Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 1643–1646

BIOORGANIC &
MEDICINAL
CHEMISTRY
LETTERS

Expedited Discovery of Second Generation NK-1 Antagonists: Identification of a Nonbasic Aryloxy Substituent

James E. Fritz,* Philip A. Hipskind, Karen L. Lobb, James A. Nixon,
Penny G. Threlkeld, Bruce D. Gitter, Carl L. McMillian and Stephen W. Kaldor

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA

Received 7 August 2000; accepted 6 April 2001

Abstract—Solution-phase, parallel-synthesis techniques were used to optimize a series of nonbasic NK-1 antagonists, resulting in the identification of (*R*)-**26**, an orally bioavailable compound with subnanomolar potency. © 2001 Elsevier Science Ltd. All rights reserved.

Substance P (SP) is a member of the tachykinin neuropeptide family and acts through three recognized receptor subtypes: NK-1, NK-2, and NK-3.[1] Studies with NK-1 receptor agonists and antagonists indicate SP may be associated with a wide variety of disease states including persistent pain,[2a] asthma,[2b] arthritis,[2c] and migraine.[2d] Previously, we reported on compound **1** (Fig. 1), a potent NK-1 antagonist currently under clinical evaluation.[3] Despite its desirable features, **1** possesses suboptimal oral bioavailability and causes irritation upon iv injection. In an effort to improve upon the properties of **1**, expedited synthesis techniques were employed to facilitate discovery of a second generation clinical candidate.

We hypothesized that the dibasic 2-[4-(piperidin-1-yl)piperidin-1-yl]acetyl side chain of **1** was a potential source of its shortcomings, and therefore examined earlier SAR work surrounding this side chain.[3] In particular, we noted that compound **2**, a relatively weak NK-1 antagonist ($IC_{50} = 34$ nM), and others like it without a basic side chain, did not cause irritation upon iv administration. Furthermore, the physical properties of the compounds were different and we hoped that this would translate into a better pharmacokinetic profile. As a result, database similarity searching techniques were employed to identify a diverse and novel set of nonbasic acylating agents analogous to the amide side chains of **1** and **2**.[4]

In the original SAR study, the (*R*)-enantiomer had consistently been the more potent. We elected to use racemic starting material (**3**, Scheme 1) to ensure that

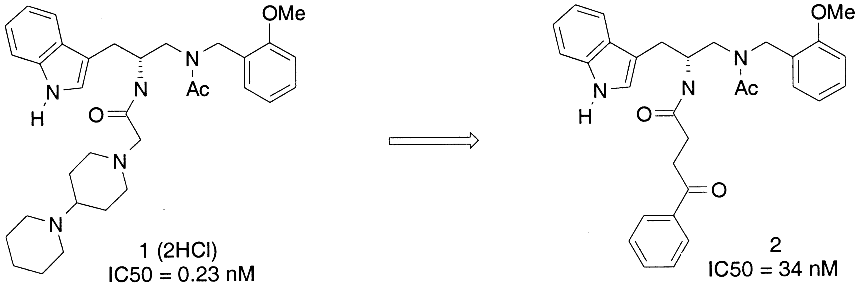


Figure 1.

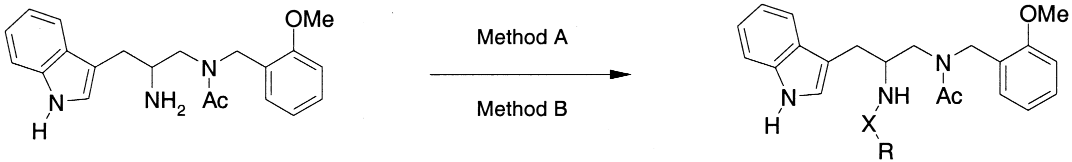
---

*Corresponding author. Fax: +1-317-433-1685; e-mail: j.fritz@lilly.com

PII: S0960-894X(01)00250-5

we identified active compounds in the event the diverse side chains caused an inversion of stereochemical preference by the receptor.[3] Initially, in vitro binding affinities were obtained in triplicate at a single concentration of 10 nM using human IM-9 cells. This allowed us to more readily assay larger sets of analogues.[5] Full IC_{50} determinations were performed on compounds exhibiting $>40\%$ inhibition at 10 nM. Expedited solution-phase synthesis was employed to construct amides, sulfonamides, carbamates, and ureas wherein polymer-supported scavengers (e.g., aminomethylpolystyrene) were used to facilitate removal of excess acylating agent.[6] Amides were also prepared using polymer-supported 1-(3-pyrrolidinylpropyl)-3-ethylcarbodiimide and carboxylic acids, thus expanding the number and diversity of possible side-chain replacements.[7] Additional scavengers or ion-exchange resins were utilized to remove any unreacted starting material or byproducts as necessary.[8] To ensure meaningful results, only compounds of purity $\geq 90\%$ as determined by HPLC analysis at two wavelengths were submitted for bioassay.[9]

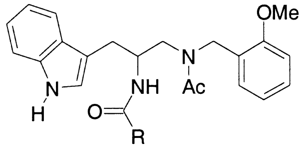
Representative SAR highlights from the initial synthesis run are shown in Table 1. Compounds with urea, sulfonamide, or carbamate side chains were generally less potent than **2** (results not shown). However, amides **11–14** showed significant improvement over the lead. Aromatic side chains, where the aromatic group was separated from the carboxamide by a 1–3 atom spacer, provided compounds with greater potency. A heteroatom in the spacer and polar groups on the aromatic ring appeared to contribute to the increased potency. A second synthesis run focusing on substituted benzoylpropionic



(3)

Scheme 1. Method A: $CHCl_3$, (**3**) (1 equiv), acylating agent (acid chloride, sulfonyl chloride, isocyanate, carbamoyl chloride) (1–1.5 equiv), (piperidinomethyl)-polystyrene (3.5 equiv if required), rt, 24 h followed by aminomethyl polystyrene; method B: $CHCl_3$, (**3**) (1 equiv), (piperidinomethyl) polystyrene (3 equiv), polymer-supported 1-(3-pyrrolidinylpropyl)-3-ethylcarbodiimide (4.5 equiv), carboxylic acid (1.5 equiv), 65 °C, 24 h followed by methylisocyanate polystyrene (1–2 equiv).

Table 1. In vitro activity for representative products from synthesis run 1



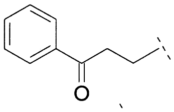
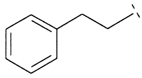
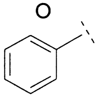
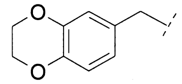
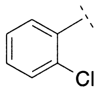
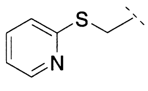
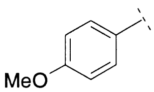
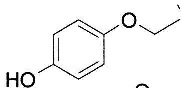
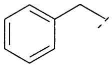
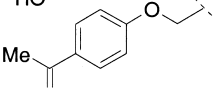
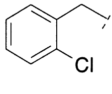
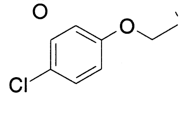
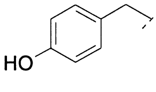
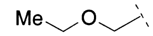
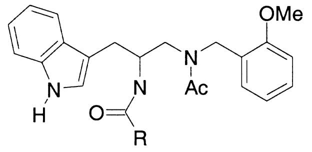
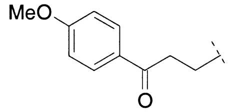
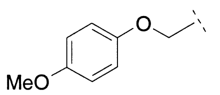
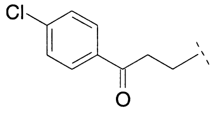
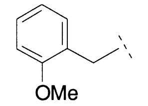
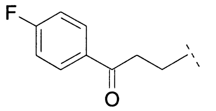
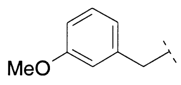
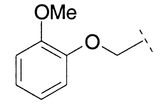
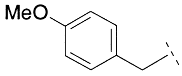
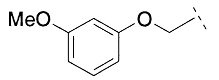
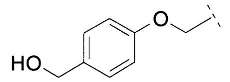
Entry	R	% Inhibition @ 10 nM	IC_{50} (nM)	Entry	R	% Inhibition @ 10 nM	IC_{50} (nM)
2		20	34	**10**		20	—
4		0	—	**11**		46	8.3
5		0	—	**12**		41	10.8
6		13	—	**13**		59	3.2
7		18	—	**14**		68	3.5
8		30	—	**15**		19	—
9		25	—	**16**		4	—

Table 2. In vitro activity for products from synthesis run 2



Entry	R	% Inhibition @ 10 nM	IC_{50} (nM)	Entry	R	% Inhibition @ 10 nM	IC_{50} (nM)
17		63	3.3	**22**		52	10.2
18		49	—	**23**		23	—
19		66	6.0	**24**		22	—
20		42	24	**25**		81	9.7
21		3	—	**26**		87	0.82

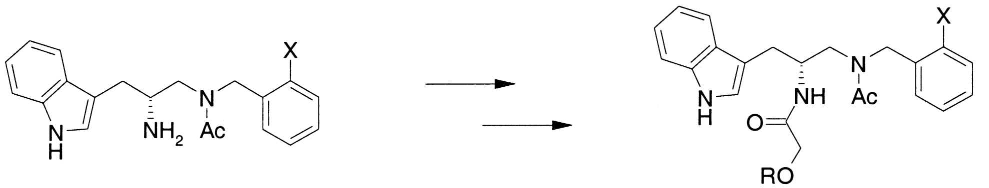
acids, phenylacetic acids, and phenoxyacetic acids was performed: representative SAR results are highlighted in Table 2. A systematic study of the aromatic ring revealed a strong preference for the *para* position (**22** and **25**).

Similar substitution enhanced the potency of the benzoylpropionic acids as well (**17** and **19**). To our surprise, an additional increase in potency was obtained with 4-(hydroxymethyl)phenoxy acetic acid as the side chain (**26**). At this point, the (*R*)- and (*S*)-enantiomers of 13 of the more potent compounds were independently synthesized to examine NK-1 receptor stereopreference. In accord with previous SAR work, the receptor exhibited a uniform and overwhelming preference for the (*R*)-enantiomers (data not shown).[10] In further SAR work, the active enantiomer (*R*) of **3** was used as starting material. Compound (*R*)-**26**, in contrast to **1**, proved to be non-irritating in an ocular irritation assay.[11] Additionally, (*R*)-**26** showed a modest improvement over **1** in both bioavailability (17% vs 9%) and peak blood levels (C_{max} 426 ng/mL vs 302 ng/mL).[12] Finally, we desired a route to further explore the 4-substituted phenoxyacetic acid side chains. Unfortunately less than 20 aryloxyacetic acids with polar *o*-, *m*-, or *p*-substituents are commercially available.

The solution came from earlier work on the SAR wherein amine **3** was acylated with bromoacetyl bromide and alkylated with amines in the presence of base. Using the appropriately substituted phenols (>2000 commercially available) in the presence of potassium *t*-butoxide we were able to construct the desired substituted aryloxyacetic acid side chains (Scheme 2).

To our satisfaction, we have been able to identify additional 4-substituted aryloxyacetic acid side chains with subnanomolar potency (data not shown). Three of the better examples from the third iteration are illustrated above.

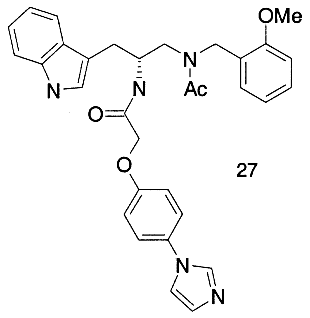
Evaluation of the third generation of the SAR shows that these compounds remain nonirritating, but show further improvements in bioavailability and microsomal stability (Table 3).



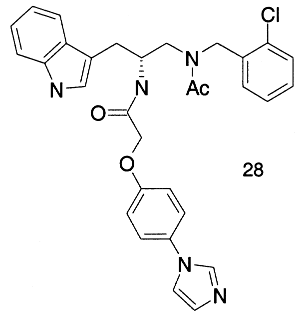
(3)

X = Cl, OMe

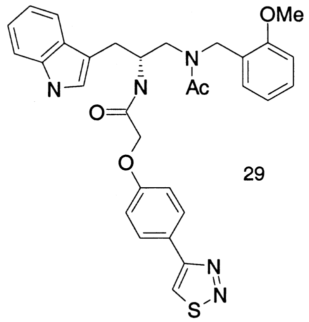
Scheme 2. Step 1: THF, DIEA, bromoacetyl bromide (1.1 equiv), 0 °C; step 2: THF, phenol (3 equiv), potassium *t*-butoxide (3 equiv), 2 h, 80 °C.



27



28



29

Table 3.

Compound	IC_{50} (nM)	Microsome stability dog liver (% remaining)	%F (dog)
(*R*)-**26**	0.43	28	17
27	0.48	87	14
28	0.65	96	36
29	0.98	67	47

In summary, solution-phase, combinatorial techniques have been used to rapidly identify potent, nonbasic side-chain replacements for the dibasic side chain of the clinical candidate **1**. Further studies to improve the in vitro and in vivo properties of these leads using expedited synthesis will be reported in subsequent communications.

Acknowledgements

The authors would like to thank Process Research at Eli Lilly and Company for supplying us with sufficient quantities of **3** including both enantiomers, and Dr. Dennis A. Laska for his work with the ocular irritation assay.

References and Notes

1. (a) *Substance P and Neurokinins*; Henry, J. L., Couture, R., Cuello, A. C., Pelletier, G., Quirion, R., Regoli, D., Eds.; Springer: New York, 1987; pp 17–18. (b) Guard, S.; Watson, S. P. *Neurochem. Int.* **1991**, *18*, 149.

2. (a) Otsuka, M.; Yanagisawa, M. *Cell Mol. Neurobiol.* **1990**, *10*, 293. (b) Laird, J. M. A.; Hargreaver, R. J.; Hill, R. G. *Br. J. Pharmacol.* **1993**, *109*, 259. (c) Lotz, M.; Carson, D. A.; Vaughan, J. H. *Science* **1987**, *235*, 893. (d) Moskowitz, M. A. *Trends Pharmacol. Sci.* **1992**, *13*, 307.

3. (a) Hipskind, P. A.; Howbert, J. J.; Bruns, R. F.; Cho, S. S. Y.; Crowell, T. A.; Foreman, M. M.; Gehlert, D. R.; Iyengar, S.; Johnson, K. W.; Krushinski, J. H.; Li, D. L.; Lobb, K. L.; Mason, N. R.; Muehl, B. S.; Nixon, J. A.; Phebus, L. A.; Regoli, D.; Simmons, R. M.; Threlkeld, P. G.; Waters, D. C.; Gitter, B. D. *J. Med. Chem.* **1996**, *39*, 736. (b) Hipskind, P. A.; Howbert, J. J.; Cho, S. S. Y.; Cronin, J. S.; Fort, S. L.; Ginah, F. O.; Hansen, G. J.; Huff, B. E.; Lobb, K. L.; Martinelli, M. J.; Murray, A. R.; Nixon, J. A.; Staszak, M. A.; Copp, J. D. *J. Org. Chem.* **1995**, *60*, 7033.

4. Structure searches were performed using the ACD provided by MDL information systems, Inc., 14600 Catalina St., San Leandro, CA 94577, USA.

5. (a) NK-1 receptor binding affinities (IC_{50}s) for all compounds were determined in [^{125}I]Bolton-Hunter SP binding experiments using a human IM-9 cell line expressing NK-1 receptors. See: Gitter, B. D.; Bruns, R. F.; Howbert, J. J.; Waters, D. C.; Threlkeld, P. G.; Cox, L. M.; Nixon, J. A.; Lobb, K. L.; Mason, N. R.; Stengel, P. W.; Cockerham, S. L.; Silbaugh, S.; Gehlert, D. R.; Schober, D. A.; Phebus, L. A.; Iyengar, S.; Calligaro, D. O.; Regoli, D.; Hipskind, P. *J. Pharmacol. Exp. Ther.* **1995**, *275*, 737. (b) Payne, D. G.; Brewster, D. R.; Goetzl, E. J. *J. Immunol.* **1984**, *133*, 3260. IC_{50} values were determined from 11-point concentration response curves with each concentration in triplicate.

6. Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193.

7. Kaldor, S. W.; Siegel, M. G. *Curr. Opin. Chem. Biol.* **1997**, *1*, 101.

8. Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett.* **1997**, *38*, 3357.

9. Reverse-phase HPLC analysis using a 8×200 mm C^{18} prep Nova pak cartridge 1% NH_4OAc in 10% H_2O, 45% CH_3CN, 45% MeOH monitored at 254 and 280 nm was used to establish purity. All compounds provided satisfactory MS, ^{1}H NMR, and TLC.

10. For example, (*R*)-**26** provided an IC_{50} of 0.4 nM, whereas its corresponding (*S*)-enantiomer was greater than 100-fold less potent.

11. Compound **1** had an ADC (in mm) score of 48, which classifies it as a severe irritant while (*R*)-**26** had an ADC score of 10 classifying it as nonirritating. For experimental detail see: Laska, D. A.; Hoffman, W. P.; Reboulet, J. T.; Poole, J. W. *In Vitro Tox.* **1996**, *9*, 201.

12. Male F344 rats were administered (*R*)-**26** as both an oral acacia suspension (10% w/v) 25 mg/kg and an intravenous 1 mg/kg in 10% Emulphor® solution. Plasma samples were collected at 0.5, 1, 2, 4, 6, 8, and 12 h after oral dosing with measurable concentrations persisting for 4 h. Reverse-phase HPLC was use to quantify the concentration of (*R*)-**26** in the plasma.