25-29 June 2018, Strasbourg

Adventures in Computer-Aided Molecular Design

Thierry Langer

universität wien

inte:ligand
Your partner for in-silico drug discovery.

First Pharmacophore Adventures

universität wien

Begin: University of Strasbourg, 1992

Camille G. Wermuth (1933-2015)

"A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supra-molecular interactions with a specific biological target and to trigger (or block) its biological response."

C.-G. Wermuth et al., *Pure Appl. Chem.* 1998, 70: 1129-1143

inte:ligand
Advance Your Molecular Design

First Pharmacophore Adventures

universität wien

Continuation @ University of Innsbruck, 1993 ...

J. Chem. Inf. Comput. Sci. **1998,** *38,* 325−330

On the Use of Chemical Function-Based Alignments as Input for 3D-QSAR

Thierry Langer*,† and Rémy D. Hoffmann‡

University of Innsbruck, Institute of Pharmaceutical Chemistry, Innrain 52a, A-6020 Innsbruck, Austria, and Molecular Simulations SARL, Parc Club Orsay Université, 20 rue Jean Rostand, F-91838 Orsay, France

Received August 24, 1997

A set of 15 highly flexible competitive inhibitors of rat liver squalene epoxidase (EC.1.14.99.
wide activity range (IC_{50} = 2 nM− 10 μM) has been investigated by three-dimensional quantitati
activity relationships (3D-QSAR). Conformational analysis of the ligands was done by a
sampling approach with sequential poling. The alignment rule has been defined by a chem
mapping based method. A comparative molecular field analysis (CoMFA) was performed usi
energy matrices generated within the GRID program. This approach was shown to yield prec
models.

T. Langer © 2018

inte:ligand
Advance Your Molecular Design

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 8072–8077, July 1996
Pharmacology

Purification, molecular cloning, and expression of the mammalian sigma$_1$-binding site

MARKUS HANNER*, FABIAN F. MOEBIUS*†, ASTRID FLANDORFER*, HANS-GÜNTHER KNAUS*, JÖRG STRIESSNIG*, ELLIS KEMPNER‡, AND HARTMUT GLOSSMANN*

*Institut für Biochemische Pharmakologie, Universität Innsbruck, Peter Mayr Strasse 1, A-6020 Innsbruck, Austria; and ‡National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892

Communicated by James Black, King's College School of Medicine and Dentistry, London, United Kingdom, April 18, 1996 (received for review March 1, 1996)

ABSTRACT **Sigma-ligands comprise several chemically unrelated drugs such as haloperidol, pentazocine, and ditolylguanidine, which bind to a family of low molecular mass proteins in the endoplasmic reticulum. These so-called sigma-receptors are believed to mediate various pharmacological effects of sigma-ligands by as yet unknown mechanisms. Based on their opposite enantioselectivity for benzomorphans and different molecular masses, two subtypes are differentiated. We purified the sigma$_1$-binding site as a single 30-kDa protein from guinea pig liver employing the benzomorphan (+)[^{3}H]pentazocine and the arylazide (−)[^{3}H]azidopamil as specific probes. The purified (+)[^{3}H]pentazocine-binding protein retained its high affinity for haloperidol, pentazocine, and ditolylguanidine. Partial amino acid sequence obtained after trypsinolysis revealed no homology to known proteins. Radiation inactivation of the pentazocine-labeled sigma$_1$-binding site yielded a molecular mass of 24 ± 2 kDa. The corresponding cDNA was cloned using degenerate oligonucleotides and cDNA library screening. Its open reading frame encoded a 25.3-kDa protein with at least one putative transmembrane segment. The protein expressed in yeast cells transformed with the cDNA showed the pharmacological characteristics of the brain and liver sigma$_1$-binding site. The deduced amino acid sequence was structurally unrelated to known mammalian proteins but it shared homology with fungal proteins involved in sterol synthesis. Northern blots showed high densities of the sigma$_1$-binding site mRNA in sterol-producing tissues. This is also in agreement with the known ability of sigma$_1$-binding sites to interact with steroids, such as progesterone.**

The verapamil-like calcium-antagonists azidopamil (a photoligand) and emopamil (an antiischemic drug) are also high-affinity sigma-ligands that were previously employed as specific probes to purify and clone a novel drug-binding membrane protein from liver. This was distinct from the sigma$_1$-binding site, although it showed substantial pharmacological and biochemical similarities with sigma-receptors (26–29). Until now, sigma-ligand studies suffered from the lack of structural information. To clarify its primary structure, we purified the protein carrying the sigma$_1$-binding site and cloned the corresponding cDNA using reverse transcriptase-PCR and degenerate oligonucleotides. Expression in *Saccharomyces cerevisiae* revealed that this cDNA was sufficient to form a high-affinity drug-binding domain with all characteristics of mammalian sigma$_1$-binding sites.

EXPERIMENTAL PROCEDURES

Materials. (+)[^{3}H]Pentazocine (32 Ci/mmol) was obtained from NEN. (−)[^{3}H]Azidopamil (87 Ci/mmol) and the unlabeled phenylalkylamines were kindly provided by Knoll (Ludwigshafen, Germany). Sigma-ligands were a gift of J. Traber (Tropon, Cologne, Germany). The following chemicals were obtained from the indicated sources: opipramol, CIBA–Geigy (Vienna); ceramic hydroxyapatite, Bradford protein reagent, and molecular weight markers, Bio-Rad; Q-, SP-, heparin-, and lysine-Sepharose, Pharmacia; phosphatidylcholine, Avanti Polar Lipids (Alabaster, AL); and all other chemicals, Sigma (Deisenhofen, Germany).

Binding Assays. (+)[^{3}H]Pentazocine binding experiments with membrane-bound and solubilized proteins were carried

M. Hanner et al., PNAS 93, 8072-8077 (1996)

The mysteries of sigma receptors: new family members reveal a role in cholesterol synthesis

Fabian F. Moebius, Jörg Striessnig and Hartmut Glossmann

In the past decade, extensive research has been performed on sigma receptors in the brain and other (e.g. endocrine) tissues[1–3]. These receptors are believed to mediate the immunosuppressant, antipsychotic and neuroprotective effects elicited by sigma ligands such as haloperidol, ditolylguanidine and pentazocine[4]. Since endogenous agonists are not known (progesterone is a possible but controversial candidate)[5,6], sigma sites cannot be classified as receptors in the sense of being agonist-activated mediators of signal transduction. Although their preferential localization in the membrane of the endoplasmic reticulum is different from neurotransmitter

the sigma$_1$ receptor and the discovery of two new members of the sigma receptor family, strongly suggest a role for these binding proteins in postsqualene sterol biosynthesis. The implications of these findings for the interpretation of the biological effects of sigma ligands and their potential use in drug development are discussed below.

The sigma$_1$ receptor: a mammalian homologue of the yeast sterol C_8–C_7 isomerase

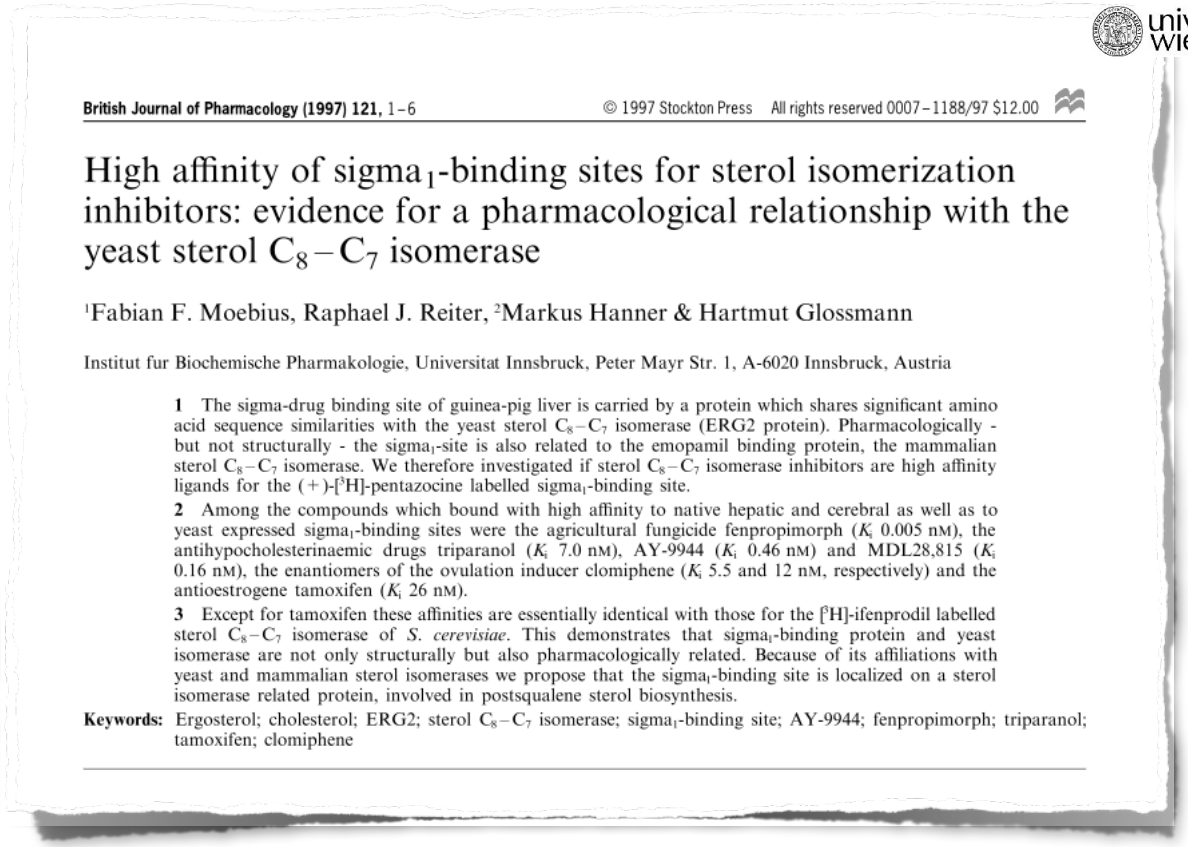
The high-affinity sigma$_1$ receptor probes pentazocine[3] and azidopamil (an arylazide photoaffinity label[10]) allowed the isolation, amino acid sequencing and cDNA cloning of

but also from identical transmembrane topologies (Fig. 1b). The sigma$_1$ receptor and the fungal ERG2 proteins (cloned from *Saccharomyces cerevisiae*, *Magnaporthe grisea* and *Ustilago maydis*) have in common an aminoterminal membrane anchor and two additional stretches of hydrophobic residues involved in substrate binding (see Ref. 11 and references therein). Despite this intimate structural relationship the function of the sigma$_1$ receptor is not yet known. In contrast to the emopamil binding protein (EBP) (see overleaf), sigma$_1$ receptors failed to complement isomerization-deficient yeast mutants[11]. It is unknown whether the yeast ERG2 protein exhibits isomerase activity in mammalian cells or whether additional cofactors are needed.

The yeast sterol C_8–C_7 isomerase: an ancestral sigma receptor

The structural similarity between the sigma$_1$ receptor and yeast iso-

F. F. Moebius et al., Trends in Pharmacological Sciences 18, 67-70 (1997)



British Journal of Pharmacology (1997) 121, 1–6

High affinity of sigma$_1$-binding sites for sterol isomerization inhibitors: evidence for a pharmacological relationship with the yeast sterol C_8-C_7 isomerase

[1]Fabian F. Moebius, Raphael J. Reiter, [2]Markus Hanner & Hartmut Glossmann

Institut fur Biochemische Pharmakologie, Universitat Innsbruck, Peter Mayr Str. 1, A-6020 Innsbruck, Austria

1 The sigma-drug binding site of guinea-pig liver is carried by a protein which shares significant amino acid sequence similarities with the yeast sterol C_8-C_7 isomerase (ERG2 protein). Pharmacologically - but not structurally - the sigma$_1$-site is also related to the emopamil binding protein, the mammalian sterol C_8-C_7 isomerase. We therefore investigated if sterol C_8-C_7 isomerase inhibitors are high affinity ligands for the (+)-[^{3}H]-pentazocine labelled sigma$_1$-binding site.

2 Among the compounds which bound with high affinity to native hepatic and cerebral as well as to yeast expressed sigma$_1$-binding sites were the agricultural fungicide fenpropimorph (K_i 0.005 nM), the antihypocholesterinaemic drugs triparanol (K_i 7.0 nM), AY-9944 (K_i 0.46 nM) and MDL28,815 (K_i 0.16 nM), the enantiomers of the ovulation inducer clomiphene (K_i 5.5 and 12 nM, respectively) and the antioestrogene tamoxifen (K_i 26 nM).

3 Except for tamoxifen these affinities are essentially identical with those for the [^{3}H]-ifenprodil labelled sterol C_8-C_7 isomerase of *S. cerevisiae*. This demonstrates that sigma$_1$-binding protein and yeast isomerase are not only structurally but also pharmacologically related. Because of its affiliations with yeast and mammalian sterol isomerases we propose that the sigma$_1$-binding site is localized on a sterol isomerase related protein, involved in postsqualene sterol biosynthesis.

Keywords: Ergosterol; cholesterol; ERG2; sterol C_8-C_7 isomerase; sigma$_1$-binding site; AY-9944; fenpropimorph; triparanol; tamoxifen; clomiphene

F. F. Moebius et al., Brit. J. Pharmacol 121, 1-6 (1997)

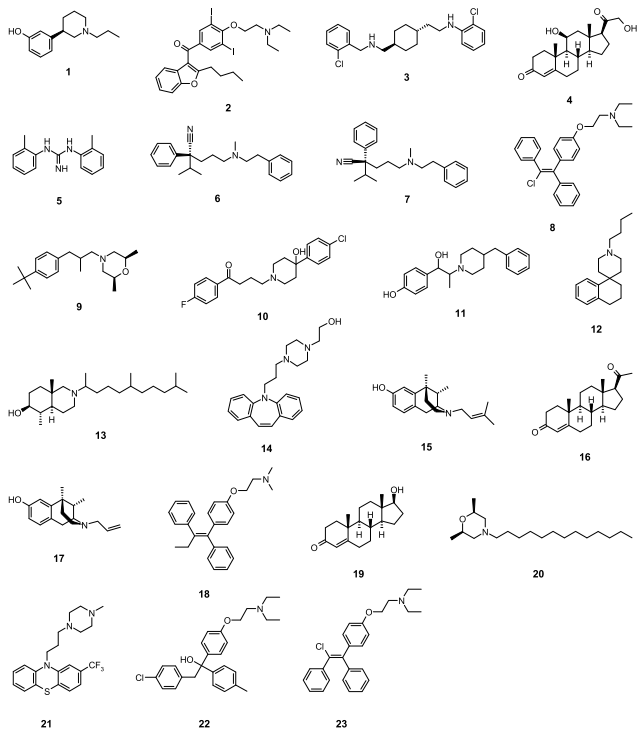
Sigma-1 Receptor Ligands

Search for potent and selective ligands

- 3D Structure of the target unknown at that time
- No significant sequence homology to other proteins (functional homology to ERG2P and EBP)
- Many sigma-1 ligands known, however with low selectivity (sigma-2, hERG, etc ...)
- Appealing clinical potential: antipsychotic, antidepressant, antiepileptic, neuropathic pain ...
- Excellent data set available

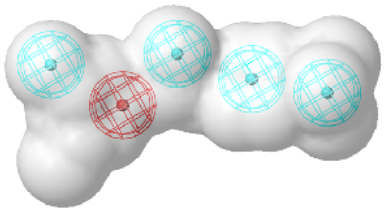
Sigma-1 Pharmacophore Model

universität wien



23 molecules

Ki = 0.1 nM - 35 µM



4 hydrophobic features

1 positive ionizable

How about prospective experimental validation ?

inte:ligand
Advance Your Molecular Design

Experimental Validation

universität wien

Articles

Discovery of High-Affinity Ligands of σ_1 Receptor, ERG2, and Emopamil Binding Protein by Pharmacophore Modeling and Virtual Screening

Christian Laggner,[†] Claudia Schieferer,[†] Birgit Fiechtner,[‡] Gloria Poles,[‡] Rémy D. Hoffmann,[§] Hartmut Glossmann,[†] Thierry Langer,*[,†] and Fabian F. Moebius*[,†]

Institute of Pharmacy, Department of Pharmaceutical Chemistry, and Center for Molecular Biosciences (CMBI), University of Innsbruck, Innrain 52, A-6020 Innsbruck, Austria; Department of Biochemical Pharmacology, Innsbruck Medical University, Peter-Mayr-Str. 1, A-6020 Innsbruck, Austria; and Accelrys SARL, Parc Club Orsay Université, 20, rue Jean Rostand, 91898 Orsay Cédex, France

Received November 17, 2004

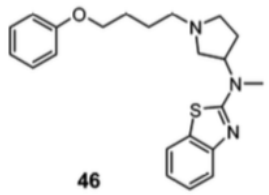
ERG2, emopamil binding protein (EBP), and sigma-1 receptor (σ_1) are enzymes of sterol metabolism and an enzyme-related protein, respectively, that share high affinity for various structurally diverse compounds. To discover novel high-affinity ligands, pharmacophore models were built with Catalyst based upon a series of 23 structurally diverse chemicals exhibiting K_i values from 10 pM to 100 µM for all three proteins. In virtual screening experiments, we retrieved drugs that were previously reported to bind to one or several of these proteins and also tested 11 new hits experimentally, of which three, among them raloxifene, had affinities for σ_1 or EBP of <60 nM. When used to search a database of 3525 biochemicals of intermediary metabolism, a slightly modified ERG2 pharmacophore model successfully retrieved 10 substrate candidates among the top 28 hits. Our results indicate that inhibitor-based pharmacophore models for σ_1, ERG2, and EBP can be used to screen drug and metabolite databases for chemically diverse compounds and putative endogenous ligands.

C. Laggner et al., J. Med. Chem. 48, 4754 - 4764 (2005)

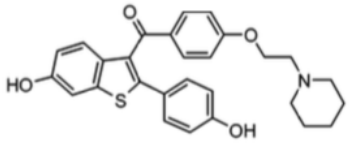
inte:ligand
Advance Your Molecular Design

Experimental Validation

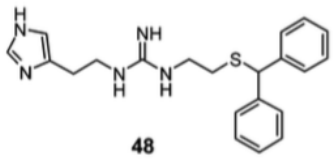
universität wien



46



47



48

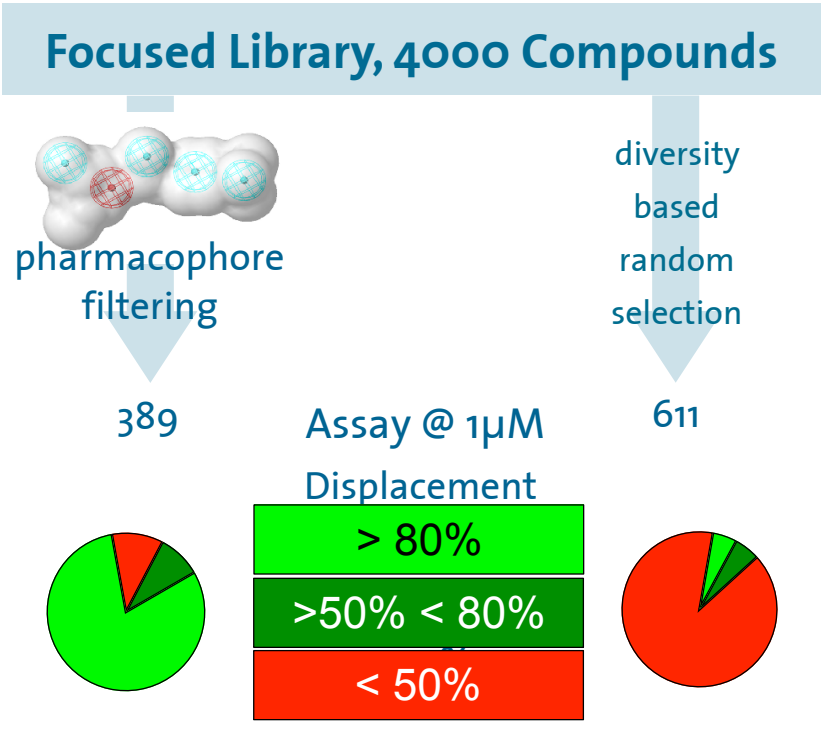
	K_i (nM)		
	EBP	σ_1	ERG2
43	60	1290	7150
44	8500	26700	31700
45	51	230	2800
46	450	1.3	169
47	1	38	66
48	39	6	170
50	583	81	387
51	>100000	207	1170
52	441	74	>100000
53	654	>100000	500
54	>100000	>100000	284

C. Laggner et al., J. Med. Chem. 48, 4754 - 4764 (2005)

inte:ligand
Advance Your Molecular Design

Industrial Application

universität wien

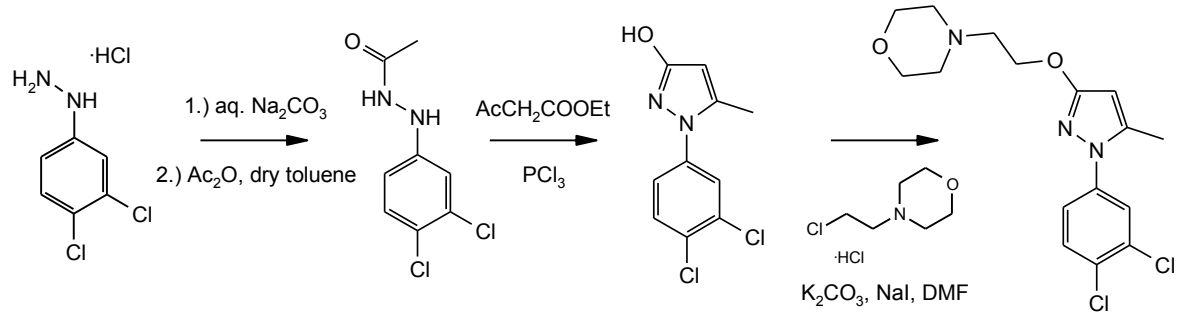


T. Langer © 2018

inte:ligand
Advance Your Molecular Design

From This Collaboration ...

universität wien



CL-142

CL-142 IC_{50} sigma-1 = 1,5 nM IC_{50} sigma-2 > 10000 nM

Pre-clinical profiling:

- no significant interaction with hERG and 21 more anti-targets
- active in animal model for neuropathic pain (oral application)
- a close analogue of CL-142 was developed
- successfully passed clinical phase I and phase II studies

C. Laggner, W. Holzer, T. Langer, *manuscript in preparation*

inte:ligand
Advance Your Molecular Design

t

ESTEVE

mundi pharma

Mundipharma and Purdue reach a new deal to in-licence from ESTEVE full global rights and development responsibilities for novel first-in-class sigma-1 antagonist (S1A or MR309/E-52862)

- Sigma-1 antagonism offers potential for a novel mechanism of action and first-in-class treatment for the management of pain.
- Phase II study results on patients treated with S1A indicate an encouraging efficacy profile in the treatment of neuropathic pain and are awaiting publication.
- Comprehensive Phase I programme involving human subjects administered with S1A showed good overall safety, tolerability, pharmacodynamics and pharmacokinetics.
- Mundipharma, Purdue and ESTEVE announced in 2015 an agreement to bring to patients next generation products for the management of pain.

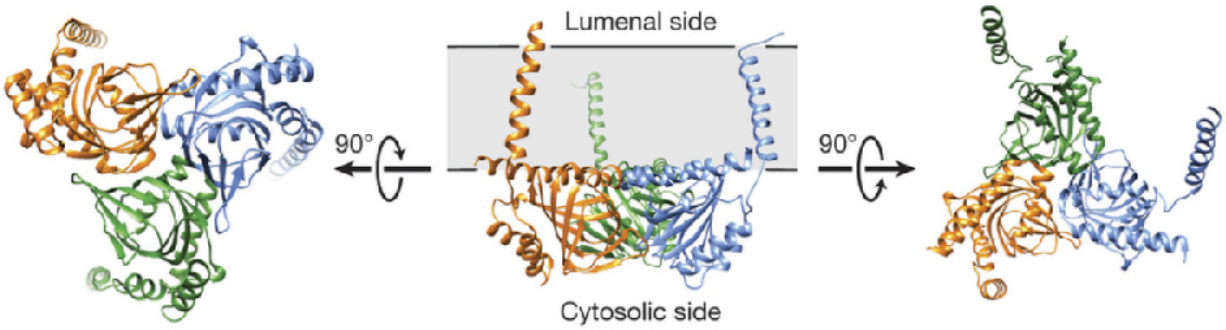
Cambridge (UK) / Barcelona (Spain), 16 May, 2016: Mundipharma Medical Company Limited and its independent associated company, Purdue Pharma L.P., today announced that, following completion of Phase II studies, they have exercised their option and taken over full responsibility from Laboratorios Esteve, S.A.U. (ESTEVE) for the clinical, regulatory and commercial development of a potential first-in-class sigma-1 antagonist (S1A or MR309/E-52862).

inte:ligand
Advance Your Molecular Design

Sigma-1 Recent Findings

universität wien

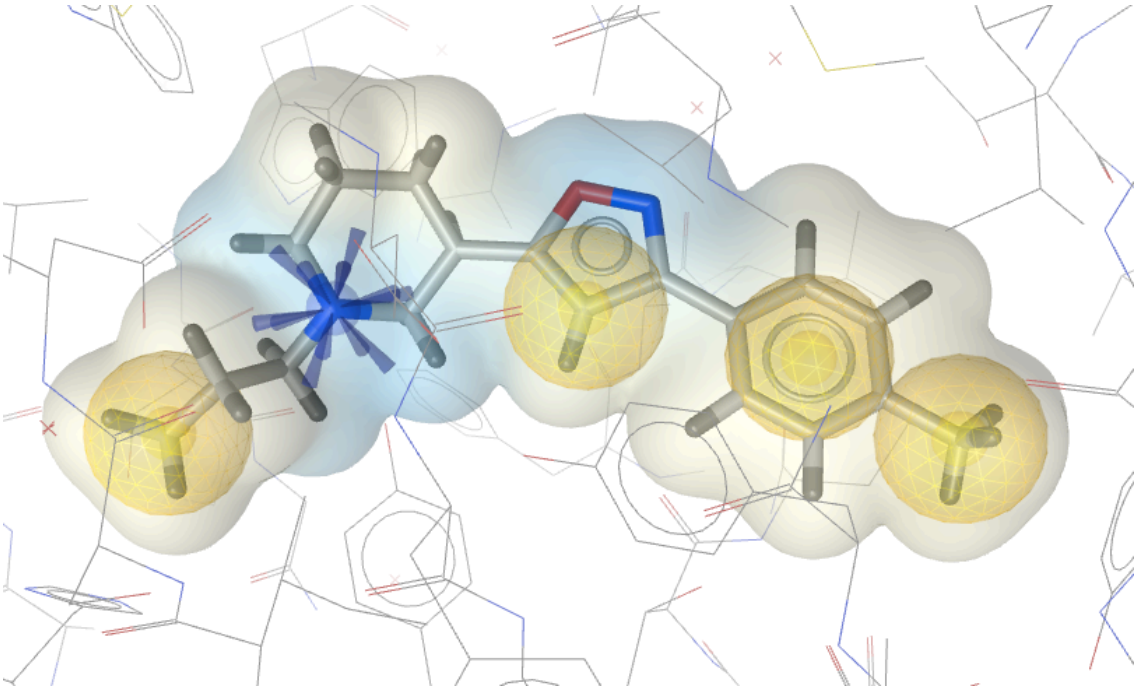
- Sigma-1 is a chaperone protein at the endoplasmic reticulum (ER) that modulates calcium signaling through the IP3 receptor, located mainly in the CNS
- Crystal structure available since April 2016:
  H. R. Schmidt et al., Nature (2016) 523, 527-530



inte:ligand
Advance Your Molecular Design

Sigma-1 Structure-based Model

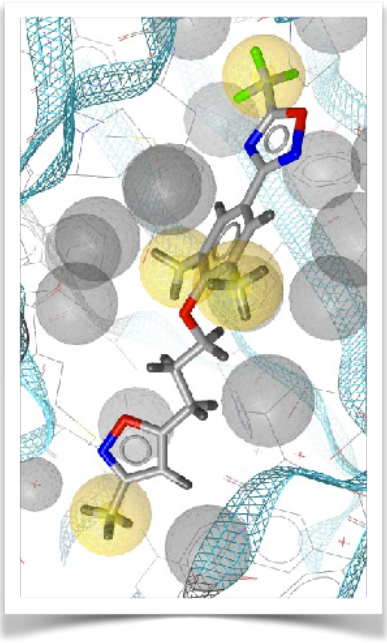
universität wien

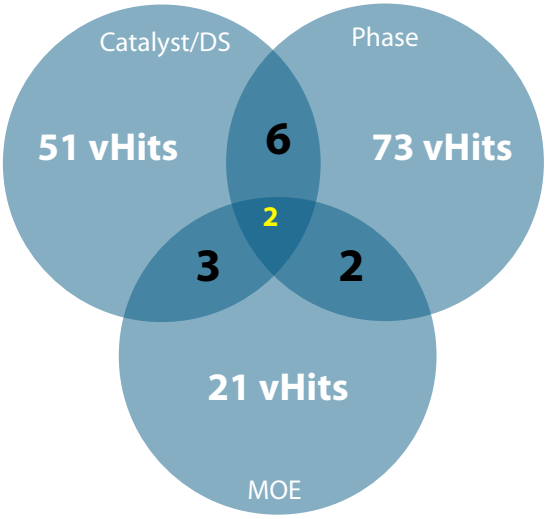


PDB 5HK1

inte:ligand
Advance Your Molecular Design

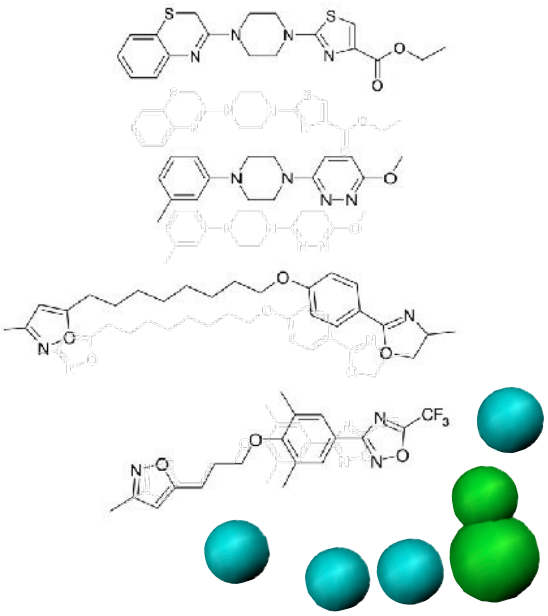
Pharmacophore Limitations

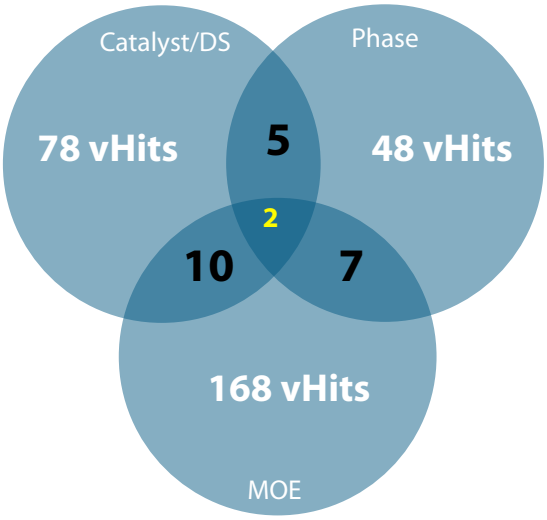




[Mangold 2006] Martina Mangold. *Human Rhinovirus Coat Protein Inhibitors - A Pharmacophore Modeling Approach.* Master's thesis at the University of Innsbruck (2006)

Pharmacophore Limitations (2)





[Mangold 2006] Martina Mangold. *Human Rhinovirus Coat Protein Inhibitors - A Pharmacophore Modeling Approach.* Master's thesis at the University of Innsbruck (2006)

There was a problem ...

universität wien

- "Old" 3D pharmacophore methods suffer from severe limitations
  - different tools return inconsistent results
  - alignment by graph matching ----> slow
  - low number of features ----> inaccurate

What is the solution ?

inte:ligand
Advance Your Molecular Design

We Need Speed & Accuracy

universität wien

- Revisit the alignment algorithm
- No upper limit for number of features
  - high number of features will give good selectivity
- No exponential growth of search time with growing number of features
- No graph matching necessary ...

Work exclusively in the pharmacophore domain !

inte:ligand
Advance Your Molecular Design

… Breaking the Code

universität wien

- Why Yuor Barin Can Raed Tihs

http://www.livescience.com/18392-reading-jumbled-words.html

inte:ligand
Advance Your Molecular Design

… Breaking the Code

universität wien

- It deson’t mttaer in waht oredr the ltteers in a wrod aepapr, the olny iprmoatnt tihng is taht the frist and lsat ltteer are in the rghit pcale. The rset can be a toatl mses and you can sitll raed it wouthit pobelrm.

http://www.livescience.com/18392-reading-jumbled-words.html

T. Langer © 2018

inte:ligand
Advance Your Molecular Design

... Breaking the Code

universität wien

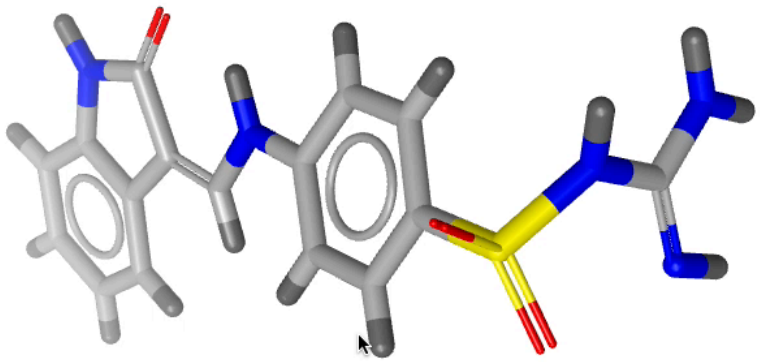
- S1M1L4RLY, YoUR M1ND 15 R34D1NG 7H15 4U70M471C4LLY W17HoU7 3V3N 7H1NK1NG 4BoU7 17

http://www.livescience.com/18392-reading-jumbled-words.html

inte:ligand
Advance Your Molecular Design

It's all about pattern recognition !

universität wien

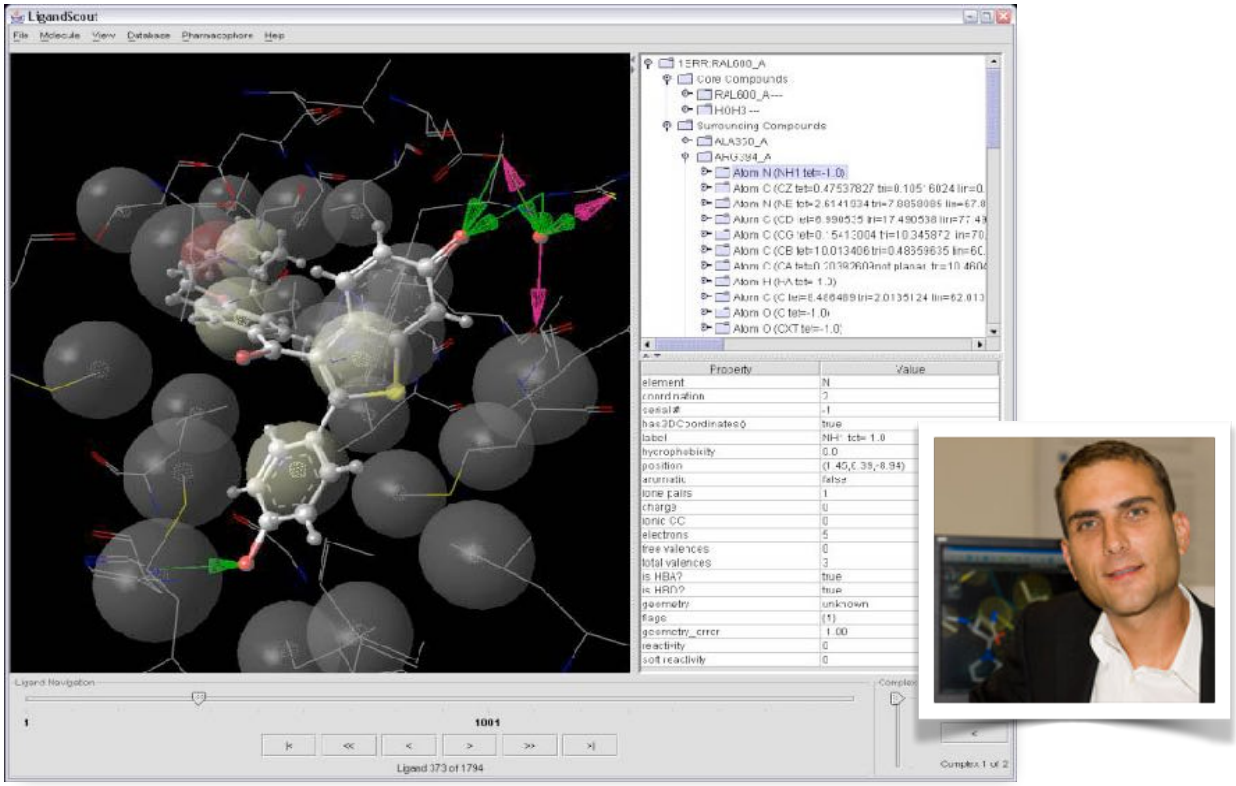


T. Langer © 2018

inte:ligand
Advance Your Molecular Design

LigandScout Prototype

universität wien



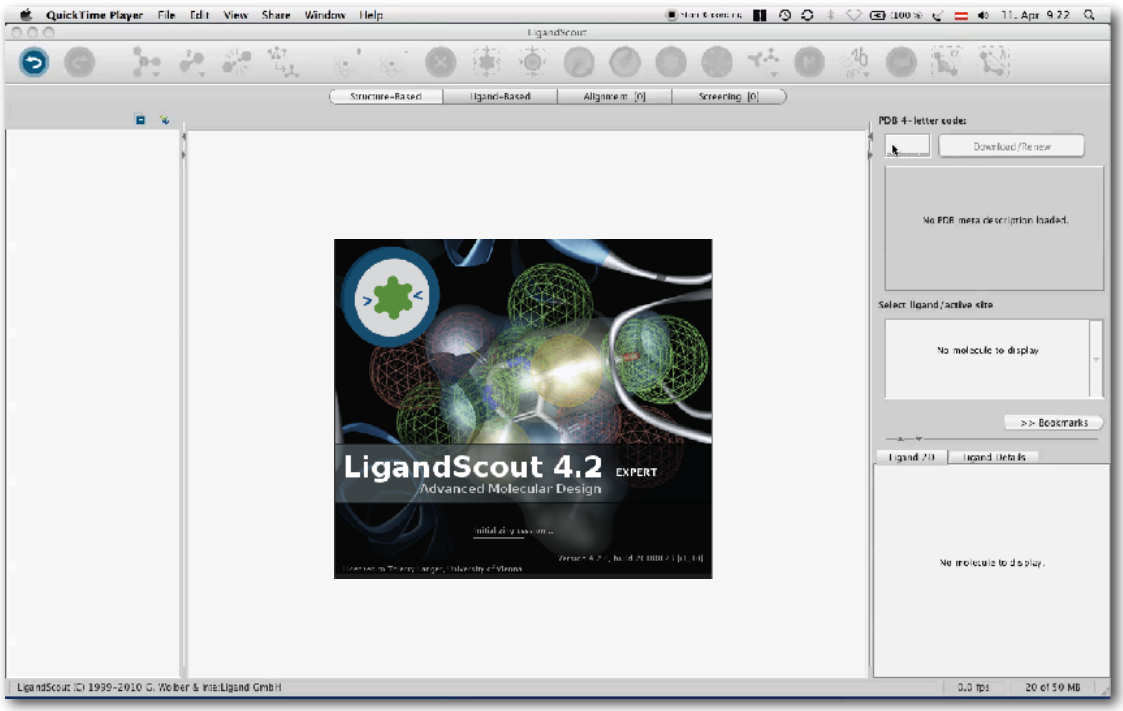
T. Langer © 2018

G. Wolber, PhD Thesis, Univ. Innsbruck, 2003

inte:ligand
Advance Your Molecular Design

LigandScout 4.2 Expert

universität wien



inte:ligand
Advance Your Molecular Design

Why is LigandScout better ?

universität wien

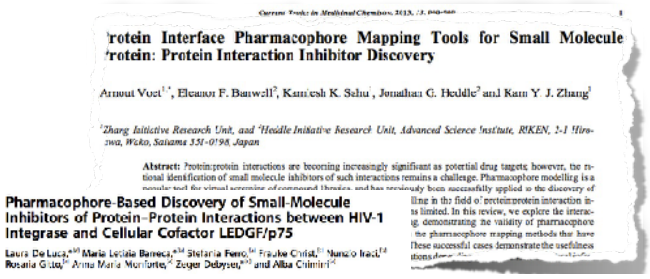
- More appropriate science: Pattern recognition
- Comprehensive models: Higher accuracy
- Smart indexing/screening: Higher speed
- Elaborated graphical user interface
  - for fast learning
  - for true productivity enhancement

inte:ligand
Advance Your Molecular Design

LigandScout Scientific Articles

universität wien

- More than 1550 papers
  - structure-based modeling
  - ligand-based modeling
  - virtual screening
- Hit identification
- Fragment-based design
- Lead structure optimization
- Protein-Protein Interactions
- Drug repurposing
- Profiling (side-effects)



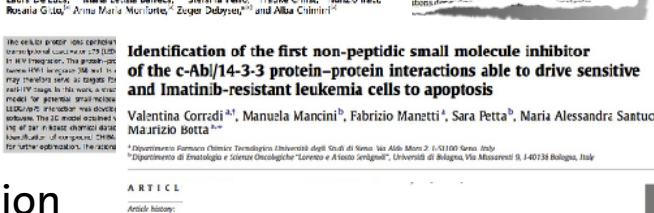
rotein Interface Pharmacophore Mapping Tools for Small Molecule rotein: Protein Interaction Inhibitor Discovery

Arnaud Voet[1,*], Eleanor F. Barwell[2], Kamlesh K. Sahu[1], Jonathan G. Heddle[2] and Kam Y. J. Zhang[1]

[1]Zhang Initiative Research Unit, and [2]Heddle Initiative Research Unit, Advanced Science Institute, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

Abstract: Protein:protein interactions are becoming increasingly significant as potential drug targets; however, the rational identification of small molecule inhibitors of such interactions remains a challenge. Pharmacophore modelling is a popular tool for virtual screening of compound libraries, and has previously been successfully applied to the discovery of

lling in the field of protein:protein interaction inis limited. In this review, we explore the interacg. demonstrating the validity of pharmacophore the pharmacophore mapping methods that have These successful cases demonstrate the usefulness



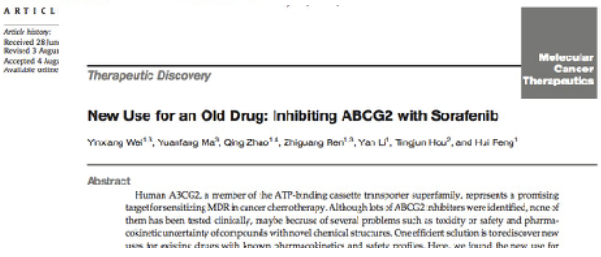
Pharmacophore-Based Discovery of Small-Molecule Inhibitors of Protein–Protein Interactions between HIV-1 Integrase and Cellular Cofactor LEDGF/p75

Laura De Luca,[a,b] Maria Letizia Barreca,[a,c] Stefania Ferro,[a] Frauke Christ,[b] Nunzio Iraci,[a] Rosalia Gitto,[a] Anna Maria Monforte,[a] Zeger Debyser,[b,*] and Alba Chimirri[a,*]

Identification of the first non-peptidic small molecule inhibitor of the c-Abl/14-3-3 protein–protein interactions able to drive sensitive and Imatinib-resistant leukemia cells to apoptosis

Valentina Corradi[a,†], Manuela Mancini[b], Fabrizio Manetti[a], Sara Petta[b], Maria Alessandra Santucci[b], Maurizio Botta[a,*]

[a]Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via Aldo Moro 2, I-53100 Siena, Italy
[b]Dipartimento di Ematologia e Scienze Oncologiche "Lorenzo e Ariosto Seràgnoli", Università di Bologna, Via Massarenti 9, I-40138 Bologna, Italy



ARTICL

Article history:
Received 28 Jun
Revised 3 Augu
Accepted 4 Augu
Available online

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 Feng[1]

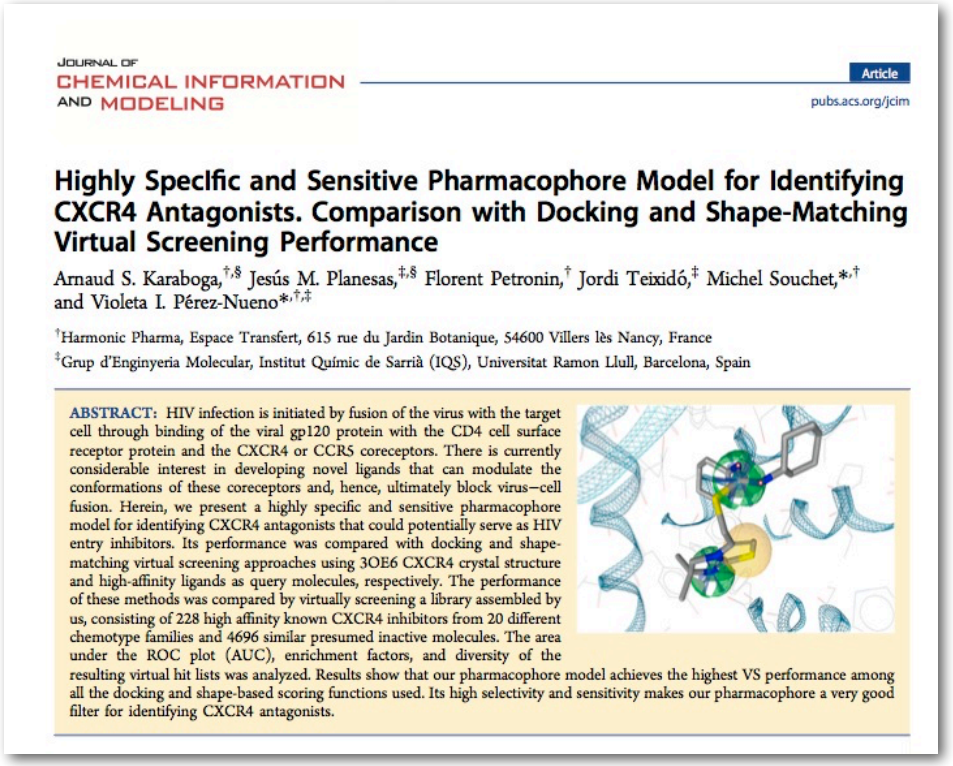
Abstract

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

inte:ligand
Advance Your Molecular Design

An Interesting Article To Read ...

universität wien



JOURNAL OF CHEMICAL INFORMATION AND MODELING — Article — pubs.acs.org/jcim

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*[,†,‡]

[†]Harmonic Pharma, Espace Transfert, 615 rue du Jardin Botanique, 54600 Villers lès Nancy, France

[‡]Grup d'Enginyeria Molecular, Institut Químic de Sarrià (IQS), Universitat Ramon Llull, Barcelona, Spain

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.

Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043−1056

inte:ligand Advance Your Molecular Design

LigandScout for VS

universität wien

Pharmacophore from PDB entry 3OE6

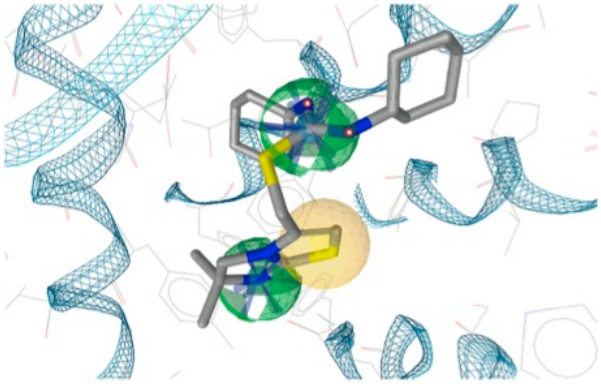


Figure 2. CXCR4 pharmacophore model with a high activity CXCR4 antagonist aligned. Five-featured manually refined final pharmacophore model. The pharmacophore hydrophobic features are shown in yellow. Positively charged features are shown in blue, and hydrogen bond donor features are shown in green.

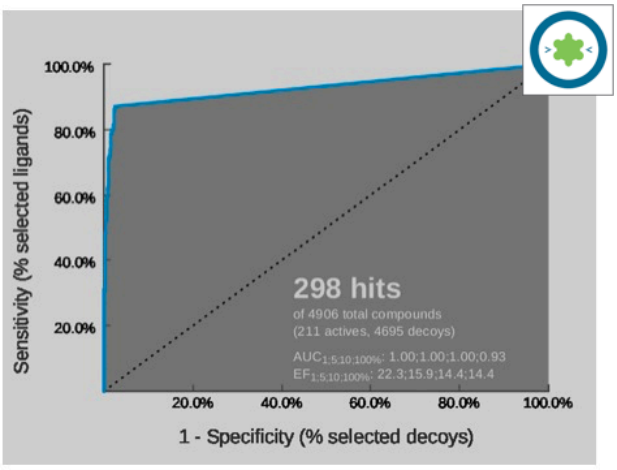
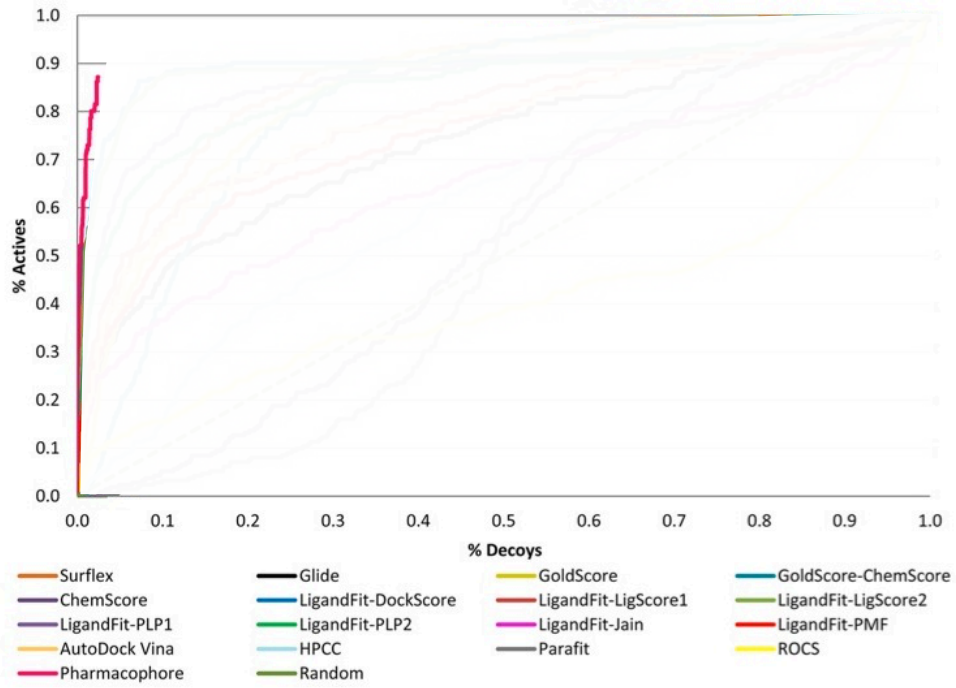


Figure 3. ROC plot validation of the pharmacophore model applied to CXCR4 antagonists. Values of area under the curve (AUC) and enrichment factor (EF) are displayed at 1, 5, 10, and 100% of screened database, respectively. These values highlight the high sensitivity and specificity of the designed pharmacophore model.

Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043−1056

inte:ligand Advance Your Molecular Design

Virtual Screening Performance



Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043−1056

The Conclusions

- Overall, the total area under de curve of the ROC plot and the early recovery results of the present pharmacophore model show that it is a highly specific and sensitive screening filter, which makes it very appropriate for identifying CXCR4 antagonists.
- Moreover, the scaffold retrieval analysis shows that the pharmacophore model is able to retrieve a diverse scaffold pool.

T. Langer © 2018

Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043−1056

Vol 448|9 August 2007 nature

COMMENTARY

New uses for old drugs

It takes too long and costs too much to bring new drugs to market. So let's beef up efforts to screen existing drugs for new uses, argue Curtis R. Chong and David J. Sullivan Jr.

Fast, affordable drug development is a vision that contrasts starkly with the current state of drug discovery — which also neglects too many diseases of the poor. An analysis[1] of 68 approved drugs estimated that it takes an average of 15 years and US$800 million to bring a single drug to market. And despite a doubling in research spending by the US National Institutes of Health (NIH) to $27 billion in 2003, the number of new drugs approved by the US Food and Drug Administration (FDA) each year remains constant at 20–30 compounds[2]. At this rate it will take more than 300 years for the number of drugs in the world to double.

The current costly and time-consuming paradigm of drug discovery is ill-equipped to combat rapidly emerging diseases, such as avian flu, drug-resistant pathogens and diseases that have a small financial market. One solution is to identify new uses for existing drugs. As the pharmacologist and Nobel laureate James Black said, "the most fruitful basis for the discovery of a new drug is to start with an old drug." Because existing drugs have known pharmacokinetics and safety profiles and are often approved by regulatory agencies for human use, any newly identified use can be rapidly evaluated in phase II clinical trials, which typically last two years and cost $20 million. In this way, drug developers can bypass about 40% of the overall cost of bringing a drug to market by eliminating much of the toxicological and pharmacokinetic assessments[3].

This back-to-basics approach is growing in popularity. At least 17 existing drugs are in various stages of clinical and animal testing for new uses (see Supplementary information), and a further 24 are already being remarketed by the pharmaceutical industry for new uses[3]. Although most successful crossovers have been the result of chance observations or educated guesses, exceptions include the antibiotic ceftriaxone, which is a potential treatment for amyotrophic lateral sclerosis[4], and whose new activity was discovered following the screening of 1,040 compounds from the National Institute of Neurological Disorders and Stroke (NINDS) custom collection in Gaithersburg, Connecticut. In the past, individual labs were limited to screening perhaps hundreds of compounds from clinical drug collections like the NINDS library and the Walter Reed Chemical Library in Washington DC, but more than 35,000 approved drugs for small-scale screening. In our view, what is needed is a more systematic approach to drug rediscovery that takes the valuable resources to the next level.

Historically, 'repurposing' old drugs has proved successful in bringing new therapies to the developing world. Today, even with the billions of research dollars available to create new drugs through public–private partnerships, and the promise of genomic data, these remains an enormous unmet need for therapies for neglected diseases'. A recent example of a repurposed drug is miltefosine, initially developed for breast cancer but now used for treating visceral leishmaniasis[5]. This disease is caused by a sandfly-transmitted parasite and kills an estimated 500,000 people each year. In fact, miltefosine failed phase II testing for tumour reduction and the drug was never approved by the FDA for cancer therapy. However, in vitro and animal studies indicated anti-infective activity, and phase II trials confirmed miltefosine as a viable treatment for visceral leishmaniasis[5].

"The most fruitful basis for the discovery of a new drug is to start with an old drug."

Cost cutting

Cost is one reason to revisit existing drugs: roughly 1,000 of the 10,000 or so drugs ever tested in clinical medicine are covered by patents, so most drugs can affordably be redeployed in the developing world. Safety is another compelling reason. Phase IV clinical studies, which monitor post-marketing safety, cost around $100 million per drug to perform in developed countries[3] and are nearly impossible in countries without an established healthcare infrastructure. Because many existing drugs have undergone phase IV surveillance in millions of patients, the same stringent safety standards required by users in developed countries can be offered to patients with neglected diseases in the developing world.

Despite the promise of finding new uses for existing drugs, a comprehensive collection of the approximately 9,990 drugs known to clinical medicine does not exist. This number includes 2,933 unique drugs approved by the FDA since 1938 (ref. 7), 1,107 drugs in the 2006 FDA Orange Book, 838 drugs in the 2006 Physician Desk Reference, and 7,057 drugs that are either approved abroad or have entered phase II clinical trials, as indicated by a US Adopted Name or International Non-proprietary Name. Excluding antiseptics, pharmaceutical aids, therapeutic plant or animal extracts, and vaccines, we estimate that there are 8,850

645

©2007 Nature Publishing Group

Sir James Black

Camille G. Wermuth:
SOSA: Selective Optimization of Side Activities (1993)

Chong & Sullivan,
Nat. Drug Discov. 2007, 448, 645-646

inte:ligand
Advance Your Molecular Design

An Example

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.

inte:ligand
Advance Your Molecular Design

An Example

universität wien

Molecular Cancer Therapeutics

Therapeutic Discovery

New Use for an Old Drug: Inhibiting ABCG2 with Sorafenib

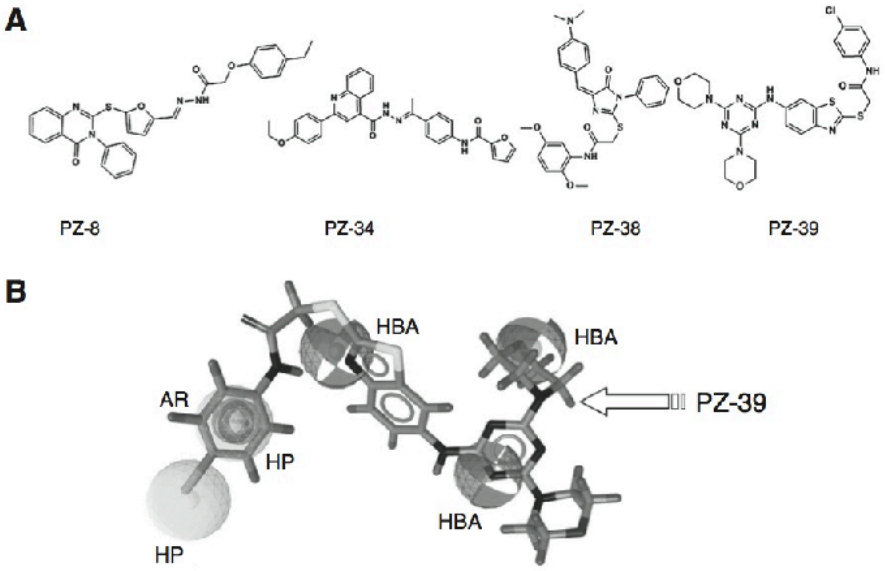
Yinxiang Wei[1,3], Yuanfang Ma[3], Qing Zhao[1,4], Zhig… and Hui Peng[1]

Bernd Riedl, Bayer Pharma, Wuppertal

inte:ligand
Advance Your Molecular Design

LigandScout Model of ABCG2-I

universität wien

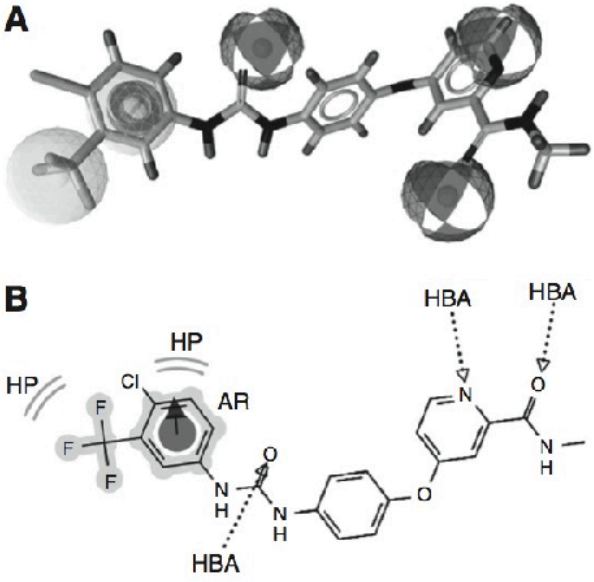


Yinxiang Wei et al., Mol. Cancer Ther.,11, 1693-1702 2012

inte:ligand
Advance Your Molecular Design

Inhibiting ABCG2 With Sorafenib

universität wien



... at a concentration up to 2,5µM/L no cytotoxic effect was observed ...

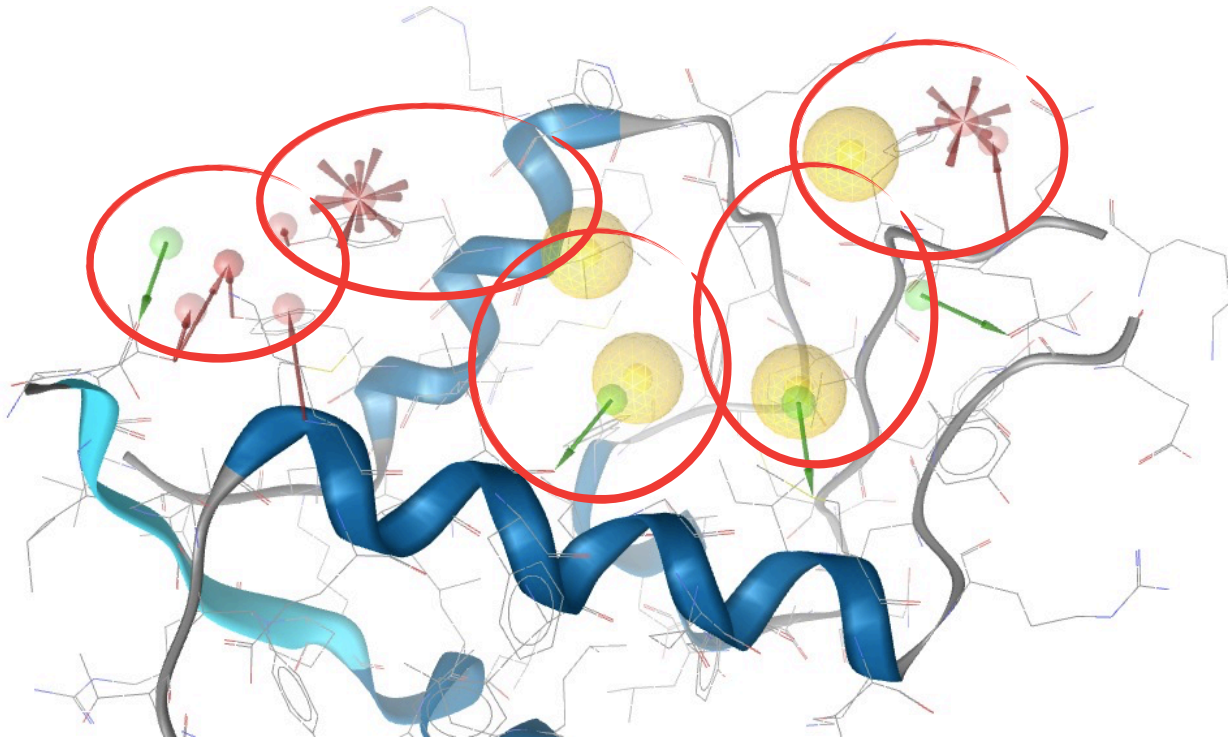
.... led us to conclude that sorafenib behaves like ABCG2 degradation-induced inhibitor. Sorafenib may, therefore, be a good candidate for MDR chemosensitizing agent.

Yinxiang Wei et al., Mol. Cancer Ther.,11, 1693-1702 2012

inte:ligand
Advance Your Molecular Design

Pharmacophores for FBDD

universität wien



T. Langer © 2018

inte:ligand
Advance Your Molecular Design

In Silico FBDD Strategy

universität wien

- Use set of smart, recombinable fragments
- Perform pharmacophore-based screening
- Recombine fragments in silico
- Synthesize the highest ranked solutions
  - IP situation
  - Fit for the target
  - Chemical tractability
  - Physicochemical properties

PRESTWICK CHEMICAL
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design

Real Life - The Numbers

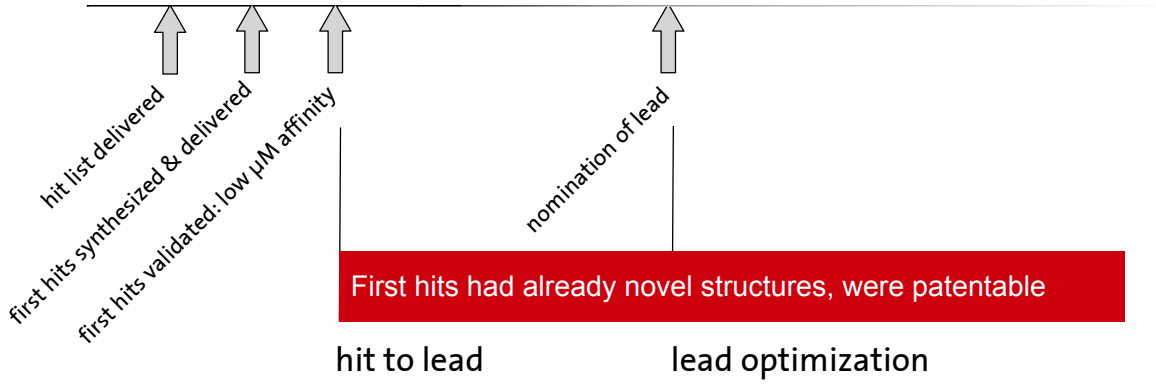
universität wien

- PPI target with known 3D structure (x-ray)
- Pharmacophore derived in direct approach
- Chemistry based fragment library design: 274 -> 837 -> 582
- Virtual combination of 2 fragments: 91k compounds
- LigandScout virtual screening delivered a reasonably small number of hits: 0.005% range
- Synthesis and biological testing: Novel IP, low µM hits

PRESTWICK CHEMICAL
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design

Real Life - Timelines



MedChemComm

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

CrossMark click for updates

Cite this: *Med. Chem. Commun.*, 2016, 7, 506

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

Laurence Deyon-Jung,*[a] Christophe Morice,*[a] Florence Chéry,[a] Julie Gay,[a] Thierry Langer,[ab] Marie-Céline Frantz,[c] Roger Rozot[c] and Maria Dalko-Csiba[c]

Received 5th October 2015,
Accepted 28th December 2015

DOI: 10.1039/c5md00444f

www.rsc.org/medchemcomm

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.

L. Deyon-Jung et al., Med. Chem. Comm. 7, 506-511, 2015

Another Success Story

PRESTWICK CHEMICAL
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design

Another Success Story

DOMAIN THERAPEUTICS

- Collaboration with Domain Therapeutics (F)
  - Target: mGluR4 positive allosteric modulators
  - Disease area: Parkinson, Schizophrenia
- Project Setup
  - 3 years, 2.5 FTEs at Prestwick for med. chem. (hit to lead & and lead optimization)
- Result
  - Optimized lead family, in vivo proof of concept
  - Patent filed by October 2009

PRESTWICK CHEMICAL
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design

mGluR4 PAMs

DOMAIN THERAPEUTICS

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 May 2011 (05.05.2011)

PCT

(10) International Publication Number
WO 2011/051478 A1

(51) International Patent Classification:
C07D 311/68 (2006.01) *A61K 31/473* (2006.01)
C07D 405/04 (2006.01) *A61P 3/10* (2006.01)
C07D 405/14 (2006.01) *A61P 25/28* (2006.01)
C07D 471/04 (2006.01) *A61P 25/22* (2006.01)
C07D 487/04 (2006.01) *A61P 25/14* (2006.01)
C07D 495/04 (2006.01) *A61P 25/16* (2006.01)
C07D 513/04 (2006.01) *A61P 25/18* (2006.01)
C07D 519/00 (2006.01)

(21) International Application Number:
PCT/EP2010/066537

(22) International Filing Date:
29 October 2010 (29.10.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09360049.2 30 October 2009 (30.10.2009) EP

(71) Applicants *(for all designated States except US)*: **DOMAIN THERAPEUTICS** [FR/FR]; Bioparc, Boulevard Sébastien Brandt, F-67400 Illkirch Graffenstaden (FR). **PRESTWICK CHEMICAL, INC.** [FR/FR]; Boulevard Gonthier d'Andernach, F-67400 Illkirch Graffenstaden (FR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SCHANN, Stephan** [FR/FR]; 31, rue des Chaumes, F-67400 Illkirch (FR). **MAYER, Stanislas** [FR/FR]; 10, rue des Jardins, F-67114 Eschau (FR). **MORICE, Christophe** [FR/FR]; 20, rue Saint-Nicolas, F-68320 Widensolen (FR). **GIETHLEN, Bruno** [FR/FR]; 12, route des Romains, F-67120 Altorf (FR).

(74) Agent: **Vossius & Partner (No. 31)**; Siebertstraße 4, 81675 München (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

PRESTWICK CHEMICAL
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design

mGluR4 PAMs Project

- Starting point: (-)-PHCCC

Available online at www.sciencedirect.com
SCIENCE DIRECT®
NEURO PHARMACOLOGY
ELSEVIER
Neuropharmacology 45 (2003) 895–906
www.elsevier.com/locate/neuropharm

(−)-PHCCC, a positive allosteric modulator of mGluR4: characterization, mechanism of action, and neuroprotection

M. Maj [a,1], V. Bruno [b,1], Z. Dragic [a], R. Yamamoto [a], G. Battaglia [b], W. Inderbitzin [a], N. Stoehr [a], T. Stein [a], F. Gasparini [a], I. Vranesic [a], R. Kuhn [a], F. Nicoletti [b,c], P.J. Flor [a,*]

[a] *Novartis Institutes for BioMedical Research, Neuroscience Disease Area, WKL-125.6.98, Basel CH-4002, Switzerland*
[b] *Istituto Neurologico Mediterraneo, Neuromed, Pozzilli, Italy*
[c] *Department of Human Physiology and Pharmacology, University of Rome, Rome, Italy*

Received 25 February 2003; received in revised form 27 May 2003; accepted 23 June 2003

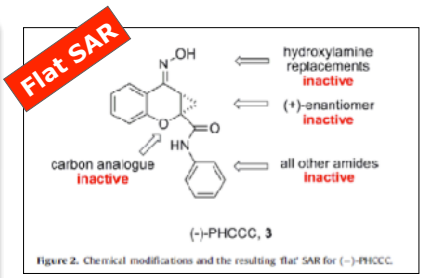
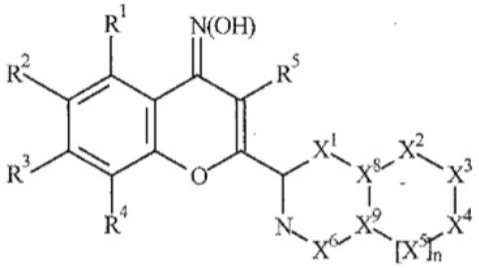


Figure 2. Chemical modifications and the resulting 'flat' SAR for (−)-PHCCC.

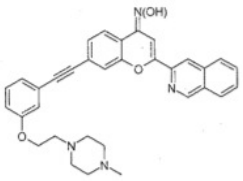
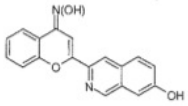
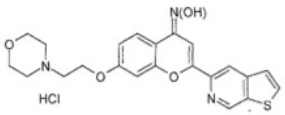
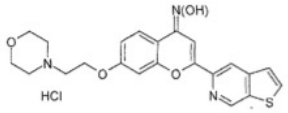
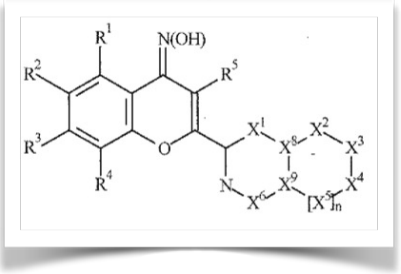
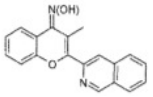
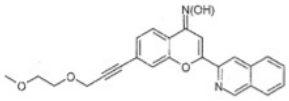
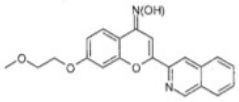
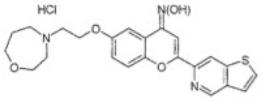
- The result:



PRESTWICK CHEMICAL
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design

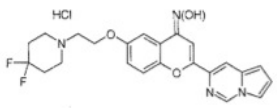
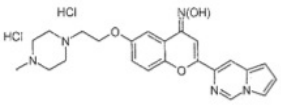
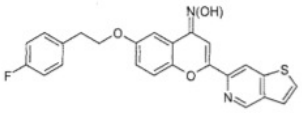
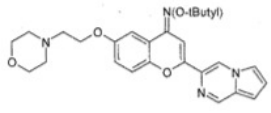
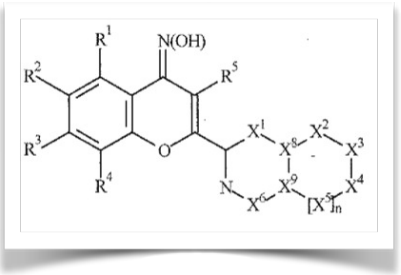
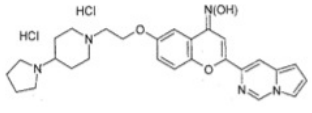
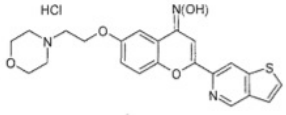
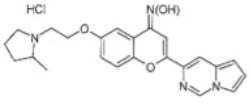
mGluR4 PAMs Patent WO2011051478A1

PRESTWICK CHEMICAL
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design

mGluR4 PAMs Patent WO2011051478A1

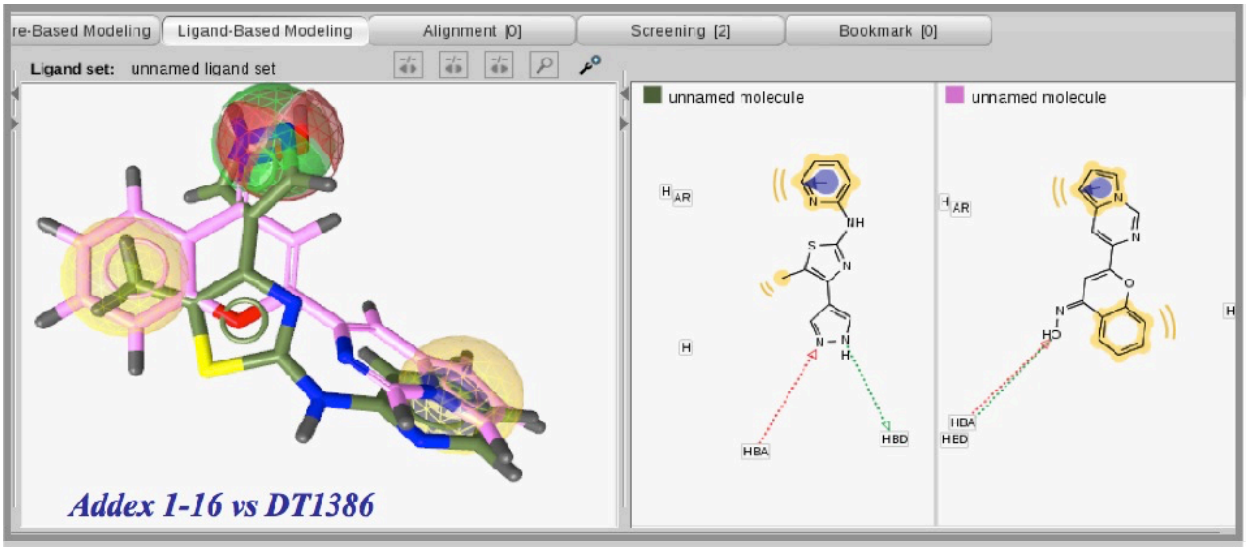
in total:
124 examples
described

PRESTWICK CHEMICAL
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design

Pharmacophore Modeling

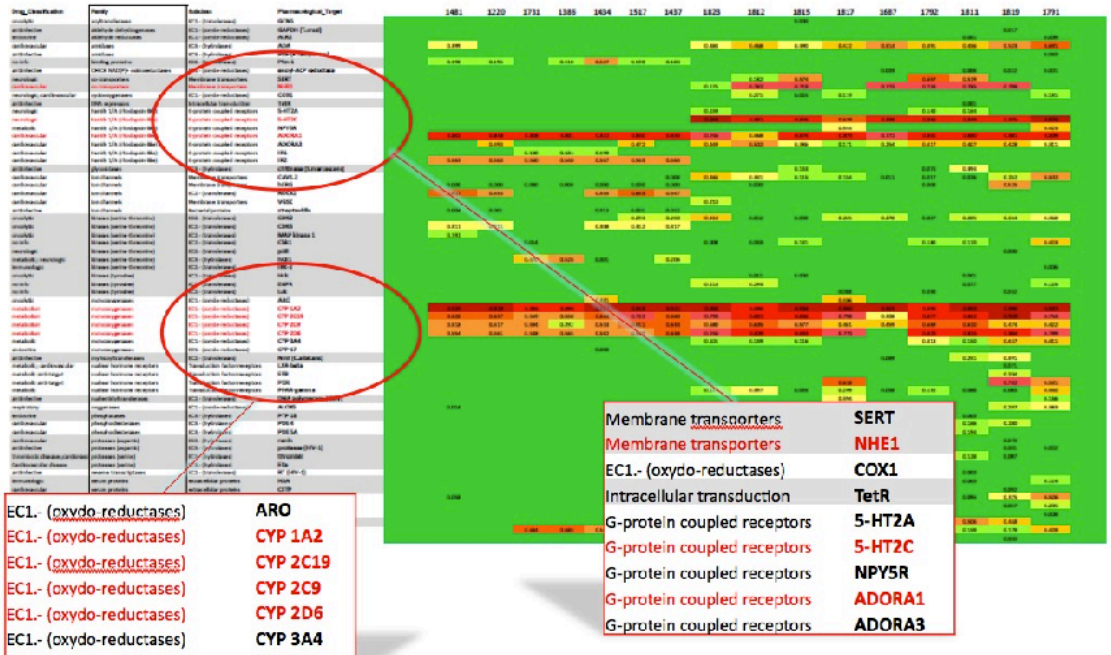
For benchmarking against Addex compounds …



PRESTWICK CHEMICAL
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design

In silico Profiling: Adverse Effects ?



PRESTWICK CHEMICAL
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design

The Result

- Collaboration with Domain Therapeutics (F)
  - Target: mGluR-4 positive allosteric modulators
  - Disease area: Parkinson, Schizophrenia
- Project Setup
  - 3 Years, 2.5 FTEs at Prestwick for med chem (hit to lead & and lead optimization)
- Result
  - Optimized lead family, in vivo proof of concept
  - License agreement signed in Q4 2010

Merck Serono
Living science, transforming lives

Prestwick Chemical
A medicinal chemistry company

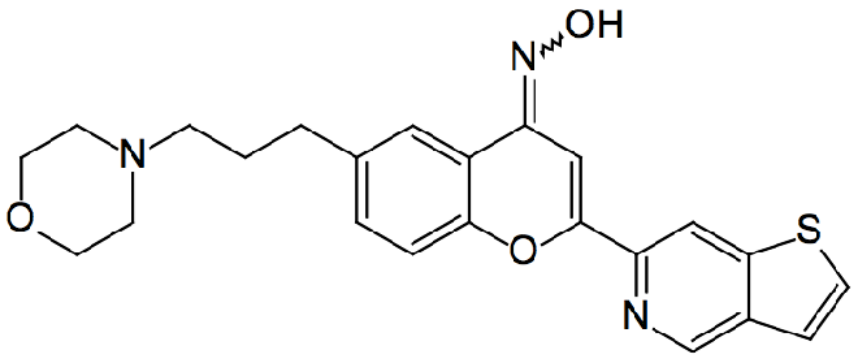
inte:ligand
Advance Your Molecular Design

How did the story continue ?

- Merck Serono closed their site in Geneva in 2012 and gave up all their neuroscience projects
- An ex-Merck team started Prexton Therapeutics and acquired the mGluR4 PAM project
- Foliglurax was selected as candidate and was developed into the clinics up to Phase II
- March 2018: Lundbeck acquired Prexton Therapeutics (total deal volume 1.12 billion USD)

Prestwick Chemical
A medicinal chemistry company

inte:ligand
Advance Your Molecular Design



Foliglurax

Lundbeck to acquire Prexton Therapeutics adding foliglurax in clinical phase II to its pipeline of innovative treatments for patients suffering from Parkinson's disease

- *Lundbeck will make an upfront payment of EUR 100 million and the deal terms also include up to EUR 805 million in development, regulatory and sales milestones*
- *Foliglurax is a first-in-class treatment which entered clinical phase II testing in Parkinson's disease in July 2017*
- *There remains a large unmet need for effective treatments for Parkinson's patients to sustain the utility of dopaminergic therapies*

Valby, Denmark, Oss, The Netherlands, 16 March 2018 - H. Lundbeck A/S (Lundbeck) and Prexton Therapeutics BV (Prexton) today announced signing of a definitive agreement in which Lundbeck will acquire Prexton. Under terms of the agreement, Lundbeck will pay EUR 100 million (approximately DKK 750 million) upfront and is furthermore required to later pay up to EUR 805 million (approximately DKK 6 billion) in development and sales milestones to the group of current owners.

By acquiring Prexton, Lundbeck will obtain global rights of an attractive compound (foliglurax) which currently is in clinical phase II testing for symptomatic treatment of *OFF*-time reduction in Parkinson's disease and dyskinesia including Levodopa Induced Dyskinesia (LID). First data from the ongoing clinical phase II programme is expected to be available during the first half of 2019.

Conclusions

universität wien

- Our pattern recognition-base pharmacophore technique is superior to all other P4 methods with respect to speed and accuracy

  ➡ Highly useful for hit identification, hit2lead, and LO

- There is a lot of new aspects to add to pharmacophore modeling, such as integration with molecular dynamics, or machine learning

  ➡ We are working on that … expect exciting results !

inte:ligand
Advance Your Molecular Design

universität wien

Thank you for your attention

T. Langer © 2018

inte:ligand
Advance Your Molecular Design