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Symposium-in-Print

Chemoinformatics in Drug Discovery

Edited by:

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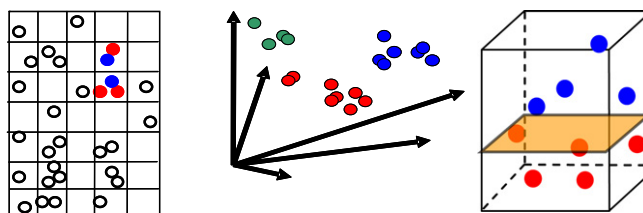
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Jürgen Bajorath*

Chemoinformatics: A view of the field and current trends in method development pp 5317–5323

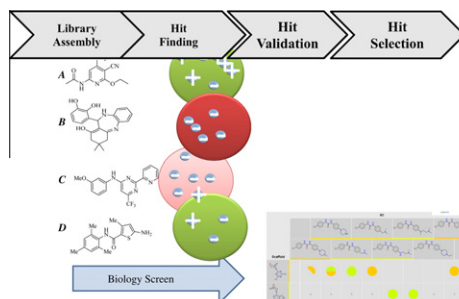
Martin Vogt, Jürgen Bajorath*



Compound classification approaches are illustrated including (from the left to the right) data set partitioning, an activity-sensitive chemical reference space, and a separating hyperplane in chemical space constructed by a support vector machine algorithm.

Early phase drug discovery: Cheminformatics and computational techniques in identifying lead series pp 5324–5342

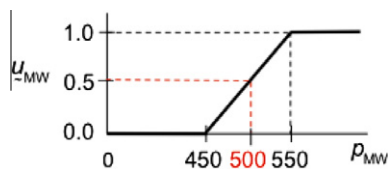
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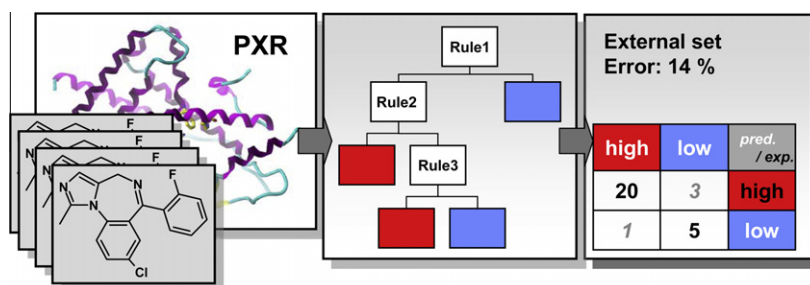
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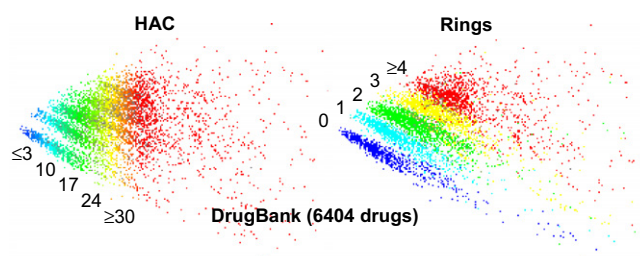
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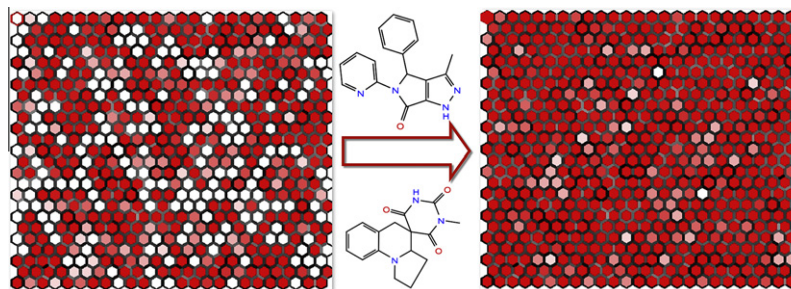
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Hole filling and library optimization: Application to commercially available fragment libraries

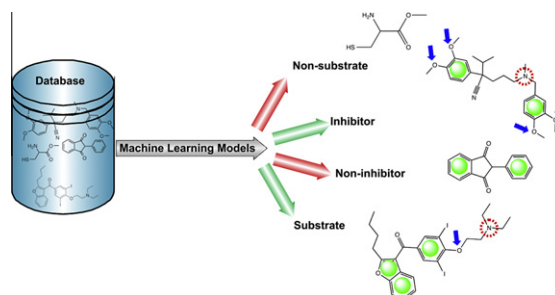
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Yuling An, Woody Sherman, Steven L. Dixon*

**Fingerprint-based in silico models for the prediction of P-glycoprotein substrates and inhibitors**

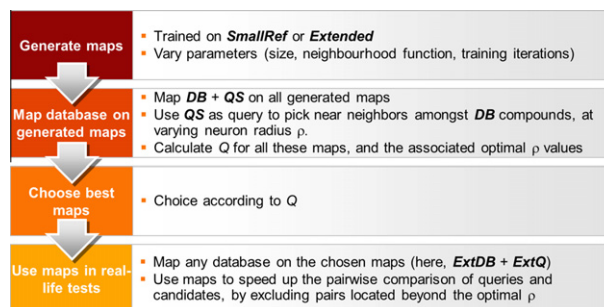
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Vasanthanathan Poongavanam, Norbert Haider, Gerhard F. Ecker*

**Using self-organizing maps to accelerate similarity search**

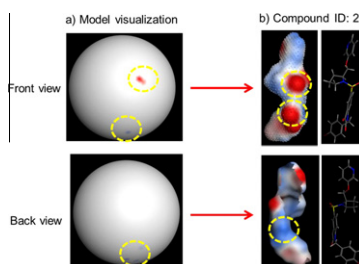
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Fanny Bonachera, Gilles Marcou, Natalia Kireeva, Alexandre Varnek, Dragos Horvath*

**New description of protein–ligand interactions using a spherical self-organizing map**

pp 5410–5415

Kiyoshi Hasegawa, Kimito Funatsu*

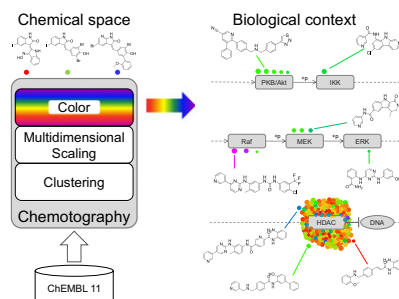


In this study, we perform a QSAR study of caspase-3 inhibitors based on the SSOM technique. The MEP values on the ligand SSOM sphere were used as chemical descriptors. The correlation of the chemical descriptors and the inhibitory activities was investigated by the SVR method. The important MEP descriptors were derived from the final SVR model. Based on the X-ray crystal structure of the protein, the descriptors matched the structural requirements of caspase-3 inhibitors.

Chemotography for multi-target SAR analysis in the context of biological pathways

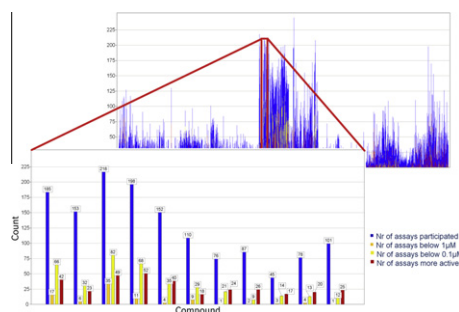
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**BioProfile—Extract knowledge from corporate databases to assess cross-reactivities of compounds**

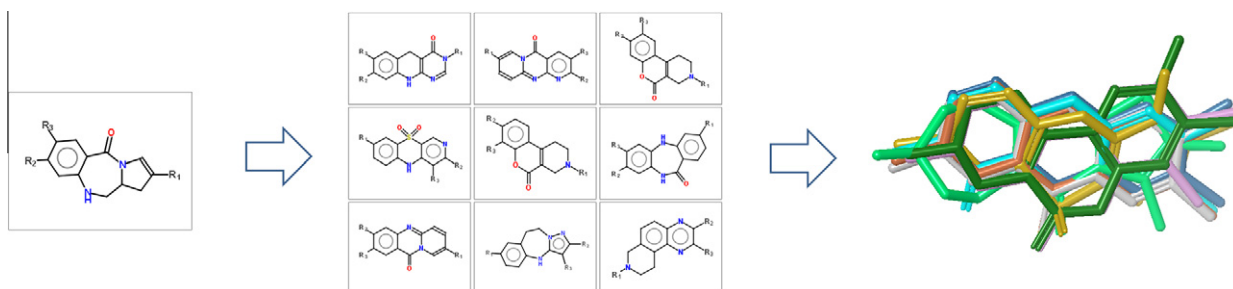
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**Database of bioactive ring systems with calculated properties and its use in bioisosteric design and scaffold hopping**

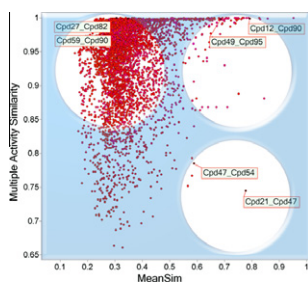
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Peter Ertl*

**Bioactivity landscape modeling: Chemoinformatic characterization of structure–activity relationships of compounds tested across multiple targets**

pp 5443–5452

Jacob Waddell, José L. Medina-Franco*



We report the Structure multiple Activity Similarity (SmAS) maps and the Structure multiple Activity Landscape Index (SmALI) as general approaches to explore and quantify the most informative regions of multi-target activity landscapes.



Who cares for the protons?

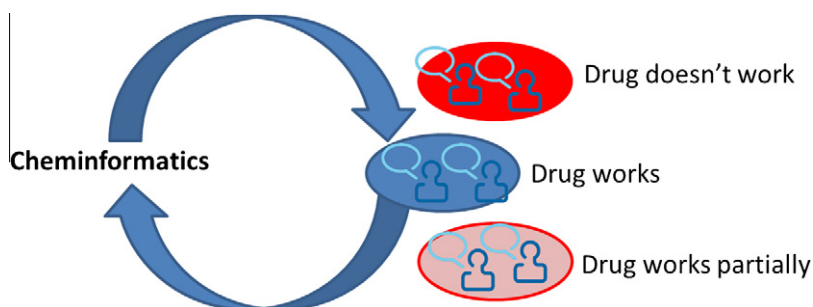
Paul Czodrowski

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**Backtranslating clinical knowledge for use in cheminformatics—What is the potential?**

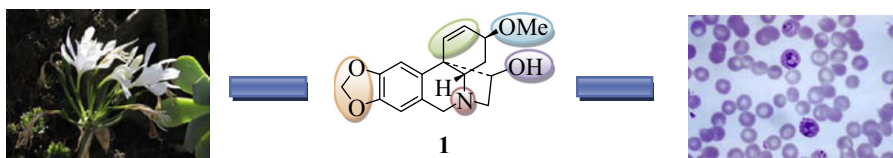
Josef Scheiber*

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**REGULAR ARTICLES****Synthesis and antimalarial activity of new haemanthamine-type derivatives**

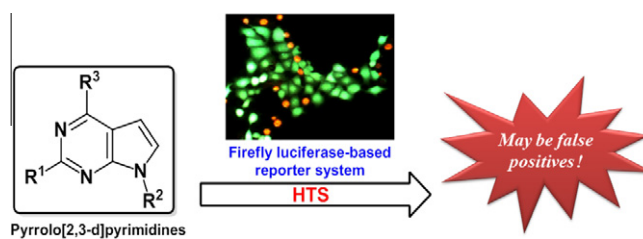
Juan C. Cedrón, David Gutiérrez, Ninoska Flores, Ángel G. Ravelo*, Ana Estévez-Braun*

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**Identification and synthesis of substituted pyrrolo[2,3-d]pyrimidines as novel firefly luciferase inhibitors**

Yang Liu, Jianping Fang, Haiyan Cai, Fei Xiao, Kan Ding*, Youhong Hu*

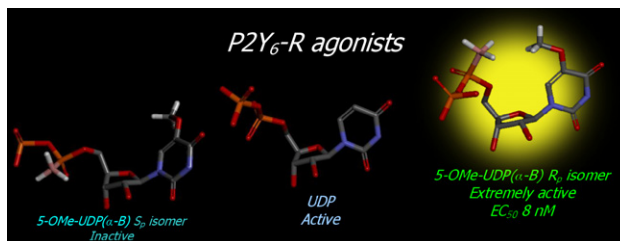
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UDP made a highly promising stable, potent, and selective P2Y₆-receptor agonist upon introduction of a boranophosphate moiety

pp 5483–5495

Tamar Ginsburg-Shmuel, Michael Haas, Djordje Grbic, Guillaume Arguin, Yael Nadel, Fernand-Pierre Gendron, Georg Reiser, Bilha Fischer*



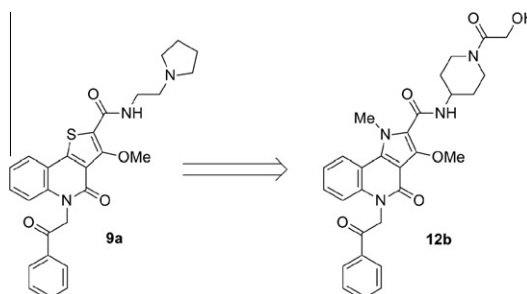
R_p isomer of 5-OMe-UDP(α-B), is the most potent P2Y₆-R agonist currently known. It is chemically and enzymatically stable under conditions mimicking gastric juice acidity, in the presence of NPP1,3 and in blood serum.



Discovery of pyrrolo[3,2-c]quinoline-4-one derivatives as novel hedgehog signaling inhibitors

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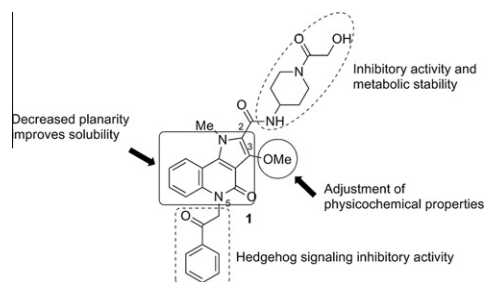
Tomohiro Ohashi*, Yuya Oguro, Toshio Tanaka, Zenyu Shiokawa, Sachio Shibata, Yoshihiko Sato, Hiroko Yamakawa, Harumi Hattori, Yukiko Yamamoto, Shigeru Kondo, Maki Miyamoto, Hideaki Tojo, Atsuo Baba, Satoshi Sasaki



Discovery of the investigational drug TAK-441, a pyrrolo[3,2-c]pyridine derivative, as a highly potent and orally active hedgehog signaling inhibitor: Modification of the core skeleton for improved solubility

pp 5507–5517

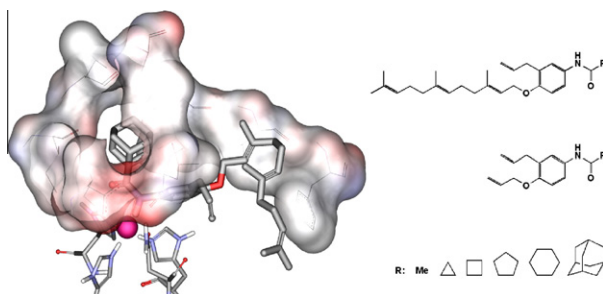
Tomohiro Ohashi, Yuya Oguro, Toshio Tanaka, Zenyu Shiokawa, Yuta Tanaka, Sachio Shibata, Yoshihiko Sato, Hiroko Yamakawa, Harumi Hattori, Yukiko Yamamoto, Shigeru Kondo, Maki Miyamoto, Mitsuhiro Nishihara, Yoshimasa Ishimura, Hideaki Tojo, Atsuo Baba, Satoshi Sasaki*



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

pp 5518–5526

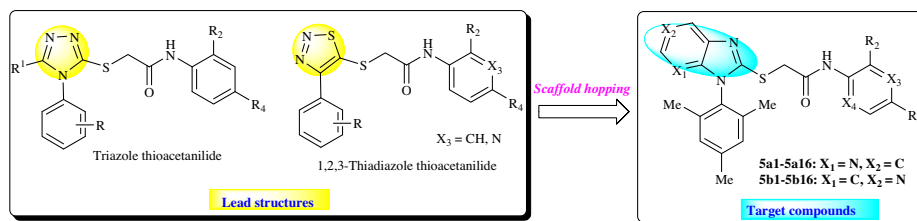
Atena Jabbari, Mahdiah Davoodnejad, Maliheh Alimardani, Amir Assadieskandar, Ali Sadeghian, Hadi Safdari, Jebraeel Movaffagh, Hamid Sadeghian*



Arylazolyl(azinyl)thioacetanilides. Part 10: Design, synthesis and biological evaluation of novel substituted imidazopyridinylthioacetanilides as potent HIV-1 inhibitors

pp 5527–5536

Xiao Li, Peng Zhan*, Hong Liu, Dongyue Li, Liu Wang, Xuwang Chen, Huiqing Liu, Christophe Pannecouque, Jan Balzarini, Erik De Clercq, Xinyong Liu*

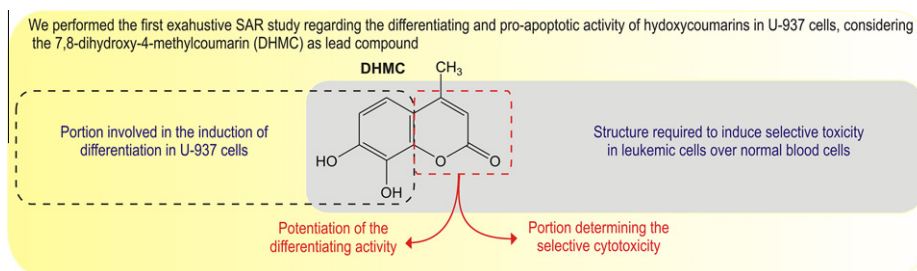


By means of scaffold hopping strategy, imidazopyridine was used as a new bioisostere to replace the five-membered heterocyclic lead structures. This strategy led to the identification of imidazopyridinylthioacetanilide NNRTIs with potency against HIV-1 replication in the low micromolar concentration range.

Structure-anti-leukemic activity relationship study of *ortho*-dihydroxycoumarins in U-937 cells: Key role of the δ -lactone ring in determining differentiation-inducing potency and selective pro-apoptotic action

pp 5537–5549

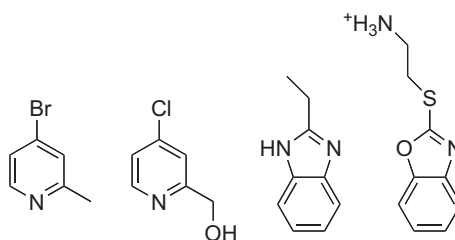
Ramiro Vázquez*, María E. Riveiro, Mónica Vermeulen, Eliana Alonso, Carolina Mondillo, Graciela Facorro, Lidia Piehl, Natalia Gómez, Albertina Moglioni, Natalia Fernández, Alberto Baldi, Carina Shayo, Carlos Davio*



Discovery of structurally-diverse inhibitor scaffolds by high-throughput screening of a fragment library with dimethylarginine dimethylaminohydrolase

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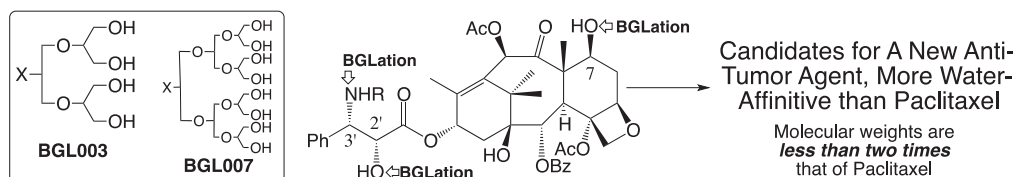
Thomas W. Linsky, Walter Fast*



Synthesis of Paclitaxel–BGL Conjugates

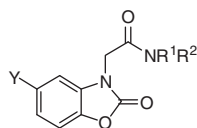
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Hisao Nemoto*, Ayato Katagiri, Masaki Kamiya, Tomoyuki Kawamura, Tsuyoshi Matsushita, Kosuke Matsumura, Tomohiro Itou, Hatsuhiko Hattori, Miho Tamaki, Keisuke Ishizawa, Licht Miyamoto, Shinji Abe, Koichiro Tsuchiya



Design, synthesis and structure–activity relationships of novel benzoxazolone derivatives as 18 kDa translocator protein (TSPO) ligands pp 5568–5582

Takayuki Fukaya*, Toru Kodo, Takeo Ishiyama, Hiroyoshi Kakuyama, Hiroyuki Nishikawa, Satoko Baba, Shuji Masumoto



14 (Y = Ph, R¹ = Me, R² = Ph) TSPO K_i = 1.6 nM

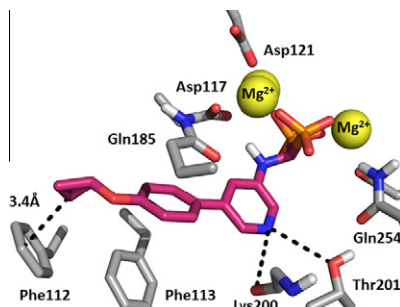
74 (Y = 3-Py, R¹ = Me, R² = Ph) TSPO K_i = 11 nM

Benzoxazolone derivatives were designed and synthesized as novel TSPO ligands. In view of initial SAR study, we selected compound **14** as lead compound. Further optimization of pharmacokinetic properties of compounds led to discovery of compound **74** which exhibited anxiolytic effect in the rat Vogel model.



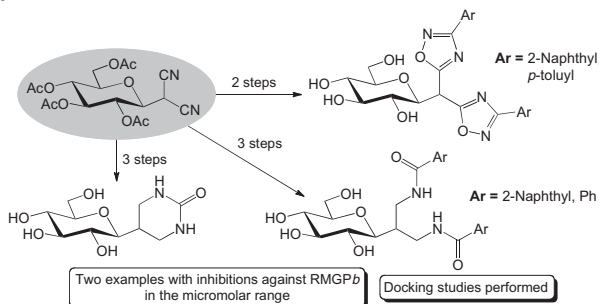
Design of potent bisphosphonate inhibitors of the human farnesyl pyrophosphate synthase via targeted interactions pp 5583–5591

Joris W. De Schutter, Joseph Shaw, Yih-Shyan Lin, Youla S. Tsantrizos*



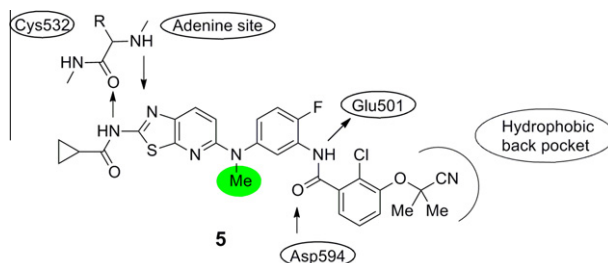
C-Glucosylated malonitrile as a key intermediate towards carbohydrate-based glycogen phosphorylase inhibitors pp 5592–5599

Sophie Feuillastre, Aikaterini S. Chajistamatiou, Constantinos Potamitis, Maria Zervou, Panagiotis Zoumpoulakis, Evangelia D. Chrysina*, Jean-Pierre Praly*, Sébastien Vidal*



Design and synthesis of novel DFG-out RAF/vascular endothelial growth factor receptor 2 (VEGFR2) inhibitors: 3. Evaluation of 5-amino-linked thiazolo[5,4-d]pyrimidine and thiazolo[5,4-b]pyridine derivatives pp 5600–5615

Masaaki Hirose*, Masanori Okaniwa*, Tohru Miyazaki, Takashi Imada, Tomohiro Ohashi, Yuta Tanaka, Takeo Arita, Masato Yabuki, Tomohiro Kawamoto, Shunichiro Tsutsumi, Akihiko Sumita, Terufumi Takagi, Bi-Ching Sang, Jason Yano, Kathleen Aertgeerts, Sei Yoshida, Tomoyasu Ishikawa*



pp 5616–5622

Figure 1 displays the chemical structures of compounds 1 and 2, and their antiviral activity against HCV and VSV.

Chemical Structures:

- Compound 1:** A cage-like structure with a central carbon atom bonded to four oxygen atoms, each connected to a hexamethylene chain ($\text{O}(\text{CH}_2)_6\text{O}$).
- Compound 2:** A truncated cone-shaped structure with a central carbon atom bonded to four oxygen atoms, each connected to a hexamethylene chain ($\text{O}(\text{CH}_2)_6\text{O}$).

Antiviral Assays:

The antiviral activity of compounds 1 and 2 was evaluated using the Anti-HCV assay and the Anti-VSV assay. The results are shown in the bar charts below.

Anti-HCV assay:

The Anti-HCV assay results show the relative luciferase activity (RLU) for compounds 1 and 2 at concentrations of 1 μM (light gray bars) and 5 μM (dark gray bars). The compounds tested are DMSO, CD-CD, C₂₁, and CD-C₂₁-CD.

Compounds	1 μM (RLU)	5 μM (RLU)
DMSO	~350,000	~350,000
CD-CD	~340,000	~350,000
C ₂₁	~360,000	~320,000
CD-C ₂₁ -CD	~80,000	~20,000

Anti-VSV assay:

The Anti-VSV assay results show the relative luciferase activity (RLU) for compounds 1 and 2 at concentrations of 1 μM (light gray bars) and 5 μM (dark gray bars). The compounds tested are DMSO, CD-CD, C₂₁, and CD-C₂₁-CD.

Compounds	1 μM (RLU)	5 μM (RLU)
DMSO	~650,000	~650,000
CD-CD	~680,000	~650,000
C ₂₁	~680,000	~620,000
CD-C ₂₁ -CD	~700,000	~650,000



pp 5623–5636

1

14f

hGHSR1a Binding, K_i = 8 nM
hGHSR1a CreLuc, IC_{50} = 7 nM

pp 5637–5641

Chemical structures of the linker and its attachment to the CCRF-CEM and CEM/ADR5000 cell lines. The linker is shown as a green box labeled "Linker". The linker is attached to the CCRF-CEM and CEM/ADR5000 cell lines via a linker group. The linker is shown as a green box labeled "Linker".

Cell Line	IC ₅₀ (CCR-CEM) [μM]	IC ₅₀ (CEM/ADR5000) [μM]
Linker	2.16	1.60
Linker	4.21	3.04



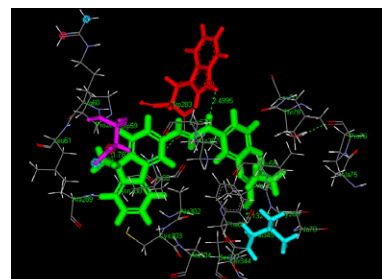
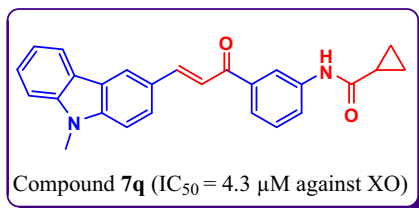
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Synthesis, biological evaluation, and molecular docking of *N*-[3-[3-(9-methyl-9*H*-carbazol-3-yl)-acryloyl]-phenyl]-benzamide/amide derivatives as xanthine oxidase and tyrosinase inhibitors

pp 5649–5657

Babasaheb P. Bandgar*, Laxman K. Adsul,
Hemant V. Chavan, Sadanand N. Shringare,
Balaji L. Korbadi, Shivkumar S. Jalde,
Shrikant V. Lonikar, Shivraj H. Nile, Amol L. Shirfule



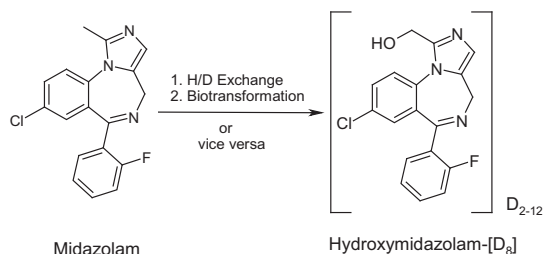
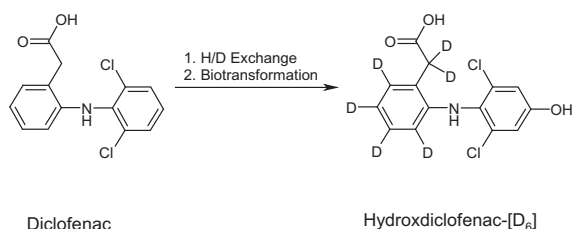
A series of *N*-[3-[3-(9-methyl-9*H*-carbazol-3-yl)-acryloyl]-phenyl]-benzamide/amide derivatives have been synthesized and investigated for their in vitro xanthine oxidase and tyrosinase inhibitory activities.



Synthesis of stable isotope labelled internal standards for drug–drug interaction (DDI) studies

pp 5658–5667

J. Atzrodt*, J. Blankenstein, D. Brasseur, S. Calvo-Vicente, M. Denoux, V. Deraud, M. Lavis, S. Perard, S. Roy, M. Sandvoss,
J. Schofield, J. Zimmermann



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
Corrigendum

p 5668

Bioorganic & Medicinal Chemistry Reviews and Perspectives

pp I–III

*Corresponding author

 Supplementary data available via SciVerse ScienceDirect

COVER

Shown are alternative activity landscape views for a set of adenosine A2 receptor ligands including a similarity-based compounds network (left) and a three-dimensional activity landscape representation (right). An arrow indicates corresponding areas of relatively low SAR information content. On the left, selected compound subsets are encircled. The color code reflects the potency distribution within the data set, ranging from low (green) over intermediate (yellow) to high (red) compound potency. Cover illustration provided by J. Bajorath.

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