monitor

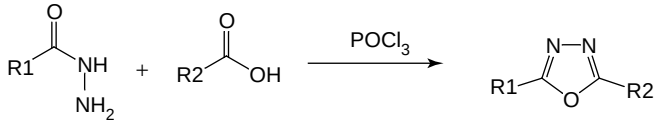
MOLECULES

1,3,4-Oxadiazole analogues as tyrosinase inhibitors

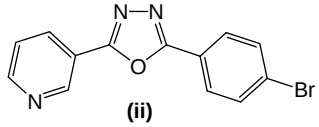
Polyphenol oxidase, or tyrosinase, is a copper-containing enzyme catalyzing the *o*-hydroxylation of monophenols and the oxidation of *o*-diphenols into *o*-quinines. Tyrosinase is a key enzyme for melanin biosynthesis and, as a result, it is reasonable to expect that tyrosinase inhibitors could potentially be clinically useful for treating dermatological disorders that are associated with melanin hyperpigmentation. Thus, recent work [1] intended to identify tyrosinase inhibitors has focused on the synthesis of a small library of 2,5-disubstituted-1,3,4-oxadiazoles.

These entities were synthesized using a microwave-assisted combinatorial synthesis. The use of microwave radiation allows the liquid and solids contained within the reaction to convert electromagnetic energy into heat; the absorption and transmission of energy being completely different from conventional heating. This technique was therefore employed to good effect in the synthesis of these 1,3,4-oxadiazoles. According to the scheme, several hydrazides were treated with a range of carboxylic acids in the presence of phosphorous oxychloride to give the 2,5-disubstituted-1,3,4-oxadiazoles of general structure **(i)**. One-pot microwave-assisted syntheses were carried out in a reaction time of 6–16 minutes, whereas under traditional reflux a reaction time of 4–10 hours was required for conversion.

When the library compounds were screened for the *o*-diphenolase inhibitory activity of tyrosinase using L-DOPA as the substrate, several moderately active compounds were discovered. One of the most potent compounds isolated was **(ii)**, which possessed an IC_{50} of 2.18 μM. Thus, this work has identified a novel series of tyrosinase inhibitors that serve as a starting point for the ultimate clinical development of a potential treatment for several skin disorders and, therefore, further optimization is therefore warranted.



(i)

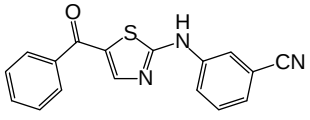


(ii)

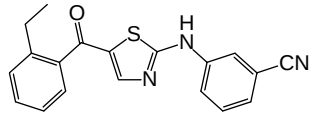
NPY5 receptor antagonists derived from iterative parallel chemistry design

Neuropeptide Y (NPY), a 36 amino acid neuropeptide, is a member of the pancreatic polypeptide family. Antagonists of the NPY5 receptor cause the reduction of food intake in animal feeding models and, so, antagonists of the NPY5 receptor have been targeted as potential antiobesity drugs. Recent work [2] has combined a topological similarity approach in virtual screening, likely to deliver compounds with similar binding affinity to the seed compound because the derived compounds are similar in structure, with a pure 3D pharmacophore approach, more likely to deliver structural novelty but with the potential penalty of a reduced binding affinity.

From this work, 632 pre-existing compounds were chosen from a corporate compound collection and screened for antagonist activity at the mouse Y5 receptor. From this chosen set, 31 compounds had an IC_{50} <10 μM, with **(iii)** possessing an IC_{50} of 40 nM. This compound was also active at 10 mg kg^{-1} i.p. (intraperitoneal) in a mouse feeding model. Hit compound **(iii)** then underwent two rounds of optimization using parallel chemistry and ~140 compounds were synthesized in solution during this optimization process. Library compounds were tested for NPY5 receptor antagonism and several active compounds were discovered. One of the most potent compounds was **(iv)** with an IC_{50} of 2.8 nM.



(iii)



(iv)

This work is of interest because the authors [2] have not focused solely on high hit rates, but rather to yield the correct balance between maintaining the pharmacophoric pattern and shape of seed compounds while concomitantly allowing for topological variability of the

scaffold. The establishment in this work of SAR within this compound class could form the basis for further optimization cycles, allowing access to more-potent NPY5 receptor antagonists that maintain a balanced pharmacokinetic and pharmacodynamic profile.

References

1 Khan, M.T.H. *et al.* (2005) Structure-activity relationships of tyrosinase inhibitory combinatorial library of 2,5-disubstituted-1,3,4-oxadiazole analogues. *Bioorg. Med. Chem.* 13, 3385–3395

2 Guba, W. *et al.* (2005) Novel and potent NPY5 receptor antagonists derived from virtual screening and iterative parallel chemistry design. *Bioorg. Med. Chem. Lett.* 15, 1599–1603

Paul Edwards
mepauledwards@fsmail.net

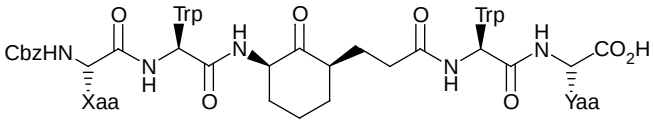
PII: S1359-6446(05)03708-6

Inhibitors of the serine protease plasmin

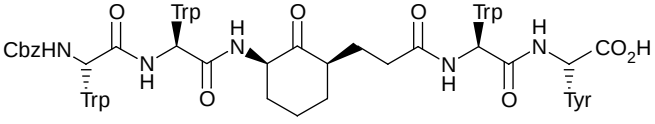
Proteases are involved in the regulation of a multitude of physiological processes, including diverse events such as growth, cellular migration and remodelling of the extracellular matrix (ECM) [1]. Plasmin is a serine protease that is crucial for ECM remodelling because of its role in degrading ECM components such as fibrin, fibronectin, laminin and proteoglycans. In addition to this direct role, plasmin also plays a more indirect role by initiating a protease cascade via the activation of the matrix metalloproteases (MMPs) MMP-1, -3, and -9. In turn, these MMPs regulate matrix deposition and remodelling.

Recently, several studies have shown that ECM remodelling is one of key processes associated with angiogenesis, tumour growth and invasion [2,3]. Thus, potent and selective inhibitors of plasmin could represent potent chemotherapeutic agents through the inhibition of angiogenesis, blocking the rapid growth of primary tumours, as well as the spread of secondary metastases. Recent work [4] has disclosed the generation of a library of putative inhibitors with the general structure **(i)**. This library of 400 compounds, synthesized in mixtures of 20, was prepared on solid support (Wang resin). Compounds were screened against plasmin, a serine protease, identifying several active mixtures. Following a deconvolution procedure, several active compounds, now as singletons, were discovered. One of the most potent inhibitors of plasmin was **(ii)**, which possessed an IC_{50} of 2.7 μM.

The specificity of **(ii)** was determined against three other trypsin-like serine proteases (kallikrein, thrombin and trypsin). Against these enzymes, no inhibition was observed at a concentration of 400 μM, indicating that **(ii)** possessed >150-fold selectivity for plasmin over kallikrein, thrombin and trypsin. Given that compounds in the series typified by **(i)** have high molecular weights and are peptide-like



(i)



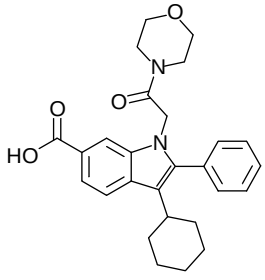
(ii)

compounds, it is unlikely they will have good oral bioavailability. However, because they are designed to control remodelling and degradation of the ECM, the inhibitors do not need to penetrate through the cell membrane. One way to improve their pharmacokinetic characteristics would be to replace the amide bonds by appropriate nonhydrolyzable analogues, decreasing their susceptibility to hydrolysis by proteases. Further work in this area is warranted to achieve these aims.

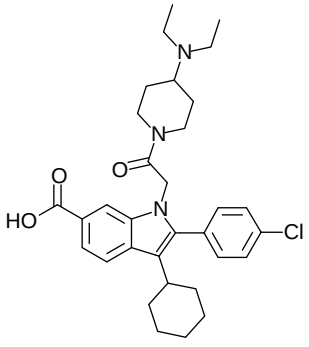
Inhibitors of subgenomic hepatitis C virus RNA replication

The hepatitis C virus (HCV) has been identified as the pathogen responsible for most cases of non-A and non-B hepatitis [5]. HCV infection represents a significant global health problem and it is now thought that there could be as many as 170 million carriers of the virus around the world. HCV can lead to life-threatening liver disorders, such as cirrhosis, and is now recognized as the largest single factor necessitating liver transplantation [6]. New therapies aimed at tackling HCV are urgently required but efforts to discover and develop them have been impeded by the problems arising with HCV replication in cell culture or in small-animal models. The recent introduction of the HCV replicon assay [7], a surrogate cell-based system in which replication of subgenomic viral RNA is studied, has facilitated drug discovery efforts that target HCV proteins. Using this assay, a potent inhibitor of the HCV nonstructural (NS)3 protease was shown to be capable of eliciting a strong reduction in viral titre in a clinical setting. In addition to NS3, the nonstructural region of the HCV genome encodes additional enzymes that are believed to play important roles in the viral life cycle, and are thus viable targets for drug discovery. The NS5B protein is one such target and it has been characterized as the RNA polymerase, which catalyzes the synthesis of a complementary (–)-stranded HCV RNA intermediate and the (+)-stranded viral genome itself. NS5B has emerged as an attractive target for drug discovery efforts aimed towards antivirals for HCV, and it has been described as the most druggable HCV protein [8].

Several series of NS5B inhibitors that show activity in the replicon assay have been reported and it is hoped that they could represent potential new HCV therapeutics. Although, to date, no non-nucleoside inhibitors capable of binding at the active site of NS5B, as well as possessing cell-based activity, have been reported. However, allosteric inhibition by small-molecule inhibitors of NS5B has emerged as one potential route for the inhibition of subgenomic



(iii) NS5B IC_{50} = 26 nM



(iv) NS5B EC_{50} = 127 nM