

CHEMICAL & MEDICINAL CHEMISTRY

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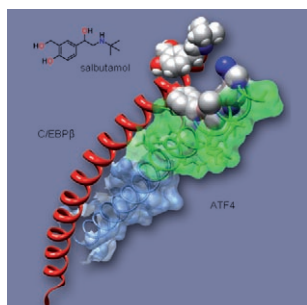
Full text:

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## COVER PICTURE



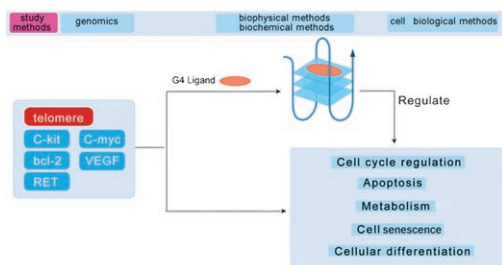
The cover picture shows a view from the X-ray crystallographic structure of activating transcription factor, ATF4, showing its molecular surface in a coiled-coil dimer with C/EBP $\beta$ , depicted in red. The interaction of the sequence highlighted in green with salbutamol is uncovered by S. R. Ladwa et al. on p. 742 ff. using the magic tag® chemical genomics approach. Key residues of the known DNA binding motif within this sequence are shown in space-filling representation to highlight how salbutamol, also depicted, might approach and modulate interaction with the nucleic acid target.

## NEWS

Spotlights on our sister journals

686 – 687

## REVIEWS



Important regions in the human genome such as telomeres and oncogene promoters have the potential to fold into G-quadruplexes. The formation or stabilization of these structures by G-quadruplex ligands may influence the

biological function of the given gene or telomere, and thus have some effect on disease control. The study of such ligands has involved genomic, biochemical, biophysical, and molecular biological methods.

T.-m. Ou, Y.-j. Lu, J.-h. Tan, Z.-s. Huang,\*  
K.-Y. Wong, L.-q. Gu\*

690 – 713

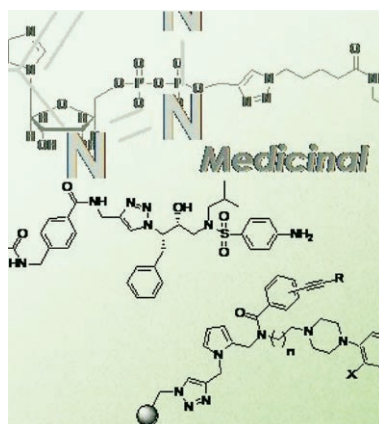
**G-Quadruplexes: Targets in Anticancer Drug Design**

## MINIREVIEWS

A. D. Moorhouse, J. E. Moses\*

715–723

## Click Chemistry and Medicinal Chemistry: A Case of “Cyclo-Addiction”



Click chemistry is chemical philosophy conceived to meet the growing demands of drug discovery. In this minireview, we discuss some of the most recent and innovative applications of click chemistry in medicinal chemistry.

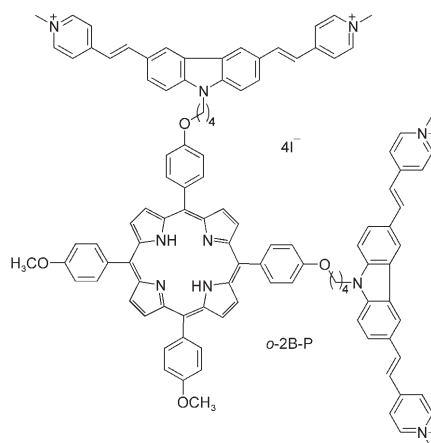
## COMMUNICATIONS

C.-C. Kang, C.-T. Chen, C.-C. Cho, Y.-C. Lin, C.-C. Chang,\* T.-C. Chang\*

725–728



## A Dual Selective Antitumor Agent and Fluorescence Probe: the Binary BMVC–Porphyrin Photosensitizer

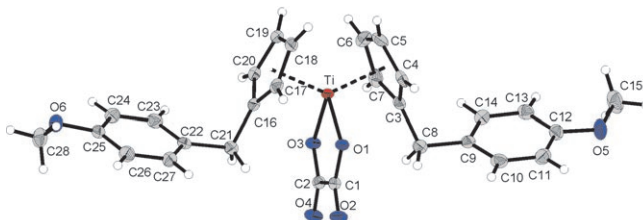


**Two in one:** *o*-2P-B (shown) generates singlet oxygen for photoinduced cytotoxicity that is highly selective for cancer cells without damaging normal cells. The required excitation wavelength is very well suited for tissue penetration in photodynamic therapy (PDT). The excellent contrast in cellular imaging of *o*-2B-P can be applied to monitor the pathway of PDT and serve as a cell death marker.

J. Claffey, M. Hogan, H. Müller-Bunz, C. Pampillón, M. Tacke\*

729–731

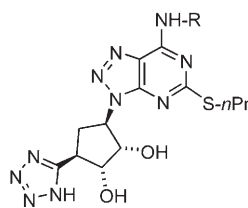
## Oxali-Titanocene Y: A Potent Anticancer Drug



**In three simple steps** the anticancer drug bis-[(*p*-methoxybenzyl)cyclopentadienyl]titanium(IV) oxalate (oxali-titanocene Y) can be synthesised from commercially available starting materials.

Oxali-titanocene Y shows twice the cytotoxicity of cisplatin in pig kidney epithelial (LLC-PK) cells and is the most cytotoxic titanocene known.

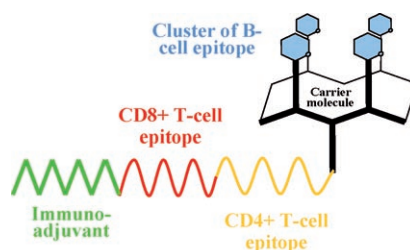
**Antagonizing a key platelet purinergic receptor.** The wide clinical use of clopidogrel has highlighted the importance of platelet ADP receptor (P2Y<sub>12</sub>) antagonists for preventing adverse cardiovascular events. We synthesized a series of novel carba-nucleosides and examined their usefulness as P2Y<sub>12</sub> antagonists. Some tetrazole derivatives were high-affinity receptor antagonists and potent inhibitors of human platelet aggregation.



*H. Ye, C. Chen, H.-C. Zhang,\* B. Haertlein, T. J. Parry, B. P. Damiano, B. E. Maryanoff\**  
732 – 736

**Carba-nucleosides as Potent Antagonists of the Adenosine 5'-Diphosphate (ADP) Purinergic Receptor (P2Y<sub>12</sub>) on Human Platelets**

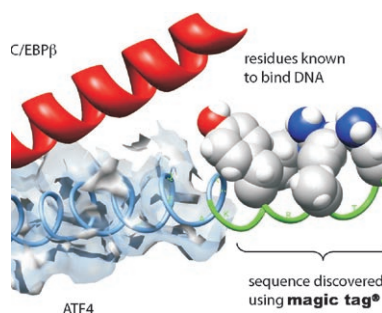
**A new generation of synthetic cancer vaccine:** the first self-adjuvanting vaccine prototype combining a cluster of B cell epitope, a CD4+ T helper cell epitope, a CD8+ T cell epitope, and an immunoadjuvant has been synthesized by a chemoselective strategy. Vaccination of mice with this molecularly defined construction induces a strong protection against tumors.



*O. Renaudet, L. BenMohamed, G. Dasgupta, I. Bettahi, P. Dumy\**  
737 – 741

**Towards a Self-Adjuvanting Multivalent B and T cell Epitope Containing Synthetic Glycolipopeptide Cancer Vaccine**

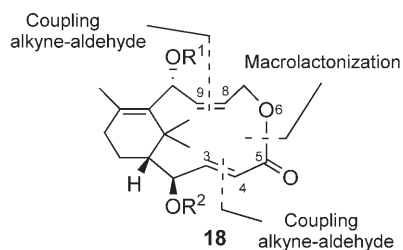
**Chemical genomics.** We have uncovered a specific interaction between the  $\beta_2$ -adrenoreceptor agonist salbutamol and the DNA binding region of transcription factor ATF4 in a chemical genomics approach using phage display combined with photoimmobilisation.



*S. R. Ladwa,\* S. J. Dilly, A. J. Clark, A. Marsh, P. C. Taylor\**  
742 – 744

**Rapid Identification of a Putative Interaction between  $\beta_2$ -Adrenoreceptor Agonists and ATF4 using a Chemical Genomics Approach**

**An efficient synthetic strategy** has been developed to prepare an oxygenated analog of Taxuspine X. Macrocyclization through Yamaguchi macrolactonization approach gave access to an original compound (**18**) showing remarkable P-gp modulating activity. Further functionalization of this versatile scaffold could lead to potential anti-cancer and/or MDR reversing agents.



*S. I. Avramova, E. Galletti, M. L. Renzulli, G. Giorgi, G. Sgaragli, D. Alderighi, C. Ghiron, F. Corelli, M. Radi, M. Botta\**  
745 – 748

**Synthesis of an Original Oxygenated Taxuspine X Analogue: a Versatile "Non-Natural" Natural Product with Remarkable P-gp Modulating Activity**

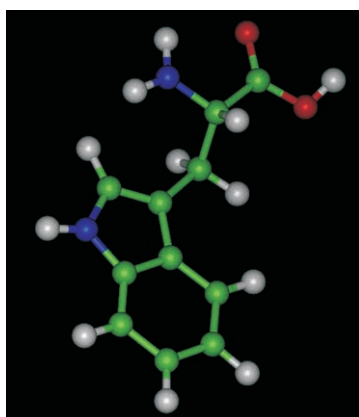
## FULL PAPERS

J. Dietz, J. Koch, A. Kaur, C. Raja, S. Stein, M. Grez, A. Pustowka, S. Mensch, J. Ferner, L. Möller, N. Bannert, R. Tampé, G. Divita, Y. Mély, H. Schwalbe, U. Dietrich\*

749 – 755



**Inhibition of HIV-1 by a Peptide Ligand of the Genomic RNA Packaging Signal  $\Psi$**



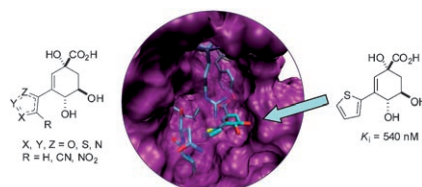
**Inhibiting HIV-1 replication:** During HIV-1 assembly the viral genome is efficiently encapsidated over cytoplasmic mRNA because of the specific recognition of the highly structured RNA packaging signal  $\Psi$  by the two zinc fingers of the viral NCp7 domain of the Gag polyprotein precursor. A short tryptophan-rich peptide optimized for binding to RNA derived from  $\Psi$  and if expressed in cells, this peptide inhibits HIV-1 replication.

C. Sánchez-Sixto, V. F. V. Prazeres, L. Castedo, S. W. Suh, H. Lamb, A. R. Hawkins, F. J. Cañada, J. Jiménez-Barbero, C. González-Bello\*

756 – 770



**Competitive Inhibitors of *Helicobacter pylori* Type II Dehydroquinase: Synthesis, Biological Evaluation, and NMR Studies**



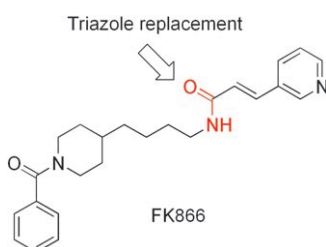
***Helicobacter pylori*** causes gastric and duodenal ulcers and has been classified as a class I carcinogen. A search for inhibitors of *Helicobacter pylori* dehydroquinase, an enzyme present in this pathogenic bacterium is reported. A potent 2-thienyl derivative has identified and its conformation when bound in the active site of the enzyme was elucidated by several NMR techniques.

U. Galli, E. Ercolano, L. Carraro, C. R. Blasi Roman, G. Sorba, P. L. Canonico, A. A. Genazzani, G. C. Tron,\* R. A. Billington

771 – 779



**Synthesis and Biological Evaluation of Isosteric Analogues of FK866, an Inhibitor of NAD Salvage**

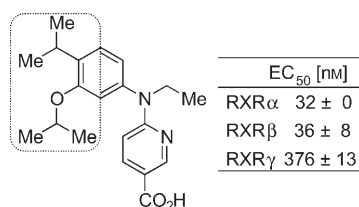


**Clicking NAD levels off.** One of the great challenges of medicinal chemistry is to create novel, effective, chemotherapeutic agents that show specificity for cancer cells combined with low systemic toxicity. A novel idea is to target the enzymes of the NAD biosynthesis and recycling pathways given that cancer cells display a higher NAD turnover rate than healthy cells.

K. Takamatsu, A. Takano, N. Yakushiji, K. Morohashi, K.-i. Morishita, N. Matsuura, M. Makishima, A. Tai, K. Sasaki, H. Kakuta\*

780 – 787

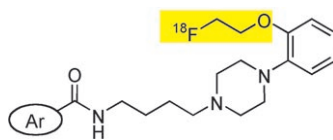
**The First Potent Subtype-Selective Retinoid X Receptor (RXR) Agonist Possessing a 3-Isopropoxy-4-isopropylphenylamino Moiety, NEt-3IP (RXR $\alpha$ / $\beta$ -dual agonist)**



**7a** (NEt-3IP): RXR  $\alpha$ / $\beta$ -selective agonist

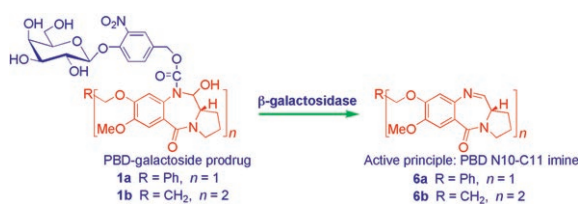
**The first subtype-selective RXR agonist.** NEt-3IP (**7a**) was found to be the first RXR $\alpha$ / $\beta$ -selective (or RXR $\alpha$ / $\beta$ -dual) agonist. Being potent, less lipophilic than previous agonists, and having RXR subtype-selective activity, NEt-3IP (**7a**) is expected to become a new drug candidate and to be a useful biological tool for clarifying each RXR subtype function.

**The dopamine D3 receptor** has attracted special attention in recent year because of its potential importance in psychiatric illness. However, there exists a lack of subtype-selective ligands for the D3 receptor. Based on 3D-QSAR models predicting subtype selectivities of dopaminergic test compounds, the [ $^{18}\text{F}$ ]-labeled D3 receptor ligands [ $^{18}\text{F}$ ]**4 a–d** were synthesized and tested in vitro.



C. Hocke,\* O. Prante, I. Salama, H. Hübner, S. Löber, T. Kuwert, P. Gmeiner  
788 – 793

**$^{18}\text{F}$ -Labeled FAUC 346 and BP 897 Derivatives as Subtype-Selective Potential PET Radioligands for the Dopamine D3 Receptor**



**Selective and effective:** Two PBD-galactoside prodrugs **1 a–b** have been synthesized and evaluated for use in selective therapy of cancer by ADEPT and PMT

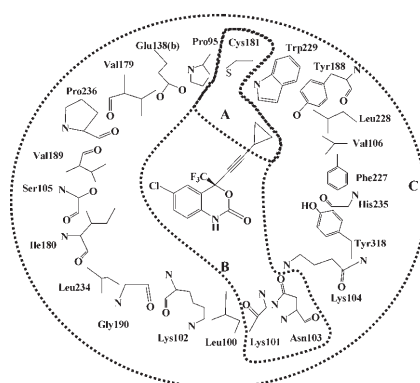
protocols. The two prodrugs display antitumor activity closely resembling their parent moieties, when activated by the enzyme  $\beta$ -galactosidase.

A. Kamal,\* V. Tekumalla, A. Krishnan, M. Pal-Bhadra, U. Bhadra\*

794 – 802

**Development of Pyrrolo[2,1-c][1,4]-benzodiazepine  $\beta$ -Galactoside Prodrugs for Selective Therapy of Cancer by ADEPT and PMT**

**Efavirenz in complex** with a mutant HIV-1 reverse transcriptase binding site is represented, based on an ONIOM3 modeling method. Interactions with Lys101, Cys181, and Asn103 (highlighted with internal dotted lines) are particularly important.

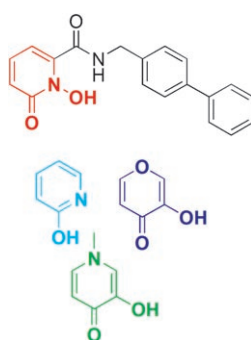


P. Srivab, S. Hannongbua\*

803 – 811

**A Study of the Binding Energies of Efavirenz to Wild-Type and K103N/Y181C HIV-1 Reverse Transcriptase Based on the ONIOM Method**

**Improving MMP inhibition.** Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases. The zinc-binding group (ZBG) of matrix metalloproteinase inhibitors (MMPi) is shown to be effective in obtaining isoform selectivity. This suggests a novel route to obtaining targeted MMPi, which elicit specificity through both the ZBG and the peptidomimetic backbone.



A. Agrawal, D. Romero-Perez, J. A. Jacobsen, F. J. Villarreal, S. M. Cohen\*

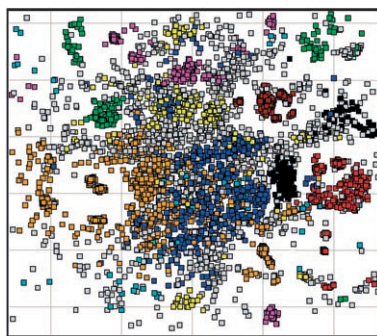
812 – 820

**Zinc-Binding Groups Modulate Selective Inhibition of MMPs**

L. Ridder,\* M. Wagener\*

821 – 832

## SyGMA: Combining Expert Knowledge and Empirical Scoring in the Prediction of Metabolites



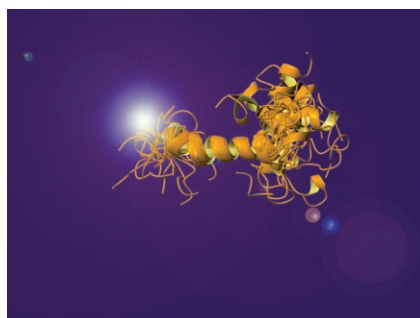
A dataset of 6187 metabolic reactions reported to occur in man has been used to develop a rule-based method that systematically predicts and ranks potential metabolites of a given parent compound. The graphic shows a projection of the training set with various types of correctly predicted metabolic reactions represented by different colors.

M. Valerio, F. Porcelli, J. P. Zbilut,  
A. Giuliani, C. Manetti, F. Conti\*

833 – 843



## pH Effects on the Conformational Preferences of Amyloid $\beta$ -Peptide (1–40) in HFIP Aqueous Solution by NMR Spectroscopy



**Conformational flexibility and aggregation propensity:** a rational basis for the different aggregation propensities of amyloid  $\beta$ -peptide in aqueous hexafluoroisopropanol, simulating the membrane environment, at different pHs as displayed by the combined use of  $^1\text{H}$  NMR spectroscopy and molecular dynamics-simulated annealing calculations.



Supporting information on the WWW (see article for access details).



A video clip is available as Supporting Information on the WWW (see article for access details).

\* Author to whom correspondence should be addressed.

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