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Novel, selective indole-based ECE inhibitors: Lead optimization via solid-phase and classical synthesis

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Abstract—A novel class of indole-based endothelin-converting enzyme (ECE) inhibitors was identified by high throughput screening. We report systematic optimization of this compound class by means of classical and solid-phase chemistry. Optimized compounds with a bisarylamide side chain at the 2-position of the indole skeleton exhibit low-nanomolar activity on ECE.

1. Introduction

Since its discovery in 1988, endothelin (ET-1), its metabolism, and potential implications in several diseases have attracted considerable attention.[1] Blockade of the action of ET-1 by ET-receptor antagonists has been widely studied in animal models as well as in clinical trials aimed at evaluating their use in the treatment of various diseases such as hypertension, congestive heart failure, and cancer.[2] Notably, bosentan, the first marketed ET-receptor antagonist, was approved for the treatment of pulmonary arterial hypertension in 2001.[3] Since the 21-amino acid peptide ET-1 is formed by cleavage of its precursor big-ET via the action of endothelin-converting enzyme (ECE), inhibition of this metalloprotease has become an attractive target to modulate ET-1 levels. Several inhibitors of ECE have been described in recent years.[4] The majority of those investigational compounds typically contains structural motifs such as thiols or phosponates addressing the Zn-bearing catalytic center of the enzyme. Such pharmacophoric groups, however, can lead to detrimental pharmacokinetic properties. In addition, selectivity versus related metalloproteases such as neutral endopeptidase 24.11 (NEP) or angiotensin-converting enzyme (ACE) has been reported to be difficult to achieve.[4] Thus, there is still need to discover novel, selective lead structures for the inhibition of ECE.

Through screening of the Bayer compound collection, indole derivative **1** has been identified to be a potent ECE inhibitor.[5] In a standard enzyme-linked immunosorbent assay (ELISA) format,[6] **1** had an IC_{50} value of 1.8 μM. The interesting in vitro activity, the unprecedented structure as well as high selectivity observed for this compound versus the related enzymes NEP and ACE (IC_{50} values >10μM) rendered indole **1** into an attractive starting point for a medicinal chemistry optimization program.

In this article, we describe a systematic approach towards the optimization of ECE inhibitor **1** and disclose the details of the resulting structure–activity relationship (SAR).

2. Chemistry

As no obvious Zn-chelating group is present in ECE inhibitor **1**, we decided to systematically vary the structural features of the lead compound. For this, we focused on the three substituents at positions 1, 2, and 5 of the indole core (see Fig. 1) which can be subjected

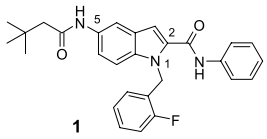

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Figure 1. Lead structure **1** from HTS.

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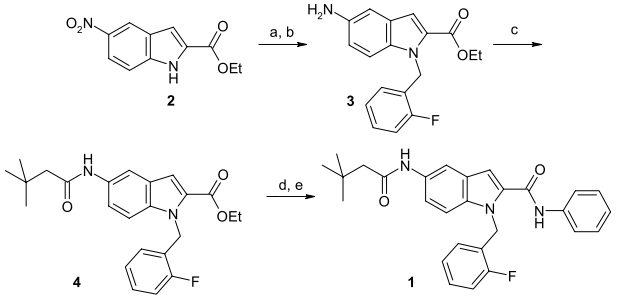
to variations independently from each other. In addition, changes in the indole scaffold itself and position shifts of the side chains were envisaged.

Synthesis of indole derivatives was achieved by starting from commercially available indole **2** through a standard sequence (Scheme 1). Alkylation of the indole nitrogen in **2** was accomplished by treatment with 2-fluorobenzylbromide under basic conditions. After reduction, the resulting aminoindole **3** was treated with pivaloyl chloride to give the corresponding amide **4**. Saponification of the ester moiety and coupling with aniline yielded the final indole-2-carboxamide **1**.

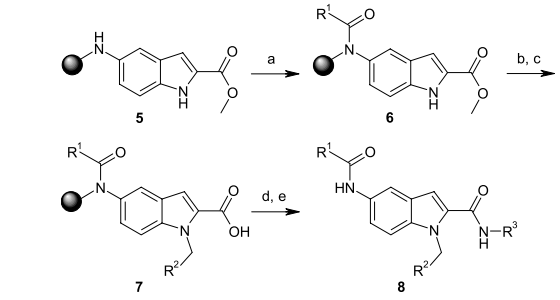
Synthetic throughput was dramatically increased by employing solid-phase organic chemistry as outlined in Scheme 2. Thus, library synthesis began with indole **5** that was obtained from reductive amination of 4-(4-formyl-3-methoxyphenoxy)butyrylamide resin with methyl-5-amino-1*H*-indole-2-carboxylate. Acylation of **5** with diverse carboxylic acid chlorides generated **6**. N-alkylation with benzyl and alkyl halides using LiHMDS followed by ester hydrolysis afforded the indole carboxylic acid **7**. Amide formation of **7** with anilines was most efficient using HATU (method A), whereas coupling of amino phenols worked best with PPh_3 and NBS (method B). Finally, **8** was released from the resin with TFA in CH_2Cl_2. The combinatorial library was synthesized using a split-and-pool IRORI Kan® method.[7] Using this synthetic route, 1332 new compounds were prepared, which gave satisfactory spectral and analytical data, and were therefore tested for their ECE inhibitory activity.

For the synthesis of the inverse amide at the 5-position (**12**, Scheme 3), commercially available 4-hydrazinobenzoic acid (**9**) was refluxed with ethylpyruvate in *i*-PrOH/AcOH, followed by coupling with neopentyl amine. The resulting phenylhydrazone was treated under Fischer-indole type reaction conditions using polyphosphoric acid[8] to yield the desired indole-5-carboxamide **10**. Alkylation of indole nitrogen and subsequent installation of a C-2 amide side chain was carried out as described in Scheme 1.

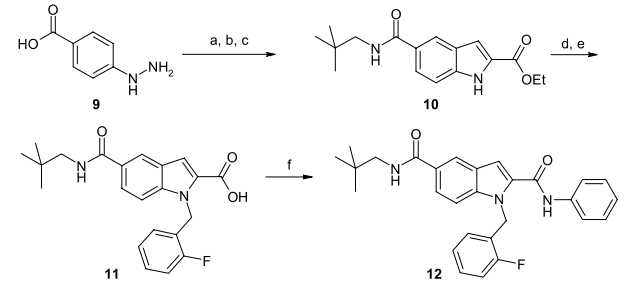
Synthesis of benzimidazole derivative **17** (Scheme 4) was achieved starting from commercially available 4-nitrobenzene-1,2-diamine (**13**) through a standard synthesis sequence.[9] After treatment with a trichloroacetimidate, the resulting intermediate **14** was converted into ester **15** under standard conditions. N-benzylation of **15** employing basic conditions resulted in a 1:1 mixture of regioisomers from which the desired 5-nitrobenzimidazole isomer was separated by flash chromatography (cyclohexane/ethyl acetate) and



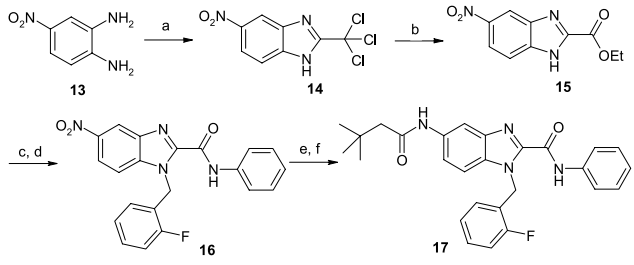
Scheme 1. Synthesis of indole-2-carboxamide **1**. Reagents and conditions: (a) KO*t*-Bu, 18-crown-6, 0 °C, 2-fluorobenzylbromide, THF, rt, 86%; (b) Pd/C, ammonium formate, EtOH/ethyl acetate, 95%; (c) $C(CH_3)_3CH_2COCl$, NEt_3, CH_2Cl_2, 0 °C to rt, 98%; (d) LiOH, MeOH/H_2O 3:1, rt, 89%; and (e) HATU, DIPEA, DMF, aniline, rt, 84%.



Scheme 2. Solid-phase synthesis of **8**. Reagents and conditions: (a) $R^1C(O)Cl$, acetone, Et_3N, rt; (b) LiHMDS, R^2CH_2Br, DMF, rt; (c) KOH, MeOH/dioxane (1:2), rt; (d) method A (anilines): HATU, DMF/Pyr (1:2), rt, or method B (amino phenols): PPh_3, NBS, CH_2Cl_2, Pyr, THF, −25 °C to rt; and (e) TFA, CH_2Cl_2, rt.



Scheme 3. Synthesis of indole-5-carboxamide **12**. Reagents and conditions: (a) ethyl pyruvate, AcOH, *i*-PrOH, reflux, 76%; (b) TBTU, DIPEA, $C(CH_3)_3CH_2NH_2$, CH_2Cl_2, 0 °C to rt, 59%; (c) PPA, 120 °C, 5 h, 34%; (d) KO*t*-Bu, 18-crown-6, 0 °C, 2-fluorobenzylbromide, THF, rt, 55%; (e) LiOH, MeOH/H_2O 3:1, rt, 98%; and (f) HATU, pyr/DMF 2:1, aniline, rt, 47%.



Scheme 4. Synthesis of benzimidazole **17**. Reagents and conditions: (a) methyl 2,2,2-trichloroacetimidate, AcOH, rt, 3 h, 92%; (b) $AgNO_3$, EtOH, reflux, 15 h, 99%; (c) KO*t*-Bu, 18-crown-6, 0 °C, *o*-fluorobenzylbromide, THF, rt, 29% desired regioisomer; (d) aniline, NaH, THF, reflux, 65%; (e) $SnCl_2$, EtOH, 32%; and (f) $C(CH_3)_3CH_2COCl$, NEt_3, CH_2Cl_2, 0 °C to rt, 20%.