X-ray Irradiation Promoted Activation of Prodrugs

**Significance:** Activating an anticancer prodrug with clinical doses of ionizing radiation could enable localized release of a drug at the tumor site and potentially eliminate the global systemic toxicity of conventional chemo-radiotherapy. In a tumor-bearing mice model, the combination of caged prodrug and X-ray treatment not only inhibited tumor growth but also reduced doxorubicin-induced heart toxicity.

**Comment:** The caged doxorubicin prodrug was synthesized in two steps, by following a reported procedure (*Bioconjugate Chem.* 2018, 29, 324). Decaging of doxorubicin was achieved using X-ray irradiation (from 0 to 60 Gy) through radical reduction of the tetrafluorophenyl azide followed by 1,6-self-immolation linker cleavage.

**Synthesis of prodrug:**

1. A, py
2. doxorubicin, Et$_3$N

81% over 2 steps

caged doxorubicin prodrug

**Prodrug activation by X-ray irradiation:**

inactive prodrug

H$_2$N

active drug

X-ray

– N$_2$

decarboxylation

**Key words**

cancer prodrugs
radiotherapy
X-ray irradiation
Go Bi-Steric for Selectivity

Significance: The kinase mTOR exists as two complexes, mTORC1 and 2 and is often hyperactive in cancer. Clinical inhibitors of mTOR include rapamycin and its analogs (rapalogs) and mTOR kinase inhibitors. While rapalogs are mTORC1 selective, they only partially inhibit mTORC1 and its downstream targets such as 4EBP. Inhibitors of mTOR kinase on the other hand are pan-mTOR inhibitors, potently inhibiting mTORC1/2 and 4EBP phosphorylation. The clinical benefit of mTOR kinase inhibitors however is limited by their toxicity, partly due to inhibition of mTORC2 and its downstream target Akt. Selective and potent inhibitors of mTORC1 could therefore overcome the limitations of rapalogs and mTOR kinase inhibitors.

Comment: The reported mTORC1 inhibitors were based on RapaLink-1. Several bi-steric inhibitors, consisting of a rapalog and an active site inhibitor were designed and evaluated. Notably, with their bi-steric mTORC1 inhibitor RCM-4529, the authors were able to achieve 31-fold inhibition of mTORC1 over mTORC2. RCM-4529 is a potent inhibitor of both mTORC1 and phosphorylation of 4EBP. Additionally, RCM-4529 shows comparable antitumor activity to clinical candidates, while showing significantly less metabolic side effects such as weight loss in mouse xenograft models. RCM-4529 was synthesized from rapamycin by reduction at C32, attachment of an alkyne via an oxime yielding A, and CuAAC with B.
Goyazensolide, a Covalent Importin-5 (IPO5) Inhibitor

**Significance:** The synthesis of goyazensolide and its two alkyne-tagged probes revealed the covalent inhibition of IPO5, a protein that transports cargo to the nucleus and poses as an interesting target for potential anticancer and antiviral treatments.

**Comment:** This versatile synthesis enabled access to sixteen structurally related sesquiterpene natural products, structural revision of two natural products, and the exploration of the covalent interactome of goyazensolide.
Truncated Mycalolide B Analog to Prevent Cancer Metastasis

**Significance:** Mycalolide B (MycB) is an actin-targeting biologically active natural product that is known to suppress cancer metastasis. The limited availability of MycB from natural sources and its challenging total synthesis have impeded its development as an anticancer agent. The authors identified and synthesized a highly potent truncated derivative of MycB through a structure-activity relationship study.

**Comment:** The linear skeleton of the MycB analog was prepared using a Hoveyda–Grubbs II catalyzed olefin metathesis between alkene fragments A and B. An elegant two-step sequence of a Takai olefination followed by a Goldberg coupling with N-ethylformamide installed the requisite N-vinylformamide moiety. The truncated analog greatly impaired cancer cell motility and prevented their invasion of the extracellular matrix.
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Macrodiolide Diversification Reveals Broad Immunosuppressive Activity That Impairs the cGAS-STING Pathway
Angew. Chem. Int. Ed. 2021, 60, 18734–18741, DOI: 10.1002/anie.202105793.

Macrodiolide Library Synthesis of cGAS-STING Inhibitors

Significance: The natural product (−)-vermiculine is a C₂-symmetric macrodiolide that possesses immunosuppressive and cytotoxic activity. With a limited supply of the compound from natural sources, total synthesis enables the preparation of vermiculine and analogs thereof for biological studies and elucidation of structure–activity relationships. In this report, Liu et al. develop a library synthesis strategy by which they prepare vermiculine and 18 analogs, resulting in newly identified cGAS-STING pathway inhibitors.

Comment: Starting with a versatile epoxide building block, the authors prepared vermiculine in 14 linear steps. By using this general sequence, a diverse library of analogs was prepared by changing the nucleophile for epoxide ring-opening and altering the Wittig reagent. The authors tested the analogs in growth inhibition and immunosuppression assays and concluded that LH519 is of interest for future studies due to its immunosuppressive activity and low toxicity.
Significance: Erythrina alkaloids act as competitive antagonists of nicotinic acetylcholine receptors (nAChRs). (+)-Dihydro-β-erythroidine, one of the most potent members of this family, was previously used in the treatment of Parkinson’s disease. The authors provide a concise synthesis of the key tricyclic intermediate E, which was used in the total synthesis of (+)-cocculine and (+)-cocculidine. The same intermediate allowed for the preparation of a series of analogues that were used in SAR studies of their binding affinities to four nAChRs. None of the analogues were more potent than the natural products, but higher selectivity was observed for different types of nAChRs, particularly β2 over β4 selectivity.

Comment: A Tsuji–Trost enantioselective allylic alkylation introduced a tetrasubstituted stereocenter with excellent enantioselectivity (95% ee). An allylboration using a chiral allyl boronate provided a homoallylic alcohol with low diastereoselectivity (J. Am. Chem. Soc. 2019, 141, 8783). Both epimers were converted into E using two cyclizations: a ring-closing metathesis and a Dieckmann condensation. The major epimer was applied in the total synthesis of two Erythrina alkaloids. Both epimers were converted into a series of ten pairs of analogues containing either heteroaromatic scaffolds or aryl/styryl side chains.
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TF-PROTACs Enable Targeted Degradation of Transcription Factors

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**Targeting Transcription Factors for Degradation**

**Significance:** Transcription factors (TFs) are promising potential targets for cancer therapeutics; however, their lack of activation sites or allosteric regulatory pockets makes targeting them with small molecule inhibitors difficult. The Jin and Wei groups have recently reported the development of TF-PROTACs, a generalizable platform. They demonstrate the selective degradation of TFs of interest and show the potential for targeting ‘undruggable’ TFs. Their work showcases the modularity of the approach by developing degraders for both NF-κB and E2F.

**Comment:** To evaluate this new PROTAC platform, NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) was chosen as the target, and 18 different TF-PROTACs were synthesized. Key to the synthesis of various TF-PROTACs was the use of a bioorthogonal copper-free strain-promoted azide-alkyne cycloaddition (SPAAC). Five of the 18 TF-PROTACs demonstrated greater than 50% reduction of p65, a subunit of NF-κB heterodimer. Furthermore, this work was successfully extended to enable degradation of E2F by changing the DNA oligomer.
Fighting Malaria with Endoperoxides

**Significance:** Endoperoxides are a family of bioactive compounds that are well-known for their antimalarial properties. In 2015, the Nobel Prize in Physiology or Medicine was awarded to Youyou Tu for discovering artemisinin, an important member of this family, as an antimalarial drug. Furthermore, endoperoxides containing natural products are reported to have antiprotozoal, anti-HIV, antibacterial or cytotoxic activities. Despite the importance of endoperoxides, synthetic access is limited by the few existing methods.

**Comment:** The authors reported a synthetic route for the preparation of a series of 1,2-dioxolanes (related: *Tetrahedron Lett.* 2016, 57, 5286; *Org. Lett.* 2019, 21, 4729.) A range of cyclopropanols were synthesized through either a Kulinkovich reaction or a reductive cyclization, then oxidative ring expansion was achieved with Mn(acac)2 under O2 to give 1,2-dioxolanes. Lastly, Lewis acid catalyzed acetylation and nucleophilic addition produced a variety of 3,5-disubstituted 1,2-dioxolanes.
Cyclic Disulfides as Selective Thioredoxin Probes

Significance: Current techniques to study redox protein dynamics are limited by nonspecific interactions with intracellular monothiols. The authors developed a series of monothiol-resistant probes that selectively release fluorescent cargo when triggered by thioredoxin.

Comment: The most promising probe motif, SS66C, was synthesized beginning with a diastereoselective hydrogenation. The fully assembled probe is fluorescently silent until a disulfide redox effector protein triggers the irreversible phenolic release of the fluorophore.
**Significance:** Malaria is a parasitic infectious disease caused by *Plasmodium* and remains a global burden in light of emerging drug resistances. Prodigiosins and tambjamines are pyrrolypyrromethane alkaloid antibiotics that are of marine and terrestrial origin. Here, isoheptylprodigiosin and (E/Z)-tambjamine MYP1 were synthesized for the first time. They showed high antiplasmodial activity and likely function through a novel mode of action.

**Comment:** Azafulvene 1 was prepared in one step. Suzuki coupling and deprotection yielded bispyrrole, which underwent condensation to isoheptylprodigiosin with pyrrole B without dimerization. Similarly, several side chain prodigiosin derivatives were prepared, and all products were orally curative of malaria infection in vivo. The total synthesis of tambjamine MYP1 was achieved using a condensation step as macrocyclization strategy, while RCM was less effective.
Total Synthesis and Configurational Assignment of Mutanobactin D

**Significance:** Mutanobactin D is a nonribosomal peptide isolated from the human oral pathogen *Streptococcus mutans*. It inhibits biofilm formation of the fungus *Candida albicans*, which naturally populates the oral cavity, skin, and gastrointestinal tract. Biofilms can initiate or prolong infections caused by encapsulated pathogens and complicate treatment of infectious diseases by diminishing their susceptibility to antibiotics. Accordingly, biofilm inhibitors are highly desired in the clinical treatment of microbial infections.

**Comment:** The first total synthesis of mutanobactin D was accomplished using *trans*-substituted isoxazoline A as a mask for the key lipidated ω-amino acid moiety found in the natural product. *trans*-A was synthesized through an enantioselective, zinc-mediated [3+2] cycloaddition and coupled with the peptide backbone to give the natural product after further manipulations. In addition, the researchers elucidated the configuration of the previously unassigned stereocenters at C-25 and C-26 using a variety of methods, including a novel infrared sequence alignment algorithm.
Total Synthesis and Structure-Activity Studies of Geodiamolide H

**Significance:** Geodiamolides bind and stabilize actin fibers (F-actin) and such blocking of cytoskeletal dynamics leads to cytotoxicity. The authors synthesized geodiamolide H using a flexible synthetic route amenable to the preparation of analogues. The potency of the compounds against cancer cell lines was inferred by measuring cytotoxicity (HeLa), antiproliferative activity (HUVEC and K-562) and actin polymerization induction, which, together with docking studies, provided valuable structure-activity relationship (SAR) data.

**Comment:** A Shiina esterification combined the polyketide and the tripeptide fragments. The 19-membered ring was obtained through a challenging ring-closing metathesis (J. Am. Chem. Soc. 2020, 142, 9240). In vitro and in cellulo SAR studies identified a strong dependence on the geometry of the double bond, and the presence of a halogen and an allylic methyl-group. In silico studies provided support for the experimental findings.
**Drugging the Undruggable using Irreversible Covalent K-Ras G12C Inhibitors**

**Significance:** Mutations in the important regulatory signal transduction protein K-Ras are found in approximately 25% of human cancers. Attempts to target this notorious GTPase resulted in many failures and the protein became known as 'the undruggable'. Shokat and co-workers took advantage of the nucleophilic cysteine of the G12C mutant and developed acrylamide-based inhibitors that bind covalently and irreversibly.

**Comment:** A library of nearly 500 acrylamides and vinyl sulfonamides was synthesized and tested for K-Ras G12C inhibition. Various aromatic building blocks were combined with the electrophilic portion using amide bond couplings. Based on these discoveries, many companies continued their discovery programs towards K-Ras anticancer drugs. Amgen's Sotorasib became the first FDA-approved K-Ras G12C inhibitor in May 2021.