

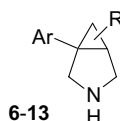
Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 13, 2008

Contents

ARTICLES

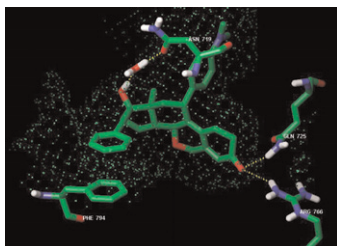
Studies on the structure–activity relationship of bicifadine analogs as monoamine transporter inhibitors pp 3682–3686

Mingzhu Zhang, Florence Jovic, Troy Vickers, Brian Dyck, Junko Tamiya, Jonathan Grey,
Joe A. Tran, Beth A. Fleck, Rebecca Pick, Alan C. Foster, Chen Chen*



Insight from molecular modeling into different conformation and SAR of natural steroids and unnatural 7-oxa-steroids pp 3687–3690

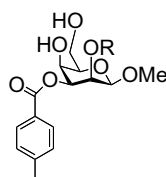
Fu-An Kang*, Xin Chen, Nareshkumar Jain, George Allan, Pamela Tannenbaum, Scott Lundeen, Zhihua Sui



Molecular modeling, in vivo activity, pharmacokinetic and metabolic properties of unnatural 7-oxa-steroids are reported.

Protein subtype-targeting through ligand epimerization: Talose-selectivity of galectin-4 and galectin-8 pp 3691–3694

Christopher T. Öberg, Helen Blanchard, Hakon Leffler, Ulf J. Nilsson*



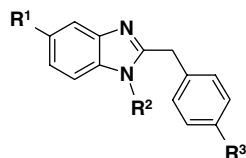
Galectin-4 C-terminal domain and galectin-8 N-terminal domain were found to prefer the α -talopyranose configuration to the natural ligand α -galactopyranose configuration. Methyl β - α -talopyranosides derivatized at O2 and O3 were synthesized and discovered to be selective submillimolar inhibitors of galectin-4C and galectin-8N.



Novel benzimidazole derivatives as selective CB2 agonists

pp 3695–3700

Daniel Pagé*, Elise Balaux, Luc Boisvert, Ziping Liu, Claire Milburn, Maxime Tremblay, Zhongyong Wei, Simon Woo, Xuehong Luo, Yun-Xing Cheng, Hua Yang, Sanjay Srivastava, Fei Zhou, William Brown, Mirosław Tomaszewski, Christopher Walpole, Leila Hodzic, Stéphane St-Onge, Claude Godbout, Dominic Salois, Keymal Payza

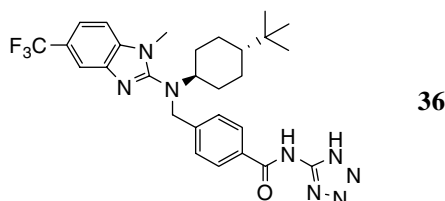


The preparation and evaluation of a novel class of CB2 agonists based on a benzimidazole scaffold are reported.

Discovery of potent, orally active benzimidazole glucagon receptor antagonists

pp 3701–3705

Ronald M. Kim*, Jiang Chang, Ashley R. Lins, Ed Brady, Mari R. Candelore, Qing Dallas-Yang, Victor Ding, Jasminka Dragovic, Susan Iliff, Guoqiang Jiang, Steven Mock, Sajjad Qureshi, Richard Saperstein, Deborah Szalkowski, Constantin Tamvakopoulos, Laurie Tota, Michael Wright, Xiaodong Yang, James R. Tata, Kevin Chapman, Bei B. Zhang, Emma R. Parmee

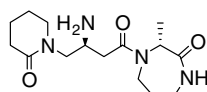


Potent and selective aminobenzimidazole glucagon receptor antagonists are described. Compound **36** was orally efficacious in blocking glucagon-dependent glucose production and in lowering glucose levels in an animal model of diabetes.

Discovery of new binding elements in DPP-4 inhibition and their applications in novel DPP-4 inhibitor design

pp 3706–3710

Gui-Bai Liang*, Xiaoxia Qian, Tesfaye Biftu, Suresh Singh, Ying-Duo Gao, Giovanna Scapin, Sangita Patel, Barbara Leiting, Reshma Patel, Joseph Wu, Xiaoping Zhang, Nancy A. Thornberry, Ann E. Weber



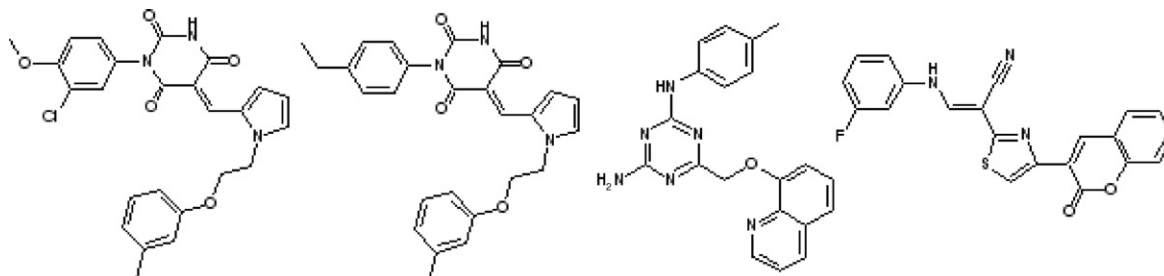
20a: IC₅₀ = 20 nM

The newly discovered aromatic fluorine H-bond and other binding elements in the DPP-4 inhibition were successfully incorporated into novel DPP-4 inhibitors such as **20a**.

Discovery and biological evaluation of novel α-glucosidase inhibitors with in vivo antidiabetic effect

pp 3711–3715

Hwangseo Park*, Kyo Yeol Hwang, Young Hoon Kim, Kyung Hwan Oh, Jae Yeon Lee, Keun Kim*

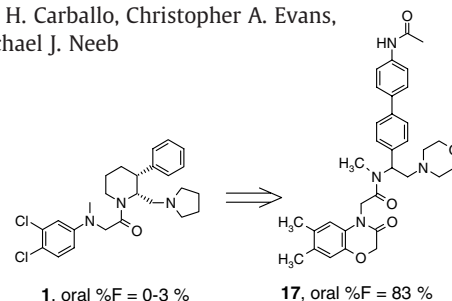


We have discovered four novel α-glucosidase inhibitors with in vivo antidiabetic effects by means of a drug design protocol involving the virtual screening with docking simulations, in vitro enzyme assay, and in vivo efficacy test.

Potent and selective small-molecule human urotensin-II antagonists with improved pharmacokinetic profiles pp 3716–3719

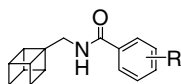
John J. McAtee*, Jason W. Dodson, Sarah E. Dowdell, Karl Erhard, Gerald R. Girard, Krista B. Goodman, Mark A. Hilfiker, Jian Jin, Clark A. Sehon, Deyou Sha, Dongchuan Shi, Feng Wang, Gren Z. Wang, Ning Wang, Yonghui Wang, Andrew Q. Viet, Catherine C. K. Yuan, Daohua Zhang, Nambi V. Aiyar, David J. Behm, Luz H. Carballo, Christopher A. Evans, Harvey E. Fries, Rakesh Nagilla, Theresa J. Roethke, Xiaoping Xu, Stephen A. Douglas, Michael J. Neeb

Redesign of the potent human urotensin-II antagonist **1** with the 2-pyrrolidinylmethyl-3-phenyl-piperidine core to a new chemical series with a substituted *N*-methyl-2-(1-pyrrolidinyl)ethanamine core as in **17** resulted in compounds with improved PK profiles.

**Cubyl amides: Novel P2X₇ receptor antagonists**

pp 3720–3723

Hendra Gunosewoyo, Jun Liu Guo, Maxwell R. Bennett, Mark J. Coster, Michael Kassiou*

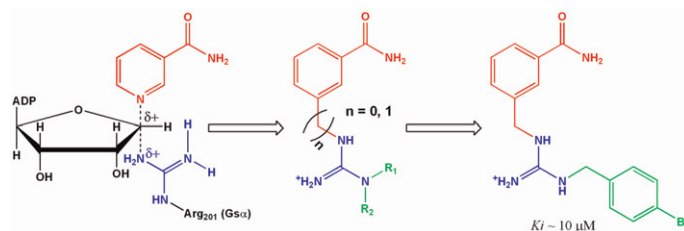


Cubyl amides were successfully synthesised. All synthesised compounds possessed P2X₇R antagonistic properties when tested on rat spinal cord microglia cells.

**Design, synthesis, and evaluation of bisubstrate analog inhibitors of cholera toxin**

pp 3724–3727

Guangtao Zhang*

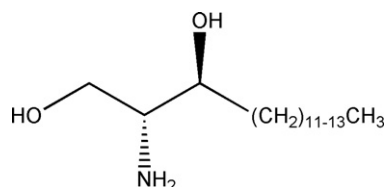


Bisubstrate analog inhibitors in which a nicotinamide mimetic is attached to a series of structurally diversified guanidines (arginine mimic) were synthesized and evaluated for inhibition of cholera toxin. Our results demonstrated that the mechanism-based bisubstrate inhibitors were up to 1400-fold more potent than natural substrate NAD⁺ and 400-fold more potent than the artificial substrate diethylamino (benzylidene-amino)guanidine (DEABAG) in an assay toward an intrinsically active mutant of wild-type cholera toxin.

Fungicidal activity of truncated analogues of dihydrosphingosine

pp 3728–3730

Karin Thevissen, Ulrik Hillaert, Els M. K. Meert, Kuen K. Chow, Bruno P. A. Cammue*, Serge Van Calenbergh, Isabelle E. J. A. François

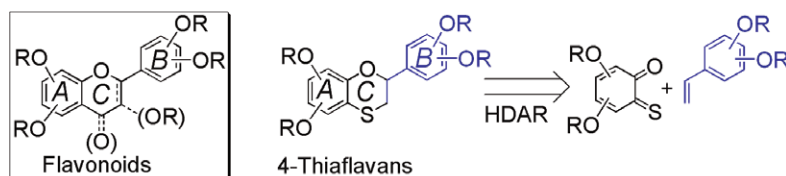


Truncated dihydrosphingosine (DHS) derivatives have been evaluated for antifungal activity. DHS derivatives with C15 or C17 showed 10-fold increased fungicidal activity against *Candida albicans* as compared to native DHS.

Antimycotic activity of 4-thioisosteres of flavonoids towards yeast and yeast-like microorganisms

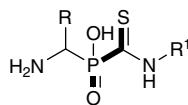
pp 3731–3733

Pietro Buzzini*, Stefano Menichetti*, Chiara Pagliuca, Caterina Viglianisi, Eva Branda, Benedetta Turchetti

Twelve derivatives tested on 21 microorganisms. MICs $\geq 8 \mu\text{g/mL}$ were observed.**First synthesis of α -aminoalkyl-(N-substituted)thiocarbamoyl-phosphinates: Inhibitors of aminopeptidase N (APN/CD13) with the new zinc-binding group**

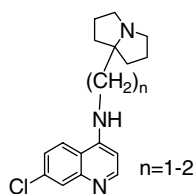
pp 3734–3736

Renata Grzywa, Józef Oleksyszyn*

Synthesis of new group of α -aminoalkyl-(N-substituted)thiocarbamoyl-phosphinates and their inhibitory activity towards aminopeptidase N are reported.**Antimalarial activity of novel pyrrolizidinyl derivatives of 4-aminoquinoline**

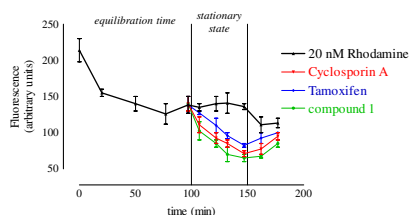
pp 3737–3740

Anna Sparatore*, Nicoletta Basilico, Manolo Casagrande, Silvia Parapini, Donatella Taramelli, Reto Brun, Sergio Wittlin, Fabio Sparatore

New orally efficacious chloroquine analogs with excellent activity on CQ-R strains of *P. falciparum*.**Effect of some P-glycoprotein modulators on Rhodamine-123 absorption in guinea-pig ileum**

pp 3741–3744

Nicola Antonio Colabufo*, Francesco Berardi, Marialessandra Contino, Carmela Inglese, Mauro Niso, Roberto Perrone

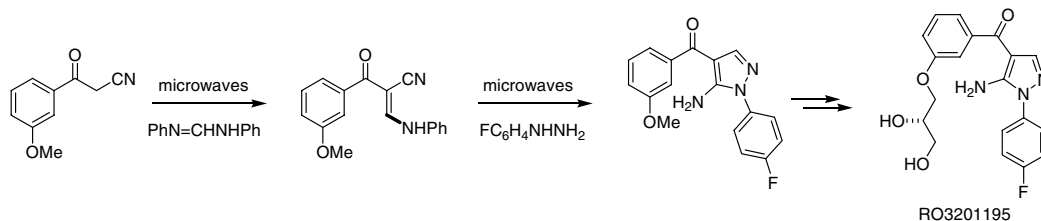


The inhibition of Rhodamine-123 efflux in guinea-pig ileum by several P-gp inhibitors is reported.

Microwave-assisted synthesis of 5-aminopyrazol-4-yl ketones and the p38^{MAPK} inhibitor RO3201195 for study in Werner syndrome cells

pp 3745–3748

Mark C. Bagley*, Terence Davis*, Matthew C. Dix, Paola G. S. Murziani, Michal J. Rokicki, David Kipling*

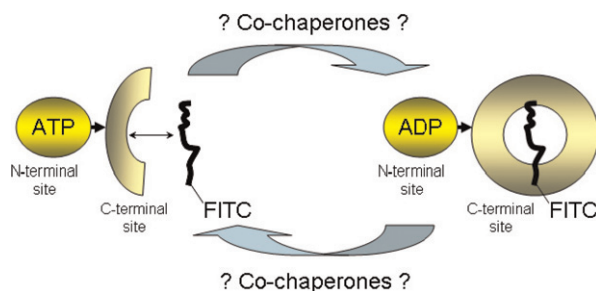


5-Aminopyrazol-4-yl ketones can be prepared rapidly and efficiently using microwave heating for elaboration to the p38 α MAP kinase inhibitor, RO3201195, which shows very high selectivity in Werner syndrome cells over JNK kinase.

Design of a fluorescence polarization assay platform for the study of human Hsp70

pp 3749–3751

Yanlong Kang, Tony Taldone, Cristina C. Clement, Sheara W. Fewell, Julia Aguirre, Jeffrey L. Brodsky, Gabriela Chiosis*

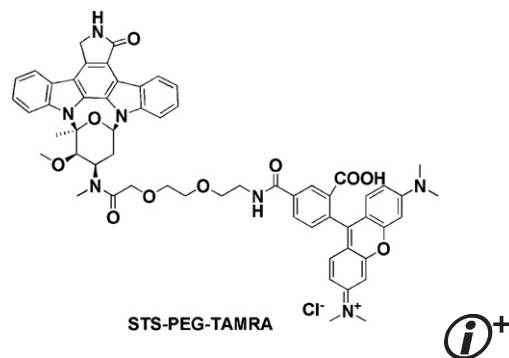


Development of a novel fluorescent probe for fluorescence correlation spectroscopic detection of kinase inhibitors

pp 3752–3755

Mitsuyasu Kawaguchi, Takuya Terai, Rei Utata, Miki Kato, Keiko Tsuganezawa, Akiko Tanaka, Hirotatsu Kojima, Takayoshi Okabe, Tetsuo Nagano*

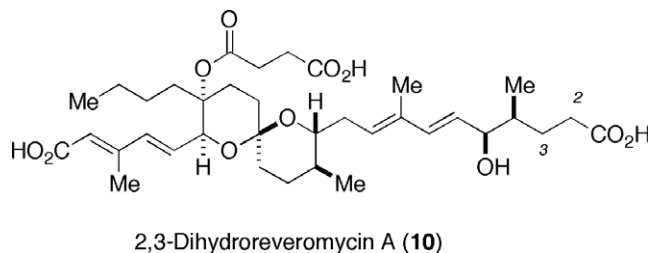
With this probe, we successfully evaluated the inhibitory activities of known inhibitors of ASK1.



Synthesis and biological activities of reveromycin A and spirofungin A derivatives

pp 3756–3760

Takeshi Shimizu*, Takeo Usui, Makoto Fujikura, Makoto Kawatani, Tomoharu Satoh, Kiyotaka Machida, Naoki Kanoh, Je-Tae Woo, Hiroyuki Osada, Mikiko Sodeoka



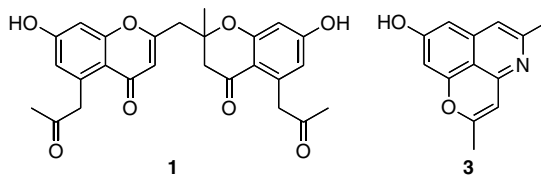
2,3-Dihydroreveromycin A (10)

Various derivatives of reveromycin A and spirofungin A were synthesized and their inhibitory effects on both the isoleucyl-tRNA synthetase activity and the survival of osteoclasts were examined.

Chrobisiamone A, a new bischromone from *Cassia siamea* and a biomimetic transformation of 5-acetonil-7-hydroxy-2-methylchromone into cassiarin A

pp 3761–3763

Shiori Oshimi, Yuichiro Tomizawa, Yusuke Hirasawa, Toshio Honda, Wiwied Ekasari, Aty Widyawaruyanti, Marcellino Rudyanto, Gunawan Indrayanto, Noor Cholies Zaini, Hiroshi Morita*

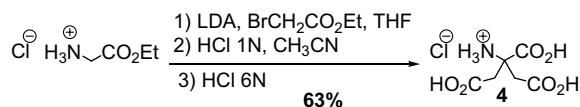


A new bischromone, chrobisiamone A (**1**) with an antiplasmodial activity has been isolated from the leaves of *Cassia siamea* and the structure was elucidated by 2D NMR analysis. Cyclization of 5-acetonil-7-hydroxy-2-methylchromone (**2**) in the presence of ammonium acetate resulted in generation of cassiarin A (**3**) with an unprecedented tricyclic skeleton, supporting a biogenetic pathway proposed for **3**.

2-Aminopropane-1,2,3-tricarboxylic acid: Synthesis and co-crystallization with the class A β -lactamase BS3 of *Bacillus licheniformis*

pp 3764–3768

Joséphine Beck, Eric Sauvage, Paulette Charlier, Jacqueline Marchand-Brynaert*

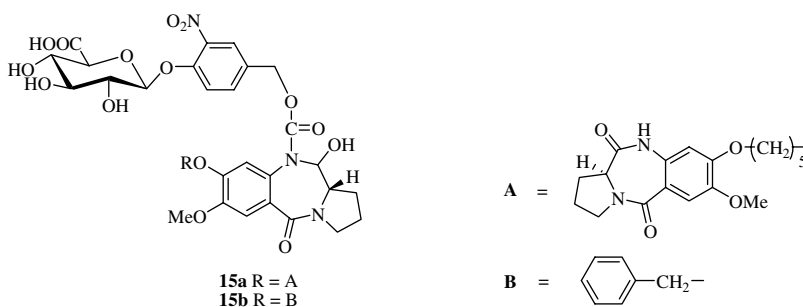


Synthesis and biochemical evaluation against β -lactamases of amino analog of citric acid are presented. The structure of the complex aminocitrate-BS3 has been analyzed by X-ray diffraction and compared to ones with citrate and isocitrate.


Pyrrolo[2,1-c][1,4]benzodiazepine- β -glucuronide prodrugs with a potential for selective therapy of solid tumors by PMT and ADEPT strategies

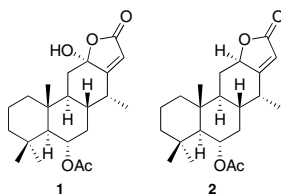
pp 3769–3773

Ahmed Kamal*, Venkatesh Tekumalla, P. Raju, V. G. M. Naidu, Prakash V. Diwan, Ramakrishna Sistla


Sucutiniranes A and B, new cassane-type diterpenes from *Bowdichia nitida*

pp 3774–3777

Yosuke Matsuno, Jun Deguchi, Yusuke Hirasawa, Kunio Ohyama, Hiroo Toyoda, Chieko Hirobe, Wiwied Ekasari, Aty Widyawaruyanti, Noor Cholies Zaini, Hiroshi Morita*

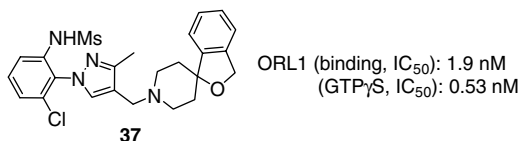


Two new diterpenes, sucutiniranes A (**1**) and B (**2**), have been isolated from *Bowdichia nitida*. Sucutinirane A (**1**) and 6 α -acetoxyvouacapanone (**3**) showed a moderate cytotoxicity and 6 α ,7 β -diacetoxyvouacapanone (**4**) showed in vitro antiplasmodial activity against parasite *Plasmodium falciparum* 3D7.

Design, synthesis, and structure–activity relationship study of a novel class of ORL1 receptor antagonists based on *N*-biaryl methyl spiropiperidine

pp 3778–3782

Takashi Yoshizumi*, Hiroshi Miyazoe, Hirokatsu Ito, Tomohiro Tsujita, Hirobumi Takahashi, Masanori Asai, Satoshi Ozaki, Hisashi Ohta, Osamu Okamoto

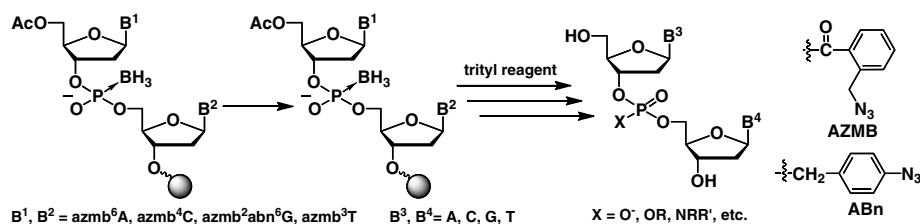


A focused library of biaryl methyl bound to the nitrogen atom of spiropiperidine was designed. Systematic modifications allowed the discovery of a synthetically feasible and highly potent ORL1 antagonist **37**.

Solid-phase synthesis of backbone-modified DNA analogs by the boranophosphotriester method using new protecting groups for nucleobases

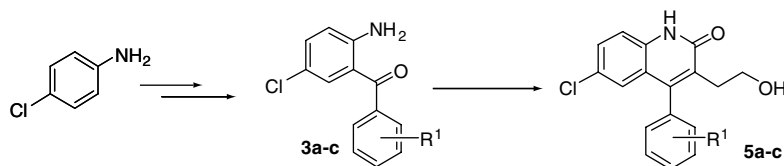
pp 3783–3786

Toshihide Kawanaka, Mamoru Shimizu, Noriko Shintani, Takeshi Wada*

**Synthesis and in vitro anti-hepatitis B virus activities of 4-aryl-6-chloro-quinolin-2-one and 5-aryl-7-chloro-1,4-benzodiazepine derivatives**

pp 3787–3789

Pi Cheng, Quan Zhang, Yun-Bao Ma, Zhi-Yong Jiang, Xue-Mei Zhang, Feng-Xue Zhang, Ji-Jun Chen*

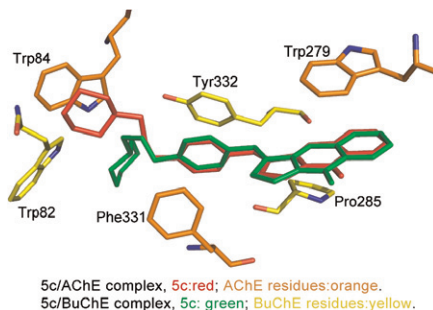


3-Hydroxyethyl-4-aryl-6-chloro-quinolin-2-ones (**5a-c**) exhibited inhibitory activities on the secretion of HBsAg and HBeAg in HBV infected Hep G2.2.15 cells.

**Design, synthesis and evaluation of isaindigotone derivatives as acetylcholinesterase and butyrylcholinesterase inhibitors**

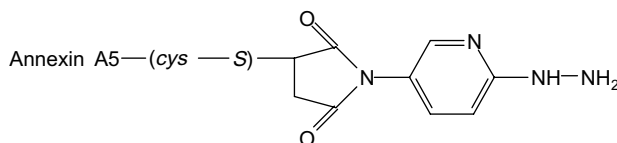
pp 3790–3793

Li Pan, Jia-Heng Tan, Jin-Qiang Hou, Shi-Liang Huang, Lian-Quan Gu, Zhi-Shu Huang*



Preliminary in vivo evaluation of a novel ^{99m}Tc -Labeled HYNIC-cys-annexin A5 as an apoptosis imaging agent pp 3794–3798

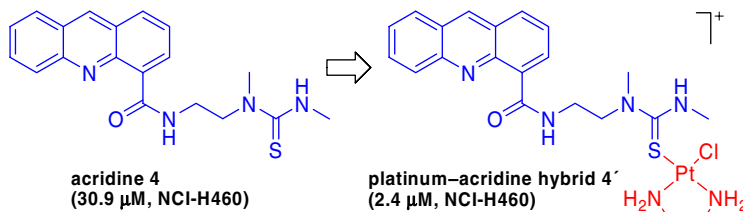
Humphrey Fonge, Marijke de Saint Hubert, Kathleen Vunckx, Dirk Rattat, Johan Nuyts, Guy Bormans, Yicheng Ni, Chris Reutelingsperger, Alfons Verbruggen*



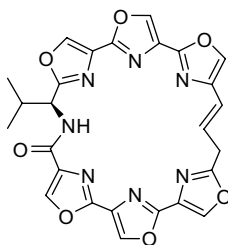
The study describes the preliminary evaluation of technetium-99m-labeled novel 'site-specific' HYNIC-cys-annexin A5 as an apoptosis imaging radiotracer in animal models of hepatic apoptosis and acute myocardial infarction.

Effect of linkage geometry on biological activity in thiourea- and guanidine-substituted acridines and platinum-acridines pp 3799–3801

Zhidong Ma, Gilda Saluta, Gregory L. Kucera, Ulrich Bierbach*

**Ring-closing metathesis for the synthesis of a highly G-quadruplex selective macrocyclic hexaoxazole having enhanced cytotoxic potency** pp 3802–3804

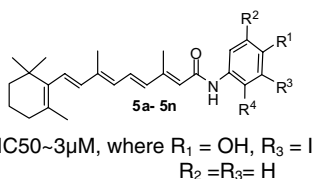
Mavurapu Satyanarayana, Suzanne G. Rzuczek, Edmond J. LaVoie, Daniel S. Pilch, Angela Liu, Leroy F. Liu, Joseph E. Rice*



Ring-closing metathesis was employed for the synthesis of a highly G-quadruplex selective and cytotoxic macrocyclic hexaoxazole.

Design and synthesis of 4-HPR derivatives for rhabdoid tumors pp 3805–3808

Bhaskar C. Das*, Melissa E. Smith, Ganjam V. Kalpana*



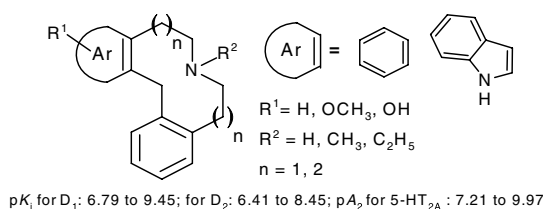
Synthetic Derivatives of 4-HPR with halogen substitutions are active against rhabdoid tumors.



**Dopamine/serotonin receptor ligands. Part 17: A cross-target SAR approach:
Affinities of azecine-styled ligands for 5-HT_{2A} versus D₁ and D₂ receptors**

pp 3809–3813

Christoph Enzensperger, Tilo Görnemann, Heinz H. Pertz, Jochen Lehmann*

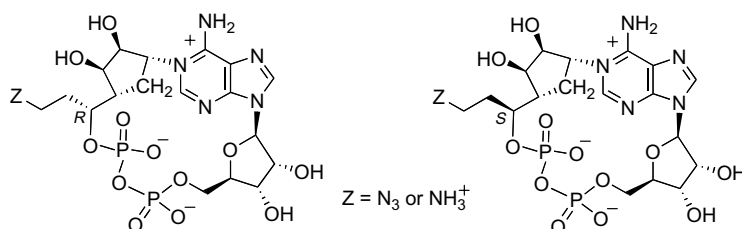


A cross-target SAR was conducted with 13 azecine-styled compounds on D₁, D₂ and 5-HT_{2A} receptors. Surprisingly, molecular modifications affect the affinity for the D₁ receptor in the same manner as the 5-HT_{2A} receptor. The protein–ligand interactions were discussed with respect to the different binding pockets.

**Synthesis of 5''-branched derivatives of cyclic ADP-carbocyclic-ribose, a potent Ca²⁺-mobilizing agent:
The first antagonists modified at the N1-ribose moiety**

pp 3814–3818

Natsumi Sakaguchi, Takashi Kudoh, Takayoshi Tsuzuki, Takashi Murayama, Takashi Sakurai, Akira Matsuda, Mitsuhiro Arisawa, Satoshi Shuto*

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*Corresponding author

Supplementary data available via ScienceDirect

COVER

Overlay of high resolution co-crystal structures of **R-22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5677.]

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