Bioorganic & Medicinal Chemistry Letters 25 (2015) 3039–3043

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Biaryls as potent, tunable dual neurokinin 1 receptor antagonists and serotonin transporter inhibitors

Andrew P. Degnan *, George O. Tora, Ying Han, Ramkumar Rajamani, Robert Bertekap, Rudolph Krause, Carl D. Davis, Joanna Hu, Daniel Morgan, Sarah J. Taylor, Kelly Krause, Yu-Wen Li, Gail Mattson, Melissa A. Cunningham, Matthew T. Taber, Nicholas J. Lodge, Joanne J. Bronson, Kevin W. Gillman, John E. Macor

Bristol-Myers Squibb Co., Research and Development, 5 Research Parkway, Wallingford, CT 06492, United States

ARTICLE INFO

Article history:
Received 9 February 2015
Accepted 30 April 2015
Available online 2 June 2015

Keywords:
Neurokin 1
NK_1
SERT
SSRI
Serotonin transport inhibitors
Neuroscience discovery

ABSTRACT

Depression is a serious illness that affects millions of patients. Current treatments are associated with a number of undesirable side effects. Neurokinin 1 receptor (NK_1R) antagonists have recently been shown to potentiate the antidepressant effects of serotonin-selective reuptake inhibitors (SSRIs) in a number of animal models. Herein we describe the optimization of a biaryl chemotype to provide a series of potent dual NK_1R antagonists/serotonin transporter (SERT) inhibitors. Through the choice of appropriate substituents, the SERT/NK_1R ratio could be tuned to afford a range of target selectivity profiles. This effort culminated in the identification of an analog that demonstrated oral bioavailability, favorable brain uptake, and efficacy in the gerbil foot tap model. Ex vivo occupancy studies with compound **58** demonstrated the ability to maintain NK_1 receptor saturation (>88% occupancy) while titrating the desired level of SERT occupancy (11–84%) via dose selection.

Major depressive disorder is a serious and debilitating illness that has a lifetime prevalence in the United States of >16%.[1] It is a leading cause of disability as measured by years lost to disability and is the fourth leading contributor to the global burden of disease as measured by disability-adjusted life years.[2] The treatment of depression was revolutionized in 1988 with the approval of fluoxetine, the first serotonin-selective reuptake inhibitor (SSRI), in the United States.[3] Despite the improvements in safety and tolerability made by the advent of this and other SSRIs, these agents have been associated with a number of negative side effects, including sexual dysfunction, weight gain, nausea, insomnia, and somnolence.[3] As such, there remains a serious unmet medical need that awaits the identification of new pharmacological approaches for the treatment of depression.

Neurokinin 1 receptor (NK_1R) antagonists were first reported to have anti-depressant activity in clinical trials in 1998 by Kramer and co-workers.[4] In these trials, aprepitant (**1**) showed improvement in symptoms of anxiety and depression that was comparable to the well-established SSRI, paroxetine. Aprepitant was found to be well-tolerated at all doses, with adverse events comparable to those of placebo. For example, sexual side effects occurred in 26% of study participants given paroxetine versus 3% given aprepitant. Despite this early promising result, a subsequent dose-finding study with aprepitant failed to show superior efficacy to placebo and development for depression was discontinued.[5]

More recently, it has been suggested that NK_1R antagonists potentiate the antidepressant effects of SSRIs.[6] For instance, it has been shown that combination of sub-active doses of citalopram or paroxetine with an inactive dose of NK_1R antagonist GR205171 reduces immobility of Swiss mice in the forced swim test.[7] A similar result was observed in our own labs using paroxetine and aprepitant in the gerbil forced swim test.[8] As a part of our studies, ex vivo occupancy of both the NK_1 receptor and the serotonin transporter (SERT) was measured. It was found that by maintaining high NK_1 receptor occupancy, the SERT occupancy could be reduced while retaining activity in the gerbil forced swim test. This result offered the hope of delivering an antidepressant with fewer side effects than with an SSRI alone.

It was in this context that we undertook the development of a dual NK_1R/SERT antagonist.[9] From the occupancy experiments described above, it appeared that high NK_1 receptor occupancy would allow us to reduce SERT occupancy and, theoretically, reduce the potential for SSRI-related side effects. Our studies suggested a SERT inhibition/NK_1R antagonism IC_{50} ratio of approximately 10

* Corresponding author. Tel.: +1 203 677 5750; fax: +1 203 677 7702.
E-mail address: andrew.degnan@bms.com (A.P. Degnan).

http://dx.doi.org/10.1016/j.bmcl.2015.04.098
0960-894X/

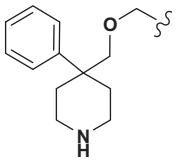
or greater would allow us to achieve the desired receptor/transporter occupancy profile.

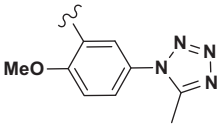
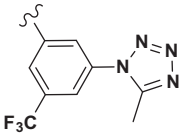
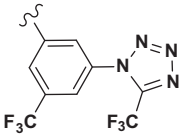
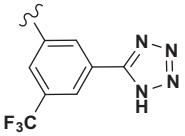
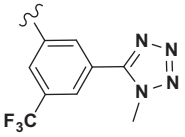
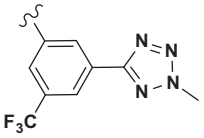
In an earlier paper,[9b] we reported that **2** was a potent dual NK_1R antagonist and SERT inhibitor. We sought to improve the NK_1R potency of this series (and consequently increase the SERT/NK_1R ratio) and focused our initial work around modification of the bis-trifluoromethylphenyl ring. We were inspired in this endeavor by the work of Ward and co-workers,[10] who showed that the 3,5-bistrifluoromethylphenyl of NK_1R antagonists such as aprepitant (**1**) could be replaced with a 2-methoxy-5-tetrazolylphenyl to afford compounds such as **3** (Fig. 1). Importantly, this substitution gave dramatic improvements in both metabolic stability and oral bioavailability. In a subsequent disclosure,[11] it was reported that substitution of C-5 of the tetrazole with small alkyl groups was also well-tolerated to afford compounds **4** and **5**. We sought to apply this modification to our series.

The first compound prepared in this endeavor was **6** (Table 1). Although this analog retained nanomolar potency against both targets, we were disappointed to find that it was significantly less potent than the parent bis-trifluoromethylphenyl derivative, **2**. Additionally, this analog was somewhat more potent against SERT than NK_1R, contrary to our desired profile (vide supra). Given this result, we investigated the possibility of replacement of the 2-methoxy substituent with the 3-trifluoromethyl group of our earlier lead series. Unfortunately, compound **7** was less potent than our earlier lead (**2**) and had an unfavorable SERT/NK_1R ratio. In earlier work,[11] substitution of the tetrazole with a trifluoromethyl group gave maximum NK_1R potency, however on our substrate, just the opposite trend was observed with compound **8** having a still lower SERT/NK_1R ratio. Our most favorable balance of potency and ratio was realized with the C-linked tetrazole **10**, which had an NK_1R antagonism and SERT inhibition ratio of ~1. Interestingly, the desmethyl tetrazole **9** and the isomeric *N*-methyltetrazole **11** achieved a desirable potency for SERT inhibition but did not have sufficient potency for NK_1R antagonism to achieve the targeted potency profile.

Encouraged by the result with **10**, we sought to more extensively explore SAR around biaryl ring systems, focusing most of our work on C-linked aryl and heteroaryl substituents. The results of these studies are summarized in Table 2. In general, 6-membered aromatic systems gave the best combination of potency and reasonable SERT/NK_1R ratios. We were especially encouraged by phenyl-containing **12**, having single digit nanomolar potency at both targets and 4-pyridyl **13**, having single digit nanomolar potency against NK_1R and an ideal SERT/NK_1R ratio (10). Smaller heterocycles such as furan (**15**), thiazole (**16**), and those in Table 1 tended to have lower NK_1R potency and lower SERT/NK_1R ratios. Larger bicyclic aromatics (compounds **17** and **18**) tended toward lower affinities at both targets and were not pursued further.

Table 1
SAR studies: in vitro potency of tetrazoles **6**–**11**[a,b]



Compound	R	NK_1R IC_{50} (nM)	SERT IC_{50} (nM)	SERT/NK_1R ratio
6		87	37	0.4
7		180	70	0.4
8		700	57	0.08
9		200	8.6	0.04
10		65	50	0.8
11		36	9.6	0.3

[a] Binding assays performed by methods described in Ref. 8.
[b] All binding values represent a minimum of 2 replicates.

Encouraged by these results, we expanded our understanding around the SAR of 6-membered aryls through the preparation of an extensive biaryl library using a combination of Suzuki and Stille coupling approaches. The requisite precursors were prepared

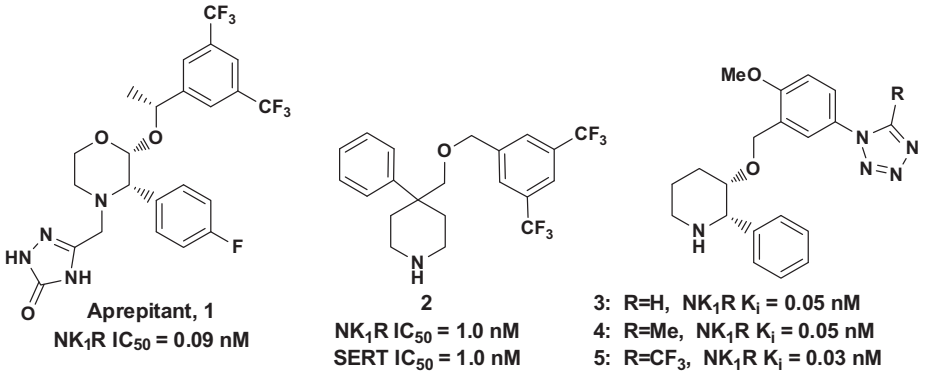


Figure 1. Structures of literature NK_1R antagonists.