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Synthesis and biological evaluation of picolinamides as potent inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1)

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ABSTRACT

Synthesis of a series of 6-substituted picolinamide derivatives and their inhibitory activities against 11β-hydroxysteroid dehydrogenase type 1 are described. Optimization of the initial hit compound, *N*-cyclohexyl-6-(piperidin-1-yl)picolinamide (**1**) from high throughput screening of in-house library resulted in the discovery of the highly potent and metabolically stable compound **25**, which was efficacious in a mouse ex vivo pharmacodynamic model and reduced the fasting blood glucose and insulin levels in a HF/STZ mouse model after oral dosing.

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is a key enzyme that acts as an NADPH-dependent reductase and converts inactive cortisone into active cortisol, which is an actual circulating glucocorticoid in humans. 11β-HSD1 is mainly distributed in specific tissues, such as liver, adipose, and brain, and regulates tissue-specific glucocorticoid levels.[1]

Chronic high level of glucocorticoids can result in insulin resistance from impairment of insulin-dependent glucose uptake, increased hepatic gluconeogenesis, and reduced insulin secretion from the pancreas. Due to the physiological relationship between glucocorticoids and metabolic disease risk factors, 11β-HSD1 has been regarded to be a potential target for the treatment of metabolic syndrome as well as type II diabetes.[2] Several studies using a genetic mouse model have supported this idea. For example, liver or adipose tissue-specific overexpression of 11β-HSD1 in transgenic mice showed several features of metabolic syndrome, including abdominal obesity, dyslipidemia, glucose intolerance, and insulin resistance.[3] In contrast, 11β-HSD1 knock-out mice demonstrated a reduction in body weight, improved lipid profiles, and increased insulin sensitivity under the conditions of a high fat diet.[4]

In the last decade, extensive research in the pharmaceutical industry has disclosed various chemical classes of 11β-HSD1 inhibitors[5] (Fig. 1), including sulfonamides (PF-915275),[6] triazoles (Merck 544),[7] thiazolones (AMG-221),[8] and carboxamides (AZD-4071).[9]

As one of our research projects for the development of new therapeutics for the treatment of type II diabetes, high throughput screening of an in-house compound library utilizing the microsomal fractions overexpressing human 11β-HSD1 enzyme was performed, and hit compound **1** was identified to be a novel inhibitor of 11β-HSD1. Interestingly, compound **1** shared the same picolinamide core structure with the previously reported 11β-HSD1 inhibitor, BMS30[10] (Fig. 2). To guide the medicinal chemistry program,

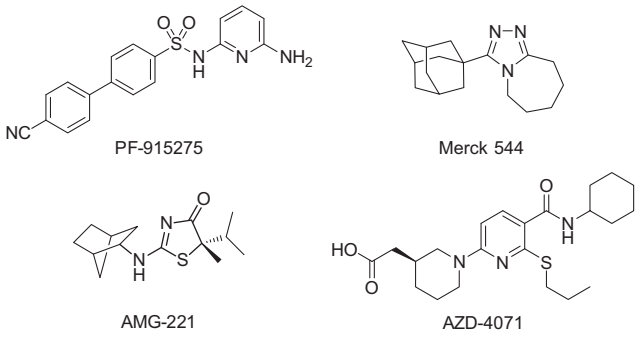

Figure 1. Previously reported 11β-HSD1 inhibitors.

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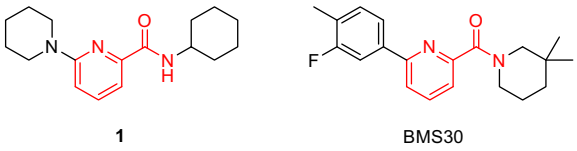


Figure 2. Chemical structures of hit compound **1** and BMS30.

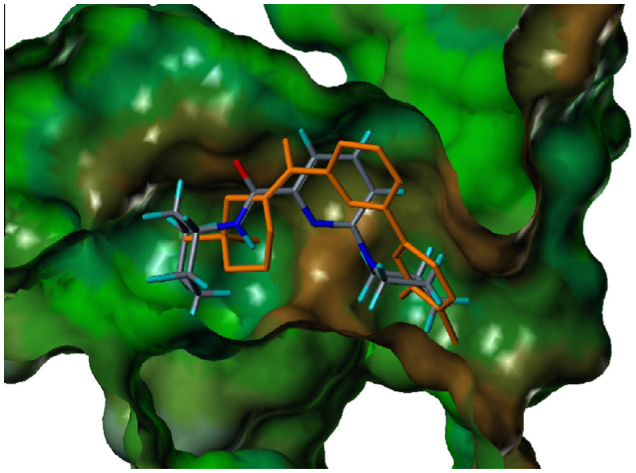


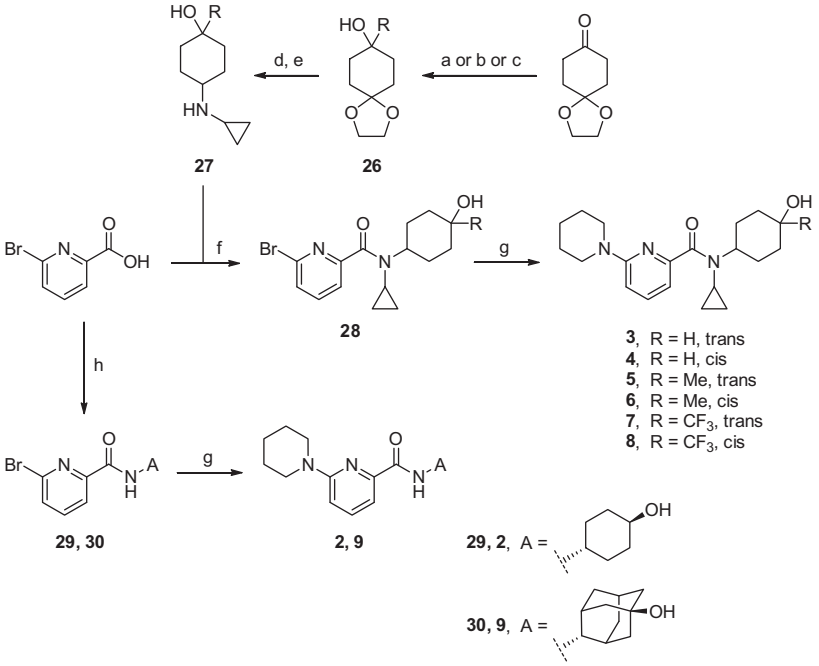
Figure 3. Overlap of BMS30 (in brown stick) and compound **1** in the binding site of human 11β-HSD1. The protein structure and pose of BMS30 were taken from 3CH6. Predicted binding mode of **1** was generated by Surflex-Dock.

the hit compound **1** was docked into the human 11β-HSD1-BMS30 co-crystal structure (PDB code 3CH6). The overall binding mode of **1** in the binding site of human 11β-HSD1 was similar to that of BMS30. However, detailed analysis revealed that the carbonyl group of **1** did not establish hydrogen bonds with the key interaction residues (hydroxyl groups of Ser170 and Tyr183), whereas the cyclohexyl moiety of **1** was located more closely to the hydrophobic binding pocket. The piperidine ring of **1** was positioned toward the solvent-exposed area of the dimer interface region of the protein and interacted with hydrophobic residues (Fig. 3).

Despite its moderate to high inhibitory activity against 11β-HSD1 (human 11β-HSD1, IC_{50} = 58 nM), compound **1** showed poor metabolic stability in the mouse microsomal assay (% remaining at 30 min = 15%). We planned to modify cyclohexyl and piperidine rings of **1** because these lipophilic moieties are expected to be metabolically unstable despite their important hydrophobic interactions with the binding site of the enzyme. In this communication, we describe our optimization efforts to improve both the potency and metabolic stability of our hit compound **1** as an 11β-HSD1 inhibitor.

First of all, we planned to modify the structure of **1** in two regions, the cyclohexyl amide position and the piperidine ring at the 2-position of the pyridine. Additionally, the derivatization was focused on improving not only the enzymatic inhibitory activity but also the metabolic stability by introducing polar groups, such as a hydroxyl group or carboxylic acid group. Cyclohexyl ring modified analogs **2**–**9** were prepared as outlined in Scheme 1. 1,4-Cyclohexanedione mono-ethylene ketal was either reduced by $NaBH_4$ or treated with MeMgCl or $TMSCF_3$ to yield the 4-substituted cyclohexanone ketal **26**. Treatment of **26** with 1 N HCl, followed by reductive amination with cyclopropylamine, produced the cyclohexylamine **27**, which was then coupled with 6-bromopicolinic acid in the presence of HBTU and separated by silica gel column chromatography to yield both *cis* and *trans* intermediates **28**.[11] Reaction of **28** with piperidine under microwave irradiation afforded the corresponding amides **3**–**8**. In a similar fashion, compounds **2** and **9** were obtained simply by microwave irradiation of piperidine and the picolinamides **29**–**30**, which were also synthesized by a HBTU-assisted coupling reaction between the appropriate cycloalkylamine and 6-bromopicolinic acid.

Piperidine ring-modified compounds **10**–**25** were synthesized via the routes outlined in Schemes 2 and 3. Compounds **10**–**13** were prepared by the reaction of picolinamide **30** with 4-substituted



Scheme 1. Reagents and conditions: (a) $NaBH_4$, MeOH, 98%, (R = H); (b) MeMgCl, THF, 59% (R = Me); (c) $TMSCF_3$, TBAF, THF, 97% (R = CF_3); (d) 1 N-HCl, THF, 62–92%; (e) cyclopropylamine, $NaBH(OAc)_3$, AcOH, DCM, 87–95%; (f) HBTU, DIPEA, ACN, 65–90%; (g) piperidine, ACN, 150 °C, microwave, 82–99%; (h) *trans*-4-aminocyclohexanol or *trans*-4-aminoadamantan-1-ol, HBTU, DIPEA, ACN, 73–85%.