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Synthesis and 5-HT$_3$ Receptor Antagonist Potency of Novel (*endo*) 3,9-Diazabicyclo[3.3.1]nonan-7-amino Derivatives.

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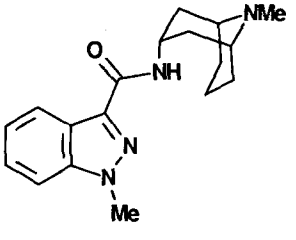
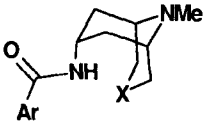
Abstract. The synthesis and 5-HT$_3$ receptor affinity and/or antagonist activity of a series of novel N-(3,9-diazabicyclo[3.3.1]nonan-7-yl)amides (3-azagranatanes) are described. High potency is retained with relatively bulky 3-N substituents indicative of a large sterically allowed volume "underneath" the piperidine ring.

Granisetron (**1**) is a potent and selective 5-HT$_3$ receptor antagonist used clinically in the treatment of chemotherapy-induced emesis in cancer patients[1]. A key structural feature of granisetron is the 9-azabicyclo[3.3.1]nonane (granatane) basic side chain which is believed to form a key binding interaction with the 5-HT$_3$ receptor, probably an ionic interaction with an aspartate. We have recently shown that the pK_a of the side chain can be modified by introduction of the 3-hetero atoms, O and S (**2**), with retention of activity[1,2]. The current paper describes the extension of this work to 3-aza analogues (**3**) and describes both their synthesis and preliminary pharmacological evaluation.



(**1**) granisetron



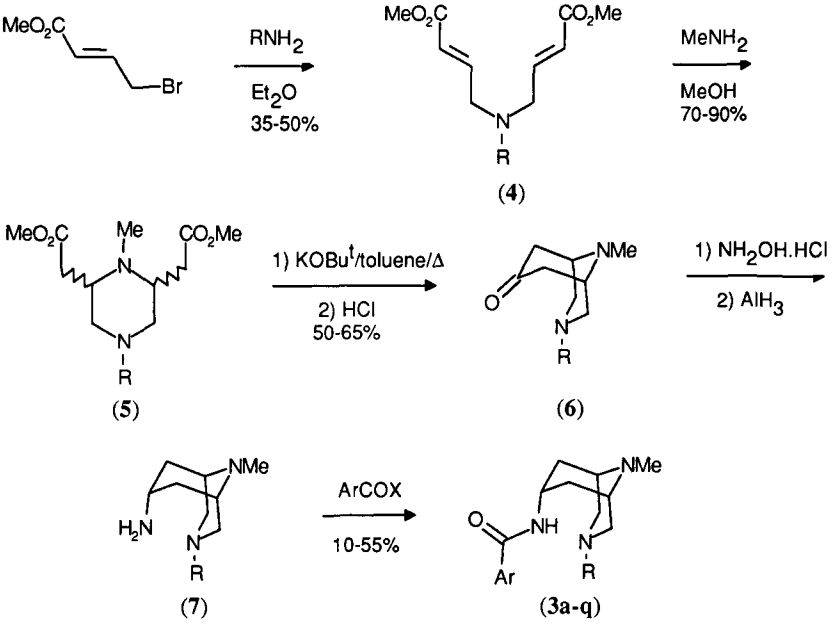
(**2**) X = O, S

(**3**) X = NR

A potential intermediate ketone (**6**) for the stereoselective synthesis of the *endo*-amines (**7**) was originally prepared in 1932 by Robinson-Schopf cyclisation in only a 7.5% yield[3]. This method was not suitable for the rapid synthesis of a number of analogues and therefore an alternative synthesis of the diazabicyclic system was required. Based on retro-synthetic analysis, we decided to adopt a Dieckmann cyclisation strategy to the ketones (**6**, see Scheme). This required the synthesis of the symmetrical 2,6-disubstituted piperazines (**5**) which we believed could be synthesised by conjugate, Michael-type addition of methylamine to an amino-di-crotonate (**4**). Although this addition would be expected to give both *cis* and *trans* isomers (**5**), we hoped that, under the basic conditions of the Dieckmann cyclisation, a retro-Michael reaction might result in isomer equilibration. The di-crotonate derivatives (**4**) were readily prepared from commercial methyl 4-bromocrotonate and the appropriate primary amine in good yield. Reaction with methylamine did

give a mixture of *cis* and *trans* piperazines, which was cyclised using potassium t-butoxide followed by acid hydrolysis and decarboxylation to give the 3,9-diazabicyclo[3.3.1]nonan-7-ones (**6**) in low to moderate yields (25-50%). Unfortunately, the anticipated isomer equilibration probably did not occur and it is presumed that only the *cis* isomers cyclised, a possible explanation for the relatively moderate yields. However, we were unable to isolate the *trans* piperazine dicarboxylic acid, the expected by-product, to confirm this presumption.

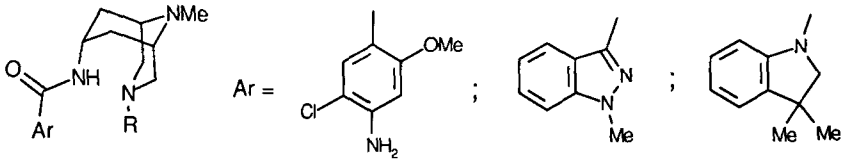
Scheme:



Reduction of the oxime derivative of (**6**) with alane using standard methodology[2] gave the intermediate amines (**7**). Surprisingly, whereas we have found that all our previous examples of alane reduction of oximes in related [3.3.1] and [3.2.1] systems give almost exclusively the *endo* or axial isomer, for the 3,9-diaza system, the isomer ratio depended upon the size of the 3-alkyl group[4]. For the 3-methyl, an isomer ratio of 4:1 *exo:endo* was obtained which reduced to 1:3 *exo:endo* for 3-ethyl and exclusively *endo* for 3-n-propyl and for larger R groups. The amines (**7**) were coupled with the suitably activated aromatic carbonyl species by the previously described standard methods[1] to give the desired compounds (**3**) (purified by flash column chromatography on silica, $CHCl_3$/EtOH, relative proportions depending upon the compound, yields not optimised) for determination of their 5-HT_3 receptor affinity.[5] The aromatic nuclei chosen for investigation were those which we had previously found to be of particular interest, the 4-amino-5-chloro-2-methoxybenzoyl, the 1-methylindazol-3-yl and 3,3-dimethylindolin-1-yl.[1] The 3-acetyl (**3p**) and 3-benzoyl (**3q**) analogues were prepared from the 3-benzyl (**3o**) by catalytic hydrogenolysis to the 3-H (**3a**) followed by acylation.

The 5-HT_3 receptor affinity of the compounds was assessed by their ability to displace [^{3}H]-granisetron from rat cortex[6] and/or their antagonist potency by their ability to inhibit the reflex bradycardia induced by an iv bolus injection of 5-HT, the von Bezold-Jarisch reflex[7]. Previous work in our laboratories has demonstrated an excellent correlation (coefficient of 0.98) between potency as assessed by these two methods[6]. The following Table summarises the results obtained.

Table:



A B C

No.	R	Ar	Inhibition of Bezold-Jarisch reflex μg/kg iv	Binding Affinity pK_i
3a	H	C	-	9.0
3b	Me	A	2.5 (n=2)	-
3c	Me	C	-	9.0
3d	Et	B	0.8 ± 0.3	8.8
3e	Et	C	0.6 ± 0.2	8.6
3f	n-Pr	B	-	8.5
3g	i-Pr	B	0.65 ± 0.30	9.1
3h	i-Pr	C	0.43 ± 0.09	8.9
3i	n-Bu	B	-	8.6
3j	n-Bu	C	-	7.7
3k	i-Bu	B	-	8.5
3l	Ph	B	3.0 ± 1.0	-
3m	-CH_2Ph	A	0.5 ± 0.2	-
3n	-CH_2Ph	B	0.16 ± 0.04	9.3
3o	-CH_2Ph	C	1.8 ± 0.6	-
3p	$COCH_3$	C	-	8.4
3q	COPh	C	-	8.0
1	granisetron		0.7	9.6

All compounds investigated in the Bezold-Jarisch model were antagonists. High potency was achieved with all three aromatic nuclei and with a wide range of sizes of side chain 3-substituent up to N-benzyl. However, the dimethylindoline aromatic (C) appears to be less tolerant of size, for example (**3j**) vs. (**3i**) and (**3o**) vs (**3n**). This lack of steric tolerance with indolines has been noted in other related azabicyclo series[1]. However, the high potency of (**3a**), (**3c**) and (**3h**) shows that the steric effect of the 3 position with this azagranatane side chain is akin to the previously reported oxa-granatanes[2] rather than the more sterically demanding granatanes. This reduced steric effect may be due to the lack of an axial proton, or even to an intramolecular H-bond between the 3-hetero atom and the amide NH. Both 3-acyl compounds were less potent than 3-alkyl which may be a result of a combination of the increased bulk close to the 3-nitrogen and the desire of the amide to be planar.

In conclusion, we have developed a new synthesis of the 3,9-diazabicyclo[3.3.1]nonane system and shown that the aryl amides (**3**) retain good 5-HT_3 receptor affinity and/or antagonist potency despite the introduction of a second basic nitrogen. In common with most other 5-HT_3 receptor antagonists, the compound identified for further evaluation, (**3h**), had no significant affinity for other 5-HT and related G-protein receptors (pK_i <6). In addition, we have shown that there is a large sterically allowed region "underneath" the piperidine ring occupied by substituents attached to the 3-position of the aza-granatane, an area of space not previously explored and which would be difficult to explore in the standard granatane series.

References:

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