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Bioorganic & Medicinal Chemistry Letters 17 (2007) 3421–3425
Bioorganic & Medicinal Chemistry Letters

Piperidine amides as 11β-hydroxysteroid dehydrogenase type 1 inhibitors

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Received 27 February 2007; revised 27 March 2007; accepted 27 March 2007
Available online 30 March 2007

Abstract—A series of piperidine amide inhibitors of human 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) were identified via modifications of the HTS hit compound **1**. The synthesis, in vitro biological evaluation, and structure–activity relationship of these compounds are presented.

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) has attracted attention during the last few years due to its potential as a target for the treatment of diseases associated with the metabolic syndrome.[1–3] The enzyme, which is mainly expressed in liver and adipose tissue, catalyzes the conversion of inactive cortisone to glucocorticoid receptor-active cortisol (Fig. 1). The type II isoform (11β-HSD2) is located primarily in the kidney and catalyzes the inactivation of cortisol.[4]

A growing number of research results indicate that glucocorticoid excess in tissues such as the liver and adipose might contribute to the development of the metabolic syndrome. In the liver, cortisol has been shown to promote gluconeogenesis via the glucocorticoid receptor by activation of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase enzymes.[5] In the adipose tissue, cortisol is involved in the stimulation of adipogenesis, lipolysis, and release of free fatty acids.[6] The significance of 11β-HSD1 in metabolic diseases such as type 2 diabetes and obesity has been demonstrated in various rodent studies.[7–9] In addition, indirect clinical evidence in humans has been found in patients with Cushing's syndrome where elevated cortisol levels are

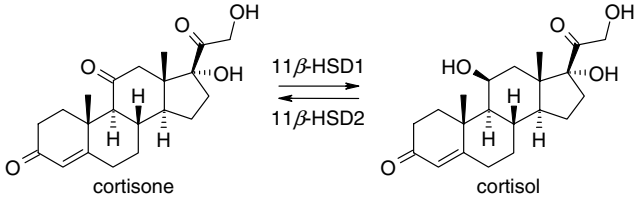

Figure 1. Interconversion of cortisone and cortisol by 11β-HSD1 and 11β-HSD2.

accompanied by characteristic features of the metabolic syndrome, that is, visceral obesity, impaired glucose tolerance, and hyperglycemia.[10] These findings have led to the hypothesis that selective inhibition of 11β-HSD1 would provide a beneficial therapy against metabolic syndrome related diseases.[11–16]

In our ongoing research program on selective 11β-HSD1 inhibitors,[17] the piperidinylbenzimidazolone **1** (K_i = 0.30 μM) was identified in a HTS-campaign (Fig. 2). Based on synthetic accessibility of a wide range of analogs, an expansion of the hit was performed aimed at improving in vitro potency. The inhibitory properties of the molecules were evaluated in a SPA-based human 11β-HSD1 enzymatic binding assay.[18]

It was found that isosteric alternatives to the piperidine amide functionality, for example, sulfonamides, ureas or carbamates, gave decreased 11β-HSD1 binding potencies. Therefore, it was decided to retain the piperidine

Keywords: 11β-HSD1 inhibitors; Piperidine amides; Metabolic syndrome.
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doi:10.1016/j.bmcl.2007.03.083

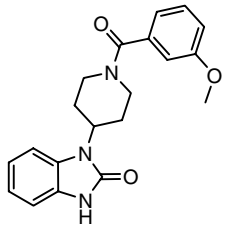


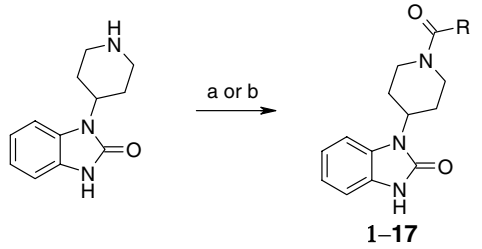
Figure 2. HTS hit compound **1**.

amide moiety as featured in **1** and to focus the investigations on synthetic analogs to the 3-methoxybenzoyl group as well as substitutions/variations on the benzimidazolone ring system.

To determine the SAR around the *N*-acyl substituent at the piperidyl nitrogen, a series of aryl, heteroaryl, saturated cyclic, and aliphatic piperidine amides were synthesized from commercially available 1-piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one and acyl chlorides or carboxylic acids (Scheme 1). The 11β-HSD1 SPA binding assay results of representative examples of these compounds are shown in Table 1.

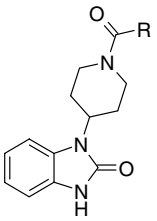
Compounds with aliphatic substituents (**2** and **3**) were >10 μM in the SPA assay, and attempts to introduce alternative heterocycles such as furan (**4**) also resulted in poor binding, although the 2-chloro-4-methoxypyridine derivative **5** retained activity. Electron-rich *meta*-, *para*-disubstituted aromatic amides appeared more favored (**6**–**10**), and the most potent compounds (**6** and **7**) showed a threefold increase in potency when compared to the hit compound **1**. Phenyl groups containing electron-withdrawing substituents such as fluorine (**13** and **14**) and trifluoromethyl (**15**–**17**) gave, on the other hand, reduced activity. To confirm selectivity, compound **7** was tested against 11β-HSD2 and showed very weak activity (K_i > 10 μM).

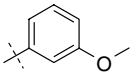
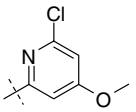
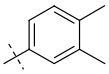
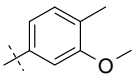
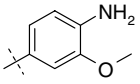
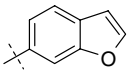
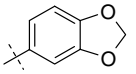
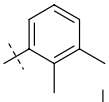
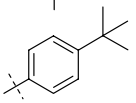
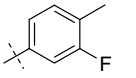
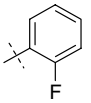
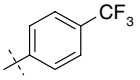
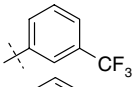
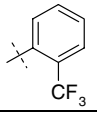
Synthetic variations on the benzimidazole scaffold are described in Schemes 2–5. For comparison purposes, and since **7** was one of the most potent compounds in Table 1, the 3-methoxy-4-methylbenzoyl moiety was retained as the piperidyl *N*-acyl substituent in all of these compounds. Synthesis of the benzoxazolone **18** was achieved in four steps from *N*-Boc-4-piperidone (Scheme 2). Reductive amination with 2-aminophenol and sodium triacetoxyborohydride in DCE at room

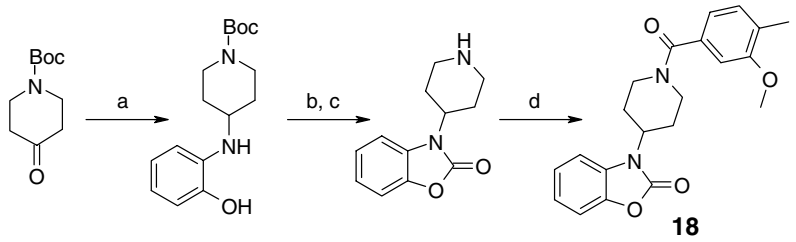


Scheme 1. Reagents and conditions: (a) RCOCl, 10% NaOH (aq), 16 h, rt; (b) RCOOH, EDC, Et_3N, DCM, rt.

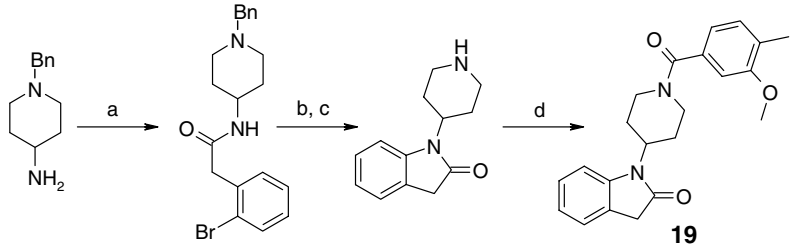
Table 1. Inhibitory activities of selected compounds



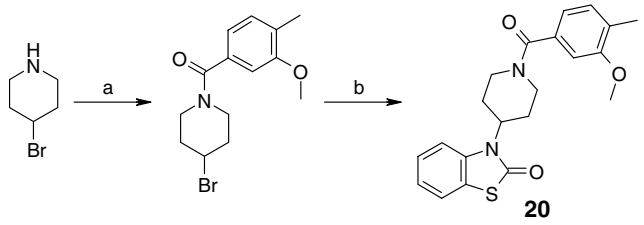
Compound	R	Human 11β-HSD1 SPA K_i (μM)
1		0.30
2		>10
3		>10
4		>10
5		0.45
6		0.10
7		0.11
8		0.18
9		0.50
10		1.1
11		1.1
12		1.6
13		1.7
14		3.5
15		2.6
16		3.1
17		1.3



Scheme 2. Reagents and conditions: (a) 2-aminophenol, DCE, $NaBH(OAc)_3$, rt; (b) pyridine, THF, triphosgene, 60 °C; (c) HCl, 50 °C; (d) 3-methoxy-4-methylbenzoic acid, EDC, Et_3N, DCM, rt.



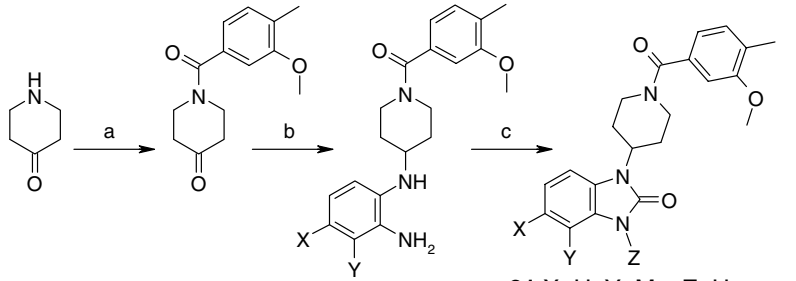
Scheme 3. Reagents and conditions: (a) 2-bromophenylacetyl chloride, K_2CO_3, MeCN, rt; (b) phenylboronic acid, X-Phos, $Pd(OAc)_2$, K_2CO_3, ^{t}BuOH, 85 °C, 2 h; (c) ammonium formate, Pd/C, MeOH, MW, 140 °C, 3 min; (d) 3-methoxy-4-methylbenzoic acid, EDC, Et_3N, DCM, rt, overnight.



Scheme 4. Reagents and conditions: (a) 3-methoxy-4-methylbenzoic acid, EDC, Et_3N, DCM, rt; (b) 2-hydroxybenzothiazole, K_2CO_3, 90 °C.

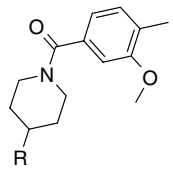
temperature overnight yielded the corresponding 2-[1-Boc-piperidine-4-yl-amino]phenol. Ring-closure to the benzoxazolidinone was achieved with triphosgene and pyridine as previously described.[19] Deprotection with concentrated HCl and subsequent amide formation using EDC and Et_3N gave the desired benzoxazolone **18**.

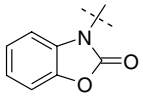
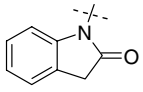
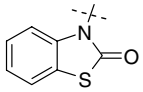
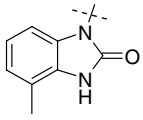
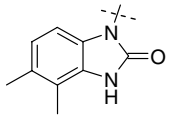
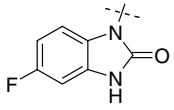
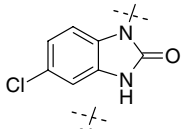
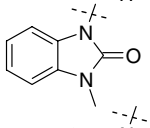
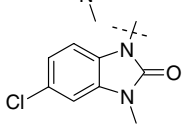
The synthesis of the indolone **19** was performed in four steps, the first being acylation of 4-amino-1-benzylpiperidine with 2-bromophenylacetyl chloride (Scheme 3). Subsequent ring closure with $Pd(OAc)_2$, $PhB(OH)_2$, X-Phos, and K_2CO_3 yielded the benzyl protected 1-(4-piperidyl)indolone.[20] Benzyl deprotection with ammonium formate and Pd/C in MeOH under microwave irradiation and subsequent EDC-catalyzed amide formation with triethylamine gave the desired target compound **19**.



Scheme 5. Reagents and conditions: (a) 3-methoxy-4-methylbenzoic acid, EDC, Et_3N, DCM, rt; (b) X,Y-aryl substituted *o*-phenylenediamine, $NaBH(OAc)_3$, AcOH, DCE rt; (c) DSC, MeCN, rt; (d) NaH, MeI, THF, 0 °C.

Table 2. Inhibitory activities of selected compounds



Compound	R	Human 11β-HSD1 SPA K_i (μM)
18		0.27
19		0.24
20		0.17
21		0.14
22		0.33
23		0.20
24		0.50
25		0.18
26		0.36

The corresponding benzothiazolone **20** was synthesized by coupling of 4-bromopiperidine and 3-methoxy-4-methylbenzoic acid followed by alkylation of 2-hydroxybenzothiazole with potassium carbonate[21] to give the desired product according to Scheme 4.

Amide coupling of piperidone and 3-methoxy-4-methylbenzoic acid using EDC and Et_3N in dichloromethane (DCM) yielded the desired *N*-acyl piperidone amide intermediate (Scheme 5). Reductive amination with aryl-substituted *o*-phenylenediamines, $NaBH(OAc)_3$, and AcOH in DCE at room temperature gave the corresponding benzimidazolones. Ring-closure was achieved using disuccinimido carbonate (DSC) in MeCN at ambient temperature to give compounds **21**–**23** in >80% regioisomeric purity.[22] Compound **24** was synthesized directly from commercially available 5-chloro-1-piperidin-4-yl-1,3-dihydro-2*H*-benzimidazol-2-one according to Scheme 1. Alkylation of compounds **7** and **24** using NaH in dry THF followed by addition of excess MeI yielded the *N*-methylated benzimidazolones **25** and **26**, respectively.

Table 2 illustrates the variations of the benzimidazolone scaffold where the SAR was found to be relatively flat in comparison to the dramatic shifts in activity observed when altering the *N*-acyl substituent at the piperidyl nitrogen. Changing the peripheral scaffold from benzimidazolone (**7**) to the corresponding benzoxazolone (**18**), indolone (**19**), or benzothiazolone (**20**) gave essentially equipotent compounds. Various substitution patterns on the benzimidazolone were tolerated (**21**–**24**) but did not improve potency; however, monosubstituted benzimidazolone **21** appeared more favored than the disubstituted derivative **22**. *N*-Methylation of the benzimidazole (**25** and **26**) gave compounds with similar or slightly improved activities when compared to their non-alkylated analogs (**7** and **24**). Thus, none of the performed modifications on the benzimidazolone scaffold resulted in an increase in inhibitory activity when compared to compound **7**.

In conclusion, we have identified a novel class of piperidine amide inhibitors of the human 11β-HSD1 enzyme. Modification of the hit compound **1** resulted in a threefold increase in potency (compounds **6** and **7**). Alternatives to the piperidine amide linker, variations of the *N*-acyl substituent, and substitutions/variations on the benzimidazolone moiety of **1** were investigated.

Acknowledgments

We thank Lars Hammarström at Biovitrum for help and discussions during the preparation of this manuscript.

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18. Human 11β-HSD1 Scintillation Proximity Assay (SPA) was carried out in triplicate, each replica containing 10 μL of diluted compound (from a 3-fold dilution series), 50 μL assay buffer, and 25 μL substrate mixture [^{3}H]-Cortisone / NADPH (175 nM/200 μM). Reactions were initiated by the addition of 25 μL of purified *Escherichia coli* derived human 11β-HSD1 (40–60 nM final concentration, depending on the batch). Following mixing, the plates were incubated on a shaker for 30–60 min at room temperature. The reactions were terminated with 10 μL stop solution (1 mM 18β-glycyrrhetinic acid in ethanol). Monoclonal mouse anticortisol antibody was then added (10 μL of 1.92 μM working solution) followed by 50 μL of YSi SPA beads coated with monoclonal antimouse antibodies. As reference substance, carbenoxolone was run in each plate. The plates were sealed with plastic film (Perkin Elmer, Top Seal-A) and incubated on a shaker for 30 min at rt before counting. The amount of [^{3}H]-cortisol captured on the beads was determined in a microplate liquid scintillation counter. Kinetic constants were calculated employing the Microsoft Excel integrated application XLfit (Version 5.3.0.19, ID Business Solutions Ltd.) using the sigmoidal dose–response model 205 which is based on the non-linear curve fitting based on Levenberg–Marquardts algorithm.
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