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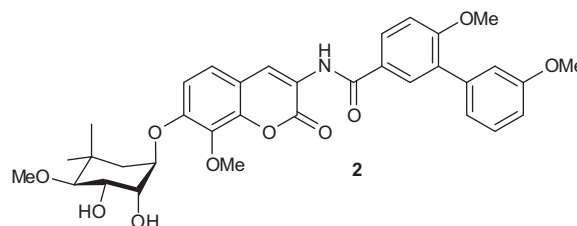
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1. Current literature highlights

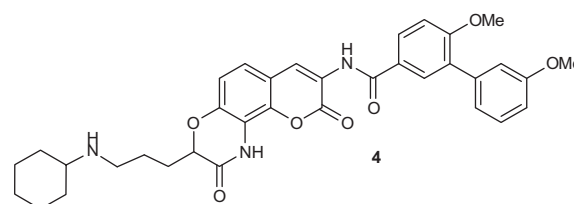
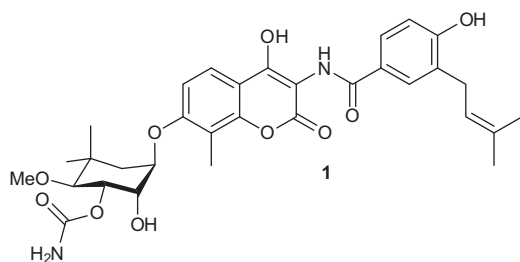
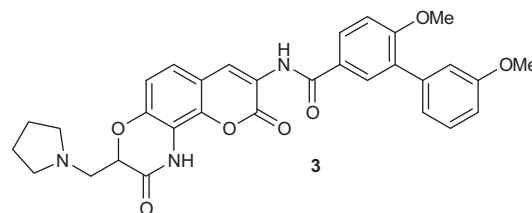
1.1. Synthesis of novobiocin analogs as Hsp-90 C-terminal inhibitors

The 90 kDa heat shock protein (Hsp90) plays a key role in maintaining cell function by being a component of the protein folding machinery, and in regulation of protein maturation, activation and integrity of function. However, as many of the client proteins are mutated or overexpressed in cancer cells, Hsp90 inhibition has been widely investigated as a potential target for anticancer therapeutics. Hsp90 functions as a dimer, each monomer of which contains an *N*-terminal ATP-binding domain, a middle domain and a *C*-terminal dimerization domain. Much research has focused on the design of inhibitors of the *N*-terminal domain, but *C*-terminal inhibitors are emerging as an alternative mode of intervention. A recent publication has described the use of several small compound libraries based on novobiocin to find novel antiproliferative agents that bind to Hsp90 *C*-terminal [1].

Novobiocin (**1**) is a DNA gyrase inhibitor that was discovered to bind to the *C*-terminal of Hsp90, but has only weak antiproliferative activity and thus limited therapeutic potential. Early studies indicated that key structural modifications resulted in a shift in the profile from DNA gyrase inhibition to Hsp90 binding. In particular, the incorporation of a biphenyl unit as in KU174 (**2**) enhanced antiproliferative activity in SkBr3 cells (an estrogen receptor negative, Her2 overexpressing breast cancer cell) from an IC_{50} of 700 μ M down to 14 μ M. Subsequent work with new compounds and molecular docking studies indicated that the sugar moiety in both novobiocin and KU174 could be replaced with an α -substituted fused lactam ring, as found in compound **3**.



As no co-crystal structure of Hsp90 with ligands bound to the *C*-terminal domain have been generated, not a great deal is known about the pocket that accommodates the sugar moiety, so a series of small compound libraries were created to investigate optimization of the lactam substituents. New compounds were evaluated for their antiproliferative activity against SKBr3 and MCF-7 (estrogen receptor positive breast cancer cells) cell lines. In these assays, compound **3** appeared to be as active as KU174, but other analogs were found to be even more active. In particular, extending a basic amine group on a two- or three-carbon tether resulted in improved antiproliferative activity. Compound **4** was one of the best compounds made with IC_{50} values against the SKBr3 and MCF-7 cells lines of 200 and 350 nM, respectively.



Treating cell lysates with **4** and other related analogs, and investigating protein levels using Western blot analysis, revealed that degradation of Hsp90 client proteins, Her2, Raf-1, and Akt was induced. Actin levels were unaffected as this is an Hsp90-independent protein. Overall, this study has revealed new ring-constrained analogs of novobiocin that are effective in preventing proliferation of breast cancer cell lines.

2. A summary of the papers in this month's issue

2.1. Polymer supported synthesis

An efficient and practical method for macrocyclic lipoglycopeptide synthesis has been developed and utilized to synthesize lipoglycosylated derivatives of Tyrocidine A. The method is based on solid-phase peptide synthesis using 2-chlorotrityl resin as the solid-phase support and lipoglycosyl amino acids as building blocks. This synthetic method should be generally applicable to various macrocyclic lipoglycopeptides [2].

2.2. Solution-phase synthesis

An efficient, convenient, and novel one pot approach has been described for the synthesis of triarylmethanes by *in situ* oxidation of benzyl alcohols followed by the Friedel–Crafts alkylation of di/trimethoxybenzenes in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. The generality of this method is demonstrated by running the reaction with a variety of aromatic, aliphatic, and heteroaromatic alcohols with methoxy arenes [3].

The first one-pot synthesis of structurally diverse pyrrolo[3,4-c]quinoline-1-one derivatives *via* a three-component cascade reaction of enamines, amines, and isatin under acidic conditions has been reported. This reaction proceeds through an unusual hydride transfer from *in situ* formed dimethylamine to a carbocation intermediate to generate the 3-methylene group. The method is straightforward, high-yield, easy to operate, and shows a broad substrate scope, thus potentially useful for diversity-oriented synthesis [4].

2.3. Scaffolds and synthons for combinatorial libraries

No papers this month.

2.4. Solid-phase supported reagents

A solvent-free environmentally benign approach for the synthesis of diversified pyrrole derivatives has been described using a one-pot multicomponent reaction of aldehydes, nitroalkanes, amines, and an enolizable active C–H reactant. The reaction proceeds using polystyrene supported *p*-toluenesulfonic acid (PS-PTSA) under microwave irradiation. In comparison to conventional methods, this efficient green protocol provides remarkable advantages such as good to excellent yields, shorter reaction time, low cost, easy work-up procedure, and bypasses the use of hazardous transition metal catalysts and organic solvents [5].

A solvent-selective methodology for the phenyl selenylation and phenyl tellurylation of aryl boronic acids using a polymer supported Cu(II) catalyst has been developed. The catalyst was synthesized by anchoring $\text{Cu}(\text{OAc})_2$ onto a functionalized polystyrene with pyridine thiosemicarbazone ligand. A wide variety of unsymmetrical organodiaryl or aryl-heteroaryl selenides and tellurides have been synthesized by this protocol, and the catalyst was recycled for up to six runs without any appreciable loss of catalytic activity [6].

2.5. Novel resins, linkers and techniques

Peptide hydrazides can be easily synthesized using a new hydrazone resin, obtained *via* acylation of aminomethyl polystyrene by the Fmoc-hydrazone of pyruvic acid. It has been shown that the hydrazone linker is completely stable during standard Fmoc solid phase peptide synthesis. Moreover, it can tolerate 5% TFA in dichloromethane thus permitting selective removal of Mtt or related acid-labile protecting groups [7].

Interactions between analyte proteins and *de novo* designed structured peptides as capture molecules cause structural changes. These are reflected in fluorescence-intensity changes of labeled peptides in a dose-dependent manner. A new detection method uses the principle of the differences in fluorescence intensity of capture peptides upon addition of analytes, and monitoring these structural changes by an array of *de novo* designed synthetic and structured peptides has been undertaken. One study involved 5-fluorouracil (5-FU), as a low molecular weight antigen, and a monoclonal antibody against 5-FU. The fluorescence intensity changes of labeled peptides have been measured after incubation with a monoclonal antibody and again after further incubation with the antigen, 5-FU. This approach offers a useful detection system for molecule capture by peptide-based microarrays [8].

2.6. Library applications

The development of a novel tumor-targeting photosensitizer delivery system, with potential ability to selectively transport the photosensitizer prodrug 5-aminolevulinic acid methyl ester (MAL) into the tumor site has been described. Conjugation of MAL to folic acid *via* an unnatural β -peptide linker has been carried out almost entirely by an efficient solid phase approach. This molecular system has been devised for possible applications in selective photodynamic diagnosis and therapy [9].

A recent publication describes continued optimization of a highly selective M5 negative allosteric modulator (NAM) probe, ML375, through a combination of matrix libraries and iterative parallel synthesis. SAR was found to be shallow, and the matrix library approach highlighted the challenges with M5 NAM SAR within this chemotype. Enantiospecific activity was noted, and potency at rat and human M5 were improved over ML375, along with slight enhancement in physicochemical properties, certain *in vitro* DMPK parameters and CNS distribution [10].

A small molecule has been identified as a selective partial agonist of Opioid Receptor Like-1 (ORL-1) with potential utility for the treatment of anxiety and other disorders. The synthesis of the key compound involved using a molecular diversity approach, to rapidly advance a library of compounds for biological testing. A lead selective potent partial agonist (35-fold ORL-1/Mu) was progressed to ORL-1 proof of concept testing in advanced studies [11].

A 26-member library of novel *N*-hydroxyquinolinone derivatives has been synthesized by a one-pot Buchwald-type palladium catalyzed amidation and condensation sequence. The design of these rare scaffolds was inspired by *N*-hydroxypyridone and 2-quinolinone classes of compounds which have been shown to have rich biological activities. The synthesized compounds were evaluated for their anti-plasmodial and anti-bacterial properties, and in addition, these compounds were screened for their iron(II)-chelation properties. Notably, four of these compounds exhibited anti-plasmodial activities comparable to that of the natural product cordypyridone B [12].

The derivatization of resin-bound aminobenzimidazole toward the parallel solid-phase synthesis of aminobenzimidazole tethered pharmacologically important heterocycles such as quinazoline-2,4-diones, thioxoquinazolin-4-ones, benzodiazepine-2,3,5-triones,

isoxazoles and isoxazolines has been reported. All the compounds were tested for IKK inhibition, but only one compound elicited significant inhibition of IKK ϵ , TBK-1 and IKK2 [13].

To further extend the scope of iminosugar biological activity, a systematic structure–activity relationship investigation has been performed by synthesizing a library of twenty-three iminoalditols and evaluating these as cholinesterase inhibitors. The compounds were evaluated *in vitro* for the inhibition of cholinesterases and some compounds were found to have IC₅₀ values in the micromolar range and display significant inhibition selectivity for butyrylcholinesterase over acetylcholinesterase [14].

Design strategies that led to the discovery of novel pyridopyrazine-1,6-dione γ -secretase modulators incorporating an indole motif have been described. Tactics involving parallel medicinal chemistry and *in situ* monomer synthesis to prepare focused libraries were employed. One optimized indole exhibited good alignment of *in vitro* potency and physicochemical properties, and moderate reduction of brain A β 42 was achieved in a rat efficacy model when dosed orally at 30 mg/kg [15].

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Further reading

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