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Design and synthesis of a novel series of orally active, selective somatostatin receptor 2 agonists for the treatment of type 2 diabetes

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ABSTRACT

The discovery of a novel series of β-methyltryptophan (β MeTrp) derivatives as selective and orally active non-peptide somatostatin receptor 2 (SSTR2) agonists for the treatment of Type 2 diabetes is described. In our previous research, Compound **A**, β-MeTrp derivative with highly potent and selective SSTR2 agonistic activity IC_{50} (SSTR2/SSTR5) = 0.3/>100 (nM), was identified as a drug candidate for treatment of Type 2 diabetes which lowers significantly plasma glucose level in Wistar fatty rats in its oral administrations. However, as serious increase in AUC and phospholipidosis (PLsis) were observed in its toxicological studies in rats, follow-up compounds were searched to avoid risk of PLsis with reference to their in vitro PLsis potentials evaluated on the basis of accumulation of phospholipids in HepG2 cells exposed to the compounds.

It has been found that introduction of a carbonyl group onto the piperidine and piperazine or aniline moiety of compounds **A** and **B** reduced markedly the in vitro PLsis potentials. And further modification of the compounds and their evaluation led to a discovery of compounds **3k** with lower in vitro PLsis potentials exhibiting lowering effect of hypoglycemia-induced glucagon secretion in SD rats (ED_{50} = 1.1 mg/kg) and glucose excursion in meal tolerance test in Wistar fatty diabetic rats (MED = 3.0 mg/kg) in oral administrations.

Compound **3k** was selected as a new drug candidate of selective and orally active non-peptide SSTR2 agonists for treatment of Type 2 diabetes with low in vivo PLsis potential.

1. Introduction

It is studied well that excessive secretion of glucagon in Type 2 diabetics causes fasting and postprandial hyperglycemia through acceleration of glycogenolysis and gluconeogenesis in liver in patients.[1]

Somatostatin is a well-known regulatory hormone in endocrine and exocrine systems which suppresses secretion of glucagon, insulin, gastrin, and growth hormone depending on its binding to 5-subtypes of G-protein coupled receptors (SSTR1–5).[2,3] Among them SSTR2 has been revealed to affect significantly suppression of secretion of glucagon, and a SSTR2 agonist is anticipated to lower plasma glucose levels in hyperglycemia through inhibition of glycogenolysis and gluconeogenesis induced by glucagon and accordingly would be a novel class of therapeutic drug for type 2 diabetes without side effect of increase in body weight caused by PPARγ agonist.[4]

The research group in Merck reported selective SSTR2 agonists L-054,522, L-779,967[5] bearing β-methyltryptophan (β-MeTrp) structure and also we developed β-MeTrp derivative **A**[6,7] as an orally active SSTR2 agonist exhibiting full agonistic activity and high selectivity over SSTR5 (IC_{50} (SSTR2/5) = 0.2/>100 (nM)). In compound **A**, (*N,N*-dimethylaminomethyl)aniline may mimic the amino group of Lys9 and 4-phenyl-1-piperidinecarboxamide moiety would serve as a surrogate for Phe7 in the active site of SST-14.

We found that compound **A** lowers significantly plasma glucagon levels with single dosing and decrease glucose excursion after meal challenge in Wister fatty rats. However, repeated dose toxicity study of the candidate compound revealed that it induces serious phospholipidosis (PLsis) in rats and thus following drug candidates without induction of PLsis had to be searched.

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To avoid the potential risk of PLsis probably due to the cationic amphiphilic drugs (CAD) structure of β-MeTrp derivatives bearing an amino functionality essential for SSTR2 agonists activity, compounds **1**–**3** with a hydrophilic side chain were designed and synthesized for evaluation because displacement of *N,N*-dimethylaminomethyl group of compounds **A** and **B**[7] with weakly basic or non-basic functionalities resulted in significant decrease in activity.

In the present paper, we describe syntheses of β-MeTrp derivatives, their SAR and in vitro PLsis potentials evaluated on the basis of accumulation of phospholipids in HepG2 cells exposed to the compounds to find out a new orally active and selective non-peptide SSTR2 agonist as a therapeutic drug for Type 2 diabetes (Fig. 1).

2. Chemistry

Generally, compounds **1**–**3** were synthesized from **4** via urea formation with potential surrogates **8** for Phe7 followed by a peptide coupling with (*N,N*-dimethylaminomethyl)anilines **9** mimicking Lys9 (Scheme 1): The *N*-ureido- β-MeTrp intermediates **6** was prepared from **4** and **8** using *N,N′*-disuccinimidyl carbonate (DSC).[6] Hydrolysis of **6** followed by peptide coupling of **7** with **9** afforded the desired compounds without racemization.

Compounds **8a**–**f** were synthesized by the reactions of **10** with Grignard reagents or lithiated reagents followed by the removal of the Boc group of **11a**–**f** by treatment with HCl (Scheme 2). Alternatively, compound **8g** was prepared by the reaction of **12** with 2-furyl lithium followed by oxidation of **13** and removal of the Boc group of **14** by treatment with HCl (Scheme 3).

Compounds **8h** and **8i** were synthesized by acylation of **15** followed by the removal of the Boc group of **16a** and **16b** by treatment with HCl (Scheme 4).

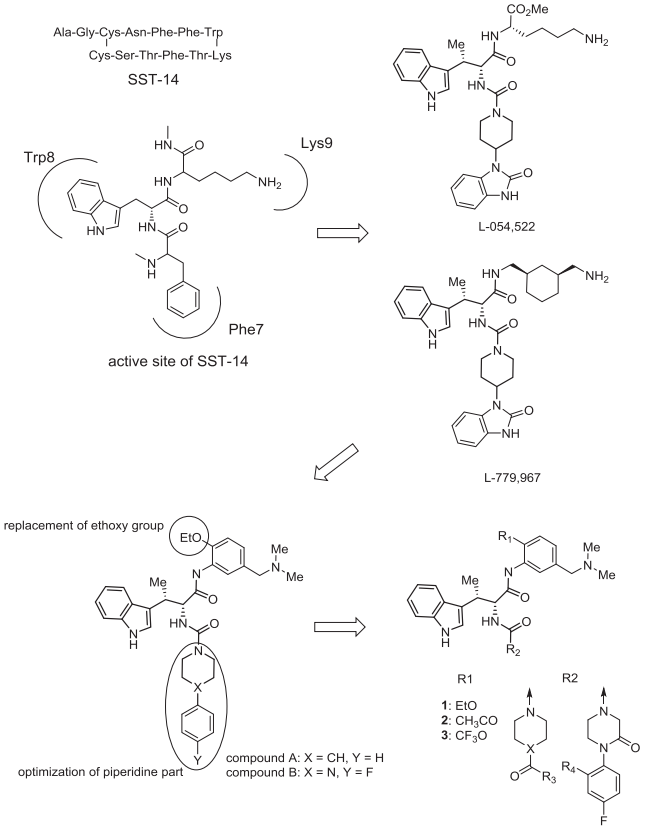
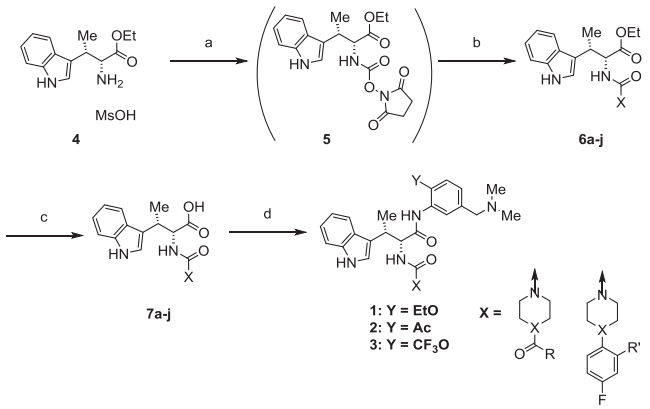
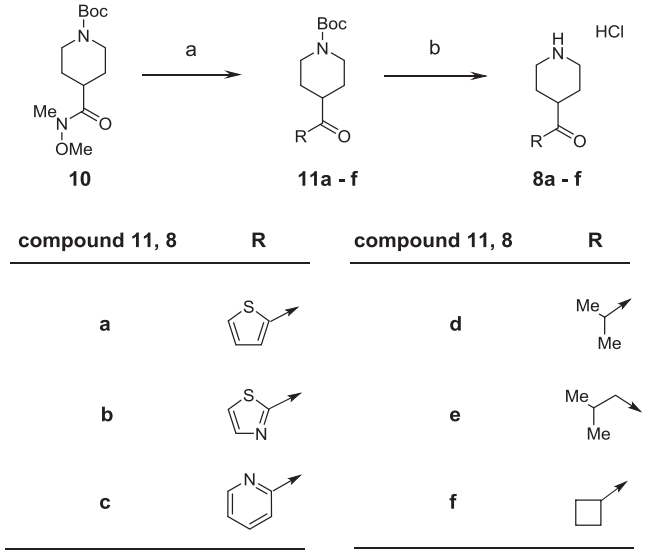


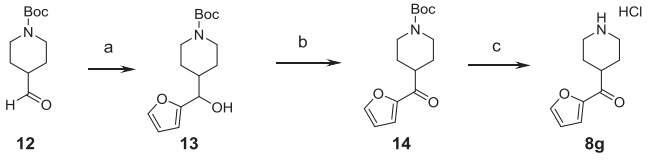
Fig. 1. Drug design of Selective and orally active non-peptide SSTR agonist.



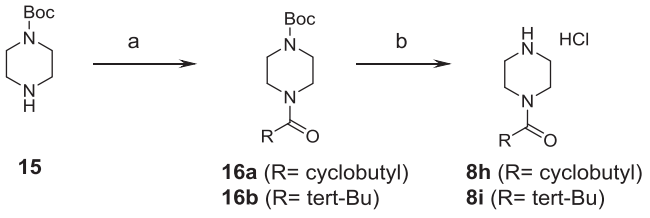
Scheme 1. General synthetic method of compounds **1**–**3**. Reagents and conditions: (a) DSC, $^{i}Pr_2NEt$, MeCN; (b) piperidine derivatives or piperazine derivatives (**8a**–**j**), $^{i}Pr_2NEt$, MeCN; (c) aq. NaOH, MeOH; (d) **9a**–**c**, WSC, HOBt, $^{i}Pr_2NEt$, THF, MeCN.



Scheme 2. Syntheses of compounds **8a**–**f**. Reagents and conditions: (a) RMgX (X = Cl or Br) or RLi, THF, −78 °C; (b) 4 N HCl-AcOEt, rt.



Scheme 3. Synthesis of compound **8g**. Reagents and conditions: (a) nBuLi, furan, THF, −78 °C; (b) $PySO_3$, Et_3N, DMSO, CH_2Cl_2, rt; (c) 4 N HCl-AcOEt, rt.



Scheme 4. Syntheses of compounds **8h** and **8i**. Reagents and conditions: (a) acyl chloride, Et_3N, THF, rt; (b) 4 N HCl-AcOEt, rt.