dezli; Vecsei, 2017), entacapone, tolcapone, and 8-hydroxy quinoline [COMT enzyme antagonists] (Fabri et al., 2022) were used as controls in a DockingServer program (Lopez-Ramos et al., 2024).

2.4 Pharmacokinetic analysis

Pharmacokinetic factors for steroid derivatives 1, 2, 3, 7, 9, 10, 12, 13, 21, 25, and 26 were determined using the SwissADME software (Backchi et al., 2022).

2.5 Toxicology analysis

Toxicology evaluation for steroid derivatives 1, 2, 3, 7, 9, 10, 12, 13, 21, 25, and 26 were determined using the Gussar software (Khrapova et al., 2023).

3. Results and Discussion

For several years, different theoretical methods have been used to design new drugs to treat some diseases. Analyzing these data, in this study two theoretical methods such as pharmacophore and docking were used to address or characterize the possible interaction of dihydrofuran-2-one derivatives with MAO-B or COMT enzymes.

3.1 Pharmacophore model

For example, the pharmacophore model is a theoretical tool to design new molecules that could be useful in designing drugs that could interact with some biomolecules. In the literature, there are several programs for the design of different drugs such as catalysts (Patel et al., 2002), Elixir (Wang et al., 2022), Biovia (Baskaran et al., 2020), and LigandScout (Wolbe; Langer, 2005). In this research, LigandScout 4.4 was used to design a pharmacophore for Dihydrofuran-2-one and its derivatives (compounds 2-30). It is noteworthy, LigandScout is a program that allows design three-dimensional pharmacophores from the chemical structure of different compounds which involve various functional groups that can act as hydrogen bond donors, hydrogen bond acceptors, lipophilic areas, and positive-negatively ionizable chemical groups.

For this reason, this research aimed to develop some pharmacophores from Dihydrofuran-2-one (compound 1) and its derivatives (2-30). Figures 2-4 display some hydrogen bond donors and acceptors, lipophilic areas, and positively and negatively ionizable chemical groups that are involved in their chemical structure. It is noteworthy that chemical characteristics of each steroid derivative could be a determining factor for its interaction with some biomolecule, which could result in the ligand-protein complex formation.

3.2 Ligand-MAO complex formation

Monoamine oxidase (MAO) is an enzyme that metabolizes several biogenic amines such as norepinephrine, dopamine, and serotonin through oxidative deamination (Edmondson; Binda, 2018). There are some studies, which indicate that serotonin, norepinephrine, and dopamine deficiency may be involved in some neurodegenerative processes; these phenomena can indirectly cause Parkinson's disease (Scatton et al., 1983). It is important to mention that several drugs such as rasagiline, and selegiline, (MAO inhibitors) are used to try of Parkinson's disease (Lee, 1993); however, some of these drugs can produce some secondary effects such as somnolence/dizziness (Shen; Kong, 2018).

In the search for a therapeutic alternative for try of Parkinson´s disease, some drugs have been developed (Niswender et al., 2008; Panarese et al., 2018; Abdel-Magid, 2019); nevertheless, the interaction of these compounds is not clear. For this reason, in this study, the possible interaction of Dihydrofuran-2-one (compound

1) and its derivatives (compounds 2-30) with MAO enzyme surface was determined using the DockingServer program (Figueroa-Valverde et al., 2024). It is important to mention that DockingServer software uses MMFF94 model, which is a molecular modeling force field, which is designed to address condensed phase processes in molecular dynamics simulation and optimization of molecular geometry in proteins and other biological systems (Halgren, 1996). Besides, DockingServer uses the Autodock program as theoretical support, which uses the Lamarckian Genetic Algorithm to determine the optimal docking position between ligands and macromolecules, and then evaluates the results with an empirical binding free energy function (Morris et al., 2008).

The results of the interaction of Dihydrofuran-2-one and its derivatives with MAO-B enzyme surface were determined using the 1gos protein (PDB: https://doi.org/10.2210/pdb1GOS/pdb), and selegiline, rasagiline and safinamide drugs as theoretical tools in DockingServer software. Besides, some thermodynamic parameters and inhibition constants were determined to evaluate the possible interaction of Dihydrofuran-2-one and its derivatives with the 6rv2 protein surface. The results (Table 1) displayed different amino acid residues involved in the interaction of Dihydrofuran-2-one derivatives with 1gos protein surface compared to selegiline, rasagiline, and safinamide drugs. It is noteworthy that aminoacid residues involved in the interaction of Dihydrofuran-2-one and its derivatives 2 and 3 with the 1gos-protein surface involve the same type of aminoacid residues such as Val_{173}; Thr_{174}; Trp_{184}; Tyr_{188}; Tyr_{398}; Thr_{399} compared to compounds 4-30; this phenomenon could be due to differences in their chemical structure of each compound.

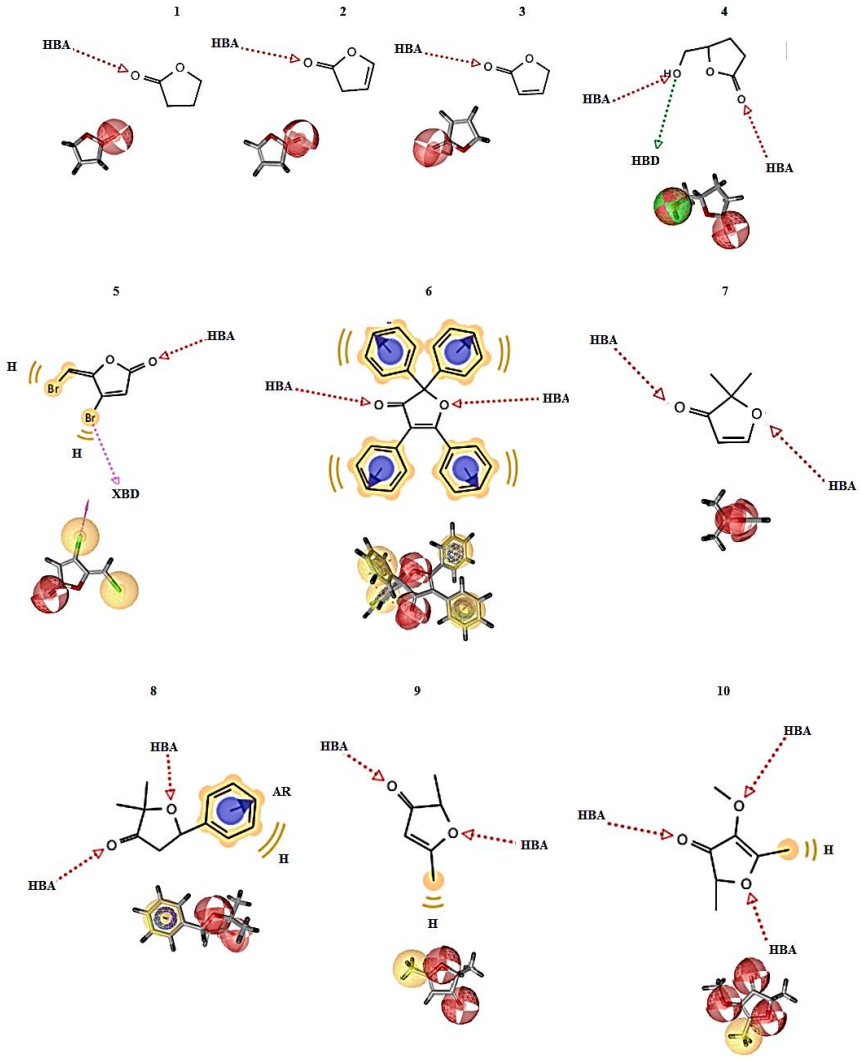

Figure 2. Pharmacophore model for Dihydrofuran-2-one (1) and its derivatives (2-10). Visualized with the LigandScout 4.4 program. The results showed different types of hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA) and lipophilic areas. Source: Authors, 2024.

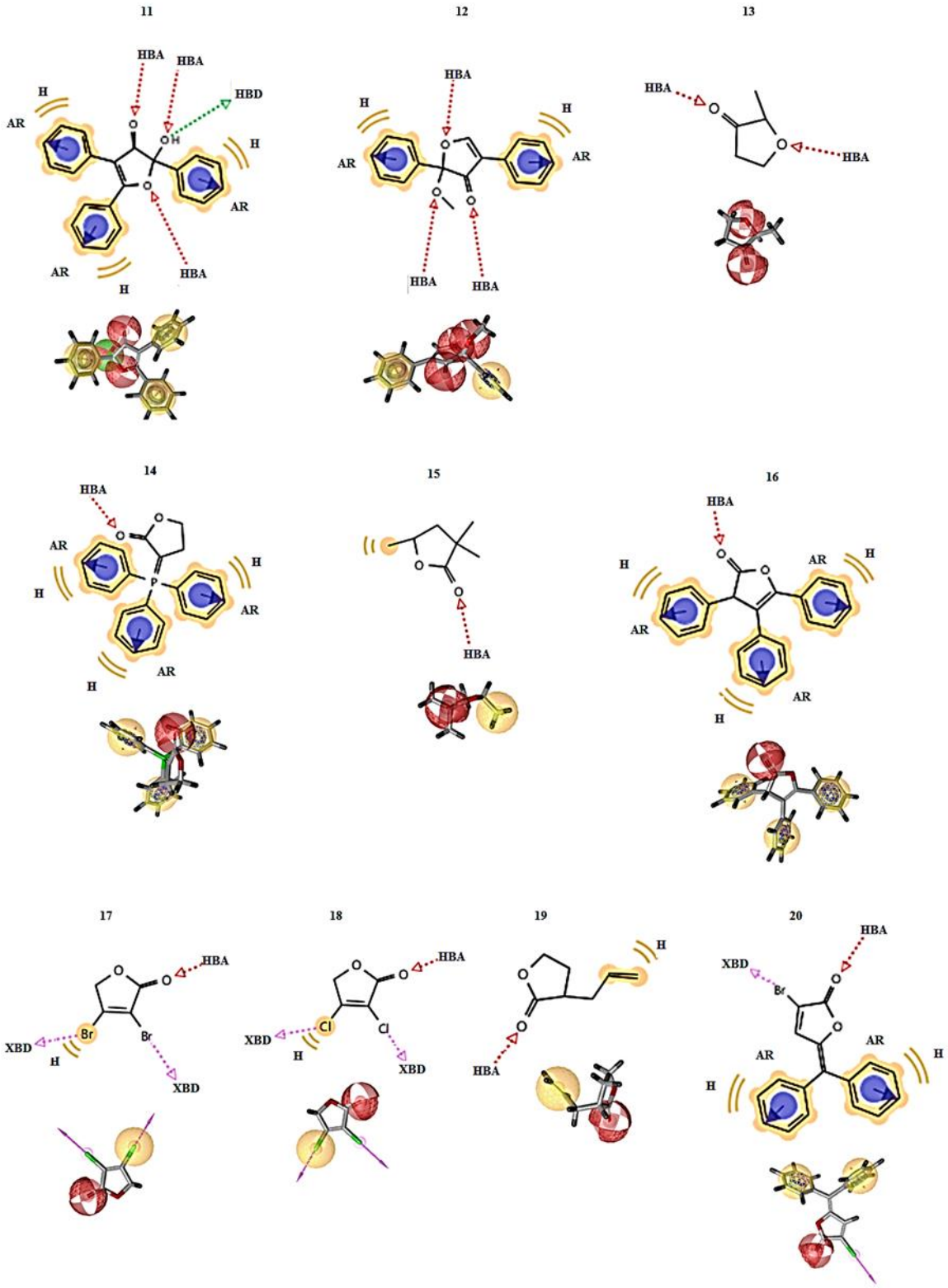

Figure 3. Chromophore models for Dihydrofuran-2-one (11-20) derivatives. Visualized with LigandScout 4.4 program. Source: Authors, 2024.

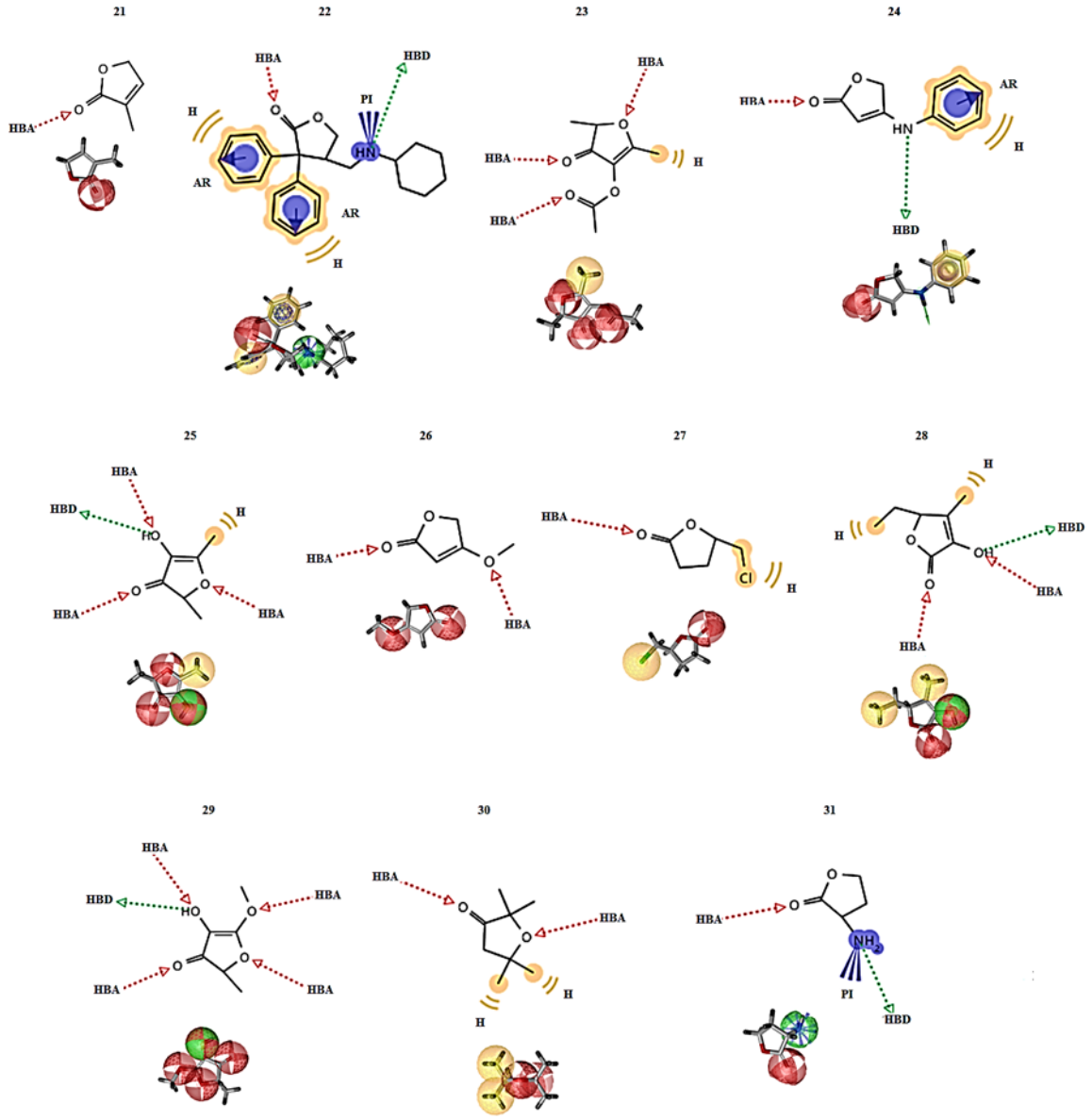

Figure 4. Design of Chromophores for Dihydrofuran-2-one (21-31) derivatives. Visualized with LigandScout 4.4 program. Source: Authors, 2024.

Table 1. Aminoacid residues involved in the interaction of selegiline, rasagiline, safinamide, dihydrofuran-2-one (1), and their derivatives (2-31) with 1gos protein surface.

Compound	Aminoacid Residues
Selegiline	Ile_{14}; Arg_{42}; Thr_{43}; Tyr_{60}; Gln_{206}; Phe_{343}; Tyr_{398}; Tyr_{435}; Met_{436}; Ala_{439}
Rasagiline	Glu_{34}; Ala_{35}; Arg_{36}; Ile_{264}; Pro_{265}; Leu_{268}; Tyr_{393}
Safinamide	Ile_{14}; Arg_{42}; Thr_{43}; Tyr_{60}; Gln_{206}; Phe_{343}; Tyr_{398}; Tyr_{435}; Met_{436}; Ala_{439}
1	Val_{173}; Thr_{174}; Trp_{184}; Tyr_{188}; Tyr_{398}; Thr_{399}
2	Val_{173}; Thr_{174}; Trp_{184}; Tyr_{188}; Tyr_{398}; Thr_{399}
3	Val_{173}; Thr_{174}; Trp_{184}; Tyr_{188}; Tyr_{398}; Thr_{399}
4	Pro_{266}; Arg_{282}; Phe_{423}; Glu_{427}; Thr_{428}

5	Arg_{42}; Lys_{296}; Phe_{343}; Trp_{388}; Cys_{397}; Tyr_{398}
6	Arg_{42}; Tyr_{60}; Gln_{65}; Tyr_{188}; Gln_{206}; Cys_{397}; Tyr_{398}; Thr_{426}; Tyr_{435}; Met_{436}
7	Ser_{262}; Pro_{266}; Arg_{282}; Phe_{423}; Glu_{427}; Thr_{428}
8	Arg_{42}; Lys_{296}; Phe_{343}; Trp_{388}; Cys_{397}; Tyr_{398}; Met_{436}
9	Val_{294}; Lys_{296}; Phe_{343}; Trp_{388}; Cys_{397}; Tyr_{398}
10	Arg_{42}; Lys_{296}; Phe_{343}; Cys_{397}; Tyr_{398}
11	Ile_{14}; Thr_{43}; Tyr_{60}; Phe_{343}; Trp_{388}; Cys_{397}; Tyr_{398}; Met_{436}
12	Arg_{42}; Cys_{397}; Tyr_{398}; Thr_{426}; Met_{436}; Ala_{439}
13	Ser_{262}; Pro_{266}; Leu_{414}; $Phe_{423}Glu_{427}$; Thr_{428}
14	Arg_{42}; Tyr_{188}; Lys_{296}; Phe_{343}; Tyr_{398}; Tyr_{435}; Met_{436}
15	Val_{10}; Glu_{34}; Ala_{35}; Ile_{264}; Tyr_{393}
16	Arg_{42}; Phe_{343}; Trp_{388}; Cys_{397}; Tyr_{398}; Tyr_{435}; Met_{436}
17	Val_{10}; Leu_{33}; Ala_{35}; Arg_{233}; Val_{235}; Ile_{264}; Tyr_{393}
18	Glu_{34}; Ala_{35}; Tyr_{393}
19	Arg_{42}; Val_{294}; Lys_{296}; Phe_{343}
20	Arg_{42}; Lys_{296}; Phe_{343}; Trp_{388}; Cys_{397}; Tyr_{398}; Tyr_{435}; Met_{436}
21	Ser_{262}; Pro_{266}; Leu_{414}; Phe_{423}; Glu_{427};Thr_{428}
22	Val_{10}; Ser_{15}; Glu_{34}; Ala_{35}; Arg_{36}; Arg_{42}; Val_{235}; Ala_{263}; Ile_{264}; Pro_{265}; Tyr_{393}; Ser_{394}
23	Val_{10}; Glu_{34}; Ala_{35}; Ile_{264}; Leu_{268}; Lys_{271}; Tyr_{393}
24	Val_{10}; Glu_{34}; Ala_{35}; Pro_{265}; Ser_{394}
25	Lys_{296}; Phe_{343}; Trp_{388}; Cys_{397}; Tyr_{398}
26	Val_{294}; Lys_{296}; Phe_{343}; Trp_{388}; Cys_{397}; Tyr_{398}
27	Val_{10}; Glu_{34}; Ala_{35}; Val_{235}
28	Arg_{42}; Lys_{296}; Phe_{343}; Trp_{388}; Cys_{397}; Tyr_{398}
29	Lys_{296}; Phe_{343}; Trp_{388}; Cys_{397}; $Tyr3_{398}$
30	Val_{10}; Glu_{34}; Ala_{35}; Ile_{264}; Tyr_{393}
31	Val_{10}; Leu_{33}; Glu_{34}; Ala_{35}; Val_{264}; Ile_{264}

Source: Authors, 2024.

3.3 Thermodynamic parameters analysis

Thermodynamic parameters (Table 2, Figure 5) involved in the interaction of Dihydrofuran-2-one and its derivatives with the 1gos-protein surface showed differences in energy levels compared to selegiline, rasagiline, and safinamide drugs. In addition, the inhibition constant of Dihydrofuran-2-one and its derivatives (2, 3, 7, 12, and 26) were lower than those of selegiline, rasagiline, and safinamide. These data suggest that Dihydrofuran-2-one and its derivatives (2, 3, 7, 12, and 26) could act as MAO-B enzyme inhibitors, resulting in increased dopamine levels. Therefore, Dihydrofuran-2-one and its derivatives 2, 3, 7, 12, and 26 could be good therapeutic alternatives for the treatment of Parkinson disease.

Table 2. Thermodynamic parameters involved in the interaction of selegiline, rasagiline, safinamide, Dihydrofuran-2-one (1), and its derivatives (2-31) with 1gos protein surface.

Compound	A	B	C	D	E	F
Selegiline	-6.38	20.94	-8.37	0.29	-8.08	974.41
Rasagiline	-7.02	7.13	-6.72	-1.22	-7.94	975.30

Safinamide	-6.38	20.94	-8.37	0.29	-8.08	974.41
1	-4.03	1.12	-4.05	-0.02	-4.03	220.54
2	-3.82	1.54	-3.79	-0.04	-3.82	217.38
3	-3.79	1.67	-3.79	-0.04	-3.84	217.50
4	-4.37	623.15	-4.07	0.00	-4.07	255.60
5	-4.89	260.10	-4.80	-0.09	-4.89	302.12
6	-9.51	107.11	-10.92	-0.00	-10.92	1039.11
7	3.97	1.23	-3.93	-0.04	-3.97	841.13
8	-6.67	12.95	-6.93	-0.03	-6.97	763.69
9	-4.66	383.04	-3.93	-0.73	-4.66	336.51
10	-4.27	739.69	-4.02	-0.55	-4.57	666.44
11	-10.14	37.15	-10.97	-0.04	-11.01	968.73
12	-7.24	4.94	-8.19	0.05	-8.14	929.92
13	-4.76	326.74	-4.68	-0.08	-4.76	245.96
14	-8.42	677.26	-10.18	0.03	-10.15	949.48
15	-5.02	207.95	-4.90	-0.12	-5.02	861.16
16	-8.74	389.67	-10.09	-0.02	-10.12	909.90
17	-4.41	582.92	-4.35	-0.06	-4.41	791.32
18	-5.48	96.06	-5.56	0.08	-5.48	868.84
19	-4.56	456.08	-4.93	-0.18	-5.11	355.17
20	-8.33	777.54	-8.85	-0.08	-8.93	875.04
21	-4.32	686.73	-4.22	-0.10	-4.32	242.99
22	-9.47	114.91	-9.72	-0.58	-10.30	1177.15
23	-4.81	297.51	-5.35	-0.08	-5.45	946.99
24	-5.51	91.93	-5.91	-0.19	-6.10	956.73
25	-4.81	297.80	-3.89	-0.92	-4.81	599.24
26	-3.31	3.78	-3.53	-0.07	-3.60	327.02
27	-4.70	361.54	-4.84	-0.16	-4.99	856.65
28	-4.55	464.99	-3.93	-0.92	-4.84	671.86
29	-4.64	394.29	-4.07	-0.87	-4.94	647.94
30	-5.53	88.50	-5.50	-0.03	-5.53	916.79
31	-4.80	301.99	-4.23	-0.87	-5.10	822.79

Note: A = Est: Free Energy of Binding (kcal/mol^{-1}); **B** = Inhibition Constant, Ki (mM); **C** = vdW + Hbond + desolv Energy (kcal/mol^{-1}); **D** = Electrostatic Energy (kcal/mol^{-1}); **E** = Total Intermolec. Energy (kcal/mol^{-1}); **F** = Interact. Surface. Source: Authors, 2024.

3.4 Ligand-COMT complex

Catechol-O-methyltransferase (COMT) plays an important role in the metabolism of biogenic molecules, such as dopamine, epinephrine, and norepinephrine (Borchardt, 1973). It is important to mention that several COMT inhibitors are used to treat Parkinson's disease, including tolcapone, L-DOPA/carbidopa, and amantadine. It is important to mention that some of these drugs may produce side effects, such as hepatotoxicity (Olanow, 2000), arrhythmia (Churchyard et al., 1997), somnolence, and dizziness (Shen; Kong, 2018). In the search for new therapeutic alternatives, several drugs have been developed to evaluate their biological activity against Parkinson's disease (Harrison et al., 2015; Ernst et al., 2019); however, the interaction with the COMT enzyme surface is

unclear. Analyzing these data, this research aimed to evaluate the interaction of dihydrofuran-2-one and its derivatives with the COMT enzyme using the 1vid protein as a theoretical tool. Besides, entacapone, tolcapone, and 8-Hydroxyquinoline drugs were used as controls in the DockingServer software. The results (Table 3) showed some differences in the aminoacid residues for dihydrofuran-2-one (1) and its derivatives (2-31) involved in ligand-COMT complex formation compared with entacapone, tolcapone, and 8-hydroxyquinoline; however, compounds 1-3 present similar amino acid residues such as Asn_{41}; Tyr_{68}; Tyr_{71}; Ser_{72}; Asp_{141} compared to dihydrofuran-2-one derivatives (4-31). This phenomenon could produce changes in the biological activity of the COMT enzyme, which could translate into a better life quality for Parkinson's disease patients.

Table 3. Aminoacid residues involved in the interaction of entacapone, tolcapone, 8-hydroxyquinoline, dihydrofuran-2-one (1), and its derivatives (2-31) with 1vid protein surface.

Compound	Amino acid Residues
Entacapone	Trp_{38}; Met_{40}; Asp_{141}; Trp_{143}; Lys_{144}; Asp_{169}; Asn_{170}; Glu_{199}
Tolcapone	Tyr_{68}; Met_{89}; Glu_{90}; Met_{91}; Ser_{119}; Gln_{120}; His_{142}; Trp_{143}
8-Hydroxiquinoline	Met_{91}; Ser_{119}; Gln_{120}; His_{142}; Trp_{143}; Arg_{146}
1	Asn_{41}; Tyr_{68}; Tyr_{71}; Ser_{72}; Asp_{141}
2	Asn_{41}; Tyr_{68}; Tyr_{71}; Ser_{72}; Asp_{141}
3	Asn_{41}; Tyr_{68}; Tyr_{71}; Ser_{72}; Asp_{141}
4	Met_{40}; Tyr_{68}; Glu_{90}; His_{142}; Trp_{143}
5	Met_{89}; Glu_{90}; Ser_{119}; His_{142}; Trp_{143}; Arg_{146}
6	Trp_{38}; Asp_{141}; Trp_{143}; Lys_{144}; Asn_{170}; Pro_{174}; Leu_{198}; Glu_{199}
7	Leu_{65}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}
8	Met_{40}; Glu_{90}; Met_{91}; Tyr_{95}; Ser_{119}; His_{142}; Trp_{143}
9	Met_{89}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}
10	Met_{89}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}; Trp_{143}; Arg_{146}
11	Trp_{38}; Met_{40}; Asp_{141}; Trp_{143}; Lys_{144}; Asn_{170}; Pro_{174}
12	Met_{40}; Tyr_{68}; Glu_{90}; Met_{91}; Tyr_{95}; Asp_{141}; His_{142}; Trp_{143}; Lys_{144}
13	Met_{89}; Met_{91}; Ser_{119}; His_{142}
14	Trp_{38}; Met_{40}; Asp_{141}; Trp_{143}; Lys_{144}; Asn_{170}; Pro_{174}
15	Leu_{65}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}
16	Trp_{38}; Met_{40}; Asp_{141}; Trp_{143}; Lys_{144}; Asn_{170}
17	Met_{89}; Glu_{90}; Met_{91}; Gly_{117}; Ser_{119}; His_{142}; Trp_{143}
18	Glu_{90}; Met_{91}; Ser_{119}; Gln_{120}; His_{142}; Trp_{143}
19	Met_{89}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}; Trp_{143}
20	Met_{40}; Asn_{41}; Tyr_{68}; Ser_{72}; Glu_{90}; Asp_{141}; Trp_{143}; Lys_{144}; Asn_{170}; Glu_{199}
21	Met_{89}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}
22	Trp_{38}; Met_{40}; Asp_{141}; Trp_{143}; Lys_{144}; Asp_{169}; Asn_{170}; Pro_{174}; Glu_{199}
23	Glu_{90}; Met_{91}; His_{142}; Trp_{143}
24	Met_{40}; Tyr_{68}; Met_{89}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}; Trp_{143}
25	Glu_{90}; Met_{91}; Ser_{119}; His_{142}; Trp_{143}
26	Met_{89}; Glu_{90}; Met_{91}; His_{142}
27	Met_{89}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}
28	Leu_{65}; Met_{89}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}; Trp_{143}
29	Leu_{65}; Met_{89}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}; Trp_{143}

30	Met_{89}; Glu_{90}; Met_{91}; Ser_{119}; His_{142}; Trp_{143}
31	Met_{40}; Asp_{141}; Lys_{144}; Asp_{169}; Asn_{170}; Glu_{199}

3.5 Thermodynamic parameters

The results showed differences in the energy levels of dihydrofuran-2-one and its derivatives compared to tolcapone entacapone, and 8-Hydroxyquinoline (Table 4 and Figure 6). In addition, the inhibition constant (Ki) was lower for compounds 1, 2, 3, 7, 9, 10, 13, 21, and 25 than for tolcapone entacapone, and 8-Hydroxyquinoline. These data suggest that Dihydrofuran-2-one and its derivatives, 1, 2, 3, 7, 9, 10, 13, 21, and 25, could act as COMT inhibitors. This phenomenon could be translated into a good compound for treating Parkinson´s disease.

Table 4. Thermodynamic parameters involved in the interaction of entacapone, tolcapone, 8-Hydroxyquinoline, dihydrofuran-2-one (1), and its derivatives (2-31) with 1vid protein surface.

Compound	A	B	C	D	E	F
Entacapone	-4.27	737.92	-5.33	-0.02	-5.35	524.17
Tolcapone	-8.85	327.84	-9.47	0.35	-9.12	680.58
8-Hydroxyquinoline	-5.66	71.42	-5.86	-0.09	-5.95	416.83
1	-3.72	1.88	-3.34	-0.38	-3.72	256.38
2	-3.43	3.07	-3.07	-0.36	-3.43	250.54
3	-3.46	2.90	-3.10	-0.37	-3.46	251.38
4	-4.23	787.10	-3.83	-0.18	-4.01	385.63
5	-4.93	243.89	-4.90	-0.03	-4.93	313.27
6	-6.91	8.68	-8.22	-0.07	-8.30	728.94
7	3.94	1.29	-4.01	0.07	-3.94	342.28
8	-7.35	4.12	-7.69	0.05	-7.64	542.05
9	-3.83	1.55	-4.08	0.25	-3.83	368.77
10	-3.89	1.41	-4.61	0.42	-4.19	442.32
11	-6.41	19.94	-7.23	-0.06	-7.29	630.80
12	-5.56	84.32	-6.38	-0.12	-6.51	706.24
13	-3.96	1.26	-3.89	-0.06	-3.96	324.11
14	-5.45	101.00	-6.97	-0.03	-7.01	655.25
15	-5.14	171.90	-5.05	-0.08	-5.14	383.50
16	-5.72	63.93	-6.59	-0.10	-6.69	598.30
17	-4.24	778.59	-4.27	0.03	-4.24	289.21
18	-5.48	95.57	-5.53	0.05	-5.48	387.87
19	-4.56	454.93	-4.97	-0.17	-5.14	396.69
20	-8.38	715.19	-8.76	-0.24	-9.00	643.04
21	-3.57	2.40	-3.50	-0.08	-3.57	320.64
22	-6.76	11.15	-6.29	-0.46	-6.75	630.71
23	-4.57	447.23	-5.51	0.39	-5.12	498.68
24	-5.95	43.44	-6.45	-0.10	-6.54	546.83
25	-3.88	1.43	-4.44	0.26	-4.18	445.08GO
26	-3.19	4.58	-3.45	-0.04	-3.49	360.75
27	-4.76	326.07	-5.06	0.00	-5.05	402.09

28	-4.32	685.58	-4.79	0.17	-4.61	401.26
29	-4.00	1.18	-4.62	0.33	-4.29	422.37
30	-5.43	105.37	-5.44	0.01	-5.43	441.37
31	-6.59	14.75	-3.30	-3.59	-6.89	323.53

Note: **A =** Est: Free Energy of Binding (kcal/mol^{-1}); **B** = Inhibition Constant, Ki (mM); **C** = vdW + Hbond + desolv Energy (kcal/mol^{-1}); **D** = Electrostatic Energy (kcal/mol^{-1}); **E** = Total Intermolec. Energy (kcal/mol^{-1}); **F** = Interact. Surface. Source: Authors, 2024.

3.6 Pharmacokinetic parameters

For several years, some models have been used to evaluate different pharmacokinetic properties, such as absorption, distribution, metabolism, and elimination (ADME), for the development of new drugs (Butina et al., 2002). In this study, the pharmacokinetic parameters of Dihydrofuran-2-one (1) and its derivatives (2-31) were determined using SwissADME software. The results (Table 5) suggest that metabolism of Dihydrofuran-2-one (1) and its derivatives (1, 2-3, 7, 9, 10. 12. 13, 21, 25, and 26) may involve different Cyps (P450 family). This phenomenon could be due to differences in the chemical structure or lipophilicity of the compounds.

Table 5. Pharmacokinetic parameters for of selegiline (Sel), rasagiline (Ras), safinamide (Saf), entacapone (Enta), tolcapone (Tolc) and 8-Hidroxyquinoline (8-OH-Q), dihydrofuran-2-one (1) and its derivatives (1, 2-3, 7, 9, 10. 12. 13, 21, 25, and 26) using SwissADME.

Compound	I	II	III	IV	V	VI	VII	VII
Sel	High	Yes	No	Yes	No	No	Yes	No
Ras	High	Yes	No	No	No	No	Yes	No
Saf	High	Yes	No	No	Yes	No	Yes	Yes
Enta	High	No	No	No	No	No	No	No
Tolc	High	No	No	No	No	Yes	No	Yes
8-OH	Low	No	No	No	No	Yes	No	No
1	High	No	No	No	No	No	No	No
2	High	No	No	No	No	No	No	No
3	High	No	No	No	No	No	No	No
7	High	Yes	No	No	No	No	No	No
9	High	Yes	No	No	No	No	No	No
10	High	Yes	No	No	No	No	No	No
12	High	Yes	No	Yes	Yes	Yes	No	No
13	High	No	No	No	No	No	No	No
21	High	No	No	No	No	No	No	No
25	High	Yes	No	No	No	No	No	No
26	High	No	No	No	No	No	No	No

Source: Authors, 2024.

3.7 Lipophilicity analysis

The lipophilicity degree for dihydrofuran-2-one (1) and its derivatives (1, 2-3, 7, 9, 10, 12, 13, 21, 25 and 26) was determined using SwissADME software [42]. The results (Table 6) displayed differences in the lipophilicity degree of dihydrofuran-2-one compared to its derivatives.

Table 6. Theoretical determination of lipophilicity degree values for dihydrofuran-2-one and its derivatives using the SwissADME program.

Parameter	1	2	3	7	9	10	12	13	21	25	26
Log $P_{o/w}$ (iLOGP)	1.13	1.19	1.10	1.70	1.77	2.07	2.86	1.43	1.39	1.52	1.36
Log $P_{o/w}$ (XLOGP3)	0.64	0.22	-0.60	0.65	0.83	1.01	3.16	0.03	0.59	0.68	-0.09
Log $P_{o/w}$ (WLOGP)	0.32	0.45	0.10	0.88	0.88	0.85	3.02	0.36	0.49	0.76	0.07
Log $P_{o/w}$ (MLOGP	0.09	-0.01	-0.01	-0.04	-0.04	-0.57	2.41	-0.31	0.40	-0.92	-0.48
Log $P_{o/w}$ (SILICOS-IT)	1.43	1.02	1.02	1.28	1.28	1.23	3.69	1.32	1.31	0.77	0.82
Consensus Log $P_{o/w}$	0.47	0.57	0.32	0.89	0.94	0.92	3.01	0.57	0.84	0.56	0.34

Source: Authors, 2024.

3.8 Toxicity analysis

Several methods, such as TosCast (Martin et al., 2010), ToxAlert (Perez et al., 2001), Stop-Tox (Shinde and Hoelting, 2017), and Gusar (Visha et al., 2020) have been used to predict the degree of toxicity of several drugs. This research aimed to evaluate the possible toxicity produced by Dihydrofuran-2-one (1) and its derivatives (2-3, 7, 9, 10, 12, 13, 21, 25, and 26) using GUSAR software. The results (Table 7) indicated that the degree of toxicity could depend on the dose administered to Dihydrofuran-2-one and its derivatives through different routes of administration. Perhaps, this phenomenon could depend on the different functional groups involved in the chemical structure of each Dihydrofuran-2-one and its derivatives 2-3, 7, 9, 10. 12. 13, 21, 25, and 26.

Table 7. Theoretical toxicity analysis produced by Dihydrofuran-2-one (1) and its derivatives (1, 2, 3, 7, 9, 10, 12, 13, 21, 25, and 26) using the GUSAR program.

Compound	IP LD_{50} (mg kg^{-1})	IV LD_{50} (mg kg^{-1})	Oral LD_{50} (mg kg^{-1})	SC LD_{50} (mg kg^{-1})
1	371.20	31.29	2525.00	960.50
2	173.10	17.40	841.40	181.90
3	261.50	12.36	782.90	323.40
7	166.40	18.75	985.60	432.10
9	225.60	25.65	764.70	594.40
10	263.20	40.96	872.00	651.50
12	449.50	63.84	1226.00	783.10
13	210.70	16.29	1009.00	178.20
21	345.70	19.06	1679.00	813.60
25	125.90	42.37	861.10	565.80
26	220.50	23.45	907.70	1327.00

Source: Authors, 2024.

4. Conclusions

The theoretical models used in this study are suitable for the following reasons. i) To develop a pharmacophore model for Dihydrofuran-2-one (1) and its derivatives (2-31) which allows analysis of the different possibilities of their interaction with either MAO-B or COMT enzymes; ii) to evaluate different energy levels involved in the interaction of Dihydrofuran-2-one and its derivatives (2-31) with either MAO-B or COMT enzyme surface; and ii) to evaluate some pharmacokinetic and toxicological aspects that could determine the biological activity of Dihydrofuran-2-one and its derivatives (1, 2, 3, 7, 9, 10, 12, 13, 21, 25, and 26). Finally, the results obtained suggest that Dihydrofuran-2-one and its derivatives 1, 2, 3, 7, 9, 10, 12, 13, 21, 25, and 26 could be good therapeutic alternatives for the treatment of Parkinson´s disease.

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None.

6. Authors' Contributions

Figueroa Valverde Lauro: Theoretical experimental design, article writing, data analysis, corrections, and publication; *Alvarez Ramirez Magdalena*: data analysis, writing, and evaluating data; *Rosas Nexticapa Marcela*: article writing, data evaluation, and corrections; *Aguilar Sanchez Emilio*: analysis data, and corrections; *Mateu Armad Maria Virginia*: analysis data, corrections, and publication.

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Does not apply.

9. References

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