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Special Section: Symposium-in-Print

G-Protein-Coupled Receptors in Drug Discovery

Guest Editor: John Saunders

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Bioorganic & Medicinal Chemistry Letters Symposia-in-Print
Introduction: G-protein-coupled receptors in drug discovery

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SYMPOSIUM-IN-PRINT COMMUNICATIONS

Structural biology of G protein-coupled receptors
Kenneth Lundstrom

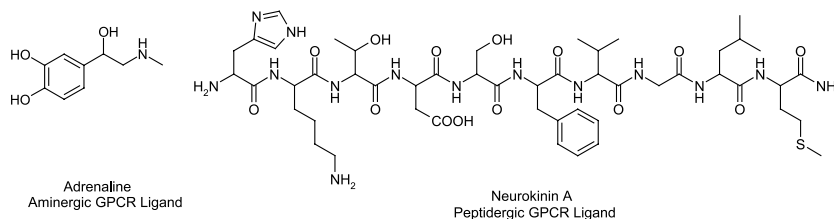
pp 3654–3657

More than 60% of the current drugs are based on G protein-coupled receptors. Paradoxically, high-resolution structures are not available to facilitate rational drug design. Difficulties in expression, purification, and crystallization of these transmembrane receptors are the reasons for the low success rate. Recent individual and network-based technology development has significantly improved our knowledge of structural biology and might soon bring a major breakthrough in this area.

Oral delivery of G protein-coupled receptor modulators: An explanation for the observed class difference

pp 3658–3664

Kevin Beaumont,* Esther Schmid and Dennis A. Smith



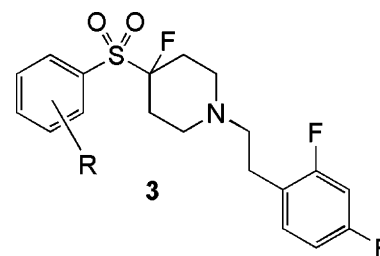
There is a distinct class difference between the number of drugs against aminergic and non-aminergic GPCRs. The difference lies with the natural ligands.

4-Fluorosulfonylpiperidines: Selective 5-HT_{2A} ligands for the treatment of insomnia

pp 3665–3669

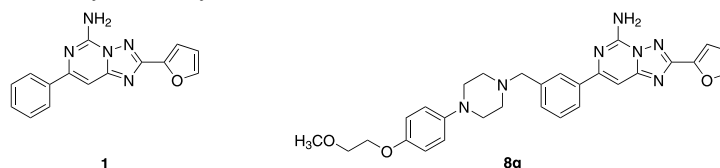
L. Rebecca Fish, Myra T. Gilligan, Alexander C. Humphries,* Magnus Ivarsson, Tammy Ladduwahetty,* Kevin J. Merchant, Desmond O'Connor, Smita Patel, Elisabeth Philipps, Hugo M. Vargas, Peter H. Hutson and Angus M. MacLeod

α -Fluorosulfones, of general structure **3**, were synthesized as an alternative approach to reduce the pK_a of the piperidine ring in an existing series of sulfonyl piperidine 5-HT_{2A} antagonists. This work led to the identification of **3b**, a selective 5-HT_{2A} antagonist that gave no significant increase in QT_c in the anesthetized dog.

**2-(2-Furanyl)-7-phenyl[1,2,4]triazolo[1,5-c]pyrimidin-5-amine analogs: Highly potent, orally active, adenosine A_{2A} antagonists. Part 1**

pp 3670–3674

Julius J. Matasi, John P. Caldwell, Hongtao Zhang, Ahmad Fawzi, Mary E. Cohen-Williams, Geoffrey B. Varty and Deen B. Tulshian*

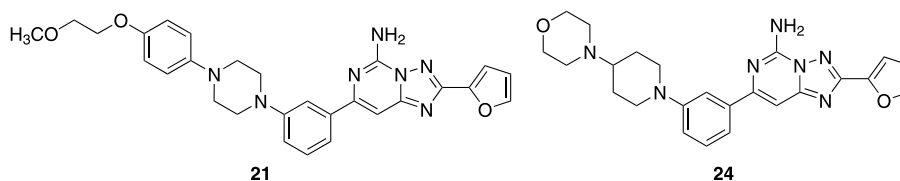


The structure–activity relationship of this novel class of compounds based on 2-(2-furanyl)-7-phenyl[1,2,4]triazolo[1,5-c]pyrimidin-5-amine, **1**, and its analogs was evaluated for their in vitro and in vivo adenosine A_{2A} receptor antagonism. Compound **8g** displayed an excellent in vitro profile as well as a highly promising in vivo profile.

2-(2-Furanyl)-7-phenyl[1,2,4]triazolo[1,5-c]pyrimidin-5-amine analogs as adenosine A_{2A} antagonists: The successful reduction of hERG activity. Part 2

pp 3675–3678

Julius J. Matasi, John P. Caldwell, Hongtao Zhang, Ahmad Fawzi, Guy A. Higgins, Mary E. Cohen-Williams, Geoffrey B. Varty and Deen B. Tulshian*



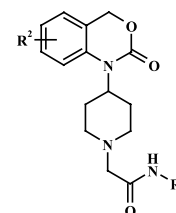
This report discusses the strategy and outcome of an expanded SAR focused on addressing the hERG liability. As a result, compounds **21** and **24** possess excellent in vitro profiles, highly promising in vivo profiles, and acceptable levels of hERG channel inhibition.

A preliminary study of the metabolic stability of a series of benzoxazinone derivatives as potent neuropeptide Y5 antagonists

pp 3679–3684

Alberto Dordal, Mike Lipkin, Jackie Macritchie,* Josep Mas, Adriana Port, Sally Rose, Leonardo Salgado, Vladimir Savic, Wolfgang Schmidt, Maria Teresa Serafini, William Spearing, Antoni Torrens* and Sandra Yeste

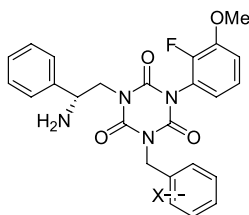
The metabolic stability of benzoxazinone derivatives, a potent series of NPY5 antagonists, has been investigated. This study identified the moieties prone to metabolic transformation and provides the opportunity to optimize the structure of this new class of NPY5 antagonists.



Structure–activity relationships of 1,3,5-triazine-2,4,6-triones as human gonadotropin-releasing hormone receptor antagonists

pp 3685–3690

Zhiqiang Guo,* Dongpei Wu, Yun-Fei Zhu, Fabio C. Tucci, Collin F. Regan, Martin W. Rowbottom, R. Scott Struthers, Qiu Xie, Shelby Reijmers, Susan K. Sullivan, Yang Sai and Chen Chen*

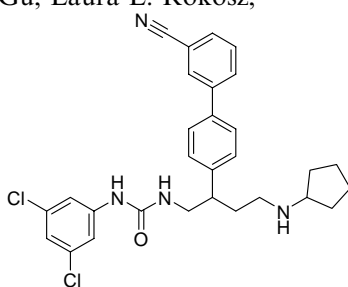


SAR studies of 1,3,5-triazine-2,4,6-triones as human gonadotropin-releasing receptor antagonists resulted in potent compounds. The best compound from the series had a binding affinity of 2 nM.

Discovery and SAR of 4-amino-2-biarylbutylurea MCH 1 receptor antagonists through solid-phase parallel synthesis

pp 3691–3695

Tao Guo,* Rachael C. Hunter, Huizhong Gu, Laura L. Rokosz, Tara M. Stauffer and Doug W. Hobbs

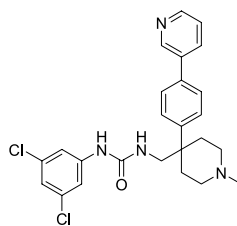


11g
MCH1R K_i = 3.0 nM

Discovery and SAR of biaryl piperidine MCH1 receptor antagonists through solid-phase encoded combinatorial synthesis

pp 3696–3700

Tao Guo,* Yuefei Shao, Gang Qian, Laura L. Rokosz, Tara M. Stauffer, Rachael C. Hunter, Suresh D. Babu, Huizhong Gu and Doug W. Hobbs

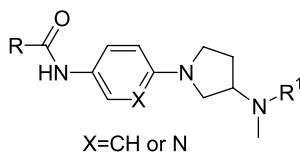


8e
MCH1R K_i = 3.1 nM

1-(4-Amino-phenyl)-pyrrolidin-3-yl-amine and 6-(3-amino-pyrrolidin-1-yl)-pyridin-3-yl-amine derivatives as melanin-concentrating hormone receptor-1 antagonists

pp 3701–3706

Charles Q. Huang, Tracy Baker, David Schwarz, Jun Fan, Christopher E. Heise, Mingzhu Zhang, Val S. Goodfellow, Stacy Markison, Kathleen R. Gogas, Takung Chen, Xiao-Chuan Wang and Yun-Fei Zhu*



I

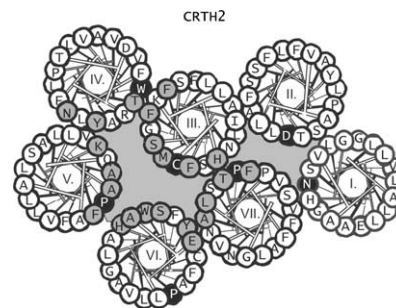
Derivatives of 1-(4-amino-phenyl)-pyrrolidin-3-yl-amine and 6-(3-amino-pyrrolidin-1-yl)-pyridin-3-yl-amine (**I**) were identified as potent and functionally active MCH receptor-1 (MCH-R1) antagonists. The compound **10** with K_i = 2.3 nM demonstrated good oral bioavailability (32%) and in vivo efficacy in rats.

A phylogenetic method to assign ligand-binding relationships between 7TM receptors

pp 3707–3712

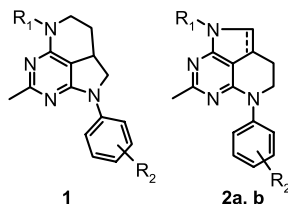
Thomas M. Frimurer, Trond Ulven, Christian E. Elling, Lars-Ole Gerlach,
Evi Kostenis and Thomas Högberg*

A computational protocol has been devised to relate 7TM receptor proteins (GPCRs) with respect to physicochemical features of the core ligand-binding site. A case targeting the newly identified prostaglandin D2 receptor CRTH2 serves as a primary example to illustrate the procedure.

**Substituted tetraazaacenaphthylenes as potent CRF₁ receptor antagonists for the treatment of depression and anxiety**

pp 3713–3716

Y. St-Denis,* R. Di Fabio,* G. Bernasconi, E. Castiglioni, S. Contini, D. Donati,
E. Fazzolari, G. Gentile, D. Ghirlanda, C. Marchionni, F. Messina, F. Micheli,
F. Pavone, A. Pasquarello, F. M. Sabbatini, M. G. Zampori, R. Arban and G. Vitulli

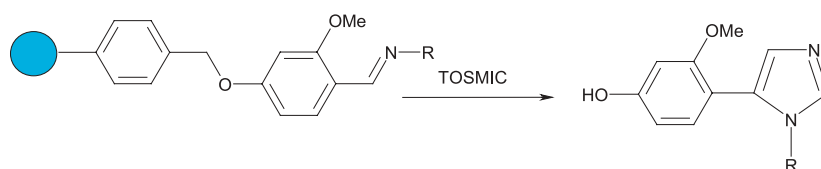


The synthesis, SAR, and in vivo characterization of a novel class of CRF₁ antagonist are reported.

REGULAR COMMUNICATIONS**Microwave-assisted synthesis of imidazoles: Reaction of *p*-toluenesulfonylmethyl isocyanide and polymer-bound imines**

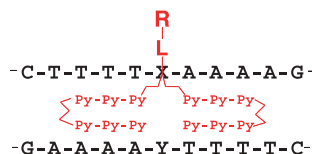
pp 3717–3719

Swapan K. Samanta, Irene Kylänlahti and Jari Yli-Kauhaluoma*

**Functionalized head-to-head hairpin polyamides: Synthesis, double-stranded DNA-binding activity and affinity**

pp 3720–3724

Ludovic Halby, Vladimir A. Ryabinin, Alexandre N. Sinyakov and Alexandre S. Boutorine*



In vitro binding of leukotriene B₄ (LTB₄) to human serum albumin: Evidence from spectroscopic, molecular modeling, and competitive displacement studies

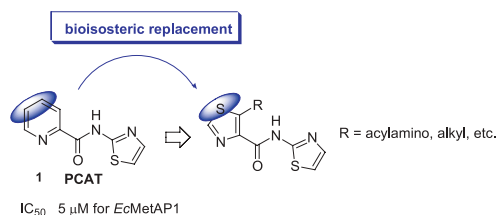
pp 3725–3731

Ferenc Zsila,* Zsolt Bikádi and Samuel F. Lockwood

Binding of leukotriene B₄ to the IIIA domain of human serum albumin is reported.**Identification of potent type I MetAP inhibitors by simple bioisosteric replacement. Part 1: Synthesis and preliminary SAR studies of thiazole-4-carboxylic acid thiazol-2-ylamide derivatives**

pp 3732–3736

Yong-Mei Cui, Qing-Qing Huang, Jie Xu, Ling-Ling Chen, Jing-Ya Li, Qi-Zhuang Ye, Jia Li* and Fa-Jun Nan*

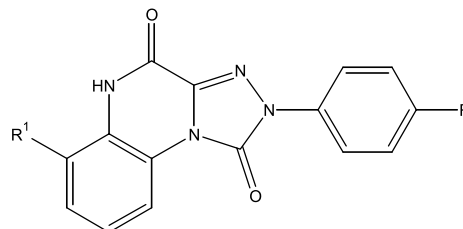


A new series of potent type I MetAP inhibitors were obtained by simple bioisosteric replacement of previously reported pyridine-2-carboxylic acid thiazol-2-ylamide (PCAT) MetAP inhibitors.

QSAR of adenosine A₃ receptor antagonist 1,2,4-triazolo[4,3-*a*]quinoxalin-1-one derivatives using chemometric tools

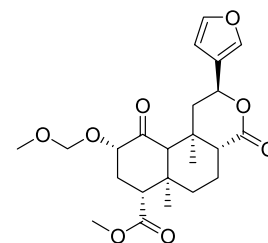
pp 3737–3743

Prosenjit Bhattacharya and Kunal Roy*

Considering the potential of selective adenosine A₃ receptor subtype ligands in the development of prospective therapeutic agents, an attempt has been made to explore physicochemical requirements of 1,2,4-triazolo[4,3-*a*]quinoxalin-1-one derivatives for A₃ receptor binding.**Synthesis and in vitro pharmacological studies of new C(2) modified salvinorin A analogues**

pp 3744–3747

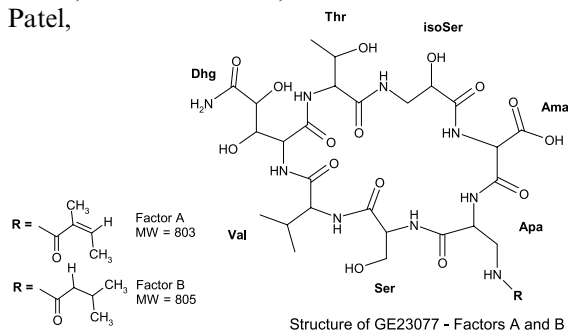
David Y. W. Lee, Vishnu V. R. Karnati, Minsheng He, Lee-Yuan Liu-Chen, Leelakrishna Kondaveti, Zhongze Ma, Yulin Wang, Yong Chen, Cecile Beguin, William A. Carlezon, Jr. and Bruce Cohen*

A series of salvinorin A derivatives modified at the C(2) position were prepared and screened for binding and functional activities at the human κ -opioid receptor. A highly selective κ -agonist (EC_{50} = 0.6 nM) was identified.4 ED_{50} = 0.6 nM

Antibiotics GE23077, novel inhibitors of bacterial RNA polymerase. Part 3: Chemical derivatization pp 3748–3752

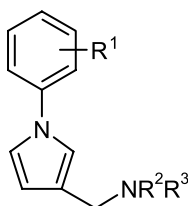
Riccardo Mariani,* Giorgio Granata, Sonia I. Maffioli, Stefania Serina, Cristina Brunati, Margherita Sosio, Alessandra Marazzi, Alfredo Vannini, Dinesh Patel, Richard White and Romeo Ciabatti

Chemical derivatization of a novel inhibitor of bacterial RNA polymerase GE23077 ($IC_{50} = 0.02$ mg/l) is reported.

**Phenylpyrroles, a new chemolibrary virtual screening class of 5-HT₇ receptor ligands**

pp 3753–3757

Magalie Paillet-Loilier, Frédéric Fabis, Alban Lepaillieur, Ronan Bureau, Sabrina Butt-Gueulle, François Dauphin, Catherine Delarue, Hubert Vaudry and Sylvain Rault*

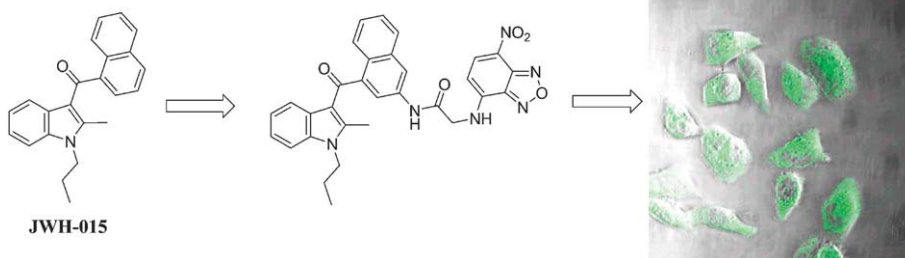


Virtual screening studies have identified a series of phenylpyrroles as novel 5-HT₇ receptor ligands. The synthesis and the affinity for the 5-HT₇ receptor of these phenylpyrroles are described. Some of these compounds exhibited high affinity for the 5-HT₇ receptors.

Chemical modification of the naphthoyl 3-position of JWH-015: In search of a fluorescent probe to the cannabinoid CB₂ receptor

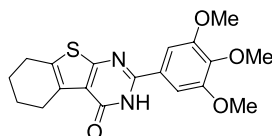
pp 3758–3762

Andrew S. Yates, Stephen W. Doughty, David A. Kendall and Barrie Kellam*

**Inhibition of tumor cell proliferation by thieno[2,3-*d*]pyrimidin-4(1*H*)-one-based analogs**

pp 3763–3766

Yanong D. Wang,* Steven Johnson, Dennis Powell, John P. McGinnis, Miriam Miranda and Sridhar K. Rabindran

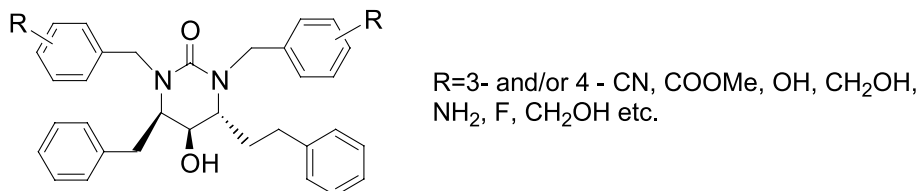


The synthesis of a series of novel tricyclic thieno[2,3-*d*]pyrimidin-4(1*H*)-one-based analogs and their anti-proliferative activities are described.

Hydrophobicity in the design of P2/P2' tetrahydropyrimidinone HIV protease inhibitors

pp 3767–3770

Rajni Garg* and Disha Patel

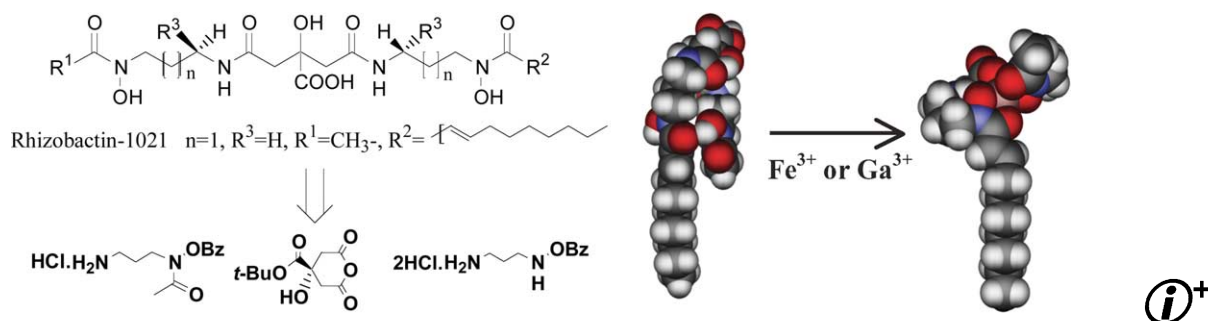


Balance of hydrophobicity and volume dependent polarizability has been found to play a key role in the inhibition of HIV protease by these inhibitors.

Synthesis and structural modeling of the amphiphilic siderophore rhizobactin-1021 and its analogs

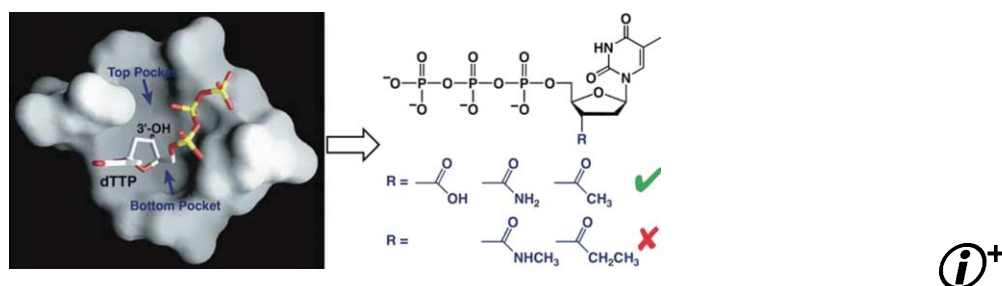
pp 3771–3774

Evgeny A. Fadeev, Minkui Luo and John T. Groves*

**Structure-based design, synthesis, and in vitro assay of novel nucleoside analog inhibitors against HIV-1 reverse transcriptase**

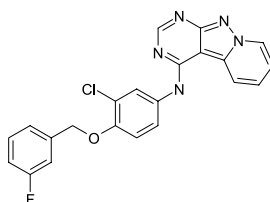
pp 3775–3777

Xianjun Liu, Wei Xie and Raven H. Huang*

**Discovery and in vitro evaluation of potent kinase inhibitors: Pyrido[1',2':1,5]pyrazolo[3,4-d]pyrimidines**

pp 3778–3781

Michael J. Alberti, Elizabeth P. Auten, Karen E. Lackey, Ochterloney B. McDonald, Edgar R. Wood, Frank Preugschat, Geoffrey J. Cutler, Laurie Kane-Carson, Wei Liu and David K. Jung*

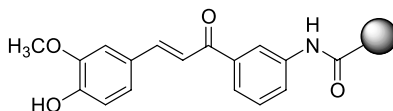


The discovery, synthesis, and in vitro kinase profile of several pyrido[1',2':1,5]pyrazolo[3,4-d]pyrimidines as potent kinase inhibitors are discussed.

Synthesis of novel curcumin mimics with asymmetrical units and their anti-angiogenic activity

pp 3782–3786

Ho Bum Woo, Woon-Seob Shin, Seokjoon Lee and Chan Mug Ahn*

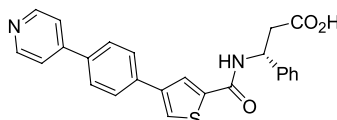


● : alkyl, chloro-substituted phenyl and heteroaromatic

Structure-based design and synthesis of novel non-zinc chelating MMP-12 inhibitors

pp 3787–3790

Anne-Claude Dublanchet,* Pierre Ducrot, Charles Andrianjara, Margaret O’Gara, Renaud Morales, Delphine Compère, Alexis Denis, Stéphane Blais, Philippe Cluzeau, Karine Courté, Jacques Hamon, François Moreau, Marie-Laure Prunet and Anita Tertre

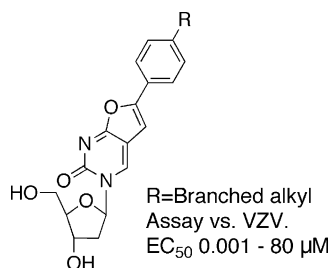


A new class of MMP-12 inhibitors was discovered and optimized using structure-based drug design methods. Optimization resulted in the discovery of a compound displaying nanomolar activity against MMP-12 which was co-crystallized with MMP-12.

Bicyclic nucleoside inhibitors of Varicella–Zoster virus: The effect of branching in the *p*-alkylphenyl side chain

pp 3791–3796

Giovanna Luoni, Christopher McGuigan,* Graciela Andrei, Robert Snoeck, Erik De Clercq and Jan Balzarini



R=Branched alkyl
Assay vs. VZV.
EC₅₀ 0.001 - 80 μM

Effects of B group vitamins on reactions of various α-hydroxyl-containing organic radicals

pp 3797–3800

P. Yu. Lagutin and O. I. Shadyro*

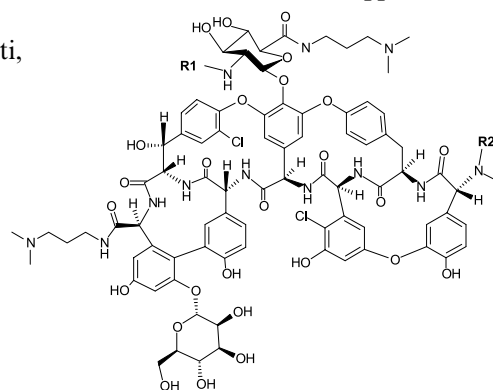
The interaction of α-hydroxyl-containing organic radicals with B group vitamins is reported.

Synthesis and antibacterial activity of alkyl derivatives of the glycopeptide antibiotic A40926 and their amides

pp 3801–3805

Sonia I. Maffioli,* Romeo Ciabatti, Gabriella Roman, Ettore Marzorati, Maria Preobrazhenskaya and Andrej Pavlov

Lipophilic alkylated derivatives of A40926 containing basic amides showed a strong increase in antibiotic activity.

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Contributors to this issue

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Instructions to contributors

pp III–VI

*Corresponding author

 Supplementary data available via ScienceDirect**COVER**

Schematic representation of the secondary structure elements of a rhodopsin-like 7TM receptor. The conserved key residues numbered according to the generic numbering system are highlighted in black. [Frimurer, T. M.; Ulven, T.; Elling, C. E.; Gerlach, L.-O.; Kostenis, E.; Högberg, T. *Bioorg. Med. Chem. Lett.* **2005**, 15, 3707.]



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