Design and In Silico Evaluation of Coumarin-Triazole Hybrids as EGFR Inhibitors: Molecular Docking and ADMET Analysis

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Abstract: **A series of coumarin-triazole hybrids (1a-1j) were designed and evaluated as Epidermal Growth Factor Receptor (EGFR) inhibitors using molecular docking and in silico pharmacokinetic analysis. Molecular docking was carried out against the EGFR tyrosine kinase domain using the crystal structures PDB 1M17 and PDB 4HJO with Erlotinib serving as the reference inhibitor. The docking investigations displayed that some derivatives had a high binding affinity within the EGFR's ATP-binding region. Compound 1e had the greatest binding affinity, with docking scores of -9.5 kcal/mol (1M17) and -11.9 kcal/mol (4HJO), outperforming the conventional medication in the inactive EGFR configuration. Interaction analysis indicated the formation of hydrogen bonding, π–π stacking, and hydrophobic interactions with key residues such as LYS721, MET742, VAL702 and LEU820, contributing to the stability of the ligand–protein complex. The designed hybrids were further assessed for their pharmacokinetic properties using in-silico ADMET prediction. Most derivatives complied with Lipinski's Rule of Five and Veber's Rule indicating good drug-likeness and oral bioavailability. Furthermore, compounds 1e and 1f have good pharmacokinetic characteristics, moderate solubility, adequate absorption, and non-mutagenic toxicity profiles.**

Keywords: Coumarin; Triazole; In silico; Molecular docking; ADMET.

I. INTRODUCTION.

Cancer is the largest cause of illness and death globally, and it continues to pose a significant public health problem. GLOBOCAN 2020 anticipated around 19.3 million new cancer cases and 10.0 million deaths worldwide, with the burden projected to climb to 28.4 million new cases by 2040, a 47% increase driven mostly by population aging and growth [1, 2]. Cancer is already the second biggest cause of mortality globally and a main cause of disability-adjusted life years (DALYs), second only to cardiovascular illnesses [3]. This growing burden is particularly alarming in low- and middle-income countries, where limited access to prevention, early diagnosis, and effective therapies leads to higher mortality despite sometimes lower incidence [4]. The EGFR a tyrosine kinase is crucial for normal epithelial development and homeostasis but it is commonly mis regulated in cancer [5]. EGFR overexpression, gene amplification, activating point mutations and truncations are prevalent in malignancies such as non-small cell lung, glioblastoma, colorectal, gastric, head and neck, pancreatic and breast [6]. Aberrant EGFR activation activates critical oncogenic pathways including as RAS-RAF-MEK-ERK and PI3K-AKT-mTOR, boosting proliferation, survival, invasion, and resistance to apoptosis. EGFR is also becoming more well recognized as a biomarker of resistance, with secondary mutations or amplification occurring under therapeutic pressure and contributing to treatment failure and disease progression [5, 7, 8].

Traditional cancer remedies like radiation, surgery, chemotherapy and hormonal therapy remain the foundation of cancer care but each has significant limits [9]. Due to tumor heterogeneity and microscopic dissemination surgery frequently fails to eliminate all malignant cells [10]. Chemotherapy and many cytotoxic medicines suffer from systemic toxicity, poor selectivity, limited stability, pharmacokinetic limitations and multidrug resistance, all of which impair efficacy and affect quality of life. Radiation therapy, while more accurate with contemporary equipment nevertheless risks harm to adjacent normal tissues and is unavailable in many places [10, 11]. Targeted therapy such as EGFR tyrosine kinase inhibitors (TKIs) and monoclonal antibodies has considerably improved outcomes in patients with EGFR mutant lung cancer [5, 6]. However, inherent and developed resistance such as on-target mutations, bypass signalling activation, altered receptor trafficking and tumor microenvironmental adaptations, restrict the response's duration [8]. New EGFR directed medicines with superior profiles are needed to address resistance mechanisms, off-target toxicity and poor effectiveness across various mutation spectra [10, 12].

Despite improvements in immunotherapy, kinase inhibitors and precision medicine, no single therapeutic approach is effective for all cancer kinds and stages and drug resistance remains a significant hurdle. Treatment failure is caused by numerous features, comprising inadequate drug concentrations at the tumor site, non-selective tissue distribution, evasion of drug-induced apoptosis and mutation or change of therapeutic targets [10, 11, 13]. The rise of resistant variants and noncanonical EGFR activities in EGFR driven malignancies highlights the necessity for innovative, powerful and selective inhibitors that can conquer resistance while limiting harm. Hybrid scaffolds that include favored pharmacophores, such as coumarins and triazoles provide options to improve binding interactions within the EGFR kinase domain while also modulating pharmacokinetic and safety aspects [6, 7].

Modern anticancer drug development relies heavily on structure-based computational approaches, especially for kinase targets like EGFR [14]. Molecular docking predicts the ideal orientation and binding affinity of small molecules inside a protein's active site, allowing for virtual screening of huge libraries to select candidates with favourable interactions and low binding free energy [15]. Docking in cancer therapy makes it easier to discover small compounds that precisely inhibit oncogenic proteins, speeds up lead optimization and lowers the cost and time involved with purely experimental campaigns. Integrating docking with in vitro tests has demonstrated high concordance in breast cancer and other models indicating its relevance in directing the synthesis of novel compounds and repurposing current therapies [15, 16]. In silico evaluation of ADMET (absorption, distribution, metabolism, excretion, and toxicity) further refines candidates by predicting pharmacokinetic behaviour and safety, helping to address the persistent challenges of toxicity, poor bioavailability, and instability associated with many anticancer agents [11].

Against this background, the rational design and in-silico evaluation of coumarin–triazole hybrids as inhibitors of the EGFR, employing molecular docking and ADMET prediction, represents a promising strategy for the identification of novel, selective, and potentially resistance-overcoming anticancer candidates.

II. DESIGN STRATEGY

Coumarin-triazole hybrids were designed using a molecular hybridization technique (Figure 1), which included merging two pharmacologically active scaffolds to increase biological activity. The coumarin nucleus is a well-known heterocyclic structure with several biological features, including anticancer action. The 1,2,3-triazole ring adds structural rigidity, metabolic stability, and the capacity to form hydrogen bonds and π-π interactions with amino acid residues. In this work, the coumarin moiety was connected to aromatic acid via a triazole bridge to strengthen interactions inside the EGFR's ATP binding pocket with the goal of increasing binding affinity, selectivity and possible anticancer activity.

III. MOLECULAR DOCKING STUDIES

The molecular docking investigations were accomplished for the designed hybrids against Epidermal Growth Factor Receptor tyrosine kinase domain (PDB: 1M17) and inactive EGFR tyrosine kinase (PDB: 4HJO) proteins to evaluate their binding affinity and interaction patterns within the active sites of these proteins. The structure of EGFR tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib (PDB: 1M17) [17] and Crystal structure of the inactive EGFR tyrosine kinase domain with erlotinib (PDB: 4HJO) [18] was downloaded from the protein database (www.rcsb.org) Prior to protein preparation, all co-crystallized inhibitors, bound ligands, and water molecules were removed to obtain a purified and receptor-ready protein structure. Subsequently, polar hydrogen atoms were incorporated, and Kollman charges were assigned to the protein to prepare it for molecular docking investigations [19]. The protein (PDB ID: 1M17) grid box's centre was set to 38, 34 and 42 while the number of points in the x, y, and z dimensions was set to 24.016 -0.886 and 55.425 Å, respectively. The protein (PDB ID: 4HJO) grid box's centre was set to 40, 36 and 42 while the number of points in the x, y, and z dimensions was set to 24.863 11.117 and -0.834 Å, respectively. The ChemDraw program was utilized to generate 2D representations of the designed compounds, which were subsequently transformed into energetically optimized 3D conformations through an energy minimization procedure. In addition, Gasteiger charge parameters were applied, and rotatable bonds along with nonpolar hydrogen atoms were

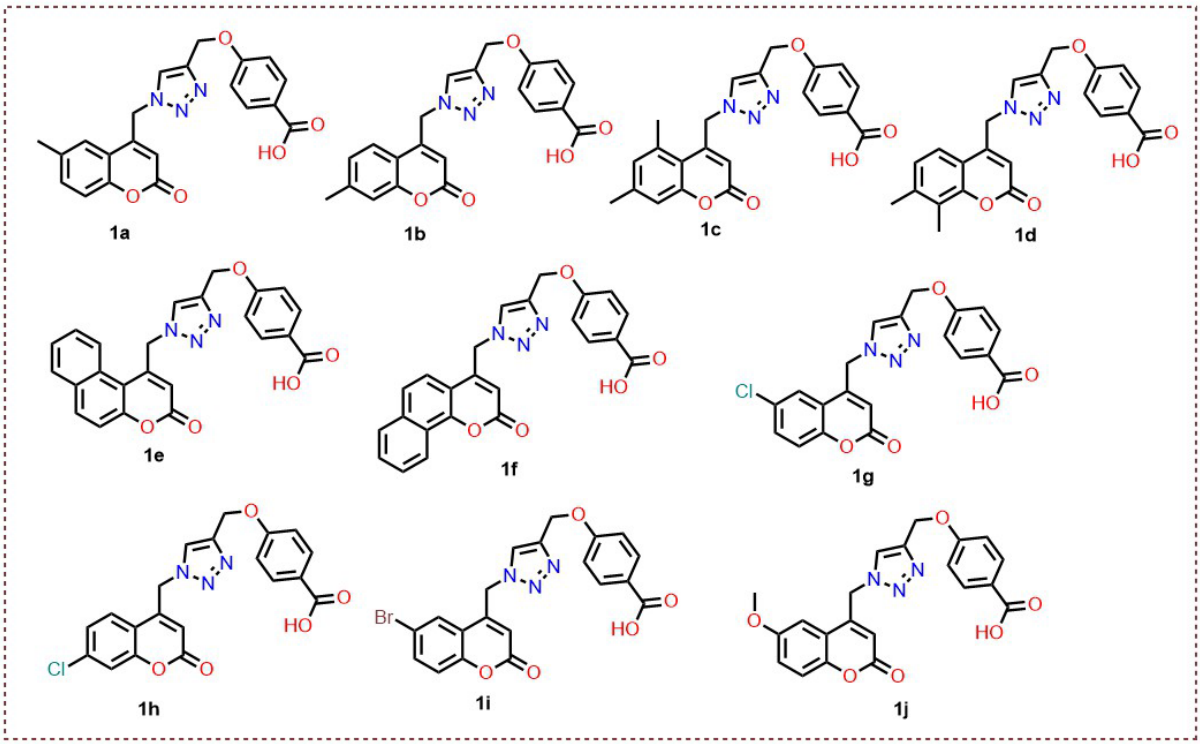

Fig. 1. Designed coumarin–triazole compounds.

defined using AutoDock 4.2. Each ligand was then subjected to docking analysis employing AutoDock Vina. The resulting docking conformations and interactions were finally visualized and analyzed using Discovery Studio [20].

TABLE I. DOCKING RESULTS OF THE DESIGNED DERIVATIVES AGAINST EGFR TYROSINE KINASE DOMAIN (PDB: 1M17) AND INACTIVE EGFR TYROSINE KINASE DOMAIN (PDB: 4HJO).

Compound Code	Binding Affinity (kcal/mol)	
	PDB: 1M17	PDB: 4HJO
1a	-9.0	-10.4
1b	-9.0	-10.5
1c	-9.3	-10.6
1d	-8.7	-10.7
1e	-9.5	-11.9
1f	-9.1	-11.4
1g	-8.8	-10.4
1h	-9.0	-10.3
1i	-9.0	-10.4
1j	-8.5	-10.2
Erlotinib	-10.6	-11.3

The docking investigations displayed that all compounds exhibited favourable binding affinities within the receptor's active site, with binding energies ranging from −8.5 to −9.5 kcal/mol for PDB 1M17 and −10.2 to −11.9 kcal/mol for PDB 4HJO (**Table 1**), indicating strong interactions with the kinase binding pocket. These results are comparable to the conventional inhibitor Erlotinib, which demonstrated docking scores of -10.6 kcal/mol (1M17) and -11.3 kcal/mol (4HJO) respectively. Compound **1e** has the greatest binding affinity to both protein structures with docking scores of −9.5 kcal/mol for PDB 1M17 and −11.9 kcal/mol for PDB 4HJO indicating a robust and consistent engagement with the EGFR active site. Compound **1e** has higher binding affinity due to many stabilizing interactions, such as hydrogen bonding, stacking, sigma interactions, and hydrophobic interactions with pivotal residues in the binding pocket. The interaction analysis indicated that numerous key amino acid residues of the EGFR kinase domain were involved in ligand stabilization. Residues including LYS721, MET742, CYS773, LEU694, VAL702, LEU820, and ASP831 were commonly engaged in ligand interactions. Hydrogen bonding interactions were often seen with residues LYS721, MET769, THR766, and CYS773, which are critical in anchoring the ligand inside the ATP-binding site. Furthermore, the ligand-protein complex was stabilized by π-π stacking and π-alkyl interactions between the aromatic rings of the coumarin-triazole framework and hydrophobic residues like LEU694, VAL702 and LEU820.

Compounds 1c, 1e and 1f showed greater binding interactions with the PDB 1M17 complex than the other derivatives. Compound 1c developed hydrogen bonding connections with residues such as MET742 and ASP831, as well as hydrophobic contacts with VAL702 and LEU820 which contributed to its high binding energy. Compound 1f had several hydrophobic and π-interactions with LEU820, VAL702 and MET769, stabilizing the complex inside the kinase pocket. The binding interactions of hybrid 1e at the active site of the protein EGFR tyrosine kinase domain is shown in Figure 3.

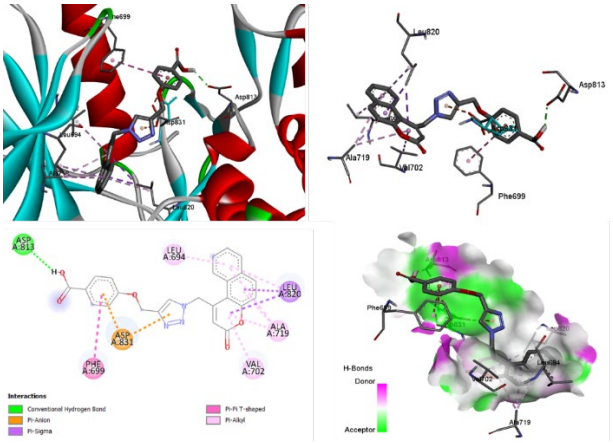

Fig. 2. Binding interactions of compound 1e at the active site of the protein EGFR tyrosine kinase domain (PDB: 1M17).

Most molecules in the PDB: 4HJO complex have increased binding energies than the 1M17 structure indicating greater ligand accommodation in the receptor's inactive state. Compounds 1e and 1f formed strong hydrogen bonds with LYS721 and MET742, along with broad hydrophobic contacts with LEU694, VAL702 and LEU820. These interactions are comparable with those shown with the co-crystallized inhibitor Erlotinib which interacts with similar residues in the ATP-binding pocket. The binding interactions of compound 1e at the active site of the protein inactive EGFR tyrosine kinase domain is displayed in Figure 2.

Overall, the docking data show that the coumarin-triazole scaffold conforms well to the EGFR kinase active site, generating several stabilizing contacts with critical catalytic residues. The inclusion of aromatic rings and heteroatoms in the proposed compounds promotes strong π-interactions and hydrogen bonding which are essential for successful receptor inhibition. Among the designed derivatives, compound 1e emerged as the most promising contender, with binding affinity equivalent to or even superior to the standard inhibitor in the EGFR complexes of PDB 1M17 and PDB 4HJO.

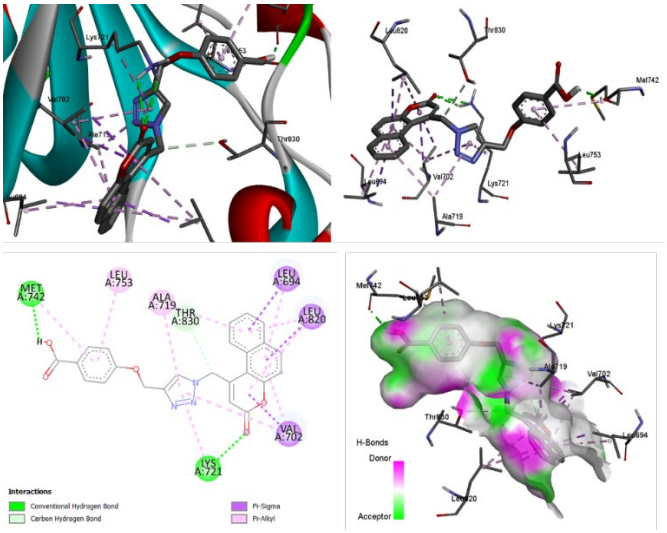

Fig. 3. Binding interactions of compound 1e at the active site of the protein inactive EGFR tyrosine kinase domain (PDB: 4HJO).

IV. ADMET STUDIES

The well recognized Lipinski's Rule of Five [21] and Veber Rule guidelines [22] were used to analyze the ADMET-related physicochemical properties of the designed compounds (1a–1j) in order to determine their drug-likeness and oral bioavailability. The results were deduced using Swiss ADME webserver [23] (Table 2). The designed compounds have a molecular weight range of 391.38 to 456.25 g/mol which is within the permissible limit (≤500) specified by Lipinski's Rule of Five, suggesting excellent drug like properties. Similarly, the computed lipophilicity values (iLogP) ranged from 1.87 to 3.06, which is much lower than the threshold value of 5 indicating balanced hydrophilic lipophilic characteristics crucial for membrane permeability and absorption. The compounds' hydrogen bonding capacity was likewise within the required range with HBA values ranging from 7 to 8 and HBD values equal to 1 showing their potential to form stabilizing contacts with biological targets while preserving appropriate pharmacokinetic behaviour.

TABLE II. PHYSICOCHEMICAL DESCRIPTORS OF THE DESIGNED COUMARIN-TRIAZOLE COMPOUNDS

Compound	MW	iLog P	Log S	HBA	HBD	nRB	TPSA
Lipinski	≤500	≤5	-	≤10	≤5	-	-
Veber	-	-	-	-	-	≤10	≤140
1a	391.38	2.35	-4.1	7	1	6	107.45
1b	391.38	2.5	-4.1	7	1	6	107.45
1c	405.4	3.06	-4.48	7	1	6	107.45
1d	405.4	2.52	-4.48	7	1	6	107.45
1e	427.41	2.68	-5.02	7	1	6	107.45
1f	427.41	2.66	-5.02	7	1	6	107.45
1g	411.8	1.87	-4.38	7	1	6	107.45
1h	411.8	2.5	-4.38	7	1	6	107.45
1i	456.25	2.15	-4.44	7	1	6	107.45
1j	407.38	2.42	-3.89	8	1	7	116.68

The compounds have 6 to 7 rotatable bonds, meeting Veber's Rule criterion of ≤10. This implies appropriate molecular flexibility and oral bioavailability. The compounds' topological polar surface area (TPSA) values ranged from 107.45 to 116.68 Å², below the threshold of 140 Å², indicating adequate intestinal absorption and permeability. The projected water solubility (Log S) values varied from -3.89 to -5.02, indicating moderate solubility, suitable for drug-like compounds. Furthermore, the bioavailability radar plots of the most promising compounds 1e and 1f (Figure 4) disclose that their physicochemical properties are within the ideal range for oral medication candidates. These radar plots show balanced qualities in terms of lipophilicity, size, polarity, solubility, flexibility and saturation indicating good pharmacokinetics.

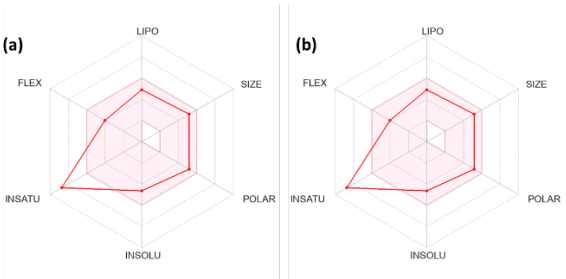

Fig. 4. Radar plots of compound (a) 1e and (c) 1f.

The pharmacokinetic behaviour and toxicity profile of the most promising coumarin-triazole derivatives 1e and 1f were assessed using the pkCSM online server and the findings were compared to the reference medication Erlotinib (Table 3), a recognized EGFR inhibitor. Compounds 1e and 1f have moderate aqueous solubility (-3.477 and -3.472 log mol/L, respectively) somewhat greater than the typical medication. The Caco-2 permeability values (0.529 and 0.543 log cm/s) suggest moderate intestinal permeability when compared to the benchmark. Compound 1f showed reasonably high expected intestinal absorption (77.915%), although somewhat lower than the reference medication (95.549%). Both chemicals were projected to be substrates of P-glycoprotein, not inhibitors. Compounds 1e and 1f showed lower tissue distribution than the reference medication, with anticipated steady-state volume of distribution (VDss) values of -0.85 and -0.853 log L/kg, respectively. The percent unbound (Fu) values of 0.165 and 0.173 indicate considerable plasma protein binding. The anticipated blood-brain barrier permeability values (logBB −1.101 and −1.107) show limited penetration across the BBB. This is reliable with the low CNS permeability values (logPS −3.153 and −3.161), indicating that these compounds are unlikely to accumulate in the CNS.

The metabolism prediction unveiled that both hybrids are non-substrates of CYP2D6, indicating a lesser possibility of metabolic liability via this enzyme although both operate as CYP1A2 inhibitors comparable to the reference medication. In terms of excretion, compounds 1e and 1f had moderate total clearance values of 0.843 and 0.897 log mL/min/kg respectively, that are fairly higher than the reference drug, indicating effective removal from the body. Furthermore, neither molecule was expected to be a substrate of the renal organic cation transporter OCT2. Toxicity projections further established that both chemicals are non-mutagenic according to the AMES test and do not produce skin sensitization indicating acceptable safety profiles. However, comparable to the reference medicine both compounds demonstrated expected hepatotoxicity that might require further experimental confirmation. Overall, ADMET predictions indicate that the designed coumarin-triazole derivatives particularly compounds 1e and 1f have favourable pharmacokinetic properties and acceptable safety profiles supporting their potential as promising EGFR inhibitors for future anticancer drug development.

TABLE III. IN-SILICO PREDICTED PHARMACOKINETIC PARAMETERS (ADMET)

Parameters		1e	1f	Standard
Absorption	Water solubility	-3.477	-3.472	-4.403
	Caco-2	0.529	0.543	1.238
	Intestinal absorption	0.529	77.915	95.549
	P-gp substrate	Yes	Yes	No
	P-gp inhibitor	No	No	Yes
Distribution	VDss	-0.85	-0.853	-0.053
	Fu	0.165	0.173	0.04
	BBB	-1.101	-1.107	-0.67
	CNS	-3.153	-3.161	-3.384
Metabolism	CYP2D6 Substrate	No	No	No
	CYP1A2 Inhibitor	Yes	Yes	Yes
Excretion	Total clearance	0.843	0.897	0.591
	Renal OCT2 substrate	No	No	No
Toxicity	AMES toxicity	No	No	No
	Hepatotoxicity	Yes	Yes	Yes
	Skin sensitization	No	No	No

Abbreviations and corresponding threshold values: Caco-2 (colon carcinoma-2 cell permeability); > 0.9 log cm/s indicates high permeability. VDss (volume of distribution at steady state); log VDss < −0.15 denotes low distribution, whereas log VDss > 0.45 signifies high distribution. BBB (blood–brain barrier permeability); logBB > 0.3 suggests efficient penetration across the BBB, while logBB < −1 indicates poor permeability. CNS (central nervous system permeability); logPS > −2 reflects the ability to penetrate the CNS, whereas logPS < −3 implies an inability to access the CNS. CYP (cytochrome P450 enzyme family) and OCT2 (organic cation transporter 2) are also considered important pharmacokinetic parameters.

V. CONCLUSION

In conclusion, a series of coumarin-triazole hybrids were rationally developed and assessed using molecular docking and in-silico ADMET analysis to investigate their potential as EGFR receptor inhibitors. The docking investigations utilizing PDB 1M17 and PDB 4HJO revealed that the proposed compounds had favourable binding interactions within the EGFR's ATP-binding pocket, with docking scores equivalent to the reference drug Erlotinib. Among the studied derivatives compounds 1e and 1f had especially significant binding affinities and persistent interactions with critical amino acid residues, showing their potential as EGFR inhibitors. Furthermore, ADMET predictions indicated that the proposed compounds had acceptable pharmacokinetic and toxicity profiles meeting the primary drug-likeness criteria. These findings emphasize the importance of the coumarin-triazole hybrid framework as a useful conjugate for anticancer drug development. Further experimental validation is required to confirm these drugs' therapeutic potential.

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Conflicts of Interest

There are no conflicts to declare.

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