Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 3073–3076

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Parallel Solution- and Solid-Phase Synthesis of Spiropyrrolo-Pyrroles as Novel Neurokinin Receptor Ligands

Konrad H. Bleicher,* Yves Wüthrich, Geo Adam, Torsten Hoffmann and Andrew J. Sleight

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

Received 17 May 2002; revised 24 July 2002; accepted 5 August 2002

Abstract—The combination of a 3,5-bis(trifluoromethyl)phenyl needle with the spiropyrrolo-pyrrole motive as a privileged GPCR scaffold was the basis for designing a focused combinatorial library targeted towards the neurokinin-1 receptor. A solution- and solid-phase method is described and binding affinities of representative compounds are presented.

Currently three subtypes of neurokinin receptors are described as being 7-transmembrane G-protein coupled, namely the NK-1, NK-2 and the NK-3 receptors. All three belong to the peptide receptor subgroup of GPCR family 1.[1] Their endogenous ligands are the tachykinins, a group of well known peptide amides that all share the common C-terminal amino acid sequence Phe-X-Gly-Leu-Met-NH_2 where X is either Phe or Val. 'Substance P' (or SP) is an undecapeptide (where X = Phe) which shows highest binding affinity for the NK-1 receptor. NKA and NKB (X = Val) are both decapeptides that bind preferentially to the NK-2 and NK-3 receptor, respectively.[2]

All three receptors have been described as being of pharmacological relevance in various areas. NK-1 and NK-3 receptors are discussed as potential CNS disease targets since both receptors are mainly expressed in the brain. Antagonists of these receptors are currently investigated as potential treatments for diseases such as anxiety and depression (NK-1 antagonists) or chemotherapy-induced emesis (NK-3 antagonists). The NK-2 receptor is mainly expressed in the periphery and described as a pharmacologically relevant target for respiratory diseases such as asthma as well as urinary dysfunction.[3]

Due to the fact that neurokinin receptors are G-protein coupled receptors, biostructural information is very limited. Thus for the initiation of a research program on the NK-1 receptor we started with the classical route of high-throughput screening (HTS) as a first step for the identification and validation of hit series.

As a complementary approach to the HTS campaign we envisaged an NK-1 focused library design based on the combination of two concepts—the 'privileged structure' and the 'needle' approach as already stated in an earlier communication.[4]

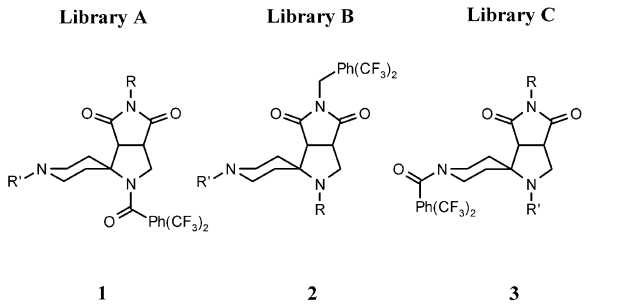
Since spiropiperidines are considered as pharmacologically relevant molecules for various targets within the area of G-protein coupled receptors, this class of chemical motives is often referred to as 'privileged GPCR-structures'.[5,6]

Complementary to the 'privileged structure' motive the terminus 'needle' was described in the literature as the fragment of an active molecule showing very specific interactions with one particular biological target.[7] Within the neurokinin family one such example is the 3,5-bis(trifluoromethyl)phenyl moiety which has been described as an essential fragment for several NK-1 receptor ligands.[3]

Spiropyrrolo-pyrroles were already described by us as ligands for the orphanin FQ receptor (OFQ).[8] This protein was characterized as being a member of the G-protein coupled receptors. Similar to neurokinin receptors the OFQ receptor belongs to the GPCR subfamily 1 where a 17 amino acid neuropeptide was identified as the endogenous ligand.[9] Since these OFQ ligands also

*Corresponding author. Tel.: +41-6168-70387; fax: +41-6168-86459; e-mail: konrad.bleicher@roche.com

0960-894X/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0960-894X(02)00659-5

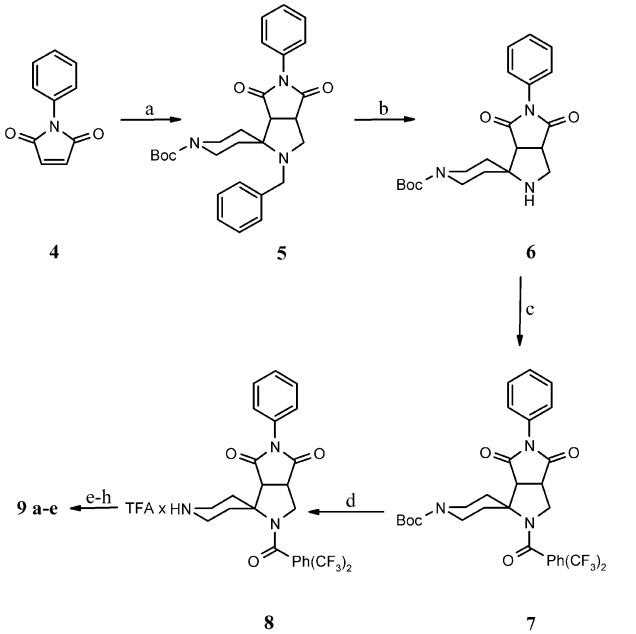


Scheme 1. Targeted library design for NK-1 receptor ligands by combination of a GPCR 'privileged structure' motive with the 3,5-bis(trifluoromethyl)phenyl 'needle' ($Ph(CF_3)_2$).

contain the piperidine architecture we envisaged this template as a 'privileged structure' for G-protein coupled receptors.

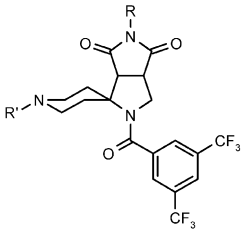
Following the approach of combining such promiscuous motives with the 'needle' concept, a focused library synthesis was initiated as depicted in Scheme 1. Three sets of sublibraries were prepared in a parallel fashion using either solution- or solid-phase methodologies.

A compound collection of type A was generated via parallel solution phase synthesis. The core scaffold was thereby obtained from a (3 + 2) cycloaddition reaction starting from *N*-phenylmaleimide **4** as a dienophile and the corresponding diene generated in situ from 1-Boc-piperidone and *N*-benzylglycine via base catalysis.[10] Under the reaction conditions described in Scheme 2 a spontaneous decarboxylation takes place leading to the

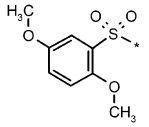
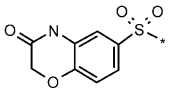
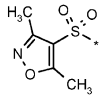
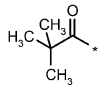


Scheme 2. (a) 1 equiv Boc-piperidone, 1 equiv *N*-benzylglycine, 2.5 equiv DIPEA, toluene, reflux, 16 h; (b) Pd/C, H_2, 2 atm, MeOH/CH_2Cl_2 (4:1), rt, 16 h; (c) 1.2 equiv 3,5-bis(trifluoromethyl)benzoyl chloride, 1.2 equiv BSA, CH_2Cl_2, 0 °C–rt, 72 h; (d) TFA/DCM (1:1), rt, 2 h; (e) 1.1 equiv RCOOH, 1.1 equiv DIC, CH_2Cl_2, rt, 16 h; (f) 1.1 equiv RSO_2Cl, 1.1 equiv TEA, CH_2Cl_2, rt, 16 h; (g) 1.1 equiv RNCO, CH_2Cl_2, rt, 16 h; (h) 1.1 equiv RCHO, 1.3 equiv $NaBH_3CN$, DMF/MeOH/CH_3COOH (87:10:3), rt, 16 h.

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



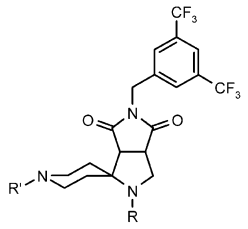
1

Compd	R	R′	pK_i (hNK-1)
9a	Phe		7.52
9b	Phe		7.51
9c	Phe		7.12
9d	Phe		6.52
9e	Phe		5.97

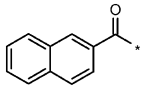
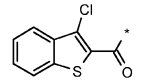
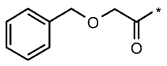
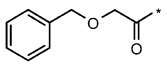
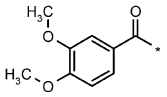
spiropyrrolo-pyrrole intermediate **5**. Subsequent debenzylation using standard Pd/C hydrogenation conditions gave deprotected intermediate **6**. The nucleophilicity of the resulting α,α-disubstituted pyrrolidine nitrogen turned out to be very low due to steric hindrance of the neighboring spiropiperidine ring. Reactivity enhancement was achieved by silylation of the pyrrolidine nitrogen prior to the acylation step.

Therefore, intermediate **6** was treated with bis(-trimethylsilyl)acetamide (BSA) at room temperature and stirred for 1 h. Subsequently the reaction mixture was cooled down to 0 °C. The dropwise addition of 3,5-bis(trifluoromethyl)benzoyl chloride and subsequent warming to room temperature gave the benzoylated intermediate **7** in mediocre yield only. Kieselgel chromatography and final treatment with trifluoroacetic acid resulted in the TFA salt of precursor **8** ready for further modification. To generate a compound collection of type A spiropyrrolo-pyrrole **8** was treated under DIC coupling conditions with a set of carboxylic acids to form the corresponding amides. Sulfonylchlorides were coupled to give sulfonamides, isocyanates yielded the corresponding ureas and finally reductive alkylation reactions were performed to introduce a basic tertiary nitrogen into the molecular framework. The compounds were generated using standard in-house developed parallel synthesis equipment. All products were worked up by a liquid/liquid extraction step and finally purified using preparative HPLC. For quality control and compound

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

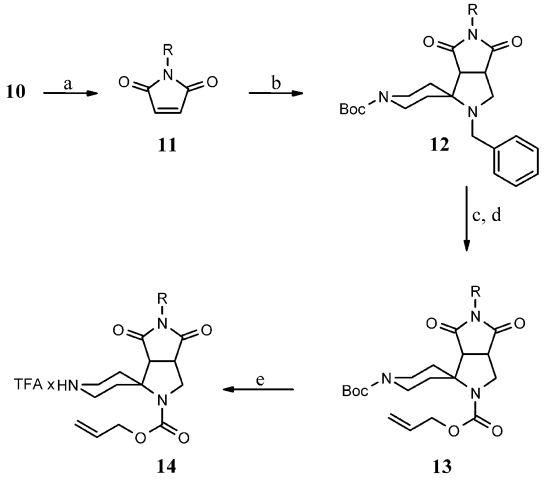


2

Compd	R′	R	pK_i (hNK-1)
19a			6.58
19b	H		6.30
19c	H		5.64
19d			5.63
19e	H		5.37

characterization online-coupled LCMS was applied to check the purity of generated material.

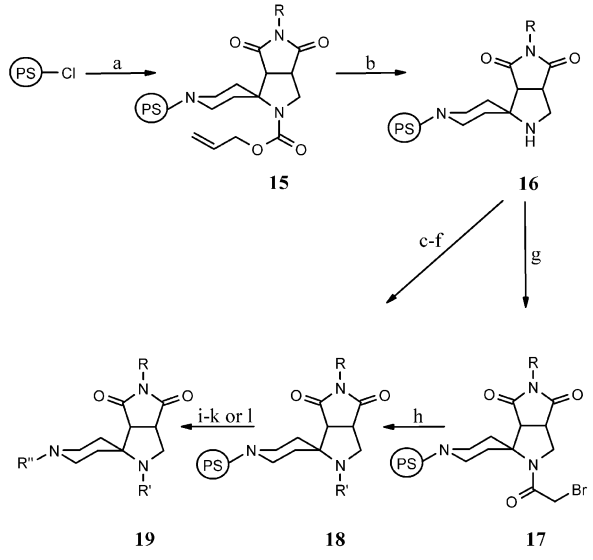
Five representative compounds (**9a–e**) showing reasonable activities for the NK-1 receptor are depicted in Table 1.



Scheme 3. (a) 1 equiv primary amine, CH_2Cl_2, rt, 1 h, evaporation, 1.25 equiv sodium acetate, acetic anhydride, 90 °C, 16 h; (b) 1 equiv Boc-piperidone, 1 equiv *N*-benzylglycine, 2.5 equiv DIPEA, toluene, reflux, 16 h; (c) Pd/C, H_2, 2 atm, MeOH/CH_2Cl_2 (4:1), rt, 2 h; (d) 1.2 equiv Alloc-chloride, 1.2 equiv BSA, CH_2Cl_2, 0 °C–rt, 72 h; (e) TFA/DCM (1:1), rt, 2 h.

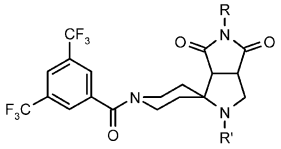
Due to low reactivity of the pyrrolidine nitrogen observed during the 3,5-bis(trifluoromethyl)benzoylation reaction we considered a solid-phase protocol for this particular modification step to generate compounds of type B and C. This would allow the use of a large excess of reagents to drive the reaction to completion. Unconsumed material can be washed away and product isolation is obtained via simple filtration. For the ease of parallel processing we considered an acid labile polymer support as most convenient. The allyloxycarbonyl-(Alloc) group was considered as an orthogonal protecting group that can be cleaved under very mild conditions. The solution phase synthesis of the corresponding precursors **14** is shown in Scheme 3. Analogous to Scheme 2, the spiropyrrolo-pyrrole is obtained via a thermal (3 + 2) cycloaddition reaction starting from either commercially available *N*-substituted maleimides **11** or from intermediates prepared via maleic acid anhydride **10** and primary amines. Debenzylation of intermediates **12** and subsequent acylation with allyl chloroformate resulted in intermediates **13**. Boc cleavage by TFA treatment gave scaffolds **14**.

For the immobilization of precursors **14** the compounds were added to trityl chloride resin resulting in solid supported intermediate **15**. Palladium catalyzed Alloc cleavage gave resin **16**. Compound subset B was generated via modification at the pyrrolidine nitrogen by coupling of carboxylic acids, isocyanates, sulfonyl chlorides and aldehydes resulting in resins **18**. After TFA cleavage the compounds were either purified or further modified by treating with acetic anhydride or mesyl chloride for capping of the piperidine nitrogen. Excess of reagent was removed by simple evaporation

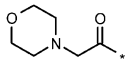
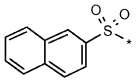
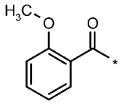


Scheme 4. (a) 1 equiv **14**, 3 equiv DIPEA, CH_2Cl_2, rt, 16 h; (b) 0.05 equiv $Pd(PPh_3)_4$, 10 equiv morpholine, CH_2Cl_2, rt, 16 h; (c) 3 equiv RCOOH, 3 equiv DIC, DMF, rt, 16 h; (d) 3 equiv RNCO, CH_2Cl_2, rt, 16 h; (e) 3 equiv RSO_2Cl, 3 equiv TEA, CH_2Cl_2, rt, 16 h; (f) 10 equiv RCHO, 5 equiv $NaBH_3CN$, DMF/MeOH/CH_3COOH (87:10:3), rt, 16 h; (g) 3 equiv bromoacetic acid, 3 equiv DIC, DMF, rt, 16 h; (h) 3 equiv amine, DMF, rt, 4 h; (i) TFA, CH_2Cl_2 (1:1), rt, 2 h; (j) 2 equiv Ac_2O, 2 equiv TEA, CH_2Cl_2, rt, 16 h; (k) 2 equiv $MeSO_2Cl$, 2 equiv TEA, CH_2Cl_2, rt, 16 h; for library C: (l) 2 equiv 3,5-bis(trifluoromethyl)benzoyl chloride, 2 equiv DIPEA, CH_2Cl_2, rt, 16 h.

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



3

Compd	R	R′	pK_i (hNK-1)
19f	Phe		8.29
19g	Phe		8.08
19h	Me		7.41
19i	Me		6.29
19j	Me		6.10

after quenching the reaction mixture with methanol. All compounds were purified by preparative HPLC.

Table 2 shows five representative compounds of library B (**19a**–**e**) with moderate NK-1 receptor activities.

Compounds generated for library C were designed to have the NK-1 specific 3,5-bis(trifluoromethyl)phenyl needle at the piperidine nitrogen. Since this was foreseen as the attachment point to the resin as described in Scheme 4, a solid supported synthesis approach is not obvious. We anyway decided to proceed via a solid-phase synthesis route due to low reactivity of the pyrrolidine nitrogen allowing the use of an excess of reagents for this particular coupling step. Additionally a two step modification procedure was envisaged by first DIC coupling of resin **16** with bromoacetic acid resulting in resin **17** and subsequent nucleophilic displacement of the bromide with a set of available secondary amines. The compounds were cleaved from the trityl resin under TFA treatment to give the free piperidine analoges. Subsequent coupling of 3,5-bis(trifluoromethyl)benzoyl chloride was applied to crude material after evaporation of the cleavage reagent providing compounds of type C. The excess of unconsumed carboxylic acid chloride was scavenged with aminomethylated polystyrene resin resulting in highly pure material. To guarantee solid biological data all compounds were further purified with preparative HPLC and characterized as already described.

Table 3 shows five representative compounds generated for library C (**19f**–**j**) with reasonable to high NK-1 receptor affinities.

In summary, we described the parallel solution- and solid-phase synthesis of a focused compound library targeted towards the neurokinin-1 receptor. The basis for the library design was a combination of the spiro-pyrrolo-pyrrole template envisaged as a 'privileged structure' for G-protein coupled receptors with the 3,5-bis(trifluoromethyl)phenyl motive as an NK-1 specific 'needle'. As a result novel neurokinin receptor ligands with low nanomolar affinities were identified.

Acknowledgements

The authors would like to thank Dr. Mark Rogers-Evans for critical reading of the manuscript and Alain Rudler for biological testing.[11]

References and Notes

1. Beck-Sickinger, A. *Drug Discov. Today* **1996**, *1*, 502.
2. Leroy, V.; Mauser, P.; Gao, Z.; Peet, N. P. *Exp. Opin. Invest. Drugs* **1999**, *9*, 735.
3. Seward, E. M.; Swain, C. *Exp. Opin. Ther. Pat.* **1999**, *9*, 571.
4. Bleicher, K. H.; Wüthrich, Y.; De Boni, M.; Kolczewski, S.; Hoffmann, T.; Sleight, A. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2519.
5. Mason, J. S.; Morize, I.; Menard, P. R.; Cheney, D. L.; Hulme, C.; Labaudiniere, R. F. *J. Med. Chem.* **1999**, *42*, 3251.
6. Patchett, A. A.; Nargund, R. P. *Annu. Rep. Med. Chem.* **2000**, *35*, 289.
7. 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.
8. Adam, G.; Dautzenberg, F.; Kolczewski, S.; Roever, S.; Wichmann, J. Eur. Pat. Appl. 963987 1999; *Chem. Abstr.* **1999**, 132, 35624.
9. Reinscheid, R. K.; Nothacker, H. P.; Bourson, A.; Ardati, A.; Henningsen, R. A.; Bunzow, J. R.; Grandy, D. K.; Langen, H.; Monsma, F. J., Jr.; Civelli, O. *Science* **1995**, *270*, 792.
10. Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4067.
11. Affinities of the compounds 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 of the compound.