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Design, ADME study, and molecular docking of serine derivatives of isatin – para-aminobenzoic acid conjugates

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ABSTRACT

A total of 20 novel isatin – para-aminobenzoic acid derivatives of serine have been designed in order to assess their potential effectiveness against some promising targets. Molecular docking was accomplished with the crystal structure of some of the predicted targets (i.e., 5UEN, 5FL4, 6QNG, 5SDB, and 6SUK), and we analysed the binding affinity between the compounds and each of the proteins of interest. Moreover, absorption, distribution, metabolism, and excretion (ADME) studies were conducted for the compounds with the best docking poses, thereby providing sufficient information about their pharmacokinetic, physicochemical, and drug-likeness properties.

KEY WORDS:
MOE software; ADME study; Molecular docking; isatin Schiff base; para-aminobenzoic acid

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1. Introduction

Heterocyclic compounds are pivotal sets of organic molecules as they are characterized by sizable biological profiles; this makes these compounds continuously being employed by researchers dealing with drug design and development[1,2]. Isatin (1H-indole-2,3-dione) is an invaluable aromatic heterocyclic organic compound; itself and its corresponding compounds constitute an auspicious genre of heterocyclic molecules with many substantial activities and are benign in humans[3]. The isatin molecule is endowed with myriad pharmacological activities, including antimicrobial, antitubercular, antiviral, antitumour, antioxidant, anticonvulsant, anti-inflammatory, analgesic, antifungal, and central nervous system-depressant activities[4,5]. Isatin and

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a primary amine undergo a condensation reaction to generate Schiff bases of isatin. Those Schiff bases are useful intermediates in the preparation of medicines, dyes, and other organic molecules due to their manifold chemical and biological characteristics[6]. Some clinically significant drugs comprise an isatin moiety, like the tyrosine kinases inhibitor nintedanib, the mRNA and protein synthesis inhibitor antiviral agent methisazone, and the receptor tyrosine kinase inhibitor anticancer drug sunitinib[3].

2. Methodology

The present study utilized an HP system with 8 GB of RAM and Intel Core i7-8550U processors running at 2 GHz. Chem Draw Ultra 22.0.0 and MOE 2024.06 were both installed and configured. The molecular docking simulation was performed inside the active site of the following proteins (herein abbreviated as in the Protein Data Bank; PDB): (i) human carbonic anhydrase IX (5FL4), human carbonic anhydrase XII (6QNG), and human dihydrofolate reductase in complex with NADP and N10-formyl-tetrahydrofolate (5SDB) that were selected for the screening of anticancer activity, as well as (ii) human adenosine A1 receptor (5UEN) and neprilysin (6SUK) that were used for the screening of cardioprotective effects. The crystal structures of these proteins were downloaded from the PDB. The proteins were prepared by removing the solvent molecules, other associated molecules, and other chains of proteins of interest in order to facilitate the interaction of ligands with the complementary functional groups in the binding site of the selected receptors, followed by the addition of protons to the downloaded protein format from PDB, then the addition of broken bonds, and the fixation of the potential of the protein molecule. Finally, the active site of the receptors was selected in MOE depending on the site occupied by the co-crystallized ligands. The molecular structures of the ligands were precisely outlined using ChemDraw Professional (22.0.0). The ligands were subsequently protonated into a three-dimensional configuration, partial charges were incorporated, energy was minimized, and the outcomes were stored. The absorption, distribution, metabolism, and excretion (ADME) properties' determination was accomplished by utilizing the SwissADME server: we evaluated the pharmacokinetic profiles of the compounds as well as their blood-brain barrier (BBB) penetration and bioavailability.

3. Results and Discussion

The docking and ADME outcomes offer valuable insights into the drug-likeness of the tested ligands (Table 1). Among them, ligands 1b, 1c, 1d, 3b, and 4b demonstrate strong binding affinities across multiple goal proteins, with docking scores as low as -10.34 kcal/mol (1b with 6SUK) and -10.05 kcal/mol (3b with 6SUK), thereby indicating robust interactions with their respective binding sites. These ligands also showcase high gastrointestinal (GI) absorption, suitable bioavailability (0.56), and no violations of Lipinski's Rule of Five, making them favourable candidates for oral drug development[7]. In our assessment, ligands 2a, 2b, 2c, and 2d display even more potent binding affinities, with 2c accomplishing a docking score of -10.23 kcal/mol with 6QNG and 2a attaining a -10.17 kcal/mol with 5FL4, thereby suggesting brilliant docking capacity. However, these ligands are afflicted by a low GI absorption and terrible bioavailability (0.11) due to their excessive hydrogen bond acceptor and topological polar floor area (>140 $Å^2$) performance, which limits their passive intestinal permeability[8]. The presence of extra polar practical corporations in those ligands in all likelihood contributes to their stronger protein-ligand interactions and reduces their absorption performance, suggesting an alternate-off between binding power and pharmacokinetic residences[9]. Importantly, none of the ligands are expected to penetrate the BBB, which may be beneficial only when targeting peripheral conditions.

4. Conclusion

All the designed compounds manifest vigorous binding affinities with the target proteins, highlighting their potential as therapeutic agents in cancer and cardiovascular diseases. Their interactions with proteins like neprilysin and adenosine A1 receptor suggest their function

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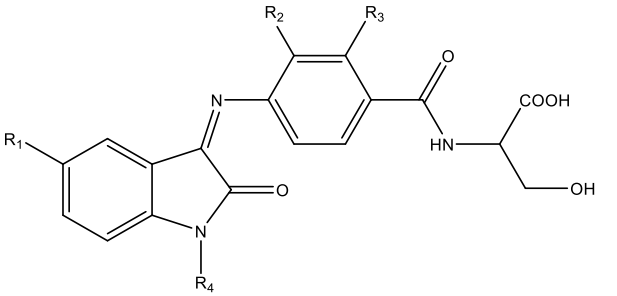
Table 1. *The molecular docking and ADME results of the designed compounds. Abbreviations used: 1a (R_1=H, R_2=H, R_3=H, R_4=H), 1b (R_1=H, R_2=H, R_3=CH_3, R_4=H), 1c (R_1=H, R_2=H, R_3=OCH_3, R_4=H), 1d (R_1=H, R_2=Cl, R_3=H, R_4=H), 2a (R_1=NO_2, R_2=H, R_3=H, R_4=H), 2b (R_1=NO_2, R_2=H, R_3=CH_3, R_4=H), 2c (R_1=NO_2, R_2=H, R_3=OCH_3, R_4=H), 2d (R_1=NO_2, R_2=Cl, R_3=H, R_4=H), 3a (R_1=F, R_2=H, R_3=H, R_4=H), 3b (R_1=F, R_2=H, R_3=CH_3, R_4=H), 3c (R_1=F, R_2=H, R_3=OCH_3, R_4=H), 3d (R_1=F, R_2=Cl, R_3=H, R_4=H), 4a (R_1=Br, R_2=H, R_3=H, R_4=H), 4b (R_1=Br, R_2=H, R_3=CH_3, R_4=H), 4c (R_1=Br, R_2=H, R_3=OCH_3, R_4=H), 4d (R_1=Br, R_2=Cl, R_3=H, R_4=H), 5a (R_1=Br, R_2=H, R_3=H, R_4=CH_3), 5b (R_1=Br, R_2=H, R_3=CH_3, R_4=CH_3), 5c (R_1=Br, R_2=H, R_3=OCH_3, R_4=CH_3), 5d (R_1=Br, R_2=Cl, R_3=H, R_4=CH_3), 5FL4 (human carbonic anhydrase IX), 5SDB (human dihydrofolate reductase in complex with NADP and N10-formyl-tetrahydrofolate), 5UEN (human adenosine A1 receptor), 6QNG (human carbonic anhydrase XII), 6SUK (neprilysin), ADME (absorption, distribution, metabolism, and excretion), BBB (blood-brain barrier), F (absolute bioavailability), GI (gastrointestinal), TPSA (topological polar surface area).*



R_1= H, NO_2, F, Br

R_2= H. Cl

R_3= CH_3, OCH_3

R_4= H, CH_3

Ligands	**Molecular docking results** (kcal/mol)					**ADME results**							
	5UEN	**5FL4**	**6QNG**	**5SDB**	**6SUK**	**H-donor**	**H-acceptor**	**Molar refractivity**	**TPSA** (Å^2)	**GI absorption**	**BBB permeability**	***F***	**Lipinski's Rule of Five**
1a	-6.73	-9.44	-9.55	-7.98	-9.89	4	6	96.01	128.09	high	no	0.56	0
1b	-7.16	-9.58	-9.06	-8.20	-10.34	4	6	100.97	128.09	high	no	0.56	0
1c	-7.15	-9.54	-9.74	-8.30	-9.70	4	7	102.50	137.32	high	no	0.56	0
1d	-6.92	-9.66	-9.33	-8.14	-10.61	4	6	101.02	128.09	high	no	0.56	0
2a	-7.35	-10.17	-10.02	-8.92	-9.77	4	8	104.83	173.91	low	no	0.11	1 [N or O>10]
2b	-7.39	-9.73	-9.94	-8.73	-10.58	4	8	109.80	173.91	low	no	0.11	1 [N or O>10]
2c	-8.06	-9.60	-10.23	-8.95	-9.68	4	9	111.32	183.14	low	no	0.11	1 [N or O>10]
2d	-7.69	-9.64	-10.10	-8.56	-10.47	4	8	109.84	173.91	low	no	0.11	1 [N or O>10]
3a	-6.74	-9.99	-9.94	-8.02	-9.52	4	7	95.97	128.09	high	no	0.56	0
3b	-7.35	-9.70	-9.62	-8.13	-10.05	4	7	100.93	128.09	high	no	0.56	0
3c	-7.29	-9.78	-9.64	-8.56	-8.77	4	8	102.46	137.32	high	no	0.56	0
3d	-6.92	-9.35	-9.60	-8.08	-10.42	4	7	100.98	128.09	high	no	0.56	0
4a	-6.89	-9.21	-9.66	-8.03	-9.22	4	6	103.71	128.09	high	no	0.56	0
4b	-7.38	-9.40	-9.80	-8.45	-10.47	4	6	108.67	128.09	high	no	0.56	0
4c	-7.15	-9.68	-10.15	-8.56	-9.30	4	7	110.20	137.32	high	no	0.56	0
4d	-7.36	-9.32	-9.83	-8.35	-10.65	4	6	108.72	128.09	high	no	0.56	0
5a	-7.30	-9.79	-9.85	-8.74	-8.97	3	6	108.61	119.30	high	no	0.56	0
5b	-7.50	-9.39	-10.02	-8.82	-10.15	3	6	113.58	119.30	high	no	0.56	0
5c	-7.12	-9.37	-10.04	-9.12	-10.45	3	7	115.10	128.53	high	no	0.56	0
5d	-7.48	-9.14	-10.10	-8.85	-10.18	3	6	113.62	119.30	high	no	0.56	0

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in modulating cardiovascular functions such as vasodilation, diuresis, and natriuresis, besides their potential in modulating the pH homeostasis maintained by carbonic anhydrases. Additionally, the deprivation of an important cofactor required for cancer cell multiplication (offered by the herein observed dihydrofolate reductase inhibition) warrants further research into their pharmacological applications.

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Conflicts of interest

None exist.

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