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Design, synthesis, and biological evaluation of a novel series of peripheral-selective noradrenaline reuptake inhibitors: Part 3

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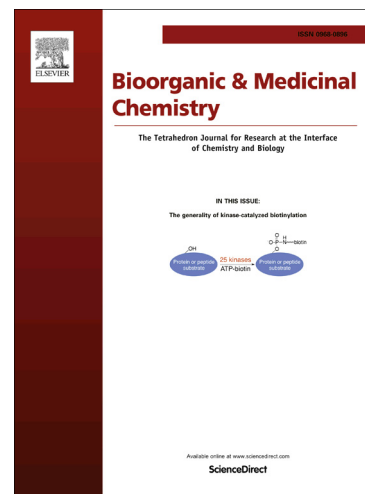
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Design, synthesis, and biological evaluation of a novel series of peripheral-selective noradrenaline reuptake inhibitors: Part 3

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

Abstract

Peripheral-selective inhibition of noradrenaline reuptake is a novel mechanism for the treatment of stress urinary incontinence to overcome adverse effects associated with central action. Here, we describe our medicinal chemistry approach to discover a novel series of highly potent, peripheral-selective, and orally available noradrenaline reuptake inhibitors with a low multidrug resistance protein 1 (MDR1) efflux ratio by cyclization of an amide moiety and introduction of an acidic group. We observed that the MDR1 efflux ratio was correlated with the pK_a value of the acidic moiety. The resulting compound **9** exhibited favorable PK profiles, probably because of the effect of intramolecular hydrogen bond, which was supported by its single-crystal structure. The compound **9**, 1-[[[(6*S*,7*R*)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl]-2-oxo-1,2-dihydropyridine-3-carboxylic acid hydrochloride, which exhibited peripheral NET-selective inhibition at tested doses in rats by oral administration, increased urethral resistance in a dose-dependent manner.

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