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INDOLIZIDINE DERIVATIVES AS POTENTIAL SUBSTANCE P ANTAGONISTS

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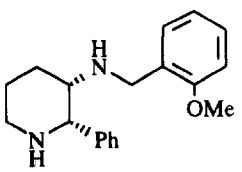
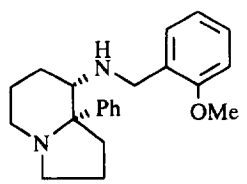
Abstract: Two novel indolizidine analogues, (**7a**) and (**7b**), of the substance P antagonist CP 99,994 have been prepared. Possible conformational factors for their low biological activity are discussed.

Through the neurokinin-1 (NK_1) receptor, substance P, an eleven amino acid neuropeptide, is implicated in numerous disease states including arthritis,[1] asthma,[2] migraine[3] and pain.[4] Recently the discovery of functionalised quinuclidines[5] as potent non-peptide NK_1 receptor antagonists has stimulated the search for other non-peptide antagonists.[6] One of the most potent antagonists reported to date is CP 99,994,[7] a derivative of 2-phenylpiperidine. It has been demonstrated that CP 99,994 shows a broad spectrum of anti-emetic activity[8,9] in animal models and therefore may offer a valuable novel therapy for the treatment of emesis associated with cancer chemotherapy. A potential factor limiting the oral bioavailability of CP 99,994 is its susceptibility to metabolism by liver enzymes. As part of a program to address this potential problem as well as to examine the effect of additional bulk at the receptor, we undertook the synthesis of the novel 8,8a-disubstituted indolizidine (**1**), incorporating the pharmacophore present in CP 99,994.

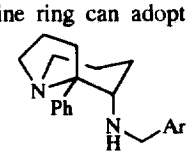


CP 99,994

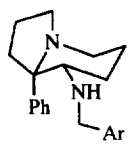


(**1**)

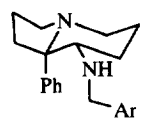
We have shown previously that potent NK_1 receptor binding affinity is retained in analogues of CP 99,994 in which the piperidine ring is locked in a chair conformation.[10] In the indolizidine analogue (**1**) the piperidine ring can adopt three possible chair conformations at the ring junction, due to the possibility of



(**1a**)



(**1b**)

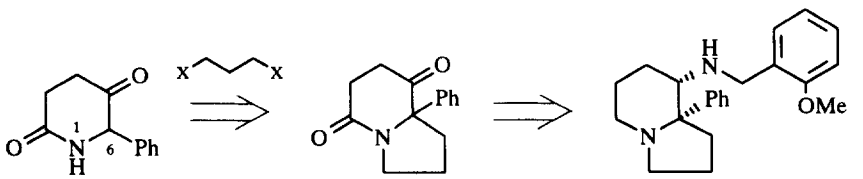


(**1c**)

† Deceased 15th February 1994

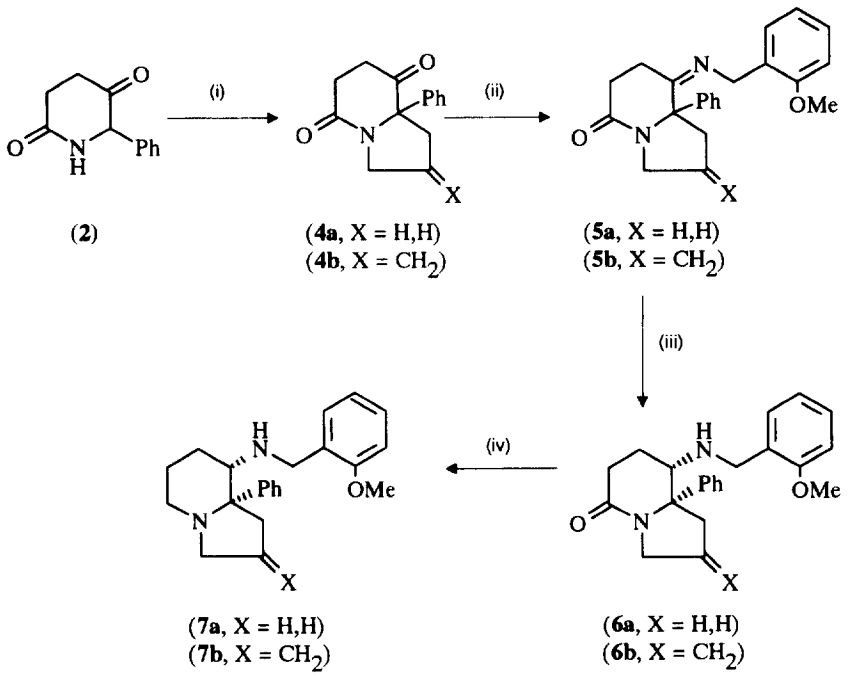
invertomers at the bridgehead nitrogen atom. Two conformers (**1a**) and (**1b**) possess a *cis*-fused ring junction, and the third (**1c**) a *trans*-fused junction. Of these three conformers the energetically preferred[11] *cis*-conformer (**1a**) overlays very closely with the low energy chair conformer of CP 99,994 (Figure 1).

Scheme 1



(**2**) (**3**) (**1**)

Two syntheses of indolizidines substituted by an aryl group at the ring junction have been reported.[12,13] Neither of these were suitable for our target. Our approach to this class of compounds involved coupling a suitable bifunctional three carbon unit with the N-1 and C-6 positions of the ketopiperidine (**2**)[14] to give the ketoindolizidine (**3**) which is a suitable substrate for elaboration to the amino compound (**1**) (Scheme 1).



(**2**) (**4a**, X = H,H) (**4b**, X = CH_2) (**5a**, X = H,H) (**5b**, X = CH_2)

(**7a**, X = H,H) (**7b**, X = CH_2) (**6a**, X = H,H) (**6b**, X = CH_2)

Reagents and Conditions

(i) **4a** 1,3-diiodopropane, K_2CO_3, N_2, DMF, 45°C, 1.75h; **4b** 3-Chloro-2-chloromethyl propene, NaH, N_2, DMF, - 20°C, 4.5h; K_2CO_3, MeOH; (ii) For both **5a** and **5b** *o*-methoxybenzylamine, $PhCH_3$, PTSA, reflux, 20h, (iii) For both **6a** and **6b** $NaBH_4$, MeOH, 21°C, 2.0h; (iv) **7a** Borane, THF, 21°C, 14h, N_2, HCl, dioxan; **7b** $LiAlH_4$. THF, 21°C, 15h.

Our initial attempts at base-catalysed alkylation of the ketopiperidine (**2**), with 1,3-diiodopropane, were complicated by oxidative breakdown of the piperidine ring.[15] When the reaction was carried out in degassed solvents, under nitrogen, 47% of the crystalline indolizidine (**4a**, X = H, H) was isolated. Using the more reactive three carbon progenitor 3-chloro-2-chloromethylpropene, ring cleavage was not a problem, and the corresponding exomethylene indolizidinone (**4b**, X = CH_2) was obtained. Attempted transformation of the keto group of (**4a**) into an amino function *via* hydrogenation of the methoxime derivative failed, presumably due to steric factors. The only product isolated was the methoxime of the reduced cyclohexyl derivative.[16] To overcome this problem the following strategy was employed. Treatment of the ketones (**4a**) and (**4b**) with *o*-methoxybenzylamine, under azeotropic conditions in the presence of acid, gave the imines (**5a**) and (**5b**) respectively. Reduction of the imines with sodium borohydride occurred stereospecifically, to give the corresponding *cis*-aminoamides (**6a**) and (**6b**). Reduction of the amide group of (**6a**) was achieved with diborane and the resultant diamine (**7a**) was characterised as the crystalline dihydrochloride salt. In the case of the exomethylene amide (**6b**) the reduction to the diamine (**7b**) was achieved with lithium aluminium hydride.

Figure 1 (Grey **7a**, Green CP 99,994)

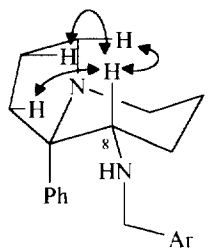


Figure 2

The NK_1 receptor binding affinities[17] of the two indolizidine analogues (**7a**) and (**7b**) were weak (pKi < 7.0) when compared to that of CP 99,994 (pKi 9.4). We ascribed the low receptor affinities to their inability to acquire the proposed bioactive conformation (**1a**), predicted from the energy calculations, or to the additional bulk of the bridging atoms which might not be tolerated at the receptor. The former explanation was supported by a NOESY experiment on a solution of the dihydrochloride salt of (**7a**) in CD_3OD. NOE's were observed between the axial proton at C-8 and the three protons on the β-face of the indolizidone 5-membered ring (Figure 2). The data were consistent with conformer (**1b**) and clearly excluded conformations (**1a**) and (**1c**). However we could not exclude the alternative possibility that the extra bulk associated with the additional methylene groups present in the indolizidine analogues was responsible for steric hindrance to receptor fit.

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11. Conformational analysis on structure (**1**) was carried out by a Monte Carlo-style search and minimised with MM3 force field within MacroModel 4.5. Based on these studies (**1b**) was found to have 3.4 kJ/mol and (**1c**) 10.6 kJ/mol higher energy than the lowest energy conformer (**1a**). However these data could not exclude the accessibility of conformer (**1b**).
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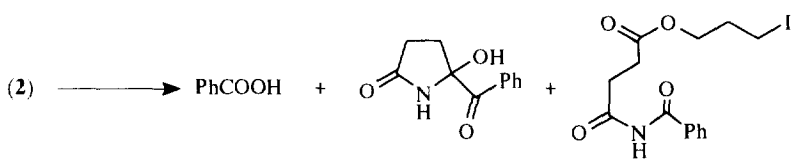
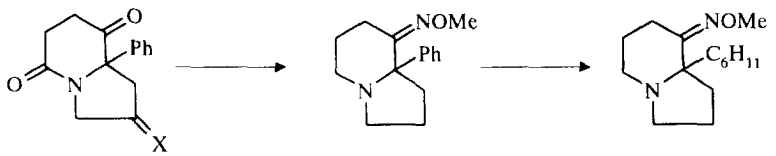
15. Treatment of the ketopiperidine (**2**) with 1,3-diidopropane and sodium hydrogen carbonate at 21°C, without the exclusion of air, gave a complex mixture from which was isolated benzoic acid (**i**), pyrrolidine (**ii**) and the iodoester (**iii**):-



(i) (ii) (iii)

16. The ketone (**4a**, X = H,H) was converted into the corresponding methoxime and the amide function reduced with diborane. Hydrogenation of the resultant methoxime (**i**) in the presence of a platinum catalysts gave the cyclohexyl derivative (**ii**):-



(**4a**) (**i**) (**ii**)

17. Binding affinities of these compounds were carried out with NK_1 receptors from U-373MG human astrocytoma cell line. For details of the receptor binding protocol, see reference 10.

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