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# Bioorganic & Medicinal Chemistry Letters

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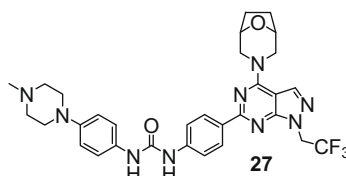
## Bioorganic & Medicinal Chemistry Letters Volume 19, Issue 24, 2009

### Contents

#### ARTICLES

- Incorporation of water-solubilizing groups in pyrazolopyrimidine mTOR inhibitors: Discovery of highly potent and selective analogs with improved human microsomal stability** pp 6830–6835

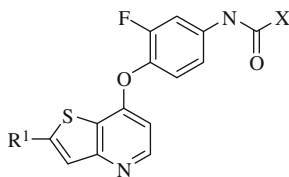
David J. Richard<sup>\*</sup>, Jeroen C. Verheijen, Kevin Curran, Joshua Kaplan, Lourdes Toral-Barza, Irwin Hollander, Judy Lucas, Ker Yu, Arie Zask



A series of pyrazolopyrimidine mTOR inhibitors which contain basic amines or polar substituents attached to the 6-arylureidophenyl moiety demonstrate enhanced cellular potency and significantly improved stability towards human microsomes.

- N*<sup>3</sup>-Arylmalonamides: A new series of thieno[3,2-*b*]pyridine based inhibitors of c-Met and VEGFR2 tyrosine kinases** pp 6836–6839

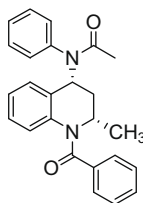
Oscar Saavedra, Stephen Claridge<sup>\*</sup>, Lijie Zhan, Franck Raeppe, Marie-Claude Granger, Stéphane Raeppe, Michael Mannion, Frédéric Gaudette, Nancy Zhou, Ljubomir Isakovic, Naomy Bernstein, Robert Déziel, Hannah Nguyen, Normand Beaulieu, Carole Beaulieu, Isabelle Dupont, James Wang, A. Robert Macleod, Jeffrey M. Besterman, Arkadii Vaisburg



A series of thieno[3,2-*b*]pyridine inhibitors of the receptor tyrosine kinases c-Met and VEGFR2, bearing the *N*<sup>3</sup>-arylmalonamides functionality, is described.

- Tetrahydroquinoline derivatives as CRTH2 antagonists** pp 6840–6844

Jiwen Liu<sup>\*</sup>, Yingcai Wang, Ying Sun, Derek Marshall, Shichang Miao, George Tonn, Penny Anders, Joel Tocker, H. Lucy Tang, Julio Medina

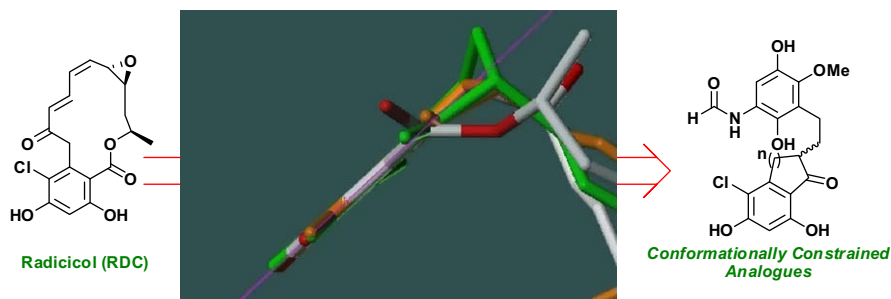


A series of tetrahydroquinoline-derived inhibitors of the CRTH2 receptor was discovered by a high throughput screen. Optimization of these compounds for potency and pharmacokinetic properties led to the discovery of potent and orally bioavailable CRTH2 antagonists.

**Design, synthesis, and biological activity of bicyclic radester analogues as Hsp90 inhibitors**

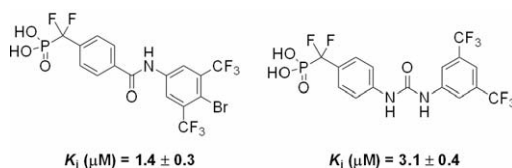
pp 6845–6850

Vinod D. Jadhav, Adam S. Duerfeldt, Brian S. J. Blagg \*

**Fragment-based discovery of selective inhibitors of the *Mycobacterium tuberculosis* protein tyrosine phosphatase PtpA**

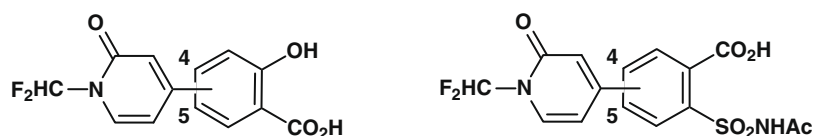
pp 6851–6854

Katherine A. Rawls, P. Therese Lang, Jun Takeuchi, Shinichi Imamura, Tyler D. Baguley, Christoph Grundner \*, Tom Alber \*, Jonathan A. Ellman \*

The development of low  $\mu$ M inhibitors of the *Mycobacterium tuberculosis* phosphatase PtpA is reported.**Synthesis and biological evaluation of salicylic acid and *N*-acetyl-2-carboxybenzenesulfonamide regioisomers possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore: Dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity**

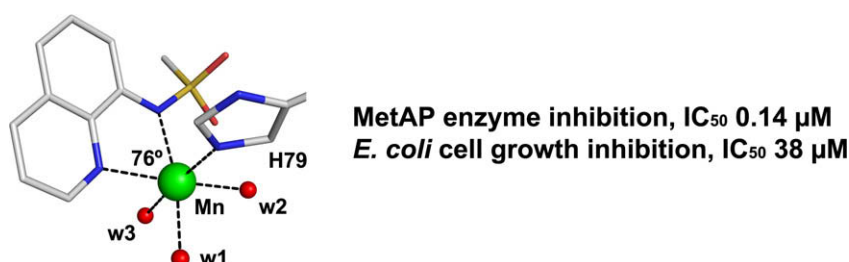
pp 6855–6861

Morshed A. Chowdhury, Khaled R. A. Abdellatif, Ying Dong, Dipankar Das, Gang Yu, Carlos A. Velázquez, Mavanur R. Suresh, Edward E. Knaus \*

**Metal-mediated inhibition is a viable approach for inhibiting cellular methionine aminopeptidase**

pp 6862–6864

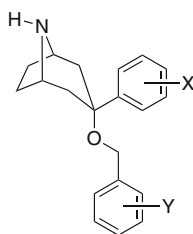
Sergio C. Chai, Qi-Zhuang Ye \*



**Synthesis and monoamine transporter affinity of 3 $\alpha$ -arylmethoxy-3 $\beta$ -arylnortropanes**

pp 6865–6868

Harneet Kaur, Sari Izenwasser, Abha Verma, Dean Wade, Amy Housman, Edwin D. Stevens,  
David L. Mobley, Mark L. Trudell \*

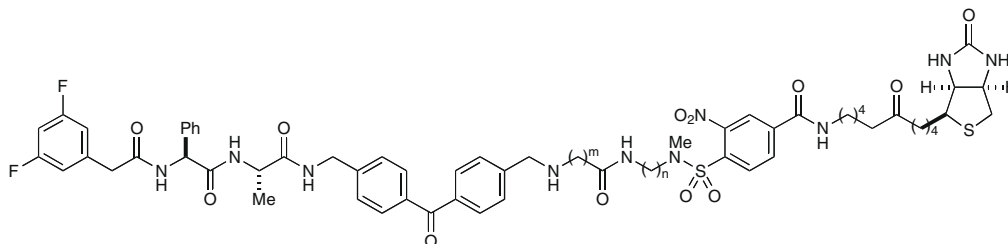


The design, synthesis and monoamine transporter affinity of a series of nortropane derivatives is described.

**Development of photoaffinity probes for  $\gamma$ -secretase equipped with a nitrobenzenesulfonamide-type cleavable linker**

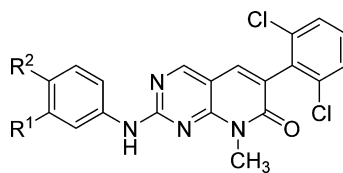
pp 6869–6871

Satoshi Yokoshima, Yuzo Abe, Naoto Watanabe, Yoichi Kita, Toshiyuki Kan, Takeshi Iwatsubo, Taisuke Tomita,  
Tohru Fukuyama \*

**Structure–activity relationships of 6-(2,6-dichlorophenyl)-8-methyl-2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7-ones: Toward selective Abl inhibitors**

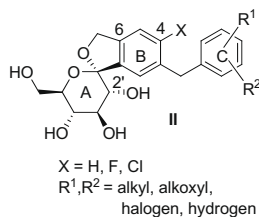
pp 6872–6876

Christophe Antczak \*, Darren R. Veach, Christina N. Ramirez, Maria A. Minchenko, David Shum, Paul A. Calder,  
Mark G. Frattini, Bayard Clarkson, Hakim Djaballah

**Exploration of *O*-spiroketal *C*-arylglucosides as novel and selective renal sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors**

pp 6877–6881

Binhua Lv \*, Baihua Xu, Yan Feng, Kun Peng, Ge Xu, Jiyan Du, Lili Zhang, Wenbin Zhang, Ting Zhang,  
Liangcheng Zhu, Haifeng Ding, Zelin Sheng, Ajith Welihinda, Brian Seed, Yuanwei Chen \*

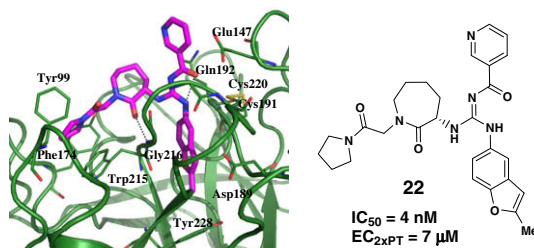


The novel spiro[isobenzofuran-1,2'-pyran] structure is proved to be an effective scaffold for diversification of SGLT2 inhibitors and a number of compounds with single digit nanomolar potency and high selectivity have been synthesized.

**Aroylguanidine-based factor Xa inhibitors: The discovery of BMS-344577**

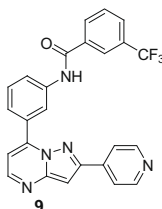
pp 6882–6889

Yan Shi <sup>\*</sup>, Chi Li, Stephen P. O'Connor, Jing Zhang, Mengxiao Shi, Sharon N. Bisaha, Ying Wang, Doree Sitkoff, Andrew T. Pudzianowski, Christine Huang, Herbert E. Klei, Kevin Kish, Joseph Yanchunas Jr., Eddie C.-K. Liu, Karen S. Hartl, Steve M. Seiler, Thomas E. Steinbacher, William A. Schumacher, Karnail S. Atwal, Philip D. Stein

**Hit to lead optimization of pyrazolo[1,5-a]pyrimidines as B-Raf kinase inhibitors**

pp 6890–6892

Ariamala Gopalsamy <sup>\*</sup>, Greg Ciszewski, Mengxiao Shi, Dan Berger, Yongbo Hu, Frederick Lee, Larry Feldberg, Eileen Frommer, Steven Kim, Karen Collins, Donald Wojciechowicz, Robert Mallon

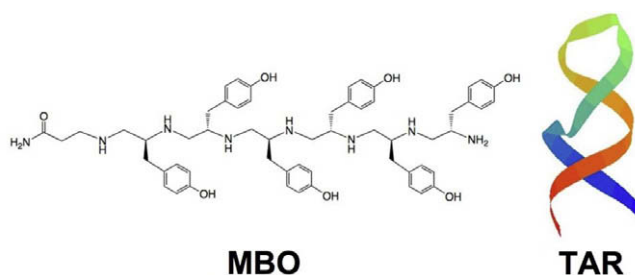


Structure guided design was utilized to optimize the pyrazolo[1,5-a]pyrimidine scaffold by introducing kinase hinge region interacting groups in the 2-position. This strategy led to the identification of lead compound **9** with enhanced enzyme and cellular potency, while maintaining good selectivity over a number of kinases.

**Multivalent binding oligomers inhibit HIV Tat–TAR interaction critical for viral replication**

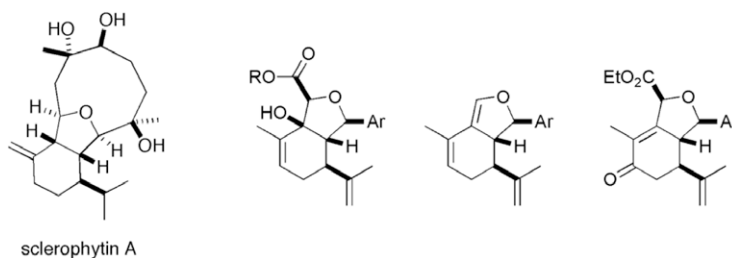
pp 6893–6897

Deyun Wang, Jaclyn Iera, Heather Baker, Priscilla Hogan, Roger Ptak, Lu Yang, Tracy Hartman, Robert W. Buckheit Jr., Alexandre Desjardins, Ao Yang, Pascale Legault, Venkat Yedavalli, Kuan-Teh Jeang, Daniel H. Appella <sup>\*</sup>

**Synthesis and anticancer activity of sclerophytin-inspired hydroisobenzofurans**

pp 6898–6901

T. David Bateman, Aarti L. Joshi, Kwangyul Moon, Elena N. Galitovskaya, Meenakshi Upreti, Timothy C. Chambers <sup>\*</sup>, Matthias C. McIntosh <sup>\*</sup>



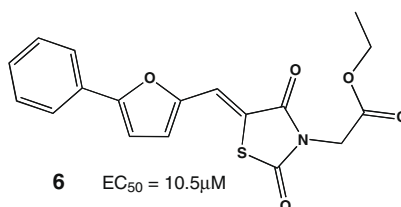
Seco analogs of sclerophytin A prepared in three or four steps exhibit sub-micromolar growth inhibitory activity against the RPMI-8226 leukemia and HOP-92 non-small cell lung cancer cell lines.



**Identification of novel agonists of the integrin CD11b/CD18**

pp 6902–6906

Mohd. Hafeez Faridi, Dony Manguel, Constantinos J. Barth, Darren Stoub, Ruth Day, Stephan Schürer\*, Vineet Gupta\*

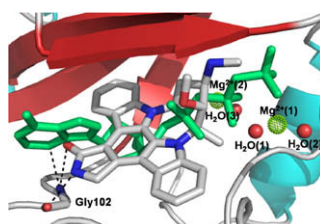


Novel allosteric agonists of integrin CD11b/CD18 were identified. Initial SAR exploration and structural model of binding site are presented.

**Structural insights into IKK $\beta$  inhibition by natural products staurosporine and quercetin**

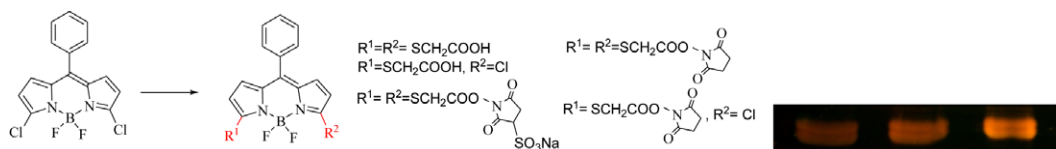
pp 6907–6910

Carolina M. Avila, Nelilma C. Romeiro, Carlos M. R. Sant'Anna, Eliezer J. Barreiro, Carlos A. M. Fraga\*

This work describes the structural basis of the IKK $\beta$  inhibition by staurosporine and quercetin in ATP binding site.**Synthesis, spectroscopic properties and protein labeling of water soluble 3,5-disubstituted boron dipyrromethenes**

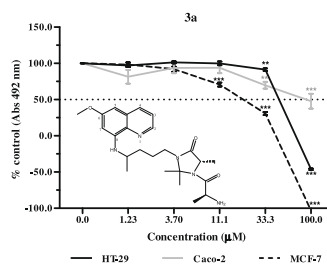
pp 6911–6913

Özlem Dilek, Susan L. Bane\*

**Anti-tumoral activity of imidazoquinones, a new class of antimalarials derived from primaquine**

pp 6914–6917

Iva Fernandes, Nuno Vale, Victor de Freitas, Rui Moreira, Nuno Mateus, Paula Gomes\*

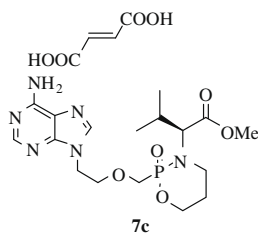


The anti-proliferative activity of primaquine, and related quinolinic antimalarials, against three human tumoral cell lines is reported.



## Design, synthesis and evaluation of novel oxazaphosphorine prodrugs of 9-(2-phosphonomethoxyethyl)adenine (PMEA, adefovir) as potent HBV inhibitors

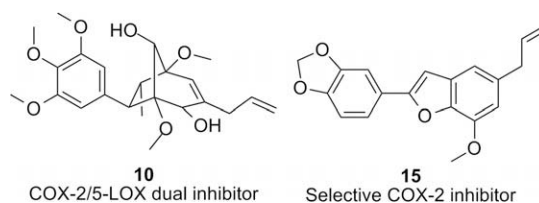
pp 6918–6921

Peng Lu, Jiangxia Liu, Yuya Wang, Xiaoyan Chen, Yushe Yang<sup>\*</sup>, Ruyun Ji

A series of novel oxazaphosphorine prodrugs of PMEA is disclosed. L-valine methyl ester (**7c**) demonstrated highly potent anti-HBV activity, excellent stability in human plasma and release of the parent compound PMEA in human microsomes.

## COX, LOX and platelet aggregation inhibitory properties of Lauraceae neolignans

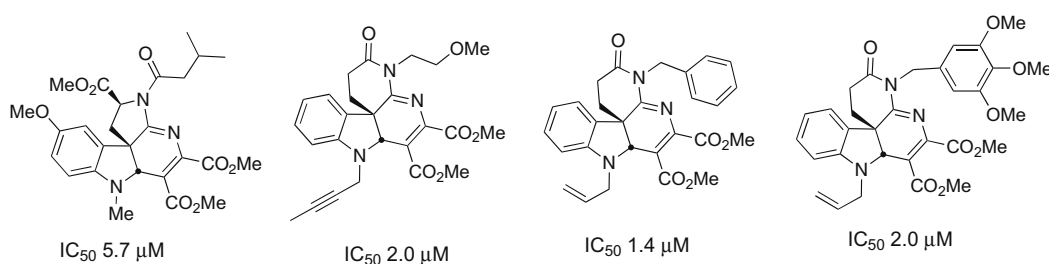
pp 6922–6925

Ericsson David Coy<sup>\*</sup>, Luis Enrique Cuca<sup>\*</sup>, Michael Sefkow

Inhibition of COX-1, COX-2, 5-LOX and agonist-induced platelet aggregation for 26 neolignans is reported.

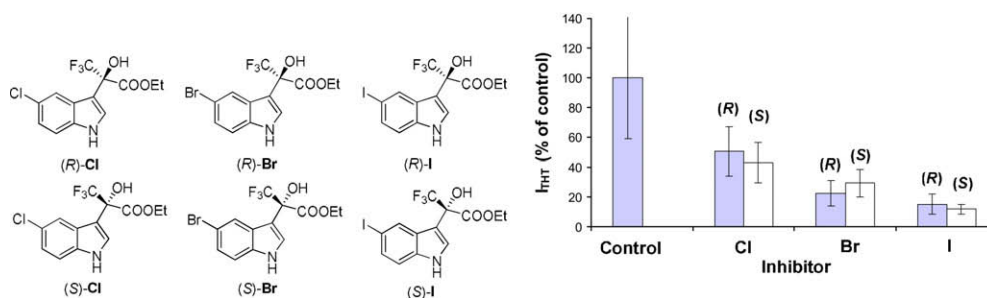
## New small molecule inhibitors of hepatitis C virus

pp 6926–6930

Wanguo Wei, Cuifang Cai, Smitha Kota, Virginia Takahashi, Feng Ni, A. Donny Strosberg<sup>\*</sup>, John K. Snyder<sup>\*</sup>

## Effect of chirality of small molecule organofluorine inhibitors of amyloid self-assembly on inhibitor potency

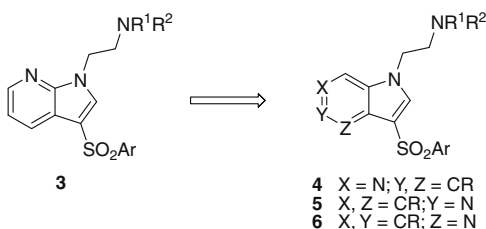
pp 6931–6934

Abha Sood, Mohammed Abid, Samson Hailemichael, Michelle Foster, Béla Török, Marianna Török<sup>\*</sup>

**1-(2-Aminoethyl)-3-(arylsulfonyl)-1H-pyrrolopyridines are 5-HT<sub>6</sub> receptor ligands**

pp 6935–6938

Ronald C. Bernotas<sup>\*</sup>, Schuyler A. Antane, Steven E. Lenicek, Simon N. Haydar, Albert J. Robichaud, Boyd L. Harrison, Guo Ming Zhang, Deborah Smith, Joseph Coupet, Lee E. Schechter

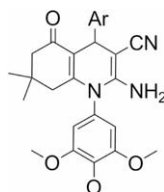


Pyrrolopyridines **4**, **5**, and **6** have been prepared and tested as 5-HT<sub>6</sub> ligands.

**Synthesis and biological evaluation of 2-amino-7,7-dimethyl 4-substituted-5-oxo-1-(3,4,5-trimethoxy)-1,4,5,6,7,8-hexahydro-quinoline-3-carbonitrile derivatives as potential cytotoxic agents**

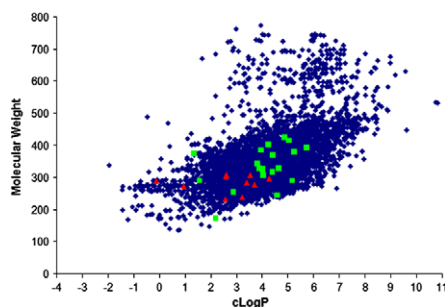
pp 6939–6942

Saleh I. Alqasoumi, Areej M. Al-Taweel, Ahmed M. Alafeefy, Mostafa M. Hamed, Eman Noaman, Mostafa M. Ghorab<sup>\*</sup>

**Physicochemical property profiles of marketed drugs, clinical candidates and bioactive compounds**

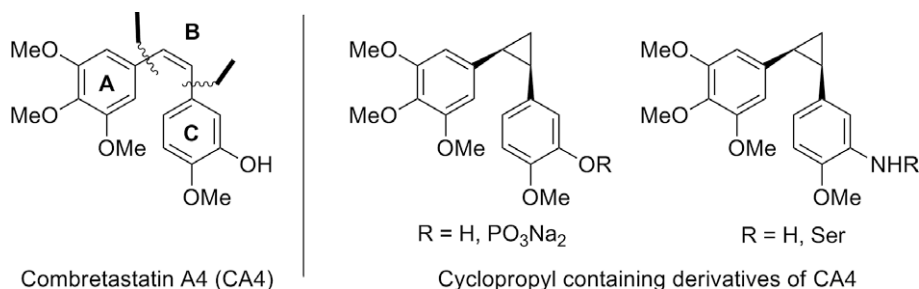
pp 6943–6947

Christian Tyrchan, Niklas Blomberg, Ola Engkvist, Thierry Kogej, Sorel Muresan<sup>\*</sup>

**Synthesis and antitumor-evaluation of cyclopropyl-containing combretastatin analogs**

pp 6948–6951

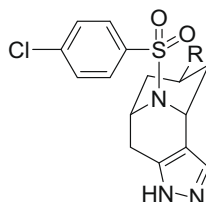
Rita Fürst, István Zupkó, Ágnes Berényi, Gerhard F. Ecker, Uwe Rinner<sup>\*</sup>



**N-Bridged bicyclic sulfonamides as inhibitors of  $\gamma$ -secretase**

pp 6952–6956

Simeon Bowers<sup>\*</sup>, Gary D. Probst, Anh P. Truong, Roy K. Hom, Andrei W. Konradi, Hing L. Sham, Albert W. Garofalo, Karina Wong, Erich Goldbach, Kevin P. Quinn, John-Michael Sauer, William Wallace, Lan Nguyen, Susanna S. Hemphill, Michael P. Bova, Guriqbal S. Basi



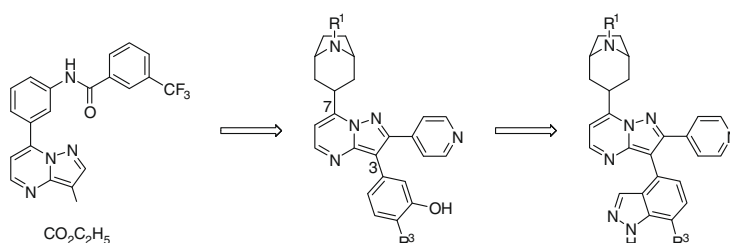
The structural modification of a series of [3.3.1] bicyclic sulfonamide based  $\gamma$ -secretase inhibitors is described. Appropriate substitution on the bicyclic scaffold provides a significant increase in the metabolic stability of the compounds resulting in an improved in vivo metabolic profile.

**Novel pyrazolopyrimidines as highly potent B-Raf inhibitors**

pp 6957–6961

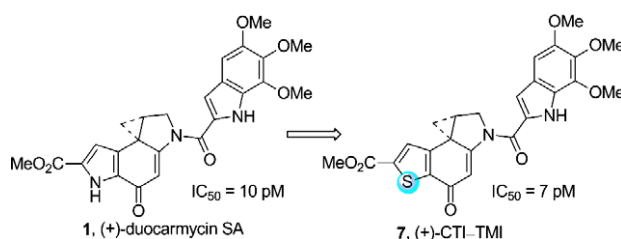
Martin J. Di Grandi<sup>\*</sup>, Dan M. Berger, Darrin W. Hopper, Chunchun Zhang, Minu Dutia, Alejandro L. Dunnick, Nancy Torres, Jeremy I. Levin, George Diamantidis, Christoph W. Zapf, Jonathan D. Bloom, YongBo Hu, Dennis Powell, Donald Wojciechowicz, Karen Collins, Eileen Frommer

A novel series of pyrazolo[1,5-*a*]pyrimidines bearing a 3-hydroxyphenyl group at C(3) and substituted tropanes at C(7) have been identified as potent B-Raf inhibitors. Exploration of alternative functional groups as a replacement for the C(3) phenol demonstrated indazole to be an effective isostere. Several compounds possessing substituted indazole residues, such as **4e**, **4p**, and **4r**, potently inhibited cell proliferation at submicromolar concentrations in the A375 and WM266 cell lines, and the latter two compounds also exhibited good therapeutic indices in cells.

**Synthesis and evaluation of a thio analogue of duocarmycin SA**

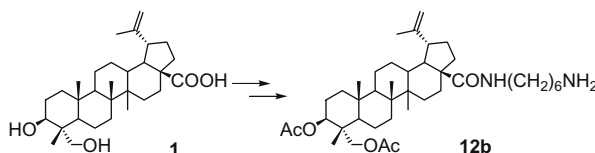
pp 6962–6965

Karen S. MacMillan, James P. Lajiness, Carlota Lopez Cara, Romeo Romagnoli, William M. Robertson, Inkyu Hwang, Pier Giovanni Baraldi<sup>\*</sup>, Dale L. Boger<sup>\*</sup>

**Terpenoids. III: Synthesis and biological evaluation of 23-hydroxybetulinic acid derivatives as novel inhibitors of glycogen phosphorylase**

pp 6966–6969

Peiqing Zhu, Yi Bi, Jinyi Xu<sup>\*</sup>, Zan Li, Jun Liu, Luyong Zhang, Wencai Ye, Xiaoming Wu<sup>\*</sup>



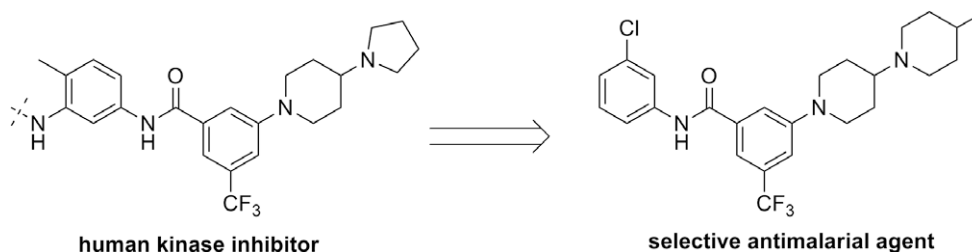
A series of 23-hydroxybetulinic acid derivatives were prepared and evaluated as a new class of inhibitors of glycogen phosphorylase (GP), among which **12b** was the most potent GP<sub>a</sub> inhibitor ( $IC_{50} = 3.5 \mu M$ ).



**Cell-based optimization of novel benzamides as potential antimalarial leads**

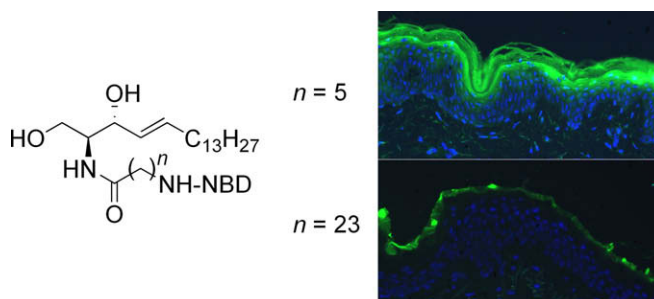
pp 6970–6974

Tao Wu, Advait Nagle, Tomoyo Sakata, Kerstin Henson, Rachel Borboa, Zhong Chen, Kelli Kuhen, David Plouffe, Elizabeth Winzeler, Francisco Adrian, Tove Tuntland, Jonathan Chang, Susan Simerson, Steven Howard, Jared Ek, John Isbell, Xianming Deng, Nathanael S. Gray, David C. Tully, Arnab K. Chatterjee \*

**Synthesis of fluorescent C<sub>24</sub>-ceramide: Evidence for acyl chain length dependent differences in penetration of exogenous NBD-ceramides into human skin**

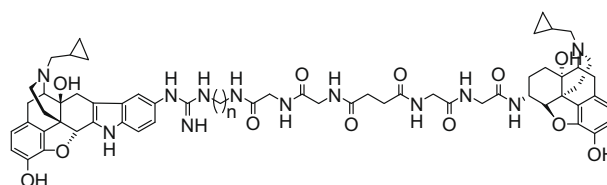
pp 6975–6977

Jakub Novotný, Kateřina Pospěchová, Alexandr Hrabálek, Robert Čáp, Kateřina Vávrová \*

**A bivalent ligand (KMN-21) antagonist for  $\mu/\kappa$  heterodimeric opioid receptors**

pp 6978–6980

Shijun Zhang, Ajay Yekkirala, Ye Tang, Philip S. Portoghese \*

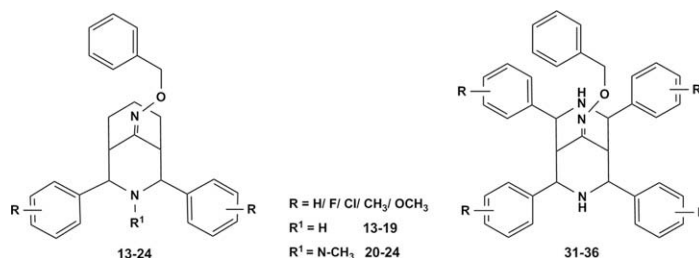


A series of bivalent ligands containing  $\kappa$ - and  $\mu$ -antagonist pharmacophores were designed and reported as chemical tools for studying  $\kappa$ - $\mu$  heterodimers.

**Synthesis, stereochemistry and antimicrobial studies of novel oxime ethers of aza/diazabicycles**

pp 6981–6985

Paramasivam Parthiban, Gopalakrishnan Aridoss, Paramasivam Rathika, Venkatachalam Ramkumar, Senthamaraikannan Kabilan \*



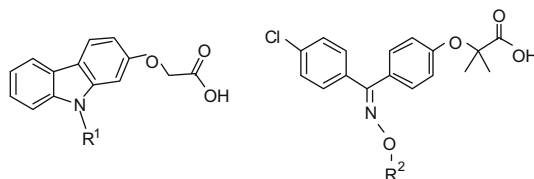
Two series of heterobicyclic oxime ethers viz, 3-ABN-9-one and 3,7-DABN-9-one O-benzyloximes were synthesized and stereochemistry was established by their spectral and crystal studies. All the synthesized oxime ethers were screened against a set of pathogenic bacteria and fungi. From the results, structure-activity relationship was discussed.



**NSAID-derived  $\gamma$ -secretase modulators. Part III: Membrane anchoring**

pp 6986–6990

Stefanie Baumann, Nicole Höttecke, Robert Schubel, Karlheinz Baumann, Boris Schmidt \*

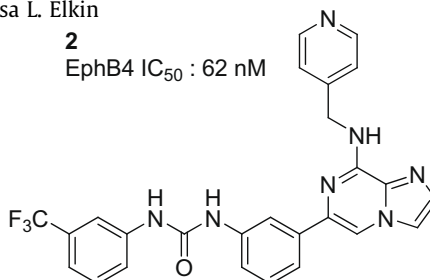


The synthesis and activity data of N-substituted carbazole- and O-substituted fenofibrate-derived  $\gamma$ -secretase modulators are presented. Out of 19 screened compounds, seven exhibited promising activity against  $A\beta_{42}$  secretion at a low micromolar level. We suggest that the  $\gamma$ -secretase modulators interact with lys624 at the membrane interface and that the lipophilic substituent anchors the compound in the membrane.

**Imidazo[1,2-a]pyrazine diaryl ureas: Inhibitors of the receptor tyrosine kinase EphB4**

pp 6991–6995

Scott A. Mitchell \*, Mihaela Diana Danca, Peter A. Blomgren, James W. Darrow, Kevin S. Currie, Jeffrey E. Kropf, Seung H. Lee, Steven L. Gallion, Jin-Ming Xiong, Douglas A. Pippin, Robert W. DeSimone, David R. Brittelli, David C. Eustice, Aaron Bourret, Melissa Hill-Drzewi, Patricia M. Maciejewski, Lisa L. Elkin

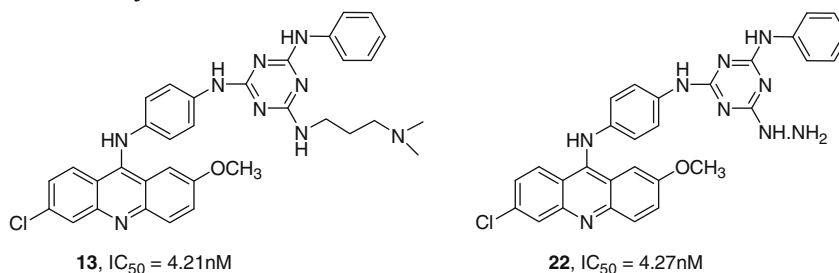


The identification of imidazo[1,2-a]pyrazine diarylureas as potent inhibitors of the receptor tyrosine kinase EphB4 is reported.

**Synthesis of 9-anilinoacridine triazines as new class of hybrid antimalarial agents**

pp 6996–6999

Ashok Kumar, Kumkum Srivastava, S. Raja Kumar, S. K. Puri, Prem M. S. Chauhan \*

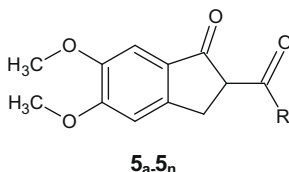


A series of new class of hybrid 9-anilinoacridine triazines were synthesized and screened in vitro for their antimalarial activity against CQ-sensitive 3D7 strain of *Plasmodium falciparum*. The compounds **13** and **29** displayed >96.59% and 98.73% suppression, respectively, orally against N-67 strain of *Plasmodium yoelii* in swiss mice at dose 100 mg/kg for four days.

**Synthesis and antimycobacterial evaluation of novel 5,6-dimethoxy-1-oxo-2,5-dihydro-1H-2-indenyl-5,4-substituted phenyl methanone analogues**

pp 7000–7002

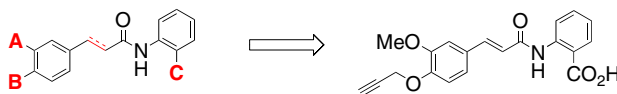
Mohamed Ashraf Ali \*, Jeyabalan Govinda Samy, Elumalai Manogaran, Velmurugan Sellappan, Mohamed Zaheen Hasan, Mohamed Jawed Ahsan, Suresh Pandian, Mohammad ShaharYar



In present investigation, a series of substituted phenyl-5,6-dimethoxy-1-oxo-2,5-dihydro-1H-2-indenylmethanone analogues were synthesized and were evaluated for antimycobacterial activity against *Mycobacterium tuberculosis* H<sub>57</sub>Rv and INH resistant *M. tuberculosis*. All the newly synthesized compounds were showing moderate to high inhibitory activities, with compound 5,6-dimethoxy-1-oxo-2,5-dihydro-1H-2-indenyl-4-fluorophenylmethanone (**5g**) produced was found to be the most promising compounds active against *M. tuberculosis* H<sub>57</sub>Rv and isoniazid (INH) resistant *M. tuberculosis* with Minimum inhibitory concentration 0.10 and 0.10  $\mu$ M.

**Evaluation and optimization of antifibrotic activity of cinnamoyl anthranilates**

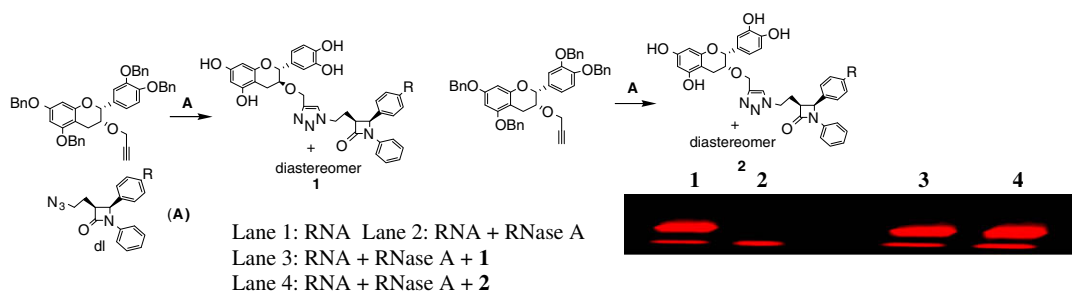
pp 7003–7006

Steven C. Zammit, Alison J. Cox, Renae M. Gow, Yuan Zhang, Richard E. Gilbert, Henry Krum, Darren J. Kelly<sup>\*</sup>, Spencer J. Williams<sup>\*</sup>

A panel of cinnamoyl anthranilates were investigated for their antifibrotic activity through their ability to reduce collagen formation stimulated by the cytokine transforming growth factor- $\beta$ . The most active compound was shown to reduce albuminuria in a hypertensive rat model of progressive type II diabetes.

**Design, synthesis and bioactivity of catechin/epicatechin and 2-azetidinone derived chimeric molecules**

pp 7007–7010

Basab Roy, Arindam Chakraborty, Sudip K. Ghosh, Amit Basak<sup>\*</sup><sup>\*</sup>Corresponding author

Supplementary data available via ScienceDirect

**COVER**

MW versus cLogP for drugs (red), clinical candidates (green) and bioactive compounds (blue) for Cannabinoid receptor CNR1. [Tyrchan, C.; Blomberg, N.; Engkvist, O.; Kogej, T.; Muresan, S. *Bioorg. Med. Chem. Lett.* **2009**, 19, 6943.]

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