Molecular Pharmacophore Determination of Lipid Lowering Drugs with the Receptor Mapping Method

M. Ablise [1, 2.b] *, A. Cartier [2.a], G. Siest [2.b], S. Visvikis [2.b] and V. Loppinet [2.b]

[1] Xinjiang Medical University, College of Pharmacy, China; [2] Université Henri Poincaré, 54000 Nancy, France: (2.a) UMR 7565 (Fac. Sciences); 2.b / INSERM 525 (Fac. Pharmacie)

Abstract: Hypolipidemic pharmacophoric moieties of statins, fibrates, ACAT inhibitors and beta-sitosterol analog series were identified by computational modeling, and compared with the computed structure of new potential glycyrrhetinic acid derivatives lipid-lowering drugs. Their electronic and geometric domains, similar to those of fibrates, suggest a fibrate -like mechanism matching biochemical data.

Key Words: molecular modeling, hypolipidemic pharmacophore, EMO and GEOMOS programs, semi-empirical PM3 method, glycyrrhetinic acid derivatives.

I-INTRODUCTION

Over the last ten years, numerous hypolipidemic drugs have been investigated for their cooperative therapeutic action upon atherosclerosis which is the first cause of morbidity and mortality in the western world.

The chemical structures of lead series (**I**: statins / HMG Co A reductase inhibitors; **II:** fibrates /ACoAC inhibitors; **III:** ACAT inhibitors [1]; **IV**: beta-sitosterol compounds / cholesterol absorption inhibition in the intestinal tract, was very heterogeneous, due to their various mechanisms (Figure **1**).

Zakirov [2] has recently demonstrated the effective hypolipidemic and antiatherosclerotic properties of a triterpenoides **V :** Glycyrrhetinic acid (GA, aglycone of glycyrrhizin which is a major saponin of *Glycyrrhiza glabra* L) (Figure **1**). Ammonium salt of GA and 18-dehydro-GA could considerably lower cholesterol and triglycerides level in atherosclerotic and hypercholesterolemic rabbits. However, their hypolipidemic pharmacophore is unknown and their action mechanism is still controversial [2,3].

The goal of this paper is to define pharmacophoric moieties for each family and to identify the hypolipidemic pharmacophore of the potential drug series, namely GA derivatives.

In order to achieve this aim, we have undertaken comparative studies with the help of the computer system to model the pharmacophore of different series of hypolipidemic drugs whose action mechanism is known. The result of this molecular model makes it possible to identify the hypolipidemic pharmacophore of glycyrrhetinic acid derivative series. This model lists the characteristics of their possible action mechanisms .

II- METHODS

II-1. Software Implemented

"EMO program - Molecular mechanics: geometry and steric energy of a molecule": Copyright Bruno Blaive, CNRS - 1998; Ecole Nationale Supérieure de Chimie, Faculté St-Jerome, F-13397 Marseille Cedex 20.

GEOMOS program with the Quantum Mechanic semi-empirical PM3 method [4] and Insight II Ver 97ª for superposition": <Silicon Graphics, Iris Indigo> 2011N, Shoreline BLDV, Mitsubishi Electric Corporation, Japan.

II-2. The Main Stages of Modelisation

We performed:

II.2.1. The Geometric Structure Optimization

The geometric structure optimization for 32 compounds by global energy minimization: This enabled us to create files containing optimized structure coordinates on a microcomputer.

The EMO program automatically performs all the iterations, on energy increments ($E_{binding}$, E_{angle}, $E_{torsion}$, $E_{Van\ der\ Waals}$), until a first minimum is reached. These results led us to verify the configuration of each chiral center, on which the final molecular geometry depends. The total energies of the different structures are recorded for further exploitation.

II-2.2. The Superposition

The superposition of the geometry and the determination of common architectural moieties: The files under EMO

*Address correspondence to this author at the Xinjiang Medical University (XMU), College of Pharmacy, 8, Xin Yi Road, 830054-ÜRÜMQI, P R of China, Tel: 0086 991 4841 491, Fax: 0086 991 4830 924, E-mail: mourboul@hotmail.com, mourboul@mail.xj.cninfo.net

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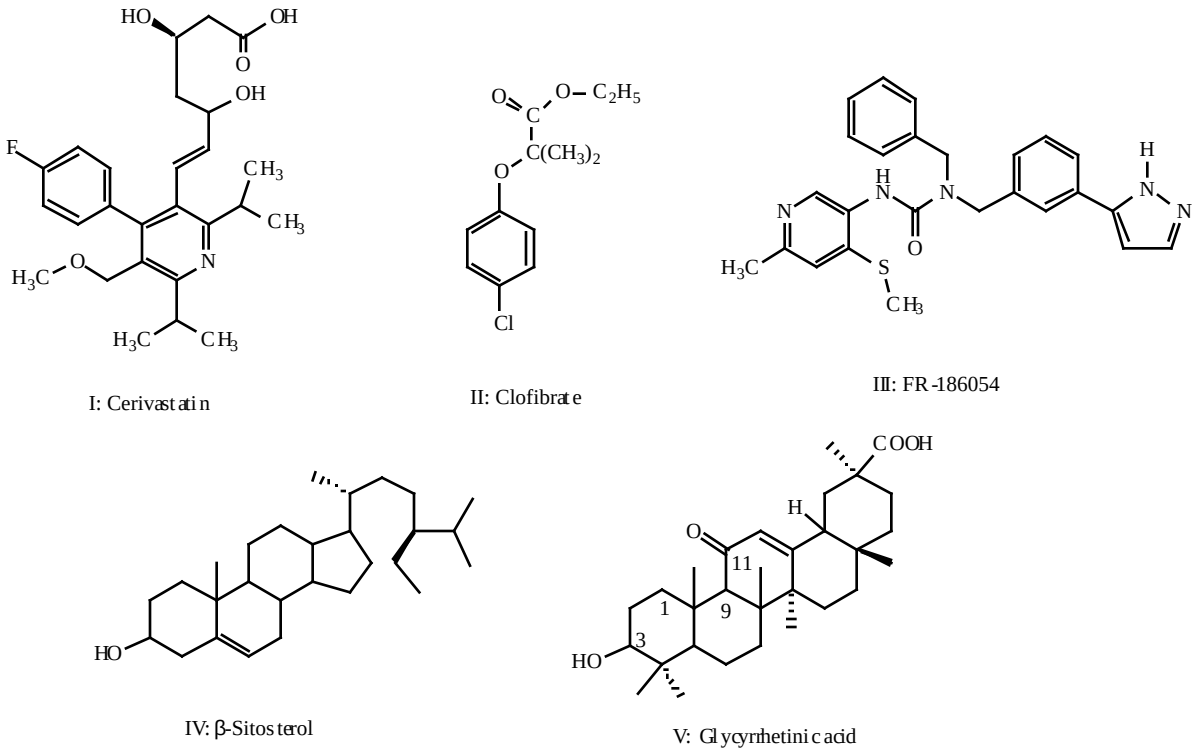


Fig. (1). Chemical structures of five hypolipidemic lead series.

were transferred to a Silicon graphic station calculating molecular modeling (Pro-software Insight II version 97) by the semi-empirical PM3 method (GEOMOS program). The wave function attached to each structure allows us to calculate most of its molecular and atomic characteristics such as:

- Electronic characteristics: net charge (positive or negative) on each atom or atomic groups, identification of charged poles, dipolar moment.
- Geometrical characteristics: interatomic distances, interfunctional group distances and distances between charged poles; torsion angles, dihedral angles, etc.
- Energetic characteristics: heat of formation, global energy...

Then, we undertook a systematic comparison of the molecules belonging to the same chemical class. We also identified their common molecular characteristics(electronic, geometrical and energetic), and defined the hypolipidemic pharmacophores of each family, which were correlated with its action mechanism.

More over, a superposition based on the similarity of some of the parameters obtained, was achieved between the optimized geometry of GA derivatives and that of each hypolipidemic series introduced into therapeutics, in order to seek common architectural fragments. The superposition of two structures rests on a minimum of 5 structurally determinant points and the superposition is validated statistically by their Root Mean Square values (RMS).

III- RESULTS

After this model, was achieved different hypolipidemic pharmacophoric moieties representing the characteristic of each hypolipidemic drug series were identified (Table I).

Furthermore, an electronic and geometrical similarity was observed between the structural characteristics of GA derivatives and those of the fibrates : in the optimized geometrical structure of GA derivatives (especially 11-cetonic compounds), there is a domain (A, B and C poles) mainly corresponding to the pharmacophore of fibrates (Tables II & III).

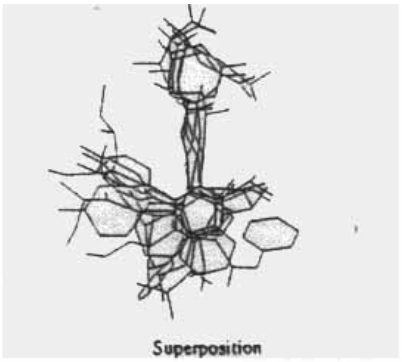
Three negatively charged moieties (C3-OH; C9; O /11 C=O) were identified and their interatomic distances (4 data on average) which are very similar to those of the fibrates were measured (Table IV). The statistical values of RMS validate their superposition (Table V).

Besides, a degree of geometrical structure similarity was observed between the beta configuration of GA derivatives and that of the beta sitosterol.

IV- CONCLUSION

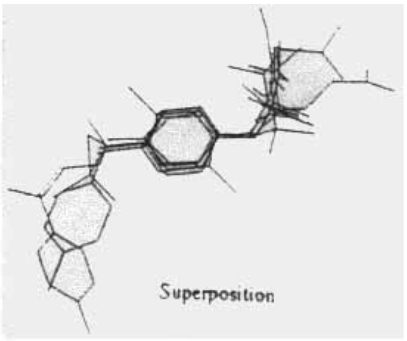
These results induce us to put forward a hypothesis for the hypolipidemic mechanism of GA derivatives, which may inhibit ACoA-Carboxylase enzyme activity like the fibrates [5,6]. This hypolipidemic activity is characterized by lower rates of triglycerides, cholesterol and VLDL formation. This hypothesis is keeping with pharmacological results for these

Table I. Pharmacophoric Characteristics of Different Hypolipidemic Molecules Series



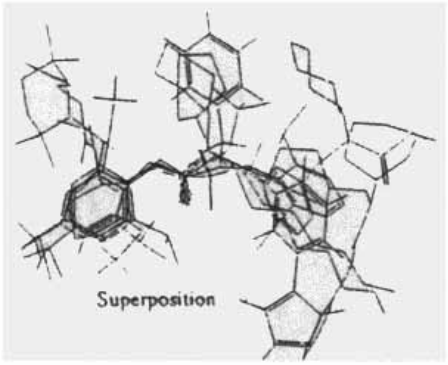
I a : Statin model

(Series I, 7 molecules: HMG Co-A reductase inhibitors)



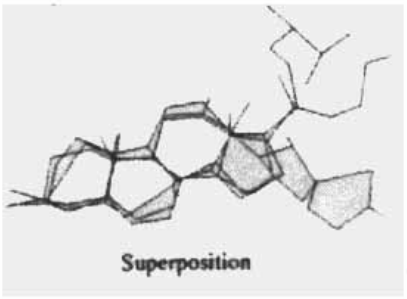
I b : Fibrate model

(Series II, 7 molecules: Acetyl Co-A carboxylase inhibitors)



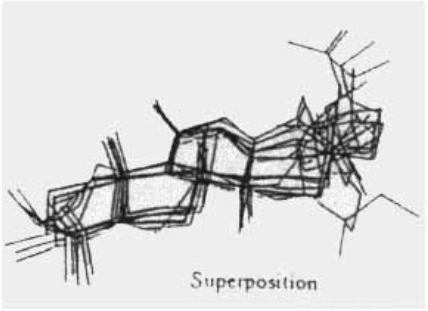
I c : ACAT inhibitors model

(Series III, 7 molecules: Acyl-CoA : cholesterol O-acyltransferase inhibitors)



I d : β-sitosterol analog model

(Series IV, 3 molecules: Cholesterol absorption inhibitors)



I e : GA derivative model

(Series V, 8 molecules: Unknown mechanism of action)

Table II. Superposition of Energy Minimized Fibrate Structures upon Energy Minimized GA Derivatives

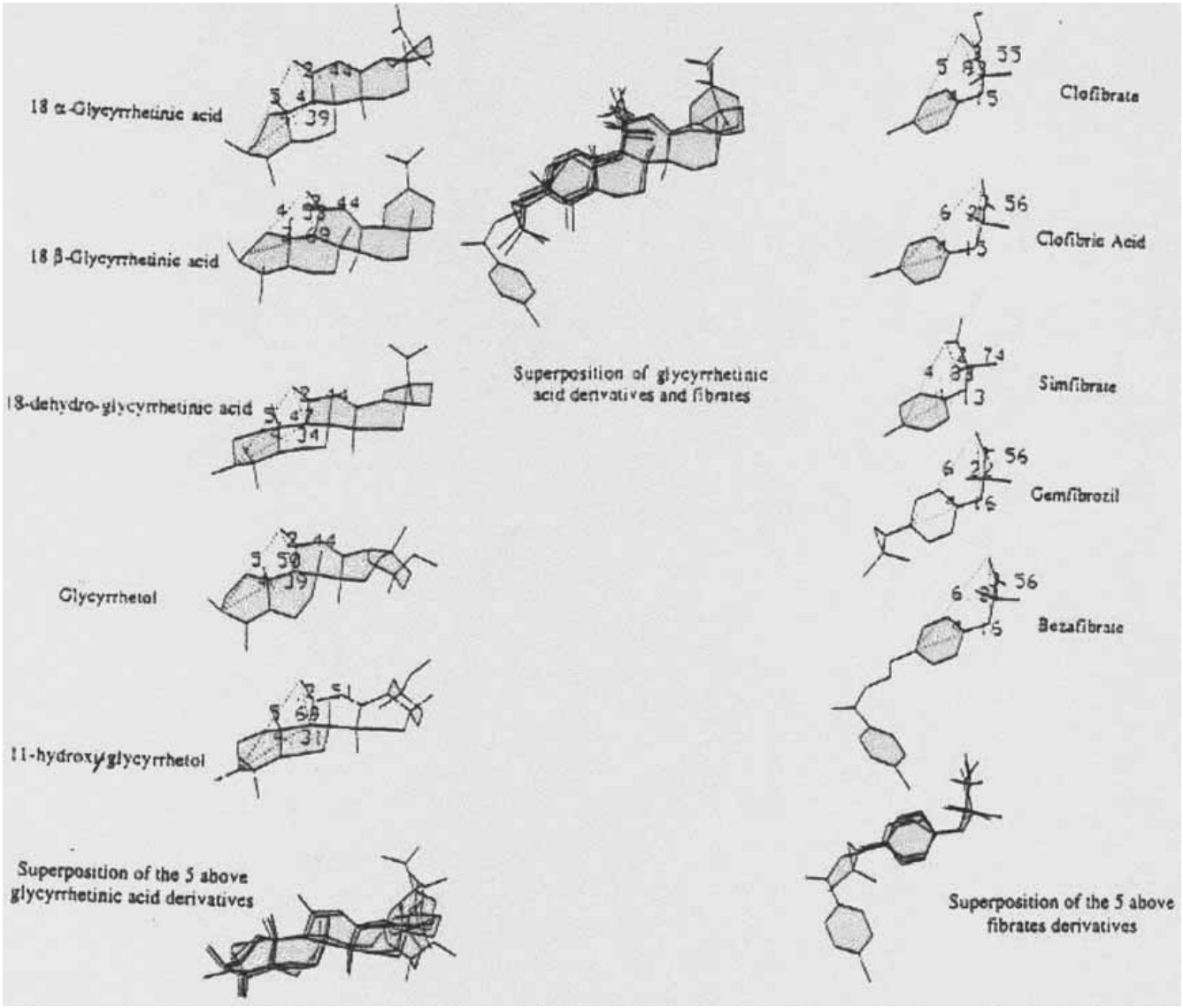
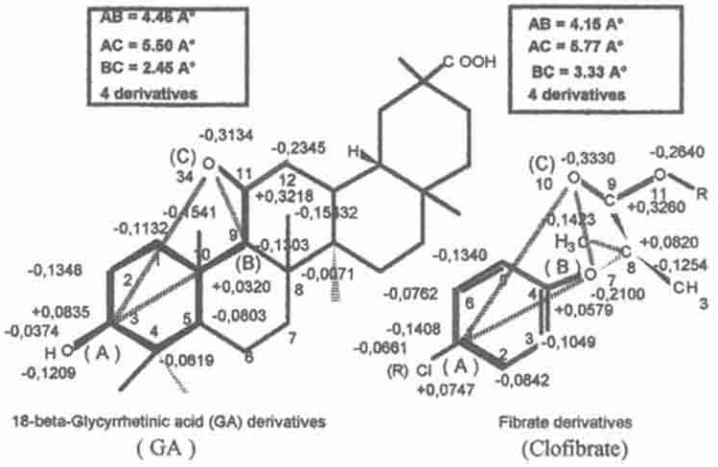


Table III. Comparison of Geometric Characteristics and Net Charge Distribution of Glycyrrhetinic Acid Derivatives with those of Fibrates



(Table III). contd.....

III a: Net charge distribution in glycyrrhetinic acid (GA) derivatives

Charge poles	Atomic charges	18β-GA	18α-GA	18-DHGA	GT	11-OH GT	11-DO GT	Δ 9,12-GT	Δ 11,13-GT
	1.C_3	+0.0835	+0.0834	+0.0794	+0.0851	+0.0828	+0.0809	+0.0739	+0.0861
	2.OH	-0.1209	-0.1260	-0.1121	-0.1225	-0.1223	-0.1219	-0.1226	-0.1134
(A)	**1**+**2**./C_3+OH	-0.0374	-0.0372	-0.0427	-0.0274	-0.0395	-0.0410	-0.0487	-0.0273
	3.C_{10}	+0.0032	+0.0028	+0.0028	-0.0082	-0.0001	-0.0207	+0.0209	-0.0128
	4.C_1	-0.1132	-0.1129	-0.1120	-0.1109	-0.1048	-0.1048	-0.1171	-0.1184
(B)	**5**.C_9	-0.1303	-0.1296	-0.1258	-0.1447	-0.1259	-0.1259	-0.0926	-0.0596
	6.C_{11}	+0.3213	+0.3296	+0.3237	+0.3326	+0.1309	+0.1309	-0.1293	-0.1314
(C)	**7**.O_{34}	-0.3134	-0.3134	-0.3144	-0.3174	-0.1224	-0.1224	---	---
	8.C_{12}	-0.2345	-0.1566	-0.2321	-0.2494	-0.2207	-0.2207	-0.1458	-0.1152

(**GT**: glycyrrhetol; **Δ-9, 12-GT**: 18β-olean-9 (11),12-diene-3β, 30-diol ; **Δ−11, 13-GT** : 18β-olean-11, 13 (18)-diene-3β, 30-diol)

III b : Net charge distribution in fibrates

Charged moieties	Charged atom or groups (net charge)	Clofibric acid	Clofibrate	Simfibrate	Fenofibrate	Bezafibrate
	1. C_1	-0.1408	-0.1307	-0.1818	-0.1631	-0.0944
	2. Cl_{14} /C-R	+0.0747 (Cl)	+0.0694 (Cl)	+0.0667 (Cl)	+0.0767 (CO-R)	+0.0401 (CH_2-R)
(A)	**1**+**2**. C_1+CI_{14}	-0.0661	-0.0613	-0.1158	-0.0867	-0.0543
	3. C_4	+0.0579	+0.0472	+0.0897	+0.0763	+0.0594
	4.C_5	-0.1340	-0.1048	-0.1832	-0.1261	-0.1423
(B)	**5**.O_7	-0.2100	-0.1916	-0.1813	-0.2001	-0.2104
	6.C_9	+0.3260	+0.3436	+0.2526	+0.3726	+0.3265
(C)	**7**.O_{10}	-0.3330	-0.3736	-0.3025	-0.3759	-0.3332

Table IV. Characteristics of Charged Poles and Distances Between the Charged Poles of GA Derivatives and those of Fibrates

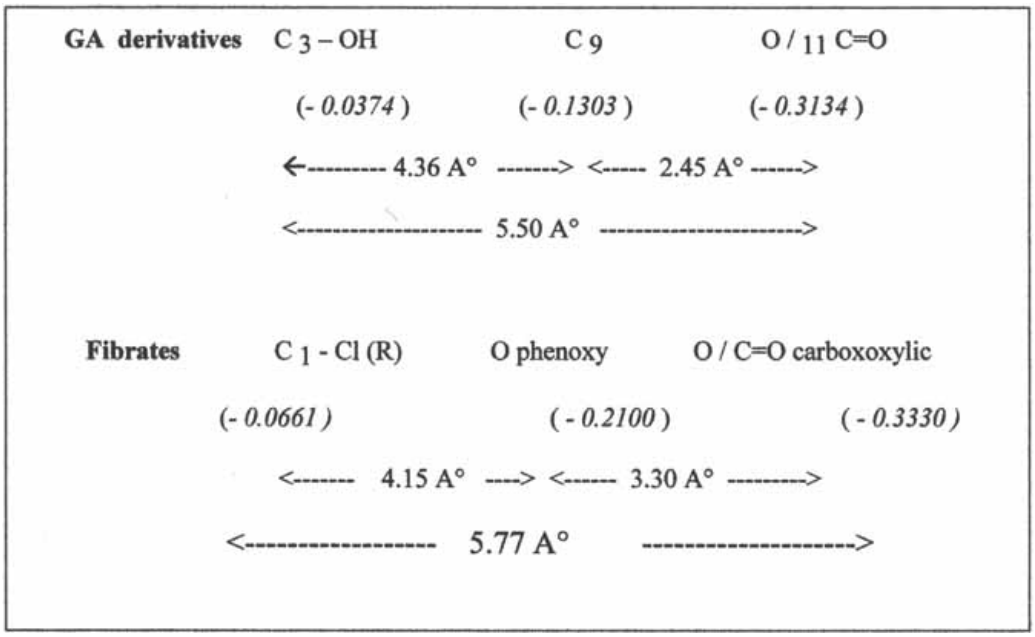
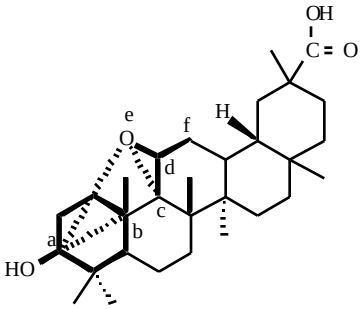
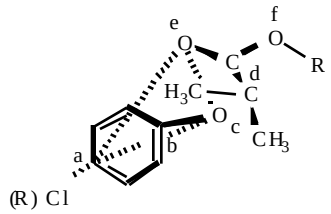


Table V. Root Mean Square / Superposition of Fibrates upon 18 β-Glycyrrhetinic Acid



18 β-GA



Clofibrate derivatives

Molecules	a c e 3 points	a b c e 4 points	a b c d e 5 points	a b c d e f 6 points
18β-GA	0.0000	0.0000	0.0000	0.0000
Clofibric acid	0.3178	0.5430	0.5730	0.0971
Clofibrate	0.3638	0.4987	0.5493	0.9551
Simfibrate	0.3744	0.5042	0.5883	0.1261
Bezafibrate	0.3142	0.5883	0.5696	0.9307
Ciprofibrate	0.3163	0.5414	0.5718	0.9357

derivatives: GA and 18-dehydroGA exhibiting a decrease of 71.3 % in triglycerides and 50.6% in total cholesterol of atherosclerotic and hypercholesterolemic rabbits [2]. These results are similar to the behavior of fibrates [5].

Furthermore, all GA beta configuration derivatives present a geometry equally superposable on that of the beta sitosterol. Consequently, a second action mechanism can be suggested for GA derivatives, that is to say a hypolipidemic activity fixing the cholesterol absorption site on the intestine, as it is the case for the β-sitosterol [3].

This method may also prove valuable both for the recognition of pharmacophoric moieties and for further study of the action mechanism of some natural molecules, especially drugs derived from medicinal plants.

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