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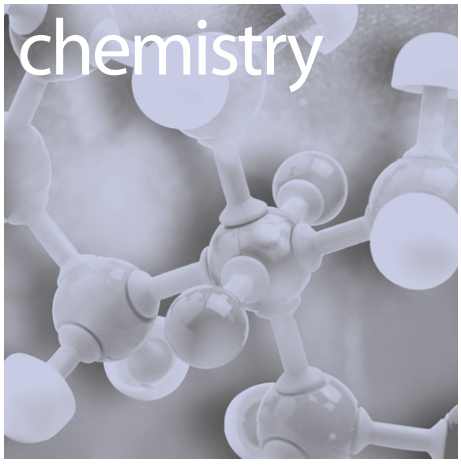
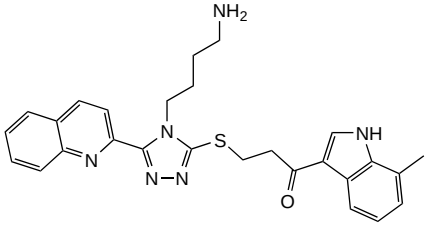


MOLECULES

Somatostatin sst_2/sst_5 agonists

The cyclic peptidic hormone somatostatin (or somatotropin release-inhibiting factor, SRIF) is widely distributed throughout the body. It is mainly expressed in the central and peripheral nervous system and in the gastrointestinal tract, but also in the immune system, the kidney, retina and vessel walls. Somatostatin has regulatory effects on a number of endocrine and exocrine functions such as inhibition of growth hormone [1] and inhibition of the pancreatic secretion of insulin and glucagons [2]. The biological effects of somatostatin are mediated through five distinct G protein-coupled receptor subtypes (sst_{1-5}), which have been cloned and characterized.

Somatostatin displays a wide range of physiological functions, and it could be a significant target for the treatment of various human diseases. For example, if several receptors mediate the antiproliferative activity of somatostatin, then only sst_2 and sst_3 have been reported to induce apoptosis, and to be involved in angiogenesis [3]. In the brain, sst_2 and sst_5 exert a predominant role in the inhibition of GH, prolactin, and thyroid-stimulating hormone (TSH) release. In the pancreas, sst_5 is responsible for the regulation of insulin secretion, whereas sst_2 mediates the inhibition of glucagon release.



(i)

However, somatostatin has a very short half-life in the circulation and its lack of selectivity has been one of the major factors driving the preparation of selective, potent, drug-like peptidic and non-peptidic analogues. Recent work [4] has focused on a new heterocyclic scaffold which could be considered an amide isostere. Thus, these authors have concentrated on the synthesis of 3-thio-1,2,4-triazoles, a template with three points of diversity for combinatorial exploration. More than 700 3-thio-1,2,4-triazole compounds were rapidly prepared by parallel synthesis methods. Competitive inhibition of [^{125}I-Tyr11]SRIF-14 binding to membranes isolated from CHO-K1 cells stably expressing each human somatostatin receptor subtype was measured in 96-well plates. Compounds were first tested at 10 μM. Inhibition constants (K_i) were determined for compounds eliciting more than 70% inhibition at 10 μM. Binding affinities of the most potent compounds toward subtypes 1, 3, and 4 receptors revealed a 10- to 2100-fold selectivity for sst_5 and 20-to 400-fold selectivity for sst_2. In a functional assay based on the inhibition of forskolin-induced intracellular accumulation of cyclic AMP in CHO-K1 cells expressing human sst_2 or sst_5 receptors, one of the most potent agonists discovered **(i)** possessed an EC_{50} value of 4.0 and 2.3 nM on cells expressing the human sst_2 and sst_5 receptors, respectively. Further work to evaluate the therapeutic potential of this new class of non-peptidic somatostatin receptor ligands is warranted.

Factor VIIa inhibitor

Tissue factor (TF) is a membrane-bound protein not normally found in circulating plasma. Damage to the integrity of the vascular system or activation of monocytes or endothelial cells results in release of TF to the blood. After this, TF forms a complex with factor VIIa (fVIIa) to activate factor IX to factor IXa and factor X to factor Xa, which in turn activates prothrombin to thrombin. Active thrombin then cleaves fibrinogen to fibrin, which is the major structural component of blood clots. The fVIIa/TF complex is recognized as the primary initiator of blood coagulation *in vivo*. Although progress has been made in the discovery of potent and selective inhibitors of thrombin and factor Xa as anticoagulant drugs (see, for examples [5,6]), less effort has been focused on the discovery of inhibitors of fVIIa/TF. Recently, for example, studies using anti-factor VIIa antibodies, active-site-inhibited factor VIIa, and recombinant anticoagulant tissue factor pathway inhibitor (TFPI) have yielded promising results (see, for examples [7,8]).

Thus, there is increasing interest in the generation of potent and selective small-molecular factor VIIa inhibitors as candidates for novel anticoagulants [9]. This work describes the optimization of potency and selectivity for inhibition of fVIIa/TF based on scaffold **(ii)**. The original lead **(ii)** was discovered from a combinatorial chemistry library. Further optimization by computational modeling led to one of the most potent compounds discovered in this work **(iii)**, which possessed a K_i for fVIIa/TF of 1 nM, with good selectivity over fXa and Thrombin (K_is of 1.8 μM and >150 μM, respectively). This compound was also shown to preferentially inhibit the TF-dependent

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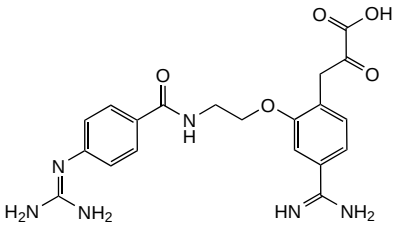
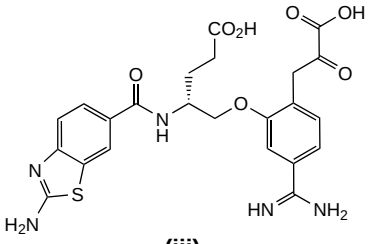


(ii)



(iii)

extrinsic clotting pathway. Here, **(iii)** displayed a prothrombin time (% of control at the drug concentration of 32 μM) of 4500 and an activated partial thromboplastin time (% of control at the drug concentration of 32 μM) of 370. Inhibition of the TF-dependent extrinsic clotting pathway was evaluated in terms of the prolongation of the prothrombin time. The prothrombin time prolongation correlated with fVIIa-inhibitory activity. Optimization of a lead discovered library by combinatorial chemistry methods from a fXa inhibitor library led to a potent and selective fVIIa/TF inhibitor which preferentially inhibits the TF-dependent extrinsic clotting pathway.

The potential advantages of small-molecular fVIIa/TF inhibitors as compared with fXa or thrombin inhibitors in the treatment of thrombotic disorders are not well established. Thus, further work is warranted in this area to examine the separation of antithrombotic efficacy and bleeding side effect by using a selective fVIIa/TF inhibitor such as **(iii)** in intravenous studies in animal models.

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