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QUATERNISED RENZAPRIDE AS A POTENT AND SELECTIVE 5-HT$_4$ RECEPTOR AGONIST.

G.S. Baxter, P. Boyland, L.M. Gaster and F.D. King*

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

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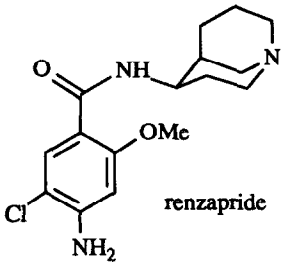
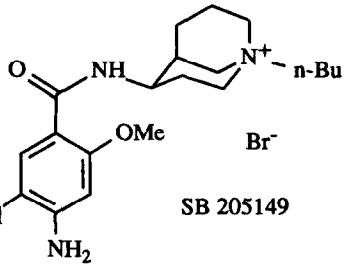
Abstract: The n-butyl quaternary salt of the 5-HT$_4$ receptor agonist and 5-HT$_3$ receptor antagonist, renzapride, is reported to be a potent and selective 5-HT$_4$ receptor agonist.

Serotonin - 5-HT$_4$ receptors have been identified in mouse embryo coliculli neurones,[1] guinea pig hippocampus[2], the gastro-intestinal tract[3,4] and in both piglet[5] and human atrium.[6] The present communication describes the results we have obtained by quaternising the potent 5-HT$_4$ receptor agonist, renzapride (BRL 24924).[7,8] Renzapride is also a potent 5-HT$_3$ receptor antagonist,[9] and for selectivity for the 5-HT$_4$ receptor, we required a relative reduction in this activity. It has been reported that methyl quaternary salts of 5-HT$_3$ receptor antagonists, such as ICS 205-930, retain or even increase 5-HT$_3$ receptor antagonist potency.[10] However, for free bases, N-substituents larger than methyl dramatically reduce this activity.[11] We therefore quaternised renzapride by reaction with n-butyl bromide in EtOH at reflux to give SB 205149 to investigate its pharmacological properties.



renzapride



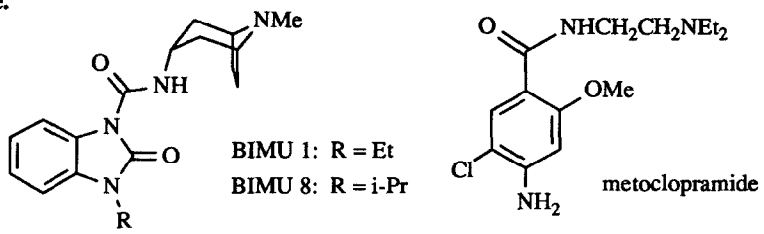
SB 205149

SB 205149 was assessed for its agonist potency and efficacy at the 5-HT$_4$ receptor located in the rat oesophageal tunica muscularis mucosae[3] and its 5-HT$_3$ receptor affinity by its ability to displace [^{3}H] granisetron from rat cortex[16] (see Table). The previously published results for metoclopramide, renzapride,[3] BIMU 1 and BIMU 8[12,13] are included for comparison.

SB 205149 was found to be a potent and highly effective 5-HT$_4$ receptor agonist with a potency approximately 6 fold greater than renzapride, equivalent to 5-HT and almost 100 fold more potent than metoclopramide. However, as expected, SB 205149 was found to be only a weak 5-HT$_3$ receptor antagonist with a pK$_i$ of 6.9, similar to that of metoclopramide. In contrast both BIMU 1 and BIMU 8, although highly potent 5-HT$_4$ receptor agonists, are also highly potent 5-HT$_3$ receptor antagonists.

In conclusion, n-butyl quaternisation of renzapride both reduced 5-HT$_3$ receptor affinity and increased 5-HT$_4$ receptor agonist potency to give a potent and selective 5-HT$_4$ receptor agonist. In addition, being a quaternary derivative, the compound is very polar and, if radiolabelled, could provide a suitable ligand for radioligand binding studies.

Table.



Compound	5-HT_4 agonism -Log EC_{50} (SEM)	Intrinsic activity (SEM)	5-HT_3 binding pK_i
5-HT	8.01 (0.04)**	1	6.8±0.1*
metoclopramide	6.1[3]	0.8	6.8[16]
renzapride	7.2[3]	0.8	8.3[14]
BIMU 1	8.0[12]	0.7	8.4[13]
BIMU 8	7.9[12]	0.9	8.8[13]
SB 205149	8.02 (0.09)**	0.79 (0.03)	6.9±0.1*

* rat cortex, [^{3}H]-granisetron, 5-HT an agonist[16] **rat oesophagus [3] n = 4.

References

1. Dumius, A.; Sebben, M.; Bockaert, J. *Naunyn-Schmied. Arch. Pharmacol.* **1989,** *340,* 403.
2. Bockaert, J.; Sebben, M.; Dumius, A. *Mol. Pharmacol.* **1990,** *37,* 408.
3. Baxter, G.S.; Craig, D.A.; Clarke, D.E. *Naunyn-Schmied. Arch. Pharmacol.* **1991,** *343,* 439.
4. Sanger, G.J.; Wardle, K.A. *Serotonin: From Cell Binding to Pharmacology and Therapeutics;* Paoletti *et al.*, Ed.; Kluwer Academic publishers: Dordrecht, 1990; pp. 251-255.
5. Kaumann, A.J.; Brown, A.M.; Raval, P. *Br. J. Pharmacol.* **1991,** *102,* 98P.
6. Kauman, A.J. *Naunyn-Schmied. Arch. Pharmacol.* **1990,** *342,* 619.
7. Craig, D.A.; Clarke, D.E. *Br. J. Pharmacol.* **1991,** *102,* 563.
8. King, F.D.; Hadley, M.S.; Joiner, K.T.; Martin, R.T.; Sanger, G.J.; Smith, D.M.; Smith, G.E.; Smith, P.; Turner, D.H.; Watts, E.A. *J. Med Chem* (in press).
9. Dunbar, A.W.; McClelland, C.M.; Sanger, G.J. *Br. J. Pharmacol.* **1986,** *88,* 319P.
10. Richardson, B.P.; Engel, G.; Donatsch, P.; Stadler, P.A. *Nature* **1985,** *316,* 126.
11. Turconi, M.; Nicola, M.; Quintera, M.G.; Maiocchi, L.; Micheletti, R.; Giraldo, E.; Donetti, A. *J. Med. Chem.* **1990,** *33,* 2101.
12. Baxter, G.S.; Clarke, D.E. *Eur. J. Pharmacol.* **1992,** *212,* 225.
13. Turconi, M.; Schiantarelli, P.; Borsini, F.; Rizzi, C.A.; Ladinsky, H.; Donetti, A. *Drugs of the Future* **1991,** *16,* 1011.
14. Flynn, D.L.; Zabrowski, D.L.; Becker, D.P.; Nosal, R.; Villamil, C.I.; Gullikson, G.W.; Moummi, C.; Yang, D-C. *J. Med. Chem.* **1992,** *35,* 1486.
15. Sanger, G.J. *Br. J. Pharmacol.* **1987,** *91,* 77.
16. Nelson, D.R.; Thomas, D.R. *Biochem. Pharmacol.* **1989,** *38,* 1693.