Bioorganic & Medicinal Chemistry 20 (2012) 5518–5526

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and SAR studies of 3-allyl-4-prenyloxyaniline amides as potent 15-lipoxygenase inhibitors

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ARTICLE INFO

Article history:
Received 9 June 2012
Revised 14 July 2012
Accepted 16 July 2012
Available online 24 July 2012

Keywords:
SLO
MBTH
DMAB
Radical scavenger
DPPH

ABSTRACT

15-Lipoxygenases are one of the nonheme iron-containing proteins with ability of unsaturated lipid peroxidation in animals and plants. The critical role of the enzymes in formation of inflammations, sensitivities and some of cancers has been demonstrated in mammalians. Importance of the 15-lipoxygenases leads to development of mechanistic studies, products analysis and synthesis of their inhibitors. In this work new series of the 3-allyl-4-allyoxyaniline amides and 3-allyl-4-prenyloxyaniline amides were designed, synthesized and their inhibitory potency against soybean 15-lipoxygenase were determined. Among the synthetic amides, 3-allyl-4-(farnesyloxy)-adamantanilide showed the most potent inhibitory activity by IC_{50} value of 0.69 μM. SAR studies showed that in spite of prenyl length increases, the effects of the amide size and its electronic properties on the inhibitory potency became predominant. The SAR studies was also showed that the orientation of allyl and prenyloxy moieties toward Fe core of the SLO active site pocket is the most suitable location for enzyme inhibition.

1. Introduction

Lipoxygenases (LO) are a main group of the nonheme iron-containing proteins which can catalyze hydroperoxidation of poly unsaturated fatty molecules containing a *cis*,*cis*-1,4-pentadiene structure such as arachidonic and linoleic acid.[1] In mammalians, three classes of signaling compounds leukotrienes, eoxines and lipoxins are formed via hydroperoxidation at 5 and 15 carbon position of the arachidonic acid, respectively.[2,3] Among the mammalian lipoxygenases involved in the human disease, 5-lipoxygenase (5-LO) is now well documented as a target for reducing the biosynthesis of leukotrienes one of the known proinflammatory mediators.[4] The immediate products of 15-LO hydroperoxidation of arachidonic acid and linoleic acid have been shown to be pro-inflammatory.[3,5] The critical role of the 15-LO-1 metabolite, 13-(*S*)-hydroxyoctadecadienoic acid, in the progression of prostate cancers and inhibition of 15-LO-1 activity for apoptosis induction in PC3 cells has been demonstrated.[6,7] It has been also found that 15-LO involves in oxidative modification of low-density lipoproteins (LDL) lead to development of atherosclerosis.[8–10] A recent study on human airway epithelial cells, in cell culture and in human asthmatic epithelial cells, showed that high levels of 15-LO-1 interact with phosphatidylethanolamine-binding protein-1 to displace Raf-1 and sustain MAPK/ERK activation.[11]

There has been considerable interest in the development of LO inhibitors for therapeutic applications. Although a numerous LO inhibitors has been prepared and biologically studied, consuming of them, due to their side effects, is usually forbidden or limited.[12] Explore the alternative strategies to reduce the lipoxygenase activity with the help of natural products is necessary. A group of these natural products are allylbenzenes. The well known example of this group of natural compounds is eugenol first reported as 5-lipoxygenase inhibitors by Raghavenra et al.[13] Afterwards, some aliphatic and aromatic esters of eugenol was synthesized and evaluated for inhibition of soybean 15-lipoxygenase (SLO) activity.[14] The results indicated an increase in inhibitory potency of some esters when compared with eugenol. It showed that the more lipophylic and bulky esters posses the best inhibitory activity.[14] Further evaluation was done by Horchani et al. on eugenyl benzoate to explore the inhibitory mechanism.[15] They showed eugenol and eugenyl benzoate have the same potency for scavenging of DPPH radical while antioxidant and bleaching property of eugenol was more predominant. With respect to previous researches, it was

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http://dx.doi.org/10.1016/j.bmc.2012.07.025

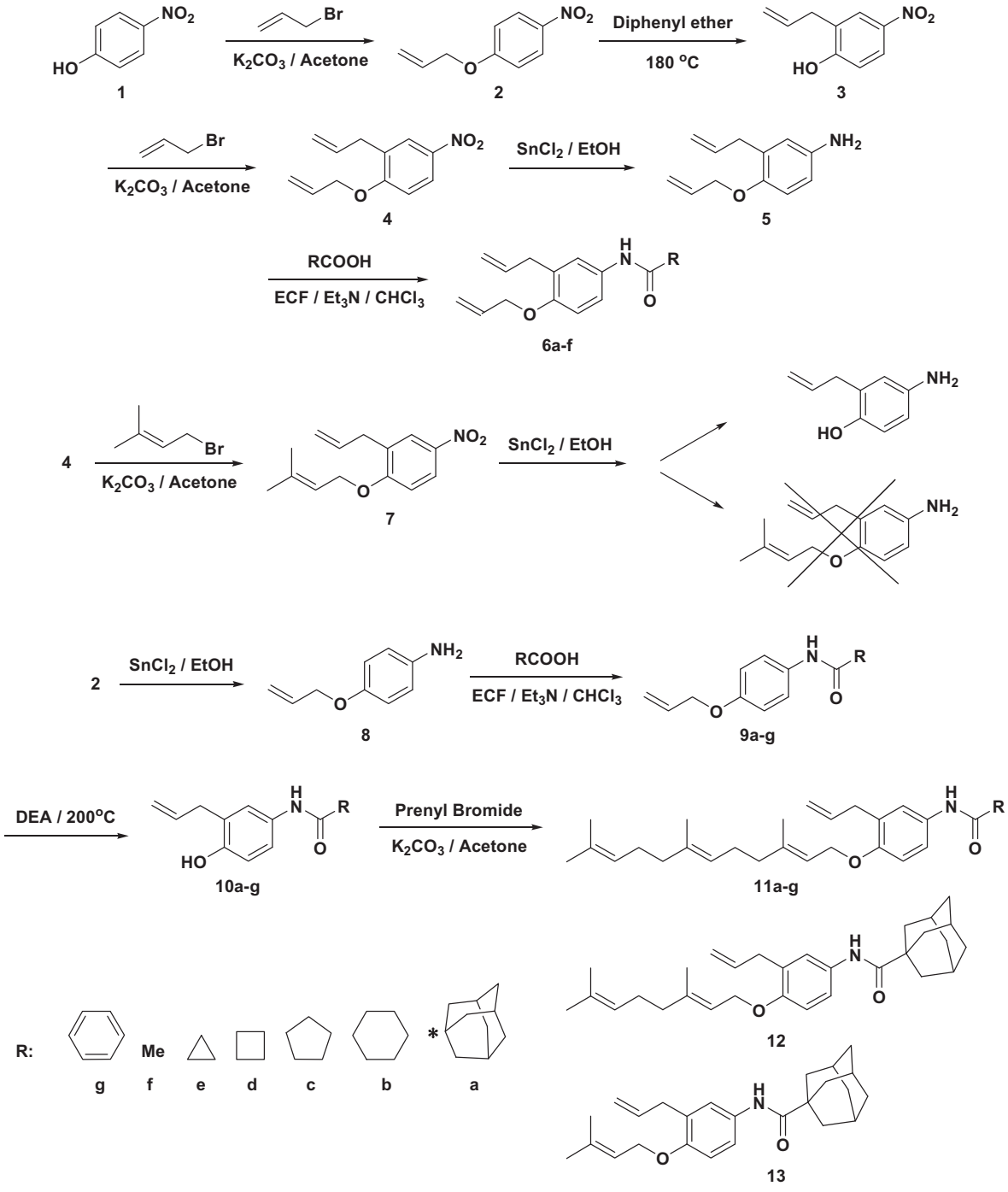
concluded that the radical scavenging by methylene hydrogen of eugenol and its esters, play a key role in lipoxygenase inhibition.

In another work, it was shown that the allyloxybenzenes such as 4-allyloxyaniline amides inhibited the lipoxygenase activity and this functionality was enhanced by increasing in size and lipophilic property of the amide moiety. In a comprehensive study by Yang et al., it was found that the iron chelating property of allyoxy group was the main factor in lipoxygenase inhibition.[16]

In this study, a new series of aniline amides possessing both allyl and allyloxy moieties were designed and synthesized. In the designing, allyl and allyloxy moieties were placed at the *meta* and *para* position towards amide group, respectively. Afterwards inhibitory potency of the synthesized amides was assessed against SLO. In the next step the allyoxy moiety replaced by isopentenyloxy, geranyloxy and farnesyloxy groups to study the effect of prenyl chain length on the inhibitory activity. All of the resulted IC_{50} values were compared with the theoretical inhibitory constant (K_i) calculated by the molecular interaction simulator software to describe the structure activity relationships.

2. Result and discussion

A series of cycloalkyl amides of 3-allyl-4-allyoxyaniline were synthesized according to the synthetic procedure reported in the previous work.[17] In the synthetic pathways, after allylation of 4-nitrophenol by allyl bromide in the presence of potassium



Scheme 1. General procedure for the synthesis of compounds **6a–f**, **11a–g**, **12** and **13**.

carbonate, the related 3-allyl-4-nitrophenol (**3**) produced via Claisen rearrangement.[18] The prepared phenol was reacted with allyl bromide in the presence of potassium carbonate to produce 2-allyl-1-allyoxy-4-nitrobenzene (**4**). The desired 3-allyl-4-allyoxyaniline (**5**) was synthesized by reduction of nitro group with stannous chloride. Various amide derivatives **6a**–**f** were prepared from amine **5** and intermediate carbonic acid chlorides which were formed from reacting of acids **a**–**f** with ethyl chloroformate (ECF) in the presence of triethylamine (TEA) (Scheme 1).[19]

Attempt for synthesis of *O*-prenylated allylaniline **7** via the described method was inconclusive. In this procedure reduction of 1-isopentenyloxy-2-allyl-4-nitrobenzene produced 2-allyl-4-aminophenol (Scheme 1).

In another synthetic procedure, 1-allyloxy-4-nitrobenzene (**2**) was reduced to 4-allyloxyaniline (**8**) and then was reacted with the intermediate carbonic acid chlorides to produce **9a**–**g**. The synthetic amides **9a**–**g** was converted to 3-allyl-4-amidophenols **10a**–**g** by using Claisen rearrangement at 200 °C in diethylaniline under the hydrogen atmosphere. Using of the dimethylaniline reported in the literatures led to low yield of the products.[18] The crude products of **9a**–**g** were directly reacted with prenyl bromides to produce **11a**–**g**, **12** and **13** (Scheme 1).

The chemical structure of the products was confirmed by ^{13}C NMR, ^{1}H NMR and CHN analyses. HH-NOESY spectrum of the farnesyl derivatives showed that the *trans trans* configuration of farnesyl moiety leaves conserved over the alkylation step. In the spectrum, 2D correlation between the first methyl hydrogens and $-O-CH_2$ implies that the *trans* configuration of $-O-CH_2CH{=}C(CH_3)R$ through the carbocation intermediate formation has been left intact (Fig. 1). It was interesting to see an excellent correlation between aromatic H_5 and $-O-CH_2$. The observed correlations confirmed the 3D structure shown in (Fig. 1).

The inhibitory activity of the synthetic compounds against SLO was determined using modified DMAB-MBTH method reported by Anthon et al.,[20] In this method the basis of the lipoxygenase assay is the peroxide concentration measurement. The enzyme assay was performed according to the end point protocol while in the previous work it had been down pursuant to the kinetic procedure (measurement of the enzyme activity within 60–120 s after addition of the substrate to the enzyme-inhibitor mixture).[14,17] By using of the last protocol the lower IC_{50} values were obtained versus the former one. For example the IC_{50} of compound **9a** is 27.8 μM while it was 0.67 μM in the previous work.[17]

The synthetic amides **6a**–**f** showed better inhibition activity on the enzyme in comparison with their related analogueues **9a**–**f**. Compound **6a** including an adamantanecarboxylate substituent was the most potent inhibitor (IC_{50} = 9.8 ± 1.2 μM) while the acetamide analogue (**6f**) showed the least activity (IC_{50} = 67.8 ± 1.8 μM,

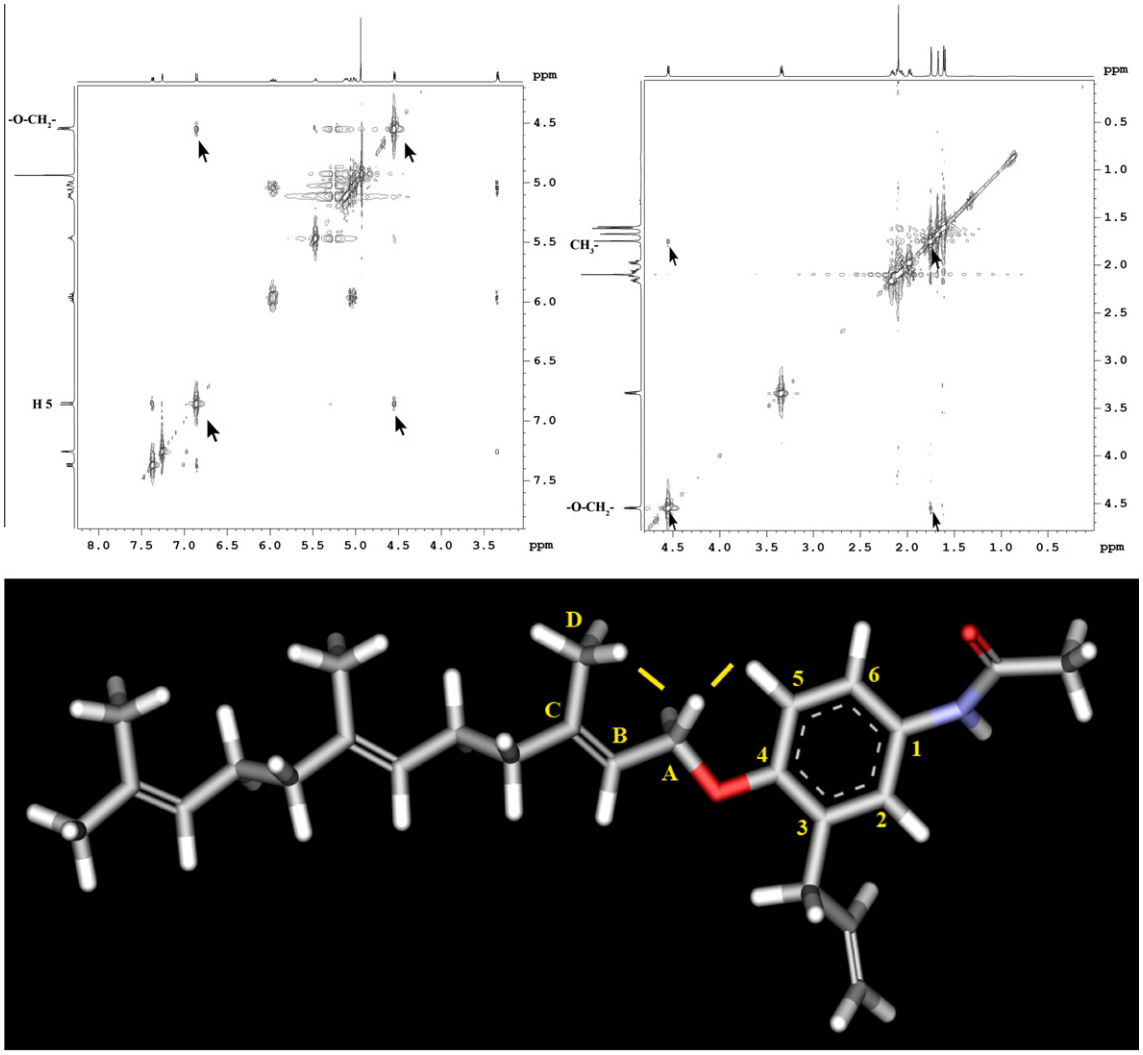


Figure 1. (Above) HH-NOESY spectrum of compound **11g**. The 2D correlations are distinguished by black cursor. (Below) geometry optimized 3D structure of **11g** in stick view. The intramolecular interactions are showed by yellow lines.

Table 1
Enzyme inhibitory assessment data of the synthetic compounds in comparison with 4-allylbenzene-1-adamantanamide (**9a**),[17] caffeic acid and 4-methyl-2-(4-methyl-piperazinyl)pyrimido[4,5-*b*]benzothiazine (CAS 928853-86-5)

Compounds	IC_{50} (μM)	Compounds	IC_{50} (μM)
6a	9.8 ± 1.2	**11d**	2.1 ± 0.10
6b	18.5 ± 1.1	**11e**	16.5 ± 1.1
6c	58.0 ± 3.4	**11f**	24.8 ± 2.1
6d	19.6 ± 1.0	**12**	3.6 ± 0.10
6e	54.1 ± 1.4	**13**	10.3 ± 0.32
6f	67.8 ± 1.8	**9a**	27.8 ± 1.6
11a	0.69 ± 0.04	Caffeic Acid	37.1 ± 1.5
11b	5.2 ± 0.47	4-MMPB	28.2 ± 1.1
11c	35.7 ± 3.3		

respectively) (Table 1). The enzyme assessment demonstrated that introducing allyl group on the allyloxyaniline moiety, resulted in increscent lipoxygenase inhibition potency. Radical scavenging property of allylbenzenes,[15,21–23] could be the good reasons for explanation our experimental observations. This means that the new synthetic inhibitors can inhibit the lipoxygenase activity by their radical scavenging properties. To explore the effect of alkene bond on inhibition potency, isopentenyloxy, geranyloxy and farnesyloxy analogues of **6a** which was the best inhibitor among the tested compounds, were synthesized and their inhibitory potency were assayed. The experiment showed that, the elongation of the prenyl length led to increase the inhibitory potency. The IC_{50} values of the three synthetic prenylated allylaniline amide, **11a**, **12** and **13**, were 0.69 ± 0.04, 3.6 ± 0.10 and 10.3 ± 0.32 μM, respectively. To go forward the effect of the amide moiety size on inhibitory activity was studied. To do this, a series of cyclic amides of farnesyloxy derivative were synthesized and the inhibitory potency of them was measured. The inhibitory results were compared with acetamide analogue (**11f**) as smallest amide moiety. With the exception of **11d** and **11c**, an acceptable relationship between the size of amide group and IC_{50} values was observed. Among the synthetic amides, adamantyl analogue was the most potent inhibitor and **11d** with the IC_{50} value of 2.1 ± 0.17 located in the second rank while the cyclopentyl amide analogue **11c** was the weakest inhibitor (IC_{50} = 35.7 ± 3.3 μM).

To rationalize the observed variation in inhibitory potency of the synthetic compounds, computer-assisted modeling studies were performed on intermolecular interactions of SLO-inhibitor complex. To approach this aim, semi-empirical energy minimized 3D structure of the best inhibitors **11a–f**, **12** and **13** were docked into the SLO (PDB entry: 1IK3) active site pocket while the Fe core had been modified to Fe^{III}-OH and side chain of Leu227, Leu557, Leu560, Leu565, Ile572, Phe576, Leu773 and Ile857 had been made flexible. Bonding affinity of the designed molecular structures toward SLO was studied. 200 docked conformers of the compounds were generated in ADT (Auto Dock Tools) software.[24] A detailed assessment of the output clusters (cluster tolerance/Å = 2.0) of the enzyme revealed that for each of the docked molecules two most popular clusters (cluster A and B) exist. The numbers of conformations (22–41%) belong to cluster A in which prenyl moiety orients toward Fe-OH and amide portion surrounded by Val372, Ser510, His513, Gln716, Gly720, Arg726, Thr728, Asp766, and Ile770 while it was invert in cluster B so that in this (number of the biding conformers = 18–24%), amide portions oriented toward Fe-OH and prenyl moiety is covered by Val372, Ser510, His513, Val571, Ile572, Phe576, Gln716, Thr728, Asp766, Val769 and Ile770 (Fig. 2). Among the amino acids, His513, Val571, Ile572, Gln716, Asp766 and Ile770 are the conserved residues.[17,25,26] It was notable that the binding conformers with the least estimated inhibitory constant (K_i) belonged to the aforementioned clusters. With exception of **11e**, analysis of docking results showed an acceptable conformity between the IC_{50} variations and K_i of the clusters B binding conformer in which allyl moiety situated close to the Fe-OH core (Figs. 3 and 4). The allyl orientation could be suitable for its interference with hydrogen abstracting step down by Fe-OH during the peroxidation process.[27] Amongst all of the conformers in each cluster B of the docked inhibitors, ones with the least K_i was named as 'consensus structure' and used for further analysis (Fig. 5). In cluster B, we could found a hydrogen bond between the amide group of the consensus structures and hydroxyl of Fe-OH. Cycloalkyl portion of the amide moiety is covered by Leu227, Leu557, Leu560, Leu565, Leu773 and Ile857 side chains (Fig. 2). Among the mentioned amino acids, Leu557, Leu565, Val566, Ile572, Leu773 and Ile857 are conserved types.[17,25,26] In 3D view of the consensus structures we could see vertical orientation of Leu565 isobutyl hydrogens towards horizontal aromatic ring of allylbenzene. In this arrangement, intermolecular π (aromatic ring) → σ^* (H–C) could further stabilize the ligand–protein junction (Fig. 3).[28]

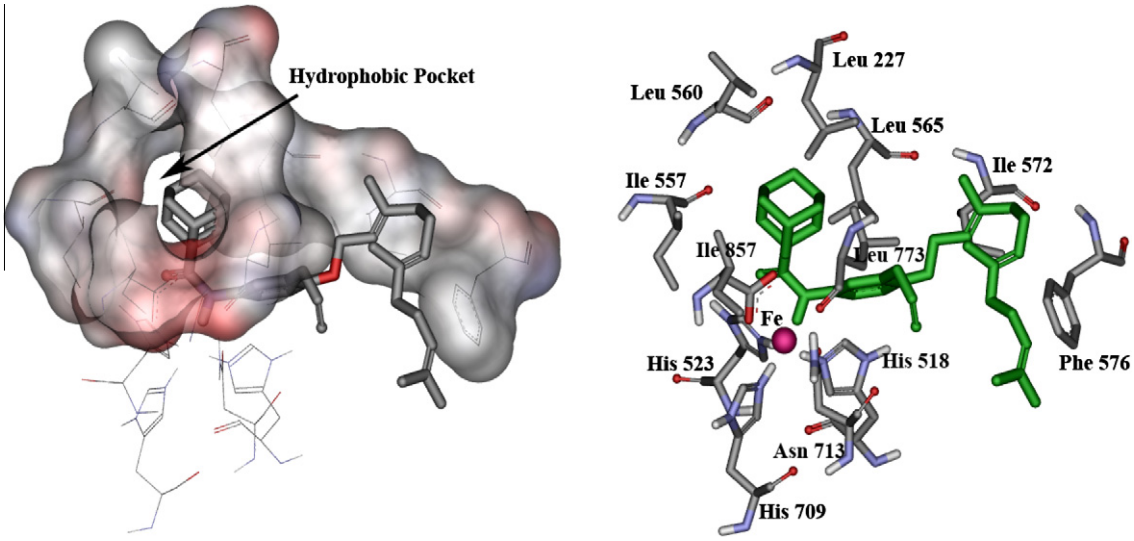


Figure 2. (Right) Stick view of the consensus bonding conformation of **11a** which has lipophilic interactions with flexible hydrophobic residues in cluster B. The Fe atom coordinated with His518, His523, His709, Asn713 and Ile857 is distinguished by purple. (Left) Solvent surface view of the aforementioned residues. Hydrophobic pocket covering the adamantane moiety is pointed by arrow.

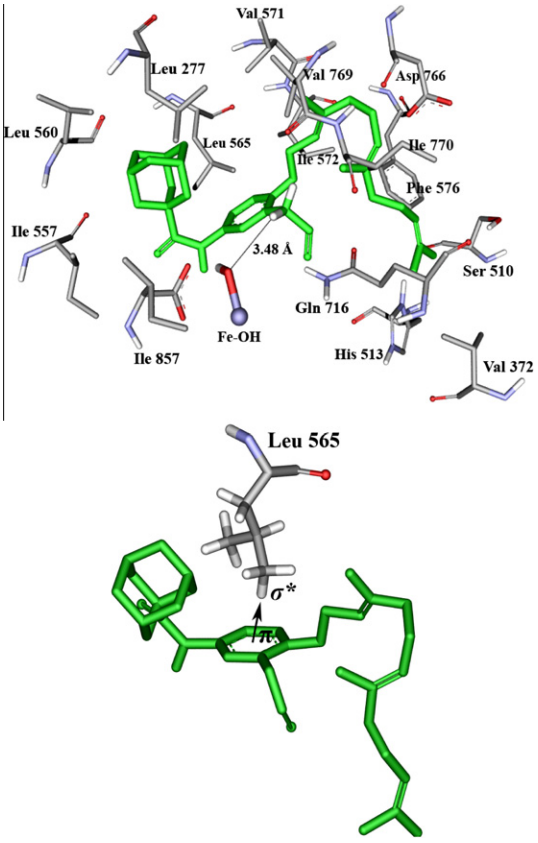


Figure 3. (above) Stick view of the residues surrounding the consensus bonding conformation of **11a** (green). The distance between oxygen of Fe^{III}-OH and 11a allyl hydrogen is distinguished by a black line. (Below) suitable situation of flexible Leu565 and 11a for formation of π (aromatic ring) → σ^* (H-C).

Docking analysis could help us to rationalize the structure–activity relationships for the synthetic compounds, but could not describe **11e** (Fig. 4). To explain this exception, it was decided to check the other reactivity of the compounds which could be related to their LOX inhibitory activity. As was mentioned, literature review showed that the allylbenzenes possess radical scavenging activity.[15,21–23] So the radical quenching capacity of **11a–f**, **12** and **13** having both ally and prenyloxy moiety was assayed using DPPH radical scavenging method. In vitro bleaching method of DPPH free radical is a widely adopted assay to evaluate the scavenging potential of stable free radicals.[16] Amongst **11a–f**, **12** and **13** adamantyl, methyl, cyclopropyl and cyclobutyl analogues showed the best radical scavenging activity (Table 2). It was interesting that the cyclopropyl analogous showed the most potent activity (IC_{50} = 8.9 ± 0.4 μM). It was an explanation for the unexpected LO inhibitory activity of **11e**. In this case the radical scavenging potency of **11e** can compensates its low binding affinity. The results of the DPPH bleaching showed that beside of the allyl group the size of the amide moiety played an important role in radical scavenging.

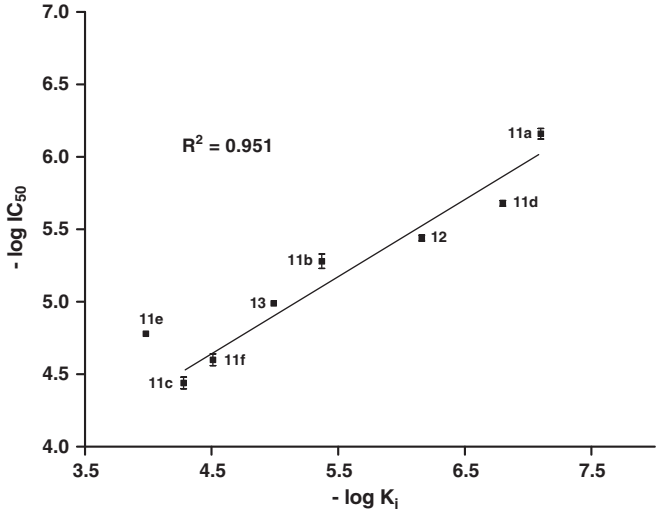


Figure 4. Diagram of –log IC_{50} versus –logK_i for consensus structure of compounds **11a–f**, **12** and **13**.

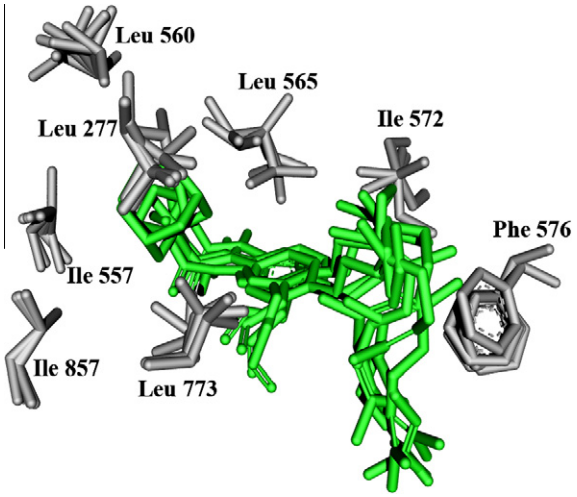


Figure 5. Stick view of flexible residues (gray), surrounding the consensus bonding conformations of **11a–g** (green) in the SLO active site pocket.

Lack of the allyl group lead to radical scavenging deletion, therefore DPPH bleaching activity was not observed for **9a–f** compared with **6a–f** up to 1000 μM. Electron rich amide groups can increase the allyl benzene radical stability so it raises the radical scavenging potency. As it was known, low contribution of P orbital in cyclopropyl hybrids make its strained C–C bonds (bent bonds[28]) as σ-electron donor system which could inductively donate

Table 2
DPPH bleaching IC_{50} of the synthetic compounds and docking analysis data of consensus conformers. (K_i: estimated inhibition constant, RMSD: root mean square deviation, NDGA = nordihydroguaiaretic acid)

Compound	Cluster	K_i (μM)	Number of conformers in cluster	cluster RMSD	IC_{50} (μM)(DPPH bleaching)
11a	A	2.62	22	2.00	114.3 ± 2.8
	B	0.078	24	1.41	
11b	A	2.51	14	1.79	529.1 ± 5.4
	B	4.22	18	0.00	
11c	A	0.710	31	0.00	461.4 ± 5.1
	B	52.32	18	1.69	
11d	A	0.096	33	0.00	139.5 ± 2.9
	B	0.148	21	1.16	
11e	A	53.04	31	1.37	8.9 ± 0.4
	B	104.0	19	1.64	
11f	A	29.72	39	1.87	224.8 ± 2.7
	B	31.01	18	0.00	
12	A	0.18	22	1.67	120.8 ± 2.1
	B	0.69	20	1.36	
13	A	1.48	41	1.66	104.6 ± 1.7
	B	10.11	21	1.43	
NDGA					6.2 ± 0.4

electron density to carbonyl π^* of amide group. Such a phenomenon is detected weakly for cyclobutyl in which the bent bonds make it as electron inductive like adamantan tertiary carbon.[28] To test the mesomeric effect of amide moiety on allylbenzene radical stability, benzamide analogue (**11g**) was synthesized. The observed low potency of **11g** for DPPH bleaching (IC_{50} = 548 μM) revealed the main role of the inductive effect on radical stability. It was interesting that by decreasing the prenyl length, the radical scavenging activity did not change significantly.

Conclusion could be made that the prenyl length increasing resulted in the effects of the amide size and electronic properties on the inhibitory potency more predominant. Also it could lead us to design and synthesis of other more potent and selective inhibitors. On the other hands, the SAR studies could help us to find the best binding conformation of these series of the inhibitors in SLO active site pocket. We also found the importance of the inductive electron donating effect on the allylbenzene radical stability.

3. Materials and methods

3.1. Molecular modeling, docking and SAR study

3.1.1. Structure optimization

The structures were designed in chem3D professional; Cambridge software.[29] Output files were minimized under semi-empirical PM3 method (Convergence limit = 0.01; Iteration limit = 50; RMS gradient = 0.05 kcal/mol; Fletcher-Reeves optimizer algorithm) in HyperChem7.5.[29,30]

Crystal structure of soybean lipoxygenase-3 (arachidonate 15-lipoxygenase) complex with 13(*S*)-hydroproxy-9(*Z*)-2,11(*E*)-octadecadienoic acid was retrieved from RCSB Protein Data Bank (PDB entry: 1IK3).

3.1.2. Molecular docking

The fatty acid peroxide bonded to Fe^{III} atom of the SLO 3D structure was omitted. Then the Fe was modified to Fe^{III}-OH, geometrically optimized by MM+ method in HyperChem7.5 and outputted in .pdb format for docking process.

Automated docking simulation was implemented to dock the minimized structures into the active site of SLO with AutoDock 4.2[31] using Lamarckian genetic algorithm.[32] This method has been previously shown to produce binding models similar to the experimentally observed models.[25,26] The torsion angles of the ligands were identified, hydrogens were added to the macromolecule, bond distances were edited and solvent parameters were added to the enzyme 3D structure. Partial atomic charges were then assigned to the macromolecule as well as ligands (Gasteiger for the ligands and Kollman for the protein).

The docking regions of the enzyme were defined by considering cartesian chart 18.3, 4.8 and 19.2 as the central of a grid size with 44, 56 and 62 points in *X*, *Y* and *Z* axises. The docking parameter files were generated using Genetic Algorithm and Local Search Parameters (GALS) while number of generations and maximum number of energy evaluations was set to 200 and 2500,000, respectively. The 200 docked complexes were clustered with a root mean square deviation tolerance (RMSD) of 2.0 Å. Docking results were submitted to Accelrys DS Visualizer 2.0.1[33] for further evaluations. The results of docking processing (K_i: estimated inhibition constant, number of conformers in cluster and cluster RMSD) are outlined in Table 2.

3.1.3. 15-LO inhibitory assessment

Linoleic acid and two assay solutions (A and B) were prepared in advance.

Solution A was 50 mM DMAB (3-dimethylaminobenzoic acid) in a l00 mM phosphate buffer (pH 7.0). Solution B was a mixture of l0 mM MBTH (3-methyl-2-benzothiazolonhydrazone) (3 mL), hemoglobin (5 mg/mL, 3 mL) in 50 mM phosphate buffer at pH 5.0 (25 mL). A linoleic acid solution was prepared by mixing 5 mg of linoleic acid with 0.5 mL ethanol and then diluting with KOH 100 mM to a final volume of 5 mL.

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 pre-incubation was carried out for 5 min at room temperature. A control test was done with the same volume of ethanol. After the pre-incubation, linoleic acid solution (50 μL) was added to start the peroxidation reaction, and, 7 min later, solution A (270 μL) and then solution B (130 μL) was added to start the color formation. Further 5 min later, 200 μL of a 2% SDS solution was added to terminate the reaction. The absorbance at 598 nm was compared with control test.

3.1.4. Determination of DPPH bleaching

25 μM solution of DPPH in absolute ethanol was prepared. This solution was added to an equal volume of the solution of the test compounds (dissolved in ethanol) to obtain a desired concentration. Ethanol was used as control solution. After 30 min at room temperature, the absorbance was recorded at 517 nm and compared to NDGA (nordihydroguaiaretic acid).

4. Experimental section

4.1. Instruments

^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz) and HH-NOESY were obtained by using a Bruker Avance DRX-500 Fourier transformer spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS). Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer. All measurements of lipoxygenase activities were carried out using an Spekol 1500 spectrophotometer. The soybean 15-lipoxygenase and other chemicals were purchased from Sigma, Aldrich and Merck Co., respectively.

4.2. General procedure for preparation of 6a–f

A mixture of 69.5 g (0.50 mol) of 4-nitrophenol (**1**), 66.0 g (0.55 mmol) of allyl bromide and 70.0 g of anhydrous potassium carbonate (0.50 mol) in dry acetone (150 mL) was refluxed for 16 h and cooled. The mixture was diluted with water (250 mL) and then extracted with ether (2 × 150 mL). The combined extracts were washed with NaOH 10% (2 × 100 mL) and dried with anhydrous sodium carbonate. After removal of the solvent the residual oil of **2** was distilled under reduced pressure (74.4 g, 83% yield).

An equal mixture of allyl ether **2** and diphenyl ether (35 g) was heated (210 °C) for 5 h under nitrogen atmosphere, and then cooled. The oil was dissolved in 200 mL of ethyl acetate and the solution was extracted with 10% NaOH (3 × 70 mL). The combined alkaline extracts were then acidified with concentrated HCl, and the mixture was extracted with ether (3 × 70 mL). The ether extract were dried with anhydrous sodium sulfate, evaporated and the residual sticky solid was recrystallized with heptane to produce pure yellow crystals of **3** (23.0 g, 65% yield).

A mixture of 17.9 g (0.10 mol) of **3**, 14.5 g (0.12 mol) of allyl bromide and 14.0 g of anhydrous potassium carbonate (0.10 mol) in dry acetone (40 mL) was refluxed for 12 h and then cooled. The mixture was diluted with water (150 mL) and then extracted with ether (2 × 150 mL). The combined extracts were washed with NaOH 10% (2 × 100 mL) and dried with anhydrous sodium carbonate. After removal of the solvent, the residual oil of **4** was distilled under reduced pressure (18.4 g, 84% yield).

A mixture of 18.0 g (0.082 mol) of **4** and 113.0 g (0.50 mol) of $SnCl_2.2H_2O$ in 160 mL of absolute ethanol was refluxed under nitrogen for 20 min. After cooling; the mixture was poured into cold water (400 mL). The pH was made basic by adding sodium bicarbonate. 3-Allyl-4-(allyloxy)aniline (**5**) was extracted by ethyl acetate (3 × 80 mL). The combined organic phase dried with anhydrous sodium sulfate. After removal of the solvent the residual oil of **5** was distilled under reduced pressure (12.3 g, 79% yield).

Ethyl chloroformate (0.60 g, 5.5 mmol) was added dropwise to a solution of desired carboxylic acid (5 mmol) and 0.6 g of TEA in 10 mL chloroform while stirring in ice-water. After removing the ice-bath, the reaction mixture was stirred at room temperature for 15 min. The amine **5** (0.85 g, 5 mmol) was then added dropwise and stirring continued for 20 min and 10 min further at 50 °C. The resulting solution was washed with 0.5 N NaOH (2 × 15 mL), dilute HCl (2 × 15 mL) and water (2 × 15 mL). The organic layer was dried over sodium sulfate. After removing of the solvent under reduced pressure, the residue was recrystallized from methanol to give **6a**–**f**.

4.2.1. *N*-(3-Allyl-4-(allyloxy)phenyl)adamantanecarboxamide (6a)

White solid, mp: 126–127 °C; ^{1}H NMR ($CDCl_3$): δ 1.73–180 (m, 6H, –CH_2– (adamantyl)), 1.97 (m, 6H, –CH_2– (adamantyl)), 2.10 (m, 3H, –CH–(adamantyl)), 3.41 (d, J = 7.0 Hz, 2H, –CH_2– (allyl)), 4.52–4.53 (m, 2H, –CH_2O–), 5.04–5.44 (m, 4H, =CH_2 (allyl & allyloxy)), 5.97–6.08 (m, 2H, –HC= (allyl & allyloxy)), 6.80 (d, J = 8.5 Hz, 1H, H-2), 7.18 (s, 1H, NH), 7.24 (d, J = 3.0 Hz, 1H, H-5), 7.40 (dd, J = 8.8, 2.5 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ 175.90, 152.89, 136.64, 133.45, 131.17, 129.47, 122.14, 119.18, 116.97, 115.78, 112.09, 69.12, 41.31, 39.29, 36.46, 34.39, 26.14. Found: C, 79.06; H, 8.76; N, 3.98. $C_{23}H_{29}NO_2$ requires: C, 78.59; H, 8.32; N, 3.99.

4.2.2. *N*-(3-Allyl-4-(allyloxy)phenyl)cyclohexanecarboxamide (6b)

White solid, mp: 105–106 °C; ^{1}H NMR ($CDCl_3$): δ 1.24–1.31 (m, 3H, –CH_2– (cyclohexyl)), 1.49–1.57 (m, 2H, –CH_2– (cyclohexyl)), 1.69–1.71 (m, 2H, –CH_2– (cyclohexyl)), 1.81–1.86 (m, 2H, –CH_2– (cyclohexyl)), 1.91–1.96 (m, 2H, –CH_2– (cyclohexyl)), 2.20 (m, 1H, CH (cyclohexyl)), 3.39 (d, J = 6.5 Hz, 2H, –CH_2– (allyl)), 4.52 (m, 2H, -CH_2O-), 5.03–5.44 (m, 4H, =CH_2 (allyl & allyloxy)), 5.95–6.08 (m, 2H, –H C= (allyl & allyloxy)), 6.77 (d, J = 8.5 Hz, 1H, H-2), 7.24 (d, J = 2.5 Hz, 1H, H-5), 7.28 (s, 1H, NH), 7.40 (dd, J = 8.5, 2.5 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ 174.26, 152.86, 136.61, 133.45, 131.27, 129.47, 122.01, 119.06, 116.97, 115.78, 112.08, 69.12, 46.38, 34.36, 29.70, 25.70. Found: C, 75.21; H, 8.71; N, 4.66. $C_{19}H_{25}NO_2$ requires: C, 76.22; H, 8.42; N, 4.68.

4.2.3. *N*-(3-Allyl-4-(allyloxy)phenyl)cyclopantanecarboxamide (6c)

White solid, mp: 97–98 °C; ^{1}H NMR ($CDCl_3$): δ 1.60–1.62 (m, 2H, –CH_2– (cyclopentyl)), 1.76–1.82 (m, 2H, –CH_2– (cyclopentyl)), 1.87–1.96 (m, 4H, –CH_2– (cyclopentyl)), 2.65 (m, 1H, CH (cyclopentyl)), 3.41 (d, J = 6.5 Hz, 2H, –CH_2– (allyl)), 4.52–4.54 (m, 2H, -CH_2O-), 5.04–5.44 (m, 4H, =CH_2 (allyl & allyloxy)), 5.95–6.08 (m, 2H, –HC= (allyl & allyloxy)), 6.80 (d, J = 8.5 Hz, 1H, H-2), 7.04 (s, 1H, NH), 7.24 (d, J = 2.5 Hz, 1H, H-5), 7.40 (dd, J = 8.8, 2.5 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ 174.51, 152.84, 136.62, 133.45, 131.38, 129.46, 122, 119.02, 116.95, 115.74, 112.07, 69.13, 46.67, 34.37, 30.57, 26.03. Found: C, 75.77; H, 7.99; N, 4.85. $C_{18}H_{23}NO_2$ requires: C, 75.76; H, 8.12; N, 4.91.

4.2.4. *N*-(3-Allyl-4-(allyloxy)phenyl)cyclobutanecarboxamide (6d)

White solid, mp: 96–98 °C; ^{1}H NMR ($CDCl_3$): δ 1.90–2.06 (m, 2H, –CH_2– (cyclobutyl)), 2.21–2.23 (m, 2H, –CH_2– (cyclobutyl)), 2.37–2.41 (m, 2H, –CH_2– (cyclobutyl)), 3.11–3.15 (m, 1H, CH (cyclobutyl)), 3.41 (d, J = 6.5 Hz, 2H, –CH_2– (allyl)), 4.52–4.54 (m, 2H, –CH_2O–), 5.04–5.44 (m, 4H, =CH_2 (allyl & allyloxy)), 5.96–6.06 (m, 2H, –HC= (allyl & allyloxy), 6.80 (d, J = 9.0 Hz, 1H, H-6), 6.90 (s, 1H, NH), 7.23 (d, J = 3.0 Hz, 1H, H-3), 7.41 (dd, J = 9.0, 2.5 Hz, 1H, H-2). ^{13}C NMR ($CDCl_3$) δ 173.10, 152.87, 136.61, 133.44, 131.20, 129.47, 212.97, 119.02, 116.97, 115.77, 112.05, 69.11, 40.70, 34.35, 25.33, 18.07. Found: C, 75.16; H, 7.70; N, 5.12. $C_{17}H_{21}NO_2$ requires: C, 75.25; H, 7.80; N, 5.16.

4.2.5. *N*-(3-Allyl-4-(allyloxy)phenyl)cyclopropanecarboxamide (6e)

White solid, mp: 96–98 °C; ^{1}H NMR ($CDCl_3$): δ 0.80–0.847 (m, 2H, –CH_2– (cyclopropyl)), 1.06–1.095 (m, 2H, –CH_2– (cyclopropyl)), 1.45–1.49 (m, 1H, –CH– (cyclopropyl)), 3.40 (d, J = 6.5 Hz, 2H, –CH_2– (allyl)), 4.53 (d, 2H, J = 5.0 Hz –CH_2O–), 5.04–5.44 (m, 4H, =CH_2 (allyl & allyloxy)), 5.94–6.00 (m, 2H, –HC= (allyl & allyloxy), 6.79 (d, J = 8.5 Hz, 1H, H-2), 7.24 (d, J = 2.0 Hz, 1H, H-5), 7.28 (br, 1H, NH), 7.36 (dd, J = 9.0, 2.5 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ 171.78, 152.85, 136.61, 133.45, 131.35, 129.45, 122.05, 119.08, 116.97, 115.77, 112.03, 69.11, 34.35, 15.53, 7.72. Found: C, 74.65; H, 7.36; N, 5.39. $C_{16}H_{19}NO_2$ requires: C, 74.71; H, 7.40; N, 5.45.

4.2.6. *N*-(3-Allyl-4-(allyloxy)phenyl)acetamide (6f)

White solid, mp: 96–98 °C; ^{1}H NMR ($CDCl_3$): δ 2.1 (s, 3H, CH_3) 3.43 (d, J = 6.5 Hz, 2H, –CH_2– (allyl)), 4.54 (d, 2H, J = 5.0 Hz –CH_2O–), 5.00–5.44 (m, 4H, =CH_2 (allyl & allyloxy)), 5.94–6.00 (m, 2H, –HC= (allyl & allyloxy), 6.80 (d, J = 8.5 Hz, 1H, H-2), 7.26(d, J = 2.0 Hz, 1H, H-5), 7.30(br, 1H, NH), 7.38 (dd, J = 9.0, 2.5 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ 165.66, 153.27, 136.56, 133.41, 131.64, 129.62, 122.55, 119.67, 117.04, 115.88, 112.11, 69.12, 45.17, 34.35. Found: C, 72.68; H, 7.32; N, 6.00. $C_{14}H_{17}NO_2$ requires: C, 72.72; H, 7.36; N, 6.06.

4.2.7. General procedure for preparation of 11a–g, 12 and 13

A mixture of 32.2 g (0.18 mol) of **2** and 203.0 g (0.90 mol) of $SnCl_2{\cdot}2H_2O$ in 300 mL of absolute ethanol was refluxed under nitrogen for 20 min. After cooling; the mixture was poured into cold water (700 mL). The pH was made basic by adding sodium bicarbonate. The 4-(allyloxy)aniline (**8**) was extracted by ethyl acetate (3 × 150 mL). The combined organic phase dried with anhydrous sodium sulfate. After removal of the solvent the residual oil of **8** was distilled under reduced pressure (21.3 g, 79% yield).

Ethyl chloroformate (1.20 g, 11 mmol) was added dropwise to a solution of desired carboxylic acid (10 mmol) and 1.20 g of TEA in 15 mL chloroform while stirring in ice-water. After removing the ice-bath, the reaction mixture was stirred at room temperature for 15 min. The amine **5** (1.9 g, 10 mmol) was then added dropwise and stirring continued for 20 min and 10 min further at 50 °C. The resulting solution was washed with 0.5 N NaOH (2 × 20 mL), dilute HCl (2 × 20 mL) and water (2 × 20 mL). The organic layer was dried over sodium sulfate. After removing of the solvent under reduced pressure, the residue was recrystallized from methanol to give **9a**–**g**.

A mixture of 1.5 g of each synthesized amides **9a**–**g** and diethylaniline (4.5 mL) was heated (200 °C) for 6 h under hydrogen atmosphere, and then cooled. The oil was dissolved in 200 mL of ethyl acetate and the solution was extracted with 10% NaOH (3 × 10 mL). The combined alkaline extracts were then acidified with concentrated HCl, and the mixture was extracted with ether (3 × 20 mL). The ether extract were dried with anhydrous sodium sulfate, evaporated and the residual solid without purification was used in the next step.

A mixture of ~5 mmol of each crud products **10a**–**g**, prenyl bromide (6 mmol) and anhydrous potassium carbonate (0.70 g; 5 mmol) in dry acetone (3 mL) was refluxed for 12 h and then

cooled. The mixture was diluted with water (10 mL) and then extracted with ether (2 × 20 mL). The combined extracts were washed with NaOH 10% (2 × 10 mL) and dried with anhydrous sodium carbonate. After removal of the solvent the products **11a–g, 12** and **13** were purified by column chromatography (Silicagel 60; 230–400; heptane).

4.2.8. 4-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyloxy)-3-allyl-*N*-adamantylbenzenamine (11a)

White solid, mp: 75–76 °C; ^{1}H NMR ($CDCl_3$): δ 1.61, 1.62, 1.69 & 1.73 (s, 12H, CH_3– (farnesyl)), 1.74–1.76 (m, 6H, –CH_2– (adamantyl)), 1.97 (m, 6H, –CH_2– (adamantyl)), 1.99 (m, 2H, –CH_2– (farnesyl)) 2.05–2.15 (m, 9H, –CH– (adamantyl) & –CH_2– (farnesyl)), 3.38 (d, J = 6.5 Hz, 2H, –CH_2– (allyl)), 4.52 (d, J = 5.0 Hz, 2H, (–CH_2O–), 5.04–5.11 (m, 4H, =CH_2 (allyl) & =CH– (farnesyl)), 5.47 (t, J = 6.5 Hz, 1H, =CH– (farnesyl)), 5.95–6.01 (m, 1H, -H C= (allyl), 6.81 (d, J = 9.0 Hz, 1H, H-2), 7.19 (s, 1H, NH), 7.22 (d, J = 2.5 Hz, 1H, H-5), 7.40 (dd, J = 8.5, 3.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ 175.84, 153.30, 140.45, 136.76, 135.38, 131.31, 130.93, 129.61, 124.33, 123.72, 122.05, 119.99, 119,19, 115.71, 112.72, 65.61, 41.31, 39.69, 39.52, 39.32, 36.47, 34.32, 28.16, 26.72, 26.27, 25.70, 17.70, 16.69, 16.03. Found: C, 81.81; H, 9.13; N, 2.69. $C_{35}H_{49}NO_2$ requires: C, 81.50; H, 9.58; N, 2.72.

4.2.9. 4-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyloxy)-3-allyl-N-cyclohexylbenzenamine (11b)

White solid, mp: 69–71 °C; ^{1}H NMR ($CDCl_3$): δ 1.25–1.35 (m, 4H, –CH_2– (cyclohexyl)), 1.52–1.55 (m, 2H, –CH_2– (cyclohexyl)), 1.61, 1.62, 1.69 & 1.72 (s, 12H, CH_3– (farnesyl)), 1.82–1.86 (m, 2H, –CH_2– (farnesyl)), 1.94–2.00 (m, 4H, –CH_2– (cyclohexyl & farnesyl)), 2.05–2.13 (m, 6H, –CH_2– (cyclohexyl & farnesyl)), 2.17–2.20 (m, 1H, CH, (cyclohexyl)), 3.38 (d, J = 7.0 Hz, 2H, –CH_2– (allyl)), 4.52 (d, J = 6.5 Hz, 2H, (–CH_2O–), 5.03–5.11 (m, 4H, =CH_2 (allyl) & =CH– (farnesyl)), 5.48 (t, J = 6.5 Hz, 1H, =CH– (farnesyl)), 5.95–6.01 (m, 1H, –HC= (allyl), 6.80 (d, J = 9.0 Hz, 1H, H-2), 7.13 (s, 1H, NH), 7.22 (d, J = 2.5 Hz, 1H, H-5), 7.41 (dd, J = 8.5, 2.5 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 174.1, 153.26, 140.47, 136.72, 135.38, 131.32, 130.99, 129.60, 124.33, 123.72, 121.88, 118.98, 118.02, 115.74, 112.23, 65.50, 46.43, 39.70, 39.52, 34.30, 29.72, 26.71, 26.62, 25.72, 17.71, 16.70, 16.04. Found: C, 80.29; H, 9.70; N, 2.98. $C_{31}H_{45}NO_2$ requires: C, 80.30; H, 9.78; N, 3.02.

4.2.10. 4-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyloxy)-3-allyl-*N*-cyclopentyl benzenamine (11c)

White solid, mp: 29–30 °C; ^{1}H NMR ($CDCl_3$): δ 1.57 (m, 2H, –CH_2– (cyclopentyl)),, 1.61, 1.62, 1.69 & 1.72 (s, 12H, CH_3– (farnesyl)), 1.83 (m, 2H, –CH_2– (cyclopentyl)), 1.82–1.86 (m, 2H, –CH_2– (farnesyl)), 1.94–2.00 (m, 4H, –CH_2– (adamantyl & farnesyl)), 2.05–2.13 (m, 6H, –CH_2– (adamantyl & farnesyl)), 2.18 (m, 1H, CH, (cyclohexyl)), 3.38 (d, J = 7.0 Hz, 2H, –CH_2– (allyl)), 4.52 (d, J = 6.5 Hz, 2H, (-CH_2O-), 5.03–5.11 (m, 4H, =CH_2 (allyl) & =CH– (farnesyl)), 5.48 (t, J = 6.5 Hz, 1H, =CH– (farnesyl)), 5.97 (m, 1H, –HC= (allyl), 6.80 (d, J = 9.0 Hz, 1H, H-2), 7.13 (s, 1H, NH), 7.22 (d, J = 2.5 Hz, 1H, H-5), 7.41 (dd, J = 8.5, 2.5 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ 173, 153, 140.50, 137, 135.60, 131.43, 131, 129.96, 124.45, 124, 122, 120, 119, 115.86, 112, 65.90, 34.42, 32.33, 27, 26.61, 26, 25.50, 18.08, 17.71, 16.73, 16.04. Found: C, 80.13; H, 69.52; N, 3.10. $C_{30}H_{43}NO_2$ requires: C, 80.18; H, 9.58; N, 3.12.

4.2.11. 4-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyloxy)-3-allyl-*N*-cyclobutylbenzenamine (11d)

Yellow solid, mp: 29–30 °C; ^{1}H NMR ($CDCl_3$): δ 1.61, 1.62, 1.69 & 1.72 (s, 12H, CH_3– (farnesyl)), 1.82–1.86 (m, 2H, –CH_2– (farnesyl)), 1.94–2.15 (m, 10H, –CH_2– (cyclobutyl & farnesyl)), 2.22–2.24 (m, 2H, –CH_2– (cyclobutyl)), 2.35–2.41 (m, 2H, –CH_2–, (cyclobutyl)), 3.11–3.14 (m, 1H, CH, (cyclobutyl)), 3.38 (d, J = 7.0 Hz, 2H, –CH_2– (allyl)), 4.52 (d, J = 6.0 Hz, 2H, (–CH_2O–), 5.03–5.11 (m, 4H, =CH_2 (allyl) & =CH– (farnesyl)), 5.47 (t, J = 6.5 Hz, 1H, =CH– (farnesyl)), 5.95–6.01 (m, 1H, –HC= (allyl), 6.81 (d, J = 8.5 Hz, 1H, H-2), 7.02 (s, 1H, NH), 7.21 (d, J = 2.5 Hz, 1H, H-5), 7.41 (dd, J = 8.5, 3.0 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 172.94, 153.27, 140.47, 136.72, 135.38, 131.32, 130.91, 129.60, 124.33, 123.72, 121.80, 119.98, 118.94, 115.74, 112.22, 65.57, 40.47, 39.70, 39.52, 34.29, 26.71, 26.26, 25.72, 25.34, 18.06, 17.71, 16.70, 16.04. Found: C, 79.94; H, 9.40; N, 3.18. $C_{29}H_{41}NO_2$ requires: C, 80.00; H, 9.42; N, 3.22.

4.2.12. 4-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyloxy)-3-allyl-*N*-cyclopropylbenzenamine (11e)

White liqud; ^{1}H NMR ($CDCl_3$): δ 0.81–0.85 (m, 2H, –CH_2–, (cyclopropyl)), 1.06–1.09 (m, 2H, –CH_2–, (cyclopropyl)), 1.44–1.47 (m, 1H, CH, (cyclopropyl)), 1.61, 1.62, 1.69 & 1.72 (s, 12H, CH_3– (farnesyl)), 1.97–2.15 (m, 8H, –CH_2– (farnesyl)), 3.38 (d, J = 6.5 Hz, 2H, –CH_2– (allyl)), 4.52 (d, J = 6.5 Hz, 2H, (–CH_2O–), 5.04–5.14 (m, 4H, =CH_2 (allyl) & =CH– (farnesyl)), 5.46 (t, J = 6.5 Hz, 1H, =CH– (farnesyl)), 5.94–6.00 (m, 1H, –HC= (allyl), 6.81 (d, J = 8.5 Hz, 1H, H-2), 7.21 (d, J = 2.0 Hz, 1H, H-5), 7.25 (s, 1H, NH), 7.38 (dd, J = 8.5, 2.0 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 171.50, 153.24, 140.47, 136.73, 135.39, 131.34, 131.05, 129.60, 124.33, 123.71, 121.84, 119.98, 118.94, 115.74, 112.21, 65.65, 39.70, 39.51, 34.29, 26.71, 26.25, 25.72, 17.71, 16.70, 16.04, 15.63. Found: C, 79.75; H, 9.21; N, 3.28. $C_{28}H_{39}NO_2$ requires: C, 79.81; H, 9.26; N, 3.32.

4.2.13. 4-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyloxy)-3-allyl-*N*-methylbenzenamine (11f)

White solid, mp: 60–61 °C; ^{1}H NMR ($CDCl_3$): δ 1.61, 1.62, 1.69 & 1.72 (s, 12H, CH_3– (farnesyl)), 1.97–2.00 (m, 2H, –CH_2– (farnesyl)), 2.05–2.10 (m, 4H, –CH_2– (farnesyl)), 2.12–2.17 (m, 5H, –CH_2– (farnesyl) & CH_3– (acetyl)), 3.37 (d, J = 6.5 Hz, 2H, –CH_2– (allyl)), 4.52 (d, J = 6.5 Hz, 2H, (–CH_2O–), 5.03–5.14 (m, 4H, =CH_2 (allyl) & =CH– (farnesyl)), 5.48 (t, J = 6.5 Hz, 1H, =CH– (farnesyl)), 5.93–5.99 (m, 1H, –HC= (allyl), 6.80 (d, J = 8.5 Hz, 1H, H-2), 7.15 (d, J = 3.0 Hz, 1H, H-5), 7.30 (s, 1H, NH), 7.38 (dd, J = 8.5, 2.5 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 168.24, 153.49, 140.51, 136.72, 135.39, 131.32, 130.70, 129.58, 124.33, 123.71, 118.98, 118.49, 115.75, 111.15, 65.54, 39.70, 39.52, 34.29, 26.71, 26.26, 25.72, 24.36, 17.71, 16.70, 16.04. Found: C, 78.93; H, 9.34; N, 3.50. $C_{26}H_{37}NO_2$ requires: C, 78.99; H, 9.37; N, 3.54.

4.2.14. 4-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyloxy)-3-allylphenylbenzenamine (11g)

White solid, mp: 51–52 °C; ^{1}H NMR ($CDCl_3$): δ 1.62, 1.63, 1.70 & 1.75 (s, 12H, CH_3– (farnesyl)), 1.99–2.19 (m, 8H, –CH_2– (farnesyl)), 3.40 (d, J = 7.0 Hz, 2H, –CH_2– (allyl)), 4.55 (d, J = 6.5 Hz, 2H, (–CH_2O–), 5.05–5.16 (m, 4H, =CH_2 (allyl) & =CH– (farnesyl)), 5.50 (t, J = 5.5 Hz, 1H, =CH– (farnesyl)), 5.95–6.00 (m, 1H, –HC= (allyl), 6.85 (d, J = 8.5 Hz, 1H, H-2), 7.32 (s, 1H, NH), 7.44–7.47 (m, 2H, aromatic), 7.51–7.56 (m, 2H, aromatic), 7.85–7.88 (m, *2*H, aromatic); ^{13}C NMR ($CDCl_3$) δ 165.60, 153.66, 140.55, 136.60, 135.40, 135.11, 131.60, 131.32, 130.79, 129.71, 128.68, 127.00, 124.36, 123.73, 122.43, 120.77, 119.96, 119.62, 115.62, 109.75, 65.57, 39.71, 39.53, 32.48, 26.73, 26.28, 25.70, 17.71, 16.72, 16.06. Found: C, 81.34; H, 8.50; N, 3.00. $C_{31}H_{39}NO_2$ requires: C, 81.40; H, 8.53; N, 3.06.

4.2.15. 4-((*E*)-3,7-Dimethyllocta-2,6-dienyloxy)-3-allyl-*N*-adamantylbenzenamine (12)

White solid, mp: 106–107 °C; ^{1}H NMR ($CDCl_3$): δ 1.62, 1.69 & 1.72 (s, 9H, CH_3– (geranyl)), 1.72–1.80 (m, 6H, –CH_2– (adamantyl)), 1.97 (m, 6H, –CH_2– (adamantyl)), 2.05–2.16 (m, 9H, –CH– (adamantyl) & –CH_2– (geranyl)), 3.38 (d, J = 6.5 Hz, 2H, –CH_2– (allyl)),

4.53 (d, J = 6.5 Hz, 2H, (–CH_2O–), 5.02–5.10 (m, 4H, =CH_2 (allyl) & =CH– (geranyl)), 5.47 (m, 1H, =CH– (geranyl)), 5.96–6.02 (m, 1H, –HC= (allyl), 6.81 (d, J = 8.5 Hz, 1H, H-2), 7.19 (s, 1H, NH), 7.22 (d, J = 3.0 Hz, 1H, H-5), 7.42 (dd, J = 8.5, 3.0 Hz, 1H, H-6); δ ^{13}C NMR ($CDCl_3$) δ 175.84, 153.30, 140.45, 136.76, 135.38, 131.31, 130.93, 129.61, 124.33,123,72, 119.99. 119.19, 115.71, 112.50, 65.61, 41.31, 39.52, 36.47, 34.32, 28.16, 26.72, 26.27, 25.70, 17.70, 16.69, 16.03. Found: C, 80.87; H, 8.71; N, 3.90. $C_{30}H_{39}NO_2$ requires: C, 80.90; H, 8.76; N, 3.15.

4.2.16. 4-(3-Methylbut-2-enyloxy)-3-allyl-*N*-adamantylbenzenamine 13

White solid, mp: 129–131 °C; ^{1}H NMR ($CDCl_3$): δ 1.72–1.80 (m, 12H, –CH_2– (adamantyl) & CH_3– (isopentenyl)), 1.96 (m, 6H, CH_3–(adamantyl)), 2.01 (m, 3H, –CH– (adamantyl)), 3.37 (d, J = 6.5 Hz, 2H, –CH_2– (allyl)), 4.49 (d, J = 6.5 Hz, 2H, (–CH_2O–), 5.03–5.10 (m, 4H, =CH_2 (allyl) & =CH– (isopentenyl)), 5.455.50 (m, 1H, =CH–(isopentenyl)), 5.94–6.02 (m, 1H, –HC= (allyl), 6.80 (d, J = 8.5 Hz, 1H, H-2), 7.23–7.24 (m, *2*H, H-5 & NH), 7.41 (dd, J = 8.5, 3.0 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 175.90, 153.28, 136.75, 130.93, 129.61, 121.79, 119.69, 119.24, 116.37, 112.52, 65.56, 41.31, 39.31, 36.47, 34.30, 28.16, 25.76, 18.26. Found: C, 79.53; H, 8.17; N, 3.66. $C_{25}H_{33}NO_2$ requires: C, 79.11; H, 8.76; N, 3.69.

Acknowledgement

We are grateful to Mashhad University of Medical Sciences for financial support of this work (project 88210).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.07.025.

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