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Medicinal
Chemistry

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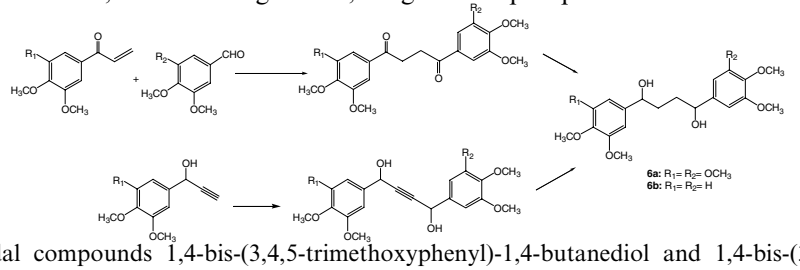
# Contents

## ARTICLES

**Synthesis and trypanocidal activity of 1,4-bis-(3,4,5-trimethoxy-phenyl)-1,4-butanediol and 1,4-bis-(3,4-dimethoxyphenyl)-1,4-butanediol** **pp 7075–7082**

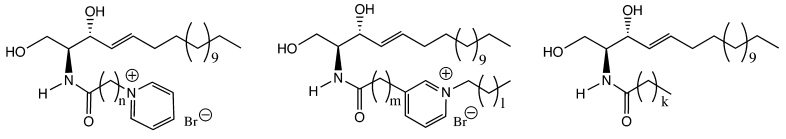
Lilian Sibelle Campos Bernardes, Massuo Jorge Kato, Sérgio Albuquerque and Ivone Carvalho*




Two potential trypanocidal compounds 1,4-bis-(3,4,5-trimethoxyphenyl)-1,4-butanediol and 1,4-bis-(3,4-dimethoxyphenyl)-1,4-butanediol, prepared from 1,4-diaryl-1,4-diketones and 1,4-diarylacetylenic-1,4-glycols, are described.

**Tailoring structure–function and targeting properties of ceramides by site-specific cationization** **pp 7083–7104**

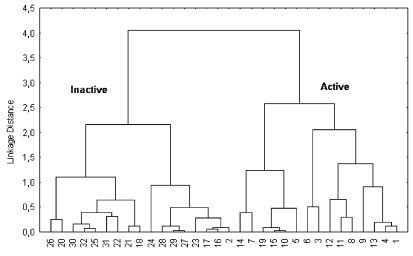
Zdzislaw M. Szulc, Jacek Bielawski, Hanna Gracz, Marietta Gustilo, Nalini Mayroo, Yusuf A. Hannun, Lina M. Obeid and Alicja Bielawska*



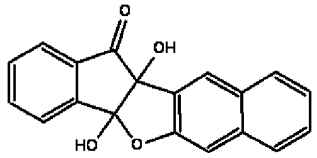
| | **D-e-C12-ω-CCPS** (n = 11) | **D-e-C1-α-CCPS** (m = 0, l = 6) | **D-e-C6-Cer** (k = 4) |
|---|---|---|---|
| $IC_{50}$ (MCF7 cells, μM): | 0.6 | 20 | 15 |
| water solubility (mg/mL): | 495 | 120 | 0.0014 |
| hydrophobicity ($R_M$): | 0.21 | 0.05 | - |

**Structure–activity relationship study of flavone compounds with anti-HIV-1 integrase activity: A density functional theory study** **pp 7105–7112**

J. Lameira, I. G. Medeiros, M. Reis, A. S. Santos and C. N. Alves*

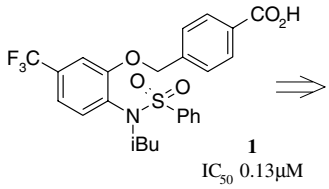


**Identification and evaluation of antioxidant, analgesic/anti-inflammatory activity of the most active ninhydrin–phenol adducts synthesized** **pp 7113–7120**
K. R. Prabhakar, V. P. Veerapur, Punit Bansal, K. Parihar Vipan, K. M. Reddy, Atanu Barik, Bharat Kumar D. Reddy, P. Reddanna, K. I. Priyadarsini and M. K. Unnikrishnan*

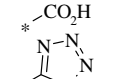
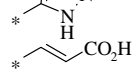
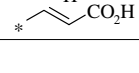


Phenol–ninhydrin adducts were synthesized and the best free radical scavenger, lipoxgenase inhibitor was identified and studied for its in vivo analgesic, anti-inflammatory studies.

**Further optimization of sulfonamide analogs as EP1 receptor antagonists: Synthesis and evaluation of bioisosteres for the carboxylic acid group** **pp 7121–7137**
Atsushi Naganawa,* Toshiaki Matsui, Masaki Ima, Tetsuji Saito, Masayuki Murota, Yoshiyuki Aratani, Hideomi Kijima, Hiroshi Yamamoto, Takayuki Maruyama, Shuichi Ohuchida, Hisao Nakai and Masaaki Toda

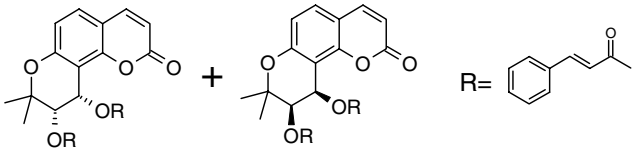


**1**
$IC_{50}$ 0.13μM

| | R | $IC_{50}$, μM |
|---|---|---|
| **2b** |  | 0.0056 |
| **8** |  | 0.00074 |
| **16** |  | 0.0053 |

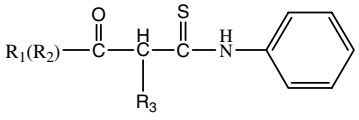
Further optimization of **1** as EP1 antagonist afforded **2b**, **8**, and **16**.

**(±)-3′-*O*, 4′-*O*-dicynnamoyl-*cis*-khellactone, a derivative of (±)-praeruptorin A, reverses P-glycoprotein mediated multidrug resistance in cancer cells** **pp 7138–7145**
Xiaoling Shen, Guangying Chen, Guoyuan Zhu and Wang-Fun Fong*



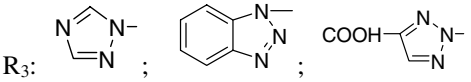
**Synthesis and QSAR studies of novel triazole compounds containing thioamide as potential antifungal agents** **pp 7146–7153**
Qing-Li Wei, Shu-Sheng Zhang,* Jun Gao, Wei-hua Li, Liang-Zhong Xu and Zhi-Gang Yu

Eighteen novel triazole compounds were synthesized and confirmed by elemental analysis, $^1H$ NMR, IR, and MS. The title compounds exhibited certain antifungal activity. A correlative equation between *FA* and DELH, *V* was well established by using the multiple linear regression (MLR).

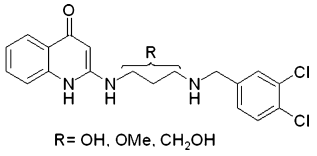


$R_1$: $C_6H_5$; 4-$ClC_6H_4$; 2,4-$Cl_2C_6H_3$; 3,4-$Cl_2C_6H_3$; 4-Ph- $C_6H_4$; 4-$MeOC_6H_4$; 4-$MeC_6H_4$

$R_2$: 4-$FC_6H_4$; 2,4-$F_2C_6H_3$; 2-F-5-$MeC_6H_4$; 2-F-4-$MeC_6H_3$

$R_3$: 

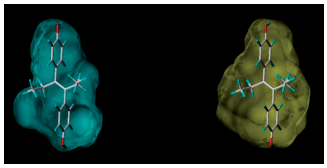
**Design and synthesis of quinolinones as methionyl-tRNA synthetase inhibitors** **pp 7154–7159**
Farhanullah, Su Yeon Kim, Eun-Jeong Yoon, Eung-Chil Choi, Sunghoon Kim, Taehee Kang, Farhana Samrin, Sadhna Puri and Jeewoo Lee*



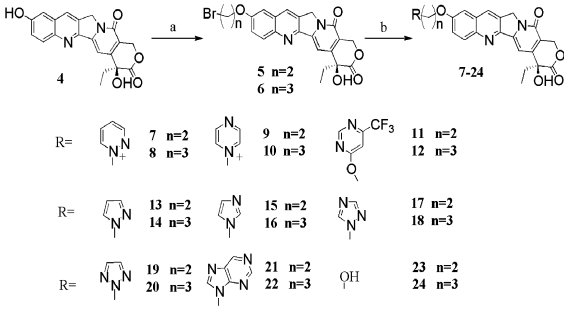

Synthesis and *Staphylococcus aureus* methionyl-tRNA synthetase inhibitory activities of substituted-1*H*-quinolones are described.

**Structural basis for androgen receptor agonists and antagonists: Interaction of SPEED 98-listed chemicals and related compounds with the androgen receptor based on an in vitro reporter gene assay and 3D-QSAR** **pp 7160–7174**
Hiroto Tamura,* Yoichi Ishimoto, Tomoko Fujikawa, Hiroaki Aoyama, Hiromichi Yoshikawa and Miki Akamatsu

The analysis of the structural requirements necessary to disrupt androgen receptor (AR) function shows that the steric and electrostatic properties were sufficient to describe the structural requirements for AR antagonist activity and the structural difference of AR agonists and antagonists was explained based on 3D-QSAR results and the AR crystal structure. The subtle difference of the surface areas of the ligand binding domain between AR and ER determines whether an ER agonist acts as an AR antagonist or an agonist.

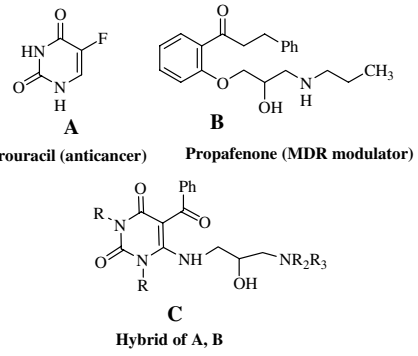


**Synthesis and antitumor activity of novel 10-substituted camptothecin analogues** **pp 7175–7182**
Qingyong Li, Yuangang Zu,* Rongzhen Shi, Liping Yao, Yujie Fu, Zhiwei Yang and Lei Li

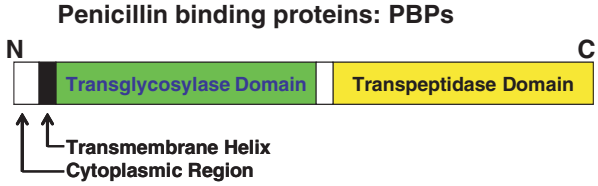



**Studies of interactions between uracil-based hybrid molecules and P-glycoprotein—Search for multidrug resistance modulators** **pp 7183–7186**
Palwinder Singh* and Kamaldeep Paul

The hybrid molecules (**C**), having the structural features of anticancer drug 5-fluorouracil (**A**) and MDR modulator, propafenone (**B**), have been studied for their interactions with P-glycoprotein.

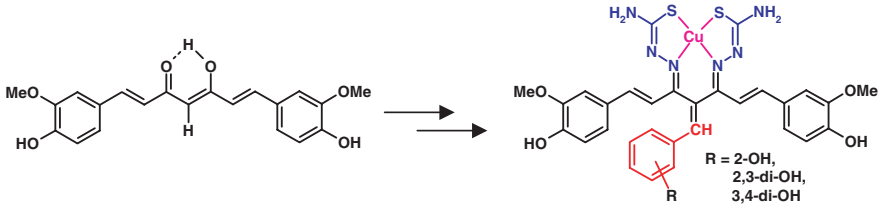


**Characterization of a transglycosylase domain of *Streptococcus pneumoniae* PBP1b** **pp 7187–7195**
Haitian Liu and Chi-Huey Wong*



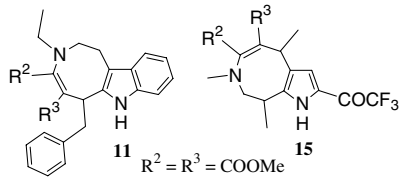

The bacterial cell-wall biosynthesis pathway is an attractive target for antibiotics. PBP1b catalyzes the polymerization of Lipid II forming uncrosslinked peptidoglycan. A transglycosylase domain from PBP1b was cloned, expressed, and characterized.

**Novel curcumin analogs targeting TNF-induced NF-κB activation and proliferation in human leukemic KBM-5 cells** **pp 7196–7204**
Ajit P. Zambre, V. M. Kulkarni, Subhash Padhye,* Santosh K. Sandur and Bharat B. Aggarwal



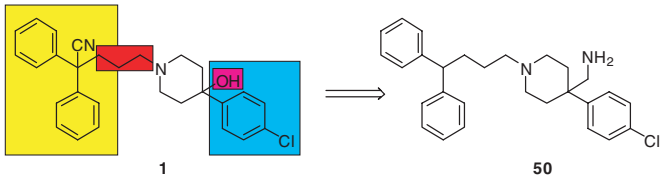

The work describes new curcumin analogs targeting NF-κB protein, where the diketo motif is functionalized through Knoevenagel condensation at the active methylene site yielding Schiff base ligands. Conjugation with copper shows synergistic enhancement in the inhibitory activity of these ligands.

**Ester derivatives of annulated tetrahydroazocines: A new class of selective acetylcholinesterase inhibitors** **pp 7205–7212**
Andrea Carotti, Modesto de Candia, Marco Catto, Tatiana N. Borisova, Alexey V. Varlamov, Estefanía Méndez-Álvarez, Ramón Soto-Otero, Leonid G. Voskressensky and Cosimo Altomare*



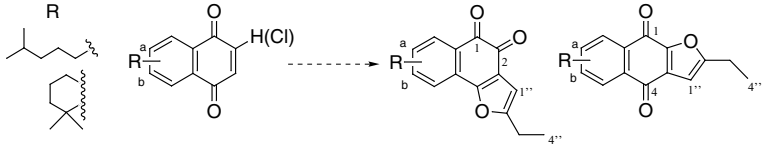

Several mono- and diester derivatives of annulated tetrahydroazocines, synthesized through an efficient 6 → 8 membered ring expansion procedure, exhibited acetylcholinesterase (AChE) inhibitory activity. The most potent derivatives **11** and **15** ($IC_{50}$ ca. 5 μM) proved selective, with selectivity ratios versus BuChE of ca. 15 and more than 20, respectively.

**Synthesis and pharmacological characterization of novel inverse agonists acting on the viral-encoded chemokine receptor US28** **pp 7213–7230**
Janneke W. Hulshof, Henry F. Vischer, Mark H. P. Verheij, Silvina A. Fratantoni, Martine J. Smit, Iwan J. P. de Esch and Rob Leurs*




The synthesis and structure–activity relationships of a new series of nonpeptidergic molecules acting as inverse agonists on the viral-encoded GPCR US28 are described. Our studies resulted in the identification of compound **50**, which is the highest affinity inverse agonist for US28 described in the literature.

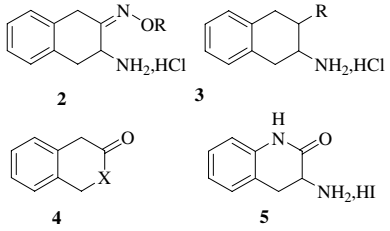
**New cytotoxic furoquinones obtained from terpenyl-1,4-naphthoquinones and 1,4-anthracenediones** **pp 7231–7240**
José M. Miguel del Corral,* M. Angeles Castro, Alaide B. Oliveira, Simone A. Gualberto, Carmen Cuevas and Arturo San Feliciano



Several new cytotoxic furoterpenyl-1,4-naphtho(anthra)quinones and furoterpenyl-1,2-naphtho(anthra)quinones have been prepared via oxidative cyclization from the corresponding 1,4-naphtho(anthra)quinones.

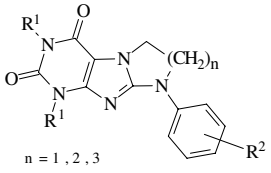
**Synthesis and structure activity relationships of novel non-peptidic metallo-aminopeptidase inhibitors** **pp 7241–7257**
Sébastien Albrecht, Albert Defoin,* Emmanuel Salomon, Céline Tarnus,* Anders Wetterholm and Jasper Z. Haeggström

Racemic derivatives **2**, **3** and analogues **4**, **5** of 3-amino-2-tetralone were synthesised and evaluated as inhibitors of four representative members of zinc-dependent aminopeptidases. $K_i$ values in the low micromolar range against 'one-zinc' aminopeptidases are obtained.

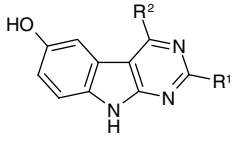


**Synthesis and biological activity of tricyclic aryloimidazo-, pyrimido-, and diazepinopurinediones** **pp 7258–7281**
Anna Drabczyńska, Christa E. Müller, Svenja K. Lacher, Britta Schumacher, Janina Karolak-Wojciechowska, Antony Nasal, Piotr Kawczak, Olga Yuzlenko, Elżbieta Pękala and Katarzyna Kieć-Kononowicz*

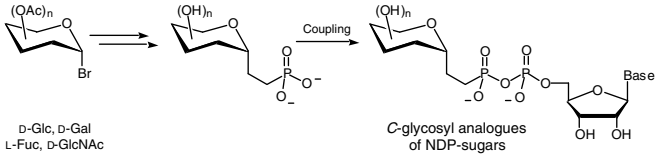
New 1,3-dimethyl 8-, 9-, 10-arylimidazo-, pyrimido-, and 1,3-diazepino[2,1-*f*]purinediones were obtained and evaluated in vitro for their affinity to $A_1$ and $A_{2A}$ adenosine receptors and in vivo as anticonvulsants. Physicochemical properties of the compounds were examined by means of calculations and experimental methods (HPLC). The obtained compounds showed affinity and $A_{2A}$ AR selectivity, pyrimido derivatives displayed anticonvulsant activity. The pyrimidine annelated ring is beneficial for both receptor and anticonvulsant activity.



**2,4-Diamino-9*H*-pyrimido[4,5-*b*]indol-5-ols: Synthesis, in vitro cytotoxic activity, and QSAR investigations** **pp 7282–7292**
Bernd Dotzauer, Renate Grünert, Patrick J. Bednarski, Harald Lanig, Jens Landwehr and Reinhard Troschütz*

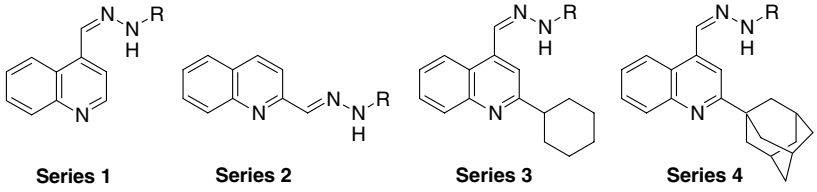


**Non-isosteric *C*-glycosyl analogues of natural nucleotide diphosphate sugars as glycosyltransferase inhibitors** pp 7293–7301
Sébastien Vidal, Isabelle Bruyère, Annie Malleron, Claudine Augé and Jean-Pierre Praly*



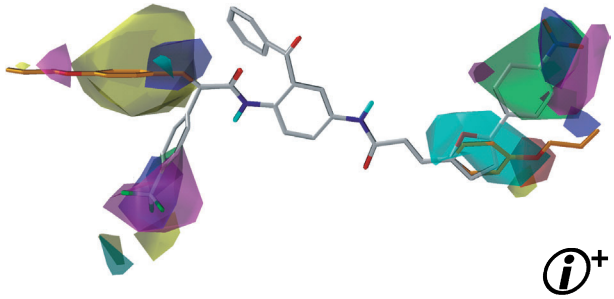

A series of glycosyltransferase inhibitors were synthesized through photo-induced radical addition of glycosyl bromides to diethyl vinylphosphonate followed by deprotection then coupling with activated nucleoside monophosphates. Inhibition of each analogue was tested through a competition assay using a fluorescent acceptor substrate and analysis by RP-HPLC. Each analogue displayed reasonable inhibition towards the corresponding glycosyltransferase with a noticeable inhibition (similar to the $K_m$ of the natural substrate) for the UDP-Gal analogue.

**Synthesis, anti-tuberculosis activity, and 3D-QSAR study of ring-substituted-2/4-quinolinecarbaldehyde derivatives** pp 7302–7310
Amit Nayyar, Alpeshkumar Malde, Evans Coutinho* and Rahul Jain*

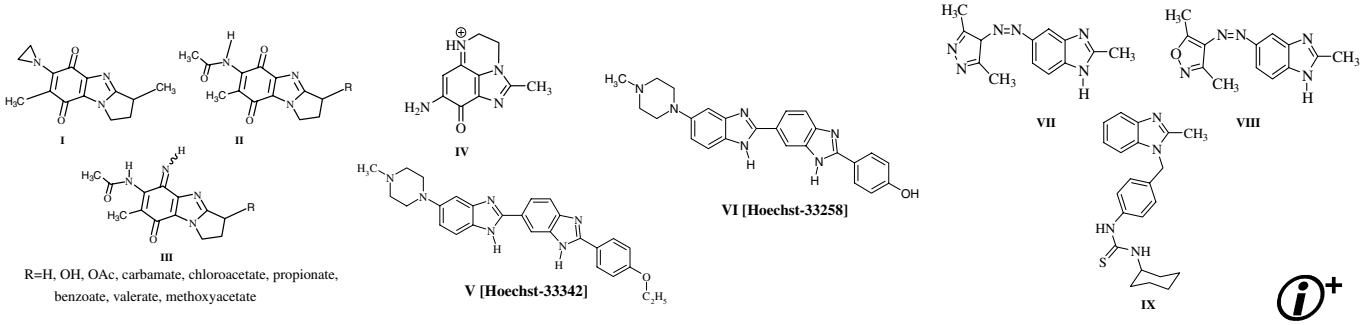



**3D-QSAR analysis of antimalarial farnesyltransferase inhibitors based on a 2,5-diaminobenzophenone scaffold** pp 7311–7323
Aihua Xie, Prasanna Sivaprakasam and Robert J. Doerksen*

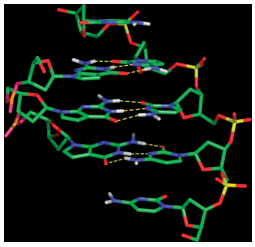
Steric, electrostatic and hydrophobic favored and disfavored regions for optimizing antimalarial activity of the title ligands.



**Synthesis and antitumor activity of 1-substituted-2-methyl-5-nitrobenzimidazoles** pp 7324–7332
Mostafa M. Ramla,* Mohamed A. Omar, Abdel-Momen M. El-Khamry and Hoda I. El-Diwani



**Solid-phase synthesis of positively charged deoxynucleic guanidine (DNG) oligonucleotide incorporating 7-deazaguanine bases** **pp 7333–7346**
Moti L. Jain and Thomas C. Bruice*



**QSAR studies about cytotoxicity of benzophenazines with dual inhibition toward both topoisomerases I and II: 3D-MoRSE descriptors and statistical considerations about variable selection** **pp 7347–7358**
Liane Saíz-Urra, Maykel Pérez González* and Marta Teijeira

A QSAR study was developed employing the 3D-MoRSE descriptors and a set of benzophenazines in order to model, the inhibition of the topoisomerases I and II, expressed by the cytotoxicity of these compounds ($IC_{50}$) against drug resistant human small cell lung carcinoma line cell H69/LX4. A comparison with other approaches such as the Topological, BCUT, Galvez topological charge indexes, 2D autocorrelations, Randic molecular profile, Geometrical, RDF and WHIM descriptors, was carried out.


## OTHER CONTENTS

**Addendum and Corrigendum** **pp 7359–7361**
**Summary of instructions to authors** **p I**

*Corresponding author
Supplementary data available via ScienceDirect

## COVER

2006: The cover figure shows a synthetic multifunctional pore that is composed of rigid-rod staves (para-octiphenyls, tan) and beta-sheet hoops (arrows) and can be activated with external ligands (fullerenes, golden spheres) and closed with internal blockers (alpha-helix, red ribbon) [Gorteau, V.; Bollot, G.; Mareda, J.; Pasini, D.; Tran, D.-H.; Lazar, A. N.; Coleman, A. W.; Sakai, N.; Matile, S. *Bioorg. Med. Chem.* **2005**, *13*, 5171–5180].



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