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SUBSTITUTED 2,4-DIAMINOQUINAZOLINES AND 2,4-DIAMINO-8-ALKYLPURINES AS ANTAGONISTS OF THE NEUROKININ-2 (NK_2) RECEPTOR

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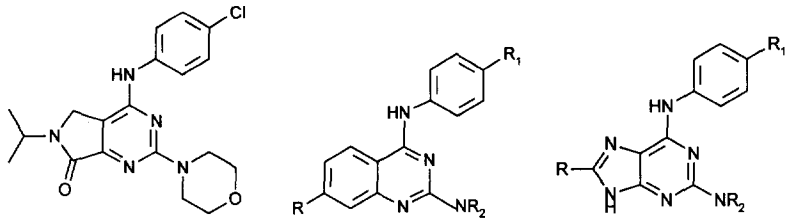
Abstract: Modification of the heterocyclic nucleus of a lead pyrrolopyrimidine (**1**) found to be active as an antagonist at the neurokinin-2 (NK_2) receptor is described. Compounds based on the purine nucleus (**3**) were found to be particularly interesting, and were modified in the C(2), C(4) and C(8) substituents to afford compounds with high potency.

Asthma is an inflammatory disease which affects a significant portion of the population, with recent data suggesting that the numbers of asthma sufferers is increasing.[1] One of the hallmark symptoms of asthma is a hyperresponsiveness of the bronchial airways to a variety of stimuli including allergens and cold air.[2] It has been proposed that a significant contributing factor to this hyperresponsiveness is the exposure of sensory afferent neurons known as C-fibers to the interstitial airspace as a result of damage to the epithelial layer of the lung.[3] It has been discovered that the neurotransmitters utilized by these neurons are a family of neuropeptides known collectively as tachykinins, including substance P, neurokinin A and neurokinin B. In the human, it has been suggested that neurokinin A is the tachykinin predominantly responsible for bronchoconstriction while substance P has a role in control of mucus secretion. The receptor at which neurokinin A has strongest affinity has been designated the NK_2 receptor, while the NK_1 receptor shows some preference for substance P.[4]

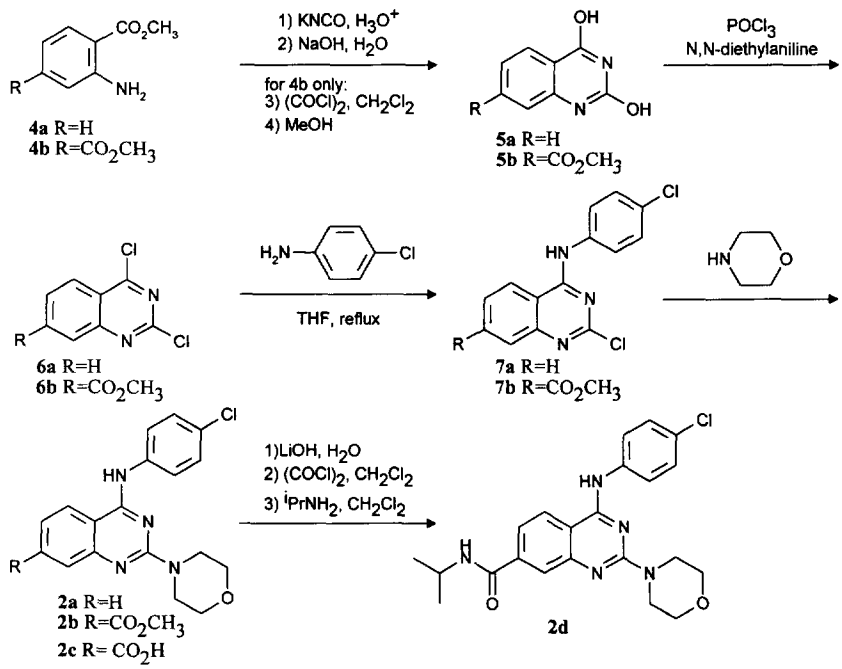
In the course of screening our company compound collection for activity opposite the NK_2 receptor, the pyrrolopyrimidine **1** was found to effectively displace [^{3}H]-NKA from the NK_2 receptor found in hamster urinary bladder membrane (HUBM), with a K_i= 0.015 μM.[5] Given the simplicity of this structure as opposed to the peptide agonist, an extensive study of the structure-activity relationships (SAR) in this series was initiated. In addition to modifications of the various substituents on the pyrrolopyrimidine nucleus,[6] we also sought to examine the role of the heterocyclic nucleus on biological activity. One strategy employed in this regard was to replace the bicyclic lactam with an aromatic bicycle such as a quinazoline **2** or purine **3**. We designed our synthetic routes to such structures to be sufficiently versatile to allow us to vary the substituents on the heterocyclic nucleus.



1 2 3

Initial targets in the quinazoline series incorporated an amide moiety at the 7-position of the quinazoline nucleus to mimic the lactam of **1**. These compounds were prepared using standard methods as depicted in Scheme 1. The anthranilic acid ester **4** was treated with potassium isocyanate under acidic conditions, followed by ring closure to the dihydroxyquinazolines **5** by treatment with aqueous base. In the case of the diester **4b**, the resulting carboyxlic acid was re-esterified by sequential treatment with oxalyl choride and methanol. Treatment of **5** with phosphorus oxychloride and N,N-diethylaniline afforded the dichloroquinazolines **6**, which when treated with 4-chloroaniline in refluxing THF afforded the 4-anilino derivatives **7**. Displacement of the less reactive 2-chloro substituent was achieved by heating **7** in morpholine to give the diamino derivatives **2**. The ester **2b** was saponified to the carboxylic acid **2c**, which was then converted to the amide **2d** via the acid chloride.

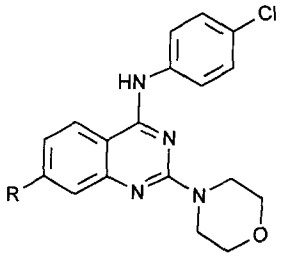
Scheme 1. Preparation of Quinazoline Derivatives **2**.



The unsubstituted quinazoline **2a** exhibited very poor binding affinity, as expected. The methyl ester **2b** was significantly more active, exhibiting a K_i of 0.82 μM. The carboxylic acid derivative **2c** was poorly active, as

expected, but we were surprised to find that the isopropyl amide **2d**, representative of several amides prepared, was no better than the carboxylic acid **2c** or the unsubstituted quinazoline **2a**. The binding data for the quinazoline derivatives is summarized in Table I.

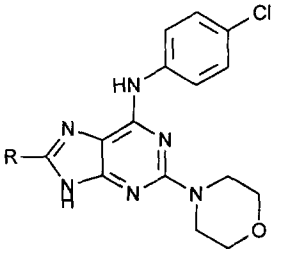
Table I. Quinazoline Derivatives



Compound No.	R	K_i (HUBM), μM
2a	H	29.5
2b	CO_2CH_3	0.82
2c	CO_2H	20.3
2d	CONHiPr	58.7

Based on this data, it was concluded that the increased binding affinity observed for **2b** was due to hydrophobic interactions rather than the hydrogen bonding interaction originally anticipated. Attempts to exploit this trend in the in the quinazoline series were not pursued, as the purine series appeared to be more interesting, and was synthetically more readily accessible. Simple aliphatic substituents placed at C(8) of the purine nucleus provided increasingly potent compounds as the chain length substituent was increased from methyl (**3a**) through propyl (**3c**), as summarized in Table II.

Table II. Purine Derivatives



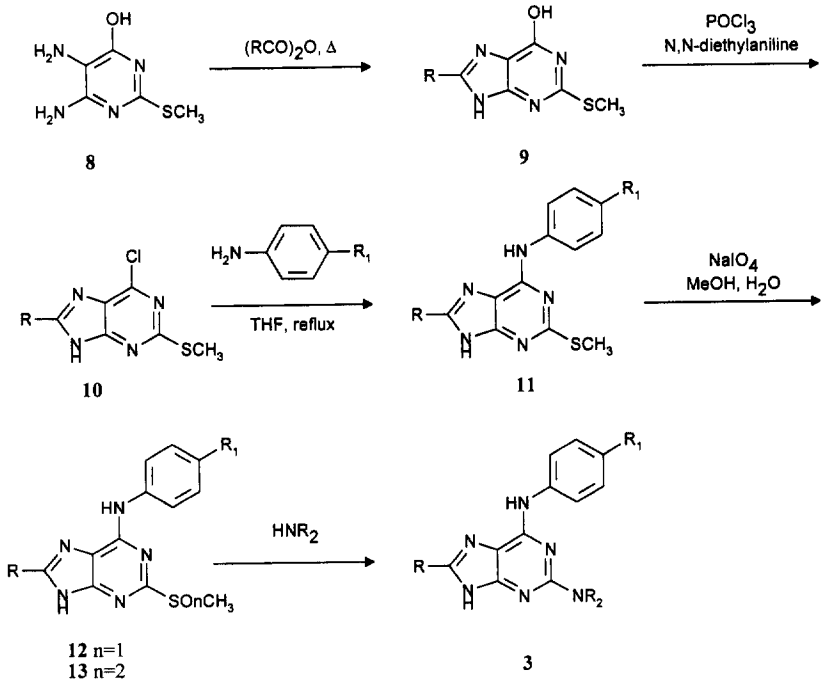
Compound No.	R	K_i (HUBM), μM	K_i (chNH2r), μM
3a	CH_3	6.6	17.5
3b	Et	0.52	6.94
3c	^nPr	0.054	2.34
3d	^iPr	0.067	3.07

Both the n-propyl (**3c**) and isopropyl (**3d**) compounds exhibited binding affinities similar to that observed for **1**, suggesting that the lactam carbonyl was not crucial for binding to the NK_2 receptor. Subsequent evaluation of **3a-3d** in a cloned human NK_2 receptor assay[7] revealed these compounds to have only micromolar affinity in this system. The discrepancy between the hamster and human receptor affinities was not limited to the purine derivatives **3**, as when screened in the same human NK_2 receptor system, our lead pyrrolopyrimidine **1** was found to have a K_i of 0.55 μM. Since the information available[8] suggested that the hamster and human receptors were different subtypes, optimization of the purine series in the cloned human receptor was our highest priority, and subsequent compounds were screened in the cloned human NK_2 receptor assay.

The synthetic route employed to prepare the purine derivatives, summarized in Scheme 2, allowed for straightforward modification of both the C(2) and C(4) substituents. Condensation of 4,5-diamino-6-hydroxy-2-methylthiopyrimidine[9] **8** with a carboxylic acid anhydride afforded the purine derivative **9**.[10] Introduction of the 4-substituent began by treatment of **9** with phosphorus oxychloride in the presence of N,N-diethylaniline[8]

to give the reactive 4-chloropurine derivative **10**, followed by displacement of the chloride by a substituted aniline to yield **11**. The thioether at C(2) was then oxidized by sodium periodate to give a mixture of sulfoxide **12** and sulfone **13** , which were reactive toward displacement by amines to give the final drug candidates **3**.

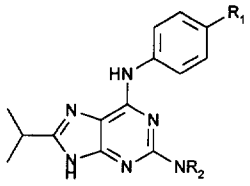
Scheme 2. Synthesis of Purine Derivatives **3**.

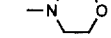
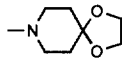
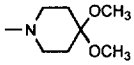
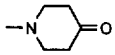
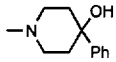
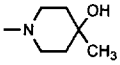
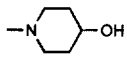


Attempts to improve binding affinity further by modification of either the C(2) substituent or the substitution pattern on the anilino group at C(4) were marginally successful. The C(2) substituent appeared to be a region which tolerated a wide variety of functionality: secondary and tertiary amines were of similar activity, sterically demanding groups such as the 4-hydroxy-4-phenylpiperidinyl derivative were all active with K_i's in the micromolar range (Table III). From SAR studies in the pyrrolopyrimidine series (e.g., **1**), it was known that replacement of the 4-chloro substituent of the aniline ring with trifluoromethyl afforded compounds of superior potency. This substitution was less beneficial in the purine series, giving only a small increase in binding affinity (compare **3d** with **3j**). Unfortunately, none of these substituents provided a compound with submicromolar affinity for the human receptor.

Finally, when these derivatives were tested for their ability to inhibit contractions of guinea pig trachea induced by an NK_2 receptor agonist,[11] only the 4-hydroxy-4-methylpiperidine derivative **3i** exhibited activity in the 10μM range. Given the discovery by Sanofi of their remarkably potent NK_2 receptor antagonist SR-48968,[12] which has a reported K_i =1 nM (rat) and a K_B = 1 nM (guinea pig), further work on the purine series was discontinued. Nonetheless, we feel that compounds of general structure **3** offer an interesting starting point for further optimization, and may provide some insight into the differences between the NK_{2a} and NK_{2b} subtypes.[13]

Table III. Purine Derivatives-Modification of the C(2) Substituent and C(4) Anilino Substitution Pattern.



Compound	R_1	NR_2	K_i (chNK2r), μM[a]	K_B (μM, gpt)[b]
3d	Cl		3.07	70.8
3e	Cl		4.36	NT
3f	Cl		3.44	NT
3g	Cl		5.89	NT
3h	Cl		2.24	100
3i	Cl		2.10	10.7
3j	CF_3		2.85	>100
3k	CF_3		1.77	>100
3l	Cl	-NH $(CH_2)_2CH_3$	3.49	NT
3m	Cl	$-NHCH_2Ph$	5.58	NT
3n	Cl	$-NH(CH_2)_3NH_2$	2.55	NT

[a] Inhibition constant for displacement of [^{3}H]NKA from a cloned human NK_2 receptor which has been expressed in Baculovirus infected insect sf21 cells. For a complete description of the characterization of this assay system, see reference 5. [b] K_B determined in guinea pig trachea for inhibition of contractions induced by [b-Ala^8-NKA(4-10)]. For details of this assay system, see reference 7.

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