Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 2519–2522

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Parallel Solution- and Solid-Phase Synthesis of Spirohydantoin Derivatives as Neurokinin-1 Receptor Ligands

Konrad H. Bleicher,* Yves Wüthrich, Maxime De Boni, Sabine Kolczewski, Torsten Hoffmann and Andrew J. Sleight

F. Hoffmann-La Roche AG, Pharma Research, CH-4070 Basel, Switzerland

Received 9 April 2002; revised 3 June 2002; accepted 28 June 2002

Abstract—The combination of the 3,5-bis(trifluoromethyl)phenyl group with a spirohydantoin motive as a central scaffold was the basis for the design of a combinatorial library targeted towards the neurokinin-1 receptor. A solution- and solid-phase procedure is described and binding affinities of representative compounds presented. © 2002 Elsevier Science Ltd. All rights reserved.

The neurokinin receptors (NK-1, NK-2 and NK-3) all belong to the target family of 7-transmembrane G-protein coupled receptors.[1,2] They are both expressed in the periphery (mainly NK-2) as well as in the central nervous system (NK-1 and NK-3). Hence, their therapeutic utility ranges from CNS indications to the potential treatment of respiratory and gastric diseases.

The endogenous ligands for the neurokinin receptors are the tachykinins, a group of peptides that all share a common C-terminal amino acid sequence Phe-X-Gly-Leu-Met-NH_2 where X is either Phe or Val. The most prominent member of this peptide family is the undecapeptide 'Substance P' (X = Phe) which shows highest affinity for the NK-1 receptor, whereas NKA and NKB (X = Val) are both decapeptides that bind preferentially to the NK-2 and NK-3 receptor, respectively.[3]

In the search for novel small molecule ligands targeting the NK-1 receptor, we initiated a focused library synthesis based on a design strategy that combines the concepts of both 'privileged structure' motives[4,5] as well as the 'needle' approach.[6] Although both terms have been widely discussed in public, their differentiation is somewhat unclear. Therefore, we would like to outline our understanding of these two terms in some more detail here.

Spiropiperidines belong to a well-known class of pharmacologically relevant molecules showing biological activity for various target families ranging from enzyme inhibitors[7] to ion channel blockers.[8] Such molecular frameworks are of special interest in the area of G-protein coupled receptors. Therefore this class of chemical motives are often referred to as 'privileged structures'. Elements of this type are recognized not only by a particular receptor or enzyme but by various protein family members. One such representative class of spiropiperidines is the spiropiperidino-hydantoin which is a well-known motive in the serotonin receptor area with Spiperone as a very close analogue.[9] In addition we recently reported this scaffold as novel NK-1 antagonists.[10] This molecular architecture is of particular interest as a scaffold for combinatorial design due to its rigid three-dimensional organization and its low molecular weight. Additionally it can be modified in a straightforward manner at three sites of the core moiety which allows the rapid generation of a diverse set of drug-like compounds.

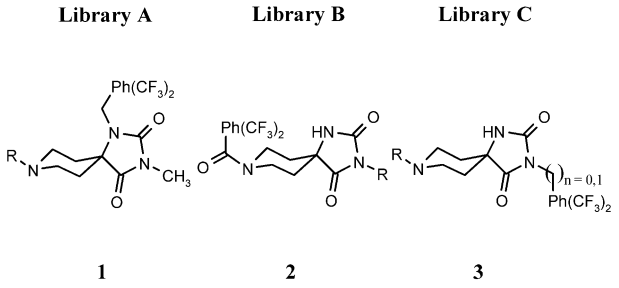
In contrast to the 'privileged structure' motive, the terminus 'needle' was described in the literature as a fragment of an active molecule showing very specific interactions with one particular biological target. One well known example for such a needle within the GPCR area is the *ortho*-substituted biphenyl tetrazole (or bioisosteres), an element present in most angiotensin-1 antagonists currently on the market.[11] Within the neurokinin area, one example of such a needle is the 3,5-bis(trifluoromethyl)phenyl moiety which has been described for several NK-1 receptor ligands.[12]

*Corresponding author. Tel.: +41-6168-70387; fax: +41-6168-81745; e-mail: konrad.bleicher@roche.com

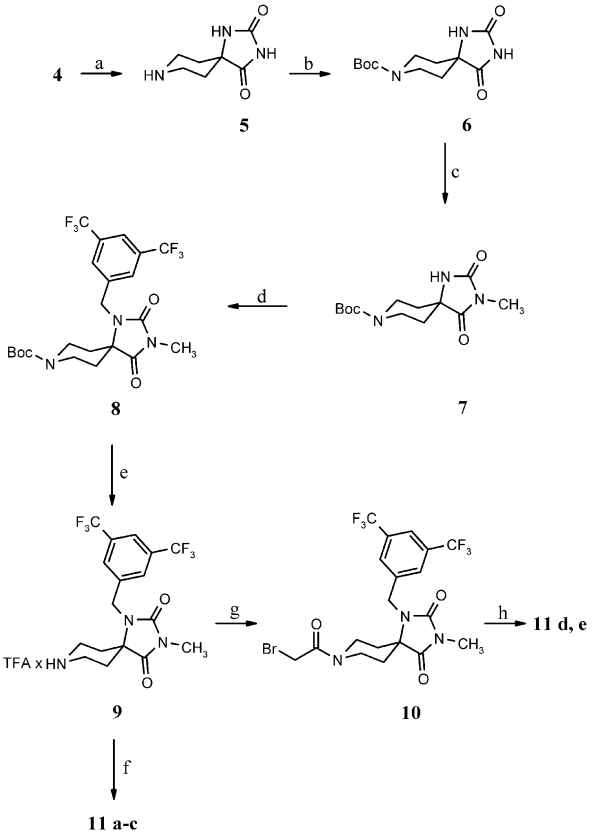
0960-894X/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0960-894X(02)00488-2

Following the idea of combining a 'privileged structure' motive with the 'needle' concept, a library design was generated as depicted in Scheme 1. The intention was to couple the 3,5-bis(trifluoromethyl)phenyl needle to all positions available in the core structure and decorate one of the remaining nitrogens with various residues. The three sets of compounds were prepared in a parallel fashion using solution- and solid-phase methodologies.

First, a collection of compounds for library A was synthesized in solution by modification of the piperidine nitrogen of template **9** as outlined in Scheme 2. This



Scheme 1. Targeted library design for NK-1 receptor ligands by combination of a GPCR 'privileged structure' motive with the 3,5-bis(trifluoromethyl)phenyl 'needle' [$Ph(CF_3)_2$].



Scheme 2. (a) 1.5 equiv NaCN, 5 equiv $(NH_4)_2CO_3$, EtOH/water (4:1), 80 °C, 3.5 atm, 18 h; (b) 1.1 equiv Boc_2O, 1.1 equiv Et_3N, dioxane/water (1:1), rt, 2 h; (c) 1.1 equiv NaH, 1.1 equiv MeI, DMA, rt, 72 h; (d) 1.1 equiv NaH, 1.1 equiv 3,5-bis(trifluoromethyl)benzyl bromide, DMA, rt, 48 h; (e) TFA/DCM (1:1), rt, 2 h; (f) 2.2 equiv RCOOH, 1.1 equiv DIC, rt, 16 h; (g) 2.2 equiv bromoacetic acid, 1.1 equiv DIC, rt, 16 h; (h) 2 equiv amine, rt, 16 h.

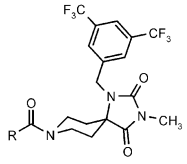
intermediate was generated starting from commercially available piperidone monohydrate **4**. The resulting spirohydantoin **5** was further modified to give the corresponding *N*-Boc-protected intermediate **6** using standard conditions. Regioselective *N*-methylation of the imide nitrogen of the hydantoin moiety yielded in compound **7**. Subsequent 3,5-bis(trifluoromethyl)benzylation led to the desired Boc-protected spirohydantoin **8**. Finally, deprotection of the piperidine nitrogen by treatment with trifluoroacetic acid gave the TFA salt of spirohydantoin **9** ready for further modification.

In addition, compound **9** was further coupled with bromoacetic acid to yield intermediate **10**. Both derivatives were used as precursors for additional modification to result in products of type **11a–e** (Table 1). For the synthesis of the first set of compounds a collection of aliphatic and aromatic carboxylic acids were coupled under standard conditions to compound **9** resulting in spiropiperidine amides of type **11a–c**. For the generation of a second subset of compounds intermediate **10** was treated with secondary amines resulting in the corresponding chemotype **11d,e**. For the library generation in-house developed parallel synthesis equipment was applied. The compounds were worked up via liquid/liquid extraction and further purified by preparative HPLC. All products were analyzed and characterized by LC–MS.

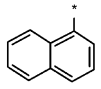
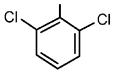
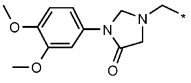
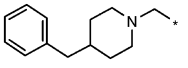
Table 1 summarizes five representative compounds **11a–e** generated for this particular series showing moderate NK-1 receptor binding affinities.

For the generation of libraries B and C, a solid-phase protocol was envisaged since the synthesis of hydantoins from the corresponding α-amino acids is well

Table 1. NK-1 receptor affinities of representatives from library A



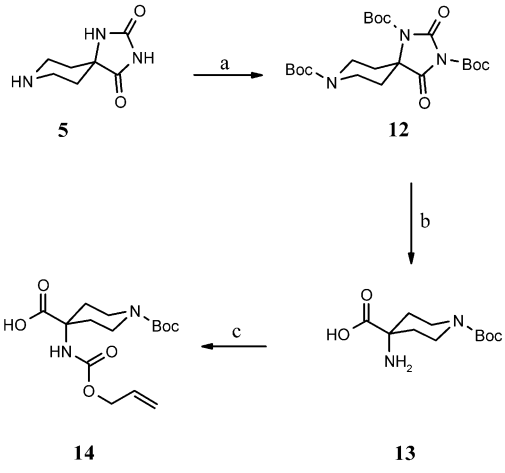
11 a-e

Compd	R	pK_i (hNK-1)
11a		6.34
11b		6.19
11c		5.83
11d		5.77
11e		5.43

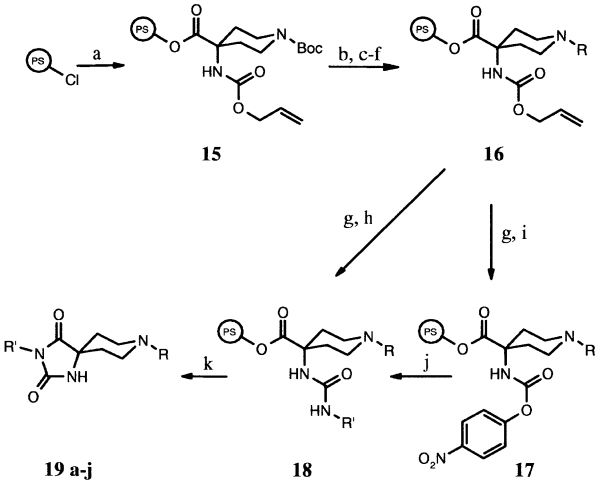
documented[13] and the advantages of solid-phase synthesis for library generation were recognized. Therefore, the orthogonally protected amino acid **14** was generated starting from the spirohydantoin **5** as outlined in Scheme 3. Treatment with excess of Boc anhydride gave the fully Boc-protected spirohydantoin **12**. Ring opening under basic conditions gave the corresponding Boc-protected amino acid **13**. Final protection of the α-nitrogen resulted in orthogonally protected amino acid **14** ready for coupling to the solid support.

The solid supported synthesis protocol for the generation of libraries B and C is schematically outlined in Scheme 4.

As a first step, amino acid **14** was immobilized on chloromethylated polystyrene beads (Merrifield resin).



Scheme 3. (a) 5 equiv Boc_2O, 1 equiv DMAP, 1 equiv Et_3N, DME, rt, 18 h; (b) 1 N NaOH/DME (2:1), rt, 20 h; (c) 1.5 equiv allyl chloroformate, 5% aq Na_2CO_3 dioxane/water (1:2), rt, 16 h.



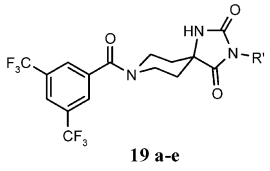
Scheme 4. (a) 1 equiv Cs_2CO_3, cat. KI, **14**, 60 °C, 16 h; (b) TFA/CH_2Cl_2 (1:1), rt, 2 h; (c) 3 equiv RCOCl, 3 equiv Et_3N, CH_2Cl_2, rt, 1 h; (d) 3 equiv RNCO, CH_2Cl_2, rt, 2 h; (e) 3 equiv RSO_2Cl, 3 equiv Et_3N, rt, 4 h; (f) 10 equiv RCHO, 5 equiv $NaBH_3CN$, DMF/MeOH/CH_3COOH (87:10:3), rt, 16 h; (g) 0.2 equiv $Pd(PPh_3)_4$, 10 equiv morpholine, CH_2Cl_2, rt, 2 h; (h) 3 equiv RNCO, CH_2Cl_2, rt, 2 h; (i) 2 equiv 4-nitrophenyl chloroformate, 2 equiv Et_3N, CH_2Cl_2, rt, 1 h; (j) 2 equiv amine, CH_2Cl_2, rt, 16 h; (k) isopropyl amine, 80 °C, 2 h.

Therefore the cesium salt of **14** was generated and coupled under standard conditions to give resin bound compound **15**. For the generation of compounds of library B the Boc protecting group was cleaved first via TFA treatment of resin **15** which resulted in the free piperidine nitrogen. Standard coupling of 3,5-bis(trifluoromethyl)phenyl carboxylic acid chloride resulted in resin **16** where R represents the NK-1 needle. Pd(0) catalyzed Alloc deprotection was achieved under mild conditions using morpholine as a nucleophile. Subsequently, the resin was treated with 4-nitrophenyl chloroformate to yield resin **17**. This activated carbamate was converted into the corresponding urea by treating the resin with primary amines to generate resin bound urea derivatives **18**. A bright yellow color indicated the liberation of 4-nitrophenolate and was therefore used for real time monitoring of the reaction progress. The advantage of this two-step procedure is obvious due to the accessibility of far more primary amines compared to the limited number of available isocyanates. The final step to generate compounds of type **19a–j** was a cyclization and cleavage approach. This can be achieved under either acidic[14] or basic conditions.[15] We preferred the resin cleavage via isopropyl amine treatment due to higher yielding reactions and ease of parallel handling. Although the compounds showed very high purity due to the cyclization/cleavage strategy an additional HPLC purification step was undertaken to ensure reliable biological data. All compounds were analyzed and characterized by LC–MS.

Five representative compounds of collection B with moderate NK-1 binding affinities are shown in Table 2.

The compounds generated for library C mainly differ at the piperidine moiety. Once again, a compound subset of type **3** was obtained by standard coupling of

Table 2. NK-1 receptor affinities of representatives from library B



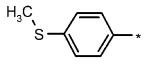
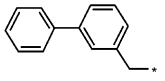
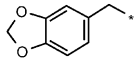
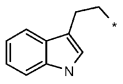
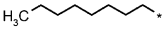
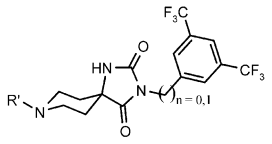
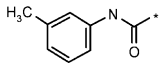
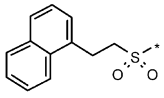
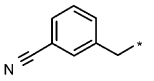
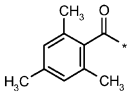
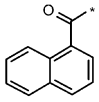
Compd	R′	pK_i (hNK-1)
19a		6.88
19b		6.86
19c		6.61
19d		6.24
19e		5.69

Table 3. NK-1 receptor affinities of representatives from library C



19 f-j

Compd	R′	pK_i (hNK-1)
19f/$n=1$		7.34
19g/$n=1$		7.13
19h/$n=1$		6.97
19i/$n=0$		6.49
19j/$n=0$		6.47

carboxylic acid chlorides onto the deprotected piperidine nitrogen of resin bound amino acid **16** (R = H) for tertiary amid formation. Treatment of resin **16** with sulfonyl chlorides resulted in the corresponding sulfonamides as a second subset. In addition, isocyanates were coupled to the piperidine nitrogen to form the corresponding piperidine urea derivatives. For the introduction of a basic nitrogen to the molecular framework of compounds **3**, a reductive alkylation step was applied using aldehydes as building blocks resulting in resin bound tertiary amines of type **16**. Subsequent urea formation after Alloc cleavage at the α-nitrogen was either achieved via coupling of commercially available 3,5-bis(trifluoromethyl)phenyl isocyanate directly to the α-nitrogen of the immobilized amino acid or via activation of resin **16** and subsequent treatment of activated carbamate resin **17** with 3,5-bis(trifluoromethyl)benzyl amine to yield resin **18**. The generated urea derivatives were again cleaved under basic conditions to result in compounds of type **19f–j** (Table 3) where *n* equals either 0 or 1.

A subset of NK-1 active compounds from library C is depicted in Table 3 showing moderate to high binding affinities.

In summary, we have described the generation of a focused compound library targeted towards the neurokinin-1 receptor. The basis for the library design were both the identification of spiropiperidino-hydantoin as a 'privileged structure' motive for G-protein coupled receptors as well as an NK-1 specific 3,5-bis(trifluoromethyl)phenyl 'needle'. Follow up work on the privileged structure/needle design concept for the identification of further NK-1 ligands will be reported in due course.

Acknowledgements

The authors would like to thank Dr. Mark Rogers-Evans for critical reading of the manuscript and Mr. Alain Rudler for biological testing.[16]

References and Notes

1. Watson, S.; Arkinstall, S. *The G-Protein Linked Receptors Facts Book*; Academic: New York, 1994.
2. Flower, D. R. *Biochim. Biophys. Acta* **1999**, *1422*, 207.
3. Leroy, V.; Mauser, P.; Gao, Z.; Peet, N. P. *Exp. Opin. Invest. Drugs* **1999**, *9*, 735.
4. Mason, J. S.; Morize, I.; Menard, P. R.; Cheney, D. L.; Hulme, C.; Labaudiniere, R. F. *J. Med. Chem.* **1999**, *42*, 3251.
5. Patchett, A. A.; Nargund, R. P. *Annu. Rep. Med. Chem.* **2000**, *35*, 289.
6. Boehm, H.-J.; Boehringer, M.; Bur, D.; Gmuender, H.; Huber, W.; Klaus, W.; Kostrewa, D.; Kuehne, H.; Luebbers, T.; Meunier-Keller, N.; Mueller, F. *J. Med. Chem.* **2000**, *43*, 2664.
7. Anon. *Expert Opion. Ther. Pat.* **2000**, *10*, 125
8. Kolocouris, N.; Kolocouris, A.; Foscolos, G. B.; Fytas, G.; Neyts, J.; Padalko, E.; Balzarini, J.; Snoeck, R.; Andrei, G.; De Clercq, E. *J. Med. Chem.* **1996**, *39*, 3307.
9. Weinhardt, K. K.; Bonhaus, D. W.; De Souza, A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2687.
10. Galley, G.; Godel, T.; Goergler, A.; Hoffmann, T.; Kolczewski, S.; Roever, S. WO 0194346 2001; *Chem. Abstr.* **2001**, *136,* 37519.
11. Burnier, M.; Brunner, H. R. *Lancet* **2000**, *355*, 637.
12. Seward, E. M.; Swain, C. *Exp. Opin. Ther. Pat.* **1999**, *9*, 571.
13. Chong, P. Y.; Petillo, P. A. *Tetrahedron Lett.* **1999**, *40*, 2493.
14. DeWitt, S. H.; Kiley, J. S.; Stankovic, C. H.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6900.
15. Kim, S. W.; Anh, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, *38*, 4603.
16. Affinities for the human NK_1 receptor were evaluated in CHO cells infected with the human NK_1 receptor (using the Semliki virus expression system) and radiolabelled with [^{3}H] substance P. Displacement curves were determined with at least seven concentrations.