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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

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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).

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0960-894X/

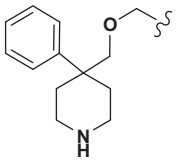
or greater would allow us to achieve the desired receptor/transporter occupancy profile.

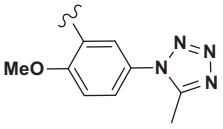
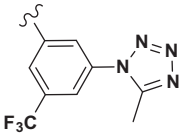
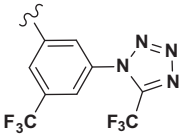
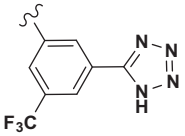
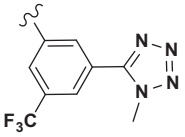
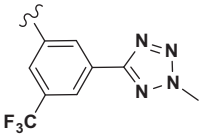
In an earlier paper,[9b] we reported that **2** was a potent dual NK_1R antagonist and SERT inhibitor. We sought to improve the NK_1R potency of this series (and consequently increase the SERT/NK_1R ratio) and focused our initial work around modification of the bis-trifluoromethylphenyl ring. We were 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

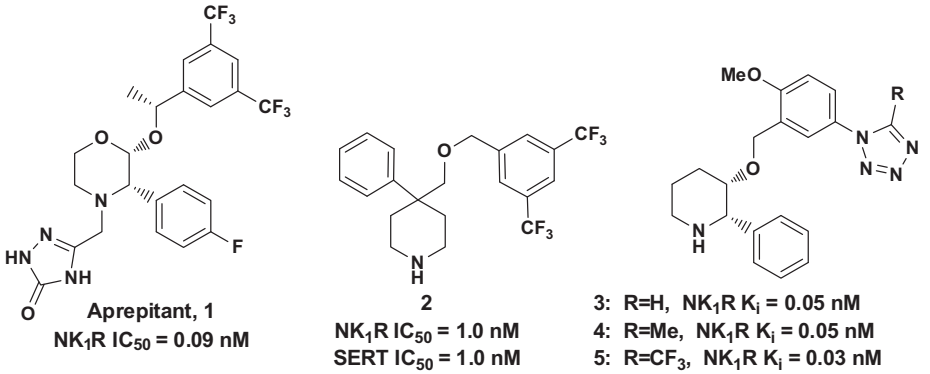
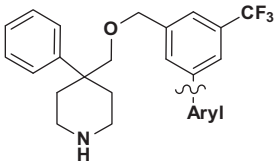
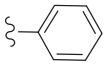
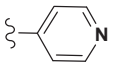
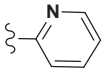
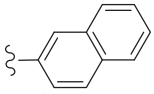
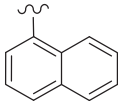


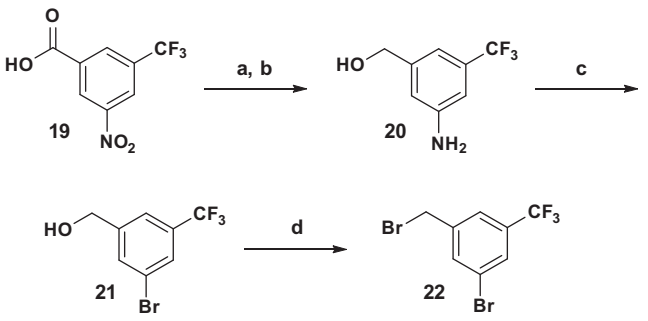
Figure 1. Structures of literature NK_1R antagonists.

Table 2
SAR studies: in vitro potency of diverse biaryls **12–18**

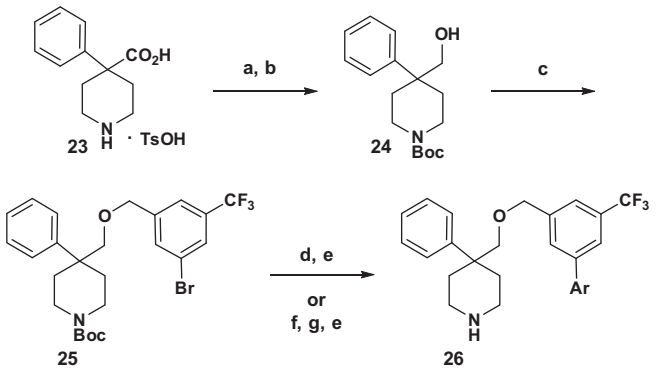


Compound	Aryl	NK_1R IC_{50} (nM)	SERT IC_{50} (nM)	SERT/NK_1R ratio
12		6.3	3.7	0.6
13		1.6	16	10
14		41	7.4	0.2
15		47	18	0.4
16		70	4.1	0.06
17		120	110	0.9
18		540	120	0.2

as outlined in Schemes 1 and 2. To begin, nitro acid **19** was reduced in two steps to hydroxy aniline **20**. A modified Sandmeyer reaction[12] converted the aniline to the corresponding aryl bromide **21**. Conversion of the hydroxyl group to the benzyl bromide provided intermediate **22** (Scheme 1) for coupling to the piperidine. Preparation of the piperidine began with the commercially available piperidine acid **23** (Scheme 2). Protection of the nitrogen as the *tert*-butyl carbamate and reduction of the acid by the action of borane-THF yielded alcohol **24**. Benzyl bromide **22** and alcohol **24** were efficiently coupled by the action of sodium hydride in DMF to afford the corresponding ether in 96% yield (Scheme 2). Aryl bromide **25** proved itself to be a competent coupling partner in Suzuki reactions with arylboronic acids. Alternately, the bromide could be converted to the corresponding stannane for use in Stille couplings. This greatly increased the number of commercially available coupling partners by expanding the potential coupling partners from arylboronic acids to arylhalides. Removal of



Scheme 1. Reagents and conditions: (a) BH_3-THF, THF (85%); (b) Pd/C, H_2, MeOH (85%); (c) $CuBr_2$, *t*-butylnitrite, MeCN (69%); (d) NBS, PPh_3, THF (76%).

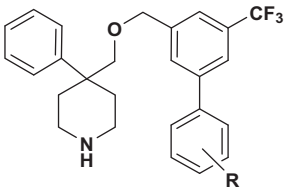


Scheme 2. Reagents and conditions: (a) Boc_2O, Et_3N, THF (98%); (b) BH_3–THF, THF (97%); (c) NaH, **22**, DMF (96%); (d) $ArB(OH)_2$, $Pd(PPh_3)_4$, 1 N KOH; (e) 33% TFA in DCM; (f) *n*-BuLi, THF then Bu_3SnCl (79%); (g) ArBr, $PdCl_2(PPh_3)_2$, MeCN.

the *tert*-butyl carbamate by treatment with TFA/DCM completed the synthesis. In all, approximately 150 compounds were prepared by these methods.

Following up on lead **13**, a variety of substituted 4-pyridines were prepared. While several retained useful levels of potency against both targets (data not shown), none gave a better combination of potency and SERT/NK_1R ratio than that of the unsubstituted 4-pyridyl (**13**). On the other hand, a number of phenyl substituents were found to have beneficial effects on both potency and SERT/NK_1R ratio in the biphenyl-containing series (Table 3). In general, substitution of the 4-position was preferred relative to substitution of other positions. Substitution of the 4-position with either cyano or alkoxy groups gave compounds with potent NK_1R

Table 3
SAR studies: effect of biphenyl substitution on potency

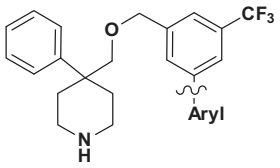


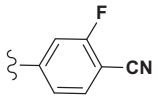
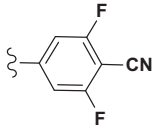
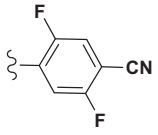
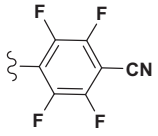
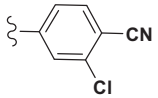
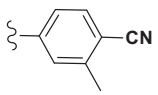
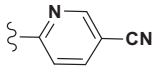
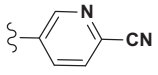
Compound	R	NK_1R IC_{50} (nM)	SERT IC_{50} (nM)	SERT/NK_1R ratio
27	2-Cl	68	6.4	0.1
28	2-F	23	7.6	0.3
29	2-Me	130	13	0.1
30	2-NO_2	6.5	3.5	0.5
31	2-OMe	54	4.2	0.1
32	3-CH_3	24	14	0.6
33	3-CN	49	10	0.2
34	3-F	5.0	6.3	1
35	3-NH_2	25	30	1
36	3-NO_2	5.2	4.2	0.8
37	3-OH	13	27	2
38	3,4-OCH_2O	7.1	45	6
39	4-CF_3	30	36	1
40	4-Cl	2.8	1.8	0.6
41	4-CO_2Me	17	25	1
42	4-F	2.2	1.5	0.7
43	4-Me	8.4	6.4	0.8
44	4-NMe_2	18	3.5	0.2
45	4-NO_2	3.8	7.3	2
46	4-OEt	3.4	14	4
47	4-OH	3.6	27	8
48	4-OMe	0.93	15	16
49	4-CN	0.45	4.0	9

antagonism and favorable SERT/NK_1R ratios. The most attractive compound identified was the 4-cyanophenyl analog **49**, which had potent NK_1R antagonism and SERT inhibition (NK_1R IC_{50} = 0.45 nM; SERT IC_{50} = 4.0 nM) and a nearly ideal ratio (9).

Additional analogs were prepared around the 4-alkoxy and 4-cyano 6-membered aryls to further refine our leads. No analogs were identified within the 4-alkoxy series that showed any improvements in potency over those outlined in Table 3 (data not shown). A number of compounds in the 4-cyano series were found to have attractive potencies and ratios and led to the identification of a number of related compounds with varying SERT/NK_1R profiles (Table 4). Incorporation of fluorine onto C-2 (**50**), gave a compound with a profile very similar to that of 4-cyanophenyl lead **49**. Replacement of both the C-2 and C-6 protons with fluorine (**51**), boosted the SERT/NK_1R ratio to 22 while retaining single digit nanomolar potency against SERT. Alternately, substitution with 2,5-difluoro (**52**), 2-chloro (**54**), 2-methyl (**55**), or 2-aza (**57**) gave compounds with high potency (<10 nM) against both NK_1R and SERT, but lower levels of NK_1R selectivity (SERT/NK_1R IC_{50}'s = 2–5). In this series, only compound **56** was found to be more selective for SERT. This compound had low nanomolar potency against both targets with a SERT/NK_1R ratio of 0.5.

Table 4
SAR studies: impact of cyanobiphenyl functionalization on SERT/NK_1R ratio



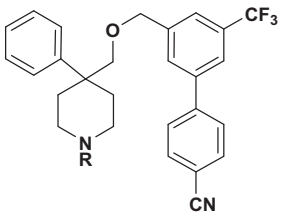
Compound	Aryl	NK_1R IC_{50} (nM)	SERT IC_{50} (nM)	SERT/NK_1R ratio
50		1.1	8.9	8
51		0.32	7.0	22
52		0.91	3.7	4
53		4.8	47	10
54		1.1	3.1	3
55		1.2	2.7	2
56		8.1	4.0	0.5
57		1.9	10	5

Given its excellent potency and its near ideal SERT/NK_1R ratio, **49** was prioritized for advancement into behavioral studies. NK_1R radioligand binding studies have shown significant species differences. Whilst mouse and rat receptor binding have proven poor predictors for human pharmacology, the gerbil and guinea pig have demonstrated good receptor homology with human.[13] As such, our screening tier utilized the gerbil foot tap model[14] as an in vivo target engagement model. In this assay, the ability of an NK_1R antagonist, dosed orally, to block foot tapping induced by i.c.v. administration of an NK_1R agonist (GR-73632) was measured. We were disappointed to find that **49**, despite its excellent in vitro potency, failed to give a significant reduction in foot tapping. Measurement of drug concentration in the plasma and brain indicated poor brain uptake (Table 6), and suggested that poor brain penetrance was to blame for the lack of behavioral efficacy.

It was hypothesized that brain penetration could be improved by removal of a hydrogen bond donor via substitution of the nitrogen of the piperidine. To this end, a small library of N-alkylated piperidines was prepared (Table 5). Although substitution had little effect on NK_1R potency, it was found that SERT potency was exquisitely sensitive to the steric bulk of the substituent. Only substitution with a methyl group (**58**) was tolerated, affording only a small (ca. 2 fold) loss in potency at SERT. Substitution with larger groups (compounds **59**–**62**) was accompanied by dramatic reductions in SERT potency (>100 fold).

Compound **58** was advanced into the gerbil foot tap model. We were gratified to find that **58**, differing by only a single methyl group, gave a robust reduction in foot tapping (Table 6). Again, plasma and brain concentrations were measured. They indicated greatly enhanced brain uptake ([brain] = 1.3 μM; B:P = 2.5) relative to unmethylated derivative **49** ([brain] = 0.19 μM; B:P = 0.52). Activity in the gerbil foot tap model, suggested significant occupancy of the NK_1 receptor, but said nothing about the occupancy of serotonin transporters. To assess the absolute and relative level of occupancy at both targets, ex vivo occupancy experiments were performed with compound **58** across a range of doses in gerbil (Fig. 2). ^{125}I-substance P and ^{3}H-citalopram were used to assess NK_1R and SERT occupancy, respectively. To our delight, NK_1 receptor occupancy was high (88–102% across all doses) while serotonin transporter occupancy increased in a dose-dependent manner from 11% (@3 mg/kg) to 84% (@30 mg/kg). This target profile suggested the ability to maintain NK_1 receptor saturation while titrating (via dose selection) SERT occupancy up to a level which achieves clinical efficacy without the mechanism-based side effects that can occur at high SERT occupancies.

Table 5
SAR studies: impact of piperidine alkylation on potency



Compound	R	NK_1R IC_{50} (nM)	SERT IC_{50} (nM)	SERT/NK_1R ratio
49	H	0.45	4.0	9
58	Me	0.29	9.5	33
59	Et	0.25	420	1700
60	*i*-Pr	0.39	450	1200
61	*c*-Pr	1.8	2100	1200
62	Bn	2.0	800	400

Table 6
Impact of piperidine alkylation on activity in gerbil foot tap model and brain uptake

Compound	**49**	**58**
hNK_1R IC_{50} (nM)	0.59	0.20
Foot Tapping[a] (% inh @ 10 mpk, po)	29% (ns)[b]	73%
Plasma Conc. (nM)	365	526
Brain Conc. (μM)	0.19	1.3
Brain:Plasma	0.52	2.5

[a] Gerbils treated with test compound (10 mg/kg p.o.). After 4 h, animals anesthetized with isoflurane and treated with GR-73632 (3 pmol, i.c.v.). Foot tapping recorded for 5 min after animal regains righting reflex (2–3 min post-injection).
[b] ns = not significant.

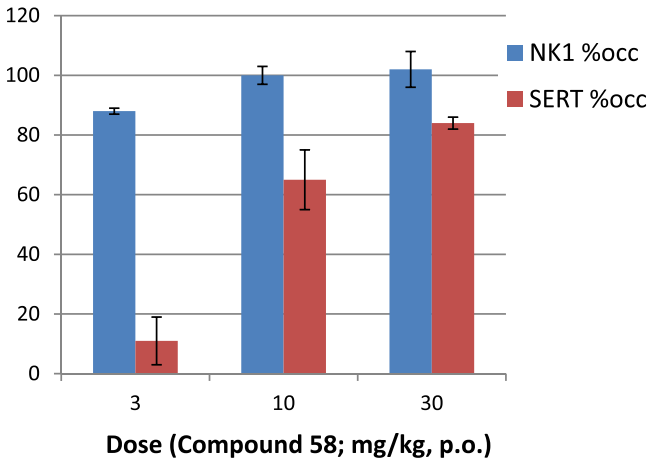


Figure 2. Ex vivo NK_1R and SERT occupancy in gerbils: Dose response of compound **58**. Gerbils treated with test compound (po). Ex vivo occupancy assessed at 4 h.

In conclusion, it was found that biaryls are suitable replacements for the bis-trifluoromethyl group of **1**. Replacement of one of the trifluoromethyl groups with a 4-cyanophenyl gives a compound with significantly improved potency against NK_1R to afford a compound with an improved SERT/NK_1R ratio. By selection of appropriate substitutions around the 4-cyanophenyl ring, a number of highly potent compounds were identified which were differentiated primarily by their SERT/NK_1R ratio. Methylation of the piperidine afforded a compound that enhanced oral bioavailability and greatly improved brain penetration. 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. Additional characterization of compound **58** will be disclosed in due course.

References and notes

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