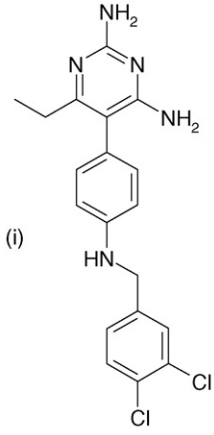
monitor

MOLECULES

Novel compounds directed against the inhibition of protease cascades

Small molecule nonchiral renin inhibitors

One of the major risk factors for cardiovascular diseases, such as congestive heart failure, stroke and myocardial infarction, is hypertension. Hypertension is the leading cause of death in the Western world and it is estimated that there are approximately 1 billion people worldwide that suffer from high blood pressure. Despite currently available therapies, the majority of patients diagnosed with hypertension do not reach their target blood pressure levels. Opportunities remain for improved treatment options [1]. The renin–angiotensin system (RAS) is well established as an endocrine system involved in blood pressure and fluid electrolyte balance. Renin is the aspartyl protease that cleaves angiotensinogen to produce angiotensin I, which is further converted by angiotensin-converting enzyme (ACE) to the potent vasoconstrictor, angiotensin II. It is believed that inhibition of renin would be a good strategy for the control of hypertension because angiotensinogen is the only substrate known for renin, and cleavage of angiotensinogen by renin is the rate-determining step in the RAS [2]. Attempts to inhibit renin, at first concentrated on high molecular weight transition state mimetics, designed from the angiotensinogen backbone. As is often the case with peptidomimetics, these inhibitors suffered from poor PK properties, such as low oral bioavailability and short duration of action. For a long time, these observations led many to believe that renin was an 'nondruggable' target. Recently, in 2006, Novartis Pharmaceuticals filed the first NDA for an inhibitor of renin for the treatment of hypertension. Tekturna® (Aliskerin) was approved in March 2007 and represents the first of a new structural class of antihypertensive drugs. Based on the positive results exhibited by Tekturna®, interest has been rekindled in renin as a viable drug target for the control of hypertension. Recent work [3] describes efforts into the discovery of novel small molecule renin inhibitors for the treatment of hypertension. Workers here ran an HTS campaign and identified (i) as a weak hit (IC_{50} = 27 μM), representing a novel small molecule start point. Parallel chemistry was then undertaken to optimize this hit. A series of reductive aminations was undertaken to prepare 450 compounds, leading to the identification of (ii), which possessed an IC_{50} of 4 μM. Utilizing X-ray crystallography, molecular modeling and an earlier series [4], these workers were able to identify a new chemotype (iii), which itself possessed an IC_{50} of 650 nM against renin. These compounds served as a starting point for further exploration. Other side chains were introduced, with the intention of probing for interactions within other areas in the renin-binding site. This work then led to the identification of (iv) as one of the most potent inhibitors of renin obtained in this series, with an IC_{50} of 91 nM. This work is important because it has identified a novel series of nonpeptidic small molecule renin inhibitors that are not only nonpeptidic but also nonchiral. Further work in the area is warranted in order to optimize for potency and pharmacokinetic/pharmacodynamic parameters within this novel scaffold series.



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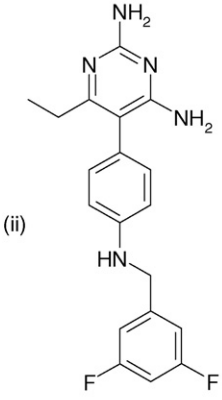

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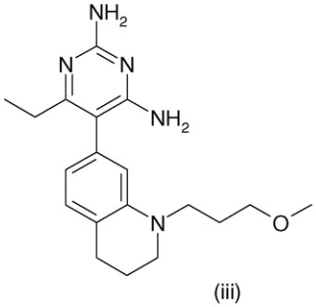

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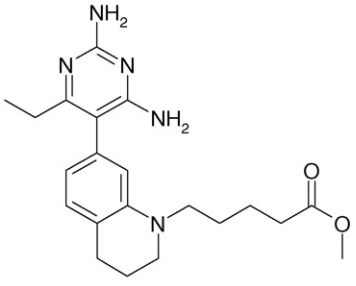

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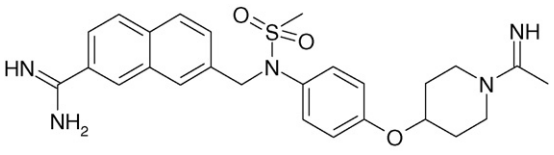
Prodrug-based design, synthesis and biological evaluation of novel factor Xa inhibitors

Thromboembolic diseases, such as ischemic stroke and deep vein thrombosis, result from intravascular clot formation. Clot formation is a major cause of morbidity and mortality in patients in the industrialized world. Until recently, the main medical strategy for treating and preventing such diseases has been the use of the anticoagulants heparin, low molecular weight heparins and the vitamin K antagonist warfarin. All of these drugs, however, have therapeutic limitations. Heparin administration for example, does not allow for an oral route of administration. The use of warfarin as a treatment suffers from a slow onset of action and also requires individual dose titration and periodic monitoring because of its indirect mechanism of action [5]. Thus, the search for novel, orally active anticoagulants that directly inhibit blood coagulation enzymes has emerged as a very active area of current research in drug discovery. Thrombin, which promotes blood clot formation by catalyzing the conversion of fibrinogen to insoluble fibrin, as well as strongly inducing platelet aggregation, plays a central role in thrombosis [6]. However, direct thrombin inhibitors display a tendency to prolong bleeding at levels approaching the effective dose. An attractive alternative to direct thrombin inhibition is by blocking the biosynthesis of thrombin itself. Thrombin formation from prothrombin in the prothrombinase complex is catalyzed by factor Xa (fXa). fXa inhibitors theoretically have less potential to increase the risk of bleeding because they affect coagulation specifically, and do not affect platelet function [7]. Thus, fXa has emerged as an attractive target for the development of new therapeutic agents with potential for the treatment of arterial and venous thrombosis. Recent work [8] has utilized compound (v) as a starting point for drug design optimization. These researchers planned that the benzamidine group of (v) would be transformed into an *N*-hydroxybenzamidine, to enable a prodrug strategy. Till date, there have been no promoieties revealed for the acetimidoyl group contained within (v), so surrogates for the *N*-acetimidoylpiperidine moiety was sought. A further round of design exploited the knowledge that compounds with amidine groups can cause cardiovascular side effects, such as reduced blood pressure and heart rate, probably because of the high basicity of the amidine group [9]. The introduction of an acidic carboxyl group into the amidine derivative with its concomitant reduction of the basicity of the whole chemical compound are important for the avoidance of these side effects [10]. In order to optimize compounds based on the foregoing design hypotheses, a library of piperidine derivatives typified by template (vi) was prepared using solid-phase parallel synthesis. All compounds synthesized were tested for their potency in inhibiting human fXa in a purified enzyme system. The anticoagulant activity for selected compounds was evaluated by measuring the prolongation of prothrombin time (PT) in mouse and human plasma. After testing compounds synthesized in these assays, one of the most potent analogs obtained (vii) which is an *N*-hydroxyamidine prodrug. Compound (vii) itself had no *in vitro* activity but demonstrated an evident PT-prolongation effect in mice when administered orally. Its parent amidine (viii) showed no oral anticoagulant potency. These results indicated that the prodrug (vii) was absorbed via oral dosing and bioconverted into the corresponding active compound. Further work in this area is warranted to improve the potency and oral activity of this series of fXa inhibitors.



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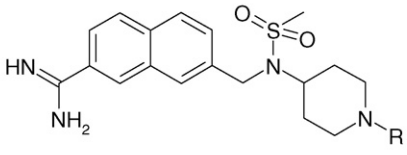

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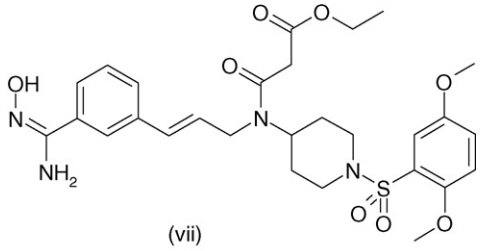

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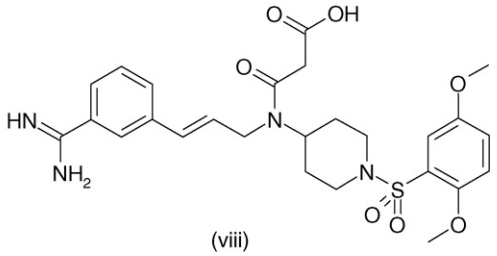

(viii)

1 Ferro, A. *et al.* (2006) Importance of renin in blood pressure regulation and therapeutic potential of renin inhibitors. *Int. J. Clin. Pract.* 60, 577–581

2 Rosenberg, S.H. and Boyd, S.A. (1997) Renin inhibitors. *Antihypertensive Drugs* 77–111

3 Holsworth, D.D. *et al.* (2007) Discovery of 6-ethyl-2,4-diaminopyrimidine-based small molecule renin inhibitors. *Bioorg. Med. Chem. Lett.* 17, 3575–3580

4 Holsworth, D.D. *et al.* (2005) Discovery of novel non-peptidic ketopiperazine-based renin inhibitors. *Bioorg. Med. Chem.* 13, 2657–2664

5 Bona, R.D. (1997) Efficacy and safety of oral anticoagulation in patients with cancer. *Thromb. Haemost.* 78, 137–140

6 Davie, E.W. *et al.* (1991) The coagulation cascade: initiation, maintenance, and regulation. *Biochemistry* 30, 10363–10370

7 Sato, K. *et al.* (1998) Antithrombotic effect of YM-60828, a newly synthesized factor Xa inhibitor, in rat thrombosis models and its effects on bleeding time. *Br. J. Pharmacol.* 123, 92–96

8 Ishihara, T. *et al.* (2007) Prodrug-based design, synthesis, and biological evaluation of *N*-benzenesulfonylpiperidine derivatives as novel, orally active factor Xa inhibitors. *Bioorg. Med. Chem.* 15, 4175–4192

9 Fevig, J.M. *et al.* (1998) Rational design of boropeptide thrombin inhibitors: β,β-dialkyl-phenethylglycine P2 analogs of DuP 714 with greater selectivity over complement factor 1 and an improved safety profile. *Bioorg. Med. Chem. Lett.* 8, 301–306

10 Kikumoto, R. *et al.* (1980) Thrombin inhibitors. 3. Carboxyl-containing amide derivatives of Nα-substituted L-arginine. *J. Med. Chem.* 23, 1293–1299

Paul Edwards
mepauledwards@fsmail.net