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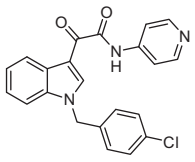
1. Current literature highlights

1.1. A library revealing orally bioavailable tubulin polymerase inhibitors

Microtubule-targeting agents (MTAs) comprise a class of anti-cancer compounds that have shown clinical success in a range of cancer types. The drugs bind to heterodimers of α- and β-tubulin and consequently interfere with natural microtubule function. MTAs can either stabilise or destabilise microtubules, but the result either way is disruption of cell function leading to apoptosis. Several drugs that work as binders to microtubules suffer from some significant disadvantages. For example, drug resistance or adverse toxicities can prove dose-limiting. Thus, there is still an ongoing search for new MTAs, and towards this end, a recent paper describes the synthesis of a library of indole-3-glyoxylamide derivatives based on the tubulin polymerase inhibitor indibulin (**1**) [1].



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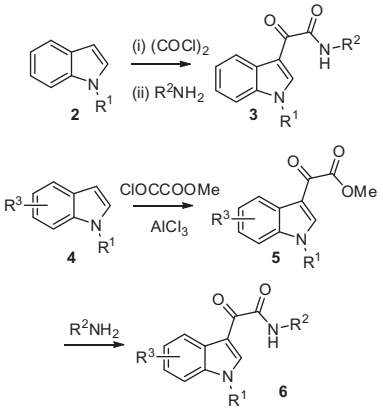
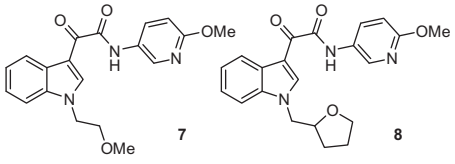
The new library of compounds focussed initially on removing the chlorophenyl sidechain with a particular aim of increasing the count of sp^3 carbon atoms as such changes are known to improve the solubility of small molecules. The tubulin polymerisation inhibitors identified from this study were investigated in models of head and neck cancer (HNC) where existing MTAs have shown benefit.

The glyoxylamides were derived from *N*-substituted indoles by one of two routes. *N*-substituted indoles (**2**) were reacted with oxalyl chloride and then amines to generate the amide products (**3**). However, as this route proved to be unsatisfactory for indoles substituted on positions 4 to 7, these indoles (**4**) were reacted under Friedel–Crafts conditions with aluminium chloride to give glyoxalate ester intermediates (**5**) which were then reacted with amines to give the target compounds (**6**).



The library compounds prepared by these methods were first assessed for cytotoxicity against FaDu, an HNC cell line derived from a squamous cell carcinoma from the larynx. LC_{50} values were derived for compounds showing cytotoxicity at or below 10 μM at the 72 h time point. In particular it was found that alkyl groups on the indole nitrogen were generally lacking in activity unless the glyoxylamide derivative contained a methoxypyridine group (e.g. compound **7**, LC_{50} = 17 nM).



The study examined variation in several positions around the glyoxylamide structure, making over 60 compounds in total and these compounds were additionally profiled in solubility, microsomal stability and CACO-2 permeability assays. A subset of compounds was chosen for evaluation in a tubulin polymerisation assay, and several were found to suppress polymerisation in a dose-dependent manner. Ultimately two compounds were selected for an *in vivo* efficacy study in a mouse HNC model

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employing FaDu cell xenografts. These compounds both exhibited LC_{50} values below 100 nM and a microsomal half-life exceeding 30 min. Mice were dosed orally with compound **8** at 10 mg/kg daily for 10 days over which time there was a significant reduction in tumour growth relative to the control group.

Overall, this study has used a library synthesis of indole-3-glyoxylamides to find compounds which are inhibitors of tubulin polymerisation, that show cancer cell toxicity, and were active in a mouse xenograft model. Although improvements in pharmacokinetics are still required, the compounds reveal a new SAR pattern that might lead to the discovery of MTA compounds with improved activity and potential clinical efficacy.

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

2.1. Polymer supported synthesis

A solid-phase synthesis procedure for the parallel preparation of 6,7-cycloalkane-fused 1,4-diazepane-2,5-diones has been described. The methodology applied α- and alicyclic β-amino acid building blocks to construct the seven-membered heterocyclic core, while alcohols were used for further skeletal decoration. The use of a cyclisation/release strategy permitted the isolation of the target cyclic α,β-dipeptides in good purities and generally moderate to good yields. A 26-membered model library has been reported and NMR spectroscopic data used to describe the overall conformational behaviour of the obtained homodiketopiperazines [2].

2.2. Solution-phase synthesis

The synthesis of novel 7-amino-substituted pyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitriles has been achieved *via* a three-component reaction of 3-amino-substituted 5-aminopyrazole-4-carbonitriles, cyanamide and triethyl orthoformate under microwave irradiation. Under catalyst-free conditions, this three-component reaction accommodated a generous diversity of amino substituents making it ideal for the generation of compound libraries for drug discovery processes [3].

An efficient and concise synthesis of structurally diverse thiazolo[3,2-*a*]chromeno[4,3-*d*]pyrimidin-6(7*H*)-one derivatives in good to excellent yields has been developed. This reaction is a versatile one-pot multicomponent condensation of 4-hydroxycoumarins, 2-aminobenzothiazoles, and various aldehydes catalysed by eco-friendly and reusable 1-butyl-3-methylimidazolium tetrafluoroborate ionic liquid under solvent-free conditions. Several advantages of this protocol include operational simplicity, short reaction time, efficient utilisation of the reactants, non-chromatographic purification procedure, wide functional group tolerance, and ease of recovery and reuse of the catalyst for at least five consecutive cycles without loss of activity [4].

2.3. Scaffolds and synthons for combinatorial libraries

A new methodology has been developed for the synthesis of hexahydro-1*H*-pyrido[2,3-*b*]indol-2-one scaffolds *via* a sequential Michael addition/amidation/reductive cyclisation process. A wide variety of products bearing a hexahydro-1*H*-pyrido[2,3-*b*]indol-2-one core with varying degrees of substitution around it were obtained smoothly with high efficiency (up to overall yield of 67%). Furthermore, biological activities have been preliminarily demonstrated by *in vitro* evaluation against human prostate cancer cells PC-3, human lung cancer cells A549 and human leukemia cells K562 using MTT-based assays. The results demonstrated that many compounds showed considerable cytotoxicities against these three cell lines, and that hexahydro-1*H*-pyrido[2,3-*b*]indol-2-one scaffolds may be potential leads for further antitumour activity screenings [5].

2.4. Solid-phase supported reagents

Various primary and secondary alcohols have been selectively oxidised to the corresponding aldehydes and ketones using silica supported TEMPO as a heterogeneous catalyst and nitrosonium tetrafluoroborate as a cocatalyst. No over-oxidation of aldehydes to acids, nitration processes or oxidation of double bonds was observed. The reported procedure is very convenient, and uses mild experimental conditions (room temperature and dioxygen as the terminal oxidant). Furthermore, the reactions proceeded cleanly and isolation of the desired compounds required minimal work-up [6].

A simple, highly efficient and environmentally benign method for the synthesis of pyrrolo[1,2-*a*]quinoxalines has been developed using a green and recyclable catalyst, Amberlite IR-120H resin under solvent-free conditions. The method provides several advantages such as mild conditions, no use of oxidant, and an environmentally compatible and inexpensive catalyst. Moreover, the catalyst can be recovered after completion of the reaction and can be reused as the catalytic property of the resin is not affected even up to five cycles [7].

The catalytic activity of palladium supported on magnetic nanoparticles in the amination coupling reaction of different nitrogen containing substrates with aryl halides has been investigated. C–N bond formation was achieved in moderate to excellent yields and the catalyst could be separated by magnetic decantation [8].

A ligand-free $Pd/Al(OH)_3$ nano-catalyst which has been prepared by a one-pot three-component method using $Pd(PPh_3)_4$, tetra(ethylene glycol), and aluminium tri-*sec*-butoxide has exhibited excellent catalytic activity in Stille cross-couplings of (het)aryl chlorides, arenediazonium tetrafluoroborate salts with phenyltributylstannane, respectively, and Kumada couplings of (het)aryl chlorides with various Grignard reagents. More importantly, these two processes have shown excellent functional group compatibility with moderate to good yields and they are also versatile with respect to not only (het)aryl chlorides, but also diazonium salts, and heteroaryl Grignard reagents. The nano-catalyst could also be recycled and reused five times without loss of activity or decrease of yield [9].

2.5. Novel resins, linkers and techniques

Side-chain to side-chain lactam-bridged cyclic peptides have been used as therapeutic agents and biochemical tools. An efficient microwave-assisted synthesis of side-chain to side-chain lactam-bridge cyclic peptides has been reported. The synthesis time and efforts are significantly reduced with this method, and it avoids side product formation. Analytical and pharmacological data of the synthesised cyclic peptides are in accordance with the commercially obtained compounds. This new method could be used to synthesise other side-chain to side-chain lactam-bridge peptides and amenable to automation and extensive SAR compound derivatisation [10].

2.6. Library applications

A novel molecular framework with a lysine core has been explored to prepare a probe library for protein kinases. Active site-directed probes, identified through screening of the library, displayed desirable labelling properties, including target specificity, good linear response to the corresponding enzymatic activity and cell permeability. Finally, a two-stage protocol utilising the newly developed probe with an immunoprecipitation step was

successfully established to monitor intracellular Src kinase activity in RK3E-v-Src cells [11].

A library of triazole-based analogues of bromotyramine alkaloids such as verongamines, hemibastadins, pseudoceramine D and clavatidine E has been designed in order to identify promising leads that may help in the control of bacterial biofilms. Twenty-three compounds were screened for their biofilm inhibitory activity against three strains of Gram-negative bacteria. SAR studies revealed that hemibastadin analogues were the most active compounds which act as inhibitors of biofilm development (EC_{50} 8.8–29 μM) without effect on bacterial growth even at high concentrations (100 μM) [12].

N-Aryl derivatives of edaravone have been identified as potentially effective small molecule inhibitors of tau and beta-amyloid aggregation in the context of developing disease-modifying therapeutics for Alzheimer's disease. Palladium-catalysed hydrazine monoarylation protocols have been employed as an expedient means of preparing a focussed library of 21 edaravone derivatives featuring varied *N*-aryl substitution, enabling structure–activity relationship studies. On the basis of data obtained from two functional biochemical assays examining fibril and oligomer formation, it was determined that derivatives featuring an *N*-biaryl motif were fourfold more potent than edaravone [13].

BACE-1 (β-secretase) is considered to be a promising targets for treatment of Alzheimer's disease as it catalyses the rate limiting step of Aβ-42 production. A novel class of allylidene hydrazinecarboximidamide derivatives have been disclosed as moderately potent BACE-1 inhibitors, having aminoguanidine substitution on an allyl linker with two aromatic groups on either side. A library of derivatives was designed based on the docking studies, synthesised and evaluated for BACE-1 inhibition *in vitro* [14].

The synthesis and SAR studies that led to the discovery of benzamide (reverse amide) as potent and selective human β3-adrenergic receptor agonists has been described. Based on a conformationally restricted pyrrolidine scaffold, a pyrrolidine benzoic acid intermediate was previously synthesised, and from library synthesis and further optimisation efforts, several structurally diverse reverse amides were found to have excellent human β3-adrenergic potency and good selectivity over the β1 and β2 receptors [15].

Diversity-oriented construction of new indolizine scaffolds has been accomplished by employing domino Knoevenagel condensation/intramolecular aldol cyclisation reactions. Biological evaluation revealed anticancer activity of these compounds through inhibition of β-catenin and activation of p53 [16].

A novel and green approach for the synthesis of 2-substituted benzothiazole analogues has been reported. A number of 2-aryl and heteroaryl benzothiazole scaffolds were synthesised using Amberlite IR-120 resin under microwave irradiation. The catalytic role and reusability of the resin has been fully described and 2-substituted benzothiazole analogues were also tested against several bacterial strains (*Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Salmonella*) and cancer cell lines (MCF-7 and HeLa) [17].

Antimitotic agents are widely used in cancer chemotherapy but the numerous side effects and the onset of resistance limit their clinical efficacy. With the purpose of discovering more selective and efficient anticancer agents to be administered alone or in combination with traditional drugs, a large library of 1,3,4-thiadiazoline analogues has been synthesised. This library maintained the pharmacophoric structure of an antiproliferative compound known as K858;a new kinesin Eg5 inhibitor, able to induce the mitotic arrest in colorectal cancer cells and in xenograft ovarian cancer cells. 103 compounds were screened to assess their antiproliferative activity on a PC3 prostate cancer cell line [18].

A recent study involved the synthesis and lead structure selection of the best anti-leukemic agent from a library of azapodophyllotoxin analogues (APTs). A scalable, modified multicomponent reaction has been reported that uses a 'sacrificial' aniline partner as a more general route to rapidly construct the pivotal library of 50 APT analogues. Preliminary structure activity relationship studies for anti-leukemic activity also addressed the innate toxicity of these compounds against non-malignant cells. Two novel compounds were discovered to be more potent than etoposide, having high selectivity against the human THP-1 leukemia cell line and a minimal toxicity [19].

A new library of phenothiazine and 1,3,4-thiadiazole hybrid derivatives has been designed based on the molecular hybridisation approach and the molecules were synthesised in excellent yields using a facile single-step chloro-amine coupling reaction between 2-chloro-1-(10*H*-phenothiazin-10-yl)ethanones and 2-amino-5-subsituted-1,3,4-thiadiazoles. The compounds were evaluated for their *in vitro* inhibition activity against *Mycobacterium tuberculosis* H37Rv [20].

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