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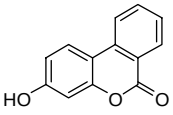
Contents

ARTICLES

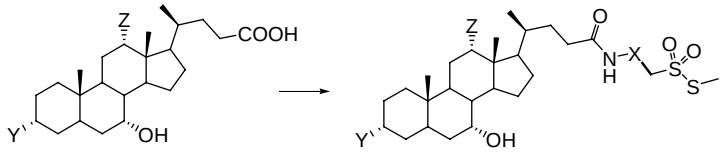
6*H*-Benzo[*c*]chromen-6-one derivatives as selective ERβ agonists **pp 1468–1472**
Wanying Sun,* Lovji D. Cama, Elizabeth T. Birzin, Sudha Warrier, Louis Locco, Ralph Mosley, Milton L. Hammond and Susan P. Rohrer



3-Hydroxy-6H-benzochromen-6-one

A series of 6*H*-benzo[*c*]chromen-6-one and 6*H*-benzo[*c*]chromene derivatives were prepared. Many of the analogs were found to be potent and selective ERβ agonists. Bis hydroxyl at positions 3 and 8 are essential for activity in a HTRF coactivator recruitment assay. Additional modifications at both phenyl rings led to compounds with ERβ <10 nM potency and >100-fold selectivity over ERα.

Design of novel synthetic MTS conjugates of bile acids for site-directed sulfhydryl labeling of cysteine residues in bile acid binding and transporting proteins **pp 1473–1476**
Abhijit Ray, Antara Banerjee, Cheng Chang, Chandra M. Khantwal and Peter W. Swaan*

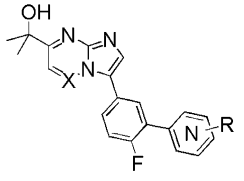


X= CH_2, $CH(COOH)CH_2CONHCH_2$
Y=OH, NH_2
Z= H,OH

Novel MTS containing bile acid conjugates were designed and synthesized to selectively probe cysteine residues in bile acid transporting proteins, providing valuable tool for their characterization.

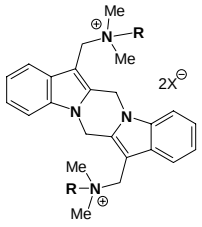
Imidazo[1,2-*b*][1,2,4]triazines as α2/α3 subtype selective $GABA_A$ agonists for the treatment of anxiety **pp 1477–1480**
Andrew S. R. Jennings,* Richard T. Lewis, Michael G. N. Russell, David J. Hallett, Leslie J. Street, José L. Castro, John R. Atack, Susan M. Cook, Rachael Lincoln, Joanna Stanley, Alison J. Smith, David S. Reynolds, Bindi Sohal, Andrew Pike, George R. Marshall, Keith A. Wafford, Wayne F. A. Sheppard and Spencer J. Tye

Imidazo[1,2-*a*]pyrimidines and imidazo[1,2-*b*][1,2,4]triazines are ligands for the benzodiazepine binding site of $GABA_A$ receptors that are functionally selective for the α2/α3 subtypes over the α1 subtype. SAR studies to optimise this functional selectivity, pharmacokinetic and behavioural data are described.

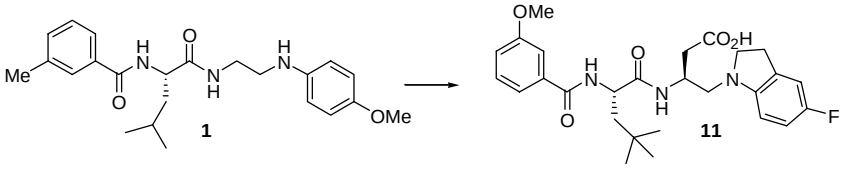


X = CH, N

6*H*,13*H*-Pyrazino[1,2-*a*;4,5-*a*′]diindole analogs: Probing the pharmacophore for allosteric ligands of muscarinic M_2 receptors **pp 1481–1485**
Darius P. Zlotos,* Christian Tränkle, Aliaa Abdelrahman, Daniela Gündisch, Krzysztof Radacki, Holger Braunschweig and Klaus Mohr

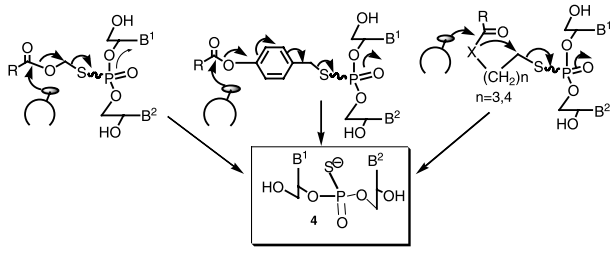


Arylaminoethyl amides as noncovalent inhibitors of cathepsin S. Part 2: Optimization of P1 and *N*-aryl **pp 1486–1490**
Phillip B. Alper,* Hong Liu, Arnab K. Chatterjee, KhanhLinh T. Nguyen, David C. Tully, Christine Tumanut, Jun Li, Jennifer L. Harris, Tove Tuntland, Jonathan Chang, Perry Gordon, Thomas Hollenbeck and Donald S. Karanewsky



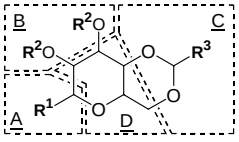
A systematic study of anilines led to the discovery of a metabolically robust fluoroindoline replacement for the alkoxy aniline toxicophore in **1**. Investigations of the P1 pocket resulted in the discovery of a wide tolerance of functionality leading to the discovery of **11** as a potent and selective inhibitor of cathepsin S.

Anti-HBV nucleotide prodrug analogs: Synthesis, bioreversibility, and cytotoxicity studies **pp 1491–1494**
Seetharamaiyer Padmanabhan, John E. Coughlin, Guangrong Zhang, Cassandra J. Kirk and Radhakrishnan P. Iyer*



Synthesis and evaluation of a number of dinucleotide prodrugs are described.

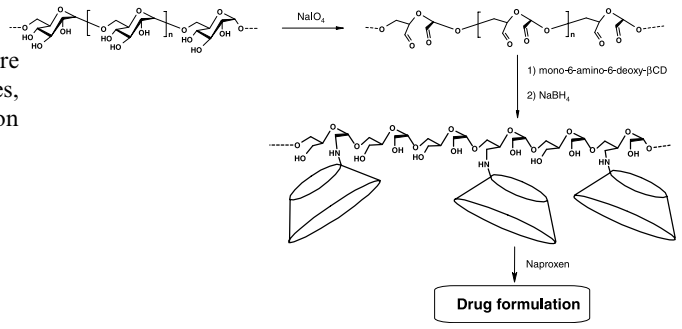
Synthesis and screening of bicyclic carbohydrate-based compounds: A novel type of antivirals **pp 1495–1498**
Steven Van Hoof, Bart Ruttens, Idzi Hubrecht, Gert Smans, Petra Blom, Benedikt Sas, Johan Van hemel, Jan Vandenkerckhove and Johan Van der Eycken*



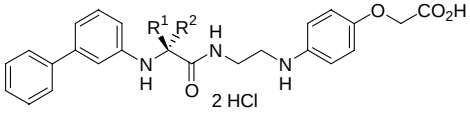
A small library of bicyclic carbohydrate derivatives was synthesized and screened. A strong and selective activity against cytomegalovirus was found. Structure–activity relationship for this new type of antivirals is discussed.

Cyclodextrin-grafted polysaccharides as supramolecular carrier systems for naproxen **pp 1499–1501**
Héctor L. Ramírez, Aymara Valdivia, Roberto Cao,* Juan J. Torres-Labandeira, Alex Fragoso and Reynaldo Villalonga*

New polymeric carriers for low molecular weight drugs were synthesized by grafting β-cyclodextrins into polysaccharides, evaluating the influence of their supramolecular associations on the improved anti-inflammatory activity of naproxen.



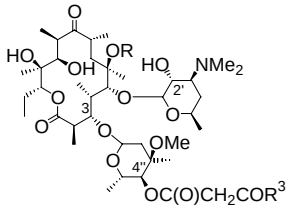
4-Aminophenoxyacetic acids as a novel class of reversible cathepsin K inhibitors **pp 1502–1505**
Tsuyoshi Shinozuka,* Kousei Shimada, Satoshi Matsui, Takahiro Yamane, Mayumi Ama, Takeshi Fukuda, Motohiko Taki and Satoru Naito



43: R^1 = *i*-Bu, R^2 = H; IC_{50} = 4.5 nM
47: $R^1 = R^2 = -(CH_2)_5-$; IC_{50} =4.8 nM

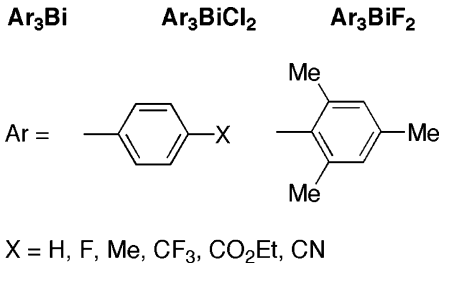
The synthesis and SAR of 4-aminophenoxyacetic acids as cathepsin K inhibitors are reported.

Synthesis and biological investigation of new 4″-malonyl tethered derivatives of erythromycin and clarithromycin **pp 1506–1509**
Daniel Sherman, Liqun Xiong, Alexander S. Mankin and Artem Melman*

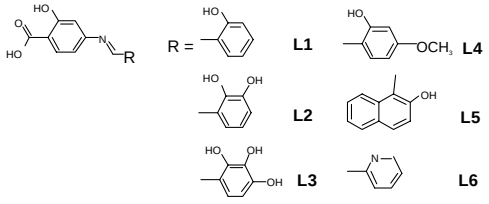


Inhibition of jack bean urease by organobismuth compounds **pp 1510–1513**
Toshihiro Murafuji,* Takako Azuma, Youhei Miyoshi, Motoko Ishibashi, A. F. M. Mustafizur Rahman, Kouto Migita,* Yoshikazu Sugihara* and Yuji Mikata

Inhibitory activity of organobismuth compounds was tested against jack bean urease. Triphenylbismuth difluoride showed the highest activity. The tendency of the inhibition is in good agreement with that observed in the antibacterial activity against *Helicobacter pylori*.

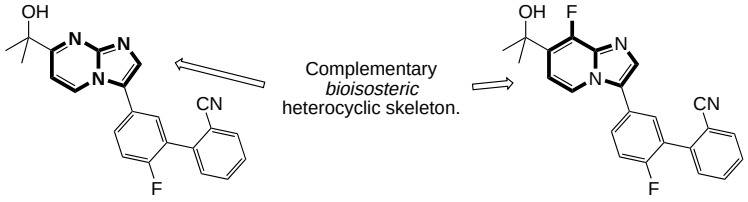


Schiff base conjugates of *p*-aminosalicylic acid as antimycobacterial agents **pp 1514–1517**
Jayendra Patole, Dipti Shingnapurkar, Subhash Padhye* and Colin Ratledge

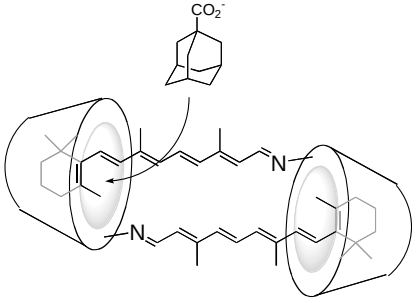


Schiff base conjugates of *p*-aminosalicylic acid containing hydroxyl-rich side chains show enhanced antimycobacterial activity against *Mycobacterium smegmatis* and *Mycobacterium bovis* BCG. Higher Clog *P* values and superior radical scavenging activities are thought to be the contributing factors for their enhanced antimycobacterial activities.

8-Fluoroimidazo[1,2-*a*]pyridine: Synthesis, physicochemical properties and evaluation as a bioisosteric replacement for imidazo[1,2-*a*]pyrimidine in an allosteric modulator ligand of the $GABA_A$ receptor **pp 1518–1522**
Alexander C. Humphries,* Emanuela Gancia, Myra T. Gilligan, Simon Goodacre, David Hallett, Kevin J. Merchant and Steve R. Thomas

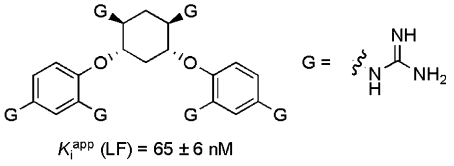


Cyclodextrin retinylidene: A biomimetic kinetic trap model for rhodopsin **pp 1523–1526**
Kafui Kpegba, Matthew Murtha and Nasri Nesnas*



Displacement of the β-ionone ring by adamantane carboxylate increases the rate of Schiff base hydrolysis.

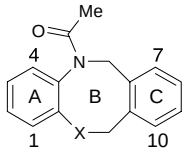
Guanidinylated 2,5-dideoxystreptamine derivatives as anthrax lethal factor inhibitors **pp 1527–1531**
Guan-Sheng Jiao,* Lynne Cregar, Mark E. Goldman, Sherri Z. Millis and Cho Tang



Anthrax lethal factor is a Zn^{2+}-dependent metalloprotease and the key virulence factor of tripartite anthrax toxin secreted by *Bacillus anthracis*, the causative agent of anthrax. A series of guanidinylated 2,5-dideoxystreptamine derivatives were designed and synthesized as inhibitors of lethal factor, some of which show strong inhibitory activity against lethal factor in an in vitro FRET assay. Preparation and structure–activity relationships of these compounds are presented.

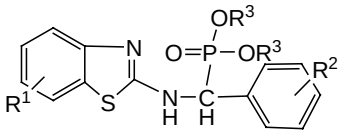
Identification of a novel series of tetrahydrodibenzazocines as inhibitors of 17β-hydroxysteroid dehydrogenase type 3 **pp 1532–1536**
Brian E. Fink,* Ashvinikumar V. Gavai, John S. Tokarski, Bindu Goyal, Raj Misra, Hai-Yun Xiao, S. David Kimball, Wen-Ching Han, Derek Norris, Thomas E. Spires, Dan You, Marco M. Gottardis, Matthew V. Lorenzi and Gregory D. Vite

A novel series of 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) inhibitors has been identified. These inhibitors, based on a dibenzazocine core, exhibited picomolar to low nanomolar inhibition of 17β-HSD3 in cell-free enzymatic as well as in cell-based transcriptional reporter assays.



Synthesis, X-ray crystallographic analysis, and antitumor activity of *N*-(benzothiazole-2-yl)-1-(fluorophenyl)-*O*,*O*-dialkyl-α-aminophosphonates **pp 1537–1543**
Linhong Jin, Baoan Song,* Guoping Zhang, Ruiqing Xu, Sumei Zhang, Xingwen Gao, Deyu Hu and Song Yang

The Mannich-type addition of 2-aminobenzothiazole and *O*,*O*-dialkylphosphite to 2-fluorobenzoaldehyde or 4-trifluorobenzoaldehyde in ionic liquids is used to synthesize the corresponding product α-aminophosphonate with benzothiazole and fluorine moiety. And their inhibitory activities against cancer cells are preformed.



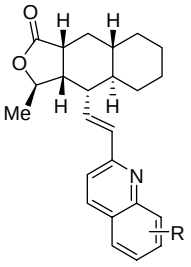
R^1: 4-CH_3, 6-OCH_3

R^2: 2-F, 4-F, 4-CF_3

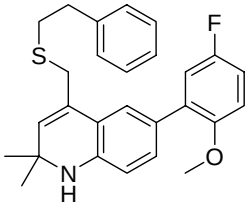
R^3: Me, Et, n-Pr, i-Pr, n-Bu

Discovery and synthesis of a novel series of quinoline-based thrombin receptor (PAR-1) antagonists **pp 1544–1548**
Martin C. Clasby,* Samuel Chackalamannil, Michael Czarniecki, Dario Doller, Keith Eagen, William J. Greenlee, Yan Lin, Hsingan Tsai, Yan Xia, Ho-Sam Ahn, Jacqueline Agans-Fantuzzi, George Boykow, Madhu Chintala, Carolyn Foster, Matthew Bryant and Janice Lau

The synthesis and SAR studies of a structurally novel series of highly potent thrombin receptor (PAR-1) antagonists are described.



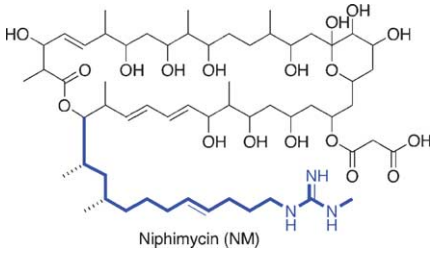
Discovery and SAR study of novel dihydroquinoline containing glucocorticoid receptor ligands **pp 1549–1552**
Hidenori Takahashi,* Younes Bekkali, Alison J. Capolino, Thomas Gilmore, Susan E. Goldrick, Richard M. Nelson, Donna Terenzio, Ji Wang, Ljiljana Zuvela-Jelaska, John Proudfoot, Gerald Nabozny and David Thomson
The SAR study of novel class of glucocorticoid receptor ligands is reported.



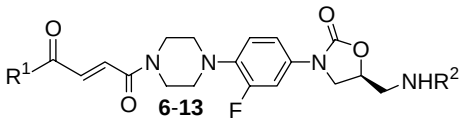
44 GR IC_{50} = 84 nM

Structure–activity relationship studies on niphimycin, a guanidylpolyol macrolide antibiotic. Part 1: The role of the *N*-methyl-*N*′-alkylguanidinium moiety pp 1553–1556
Yoshinosuke Usuki,* Keiji Matsumoto, Takatsugu Inoue, Koichi Yoshioka, Hideo Iio and Toshio Tanaka

Several *N*-methyl-*N*′-alkylguanidinium derivatives were synthesized and used as simplified analogues of niphimycin (NM), a guanidylpolyol macrolide, in structure–activity relationship studies. The C16-alkylated derivative exerted fungicidal activity by directly damaging the fungal plasma membrane and inducing oxidative stress in a manner similar to niphimycin. These results indicate that the *N*-methyl-*N*′-alkylguanidinium moiety is required for antifungal activity by NM.



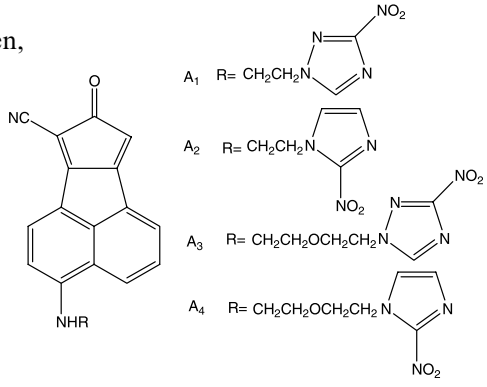
Novel 4-N-substituted aryl pent-2-ene-1,4-dione derivatives of piperazinyloxazolidinones as antibacterials pp 1557–1561
Braj Bhushan Lohray,* Vidya Bhushan Lohray, Brijesh Kumar Srivastava, Sunil Gupta, Manish Solanki, Purvi Pandya and Prashant Kapadnis



A few substituted piperazinylphenyloxazolidinone compounds **6–13** having substitution on the distant nitrogen atom of piperazine ring scaffold have been synthesized and evaluated for their antibacterial activity in Gram-positive bacteria. A few compounds showed superior in vitro antibacterial activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Streptococcus pyogenes* than linezolid and eperezolid.

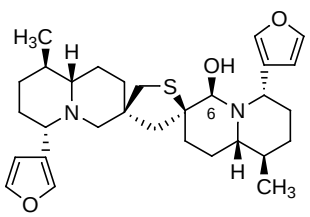
Synthesis and evaluation of novel 8-oxo-8*H*-cyclopenta[*a*]acenaphthylene-7-carbonitriles as long-wavelength fluorescent markers for hypoxic cells in solid tumor pp 1562–1566
Yan Liu, Yufang Xu,* Xuhong Qian,* Yi Xiao, Jianwen Liu, Liyun Shen, Junhui Li and Yuanxing Zhang

Novel bioreductive and long-wavelength fluorescent markers for hypoxic cells in solid tumor, 8-oxo-8*H*-cyclopenta[*a*]acenaphthylene-7-carbonitriles with 2-nitroimidazole were designed, synthesized, and evaluated in V79 379 A Chinese hamster cells in vitro.

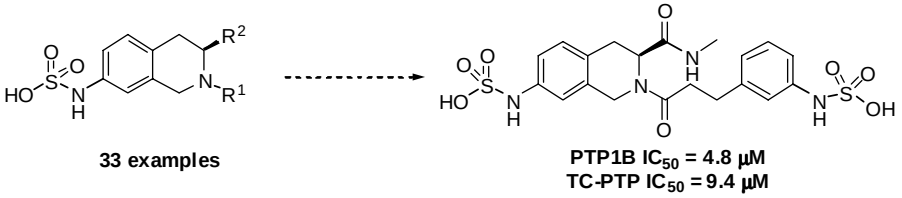


Nuphar alkaloids with immediately apoptosis-inducing activity from *Nuphar pumilum* and their structural requirements for the activity pp 1567–1573
Hisashi Matsuda, Kazutoshi Yoshida, Katsutoshi Miyagawa, Yumiko Nemoto, Yasunobu Asao and Masayuki Yoshikawa*

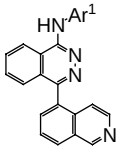
The methanolic extract and its alkaloid fraction from the rhizomes of *Nuphar pumilum* showed cytotoxic effects on human leukemia cell (U937), mouse melanoma cell (B16F10), and human fibroblast (HT1080). Among the isolated constituents, dimeric sesquiterpene thioalkaloids with the 6-hydroxyl group (6-hydroxythiobinupharidine, 6,6′-dihydroxythiobinupharidine, and 6-hydroxythionuphlutine B) showed potent cytotoxic activity at 10 μM, Apoptosis-inducing activity of a principal active constituent, 6-hydroxythiobinupharidine, on U937 was examined using morphological examination and DNA fragmentation assay (TUNEL method). Apoptosis of U937 was immediately observed within 1 h after treatment of 6-hydroxythiobinupharidine at 2.5–10 μM.


6-hydroxythiobinupharidine

1,2,3,4-Tetrahydroisoquinolinyl sulfamic acids as phosphatase PTP1B inhibitors **pp 1574–1578**
Sean R. Klopfenstein,* Artem G. Evdokimov, Anny-Odile Colson, Neil T. Fairweather, Jeffrey J. Neuman, Matthew B. Maier, Jeffrey L. Gray, Gina S. Gerwe, George E. Stake, Brian W. Howard, Julie A. Farmer, Matthew E. Pokross, Thomas R. Downs, Bhavani Kasibhatla and Kevin G. Peters



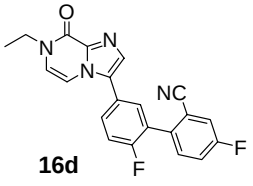
Arylphthalazines. Part 2: 1-(Isoquinolin-5-yl)-4-arylamino phthalazines as potent inhibitors of VEGF receptors I and II **pp 1579–1581**
Matthew A. J. Duncton,* Evgueni L. Piatnitski, Reeti Katoch-Rouse, Leon M. Smith, II, Alexander S. Kiselyov, Daniel L. Milligan, Chris Balagtas, Wai C. Wong, Joel Kawakami and Jacqueline F. Doody



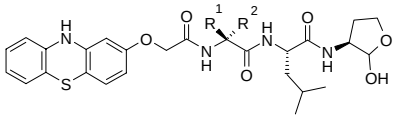
The synthesis and structure–activity relationships for a sub-class of arylphthalazine derivatives which have found use as inhibitors of VEGF receptors I and II are reported.

Imidazo[1,2-*a*]pyrazin-8-ones, imidazo[1,2-*d*][1,2,4]triazin-8-ones and imidazo[2,1-*f*][1,2,4]triazin-8-ones as α2/α3 subtype selective $GABA_A$ agonists for the treatment of anxiety **pp 1582–1585**
Simon C. Goodacre,* David J. Hallett, Robert W. Carling, José L. Castro, David S. Reynolds, Andrew Pike, Keith A. Wafford, Robert Newman, John R. Atack and Leslie J. Street

Imidazo[1,2-*a*]pyrazin-8-ones, imidazo[1,2-*d*][1,2,4]triazin-8-ones and imidazo[2,1-*f*][1,2,4]triazin-8-ones are high affinity $GABA_A$ agonists. Compound **16d** has good oral bioavailability in rat, functional selectivity for the $GABA_A$α2 and α3-subtypes and is anxiolytic in a conditioned animal model of anxiety with minimal sedation observed at full BZ binding site occupancy.



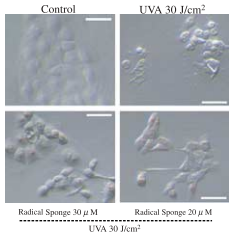
Novel dual inhibitors of calpain and lipid peroxidation with enhanced cellular activity **pp 1586–1589**
Serge Auvin,* Bernadette Pignol, Edith Navet, Morgane Troadec, Denis Carré, José Camara, Dennis Bigg and Pierre-E. Chabrier



The synthesis of hybrid molecules possessing calpain inhibitory and antioxidant properties is reported. Two of them, **6d-05** and **6d-08**, exhibit potent intracellular calpain inhibition (IC_{50} = 0.6 μM). According to a theoretical calculation approach, the polar surface area and the number of rotors of the molecules adequately describe their cellular behavior.

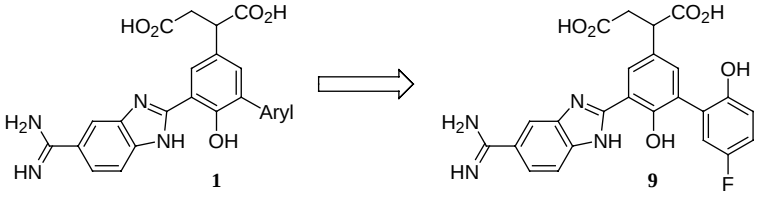
The water-soluble fullerene derivative 'Radical Sponge®' exerts cytoprotective action against UVA irradiation but not visible-light-catalyzed cytotoxicity in human skin keratinocytes **pp 1590–1595**
Li Xiao, Hiroya Takada, Xue hui Gan and Nobuhiko Miwa*

Radical Sponge®, a water-soluble derivative of fullerene is composed of the purified fullerene BioFullerene® and PVP (polyvinylpyrrolidone), which exhibited a particle diameter of 120–230 nm in the dry state (shown in another photograph) in contrast to mean 688 nm in the aqueous dispersion (the MicroTrak histogram shown in the text), could protect human skin keratinocytes HaCaT from UVA injures via the preventive effect without any cytotoxicity or phototoxicity at 10–40 μM.



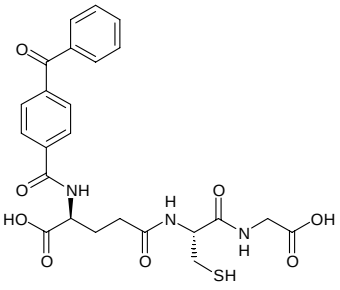
Factor VIIa inhibitors: Gaining selectivity within the trypsin family **pp 1596–1600**
William D. Shrader,* Aleksandr Kolesnikov, Jana Burgess-Henry, Roopa Rai, John Hendrix, Huiyong Hu, Steve Torkelson, Tony Ton, Wendy B. Young, Bradley A. Katz, Christine Yu, Jie Tang, Ronnel Cabuslay, Ellen Sanford, James W. Janc and Paul A. Sprengeler

A series of highly selective and potent factor VIIa-tissue factor (fVIIa/TF) complex inhibitors were generated via a Suzuki-based synthesis strategy. With this scaffold class (**9**), we propose that a unique hydrogen bond interaction between a hydroxyl on the biaryl system and the backbone carbonyl of fVIIa Lys-192 provides a basis for enhanced selectivity and potency.

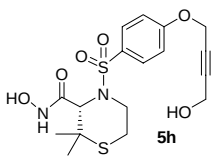


Synthesis and evaluation of an N-acylated photoactivatable analogue of glutathione as probe for glutathione-utilizing enzymes **pp 1601–1604**
Dan Bernardi, Eric Battaglia and Gilbert Kirsch*

The synthesis of *N*-(4-benzoylbenzoyl)glutathione an inhibitor and a photoaffinity probe of purified rat liver glutathione *S*-transferases is reported.

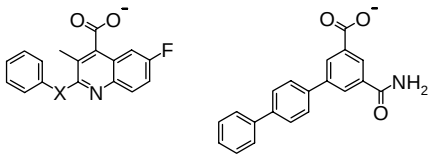


Acetylenic TACE inhibitors. Part 3: Thiomorpholine sulfonamide hydroxamates **pp 1605–1609**
J. I. Levin,* J. M. Chen, L. M. Laakso, M. Du, J. Schmid, W. Xu, T. Cummons, J. Xu, G. Jin, D. Barone and J. S. Skotnicki



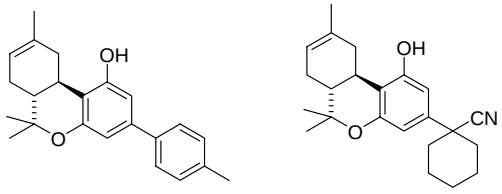
Compound **5h** with excellent in vitro potency against isolated TACE enzyme and in cells, oral activity in a model of TNF-α production and a collagen-induced arthritis model, was selected as a clinical candidate for the treatment of RA.

Brequinar derivatives and species-specific drug design for dihydroorotate dehydrogenase **pp 1610–1615**
Darrell E. Hurt, Amanda E. Sutton and Jon Clardy*

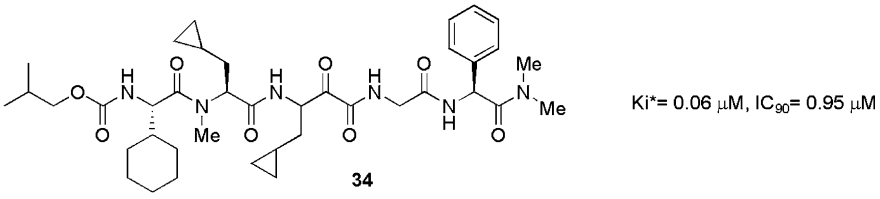


Brequinar analogs were evaluated through bioassays and in silico screening as species-specific inhibitors of dihydroorotate dehydrogenase (DHODH). A class of analogs known to not inhibit human DHODH dock well to *Plasmodium falciparum* DHODH.

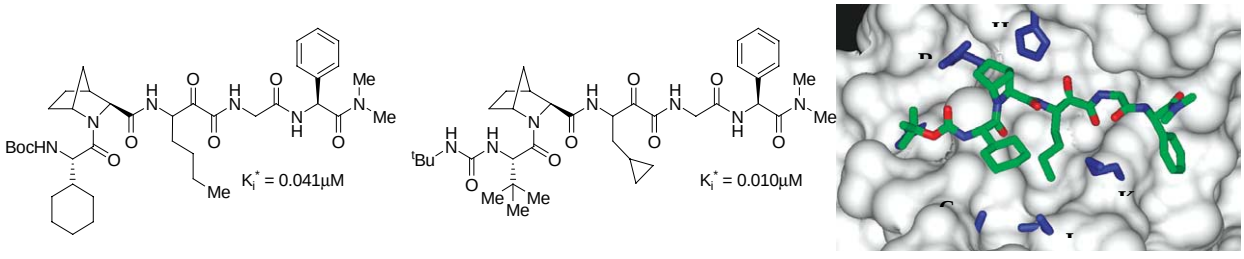
Structural modifications of the cannabinoid side chain towards C3-aryl and 1′,1′-cycloalkyl-1′-cyano cannabinoids **pp 1616–1620**
Demetris P. Papahatjis,* Victoria R. Nahmias, Thanos Andreou, Pusheng Fan and Alexandros Makriyannis



Depeptidization efforts on P_3–P'_2 α-ketoamide inhibitors of HCV NS3-4A serine protease: Effect on HCV replicon activity **pp 1621–1627**
Stéphane L. Bogen,* Sumei Ruan, Rong Liu, Sony Agrawal, John Pichardo, Andrew Prongay, Bahige Baroudy, Anil K. Saksena, Viyyoor Girijavallabhan and F. George Njoroge

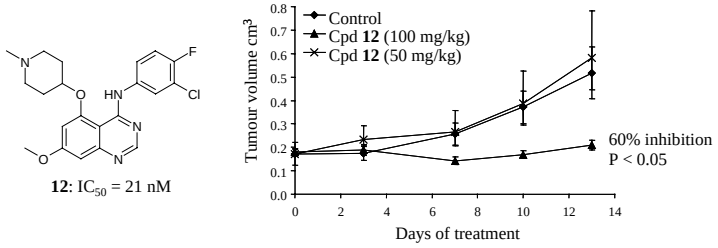


Novel inhibitors of hepatitis C NS3–NS4A serine protease derived from 2-aza-bicyclo[2.2.1]heptane-3-carboxylic acid **pp 1628–1632**
Srikanth Venkatraman,* F. George Njoroge, Wanli Wu, Viyyoor Girijavallabhan, Andrew J. Prongay, Nancy Butkiewicz and John Pichardo



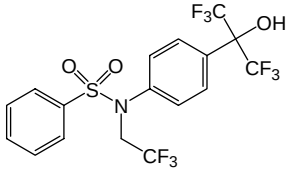
Inhibitors of epidermal growth factor receptor tyrosine kinase: Novel C-5 substituted anilinoquinazolines designed to target the ribose pocket **pp 1633–1637**

Peter Ballard, Robert H. Bradbury, Craig S. Harris, Laurent F.A. Hennequin, Mark Hickinson, Paul D. Johnson, Jason G. Kettle,* Teresa Klinowska, Andrew G. Leach, Remy Morgentin, Martin Pass, Donald J. Ogilvie, Annie Olivier, Nicolas Warin and Emma J. Williams



Discovery and optimization of a novel series of liver X receptor-α agonists **pp 1638–1642**

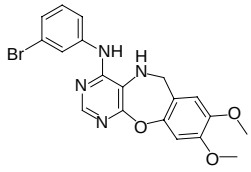
Leping Li,* Jiwen Liu, Liusheng Zhu, Serena Cutler, Hirohiko Hasegawa, Bei Shan and Julio C. Medina



A novel series of Liver X Receptor-α activators have been synthesized and their receptor activation potentials were evaluated. Compounds with enhanced potency and similar efficacy to those of the endogenous ligands, oxysterols, were identified.

Tricyclic azepine derivatives: Pyrimido[4,5-*b*]-1,4-benzoxazepines as a novel class of epidermal growth factor receptor kinase inhibitors **pp 1643–1646**

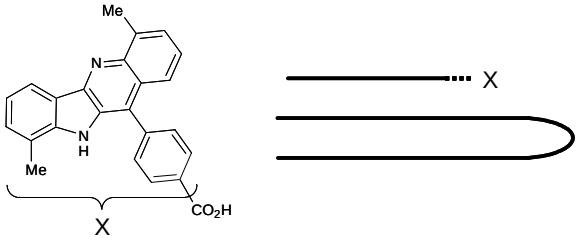
Leon Smith, II, Evgueni L. Piatnitski,* Alexander S. Kiselyov, Xiaohu Ouyang, Xiaoling Chen, Sabina Burdzovic-Wizemann, Yongjiang Xu, Ying Wang, Robin L. Rosler, Sheetal N. Patel, Hui-Hsien Chiang, Daniel L. Milligan, John Columbus, Wai C. Wong, Jacqueline F. Doody and Yaron R. Hadari



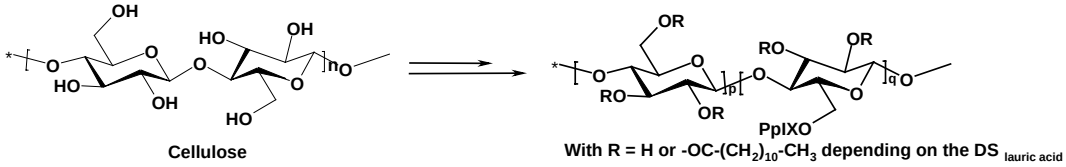
The synthesis and SAR studies of benzoxazepines as a novel EGFR kinase inhibitor class are reported.

DNA triplex stabilization by a δ-carboline derivative tethered to third strand oligonucleotides **pp 1647–1650**

Nina Todorović, Nguyen Thi Bich Phuong, Peter Langer* and Klaus Weisz*

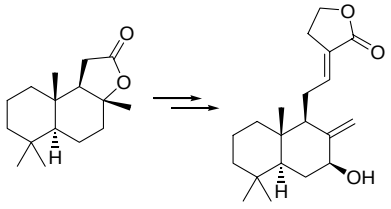


New photoantimicrobial films composed of porphyrinated lipophilic cellulose esters **pp 1651–1655**
Mohammed Krouit, Robert Granet, Pierre Branland, Bernard Verneuil and Pierre Krausz*



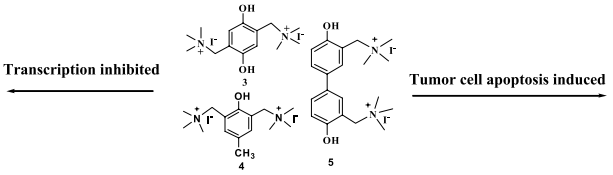
New photobactericidal polymers have been prepared in homogeneous medium starting from cellulose, protoporphyrin IX (PpIX), and lauric acid, using a TsCl/pyridine system. They showed photobactericidal activity against Gram-positive and Gram-negative bacteria.

Synthesis and biological activity of (+)-hedychilactone A and its analogs from (+)-sclareolide **pp 1656–1659**
Sangtae Oh, In Howa Jeong, Woon-Seob Shin, Qian Wang* and Seokjoon Lee*

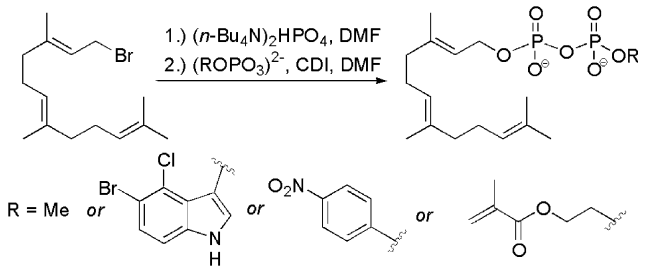


Biological studies of photoinducible phenol quaternary ammonium derivatives **pp 1660–1664**
Yang Song, Ping Wang, Juanjuan Wu, Xiang Zhou,* Xiao-Lian Zhang,*
Linhong Weng, Xiaoping Cao and Feng Liang

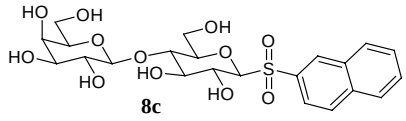
Three water-soluble DNA cross-linking phenol quaternary ammonium derivatives **3**, **4**, and **5** could inhibit the transcription in vitro by photoactivation. DNA interstrand cross-linking action might be the key factor to inhibit transcription by these compounds. Further tumor cell apoptosis was observed by flow cytometry and it indicated that cross-linking agent **5** could significantly induce the late apoptosis of tumor cells.



Convenient methods for the synthesis of P^1-farnesyl-P^2-indicator diphosphates **pp 1665–1667**
Birte K. Feld and Gregory A. Weiss*



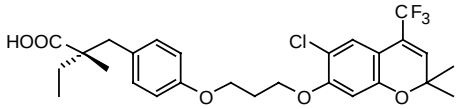
Aryl *O*- and *S*-galactosides and lactosides as specific inhibitors of human galectins-1 and -3: Role of electrostatic potential at O-3 pp 1668–1672
Denis Giguère, Sachiko Sato, Christian St-Pierre, Suzanne Sirois and René Roy*



8c

Aryl *O*- and *S*-galactosides, and lactosides were prepared and used for the specific inhibition of galectins-1 and -3. In inhibition of hemagglutination assay against red blood cells, the best inhibitor for galectin-1 was the β-napthylsulfonyl lactoside **8c** (40 μM). Electrostatic potential at O-3 correlated with the relative potency.

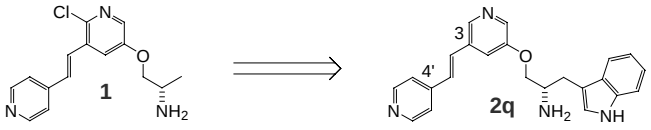
Design and synthesis of potent and subtype-selective PPARα agonists pp 1673–1678
Ranjit C. Desai,* Edward Metzger, Conrad Santini, Peter T. Meinke, James V. Heck, Joel P. Berger, Karen L. MacNaul, Tian-quan Cai, Samuel D. Wright, Arun Agrawal, David E. Moller and Soumya P. Sahoo*



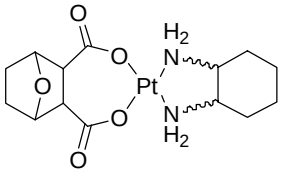
39

A series of potent and subtype-selective PPARα agonists was synthesized. The optimized compound **39** was selected for further profiling.

Discovery of *trans*-3,4′-bispyridinylethylenes as potent and novel inhibitors of protein kinase B (PKB/Akt) for the treatment of cancer: Synthesis and biological evaluation pp 1679–1685
Qun Li,* Tongmei Li, Gui-Dong Zhu, Jianchun Gong, Akiyo Claibone, Chris Dalton, Yan Luo, Eric F. Johnson, Yan Shi, Xuesong Liu, Vered Klinghofer, Joy L. Bauch, Kennan C. Marsh, Jennifer J. Bouska, Shannon Arries, Ron De Jong, Tilman Oltersdorf, Vincent S. Stoll, Clarissa G. Jakob, Saul H. Rosenberg and Vincent L. Giranda

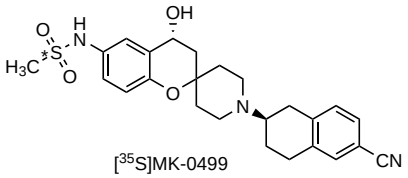


Anticancer activity of a series of platinum complexes integrating demethylcantharidin with isomers of 1,2-diaminocyclohexane pp 1686–1691
Chun-Wing Yu, Kay K. W. Li, Siu-Kwong Pang, Steve C. F. Au-Yeung and Yee-Ping Ho*



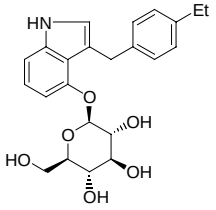
Anticancer activity and flow cytometric analysis of a series of *trans*-DACH–Pt–DMC analogues are compared with those of oxaliplatin, cisplatin, and carboplatin.

Synthesis of the first sulfur-35-labeled hERG radioligand **pp 1692–1695**
Conrad E. Raab,* John W. Butcher, Thomas M. Connolly, Jerzy Karczewski, Nathan X. Yu, Steven J. Staskiewicz, Nigel Liverton, Dennis C. Dean and David G. Melillo



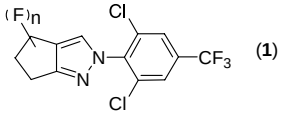
The synthesis of hERG radioligand [^{35}S]MK-0499 for use in an HTS assay for I_{Kr} activity is reported.

Indole-glucosides as novel sodium glucose co-transporter 2 (SGLT2) inhibitors. Part 2 **pp 1696–1701**
Xiaoyan Zhang,* Maud Urbanski, Mona Patel, Geoffrey G. Cox, Roxanne E. Zeck, Haiyan Bian, Bruce R. Conway, Mary Pat Beavers, Philip J. Rybczynski and Keith T. Demarest



A series of indole-*O*-glucosides and *C*-glucosides was synthesized and evaluated in SGLT1 and SGLT2 cell-based functional assays. Compounds **2a** and **2o** were identified as potent SGLT2 inhibitors and screened in ZDF rats.

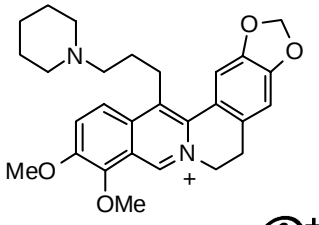
Synthesis and insecticidal activity of fluorinated 2-(2,6-dichloro-4-trifluoromethylphenyl)-2,4,5,6-tetrahydrocyclopentapyrazoles **pp 1702–1706**
Sanath K. Meegalla,* Dario Doller, Ruiping Liu, DeYou Sha, YuKai Lee, Richard M. Soll, Nancy Wisnewski, Gary M. Silver and Dale Dhanoa



Synthesis and insecticidal activities of fused fluorinated tetrahydrocyclopentapyrazoles (generic structure **1**) will be presented.

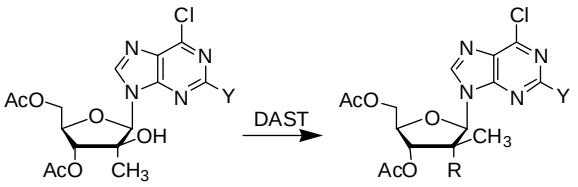
Natural and synthetic G-quadruplex interactive berberine derivatives **pp 1707–1711**
Marco Franceschin, Luigi Rossetti, Anna D'Ambrosio, Stefano Schirripa, Armandodoriano Bianco, Giancarlo Ortaggi, Maria Savino, Christoph Schultes and Stephen Neidle*

The interaction of the natural alkaloid berberine with various G-quadruplex DNA structures and its ability to inhibit telomerase have been examined and compared with those of a synthetic piperidino derivative and the related compound coralyne.



Synthesis and antiviral activity of 2′-deoxy-2′-fluoro-2′-*C*-methyl purine nucleosides as inhibitors of hepatitis C virus RNA replication **pp 1712–1715**

Jeremy L. Clark,* J. Christian Mason, Laurent Hollecker, Lieven J. Stuyver, Phillip M. Tharnish, Tamara R. McBrayer, Michael J. Otto, Phillip A. Furman, Raymond F. Schinazi and Kyoichi A. Watanabe

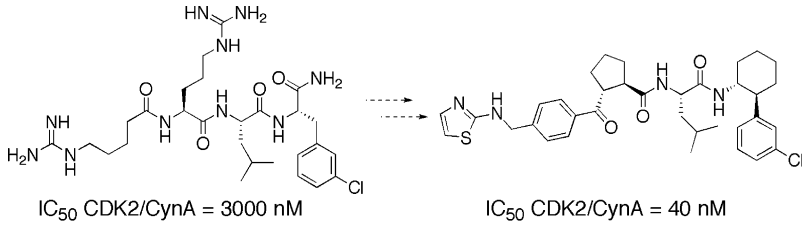


6a: Y = NHTr
6b: Y = H

7a: R = F, Y = NHTr
7b: R = F, Y = H
8a: R = OH, Y = NHTr
8b: R = OH, Y = H

CDK2/cyclinA inhibitors: Targeting the cyclinA recruitment site with small molecules derived from peptide leads **pp 1716–1720**

Georgette Castanedo, Kevin Clark, Shumei Wang, Vickie Tsui, Mengling Wong, John Nicholas, Dineli Wickramasinghe, James C. Marsters, Jr. and Daniel Sutherlin*



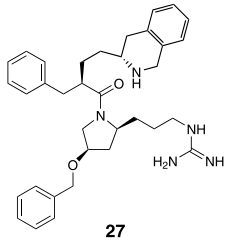
IC_{50} CDK2/CynA = 3000 nM
19 rotatable bonds, +2 charge

IC_{50} CDK2/CynA = 40 nM
11 rotatable bonds, neutral

Synthesis of Tic-D-Phe Ψ[CH_2–CH_2] isostere and its use in the development of melanocortin receptor agonists **pp 1721–1725**

Xinrong Tian,* Xuemei Chen, Lixian Gan, Jeffery C. Hayes, Adrian G. Switzer, Mark G. Solinsky, Frank H. Ebetino, John A. Wos, Beth B. Pinney, Julie A. Farmer, Doreen Crossdoersen and Russell J. Sheldon

The first synthesis of Tic-D-Phe Ψ[CH_2–CH_2] isostere is described, which features diastereoselective alkylation of the tricyclic lactam **14**. The use of this novel dipeptide isostere in the development of melanocortin agonists has been demonstrated by the synthesis of peptidomimetic **7** and non-peptidic ligand **27**. Both compounds displayed significant binding and agonist potency at the MC4R.



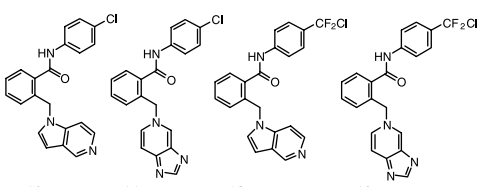
27

MC4R: Ki 76 nM; EC50 (Emax) 142 nM(76%)

2-((1*H*-Azol-1-yl)methyl)-*N*-arylbenzamides: Novel dual inhibitors of VEGFR-1/2 kinases **pp 1726–1730**

Alexander S. Kiselyov,* Marina Semenova, Victor V. Semenov and Evgueni Piatnitski

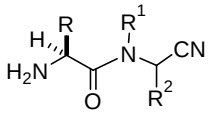
Novel potent derivatives of (azol-1-yl)methyl-*N*-arylbenzamides with improved solubility (>3 mM) are described as ATP-competitive inhibitors of vascular endothelial growth factor receptor 2 (VEGFR-2). Many compounds display VEGFR-2 inhibitory activity reaching IC_{50} < 100 nM in the enzymatic assay. The compounds also inhibit the related tyrosine kinase, VEGFR-1, with similar potencies. Several compounds containing bulky lipophilic substituents at the benzamide pharmacophore yielded 10- to 17-fold selectivity for the VEGFR-2 versus VEGFR-1 kinase.



10 **11** **18** **19**

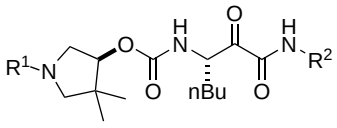
Cmpd	VEGFR-2, IC_{50}, μM	VEGFR-1, IC_{50}, μM
10	0.092±0.008	0.22±0.07
11	0.047±0.005	0.14±0.02
18	***0.073±0.02***	***1.25±0.12***
19	***0.095±0.02***	***1.16±0.11***

Seco-prolinenitrile inhibitors of dipeptidyl peptidase IV define minimal pharmacophore requirements at P1 **pp 1731–1734**
David R. Magnin, Prakash C. Taunk, James G. Robertson, Aiying Wang, Jovita Marcinkeviciene, Mark S. Kirby and Lawrence G. Hamann*



The synthesis and dipeptidyl peptidase IV inhibitory activity of glycine- and alaninenitrile dipeptides are reported.

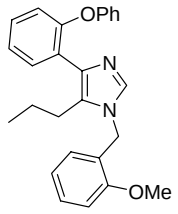
Novel, potent P^2–P^3 pyrrolidine derivatives of ketoamide-based cathepsin K inhibitors **pp 1735–1739**
David G. Barrett, John G. Catalano,* David N. Deaton, Anne M. Hassell, Stacey T. Long, Aaron B. Miller, Larry R. Miller, John A. Ray, Vicente Samano, Lisa M. Shewchuk, Kevin J. Wells-Knecht, Derril H. Willard, Jr. and Lois L. Wright



Starting from a potent pantolactone ketoamide cathepsin K inhibitor derived from structural screening, conversion of the lactone scaffold to a pyrrolidine scaffold allowed exploration of the S^3 subsite of cathepsin K. Manipulation of P^3 and $P^{1'}$ groups afforded potent inhibitors with drug-like properties.

Design and modular parallel synthesis of a MCR derived α-helix mimetic protein–protein interaction inhibitor scaffold **pp 1740–1743**
Walfrido Antuch, Sanjay Menon, Quin-Zene Chen, Yingchun Lu, Sukumar Sakamuri, Barbara Beck, Vesna Schauer-Vukašinović, Seema Agarwal, Sibylle Hess and Alexander Dömling*

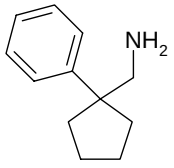
Design, synthesis and biological activity of Bcl family imidazole protein interaction antagonists is reported.



GI_{50} (HL-60) = 12 μM

The reversed binding of β-phenethylamine inhibitors of DPP-IV: X-ray structures and properties of novel fragment and elaborated inhibitors **pp 1744–1748**
Sonja Nordhoff,* Silvia Cerezo-Gálvez, Achim Feurer, Oliver Hill, Victor G. Matassa, Günther Metz, Christian Rummey, Meinolf Thiemann and Paul J. Edwards

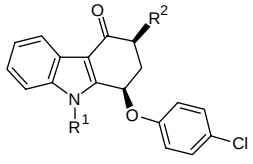
The co-crystal structure of β-phenethylamine fragment inhibitor **5** bound to DPP-IV revealed that the phenyl ring occupied the proline pocket of the enzyme. This finding provided the basis for a general hypothesis of a reverse binding mode for β-phenethylamine-based DPP-IV inhibitors, allowing novel inhibitor design concepts that obviate substrate-like structure–activity relationships (SAR).



5

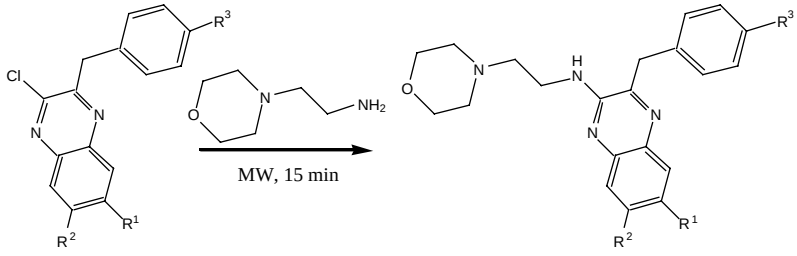
DPP-IV IC_{50} = 33 μM (human);
DPP-IV IC_{50} = 30 μM (porcine)

Synthesis and SAR of substituted tetrahydrocarbazole derivatives as new NPY-1 antagonists **pp 1749–1752**
Romano Di Fabio,* Riccardo Giovannini, Barbara Bertani, Manuela Borriello, Andrea Bozzoli, Daniele Donati, Alessandro Falchi, Damiano Ghirlanda, Colin P. Leslie, Angelo Pecunioso, Giovanna Rumboldt and Simone Spada



The synthesis and the SAR of new series of NPY-1 antagonists are reported.

Synthesis of 3-benzyl-2-substituted quinoxalines as novel monoamine oxidase A inhibitors **pp 1753–1756**
Seham Y. Hassan, Sherine N. Khattab, Adnan A. Bekhit* and Adel Amer*



OTHER CONTENTS

Erratum **p 1757**
Summary of instructions to authors **p I**

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

View of the crystal structure of the DB819-d(CGCGAATTCGCG)$_2$ complex, looking down the minor groove of the DNA (see Campbell, N.H.; Evans, D.A.; Lee, M.P.H.; Parkinson, G.N.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 15.). The DB819 molecule is shown in space-filling mode. Visualisation produced with the VMD program. [Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33.]

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