

Bioorganic & Medicinal Chemistry Vol. 14, No. 14, 2006

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Gopal Bose, Karin Bracht, Patrick J. Bednarski, Michael Lalk* and Peter Langer*

Synthesis and antibacterial activity of substituted flavones, 4-thioflavones and 4-iminoflavones

pp 4704-4711

Ehsan Ullah Mughal, Muhammad Ayaz, Zakir Hussain,* Aurangzeb Hasan, Amina Sadiq, Muhammad Riaz, Abdul Malik, Samreen Hussain and M. Iqbal Choudhary

OH
$$R_1$$

$$S \text{ steps}$$

$$R_2$$

$$R_3$$

$$R_4$$

$$X = O, S, 2,4-DNPH$$

Closing in on the AMPA receptor: Synthesis and evaluation of 2-acetyl-1-(4'-chlorophenyl)-6-methoxy-7-[11C]methoxy-1,2,3, 4-tetrahydroisoquinoline as a potential PET tracer

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Erik Årstad,* Rosaria Gitto, Alba Chimirri, Roberta Caruso, Andrew Constanti, David Turton, Sue P. Hume, Rabia Ahmad, Lyn S. Pilowsky and Sajinder K. Luthra

Design, synthesis, and biological activity of N^6 -substituted-4'-thioadenosines at the human A_3 adenosine receptor

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Lak Shin Jeong,* Hyuk Woo Lee, Hea Ok Kim, Ji Young Jung, Zhan-Guo Gao, Heng T. Duong, Srikar Rao, Kenneth A. Jacobson, Dae Hong Shin, Jeong A Lee, Prashantha Gunaga, Sang Kook Lee, Dong Zhe Jin, Moon Woo Chun and Hyung Ryong Moon

Structure-activity relationship of N⁶-substituted-4'-thioadenosines as potent human A₃ adenosine receptor agonists is described.

Novel antibiotics: C-2 symmetrical macrocycles inhibiting Holliday junction DNA binding by *E. coli* RuvC

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Po-Shen Pan, Fiona A. Curtis, Chris L. Carroll, Irene Medina, Lisa A. Liotta, Gary J. Sharples* and Shelli R. McAlpine*

Macrocyclic hexa- and octapeptides designed to trap Holliday junctions

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Structure-activity studies of a novel series of 5,6-fused heteroaromatic ureas as TRPV1 antagonists

pp 4740-4749

Irene Drizin,* Arthur Gomtsyan, Erol K. Bayburt, Robert G. Schmidt, Guo Zhu Zheng, Richard J. Perner, Stanley DiDomenico, John R. Koenig, Sean C. Turner, Tammie K. Jinkerson, Brian S. Brown, Ryan G. Keddy, Heath A. McDonald, Prisca Honore, Carol T. Wismer, Kennan C. Marsh, Jill M. Wetter, James S. Polakowski, Jason A. Segreti, Michael F. Jarvis, Connie R. Faltynek and Chih-Hung Lee

Novel potent and selective calcium-release-activated calcium (CRAC) channel inhibitors. Part 1: Synthesis and inhibitory activity of 5-(1-methyl-3-trifluoromethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamides

pp 4750-4760

Yasuhiro Yonetoku,* Hirokazu Kubota, Yoshinori Okamoto, Akira Toyoshima, Masashi Funatsu, Jun Ishikawa, Makoto Takeuchi, Mitsuaki Ohta and Shin-ichi Tsukamoto

5-(1-Methyl-3-trifluoromethyl-1*H*-pyrazol-5-yl)thiophene-2-carboxamide derivatives were prepared and evaluated for their CRAC channel inhibitory activity.

Synthesis of new class dipeptide analogues with improved permeability and antithrombotic activity

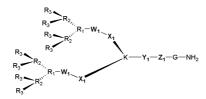
pp 4761-4774

Ming Zhao, Lanrong Bi, Wei Bi, Chao Wang, Zhe Yang, Jingfang Ju* and Shiqi Peng*

Synthesis of a library of polycationic lipid core dendrimers and their evaluation in the delivery of an oligonucleotide with hVEGF inhibition

pp 4775-4780

Harendra S. Parekh,* Robert J. Marano, Elizabeth P. Rakoczy, Joanne Blanchfield and Istvan Toth



Synthesis of a library of new polycationic dendrimers and their evaluation in downregulation of human vascular endothelium growth factor is presented.

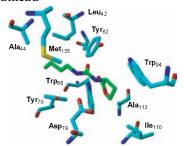


Synthesis and biological evaluation of homoserine lactone derived ureas as antagonists of bacterial quorum sensing

pp 4781-4791

Marine Frezza, Sandra Castang, Jane Estephane, Laurent Soulère, Christian Deshayes, Bernard Chantegrel, William Nasser, Yves Queneau, Sylvie Reverchon and Alain Doutheau*

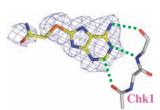
A series of homoserine lactone derived ureas were synthesized and evaluated for their ability to inhibit the quorum sensing in *Vibrio fischeri* bacteria.



Identification of chemically diverse Chk1 inhibitors by receptor-based virtual screening

pp 4792-4802

Nicolas Foloppe,* Lisa M. Fisher, Rob Howes, Andrew Potter, Alan G.S. Robertson and Allan E. Surgenor



Chk1 structure \rightarrow virtual screening \rightarrow binding assay \rightarrow compound QC \rightarrow diverse new ligands \rightarrow crystallography.

Discovery of thiochroman and chroman derivatives as pure antiestrogens and their structure-activity relationship

pp 4803-4819

Yoshitake Kanbe,* Myung-Hwa Kim, Masahiro Nishimoto, Yoshihito Ohtake, Nobuaki Kato, Toshiaki Tsunenari, Kenji Taniguchi, Iwao Ohizumi, Shin-ichi Kaiho, Kazumi Morikawa, Jae-Chon Jo, Hyun-Suk Lim and Hak-Yeop Kim

In order to develop pure antiestrogens, a series of 7-hydroxy-3-(4-hydroxyphenyl)chroman and 7-hydroxy-3-(4-hydroxyphenyl)thiochroman derivatives with sulfoxide containing side chains at the 4-position were designed, synthesized, and evaluated.

$$S(O)_{m} \ \ R_2$$

$$(CH_2)_n \ \ OH \ \ \ R_1 = Me, \ H$$

$$R_2 = (CH_2)_3CF_2CF_3, \ (CH_2)_4CH_3,$$

$$n = 8, 9, 10$$

$$m = 0, 1, 2$$

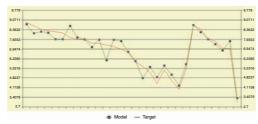
Evaluation of glycolamide esters of indomethacin as potential cyclooxygenase-2 (COX-2) inhibitors

pp 4820-4833

Smriti Khanna, Manjula Madan, Akhila Vangoori, Rahul Banerjee, Ram Thaimattam, S.K. Jafar Sadik Basha, Mullangi Ramesh, Seshagiri Rao Casturi and Manojit Pal*

 R^{1} = alkyl, aryl, heteroaryl; R = H R^{1} & R = heterocyclyl

QSAR study of 1,4-dihydropyridine calcium channel antagonists based on gene expression programming pp 4834–4841 Hong Zong Si,* Tao Wang, Ke Jun Zhang, Zhi De Hu* and Bo Tao Fan



The log (1/IC₅₀) for 45 1,4-dihydropyridines was modeled using the descriptors calculated from the molecular structure along with a quantitative structure–activity relationship (QSAR) technique. The heuristic method (HM) and gene expression programming (GEP) were utilized to construct the linear and nonlinear prediction models, leading to a good prediction.

Synthesis, study of 3D structures, and pharmacological activities of lipophilic nitroimidazolyl-1,4-dihydropyridines as calcium channel antagonist

pp 4842-4849

Ramin Miri,* Katayoun Javidnia, Hasti Sarkarzadeh and Bahram Hemmateenejad*

A group of alkyl ester analogues of new derivatives of nifedipine, in which the orthonitrophenyl group at position 4 is replaced by a 1-methyl-5-nitro-2-imidazolyl substituent, and the methyl group at position 6 is replaced by a phenyl substituent, were synthesized and evaluated as calcium channel antagonist using the high K⁺ contraction of guinea-pig ileal longitudinal smooth muscle.

$$\begin{array}{c} R_1 = \\ \text{Me, Et} \\ \text{n-Pr, i-Pr} \\ \text{n-Bu, i-Bu} \\ \\ R_1O_2C \\ \\ R_2 \\ \\ \text{H} \end{array}$$

Nonsteroidal progesterone receptor ligands (I): Synthesis and SAR of new tetrahydronaphthofuranone derivatives

pp 4850-4861

Rie Shinei.* Ken-ichi Kurihara, Kivoshi Tanabe, Yuji Tabata, Yasushi Kurata, Shigeru Hoshiko and Tsuneo Okonogi

$$R^3$$
 8 9 1 0 PF1092C: R^1 = H, R^2 = OH, R^3 = H 8b: R^1 = EtCO, R^2 = EtCOO, R^3 = H 19i: R^1 = cyclopropyl-NHCO, R^2 = H, R^3 = MeO

Tetrahydronaphthofuranones, based on the fungal metabolite PF1092C, was synthesized and evaluated for progesterone receptor (PR) binding affinities. Compounds 8b and 19i exhibited high affinity and acted as selective PR antagonists.

Nonsteroidal progesterone receptor ligands (II); synthesis and SAR of new tetrahydrobenzindolone derivatives

pp 4862-4878

 $R = Me_2NCO$

Ken-ichi Kurihara,* Rie Shinei, Kiyoshi Tanabe, Yuji Tabata, Yasushi Kurata, Shigeru Hoshiko and Tsuneo Okonogi

We have developed a new lead compound, tetrahydrobenzindolone, possessing a lactam ring, which shows sufficient stability for easy modification at the 6- and/or 7-positions. We succeeded in separating the agonistic and antagonistic activities by choosing suitable substituent groups at the 6- and/or 7-position(s) of the tetrahydrobenzindolone.

Me MeO, N PR agonist:
$$R = n$$
-PrNHCO $R = Me_2NCO$ PR antagonist: $R = (CH_3)_2CH(CH_2)_2$ -

tetrahydrobenzindolone deriv.

Cytoprotective effect of caffeic acid phenethyl ester (CAPE) and catechol ring-fluorinated CAPE derivatives against menadione-induced oxidative stress in human endothelial cells

pp 4879-4887

Xinyu Wang, Salomon Stavchansky,* Phillip D. Bowman and Sean M. Kerwin*

$$\begin{array}{c} CI \\ \bigoplus \\ Ph_3P \\ O \\ \end{array}$$

$$\begin{array}{c} R_5 \\ R_4O \\ \end{array}$$

$$\begin{array}{c} R_5 \\ R_3 \\ \end{array}$$

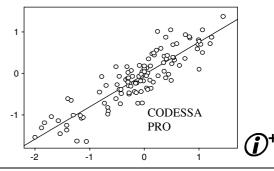
$$\begin{array}{c} R_2 = H, F \\ R_3 = H, OH, OMe \\ R_4 = H, Me \\ R_5 = F, OH, OMe \\ \end{array}$$

Correlation of blood-brain penetration using structural descriptors

pp 4888-4917

Alan R. Katritzky,* Minati Kuanar, Svetoslav Slavov, Dimitar A. Dobchev, Dan C. Fara, Mati Karelson, William E. Acree Jr., Vitaly P. Solov'ev and Alexandre Varnek

QSAR models of log BB for a diverse set of 113 drug molecules were developed employing structural descriptors using CODESSA-PRO and ISIDA approaches. The models were successfully validated using the central nervous system activity data of an external test set of 40 drug molecules.



Asymmetric reduction of 3-aryl-3-keto esters using Rhizopus species

pp 4918-4922

Neeta A. Salvi and Subrata Chattopadhyay*

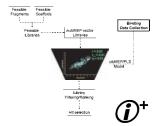
CO₂Et Rhizopus species
$$R = H, 2-F, 3-NO_2, 4-NO_2$$
 $Vield: 42-80\%$ $Vield: 42-80\%$ $Vield: 42-80\%$ $Vield: 42-80\%$

The application of a 3D-QSAR (*auto*MEP/PLS) approach as an efficient pharmacodynamic-driven filtering method for small-sized virtual library: Application to a lead optimization of a human A₃ adenosine receptor antagonist

pp 4923–4932

Stefano Moro,* Magdalena Bacilieri, Barbara Cacciari, Chiara Bolcato, Claudia Cusan, Giorgia Pastorin, Karl-Norbert Klotz and Giampiero Spalluto*

We present the application of 3D-QSAR (*auto*MEP/PLS) approach as an efficient and alternative pharmacodynamic filtering method for small-sized virtual library. For this purpose, a small-sized combinatorial library (841 compounds) was derived from the scaffold of the known human A₃ antagonist pyrazolo-triazolo-pyrimidines.

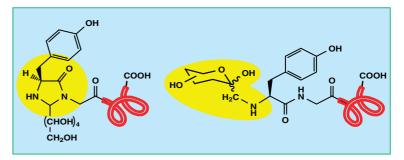


Transformations of bioactive peptides in the presence of sugars—Characterization and stability studies of the adducts generated via the Maillard reaction

pp 4933-4943

Maja Roščić and Štefica Horvat*

Glycation—a sweet hazard. Mechanism of formation in correlation with analysis in human serum improved our understanding of the underlying chemistry in the Maillard reaction.



Antagonists of the myelin-associated glycoprotein: A new class of tetrasaccharide mimics

pp 4944-4957

Daniel Schwizer, Heiko Gäthje, Soerge Kelm, Michele Porro, Oliver Schwardt and Beat Ernst* OH

Simplified mimics of tetrasaccharide 1, where the core disaccharide $Gal\beta(1-3)GalNAc$ was replaced with a biphenyl, were synthesized and biologically evaluated as inhibitors of the myelin-associated glycoprotein (MAG).

Toward the control of *Leptosphaeria maculans*: Design, syntheses, biological activity, and metabolism of potential detoxification inhibitors of the crucifer phytoalexin brassinin

pp 4958-4979

M. Soledade C. Pedras* and Mukund Jha

Potential inhibitors of brassinin detoxification were designed by replacement of the moiety A with carbamate, dithiocarbonate, urea, thiourea, sulfamide, sulfonamide, dithiocarbazate, amide, and ester groups, and moiety B with naphthalenyl and phenyl.

3'-Fluoro-3'-deoxy-5'-noraristeromycin derivatives: Synthesis and antiviral analysis

pp 4980-4986

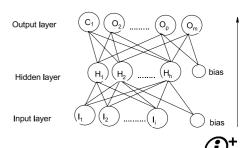
Atanu Roy, Tesfaye Serbessa and Stewart W. Schneller*

OSAR modeling of the inhibition of Glycogen Synthase Kinase-3

pp 4987-5002

Alan R. Katritzky,* Liliana M. Pacureanu, Dimitar A. Dobchev, Dan C. Fara, Pablo R. Duchowicz and Mati Karelson

QSAR modeling of the biological activity (pIC_{50}) of 277 inhibitors of GSK-3 is developed using linear (multilinear regression) and nolinear (artificial neural network) models. The results gave an insight into the dominant role played by the electrostatic, bonding, and steric interactions on the modulation of inhibitory activity.



Studies on quinones. Part 41: Synthesis and cytotoxicity of isoquinoline-containing polycyclic quinones pp 5003–5011

Jaime A. Valderrama,* M. Florencia González, David Pessoa-Mahana,

Distriction of the Polyconia González, David Pessoa-Mahana,

Ricardo A. Tapia, Houda Fillion, Felix Pautet, Jaime A. Rodriguez, Cristina Theoduloz and Guillermo Schmeda-Hirschmann

The regioselective synthesis of fused isoquinolinequinones (i.e., 6, 8, 13, and 15) through highly regiocontrolled cycloaddition reactions from methyl 1,3-dimethyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate 3 and 1,3-dienes is reported. The 2-aza- and 1,6-diaza-anthraquinone derivatives displayed significant in vitro activity on normal fibroblast and four tumor cell lines.

New Taxol® (paclitaxel) prodrugs designed for ADEPT and PMT strategies in cancer chemotherapy
Abdessamad El Alaoui, Nabendu Saha, Frédéric Schmidt,* Claude Monneret and
Jean-Claude Florent

Two new glucuronide paclitaxel prodrugs were synthesized. One of them fulfils all the stability and enzymatic cleavage requirements for an ADEPT or a PMT strategy in cancer chemotherapy.

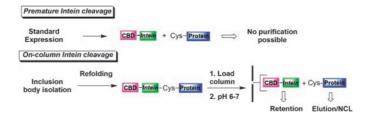


Targeting the α-folate receptor with cyclopenta[g]quinazoline-based inhibitors of thymidylate synthase pp 5020–5042 Elisa A. Henderson, Vassilios Bavetsias,* Davinder S. Theti, Stuart C. Wilson, Rainer Clauss and Ann L. Jackman

Expression of N-terminal Cys-protein fragments using an intein refolding strategy

pp 5043-5048

Christian P.R. Hackenberger, Mark M. Chen and Barbara Imperiali*



An amphiphilic N-terminal Cys-protein fragment for NCL, which undergoes premature cleavage from a pH-sensitive intein fusion under standard conditions, has been isolated by expression and refolding of inclusion bodies.



Antisense oligonucleotides: Efficient synthesis of 2'-O-methoxyethyl phosphorothioate oligonucleotides using 4,5-dicyanoimidazole. Are these oligonucleotides comparable to those synthesized using 1*H*-tetrazole as coupling activator?

Zhiwei Wang, Andy Siwkowski, Walt F. Lima, Phil Olsen and Vasulinga T. Ravikumar*

Multiple 2'-O-methoxyethyl modified phosphorothioate oligonucleotides of 18–20-mer in length were synthesized at various scales using 4,5-dicyanoimidazole (DCI) as coupling activator. Extensive synthetic, analytical (using ion-pair LC–MS), and in vivo pharmacological, toxicological studies showed that oligonucleotides made with DCI and 1*H*-tetrazole are chemically and biologically equivalent. This extensive study will help the oligonucleotide therapeutic industry to move from using a potentially explosive activator (1*H*-tetrazole) to a safe activator (DCI).

DMTO Base

O R

1H-tetrazole = DCI

b) thiolation

$$R = H \text{ or } OCH_2CH_2OMe$$

DMTO Base

 $R = H \text{ or } OCH_2CH_2OMe$

DMTO R

CEO P = S

O R

Synthesis of pyrazole-based hybrid molecules: Search for potent multidrug resistance modulators Palwinder Singh,* Kamaldeep Paul and Wolfgang Holzer

pp 5061-5071

The hybrid molecules C and D obtained by combining the structural features of pyrazole-based drugs (A) and propafenone (a modulator) (B) have been synthesized and evaluated for their interactions with P-glycoprotein.

OTHER CONTENTS

Summary of instructions to authors

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- *Corresponding author
- ** Supplementary data available via ScienceDirect

COVER

The figure shows the synthetic approach to 6RS CB300945; an inhibitor of thymidylate synthase targeted at α-folate receptor overexpressing tumours. This compound and related derivatives were synthesised via multistep routes [Henderson, E.A.; Bavetsias, V.; Theti, D.S.; Wilson, S.C.; Clauss, R.; Jackman, A.L. Bioorg. Med. Chem. 2006, 14, 5020].



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