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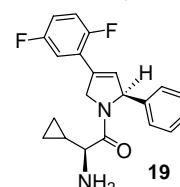
ARTICLES

Kinesin spindle protein (KSP) inhibitors. Part 2: The design, synthesis, and characterization of 2,4-diaryl-2,5-dihydropyrrole inhibitors of the mitotic kinesin KSP

pp 1775–1779

Mark E. Fraley,* Robert M. Garbaccio, Kenneth L. Arrington, William F. Hoffman, Edward S. Tasber, Paul J. Coleman, Carolyn A. Buser, Eileen S. Walsh, Kelly Hamilton, Christine Fernandes, Michael D. Schaber, Robert B. Lobell, Weikang Tao, Victoria J. South, Youwei Yan, Lawrence C. Kuo, Thomayant Prueksaritanont, Cathy Shu, Maricel Torrent, David C. Heimbrook, Nancy E. Kohl, Hans E. Huber and George D. Hartman

2,4-Diaryl-2,5-dihydropyrroles are reported as potent inhibitors of the mitotic kinesin KSP.



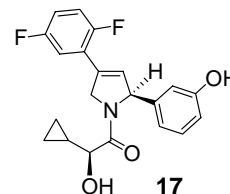
KSP IC₅₀ = 2.0 nM
Cell EC₅₀ = 8.6 nM

Kinesin spindle protein (KSP) inhibitors. Part 3: Synthesis and evaluation of phenolic 2,4-diaryl-2,5-dihydropyrroles with reduced hERG binding and employment of a phosphate prodrug strategy for aqueous solubility

pp 1780–1783

Robert M. Garbaccio,* Mark E. Fraley, Edward S. Tasber, Christy M. Olson, William F. Hoffman, Kenneth L. Arrington, Maricel Torrent, Carolyn A. Buser, Eileen S. Walsh, Kelly Hamilton, Michael D. Schaber, Christine Fernandes, Robert B. Lobell, Weikang Tao, Vicki J. South, Youwei Yan, Lawrence C. Kuo, Thomayant Prueksaritanont, Donald E. Slaughter, Cathy Shu, David C. Heimbrook, Nancy E. Kohl, Hans E. Huber and George D. Hartman

Phenolic 2,4-diaryl-2,5-dihydropyrroles are reported as potent inhibitors of the mitotic kinesin KSP.



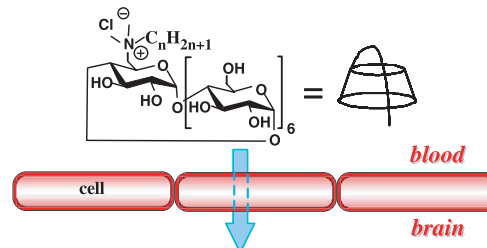
KSP IC₅₀ = 3.0 nM
Cell EC₅₀ = 3.3 nM

How cyclodextrins can mask their toxic effect on the blood–brain barrier

pp 1784–1787

Cécile Binkowski-Machut, Frédéric Hapiot,* Patrick Martin, Roméo Cecchelli and Eric Monflier

The toxicity and permeability of monosubstituted *n*-alkyldimethylammonium- β -cyclodextrins towards endothelial cells of an in vitro model of the blood–brain barrier (BBB) was evaluated and compared to that of the native β -CD.



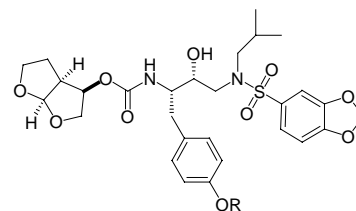
For $n=12$, weaker toxicity threshold and better transport through the BBB than the native β -CD

Ultra-potent P1 modified arylsulfonamide HIV protease inhibitors: The discovery of GW0385

pp 1788–1794

John F. Miller,* C. Webster Andrews, Michael Brieger, Eric S. Furfine, Michael R. Hale, Mary H. Hanlon, Richard J. Hazen, Istvan Kaldor, Ed W. McLean, David Reynolds, Douglas M. Sammond, Andrew Spaltenstein, Roger Tung, Elizabeth M. Turner, Robert X. Xu and Ronald G. Sherrill*

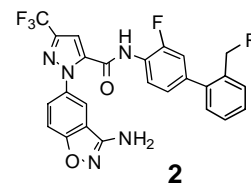
A novel series of P1 modified HIV protease inhibitors was synthesized and evaluated for in vitro antiviral activity against wild-type virus and protease inhibitor-resistant viruses. Optimization of the P1 moiety resulted in compounds with femtomolar enzyme activities and cellular antiviral activities in the low nanomolar range culminating in the identification of clinical candidate GW0385.

**Aminobenzisoxazoles with biaryl P4 moieties as potent, selective, and orally bioavailable factor Xa inhibitors**

pp 1795–1798

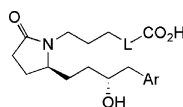
Mimi L. Quan,* Qi Han,* John M. Fevig, Patrick Y. S. Lam, Steve Bai, Robert M. Knabb, Joseph M. Luetgten, Pancras C. Wong and Ruth R. Wexler

We have previously reported on a series of aminobenzisoxazoles as potent, selective, and orally bioavailable factor Xa inhibitors, which culminated in the discovery of razaxaban. Herein, we describe another approach to improve factor Xa inhibitory potency and pharmacokinetic profile by incorporating basic and water soluble functionalities on the terminal ring of the P4 biaryl group found in our earlier Xa inhibitors. This approach resulted in a series of potent, selective, and orally bioavailable factor Xa inhibitors.

**Discovery of highly selective EP4 receptor agonists that stimulate new bone formation and restore bone mass in ovariectomized rats**

pp 1799–1802

Kimberly O. Cameron,* Bruce A. Lefker, Margaret Y. Chu-Moyer, David T. Crawford, Paul DaSilva Jardine, Shari L. DeNinno, Sandra Gilbert, William A. Grasser, HuaZhu Ke, Bihong Lu, Thomas A. Owen, Vishwas M. Paralkar, Hong Qi, Dennis O. Scott, David D. Thompson, Christina M. Tjoa and Michael P. Zawistoski



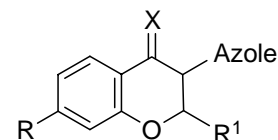
We describe the synthesis, SAR, and in vivo efficacy of a series of EP4-selective lactam derivatives.

Azolychromans as a novel scaffold for anticonvulsant activity

pp 1803–1806

Saeed Emami,* Abbas Kebriaeezadeh, Mohammad Jafar Zamani and Abbas Shafiee

A series of azolychroman derivatives were prepared as conformationally constrained analogs of (arylalkyl)azole anticonvulsants. The anticonvulsant activities of the compounds were determined against pentylenetetrazole (PTZ)-induced lethal convulsions in mice. Among these compounds, 7-chloro-3-(1H-imidazol-1-yl)chroman-4-one and 3-(1H-1,2,4-triazol-1-yl)chroman-4-one exhibited significant action in delaying seizures as well as effective protection against PTZ-induced seizures and deaths.



R= H, Cl; R¹ = H, CH₃ (*trans* respect to Azole)

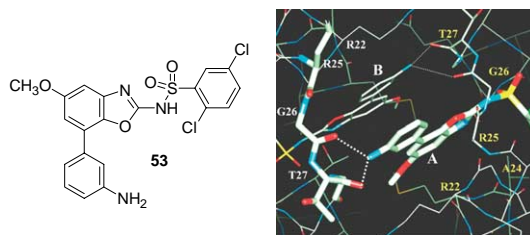
X= O, NOH

Azole=1H-imidazol-1-yl, 1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-4-yl

Benzoxazole benzenesulfonamides as allosteric inhibitors of fructose-1,6-bisphosphatase

pp 1807–1810

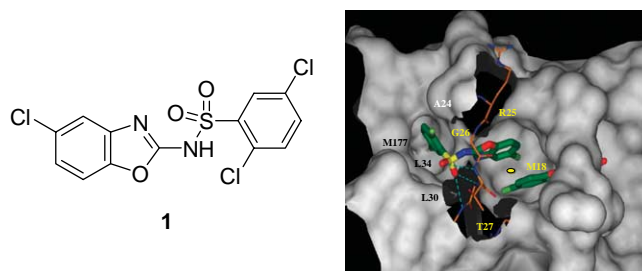
Chunqiu Lai,* Rebecca J. Gum, Melissa Daly, Elizabeth H. Fry, Charles Hutchins, Celerino Abad-Zapatero and Thomas W. von Geldern*



Benzoxazole benzenesulfonamides are novel allosteric inhibitors of fructose-1,6-bisphosphatase with a distinct binding mode

pp 1811–1815

Thomas W. von Geldern,* Chunqiu Lai, Rebecca J. Gum, Melissa Daly, Chaohong Sun, Elizabeth H. Fry and Celerino Abad-Zapatero

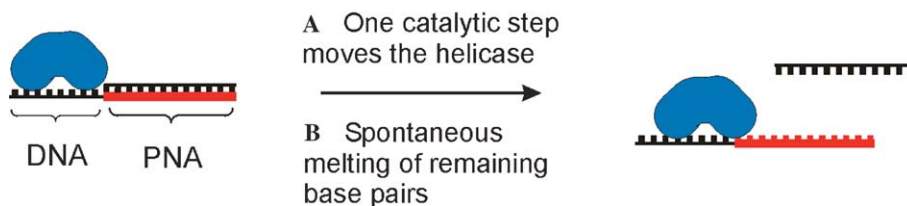


Dda helicase unwinds a DNA–PNA chimeric substrate: Evidence for an inchworm mechanism

pp 1816–1820

Travis L. Spurling, Robert L. Eoff and Kevin D. Raney*

Helicase-catalyzed unwinding of a DNA-PNA Chimeric Substrate

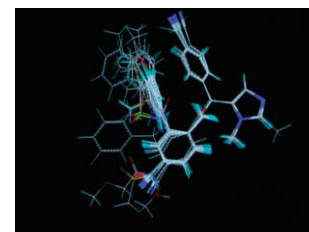


3D-QSAR studies of farnesyltransferase inhibitors: A comparative molecular field analysis approach

pp 1821–1827

Devendra Puntambekar, Rajani Giridhar and Mange Ram Yadav*

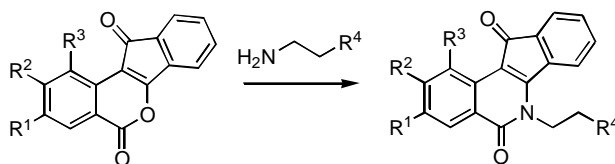
Three-dimensional quantitative structure–activity relationship studies using comparative molecular field analysis (CoMFA) approach were carried out on a series of benzonitrile derivatives as potent and selective farnesyltransferase inhibitors.



Synthesis of benz[*d*]indeno[1,2-*b*]pyran-5,11-diones: Versatile intermediates for the design and synthesis of topoisomerase I inhibitors

pp 1846–1849

Andrew Morrell, Smitha Antony, Glenda Kohlhaugen, Yves Pommier and Mark Cushman*

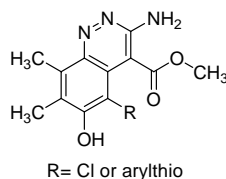


A one-pot, two-step synthesis of indenopyrans and their conversion to indenoisoquinoline topoisomerase I inhibitors are reported.

**Synthesis and antifungal activity of 6-hydroxycinnolines**

pp 1850–1853

Chung-Kyu Ryu* and Jung Yoon Lee

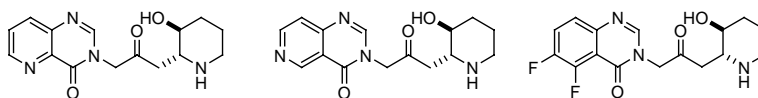


6-Hydroxycinnolines and cyclohexa-2,5-diene-1,4-dione derivatives were synthesized and tested for in vitro antifungal activity against *Candida* species and *Aspergillus niger*. Among them, 2-amino-7,8-dimethyl-6-hydroxycinnolines exhibited potent antifungal activity.

Synthesis and evaluation of febrifugine analogues as potential antimalarial agents

pp 1854–1858

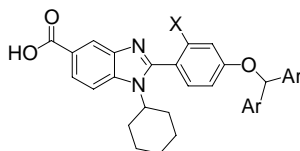
Shuren Zhu,* Li Meng, Quan Zhang and Lai Wei

**Benzimidazole inhibitors of hepatitis C virus NS5B polymerase:**

pp 1859–1863

Identification of 2-[(4-diarylmethoxy)phenyl]-benzimidazole

Tomio Ishida, Takayoshi Suzuki, Shintaro Hirashima, Kenji Mizutani, Atsuhito Yoshida, Izuru Ando, Satoru Ikeda, Tsuyoshi Adachi and Hiromasa Hashimoto*



A series of 1-cycloalkyl-2-phenyl-1*H*-benzimidazole-5-carboxylic acid derivatives was synthesized and evaluated for their ability to inhibit HCV NS5B polymerase and subgenomic HCV RNA replication in the replicon cells.

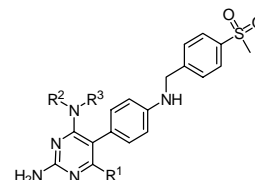


Optimization of 2,4-diaminopyrimidines as GHS-R antagonists: Side chain exploration

pp 1864–1868

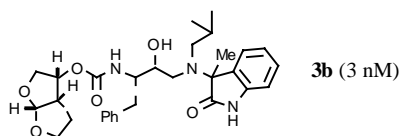
Bo Liu, Mei Liu, Zhili Xin, Hongyu Zhao, Michael D. Serby, Christi Kosogof, Lissa T. J. Nelson, Bruce G. Szczepankiewicz, Wiweka Kaszubska, Verlyn G. Schaefer, H. Douglas Falls, Chun Wel Lin, Christine A. Collins, Hing L. Sham and Gang Liu*

The synthesis and structure–activity relationships of the 4- and 6-substituents of 2,4-diaminopyrimidine-based growth hormone secretagogue receptor (GHS-R) antagonists are described. Diaminopyrimidines with 6-norbornenyl (**4n**) and 6-tetrahydrofuranly (**4p**) substituents exhibited potent GHS-R antagonism and good selectivity (~1000-fold) against dihydrofolate reductase.

**Design and synthesis of novel HIV-1 protease inhibitors incorporating oxyindoles as the P₂'-ligands**

pp 1869–1873

Arun K. Ghosh,* Gary Schiltz, Ramu Sridhar Perali, Sofiya Leshchenko, Stephanie Kay, D. Eric Walters, Yasuhiro Koh, Kenji Maeda and Hiroaki Mitsuya



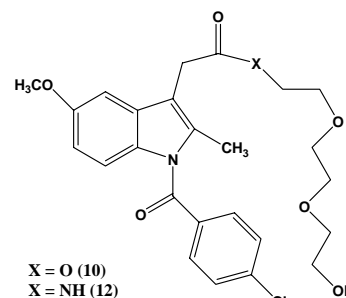
A series of novel oxyindole-derived HIV-1 protease inhibitors were designed and synthesized. A number of inhibitors exhibited low nanomolar inhibitory potencies against HIV protease.

Synthesis and stability of two indomethacin prodrugs

pp 1874–1879

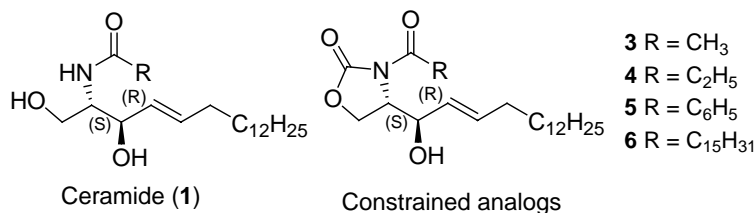
Shyamala Chandrasekaran, Abeer M. Al-Ghananeem, Robert M. Riggs and Peter A. Crooks*

The purpose of this study was to synthesize and study the in vitro enzymatic and non-enzymatic hydrolysis of indomethacin–TEG ester and amide prodrugs. It was found that the ester conjugate **10** was comparatively stable between pH 3 and 6 (half-life >90 h), with a half-life equal to 5.2 h in 80% buffered plasma. In contrast, the amide conjugate **12** appeared to be stable over the entire pH range studied with the only observed degradation being cleavage of the indolic *N*-4-chlorobenzoyl moiety.

**Synthesis of constrained ceramide analogs and their potent antileukemic activities**

pp 1880–1883

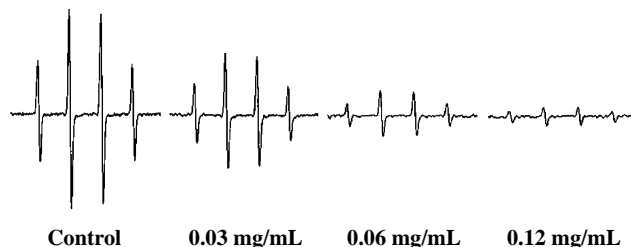
Hyun-Joon Ha,* Myeng Chan Hong, Seung Whan Ko, Yong Woo Kim, Won Koo Lee* and Jungchan Park



Antioxidant activity of novel chitin derivative

pp 1884–1887

Jae-Young Je and Se-Kwon Kim*



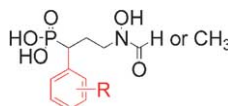
Novel chitin derivative was prepared by chemical modification. Aminoethyl-chitin (AEC) exhibited free radical scavenging effects against DPPH, hydroxyl, superoxide, and peroxy radicals. Especially, AEC was more active against hydroxyl radical.

Synthesis of α -substituted fosmidomycin analogues as highly potent

pp 1888–1891

***Plasmodium falciparum* growth inhibitors**

Timothy Haemers, Jochen Wiesner, Sara Van Poecke, Jan Goeman, Dajana Henschker, Edwald Beck, Hassan Jomaa and Serge Van Calenbergh*



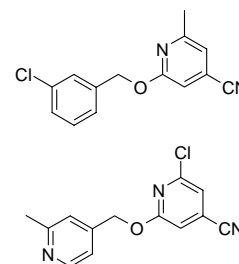
A series of α -substituted fosmidomycin analogues was synthesized and evaluated for DOXP reductoisomerase inhibition and *Plasmodium falciparum* growth inhibition. In the latter assay, most analogues proved superior to fosmidomycin.

Arylmethoxypyridines as novel, potent and orally active mGlu5 receptor antagonists

pp 1892–1897

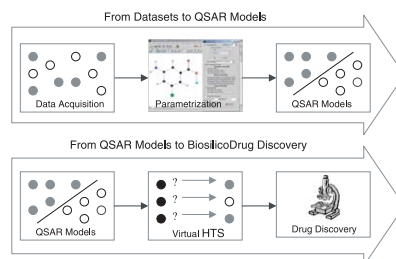
Bernd Büttelmann,* Jens-Uwe Peters,* Simona Ceccarelli, Sabine Kolczewski, Eric Vieira, Eric P. Prinssen, Will Spooren, Franz Schuler, Jörg Huwyler, Richard H. P. Porter and Georg Jaeschke

The optimisation of a chemically unstable HTS hit led to mGluR5 antagonists with high affinity for the allosteric MPEP binding site and anxiolytic-like activity in vivo.

**New ligand-based approach for the discovery of antitrypanosomal compounds**

pp 1898–1904

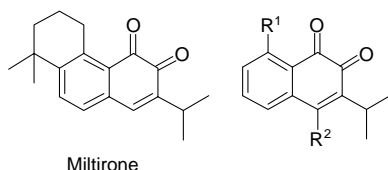
María Celeste Vega, Alina Montero-Torres,* Yovani Marrero-Ponce, Miriam Rolón, Alicia Gómez-Barrio, José Antonio Escario, Vicente J. Arán, Juan José Nogal, Alfredo Meneses-Marcel and Francisco Torrens



Synthesis of miltirone analogues as inhibitors of Cdc25 phosphatases

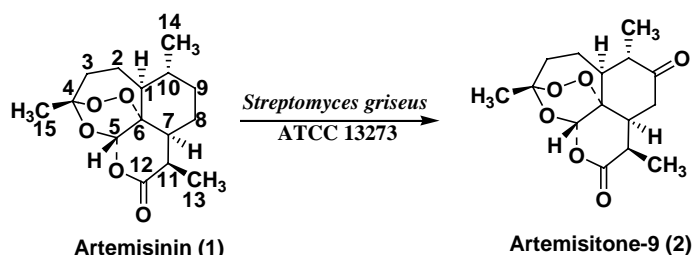
pp 1905–1908

Weigang Huang, Jingya Li, Wei Zhang, Yueyang Zhou, Chuanming Xie,
Yu Luo, Yunfei Li, Jingli Wang, Jia Li* and Wei Lu*

**A novel ketone derivative of artemisinin biotransformed by *Streptomyces griseus* ATCC 13273**

pp 1909–1912

Ji-Hua Liu, You-Gen Chen, Bo-Yang Yu* and Yi-Jun Chen*

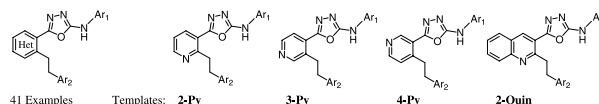


Artemisinin (1) was regioselectively converted to artemisitone-9 (2) and three other oxidative metabolites by *Streptomyces griseus* ATCC 13273.

**Inhibitors of VEGF receptors-1 and -2 based on the 2-((pyridin-4-yl)ethyl)pyridine template**

pp 1913–1919

Alexander S. Kiselyov,* Marina Semenova, Victor V. Semenov and Daniel Milligan

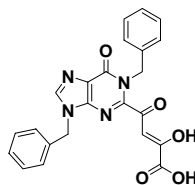


We have developed a series of novel potent ((pyridin-4-yl)ethyl)pyridine derivatives active against kinases VEGFR-1 and -2. Both specific and dual ATP-competitive inhibitors of VEGFR-2 were identified. Kinase selectivity could be controlled by varying the arylamino substituent at the 1,3,4-oxadiazole ring. Most specific molecules displayed >10-fold selectivity for VEGFR-2 over VEGFR-1. Compound activities in both in vitro and cell-based assays ($IC_{50} < 100$ nM) were similar to those of reported clinical and development candidates, including PTK787 (Vatalanib). High permeability of the active compounds across Caco-2 cell monolayer ($>30 \times 10^{-5}$ cm/min) is indicative of their potential for intestinal absorption upon oral administration.

 β -Diketo acids with purine nucleobase scaffolds: Novel, selective inhibitors of the strand transfer step of HIV integrase

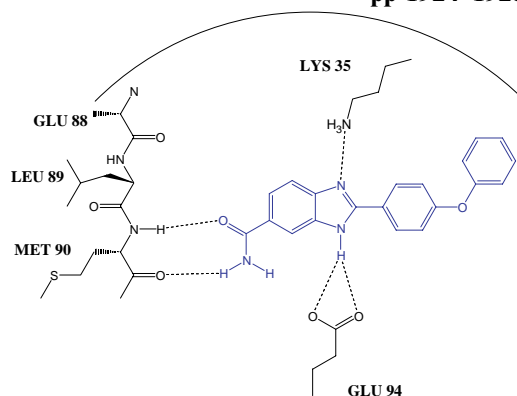
pp 1920–1923

Vasu Nair,* Vinod Uchil and Nouri Neamati



pp 1924–1928

A number of benzimidazole replacements were synthesized and examined to gain a greater understanding of the SAR around this novel series of chk2 kinase inhibitors.



pp 1929–1933

The image shows a complex macrocyclic chemical structure. It consists of a large ring with several amide bonds (peptide linkages). A hydroxyl group (-OH) is attached to one of the ring carbons. A methyl group (-CH₃) is attached to another carbon. A substituent 'R' is attached to one of the amide groups via a methylene group (-CH₂-). The structure is drawn with stereochemistry indicated by wedges and dashes.

pp 1934–1937

Cc1ccc(cc1C2=CC=CC=C2C3=CC=CC=C3C4=CC=CC=C4C5=CC=CC=C5C6=CC=CC=C6C7=CC=CC=C7C8=CC=CC=C8C9=CC=CC=C9C10=CC=CC=C10C11=CC=CC=C11C12=CC=CC=C12C13=CC=CC=C13C14=CC=CC=C14C15=CC=CC=C15C16=CC=CC=C16C17=CC=CC=C17C18=CC=CC=C18C19=CC=CC=C19C20=CC=CC=C20C21=CC=CC=C21C22=CC=CC=C22C23=CC=CC=C23C24=CC=CC=C24C25=CC=CC=C25C26=CC=CC=C26C27=CC=CC=C27C28=CC=CC=C28C29=CC=CC=C29C30=CC=CC=C30C31=CC=CC=C31C32=CC=CC=C32C33=CC=CC=C33C34=CC=CC=C34C35=CC=CC=C35C36=CC=CC=C36C37=CC=CC=C37C38=CC=CC=C38C39=CC=CC=C39C40=CC=CC=C40C41=CC=CC=C41C42=CC=CC=C42C43=CC=CC=C43C44=CC=CC=C44C45=CC=CC=C45C46=CC=CC=C46C47=CC=CC=C47C48=CC=CC=C48C49=CC=CC=C49C50=CC=CC=C50C51=CC=CC=C51C52=CC=CC=C52C53=CC=CC=C53C54=CC=CC=C54C55=CC=CC=C55C56=CC=CC=C56C57=CC=CC=C57C58=CC=CC=C58C59=CC=CC=C59C60=CC=CC=C60C61=CC=CC=C61C62=CC=CC=C62C63=CC=CC=C63C64=CC=CC=C64C65=CC=CC=C65C66=CC=CC=C66C67=CC=CC=C67C68=CC=CC=C68C69=CC=CC=C69C70=CC=CC=C70C71=CC=CC=C71C72=CC=CC=C72C73=CC=CC=C73C74=CC=CC=C74C75=CC=CC=C75C76=CC=CC=C76C77=CC=CC=C77C78=CC=CC=C78C79=CC=CC=C79C80=CC=CC=C80C81=CC=CC=C81C82=CC=CC=C82C83=CC=CC=C83C84=CC=CC=C84C85=CC=CC=C85C86=CC=CC=C86C87=CC=CC=C87C88=CC=CC=C88C89=CC=CC=C89C90=CC=CC=C90C91=CC=CC=C91C92=CC=CC=C92C93=CC=CC=C93C94=CC=CC=C94C95=CC=CC=C95C96=CC=CC=C96C97=CC=CC=C97C98=CC=CC=C98C99=CC=CC=C99C100=CC=CC=C100C101=CC=CC=C101C102=CC=CC=C102C103=CC=CC=C103C104=CC=CC=C104C105=CC=CC=C105C106=CC=CC=C106C107=CC=CC=C107C108=CC=CC=C108C109=CC=CC=C109C110=CC=CC=C110C111=CC=CC=C111C112=CC=CC=C112C113=CC=CC=C113C114=CC=CC=C114C115=CC=CC=C115C116=CC=CC=C116C117=CC=CC=C117C118=CC=CC=C118C119=CC=CC=C119C120=CC=CC=C120C121=CC=CC=C121C122=CC=CC=C122C123=CC=CC=C123C124=CC=CC=C124C125=CC=CC=C125C126=CC=CC=C126C127=CC=CC=C127C128=CC=CC=C128C129=CC=CC=C129C130=CC=CC=C130C131=CC=CC=C131C132=CC=CC=C132C133=CC=CC=C133C134=CC=CC=C134C135=CC=CC=C135C136=CC=CC=C136C137=CC=CC=C137C138=CC=CC=C138C139=CC=CC=C139C140=CC=CC=C140C141=CC=CC=C141C142=CC=CC=C142C143=CC=CC=C143C144=CC=CC=C144C145=CC=CC=C145C146=CC=CC=C146C147=CC=CC=C147C148=CC=CC=C148C149=CC=CC=C149C150=CC=CC=C150C151=CC=CC=C151C152=CC=CC=C152C153=CC=CC=C153C154=CC=CC=C154C155=CC=CC=C155C156=CC=CC=C156C157=CC=CC=C157C158=CC=CC=C158C159=CC=CC=C159C160=CC=CC=C160C161=CC=CC=C161C162=CC=CC=C162C163=CC=CC=C163C164=CC=CC=C164C165=CC=CC=C165C166=CC=CC=C166C167=CC=CC=C167C168=CC=CC=C168C169=CC=CC=C169C170=CC=CC=C170C171=CC=CC=C171C172=CC=CC=C172C173=CC=CC=C173C174=CC=CC=C174C175=CC=CC=C175C176=CC=CC=C176C177=CC=CC=C177C178=CC=CC=C178C179=CC=CC=C179C180=CC=CC=C180C181=CC=CC=C181C182=CC=CC=C182C183=CC=CC=C183C184=CC=CC=C184C185=CC=CC=C185C186=CC=CC=C186C187=CC=CC=C187C188=CC=CC=C188C189=CC=CC=C189C190=CC=CC=C190C191=CC=CC=C191C192=CC=CC=C192C193=CC=CC=C193C194=CC=CC=C194C195=CC=CC=C195C196=CC=CC=C196C197=CC=CC=C197C198=CC=CC=C198C199=CC=CC=C199C200=CC=CC=C200C201=CC=CC=C201C202=CC=CC=C202C203=CC=CC=C203C204=CC=CC=C204C205=CC=CC=C205C206=CC=CC=C206C207=CC=CC=C207C208=CC=CC=C208C209=CC=CC=C209C210=CC=CC=C210C211=CC=CC=C211C212=CC=CC=C212C213=CC=CC=C213C214=CC=CC=C214C215=CC=CC=C215C216=CC=CC=C216C217=CC=CC=C217C218=CC=CC=C218C219=CC=CC=C219C220=CC=CC=C220C221=CC=CC=C221C222=CC=CC=C222C223=CC=CC=C223C224=CC=CC=C224C225=CC=CC=C225C226=CC=CC=C226C227=CC=CC=C227C228=CC=CC=C228C229=CC=CC=C229C230=CC=CC=C230C231=CC=CC=C231C232=CC=CC=C232C233=CC=CC=C233C234=CC=CC=C234C235=CC=CC=C235C236=CC=CC=C236C237=CC=CC=C237C238=CC=CC=C238C239=CC=CC=C239C240=CC=CC=C240C241=CC=CC=C241C242=CC=CC=C242C243=CC=CC=C243C244=CC=CC=C244C245=CC=CC=C245C246=CC=CC=C246C247=CC=CC=C247C248=CC=CC=C248C249=CC=CC=C249C250=CC=CC=C250C251=CC=CC=C251C252=CC=CC=C252C253=CC=CC=C253C254=CC=CC=C254C255=CC=CC=C255C256=CC=CC=C256C257=CC=CC=C257C258=CC=CC=C258C259=CC=CC=C259C260=CC=CC=C260C261=CC=CC=C261C262=CC=CC=C262C263=CC=CC=C263C264=CC=CC=C264C265=CC=CC=C265C266=CC=CC=C266C267=CC=CC=C267C268=CC=CC=C268C269=CC=CC=C269C270=CC=CC=C270C271=CC=CC=C271C272=CC=CC=C272C273=CC=CC=C273C274=CC=CC=C274C275=CC=CC=C275C276=CC=CC=C276C277=CC=CC=C277C278=CC=CC=C278C279=CC=CC=C279C280=CC=CC=C280C281=CC=CC=C281C282=CC=CC=C282C283=CC=CC=C283C284=CC=CC=C284C285=CC=CC=C285C286=CC=CC=C286C287=CC=CC=C287C288=CC=CC=C288C289=CC=CC=C289C290=CC=CC=C290C291=CC=CC=C291C292=CC=CC=C292C293=CC=CC=C293C294=CC=CC=C294C295=CC=CC=C295C296=CC=CC=C296C297=CC=CC=C297C298=CC=CC=C298C299=CC=CC=C299C300=CC=CC=C300C301=CC=CC=C301C302=CC=CC=C302C303=CC=CC=C303C304=CC=CC=C304C305=CC=CC=C305C306=CC=CC=C306C307=CC=CC=C307C308=CC=CC=C308C309=CC=CC=C309C310=CC=CC=C310C311=CC=CC=C311C312=CC=CC=C312C313=CC=CC=C313C314=CC=CC=C314C315=CC=CC=C315C316=CC=CC=C316C317=CC=CC=C317C318=CC=CC=C318C319=CC=CC=C319C320=CC=CC=C320C321=CC=CC=C321C322=CC=CC=C322C323=CC=CC=C323C324=CC=CC=C324C325=CC=CC=C325C326=CC=CC=C326C327=CC=CC=C327C328=CC=CC=C328C329=CC=CC=C329C330=CC=CC=C330C331=CC=CC=C331C332=CC=CC=C332C333=CC=CC=C333C334=CC=CC=C334C335=CC=CC=C335C336=CC=CC=C336C337=CC=CC=C337C338=CC=CC=C338C339=CC=CC=C339C340=CC=CC=C340C341=CC=CC=C341C342=CC=CC=C342C343=CC=CC=C343C344=CC=CC=C344C345=CC=CC=C345C346=CC=CC=C346C347=CC=CC=C347C348=CC=CC=C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pp 1938–1940

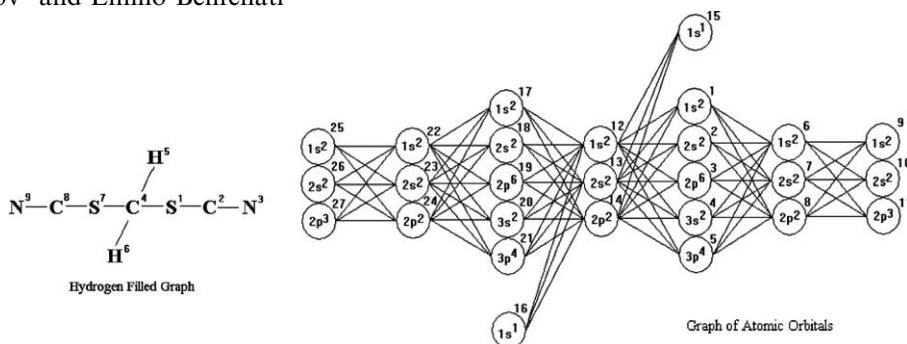
Chemical structures of compounds 1 and 2 are shown. Compound 1 is a piperidine ring connected via a chain of length n to a 1-cyano-2-(1H-indol-1-yl)ethanimine group. Compound 2 is a piperidine ring connected via a chain of length n to a 1-(2-nitro-1H-indol-1-yl)ethanimine group. Both structures show the piperidine ring with a nitrogen atom and the chain length n indicated by a subscript n in parentheses.

Synthesis and fluorescent properties of histamine H₃ receptor ligands in 2-cyanoisindole and nitrobenzofurazan series with nanomolar binding affinities are reported.

QSAR models of quail dietary toxicity based on the graph of atomic orbitals

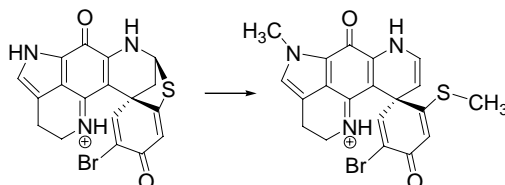
pp 1941–1943

Andrey A. Toropov* and Emilio Benfenati

**Semi-synthetic preparation of the rare, cytotoxic, deep-sea sourced sponge metabolites discorhabdins P and U**

pp 1944–1946

Tanja Grkovic, Balwinder Kaur, Victoria L. Webb and Brent R. Copp*



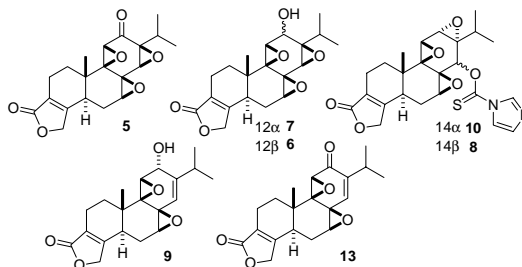
Semi-synthetic routes to the enzyme inhibitory and potently anti-proliferative marine natural products discorhabdins P and U were developed by one-step methylation reactions of discorhabdins C and B, respectively. Two novel semi-synthetic derivatives of discorhabdin U were also prepared, one of which (**6**) exhibited significant anti-proliferative activity.

Semisynthesis of C-ring modified triptolide analogues and their cytotoxic activities

pp 1947–1949

Yutaka Aoyagi, Yukio Hitotsuyanagi, Tomoyo Hasuda, Haruhiko Fukaya, Koichi Takeya,* Ritsuo Aiyama, Takeshi Matsuzaki and Shusuke Hashimoto

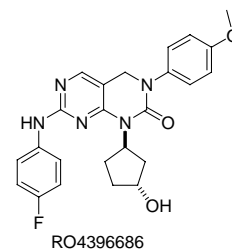
The semisynthesis and SAR study of C-ring modified cytotoxic triptolide analogues were reported.

**Biological evaluation of a multi-targeted small molecule inhibitor of tumor-induced angiogenesis**

pp 1950–1953

Lee A. McDermott,* Brian Higgins, Mary Simcox, Kin-Chun Luk, Tom Nevins, Kenneth Kolinsky, Melissa Smith, Hong Yang, Jia K. Li, Yingsi Chen, June Ke, Navita Mallalieu, Tom Egan, Stan Kolis, Aruna Railkar, Louise Gerber, Jin-Jun Liu, Fred Konzelmann, Zhuming Zhang, Tom Flynn, Omar Morales and Yi Chen

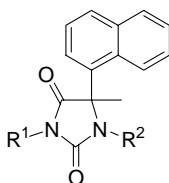
The biological evaluation of RO4396686, an inhibitor of the key pro-angiogenic kinases KDR, FGFR, and PDGFR is reported.



Hydantoin derivatives as non-peptidic inhibitors of Ras farnesyl transferase

pp 1954–1956

Jinho Lee,* Jonghyun Kim, Jong Sung Koh, Hyun-Ho Chung and Kyoung-Hee Kim

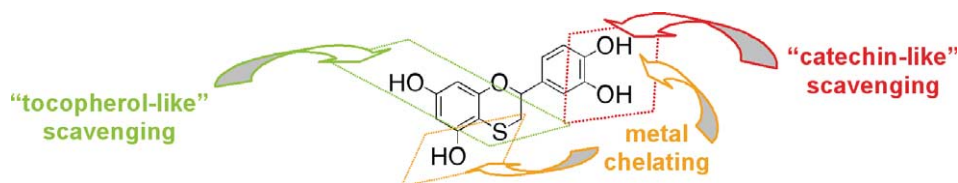


1,3,5,5-Tetrasubstituted 2,4-imidazolidinedione (hydantoin) derivatives were evaluated as Ftase inhibitors. Potent Ftase inhibitors without thiol or peptide were obtained in three steps.

Polyhydroxylated 4-thiaflavans as multipotent antioxidants: Protective effect on oxidative DNA damage in vitro

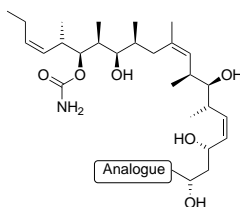
pp 1957–1960

Maura Lodovici,* Stefano Menichetti,* Caterina Viglianisi, Silvia Caldini and Elisa Giuliani

**A series of 23,24-dihydrodiscodermolide analogues with simplified lactone regions**

pp 1961–1964

Simon J. Shaw,* Kurt F. Sundermann, Mark A. Burlingame, Dan Zhang, Joseph Petryka and David C. Myles

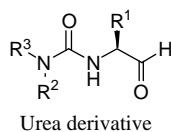
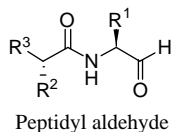


A collection of seven new 23,24-dihydrodiscodermolide analogues have been synthesized with modifications to the lactone ring, some of which show antiproliferative activities similar to discodermolide.

**A novel series of urea-based peptidomimetic calpain inhibitors**

pp 1965–1968

M. Lee Sanders and Isaac O. Donkor*

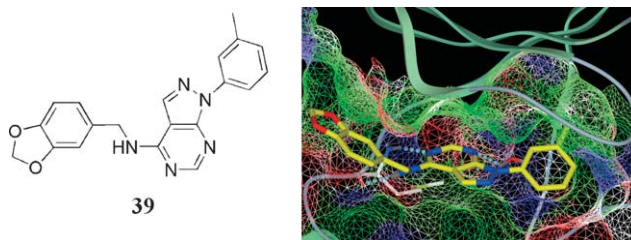


A series of peptide aldehyde derivatives in which the P₂ chiral carbon has been replaced with a nitrogen atom were synthesized as urea-based peptidomimetic inhibitors of μ -calpain.

In silico identification of novel EGFR inhibitors with antiproliferative activity against cancer cells

pp 1969–1974

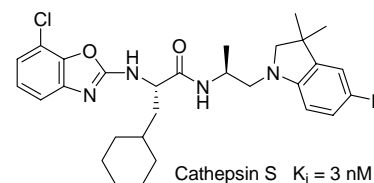
Claudio N. Cavasotto,* María A. Ortiz, Ruben A. Abagyan and F. Javier Piedrafitá*

**Synthesis and evaluation of arylaminoethyl amides as noncovalent inhibitors of cathepsin S. Part 3: Heterocyclic P3**

pp 1975–1980

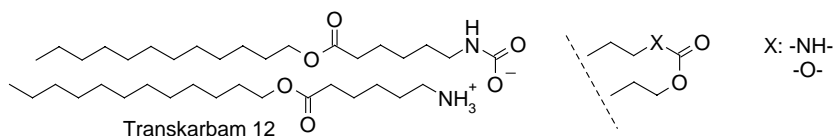
David C. Tully,* Hong Liu, Phil B. Alper, Arnab K. Chatterjee, Robert Epple, Michael J. Roberts, Jennifer A. Williams, KhanhLinh T. Nguyen, David H. Woodmansee, Christine Tumanut, Jun Li, Glen Spraggon, Jonathan Chang, Tove Tuntland, Jennifer L. Harris and Donald S. Karanewsky

A series of N_α -2-benzoxazolyl- α -amino acid-(aryl-aminoethyl)amides were identified as potent, selective, and noncovalent inhibitors of cathepsin S. Structure–activity relationships including strategies for modulating the selectivities among cathepsins S, K, and L, and in vivo pharmacokinetics are discussed. A X-ray structure of compound 3 bound to the active site of cathepsin S is also reported.

**Synthesis and transdermal penetration-enhancing activity of carbonic and carbamic acid esters—Comparison with transkarbam 12**

pp 1981–1984

Jana Klimentová, Alexandr Hrabálek,* Kateřina Vávrová, Tomáš Holas and Aleš Kroutil

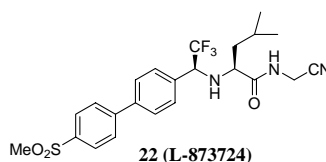


Series of carbamic and carbonic acid esters has been prepared as analogues of transkarbam 12 and their transdermal penetration-enhancing activity has been evaluated in vitro.

**Identification of a potent and selective non-basic cathepsin K inhibitor**

pp 1985–1989

Chun Sing Li,* Denis Deschenes, Sylvie Desmarais, Jean-Pierre Falgueyret, Jacques Yves Gauthier, Donald. B. Kimmel, Serge Léger, Frédéric Massé, Mary E. McGrath, Daniel J. McKay, M. David Percival, Denis Riendeau, Sevgi B. Rodan, Michel Thérien, Vouy-Linh Truong, Gregg Wesolowski, Robert Zamboni and W. Cameron Black

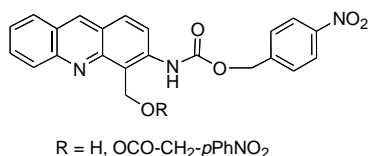


Based on our previous study with trifluoroethylamine as a P2–P3 amide isostere of cathepsin K inhibitor, further optimization led to identification of compound 22 (L-873724) as a potent and selective non-basic cathepsin K inhibitor.

Nitrobenzylcarbamate prodrugs of cytotoxic acridines for potential use with nitroreductase gene-directed enzyme prodrug therapy

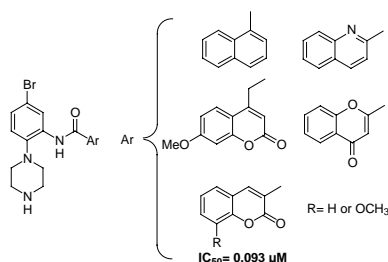
pp 1990–1994

Christian Asche, Pascal Dumy, Danièle Carrez, Alain Croisy and Martine Demeunynck*

**BACE-1 inhibitory activities of new substituted phenyl-piperazine coupled to various heterocycles: Chromene, coumarin and quinoline**

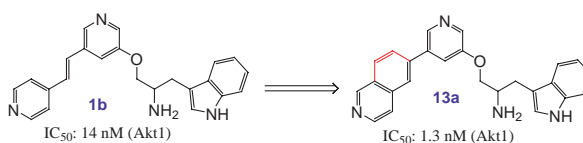
pp 1995–1999

Cédrik Garino, Nicolas Pietrancosta, Younes Laras, Vincent Moret, Amandine Rolland, Gilles Quéléver and Jean-Louis Kraus*

**Synthesis and structure–activity relationship of 3,4'-bispyridinylethylenes: Discovery of a potent 3-isoquinolinylpyridine inhibitor of protein kinase B (PKB/Akt) for the treatment of cancer**

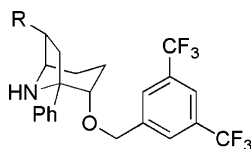
pp 2000–2007

Qun Li,* Keith W. Woods, Sheela Thomas, Gui-Dong Zhu, Garrick Packard, John Fisher, Tongmei Li, Jianchun Gong, Jurgen Dinges, Xiaohong Song, Jason Abrams, Yan Luo, Eric F. Johnson, Yan Shi, Xuesong Liu, Vered Klinghofer, Ron Des Jong, Tilman Oltersdorf, Vincent S. Stoll, Clarissa G. Jakob, Saul H. Rosenberg and Vincent L. Giranda

**1-Phenyl-8-azabicyclo[3.2.1]octane ethers: A novel series of neurokinin (NK₁) antagonists**

pp 2008–2012

Ian T. Huscroft,* Emma J. Carlson, Gary G. Chicchi, Marc M. Kurtz, Clare London, Piotr Raubo, Alan Wheeldon and Janusz J. Kulagowski

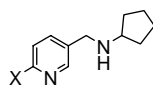


1-Phenyl-8-azabicyclo[3.2.1]octane ethers are NK₁ receptor antagonists. Substitution at the 6-*exo*-position leads to high affinity NK₁ antagonists with a prolonged duration of action in vivo. Incorporation of an α -methyl substituent in the pendent benzyl ether side chain gave compounds with increased selectivity over the hERG channel.

Synthesis and analgesic activity of secondary amine analogues of pyridylmethylamine and positional isomeric analogues of ABT-594

pp 2013–2016

Chuan-Xin Zhang, Ze-Mei Ge, Tie-Ming Cheng and Run-Tao Li*

**7a:** X= H**7d:** X= Cl

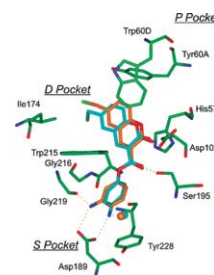
The highly sterically hindered secondary amine analogues of 3-pyridylmethylamine **7a** and **7d** showed potent in vivo analgesic activity and lower toxicity.

Investigation of mechanism-based thrombin inhibitors: Implications of a highly conserved water molecule for the binding of coumarins within the S pocket

pp 2017–2021

Raphaël Frédérick, Caroline Charlier, Séverine Robert, Johan Wouters, Bernard Masereel and Lionel Pochet*

The synthesis, thrombin inhibiting properties and docking of novel coumarins bearing an amine or a guanidine on the ester lateral side chain in the 3-position are reported.

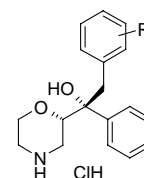


Discovery of novel and selective tertiary alcohol containing inhibitors of the norepinephrine transporter

pp 2022–2025

Manuel J. Cases-Thomas,* John J. Masters, Magnus W. Walter, Gordon Campbell, Louise Haughton, Peter T. Gallagher, David R. Dobson, Vincent Mancuso, Benjamin Bonnier, Thierry Giard, Thierry Defrance, Michel Vanmarsenille, Andrew Ledgard, Craig White, Sivi Ouwerkerk-Mahadevan, Francoise J. Brunelle, Nancy A. Dezutter, Camy A. Herbots, Joel Y. Lienard, Jeremy Findlay, Lorna Hayhurst, John Boot, Linda K. Thompson and Susan Hemrick-Luecke

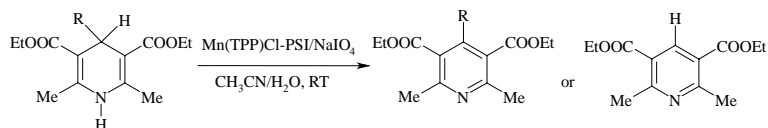
An efficient synthetic route to novel norepinephrine reuptake inhibitors, their in vitro binding affinity and selected in vivo data are presented.



Mild and efficient oxidation of Hantzsch 1,4-dihydropyridines with sodium periodate catalyzed by a new polystyrene-bound Mn(TPP)Cl

pp 2026–2030

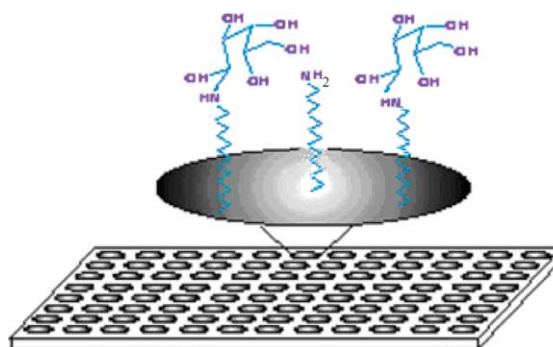
Majid Moghadam,* Masoud Nasr-Esfahani,* Shahram Tangestaninejad and Valiollah Mirkhani



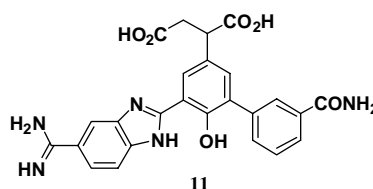
Mild and efficient oxidation of Hantzsch 1,4-dihydropyridines with sodium periodate catalyzed by Mn(TTP)Cl supported on polystyrene-bound imidazole is reported.

Fabrication and application of neoglycolipid arrays in a microtiter plate

pp 2031–2033

Gang-Liang Huang, Hou-Cheng Zhang
and Peng-George Wang ***Small molecule inhibitors of plasma kallikrein**

pp 2034–2036

Wendy B. Young,* Roopa Rai, William D. Shrader, Jana Burgess-Henry, Huiyong Hu,
Kyle C. Elrod, Paul A. Sprengeler, Bradley A. Katz, Juthamas Sukbuntherng and
Joyce Mordenti

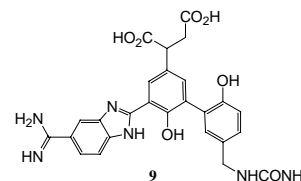
Plasma kallikrein is a serine protease that is involved in pathways of inflammation, complement fixation, coagulation, and fibrinolysis. Herein, we describe the SAR and structural binding modes of a series of inhibitors of plasma kallikrein as well as the pharmacokinetics of a lead analog **11** in rat.

Factor VIIa inhibitors: Chemical optimization, preclinical pharmacokinetics, pharmacodynamics, and efficacy in an arterial baboon thrombosis model

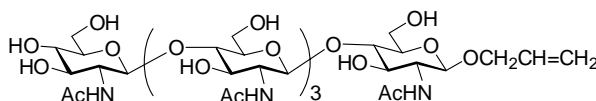
pp 2037–2041

Wendy B. Young,* Joyce Mordenti, Steven Torkelson, William D. Shrader, Aleksandr Kolesnikov, Roopa Rai,
Liang Liu, Huiyong Hu, Ellen M. Leahy, Michael J. Green, Paul A. Sprengeler, Bradley A. Katz, Christine Yu,
James W. Janc, Kyle C. Elrod, Ulla M. Marzec and Stephen R. Hanson

Highly selective and potent factor VIIa–tissue factor (fVIIa·TF) complex inhibitors were generated through structure-based design. The pharmacokinetic properties of an optimized analog (**9**) were characterized in several preclinical species, demonstrating pharmacokinetic characteristics suitable for once-a-day dosing in humans. Analog **9** inhibited platelet and fibrin deposition in a dose-dependent manner after intravenous administration in a baboon thrombosis model, and a pharmacodynamic concentration–response model was developed to describe the platelet deposition data. Results for heparin and enoxaparin (Lovenox®) in the baboon model are also presented.

**Chemo-enzymatic synthesis of allyl penta-N-acetyl-chitopentaose**

pp 2042–2043

Gang-Liang Huang, Da-Wei Zhang, Hong-Juan Zhao,
Hou-Cheng Zhang and Peng-George Wang*

QSAR study on topically acting sulfonamides incorporating GABA moieties: A molecular connectivity approach

pp 2044–2051

Vijay K. Agrawal, Jyoti Singh, Padmakar V. Khadikar* and Claudiu T. Supuran

A quantitative Structure–activity relationship study (QSAR) on a set of carbonic anhydrase inhibitors is presented using first-order valence connectivity index ($^1\chi^v$). The inhibitory activity against three isozymes CAI, CAII (cystolic forms), and CAIV (membrane bound form), some of which are involved in important physiological processes, were considered for this purpose. All the three activities were well modeled by $^1\chi^v$ in multi-parametric regression containing indicator parameters. The results are critically discussed on the basis of variety of statistical analyses.

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Summary of instructions to authors

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*Corresponding author

①⁺ Supplementary data available via ScienceDirect**COVER**

Crystal structures of **19** bound to the allosteric site of KSP. Protein shown in solid ribbon. Green patch indicates location of a hydrophobic region in the binding site. [Fraleigh, M. E.; Garbaccio, R. M.; Arrington, K. L.; Hoffman, W. F.; Tasber, E. S.; Coleman, P. J.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Fernandes, C.; Schaber, M. D.; Lobell, R. B.; Tao, W.; South, V. J.; Yan, Y.; Kuo, L. C.; Prueksaritanont, T.; Shu, C.; Torrent, M.; Heimbrook, D. C.; Kohl, N. E.; Huber, H. E.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2006**, 16, 1775.]



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