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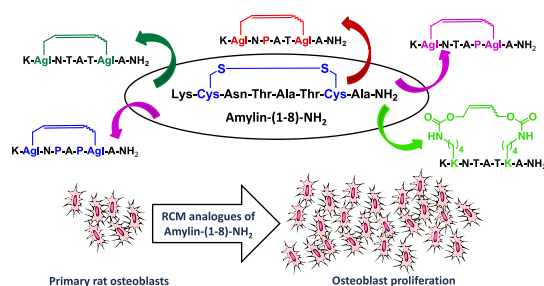
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ARTICLES

How to blast osteoblasts? Novel dicarba analogues of amylin-(1–8) to treat osteoporosis

pp 6011–6018

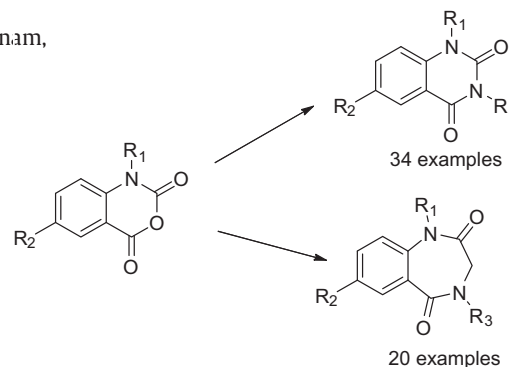
Renata Kowalczyk, Margaret A. Brimble*, Karen E. Callon, Maureen Watson, Jillian Cornish



Identification and development of the 1,4-benzodiazepin-2-one and quinazoline-2,4-dione scaffolds as submicromolar inhibitors of HAT

pp 6019–6033

Rachel L. Clark, Carol J. Clements, Michael P. Barrett, Simon P. Mackay, Rajendra P. Rathnam, George Owusu-Dapaah, John Spencer, Judith K. Huggan*

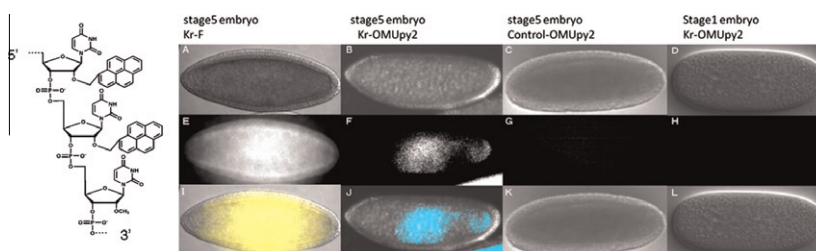


A library of 1,4-benzodiazepines and quinazoline-2,4-diones has been synthesised that display MIC values as low as 0.97 μ M against *Trypanosoma brucei*.

RNA-based diagnosis in a multicellular specimen by whole mount in situ hybridization using an RNA-specific probe

pp 6034–6039

Takako Ueda, Akio Kobori, Asako Yamayoshi, Hideki Yoshida, Masamitsu Yamaguchi, Akira Murakami*



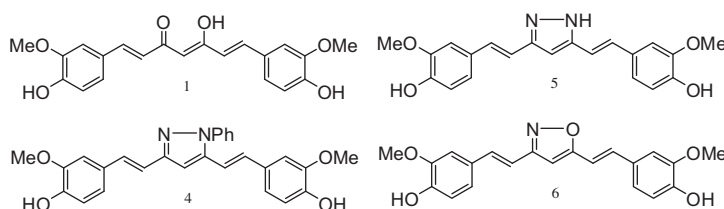
RNA-specific probe (OMUp2) was found to be applicable to the detection of specific mRNA in *Drosophila* embryos from the view point of temporal and spatial localization in multi cellular specimens.



Curcumin is an inhibitor of calcium/calmodulin dependent protein kinase II

pp 6040–6047

M. Mayadevi, D.R. Sherin, V.S. Keerthi, K.N. Rajasekharan, R.V. Omkumar*



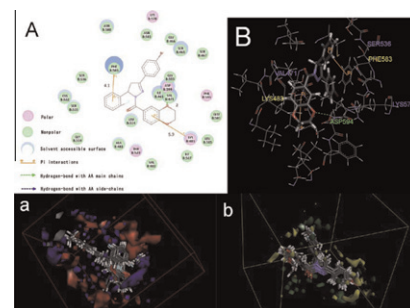
The inhibition of CaMKII kinase activity by natural curcumin I (1) and its two pyrazole derivatives (4, 5) and one isoxazole derivative (6) is reported.

Design, modification and 3D QSAR studies of novel 2,3-dihydrobenzo[b][1,4]dioxin-containing 4,5-dihydro-1H-pyrazole derivatives as inhibitors of B-Raf kinase

pp 6048–6058

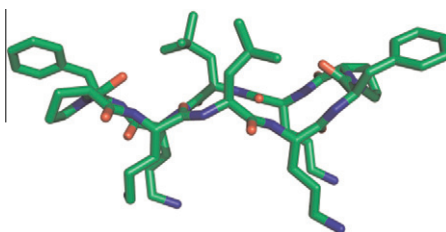
Yu-Shun Yang, Qing-Shan Li, Shuai Sun, Yan-Bin Zhang, Xiao-Liang Wang, Fei Zhang, Jian-Feng Tang, Hai-Liang Zhu*

Two series of novel 2,3-dihydrobenzo[b][1,4]dioxin-containing 4,5-dihydro-1H-pyrazole derivatives **C1–C15** and **D1–D15** have been synthesized and evaluated for their B-Raf inhibitory and anti-proliferation activities. Compound **C14** ((3-(4-bromophenyl)-5-(2-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methanone) showed the most potent biological activity against B-Raf^{V600E} (IC₅₀ = 0.11 μM) and WM266.4 human melanoma cell line (GI₅₀ = 0.58 μM), being comparable with the positive control Erlotinib and more potent than our previous best compound, while **D10** ((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)(5-(3-fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone) performed the best in the **D** series (IC₅₀ = 1.70 μM; GI₅₀ = 1.45 μM). The docking simulation was performed to analyze the probable binding models and poses and the QSAR model was built for reasonable design of B-Raf inhibitors in future. The introduction of 2,3-dihydrobenzo[b][1,4]dioxin structure reinforced the combination of our compounds and the receptor, resulting in progress of bioactivity.

**'Inverted' analogs of the antibiotic gramicidin S with an improved biological profile**

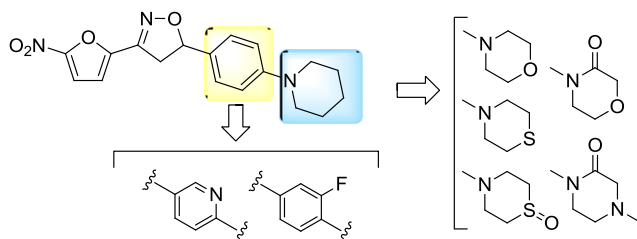
pp 6059–6062

Varsha V. Kapoerchan, Annemiek D. Knijnenburg, Peter Keizer, Emile Spalburg, Albert J. de Neeling, Roos H. Mars-Groenendijk, Daan Noort, José M. Otero, Antonio L. Llamas-Saiz, Mark J. van Raaij, Gijts A. van der Marel, Herman S. Overkleef, Mark Overhand*

**Antitubercular nitrofuran isoxazolines with improved pharmacokinetic properties**

pp 6063–6072

Rakesh, David Bruhn, Dora B. Madhura, Marcus Maddox, Robin B. Lee, Ashit Trivedi, Lei Yang, Michael S. Scherman, Janet C. Gilliland, Veronica Gruppo, Michael R. McNeil, Anne J. Lenaerts, Bernd Meibohm, Richard E. Lee*

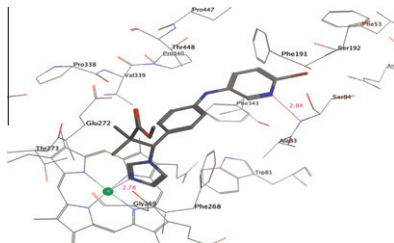


A series of tetracyclic nitrofuran isoxazoline antimicrobial agents was designed and synthesized to increase pharmacokinetic properties including solubility and metabolic stability over on an initial lead.

pp 6073–6079



Mohamed S. Gomaa, Andrew S.T. Lim, S.C. Wilson Lau, Ann-Marie Watts, Nicola A. Illingworth, Caroline E. Bridgens, Gareth J. Veal, Christopher P.F. Redfern, Andrea Brancale, Jane L. Armstrong, Claire Simons*



A series of 3-[4-(arylamino)phenyl]-3-(azole)-2,2-dimethylpropanoates were prepared and evaluated for their inhibitory activity against CYP26A1 with molecular modeling studies to determine key binding interactions within the CYP26A1 active site.

Jia-Jia Liu, Hui Zhang, Juan Sun, Zhong-Chang Wang, Yu-Shun Yang, Dong-Dong Li, Fei Zhang, Hai-Bin Gong*, Hai-Liang Zhu*

The reaction scheme illustrates the synthesis of 3a-3t in three steps:

- Step a:** 4- R_1 -benzoyl (a benzene ring with a R_1 substituent at the para position and a $-C(=O)CH_3$ group at the other para position) reacts with 2,6-dihydroxy-3- R_2 -benzaldehyde (a benzene ring with $-OH$ groups at positions 2 and 6, a $-CHO$ group at position 3, and a R_2 substituent at position 1) to form intermediate 1a-1t. The structure of 1a-1t is a chalcone derivative where the benzoyl group has been converted to a $-CH=CH-$ bridge.
- Step b:** Intermediate 1a-1t undergoes cyclization to form 2a-2t. The structure of 2a-2t is a 2-aryl-2,3-dihydro-1H-imidazole derivative, where the $-CH=CH-$ bridge has cyclized to form an imidazole ring.
- Step c:** Intermediate 2a-2t undergoes cyclization to form the final product 3a-3t. The structure of 3a-3t is a 2-aryl-2,3-dihydro-1H-imidazole derivative, where the imidazole ring has cyclized to form a 2,3-dihydro-1H-imidazole ring.

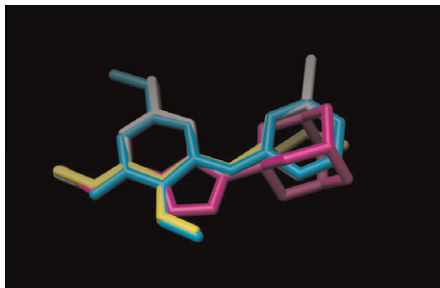
pp 6097–6108

Synthesis and SAR of novel 5-, 6-, 7-, 8-aza, 5,8-diazaphthalazinone derivatives **2**, and dual H₁ H₃ receptor antagonist **44**.

Structure–activity relationship study of nitrosopyrimidines acting as antifungal agents

pp 6109-6122

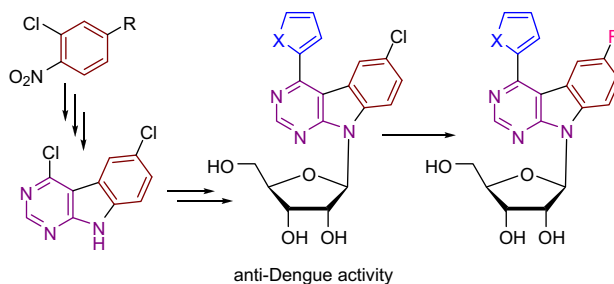
Monica Olivella, Antonio Marchal, Manuel Nogueras, Adolfo Sánchez, Manuel Melguizo, Marcela Raimondi, Susana Zacchino, Fernando Giannini, Justo Cobo*, Ricardo D. Enriz*



Synthesis and antiviral activity of 4,6-disubstituted pyrimido[4,5-*b*]indole ribonucleosides

pp 6123–6133

Michal Tichý, Radek Pohl, Hao Ying Xu, Yen-Liang Chen, Fumiaki Yokokawa, Pei-Yong Shi, Michal Hocek*



Minutissamides E–L, antiproliferative cyclic lipodecapeptides from the cultured freshwater cyanobacterium cf. *Anabaena* sp.

pp 6134–6143

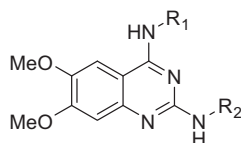
Hahk-Soo Kang, Megan Sturdy, Aleksej Krunic, Hyunjung Kim, Qi Shen, Steven M. Swanson, Jimmy Orjala*



Development of erlotinib derivatives as CIP2A-ablating agents independent of EGFR activity

pp 6144-6153

Kuen-Feng Chen, Kuan-Chuan Pao, Jung-Chen Su, Yi-Chieh Chou, Chun-Yu Liu, Hui-Ju Chen, Jui-Wen Huang, InKi Kim, Chung-Wai Shiau*



Quinazoline derivatives were synthesized with two steps. These derivatives induced cell apoptosis without the inhibition of EGFR activity. The novel compounds were tested in the ability of CIP2A down-regulation.



Novel fluorescent ceramide derivatives for probing ceramidase substrate specificity

pp 6154–6161

Krishna P. Bhabak, Denny Proksch, Susanne Redmer, Christoph Arenz*



In this study we have synthesized novel Nile Red (NR)-labeled ceramides as substrates of acid and neutral ceramidases. Structure–activity–relationship and kinetic studies with NR- and commercially available NBD-ceramides provide insights into their substrate specificities toward recombinant acid and neutral ceramidases.

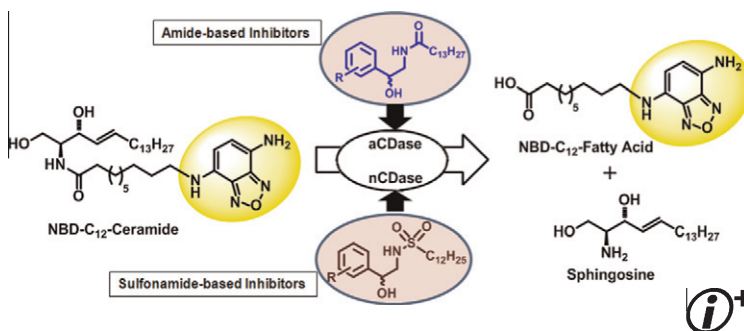


Novel amide- and sulfonamide-based aromatic ethanolamines: Effects of various substituents on the inhibition of acid and neutral ceramidases

pp 6162–6170

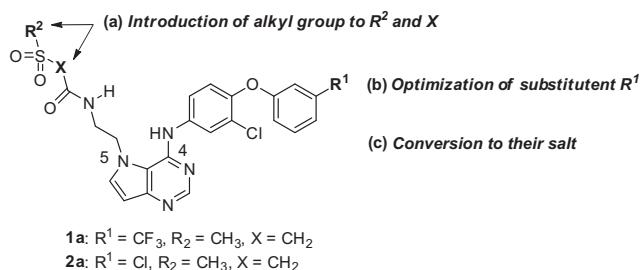
Krishna P. Bhabak, Christoph Arenz*

In the present study we describe the design and synthesis of series of amide- and sulfonamide-based compounds as inhibitors of recombinant acid and neutral ceramidases. Our results suggest that the electronic effects of the substituents on phenyl ring in B-13 and D-e-MAPP analogues have negligible effects either in enhancing the inhibition potencies or for selectivity towards aCDase over nCDase. However, the hydrophobicity and the steric effects of longer alkyl chains (*n*-Pr, *n*-Bu or *t*-Bu groups) at the phenyl ring were found to be important for an enhanced selectivity towards aCDase over nCDase.



Design and synthesis of pyrrolo[3,2-*d*]pyrimidine HER2/EGFR dual inhibitors: Improvement of the physicochemical and pharmacokinetic profiles for potent in vivo anti-tumor efficacy

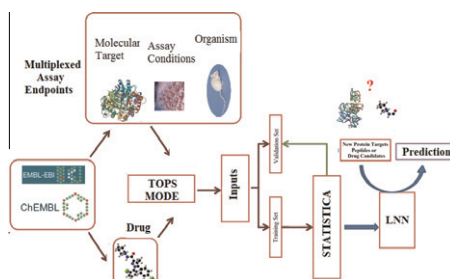
Youichi Kawakita*, Kazuhiro Miwa, Masaki Seto, Hiroshi Banno, Yoshikazu Ohta, Toshiya Tamura, Tadashi Yusa, Hiroshi Miki, Hidenori Kamiguchi, Yukihiro Ikeda, Toshimasa Tanaka, Keiji Kamiyama, Tomoyasu Ishikawa*



ANN multiplexing model of drugs effect on macrophages; theoretical and flow cytometry study on the cytotoxicity of the anti-microbial drug G1 in spleen

pp 6181–6194

Esvieta Tenorio-Borroto, Claudia G. Peñuelas Rivas, Juan C. Vásquez Chagoyán, Nilo Castañedo, Francisco J. Prado-Prado, Xerardo García-Mera, Humberto González-Díaz*



OTHER CONTENT**Corrigendum****pp 6195–6197**

*Corresponding author

* Supplementary data available via SciVerse ScienceDirect**COVER**

The 2011 Nobel Prize in Physiology or Medicine was awarded for the discovery of mechanisms triggering the activation of innate immunity and mediating the communication between innate and adaptive immunity, many of which through the toll-like receptor (TLR) protein family. Thirteen years after the landmark discovery, targeting TLR signaling has become an important strategy in medicinal chemistry. In this report, we showed that arylidene malonate derivatives (shown in spacefilling representation in magenta) are effective regulators of the horseshoe-shaped TLR4 (shown in ribbon) signaling by targeting the TLR4/MD-2 protein-protein interface. [Zhang, S.; Cheng, K.; Wang, X.; Yin, H. *Bioorg. Med. Chem.* **2012**, 20, 6074–6080.]

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