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Synthesis, ADMET and Docking Studies of Novel Pyrazoles Incorporating Coumarin Moiety as Tyrosine Kinase (Src) Inhibitors

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Abstract: Novel pyrazoles incorporating coumarin moiety have been synthesized by the 1,3-dipolar cycloaddition reaction of the nitrilimines that were generated *in situ* from hydrazonyl halides by the action of triethylamine and the enaminone named *E*-3-(3-(dimethylamino)acryloyl)-8-methoxy-2H-chromen-2-one (1) in dry benzene for 6 h. These novel compounds' chemical structures were elucidated by physical and spectral techniques, including FTIR, ^{1}H-NMR, ^{13}C-NMR, ^{1}H-^{13}C HMBC NMR, and mass spectra. These molecules were predicted to show tyrosine kinase inhibition activity, which was further validated by docking studies. These molecules also showed good ADMET properties and passed Lipinski's filters for drug-likeness. These results collectively paved the way for developing pyrazoles incorporating coumarin moiety as possible tyrosine kinase inhibitors.

Keywords: 1,3-dipolar cycloaddition; pyrazoles; coumarin; tyrosine kinase; docking.

1. Introduction

Coumarins are an important class of phytochemicals and comprise a benzopyrones family, widely distributed in nature [1]. These oxygen-containing heterocycles, bearing a typical benzopyrone framework, either synthetic or natural, are interested in contemporary drug discovery [2, 3]. Coumarin derivatives are being actively studied for their pharmacological activities and enormous efforts have been put into the design and development of coumarin-based anticoagulants, antioxidant [4], antimicrobial (anti-viral, antifungal, and anti-parasitic) [5, 6], anticancer [7-9], anti-diabetic, analgesic, anti-neurodegenerative, and anti-inflammatory agents [10]. Coumarin-based compounds are also believed to occupy an important place in medicinal chemistry and drug discovery due to the possibility of getting structurally diverse molecules with interesting biological activities from this ring structure [11, 12].

An efficient medicinal chemistry strategy to discover new drug molecules has been the clubbing together of two or more biologically important structural motifs in one molecule. These molecules, often in the form of hybrid molecules, sometimes known as hybrid drugs, are more efficient with better efficacy than the individual molecules [13, 14]. Many synthetic intermediates are quite useful to synthesize such hybrid molecules, among which enaminones are considered important synthetic intermediates for the synthesis of various heterocyclic compounds [15, 16]. The importance of the enaminone such as *E*-3-(3-(dimethylamino)acryloyl)-8-methoxy-2H-chromen-2-one (1) due to its unique structure (Fig.

1), which facilitates the 1,3-dipolar cycloaddition with nitrilimines (liberated, *in situ*, by the action of the base on the corresponding hydrazonyl halides), to synthesize the pyrazoles. In turn, pyrazoles are considered to be pharmacologically important and active scaffolds that possess almost all types of pharmacological activities [17-19]. In continuation of our research work in the area of synthesis of heterocyclic compounds for different applications [20-22], we present this work that aims to synthesize novel pyrazole derivatives containing coumarin moiety utilizing efficient synthetic strategies. In silico studies of these molecules were also conducted to unravel their potential as biologically important scaffolds.

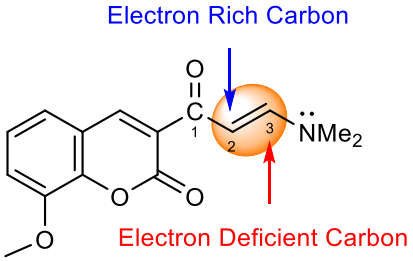


Figure 1. Structure of enaminone 1.

2. Materials and Methods

2.1. Chemistry.

All organic solvents were purchased from commercial sources and used as received unless otherwise stated. All other chemicals were purchased from Merck, Aldrich, or Acros and used without further purification. Thin-layer chromatography (TLC) was performed on precoated Merck 60 GF254 silica gel plates with a fluorescent indicator and detection by means of UV light at 254 and 360 nm. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, an ultra-high-performance, versatile Attenuated Total Reflectance (ATR) sampling accessory on the Nicolet iS10 FT-IR spectrometer. The NMR spectra were recorded on a Bruker Avance III 400 (9.4 T, 400.13MHz for ^{1}H, 100.62 MHz for ^{13}C and 376.25 MHz for ^{19}F) spectrometer with a 5-mm BBFO probe, at 298 K. Chemical shifts (δ in ppm) are given relative to internal solvent, DMSO-d_6 2.50 for ^{1}H and 39.50 for ^{13}C was used as an external standard. (^{1}H-^{13}C) gs-HMBC was acquired and processed using standard Bruker NMR software (Topspin 3.2). Mass spectra were recorded on a Thermo ISQ Single Quadrupole GC-MS. Elemental analyses were carried out on a EuroVector instrument C, H, N, S analyzer EA3000 Series.

E-3-(3-(dimethylamino)acryloyl)-8-methoxy-2H-chromen-2-one (1) [23] and *N*-Aryl-2-oxopropanehydrazonoyl chloride 2a-c [24] were synthesized according to literature procedures.

2.1.1. General procedure for 1,3-dipolar cycloaddition reaction.

To a hot solution of enaminone 1 (10 mmol) and the appropriate hydrazonyl halide 2a-c(10 mmol) in benzene (25 mL), triethylamine (10 mmol) was added. The reaction mixture was refluxed for 7 h. (until no starting materials showed by in TLC). The solvent was evaporated under reduced pressure. The solid product was crystallized from ethanol to afford the corresponding pyrazole derivatives 5a-c.

2.1.2. 3-(3-acetyl-1-phenyl-1H-pyrazole-4-carbonyl)-8-methoxy-2H-chromen-2-one (5a).

m.p. = 165 °C; IR (KBr) ν/cm^{-1}:1644, 1718, 1738 (3C=O), 1593 (C=N); ^{1}HNMR(DMSO-*d*$_6$):δ 2.56 (s, 3H, COMe), 3.92 (s, 3H, OMe), 7.34-7.60 (m, 6H, Ar H), 8.02 (d, 2H, J = 8Hz, ArH), 8.57 (s, 1H, coumarin H4), 9.22 (s, 1H, pyrazole H); ^{13}C NMR(DMSO-d6): δ 27.7, 56.6, 119.4, 119.8, 119.9, 121.8, 124.1, 124.9, 125.4, 130.3, 134.1, 146.6,146.8,158.9, 185.9,193.4; MS (m/z): 388 (M^+); $C_{22}H_{16}N_2O_5$:Anal. Calcd: C, 68.04; H, 4.15; N, 7.21. Found: C, 68.27; H, 4.05; N, 7.08.

2.1.3. 3-(3-acetyl-1-(4-tolyl)-1H-pyrazole-4-carbonyl)-8-methoxy-2H-chromen-2-one (5b).

m.p. = 200°C; IR (KBr) ν/cm^{-1}:1648, 1718, 1736 (3C=O), 1601 (C=N); ^{1}HNMR(DMSO-*d*$_6$):δ 2.39 (s, 3H, Me), 2.87 (s, 3H, COMe), 3.92 (s, 3H, OMe), 7.30-7.48 (m, 5H, Ar H), 7.99 (d, 2H, J = 8.4 Hz, ArH), 8.55 (s, 1H, coumarin H4), 9.16 (s, 1H, pyrazole H); ^{13}C NMR(DMSO-d6): δ 21.0, 27.7, 56.5, 116.5, 119.4, 119.8, 121.2, 121.7, 124.0, 124.9, 125.4, 127.3, 130.6, 133.9, 136.6, 146.1, 146.6, 158.9, 184.9,194.5; MS (m/z): 402 (M^+); $C_{23}H_{18}N_2O_5$:Anal. Calcd: C, 68.65; H, 4.51; N, 6.96. Found: C, 68.94; H, 4.43; N, 6.75.

2.1.4. 3-(3-acetyl-1-(4-trifluromethylphenyl)-1H-pyrazole-4-carbonyl)-8-methoxy-2H-chromen-2-one (5c).

m.p. = 224 °C; IR (KBr) ν/cm^{-1}:1645, 1718, 1735 (3C=O), 1601 (C=N); ^{1}HNMR(DMSO-*d*$_6$):δ 2.58 (s, 3H, COMe), 3.83 (s, 3H, OMe), 7.32-7.49 (m, 7H, Ar H), 8.60 (s, 1H, coumarin H4), 9.22 (s, 1H, pyrazole H); ^{13}C NMR(DMSO-d6): δ 30.5, 56.7, 116.9, 119.1, 121.3, 121.9, 122.1, 124.9, 125.3, 126.2, 127.4, 130.1, 132.8, 144.4, 146.7, 147.7, 158.6, 183.6,195.6; MS (m/z): 456 (M^+); $C_{23}H_{15}F_3N_2O_5$:Anal. Calcd: C, 60.53; H, 3.31; N, 6.14. Found: C, 60.76; H, 3.22; N, 6.00.

2.2. In silico Studies

2.2.1. Target prediction.

To estimate the most probable macromolecular target for the synthesized compounds (5a-5c) they were screened by an online web tool: Swiss TargetPrediction [25]. SwissTargetPrediction is a web-based tool to perform ligand-based target prediction for any small bioactive molecule. Prediction of the target is based on the similarity principle through reverse screening.

2.2.2. ADMET and pharmacokinetic studies.

ADMET and pharmacokinetic properties were checked using pkCSM (A Cambridge online source, link: http://bleoberis. bioc.cam.ac.uk/pkcsm/prediction) and validated using MedChemDesigner^{TM} software version 3.0 [26]. The structures of the compounds 5a-5c and their physicochemical properties were drawn and calculated using MarvinSketch.

2.2.3. Docking studies.

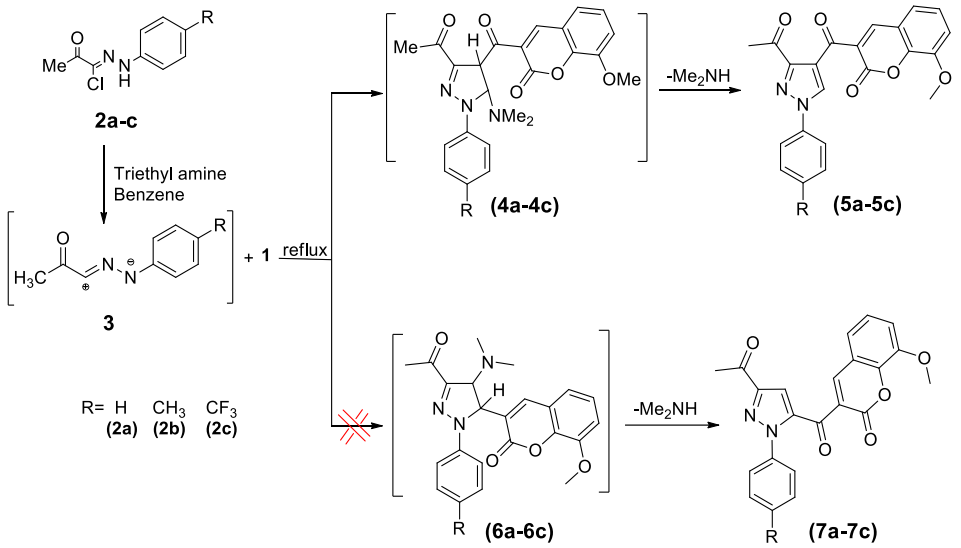
The molecules (5a-5c) as ligands were drawn in ChemDraw Ultra 12.0 (Chem Office package) assigned with proper 2D orientation and analyzed for connection error in bond order. OSIRIS, an ADMET-based Java library layer that provides reusable cheminformatics

functionality, an entirely in-house developed drug discovery informatics system, was used to predict the total drug score. Dundee PRODRG2 server was used to minimize the energy of the molecules [27, 28]. The energy minimized compounds were then read as input for AutoDock4.2 in order to carry out the docking simulation. Auto Dock used the local search to search for small molecules' optimum binding site to the protein. The active site was defined by a grid box of 85×80×90 points and spacing of 0.375 Å with the ligand-binding site as the center. The final structure was then saved in pdbqt format. During the docking process, a maximum of 10 conformers was considered for each compound. AutoDock 4.2 and AutoDockvina were compiled and run under Windows 7 operating system [29]. The images were visualized using PyMoL.

3. Results and Discussion

3.1. Synthesis.

The enaminone 1 reacted with α-ketohydrazonylhalide2a-c in a regioselective manner to afford only one isolable product as examined by TLC. The structures of the products formed may be 5a-5cor other regioisomers 7a-7c(Scheme 1).



Scheme 1. Regioselective reaction between enaminone and hydrazonyl halides.

As mentioned before, the differentiation between the two possible regioisomers can be easily done via the long-range C-H connectivitiesutilizing ^{1}H-^{13}C HMBC depending on the correlation between the pyrazole proton with the carbons of the two carbonyl groups [24,30]. Here in our case, we first can assign the three carbons of carbonyl groups from the ^{1}H-^{13}C HMBC full spectrum of the isolated product 5a or 7a. In which a signal was observed at δ 158.9 ppm corresponding to the carbonyl carbon of coumarin; it exhibited a correlation peak with the signal at δ 8.57 ppm assigned to the coumarin H-4. A signal at δ 193.4 ppm corresponds to the carbonyl carbon due to its correlation peak with the signal at δ 2.56 ppm assigned to the acetyl group's methyl protons. On the other hand, the signal at δ 185.9 ppm is attributed to the other carbonyl group, owing to its correlation peak with the signal at δ 9.22 ppm, easily assigned to the pyrazole proton (Figure2). These observations indicate that only one carbonyl functional group correlates to the pyrazole proton ($^{3}J_{H-C}$), following the structure 7a, in addition to the other observed correlations of the pyrazole protons with C-4 pyrazole

($^2J_{H-C}$), C-3 pyrazole ($^3J_{H-C}$), and the deshielded quaternary carbon of the phenyl group ($^3J_{H-C}$) (Fig. 1 and see supporting information).

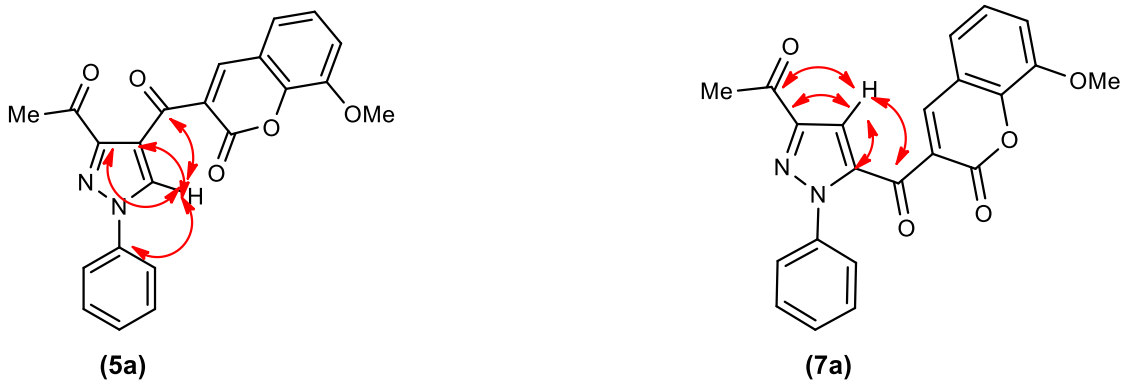


Figure 2. Diagnostic correlations in the ^{1}H-^{13}C HMBC (red arrows) for two regioisomers5a and 7a.

Therefore, these results confirm the existence of regioisomer 5a and rule out the alternative structure 7a. The formation of novel pyrazole derivative 5a was assumed to be formed via initial 1,3-dipolar cycloaddition of the nitrilimine 3 (generated in situ form of hydrazonyl halid 2a upon treatment with triethylamine) to the activated double bond in the enaminone 1 to afford the dihydropyrazole transition state 4a, followed by elimination of dimethylamine, yielding the pyrazole derivative 5a (Scheme 1). The other derivatives follow the same reaction route.

3.2. ADMET and pharmacokinetic studies.

To make sure that the synthesized molecules show the potential of a drug, their ADMET and pharmacokinetic properties were checked using pkCSM (A Cambridge online source, link: http://bleoberis. bioc.cam.ac.uk/pkcsm/prediction) and validated using MedChemDesigner^{TM} software version 3.0 [26] which predicts the values with great precision. The predicted values showed that the molecules have a great solubility potential, both in water (5a) -3.969 (log mol/L), (5b) -4.021 (5c)-4.086 and $CaCO_2$permeability (5a) 1.557, (5b) 1.41, (5c) 0.856 (log Papp in 10 cm/s). Intestinal absorption (human) (5a) 100(5b) 100, (5c) 97.06(% Absorbed) and skin permeability (5a, 5b & 5c) -2.735, (log Kp). BBB permeability (5a) -0.966,(5b) -0.98, (5c)-1.404 (log BB) and CNS permeability (5a) -2.433, (5b) -2.359, (5c) -2.275(log PS). The molecule's ability to inhibit CYP1A2, CYP3A4, CYP2C9, and CYP2C19 shows that the molecule will not allow the metabolism of xenobiotics in the body. The value of clearance, which is the pharmacokinetic parameter that represents the rate of drug elimination divided by its plasma concentration, is quite favorable for the molecules (5a) 0.813(5b) 0.815, and (5c) 0.334 log ml/min/kg and implies that the molecule would not accumulate in the body and hence is nontoxic. Oral Rat Acute Toxicity (LD50) was (5a) 2.702(5b) 2.715, (5c) 2.787mol/kg and Oral Rat Chronic Toxicity (LOAEL) was (5a) 1.092 (5b) 1.166, (5c) 0.589 (log mg/kg_bw/day). These results depict that the compound has good ADMET properties, which are a requisite for a molecule to show drug-like properties.

The predicted pharmacokinetic parameters and other physicochemical properties, often known as Lipinski's filters, are important for both *in silico* and *in vitro* evaluation of drug-like properties [31-33]. A molecule that lacks good pharmacokinetic parameters and does not obey Lipinski's filters fails in the later stages of drug development. From the predicted pharmacokinetic parameters and after applying Lipinski's filters (shown in Table 1) it appears

that the molecules show good drug-likeness properties and could be a good drug candidate for further studies.

Table 1. ADMET and Lipinski's filters for drug-likeness.

Compound	M.Wt	ClogP*	LogD#	[a]HBA	HBD	PSA	Ro5 (Y/N)
5a	388.37	2.51	3.00	7	0	87.49	Y
5b	402.12	2.99	3.51	7	0	85.27	Y
5c	456.37	3.43	3.87	7	0	85.27	Y

*At PH 7.4;#calculated using ChemAxonLogDpredictor [a]HBA—hydrogen bond acceptor, HBD—hydrogen bond donor, PSA—polar surface area obtained by Marvin Sketch 5.1. #Values adopted from referred sources. Ro5 (Y/N): Rule of five followed or not; Y: Yes; N: No

3.3. Molecular docking studies.

A molecular docking study of the compounds (5a-5c) was performed to validate the predicted target. 2D structures of the molecules were converted to energy minimized 3D structures and were further used for docking. The molecules were docked into the active sites of tyrosine kinase (PDB ID: 2SRC). It was found that the molecules interact with different residues inside the active site of the enzyme. The binding free energy for these molecules was found to be in the range of -15.55 to -17.92 kcal/mol, which shows that the inhibitor binds well inside the active site pocket (see Figure 3). The molecule also showed hydrogen bonding, hydrophobic and other interactions with the target, explaining its good antibacterial activity.

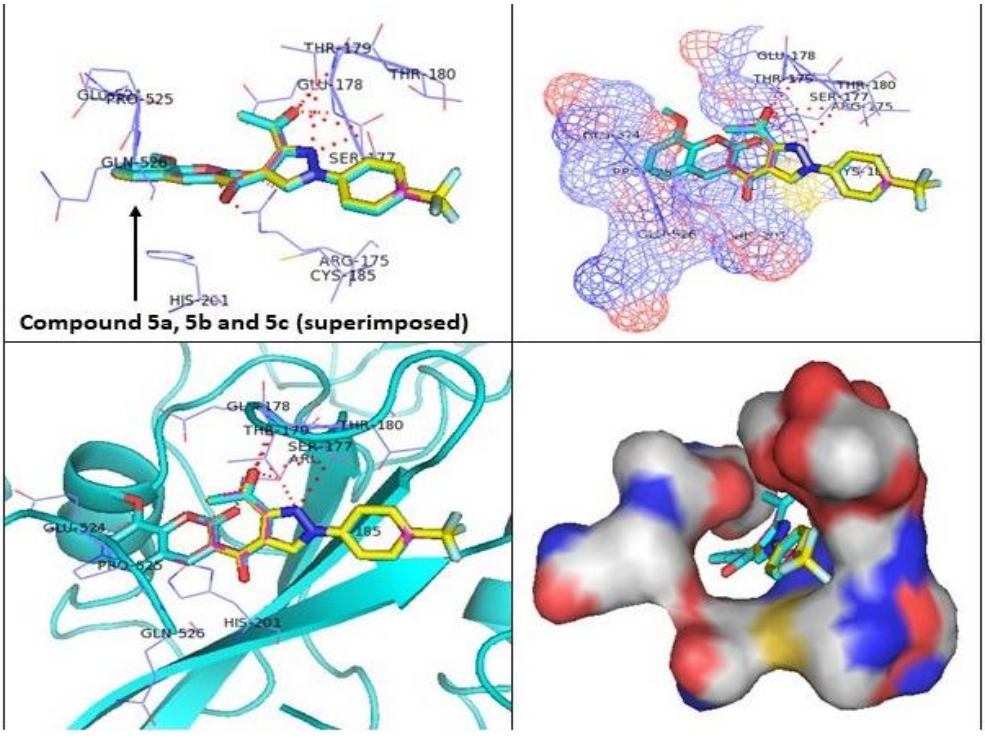


Figure 3. Docking poses of the compounds (5a-5c) inside the active site pocket of tyrosine kinase (2SRC). All the molecules show similar binding interactions, and their structures are superimposed in the images.

The acetyl group's oxygen atom attached to the pyrazole ring showed hydrogen bonding interaction with SER177, GLU178, and THR179 amino acid residues of the target enzyme. The nitrogen atom of the pyrazole ring showed hydrogen bonding interaction with SER177 and THR179. The coumarin ring formed hydrogen bonds with ARG175 amino acid residue of the target enzyme. The other active pocket residues THR180, CYS185, HIS201, GLU524,

PRO525, and GLN526 of the enzyme were involved in van der Waal's interactions, hydrophobic and π-π staking interactions.

Tyrosine kinase inhibitors (TKI) are effective in the targeted treatment of different types of malignancies. Tyrosine kinase (sar) enzymes catalyze the transfer of γ- phosphate group from adenosine triphosphate to the target proteins, which play an important role in diverse normal cellular regulatory processes [34]. Several tyrosine kinase inhibitors as drug molecules are already used in the clinic, such as Imatinib, the first clinically approved TKI. Imatinib was later followed by drugs such as gefitinib, erlotinib, sorafenib, sunitinib, and dasatinib. The 2-amino benzoxazole and benzimidazole derivatives and pyrazolyl-benzoxazole derivatives have been proved to be active tyrosine kinase inhibitors due to strong binding affinity enzyme [35, 36, 37]. Our results also corroborate these findings. Therefore, these hybrid molecules containing a coumarin ring and pyrazole moiety could be good scaffolds for designing new tyrosine kinase inhibitors. These molecules also showed good ADMET properties and passed Lipinski's filters for drug-likeness. These results collectively paved the way for the development of pyrazoles incorporating coumarin moiety as tyrosine kinase inhibitors.

4. Conclusions

1,3-dipolar cycloaddition reaction of the nitrilimines that were generated *in situ* from hydrazonyl halides by the action of triethylamine and the enaminone named *E*-3-(3-(dimethylamino)acryloyl)-8-methoxy-2H-chromen-2-one (1) in dry benzene for 6 h gave rise to new pyrazoles incorporating coumarin moiety in their skeleton. These compounds' structures were elucidated by different physical and spectral techniques, including FTIR, ^{1}H-NMR, ^{13}C-NMR, ^{1}H-^{13}C HMBC NMR, and mass spectra. These molecules were predicted to target tyrosine kinase, which was further validated by docking studies. These molecules fit well in the active site pocket of the target enzyme and displayed good drug-likeness properties. Overall, these molecules possessed good ADMET properties, passed Lipinski's filters for drug-likeness, and showed a good binding affinity with the target. These results are quite encouraging owing to the development of new tyrosine kinase inhibitors as potential drug molecules.

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Conflicts of Interest

The authors declare no conflict of interest.

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