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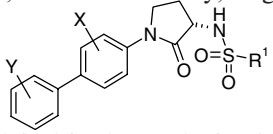
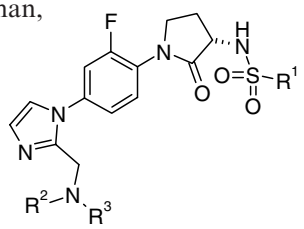
Structure and property based design of factor Xa inhibitors: Pyrrolidin-2-ones with biaryl P4 motifs **pp 23–27**
Robert J. Young*, Alan D. Borthwick, David Brown, Cynthia L. Burns-Kurtis, Matthew Campbell, Chuen Chan, Marie Charbaut, Chun-wa Chung, Máire A. Convery, Henry A. Kelly, N. Paul King, Savvas Kleanthous, Andrew M. Mason, Anthony J. Pateman, Angela N. Patikis, Ivan L. Pinto, Derek R. Pollard, Stefan Senger, Gita P. Shah, John R. Toomey, Nigel S. Watson and Helen E. Weston



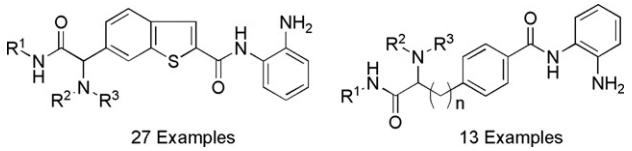
Structure and property based drug design was exploited in the synthesis of sulfonamidopyrrolidin-2-one-based factor Xa (fXa) inhibitors, incorporating biaryl P4 groups, producing highly potent inhibitors with encouraging oral pharmacokinetic profiles and significant but sub-optimal anticoagulant activities.

Structure and property based design of factor Xa inhibitors: Biaryl pyrrolidin-2-ones incorporating basic heterocyclic motifs **pp 28–33**
Robert J. Young,* Alan D. Borthwick, David Brown, Cynthia L. Burns-Kurtis, Matthew Campbell, Chuen Chan, Marie Charbaut, Máire A. Convery, Hawa Diallo, Eric Hortense, Wendy R. Irving, Henry A. Kelly, N. Paul King, Savvas Kleanthous, Andrew M. Mason, Anthony J. Pateman, Angela N. Patikis, Ivan L. Pinto, Derek R. Pollard, Stefan Senger, Gita P. Shah, John R. Toomey, Nigel S. Watson, Helen E. Weston and Ping Zhou



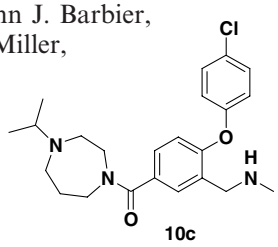
Structure and property based drug design was exploited in the synthesis of sulfonamido-pyrrolidin-2-one-based factor Xa (fXa) inhibitors, incorporating basic biaryl P4 groups, producing highly potent inhibitors with significant anticoagulant activities and encouraging oral pharmacokinetic profiles.

Amino acid derivatives as histone deacetylase inhibitors **pp 34–38**
Jed L. Hubbs,* Hua Zhou, Astrid M. Kral, Judith C. Fleming, William K. Dahlberg, Bethany L. Hughes, Richard E. Middleton, Alexander A. Szewczak, J. Paul Secrist and Thomas A. Miller



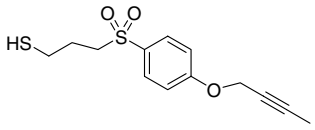
Synthesis and biological activity of piperazine and diazepane amides that are histamine H_3 antagonists and serotonin reuptake inhibitors pp 39–43
Kiev S. Ly, Michael A. Letavic,* John M. Keith, Jennifer M. Miller, Emily M. Stocking, Ann J. Barbier, Pascal Bonaventure, Brian Lord, Xiaohui Jiang, Jamin D. Boggs, Lisa Dvorak, Kirsten L. Miller, Diane Nepomuceno, Sandy J. Wilson and Nicholas I. Carruthers

The synthesis and biological activity of a new series of piperazine and diazepane amides is described.



10c
H_3 K_i =0.5 nM
SERT K_i=6.4 nM

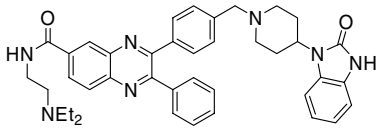
Novel thiol-based TACE inhibitors. Part 2: Rational design, synthesis, and SAR of thiol-containing aryl sulfones pp 44–48
Upul K. Bandarage,* Tiansheng Wang, Jon H. Come, Emanuele Perola, Yunyi Wei and B. Govinda Rao



8b TACE K_i = 10 nM

A series of potent thiol-containing aryl sulfone TACE inhibitors were designed and synthesized. The SAR and MMP selectivity of the series were investigated. In particular, compound **8b** has shown excellent in vitro potency against the isolated TACE enzyme and good selectivity over MMP-2, -7, -8, -9, and -13. The X-ray structure of **8b** bound to TACE was also obtained.

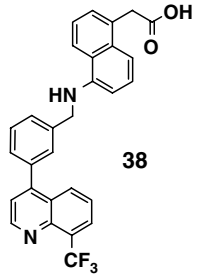
Development of potent, allosteric dual Akt1 and Akt2 inhibitors with improved physical properties and cell activity pp 49–53
Zhijian Zhao,* Ronald G. Robinson, Stanley F. Barnett, Deborah Defeo-Jones, Raymond E. Jones, George D. Hartman, Hans E. Huber, Mark E. Duggan and Craig W. Lindsley



	Akt 1 (IC_{50})	Akt 2 (IC_{50})	Akt 3 (IC_{50})
in vitro	138 nM	212 nM	7200 nM
cell IPKA	253 nM	276 nM	>10,000 nM

Soluble in 98% Saline (18 mg/mL)

Carboxylic acid based quinolines as liver X receptor modulators that have LXRβ receptor binding selectivity pp 54–59
Baihua Hu,* Elaine Quinet, Rayomand Unwalla, Mike Collini, James Jetter, Rebecca Dooley, Diane Andraka, Lisa Nogle, Dawn Savio, Anita Halpern, Annika Goos-Nilsson, Anna Wilhelmsson, Ponnal Nambi and Jay Wrobel



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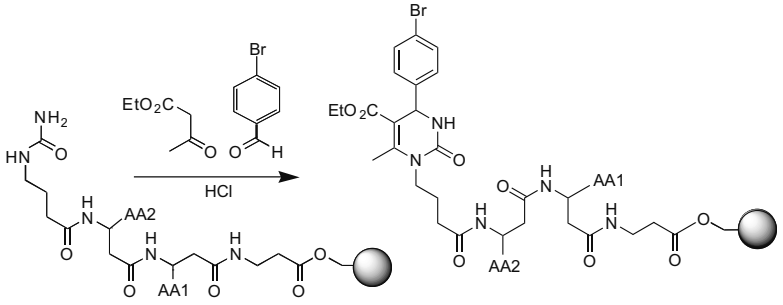
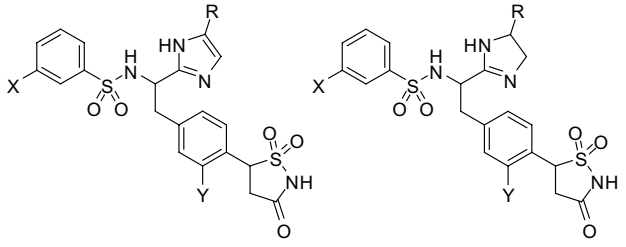
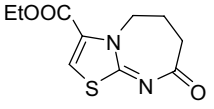
Chemical modulators of heat shock protein 70 (Hsp70) by sequential, microwave-accelerated reactions on solid phase **pp 60–65**
Susanne Wisén, John Androsavich, Christopher G. Evans, Lyra Chang and Jason E. Gestwicki*



Isothiazolidinone inhibitors of PTP1B containing imidazoles and imidazolines **pp 66–71**
Brent Douty,* Brian Wayland, Paul J. Ala, Michael J. Bower, James Pruitt, Lori Bostrom, Min Wei, Ronald Klabe, Lucie Gonneville, Richard Wynn, Timothy C. Burn, Phillip C. C. Liu, Andrew P. Combs and Eddy W. Yue

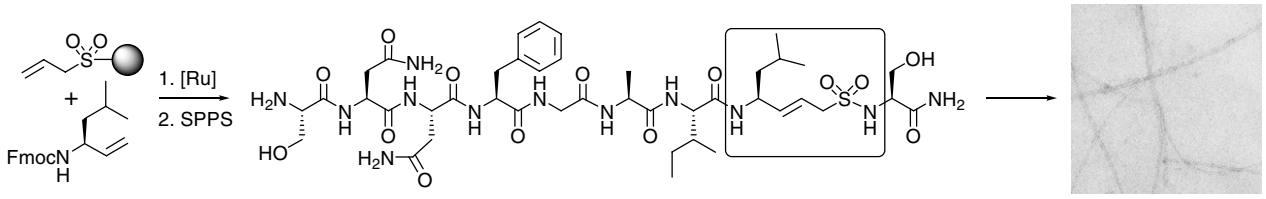


New ultra-short acting hypnotic: Synthesis, biological evaluation, and metabolic profile of ethyl 8-oxo-5,6,7,8-tetrahydro-thiazolo[3,2-*a*][1,3]diazepin-3-carboxylate (HIE-124) **pp 72–77**
Hussein I. El-Subbagh,* Hassan A. El-Kashef, Adnan A. Kadi, Alaa A.-M. Abdel-Aziz, Ghada S. Hassan, Justice Tettey and Jochen Lehmann



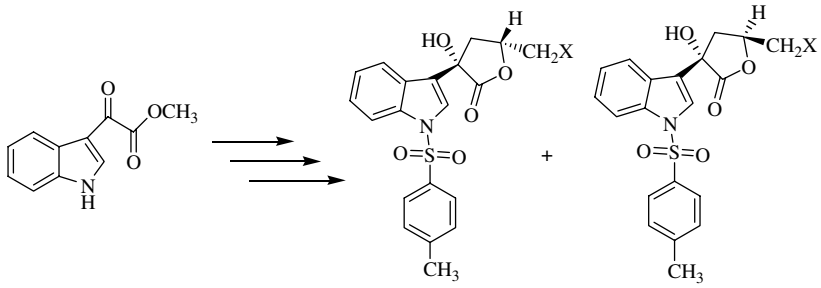
HIE-124 (4)

Delayed fibril formation of amylin(20–29) by incorporation of alkene dipeptidosulfonamide isosteres obtained by solid phase olefin cross metathesis **pp 78–84**
Arwin J. Brouwer, Ronald C. Elgersma, Monika Jagodzinska, Dirk T. S. Rijkers and Rob M. J. Liskamp*

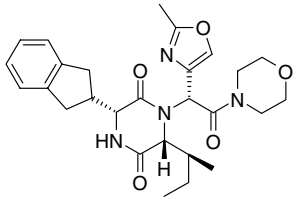


1-Toluene-sulfonyl-3-[(3′-hydroxy-5′-substituted)-γ-butyrolactone]-indoles: Synthesis, COX-2 inhibition and anti-cancer activities pp 85–89
Palwinder Singh,* Anu Mittal, Atul Bhardwaj, Satwinderjeet Kaur and Subodh Kumar

Allylation-iodocyclisation and nucleophilic replacement reactions on 3-indoleglyoxylate, have provided butyrolactone substituted indoles with high COX-2 inhibitory activities and remarkable anti-cancer activities.

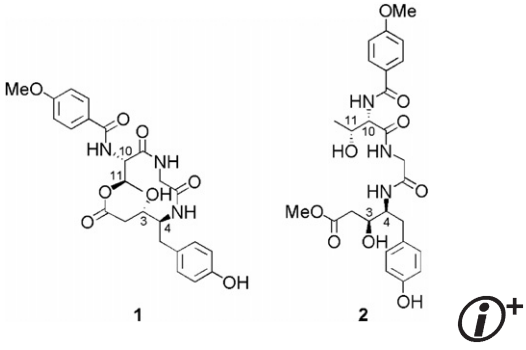


The discovery of GSK221149A: A potent and selective oxytocin antagonist pp 90–94
John Liddle,* Michael J. Allen, Alan D. Borthwick, David P. Brooks, David E. Davies, Richard M. Edwards, Anne M. Exall, Chris Hamlett, Wendy R. Irving, Andrew M. Mason, Gerald P. McCafferty, Fabrizio Nerozzi, Simon Peace, Joanne Philp, Derek Pollard, Mark A. Pullen, Shaila S. Shabbir, Steve L. Sollis, Timothy D. Westfall, Pat M. Woollard, Charlene Wu and Deirdre M. B. Hickey

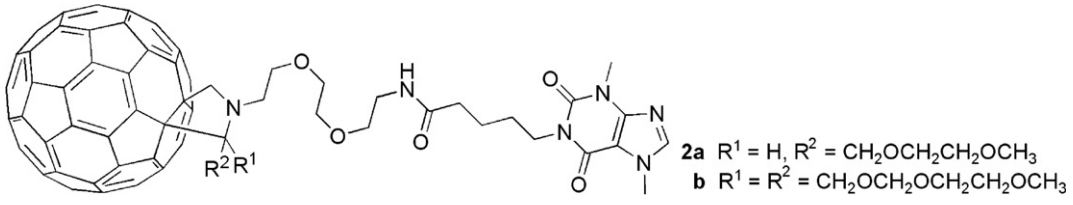


Determination of absolute stereochemistry, total synthesis, and evaluation of peptides from the myxomycete *Physarum melleum* pp 95–98
Shuwa Hanazawa, Midori A. Arai, Xiaofan Li and Masami Ishibashi*

We determined the absolute stereochemistry of melleumin A (**1**) and B (**2**). Total synthesis of **2** was achieved and the epimer showed moderate inhibition of Wnt signal transcription.

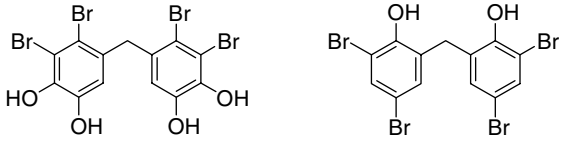


Synthesis and anti-inflammation evaluation of new C_{60} fulleropyrrolidines bearing biologically active xanthine pp 99–103
Sheng-Tung Huang,* Jian-Sheng Liao, Hsu-Wei Fang and Chun-Mao Lin



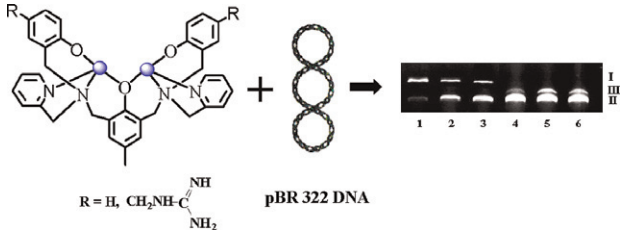
We prepared new C_{60} fullerene hybrids bearing a xanthine moiety and it is a potent agent to reduce the LPS-induced NO and TNF-α released by the macrophages J774A.1.

Antimicrobial activities of the bromophenols from the red alga *Odonthalia corymbifera* and some synthetic derivatives **pp 104–108**
Ki-Bong Oh, Ji Hye Lee, Soon-Chun Chung, Jongheon Shin, Hee Jae Shin, Hye-Kyeong Kim* and Hyi-Seung Lee*



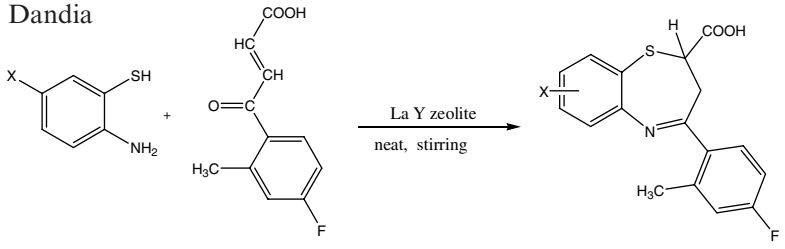
The isolation, synthesis, and bioactivity of bromophenols are described.

Efficient enhancement of DNA cleavage activity by introducing guanidinium groups into diiron(III) complex **pp 109–113**
Xiaoqiang Chen, Jingyun Wang,* Shiguo Sun, Jiangli Fan, Song Wu, Jianfeng Liu, Saijian Ma, Lizhu Zhang and Xiaojun Peng*



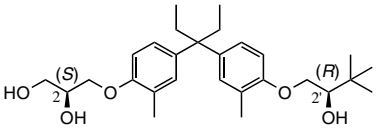
Guanidinium groups were introduced into diferric system and led to efficient enhancement in DNA cleavage activity.

The expedient synthesis of 1,5-benzothiazepines as a family of cytotoxic drugs **pp 114–119**
Kapil Arya* and Anshu Dandia



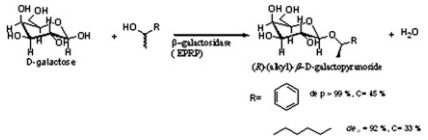
The expedient synthesis of 1,5-benzothizeopines using LaY zeolite under stirring condition is reported and synthesized compound screened for cytotoxic activity.

(2*S*,2′*R*)-Analogue of LG190178 is a major active isomer **pp 120–123**
Wataru Hakamata, Yukiko Sato, Haruhiro Okuda, Shinobu Honzawa, Nozomi Saito, Seishi Kishimoto, Atsushi Yamashita, Takayuki Sugiura, Atsushi Kittaka and Masaaki Kurihara*

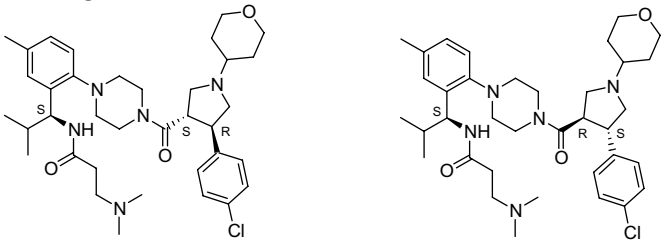


YR301 was the (2*S*,2′*R*)-analogue of LG190178 and had strong activity.

Diastereoselective synthesis of (*R*)-(alkyl)-β-D-galactopyranoside by using β-galactosidase (*Aspergillus oryzae*) in low-water media **pp 124–128**
Abir B. Majumder, Bhupender Singh and Munishwar N. Gupta*



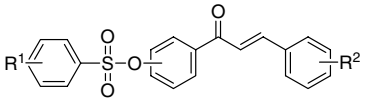
Identification and characterization of pyrrolidine diastereoisomers as potent functional agonists and antagonists of the human melanocortin-4 receptor **pp 129–136**
Chen Chen,* Wanlong Jiang, Joe A. Tran, Fabio C. Tucci, Beth A. Fleck, Stacy Markison, Jenny Wen, Ajay Madan, Sam R. Hoare, Alan C. Foster, Dragan Marinkovic, Caroline W. Chen, Melissa Arellano and John Saunders



13b-1 (*S,S,R*-isomer):
K_i = 1.0 nM, EC_{50} = 3.8 nM, IA = 122%

13b-2 (*S,R,S*-isomer):
K_i = 4.7 nM, IA = 10%, IC_{50} = 64 nM

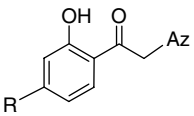
Sulfonate chalcone as new class voltage-dependent K^+ channel blocker **pp 137–140**
Oleg V. Yarishkin, Hyung Won Ryu, Jae-Yong Park, Min Suk Yang, Seong-Geun Hong* and Ki Hun Park*



Sulfonate Chalcones **9**–**17** were found to exhibit the potential to act as a new class of voltage-dependent K^+ channel blockers.

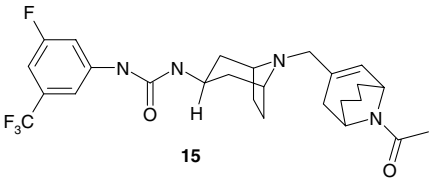
2-Hydroxyphenacyl azoles and related azolium derivatives as antifungal agents **pp 141–146**
Saeed Emami,* Alireza Foroumadi, Mehraban Falahati, Ensieh Lotfali, Saeed Rajabalian, Soltan-Ahmed Ebrahimi, Shirin Farahyar and Abbas Shafiee

2-Hydroxyphenacyl azole and 2-hydroxyphenacyl azolium compounds have been described as a new class of azole antifungals. Most target compounds showed significant in vitro antifungal activities against tested fungi with low MIC values included in the range of 0.25–32 μg/mL comparable to reference drug fluconazole.



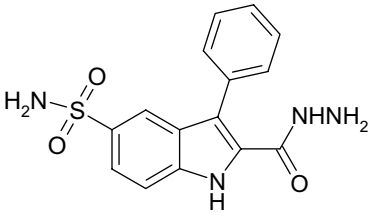
R = H, Cl, OMe
Az = 1*H*-imidazol-1-yl; 1*H*-1,2,4-triazol-1-yl; 4*H*-1,2,4-triazol-4-yl; 1*H*-1,2,4-triazolium; 4-amino-4*H*-1,2,4-triazoliumyl

Development of CXCR3 antagonists. Part 3: Tropenyl and homotropenyl-piperidine urea derivatives **pp 147–151**
Robert J. Watson,* Daniel R. Allen, Helen L. Birch, Gayle A. Chapman, Frances C. Galvin, Louise A. Jopling, Roland L. Knight, Dorica Meier, Kathryn Oliver, Johannes W. G. Meissner, David A. Owen, Elizabeth J. Thomas, Neil Tremayne and Sophie C. Williams

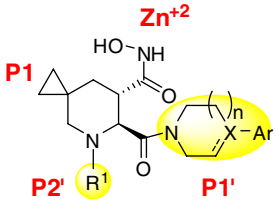


The optimization of a series of 1-aryl-3-piperidinyl urea derivatives is described in which incorporation of tropenyl and homotropenyl moieties has led to significant improvements in activity and drug-like properties. Replacement of the central piperidine with an *exo*-tropanyl unit led to the identification of compound **15** which provides a combination of excellent potency against human and murine receptors, drug-like properties and pharmacokinetics, thus providing a valuable tool for the evaluation of CXCR3 antagonists in models of human disease.

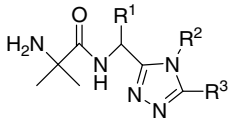
Carbonic anhydrase inhibitors. Interaction of 2-(hydrazinocarbonyl)-3-phenyl-1*H*-indole-5-sulfonamide with 12 mammalian isoforms: Kinetic and X-ray crystallographic studies **pp 152–158**
Özlen Güzel, Claudia Temperini, Alessio Innocenti, Andrea Scozzafava, Aydın Salman and Claudiu T. Supuran*



Design and identification of selective HER-2 sheddase inhibitors via P1′ manipulation and unconventional P2′ perturbations to induce a molecular metamorphosis **pp 159–163**
Wenqing Yao,* Jincong Zhuo, David M. Burns, Yun-Long Li, Ding-Quan Qian, Colin Zhang, Chunhong He, Meizhong Xu, Eric Shi, Yanlong Li, Cindy A. Marando, Maryanne B. Covington, Gengjie Yang, Xiangdong Liu, Max Pan, Jordan S. Fridman, Peggy Scherle, Zelda R. Wasserman, Gregory Hollis, Kris Vaddi, Swamy Yeleswaram, Robert Newton, Steve Friedman and Brian Metcalf

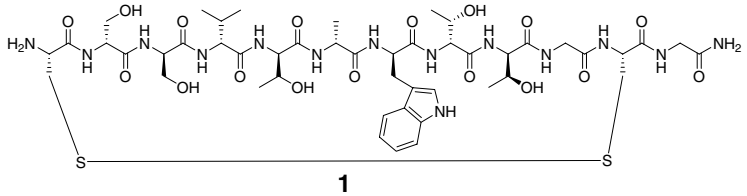


Trisubstituted 1,2,4-triazoles as ligands for the ghrelin receptor: On the significance of the orientation and substitution at position 3 **pp 164–168**
Aline Moulin, Luc Demange, Joanne Ryan, Céline M'Kadmi, Jean-Claude Galleyrand, Jean Martinez and Jean-Alain Fehrentz*



The importance of R_1 substitution and orientation was studied. The (D) Trp residue as starting material was found to lead to the best agonist or antagonist compounds.

Discovery of new small molecules that influence neuroblast cell migration from the subventricular zone **pp 169–174**
Amandine Rolland, Isabelle Boquet, Jean-Chrétien Norreel, Vincent Moret, Younes Laras and Jean-Louis Kraus*



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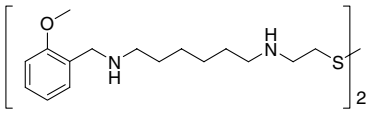
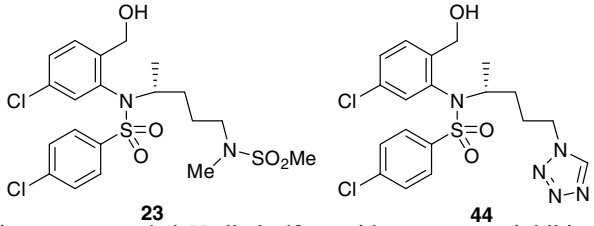


8

Structures of compound **1** and compound **8** which are, respectively, activator and inhibitor for neuronal SVZ cell migration. **8** antagonizes the activating effect of **1**.

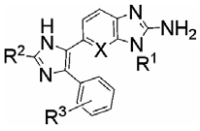
Nitrogen-appended *N*-alkylsulfonamides as inhibitors of γ-secretase **pp 175–178**
Carl P. Bergstrom,* Charles P. Sloan, Henry H. Wang, Michael F. Parker, David W. Smith, Ming Zheng, Steven B. Hansel, Craig T. Polson, Lauren E. Barber, Isia Bursuker, Valerie L. Guss, Jason A. Corsa, Donna M. Barten, Kevin M. Felsenstein and Susan B. Roberts



23 **44**

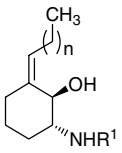
Structure–activity relationships of nitrogen-appended *N*-alkylsulfonamide γ-secretase inhibitors are reported.

Imidazolyl benzimidazoles and imidazo[4,5-*b*]pyridines as potent p38α MAP kinase inhibitors with excellent in vivo antiinflammatory properties **pp 179–183**
Mary Mader,* Alfonso de Dios,* Chuan Shih, Rosanne Bonjouklian, Tiechao Li, Wesley White, Beatriz López de Uralde, Concepción Sánchez-Martinez, Miriam del Prado, Carlos Jaramillo, Eugenio de Diego, Luisa M. Martín Cabrejas, Carmen Dominguez, Carlos Montero, Timothy Shepherd, Robert Dally, John E. Toth, Arindam Chatterjee, Sehila Pleite, Jaime Blanco-Urgoiti, Leticia Perez, Mario Barberis, María José Lorite, Enrique Jambrina, C. Richard Nevill, Jr., Paul A. Lee, Richard C. Schultz, Jeffrey A. Wolos, Li C. Li, Robert M. Campbell and Bryan D. Anderson



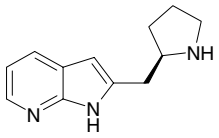
The p38 MAP kinase activity of two series of trisubstituted imidazoles (X = C, N) is reported, leading to compounds with highly potent cellular and in vivo activity.

Leishmanicidal and trypanocidal activities of 2-aminocyclohexanol and 1,2-cyclohexanediamine derivatives **pp 184–187**
Oscar Rebollo, Esther del Olmo,* Grace Ruiz, José L. López-Pérez, Alberto Giménez and Arturo San Feliciano



Alkyl(alkylidene) substituted aminocyclohexanol derivatives and related compounds display in vitro anti-*Leishmania* and anti-*Trypanosoma* activities, with potencies higher than those of the clinically used reference drugs pentamidine, amphotericin B and benznidazol.

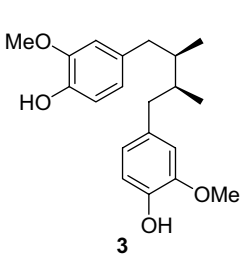
7-Azaindole derivatives as potential partial nicotinic agonists **pp 188–193**
Axel R. Stoit,* Arnold P. den Hartog, Harry Mons, Sjoerd van Schaik, Nynke Barkhuijsen, Cees Stroomer, Hein K. A. C. Coolen, Jan Hendrik Reinders, Tiny J. P. Adolfs, Martina van der Neut, Hiskias Keizer and Chris G. Kruse



A series of 7-azaindoles was investigated as potential partial agonists of the α4β2 nicotinic acetylcholine receptor (nAChR).

Low-density lipoprotein (LDL)-antioxidant lignans from *Myristica fragrans* seeds **pp 194–198**
Hyun Sook Kwon, Min-Jung Kim, Hyung Jae Jeong, Min Suk Yang, Ki Hun Park, Tae-Sook Jeong* and Woo Song Lee*

Six diarylbutane lignans **1**–**5** and one aryltetralin lignan **6** were isolated from the ethyl acetate extracts of *Myristica fragrans* seeds and then 7-methyl ether diarylbutane lignan **4** has proven to be a new compound. Their compounds **1**–**7** were evaluated for LDL-antioxidant activity to identify the most potent LDL-antioxidant compound **3** with an IC_{50} value of 2.6 μM.



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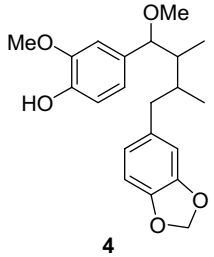
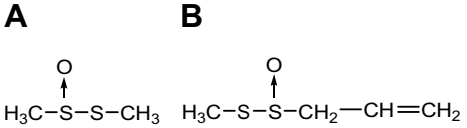


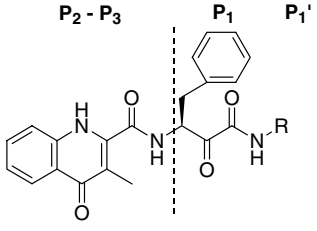
4

Thiosulfinates from *Allium tuberosum* L. induce apoptosis via caspase-dependent and -independent pathways in PC-3 human prostate cancer cells **pp 199–204**
So-Yeon Kim, Kyoung-Wuk Park, Jae-Yong Kim, Il-Yun Jeong, Myung-Woo Byun, Jung-Eun Park, Sung-Tae Yee, Kee-Hong Kim, Johng S. Rhim, Koji Yamada and Kwon-Il Seo*



Design and synthesis of 4-quinolinone 2-carboxamides as calpain inhibitors **pp 205–209**
Dong Hyuk Nam, Kwang Seob Lee, Sang Hoon Kim, Sung Min Kim, Seo Yun Jung, Sung Hyun Chung, Hyoung Ja Kim, Nam Doo Kim, Changbae Jin and Yong Sup Lee*

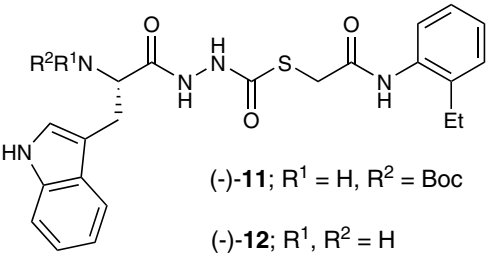
4-Quinolinone 2-carboxamide derivatives were prepared and evaluated for μ-calpain inhibition. Of the derivatives synthesized, compound **3a** and **3k**, which have a primary amide and 4-methoxyphenethy amide at P_1' region, were the most potent μ-calpain inhibitor with an IC_{50} values of 0.71 and 0.73 μM, respectively.



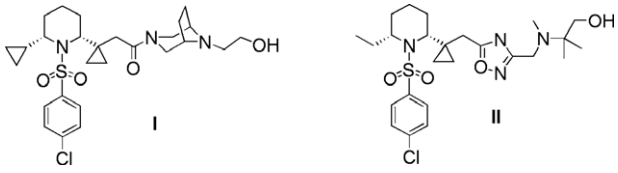
3,**4**-Quinolinone 2-carboxamide

Identification and synthesis of a unique thiocarbazate cathepsin L inhibitor **pp 210–214**
Michael C. Myers, Parag P. Shah, Scott L. Diamond,* Donna M. Huryn* and Amos B. Smith, III

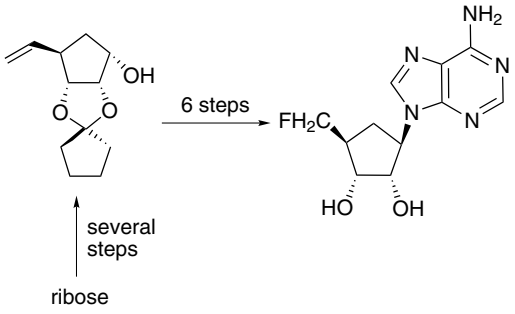
Library samples containing 2,5-disubstituted oxadiazoles were identified as potent hits in a high throughput screen (HTS) of the NIH Molecular Libraries Small Molecule Repository (MLSMR) directed at discovering inhibitors of cathepsin L. However, when synthesized in pure form, the putative actives were found to be devoid of biological activity. Analyses by LC–MS of original library samples indicated the presence of a number of impurities, in addition to the oxadiazoles. Synthesis and bioassay of the probable impurities led to the identification of a thiocarbazate that likely originated via ring opening of the oxadiazole. Previously unknown, thiocarbazates (−)-**11** and (−)-**12** were independently synthesized as single enantiomers and found to inhibit cathepsin L in the low nanomolar range.



Discovery of amide and heteroaryl isosteres as carbamate replacements in a series of orally active γ-secretase inhibitors **pp 215–219**
Mark D. McBriar,* John W. Clader, Inhou Chu, Robert A. Del Vecchio, Leonard Favreau, William J. Greenlee, Lynn A. Hyde, Amin A. Nomeir, Eric M. Parker, Dmitri A. Pissarnitski, Lixin Song, Lili Zhang and Zhiqiang Zhao

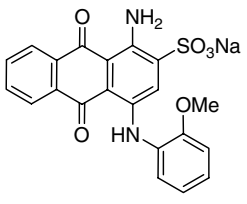


5′-Fluoro-5′-deoxyaristeromycin **pp 220–222**
Weikuan Li, Xueqiang Yin and Stewart W. Schneller*

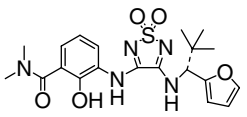


Combinatorial synthesis of anilinoanthraquinone derivatives and evaluation as non-nucleotide-derived $P2Y_2$ receptor antagonists **pp 223–227**
Stefanie Weyler, Younis Baqi, Petra Hillmann, Marko Kaulich, Andrea M. Hunder, Ingrid A. Müller and Christa E. Müller*

A library of anilinoanthraquinone derivatives was synthesized by a parallel Ullmann coupling reaction in solution and evaluated as $P2Y_2$ receptor antagonists. PSB-716 was found to be a potent $P2Y_2$ antagonist with an IC_{50} of 9 μM.



3,4-Diamino-2,5-thiadiazole-1-oxides as potent CXCR2/CXCR1 antagonists **pp 228–231**
Purakkattle Biju,* Arthur Taveras, Younong Yu, Junying Zheng, Jianhua Chao, Diane Rindgen, James Jakway, R. William Hipkin, James Fossetta, Xuedong Fan, Jay Fine, Hongchen Qiu, J. Robert Merritt and John J. Baldwin



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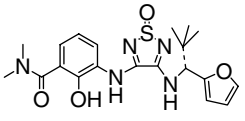
CXCR2 Ki = 11nM
CXCR1 Ki = 61nM



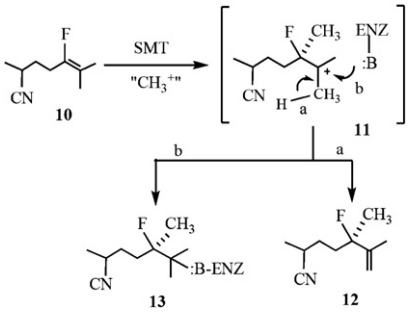
27

CXCR2 Ki = 2.3nM
CXCR1 Ki = 21nM

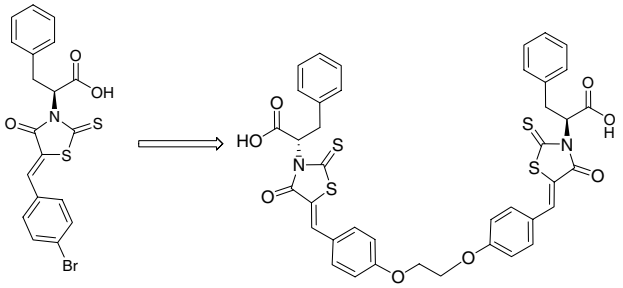
A novel series of structurally related 3,4-diamino-2,5-thiadiazole-1,1-dioxides and 3,4-diamino-2,5-thiadiazole-1-oxides prepared as CXCR2/CXCR1 receptor antagonists is described.

Sterol C24-methyltransferase: Mechanistic studies of the C-methylation reaction with 24-fluorocycloartenol **pp 232–235**
Junqing Wang, Jialin Liu, Zhihong Song and W. David Nes*

The mechanism of the C-methylation reaction was studied with 24-fluorocycloartenol **10** incubated with the soybean sterol C24-methyltransferase. **10** suppresses the rate of the C-methylation reaction by one order of magnitude relative to the cycloartenol substrate, $k_{cat} = 0.02\ min^{-1}$ versus $0.6\ min^{-1}$; alternately **10** can inhibit activity ($K_i = 32\ \mu M$) to afford time-dependent inactivation of SMT ($k_{inact} = 0.32\ min^{-1}$).

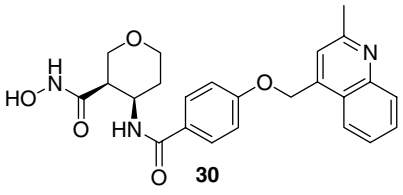


Development of dimeric modulators for anti-apoptotic Bcl-2 proteins **pp 236–240**
Liangyou Wang, Fansen Kong, Candis L. Kokoski, David W. Andrews and Chengguo Xing*



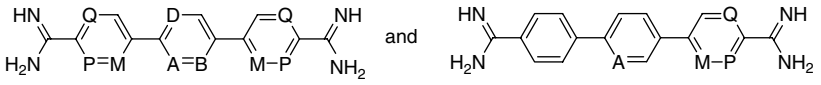
3e **3e-D2**

Discovery of β-benzamido hydroxamic acids as potent, selective, and orally bioavailable TACE inhibitors **pp 241–246**
James J.-W. Duan,* Lihua Chen, Zhonghui Lu, Chu-Biao Xue, Rui-Qin Liu, Maryanne B. Covington, Mingxin Qian, Zelda R. Wasserman, Krishna Vaddi, David D. Christ, James M. Trzaskos, Robert C. Newton and Carl P. Decicco



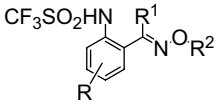
30

Azaterphenyl diamidines as antileishmanial agents **pp 247–251**
Laixing Hu, Reem K. Arafa, Mohamed A. Ismail, Tanja Wenzler, Reto Brun, Manoj Munde, W. David Wilson, Sandra Nzimiro, Serene Samyesudhas, Karl A. Werbovetz* and David W. Boykin*



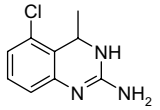
A, B, D, M, P, Q = CH, N

Parasiticidal 2-alkoxy- and 2-aryloxyiminoalkyl trifluoromethanesulfonanilides **pp 252–255**
Abdelselam Ali, Timothy M. Altamore, Marianne Bliese, Petr Fisara, Andris J. Liepa, Adam G. Meyer,* Oahn Nguyen, Roger M. Sargent, David G. Sawutz, David A. Winkler, Kevin N. Winzenberg and Angela Ziebell



Novel 2-alkoxy- and 2-aryloxyiminoalkyl trifluoromethanesulfonanilide derivatives with significant in vitro parasiticidal activity against *Ctenocephalides felis*, *Rhipicephalus sanguineus* and *Haemonchus contortus* are reported.

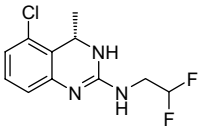
Cyclic guanidines as dual 5-HT$_{5A}$/5-HT$_7$ receptor ligands: Structure–activity relationship elucidation **pp 256–261**
Jens-Uwe Peters,* Thomas Lübbers, Alexander Alanine, Sabine Kolczewski, Francesca Blasco and Lucinda Steward



Ki (5-HT$_{5A}$) = 5.1nM
Ki (5-HT$_7$) = 16nM
brain / plasma = 0.2

The optimisation of affinity and selectivity in a novel series of dual 5-HT$_{5A}$/5-HT$_7$ receptor ligands is described.

Cyclic guanidines as dual 5-HT$_{5A}$/5-HT$_7$ receptor ligands: Optimising brain penetration **pp 262–266**
Jens-Uwe Peters,* Thomas Lübbers, Alexander Alanine, Sabine Kolczewski, Francesca Blasco and Lucinda Steward

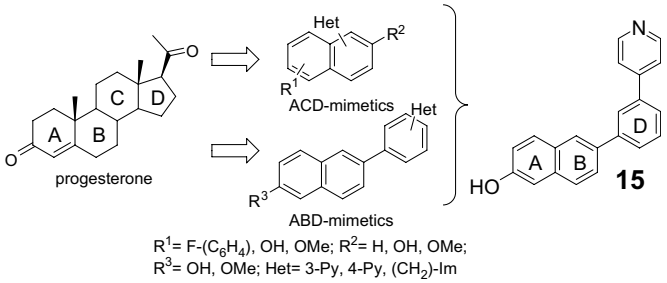


Ki (5-HT$_{5A}$) = 6.8nM
Ki (5-HT$_7$) = 25nM
brain / plasma ~ 4

The optimisation of molecular properties within a series of guanidine-type dual 5-HT$_{5A}$/5-HT$_7$ receptor ligands led to an improved brain-to-plasma ratio. The best representative of optimised compounds reached micromolar brain concentrations after oral administration.

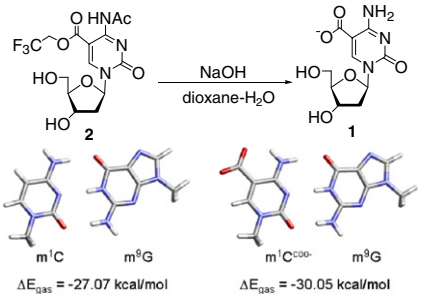
Synthesis, biological evaluation and molecular modelling studies of novel ACD- and ABD-ring steroidomimetics as inhibitors of CYP17 **pp 267–273**
Mariano A. E. Pinto-Bazurco Mendieta, Matthias Negri, Carsten Jagusch, Ulrike E. Hille, Ursula Müller-Vieira, Dirk Schmidt, Klaus Hansen and Rolf W. Hartmann*

Novel ACD- and ABD-ring mimetics of progesterone were synthesised and evaluated as CYP17 inhibitors. One promising lead structure (**15**) was found, suitable for further optimisation.

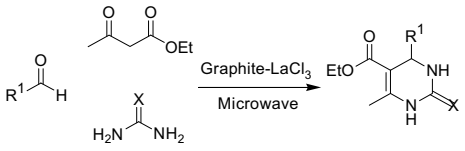


Synthesis and properties of oligodeoxynucleotides containing 5-carboxy-2′-deoxycytidines **pp 274–277**
Masanori Sumino, Akihiro Ohkubo, Haruhiko Taguchi, Kohji Seio and Mitsuo Sekine*

We synthesized ODN incorporating 5-carboxy-2′-deoxycytidine. The ODN could form the duplex with the complementary ODN which was more stable than the natural-type duplex.

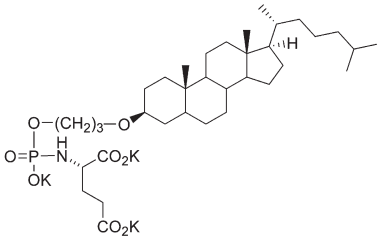


Microwave-assisted synthesis of dihydropyrimidin-2(1*H*)-ones using graphite supported lanthanum chloride as a mild and efficient catalyst **pp 278–280**
Hojatollah Khabazzadeh, Kazem Saidi* and Hassan Sheibani



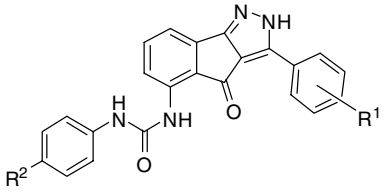
Graphite supported lanthanum chloride was employed for the synthesis of dihydropyrimidinones under microwave irradiation.

Phosphoramidate derivatives of hydroxysteroids as inhibitors of prostate-specific membrane antigen **pp 281–284**
Lisa Y. Wu, Jacinda C. Do, Marat Kazak, Helen Page, Yoko Toriyabe, Marc O. Anderson and Clifford E. Berkman*



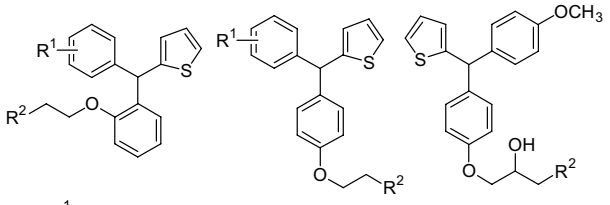
IC_{50} against PSMA enzymatic activity = 125 nM (five other steroid derived phosphoramidates were found with IC_{50} values ranging from 140-569 nM)

Discovery of indenopyrazoles as EGFR and VEGFR-2 tyrosine kinase inhibitors by in silico high-throughput screening pp 285–288
Taikou Usui, Hyun Seung Ban, Junpei Kawada, Takatsugu Hirokawa and Hiroyuki Nakamura*



In silico high-throughput screening targeting to EGFR tyrosine kinase was carried out and indenopyrazoles were found to possess inhibitory activities toward EGFR and/or VEGFR tyrosine kinases.

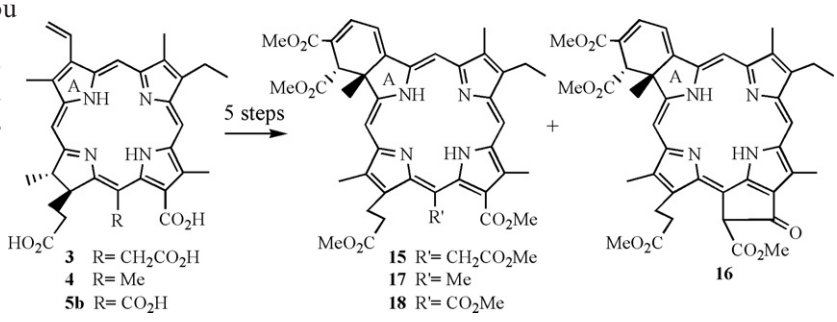
Thiophene containing triarylmethanes as antitubercular agents pp 289–292
Maloy Kumar Parai, Gautam Panda,* Vinita Chaturvedi, Y. K. Manju and Sudhir Sinha



R^1= m-OCH_3, p-OCH_3, p-SCH_3, p-Cl
R^2= 1°, 2° and 3° amines

Design, synthesis, and in vitro photodynamic activities of benzochloroporphyrin derivatives as tumor photosensitizers pp 293–297
Jianzhong Yao, Wannian Zhang,* Chunquan Sheng, Zhenyuan Miao, Feng Yang, Jianxin Yu, Ling Zhang, Yunlong Song, Ting Zhou and Youjun Zhou

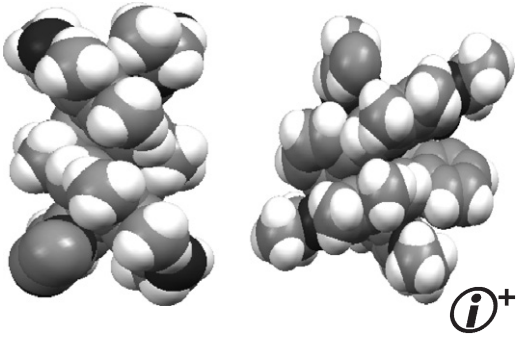
The synthesis and preliminary in vitro photodynamic efficacy on human hepatoma BEL-7402 cells of novel benzochloroporphyrin derivatives (BCPDs) **15**–**18** are reported.



3 R= CH_2CO_2H
4 R= Me
5b R= CO_2H
5 steps
15 R'= CH_2CO_2Me
17 R'= Me
18 R'= CO_2Me
16

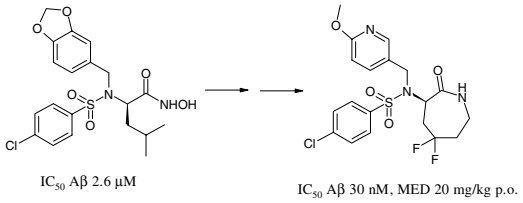
Synthesis, characterization and DNA-binding properties of four Zn(II) complexes with bis(pyrrol-2-yl-methyleneamine) ligands pp 298–303
Yuan Wang, Zheng-Yin Yang* and Zhong-Ning Chen

A novel series of bis(pyrrol-2-yl-methyleneamine) ligands H_2L^n and their Zn(II) complexes were synthesized. The crystal structures of $[ZnL^1]_2$ and $[ZnL^4]_2$ show that each of them possesses a double-stranded helical geometry. In addition, the DNA-binding properties of the compounds have been fully investigated.



Substituted 2-oxo-azepane derivatives are potent, orally active γ-secretase inhibitors **pp 304–308**
Eric A. Kitas,* Guido Galley, Roland Jakob-Roetne, Alexander Flohr, Wolfgang Wostl, Harald Mauser, André M. Alker, Christian Czech, Laurence Ozmen, Pascale David-Pierson, Dieter Reinhardt and Helmut Jacobsen

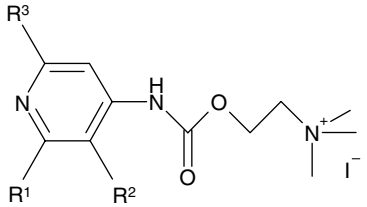
A hydroxamic acid screening hit was elaborated to 5,5-difluoro-2-oxoazepane derivatives exhibiting low nanomolar inhibition of γ-secretase, a key proteolytic enzyme involved in Alzheimer's disease (AD). Oral activity was observed in a transgenic mouse model for AD.



IC_{50} Aβ 2.6 μM

IC_{50} Aβ 30 nM, MED 20 mg/kg p.o.

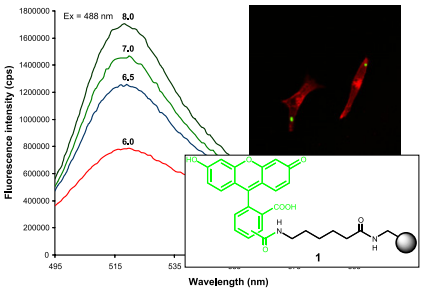
4-Aminopyridine derivatives with anticholinesterase and antiamnesic activity **pp 309–312**
Luigi Scipione,* Daniela De Vita, Alessandra Musella, Lisa Flammini, Simona Bertoni and Elisabetta Barocelli



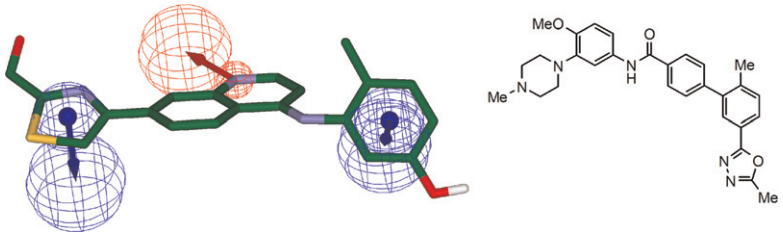
The synthesis and biological evaluation of 4-aminopyridine derivatives with anticholinesterase and antiamnesic activity is reported.

pH sensing in living cells using fluorescent microspheres **pp 313–317**
Mark Bradley, Lois Alexander, Karen Duncan, Mourad Chennaoui, Anita C. Jones and Rosario M. Sánchez-Martín*

Intracellular pH in living cells is measured by flow cytometry and microscopy using fluorescently loaded microspheres as efficient carrier systems and stable sensors.



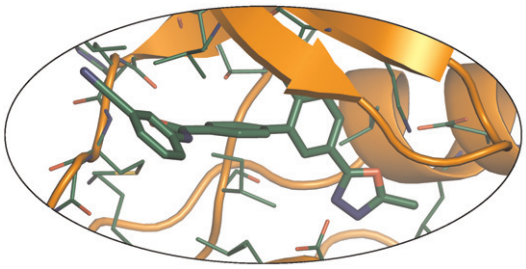
Biphenyl amide p38 kinase inhibitors 1: Discovery and binding mode **pp 318–323**
Richard M. Angell, Paul Bamborough,* Anne Cleasby, Stuart G. Cockerill, Katherine L. Jones, Christopher J. Mooney, Donald O. Somers and Ann L. Walker

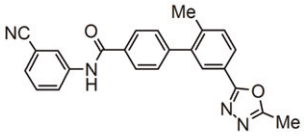


The biphenyl amides (BPAs) are a novel series of p38α MAP kinase inhibitors. The discovery of the series through structure-based focused screening is described, and the binding mode of the compounds is explained with reference to X-ray crystal structures.

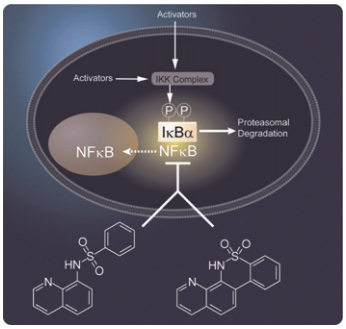
Biphenyl amide p38 kinase inhibitors 2: Optimisation and SAR pp 324–328
Richard M. Angell, Tony D. Angell, Paul Bamborough,* David Brown, Murray Brown, Jacky B. Buckton, Stuart G. Cockerill, Chris D. Edwards, Katherine L. Jones, Tim Longstaff, Penny A. Smee, Kathryn J. Smith, Don O. Somers, Ann L. Walker and Malcolm Willson

Structure–activity relationships of the biphenyl amide (BPA) series against p38α are discussed with reference to the X-ray crystal structure of an example. The series was optimised rapidly to a selective compound showing oral activity in an in vivo disease model.

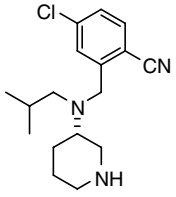




Identification of *N*-(quinolin-8-yl)benzenesulfonamides as agents capable of down-regulating NFκB activity within two separate high-throughput screens of NFκB activation pp 329–335
Yuli Xie, ShiXian Deng, Craig J. Thomas, Yidong Liu, Ya-Qin Zhang, Alison Rinderspacher, Wenwei Huang, Gangli Gong, Michael Wyler, Efithia Cayanis, Nathalie Aulner, Udo Többen, Caty Chung, Sergey Pampou, Noel Southall, Dušica Vidović, Stephan Schürer, Lars Branden, R. Eric Davis, Louis M. Staudt, James Inglese, Christopher P. Austin, Donald W. Landry,* Deborah H. Smith and Douglas S. Auld*

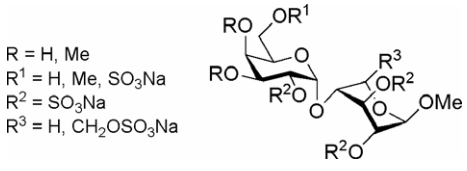


Discovery of a series of aminopiperidines as novel iNOS inhibitors pp 336–343
Bertrand Le Bourdonnec,* Lara K. Leister, Christopher A. Ajello, Joel A. Cassel, Pamela R. Seida, Heather O'Hare, Minghua Gu, Guo-Hua Chu, Paul A. Tuthill, Robert N. DeHaven and Roland E. Dolle



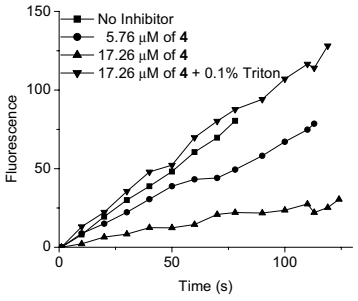
The design and synthesis of a novel class of iNOS inhibitors are described.

Design, synthesis, FGF-1 binding, and molecular modeling studies of conformationally flexible heparin mimetic disaccharides pp 344–349
Ligong Liu, Ian Bytheway, Tomislav Karoli, Jon K. Fairweather, Siska Cochran, Caiping Li and Vito Ferro*

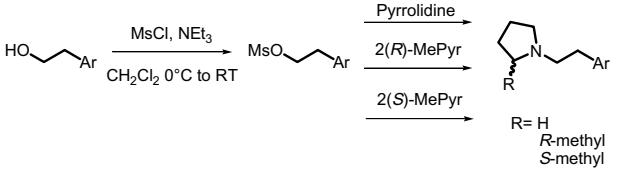


Uncovering false positives on a virtual screening search for cruzain inhibitors **pp 350–354**
Alberto Malvezzi, Leandro de Rezende, Mario Augusto Izidoro, Maria Helena Sedenho Cezari, Luiz Juliano and Antonia T.-do Amaral*

Promiscuous inhibition of cruzain is reported for three out of six virtual screening selected compounds. The promiscuous mechanism was assumed after the recovery of the enzyme activity following the addition of 0.1% Triton.

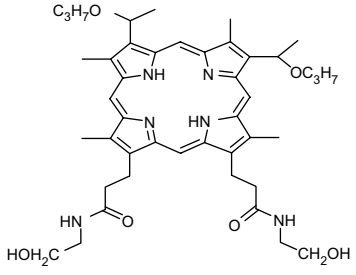


In vitro SAR of pyrrolidine-containing histamine H_3 receptor antagonists: Trends across multiple chemical series **pp 355–359**
Diana L. Nersesian,* Lawrence A. Black, Thomas R. Miller, Timothy A. Vortherms, Timothy A. Esbenshade, Arthur A. Hancock and Marlon D. Cowart

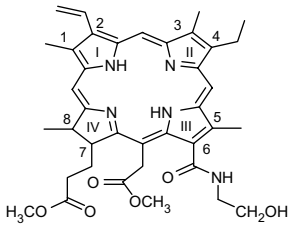


The SAR of a 60-compound library of H_3 antagonists comprising 20 different core moieties each incorporating pyrrolidine, (*R*)-2-methylpyrrolidine, and (*S*)-2-methylpyrrolidine is discussed.

Preparation and in vitro biological evaluation of tetrapyrrole ethanolamide derivatives as potential anticancer agents **pp 360–365**
Denis Girard, Glenn Weagle, Atul Gupta, Gervais Bérubé and Camille Chapados*

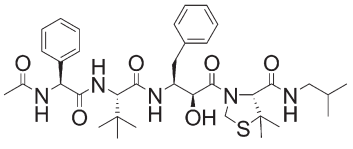


1, HPPEEA



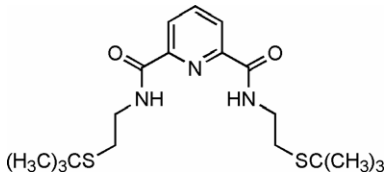
2, PEA

Truncation and non-natural amino acid substitution studies on HTLV-I protease hexapeptidic inhibitors **pp 366–370**
Jeffrey-Tri Nguyen, Meihui Zhang, Henri-Obadja Kumada, Ayako Itami, Keiji Nishiyama, Tooru Kimura, Maosheng Cheng, Yoshio Hayashi and Yoshiaki Kiso*

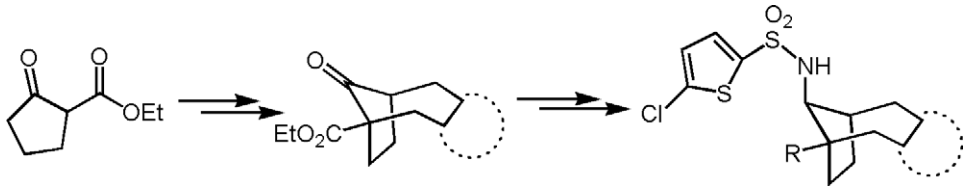


KNI-10516

Antiviral activities against herpes simplex virus type 1 by HPH derivatives and their structure–activity relationships pp 371–374
Tetsuji Hosono,* Kazumi Yokomizo, Akiyuki Hamasaki, Yoshinari Okamoto, Tadashi Okawara, Masami Otsuka, Ryozaburo Mukai and Keitarou Suzuki

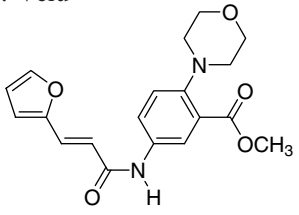


Sulfonamide derivatives of bridgehead substituted bicyclo[4.2.1]nonanes as γ-secretase inhibitors pp 375–379
Tim Sparey,* Earl Clarke, Joanne Hannam, Timothy Harrison, Andrew Madin, Mark Shearman and Bindi Sohal



A range of substituents was appended from the bridgehead position of sulfonamide substituted bicyclo[4.2.1]nonanes. No improvement in potency for inhibition of γ-secretase was found compared with unsubstituted parent compound, but two compounds displayed improved pharmacokinetic properties in vivo.

Identification of novel inhibitors of bacterial surface enzyme *Staphylococcus aureus* Sortase A pp 380–385
Bala Chandra Chenna, Bidhan A. Shinkre, Jason R. King, Aaron L. Lucius, Sthanam V. L. Narayana and Sadanandan E. Velu*

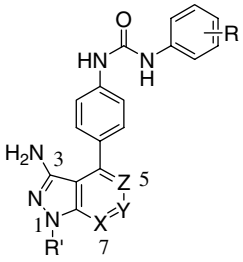


IC_{50} = 58μM

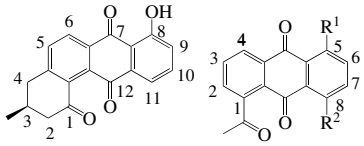
A novel class of inhibitors of *Staphylococcus aureus* Sortase A is discovered by in-silico virtual screening and structure activity relationship studies.

Identification of aminopyrazolopyridine ureas as potent VEGFR/PDGFR multitargeted kinase inhibitors pp 386–390
Yujia Dai,* Kresna Hartandi, Niru B. Soni, Lori J. Pease, David R. Reuter, Amanda M. Olson, Donald J. Osterling, Stella Z. Doktor, Daniel H. Albert, Jennifer J. Bouska, Keith B. Glaser, Patrick A. Marcotte, Kent D. Stewart, Steven K. Davidsen and Michael R. Michaelides

Tumor angiogenesis is mediated by KDR and other VEGFR and PDGFR kinases. Their inhibition presents an attractive approach for developing anticancer therapeutics. Here, we report a series of aminopyrazolopyridine ureas as potent VEGFR/PDGFR multitargeted kinase inhibitors. A number of compounds have been identified to be orally bioavailable and efficacious in the mouse edema model.

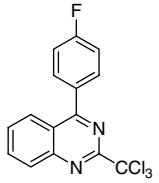


Design, synthesis, and studies of small molecule STAT3 inhibitors **pp 391–395**
Deepak Bhasin, Katryna Cisek, Trupti Pandharkar, Nicholas Regan, Chenglong Li, Bulbul Pandit, Jiayuh Lin and Pui-Kai Li*



Compound	R^1	R^2
1	OH	H
2	H	OH
3	OMe	H
4	H	OMe

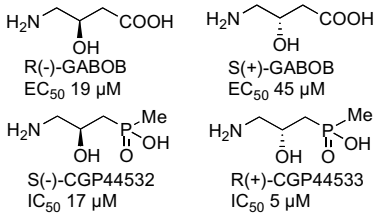
Synthesis and antiplasmodial activity of new 4-aryl-2-trichloromethylquinazolines **pp 396–401**
Pierre Verhaeghe, Nadine Azas, Monique Gasquet, Sébastien Hutter, Christophe Ducros, Michèle Laget, Sylvain Rault, Pascal Rathelot and Patrice Vanelle*



$IC_{50\ (w2)}$: 2.5 μM

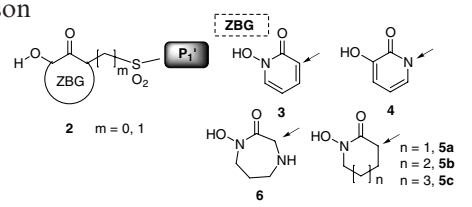
A series of original 4-aryl-substituted 2-trichloromethylquinazoline derivatives was synthesized using a microwave-assisted Suzuki-Miyaura cross-coupling approach. Antiplasmodial activity was evaluated on both chloroquino-resistant and -sensitive *Plasmodium falciparum* strains, and the selectivity indexes for THP1 and HepG2 human cells were also calculated, revealing their antiplasmodial potential.

Enantioselective actions of 4-amino-3-hydroxybutanoic acid and (3-amino-2-hydroxypropyl)methylphosphinic acid at recombinant $GABA_C$ receptors **pp 402–404**
Tina Hinton, Mary Chebib and Graham A. R. Johnston*



Different enantioselectivity for these hydroxy-substituted agonists and antagonists at $GABA_C$ receptors.

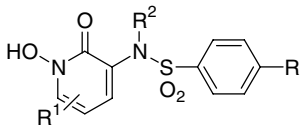
Syntheses and in vitro evaluation of arylsulfone-based MMP inhibitors with heterocycle-derived zinc-binding groups (ZBGs) **pp 405–408**
Yue-Mei Zhang,* Xiaodong Fan, Shyh-Ming Yang, Robert H. Scannevin, Sharon L. Burke, Kenneth J. Rhodes and Paul F. Jackson



Several classes of arylsulfone-based MMP-2/-9 inhibitors utilizing 6-to 8-membered heterocyclic rings as zinc-binding groups (ZBGs) have been synthesized and their enzyme inhibitory activities were evaluated. The most potent arylsulfone inhibitors are based on the rigid 1- or 3-hydroxypyridone ZBG.

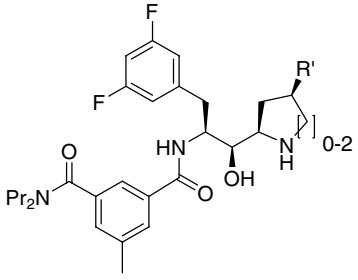
1-Hydroxy-2-pyridinone-based MMP inhibitors: Synthesis and biological evaluation for the treatment of ischemic stroke pp 409–413
Yue-Mei Zhang,* Xiaodong Fan, Devraj Chakaravarty, Bangping Xiang, Robert H. Scannevin, Zhihong Huang, Jianya Ma, Sharon L. Burke, Prabha Karnachi, Kenneth J. Rhodes and Paul F. Jackson

A series of 1-hydroxy-2-pyridinone synthesized have excellent in vitro potency in inhibiting MMP-9 in addition to MMP-2 and representative compounds demonstrate good efficacy in the mouse transient mid-cerebral artery occlusion (tMCAO) model of cerebral ischemia.



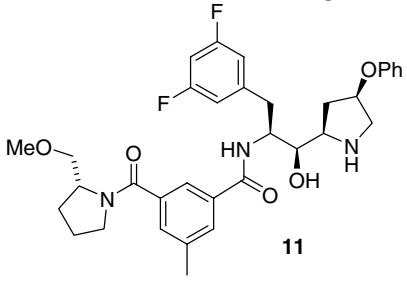
1-HO-2-pyridinone 3

Potent pyrrolidine- and piperidine-based BACE-1 inhibitors pp 414–417
U. Iserloh,* Y. Wu, J. N. Cumming, J. Pan, L. Y. Wang, A. W. Stamford, M. E. Kennedy, R. Kuvelkar, X. Chen, E. M. Parker, C. Strickland and J. Voigt



The discovery and development of novel BACE-1 inhibitors incorporating a cyclic amine scaffold is described.

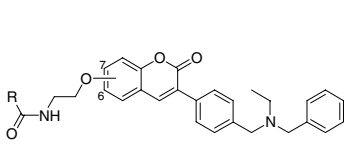
Discovery of an orally efficaceous 4-phenoxypyrrolidine-based BACE-1 inhibitor pp 418–422
U. Iserloh,* J. Pan, A. W. Stamford, M. E. Kennedy, Q. Zhang, L. Zhang, E. M. Parker, N. A. McHugh, L. Favreau, C. Strickland and J. Voigt

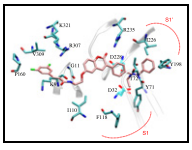


11

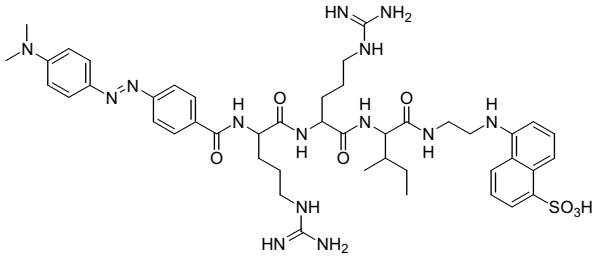
Extensive SAR studies led to the identification of **11**, which has been extensively profiled in various in vivo settings.

Multi-target-directed coumarin derivatives: hAChE and BACE1 inhibitors as potential anti-Alzheimer compounds pp 423–426
Lorna Piazzi,* Andrea Cavalli, Francesco Colizzi, Federica Belluti, Manuela Bartolini, Francesca Mancini, Maurizio Recanatini, Vincenza Andrisano and Angela Rampa



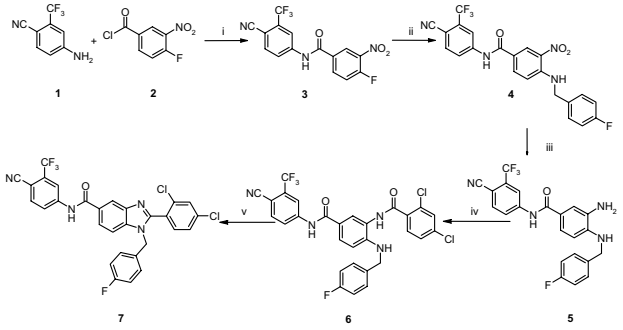


Substrate specificity and screening of the integral membrane protease Pla **pp 427–431**
Anton Agarkov, Sadhana Chauhan, Pedro J. Lory, Scott R. Gilbertson* and Vladimir L. Motin

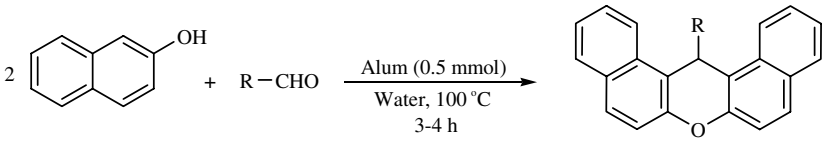


The development of series of small peptide substrates for the protease Pla is reported.

Synthesis, characterization and evaluation of benzimidazole derivative and its precursors as inhibitors of MDA-MB-231 human breast cancer cell proliferation **pp 432–435**
N. R. Thimmegowda, S. Nanjunda Swamy, C. S. Ananda Kumar, Y. C. Sunil Kumar, S. Chandrappa, George W. Yip* and K. S. Rangappa*



Eco-friendly and efficient one-pot synthesis of alkyl- or aryl-14*H*-dibenzo[*a*,*j*]xanthenes in water **pp 436–438**
Minoo Dabiri,* Mostafa Baghbanzadeh, Maryam Shakouri Nikcheh and Elham Arzroomchilar



OTHER CONTENTS

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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