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# CONFORMATIONALLY RESTRICTED PIPERIDINYL BENZAMIDES AS 5-HT$_3$ RECEPTOR ANTAGONISTS.

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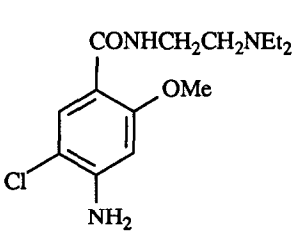
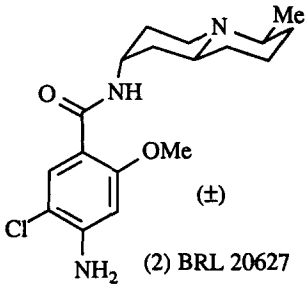
**Abstract.** The synthesis and 5-HT$_3$ receptor antagonist activity of indolizidin-7-yl and 8-oxaquinolizidin-2-yl benzamides related to the quinolizidine, BRL 20627 (2), are described. High potency is restricted to axial isomers and both the indolizidines and oxa-quinolizidines are much more potent than (2), an effect which appears to be unrelated to basicity.

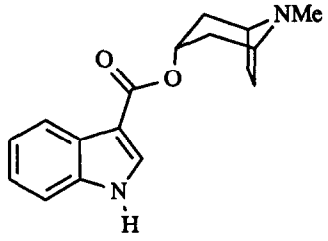
Metoclopramide is a benzamide marketed as a gastric motility stimulant and anti-emetic. Pharmacologically it has at least three modes of action; 5-HT$_3$ receptor antagonism, dopamine D$_2$ receptor antagonism[1] and 5-HT$_4$ receptor agonism.[2] In an earlier publication we showed that, by conformational restriction of the diethylaminoethyl basic side chain in the form of the fused azabicycle, quinolizidine, it was possible to separate the gastric motility stimulant activity, recently correlated with 5-HT$_4$ receptor agonism, from the dopamine receptor antagonist activity.[3] In particular BRL 20627(2) was identified as a selective stimulant of gastrointestinal motility. We have subsequently investigated (2) and other fused azabicycles related to quinolizidine for 5-HT$_3$ receptor antagonist activity and the significant findings are now reported. Their 5-HT$_4$ agonist and dopamine antagonist properties will be reported separately as a part of a more comprehensive study.




(1) Metoclopramide



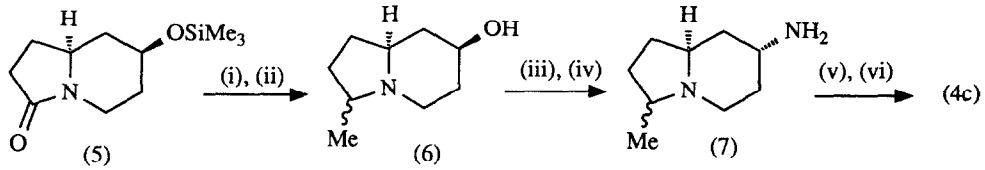

(±) (2) BRL 20627




(3) ICS 205-930

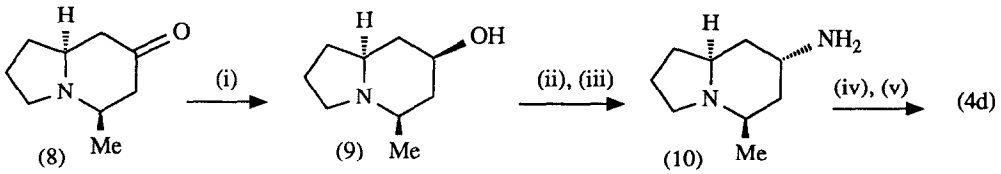
Metoclopramide is a relatively weak 5-HT$_3$ receptor antagonist (see Table). Conformational restriction of the diethylaminoethyl side chain in the form of the axially substituted quinolizidine (2) only increased 5-HT$_3$ receptor antagonist potency by a factor of 2. However it has previously been reported that increasing the bulk of the tropanyl N-substituent of the indole ester ICS 205-930 (3) to ethyl or iso-propyl dramatically reduced 5-HT$_3$ receptor antagonist potency.[4] This apparent desirability of a small N-substituent prompted us to investigate the smaller, less

sterically hindered fused azabicycles related to (2), the indolizidines (4a-d) and the 8-oxaquinolizidines (4e-f) shown in the Table. The parent indolizidines (4a) and (4b) were prepared by conversion of indolizidin-7-one[5] to the indolizine-7-amines by the methods described for the equivalent quinolizidines.[3] For all the compounds (4a-f), the intermediate amines were converted to the benzamides by reaction with 4-acetylamino-5-chloro-2-methoxybenzoyl chloride followed by selective base hydrolysis of the N-acetyl group by the method previously described for (2).[3] The 3-methyl compound (4c) was prepared as an inseparable mixture of isomers from the TMS protected indolizin-7-ol-3-one (5)[6] by addition of methyl magnesium bromide followed by sodium borohydride reduction to give the alcohol (6). This was converted to the axial amine (7) by activation and azide displacement using the Mitsunobu procedure followed by reduction with LAH.



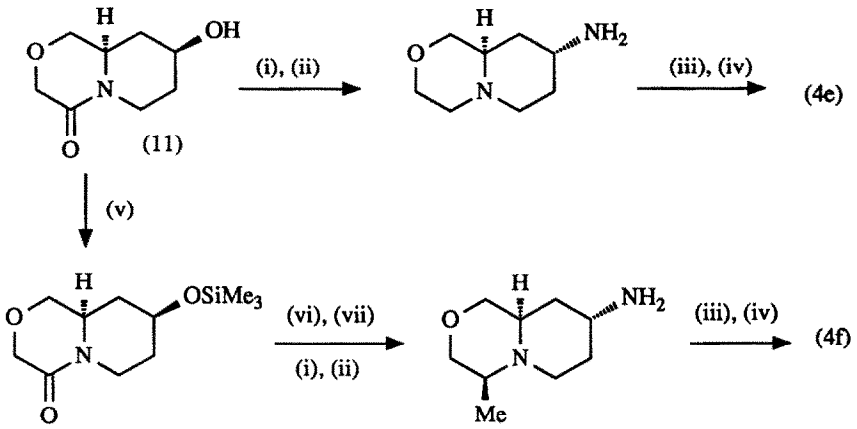

(i) MeMgBr; (ii) $H^+/NaBH_4$; (iii) $Ph_3P/DEAD/(PhO)_2PON_3$; (iv) LAH; (v) N-Ac-ArCOCl; (vi) NaOH

The 5-methylindolizidine (4d) was prepared from the ketone (8)[7] by dissolving metal reduction to the equatorial alcohol (9), then conversion to the axial amine (10) by the procedure described for (7).



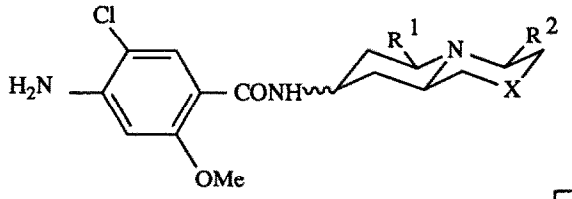

(i) $Na/C_5H_{11}OH$; (ii) $Ph_3P/DEAD/(PhO)_2PON_3$; (iii) LAH; (iv) N-Ac-ArCOCl; (v) NaOH

For the 8-oxaquinolizidines (4e, 4f), the introduction of the oxygen atom would be expected to have three major effects. First a reduction in steric bulk ($CH_2OCH_3$; $E_s$= -0.19; $CH_2CH_2CH_3$; $E_s$= -0.36[8]), second a change in electronic characteristics and third, by analogy with piperidine ($pK_a$ 11.1) and morpholine ($pK_a$ 8.3), a reduction in basicity. The parent 8-oxaquinolizidine (4e) was prepared from the previously reported 8-oxaquinolizidin-2-ol-6-one (11)[9] by the Mitsunobu reaction followed by simultaneous LAH reduction of both the lactam and azide. The 6-methyl analogue (4f) was prepared by the procedure analogous to that described for (4c). However, for the 6-membered ring, only the equatorially orientated methyl isomer was obtained.




(i) $Ph_3P/DEAD/(PhO)_2PON_3$; (ii) LAH; (iii) N-Ac-ArCOCl; (iv) NaOH; (v) $(Me_3Si)_2NH$; (vi) MeMgBr; (vii) $H^+/NaBH_4$

**Table:** 5-$HT_3$ Receptor Antagonist Activity




| Compound No. | Isomer | X | $R^1$ | $R^2$ | Inhibition of Bezold-Jarisch* $ID_{50}$ µg/kg iv |
|---|---|---|---|---|---|
| 1 | metoclopramide | | | | 500 |
| 3 | ICS 205930 | | | | 1.4 |
| 2 | Ax. | $CH_2$ | H | Me | 225 |
| 4a | Eq | bond | H | H | >1000 |
| 4b | Ax | bond | H | H | 24 |
| 4c** | Ax | bond | H | Me | 12 |
| 4d | Ax | bond | Me | H | 290 |
| 4e | Ax | O | H | H | 17 |
| 4f | Ax | O | H | Me | 9.5 |

* Mean of at least 3 determinations., standard error ±20% ** Mixture of isomers.

The 5-$HT_3$ receptor antagonist potency was assessed in the anaesthetised rat by the inhibition of the 5-HT induced bradycardia, the Bezold-Jarisch reflex, by the method previously described (Table).[10] For comparison the potency of ICS 205-930 is included.

The equatorial indolizidine (4a) was much less potent than either metoclopramide (1) or BRL 20627 (2). The low potency of the equatorial isomer correlates with the relatively low potency of previously reported equatorial tropanyl esters.[4] However, both the axial indolizidine (4b) and the 3-methyl-substituted indolizidine (4c) were much more potent than either (1) or (2). The high potency of (4c) was surprising considering the previously reported low potency of bulky N-substituted analogues of (3).[4] In contrast, methyl-substitution in the 6-membered ring (4d) resulted in a 12-fold reduction in potency compared to (4b). The increased potency of (4b) and (4c) over the quinolizidine (2) could be a result of either the greater basicity of indolizidines compared to quinolizidines or the smaller size of the 5-membered ring.

In considering the effect of basicity on 5-$HT_3$ receptor antagonist potency, the weakly basic oxa-quinolizidine (4e) (measured $pK_A$ 6.3) was also much more potent than (2) (measured $pK_A$ 9.2) and, again, greater potency was observed with the methyl-substituted analogue (4f). From these results it can be concluded that the basicity of the amine may not be a crucial factor contributing to 5-$HT_3$ receptor antagonist potency. This is surprising considering that the reported high potency of the methyl-quaternary salt of ICS 205-930 would suggest that the antagonists bind to the receptor in their protonated form.[4] Any reduction in basicity, and hence degree of protonation at physiological pH would be expected to result in a lower receptor binding efficacy, and hence potency. It may be, therefore, that for the oxaquinolizidines an additional, weak interaction of the ether oxygen with the receptor may compensate for the reduced basicity. Certainly for both the indolizidines (4b), (4c) and the oxaquinolizidines (4e), (4f), the smaller size of the fused ring has resulted in a marked increase in potency and, surprisingly, with bulk in the plane of the fused system being tolerated.

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