

## Contents

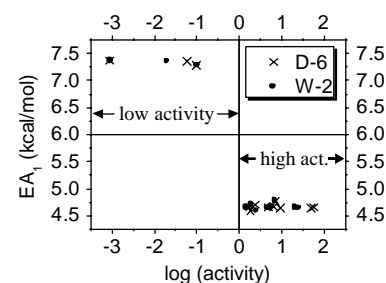
### ARTICLES

**Effective discrimination of antimalarial potency of artemisinin compounds based on quantum chemical calculations of their reaction mechanism**

pp 2082–2088

Somsak Tonmunphean, Vudhichai Parasuk and Sirirat Kokpol\*

Effective discrimination between high and low antimalarial activities compounds was accomplished using  $EA_1$ ,  $\Delta E_1$ , and  $\Delta E(1A - 2A)$  energies obtained from quantum chemical calculations on their reaction mechanism.

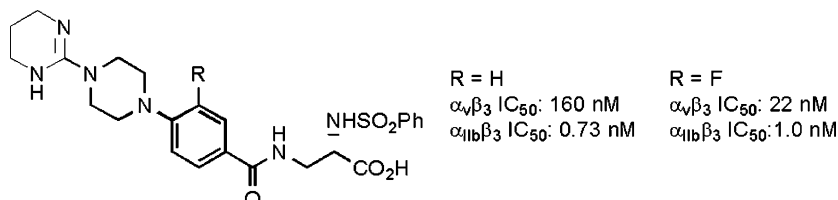


**Tricyclic pharmacophore-based molecules as novel integrin  $\alpha_v\beta_3$  antagonists. Part 1:**

pp 2089–2108

**Design and synthesis of a lead compound exhibiting  $\alpha_v\beta_3/\alpha_{IIb}\beta_3$  dual antagonistic activity**

Dai Kubota, Minoru Ishikawa, Mikio Yamamoto, Shoichi Murakami, Mitsugu Hachisu, Kiyoaki Katano and Keiichi Ajito\*



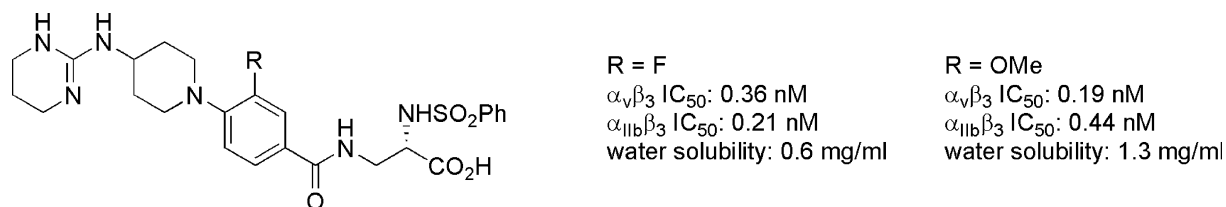
A linear and unfused-tricyclic pharmacophore, which was designed from an RGD tripeptide sequence, was synthesized as a novel non-peptide integrin  $\alpha_v\beta_3$  antagonist.

**Tricyclic pharmacophore-based molecules as novel integrin  $\alpha_v\beta_3$  antagonists. Part 2:**

pp 2109–2130

**Synthesis of potent  $\alpha_v\beta_3/\alpha_{IIb}\beta_3$  dual antagonists**

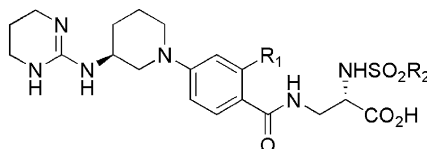
Minoru Ishikawa, Dai Kubota, Mikio Yamamoto, Chizuko Kuroda, Maki Iguchi, Akihiro Koyanagi, Shoichi Murakami and Keiichi Ajito\*



**Tricyclic pharmacophore-based molecules as novel integrin  $\alpha_v\beta_3$  antagonists. Part III: Synthesis of potent antagonists with  $\alpha_v\beta_3/\alpha_{IIb}\beta_3$  dual activity and improved water solubility**

pp 2131–2150

Minoru Ishikawa,\* Yukiko Hiraiwa, Dai Kubota, Masaki Tsushima, Takashi Watanabe, Shoichi Murakami, Shokichi Ouchi and Keiichi Ajito



$R_1 = H, R_2 = Ph$   
 $\alpha_v\beta_3$  IC<sub>50</sub>: 0.48 nM  
 $\alpha_{IIb}\beta_3$  IC<sub>50</sub>: 0.56 nM  
 water solubility: 3.5 mg/ml

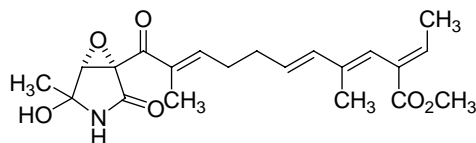
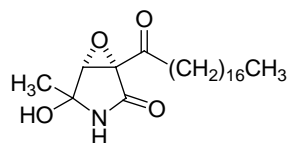
$R_1 = F, R_2 = Ph$   
 $\alpha_v\beta_3$  IC<sub>50</sub>: 0.23 nM  
 $\alpha_{IIb}\beta_3$  IC<sub>50</sub>: 0.78 nM  
 water solubility: 2.8 mg/ml

$R_1 = H, R_2 = 2\text{-thienyl}$   
 $\alpha_v\beta_3$  IC<sub>50</sub>: 0.25 nM  
 $\alpha_{IIb}\beta_3$  IC<sub>50</sub>: 0.40 nM  
 water solubility: 3.3 mg/ml

**Apoptosis-inducing effect of epolactaene derivatives on BALL-1 cells**

pp 2151–2161

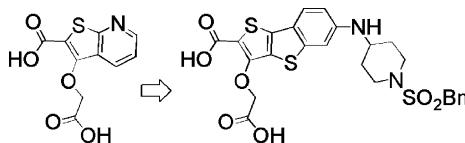
Kouji Kuramochi, Rie Matsui, Yasuaki Matsubara, Junko Nakai, Takashi Sunoki, Satoshi Arai, Seigo Nagata, Yukitoshi Nagahara, Yoshiyuki Mizushima, Masahiko Ikekita and Susumu Kobayashi\*


 Epolactaene IC<sub>50</sub> 3.82  $\mu$ M

 1e IC<sub>50</sub> 0.70  $\mu$ M

**Bicyclic and tricyclic thiophenes as protein tyrosine phosphatase 1B inhibitors**

pp 2162–2177

A. F. Moretto, S. J. Kirincich, W. X. Xu, M. J. Smith, Z.-K. Wan, D. P. Wilson, B. C. Follows, E. Binnun, D. Joseph-McCarthy, K. Foreman, D. V. Erbe, Y. L. Zhang, S. K. Tam, S. Y. Tam and J. Lee\*

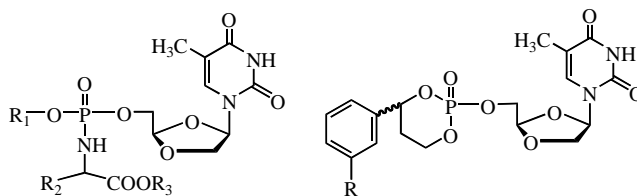


Novel bicyclic and tricyclic thiophene PTP1B inhibitors were discovered and optimized by structure-based design. Excellent consistency has been observed between structure–activity relationships and structural information from PTP1B-inhibitor complexes.

**Phosphoramidate and phosphate prodrugs of (–)- $\beta$ -D-(2R,4R)-dioxolane-thymine: Synthesis, anti-HIV activity and stability studies**

pp 2178–2189

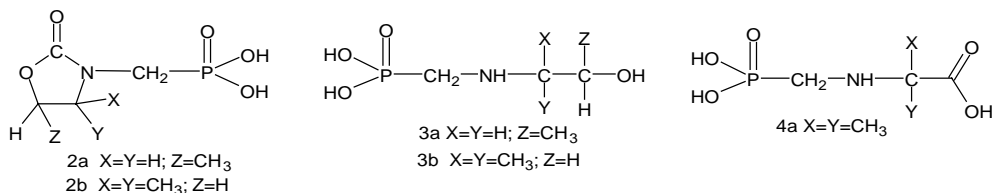
Yuzeng Liang, Janarthanan Narayanasamy, Raymond F. Schinazi and Chung K. Chu\*



**Novel  $\alpha$ -aminophosphonic acids. Design, characterization, and biological activity**

pp 2190–2196

Emilia Naydenova, Margarita Topashka-Ancheva, Petar Todorov,  
Ts. Yordanova and Kolio Troev\*

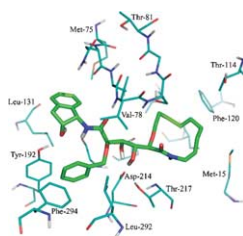


The genotoxic, clastogenic and antiproliferative effects of newly synthesized original aminophosphonic acids were investigated for the first time.

**Macrocyclic inhibitors of the malarial aspartic proteases plasmepsin I, II, and IV**

pp 2197–2208

Karolina Ersmark, Martin Nervall, Hugo Gutiérrez-de-Terán, Elizabeth Hamelink,  
Linda K. Janka, Jose C. Clemente, Ben M. Dunn, Adolf Gogoll, Bertil Samuelsson,  
Johan Åqvist and Anders Hallberg\*

**Discovering novel chemical inhibitors of human cyclophilin A: Virtual screening, synthesis, and bioassay**

pp 2209–2224

Jian Li, Jing Chen, Chunshan Gui, Li Zhang, Yu Qin, Qiang Xu, Jian Zhang,  
Hong Liu,\* Xu Shen\* and Hualiang Jiang\*

By using structure-based virtual screening approach in conjunction with chemical synthesis and bioassay, four potent CypA inhibitors have been discovered. Compound **16h** is active with very close potency to CsA in inhibiting the proliferation of spleen cells, demonstrating that this compound may be a good lead for discovering new immunosuppressive agents.

**Effect of cholesterol on DMPC phospholipid membranes and QSAR model construction in membrane-interaction QSAR study through molecular dynamics simulation**

pp 2225–2234

Jianzhong Liu\* and Liu Yang

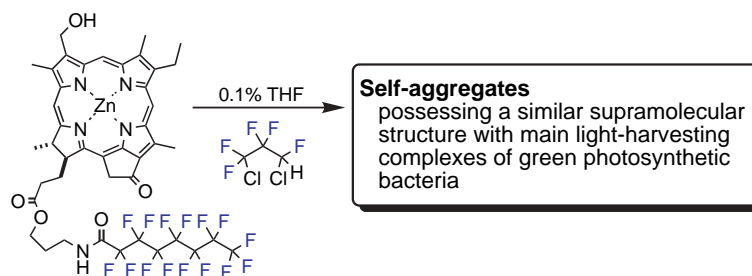


Molecular dynamics simulations were applied to explore the effect on the membrane and the construction of the MI-QSAR model due to the addition of cholesterol into the DMPC membrane system.

### Self-aggregation of synthetic zinc chlorophyll derivative possessing a perfluoroalkyl group in a fluorinated solvent

pp 2235–2241

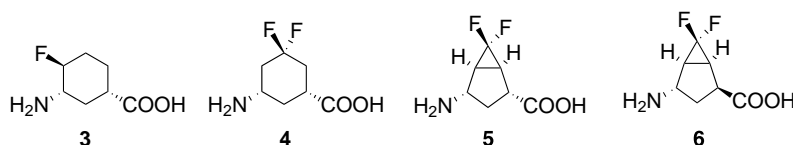
Reiko Shibata and Hitoshi Tamiaki\*



### Syntheses and evaluation of fluorinated conformationally restricted analogues of GABA as potential inhibitors of GABA aminotransferase

pp 2242–2252

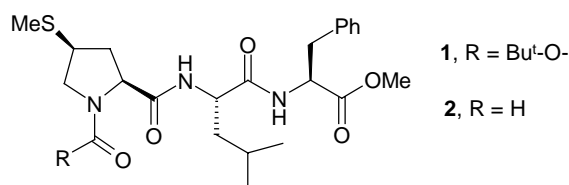
Zhiyong Wang and Richard B. Silverman\*



### Chemotactic peptides: fMLF-OMe analogues incorporating proline–methionine chimeras as N-terminal residue

pp 2253–2265

Adriano Mollica, Mario Paglialunga Paradisi, Katia Varani, Susanna Spisani and Gino Lucente\*

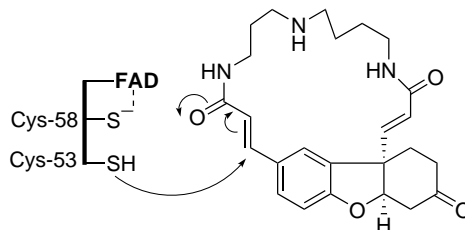


Novel analogues of the potent chemotactic tripeptide fMLF were designed and synthesized. The representative compound (1) containing the *cis*-4(*S*)-methylthio-(*S*)-proline residue at position 1 and the *N*-Boc-protecting group resulted to be a pure chemoattractant with the highest activity.

### Time-dependent inhibitors of trypanothione reductase: Analogues of the spermidine alkaloid lunarine and related natural products

pp 2266–2278

Chris J. Hamilton, Ahilan Saravanamuthu, Christiane Poupat, Alan H. Fairlamb and Ian M. Eggleston\*

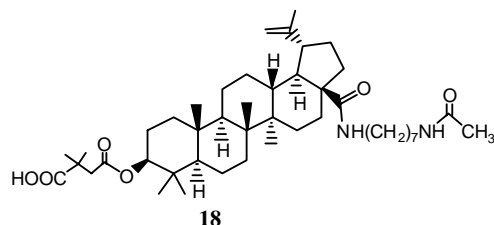


The molecular mechanism and minimal structural requirements for time-dependent inactivation of trypanothione reductase by the spermidine alkaloid lunarine and other natural product-derived compounds are described.

**Synthesis and anti-HIV activity of bi-functional betulinic acid derivatives**

pp 2279–2289

Li Huang, Phong Ho, Kuo-Hsiung Lee and Chin-Ho Chen\*

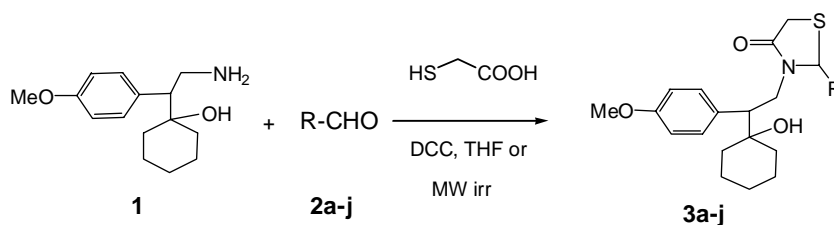


Synthesis of betulinic acid derivatives with both anti-HIV entry and anti-HIV maturation activities.

**Synthesis of new bioactive venlafaxine analogs: Novel thiazolidin-4-ones as antimicrobials**

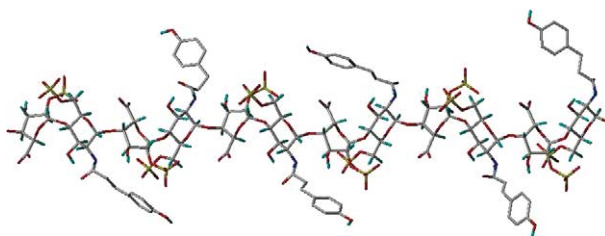
pp 2290–2299

C. V. Kavitha, Basappa, S. Nanjunda Swamy, K. Mantelingu, S. Doreswamy, M. A. Sridhar, J. Shashidhara Prasad and Kanchugarakoppal S. Rangappa\*

**Diversity-oriented chemical modification of heparin: Identification of charge-reduced N-acyl heparin derivatives having increased selectivity for heparin-binding proteins**

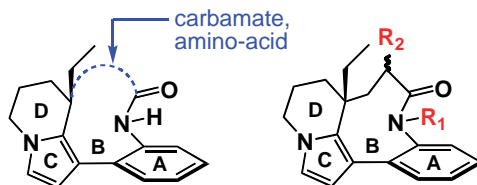
pp 2300–2313

Liusheng Huang and Robert J. Kerns\*

**Synthesis and biological evaluation of B-ring analogues of (–)-rhazinilam**

pp 2314–2332

Anne Décor, Barbara Monse, Marie-Thérèse Martin, Angèle Chiaroni, Sylviane Thoret, Daniel Guénard, Françoise Guéritte and Olivier Baudoin\*

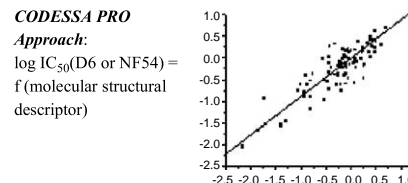


**Antimalarial activity: A QSAR modeling using CODESSA PRO software**

pp 2333–2357

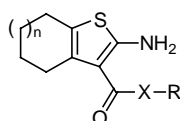
Alan R. Katritzky,\* Oleksandr V. Kulshyn, Iva Stoyanova-Slavova,  
Dimitar A. Dobchev, Minati Kuanar, Dan C. Fara and Mati Karelson

QSAR modeling of the antimalarial activity of two strains D6 and NF54 of *Plasmodium falciparum* for a diverse set of organic compounds is presented. Satisfactory multilinear regression models ( $R^2 = 0.84$  and  $0.89$ ) were obtained for D6 and NF54 using molecular structural descriptors calculated solely from the structure of a compound using the CODESSA PRO software. *CODESSA PRO Approach*:  $\log IC_{50}(\text{D6 or NF54}) = f(\text{molecular structural descriptor})$ .

**2-Aminothiophene-3-carboxylates and carboxamides as adenosine A<sub>1</sub> receptor allosteric enhancers**

pp 2358–2365

George Nikolakopoulos, Heidi Figler, Joel Linden and Peter J. Scammells\*

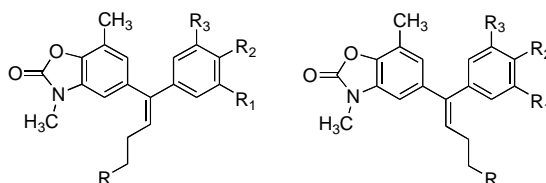


Three series of 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene and 2-amino-5,6,7,8-tetrahydrocyclohepta[b]thiophenes with 3-carboxylates and carboxamides have been prepared using the Gewald synthesis and evaluated as A<sub>1</sub>AR allosteric enhancers. The structure–activity relationships of these classes of compound are described. A number of compounds, notably **7b**, are more potent and efficacious than PD81,723 (**1**).

**Synthesis and anti-HIV activity of new alkenyldiarylmethane (ADAM) non-nucleoside reverse transcriptase inhibitors (NNRTIs) incorporating benzoxazolone and benzisoxazole rings**

pp 2366–2374

Bo-Liang Deng, Matthew D. Cullen, Zhigang Zhou, Tracy L. Hartman, Robert W. Buckheit, Jr.,  
Christophe Pannecouque, Erik De Clercq, Phillip E. Fanwick and Mark Cushman\*

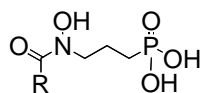


The syntheses and antiviral activities for a new set of alkenyldiarylmethane (ADAM) HIV-1 reverse transcriptase inhibitors bearing benzoxazolone and benzisoxazole rings are described.

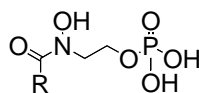
**Evaluation of fosmidomycin analogs as inhibitors of the *Synechocystis* sp. PCC6803 1-deoxy-D-xylulose 5-phosphate reductoisomerase**

pp 2375–2385

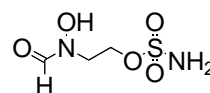
Youn-Hi Woo, Roberta P. M. Fernandes and Philip J. Proteau\*



R = H, fosmidomycin  
R = CH<sub>3</sub>, FR900098



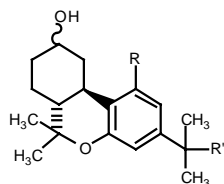
R = H, fosfoxacin  
R = CH<sub>3</sub>



# Synthesis and pharmacology of 11-nor-1-methoxy-9-hydroxyhexahydrocannabinols and 11-nor-1-deoxy-9-hydroxyhexahydrocannabinols: New selective ligands for the cannabinoid CB<sub>2</sub> receptor

pp 2386–2397

Karla-Sue C. Marriott, John W. Huffman,\* Jenny L. Wiley and Billy R. Martin

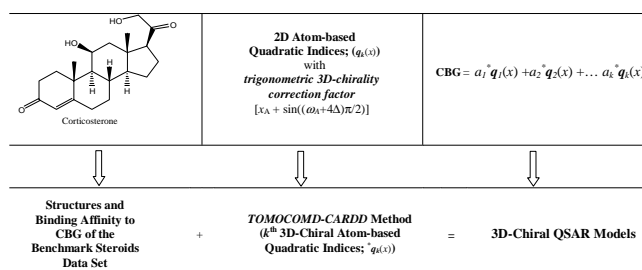


The synthesis and pharmacology of two series of 11-nor-9-hydroxy-HHCs are described. R = H, OCH<sub>3</sub>; R' = *n*-propyl to *n*-hexyl.

## Atom-based 3D-chiral quadratic indices. Part 2: Prediction of the corticosteroid-binding globulin-binding affinity of the 31 benchmark steroids data set

pp 2398–2408

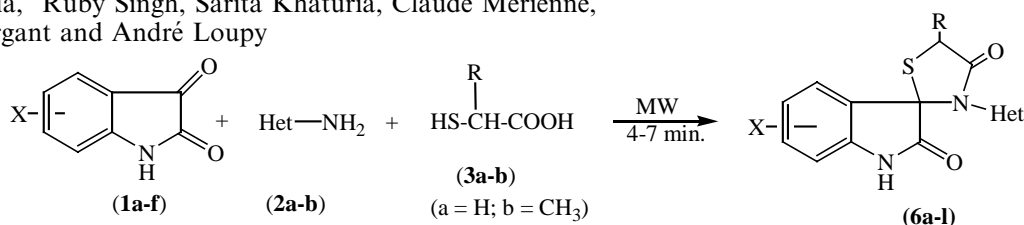
Juan A. Castillo-Garit,\* Yovani Marrero-Ponce and Francisco Torrens



## Efficient microwave enhanced regioselective synthesis of a series of benzimidazolyl/triazolyl spiro [indole-thiazolidinones] as potent antifungal agents and crystal structure of spiro[3*H*-indole-3,2'-thiazolidine]-3'-(1,2,4-triazol-3-yl)-2,4'(1*H*)-dione

pp 2409–2417

Anshu Dandia,\* Ruby Singh, Sarita Khaturia, Claude Mérienne, Georges Morgant and André Loupy

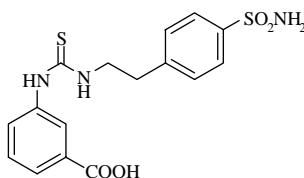


A microwave-assisted three-component, regioselective one-pot synthesis of spiro[indole-thiazolidinones] (**6a-l**) is carried out using montmorillonite KSF as solid support.

## Carbonic anhydrase inhibitors: Transepithelial transport of thioureido sulfonamide inhibitors of the cancer-associated isozyme IX is dependent on efflux transporters

pp 2418–2427

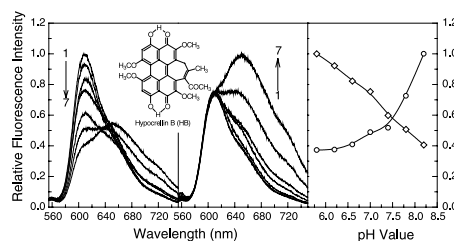
Daniela Vullo, Bente Steffansen, Birger Brodin, Claudiu T. Supuran,\* Andrea Scozzafava and Carsten Uhd Nielsen\*



**Spectroscopic studies of the interaction between hypocrellin B and human serum albumin**

pp 2428–2432

Baozhong Zhao, Liming Song, Xin Liu, Jie Xie and Jingquan Zhao\*

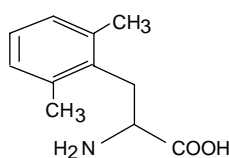


Bound to human serum albumin, hypocrellin B (HB) fluorescence was very sensitive to pH values in physiological range (6.0–8.0).

**ORL1 and opioid receptor preferences of nociceptin and dynorphin A analogues with Dmp substituted for N-terminal aromatic residues**

pp 2433–2437

Yusuke Sasaki,\* Susumu Kawano, Hirokazu Kohara, Hideko Watanabe and Akihiro Ambo



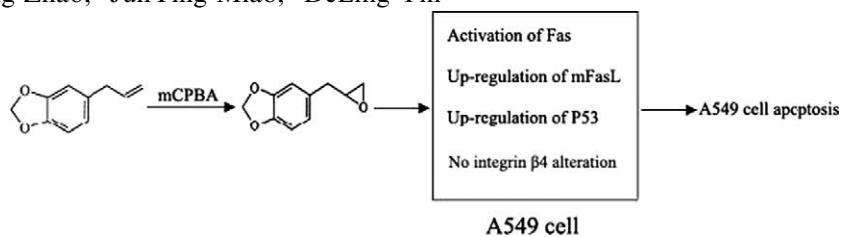
Dmp = 2,6-dimethylphenylalanine

Nociceptin and dynorphin A analogues containing Dmp in position 1 and/or 4 were synthesized. Dmp is a useful surrogate in producing analogues with novel receptor-binding profiles.

**Safrole oxide induces apoptosis by up-regulating Fas and FasL instead of integrin  $\beta 4$  in A549 human lung cancer cells**

pp 2438–2445

AiYing Du, BaoXiang Zhao,\* JunYing Miao,\* DeLing Yin and ShangLi Zhang

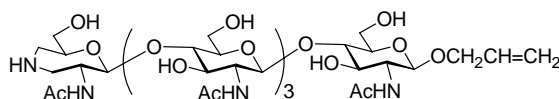


Safrole reacted with 3-chloroperoxybenzoic acid (mCPBA) in chloroform or in benzene to yield 3,4-(methylenedioxy)-1-(2',3'-epoxypropyl)-benzene (safrole oxide). Safrole oxide induced apoptosis in A549 human lung cancer cells perhaps through Fas/FasL pathway.

**Chemo-enzymatic synthesis of 1,4-oxazepanyl sugar as potent inhibitor of chitinase**

pp 2446–2449

Gang-Liang Huang, Da-Wei Zhang, Hong-Juan Zhao, Hou-Cheng Zhang and Peng-George Wang\*

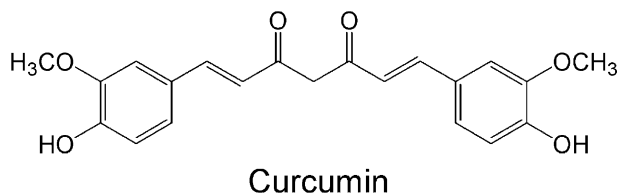




**Activation of NFκB is inhibited by curcumin and related enones**

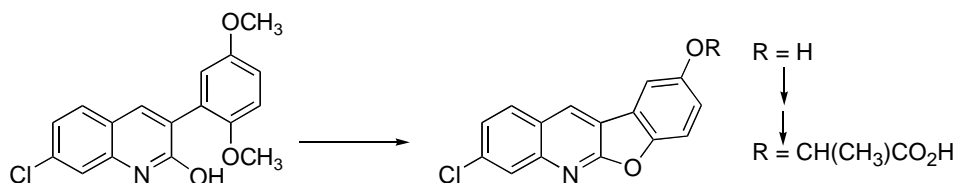
pp 2450–2461

Waylon M. Weber, Lucy A. Hunsaker, C. Nathaniel Roybal,  
Ekaterina V. Bobrovnikova-Marjon, Steve F. Abcouwer, Robert E. Royer,  
Lorraine M. Deck\* and David L. Vander Jagt\*

**Synthesis and biological evaluation of conformationally constrained analogs of the antitumor agents XK469 and SH80. Part 5**

pp 2462–2467

Stuart T. Hazeldine, Lisa Polin, Juiwanna Kushner, Kathryn White,  
Thomas H. Corbett and Jerome P. Horwitz\*

**OTHER CONTENTS**

Summary of instructions to authors

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\*Corresponding author

Supplementary data available via ScienceDirect

**COVER**

The figure shows a snapshot from a molecular dynamics simulation of a macrocyclic inhibitor in complex with one of its targets, plasmepsin IV from *Plasmodium falciparum*. The inhibitor is active also on the other aspartic proteases found in the food vacuole of this malarial parasite. The macrocyclic part of the ligand binds to the S1–S3 pocket of the enzyme, while the indanol and benzyloxy moieties bind to the S2' and S1 sites, respectively [Ersmark, K.; Nervall, M.; Gutiérrez-de-Terán, H.; Hamelink, E.; Janka, L. K.; Clemente, J. C.; Dunn, B. M.; Gogoll, A.; Samuelsson, B.; Åqvist, J.; Hallberg, A. *Bioorg. Med. Chem.* **2006**, *14*, 2197–2208].

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE



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