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# New chemical structures of hypolipidemic and antiplatelet activity*

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*Abstract*: Elevated lipid level is supposed to be one of the main risk factors of atherosclerosis and subsequent cardiovascular disease (and is connected to mortality). Therefore, lipid lowering is one of the major targets in cardiovascular disease treatment and prevention. Also, blood platelets play a pivotal role in the development of atherosclerosis and fatal thrombus formation in the course of coronary heart disease. Therefore, there is a great necessity to acquire drugs inhibiting platelet aggregation and clot generation. The present paper reviews new chemical structures in development for the treatment and prevention of hyperlipidemia, atherosclerosis, and subsequent cardiovascular disease. The authors' recent results are also reported regarding synthesis of a new group of α-asarone analogs. These compounds were identified as an original class of agents exhibiting hypolipidemic and antiplatelet (mice, rats) activities. Although the mechanism of the compounds' pharmacological activity has not been identified, quantum-mechanical calculations allowed structural requirements to be described that correspond to the activity (a hypothetical pseudoreceptor structure). Since it is known that asarone and its derivatives may exhibit genotoxicity, calculations were carried out to identify derivatives of possibly low genotoxic activity.

## SIGNIFICANCE OF HYPOLIPIDEMIC AND ANTIPLATELET AGENTS IN ATHEROSCLEROSIS

Atherosclerosis and subsequent cardiovascular diseases, especially myocardial infarction, still remain the major cause of mortality in modern societies. Plausible cardiovascular disease biological risk factors include lipid abnormalities, glucose intolerance and insulin resistance, hypertension, abnormalities in hemocoagulation [1], or serum hyperhomocysteinemia [2–4].

Hypercholesterolemia is an important cause of coronary heart disease (CHD), and the role of cholesterol in the formation of atherosclerotic lesions has been confirmed experimentally [5]. Basically, cells—except for hepatic and ileum cells—do not synthesize cholesterol *de novo* but obtain it from the blood and the cholesterol that accumulates in atherosclerotic lesion originates primarily in plasma liopoproteins. Among several lipoproteins, low-density lipoprotein (LDL) is the main lipoprotein delivering cholesterol to the target cells, which acquire it with the aid of LDL-receptors (for a review, see [6,7]).

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Various clinical and experimental studies established that elevated plasma concentrations of LDL-cholesterol were associated with atherogenesis. Another lipoprotein—high-density lipoprotein (HDL)—takes part in the reverse cholesterol transport, and it is known that HDL-cholesterol is negatively associated with the incidence of CHD in humans [8]. The oxidation of LDL and very low density lipoproteins (VLDLs) is strongly suggested to be involved in lipid accumulation in the arterial wall and subsequent plaque formation. The following sequence has been postulated as leading to the fatty streak formation [9]. In the presence of high plasma LDL level, the concentration of LDL in the intima is increased, and it can be modified via oxidative process. Then, circulated monocytes can be recruited into the arterial wall where they undergo phenotypic modification into macrophages. However, the macrophage's return into circulating plasma is now inhibited by the oxidized LDL. The macrophages resident in subendothelium express the acetyl-LDL receptors and may more rapidly accumulate the oxidized LDL. The cells are now loaded with cholesterol and become foam cells in fatty streak lesion.

Several lipoproteins, including VLDL, LDL, oxidatively modified LDL, and lipoprotein(a), can promote procoagulant and antifibrinolytic responses in endothelium, macrophages, platelets, and neutrophils [10,11]. In early atherogenesis, oxidatively modified lipoproteins can express specific adhesion molecules to mediate leucocyte adhesion [12]. Progression of aetheroma is mediated by smooth muscle cell migration and cellular proliferation resulting from cytokine and mitogens activity. Endothelium equilibrium between anticoagulant and procoagulant properties in response to atherosclerosis development becomes unbalanced and shifts toward procoagulant state [13]. During lesion formation, platelets release clotting factors, chemotaxins, and vasoconstrictors such as thromboxane $A_2$, platelet-activating factor (PAF), and leucotriens that may result in mural microtrombi formation. At a later stage, a plaque rupture can take place, exposing subendothelium to circulating blood elements. Exposure to collagen and tissue factor results in platelet adhesion, activation, and aggregation and in initiation of the coagulation cascade, and subsequently in thrombus formation [14].

In recent years, it has been established that atherosclerosis can be slowed and even regressed (for a review, see [15]). Atherosclerotic plaques are, however, known to progress, stabilize, or regress for various reasons, some of them still unknown. Numerous different processes, such as competitive inhibition, reverse cholesterol transport, and low-serum cholesterol, contribute to plaque regression [15]. Plaque regression occurs more readily by the removal of exchangeable components in the plaque's lipid pool—reverse transport of exchangeable cholesterol and HDL-cholesterol is believed to play a significant role in this process [8]. Therefore, regressions occur more frequently in patients with low levels of trigliceride-rich lipoproteins and LDL and high levels of HDL [16,17]. While plasma cholesterol is a major contributor to the lesion, cholesterol exchange and controlling plasma cholesterol levels indirectly help restrict the volume of lesion lipid pools [17] and lower the incidence of death and major coronary events [18–20].

Although even under favorable conditions of low triglicerides and LDL and high HDL levels, atherosclerosis still may progress [16,21,22], yet lipid-lowering therapy is one of the major targets in the CHD treatment and prevention. Drugs prescribed for hyperlipidemia treatment in general can be put into the following categories:

- Bile acid binding resins (colestipol, cholestyramine)—large polymeric cationic exchange resins insoluble in water. These resins bind bile acids in the intestinal lumen, prevent their reabsorption, and promote their excretion.
- Fibric acid derivatives (clofibrate, bezafibrate, fenofibrate, gemfibrozil, etofibrate, ciprofibate, clofibride, nicofibrate, eniclobrate)—lower triglyceride and cholesterol-rich lipoprotein levels and increase lipolysis of lipoprotein triglyceride via lipoprotein lipase.
- Statins (lovastatin, simvastatin, pravastatin, mevastatin, fluvastatin, atorvastatin, cerivastatin)—cholesterol biosynthesis inhibitors. Act as structural analogs and competitive inhibitors of 3-HMG-CoA reductase, an enzyme involved in the transformation of (S)-3-hydroxy-3-methylglutaryl-CoA into (R)-mevalonate and determining the kinetics of cholesterol synthesis.

- Nicotinic acid (niacin) and its analog acipimox—inhibit triglyceride lipolysis (liberation from adipocytes) lowering influx of free fatty acids to the liver and cholesterol esterification.
- Unsaturated fatty acids (esters of linolic, linolinolic and oleic acids with phospholipids)—decrease cholesterol and triglyceride levels.
- Probucol—mechanism of activity unclear. It was found to be a lipophilic antioxidant, more powerful than vitamin E (for a review, see [23]).

Blood platelets play a pivotal role in the development of atherosclerosis and fatal thrombus formation in the course of coronary heart disease. Therefore, various drugs are commonly used to inhibit platelet aggregation and clot generation. Agents currently used in antiplatelet treatment may be classified as follows:

- Drugs targeting arachidonic acid metabolism—cyclooxygenase (aspirin and other nonsteroidal anti-inflammatory drugs: indobufen, triflusal, sulfinpyrazone) and other thromboxane synthesis inhibitors (ozagrel, camonagrel, dazoxiben, ridogrel), as well as prostacyclin mimetics (beraprost).
- ADP-receptor inhibitors/antagonists (thienopyridines ticlopidine and clopidogrel).
- Phophodiestherase inhibitor (dipyridamole).
- Glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban, fradafiban, lamifiban, xemlofiban, sibrafiban).
- Thrombin inhibitors (heparin and direct thrombin inhibitors: hirudin, bivalirudin, argatroban, efegatran, inogatran).

## NEW HYPOLIPIDEMIC AND ANTIPLATELET AGENTS

### Hypolipidemics

Recently disclosed (1997–2000) hypolipidemic structures may be put into such categories as:

- Cholesterol biosynthesis inhibitors [24–26]—compounds inhibiting one of the steps in the cholesterol biosynthetic pathway.
- Acyl-coenzyme A cholesteryl acyltransferase (the enzyme catalyzing the formation of cholesterol esters) inhibitors [27,28].
- LDL uptake promoters—increase the uptake of LDL by Hep G2 cells [29] and exhibit ability to increase LDL receptor expression in HepG2 cells [30].
- Taurocholate receptor antagonists [31]. The compounds are stated to be [3H]-taurocholate receptor antagonists (for a review concerning conjugated bile acids uptake, see [32]).
- aP2 (an intracellular lipid-binding protein postulated to facilitate the intracellular trafficking of lipids [33–35]) inhibitors [36]. It has been shown that aP2-depleted mice exhibited significant decrease in both basal and isoproterenol-stimulated lipolysis in adipose tissue and increased cellular fatty acid levels, suggesting that lipid-binding proteins function as lipid chaperones, facilitating the movement of fatty acids out of the fat cell [37].
- Peroxisome proliferator-activated receptors $\alpha$, $\beta$, and $\gamma$ (PPARs) activators [38,39]. PPARs regulate fatty acids $\beta$-oxidation [40–42]. It has been shown that a variety of fatty acids can activate the receptors and suggest that fatty acids (or their acyl-CoA derivatives) may be the natural ligands of PPARs [43].
- Antioxidants [44–47]. Oxidation of LDL in the vessel wall is thought to be one of the steps involved in atherogenesis [48].

### Antiplatelet agents

Newly patented compounds claimed as antiplatelet agents may be classified as:

- Fibrinogen receptor antagonists [49–54]. Some of the compounds are claimed to be the GP IIb/IIIa modulators.
- Vitronectin receptor antagonists [55]. Vitronectin, a glycoprotein present in platelets, plasma, endothelium, and in extracellular matrix, intermediates interactions between fibroblasts, endothelium, and thrombocytes. Thus, vitronectin is an important factor, whose activity may result in the binding platelets to subendothelium.
- Thrombin inhibitors (a stress being made on direct thrombin inhibitors) [56–63].
- Factor Xa inhibitors [64–72]. Factor Xa is known as a site where intrinsic and extrinsic pathways of coagulation links together. Factor X is activated to factor Xa by factor VIIa or factor IXa and, in connection with factor Va, phospholipids, and calcium ions, forms a prothrombinase complex, which converts prothrombin to thrombin. Thus, factor Xa is a valuable antithrombotic target.
- Serine protease inhibitors with no marked specificity [73–75].
- Calmodulin modulators [76,77]. Camodulin is a $Ca^{2+}$-dependent regulatory protein. Besides acting on calcium ions transport and several enzymes (especially those involved in synthesis and decomposition of cyclic nucleotides), it regulates activity of numerous cell structure elements connected with cell motility, conformational changes, mitosis, and endocitosis.

### Miscellaneous

The above-reviewed compounds are claimed for treating hyperlipidemia and atherosclerosis to be of use in cardiovascular diseases. Some of the agents exhibit the mechanism of activity similar to those of known hypolipidemic and antiplatelet drugs and some are claimed to be directed at new molecular targets. There is, however, quite a numerous group of structures that are claimed as hypoglycemic and/or hypolipidemic (and antiplatelet, etc.) agents without specifying a definite mechanism of activity.

The compounds stated for the use in hyperlipidemia, obesity, and the insulin-resistance syndrome represent diversified chemical structures. Most of the structures contain aza [78,79], tia [80,81], oxaza [82–88], tiaza [89–91], diaza [92–94], oxaza and tiaza [95], or tia and oxaza [96] five-membered heteroaromatic rings. Natural products derivatives, such as liberomycins [97] and steroids [98], can also be found. The latter group of compounds, claimed to be of use for diabetes and obesity, reached relatively a high level of preclinical studies being tested on monkeys [98].

Novel substituted terphenyl [99] and pyrazolone derivatives [100] were disclosed as platelet aggregation inhibitors, without revealing the specified mechanisms of action. Thrombolytic agents with antithrombotic activity, comprising a protease conjugated to GP IIb/IIIa targeting compounds, were claimed by Diatide, Inc. [101]. Antithrombotic activity exhibited novel fucan sulfate compounds isolated from brown algae [102]. Organic nitrates derived from known cardiovascular agents, such as timolol and enalaprilate, with lower toxicities than reference compounds, were stated to possess antithrombotic activity and to be useful as antihypertensive and cardioprotective agents [103]. One of the processes occurring in atherogenesis is smooth muscle cell proliferation. Sulfated oligosaccharides, prepared by degradation of a polysaccharide from the yeast Pichia holstii, known as inhibitors of mammalian heparanases with anticoagulant/antithrombotic activity, were disclosed as smooth muscle cell proliferation inhibitors [104].

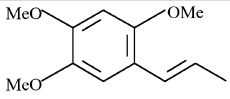
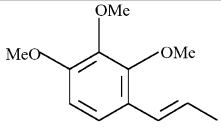
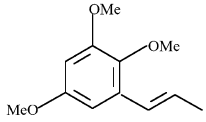
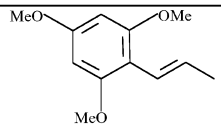
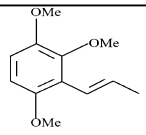
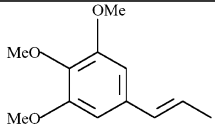
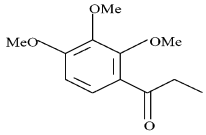
## NEW α-ASARONE DERIVATIVES

### Hypolipidemic activity

In our laboratories, several asarone analogs **1**–**33** (Table 1) were obtained. All the compounds were examined for their hypolipidemic activity on Wistar male rats weighting 200–300 g. All rats were fed a high cholesterol diet (Murigran enriched with cholesterol 1%, sodium cholate 0.2%, and olive oil 5%) for 7 days. Rats fed with laboratory chow for the same duration as above were used as a noncholesterol

control group. Group receiving clofibrate and fenofibrate served as positive control. Total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglicerydes were determined using BioMerieux (Marcy–l'Etuoile, France) kits on a Shimadzu UV-1202 Spectrophotometer. All the data were statistically analyzed by Student's t-test.

**Table 1** Hypolipidemic activity of α-asarone isomers (% of control I).

| Entry | Compound | TC | HDL | LDL | TG |
|---|---|---|---|---|---|
| 1 | Control 0 | –38,0 | +56 | –79 | –39 |
| 2 | Control I | 100 | 100 | 100 | 100 |
| 3 | CLOFIBRATE | –23 | +24 | +7 | –27 |
| 4 | FENOFIBRATE | –41 | +213 | –63 | +136 |
| 5 |  **1** (α-asarone) | +2 | +57 | –43 | +75 |
| 6 |  **2*** | –13 | +48 | –30 | +0 |
| 7 |  **3*** | –12 | +35 | –17 | +12 |
| 8 |  **4*** | –12 | +31 | –15 | –7 |
| 9 |  **5*** | +4 | +4 | +12 | +30 |
| 10 |  **6*** | –16 | +56 | –54 | +8 |
| 11 |  **7** | –16 | +20 | –35 | +21 |

(*Continued on next page*)

**Table 1** (*Continued*)

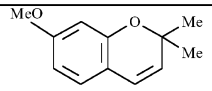
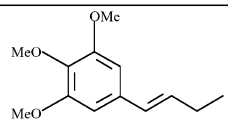
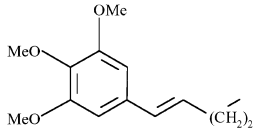
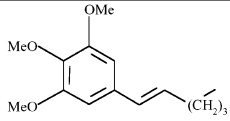
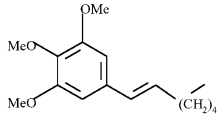
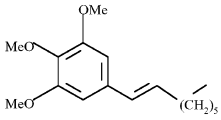
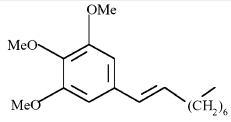
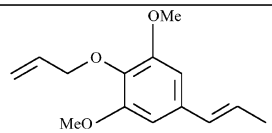
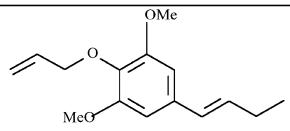
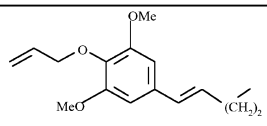
| Entry | Compound | TC | HDL | LDL | TG |
|---|---|---|---|---|---|
| 12 |  **8** | +26 | –45 | +94 | +42 |
| 13 |  **9** | –10 | +7 | –16 | +133 |
| 14 |  **10** | +17 | –4 | +21 | +167 |
| 15 |  **11** | +6 | +4 | +4 | 0 |
| 16 |  **12** | +5 | +29 | –5 | +111 |
| 17 |  **13** | –28 | +2 | –38 | –22 |
| 18 |  **14** | +1 | +4 | +2 | –11 |
| 19 |  **15** | +52 | –22 | +78 | +122 |
| 20 |  **16** | +32 | +20 | +34 | +11 |
| 21 |  **17** | +8 | +33 | +1 | –22 |

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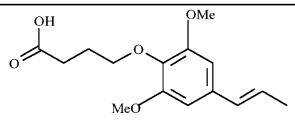
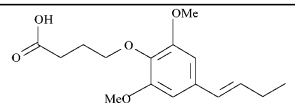
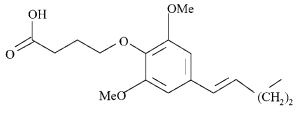
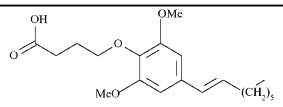
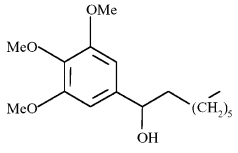
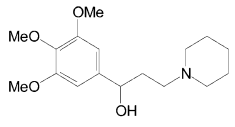
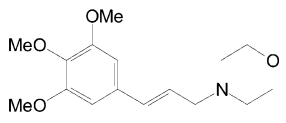
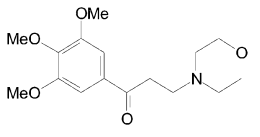
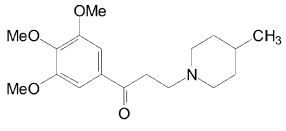
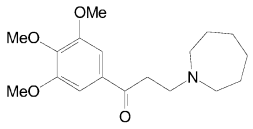
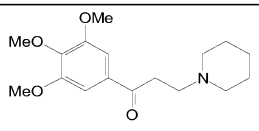
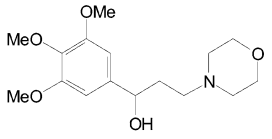
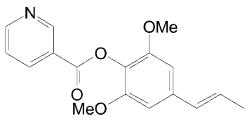
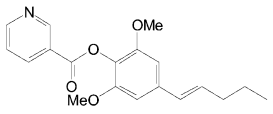
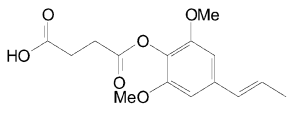
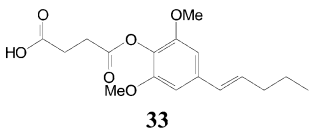
**Table 1** (*Continued*)

| Entry | Compound | TC | HDL | LDL | TG |
|---|---|---|---|---|---|
| 22 |  **18** | +37 | +16 | +40 | +222 |
| 23 |  **19** | +36 | +16 | +44 | +56 |
| 24 |  **20** | +17 | +25 | +16 | 0 |
| 25 |  **21** | +4 | −18 | +15 | −5 |
| 26 |  **22** | +57 | −25 | +107 | −21 |
| 27 |  **23** | +13 | +10 | +20 | −15 |
| 28 |  **24** | +13 | +26 | +12 | +16 |
| 29 |  **25** | +7 | +71 | −7 | +54 |
| 30 |  **26** | −10 | +35 | −16 | −16 |

(*Continued on next page*)

**Table 1** (*Continued*)

| Entry | Compound | TC | HDL | LDL | TG |
|---|---|---|---|---|---|
| 31 |  **27** | +18 | +68 | +12 | +12 |
| 32 |  **28** | +6 | +65 | –5 | +26 |
| 33 |  **29** | 0 | +36 | –2 | –23 |
| 34 |  **30** | –11 | +7 | –21 | +51 |
| 35 |  **31** | –29 | +42 | –42 | –3 |
| 36 |  **32** | –3 | +10 | –2,9 | –12 |
| 37 |  **33** | +28 | –7 | +28 | +38 |

TC: total cholesterol; HDL: HDL-cholesterol; LDL: LDL-cholesterol; TG: triglycerides; Control 0: animals receiving standard laboratory chow; Control I: control animals receiving cholesterol-rich chow

*Data taken from ref. [105]

The compounds exhibited differentiated hypolipidemic activity. The differences were observed between particular compounds, as well as for the same compounds in different tests (i.e., influence on total, HDL- and LDL-cholesterol and triglyceride levels). Compounds **1**–**4**, **6**, **7**, **12**, **13**, **26**, **31**, and **32** were able to decrease total and LDL-cholesterol levels with simultaneous elevating of HDL-cholesterol levels. Since both an increase of HDL-cholesterol and a decrease of LDL-cholesterol concentrations have a positive effect on stopping atherosclerosis, a sum of the effects was calculated {atherogenic index = log ($[\text{HDL-cholesterol}]_{\text{sample}}/[\text{HDL-cholesterol}]_{\text{control}}$ ) – log ($[\text{LDL-cholesterol}]_{\text{sample}}/[\text{LDL-cholesterol}]_{\text{control}}$)} as a most natural way to show the compounds' parallel activity. The highest atherogenic indices possessed compounds **1**, **2**, **3**, **4**, **6**, **7**, and **13** (0.44, 0.33, 0.21, 0.18, 0.52, 0.27, 0.22,

respectively). Additionally, compounds **1** and **3** exhibited antithrombotic activity in collagen and epinephrine-induced pulmonary thromboembolism in mice [105].

### *QSAR of α-asarone derivatives*

While the mechanism of the compounds' pharmacological activity has not been determined, a model of pseudoreceptor for the most active compounds has been constructed. As the measure of the molecules' activities, previously defined atherogenic indices were used.

Structures of all molecules were generated in Cerius$^2$ package [106]. Optimizations were performed using universal force field [107], also in Cerius$^2$. For an alignment of training (reference), as well as test sets of molecules, a flexible fitting was used. For target molecules, the most active compounds were chosen in four main conformations. The QSAR analysis was performed by Cerius$^2$ module, receptor surface analysis (RSA).

Pseudoreceptors were created for each of four alignments. The seven molecules (**1**, **4**, **6**, **7**, **13**) with the highest atherogenic indices served as a scaffold for building these pseudoreceptors as an envelope coating the aligned molecules. Then, interaction energies between pseudoreceptor surface and respective molecules were calculated. The interaction energies were calculated at each point on the surface of a receptor model. Then, 90% points with lowest variance were excluded from calculations of QSAR regression. After selecting a set of molecular field points, they were used as molecular descriptors. All of the descriptors were used as independent variables in a statistical method to generate QSAR correlation, and a genetic function approximation (GFA) from Cerius$^2$ package was used as a regression method. A major advantage of this approach is that diverse, small models are generated that all have roughly the same high predictability. To estimate validity of the model, a cross-validation procedure was used. Each molecule was left out, in turn, and the correlation coefficient was computed using the predicted values of the missing molecules. At each surface point, the potentials (hydrophobicity, hydrogen bonding inclination, etc.) were mapped based on complementarities between a respective molecule potential and a surface point. The resulting models, together with the seven molecules used for construction of the pseudoreceptors, are shown in the Fig. 1.

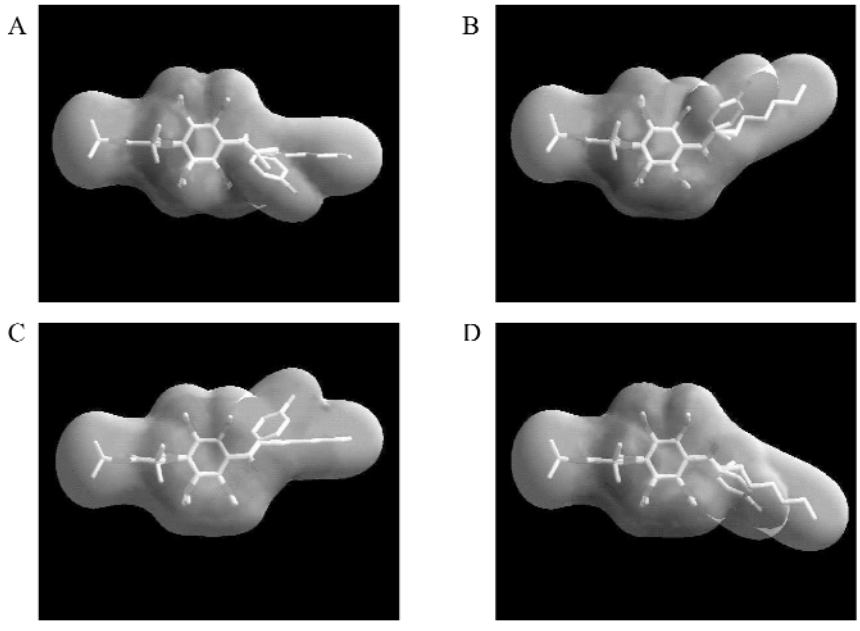



**Fig. 1** Pseudoreceptors generated for four main alignments of the reference set of molecules.

All molecules were minimized inside the pseudoreceptor surface, and total interaction energies at each surface point of the pseudoreceptor were analyzed by statistical method GFA. Resulting regressions with correlation coefficient (R), root mean square for training set (RMS), cross-validated $R^2$ ($cvR^2$), and root mean square for test set ($RMS_{test}$) are presented in Table 2. For all regressions, the number of observations was $N_{obs} = 20$, and the number of variables was $N_{var} = 4$ (including constant). The GFA method can build several QSAR regressions for single pseudoreceptor, and the best ones were collected in Table 1. The regression line drawn for the best C model is shown in Fig. 2.

**Table 2** Results of pseudoreceptor fit for the training set of molecules.

| Pseudoreceptor | R | RMS | $cvR^2$ | $RMS_{test}$ |
|---|---|---|---|---|
| **A** | 0.872 | 0.154 | 0.645 | 0.164 |
| **B** | 0.839 | 0.171 | 0.569 | 0.170 |
| **C** | 0.918 | 0.125 | 0.663 | 0.108 |
| **D** | 0.837 | 0.169 | 0.605 | 0.632 |

The obtained regression was tested on six compounds with known activities, but not included in the set used to create the models. As one can see from Fig. 2, all predictions for the tested set of compounds lie within experimental errors. Thus, it seems that the model may have a predictive value, although its validity has to be examined by the preparation of new molecules.

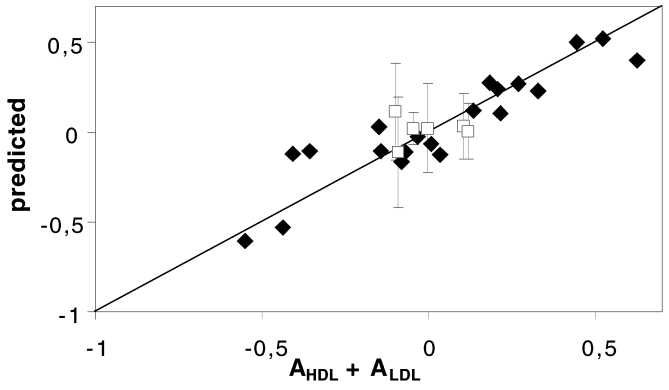



**Fig. 2** Predictivity of the pseudoreceptor model C. Reference set of molecules—dark diamonds; test set—light squares. R = 0.998; RMS = 0.019; $RMS_{test}$ = 0.240.

### *Genotoxic activity*

It has been found that α-asarone isomers may exhibit genotoxic activity [108,109]. According to Testa *et al.*, the relative stability formed during the metabolic pathway carbonium ions (Fig. 3) may be one of the key factors in the genotoxicity of some allylbenzenes (asarones) and propenylbenzenes, the non-genotoxicity being due to a greater difficulty of the carbonium ions formation [110]. Calculated according to Testa's method, the stabilities of putative carbonium ions for α-asarone and compounds **2**–**6** revealed that compound **6** (and perhaps compound **3**) might be lacking genotoxic activity (Table 3).

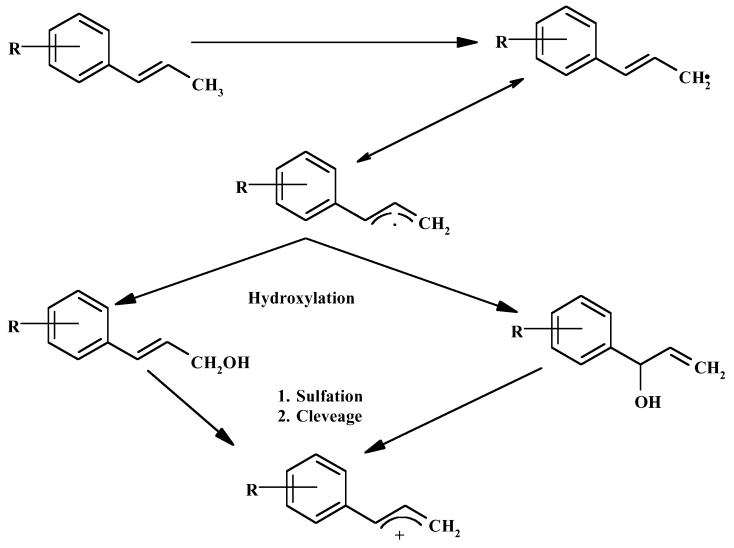



**Fig. 3** Postulated mechanism of metabolic activation of allylbenzenes [110].

**Table 3** Heat of formations of different metabolic intermediates (Fig. 3) for α-asarone and its isomers (calculated with the semiempirical AM1 method in kcal/mol).

| Compound | $\Delta H_{f(substrate)}$ [a] | $\Delta H_{f(radical)}$ [b] | $\Delta H_{f(alcohol)}$ [c] | $\Delta H_{f(carbocat.)}$ [d] | $\Delta H_{R(carbocat.)}$ [e] |
|---|---|---|---|---|---|
| **1** (α-asarone) | –80.1 | –61.7 | –124.5 | 103.0 | 227.5 |
| **2** | –77.7 | –60.1 | –123.4 | 105.9 | 229.3 |
| **3** | –78.8 | –61.0 | –122.9 | 110.6 | 232.9 |
| **4** | –79.8 | –63.5 | –122.6 | 94.7 | 217.3 |
| **5** | –76.8 | –60.2 | –122.5 | 105.4 | 227.9 |
| **6** | –79.2 | –62.2 | –124.7 | 111.2 | **235.9**[f] |

Heat of formations for: [a]substrates, [b]radicals, [c]alcohols, [d]carbocations, [e]stabilized carbocations $\Delta H_R = \Delta H_{f(carbocation)} - \Delta H_{f(alcohol)}$; [f]according to Testa [110], the heat of the radical formation for compounds exhibiting genotoxic activity should be less than 231.0 kcal/mol, with the mean value 227.7 ± 2.2 kcal/mol

## CONCLUSIONS

Hypolipidemic therapy has been developing rapidly within the last few years and is attaining very high therapeutic and market significance. Blood platelets play a pivotal role in the development of atherosclerosis and fatal thrombus formation in the course of coronary heart disease. Therefore, there is a great necessity to acquire drugs inhibiting platelet aggregation and clot generation. Since the atherosclerosis pathogenesis seems to be a complicated process, co-existing with such disorders as hyperlipidemia, obesity, and insulin-resistance syndrome, the great number of compounds do not have clearly defined molecular targets for the treatment of the above complex disorders.

Some of the obtained new asarone derivatives exhibited both hypolipidemic (high atherogenic index) and antithrombotic [105] activity *in vivo*. Pharmacological properties of those derivatives are thus unique, but it is known that the type of compounds may be potentially genotoxic. However, theoretical evaluation of the compounds' genotoxic activity has shown that two of them may potentially be non-genotoxic. Although the mechanism of the compounds' activity has not been determined, the

obtained pseudoreceptor model with a predictive ability may suggest that the compounds could follow the same mechanism of action. Compounds **3** and **6** are thus worth further pharmacological evaluation and could serve as leading structures for the design of new synthetic drug candidates.

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