

## Contents

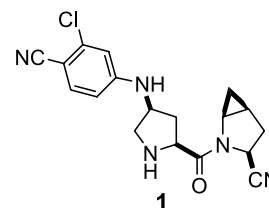
### ARTICLES

#### Diprolyl nitriles as potent dipeptidyl peptidase IV inhibitors

pp 3992–3995

Guohua Zhao,\* Prakash C. Taunk, David R. Magnin, Ligaya M. Simpkins, Jeffrey A. Robl, Aiying Wang, James G. Robertson, Jovita Marcinkeviciene, Doree F. Sitkoff, Rex A. Parker, Mark S. Kirby and Lawrence G. Hamann

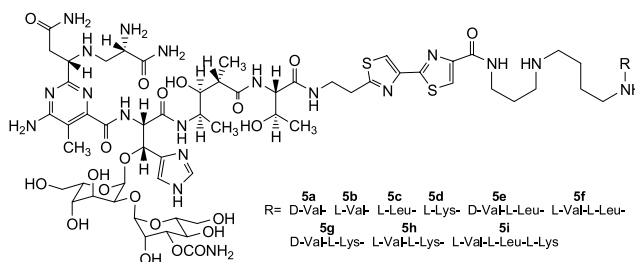
Dipeptidyl peptidase IV (DPP4) is a multifunctional type II transmembrane serine peptidase which regulates various physiological processes, most notably plasma glucose homeostasis by cleaving peptide hormones glucagon-like peptide-1 and glucose-dependent insulintropic polypeptide. Inhibition of DPP4 is a potentially valuable therapy for type 2 diabetes. Synthesis and structure–activity relationships of a series of substituted diprolyl nitriles are described, leading to the identification of compound **1** with a measured DPP4  $K_i$  of 3.6 nM.



#### Novel peptide derivatives of bleomycin A<sub>5</sub>: Synthesis, antitumor activity and interaction with DNA

pp 3996–3999

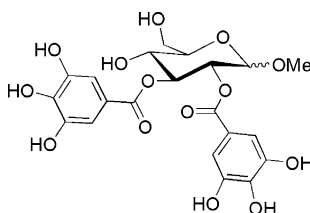
Zhi-Dong Xu, Min Wang, Su-Long Xiao and Ming Yang\*



#### O-Methylglucogalloyl esters: Synthesis and evaluation of their antimycotic activity

pp 4000–4003

Annalisa Romani, Stefano Menichetti,\* Panagiotis Arapitsas, Cristina Nativi, Benedetta Turchetti and Pietro Buzzini

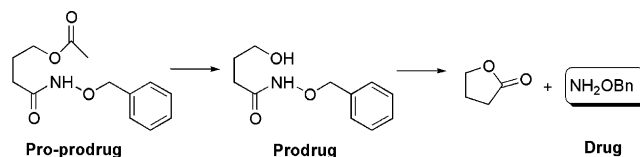


Both anomers of *O*-methylgluco-2,3-digalloyl esters, used in subinhibitory concentration, enhance the antimycotic activity of Amphotericin B towards yeasts of biomedical relevance.

**A prodrug system for hydroxylamines based on esterase catalysis**

pp 4004–4009

Ana Conejo-Garcia and Christopher J. Schofield\*

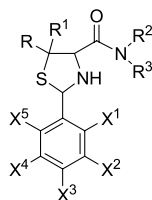


The synthesis and reactivity of hydroxy hydroxamates as models for a prodrug form of hydroxylamine are described.  $\gamma$ -Hydroxy hydroxamates were found to enable hydroxylamine release via lactonisation. Hydroxamates were found to undergo esterase catalysed hydrolysis.

**SAR studies of 2-arylthiazolidine-4-carboxylic acid amides: A novel class of cytotoxic agents for prostate cancer**

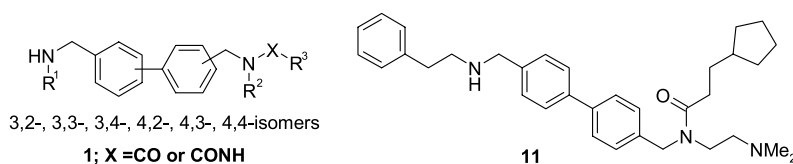
pp 4010–4013

Veeresa Gududuru, Eunju Hurh, Joshua Sullivan, James T. Dalton and Duane D. Miller\*

**Discovery of a potent and selective 5-HT<sub>5A</sub> receptor antagonist by high-throughput chemistry**

pp 4014–4018

David F. Corbett,\* Tom D. Heightman, Stephen F. Moss, Steven M. Bromidge, Sara A. Coggon, Mark J. Longley, Ana Maria Roa, Jennifer A. Williams and David R. Thomas

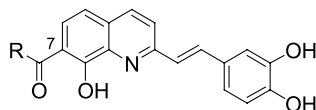


A series of biphenylmethanamines with affinity for the 5-HT<sub>5A</sub> receptor was identified by high-throughput screening of array **1**, synthesised by high-throughput solid-phase chemistry. Compound **11** was identified as the most potent and selective 5-HT<sub>5A</sub> receptor antagonist from this series.

**New HIV-1 replication inhibitors of the styrylquinoline class bearing aryl/acyl groups at the C-7 position: Synthesis and biological activity**

pp 4019–4022

Marie Normand-Bayle, Christophe Bénard, Fatima Zouhiri, Jean-François Mouscadet, Hervé Leh, Claire-Marie Thomas, Gladys Mbemba, Didier Desmaële\* and Jean d'Angelo\*



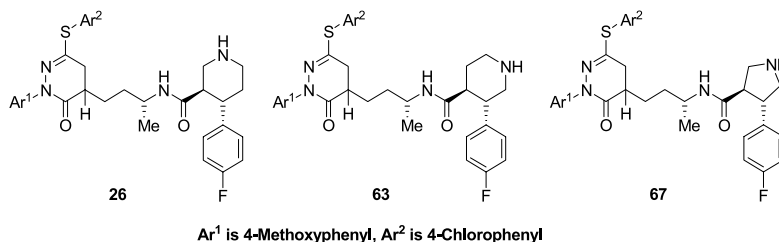
Novel variants of HIV-1 replication inhibitors of the styrylquinoline class harboring aryl/acyl group at the C-7 position have been synthesized. In sharp contrast with styrylquinolines bearing a carboxylic acid group at C-7, these compounds proved to be inactive toward HIV-1 integrase in *in vitro* assays.

**Design and syntheses of melanocortin subtype-4 receptor agonists. Part 2: Discovery of the dihydropyridazinone motif**

pp 4023–4028

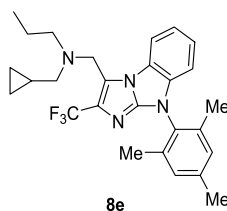
Feroze Ujjainwalla,\* Daniel Warner, Christine Snedden, Ricky D. Grisson, Thomas F. Walsh, Matthew J. Wyvratt, Rubana N. Kalyani, Tanya MacNeil, Rui Tang, David H. Weinberg, Lex Van der Ploeg and Mark T. Goulet

Optimization of the biological activity of a new class of non-peptidyl, pyridazinone derived human melanocortin subtype-4 receptor agonists is disclosed. This work culminated in the identification of 26, 63, and 67, which are potent and subtype selective agonists of human MC4R.

**Synthesis and structure–activity relationship of imidazo[1,2-*a*]benzimidazoles as corticotropin-releasing factor 1 receptor antagonists**

pp 4029–4032

Xiaojun Han,\* Sokhom S. Pin, Kevin Burris, Lawrence K. Fung, Stella Huang, Matthew T. Taber, Jie Zhang and Gene M. Dubowchik\*



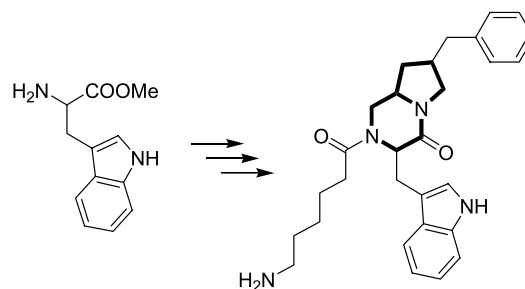
The synthesis and SAR of imidazo[1,2-*a*]benzimidazoles and pharmacokinetic properties of compound **8e** ( $K_i = 23$  nM) are reported.

**Utilizing the intramolecular Fukuyama–Mitsunobu reaction for a flexible synthesis of novel heterocyclic scaffolds for peptidomimetic drug design**

pp 4033–4036

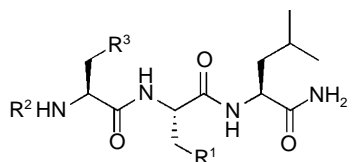
Christoph W. Zapf,\* Juan R. Del Valle and Murray Goodman

We report the flexible syntheses of two scaffolds which derive from amino acids and can be decorated with a variety of pharmacophores while retaining full control over all stereocenters.

**Synthesis of tripeptides as potent *Yersinia* protein tyrosine phosphatase inhibitors**

pp 4037–4042

Kyeong Lee, Shanthaveerappa K. Boovanahalli, Ky-Youb Nam, Sang-Uk Kang, Mijeoung Lee, Jason Phan, Li Wu, David S. Waugh, Zhong-Yin Zhang, Kyoung Tai No, Jung Jun Lee and Terrence R. Burke, Jr.\*



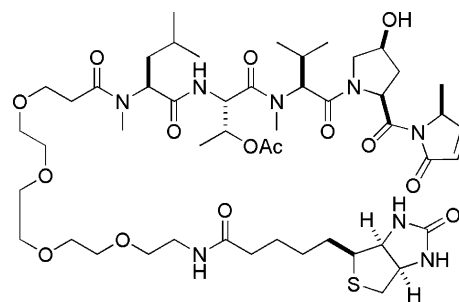
R<sup>1</sup> = Mono-Carboxy based pTyr mimetic  
 R<sup>2</sup> = Fmoc, Heterocycles  
 R<sup>3</sup> = CH<sub>2</sub>CO<sub>2</sub>Bn, NHCO<sub>2</sub>Bn.

**Developing microcolin A analogs as biological probes**

pp 4043–4047

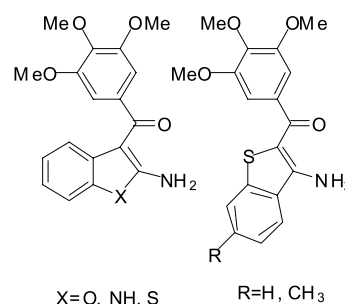
Amit K. Mandal, John Hines, Kouji Kuramochi and Craig M. Crews\*

The synthesis and biological evaluation of microcolin A and B analogs are reported. Design, synthesis, and biological activity profile of a biotinylated microcolin A analog as a molecular probe are also discussed.

**Synthesis and preliminary biological evaluation of new anti-tubulin agents containing different benzoheterocycles**

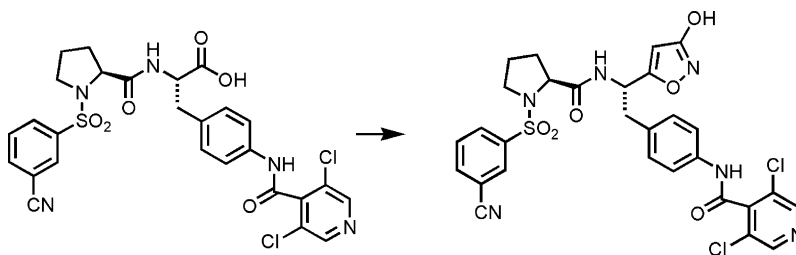
pp 4048–4052

Romeo Romagnoli,\* Pier Giovanni Baraldi, M. Katherine Jung, Maria Antonietta Iaconinoto, Maria Dora Carrion, Vincent Remusat, Delia Preti, Mojgan Aghazadeh Tabrizi, Fruttarolo Francesca, Erik De Clercq, Jan Balzarini and Ernest Hamel

**Influence of acid surrogates toward potency of VLA-4 antagonist**

pp 4053–4056

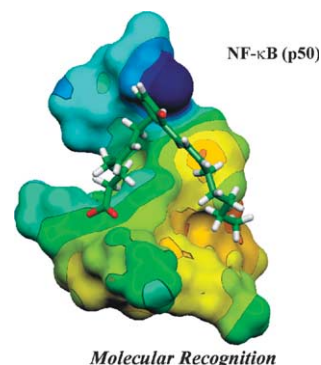
Shankar Venkatraman,\* Jongwon Lim, Merryl Cramer, Michael F. Gardner, Joyce James, Kenneth Alves, Russell B. Lingham, Richard A. Mumford and Benito Munoz

**Molecular recognition of 15-deoxy- $\Delta^{12,14}$ -prostaglandin J<sub>2</sub> by nuclear factor-kappa B and other cellular proteins**

pp 4057–4063

Vineet Pande and Maria J. Ramos\*

15-Deoxy- $\Delta^{12,14}$ -prostaglandin J<sub>2</sub> (15d-PGJ<sub>2</sub>) binds to its target proteins and covalently modifies critical cysteine residues. A computational docking and electrostatics study is performed to understand the structural basis of this binding, providing fertile ground for rational design of 15d-PGJ<sub>2</sub> analogs.

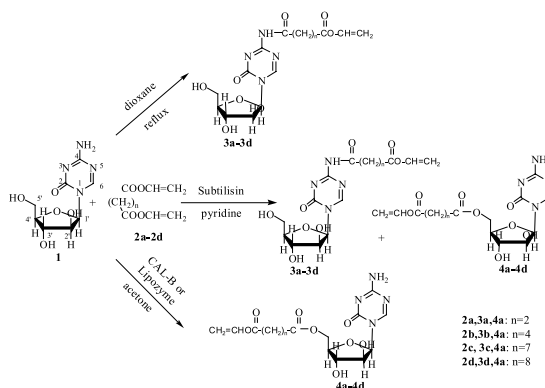


## Controllable selective synthesis of a polymerizable prodrug of cytarabine by enzymatic and chemical methods

Na Wang, Zhi Chun Chen, De Shui Lu and Xian Fu Lin\*

pp 4064–4067

Selectivity of enzymatic and chemical methods for the synthesis of polymerizable cytarabine derivatives was described. The obtained series of cytarabine derivatives would be useful as a significant monomer for macromolecular anticancer drugs.

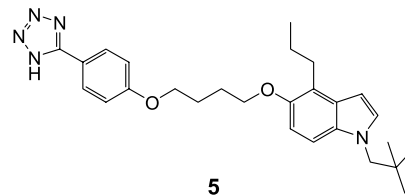


## Benzazoles as allosteric potentiators of metabotropic glutamate receptor 2 (mGluR2): Efficacy in an animal model for schizophrenia

Steven P. Govek,\* Celine Bonnefous, John H. Hutchinson, Theodore Kamenecka, Jeffrey McQuiston, Richard Pracitto, Lucy X. Zhao, Michael F. Gardner, Joyce K. James, Lorrie P. Daggett, Blake A. Rowe, Hervé Schaffhauser, Linda J. Bristow, Una C. Campbell, Dana E. Rodriguez and Jean-Michel Vernier

pp 4068–4072

Metabotropic glutamate receptor 2 (mGluR2) has been implicated in a variety of CNS disorders, including schizophrenia. Disclosed herein is the development of a new series of allosteric potentiators of mGluR2. Structure–activity relationship studies in conjunction with pharmacokinetic data led to the discovery of indole **5**, which is active in an animal model for schizophrenia.

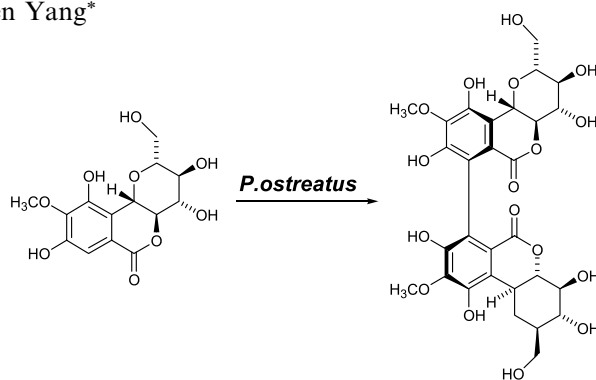


## A carbon–carbon-coupled dimeric bergenin derivative biotransformed by *Pleurotus ostreatus*

Dong Wang, Hong-Tao Zhu, Ying-Jun Zhang\* and Chong-Ren Yang\*

pp 4073–4075

A novel C–C-coupled dimer derivative of bergenin was produced by the biotransformation of cultured mycelia of white rot fungus *Pleurotus ostreatus*. Its structure was elucidated by detailed spectroscopic analysis.

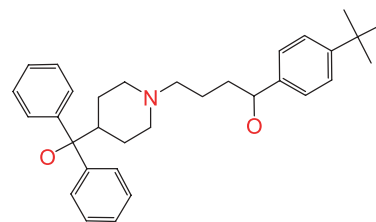


## Modeling $K_m$ values using electrotopological state: Substrates for cytochrome P450 3A4-mediated metabolism

Yong-Hua Wang, Yan Li, Yan-Hong Li, Sheng-Li Yang and Ling Yang\*

pp 4076–4084

Using electrotopological state (E-state) indices, together with Bayesian-regularized artificial neural network, we describe an in silico approach for modeling the CYP3A4 enzyme kinetics.

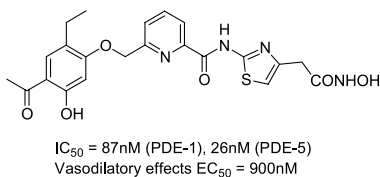


(terfenadine, a typical substrate of CYP3A4)

**Discovery of hydroxamic acid analogs as dual inhibitors of phosphodiesterase-1 and -5**

pp 4085–4090

Akihito Dan, Takaaki Shiyama, Kazuto Yamazaki,\* Naoto Kusunose, Katsuya Fujita, Hideshi Sato, Kazutaka Matsui and Masafumi Kitano

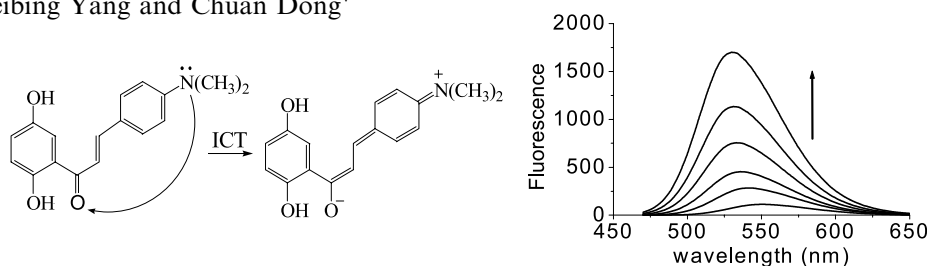


HTS and the following synthesis of a series of compounds led us to the discovery of hydroxamic acid analogs as potent dual inhibitors of phosphodiesterase (PDE)-1 and -5. Some of them showed the expected potent vasodilatory effects with a rising level of cGMP.

**Determination of human serum albumin using an intramolecular charge transfer fluorescence probe: 4'-Dimethylamino-2,5-dihydroxychalcone**

pp 4091–4096

Zhicheng Xu, Weibing Yang and Chuan Dong\*

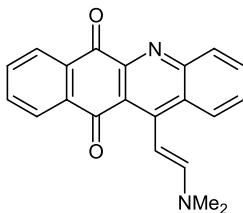


Intramolecular charge transfer fluorescence probe 4'-dimethylamino-2,5-dihydroxychalcone binding to human serum albumin exhibited dramatic enhancement of fluorescence intensity with accompanying blue shift of the emission maximum.

**Identification of heteroarylenamines as a new class of antituberculosis lead molecules**

pp 4097–4099

Brent R. Copp,\* Holly C. Christiansen, Brent S. Lindsay and Scott G. Franzblau



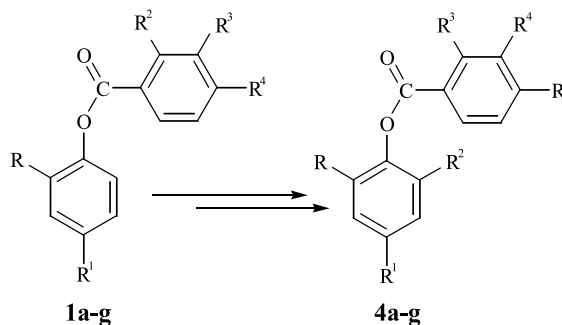
A range of heteroarylenamines were prepared and evaluated against *Mycobacterium tuberculosis* H<sub>37</sub>Rv (Mtb). Cell-based studies indicate that the compounds exhibit activity via a novel mechanism of action compared to current front-line therapies.

**Synthesis of benzoyl phenyl benzoates as effective inhibitors for phospholipase A<sub>2</sub> and hyaluronidase enzymes**

pp 4100–4104

Shaukath Ara Khanum, Satish Kumar Murari, Bannikuppe Sannanaik Vishwanth and Sheena Shashikanth\*

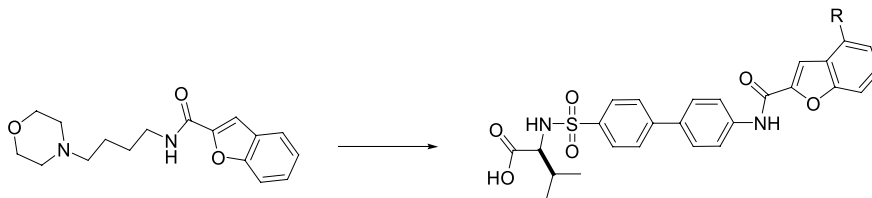
Benzoylation of (hydroxy phenyl) phenyl methanone **2a–g** to benzoyl phenyl benzoates **4a–g** was achieved in good yield. All the newly synthesized compounds were evaluated for their phospholipase A<sub>2</sub> [E.C. 3.1.1.4] and hyaluronidase [E.C. 3.2.1.35] enzyme inhibitory activity in snake venom as source and their structure–activity relationship with respect to different groups is reported for the first time.



**Identification of potent and selective MMP-13 inhibitors**

pp 4105–4109

Junjun Wu, Thomas S. Rush III, Rajeev Hotchandani, Xuemei Du, Mary Geck, Elisabeth Collins, Zhang-Bao Xu, Jerry Skotnicki, Jeremy I. Levin and Frank E. Lovering\*

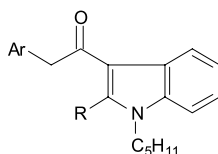


A potent, selective series of MMP-13 inhibitors has been derived from a weak inhibitor that did not bear a zinc chelator.

**1-Pentyl-3-phenylacetylindoles, a new class of cannabimimetic indoles**

pp 4110–4113

John W. Huffman,\* Paul V. Szklennik, Amanda Almond, Kristen Bushell, Dana E. Selley, Hengjun He, Michael P. Cassidy, Jenny L. Wiley and Billy R. Martin



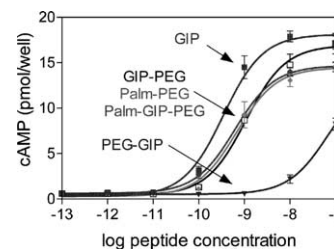
The synthesis and pharmacology of 30 1-pentyl-3-arylacetylindoles ( $R = H$  and  $CH_3$ ) are described. Two of these compounds are highly efficacious and selective ligands for the  $CB_1$  receptor.

**Contribution of site-specific PEGylation to the dipeptidyl peptidase IV stability of glucose-dependent insulinotropic polypeptide**

pp 4114–4117

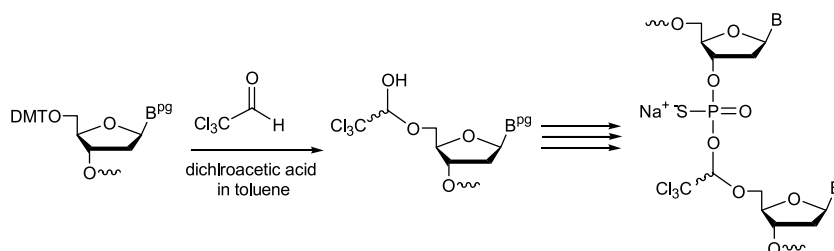
Arthur I. Salhanick, Kevin B. Clairmont, Thomas M. Buckholz, Carla M. Pellegrino, Sha Ha and Kevin J. Lumb\*

Potent and DPP-IV-stable PEGylated GIP peptides are reported.

**Trichloroacetaldehyde modified oligonucleotides**

pp 4118–4124

Hans Gaus, Phil Olsen, Kent Van Sooy, Claus Rentel, Brett Turney, Kathleen L. Walker, James V. McArdle and Daniel C. Capaldi\*

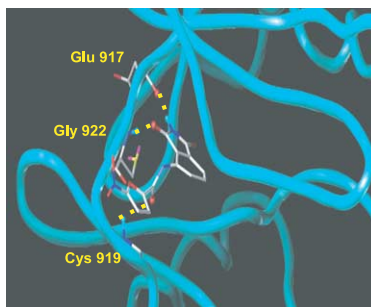


The presence of chloral in dichloroacetic acid leads to the formation of trichloroacetaldehyde modified oligonucleotides.

**Identification of novel angiogenesis inhibitors**

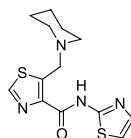
pp 4125–4129

Jayalakshmi Sridhar, Nagaraju Akula, Dakshanamurthy Sivanesan, Madhusudhanan Narasimhan, Appu Rathinavelu and Nagarajan Pattabiraman\*


**Identification of potent type I MetAPs inhibitors by simple bioisosteric replacement. Part 2: SAR studies of 5-heteroalkyl substituted TCAT derivatives**

pp 4130–4135

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



TCAT

**9b** IC<sub>50</sub> 10 nM for EcMetAP1  
75 nM for ScMetAP1

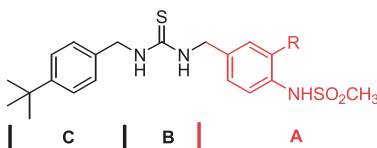
Systematic SAR studies on the thiazole ring 5-substituent of TCAT inhibitors of *EcMetAP1* and *ScMetAP1* revealed that the introduction of a  $\beta$ -alkoxy or an amino group enhanced the inhibitory activity significantly.

**Analysis of structure–activity relationships for the ‘A-region’**

pp 4136–4142

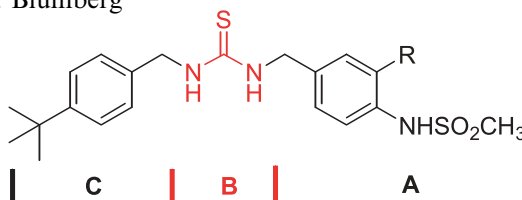
**of *N*-(4-*t*-butylbenzyl)-*N'*-[4-(methylsulfonylamino)benzyl]thiourea analogues as TRPV1 antagonists**

Jeewoo Lee,\* Sang-Uk Kang, Min-Jung Kil, Myoungyoun Shin, Ju-Ok Lim, Hyun-Kyung Choi, Mi-Kyoung Jin, Su Yeon Kim, Sung-Eun Kim, Yong-Sil Lee, Kyung-Hoon Min, Young-Ho Kim, Hee-Jin Ha, Richard Tran, Jacqueline D. Welter, Yun Wang, Tamas Szabo, Larry V. Pearce, Daniel J. Lundberg, Attila Toth, Vladimir A. Pavlyukovets, Matthew A. Morgan and Peter M. Blumberg


**Analysis of structure–activity relationships for the ‘B-region’ of *N*-(4-*t*-butylbenzyl)-*N'*-[4-(methylsulfonylamino)benzyl]thiourea analogues as TRPV1 antagonists**

pp 4143–4150

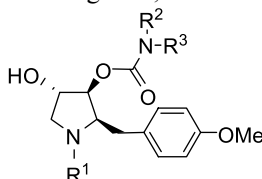
Jeewoo Lee,\* Mi-Kyoung Jin, Sang-Uk Kang, Su Yeon Kim, Jiyoung Lee, Myoungyoun Shin, Jaemin Hwang, Sookhyun Cho, Yeon-Sil Choi, Hyun-Kyung Choi, Sung-Eun Kim, Young-Ger Suh, Yong-Sil Lee, Young-Ho Kim, Hee-Jin Ha, Attila Toth, Larry V. Pearce, Richard Tran, Tamas Szabo, Jacqueline D. Welter, Daniel J. Lundberg, Yun Wang, Jozsef Lazar, Vladimir A. Pavlyukovets, Matthew A. Morgan and Peter M. Blumberg





**Solid-phase synthesis and anti-infective activity of a combinatorial library based on the natural product anisomycin** pp 4151–4154

Shuhao Shi,\* Shirong Zhu, Samuel W. Gerritz, Kim Esposito, Ramesh Padmanabha, Wenying Li, John J. Herbst, Henry Wong, Yue Zhong Shu, Kin S. Lam and Michael J. Sofia



Solid-phase synthesis of a library based on the natural product anisomycin is described. The resulting library was tested against a panel of bacterial and fungal targets, and active compounds were identified in a *Staphylococcus aureus* whole-cell assay and an efflux-deficient fungal whole-cell assay.

**OTHER CONTENTS**


Contributors to this issue

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Summary of instructions to authors 2005

p III

\*Corresponding author

 Supplementary data available via ScienceDirect

**COVER**

Amerlizing transthyretin amyloidogenesis by native state kinetic stabilization mediated by small molecule binding. Small molecule binding to the amyloidogenic protein transthyretin kinetically stabilizes the native tetrameric state, preventing dissociation to folded monomers that misfold and misassemble into toxic intermediates, amorphous aggregates, and amyloid fibrils. The Kelly laboratory has developed several structurally distinct inhibitor families, depicted in the background, that are undergoing pharmacological evaluation. Created by Steven M. Johnson, graduate student in Professor Jeffery W. Kelly's laboratory, Department of Chemistry, The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA.



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