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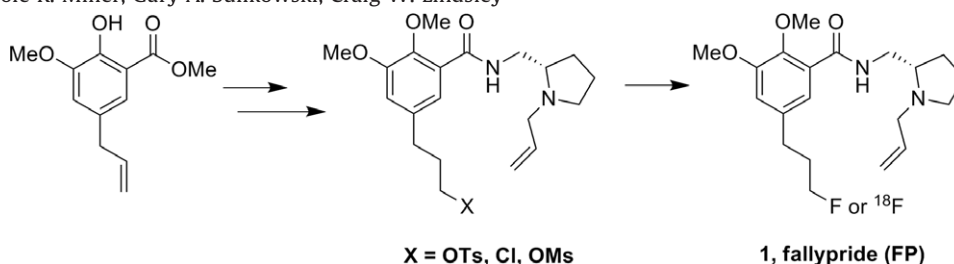
Contents

ARTICLES

A new multi-gram synthetic route to labeling precursors for the $D_{2/3}$ PET agent ^{18}F -fallypride

pp 4467–4469

Kwangho Kim, Nicole R. Miller, Gary A. Sulikowski, Craig W. Lindsley*



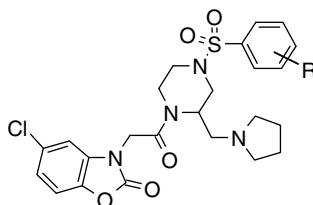
This Letter describes a new multi-gram synthetic protocol for the preparation of the classic tosylate labeling precursor for the $D_{2/3}$ PET agent [^{18}F]fallypride. In the course of our studies, we also discovered two novel labeling precursors, the previously undescribed mesylate and chloro congeners of fallypride.



Aminomethylpiperazines as selective urotensin antagonists

pp 4470–4473

Mark A. Hilfiker*, Daohua Zhang, Sarah E. Dowdell, Krista B. Goodman, John J. McAtee, Jason W. Dodson, Andrew Q. Viet, Gren Z. Wang, Clark A. Sehon, David J. Behm, Zining Wu, Luz H. Carballo, Stephen A. Douglas, Michael J. Neeb

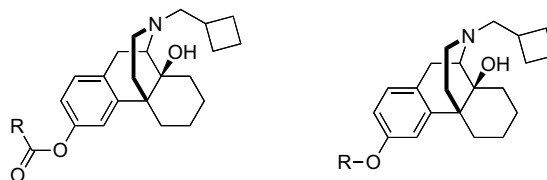


Aminomethylpiperazines, reported previously as being κ -opioid receptor agonists, have been developed into selective, high affinity human urotensin-II antagonists.

Synthesis and pharmacological evaluation of hydrophobic esters and ethers of butorphanol at opioid receptors

pp 4474–4476

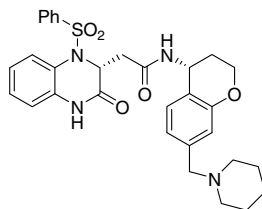
Brian S. Fulton, Brian I. Knapp, Jean M. Bidlack, John L. Neumeyer*



Hydrophobic esters and ethers of butorphanol were synthesized and their affinities at opioid receptors determined. Tested compounds displayed moderate to high affinities to the μ and κ receptors. The findings accord with previous evidence of a lipophilic binding pocket in the opioid receptors that can be accessed to afford good binding affinity without the need for a phenolic hydrogen-bond donor group.

Discovery of dihydroquinoxalinone acetamides containing bicyclic amines as potent Bradykinin B1 receptor antagonists pp 4477–4481

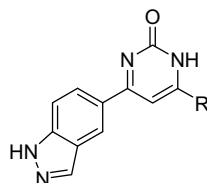
Jian Jeffrey Chen*, Wenyuan Qian, Kaustav Biswas, Vellarkad N. Viswanadhan, Benny C. Askew, Stephen Hitchcock, Randall W. Hungate, Leyla Arik, Eileen Johnson



Novel dihydroquinoxalinone acetamides containing bicyclic aminotetralins or chromans were found to be potent Bradykinin B1 receptor antagonists.

4-(1*H*-Indazol-5-yl)-6-phenylpyrimidin-2(1*H*)-one analogs as potent CDC7 inhibitors pp 4482–4485

Cynthia M. Shafer*, Mika Lindvall, Cornelia Bellamacina, Thomas G. Gesner, Asha Yabannavar, Weiping Jia, Song Lin, Annette Walter

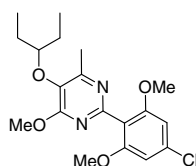


A series of 4-(4-hydroxyphenyl)-6-phenylpyrimidin-2(1*H*)-ones were identified by HTS as inhibitors of CDC7. Molecular modeling and medicinal chemistry techniques were employed to explore the SAR for this series with a focus on removing potential metabolic liabilities and improving cellular potency.



2-Arylpyrimidines: Novel CRF-1 receptor antagonists pp 4486–4490

Taeyoung Yoon, Stéphane De Lombaert, Robbin Brodbeck, Michael Gulianello, James E. Krause, Alan Hutchison, Raymond F. Horvath, Ping Ge, John Kehne, Diane Hoffman, Jayaraman Chandrasekhar, Darío Doller, Kevin J. Hodgetts*

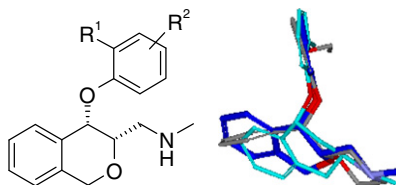


12b, CRF-1 K_i = 9 nM

The design, synthesis, and structure–activity relationship studies of a novel series of CRF-1 receptor antagonists, the 2-arylpyrimidines, are described. The effects of substitution on the aromatic ring and the pyrimidine core on CRF-1 receptor binding were investigated. A number of compounds with K_i values below 10 nM and lipophilicity in a minimally acceptable range for a CNS drug ($cLog P < 5$) were discovered.

Structure–activity relationships of chiral selective norepinephrine reuptake inhibitors (sNRI) with increased oxidative stability pp 4491–4494

Sarah Hudson, Mehrak Kiankarimi, Wendy Eccles, Wesley Dwight, Yalda S. Mostofi, Marc J. Genicot, Beth A. Fleck, Kathleen Gogas, Anna Aparicio, Hua Wang, Jenny Wen, Warren S. Wade*



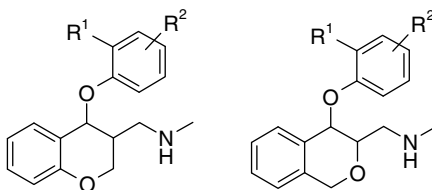
A series of chiral ring-constrained norepinephrine reuptake inhibitors equivalent to atomoxetine in potency, selectivity, and inhibition of CYP2D6 but more stable to oxidative metabolism.



Synthesis and structure–activity relationships of selective norepinephrine reuptake inhibitors (sNRI) with a heterocyclic ring constraint

pp 4495–4498

Sarah Hudson*, Mehrak Kiankarimi, Wendy Eccles, Yalda S. Mostofi, Marc J. Genicot, Wesley Dwight, Beth A. Fleck, Kathleen Gogas, Warren S. Wade*



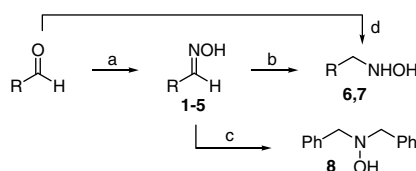
A series of heterocyclic ring-constrained norepinephrine reuptake inhibitors have activities as racemates equivalent to atomoxetine (IC_{50} 's < 10 nM).



Metal-free artificial nucleases based on simple oxime and hydroxylamine scaffolds

pp 4499–4502

Luciano Fernandes, Franciele L. Fischer, Carolina W. Ribeiro, Gustavo P. Silveira, Marcus M. Sá, Faruk Nome, Hernán Terenzi*



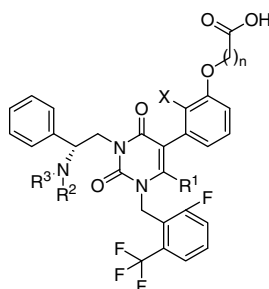
Hydrolysis of DNA is of increasing importance in biotechnology and medicine. In this Letter, we present the DNA-cleavage potential of metal-free hydroxylamines and oximes as new members of nucleic acid cleavage agents.



Zwitterionic uracil derivatives as potent GnRH receptor antagonists with improved pharmaceutical properties

pp 4503–4507

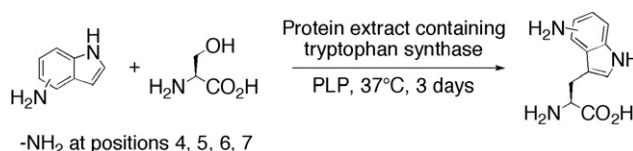
Colin F. Regan, Zhiqiang Guo, Yongsheng Chen, Charles Q. Huang, Mi Chen, Wanlong Jiang, Jaimie K. Rueter, Timothy Coon, Chen Chen, John Saunders, Michael S. Brown, Steve F. Betz, R. Scott Struthers, Chun Yang, Jenny Wen, Ajay Madan, Yun-Fei Zhu*



A convenient one-step synthesis of L-aminotryptophans and improved synthesis of 5-fluorotryptophan

pp 4508–4510

Michael Winn, Abhijeet Deb Roy, Sabine Grüşchow, Raj S. Parameswaran, Rebecca J. M. Goss*



A one-pot biotransformation for the generation of a series of L-aminotryptophans using tryptophan synthase-containing bacterial cell free extract is reported. The extract can be freeze-dried and stored without appreciable loss of activity.

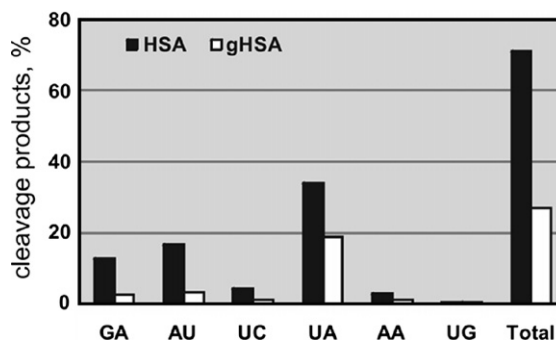


Interaction of human serum albumin and its clinically relevant modification with oligoribonucleotides

pp 4511–4514

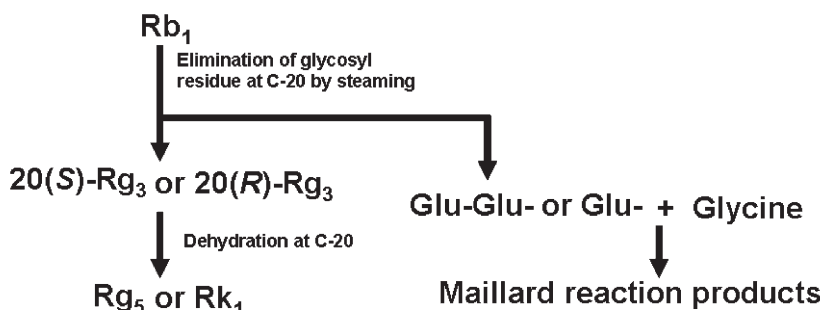
Yuliya V. Gerasimova, Irina A. Erchenko, Makhmut M. Shakirov, Tatyana S. Godovikova*

RNA hydrolysis in the presence of HSA proceeds via 2',3'-cyclophosphate intermediates. Nonenzymatic glycation of HSA decreases protein-mediated oligoribonucleotide cleavage with no influence on the cleavage specificity.

**The chemical and hydroxyl radical scavenging activity changes of ginsenoside-Rb₁ by heat processing**

pp 4515–4520

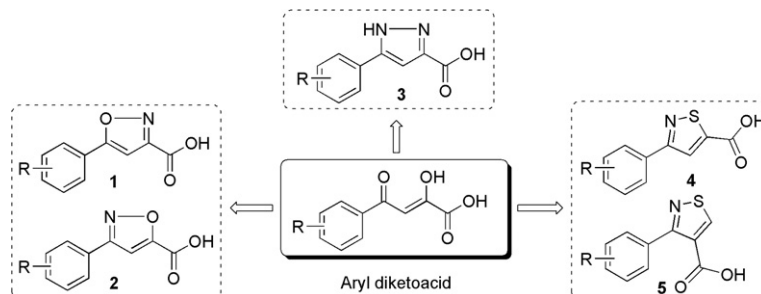
Yong Jae Lee, Hyun Young Kim, Ki Sung Kang, Jin Gyun Lee, Takako Yokozawa, Jeong Hill Park*

**Efficient synthesis and utilization of phenyl-substituted heteroaromatic carboxylic acids as aryl diketo acid isosteres in the design of novel HIV-1 integrase inhibitors**

pp 4521–4524

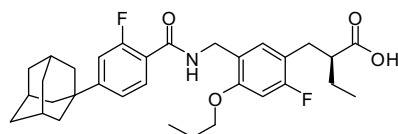
Li-Fan Zeng, Hu-Shan Zhang, Yun-Hua Wang, Tino Sanchez, Yong-Tang Zheng, Nouri Neamati, Ya-Qiu Long*

Three types of aryl diketo acid isosteres were designed and synthesized by conversion of the biologically labile 1,3-diketo unit into isoxazole, isothiazole or 1H-pyrazole to improve the bioavailability of ADK-based HIV-1 integrase inhibitors, affording potent antiviral effect and high therapeutic index.

**Improvement of the transactivation activity of phenylpropanoic acid-type peroxisome proliferator-activated receptor pan agonists: Effect of introduction of fluorine at the linker part**

pp 4525–4528

Jun-ichi Kasuga*, Takuji Oyama, Yuko Hirakawa, Makoto Makishima, Kosuke Morikawa, Yuichi Hashimoto, Hiroyuki Miyachi*



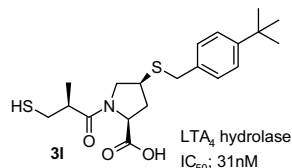
PPAR pan agonist

Activity (EC ₅₀)		
PPARα	PPARδ	PPARγ
13 nM	23 nM	31 nM

Synthesis and biological evaluation of *N*-mercaptoacylproline and *N*-mercaptoacylthiazolidine-4-carboxylic acid derivatives as leukotriene A₄ hydrolase inhibitors

pp 4529–4532

Hiroshi Enomoto*, Yuko Morikawa, Yurika Miyake, Fumio Tsuji, Maki Mizuchi, Hiroshi Suhara, Ken-ichi Fujimura, Masato Horiuchi, Masakazu Ban

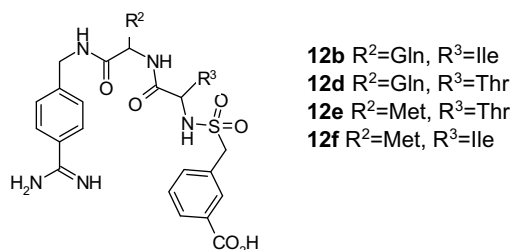


Synthesis and leukotriene A₄ (LTA₄) hydrolase inhibitory activity of *N*-mercaptoacylproline and (4*R*)-*N*-mercaptoacylthiazolidine-4-carboxylic acid derivatives are reported. An *N*-mercaptoacyl group, (2*S*)-3-mercapto-2-methylpropionyl group, was effective for both scaffolds. Additional introduction of a substituent, such as 4-*tert*-butyl benzylthio, with (*S*)-configuration at the C₄ position of proline yielded potent LTA₄ hydrolase inhibitors.

**Factor VIIa inhibitors: Target hopping in the serine protease family using X-ray structure determination**

pp 4533–4537

Takuya Shiraishi*, Shojiro Kadono, Masayuki Haramura, Hirofumi Kodama, Yoshiyuki Ono, Hitoshi Iikura, Tohru Esaki, Takaki Koga, Kunihiro Hattori, Yoshiaki Watanabe, Akihisa Sakamoto, Kazutaka Yoshihashi, Takehisa Kitazawa, Keiko Esaki, Masateru Ohta, Haruhiko Sato, Toshiro Kozono



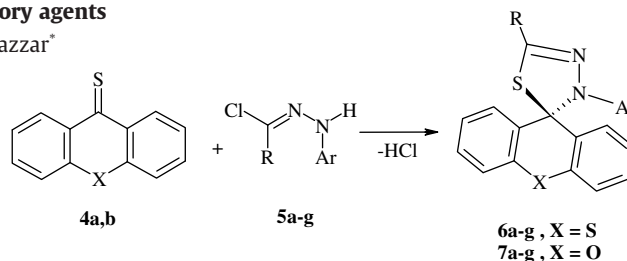
12b R²=Gln, R³=Ile
 12d R²=Gln, R³=Thr
 12e R²=Met, R³=Thr
 12f R²=Met, R³=Ile

We succeeded in target hopping in the serine protease family using crystal structures of human FVIIa/TF in complex with peptide mimetic inhibitors.

A facile regioselective synthesis of novel spiro-thioxanthene and spiro-xanthene-9',2-[1,3,4]thiadiazole derivatives as potential analgesic and anti-inflammatory agents

pp 4538–4543

H. N. Hafez, M. I. Hegab, I. S. Ahmed-Farag, A. B. A. El-Gazzar*

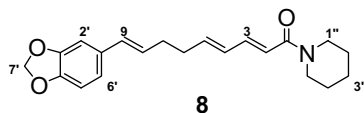


The 1,3-dipolar cycloaddition of nitrile imines to 9*H*-thioxanthene-9-thione and 9*H*-xanthone-9-thione afforded novel spiro-thioxanthene-9',2-[1,3,4]thiadiazoles **6a–g** and spiro-xanthene-9',2-[1,3,4]thiadiazoles **7a–g** in good yields. Some of the newly synthesized compounds were tested for anti-inflammatory and analgesic activities comparable to ibuprofen. Compounds **6a,d,e** and **7a,d,e** showed significant activity compared to standard drug. The toxicity studies revealed that neither death nor other behavioral or toxicological changes were observed on rats up to a dose as high as 200 mg/kg.

Alkamides from the fruits of *Piper longum* and *Piper nigrum* displaying potent cell adhesion inhibition

pp 4544–4546

Seung Woong Lee, Young Kook Kim, Koanhui Kim, Hyun Sun Lee, Jung Ho Choi, Woo Song Lee, Chang-Duk Jun, Jee Hun Park, Jeong Min Lee, Mun-Chual Rho*

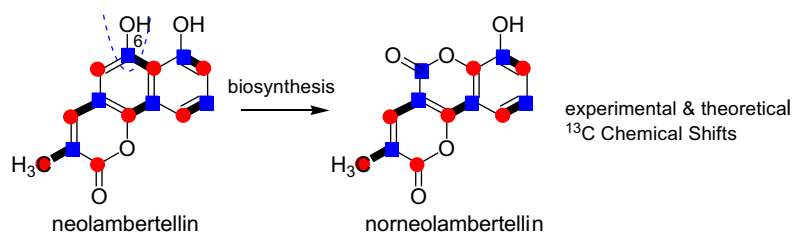


Eight alkamides **1–8** were isolated from EtOH extracts of the fruits of *Piper longum* and *nigrum*. Among the tested alkamide derivatives **1–8**, dehydropipernonaline (**8**) showed the most inhibition of the direct binding between sICAM-1 and LFA-1 of THP-1 cells in a dose-dependent manner, with an IC₅₀ value of 6.0 μg/mL.

Structure and biosynthesis of norneolambertellin produced by *Lambertella* sp. 1346

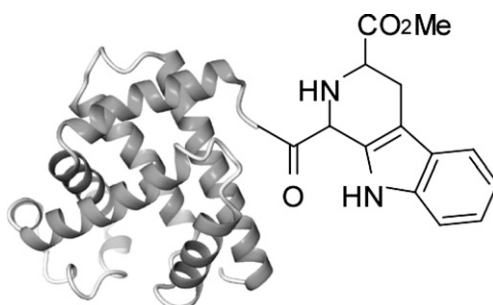
pp 4547–4549

Takanori Murakami, Noboru Takada, Warren Hehre, Masaru Hashimoto*

**N-terminal labeling of proteins by the Pictet–Spengler reaction**

pp 4550–4553

Tsubasa Sasaki, Koichiro Kodama, Hiroaki Suzuki, Seketsu Fukuzawa*, Kazuo Tachibana*

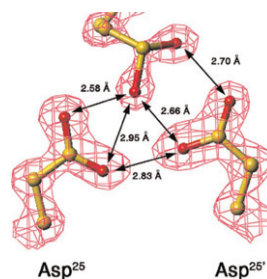


This work describes the methodology for the N-terminal modification of proteins by the Pictet–Spengler reaction.

**Crystal structure of chemically synthesized HIV-1 protease and a ketomethylene isostere inhibitor based on the p2/NC cleavage site**

pp 4554–4557

Vladimir Yu. Torbeev*, Kalyaneswar Mandal, Valentina A. Terechko, Stephen B. H. Kent

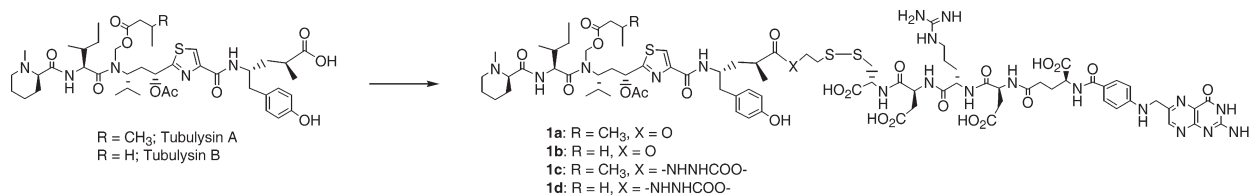


Crystal structure of HIV-1 protease with its ketomethylene isostere inhibitor is reported.

**Design and regioselective synthesis of a new generation of targeted chemotherapeutics. Part II: Folic acid conjugates of tubulysins and their hydrazides**

pp 4558–4561

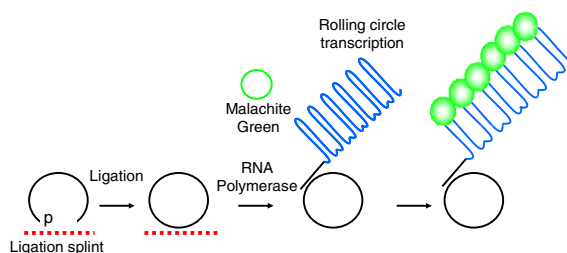
Iontcho R. Vlahov*, Yu Wang, Paul J. Kleindl, Christopher P. Leamon



Fluorescence generation from tandem repeats of a malachite green RNA aptamer using rolling circle transcription

pp 4562–4565

Kazuhiro Furukawa, Hiroshi Abe*, Naoko Abe, Mitsuru Harada, Satoshi Tsuneda, Yoshihiro Ito

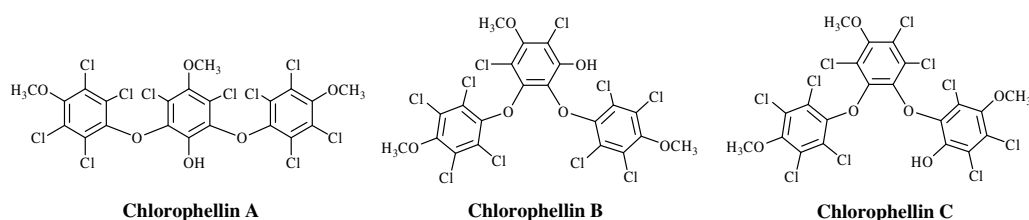


We demonstrate a fluorescence generation of tandem repeats of a malachite green (MG) RNA aptamer using rolling circle transcription.

Polychlorinated compounds with PPAR- γ agonistic effect from the medicinal fungus *Phellinus ribis*

pp 4566–4568

In-Kyoung Lee, Jeong-Hyung Lee, Bong-Sik Yun*

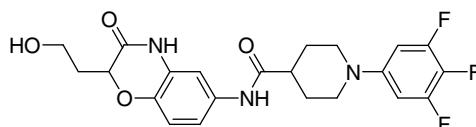


Polychlorinated compounds with PPAR- γ agonistic effect have been isolated together with the known compound, drosophilin A, from the methanolic extract of the fruiting body of the fungus *Phellinus ribis*. Chemical structures were assigned on the basis of NMR and mass spectrometric analyses. Chlorophellin C of compounds exhibited the most potent PPAR- γ agonistic effect and was comparable to rosiglitazone.

Discovery of piperidine carboxamide TRPV1 antagonists

pp 4569–4572

Wing S. Cheung, Raul R. Calvo, Brett A. Tounge, Sui-Po Zhang, Dennis R. Stone, Michael R. Brandt, Tasha Hutchinson, Christopher M. Flores, Mark R. Player*

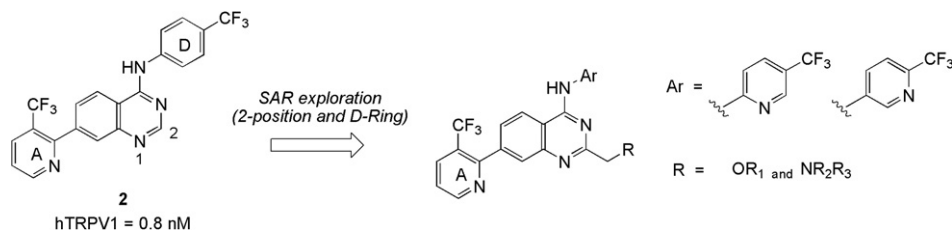


A series of piperidine carboxamides were developed as potent antagonists of the transient receptor potential receptor vanilloid 1 (TRPV1), an emerging target for the treatment of pain. A focused library of polar head groups led to the identification of a benzoxazinone amide that afforded good potency in cell-based assays. Synthesis and a QSAR model will be presented.

Aminoquinazolines as TRPV1 antagonists: Modulation of drug-like properties through the exploration of 2-position substitution

pp 4573–4577

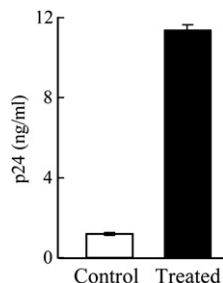
Charles A. Blum*, Xiaozhang Zheng, Harry Brielmann, Kevin J. Hodgetts, Rajagopal Bakthavatchalam, Jayaraman Chandrasekhar, James E. Krause, Daniel Cortright, David Matson, Marci Crandall, Chu K. Ngo, Lawrence Fung, Marta Day, Mark Kershaw, Stéphane De Lombaert, Bertrand L. Chenard



Selective inhibitory effects of hybrid liposomes on the growth of HIV type 1-infected cells in vitro

pp 4578–4580

Ryuichi Ueoka*, Yuji Komizu, Yoko Matsumoto, Yu Zhong, Ritsuko Tanaka, Naoki Yamamoto*

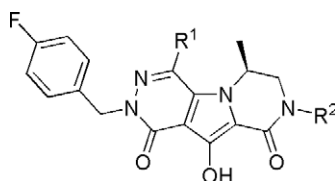


A good correlation between fifty-percent inhibitory concentration of hybrid liposomes (HL) on the growth of MOLT-4 cells chronically infected with human immunodeficiency virus and the membrane fluidity of HL was obtained.

10-Hydroxy-7,8-dihydropyrazino[1',2':1,5]pyrrolo[2,3-d]pyridazine-1,9(2H,6H)-diones: Potent, orally bioavailable HIV-1 integrase strand-transfer inhibitors with activity against integrase mutants

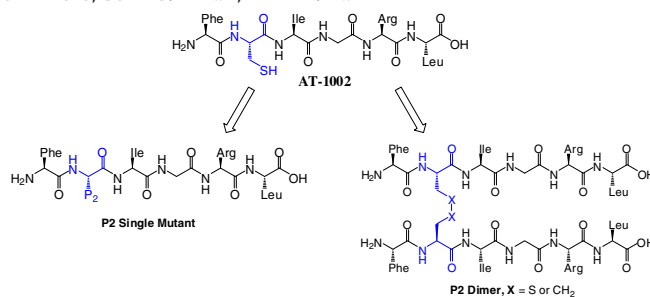
pp 4581–4583

Catherine M. Wiscount*, Peter D. Williams, Lekhanh O. Tran, Mark W. Embrey, Thorsten E. Fisher, Vanessa Sherman, Carl F. Homnick, D. Donnette Staas, Terry A. Lyle, John S. Wai, Joseph P. Vacca, ZiQiang Wang, Peter J. Felock, Kara A. Stillmock, Marc V. Witmer, Michael D. Miller, Daria J. Hazuda, Alysha M. Day, Lori J. Gabryelski, Linda T. Ecto, William A. Schleif, Daniel J. DiStefano, Christopher J. Kochansky, M. Reza Anari

**Structure–activity relationship studies of permeability modulating peptide AT-1002**

pp 4584–4586

Min Li, Ed Oliver, Kelly M. Kitchens, John Vere, Sefik S. Alkan, Amir P. Tamiz*

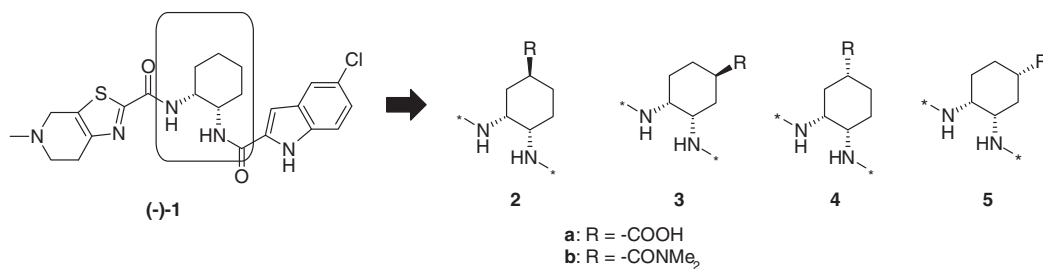


The structure–activity relationship of a permeability modulating peptide **AT-1002** was elaborated with the specific goal to replace P2 cysteine amino acid. We report herein, the discovery of peptides that exhibit reversible permeability enhancement properties with increased stability profile.

Stereoselective synthesis and biological evaluation of 3,4-diaminocyclohexanecarboxylic acid derivatives as factor Xa inhibitors

pp 4587–4592

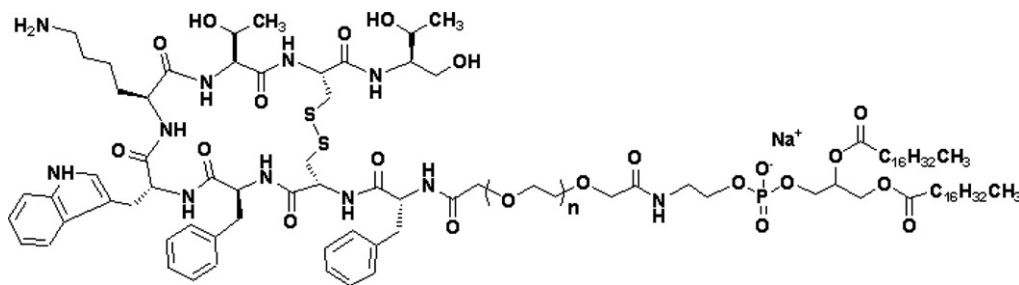
Tsutomu Nagata*, Masatoshi Nagamochi, Shozo Kobayashi, Satoshi Komoriya, Toshiharu Yoshino, Hideyuki Kanno



A synthetic method for peptide-PEG-lipid conjugates: Application of Octreotide-PEG-DSPE synthesis

pp 4593–4596

Jian-Chiou Su, Chin-Lu Tseng, Ting-Gung Chang, Wen-Jen Yu, Shih-Kwang Wu*

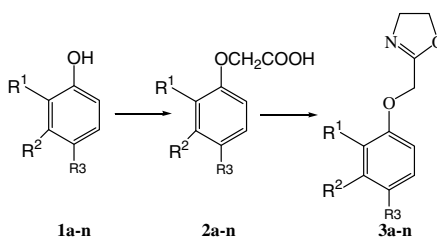


Chemical structure of Octreotide-PEG-DSPE.

**Synthesis and anti-inflammatory activity of 2-aryloxy methyl oxazolines**

pp 4597–4601

Shaukath Ara Khanum*, Noor Fatima Khanum, M. Shashikanth

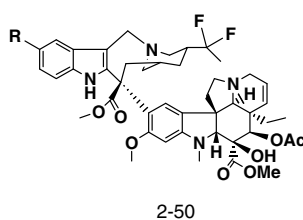


A series of potential biologically active 2-aryloxy methyl oxazolines **3a–n**, have been synthesized from substituted hydroxybenzenes **1a–n** with good chemical yield and screened for their anti-inflammatory, ulcerogenic, cyclooxygenase activities and also for their acute toxicity.

Synthesis and biological evaluation of C-12' substituted vinflunine derivatives

pp 4602–4605

Lei Xin Sheng, Yu Xiang Da, Yin Long, Liu Zhen Hong, Tang Peng Cho*

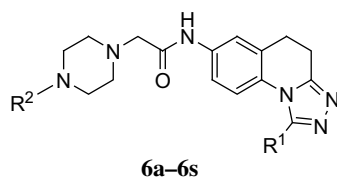


A series of novel C-12' substituted vinflunine derivatives have been synthesized. Several compounds in this series possess comparable in vitro cytotoxic potency against A549 cell lines.

Synthesis and positive inotropic activity of *N*-(4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinolin-7-yl)-2-(piperazin-1-yl)acetamide derivatives

pp 4606–4609

Chun-Bo Zhang, Xun Cui, Lan Hong, Zhe-Shan Quan, Hu-Ri Piao*

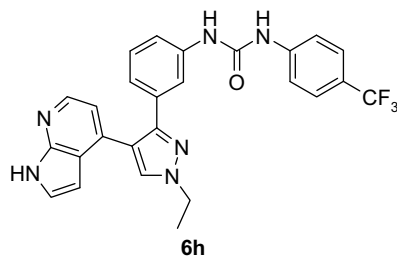


A series of *N*-(4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinolin-7-yl)-2-(piperazin-1-yl)acetamide derivatives were synthesized and their positive inotropic activity was evaluated by measuring left atrium stroke volume on isolated rabbit heart preparations.

Knowledge-based design of 7-azaindoles as selective B-Raf inhibitors

pp 4610–4614

Jun Tang*, Toshihiro Hamajima, Masato Nakano, Hideyuki Sato, Scott H. Dickerson, Karen E. Lackey

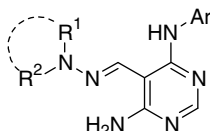


We have identified the title compound **6h** as a novel, potent, and selective B-Raf kinase inhibitor using knowledge-based design.

4-Amino-6-arylamino-pyrimidine-5-carbaldehyde hydrazones as potent ErbB-2/EGFR dual kinase inhibitors

pp 4615–4619

Guozhang Xu*, Marta C. Abad, Peter J. Connolly, Michael P. Neeper, Geoffrey T. Struble, Barry A. Springer, Stuart L. Emanuel, Niranjana Pandey, Robert H. Gruninger, Mary Adams, Sandra Moreno-Mazza, Angel R. Fuentes-Pesquera, Steven A. Middleton

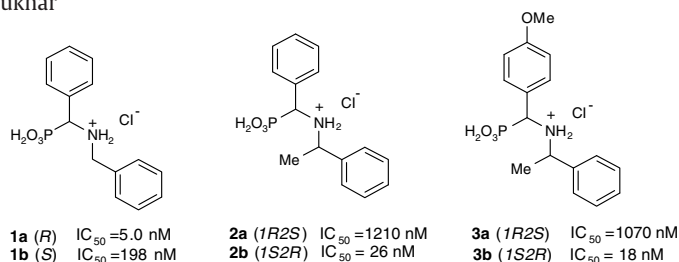


Members of a novel class of 4-amino-6-arylamino-pyrimidine-5-carbaldehyde hydrazones were identified as potent dual ErbB-2/EGFR kinase inhibitors using concept-guided design approach.

Stereoselectivity of binding of α -(N-benzylamino)benzylphosphonic acids to prostatic acid phosphatase

pp 4620–4623

Andriy I. Vovk*, Iryna M. Mischenko, Vsevolod Yu. Tanchuk, Georgiy A. Kachkovskii, Sergiy Yu. Sheiko, Oleg I. Kolodyazhnyi, Valery P. Kukhar

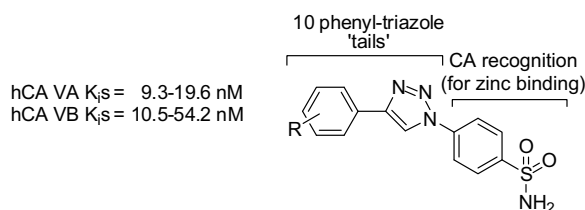


The evaluation of inhibitory activity of enantiomerically pure α -(N-benzylamino)benzylphosphonic acids toward human prostatic acid phosphatase is reported. The enantioselectivity has been explained using a molecular docking approach.

Inhibition of human mitochondrial carbonic anhydrases VA and VB with *para*-(4-phenyltriazole-1-yl)-benzenesulfonamide derivatives

pp 4624–4627

Sally-Ann Poulsen*, Brendan L. Wilkinson, Alessio Innocenti, Daniela Vullo, Claudiu T. Supuran*



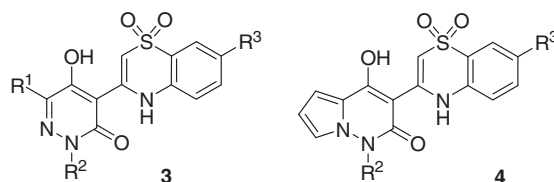
This paper describes the synthesis of and mitochondrial carbonic anhydrase inhibition for a novel library of benzenesulfonamides with variously substituted 4-phenyl-1,2,3-triazole 'tail' moieties.



4-(1,1-Dioxo-1,4-dihydro-1λ⁶-benzo[1,4]thiazin-3-yl)-5-hydroxy-2H-pyridazin-3-ones as potent inhibitors of HCV NS5B polymerase

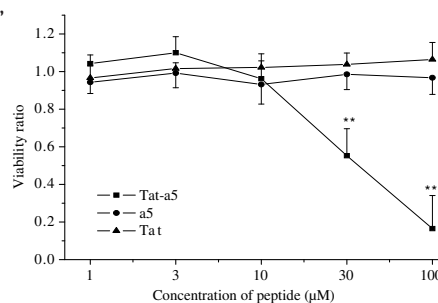
pp 4628–4632

David A. Ellis, Julie K. Blazel, Stephen E. Webber, Chinh V. Tran*, Peter S. Dragovich, Zhongxiang Sun, Frank Ruebsam, Helen M. McGuire, Alan X. Xiang, Jingjing Zhao, Lian-Sheng Li, Yuefen Zhou, Qing Han, Charles R. Kissinger, Richard E. Showalter, Matthew Lardy, Amit M. Shah, Mei Tsan, Rupal Patel, Laurie A. LeBrun, Ruhi Kamran, Darian M. Bartkowski, Thomas G. Nolan, Daniel A. Norris, Maria V. Sergeeva, Leo Kirkovsky

**A novel peptide from α5 helix of *Asterina pectinifera* cyclin B conjugated to HIV-Tat^{49–57} with cytotoxic and apoptotic effects against human cancer cells**

pp 4633–4637

Huiping Lou, Yanfeng Gao*, Mingxia Zhai, Yuanming Qi*, Lixiang Chen, Hong Lv, Jibing Yu, Yongxin Li

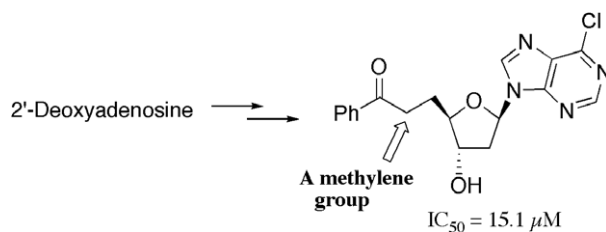


KAQIRAMECNILGRKKRRQRRR (Tat-a5)HIV-Tat (49–57): RKRRQRRR (Tat)Cyclin B (285–296): KAQIRAMECNIL (a5).

**Synthesis and evaluation of 5'-modified 2'-deoxyadenosine analogues as anti-hepatitis C virus agents**

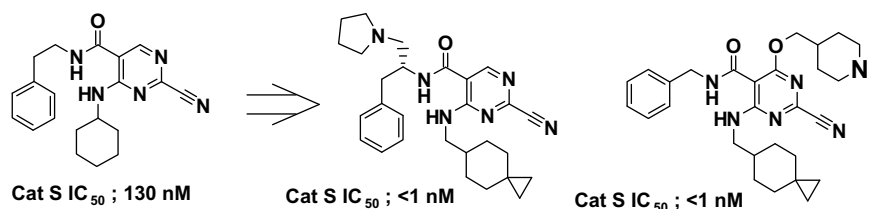
pp 4638–4641

Masahiro Ikejiri*, Takayuki Ohshima, Akemi Fukushima, Kunitada Shimotohno, Tokumi Maruyama*

**4-Amino-2-cyanopyrimidines: Novel scaffold for nonpeptidic cathepsin S inhibitors**

pp 4642–4646

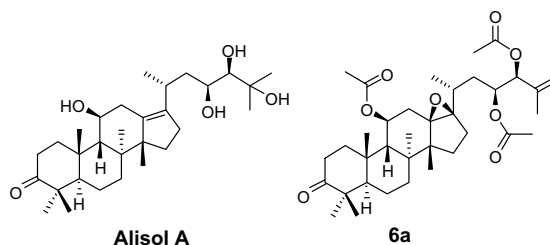
Osamu Irie*, Fumiaki Yokokawa, Takeru Ehara, Atsuko Iwasaki, Yuki Iwaki, Yuko Hitomi, Kazuhide Konishi, Masashi Kishida, Atsushi Toyao, Keiichi Masuya, Hiroki Gunji, Junichi Sakaki, Genji Iwasaki, Hajime Hirao, Takanori Kanazawa, Keiko Tanabe, Takatoshi Kosaka, Terance W. Hart, Allan Hallett



Anti-HBV agents. Part 1: Synthesis of alisol A derivatives: A new class of hepatitis B virus inhibitors

pp 4647–4650

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

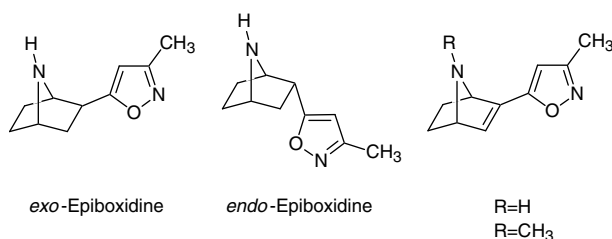


A series of alisol A derivatives were synthesized and assayed for their anti-HBV activities in vitro. The most active compound **6a** showed IC_{50} of 0.024 and 0.028 mM to HBsAg and HBeAg, respectively, with $CC_{50} > 2.6$ mM, resulting remarkable selective indices ($SI_{HBsAg} > 108$, $SI_{HBeAg} > 93$).

**Epiboxidine and novel-related analogues: A convenient synthetic approach and estimation of their affinity at neuronal nicotinic acetylcholine receptor subtypes**

pp 4651–4654

Luca Rizzi, Clelia Dallanocce*, Carlo Matera, Pietro Magrone, Luca Pucci, Cecilia Gotti, Francesco Clementi, Marco De Amici

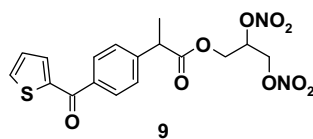


An efficient Stille coupling-based synthesis of epiboxidine and unsaturated analogues is reported. The compounds were assayed for their binding affinity at neuronal $\alpha 4\beta 2$ and $\alpha 7$ nicotinic acetylcholine receptors.

New NSAIDs-NO hybrid molecules with antiproliferative properties on human prostatic cancer cell lines

pp 4655–4657

Nicolas Bézière, Laurence Goossens, Jean Pommery, Hervé Vezin, Nadia Touati, Jean-Pierre Hénichart, Nicole Pommery*



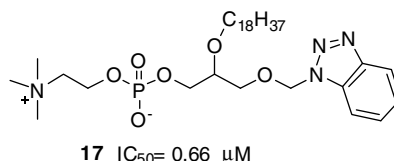
Compound **9**:
PC3 cell growth inhibition at 10 μ M :
- 52 % after 24h incubation time
- 0 % after 72h incubation time

A study of the action mechanism of new NO-donating profens on prostatic cancer cell lines is reported.

Parallel synthesis and antileishmanial activity of ether-linked phospholipids

pp 4658–4660

Paolo Coghi, Nadia Vaiana, Maria G. Pezzano, Luca Rizzi, Marcel Kaiser, Reto Brun, Sergio Romeo*

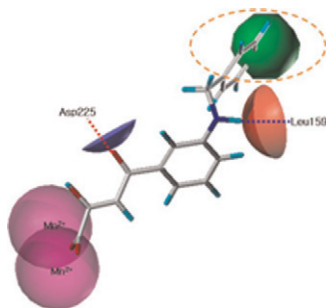


The parallel synthesis of a series of alkyl ether phospholipids is reported. Compound **17** showed good inhibition of *L. donovani* growth.

Effects of the aryl linker and the aromatic substituent on the anti-HCV activities of aryl diketoacid (ADK) analogues

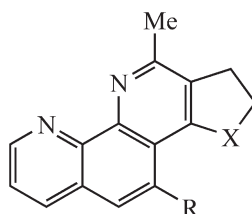
pp 4661–4665

Jinyoung Kim, Ki-Sun Kim, Hyo Seon Lee, Kwang-Su Park, Sun Young Park, Seock-Yong Kang, Soo Jae Lee, Hyung Soon Park, Dong-Eun Kim, Youhoon Chong*

**Design, synthesis, and biological activities of conformationally restricted analogs of primaquine with a 1,10-phenanthroline framework**

pp 4666–4669

Cheikh Sall, Ange-Désiré Yapi, Nicolas Desbois, Séverine Chevalley, Jean-Michel Chezal, Kimny Tan, Jean-Claude Teulade, Alexis Valentin, Yves Blache*

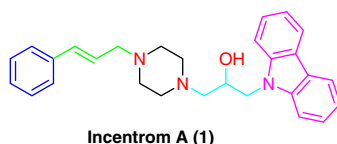


A novel series of 1,10-phenanthrolines derivatives were designed and prepared. All compounds showed potent antiplasmodial activities in vitro against both sensitive and chloroquine-resistant lines and also potent antigametocytal activity.

Structure–activity relationship studies of the chromosome segregation inhibitor, Incentrom A

pp 4670–4674

Hee-Yoon Lee*, Yongsik Jung, Wonyeob Kim, Jin Hee Kim, Min-Soo Suh, Seung Koo Shin*, Hye-Joo Yoon*

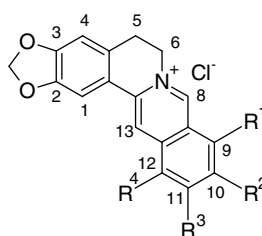


Pharmacophore and structure–activity relationship of Incentrom A that inhibits the chromosome segregation process in yeast were established. A series of Incentrom A analogs were synthesized and tested for the anti-yeast activity.

Synthesis and structure–activity relationships of berberine analogues as a novel class of low-density-lipoprotein receptor up-regulators

pp 4675–4677

Peng Yang, Dan-Qing Song*, Ying-Hong Li, Wei-Jia Kong, Yan-Xiang Wang, Li-Mei Gao, Shu-Yu Liu, Rui-Qiang Cao, Jian-Dong Jiang*



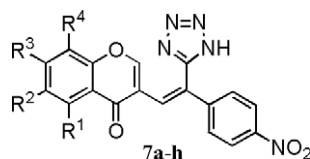
R¹–R⁴ = H, OH, OCH₃, OC₂H₅, OC₃H₇ etc.



Substituted 3-((Z)-2-(4-nitrophenyl)-2-(1H-tetrazol-5-yl) vinyl)-4H-chromen-4-ones as novel anti-MRSA agents: Synthesis, SAR, and in-vitro assessment

pp 4678–4681

Santosh D. Diwakar, Sachin S. Bhagwat, Murlidhar S. Shingare, Charansing H. Gill*

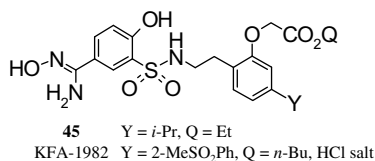


The synthesis of the potent antibacterial tetrazolyl chromones **7a-h** is reported. Introduction of a '-F' at **R**² and -Cl at **R**², and **R**⁴ position led to compounds having anti-MRSA (methicillin resistant *S. aureus*) potential and antibacterial superior to Gentamicin, Erythromycin, Ampicillin and Ciprofloxacin.

Orally active factor Xa inhibitors: Investigation of a novel series of 3-amidinophenylsulfonamide derivatives using an amidoxime prodrug strategy

pp 4682–4687

Masahiko Uchida*, Kosuke Okazaki, Harunobu Mukaiyama, Hidetoshi Isawa, Hiroaki Kobayashi, Hiroaki Shiohara, Hideyuki Muranaka, Yuichiro Kai, Norihiko Kikuchi, Hideki Takeuchi, Kenji Yokoyama, Eiichi Tsuji, Tomonaga Ozawa, Yuji Hoyano, Takashi Koizumi, Keiko Misawa, Kiyoto Hara, Shigeru Nakano, Yasuoki Murakami, Hiroaki Okuno

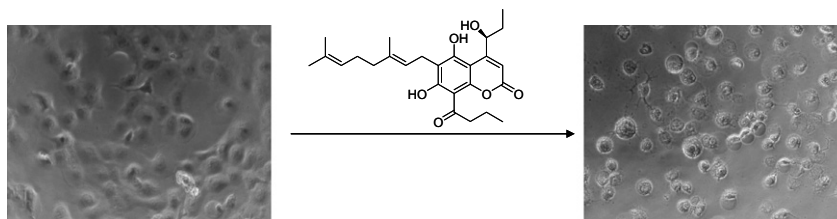


An amidoxime/ester double prodrug **45** demonstrated sufficient oral bioavailability and encouraging oral antithrombotic activity in mice. Among the various compounds under investigation, KFA-1982 was selected for clinical development.

Novel anticancer agents, kayeassamins A and B from the flower of *Kaya assamica* of Myanmar

pp 4688–4691

Nwet Nwet Win, Suresh Awale*, Hiroyasu Esumi, Yasuhiro Tezuka, Shigetoshi Kadota*

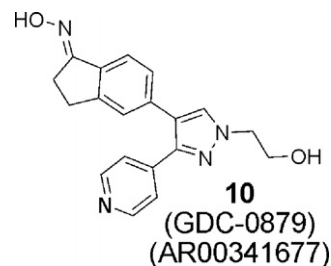


Potent and selective pyrazole-based inhibitors of B-Raf kinase

pp 4692–4695

Joshua D. Hansen,* Jonas Grina, Brad Newhouse, Mike Welch, George Topalov, Nicole Littman, Michele Callejo, Susan Gloor, Matthew Martinson, Ellen Laird, Barbara J. Brandhuber, Guy Vigers, Tony Morales, Rich Woessner, Nikole Randolph, Joseph Lyssikatos, Alan Olivero

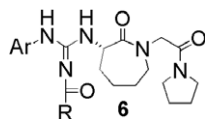
We report herein a series of substituted pyrazoles as inhibitors of B-Raf kinase. Through structure–activity relationship studies, cellular potency, pharmacokinetics, and kinase selectivity were optimized to afford GDC-0879 (**10**), a compound with good preclinical in vivo activity against tumor xenograft models.



Synthesis and evaluation of acylguanidine FXa inhibitors

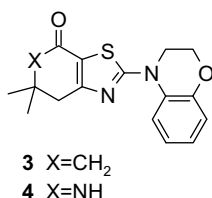
pp 4696–4699

Stephen P. O'Connor*, Karnail Atwal, Chi Li, Eddie C.-K. Liu, Steven M. Seiler, Mengxiao Shi, Yan Shi, Philip D. Stein, Ying Wang

**Achieving multi-isoform PI3K inhibition in a series of substituted 3,4-dihydro-2H-benzo[1,4]oxazines**

pp 4700–4704

Benjamin Perry*, Rikki Alexander, Gavin Bennett, George Buckley, Tom Ceska, Tom Crabbe, Verity Dale, Lewis Gowers, Helen Horsley, Lynwen James, Kerry Jenkins, Karen Crépy, Claire Kulisa, Helen Lightfoot, Chris Lock, Stephen Mack, Trevor Morgan, Anne-Lise Nicolas, Will Pitt, Verity Sabin, Sara Wright

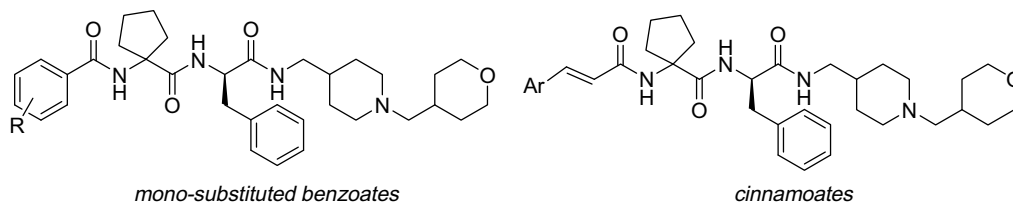


The SAR and pharmacokinetic profiles of a series of multi-isoform PI3K inhibitors based on a 3,4-dihydro-2H-benzo[1,4]oxazine scaffold are disclosed.

Cinnamic acids and mono-substituted benzoic acids as useful capping groups for the preparation of hNK₂ receptor antagonists

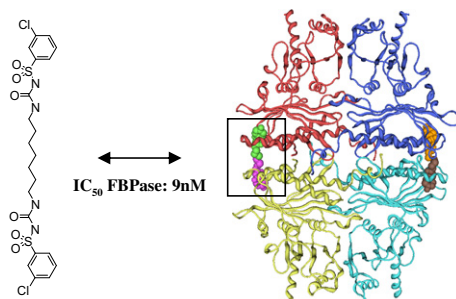
pp 4705–4707

Marina Porcelloni, Piero D'Andrea, Maria Altamura, Rose-Marie Catalioto, Sandro Giuliani, Stefania Meini, Daniela Fattori*

Starting from an in-house prepared library of capped dipeptides, we have identified a series of molecules with subnanomolar binding affinity for the hNK₂ receptor containing a dipeptide cyclopentanglycine-D-phenyl alanine as a core and C- and N-terminal capping groups. Here we report how we were able to manipulate the N-terminal capping group to obtain significant in vivo activity after iv and id administration.**Allosteric FBPsase inhibitors gain 10⁵ times in potency when simultaneously binding two neighboring AMP sites**

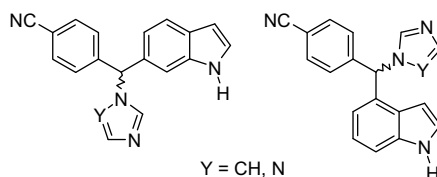
pp 4708–4712

Paul Hebeisen*, Bernd Kuhn, Philipp Kohler, Marcel Gubler, Walter Huber, Eric Kitas, Brigitte Schott, Jörg Benz, Catherine Joseph, Armin Ruf



Synthesis of 6- or 4-functionalized indoles via a reductive cyclization approach and evaluation as aromatase inhibitors pp 4713–4715

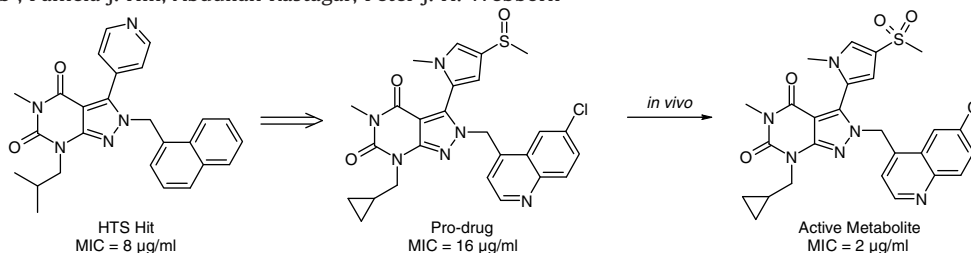
Marie-Pierre L    , Anja Paluszczak, Rolf W. Hartmann, Marc Le Borgne*



Two new series of benzonitrile derivatives on position 6 or 4 of the indole ring were successfully synthesized via a Leimgruber–Batcho reaction. The target compounds were further evaluated as aromatase inhibitors.

Design of *Helicobacter pylori* glutamate racemase inhibitors as selective antibacterial agents: A novel pro-drug approach to increase exposure pp 4716–4722

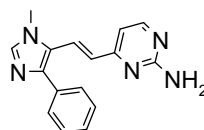
Gregory S. Basarab*, Pamela J. Hill, Abdullah Rastagar, Peter J. H. Webborn



To achieve high bioavailability towards the design of *Helicobacter pylori* antibacterial drugs, a pro-drug approach was implemented wherein a sulfoxide moiety is oxidized in vivo to the more potent sulfone.

Discovery of imidazole vinyl pyrimidines as a novel class of kinase inhibitors which inhibit Tie-2 and are orally bioavailable pp 4723–4726

David Buttar, Mike Edge, Steve C. Emery, Martina Fitzek, Cheryl Forder, Alison Griffen, Barry Hayter, Chris F. Hayward, Philip J. Hopcroft, Richard W. A. Luke*, Ken Page, John Stawpert, Andy Wright

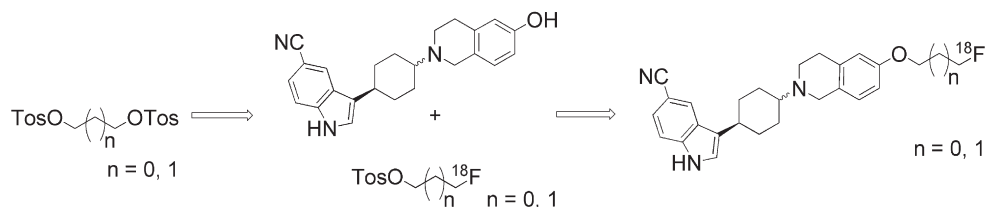


pTie-2 Cell IC₅₀ = 340 nM

The discovery and SAR of a novel class of imidazole-alkene-pyrimidine kinase inhibitors, which inhibit Tie-2 in vitro and in cells is reported. These compounds are lead-like with low molecular weight and good physical properties, and are orally bioavailable.

3-(4-(6-Fluoroalkoxy-3,4-dihydroisoquinoline-2(1H)-yl)cyclohexyl)-1H-indole-5-carbonitriles for SERT imaging: Chemical synthesis, evaluation in vitro and radiofluorination pp 4727–4730

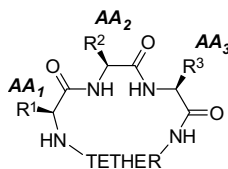
Uta Funke*, Steffen Fischer, Achim Hiller, Matthias Scheunemann, Winnie Deuther-Conrad, Peter Brust, J  rg Steinbach



Efficient parallel synthesis of macrocyclic peptidomimetics

pp 4731–4735

Eric Marsault*, Hamid R. Hoveyda*, René Gagnon, Mark L. Peterson, Martin Vézina, Carl Saint-Louis, Annick Landry, Jean-François Pinault, Luc Ouellet, Sophie Beauchemin, Sylvie Beaubien, Axel Mathieu, Kamel Benakli, Zhigang Wang, Martin Brassard, David Lonergan, François Bilodeau, Mahesh Ramaseshan, Nadia Fortin, Ruoxi Lan, Shigui Li, Fabrice Galaud, Véronique Plourde, Manon Champagne, Annie Doucet, Patrick Bhérer, Maude Gauthier, Gilles Olsen, Gérald Villeneuve, Shridhar Bhat, Laurence Foucher, Daniel Fortin, Xiaowen Peng, Sylvain Bernard, Alexandre Drouin, Robert Déziel, Gilles Berthiaume, Yves L. Dory, Graeme L. Fraser, Pierre Deslongchamps

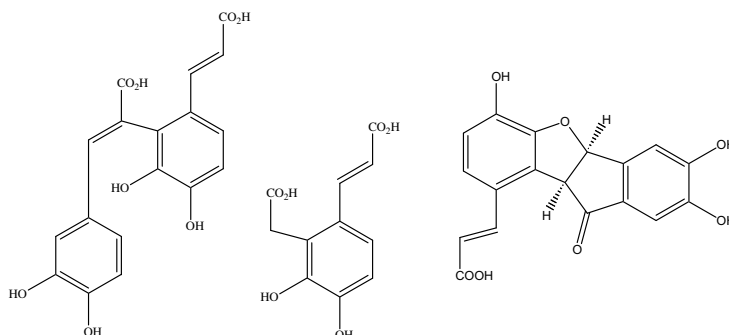


A new method for solid phase parallel synthesis of chemically and conformationally diverse macrocyclic peptidomimetics is reported.

**Synthesis and antiviral properties of some polyphenols related to Salvia genus**

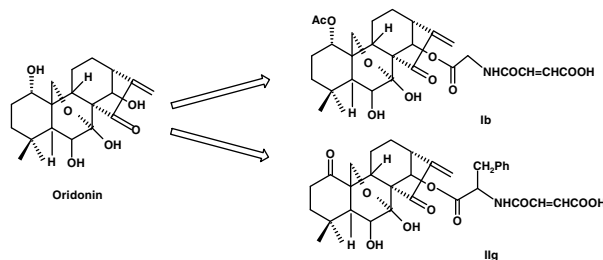
pp 4736–4740

Clémence Queffélec, Fabrice Bailly, Gladys Mbemba, Jean-François Mouscadet, Sean Hayes, Zeger Debyser, Myriam Witvrouw, Philippe Cotellet*

**Synthesis and biological evaluation of novel 1-O- and 14-O-derivatives of oridonin as potential anticancer drug candidates**

pp 4741–4744

Jinyi Xu*, JingYi Yang, Qian Ran, Lei Wang, Jie Liu, Zhixuan Wang, Xiaoming Wu*, WeiYi Hua, Shengtao Yuan, Luyong Zhang, Mingqin Shen, Yongfang Ding



1-O- and 14-O-derivatives of oridonin exhibited stronger cytotoxicity against six cancer cell lines than oridonin in vitro, compounds **Ib** and **IIg** were more potent than oridonin and cyclophosphamide in vivo.

OTHER CONTENTS**Corrigendum**

p 4745

Summary of instructions to authors

p I

*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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