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Synthesis of a novel series of tetracyclic opioid antagonists incorporating an 8-aminobicyclo[3.2.1]oct-6-ene sub-unit

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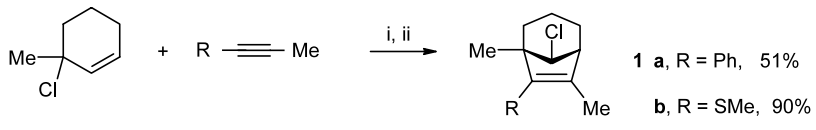
Abstract—The bridged bicyclo[3.2.1]oct-ene and -ane amines **9**–**13** have been prepared via [3+2]cycloaddition of allylic alcohols **6** to alkynes **7**, and assessed as ligands at opioid receptors. Amine **10b** is a potent antagonist at μ receptors.

Zinc chloride-mediated [3+2]cycloaddition of simple allylic chlorides to alkynes to produce 4-chlorocyclopentenes was first reported several years ago.[1] Subsequently, incorporation of the allyl unit into a cyclohexenyl system allowed a facile entry to 8-chlorobicyclo[3.2.1]oct-6-enes,[2,3] via a process which is stereospecific at C-8 and is often highly regioselective—see the synthesis of compounds **1** (Scheme 1).

Further study revealed that Lewis acid-mediated replacement of the 8-chloride by other donor ligands, such as -OH or $-N_3$, was readily achievable, and that the relative configuration at C-8 was retained in the substituted product.[4,5] Due to the considerable rigidity of these bridged bicyclic structures, it was also apparent that the [3+2]cycloaddition methodology could be applied to polycyclic substrates such that the C-8 ligand (e.g. -OH or $-NH_2$) in the bicyclo[3.2.1]oct-6-ene moiety of the product would often have a tightly defined distance and orientation with respect to other points in the structure. In effect, this gives a kind of template capable of being matched with known pharmacophores—a favoured approach to drug design when there is extensive historical QSAR but inadequate X-ray or other structural data.

It is this kind of 3D-relationship which has provoked the design of ligands for opioid receptors over the last 50 years or so.[6] In particular, morphine and its congeners are rigid enough to present to the enquiring mind a relatively tight set of options for distance from the quaternary or otherwise charged nitrogen to the centroid of the benzene ring (about 4.4–4.6 Å) and for the distance of the same centre above the plane of the benzene ring (range 0.8–1.3 Å). Indeed, such imagery still drives the search for new morphinoids, as in the elegant work of Hanessian et al. on potent and selective μ receptor agonists based on the isopavane nucleus.[7]

Our interest in this topic was partially stimulated by the work of Freed and his colleagues,[8–10] who sought to combine the bridged tricyclic framework of established analgesics like the benzomorphans, as in metazocine **2**, with that of the 2-aminotetralins **3**. The outcome was the bridged tricyclic opiate antagonist dezocine **4** which was subsequently licensed as an analgesic in USA,



Scheme 1. *Reagents and conditions*: (i) $ZnCl_2$, CH_2Cl_2, 0–20°C, 1 h; (ii) chromatography.

Keywords: [3+2]cycloaddition; allyl cations; alkynes; bicycle[3.2.1]oct-ene/-ane amines; opioid antagonist; dezocine; μ receptors.
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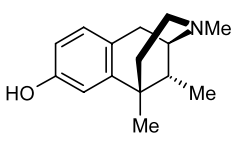
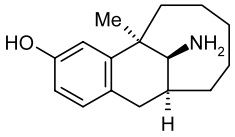
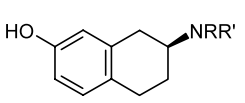
following detailed animal pharmacology,[11] pharmacokinetic studies,[12] and a favourable clinical profile.[13] We performed a molecular modelling study on dezocine and predicted that, in the active diastereoisomer, the amino group nitrogen is about 5.2 Å from the benzene centroid, and about 0.25 Å above its plane.[14] When the modelling was extended to a bicyclo[3.2.1]oct-6-ene prototype, **5**, the above geometric features were predicted to be 5.8–5.9 Å apart, and the nitrogen to be 1.6–1.8 Å above the benzenoid ring. This geometry was sufficiently different from that in morphine and dezocine (both of which are selective for μ-type opioid receptors, through which most clinically useful analgesics are believed to act[15]) to raise the question as to whether any degree of analgesic effect might be retained in substituted variants of **5**. In this short paper we describe the synthesis of a range of analogues of **5** and report briefly the results of biochemical and functional assays on selected compounds.



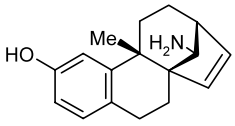
2 metazocine



4 dezocine



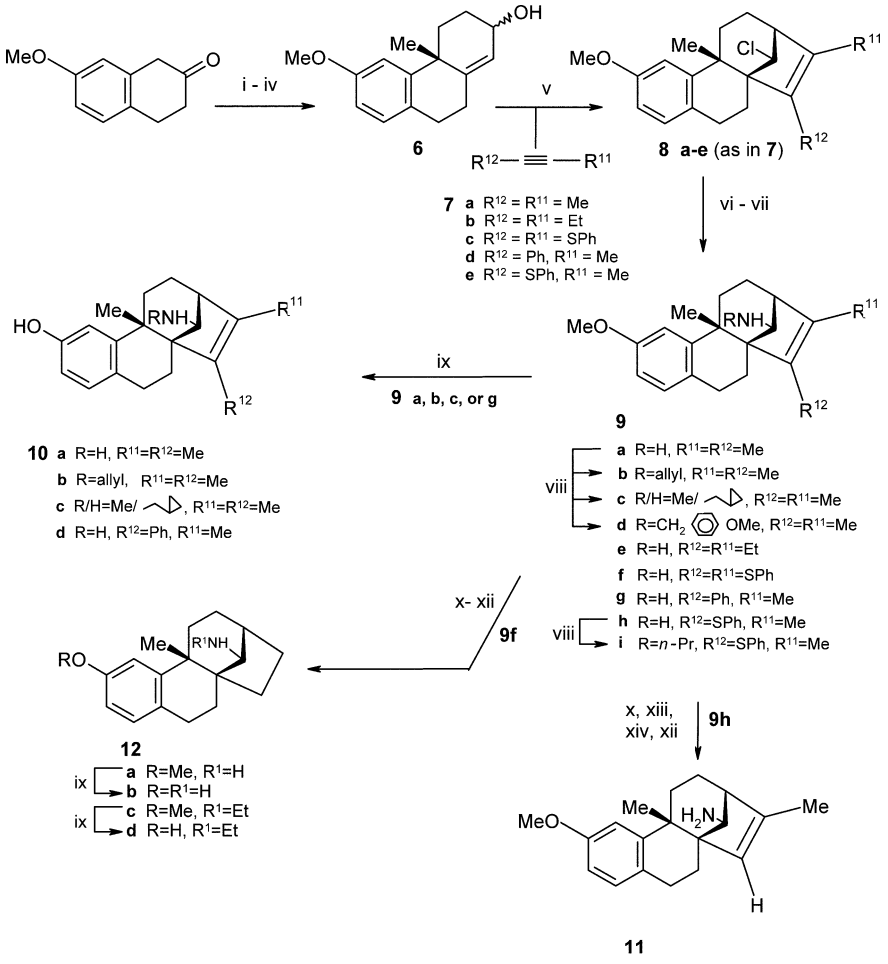
3 aminotetralin



5

The starting materials for the allylic components of the proposed [3+2]cycloadditions were 6- and 7-methoxy-2-tetralone, and an illustrative synthesis originating with the latter is set out in Scheme 2. The tetralone was converted by standard methodology[16,17] into the diastereomeric alcohols **6**, which are racemic but here are depicted as one pair of diastereoisomers. The mixtures of allylic chlorides corresponding to the alcohols **6** were found to be unstable due to ready elimination of HCl. We therefore generated the allylic chlorides in situ, using HCl and $ZnCl_2$, and otherwise followed the previously described procedure[5] to give the key bridged chlorides **8a**–**e** in moderate yields (30–65%) from the alkynes **7a**–**e**. These chlorides all had the same 'up' geometry, as observed in other simpler series,[4,5] and revealed consistently in proton NMR by a doublet at about 3.9–4.1 ppm for the -C*H*Cl- proton with a vicinal coupling of 5.0 Hz to the bridgehead hydrogen.[18] Another feature of the cycloaddition is that the alkyne could, in principle, approach the cyclohexenyl ring from either face, i.e. *syn* or *anti* to the angular methyl group. Moderate to high stereoselectivity in [3+2]-cycloaddition to 4-substituted mono- and bicyclic cyclohexenyl cations has been observed previously,[19] and in all such cases the 4-substituent directed the addition of the alkyne to occur predominantly from the opposite face of the cation, provided that the alkyne was disubstituted. In the event, only one diastereoisomer was detected in each sequence leading to the bicyclic chlorides **8a**–**e**, and their stereochemistry was later confirmed in the amine **9e** by a combination of COSY and NOE.[20] This stereoselectivity is significant, because the opposite mode of addition would lead to structures in which the geometric parameters discussed above were unachievable, e.g. the nitrogen to benzene centroid distance drops to around 3.0Å. A similar situation was observed with dezocine and its congeners.[8] The synthesis of our targets was completed by exchange of azide for chloride at the bridge (again with retention of configuration, as indicted by vicinal coupling of 5.0 Hz between the bridge and bridgehead methine protons), followed by azide reduction to give amines **9a** and **9e**–**h**, the precursors for most of the compounds reported here. Subsequent simple transformations, such as *N*-alkylation, gave **9b**–**d** and **9i**, and *O*-demethylation, with or without *N*-alkylation, gave phenols **10a**–**d**. In two cases we used alkynyl sulphides **7c** or **7e** as [3+2]cycloaddition partners, because they give good yields[3] and the PhS group controls the regiochemistry of the addition, as did the MeS group in **1b**.[3,19] More significantly, [3+2]cycloaddition fails with ethyne and propyne, and this denied us direct access to simpler targets like **11** and **12a**,**b**. This problem can be circumvented by reductive removal of either S(II) or S(VI) ligands from cycloadducts of **7c** or **7e**, so that mono-sulphenyl alkyne **7e** and bis-sulphenyl alkyne **7c** become the functional equivalent of propyne, as in **11**, or ethene, as in **12**, respectively. Initial attempts to prepare **12a** from **9f** yielded only **12c** which accidentally arose in the Raney-nickel reaction, presumably as a result of in situ reduction of an acetaldehyde imine, formed by oxidation of the solvent ethanol to acetaldehyde and then reaction with the free amino group of **9f**. Prior conversion of **9f** to a bridge amide prevented the *N*-ethylation and allowed synthesis of **12a** and hence the corresponding phenol **12b**.

Table 1 shows the amines that were synthesised[21] and then tested as hydrochlorides in relevant bioassays, all of which were routine and widely available. Opioid receptor affinity (IC_{50} in μM) was established via competition with [^{3}H]naloxone, and the effect of compounds on contractions of guinea-pig ileum (GPI) was used as a functional assay for opioid activity. About half of the reported compounds were tested in the GPI assay, but all were inactive. From the naloxone displacement studies, especially those on structures where



Scheme 2. *Reagents and conditions*: (i) pyrrolidine in toluene, reflux; (ii) MeI, dioxane; (iii) 4(*N*,*N*-diethylamino)butan-2-one, MeI, KOEt, benzene–ethanol (45–78% for i–iii); (iv) LAH in ether (90–95%); (v) alkyne 1.0–1.2 mol equiv., $ZnCl_2$ 1.5–2 mol. equiv., DCM, HCl in ether, 0°C to rt (30–65%); (vi) NaN_3 5 mol equiv., $ZnCl_2$ 5 mol equiv., DCM, 5d at rt (51–68%); (vii) LAH in ether, 0°C to rt (92–95%); or cat. H_2 over Pd-charcoal, EtOH (80–88%); (viii) RBr, K_2CO_3, EtOH, reflux (69–90%); (ix) BBr_3, DCM, −20°C to rt (80–85%); (x) Ac_2O, pyridine, DMAP; (xi) Raney-Ni, EtOH; (xii) HCl, aq. EtOH, reflux (62–78% for x–xii); (xiii) mCPBA, DCM (86%); (xiv) Na(Hg), Na_2HPO_4, THF–MeOH (62%).

$R^{11} = R^{12} = Me$, some broad SAR emerged-notably that phenols are generally 20–40 fold more active than their parent ethers and that certain small *N*-alkyl groups, especially allyl, induce antagonism and raise affinity (known features of morphine-like opioids[6]). From the data on compounds with other combinations of R^{11} and R^{12}, the clearest indication is that bulky ligands are not tolerated on the isolated double bond. These data suggested that compound **10b** (IC_{50} 0.026 μM), which had an affinity comparable to morphine (IC_{50} 0.013–0.031 μM in our assay), be studied further. In a full dose–response study, this compound was shown to be a competitive antagonist versus naloxone. Moreover, its receptor affinity was not greatly affected by sodium ion, thus confirming that it is an antagonist.[22] A study of binding to the main opioid receptors (μ, δ, and κ) confirmed our lead as μ-selective, and that it had some affinity for δ receptors. Finally, it was shown to be inactive in the acetic acid writhe model of pain, commonly used to study μ receptor agonists.

These additional data confirm **10b** as a potent, naloxone-like opioid antagonist of the μ/δ-type but it was judged not worthy of further development. In contrast, mixed μ/δ agonists[23] remain of interest in an opioid scenario which a current review[24] described as being 'far from successful' over the last 20 years in the search for a replacement for morphine.

Acknowledgements

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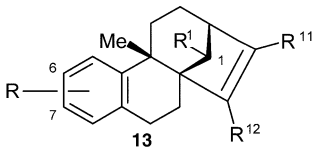
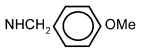
Table 1. [^{3}H]naloxone displacement data for a series of bicyclo[3.2.1]oct-6-ene/-ane amines of general structure **13**



13

ENTRY	R	R^1	R^{11}	R^{12}	Naloxone (IC_{50} μM) [a]
1	6-OMe	NH_2	Me	Me	17
2	6-OH	NH_2	Me	Me	0.4
3	7-OMe	NH_2	Me	Me	3.7
4	7-OH	NH_2	Me	Me	1.5
5	6-OMe	NH allyl	Me	Me	5.4
6	6-OH	NH allyl	Me	Me	0.026
7	7-OH	NH allyl	Me	Me	0.6
8	H	NH allyl	Me	Me	1.8
9	6-OMe		Me	Me	91
10	6-OH		Me	Me	1.4
11	7-OH		Me	Me	0.5
12	6-OMe		Me	Me	21.5
13	6-OMe	NHEt	H	H	10
14	6-OH	NHEt	H	H	0.6
15	6-OMe	NH_2	H	H	20
16	6-OH	NH_2	H	H	0.9
17	6-OMe	NH_2	Me	H	Not tested
18	6-OMe	NH_2	Me	Ph	42
19	6-OH	NH_2	Me	Ph	4
20	6-OMe	NH_2	Me	SPh	100
21	6-OMe	NH*n*-Pr	Me	SPh	>100
22	6-OMe	NH_2	Et	Et	29
23	6-OMe	NH_2	SPh	SPh	>100

[a] Data from three determinations and where IC_{50} is the concentration of ligand (μM) required to displace 50% of [^{3}H]naloxone bound to opioid receptor.

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