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Bioorganic & Medicinal Chemistry Volume 21, Issue 1, 2013

Contents

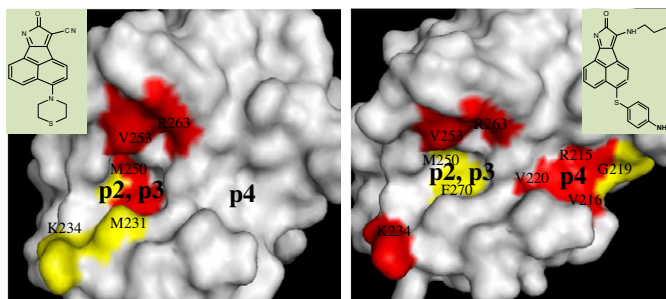
ARTICLES

3-Thiomorpholin-8-oxo-8H-acenaphtho [1,2-b] pyrrole-9-carbonitrile (S1) derivatives as pan-Bcl-2-inhibitors of Bcl-2, Bcl-x_L and Mcl-1

pp 11–20

Ting Song, Xiangqian Li, Xilong Chang, Xiaomeng Liang, Yan Zhao, Guiye Wu, Shenghui Xie, Pengchen Su, Zhiyong Wu, Yingang Feng, Zhichao Zhang*

S1 derivatives spanning p2–p4 pockets of Mcl-1, Bcl-2 and Bcl-x_L were synthesized. Compound **6d** exhibited 9- to 35-fold improved affinity toward the three targets than S1 (IC₅₀ = 10, 20 and 18 nM, respectively). Different contribution of p4 to binding Bcl-2 and Mcl-1 was investigated by plotting the potency and the HAC of the derivatives.

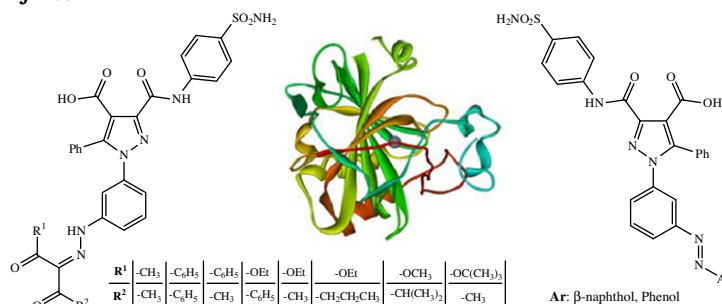


Facile synthesis and characterization of novel pyrazole-sulfonamides and their inhibition effects on human carbonic anhydrase isoenzymes

pp 21–27

Havva Balseven, M. Mustafa İşgör, Samet Mert, Zuhail Alım, Şükrü Beydemir, Salim Ok, Rahmi Kasımoğlu*

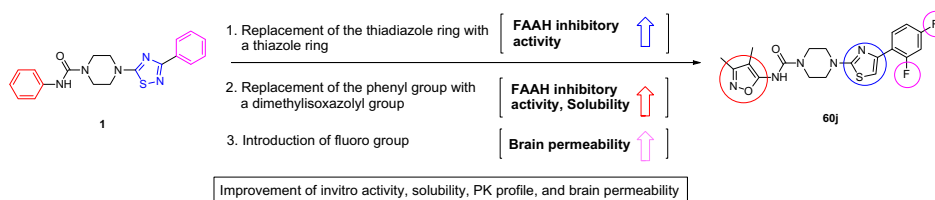
This work reports the synthesis and biological activity of new pyrazole-sulfonamides, 1-(3-substituted)-5-phenyl-3-(4-sulfamoylphenylcarbamoyl)-1H-pyrazole-4-carboxylic acid. Almost all of the compounds have good inhibition effects on the CA I and CA II isoenzymes.



Synthesis, SAR study, and biological evaluation of a series of piperazine ureas as fatty acid amide hydrolase (FAAH) inhibitors

pp 28–41

Mitsunori Kono*, Takahiro Matsumoto, Toru Kawamura, Atsushi Nishimura, Yoshihiro Kiyota, Hideyuki Oki, Junichi Miyazaki, Shigeru Igaki, Craig A. Behnke, Masato Shimojo, Masakuni Kori

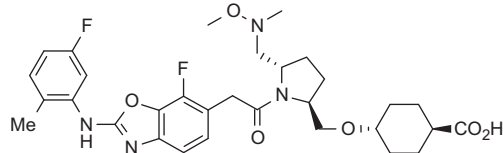


A series of piperazine ureas was designed, synthesized, and evaluated for their potential as novel orally available fatty acid amide hydrolase (FAAH) inhibitors that are therapeutically effective against pain.

A novel, potent, and orally active VLA-4 antagonist with good aqueous solubility: *trans*-4-[1-[[2-(5-Fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl]acetyl]-(5*S*)-[methoxy(methyl)amino]methyl-(2*S*)-pyrrolidinylmethoxy]cyclohexanecarboxylic acid

pp 42–61

Masaki Setoguchi*, Shin Iimura, Yuuichi Sugimoto, Yoshiyuki Yoneda, Jun Chiba, Toshiyuki Watanabe, Fumihito Muro, Yutaka Iigo, Gensuke Takayama, Mika Yokoyama, Tomoe Taira, Misato Aonuma, Tohru Takashi, Atsushi Nakayama, Nobuo Machinaga



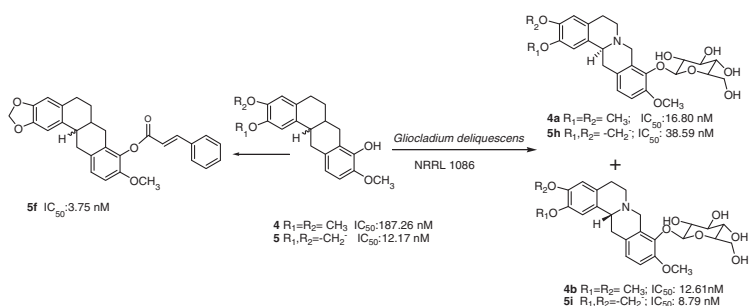
Compound **7n** with favorable aqueous solubility significantly alleviated bronchial hyper-responsiveness to acetylcholine chloride at 12.5 mg/kg, p.o. in an actively sensitized murine asthma model.

7n: VLA-4/VCAM-1 binding assay, IC_{50} (-/+3% HSA) = 1.7, 86 nM
aqueous solubility, JP1 (at pH 1.2), 89 µg/mL; JP2 (at pH 6.8), 462 µg/mL

Chemical and microbial semi-synthesis of tetrahydroprotoberberines as inhibitors on tissue factor procoagulant activity

pp 62–69

Hai-Xia Ge, Jian Zhang, Ling Chen, Jun-Ping Kou*, Bo-Yang Yu*

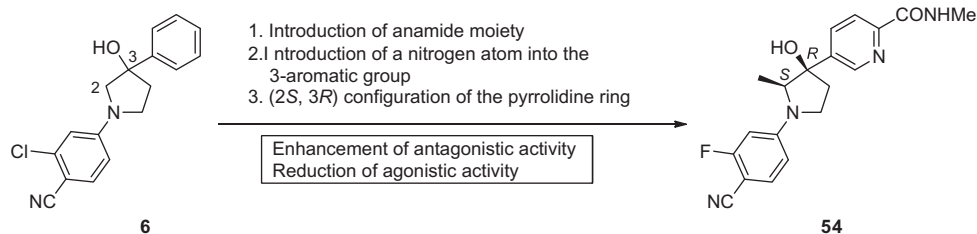


A series of THPBs derivatives were prepared by chemical and microbial semi-synthesis and screened for their inhibitory effect on TF procoagulant activity in human THP-1 cells stimulated by LPS.

Design, synthesis, and biological evaluation of 3-aryl-3-hydroxy-1-phenylpyrrolidine derivatives as novel androgen receptor antagonists

pp 70–83

Satoshi Yamamoto*, Hiromi Kobayashi, Tomohiro Kaku, Katsuji Aikawa, Takahito Hara, Masuo Yamaoka, Naoyuki Kanzaki, Atsushi Hasuoka, Atsuo Baba, Mitsuhiro Ito

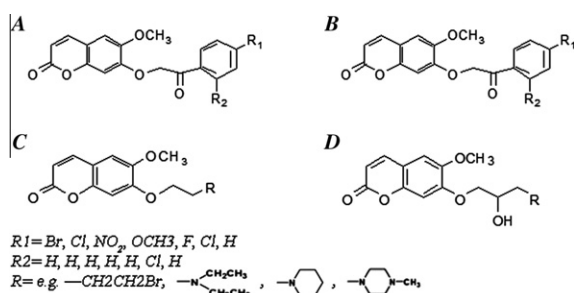


A series of 3-aryl-3-hydroxy-1-phenylpyrrolidine compounds were designed, synthesized, and evaluated for their potential as novel orally available androgen receptor antagonists therapeutically effective against castration-resistant prostate cancers.

Synthesis and biological evaluation of scopoletin derivatives

pp 84–92

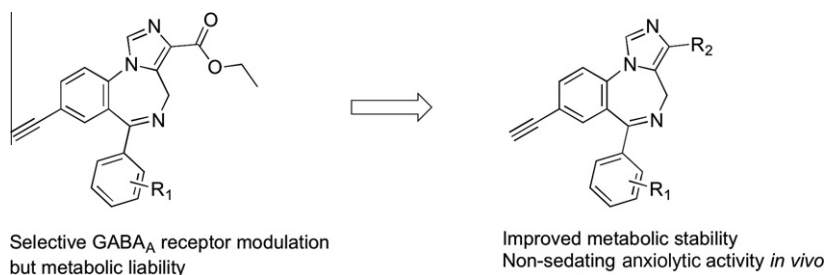
Xueting Cai, Jie Yang, Jinpei Zhou, Wuguang Lu, Chunping Hu, Zhenhua Gu, Jiege Huo, Xiaoning Wang, Peng Cao*



Search for $\alpha 3\beta 2/\gamma 2$ subtype selective ligands that are stable on human liver microsomes

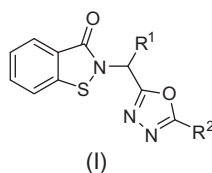
pp 93–101

Ojas A. Namjoshi, Zhi-jian Wang, Sundari K. Rallapalli, Edward Merle Johnson Jr., Yun-Teng Johnson, Hanna Ng, Joachim Ramerstorfer, Zdravko Varagic, Werner Sieghart, Samarpan Majumder, Bryan L. Roth, James K. Rowlett, James M. Cook*

**Design, synthesis and characterization of novel 1,2-benzisothiazol-3(2H)-one and 1,3,4-oxadiazole hybrid derivatives: Potent inhibitors of Dengue and West Nile virus NS2B/NS3 proteases**

pp 102–113

Huiguo Lai, Dengfeng Dou, Sridhar Aravapalli, Tadahisa Teramoto, Gerald H. Lushington, Tom M. Mwanja, Kevin R. Alliston, David M. Eichhorn, Radhakrishnan Padmanabhan, William C. Groutas*

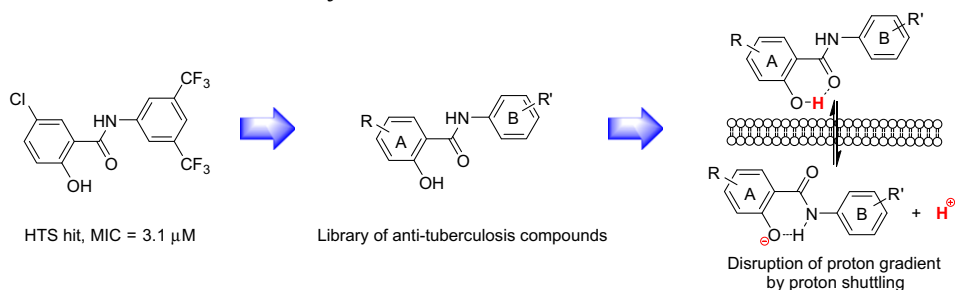


A series of functionalized 1,2-benzisothiazol-3(2H)-one–1,3,4-oxadiazole hybrid derivatives (I) were synthesized and shown to inhibit Dengue and West Nile virus proteases. The IC₅₀ values of compound **7n** against DENV2 and WNV proteases were determined to be 3.75 ± 0.06 and 4.22 ± 0.07 μM, respectively. The kinetics data support a competitive mode of inhibition by compound **7n**. The results of docking studies corroborate some general activity trends observed in the tested compounds.

Structure–activity relationships of antitubercular salicylanilides consistent with disruption of the proton gradient via proton shuttling

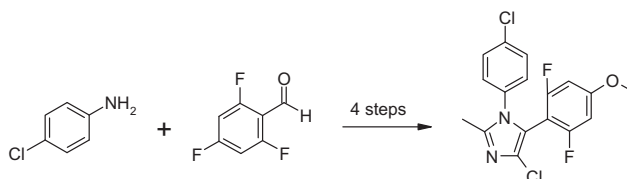
pp 114–126

Ill-Young Lee, Todd D. Gruber, Amanda Samuels, Minhan Yun, Bora Nam, Minseo Kang, Kathryn Crowley, Benjamin Winterroth, Helena I. Boshoff, Clifton E. Barry III*

**Synthesis and fungicidal activity of tubulin polymerisation promoters. Part 3: Imidazoles**

pp 127–134

Clemens Lamberth*, Raphael Dumeunier, Stephan Trah, Sebastian Wendeborn, Jeremy Godwin, Peter Schneider, Andy Corran

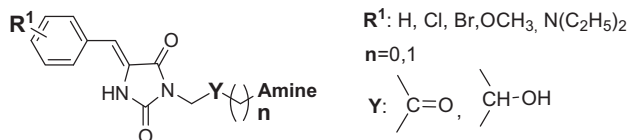


Highly active against *Botrytis cinerea* (grey mould), *Ucinula necator* (grape powdery mildew), *Mycosphaerella graminicola* (wheat leaf blotch) and *Alternaria solani* (potato and tomato early blight).

Search for new tools to combat Gram-negative resistant bacteria among amine derivatives of 5-arylidenehydantoin

pp 135–145

Jadwiga Handzlik*, Ewa Szymańska, Sandrine Alibert, Jacqueline Chevalier, Ewa Otrębska, Elżbieta Pękala, Jean-Marie Pagès, Katarzyna Kieć-Kononowicz

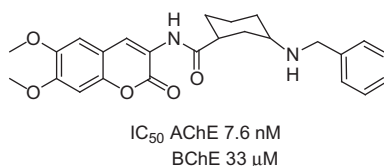


Nineteen amine derivatives of 5-arylidenehydantoin were tested on their potency to improve antibiotic efficacy in multidrug resistant strains of *E. aerogenes*. Synthesis, molecular modeling and SAR-studies were performed.

**Design, synthesis and biological evaluation of coumarin alkylamines as potent and selective dual binding site inhibitors of acetylcholinesterase**

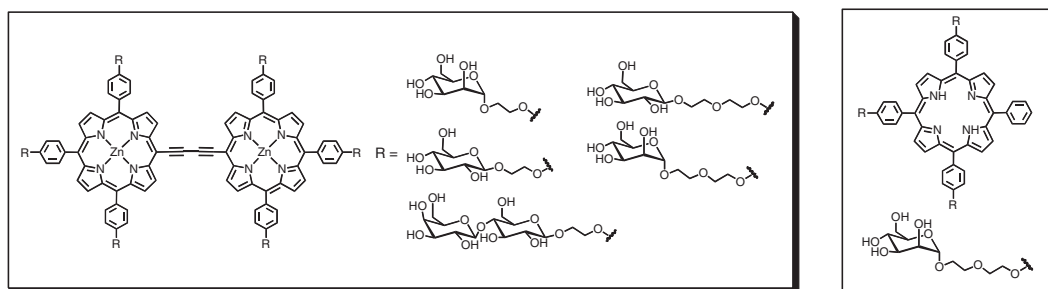
pp 146–152

Marco Catto*, Leonardo Pisani, Francesco Leonetti, Orazio Nicolotti, Paolo Pesce, Angela Stefanachi, Saverio Cellamare, Angelo Carotti*

**Carbohydrate-conjugated porphyrin dimers: Synthesis and photobiological evaluation for a potential application in one-photon and two-photon photodynamic therapy**

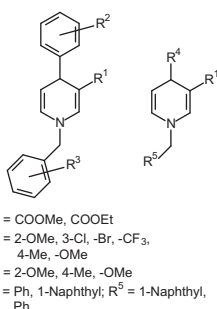
pp 153–165

Guillaume Garcia*, Fabien Hammerer, Florent Poyer, Sylvain Achelle, Marie-Paule Teulade-Fichou, Philippe Maillard

**Development of small-molecule P-gp inhibitors of the N-benzyl 1,4-dihydropyridine type: Novel aspects in SAR and bioanalytical evaluation of multidrug resistance (MDR) reversal properties**

pp 166–177

Christiane Baumert, Marianne Günthel, Sören Krawczyk, Marc Hemmer, Tom Wersig, Andreas Langner, Josef Molnár, Hermann Lage, Andreas Hilgeroth*

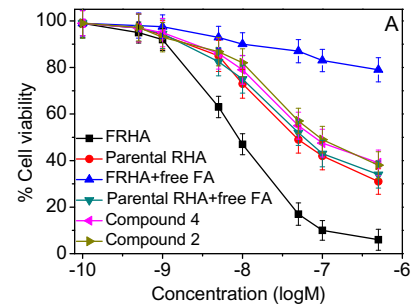


Synthesis and biological evaluation of a folate-targeted rhaponticin conjugate

pp 178–185

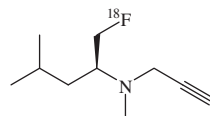
Xuhua Liang, Yang Sun, Wenyuan Zeng, Lusha Liu, Xuan Ma, Yingyong Zhao*, Jun Fan*

Viability of FR-positive KB cells after exposure to FRHA or parental RHA or the RHA derivative (compound **2** or compound **4**) with increasing concentrations in the presence or absence of 0.01 mM FA (as a competitor) at 37 °C for 48 h.

**Synthesis and biological evaluation of novel propargyl amines as potential fluorine-18 labeled radioligands for detection of MAO-B activity**

pp 186–195

S. Nag*, G. Ketschau, T. Heinrich, A. Varrone, L. Lehmann, B. Gulyas, A. Thiele, É. Keller, C. Halldin

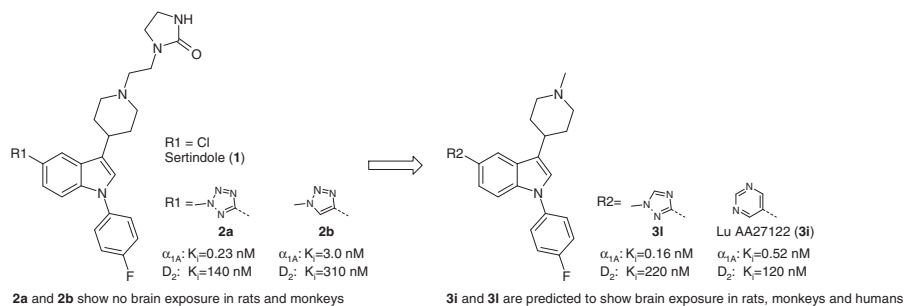


(S)-1-[18F]fluoro-N,4-dimethyl-N-(prop-2-ynyl)pentan-2-amine a new fluorine-18 labelled radioligands for detection of MAO-B activity by PET.

Discovery of novel α_1 -adrenoceptor ligands based on the antipsychotic sertindole suitable for labeling as PET ligands

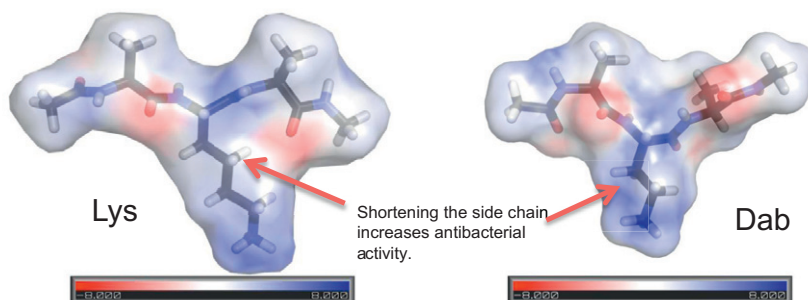
pp 196–204

Morten Jørgensen, Pernille N. Jørgensen, Claus T. Christoffersen, Klaus G. Jensen, Thomas Balle, Benny Bang-Andersen*

**Antimicrobial peptides containing unnatural amino acid exhibit potent bactericidal activity against ESKAPE pathogens**

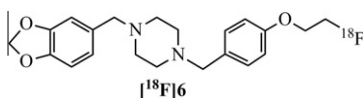
pp 205–214

R. P. Hicks, J. J. Abercrombie, R. K. Wong, K. P. Leung*



Synthesis and biological evaluation of ^{18}F labeled fluoro-oligo-ethoxylated 4-benzylpiperazine derivatives for sigma-1 receptor imaging pp 215–222

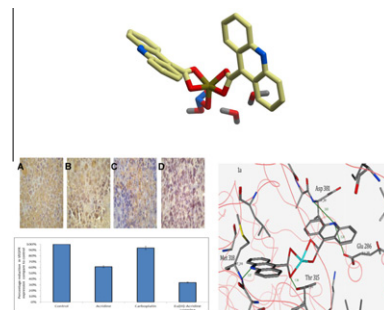
Xia Wang, Yan Li, Winnie Deuther-Conrad, Fang Xie, Xin Chen, Meng-Chao Cui, Xiao-Jun Zhang, Jin-Ming Zhang, Jörg Steinbach, Peter Brust, Bo-Li Liu, Hong-Mei Jia*



Bis(acridine-9-carboxylate)-nitro-europium(III) dihydrate complex a new apoptotic agent through Flk-1 down regulation, caspase-3 activation and oligonucleosomes DNA fragmentation pp 223–234

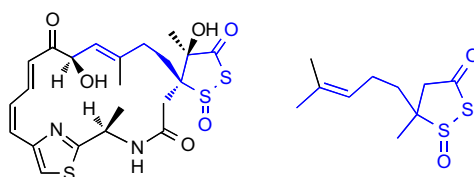
Hassan A. Azab, Belal H. M. Hussein, Mona F. El-Azab, Mohamed Gomaa, Abdullah I. El-Falouji*

New bis(acridine-9-carboxylate)-nitro-europium(III) dihydrate complex was synthesized and characterized, the in vivo activity of the new complex showed that europium(III)-acridine-9-carboxylate complex is a promising antitumor agent with a good antiangiogenic and apoptotic activity.



Synthesis and characterization of a small analogue of the anticancer natural product leinamycin pp 235–241

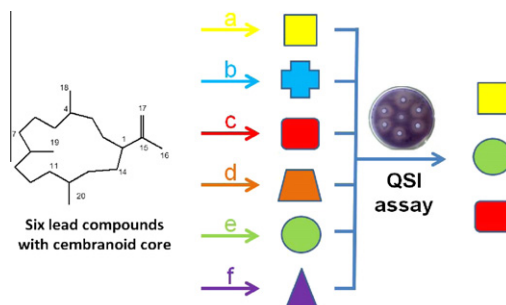
Kripa Keerthi, Anuruddha Rajapakse, Daekyu Sun, Kent S. Gates*



A small analogue of the natural product leinamycin was prepared containing the core set of functional groups required to enable thiol-triggered generation of both redox active polysulfides and an episulfonium ion intermediate via the complex reaction cascade first seen in the natural product leinamycin.

Synthesis of cembranoid analogues and evaluation of their potential as quorum sensing inhibitors pp 242–256

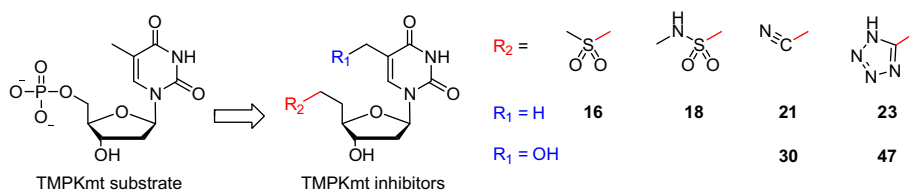
Edisson Tello, Leonardo Castellanos, Carmenza Duque*



Synthesis and evaluation of 5'-modified thymidines and 5-hydroxymethyl-2'-deoxyuridines as *Mycobacterium tuberculosis* thymidylate kinase inhibitors

pp 257–268

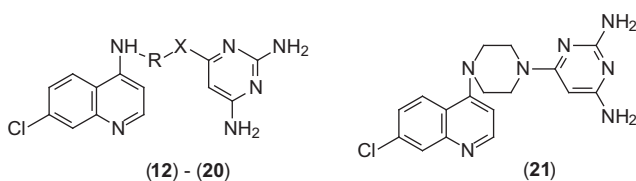
Kiran S. Toti, Frederick Verbeke, Martijn D. P. Risseuw, Vladimir Frecer, Hélène Munier-Lehmann, Serge Van Calenbergh*



Synthesis, characterization and antimalarial activity of quinoline–pyrimidine hybrids

pp 269–277

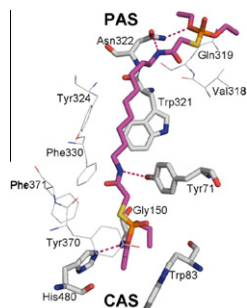
Stefan I. Pretorius, Wilma J. Breytenbach, Carmen de Kock, Peter J. Smith, David D. N'Da*

 $IC_{50}/D10$: 0.157–0.85 μM $IC_{50}/D10$: 0.07 μM $IC_{50}/Dd2$: 0.107–0.58 μM $IC_{50}/Dd2$: 0.157 μM 

Design, synthesis and biological evaluation of organophosphorous-homodimers as dual binding site acetylcholinesterase inhibitors

pp 278–282

Ruliang Xie, Qianfei Zhao, Tao Zhang, Jing Fang, Xiangdong Mei, Jun Ning*, Yun Tang*



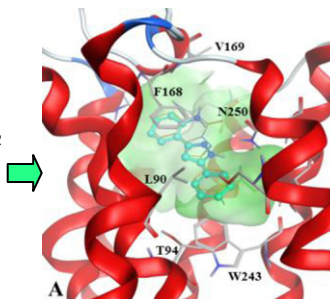
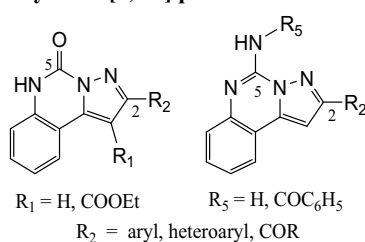
The molecular docking between 4H and 1QO9

Pyrazolo[1,5-c]quinazoline derivatives and their simplified analogues as adenosine receptor antagonists: Synthesis, structure–affinity relationships and molecular modeling studies

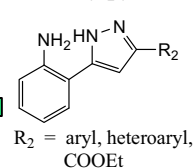
pp 283–294

Daniela Catarzi*, Vittoria Colotta, Flavia Varano, Daniela Poli, Lucia Squarcialupi, Guido Filacchioni, Katia Varani, Fabrizio Vincenzi, Pier Andrea Borea, Diego Dal Ben, Catia Lambertucci, Gloria Cristalli

Pyrazolo[1,5-c]quinazolines

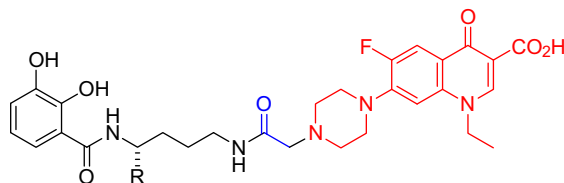


Simplified analogues: 3,5-diarylpyrazoles



Synthesis and antibacterial activity of conjugates between norfloxacin and analogues of the siderophore vanchrobactin pp 295–302

Alba Souto, Marcos A. Montaños, Miguel Balado, Carlos R. Osorio, Jaime Rodríguez*, Manuel L. Lemos, Carlos Jiménez*

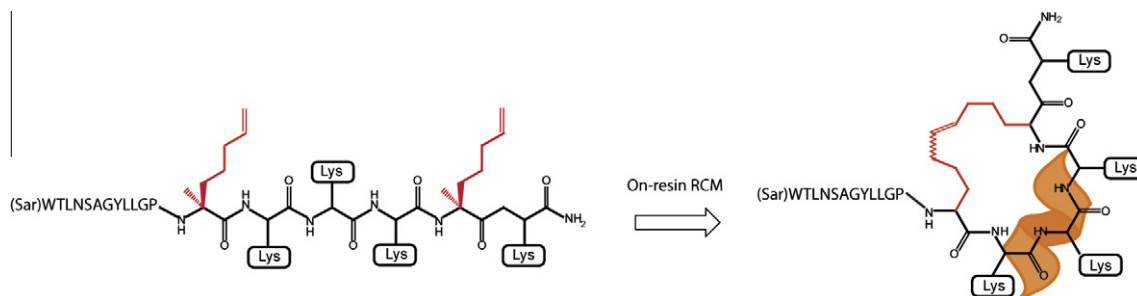


R = -H, -COOMe, -COOH, -(C=O)-L-Ser



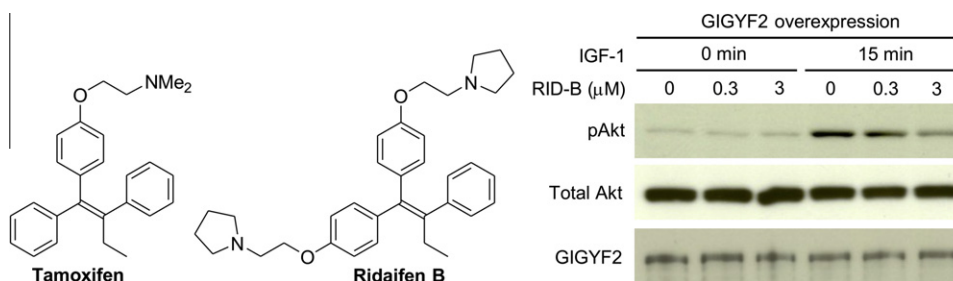
Cyclic analogs of galanin and neuropeptide Y by hydrocarbon stapling pp 303–310

Brad R. Green*, Brian D. Klein, Hee-Kyoung Lee, Misty D. Smith, H. Steve White, Grzegorz Bulaj



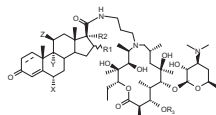
Ridaifen B, a tamoxifen derivative, directly binds to Grb10 interacting GYF protein 2 pp 311–320

Senko Tsukuda, Tomoe Kusayanagi, Eri Umeda, Chihiro Watanabe, Yu-ta Tosaki, Shinji Kamisuki, Toshifumi Takeuchi, Yoichi Takakusagi, Isamu Shiina, Fumio Sugawara*



Macrolactonolides: A novel class of anti-inflammatory compounds pp 321–332

Linda Tomašković*, Marijana Komac, Oresta Makaruha Stegić, Vesna Munić, Jovica Ralić, Barbara Stanić, Mihailo Banjanac, Stribor Marković, Boška Hrvačić, Hana Čipčić Paljetak, Jasna Padovan, Ines Glojnarčić, Vesna Eraković Haber, Milan Mesić, Mladen Merćep



Comp.	X	Y	Z	A	R ¹	R ²	R ³
1	H	F	OH	+	α-CH ₃	OH	-
44	H	F	OH	+	α-CH ₃	OH	Lactid.
45	H	F	OH	+	α-CH ₃	H	Lactid.
46	F	H	OH	+	α-CH ₃	OH	Lactid.
47	H	Cl	OH	+	β-CH ₃	OH	Lactid.
48	F	F	OH	+	α-CH ₃	OH	Lactid.
49	F	F	OH	+	α-CH ₃	H	Lactid.
50	F	Cl	OH	+	α-CH ₃	OH	Lactid.
51	H	H	OH	+	H	OH	Lactid.
52	H	H	OH	-	H	H	Lactid.
53	H	H	OH	-	H	OH	Lactid.
54	H	F	OH	+	α-CH ₃	H	H
55	F	H	OH	+	α-CH ₃	OH	H
56	F	F	OH	+	α-CH ₃	OH	H
57	F	Cl	OH	+	α-CH ₃	OH	H
58	H	H	OH	-	H	OH	H



pp 333–347

Ar ₁	Ar ₂

focused library synthesis = enhanced activity



pp 348–358

$\text{X} = \text{CH}_2$: chaetomelic acid A sodium salt; yeast FTase $\text{IC}_{50} = 16.7 \text{ } (\mu\text{M})$
 NaOOC  X 
 rat FTase $\text{IC}_{50} = 0.91 \text{ } (\mu\text{M})$
 $\text{X} = \text{S}$: thia-analogue; yeast FTase $\text{IC}_{50} = 3.5 \text{ } (\mu\text{M})$; rat FTase $\text{IC}_{50} = 0.19 \text{ } (\mu\text{M})$



pp 359–364

Chemical reaction scheme showing the synthesis of a bicyclic nucleoside derivative. The reaction involves 2-chloro-6-aminopyrimidine-4-carboxamide and a substituted cyclopentene derivative (with HO and OAc groups) reacting to form a bicyclic nucleoside derivative. The product has a purine-like core with an amino group, a substituent X, and a hydroxyl group. The substituent X is defined as Cl, Br, I, or Me.

pp 365–372


3a-l

R =

X = -Cl, -SCH₂Ph, -SO₂NH₂

3k IC₅₀ ~ 6.2 (nM)

*Corresponding author

* Supplementary data available via SciVerse ScienceDirect

COVER

Dipyrone (metamizol) is a common antipyretic drug and the most popular non-opioid analgesic in many countries. In spite of its long and widespread use, molecular details of its fate in the body are not fully known. Two unknown metabolites were now found, viz. arachidonoyl amides, and positively tested for cannabis receptor binding (CB1 and CB2) and cyclooxygenase inhibition. Two more puzzle pieces of the dipyrone story found! (Rogosch, T.; Sinning, C.; Podlewski, A.; Watzer, B.; Schlosburg, J.; Lichtman, A.H.; Cascio, M.G.; Bisogno, T.; Di Marzo, V.; Nüsing, R.; Imming, P. *Bioorg. Med. Chem.* **2012**, 20, 103–109.)

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