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1-Phenyl-8-azabicyclo[3.2.1]octane ethers: A novel series of neurokinin (NK_1) antagonists

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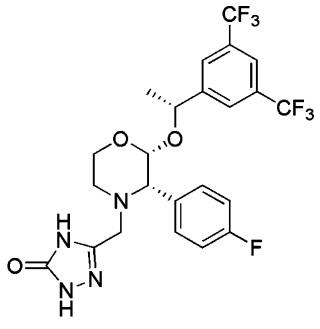
Abstract—1-Phenyl-8-azabicyclo[3.2.1]octane ethers are NK_1 receptor antagonists. Substitution at the 6-*exo*-position led to high affinity NK_1 antagonists with a prolonged duration of action in vivo. Incorporation of an α-methyl substituent in the pendent benzyl ether side chain gave compounds with increased selectivity over the hERG channel.

Research at Merck into selective non-peptide NK_1 antagonists culminated in the identification of Aprepitant (Emend®)[1] as a potent, orally active drug suitable for the treatment of both the acute and delayed phases of chemotherapy induced nausea and vomiting.[2]

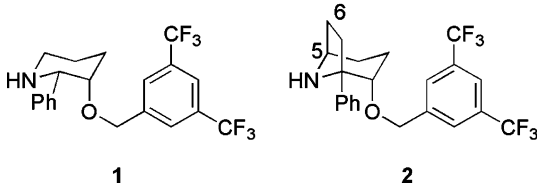
Since 1991, when the first non-peptidic NK_1 receptor antagonist was reported by Pfizer,[3] numerous selective and structurally diverse NK_1 antagonists have been identified (e.g., **1**).[4] As part of our effort in this area, we have been actively investigating conformationally restricted piperidine derivatives (e.g., **2**) of known NK_1 receptor antagonists (Fig. 1).

The key synthetic transformation used in the preparation of analogues of **2** and a related benzylamine series[5] was a [3 + 2] cycloaddition reaction[6] (Schemes 1 and 2). C-6 bridge substituents were introduced using this methodology. Herein, we will focus on the preparation of tetrazoles as the C-6 substituent (Schemes 2 and 3).

1-Benzyl-3-hydroxy-2-phenylpyridinium bromide **3** was prepared in two steps from commercially available 2-bromo-3-hydroxypyridine (Scheme 1). 1,3-Dipolar cycloaddition of the betaine **3** with phenyl vinyl sulfone afforded the cycloadduct **4** as the predominant epimer. Hydrogenation of the double bond followed by reduc-



Aprepitant, Emend ®



1 **2**

Figure 1.

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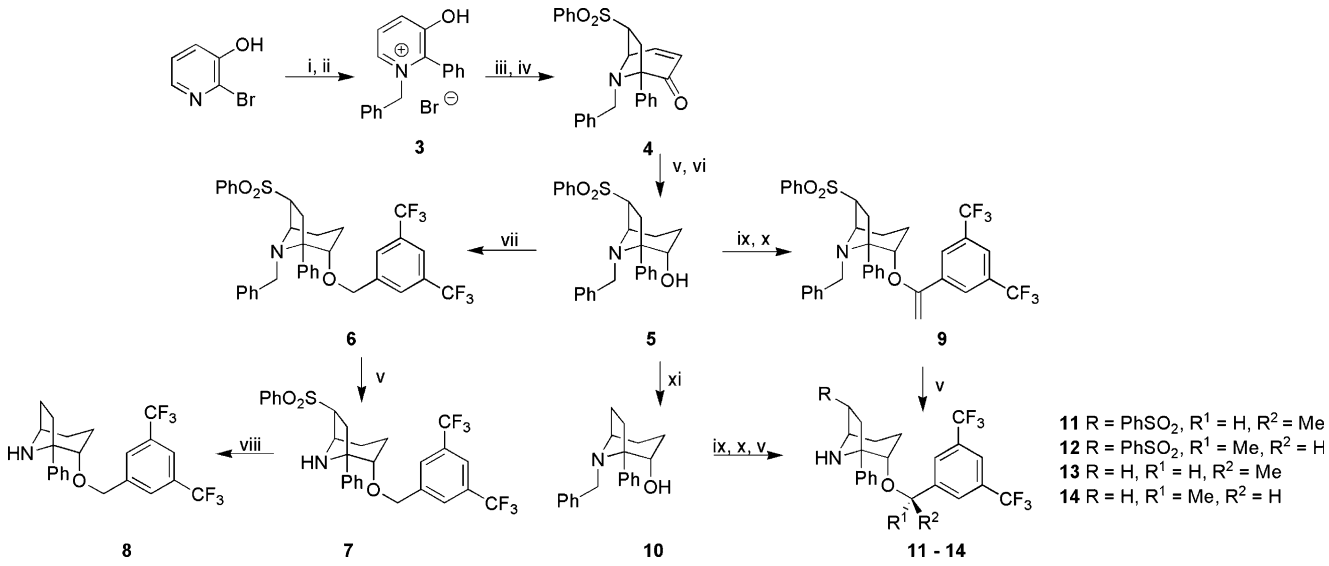
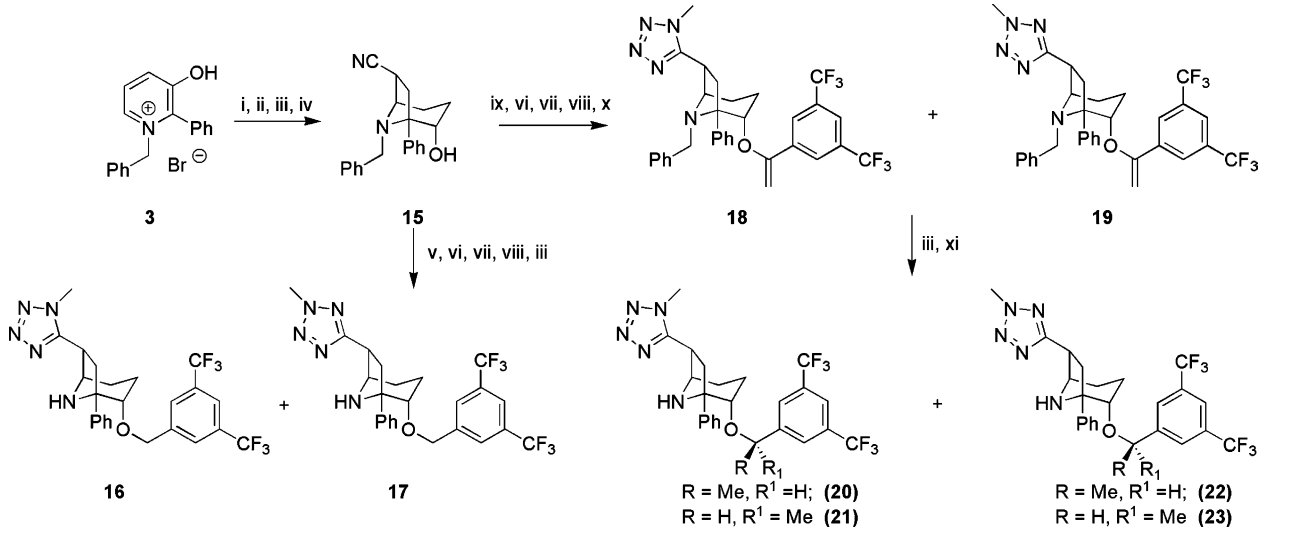


Scheme 1. Reagents and conditions: (i) $PhB(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, toluene, H_2O; (ii) benzyl bromide, toluene; (iii) phenyl vinyl sulfone, 1,4-dioxane, Et_3N; (iv) separation of cycloadducts, SiO_2; (v) Pd/C, H_2, EtOH; (vi) $NaBH_4$, MeOH, THF; (vii) 3,5-bis(trifluoromethyl)benzylbromide, NaH, THF; (viii) Na(Hg), MeOH, THF; (ix) 3,5-bis(trifluoromethyl)benzoyl chloride, Et_3N, DMAP, DCM; (x) dimethyl titanocene, toluene; (xi) lithium naphthalenide, THF, −78 °C.

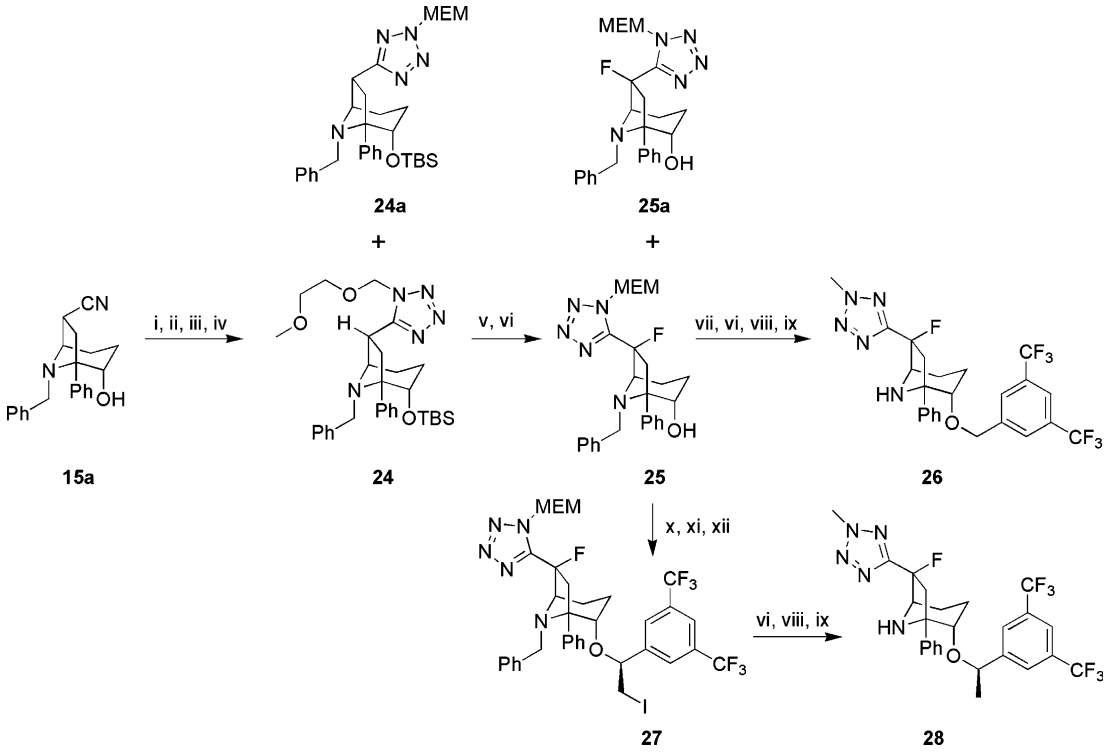


Scheme 2. Reagents and conditions: (i) acrylonitrile, 1,4-dioxane, Et_3N; (ii) separation of cycloadducts, SiO_2; (iii) Pd/C, H_2, EtOH; (iv) $NaBH_4$, MeOH, THF; (v) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, THF; (vi) NaN_3, NH_4Cl, DMF; (vii) MeI, K_2CO_3, DMF; (viii) regioisomer separation, SiO_2; (ix) 3,5-bis(trifluoromethyl)benzoyl chloride, Et_3N, DMAP, DCM; (x) dimethyl titanocene, toluene; (xi) diastereomer separation, SiO_2.

tion of the ketone to the *exo*-alcohol **5** and alkylation with 3,5-bis(trifluoromethyl)benzyl bromide afforded the ether **6** from which the *N*-benzyl and phenyl sulfone groups were successively removed to give **7** and **8**.

Esterification of the *exo*-alcohol **5** with 3,5-bis(trifluoromethyl)benzoyl chloride was followed by formation of the enol ether **9** using the conditions developed by Petasis.[7] Hydrogenation and diastereomer separation gave the α-methylbenzyl derivatives **11** and **12**. Unsubstituted compounds **13** and **14** were prepared in an analogous fashion from **10** following reductive removal of the phenyl sulfone from **5** (Scheme 1). Compound **11** (hNK_1 0.6 nM) displayed only modest brain penetration in the gerbil foot-tapping assay (Table 1). We reasoned that the polar phenyl sulfone fragment found in **11** would not be optimal for good brain penetration and hence sought to replace this group in subsequent compounds.

1,3-Dipolar cycloaddition of the betaine **3** with acrylonitrile followed by chromatographic separation of the cycloadducts and elaboration analogous to that described in Scheme 1 gave the 6-*exo*-cyano alcohol **15**. The 6-*endo*-cyano analogue, **15a**, was also isolated and utilized subsequently (Scheme 3). Alkylation with 3,5-bis(trifluoromethyl)benzyl bromide followed by tetrazole formation, alkylation and *N*-benzyl deprotection gave the



Scheme 3. Reagents and conditions: (i) TBSOTf, Et_3N, DCM; (ii) NaN_3, $Et_3N{\cdot}HCl$, DMF; (iii) MEM-Cl, K_2CO_3, DMF; (iv) regioisomer separation, SiO_2, **24**:**24a** = 1:1.5; (v) ^{n}BuLi, $(PhSO)_2NF$, THF, **25**:**25a** = 1:1; (vi) HCl, Et_2O, MeOH; (vii) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, THF; (viii) PPh_3, DEAD, THF, MeOH; (ix) Pd/C, H_2, EtOH; (x) 3,5-bis(trifluoromethyl)phenyl diazo acetic acid methyl ester, $Rh_2(OAc)_4$, DCE; (xi) $LiBH_4$, Et_2O; (xii) PPh_3, I_2, imidazole, DCM.

isomeric tetrazoles **16** and **17** (Scheme 2). Introduction of an α-methylbenzyl substituent was achieved by esterification of the *exo*-alcohol **15** with 3,5-bis(trifluoromethyl)benzoyl chloride followed by tetrazole formation, alkylation and chromatographic regioisomer separation. Formation of the enol ethers **18** and **19** was carried out as described previously. Subsequent hydrogenation and diastereomer separation gave the isomeric pairs of α-methylbenzyl ethers, **20** and **21**; **22** and **23** (Scheme 2).

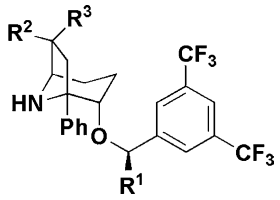
Fluorine is commonly incorporated into biologically active compounds since it gives rise to minimal steric impact, whilst its electronegativity influences pK_a.[8] We wished to examine the effect of reducing pK_a on the hERG channel liability.[9] Elaboration of **15a** gave the regioisomers **24** and **24a** after chromatography (Scheme 3). Tetrazole derivatives bearing a fluorine atom at the 6-*endo*-position were prepared by fluorination of **24** with *N*-fluorobenzenesulfonamide. During the course of this transformation, epimerization of the C-6 position was observed. Removal of the TBS group revealed the diastereomeric fluorides **25** and **25a**. Etherification of **25** followed by removal of the MEM group, regioselective tetrazole N-2 methylation under Mitsunobu[10] conditions and hydrogenation yielded the fluorinated benzylether **26**.

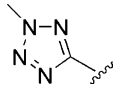
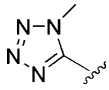
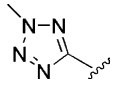
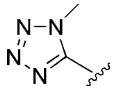
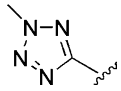
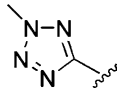
Hydrogenation of either of the enol ethers **18** or **19** resulted in variable ratios of epimers, typically with the undesired (α) isomer predominant. Hence, an alternate synthesis towards the α-methylbenzyl ethers was required. Rhodium (II) catalysed insertion of alcohol **25** with [3,5-bis(trifluoromethyl)phenyl]-diazo acetic acid methyl ester[11] yielded a 3.4:1 ratio of isomers with the preferred (β) isomer the major product. Chromatographic separation of the isomers followed by reduction of the methyl ester and iodination of the resulting alcohol gave **27**. Elaboration of **27** via MEM deprotection, tetrazole N-methylation and hydrogenation resulted in the desired α-methylbenzyl ether **28**.

The data in Table 1 reveal that substitution at the 6-position of the bicyclic[3.2.1] ring system is tolerated. Compound **7** bearing a 6-*exo*-phenylsulfonyl group shows similar binding affinity for the hNK_1 receptor as the parent **8**. Substitution of the pendent benzyl ether shows the β-diasteromer **13** to be more potent than the α-analogue **14** (hNK_1 IC_{50} 200 nM). However, substitution at the benzylic position on its own does not improve affinity relative to the parent, **8**. Interestingly, a combination of 6-substituent coupled with an α-methylbenzyl fragment gives rise to a more potent compound, **11**.

The N-2 methyl tetrazole derivative **17** exhibits high affinity for the hNK_1 receptor. The ability of **17** to occupy central hNK_1 receptors in vivo was studied further. Foot-tapping in gerbils is induced after central infusion of the NK_1 agonist GR 73632. This is a centrally mediated response; dosing immediately prior to the agonist challenge ($GFT_{t=0}$) demonstrates that a compound is brain penetrant. Dosing with **17** twenty-four hours prior to the agonist challenge demonstrates duration of action

Table 1. NK_1 receptor binding, hERG channel activity and gerbil foot-tapping results for the azabicyclic series



Compound	R^1	R^2	R^3	hNK_1 IC_{50}[a] (nM)	hERG K_i[b] (nM)	Gerbil foot tapping ID_{50} mg/kg iv[c]	
						$t = 0$ h	$t = 24$ h
8	H	H	H	3	300		
7	H	$PhSO_2$	H	2.8	1300		
13	Me	H	H	4.2			
11	Me	$PhSO_2$	H	0.6	1930	39% at 3	
17	H		H	1.0	100	0.3	0.6
16	H		H	9.0	1250		
22	Me		H	0.5	1800	0.4	1.1
20	Me		H	1.2	2800	0.2	0.8
26	H		F	1.5	>10,000		11% at 3
28	Me		F	0.4	>5000		23% at 3

Data are geometric means of 3–6 determinations.

[a] Displacement of [^{125}I]-labelled substance P from the cloned hNK_1 receptor expressed in CHO cells.[12]

[b] Displacement of [^{35}S]-labelled MK-499 from the cloned receptor expressed in HEK cells.[13]

[c] Inhibition of GR 73632 induced foot-tapping in gerbils.[14] Where an ID_{50} value was not determined, % inhibition at 3 mg/kg is quoted.

($GFT_{t=24h}$). Despite the excellent in vivo properties of **17**, it is compromised by its hERG liability. In comparison the N-1 methyl tetrazole, **16** displayed a lower potency for the hERG channel although coupled with lower affinity for the target receptor. Installation of an α-methyl group (**20** and **22**) in the pendent bis(trifluoromethyl)benzyl ether resulted in an increase in hNK_1 affinity over the corresponding unsubstituted analogues (**16** and **17**). Both **20** and **22** retain excellent brain penetration, duration of action and interestingly, an increase in selectivity over hERG channel activity in both the N-1 and N-2 methyl tetrazoles. There was a particularly striking eighteen-fold reduction observed in the N-2 methyl tetrazole analogue **22** over the unsubstituted derivative **17**. Introduction of a fluorine atom (**26** and **28**) at the C-6 position of the azabicyclic ring maintained the hNK_1 affinity observed in the des-fluoro analogues **17** and **22** but dramatically increases the selectivity over the hERG channel. Unfortunately, however, this was accompanied by a reduction in the duration of action in vivo (Table 1).

In conclusion, we have identified and evaluated a novel series of NK_1 receptor ligands. Introduction of a tetrazole moiety at the 6-*exo*-position of the 8-azabicyclo[3.2.1]octane core led to the identification of **17** which showed both rapid CNS penetration and extended duration of action in vivo.

Introduction of an α-methyl substituent into the pendent benzyl ether side chain attenuated the hERG activity whilst maintaining efficacy in the gerbil foot-tapping assay. Finally we found that modulating the pK_a of the azabicycle significantly affected the hERG affinity in vitro. However, incorporation of the fluorine atom resulted in a reduction of efficacy in vivo.

References and notes

1. Hale, J. J.; Mills, S. G.; MacCoss, M.; Finke, P. E.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Chicchi, G. G.; Kurtz, M.; Metzger, J.; Eirmann, G.; Tsou, N. N.; Tattersall, F. D.; Rupniak, N. M. J.; Williams, A. R.; Rycroft, W.; Hargreaves, R.; MacIntyre, D. E. *J. Med. Chem.* **1998**, *41*, 4607.
2. Dando, T. M.; Perry, C. M. *Drugs* **2004**, *64*, 777.
3. Snider, R. M.; Constantine, J. W.; Lowe, J. A., III; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H. J. *Science* **1991**, *251*, 435.
4. Harrison, T.; Wiliams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545.
5. Thomson, C. G.; Carlson, E.; Chicchi, G. G.; Kulagowski, J. J.; Kurtz, M. M.; Swain, C. J.; Tsao, K. C.; Wheeldon, A. *Bioorg. Med. Chem. Lett.*, in press.;
6. Kozikowski, A. P.; Araldi, G. L.; Ball, R. G. *J. Org. Chem.* **1997**, *62*, 503.
7. Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
8. Welch, J. T.; Eswarakrishnan, S. In *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991; p 1.
9. Inhibition of the hERG channel is implicated as the underlying cause of cardiac disfunctions such as QT interval prolongation and Torsades de Pointes: Finlayson, K.; Withel, H. J.; McCulloch, J.; Sharkey, J. *Eur. J. Pharmacol.* **2004**, *500*, 129.
10. Purchase, C. F.; White, A. D. *Synth. Commun.* **1996**, *26*, 2687.
11. Lewis, R. T.; Ladduwahetty, T.; Merchant, K. J.; Keown, L. E.; Hitzel, L.; Verrier, H.; Stevenson, G. I.; MacLeod, A. M. *J. Org. Chem.* **2000**, *65*, 2615.
12. Cascieri, M. A.; Ber, E.; Fong, T. M.; Sadowski, S.; Bansal, A.; Swain, C. J.; Seward, E. M.; Frances, B.; Burns, D.; Strader, C. D. *Mol. Pharmacol.* **1992**, *42*, 458.
13. Cooper, L. C.; Carlson, E.; Castro, J. C.; Chicchi, G.; Dinnell, K.; Di Salvo, J.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Ridgill, M. P.; Rycroft, W.; Tsao, K.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1759.
14. Rupniak, N. M. J.; Tattersall, F. D.; Williams, A. R.; Rycroft, W.; Carlson, E. J.; Casieri, M. A.; Sadowski, S.; Ber, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Seward, E.; Huscroft, I.; Owen, S.; Swain, C. J.; Hill, R. G.; Hargreaves, R. J. *Eur. J. Pharmacol.* **1997**, *326*, 201.