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Synthesis and structural studies of a novel scaffold for drug discovery: a 4,5-dihydro-3*H*-spiro[1,5-benzoxazepine-2,4′-piperidine] ☆

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Abstract—We describe the three-step synthesis of a novel 4,5-dihydro-3*H*-spiro[1,5-benzoxazepine-2,4′-piperidine] scaffold from *ortho*-hydroxyacetophenone and *N*-benzylpiperidone. The structure of one disubstituted derivative, studied by NOESY NMR in an aqueous medium and X-ray diffraction, demonstrates that this scaffold presents side chains in a well-defined orientation. The Boc protected derivative represents a key intermediate for the combinatorial synthesis of drug-like molecules.

1. Privileged structures in drug discovery

Privileged structures represent molecular frameworks capable of binding to several diverse biological receptors with high affinity. Since its introduction by Evans et al.[1] for 1,4-benzodiazepine-2-ones, the term privileged structures has appeared in the literature many times to define structures as diverse as 1,4-dihydropyridines, benzylpiperidines or even cyclic peptides. These structures need to be distinguished from 'frequent hitters' such as those described by Roche et al.,[2] which either bind nonspecifically to a variety of targets or interfere with the read-out of biological assays. A structural rather than biological definition of a privileged structure was thus provided by IUPAC as a 'substructural feature which confers desirable (often drug like) properties on compounds containing that feature. It often consists of a semi-rigid scaffold, which is able to present multiple hydrophobic residues without undergoing hydrophobic collapse'.[3] With the generalisation of high throughput screening in the drug discovery process, there has been significant interest in the incorporation of structural features (substructures or scaffolds) of privileged structures in the design of chemical libraries.[4] It has been shown that biological activity and specificity of compounds based on privileged structures can easily be modulated with minor changes in the nature of the substituents.[5,6]

1.1. 4,5-Dihydro-3*H*-spiro[1,5-benzoxazepine-2,4′-piperidine]: a new scaffold for library design

We report here the design of a scaffold suitable for the preparation of combinatorial libraries. In designing our new scaffold, our intention was to meet the IUPAC requirements for a privileged structure. This scaffold combines two substructures: 1,5-benzoxazepine and spiro piperidine leading to the 4,5-dihydro-3*H*-spiro[1,5-benzoxazepine-2,4′-piperidine] semi-rigid scaffold (structure A in Fig. 1). Although the preparation of spirocyclic systems of this type has not yet been published, related spirocycles endowed with various bioactivities have been reported. Spiro[piperidine-pyrrolo[2,1-*c*]-[1,4]-benzoxazepines] (type B) have been shown to be analgesic and antihypertensive agents,[7] whilst

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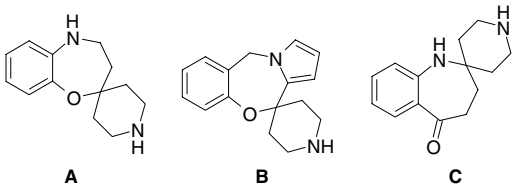


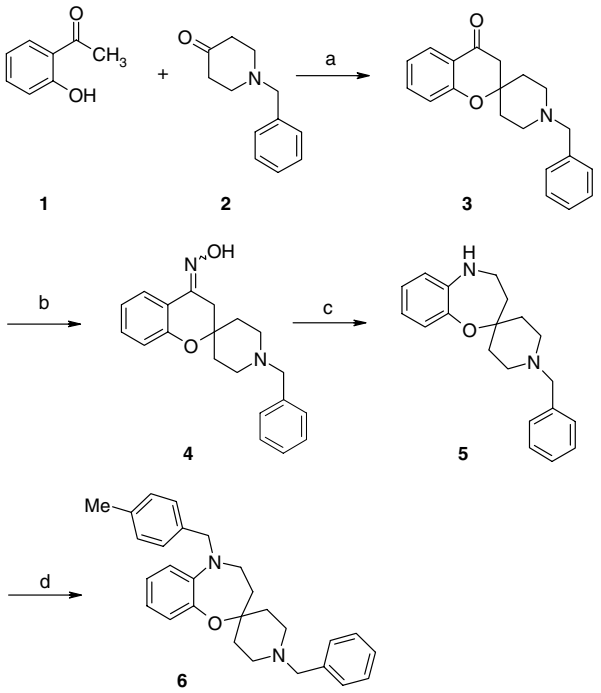
Figure 1. Structures of scaffold type A and spiro scaffolds of types B and C.

spiro[benzoxazepine-2,4′-piperidine] (type C) bind to sigma receptors (Fig. 1).[8]

Due to the presence of two nitrogen atoms of well-defined chemical reactivity, various substituents can be attached and projected in a conformationally restricted manner in the three spatial directions. Moreover the HCl salt of **6**, despite bearing two hydrophobic substituents, displays remarkable water solubility (>10 mg/mL at pH = 1 and >50 μg/mL at pH = 7.4).

2. Synthetic approach

In our synthetic approach, we designed a strategy that permits the rapid and efficient synthesis of derivatives from simple and commercially available *ortho*-hydroxyacetophenones and *N*-benzyl-piperidone (Scheme 1). Compound **3** was obtained in quantitative yield by refluxing bis-nucleophile **1** (1 equiv) with **2** (1 equiv) in methanol, in the presence of a catalytic amount of pyrrolidine (0.5 equiv). Oxime **4** was formed in a refluxing ethanolic solution of hydroxylamine hydrochloride (2 equiv), pyridine (2 equiv) and compound **3** (1 equiv). The key step for the preparation of **5** was the ring expansion. The one-pot synthesis of heterocyclic fused azepines using diisobutylaluminium hydride (DIBAL-H) from oximes has been studied by Cho et al.[9] In contrast to the classical two-step Beckmann synthesis, which requires the preparation of a lactam intermediate and its reduction, this procedure yields the desired oxazepine directly. However, when using the described conditions, the product decomposed rapidly during work-up. Exchanging potassium fluoride for 20% sulfuric acid for the cleavage of the nitrogen–aluminium complex, the desired compound **5** was recovered in dichloromethane after basification to pH 9 using a 30% sodium hydroxide solution. The target compound **5** was obtained as an oil, which crystallised, in three steps with an overall yield of 31% (Scheme 2).[10]

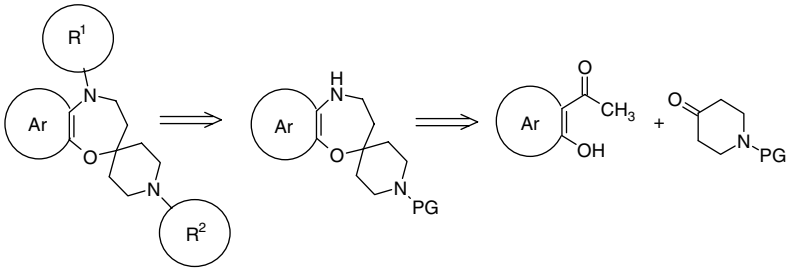


Scheme 2. Reagents and conditions: (a) pyrrolidine, MeOH, reflux 18 h, 98%; (b) $NH_2OH{\cdot}HCl$, pyridine, EtOH, reflux 2 h, 64%; (c) DIBAL-H, CH_2Cl_2, 0 °C, 3 h then MeOH, H_2O, 20% H_2SO_4 (30 min), then 30% NaOH to pH 9, 50%; (d) 4-methylbenzaldehyde, $NaBH(OAc)_3$, CH_2Cl_2, 18 h, rt, 70%.

3. Structural studies

In order to exemplify the possibility of introducing an additional substituent on the azepine nitrogen, **5** was alkylated with 4-methylbenzaldehyde (1.1 equiv) and sodium triacetoxyborohydride (2 equiv) in CH_2Cl_2 to give **6** in 70% yield. The relative orientations of the scaffold and the two side-chains in **6** were studied by 2D NMR in $CDCl_3$ and D_2O/DCl and by X-ray crystallography. The ^1H NMR spectrum of compound **6**, in D_2O/DCl and in $CDCl_3$, showed only one set of signals that could be attributed to **6a**, one of the two possible chair conformations of the piperidine illustrated in Figure 2.

The $H12_{ax}$ and $H16_{ax}$ protons appeared as a multiplet, showing one large geminal coupling ($J^2 = 12.65$ Hz), one large *trans*-axial coupling with $H13_{ax}$ and $H15_{ax}$ ($J^3 = 12.04$ Hz), and one *cis* coupling ($J^3 = 4.71$ Hz) with $H13_{eq}$ and $H15_{eq}$. In addition the $H12_{eq}$, $H16_{eq}$ and



Scheme 1.

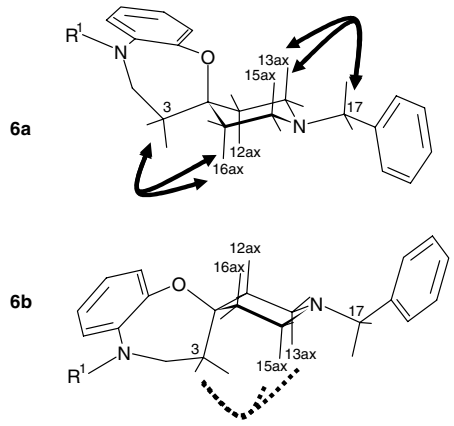


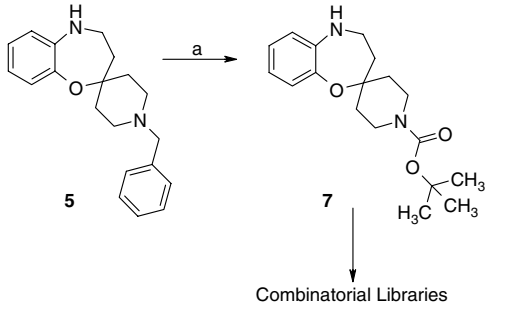
Figure 2. NOESY NMR spectrometry in $CDCl_3$ and D_2O/DCl. Solid arrows: observed cross-signals, dotted lines: cross-signals not observed, $R^1 = 4$-methylbenzyl.

$H13_{eq}$, $H15_{eq}$ protons appeared as doublets showing one large geminal coupling. In the NOESY spectrum, H3 of the azepine ring gave cross-signals with $H12_{ax}$ and $H16_{ax}$. Both H17 protons gave cross-signals with $H13_{ax}$ and $H15_{ax}$. No cross-signals between H3 and $H13_{ax}$, or $H15_{ax}$ could be detected (Fig. 1). This experiment confirmed the presence of conformation **6a**, which is energetically favoured both in $CDCl_3$ and D_2O/DCl.

Compound **6** also adopts the same conformation in the crystal as shown by the ORTEP drawing of the X-ray diffraction analysis. Thus 4,5-dihydro-3*H*-spiro[1,5-benzoxazepine-2,4′-piperidine] acts as a semi-rigid scaffold, able to present various substituents without undergoing hydrophobic collapse and behaves structurally as a privileged structure.

4. A key intermediate for combinatorial synthesis

To exploit fully the potential of this scaffold in parallel synthesis, compound **5** was debenzylated by Pd-catalysed hydrogenation and selectively protected with a Boc group, to yield compound **7** (Scheme 3). This scaffold is currently being substituted with target-specific pharmacophores to demonstrate that it is able to provide ligands for diverse receptors (GPCRs, metallo-protease) depending on the side-chains attached and other modifications.



Scheme 3. Reagents and conditions: (a) (i) H_2, Pd/C (10%), MeOH, 18 h; (ii) Boc_2O (1.05 equiv), Et_3N (2 equiv), DCM/dioxane, 2 h, 66% (two steps).

Supplementary material

Experimental procedures for syntheses of **3**, **4**, **6**, **7** and an ORTEP drawing of compound **6** (CCDC 224676).

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10. Oxime **4** (3 g, 9.3 mmol, 1 equiv) was solubilised in anhydrous dichloromethane (20 mL). The mixture was stirred at 0 °C for 30 min, and (1 N) diisobutylaluminium hydride in dichloromethane (54 mL, 54 mmol, 5.8 equiv) was added dropwise over 1 h. The mixture was stirred for 3 h under nitrogen at 0 °C. The reaction was quenched by slowly adding MeOH (9 mL), followed by distilled water (9 mL) and 20% sulfuric acid (50 mL). The solution was stirred for a further 20 min. The solution was basified to pH 9 using a 30% sodium hydroxide solution. The resulting mixture was extracted with ethyl acetate (2×100 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a yellow oil. The residue was purified by chromatography on alumina oxide with cyclohexane/ethyl acetate (1/1, v/v) to give 1.5 g of a yellow oil, which

crystallised. Yield: 52%. Mp: 99.0–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.54 (ddd, 2H, $J = 12.85$ Hz, $J = 12.60$ Hz, $J = 4.62$ Hz); 1.82 (t, 2H, $J = 5.16$ Hz); 1.86 (dm, 2H, $J = 12.60$ Hz); 2.40 (ddm, 2H, $J = 12.60$ Hz, $J = 11.41$ Hz); 2.51 (dm, 2H, $J = 11.41$ Hz); 3.18 (t, 2H, $J = 5.16$ Hz), 3.47 (s, 2H); 6.53 (dd, 1H, $J = 7.73$ Hz, $J = 1.62$ Hz); 6.63 (td, 1H, $J = 7.55$ Hz, $J = 1.59$ Hz); 6.77 (td, 1H, $J = 7.45$ Hz, $J = 1.52$ Hz); 6.87 (dd, 1H, $J = 7.78$ Hz, $J = 1.55$ Hz); 7.15–7.30 (m, 5H). ^{13}C NMR δ: 34.3; 40.2; 40.9; 48.7; 62.6; 117.7; 119.1; 123.0; 123.8; 126.2; 127.4; 127.4; 128.5; 137.7; 141.8. MS $(MH)^+$ m/z 309 (100%).