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Synthesis of 5-(3,4-dichlorophenyl)-4-[(methyloxy)methyl]-2-azabicyclo [3.2.1]octane derivatives as constrained aryl-piperidines with activity as triple re-uptake inhibitors

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ABSTRACT

Stereochemical and synthetic aspects encountered during the preparation of the four possible isomers of **1** are reported. The 5-aryl 2-azabicyclo [3.2.1] octane derivatives represent a novel class of compounds which can be deemed as an example of aryl-piperidine conformationally constrained of potential interest for medicinal chemistry exploration. In particular isomers of **1** are characterised by a potent in vitro serotonine, dopamine and noradrenaline re-uptake inhibitor (TRUI) activity superior/comparable to standard compounds such as DOV 21,947 and DOV 102,677.

Exploration of aryl-piperidine motifs by several pharmaceutical industries has resulted in the identification of interesting biologically active molecules particularly for application in the CNS area. In fact, these compounds have been widely investigated as NMDA receptor antagonists, serotonin re-uptake inhibitors (SSRI), dual or triple re-uptake inhibitors (TRUI—inhibitors of the re-uptake of three important neurotransmitters namely 5-HT [serotonin], DA [dopamine] and NE [noradrenaline]) and other mechanisms for indications such as unipolar depression, Alzheimer's and Parkinson's diseases.[1] The constraint of the piperidine ring represents an efficient expedient to achieve biological potency and selectivity within a receptor family.

A few examples of constrained aryl-piperidines that are CNS active are listed in Figure 1: tropane derivatives and benzomorfane scaffolds are classical examples[2] of constrained aryl-piperidines. In these cases the piperidine ring has been constrained, respectively, by a C2 and C3 carbon linkage between 1 and 5 positions or as in the case of DOV 21,947 and DOV 102,67 where positions 1 and 5 are directly linked to give a [3.1.0] bicyclic motif.[3] Likewise for cocaine analogues, often the 2 position is a point of further diversification of the molecule that enables the modulation of its physico-chemical and biological properties. The anti-depressant paroxetine, which bears both substituents in the equatorial positions, can also be considered as a 4-aryl-piperidine with a restricted conformation.[4] Also the well-known Parkinson's disease animal model inducer MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), that is, characterised by the presence of a double bond can be considered as an example of an aryl-piperidine with a reduced degree of freedom.[5] Recently GSK has published[6] a further example of a constrained 4-aryl-piperidine, see compound **2** in Figure 1. Single enantiomers have been characterised both in vitro and in vivo as a CNS penetrant TRUI with potential application for unipolar depression.

During our research activity we were interested in preparing a novel class of compounds such as TRUIs and we envisaged the possibility to achieve this with a new class of constrained 4-aryl-piperidines,[7] with a more rigid C2 carbon linkage and that was amenable to further chemical manipulations. A schematic example is reported in Figure 2. In particular, to evaluate whether this class of compounds can deliver a triple re-uptake inhibitor, compound **1** was designed. We choose the 5-aryl 2-azabicyclo [3.2.1] octane lactam **3**, as a key intermediate (Scheme 1). It contains multiple functional groups that can allow versatile manipulations and decorations. It represents an ideal starting point for a SAR exploration around this template. The 5-aryl 2-azabicyclo [3.2.1] octane template is a very rigid structure and the substituents are locked in their positions as depicted in Figure 3.

It is clear that among the three chiral centres present in compound **3**, two of them are mutually related by the C2 carbon atoms sequence bridging the 1 and 5 positions of the piperidine ring.

The 5-aryl substituent assumes an equatorial position whilst the substituent at 4 position could either be in an equatorial (*anti* diastereoisomer) or an axial position (*syn* diastereoisomer).

Clearly, the biological response to this variation and to the absolute stereochemistry will be diverse and important to investigate. Therefore, in the first instance all possible isomers of **1** were of potential interest.

The malonamide motif present in **3** is a key strategic feature for preparation of **1** and the ester moiety can allow a relatively easy functionalisation at the 4 position. Synthesis of intermediate **3** is reported in Scheme 1.

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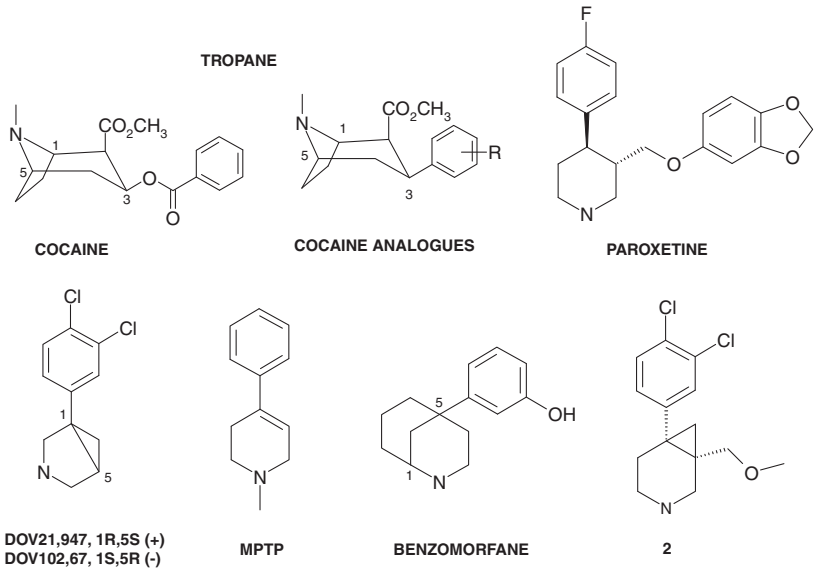


Figure 1. Constrained piperidine examples active in CNS.

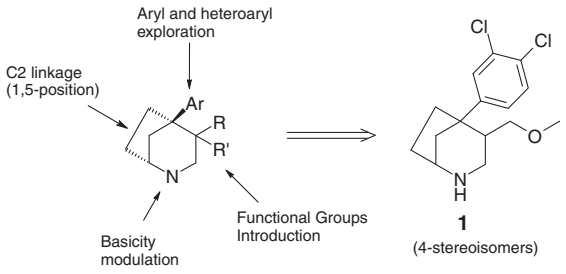


Figure 2. 5-Aryl 2-azabicyclo [3.2.1] octane as new triple re-uptake inhibitor.

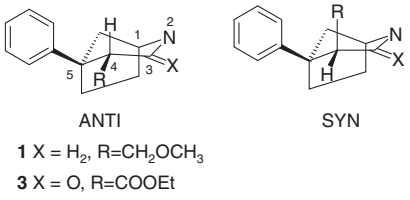


Figure 3. Relative stereochemistry of the two possible diastereoisomers.

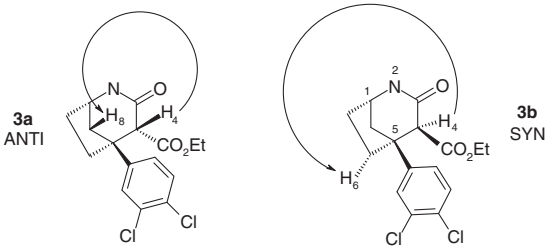
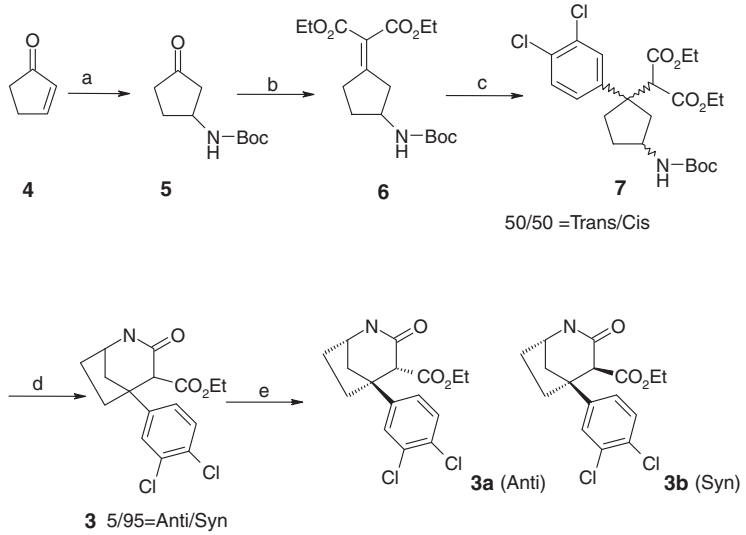


Figure 4. Homonuclear dipolar interactions (^{1}H–^{1}H-ROE) exploited to assign the relative *anti* and *syn* stereochemistry of **3a** and **3b**.

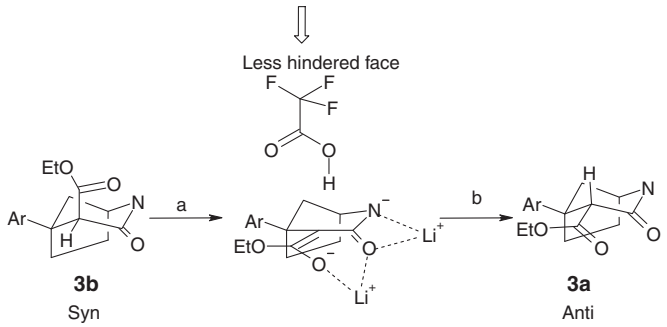
The first problem to address was the preparation of the intermediate β-amino ketone **5**.

Despite the fact that several 1,4-Michael additions of benzyl and dibenzyl amines catalysed by Lewis acids on α,β-unsaturated ketones are reported in the literature,[8] in our hands, only traces of target product were detected applying these procedures onto



Scheme 1. Reagent and conditions: (a) (1) $TMSN_3$, CH_3COOH, Et_3N, DCM, rt; (2) H_2, Pd/C, EtOAc; (3) Boc_2O, 30%; (b) diethylmalonate, $TiCl_4$, CCl_4/THF, 58%; (c) 3,4-dichlorophenyl magnesium bromide, CuI, THF, rt; (d) (1) TFA, DCM; (2) Et_3N, DCM, 120 °C MW, 40 min, 43% after three steps; (e) prep HPLC separation.

cyclopentenone **4**. This finding prompted us to consider a more conservative two-step sequence involving a 1,4-Michael addition of azide followed by reduction and in situ protection to give a stable *N*-Boc cyclopentanone[9] **5** in an overall 30% yield. Due to the presence of the acid-labile protective group *N*-Boc on intermediate 5, the α,β-unsaturated malonic system **6** was obtained by applying a mild version of the Knoevenagel condensation reaction, using $TiCl_4$ as the activator in THF/CCl_4 solution at 0 °C followed by pyridine treatment to complete the formation of the α,β-unsaturated system.

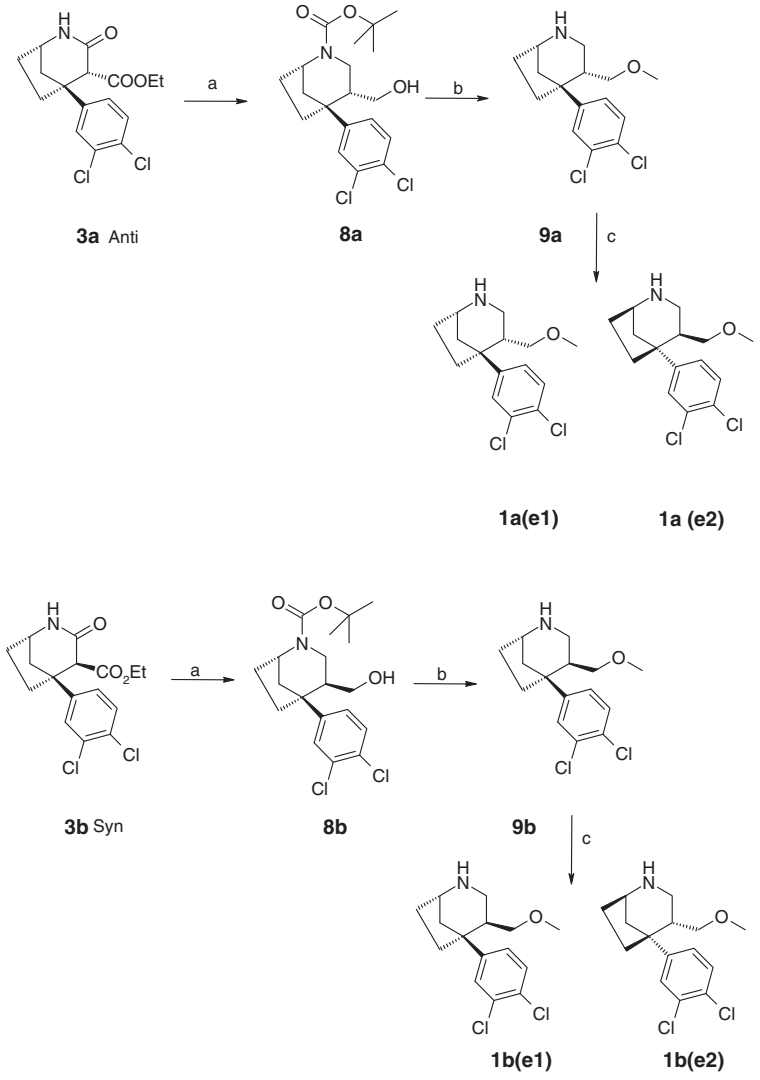


Scheme 2. Stereochemical inversion of **3b** to **3a**. Reagents and conditions: (a) LiHMDS, −78 °C, THF; (b) TFA, from −78 °C to rt, 90%.

Intermediate **6** was then reacted via 1,4-Michael addition with an excess of 3,4-dichloro phenylmagnesium bromide due to the presence of the acidic NH-Boc moiety using CuI as the catalyst. The aryl group was expected to mainly enter from the less hindered face of **6**, however, the coordination of the Grignard with the NH-Boc might have counterbalanced the expected favourable steric effect giving rise to **7** as a ~1:1 ratio of trans:cis isomers. Separation of the two isomers **7** was achieved in the next steps; cleavage of the *N*-Boc-protecting group using TFA followed by basic treatment to obtain the corresponding free amine, which in turn was cyclised to lactam **3**.

Of course, only the isomer with the right geometry underwent intramolecular cyclisation affording the corresponding lactam **3**. The polar nature of the unreacted isomer facilitated the isolation of the desired product **3** which was obtained as a mixture of two isomers **3a** and **3b** (*anti*/*syn* = 5/95). Relative stereochemistry of **3a** and **3b** was assessed by homonuclear dipolar interactions (^{1}H–1H-ROE), Figure 4.

Only the major diastereoisomer **3b** (syn) showed a strong H4–H6 ROE supporting the view that these two hydrogens are on the



Scheme 3. Reagents and conditions: (a) (1) BH_3 * THF, reflux then MeOH/HCl; (2) NaOH, THF, Boc_2O; (b) (1) NaH, MeI, THF; (2) TFA, DCM, 30% over five steps; (c) Chiral Prep HPLC. **1a**(**e1**), **1a**(**e2**), **1b**(**e1**) and **1b**(**e2**) are single enantiomers and their relative stereochemistry is shown. Absolute stereochemistry has not been determined.

Table 1
Binding values at three transporters (DAT, SERT, NET) expressed as pK_i

Compounds	hDAT pK_i	hSERT pK_i	hNET pK_i
DOV 21,947	7.10	6.85	6.83
DOV 102,677	7.42	7.09	7.23
9b	8.50	8.50	8.10
1b(**e1**)	8.68	8.85	8.24
1b(**e2**)	8.00	8.50	8.30
9a	8.80	10.00	8.80
1a(**e1**)	8.90	10.10	8.82
1a(**e2**)	7.50	8.20	7.10

SEM for hDAT/hSERT/hNET data sets is ±0.1.

same side of the molecule, while isomer **3a** (anti) showed a significant correlation between H4 and H8 permitting to assign the anti-relationship to this isomer as depicted in Figure 4. It was surprising to us to find out that isomer **3b** bearing the ethyl ester in a pseudo-axial position was the major one. Likely, the experimental condition used to obtain lactam **3** reflects the relative thermodynamic stability of the two diastereoisomers, see Figure 3. Although, molecular mechanic and quantum mechanic calculations[10] are in agreement with the result obtained predicting the *syn* isomer as the favourable form, these studies cannot explain the high degree of stereoselectivity observed (*anti*/*syn* = 5/95).

Separation of these two isomers has proven difficult; from a practical point of view only isomer **3b** was recovered as a pure material by flash chromatography whilst a pure sample of the isomer **3a** was obtained by preparative HPLC separation.

Reduction of isomer **3b** to the corresponding **8b** was achieved using borane in THF at reflux followed by in situ protection of the secondary nitrogen by reaction with $(Boc)_2O$ under Schotten–Baumann conditions.[11] With the aim of converting the *syn* isomer **3b** to the corresponding anti-form, **3a**, we started to investigate different conditions for inverting the stereochemistry of the ethyl ester. Among them, we found that treatment of **3b** with lithium hexamethyldisilazane (2 equiv) as a base in THF at −78 °C followed by addition of TFA was particularly successful, Scheme 2. We assumed that the proton would have entered from the less hindered face of the molecule, opposite to the C2 carbon bridge, to give the *anti* isomer **3a**. We were pleased to see that our assumption was fully supported by the experimental results and complete epimerisation from **3b** to **3a** was obtained. However, as expected the isolated pure **3a** *anti* isomer proved to have limited stability and after 36–48 h at room temperature we observed re-conversion to the **3b** *syn* isomer.

Nevertheless, this finding did not limit the possibility of obtaining the desired amino-alcohol **8a**, which retained the relative stereochemistry, through reduction of a freshly prepared sample of **3a**. Separately, both compounds **8a** and **8b** were methylated using the same reaction conditions, NaH and MeI in THF. Then removal of the *N*-Boc-protecting groups, using TFA, gave **9a** and **9b**, both in 30% overall yield. Eventually, racemic **9a** and **9b** were resolved by chiral preparative HPLC[12] to obtain the corresponding single enantiomers **1a**(**e1**), **1a**(**e2**), **1b**(**e1**) and **1b**(**e2**) as shown in Scheme 3. All of these were tested as TRUIs in comparison with two standard compounds DOV 21,947 and DOV 102,677. All four compounds showed excellent in vitro potency in blocking the binding of the three human transporters DAT, SERT and NET.[13]

Additionally, the relative potency ratio for the three neurotransmitter transporters is more balanced in the case of the *syn* isomers **1b**(**e1**) and **1b**(**e2**) rather than in the case of the *anti* isomers **1a**(**e1**) and **1a**(**e2**) see Table 1. In conclusion, the synthesis of a new conformationally constrained 4-aryl-piperidine class such as **1** has been achieved. Both isomers **9b** and **9a** have been isolated using a suitable chemical strategy that has allowed to epimerise the *syn* isomer **3b** to the anti **3a** isomer. Final compounds **1a**(**e1**), **1a**(**e2**), **1b**(**e1**) and **1b**(**e2**) were isolated as single enantiomers and showed to be potent in vitro TRUIs with different potency ratios for the three transporters, SERT, DAT and NET.

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