CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY

05/2008

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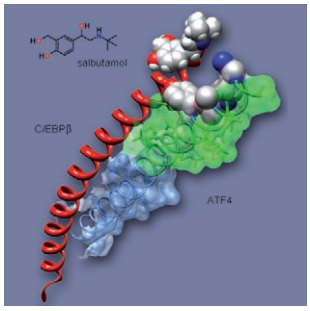
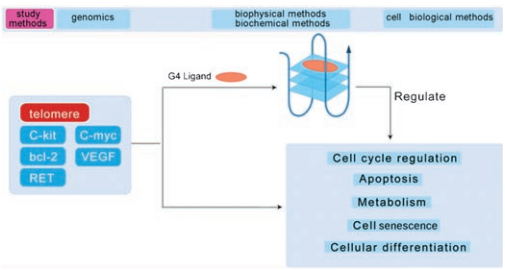
COVER PICTURE



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/EBPβ, 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.

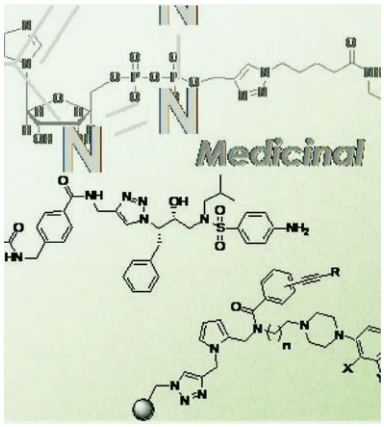
NEWS

REVIEWS



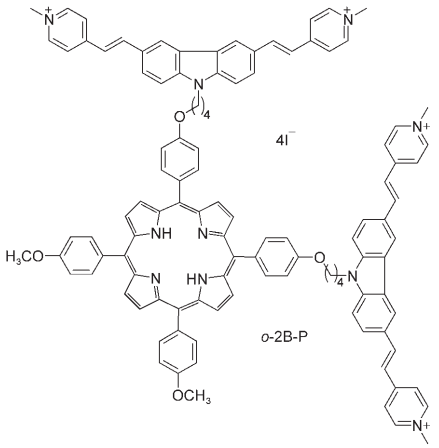
Important regions in the human genome such as telomeres and oncogene promoters have the potential to fold into G-quadruplexes. The formation or stabilization of these structures by G-quadruplex ligands may influence the biological function of the given gene or telomere, and thus have some effect on disease control. The study of such ligands has involved genomic, biochemical, biophysical, and molecular biological methods.

MINIREVIEWS

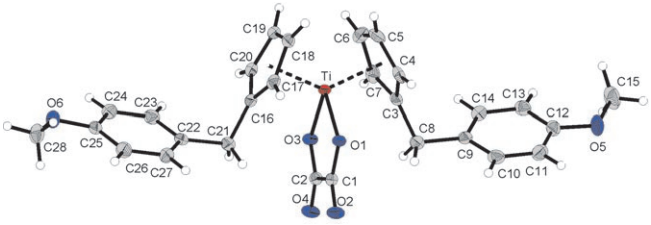


Click chemistry is chemical philosophy conceived to meet the growing demands of drug discovery. In this minireview, we discuss some of the most recent and innovative applications of click chemistry in medicinal chemistry.

COMMUNICATIONS



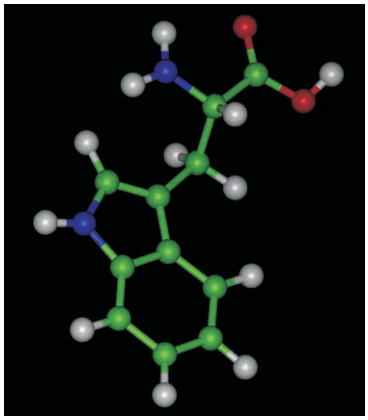
Two in one: *o*-2P-B (shown) generates singlet oxygen for photoinduced cytotoxicity that is highly selective for cancer cells without damaging normal cells. The required excitation wavelength is very well suited for tissue penetration in photodynamic therapy (PDT). The excellent contrast in cellular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



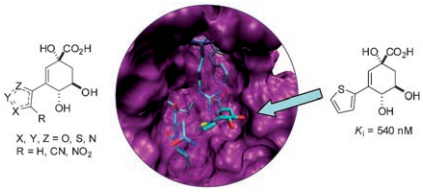
In three simple steps the anticancer drug bis-[(*p*-methoxybenzyl)cyclopentadienyl]titanium(IV) oxalate (oxali-titanocene Y) can be synthesised from commercially available starting materials.

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

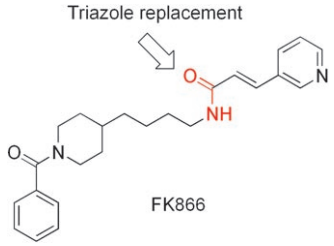
FULL PAPERS



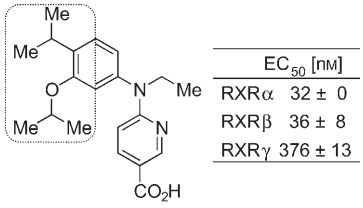
Inhibiting HIV-1 replication: During HIV-1 assembly the viral genome is efficiently encapsidated over cytoplasmic mRNA because of the specific recognition of the highly structured RNA packaging signal Ψ by the two zinc fingers of the viral NCp7 domain of the Gag polyprotein precursor. A short tryptophan-rich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



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.

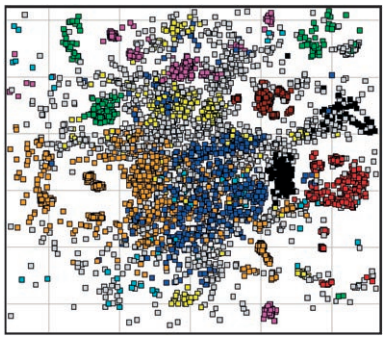


Clicking NAD levels off. One of the great challenges of medicinal chemistry is to create novel, effective, chemotherapeutic agents that show specificity for cancer cells combined with low systemic toxicity. A novel idea is to target the enzymes of the NAD biosynthesis and recycling pathways given that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

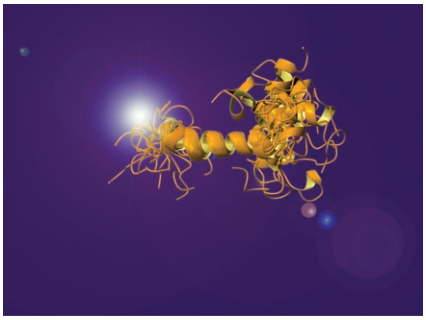


7a (NEt-3IP): RXR *α/β*-selective agonist

The first subtype-selective RXR agonist. NEt-3IP (**7a**) was found to be the first RXRα/β-selective (or RXRα/β-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.



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.



Conformational flexibility and aggregation propensity: a rational basis for the different aggregation propensities of amyloid β-peptide in aqueous hexafluoroisopropanol, simulating the membrane environment, at different pHs as displayed by the combined use of ^{1}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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