Synthesis, crystal structure, hirshfeld surface analysis, molecular docking and molecular dynamics studies of novel olanzapinium 2,5-dihydroxybenzoate as potential and active antipsychotic compound

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ABSTRACT

The antipsychotic drug Olanzapine was crystallized with aromatic acid, 2,5-dihydroxybenzoic acid in isopropyl alcohol by slow evaporation which led to the formation of olanzapinium 2,5-dihydroxybenzoate crystalline salt. The structure of the compound was characterized by 1H-NMR, 13C-NMR, and single-crystal X-ray diffraction analysis. The Hirshfeld analyses were performed to quantify the order and nature of intermolecular interactions in the crystal network. Employing computational approaches, the compound was tested for its affinity against antipsychotic activity by molecular docking and molecular dynamic simulation to attest the conformational stability over time step of 100 ns. Besides, bioactivity and ADMET properties were also predicted to ratify the result. The compound asserted neither carcinogenic nor mutagenic activity and has high oral bioavailability. Hence, this synthesized novel compound Olanzapinium 2,5-dihydroxybenzoate recognized in the study possesses high potential as an effective antipsychotic compound, and can further be examined for its efficiency by in vivo studies. The synthesized compound was submitted to NCBI PubChem database using accession substance ID: 441329256. The crystal structure was submitted to CCDC (Cambridge Crystallographic Data Centre) with submission ID: 2010899.

ARTICLE HISTORY

Received 14 February 2022
Accepted 17 March 2022

KEYWORDS

Olanzapinium 2,5-dihydroxybenzoate; X-ray structures; Co-crystal; Hirshfeld surface; molecular docking; molecular dynamics simulation; ADMET property prediction

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1. Introduction

Antipsychotic medication, also known as neuroleptics is a class of psychotropics primarily manoeuvred for short- or long-term treatments of psychotic disorders (bipolar depression, delusions, paranoia, schizophrenia, etc.). Studies have revealed that Olanzapine, a novel atypical antipsychotic drug elicits a high response with low dosage on the patients suffering from psychotic ailments. It consists of a thieno-benzodiazepinyl structure and exhibits a similar *in vitro* binding profile with an atypical anti-psychotic agent; an FDA-approved drug, Clozapine [1,2]. According to the Biopharmaceutical Classification System (BCS), Olanzapine belongs to class II (low solubility, high permeability) cadre, and is highly effective in positive, negative, and cognitive symptoms for acute and relapsing schizophrenics. This drug is marketed under the trademark, Zyprexa by Eli Lilly and Company [3,4].

Pharmacokinetic studies have indoctrinated that the efficacy of Olanzapine is mediated through the combined effect of dopamine and serotonin type 2 form but in an antagonistic manner. Olanzapine shows a selective monoaminergic antagonistic property with augmented binding affinity to serotonin 5HT_{2A/2C}, dopamine D_{14}, muscarinic M_{1-5}, and adrenergic α_{1} receptors, thereby manifesting a broad pharmacological profile [5–7]. Despite myriad studies, the complete mechanism of action and efficiency of the drug Olanzapine is obfuscated, chiefly while dealing with schizophrenia.

For decades, an innumerable amount of antipsychotic drugs have emerged as therapeutic agents for schizoaffective disorders, bipolar mania, delusional ailments, etc. [8–11]. Moreover, most of them encompass high affinity for blocking D_{2} receptors but exhibit severe side effects, such as motor abnormalities, weight gain, diabetes, cardiovascular disorders, etc.[12,13] Therefore, there is a requirement for new chemically tailored drugs with abridged after-effects.

In the current study, synthesis, and crystallization of a new compound, Olanzapinium 2,5-dihydroxybenzoate has been done by solution method with slow evaporation technique. Identification of the crystal structure with potentiation points is appraised *via* X-ray diffraction technique. The intermolecular interactions in the crystal lattice were assessed by employing the Hirshfeld surface analysis [14]. Further analysis was performed using computational approaches for testing the affinity against potassium protein structure by molecular docking and molecular dynamic tools. Bioactivity and ADMET properties were also gauged *via* computer-aided programs. The molecular structure of the Olanzapinium 2,5-dihydroxybenzoate is illustrated in Figure 1.
2. Materials and methods

2.1. Chemicals and reagents

Olanzapine and 2,5-dihydroxybenzoic acid were used as generic from Sigma-Aldrich (Steinheim, USA). Isopropyl Alcohol was purchased from Merck scientific Inc. (Darmstadt, Germany) and used as an effective solvent. All the chemicals and solvent were used without further purification.

Melting Points (mp) were measured in open capillaries on Nessler digital Auto melting point apparatus and were uncorrected. The $^1$H-NMR spectra was recorded on a 300 MHz (Bruker) spectrometer in appropriate solvents using Tetra methyl silane (TMS) as an internal standard. The solvent signals as secondary standards and the chemical shifts were reported in δ values (ppm). Coupling constants $J$ were expressed in Hertz (Hz). The Signal multiplicities are represented by the following abbreviations: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), and m (multiplet). $^{13}$C-NMR spectra was recorded on 75 MHz spectrometers.

2.2. Synthesis and crystallization

Olanzapine (156 mg, 0.5 mmol) and 2,5-dihydroxybenzoic acid (77 mg, 0.5 mmol) were dissolved in 30 mL of isopropyl alcohol and stirred for 5 hours at 330K. The mixture was filtered and allowed slow evaporation of the solvent at room temperature; crystals were obtained within 2 weeks. To maintain a constant temperature of the solution, the growth vessel was kept in a constant temperature bath. The compound was fully characterized by $^1$H-NMR, $^{13}$C-NMR analysis (Figures 2 and 3). Further single-crystal X-ray diffraction analyses of the compound was unambiguously confirmed. The structure and stereochemistry of the compounds is illustrated in Figure 4.

2.3. Structural analysis of the compound

Good optical quality and well-shaped single crystal were selected under high-resolution microscope for the single-crystal X-ray diffraction data collection. The intensity data were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation ($λ = 0.71073$ Å) by the ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Integration and scaling of intensity data were accomplished using the program SAINT [15]. The structures were solved by direct methods using SHELXS97 and refinement was carried out by full-matrix least-squares technique using SHELXL97.

2.4. Ligand and protein preparation

The module of the Schrodinger suite, PrepWiz was used to prepare the protein [16–23]. The protein was pre-processed by assigning the bond orders and hydrogen, creating zero-order bonds to metals, and adding disulphide bonds. Further, the module of Schrodinger was used to fill up missing side chains and loops. Beyond 5 Å, all the water molecules were eliminated from the hetero groups. The H bonds were assigned, followed by energy minimization by OPLS 2005 force field after obtaining the pre-processed protein structure [24–39]. The final refined structure of the protein was saved in.pdb format for further investigation and research. The OPLS 2005 force field algorithm embedded in the LigPrep module of Schrödinger suite, 2013 (Schrodinger. LLC, New York, NY) was used to
optimize the ligand. The original state was retained by the ionizations of the ligand and was further desalted. The optimized protein structure was stored in an .sdf format for further docking studies [40–47].

2.5. Prediction of B-factor and evaluation

The B-factor value was calculated from the newly obtained folded template protein in combination with the human potassium voltage-gated channel (KCNA) protein sequence-profiles derived from the SwissProt - UniProt database [48–55]. The Debye–Waller factor is also known as the B-factor when measuring the flexibility of the protein structure [24]. The B-factor parameters (Figure 6) represent the normalized B-factor of the target KCNA, defined by $B = (B' - u)/s$, where $B'$ is the raw B-factor value, $u$ and $s$ are the mean and the standard deviation of the raw B-factors, respectively, along with the target KCNA (Figure 6) [24, 56–69].

2.6. Prediction of channel in the protein

EBI’s PORE WALKER 1.0 server (Pellegrini-Calace et al., 2019) (http://www.dev.ebi.ac.uk/thornton-srv/software/PoreWalker) which includes a fully-automated method for the detection and characterization of transmembrane protein channels from their 3D structure was employed to detect the cavity in the protein [46]. The channel is predicted by the identification of the longest and widest cavity across the protein [70–75].

Figure 2. $^1$H-NMR spectrum of Olanzapinium 2,5-dihydroxybenzoate in CDCl$_3$. 
2.5. Molecular docking

Molecular virtual Docker (MVD) is a flexible platform that offers high-quality docking based on high potential pair-wise linear potential (PLP), and the Mol Dock scoring function was utilized for molecular docking. The compound was docked at the predicted active site of the protein [76–87]. The cavity bearing the highest volume was selected for the docking of the compound [88–95]. The docking parameters were set to 0.20 Å as grid resolution, maximum iteration of 1500 and maximum population size of 50. For optimizing the complex energy of ligand–protein interaction, the Nelder Mead Simplex Minimization (using non-grid force field and H-bond directionality) was used after the docking [96–105]. The parameter of the Simplex evolution was set at maximum steps of 300 with a neighbourhood distance factor of 1 [106–115]. Binding affinity and interactions of the compound with protein were evaluated based on the internal hydrogen bond interactions, the internal electrostatic interaction, and sp²–sp² torsions [116–125]. The efficient interacting compound was selected based on the re-rank score from the dataset, which determines the most promising docking result [113, 126–135].

2.6. ADMET

The free interface of the admetSAR database (http://lmmd.ecust.edu.cn:8000) was used to calculate ADMET properties of a compound to deal with its absorption, distribution,
Figure 4. ORTEP representation of Olanzapinium 2,5-dihydroxybenzoate, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

Figure 5. Views of the Hirshfeld surfaces of title compound mapped with $d_{norm}$ in two different orientations. The HS is plotted in the range $-0.1500$ to $1.4938$ a.u.
metabolism, excretion, and toxicity in the human body which play an essential role in the discovery of a compound [133, 136–143]. The admetSAR database is based on the 5 quantitative regressions and 22 qualitative classification models which provide a more precise result and were essential in evaluating pharmacodynamics activities [144–153].

2.7. Molecular dynamics simulation

The molecular dynamic stimulation is for entailing time-dependent molecular motion of the biological macromolecules. It has replaced the single-point model with the complex dynamic model to explore the conformational space of the compound [154–162]. The simulation was run for 100 ns timestep in Desmond module of Schrodinger Suite wield the OPLS5 force field for molecular modeling. The geometry and thermodynamic property of the solution were fluctuated during the simulation period and the structural and the functional details of the molecule was obtained; which was studied with simulation diagram, wherein, RMSD, RMSF, protein–ligand interaction and ligand properties were analyzed [163–168].

2.8. Computing details

Crystallographic data collection: SMART [169]; cell refinement: SAINT [169]; data reduction: SAINT [169]; program(s) used to solve structure: SHELXS97 [170]; program(s) used to refine structure: SHELXL97 [171]; molecular graphics: SHELXTL [171] and Mercury [172]; software used to prepare material for publication: SHELXL97 [171] and PLATON [173].

3. Results and discussion

3.1. Analysis of spectral data

**Novel olanzapinium 2,5-dihydroxybenzoate:**

| Melting Point (mp):          | 110–112 °C |
|------------------------------|------------|
| $^1$H NMR (300 MHz, CDCl$_3$): | δ7.65 – 7.63 (m, 1H), 7.37 – 7.26 (m, 2H), 6.97 – 6.85 (m, 5H), 6.75 – 6.68 (m, 3H), 6.34 – 6.22 (m, 2H), 3.98 – 3.88 (m, 1H), 3.72 – 3.65 (m, 4H), 2.95 – 2.92 (m, 4H), 2.67 – 2.56 (m, 3H), 2.36 – 2.25 (m, 3H), 1.22 – 1.08 (m, 6H) |
| $^{13}$C NMR (75 MHz, CDCl$_3$ + DMSO-d$_6$): | δ 172.3, 156.7, 155.1, 153.5, 147.7, 143.6, 137.2, 127.8, 126.5, 123.8, 122.8, 121.0, 120.7, 118.3, 115.7, 115.1, 114.6, 77.6, 77.1, 76.7, 61.8, 52.0, 44.3, 42.7, 24.3, 14.2 |
3.2. Structural commentary

The ORTEP diagram of Olanzapinium 2,5-dihydroxybenzoate with thermal displacement ellipsoids are drawn at the 30% probability is shown in Figure 4. The bond length, bond angles of atoms are given in Tables 1 and 2, respectively. The bond lengths of C14–N4, C15–N4 and C17–N4 are 1.484 (4), 1.484 (4) and 1.483 (4) Å, respectively. These distances are longer than the bond length of a C18–O1 (1.251 (4) Å) and the system formed by the O–H (ionic) bond and the aromatic systems (Table 1 and Figure 4). The bond angle of acetate group (O1–C18¼O2) and C20–C19–C18 are 123.9° and 121.3°, respectively (Table 2).

Naturally, the number of OH groups capable of binding the drug would define the amount of the drug that can be carried by the matrix or the carrier agent. Many investigations indicated that the presence of at least one aryl group, one or two-electron donor atoms, and/or an NH group in a special spatial arrangement is necessary for anticonvulsant activity. Currently clinically used mostly anticonvulsant agents possess cyclic amide or acyclic amide or hetero atom present in the ring. According to them, the most common structural elements of clinically active drugs against epilepsy appeared to be a

### Table 1. Bond length (Å) of Olanzapinium 2,5-dihydroxybenzoate.

| Atom | Bond length (Å) | Atom | Bond length (Å) |
|------|----------------|------|----------------|
| C1—C2 | 1.495 (5) | C16—N3 | 1.451 (4) |
| C1—H1A | 0.9600 | C16—H16A | 0.9700 |
| C1—H1B | 0.9600 | C16—H16B | 0.9700 |
| C1—H1C | 0.9600 | C17—N4 | 1.483 (4) |
| C2—C3 | 1.343 (4) | C17—H17A | 0.9600 |
| C2—S1 | 1.736 (3) | C17—H17B | 0.9600 |
| C3—C4 | 1.433 (4) | C17—H17C | 0.9600 |
| C3—H3 | 0.9300 | N2—H2N | 0.87 (3) |
| C4—C5 | 1.364 (4) | N4—H4N | 0.89 (4) |
| C4—C12 | 1.475 (4) | C18—O1 | 1.251 (4) |
| C5—N2 | 1.389 (4) | C18—O2 | 1.261 (4) |
| C5—S1 | 0.9300 | C18—C19 | 1.379 (4) |
| C5—C16 | 1.387 (5) | C18—C20 | 1.376 (4) |
| C6—C7 | 1.383 (4) | C19—C20 | 0.9300 |
| C6—C11 | 1.401 (4) | C19—C21 | 1.374 (4) |
| C6—N2 | 1.429 (4) | C20—C21 | 1.373 (4) |
| C7—C8 | 1.378 (5) | C20—C22 | 1.374 (4) |
| C7—H7 | 0.9300 | C21—O4 | 0.9300 |
| C8—C9 | 1.371 (5) | C21—C22 | 1.381 (4) |
| C8—H8 | 0.9300 | C22—C23 | 0.9300 |
| C9—C10 | 1.386 (5) | C22—H22 | 1.381 (4) |
| C9—H9 | 0.9300 | C23—C24 | 0.9300 |
| C10—C11 | 1.388 (4) | C23—H23 | 0.9300 |
| C10—H10 | 0.9300 | C24—O3 | 1.362 (4) |
| C11—N1 | 1.408 (4) | O3—H3O | 0.89 (4) |
| C12—N1 | 1.287 (4) | O4—H4O | 0.84 (4) |
| C12—N3 | 1.389 (4) | C25—C26 | 1.485 (5) |
| C13—N3 | 1.463 (4) | C25—H25A | 0.9600 |
| C13—C14 | 1.504 (4) | C25—H25B | 0.9600 |
| C13—H13A | 0.9700 | C25—H25C | 0.9600 |
| C13—H13B | 0.9700 | C26—O5 | 1.440 (4) |
| C14—N4 | 1.484 (4) | C26—C27 | 1.495 (5) |
| C14—H14A | 0.9700 | C26—H26 | 0.9800 |
| C14—H14B | 0.9700 | C27—H27A | 0.9600 |
| C15—N4 | 1.484 (4) | C27—H27B | 0.9600 |
| C15—C16 | 1.504 (5) | C27—H27C | 0.9600 |
| C15—H15A | 0.9700 | O5—H5O | 0.88 (4) |
| C15—H15B | 0.9700 |
| Atoms   | Angle in degree | Atoms   | Angle in degree |
|---------|-----------------|---------|-----------------|
| C2—C1—H1A | 109.5           | N4—C17—H17A | 109.5          |
| C2—C1—H1B  | 109.5           | N4—C17—H17B | 109.5          |
| H1A—C1—H1B | 109.5           | H17A—C17—H17B | 109.5         |
| C2—C1—H1C  | 109.5           | N4—C17—H17C | 109.5          |
| H1A—C1—H1C | 109.5           | H17A—C17—H17C | 109.5         |
| H1B—C1—H1C | 109.5           | H17B—C17—H17C | 109.5         |
| C3—C2—C1   | 130.5 (3)       | C12—N1—C11 | 124.2 (3)      |
| C3—C2—S1   | 110.4 (2)       | C5—N2—C6  | 114.5 (2)      |
| C1—C2—S1   | 119.1 (3)       | C5—N2—H2N | 113 (2)        |
| C2—C3—C4   | 114.6 (3)       | C6—N2—H2N | 111 (2)        |
| C2—C3—H3   | 122.7           | C12—N3—C16 | 118.9 (3)     |
| C4—C3—H3   | 122.7           | C12—N3—C13 | 121.3 (2)     |
| C5—C4—C3   | 111.5 (3)       | C16—N3—C13 | 111.0 (2)     |
| C5—C4—C12  | 120.9 (3)       | C17—N4—C15 | 111.5 (3)     |
| C3—C4—C12  | 127.6 (3)       | C17—N4—C14 | 111.7 (3)     |
| C4—C5—N2   | 126.8 (3)       | C15—N4—C14 | 111.1 (2)     |
| C4—C5—S1   | 111.5 (2)       | C17—N4—H4N | 111 (2)       |
| N2—C5—S1   | 121.6 (2)       | C15—N4—H4N | 109 (2)       |
| C7—C6—C11  | 120.1 (3)       | C14—N4—H4N | 103 (2)       |
| C7—C6—N2   | 119.9 (3)       | C5—S1—C2  | 91.97 (15)    |
| C11—C6—N2  | 119.9 (3)       | O1—C18—O2 | 123.9 (3)     |
| C8—C7—C6   | 121.4 (3)       | O1—C18—C19 | 118.6 (3)    |
| C8—C7—H7   | 119.3           | O2—C18—C19 | 117.4 (3)    |
| C6—C7—H7   | 119.3           | C20—C19—C24 | 118.7 (3) |
| C9—C8—C7   | 119.3 (3)       | C20—C19—C18 | 121.3 (3) |
| C9—C8—H8   | 120.3           | C24—C19—C18 | 120.0 (3) |
| C7—C8—H8   | 120.3           | C21—C20—C19 | 121.1 (3) |
| C8—C9—C10  | 119.6 (3)       | C21—C20—H20 | 119.4      |
| C8—C9—H9   | 120.2           | C19—C20—H20 | 119.4      |
| C10—C9—H9  | 120.2           | C20—C21—O4  | 117.8 (3)    |
| C9—C10—C11 | 122.3 (3)       | C20—C21—C22 | 119.5 (3)    |
| C9—C10—H10 | 118.9           | O4—C21—C22 | 122.7 (3)    |
| C11—C10—H10 | 118.9          | C23—C22—C21 | 120.3 (3)    |
| C10—C11—C6 | 117.3 (3)       | C23—C22—H22 | 119.9      |
| C10—C11—N1 | 116.3 (3)       | C21—C22—H22 | 119.9      |
| C6—C11—N1  | 126.2 (3)       | C22—C23—C24 | 120.7 (3)    |
| N1—C12—N3  | 117.6 (3)       | C22—C23—H23 | 119.7      |
| N1—C12—C4  | 126.6 (3)       | C24—C23—H23 | 119.7      |
| N3—C12—C4  | 115.7 (3)       | O3—C24—C23 | 119.2 (3)    |
| N3—C13—C14 | 109.8 (3)       | O3—C24—C19 | 121.1 (3)    |
| N3—C13—H13A | 109.7          | C23—C24—C19 | 119.7 (3)    |
| C14—C13—H13A | 109.7          | C24—O3—H3O | 103 (3)     |
| N3—C13—H13B | 109.7          | C21—O4—H4O | 108 (3)     |
| C14—C13—H13B | 109.7          | C26—C25—H25A | 109.5   |
| H13A—C13—H13B | 108.2          | C26—C25—H25B | 109.5    |
| N4—C14—C13  | 110.8 (3)       | H25A—C25—H25B | 109.5 |
| N4—C14—H14A | 109.5          | C26—C25—H25C | 109.5    |
| C13—C14—H14A | 109.5          | H25A—C25—H25C | 109.5    |
| N4—C14—H14B | 109.5          | H25B—C25—H25C | 109.5    |
| C13—C14—H14B | 109.5          | O5—C26—C25 | 106.9 (3)    |
| H14A—C14—H14B | 108.1          | O5—C26—C27 | 112.0 (3)    |
| N4—C15—C16  | 112.1 (3)       | C25—C26—C27 | 113.3 (4)    |
| N4—C15—H15A | 109.2          | O5—C26—H26 | 108.2       |
| C16—C15—H15A | 109.2          | C25—C26—H26 | 108.2       |
| N4—C15—H15B | 109.2          | C27—C26—H26 | 108.2       |
| C16—C15—H15B | 109.2          | C26—C27—H27A | 109.5    |
| H15A—C15—H15B | 107.9          | C26—C27—H27B | 109.5    |
| N3—C16—C15  | 109.9 (3)       | H27A—C27—H27B | 109.5   |
| N3—C16—H16A | 109.7          | C26—C27—H27C | 109.5       |
| C15—C16—H16A | 109.7          | H27A—C27—H27C | 109.5    |
| N3—C16—H16B | 109.7          | H27B—C27—H27C | 109.5    |
| C15—C16—H16B | 109.7          | C26—O5—H5O | 110 (2)     |
| H16A—C16—H16B | 108.2          |                  |            |
nitrogen hetero atomic system. The new compound possesses two Hetro atom –NH functional groups present in the ring lead to improve anticonvulsant activity. In this study, it is the NH group and C =O group, which define both the binding and diffusion of the drug (Olanzapine) to the attached molecule (2,5-dihydroxybenzoic acid). The solid-state $^{13}$C NMR study allowed us to determine the drug (Olanzapine) which is attached to the supporting molecule (2,5-dihydroxybenzoic acid).

### 3.3. Refinement

Crystal data collection and structure refinement details are presented in Supplementary Table S1. The hydroxy-H atom was located in a different Fourier map and freely refined. The C-bound H atoms were positioned geometrically and allowed to ride on their parent atoms: C–H = 0.93–0.96 Å with $U_{iso}$ (H) = 1.5 $U_{eq}$ (C-methyl) and 1.2 $U_{eq}$ (C) for other H atoms. Molecular graphics were done using DIAMOND program [174]. Olanzapinium 2,5-dihydroxybenzoate was crystallized with centro symmetric space group P2(1)/n in the monoclinic system. The unit cell parameters of the compound are: $a = 8.4867(6)$ Å, $b = 29.764(2)$ Å, $c = 10.6334(8)$ Å, $\alpha = 90^\circ$, $\beta = 94.3810^\circ$ (10), $\gamma = 90^\circ$.

### 3.4. Hirshfeld surface (HS) analysis

The Hirshfeld surface analysis [175–177] was performed to understand the intermolecular interactions in the crystal structure of the compound and was constructed in the crystal environment using CrystalExplorer 17.5 [178]. The various non-covalent interactions were quantified with decomposed, two-dimensional fingerprint plots [178].

The Hirshfeld surface plotted over $d_{norm}$ is shown in Figure 5 with red areas indicating distances shorter (in closer contact) and blue those longer (distant contact) than the van der Waals radii. The contacts with distances equal to the sum of van der Waals radii are indicated in white [178]. From Figure 5, the bright red spots appearing near the hydrogen atoms H2N, H4N, H10 and H13 in the cation indicate that these hydrogen atoms are involved in the intermolecular interactions. The shape-index (SI) diagram, a tool to visualize $\pi$-$\pi$ stacking interactions, for the cation, anion, and the solvent molecule is shown in Figure 6. The overall two-dimensional fingerprint (2D–FP) plots are illustrated in Figure 5. The $H\cdots H$ contacts make the highest contribution (53.8%) to the total crystal packing (broad peaks at $d_{c}+d_{i} = \sim 2.3$ Å). The second highest contribution is from $H\cdots C/C\cdots H$ contacts (25.7%) and is indicated by the broad wing-like structure at $d_{c}+d_{i} = \sim 2.1$ Å. The symmetrical sharp spikes at $d_{c}+d_{i} = \sim 1.6$ Å are attributed to $H\cdots O/O\cdots H$ contacts (14.3%).

### 3.5. Protein preparation

KCNA gene is a comparably conserved region; however, some substitutions in its amino acids have resulted in significant antipsychotic activity, indicating that KCNA docks against antipsychotic compound Olanzapinium 2,5-dihydroxybenzoate. A comprehensive set of the amino acid sequence and atomic coordinates were analyzed from the obtained 3D structure of the KCNA (PDB ID: 4BGC) [179] using EMBOSS. All proteinogenic amino acids possess common structural features directly proportional to the biochemical properties of the model, which contain 117 aliphatic residues, 66 aromatic residues, 224 polar amino acids, 271 non-polar residues, 65 acidic amino acids, 65 negative residues and 47 positive residues. The X-ray diffraction data of the protein was visualized with
RasMol software, which suggests the target protein has two chains: chain A and chain B with 101 groups and total of 913 atoms. There are 952 absolute bonds with four alpha-helices in red colour and four beta-strands in green colour; however, there is no mention of turns or loops in data. The ribbon backbone model of potassium voltage-gated channel obtained from the protein database bank is depicted in Figure 7. These predicted values of the KCNA are proved to be useful in the analysis of protein packing, protein recognition, and ligand design.

### 3.6. Protein channel detection

Pore Walker detected the transmembrane protein channels and characterised them from the 3D structure of KCNA protein. It represents that the funnel prediction shape of the protein is DUD (Hourglass–Diamond–Complex). In Figure 8A, the red spheres represent pore centres at 3D steps, and their radii are directly proportional to the corresponding measured diameters. In contrast, grey and blue areas show pore-lining atoms and corresponding residues, respectively. The remaining portions of the proteins are shown in green. The number of found lines is 4, the points in straight areas were 54.55, and the total RMSD value is 2.33. Hence, the cavity predicted was close to that of the potassium channel protein structure available in PDB (Figure 8), therefore, we proceeded for the docking analysis to estimate the affinity of the compound against the channel. Evident from the re-rank score, the compound shows appreciably good affinity against the channel.

### 3.6. Molecular docking results

The molecular docking of the compound was performed using Molegro Virtual Docker to estimate the affinity of the compound Olanzapinium 2,5-dihydroxybenzoate against the KCNA. Evident from re-rank score ranging between $\Delta C_0$ 83.2566 KJ/mol and $\Delta C_0$ 60.6982 KJ/mol of the compound in different poses shows appreciably good affinity against the KCNA. The complete affinity analysis with different interacting descriptors is shown in Table 3.

### 3.7. Molecular dynamics simulation

The MD simulation provided details of conformational changes in protein and ligand over the trajectory of 100 ns. The simulation diagram is for structural analysis by RMSD and RMSF, ligand properties, and protein–ligand interaction. Based on the structural
assessment, the functionality of ligand molecules could be anticipated. The RMSD (root mean square deviation) graph suggests structural activity of protein–ligand interaction; lower the RMSD confers greater stability of the interface. Whilst RMSF (root mean square fluctuation) graph refers to the mobility of proteins Ca residue; a greater number of peaks stipulates more flexibility in proteins backbone.

The inter-residue interaction of olanzapinium 2,5-dihydroxybenzoate against the KCNA is in Figure 9. The RMSD value for protein ranged from 0.9 to 2.4 Å with recurrent deviation. The graph was in equilibrium amid 20–50 ns followed by trough around 60 ns. Again, the protein graph was stable for few nanoseconds, next ascend to maximum 2.4 Å then decreased further till 100 ns (Figure 9I). The ligand graph for this complex span between 3 and 45 Å, it was stable for first 20 ns with scarce variation followed by gradual increase to 20 Å for next 10 ns and sudden spike around 30 ns. Thereafter, it was stable from 40 to 100 ns with mini-fluctuation. The sudden spike around 30 ns indicates toward flexible atom in ligand around which the configuration of the ligand can change. The RMSF graph remained less than 2 Å throughout the simulation with few blunt peaks around 20 and 40 ns (Figure 9II).

### 3.8. Protein–ligand interaction

Protein–ligand interactions elucidate the stability of the interaction by taking into account hydrogen bonds, hydrophobic bonds, ionic interactions, and water bridges analyzed with histogram and heatmap in Figure 10. ARG_53, VAL_55, PRO_81, ARG_84, PHE_88, ASN_93, PHE_151 and GLU_140 residues were predominantly interacting with the ligand. Hydrogen bond is formed between hydrogen atom of ligand and strongly electro-negatively charged group of reside atom, it plays crucial role in ligand binding and drug specificity. VAL_55, ASN_93, and GLU_140 residues are bounded by hydrogen bond

| Name | Ligand | Filename | MolDock dcore | Rerank score | MW     |
|------|--------|----------|---------------|--------------|--------|
| [03] | Compound 1 | Compound 1 | [03] Compound1.mol2 | -107.729 | -83.2566 | 506.617 |
| [01] | Compound 1 | Compound 1 | [01] Compound1.mol2 | -111.855 | -83.1217 | 506.617 |
| [02] | Compound 1 | Compound 1 | [02] Compound1.mol2 | -107.028 | -81.9834 | 506.617 |
| [00] | Compound 1 | Compound 1 | [00] Compound1.mol2 | -120.044 | -79.2459 | 506.617 |
| [04] | Compound 1 | Compound 1 | [04]Compound1.mol2 | -108.893 | -60.6982 | 506.617 |
The hydrophobic bonds are π-π, π-cation and other non-specific interaction involving hydrophobic amino acid and aromatic or aliphatic group of the ligand. The inter-residue interaction come across as more hydrophobic, as most of residues are hydrophobically interacting with ligand of which PHE_88, PRO_81, PRO_90, and PHE_151 are predominant (Figure 10C). Also, there are ionic (polar) interaction by GLU_140 residue, formed by attraction forces other than hydrogen bonds. In detailed structural study of ligand is in pharmacophore mapping. Water bridges are water mediated hydrogen bonds. Majority of residues are forming water bridges: ARG_53, ARG_84, ASN_93, GLU_149, and PHE_151. The timeline of residue contacts with ligand is in Figure 10B. The top panel illustrate number of specific contacts the target protein makes with ligand in each and every trajectory frame, it varies from zero to nine. First 20 ns there are more interactions and equilibrium fluctuate between 3 and 6, afterwards the contact ratio declines and equilibrium shifts to 0–3 for further time-step. The bottom panel affirm contribution of each amino acid residue interaction in each trajectory. The number of contacts is represented with orange shade; darker the shade means a greater number of contacts and lighter shade indicates lesser contacts.
Figure 10. Interaction diagram of human potassium voltage-gated channel complex with Olanzapinium 2,5-dihydroxybenzoate observed during the molecular dynamics simulation. (A) The protein-ligand interaction diagram. (B) The residues that interact with the ligand in each trajectory frame. (C) Schematic diagram of ligand interaction with the amino acid residues of protein during MD simulation.
Figure 10. Continued.

Figure 11. The ligand property trajectory of the human potassium voltage-gated channel complex with Olanzapinium 2,5-dihydroxybenzoate during the 100 ns simulation.

GLU_140, ASN_93, ARG_84 residues show deeper shade of orange asserting they have more than one type of interaction.

3.9. Ligand property

The ligand property of the olanzapinium 2,5-dihydroxybenzoate against the KCNA, includes parameters: ligand RMSD, radius of gyration (rGyr), polar surface area (PSA), molecular surface area (MolSA), and solvent surface area (SAS) (Figure 11). The RMSD value is around 1–3 Å with scarce fluctuation over span of 100 ns and equilibrium at 2 Å. The rGyr graph signifies the moment of inertia of the ligand and distribution of mass, it
ranged from 5 to 6 Å and was stable around 20–35 ns with few peaks then gradually coming to equilibrium towards 5.50 Å. The molecular surface area is calculated with probe radius 1.4 Å and indicates the Van Der Waal surface area, it ranged between 456 and 472 Å² with minimal fluctuations and sharp trough near 20 ns, the equilibrium is around 464 Å². The solvent surface area signifies area accessible by a water molecule. It ranges from 300 to 800 Å², for 20 ns it was between 300 and 450 Å², followed by sudden spike where it reaches more than 750 Å² then gradually descend to 600Å² for further time lapse, the equilibrium is around 600Å². The polar surface area is surface accessible for binding of polar residues. The PSA of ligand is constant throughout the simulation with recurrent fluctuations, the equilibrium is at 105Å². The overall ligand property shows stability of the KCNA-Olanzapinium 2,5-dihydroxybenzoatecomplex.

3.10. Pharmacophore studies

The docking profile of the compound energy values of descriptors of external ligand interactions contributes to higher stability than internal ligand interactions. Moreover, the external ligand interactions were stabilized mostly by stearic energy guided by PLP while in internal ligand interactions; the torsional strain contributes to the stability of the ligand–receptor interactions. We speculate the 3H-bond interactions of the compound Olanzapinium 2,5-dihydroxybenzoate which are present between MET_51, ASN_93 and VAL_55 in KCNA as shown in Figure 12.

Electrostatic interactions of the compound Olanzapinium 2,5-dihydroxybenzoate within the channel shown in Figure 13. In general, the Potassium voltage-gated channel subfamily A member 1 protein there exhibits a dominant in electronegativity. But when the compound is introduced, the electro positivity it also enhances, thus creating a neutral tendency to facilitate the activity of the compound. Arginine is one of the dominant residues in the region of potassium voltage-gated channel. The electrostatic interaction manifests that clusters of charged and polar residues that are detected on protein–protein interfaces may intensify complex stability, although the total effect of electrostatics is generally net destabilizing. The compound Olanzapinium 2,5-dihydroxybenzoate is embedded

![Figure 12. The most effective pose of compound Olanzapinium 2,5-dihydroxybenzoate with lowest re-rank score shows hydrogen bond interaction with a channel protein KCNA 1 (Residues in colour cyan, ligand in colour pink and hydrogen bond in black dots.)](image)
in the protein cavity and were sheltered more towards the highly electronegative residues which are shown in red shades. The compound possesses less toxic, low melting point, average molecular weight and electronegative nature to facilitate oxygen enrichment, as self-supporting transporter through transvascular route (TVR) at blood–brain barrier (BBB) and blood cerebral spinal fluid barrier (BCSFB) that shuttle compound toward and away from neural tissue [94].

The van der Waals and some covalent interaction of the Olanzapinium 2,5-dihydroxybenzoate is illustrated in Figure 14. This also includes electrostatic forces, water bridges and ionic bonds. As predicted from MD simulation the ARG_53, VAL_55, MET_51, ARG_84, PHE_88, ASN_93, TYR_95 and GLU_94 residues strongly interact with the compound. The residues encircled in pink are polar in nature forming electrostatic bonds. The residues encircled in green are making non-covalent interaction, i.e., Van der Waals interaction hence loosely bonded. The green arrow suggests TYR_95, VAL_55 and MET_51 residues are forming hydrogen bond by accepting with
side chain atom, among these, TYR_95 is forming strong bonding by backbone acceptor of methyl atom. The orange line evinces $\pi-\pi$ interaction of the residue with aromatic ring. PHE_88, TYR_95 and ARG_84 are interacting by $\pi-\pi$ bond while MET_51 is forming $\pi$-cation interaction. The blue shadowed atoms are exposure of the ligand. It could be said that TYR_95 and ARG_84 residues are strongly interacting with the Olanzapinium 2,5-dihydroxybenzoate. This concurs with the simulation histogram of protein–ligand interaction.

3.10. ADMET studies

The compound Olanzapinium 2,5-dihydroxybenzoate further tested for their in silico ADMET profile and solubility properties (Table 4). We anticipate that the compound had appreciable ADMET profile, in addition, was neither carcinogenic nor mutagenic.

| Model                                         | Result          | Probability |
|-----------------------------------------------|-----------------|-------------|
| Blood–brain barrier                          | BBB-            | 0.8474      |
| Human intestinal absorption                   | HIA+            | 0.8807      |
| Caco-2 permeability                          | Caco2-          | 0.5852      |
| P-glycoprotein substrate                     | Substrate       | 0.93        |
| P-glycoprotein inhibitor                     | Non-inhibitor   | 0.7854      |
| Renal organic cation transporter             | Non-inhibitor   | 0.8543      |
| Subcellular localization                     | Nucleus         | 0.4491      |
| CYP450 2C9 substrate                         | Non-substrate   | 0.6695      |
| CYP450 2D6 substrate                         | Non-substrate   | 0.7364      |
| CYP450 3A4 substrate                         | Substrate       | 0.5738      |
| CYP450 1A2 inhibitor                         | Non-inhibitor   | 0.7022      |
| CYP450 2C9 inhibitor                         | Non-inhibitor   | 0.7599      |
| CYP450 2D6 inhibitor                         | Non-inhibitor   | 0.8014      |
| CYP450 2C19 inhibitor                        | Non-inhibitor   | 0.7163      |
| CYP450 3A4 inhibitor                         | Non-inhibitor   | 0.8929      |
| CYP inhibitor promiscuity                    | Low CYP inhibitory promiscuity | 0.8445 |
| Human ether-a-go-go-related                  | Weak inhibitor  | 0.9763      |
| Gene inhibition                              | Non-inhibitor   | 0.5895      |
| AMES toxicity                                | Non AMES toxic  | 0.6047      |
| Carcinogens                                  | Non-carcinogens | 0.8607      |
| Fish toxicity                                | High FHMT       | 0.9991      |
| Tetrahymena pyriformis toxicity              | High TPT        | 0.9449      |
| Honey bee toxicity                           | Low HBT         | 0.7284      |
| Biodegradation                               | Not ready biodegradable | 0.9914 |
| Acute oral toxicity                          | III             | 0.6079      |
| Carcinogenicity (three-class)                | Non-required    | 0.6409      |

Table 5. ADMET predicted profile – regression.

| Model                                         | Value   | Unit       |
|-----------------------------------------------|---------|------------|
| Aqueous solubility                            | -3.1394 | Log S      |
| Caco-2 Permeability                           | 0.8479  | Log Papp, cm/s |
| Rat Acute Toxicity                            | 2.6271  | LD50, mol/kg |
| Fish Toxicity                                 | 1.2842  | pLC50, mg/L |
| Tetrahymena pyriformis toxicity               | 0.6645  | pIGC50, $\mu$g/L |
optimal probabilistic values of ADMET models, in addition, show the compound to have drug-like properties. As shown in Tables 4 and 5, the predicted bioactivity score of the compound is highest against Potassium channel modulator target, showing compound to have a high and targeted affinity for potassium voltage-gated channel. The targeted activity we assume is important, as needless activation of the targets may raise serious physiological concerns. In the next approaches, we tested for the compound for its solubility and bioavailability. The compound showed excellent soluble properties along with high oral bioavailability.

4. Conclusions

In the study conducted, the antipsychotic drug olanzapine was synthesized and crystallized with aromatic acid 2,5-dihydroxybenzoic in isopropyl alcohol that led to the formation of novel Olanzapinium 2,5-dihydroxybenzoate. From the profile, it is evident that the external ligand’s contribution is predominant than the internal which in turn stabilizes the compound’s integrity. The simulation trajectory validates the conformational stability of the compound. Further, when the new compound is introduced in the KCNA environment, it completely neutralizes the environment to facilitate the activity of the compound viz., KCNA is highly electronegative where as our compound is highly electropositive. Besides, protein–ligand interaction contemplated the hydrophobic nature of the compound. The predicted ADMET properties completely support the affinity of the compound through the KCNA channel, viz., the predominance of arginine and tyrosine residue in all directions. The bio activity score is also very high. In conclusion, together with molecular docking analysis, bioavailability analysis, and ADMET predictions, we foresee that this new compound Olanzapinium 2,5-dihydroxybenzoate may serve as a highly potent and active antipsychotic drug.

Acknowledgements

This work was supported by Taif University Researchers Supporting Program (project number: TURSP-2020/128), Taif University, Saudi Arabia. The authors are grateful to the Deanship of Scientific Research, King Saud University for funding through Vice Deanship of Scientific Research Chairs.

Author contributions

All authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves jointly and individually responsible for its content.

Compliance with ethical standards

Disclosure statement

The authors declare that they have no conflict of interest.

Ethical approval

Ethical approval and informed consent not required for this manuscript.
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