Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 2065–2068

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Biphenyl Derivatives as Novel Dual NK_1/NK_2-Receptor Antagonists

Robert Mah,[a,b,*] Marc Gerspacher,[a] Andreas von Sprecher,[a] Stefan Stutz,[b] Vincenzo Tschinke,[a,b] Gary P. Anderson,[c] Claude Bertrand,[d] Natarajan Subramanian[a] and Howard A. Ball[a]

[a]*Pharma Research, Novartis Pharma AG, CH-4002 Basel, Switzerland*
[b]*Speedel Experimenta AG, Gewerbestrasse 14, CH-4123 Allschwil, Switzerland*
[c]*Department of Pharmacology, University of Melbourne, Parkville, 3052 VIC, Australia*
[d]*Inflammatory Disease Unit, Roche Biosciences, Palo Alto, CA, USA*

Received 26 March 2002; accepted 23 May 2002

Abstract—In a continuation of our efforts to simplifly the structure of our neurokinin antagonists, a series of substituted biphenyl derivatives has been prepared. Several compounds exhibit potent affinities for both the NK_1 receptor (<10 nM) and for the NK_2 receptor (<50 nM). Details on the design, synthesis, biological activities, SAR and conformational analysis of this new class of dual NK_1/NK_2 receptor antagonists are presented.

Neurokinins (NKs), also referred to as tachykinins (TKs), are a family of peptide neurotransmitters and neuromodulators implicated in a variety of biological disorders such as anxiety, arthritis, asthma and airway diseases, cancer, depression, emesis, migraine and schizophrenia.[1] Within the lungs, the release of neuropeptides, notably substance P (SP) and neurokinin A (NKA), from sensory nerves as well as from inflammatory cells results in an inflammatory response characterized by bronchoconstriction, microvascular leakage and mucus hypersecretion—typical pathological features of asthma and chronic bronchitis.[2] The effects of SP (primarily microvascular leakage and mucus hypersecretion) and NKA (predominantly hyper-responsiveness) are mediated through specific receptors—mainly NK_1 for SP and mainly NK_2 for NKA—and thus the simultaneous blockade of both receptors offers an attractive strategy for the treatment of asthma and airway diseases.[3]

In a continuation of our efforts to simplify the structures of our NK-antagonists (e.g., the selective NK_1 antagonist **CGP49823**[4] and the dual NK_1/NK_2 antagonists such as 5-aryl-4-benzoylamino-pent-2-ene-carboxamides, **A**[5]), analysis with molecular models suggested that a suitably substituted biphenyl derivative (**B**) would place the two aromatic rings—comprising the postulated pharmacophore elements (for the NK_1 receptor)—in the correct orientation as required for receptor binding[6] (Fig. 1). In addition to eliminating an additional stereocenter,[7] molecules of this type were envisioned to be amenable for rapid optimization of biological activity as a result of the projected synthesis (aryl–aryl coupling).

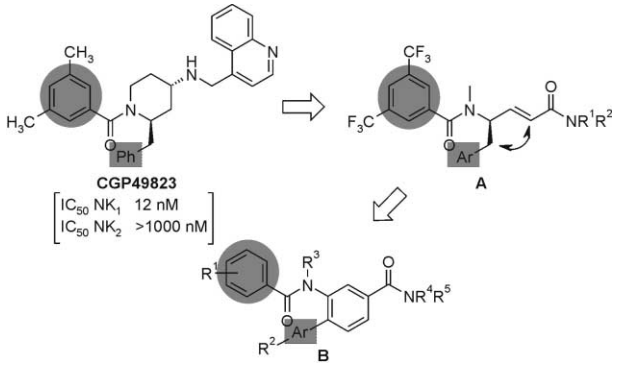
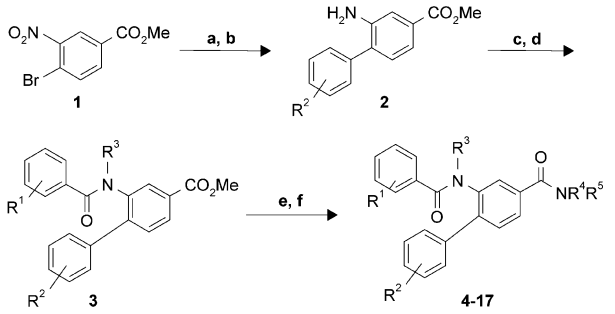


Figure 1. Simplification of NK-antagonist structures leading to substituted biphenyls.

*Corresponding author. Tel.: +41-61-206-4074; fax: +41-61-206-4001; e-mail: robert.mah@speedelgroup.com

0960-894X/02/$ - see front matter
PII: S0960-894X(02)00382-7

The requisite 1,3-disubstituted biphenyl derivatives (**2**) were prepared using a Cu-catalyzed cross-coupling reaction between bromide **1** and a suitably substituted aryl iodide, and subsequent Raney nickel reduction of the nitro group. Sequential acylation and alkylation of the free amine provided esters **3**. The target compounds (**4**–**17**) were obtained following saponification and ensuing reaction of the acid intermediates with various amines under standard peptide coupling conditions (Scheme 1).

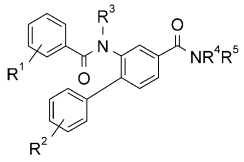


Scheme 1. Preparation of compounds **4**–**17**: (a) R^2-aryl-I, Cu; (b) H_2, Ra(Ni); (c) R^1-aryl-COCl, Et_3N, DMAP; (d) R^3-I, NaH; (e) LiOH, H_2O, THF, MeOH; (f) R^4R^5-NH, Et_3N, EDC, DMAP.

The affinity of **4**–**17** for the NK_1 receptor was determined by measuring the inhibition of binding of ^{3}H-Sar^9-SP in bovine retina membranes.[8] For the NK_2 receptor, the inhibition of ^{125}I-NKA binding to transfected CHO-cells expressing human recombinant NK_2 receptors was assessed.[9] (Table 1). A number of compounds (**9**, **13**–**14**) demonstrated potent affinities for both the NK_1 and NK_2 receptors—comparable to the reference compound.[5] It was found that a wide variety of substituents are tolerated at various positions in the molecule leading to compounds with high affinity to the NK_1 receptor, thus suggesting that the orientation of the two pendant aromatic rings (vide infra) is solely responsible for the binding activity to the NK_1 receptor. NK_2 receptor affinity, however, is much more dependent on the nature of the substitution pattern—the largest effects resulted from variations of the R^4R^5-substituents (**8**, **14**–**17**) and of the R^1-substituent (**4**–**5**, **14**). Moreover, in addition to the potent NK receptor binding affinities, several compounds exhibited good inhibition of either Sar^9-SP-induced bronchoconstriction[10] (79 and 60% for **6** and **7** respectively, 1 mg kg^{-1} po) or β-Ala^8-NKA-induced bronchoconstriction[10] (72% for **8**, 10 mg kg^{-1} po) when administered to guinea pigs 2 h prior to agonist challenge.

Subsequent to the initiation of synthetic activities, modelling studies[11] with **CGP49823**, **A** (Ar = 4-Cl-phenyl, NR^1R^2 = 2-piperidin-1-yl-ethylamine) and **8** were undertaken to test the validity of the original hypothesis and to aid in the identification of specific structural features for enhancing the NK_2-antagonistic activity. In confirmation of the original supposition, analysis of the lowest energy conformations highlighted

Table 1. In vitro binding affinities of compounds **4**–**17** to NK_1- and NK_2-receptors



Compd	R^1	R^2	R^3	NR^4R^5	NK_1 IC_{50} (nM)[a]	NK_2 IC_{50} (nM)[a]
4	H	4-F	CH_3		3.5	>1000
5	3,5-$(CF_3)_2$	4-F	CH_3		34	168
6	3,5-$(CF_3)_2$	4-H	CH_3	 (D,L)	1.5	560
7	3,5-$(CF_3)_2$	4-CH_3	CH_3	D-α-Amino-ε-caprolactam	6	181
8	3,5-$(CF_3)_2$	4-Cl	CH_3	D-α-Amino-ε-caprolactam	2.7	70
9	3,5-$(CF_3)_2$	4-F	CH_3	D-α-Amino-ε-caprolactam	1	28
10	3,5-$(CF_3)_2$	3,4-$(Cl)_2$	CH_3	D-α-Amino-ε-caprolactam	0.8	43
11	3,4,5-$(OCH_3)_3$	4-Cl	H	D-α-Amino-ε-caprolactam	0.7	>1000
12	3,4,5-$(OCH_3)_3$	4-Cl	CH_3	D-α-Amino-ε-caprolactam	13	162
13	3,4,5-$(OCH_3)_3$	4-Cl	H		9	30
14	3,5-$(CF_3)_2$	4-Cl	CH_3		3	51
15	3,5-$(CF_3)_2$	4-Cl	CH_3	$N(CH_2)_3N(CH_3)_2$	1	108
16	3,5-$(CF_3)_2$	4-Cl	CH_3	$N(CH_3)_2$	4	500
17	3,5-$(CF_3)_2$	4-Cl	CH_3	$N(OH)CH_3$	0.6	>1000

[a]Values are means of three experiments.

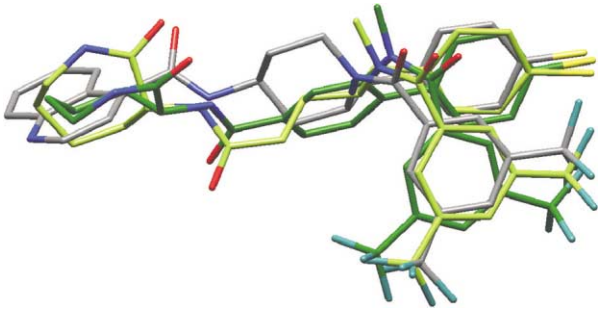


Figure 2. Overlap of **CGP49823** (gray), **A** (light green) and **8** (dark green).

the pair of closely spaced, staggered aromatic rings[6] as the most striking common feature. Furthermore, the presence of a H-bond accepting group (e.g., a carbonyl) at approximately 6 Å from the centroid of the first of the two staggered rings was identified as an important contributor for NK_2 binding activity (Fig. 2)

In conclusion, a novel class of dual NK_1/NK_2 receptor antagonists has been discovered. Several of the reported compounds exhibit potent affinities for both the NK_1 receptor (IC_{50} <10 nM) and for the NK_2 receptor (IC_{50} <50 nM). Additionally, some of the compounds displayed potent in vivo po activities in guinea pigs against either NK_1 or NK_2 agonist-induced bronchoconstriction. In addition to eliminating a stereocenter, the rigid nature of the target molecules allows for rapid conformational analysis using computer-assisted molecular modeling which, in turn, may aid in the optimization of binding activities.

Acknowledgements

The authors wish to thank H. Bammerlin, E. Braun, A. Cosenti, M. Erard, C. Ferraretto, S. Fuhrer, H. Hettrich, S. Kimmel, M. Kuhn, Th. Kull, M. Modena, C. Mouzo, T. Osman, V. Pawelzik, C. Ruesch, K. Ryffel, N. Stuber, A. Widmer and D. Wyss for their excellent technical assistance.

References and Notes

1. (a) Longmore, J.; Swain, C. J.; Hill, R. G. *Drug News Perspec*. **1995**, *8*, 5. (b) Kucharczyk, N. *Exp. Opin. Invest. Drugs* **1995**, *4*, 299. (c) Elliott, J.; Seward, E. M. *Exp. Opin. Ther. Pat*. **1997**, *7*, 43. (d) Longmore, J.; Hill, R. G.; Hargreaves, R. J. *Can. J. Phys. Pharmacol*. **1997**, *75*, 612. (e) von Sprecher, A.; Gerspacher, M.; Anderson, G. P. *Idrugs* **1998**, *1*, 73.
2. (a) Ford-Hutchinson, A. W.; Rodger, I. W.; Jones, T. R. *Drug. News Perspec*. **1992**, *5*, 542. (b) Geppetti, P.; Bertrand, C.; Ricciardolo, F. M. L.; Nadel, J. A. *Can. J. Phys. Pharmacol*. **1995**, *7*, 843. (c) Advenier, C.; Lagente, V.; Boichot, E. *Eur. Respir. J*. **1997**, *10*, 1892. (d) Chapman, R. W.; Hey, J. A.; McLeod, R.; Minnicozzi, M.; Rizzo, Ch. *Drug News Perspect*. **1998**, *11*, 480.
3. (a) Murai, M.; Morimoto, H.; Maeda, Y.; Kiyotoh, S.; Nishikawa, M.; Fujii, T. *J. Pharmacol. Exp. Ther*. **1992**, *262*, 403. (b) Joos, G. F.; Van Schoor, J.; Kips, J. C.; Pauwels, R. A. *Am. J. Respir. Crit. Care Med*. **1996**, *153*, 1781. (c) Gerspacher, M.; von Sprecher, A. *Drugs Future* **1999**, *24*, 883. (d) Ting, P. C.; Lee, J. F.; Anthes, J. C.; Shih, N.-Y.; Piwinski, J. J. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2333. (e) Bernstein, P. R.; Aharony, D.; Albert, J. S.; Andisik, D.; Barthlow, H. G.; Bialecki, R.; Davenport, T.; Dedinas, R. F.; Dembofsky, B. T.; Koether, G.; Kosmider, B. J.; Kirkland, K.; Ohnmacht, C. J.; Potts, W.; Rumsey, W. L.; Shen, L.; Shenvi, A.; Sherwood, S.; Stollman, D.; Russell, K. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2769.
4. Ofner, S.; Hauser, K.; Schilling, W.; Vassout, A.; Veenstra, S. J. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1623.
5. Gerspacher, M.; von Sprecher, A.; Mah, R.; Roggo, S.; Ofner, S.; Auberson, Y.; Betschart, C.; Schilling, W.; Anderson, G. P.; Ball, H.; Bertrand, C.; Subramanian, N.; Hauser, K. 5-Aryl-4-benzoyl-amino-pent-2-ene-carboxamides: a new class of NK_1 and dual NK_1/NK_2 antagonists. *212th ACS National Meeting,* Aug 23–27, 1998, Boston, USA; MEDI 52. For example, the compound with Ar = 4-Cl-phenyl and NR^1R^2 = 2-piperidin-1-yl-ethylamine exhibited IC_{50} values of 10 nM (NK_1) and 49 nM (NK_2).
6. (a) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 2545. (b) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem*. **1992**, *35*, 4911.
7. See also: Gerspacher, M.; La Vecchia, L.; Mah, R.; von Sprecher, A.; Anderson, G. P.; Subramanian, N.; Hauser, K.; Bammerlin, H.; Kimmel, S.; Pawelzik, V.; Ryffel, K.; Ball, H. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 3081.
8. For experimental details see: Bittiger, H; Heid, J. In *Substance P*; Skrabanek, P., Powell, D. Boole; Dublin, 1983; p. 198.
9. Inhibition of ^{125}I-NKA binding to transfected chinese hamster ovary cells (CHO cells) expressing recombinant human neurokinin 2 receptors: The assay was performed in 96-well plates (Nunclon) containing 200 µL 20 mM HEPES buffer, pH 7.4 containing 2 mM $MnSO_4$ and 6 mM $MgCl_2$, 3×10^5 h NK_2 CHO cells, 0.05 nM ^{125}I-NKA (2200 Ci mmol^{-1}) and various drug concentrations. Nonspecific binding was estimated in the presence of 50 nM NKA. The mixture was incubated for 20 min at room temperature after which the unbound ligand was removed by rapid filtration and washed four times with ice-cold Tricine buffer. Filter bound radioactivity was counted in Microscint 20 in a scintillation counter. All samples were measured in triplicate. Culture conditions and cell isolation for hr NK_2 CHOcells: Subramanian, N.; Ruesch, C.; Bertrand, C. *Biochem. Biophys. Res. Comm*. **1994**, *200*, 1512.
10. Dunkin-Hartley guinea-pigs (500–700 g) were anaesthetized with ip urethane (1.5 g kg^{-1}), tracheotomized and ventilated with a constant-volume ventilator (Model 683; Harvard apparatus Co., S. Natick, MA, USA) at a frequency of 60 breaths min^{-1}. Pavulon (pancuronium bromide, Organon, 1 mg kg^{-1}) and atropine (Fluka, 1 mg kg^{-1}) were administered (iv) to prevent spontaneous breathing and cholinergic reflexes, respectively. The tidal volume was adjusted to about 1 mL 100 g^{-1} body weight so as to maintain normal arterial blood gases. Intratracheal pressure was measured with a differential pressure transducer (Model DP 45–28, Validyne Engineering Corp., Northridge, CA, USA). Polyethylene catheters (250 I.U. mL^{-1} heparin in 0.9% NaCl) were inserted into the right jugular vein for drug injection and the left carotid for blood pressure measurements (Statham transducer P23XL). All signals were recorded using a computer data-acquisition system (Mi^2 Bio Report software, Modular Instruments). The timing of anaesthesia and animal preparation were such that after a baseline period was obtained, Sar^9-SP (3 µg kg^{-1}; ED_{80} dose for increase in intratracheal pressure) or β-Ala^8-NKA (0.8 µg kg^{-1} ED_{80} dose) was injected, corresponding to a time of 2, 4 or 12 h since the oral dosing of vehicle or drug. The antagonists were given in doses ranging

from 0.01 to 1 mg kg^{-1} in a vehicle consisting of 0.0067–0.67% DMSO in 0.5% methylcellulose, in a volume of 10 mL kg^{-1}. Five to six animals per dose were studied. The percent inhibition for each animal was calculated by dividing the elicited change in intratracheal pressure for the antagonist-treated animals by the mean value obtained for the vehicle-treated group. A linear regression analysis was then performed of the logarithmically transformed dose data and the ED_{50} value interpolated.

11. Conformation analysis simulations were carried out using the Monte Carlo method as implemented in MacroModel 5.0, including solvation effects in water. Visualization, clustering and superposition of the molecular structures were performed using Insight II.