Bioorganic & Medicinal Chemistry Letters 20 (2010) 5925–5932

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Fused tricyclic pyrrolizinones that exhibit pseudo-irreversible blockade of the NK_1 receptor

Gregori J. Morriello [a,*], Gary Chicchi [b], Tricia Johnson [a], Sander G. Mills [a], Julie DeMartino [b], Marc Kurtz [b], K. L. C. Tsao [b], Song Zheng [c], Xinchun Tong [c], Emma Carlson [d], Karen Townson [d], Alan Wheeldon [d], Susan Boyce [d], Neil Collinson [d], Nadia Rupniak [d], Robert J. DeVita [a]

[a] Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[b] Department of Immunology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[c] Department of Drug Metabolism, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA
[d] Department of Behavioral Neuroscience, Merck Research Laboratories, Terlings Park, UK

ARTICLE INFO

Article history:
Received 19 February 2010
Revised 12 July 2010
Accepted 14 July 2010
Available online 19 July 2010

Keywords:
Neurokinin
Neurokinin-1 antagonists
Functional IP

ABSTRACT

Previously, we had disclosed a novel class of hNK_1 antagonists based on the 5,5-fused pyrrolidine core. These compounds displayed subnanomolar hNK_1 affinity along with good efficacy in a gerbil foot-tapping (GFT) model, but unfortunately they had low to moderate functional antagonist (IP-1) activity. To elaborate on the SAR of this class of hNK_1 compounds and to improve functional activity, we have designed and synthesized a new class of hNK_1 antagonist with a third fused ring. Compared to the 5,5-fused pyrrolidine class, these 5,5,5-fused tricyclic hNK_1 antagonists maintain subnanomolar hNK_1 binding affinity with highly improved functional IP-1 activity (<10% SP remaining). A fused tricyclic methyl, hydroxyl geminally substituted pyrrolizinone (compound **20**) had excellent functional IP (<2% SP remaining), hNK_1 binding affinity, off-target selectivity, pharmacokinetic profile and in vivo activity. Complete inhibition of agonist activity was observed at both 0 and 24 h in the gerbil foot-tapping model with an ID_{50} of 0.02 mpk at both 0 and 24 h, respectively.

Interest in neurokinin-1 (NK_1) antagonists for treatment of CNS disorders greatly increased in the 1990s and resulted in the discovery of Emend® for the treatment of chemotherapy induced nausea and vomiting.[1] Considerable research has been done in the last decade on the physiological effects of substance P (SP) on the NK_1 receptor, which led to other potential medicinal uses for hNK_1 antagonists including the treatment of anxiety, depression, and urge urinary incontinence.[2]

Previously, we had disclosed a new structurally diverse class of 5,5-fused pyrrolidine-based NK_1 antagonists that displayed good binding affinity, bioavailability, and efficacy profiles.[3] However, these compounds proved to have low to moderate activity in the functional IP-1 assay.[3,4] The functional IP-1 assay,[5] measures the activity of substance P (at 10 μM concentrations) remaining in hNK_1 overexpressing CHO cells after pre-treatment with the antagonist at 100 nM. We find that those compounds with low substance P response remaining (<10% SPRR) display pseudo-irreversible blockade of the NK_1 receptor. In turn, we have found that this property (low SPRR) correlates well with receptor off-rates,[6] leading to lower plasma concentrations necessary for high central receptor occupancy in an in vivo rhesus receptor occupancy model.[1,17]

Therefore, compounds with poor functional IP-1 require higher drug levels to maintain high receptor occupancy (RO), and thus necessitates a higher initial dose of the compound. This, in turn, could reduce the safety margins due to the higher drug concentrations. It was desired to find compounds with greater functional IP-1 that in turn would lead to a higher RO at much lower drug concentrations and thereby increasing the margin of safety.

In an attempt to improve functional activity, it was proposed that a more rigid structure might be advantageous since substituents at the α and β positions of the cyclic lactam fused to the pyrrolidine core exhibited moderate increases in functional IP-1 activity.[4] A more rigid structure may also give the desired steric interactions which may enable it to bind more tightly to the receptor, in essence, improving the functional activity of NK_1 antagonism. In addition, other series of fused bicyclic tetrahydroquinoline NK_1 antagonists[7] and 5,5-fused pyrrolidines inspired our interest in fused tricyclic pyrrolidines. (Fig. 1) Thus, chemistry was developed to make fused tricyclic pyrrolidines in the hopes that this modification would retain NK_1 binding affinity while improving other physical–chemical and pharmacological properties.

Two types of tricyclic compounds were of interest to us: (1) the fusion of a pyrrolidine ring and (2) the fusion of a cyclopentyl ring with the ability for addition of substitutions on each ring. The

* Corresponding author. Tel.: +1 732 594 3867; fax: +1 732 594 5350.
E-mail address: greg_morriello@merck.com (G.J. Morriello).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.07.058

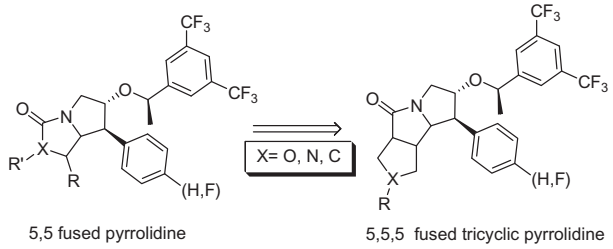


Figure 1. Tricyclic design derived from bicyclic scaffold.

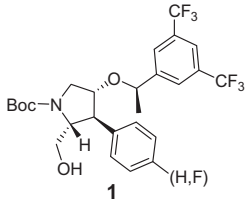


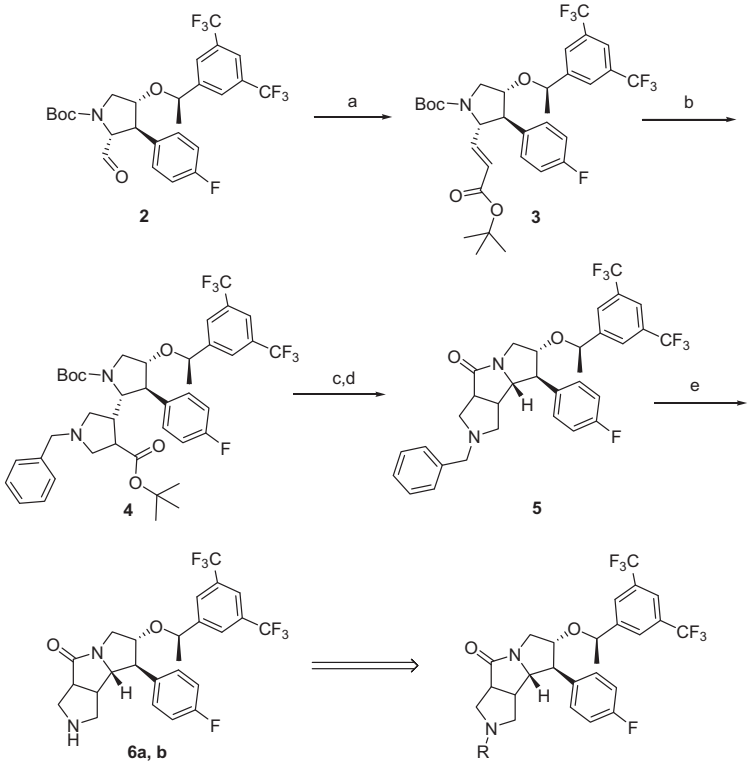
Figure 2. Enantiomerically pure starting material.

chemistry was first developed in which a pyrrolidine was incorporated as the third fused ring (Scheme 1).

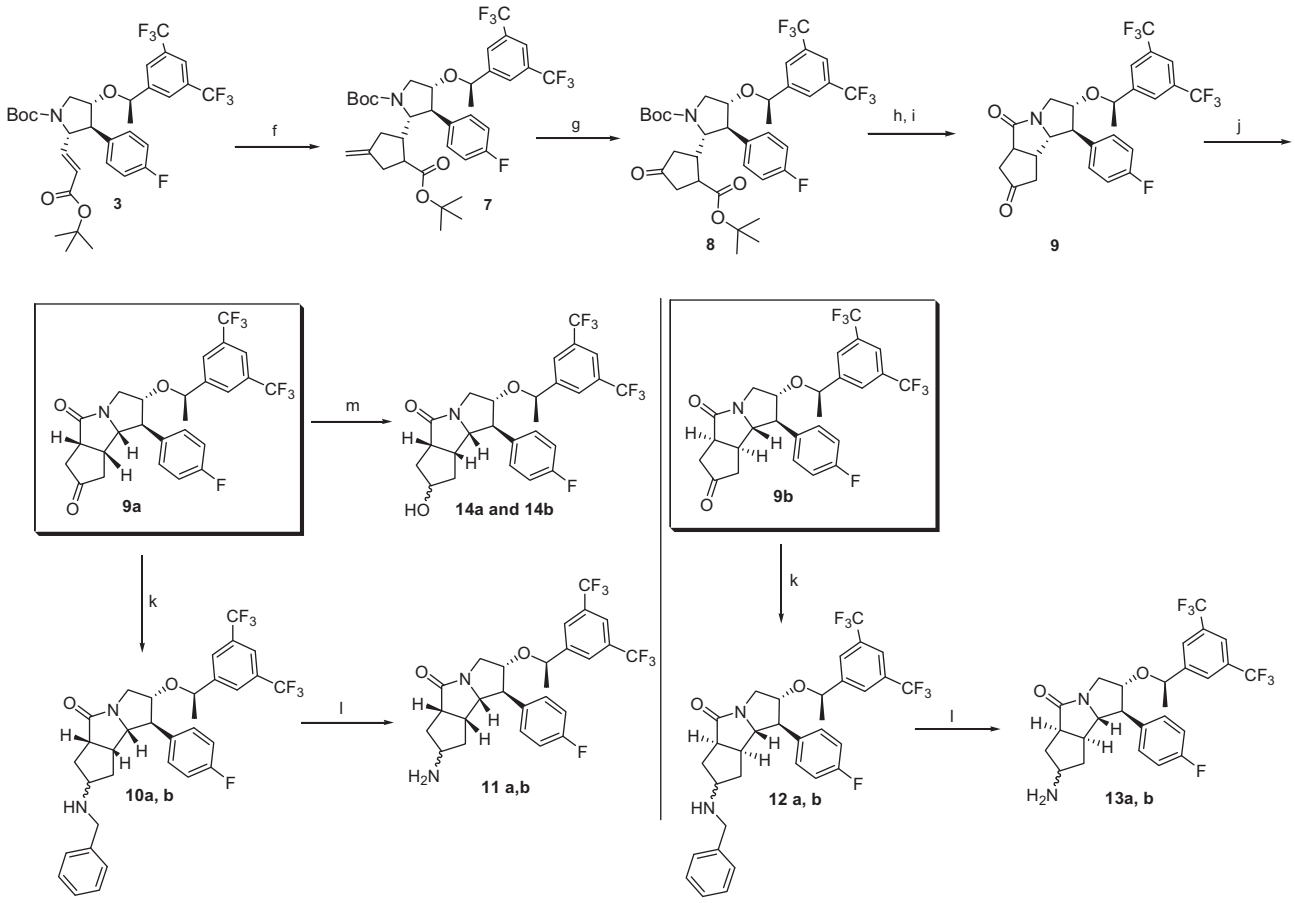
The more active enantiomerically pure alcohol (intermediate **1**) was already determined from previous chemistry in the synthesis of the 5,5-fused pyrrolidine compounds,[3] Figure 2. Therefore, simple chemical manipulations of this known intermediate **1** led to the desired fused tricyclic pyrrolidine core hNK_1 antagonists.

First, the alcohol **1** was oxidized to the aldehyde **2** via Swern oxidation.[8] This intermediate was then immediately used without purification in a Wittig reaction[9] to give the α,β-unsaturated ester **3**. Treatment of the unsaturated ester with *N*-benzyl-1-methoxy-*N*-[(trimethylsilyl)methyl]methanamine, in the presence of 0.4 M equiv of TFA overnight afforded the cyclic *N*-benzyl pyrrolidine **4**.[10] Simultaneous removal of the Boc and *t*-butyl ester with 4 N HCl in dioxane followed by treatment with EDC and DMAP in the presence of DIEA gave the penultimate tricyclic fused pyrrolidine lactam **5**. The benzyl group was then removed via hydrogenolysis to afford the 5,5,5-fused cis pyrrolidine lactam diastereomers **6a**,**b**.[11] Other analogs were synthesized via substitutions on the available nitrogen of the pyrrolidine ring.

The cyclopentyl lactam compounds were slightly more complicated to prepare: however, the α,β-unsaturated ester intermediate **3** from the synthesis of the pyrrolidine compounds could be utilized for the cyclopentyl series, by reaction with 2-[(trimethylsilyl)methyl]prop-2-en-1-yl acetate in the presence of palladium acetate and tri-isopropoxy-phosphite refluxed in toluene for 5 h[12] (Scheme 2). This afforded a cyclopentyl ring with an exo-double bond **7** that could be manipulated into different functional groups. Oxidation of the methylene with ozone followed by reduction of the ozonide with triphenylphosphine afforded the cyclopentyl ketone **8**. Then, using the conditions similar to the prior chemistry, acidic deprotection and EDC coupling of the amino acid gave the tricyclic fused cyclopentyl lactam **9**. Separation of the two cis cyclopentyl diastereomers (**9a**,**b**)[11] at this stage was accomplished via MPLC purification using a Biotage flash 40 + silica gel cartridge and eluting with a gradient of 10–60% ethyl acetate in hexane. The primary amino compounds were prepared via treatment of the ketones with sodium(triacetoxy)borohydride in the presence of benzyl amine and molecular sieves to afford the benzyl protected amines **10a**,**b** and **12a**,**b**. Then the resulting benzyl protected amines were hydrogenated to give **11a**,**b** and **13a**,**b** as a mixture of amino diastereomers. The alcohol compounds were also of

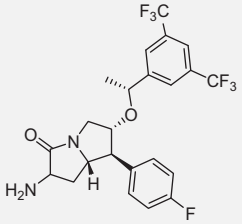
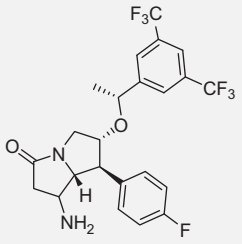


Scheme 1. Reagents and conditions: (a) (*t*-butoxycarbonylmethylene)triphenylphosphorane, DCM rt overnight (78%); (b) *N*-benzyl-1-methoxy-*N*-[(trimethylsilyl)methyl]methanamine, TFA, DCM, rt overnight (89%); (c) 4 N HCl in dioxane, 1 h quantitative; (d) EDC, DMAP, DIEA, DCM, rt, overnight (65%); (e) 10% palladium on carbon, H_2, MeOH, 1 equiv HCl, 3 h (82%).



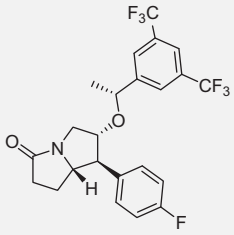
Scheme 2. Reagents and conditions: (f) 2-[(trimethylsilyl)methyl]prop-2-en-1-yl acetate, $Pd(OAc)_2$, $P(OiPr)_3$, toluene, reflux 5 h (74%); (g) ozone, DCM −78 °C followed by PPh_3 rt overnight (78%); (h) 4 N HCl in dioxane, 1 h. (quantitative); (i) EDC, DMAP, DIEA, DCM, rt, overnight (74% mixture of isomers); (j) separation of isomers by MPLC eluting with 100% ethyl acetate; (k) benzyl amine, $Na(OAc)_3BH$, DCM, 4 Å MS rt 16 h (59–70%); (l) 10% Pd/C, methanol, 1 equiv HCl under H_2 atm 2 h (82–94%); (m) $NaBH_4$, methanol, rt 5 h (54–61%).

Table 1
Sample structural activity relationship (SAR) from 5,5-fused bicyclic pyrrolidinones

Compound[a,4]	Structure [a]	hNK_1[b] IC_{50} (nM)/50% HS	IP-1[c] % SP remaining	hPXR induction[d] IC_{50} (μM) (%max)	Ion channels[d] IC_{50} (μM)	Gerbil foot-tapping[e] (GFT)
15		0.06/0.38	59	>25 (7)	Ikr: 6.5 Dz: 0.21 Na: 0.24	100% inh. at 3 mpk (24 h) ED_{50} = 0.61 mpk (24 h)
16		0.09/0.60	75	>25 (1)	Ikr: 9.5 Dz: 1.88 Na: 7.72	100% inh. at 3 mpk (24 h) ED_{50} = 0.92 mpk (24 h)

(*continued on next page*)

Table 1 (*continued*)

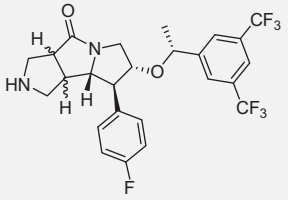
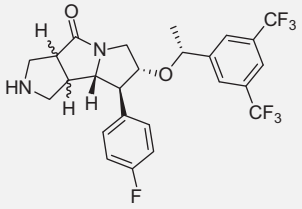
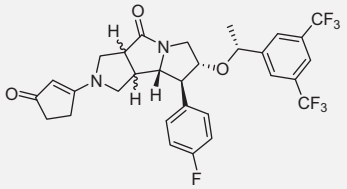
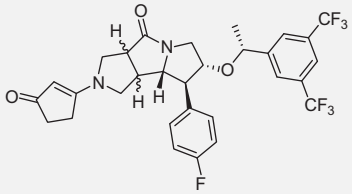
Compound[a,4]	Structure [a]	hNK_1 [b] IC_{50} (nM)/50% HS	IP-1[c]% SP remaining	hPXR induction[d] IC_{50} (μM) (%max)	Ion channels[d] IC_{50} (μM)	Gerbil foot-tapping[e] (GFT)
17		0.06/2.20	88	4.8 (50)	Ikr: 5.7 Dz: 1.58 Na: 1.75	100% inh. at 3 mpk (24 h) ED_{50} = 0.20 mpk (24 h)

[a] All compounds gave satisfactory ^1H NMR and mass spectral data.
[b] Displacement of [^{125}I]SP from the human hNK_1 receptor expressed in CHO cells. See also Ref. 13 and note 14.
[c] IP-1 assay: measures the response of inositol phosphate generation to substance P (10 mM) and is reported as the percentage of substance P remaining (SPRR) at 100 nM NK_1 antagonist concentration; Ref. 5.
[d] Ion channels: binding assay in which IC_{50}'s are calculated for both sodium and calcium (Dlz) channels. hPXR induction %max at 10 μM.
[e] Inhibition of GR73632 induced foot tapping in gerbils at concentration and time point given in the table (i.e., 3 mpk (24 h)); Ref. 15.

interest, and therefore, reduction of ketone **9a** to the corresponding alcohols **14a**,**b**[11] was completed upon treatment with sodium borohydride. Further manipulations of the desired isomer of the ketone intermediate (**9a**) with Grignard reagents offered another modification to the compounds as exhibited in the examples shown in Table 4.

Table 1 shows a subset of 5,5-fused pyrrolidine hNK_1 antagonists previously disclosed in the literature.[3,4] They proved to have excellent hNK_1 binding affinity along with moderate efficacy as exhibited in the GFT[15] assay. However, the major concern with these compounds was the high percent of substance P remaining in the functional IP-1 assay. High percentage numbers in this assay

Table 2
SAR of the tri-cyclic fused pyrroline/pyrrolidinone

Compound[a]	Structure[a]	hNK_1 [b] IC_{50} (nM)/50% HS	IP-1[c]% SP remaining	Ion channels[d] IC_{50} (μM)	Gerbil foot tapping[e] (GFT)
6a		1.5/15.0	46	n/a[f]	n/a[f]
6b		0.31/3.2	60	Ikr: 2.71 Dz: 0.31	12% inh. at 3 mpk (24 h)
18a[d]		0.17/1.9	11	Ikr: 1.43 Dz: 8.81	32% inh. at 3 mpk (24 h)
18b[e]		0.09/1.0	7	Ikr: 0.73 Dz: 4.81	92% inh. at 1 mpk (1 h) 74% inh. at 3 mpk (24 h)

[a] All compounds gave satisfactory mass spectral data. Stereochemistry was not assigned and isomers were labeled in order of retention (a: first isomer eluded, b: second isomer).
[b] Displacement of [^{125}I]SP from the human hNK_1 receptor expressed in CHO cells. See also Ref. 13 and note 14.
[c] IP-1 assay: measures the response of inositol phosphate generation to substance P (10 mM) and is reported as the percentage of substance P remaining (SPRR) at 100 nM NK_1 antagonist concentration; Ref. 5.
[d] Ion channels: binding assay in which IC_{50}'s are calculated for both sodium and calcium (Dlz) channels.
[e] Inhibition of GR73632 induced foot tapping in gerbils at concentration and time point given in the table (i.e., 3 mpk (24 h)); Ref. 15.
[f] n/a stands for no data available.

were associated with fast off-rates on the hNK_1 receptor which correlated to the need for much higher dosing levels for good duration of pharmodynamic (PD) activity.[16]

This is illustrated by compound **16** with a measured receptor occupancy off-rate of less than 100 min. To maintain good receptor occupancy, the dose of drug would have to be rather high which would drastically reduce safety margins. As can also be seen in Table 1, α (**15**) and β (**16**) substitutions on the fused bicyclic series did give slightly better functional IP numbers. As we extended the substitution out, the numbers seem to improve.[4] Thus, we decided to explore the 5,5,5-fused tricyclic pyrrolidines in the hope of seeing improvement in the functional activity of these hNK_1 antagonist to less than 10% remaining.

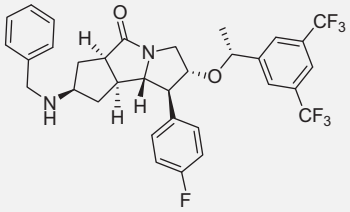
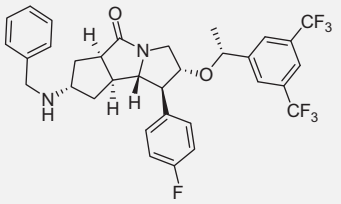
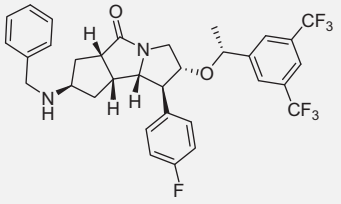
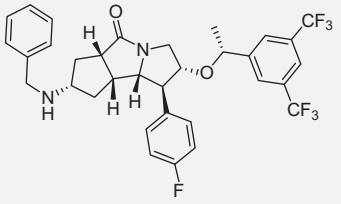
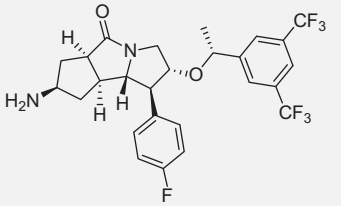
The first series of compounds, shown in Table 2, contained the fused pyrrolidine ring as the third fused ring. During formation of the pyrrolidine ring, two diastereomers were formed and separated during the synthesis of pyrrolidine compound **6**. Compounds **6a** and **6b** displayed slightly increased IP-1 functional activity (60% and 46% SP remaining, respectively). The addition of a substituent, such as the vinylogous amide moiety, greatly improved results in the functional antagonist IP-1 assay. In vivo efficacy for compound (**18b**) was 74% inh. at 3 mpk seen at 24 h, a promising result; however, loss of IKr selectivity proved to be a liability for this series of compounds. Having demonstrated that an additional ring substantially increased the functional receptor blockade, exploration of the substituted cyclopentane ring was deemed important to reduce Dlz binding affinity.

Table 3 contains the data for the key compounds synthesized in the cyclopentane 5,5,5-fused tricyclic hNK_1 antagonist series. As can be seen, the conformational differences of the diastereomers had a great impact on the observed functional IP-1 activity.

The desired (more active) conformation greatly enhanced functional activity exhibiting less than 5% substance P remaining. In the case of the amino substituted compounds, all four diastereomers were synthesized. After inspection of the intrinsic binding data, only the diastereomers of the hydroxyl compounds formed from intermediate **9a** were selected to be assayed for hNK_1 binding affinity.

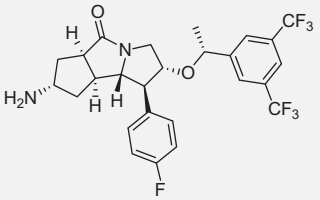
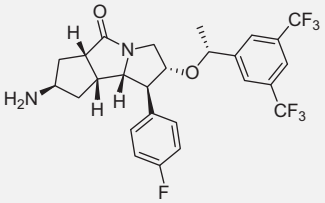
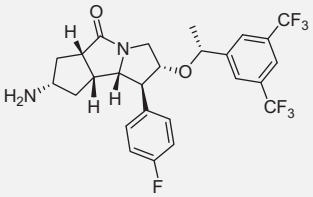
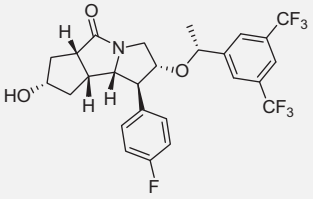
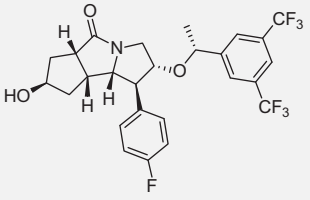
Analogs **12a** and **12b**, in which the fused ring was in the less active stereochemical series, had reasonable intrinsic binding activ-

Table 3
SAR of the tri-cyclic fused substituted cyclopentane/pyrrolidinone

Compound[a]	Structure[a,g]	hNK_1[b] IC_{50} (nM)/50% HS	IP-1[c] % SP remaining	PXR Induction IC_{50} (μM) (%max)	Ion channels[d] IC_{50} (μM)	Gerbil foot tapping[e] (GFT)
12a		1.2/13.0	94	n/a[f]	n/a[f]	n/a[f]
12b		0.14/2.3	58	n/a[f]	n/a[f]	81% inh. at 1 mpk (1 h) 6% inh. at 3 mpk (24 h)
10a		0.14/1.3	4	>25 (0)	Ikr: 0.30 Dz: 0.21 Na: 0.21	94% inh. at 3 mpk (24 h)
10b		0.17/1.8	2	>25 (0)	Ikr: 0.28 Dz: 0.14 Na: n/a	100% inh. at 3 mpk (24 h) ED_{50} = 0.47 mpk (24 h)
13a		1.5 /47.0	93	n/a	n/a	n/a

(*continued on next page*)

Table 3 (*continued*)

Compound[a]	Structure[a,g]	hNK_1[b] IC_{50} (nM)/50% HS	IP-1[c]% SP remaining	PXR Induction IC_{50} (μM) (%max)	Ion channels[d] IC_{50} (μM)	Gerbil foot tapping[e] (GFT)
13b		0.66/13.0	61	n/a	n/a	n/a
11a		0.11/1.0	10	>25 (0)	Ikr: 1.73 Dz: 0.59 Na: 0.52	100% inh. at 3 mpk (24 h) ED_{50} = 1.33 mpk (24 h)
11b		0.09/1.0	6	>25 (0)	Ikr: 0.99 Dz: 1.23 Na: 0.71	91% inh. at 3 mpk (24 h)
14a		0.06/0.77	3	4.5 (65)	n/a[f]	100% inh. at 1 mpk (1 h) 100% inh. at 3 mpk (24 h)
14b		0.08/1.7	35	n/a[f]	n/a[f]	n/a[f]

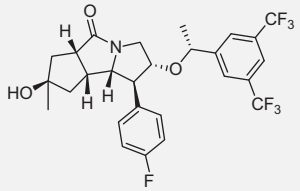
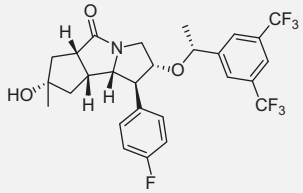
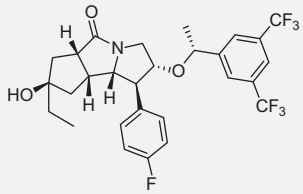
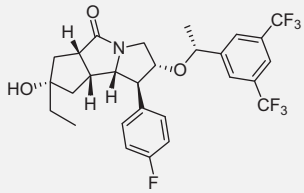
[a] All compounds gave satisfactory ^1H NMR and mass spectral data.
[b] Displacement of [^{125}I]SP from the human hNK_1 receptor expressed in CHO cells. See also Ref. 13 and note 14.
[c] IP-1 assay: measures the response of inositol phosphate generation to substance P (10 mM) and is reported as the percentage of substance P remaining (SPRR) at 100 nM NK_1 antagonist concentration; Ref. 5.
[d] Ion channels: binding assay in which IC_{50}'s are calculated for both sodium and calcium (Dlz) channels. hPXR induction %max at 10 μM.
[e] Inhibition of GR73632 induced foot tapping in gerbils at concentration and time point given in the table (i.e., 3 mpk (24 h)); Ref. 15.
[f] n/a stands for no data available.
[g] Stereochemistry of the amino substituent was not confirmed and are drawn on the assumption that they follow the same stereochemistry as their related hydroxyl substituted compounds. (i.e., **14a** known stereochemistry relative to **11b** since they are the more potent diastereomers in their related series).

ity, however, they were shown to be ineffective at blocking the effects of substance P in the IP-1 assay with 58–94% substance P remaining. Analog **12b** also proved to have a short duration of activity in the GFT assay with good response of 81% inh. at 1 mpk at 1 h but only 6% inh. at 3 mpk at the 24 h time point. As for the diastereomers, analogs **10a** and **10b** had similar, if not slightly better, binding affinities and were able to block the substance P response by greater than 95% (4% and 2% SPRR) at 100 nM. This also correlated with excellent efficacy and duration of activity with 100% inh. at 3 mpk at 24 h with an IC_{50} of 0.47 mpk. This compound demonstrated rapid brain penetration with a good duration of action in blocking the agonist induced foot tapping response in the gerbil model. Although, the ion channel selectivity was greatly compromised with both IKr and calcium channel (Dlz) activity of less than 300 nM.

Analogs **11a** and **11b** IKr selectivity had significantly improved along with their sodium and calcium channel selectivity. However, the in vivo efficacy was disappointing and, therefore, we moved on to examining the hydroxyl substitution.

Since we had now determined the desired, more active diastereomer from the amino compounds, the corresponding ketone intermediate (**9a**) was taken on to the hydroxyl analogs via simple sodium borohydride reduction to give a mixture of two isomers (**14a** and **14b**) which were separated via chiral HPLC purification on a ChiralCel OD column. The two analogs exhibited excellent intrinsic binding activity with minimal serum shifts. The functional IP-1 assay distinguished the superior isomer (**14a**) with 3% substance P remaining (as compared to **14b** with 35%). The GFT proved to be extremely promising with 100% inhibition of the foot-tapping response at both 1 h (1 mpk dose) and 24 h (3 mpk dose) time

Table 4
SAR of the Grignard addition products

Compound	Structure[a]	hNK_1[b] IC_{50} (nM)/50% HS	IP-1[c] % SP remaining	hPXR induction IC_{50} (μM) (%max)	Ion channels[d] IC_{50} (μM)	Gerbil foot tapping [e](GFT) IC_{50} (μM)
19		0.066/1.20	24	n/a[f]	n/a[f]	n/a[f]
20		0.061/0.70	3	8.4 (37)	Ikr: 2.47 Dz: >10 Na: >10	100% inh. at 3 mpk (24 h) ED_{50} = 0.02 mpk (24 h)
21		0.21/2.3	31	n/a[f]	n/a[f]	n/a[f]
22		0.16/1.7	4	3.3 (51)	Ikr: 1.77 Dz: 8.42 Na: n/a	100% inh. at 3 mpk (24 h) ED_{50} = 0.06 mpk (24 h)

[a] All compounds gave satisfactory ^1H NMR and mass spectral data.
[b] Displacement of [^{125}I]SP from the human hNK_1 receptor expressed in CHO cells. See also Ref. 13 and note 14.
[c] IP-1 assay: measures the response of inositol phosphate generation to substance P (10 mM) and is reported as the percentage of substance P remaining (SPRR) at 100 nM NK_1 antagonist concentration; Ref. 5.
[d] Ion channels: binding assay in which IC_{50}'s are calculated for both sodium and calcium (Dlz) channels. hPXR induction %max at 10 μM.
[e] Inhibition of GR73632 induced foot tapping in gerbils at concentration and time point given in the table (i.e., 3 mpk (24 h)); Ref. 15.
[f] n/a stands for no data available.

points. Unfortunately, the off-target activity proved to be a concern with the hPXR inhibition at IC_{50} of 4.5 μM with 65% inhibition seen at 10 μM concentration.

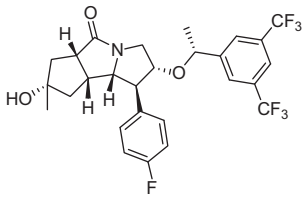
As stated previously, a Grignard addition to the ketone gave another set of analogs that could be examined in the functional IP-1 assay. Grignard addition to the desired ketone intermediate (**9a**) with both methyl and ethyl magnesium bromide was carried out to give the four geminal substituted analogs shown in Table 4. The two sets of diastereomers **19**, **20** and **21**, **22** were equipotent in terms of the receptor binding affinity, however, analogs **20** and **22** demonstrated superior functional receptor blockade with 3% and 4% substance P remaining, respectively. Both compounds proved to be extremely efficacious in the GFT assay with ID_{50}'s of 0.02 and 0.06 mpk at 24 h. Ion channels for both were much improved versus the amino compounds along with a minimal potency shift in the presence of 50% human serum. The difference in the two finally became apparent with the measurement of hPXR induction. The ethyl substituted compound **22** had twice the potency of the methyl substituted compound **20** with an IC_{50} of 3.3 versus 8.4 μM, respectively. Thus, compound **22**, with intrinsic hNK1 activity of 0.16 nM, had sevenfold worst off-target selectivity on hPXR than compound **20**, with 0.06 nM hNK1 activity. Therefore, compound **20** was selected for further follow-up assays to determine its viability as a drug candidate.

Table 5 summarizes the activity and p*K* profile of the gem substituted hydroxyl, methyl analog **20**. The cross species intrinsic binding affinities in the presence of 50% serum were surprisingly equipotent with IC_{50}'s still less than 2 nM. The functional IP was titrated down to 1 nM with a receptor blockade of 64% (36% SPRR).

Microsomal stability was excellent across species with greater than 90% parent remaining after a 60 min incubation with microsomes. The ancillary activity was minimal and the compound's brain/plasma ratio was 0.5 in the gerbil PK/PD study. Looking at the p*K* values in rat, the clearance was very low and the compound had an excellent half life of 14.6 h with bioavailability of ~88%. The dog p*K* also proved to have a particularly long half-life of 58 h. The compound proved to have long duration of activity in vivo and the p*K* profile seemed to justify this result with long half-lives and low clearance in two species.

Thus, we have presented a series of 5,5,5-tricyclic fused pyrrolidines that displayed excellent hNK1 intrinsic binding affinity and good functional IP-1 activities with the better diastereomers having less than 5% substance P remaining. This series clearly showed much improvement in functional activity versus the prior 5,5-fused compounds. Compound **20** in particular exhibited drug-like pharmacokinetics with reduced potential for inhibition or induction of the CYP enzymes and good off-target activity. The p*K* profile across species was also extremely promising.

Table 5
Lead compound of tricyclic hNK_1 antagonists



IC_{50}: 0.06 nM		
IC_{50} + 50% serum:	Ancillary activity:	
Human: 0.7 nM	CYP inhibition	
Dog: 1.5 nM	2D6: 17.38 μM	
Rhesus: 0.4 nM	3A4: 22.68 μM	
Rat: 0.4 nM	2C9: 43.12 μM	
Gerbil: 1.9 nM	hPXR: 3.77 μM (38%)	
IP-1: 2% SP remaining [*] (36%SP at 1 nM dose)		
GFT:	Gerbil PK/PD iv study:	
ID_{50} = 0.02 mg/kg (1 h)	IC_{50} = 2.2 nM (1 h brain)	
ID_{50} = 0.02 mg/kg (24 h)	IC_{50} = 4.3 nM (1 h plasma)	
Microsomal stability % remaining (60 min)		
Dog: 90%		
Human: 96%		
Rat: 96%		
Rhesus: 99%		
Pharmocokinetics		
	Rat	Dog
Clp (ml/min/kg)	3.24	0.50
$t_{1/2}$: (h)	14.60	58.02
MRT: (h)	4.67	n/a
V_d: (L/Kg)	4.03	
F%	88.83	n/a

Acknowledgments

The authors thank George Doss for the NMR characterizations of compounds **1**, **9a**,**9b, 14a**, **14b**, **20**, and Paul Finke for his assistance in the preparation of this Letter.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.07.058.

References and notes

1. (a) Hale, J. J.; Mills, S. G.; MacCoss, M.; Shah, S. K.; Qi, H.; Mathre, D. J.; Cascieri, M. A.; Sadowski, S.; Strader, C. D.; MacIntyre, D. E.; Metzger, J. M. *J. Med. Chem.* **1996**, *39*, 1760; (b) Campos, D.; Pereira, J. R.; Reinhardt, R. R.; Carracedo, C.; Poli, S.; Vogel, C., et al *J. Clin. Oncol.* **2001**, *19*, 1759; (c) Poli-Bigelli, S.; Rodrigues-Pereira, J.; Carides, A. D.; Ma, G. J.; Eldridge, K.; Hipple, A., et al *Cancer* **2003**, *97*, 3090; (d) Gale, J. D.; O'Neill, B. T.; Humphrey, J. M. *Exp. Opin. Ther. Pat.* **2001**, *11*, 1837.
2. (a) Stahl, S. M. *J. Clin. Psychiatry [Brainstorms]* **1990**, *60*, 77; (b) Quatara, L.; Maggi, C. A. *Neuropeptide* **1998**, *32*, 1; (c) Kramer, M. S.; Cutler, N.; Feighner, J.; Shrivastava, R.; Carmen, J.; Sramek, J. J.; Reines, S. A.; Liu, G.; Snavely, D.; Wyatt-Knowles, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Swain, C. J.; Harrison, T.; Hill, R. G.; Hefto, F.; Scolnick, E. M.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Williams, A. R.; Hewson, L.; Smith, D.; Carlson, E. J.; Hargreaves, R. J.; Rupniak, N. M. J. *Science* **1998**, *22*, 1640; (d) Rupniak, N. M. J.; Kramer, M. S. *Trends Pharmocol. Sci.* **1999**, *20*, 485; (e) Green, S. A.; Alon, A.; Ianus, J.; McNaughton, K. S.; Tozzi, C. A.; Reiss, T. F. *J. Urol.* **2006**, *176*, 2535.
3. Morriello, G. J.; DeVita, R. J.; Mills, S. G.; Young, J. R.; Lin, P.; Doss, G.; Chicchi, G. G.; DeMartino, J.; Kurzt, M. M.; Tsao, K.-L. C.; Carlson, E.; Townson, K.; Wheeldon, A.; Boyce, S.; Collinson, N.; Rupniak, N.; Moore, S. *Bioorg. Med. Chem.* **2008**, *16 5*, 2156.
4. Morriello, G. J.; DeVita, R. J.; Mills, S. G.; Young, J. R.; Lin, P.; Doss, G.; Chicchi, G. G.; DeMartino, J.; Kurzt, M. M.; Tsao, K.-L. C.; Carlson, E.; Townson, K.; Wheeldon, A.; Boyce, S.; Collinson, N.; Rupniak, N.; Moore, S. *Bioorg. Med Chem. Lett.* **2010**.
5. CHO cells (2.5×10^4) expressing recombinant human NK_1 receptors were plated in 96-well tissue culture dishes and left overnight. This was then followed by prelabeling overnight with [H^3]-myo-inositol (10–25 Ci/mmol) in inositol-free medium with 0.02% BSA at 37 °C. The cells were then incubated with 10 mM LiCl in Hepes-buffered inositol-free (DMEM) medium with 0.02% BSA for 15 min. Antagonists (100 nM) or anhydrous DMSO were added for 30 min before substance P (up to 10 μM) was added for another 30 min. The reaction was terminated by removal of the medium and addition of formic acid. The supernatant was aged for 60 min at 22 °C. Lysates (15 μL) were incubated with 1 mg RNA Binding Yittrium Silicate (2–5 μm) SPA beads (Amersham) in Optiplates with shaking for 2 h. [H^3]-inositol phosphate generation was quantitated on a Packard Topcount and the data were analyzed using Prism (GraphPad).
6. Young, J. R.; Eid, R.; Turner, C.; DeVita, R. J.; Kurtz, M. M.; Tsao, K.-L. C.; Chicchi, G. G.; Wheeldon, A.; Carlson, E.; Mills, S. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5310.
7. (a) Devita, R.; Mills, S. G.; Jiang, J.; et al. World Patent 2006/060344, 2006.; (b) Devita, R.; Mills, S. G.; Jiang, J.; et al. World Patent 2006/060346, 2006.
8. (a) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480; (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, *3*, 165.
9. (a) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44; (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *7*, 1733.
10. (a) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 2762; (b) Luci, D. K.; Santulli, R. J.; Gauthier, D. A.; Tounge, B. A.; Ghosh, S.; Proost, J. C.; Kinney, W. A.; De Corte, B.; Galemmo, R. A.; Lewis, J. M.; Dorsch, W. E.; Wagaman, M. W.; Daimiano, B. P.; Maryanoff, B. E. *Heterocycles* **2004**, *62*, 543.
11. Compounds **1**, **6a**, **6b**, **9a**, **9b**, **14a**, and **14b** relative stereochemistry was assigned via NOEsy, HMQC, ^{1}H NMR, and ^{13}C NMR. Isomers were compared to one another and assignments were based on the observation (or absence) of NOE signal in relation to the surrounding hydrogens of known stereochemistry.
12. (a) Cossy, J.; Belotti, D.; Pete, J. P. *Tetrahedron Lett.* **1987**, *28*, 4547; (b) Trost, B. M.; Crawley, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 9328.
13. Cascieri, M. A.; Ber, E.; Fong, T. M.; Sadowski, S.; Bansal, A.; Swain, C. J.; Seward, E. M.; Frances, B.; Burns, D.; Strader, C. D. *Mol. Pharmacol.* **1992**, *42*, 458.
14. All values represent the average of 2–6 independent experiments. Variability between experiments was typically less than twofold.
15. (a) Rupniak, N. M. J.; Williams, A. R. *Eur. J. Pharmcol.* **1994**, *265*, 179; (b) Rupniac, N. M. J.; Tattersall, F. D.; Williams, A. R.; Rycroft, W.; Carlson, E. J.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Seward, E.; Huscroft, I.; Owen, S.; Swain, C. J.; Hill, R. G.; Hargreaves, R. J. *Eur. J. Pharmcol.* **1997**, *326*, 201.
16. Lin, P.; Chang, L.; DeVita, R. J.; Young, J. R.; Eid, R.; Tong, X.; Zheng, S.; Ball, R. G.; Tsou, N. N.; Chicchi, G.; Kurtz, M.; Tsao, K.-L. C.; Wheeldon, A.; Carlson, E. J.; Eng, W.; Burns, D. H.; Hargreaves, R. J.; Mills, S. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5191.
17. Jiang, J.; Bunda, J. L.; Doss, G. A.; Chicchi, G. G.; Kurtz, M. M.; Tsao, K.-L. C.; Tong, X.; Zheng, S.; Upthagrove, A.; Samuel, K.; Tschirret-Guth, R.; Kumar, S.; Wheeldon, A.; Carlson, E. J.; Hargreaves, R.; Burns, D.; Hamill, T.; Ryan, C.; Krause, S. M.; End, W.; Devita, R. J.; Mills, S. G. *J. Med. Chem.* **2009**, *52*, 3039.