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Discovery of DS79182026: A potent orally active hepcidin production inhibitor

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ABSTRACT

Hepcidin has emerged as the central regulatory molecule of systemic iron homeostasis. Inhibition of hepcidin could be a strategy favorable to treating anemia of chronic disease (ACD). We report herein the synthesis and structure-activity relationships (SARs) of a series of benzisoxazole compounds as orally active hepcidin production inhibitors. The optimization study of multi kinase inhibitor **1** led to a potent and bioavailable hepcidin production inhibitor **38** (DS79182026), which showed serum hepcidin lowering effects in a mouse IL-6 induced acute inflammatory model.

Hepcidin is a peptide hormone, and is known as the master regulator for systemic iron mobilization.[1] The maintenance of serum iron level is important since a high iron concentration induces oxidative organ damage, and a low iron concentration results in iron deficiency anemia.[2] As hepcidin was originally discovered as an antibacterial peptide,[3] this hormone is inducible by inflammatory cytokines such as IL-6,[4] in addition to iron signaling.

Anemia of chronic disease (ACD), which includes anemia of inflammation, is a heterogenic anemic condition due to chronic inflammation from a basic disease, such as rheumatoid arthritis.[5] Some ACD patients are known to present iron deficiency despite abundant body iron store (termed *functional iron deficiency*). Recently, high hepcidin induction based on inflammatory status was recognized as the cause of functional iron deficiency. Hepcidin expression deficiency is a common phenotype of hereditary hemochromatosis. The controlling of hepcidin level would be a promising therapeutic strategy for treating hepcidin caused functional iron deficiency. Indeed, a few such biologics (e.g. NOX-H94, LY2928057 and LY2787106) are entering clinical trials for treatment of anemia. Herein we describe the derivatization aimed at the enhancement of bioavailability and lowering of the multi kinase inhibitory activity of **1** to discover methyl {6-[5-methyl-3-(pyridin-2-yl)-1*H*-pyrazol-4-yl]-1,2-benzisoxazol-3-yl}carbamate (DS79182026, **38**), a potent orally available hepcidin production inhibitor.

As previously reported,[6] we identified the indazole derivative **1** as a potent active lead compound (IC_{50} = 0.13 μM).[7] Although compound **1** showed hepcidin lowering effect in mice by the intraperitoneal administration, pharmacokinetic (PK) profiles supported a lack of exposure to blood in the oral administration (Table 1).

The indispensable *para*-hydroxyphenyl group also might be responsible for this low exposure because of the *O*-glucuronidation via UDP-glucuronosyltransferase (UGT). As an entirely fresh start, we started to explore the alternatives of the *para*-hydroxyphenyl group.

First, we examined the bicyclic phenolic bioisosteres. The bicyclic mimetics were designed to address the phenolic H-bond donor based on the localization afforded by the complementary fused heterocyclic rings.[8] However, the benzimidazole **3**, pyrolopyridine **4** and oxindole **5** were found to be surprisingly poor mimetics. Then, we investigated the monocyclic heteroaromatics. The transformations to pyrrole **6** drastically lost and 4-pyridyl group **7** deteriorated hepcidin inhibitory activity. However, the dimethylisoxazole **8** showed moderate inhibitory activity.

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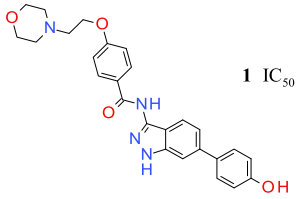
0960-894X/

Table 1
IC_{50} values and physicochemical properties and PK parameters of **1**.



1 IC_{50} = 0.13 μM

LogD	MS[a] (%)	UGT[a] (%)	Cmax (μg/mL)	Tmax (h)	AUC (h*μg/mL)
3.4	89	76	2.64[b] 0.32[c]	1.33[b] 1.50[c]	6.93[b] 0.89[c]

[a] Remaining (%) of the tested compound after 0.5 h incubation with mouse liver microsomes (0.5 mg/mL).
[b] Average of two values dosed at 30 mg/kg i.p. with C57BL/6J mice (0.5% Methylcellulose, suspension).
[c] Average of two values dosed at 30 mg/kg p.o. with C57BL/6J mice (0.5% Methylcellulose, suspension).

Surprisingly, the dimethylpyrazole **9** showed inhibitory activity comparable to compound **2** (Table 2).

Subsequently, we investigated the combinations of the alternative pyrazole and potent benzamide moieties.[6]

The compounds **10** and **11** retained potent *in vitro* activity (Table 3).

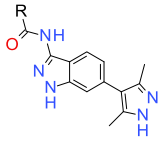
PK parameters of compound **11** are summarized in Table 4.

Compound **11** showed high stability against UGT. PK profiles of **11** were evaluated and found to be improved compared to compound **1**, presumably due to the interruption of the glucuronidation.

Indeed, **11** showed higher plasma exposure than **1** and was considered to be a suitable profile as an oral agent.

Next, the hepcidin lowering effect of compound **11** was evaluated by a mouse interleukin-6 (IL-6) induced acute inflammatory model.

Table 3
SAR of 6-dimethylpyrazole derivatives.



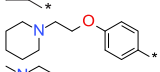
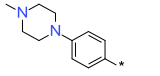
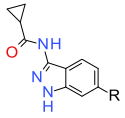
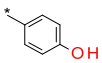
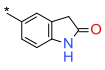
Compound	R	IC_{50} (μM)
9		0.33
10		0.26
11		0.23

Table 2
Alternatives of *para*-hydroxyphenyl group.



Compound	R	IC_{50} (μM)	Compound	R	IC_{50} (μM)
2		0.40	**6**		>30
3		>3	**7**		7.2
4		11	**8**		1.0
5		>30	**9**		0.33