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Tetrahydroindolizinone NK_1 antagonists

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ABSTRACT

A new class of potent NK_1 receptor antagonists with a tetrahydroindolizinone core has been identified. This series of compounds demonstrated improved functional activities as compared to previously identified 5,5-fused pyrrolidine lead structures. SAR at the 7-position of the tetrahydroindolizinone core is discussed in detail. A number of compounds displayed high NK_1 receptor occupancy at both 1 h and 24 h in a gerbil foot tapping model. Compound **40** has high NK_1 binding affinity, good selectivity for other NK receptors and promising in vivo properties. It also has clean P_{450} inhibition and hPXR induction profiles.

The neurokinin-1 receptor (NK_1) is present in high concentrations in central and peripheral nerve systems.[1] Through the studies of the physiological effect of the ligand substance P, the NK_1 receptor has been selected as a therapeutic target for treatment of chemotherapy-induced nausea and vomiting (CINV), post-operative nausea and vomiting (PONV),[2,3] urinary incontinence[4] and other disorders. Aprepitant (Emend™)[5] is currently the only NK_1 antagonist on market, and it is approved for the treatment of CINV and PONV. In our NK_1 antagonist backup program, we focused our efforts on the discovery of efficacious compounds that are orally bioavailable and brain-penetrating with minimum potential for drug–drug interactions.

Previously, we have disclosed a novel class of NK_1 antagonists based on the 5,5-fused pyrrolidine core (**1**) (Fig. 1).[6,7a] These compounds displayed sub-nanomolar NK_1 affinity,[8] moderate functional activity,[9] and had good efficacy in the gerbil foot tapping model.[10] We have designed and synthesized a new class of NK_1 antagonist with a 6,5-fused tetrahydroindolizinone core (**1a**) in order to expand the scope of this class of compounds, to improve functional activity and to minimize potential P_{450} inhibition and hPXR induction issues. Herein, the initial SAR results at the 7-position of this fused system are presented.

The tetrahydroindolizinone derivatives[7b] were synthesized as illustrated in Scheme 1. The intermediate **2**[7a] was oxidized to its aldehyde, which was further oxidized to carboxylic acid **3** with $NaClO_2$. One carbon homologation of acid **3** with diazomethane and AgOBz provided ester **5**. Ester **5** was partially reduced to aldehyde **6** by DIBAL-H. Addition of the anion of *t*-BuOAc to aldehyde **6** afforded aldol product **7**, which upon deprotection by HCl and intramolecular EDC coupling provided hexahydroindolizinone **8** (Scheme 1). Oxidation of alcohol **8** to ketone **9** was achieved with PCC-alumina in 63% yield. The enolate of ketone **9** reacted with 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine to provide vinyl triflate **10**. Compounds **11**–**29** and **37** were prepared from intermediate **10** by the Suzuki coupling reaction. Compounds **38** and **40** were prepared from triflate **10** by Stille coupling reactions. Compounds **39** and **41** were prepared from olefenic compounds **38** and **40**, respectively by selective hydrogenation (25 psi H_2, 10%

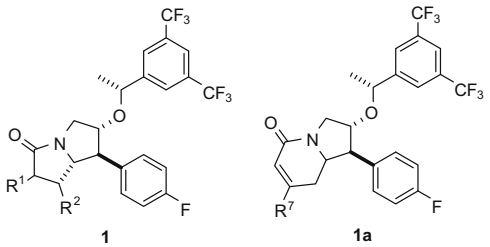

Figure 1. Structure of 5,5-fused pyrrolidine NK_1 antagonists **1** and proposed 6,5-fused tetrahydroindolizinone **1a**.

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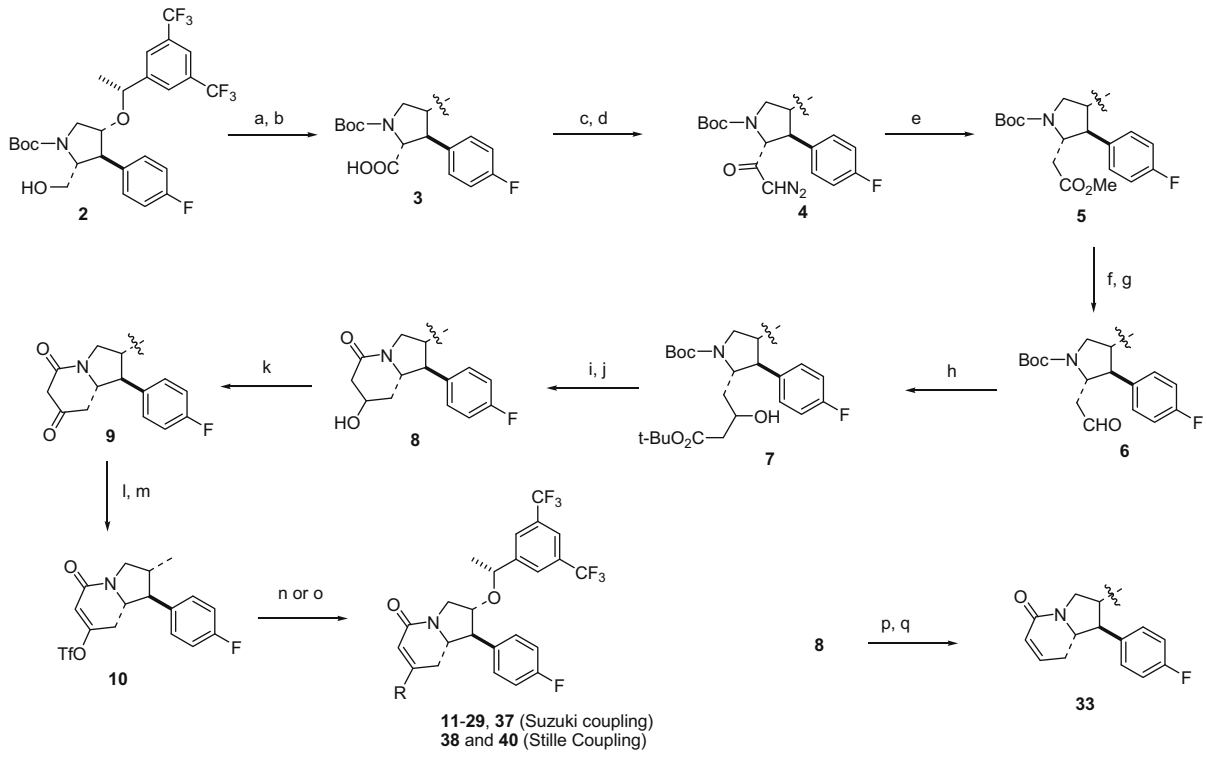
Pd–C in MeOH). Alkene **33** was prepared from **8** through formation of its mesylate followed by elimination of MsOH under basic condition.

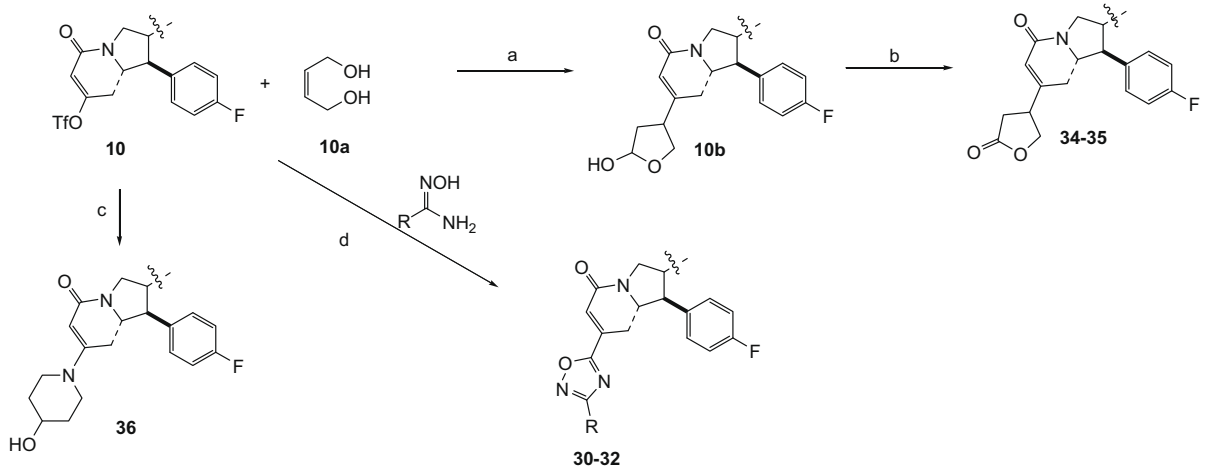
Lactone compounds **34** and **35** were prepared according to Scheme 2. Palladium catalyzed coupling reaction of **10** with diol **10a** provided lactol **10b**, which was oxidized with Ag_2CO_3 to afford lactones **34** and **35**.[11]

Oxadiazoles **30**–**32** were prepared by palladium catalyzed reaction of **10** with CO to generate an acyl-palladium intermediate, which reacts with amidoximes to afford **30**–**32** (Scheme 2).[12] Direct displacement of OTf of **10** with 4-OH piperidine provided **36**.

Biological results for compounds with β-aromatic substituents are shown in Table 1. With a few exceptions (**12**–**14**, **20**, **27** and **32**), most of the analogs in Table 1 displayed potent sub-nanomolar NK_1 binding affinities. In presence of 50% human serum, their NK_1 binding activities varied widely. Polar compounds had smaller serum shifts (**16** vs **17**, **20** vs **21** and **22** vs **23**). A significant improvement in IP-1 functional activity was observed for these 6,5-fused

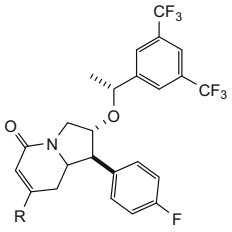


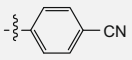
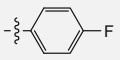
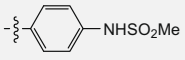
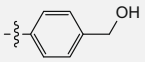
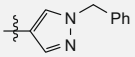
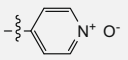
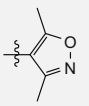
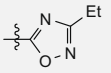
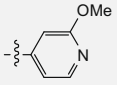
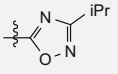
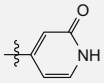
Scheme 1. Synthesis of **11**–**29**, **33**, **37**–**38** and **40**. Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 15 min, then Et_3N, −78 °C 15 min; (b) $NaClO_2$, *t*-BuOH, rt, 16 h, 100%, two steps; (c) *i*-BuOCOCl, Et_3N, THF, 0 °C, 1 h; (d) CH_2N_2, THF, 0 °C to rt, 2 h, 68%, two steps; (e) AgOBz, Et_3N, MeOH, rt, 16 h, 77%; (f) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (g) MeOH, −78 °C to rt; (h) LHMDS/*t*-butyl acetate, THF, −78 to 30 °C, 3 h, 87%, two steps); (i) HCl, 1,4-dioxane, rt, 2 h; (j) EDC, DMAP, CH_2Cl_2, 75%, two steps; (k) PCC-alumina, CH_2Cl_2, rt, 18 h, 63%; (l) KHMDS, THF, −78 °C, 0.5 h; (m) 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine, THF, −78 °C, 1.5 h, 99%, two steps; (n) Suzuki coupling, $Pd(PPh_3)_4$, boronic acid, toluene, water, 120 °C, 18 h; (o) Stille coupling, $Pd(PPh_3)_4$, vinyl tin reagent, dioxane, 108 °C, 18 h; (p) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, 100%; (q) piperidine, toluene, 64 °C, 18 h, 73%.



Scheme 2. Synthesis of **30**–**32** and **34**–**36**. Reagents and conditions: (a) $Pd(OAc)_2$, *n*-Bu_4NCl, DMF, 70 °C, 3 h; (b) Ag_2CO_3-Celite, toluene, 80 °C, 24 h, 78%; (c) 4-hydroxypiperidine, THF, 80 °C, 1 h, 100%; (d) $Pd(PPh_3)_4$, CO, toluene, 95 °C, 16 h, 65–73%, two steps.

Table 1
Activities of compounds with β-aromatic substituents



Compd	R	NK1 IC_{50}[a] (nM)	+50 %HS IC_{50} (nM)	IP-1[b] %SPRR	Gerbil FT[c] % Inhibition	Compd	R	NK1 IC_{50} (nM)	+50 %HS IC_{50} (nM)	IP-1 %SPRR	Gerbil FT % Inhibition
33	H	0.013	0.53	48		**22**		0.18	8.5	9	25
11	Ph	0.93	89.5	17	–	**23**		0.15	2.3	11	42
12		1.8	53	3	–	**24**		0.16	4	84	98
13		2	100	7	–	**25**		0.15	7.7	55	82
14		1.0	54	11	–	**26**		0.13	5.4	14	94
15		0.39	23	3	–	**27**		1.9	66	3	–
16		0.14	8.1	4	100	**28**		0.11	6.4	31	–
17		0.10	2.1	11	100	**29**		0.11	5.6	59	–
18		0.11	11.7	7	96	**30**		0.15	5.1	35	–
19		0.51	34	12	85	**31**		0.40	27	32	–
20		1.1	44	5	–	**32**		1.7	72	21	–
21		0.27	3.9	17	0						

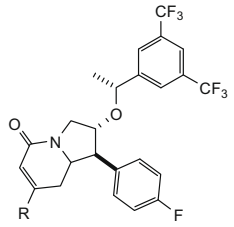
[a] Displacement of [^{125}I] labelled substance P from the cloned hNK$_1$ receptor expressed in CHO cells. Data are mean (n = 3).[8]
[b] IP-1 assay: Measures the response of inositol phosphate generation to substance P (10 μM) and is reported as the percent of substance P response remaining (SPRR) at 100 nM NK$_1$ antagonist concentration.[9]
[c] Inhibition of GR73632 induced foot tapping in gerbils@ 3 mg/kg iv at 24 h.[10]

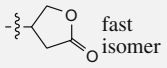
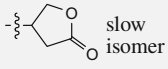
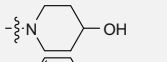
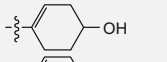
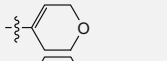
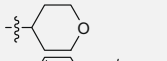
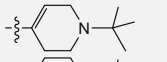
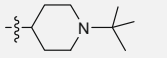
compounds with β-substituents compared with unsubstituted compound **33**. In general, the IP-1 functional activity of these 6,5-fused compounds was also significantly better than that of the 5,5-fused pyrrolidine compounds previously disclosed (IP-1: 28–90%).[7a] A majority of these compounds had IP-1 activities below 20% substance P response remaining (SPRR) at 100 nM antagonist concentration. Among compounds with a six-membered ring substituents at the 7-position, compared to compound **11**, a substituent at the 4-position of the phenyl group had a positive impact on the IP-1 activity (**11** vs **12**–**16**). Compounds with a pyridyl substituent also had improved IP-1 activities compared to compound **11**. Except compounds **26** and **27**, compounds with a five-membered ring substituent were less potent than compounds with a six-membered ring substituents in the IP-1 assay. The NK$_1$ binding affinity and the functional activity did not always directly correlate (for example, compound **12** had weaker NK$_1$ binding activity and excellent IP-1 activity). There was also no correlation between the polarity of a compound and its IP-1 functional activity (**25** vs **26** and **27**).

Some of the compounds with potent NK$_1$ binding and functional activity were also tested in the gerbil foot tapping assay[10], which measured how effective the compound blocked the NK$_1$ receptor at 24 h in the gerbil brain (Table 1). Data from this assay also provided an indication of the duration of parent or active metabolites, and an indication of brain penetration. Compounds **16** and **17** demonstrated complete inhibition of gerbil foot tapping at 24 h at an iv dose of 3 mg/kg.

The SAR learned from Table 1 was applied in the design of compounds with non-aromatic β substituents at the 7-position and data are presented in Table 2. These compounds all have a polar

Table 2
Activities of compounds with β non-aromatic substituents



Compd	R	NK1 IC_{50}[a] (nM)	+50 %HS	IP-1[b] %	Gerbil FT[c] % Inhibition
34	 fast isomer	0.066	1.4	5	98[d]
35	 slow isomer	0.11	2.4	5	96[d]
36		0.16	11	4	82
37		0.18	13	8	—
38		0.18	9.6	14	—
39		0.09	3.2	3	100[d]
40		0.18	1.9	2	100
41		0.041	0.21	4	91

[a] Displacement of [^{125}I] labelled substance P from the cloned hNK_1 receptor expressed in CHO cells. Data are mean ($n = 3$).[8]
[b] IP-1 assay[9]: Measure the response of inositol phosphate generation to substance P (10 μM) and reported as the percent of substance P response remaining (SPRR) at 100 nM NK_1 antagonist concentration *x*.
[c] Inhibition of GR73632 induced foot tapping in gerbils@ 3 mg/kg iv at 24 h.[10]
[d] 1 h at 1 mg/kg.

group at the far side of the attachment to reduce serum shifts. All of them exhibited sub-nanomolar binding potency on the NK_1 receptor. They had lower shifts in affinity in the presence of human serum as compared to the compounds with β-aromatic substituents, probably due to higher polarity. Importantly, all of them had excellent functional activities. In the gerbil foot tapping assay, all tested compounds displayed potent efficacy at 1 h or 24 h. Compound **40** was prepared initially as an intermediate for compound **41**. The *t*-Bu group of compound **41** was used to block possible metabolism of the piperidine group. It was surprising to find that compound **40** is more potent than **41** in the gerbil foot tapping assay despite the fact that compound **41** is about fourfold (ninefold with human serum) more potent than compound **40** in the binding assay.

Given its single dose potency in the gerbil foot tapping assay, compound **40** was titrated to have an $ID_{50} = 0.05$ mg/kg at 1 h and an $ID_{50} = 0.49$ mg/kg at 24 h (Table 3). These data indicate that compound **40** was one of the most potent compounds in this assay.

Table 3
In vivo activity of compound **40** in Gerbil[a]

Time (h)	ID_{50}	ID_{50} (at 1 mpk, iv) Plasma	Brain
1	0.05	0.57	6.9
24	0.49	—	—

[a] Plasma drug levels determined by LC–MS following protein precipitation.

Table 4
Pharmacokinetic profile of **40**

	$t_{1/2}$ (h)	Vd (L/kg)	Clp (mL/mg/kg)	nAUC (po) (μM h kg/mg)	*F* (%)
Rat	2.8	7.2	33	0.05	5.3
Dog	8.8	11	17	0.69	44

Table 5
P_{450} inhibition and hPXR induction data for compound **40**

	Cyp 2C9	Cyp 2D6	Cyp 3A4	PXR
IC_{50} (μM)	36.5	35.7	>50	>30

At 1 h, the IC_{50} values in plasma and brain are 0.57 and 6.9 nM, respectively indicating that low plasma and brain concentrations drive efficacy in gerbil and a high b/p ratio.

Compound **40** was evaluated for PK properties in rat and dog (Table 4). In rat, it showed high clearance (33 mL/min/kg), very low oral AUC (0.05), desirable plasma half-life (2.8 h) and poor oral bioavailability. However, in dog, the PK profile improved with moderate clearance (11 mL/min/kg), better oral AUC (0.69), good half-life, and improved oral bioavailability.

Compound **40** had a low affinity for cytochrome P_{450} enzymes and a reduced potential for induction as measured by a hPXR induction assay (Table 5), which indicated that compound **40** may have reduced liability for drug–drug interactions.

In summary, a new class of NK_1 receptor antagonists based on a tetrahydroindolizinone core with substitutions at the 7-position has been identified. These 6,5-fused pyrrolidine NK_1 antagonists generally had sub-nanomolar NK_1 binding affinities and excellent functional IP-1 activities. Many of these analogs have potent in vivo efficacy in the gerbil model at 24 h. Compound **40** had excellent efficacy in the gerbil foot tapping model at both 1 h and 24 h. It also had a clean profile in human P_{450} inhibition and PXR induction assays, thus reducing the potential for drug–drug interactions.

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