

## European Journal of Medicinal Chemistry Vol 43, No 9, 2008

### Contents

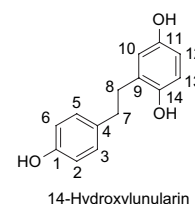
#### ORIGINAL ARTICLES

##### Activity of a hydroxybibenzyl bryophyte constituent against *Leishmania* spp. and *Trypanosoma cruzi*: In silico, in vitro and in vivo activity studies

pp. 1797–1807

Virginia Roldos, Hector Nakayama, Miriam Rolón, Alina Montero-Torres, Fernando Trucco, Susana Torres, Celeste Vega, Yovanni Marrero-Ponce, Viviana Huguaburu, Gloria Yaluff, Alicia Gómez-Barrio, Luis Sanabria, Maria Elena Ferreira, Antonieta Rojas de Arias\* and Enrique Pandolfi\*\*

The synthesis and potent antiprotozoal activity of 14-hydroxylunularin, a natural hydroxybibenzyl constituent from *Ricciocarpus natans*, is reported.

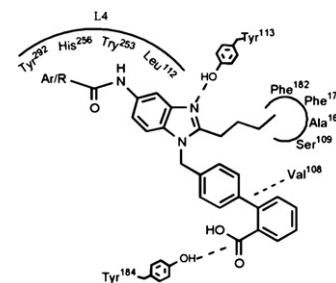


##### Angiotensin II – AT<sub>1</sub> receptor antagonists: Design, synthesis and evaluation of substituted carboxamido benzimidazole derivatives

pp. 1808–1812

Dhvanit I. Shah, Manu Sharma, Yogita Bansal, Gulshan Bansal\* and Manjeet Singh

A series of 5-(alkyl and aryl)carboxamido benzimidazole derivatives had been designed, synthesized and evaluated for in vitro angiotensin II – AT<sub>1</sub> receptor antagonism and in vivo antihypertensive activities. The pharmacological activities were inversely related to the size of alkyl and aryl substituents. It can be suggested that compounds with lower alkyl groups at 5-position of benzimidazole nucleus demonstrated potent antihypertensive activity.

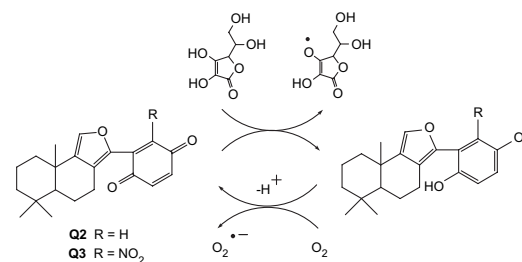


##### Part 1: Effect of vitamin C on the biological activity of two euryfurylbenzoquinones on TLT, a murine hepatoma cell line

pp. 1813–1817

Julio Benites, Leonel Rojo, Jaime A. Valderrama, Henryk Taper and Pedro Buc Calderon\*

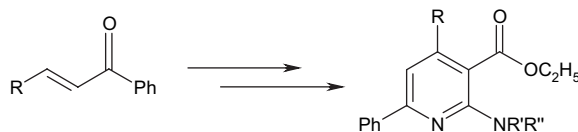
2-Euryfuryl- and 2-euryfuryl-3-nitro-1,4-benzoquinone (compounds **Q2** and **Q3**) were assessed for their cytotoxicity against TLT cells in the absence and in the presence of vitamin C.



### Synthesis of new 3-pyridinecarboxylates of potential vasodilation properties

pp. 1818–1827

Adel S. Girgis\*, Nawal Mishriky, Ahmad M. Farag, Wafaa I. El-Eraky and Hanaa Farag

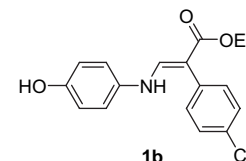


### Enamines as novel antibacterials and their structure–activity relationships

pp. 1828–1836

Zhu-Ping Xiao, Rui-Qin Fang, Huan-Qiu Li, Jia-Yu Xue, Yi Zheng and Hai-Liang Zhu\*

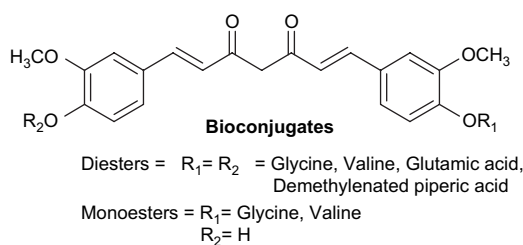
The most active compound, (*E*)-ethyl 3-(4-hydroxyphenylamino)-2-(4-chlorophenyl)acrylate (**1b**), showed considerable antibacterial activities against *Staphylococcus aureus* ATCC 6538 and against *Pseudomonas fluorescens* ATCC 13525, which was superior to the positive controls penicillin and kanamycin respectively.



### Design, synthesis and characterization of some bioactive conjugates of curcumin with glycine, glutamic acid, valine and demethylenated piperic acid and study of their antimicrobial and antiproliferative properties

pp. 1837–1846

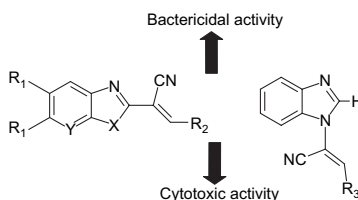
Shiv K. Dubey, Anuj K. Sharma, Upma Narain, Krishna Misra\* and Uttam Pati



### Structure–activity relationships of novel heteroaryl-acrylonitriles as cytotoxic and antibacterial agents

pp. 1847–1857

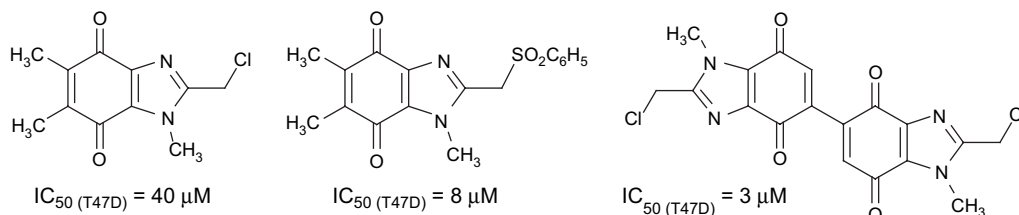
Franciszek Sączewski\*\*, Agnieszka Stencel, Andrzej M. Bieńczyk, Karolina A. Langowska, Martin Michaelis, Władysław Werel, Rafał Hałasa, Przemysław Reszka and Patrick J. Bednarski\*



**Synthesis and cytotoxicity evaluation of some benzimidazole-4,7-diones as bio-reductive anticancer agents pp. 1858–1864**

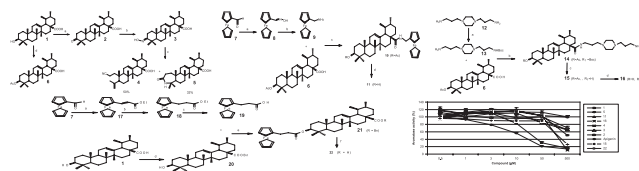
Armand Gellis, Hervé Kovacic, Narimène Boufatah and Patrice Vanelle\*

New benzimidazole-4,7-diones, substituted at 2-position, were synthesized via a microwave-assisted reaction. Their cytotoxicity has been evaluated on colon, breast and lung cancer cell lines. Some derivatives demonstrate excellent activity and exhibit a similar dose effect to mitomycin C.

**Evaluation of ursolic acid isolated from *Ilex paraguariensis* and derivatives on aromatase inhibition pp. 1865–1877**

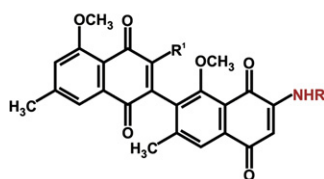
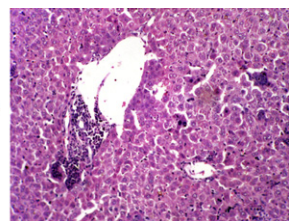
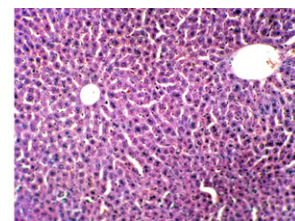
Simone C.B. Gnoatto, Alexandra Dassonville-Klimpt, Sophie Da Nascimento, Philippe Galéra, Karim Boumediene, Grace Gosmann, Pascal Sonnet\* and Safa Moslemi\*\*

The inhibitory potency of ursolic acid isolated from *Ilex paraguariensis* and its derivatives to inhibit aromatase activity was assessed. Only ursolic acid **1** showed an efficient and dose-dependent aromatase inhibition.

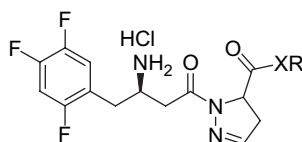
**Synthesis of novel aminoquinonoid analogues of diospyrin and evaluation of their inhibitory activity against murine and human cancer cells pp. 1878–1888**

Madhushree Das Sarma, Rina Ghosh, Amarendra Patra and Banasri Hazra\*

Site-specific amination of diospyrin, isolated from *Diospyros montana* Roxb., produced derivatives with variable anti-tumor activity against two human cell lines and a murine tumor model.

Amino derivatives of diospyrin  
3a – e ; 4 ; 5EAC tumor bearing control  
(Untreated)Treated with  
5 : R = CH<sub>3</sub>CO : R<sup>1</sup> = H**Synthesis and biological evaluation of pyrazoline analogues with β-amino acyl group as dipeptidyl peptidase IV inhibitors pp. 1889–1902**

Mi Ae Jun, Woul Seong Park, Seung Kyu Kang, Ki Young Kim, Kwang Rok Kim, Sang Dal Rhee, Myung Ae Bae, Nam Sook Kang, Sang-Kwon Sohn, Sung Gyu Kim, Jie Oh Lee, Duck Hyung Lee, Hyae Gyeong Cheon, Sung Soo Kim\* and Jin Hee Ahn\*

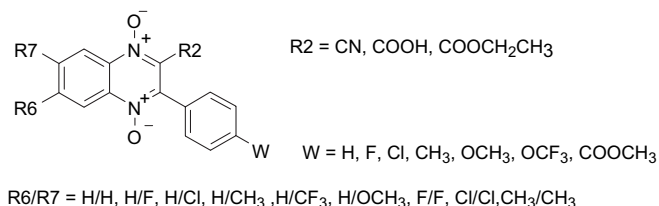


### Synthesis and structure–activity relationship of 3-phenylquinoxaline 1,4-di-*N*-oxide derivatives as antimalarial agents

pp. 1903–1910

Esther Vicente, Lidia M. Lima, Emily Bongard, Sarah Charnaud, Raquel Villar, Beatriz Solano, Asunción Burguete, Silvia Perez-Silanes, Ignacio Aldana\*, Livia Vivas and Antonio Monge

In vitro antiplasmodial activity, cytotoxicity and selectivity parameters of new 3-phenylquinoxaline 1,4-di-*N*-oxide derivatives are reported. These derivatives emerge as new valid lead-compounds for synthesizing new structures that possess improved activity.

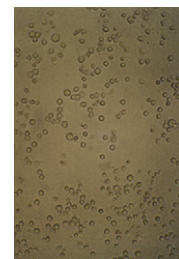


### Synthesis and characterization of polyoxometalates loaded starch nanocomplex and its antitumoral activity

pp. 1911–1917

Fengying Zhai, Dongliu Li, Chunli Zhang, Xiaohong Wang\* and Rui Li\*

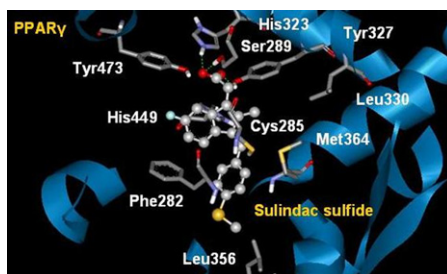
Using starch nanoparticles, by a water-in-oil emulsion technique, loaded polyoxometalates (POMs)  $\alpha$ -K<sub>8</sub>H<sub>6</sub>[Si<sub>2</sub>W<sub>18</sub>Ti<sub>6</sub>O<sub>77</sub>] (Si<sub>2</sub>W<sub>18</sub>Ti<sub>6</sub>) have been prepared. This new complex exhibited higher stability, antitumoral activity and extending the survival days of the mice with tumor than its parent owing to the encapsulation by starch nanoparticles.



### NSAIDs revisited: Putative molecular basis of their interactions with peroxisome proliferator-activated gamma receptor (PPAR $\gamma$ )

pp. 1918–1925

Nelilma C. Romeiro\*, Carlos M.R. Sant'Anna, Lidia M. Lima, Carlos A.M. Fraga and Eliezer J. Barreiro\*\*

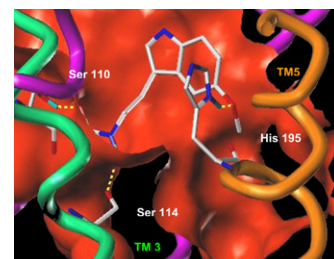


### Homology modeling of MT<sub>1</sub> and MT<sub>2</sub> receptors

pp. 1926–1944

Amaury Farce, Anton O. Chugunov, Cédric Logé, Ahmed Sabaouni, Saïd Yous, Sébastien Dilly, Nicolas Renault, Gérard Vergoten, Roman G. Efremov, Daniel Lesieur and Philippe Chavatte\*

We report here the construction of a 3D structure for both human MT<sub>1</sub> and MT<sub>2</sub> receptors and their careful modification in an attempt to propose a valid melatonin binding site.

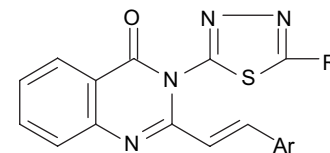


### CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones

pp. 1945–1954

Varsha Jatav, Pradeep Mishra, Sushil Kashaw\* and J.P. Stables

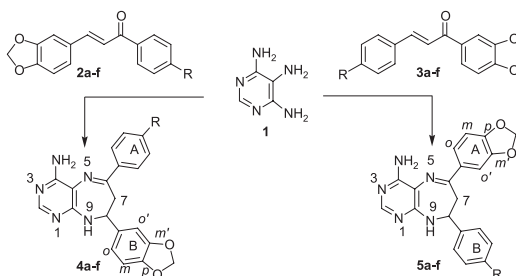
Eighteen new 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones have been synthesized and evaluated for anticonvulsant, sedative–hypnotic and CNS depression activities. Maximal electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice were used to screen anticonvulsant activity. The synthesized compounds were found to be better sedative–hypnotic and CNS depressant agents than anticonvulsant agent.



### Microwave induced synthesis of novel 8,9-dihydro-7*H*-pyrimido[4,5-*b*][1,4]diazepines as potential antitumor agents

pp. 1955–1962

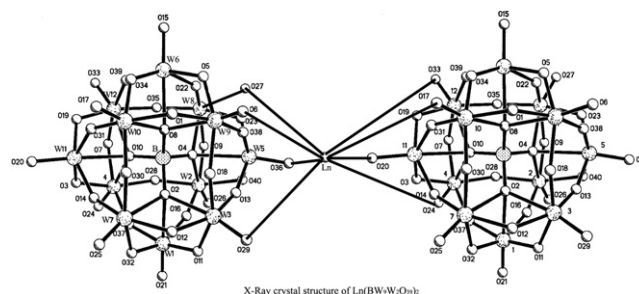
Braulio Insuasty\*, Fabián Orozco, Jairo Quiroga, Rodrigo Abonia, Manuel Nogueras and Justo Cobo



### *In vitro* and *in vivo* investigations on the antiviral activity of a series of mixed-valence rare earth borotungstate heteropoly blues

pp. 1963–1970

Ya-Nan Liu, Shuo Shi, Wen-Jie Mei, Cai-Ping Tan, Lan-Mei Chen, Jie Liu\*, Wen-Jie Zheng\* and Liang-Nian Ji

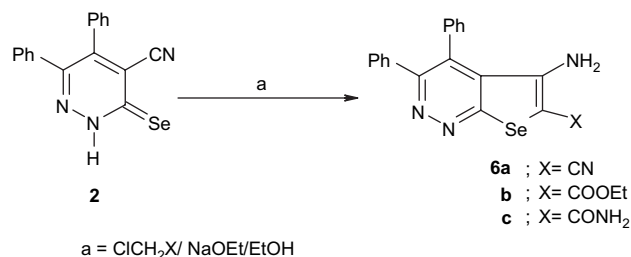


### Selenium containing heterocycles: Synthesis, anti-inflammatory, analgesic and anti-microbial activities of some new 4-cyanopyridazine-3(2*H*)selenone derivatives

pp. 1971–1977

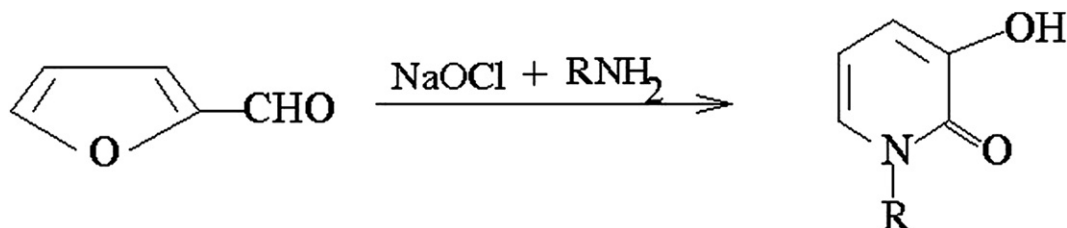
Sh.H. Abdel-Hafez\*

New series of selenolo[2,3-*c*]pyridazine and pyrimido[4',5':4,5]selenolo[2,3-*c*] pyridazine derivatives were prepared from new 4-cyano-5,6-diphenylpyridazine-3(2*H*)selenone (**2**).



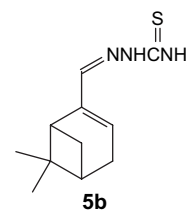
## SHORT COMMUNICATIONS

**Synthesis of 3-hydroxypyrid-2-ones from furfural for treatment against iron overload and iron deficiency** pp. 1978–1982  
 Bhupesh S. Samant\*



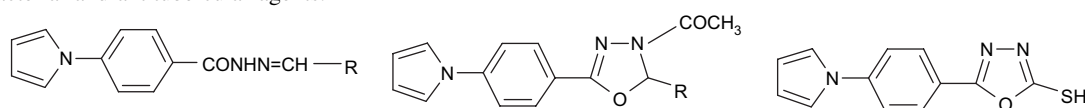
**Synthesis and antimalarial activity of semicarbazone and thiosemicarbazone derivatives** pp. 1983–1988  
 Renata B. de Oliveira, Elaine M. de Souza-Fagundes, Rodrigo P.P. Soares, Anderson A. Andrade, Antoniana U. Krettli and Carlos L. Zani\*

Semicarbazone and thiosemicarbazone derivatives were prepared and tested in vitro against a chloroquine resistant strain of *Plasmodium falciparum* (W2) to evaluate their antiplasmodial potential. The thiosemicarbazone **5b** was selected for in vivo tests on mice infected with *Plasmodium berghei* (strain NK-65). The in vitro and in vivo results make **5b** an interesting lead for further development.

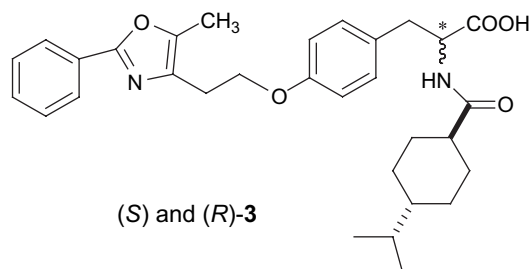


**Synthesis of new 4-pyrrol-1-yl benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole ring systems: A novel class of potential antibacterial and antitubercular agents** pp. 1989–1996  
 S.D. Joshi, H.M. Vagdevi\*, V.P. Vaidya and G.S. Gadaginamath

A series of 4-pyrrol-1-yl benzoic acid hydrazide analogs and some derived ring systems were synthesized. The structures of new compounds were established on the basis of their elemental analysis and IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectral data. All compounds were subjected to in vitro antibacterial testing against six pathogenic strains and antitubercular screening against *Mycobacterium tuberculosis*. Preliminary results indicate that some of them exhibited promising activities and they deserve more consideration as potential antibacterial and antitubercular agents.



**Insulin-releasing activity of a series of phenylalanine derivatives** pp. 1997–2003  
 Lei Tang, Juanhong Yu, Haoshu Wu, Houxing Fan, Yushe Yang\* and Ruyun Ji

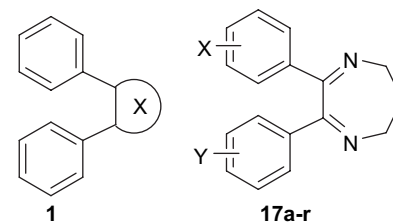


**Synthesis, antileukemic and antiplatelet activities of 2,3-diaryl-6,7-dihydro-5H-1,4-diazepines**

pp. 2004–2010

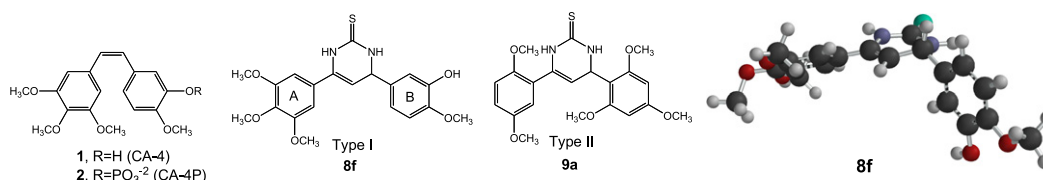
R. Ramajayam, Rajani Giridhar\*, M.R. Yadav, R. Balaraman, Hakim Djaballah, David Shum and Constantin Radu

Various vicinal diaryl heterocycles (**1**) are found to be pharmacologically important in medicinal chemistry. In this paper 2,3-diaryl-6,7-dihydro-5H-1,4-diazepines (**17a–r**) were synthesized and evaluated for antileukemic and antiplatelet activities. The 2,3-diaryl-1,4-diazepine motif showed an interesting antiplatelet activity profile.

**1,2,3,4-Tetrahydro-2-thioxopyrimidine analogs of combretastatin-A4**

pp. 2011–2015

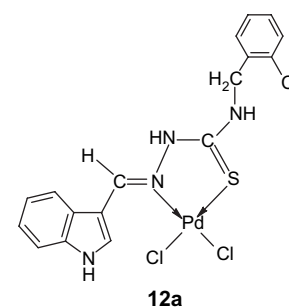
Lauren Lee, Ryan Davis, Jenna Vanderham, Patrice Hills, Hilary Mackay, Toni Brown, Susan L. Mooberry and Moses Lee\*

**New Pd(II) complexes of the synthesized 1-N-substituted thiosemicarbazones of 3-indole carboxaldehyde: Characterization and antiamoebic assessment against *E. histolytica***

pp. 2016–2028

Kakul Husain, Abdul Roouf Bhat and Amir Azam\*

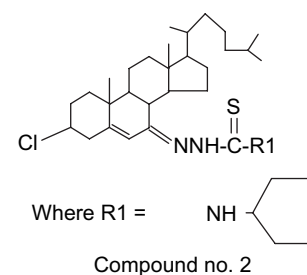
Reaction of 3-indole carboxaldehyde with aminothiocabonyl hydrazines resulted in the formation of 3-indole carboxaldehyde thiosemicarbazones (TSCs) **1–13**. The synthesized thiosemicarbazones were used as ligands in the formation of  $[\text{Pd}(\text{TSC})\text{Cl}_2]$  complexes with palladium(II) metal ion precursor,  $[\text{Pd}(\text{DMSO})_2\text{Cl}_2]$ . The testing of the antiamoebic activity against the protozoan parasite *Entamoeba histolytica* showed that compound **12a** displays remarkable antiamoebic activity than metronidazole ( $\text{IC}_{50}$  values of **0.29** vs **1.81**  $\mu\text{M}$ , respectively). MTT assay showed that the compounds are non-toxic to human kidney epithelial cell line.

**Synthesis and *in vitro* antibacterial activity of new steroidal thiosemicarbazone derivatives**

pp. 2029–2034

Salman Ahmad Khan, Praveen Kumar, Rajkumar Joshi, Prince F. Iqbal and Kishwar Saleem\*

We investigated the antibacterial activity of some new steroidal thiosemicarbazone derivatives, prepared from the reaction of cholest-5-en-7-one with thiosemicarbazides, in ethanol in the presence of a few drops of HCl at 80 °C in high yield. All the compounds have been characterized by means of elemental analyses, IR,  $^1\text{H}$  NMR and mass spectroscopic data, to find an effective antibacterial agent. The antibacterial activity was first tested *in vitro* by the disk diffusion assay against two Gram-positive and two Gram-negative bacteria, and then the minimum inhibitory concentration (MIC) of compounds was determined. The results showed that the steroidal thiosemicarbazones derivatives inhibit growth of both types of the bacteria (Gram-positive and Gram-negative). The acetoxy and chloro derivatives of cyclopentyl and cyclohexyl amine thiosemicarbazones were found to have more antibacterial activity than the other derivatives.



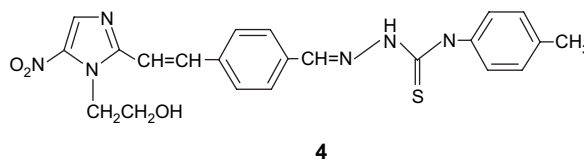


**Synthesis and antiamoebic activity of metronidazole thiosemicarbazone analogues**

pp. 2035–2039

Mohammad Abid, Subhash M. Agarwal and Amir Azam\*

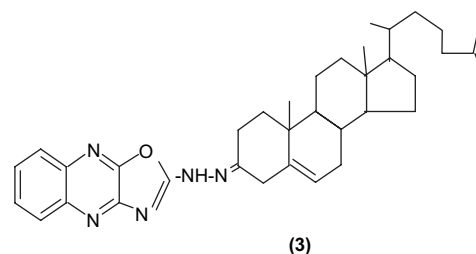
Eleven  $N^4$ -substituted thiosemicarbazone analogues of metronidazole were synthesized and evaluated for their antiamoebic activity by the microdilution method against *HML:IMSS* strain of *Entamoeba histolytica*. As many as eight (**1–4**, **7–9** and **11**) out of eleven compounds were found better inhibitors of *E. histolytica* growth and compound **4** showed the most promising antiamoebic activity.

**Synthesis, characterization and *in vitro* antibacterial activity of new steroidal 5-en-3-oxazolo and thiazoloquinoxaline**

pp. 2040–2044

Salman A. Khan\*

Steroidal heterocyclic systems namely cholest-5-en-3-oxazolo and thiazoloquinoxaline have been synthesized *via* the reaction of cholest-5-en-3-one semicarbazone/thiosemicarbazone with 2,3-dichloroquinoxaline at 80 °C in high yield. Cholest-5-en-3-one semicarbazone is obtained by the condensation of cholest-5-en-3-one with semicarbazide in the presence of AcONa in ethanol and cholest-5-en-one thiosemicarbazone is obtained by the condensation of cholest-5-en-3-one with thiosemicarbazide in ethanol in the presence of a few drops of HCl. The structures of these compounds were evident by elemental analysis, IR,  $^1\text{H}$  NMR and FAB mass spectral analysis. These synthesized compounds were investigated for antibacterial activity first by the disk-diffusion assay against two Gram-positive and two Gram-negative bacteria and then the minimum inhibitory concentration (MIC). The results showed that these compounds oxazolo/thiazoloquinoxaline are better antibacterial agent as compared to standard drug Amoxicillin. The results showed that these compounds oxazolo/thiazoloquinoxaline are better antibacterial agents as compared to the standard drug Amoxicillin.





**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 Spyrakis, Alessio Amadasi, Micaela Fornabaio, Donald J. Abraham, Andrea Mozzarelli, Glen E. Kellogg, Pietro Cozzini. © 2008. Published by Elsevier Masson SAS

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\* Corresponding authors.

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