Piperidones: from alkaloids to pseudopeptides

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1. Introduction

In the early 1980’s our group was working on the synthesis of monoterpene indole alkaloids and their derivatives. We were particularly interested in four families: Corynanthe, Vinca-Eburnane, Strychnos and Aspidosperma (Figure 1). Some representatives of these families still find clinical use; vincamine, is used as a brain vasodilator in geriatric patients, and vincristine is used as an antineoplasic agent in the treatment of certain cancers. The widespread use of these drugs is only possible, however, because chemical synthesis provides them in quantities not obtainable from natural sources, where the amounts of the active principles are too low. In addition, these drugs are highly toxic. Less toxic and more specific synthetic analogues could lead to the improvement of the quality of life of patients under treatment.

The four families of indole alkaloids mentioned above were attractive as targets for synthesis because they share a common structural feature, a 2-indolylpiperidine unit. Our general synthetic approach was to focus on this moiety, using functionalized piperidine synthons as scaffolds to build more complex molecules. The first piperidine synthon we prepared was a 2-aryl-4-piperidone, reviewed in Section 2. We have subsequently developed a number of piperidones and applied them to the preparation of piperidine compounds with biological interest.

Abstract

Our early work on the synthesis of alkaloids that contain a piperidine ring led us to prepare diversely functionalised piperidines as scaffolds for building more complex structures. Since then we have prepared a number of piperidone synthons, and we have applied these to the preparation of biologically interesting compounds which range from alkaloids to conformationally constrained pseudopeptides. We provide here a brief historical introduction, followed by eight sections, dedicated to our most relevant piperidine synthons: i) 2-aryl-4-piperidones, ii) \( \Delta^1 \)-piperidein-2-ones and 2-cyanopiperideines, iii) 3-amino-2-arylpireridin-4-ones, iv) 3-aminopiperidin-2-ones, v) glutarimides, vi) 3-amino-\( \Delta^2 \)-piperidein-2-ones, vii) oxazolopiperidones, and viii) hydroxylactams.

Keywords: 2-aryl-4-piperidones, 3-aminolactams, indole alkaloids, pseudopeptides, peptidomimetics.

Resum

Els nostres treballs inicials sobre la síntesi d’alcaloides que contenen un anell de piperidina en llur estructura, ens va portar a la preparació de sintons piperidínics diversament funcionalitzats sobre els quals construir molècules més complexes. Des de llavors hem sintetitzat algunes piperidones, que hem emprat per a la obtenció de compostos amb interès biològic. Al llarg dels anys, aquests compostos van des dels alcaloides fins a pseudopèptids de conformació restringida. Aquest article consta, per tant, d’una breu introducció històrica, seguida de vuit capítols corresponents als sintons piperidínics més rellevants que hem desenvolupat: i) 2-aryl-4-piperidones, ii) \( \Delta^1 \)-piperidein-2-ones i 2-ciano-piperideïnes, iii) 3-amino-2-arylpireridin-4-ones, iv) 3-aminopiperidin-2-ones, v) glutarimides, vi) 3-amino-\( \Delta^2 \)-piperidein-2-ones, vii) oxazolopiperidones i viii) hidroxilactams.

Keywords: 2-aryl-4-piperidones, 3-aminolactams, indole alkaloids, pseudopeptides, peptidomimetics.

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At about this time, models to explain how biological receptors operate were beginning to appear [1], although the relationship between structure and biological activity remained largely mysterious. Thus, compounds of similar structure proved to have different biological properties, and compounds with very different structures were found to be useful against the same disease. The possibility of using rational design to improve molecules showing potential clinical efficacy was, consequently, very tempting. Indeed, progress in understanding the modes of action of compounds has since aided the rational design of new «drug leaders». Many compounds act by mimicking the action of endogenous peptides, and peptide mimetics has become an intensely active field of pharmacological study. As our research has advanced, we have continued to seek structures that contain the piperidine core and that have potential use in the pharmacological field. By modifying our piperidine synthons we have widened their scope, and our research has evolved towards molecules that might act as small peptidomimetics. The focus of our most recent work is the preparation of 3-aminopiperdin-2-ones (Figure 2) whose backbone makes them intrinsically biologically interesting (see for example, Section 4.1). In addition, they can be considered as conformationally constrained dipeptide surrogates (see section 5), and can be used to improve the activity of known peptides.

This review is organized into eight sections, each devoted to one of the most relevant synthons on which we have focused our work: 2-aryl-4-piperidones (I), unsaturated valerolactams and 2-cyanopiperideines (II), 3-amino-2-aryl(piperidin-4-ones (III), 3-aminopiperidin-2-ones (IV), glutarimides (V), enamides (VI), oxazolopiperidinones (VII), and hydroxylactams (VIII).

2. 2-Aryl-4-piperidones (I)

We developed our first synthon, 2-aryl-4-piperidone I (Figure 2), with the aim of forging a new route to the benzoquinolizidine alkaloids. At the time, the known methods for obtaining this tricyclic structure were closure of ring C by either Dieckmann cyclization or the Mannich reaction, and formation of the 11a-11b bond through a Bishler-Napieralsky reaction (Figure 3). Our approach was to close ring B by formation of the 7-7a bond [2], for which we had first to prepare the appropriate 2-phenyl-4-piperidone, a system that had never been described.
The synthesis of the required 2-phenylpiperidin-4-one was achieved by condensation of the suitable primary aminoacetals with benzaldehyde, followed by an acid-promoted Mannich-type cyclisation (Figure 4) [3]. Indeed, in a dry acid medium the protonation of the acetal allows the formation of an enol ether which attacks the intramolecular iminium salt.

This proved to be a general method for obtaining protected 2-aryl-4-piperidones 1, by using any aromatic aldehyde.

2.1. Corynanthe alkaloids

Our interest in the quinolizidines led us to attempt the preparation of Corynanthe indole alkaloids. The reported methods for synthesis of the indolo[2,3-α]quinolizidine ring system were based on closure either of ring C through formation of the C12a-C12b bond, or of ring D (Figure 5). We planned to explore the possibility of applying our method to close ring C by formation of the C7-C7a bond.

We discovered that the treatment with K’BuO of a 2-(2-indolyl)piperidine 2, whose indole nucleus was protected with a phenylsulfonyl group and whose piperidine nitrogen atom carried 2-hydroxyethyl chain, yielded directly the indoloquinolizidine system 3 (Figure 6). We planned to explore the possibility of applying our method to close ring C by formation of the C7=C7a bond.

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those of other experiments, allowed us to give a mechanistic explanation [4].

The KtBuO acted as a nucleophile on the sulfonyl group, allowing its migration to the alcoholate via transesterification. The resulting intermediate 5 underwent intramolecular attack of the bidentated indole anion on the sulfoxyl leaving group. Thus, the indoloquinolizidine system was obtained in one step as a product of cyclisation on the indole 3-position, although inevitably accompanied by the pyridopyrazinoidole that results from cyclisation on the indole nitrogen atom.

To avoid the formation of the undesired regioisomer, we applied the reaction to a 2-(3-indolyl)piperidine 6. In this case, the intermediate formed with KtBuO would be a spiroindolenine 7, which was known to rearrange to the desired quinolizidine upon treatment with a Lewis acid (Figure 7) [5].

Structurally, the intermediate spiroindolenines 7 constitute the ABCD ring system characteristic of Aspidosperma and Strychnos alkaloids, so we considered the possibility of building the fifth E ring by integrating a carbonated chain between the imine carbon atom and positions 3 or 4 of the piperidine ring, respectively (Figure 8). In addition, an appropriate substitution on the piperidine C3 position might also be used to obtain the Eburnane framework after rearrangement to an indoloquinolizidine.

2.2. Synthesis of Strychnos-type compounds via protected 2-indolyl-4-piperidones
To synthesize Strychnos-type compounds, we first prepared 2-(3-indolyl)piperidines 8a and 8b following our methodology (Figure 9) [6]. Piperidines 8a and 8b bear an acetate chain on the 4-position, cis with respect to the indole substituent, and are epimeric on C-5. Treatment of the mixture of 8a and 8b with an excess of KtBuO followed by addition of BF3·Et2O to the reaction medium provided a mixture of compounds 10 and 11 (Figure 9). Indoloquinolizidine 11 was already known to be a precursor of dihydrocorynantheol [7], and compound 10 was identified as tetrahydroakamicine. We had thus achieved a formal synthesis of dihydro-
corynantheol, and opened a new synthetic route to the pentacyclic *Strychnos* structure [8,9].

2.3. Attempts to synthesize the *Eburnane* and *Aspidosperma* alkaloids

According to our reasoning (Figure 8), it should be possible to synthesize the *Eburnane*-type structure 12 by closing the C16–N1 bond after rearrangement of a spiroindolizidine 13 to the corresponding quinolizidine (Figure 10). Compound 13 would be obtained from 2-indolylpiperidine 14 by treatment with KBuO.

However, when we treated piperidine 14 with KBuO under the conditions normally used to obtain spiroindolenine 13, and then induced rearrangement to the indoloquinolizidine 15 using BF3·Et2O, the only products obtained were tryptophylpiperidines 16 (Figure 11) [10].

We had already observed that spiroindolenines carrying substituents on the piperidine C3 [11] or the indole C2 [12] positions evolve naturally to tryptophylpiperidines type 17 through opening of the pyrrole ring by anchimeric assistance of the nitrogen atom. It appeared that the ring opening was quicker than the rearrangement because of the steric interaction. In the absence of a nucleophile or oxidizing agent [5b], the resulting iminium salt (type 17) would usually evolve to the corresponding enamine. However, in the present case, the lack of a hydrogen atom on C3 prevents the tautomeric equilibrium of 17, and a Wagner-Meerwein rearrangement of the ethyl chain takes place, followed by elimination to give the stable unsaturated ester 16.

In any case, the high instability of the intermediate spiroindolenine 13 rendered our strategy unsuitable for obtaining either *Eburnane* or *Aspidosperma* alkaloids.
3. Unsaturated valerolactams and 2-cyanopiperidines (II)

In the light of our previous results, we planned to obtain both the Aspidosperma and the Strychnos frameworks by closing the pyrrole C ring (Figure 8) on a suitable ABED tetracyclic system, a strategy that had already been reported [13]. The bridged tetracyclic framework of the Strychnos alkaloids constitutes the structure of dasycarpidine alkaloids. In the case of Aspidosperma, the preparation of a pyridocarbazole was necessary.

We devised a single approach for synthesis of both tetracyclic ring systems, with the key step being the closure of the bond between the indole nucleus and the piperidine C2-position (Figure 12). We chose 2-cyanopiperidines 19 and 22 as latent iminium salts, with lactams 20 and 23, whose partial reduction would also provide the desired iminium salts, as alternatives. The nucleophile indole synthon in both cases would be 2-(1,3-dithian-2-yl)indole 21.

3.1. Synthesis of Aspidosperma-type compounds

We first carried out the condensation of 3-chloromethylpiperideine 19 with the dianion of indolyldithiane 21, to obtain compound 24. Sequential Ni-Raney reduction and cyclization with rhodium chloride triphenylphosphine complex [14] then led to the target compound 26 (Figure 13) [15]. However, this method did not allow cyclization in the presence of the sulfur atoms, and thus limited considerably the possibilities of functionalizing the system.

To circumvent this problem, we prepared the pyridocarbazole tetracycles 28 by conjugate addition of the dianion of dithiane 21 on 3-methylenelactams 20a, followed by treatment of the adduct with DIBAH (Figure 14). The reduction takes place with spontaneous cyclization of the iminium salt to give the desired pyridocarbazoles 28 (C/D ring junction cis and trans) and their regioisomers, the naphthyridindoindole 29 [16]. Naphthyridindoindole 29 was isomerised to compound 28 in 50% aqueous AcOH.

Subsequently, we introduced an ethyl chain on C3 by a tandem conjugate addition-alkylation reaction, using lactam 20b as the starting material. In this case, only the C/D cis pyridocarbazole was obtained, and closure of the pyrroldine ring followed by reduction of the dithiane ring yielded the alkaloid aspidospermidine (Figure 15) [16].

3.2. Synthesis of dasycarpidine-type alkaloids

Previous synthesis of the dasycarpidine ring system (Fig. 16) had been based on closure of ring C (a, b) or ring D (c), or by indolization (d).

To obtain the dasycarpidine ring system, we generated the iminium salt 35 by treating the 2-cyanopiperidine 22a with AgBF4 (Figure 17). The dianion of indolyldithiane 21 was generated in an adjacent reaction, and then added via cannula to the dihydropyridinium salt. The major adducts derived from this reaction were 37, derived from condensation on the indole 3-position. The minor products were compound 39a, identified as the direct precursor of 20-epidasycarpidine.
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Thus, the target compounds were obtained, but in very low yield owing to the poor regioselectivity of the condensation. To avoid the regioselectivity problem, we performed the conjugate addition of the indolyldithiane anion on the 3-position and subsequent oxidation/elimination of the selenide by treatment with MCPBA. The Michael-type addition of the dianion of indolyldithiane 21 on lactam 23c or 23d in THF yielded the expected adduct 40 as the only product (Figure 19). Partial reduction of lactam 39 was achieved with LiAlH4 in the presence of cyanide anions, and led to a mixture of piperidine 41, 2-cyanopiperidine 42 and methanodiazocinoidole 43. Treatment of compounds 42 and 43 with 50% aqueous AcOH transformed both to the target dasycarpidone-type tetracycle 44, in high yield.

We envisioned the isomerization of methanodiazocinoidole 44 occurring as depicted in Figure 20. In the acid medium the indole 3-position is rapidly protonated leading to formation of the iminium salt 45. This, through an imine-enamine tautomerism, then cyclises to give the regiosomeric dasycarpidone methanodiazocinoidole ring system.

We subsequently applied this strategy to the diastereoselective synthesis of compounds 47 and 48 (Figure 21), using the chiral lactam 23e as the electrophile [18]. Lactam 23e, an (R)-(-)-phenylglycinol derivative, was prepared by oxidation of the corresponding saturated lactam [19]. In this study, the reduction/cyclisation step was improved by the use of Red-Al®.

We also applied the methodology to the preparation of compounds 49 (R = Bn, Me), which were converted to the corresponding acylindole derivatives 50 and the alkaloid 20-epidasycarpidone, respectively (Figure 22) [20]. In this case, the unsaturated valerolactams required 23a and 23b were obtained by DMD oxidation [21] of the corresponding 2-cyano-3-ethyl-Δ^3-piperidein-2-ones 22a and 22b.

3.3. Lactam Pseudopeptides: 3-Amino-4-indolyl-2-piperidine
The use of unsaturated lactams as Michael acceptors had proved to be a very efficient synthetic procedure. Moreover, the conjugate addition of aromatic moieties on Δ^3-piperidein-2-ones indicated a possible entry to 4-aryl-2-piperidine synthons, which, together with our experience in the preparation of 3-aminopiperidine derivatives (see Section 4.1), led us to focus on the preparation of 3-amino-4-indolylpiperidin-2-ones type 54 (Figure 23). Compound 54 was designed as a conformationally constrained analogue of the dipeptide Trp-Gly (see Section 6), in which the restriction caused by...
cyclization between the β-carbon of tryptophan and the nitrogen atom of glycine constrains the conformational space occupied by the indole nucleus of Trp. Furthermore, the dynamics of the ring imposes the orientation of its substituents, and as a result, the φ torsion angles of both Trp and Gly are also restricted. The synthesis of compound 54 was envisaged as occurring through a conjugate addition of indole on lactam 52 followed by a Curtius rearrangement to introduce the amino group on C3 (Figure 23) [22].

The synthesis of the unsaturated lactam 52 was started from N-Boc-α-valerolactam 55 (Figure 24). Acylation on C3 with benzylchloroformate, followed by phenylselenylation on the same position, yielded lactam 56. The successive deprotection of the nitrogen atom and introduction of the acetate chain was done at this stage, since the unsaturated secondary lactam 57 was highly unstable. Alkylation of 58 in basic medium, and addition of MCPBA to the reaction, gave the desired lactam in 60% yield.

The conjugate addition of indole was performed in the presence of Montmorillonite® [23], yielding a mixture of the racemics cis and trans 59 (Figure 25). Compounds 59a and 59b were separated by analytical reverse phase HPLC. However, in the presence of SiO2, epimerization of C3 resulted in partial interconversion of 59a and 59b.

When the mixture of lactams 59 was submitted to the Curtius rearrangement using DPPA and Et3N in the presence of dibutyltin dilaurate, carbamate 60 (Cbz/OtBu) was obtained. Only the trans-isomer was observed. In order to adapt our [Trp-Gly] pseudodipeptide for solid phase peptide synthesis, we also prepared the Fmoc/OtBu derivative 61 by standard methods.

4. 3-amino-2-arylpiperidin-4-ones

4.1. 3-Aminopiperidines as Substance P inhibitors

In the early 1990’s we became interested in prepa-
thetic target potentially able to inhibit SP.

The first problem was to establish a method for introducing an amino group on the 3-position. Of the known amination methods, we chose to try the Neber rearrangement, an old reaction that allows the introduction of an amino group on the α-position of ketones [26]. On the other hand this reaction had never been shown to work on nitrogenated substrates. We first verified that the method works on N-benzylpiperidin-4-one, by formation of the oxime, tosylation, and treatment of the tosyloxime with NaEtO in EtOH (Figure 28). When the method was applied to substrates arylated on C2, the rearrangement yielded both, the 3- and the 5-amino derivatives 66 and 67. We observed that the regioselectivity of the rearrangement depended on the stereochemistry of the intermediate tosyloxime. Thus, the amination took place «anti» with respect to the tosyloxime, which indicated that the intermediate azirine 69 was formed by a backside attack of the anion on the nitrogen atom. The subsequent opening of the azirine ring occurred by the action of the EtOH used as solvent, to give acetal 70. In this way we obtained a small collection of 3-amino-2-arylpiperidin-4-ones. These proved to be inactive as SP inhibitors. However, we had demonstrated for the first time the usefulness of the Neber rearrangement on a piperidone.

4.2. Aza-\textit{Eburnane} alkaloids

In connecting our studies on the Neber rearrangement to the indolo[2,3-a]quinolizidine alkaloids (see Section 2), we decided to prepare 1- and 3-aminoindolo[2,3-a]quinolizidin-2-ones (Figure 29). These compounds would lead respectively to the pentacyclic aza-\textit{Eburnane} and aza-\textit{Yohimbe} alkaloids, in which the extra nitrogen atom is located in ring E. Similar aza-\textit{Eburnane} systems had shown to be able to modify the induction of tyrosine hydroxylase [27]. We planned two approaches for the synthesis of aza-\textit{Eburnane} compounds, via closure of ring C or of ring E in the last step.

Since the pyridopirimidinoindole tetracyclic system of compound 71 (Figure 30) was unprecedented in the literature, we studied its preparation first. Treatment of 3-amino-2-indolylpiperidine 72 with benzyl chloroformate yielded only compound 73 in very low yields, whose structure was inferred from its analytical data. We concluded that even if the ABED tetracycle was formed, its functionalization provoked a spontaneous elimination in the reaction conditions, and that the loss of the ma-
majority of the product could be the result of a subsequent aromatization.

Closure of ring C on compound 73 to give the aza-Eburnane type compound 74 was unsuccessful, which was explained by the high rigidity of the substrate and the decreased nucleophilicity of the indole C3-position.

The second approach to the synthesis of aza-Eburnane systems was started by the preparation of 1-aminindoquinolizidine 75 (Figure 31). This was done either by closure of ring C on aminopiperidine 76, or by amination of indoloquinolizidin-2-one 77. The pentacyclic system was obtained quantitatively from 75 by formation of the carbamate 78 followed by base-induced cyclization [28].

5. 3-aminolactams

5.1. Introduction

In the early 1990s we became interested in the possibility that piperidones might be used as pseudopeptides and as peptide mimetics. As drugs, peptides and proteins tend to suffer from low bioavailability and rapid degradation. Furthermore, the larger and more flexible the molecule, the more likely it is to interact with a wide range of receptors, with corresponding loss of specificity. Small molecules with a longer half-life that bind to a particular receptor may thus be more active than the native peptides or proteins they mimic. Another aspect to be taken into account is that the interaction between the receptor and the peptide active site depends on the conformation of both. Since small molecules have more limited conformational variability, productive interaction with their receptors is likely to be more frequent than that of larger peptides.

One of the major structural motifs that characterise receptor recognition sites of peptides is the β-turn (Figure 32) [29]. 3-Aminolactams were first reported to be able to induce β-turns by Freidinger in 1982 [30]. Since then numerous structures that mimic or induce β-turns have been developed. In 1992 Siegl reported a synthesis of 4-phenyl lactam 80, as a constrained analogue of phenylalanine [31]. This, together with the relevance that peptide mimetics were acquiring in the pharmacological field, focused our attention on the synthesis of diversely functionalized 3-aminopiperidin-2-ones. Not only do our structures present interesting biological activities per se as enzyme inhibitors, but they can also be used as dipeptide surrogates to study structure-activity relationships of known active peptides.
5.2. Simple 3-aminolactams as conformationally restricted surrogates of alanine

We envisaged the synthesis of diversely N₁-substituted 3-aminovalerolactams, since we regarded these as one of the simplest structures that can be considered as constrained derivatives of alanine. The Ala-Gly surrogate 84, described as an ACE inhibitor [32], has been prepared by two methods: N-alkylation of Cbz-cyclo-ornithine with benzyl bromoacetate [33], and lactamisation of N₁-substituted ornithine (Figure 33) [32,34]. Since our intention was to be able to introduce any substituent on the lactam nitrogen atom, we explored the possibility of closing the C6-N1 bond by intramolecular nucleophilic substitution of an α-bromoamide [35].

Coupling of bromoacid 81 [36] with glycine-OBn using DCC/HOBt yielded the desired bromoamide 82, whose treatment with NaH led to the expected valerolactam 83. Reduction of the azido group by hydrogenation in the presence of Lindlar catalyst yielded the target Ala-Gly surrogate 84.

We then applied the cyclisation method to the preparation of [Ala-Leu] 88. Coupling of bromovaleric acid 81 to Leu-OBn using DCC/HOBt gave amide 85 in 38% yield, and treatment of 85 with NaH furnished the expected lactam 87 (Figure 35). However, this series of reactions had two drawbacks. Compound 86, resulting from nucleophilic attack of HOBt on the bromide, was identified as a by-product of the coupling, which accounted for the mediocre yields obtained, and, most importantly, the NaH cyclisation occurred with racemisation at C3.

In order to avoid the SN reaction competing with the coupling, we performed the condensation of the bromoacid with Leu-OBn in the presence of Et₃N. In this manner, the intermediate lactone 89 was generated by cyclisation of the carboxylate, which then reacted with Leu-OBn to give hydroxyamide 90 quantitatively. Treatment of 90 with DEAD/PPh₃ led to the desired azidolactam 91 without racemisation.

In parallel with the previous study, we assayed the solid phase synthesis of 3-aminovalerolactams by formation of the N1-C2 bond through intramolecular coupling of a secondary amine and a carboxyl group (Figure 36). As noted earlier, this strategy had been reported to cyclise N₁-substituted ornithine [33]. However, we needed to be able to introduce an asymmetric centre with respect to the N₁ nitrogen atom. For this purpose, we decided to use a suitable amine as a nucleophile on the mesylate of 5-hydroxynorvaline.

We first established a new method for the preparation of (S)-5-hydroxynorvaline (Figure 37) [37]. This involved protection of the aminocarboxyl extremity of glutamic acid using BEt₃, and reduction of the α-carboxylate with BH₃. (S)-5-Hydroxynorvaline was anchored to a solid support (PS(BHA)-IRAA-HMPP resin) by carbonate activation of the resin. The hydroxyl group was replaced by 4-aminobenzylamine via
mesylation, to give the open chain amino acid in high yields (Figure 38). Subsequent cyclisation was effected by intramolecular DIPCDI/HOBt coupling of the secondary amine. The final cleavage from the resin was carried out by a 20% TFA/CH₂Cl₂ treatment to give lactam [38].

We are currently studying the generality and scope of these two methods by the preparation of small libraries of 3-aminovalerolactams, both in solution and on solid support.

6. Glutarimides

A somewhat more ambitious goal was the preparation of 3-aminovalerolactams substituted on positions C4, C5 and C6. In particular we wished to prepare 4-indolylvalerolactam 99 and 5-methylthiolactam 100, constrained analogues of Trp and Met, respectively (Figure 39).

Various constrained derivatives of tryptophan had already been reported. These can be classified as shown in Figure 40. A first group of derivatives contain the α-position of Trp linked to the indole nucleus 4-position, via a carbon bridge that renders Cα quaternary. A variation of this method consists of linking the amino group to the indole 4-position, by either a carbon chain or another amino acid (here Val) to yield rings of 7, 8, or 9 members. A third class of derivative includes the α- and β-carbons of Trp in a 3-amino lactone ring, whose synthesis was achieved starting from an appropriate carbohydrate. Other derivatives show the cyclisation between the amino group and the indole 2-position, either directly to form a fisostigmine-type compound, or through a carbon atom to yield a β-carboline, via a Bishler-Napieralsky condensation of Trp with the aldehyde of Ser followed by coupling.

Our 3-aminovalerolactam was therefore a new derivative of Trp, in which the α-position was tethered to the amino group of the following amino acid residue (aa₂) by a 2-carbon bridge. In this fashion, the ω, ψ₁(Trp), and χ₂(Trp) dihedral angles are constrained by the six-membered ring, with a concurrent effect on the ψ(Trp), χ₁(Trp), and ϕ(aa₂) dihedral angles which are obliged to move cooperatively with the ring.

Because of our experience with synthesis of (R)-phenylglycinol-derived lactams in the dasy-carpidine alkaloids (see Section 3.2), we decided to establish the synthetic strategy by preparing 3-amino-4-indolylpiperidin-2-one 101, by reduction of a 4-indolylglutarimide (Figure 41). We considered two different approaches: performing the amination as the final step of the synthesis, or introducing the C3 amino group on the starting substrate. In both cases the imides would be prepared by reaction of an appropriate anhydride with (R)-phenylglycinol, a strategy that should allow us to diversify the synthesis by the use of any primary amine.

6.1. Tryptophan-phenylglycinol derivatives

We first obtained the 4-indolylglutaric anhydride 103 from N-benzylindole-3-carbaldehyde (106). A Wadsworth-Emmons condensation with ethyl diethylphosphoroacetate, followed by a malonic synthesis, yielded 4-indolylglutaric acid (Figure 42), which was then cyclized by mesylation and base treatment. The condensation of anhydride 103 with (R)-...
phenylglycinol and the subsequent addition of AcCl led to the desired prochiral glutarimide \[102\].

Reduction of imide \[102\] was performed by treatment with NaBH\(_4\) in acid medium, and yielded a mixture of the 6-hydroxylactams \[110\] and \[111\], together with a small proportion of hydroxyamide \[112\] (Figure 43). Formation of hydroxylactam results from the reduction of the intermediate open-chained aldehyde \[39\]. Reduction of position C6 by Et\(_3\)SiH/TFA, followed by chromatography on SiO\(_2\) and saponification of the acetyl group led to the desired lactam \[113\]. Lactam \[113\] was also obtained by cyclisation of the hydroxyamide \[112\] through mesylation and subsequent treatment with NaH.

The assays of direct amination on C3 using trisylazide did not yield the expected 3-azidolactam \[117\], but rather the diazoderivative \[116\] which we were unable to reduce to the amine (Figure 44). We then prepared 3-bromolactam \[114\], but unfortunately the acidity of the proton on C4 was sufficient to make the bromolactam undergo a dehydrohalogenation upon treatment with benzylamine or with NaN\(_3\), resulting in piperideinone \[115\].

The second approach circumvented this problem by using a starting substrate bearing the amino group on the C3 position. Thus, 4-indolylglutaric anhydride \[122\] was prepared from indolyl-3-carboxaldehyde \[106\] in a sequence that involved a Henry-type reaction, followed by a conjugate addition of di-tert-butyl malonate to yield triester \[119\] (Figure 45). The reduction of the nitro group was performed at this stage, and the amino function was Alloc-protected. In this fashion, the erythro and threo racemic mixtures \[120a,b\] were obtained, and were separated by column chromatography. The major threo triester \[120b\] was used to prepare the corresponding diacid \[121\], which was cyclized as in the previous series to obtain the trans-anhydride \[122\].

The synthesis of the target lactam \[126\] from anhydride \[122\] was carried out by applying the sequence that we had established previously, i.e. by formation of the glutarimide (two trans diastereomers), reduction and cyclisation \[40\]. However, in this case, the reduction of imide \[123\] with NaBH\(_4\)/HCl led only to the open chain hydroxyamide \[124\], whose mesylate \[125\] was cyclized using DBU as the base (Figure 46). The same chemistry was applied using the minor erythro-triester \[120a\], to obtain the cis diastereomers.

### 6.2 Tryptophan-serine derivatives

We next tried to apply the method the synthesis of Trp-Ser surrogates. Thus, condensation of the threo anhydride \[122\] (2 diastereomers) with di-tert-butylserine yielded \[127\], the glutarimide necessary for our study (Figure 47).

Since, in our experience, the use of NaBH\(_4\)/HCl as the reducing agent for glutarimides led to mixtures of the open chain hydroxyamide and the hydroxylactam in very variable proportions \[41\], we tried the reduction of \[127\] using LiBEt\(_3\)H. Of the two possible products, only hydroxylactam \[128\] was obtained. The dehydroxylation was effected by treatment with TFA/Et\(_3\)SiH to obtain the desired 3-amino 4-indolylpiperidin-2-one \[129\]. The selective cleavage of the Alloc protecting group was performed with NaBH\(_4\) in the presence of a Pd catalyst to yield the H-{Trp(Bn)-Ser(tBu)}-O\(_2\)Bu pseudopeptide \[130\].

However, we were confronted to two major problems: failure to separate the diastereomeric anhydrides, glutarimides, or lactams by standard chromatographic methods, and inability to debenzylate the indole nucleus (Figure 48).

The pseudopeptides obtained were therefore neither pure nor easily and selectively deprotected, and were hence unsuitable for further synthetic purposes.

However, we later succeeded in preparing Trp constrained derivatives by using conjugate addition of indole on an appropriate unsaturated lactam, as described in Section 3.3.
As outlined in the introduction to Section 6 (Figure 39), we also aimed to synthesize 3-amino-5-methylthiolactams 100, as constrained surrogates of Met. In conjunction with the studies on glutarimides, we envisaged the possibility of using 6-hydroxylactams to yield cyclic enamides by dehydration, and of using the double bond to functionalize position C5 (Figure 49). Since there was little information on the reactivity of enamides, we decided to prepare the methionine-phenylglycinol derivative 138, using the intermediate enamide 133 as a model.

The enamides appeared to be very attractive synthons; not only can they be regarded as constrained derivatives of Ala, their potential reactivity should allow functionalization on positions C4, C5, and C6 of the valerolactam ring.

7.1. Methionine-phenylglycinol [42]

Several ways to constrain the mobility of the methionine side-chain had been reported in the literature (Figure 51). When a thirane ring [43] or of a double bond [44] is introduced the α-position remains tertiary. Otherwise, the α-position is involved in the formation of a bridged bicycle [45] or of a cyclopropane ring [46], yielding quaternary derivatives. Finally, a compound isolated from human urine, contains the structure of methionine as part of a seven-membered ring [47]. Our 3-amino-5-methylthiolactam maintains both the methylsulfide function and the tertiary α-position, and binds the side chain to the nitrogen atom of the following amino acid with an ethylene bridge. As in the case of the Trp derivatives, the level of constraint is high, affecting most dihedral angles of the amino acid.

To prepare compounds 134, glutarimide 131 was partially reduced with Superhydride®, and the resulting hydroxylactams 132 were dehydrated using TFA to produce the expected enamide 133 in 60% yield (Figure 52). The methylthiolation of C5 was achieved by addition of MeSH to the double bond in the presence of AlBN, whereas the enamide did not react with electrophilic reagents such as MeS-S(O)Me. This demonstrated that the electron-withdrawing effect of the carbonyl group (C2) was sufficiently strong to make the double bond of the enamide behave as an isolated alkene rather than as an enamine. As expected, the radical addition yielded an equimolar mixture of the antiMarkovnikov regioisomers, 134a and 134b, which were separated by column chromatography.

Amination of the 3-position was carried out by bromination and substitution (Figure 53). Thus, treatment of the methylthiolactam (αR,5S)-135 with sec-BuLi and bromine yielded a 5:1 diastereomeric mixture of 3-bromolactams 136a and 136b, both in solution and in the presence of SiO2. Substitution of the bromine atom by NaN3 yielded compound 137 as a single isomer, which was reduced to obtain the (αR,3S,5S) {Met-phenylglycinol} 138a. When the bulkier potassium phthalimide was used as the nucleophile, we obtained a 5:1 C3 epimeric mixture of 3-phthalimidolactams 139, which were separated by chromatography. Deprotection of isomer 139b yielded the (αR,3S,5S) {Met-phenylglycinol} 138b.

7.2. Methionine-serine [48]

Since amination on C3 using a strong base is incompatible with the acidity of the α-proton of amino acids, it appeared advisable to use glutamic anhydride as the starting substrate for the preparation of dipeptide analogues. The key enamides could then be obtained either by partial reduction of the corresponding imide, or by closure of the N1-C6 bond from a formylamide (Figure 54). Both general approaches should...
enable us to prepare small series of pseudodipeptides, first by diversifying the second amino acid (aa2), and eventually, by diversifying the functionalisation of the lactam ring.

Condensation of glutamic anhydride 140 with di-tert-butyl serine led to the corresponding imide in 60% yield (Figure 55). The reduction of imide 141 with Superhydride gave the expected 6-hydroxylactam 142 in 50% yield. When we tried the reaction using NaBH₄/HCl as the reducing agent, only the open chain hydroxyamide 143 was obtained, and DIBAH led to a mixture of 142 and 143, but in variable proportions. Although we tried to dehydrate hydroxylactam 142, the starting substrate remained unaltered under all conditions used (TFA; p-TsOH; 1. MsCl/TEA, 2. DBU; POCl₃, pyridine; NH₄Br). These unexpected results made us turn our attention to the second approach.

The alternative was to prepare an open chain formylamide 148, whose cyclisation would yield the target enamide 149 (Figure 56). We decided to generate the aldehyde function by reduction of the corresponding thioester. Thus, treatment of glutamic anhydride 145 with phenylthiol in the presence of dicyclohexylamine yielded thioester 146 quantitatively, and this was condensed with di-tert-butyl serine under standard conditions to obtain amide 147. The reduction of compound 147 using Et₃SiH in the presence of Pd/C in CH₃CN:CH₂Cl₂ led to the key aldehyde 148, and treatment of 148 with acid generated the desired enamide 149 in 45% yield (2 steps) after column chromatography on SiO₂.

Once the enamide had been obtained, methylhiolation with MeSH in the presence of AIBN in THF gave the target {Met-Ser} constrained derivative 150.

In order to test the generality of this method for synthesizing {Met-aa₂} derivatives, we repeated the synthetic sequence using other amino acids. Since one of our aims is to determine whether our pseudodipeptides can induce particular conformations once inserted in longer peptide chains, we chose to prepare {Met-Val} and {Met-Leu}. The Ramachandran plots of valine and leucine show that they show high potential for β-sheet and α-helix conformation, respectively.

Condensation of thioester 146 with Val and Leu, followed by the reduction of the thioester function and final acid cycli...
sation of the aldehydes, yielded enamides 153 and 154 (Figure 57). In each case the separation of the two diastereomers was done by serial chromatography. Methylthiolation was performed on the pure diastereomers 153a and 154a to give a 3:1 proportion of the methionine-derived pseudopeptides. The major isomers were always the 3,5-trans forms (a), in which the methylsulfide group was axially disposed. We attributed the unequal proportion to a steric effect of the bulky C3 phthalimido substituent.

### 7.3. Application to the solid phase synthesis of enamides [49]

Our next aim was to synthesize enamides on solid phase. In this fashion we would be able to diversify their N1-substituent, and subsequently carry out parallel functionalizations of the ring. This exponential diversification would result in small libraries of lactam pseudopeptides. For this purpose, the above sequence (Figure 57) had to be modified to make it compatible with the resin. The first step was to test the feasibility of the procedure using a carbamate N-protection such as Cbz. Since there was no regioselectivity in the ring opening of anhydride 157 (Figure 58) we could not apply the same strategy as that used in the phthalimido series (Figure 56). Hence, Cbz-Glu was transformed to the amidocid 161 after condensation of the oxazolidinone 160 [50] with Leu-OMe. The reduction of the acid group in 161 via an acid chloride yielded the pyrrolidone 162, as a result of cyclisation on the carbamate nitrogen atom (Figure 58).

In order to avoid the formation of the pyrrolidone ring, the reduction of the acid group was carried out on compounds 160 [51] via a thioester intermediate 163. The aldehyde was protected as a dimethylacetal, and compound 165 was coupled with Leu-OMe to yield 167. Various cyclisation conditions were assayed, but only with p-TsOH was the desired enamide 168 obtained (6%), together with a more polar compound identified as 5-hydroxyproline 169 (Figure 59).

At present we are optimising this cyclisation to enable us to start the sequence on solid phase using a Tentagel®-IRAA-HMPP-O-CO resin.

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8. Oxazolopiperidines [52]

#### 8.1. Introduction

As explained in Section 5, we are interested in obtaining pseudopeptides that can induce a particular conformation once inserted in a longer peptide chain. More specifically, one of the conformations that we seek is the β-turn, since it is known that bicyclic compounds can be good β-turn mimetics [53]. For instance, compound 170 (Figure 60) [54] has been extensively studied in the context of building active peptide analogues [55-61]. Despite the role played by the β-turn position itself in the interaction with the receptor and the fact that 170 induces a β-turn conformation in collaboration with the adjacent residues, this β-turn dipeptide seems not to be very useful for improving the activity of small peptides, in which the β-turn position itself plays some role in the interaction with the receptor site [62]. Interestingly, recent molecular modeling calculations on the tetrapeptide Ac-Ala-{170a}-Ala-NHMe indicate that the geometry of a turn induced by thiazolopiperidone 170...
differs significantly from that of an ideal β-turn [63]. In addition, the incorporation of either epimer 170a or 170b in a bioactive peptide has been shown to provoke distinct changes in its bioactivity [60a].

We thought that the isosteric substitution of the sulfur in the 7-position by an oxygen atom might improve the binding properties of the β-turn dipeptide, since oxygen could act as a better hydrogen bond acceptor on the «external part» of the turn. With the aim of establishing the possible utility of oxazolopiperidones 171 as β-turn mimetics, we have prepared these bicyclic lactams and their derivatives 173 (Figure 61). The conformational analysis of 173, both by NMR and by molecular modeling calculations, indicate that oxazolopiperidone 173a mimics a βII' turn and that 173b adopts a β-turn conformation that does not correspond to the classified types [1b-e,2].

8.2. Synthesis and structural studies
The preparation of oxazolopiperidones 172 was achieved by condensation of aldehyde 164 [50] with methyl serine hydrochloride (Figure 61). When the reaction was conducted at room temperature, isomer (3S,6S,9S)-172a was obtained pure, whilst the condensation in refluxing toluene yielded a 1:5 mixture of 172a and its C6 epimer 172b. The absolute configuration of each isomer was determined by NOESY experiments. Amidation of compounds 172 with MeNH2 led to compounds 173, which fulfill all the requirements necessary for studying the conformational tendencies of the bicyclic oxazolopiperidone system.

The conformation of 173a and 173b was studied by combining molecular modeling calculations and NMR techniques. NMR experiments were used to determine the existence of an intramolecular hydrogen bond between the oxygen atom of the Cbz carbonyl group and the amide NH proton, which is the sine qua non for pseudodipeptide occupation of the (i+1) and (i+2) positions of a standard β-turn. Molecular modeling calculations were used to find the most probable conformations of each isomer (6H-α and 6H-β), and to determine, according to the dihedral angles involved, which kind of β-turn they correspond to.

Similar results were obtained for both isomers 173a and 173b by NMR experiments (Figure 62). Thus, following the classification of Scolastico and co-workers [64], chemical shifts in CDCl3, temperature coefficients in CDCl3, and the results of competitive solvent addition (DMSO) experiments...
showed that the NH carbamate proton was not hydrogen-bonded, and that the NH$_{i+3}$ amide proton was intramolecularly hydrogen-bonded, though weakly. Therefore both isomers showed reasonable potential for action as β-turn mimetics.

Molecular mechanics/dynamics (MM/MD) calculations were performed in continuum, in DMSO, and in H$_2$O. These demonstrate that 173a is an excellent β'II turn mimetic, whereas 173b is more flexible and adopts either unusual β-turns or L-shaped conformations.

The bicyclic system (3S,6S,9S)-171a is therefore a new dipeptide scaffold for the synthesis of β'II turn mimetics, which might find application in bioactive peptide-based rational drug design.

9. Hydroxylactams

9.1. Introduction

The last synthon that we present in this review is the polyhydroxylated piperidin-2-one 174 (Figure 63). Since polyhydroxylated lactams have been reported as having interesting biological activities, such as inhibition of glycosidase activity [65], cancer cell metastasis [66], and inflammation [67], we considered the possibility of synthesising a small collection of 3,4,5-trihydroxy piperidin-2-ones 174, whose activities might be modulated by side chain functionalisation of the amino acid moiety. In addition, transformation of the hydroxyl groups of this synthon offered a wide range of synthetic possibilities. Thus, our first aim was to employ the polyhydroxylated synthon in the preparation of 3-aminovalerolactam 189, a constrained surrogate of the Ser-Leu dipeptide.

9.2. Synthesis of 3,4,5-trihydroxyvalerolactam 174

The synthesis of compound 174 was directly inspired by the lactamisation reaction of aminolactones derived from carbohydrates (Figure 64). This procedure produces a valerolactam ring with three stereocentres of predefined configuration. Thus, ribonolactone, protected [68] or not [69], can be transformed to its 5-azido derivative, whose hydrogenation yields N-unsubstituted valerolactams by spontaneous cyclisation of the primary amine.

In contrast, our synthesis demanded the cyclisation of an intermediate 5-aminolactone 176 which presented a secondary amino group, since we wanted to introduce a stereocentre adjacent to the N$_1$-position (Figure 65) [70]. Hydrolysis of the acetal would lead to the target synthon 174.

Quantitative protection of commercial ribonolactone was carried out by transacetalisation using acetone dimethyl acetal (Figure 66). To introduce the suitable amino moiety, C5 was brominated using NBS-PPh$_3$ in CH$_2$Cl$_2$, and the resulting bromine 179 was treated with Leu-O'Bu in the presence...
of Et₃N. However, the product obtained was identified as the amide 181, resulting from opening of the lactone ring, instead of the expected substitution product 176 [71]. When iodide was assayed as the leaving group the same result was obtained. Treatment of amides 181 and 182 with K₂CO₃ led quantitatively to the corresponding epoxide 183, which was transformed to the desired lactam 175 on NaH treatment, but in very low yields.

As an alternative, we prepared triflate 184, whose reaction with Leu-OtBu yielded the aminolactone 176, which led to the protected lactam 175 in 90% yield upon treatment with NaAcO (Figure 67). Hydrolysis of the acetal furnished the target trihydroxyvalerolactam 174.

9.3. Serine-Leucine constrained analogues

Once the synthesis of compound 174 had been established, we could proceed to the synthesis of pseudopeptide 189 as a conformationally restricted Ser-Leu surrogate (Figure 68) [70]. The free alcohol of compound 175 was protected as a benzyl ether, and the acetal was hydrolysed to give compound 186. The C3 was aminated by reaction of the sulphite 187 with NaN₃ in the presence of HMPA [72]. The sulphite 187 was obtained as a mixture of the 2 epimers on the sulfur atom, which could be separated by chromatography and fully characterized. The subsequent attack by NaN₃ on each isomer led only to the 3S isomer of compound 188. Subsequent reduction of the azide group led to the target [Ser-Leu] pseudopeptide 189. Compound 189 was suitably N-protected and C-deprotected to yield the Fmoc/OH derivative 190, appropriate for further peptide synthesis on solid phase.

We intend now to introduce compound 190 in a small cyclic peptide in order to evaluate its possible application as a β-turn mimetic.

9.4. Solid phase synthesis of hydroxylactams

Once we had established the synthesis of hydroxylated lactams in solution, we examined modified versions of it applicable to solid phase synthesis, which would allow the preparation of a small library of derivatives with various substituents on the N1 position. Our strategy consisted of anchoring the terminal carboxyl of the aminoacid moiety to a Tentagel™ resin [73], performing the condensation with D-ribonolactone 177, and lactamisation (Figure 69). Since lactamisation is accomplished using NaOAc/MeOH, the cleavage of the molecule from the resin would be concomitant with the cyclisation [74], and no linker would be necessary [75].
First, we explored the possibility of aminating ribonolactone 177 using a Mitsunobu reaction, which is mild and suitable for solid phase synthesis [76]. This was satisfactorily achieved by N-alkylation of the sulfonamide derived from Leu (194) with 177 in the presence of DEAD and PPh3, followed by cleavage of the arylsulfone group of compound 195 with PhSH (Figure 70) [77]. Treatment of the resulting secondary amine 196 with NaOAc/MeOH yielded the expected lactam 197a.

For the solid phase synthesis we followed Liskamp’s method [74] since the TentaGel(r) resin conveniently swells in MeOH, a necessary condition for efficient lactamisation/cleavage. Parallel anchoring of the Fmoc protected aminocids to the Tentagel(r) resin via a Mitsunobu-type reaction [78] yielded compounds 199a-c which, after capping with Ac2O, were deprotected to obtain amines 200a-c (Figure 72). Standard sulfonation of the amines gave the desired compounds 193a-c [79] which were N-alkylated by treatment with ribonolactone 177 in the presence of DEAD and PPh3 to obtain the corresponding tertiary sulfonamides 201a-c (Figure 72). The sulfone group was cleaved using PhSH, and subsequent treatment of the secondary amines 192a-c with NaOAc/MeOH yielded the expected hydroxylactams 197a-c. After removal of the resin, the MeOH solvent was replaced by CH2Cl2 and the products filtered to obtain lactams 191a-c (75%) and 191b (65%) and 191c (80%) (Figure 72).

Figure 72

10. Conclusion

As every painter has a particular colour that helps him capture very specific feelings or images, we have used the synthetic scope of piperidine to prepare pharmacologically interesting compounds. Thus, by modifying the functionalisation of the piperidine ring we have been able to obtain compounds ranging from alkaloids to pseudopeptides. The reader will realise that this is a dynamic field: we intend to continue contributing to its development.

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References and Notes


[9] Diez, A.; Vila, C.; Sinibaldi, M.-E.; Troin, Y.; Rubiralta,


[29] a. β-Turns are non-periodic tetrapeptide segments which reverse the orientation of the peptide chain, and are known to participate in molecular recognition processes. The most general β turn features are the distance R (R < 7 Å) between the Cx atoms of the first and the fourth amino acids, and the torsion angle R (90° < x < +90°) formed by the four Cx atoms. Many conformers fulfil these requirements.[29b] The major types [29d] show a characteristic hydrogen bond between the carbonyl function of the first amino acid and the amide group of the fourth. The major β turns are classified according to the torsion angles of the second and of the


[41] Only reduction of the C6 position was observed in all our examples. For a different regioselectivity, see: Ducrot, P.; Thal, C. «A Short Diastereoselective Synthesis of 1-Aminooindolo-[2,3-a]quinolizidines Via an N-Acyliminium Ion Cyclization», Tetrahedron Lett., 1999, 40, 9037-9040.


[51] Compounds 160, 163, and 164 when P = Cbz, are reported in reference [50].


Piró, J.; Rubiralta, M.; Giralt, E.; Diez, A. «3-Amino-2-

[71] The analysis of the TOCSY NMR spectrum was necessary to unequivocally assign the structure.


[73] NovaSyn(r) TG hydroxy resin, loading = 0.27 mmol/g, Novabiochem (ref. No. 01-64-0096).


[79] The synthesis of compound 193a is reported in reference [74] through another method.

**About the authors**

The authors belong to the Department of Pharmacology and Medicinal Chemistry of the University of Barcelona. The group is specialised in the preparation and the synthetic applications of piperidone building blocks. They first developed two main families of substituted piperidones: 2-arylpiperidin-4-ones and 4-arylpiperidin-2-ones. The former were used to obtain natural alkaloids and derivatives of reserpine and corynantheol. The latter to obtain Aspidosperma and dasycarpine done alkaloids. More recently, with the better understanding of the mode of action of drugs, and the technical development for the design of new potential drugs, the authors developed a collection of 3-aminopiperidin-2-ones. These have a double interest: as peptidomimetics and as restricted pseudopeptides to be used as surrogates in longer peptide chains. The targets are mostly enzyme inhibitors for diverse therapeutic applications, such as antiinflammatories, antibiotics, and anticancer agents.

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