CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY

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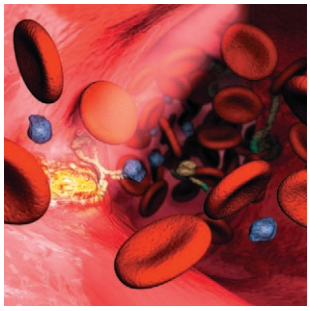
Some articles in this issue have already appeared online in Wiley InterScience. See www.chemmedchem.org under EarlyView®

COVER PICTURE

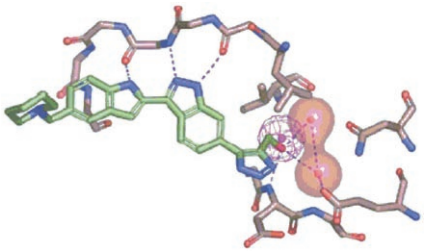


The cover picture shows an impression of a photoactivatable bispecific antibody bound to a tumour. Only the antitumour portion is initially active, allowing tumour cell binding. On irradiation with UV light the T-cell binding site is reactivated, allowing T-cell binding and activation. As anti-T-cell activity is not reactivated outside of the illuminated treatment area, immune activation is highly specific targeted to tumour tissues. For details, see the two back-to-back Communications by C. H. Self, S. Thompson, et al. on pp. 1587 and 1591 ff. (BioTransformations Ltd. Image courtesy of the Centre for Design Research.)

NEWS

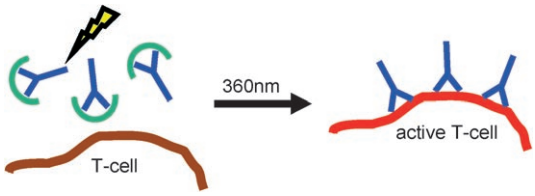
REVIEWS

MINIREVIEWS

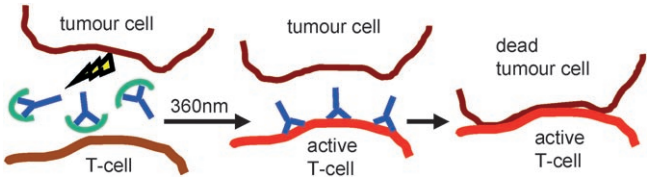


Inhibition of Chk1 kinase has garnered attention as a possible complement to DNA-damaging chemotherapeutic agents, widening their therapeutic window. As a result, several distinct classes of Chk1 inhibitors have been recently identified with selected compound advancing to clinical trials stage. This review focuses on the challenges and recent progress achieved in this area from a medicinal chemistry perspective.

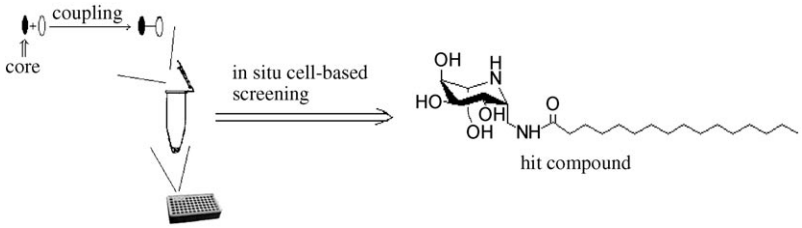
COMMUNICATIONS



Anti-human CD3 antibodies are rendered inert with a coating of photolabile 2-nitrobenzyl groups until their activity is restored by irradiation with UVA light, at which point the antibodies are free to bind and activate T-cells. Such antibodies should enable the regulation of cytotoxic T-cell activity at required times and locations in the body. This would have widespread medical application, particularly in the treatment of cancer.

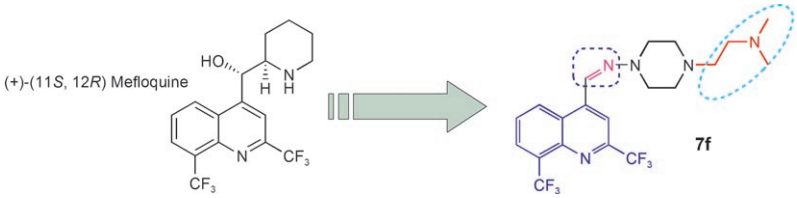


A photoactivatable anti-murine CD3 antibody was constructed. When reactivated in vivo in the presence of tumour pieces it markedly reduces the growth of ovarian carcinoma. Such antibodies provide a means to target T-cells with a much higher degree of specificity to tumours, whilst minimising side effects in other non-illuminated areas of the body.

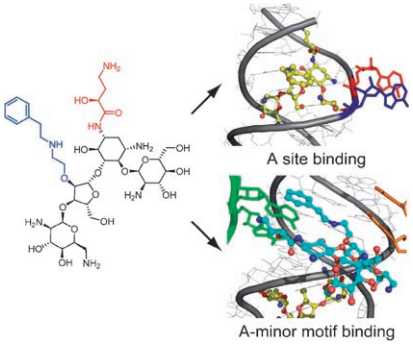


Effective and efficacious drug screening methods are imperative in the drug discovery process. A library has been constructed efficiently and followed by in situ cell-based screening without product purification. This method led to discovery of several iminosugar derivatives with anticancer activity.

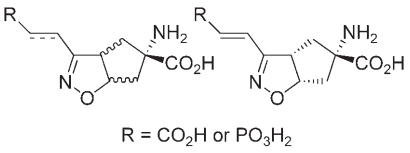
FULL PAPERS



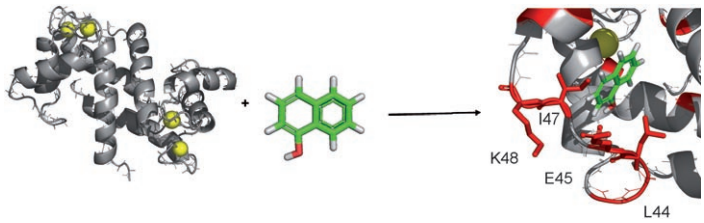
Tuberculosis is among the top five deadly diseases in developing countries. The current TB chemotherapy regimen requires patients to take three to four drugs for a minimum of six months. The key to shortening the current long regimen lies in effectively targeting this NRP-TB. To this end, we report herein the design and synthesis of mefloquine-based analogues and the evaluation of their activity against R-TB and NRP-TB.



The synthetic paromomycin analogue with the L-haba group and an ether chain with an *O*-phenethylaminoethyl group could specifically bind to ribosomes in two different modes: 1) the classical binding to the A site and 2) binding to an A-minor motif participating in the recognition of the codon–anticodon helix or in the intersubunit bridges.



Structurally constrained homologues of glutamic acid were prepared and tested against iGluRs and mGluRs. Amino acid (±)-**5** (shown at right, R = CO_2H) emerged as a selective group I mGluR antagonist capable of protecting DBA/2 mice from audiogenic seizures after i.c.v. administration.



NMR screening of two S100 proteins which are potential drug targets has been performed with a fragment library. A relatively large variety of interaction regions for various ligands for the two S100 proteins were identified even applying computer-aided drug design. Our results show that they have only few ligands in common, suggesting that selective leads could be developed starting from the different hits identified in the present work.

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

* Author to whom correspondence should be addressed.

SERVICE

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