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Design, synthesis, and structure–activity relationship study of *O*-prenylated 3-acetylcoumarins as potent inhibitors of soybean 15-lipoxygenase

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Abstract

In this work, the design, synthesis, and structure–activity relationships of a novel array of geranyloxy and farnesyloxy 3-acetylcoumarin**s** were reported as potent soybean 15-lipoxygenase inhibitors. Among the prepared coumarins, 7-farnesyloxy-3-acetylcoumarin (**12b**) was found to be the most potent inhibitor by IC_{50} = 0.68 μM while *O*-geranyl substituents at positions 5 and 6 of 3-acetylcoumarin (**10a** and **11a**) were not inhibitors. Using docking studies, the binding affinity and the preferred pose of synthetic compounds were considered. It was found that lipoxygenase inhibitory activity and prenyl length chain were directly related. The hydrophobic cavity of the enzyme was more effectively occupied by the farnesyl moiety of the potent inhibitor **12b** rather than other derivatives. Also, with this pose of farnesyl chain in 7-farnesyloxy-3-acetylcoumarins, the acetyl group could be directed to the hydrophilic pocket in the active site.

KEYWORDS
15-lipoxygenase inhibitor, acetyl-moiety, prenyloxycoumarins, SAR studies

1 | INTRODUCTION

Lipoxygenases are nonheme iron-containing proteins that contribute to a new successful eicosanoid pathway by acting as biocatalysts in arachidonic acid's peroxidation at positions 5, 8, 12, and 15 to the corresponding hydroperoxide derivatives (Segraves et al., 2004).

Plants, fungi, and animals are the primary sources of lipoxygenases. The large family of these isoenzymes has broad biological implications, meaning that in mammalians, lipoxygenases are involved in the early formation of pro-inflammatory mediators (Jeon et al., 2009), asthma, immune disorders (Segraves et al., 2004), various cancer promoters, especially prostate and breast cancers (Das et al., 2007), atherosclerosis (Bocan et al., 1998), neurodegeneration (van Leyen et al., 2006), obesity, and diabetes (Menteşe et al., 2016).

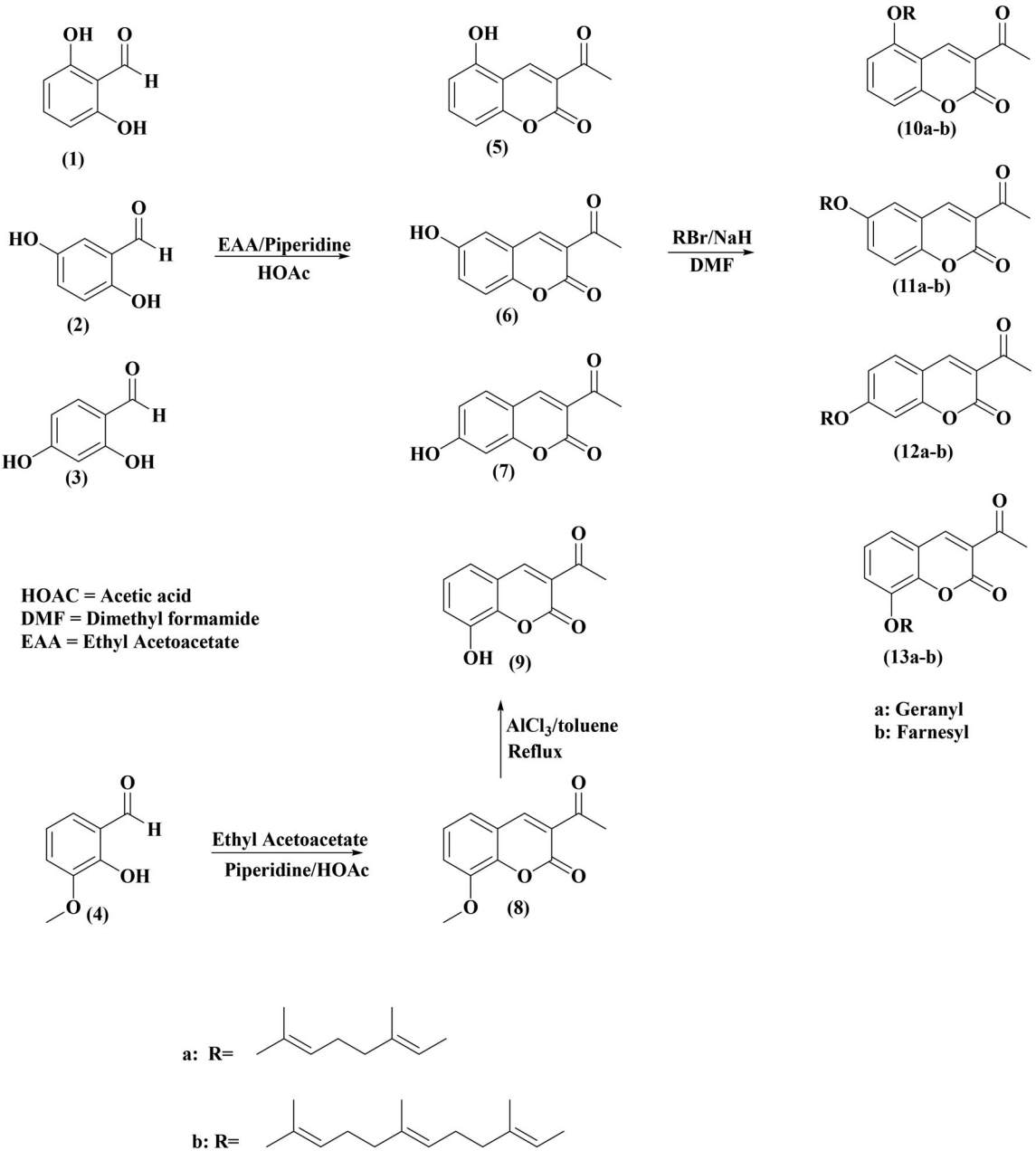
Today, the use of lipoxygenase inhibitors for therapeutic purposes has received increasing attention. So far, a variety of 15 LOX inhibitors have been synthesized and categorized based on their chemical structure, including heterocyclic, phenolic, allyl, and allyloxy benzene derivatives (Sadeghian & Jabbari, 2016).

Coumarin is among the widely acclaimed heterocyclic structures that have been recorded as lipoxygenase inhibitors. Coumarins are classified as lactones with a benzopyrone scaffold, consisting of benzene joined to a pyrone ring. They were mainly synthesized through Pechmann (Panetta & Rapoport, 1982), Perkin (Matos et al., 2009), Knoevenagel (Kumar et al., 2011), Wittig (Upadhyay & Kumar, 2009), Baylis–Hillman (Kaye & Robinson, 1996), Michael addition (Rao & Sivakumar, 2006), and Palladium-catalyzed (Trost et al., 2003) reactions.

Based on its structure, coumarin can be parted into (a) substituted coumarins, (b) ring-fused coumarins, and (c) *C*-, and *O*-prenylcoumarins (Curini et al., 2006). Prenyloxycoumarins (isopentenyloxy, geranyloxy, farnesyloxy, and other biosynthetic derivatives) are secondary metabolites commonly extracted from plants that belong to Rutaceae and Umbelliferae families. Until

recently, oxyprenylated compounds were regarded as biosynthetic intermediates of C-prenylated coumarins. Thus, scant attention has been paid to the biological activities of prenyloxycoumarins, which were either isolated or synthesized. Maleki et al. analyzed the structure–activity relationship (SAR) study of 18 *O*-prenylated coumarin derivatives. They revealed they were not toxic in normal cells, and oxyprenylation in position 6 of the coumarin ring largely inhibited HeLa cell (cervical cancer) growth (Maleki et al., 2020). Geovese and coworkers introduced oxyprenylated coumarins with electron-withdrawing groups as whitening agents in melanogenesis (Genovese et al., 2019). They reported that 7-geranyloxycoumarin exerted remarkable effects in various inflammatory diseases associated with the activation of the acquired immune system, such as asthma and multiple sclerosis (Askari et al., 2020). Also, recent studies have demonstrated that prenyloxycoumarins are potent inhibitors of different types of LOX isoenzymes (Fiorito et al., 2018; Iranshahi et al., 2012; Jabbari et al., 2017; Kavetsou et al., 2017; Kavetsou et al., 2020).

In recent years, a growing number of studies have explored a variety of 3-acetyl coumarin scaffolds, which are completely synthesized through the Knoevenagel condensation of 2-hydroxybenzaldehyde derivatives with ethyl acetoacetate. Some of the 3-acetyl coumarin derivatives have been recognized to possess plentiful remedial functions, including cytotoxic activity (Molaverdi et al., 2013), the inhibition of human monoamine oxidase enzymes A and B (Secci et al., 2011), antibacterial properties, radical scavenging effects, and antiretroviral activity against HIV-1 infection (Srivastav et al., 2018).



SCHEME 1 General procedure for the synthesis of *O*-prenylated-3-acetylcoumarins

In this project, in line with our previous studies on *O*-prenylated coumarin and *O*-prenylated 3-carboxycoumarin derivatives, which were highly effective 15-LOX inhibitors (Iranshahi et al., 2012; Jabbari et al., 2017), we give an introduction of the synthesis, structural characterization and, in vitro inhibitory potency of 15-soybean lipoxygenase, along with SAR studies on new derivatives of oxyprenylated coumarins. This research aimed to design and synthesis of new *O*-prenylated-3-acetylcoumarin analogs to investigate the role of acetyl groups in the soybean LOX inhibitory activity of prenyloxy coumarins.

2 | RESULTS AND DISCUSSION

The synthesis of novel *O*-prenylated-3-acetylcoumarin derivatives is depicted in Scheme 1. All eight analogs including geranyloxy and farnesyloxy moiety at positions 5, 6, 7, and 8 of 3-acetyl coumarin (**10a-b**, **11a-b**, **12a-b**, and **13a-b**) were synthesized through the prenylation of desired 3-acetyl hydroxycoumarin compounds (**5**, **6**, **7**, **and 9**) with prenyl bromide and sodium hydride as a base in dry DMF (Jabbari et al., 2017). All *O*-prenylated-3-acetylcoumarins were purified by column chromatography and were also structurally determined by ^{1}H and ^{13}C NMR spectroscopy. Compounds **5**, **6**, as well as **7**, were prepared by Knoevenagel reaction of dihydroxybenzaldehyde (**1**, **2**, and **3**) with ethyl acetoacetate (KhanYusufzai et al., 2017), while 8-hydroxy-3-acetyl coumarin (**9**) was obtained from Knoevenagel condensation of 2-hydroxy- 3-methoxy benzaldehyde (**4**) with ethyl acetoacetate. It was then followed by the demethylation of the resulted methoxy-3-acetyl coumarins (**8**) via refluxing with anhydrous aluminum chloride in dry toluene (Kalaiarasi et al., 2018) (Scheme 1).

The inhibitory potency of synthetic compounds toward soybean 15-lipoxygenase (SLO) was measured using the rectified catalytic oxidative coupling of 3-methyl-2-benzothiazolinone (MBTH) with 3-(dimethylamino)benzoic acid (DMAB), just as announced in an initial survey.(Jabbari et al., 2012). In this procedure, the 15-SLO enzyme assay is conducted to determine fatty acid peroxide concentration. The analyses were performed in the presence of a widely known lipoxygenase inhibitor, 4-methyl-2-(4-methylpiperazinyl)pyrimido [4,5-b]benzothiazine (4-MMPB; CAS 928853-86-5) as the standard.

According to our previous studies, given the shallow inhibitory potential of allyloxy and isopentenyloxy chain in coumarins (Iranshahi et al., 2012) and coumarin-3-carboxylic acid (Jabbari et al., 2017), in this project, only *O*-geranyl and *O*-farnesyl of 3-acetylcoumarin were synthesized and studied. Prenylated-3-acetylcoumarins in positions 7, 8 of aromatic ring demonstrated the best inhibitory activity at IC_{50} value less than 5 μM compared with 4-MMPB (IC50 = 18.00 μM) as a standard (Table 1). Among the prepared coumarins, farnesyloxy series exhibited the best inhibitory activity toward soybean15-lipoxygenase while compounds (**10a** and **11a**) were inactive (Table 1). As shown by data, 7-farnesyloxy analog (**12b**) was a potent inhibitor by an IC_{50} value of 0.68 μM. Compound **10b** was a low active inhibitor by an IC_{50} value of 34.16 μM among the farnesyloxy derivatives. The most active LOX inhibitor among *O*-geranylated series was compound **12a**

TABLE 1 Inhibitory assessment data of *O*-prenylated-3-acetylcoumarins in comparison with 4-MMPB against soybean 15-lipoxygenase. The data are shown as ±*SD*

Compound	IC_{50}	Compound	IC_{50}
10a	<100	**13b**	1.46 ± 0.02
10b	34.16 ± 0.2	**10b′**	0.8 ± 0.1
11a	<100	**11b′**	2.1 ± 0.1
11b	13.5 ± 0.2	**12b′**	3.1 ± 0.1
12a	3.3 ± 0.18	**13b′**	5.8 ± 0.2
12b	0.68 ± 0.2	4-MMPB	18 ± 0.8
13a	4.1 ± 0.2		

Abbreviation: 4-MMPB, 4-methyl-2-(4-methylpiperazinyl)pyrimido[4,5-b] benzothiazine.

with IC_{50} 3.3 μM. The result suggested that the soybean LOX inhibitory activity was improved by increasing the prenyl chain. It is remarkably enhanced in *O*-prenylated-3-acetyl coumarins from geranyl to farnesyl moiety on positions 5 and 6, while in other positions (7, 8), its effect was less significant (five- and three-fold increase, respectively).

To obtain a profound understanding of the structural parameters responsible for desired coumarins' inhibitory potency, docking studies of these molecules into the active site of 15-soybean lipoxygenase (PDB Code: 1IK3) were performed. To do so, AutoDockTools (ADT) software was used to analyze 100 conformers of the compounds generated. In docking, rotatability of the flexible side chain of the active site pocket remains was authorized (Leu277, Leu515, Leu557, Leu560, Leu565, Val566, Ile572, Phe576, Leu773, and Ile857). Also, the Fe core was modified to Fe^{III}–OH based on our previous study (Iranshahi et al., 2012). The docking analysis showed versatile interactions between these molecules and nonpolar and polar amino acids. Analysis of the proposed binding of the best inhibitor **12b** (Figure 1) within the active site revealed that the farnesyloxy chain was surrounded by Leu277, Lys278, Leu515, His518, Trp519, His523, Ile557, Leu560, Leu565, Val566, Leu773, and Ile857. At the same time coumarin scaffold was shielded by side chains of Val 372, Ser510, His513, Gln514, His 518, Thr575, Phe576, Gln716, Thr717, Gly720, Gln721, Arg726, Thr728, Asp766, Val769, Ile770, Phe848, and Arg849. Among these amino acids, Ser510, Gly720, Gln721, Arg726, and Thr728 provided a suitable hydrophilic pocket for the acetyl functional group. Eleven residues from cited amino acids, including Ile557, Leu560, Leu565, Val566, Ile572, Leu773, Ile857, His513, Gln514, Gln716, and Asp766 were highly conserved (Sadeghian et al., 2009). The docking results with compound **12b** exhibited π-π interaction between Phe576 and the aromatic ring of coumarin.

It also was observed that the carbonyl group in the pyranone ring and acetyl group were able to make a hydrogen bond with the side chain of His513 and Ser510 amino acids residue, respectively. A strong relationship was detected between binding energies and the inhibitory activities of compounds, **12b** and **10a** and **11a** (ΔGbinding = −11.7 and −10.05 and −9.41 kcal/mol), which were the most and least active inhibitors, respectively. By considering the

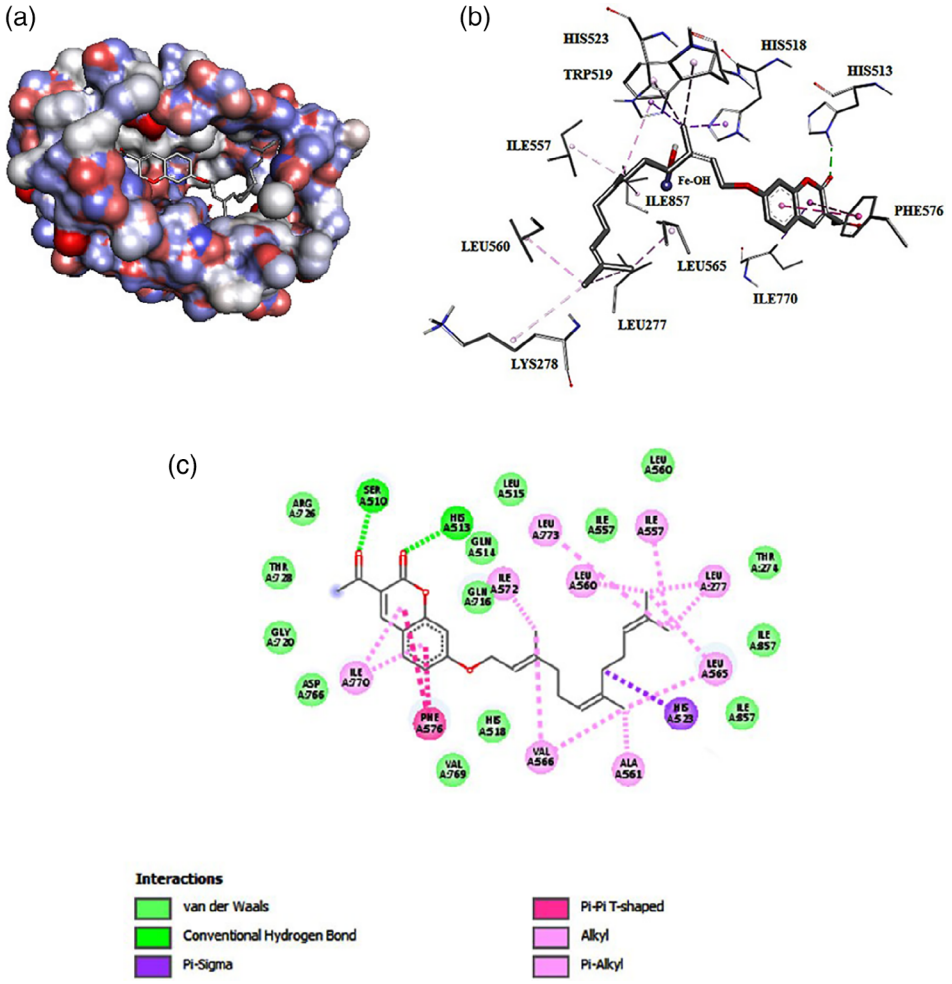


FIGURE 1 (a) Stick and solvent surface view of the 15-soybean 15-lipoxygenase (SLO) (PDB code: 1IK3) active site residues interactions with the conformer with the least Ki of **12b**. (b) The docking pose of the conformer with the least Ki of **12b** in active site pocket of 15-SLO. (c) 2D representation of the interaction of conformer with the least Ki of compound **12b** in 15-soybean 15-lipoxygenase (SLO)

docked conformers of synthetic compounds it was found that the lipoxygenase inhibition potency and prenyl length chain were directly related due to the ability of the more extended prenyl moiety (farnesyl) of prenyloxy-3-acetylcoumarins to occupy the lipophilic cavity, which is created by Leu277, Leu515, Trp519, Ile557, Leu560, Leu565, Val566, Ile572, Leu773, and Ile857.

To examine the effect of acetyl functional group on inhibitory activity, a comparison was made between the lipoxygenase inhibition of synthetic compounds and analogs without acetyl substituents. For this aim, soybean 15-LOX inhibitory potency of all farnesyloxy derivatives at position 5-, 6-, 7-, and 8-coumarin (**10b**′, **11b**′, **12b**′, and **13b**′, respectively), reported in our previous study (Iranshahi et al., 2012) were compared to the *O*-farnesyl derivatives of 3-acetylcoumarins (**10a-b**, **11a-b**, **12a-b**, **13a-b**) (Figure 2). It was worth noting that **12b** and **13b** with the farnesyloxy moiety at positions 7 and 8 demonstrated a higher lipoxygenase inhibitory activity than the corresponding analogs with no acetyl group (4.5–1.4 folds higher, respectively). However, **10a** and **11a** inhibitors were 43–7 times weaker than similar coumarin derivatives, respectively. The preferred docking pose of **12b** and **12b'**in soybean 15-LOX was shown in Figure 3. The superimposition of two compounds demonstrated that the status of coumarin scaffold (due to two hydrogen bond with HIS513 and SER510) and prenyl moiety of the docked conformers of 7-farnesyloxy-3-acetylcoumarins (**12b**) and 7-farnesyloxycoumarins (**12b**′) were not identical. The hydrophobic cavity was filled entirely by the farnesyl chain of **12b**. Hence, it was the more desirable inhibitor. Generally, the significant parameter of the inhibitor bonding propensity to SLO is the hydrophobic nature of the active site pocket, which is formed by the lipophilic side-chain of Leu277, Leu515, Trp519, Ile557, Leu560, Leu565, Val566, Ile572, Leu773, and Ile857. It can contribute to a lead for designing brand-new inhibitors. Despite the same remarkable inhibitory constant for **12b** and **10b**′ (IC_{50} = 0.68 μM), 7-*O*-farnesyl-3-acetylcoumarin seems to be a better candidate for further development and studies. The synthesis procedure of these analogs was more convenient than that of 5-*O*-farnesylcoumarin (**10b**′). Several studies have led to synthesizing brand-new coumarins' derivatives to disclose desirable functional groups at various positions (from C-3 to C-8) of coumarin nucleus to come by a higher biological activity. The analysis of related SAR studies revealed that a coumarin ring bearing a polar substitution (—OR, —OH, —NH) at position 7 further improved the biological activity. Regarding the results of this research and our previous study (Iranshahi et al., 2012), it could be concluded that the acetyl as a mild electron-withdrawing group at position 3, led to positive effect on

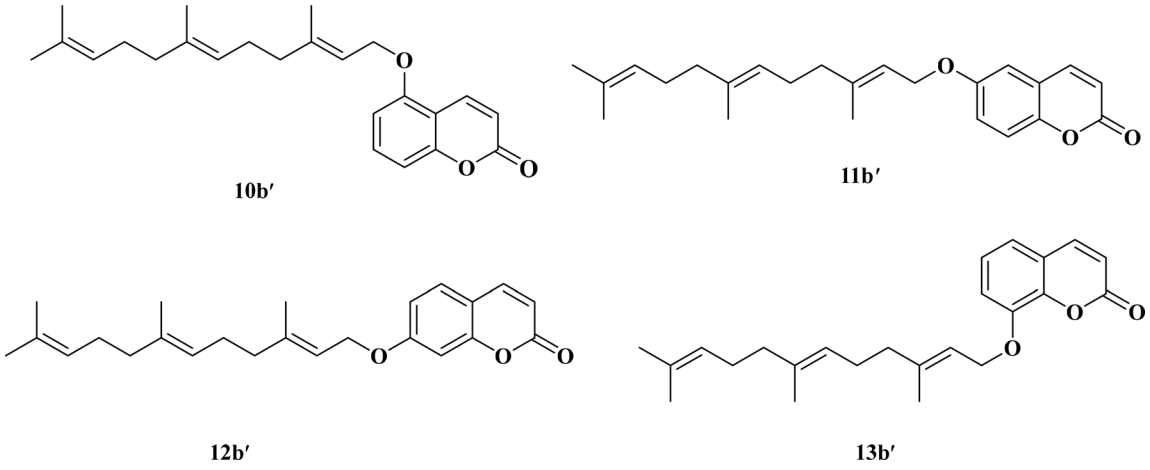


FIGURE 2 Structure of compounds **10b′**, **11b′**, **12b′**, and **13b′**

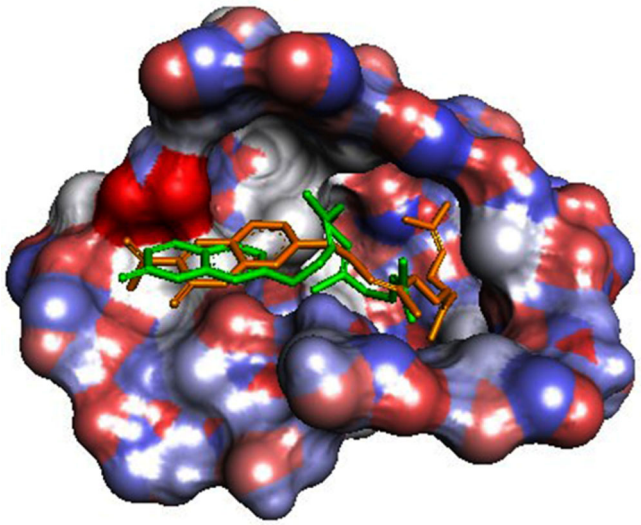


FIGURE 3 Superimposition of conformer with the least Ki of compounds 12b (orang stick) and **12b′** (green stick) in soybean 15-LOX active site

15-LOX inhibitory activity of *O*-prenyl chain as polar moiety at positions 7, and 8 rather than 5,6 positions.

3 | CONCLUSION

In conclusion, new geranyloxy and farnesyloxy derivatives in all positions of the aromatic ring of 3-acetylcoumarin were synthesized, characterized, and assessed in vitro as soybean 15-LOX inhibitors. Among eight newly synthesized coumarins, **12a**, **12b**, **13a**, and **13b** showed excellent inhibitory activities against 15-LOX and were more potent than 4-MMPB as the standard (IC_{50} = 18.00 μM). In this work, 3-acetylcoumarin with farnesyloxy chain at position 7 was found to be the best inhibitor (IC_{50} = 0.68 μM). According to the SAR, the inhibitory activity of **12b** is possibly due to the H-bond interaction of coumarin nucleus with His513, and SER510 as well as hydrophobic-hydrophobic interaction of prenyl chain with the lipophilic side chain of amino acids in the active site.

4 | MATERIALS AND METHODS

4.1 | Structure optimization

ChemDraw Ultra 12.0 used to sketch the required structures transported to the HyperChem 8.07 software and geometrical form optimized by classic MM^+ (RMS gradient = 0.05 kcal mol^{-1}) to simulating of the 3D scaffolds. Crystal skeleton of SLO in combination with 13(S) - hydroproxy-9(Z)-2,11(E)-octadecadienoic acid was repossessed from RCSB Protein Data Bank (PDB entry: 1IK3).

4.2 | Molecular docking

The ligand of the SLO 3D structure was eliminated. Then, the Fe was altered to Fe^{III}-OH, in terms of geometrical form optimized using MM^+ approach in HyperChem12.0 and embedded in pdb format for docking procedure (Iranshahi et al., 2012). Docking of the minimized structures into the active site of 1IK3 was carried out using AutoDock 4.2 (Morris et al., 2009). The torsion angles of the ligands were determined, bond lengths were edited out, hydrogens and solvent parameters were added to the enzyme 3D structure. Partial atomic charges were then dedicated to the macromolecule and ligands (Gasteiger for the ligands and Kollman for the protein). The docking areas of the enzyme were determined by supposing a Cartesian chart 18.3, 4.8, and 19.2 as the center of a grid size with 44, 56, and 62 points in X, Y, and Z axes. The docking parameter files were generated utilizing Lamarckian genetic algorithm Parameters while the number of generations and the maximum number of energy assessments was set to 100 and 2,500,000, successively. The 100 docked complexes were clustered with a root-mean-square deviation tolerance of 2.5 Å.

Docking outcomes were submitted to Accelrys Discovery Studio v4.5 for further simulation.

4.3 | Lipoxygenase inhibitory assessment

Linoleic acid and two assay solutions (A and B) were arranged beforehand. Solution A was 50 mM DMAB in an l00 mM phosphate buffer (pH 7.0). Solution B was a mixture of 10 mM MBTH (3 ml), hemoglobin (5 mg/ml, 3 ml) in 50 mM phosphate buffer at pH 5.0 (25 ml). A linoleic acid solution was arranged using mixing 5.6 mg of linoleic acid (Sigma Aldrich, L1376) with 0.5 ml methanol and then diluted with KOH 100 mM to a final volume 5 ml (4 mM). In the standard assay, the sample in ethanol (25 μl), SLO (4000 units/ml in 50 mM phosphate buffer pH 7.0; 25 μl) and phosphate buffer pH 7.0 (50 mM; 900 μl) were mixed in a test tube, and preincubation was done for 5 min at ambient temperature. A control test was carried out by an equal volume of ethanol. After the preincubation, linoleic acid solution (50 μl) was added to start the peroxidation reaction at 30°C, and, 7 min later, solution A (270 μl) and afterward solution B (130 μl) was added to commence the color formation. Moreover, in 3 min then 200 μl of a 2% SDS solution was added to conclude the reaction. The absorbance at 598 nm was compared with the control test. These experiments were carried out in triplicate. The data evaluation was accomplished utilizing GraphPad Prism 5.01.

5 | EXPERIMENTAL SECTION

5.1 | Instruments

The IR spectra were acquired by a 4300 Shimadzu Spectrometer. ^{1}H NMR (300 MHz) was acquired by a Bruker Avance DRX-300 Fourier transformer spectrometer. Chemical shifts are stated in parts per million (δ) downfield from tetramethylsilane. The mass spectra were recorded on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer. Performance of lipoxygenase was analyzed utilizing BioTek Synergy HTX Multi-Mode reader. Chemicals were bought from Aldrich and Merck Co.

5.1.1 | General procedure for preparation of 3-acetylhydroxycoumarins (5), (6), and (7)

Desired hydroxysalicylaldehyde (2,6-dihydroxybenzaldehyde (**1**), 2,5-dihydroxybenzaldehyde (**2**), and 2,4-dihydroxybenzaldehyde (**3**)) (3 mmol, 0.411 g), ethyl acetoacetate (4.0 mmol, 0.5 ml), acetic acid (2 drops), piperidine (5 drops) and ethanol (8 ml) were refluxed for 4 h. After the reaction was finished (control with TLC), the solvent volume reduced, and the crude products were crystallized by ethanol (Martínez-Martínez et al., 2012).

5.1.2 | 3-Acetyl-5-hydroxy-2H-chromen-2-one (5)

Yellow solid, yield 45%, m.p. 238–240°C; IR (KBr disc) ν 3484, 3178, 3080, 3047, 2920, 2735, 1735, 1640 cm^{-1}; MS (*m/z*) 204 (M^+), 187, 161; Anal. calcd for $C_{11}H_8O_4$: C 64.71, H 3.95, found: C 64.02, H 4.00%.

5.1.3 | 3-Acetyl-6-hydroxy-2H-chromen-2-one (6)

Green crystals, yield 65%, m.p. 246–249°C; Lit: 247–248°C (Martínez-Martínez et al., 2012); IR (KBr disc) ν 3468.79,3168, 3063, 3047, 2945, 2735, 1740, 1644, 1567, 1119 cm^{-1}; MS (*m/z*) 204 (M^+).

5.1.4 | 3-Acetyl-7-hydroxy-2H-chromen-2-one (7)

White crystals, yield 65%, m.p. 226–228°C; Lit: 236–238°C (Durgapal et al., 2020); IR (KBr disc) ν 3490, 3065, 2982, 2929, 1716, 1662, 1603, 1451, 1049 cm^{-1}; MS (*m/z*) 204 (M^+).

5.2 | General procedure for preparation of 3-acetyl-8-hydroxycoumarin (9)

3-Methoxysalicylaldehyde (**4**) (3 mmol; 0.45 g), ethyl acetoacetate (4.0 mmol, 0.5 ml), acetic acid (2 drops), piperidine (5 drops) and ethanol (8 ml) were refluxed. After 4 h, the reaction mixture was cooled, and the crude precipitate was formed by adding water. The produced methoxy-3-acetylcoumarin (**8**) was recrystallized by ethanol and after drying, used for the next step.

5.2.1 | 3-Acetyl-8-methoxy-2H-chromen-2-one (8)

Orange crystals, yield 60%, m.p. 143–144°C; IR (KBr disc) ν 3076, 3015, 2941, 1734, 1685, 1601, 1092 cm^{-1}; MS (*m/z*) 218 (M^+), 175 (M-COMe).

A mixture of 8-methoxy-3-acetylcoumarin (**8**) (0.3 mmol, 0.07 g) and $AlCl_3$ (0.9 mmol, 0.12 g) were suspended in dry toluene (25 ml) and refluxed for 24 h. The precipitate was poured into HCl (10%) solution and extracted with chloroform. After washing with water, 8-methoxy-3-acetylcoumarin (**9**) was prepared with good purity and yield in brick color (Kalaiarasi et al., 2018).

5.2.2 | 3-Acetyl-8-hydroxy-2H-chromen-2-one (9)

Brick crystals, yield 50%, m.p. 249–251°C; Lit: 253°C (la Pietra et al., 2012) IR (KBr disc): ν 3227, 3039, 2921, 1696, 1679, 1600 cm^{-1}; MS (*m/z*) 204 (M^+).

5.3 | General procedure for preparation of prenyloxy-3-acetylcoumarins (10a-b, 11a-b, and 12a-b, 13a-b)

To cold desired 3-acetyl hydroxycoumarins (compounds: 5, 6, 7, 9) (0.9 mmol, 0.20 g) in dry dimethylformamide (4 ml), sodium hydride (2 mmol, 0.064 g) was added, stirred for 30 minutes. Then prenyl bromide (1.0 mmol) was added slowly to the reaction mixture at 50°C. After controlling the reaction completion using TLC within 5–10 h, the reaction mixture was poured into cold hydrochloric acid (10%). The resulting extracted with chloroform three times (3 × 10 ml) then the solution of sodium hydroxide (2 × 5) was utilized for washing up the organic layer to remove unreacted hydroxycomarin derivatives. Finally, organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The remains were purified by silica-gel thin-layer chromatography (EtOAc/n-hexane 1:20).

5.3.1 | 3-Acetyl-5-((E)-3,7-dimethylocta-2,6-dienyloxy)-2H-chromen-2-one (10a)

Yellow amorphous solid, 47% yield; m.p.: 43–45°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (s, 3H, CH_3 (geranyl)), 1.70 (s, 3H, CH_3 (geranyl)), 1.79 (s, 3H CH_3 (geranyl)), 2.15-2.20 (m, 2-CH_2 (geranyl)), 2.63 (s, 3H, H(Acetyl)), 4.73 (d, *J* = 6.3 Hz, 2H, -OCH_2 (geranyl)), 5.08–5.11 (m, 1H, =CH (geranyl)), 5.52–5.55 (t, *J* = 6 Hz, 1H, =CH (geranyl)), 6.85 (d, *J* = 8.1 Hz, 1H, H-8 (coumarin)), 7.03 (d, *J* = 8.1 Hz, 1H, H-6 (coumarin)), 7.65–7.70 (t, *J* = 8.1 Hz, 1H, H-7 (coumarin)), 9.36 (s, 1H, H-4 (coumarin)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16, 16.8, 17.7, 25.7, 26., 26.6, 39.5, 65.8, 100.9, 111.9, 114.4, 117.9, 120.4, 123.3, 131.3, 135.6, 142.9, 147.8, 157.7, 159.8, 164.6, 195.5 ppm; IR (KBr): 3060, 2966, 1759, 1679, 1606 cm^{-1}; MS (*m/z*) 340 (M^+), 203, 187, 160; Anal. calcd for $C_{21}H_{24}O_4$: C 74.09, H 7.11, found: C 73.02, H 7.14%.

5.3.2 | 3-Acetyl-5-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyloxy)-2H-chromen-2-one (10b)

Yellow amorphous solid, yield 40%; m.p. 39–41°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 3H, CH_3 (farnesyl)), 1.54 (s, 3H, CH_3 (farnesyl)), 1.60 (s, 3H CH_3 (farnesyl)), 1.70 (s, 3H, CH_3 (farnesyl)), 1.89–2.08 (m, 8H, 4-CH_2 (farnesyl)), 2.60 (s, 3H, H(Acetyl)), 4.64 (d, *J* = 6.6 Hz, 2H, -OCH_2 (farnesyl)), 4.98–5.03 (m, 2H=CH (farnesyl)), 5.41–5.45 (t, *J* = 6.3 Hz, 1H, =CH (farnesyl)), 6.76 (d, *J* = 8.4 Hz, 1H, H-8 (coumarin)), 6.93 (d, *J* = 8.4 Hz, 1H, H-6 (coumarin)), 7.55–7.61 (t, *J* = 8.4 Hz, 1H, H-7 (coumarin)), 9.26 (s, 1H, H-4 (coumarin)), 2H, -OCH_2 (farnesyl)), 5.08–5.13 (m, 2H, =CH (farnesyl)), 5.48–5.52 (t, *J* = 6.39 Hz, 1H, =CH (farnesyl)), 7.08 (d, *J* = 2.67 Hz, 1H, H-5 (coumarin)), 7.26 (d, *J* = 2.73 Hz, 1H, H-7 (coumarin)), 7.34 (d, *J* = 10.98 Hz, 1H, H-8 (coumarin)), 9.26 (s, 1H, H-4 (coumarin)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16, 16.8, 17.7, 25.7, 26.1, 26.6, 30.6, 39.5, 39.6, 65.8, 101, 111.9, 114.4, 117.9, 120.4, 123.3, 124.2, 131.3, 131.4, 135.6, 142.9, 147.8, 157.7, 159.4, 195.8, 164.6, 195.6 ppm; IR (KBr): 2962, 2925–2851, 1735, 1617, 1200 cm^{-1}; MS (*m/z*) 408 (M^+), 203, 187; Anal. calcd for $C_{26}H_{32}O_4$: C 76.44, H 7.90, found: C 76.78, H 7.98%.

5.3.3 | 3-Acetyl-6-((E)-3,7-dimethylocta-2,6-dienyloxy)-2H-chromen-2-one (11a)

Green crystals, yield 55%; m.p. 86–87°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (s, 3H, CH_3 (geranyl)), 1.59 (s, 3H, CH_3 (geranyl])), 1.69 (s, 3H, CH_3 (geranyl)), 2.00–2.10 (m, 4H, 2-CH_2 (geranyl)), 2.66 (s, 3H, H(Acetyl)), 4.51 (d, *J* = 6.3 Hz, 2H, -OCH_2 (geranyl)), 4.99–5.01 (m, 1H, =CH (geranyl)), 5.38–5.42 (t, *J* = 6.42 Hz, 1H, =CH (geranyl)), 6.97 (d, *J* = 2.64 Hz, 1H, H-5 (coumarin)), 7.16 (d, *J* = 2.67 Hz, 1H, H-7 (coumarin)), 7.25 (d, *J* = 9.09 Hz, 1H, H-8 (coumarin)), 8.38 (s, 1H, H-4 (coumarin)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7, 17.7, 25.7, 26.2, 30.7, 39.5, 65.6, 112.2, 119.9, 123.6, 124.5, 132, 142.2, 147.4, 159.4, 168.6, 195.7 ppm; IR (KBr): 3076, 2958, 1736, 1685, 1614, 1187 cm^{-1}; MS (*m/z*) 340 (M^+), 203, 187, 160; Anal. calcd for $C_{21}H_{24}O_4$: C 74.09, H 7.11, found: C 74.02, H 6.94%.

5.3.4 | 3-Acetyl-6-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyloxy)-2H-chromen-2-one (11b)

Green crystals, yield 50%; m.p. 72–74°C; 1H NMR (300 MHz, CDCl3): δ = 1.63 (s, 6H, CH3 (farnesyl)), 1.71 (s, 3H, CH3 (farnesyl)), 1.80 (s, 3H CH3 (farnesyl)), 1.99–2.15 (m, 8H, 4-CH2 (farnesyl)), 2.76 (s, 3H, H(Acetyl)), 4.61 (d, J = 6.51 Hz, 2H, -OCH2 (farnesyl)), 5.08–5.13 (m, 2H, =CH (farnesyl)), 5.48–5.52 (t, J = 6.39 Hz, 1H, =CH (farnesyl)), 7.08 (d, J = 2.67 Hz, 1H, H-5 (coumarin)), 7.26 (d, J = 2.73 Hz, 1H, H-7 (coumarin)), 7.34 (d, J = 10.98 Hz, 1H, H-8 (coumarin)), 8.48 (s, 1H, H-4 (coumarin)); 13C NMR (75 MHz, CDCl3): δ = 16, 16.7, 17.6, 25.6, 26.1, 26.7, 30.5, 39.5, 39.6, 65.7, 112.2, 123.5, 123.5, 124.2, 124.6, 131.3, 135.6, 142.2, 147.3, 149.9, 155.6, 159.4, 195.7 ppm; IR (KBr): 2962, 2925–2851, 1735, 1617, 1200 cm^{-1}; MS (*m/z*) 408 (M^+), 203, 187; Anal. calcd for $C_{26}H_{32}O_4$: C 76.44, H 7.90, found: C 76.08, H 7.68%.

5.3.5 | 3-Acetyl-7-((E)-3,7-dimethylocta-2,6-dienyloxy)-2H-chromen-2-one (12a)

Creamy crystals, yield 67%; m.p. 60–64°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (s, 3H, CH_3 (geranyl)), 1.69 (s, 3H, CH_3 (geranyl)), 1.79 (s, 3H CH_3 (geranyl)), 2.00–2.07 (m, 4H, 2-CH_2 (geranyl)), 2.73 (s, 3H, H(Acetyl)), 4.66 (d, *J* = 6.48 Hz, 2H, -OCH_2 (geranyl)), 5.09–5.11 (m, 1H, =CH (geranyl)), 5.47–5.51 (t, *J* = 6.21 Hz,1H, =CH (geranyl)), 6.85 (s, 1H, H-8 (coumarin)), 6.9–6.93 (dd, *J* = 1.89 and 8.64 Hz, 1H, H-6 (coumarin)), 7.55 (d, *J* = 8.67 Hz, 1H, H-5 (coumarin)), 8.52 (s, 1H, H-4 (coumarin)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16, 16.8, 17.7, 25.7, 26.1, 30.6, 65.8, 101, 117.9, 123.4, 124.2, 131.4, 135.6, 142.9, 147.8, 157.7,

159.8, 164.6, 195.5 ppm; IR (KBr): 3068, 2965, 2855, 1736, 1670, 1618, 1129 cm^{-1}; MS (*m/z*) 340 (M^+), 340, 203, 187; Anal. calcd for $C_{21}H_{24}O_4$: C 74.09, H 7.11, found: C 74.20, H 7.22%.

5.3.6 | 3-Acetyl-7-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyloxy)-2H-chromen-2-one (12b)

Creamy crystals, yield 57%; m.p. 70–72°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 6H, CH_3 (farnesyl)), 1.59 (s, 3H, CH_3 (farnesyl)), 1.7 (s, 3H CH_3 (farnesyl)), 1.88–2.05 (m, 8H, 4-CH_2 (farnesyl)), 2.63(s, 3H, H (Acetyl)), 4.57 (d, *J* = 5.88 Hz, 2H, -OCH_2 (farnesyl)), 4.99–5.01 (m, 2H, =CH (farnesyl)), 5.39 (t, *J* = 5.58 Hz, 1H, =CH (farnesyl)), 6.47 (s, 1H, H-8 (coumarin)), 6.80–6.83 (d, *J* = 8.22 Hz, 1H, H-6 (coumarin)), 6.7–7.54 (d, *J* = 8.4 Hz,1H H-5 (coumarin)), 8.42 (s, 1H, H-4 (coumarin)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16, 16.8, 17.7, 25.7, 26.1, 26.6, 30.6, 39.5, 39.6, 65.8, 100.9, 118, 120.4, 123.4, 124.2, 131.3, 131.4, 135.6, 142.9, 147.8, 157.7, 159.8, 164.6, 195.5 ppm; IR (KBr): 3071, 2920, 2851, 1735, 1674, 1618, 1130 cm^{-1}; MS (*m/z*) 408 (M^+), 203; Anal. calcd for $C_{26}H_{32}O_4$: C 76.44, H 7.90, found: C 76.68, H 8.00%.

5.3.7 | 3-Acetyl-8-((E)-3,7-dimethylocta-2,6-dienyloxy)-2H-chromen-2-one (13a)

Orange liquid, yield 58%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62(s, 3H, CH_3 (geranyl)), 1.69 (s, 3H, CH_3 (geranyl)), 1.78 (s, 3H, CH_3 (geranyl)), 2.12 (m, 4H, 2-CH_2 (geranyl)), 2.75(s, 3H, CH_3 (Acetyl)), 4.75 (d, *J* = 6.3 Hz, 2H, -OCH_2 (geranyl)), 5.09 (m, 1H, =CH (geranyl)), 5.52–5.56 (t, *J* = 6.3 Hz, 1H, =CH (geranyl)), 7.18–7.29 (m, 3H, H-7, H-6, H-5 (coumarin)), 8.5 (s, 1H, H-4 (coumarin)); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8, 17.7, 25.7, 26.2, 30.7, 39.5, 66.4, 117.7, 121.3, 123.6, 124.5, 124.7, 132, 141.9, 145.4, 158.8, 195.8; IR ($CHCl_3$): 3035, 2966, 2827, 1734, 1681, 1604, 1186 cm^{-1}; MS (*m/z*) 340 (M^+), 203, 187, 160; Anal. calcd for $C_{21}H_{24}O_4$: C 74.09, H 7.11, found: C 73.50, H 6.67%.

5.3.8 | 3-Acetyl-8-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien1yloxy)-2H-chromen-2-one (13b)

Orange liquid, yield 56%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (s, 6H, 2-CH_3 (farnesyl)), 1.70 (s, 3H, CH_3 (farnesyl)), 1.79 (s, 3H, CH_3 (farnesyl)), 1.96–2.20 (m, 8H, 4-CH_2 (farnesyl)), 2.75(s, 3H, CH_3(Acetyl)), 4.76 (d, *J* = 6.4 Hz, 2H, -OCH_2 (farnesyl)), 5.08–5.12 (m, 2H, =CH (farnesyl)), 5.53–5.57 (t, *J* = 6.3 Hz, 1H, =CH (farnesyl)), 7.18–7.29 (m, 3H, H-7,H-6, H-5 (coumarin)), 8.5 (s, 1H, H-4 (coumarin)); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16, 16.8, 17.7, 25.7, 26.1, 26.7, 30.6, 39.5, 39.7, 66.4, 117.8, 121.4, 123.5, 124.3, 124.6, 124.7, 131.3, 135.5, 142, 145.4, 158.8, 195.69 ppm; IR ($CHCl_3$): 3031, 2965, 1737, 1690, 1604, 1184 cm^{-1}; MS (*m/z*) 408 (M^+), 203, 188; Anal. calcd for $C_{26}H_{32}O_4$: C 76.44, H 7.90, found: C 76.20, H 7.77%.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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