

Comparative ADMET, Docking and Molecular Dynamics Investigation of Novel Urea Scaffolds and Mesotrione for Sustainable Herbicide Development

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ABSTRACT:

The upward dominance of herbicide-resistant weeds has intensified the search for new herbicidal agents with improved efficacy, selectivity and environmental compatibility. In this study, a series of substituted urea derivatives were designed and computationally evaluated as potential inhibitors of 4-hydroxyphenylpyruvate dioxygenase (HPPD), a key enzymatic target in weed management. Molecular docking exploration discovered that several of the designated compounds unveiled resilient binding attraction toward the HPPD active points than the commercial herbicide Mesotrione. Among the evaluated derivatives, Compound -2 demonstrated the maximum satisfactory interaction contour with a MolDock score of -166.256Kcal/mol, significantly outperforming Mesotrione (-118.689Kcal/mol). The enhanced binding enactment of the nominated compounds was attributed to promising hydrogen bonding, hydrophobic interactions, aromatic stacking and van der Waals associations indoors of the catalytic central point. In addition, physicochemical, ADMET and radar plot analyses indicated that the majority of the derivatives possessed acceptable agrochemical properties, including balanced lipophilicity, suitable molecular size, moderate solubility and favorable permeability characteristics. Toxicity predictions further suggested improved safety profiles for the selected compounds, with no major indications of carcinogenicity, mutagenicity, skin sensitization, respiratory failure, or eye irritation. To further validate the stability of the ligand-protein systems, molecular dynamics simulations remained accomplished over a 100ns trajectory. The simulation findings demonstrated that Compound -2 maintained superior conformational stability and stronger interaction persistence within the HPPD active site compared with Mesotrione. This was evidenced by lower RMSD and RMSF fluctuations, stable solvent accessibility of surface area (SASA), consistent radius of gyration (Rg) values, and sustained hydrogen bond interactions through the simulation period. In contrast, the Mesotrione complex exhibited greater structural fluctuations and weaker dynamic stability. Collectively, the integrated docking, ADMET, toxicity and molecular dynamics results identify Compound -2 as a promising lead scaffold with enhanced inhibitory potential, favorable physicochemical behavior, improved predicted safety and strong structural stability. These findings support the potential application of substituted urea derivatives as next-generation HPPD-targeting herbicidal candidates for sustainable weed management strategies.

1.0 Introduction

Chemical weed control remains a cornerstone of modern agricultural practice because of its steadfast performance, operational efficiency, and suitability for large-scale farming systems [1]. Although marginal weed controlling approaches, counting biological control using rhizobacteria and other environmentally friendly approaches have stood discovered, these approaches often struggle to transport the level of evenness and practicality required for routine field use [2]. Within the continuum of chemical herbicides, urea-based compounds have extended substantial curiosity as effective weed management tools due to their adaptable chemical structures and potential for selective biological activity [3]. The overall success of herbicide application is determined by several interacting factors, such as the applied dose, formulation characteristics, method of delivery, and prevailing environmental conditions. In appraisal with automated weed control, biochemical approaches typically reduce labor demand, shorten field operation time, and improve cost efficiency, particularly in large-scale agricultural settings [4]. Nevertheless, the continuous evolution of herbicide resistance in weed populations remains a major challenge, underscoring the ongoing need for the upgrading of new and more effective herbicidal agents [5].

Urea and its derivatives constitute an important class of herbicides known for their ability to disrupt essential physiological and biochemical processes in plants [6]. Many compounds within this group exert their herbicidal effects by interfering with photosynthetic pathways or enzyme-mediated metabolic utilities that are precarious for plant survival [7]. Notable examples include Diuron and Linuron, which have been broadly scrutinized for their broad-spectrum weed control activity. These herbicides are commonly absorbed through plant roots or leaf surfaces and are subsequently transported inside plant materials, somewhere they inhibit the key enzymatic systems such as 4-hydroxyphenylpyruvate dioxygenase (HPPD) [8]. This inhibition disrupts pigment synthesis, leading to visible symptoms such as leaf bleaching (chlorosis) and, ultimately, plant death. The performance of urea-based herbicides can be further enhanced through optimized formulation strategies, including the incorporation of adjuvants [9]. Additives such as urea, ammonium sulfate, and ammonium nitrate are frequently used to improve herbicide absorption and biological activity, often producing synergistic effects that strengthen weed control outcomes while potentially helping to slow the emergence of resistance [10]

The use of urea-derived herbicides is particularly important in conservation-oriented farming systems, especially those based on minimum or reduced tillage practices where soil disturbance is intentionally minimized [11]. While conventional tillage methods remain widely practiced due to established agricultural traditions, they are frequently concomitant with soil structure degradation and long-term reductions in productivity [12]. In contrast, minimum tillage systems support improved soil health and sustainability but depend heavily on reliable chemical weed management to regulator prevailing vegetation beforehand implanting [2, 13]. In modern years, computational practices have emerged as powerful tools for accelerating herbicide discovery and optimization [14]. Approaches such as molecular docking, quantitative structure activity relationship (QSAR) analysis and molecular dynamics (MD) simulations enable researchers to design and evaluate urea derivatives with enhanced binding affinity and specificity toward biological targets like the HPPD enzyme [15]. These *in silico* strategies significantly reduce reliance on time-consuming experimental screening, allowing for faster identification of promising compounds with desirable physicochemical and biological characteristics [16]. As a result, the integration of conservation agriculture practices with computationally guided herbicide development represents a forward-looking and sustainable strategy for improving weed management in modern agricultural systems [17].

2.0 Materials and Methods

2.1. Software bundles and website usage exploitation

All computational procedures shepherded in this study were performed on a Samsung laptop powered by an Intel® Core™ i5-2467M processor operating at a clock speed of 2.0 GHz and supported by 16.0 GB of random-access memory (RAM), running on the Windows 10 operating system. A range of specialized computational chemistry and molecular modeling software packages were employed throughout the research workflow [18]. These included ChemDraw 19.1 for molecular structure design and visualization, Molegro Fundamental Docker for docking simulations, Spartan '14 v1.1.4 for molecular optimization and quantum chemical calculations, and Discovery Studio for structural analysis and interaction profiling [19]. In addition, web-based computational platforms were utilized to assess the pharmacokinetic behavior, physicochemical characteristics, and herbicide-likeness profiles of the investigated compounds [20]. Specifically, the online interfaces of SwissADMET and ADMETlab 3.0 were employed to envisage metabolism, absorption, excretion, distribution,

and toxicity (rearranged as ADMET) parameters, thereby supporting the evaluation of the environmental compatibility and biological performance potential of the designed herbicidal candidates [21].

2.2. Conversion of 2D and 3D geometry optimization

The two-dimensional (2D) molecular structures of all designed compounds were initially generated and subsequently imported into the interface of Spartan '14 v1.1.4, where they remained transformed into three-dimensional (3D) configurations suitable for computational analysis. Following structure generation, geometry optimization of the fragments were achieved expending density functional theory (DFT)-based quantum mechanical calculations [22]. The optimization process employed the B3LYP functional in combination with the 6-31G* basis set to obtain energetically favorable molecular conformations [23]. This geometry optimization step was essential for identifying the most stable conformers of each compound prior to subsequent molecular modeling and docking analyses [24]. Upon completion of the optimization procedure, the resulting structures were carefully stored in a designated directory and exported in Protein Data Bank (PDB) file format to ensure compatibility with downstream computational tools used in the study [25].

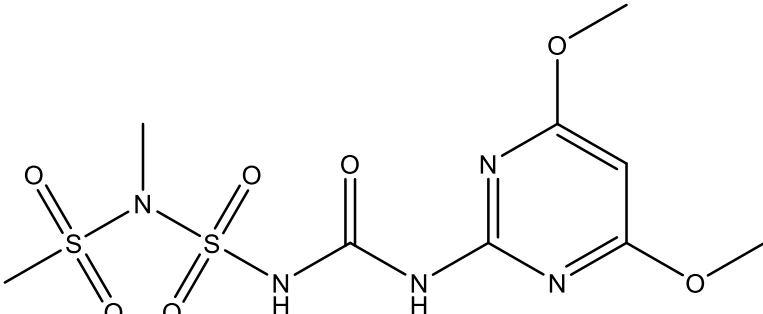
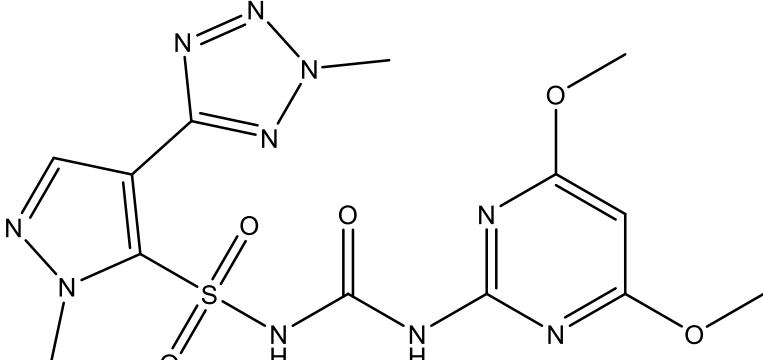
2.3. Receptor download and fundamental structural preparation

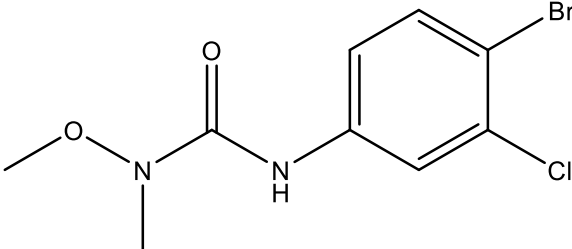
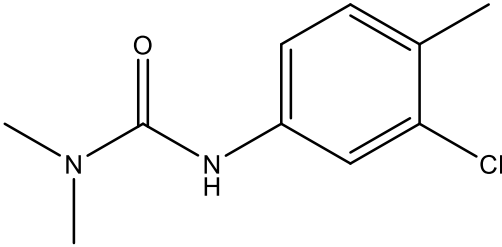
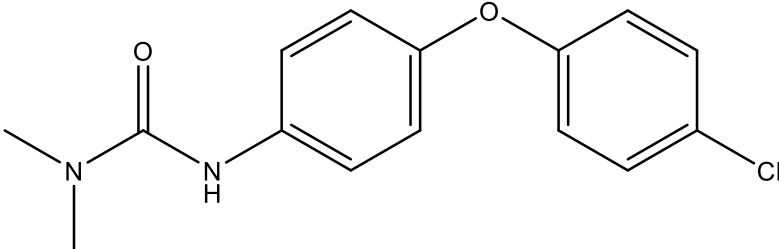
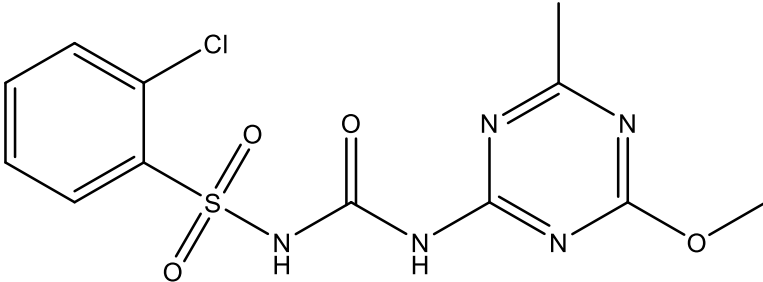
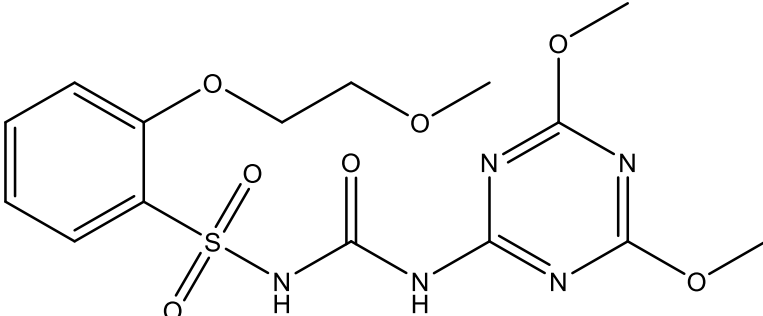
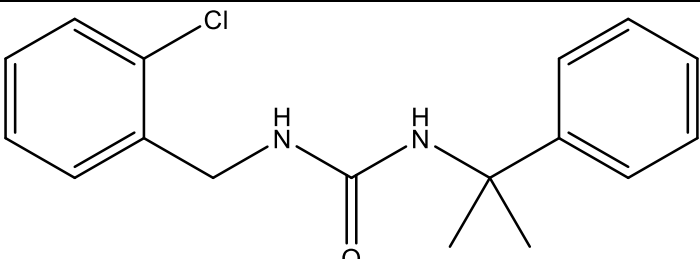
The crystallographic structure of the target protein, 4-hydroxyphenylpyruvate dioxygenase (HPPD) co-crystallized with its native ligand (PDB ID: 1TFZ), was repossessed from the Bank of Protein Data (PDB) repository using the reference Digital Object Identifier (DOI): <https://doi.org/10.2210/pdb1TFZ/pdb> [26]. The downloaded protein structure was subsequently imported into the working environment of Molegro Virtual Docker for comprehensive structural preparation prior to docking simulations [27]. During this preparation stage, amino acid residues exhibiting structural inconsistencies such as distortions or irregular bond geometries that may ascend throughout file acquisition or conversion were carefully corrected and reconstructed to ensure structural integrity [28]. In addition, the co-crystallized ligand molecules and non-essential water molecules present within the protein structure were systematically removed to eliminate potential interference and to define a clean and reliable binding environment for subsequent molecular docking analyses [29].

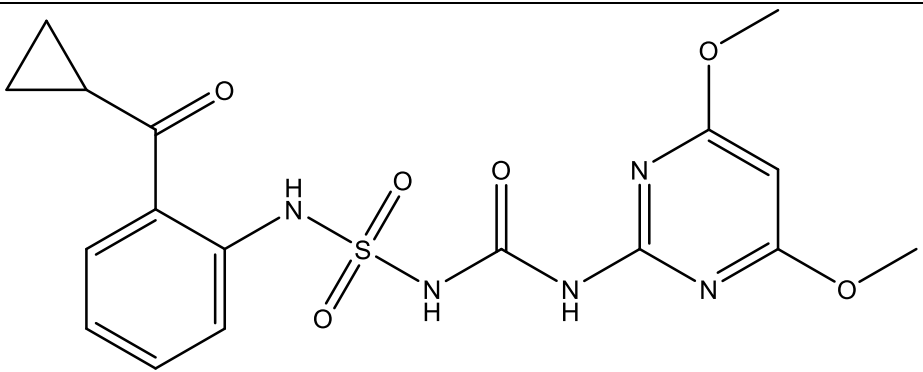
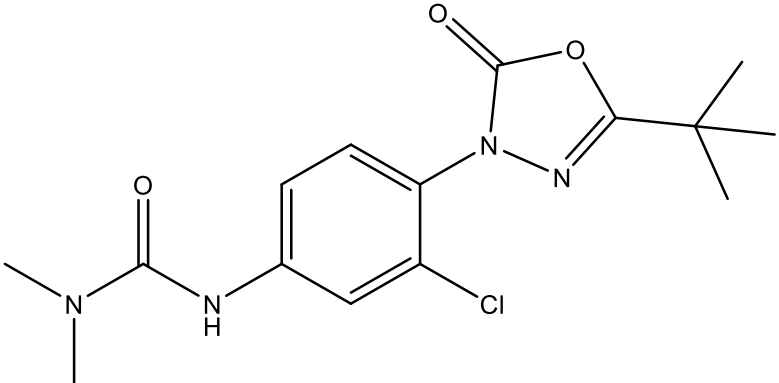
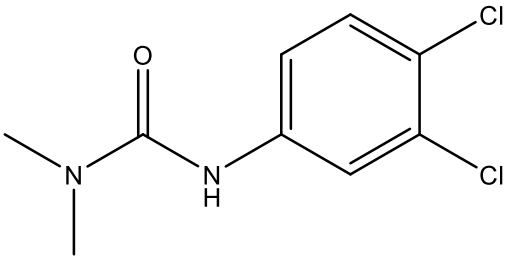
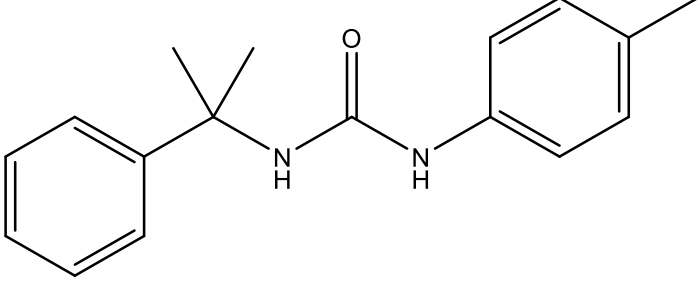
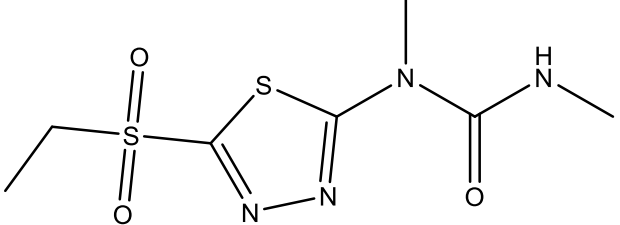
2.4. Dataset accessibility

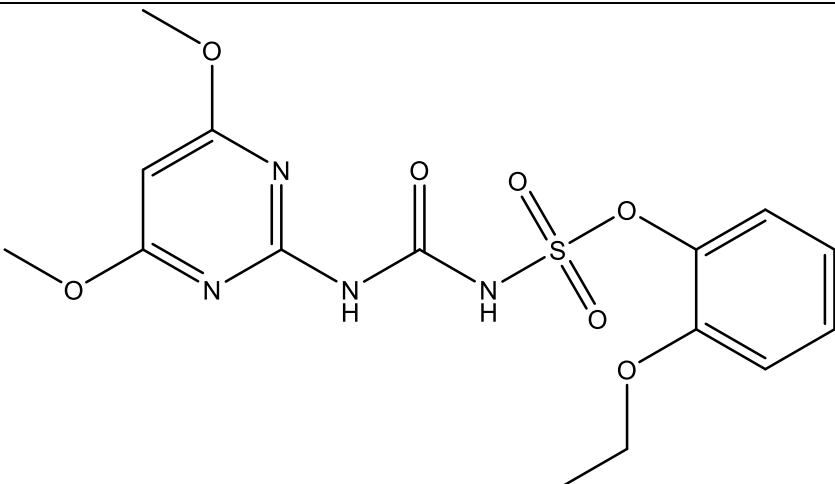
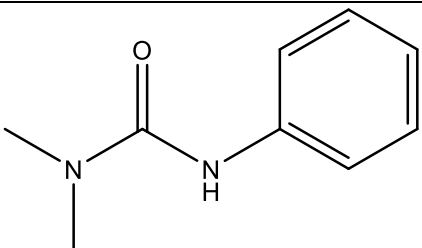
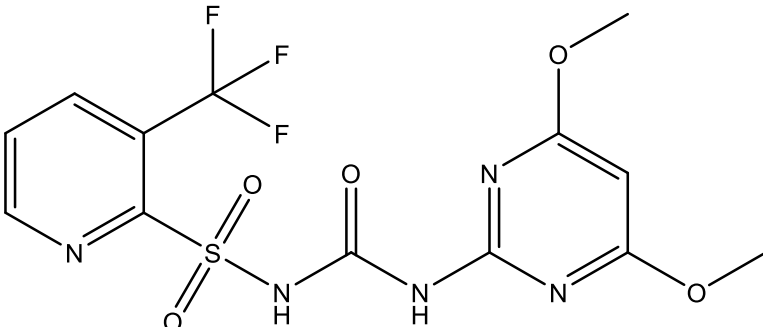
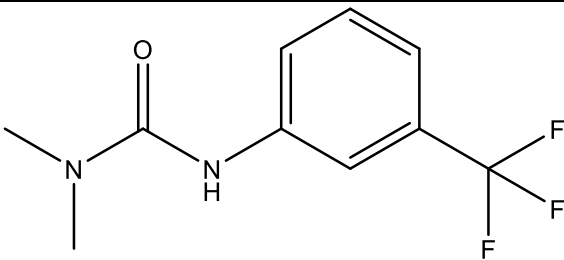
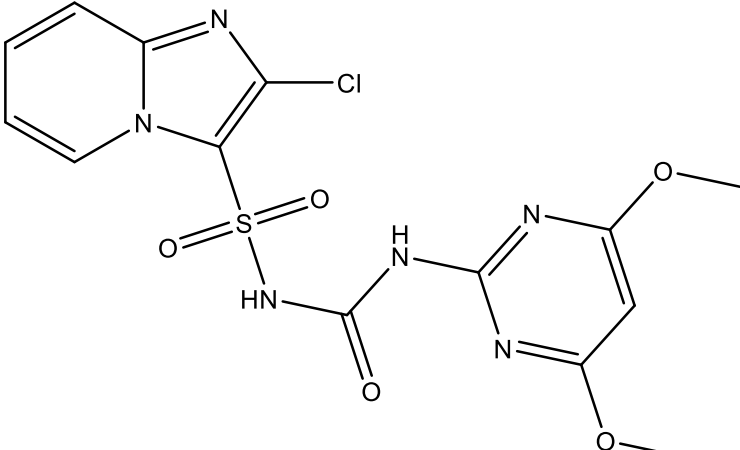
The dataset covered a total of 41 substituted urea derivatives previously reported as potential herbicidal inhibitors of 4-hydroxyphenylpyruvate dioxygenase (HPPD) [30]. The inhibitory activity of individually compound was estimated centered on its half-maximal inhibitory concentration (IC_{50}), expressed in micro molar (μM), which serves as a standard measure of biological potency [30]. To improve the statistical robustness and linearity of the dataset for quantitative modeling and comparative analysis, the IC_{50} values stayed transformed into their corresponding logarithmic form, known as pIC_{50} [31]. This conversion simplifies easier clarification of activity trends and enhances the enactment of regression-based computational models. The relationship used for this conversion is presented is given by the equation ($pIC_{50} = -\log IC_{50} \times 10^{-6}$) [32]. The calculated pIC_{50} values were subsequently organized and presented in Table 1 to provide a standardized dataset for further computational routinization, counting molecular docking, quantitative structure activity relationship (QSAR) modeling, and other in silico evaluations.

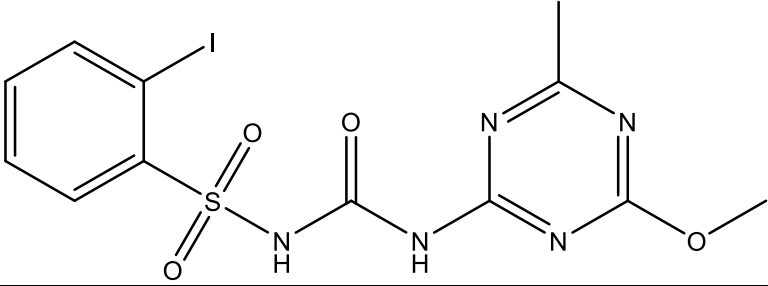
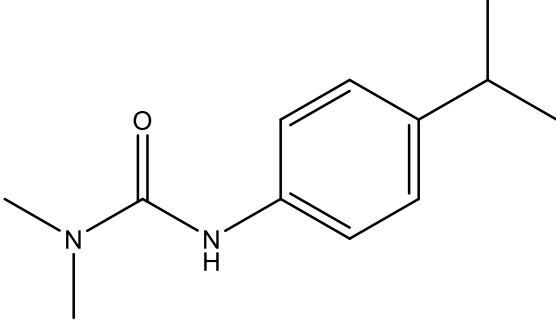
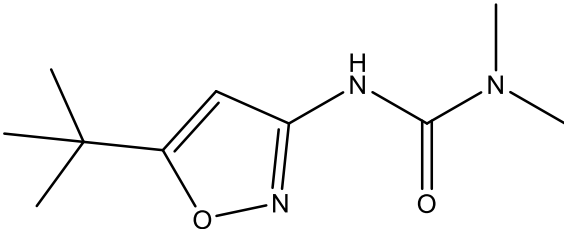
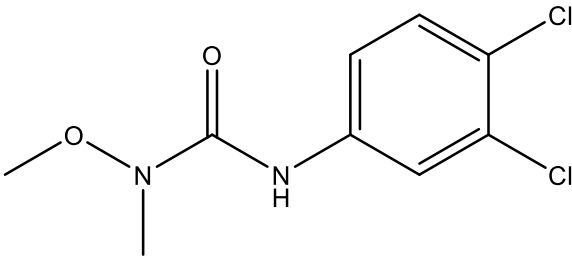
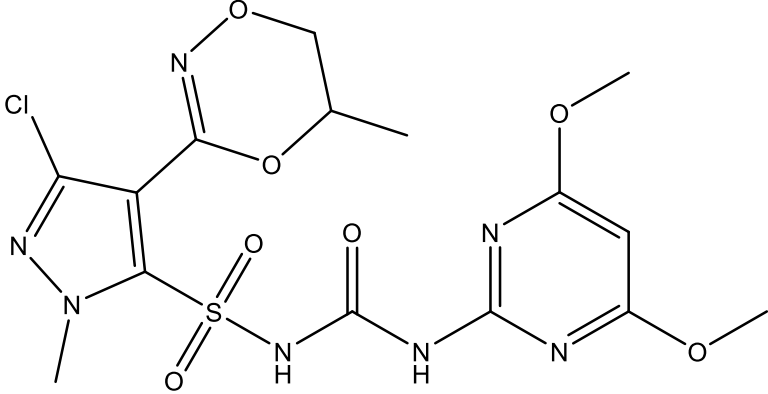
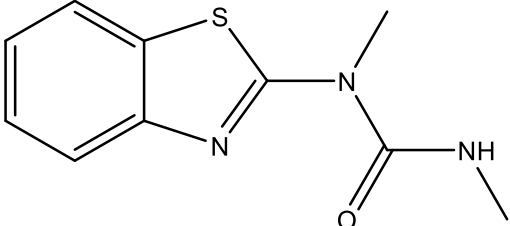
Table 1 2D Structures and experimental pIC_{50} values of substituted urea derivatives

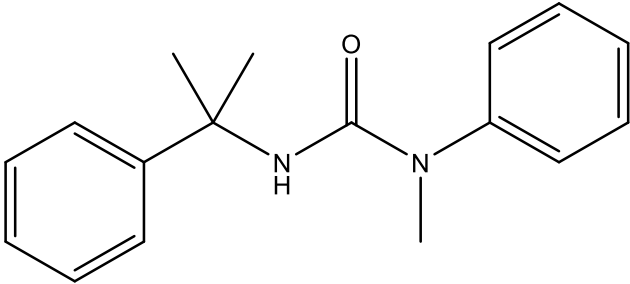
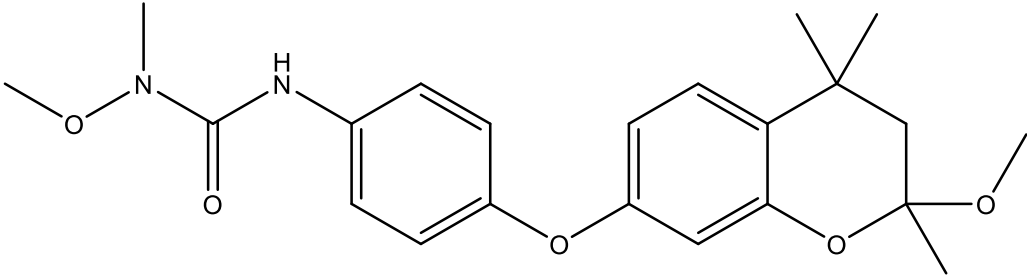
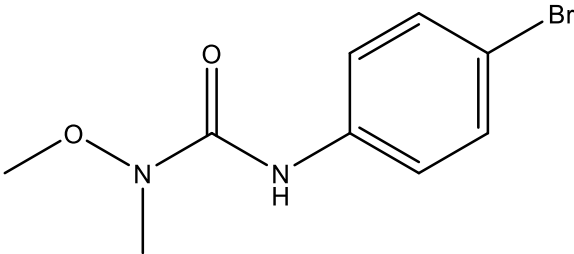
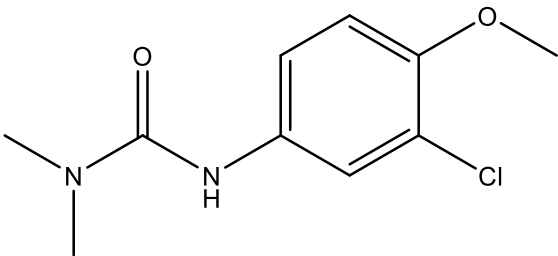
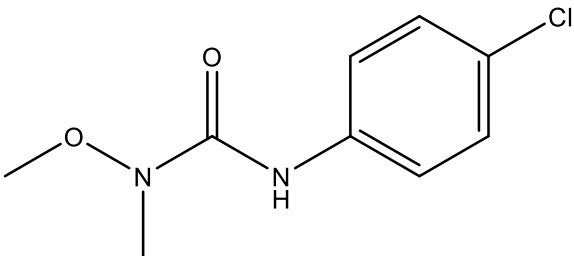
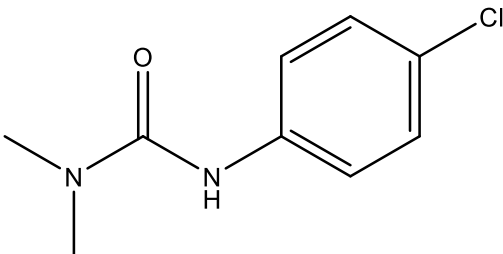
S/no.	2D Structures	pIC_{50} (μM)
1		5.478862
2		5.583359

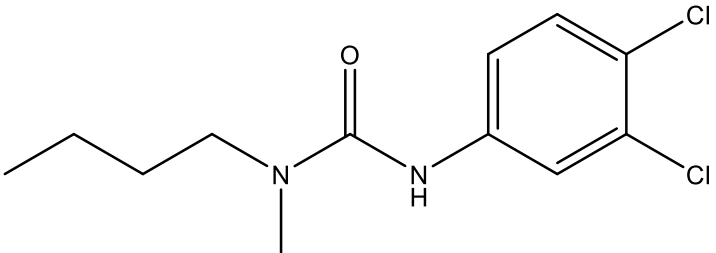
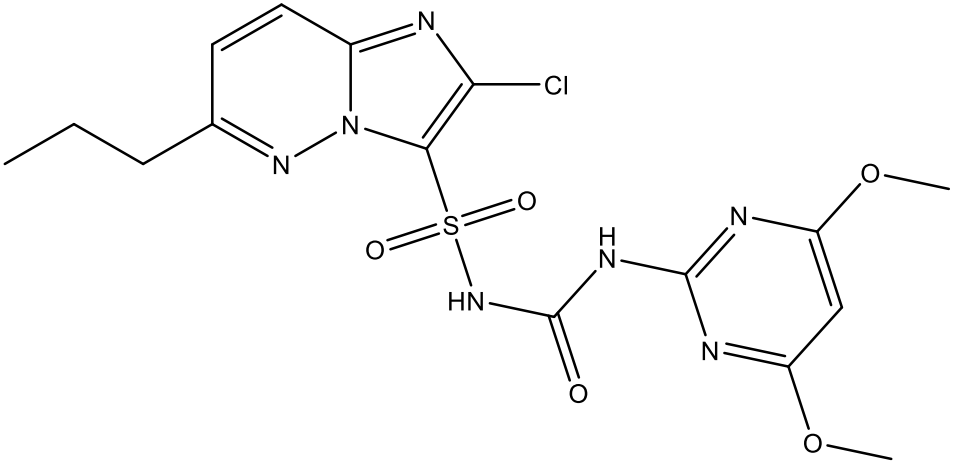
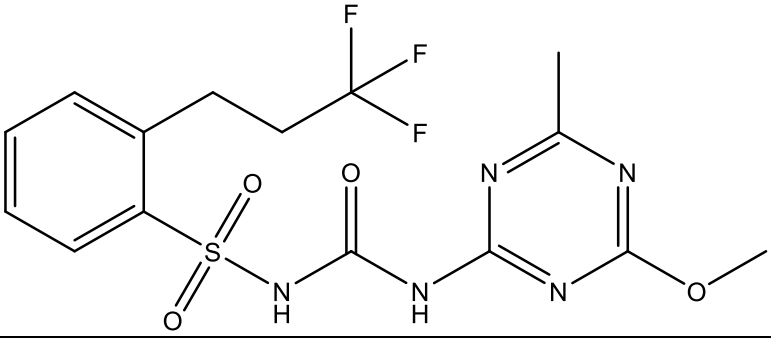
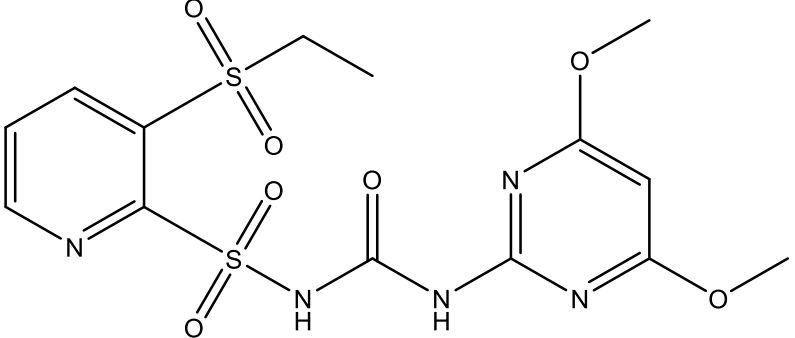
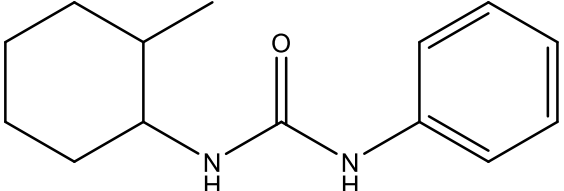
3	 <chem>CN(C)C(=O)Nc1cc(Br)cc(Cl)c1</chem>	5.486782
4	 <chem>CN(C)C(=O)Nc1cc(C)cc(Cl)c1</chem>	5.542118
5	 <chem>CN(C)C(=O)Nc1ccc(Oc2ccc(Cl)cc2)cc1</chem>	5.310691
6	 <chem>COC1=CN=C(NC(=O)NS(=O)(=O)c2ccccc2Cl)N1</chem>	5.38300
7	 <chem>COC1=CN=C(NC(=O)NS(=O)(=O)c2ccccc2Cl)N1COC</chem>	5.443697
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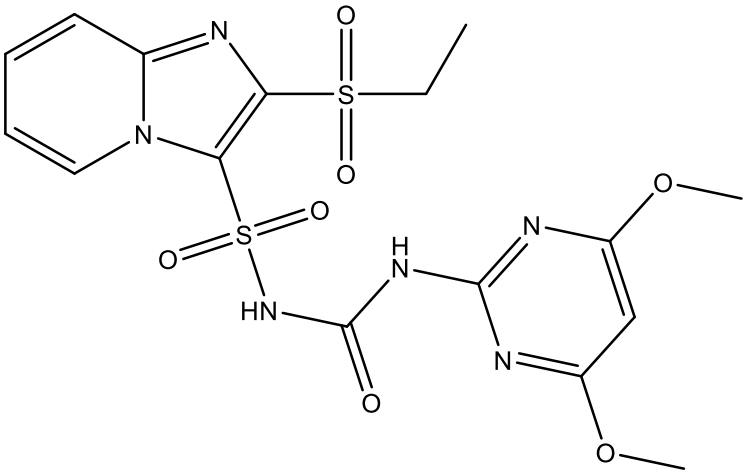
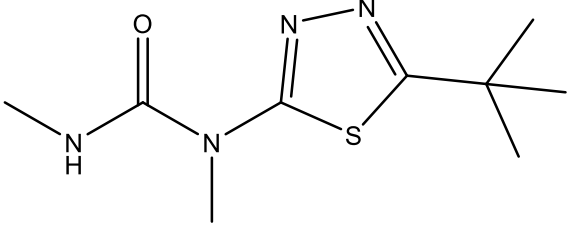
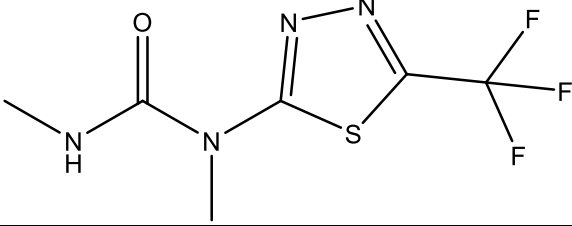
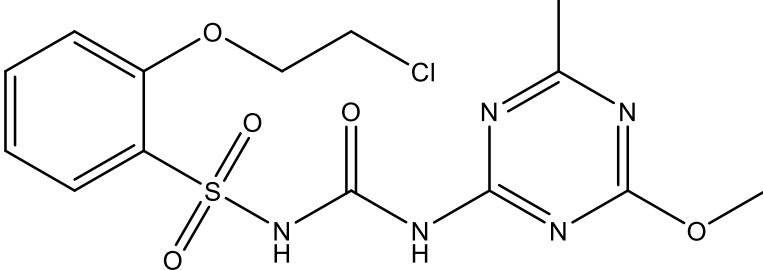
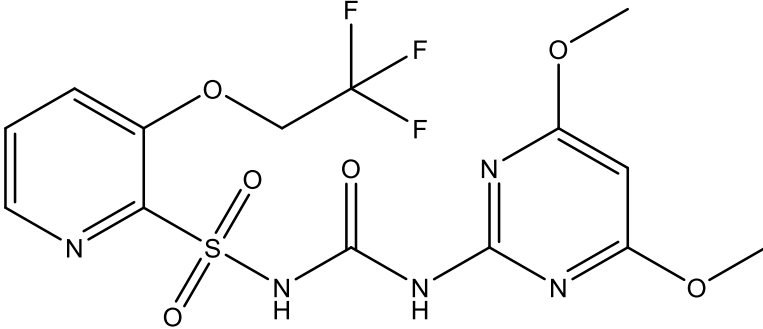
9	 <chem>COc1cc(OC)c(NC(=O)NS(=O)(=O)NC(=O)c2ccccc2C3CC3)c[nH]1</chem>	5.36251
10	 <chem>CC1=CN(C(=O)Nc2ccc(Cl)cc2N1C(=O)O)C(=O)N(C)C</chem>	5.465974
11	 <chem>CN(C)C(=O)Nc1cc(Cl)cc(Cl)c1</chem>	5.424812
12	 <chem>CN(C)C(=O)Nc1ccc(C)cc1</chem>	5.366532
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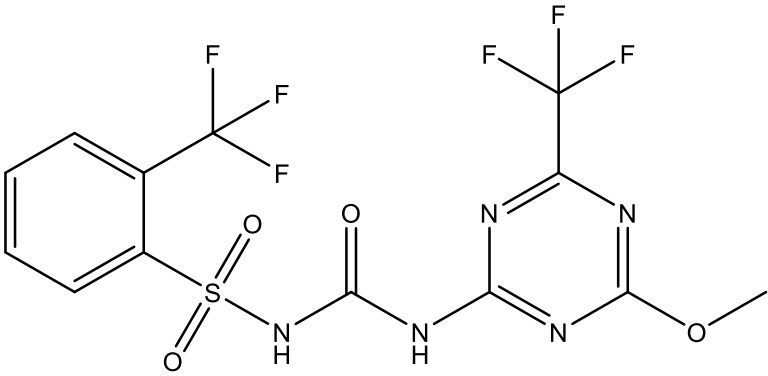
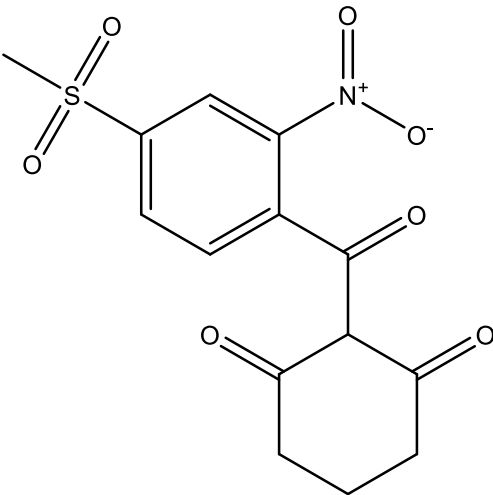
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15	 <chem>CN(C)C(=O)Nc1ccccc1</chem>	5.79588
16	 <chem>COC1=CC(=NC(=C1)NC(=O)NS(=O)(=O)c2ccncc2C(F)(F)F)OC</chem>	5.427128
17	 <chem>CN(C)C(=O)Nc1ccc(cc1)C(F)(F)F</chem>	5.464706
18	 <chem>COC1=CC(=NC(=C1)NC(=O)NS(=O)(=O)c2nc3ccccc3n2Cl)OC</chem>	5.369572

19		5.527244
20		5.450997
21		5.61261
22		5.453457
23		5.496209
24		5.548214

25		5.437707
26		5.326058
27		5.537602
28		5.567031
29		5.590067
30		5.539102

31		5.321482
32		5.367543
33		5.440093
34		5.407823
35		5.386158

36		5.374688
37		5.539102
38		5.546682
39		5.394695
40		5.458421

41		5.395774
MST	 Standard herbicide (Mesotrione)	

2.5.Molecular Docking Studies

In the contemporaneous study, molecular docking inquiry was conducted for all 41 synthesized ring-substituted urea derivatives previously reported by [30]. The binding interfaces amongst these compounds and the active-site residues of the enzyme 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) were systematically investigated using the molecular docking podium Molegro Simulated Docker [33]. The three-dimensional crystal arrangement of the target protein with the bank protein storage ID (PDB ID: 1TFZ; DOI: <https://doi.org/10.2210/pdb1TFZ/pdb>) was gotten from the Bank of Protein Data and prepared for docking simulations by removing the co-crystallized ligand and non-essential crystallographic water molecules, in accordance with standard protein preparation protocols [26]. In addition, amino acid residues displaying structural irregularities or distortions were carefully examined and corrected to ensure structural reliability prior to docking analysis [34].

In addition, a spherical search space with a ambit radius of 1.80Å was defined around the catalytic binding point of the enzyme to accurately guide ligand placement during the docking process. To verify the reliability and reproducibility of the docking protocol, the native ligand present in the crystal structure namely the reference herbicide Mesotrione was re-docked into the same active site [35]. Following successful validation of the docking procedure, all the geometry-optimized ring-substituted urea derivatives were individually docked into the active location of the 1TFZ receptor. For each ligand-protein complex, the docking software generated several key scoring parameters, including the MolDock Score, Rerank Score, and estimated hydrogen-bond interaction energy, which remained cast-off to evaluate binding attraction and interaction strength [36]. The subsequent docked complexes were supplementary considered and visually inspected using the molecular visualization and analysis platform Discovery Studio to recognize and characterize the precise intermolecular connections accountable for stabilizing ligand enzyme binding within the active site.

2.6. ADMET extrapolations

The web-based computational platforms SwissADMET and ADMETlab 3.0 were employed to predict the pharmacokinetic behavior and potential toxicity profiles of the ring-substituted urea derivatives investigated as candidate herbicides [34]. Though these apparatuses were primarily developed to assess drug-likeness properties in pharmaceutical research, they have progressively been espoused in agrochemical discovery for evaluating herbicide-likeness characteristics. Their growing application in this field is largely attributed to their ability to identify compounds that demonstrate strong biological activity while maintaining favorable environmental and safety profiles [37].

Moreover, the predictive strength of these computational platforms helps minimize dependence on extensive laboratory and field-based toxicity testing during the early stages of compound development, thereby accelerating the screening and prioritization of promising herbicidal candidates [34]. In the present study, Lipinski's Rule of Five (LRO5) was applied as an initial screening criterion to assess the physicochemical suitability of the designed compounds. This preliminary evaluation was subsequently complemented by a more comprehensive analysis of perilous ADMET parameters to ensure a thorough assessment of the compounds' overall performance and environmental compatibility [38].

2.7. Molecular dynamics simulation analysis

Molecular dynamics simulation happening with energy minimization, exploiting the steepest descent algorithm to address and remove any unfavorable steric interactions, thereby stabilizing the system. To manage non-bonded interactions, the Verlet cutoff scheme was executed, while long-range electrostatic contacts were calculated accurately using the Particle Mesh Ewald (PME) procedure. The system endured a two-phase equilibration process: first, it was imperiled to a constant number of particles, volume, and temperature (NVT) ensemble, surveyed by a constant number of particles, pressure, and temperature (NPT) ensemble at 300K and 1bar pressure. Temperature control was expedited through a velocity-rescale thermostat, while pressure stabilization was accomplished using Berendsen and Parrinello–Rahman algorithms. After numerous equilibrations, a production simulation durable 100ns was conceded out under NPT settings, with a 2 femtosecond time step and bond length constraints preserved by the LINCS algorithm. Lastly, the verified simulation trajectories were scrutinized for key metrics such as root mean square of deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), solvent accessibility of surface area (SASA), and H-bond interactions.

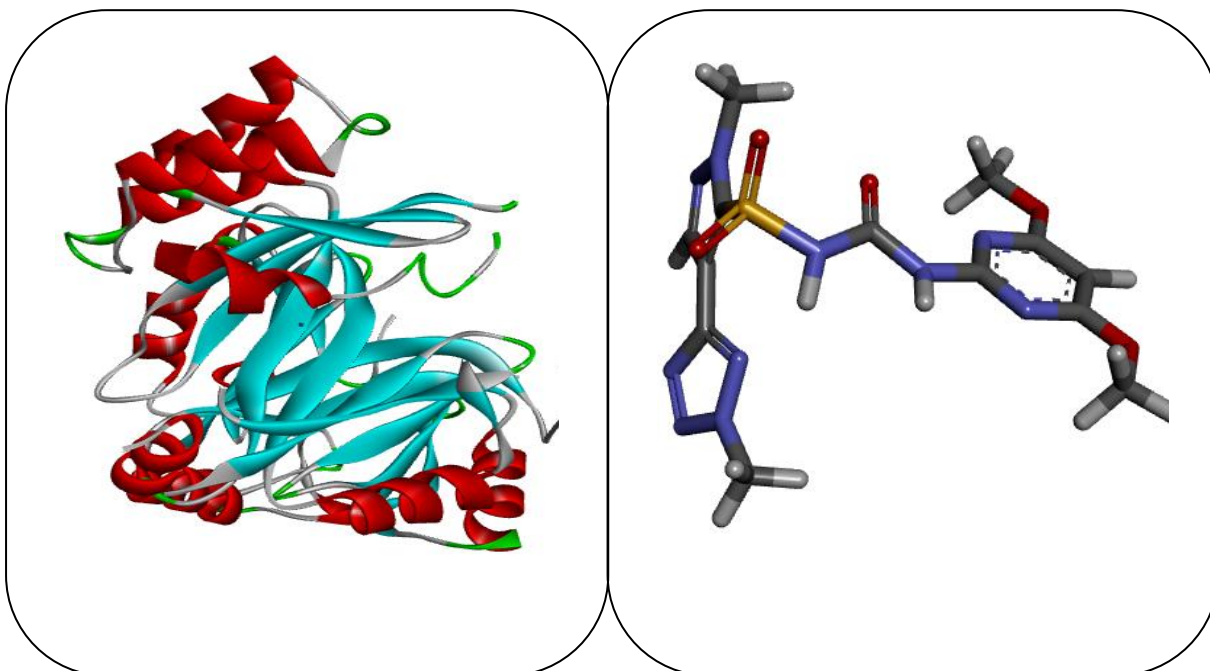


Fig. 1 Prepared crystal structure of 4-HPPD receptor and 3D structure of the prepared Ligand (Compound-2)

Fig. 1 above illustrates the finalized structural preparation of the receptor model for 4-hydroxyphenylpyruvate dioxygenase (HPPD), together with the optimized three-dimensional (3D) configuration of template ligand -2 used in the molecular docking investigation. Earlier to the docking procedure, the protein structure underwent a systematic preparation workflow designed to enhance structural accuracy and ensure reliable computational performance. This preparation stage typically included the confiscation of non-essential molecules, correction of structural inconsistencies, and the adding of hydrogen atoms to better reflect physiologically relevant chemical conditions. Furthermore, a dumpy energy minimization period was executed to relieve steric strain and stabilize the geometry of the binding pocket, thereby improving the overall reliability and reproducibility of the docking simulations.

Similarly, the molecular structure of template ligand -2 was carefully generated and optimized to obtain a stable, low-energy conformation appropriate for interaction analysis. Key refinements, including geometry optimization and proper charge assignment, were conceded out to ensure accurate depiction of the ligand's physicochemical properties and its interface potential with the receptor. Collectively, the prepared receptor and ligand structures presented in Fig. 1 represent docking-ready models that provide a robust structural foundation for assessing binding interfaces and evaluating the inhibitory likelihood of the investigated urea derivatives against the HPPD target enzyme.

3.0 Results and discussion

3.1 Molecular docking results

The molecular docking results summarized in Table 2 demonstrate a wide variation in binding affinities among the designed compounds inside the active point of the 4-hydroxyphenylpyruvate dioxygenase (HPPD) enzyme, as indicated by their MolDock and rerank scoring values. The reference herbicide Mesotrione recorded a MolDock score of -118.689Kcal/mol and served as a standard benchmark for evaluating the relative binding performance of the synthesized derivatives. Several compounds exhibited markedly stronger predicted binding interactions than the reference compound, most notably compounds 2 (-166.256Kcal/mol), 36 (-159.167Kcal/mol), 32 (-154.060Kcal/mol) and 23 (-151.845 Kcal/mol). These substantially lower energy values suggest enhanced binding empathy and improved conformational immovability of these ligands within the enzyme binding pocket. The favorable rerank scores associated with these compounds further reinforce the reliability

and energetic stability of their predicted docking conformations. Conversely, a smaller group of compounds, including compounds 3, 4, and 15, demonstrated comparatively weaker binding energies, emphasizing the significant role of molecular structure and substituent patterns in determining ligand–receptor interaction efficiency.

In addition, the Hydrogen-bond interaction examination delivers a surplus perception into the stabilization mechanisms governing ligand binding. The reference herbicide Mesotrione exhibited moderate hydrogen-bonding interactions with an estimated energy contribution of -4.53Kcal/mol. In contrast, some specially designed compounds, particularly compounds 2 and 21, exhibited stronger hydrogen-bond contributions, which may enhance binding specificity and stability within the catalytic pocket. However, it's important to note that strong binding affinity isn't solely determined by hydrogen bonding. For instance, high-performing compounds like 32 and 36 exposed only moderate hydrogen-bond energies yet achieved inspiring overall docking scores. This suggests that other non-covalent interactions, such as hydrophobic forces and van der Waals attractions, provocatively contribute to stabilizing the ligand-enzyme complexes. From a structural standpoint, certain functional features seem to greatly augment binding performance. The existence of sulfonylurea linkages, heterocyclic ring systems, and electron-withdrawing groups like halogens and trifluoromethyl substituents likely improve molecular fit within the HPPD active site, leading to stronger ligand-receptor interactions. Largely, these intuitions divulge that several of the designed urea derivatives unveil loftier binding characteristics compared to the reference herbicide Mesotrione, underscoring their potential as promising candidates for developing more effective and selective HPPD-targeting herbicides.

Table 2 SMILE Formula, MolDock Score, Rerank Score (Kcal/mol) and H-bond energies of the studies compounds

ID	SMILE Formula	MolDock Score	Rerank Score	H-Bond (Kcal/mol)
1	<chem>COC1=CC(OC)=NC(NC(=O)NS(=O)(=O)N(C)S(C)(=O)=O)=N1</chem>	-121.990	-96.7283	-4.50791
2	<chem>COC1=CC(OC)=NC(NC(=O)NS(=O)(=O)C2=C(C=NN2C)C2=NN(C)N=N2)=N1</chem>	-166.256	-132.485	-10.1816
3	<chem>CON(C)C(=O)NC1=CC=C(Br)C(Cl)=C1</chem>	-89.1095	-70.2069	-1.39856
4	<chem>CN(C)C(=O)NC1=CC=C(C)C(Cl)=C1</chem>	-76.4181	-57.7909	-2.16513
5	<chem>CN(C)C(=O)NC1=CC=C(OC2=CC=C(Cl)C=C2)C=C1</chem>	-110.493	-91.121	-1.96712
6	<chem>COC1=NC(C)=NC(NC(=O)NS(=O)(=O)C2=CC=CC=C2Cl)=N1</chem>	-125.656	-98.1744	-0.66908
7	<chem>COCCOC1=CC=CC=C1S(=O)(=O)NC(=O)NC1=NC(OC)=NC(OC)=N1</chem>	-142.873	-106.644	-2.61426
8	<chem>CC(C)(NC(=O)NCC1=CC=CC=C1Cl)C1=CC=CC=C1</chem>	-104.295	-83.8131	-1.58857
9	<chem>COC1=CC(OC)=NC(NC(=O)NS(=O)(=O)NC2=CC=CC=C2C(=O)C2CC2)=N1</chem>	-147.146	-120.515	-1.45010
10	<chem>CN(C)C(=O)NC1=CC=C(Cl)C(Cl)=C1</chem>	-118.707	-39.8625	-3.23929
11	<chem>CN(C)C(=O)NC1=CC=C(Cl)C(Cl)=C1</chem>	-78.0129	-57.2591	-1.68305
12	<chem>CC1=CC=C(NC(=O)NC(C)(C)C2=CC=CC=C2)C=C1</chem>	-116.049	-95.8651	-2.80193
13	<chem>CCS(=O)(=O)C1=NN=C(S1)N(C)C(=O)NC</chem>	-95.8917	-77.3046	-4.61451
14	<chem>CCOC1=CC=CC=C1OS(=O)(=O)NC(=O)NC1=NC(OC)=CC(OC)=N1</chem>	-125.505	-99.6672	0.00000
15	<chem>CN(C)C(=O)NC1=CC=CC=C1</chem>	-71.2065	-59.6132	-1.19911
16	<chem>COC1=CC(OC)=NC(NC(=O)NS(=O)(=O)C2=NC=CC=C2C(F)(F)F)=N1</chem>	-128.3800	-86.2665	-4.82430
17	<chem>CN(C)C(=O)NC1=CC=CC(=C1)C(F)(F)F</chem>	-88.9776	-61.9224	-2.03066
18	<chem>COC1=CC(OC)=NC(NC(=O)NS(=O)(=O)C2=C(Cl)N=C3C=CC=CN23)=N1</chem>	-146.909	-114.280	-3.74533
19	<chem>COC1=NC(C)=NC(NC(=O)NS(=O)(=O)C2=CC=CC=C2I)=N1</chem>	-128.794	-103.465	-2.42765
20	<chem>CC(C)C1=CC=C(NC(=O)N(C)C)C=C1</chem>	-82.4082	-66.9321	-2.02869
21	<chem>CN(C)C(=O)NC1=NOC(=C1)C(C)(C)C</chem>	-87.8242	-72.2791	-10.0124
22	<chem>CON(C)C(=O)NC1=CC=C(Cl)C(Cl)=C1</chem>	-91.8359	-73.9975	-1.43932
23	<chem>COC1=CC(OC)=NC(NC(=O)NS(=O)(=O)C2=C(C(Cl)=NN2C)C2=NOCC(C)O2)=N1</chem>	-151.845	-88.8134	-2.49322
24	<chem>CNC(=O)N(C)C1=NC2=CC=CC=C2S1</chem>	-91.0200	-72.0683	-2.50000
25	<chem>CN(C(=O)NC(C)(C)C1=CC=CC=C1)C1=CC=CC=C1</chem>	-105.939	-89.7800	-2.50000
26	<chem>CON(C)C(=O)NC1=CC=C(OC2=CC=C3C(OC(C)(CC3(C)C)OC)=C2)C=C1</chem>	-134.701	-108.425	0.00000
27	<chem>CON(C)C(=O)NC1=CC=C(Br)C=C1</chem>	-82.7277	-67.7942	-0.99182
28	<chem>COC1=CC=C(NC(=O)N(C)C)C=C1Cl</chem>	-79.8183	-63.6523	-0.31403
29	<chem>CON(C)C(=O)NC1=CC=C(Cl)C=C1</chem>	-82.8748	-67.8759	-0.91236
30	<chem>CN(C)C(=O)NC1=CC=C(Cl)C=C1</chem>	-75.9703	-63.1544	0.00000
31	<chem>CCCCN(C)C(=O)NC1=CC=C(Cl)C(Cl)=C1</chem>	-102.298	-82.3941	-0.18502
32	<chem>CCCC1=NN2C(C=C1)=NC(Cl)=C2S(=O)(=O)NC(=O)NC1=NC(OC)=CC(OC)=N1</chem>	-154.060	-121.631	-2.60266
33	<chem>COC1=NC(C)=NC(NC(=O)NS(=O)(=O)C2=CC=CC=C2CCC(F)(F)F)=N1</chem>	-143.871	-112.977	-3.51627
34	<chem>CCS(=O)(=O)C1=CC=CC=C1S(=O)(=O)NC(=O)NC1=NC(OC)=CC(OC)=N1</chem>	-133.473	-108.312	-5.86711

35	<chem>CC1CCCCC1NC(=O)NC1=CC=CC=C1</chem>	-102.251	-86.9463	-3.08426
36	<chem>CCS(=O)(=O)C1=C(N2C=CC=CC2=N1)S(=O)(=O)NC(=O)NC1=NC(OC)=CC(OC)=N1</chem>	-159.167	-120.033	-2.50000
37	<chem>CNC(=O)N(C)C1=NN=C(S1)C(C)(C)C</chem>	-95.661	-76.907	-2.00469
38	<chem>CNC(=O)N(C)C1=NN=C(S1)C(F)(F)F</chem>	-91.6859	-70.7656	-2.88920
39	<chem>COC1=NC(C)=NC(NC(=O)NS(=O)(=O)C2=CC=CC=C2OCCCI)=N1</chem>	-131.966	-90.5178	-2.51128
40	<chem>COC1=CC(OC)=NC(NC(=O)NS(=O)(=O)C2=NC=CC=C2OCC(F)(F)F)=N1</chem>	-143.285	-90.4627	-0.19319
41	<chem>COC1=NC(=NC(NC(=O)NS(=O)(=O)C2=CC=CC=C2C(F)(F)F)=N1)C(F)(F)F</chem>	-128.316	-108.814	-1.63361
Standard Herbicide (Mesotrione)		-118.689	-101.442	-4.52561

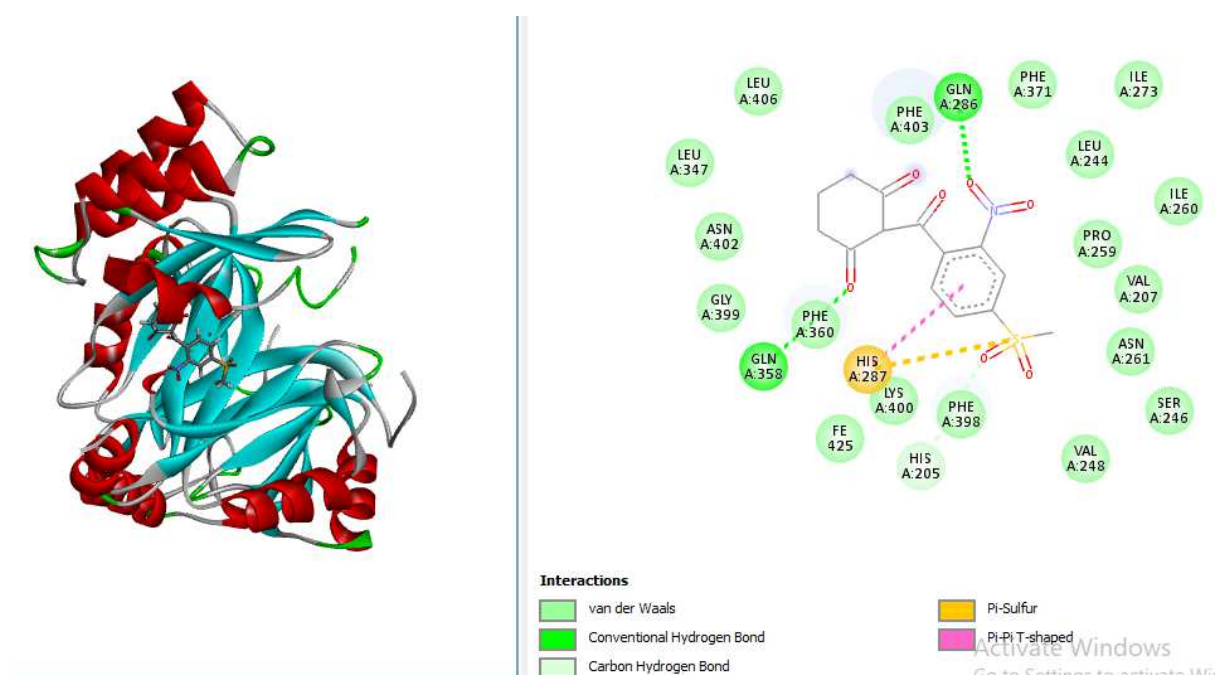


Fig. 2 3D and 2D molecular interaction of the standard mesotrione herbicide with HPPD - 1TFZ receptor binding site

The docking analysis indicates that the reference ligand mesotrione (Fig. 2) is well accommodated within the active point of the 4-hydroxyphenylpyruvate dioxygenase (HPPD) enzyme. The ligand adopts a compact and stable conformation, with its β -triketone moiety strategically positioned toward the catalytic center, which is essential for effective binding. A key interaction involves the formation of a conventional hydrogen bond with GLN286, helping to anchor the ligand securely within the binding pocket. Additionally, nearby residues like GLN358 and ASN261 provide support through scrawnier polar and van der Waals interfaces, creating a favorable binding environment. A defining characteristic of the

mentioned complex is the coordination amongst the ligand and the catalytic Fe^{2+} ion, which is considered crucial for the inhibitory action of β -triketone herbicides against HPPD.

Furthermore, the firmness of the ligand-enzyme complex is bolstered by a network of hydrophobic and aromatic interactions within the binding cavity, enhancing overall binding efficacy. π - π stacking with PHE360, along with hydrophobic contacts involving PHE398, LEU244, and VAL248, helps to firmly position the aromatic ring of the ligand in a nonpolar province of the enzyme. Superfluous influences arise from interfaces such as π -sulfur contact with HIS287 and various van der Waals contacts involving residues like LYS400, PRO259, and SER246, which promote tight packing and structural complementarity. Taken together, these interactions underline the strong binding affinity of mesotrione and reinforce its role as a reliable reference inhibitor, while also emphasizing the importance of metal coordination and balanced hydrophobic interactions in achieving effective HPPD inhibition.

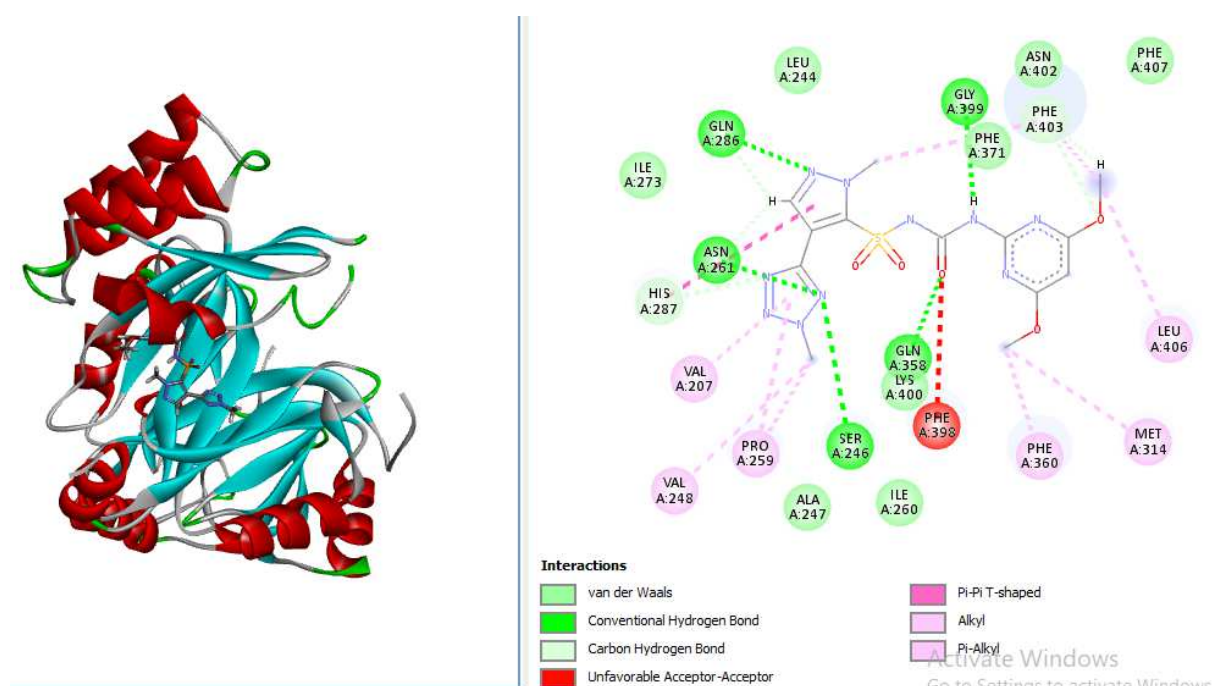


Fig. 2a 3D and 2D molecular interaction of the substituted urea derivative (Ligand -2) with HPPD -1TFZ receptor binding site

Figure 2a demonstrates the binding behavior of the substituted urea derivative, Ligand-2, inside the active point of the 4-hydroxyphenylpyruvate dioxygenase (HPPD) enzyme. The ligand occupies the catalytic cavity in a favorable and well-oriented conformation, allowing its molecular framework to fit effectively among the surrounding amino acid residues. This stable alignment promotes the establishment of multiple intermolecular interactions that collectively enhance the binding affinity of the compound toward the receptor. Notably,

conventional hydrogen-bond interactions involving GLN358, SER246, ASN261, and PHE371 contribute meaningfully to upholding the ligand inside the active point. In addition, several van der Waals interfaces with residues such as ILE273, ALA247, ILE260, LEU244, and GLY399 further reinforce the constancy of the protein-ligand complex, demonstrating a high degree of structural compatibility between the ligand and the enzyme environment.

Furthermore, the stability of the complex is supported by supplementary hydrophobic and aromatic contacts formed within the binding cavity of the enzyme. A π - π T-shaped interactions and alkyl contacts with residues like PHE360, PHE403, and MET314 help to secure the ligand in the hydrophobic region of the pocket and maintain a favorable orientation. Although a slight unfavorable acceptor-acceptor interaction is observed with PHE398, its influence appears negligible when compared to the numerous stabilizing forces present. Overall, the interaction pattern points to strong binding affinity and good structural complementarity, indicating that Ligand-2 is a promising candidate. Its behavior within the active site suggests that substituted urea derivatives could serve as operational scaffolds for emerging as new HPPD inhibitors with performance comparable to established herbicides such as mesotrione.

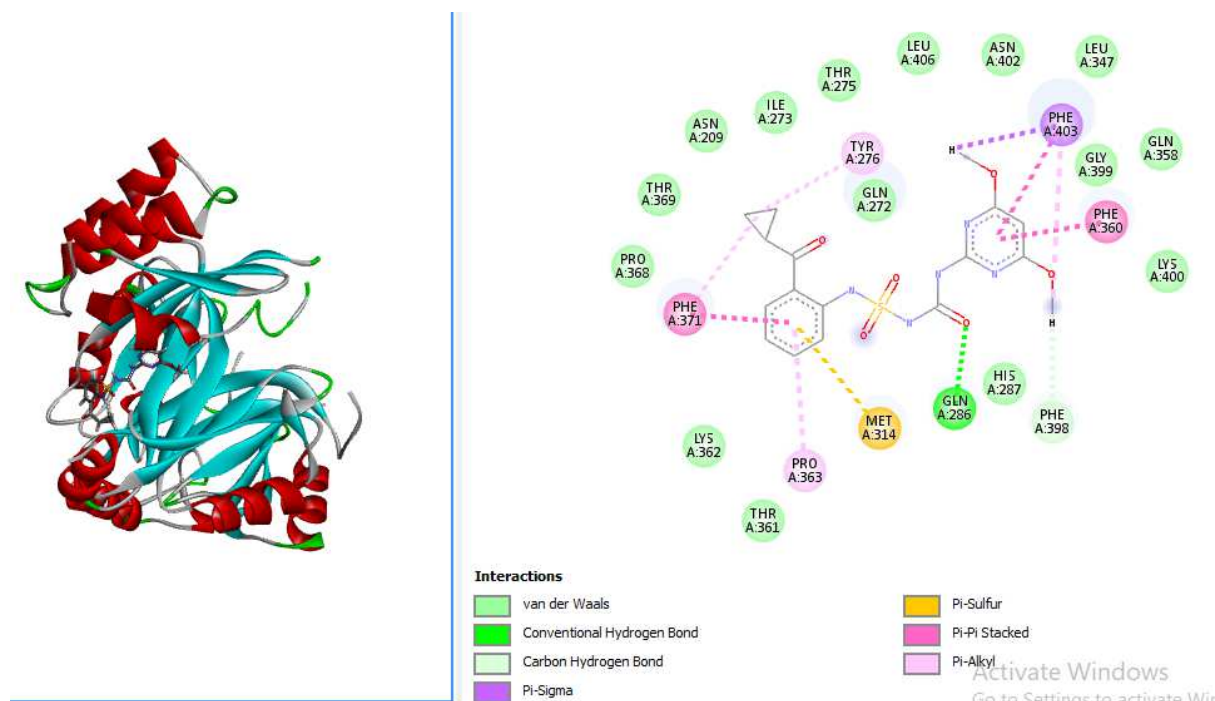


Fig. 2b 3D and 2D molecular interaction of substituted urea derivative (Ligand -9) with HPPD -1TFZ receptor binding site

Fig. 2b depicts the interaction of the substituted urea derivative within the active site of 4-hydroxyphenylpyruvate dioxygenase (HPPD), where the ligand adopts a well-oriented and energetically favorable conformation. It is positioned deep within the enzyme's hydrophobic pocket, suggesting a good steric match between the ligand structure and the surrounding amino acid environment. A key interaction stabilizing the complex is conventional hydrogen bonds with GLN286, which likely theaters a foremost role in securing the ligand within the binding site. In addition, a carbon–hydrogen bond interaction with PHE398 provides further support, helping to maintain the ligand's alignment in the catalytic region.

However, beyond these interactions, the composite is strengthened by a network of hydrophobic and aromatic contacts that enhance overall binding stability. π – π stacking contacts with deposits such as PHE403, PHE360, and PHE371 contribute to efficient packing within the hydrophobic cavity and support favorable electronic interfaces often linked to strong HPPD inhibition. A π –sulfur interaction with MET314 adds another layer of stabilization, while numerous van der Waals acquaintances involving ASN209, THR369, PRO368, TYR276, GLN272, and LYS362 help ensure a tight and complementary fit within the binding pocket. Altogether, these interaction features point to a stable ligand–receptor complex and suggest that the substituted urea scaffold holds considerable promise for the design of effective herbicidal agents, with behavior comparable to well-established inhibitors such as mesotrione.

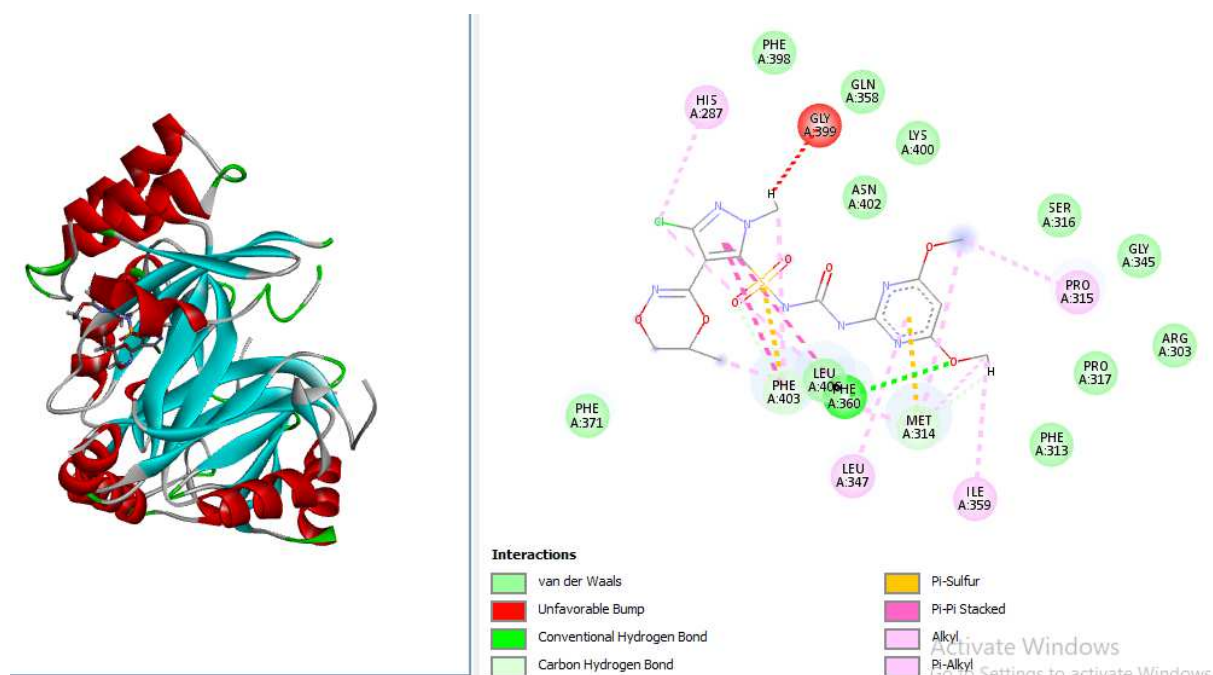


Fig. 2c 3D and 2D molecular interaction of substituted urea derivative (Ligand -23) with HPPD -1TFZ receptor binding site

Fig. 2c shows how the substituted urea derivative occupies the catalytic pocket of 4-hydroxyphenylpyruvate dioxygenase (HPPD). The ligand adopts a compact and stable conformation, fitting neatly within the active site. Its placement in a predominantly hydrophobic region allows nearby interaction with numerous neighboring residues, which helps strengthen the overall binding. A notable interaction is the construction of a conventional hydrogen bond with GLY399, which appears to piece a role in maintaining the ligand's orientation and contributing to the permanence of the complex.

Moreover, additional stabilization arises from a range of hydrophobic and aromatic interactions within the binding cavity. π - π stacking with residues such as PHE403, PHE360, and PHE371 suggests good electronic and structural complementarity among the ligand and the receptor. The actuality of a π -sulfur interaction with MET314 further supports the binding stability, while alkyl and π -alkyl contacts involving LEU347, ILE359, and PRO315 enhance hydrophobic packing. Although a slight steric clash is observed with GLY399, its effect appears minimal compared to the numerous favorable interactions across the binding interface. Overall, the interaction profile indicates strong binding compatibility and highlights the probable of this substituted urea derivative as a auspicious lead for developing HPPD-targeting herbicides, in line with the mechanism of established inhibitors such as mesotrione.

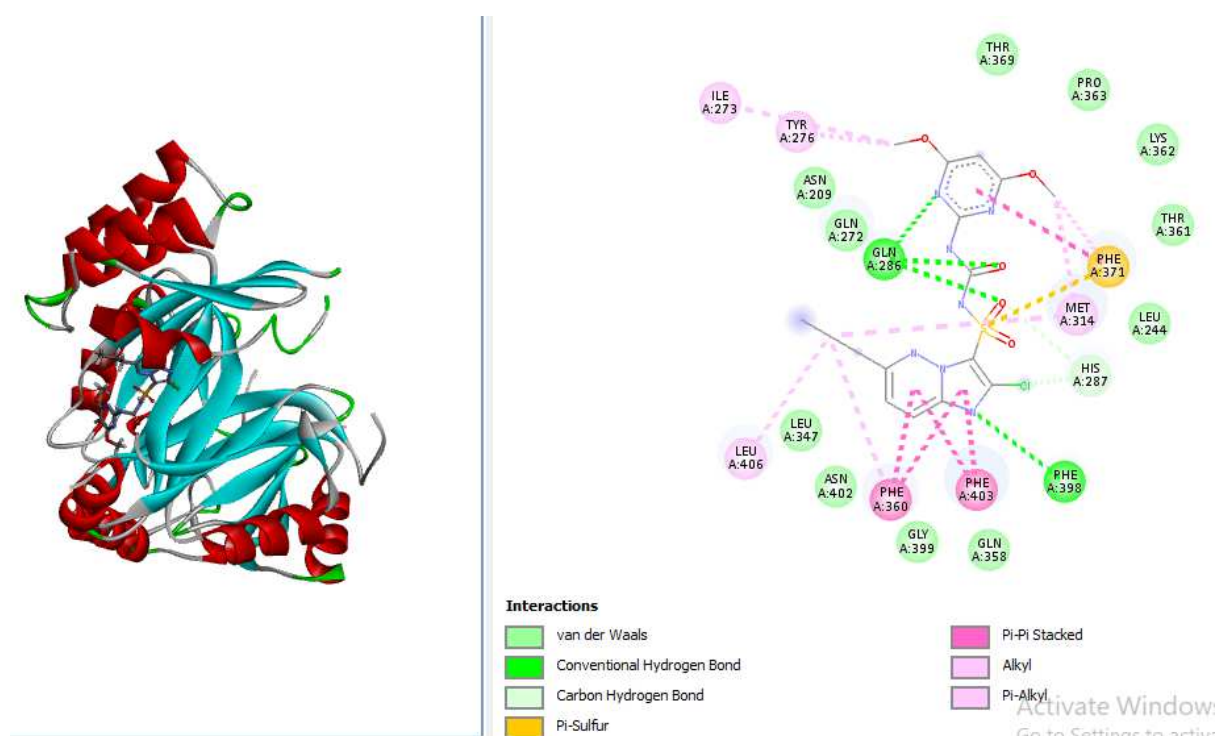
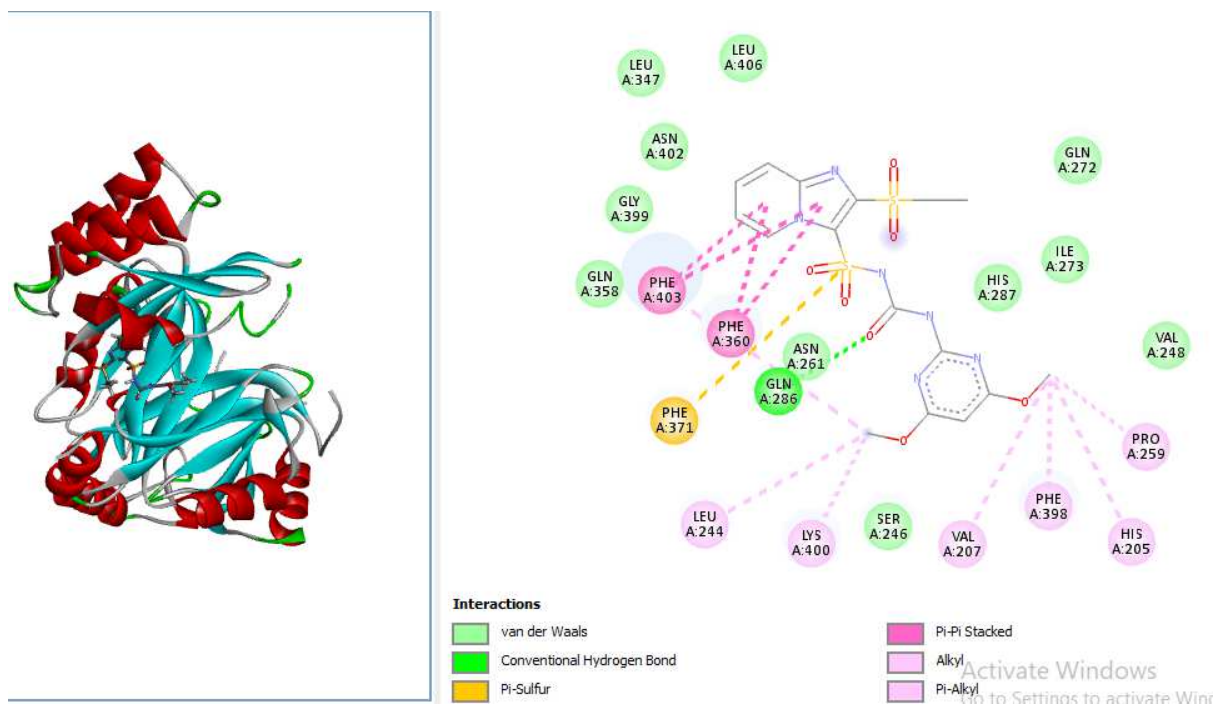


Fig. 2d- 3D and 2D molecular interaction of substituted urea derivative (Ligand -32) with HPPD -1TFZ receptor binding site

Fig. 2d above, outline the docking results for Ligand-32 indicate that the compound is well accommodated within the active site of 4-hydroxyphenylpyruvate dioxygenase (HPPD), where it adopts a stable and energetically favorable conformation. The ligand is positioned deep inside the catalytic pocket, allowing its substituted urea moiety and aromatic rings to align effectively with key residues involved in enzyme inhibition. Conventional hydrogen bonds with GLN286 and ASN209 appear to play a central role in anchoring the ligand within the binding site, helping to maintain the integrity of the ligand–receptor complex. These interactions, together with supporting carbon–hydrogen contacts, underwrite to the specificity and steadiness of binding indoors of the enzyme environment.

In addition to these polar interactions, hydrophobic and aromatic contacts significantly enhance the overall stability of the complex. π – π stacking and alkyl collaborations with deposits such as PHE371, PHE360, PHE403, and LEU244 help to retain the ligand within the nonpolar region of the binding pocket, strengthening its interaction with the receptor. A π –sulfur interaction involving MET314 provides further stabilization, while superfluous van der Waals associates with residues including HIS287, GLY399, and THR361 promote tight packing and structural complementarity. Taken together, these interaction features suggest that Ligand-32 has strong binding affinity and good compatibility with the HPPD active site, supporting its potential as a promising inhibitor and a feasible aspirant for auxiliary progress as a herbicidal agent, with performance comparable to established compounds such as mesotrione.



.Fig. 2e 3D and 2D molecular interaction of substituted urea derivative (Ligand -36) with HPPD -1TFZ receptor binding site

Fig. 2e above, presents the docking profile of Ligand-36 within the active point of 4-hydroxyphenylpyruvate dioxygenase (HPPD). The outcomes show that the compound is well billeted in the catalytic void, adopting a stable and properly aligned conformation. Its substituted urea moiety and aromatic framework are oriented in a way that enables effective interaction with both polar and nonpolar regions of the binding pocket, indicating a balanced and favorable binding mode. Conservative H- bonds with residues such as GLN286 and ASN261 appear to be particularly important, as they help anchor the ligand and maintain its orientation within the active site. Additional carbon-hydrogen interactions further contribute to stabilizing the ligand–protein complex.

Moreover, the binding is further reinforced by a network of hydrophobic and aromatic interactions. π – π stacking with key phenylalanine residues, notably PHE360 and PHE403, helps secure the aromatic rings of the ligand within the hydrophobic region of the enzyme. Other interactions, including π –alkyl and alkyl contacts with PRO259, VAL207, LYS400, and LEU244, enhance hydrophobic packing and improve overall binding stability. Van der Waals contacts with nearby residues such as HIS287, GLN272, ILE273, and GLY399 also support a tight and complementary fit within the binding pocket. Largely, these interactions

recommend that Ligand-36 has strong binding affinity and good structural compatibility with the HPPD active site, underscoring its potential as a auspicious inhibitor and an appropriate entrant for extra optimization as a new herbicidal agent, comparable in function to established compounds like mesotrione.

Generally, the comparative docking results propose that the substituted urea derivatives display binding patterns comparable to those of the reference herbicide mesotrione inside the active point of 4-hydroxyphenylpyruvate dioxygenase (HPPD). Both the standard compound and the designed ligands adopt stable conformations in the catalytic point and engage in key stabilizing interactions. These embrace hydrogen bonding with important residues, as well as extensive hydrophobic and π - π interactions with phenylalanine residues, all of which contribute to strong ligand retention and overall complex stability. Although, mesotrione is characterized by its ability to coordinate directly with the catalytic Fe^{2+} ion, the substituted urea derivatives appear to offset this difference through a rich combination of intermolecular interactions. Their binding is supported by multiple hydrogen bonds, aromatic stacking, and widespread van der Waals connections, which together promote a high degree of structural complementarity within the binding site. Lastly, these outcomes signpost that the substituted urea scaffold holds considerable promise, demonstrating interaction profiles and inhibitory potential that closely approach those of the standard herbicide and supporting its potential as a competitive framework for the proposal of new HPPD-targeting herbicidal agents.

3.2 ADMET Unique Controls of the selected substituted urea derivatives

The predicted ADMET profiles of the selected urea derivatives indicate that their physicochemical properties generally fall inside putative arrays for both herbicide- and drug-like behavior (Table 3). Their molecular weights (401.06 - 475.07g/mol) remain below the typical upper limit of 500g/mol, suggesting that the complexes are of suitable size for efficient transport and effective collaboration with the target enzyme. The numeral of H-bond donors (2-3) is within recommended limits, while a few compounds show slightly higher numbers of hydrogen bond acceptors, leading to minor deviations from ideal criteria. The calculated Log P values (0.799-2.835) reflect moderate lipophilicity, which is favorable for balancing membrane permeability with environmental mobility. In addition, the predicted aqueous solubility (Log S: -2.492 to -5.732) points to moderate solubility, a desirable feature for systemic herbicide action. Although some derivatives exhibit elevated topological polar of

surface area (TPSA >140Å²), this may improve aqueous interactions and target specificity without significantly limiting permeability.

By comparison, the reference herbicide mesotrione shows a well-balanced physicochemical profile, including lower molecular weight, optimal hydrogen bonding capacity, moderate lipophilicity (Log P $\approx$ 1.056), and full compliance with Lipinski's guidelines. Notably, certain derivatives particularly compounds 33 and 39 closely mirror these favorable properties, displaying no Lipinski rule violations and comparable TPSA values. Taken together, the ADMET results suggest that the designed urea derivatives possess acceptable pharmacokinetic and physicochemical characteristics similar to the commercial standard. This supports their prospective as viable HPPD inhibitor candidates and justifies their consideration for supplementary optimization and untried endorsement in the development of next-generation herbicides.

Table 3 Predicted ADMET characteristics properties of the designated ligands

S/no.	Molecular weight	HBA	HBD	Log S	Log P	TPSA	Lipinski rule Violation
	Selected ligands with the uppermost binding potentials						
2	424.10	15.0	2.0	-2.745	1.171	180.93	2
7	413.10	12.0	2.0	-3.857	2.217	150.86	1
9	421.11	11.0	3.0	-5.732	2.097	148.61	2
18	412.04	11.0	2.0	-4.804	2.523	136.81	1
23	475.07	14.0	2.0	-3.947	0.799	168.15	2
32	455.08	12.0	2.0	-4.309	2.824	149.70	2
33	419.09	9.00	2.0	- 4.714	2.835	123.17	0
36	470.07	13.0	2.0	-4.606	1.810	170.95	2
39	401.06	10.0	2.0	-2.492	2.170	132.40	0
40	437.06	11.0	2.0	-3.110	1.932	141.63	2
MST	339.04	8.00	0.0	-3.135	1.056	128.49	0
Lipinski's rule	≤500	≤10	≤5	≤5	Low	≤140Å	

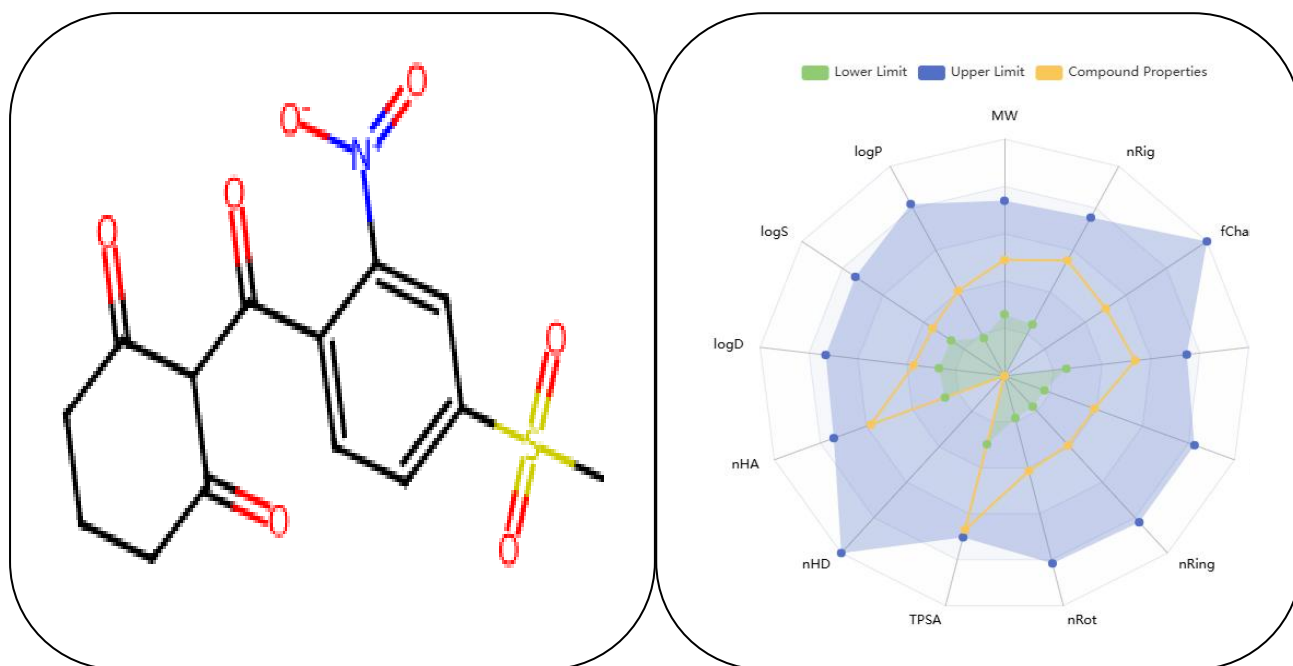


Fig. 3 Pharmacological radar chart of the standard Mesotrione herbicide

The pharmacological radar chart for the reference herbicide mesotrione (Fig. 3) highlights a well-balanced set of physicochemical and pharmacokinetic properties across key molecular descriptors relevant to herbicide performance and environmental behavior. Most of the evaluated parameters such as molecular weight, lipophilicity (logP and logD) aqueous solubility (logS), hydrogen bonding capacity (nHD and nHA), topological polar of surface area (TPSA), and molecular flexibility (nRot) fall within their recommended ranges. Structural features, including ring count, maximum ring size, heteroatom content, fraction of sp^3 carbons, and molecular rigidity, also lie within acceptable boundaries, indicating strong compliance with established herbicide-likeness criteria. Notably, the moderate lipophilicity and balanced polarity of mesotrione support effective absorption, systemic movement within plant tissues, and efficient interaction with the target enzyme. Its solubility profile and structural characteristics further contribute to good bioavailability and controlled environmental behavior. Overall, the radar chart confirms that mesotrione possesses an optimized combination of properties required for effective HPPD inhibition, reinforcing its role as a reliable benchmark for evaluating and guiding the design of new herbicidal candidates in computational studies.

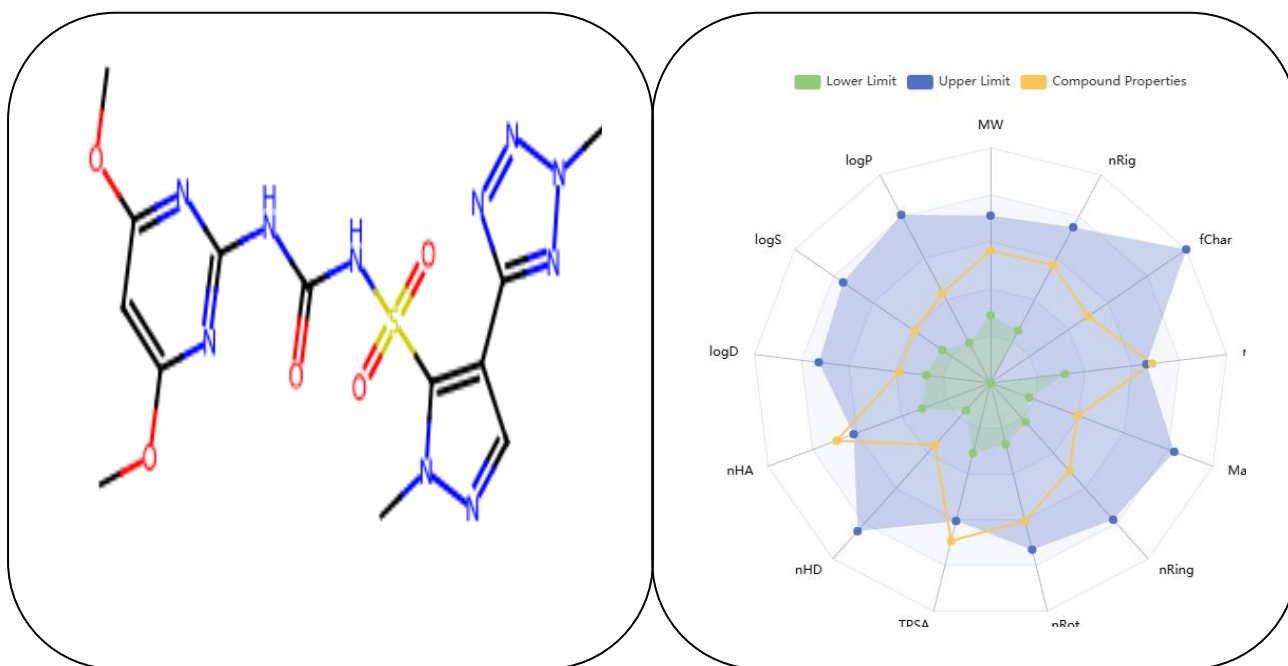


Fig. 3a Pharmacological radar chart of ligand -2

The radar chart presented in Fig. 3a, highlights the pharmacological characteristics of the urea-based compound (Ligand -2), showing a generally well-balanced physicochemical profile that aligns with standard herbicide-likeness guidelines and is comparable to that of Mesotrione. Key properties such as molecular weight, lipophilicity (logP and logD), water solubility (logS), H- bond patrons and acceptors, topological polar of surface area, and molecular flexibility all fall within the recommended ranges for effective herbicidal compounds. Structural features, counting sphere count, ring size, heteroatom presence, fraction of sp^3 carbons, and overall rigidity, also remain within acceptable limits.

Importantly, Ligand 2 demonstrates a moderate level of polarity along with a balanced capacity for hydrogen bonding. These features are critical for facilitating strong interactions within the active site of the 4-hydroxyphenylpyruvate dioxygenase (HPPD) enzyme, while also supporting efficient movement and distribution within plant tissues. Though there are negligible variances in constraints such as polar surface area and hydrogen-bonding characteristics when compared with Mesotrione, these variations remain within tolerable boundaries and are unlikely to negatively affect its pharmacokinetic behavior. Overall, the radar plot suggests that Ligand -2 possesses a well-optimized structural and physicochemical framework, reinforcing its probable as a doable aspirant for extra exploration and development in herbicide research.

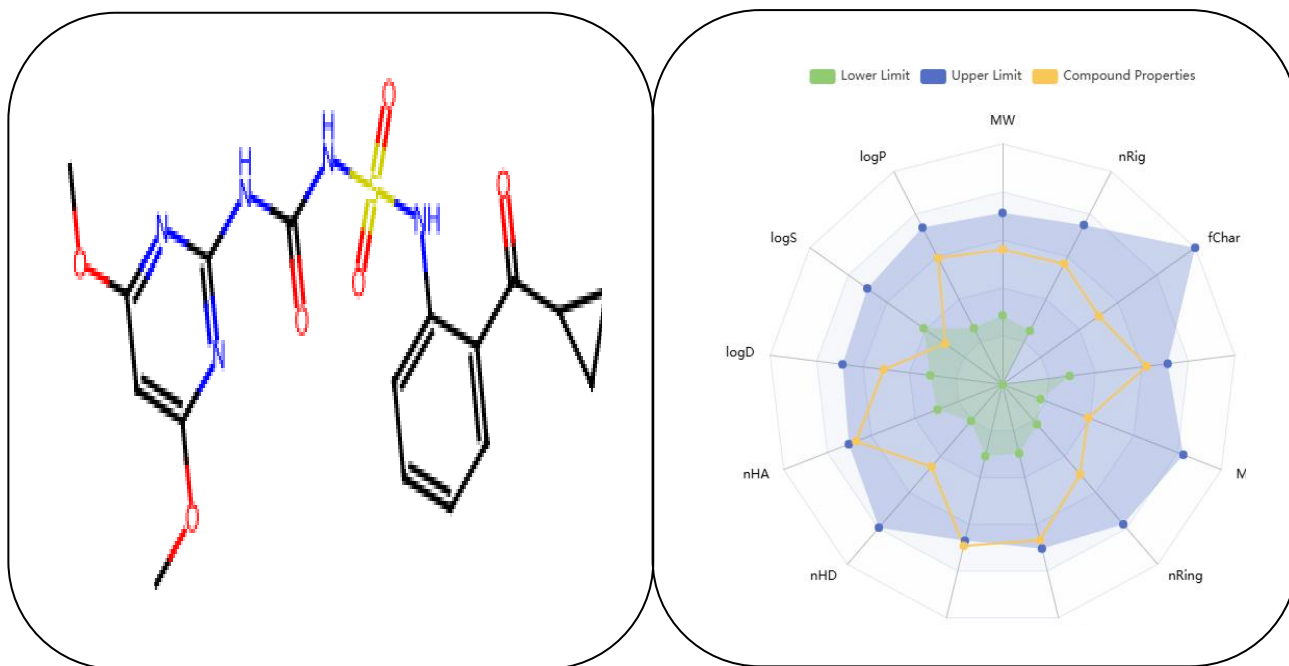


Fig. 3b Pharmacological radar chart of ligand -9

Fig. 3b, illustrates the pharmacological radar chart of the designed urea-based compound, Ligand-9, revealing a well-balanced spread of physicochemical and structural properties within the accepted herbicide-likeness space. Its overall profile closely resembles that of the reference compound, Mesotrione. Important descriptors including molecular weight, lipophilicity (logP and logD), aqueous solubility, H- bond contributors and acceptors, topological polar of surface area, molecular flexibility, and ring-related characteristics—are generally maintained within the recommended limits, suggesting favorable pharmacokinetic behavior and environmental compatibility.

Moreover, the ligand-9 displays moderate polarity and lipophilicity, along with a balanced hydrogen-bonding potential and suitable structural rigidity. These structures are imperative for effective membrane permeability, strong interaction with the biological target, and efficient translocation within plant systems. While slight variations are noted in parameters such as hydrogen bond donor capacity and ring complexity, these differences remain within acceptable ranges and are not expected to significantly impact its biological activity. In summary, the radar chart indicates that Ligand-9 possesses a stable and well-optimized physicochemical framework, supporting its promise as a likely inhibitor of HPPD and a candidate for auxiliary refinement and validation in computational herbicide design studies.

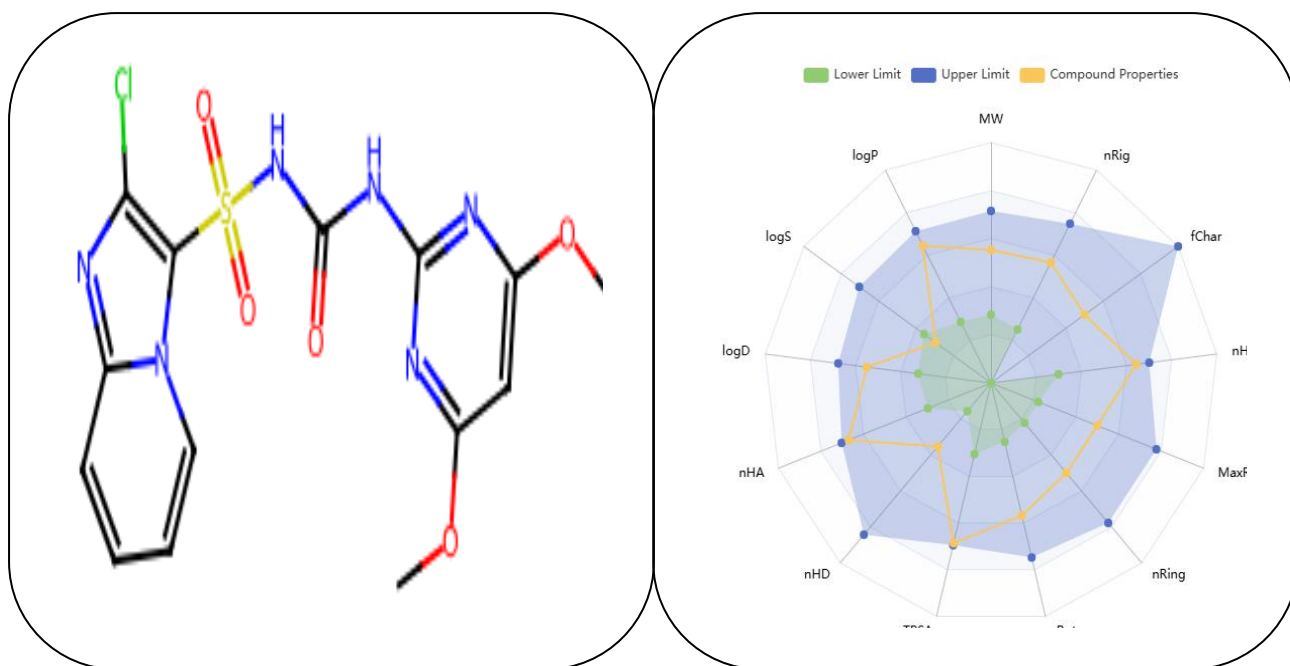


Fig. 3c Pharmacological radar chart of ligand -18

Figure 3c illustrates the radar plot of Ligand-18, showing the extent to which its physicochemical characteristics conform to recognized agrochemical design standards. The orange profile is positioned predominantly indoors the recommended blue region, indicating that the compound possesses properties generally associated with promising herbicidal agents. Its molecular weight remains inside a satisfactory range, which may support effective uptake and translocation within plant tissues. In addition, the lipophilicity-related descriptors, including logP, logD, and logS, reflect a balanced hydrophobic–hydrophilic nature. Such balance is important because it can boost penetration through the plant cuticle while still permitting agreeable distribution inside the plant system. Structurally, Ligand-18 also proves suitable values for ring count, maximum ring size and molecular rigidity, suggesting that the compound maintains a stable yet flexible outline capable of interacting efficiently with the HPPD active point.

Nevertheless, a few parameters appear close to the recommended limits and may slightly influence the biological behavior of the compound. The H- bond donor and acceptor capacities, together with the topological polar of surface area, could affect both receptor interfaces and mobility across plant tissues. Also, the moderately low proportion of sp^3 -hybridized carbons advocates a more planar molecular architecture, which may reduce conformational suppleness during enzyme binding. Despite these minor contemplations,

Ligand-18 generally displays a physicochemical profile that aligns well with the requirements for herbicide development, with no significant deviations observed. These findings support its appropriateness for surplus optimization and assessment as a potential HPPD-targeting herbicidal contender.

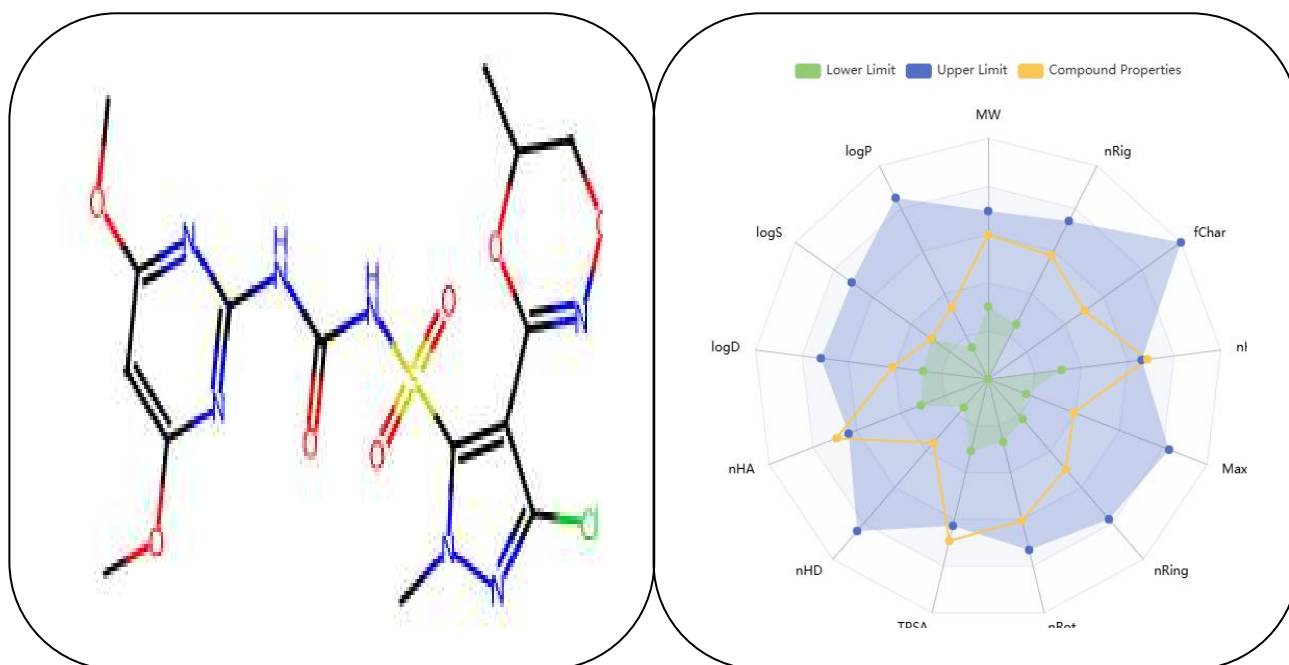


Fig. 3d Pharmacological radar chart of ligand -23

Figure 3d shows the radar chart analysis of Ligand-23, highlighting its physicochemical properties in comparison with standard agrochemical design requirements. Most of the evaluated parameters fall within the recommended region, suggesting that the compound possesses a generally suitable profile for herbicide development. Its molecular weight is indoors the desirable range, which may support efficient absorption and translocation in plants. The lipophilicity value (logP) is moderately high and close to the satisfactory limit, indicating strong hydrophobic characteristics that could improve penetration through the plant cuticle. Meanwhile, the logD value remains in the prime range, reflecting a balanced behavior under physiological conditions. However, the low logS value suggests limited water solubility, which may affect formulation and spray performance and could require further optimization.

The structural characteristics of Ligand-23 also support its potential as an HPPD-targeted herbicide entrant. Parameters such as ring count, ring size, and molecular rigidity indicate a stable structure with sufficient flexibility for collaboration within the HPPD active point. The

lower fraction of sp^3 carbons suggests a more planar molecular arrangement, which may influence binding orientation inside the enzyme pocket. In addition, the H-bond contributor and acceptor values are inside tolerable limits, supporting the possibility of strong ligand-protein exchanges. The moderate topological polar of surface area additionally suggests satisfactory permeability and movement inside plant tissues. Totally, Ligand-23 establishes auspicious physicochemical features for herbicide design, with solubility and lipophilicity steadiness identified as the main areas requiring improvement.

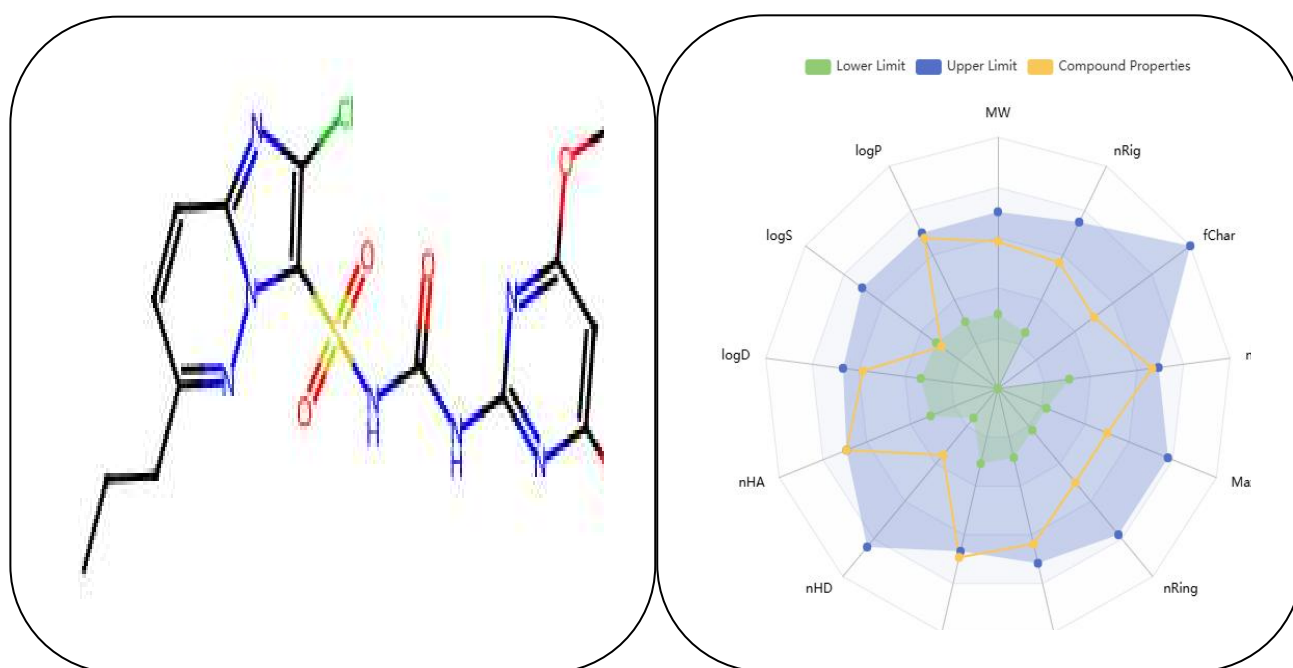


Fig. 3e Pharmacological radar chart of ligand -32

Figure 3e presents the radar chart analysis of Ligand-32, skimpily that most of its physicochemical properties fall indoors the endorsed agrochemical design region. The molecular weight is within the chosen range for herbicidal compounds, which may favor effective absorption and movement indoors of plant tissues. Its lipophilicity profile shows a logP value close to the upper satisfactory limit, portentous moderate hydrophobicity that could augment penetration through the plant cuticle. In addition, the logD value remains within the seemly range, indicating a balanced interface between lipophilicity and ionization under physiological conditions. Nevertheless, the comparatively low logS value points to reduced water solubility, which may stimulates formulation competence and field application performance.

Moreover, structurally, Ligand-32 demonstrates advantageous characteristics for collaboration with the HPPD enzyme target. Structures such as hoop count, ring size, and molecular inflexibility specify a steady molecular outline capable of fitting effectively within the enzyme active point. The restrained fraction of sp^3 carbons advocates partial planarity, which may contribute to binding orientation and interface efficiency. Furthermore, the-bond acceptor and donor profile supports strong interactions with residues in the binding pocket while upholding adequate permeability through plant systems. The moderate topological polar of surface area also indicates good transport potential within plant tissues. Overall, Ligand-32 possesses hopeful physicochemical and structural features consistent with herbicide design principles, though improvements in solubility and flexibility may further enhance its performance as an HPPD-targeted herbicidal candidate.

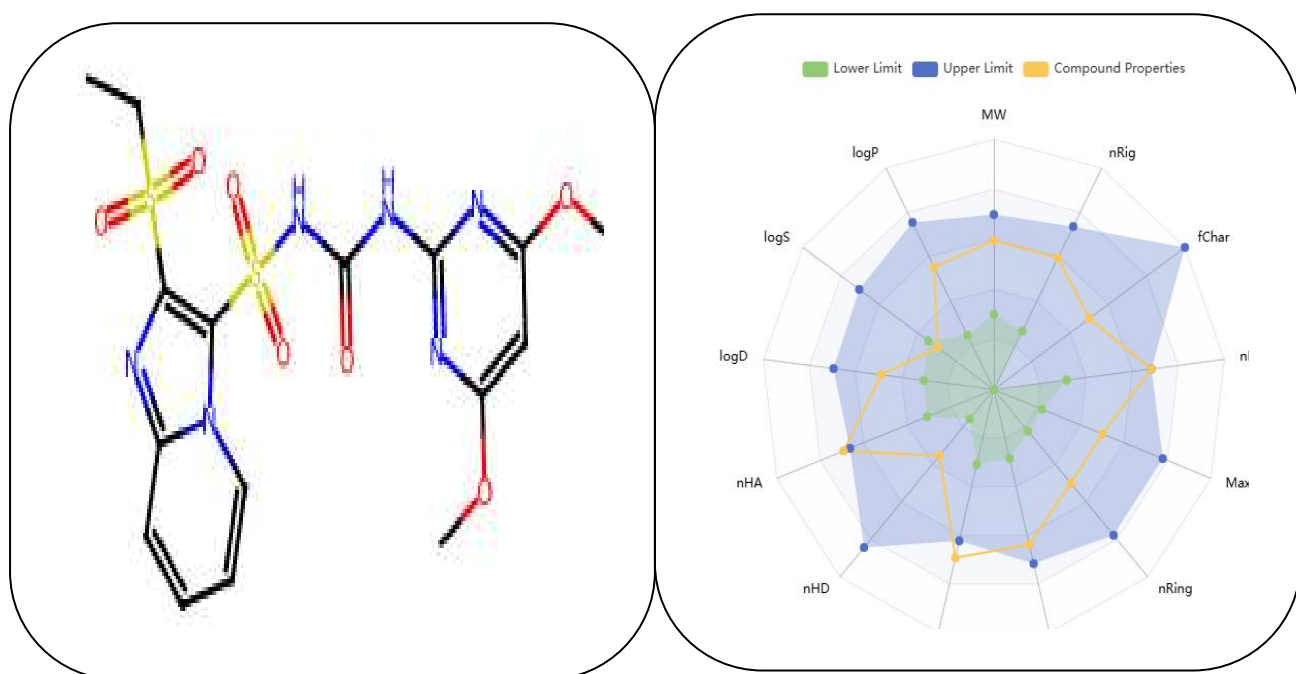


Fig. 3f Pharmacological radar chart of ligand -36

Figure 3f illustrates the radar chart analysis of the urea derivative (Ligand 36), representing that its physicochemical and environmental properties normally fall inside the tolerable range for herbicide development. Important parameters such as molecular weight, lipophilicity ($\log P/\log D$), and aqueous solubility ($\log S$) appear to be well balanced for agrochemical application. Moderate lipophilicity may supplement penetration through the waxy plant cuticle, while adequate solubility can support effective formulation; distribution and movement indoors plant tissues. In addition, the hydrogen-bond donor and acceptor properties, together with the topological polar surface area, indicate a suitable polarity profile

that may errand systemic carriage in plants, which is indispensable for herbicides targeting the HPPD enzyme.

The fundamental characteristics of Ligand 36 further support its budding as an effective herbicidal compound. Features such as rotatable bonds and ring systems propose a balance between molecular stability and flexibility, which could improve interface with the target enzyme while continuing acceptable environmental persistence. The portion of sp^3 carbons and the attendance of heteroatoms also fall indoors ranges commonly connected with agrochemicals that exhibit unswerving field activity and controlled degradation behavior. Inclusive, the radar chart suggests that Ligand 36 enjoys physicochemical properties unfailing with modern herbicide design principles, supportive it's likelihood as a encouraging HPPD-targeted herbicide candidate.

The comparative evaluation of the radar charts in Fig. 3a-3f in contradiction of the reference herbicide Mesotrione shows that the designated urea derivatives generally satisfy the important physicochemical requirements for effective herbicidal activity. Most of the compounds parade an acceptable ranges for molecular weight, lipophilicity, aqueous solubility, H-bonding capacity, topological polar of surface area and molecular flexibility. These comparisons submit that the derivatives possess well-adjusted polarity, permeability, and environmental compatibility comparable to those associated with the established performance of Mesotrione as a systemic HPPD inhibitor. Ligands 2 and 9 unveil properties that are predominantly close to the reference compound, chiefly in terms of polarity and hydrogen-bonding behavior, indicating their potential for an effectual plant uptake and target interaction.

However, some variations among the compounds, divulge areas that may require additional optimization. Ligands 18 and 23 show somewhat sophisticated lipophilicity and lower solubility, characteristics that may progress dissemination through plant surfaces but could also create formulation defies. Ligand 32 demonstrates a stable structural profile similar to the reference herbicide, though its reduced aqueous solubility may frontier formulation competence to some extent. In contrast, Ligand 36 offerings a more balanced distribution of physicochemical descriptors, supporting operational movement inside plant tissues while preserving acceptable environmental properties. Overall, the radar chart comparison designates that the urea derivatives share many positive characteristics with Mesotrione, with the main modifications linking to lipophilicity, solubility and structural flexibility rather than

biological potential. These conclusions support the aptness of the compounds as auspicious entrants for additional herbicide development and optimization.

Table 4 Toxicity studies of the selected urea derivatives with the uppermost Gibb's energy

Toxicity evaluation parameters							
ID	Carcinogenicity	Skin Sensitization	Eye Irritation	Respiratory failure	Human Hepatotoxicity	Hematotoxicity	AMES toxicity
2	NO	NO	NO	NO	YES	YES	NO
7	NO	NO	NO	NO	YES	YES	NO
9	NO	NO	NO	NO	YES	YES	NO
18	NO	NO	NO	NO	YES	YES	NO
23	NO	NO	NO	NO	YES	YES	NO
32	NO	NO	NO	NO	YES	YES	NO
33	NO	NO	NO	NO	YES	YES	NO
36	NO	NO	NO	NO	YES	YES	NO
39	NO	NO	NO	NO	YES	YES	NO
40	NO	NO	NO	NO	YES	YES	NO
Mesotrione	YES	YES	NO	YES	YES	YES	YES

Hint: Extrapolation probability values are distributed into six symbols: **0-0.1 (---)**, **0.1-0.3 (--)**, **0.3-0.5 (-)**, **0.5-0.7 (+)**, **0.7-0.9 (++)**, and **0.9-1.0 (+++)**.

The toxicity data summarized in Table 4 above indicate a generally favorable safety profile for the selected urea derivatives when compared with the reference herbicide Mesotrione. All evaluated compounds (2, 7, 9, 18, 23, 32, 33, 36, 39 and 40) were predicted to be non-carcinogenic and showed no indications of skin sensitization, eye irritation, or respiratory toxicity. These results point to a potentially safer profile in terms of both environmental exposure and occupational handling. In contrast, Mesotrione is associated with positive predictions for several toxicity endpoints, including carcinogenicity, skin sensitization, respiratory toxicity, and mutagenicity (AMES), suggesting possible health and ecological risks. Although both the designed compounds and the reference herbicide show indications of human hepatotoxicity and hematotoxicity, the absence of AMES-related mutagenicity in the urea derivatives is particularly noteworthy, as it implies a reduced potential for genetic future damage. Inclusively, these discoveries advocate that the newly designed urea-based compounds offer an improved toxicity profile relative to Mesotrione. This enhanced safety outlook supports their promise as alternative herbicidal candidates with potentially lower adverse effects on human health and the environment.

3.3 MD simulations analysis

Molecular dynamics (MD) simulations were employed to investigate the dynamic stability and interaction behavior of the selected urea-based compound (Compound 2) in comparison with the reference herbicide Mesotrione against the HPPD target protein (1TFZ). In contrast to molecular docking, which provides a static binding orientation, MD simulation enables continuous monitoring of protein–ligand interactions under simulated physiological conditions over time. To obtain a widespread thoughtful of the complexes' behavior throughout the 100 ns simulation, essential parameters such as RMSD, RMSF, SASA, radius of gyration (Rg), and hydrogen bonding patterns were evaluated to determine their conformational stability, structural compactness, residue flexibility, and binding persistence within the active site of the receptor.

3.3.1 RMSD

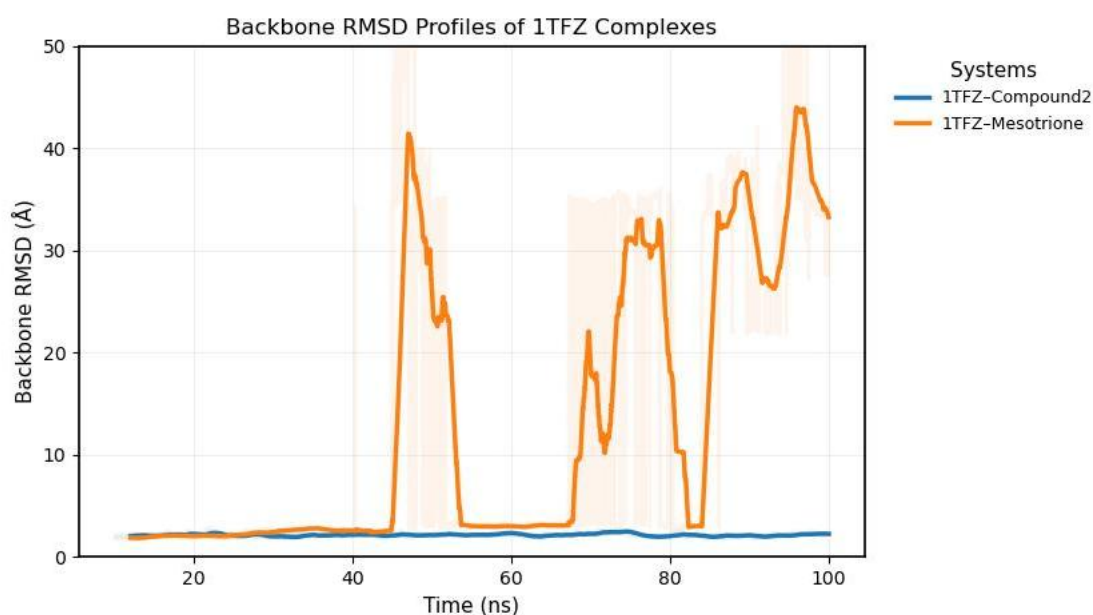


Fig. 4 Root Mean Square of Deviation (RMSD) analysis

Fig. 4 above demonstrate the RMSD analysis of the 1TFZ-Compound 2 complex which revealed an exceedingly stable trajectory through the molecular dynamics simulation, with deviations steadily maintained indoors a narrow range of approximately 2.0-3.0Å. This stability suggests that the urea derivative remained firmly accommodated within the active site of the receptor while preserving the structural integrity of the protein during the

simulation period. The small fluctuations observed are typical of normal protein–ligand adjustments during equilibration and do not indicate structural instability. Overall, the low and consistent RMSD values demonstrate strong binding persistence, conformational stability, and the formation of a well-equilibrated protein–ligand complex.

In contrast, the 1TFZ-Mesotrione complex showed substantial instability, particularly after approximately 45ns, where RMSD values increased sharply and exceeded 40Å at several points. Additional fluctuations observed between 68-85 ns and near the end of the simulation further indicate major conformational changes and disruption of structural equilibrium within the complex. These elevated deviations suggest weaker binding interactions and reduced stability of the receptor environment in the presence of Mesotrione. Comparative analysis therefore indicates that Compound -2 exhibits significantly greater dynamic stability and stronger structural compatibility with the 1TFZ protein than the reference herbicide, highlighting the potential of the urea scaffold as a promising framework for the development of improved HPPD-targeted herbicidal agents.

3.3.2. RMSF

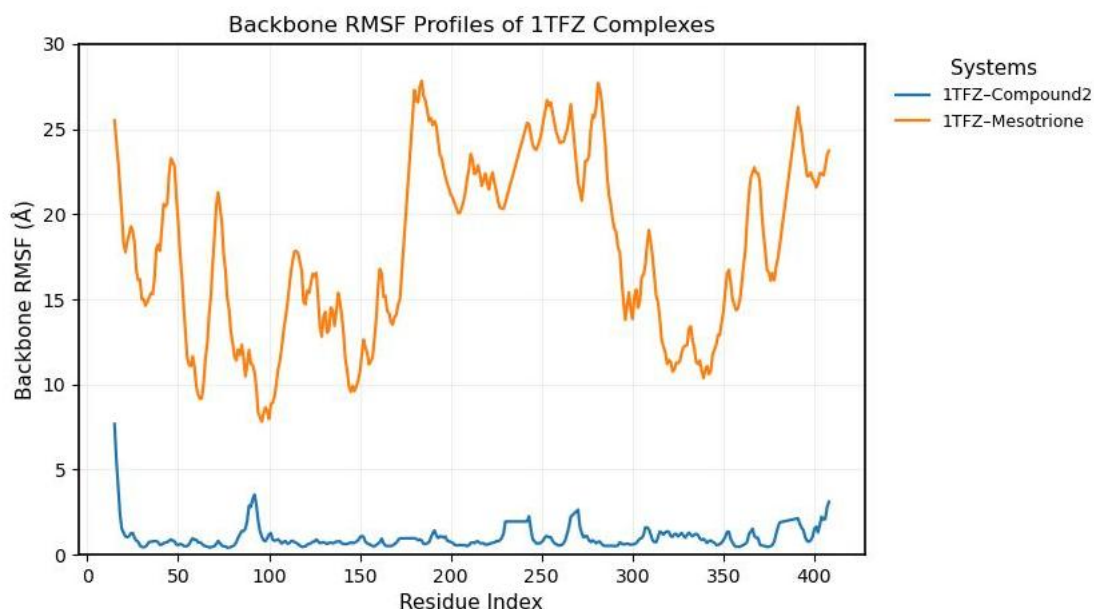


Fig. 5 Root Mean Square of Fluctuation (RMSF) Analysis

Fig. 5 above depicts the RMSF analysis of the 1TFZ protein complexes which provided meticulous awareness into residue-level flexibility and conformational dynamics during the

100ns molecular dynamics simulation. The 1TFZ -Compound 2 complex exhibited consistently low RMSF values across most residue regions, with fluctuations remaining predominantly below 2Å except for a few localized peaks associated with naturally flexible loop or terminal regions. This stable fluctuation profile indicates that the selected urea derivative effectively restricted residue mobility and preserved the structural rigidity of the protein backbone throughout the simulation. The reduced flexibility observed for Compound -2 suggests enhanced conformational equilibrium and stable accommodation of the ligand within the active site, thereby supporting the overall structural integrity of the receptor system during ligand binding.

In discrepancy, the 1TFZ- mesotrione complex displayed substantially elevated RMSF values, particularly across residue regions 170-290 and near the terminal domains, where fluctuations frequently ranged between approximately 10-28Å. These pronounced oscillations indicate excessive residue mobility and significant conformational perturbations within the protein structure, reflecting weaker stabilization of the receptor environment upon Mesotrione binding. Relative evaluation therefore demonstrates that Compound -2 possesses markedly superior residue stabilization and dynamic compatibility with the 1TFZ target protein relative to the standard herbicide. The enhanced rigidity and abridged backbone suppleness allied with the urea-based scaffold strongly support its improved binding stability and structural resilience, highlighting its promise as a potential lead framework for the development of next-generation HPPD-targeting herbicidal agents.

3.3.3. SASA

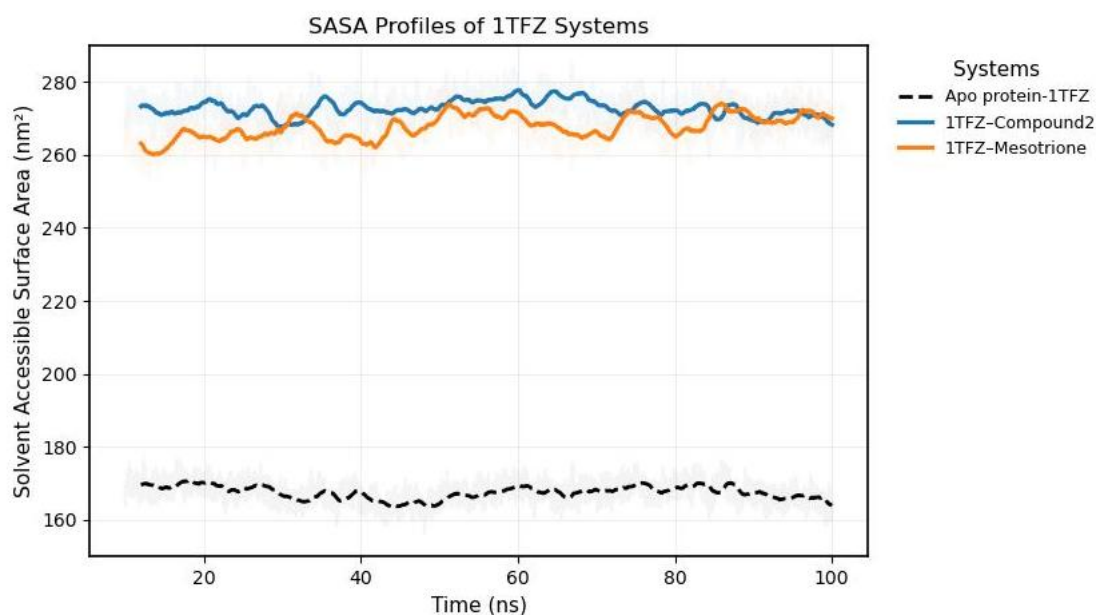


Fig. 6 Solvent Accessible Surface Area (SASA) Analysis

The solvent accessible surface area (SASA) analysis offered in Fig. 6 above provided unevenly cherished intuitions into the conformational stability and solvent exposure behavior of the 1TFZ protein complexes throughout the 100ns molecular dynamics simulation. Both ligand-bound systems exhibited higher SASA values relative to the apo protein, indicating that ligand binding altered the solvent accessibility pattern of the receptor and promoted a relatively expanded conformational state. However, the 1TFZ-Compound 2 complex displayed a notably more stable and controlled SASA trajectory, with values consistently fluctuating within a constricted array of approximately 268-278nm². The smooth and equilibrated profile observed for Compound -2 suggests that the selected urea derivative effectively maintained protein compactness and minimized excessive solvent exposure during the simulation. The limited fluctuations further indicate stable folding behavior and persistent accommodation of the ligand within the active site without inducing major structural perturbations in the receptor framework.

In dissimilarity, the 1TFZ- mesotrione complex exhibited comparatively greater oscillatory behavior throughout the simulation period, reflecting subtle conformational rearrangements and reduced structural compactness relative to the urea-based scaffold. Although the fluctuations were not excessively large, the repeated variations in SASA values suggest

weaker stabilization of the protein environment upon Mesotrione binding. Comparative evaluation therefore demonstrates that Compound -2 possesses enhanced conformational control and improved dynamic stability against the 1TFZ target protein. These discoveries are also unfailing with the earlier RMSD and RMSF analyses, collectively supporting the superior structural resilience and binding compatibility of the nominated urea derivative. Overall, the SASA results reinforce the probable of Compound -2 as a hopeful HPPD inhibitory scaffold for the rational design and development of more stable and effective herbicidal agents.

3.3.4. Radius of Gyration (Rg.)

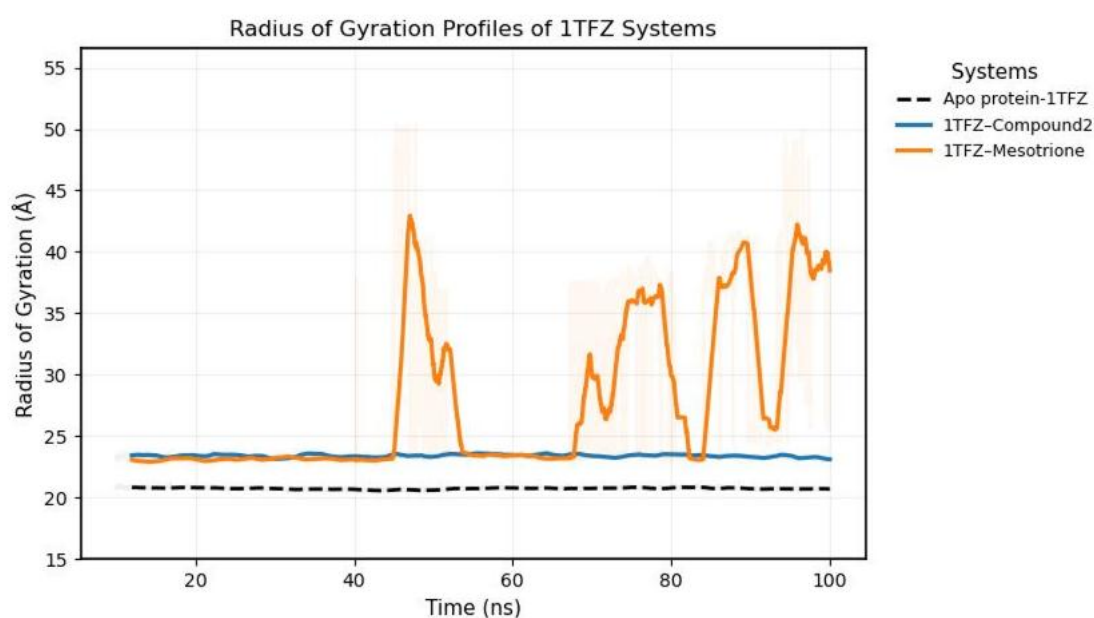


Fig. 7 Radius of Gyration (Rg) Analysis

Fig. 7 above displays the radius of gyration (Rg) analysis of the 1TFZ systems which provided imperative perceptions into the conformational compactness and folding stability of the protein during the 100ns molecular dynamics simulation. The 1TFZ-Compound 2 complex exhibited a highly stable Rg profile throughout the simulation trajectory, maintaining values indoors a tapered assortment of approximately 23-24Å with only minimal fluctuations. This regular comportment specifies that the selected urea derivative effectively preserved the structural compactness and overall integrity of the protein building during ligand binding. The absence of significant deviations further suggests stable accommodation of Compound -2 within the active site, without inducing major conformational disturbances

in the receptor framework. The observed Rg stability strongly complements the earlier RMSD, RMSF, and SASA findings, collectively confirming the enhanced dynamic equilibrium and structural resilience of the protein-ligand complex.

Conversely, the 1TFZ- mesotrione complex displayed pronounced conformational instability during the simulation period, particularly after approximately 45ns, where the Rg values increased markedly beyond 40Å at several intervals. These substantial fluctuations indicate repeated structural expansion and loss of protein compactness, suggesting significant conformational rearrangements within the receptor system upon Mesotrione binding. The persistent oscillatory behavior observed throughout the trajectory reflects weaker stabilization of the protein environment and reduced control over folding dynamics relative to Compound -2. Comparative evaluation therefore demonstrates that the selected urea scaffold possesses superior conformational stability, stronger structural compactness, and improved dynamic compatibility with the HPPD target protein. Cooperatively, these findings further support the potential of Compound -2 as a promising lead scaffold for the rational development of next-generation herbicidal agents with enhanced binding stability and inhibitory efficiency.

3.3.5. Hydrogen bond

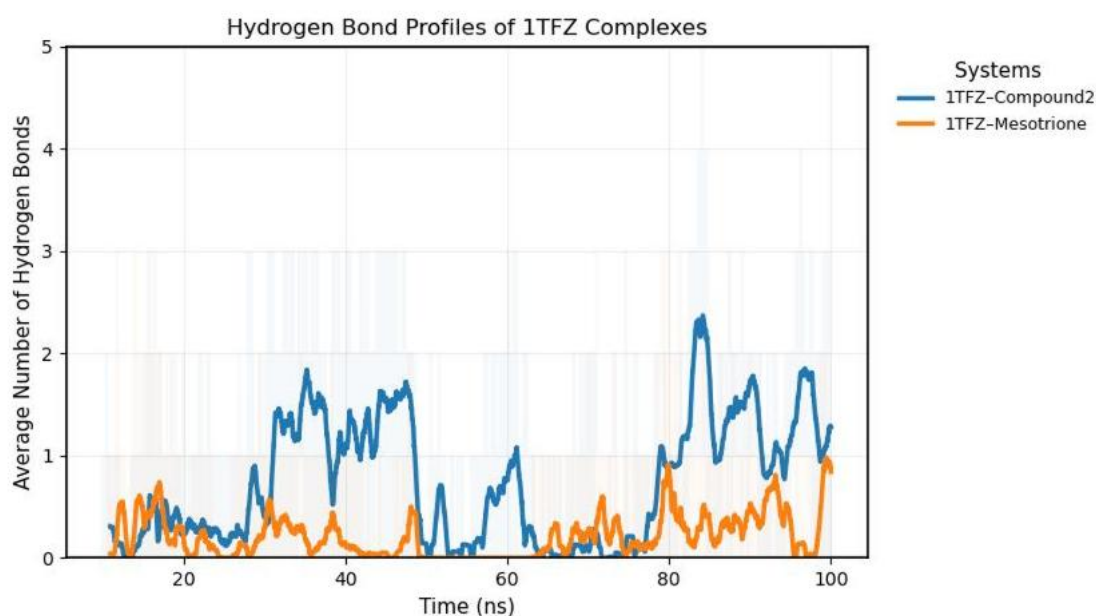


Fig. 8 Hydrogen Bond Behavior of 1TFZ complexes (Compound-2 & Mesotrione)

Hydrogen bond analysis of the 1TFZ complexes over the 100ns molecular dynamics simulation revealed notable differences in interaction stability between the selected urea

derivative (Compound -2) and the standard herbicide Mesotrione as presented in Fig. 8. The hydrogen bonding theatres a vital role in stabilizing protein–ligand complexes by enhancing intermolecular affinity, maintaining active-site orientation, and promoting long-term interaction persistence during simulation. The 1TFZ-Compound 2 complex exhibited a consistently stronger and more sustained hydrogen bonding profile throughout the simulation trajectory, maintaining approximately 1-2 hydrogen bonds over extended periods, with transient increases beyond two hydrogen bonds observed around 80-90ns. Despite minor fluctuations, the interaction network remained stable and persistent, indicating effective accommodation of the ligand within the active site and strong conformational adaptation of the protein–ligand system. These conclusions compare well with the earlier RMSD, RMSF, SASA, and radius of gyration analyses, which collectively demonstrated enhanced structural firmness and trimness of the Compound -2 complex.

In distinction, the 1TFZ- mesotrione complex displayed comparatively weak and intermittent hydrogen bond interactions, with most of the simulation trajectory remaining below one hydrogen bond on average. The irregular and short-lived interaction pattern suggests poor interaction persistence and reduced stabilization within the binding cavity, which may account for the pronounced conformational fluctuations previously observed in the RMSD and Rg analyses. Comparative evaluation therefore indicates that Compound -2 possesses superior interaction durability, stronger binding retention, and improved dynamic compatibility with the 1TFZ target protein relative to Mesotrione. The enhanced hydrogen bonding capacity of the urea-based scaffold likely contributed to the improved structural rigidity and conformational equilibrium of the complex, thereby underlining its impending as a hopeful lead candidate for the rational design and development of next-generation HPPD-targeting herbicidal agents.

In overall summary, the molecular dynamics simulation findings demonstrated that the selected urea derivative (Compound -2) exhibited markedly superior stability and binding performance against the 1TFZ target protein compared with the standard herbicide Mesotrione. Compound -2 maintained consistently squat RMSD and RMSF values, signifying greater structural stability, reduced residue flexibility, and strong conformational integrity throughout the 100 ns simulation period. The ligand also displayed stable SASA and radius of gyration profiles, suggesting improved protein compactness and minimal conformational disruption during binding. In addition, the urea derivative formed more

persistent and stable hydrogen bond interactions within the active site, which further contributed to its prolonged binding retention and overall dynamic stability. In contrast, Mesotrione showed pronounced structural fluctuations, higher residue mobility, repeated conformational expansion, and weaker hydrogen bond persistence, reflecting reduced stability within the protein environment. Cooperatively, these outcomes signpost that Compound -2 possesses stronger binding compatibility, greater conformational resilience, and improved structural stabilization of the 1TFZ protein, emphasizing its likelihood as a auspicious lead scaffold for the development of more effective HPPD-targeting herbicidal agents.

4. Conclusion

In conclusion, the present study demonstrates the significant potential of substituted urea derivatives as promising next-generation HPPD-targeting herbicidal agents for sustainable weed management. Through an integrated computational strategy involving molecular docking, physicochemical profiling, ADMET prediction, toxicity assessment and molecular dynamics simulation, in which several designed compounds exhibited superior interaction characteristics and enhanced stability relative to the commercial herbicide Mesotrione. Among the evaluated derivatives, Compound -2 consistently emerged as the most promising candidate, displaying the strongest binding affinity, favorable intermolecular interactions, balanced agrochemical properties, improved predicted safety profile and remarkable conformational stability within the HPPD active site throughout the 100ns simulation period. The improved performance of the nominated composites was strongly associated with key structural features, including sulfonylurea functionalities, heterocyclic frameworks and electron-withdrawing substituents, which collectively improved ligand-protein complementarity and interaction persistence. Importantly, the combined docking and molecular dynamics findings revealed that Compound -2 maintained superior structural integrity, reduced residue fluctuations, stable compactness and persistent hydrogen bond interactions compared with Mesotrione, indicating stronger target engagement and improved dynamic compatibility with the 1TFZ protein. Furthermore, the favorable ADMET and toxicity predictions suggest that the designed urea derivatives may provide safer and more environmentally compatible alternatives to existing commercial herbicides. Jointly, these findings establish the substituted urea scaffold as a valuable platform for the rational design of novel HPPD inhibitors and provide a strong computational sustenance for future experimental validation, optimization and agrochemical development. The study therefore

contributes meaningful insight toward the discovery of effective and environmentally sustainable herbicidal agents capable of addressing the growing global challenge of herbicide resistance.

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Human Ethics and Consent to Participate:

Not applicable

Conflicts of interest/Competing interests:

The authors declare no competing interests.

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Authors' Contributions:

- ✓ Saidu Tukur and Zakari Ya'u Ibrahim - Wrote, edited and compiled the main manuscript text.
- ✓ Gideon Adamu Shallangwa and Adamu Uzairu - Supervised and provide all the necessary software's for the research Project.
- ✓ Muhammad Tukur Ibrahim - Carried out molecular docking analysis and interpreted the result.
- ✓ Gbolahan Oladipupo Oduselu - Conducted the MD Simulation analysis and interpreted the result.
- ✓ Bitrus Dawi TARFA - Prepared all Figures and Tables.
- ✓ All authors reviewed the final edited manuscript before submission.

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