

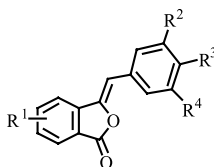
Contents

ARTICLES

Anxiolytic effects of benzalphthalides

pp 3483–3486

Alejandro Zamilpa, Maribel Herrera-Ruiz, Esther del Olmo,* José L. López-Pérez,
Jaime Tortoriello* and Arturo San Feliciano

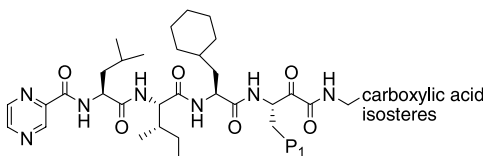


The anxiolytic activities of 12 benzalphthalides have been evaluated in the elevated plus maze test in mice. Two compounds showed significant activity.

Investigation of glycine α -ketoamide HCV NS3 protease inhibitors: Effect of carboxylic acid isosteres

pp 3487–3490

Wei Han,* Xiangjun Jiang, Zilun Hu, Zeld R. Wasserman and Carl P. Decicco



A series of tetrapeptide-based α -ketoamides with acid isosteres, such as tetrazole, sulfonic acid, and *N*-sulfonylcarboxamids, as prime groups were designed, synthesized, and evaluated as HCV NS3 protease inhibitors. Potent inhibitors with IC_{50} of 0.02–0.060 μ M were identified.

BCUT descriptors for predicting affinity toward A_3 adenosine receptors

pp 3491–3495

Maykel Pérez González,* Carmen Terán, Marta Teijeira,
Pedro Besada and Maria J. González-Moa

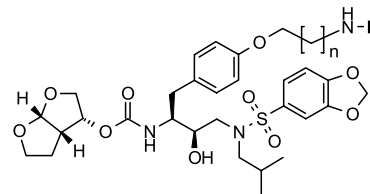
The BCUT approach has been applied to the study of the A_3 adenosine receptor agonist effect with excellent results. Four different approaches failed to give satisfactory models for this property.



Novel P1 chain-extended HIV protease inhibitors possessing potent anti-HIV activity and remarkable inverse antiviral resistance profiles pp 3496–3500

John F. Miller,* Michael Brieger, Eric S. Furfine, Richard J. Hazen, Istvan Kaldor, David Reynolds, Ronald G. Sherrill and Andrew Spaltenstein

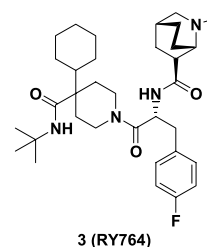
A novel series of tyrosine-derived HIV protease inhibitors was synthesized and evaluated for in vitro antiviral activity against wild-type virus and two protease inhibitor-resistant viruses. All of the compounds had wild-type antiviral activities that were similar to or greater than several currently marketed HIV protease inhibitors. In addition, a number of compounds in this series were more potent against the drug-resistant mutant viruses than they were against wild-type virus.



Discovery and activity of (1*R*,4*S*,6*R*)-*N*-[(1*R*)-2-[4-cyclohexyl-4-[(1,1-dimethylethyl)amino]carbonyl]-1-piperidinyl]-1-[(4-fluorophenyl)methyl]-2-oxoethyl]-2-methyl-2-azabicyclo[2.2.2]octane-6-carboxamide (3, RY764), a potent and selective melanocortin subtype-4 receptor agonist pp 3501–3505

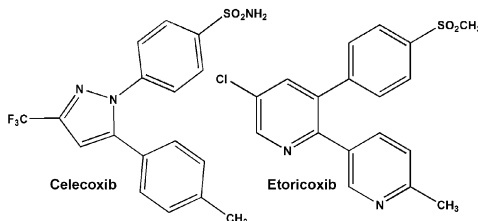
Zhixiong Ye,* Liangqin Guo, Khaled J. Barakat, Patrick G. Pollard, Brenda L. Palucki, Iyassu K. Sebbat, Raman K. Bakshi, Rui Tang, Rubana N. Kalyani, Aurawan Vongs, Airu S. Chen, Howard Y. Chen, Charles I. Rosenblum, Tanya MacNeil, David H. Weinberg, Qianping Peng, Constantin Tamvakopoulos, Randy R. Miller, Ralph A. Stearns, Doreen E. Cashen, William J. Martin, Joseph M. Metzger, Alison M. Strack, D. Euan MacIntyre, Lex H. T. Van der Ploeg, Arthur A. Patchett, Matthew J. Wyvratt and Ravi P. Nargund

A novel isoquinuclidine containing selective melanocortin subtype-4 receptor small molecule agonist, **3** (RY764), is reported. Its in vivo characterization revealed mechanism-based food intake reduction and erectile activity augmentation in rodents.



The molecular basis for coxib inhibition of p38 α MAP kinase pp 3506–3509

Gilberto M. Sperandio da Silva, Lidia M. Lima, Carlos A. M. Fraga, Carlos M. R. Sant'Anna and Eliezer J. Barreiro*



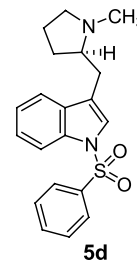
This work describes the theoretical basis of the p38 MAP kinase inhibition promoted by selective COX-2 inhibitors celecoxib and etoricoxib.



Interaction of chiral MS-245 analogs at h5-HT₆ receptors pp 3510–3513

Carmen Abate, Renata Kolanos, Malgorzata Dukat, Vince Setola, Bryan L. Roth and Richard A. Glennon*

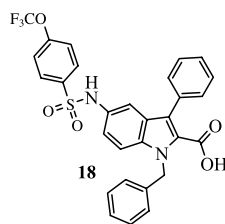
Chiral analogs of the 5-HT₆ ligand MS-245 (K_i ca. 2 nM) were examined; for example, **5d** (K_i = 0.3 nM) binds with higher affinity than its *S*-enantiomer (K_i = 1.7 nM), and with 30 times greater affinity than its counterpart lacking the benzenesulfonyl group.



Synthesis and SAR of 2-carboxylic acid indoles as inhibitors of plasminogen activator inhibitor-1

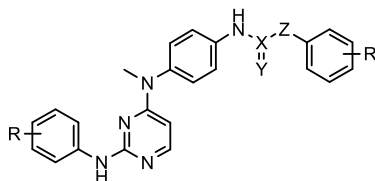
pp 3514–3518

Baihua Hu,* James W. Jetter, Jay E. Wrobel, Thomas M. Antrilli, Jean S. Bauer, Li Di, Sergiusz Polakowski, Uday Jain and David L. Crandall

**Discovery of a novel and potent series of dianilinopyrimidineurea and urea isostere inhibitors of VEGFR2 tyrosine kinase**

pp 3519–3523

Douglas M. Sammond,* Kristen E. Nailor, James M. Veal, Robert T. Nolte, Liping Wang, Victoria B. Knick, Sharon K. Rudolph, Anne T. Truesdale, Eldridge N. Nartey, Jeffrey A. Stafford, Rakesh Kumar and Mui Cheung

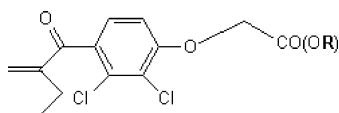


A series of dianilinopyrimidineureas show potency as VEGFR2 kinase inhibitors.

**Novel antiglaucoma prodrugs and codrugs of ethacrynic acid**

pp 3524–3527

Grazyna Cynkowska, Tadeusz Cynkowski, Abeer A. Al-Ghananeem, Hong Guo, Paul Ashton and Peter A. Crooks*

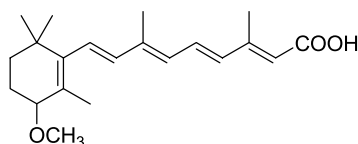


The purpose of this study was to synthesize a novel prodrug of ethacrynic acid (ECA) with short chain polyethylene glycols and codrugs of ECA with the β -adrenergic blocking agent atenolol or timolol to overcome the adverse effects of ECA and to enhance its physicochemical properties.

Impurity analysis of retinoic acid samples

pp 3528–3531

Gianna Allegrone, Elisabetta Brenna,* Giovanni Fronza, Claudio Fuganti, Tommaso Giovenzana, Luciana Malpezzi, Enrico Barlocchi and Cesare Pellegatta

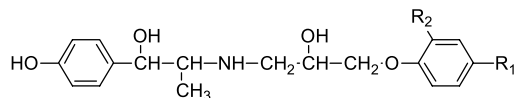


Impurity found in commercial tretinoin samples.

Design, synthesis and evaluation of racemic 1-(4-hydroxyphenyl)-2-[3-(substituted phenoxy)-2-hydroxy-1-propyl]amino-1-propanol hydrochlorides as novel uterine relaxants

pp 3532–3535

C. L. Viswanathan,* M. M. Kodgule and A. S. Chaudhari

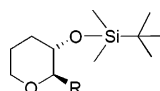


The design, synthesis and evaluation of racemic 1-(4-hydroxyphenyl)-2-[3-(substituted phenoxy)-2-hydroxy-1-propyl]amino-1-propanol hydrochlorides as novel uterine relaxants is reported.

The *tert*-butyl dimethyl silyl group as an enhancer of drug cytotoxicity against human tumor cells

pp 3536–3539

Osvaldo J. Donadel, Tomás Martín, Víctor S. Martín, Jesús Villar and José M. Padrón*

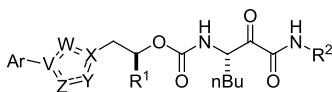
Gl₅₀ = 6–86 μ M

The synthesis of enantiomerically pure (2*R*,3*S*)-disubstituted tetrahydropyrans and their in vitro activity against HL60 promyelocytic leukemia cells and MCF7 breast cancer cells are reported. A structure–activity relationship is discussed.

P²–P³ conformationally constrained ketoamide-based inhibitors of cathepsin K

pp 3540–3546

David G. Barrett, Virginia M. Boncek, John G. Catalano, David N. Deaton,* Anne M. Hassell, Cynthia H. Jurgensen, Stacey T. Long, Robert B. McFadyen, Aaron B. Miller, Larry R. Miller, J. Alan Payne, John A. Ray, Vicente Samano, Lisa M. Shewchuk, Francis X. Tavares, Kevin J. Wells-Knecht, Derril H. Willard Jr., Lois L. Wright and Hui-Qiang Q. Zhou

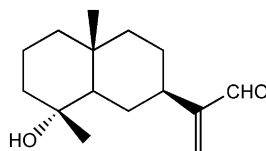


An orally bioavailable series of ketoamide-based cathepsin K inhibitors with good pharmacokinetic properties has been identified. Starting from a potent inhibitor endowed with poor drug properties, conformational constraint of the P²–P³ linker and modifications to P^{1'} elements led to an enhancement in potency, solubility, clearance, and bioavailability. These optimized inhibitors attenuated bone resorption in a rat TPTX hypocalcemic bone resorption model.

Gastric cytoprotective activity of ilicic aldehyde: Structure–activity relationships

pp 3547–3550

Osvaldo J. Donadel,* Eduardo Guerreiro, Alejandra O. María, Graciela Wendel, Ricardo D. Enriz, Oscar S. Giordano and Carlos E. Tonn

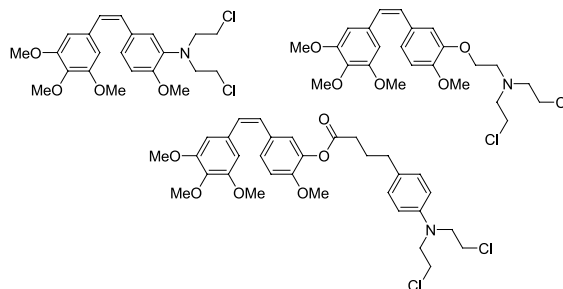


UI: 0.20 \pm 0.12
DI: 96%

A series of sesquiterpene compounds possessing both eudesmane and eremophilane skeletons were tested as gastric cytoprotective agents on rats.

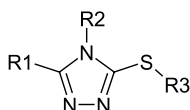
Synthesis and biological activity of mustard derivatives of combretastatins

pp 3551–3554

Beatrice Coggiola, Francesca Pagliai, Gianna Allegrone,
Armando A. Genazzani and Gian Cesare Tron***3-Thio-1,2,4-triazoles, novel somatostatin sst₂/sst₅ agonists**

pp 3555–3559

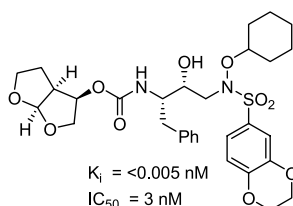
Marie-Odile Contour-Galcéra,* Alban Sidhu, Pascale Plas and Pierre Roubert



Novel 3-thio-1,2,4-triazoles have been obtained via a solution-phase parallel synthesis strategy, affording potent non-peptidic human somatostatin receptor subtypes 2 and 5 agonists.

Synthesis and antiviral activities of novel *N*-alkoxy-arylsulfonamide-based HIV protease inhibitors

pp 3560–3564

Ronald G. Sherrill,* Eric S. Furfine, Richard J. Hazen, John F. Miller, David J. Reynolds,
Douglas M. Sammond, Andrew Spaltenstein, Pat Wheelan and Lois L. Wright

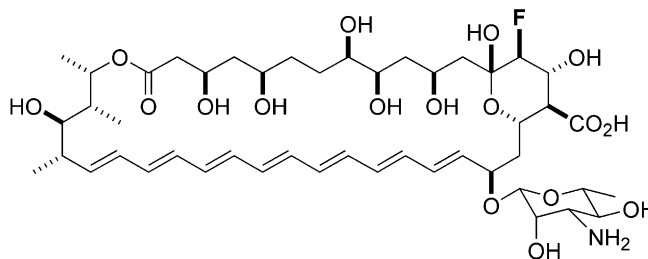
A series of novel *N*-alkoxy-arylsulfonamide HIV protease inhibitors with low picomolar enzyme activity and single digit nanomolar antiviral activity is disclosed.

Bioactive fluorinated derivative of amphotericin B

pp 3565–3567

Nobuaki Matsumori, Yuichi Umegawa, Tohru Oishi and Michio Murata*

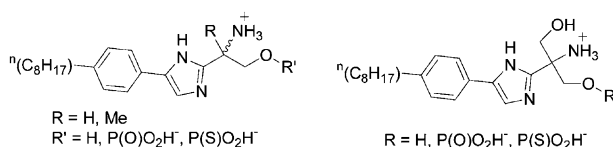
The first stably fluorinated analogue of the antifungal polyene macrolide amphotericin B has been prepared taking into account biological and ion-channel activities similar to those of the original compound.



**Synthesis of 4(5)-phenylimidazole-based analogues of sphingosine-1-phosphate and FTY720:
Discovery of potent S1P₁ receptor agonists**

pp 3568–3572

Jeremy J. Clemens,* Michael D. Davis, Kevin R. Lynch and Timothy L. Macdonald

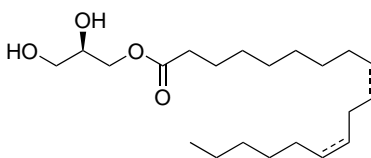


We report the syntheses, potencies and efficacies of several selective S1P receptor agonists.

Lp-PLA₂ inhibitory activities of fatty acid glycerols isolated from *Saururus chinensis* roots

pp 3573–3575

Woo Song Lee, Mi Jeong Kim, Young-Il Beck, Yong-Dae Park and Tae-Sook Jeong*



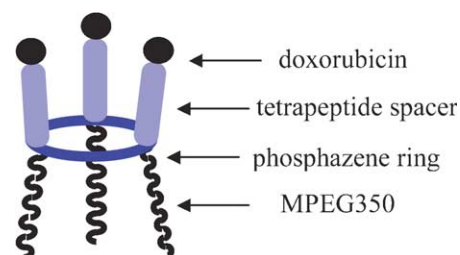
(*R*)-Glycerol-monolinoleate **4** and (*R*)-glycerol-monostearate **5** were isolated from the ethyl acetate extracts of *Saururus chinensis* roots and (*R*)- or (*S*)-fatty acid glycerols **4** and **5** were synthesized for evaluating their inhibitory activities against Lp-PLA₂.

**A macromolecular prodrug of doxorubicin conjugated
to a biodegradable cyclotriphosphazene bearing a tetrapeptide**

pp 3576–3579

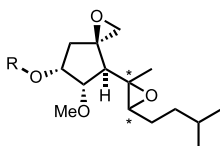
Jin Kyu Kim, Udaya S. Toti, Rita Song* and Youn Soo Sohn*

A new biodegradable water-soluble phosphazene trimer–doxorubicin conjugate was synthesized and exhibited lower than free doxorubicin ($\text{IC}_{50} = 0.10 \mu\text{M}$) but reasonably high in vitro cytotoxicity ($\text{IC}_{50} = 1.1 \mu\text{M}$) against the leukemia L1210 cell line.


Total synthesis and antiangiogenic activity of cyclopentane analogues of fumagillol

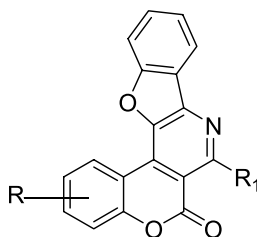
pp 3580–3583

Byeong-Seon Jeong, Nam Song Choi, Soon Kil Ahn,* Hoon Bae, Hak Sung Kim and Deukjoon Kim



Synthesis and biological evaluation of novel angularly fused polycyclic coumarins

pp 3584–3587

Imtyaz A. Khan, Manohar V. Kulkarni,* M. Gopal,
M. S. Shahabuddin and Chung-Ming Sun*

Novel angularly fused pentacyclic heterocycles with coumarin and benzofuran fused to the pyridine ring were synthesized and show promising anti-inflammatory activities.

Neuroprotective effects of naturally occurring biflavonoids

pp 3588–3591

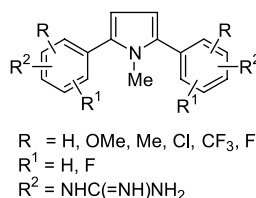
Sam Sik Kang, Ji Yeon Lee, Yoo Keum Choi, Sun Sook Song, Ju Sun Kim,
Su Jin Jeon, Yong Nam Han, Kun Ho Son and Byung Hee Han*

We examined the neuroprotective effects of naturally occurring biflavonoids on oxidative stress-induced and amyloid β peptide-induced cell death in neuronal cells. Among the nine biflavonoids tested, amentoflavone, ginkgetin, and isoginkgetin exhibited strong neuroprotection against cytotoxic insults induced by oxidative stress and amyloid β , suggesting their therapeutic potential against neurodegenerative diseases, including ischemic stroke and Alzheimer's disease.

Synthesis of some diguanidino 1-methyl-2,5-diaryl-1H-pyrroles as antifungal agents

pp 3592–3595

Gour Hari Jana, Sanjay Jain, Sudershan K. Arora and Neelima Sinha*

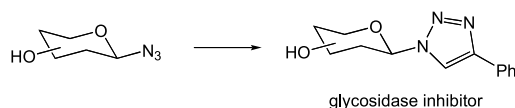


The design, synthesis, and antifungal activity profile of a series of novel 2,5-bis(guanidino-aryl)-1-methyl-1H-pyrroles are discussed.

Glycosidase inhibition by 1-glycosyl-4-phenyl triazoles

pp 3596–3599

Lauren L. Rossi and Amit Basu*

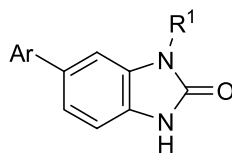


Glycosyl triazoles have been prepared by a 'click' reaction between glycosyl azides and alkynes. These triazoles are inhibitors of β -galactosidases from *Escherichia coli* and bovine liver.

SAR studies of 6-aryl-1,3-dihydrobenzimidazol-2-ones as progesterone receptor antagonists

pp 3600–3603

Eugene A. Terefenko, Jeffrey Kern, Andrew Fensome, Jay Wrobel, Yuan Zhu, Jeffrey Cohen, Richard Winneker, Zhiming Zhang and Puwen Zhang*

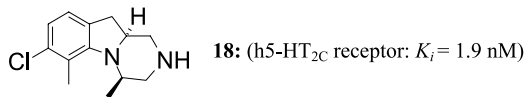


6-Aryl benzimidazol-2-ones showed progesterone receptor (PR) antagonist activity with a selection of aryl and R¹ groups examined. Prudent choice of aryl and R¹ groups led to potent PR antagonists in the T47D alkaline phosphatase assay.

Identification of 4-methyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indoles as 5-HT_{2C} receptor agonists

pp 3604–3608

S. Röver,* D. R. Adams, A. Bénardeau, J. M. Bentley, M. J. Bickerdike, A. Bourson, I. A. Cliffe, P. Coassolo, J. E. P. Davidson, C. T. Dourish, P. Hebeisen, G. A. Kennett, A. R. Knight, C. S. Malcolm, P. Mattei, A. Misra, J. Mizrahi, M. Muller, R. H. P. Porter, H. Richter, S. Taylor and S. P. Vickers

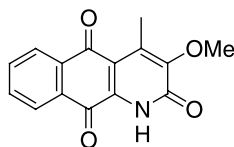


New 4-methyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indoles are 5-HT_{2C} receptor agonists. Appropriately substituted, several analogs show high potency and appreciable selectivity against the other 5-HT₂ receptor subtypes.

Concise synthesis and voltammetric studies of dielsiquinone, a cytotoxic azaanthraquinone

pp 3609–3610

Anne Brisach-Wittmeyer, Abdelkarim Sani Souana Sido, Pauline Guilini and Laurent Désaubry*

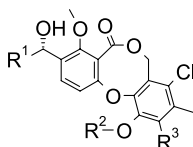


Electrochemical studies have shown that dielsiquinone is reduced to a semiquinone radical that does not react with O₂ and may therefore provide the basis for the development of safer anticancer drugs.

Dibenzodioxocinones—A new class of CETP inhibitors

pp 3611–3614

David Brückner, Frank-Thorsten Hafner, Volkhart Li, Carsten Schmeck, Joachim Telser,* Alexandros Vakalopoulos and Gabriele Wirtz

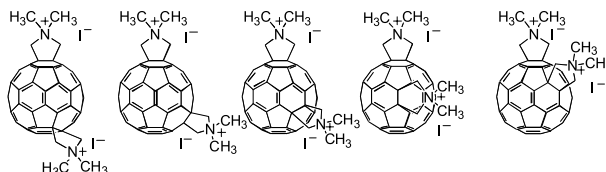


Dibenzodioxocinones with high inhibitory potential for CETP and good plasma stability were prepared by semisynthesis from a natural product precursor.

Anti-HIV properties of cationic fullerene derivatives

pp 3615–3618

Silvia Marchesan, Tatiana Da Ros,* Giampiero Spalluto, Jan Balzarini and Maurizio Prato

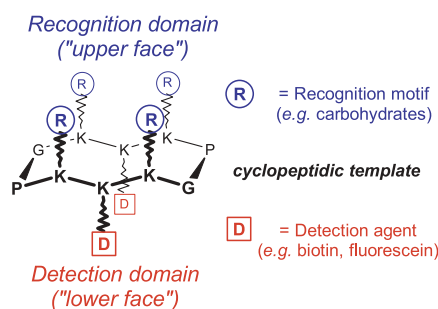


A series of regioisomeric bis-fulleropyrrolidines bearing two ammonium groups have been synthesized and their activities against HIV-1 and HIV-2 have been evaluated. Two trans isomers have been endowed with interesting antiviral properties, confirming the importance of relative positions of the substituent on a C₆₀ cage. In addition, reduced amphiphilicity of the molecules to other compounds previously reported decreases their cytotoxicity in CEM cell cultures. None of the compounds showed any inhibitory activity against a variety of DNA and RNA viruses other than HIV.

Synthesis of multitopic neoglycopeptides displaying recognition and detection motifs

pp 3619–3622

Olivier Renaudet and Pascal Dumy*

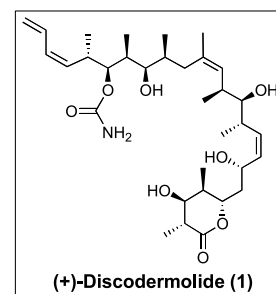


The synthesis of cyclodecapeptidic template displaying clustered carbohydrates for recognition and probes for detection is reported as a tool for glycomic research.

Discodermolide analogues as the chemical component of combination bacteriolytic therapy

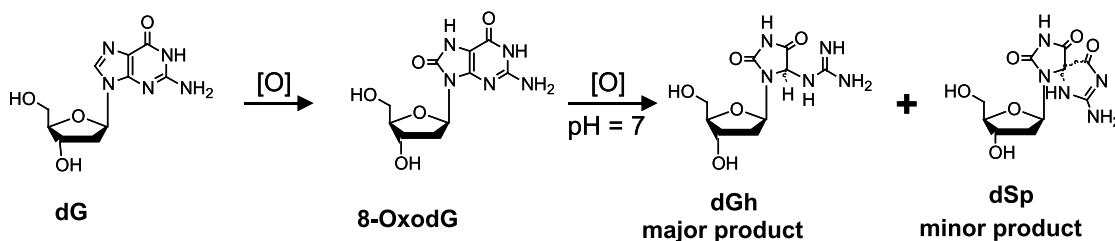
pp 3623–3626

Amos B. Smith III,* B. Scott Freeze, Matthew J. LaMarche, Jason Sager, Kenneth W. Kinzler and Bert Vogelstein*

**Hydantoin derivative formation from oxidation of 7,8-dihydro-8-oxo-2'-deoxyguanosine (8-oxodG) and incorporation of ¹⁴C-labeled 8-oxodG into the DNA of human breast cancer cells**

pp 3627–3631

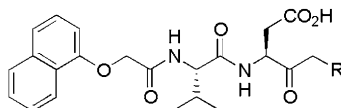
Sang Soo Hah, Hyung M. Kim, Rhoda A. Sumbad and Paul T. Henderson*



Structure–activity relationships within a series of caspase inhibitors. Part 2: Heterocyclic warheads

pp 3632–3636

Brett R. Ullman,* Teresa Aja, Ning Chen, Jose-Luis Diaz, Xin Gu, Julia Herrmann, Vincent J. Kalish, Donald S. Karanewsky, Lalitha Kodandapani, Joseph J. Krebs, Steven D. Linton, Steven P. Meduna, Kip Nalley, Edward D. Robinson, Silvio P. Roggo, Robert O. Sayers, Albert Schmitz, Robert J. Ternansky, Kevin J. Tomaselli and Joe C. Wu

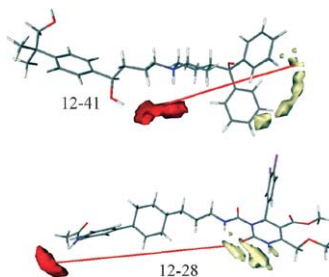


Various heterocyclic hetero-methyl ketones of the 1-naphthoxyacetyl-Val-Asp backbone have been prepared. A study of their structure–activity relationship (SAR) related to caspase-1, -3, -6, and -8 is reported. Their efficacy in a cellular model of cell death is also discussed. Potent broad-spectrum caspase inhibitors have been identified.

Predictive models for hERG potassium channel blockers

pp 3637–3642

Giovanni Cianchetta, Yi Li, Jiesheng Kang, David Rampe, Arnaldo Fravolini, Gabriele Cruciani and Roy J. Vaz*



Computational QSAR models constructed from pharmacophore-based GRIND descriptors were found to be predictive for hERG channel blockers.

**OTHER CONTENTS**

Contributors to this issue
Instructions to contributors

pp I–II
pp III–VI

*Corresponding author

Supplementary data available via ScienceDirect

COVER

Active site of the X-ray co-crystal structure of compound **60** complexed with cathepsin K. The cathepsin K carbons are colored magenta with inhibitor **60** carbons colored cyan. The semi-transparent white surface represents the molecular surface, while hydrogen bonds are depicted as yellow dashed lines. The coordinates have been deposited in the Brookhaven Protein Data Bank, Accession No. 1YT7. This figure was generated using PYMOL version 0.97 (Delano Scientific, www.pymol.org). [Barrett, D. G.; Boncek, V. M.; Catalano, J. G.; Deaton, D. N.; Hassell, A. M.; Jurgensen, C. H.; Long, S. T.; McFadyen, R. B.; Miller, A. B.; Miller, L. R.; Payne, J. A.; Ray, J. A.; Samano, V.; Shewchuk, L. M.; Tavares, F. X.; Wells-Knecht, K. J.; Willard, D. H. Jr.; Wright, L. L.; Zhou, H.-Q. Q. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2540.]

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIODISE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

