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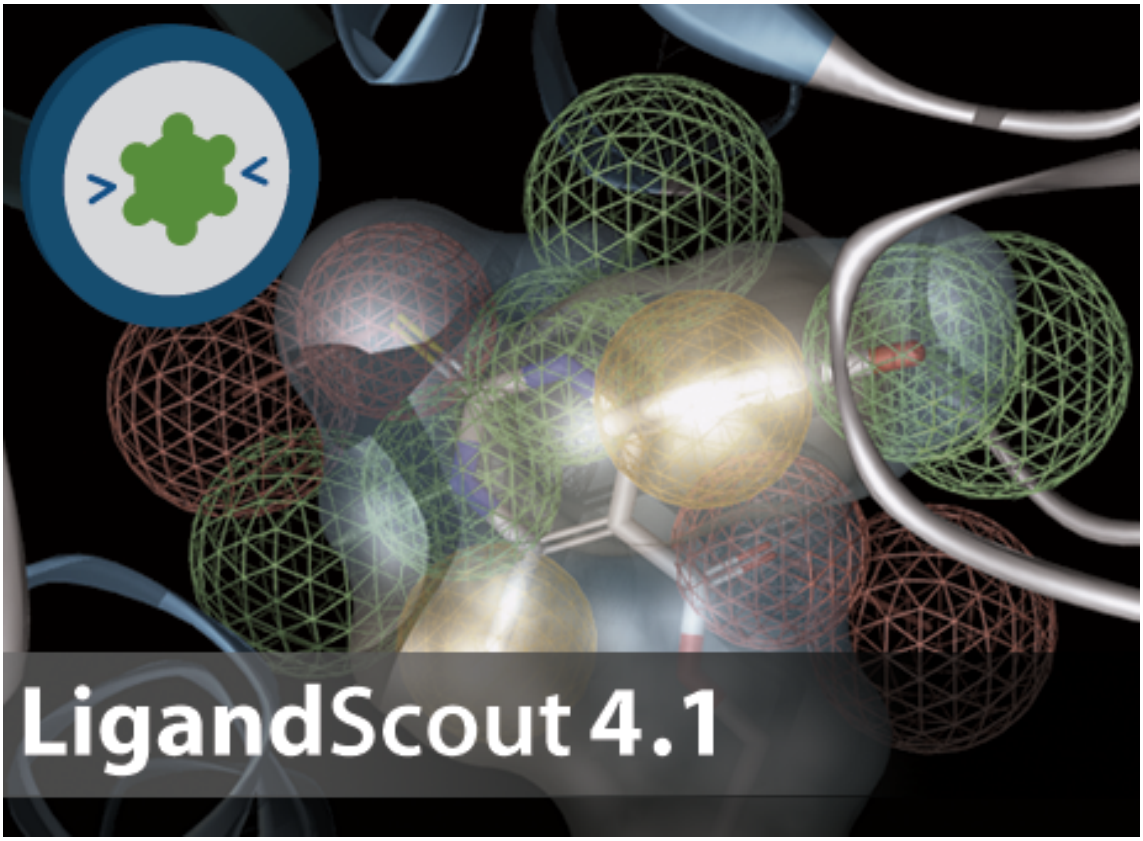
# LigandScout Research Articles

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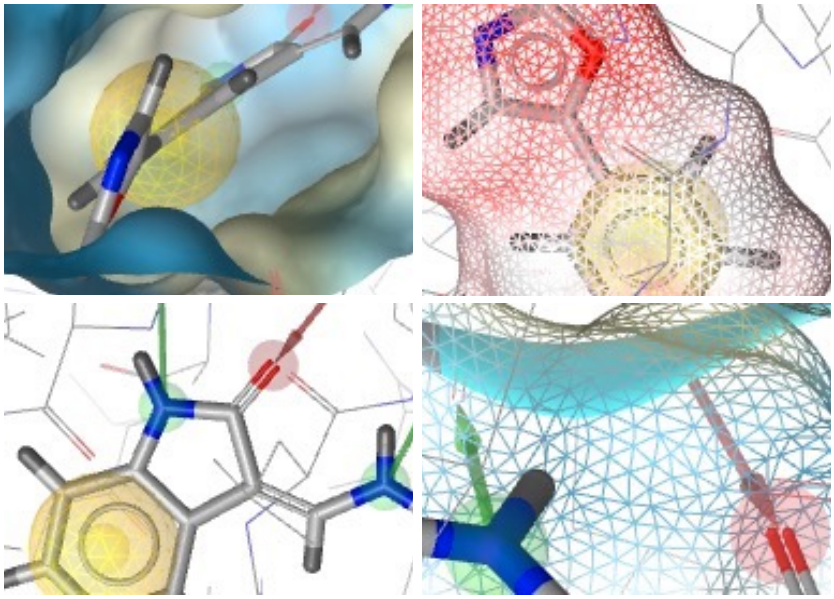
*- Alexander Varnek*



This booklet gives an overview on key publications in the area of computer aided molecular design, in which LigandScout was used for identifying and optimizing new bio-active compounds.

In more than 1000 scientific publications, researchers have reported their excellent results obtained using the LigandScout software. These outstanding scientists represent different fields of life science research, including pharmaceuticals, cosmetics, agrochemicals, and nutraceuticals areas, using LigandScout's advanced molecular design technology for efficiently discovering new bioactive molecules.

This selection only covers a small fraction of all the articles published in peer reviewed journals citing LigandScout. It covers topics ranging from performance assessment studies to hit identification in different target areas, as well as fragment-based design for lead structure generation and optimization.

# Highly Specific and Sensitive Pharmacophore Model for Identifying CXCR4 Antagonists. Comparison with Docking and Shape-Matching Virtual Screening Performance

Arnaud S. Karaboga†, Jesús M. Planesas‡, Florent Petronin†, Jordi Teixidó‡, Michel Souchet*†, and Violeta I. Pérez-Nueno*†‡

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**DOI:** 10.1021/ci400037y

Publication Date (Web): April 11, 2013



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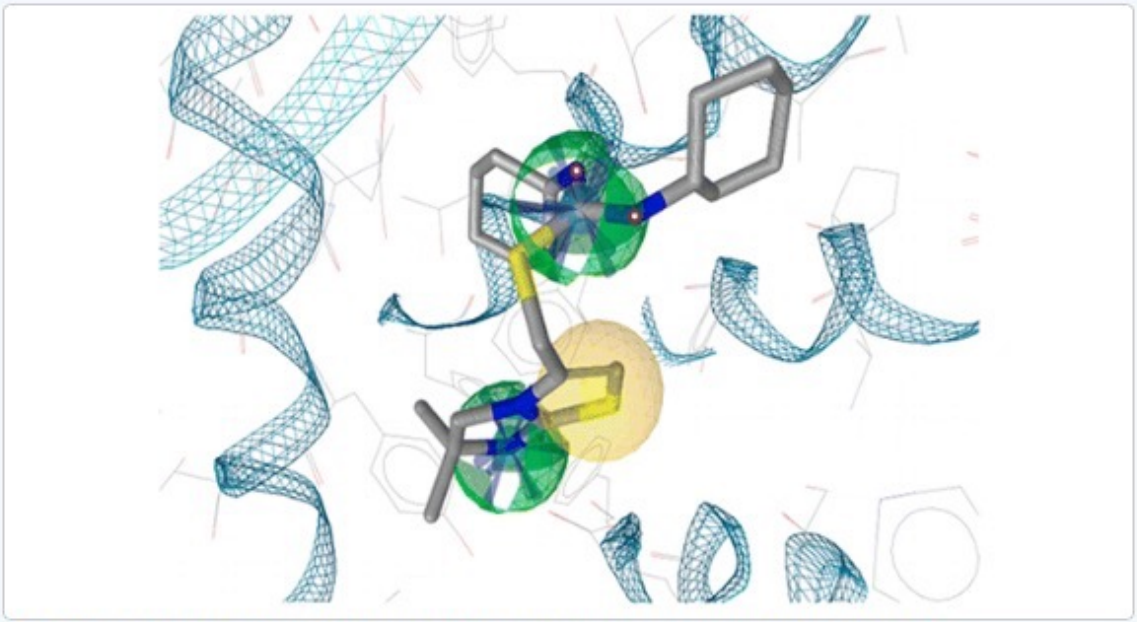
## Abstract



HIV infection is initiated by fusion of the virus with the target cell through binding of the viral gp120 protein with the CD4 cell surface receptor protein and the CXCR4 or CCR5 coreceptors. There is currently considerable interest in developing novel ligands that can modulate the conformations of these coreceptors and, hence, ultimately block virus–cell fusion. Herein, we present a highly specific and sensitive pharmacophore model for identifying CXCR4 antagonists that could potentially serve as HIV entry inhibitors. Its performance was compared with docking and shape-matching virtual screening approaches using 3OE6 CXCR4 crystal structure and high-affinity ligands as query molecules, respectively. The performance of these methods was compared by virtually screening a library assembled by us, consisting of 228 high affinity known CXCR4 inhibitors from 20 different chemotype families and 4696 similar presumed inactive molecules. The area under the ROC plot (AUC), enrichment factors, and diversity of the resulting virtual hit lists was analyzed. Results show that our pharmacophore model achieves the highest VS performance among all the docking and shape-based scoring functions used. Its high selectivity and sensitivity makes our pharmacophore a very good filter for identifying CXCR4 antagonists.

http://dx.doi.org/10.1021/ci400037y

**Article**
Journal of Computer-Aided Molecular Design
April 2014, Volume 28, Issue 4, pp 363-373

First online: 21 January 2014

# Combining in silico and in cerebro approaches for virtual screening and pose prediction in SAMPL4

Arnout R. D. Voet, Ashutosh Kumar, Francois Berenger, Kam Y. J. Zhang

10.1007/s10822-013-9702-2

## Abstract

The SAMPL challenges provide an ideal opportunity for unbiased evaluation and comparison of different approaches used in computational drug design. During the fourth round of this SAMPL challenge, we participated in the virtual screening and binding pose prediction on inhibitors targeting the HIV-1 integrase enzyme. For virtual screening, we used well known and widely used in silico methods combined with personal in cerebro insights and experience. Regular docking only performed slightly better than random selection, but the performance was significantly improved upon incorporation of additional filters based on pharmacophore queries and electrostatic similarities. The best performance was achieved when logical selection was added. For the pose prediction, we utilized a similar consensus approach that amalgamated the results of the Glide-XP docking with structural knowledge and rescoring. The pose prediction results revealed that docking displayed reasonable performance in predicting the binding poses. However, prediction performance can be improved utilizing scientific experience and rescoring approaches. In both the virtual screening and pose prediction challenges, the top performance was achieved by our approaches. Here we describe the methods and strategies used in our approaches and discuss the rationale of their performances.

### Keywords

Virtual screening – Molecular docking – Pose prediction – Pharmacophore modeling – Electrostatic similarity – EleKit – Computer aided drug design

http://dx.doi.org/10.1007/s10822-013-9702-2

Therapeutic Discovery

Molecular Cancer Therapeutics

# New Use for an Old Drug: Inhibiting ABCG2 with Sorafenib

Yinxiang Wei[1,3], Yuanfang Ma[3], Qing Zhao[1,4], Zhiguang Ren[1,3], Yan Li[1], Tingjun Hou[2], and Hui Peng[1]

## Abstract

Human ABCG2, a member of the ATP-binding cassette transporter superfamily, represents a promising target for sensitizing MDR in cancer chemotherapy. Although lots of ABCG2 inhibitors were identified, none of them has been tested clinically, maybe because of several problems such as toxicity or safety and pharmacokinetic uncertainty of compounds with novel chemical structures. One efficient solution is to rediscover new uses for existing drugs with known pharmacokinetics and safety profiles. Here, we found the new use for sorafenib, which has a dual-mode action by inducing ABCG2 degradation in lysosome in addition to inhibiting its function. Previously, we reported some novel dual-acting ABCG2 inhibitors that showed closer similarity to degradation-induced mechanism of action. On the basis of these ABCG2 inhibitors with diverse chemical structures, we developed a pharmacophore model for identifying the critical pharmacophore features necessary for dual-acting ABCG2 inhibitors. Sorafenib forms impressive alignment with the pharmacophore hypothesis, supporting the argument that sorafenib is a potential ABCG2 inhibitor. This is the first article that sorafenib may be a good candidate for chemosensitizing agent targeting ABCG2-mediated MDR. This study may facilitate the rediscovery of new functions of structurally diverse old drugs and provide a more effective and safe way of sensitizing MDR in cancer chemotherapy. *Mol Cancer Ther; 11(8); 1693–702. ©2012 AACR.*

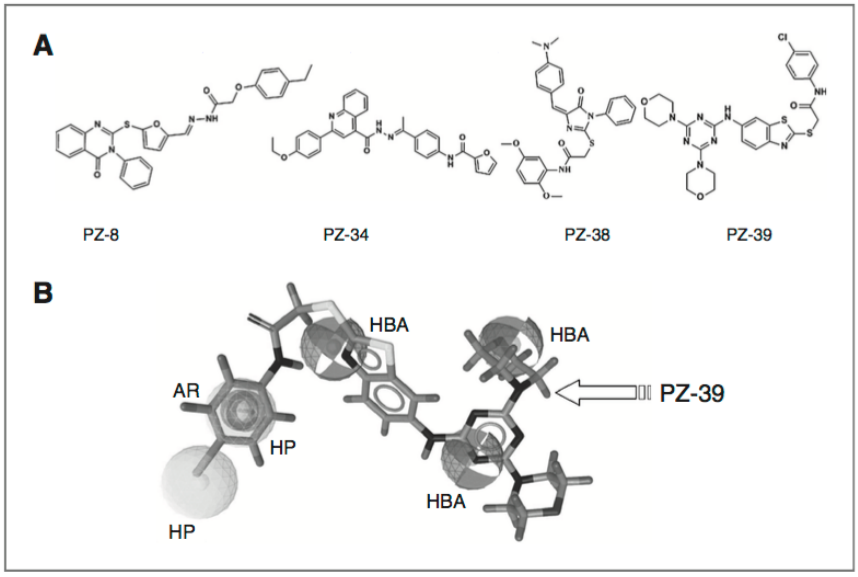



Figure 6. Chemical structures of dual-acting ABCG2 inhibitors and alignment of most active compound with the pharmacophore hypothesis. A, chemical structures of PZ-8, PZ-34, PZ-38, and PZ-39. B, the alignment of PZ-39 with the pharmacophore hypothesis. HBA, hydrogen bond acceptor; HP, hydrophobic center; AR, aromatic ring.





http://dx.doi.org/10.1158/1535-7163.MCT-12-0215

# Discovery of Potent Soluble Epoxide Hydrolase (sEH) Inhibitors by Pharmacophore-Based Virtual Screening

Birgit Waltenberger, Ulrike Garscha, Veronika Temml, Josephine Liers, Oliver Werz, Daniela Schuster, and Hermann Stuppner

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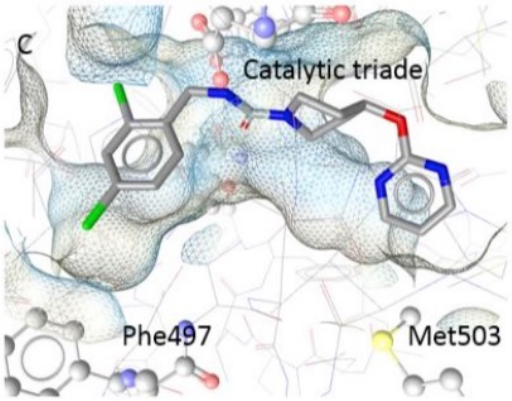
Publication Date (Web): February 16, 2016


## Abstract

There is an increasing interest in the development of soluble epoxide hydrolase (sEH) inhibitors, which block the degradation of endogenous anti-inflammatory epoxyeicosatrienoic acids. Within this study, a set of pharmacophore models for sEH inhibitors was developed. The Specs database was virtually screened and a cell-free sEH activity assay was used for the biological investigation of virtual hits. In total, out of 48 tested compounds, 19 were sEH inhibitors with IC50 < 10 $\mu$M, representing a prospective true positive hit rate of 40%. Six of these compounds displayed IC50 values in the low nanomolar range. The most potent compound 21, a urea derivative, inhibited sEH with an IC50 = 4.2 nM. The applied approach also enabled the identification of diverse chemical scaffolds, e.g. the pyrimidinone derivative 29 (IC50 = 277 nM). The generated pharmacophore model set therefore represents a valuable tool for the selection of compounds for biological testing.




http://dx.doi.org/10.1021/acs.jcim.5b00592

# Design, Virtual Screening, and Synthesis of Antagonists of $\alpha_{IIb}\beta_3$ as Antiplatelet Agents

Pavel G. Polishchuk[†], Georgiy V. Samoylenko[†], Tetiana M. Khristova[†‡], Olga L. Krysko[†], Tatyana A. Kabanova[†], Vladimir M. Kabanov[†], Alexander Yu. Kornylov[†], Olga Klimchuk[‡], Thierry Langer[§], Sergei A. Andronati[†], Victor E. Kuz'min[†], Andrei A. Krysko*[†], and Alexandre Varnek*[‡]

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Publication Date (Web): September 14, 2015


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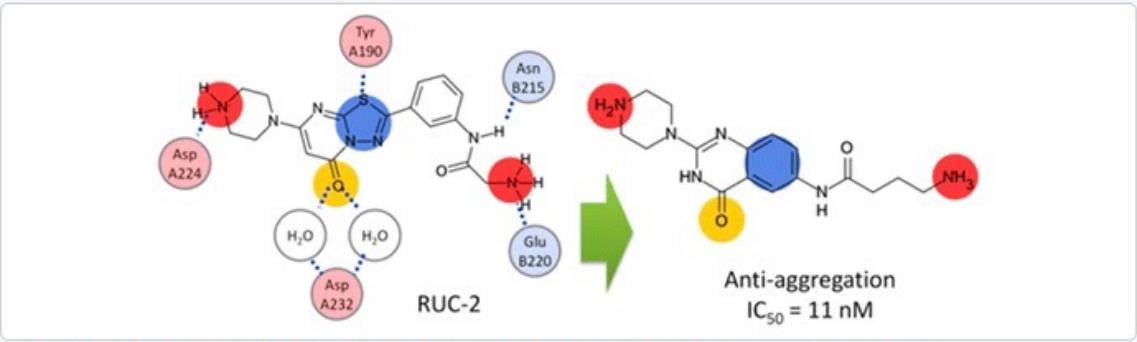
## Abstract




This article describes design, virtual screening, synthesis, and biological tests of novel $\alpha_{IIb}\beta_3$ antagonists, which inhibit platelet aggregation. Two types of $\alpha_{IIb}\beta_3$ antagonists were developed: those binding either closed or open form of the protein. At the first step, available experimental data were used to build QSAR models and ligand- and structure-based pharmacophore models and to select the most appropriate tool for ligand-to-protein docking. Virtual screening of publicly available databases (BioinfoDB, ZINC, Enamine data sets) with developed models resulted in no hits. Therefore, small focused libraries for two types of ligands were prepared on the basis of pharmacophore models. Their screening resulted in four potential ligands for open form of $\alpha_{IIb}\beta_3$ and four ligands for its closed form followed by their synthesis and *in vitro* tests. Experimental measurements of affinity for $\alpha_{IIb}\beta_3$ and ability to inhibit ADP-induced platelet aggregation ($IC_{50}$) showed that two designed ligands for the open form **4c** and **4d** ($IC_{50}$ = 6.2 nM and 25 nM, respectively) and one for the closed form **12b** ($IC_{50}$ = 11 nM) were more potent than commercial antithrombotic Tirofiban ($IC_{50}$ = 32 nM).

http://dx.doi.org/10.1021/acs.jmedchem.5b00865

# Comparative Analysis of Pharmacophore Screening Tools

Marijn P. A. Sanders†, Arménio J. M. Barbosa‡, Barbara Zarzycka§, Gerry A.F. Nicolaes§, Jan P.G. Klompı, Jacob de Vlieg†⊥, and Alberto Del Rio*‡

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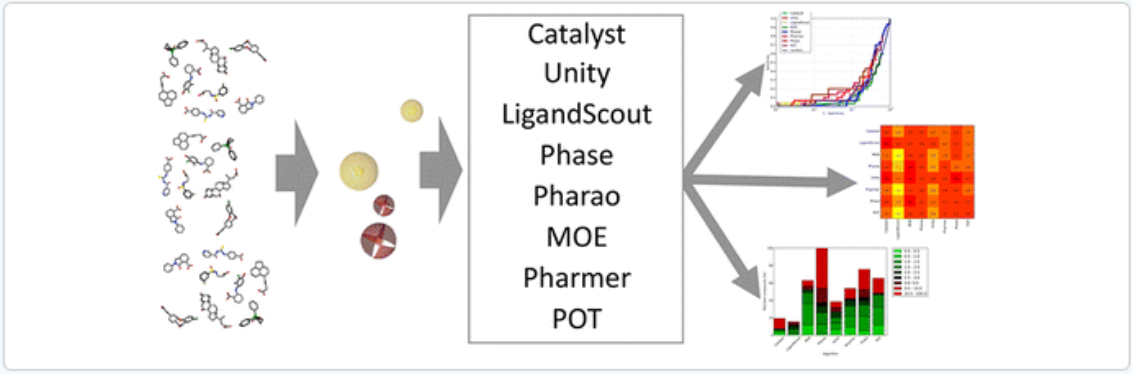
## Abstract




The pharmacophore concept is of central importance in computer-aided drug design (CADD) mainly because of its successful application in medicinal chemistry and, in particular, high-throughput virtual screening (HTVS). The simplicity of the pharmacophore definition enables the complexity of molecular interactions between ligand and receptor to be reduced to a handful set of features. With many pharmacophore screening softwares available, it is of the utmost interest to explore the behavior of these tools when applied to different biological systems. In this work, we present a comparative analysis of eight pharmacophore screening algorithms (Catalyst, Unity, LigandScout, Phase, Pharao, MOE, Pharmer, and POT) for their use in typical HTVS campaigns against four different biological targets by using default settings. The results herein presented show how the performance of each pharmacophore screening tool might be specifically related to factors such as the characteristics of the binding pocket, the use of specific pharmacophore features, and the use of these techniques in specific steps/contexts of the drug discovery pipeline. Algorithms with rmsd-based scoring functions are able to predict more compound poses correctly as overlay-based scoring functions. However, the ratio of correctly predicted compound poses versus incorrectly predicted poses is better for overlay-based scoring functions that also ensure better performances in compound library enrichments. While the ensemble of these observations can be used to choose the most appropriate class of algorithm for specific virtual screening projects, we remarked that pharmacophore algorithms are often equally good, and in this respect, we also analyzed how pharmacophore algorithms can be combined together in order to increase the success of hit compound identification. This study provides a valuable benchmark set for further developments in the field of pharmacophore search algorithms, e.g., by using pose predictions and compound library enrichment criteria.

Biochemical and Biophysical Research Communications

Volume 470, Issue 3, 12 February 2016, Pages 685–689

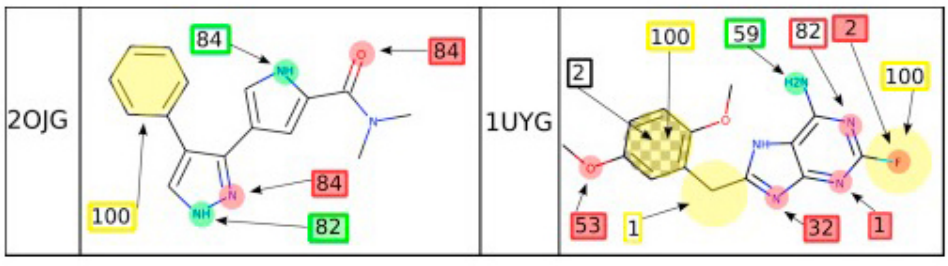
# Evaluating the stability of pharmacophore features using molecular dynamics simulations

Marcus Wieder[a, b], Ugo Perricone[c], Stefan Boresch[b], Thomas Seidel[a], Thierry Langer[a]

## Abstract

Molecular dynamics simulations of twelve protein—ligand systems were used to derive a single, structure based pharmacophore model for each system. These *merged* models combine the information from the initial experimental structure and from all snapshots saved during the simulation. We compared the merged pharmacophore models with the corresponding *PDB* pharmacophore models, i.e., the static models generated from an experimental structure in the usual manner. The frequency of individual features, of feature types and the occurrence of features not present in the static model derived from the experimental structure were analyzed. We observed both pharmacophore features not visible in the traditional approach, as well as features which disappeared rapidly during the molecular dynamics simulations and which may well be artifacts of the initial PDB structure-derived pharmacophore model. Our approach helps mitigate the sensitivity of structure based pharmacophore models to the single set of coordinates present in the experimental structure. Further, the frequency with which specific features occur during the MD simulation may aid in ranking the importance of individual features.

## Graphical abstract




## Keywords

Pharmacophore modeling; Structure-based pharmacophore modeling; Molecular dynamics; Protein flexibility

http://dx.doi.org/10.1016/j.bbrc.2016.01.081

# Structure-Based Pharmacophore Identification of New Chemical Scaffolds as Non-Nucleoside Reverse Transcriptase Inhibitors

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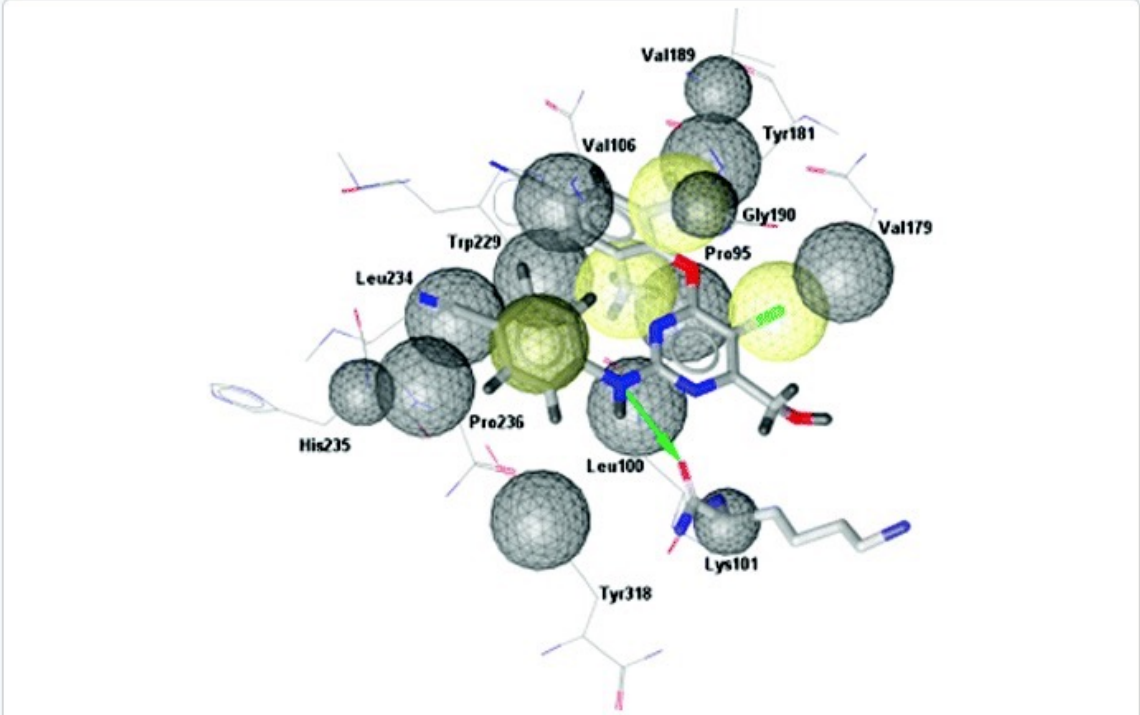
Dipartimento Farmaco-Chimico, Università di Messina, Viale Annunziata, 98168 Messina, Italy, and Istituto di Genetica Molecolare IGM-CNR, via Abbiategrasso 207, 27100 Pavia, Italy

*J. Chem. Inf. Model.*, **2007**, *47* (2), pp 557–562
**DOI:** 10.1021/ci600320q
Publication Date (Web): February 3, 2007


## Abstract




A structure-based molecular modeling approach was performed to identify novel structural characteristics and scaffolds that might represent new classes of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). The software LigandScout was used for identification and visualization of protein–ligand interaction sites and pharmacophore model generation. In the next step virtual screening of 3D multiconformational databases together with docking experiments allowed the identification of promising candidates for biological testing. The positive biological results obtained confirm the validity of our work strategy.

http://dx.doi.org/10.1021/ci600320q

Bioorganic & Medicinal Chemistry Letters

Available online 20 February 2016

In Press, Accepted Manuscript — Note to users

# *In silico* exploration for agonists/antagonists of brassinolide

Seisuke Takimoto[a, 1], Airi Sugiura[a, 1], Saki Minami[a], Tomohiko Tasaka[b], Yoshiaki Nakagawa[a], Hisashi Miyagawa[a]

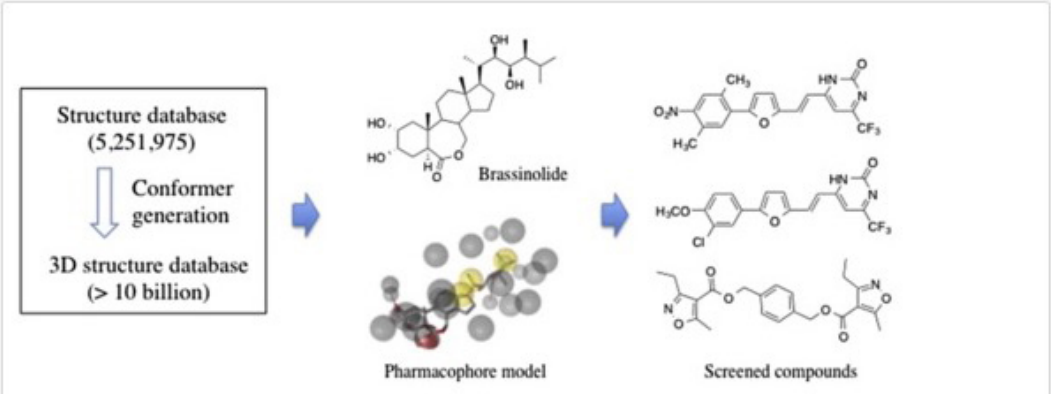
doi:10.1016/j.bmcl.2016.02.054



## Abstract

Brassinolide (BL) is a plant steroid hormone that is necessary for stem elongation and cell division. To date more than 70 steroidal BL-like compounds, which are collectively named as brassinosteroids, have been identified. However, non-steroidal compounds that mimic BL have not been reported yet, which can be used as plant growth regulators. Twenty-two non-steroidal compounds were screened from the database containing about 5 million compound structures using a pharmacophore-based *in silico* screening method. The crystal structure (PDB: 4LSX) of the BL receptor was used to generate a pharmacophore model required for *in silico* screening. Among 22 hit compounds, 15 compounds that are thought to be physicochemically acceptable were submitted to the *in vivo* rice lamina inclination assay. Although no compound showed BL like activity, three compounds were detected as BL antagonist. The most potent compound was an ester derivative of 1,4-diphenlenedimethanol and isoxazole-4-carboxylic acid, and the other two compounds contain 2-phenylfuran and pyrimidin-2(1*H*)-one moieties bridged by an ethenyl substructure. The 50% effective doses ($ED_{50}$) for the antagonistic activity were in a range of 0.6 – 5 nmole per plant. The inhibition of the lamina inclination by the most potent agonist was recovered by the co-application of BL in a dose-dependent manner.

## Graphical abstract




http://dx.doi.org/10.1016/j.bmcl.2016.02.054

# *In Silico* Prediction of Human Sulfotransferase 1E1 Activity Guided by Pharmacophores from Molecular Dynamics Simulations*

**Christin Rakers[‡], Fabian Schumacher[§,¶], Walter Meinl[‖,**], Hansruedi Glatt[**], Burkhard Kleuser[§] and Gerhard Wolber[‡1]**

[+] Author Affiliations

[1] To whom the correspondence should be addressed. E-mail: gerhard.wolber@fu-berlin.de.

## Abstract

Acting during phase II metabolism, sulfotransferases (SULTs) serve detoxification by transforming a broad spectrum of compounds from pharmaceutical, nutritional, or environmental sources into more easily excretable metabolites. However, SULT activity has also been shown to promote formation of reactive metabolites that may have genotoxic effects. SULT subtype 1E1 (SULT1E1) was identified as a key player in estrogen homeostasis, which is involved in many physiological processes and the pathogenesis of breast and endometrial cancer. The development of an *in silico* prediction model for SULT1E1 ligands would therefore support the development of metabolically inert drugs and help to assess health risks related to hormonal imbalances. Here, we report on a novel approach to develop a model that enables prediction of substrates and inhibitors of SULT1E1. Molecular dynamics simulations were performed to investigate enzyme flexibility and sample protein conformations. Pharmacophores were developed that served as a cornerstone of the model, and machine learning techniques were applied for prediction refinement. The prediction model was used to screen the DrugBank (a database of experimental and approved drugs): 28% of the predicted hits were reported in literature as ligands of SULT1E1. From the remaining hits, a selection of nine molecules was subjected to biochemical assay validation and experimental results were in accordance with the *in silico* prediction of SULT1E1 inhibitors and substrates, thus affirming our prediction hypotheses.

drug design | drug metabolism | liver metabolism | molecular dynamics | molecular modeling | sulfotransferase

http://dx.doi.org/10.1074/jbc.M115.685610

# Potent Human Telomerase Inhibitors: Molecular Dynamic Simulations, Multiple Pharmacophore-Based Virtual Screening, and Biochemical Assays

Faezeh Shirgahi Talari[†§], Kowsar Bagherzadeh[‡], Sahand Golestanian[†], Michael Jarstfer[*§], and Massoud Amanlou[*†]

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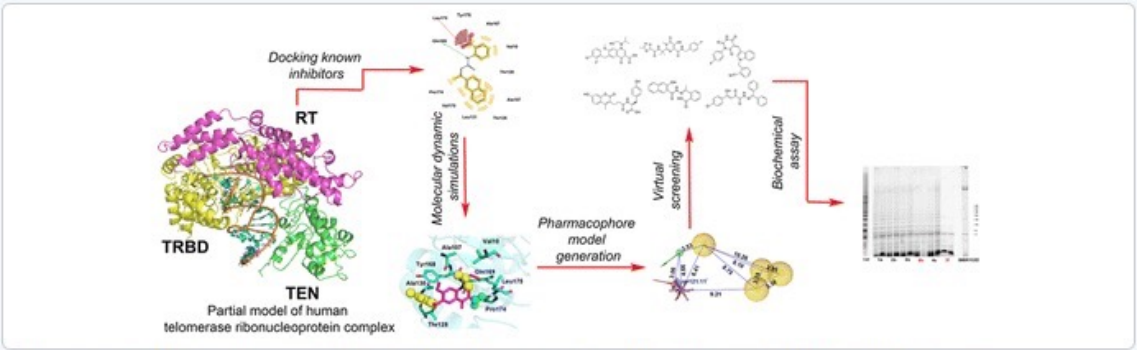
**DOI:** 10.1021/acs.jcim.5b00336
Publication Date (Web): November 3, 2015


*E-mail: amanlou@tums.ac.ir (M.A.)., *E-mail: jarstfer@email.unc.edu (M.J.).

## Abstract




Telomere maintenance is a universal cancer hallmark, and small molecules that disrupt telomere maintenance generally have anticancer properties. Since the vast majority of cancer cells utilize telomerase activity for telomere maintenance, the enzyme has been considered as an anticancer drug target. Recently, rational design of telomerase inhibitors was made possible by the determination of high resolution structures of the catalytic telomerase subunit from a beetle and subsequent molecular modeling of the human telomerase complex. A hybrid strategy including docking, pharmacophore-based virtual screening, and molecular dynamics simulations (MDS) were used to identify new human telomerase inhibitors. Docking methodology was applied to investigate the ssDNA telomeric sequence and two well-known human telomerase inhibitors' (BIBR1532 and MST-312) modes of interactions with hTERT TEN domain. Subsequently molecular dynamic simulations were performed to monitor and compare hTERT TEN domain, TEN –ssDNA, TEN–BIBR1532, TEN–MST-312, and TEN–ssDNA–BIBR1532 behavior in a dynamic environment. Pharmacophore models were generated considering the inhibitors manner in the TEN domain anchor site. These exploratory studies identified several new potent inhibitors whose $IC_{50}$ values were generated experimentally in a low micromolar range with the aid of biochemical assays, including both the direct telomerase and the telomeric repeat amplification protocol (TRAP) assays. The results suggest that the current models of human telomerase are useful templates for rational inhibitor design.

http://dx.doi.org/10.1021/acs.jcim.5b00336

Life Sciences

Volume 145, 15 January 2016, Pages 240–246

# Discovery of novel dual inhibitors against Mdm2 and Mdmx proteins by in silico approaches and binding assay

Sahand Golestanian[a, 1], Amirhossein Sharifi[a, 1], Grzegorz M. Popowicz[b], Homa Azizian[c], Alireza Foroumadi[a], Aleksandra Szwagierczak[b], Tad A. Holak[b], Massoud Amanlou[a]

doi:10.1016/j.lfs.2015.12.047

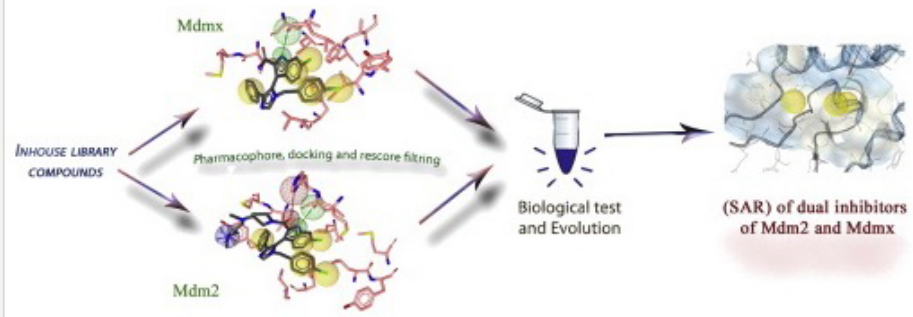


## Abstract

The p53 protein, also called guardian of the genome, has a key role in cell cycle regulation. It is activated under stressful circumstances, such as DNA damage which results in permanent arrest or cell death. The protein is disabled in several types of human cancer due to over-expression of the two regulators, Mdm2 and Mdmx. As a result, inhibiting Mdm subtypes could reactivate p53 and bring about a promising therapeutic strategy in cancers.

Here a structure-based pharmacophore search and docking simulation are presented in order to filter our in-house library which contains 1035 compounds to find novel scaffolds that inhibit Mdm2 and Mdmx concomitantly. Afterwards, fluorescence polarization binding assay was used to obtain inhibition constant of final compounds.

## Graphical abstract




http://dx.doi.org/10.1016/j.lfs.2015.12.047

Bioorganic & Medicinal Chemistry Letters

Volume 19, Issue 10, 15 May 2009, Pages 2668–2673

# Discovery of novel benzene 1,3-dicarboxylic acid inhibitors of bacterial MurD and MurE ligases by structure-based virtual screening approach

Andrej Perdih[a], Andreja Kovač[b], Gerhard Wolber[c, d], Didier Blanot[e], Stanislav Gobec[b], Tom Solmajer[a]

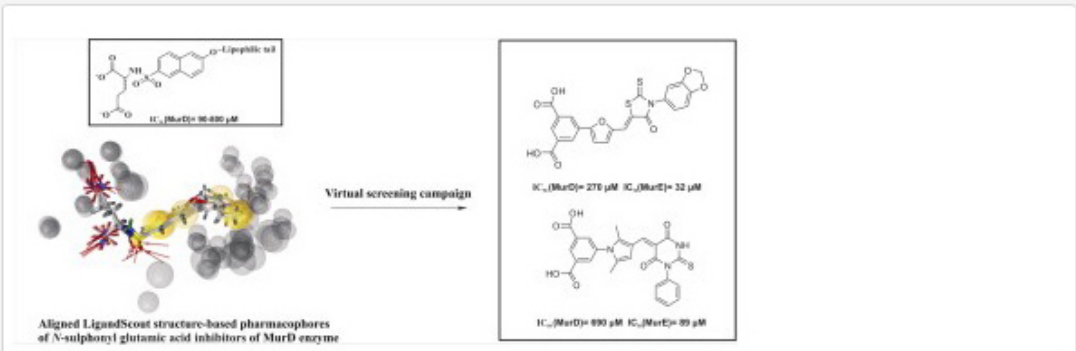
doi:10.1016/j.bmcl.2009.03.141



## Abstract

The peptidoglycan biosynthetic pathway provides an array of potential targets for antibacterial drug design, attractive especially with respect to selective toxicity. Within this pathway, the members of the Mur ligase family are considered as promising emerging targets for novel antibacterial drug design. Based on the available MurD crystal structures co-crystallised with *N*-sulfonyl glutamic acid inhibitors, a virtual screening campaign was performed, combining three-dimensional structure-based pharmacophores and molecular docking calculations. A novel class of glutamic acid surrogates—benzene 1,3-dicarboxylic acid derivatives—were identified and compounds **14** and **16** found to possess dual MurD and MurE inhibitory activity.

## Graphical abstract




http://dx.doi.org/10.1016/j.bmcl.2009.03.141

Research Article

# Fragment pharmacophore-based *in silico* screening: a powerful approach for efficient lead discovery

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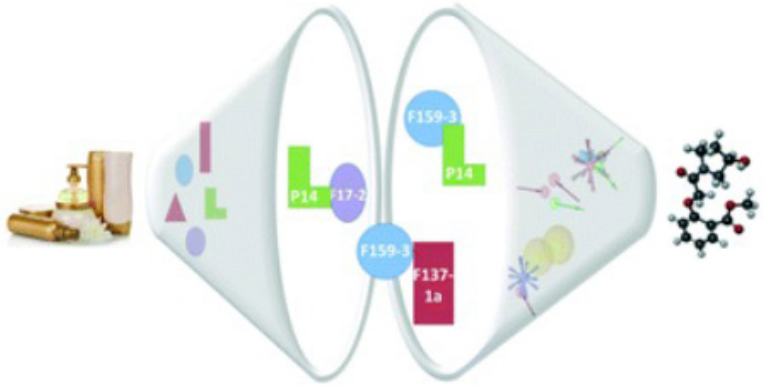
Through a process of fragmentation, functionalization, and recombination of market approved molecules for cosmetic usage, we customized an *in-house* virtual library comprising molecules ideally suited for virtual screening. Computational pharmacophore-based screening of this virtual library followed by a 3 month optimization phase led to the identification of an optimized lead with all its expected properties in hand to be developed as a candidate molecule for skin care in cosmetic applications. The success of this pilot project paves the way for other cosmetic targets of interest.




http://dx.doi.org/10.1039/c5md00444f

# Ligand-Based Pharmacophore Modeling and Virtual Screening for the Discovery of Novel 17β-Hydroxysteroid Dehydrogenase 2 Inhibitors

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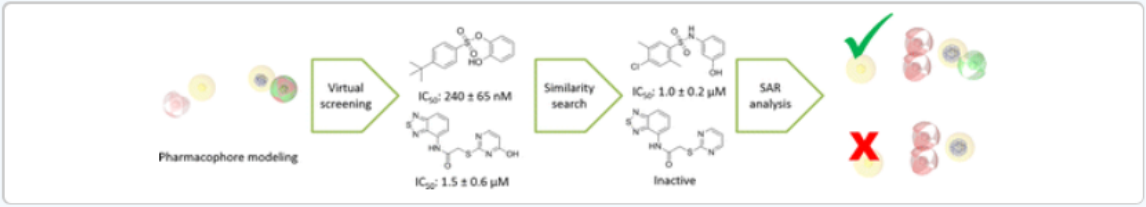
## Abstract




17β-Hydroxysteroid dehydrogenase 2 (17β-HSD2) catalyzes the inactivation of estradiol into estrone. This enzyme is expressed only in a few tissues, and therefore its inhibition is considered as a treatment option for osteoporosis to ameliorate estrogen deficiency. In this study, ligand-based pharmacophore models for 17β-HSD2 inhibitors were constructed and employed for virtual screening. From the virtual screening hits, 29 substances were evaluated in vitro for 17β-HSD2 inhibition. Seven compounds inhibited 17β-HSD2 with low micromolar $IC_{50}$ values. To investigate structure–activity relationships (SAR), 30 more derivatives of the original hits were tested. The three most potent hits, **12**, **22**, and **15**, had $IC_{50}$ values of 240 nM, 1 µM, and 1.5 µM, respectively. All but 1 of the 13 identified inhibitors were selective over 17β-HSD1, the enzyme catalyzing conversion of estrone into estradiol. Three of the new, small, synthetic 17β-HSD2 inhibitors showed acceptable selectivity over other related HSDs, and six of them did not affect other HSDs.

http://dx.doi.org/10.1021/jm5004914

# Structure–Activity Relationship of *S*-Trityl-L-Cysteine Analogues as Inhibitors of the Human Mitotic Kinesin Eg5

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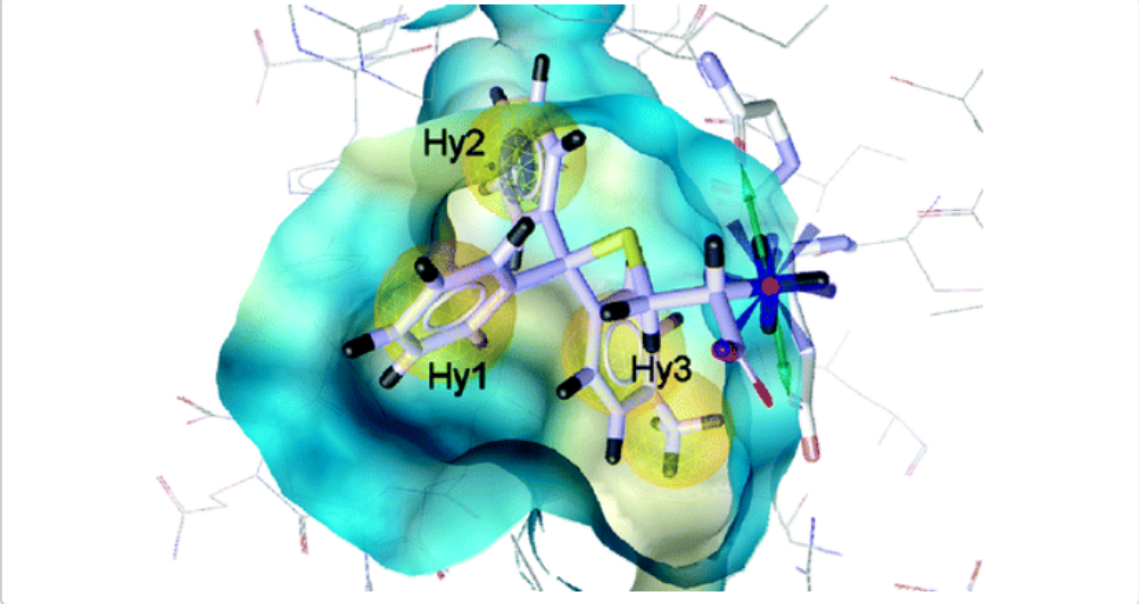
## Abstract




The human kinesin Eg5 is a potential drug target for cancer chemotherapy. Eg5 specific inhibitors cause cells to block in mitosis with a characteristic monoastral spindle phenotype. Prolonged metaphase block eventually leads to apoptotic cell death. *S*-trityl-L-cysteine (STLC) is a tight-binding inhibitor of Eg5 that prevents mitotic progression. It has proven antitumor activity as shown in the NCI 60 tumor cell line screen. It is of considerable interest to define the minimum chemical structure that is essential for Eg5 inhibition and to develop more potent STLC analogues. An initial structure–activity relationship study on a series of STLC analogues reveals the minimal skeleton necessary for Eg5 inhibition as well as indications of how to obtain more potent analogues. The most effective compounds investigated with substitutions at the *para*-position of one phenyl ring have an estimated $K_i^{app}$ of 100 nM *in vitro* and induce mitotic arrest with an $EC_{50}$ of 200 nM.

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# Structure-based discovery of potentially active semiochemicals for *Cydia pomonella* (L.)

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Jiyuan Liu[1,2,*], Zhen Tian[1,*] & Yalin Zhang[1]

**The development of physiologically active semiochemicals is largely limited by the labor-consuming searching process. How to screen active semiochemicals efficiently is of significance to the extension of behavior regulation in pest control. Here pharmacophore modeling and shape-based virtual screening were combined to predict candidate ligands for *Cydia pomonella* pheromone binding protein 1 (CpomPBP1). Out of the predicted compounds, ETrME displayed the highest affinity to CpomPBP1. Further studies on the interaction between CpomPBP1 and ETrME, not only depicted the binding mode, but also revealed residues providing negative and positive contributions to the ETrME binding. Moreover, key residues involved in interacting with ETrME of CpomPBP1 were determined as well. These findings were significant to providing insights for the future searching and optimization of active semiochemicals.**

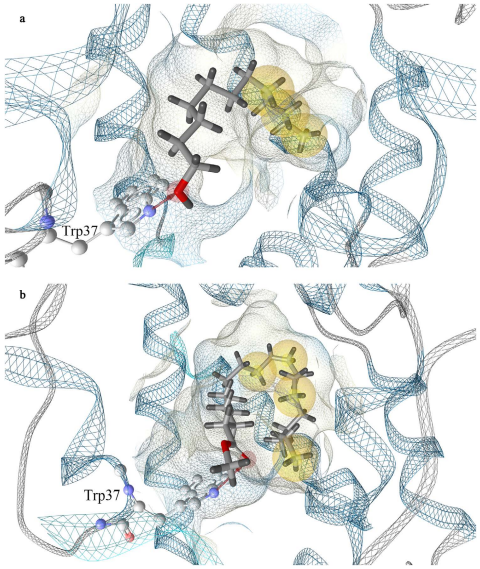


**Figure 1. Structure-based pharmacophore modeling.** (**a**) Pharmacophore model based on the binding mode of CpomPBP1-Codlemone complex. The model consists of three hydrophobic features (yellow) as well as one hydrogen bond (red arrow). (**b**) Pharmacophore model based on the binding mode of CpomPBP1-ETrME complex. The model consists of four hydrophobic features (yellow) as well as one hydrogen bond (red arrow).

http://dx.doi.org/10.1038/srep34600

Lagarde *et al. J Cheminform (2016) 8:43*
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Journal of Cheminformatics

RESEARCH ARTICLE

Open Access

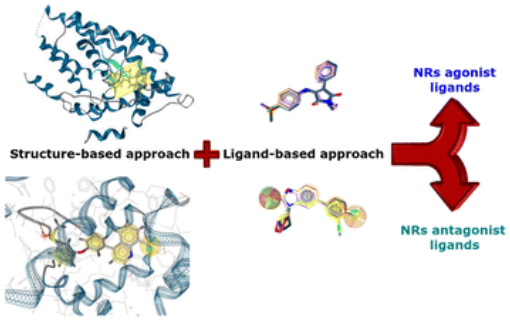
# Discriminating agonist and antagonist ligands of the nuclear receptors using 3D-pharmacophores

Nathalie Lagarde, Solenne Delahaye, Jean-François Zagury and Matthieu Montes*

**Abstract**

Nuclear receptors (NRs) constitute an important class of therapeutic targets. We evaluated the performance of 3D structure-based and ligand-based pharmacophore models in predicting the pharmacological profile of NRs ligands using the NRLiSt BDB database. We could generate selective pharmacophores for agonist and antagonist ligands and we found that the best performances were obtained by combining the structure-based and the ligand-based approaches. The combination of pharmacophores that were generated allowed to cover most of the chemical space of the NRLiSt BDB datasets. By screening the whole NRLiSt BDB on our 3D pharmacophores, we demonstrated their selectivity towards their dedicated NRs ligands. The 3D pharmacophores herein presented can thus be used as a predictor of the pharmacological activity of NRs ligands.

**Keywords:** Nuclear receptors, Agonist ligands, Antagonist ligands, Pharmacophores, Structure-based, Ligand-based, Virtual screening



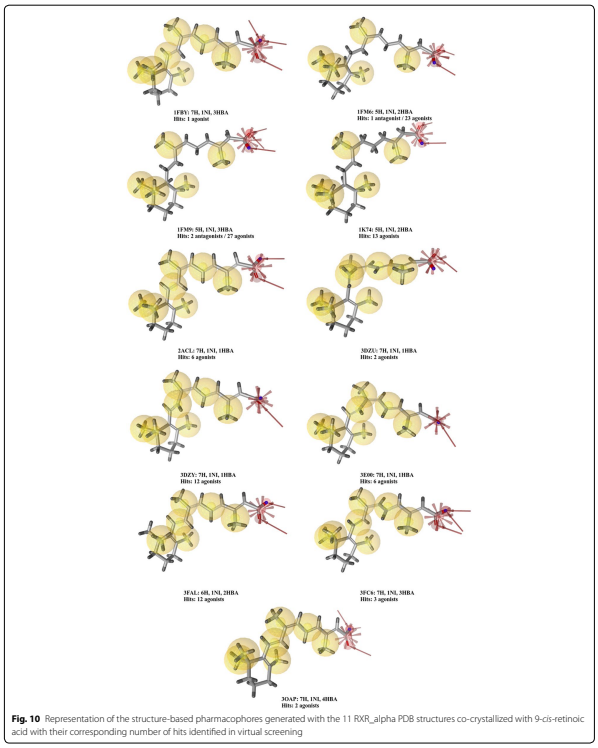



**Fig. 10** Representation of the structure-based pharmacophores generated with the 11 RXR_alpha PDB structures co-crystallized with 9-*cis*-retinoic acid with their corresponding number of hits identified in virtual screening

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New Results

# Computational evidence of a compound with nicotinic α4β2-Ach receptor partial agonist properties as possible coadjuvant for the treatment of obesity

Helena den Haan, Juan Jose Hernandez Morante, Horacio Perez-Sanchez

**doi:** http://dx.doi.org/10.1101/088138

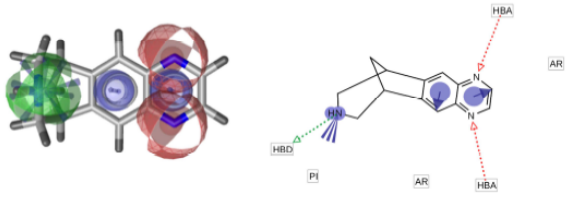
This article is a preprint and has not been peer-reviewed [what does this mean?].



## Abstract

Background. Nowadays, the search for new anti-obesity drugs is oriented to the use of anti-addiction medications like bupropion and naltrexone. Other compounds like varenicline may be also useful to treat obesity. However, the low effectiveness of the former or the high number of adverse effects of the latter makes it necessary to search for new therapeutic agents. Methods. Screening database selected for the computational experiments was DrugBank. 3D global shape comparison with varenicline was performed by means of the Ligand Based Virtual Screening tool WEGA v2015. A pharmacophore model based in the structure of varenicline was created by means of LigandScout v4.08. The in-silico screening was performed using Relative Pharmacophore Fit (RPF) scoring function implemented in LigandScout. Up to 3 mismatches with varenicline pharmacophore model were allowed for hits retrieving. Results. Drugbank database was screened in silico to find alternative molecules to varenicline, and the compound cevimeline was found to have strong similarity to varenicline in terms of 3D shape and pharmacophoric features. Thus, we propose this hit may interact with nicotinic α4β2-Ach receptor in the same mode as varenicline does. Discussion. The functional activities of this compound and its validity as a drug therapy for obesity treatment must be confirmed in further in vitro, in vivo and preclinical studies; however, attending to our screening procedure, this compound should be a promising therapy for such a complex disorder such as obesity.

Figure 1. Pharamacophore model of varenicline. Features in the model are: 1 Positive Ionizable group (blue star), 1 Hydrogen Bond Donor (green sphere), 2 Aromatic Rings (blue rings), 2 Hydrogen Bond Acceptors (red spheres). From left to right 3D and 2D figures are presented from the pharmacophore model overlapped on Varenicline.



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# Exploring new scaffolds for angiotensin II receptor antagonism

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ABSTRACT

Nowadays, $AT_1$ receptor ($AT_1R$) antagonists (ARBs) constitute the one of the most prevalent classes of antihypertensive drugs that modulate the renin-angiotensin system (RAS). Their main uses include also treatment of diabetic nephropathy (kidney damage due to diabetes) and congestive heart failure. Towards this direction, our study has been focused on the discovery of novel agents bearing different scaffolds which may evolve as a new class of $AT_1$ receptor antagonists. To fulfill this aim, a combination of computational approaches and biological assays were implemented. Particularly, a pharmacophore model was established and served as a 3D search query to screen the ChEMBL15 database. The reliability and accuracy of virtual screening results were improved by using molecular docking studies. In total, 4 compounds with completely diverse chemical scaffolds from potential ARBs, were picked and tested for their binding affinity to $AT_1$ receptor. Results revealed high nanomolar to micromolar affinity ($IC_{50}$) for all the compounds. Especially, compound **4** exhibited a binding affinity of 199 nM. Molecular dynamics simulations were utilized in an effort to provide a molecular basis of their binding to $AT_1R$ in accordance to their biological activities.



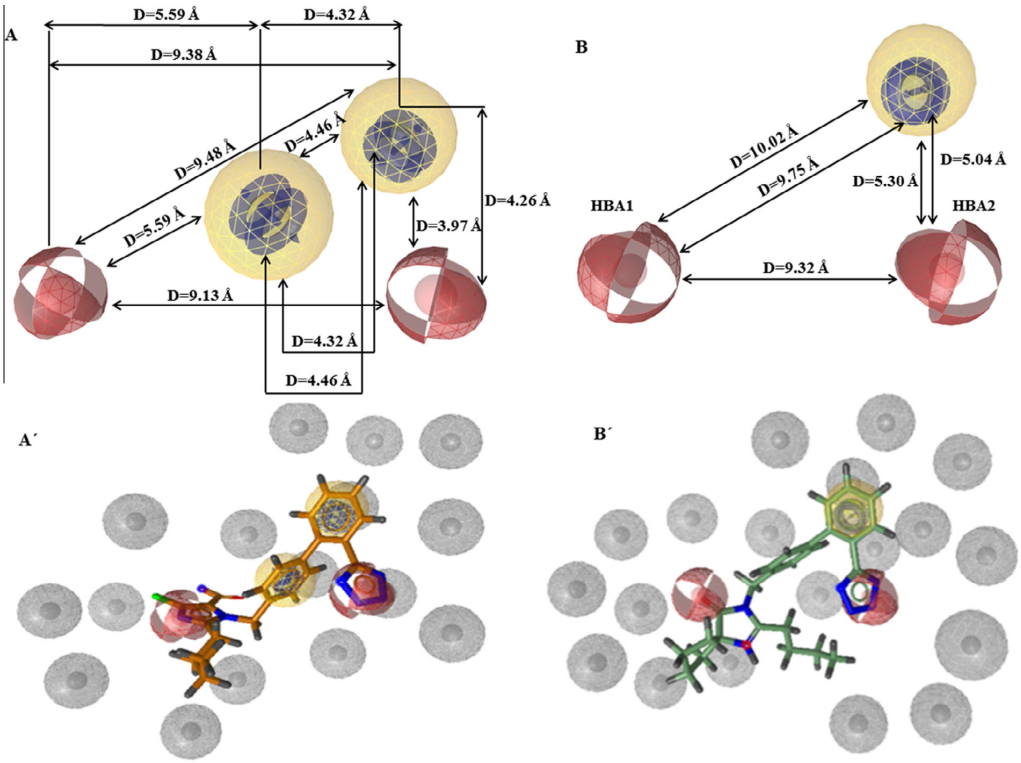


**Figure 3.** (A) Features of the initial pharmacophore model; (A′) EXP3174 fitted on the initial pharmacophore model; (B) features of the optimum pharmacophore model; (B′) irbesartan fitted on the optimum pharmacophore model. The features are depicted with the following color coding: hydrogen bond acceptors (HBA) as red spheres, hydrophobic regions (H) as yellow spheres, aromatic rings (AR) as blue rings and exclusion volumes (Ex. Vol.) as grey spheres. The distances (Å) between the chemical features are illustrated as black lines. Figure made with LigandScout 4.0 Advanced from InteLigand.[28]

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Short communication

# Pharmacophore guided discovery of small-molecule interleukin 15 inhibitors

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## Highlights

- Pharmacophore guided discovery revealed new potential IL-15 and IL-15R inhibitors.
- Twelve molecules reduced IL-15-dependent TNF-α and IL-17 synthesis *in vitro*.
- Cefazolin holds the highest promise for IL-15-directed therapeutic applications.

## Abstract

Upregulation of interleukin 15 (IL-15) contributes directly *i.a.* to the development of inflammatory and autoimmune diseases. Selective blockade of IL-15 aimed to treat rheumatoid arthritis, psoriasis and other IL-15-related disorders has been recognized as an efficient therapeutic method. The aim of the study was to identify small molecules which would interact with IL-15 or its receptor IL-15Rα and inhibit the cytokine's activity. Based on the crystal structure of IL-15Rα·IL-15, we created pharmacophore models to screen the ZINC database of chemical compounds for potential IL-15 and IL-15Rα inhibitors. Twenty compounds with the highest predicted binding affinities were subjected to *in vitro* analysis using human peripheral blood mononuclear cells to validate *in silico* data. Twelve molecules efficiently reduced IL-15-dependent TNF-α and IL-17 synthesis. Among these, cefazolin - a safe first-generation cephalosporin antibiotic - holds the highest promise for IL-15-directed therapeutic applications.

# Discovery of Novel Potent Reversible and Irreversible Myeloperoxidase Inhibitors Using Virtual Screening Procedure

Jalal Soubhye[*†], Ibaa Chikh Alard[‡], Iyas Aldib[†], Martine Prévost[§], Michel Gelbcke[†], Annelise De Carvalho[ɪ], Paul G. Furtmüller[⊥], Christian Obinger[⊥], Jörg Flemmig[#], Sara Tadrent[†], Franck Meyer[∇], Alexandre Rousseau[○], Jean Nève[†], Véronique Mathieu[ɪ], Karim Zouaoui Boudjeltia[○], François Dufrasne[*†¶], and Pierre Van Antwerpen[*†◆¶]

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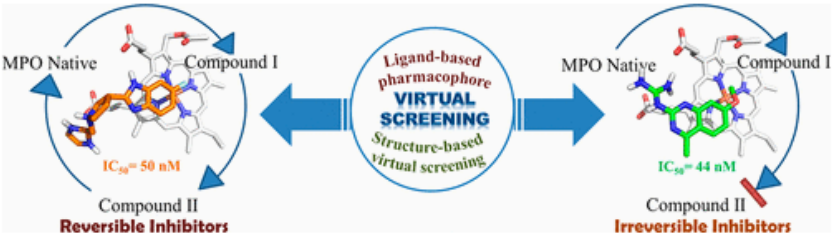
## Abstract




The heme enzyme myeloperoxidase (MPO) participates in innate immune defense mechanism through formation of microbicidal reactive oxidants. However, evidence has emerged that MPO-derived oxidants contribute to propagation of inflammatory diseases. Because of the deleterious effects of circulating MPO, there is a great interest in the development of new efficient and specific inhibitors. Here, we have performed a novel virtual screening procedure, depending on ligand-based pharmacophore modeling followed by structure-based virtual screening. Starting from a set of 727842 compounds, 28 molecules were selected by this virtual method and tested on MPO in vitro. Twelve out of 28 compounds were found to have an $IC_{50}$ less than 5 μM. The best inhibitors were 2-(7-methoxy-4-methylquinazolin-2-yl)guanidine (**28**) and (*R*)-2-(1-((2,3-dihydro-1*H*-imidazol-2-yl)methyl)pyrrolidin-3-yl)-5-fluoro-1*H*-benzo[*d*]imidazole (**42**) with $IC_{50}$ values of 44 and 50 nM, respectively. Studies on the mechanism of inhibition suggest that **28** is the first potent mechanism-based inhibitor and inhibits irreversibly MPO at nanomolar concentration.

# Trisubstituted Pyridinylimidazoles as Potent Inhibitors of the Clinically Resistant L858R/T790M/C797S EGFR Mutant: Targeting of Both Hydrophobic Regions and the Phosphate Binding Site

Marcel Günther[†∥], Jonas Lategahn[‡∥], Michael Juchum[†], Eva Döring[†], Marina Keul[‡], Julian Engel[‡§], Hannah L. Tumbrink[‡], Daniel Rauh[‡], and Stefan Laufer[*†]

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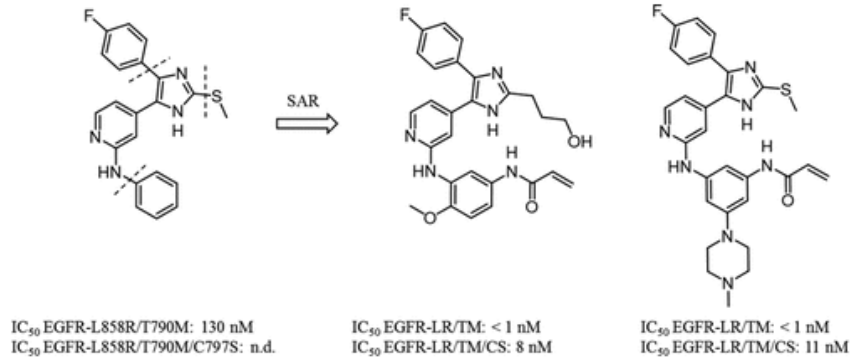
## Abstract




Inhibition of the epidermal growth factor receptor represents one of the most promising strategies in the treatment of lung cancer. Acquired resistance compromises the clinical efficacy of EGFR inhibitors during long-term treatment. The recently discovered EGFR-C797S mutation causes resistance against third-generation EGFR inhibitors. Here we present a rational approach based on extending the inhibition profile of a p38 MAP kinase inhibitor toward mutant EGFR inhibition. We used a privileged scaffold with proven cellular potency as well as in vivo efficacy and low toxicity. Guided by molecular modeling, we synthesized and studied the structure–activity relationship of 40 compounds against clinically relevant EGFR mutants. We successfully improved the cellular EGFR inhibition down to the low nanomolar range with covalently binding inhibitors against a gefitinib resistant T790M mutant cell line. We identified additional noncovalent interactions, which allowed us to develop metabolically stable inhibitors with high activities against the osimertinib resistant L858R/T790M/C797S mutant.

# Potential Antiosteoporotic Natural Product Lead Compounds That Inhibit 17β-Hydroxysteroid Dehydrogenase Type 2

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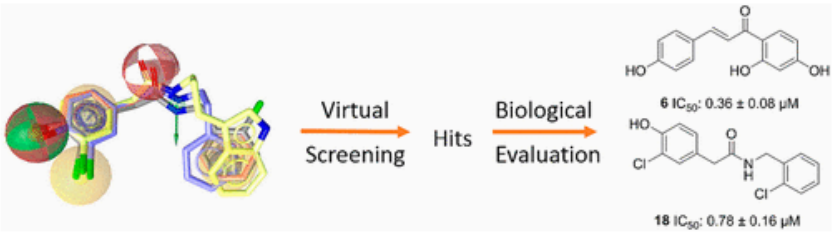
## Abstract




17β-Hydroxysteroid dehydrogenase type 2 (17β-HSD2) converts the active steroid hormones estradiol, testosterone, and 5α-dihydrotestosterone into their weakly active forms estrone, $\Delta^4$-androstene-3,17-dione, and 5α-androstane-3,17-dione, respectively, thereby regulating cell- and tissue-specific steroid action. As reduced levels of active steroids are associated with compromised bone health and onset of osteoporosis, 17β-HSD2 is considered a target for antiosteoporotic treatment. In this study, a pharmacophore model based on 17β-HSD2 inhibitors was applied to a virtual screening of various databases containing natural products in order to discover new lead structures from nature. In total, 36 hit molecules were selected for biological evaluation. Of these compounds, 12 inhibited 17β-HSD2 with nanomolar to low micromolar $IC_{50}$ values. The most potent compounds, nordihydroguaiaretic acid (**1**), $IC_{50}$ 0.38 ± 0.04 μM, (−)-dihydroguaiaretic acid (**4**), $IC_{50}$ 0.94 ± 0.02 μM, isoliquiritigenin (**6**), $IC_{50}$ 0.36 ± 0.08 μM, and ethyl vanillate (**12**), $IC_{50}$ 1.28 ± 0.26 μM, showed 8-fold or higher selectivity over 17β-HSD1. As some of the identified compounds belong to the same structural class, structure–activity relationships were derived for these molecules. Thus, this study describes new 17β-HSD2 inhibitors from nature and provides insights into the binding pocket of 17β-HSD2, offering a promising starting point for further research in this area.

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# 3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles: A New Scaffold for the Selective Inhibition of Monoamine Oxidase B

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Publication Date (Web): July 22, 2011


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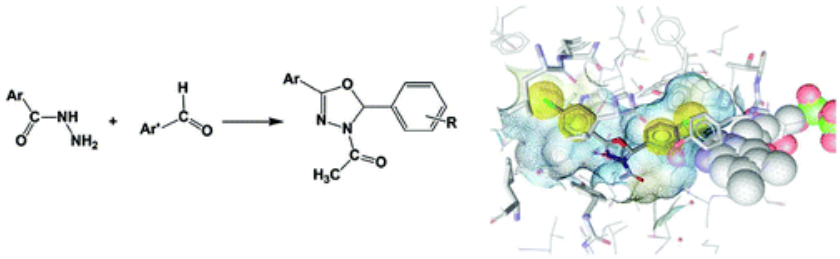
## Abstract



3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles were designed, synthesized, and tested as inhibitors against human monoamine oxidase (MAO) A and B isoforms. Several compounds, obtained as racemates, were identified as selective MAO-B inhibitors. The enantiomers of some derivatives were separated by enantioselective HPLC and tested. The *R*-enantiomers always showed the highest activity. Docking study and molecular dynamic simulations demonstrated the putative binding mode. We conclude that these 1,3,4-oxadiazoles derivatives are promising reversible and selective MAO-B inhibitors.

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# Discovery of the first dual inhibitor of the 5-lipoxygenase-activating protein and soluble epoxide hydrolase using pharmacophore-based virtual screening

Veronika Temml, Ulrike Garscha, Erik Romp, Gregor Schubert, Jana Gerstmeier, Zsofia Kutil, Barbara Matuszczak, Birgit Waltenberger, Hermann Stuppner, Oliver Werz ✉ & Daniela Schuster ✉

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Acute inflammation | Cheminformatics

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## Abstract

Leukotrienes (LTs) are pro-inflammatory lipid mediators derived from arachidonic acid (AA) with roles in inflammatory and allergic diseases. The biosynthesis of LTs is initiated by transfer of AA via the 5-lipoxygenase-activating protein (FLAP) to 5-lipoxygenase (5-LO). FLAP inhibition abolishes LT formation exerting anti-inflammatory effects. The soluble epoxide hydrolase (sEH) converts AA-derived anti-inflammatory epoxyeicosatrienoic acids (EETs) to dihydroxyeicosatetraenoic acids (di-HETEs). Its inhibition consequently also counteracts inflammation. Targeting both LT biosynthesis and the conversion of EETs with a dual inhibitor of FLAP and sEH may represent a novel, powerful anti-inflammatory strategy. We present a pharmacophore-based virtual screening campaign that led to 20 hit compounds of which 4 targeted FLAP and 4 were sEH inhibitors. Among them, the first dual inhibitor for sEH and FLAP was identified, N-[4-(benzothiazol-2-ylmethoxy)-2-methylphenyl]-N'-(3,4-dichlorophenyl)urea with $IC_{50}$ values of 200 nM in a cell-based FLAP test system and 20 nM for sEH activity in a cell-free assay.

DOI: 10.1039/C7MB00214A (Paper) *Mol. BioSyst.*, 2017, **13**, 1364-1369

# Structure based *in silico* identification of potentially non-steroidal brassinosteroids mimics

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## Abstract

Brassinosteroids (BRs) are a class of plant steroid hormones that play indispensable roles in cell elongation, division and plant development. To date, the numerous synthesis of BRs analogs and structure–activity relationship investigations have clearly revealed the key substituent groups relevant to the steroidal activity of BRs. However, due to the limited chemical space studied, the efforts for alternative non-steroidal compounds have produced no remarkable results. To identify potentially non-steroidal BR mimics in this study, vital interacting pharmacophore features were extracted starting from several complex structures of BRs that bound with the receptor Brassinosteroid-Insentive 1 (BRI1) and co-receptor BRI1-associated kinase 1 (BAK1), which were characterized and merged into one comprehensive pharmacophore model. *In silico* screening of a commercial compound database was carried out by combing pharmacophore modeling, molecular docking and visual analysis. Finally, six non-steroidal molecules were identified and subjected to the *in vivo* radish hypocotyl elongation assay. As a positive control, the hypocotyls elongation for the naturally most active BR brassinolide (BL) is 152 ± 3% at 100 nM. Moreover, two candidates (**4** and **6**) show good BRs-like activity with the hypocotyls elongation of 143 ± 1% and 128 ± 3% at the same dose, respectively. Most remarkably, compounds **4** and **6**, which have different structures, are predicted to share similar binding modes and proven to exhibit potential BRs-like activity. The two compounds obtained could be valuable leads for the development of BRs-like plant growth regulators.

# A significant mechanism of molecular recognition between bioflavonoids and P-glycoprotein leading to herb-drug interactions

Pathomwat Wongrattanakamon, Piyarat Nimmanpipug, Busaban Sirithunyalug, Sunee Chansakaow & Supat Jiranusornkul

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Download citation http://dx.doi.org/10.1080/15376516.2017.1351506 Check for updates



## Abstract

Inhibition of P-glycoprotein (P-gp)'s function may conduct significant changes in the prescription drugs' pharmacokinetic profiles and escalate potential risks in taking place of drug/herb-drug interactions. Computational modeling was advanced to scrutinize some bioflavonoids which play roles in herb-drug interactions as P-gp inhibitors utilizing molecular docking and pharmacophore analyses. Twenty-five flavonoids were utilized as ligands for the modeling. The mouse P-gp (code: 4Q9H) was acquired from the PDB. The docking was operated utilizing AutoDock version 4.2.6 (Scripps Research Institute, La Jolla, CA) against the NBD2 of 4Q9H. The result illustrated the high correlation between the docking scores and observed activities of the flavonoids and the putative binding site of these flavonoids was proposed and compared with the site for ATP. To evaluate hotspot amino acid residues within the NBD2, Binding modes for the ligands were achieved using LigandScout to originate the NBD2-flavonoid pharmacophore models. The results asserted that these inhibitors competed with ATP for binding site in the NBD2 (as competitive inhibitors) including the hotspot residues which associated with electrostatic and van der Waals interactions with the flavonoids. In MD simulation of eight delegated complexes selected from the analyzed flavonoid subclasses, RMSD analysis of the trajectories indicated the residues were stable throughout the duration of simulations.

# Targeting the apoptotic Mcl-1-PUMA interface with a dual-acting compound

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Metrics: PDF *135 views* | HTML *69 views*

**Jiyuan Liu[1,3,*], Zhen Tian[3,*], Nan Zhou[1,*], Xueying Liu[1], Chenyi Liao[2], Beilei Lei[3], Jianing Li[2], Shengyong Zhang[1,3] and Hui Chen[1]**

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## ABSTRACT

Despite intensive efforts in the search for small molecules with anti-cancer activity, it remains challenging to achieve both high effectiveness and safety, since many agents lack the selectivity to only act on cancer cells. The interface of two apoptotic proteins, myeloid cell leukemia-1 (Mcl-1) and p53 upregulated modulator of apoptosis (PUMA), has been recently affirmed as a target for treating cancers, as the disruption of Mcl-1-PUMA binding can reduce cancer cell survival and protect normal cells from apoptosis. However, therapeutic agents that target this interface are yet to be found. In this work, we combined pharmacophore modelling and biological tests to seek small molecules which target the Mcl-1-PUMA interface. For the first time, a small-molecule compound was identified. Its dual activity has been validated to reduce PUMA-dependent apoptosis while deactivating Mcl-1-mediated anti-apoptosis in cancer cells. Our results would provide a new avenue for the development of effective and safe anti-cancer agents.

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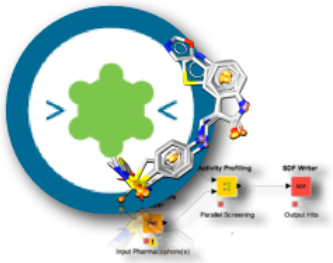

Expert

| Features | LigandScout Essential | LigandScout Advanced | LigandScout Expert/Knime |
|---|---|---|---|
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| Ligand-based Pharmacophore Modelling | ✓ | ✓ | ✓ |
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