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4-Amino-2-(aryl)-butylbenzamides and Their Conformationally Constrained Analogues. Potent Antagonists of the Human Neurokinin-2 (NK_2) Receptor

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Abstract—A library, evaluating a range of piperazines, piperidines and acyclic amines, as replacements for the 4-hydroxy-4-phenylpiperidine moiety in lead (**1b**) was prepared. These efforts identified the 4-((*N*)-benzimidazolone)piperidine analogue (**2a**) which was further optimised using classical single-compound synthesis to yield the 3-((*N*)-morpholino)azetidine (**2j**). Conformationally constrained analogues of (**2j**), generally offered no potency advantage in this particular series.

Introduction

Tachykinins and their receptors have been postulated to play a significant role in the pathophysiology of a wide variety of diseases including gastrointestinal disorders,[1] emesis,[2] chronic pain,[3] depression[4] and asthma.[5] Our own long standing efforts in this field have focused on investigating the role of neurokinin-2 antagonists in urological disorders.[6] Our initial studies in this area, however, were hampered by the lack of attractive chemical leads both as mechanistic tools and as starting points for a medicinal chemistry programme.

In 1991, however, the Sanofi group[7] reported the first examples of potent, non-peptidic NK_2 antagonists, exemplified by (**1**), Figure 1, precipitating significant activity in this structural series.[8] Benzamide, (**1a**), shows excellent potency against the human NK_2 receptor in binding studies (pIC_{50} 8.9) and functionally in the Rabbit Pulmonary Artery (RPA) assay (pA_2 9.1). Similarly, replacing the 4-*N*-acetyl group on the piperidine ring in (**1a**) with a 4-hydroxy group (**1b**) also resulted in a compound with excellent functional potency in the RPA assay (pA_2 9.5).

In this communication we wish to report our own preliminary SAR from within 4-amino-butylbenzamide series (**2**), using both parallel chemistry and single compound synthesis to explore both the role of the cyclic amine and the ring substitution in conferring potency in this series.

In addition, we also wish to report our preliminary findings from within a series of conformationally constrained analogues (**3**) containing a 3-((*N*)-morpholino)azetidine substituent, as a replacement for the 4,4-disubstituted piperidine moiety present in series (**1**).

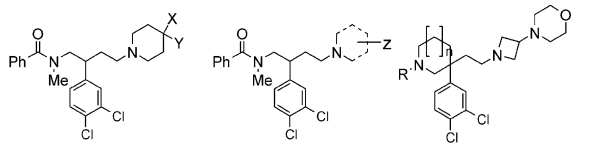

Figure 1.

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Chemistry

4-Amino-2-(3,4-dichlorophenyl)butylbenzamides (**1a**, **1b**, **1d**–**1f** and **2a**–**2j**) were prepared as shown in Scheme 1. Alkylation of commercially available 3,4-dichlorophenylacetonitrile with 2-bromoethyl tetrahydro-(2H)-pyran-2-yl ether in the presence of NaH as base and subsequent reduction of the nitrile using hydrogen in the presence of Raney nickel as catalyst under acid conditions, yielded (**4**). Formylation of the primary amine using paraformaldeheyde and borane reduction in THF as solvent, followed by treatment of the resulting secondary amine with benzoylchloride gave the benzamide (**5**). Alcohol (**5**) was then converted to the target compounds by one of two methods; oxidation to the aldehyde (**6**) under Swern conditions[9] and reductive amination of the resulting aldehyde with the appropriate amine, or alternatively, conversion to the mesylate, using methanesulphonyl chloride and displacement of the resulting mesylate using the appropriate amine in the presence of K_2CO_3 as base, in DMF at elevated temperature.

Pyrrolidines and piperidines (**3a**–-**3e**)[10] were prepared as shown in Scheme 2. Alkylation of (**7**), prepared as described in Scheme 1, with either ethyl bromoacetate or ethyl bromopropionate, using LDA as base in THF, gave (**8a**) and (**8b**), respectively. These homologues were then independently reduced to the amino esters, using hydrogen and Raney nickel as catalyst at room temperature, undergoing in situ lactamisation under the reduction conditions. Reduction of the γ- and δ-lactams to their respective cyclic amines, was then achieved using either $LiAlH_4$ or $BH_3.SMe_2$. Acylation with benzoyl chloride (for **3a** and **3b**), *ortho*-methoxybenzoyl chloride (for **3c**), 2-(cyclopropyl)acetyl chloride (**3d**) or phenylsulphonyl chloride (**3e**) and alcohol deprotection, using HCl in THF, then furnished the intermediates (**9a**) and (**9b**). The target compounds were then accessed using two separate routes. For targets (**3a**), (**3b**), and (**3d**), the appropriate alcohols (**9**) were oxidised to the aldehyde under Swern conditions and the resulting aldehyde reductively aminated using 3-((*N*)-morpholino)azetidine hydrochloride[11] in the presence of $NaBH(OAc)_3$. Targets (**3c**) and (**3e**) were accessed via conversion of the appropriate alcohols (**9**) to their mesylates using methanesulphonyl chloride in CH_2Cl_2 and subsequent displacement using 3-((*N*)-morpholino)azetidine hydrochloride in MeCN at reflux using NEt_3 and K_2CO_3 as base.

Results and Discussion

Library compounds

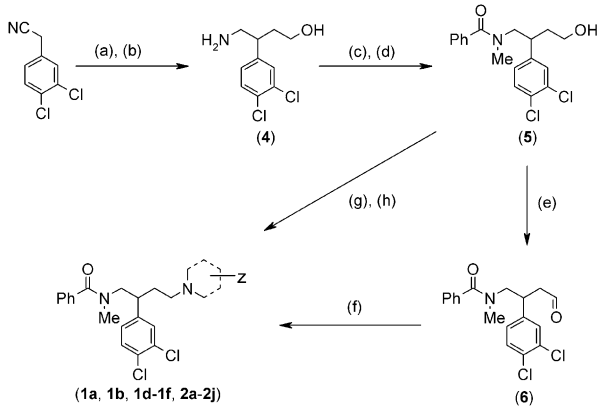
NK_2 receptor binding experiments on library compounds were carried out according to the method of Bergstrom[12] on rat duodenum membranes. Data were analysed using programmes to calculate percentage specific binding for each sample.

Singleton compounds

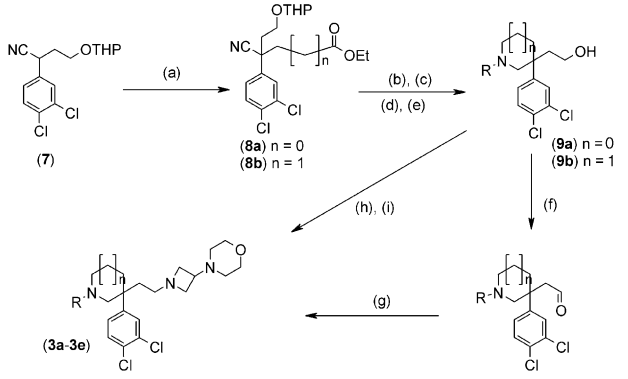
Competition binding experiments were performed in a NK_2 receptor assay using labeled ^{125}I NKA binding to human NK_2 receptors expressed in Chinese Hamster Ovary (CHO) cells. Functional activity was determined by testing their ability to antagonise the contractile effects of the selective NK_2 receptor agonist [*B*-ala^8]$NKA_{(4-10)}$ in the rabbit pulmonary artery (RPA), using the method of Pataccini and Maggi.[13]

The key objective of this work was to rapidly identify novel SAR for NK_2 activity in the piperidine region of lead (**1**). It is well precedented from the literature that the biological activity resides in the (*S*)-enantiomer of (**1**)[7c] and with this fact in mind, we chose to focus our efforts, in this initial phase of the programme, in the synthetically more accessible racemic series.

Initial exploration of the effects on potency of modifying piperidine substitution in (**1b**) produced some intriguing SAR, Table 1. For example, removal of the

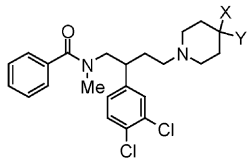


Scheme 1. Reagents and conditions: (a) Br-$(CH_2)_2$-OTHP, NaH, DMF; (b) H_2, Raney nickel; (c) (CHO)n, BH_3, THF; (d) PhCOCl, NEt_3 CH_2Cl_2, rt; (e) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (f) cyclic amine, $NaBH(OAc)_3$, AcOH, NEt_3, THF; (g), $MeSO_2Cl$, NEt_3, CH_2Cl_2; (h) amine, K_2CO_3, DMF.



Scheme 2. Reagents and conditions: (a) Ethyl bromoacetate ($n=0$) or ethyl bromopropionate ($n=1$), LDA, THF, −78 °C to rt; (b) H_2, Raney nickel, MeOH; (c) $LiAlH_4$, Et_2O or $BH_3.SMe_2$, THF, reflux; (d) acylation or sulphonylation, NEt_3, CH_2Cl_2; (e) HCl, THF, rt; (f) $(COCl)_2$, NEt_3, DMSO, CH_2Cl_2; (g) 3-((*N*)-morpholino)azetidine hydrochloride, $NaBH(OAc)_3$, AcOH, NEt_3, THF, rt; (h) $MeSO_2Cl$, NEt_3, CH_2Cl_2, rt; (i) 3-((*N*)-morpholino)azetidine hydrochloride, NEt_3, K_2CO_3, MeCN, reflux.

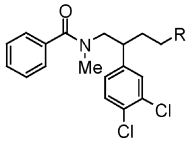
Table 1. Human NK_2 binding and RPA functional data for 4-piperidinyl-2-(3,4-dichlorophenyl)-butylbenzamides (**1b–f**)

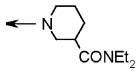
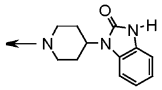


Compd[a]	X	Y	NK_2 binding (CHO, IC_{50}, nM)[b]	NK_2 Functional (RPA, pA_2)
1b	–Ph	–OH	8.9	9.5
1c	–Ph	–H	<7[c]	NT
1d	–H	–OH	6.4	NT
1e	–H	–H	6.3	NT
1f		–OH	6.6	NT

NT = not tested.
[a]All compounds are racemic.
[b]All determinations $n \geq 2$ (each experiment performed in triplicate).
[c]Literature data (ref 7c).

Table 2. NK_2 binding inhibition data for 3-(diethylcarboxamido)piperidine (**9**) and benzimidazolone analogue (**2a**)



Compd[a]	R	NK_2 binding (CHO)
9		61% inhibition @ 100nM
2a		81% inhibition @ 100nM

[a]All compounds are racemic.

4-hydroxyl group (**1c**)[7c] resulted in a precipitous drop in potency (pIC_{50} <7).[7c] Similarly, removal of the 4-phenyl ring, while retaining the 4-hydroxy substituent, (**1d**) (pIC_{50} 6.4) also resulted in a large reduction in activity relative to the 4-phenyl-4-hydroxy analogue (**1b**) (pIC_{50} 8.9).

Removal of both substituents to give the unsubstituted piperidine derivative (**1e**) gave a compound of roughly equivalent potency to either of the two mono-substituted analogues (**1c**) or (**1d**). Based on these initial data we believed that the key feature imparting activity observed in (**1b**) was the presence of an axial hydroxyl group. To explore this hypothesis further, we prepared the 4-imidazo-4-hydroxy analogue (**1f**).[14] Unfortunately, this compound was found to possess only weak activity against the human NK_2 receptor (pIC_{50} 6.6), suggesting that the two piperidine 4-substituents in (**1b**) were working synergistically to give the high NK_2 activity observed.

As a strategy to follow-up this intriguing SAR, we prepared a library[15] of compounds to rapidly explore the spatial region of the receptor occupied by the 4,4-disubstituted piperidine in (**1**). From these studies, several monosubstituted compounds emerged showing excellent inhibition profiles in the NK_2 binding assay. For example, Table 2, the 3-diethylcarboxamido analogue (**9**) and the 4-((*N*)-benzimidazolone)piperidine (**2a**) were found to possess high NK_2 inhibitory activity in the rat duodenum screen (61 and 81% inhibition, respectively, at 100 nM).

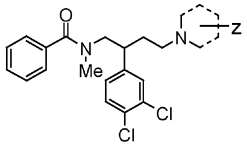
Resynthesis and rescreening of (**2a**) revealed the compound to possess excellent NK_2 binding activity (pIC_{50} 8.9) and high functional potency in the RPA assay (pA_2 8.4). Following up this exciting new lead, a series of analogues were prepared, Table 3.

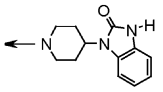
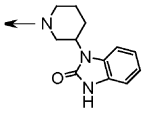
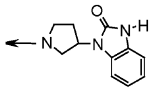
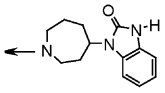
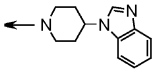
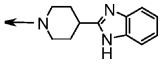
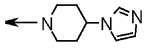
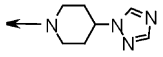
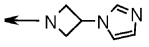
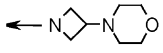
Initial analogues of library-derived lead (**2a**), focused on retaining the *N*-linked benzimidazolone and modifying both the substitution on the piperidine ring and the cyclic amine ring size. For example, 3-piperidine substituted isomer (**2b**) (pIC_{50} 7.1) was found to be significantly weaker in NK_2 binding studies than the 4-isomer (**2a**). Changing the piperidine into a pyrrolidine (**2c**) was also found to reduce potency (pIC_{50} 7.4). Increasing the amine ring size to give the homopiperidine analogue (**2d**) retained functional potency (pA_2 8.4) relative to the piperidine. Conversion of the benzimidazolone (**2a**) to the *N*-linked benzimidazole (**2e**) resulted in a small reduction in binding activity (pIC_{50} 8.1), although functional activity in the RPA assay was retained (pA_2 8.6), indicating that the imidazolone carbonyl in (**2a**) was not needed for high NK_2 activity. To explore this observation further, the (C)-2 linked benzimidazole (**2f**) isomer was also prepared. Disappointingly, this compound was found to be 20-fold weaker than the (*N*)-1 isomer (**2e**) in the RPA assay. Interestingly, removal of the fused phenyl ring in (**2e**) to give the simple 4-((*N*)-imidazolyl)piperidine (**2g**), as a strategy to reduce MWt, effectively retained functional potency (pA_2 8.3), although the triazole analogue (**2h**) was >10-fold weaker than the imidazole. Replacing the piperidine ring present in (**2g**) with the azetidine (**2i**) resulted in only a small reduction in functional potency (pA_2 7.6), suggesting that the 3-substituted azetidine effectively mimicked the directionality of the 4-substituted piperidine, placing the imidazole substituent in a similar region of space to its larger ring homologue. Building on this azetidine SAR further, we investigated non-aromatic substituents at the 3-position.[16] From these studies, the 3-(*N*)-morpholino analogue (**2j**) emerged. This compound was found to possess excellent functional potency (pA_2 8.9).

Attempts to further increase the potency of lead (**2j**) by introducing conformational constraint, Figure 2, were also explored.

Cyclisation of the amide methyl group in (**2j**) into a ring,[17] (**3**), Figure 2, gave a series of acylpyrrolidines ($n = 0$) and piperidines ($n = 1$), Table 4.

Table 3. Human NK_2 binding and RPA functional data for 4-piperidinyl-2-(3,4-dichlorophenyl)-butylbenzamides (**2a–2j**)



Compd[a]		NK_2 binding (CHO, IC_{50}, nM)[b]	NK_2 Functional (RPA, pA_2)
2a		8.9	8.4
2b		7.1	NT
2c		7.4	NT
2d		8.4	8.4
2e		8.1	8.6
2f		7.3	7.3
2g		7.7	8.3
2h		6.8	7.1
2i		6.8	7.6
2j		7.7	8.9

NT = not tested.
[a]All compounds are racemic.
[b]All determinations $n \geq 2$ (each experiment performed in triplicate).

For example, *N*-benzoylpyrrolidine (**3a**) was found to be slightly weaker than the acyclic analogue (**2j**) in both binding and functional studies, while the *N*-benzoylpiperidine was found to be equipotent with (**2j**). The *ortho*-methoxy analogue of (**3b**) was found to be 10-fold weaker in NK_2 binding studies. Similarly, the 2-(cyclopropyl)acetyl analogue (**3d**) (pIC_{50} 6.3) was also found to be weaker than the *N*-benzoyl analogue (**3b**). The phenylsulphonamide analogue (**3e**), was also found to be functionally 10-fold weaker in the RPA assay than (**3b**).

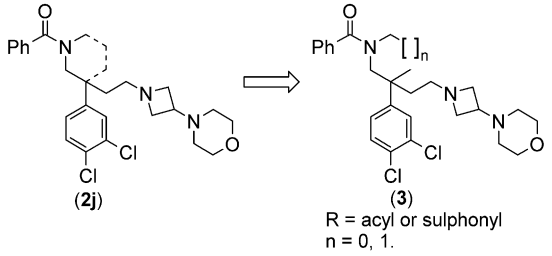
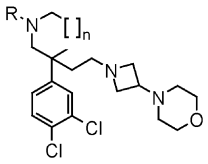
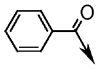
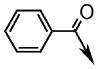
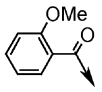
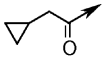


Figure 2. Cyclisation as a strategy to improve potency in lead (**2j**).

Table 4. Human NK_2 binding and RPA functional data for cyclic *N*-acylated pyrrolidines and piperidines (**3a-3e**)



Compd[a]	R	*n*	NK_2 (CHO, IC_{50}, nM)[b]	NK_2 Functional (RPA, pA_2)
2j	—	—	7.7	8.9
3a		0	7.2	8.1
3b		1	7.5	8.4
3c		1	6.5	7.7
3d		1	6.3	NT
3e	$PhSO_{2-}$	1	6.7	7.2

NT = not tested.
[a]All compounds are racemic except (**3d**) (S-enantiomer).
[b]All determinations $n \geq 2$ (each experiment performed in triplicate).

In summary, initial analogues of literature lead (**1b**) revealed that the two piperidine 4,4-disubstituents were working in a synergistic manner, with analogues possessing either substituent alone found to be only weakly active in the NK_2 binding assay. To more fully explore this intriguing SAR as rapidly as possible, we employed a library-based strategy, evaluating a range of piperazine, piperidines and acyclic amines, as replacements for the 4-hydroxy-4-phenylpiperidine moiety. These efforts identified the 4((*N*)-benzimidazolone)piperidine analogue (**2a**) as a potent 4-mono-substituted piperidine replacement for the 4-hydroxy-4-phenylpiperidine group in (**1a**), which demonstrated similar functional activity in the RPA assay. Further optimisation of this library-derived lead, using classical single-compound synthesis identified the 3-((*N*)-morpholinoazetidine (**2j**), which possessed similar functional potency to both (**1b**) and (**2a**). Conformationally constrained analogues of (**2j**), acylpyrrolidine (**3a**) and acylpiperidine (**3b**), designed to further increase NK_2 activity, whilst active, generally offered no potency advantage in this particular series.

Further studies to optimise the profiles of NK_2 antagonists from these and related, stereochemically defined, series will be the subject of future communications from these laboratories.

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References and Notes

1. Lecci, A. *Trends Pharmacol. Sci.* **2001**, *22*, 551.
2. Gale, J. D.; O'Neill, B. T.; Humphrey, J. M. *Exp. Opin. Ther. Pat.* **2001**, *11*, 1354.
3. Sakurada, T.; Sakurada, C.; Tan-No, K.; Kisara, K. *CNS Drugs* **1997**, *8*, 436.
4. Stout, S. C.; Owens, M. J.; Nemeroff, C. B. *Ann. Rev. Pharm. Toxicol.* **2001**, *41*, 877.
5. Rogers, D. F. *Exp. Opin. Ther. Pat.* **2001**, *11*, 1097 and references cited therein.
6. (a) Bushfield, M.; Metcalfe, M.; Naylor, A. M. *Br. J. Pharmacol.* **1995**, *115*, 875. (b) Newgreen, D. T. *Emerg. Drugs* **1998**, *3*, 209.
7. (a) Advenier, C.; Edmonds-Alt, X.; Vilain, P.; Goulaouic, P.; Protietto, P.; Van Broeck, D.; Naline, E.; Le Fur, G.; Breliere, J. C. *British Pharmacological Society Meeting*, **1991**, abstract C82. (b) Edmonds-Alt, X.; Goulaouic, P.; Proietto, C.; van Broeck, D. *European Patent* 0 474 561 A1, **1991**. (c) Edmonds-Alt, X.; Proietto, P.; Van Broeck, D.; Vilain, P.; Advenier, C.; Neliat, G.; Le Fur, G.; Breliere, J.-C. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 925. (d) Edmonds-Alt, X.; Vilain, P.; Proietto, V.; Van Broeck, D.; Naline, E.; Neliat, G.; Le Fur, G.; Breliere, J. C. *Life Sci.* **1992**, *50*, PL-101–PL-106.
8. For leading references see: (a) Gao, Z.; Peet, N. P. *Curr. Med. Chem.* **1999**, *6*, 375. (b) Seward, E. M.; Swain, C. J. *Exp. Opin. Ther. Pat.* **1999**, *9*, 571. (c) Swain, C. J. *Progress Med. Chem.* **1998**, *35*, 57.
9. Tidwell, T. T. *Org. React. (N.Y.)* **1990**, *39*, 297.
10. The synthesis and spectral data of all compounds has been reported previously. See: MacKenzie, A. R.; Marchington, A. P.; Middleton, D. S.; Meadows, S. D. *US Patent* **2001**, *6*, 242 438.
11. The synthesis and spectral data of 3-((*N*)-morpholino)-azetidine has been reported previously. See: MacKenzie, A. R.; Marchington, A. P.; Meadows, S. D.; Middleton, D. S. *US Patent* **1996**, *5*, 963 923.
12. Bergstrom, L.; Beaujouan, L. C.; Torrens, Y.; Saffroy, M.; Glowinski, J.; Lavielle, S.; Chassaing, G.; Marguet, A.; D'Orleans-Juste, P.; Dion, S. *Mol. Pharmacol.* **1987**, *32*, 764.
13. Patacchini, R.; Maggi, C. A. *Eur. J. Pharmacol.* **1993**, *236*, 31.
14. 4-(2-imidazo)-4-hydroxy-piperidine used in the preparation of (**1f**) was prepared in two steps from commercially available *N*-benzylimidazole and *N*-benzylpiperidine-4-one, via 2-lithiation of the imidazole at $-60\,^{\circ}C$ in THF, followed by quenching with *N*-benzylpiperidine-4-one. Following work up and chromatography of the tertiary alcohol product, hydrogenolysis of the two *N*-benzyl groups was affected using 10% Pd/C under an atmosphere of hydrogen at 30 psi, $50\,^{\circ}C$ for 4 h.
15. (a) The library was prepared by the reaction of the mesylate formed in Scheme 1 with substituted piperazines, piperidines and secondary alicyclic amines (86 reactants in total) using acetonitrile as solvent and heating the reaction mixtures in sealed reacti-vials™. The products were analysed by TLC and MS; the majority showed a single new product on TLC and the expected molecular ion by MS. (b) Selway, C. N.; Terrett, N. K. *Bioorg. Med. Chem.* **1996**, *4*, 645.
16. MacKenzie, A. R.; Marchington, A. P.; Middleton, D. S.; Newman, S. D.; Jones, B. C. *J. Med. Chem.* **2002**, *45*, 5365.
17. Goulaouic, P.; Edmonds-Alt, X.; Guele, P.; Proietto, V. *European Patent* **1992**, 512 901.