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γ-Turn Mimicry with Benzodiazepinones and Pyrrolobenzodiazepinones Synthesized from a Common Amino Ketone Intermediate

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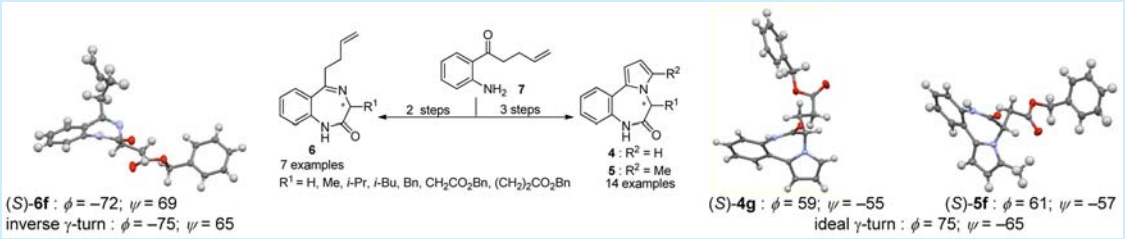
Supporting Information



ABSTRACT: To investigate diazepinone analogues as γ-turn mimics, seven 1,4-benzodiazepin-2-ones **6** and fourteen pyrrolo[1,2-*d*][1,4]benzodiazepin-6-ones **4** and **5** were synthesized from 1-(2-aminophenyl)pent-4-en-1-one (**7**). Acylation of aniline **7** with *N*-Boc-amino acids, olefin oxidation, Boc removal, and intramolecular Paal–Knorr condensation gave **4** and **5**. Alternatively, Boc removal prior to oxidation gave benzodiazepinones **6**, which were converted to **4** by ozonolysis and cyclization. Comparison of dihedral angle values for the amino acid component from X-ray analyses of **4g**, **5f**, and **6f** and related diazepinones has catalogued the manner by which ring substituents affect the component's ability to mimic the central residues of γ-turns.

Turn mimicry may lie at the heart of the wide range of biological, pharmacological, and clinical activities of 1,4-diazepin-2-ones and their aryl-fused ring analogues. Considered "privileged structures" because they exhibit high affinity to multiple receptors,[1−3] diazepinones have the capacity to mimic natural γ- and β-turn peptide secondary structures (Figure 1).[4,5]

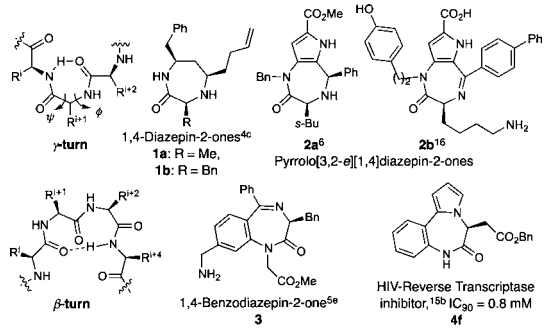


Figure 1. Representative diazepinones and γ- and β-turns.

X-ray structural analyses of diazepin-2-ones (e.g., **1** and **2**) have shown that their amino acid components adopt dihedral angle values similar to those of the central residue in a γ-turn (Figure 1).[4c,6,16] Moreover, spectroscopic and computational analyses have revealed that benzodiazepin-2-one scaffolds (e.g., **3**) can mimic β-turn backbone and side-chain geometry.[5e,f] Knowledge of ring substituent influences on turn geometry is thus valuable for rational application of such scaffolds in drug discovery.

1,4-Benzodiazepines are CNS drugs that show sedative, anxiolytic, anticonvulsant, antihypnotic, muscle relaxing, and anterograde amnesia activities.[1,2,7] They modulate hormone receptors,[1,8,9] block ion channels,[1a−c,8] and inhibit enzymes.[1a,b,5b,8,10] They exhibit antimalarial,[5b,10b] antiviral,[1a,8,10c] and antileukemic[10a] activity as well as the potential to treat lupus by inhibiting protein–DNA interactions.[1a]

Pyrrolo[2,1-*c*][1,4]benzodiazepinones exhibit anticancer and antitumor activity due to their ability to sequence-selectively bind and alkylate double-stranded DNA.[11,12] Their synthetic dimers are potent DNA cross-linking agents that have entered phase II clinical trials.[13] Pyrrolobenzodiazepinones have also shown anti-ischemic and herbicidal activity.[14] Pyrrolo[1,2-*d*][1,4]benzodiazepinones (e.g., **4f**) act as non-nucleoside HIV-1 reverse transcriptase inhibitors,[15b] albeit few publications have reported on this tricyclic system.[15]

Interested in their potential as turn mimics,[4c,6,16] we have pursued diazepinone analogues (e.g., **1** and **2**) using solution-[4c,6,18a] and solid-phase[16,17,18b] methods featuring diastereoselective Pictet–Spengler reactions[6,16,17] and copper-catalyzed cascade addition of vinyl Grignard reagents to α-aminoacyl-β-amino esters to afford γ,δ-unsaturated ketone precursors.[4c,18] Employing the latter reaction on methyl anthranilate, we synthesized effectively 1-(2-aminophenyl)-pent-4-en-1-one (**7**), which has previously served to make

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aminophenylpyrroles,[19] pyrrolo[1,2-*c*]quinazolin-5(6*H*)-ones,[19] and 2,3,4-trisubstituted quinolines (e.g., **8**−**10**, Figure 2).[20] To gain more insight into tools for γ-turn mimicry,[21] benzodiazepinone and pyrrolobenzodiazepinone analogues **4**−**6** have now been made from amino ketone **7** and examined by X-ray diffraction.

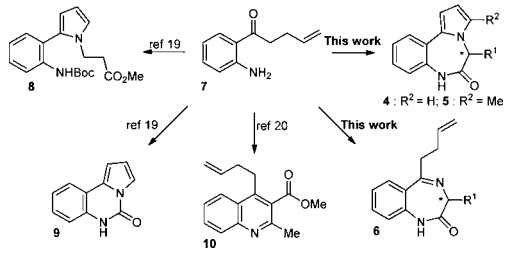


Figure 2. Amino ketone **7** as common precursor for heterocycle synthesis.

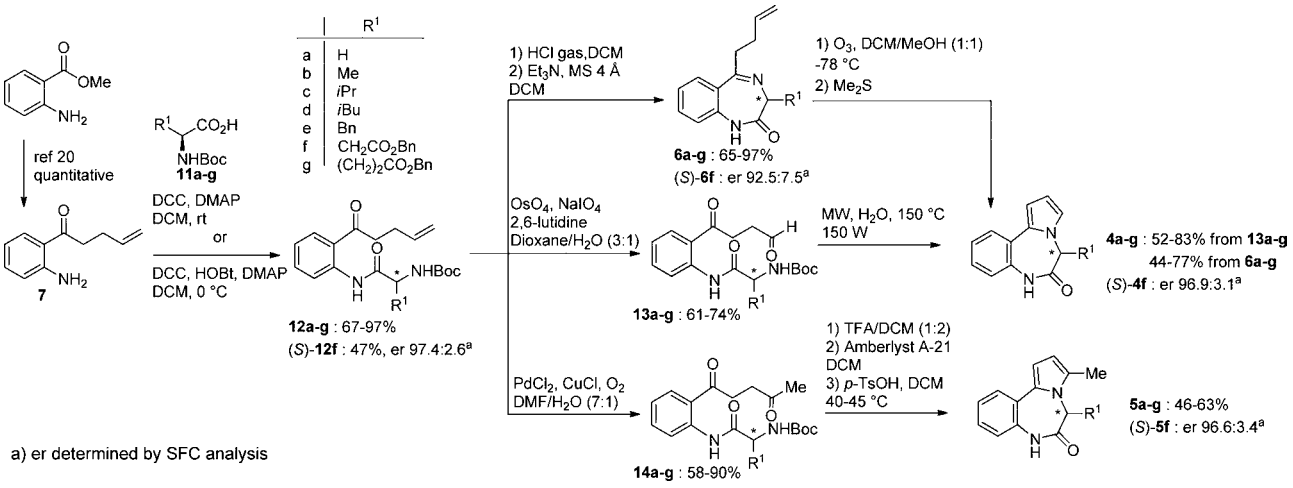
Among benzodiazepine syntheses,[22] the preparation of 1,4-benzodiazepin-2-ones has been less widely explored.[1a,5a,b,8,9a,c,10a,23,24] We perceived ring annulation by an N(4)−C(5) bond connection as an attractive route to 1,4-benzodiazepin-2-ones (e.g., **6**) because the requisite precursor may be synthesized by amino acylation of 2-aminophenones with amino acid derivatives. We have now validated this synthetic strategy by surmounting issues, low yield and racemization, in the amino acylation of electron-poor aniline **7**. Pyrrolo[1,2-*d*][1,4]benzodiazepinones **4** and **5** were also made by using 2-aminophenone **7** as a common precursor.

Electron-deficient aniline **7** was coupled to *N*-Boc-L-α-amino acids **11a**−**g** using DCC and DMAP in DCM at room temperature for 40 h to give amides **12** after chromatography on silica gel in 67−97% yields (Scheme 1). Fears of racemization from employing DMAP during peptide coupling were, however, realized by examining acylation products **12** by chiral SFC. For example, aspartate analogue **12f** exhibited a 56:44 enantiomeric ratio of (*S*)-**12f**:(*R*)-**12f**.[25,26] To overcome racemization, HOBt was added, and the DCC and DMAP procedure was run at 0 °C. In addition, the mixed anhydride method employing isobutyl chloroformate and *N*-methylmorpholine in THF at −15 °C was used to synthesize amide **12f**. The modified DCC coupling and mixed anhydride activation protocols provided material exhibiting, respectively, >94% and >93% enantiomeric excess by SFC analysis, albeit in 47% and 36% yields (92% and 71% yields based on recovered starting material, Scheme 1). With amino acids that are less susceptible to epimerization, such conditions may similarly yield high enantiomeric purity.

Benzodiazepinones **6** were synthesized in 65−97% yields from ketones **12** by Boc group removal with HCl gas in DCM, free-basing with triethylamine in the presence of 4 Å molecular sieves in DCM, and chromatography on silica gel (Scheme 1). Pyrrolo[1,2-*d*][1,4]benzodiazepinones **4** and **5** were made from olefin **12** as the common starting material. 4-Ketoaldehydes **13** and 1,4-diones **14** were obtained, respectively, by olefin oxidation using $OsO_4/NaIO_4$[27] and Tsuji−Wacker conditions.[28] 4-Ketoaldehydes **13** were isolated in 61−74% yields by chromatographic purification after oxidative cleavage of olefins **12** using sodium periodate and catalytic osmium tetraoxide in dioxane/H_2O at room temperature for 45 h. Chromatography of the products after treatment of olefins **12** with $PdCl_2$ and CuCl in DMF/H_2O at room temperature under oxygen atmosphere for 38 h afforded 1,4-diones **14** in 58−90% yields.

Various conditions were examined to synthesize pyrrolobenzodiazepinones from the dicarbonyl compounds by intramolecular Paal−Knorr condensations (Scheme 1).[29] For example, the Boc group of 1,4-diones **14** was removed with 1:2 TFA/DCM, and the resulting trifluoroacetates were free-based using Amberlyst A-21 ion-exchange resin.[30] Catalytic *p*-toluenesulfonic acid in dilute DCM at 45 °C provided pyrrolo[1,2-*d*][1,4]benzodiazepinones **5** in 46−63% yields after chromatography on silica gel. Under the same protocols, however, 4-ketoaldehydes **13** gave lower yields (10−39%) of pyrrolobenzodiazepinones **4**. Prior to chromatographic purification, the TLC profiles of crude **4** exhibited significant amounts of impurities. Attempts were unsuccessful to improve the yield of **4** by treating **13** with HCl gas in DCM to remove the Boc group prior to free-basing with triethylamine and Paal−Knorr cyclization. Limited success was also obtained by employing microwave irradiation of 4-ketoaldehyde **13** supported on silica gel at 100 °C to both remove the Boc group and effect in situ Paal−Knorr cyclization. On the other hand, pyrroles **4** were isolated in 52−83% yields from microwave irradiation of an aqueous mixture of 1,4-

Scheme 1. Synthesis of Benzodiazepinones 6a−g and Pyrrolobenzodiazepinones 4a−g and 5a−g from Amino Ketone 7



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ketoaldehydes **13** at 150 °C for 5−10 min and chromatography.[31]

Pyrrolobenzodiazepinones **4** were also prepared from benzodiazepinones **6** in 44−77% yields by ozonolysis in CH_2Cl_2/MeOH (1:1) at −78 °C, reduction of the ozonide with excess dimethyl sulfide, and chromatography on silica gel (Scheme 1). Attempts failed, however, to prepare pyrrolobenzodiazepinone **4f** by oxidation of olefin **13f** using sodium periodate/osmium tetraoxide. Employing enantiomerically enriched amide **12f** (>93% ee) in routes to pyrrolo[1,2-*d*][1,4]benzodiazepinones **4f** and **5f** featuring ozonolysis of benzodiazepinone **6f** and Tsuji−Wacker oxidations prior to Paal−Knorr cyclization of 1,4-dione **14f** gave products with high enantiomeric purity as assessed by SFC analysis (Scheme 1).

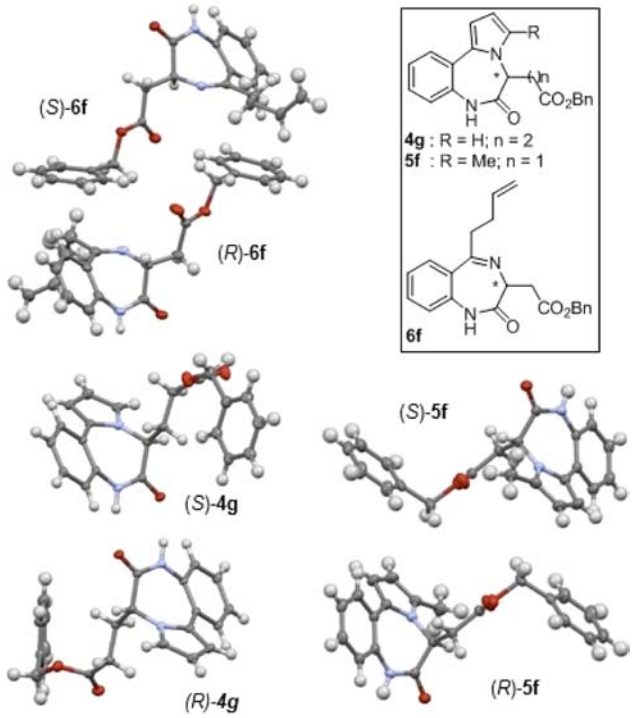

Figure 3. X-ray crystal structures of (*RS*)-**4g**, -**5f**, and -**6f**.

For X-ray analyses, crystals of benzodiazepinone (*RS*)-**6f** and pyrrolobenzodiazepinone (*RS*)-**5f** were grown by diffusion of hexanes into an ethyl acetate/hexane mixture. Crystals of pyrrolobenzodiazepinone (*RS*)-**4g** were grown by diffusion of hexanes into acetone. In both crystal structures, the enantiomers paired up in the unit cell. The amino acid side chain adopted, respectively, pseudoequatorial and pseudoaxial orientations for **6f** and for **4g** and **5f** in the solid state. The ϕ and ψ dihedral angles of the amino acid component of (*S*)-**4g**, (*S*)-**5f**, and (*R*)-**6f** and those of their enantiomers (*R*)-**4g**, (*R*)-**5**, and (*S*)-**6f** correlated, respectively, with the central residues of classical (75° ± 16 and −65° ± 10) and inverse (−75° ± 15 and 65° ± 13) γ-turns (Table 1).[32] The subtle changes of dihedral angle geometry may affect differences in receptor affinity and activity of related diazepinone ligands.

Comparing their respective crystal structures, substituent effects were observed on the dihedral angles of the amino acid component in benzodiazepinone **6f**, pyrrolobenzodiazepinones **4g** and **5f**, diazepinones **1a** and **1b**,[4c] and pyrrolodiazepinone **2a** and **2b**.[6,16] Although all of the analogues presented torsion angle values indicative of the central residue of an ideal γ-turn (75° ± 16 and −65° ± 10) and an ideal inverse γ-turn (−75° ± 18 and 65° ± 13), benzodiazepinone **6f** exhibited the best fit. Relatively smaller and larger dihedral angle values were observed, respectively, for pyrrolobenzodiazepinones **4g** and **5f** and diazepinones **1** and pyrrolodiazepinones **2** (Table 1).

Table 1. Diazepinone Crystal Analyses with ϕ and ψ Dihedral Angles Compared with Ideal γ-Turns

type of turn	ϕ	ψ
γ-turn[31]	75	−65
inverse γ-turn[31]	−75	65
diazepinone **1a**[4c]	−80	70
diazepinone **1b**[4c]	−83	67
pyrrolodiazepinone **2a**[6]	−93	72
pyrrolodiazepinone **2b**[16]	−79	74
pyrrolobenzodiazepinone (*S*)-**4g**	59	−55
pyrrolobenzodiazepinone (*R*)-**4g**	−60	52
pyrrolobenzodiazepinone (*S*)-**5f**	61	−57
pyrrolobenzodiazepinone (*R*)-**5f**	−61	57
benzodiazepinone (*S*)-**6f**	−72	69
benzodiazepinone (*R*)-**6f**	75	−68

The NMR spectra of benzodiazepinones **6** and pyrrolobenzodiazepinones **4** and **5** exhibited diastereomeric as well as broad signals due to atropisomerism contingent on ring substituent and environment. Typically, benzodiazepinones **6b−g** and pyrrolobenzodiazepinones **5b−g** and **4c** exhibited resolved spectra, with doubling of certain signals, such as the amide NH protons in chloroform. On the other hand, pyrrolobenzodiazepinones **4b−g** exhibited broad proton and missing carbon signals in chloroform, due likely to equilibrating atropisomers. Improved resolution of the NMR spectra of the benzodiazepinones was obtained in acetone, which may hydrogen bond with the amide proton. Temperature could also be varied to obtain better spectral resolution. For example, the ^{1}H and ^{13}C NMR spectra of **4b** were resolved by heating to 313 K to accelerate interconversion of the atropisomers. On the other hand, 1:1 to 3:2 diastereomeric mixtures of **4d**, **4e**, and **4g** were well resolved at low temperatures (e.g., 193 K), which slowed interconversion of the atropisomers. Finally, the ^{1}H NMR spectrum of **4f** at 193 K indicated a single set of resolved signals in acetone.

Insight has been gained into the capacity of diazepinone structures to mimic γ-turn conformations. Furthermore, by employing methyl anthranilate as common starting material, practical methods were conceived to synthesize benzodiazepinone and pyrrolobenzodiazepinone scaffolds. X-ray analyses demonstrated subtle effects of ring fusion and unsaturation in the 1,4-diazepinones on the capacity of their amino acid component to mimic the central residue of peptide γ-turns. This method offers interesting potential for applications in peptide mimicry and medicinal chemistry because of the importance of γ-turns in peptide biology[33] and the activity of related small molecules. Testing is underway to assess the biological activity of these novel diazepine analogues.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic characterization (^{1}H and ^{13}C NMR) for all compounds, SFC traces, and X-ray crystallographic data for **4g**, **5f**, and **6f**. The Supporting

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Notes

The authors declare no competing financial interest.

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