

Contents

COMMUNICATIONS

Porphyrin–DNA cross-linking agent hybrids: chemical synthesis and biological studies

pp 3013–3016

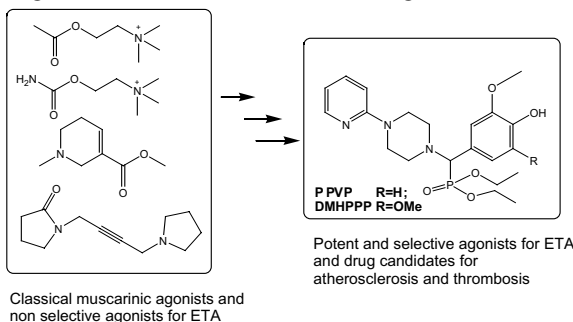
Hanping He, Tian Tian, Ping Wang, Lin Wu, Jingjing Xu, Xiang Zhou,* Xiaolian Zhang,*
Xiaoping Cao and Xiaojun Wu

Three new porphyrin–DNA cross-linking conjugates **8**, **9**, and **10** have been synthesized. Their photoinduced DNA cleavage activities and tumor cell cytotoxicities have been studied.

Discovering selective agonists of endothelial target for acetylcholine (ETA) via diversity-guided pharmacophore simplification and simulation

pp 3017–3025

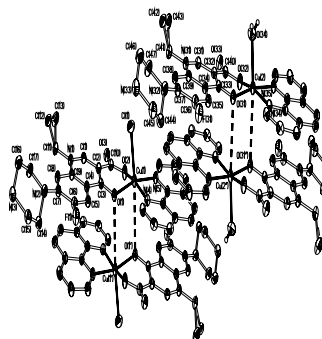
Rifang Yang,* Rusheng Zhao, Dongmei Chen, Limei Shan, Liuhong Yun and Hai Wang



A novel mixed-ligand antimycobacterial dimeric copper complex of ciprofloxacin and phenanthroline

pp 3027–3032

Dilip Kumar Saha, Uday Sandbhor, K. Shirisha,
Subhash Padhye,* Dileep Deobagkar,
Christopher E. Anson and Annie K. Powell



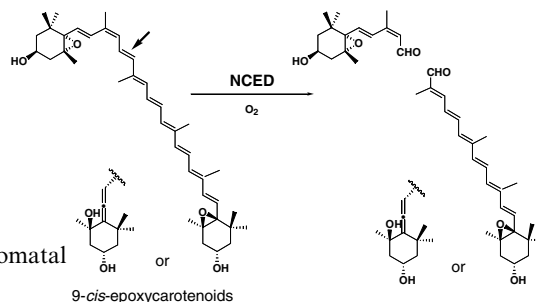
The novel mixed-ligand Cu(II) complex of ciprofloxacin (cfH) and phenanthroline (phen) [Cu(cfH)(phen)Cl][Cu(cfH)(phen)(OH₂)](BF₄)₂Cl·8H₂O contains two closely related complex units, each of which forms a weak dimeric species. The higher negative redox potential for this cluster dampens its antimycobacterial activity against *M. smegmatis*.

A new lead compound for abscisic acid biosynthesis inhibitors targeting 9-*cis*-epoxycarotenoid dioxygenase

pp 3033–3036

Sun-young Han, Nobutaka Kitahata, Tamio Saito, Masatomo Kobayashi, Kazuo Shinozaki, Shigeo Yoshida and Tadao Asami*

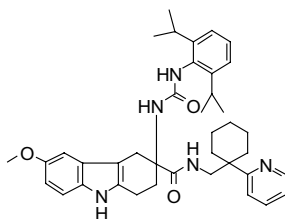
9-*cis*-Epoxy-carotenoid dioxygenase (NCED), a key enzyme in abscisic acid (ABA) biosynthesis, cleaves the olefinic double bond of 9-*cis*-epoxycarotenoid. Several analogues of nordihydroguaiaretic acid (NDGA) were designed and synthesized, and their efficacy as inhibitors of NCED was examined. One of the synthesized compounds (**20**) was found to be an inhibitor of this enzyme, and inhibited ABA accumulation and stomatal closing, suggesting that **20** should be ABA biosynthesis inhibitor.



Identification and optimization of novel partial agonists of Neuromedin B receptor using parallel synthesis

pp 3037–3042

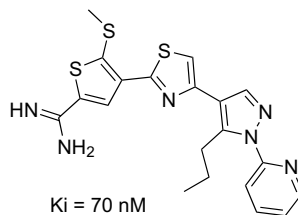
Stephen J. Shuttleworth,* Mike E. Lizarzaburu, Anne Chai and Peter Coward



A novel series of potent and selective small molecule inhibitors of the complement component C1s

pp 3043–3047

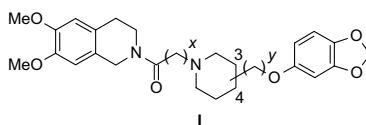
Nalin L. Subasinghe,* Farah Ali, Carl R. Illig, M. Jonathan Rudolph, Scott Klein, Ehab Khalil, Richard M. Soll, Roger F. Bone, John C. Spurlino, Renee L. DesJarlais, Carl S. Crysler, Maxwell D. Cummings, Philip E. Morris, Jr., John M. Kilpatrick and Y. Sudhakara Babu



Synthesis and pharmacological evaluation of piperidinoalkanoyl-1,2,3,4-tetrahydroisoquinoline derivatives as novel specific bradycardic agents

pp 3049–3052

Hideki Kubota,* Toshihiro Watanabe, Akio Kakefuda, Noriyuki Masuda, Kouichi Wada, Noe Ishii, Shuichi Sakamoto and Shin-ichi Tsukamoto

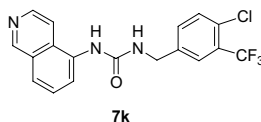


A series of piperidinoalkanoyl-1,2,3,4-tetrahydroisoquinoline derivatives (formula **I**) were synthesized, and their bradycardic activities were investigated in the isolated right atria of guinea pigs and in conscious rats.

***N*-Isoquinolin-5-yl-*N'*-aralkyl-urea and -amide antagonists of human vanilloid receptor 1**

pp 3053–3056

Michele C. Jetter, Mark A. Youngman, James J. McNally, Sui-Po Zhang, Adrienne E. Dubin, Nadia Nasser and Scott L. Dax*

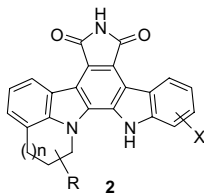


N-Isoquinolin-5-yl-*N'*-aralkyl-ureas and -amides were developed as potent ligands of human vanilloid receptor 1. *N*-Isoquinolin-5-yl-*N'*-(4-chloro-3-trifluoromethylbenzyl)urea **7k** exhibited subnanomolar binding affinity and upon capsaicin challenge, behaved as a full functional antagonist at low nanomolar concentrations.

Synthesis of 1,7-annulated indoles and their applications in the studies of cyclin dependent kinase inhibitors

pp 3057–3061

Guoxin Zhu,* Scott E. Conner, Xun Zhou, Ho-Kit Chan, Chuan Shih, Thomas A. Engler, Rima S. Al-awar, Harold B. Brooks, Scott A. Watkins, Charles D. Spencer, Richard M. Schultz, Jack A. Dempsey, Eileen L. Considine, Bharvin R. Patel, Catherine A. Ogg, Vasu Vasudevan and Michelle L. Lytle

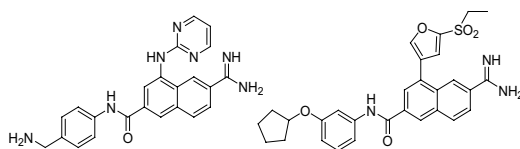


A novel series of 1,7-annulated indolocarbazoles was synthesized and their D1/CDK4 inhibitory and antiproliferative activity were evaluated.

**Interaction with the S1 β -pocket of urokinase: 8-heterocycle substituted and 6,8-disubstituted 2-naphthamidine urokinase inhibitors**

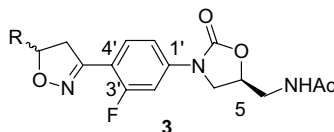
pp 3063–3068

Michael D. Wendt,* Andrew Geyer, William J. McClellan, Todd W. Rockway, Moshe Weitzberg, Xumiao Zhao, Robert Mantei, Kent Stewart, Vicki Nienaber, Vered Klinghofer and Vincent L. Giranda

**The synthesis and antimicrobial evaluation of a new series of isoxazolinyloxazolidinones**

pp 3069–3072

Michele A. Weidner-Wells,* Harvey M. Werblood, Raul Goldschmidt, Karen Bush, Barbara D. Foleno, James J. Hilliard, John Melton, Ellyn Wira and Mark J. Macielag

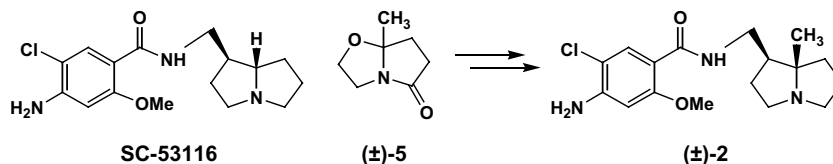


A series of oxazolidinone antibacterial agents containing a 5-substituted isoxazol-3-yl moiety were synthesized via a nitrile oxide [3+2] dipolar cycloaddition reaction. These compounds were screened against a panel of susceptible and resistant Gram-positive organisms. Several analogs from this series were comparable to or more potent than linezolid in vitro.

Bridgehead-methyl analog of SC-53116 as a 5-HT₄ agonist

pp 3073–3075

Daniel P. Becker,* Daniel L. Flynn and Clara I. Villamil



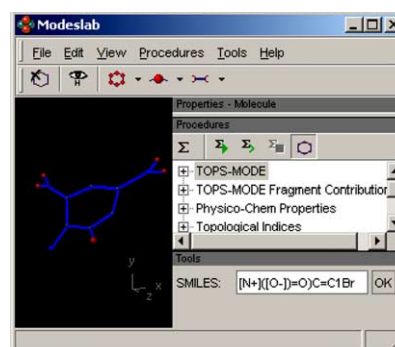
Pyrrolizidine (±)-2, the bridgehead-methyl analog of SC-53116, was prepared and evaluated for 5-HT₄ agonism activity in the rat tunica muscularis (TMM) mucosae assay. Compound (±)-2 has an EC₅₀ of 449 nM in the TMM assay, as compared to 23 nM for SC-53116, and 66 nM for the racemate of SC-53116.

A TOPS-MODE approach to predict adenosine kinase inhibition

pp 3077–3079

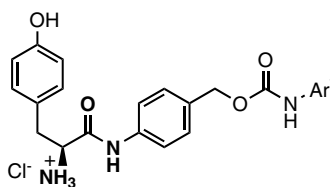
Maykel Pérez González* and Maria del Carmen Terán Moldes

The TOPological Sub-Structural Molecular Design (TOPS-MODE) approach has been applied to the study of the adenosine kinase inhibitory activity of pyrrolo[2,3-*d*]pyrimidine nucleoside analogues. A model is able to describe around 77% of the variance in the experimental activity of 32 analogues of these compounds was developed with the use of the mentioned approach.

**Image contrast agents activated by prostate specific antigen (PSA)**

pp 3081–3084

Graham B. Jones,* Longfei Xie, Ahmed El-Shafey, Curtis F. Crasto, Glenn J. Bubley and Anthony V. D'Amico

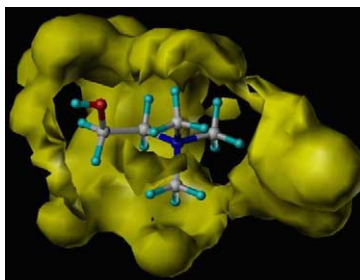


The viability of a three-component enzyme activated image contrast system was demonstrated using a family of tyrosine-chromophore conjugates linked by an inert spacer.

Molecular modeling studies on the active binding site of the blood–brain barrier choline transporter

pp 3085–3092

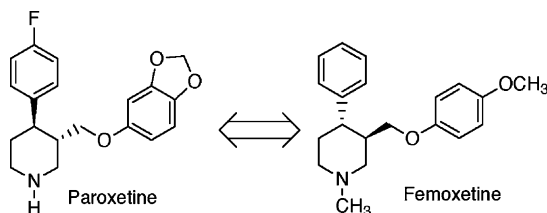
Werner J. Geldenhuys, Paul R. Lockman, James H. McAfee, Kevin T. Fitzpatrick, Cornelis J. Van der Schyf and David D. Allen*



Structural differences between paroxetine and femoxetine responsible for differential inhibition of *Staphylococcus aureus* efflux pumps

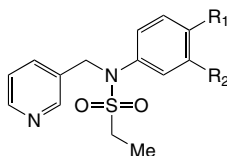
pp 3093–3097

Peng Wei, Glenn W. Kaatz and Robert J. Kerns*

**SAR study of a subtype selective allosteric potentiator of metabotropic glutamate 2 receptor, *N*-(4-phenoxyphenyl)-*N*-(3-pyridinylmethyl)ethanesulfonamide**

pp 3099–3102

David A. Barda,* Zhao-Qing Wang, Thomas C. Britton, Steven S. Henry, G. Erik Jagdmann, Darrell S. Coleman, Michael P. Johnson, Sherri L. Andis and Darryle D. Schoepp

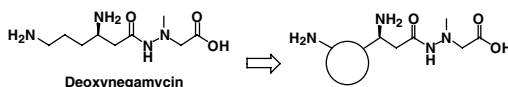


The structure–activity relationship of a subtype selective mGlu2 potentiator, LY181837 is explored.

Conformationally restricted analogs of deoxynegamycin

pp 3103–3107

B. Raju,* Sampathkumar Anandan, Shihai Gu, Prudencio Herradura, Hardwin O'Dowd, Bum Kim, Marcela Gomez, Corinne Hackbarth, Charlotte Wu, Wen Wang, Zhengyu Yuan, Richard White, Joaquim Trias and Dinesh V. Patel

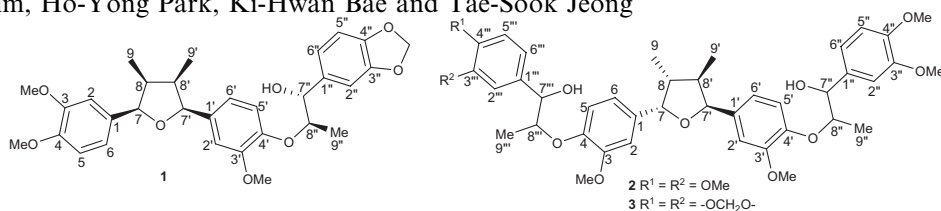


Methods were developed to synthesize a number of conformationally restricted β -amino acids. Incorporation of these β -amino acids into deoxynegamycin template has resulted in structurally novel and conformationally restricted analogs. These analogs were evaluated in whole cell assays and as inhibitors of cell-free protein synthesis to assess their antibacterial properties.

Human ACAT-1 and -2 inhibitory activities of saucerneol B, manassantin A and B isolated from *Saururus chinensis*

pp 3109–3112

Woo Song Lee, Dae-Woo Lee, Young-Il Baek, So-Jin An, Kyung-Hyun Cho, Yang-Kyu Choi, Hyoung-Chin Kim, Ho-Yong Park, Ki-Hwan Bae and Tae-Sook Jeong*

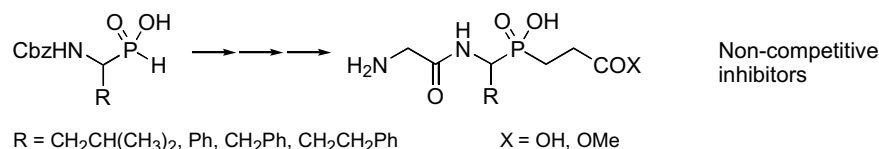


Compounds 1–3 isolated from the methanolic extracts of *Saururus chinensis* root inhibited hACAT-1 and hACAT-2 activities. The EtOAc-soluble fraction, which contained compounds 1–3, of methanol extracts of *S. chinensis* exhibited strong cholesterol-lowering effect in high cholesterol-fed mice.

Synthesis and activity of phosphinic tripeptide inhibitors of cathepsin C

pp 3113–3116

Artur Mucha,* Małgorzata Pawelczak, Józef Hurek and Paweł Kafarski

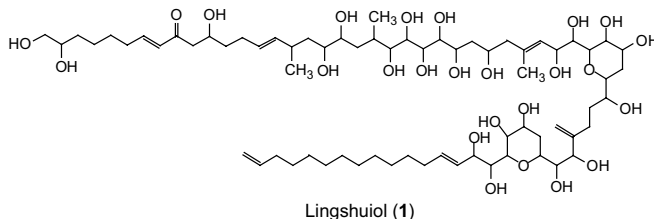


Phosphinic tripeptides were designed and synthesised as transition state analogue inhibitors of cathepsin C. Surprisingly, they revealed noncompetitive mode of binding with different kinetics for C-terminal acids comparing to the corresponding esters.

Lingshuiol, a novel polyhydroxyl compound with strongly cytotoxic activity from the marine dinoflagellate *Amphidinium* sp.

pp 3117–3120

Xiao-Chun Huang, Di Zhao, Yue-Wei Guo,* Hou-Ming Wu, Li-Ping Lin, Zhong-Hua Wang, Jian Ding and Yong-Shui Lin

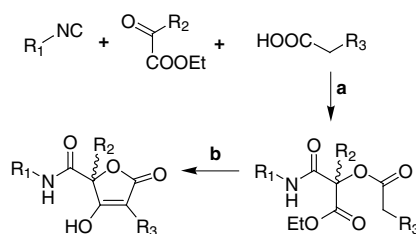


A novel polyhydroxy compound with a linear carbon-chain, lingshuiol (1), had been isolated from the cultured marine dinoflagellate *Amphidinium* sp. It possessed powerful cytotoxic activity against A-549 and HL-60 with the IC_{50} of 0.21 and 0.23 μM , respectively.

**Novel nonpeptidic inhibitors of HIV-1 protease obtained via a new multicomponent chemistry strategy**

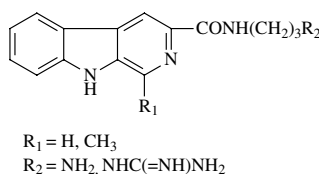
pp 3121–3125

Nasser A. M. Yehia, Walfrido Antuch, Barbara Beck, Sibylle Hess, Vesna Schauer-Vukašinović, Michael Almstetter, Patrick Furer, Eberhardt Herdtweck and Alexander Dömling*

**Synthesis and biological evaluation of novel β -carboline derivatives as Tat–TAR interaction inhibitors**

pp 3127–3130

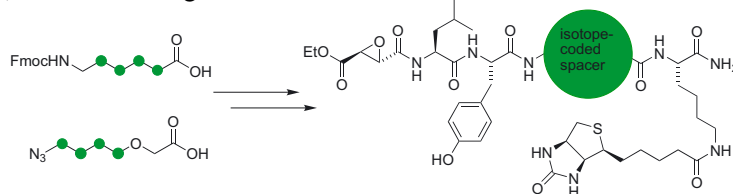
Xiaolin Yu, Wei Lin, Jingyun Li and Ming Yang*



Four new β -carboline derivatives were synthesized and their effects on Tat–TAR interaction as well as to HIV-1 in MT4 cells were evaluated. Furthermore, capillary electrophoresis was used to study the binding specificity of compound 6 to TAR RNA in inhibiting the Tat–TAR interaction.

Development of an isotope-coded activity-based probe for the quantitative profiling of cysteine proteases pp 3131–3134

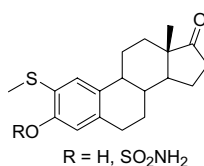
Paul F. van Swieten, Rene Maehr, Adrianus M. C. H. van den Nieuwendijk, Benedikt M. Kessler, Michael Reich, Chung-Sing Wong, Hubert Kalbacher, Michiel A. Leeuwenburgh, Christoph Driessen, Gijsbert A. van der Marel, Hidde L. Ploegh and Herman S. Overkleeft*



The synthesis of two new deuterium-containing spacers and their incorporation into quantitative functional proteomics tools, aimed at the cathepsin family of cysteine proteases is described. It is shown that the labeling pattern of these isotope-coded probes is not altered, as compared to the parent compound.

**2-Alkylsulfanyl estrogen derivatives: synthesis of a novel class of multi-targeted anti-tumour agents** pp 3135–3138

Mathew P. Leese, Simon P. Newman, Atul Purohit, Michael J. Reed and Barry V. L. Potter*

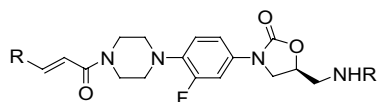


A flexible, direct, high yielding synthesis of 2-alkylsulfanyl estrogens has been developed. 2-Methylsulfanyl estradiol (2-MeSE2) and its 3-*O*-sulfamate derivative display a similar anti-proliferative activity to 2-methoxyestradiol (2-MeOE2).

Oxazolidinone: search for highly potent antibacterial

pp 3139–3142

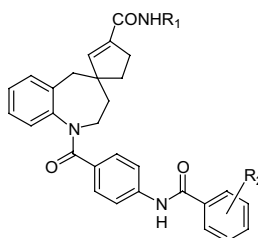
Braj Bhushan Lohray,* Vidya Bhushan Lohray, Brijesh Kumar Srivastava, Sunil Gupta, Manish Solanki, Prashant Kapadnis, Vijay Takale and Purvi Pandya



A number of substituted piperazinyl oxazolidinone derivatives have been synthesized and their antibacterial activities were evaluated. A systematic SAR was carried out to get highly potent analog of oxazolidinone.

Synthesis and evaluation of nonpeptide substituted spirobenzazepines as potent vasopressin antagonists pp 3143–3146

Min Amy Xiang, Robert H. Chen,* Keith T. Demarest, Joseph Gunnet, Richard Look, William Hageman, William V. Murray, Donald W. Combs, Philip J. Rybczynski and Mona Patel*

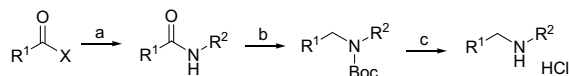


A series of spirobenzazepines have been synthesized and evaluated as selective V_{1a} and V_{1a}/V₂ dual vasopressin receptor antagonists.

An efficient sequence for the preparation of small secondary amine hydrochloride salts for focused library generation without need for distillation or chromatographic purification

pp 3147–3149

Gene M. Dubowchik,* Jodi A. Michne and Dmitry Zuev

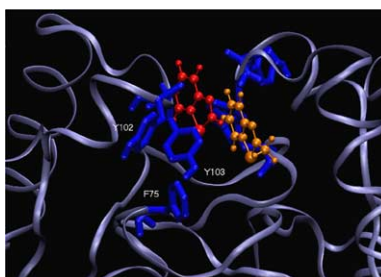


Collections of secondary amines for compound library generation can be efficiently prepared by amide reduction using BH_3 –THF or Red-Al followed by brief methanolysis, trapping with di-*tert*-butyl dicarbonate, and deprotection with HCl. The sequence requires no chromatography or distillation and provides multi-gram quantities of pure HCl salts in a short time.

Exploring the possible binding sites at the interface of triosephosphate isomerase dimer as a potential target for anti-tripanosomal drug design

pp 3151–3154

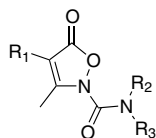
L. Michel Espinoza-Fonseca* and José G. Trujillo-Ferrara



In vitro SAR of (5-(2*H*)-isoxazolonyl) ureas, potent inhibitors of hormone-sensitive lipase

pp 3155–3159

Derek B. Lowe,* Steven Magnuson, Ning Qi, Ann-Marie Campbell, James Cook, Zhenqiu Hong, Ming Wang, Mareli Rodriguez, Furahi Achebe, Harold Kluender, Wai C. Wong, William H. Bullock, Arthur I. Salhanick, Terri Witman-Jones, Mary E. Bowling, Christine Keiper and Kevin B. Clairmont

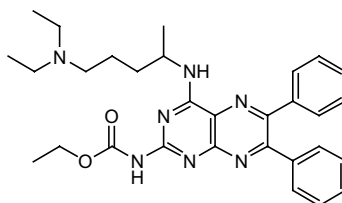


A series of (5-(2*H*)-isoxazolonyl) ureas were developed as nanomolar inhibitors of hormone-sensitive lipase, an enzyme of potential importance in the treatment of diabetes.

A new 2-carbamoyl pteridine that inhibits mycobacterial FtsZ

pp 3161–3164

R. C. Reynolds,* S. Srivastava, L. J. Ross, W. J. Suling and E. L. White

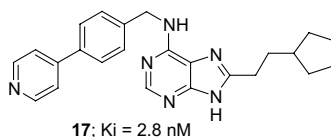


The preparation of a new 2-carbamoyl pteridine, its activity data against FtsZ from *M. tuberculosis* (Mtb), and in vitro antibacterial data against Mtb strain H37Ra are presented.

Structure-based design, synthesis, and antimicrobial activity of purine derived SAH/MTA nucleosidase inhibitors

pp 3165–3168

Martina E. Tedder, Zhe Nie, Stephen Margosiak, Shaosong Chu, Victoria A. Feher, Robert Almassy, Krzysztof Appelt and Kraig M. Yager*

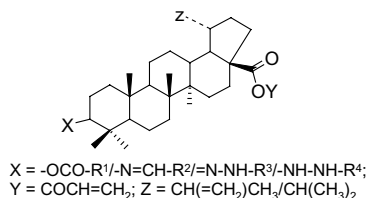


Systematic, structure-guided modifications to a series of 6-substituted purine and deaza purine derivatives provided low nM inhibitors of the bacterial enzyme S-adenosyl homocysteine/methylthioadenosine nucleosidase.

Synthesis of 3-*O*-acyl/3-benzylidene/3-hydrazone/3-hydrazine/17-carboxyacryloyl ester derivatives of betulinic acid as anti-angiogenic agents

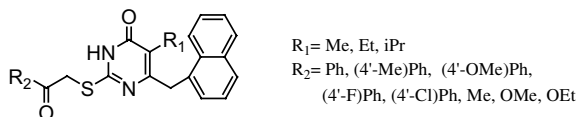
pp 3169–3172

Rama Mukherjee, Manu Jaggi,* Praveen Rajendran, Sanjay K. Srivastava,* Mohammad J. A. Siddiqui, Anand Vardhan and Anand C. Burman

**5-Alkyl-2-[(aryl and alkyloxy)carbonylmethyl]thio]-6-(1-naphthylmethyl) pyrimidin-4(3*H*)-ones as an unique HIV reverse transcriptase inhibitors of *S*-DABO series**

pp 3173–3176

Yanping He, Fener Chen,* Guangfu Sun, Yueping Wang, Erik De Clercq, Jan Balzarini and Christophe Pannecouque

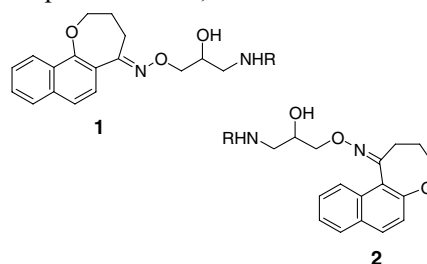


The introduction of a β -carbonyl group to the C-2 side chain of *S*-DABO led to the finding of a series of novel high potent anti-HIV agent. Interestingly, some of the novel *S*-DABOs show activity against both HIV-1 and HIV-2.

Potential hypotensive agents: synthesis and hypotensive activity of oxime ethers derived from 1-naphthoxepines and related compounds

pp 3177–3180

Vishnu K. Tandon,* Manoj Kumar, Anoop K. Awasthi, Hari O. Saxena and Gajendra K. Goswamy

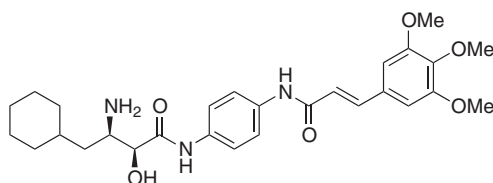


A series of oxime ethers **1** and **2** have been synthesized and evaluated for their hypotensive activity.

Design and synthesis of β -amino- α -hydroxy amide derivatives as inhibitors of MetAP2 and HUVEC growth

pp 3181–3184

Martin Sendzik,* James W. Janc, Ronnel Cabuslay, Lee Honigberg, Richard L. Mackman, Catherine Magill, Neil Squires and Nancy Waldeck

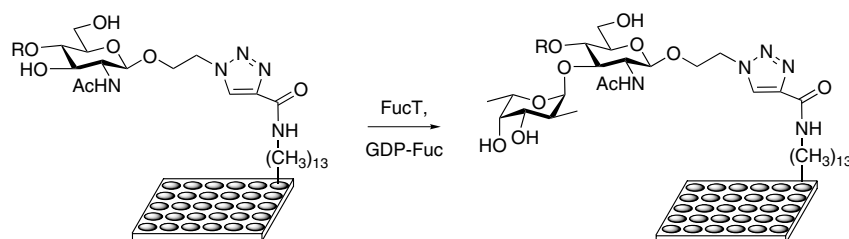


The rational design and synthesis of β -amino- α -hydroxy amide derivatives as reversible inhibitors of methionine aminopeptidase-2 (MetAP2) with anti-proliferative activity against human umbilical vein endothelial cells (HUVECs) is described.

High-throughput identification of fucosyltransferase inhibitors using carbohydrate microarrays

pp 3185–3188

Marian C. Bryan, Lac V. Lee and Chi-Huey Wong*

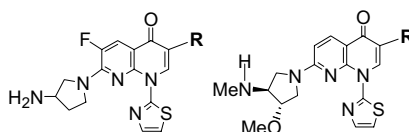


Inhibitors to fucosyltransferase were screened in a high-throughput manner using a noncovalent carbohydrate microarray strategy and four nanomolar inhibitors were identified.

Synthesis and structure–activity relationships of 3-substituted 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridines as novel antitumor agents

pp 3189–3193

Yasunori Tsuzuki,* Kyoji Tomita, Yuji Sato, Shigeki Kashimoto and Katsumi Chiba

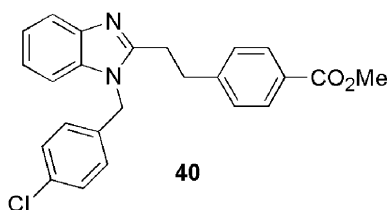


The synthesis and SARs of various 3-substituted 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridines as antitumor agents are reported. The series of novel 3-substituted analogs showed good cytotoxic activity against murine P388 leukemia while antibacterial activity of these 3-substituents was significantly less than 3-carboxy group, implying the discrepancy between antitumor SARs and antibacterial SARs.

Benzimidazoles as new potent and selective DP antagonists for the treatment of allergic rhinitis

pp 3195–3199

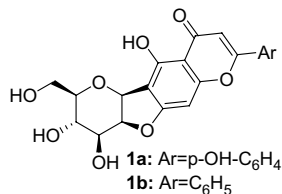
Christian Beaulieu,* Zhaoyin Wang, Danielle Denis, Gillian Greig, Sonia Lamontagne, Gary O'Neill, Deborah Slipetz and Jennifer Wang



First total synthesis of structurally unique flavonoids and their strong anti-inflammatory effect

pp 3201–3203

Takashi Nakatsuka,* Yoshiaki Tomimori, Yoshiaki Fukuda and Haruo Nukaya

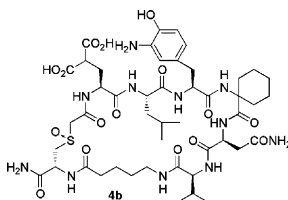


The first total synthesis of structurally unique flavonoids **1a** and **1b** is described. These compounds showed very strong anti-inflammatory effect against delayed hypersensitivity in a mouse model.

Development of L-3-aminotyrosine suitably protected for the synthesis of a novel nonphosphorylated hexapeptide with low-nanomolar Grb2-SH2 domain-binding affinity

pp 3205–3208

Yan-Li Song, Peter P. Roller and Ya-Qiu Long*

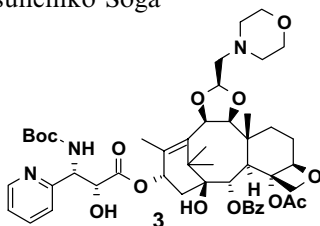


The synthesis of orthogonally protected L-3-aminotyrosine suitable for solid phase peptide synthesis and its first use for the preparation of a series of nonphosphorylated Grb2-SH2 domain antagonists were reported. The 3-aminotyrosine containing sulfoxide-cyclized hexapeptide **4b** exhibited potent Grb2-SH2 domain binding affinity (IC₅₀ = 50 nM), with only six residues free of phosphotyrosine or phosphotyrosine mimics.

New highly active taxoids from 9β-dihydrobaccatin-9,10-acetals. Part 5

pp 3209–3215

Yasuyuki Takeda, Kouichi Uoto, Michio Iwahana, Takeshi Jimbo, Motoko Nagata, Ryo Atsumi, Chiho Ono, Noriko Tanaka, Hirofumi Terasawa and Tsunehiko Soga*

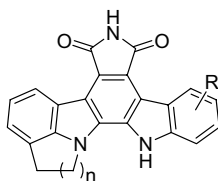


To improve the metabolic stability of **3**, new taxane analogues were synthesized. Most of the synthetic compounds maintained antitumor activity and were scarcely metabolized by human liver microsomes. And some compounds exhibited potent antitumor effects against B16 melanoma BL6 in vivo by both iv and po administration similarly to **3**.

1,7-Annulated indolocarbazoles as cyclin-dependent kinase inhibitors

pp 3217–3220

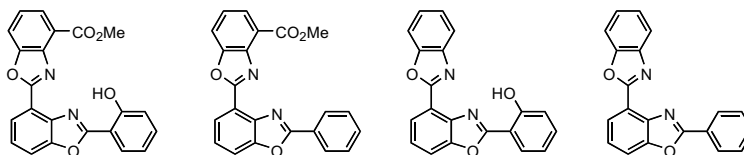
Rima S. Al-awar,* James E. Ray, Kyle A. Hecker, Jianping Huang, Philip P. Waid, Chuan Shih, Harold B. Brooks, Charles D. Spencer, Scott A. Watkins, Bharvin R. Patel, Nancy B. Stamm, Catherine A. Ogg, Richard M. Schultz, Eileen L. Considine, Margaret M. Faul, Kevin A. Sullivan, Stanley P. Kolis, John L. Grutsch and Sajjan Joseph



A series of novel 1,7-annulated indolocarbazoles was prepared and evaluated for kinase inhibitory activity.

Critical structural motif for the catalytic inhibition of human topoisomerase II by UK-1 and analogs pp 3221–3226

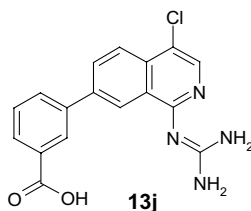
Ben B. Wang, Nima Maghami, Vanessa L. Goodlin and Paul J. Smith*



Three new analogs of UK-1 have been synthesized and their efficacies as topoisomerase II inhibitors have been determined. Results show that UK-1 and two of these analogs are catalytic inhibitors of topo II and identifies a critical structural motif necessary for enzyme inhibition.

Selective urokinase-type plasminogen activator (uPA) inhibitors. Part 3: 1-Isoquinolinylguanidines pp 3227–3230

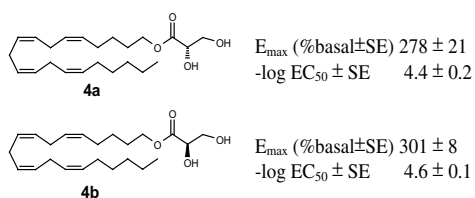
Christopher G. Barber,* Roger P. Dickinson and Paul V. Fish



A series of 1-isoquinolinylguanidines are selective inhibitors of uPA. Compound **13j** (UK-356,202) combines excellent potency and selectivity, and has been selected as a candidate for clinical evaluation.

Synthesis and CB1 receptor activities of novel arachidonyl alcohol derivatives pp 3231–3234

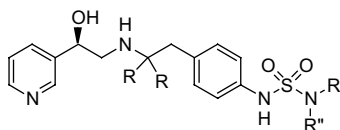
Teija Parkkari,* Juha R. Savinainen, Anu L. Rauhala, Tiina L. Tolonen, Tapio Nevalainen, Jarmo T. Laitinen, Jukka Gynther and Tomi Järvinen



Novel derivatives of arachidonyl alcohol were synthesized and evaluated for their CB1 receptor activity by [35 S]GTP $_{\gamma}$ S assay using rat cerebellar membranes.

Potent and selective, sulfamide-based human β_3 -adrenergic receptor agonists pp 3235–3240

Robert L. Dow,* Ernest S. Paight, Steven R. Schneider, John R. Hadcock, Diane M. Hargrove, Kelly A. Martin, Tristan S. Maurer, Nancy A. Nardone, David A. Tess and Paul DaSilva-Jardine

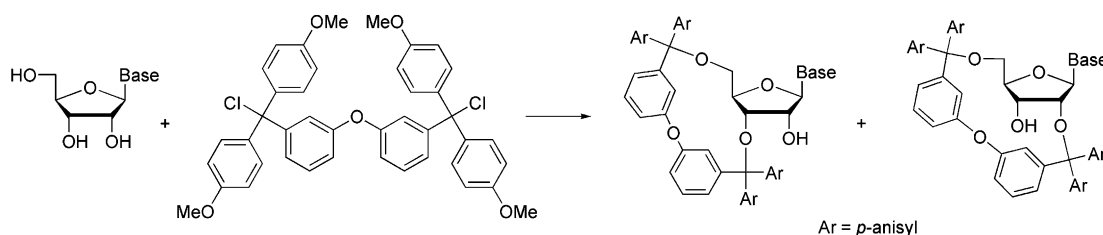


A series of sulfamide-based analogs related to L-796568 were prepared and evaluated for their biological activity at the human β_3 -adrenergic receptor (AR). This modification allows for a significant reduction in molecular weight, while maintaining single-digit nanomolar potencies at the β_3 -AR and high selectivities versus the β_1 - or β_2 -AR.

3,3'-Oxybis(dimethoxytrityl chloride) (O-DMTCl): synthesis and applications of a novel bifunctional protecting group

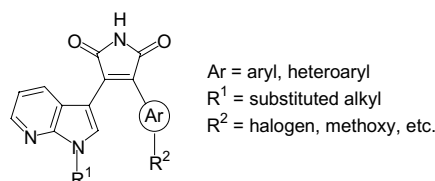
pp 3241–3244

Natsuhisa Oka, Yogesh S. Sanghvi* and Emmanuel A. Theodorakis

**3-(7-Azaindolyl)-4-arylmaleimides as potent, selective inhibitors of glycogen synthase kinase-3**

pp 3245–3250

Han-Cheng Zhang,* Hong Ye, Bruce R. Conway, Claudia K. Derian, Michael F. Addo, Gee-Hong Kuo, Leonard R. Hecker, Diane R. Croll, Jian Li, Lori Westover, Jun Z. Xu, Richard Look, Keith T. Demarest, Patricia Andrade-Gordon, Bruce P. Damiano and Bruce E. Maryanoff

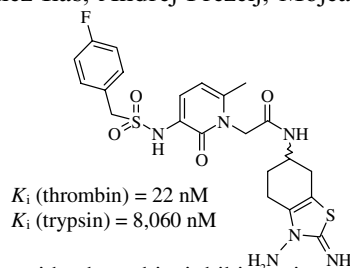


A novel series of 3-(7-azaindolyl)-4-(aryl/heteroaryl)maleimides was identified as potent GSK-3 β inhibitors with excellent selectivity over PKC- β II (>300-fold), as well as a broad panel of other protein kinases. The compounds were effective in a cell-based functional assay.

Novel thrombin inhibitors incorporating weakly basic heterobicyclic P₁-arginine mimetics: optimization via modification of P₁ and P₃ moieties

pp 3251–3256

Andreja Kranjc, Lucija Peterlin-Mašič, Janez Ilaš, Andrej Preželj, Mojca Stegnar and Danijel Kikelj*

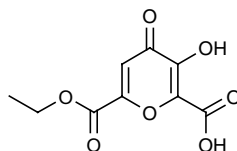


The optimization of 3-amino-2-pyridinone acetamide thrombin inhibitors incorporating weakly basic heterobicyclic P₁-arginine side-chain mimetics is described.

The monoethyl ester of meconic acid is an active site inhibitor of HCV NS5B RNA-dependent RNA polymerase

pp 3257–3261

Paola Pace,* Emanuela Nizi, Barbara Pacini, Silvia Pesci, Victor Matassa, Raffaele De Francesco, Sergio Altamura and Vincenzo Summa

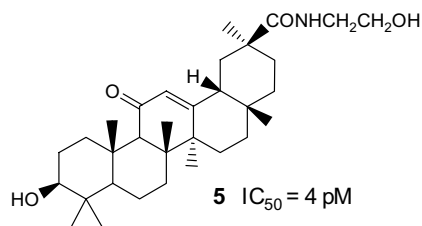


The monoethyl ester of meconic acid was discovered as novel inhibitor of HCV NS5B RNA dependent RNA polymerase. SAR around this molecule will be presented to provide an improved basis for structure-based ligand design.

A novel 18 β -glycyrrhetic acid analogue as a potent and selective inhibitor of 11 β -hydroxysteroid dehydrogenase 2

pp 3263–3267

Nigel Vicker, Xiangdong Su, Harshani Lawrence, Adrian Cruttenden, Atul Purohit, Michael J. Reed and Barry V. L. Potter*

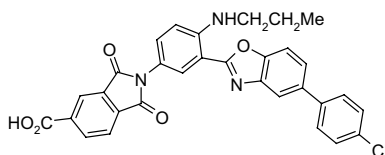


The discovery of a novel potent selective inhibitor of 11 β -HSD2 from a series of amides using 18 β -glycyrrhetic acid as a template is described.

2,3-Dihydro-1,3-dioxo-1*H*-isoindole-5-carboxylic acid derivatives: a novel class of small molecule heparanase inhibitors

pp 3269–3273

Stephen M. Courtney, Philip A. Hay,* Richard T. Buck, Claire S. Colville, David W. Porter, David I. C. Scopes, Faye C. Pollard, Martin J. Page, James M. Bennett, Margaret L. Hircok, Edward A. McKenzie, Colin R. Stubberfield and Paul R. Turner



A novel class of 2,3-dihydro-1,3-dioxo-1*H*-isoindole-5-carboxylic acids are described as inhibitors of the *endo*- β -glucuronidase heparanase. Several of the compounds display potent heparanase inhibitory activity (IC_{50} 200–500 nM).

Long chain amines and long chain ammonium salts as novel inhibitors of dynamin GTPase activity

pp 3275–3278

Timothy A. Hill, Luke R. Odell, Annie Quan, Ruben Abagyan, Gemma Ferguson, Phillip J. Robinson and Adam McCluskey*

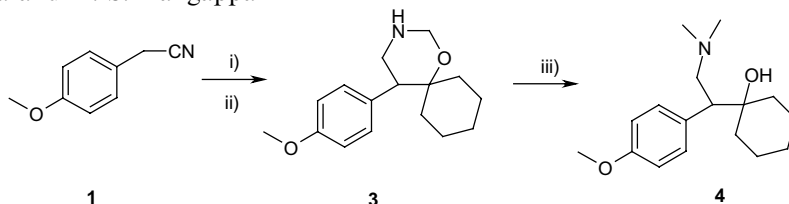


Dynamin 1 GTPase contains a pleckstrin homology (PH) domain that interacts with lipids. We report a series of simple lipid-like molecules that display moderate inhibitory activity. Inhibitory activity is linked to chain length and quaternarization of the terminal amine. A change in the counterion, Cl versus Br or I, had little effect on potency. However, introduction of a hydrophobic collar proximal to the charged site was beneficial to dynamin GTPase inhibitory action.

Simple and an efficient method for the synthesis of 1-[2-dimethylamino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol hydrochloride: (\pm) venlafaxine racemic mixtures

pp 3279–3281

Basappa, C. V. Kavitha and K. S. Rangappa*



A novel synthetic method was developed for the synthesis of venlafaxine using inexpensive reagents. An improvement in the method, in the yield was achieved for the conversion of the venlafaxine. This is an improved version, simple and efficient method for the large-scale synthesis of venlafaxine.

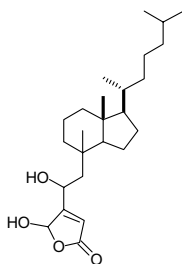
Carbonic anhydrase inhibitors: the first QSAR study on inhibition of tumor-associated isoenzyme IX with aromatic and heterocyclic sulfonamides pp 3283–3290

Mona Jaiswal, Padmakar V. Khadikar,* Andrea Scozzafava and Claudiu T. Supuran

QSAR study on the tumor-associated transmembrane carbonic anhydrase IX (CA IX) isoenzyme has been made using a large pool of distance-based topological indices: W , Sz , PI , $^0\chi$, $^1\chi$, $^2\chi$, $^0\chi^v$, $^1\chi^v$, and $^2\chi^v$. A combined set of 32 aromatic and heterocyclic compounds, including the six clinically used derivatives: acetazolamide, methazolamide, ethoxymolamide, dichlorophenamide, dorzolamide, and brinzolamide are used for this purpose. The results have shown that the inhibition of the tumor-associated isoenzyme IX with aromatic and heterocyclic sulfonamides can be modeled excellently in multiparametric regression after introduction of indicator parameters. The predictive power of the models is discussed using probable error of correlation (PE), variance-inflation factor (VIF), and cross-validation parameters: PRESS, SSY, r_{cv}^2 , S_{PRESS} , and PSE. This is the first report on QSAR study on inhibition of tumor-associated isoenzyme IX.

Design and synthesis of dysidiolide analogs from vitamin D₃: novel class of Cdc25A inhibitors pp 3291–3294

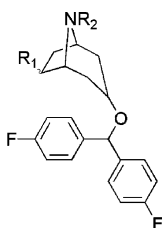
Rumiko Shimazawa, Toshiyuki Suzuki, Kosuke Dodo and Ryuichi Shirai*



Potent dysidiolide analogs were synthesized by structural hybridization of dysidiolide and vitamin D₃. These analogs exhibited strong inhibitory activity toward dual-specificity phosphatase Cdc25A (IC_{50} =0.44–0.89 μ M).

The effect of 6-substituted-4',4''-difluorobenzotropines on monoamine transporters and the muscarinic M1 receptor pp 3295–3298

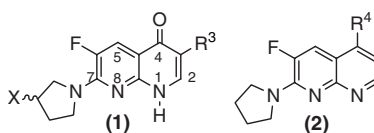
Peter Grundt,* Theresa A. Kopajtic, Jonathan L. Katz and Amy Hauck Newman*



R1 = HO, RCOO, MeSO₃
R2 = CH₃, H

Novel inhibitors of bacterial protein synthesis: structure–activity relationships for 1,8-naphthyridine derivatives incorporating position 3 and 4 variants pp 3299–3302

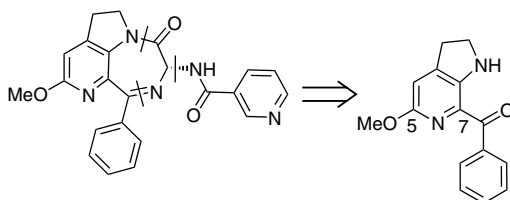
Richard F. Clark,* Sanyi Wang, Zhenkun Ma, Moshe Weitzberg, Christopher Motter, Michael Tufano, Rolf Wagner, Yu-Gui Gu, Peter J. Dandliker, Claude G. Lerner, Linda E. Chovan, Yingna Cai, Candace L. Black-Schaefer, Linda Lynch, Douglas Kalvin, Angela M. Nilius, Steve D. Pratt, Niru Soni, Tianyuan Zhang, Xiaolin Zhang and Bruce A. Beutel



New substituted triaza-benzo[*cd*]azulen-9-ones as promising phosphodiesterase-4 inhibitors

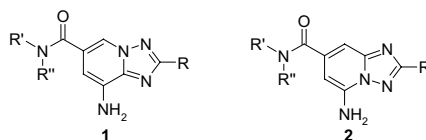
pp 3303–3306

Ingrid Devillers,* Isabelle Pevet, Henry Jacobelli, Corinne Durand, Véronique Fasquelle, Jocelyne Puaud, Bernard Gaudillière, Moulay Idrissi, François Moreau and Roger Wrigglesworth

**Comparison of inhibitory activity of isomeric triazolopyridine derivatives towards adenosine receptor subtypes or do similar structures reveal similar bioactivities?**

pp 3307–3312

Wolfgang Guba, Matthias Nettekoven,* Bernd Püllmann, Claus Riemer and Sébastien Schmitt

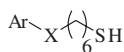


The hydrogen bond donor and acceptor strengths of two arrays of isomeric triazolopyridines derivatives **1** and **2** was analysed and compared to their affinities towards adenosine receptor subtypes.

Thiol-based SAHA analogues as potent histone deacetylase inhibitors

pp 3313–3317

Takayoshi Suzuki,* Akiyasu Kouketsu, Azusa Matsuura, Arihiro Kohara, Shin-ichi Ninomiya, Kohfuku Kohda and Naoki Miyata*



6 : Ar = Ph, X = -NHCO-

17: Ar = 3-biphenyl, X = -NHCO-

21: Ar = 3-quinoline, X = -NHCO-

24: Ar = 2-naphthalene, X = -CONH-

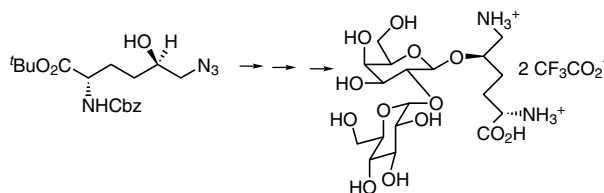
25: Ar = 2-benzofuran, X = -CONH-

A series of thiol-based SAHA analogues was designed and synthesized. Compound **6**, in which the hydroxamic acid of SAHA was replaced by a thiol, was found to be as potent as SAHA, and optimization of this series led to the identification of HDAC inhibitors (**17**, **21**, **24**, and **25**) more potent than SAHA.

The first synthesis of glucosylgalactosyl hydroxylysine (Glu-Gal-Hyl) an important biological indicator of collagen turnover

pp 3319–3321

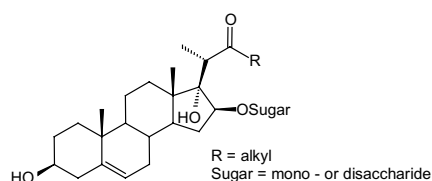
Pietro Allevi,* Mario Anastasia, Rita Paroni and Andrea Ragusa



Synthesis of analogues of a potent antitumor saponin OSW-1

pp 3323–3326

Jacek W. Morzycki,* Agnieszka Wojtkielewicz and Sławomir Wołczyński

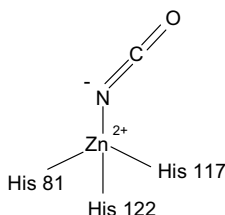


A number of analogues of a potent antitumor saponin OSW-1 were synthesized and tested for cytotoxicity.

Carbonic anhydrase inhibitors. Inhibition of the zinc and cobalt γ -class enzyme from the archaeon *Methanosarcina thermophila* with anions

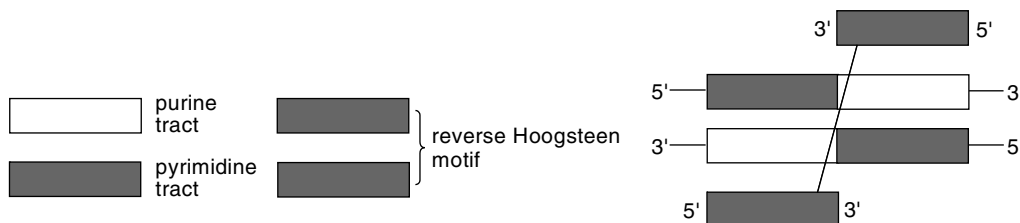
pp 3327–3331

Alessio Innocenti, Sabrina Zimmerman, James G. Ferry, Andrea Scozzafava and Claudiu T. Supuran*

**Nucleosides and nucleotides. Part 226: Alternate-strand triple-helix formation by 3'-3'-linked oligodeoxynucleotides composed of asymmetrical sequences**

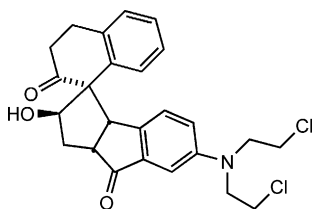
pp 3333–3336

Shuichi Hoshika, Yoshihito Ueno, Hiroyuki Kamiya and Akira Matsuda*

**Preparation of alkylation agents for bulged DNA microenvironments**

pp 3337–3339

Farid S. Fouad, Zhen Xi, Irving H. Goldberg and Graham B. Jones*

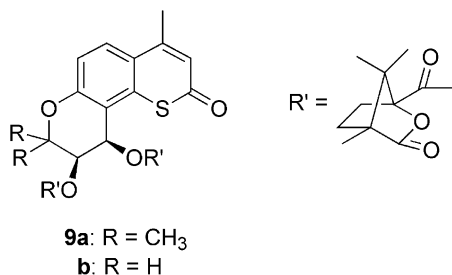


A spirocyclic agent equipped with alkylative functionality was prepared and demonstrated its ability to alkylate specific bulged sequences in a hairpin oligonucleotide substrate.

Anti-AIDS agents. Part 58: Synthesis and anti-HIV activity of 1-thia-di-*O*-(–)-camphanoyl-(+)-*cis*-khellactone (1-thia-DCK) analogues

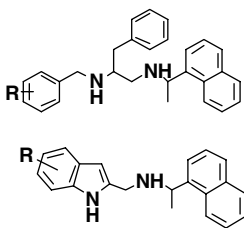
pp 3341–3343

Peng Xia,* Zhi-Jian Yin, Ying Chen, Qian Zhang, Beina Zhang, Yi Xia, Zheng-Yu Yang, Nicole Kilgore, Carl Wild, Susan L. Morris-Natschke and Kuo-Hsiung Lee*


***N*²-Benzyl-*N*¹-(1-(1-naphthyl)ethyl)-3-phenylpropane-1,2-diamines and conformationally restrained indole analogues: development of calindol as a new calcimimetic acting at the calcium sensing receptor**

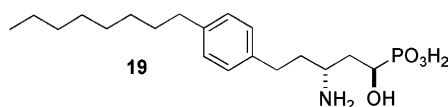
pp 3345–3349

Albane Kessler, Hélène Faure, Christophe Petrel, Martial Ruat, Philippe Dauban* and Robert H. Dodd*


Potent S1P receptor agonists replicate the pharmacologic actions of the novel immune modulator FTY720

pp 3351–3355

Jeffrey J. Hale,* William Neway, Sander G. Mills, Richard Hajdu, Carol Ann Keohane, Mark Rosenbach, James Milligan, Gan-Ju Shei, Gary Chrebet, James Bergstrom, Deborah Card, Gloria C. Koo, Sam L. Koprak, Jesse J. Jackson, Hugh Rosen and Suzanne Mandala

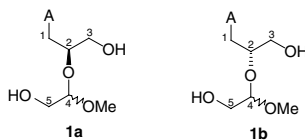


The in vitro and in vivo properties of **19** support a connection between S1P receptor agonism and immunosuppressive efficacy.

A new approach to the synthesis of optically active alkylated adenine derivatives

pp 3357–3360

N. F. Zakirova,* A. V. Shipitsyn, E. F. Belanov and M. V. Jasko




A new synthesis of chiral acyclic nucleoside and nucleotide analogues starting from D(–)- or L(+)-ribose was proposed. Antiviral properties of the synthesized compounds towards a pox virus family were evaluated.

OTHER CONTENTS

Corrigendum	p 3361
Corrigendum	p 3363
Contributors to this issue	pp I–III
Instructions to contributors	pp V–VIII

*Corresponding author

+ Supplementary data available via ScienceDirect

COVER

Cover figure provided by **Indraneel Ghosh**, Department of Chemistry, University of Arizona. The cover depicts the **Dual Surface Selection** methodology developed by the author: the blue helix of htBI (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htBI (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1389].



Full text of this journal is available, on-line from **ScienceDirect**. Visit www.sciencedirect.com for more information.

**CONTENTS
Direct**

This journal is part of **ContentsDirect**, the *free* alerting service which sends tables of contents by e-mail for Elsevier books and journals. You can register for **ContentsDirect** online at: <http://contentsdirect.elsevier.com>

Indexed/Abstracted in: Adis LMS Drug Alerts, Beilstein, Biochemistry & Biophysics Citation Index, BIOSIS previews, CAB Abstracts, CAB Health, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/Elsevier BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE



ISSN 0960-894X