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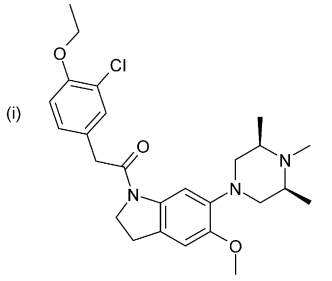
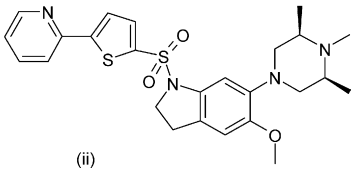
MOLECULES

Stratagems for discovery of novel biologically active compounds with the efficient use of parallel chemistry

Achiral agonists of the ghrelin receptor

The gastric hormone, ghrelin, is composed of 28 amino acids and exhibits a wide range of biological activities via its cognate G-protein-coupled receptor. In both rodents and humans, ghrelin is known to stimulate pituitary growth hormone secretion. It also increases food intake and body weight gain, and regulates energy balance [1]. Ghrelin exerts effects on the gastrointestinal tract, helping to increase gastric emptying and defecation, and also has the potential to reduce emesis [2]. Thus, agents which mimic the actions of ghrelin have potential for the treatment of diseases requiring increased nutritional intake such as cancer-associated cachexia and also in affecting an increase in gastric emptying such as functional dyspepsia [3]. The discovery and development of ghrelin-receptor agonists, to date, has focused on peptide-derived privileged fragment approaches, which have led to synthetically complex, high-molecular weight entities [4]. Recently, however, the discovery of a novel series of low-molecular weight achiral ghrelin-receptor agonists has altered the focus on purely complex peptidic molecules. The stratagem employed high-throughput screening, using a recombinant functional assay and early optimization by parallel synthesis and has been reported recently [5]. These workers at GSK performed a high-throughput screen of their compound collection and identified a moderately potent and tractable hit series represented by the indoline amide (i). Analogues of (i) were screened with the goal of generating divergent SAR data through subtle manipulation of the structure. This effort led to the identification of a series of sulphonamide derivatives which possessed improved selectivity over 5-HT_{1B} when compared to the progenitor amide series. Further synthesis ensued around this series of sulphonamides to further explore SAR. In order to facilitate the efficient parallel synthesis of sulphonamide analogues, the synthetic sequence was optimized for the use of polystyryl-*N*-methylmorpholine to allow simple parallel extraction of reaction products using solid phase cation exchange cartridges, thereby removing any minor by-products arising from sulphonylation of the more hindered piperazine nitrogen. This led to the production of two 24-member combinatorial arrays. From these libraries, a series of potent ghrelin-receptor agonists were identified. One of the most potent compounds was (ii), which possessed a pEC_{50} of 9.8 against the growth hormone secretagogue. Some of the compounds also possessed reasonable *in vitro* (such as log *D* 1.8, rat liver microsome stability of 2.6 mL/min/g and *in vivo* properties (after i.v. dosing in rats giving a $T_{1/2}$ of 2.3 hours). This work has capitalized on high-throughput screening combined with efficient parallel synthesis, and has led to the discovery of a novel achiral series of ghrelin-receptor agonists with potential as gastroprokinetic agents for the treatment of disorders such as functional dyspepsia. Further work in this series is warranted, to better optimize this novel series of inhibitors.





Substituted thioxanthen-9-one-10,10-dioxides as inhibitors of the BRCT domain of the breast cancer gene 1

Modern-day medicinal chemists will often seek to generate novel structures that are amenable to rapid and efficient lead optimization in their design plans and, so, these scaffolds amenable to parallel synthesis constitute an important strategic element in modern drug discovery. Thioxanthen-9-one-10,10-dioxides (typical structure iii) possess a number of potentially useful biological activities, including anti-tumour [6], anti-allergic [7] and monoamine oxidase (MAO) inhibitory activity [8]. An approach to the

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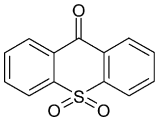
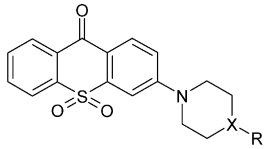
synthesis of these types of structures, utilizing parallel synthesis methods, has recently been developed [9] because of the biological potential demonstrated by this scaffold. The molecules synthesized by this approach were screened for their ability to inhibit the BRCT(BRCA1)–BACH1 interaction, known to have a role in tumour suppression, cell cycle regulation and DNA repair [10]. One of the goals of this current research was to synthesize a small focused library of such thioxanthen-9-one-10,10-dioxide derivatives. This required the development of a microwave-assisted solution-phase parallel synthesis protocol for the synthesis of 10,10-dioxo-3-piperidin-1-yl/piperizin-1-yl-thioxanthen-9-ones, general structure (iv), as well as 10,10-dioxo-3-carboxamide derivatives, general structure (v). This work led to a small library of 36 derivatives of chemotype (iv), this being synthesized via amine displacement from the parent chloride.

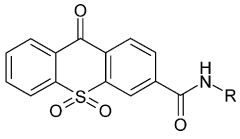
For the synthesis of compounds of general structure (v), simple amide bond formation from the corresponding commercial parent carboxylic acid was undertaken. The compounds were screened for activity in a fluorescence polarization assay for inhibition of the BRCT–BACH1 interaction. With the BRCT–BACH1 assay system, several analogues with moderate potency were identified. One of the most potent was (vi) which possessed a K_i value of 30 μM. This work has produced a focused library of two-substituted thioxanthen-9-one-10,10-dioxides through nucleophilic aromatic substitution and amide bond formation. Upon screening in biological systems, three compounds provided moderate inhibition of the BRCT–BACH1 protein–protein interaction. Further work in this area is warranted to improve the potency further and to examine the potential of these series of compounds for toxicity *in vivo*.



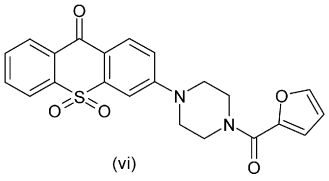
(iii)



(iv: X = C, N)



(v)



(vi)

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