

Special Section: Symposium-in-Print

Neuronal Nicotinic Receptors and Ligands

Guest Editors: Rao S. Rapaka and William A. Corrigan

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6001 Executive Blvd, Bethesda, MD 20892, USA*

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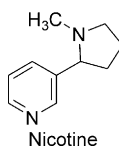
Bioorganic & Medicinal Chemistry Letters Symposia-in-Print	p 1833
Preface	p 1835

SYMPOSIUM-IN-PRINT COMMUNICATIONS

Potential applications of nicotinic ligands in the laboratory and clinic	pp 1837–1839
J. A. Dani,* M. De Biasi, Y. Liang, J. Peterson, L. Zhang, T. Zhang and F. M. Zhou	

There are many different nicotinic acetylcholine receptor subtypes constructed from a variety of different subunit combinations. This extensive diversity offers an excellent opportunity for chemists who are producing nicotinic ligands. Subunit specific ligands could have wide and varied effects in the laboratory as experimental tools and in the clinic as therapeutic agents.

$\alpha 4\beta 2$ nACh Receptor pharmacophore models	pp 1841–1844
Richard A. Glennon* and Małgorzata Dukat	



Progress towards the development of $\alpha 4\beta 2$ nicotinic acetylcholinergic (nACh) receptor pharmacophores is reviewed from the early Beers and Riech model to the more recent vector models.

Pharmacology of the agonist binding sites of rat neuronal nicotinic receptor subtypes expressed in HEK 293 cells

pp 1845–1848

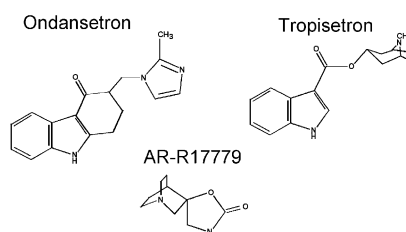
Yingxian Xiao, Maryna Baydyuk, Haizhu (Pearl) Wang, Heather E. Davis and Kenneth J. Kellar*

The binding affinities of agonists at heteromeric nicotinic receptors composed of rat $\alpha 2$, $\alpha 3$ and $\alpha 4$ subunits in combination with $\beta 2$ or $\beta 4$ subunits were examined in stably transfected HEK 293 cells. In most cases, the affinities of agonists were higher at receptors composed of an α subunit in combination with the $\beta 2$ subunit than the $\beta 4$ subunit, and in some cases this difference was quite large (> 250 times), suggesting the possibility of developing subtype-selective ligands and therapeutically useful drugs.

Activity of $\alpha 7$ -selective agonists at nicotinic and serotonin 5HT₃ receptors expressed in *Xenopus* oocytes

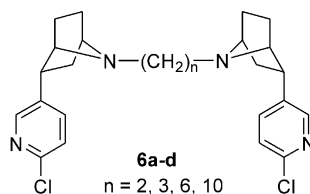
pp 1849–1853

R. L. Papke,* Julia K. Porter Papke and G. M. Rose


Synthesis and pharmacological characterization of bivalent ligands of epibatidine at neuronal nicotinic acetylcholine receptors

pp 1855–1858

Zhi-Liang Wei, Yingxian Xiao, Kenneth J. Kellar and Alan P. Kozikowski*

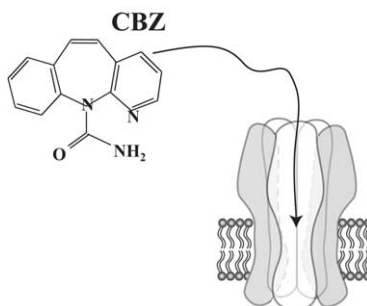


A series of bivalent ligands **6a-d** of epibatidine were synthesized and showed nanomolar binding affinities at six nAChR subtypes. In contrast to epibatidine, they are weak partial agonists at the $\alpha 3\beta 4$ nAChR as shown by functional assays.

Neuronal nicotinic receptors and epilepsy, from genes to possible therapeutic compounds

pp 1859–1861

Ronald C. Hogg and Daniel Bertrand*

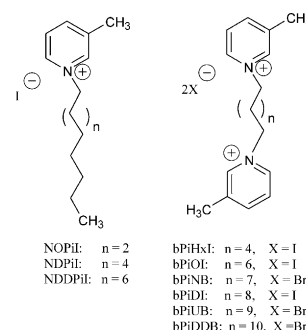


Subtype-selective nicotinic receptor antagonists: potential as tobacco use cessation agents

pp 1863–1867

Linda P. Dwoskin,* Sangeetha P. Sumithran, Jun Zhu, A. Gabriela Deaciuc, Joshua T. Ayers and Peter A. Crooks

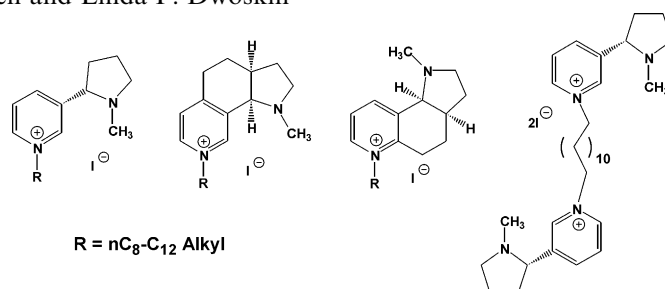
N-*n*-Alkylpicolinium and *N,N'*-alkyl-bis-picolinium analogues were assessed in nicotinic receptor (nAChR) assays. The most potent and subtype-selective analogue, *N,N'*-dodecyl-bis-picolinium bromide (bPiDDB), inhibited nAChRs mediating nicotine-evoked [³H]dopamine release (*IC*₅₀ = 5 nM; *I*_{max} of 60%), and did not interact with α4β2* or α7* nAChRs.

**Development of subtype-selective ligands as antagonists at nicotinic receptors mediating nicotine-evoked dopamine release**

pp 1869–1874

Peter A. Crooks,* Joshua T. Ayers, Rui Xu, Sangeetha P. Sumithran, Vladimir P. Grinevich, Lincoln H. Wilkins, A. Gabriela Deaciuc, David D. Allen and Linda P. Dwoskin

N-*n*-Alkylation of nicotine converts it from an agonist into an antagonist at neuronal nicotinic receptor subtypes mediating nicotine-evoked dopamine-release. Conformationally restricted analogues exhibit both high affinity and selectivity at this site and are able to access the brain due to their ability to act as substrates for the blood–brain barrier choline transporter.

**Contemporary paradigms for cholinergic ligand design guided by biological structure**

pp 1875–1877

Palmer Taylor,* Scott B. Hansen, Todd T. Talley, Ryan E. Hibbs and Zoran Radić

The identification of the various nicotinic receptor subtypes, when coupled with the recent development of three dimensional structures of surrogate extracellular receptor domains, offers new opportunities to design nicotinic ligands. Conformation and fluctuations in receptor structure are critical to ligand selectivity, and we present here how a flexible receptor template can be used in the development of selective ligands affecting cholinergic neurotransmission.

Sensitivity of neuronal nicotinic acetylcholine receptors to the opiate antagonists naltrexone and naloxone: receptor blockade and up-regulation

pp 1879–1887

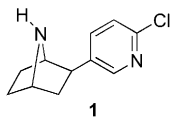
Luis E. F. Almeida, Edna F. R. Pereira, Adriana L. Camara, Alfred Maelicke and Edson X. Albuquerque*

In HEK293 cells stably expressing α4β2 nAChRs, naltrexone, but not naloxone, blocked α4β2 nAChRs via an open-channel blocking mechanism. In primary hippocampal cultures, naltrexone inhibited α7 nAChRs up-regulated by nicotine, and in organotypic hippocampal cultures naltrexone caused a time-dependent up-regulation of functional α7 nAChRs that was detected after removal of the drug. These results indicate that naltrexone could be used as a smoking cessation aid.

Epibatidine structure–activity relationships

pp 1889–1896

F. Ivy Carroll*



Epibatidine (**1**) is a potent but nonselective nAChR agonist. Its biological effects appear to be mediated largely by $\alpha 4\beta 2$ nAChRs. Surprisingly, only a limited number of epibatidine analogues have been synthesized and evaluated in in vitro assays. Even fewer analogues have received in vivo pharmacological evaluation. In this paper, SAR studies directed toward epibatidine analogues will be reviewed.

Activation and desensitization of heteromeric neuronal nicotinic receptors: implications for non-synaptic transmission

pp 1897–1900

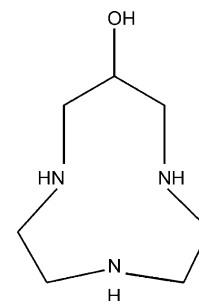
Robin A. J. Lester*

Consideration of the activation and desensitization properties of neuronal nicotinic acetylcholine receptors (nAChRs) predicts that there should be a range of concentrations over which low ambient levels of agonist can continuously open nAChR channels. These findings support the idea that postsynaptic nAChRs may participate in unconventional cellular signaling mediated by the release of acetylcholine from diffusely distributed non-synaptic cholinergic varicosities.

REGULAR COMMUNICATIONS**Nickle(II) and cobalt(II) complexes of hydroxyl-substituted triazamacrocyclic ligand as potential antitumor agents**

pp 1901–1904

Feng Liang,* Ping Wang, Xiang Zhou, Tao Li, Zhaoyan Li, Huakuan Lin, Dongzhao Gao, Congyi Zheng and Chengtai Wu*

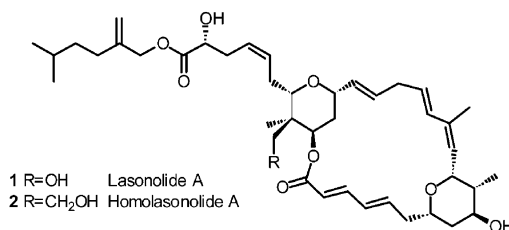


Antitumor activity evaluations of nickel and cobalt complex with triaza macrocyclic ligand were presented.

Synthesis and evaluation of lasonolide A analogues

pp 1905–1908

Jung Min Joo, Hyo Shin Kwak, Jin Hyun Park, Ho Young Song and Eun Lee*

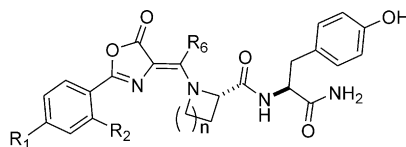


Homolasonolide A (**2**) was synthesized, and it was found that **2** was less active than lasonolide A (**1**).

Potent and selective inhibitors of bacterial methionyl tRNA synthetase derived from an oxazolone–dipeptide scaffold

pp 1909–1911

Manish Tandon, David L. Coffen, Paul Gallant, Dennis Keith and Mark A. Ashwell*

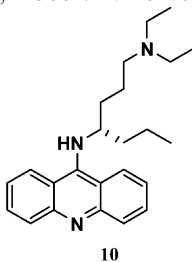


The preparation and structure–activity relationships (SARs) of potent and selective small molecule inhibitors of bacterial methionyl-tRNA synthetase (MetRS) derived from an oxazolone–dipeptide scaffold are described.

N-Acridin-9-yl-butane-1,4-diamine derivatives: high-affinity ligands of the $\alpha_2\delta$ subunit of voltage gated calcium channels

pp 1913–1916

Jongwon Lim,* Nicholas Stock, Richard Pracitto, Julia K. Boueres, Benito Munoz, Ashok Chaudhary, Angelina M. Santini, Karia Orr, Hervé Schaffhauser, Robert E. Bezverkov, Jayashree Aiyar and Shankar Venkatraman

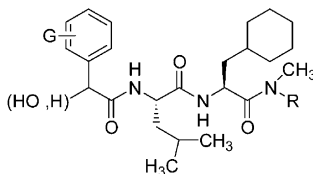


Compounds such as **10** (IC_{50} = 9 nM) are high-affinity ligands of the $\alpha_2\delta$ subunit of voltage gated calcium channels.

Hydroxytriarnides as potent γ -secretase inhibitors

pp 1917–1921

C. V. C. Prasad,* Jeffrey W. Noonan, Charles P. Sloan, Wai Lau, Shikha Vig, Michael F. Parker, David W. Smith, Steven B. Hansel, Craig T. Polson, Donna M. Barten, Kevin M. Felsenstein and Susan B. Roberts

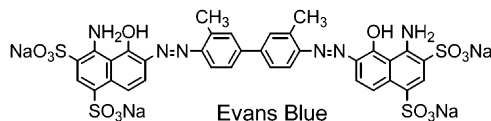


Structure–activity relationships of γ -secretase inhibitors are reported.

Evans Blue and other dyes as protein tyrosine phosphatase inhibitors

pp 1923–1926

Suja Shrestha, Yi Sup Shim, Ki Chul Kim, Keun-Hyeung Lee and Hyeongjin Cho*

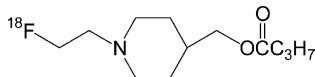


Commonly used dyes including Evans Blue and Trypan Blue were found to inhibit protein tyrosine phosphatases. Of the 13 dyes tested, four exhibited IC_{50} of less than 10 μ M, with Evans Blue lowest IC_{50} of 1.3 μ M against PTP1B.

***N*-[¹⁸F]fluoroethylpiperidin-4-ylmethyl butyrate: a novel radiotracer for quantifying brain butyrylcholinesterase activity by positron emission tomography**

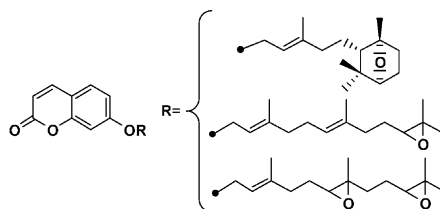
pp 1927–1930

Tatsuya Kikuchi, Ming-Rong Zhang, Nobuo Ikota, Kiyoshi Fukushi, Toshimitsu Okamura, Kazutoshi Suzuki, Yasushi Arano and Toshiaki Irie*


Farnesyloxycoumarins, a new class of squalene-hopene cyclase inhibitors

pp 1931–1934

Giancarlo Cravotto,* Gianni Balliano, Bruna Robaldo, Simonetta Oliaro-Bosso, Stefano Chimichi and Marco Boccalini

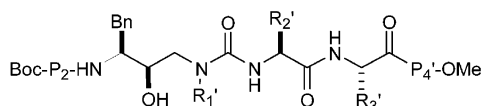


The coumarin core proved a good starting structure for the design of new SHC inhibitors. An epoxide function at the end of the prenyl chain increased the inhibitory effect, revealing a critical detail for molecular recognition.

Probing pockets S2–S4' of the γ -secretase active site with (hydroxyethyl)urea peptidomimetics

pp 1935–1938

William P. Esler, Chittaranjan Das and Michael S. Wolfe*

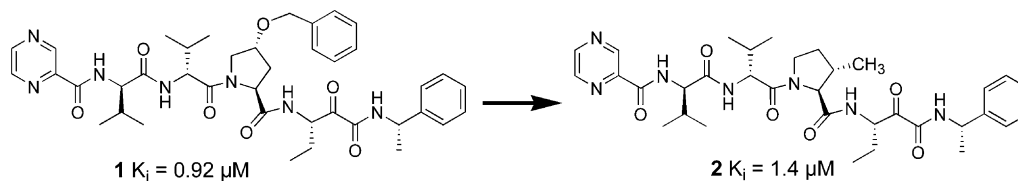


(Hydroxyethyl)urea peptidomimetics are potent inhibitors of γ -secretase that are readily accessible. Systematic alteration of P2–P4' revealed that the corresponding S2–S4' active site pockets accommodate a variety of substituents, consistent with the fact that this protease cleaves a variety of single-pass membrane proteins. A compound spanning P2–P3' was identified as a low nM inhibitor of γ -secretase activity both in cells and under cell-free conditions.

Inhibitors of hepatitis C virus NS3-4A protease. Part 3: P₂ proline variants

pp 1939–1942

Robert B. Perni,* Luc J. Farmer,* Kevin M. Cottrell, John J. Court, Lawrence F. Courtney, David D. Deininger, Cynthia A. Gates, Scott L. Harbeson, Joseph L. Kim, Chao Lin, Kai Lin, Yu-Ping Luong, John P. Maxwell, Mark A. Murcko, Janos Pitlik, B. Govinda Rao, Wayne C. Schairer, Roger D. Tung, John H. Van Drie, Keith Wilson and John A. Thomson



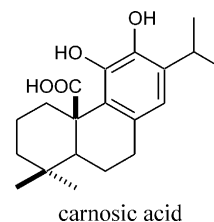
A series of potent HCV NS3-4A protease inhibitors incorporating novel 3-substituted proline moieties at the P₂ position are described.

Carnosic acid, a new class of lipid absorption inhibitor from sage

pp 1943–1946

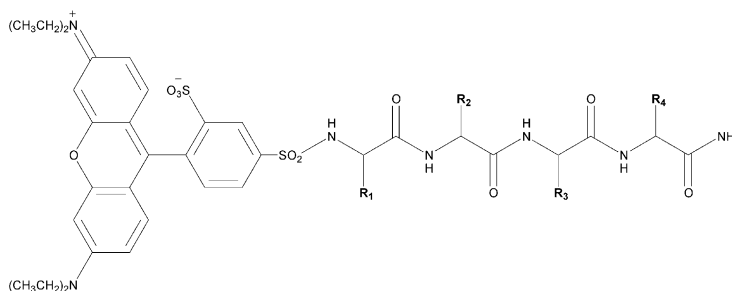
Kiyofumi Ninomiya, Hisashi Matsuda, Hiroshi Shimoda, Norihisa Nishida, Naoki Kasajima, Tomoe Yoshino, Toshio Morikawa and Masayuki Yoshikawa*

The methanolic extract from the leaves of *Salvia officinalis* L. (sage) showed significant inhibitory effect on serum triglyceride elevation in olive oil-loaded mice (500 and 1000 mg/kg, p.o.) and inhibitory activity (IC_{50} : 94 μ g/mL) against pancreatic lipase, which is participated in digestion of lipids. Through bioassay-guided separation using the inhibitory activity against pancreatic lipase activity, 4 abietan-type diterpenes (carnosic acid, carnosol, royleanonic acid, 7-methoxyrosmanol) and a triterpene (oleanolic acid) were isolated from the active fraction. Among these compounds, carnosic acid and carnosol substantially inhibited pancreatic lipase activity with IC_{50} values of 12 μ g/mL (36 μ M) and 4.4 μ g/mL (13 μ M), respectively. Carnosic acid significantly inhibited triglyceride elevation in olive oil-loaded mice at doses of 5–20 mg/kg (p.o.). However, other constituents (carnosol, royleanonic acid, oleanolic acid) did not show any effects at a dose of 200 mg/kg (p.o.). Furthermore, carnosic acid (20 mg/kg/day, p.o.) reduced the gain of body weight and the accumulation of epididymal fat weight in high fat diet-fed mice after 14 days.

**De novo identification of highly active fluorescent kappa opioid ligands from a rhodamine labeled tetrapeptide positional scanning library**

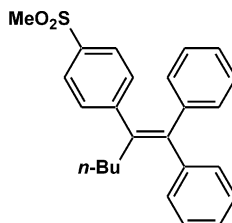
pp 1947–1951

Richard A. Houghten,* Colette T. Dooley and Jon R. Appel

**Design of acyclic triaryl olefins: a new class of potent and selective cyclooxygenase-2 (COX-2) inhibitors**

pp 1953–1956

Md. Jashim Uddin, P. N. Praveen Rao and Edward E. Knaus*



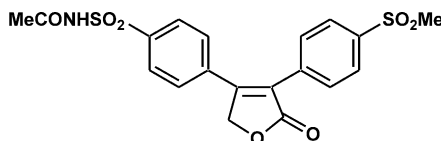
A new class of acyclic ethenes was designed from which 1,1-diphenyl-2-(4-methylsulfonylphenyl)hex-1-ene emerged as a highly potent (IC_{50} = 0.014 μ M) and selective COX-2 (selectivity index > 7142) inhibitor.

Sulfonamido, azidosulfonyl and N-acetylsulfonamido analogues of rofecoxib:

pp 1957–1960

4-[4-(N-acetylsulfonamido)phenyl]-3-(4-methanesulfonylphenyl)-2(5H)furanone is a potent and selective cyclooxygenase-2 inhibitor

Afshin Zarghi, P. N. Praveen Rao and Edward E. Knaus*

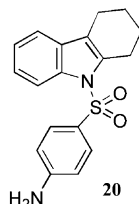


4-[4-(N-Acetylsulfonamido)phenyl]-3-(4-methanesulfonylphenyl)-2(5H)furanone, possessing a N-acetylsulfonamido pharmacophore, has been identified as a potent (IC_{50} = 0.05 μ M), and selective (S.I. > 2000), COX-2 inhibitor that has the potential to acetylate the COX-2 isozyme.

1,2,3,4-Tetrahydrocarbazoles as 5-HT₆ serotonin receptor ligands

pp 1961–1964

Jean Chang-Fong, Jagadeesh B. Rangisetty, Małgorzata Dukat, Vincent Setola, Thomas Raffay, Bryan Roth and Richard A. Glennon*

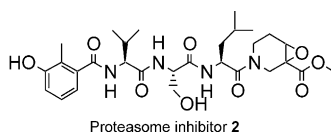


N₉-(4-Aminobenzenesulfonyl)-1,2,3,4-tetrahydrocarbazole (**20**; pA₂ = 7.0 for antagonism of cAMP hydrolysis) was demonstrated to represent a member of a novel class of 5-HT₆ receptor antagonists.

Proteasome inhibitors: synthesis and activity of arecoline oxide tripeptide derivatives

pp 1965–1968

Mauro Marastoni,* John McDonald, Anna Baldisserotto, Alessandro Canella, Carmela De Risi, Gian Piero Pollini and Roberto Tomatis

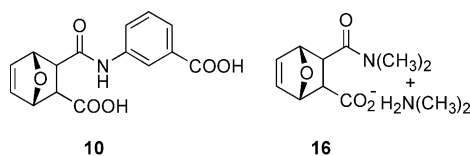


A series of C-terminal methyl 3,4-epoxypiperidine-3-carboxylate tripeptide derivatives were synthesized to evaluate their inhibitory capacity against active sites of the proteasome.

Modified norcantharidins: synthesis, protein phosphatases 1 and 2A inhibition, and anticancer activity

pp 1969–1973

Matthew E. Hart, A. Richard Chamberlin,* Cecilia Walkom, Jennette A. Sakoff and Adam McCluskey*

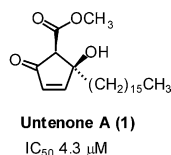


Fourteen modified norcantharidin analogues have been synthesized and screened for their ability to inhibit the serine/threonine protein phosphatases 1 and 2A. The most potent compounds found were **10** (PP1 IC₅₀ = 13 ± 5 μM; PP2A IC₅₀ = 7 ± 3 μM) and **16** (PP1 IC₅₀ = 18 ± 8 μM; PP2A IC₅₀ = 3.2 ± 0.4 μM). Overall, only analogues possessing at least one acidic residue at the former anhydride warhead displayed any PP1 or PP2A inhibitory action.

Structure–activity relationships of untenone A and its derivatives for inhibition of DNA polymerases

pp 1975–1977

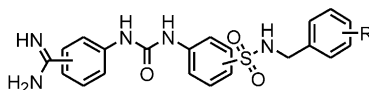
Fumiyo Saito, Ryo Takeuchi, Tomoyuki Kamino, Kouji Kuramochi, Fumio Sugawara, Kengo Sakaguchi and Susumu Kobayashi*



Sulfonyl-phenyl-ureido benzamidines: a novel structural class of potent antimalarial agents

pp 1979–1982

Johann Leban,* Stefano Pegoraro, Matthias Dormeyer, Michael Lanzer, Andrea Aschenbrenner and Bernd Kramer

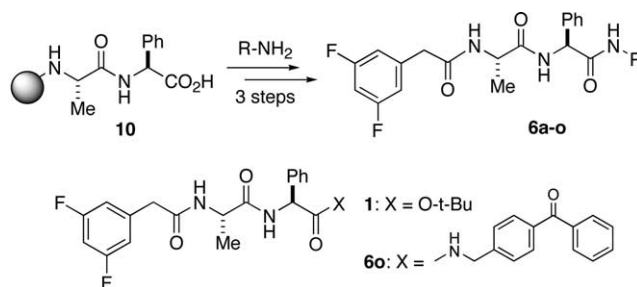


A novel structural class of antimalarial compounds was discovered. The most potent compound was more active (8 nM) in an antimalaria proliferation assay as Chloroquine (17 nM).

Parallel synthesis of DAPT derivatives and their γ -secretase-inhibitory activity

pp 1983–1985

Toshiyuki Kan, Yusuke Tominari, Kentaro Rikimaru, Yuichi Morohashi, Hideaki Natsugari, Taisuke Tomita, Takeshi Iwatsubo and Tohru Fukuyama*



Parallel synthesis of the C-terminal modified DAPT (**1**) derivatives **6a–o** was accomplished by condensation of the polymer bound *N*-acetylmethionine **10** with several amines.

Facile synthesis of metal-chelating peptides on chip for protein array

pp 1987–1990

Ching-Wen Cheng, Kuo-Chin Lin, Fu-Ming Pan, Supachok Sinchaikul, Chi-Huey Wong, Wei-Chih Su, Ching-Hsiang Hsu and Shui-Tein Chen*

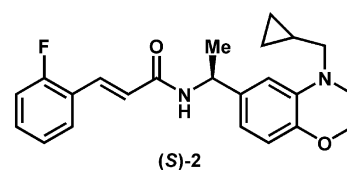
A unique peptide sequence of HGGHHG screening from a combinatorial synthetic peptide library showed a good chelating ability to bind a transition metal on a chip better than hexa-His peptide. It was directly conjugated with a His-Tagged proteins onto a chip in a mild aqueous solution and can be used this chip as a high throughput technique for protein array in order to detect and purify the His-Tagged proteins.

(*S*)-*N*-[1-(4-Cyclopropylmethyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)-ethyl]-3-(2-fluoro-phenyl)-acrylamide is a potent and efficacious KCNQ2 opener which inhibits induced hyperexcitability of rat hippocampal neurons

pp 1991–1995

Yong-Jin Wu,* Christopher G. Boissard, Jie Chen, William Fitzpatrick, Qi Gao, Valentin K. Gribkoff, David G. Harden, Huan He, Ronald J. Knox, Joanne Natale, Rick L. Pieschl, John E. Starrett, Jr., Li-Qiang Sun, Mark Thompson, David Weaver, Dedong Wu and Steven I. Dworkatzky

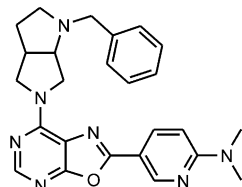
(*S*)-*N*-[1-(4-Cyclopropylmethyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)-ethyl]-3-(2-fluoro-phenyl)-acrylamide ((*S*)-**2**) was identified as a potent and efficacious KCNQ2 opener. This compound demonstrated significant activity in reducing neuronal hyperexcitability in rat hippocampal slices, and the inhibition mediated by (*S*)-**2** was reversed by the KCNQ blocker linopirdine.



Discovery and optimization of 2-aryl oxazolo-pyrimidines as adenosine kinase inhibitors using liquid phase parallel synthesis

pp 1997–2000

M. Bauser,* G. Delapierre, M. Hauswald, T. Flessner, D. D'Urso, A. Hermann, B. Beyreuther, J. De Vry, P. Spreyer, E. Reissmüller and H. Meier

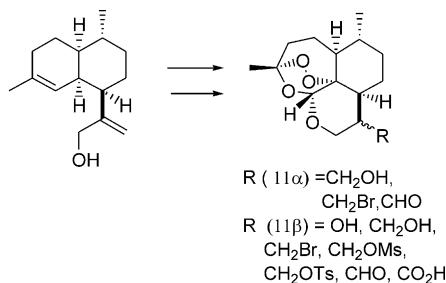


The discovery of oxazolo-pyrimidines as structurally novel adenosine kinase inhibitors is presented. High throughput derivatization of the oxazolo-pyrimidine scaffold was performed using liquid phase parallel synthesis techniques. This led to the discovery of the title compound, an adenosine kinase inhibitor with a ≤ 10 nanomolar IC_{50} value.

Antimalarial activities of (+)-deoxoartemisitenone and its novel C-11, 13 derivatives

pp 2001–2003

Mankil Jung,* Kyunghoon Lee, Hochul Jung, Howard Kendrick, Vanessa Yardley and Simon L. Croft




(+)-Deoxoartemisitenone and its C-11, 13 derivatives were synthesized from artemisinic acid via a short and regiospecific process and several derivatives show 10 to 20 times more in vitro antimalarial activities against *Plasmodium falciparum* than artemisinin.

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Instructions to contributors

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pp III–VI

*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 htB1 (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htB1 (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1389].



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