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Design, synthesis, and biological evaluation of a novel series of peripheral-selective noradrenaline reuptake inhibitors—Part 2

Tomoya Yukawa *, Ikuo Fujimori, Taku Kamei, Yoshihisa Nakada, Nobuki Sakauchi, Masami Yamada, Yusuke Ohba, Hiroyuki Ueno, Maiko Takiguchi, Masako Kuno, Izumi Kamo, Hideyuki Nakagawa, Yasushi Fujioka, Tomoko Igari, Yuji Ishichi, Tetsuya Tsukamoto

Pharmaceutical Research Division, Takeda Pharmaceutical Company Ltd, 26-1, Muraokahigashi 2-chome, Fujisawa, Kanagawa 251-8555, Japan

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ABSTRACT

Peripherally selective inhibition of noradrenaline reuptake is a novel mechanism for the treatment of stress urinary incontinence to overcome adverse effects associated with central action. Herein, we describe our medicinal chemistry approach to discover peripheral-selective noradrenaline reuptake inhibitors to avert the risk of P-gp-mediated DDI at the blood–brain barrier. We observed that steric shielding of the hydrogen-bond acceptors and donors (HBA and HBD) of compound **1** reduced the multidrug resistance protein 1 (MDR1) efflux ratio; however, the resulting compound **6**, a methoxyacetamide derivative, was mainly metabolized by CYP2D6 and CYP2C19 in the in vitro phenotyping study, implying the risk of PK variability based on the genetic polymorphism of the CYPs. Replacement of the hydrogen atom with a deuterium atom in a strategic, metabolically hot spot led to compound **13**, which was mainly metabolized by CYP3A4. To our knowledge, this study represents the first report of the effect of deuterium replacement for a major metabolic enzyme. The compound **13**, *N*-{[(6*S*,7*R*)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-[(2H^3)methyloxy]acetamide hydrochloride, which exhibited peripheral NET selective inhibition at tested doses in rats, increased urethral resistance in a dose-dependent manner.

1. Introduction

The noradrenaline transporter (norepinephrine transporter, NET), which is a membrane-bound protein, is responsible for the reuptake of extracellular noradrenaline. Selective inhibition of NET, which increases the noradrenaline concentration at synaptic cleft, has been shown to be an attractive approach for the treatment of many diseases.[1] NET is known to express in both central and peripheral nervous systems and to exhibit its own functional outputs.[2] Among the various target indications for noradrenaline reuptake inhibitor (NRI), stress urinary incontinence (SUI) seems one of good indications for peripheral-selective NRI, as our previous publication suggests that the urethral resistance-increasing effects of NRIs are mainly achieved by peripheral action.[3] Furthermore, in the case of peripheral-selective NRIs, adverse effects on the central nervous system are not a concern.[4] Target-selective distribution could also minimize clinically effective doses. Taken together, novel peripheral-selective NRIs have the potential to be safer and more effective drugs compared to traditional central-acting NRIs as anti-SUI agents.

In our previous papers, we described our approaches to design and synthesis of small molecule peripheral-selective NRIs based on 7-phenyl-6-substituted oxazepane series.[3] Among compounds in this series, compound **1** exhibits potent NET inhibitory activity, high selectivity against serotonin transporter (SERT) and dopamine transporter (DAT), and high peripheral NET selectivity in occupancy tests in rat brain (Fig. 1). However, this compound exhibits a high multidrug resistance protein 1 (MDR1) efflux ratio, and is thus a potential P-glycoprotein (P-gp) substrate. P-gp belongs the superfamily of ATP-binding cassette transporters and pumps numerous xenobiotics out of cells.[5] P-gp is also known to be the major efflux transporter at the blood brain barrier and to be responsible for the efflux of a number of xenobiotic substances from the central nervous system. Although some approved drugs

Abbreviations: SUI, stress urinary incontinence; DAT, dopamine transporter; SERT, serotonin transporter; NET, norepinephrine transporter; MDR1, multidrug resistance 1; P-gp, P-glycoprotein; CYP, cytochrome P450; hERG, human ether-a-go-go-related gene K+ channel; CNS, central nervous system.

* Corresponding author. Tel.: +81 466 32 1105; fax: +81 466 29 4454.
E-mail address: tomoya.yukawa@takeda.com (T. Yukawa).

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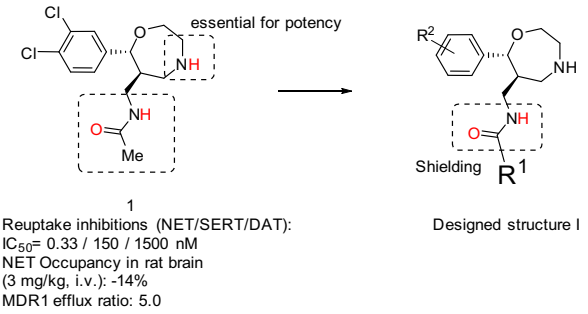


Figure 1.

inhibit P-gp,[6] drug–drug interaction (DDI) of the newly developed peripheral-selective NRIs with existing P-gp inhibitors might reduce the peripheral NET selectivity of the compounds, if they are P-gp substrates. To avoid such DDI risks, we attempted to decrease the MDR1 efflux ratio.

Removing or weakening the hydrogen-bond acceptor (HBA) and/or donor (HBD) is one of the guiding principles for reduced recognition as a P-gp substrate.[7] These modifications also increase passive diffusion of compounds, and if the passive diffusion is sufficiently fast, the efflux pumping efficiency will be overcome.[8] Our lead compound **1** has two HBDs and one HBA. In the initial SAR study, the HBD in the oxazepane ring was necessary for NET inhibitory activity. With regard to the amide motif, we have already observed that the amide is a good enhancer of the NET inhibitory activity, though several other substituents are also tolerated for NET inhibitory activity. On this basis, we decided to focus on R^1 substituent optimization in designed structure I while maintaining the amide motif. We expected that the modifications of the R^1 substituent would sterically shield the HBA and/or HBD, leading to an increase in passive diffusion and improvement of P-gp recognition (Fig. 1).[8] In addition, designed structure I might have a liability of CYP2D6 inhibition, hERG inhibition and phospholipidosis (PLsis) due to the cationic amphiphilic drug (CAD) structure. Aware of these risks, we evaluated CYP2D6 inhibitory activity and prioritized compounds based on the potency.[9] In this study, we performed the design and synthesis of 7-aryl-6-substituted oxazepine derivatives to reduce the MDR1 efflux ratio.

2. Experimental

The preparation of 6-aminomethyl 7-phenyl-1,4-oxazepane derivatives **1**–**15** is shown in Scheme 1. Morita–Baylis–Hillman reaction of 3-fluoro-4-chlorobenzaldehyde **16a**–**b** with methyl acrylate afforded ester **17a**–**b**. Michael addition of benzyl amine gave the *threo* isomer of methyl ester *rac*-**18a**–**b**. After transformation to silyl ether *rac*-**19a**–**b** via a hydroxymethyl intermediate, *N*-selective acylation with chloroacetyl chloride gave amide *rac*-**20a**–**b**. Cyclization of *rac*-**20a**–**b** under basic conditions gave 6-substituted 1,4-oxazepan-3-one *rac*-**21a**–**b**. After reduction of the amide group, the *N*-benzyl group was replaced with Boc along with deprotection of the hydroxyl group to afford *rac*-**23a**–**b**. Following optical resolution using preparative chiral HPLC, the hydroxyl group was converted into amine **26a**–**b** via the mesylate **24a**–**b** and azide **25a**–**b**. After condensation of amine **26a**–**b** with corresponding acid chloride or carboxylic acid, treatment with hydrogen chloride furnished amide **1**–**15** as the HCl salt. The absolute stereochemistry of **6** was confirmed by single-crystal X-ray analysis (Fig. 2).

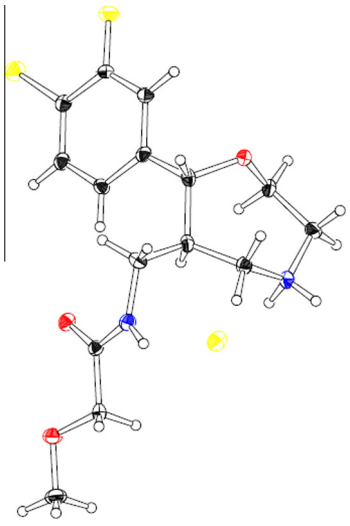
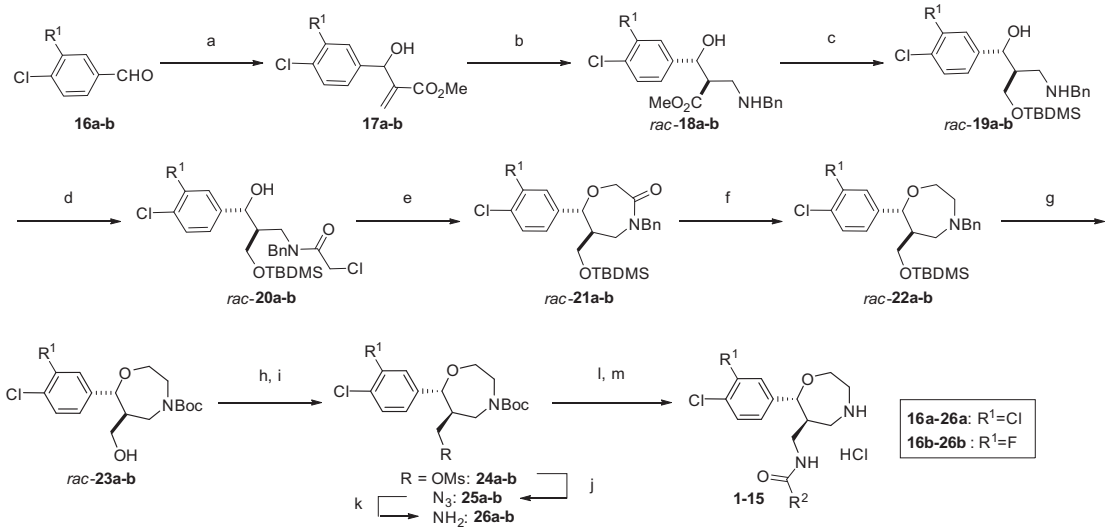


Figure 2. ORTEP drawing of compound **6**, thermal ellipsoids are drawn at 30% probability.



Scheme 1. Synthesis of compound **1**–**15**. Reagents and conditions: (a) Methyl acrylate, DABCO, DBU, MeCN, rt; (b) $BnNH_2$, Et_3N, MeOH, rt; (c) (1) $CaCl_2$, $NaBH_4$, THF, EtOH, 0 °C to rt; (2) TBDMSCl, Et_3N, imidazole, DMAP, THF, 0 °C to rt; (d) chloroacetyl chloride, Et_3N, THF, 0 °C to rt; (e) 1 M NaOH aq, THF, 0 °C to rt; (f) $LiAlH_4$, $AlCl_3$, THF, 0 °C to rt; (g) (1) 1-chloroethyl chloroformate, MeCN, rt, (2) 1 M HCl aq, MeOH, 80 °C, (3) Boc_2O, Et_3N, 0 °C to rt; (h) optical resolution by HPLC; (i) MsCl, Et_3N, THF, 0 °C to rt; (j) NaN_3, DMF, 80 °C; (k) PPh_3, THF, H_2O, rt. (l) R^2COCl, Et_3N, THF, rt or WSC, HOBt, R^2COOH, Et_3N, THF, rt; (m) 11.7 M HCl in EtOH, rt. or 4 M HCl in EtOAc, rt.