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Synthesis and SAR of sulfoxide substituted carboxyquinolines as NK3 receptor antagonists

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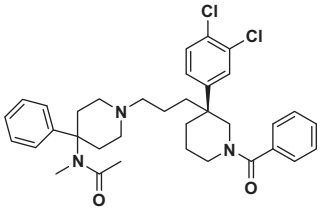
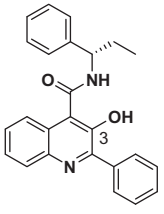
ABSTRACT

The neurokinin-3 (NK3) receptor is regarded as a potential novel target for treating patients with schizophrenia. Herein we report the synthesis and SAR of a series of C3-alkylsulfoxide substituted quinolines as potent NK3 receptor antagonists. These compounds have excellent NK3 functional activity, good selectivity and drug-like properties. Several key compounds have good in vitro/in vivo DMPK characteristics, and are active in a gerbil locomotor activity model.

Neurokinin B (NKB), a tachykinin peptide, mainly elicits its effect through the G-protein coupled neurokinin-3 (NK3) receptor. The NK3 receptor is almost exclusively expressed in the central nervous system, and has been demonstrated to affect monoaminergic and other neurotransmission. Therefore, it is considered as a potential new and druggable target for treatment of patients with schizophrenia.[1] In addition to treating schizophrenia, NK3 receptor (NK3r) antagonists may also provide benefits in the treatment of pain, mood disorder, Parkinson's disease and other CNS indications.[2]



Osanetant



Talentant

Two structurally distinct and selective NK3r antagonists, Osanetant[3] (Sanofi-Aventis) and Talentant[4] (GlaxoSmithKline) have been reported to show efficacy in improving the positive symptoms of schizophrenia in phase II clinical studies. However, development of both drug candidates have been terminated[5] without clearly demonstrating whether selective NK3r antagonists can provide sufficient antipsychotic efficacy while avoiding the undesired side-effects sometimes observed with currently marketed antipsychotics such as extra pyramidal symptoms, weight gain and cognitive deficits.

The carboxyquinoline core of Talentant has been demonstrated as a viable scaffold for selective NK3r antagonists,[6] and can tolerate a wide variety of substituents at the C3 position of the quinoline ring. This position has been extensively explored to optimize selectivity as well as drug-like properties.[7] Due to its large dipolar character and chirality, the sulfoxide is a unique functional group in medicinal chemistry and can be found in several drugs, most notably, esomeprazole (Nexium). This paper describes our entry into this area through the discovery of novel, potent and drug-like compounds based on C3-alkylsulfoxide substituted quinolines.

Chemistry: The synthesis generally started from the Pfitzinger condensation[8] of suitable isatins with aryl keto substituted alkyl sulfides to give the corresponding C3-alkylthio substituted quinoline carboxylic acids in good yields (Scheme 1). Amide coupling and subsequent sulfide oxidation led to the desired sulfoxides as a mixture of isomers. Various Pd-catalyzed coupling reactions involving aryl halide groups enabled access to substitution at various positions on the quinoline ring. As shown in Scheme 2, bromomethyl substituted carboxyl quinoline, prepared according to literature procedure,[7a] was converted into C3-methylsulfinylmethyl substituted quinoline amides in several steps.

As shown in Scheme 3, *para*-methoxybenzyl substituted intermediate, which was made in the fashion depicted in Scheme 1, was converted to free thio when heated with TFA and anisol. Alkylation and subsequent oxidation led to a variety of alkyl substituted sulfoxides.

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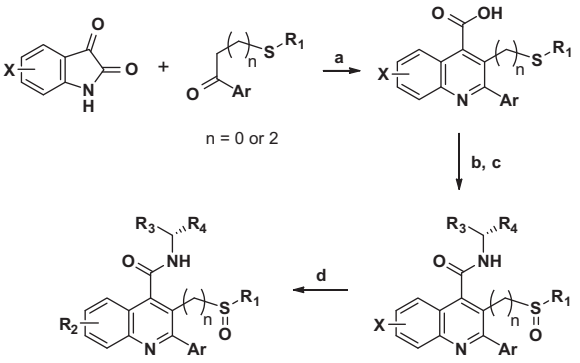
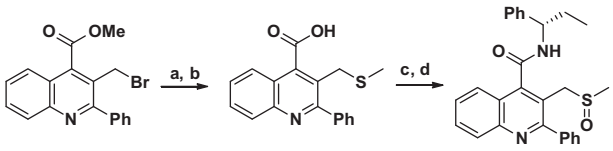
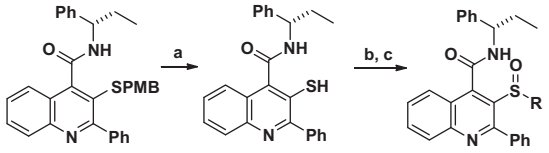


Scheme 1. Reagents and conditions: (a) NaOH, EtOH/THF, reflux; (b) amine, EDCI, HOBt, DIPEA, DCM; (c) $NaIO_4$, $MeOH/H_2O$, Δ; (d) Pd-catalyzed coupling reactions.

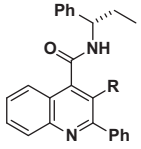


Scheme 2. Reagents and conditions: (a) MeSNa, THF; (b) LiOH, THF/H_2O; (c) amine, EDCI, HOBt, DIPEA, DCM; (d) $NaIO_4$, $MeOH/H_2O$, Δ.



Scheme 3. Reagents and conditions: (a) TFA, anisol, Δ; (b) RI, K_2CO_3, DMF; (c) $NaIO_4$, $MeOH/H_2O$, Δ.

Table 1
NK3 functional activity, solubility and permeability for **1**–**7**

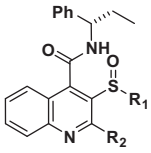


Compd	R	EC_{50}[a] (nM)	Sol.[b] (μM)	P_{app}[c]/efflux ratio
1	SMe	36 ± 10	<1	nd[e]
2	SOMe	4.9 ± 2.6	230	9.4/2.7
2a[d]	SOMe (*S*)	3.7 ± 3.4	270	28/1.3
2b[d]	SOMe (*R*)	240 ± 120	44	17/2
3	SO_2Me	14 ± 4	36	11/2.6
4	CH_2SMe	35 ± 8	2	5.9/1.1
5a[d]	CH_2SOMe (*R*)	1.8 ± 0.8	8	10/2.6
5b[d]	CH_2SOMe (*S*)	5.3 ± 2.7	53	9.9/3.7
6	CH_2SO_2Me	2.5 ± 0.7	4	11/3.1
7	CH_2CH_2SOMe	3.3 ± 0.5	360	1/21

[a] Unless noted, compounds were tested as 1:1 mixtures of diasteromers; EC_{50}'s are reported as the mean ± SEM ($n \geqslant 2$) and without SEM where $n = 1$.
[b] Equilibrium solubility.
[c] Measured in MDCK cells expressing human MDR1; unit as 10^{-6} cm/s.
[d] Single isomer.
[e] nd = not determined.

Results: The primary assay used to assess project SAR was a functional assay employing FLIPR technology in CHO cells stably expressing human recombinant NK3 receptor. Antagonism was

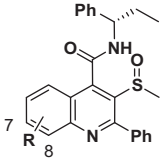
Table 2
NK3 functional activity assay results for compounds **8**–**20**



Compd[a]	R_1	R_2	EC_{50}[a] (nM)	Sol.[b] (μM)
2	Me	Ph	4.9 ± 2.6	230
8	Me	2-F phenyl	81 ± 14	53
9	Me	3-F phenyl	18 ± 3	100
10	Me	4-F phenyl	48 ± 11	88
11	Me	2-Thiophenyl	1.7 ± 0.6	47
12	Me	3-Thiophenyl	1.8 ± 1.3	28
13	Me	2-Pyridyl	1120 ± 40	360
14	Me	3-Pyridyl	690 ± 520	470
15	Me	2-Thiazol-4-yl	110 ± 12	41
16	Me	2-Thiazol-5-yl	220 ± 90	390
17	Me	3-Pyrazolyl	2500 ± 740	420
18	Ethyl	Ph	6.9 ± 1.8	170
19	*i*-Propyl	Ph	16 ± 4	83
20	CH_2CONMe_2	Ph	12 ± 0.2	52

[a,b] See footnote a in Table 1.

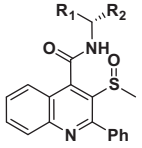
Table 3
NK3 functional activity assay results for compounds **21**–**29**



Compd[a]	R	EC_{50} (nM)[a]	Sol. (μM)[b]
2	H	4.9 ± 2.6	230
21	8-F	8.2 ± 2.3	160
22	8-Me	1900 ± 800	16
23	7-F	13 ± 10	58
24	7-Cl	7.7 ± 2.4	34
25	7-EtO	38 ± 1	69
26	$7\text{-}Me_2N$	212 ± 13	44
27	7-Br	5.1 ± 1.2	15
28	7-Me	3.6 ± 1.0	160
29	$7\text{-}Me_2NCH_2$	88 ± 58	460

[a,b] See footnote a in Table 1.

Table 4
NK3 functional activity assay results for compounds **30**–**35**



Compd	R_1	R_2	EC_{50}[a] (nM)	Sol.[b] (μM)
2	Ph	Ethyl	4.9 ± 2.6	230
30	Ph	Cyclopropyl	15 ± 7	180
31	Ph	$(CH_2)_2$	16 ± 9	1.3
32	Ph	$(CH_2)_3$	38 ± 15	4.5
33a[c]	4-Pyridyl	Cyclopropyl	>10,000	99
33b[c]	4-Pyridyl	Cyclopropyl	>9300	370
34	3-Pyridyl	Ethyl	74 ± 9	350
35a[c]	2-Pyridyl	Ethyl	77 ± 15	420
35b[c]	2-Pyridyl	Ethyl	>5200	460

[a,b,c] See footnote a in Table 1.

Table 5
Further profiling of compounds **2a**, **5a** and **5b**

Compd	EC_{50} (nM)	Selectivity versus NK1	Selectivity versus NK2	Sol. (μM)	CL_{int} (μL/min/mg)	P_{app} (10^{-6} cm/s)	Efflux ratio	Log *D*	hERG (μM)	LMA IP ED_{50} (μmol/kg)
2a	3.7 ± 3.4	>2700	1860	280	23	28	1.3	3	>33	0.75
5a	1.8 ± 0.8	nd	nd	8	5.2	10	2.6	3.5	>33	22
5b	5.3 ± 2.7	>660	170	53	8.4	9.9	3.7	3.5	>33	2

measured as inhibition of a transient Ca^{2+} flux induced by senktide, an NK3r peptide agonist, which has >3000-fold selectivity for NK3r over NK1r & NK2r. Key physical property (solubility) and DMPK characteristics (permeability, Pgp efflux ratio, metabolic clearance) were also measured. Most compounds were screened as a roughly 1:1 mixture of diastereomers. Key compounds were resolved into single diastereomers and studied further.

As shown in Table 1, the sulfoxide substitution at the C3 position of the quinoline ring generally gave very active and soluble compounds. By changing the linker length and the stereochemistry of sulfoxide, we were able to obtain superior compounds. The permeability and efflux ratios of these sulfoxide compounds was greatly improved when the sulfoxide moiety was moved closer to the quinoline ring. Therefore, shortening the methylene chain length greatly reduced the efflux ratio. The sulfoxide stereochemistry had great influence not only on the NK3 functional activity, but also on other physical properties. These compounds were quite stable under thermal conditions, but had a short half-life under light. Other oxidation states of sulfur atom were also explored. Sulfides gave very low solubility and very high clearance, while sulfones produced very good functional activity, but were less soluble than the sulfoxides.

After determining the optimal sulfur oxidation state and linker length, we explored various aryl groups at the 2 position of quinoline ring, as well as alkyl groups on the sulfoxide (Table 2). Fluorine substitution on the C2 phenyl ring led to less active compounds. Among them, *meta* F had the best activity (entry 9). Either 2-, or 3-thiophenyl groups gave highly active compounds, which were metabolically unstable in human liver microsomes (*h*CLint ~220 and 190 μl/min/mg, respectively). We attempted to further improve aqueous solubility via introduction of nitrogen containing heterocycles (pyridine, thiazole, and pyrrazole) at the C2 position. This led to greater solubility, but it also resulted in greatly reduced functional activity.Introduction of various simple alkyl groups on the sulfoxide sulfur atom was tolerated for activity, but was shown to decrease metabolic stability of the compounds in human liver microsomes. Addition of an alkyl amide group to the sulfoxide was tolerated (entry 20). However, attaching such a polar groups to the sulfoxide led to low permeability (1.5×10^{-6} cm/s) and high efflux ratio (~20).

Next we explored SAR of the C7 and C8 positions of the quinoline ring (Table 3). Fluorine substitution at the C8 position of the quinoline gave similar activity to simple phenyl analog **2**. Surprisingly, introduction of a methyl group in this position greatly reduced NK3 functional activity. This led us to hypothesize that the receptor might be very sensitive to steric hindrance around the C8 position.

Compared with C8 position, C7 position was much more tolerant of substitution. This position had a preference for small, lipophilic groups like halogen atoms or a methyl group. However, introduction of these groups led to less soluble compounds. Installation of electron donating groups, such as ethoxy- or dimethylamino- groups, afforded less active compounds. A basic amine group was introduced to improve solubility and allow for possible salt formation. However, this change also reduced the activity by ~20-fold.

Several different amides at the 4-carboxy position were examined as well (Table 4). Cyclopropyl group replacement of the ethyl group led to a slightly less active compound. Surprisingly, introduction of either achiral 1-phenylcyclopropanamine (entry 31) or 1-phenylcyclobutanamine (entry 32) still gave fairly active compounds, but this caused a precipitous drop in solubility. Replacement of the phenyl ring with a pyridyl ring was intended to introduce an ionizable basic nitrogen atom. However, 2- or 3-pyridyl groups in this position resulted in a loss of activity, while switching to a 4-pyridyl group led to even more dramatic loss of activity.

Several potent compounds were selected based on their in vitro profiles and evaluated in a gerbil locomotor activity assay (Table 5). Injection of senktide, a selective NK3 peptide agonist, into the lateral ventricle of male Mongolian gerbils acutely suppresses locomotion. The magnitude of suppression is dependent on the dose of senktide injected. This effect can be prevented by systemic preadministration of NK3r antagonists. Alkylsulfoxide **2a**, with its excellent selectivity against other neurokinin receptors, good in vitro DMPK profile and physical properties, was found to dose dependently reverse the response to senktide by ip dosing (ED_{50} of 0.75 μmol/kg). Compound **2a** exhibited acceptable pharmacokinetics in vivo, in rat (*F*% ~60%) with a high clearance in plasma (~60 mL/min/kg), and moderate $t_{1/2}$ (3 h). The total brain/plasma ratio in rat was 0.4 @ 1 h post dose (3 μmol/kg iv dosing).

Interestingly, potent compound **5a** was found to be very weak (ED_{50} 22 μmol/kg) in the gerbil locomotor assay, presumably due to its limited solubility and absorption. In contrast, its diastereomer **5b** displayed excellent in vivo activity (ED_{50} ~2 μmol/kg) and DMPK profile. The apparent oral bioavailability of this compound was very high in dog (*F*% ~89%); the plasma clearance at 2.3 mL/min/kg, and suitable half-life at 6.7 h.

The chirality of the sulfur atom in compound **5b** was determined by X-ray analysis to be (*S*)-configuration. In the crystal structure, intra-molecular hydrogen bonds form between the amide NH group and the sulfoxide O atom, resulting in an eight-membered ring. The absolute stereochemistry of the sulfoxide chiral center in compound **2a** was determined to be (*S*)-configuration as well by Vibrational Circular Dichroism (VCD) analysis.[9]

In conclusion, C3-alkylsulfoxide substituted carboxyquinolines were readily prepared, starting from the Pfitzinger condensation between arylketo sulfides and isatins. Several of these compounds were shown to have excellent NK3 functional activity, and good selectivity against other neurokinin receptors. One key SAR observation was the influence of linker length on permeability and efflux ratios. Two key compounds, **2a** and **5b**, had excellent in vitro/in vivo DMPK characteristics, and are active in the gerbil locomotor activity model. The absolute stereochemistry of the sulfoxide chiral center in compounds **2a** and **5b** was determined to be (*S*)-configuration, by VCD and X-ray analysis, respectively.

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