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Discovery of Novel, Orally Active Dual NK_1/NK_2 Antagonists

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Abstract—Exploration of the SAR around selective NK_2 antagonists, SR48968 and ZD7944, led to the discovery that naphth-1-amide analogues provide potent dual NK_1 and NK_2 antagonists. ZD6021 inhibited binding of [^{3}H]-NKA or [^{3}H]-SP to human NK_1 and NK_2 receptors, with high-affinity ($K_i = 0.12$ and 0.62 nM, respectively). In functional assays ZD6021 had, at 10^{-7} M, in human pulmonary artery $pK_B = 8.9$ and in human bronchus $pK_B = 7.3$, for NK_1 and NK_2, respectively. Oral administration of ZD6021 to guinea pigs dose-dependently attenuated ASMSP induced extravasation of plasma proteins, $ED_{50} = 0.5$ mg/kg, and NK_2 mediated bronchoconstriction, $ED_{50} = 13$ mg/kg.

The neurokinins, Substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), also known as the tachykinins, are a family of closely related peptides. They have been associated with many pathophysiological conditions including: asthma, arthritis, cough, emesis, anxiety, depression, and inflammatory bowel disease. Because of this linkage much effort has gone into the development of agents that can inhibit their effects. Since the neurokinins act, respectively, through three G-protein coupled receptors (called NK_1, NK_2, and NK_3) the development of selective tachykinin receptor antagonists has been the focus of the bulk of this effort.[1,2]

Both NK_1 and NK_2 receptors appear to be involved in pulmonary pathophysiology.[3] Therefore the hypothesis has been advanced that treatment with a dual antagonist, that blocked both of these receptors, might provide a more effective treatment for asthma.[4] This hypothesis has been based, in part, on models that showed either additive or synergistic efficacy upon combining selective NK_1 and NK_2 receptor antagonists.[5] As our approach to novel dual antagonists, as potential anti-asthmatic agents, we chose to explore structural modification of the NK_2 selective antagonists, SR48968[6] and ZD7944[7] (Fig. 1). The results we obtained are the subject of this report.

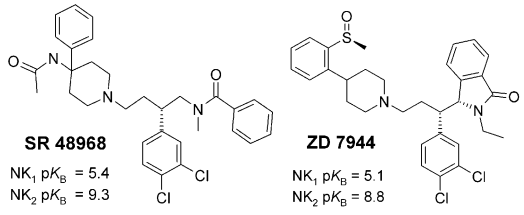
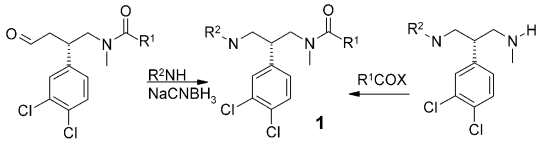


Figure 1. Functional activity (pK_B) of lead NK_2 selective antagonists, as determined on rabbit pulmonary artery (RPA).

To begin, a broad array of compounds (**1**) were prepared. In this set R^2 was varied among several substituted piperidines[8] and R^1 was chosen from over 100 aryl, heteroaryl and arylalkyl groups. This array was prepared using as the final synthetic stage, either an acylation or a reductive amination (see Scheme 1).



Scheme 1. General synthetic approach.

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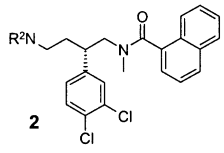
While this work was underway, several groups described identification of dual acting antagonists starting from selective NK_2 antagonists.[9–11] Alternatively, other groups succeeded in producing dual acting compounds starting with selective NK_1 antagonists.[12] The most potent, dual acting compound to come out of this array was naphthamide **2a** (see Table 1). In this compound, the piperidine substituent was the same as that found in ZD7944, a potent and selective NK_2 antagonist. Keeping the naphthamide constant we explored a larger group of piperidines[13] and found that only the corresponding sulfone **2h** and pyridyl **2m** analogues retained good dual activity. The other piperidine groups led to loss of activity either at the NK_1 receptor or at both the NK_1 and NK_2 receptors.

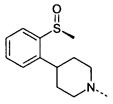
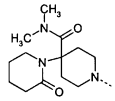
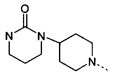
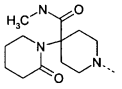
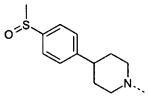
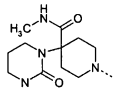
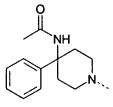
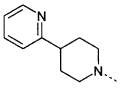
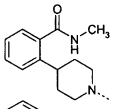
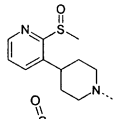
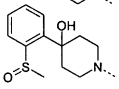
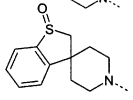
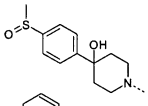
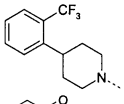
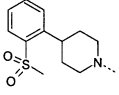
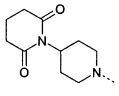
To follow-up the discovery of this naphthamide we explored the effect of substituents on the naphthalene ring. Substituents at the 3-position were a particularly interesting target. This is because an aryl group substituted in the *meta*-position with an electron-withdrawing group (e.g., CF_3) is an important structural feature of many NK_1 antagonists.[14] Commercially available 3-nitronaphth-1-oic acid was of interest, both directly for the 3-nitro analogue, and as a precursor to other 3-substituted naphth-1-oic acids via reduction to the amine and Sandmeyer type reactions. The nitro analogue **3b** proved particularly potent, both in vitro and following intravenous testing in vivo in a guinea pig pulmonary mechanics model.[15] However because of concern over its possible metabolic transformation to a β-naphthyl amine derivative, alternative 3-substituents were explored (Table 2).

Since substituent constants (π, MR, and σ_1) for cyano (−0.57, 6.3, and 0.53) highlighted it as a replacement for nitro (−0.28, 7.36, and 0.67), and as such arylnitriles are not implicated as potential toxicophores, the 3-cyano analogue (**3d**, ZD6021) was specifically targeted. The nitro **3b** and cyano **3d** analogues proved to be the most potent dual NK_1/NK_2 antagonists in this set. Unfortunately, efforts to define a broader QSAR relationship

Table 1. Exploration of piperidines while keeping naphthamide constant



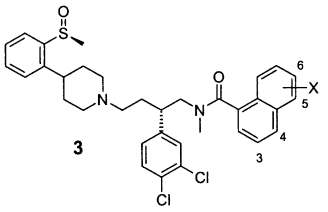
2

Compd	**2**, R^2N–=	pK_B[a] NK_1	pK_B NK_2	Compd	**2**, R^2N–=	pK_B NK_1	pK_B NK_2
2a		7.89±0.08	8.18±0.28	**2i**		6.78±0.01	8.23±0.27
2b		7.34±0.017	7.92±0.34	**2j**		6.42±0.08	8.44±0.26
2c		7.40±0.36	6.76±0.31	**2k**		6.82±0.27	8.41±0.36
2d		7.18±0.15	8.18±0.38	**2l**		6.98±0.09	NA[b]
2e		7.30±0.26	8.21±0.32	**2m**		7.69±0.04	7.82±0.05
2f		7.3±0.13	7.32±0.04	**2n**		6.98±0.12	8.10±0.06
2g		6.92±0.24	7.54±0.12	**2o**		6.03±0.25	NA
2h		7.81±0.20	7.55±0.07	**2p**		6.28±0.11	NA

[a]pK_B values were determined on rabbit pulmonary artery on $n \geq 2$ tissues. For NK_1 receptor antagonism ASMSP [Ac-[Arg6,Sar9,Met11(O2)]SP(6–11)] was used as the agonist and for NK_2 antagonism BANK [β-Ala8]NKA(4–10)] was the agonist.
[b]NA, not active (shift in dose–response curve <2) at an antagonist concentration of 1 μM.

between substituent constants for the different groups at position 3 and in vitro activity were unsuccessful.

Table 2. Exploration of varying substituents in 3-X-naphthamides



Compd	**3** X=	pK_B[a] NK_1	pK_B[a] NK_2	Dose ratio[b]	
				NK_1	NK_2
2a	H	7.89±0.08	8.18±0.28	52	262
3b	NO_2	8.16±0.10	9.03±0.18	50	321
3c	Br	8.15±0.34	7.67±0.24	43	34
3d (ZD6021)	C≡N	8.98±0.17	8.26±0.10	144	74
3e	SO_2CH_3	7.43±0.25	7.35±0.04	22	28
3f	Cl	7.15±0.12	7.10±0.09	13	31
3g	OMe	7.95±0.04	7.70±0.06	47	77
3h	CO_2H	5.68±0.14	6.86±0.11	ND[c]	ND
3i	CH_3	8.03±0.04	7.29±0.21	26	123
3j	CH_2CN	8.42±0.24	6.99±0.06	133	39
3k	Ac	7.41±0.35	7.17±0.13	41	156
3l	$C(=CH_2)CH_3$	7.24±0.19	7.24±0.29	31	75
3m	SO_2NH_2	7.54±0.04	7.02±0.21	170	7
3n	$CON(Me)_2$	5.17±0.22	7.31±0.33	ND	ND
3o	C≡CH	7.71±0.14	7.44±0.22	23	34
3p	F	7.90±0.07	8.15±0.23	12	52
3q	CF_3	7.84±0.07	6.45±0.25	ND	ND

[a]In vitro pK_B values were determined as described in Table 1 (footnote a).
[b]In vivo efficacy was determined in the anesthetized guinea pig and reported as the shift in the dose ratio for bronchoconstriction induced by a selective agonist. Animals were dosed, at 10 μmol/kg, 10 min prior to administration of the agonist, ASMSP for NK_1 and BANK for NK_2.
[c]ND, not determined.

To further elucidate what the effect of the cyano-substituent was on in vitro activity, the cyano group was moved to several other positions on the naphthyl ring system (Table 3). The results indicated that the best mixed activity was retained with the original 3-position.

To explore the impact of absolute stereochemistry on activity, isomers of ZD6021 at the aryl methine and the sulfoxide were prepared (Table 4). Previously, for both SR48968 and ZD7944, potent NK_2 antagonist activity had been linked with (*S*)-stereochemistry at the aryl methine. For ZD6021 there was an even greater effect on NK_1, than on NK_2 antagonism, as the methine stereochemistry was changed from *S* to *R*.

Table 3. Effect of moving naphthyl cyano substituent in **3** (X=CN)[a]

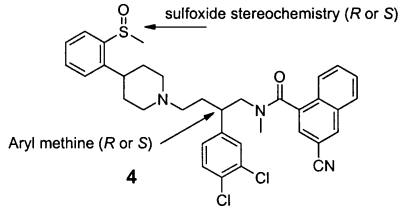
Compd	Position of cyano group	pK_B NK_1	pK_B NK_2
3r	7	8.13±0.27	8.51±0.22
3s	6	8.55±0.14	7.62±0.24
3t	4	6.31±0.09	7.34±0.42

[a]See legend in Table 2.

Broader profiling of ZD6021 was undertaken (Table 5), and comparisons made with a reference dual NK_1/NK_2 antagonist, MDL105212.[9] Binding assays showed that ZD6021 was slightly more potent than MDL105212 at the cloned human receptors.[16] However, in both animal and human functional assays, it is much more potent. Also, it is significantly more potent in vivo in the guinea pig model. In the latter model an ED_{50} of 13 mg/kg was determined for orally dosed ZD6021 against BANK-induced (NK_2) bronchoconstriction. Orally dosed ZD6021 was also examined in an ASMSP-induced (NK_1) guinea pig model of extravasation of plasma proteins, which showed an $ED_{50} = 0.5$ mg/kg.

Because of this favorable profile, ZD6021 was chosen for additional studies on its selectivity, pharmacokinetic and toxicologic profiles. Selectivity of ZD6021 was

Table 4. Relationship of stereochemistry to pharmacologic activity[a]



Compd	Stereochemistry, **4**		pK_B NK_1	pK_B NK_2	Dose ratio	
	Methine	Aryl sulfoxide			NK_2	NK_1
ZD6021	*S*	*S*	8.98±0.17	8.26±0.10	72	144
4b	*S*	*R*	8.36±0.21	8.39±0.06	51	100
4c	*R*	*S*	NA	7.10±0.25	ND	ND

[a]See legend in Table 2.

Table 5. Broader profiling of ZD6021 and comparison to MDL105212

Compound K_I (nM) in hNKx[a]	ZD6021	MDL105212
NK_1	0.1	0.3
NK_2	0.6	1.0
NK_3	74	200
pK_B[b]		
RPA NK_1	9.0	7.4
RPA NK_2	8.3	6.7
HuPA NK_1	8.9	6.9
HuBr NK_2	7.5	6.4
PO Dose ratio[c]		
NK_1	23	5
NK_2	18	1

[a]Binding affinity (K_I) was measured against the human receptor cloned and expressed in MEL cells.
[b]Functional activity was determined on: rabbit pulmonary artery (RPA) using as selective NK_1 and NK_2 agonists ASMSP and BANK, respectively; and on: human pulmonary artery (HuPA) for NK_1 antagonism and human bronchus (HuBr) for NK_2 antagonism, using ASMSP and NKA as the respective agonists.
[c]In vivo efficacy was determined in the anesthetized guinea pig and reported as the shift in the dose ratio for bronchoconstriction induced by a selective agonist. Animals were dosed orally, at 30 μmol/kg, 120 min prior to administration of the agonist, ASMSP for NK_1 and BANK for NK_2.

Table 6. Pharmacokinetics (PK) of ZD6021 in the rat and dog

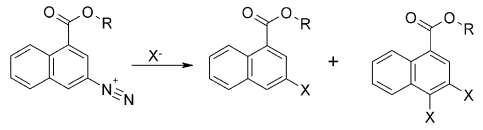
PK Parameter	Rat	Dog
IV dose (umol/kg)	10	1
Formulation	20% HPBCD[a]	20% HPBCD
AUC-IV(0-i) (ng h/mL)	3200	1100
CLp (mL/min/kg)	32.6	9.5
Vdss (L/kg)	3.7	2.0
$t_{1/2}$ (h)	1.8	3.8
Oral dose (umol/kg)	100	10
Formulation	Aq suspension	75% PEG400/saline
C_{max} (ng/mL)	421	364
T_{max} (h)	2	2
AUC-PO(0-i) (ng h/mL)	3010	2000
Bioavailability	9%	18%
$t_{1/2}$ (h)	ND[b]	2.3

[a]HPBCD, hydroxypropyl-beta-cyclodextrin.
[b]ND, not determined, data inadequate for characterization of $t_{1/2}$.

assayed in a broad array of tests, performed at PanLabs®. Assays with IC_{50} values <1 mM were (IC_{50} in mM): L-type benzothiazepine Ca^{2+} channel (0.58), muscarinic M4 (0.34), muscarinic M5 (0.65), and Sigma, σ non-selective (0.75). The pharmacokinetic profile of ZD6021 was determined in rat and dog. These studies (Table 6) showed bioavailability of 9 and 18%, respectively.

Several synthetic approaches to SR48968 and related compounds have been previously reported.[9,10] The key new synthetic need for the efforts described here was access to selectively substituted naphthoic acids. Originally we tried a Sandmeyer type approach, from 3-nitronaphthoic acid. However, decomposition of the intermediate naphthyl diazonium salts (Scheme 2) did not work well. For example, with $CuBr_2$ the predominant product was 3,4-dibromonaphthoic acid (X = Br) and not the desired 3-bromonaphthoic acid.

As an alternate key intermediate to the 3-substituted analogues (Scheme 3), we chose to utilize methyl 3-bromonaphth-1-oate. This compound was prepared from phthalic anhydride by a variation of a known



Scheme 2. Attempted use of Sandmeyer type chemistry.

approach to the 3-nitro naphthoic acid.[17] Most of the remaining 3-substituted naphthoic acids needed for the compounds in Table 2, were prepared from this intermediate by standard techniques. For example, the cyano analogue was prepared, as illustrated, by reaction with CuCN. Literature approaches were used for the naphthoic acids needed for **3g**[18] and **3p**.[19] The 4, 5, and 6 cyano-substituted naphthoic acids needed for compounds **3r**, **3s**, and **3t** were prepared as illustrated.

ZD6021 is a potent, high-affinity and selective dual NK_1/NK_2 receptor antagonist. It shows excellent functional activity in both animal and human tissue and shows good efficacy in vivo in animal models, against the effects of neurokinin agonists. It was selected for detailed preclinical evaluation and for preliminary toxicological evaluation. It may play an important part in defining the role of neurokinin antagonists in pathophysiologic conditions.

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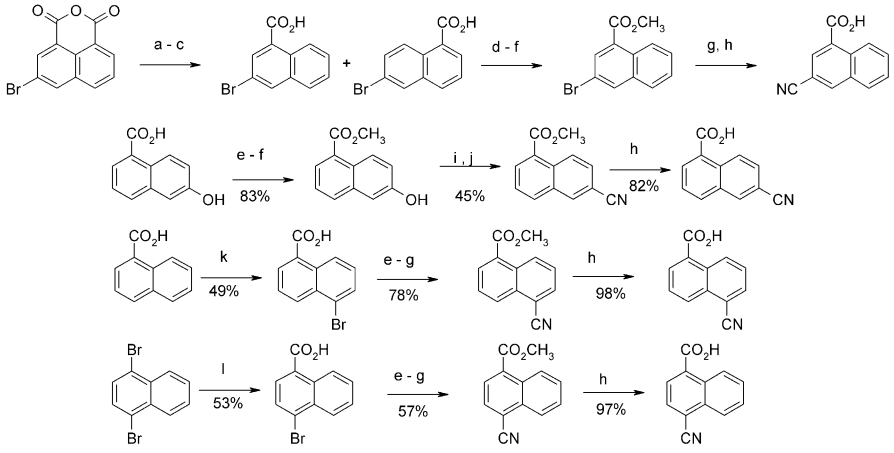

Scheme 3. Reagents and conditions: (a) NaOH, H_2O; (b) HgO (yellow), glacial HOAc, reflux 4 days; (c) 5 M aq HCl, reflux 4 h; (d) recrystallize from glacial HOAc (2×); (e) $(COCl)_2$, cat DMF, CH_2Cl_2; (f) MeOH; (g) CuCN, DMF, pyridine, 180 °C; (h) LiOH, THF, MeOH, H_2O; (i) Tf_2O, Et_3N, CH_2Cl_2; (j) $Zn(CN)_2$, $(Ph_3P)_4Pd$, DMF; (k) Br_2, HOAc; (l) (i) *n*BuLi, (ii) CO_2, (iii) HCl.

References and Notes

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