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Substituted fused bicyclic pyrrolizinones as potent, orally bioavailable hNK_1 antagonists

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ABSTRACT

Previous work on human NK_1 (hNK_1) antagonists in which the core of the structure is a 5,5-fused pyrrolizinone has been disclosed. The structural–activity-relationship studies on simple α- and β-substituted compounds of this series provided several potent and bioavailable hNK_1 antagonists that displayed excellent brain penetration as observed by their good efficacy in the gerbil foot-tapping (GFT) model assay. Several of these compounds exhibited 100% inhibition of the foot-tapping response at 0.1 and 24 h with ID_{50}'s of less than 1 mpk. One particular α-substituted compound (**2b**) had an excellent pharmacokinetic profile across preclinical species with reasonable in vivo functional activity and minimal ancillary activity.

In the 1990s several pharmaceutical companies embarked on research to discover non-peptidic hNK_1 antagonists as a possible treatment for CNS disorders.[1] Since then, extensive research has produced many patents and publications, along with the first approved drug, Emend®, for treatment of chemo-induced emesis and PONV.[2,3] Considerable research on the physiological effects of substance P (SP) on the NK_1 receptor has led to other potential medicinal uses for hNK_1 antagonists including the treatment of anxiety,[4] depression,[5] urge urinary incontinence,[6] and possibly alcoholism.[7]

Previously, we have disclosed the unsubstituted pyrrolizinone (**B**), and shown that the compound had a superior brain penetration profile compared to several of the substituted pyrrolidine compounds that preceded it.[8] However, issues with hPXR and CYP3A4 activity precluded any further studies with this compound.[8] Therefore, we chose to examine the effect on these off-target activities by the addition of small polar substituents to the lactam ring. In this manuscript, we describe the SAR on this novel substituted 5,5-fused pyrrolizinone design as potent hNK_1 antagonists (see Fig. 1).

Synthesis of hydroxyl and amino substitutents on both the α- and β-position of the lactam ring proved to significantly change the PK/PD profile of these compounds. Differences in their ancillary activities were the main distinction between the analogs.

α-Substituted analogs were directly synthesized from the 5,5-fused pyrrolizinone **1** (Scheme 1). Oxidation of the enolate, formed in situ with LHMDS, of lactam **1** with Vedejs's reagent,[9] MoOPh, afforded a 1:1 mixture of hydroxyl substituted analogs **2a**, **2b**. This mixture was then treated with mesylchloride in the presence of triethylamine to give the intermediate mesylate. Displacement of the mesyl moiety with sodium azide afforded the azido compound which was reduced under Staudinger[10] conditions to give the primary amines **3a**, **3b**. To produce the geminal substituted compounds, the hydroxyl intermediate **2a** or **2b** was oxidized to the ketone **4** with the Dess–Martin reagent[11] and treated with methyl magnesium bromide to give the hydroxyl, methyl geminally di-substituted pyrrolizinone **5a**, **5b**.

Scheme 2 describes the synthesis of the β-amino mono- and geminally substituted analogs. We selected the (R)-2-hydroxymethyl substituted pyrrolidine intermediate[8] (**6**) as a suitable starting point since it can be easily manipulated to other functional groups.

Oxidation to the aldehyde **7** was first performed to give an intermediate viable for mono-β-substitutions. The aldehyde was

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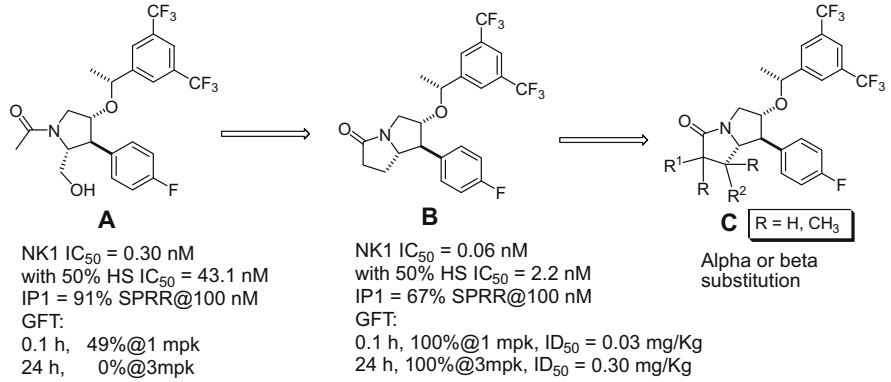
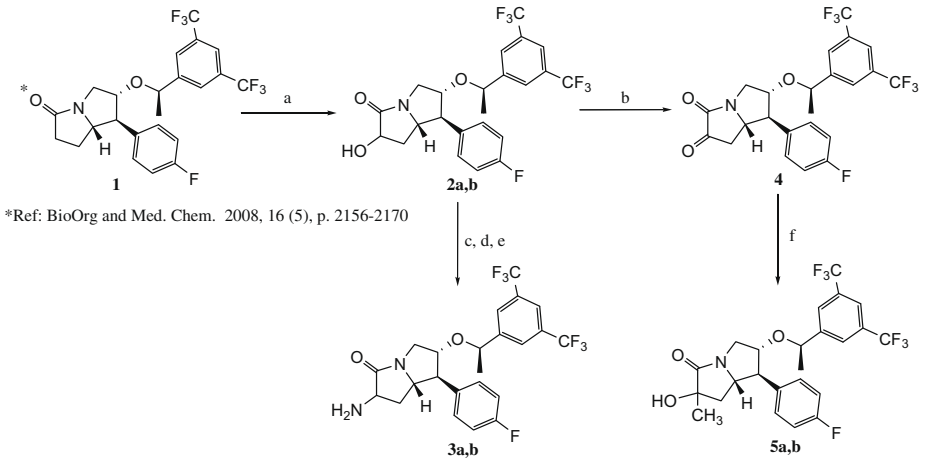
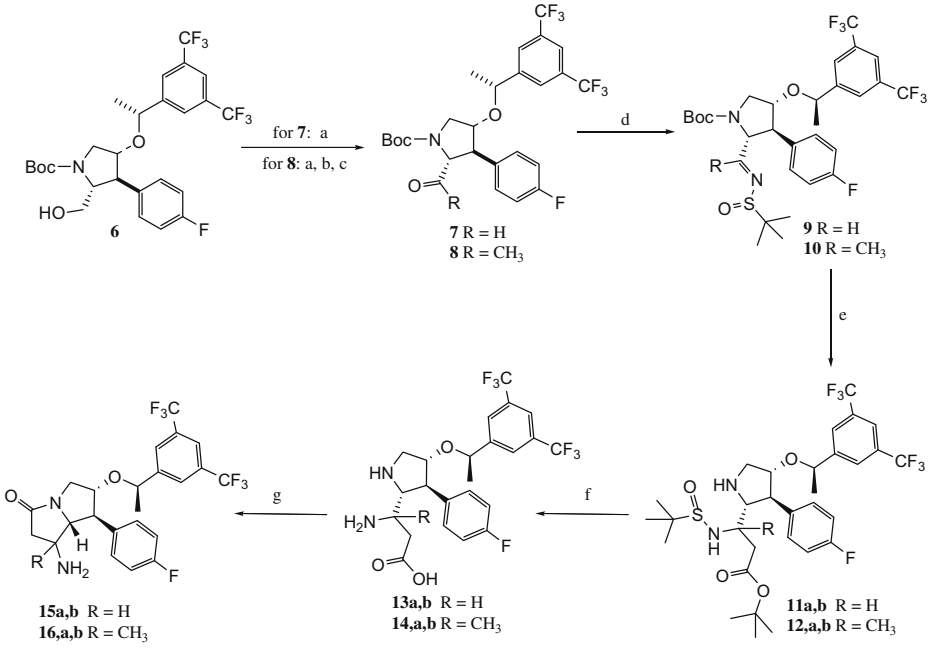


Figure 1. Alpha- and/or beta-substituted compounds derived from bicyclic scaffold.

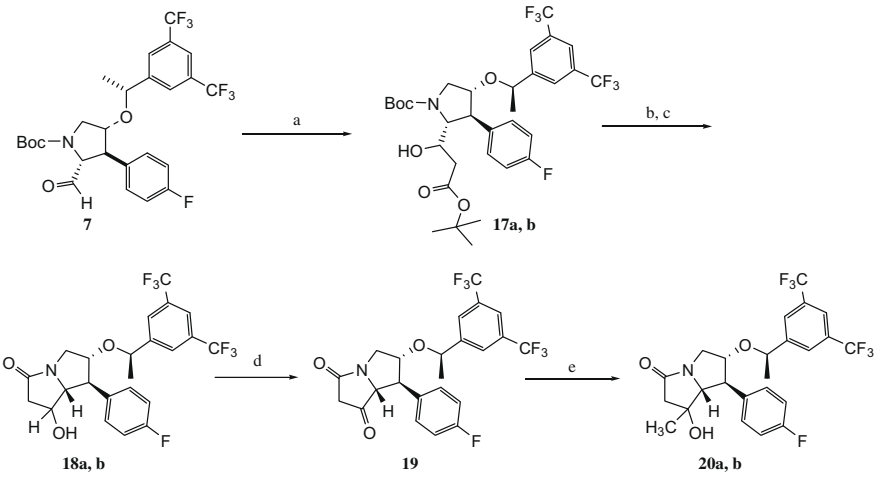


Scheme 1. Synthesis of the α-substituted analogs. Reagents and conditions: (a) MoOPh, LHMDS, THF, overnight, 0 °C to rt (1:1 mixture diastereomers, 78%); (b) 15% soln of Dess–Martin reagent in DCM, rt, 3 h (89%); (c) mesylchloride, TEA, THF, rt, 5 h (82%); (d) NaN_3, DMF, 60 °C, overnight (65%); (e) PPh_3, THF/water, rt, overnight (88%); and (f) 1.0 M methylmagnesium bromide in THF, −20 °C (1:1 mixture diastereomers, 72%).



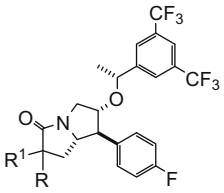
Scheme 2. Synthesis of β-amino substituted analogs. Reagents and conditions: (a) 15% soln of Dess–Martin reagent in DCM, rt, 3 h; (b) 3.0 M soln of MeMgCl in THF, −78 °C to rt, 3 h; (c) 15% soln of Dess–Martin reagent in DCM, rt, overnight; (d) R-(+)-2-methyl-2-sulfinimide, Titanium(IV) ethoxide, THF, reflux, overnight (71% over two steps); (e) *tert*-butyl acetate, NaHMDS, ether, −78 °C, 3 h, (2:1 mixture diastereomers, 63%); (f) 4.0 N HCl in dioxane, 2 h, (quantitative); and (g) EDC, DMAP, DIEA, DCM overnight, rt (54%).

then converted to the acetate **8** via methyl Grignard addition followed by oxidation of the intermediate secondary alcohol to the ketone via Dess Martin reagent. This sequence provides a second intermediate for geminal β-substituted pyrrolizinones. Thus, the Ellman[12] sulfinimide **9** from the aldehyde **7** was prepared via treatment with R-(+)-2-methyl-2-sulfinimide in the presence of a dehydrating agent such as $Ti(OEt)_4$. The sulfinimde **9** was then directly alkylated with the sodium anion of *tert*-butyl acetate,



Scheme 3. Synthesis of β-hydroxyl-substituted analogs. Reagents and conditions: (a) *tert*-butyl acetate, NaHMDS, ether, −78 °C, 3 h (3:1 mixture diastereomers, 77%); (b) 4.0 N HCl in dioxane, 2 h, (quantitative); (c) EDC, DMAP, DIEA, DCM overnight, rt (84%); (d) 15% soln of Dess–Martin reagent in DCM, rt, 3 h. (66%); and (e) 1.0 M methylmagesium bromide in THF, −20 °C, (1:1 mixture diastereomers, 55%).

Table 1
α-Substituted 5,5-fused pyrrolizinones[15]



Compound	R^1		R	NK1 IC_{50} (nM)[a]	+50 %HS IC_{50} (nM)[a]	IP-I[b] %	Gerbil FT[c] %Inhibition	Ion channels[e] Diltiazem sodium IC_{50} (nM)	
2a	·OH	Fast isomer	H	0.14	5.6	90	95[c]	8063	5138
2b	·OH	Slow isomer	H	0.08	0.91	60	100[c]	9400	4364
3a	·NH_2	Fast isomer	H	0.27	2.1	92	99c	98	2822
3b	·NH_2	Slow isomer	H	0.06	0.38	59	100[c]	214	239
5a	·OH	Fast isomer	CH_3	0.09	2.5	70	98[c]	1870	4822
5b	·OH	Slow isomer	CH_3	0.04	0.80	45	100[c]	2177	3198
21a	·N	Fast isomer	H	0.07	1.90	81	n/a	>10,000	>10,000
21b	·N	Slow isomer	H	0.05	1.80	74	0[d]	>10,000	5317
	Best set of compounds with substitutions shown below (better HS and IP-1 activity)								
22	N N H		H	0.06	0.90	55	92[c]	598	1466
23	N N=N NH N(CH3)2		H	0.13	1.4	40	88[d]	301	2412

[a] Displacement of [^{125}I] labeled substance P from the cloned hNK_1 receptor expressed in CHO cells. Data are mean (n = 3).
[b] IP-I assay: it measures the response of inositol phosphate generation to substance P (10 μM) and is reported as the percent of substance P response remaining (SPRR) at 100 nM NK1 antagonist concentration.
[c] Inhibition of GR73632 induced foot tapping in gerbils at 3 mg/kg iv at 24 h.
[d] Inhibition of GR73632 induced foot tapping in gerbils at 1 mg/kg iv at 1 h.
[e] Ion channels: binding assay in which IC_{50}'s are calculated for both sodium and calcium (Dlz) channels.

formed in situ by treatment with sodium hexamethyldisilazide, to give **11a**, **11b** as a 2:1 mixture of diastereomers. Deprotection with HCl followed by standard EDC coupling afforded the mono-amino β-substituted compounds **15a** and **15b**. These were separated via Gilson HPLC using a ChiralCel AD column eluting with 40% IPA in heptane. The compounds were labeled 'fast and slow eluting isomers' according to the order of separation since their absolute stereochemical configurations remained unknown. The same procedures as described above were also used on the ketone derivative **8** to form the geminal amino, methyl β-substituted compounds **16a**, **16b**,[13] with similar yields.

The related β-hydroxylated compounds were synthesized in a similar manner, although, the aldehyde **7** was directly alkylated with tert butyl acetate to afford **17a** and **17b** as a 3:1 mixture of diastereomers (Scheme 3). Using the same procedures described in the prior synthesis, the mono-β-hydroxyl substituted compounds **18a** and **b** were then prepared. To acquire the disubstituted analogs, intermediate **18a** or **b** was oxidized via the Dess Martin reagent to afford ketone **19** which was immediately treated with methyl magnesium bromide to afford analogs **20a**, and **b**. The ketone **19** started to decompose upon sitting at room temperature within minutes, therefore the treatment with Grignard reagent had to be performed immediately.

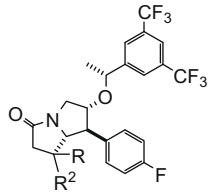
Lastly, some other nitrogen analogs were obtained via the amine substituted compounds **3**, **15**, and **16** by either reductive amination with heterocycle containing aldehydes or formation of the heterocycle 1,2,4-triazole via treatment with *N*,*N*-dimethylformamide azine in the presence of *p*-TSA refluxed in toluene overnight.[14] All compounds are shown in the two tables that follow.

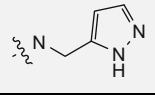
Table 1 summarizes the biological results for the α-substituted compounds. All of the compounds exhibit excellent in vitro binding potency with subnanomolar binding affinities to the hNK_1 receptor. Their human serum shift affinities were variable but still show low nanomolar activity.

Several compounds stood out due to their off target ion channel selectivity which showed considerable variability. Comparing the hydroxyl and amino compounds, it was apparent that the amino substituent caused a significant increase in the sodium and calcium channel binding, therefore, substantially decreasing their off target selectivity. For example, the amino compounds **3a**, **3b** exhibited a 40–100-fold increase in calcium channel binding along with a 3–5-fold increase against the sodium channel versus the hydroxyl compounds **2a** and **2b**. In an attempt to counteract this problem, basic heterocycles were introduced via reductive amination to the primary amine or direct formation onto the amine as in compounds **21a** and **21b**. This modification improved the off target selectivity, profoundly with compounds **21a** and **21b**, however, it also resulted in the loss of brain penetrant properties as seen in the gerbil foot-tapping[16] (GFT) assay data. Compound **21a** proved to have no GFT response when dosed in the gerbils, while both compounds **22** and **23** had decreased inhibition shown by their inability to completely block the foot-tapping response. Several other compounds were synthesized via reductive amination, however, compounds **22** and **23** were selected as representatives of the series since they proved to have the best in vitro binding activity along with adequate GFT foot-tapping inhibition.

Since the hydroxyl substituent proved to have superior off target ion selectivity versus the amine compounds with comparable

Table 2
β-Substituted 5,5-fused pyrrolizinones[15]



Compound	R^1		R	NK1 IC$_{50}$ (nM)[a]	+50 %HS IC$_{50}$ (nM)[a]	IP-I[b] %	Gerbil FT[c] %Inhibition	Ion channels[e] Diltiazem sodium IC$_{50}$ (nM)	
18a		Fast isomer	H	0.08	2.10	65	100[c]	2376	1988
18b		Slow isomer	H	0.07	2.70	79	—	—	—
15a		Fast isomer	H	0.09	0.60	75	100[c]	1877	7721
15b		Slow isomer	H	0.08	0.77	87	100[c]	1558	4983
20a		Fast isomer	CH_3	0.07	1.10	28	96[c]	2209	2214
20b		Slow isomer	CH_3	0.06	2.60	57	—	—	—
	Only the better diastereomer shown below (with better HS and IP-1 activity)								
16a			CH_3	0.08	0.42	45	100[c]	767	1397
24			H	0.07	0.83	52	o[d]	>10,000	7822
25			H	0.13	1.83	68	94[c]	2389	2966

[a] Displacement of [^{125}I] labeled substance P from the cloned hNK_1 receptor expressed in CHO cells. Data are mean (n = 3).
[b] IP-I assay: it measures the response of inositol phosphate generation to substance P (10 μM) and is reported as the percent of substance P response remaining (SPRR) at 100 nM NK1 antagonist concentration.
[c] Inhibition of GR73632 induced foot tapping in gerbils at 3 mg/kg iv at 24 h.
[d] Inhibition of GR73632 induced foot tapping in gerbils at 1 mg/kg iv at 1 h.
[e] Ion channels: binding assay in which IC$_{50}$'s are calculated for both sodium and calcium (Dlz) channels.

hNK_1 binding affinity, analogs **5a** and **5b** were synthesized. These were pursued in an effort to block possible metabolite issues, such as oxidation to the ketone, which was seen with compound **2b**.[17] These analogs also had subnanomolar binding affinity, although the ion channel selectivity was decreased. However, the compounds were of sufficient interest to be profiled as potential back-ups to compound **2b**.

Upon thorough analysis of the α-substituted compounds, the hNK_1 antagonist **2b** appeared to be superior, with subnanomolar binding affinity with or without the presence of human serum and greater than 1000-fold selectivity versus the ion channels. It also exhibited 100% inhibition of the gerbil foot-tapping response which was indicative of good brain penetration, therefore this was one of the two compounds selected for further pharmacokinetic profiling. The second compound was selected from the β-substituted hNK_1 antagonists.

In the case of the β-substituted series of compounds, the basic amino substitution seemed to be more preferred versus the hydroxyl substitution. The β-amino compounds had reduced human serum shifts and better sodium channel selectivity versus the hydroxyl analogs. This only showed that similar substitutions on different positions of the ring, even only one carbon removed, can result in drastically different biological profiles (see Table 2).

In this series of compounds, the differences in the intrinsic activities between diastereomers were also minimal, all things being equal when considering the assays standard deviation of error. Intrinsic potency did not distinguish the two diastereomers and therefore their human serum shift and off target activities became the differentiating factors.

In examination of the β-hydroxyl substituted compounds, **18a**, **18b**, **20a**, and **20b**, it became clear that the human serum shift values exhibited greater than 20-fold decrease in intrinsic potency versus the activity seen without the presence of human serum. Ion channel selectivity was reasonable with each having 2 μM binding in both the sodium and calcium channels. However, after direct comparison of these hydroxyl analogs with amino compounds **15a** and **15b**, the human serum shift values became the significant factor in deciding to abandon further biological studies on the hydroxyl analogs in favor of the amino compounds.

In this series, the amino substituent seems to be more favored with greater intrinsic potency for both isomers, 0.09 and 0.07 nM, respectively, with subnanomolar activity also in the presence of human serum. Complete inhibition of the foot-tapping response in gerbils was observed in both diastereomers at 0.1 and 24 h points. The only difference seen was in ion channel selectivity with isomer 1 having better selectivity versus both the sodium and calcium channels. This slight differentiation was enough to select compound **15a** for further biological evaluation rather than **15b**.

Similar structural variations of the α-substituted compounds (i.e. **21a,b** and **22**) were synthesized in the β-amino series, as can be seen with compounds **24** and **25**, with analogous results. Especially troublesome was the decrease in inhibition of the GFT response which led to the assumption that the analogs did not penetrate the brain as well as the non-substituted primary amines.

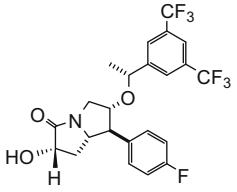
The geminal substituted methyl, amino compounds (only diastereomers 1 shown, **16a**)[18] were also prepared. Unfortunately, off-target selectivity was greatly decreased as observed with the calcium channel activity of 1.4 μM binding as compared to compounds **15a** and **15b** with 7.7 and 4.9 μM binding affinity, respectively. Therefore, after examining the preliminary data on this series of β-substituted hNK_1 antagonists, compound **15a** was selected for further evaluation (see Table 2).

Evaluation of the properties of the α-hydroxy substituted pyrrolizinone **2b** demonstrated excellent brain penetrant properties with an extremely low dose of compound needed for full inhibition of the gerbil foot-tapping response, 0.02 mg/kg at 0.1 and 24 h, respectively. Promising PK parameters were observed across species with high bioavailability, >90%, and long half lives which may be viable for once-daily dosing in man. Though, the major concern was the long half life in dogs and rhesus which were over days and not less than the preferred 24 h. Microsomal stability did not account for these considerable long half lives especially with rhesus showing the least stability with 23% parent remaining after 1 h. The ancillary activities were acceptable with greater than 60 μM inhibition observed for 2D6, 2C9, and 3A4, and a moderate response of 31% inhibition at 10 μM dose in hPXR was not of great concern. The gerbil PK/PD study exhibited an excellent ratio of compound in brain versus plasma at 1 h indicating rapid brain penetration (see Table 3).

Compound **15a** had a comparable pharmacokinetic profile as compared to compound **2b**, although it is bioavailability was somewhat lower, (78% versus 93%). hPXR activity was improved with virtually no inhibition seen at 10 μM, and the human serum shift was twofold less. However, titration of the gerbil foot-tapping assay ascertained that approximately 40X the dose was necessary for complete inhibition of the gerbil foot-tapping response versus compound **2b**. Thus, with this information, plus the observation that compound **15a** had reduced selectivity versus the ion channels when compared to **2b**, it was decided to halt further evaluation in favor of compound **2b** (see Table 4).

A new series of α- and β-substituted 5,5-fused pyrrolizinones were prepared which exhibited sub-nanomolar hNK_1 binding affinity with good off-target selectivity. Many of these analogs had potent in vivo activity in the gerbil foot-tapping model at 0.1 and 24 h and demonstrated rapid brain penetration with long duration of activity. Related work will be published in due course.[20]

Table 3
Profile of lead α-substituted hNK_1 antagonist



2b[19]

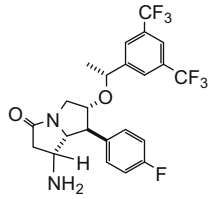
IC_{50}: 0.08 nM

IC_{50}+50% human serum: 0.91 nM

IP-1: 60% SP remaining

	Pharmacokinetics		
	Rat	Dog	Rhesus
Clp (ml/min/kg)	5.1	0.8	1.0
$t_{1/2}$: (h)	13.0	128.2	80.4
Vd: (L/Kg)	4.2	2.8	2.6
F%:	93.0	98.0	68.0
Rat brain/plasma ratio: (1 mg/kg iv.): 1.0 (4 h)			
GFT (iv):		**Gerbil PK/PD iv study:**	
ID50 = 0.02 mg/kg (1 h)		IC50 = 3.8 nM (1 h brain)	
ID50 = 0.016 mg/kg (24 h)		IC50 = 8.4 nM (1 h plasma)	
Ancillary activity:		**Microsomal stability:**	
CYP inhibition		% remaining (60 min)	
2D6:	62.2 μM	Dog:	73
3A4:	>100 μM	Human:	54
2C9:	>100 μM	Rat:	60
Ion channels: 2.6–10 μM		Rhesus:	23
hPXR: 31% at 10 μM			
hLS180: 13-fold at 10 μM (0.21 related rifamp.)			

Table 4
Profile of lead β-substituted hNK_1 antagonist



15a
IC_{50}: 0.10 nM
IC50+50% human serum: 0.6 nM
IP-1: 75% SP remaining

	Pharmacokinetics Rat
Clp (ml/min/kg)	8.9
$t_{1/2}$: (h)	7.7
Vd: (L/Kg)	5.9
F%:	78.0
Rat brain/plasma ratio: (1 mg/kg iv.): 1.4 (4 h)	
GFT (iv):	
ID50 = 0.88 mg/kg (1 h)	
ID50 = 0.92 mg/kg (24 h)	
Ancillary activity	
CYP inhibition	
2D6:	66 μM
3A4:	>100 μM
2C9:	45 μM
Ion channels: 1.2–9.1 μM	
hPXR: 0.9% at 10 μM	
Microsomal stability:	
% remaining (60 min)	
Dog:	89
Human:	66
Rat:	85
Rhesus:	91

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17. Unpublished metabolite profiling from rat PK data indicate that ketone **4** is formed in vitro and in vivo from analog **2b**.
18. In effort to conserve space in the table, the other diastereomer ,which would be **15b**, was not included. The intrinsic binding for **15b** was 0.11 nM and 1.8 nM in the presence of 50% human serum, with ion channel affinity of 558 nM for sodium and 1358 nM for the calcium channels. Functional IP-1 was 63% SP remaining and GFT inhibition was mesured at 100% inh at 3 mpk iv at 24 h.
19. The relative stereochemistry of **2b** was determined by use of 2D NOE NMR of both diasteromers (**2a** and **2b**). The most crucial evidence that determined the sterochemistry of **2b** was the presence of an NOE signal between the alpha hydrogen adjancent to the hydroxyl substituent and the bridgehead hydrogen of the fuse pyrrolidine ring. This would indicate that the hydroxyl group is in the (S)-configuration. This NOE signal was also absent in its diastereomer, **2a**.
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