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Bio-potent aryl ketoximes

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Abstract. Four aryl ketoximes were synthesized by potassium hydrogen phthalate catalyzed condensation of aryl ketones and hydroxylamine hydrochloride under conventional heating in ethanol medium. The yield of this condensation is more than 75%. The synthesized ketoximes were characterized by their physico-chemical constants and spectroscopic data. The ligand-protein interactions ability of these ketoximes were studied by molecular docking method. The antimicrobial activities of these ketoximes were assess by Bauer-Kirby disc diffusion methods against selective microorganisms.

***Keywords*:** ketoximes; potassium hydrogen phthalate; IR and NMR spectra; molecular docking; antimicrobial activities.

1. Introduction

The name oxime is an abbreviation of oxy-imine ether [1]. A methodology entails a covalent coupling of reducing glycans with aminooxy nucleophiles to form carbohydrate oxime *O*-ethers, commonly termed oximes [2]. They are the key intermediate for a variety of alkaloid synthesis. Numerous catalysts were employed for the synthesis of oximes such as Lewis's acids and bases [3, 4], organolithium compounds [5], aluminum and vanadium cyclohexyl complexes [6, 7], peroxo complexes [8], $\{RuCl_2(P\text{-cymene})\}$-$AgSbF_6$ [9], K_2CO_3 in acetone-H_2O [10], KOH in DMSO-H_2O [11], *t*-BuOK/ DMF, CS_2CO_3 [12], $Cu(OAc)_2$/ pyridine-DCE [13], xylene [14], $IrCl(cod)]_2$/Pybox, $Ba(OH)_2$ in H_2O-CH_2Cl_2 [15], MCPBA-CH_2Cl_2 [16] and DDQ/CH_2Cl_2 [17]. Manikandan *et al.* [9] synthesized some ortho and alkylated 3,4-dimethoxy ketoxime by the reaction of 3, 4-dimethoxy acetophenone and allyl acetate with yield higher than 83%. Wang *et al*. [18] introduced the best-known method for synthesis of acyclic oxime ethers by the reaction of oximes with alkyl and aryl halides. Li *et al*. [19] introduced the blue LED irradiation method for oxime synthesis. Angelone and his co-workers [10] reported an excellent method for generation of oxime ethers from oximes and epichlorohydrin. Zard *et al*. [1] synthesized more than 86% yields of *O*-propargylated oximes by the treatment of oximes with propargyl bromide. Gao *et al*. [12] synthesized more than 90% yields of *O*-arylated of oximes. Likewise, many oxime derivatives were reported including *O*-arylated acetophenone oximes, heterocyclic oxime ethers, high regio-and enantioselective synthesis of the branched oxime ethers, 3-*t*-butyl-4, 4-bis-(methythio)-4H-1,2-oxazete, enone oximes and glyoxal oximes [13-17]. Thirunarayanan *et al*. [20, 21] have prepared 2,6-diphenyl-3-methyl-piperidine-4-one oxime using conventional method by the reaction of 2,6-diphenyl-3-methyl-piperidine-4-one and hydroxylamine hydrochloride in presence of sodium acetate. As one of the prominent medicinal motifs, the oxime group is featured in a large number of pharmaceutically important compounds and is widely applied in variety pesticides like oxiconazole [1]. Oximes possess numerous biological activities such as, antibacterial [22], antifungal [23], antiviral [24], antiprotozoal [25], insecticidal [26], acaricidal [27], antidepressive [28], anticonvulsant [29], inhibition of β-receptors [30], anti-inflammatory [31], PPAR agonists [32], anti-cancer [33], antioxidant [34], antiulcer [35], antiaggregation [36], enzyme oxidase inhibitions [37], cytotoxic [38], antiproliferative [39], and herbicidal [40]. Sorenson *et al*. [41] studied the bifurcation metabolites of some natural plant oximes. The potential therapeutic properties of some unsubstituted oximes were reported by Surowiak *et al*. [42]. Kula and his coworkers [43] studied the chemical transformations of some bio-active

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oximes. Various synthetic applications of 9-anthraldehyde oxime were reported by Ahmed *et al*. [44].

Molecular docking is the study of relative binding energies of ligand-proteins and is useful finding the effective of the drug-metabolism [45]. Chemists reported the synthesis, *in vitro*, *in silico* activities, DFT and molecular docking study of various oximes including di-tert-butyl(*E*)−4-hydroxy-6-(hydroxyimino) −4-methyl-2-arylcyclohexane-1,3-dicarboxylates [45], imidazopyridine oximes [46], uncharged oximes RS41A, RS194B, RS48B, and RS182 [47], pyridinium oximes [48], syn-anti isomeric of pyridine imidazole oximes [49], 1,5-diarylpyrazole oximes [50], 1,5-diphenylpenta-1,4-dien-3-one-*O*-benzyl oximes [51], thiadiazole oximes [52], acetone *O*-((2,5-dichlorophenyl)sulfonyl) oxime [53], 3-(pyridin-2-ylmethylimino)-butan-2-one oxime [54], 3-(pyridin-2-ylmethylimino)-pentan-2-one oxime and aryl nitrone oximes [55]. A detailed literature review concluded that, there is no report availed for the synthesis, *in vitro* bio-activities and molecular docking of some substituted aryl ketoximes. Therefore, in this study, the above mentioned ketoximes for the evaluation of antimicrobial activities and protein-ligand interactions through molecular docking study.

2. Experimental

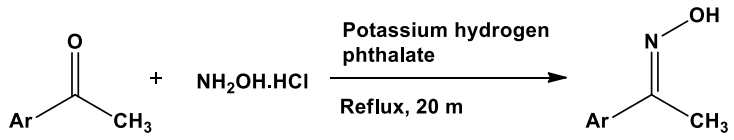
2.1. Materials and methods

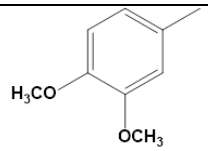
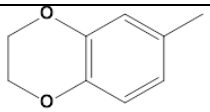
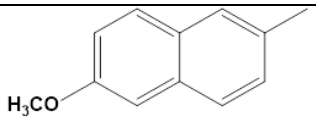
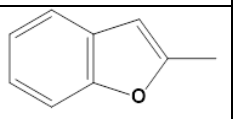
Chemicals used in this study were purchased from Sigma–Aldrich Chemical Company, Bangalore. Melting point (uncorrected) was measured on an open glass capillary on Suntex melting point apparatus.

The infrared spectra of all oximes were recorded with KBr disc in Agilent Cary 630 spectrometer. The ^{1}H- and ^{13}C-NMR spectra of synthesized oxime compounds were recorded on a Bruker Avance III 400 MHz spectrometer. Samples were prepared by dissolving about 10 mg of the compound in 0.5 mL of $CDCl_3$ containing 1% tetramethyl silane (TMS). Radio frequencies 400 and 100.61 MHz were employed for recording ^{1}H- and ^{13}C-NMR spectra. The micro analysis of the oximes was performed in Variomicro V2.2.0 elemental analyzer. The Liquid Chromatography Mass Spectrometry (LCMS) was performed and the LCMS spectra of all compounds were recorded with a Water Micro TOF Qii spectrometer in electron ionization (EI) mode.

2.2. General procedure for the synthesis of oximes

An equimolar amount of aryl methyl ketones (2 mmol) and hydroxylamine hydrochloride (2 mmol), 3 mL of 1 M solution of potassium hydrogen phthalate and 20 mL of ethanol were refluxed for 20 minutes (Scheme 1). The completion of reaction was monitored by thin-layer chromatography (TLC). After succeeded the reaction, the reaction mixture was cooled to room temperature and then it was poured into ice–cold water. The obtained white solid was filtered by vacuum pump, washed with water and dried. The crude product was recrystallized using ethanol.



Entry	1	2	3	4
Ar	 3,4-Dimethoxyphenyl	 2,3-Dihydrobenzo [b][1,4]dioxine-6-yl	 6-Methoxy-2-naphthyl	 2-Benzofuryl

Scheme 1. Synthesis of oximes by potassium hydrogen phthalate assisted condensation of aryl methyl ketones and hydroxylamine hydrochloride.

2.3. Molecular docking analysis

The structures of all synthesized compounds were designed using the Chem Draw software. The structures were optimized and converted to PDB format using Open Babel software. The assigned compounds were utilized to perform molecular docking studies. The three-dimensional structures of the molecular target were downloaded from Protein Data Bank (PDB) (www.rcsb.org): tyrosine kinase inhibitor (PDB: 1QCF) [56-58]. The procedure for receptor preparation involved the removal of heteroatoms (water and ions), the addition of polar hydrogen, and the calculation of charge. The active sites were described using grid boxes of suitable sizes around the bound ligands. The docking study was executed using AutoDock Vina software and the 2D and 3D docking poses were assigned using Discovery Studio for visualization.

2.4. Measurement of antimicrobial activity

Antimicrobial activities of the synthesized oximes were performed with a standard Bauer-Kirby disc-diffusion method [59]. Here each three-gram positive and gram-negative bacterial stains such as *Corynebacterium, Streptococcus agalactiae*, *Enterococcus*, *Acinetobacter*, *Escherichia coli* and *Pseudomonas aeruginosa* are employed for the measurement of antibacterial activity of oximes. Three antifungal microbes such as *Aspergillus niger*, *Candida albicans Mucor species*, *Fusarium oxysporum*, *Penicillium chrysogenum*, *Trichoderma viride* were utilized for the assessment of antifungal activities of oximes.

3. Results and discussion

3.1. Synthesis of ketoximes

The synthesis some ketoximes by potassium hydrogen phthalate assisted condensation of some aryl ketones and hydroxylamine hydrochloride under conventional synthetic method was performed. In this method, the obtained yields were above 75%. The electron donating substituents in the aryl groups gave higher yields than other substituents. This condensation follows the acid catalyzed nucleophilic addition and elimination of water afforded the oximes [60].

In this way the synthesized oximes were characterized using their physical constants, CHN analysis and spectroscopic data. The complete characterization data of oximes are summarized as follows:

(*E*)-1-(3,4-Dimethoxyphenyl)ethanone oxime (1): White solid, Yield: 86%, M.P. 90 – 92 ˚C. FT-IR (KBr, cm^{-1}); ν = 3425 (OH), 2922 (CH), 1412 (C-O-C), 1580 (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.173 (s, 1H, OH), 2.279 (s, 3H, CH_3), 3.912 (s, 6H, OCH_3), 6.852-7.251(m, 3H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 155.69 (CN), 12.13 (CH_3), 55.88, 55.92 (OCH_3), 108.63 – 150.16 (Ar-C). Anal. for M.F.: $C_{10}H_{13}NO_3$, Found (Calcd.): C 61.59 (61.53), H 6.69 (6.71), N 7.12 (7.18) %. MW: 195. LCMS Mass (m/z) = 195, 180, 178, 163, 137, 91, 77, 57, 31, 17, 15.

(*E*)-1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)ethanone oxime (2): White solid, Yield: 78%, M.P. 94-95 ˚C. FT-IR (KBr, cm^{-1}); ν = 3403 (OH), 3060 (CH), 1401 (C-O-C), 1587 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.851 (s, 1H, OH), 2.239 (s, 3H, CH_3), 4.271(s, 4H, -CH_2), 6.850-7.260(m, 3H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.52 (CN), 12.28 (CH_3), 64.43, 64.62 (-CH_2), 115.31 – 144.73 (Ar-C). Anal. for M.F.: $C_{10}H_{11}NO_3$, Found (Calcd.): C 62.19 (62.17), H 5.69 (5.74), N 7.16 (7.25) %. MW: 193. LCMS Mass (m/z) = 193, 178, 176, 162, 148, 135, 78, 58, 33, 30, 17, 15.

(*E*)-1-(6-Methoxynapthalanen-2-yl)ethanone oxime (3): White solid, Yield: 81%, M.P. 113-114 ˚C. FT-IR (KBr, cm^{-1}); ν = 3605 (OH), 2974 (CH), 1451 (C-O-C), 1581 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.152 (s, 1H, OH), 2.477 (s, 3H, CH_3), 3.370(s, 3H, -OCH_3), 7.227-7.238 (m, 6H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.17 (CN), 11.27 (CH_3), 55.87 (OCH_3), 106.88 – 151.81 (Ar-C). Anal. for M.F.: $C_{13}H_{13}NO_2$, Found (Calcd.): C 72.48 (72.54), H 6.02 (6.09), N 6.54 (6.51) %. MW: 215. LCMS Mass (m/z) = 215, 200, 198, 184, 170, 157, 169, 126, 91, 76, 58, 50, 46, 41, 31, 29, 17, 15.

(*E*)-1-(Benzofuran-2-yl)ethanone oxime (4): White solid, Yield: 79%, M.P. 133-105 ˚C. FT-IR (KBr, cm^{-1}); ν = 3605 (OH), 3051 (CH), 1438 (C-O-C), 1590 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.279 (s, 1H, OH), 2.378 (s, 3H, CH_3), 7.010-7.692 (m, 6H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.28 (CN), 11.43 (CH_3), 107.08 – 151.84 (Ar-C). Anal. for M.F.: $C_{10}H_9NO_2$, Found (Calcd.): C 68.61 (68.56), H 5.16 (5.18), N 7.98 (8.01) %. MW: 175. LCMS Mass (m/z) = 175, 160, 158, 144, 143, 117, 98, 83, 66, 58, 31, 23, 17, 16, 15, 126, 91, 76, 58, 50, 46, 41, 31, 29, 17, 15.

The above data are strongly supported for the formation of synthesized oximes. Also, the authors studded the effect of solvents on the condensation by means of obtained yields. This experiment was conducted with solvents like acetonitrile, dichloromethane, dioxane, ethanol, methanol, *n*-propanol and tetrahydrofuran with the same experimental conditions. The influence of solvents on the yield of the condensation of aryl methyl ketone and hydroxylamine hydrochloride was presented in Table 1.

Table 1. The influence of solvents on the yield of the condensation of aryl methyl ketone and hydroxylamine hydrochloride under conventional heating.

Ar →	**1**	**2**	**3**	**4**
Solvent ↓	**Yield (%)**			
Acetonitrile	65	63	61	54
Dichloromethane	58	53	54	50
Dioxane	46	38	51	49
Ethanol	86	78	81	79
Methanol	80	74	76	73
n-Propanol	78	73	77	75
Tetrahydrofuran	58	42	54	49

3.2. Molecular docking effect

The docking results of different substituted oximes **(1-4)** as the synthesized ligands docked with tyrosine kinase inhibitor 1QCF and the obtained binding energy values ranging from -5.18 to – 5.64 kcal/mol. These binding energy values are listed in Table 2. Oxime compound **1** showed the binding energy value -5.29 kcal/mol leads to two hydrogen bond interactions with amino acid residues such as THR A:521, TYR A:520 (Threonine, THR; Tyrosine, TYR), one hydrophobic bond interaction with PRO A:361 (proline) and one electrostatic bond interaction with ASP A:365 (aspartic acid). Oxime **2** showed -5.18 kcal/mol as the binding energy value. This displayed two hydrophobic bond interactions with amino acid residues such as LEU A:325, TRP A:260 (leucine, tryptophan) and two electrostatic bond interactions such as ASP A:258, HIS A:326 and LYS A:315 (aspartic acid, ASP; histidine, HIS; lysine, LYS).

The oxime **3** possess -5.51kcal/mol as its binding energy value and also it shows two hydrophobic bond interactions with amino acid residues such as LEU A:156, LEU A:163 (leucine) and three electrostatic bond interactions such as ASP A:365, LYS A:362, LYS A:516 (aspartic acid and lysine). The binding energy value of compound **4** is -5.64 kcal/mol. It shows three hydrophobic bond interactions with amino acid residues such as GLY A:279, LEU A:407, PHE A:278 (glycine,

leucine, phenylalanine) and two electrostatic bond interactions such as ASP A:404, LYS A:295 (aspartic acid and lysine). Finally concluded that, the compound **4** shows highest binding affinities when compared to other compounds. The 2D and 3D docking poses of all the compounds are represented in Table 2.

Table 2. The 2D and 3D docking poses of synthesized oximes.

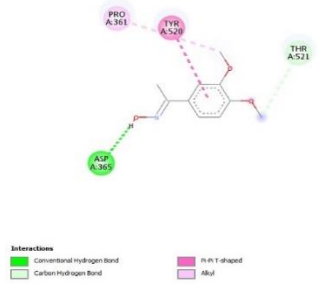
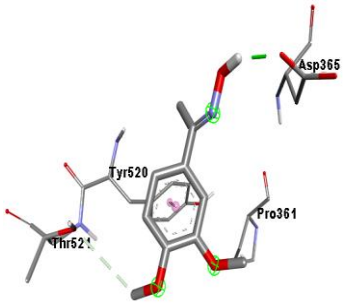
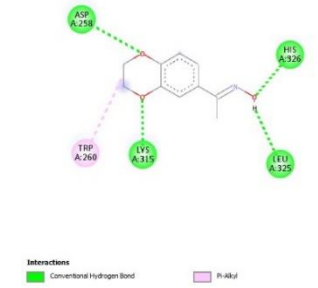
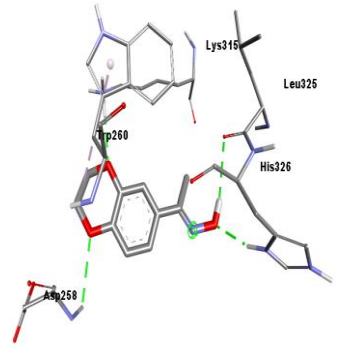
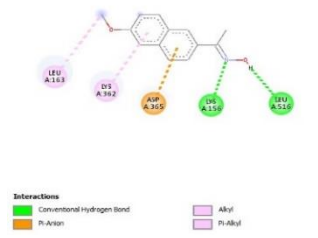
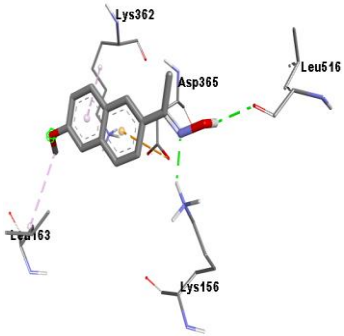
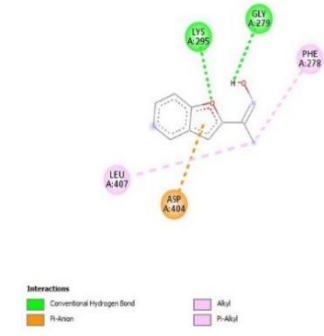
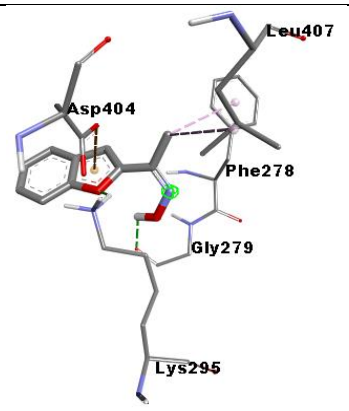
Entry	2D docking pose	3D docking pose	Binding Energy ΔG (kcal/mol)
1			-5.29
2			-5.18
3			-5.51
4			-5.64

Table 3. Antimicrobial activity by means of mm of zone of inhibitions of synthesized oximes.

Ar →	**1**	**2**	**3**	**4**
Microorganisms↓	**Antibacterial activity (zone of inhibition, mm)**			
Corynebacterium	19	12	21	20
Streptococcus agalactiae	21	19	20	19
Enterococcus	20	17	21	18
Acinetobacter	22	18	19	21
Escherichia coli	18	19	19	20

Ar →	**1**	**2**	**3**	**4**
Pseudomonas aeruginosa	20	20	21	19
Standard (Amoxicillin)	22	22	23	22
	Antifungal activity (zone of inhibition, mm)			
Aspergillus niger	14	13	14	13
Candida albicans	13	11	16	14
Mucor species	14	9	16	12
Fusarium oxysporum	15	7	15	11
Penicillium chrysogenum	14	9	14	9
Trichoderma viride	13	13	8	7
Standard (Miconazole)	15	16	17	21

3.3. Antibacterial activity

The measured antibacterial activities by means of mm of zone of inhibitions [61-66] of synthesized oximes are presented in Table 3. The statistical clustered column chart of the antibacterial activity of oximes is illustrated in Figure 1.

From the table, it can be seen that oxime **1** shows good antibacterial activity against all microbial stains.

Oxime **2** also shows good antibacterial activity against all stains, with the exception of *Corynebacterium* on which it shows less activity. Here, the dioxo group reduced the antibacterial activity against the *Corynebacterium* stain.

Oximes **3** and **4** shows good antibacterial activity against all microbial stains. In general, the inductive effect of methoxy group, oxo and furyl moieties enhances the antibacterial activity.

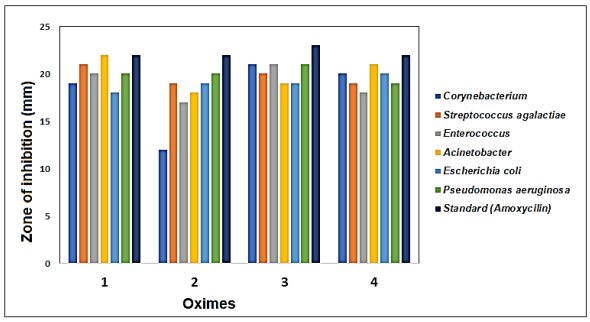


Figure 1. The clustered column chart of antibacterial activity of ketoximes **1 - 4.**

3.4. Antifungal activity

The measured antifungal activities by means of mm of zone of inhibitions [61-66] of synthesized oximes are presented in Table 3. The statistical clustered column chart of the antifungal activity of oximes are illustrated in Figure 2.

From the Table 3 it can be seen that oxime **1** demonstrates good antifungal activity against all microbial stains. Oxime **2** shows good antibacterial activity, except *Mucor species*, *Fusarium oxysporum* and *Penicillium chrysogenum* stains. Here, the dioxo group reduced the antifungal activity against the stains. Oxime **3** presents good antifungal activity except *Trichoderma viride* stain. Oxime **4** reveals only moderate antifungal activity against all fungal stains. This is due to the *+I* effect of methoxy and furyl groups were reduced the activity. In general, the inductive effect of methoxy group, oxo and moieties enhances the antifungal activity.

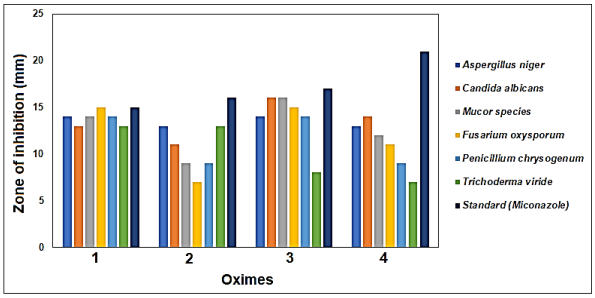


Figure 2. The clustered column chart of antifungal activity of ketoximes **1- 4**.

4. Conclusions

More than 75% yields of four ketoximes were synthesized by potassium hydrogen phthalate assisted condensation of aryl methyl ketones and hydroxylamine hydrochloride under conventional method. These oximes were characterized by their physico-chemical parameters and spectroscopic data. From the results of molecular docking analysis of the oximes, all oximes gave the binding energies of -5 to -5.7 kcal/mol. Among the four, oxime **4** shows slightly good docking character and it had the binding energy of -5.64 kcal/mol. Oximes **1, 3** and **4** presented good antibacterial activity against all bacterial stains. Oxime **2** exhibits a good anti-bacterial activity except *Corynebacterium* stain. Oxime **1** revealed good antifungal activity against all fungal stains. Oximes **2** and **3** displayed good antifungal activity except *Mucor species*, *Fusarium oxysporum*, *Penicillium chrysogenum* and *Trichoderma viride* fungal stains. Oxime **4** was found to possess moderate antifungal activity against all stains.

Conflict of interest

Authors have no conflict of interest to declare.

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