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N′,2-Diphenylquinoline-4-carbohydrazide based NK_3 receptor antagonists II

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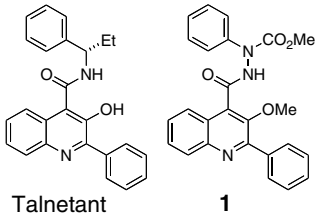
Abstract—Introduction of selected amine containing side chains into the 3-position of *N*′,2-diphenylquinoline-4-carbohydrazide based NK_3 antagonists abolishes unwanted hPXR activation. Introduction of a fluorine at the 8-position is necessary to minimize unwanted hI_{Kr} affinity and a piperazine *N*-*tert*-butyl group is necessary for metabolic stability. The lead compound (**8m**) occupies receptors within the CNS following oral dosing (Occ_{90} 7 mg/kg po; plasma Occ_{90} 0.4 μM) and has good selectivity and excellent PK properties.

In our previous paper,[1] we reported our initial studies on *N*′,2-diphenylquinoline-4-carbohydrazide based NK_3R antagonists related to Talnetant as potential treatments for schizophrenia. The lead compound **1** had good affinity (hNK_3R IC_{50} 8.8 ± 5.1 nM)[2] and was brain penetrant, occupying NK_3 receptors within the CNS following oral dosing to gerbils (Occ_{90} 30 mg/kg po; plasma Occ_{90} 0.95 μM).[1] A key liability for the series was CYP3A4 induction in human hepatocytes at high concentrations (**1**, 77% at 20 μM),[1] which could be correlated to activation of the hPXR nuclear receptor in vitro (HepG2 cells transiently transfected with hPXR; **1**, 49% of 10 μM rifampicin positive control).[3]



In order to further develop this promising lead toward a potential once a day oral drug candidate for the treatment of schizophrenia, we chose to target improvements to the in vivo occupancy and PK profile, and reduction in hPXR activation and hence CYP induction, while also ensuring that the selectivity profile was maintained.

The precursor for 3-alkoxy-substituted quinolines was the 3-hydroxy analog **2**.[1] Alkylation with methyl

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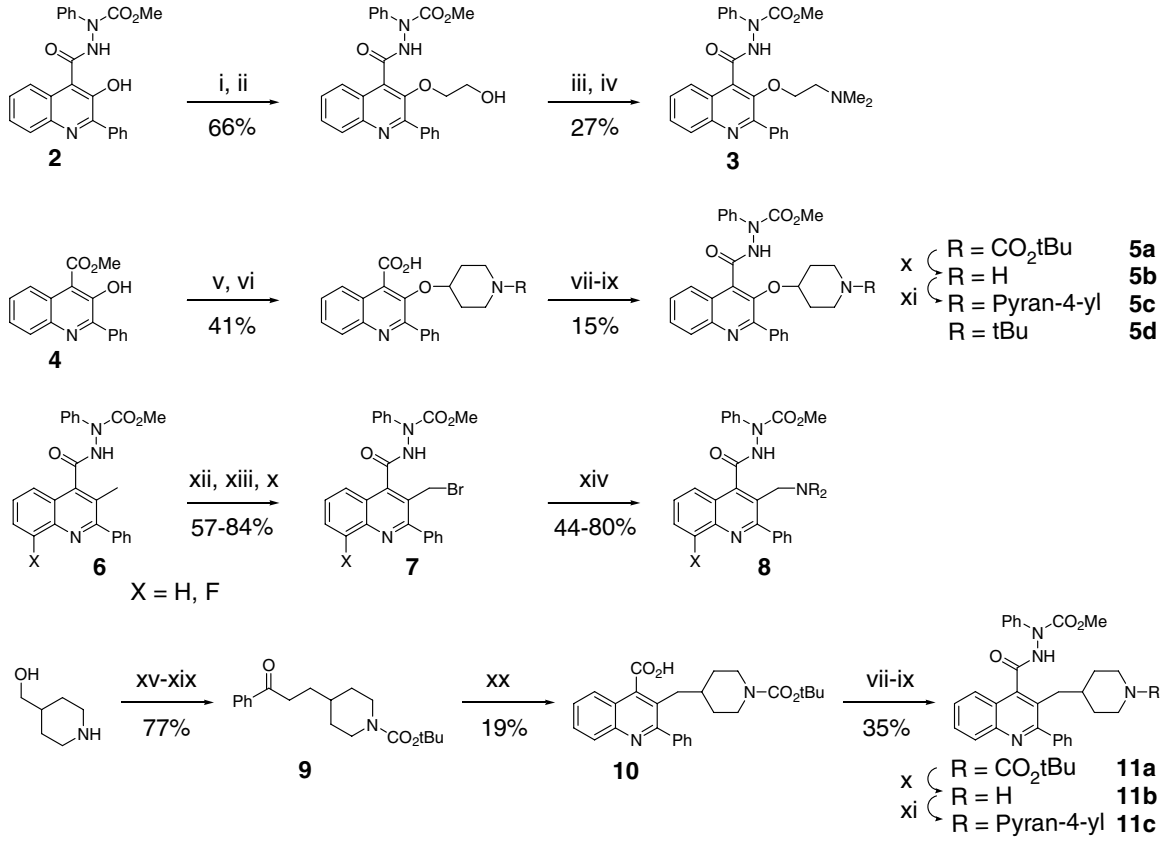


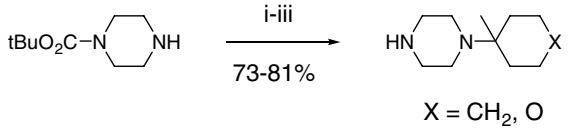
Scheme 1. Reagents and conditions: (i) $BrCH_2CO_2Me$, NaI, K_2CO_3, THF; (ii) $LiBH_4$, THF; (iii) CBr_4, Ph_3P, CH_2Cl_2; (iv) Me_2NH; (v) 1-(1,1-dimethylethyl)-4-piperidinol or 1,1-dimethylethyl 4-hydroxypiperidinecarboxylate, DTBAD, Ph_3P, THF; (vi) KOH, MeOH; (vii) $(COCl)_2$, DMF, CH_2Cl_2; (viii) $PhNHNH_2$, K_2CO_3, CH_2Cl_2, H_2O; (ix) MeOCOCl, PhMe; (x) TFA, CH_2Cl_2; (xi) tetrahydro-4*H*-pyran-4-one, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (xii) $(BOC)_2O$, NaH, THF; (xiii) NBS, CCl_4, hν; (xiv) R_2NH, Et_3N, THF, reflux; (xv) $(BOC)_2O$, CH_2Cl_2; (xvi) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (xvii) acetophenone, LiHMDS, THF; (xviii) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (xix) H_2, Pd–C, EtOAc; (xx) isatin, KOH, EtOH, H_2O.

bromoacetate followed by reduction and replacement of the terminal hydroxyl group gave **3** as shown (Scheme 1). However, alkylation of **2** to give more hindered cyclic O-linked substituents at C-3 was low yielding; it proved more efficient to O-alkylate the ester **4** with a suitable piperidin-4-ol under Mitsonobu conditions. The N-protecting group was removed and the compound was further elaborated under reductive amination conditions (Scheme 1).

In order to introduce aminomethyl groups at C-3, the versatile 3-bromomethyl precursors **7** (X = H, F) were targeted. These were most efficiently prepared via radical bromination of **6** after initial protection of the hydrazide 2-nitrogen. Deprotection and facile displacement with amines gave 3-aminomethyl derivatives (hindered *N-tert*-alkyl piperazines were prepared as shown in Scheme 2).

Compounds with a C-linked piperidine at C-3 were prepared via reaction of ketone **9** (prepared from piperidine-4-methanol) with isatin under basic Pfitzinger conditions[4] to give **10** (Scheme 1). This was further elaborated as shown.

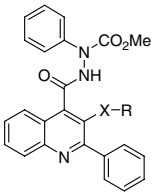
We have already reported[1] that substitution at most of the aromatic positions on the quinoline core was poorly tolerated, but a range of small substituents at the quinoline C-3 position improved hNK_3R affinity. Further exploration of the SAR showed that much larger alkoxy and amine-containing substituents were tolerated at this position (Table 1). This led, in some cases, to improved affinity relative to **1** (e.g., **8j**). Simple lipophilic groups at C-3 did not have an effect on hPXR activation, but we saw that certain amine containing side chains did reduce or abolish this unwanted activity. The disruption of hPXR activation was found to be quite selective, requiring a basic nitrogen held some distance from the quinoline core by a rigid, cyclic structure (e.g., **8b** and **11b**). If the side chain was flexible (**3**); if the basicity was reduced by benzylation (**8h**), removed by acylation (**8i**) or sulfonylation (**8j**); or if the basic center was too close to the quinoline (**8a**), hPXR activation persisted.

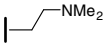
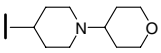
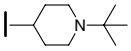
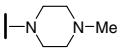
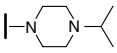
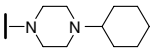
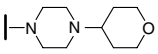
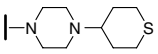
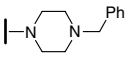
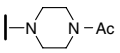
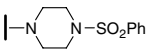
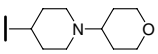


Scheme 2. Reagents and condition: (i) cyclohexanone or tetrahydro-4*H*-pyran-4-one, 1,2,3-triazole, $PhCH_3$, reflux; (ii) MeMgCl, THF; (iii) HCl, MeOH.

We next explored the effect of N-alkylation of **8b** and **11b**. We were pleased to find that the disruption of

Table 1.



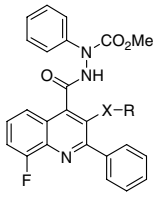
Compound	X	R	hNK_3 IC_{50}[a] (nM)	hI_{Kr} K_i[b] (μM)	hPXR response[c] (%)
3	O		11 ± 1	0.089	40
5c	O		12 ± 2	8.9	18
5d	O		17 ± 7	3.0	
8a	CH_2		160 ± 6	4.9	92
8b	CH_2		34 ± 7	0.84	7
8c	CH_2		17 ± 6	0.32	
8d	CH_2		5.8 ± 1.4	0.88	<5
8e	CH_2		2.0 ± 0.4	1.8	6
8f	CH_2		3.3 ± 0.3	6.5	10
8g	CH_2		1.9 ± 0.3	0.51	9
8h	CH_2		1.6 ± 0.2	0.53	57
8i	CH_2		7.4 ± 2.3	>9	53
8j	CH_2		0.72 ± 0.06	2.5	120
11b	CH_2		51 ± 17	0.52	<5
11c	CH_2		5.7 ± 2.7	8.0	<5

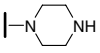
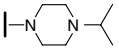
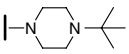
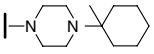
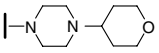
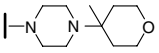
[a] Displacement of ^{125}I-labelled neurokinin B from the cloned hNK_3 receptor expressed in CHO cells. Data are means ± SD (n = 3 or more).[2]
[b] Displacement of labeled MK-499 from cloned channel expressed in HEK cells.[5]
[c] Increase in hPXR activation in HepG2 cells transiently transfected with hPXR (% of 10 μM rifampicin positive control).[3]

hPXR activation was not affected by this change and hNK_3R affinity was improved (e.g., **8c**–**g**, **11c**).

Unfortunately, this type of side chain did tend to introduce ion channel activity, especially affinity for the hERG ion channel (hI_{Kr}).[5] Blockade of this channel is linked to QT prolongation and severe cardiorhythmic side effects. We found that this affinity could be minimized by the use of a pyran-4-yl substituent (**8f** and **11c**). However, this group was found to be metabolically

Table 2.



Compound	X	R	hNK_3 IC_{50}[a] (nM)	hI_{Kr} K_i[b] (μM)	hPXR response[c] (%)
8k	CH_2		37 ± 16	8.2	<5
8l	CH_2		5.8 ± 0.8	>9	<5
8m	CH_2		4.0 ± 0.7	>9	<5
8n	CH_2		1.5 ± 0.4	2.0	
8o	CH_2		3.5 ± 0.9	>9	<5
8p	CH_2		3.5 ± 1.6	>9	7

[a] Displacement of ^{125}I-labeled neurokinin B from the cloned hNK_3 receptor expressed in CHO cells. Data are means ± SD (n = 3 or more).[2]
[b] Displacement of labeled MK-499 from cloned channel expressed in HEK cells.[5]
[c] Increase in hPXR activation in HepG2 cells transiently transfected with hPXR (% of 10 μM rifampicin positive control).[3]

labile. For example, **8f** had short half-life (rat, 1.4 h, dog, 2.4 h), with significant levels (greater than parent) of the dealkylated metabolite **8b** detected in plasma.

Metabolic N-dealkylation was a general problem for all analogs of **8f** and **11c** with primary and secondary *N*-alkyl groups. A potentially interesting approach to blocking this pathway would be to replace the pyran with a more hindered group, such as *tert*-butyl. Unfortunately, the SAR already established suggested that unacceptable hI_{Kr} affinity would be problematic with simple alkyl groups (e.g., **8d**, hI_{Kr} K_i 0.88 μM).

We have previously reported[1] that fluorination at the 8-position of the quinoline was tolerated by the hNK_3 receptor. This remained the case for molecules with amine side chains at C-3 and we were able to verify that it did not reintroduce hPXR activation (Table 2). However, we found that this substitution had the added benefit of significantly attenuating hI_{Kr} affinity (e.g., hI_{Kr} K_is: **8d**, 0.88 μM; **8l**, >9 μM). Crucially, this change expanded the scope of acceptable piperazine N-substituents, allowing us to introduce a range of groups onto the piperazine nitrogen without incurring an excessive hI_{Kr} liability (e.g., hI_{Kr} K_is: **8n**, 2 μM; **8p**, >9 μM).

We were disappointed to find that the hindered 4-methylpyran in **8p** did not improve PK properties (rat, $t_{1/2}$ 1.4 h). However, we noted that **8k** was not detected as a metabolite in plasma, suggesting that we had been successful in blocking N-dealkylation, but that a new mode of metabolism had been inadvertently introduced. This was supported by replacement of the N-substituent with a simple *tert*-butyl group (**8m**, hNK_3R IC_{50} 4.0 nM; hI_{Kr} K_i > 9 μM) which led to good metabolic stability in vitro (incubation with rat and human liver microsomes: <5% turnover after 15 min) and excellent PK properties (e.g., dog: F, 100%, $t_{1/2}$ 6.5 h) with no dealkylation to **8 k** detectable in plasma.

Cellular functional NK_3R antagonist activity of **8m** was measured in inositol phosphate generation studies using CHO/hNK_3R cells in response to eledoisin or senktide stimulation.[1] Eledoisin caused a concentration-dependent increase in inositol phosphate generation in these cells with an EC_{50} of 6.6 ± 0.1 nM (n = 2). In a Schild analysis of its antagonist behavior, **8m** caused a concentration-dependent rightward shift in the EC_{50} of eledoisin with a concomitant diminution of the maximal agonist response, indicative of a non-competitive or insurmountable antagonism. When titrated versus an approximate EC_{50} concentration (3 nM) of senktide, **8m** inhibited inositol phosphate generation with an IC_{50} of 3.0 ± 0.0 nM (n = 2).

Compound **8m** was very potent in the gerbil ex vivo central receptor occupancy assay[1] with an Occ_{90} of 7 mg/kg po and a plasma Occ_{90} of 0.4 μM when occupancy was measured 45 min post dosing. Further profiling of **8m** showed that it had modest affinity for hNK_2R (IC_{50} 50 nM) and good selectivity over hNK_1R (IC_{50} > 1 μM) as well as a panel of other receptors and ion channels.

8m also showed very low levels of CYP450 inhibition (human liver microsomes, 2C9, 2D6, 3A4, IC_{50}s > 30 μM) and had excellent physical properties (log *D* 1.7, pK_a 9.4, solubility > 5 mg/ml at pH 7.4).

In summary, we have shown that introduction of cyclic amine containing side chains onto *N*′,2-diphenylquinoline-4-carbohydrazide based NK_3R antagonists resolved the issue of unwanted activation of the hPXR receptor. A combination of fluorination at the quinoline 8-position and judicious choice of amine substituent led to a compound, **8m**, with excellent in vitro and in vivo properties.

References and notes

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2. NK_3 binding studies were conducted as a modification of a previously reported protocol[6] incubating 3×10^4 CHO cells stably expressing human NK_3 receptors with 30 pM [^{125}I]-labeled neurokinin B for 1 h at 25 °C followed by filtration over GF/C filter plates pre-soaked in 0.5% BSA.
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