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Design and synthesis of novel type VI-like β-turn mimetics. Diversity at the $i+1$ and the $i+2$ position

Wim M. De Borggraeve,* Bie M. P. Verbist, Frederik J. R. Rombouts, Vijaykumar G. Pawar, Wim J. Smets, Laila Kamoune, Jo Alen, Erik V. Van der Eycken, Frans Compernolle and Georges J. Hoornaert

K.U. Leuven, Departement Chemie, Afdeling Organische Synthese, Celestijnenlaan 200F, B-3001 Leuven, Belgium

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Abstract—In this paper, a synthetic approach for functionalised 5-aminopiperidinone-2-carboxylate (APC) systems as non-pro *cis*-peptide bond containing external β-turn mimics is presented. The scope and limitations of the synthetic method are discussed and the potential turn inducing properties of a model compound are evaluated by means of molecular modelling and NMR analysis.

1. Introduction

Analysis of a non-redundant set of proteins from the Brookhaven Protein Data Bank has revealed that non-Pro *cis*-peptide bonds might occur more often in proteins than previously thought.[1] Moreover, they appear at or near functionally important sites (such as metal binding sites, dimerisation domain, active center, cofactor/substrate binding domain) and are very likely involved in the function of the molecules. Because *cis*-peptide bonds can cause reversal of the peptide chain propagation, they can be involved in the formation of turn structures.

A turn or loop is one of the three major motifs of peptide and protein secondary structure. It plays a key role in many molecular recognition events including interactions between antigens and antibodies, peptide hormones and their receptors, and enzymes and their corresponding substrates. Different types of turns have been recognised by now, including δ-, γ-, β-, α- and π-turns corresponding to loops involving two to six residues, respectively.[2] Among the naturally occurring turns, the β-turn in which the peptide reverses direction over four residues (amino acids i, $i+1$, $i+2$ and $i+3$) is the most common one (Fig. 1). In this type of turns, an intramolecular hydrogen bond is usually observed between residue i and $i+3$ giving rise to a pseudo ten membered ring, though this is not a prerequisite.

The development of new turn stabilising structures (β-turn mimetics) has been the subject of numerous research papers.[3] Ball subdivides the different turn mimics in two classes: the ones with an internal support and those with an

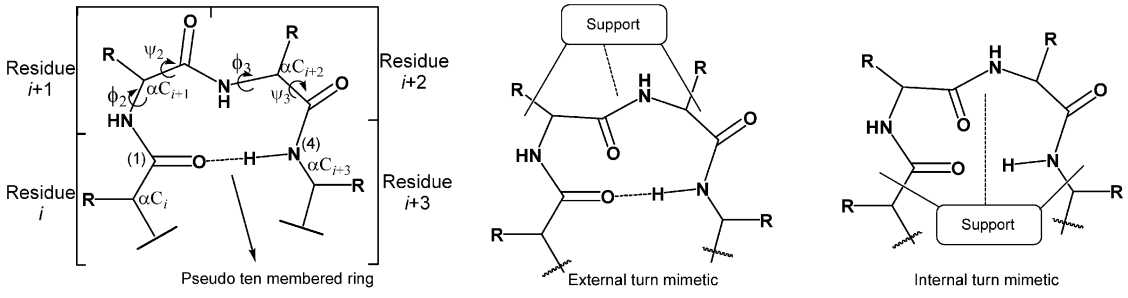

Figure 1. β-Turn mimics with internal and external support.

Keywords: Turn mimics; Pyrazinone; Diels–Alder reaction.
* Corresponding author. Tel.: +32 16 327404; fax: +32 16 327990; e-mail: wim.deborggraeve@chem.kuleuven.ac.be

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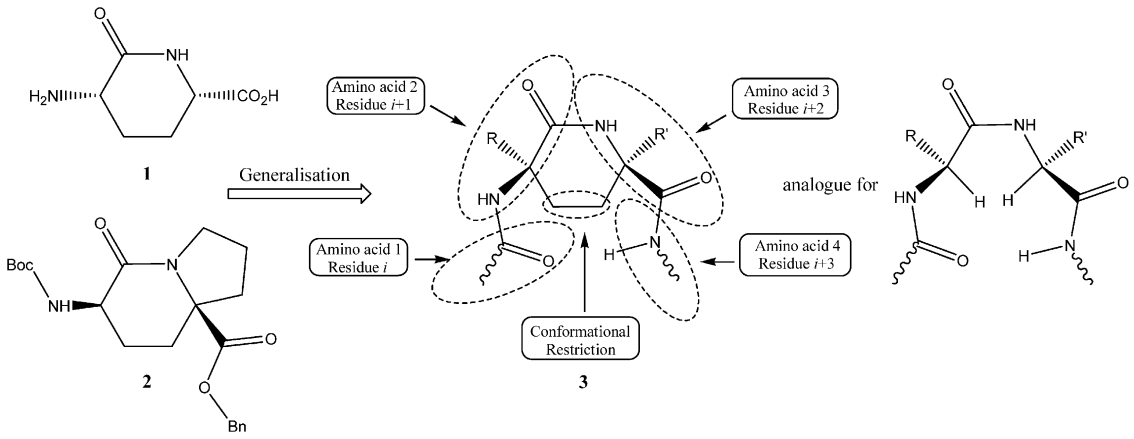


Figure 2. Design hypothesis based on known systems **1** and **2**.

external support (Fig. 1).[4] In internal support turn mimics, the emphasis of the system is on the pseudo ten membered ring of the hydrogen bonded tetrapeptides involved in the turn. The main focus in these systems is on generating scaffolds containing the side chain functionality of the β-turns they are mimicking.

In external turn mimetics on the other hand, the conformational flexibility of the peptide is diminished by an (isosteric) skeleton that is located outside the pseudo-10-membered structure: these mimics usually replace the central $i+1$ and $i+2$ residues in a turn. In these systems, incorporation of side chain functionality is less evident because the external skeleton is often not allowing this.

This is not really a problem if the turn is merely a structural prerequisite not involved in binding to the receptor.[5] However, in cases where binding to the receptor occurs at the turning position, the side chains might be involved. Hence the development of functionalised external turn mimetics, which is the subject of this paper, is an interesting topic.

2. Design hypothesis

In order to stabilise *cis*-peptide bond containing turns ('type VI-like' turns because they do not contain proline), we have to devise a synthesis for molecules which can replace the $i+1$ and the $i+2$ positions of a β-turn and which display the side chain functionality of the parent dipeptide mimicked.

Interesting examples of *cis*-peptide bond containing constrained dipeptides that have been developed as β-turn mimetics are the system **1** reported by Kemp[6] and a similar system **2** described by Robinson[7] and Germanas[8] (Fig. 2). Unfortunately, the compounds are not so easily functionalised using the synthetic strategies presented by the authors. As a consequence displaying side chain functionality at the $i+1$ and the $i+2$ position is somewhat difficult.

Based on the structural resemblance between the compounds **1** and **2**, we hypothesised that the turn inducing properties of these compounds were due to the *cis* 5-aminopiperidinone-2-carboxylate (APC) unit **3** (Fig. 2). A functionalised system of this type probably would meet the criteria we set ourselves (*cis*-peptide bond, functionalised and turn inducing). The relationship between the APC system **3** and the dipeptide mimicked is shown in Figure 2.

3. Molecular modelling

In order to verify our design hypothesis, a molecular modelling analysis was performed on a system **4** (Fig. 3). This compound **4** serves as a model for a tetrapeptide. The i and $i+3$ residues in the system are simplified to an *N*-methyl amide and an acyl amide. In this system, the hydrogen bond present in most β-turns can still be formed.

The general procedure for the computational analysis is outlined in Figure 3.[9] A conformational search was performed starting from 2000 random starting conformations (Macromodel, MCMM search, AMBER* force field, solvation model water) and all structures were energy minimised to 0.05 kcal/mol Å.[10] All conformations found within 3 kcal/mol of the global minimum conformation were checked for the accepted indicators for β-turn properties: this includes checking whether the distance between the α carbon atoms of residue 1 (residue i) and residue 4 (residue $i+3$) is smaller than 7 Å. Another criterion is the virtual dihedral angle β as defined by Ball[11] which has to be between -30 and $+30°$.[12] Finally, the presence of a hydrogen bond is also considered as indicative for a β-turn (though open turns without this hydrogen bond also exist).

Including the global minimum conformation, 11 conformations were found within 3 kcal/mol of this global minimum. The global minimum conformation (depicted in Fig. 4) fulfils all of the turn criteria. Also the other local minima within 3 kcal/mol are good turn inducing candidates. In order to get an idea about the stability of the turn conformation in the global minimum, a 1000 ps molecular dynamics analysis was performed on this structure. 10,000 snapshots were taken which were further analysed for the properties mentioned above. The results are summarised in Figure 5. According to this molecular dynamics analysis, this conformation is stable and the hydrogen bond is

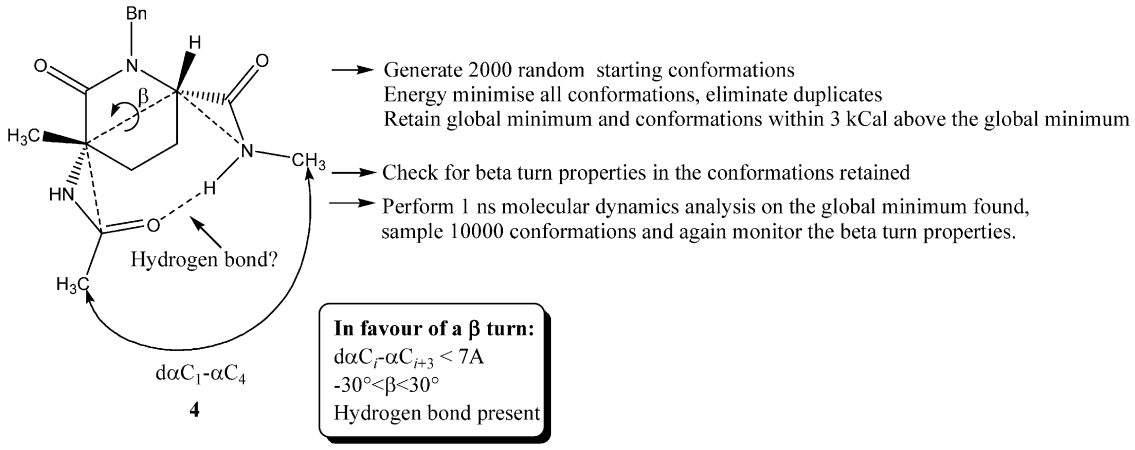


Figure 3. Analysis of model compound **4**.

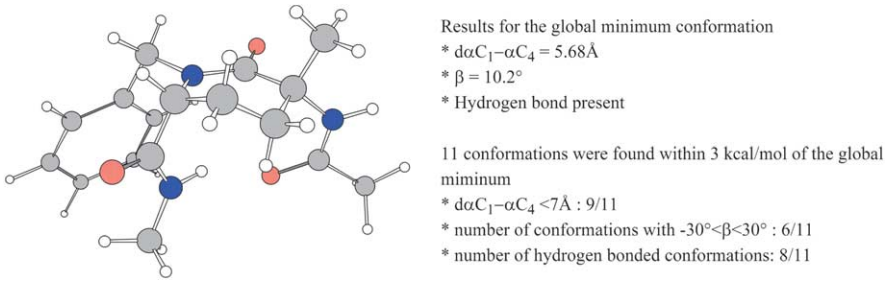


Figure 4. Global minimum conformation and its β-turn indicators.

retained in 89.4% of the samples. A narrow distribution in the sampled conformers is observed both for the distance between the α-carbon atoms and for the virtual dihedral angle β. The mean values for the distance between the α-carbon atoms of 5.68 Å and a mean dihedral angle of 9.4° in the samples are close to the observed values for the global minimum starting conformation. This also proves this conformation is a stable one.

According to this molecular modelling analysis, compound **4**, which is taken as a model for the target systems, shows good turn inducing properties in this model system. This is in agreement with our design hypothesis and urged us to start the synthesis of these compounds.

4. Synthesis

The development of a synthetic method starting from cheap commercially available starting materials was our main objective. Retrosynthetic analysis (Fig. 6) shows that the functionalised APC-systems **8** can be derived from bicyclic precursors **7**. These bicyclic lactams can be considered as the reaction product of an intermolecular Diels–Alder reaction of a functionalised 5-chloropyrazinone **6** with ethene followed by hydrolysis. A very efficient synthesis for these easily functionalisable pyrazinones has been developed in our laboratory starting from simple amino nitriles.[13]

Hence, the 4 steps in the synthesis of these compounds can

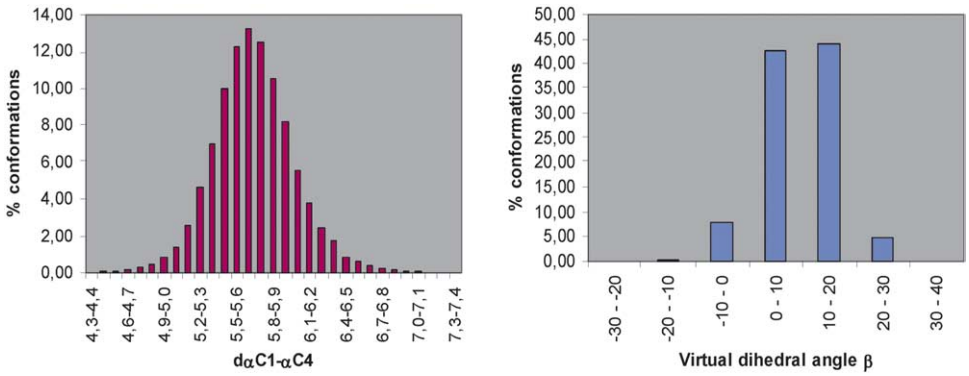


Figure 5. Results of the molecular dynamics analysis.

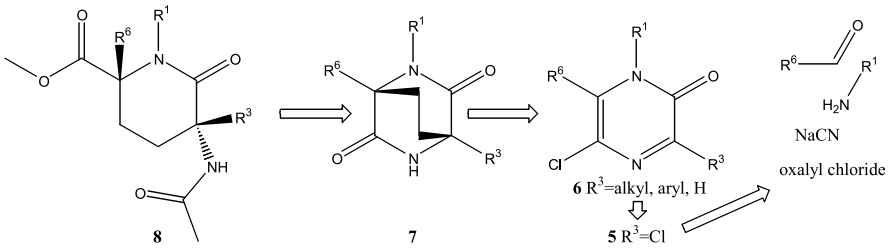


Figure 6. Retrosynthetic analysis of the APC systems.

be summarised as follows: (A) pyrazinone synthesis, (B) functionalisation of the 3-position of the pyrazinone, (C) Diels–Alder reaction, (D) methanolysis. These steps will further be discussed in more detail.[14]

4.1. Synthesis of dichloropyrazinones, introduction of the $i+2$ functionality in the target compound

In our procedure for the synthesis of 3,5-dichloropyrazinones,[13] the functional groups at positions 1 and 6 of the pyrazinone originate, respectively, from a primary amine R^1NH_2 and an aldehyde R^6CHO which are converted to an amino nitrile (or the corresponding HCl salt) via Strecker synthesis. Upon treatment with oxalyl chloride, this amino nitrile smoothly converts to a dichloropyrazinone in chlorobenzene as the solvent; in this reaction triethyl ammonium chloride is added to drive the reaction to completion by acting as an additional chloride source (Scheme 1). In the case where R^6=isopropyl, the yields of dichloropyrazinone were originally very low (10–15%). Mass spectral analysis of the crude reaction mixture revealed that the conversion of the intermediate **9** to the corresponding pyrazinone was not very efficient (Scheme 1). Addition of a catalytic amount of DMF at this stage in the reaction proved to solve this problem by increasing the yield of product **5d** up to 85%. In the ^{1}H NMR spectrum of **5d** run at room temperature, some peaks are doubled because of hindered rotation of the isopropyl and the *p*-methoxybenzyl groups. At 213 K all peaks are doubled while at 303 K all peaks are coalesced and only one compound is observed.

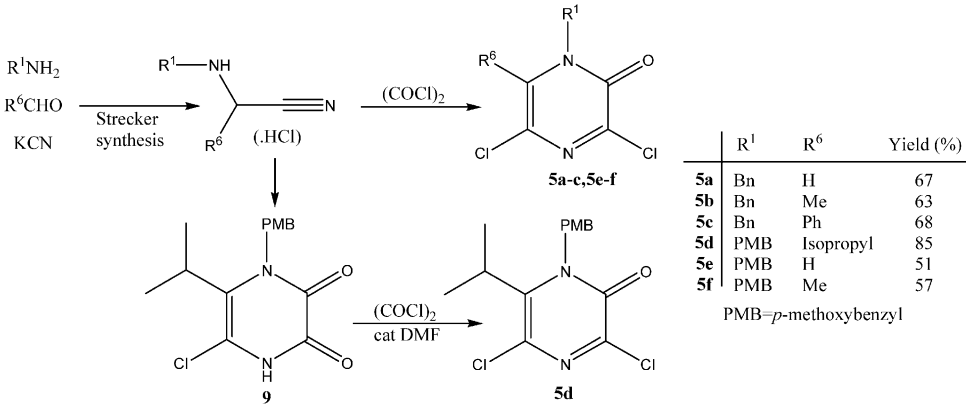
Throughout the years this pyrazinone synthesis has proven to be very robust and many substituents have been introduced on the dichloropyrazinones.[15]

At this stage of the synthesis, the functionality R^6 of what will become the $i+2$ residue of the target APC system is introduced as well as the Bn or PMB protective group (Fig. 2).[16] In the development stage of this work, we have chosen a number of 'random' substituents to prove the methodology. All yields of the compounds obtained were acceptable to good (Scheme 1). In this respect, we introduced the side chains of Gly (R^6=H), Ala (R^6=Me), Val (R^6=*iso*-propyl) and the unnatural Phg (phenylglycine, R^6=Ph). In theory, the functionality at this position is only limited by the availability of the corresponding aldehyde and its compatibility with the acidic cyclisation conditions to form a pyrazinone.

4.2. Functionalisation of the 3-position of pyrazinones, introduction of the $i+1$ functionality in the target compound

As discussed in the retrosynthetic approach (Fig. 6), the next step in the synthesis of the APC turn mimics is the functionalisation of the 3-position of the pyrazinones.

Different methods have been developed by us to functionalise these 3,5-dichloropyrazinones at the 3-position. Both carbon–heteroatom bonds[15] and carbon–carbon bonds can be formed. In our current approach towards APC systems, we are interested in forming new carbon–carbon bonds. Common organometallic reactions can be used to achieve this goal. Successful functionalisation of the 3-position is possible using Grignard reactions, Stille couplings, Suzuki reactions and Heck reactions (Scheme 2).[15] The palladium catalysed reactions are all carried out at reflux temperature of the appropriate solvent (see Section 7) while the substitution by a Grignard reagent needs deep cooling to −78 °C in order to get the compounds in a reasonable yield



	R^1	R^6	Yield (%)
5a	Bn	H	67
5b	Bn	Me	63
5c	Bn	Ph	68
5d	PMB	Isopropyl	85
5e	PMB	H	51
5f	PMB	Me	57

PMB=*p*-methoxybenzyl

Scheme 1. Synthesis of dichloropyrazinones.

(if addition of the Grignard reagent is performed at room temperature, tarry side products are formed which impede isolation of the target compound). The Stille reactions proceed smoothly, but it is sometimes difficult to get rid of the last traces of organotin impurities. We tried to overcome this problem by stirring the crude extract of the reaction with KF in ethyl acetate. Most of the organotin impurities are removed by this procedure. Reductive dechlorination using $Pd(PPh_3)_4$ and sodium formate in DMF or via H_2/Pd/C is also an option (compound **6c**).

In this step of the synthesis, the functionality R^3 of what will become the $i+1$ residue of the target APC system is introduced (Fig. 2).[16] To prove the concept of the strategy, the side chains of Ala (R^3=Me), Phe (R^3=Bn), Gly (R^3=H), Val (R^3=*iso*-propyl) and again the unnatural Phg (Phenylglycine, R^3=Ph) were introduced in the model systems (Scheme 2).

4.3. Diels–Alder reaction, introduction of the conformational restriction in the target compound

The key step in the synthesis of the APC systems is the Diels–Alder reaction of the functionalised pyrazinone systems with ethene (Scheme 3). This reaction is carried out in a steel bomb at 135 °C under 35 atm ethene pressure. Completion of the reaction takes 12 to 48 h depending on the nature of the substrate. As can be expected, it takes a longer time for the more hindered substrates to be fully converted into the adducts. In general, the reaction is left for 16 h, and if starting material is still observed on TLC after 16 h, the reaction is relaunched for another 12 h. The imidoyl chloride formed after addition is prone to hydrolysis; especially in the case where R^3=Ph this hydrolysis is very fast and almost immediately upon opening the steel bomb the bislactam is formed. In other cases, the (usually partially hydrolysed) mixture is evaporated to dryness, redissolved in chloroform and stirred in a flask open to air moisture to complete the hydrolysis.[17,18] Presumably, traces of HCl already formed accelerate autocatalytic hydrolysis.

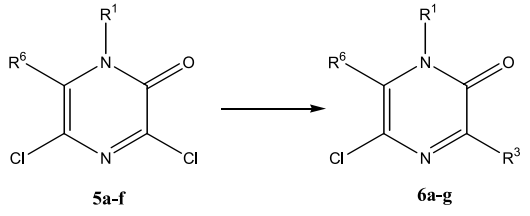
These cycloaddition reactions with ethene have also been investigated by us for similar pyrazinone compounds under somewhat milder conditions using microwave irradiation (reaction was performed in an ethene saturated solution instead of under 35 atm ethene pressure).[19] In this case, however, a specialised microwave reactor is needed. For the larger scale syntheses of these compounds we still rely on the more classical approach described above.

During this step of the reaction, two goals are achieved. First of all the conformational restriction of the target APC systems is introduced. Secondly the *cis*-relationship between the amine and the carboxylate, which we believe to be important for the β-turn inducing properties (see design hypothesis), is fixed in the precursor molecule due to the stereospecific *syn*-addition of the Diels–Alder reaction.

4.4. Conversion of bislactams into APC systems via selective methanolysis reaction: scope and limitations.[20]

The last step in the synthesis of the target compounds relies on the selectivity observed in the methanolysis reaction of a secondary lactam in the presence of a tertiary one.[21] This behaviour is in agreement with the general observation that the rate-determining step during acid catalysed hydrolysis of amides is the attack of water on an *O*-protonated amide to form a tetrahedral intermediate: indeed, steric retardation of the latter process appears to be the governing factor in many cases.[22] However, in the case of simple secondary and tertiary *N*-methyl amides, an anomalous behaviour is observed since the latter react slightly faster upon acidic hydrolysis. This result is probably due to non-steric factors, for example, σ-donation by the *N*-alkyl substituents and/or solvation effects.[22]

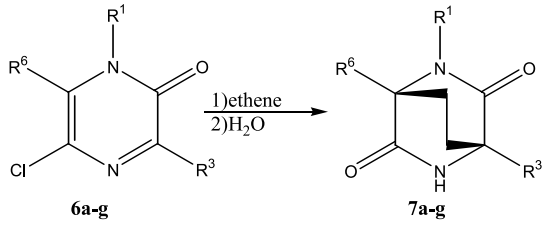
In order to check the generality of the approach, a profound study of the factors governing the selectivity and the



	R^1	R^3	R^6	Method	Yield (%)
6a	Bn	Me	H	Stille coupling	91
6b	Bn	Ph	Me	Stille coupling	92
6c	Bn	H	Ph	Pd/C	92
6d	PMB	Me	Isopropyl	Grignard reaction	45
6e	PMB	Bn	H	Grignard reaction	72
6f	PMB	Isopropyl	Me	Grignard reaction	68
6g	PMB	Me	Me	Grignard reaction/ Stille coupling	62 89

PMB=*p*-methoxybenzyl

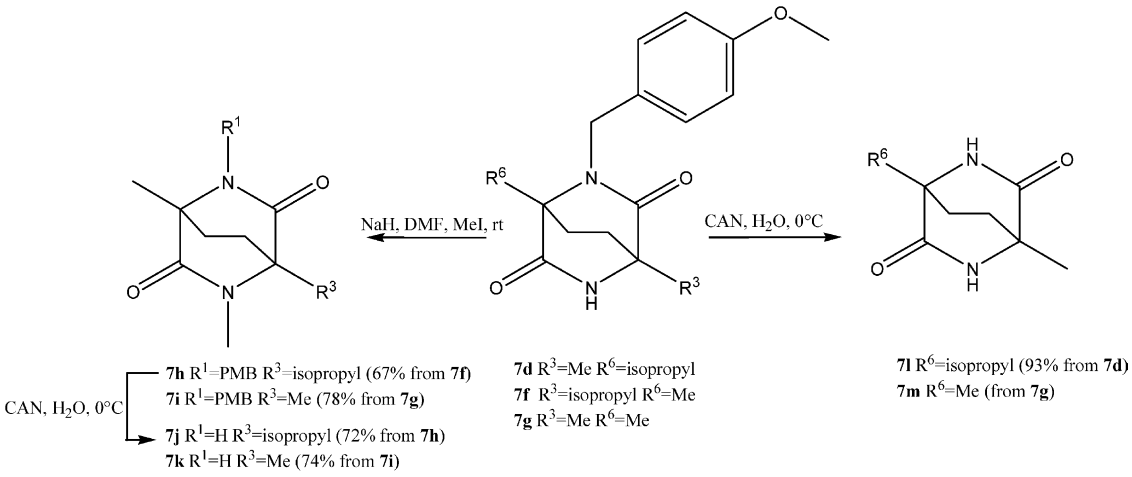
Scheme 2. Functionalisation of the 3-position of the pyrazinones.



	R^1	R^3	R^6	Yield (%)
7a	Bn	Me	H	79
7b	Bn	Ph	Me	88
7c	Bn	H	Ph	82
7d	PMB	Me	Isopropyl	56
7e	PMB	Bn	H	81
7f	PMB	Isopropyl	Me	52
7g	PMB	Me	Me	64

PMB=*p*-methoxybenzyl

Scheme 3. Diels–Alder reaction/hydrolysis of the pyrazinones.



Scheme 4. Preparation of test compounds for methanolysis study.

feasability of the methanolysis of 2,5-diazabicyclo-[2.2.2]octane-3,6-dione systems was performed.[20] The role of bulky substituents at the bridgehead positions 1 and 4 of the dione on the selectivity of the methanolysis as well as the effect of the secondary or tertiary nature of the lactam moiety was investigated.

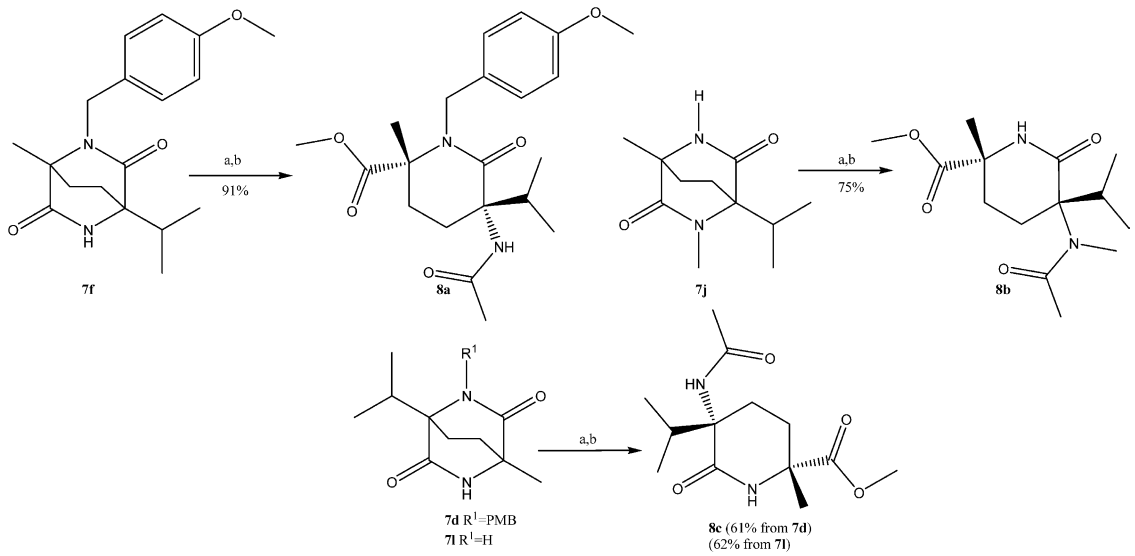
To be able to study the effects mentioned, it was necessary to synthesize a number of analogues of the bislactam systems. The conversion of **7f** and **7g** to **7j** and **7k**, respectively, was done by first methylating the secondary amide function with methyl iodide followed by removal of the PMB-group using CAN (Scheme 4). The 2-*N*-deprotected bislactam **7j** precipitated out of the reaction mixture. Direct removal of the PMB-group of bislactam **7d** and **7g** was also effected using CAN (Scheme 4). Compounds **7l** and **7m** were formed, respectively. Compound **7m** was directly used in the next methanolysis step after extraction.

4.4.1. Effect of bulky groups on the selectivity of the methanolysis process. First, we studied the effect of bulky substituents on the bridgehead positions 1 and 4 of the diones (Scheme 5). Thus treatment of 4-isopropyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione **7f** with a HCl-saturated methanol solution for 16 h resulted in a selective cleavage of the secondary lactam moiety. In order to prevent recyclisation upon neutralisation of the reaction mixture, the newly formed primary amine was trapped as the *N*-substituted acetamide by addition of triethylamine and acetic anhydride yielding compound **8a**. When compound **7j** was subjected to the acid methanolysis/*N*-acetylation sequence, selective cleavage of the tertiary lactam afforded the APC system **8b**. The 4-isopropyl group appears to shield the 'top'(2,3) lactam function irrespective of its secondary or tertiary nature. Hence, relief of the bicyclic strain can be attained only by attack of methanol at the sterically more accessible lactam carbonyl group.

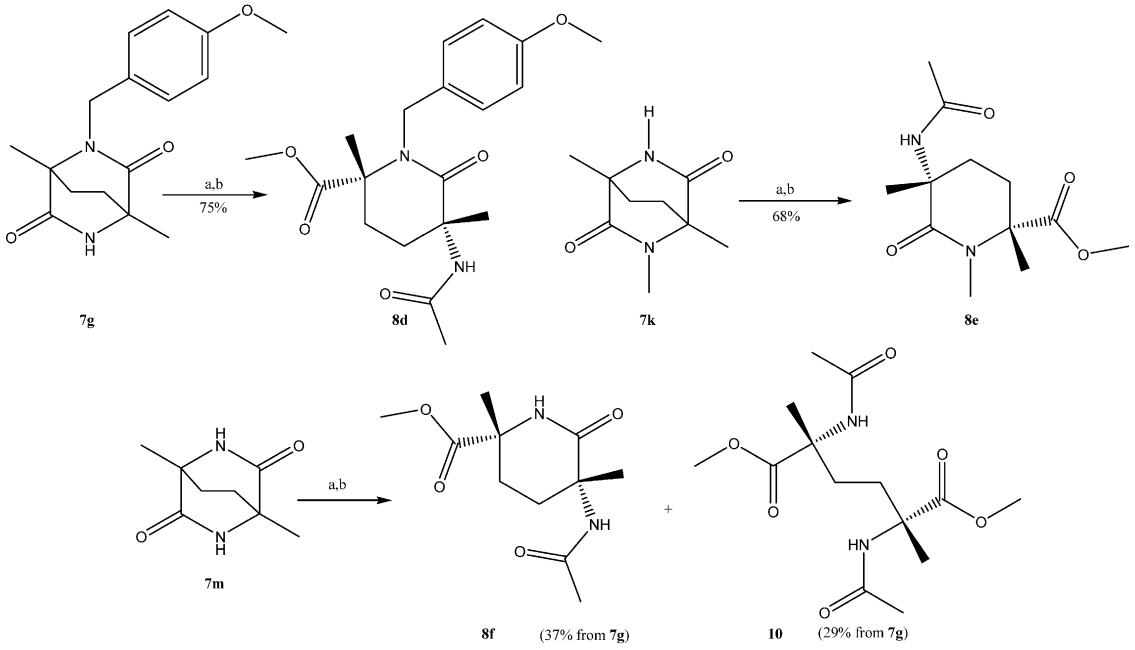
This statement also holds for the methanolysis of precursor **7l**. In this case, the 6-carbonyl function is shielded by the isopropyl group in position 1 resulting in selective cleavage of the 'upper' 2,3-amide linkage. When precursor **7d** is subjected to acid methanolysis compound **8c** is also readily formed. According to our experience the *p*-methoxybenzyl group is not easily removed from a lactam nitrogen; hence the less hindered tertiary lactam probably is cleaved first followed by removal of the benzylic group from the amine formed after cleavage.

4.4.2. Effect of secondary or tertiary lactam groups on the selectivity of the methanolysis process. In a second part, we studied the selectivity for methanolysis in the presence of two equal non bulky substituents in α-position, that is, two methyl groups (Scheme 6). Acidic methanolysis of the bicyclic system **7g** resulted in selective cleavage of the secondary amide to afford the monocyclic lactam **8d**. A comparable behaviour was observed for 2-benzyl-1,4-diphenyl-2,5-diazabicyclo[2.2.2]octane-3.6-dione.[21] When the secondary and tertiary amides were interchanged as in compound **7k** again the secondary amide was cleaved selectively to afford **8e**. Treatment of compound **7m** with an HCl-saturated methanol solution for 48 h and trapping of the intermediate amine as the *N*-acetyl derivative furnished the monocyclic secondary lactam **8f**. However, when the methanolysis was continued for one week, a mixture of singly cleaved product **8f** and doubly cleaved compound **10** was obtained. The absence of bicyclic strain accounts for the much slower second cleavage. These results indicate that a secondary lactam is cleaved preferentially without risk for a tertiary lactam cleavage if bulky substituents are absent. A second cleavage might occur if the reaction is left for a longer period of time if a secondary lactam function is present in the APC system formed.[6]

To unravel the reasons for the preferential acidic cleavage of the secondary lactam group in the bridged bislactam compounds, we performed a molecular mechanics model study of the two tetrahedral geminal diol intermediates corresponding to attack of water on either one of the two lactam functions of compound **7k** This study clearly revealed a much higher energy (difference ca. 6–7 kcal/mol) for the geminal diol formed next to the *N*-methyl group as compared to the one formed next to NH. Indeed, since the methyl group is now located on an sp^3 *N*-atom in a tight boat conformation it experiences a severe eclipsing interaction with one neighbouring OH group (Fig. 7).



Scheme 5. Effect of bulky substituents on the selectivity of the methanolysis. (a) MeOH, HCl, rt; (b) Ac_2O, Et_3N, rt.



Scheme 6. Effect of the secondary and tertiary nature of the lactam moiety on the selectivity of the methanolysis. (a) MeOH, HCl, rt; (b) Ac_2O, Et_3N, rt.

From our combined results it appears that the preferential cleavages observed for the bislactams studied here can be ascribed to two interrelated effects, that is, relief of the bicyclic strain which is modulated by the steric retardation caused by the *N*-alkyl and bridgehead substituents. While the first effect enhances the rate of acid hydrolysis of the bicyclic versus the monocyclic lactams, the latter apparently directs the attack of the nucleophile to the less sterically hindered lactam carbonyl group.

The site of cleavage in the APC systems was determined by 2D NMR spectroscopy using the long range ^{13}C–^{1}H couplings between the carbonyl groups and the neighbouring protons (HMBC). The principle is explained for compound **8b**: a coupling is noticed between the carbonyl of the methyl ester and the 2-methyl protons as well as a coupling between the *N*-methyl protons and the acetyl carbonyl group as seen in **8b**. These two couplings are not consistent with structure **11**, formed by cleavage of the other lactam group (Fig. 8).

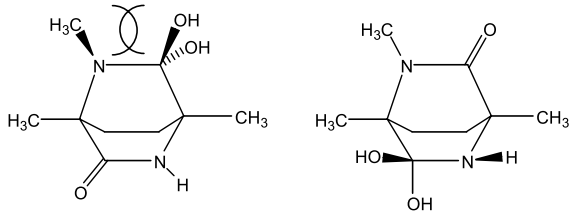


Figure 7. Eclipsing interactions in *gem*-diol intermediates corresponding to hydrolysis at CONMe and CONH groups of **7k**.

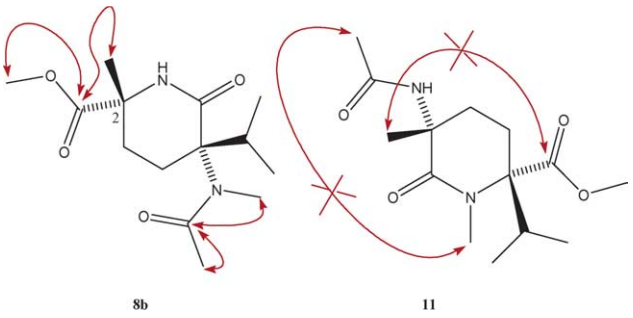


Figure 8. In theory compounds **8b** and **11** can be obtained upon methanolysis of compound **7j**. Structure **8b** is consistent with HMBC-data.

These observations can be summarised as follows: the main driving force of the reaction is alleviation of the bicyclic strain, which enhances the rate of acid hydrolysis of the bicyclic lactam relative to subsequent cleavage of the monocyclic lactam formed. The selectivity of the methanolysis reaction further depends on the steric factors involving the *N*-alkyl and bridgehead substituents. An isopropyl group at the α-position of the lactam carbonyl seems to completely prevent its sensitivity to methanolysis. In this case, the bicyclic strain will be relieved by cleaving the other lactam function, irrespective of its secondary or tertiary lactam nature. In the absence of bulky α-substituents, secondary lactam functions cleave more readily than tertiary ones. When after the first methanolysis a secondary lactam is still present, a second slow cleavage can occur but tertiary lactams seem to be stable.

The other bicyclic compounds **7a**–**7c** and **7e** also reacted in accordance with the observations made above (Scheme 7): because no bulky substituents are present, the secondary lactam function cleaves selectively during methanolysis. After trapping of the primary amine with acetic anhydride all compounds **8g**–**8j** are isolated in good yields.

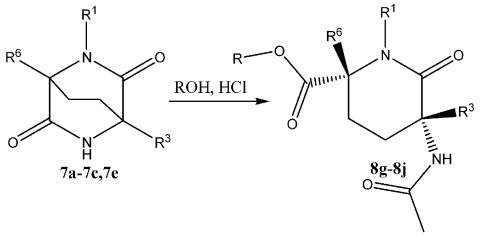
The insights gained in the reactivity of these systems in methanolysis slightly narrow the scope of the method: according to our results it will be impossible to get a secondary (or tertiary) side chain substituent at the *C*-terminal residue ($i+2$ position) of the dipeptide mimic because steric shielding prevents cleavage at the corresponding carbonyl position in the bislactam. In other cases, cleavage of the secondary lactam group is selective and our general synthesis strategy is applicable.

It has to be noted that the methanolysis reactions are somewhat difficult to monitor. TLC-monitoring is not possible in this case. Moreover, chemical ionisation mass spectral analysis of a neutralised sample extract suffers from the drawback that methanol can be lost thermally from the methyl ester products to form back the bridged bislactam starting material. However, the No-D NMR procedure described recently by Hoye et al. (using non-deuterated solvents) in this case appears to be the method of choice to get a quantitative view of what is happening in the mixture (Fig. 9).[23] The main advantage of this method is that aliquots can be taken directly from the reaction mixture to monitor the progress of the reaction.[24] The expansion of the spectrum clearly shows that the signal to noise ratio with these non deuterated solvent experiments is still sufficient to monitor the compound of interest. This is illustrated in Figure 9 where the acid catalysed methanolysis of compound **7g** is monitored by checking the disappearance of the characteristic methyl singlets in the starting material (indicated with ○ in Fig. 9). The signals of the corresponding methyl protons in the reaction product are already visible after 5 min (indicated with × in Fig. 9).

5. Analysis of β-turn properties of a model compound

In order to check the β-turn inducing properties of the APC systems synthesised, an NMR analysis was performed on compound **4** (Fig. 10). This was prepared by direct conversion of **8g** to the *N*-methyl amide by reaction with 33% $MeNH_2$ in ethanol, followed by evaporation of the reaction mixture and recrystallisation.

In the ^{1}H NMR spectrum (Fig. 10), the protons H^A and H^B on the ethylene moiety show up between 2.5 and 1.5 ppm. From the 2D COSY spectrum, the protons H^B neighbouring H^C can be identified as the signals at 2.05 and 1.19 ppm. The broader signals are assigned to the axial protons because these show mutual axial–axial couplings. The more complex signal pattern observed for H^{Bax} compared to H^{Aax} is due to coupling with H^C. In theory two conformations A and B are possible for this APC system: one with H^C pseudoaxial and one with H^C pseudoequatorial on the ring (Fig. 11). Proton H^C shows up as a broad doublet with one coupling of 7 Hz and a smaller coupling that was not resolved; this originally was interpreted as conformation B in which H^C has a big axial coupling with H^{Bax} and a small gauche coupling with H^{Beq}.[14] However, in a NOESY spectrum of this compound, a number of NOEs are observed which do not correspond with this initial proposal. For instance, the NOE found between N*H*CH_3 and the axial proton H^{Aax} is not consistent with conformer B. On the other hand this signal and the other NOEs observed fully agree with conformation A. Moreover this is also in accordance with the results of the molecular mechanics analysis (global minimum conformation) described before.



	R^1	R^3	R^6	R	Yield (%)
8g	Bn	Me	H	Me	91
8h*	Bn	Ph	Me	Et	82
8i	Bn	H	Ph	Me	84
8j	PMB	Bn	H	Me	75

* acid catalysed ethanolysis was used in this case
PMB=*p*-methoxybenzyl

Scheme 7. Methanolysis of the adducts and trapping with AcOAc.

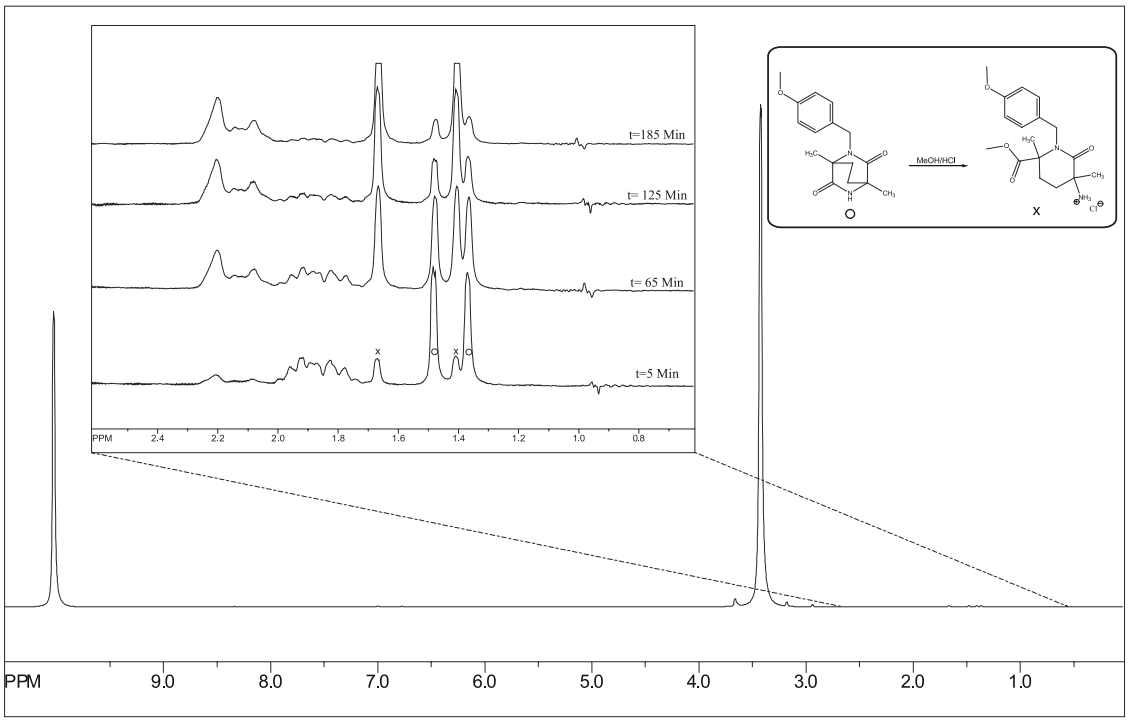


Figure 9. No-D NMR spectrum of the methanolysis mixture of **7g** at different time intervals (inset box).

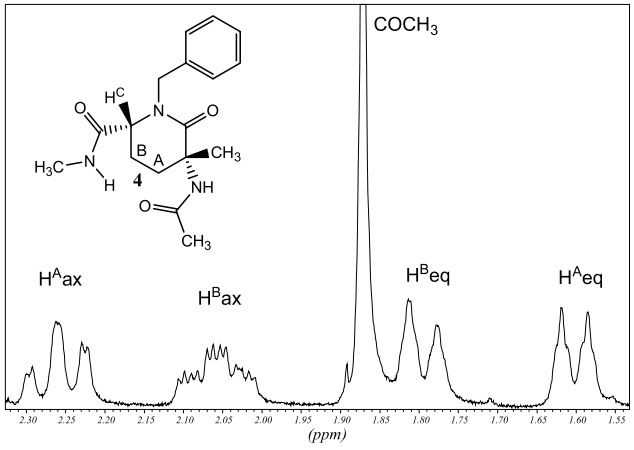


Figure 10. Ethylene bridge region in the ^{1}H NMR spectrum of the model compound.

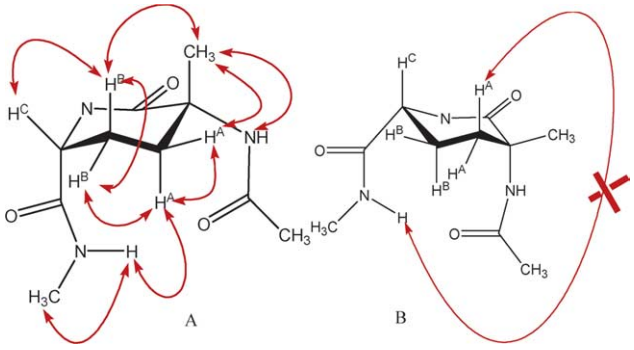


Figure 11. Structure determination based on observed NOE signals (*N*-Bn not shown in figures).

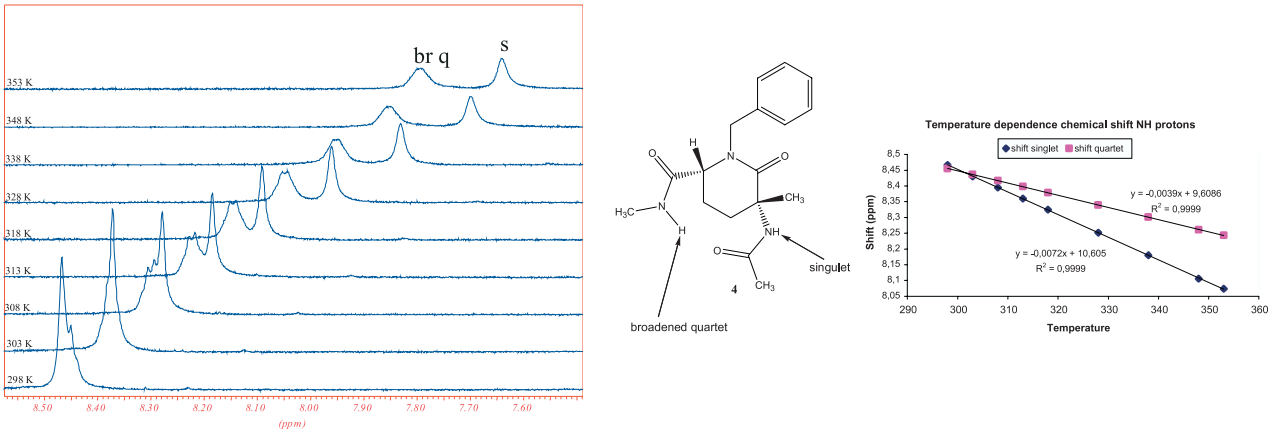


Figure 12. Hydrogen bond analysis of the model compound.

The presence of a hydrogen bond was also checked by ^{1}H NMR spectroscopy on compound **4**. The temperature dependence of the chemical shift of a hydrogen bonded amide proton is small (0 to −3 ppb/°C) when compared to the temperature dependence of a solvent exposed proton (< −7 ppb/°C).[7] The chemical shifts of the amide protons N*H*CO (singlet at $\delta = 8.47$ ppm) and N*H*Me (broadened quartet at $\delta = 8.46$ ppm) in DMSO-d_6 were recorded at different temperatures (Fig. 12). Linear regression on the collected data points provided us with the following results:the chemical shift dependence of −3.9 ppb for N*H*Me suggests this proton is shielded from the solvent and hydrogen bonding might be responsible for this shielding. The N*H*CO proton on the other hand is solvent exposed (shift dependence −7.2 ppb/°C). The value of −3.9 ppb just falls out of the region for hydrogen bonding; possibly this is due to a conformationial equilibrium with a non hydrogen bonded species or to the fact that the solvent shielding of a hydrogen bond in a model compound is less pronounced.[25] Further evidence for the presence of the hydrogen bond was obtained by checking the solvent dependency of the chemical shift of the amide protons upon changing the solvent from DMSO to $CDCl_3$. The results are summarised in Table 1. The small dependence of the chemical shift of the N*H*Me proton (0.14 ppm) also is in agreement with a hydrogen bond (or at least with shielding from the solvent). The exposed N*H*COMe proton is not shielded and therefore undergoes a large shift of 2.9 ppm upon switching the solvent.

6. Conclusion

A general non-Pro containing type VI-like β-turn mimetic was designed based on the structural resemblance between the systems of Kemp and Robinson/Germanas. In our hypothesis, we stated the turn inducing properties of these systems arise from the *cis*-relationship between an amine and a carboxylate function in an APC system. Based on this hypothesis, we developed a synthetic method for functionalised systems of this type. Key steps in the synthesis are the generation of a functionalised pyrazinone mimicking the side chains of the target compound, Diels–Alder reaction of this pyrazinone with ethene to impose the conformational restriction on the system and to fix the stereochemistry in the target compounds and finally a selective methanolysis reaction to form the APC systems. The scope and limitations of this sequence were further investigated.

Turn inducing properties were analysed by means of a combined NMR/molecular modelling analysis. Based on these results, it is concluded that our design hypothesis is correct and that these functionalised APC systems are good candidates for β-turn induction. These external turn mimics can be functionalised with the side chains of the dipeptide they are mimicking. The synthesis allows the introduction of both natural and non-natural amino acid side chains.

Introducing enantioselectivity in the system and scanning peptides with these type VI-like turn inducing systems is under current investigation.

7. Experimental

7.1. Analytical instruments

Melting points were taken using an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 Fourier transform spectrometer. Mass spectra were run using a Hewlett Packard MS-Engine 5989A apparatus for EI and CI

Table 1. Chemical shift dependence of amide protons of model compound **4**

δ_{NHMe} DMSO (ppm)	δ_{NHMe} $CDCl_3$ (ppm)	$\Delta\delta_{NHMe}$ (ppm)	δ_{NHCO} DMSO (ppm)	δ_{NHCO} $CDCl_3$ (ppm)	$\Delta\delta_{NHCO}$ (ppm)
8.46	8.32	0.14	8.47	5.88	2.59

Both the computational and the NMR analysis results indicate the design hypothesis is valid: hence this type of functionalised APC systems are promising candidates for β-turn induction.

spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10,000. For the NMR spectra (δ, ppm) a Bruker AMX 400 and a Bruker Avance 300 spectrometer were used. Analytical and preparative thin layer chromatography was carried out using Merck silica gel 60 PF-224, for column chromatography 70–230 mesh silica gel 60 (E.M. Merck) was used as the stationary phase.

7.2. Synthesis

7.2.1. Synthesis of dichloropyrazinones. For the preparation of the pyrazinones, we refer to the corresponding references:**5a**,[13] **5b**,[15g] **5c**,[21] **5e**,[21a] **5f**.[9a]

7.2.2. Synthesis of pyrazinone 5d. The general procedure for the synthesis of pyrazinones 5 is used (0.1 mol scale) with the following modification: after the addition of oxalyl chloride, the mixture is stirred at room temperature for 4 h. Subsequently 1 mL of DMF is added to the mixture. The solution is stirred for another 48 h. After evaporation, the crude mixture is treated as described in the general procedure.

7.2.3. 3,5-Dichloro-6-isopropyl-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (5d). Yield: 85%; melting point: 107–108 °C (EtOH); IR (KBr) cm^{-1}: 2930 (s, $CH(CH_3)_2$), 2827 (s, OCH_3), 1680 (s, CO), 1615 (s, CN); ^1H NMR (400 MHz, $CDCl_3$, ppm, *303 K*): 7.07 (d, 2H, $J=8.2$ Hz, ArH), 6.87 (d, 2H, $J=8.2$ Hz, ArH), 5.38 (s, 2H, CH_2Ph), 3.79 (s, 3H, OCH_3), 3.31 (br s, 1H, $CH(CH_3)_2$), 1.27 (d, 6H, $J=7.1$ Hz, $CH(CH_3)_2$); (400 MHz, $CDCl_3$, ppm, *213 K*): major conformer ($\pm$90%) 7.02 (d, 2H, $J=8.6$ Hz, ArH), 6.84 (d, 2H, $J=8.7$ Hz, ArH), 6.04 (d, 1H, $J=15.7$ Hz, CH_2Ph), 4.65 (d, 1H, $J=15.7$ Hz, CH_2Ph), 3.74 (s, 3H, OCH_3), 3.15 (heptuplet, 1H, $J=7.0$ Hz, $CH(CH_3)_2$), 1.34 (d, 3H, $J=6.8$ Hz, $CH(CH_3)_2$), 0.96 (d, 3H, $J=6.8$ Hz, $CH(CH_3)_2$). minor conformer ($\pm$10%) 7.02 (d, 2H, ArH), 6.84 (d, 2H, ArH), 5.30 (d, 1H, CH_2Ph), 5.18 (d, 1H, CH_2Ph), 3.88 (heptuplet, 1H, $J=7.0$ Hz, $CH(CH_3)_2$), 3.74 (s, 3H, OCH_3), 1.34 (d, 3H, $J=7.0$ Hz, $CH(CH_3)_2$), 1.15 (d, 3H, $J=7.0$ Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 159.5 (C*para*), 153.2 (C2), 143.9 (C3), 143.5 (C*ipso*), 127.9 (C*meta*), 126.8 (C6), 123.7 (C5), 114.6 (C*ortho*), 55.3 (OCH_3), 49.3 (CH_2Ph), 29.9 ($CH(CH_3)_2$), 18.2 (CH_3); EIMS *m/z* (%): 326 ($M^{\circ+}$, 100); HRMS: calcd for $C_{15}H_{16}Cl_2N_2O_2$: 326.0589; Found: 326.0605.

7.2.4. Functionalisation of the 3-position of pyrazinones. For the preparation of the substituted pyrazinones, we refer to the corresponding references:**6a**,[15g] **6b**,[15h] **6c**,[21] **6g**.[9a]

7.3. General procedure for the Grignard reaction on pyrazinones

To a cooled solution (−78 °C) of 1 mmol of pyrazinone in dry THF is slowly added via canula a solution of the corresponding Grignard reagent (1.3 mmol). The solution is kept at low temperature until completion of the reaction (30 min–2 h). The mixture is worked up at low temperature by addition of saturated NH_4Cl solution and extracted with ether. The organic layers are dried over $MgSO_4$, filtered and evaporated. The crude compounds are purified by column chromatography (silicagel, $CH_2Cl_2 \rightarrow CH_2Cl_2$–EtOAc 70:30).

7.3.1. 5-Chloro-6-isopropyl-1-(4-methoxybenzyl)-3-methyl-2(1*H*)-pyrazinone (6d). Yield: 45%; melting point: 97 °C (CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.06 (d, 2H, $J=8.0$ Hz, ArH), 6.87 (d, 2H, $J=8.1$ Hz, ArH), 5.36 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.26 (br s, 1H, $CH(CH_3)_2$), 2.49 (s, 3H, CH_3), 1.27 (d, 6H, $J=7.3$ Hz, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 159.5 (C*para*), 156.6 (CO), 154.4 (C3), 141.7 (C*ipso*), 128.1 (C*meta*), 128.0 (C6), 125.8 (C5), 114.8 (C*ortho*), 55.7 (OCH_3), 48.0 (CH_2Ph), 30.1 ($CH(CH_3)_2$), 21.2 ($CH(CH_3)_2$), 18.8 (CH_3); EIMS *m/z* (%): 306 ($M^{\circ+}$, 8), 121 ($C_8H_9O^+$, 100); HRMS: calcd for $C_{16}H_{19}ClN_2O_2$: 306.1131; Found 306.1147.

7.3.2. 3-Benzyl-5-chloro-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (6e). Yield: 72%; melting point: 102–103 °C; IR (KBr, cm^{-1}): 1648 (CO), 1586 (CN); ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.44 (d, 2H, $J=7$ Hz, Ar), 7.35–7.30 (m, 5H, ArH), 7.01 (s, 1H, H6), 6.9 (d, 2H, $J=8.7$ Hz, *meta* PMB), 4.93 (s, 2H, N–CH_2 of PMB), 4.12 (s, 2H, CH_2Ph), 3.8 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 159.8 (C*para*), 158.8 (C2), 154.4 (C3), 136.3 (C*ipso* Bn), 130.2 (CH-Ar), 129.3 (CH-Ar), 128.3 (CH-Ar), 126.5 (CH-Ar), 125.8 (C6), 125.7 (C*ipso* PMB), 124.3 (C5), 114.4 (*meta*PMB), 55.18 (OCH_3), 51.8 (CH_2 of PMB), 39.8 (CH_2 of Bn); EIMS *m/z* (%): 340 (8, $M^{\circ+}$), 121 (100, CH_3O–C_6H_4–$CH_2^+\cdot$); HRMS: calcd for $C_{19}H_{17}N_2O_2Cl$: 340.0978; Found: 340.0972.

7.3.3. 5-Chloro-3-isopropyl-1-(4-methoxybenzyl)-6-methyl-2(1*H*)-pyrazinone (6f). Yield: 68%; melting point: 89 °C (EtOH) IR (KBr) cm−1: (2862 (s, CH_3), 2871 (s, $CH(CH_3)_2$), 1648 (s, CONBn); ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.10 (d, 2H, $J=8.7$ Hz, ArH), 6.83 (d, 2H, $J=8.4$ Hz, ArH), 5.23 (s, 2H, CH_2Ph), 3.75 (s, 3H, OCH_3), 3.45 (heptuplet, 1H, $J=6.9$ Hz, CH), 2.34 (s, 3H, CH_3), 1.23 (d, 6H, $J=6.9$ Hz, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 161.6 (C*para*), 159.6 (C2), 155.8 (C3), 133.2 (C6), 128.7 (C*meta*), 127.4 (C5), 126.4 (C*ipso*), 114.8 (C*ortho*), 55.6 (OCH_3), 48.5 (CH_2Ph), 31.2 ($CH(CH_3)_2$), 20.4 ($CH(CH_3)_2$), 17.0 (CH_3); EIMS *m/z* (%): 306 ($M^{\circ+}$, 14); 121 ($C_8H_9O^+$, 100); HRMS: calcd for $C_{16}H_{19}ClN_2O_2$: 306.1131; Found: 306.1115.

7.4. Diels–Alder reaction. General procedure for the synthesis of compounds 7a–7g

The pyrazinone precursor (1 mmol) is dissolved in 30 mL of toluene and the solution is transferred to a steel bomb. The mixture is heated under ethene pressure (35 atm) at 135 °C for 1–2 days. Upon cooling and removal of ethene, the solvent is evaporated under reduced pressure. The imidoyl chloride intermediates are further hydrolised to the desired compounds **7a–7g** by stirring them in $CHCl_3$ open to air moisture.

These compounds are further purified by column chromatography (silica gel, CH_2Cl_2–EtOAc (95–5)). For the synthesis of compound **7c**, the imidoyl chloride intermediate is treated with 50 mL of moisturised EtOAc

containing a drop of HCl solution for 1 night. Upon addition of 10 mL of water, the solution is neutralised with K_2CO_3. The organic phase is separated and dried over $MgSO_4$ and evaporated under reduced pressure. The crude product is further purified by column chromatography (silica gel, CH_2Cl_2).

7.4.1. 5-Benzyl-1-methyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (7a). Yield: 79%; melting point: 170 °C (hexane/CH_2Cl_2); IR (KBr) cm^{-1}: 1707 (s, CO); ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.34–7.24 (m, 5H, PhH), 6.44 (s, 1H, NH), 4.77 (d, 1H, $J=14.5$ Hz, CH_2Ph), 4.38 (d, 1H, $J=14.5$ Hz, CH_2Ph), 3.89 (br s, 1H, H4), 1.95–1.65 (m, 4H, CH_2CH_2), 1.54 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 171.9 (CO, broad), 171.3 (CO), 136.2 (PhC*ipso*), 128.9;128.2;128.0 (ArC), 60.2 (C4, broad, visible in an HMQC spectrum), 58.2 (C1), 48.6, 32.5 (CH_2), 24.8 (CH_2), 18.3 (CH_3); EIMS *m/z* (%): 244 ($M^{\circ+}$, 84), 111 ($M^{\circ+}-CONCH_2Ph^{\circ}$, 43), 91 ($PhCH_2^+$, 100), 83 ($M^{\circ+}-CONCH_2$-$Ph^{\circ}$–CO, 60); HRMS: calcd for $C_{14}H_{16}N_2O_2$: 244.1212; Found: 244.1213.

7.4.2. 2-Benzyl-1-methyl-4-phenyl-2,5-diazabicyclo-[2.2.2]octane-3,6-dione (7b). Yield: 88%; melting point: 227 °C (CH_2Cl_2/hexane); IR (KBr) cm^{-1}: 1692 (s, CO); ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.20–7.48 (m, 10H, PhH), 6.36 (s, 1H, NH), 4.84 (d, 1H, $J=16$ Hz, CH_2Ph), 4.56 (d, 1H, $J=16$ Hz, CH_2Ph), 2.32 (ddd, 1H, $J=14$ Hz, 10 Hz, 5 Hz, H8′), 2.16 (ddd, 1H, $J=14$ Hz, 10 Hz, 5 Hz, H8), 2.08 (ddd, 1H, $J=13.5$ Hz, 10 Hz, 5 Hz, H7), 1.96 (ddd, 1H, $J=13.5$ Hz, 10 Hz, 5 Hz, H7′), 1.55 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 172.7 (CO), 171.1 (CO), 126.9–138.0 (ArC), 63.4 (C4), 61.8 (C1), 45.1 (CH_2Ph), 39.2 (CH_2), 29.3 (CH_2), 16.6 (CH_3); EIMS *m/z* (%): 320 ($M^{\circ+}$, 37), 187 ($M^{\circ+}-CONCH_2Ph^{\circ}$, 69), 159 ($M^{\circ+}-CONCH_2Ph^{\circ}$–CO, 100), 91 ($PhCH_2^+$, 68); HRMS: calcd for $C_{20}H_{20}N_2O_2$: 320.1525; Found: 320.1523.

For spectral data of compound **7c** we refer to Ref. 21.

7.4.3. 1-Isopropyl-2-(4-methoxybenzyl)-4-methyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (7d). Yield: 56%; melting point: 176 °C; IR (KBr) cm^{-1}: 3189 (NH), 1687 (CO); ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.12 (d, 2H, $J=8.1$ Hz, ArH), 6.81 (d, 2H, $J=8.1$ Hz, ArH), 6.74 (s, 1H, NH), 5.03 (d, 1H, $J=16.1$ Hz, CH_2Ph), 4.37 (d, 1H, $J=16.1$ Hz, CH_2Ph), 3.78 (s, 3H, OCH_3), 2.37 (heptuplet, 1H, $J=6.6$ Hz, $CH(CH_3)_2$), 1.97–1.88 (m, 2H, CH_2), 1.82–1.64 (m, 2H, CH_2), 1.50 (s, 3H, CH_3), 1.35 (d, 3H, $J=6.6$ Hz, $CH(CH_3)_2$), 1.13 (d, 3H, $J=6.6$ Hz, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 174.7 (CO), 172.7 (CO), 159.1 (C*para*), 131.0 (C*ipso*), 128.7 (C*meta*), 114.4 (C*ortho*), 68.0 (C4), 57.1 (C1), 55.6 (OCH_3), 45.4 (CH_2Ph), 32.6 (CH_2), 29.1 (CH_2), 29.1 (CH_3), 19.9 ($CH(CH_3)_2$), 18.9 ($CH(CH_3)_2$); EIMS *m/z* (%): 316 ($M^{\circ+}$, 25), 152 ($M^{\circ+}\cdot-CONHC_8H_9O$, 36), 121 ($C_8H_9O^+$, 100); HRMS: calcd for $C_{18}H_{24}N_2O_3$: 316.1787; Found: 316.1779.

7.4.4. 1-Benzyl-5-(4-methoxybenzyl)-2,5-diazabicyclo-[2.2.2]octane-3,6-dione (7e). Yield: 81%; melting point: 184 °C; IR (KBr, cm^{-1}): 3209 (NH), 1704 (CO), 1689 (CO); ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.41–7.24 (m, 5H, ArH), 7.19 (d, 2H, $J=8.5$ Hz, *ortho* PMB), 6.86 (d, 2H, $J=8.5$ Hz, *meta*PMB), 5.17 (s, 1H, NH), 4.76 (d, 1H, $J=14$ Hz, N–CH of PMB), 4.32 (d, 1H, $J=14$ Hz, N–CH of PMB), 3.86 (m, 1H, H4), 3.79 (s, 3H, OCH_3), 3.5 (d, 1H, $J=14$ Hz, Ph-CH), 3.07 (d, 1H, $J=14$ Hz, Ph-CH), 1.98 (m, 1H, bridge H), 1.88–1.64 (m, 3H, bridge H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.5 (CO), 170.7 (CO), 159.4 (C*para*), 134.7 (*ipso* benzyl), 130.4, 129.5, 129.1 (ArCH), 128.4 (C*ipso* PMB), 127.5 (ArCH), 114.3 (C*meta* PMB), 60.4 (C1), 59.0 (C4), 55.2 (OCH_3), 48.0 (CH_2 of PMB), 37.2 (CH_2-Ph), 30.8, 24.8 (C7, C8); EIMS *m/z* (%): 350 ($M^{\circ+}$, 61), 229 ($M^{\circ+}-CH_3O-C_6H_4-CH_2^{\cdot}$, 34), 186 ($C_{12}H_{12}NO^+$, 60), 121 ($CH_3O-C_6H_4-CH_2^+$, 100); HRMS: calcd for $C_{21}H_{22}N_2O_3$: 350.1630; Found: 350.1630.

7.4.5. 4-Isopropyl-2-(4-methoxybenzyl)-1-methyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (7f). Yield: 52%; melting point: 207 °C (EtOH); IR (KBr) cm^{-1}: 3347 (m, NH), 2832 (s, OCH3), 1696 (s, CO), 1668 (s, CO); ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.09 (d, 2H, $J=8.6$ Hz, ArH), 6.82 (d, 2H, $J=8.4$ Hz, ArH), 5.95 (s, 1H, NH), 4.70 (d, 1H, $J=15.6$ Hz, CH_2Ph), 4.47 (d, 1H, $J=15.6$ Hz, CH_2Ph), 3.78 (s, 3H, OCH_3), 2.44 (q, 1H, $J=6.9$ Hz, $CH(CH_3)_2$), 2.04–1.97 (m, 1H, CH_2), 1.84–1.75 (m, 3H, CH_2+CH_2), 1.48 (s, 3H, CH_3), 1.14 (d, 3H, $J=6.9$ Hz, $CH(CH_3)_2$), 1.10 (d, 3H, $J=6.9$ Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 173.4 (CO), 172.0 (CO), 158.8 (C*para*), 130.6 (C*ipso*), 128.3 (C*meta*), 114.3 (C*ortho*), 62.7 (C4), 61.4 (C1), 55.2 (OCH_3), 43.9 (CH_2Ph), 33.2 (CH_2), 29.0 ($CH(CH_3)_2$), 28.0 (CH_2), 17.9 ($CH(CH_3)_2$), 17.1 ($CH(CH_3)_2$), 16.5 (CH_3); EIMS *m/z* (%): 316 ($M^{\circ+}$, 46), 121 ($C_8H_9O^+$, 100); HRMS: calcd for $C_{18}H_{24}N_2O_3$: 316, 1787; Found: 316, 1797.

7.4.6. 2-(4-Methoxybenzyl)-1,4-dimethyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (7g). Yield: 64%; melting point: 177 °C; IR (KBr) cm^{-1}: 3180 (NH), 1692 (CO); ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.40 (s, 1H, NH), 7.08 (d, 2H, $J=8.8$ Hz, ArH), 6.81 (d, 2H, $J=8.8$ Hz, ArH), 4.71 (d, 1H, $J=16$ Hz, CH_2Ph), 4.45 (d, 1H, $J=16$ Hz, CH_2Ph), 3.77 (s, 3H, OCH_3), 1.91–1.71 (m, 4H, CH_2), 1.53 (s, 3H, CH_3), 1.46 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 174.1 (CO), 173.2 (CO), 159.2 (C*para*), 130.8 (C*ipso*), 128.4 (ArC), 114.5 (ArC), 62.1 (C1/C4), 57.8 (C1/C4), 55.6 (OCH_3), 44.4 (CH_2Ph), 33.6 (CH_2), 32.5 (CH_2), 18.9 (CH_3), 16.9 (CH_3); EIMS *m/z* (%): 288 ($M^{\circ+}$, 43), 124 ($M^{\circ+}-CONHC_8H_9O^{\cdot}$, 87), 121 ($C_8H_9O^+$, 100); HRMS: calcd for $C_{16}H_{20}N_2O_3$: 288.1474; Found: 288.1484.

7.5. General procedure for the synthesis of 7h and 7i

To a stirred solution of 1 mmol of **7f** or **7g** in DMF was added 1.4 mmol of NaH. After stirring for 5 min at room temperature 1.2 mmol of MeI was added to this mixture. The reaction was kept at room temperature for 16 h. The crude product was obtained after workup with saturated NH_4Cl solution followed by extraction and evaporation of the solvent. The products were purified by column chromatography (Silicagel, CH_2Cl_2–EtOAc, 60:40 for **6i** and 80:20 for **6h**).

7.5.1. 1-Isopropyl-5-(4-methoxybenzyl)-2,4-dimethyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (7h). Yield: 67%; melting point: colorless oil; IR (NaCl) cm^{-1}: 1679

(CO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.04 (d, 2H, J=8.4 Hz, H*meta*), 6.79 (d, 2H, J=8.4 Hz, H*ortho*), 4.70 (d, 1H, J=15.6 Hz, CH_2Ph), 4.36 (d, 1H, J=15.6 Hz, CH_2Ph), 3.74 (s, 3H, OCH_3), 2.99 (s, 3H, NCH_3), 2.34 (heptuplet, 1H, J=6.8 Hz, *CH*$(CH_3)_2$), 1.98–1.92 (m, 1H, CH_2), 1.82–1.73 (m, 2H, CH_2+CH_2), 1.63–1.57 (m, 1H, CH_2), 1.46 (s, 3H, CH_3), 1.34 (d, 3H, J=6.8 Hz, CH$(CH_3)_2$), 1.26 (d, 3H, J=6.8 Hz, CH(*CH*$_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 174.1 (*C*ONCH_3), 171.2 (CO), 158.7 (C*para*), 130.6 (C*ipso*), 128.0 (C*meta*), 114.0 (C*ortho*), 66.5 (C4), 60.5 (C1), 55.3 (OCH_3), 43.7 (CH_2Ph), 33.0 (CH_2), 29.8 (*C*H$(CH_3)_2$), 28.5 (NCH_3), 27.0 (CH_2), 19.1 (CH(*C*H$_3)_2$), 18.5 (CH(*C*H$_3)_2$), 17.2 (CH_3); EIMS *m/z* (%): 330 ($M^{\circ+}$, 88), 209 ($M^{\circ+}-C_8H_9O^{\cdot}$, 27), 167 ($M^{\circ+}-CONHC_8H_9O^{\cdot}$, 70), 121 ($C_8H_9O^+$, 100); HRMS: calcd for $C_{19}H_{26}N_2O_3$: 330.1943; Found: 330.1944.

7.5.2. 2-(4-Methoxybenzyl)-1,4,5-trimethyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (7i). Yield: 78%; melting point: 102 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.01 (d, 2H, J=8.8 Hz, ArH), 6.74 (d, 2H, J=8.8 Hz, ArH), 4.69 (d, 1H, J=16.0 Hz, CH_2Ph), 4.33 (d, 1H, J=16.1 Hz, CH_2Ph), 3.69 (s, 3H, OCH_3), 2.87 (s, 3H, NCH_3), 1.87–1.59 (m, 4H, 2×CH_2), 1.54 (s, 3H, CH_3), 1.43 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 172.6 (CO), 172.4 (CO), 159.1 (C*para*), 130.8 (C*ipso*), 128.4 (ArC), 114.4 (ArC), 61.5 (C1/C4), 61.1 (C1/C4), 55.6 (OCH_3), 44.4 (CH_2Ph), 33.1 (CH_2), 32.0 (CH_2), 27.4 (NCH_3), 17.9 (CH_3), 17.5 (CH_3); EIMS *m/z* (%): 302 ($M^{\circ+}$, 56), 138 ($M^{\circ+}-CONHC_8H_9O^{\cdot}$, 100), 121 ($C_8H_9O^+$, 98); HRMS: calcd for $C_{17}H_{22}N_2O_3$: 302.1630; Found: 302.1639.

7.6. General procedure for the CAN deprotection

The *para*-methoxybenzyl protected bislactam-system is dissolved in acetonitrile and cooled in an ice bath. 3eq of CAN, dissolved in a minimum amount of H_2O, are added dropwise. After stirring for 3 h, the solution is extracted with CH_2Cl_2 and the combined organic layers are dried with $MgSO_4$. Upon removal of the solvent, the crude product is purified by chromatography (MeOH/CH_2Cl_2). The unprotected product precipitates out of the reaction solution in case of compound **7j** or **7l**.

7.6.1. 1-Isopropyl-2,4-dimethyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (7j). Yield: 72%; melting point: 113 °C; IR (KBr) cm^{-1}: 3184 (s, NH), 1690 (s, CO); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 6.51 (s, 1H, NH), 2.99 (s, 3H, NCH_3), 2.31 (heptuplet, 1H, J=6.8 Hz, *CH*$(CH_3)_2$), 2.05–1.72 (m, 4H, 2×CH_2), 1.47 (s, 3H, CH_3), 1.30 (d, 3H, J=6.9 Hz, CH(*CH*$_3)_2$), 1.21 (d, 3H, J=6.9 Hz, CH(*CH*$_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 174.6 (CO), 172.5 (CO), 56.6 (C4), 53.4 (C1), 32.3 (CH_2), 29.6 (NCH_3), 28.8 (*C*H$(CH_3)_2$), 27.1 (CH_2), 19.3 (CH_3), 18.9 (CH_3), 18.8 (CH_3); EIMS *m/z* (%): 210 ($M^{\circ+}$, 4), 165 ($M^{\circ+}-HCONH^{\cdot}$, 100), 153 ($M^{\circ+}-CONHMe^{\cdot}$, 44); HRMS: calcd for $C_{11}H_{18}N_2O_2$: 210.1368; Found: 210.1363.

7.6.2. 1,2,4-Trimethyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (7k). Yield: 74%; melting point: oil; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 6.72 (s, 1H, NH), 2.92 (s, 3H, NCH_3), 1.98–1.79 (m, 4H, CH_2), 1.54 (s, 3H, CH_3), 1.50 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 173.8 (CO), 172.8 (CO), 61.5 (C1/C4), 57.5 (C1/C4), 32.7 (CH_2), 32.6 (CH_2), 27.3 (NCH_3), 18.9 (CH_3), 17.2 (CH_3).

7.6.3. 1-Isopropyl-4-methyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (7l). Yield: 93%; melting point: 201 °C; ^{1}H NMR (300 MHz, DMSO-d_6, ppm): 8.33 (s, 1H, NH), 8.26 (s, 1H, NH), 2.07 (heptuplet, 1H, J=6.6 Hz, *CH*$(CH_3)_2$), 1.87–1.57 (m, 4H, CH_2), 1.22 (s, 3H, CH_3), 1.02 (d, 3H, J=6.6 Hz, CH(*CH*$_3)_2$), 1.00 (d, 3H, J=6.6 Hz, CH(*CH*$_3)_2$); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): 174.3 (CO), 173.2 (CO), 62.7 (C1/C4), 56.6 (C1/C4), 32.7 (CH_2), 28.6 (CH_2), 18.0, 17.7, 17.1 (CH_3, CH); EIMS *m/z* (%): 196 ($M^{\circ+}$, 4), 151 ($M^{\circ+}-H_2NCOH$, 86), 121 ($C_8H_9O^+$, 100); HRMS: calcd for $C_{10}H_{16}N_2O_2$: 196.1212; Found: 196.1205.

7.7. Conversion of bislactams into APC systems via selective methanolysis reaction. General procedure for the methanolysis reaction

A solution of 1 mmol of bicyclic adduct **7** in 15 mL of MeOH is cooled to 0 °C. This solution is saturated with dry HCl gas for 5 min. Alternatively, 1 mL of $SOCl_2$ is slowly added to the methanol solution under cooling (CAUTION vigorous reaction). Upon completion of the reaction (check mass spectrum or NO-D NMR), the solution is evaporated under reduced pressure and the crude residue is dissolved in 8 mL of acetic anhydride. The mixture is cooled in an ice bath and Et_3N is added until precipitation of triethyl ammonium salts is observed. Upon removal of the ammonium salts, the solution is evaporated and the product **7** is purified by column chromatography (Silicagel, EtOAc).

7.7.1. Methyl 5-(acetylamino)-5-isopropyl-1-(4-methoxybenzyl)-2-methyl-6-oxo-2-piperidinecarboxylate (8a). Yield: 91%; melting point: 112 °C (CH_2Cl_2/Hex); IR (KBr) cm^{-1}: 3390 (m, NH), 2839 (w, OCH_3), 1740 (s, COOEt), 1682 (s, CO), 1648 (s, CO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.13 (d, 2H, J=8.7 Hz, H*ortho*), 6.76 (d, 2H, J=8.7 Hz, H*meta*), 6.60 (s, 1H, NH), 5.36 (d, 1H, J=15.4 Hz, CH_2Ph), 3.63 (d, 1H, J=15.4 Hz, CH_2Ph), 3.33 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 3.19 (dt, 1H, J=14.7 Hz, 3.9 Hz, $H4_{eq}$), 2.32 (td, 1H, J=14.3 Hz, 3.8 Hz, $H4_{ax}$), 2.10 (heptuplet, 1H, J=6.8 Hz, *CH*$(CH_3)_2$), 1.89 (dt, 1H, J=14.8 Hz, 4.2 Hz, $H3_{eq}$), 1.72 (td, 1H, J=14.3 Hz, 3.4 Hz, $H3_{ax}$), 1.55 (s, 3H, CH_3CO), 1.29 (s, 3H, CH_3), 1.10 (d, 3H, J=6.8 Hz, CH(*CH*$_3)_2$), 0.97 (d, 3H, J=6.8 Hz, CH(*CH*$_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 173.9 (CON+COOCH_3), 169.5 (CH_3CONH), 158.5 (C*para*), 130.4 (C*ipso*), 128.3 (C*ortho*), 113.7 (C*meta*), 65.9 (C2), 61.8 (C5), 55.1 (OCH_3), 52.7 (OCH_3), 48.6 (CH_2Ph), 35.2 (*C*H$(CH_3)_2$), 31.7 (CH_2), 25.5 (CH_3), 24.8 (CH_2), 24.5 (CH_3), 17.7 (CH_3), 17.1 (CH_3); EIMS *m/z* (%): 390 ($M^{\circ+}$, 17), 303 ($C_{18}H_{25}NO_3^+$, 41), 121 ($C_8H_9O^+$, 100); HRMS: calcd for $C_{21}H_{30}N_2O_5$: 390, 2153; Found: 390, 2155.

7.7.2. Methyl 5-[acetyl(methyl)amino]-5-isopropyl-2-methyl-6-oxo-2-piperidinecarboxylate (8b). Yield: 75%; melting point: 93.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 5.87 (s, 1H, NH), 3.79 (s, 3H, OCH_3), 2.96 (s, 3H, NCH_3), 2.49–2.43 (m, 2H, *CH*$(CH_3)_2+CH_2$), 2.23 (ddd, 1H, J=14.1 Hz, 9.7 Hz, 3.7 Hz, CH_2), 2.07 (s, 3H, $COCH_3$), 1.92 (ddd, 1H, J=13.8 Hz, 9.3 Hz, 3.7 Hz, CH_2), 1.79 (ddd, 1H, J=13.8 Hz, 7.8 Hz, 3.7 Hz, CH_2), 1.42 (s, 3H, CH_3), 1.12

(d, 3H, $J=6.8$ Hz, CH(CH_3)$_2$), 1.06 (d, 3H, $J=6.8$ Hz, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 174.2 ($COOCH_3$), 171.8 ($CONHCH_3$), 170.2 (CO), 66.5 (C5), 58.5 (C2), 52.8 (OCH_3), 34.8 (NCH_3), 33.8 (*C*H(CH_3)$_2$), 28.6 (CH_2), 27.5 (CH_3), 26.4 (CH_2), 24.3 ($COCH_3$), 19.3 (CH(*C*H_3)$_2$), 18.6 (CH(*C*H_3)$_2$); EIMS *m/z* (%): 241 ($M^{\circ+}-COCH_3^{\cdot}$, 81), 225 ($M^{\circ+}-COOCH_3^{\cdot}$, 29), 212 ($M^{\circ+}-CH_3NCOCH_3^{\cdot}$, 67), 199 (100).

7.7.3. Methyl 5-(acetylamino)-5-isopropyl-2-methyl-6-oxo-2-piperidinecarboxylate (8c). Yield: 62%; melting point: oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.00 (s, 1H, NH), 5.94 (s, 1H, NH), 3.79 (s, 3H, OCH_3), 2.46–2.43 (m, 1H, CH_2-4), 2.41–2.38 (m, 1H, CH_2-3), 2.27–2.22 (m, 1H, CH_2-4), 2.19 (heptuplet, 1H, CH(CH_3)$_2$), 1.95 (s, 3H, CH_3CO), 1.83 (dt, 1H, $J=12.6$, 10.5 Hz, CH_2-3), 1.43 (s, 3H, CH_3), 1.03 (d, 3H, CH(*C*H_3)$_2$), 1.00 (d, 3H, CH(*C*H_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 174.0 ($COOCH_3$), 173.3 (CONH), 169.7 ($COCH_3$), 61.1 (C5), 59.7 (C2), 53.0 (OCH_3), 35.0 (*C*H(CH_3)$_2$), 29.2 (CH_2-5), 27.4 (CH_3), 24.9 (CH_2-4), 24.1 (CH_3CO), 18.2 (CH(*C*H_3)$_2$), 17.0 (CH(*C*H_3)$_2$).

7.7.4. Methyl 5-(acetylamino)-1-(4-methoxybenzyl)-2,5-dimethyl-6-oxo-2-piperidinecarboxylate (8d). Yield: 75%; melting point: oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.09 (d, 2H, $J=8.6$ Hz, H*ortho*), 6.82 (d, 2H, $J=8.6$ Hz, H*meta*), 6.74 (s, 1H, NH), 5.22 (d, 1H, $J=15.8$ Hz, CH_2Ph), 3.81 (d, 1H, $J=15.8$ Hz, CH_2Ph), 3.77 (s, 3H, OCH_3), 3.74 (s, 3H, $COOCH_3$), 2.74–2.72 (m, 1H, CH_2), 2.22–2.18 (m, 1H, CH_2), 2.05–2.01 (m, 2H, CH_2), 1.96 (s, 3H, $COCH_3$), 1.65 (s, 3H, CH_3-5), 1.48 (s, 3H, CH_3-2); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 174.6 (CO), 173.9 ($COOCH_3$), 169.7 ($COCH_3$), 158.5 (C*para*), 130.7 (C*ipso*), 128.1 (C*ortho*), 114.1 (C*meta*), 65.7 (C5), 56.4 (C2), 55.2 (OCH_3), 52.9 ($COOCH_3$), 48.1 (CH_2Ph), 32.5 (CH_2), 29.4 (CH_2), 25.7 (CH_3-2), 24.7 (CH_3-5), 24.2 ($COCH_3$); EIMS *m/z* (%): 362 ($M^{\circ+}$, 15), 275 ($C_{16}H_{21}NO_3^+$, 22), 136 ($C_8H_{10}NO^+$, 100), 121 ($C_8H_9O^+$, 92); HRMS: calcd for $C_{19}H_{26}N_2O_5$: 362.1842; Found: 362.1854.

7.7.5. Methyl 5-(acetylamino)-1,2,5-trimethyl-6-oxo-2-piperidinecarboxylate (8e). Yield: 68%; melting point: oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.62 (s, 1H, NH), 3.76 (s, 3H, OCH_3), 2.88 (s, 3H, NCH_3), 2.70–2.68 (m, 1H, CH_2), 2.22–2.19 (m, 1H, CH_2), 1.99–1.96 (m, 2H, CH_2+CH_2), 1.95 (s, 3H, $COCH_3$), 1.57 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 173.8 ($CONCH_3$), 173.6 ($COOCH_3$), 169.6 (CONH), 64.5 (C2), 56.4 (C5), 52.9 (OCH_3), 32.1 (CH_2), 30.9 (NCH_3), 29.2 (CH_2), 25.1 (CH_3), 24.3 (CH_3), 24.3 (CH_3CO); EIMS *m/z* (%): 197 ($M^{\circ+}-CH_3CONH_2$, 100), 138 (($M^{\circ+}-CH_3CONH_2$)–$COOCH_3^{\cdot}$, 22).

7.7.6. Methyl 5-(acetylamino)-2,5-dimethyl-6-oxo-2-piperidinecarboxylate (8f). Yield: 37%; melting point: 155 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 6.27 (s, 1H, NH), 5.97 (s, 1H, NH), 3.80 (s, 3H, OCH_3), 2.48–2.43 (dm, 1H, $J=14$ Hz, CH_2eq), 2.30 (dt, 1H, $J=14.0$, 3.7 Hz, CH_2eq), 2.18 (td, 1H, $J=13.8$, 3.7 Hz, CH_2ax), 1.95 (s, 3H, $COCH_3$), 1.78 (td, 1H, $J=13.8$, 4.4 Hz, CH_2ax), 1.54 (s, 3H, CH_3), 1.45 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 174.7 (CO), 174.3 (CO), 170.1 (CO), 60.4 (C2/C5), 55.7 (C2/C5), 53.4 (OCH_3), 30.8 (CH_2), 30.3 (CH_2), 27.9 ($COCH_3$), 24.8 (CH_3), 24.1 (CH_3); EIMS *m/z* (%): 242 ($M^{\circ+}$, 2), 183 ($M^{\circ+}-COOCH_3^{\cdot}$, 100), 141 ($C_7H_{13}N_2O^+$, 41), 124 ($C_7H_{10}NO^+$, 36); HRMS: calcd for $C_{11}H_{18}N_2O_4$: 242.1267; Found: 242.1278.

7.7.7. Methyl 5-(acetylamino)-1-benzyl-5-methyl-6-oxo-2-piperidinecarboxylate (8g). Yield: 91%; melting point: 137 °C (hexane/CH_2Cl_2); IR (KBr) cm^{-1}: 1738 (s, CO), 1666 (br s, CO); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.36–7.26 (m, 3H, PhH), 7.19–7.15 (m, 2H, PhH), 6.58 (s, 1H, NH), 5.49 (d, 1H, $J=15$ Hz, CH_2Ph), 3.97 (dd, 1H, $J=4$ Hz, 3 Hz, H2), 3.76 (s, 3H, OCH_3), 3.70 (d, 1H, $J=15$ Hz, CH_2Ph), 2.72–2.60 (m, 1H, CH_2), 2.17–2.03 (m, 3H, CH_2CH_2), 1.97 (s, 3H, CH_3), 1.63 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.4 (CO), 171.6 (CO), 169.7 (CO), 136.2 (ArC), 128.8; 128.1; 127.8 (ArCH), 58.4 (C2), 56.8 (C5), 52.6 (OCH_3), 50.1 (CH_2Ph), 29.9 (CH_2), 24.8 (CH_3), 24.1 (CH_3), 23.0 (CH_2); EIMS *m/z* (%): 318 ($M^{\circ+}$, 32), 259 ($M^{\circ+}-NH_2COCH_3$, 49), 231 ($M^{\circ+}-NH_2COCH_3$–CO, 100), 91 ($PhCH_2^+$, 98); HRMS: calcd for $C_{17}H_{22}N_2O_4$: 318.1580; Found: 318.1578.

7.7.8. Ethyl 5-(acetylamino)-1-benzyl-2-methyl-6-oxo-5-phenyl-2-piperidinecarboxylate (8h). Yield: 82%; melting point: 61 °C (CH_2Cl_2/hexane); IR (KBr) cm^{-1}: 1722 (s, CO), 1636 (s, CO); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.48–7.25 (m, 10H, PhH), 7.23 (s, 1H, NH), 5.26 (d, 1H, $J=16$ Hz, CH_2Ph), 4.22 (q, 2H, $J=7$ Hz, OCH_2), 3.97 (d, 1H, $J=16$ Hz, CH_2Ph), 3.35 (ddd, 1H, $J=14$ Hz, 1.5 Hz, 1.5 Hz, $H3_{eq}$ or $H4_{eq}$), 2.48 (ddd, 1H, $J=14$ Hz, 14 Hz, 1.5 Hz, $H3_{ax}$ or $H4_{ax}$), 2.14 (ddd, 1H, $J=14$ Hz, 1.5 Hz, 1.5 Hz, $H3_{eq}$ or $H4_{eq}$), 1.90 (ddd, 1H, $J=14$ Hz, 14 Hz, 1.5 Hz, $H3_{ax}$ or $H4_{ax}$), 1.91 (s, 3H, $COCH_3$), 1.44 (s, 3H, CH_3), 1.29 (t, $J=7$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.3 (CO), 172.0 (CO), 169.2 (CO), 140.6 and 138.1 (PhC*ipso*), 126.9–128.5 (ArC), 66.1 (C5), 62.3 (OCH_2), 62.1 (C2), 49.7 (CH_2Ph), 31.2 (C3 or C4), 27.8 (C3 or C4), 25.7 (CH_3), 24.4 ($COCH_3$), 14.2 (CH_3); EIMS *m/z* (%): 408 ($M^{\circ+}$, 14), 335 (86), 91 ($PhCH_2^+$, 100) HRMS: calcd for $C_{24}H_{28}N_2O_4$: 408.2049; Found: 408.2055.

For the spectral data of compound **8i** we refer to Ref. 21.

7.7.9. Methyl 5-(acetylamino)-5-benzyl-1-(4-methoxybenzyl)-6-oxo-2-piperidinecarboxylate (8j). Yield: 75%; melting point: oil; IR (NaCl, cm^{-1}): 3397 (NH), 1747 (CO), 1652 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.22–7.18 (m 3H, ArH), 7.14 (d, 2H, $J=8.5$ Hz, *ortho* PMB), 7.05–6.98 (m, 2H, Ar H), 6.87 (d, 2H, $J=8.5$ Hz, *meta* PMB), 6.45 (s, 1H, NH), 5.29 (s, 1H, $J=14.5$ Hz, N–C*H* of PMB), 3.95 (br d, 1H, $J=5$ Hz, H2), 3.81 (s, 3H, Ar-OCH_3), 3.76–3.68 (m, 4H, CH_3–O–CO + N–C*H* of PMB), 3.41 (d, 1H, $J=13$ Hz, Ph-C*H*–C5), 3.14 (d, 1H, $J=13$ Hz, Ph-C*H*–C5), 2.83 (br d, 1H, $J=14$ Hz, $H4_{eq}$), 2.15 (ddd, 1H, $J=14$, 14, 4 Hz, H4ax), 2.01–1.89 (m, 4H, $NHCOCH_3+H3_{eq}$), 1.8 (dddd, 1H, $J=14$, 14, 6, 4 Hz, H3ax); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.7, 171.6 (C6 and *C*$OOCH_3$), 169.7 (*C*ONH), 159.3 (C*para*-PMB), 135.9 (*ipso*-Bn), 130.3, 130.1, 128, (Ar CH), 127.9 (*ipso*-PMB), 126.9 (ArCH), 114.0 (*meta* PMB), 60.3 (C5), 58.5 (C2), 55.2 (Ar OCH_3), 52.5 ($COOCH_3$), 50.0 (N–CH_2 of PMB), 43.1 (C5–CH_2-Ph), 29.2 (C4), 24.1 (*C*H_3CONH), 22.8 (C3); EIMS *m/z* (%): 424 (6, $M^{\circ+}$), 333 (19, $M^{\circ+}-C_6H_5$–$CH_2^{\cdot}$), 121 (100,

CH_3O–C_6H_4–CH_2^+); HRMS: calcd for $C_{24}H_{28}N_2O_5$: 424.1998; Found: 424.2006.

7.7.10. Dimethyl 2,5-bis(acetylamino)-2,5-dimethylhexanedioate (10). Yield: 29%; melting point: oil; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 6.33 (s, 2H, NH), 3.76 (s, 6H, OCH_3), 2.27–2.16 (m, 2H, CH_2), 1.99 (s, 6H, $COCH_3$), 1.96–1.94 (m, 2H, CH_2), 1.54 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 177.7 (CO), 174.9 (CO), 60.1 (C_{quat}), 53.2 (OCH_3), 30.7 (CH_2), 24.4 (CH_3), 24.0 (CH_3); EIMS *m/z* (%): 316 ($M^{\circ+}$, 1), 198 ($M^{\circ+}-(CH_3CONH_2)_2$, 45), 156 ($C_8H_{14}NO_2^+$, 100); HRMS: calcd for $C_{14}H_{24}N_2O_6$: 316.1634; Found: 316.1651.

7.8. Synthesis of model compound 4

The piperidinone derivative **8g** is dissolved in a 33% solution of $MeNH_2$ in ethanol and stirred for 12 h at room temperature. The reaction mixture is evaporated and the residue is recrystallised from hexane/dichloromethane.

7.8.1. 5-(Acetylamino)-1-benzyl-*N*,5-dimethyl-6-oxo-2-piperidinecarboxamide (4). Yield: 92%; melting point: 217 °C (hexane/CH_2Cl_2); IR (KBr) cm^{-1}: 3444 (m, NH), 3343 (s, NH), 1690 (s, CO), 1633 (br s, CO); ^{1}H NMR ($CDCl_3$, 400 MHz): 8.32 (s, 1H, N*H*Me), 7.33–7.21 (m, 5H, ArH), 5.88 (s, 1H, NH), 5.44 (d, 1H, H=15 Hz, BnH), 3.95 (br d, 1H, J=6 Hz, $H2_{eq}$), 3.67 (d, 1H, J=15 Hz, BnH), 2.84 (d, 3H, J=5 Hz, NCH_3), 2.51 (td (ddd), 1H, J=14 Hz, 4 Hz, H4ax), 2.08 (dm (dddd), 1H, J=14 Hz, H3eq), 2.03 (s, 3H, CH_3), 1.96 (tq (dddd), 1H, J=14 Hz, 4 Hz, H3ax), 1.62 (dt (ddd), 1H, J=14 Hz, 4 Hz, H4eq), 1.50 (s, 3H, CH_3); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.47 (s, 1H, NH), 8.46 (q, 1H, J=5 Hz, N*H*Me), 7.36–7.23 (m, 3H, ArH), 7.18–7.14 (br d, 2H, J=7 Hz, ArH), 5.13 (d, 1H, J=15 Hz, BnH), 3.72 (d, 1H, J=15 Hz, BnH), 3.71 (br d, 1H, J=7 Hz, H2), 2.62 (d, 3H, J=5H, NCH_3), 2.26 (td (ddd), 1H, J=13 Hz, 4 Hz, H4ax), 2.06 (tq (dddd), J=13 Hz, 4 Hz, H3ax), 1.87 (s, 3H, CH_3), 1.80 (dtm (dddd), 1H, J=13 Hz, 4 Hz, H3eq), 1.60 (dt (ddd), 1H, J=13 Hz, 4 Hz, H4eq), 1.39 (s, 3H, CH_3); Coupling between H2 and H3 is also observed in the COSY spectrum both in $CDCl_3$ and in DMSO-d_6; ^{13}C NMR ($CDCl_3$, 100 MHz): 171.1 (CO), 170.8 (CO), 170.2 (CO), 136.6 (ArC), 128.7; 128.3; 127.7 (ArCH), 61.3 (C2), 55.5 (C5), 49.9 (CH_2Ph), 30.4 (CH_2), 26.3 (CH_3), 25.6 (CH_3), 23.2 (CH_3), 23.1 (CH_2); EIMS *m/z* (%): 317 ($M^{\circ+}$, 15), 259 ($M^{\circ+}-CONHCH_3$, 100), 91 ($C_7H_7^+$, 58); HRMS: calcd for $C_{17}H_{23}N_3O_3$: 317.1739; Found: 317.1738.

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16. This is dependent on the site of cleavage of a bicyclic lactam further on in the synthesis.
17. Isolation of the pure imidoyl chlorides is possible if dry toluene is used. However, these compounds still tend to hydrolise during further purification manipulations.
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24. In our case, we performed the reaction in an NMR tube containing HCl saturated MeOH and the bicyclic lactam.
25. These values are derived from the analysis of small cyclic peptides. It is possible that for smaller model systems the shielding of the NH in a hydrogen bond is less efficient. So less stringent criteria might be adopted here.