Bioorganic & Medicinal Chemistry Letters, Vol.2, No.6, pp. 519-522, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

3-Oxagranatane (3-oxa-9-azabicyclo[3.3.1]nonane) Derivatives as Highly Potent Serotonin 5-HT_3 Receptor Antagonists.

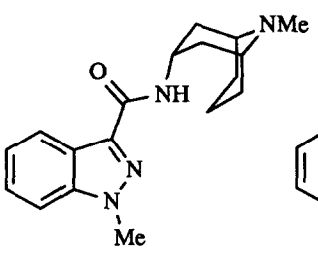
J. Bermudez, J.A. Gregory, F.D. King*, S. Starr and R.J. Summersell.

SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD. UK.

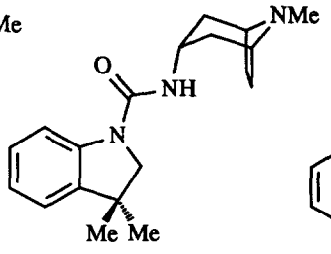
(*Received* 3 *March* 1992)

Abstract: The synthesis of 3-oxagranatane (3-oxa-9-azabicyclo[3.3.1]nonane) -7-amino derivatives is described. Their potency as 5-HT_3 receptor antagonists is compared with that of the equivalent tropanes and granatanes. Higher potency was demonstrated with the less basic and less sterically hindered oxagranatanes.

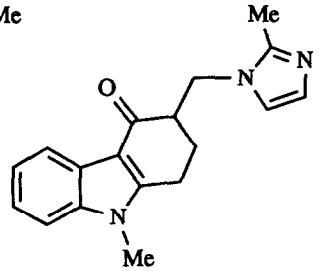
Serotonin 5-HT_3 receptor antagonists, for example granisetron (1), have been shown to be clinically effective inhibitors of emesis evoked by cancer therapies.[1] In addition 5-HT_3 receptor antagonists, for example BRL 46470 (2) and ondansetron (3), have shown activity in animal models believed to be predictive of a therapeutic role in anxiety,[2] schizophrenia[3] and migraine.[4]



granisetron (1)



BRL 46470 (2)

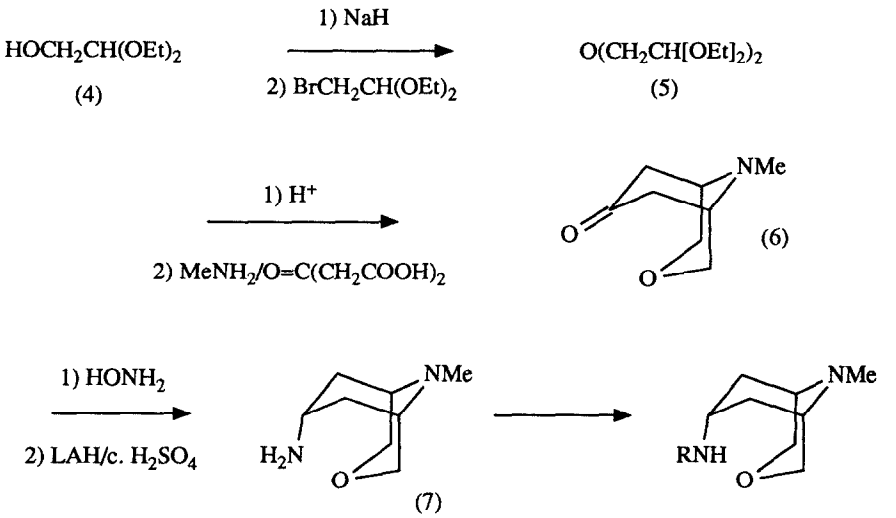


ondansetron (3)

We have previously reported that derivatives of the azabicycles tropane and granatane are potent 5-HT_3 receptor antagonists when linked via a carbonyl containing moiety to either an ortho-methoxy phenyl,[5] indazolyl,[6] 1-indolinyl[7] or ortho-substituted anilino[8] aromatic system. In addition we noted that there were differing orders of potency between the tropane and granatane derivatives depending upon the nature of the aromatic. For the ortho-methoxy phenyl and indazolyl aromatics, the tropane derivatives were more potent than the granatanes. In contrast, the opposite was true for the 1-indolinyl and ortho-substituted anilino derivatives. It was concluded that the granatane was inherently more potent, but was more

affected by unfavourble steric interactions. We therefore investigated the properties of 3-oxagranatane derivatives which would retain the favourable geometry of the granatane system, but would replace a methylene by a smaller, and electronically different oxygen. By analogy with piperidine and morpholine, the 3-oxagranatane system would be expected to be less basic, hence additional information regarding the influence of basicity on activity may also be obtained.

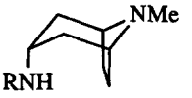
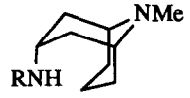
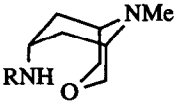
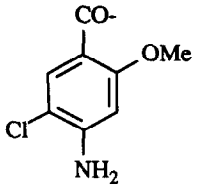
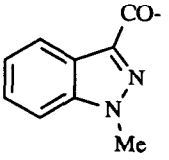
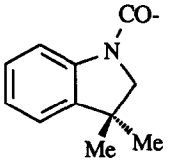
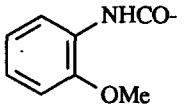
The intermediate common to all the derivatives, endo 7-amino-3-oxagranatane (7), was obtained from the 7-ketone (6) by conversion to the oxime and reduction with AlH_3 (prepared from LAH and conc. H_2SO_4 in dry THF). The 7-ketone (6) was prepared by the Robinson-Schöpf reaction using the di-2,2-diethoxyethyl ether (5), itself prepared by the literature procedure from commercially available hydroxyacetaldehyde diethylacetal (4).[9] Final conversion to the amides was achieved using the mixed anhydride (ArCO-O-COOEt) for the benzamide (10), the acid chloride for the indazole (12), the carbamoyl chloride for the indoline (13) and the isocyanate for the phenylurea (16) as described in our earlier communications.[5-8]



Scheme: Synthesis of 3-oxagranatane derivatives (10, 12, 13 and 16)

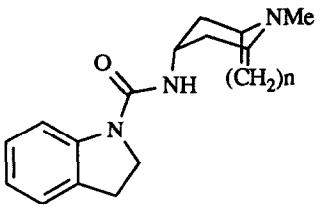
The 5-HT_3 receptor antagonist potency of the amides was assessed using the inhibition of the 5-HT evoked reflex bradycardia, the Bezold-Jarisch reflex, in the rat as previously described.[6] The ID_{50} was the dose required for 50% inhibition of a standard sub-maximal bradycardia response to 5-HT. The results for the oxagranatane derivatives, and those of the equivalent tropanes and granatanes, are shown in the Table.

Table: Comparison of 5-HT_3 receptor antagonist potencies of tropanes, granatanes and oxagranatanes ArCONHR

R	Bezold-Jarisch: ID_{50} μg/kg iv.*		
			
	0.8 compound 8	0.4 compound 9	0.09 compound 10
	1.4 compound 11	0.7 compound 1	0.16 compound 12
	0.7 compound 2	-	0.13 compound 13
	2.5 compound 14	7.5 compound 15	1.1 compound 16

* Standard error of the mean ranged from 10% to 20% with n≥3.

For both the benzamides and the indazoles, the granatanes (9 and 1) are more potent than the tropanes (8 and 11). However, as previously noted, for both the 1-indolines (17, ID_{50} 1.4 μg/kg) and (18, ID_{50} 12.5 μg/kg iv)[7] and the 2-methoxyphenylureas (14 and 15), the reverse is the case, with the tropanes being the more potent. In contrast, all the 3-oxagranatane derivatives (10, 12, 13 and 16) are more potent than either the equivalent tropanes or granatanes by a factor of between 2 and 10 times. Thus it would appear that the oxagranatane does combine both the optimum geometry of the granatane with the lower steric hinderance of the tropanes. Indeed the reduced steric hinderance may have been replaced by an attractive H-bonding interaction between the amide NH and the ether oxygen.



(17) n = 2

(18) n = 3

It has been suggested that the 5-HT_3 receptor antagonists bind in the protonated form of the amine and that the basicity of the side chain may be a factor in the determination of potency; the more basic the side chain, the more potent the compound.[10] However the results presented here with four closely related structural series suggest that this may not be so. The basicities of compounds 1, 2 and 13 were measured in a 1:1 methanol/0.2M KCl mixture by titration and the relative pK_a's were found to be 9.1, 9.4 and 7.1 respectively. The consistently higher potency found with the less basic oxagranatanes therefore suggests that, provided the optimum geometry is achievable, the basicity of the amino group may not be a significant determining factor for 5-HT_3 receptor antagonist potency.

Acknowledgement: The authors thank Dr. M. Thompson and Mr. E. Meenan for the pK_a measurements.

References and Notes

1. Carmichael, J.; Cantwell, B.M.; Edwards, C.M.; Rapeport, W.G.; Harris, A.C. *Br. Med. J.* **1988**, *297*, 110.
2. Costall, B.; Domeney, A.M.; Hendrie, C.A.; Kelly, M.E.; Naylor, R.J.; Tyers, M.B. *Br. J. Pharmacol. Proc. Suppl.* **1987**, *90*, 88P.
3. Costall, B.; Domeney, A.M.; Kelly, M.E.; Naylor, R.J.; Tyers, M.B. *Br. J. Pharmacol. Proc. Suppl.* **1987**, *90*, 89P.
4. Tell, G.P.; Fozard, J.R.; Schechter, P.J.; Centonze, V.; Beorchia, S.; Loisy, C. *Br. J. Clin. Pharmacol.* **1984**, *18*, 279P.
5. King, F.D.; Dabbs, S.; Bermudez, J.; Sanger, G.J. *J. Med. Chem.* **1990**, *33*, 2942.
6. Bermudez, J.; Fake, C.S.; Joiner, G.J.; Joiner, K.A.; King, F.D.; Miner, W.D.; Sanger, G.J. *J. Med. Chem.* **1990**, *33*, 1924.
7. Bermudez, J.; Dabbs, S.; Joiner, K.A.; King, F.D. *J. Med. Chem.* **1990**, *33*, 1929.
8. Bermudez, J.; Dabbs, S.; King, F.D. *J. Med. Chem.* **1990**, *33*, 1932.
9. Zirkle, C.L.; Gerns, F.R.; Pavloff, A.M.; Burger, A. *J. Org. Chem.* **1961**, *26*, 395.
10. Swain, C.J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E.M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. *J. Med. Chem.* **1991**, *34*, 140.