

## European Journal of Medicinal Chemistry Vol 43, No 5, 2008

### Contents

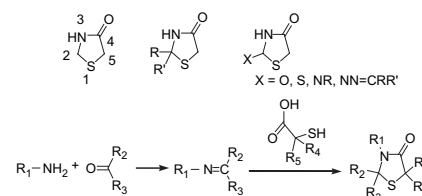
#### MINI-REVIEW

##### 4-Thiazolidinone – A biologically active scaffold

Amit Verma and Shailendra K. Saraf\*

pp. 897–905

The broad and potent activity of 4-thiazolidinones has established it as one of the biologically important scaffolds. The article has outlined the chemistry and biological activities of the 4-thiazolidinone scaffold. The synthetic methodologies indicate the simplicity, maneuverability and versatility, which offer the medicinal chemist a complete range of novel derivatives.



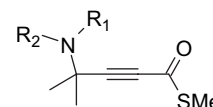
#### ORIGINAL ARTICLES

##### Aldehyde dehydrogenase inhibitors: $\alpha,\beta$ -Acetylenic *N*-substituted aminothiolesters are reversible growth inhibitors of normal epithelial but irreversible apoptogens for cancer epithelial cells from human prostate in culture

Gerard Quash, Guy Fournet\*, Charlotte Courvoisier, Rosa M. Martinez, Jacqueline Chantepie, Marie Julie Paret, Julie Pharaboz, Marie Odile Joly-Pharaboz, Jacques Goré, Jean André and Uwe Reichert

pp. 906–916

Growth-inhibitory efficacy and selectivity of  $\alpha,\beta$ -acetylenic *N*-substituted aminothiolesters obtained by the pharmacomodulation of the N atom have been addressed. Dimethylamino and morpholino compounds are *reversible* inhibitors of the growth of human prostate epithelial normal cells (HPENC) but *irreversible* inhibitors of the growth of human prostate epithelial cancer cells (DU145).

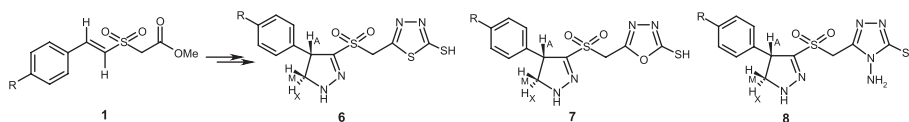


##### Synthesis and antimicrobial activity of novel sulfone-linked bis heterocycles

V. Padmavathi\*, P. Thriveni, G. Sudhakar Reddy and D. Deepthi

pp. 917–924

Novel sulfone-linked bis heterocycles pyrazolines in combination with thiadiazoles, oxadiazoles and triazoles were prepared from *E*-styrylsulfonylacetic acid methyl ester and tested for their antimicrobial activity. The compound **8** showed pronounced activity than the compounds **6** and **7**.

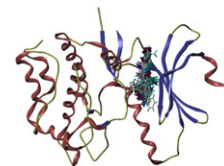


### 3D-QSAR studies of Checkpoint Kinase Weel inhibitors based on molecular docking, CoMFA and CoMSIA

pp. 925–938

Ping Yi, Xin Fang and Minghua Qiu\*

Molecular docking and three-dimensional quantitative structure-activity relationship (3D-QSAR) methods, CoMFA and CoMSIA were applied to a set of novel 4-phenylpyrrolo[3,4-c]carbazole-1,3(2*H*,6*H*)-dione Checkpoint Kinase Weel inhibitors.

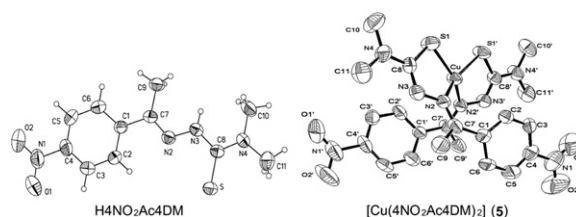


### 4-Nitroacetophenone-derived thiosemicarbazones and their copper(II) complexes with significant *in vitro* anti-trypanosomal activity

pp. 939–948

Anayive Pérez-Rebolledo, Letícia R. Teixeira, Alzir A. Batista, Antonio S. Mangrich, Gabriela Aguirre, Hugo Cerecetto, Mercedes González, Paola Hernández, Ana M. Ferreira, Nivaldo L. Speziali and Heloisa Beraldo\*

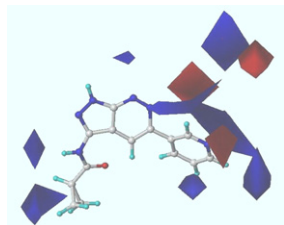
*N*<sup>4</sup>-Methyl- (H4NO<sub>2</sub>Ac4M, **1**), *N*<sup>4</sup>,*N*<sup>4</sup>-dimethyl- (H4NO<sub>2</sub>Ac4DM, **2**) and *N*<sup>4</sup>-piperidyl-4-nitroacetophenone thiosemicarbazone (H4NO<sub>2</sub>Ac4Pip, **3**) and their copper(II) complexes [Cu(4NO<sub>2</sub>Ac4M)<sub>2</sub>] (**4**), [Cu(4NO<sub>2</sub>Ac4DM)<sub>2</sub>] (**5**) and [Cu(4NO<sub>2</sub>Ac4Pip)<sub>2</sub>] (**6**) were tested for their *in vitro* ability to inhibit the growth of *Trypanosoma cruzi* epimastigote forms. H4NO<sub>2</sub>Ac4DM (**2**) as well as complexes **4** and **5** proved to be as active as the clinical reference drugs nifurtimox and benznidazol.



### Selectivity criterion for pyrazolo[3,4-*b*]pyrid[az]line derivatives as GSK-3 inhibitors: CoMFA and molecular docking studies

pp. 949–957

Dhilon S. Patel and Prasad V. Bharatam\*

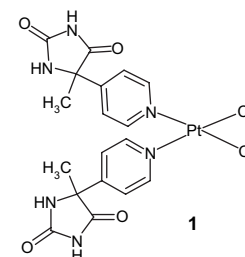


### Synthesis, characterization and biological activity of Pt(II) and Pt(IV) complexes with 5-methyl-5(4-pyridyl)-2,4-imidazolidenedione

pp. 958–965

Adriana Bakalova\*, Hristo Varbanov, Rossen Buyukliev, Georgi Momekov, Dilyan Ferdinandov, Spiro Konstantinov and Darwin Ivanov

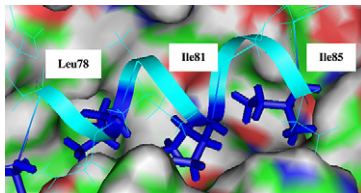
Three Pt(II) and one Pt(IV) complexes with 5-methyl-5(4-pyridyl)-2,4-imidazolidenedione and halogen ions were synthesized. Complex **1** showed superior cytotoxicity, as compared to the other complexes and was found to induce apoptosis.



**Structure–activity relationships of Bak derived peptides: Affinity and specificity modulations by amino acid replacement**

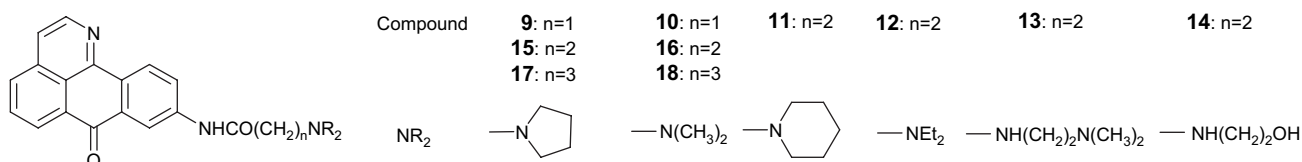
pp. 966–972

Virginie Frey, Julien Viaud, Guy Subra, Nicolas Cauquil, Jean-François Guichou, Patrick Casara, Gérard Grassy and Alain Chavanieu\*

**Oxoisoaporphine alkaloid derivatives: Synthesis, DNA binding affinity and cytotoxicity**

pp. 973–980

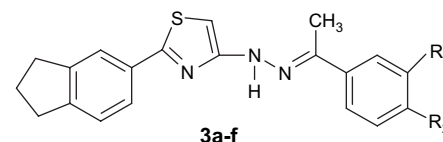
Huang Tang, Xiao-Dong Wang, Yong-Biao Wei, Shi-Liang Huang, Zhi-Shu Huang\*, Jia-Heng Tan, Lin-Kun An, Jian-Yong Wu, Albert Sun-Chi Chan and Lian-Quan Gu\*\*

**Synthesis and antituberculosis activity of new thiazolyldiazone derivatives**

pp. 981–985

Gülhan Turan-Zitouni\*, Ahmet Özdemir, Zafer Asim Kaplancikli, Kadriye Benkli, Pierre Chevallet and Gulsen Akalin

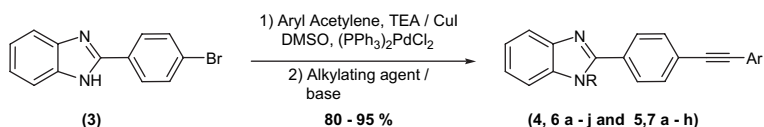
Thiazolyldiazone derivatives were investigated for antituberculosis activity against *Mycobacterium tuberculosis*. The role of the different substitution on phenyl ring on activity was explored in structure–activity relationship investigations.

**Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel N-substituted-2-(4-phenylethynyl-phenyl)-1H-benzimidazoles and N-substituted 2[4-(4,4-dimethyl-thiochroman-6-yl-ethynyl)-phenyl]-1H-benzimidazoles**

pp. 986–995

Ramanatham Vinodkumar\*, Sanjay Dashrath Vaidya, Bobba Venkata Siva Kumar, Umesh Nanasheeb Bhise, Shekhar Bhaskar Bhirud and Uday Chandrakant Mashelkar\*

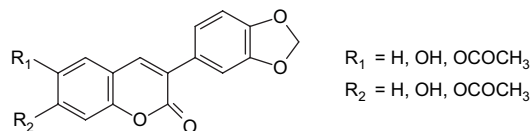
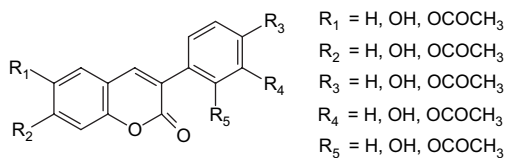
Synthesis of a series of novel and functionalized benzimidazole derivatives by the condensation of OPDA with 4-bromobenzoic acid and subsequent reactions of the product obtained with phenylacetylene and 6-ethynyl-4,4-dimethylthiochroman utilising Sonogashira coupling has been reported. The Sonogashira coupling products were then alkylated at the benzimidazole —NH with different electrophilic reagents leading to functionalized derivatives. All the compounds synthesized were screened for their potential anti-bacterial, anti-asthmatic and anti-diabetic properties, which exhibited moderate activities in screening studies in vitro.



### Inhibition of immune complex-mediated neutrophil oxidative metabolism: A pharmacophore model for 3-phenylcoumarin derivatives using GRIND-based 3D-QSAR and 2D-QSAR procedures

pp. 996–1007

Luciana M. Kabeya, Carlos H.T.P. da Silva\*, Alexandre Kanashiro, Joaquín M. Campos, Ana Elisa C.S. Azzolini, Ana Cristina M. Polizello, Mônica T. Pupo and Yara M. Lucisano-Valim\*\*

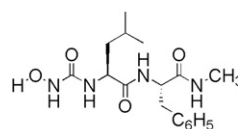


### Peptidyl 3-substituted 1-hydroxyureas as isosteric analogues of succinylhydroxamate MMP inhibitors

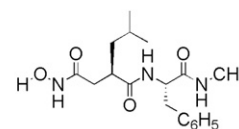
pp. 1008–1014

Cristina Campestre, Paolo Tortorella, Mariangela Agamennone, Serena Preziuso, Alessandro Biasone, Elisa Nuti, Armando Rossello and Carlo Gallina\*

Peptidyl-1-hydroxyureas are easily prepared by *N*-hydroxycarbamoylation of suitable dipeptides. Their potency against six MMPs approaches that of other *N*-hydroxyurea ligands against various zinc metalloenzymes, but is at least 50,000-fold lower than that of their succinylhydroxamate analogues.



Peptidyl-1-hydroxyurea

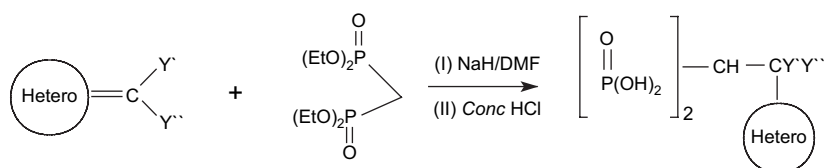


Succinyl-hydroxamic acid

### Synthesis, properties, and perspectives of *gem*-diphosphono substituted-thiazoles

pp. 1015–1024

Wafaa M. Abdou\*, Neven A. Ganoub, Athina Geronikaki and Eman Sabry

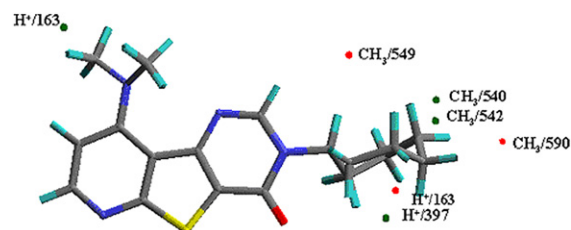


### 3D-QSAR studies of triazafluorenone inhibitors of metabotropic glutamate receptor subtype 1

pp. 1025–1034

Y. Nataraja Sekhar, Muttineni Ravikumar\*, M. Ravi Shashi Nayana, Shyam C. Mallena and Madala Kishore Kumar

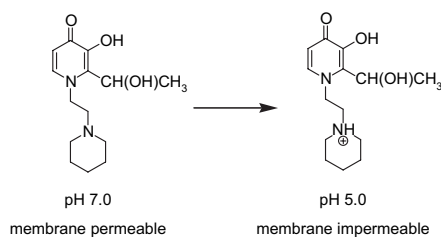
3D-QSAR studies, including MFA and RSA was performed on 46 triazafluorenone derivatives as inhibitors of metabotropic glutamate receptor subtype 1 (mGluR1) to predict the importance of proper steric and electrostatic fragments, which are necessary for higher activity.



**Basic 3-hydroxypyridin-4-ones: Potential antimalarial agents**

pp. 1035–1047

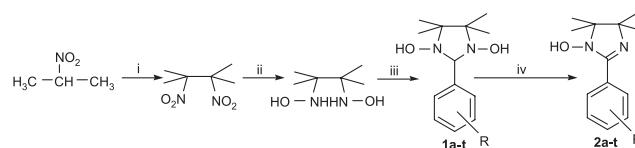
Lotfollah S. Dehkordi, Zu D. Liu and Robert C. Hider\*

**A new class of analgesic agents toward prostacyclin receptor inhibition: Synthesis, biological studies and QSAR analysis of 1-hydroxyl-2-substituted phenyl-4,4,5,5-tetramethylimidazolines**

pp. 1048–1058

Ming Zhao, Zheng Li, Li Peng, Yu-Rong Tang, Chao Wang, Ziding Zhang\* and Shiqi Peng\*\*

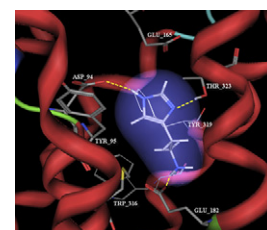
Synthetic route of 1-hydroxyl-2-substituted phenyl-4,4,5,5-tetramethylimidazolines (**2a–t**).

**Binding mode analysis and enrichment studies on homology models of the human histamine H4 receptor**

pp. 1059–1070

Róbert Kiss, Béla Noszál, Ákos Rácz, András Falus, Dániel Erős and György M. Keserű\*

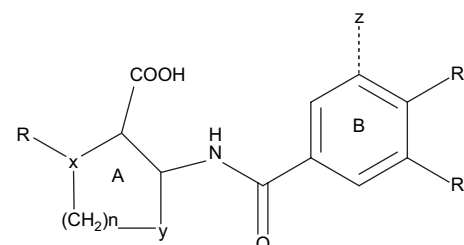
Ligand-supported homology models of the human histamine H4 receptor were developed. Our results suggest a different binding mode of histamine than proposed previously. Enrichment studies demonstrated the suitability of the models for virtual screening.

**QSAR studies on benzoylaminobenzoic acid derivatives as inhibitors of  $\beta$ -ketoacyl-acyl carrier protein synthase III**

pp. 1071–1080

Satyakam Singh, Love K. Soni, Manish K. Gupta, Yenamandra S. Prabhakar and S.G. Kaskhedikar\*

Quantitative structure–activity relationship (QSAR) studies have been carried out on a series of benzoylaminobenzoic acid derivatives as potent inhibitors of FabH and antibacterial activity against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Neisseria meningitidis* and *Escherichia coli*, which demonstrate FabH inhibitory activity in cell free and whole cell system. The QSAR studies revealed that inhibitory activity increases with increase in hydrophobicity, molar refractivity, aromaticity, and presence of OH group (on  $x$  position of the nucleus). On the other side presence of hetero-atoms like N, O, or S at  $R_1$  position of the nucleus decreases the inhibitory activity.

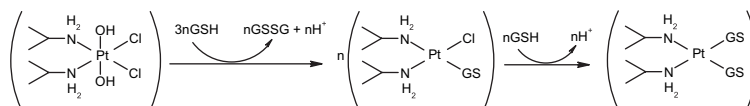


## SHORT COMMUNICATIONS

## Insight into the reactive form of the anticancer agent iproplatin

pp. 1081–1084

Erika Volckova, Evelyne Weaver and Rathindra N. Bose\*

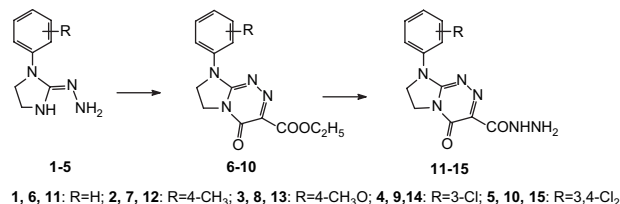


## Synthesis, structure elucidation and identification of antitumoural properties of novel fused 1,2,4-triazine aryl derivatives

pp. 1085–1094

Krzysztof Sztanke\*, Kazimierz Pasternak, Jolanta Rzymowska, Małgorzata Sztanke and Martyna Kandefer-Szerszeń

Synthesis, structure elucidation and antitumoural properties of novel fused 1,2,4-triazine aryl derivatives containing the ethoxycarbonyl (**6–10**) and carbohydrazide groups (**11–15**) are presented. Antitumour activities for the heterobicyclic hydrazides of the type **11–14** were evaluated by BrdU method for human LS180, SiHa and T47D carcinoma cells. Amongst them, hydrazide **14** has exhibited remarkable inhibitory effect against SiHa and LS180 cancer cells, and simultaneously was proved to be non-toxic towards the human normal cell line – HSF cells. Beside these, compound **14** in a concentration of 32.6  $\mu\text{M}$  was found to possess efficiency for DNA strand breakage of all the examined cancer cell lines. Furthermore, heterobicyclic hydrazide of the type **14** was able to evoke statistically significant apoptotic effects in human breast cancer (T47D) cells. The antiproliferative properties *in vitro* for heterobicyclics **6–14** were evaluated by MTT method for human leukaemic Jurkat cells. Significant viability decreases in Jurkat cells treated with different concentrations of compounds **10** and **11** were observed, suggesting their cytotoxic activities.

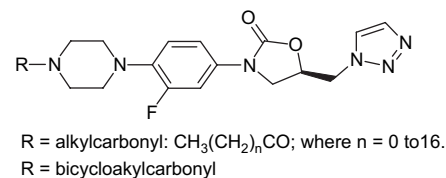


## Synthesis and structure–antibacterial activity of triazolyl oxazolidinones containing long chain acyl moiety

pp. 1095–1104

Oludotun A. Phillips\*, Edet E. Udo and Santhosh M. Samuel

Synthesis of new 5-triazolylmethyl oxazolidinone derivatives, their antibacterial activity and correlation with selected molecular descriptors are presented.

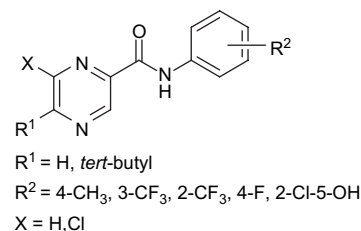


## Synthesis and antimycobacterial evaluation of substituted pyrazinecarboxamides

pp. 1105–1113

Martin Dolezal\*, Pavlina Cmedlova, Lukas Palek, Jarmila Vinsova, Jiri Kunes, Vladimir Buchta, Josef Jampilek and Katarina Kralova

Twenty potential pyrazinamide derivatives were synthesized using modification of currently known synthetic pathways. Substituted anilides of pyrazinecarboxylic acid were investigated for their antimycobacterial, antifungal, photosynthesis-inhibiting activities and their lipophilicity parameters.



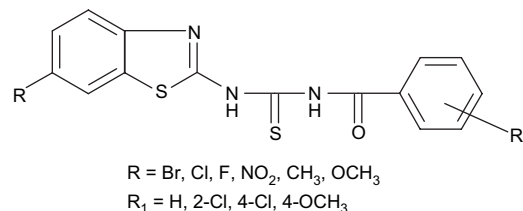
## PRELIMINARY COMMUNICATION

***N*-{[(6-Substituted-1,3-benzothiazole-2-yl)amino]carbonothioyl}-2/4-substituted benzamides:**  
**Synthesis and pharmacological evaluation**

pp. 1114–1122

Arpana Rana, Nadeem Siddiqui\*, Suroor A. Khan, Syed Ehtaishamul Haque and Mashooq A. Bhat

A series of 1,3-benzothiazol-2-yl benzamides (**11–30**) were prepared in satisfactory yield and evaluated for their anticonvulsant, neurotoxicity, CNS depressant study and other toxicity studies. All the synthesized compounds were in good agreement with elemental and spectral data. Majority of the compounds were active in MES and scPTZ screen and showed the decrease in the immobility time. None of the compounds had shown neurotoxicity or liver toxicity.



**COVER**

Overlay of the experimental and docked conformations of the ligand fluorescein in complex with an anti-fluorescein 4-4-20 Fab fragment (PDB code 1flr, 1.85 Å). The top-scoring conformation (purple) selected by the HINT force field, among the 255 poses generated by AutoDock, nearly overlays the crystallographic structure (yellow), while the conformation selected by the AutoDock scoring function (green) reverses the positions of the carbonyl and hydroxyl groups.

Image provided by Francesca Spyraakis, Alessio Amadasi, Micaela Fornabaio, Donald J. Abraham, Andrea Mozzarelli, Glen E. Kellogg, Pietro Cozzini. © 2008. Published by Elsevier Masson SAS

---

\* Corresponding authors.



Full text of this journal is available online from **ScienceDirect**. Visit [www.sciencedirect.com](http://www.sciencedirect.com) for more information.

---

*Cited/Abstracted in : Biological Abstracts, Chemical Abstracts, CABS, CNRS/Pascal, Current Contents (Life Sciences), EMBASE, Index Medicus/Medline, Science Citation Index. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®.*

---



ISSN 0223-5234