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SHORT COMMUNICATION

Quinoline-based imidazole-fused heterocycles as new inhibitors of 15-lipoxygenase

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Abstract

A series of 2-chloro-quinoline-based imidazopyridines **6a–l** and imidazothiazoles **6m–o** bearing a bulky alkylamine side chain were synthesized as soybean 15-LOX inhibitors. The target compounds **6a–o** were prepared *via* one-pot reaction of 2-chloroquinoline-3-carbaldehyde (**3**), heteroaromatic amidine **4**, and alkyl isocyanides **5**, in the presence of NH_4Cl. All compounds showed significant anti-15-LOX activity (IC_{50} values $\leq 40\,\mu M$). Among the title compounds, the imidazo[2,1-*b*]thiazole derivative **6n** bearing a *tert*-butylamine moiety showed the highest activity against soybean 15-LOX enzyme.

Keywords

Docking study, enzyme inhibitors, 15-lipoxygenase, imidazo[1,2-*a*]pyridine, imidazo[2,1-*b*]thiazole

History

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Introduction

Polyunsaturated fatty acids such as arachidonic acid are implicated in the control of several physiological processes. Lipoxygenases (LOXs) are a class of nonheme iron-containing enzymes which regio- and stereospecifically catalyze the hydroperoxidation of polyunsaturated fatty acids[1]. In humans, three major families of LOXs were found as 5-LOX, 12-LOX, and 15-LOX isoforms. These isoforms (5-, 12-, or 15-LOX) initiate the biosynthesis of leukotrienes, lipoxins, and other compounds by oxidizing the C-5, C-12, and C-15 positions of the key substrate, arachidonic acid[2,3]. For example, 15-LOX oxidizes arachidonic acid to produce mainly 15(*S*)-5*Z*,8*Z*,11*Z*,13*E*-hydroperoxyeicosatetraenic acid (15-HPETE). The bioactive metabolites of 15-LOX hydroperoxidation (e.g. HETE and leukotriene A4) are found to be potent signal transduction modifiers which affect the inflammatory processes[4]. Furthermore, 15-LOX has been implicated in neurodegenerative diseases[5], atherosclerosis[6,7], chronic obstructive pulmonary disease (COPD), and a variety of cancers[8].

Consequently, small molecules affecting the 15-LOX pathway might be therapeutically useful in chronic inflammatory diseases, cardiovascular disorders, and some types of tumors. Thus, medicinal chemists have attended extensively to find new inhibitors of 15-LOX. A part of attentions has been focused on small molecules containing fused heterocyclic systems including indolizine[9,10] and imidazo-fused heterocycles[11,12] previously described (**I**, Figure 1) as a potential inhibitors of 15-LOX. In a study by Wisniewska et al., imidazo[1,2-*a*]pyridine-3-yl-amine analog (**EP6**, **II**) was evaluated as a 5-LOX inhibitor[13]. On the other hand, a series of quinoline-based compounds were reported as potent inhibitors of LOX[14–18]. These findings convinced us to design a new core containing quinoline and imidazole-fused system as a new 15-LOX inhibitors. Thus, we describe here, synthesis, *in vitro* anti-15-LOX activity and docking study of [2-(2-chloro-quinolin-3-yl)-imidazo[1,2-*a*]pyridin-3-yl]amines **6a–l** and [6-(2-chloro-quinolin-3-yl)-imidazo[2,1-*b*]thiazol-5-yl]amines **6m–o** (Figure 1). Following our interests on the chemistry aspects of this core meaning finding new catalysis for the synthesis of imidazo[1,2-*a*]pyridine and imidazo[2,1-*b*]thiazol-quinoline derivatives and their further coupling reaction[19,20], herein, we report the synthesis of new quinolin imidazo[1,2-*a*]pyridine derivatives and also evaluate their soybean 15-LOX inhibitory activity.

Experimental

15-LOX inhibition assay

To evaluate 15-LOX (Lipoxidase from Glycine max, soybean) inhibitory activity of new synthesized compounds, the stock solution of the compounds were prepared by dissolving them in 1 mL of DMSO. To prepare substrate solution (stock concentration = 38 mM), 12 µL linoleic acid was dissolved in 988 µL ethanol. This solution should be used the same day it is

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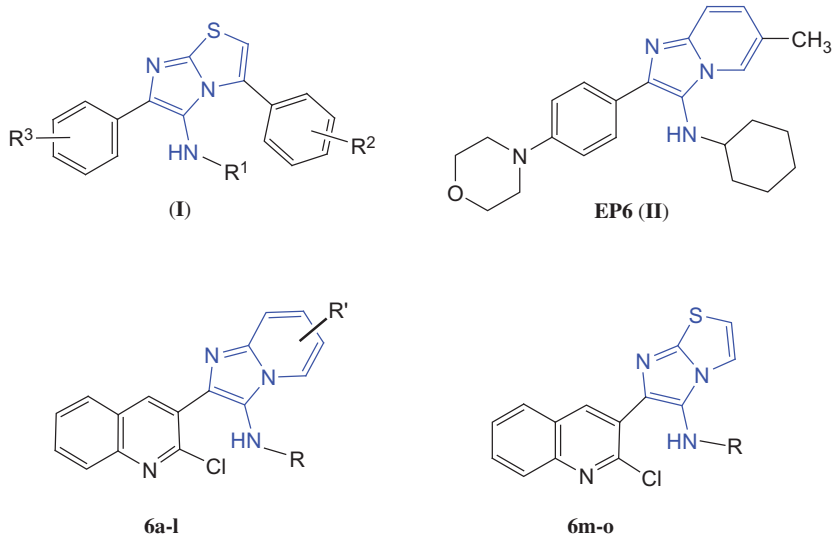


Figure 1. Structures of reported LOX inhibitors **I** and **II**, and designed compounds **6a–o** as new 15-LOX inhibitors.

made. The final concentration of substrate will be 122 μM. Five different concentrations of each compound were tested in triplicate to obtain the inhibition range between 20 and 80%. The test solution was a mixture of 3 mL phosphate buffer (0.1 M, pH = 8), 50 μL enzyme solution (final concentration: 167 U/mL), and 50 μL of target compound solution. Being incubated for 4 min, the substrate (Linoleic acid, final concentration: 122 μM) was added, and the change in absorbance was measured for 60s at 234 nm. A control test was done with the same volume of DMSO (50 μL) to eliminate the effect of DMSO on enzyme activity.

Molecular modeling and docking stimulation

All docking simulations were performed using Autodock Vina (ver. 1.1.1). First, the 3D structure of soybean LOX in complex with 13(S)-hydroproxy-9(Z)-2,11(E)-octadecadienoic acid (code ID: 1IK3) was retrieved from protein databank (www.pdb.org). Then, the co-crystallized ligand and water molecules were removed, and the protein was converted to pdbqt format using Autodock Tools (1.5.4). To prepare the ligands for docking, the 2D chemical structure of ligands was sketched using MarvinSketch 5.8.3, 2012, ChemAxon (http://www.chemaxon.com) and then converted to 3D format by Openbabel (ver 2.3.1). Finally, pdbqt format of ligands was prepared using an Autodock Tools python script, prepare_ligand4.py. The docking parameters were set as follow: size_x = 20; size_y = 20; size_z = 20; center_x = 19.693; center_y = 0.054; center_z = 17.628. The exhaustiveness was set to 100, and the max number of retrieved final docked poses was set to 15 using num_modes parameter. The other docking parameters were left as default. Finally, the most favorable docked poses in terms of free binding energy were selected for analyzing of enzyme–inhibitor interactions.

Chemistry

Commercially available chemicals and reagents were purchased from Merck and Fluka Chemical Company and used without further purification. Melting points are measured with a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were run on a Bruker FT-400 in $CDCl_3$, using TMS as an internal standard. IR spectra were recorded on a Shimadzu 470 spectrophotometer (KBr disks). MS were recorded with an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed with an Elementar Analysensysteme GmbH VarioELCHNS mode.

*General procedure for the synthesis of compounds **6a–o***

A mixture of 2-chloroquinolin-3-carbaldehyde **3** (1.0 mmol), heteroaromatic amidine **4a–f** (1.0 mmol), appropriate alkyl isocyanide (1.2 mmol), and NH_4Cl (1.0 mmol) in toluene (5 mL) was heated under reflux for 12–24 h. After completion of the reaction, as indicated by TLC, the solvent was evaporated under reduced pressure, and the residue was recrystallized from petroleum ether–EtOAc to afford target compounds **6a–o** in 65–93% yields.

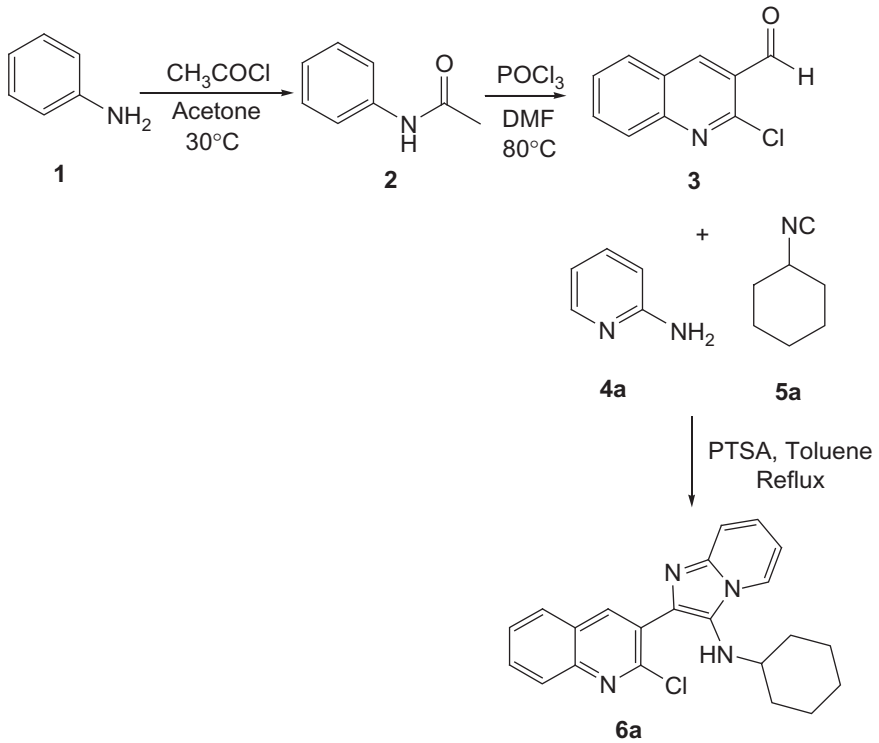
*[2-(2-Chloro-quinolin-3-yl)-imidazo[1,2-a]pyridin-3-yl]-(1,1,3,3-tetramethyl-butyl)-amine (**6c**)*

Yield: 0.32 g (80%); pale yellow solid; mp 168–170 °C; IR (KBr): 3321, 2919, 2848, 1631, 1497, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 9H, $C(CH_3)_3$), 1.29 (s, 6H, $C(CH_3)_2$), 1.42 (s, 2H, CH_2), 3.48 (s, 1H, NH), 6.94 (dd, J = 6.8, 4.0 Hz, 1H, H_6), 7.63 (t, J = 7.5 Hz, 1H, $H_{6'}$), 7.80 (t, J = 7.5 Hz, 1 H, $H_{7'}$), 7.93 (d, J = 8.0 Hz, 1H, $H_{5'}$), 8.09 (d, J = 8.4 Hz, 1H, $H_{8'}$), 8.52 (dd, J = 6.8, 1.6 Hz, 1H, H_7), 8.58–8.59 (m, 2H, H_8, H_5), 8.63 (s, 1H, $H_{4'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.0, 31.5, 31.7, 56.4, 59.4, 108.1, 112.0, 126.2, 127.2, 127.5, 127.9, 128.8, 129.0, 130.9, 131.2, 136.0, 141.8, 145.1, 148.0, 149.1, 150.0. MS: *m/z* (%) 408 (15, $[M+2]^+$), 406 (49, M^+). Anal. Calcd for $C_{24}H_{27}ClN_4$: C, 70.83; H, 6.69; N, 13.77. Found: C, 70.97; H, 6.49; N, 13.84.

*[2-(2-Chloro-quinolin-3-yl)-8-methyl-imidazo[1,2-a]pyridin-3-yl]-cyclohexyl-amine (**6d**)*

Yield: 0.35 g (91%); pale yellow solid; mp 143–145 °C; IR (KBr): 3327, 2971, 1640, 1568, 781 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01–1.69 (m, 10 H, $5CH_2$, cyclohexyl), 2.41 (s, 3H, CH_3), 2.67 (s, 1H, NCH), 3.32 (s, 1H, NH), 6.79 (t, J = 6.4 Hz, 1H, H_6), 7.02 (d, J = 6.4 Hz, 1H, H_7), 7.61 (t, J = 7.6 Hz, 1H, $H_{6'}$), 7.78–7.82 (m, 1H, $H_{7'}$), 7.92 (d, J = 8.0 Hz, 1H, $H_{5'}$), 8.10 (d, J = 8.4 Hz, 1H, $H_{8'}$), 8.24 (d, J = 6.4 Hz, 1H, H_5), 8.61 (s, 1H, $H_{4'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 24.6, 25.6, 33.8, 56.7, 111.6, 121.7, 123.4, 125.7, 127.0, 127.1, 127.3, 127.4, 128.4, 129.7, 130.5, 135.6, 140.8, 141.3, 147.1, 149.0. MS: *m/z* (%) 392 (19, $[M+2]^+$), 390 (58, M^+). Anal. Calcd for $C_{23}H_{23}ClN_4$: C, 70.67; H, 5.93; N, 14.33. Found: C, 70.45; H, 6.13; N, 14.12.

Scheme 1. Preparation of 2-chloro-quinoline-based imidazopyridines and imidazothiazoles.



*[6-Chloro-2-(2-chloro-quinolin-3-yl)-imidazo[1,2-a]pyridin-3-yl]-(1,1,3,3-tetramethyl-butyl)-amine (**6k**)*

Yield: 0.33 g (75%); yellow solid; mp 145–147 °C; IR (KBr): 3274, 2828, 1624, 1607, 1330, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (s, 6H, $C(CH_3)_2$), 0.96 (s, 9H, $C(CH_3)_3$), 1.48 (s, 2H, CH_2), 3.39 (s, 1H, NH), 7.19 (dd, $J = 9.6$, 2.0 Hz, 1H, H_7), 7.54 (dd, $J = 9.6$, 0.8 Hz, 1H, H_8), 7.61–7.65 (m, 1H, $H_{6'}$), 7.77–7.81 (m, 1H, $H_{7'}$), 7.93 (d, $J = 8.0$ Hz, 1H, $H_{5'}$), 8.11 (d, $J = 8.0$ Hz, 1H, $H_{8'}$), 8.24 (dd, $J = 2.0$, 0.8 Hz, 1 H, H_5), 8.51 (s, 1H, $H_{4'}$); ^{13}C NMR (100 MHz, $CDCl_3$):δ 30.0, 31.5, 31.7, 56.5, 59.2, 118.6, 120.7, 121.0, 126.1, 127.4, 127.7, 127.9, 128.0, 128.5, 129.0, 131.1, 134.9, 140.7, 141.0, 147.4, 149.0. MS: *m/z* (%) 444 (10, $[M + 4]^+$), 442 (58, $[M + 2]^+$), 440 (90, M^+). Anal. Calcd for $C_{24}H_{26}Cl_2N_4$: C, 65.31; H, 5.94; N, 12.69. Found: C, 65.24; H, 5.83; N, 12.76.

Results and discussion

Chemistry

In the synthetic route to target compounds **6a–o**, initially aniline (**1**) was converted to *N*-phenylacetamide (**2**) *via* the acetylation reaction in the presence of acetyl chloride and potassium carbonate under mild condition (Scheme 1). Then, 2-chloroquinolin-3-carbaldehyde (**3**) was prepared using the Vilsmeier–Haak reaction in the presence of $POCl_3$ in DMF[21]. The final compounds **6a–o** were synthesized *via* one-pot condensation reaction of aldehyde **3**, an appropriate isocyanide **5a–c** and various hetero-aromatic amidine **4a–f**, in the presence of catalytic amount of ammonium chloride in toluene. After recrystallization from petroleum ether–EtOAc, pure compounds **6a–o** were obtained in 65–93% yields.

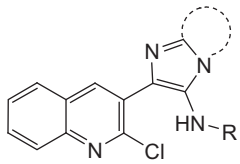
15-LOX inhibitory activity

The inhibitory activity of synthesized compounds was determined[22] against 15-LOX, and the obtained IC_{50} values (IC_{50} expressed as mean ± SD of three independent experiments) were listed in Table 1. All compounds showed significant inhibitory activity with the IC_{50} values ≤40 μM. Among them, compound **6n** possessing IC_{50} value of 11.5 μM was the most potent compound. Furthermore, compounds **6g** and **6i** with IC_{50} values of 15.3 and 14.1 μM were more active than remaining compounds. As seen in Table 1, compounds **6a–l** were imidazopyridine derivatives, and compounds **6m–o** had imidazothiazole substructure. The most potent compound **6n** was imidazothiazole derivative. On the other hand, the potent compounds **6 g** and **6i** were imidazopyridine analogs. In the imidazopyridine series, introduction of bromo or chloro substituent at 6-position decreased the inhibitory activity. The effect of methyl group at 7 or 8 position of imidazopyridine ring depended on the alkyl side chain connected to the amine group. For example, while 7-methyl-imidazopyridine derivative **6i** bearing a 1,1,3,3-tetramethyl-butylamine residue was more potent than **6c**, but 7-methyl-imidazopyridine **6h** containing a *tert*-butyl group found to be as potent as **6b**. The comparison of 7- and 8-methyl regioisomers revealed that 7-methyl derivatives **6g** and **6i** exhibiting more potent activity in respect to their 8-methyl analogs **6d** and **6f**. In contrast, (7-methyl-imidazopyridin-3-yl)amine **6h** was less potent than its 8-methyl regioisomer **6e**.

Docking study

The docking study was performed to clarify the binding mode of the target compounds in the active site of 15-LOX. For this purpose, the tested compounds were docked onto the active site of enzyme using Autodock Vina (ver. 1.1.1)[23,24]. Then, the best docked poses in terms of free binding energy were further analyzed to clarify interactions between ligands and the 15-LOX enzyme. Because of similar orientation of compounds in the active site of 15-LOX, further analysis was performed on the most active compound **6n**. As shown in Figure 2, the target compound

Table 1. Used amidine (**4**) and isocyanide (**5**) derivatives for the one-pot synthesis of compounds **6a–o** including their 15-Lox inhibitory activity.



6a-o

Compound	2-amino azines 4	Isocyanide (R) 5	IC_{50} (μM)
6a	2-amino pyridine	cyclohexyl	21.2 ± 1.0
6b	2-amino pyridine	*tert*-butyl	27.9 ± 1.3
6c	2-amino pyridine	1,1,3,3-tetramethylbutyl	40.0 ± 1.8
6d	2-amino-3-methyl pyridine	cyclohexyl	26.0 ± 1.2
6e	2-amino-3-methyl pyridine	*tert*-butyl	21.8 ± 1.0
6f	2-amino-3-methyl pyridine	1,1,3,3-tetramethylbutyl	20.5 ± 0.9
6g	2-amino-4-methyl pyridine	cyclohexyl	15.3 ± 0.7
6h	2-amino-4-methyl pyridine	*tert*-butyl	28.9 ± 1.3
6i	2-amino-4-methyl pyridine	1,1,3,3-tetramethylbutyl	14.1 ± 0.6
6j	2-amino-5-chloro pyridine	cyclohexyl	44.3 ± 2.0
6k	2-amino-5-chloro pyridine	1,1,3,3-tetramethylbutyl	39.9 ± 1.8
6l	2-amino-5-bromo pyridine	*tert*-butyl	37.6 ± 1.9
6m	2-aminothiazole	cyclohexyl	40[a]
6n	2-aminothiazole	*tert*-butyl	11.5 ± 0.5
6o	2-aminothiazole	1,1,3,3-tetramethylbutyl	19.8 ± 0.9
Quercetine	–	–	30

[a]Percentage (%) of inhibition at 25 μM.

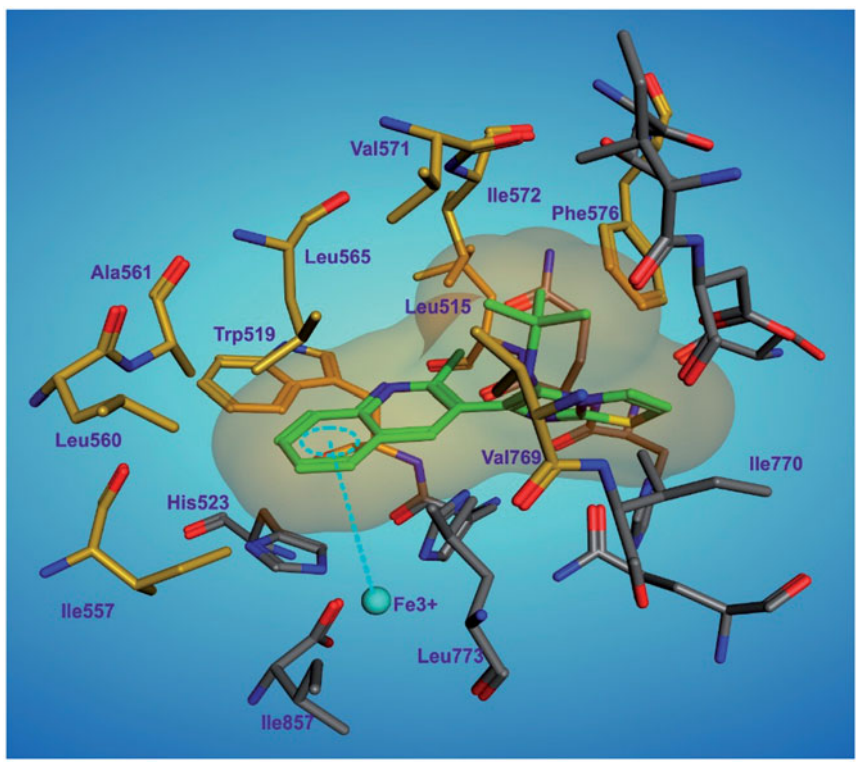


Figure 2. The best docked pose of compound **6n** in the active site of 15-LOX.

was laid near the Fe^{3+} ion in the 15-LOX active site. In this position, the ligand interacted with Fe^{3+} ion through a π-cation interaction *via* phenyl ring of its 2-chloroquinoline moiety. A careful inspection of the binding pocket indicated that this moiety oriented toward a hydrophobic cavity comprised of Trp519, Ile557, Leu560, Ala561, and Leu565. The ligand also established another remarkable hydrophobic interaction via the orientation of *tert*-butylamino group toward a hydrophobic pocket including side chains of Leu515, Val571, Ile572, Phe576, and Val769.

Conclusions

We synthesized a series of 2-chloro-quinoline-based imidazopyridines **6a–l** and imidazothiazoles **6m–o** bearing a bulky alkylamine side chain as soybean 15-LOX inhibitors. The *in vitro* evaluation of title compounds against 15-LOX demonstrated that all compounds had significant inhibitory activity (IC_{50} values $\leq$40 μM). The most potent compound **6n** with IC_{50} value of 11.5 μM was belong to the imidazo[2,1-*b*]thiazole series. However, the imidazopyridine derivatives **6g** and **6i** showed substantial inhibition against 15-LOX (IC_{50} values $\leq$15.3 μM). The limited SAR study revealed that the effect of substituent on imidazopyridine ring depended on the attached alkylamine side chain. The docking study indicated that the target compound **6n** was laid near the Fe^{3+} ion in the 15-LOX active site. A π-cation interaction of 2-chloroquinoline with Fe^{3+} ion and hydrophobic interactions had important roles in the favorable binding of the inhibitor with the enzyme active site.

Supporting information

Experimental details and ^{1}H and ^{13}C NMR spectra are available, via the supplementary content section of this article's web page.

Declaration of interest

The authors report no declarations of interest. This work was supported and funded by Research council of Tehran University of Medical Sciences (TUMS); Grant no: 95-01-92-31756; and Iran National Science Foundation (INSF).

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Supplementary materials online only – For review only at proofing stage