Available online at www.sciencedirect.com
SCIENCE DIRECT
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 3569–3573

Design, synthesis, and biological evaluation of indole derivatives as novel nociceptin/orphanin FQ (N/OFQ) receptor antagonists

Yuichi Sugimoto,* Atsushi Shimizu, Tetsuya Kato, Atsushi Satoh, Satoshi Ozaki, Hisashi Ohta and Osamu Okamoto

Banyu Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd, Okubo-3, Tsukuba 300-2611, Ibaraki, Japan

Received 6 December 2005; revised 10 March 2006; accepted 24 March 2006
Available online 18 April 2006

Abstract—A novel series of 2-(1,2,4-oxadiazol-5-yl)-1*H*-indole derivatives as nociceptin/orphanin FQ (N/OFQ) receptor antagonists was discovered. Systematic modification of our original lead by changing the pendant functional groups, linker, heterocyclic core, and basic side chain revealed the structure–activity requirements for this novel template and resulted in the identification of more potent analog with improved potency as compared to the parent compound.

Opioid receptor-like 1 (ORL1) receptor (nociceptin/orphanin FQ (N/OFQ) receptor, NOP receptor)[1] was discovered as a fourth member of the opioid receptor family in 1994 through cDNA expression cloning techniques.[2] The endogenous ligand for its receptor, a novel heptadeca neuropeptide, was independently identified in 1995 by two groups.[3] Although ORL1 receptor is a member of the G-protein-coupled receptor (GPCR) superfamily with 47% overall identity to the classical opioid (μ, δ, and κ) receptors and 64% identity in the transmembrane domains, native opioid peptides and synthetic agonists selective for μ, δ, and κ receptors do not show significant affinity for ORL1 receptor.[4]

The ORL1 receptor and N/OFQ are mainly distributed in the brain and central nervous system (CNS).[4,5] It was observed that N/OFQ is involved in modulating pain mechanisms in the spinal cord and forebrain. Several in vivo studies with N/OFQ and its peptide analogs have demonstrated that N/OFQ modulates a variety of biological functions, such as feeding, learning, diuresis, drug addiction, cardiovascular functions, and locomotor activity, and that it controls the release of neurotransmitters including serotonin and dopamine at peripheral and central sites.[6] ORL1 receptor might also be relevant in the treatment of CNS disorders such as anxiety and drug abuse.[6,7] Therefore, identification of potent small molecule agonists and antagonists of nociceptin could provide new classes of drugs for several human disorders involving pain and anxiety.

Recently, several research groups have reported their efforts in the search for small molecule ORL1 agonists and antagonists, describing nonpeptide ligands such as benzimidazolinones,[8] benzimidazoles,[9] indolinones,[10] spiropiperidines,[11] aryl piperidines,[12] and 4-aminoquinolines.[13] Some of these ligands possess very high selectivity for the ORL1 receptor versus other opioid receptors.

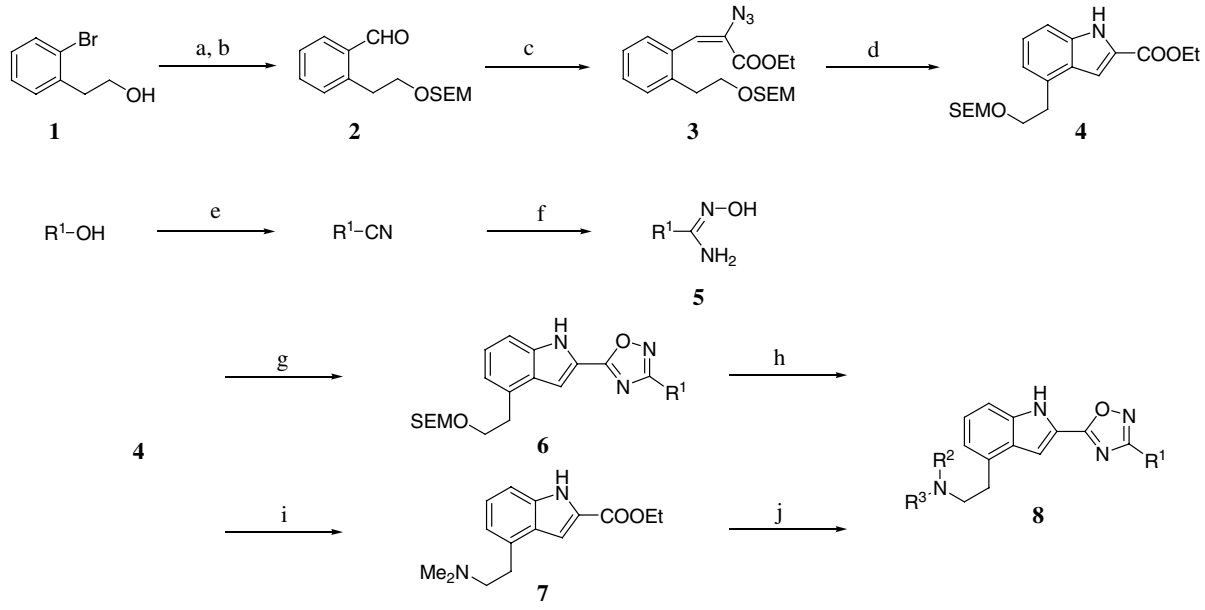
Our effort toward identifying an ORL1 antagonist started with the high-throughput screening (HTS) of various compound libraries. Among hit compounds, we identified 2-(1,2,4-oxadiazol-5-yl)-1*H*-indole **8**[14] as a novel structure that showed antagonist activity in [^{35}S]GTPγS functional assay. With regard to drug candidates, indole scaffold is a well-known representative class of privileged structures[15] with high affinity for multiple biological targets in drug discovery. Herein, we describe design, synthesis, and structure–activity relationship (SAR) studies to improve the potency of this novel lead compound (**33**, 95 nM for ORL1).

The key reaction for the preparation of the indolyl-oxadiazole **8** is a cycloaddition reaction between indole derivative **4** or **7** and appropriately substituted amide

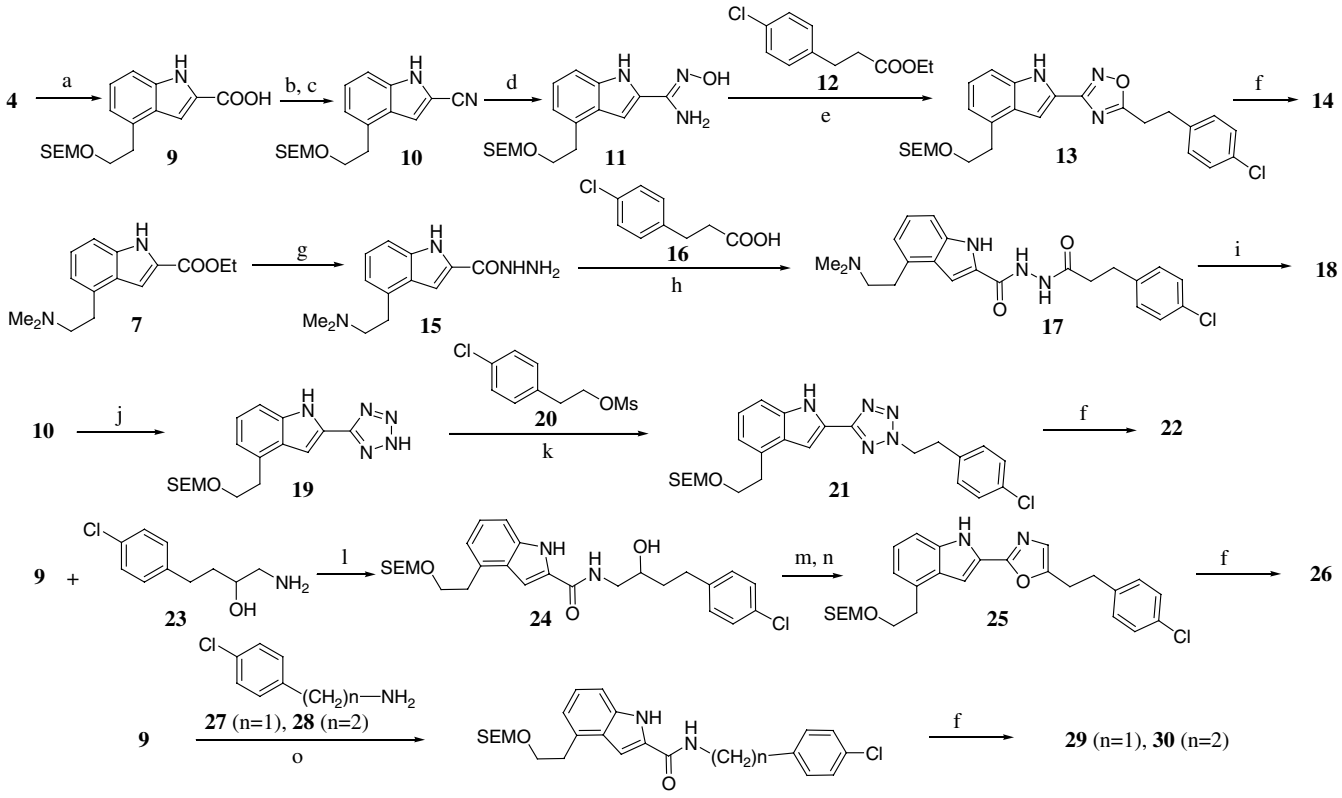
Keywords: Nociceptin; Orphanin FQ; ORL-1 receptor; Antagonist; Indole.
* Corresponding author. Tel.: +81 29 877 2000; fax: +81 29 877 2029; e-mail: yuichi_sugimoto@merck.com

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.03.086

oxime **5**. Scheme 1 depicts the synthesis of indolyl-oxadiazole **8**. 2-(2-Bromophenyl)ethanol **1** was converted in two steps, SEM protection and aldehyde formation after halogen-lithium exchange, into 2-substituted benzaldehyde **2**. 2-Azido-3-phenylacrylate **3**,[16] prepared from the benzaldehyde **2** and ethyl azidoacetate in the



Scheme 1. Reagents: (a) SEMCl, *i*-Pr_2NEt, 100%; (b) *sec*-BuLi, then DMF; (c) N_3CH_2COOEt, NaOEt; (d) heat, 29% (3 steps); (e) MsCl, Et_3N, then NaCN or KCN, 21–90%; (f) H_2NOH–HCl, Na_2CO_3, 54–95%; (g) **5**, NaH, MS4A, 54–85%; (h) i—HCl, ii—MsCl, Et_3N, iii—amine, K_2CO_3, 3 steps 10–43%; (i) i—HCl, ii—MsCl, Et_3N, iii—Me_2NH–HCl, K_2CO_3, 3 steps 59%; (j) **5**, NaH, MS4A, 15–70%.



Scheme 2. Reagents: (a) aq NaOH, 83%; (b) WSC, HOBt, then NH_4OH, quant.; (c) TFAA, pyridine, 80%; (d) H_2NOH–HCl, $NaHCO_3$, 80%; (e) **11**, NaH, MS4A, 26%;(f) i—HCl, ii—MsCl, Et_3N, iii—Me_2NH–HCl, K_2CO_3, 3 steps 12–38%; (g) H_2NNH_2–H_2O, 82%; (h) DMC, Et_3N, 6%; (i) $POCl_3$, 27%; (j) NaN_3, Et_3N–HCl, quant.; (k) **20**, K_2CO_3, 30%; (l) WSC, HOBt, 58%; (m) Deoxo-Fluor, 84%; (n) DDQ, 73%; (o) WSC, HOBt, 42% (n = 1), 69% (n = 2).