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Integrated Ugi-Based Assembly of Functionally, Skeletally, and Stereochemically Diverse 1,4-Benzodiazepin-2-ones

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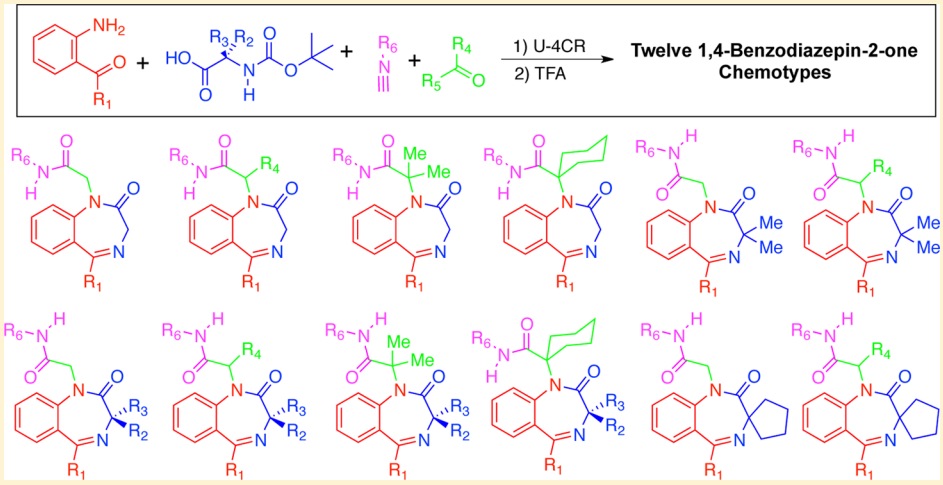
Supporting Information



ABSTRACT: A practical, integrated and versatile U-4CR-based assembly of 1,4-benzodiazepin-2-ones exhibiting functionally, skeletally, and stereochemically diverse substitution patterns is described. By virtue of its convergence, atom economy, and bond-forming efficiency, the methodology documented herein exemplifies the reconciliation of structural complexity and experimental simplicity in the context of medicinal chemistry projects.

INTRODUCTION

Extensively employed as therapeutics since the early 1960s, 1,4-benzodiazepin-2-ones (BZDs)[1] embody the archetypical privileged structure,[2] a concept coined by Evans in the late 1980s that constitutes a fruitful strategy to improve the low hit rates usually experienced during high-throughput screening campaigns. Whereas BZD scaffolds are recurrent templates in the context of CNS therapies (being extensively prescribed as sedatives, anxiolytics, anticonvulsants, or muscle relaxants),[3] the continuous appearance of reports describing novel pharmacological activities (e.g., antagonists of platelet activating factor,[4a] anti-HIV,[4b] antitumor,[4c,d] and antimalarial[4e]) unequivocally corroborate the ability of BZDs to modulate relevant biomolecules beyond CNS targets (Figure 1).

The pharmacogenicity profile of BZDs relies heavily on its constrained peptide mimic nature,[3] which dictates the geometry of the heterocyclic core and its appended functional groups, thus modulating the structural parameters ultimately governing ligand/receptor interactions. It should be emphasized that BZDs exist in a boat conformation, which confers intrinsic chirality to the heterocyclic core even in the absence of stereogenic carbons.[5] The barrier for racemization between *M* and *P* enantiomers (Figure 2) is known to be low,[5,6] unless they exhibit a single substituent at C3—which is stabilized at the pseudoequatorial position—or a relatively large substituent at position 1.[7] Consequently, the stereochemical diversity in collections of BZDs can be expanded by combining the chirality of the heterocyclic core with stereocenters at C3 or by the introduction of side chains at position 1 of the framework.

In addition to the bioactivity issues, the versatility of a privileged scaffold is heavily dependent on two key factors: its synthetic feasibility and its ability to be decorated and/or reinterpreted according to the specific requirements of distinct

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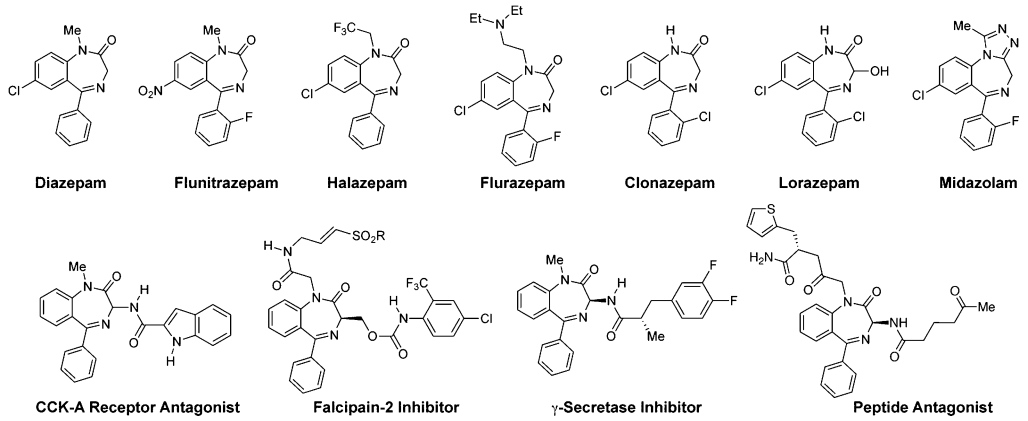


Figure 1. Representative drugs and bioactive compounds derived from the 1,4-benzodiazepin-2-one scaffold.

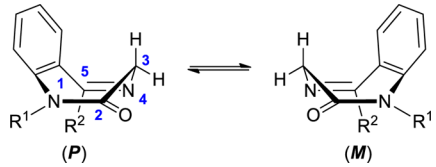


Figure 2. *P* and *M* conformational enantiomers of 1,4-benzodiazepin-2-ones.

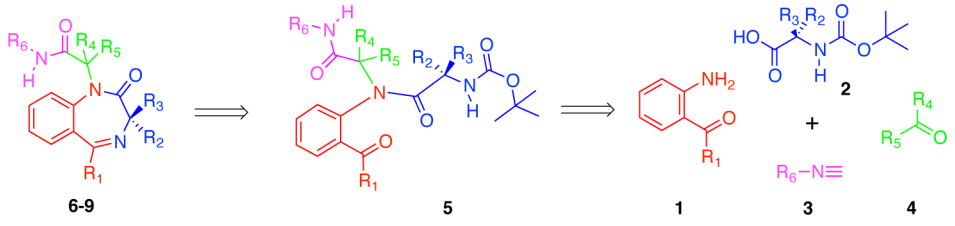
biological targets. Therefore, the implementation of concise and efficient synthetic methodologies providing integrated access to privileged molecular frameworks eliciting functional, skeletal, and stereochemical diversity, while enabling the reconciliation of the molecular complexity with experimental simplicity, constitutes a highly appreciated goal within the competitive environment of drug discovery. Notwithstanding the plethora of synthetic methods targeting BZDs,[8] established approaches consist of multistep linear pathways, where diversity elements are usually introduced at an early stage. Epimerization is often an issue, particularly during the subsequent functionalization of the heterocycle.[9] A valuable incorporation to the compendium of preparative methods targeting BZDs includes multicomponent reactions (MCR),[10] which have emerged as a tailored synthetic paradigm in drug discovery. The most powerful MCR-assisted method for generating BZD libraries[11] involves the Ugi four-component reaction (U-4CR).[12] Whereas this strategy has provided examples of elegant access to diverse BZD scaffolds,[11,12] most described protocols still require several synthetic steps and/or structurally elaborate precursors, thereby hampering its extensive application in medicinal chemistry programs. Additionally, the development of modular MCR-based approaches providing collections of privileged molecular frameworks in enantio- or diastereopure fashion remains a highly elusive challenge.[11] We herein document a conceptually simple and modular U-4CR-based approach that provides an integrated access to functionally, skeletally, and stereochemically diverse chemotypes derived from the pharmacologically useful 1,4-benzodiazepin-2-one framework.

RESULTS AND DISCUSSION

In the frame of a medicinal chemistry program series of 1,4-benzodiazepin-2-ones, simultaneous incorporation of functionalized alkyl chains at N1 and concise chemical and stereochemical substitution patterns at position 3 of the heterocyclic core were required. Being aware of the limitations of classical synthetic approaches to access the targeted chemotypes, we decided to assess the feasibility of a MCR-based approach. It was envisioned (Scheme 1) that the U-4CR reaction employing 2-aminophenyl ketones **1** as amine input, in combination with *N*-Boc-protected amino acids **2**, isocyanides **3**, and the carbonyl partner **4**, would afford Ugi adducts **5**, which upon removal of the protecting group would undergo an intramolecular cyclization to provide the targeted BZDs (Scheme 1). The feasibility of the proposed approach relies heavily on the reactivity of the carbonyl moiety of the starting 2-aminophenyl ketone **1** when it coexists with alternative carbonyl compounds during the U-4CR.

While a few reports have exemplified the use of amino ketones (**1**) toward U-4CR,[13] to the best of our knowledge, these works have employed aldehydes as carbonyl components; the reaction outcome of this transformation with ketones remains unexplored. Two recent papers have described Ugi-based benzodiazepine synthesis conceptually related to the approach documented herein. The first study, published by Torroba et al. in 2010,[14] documents an U-4CR that employs 2-aminobenzophenone and (*S*)-2-azido-3-phenylpropanoic acid as key components (in combination with cyclohexyl isocyanide and three substituted benzaldehydes), thus generating Ugi adducts that were subsequently cyclized under the Staudinger/aza-Wittig reaction conditions. This elegant approach is,

Scheme 1. Retrosynthetic Analysis to BZD Derivatives 6−9 through U-4CR



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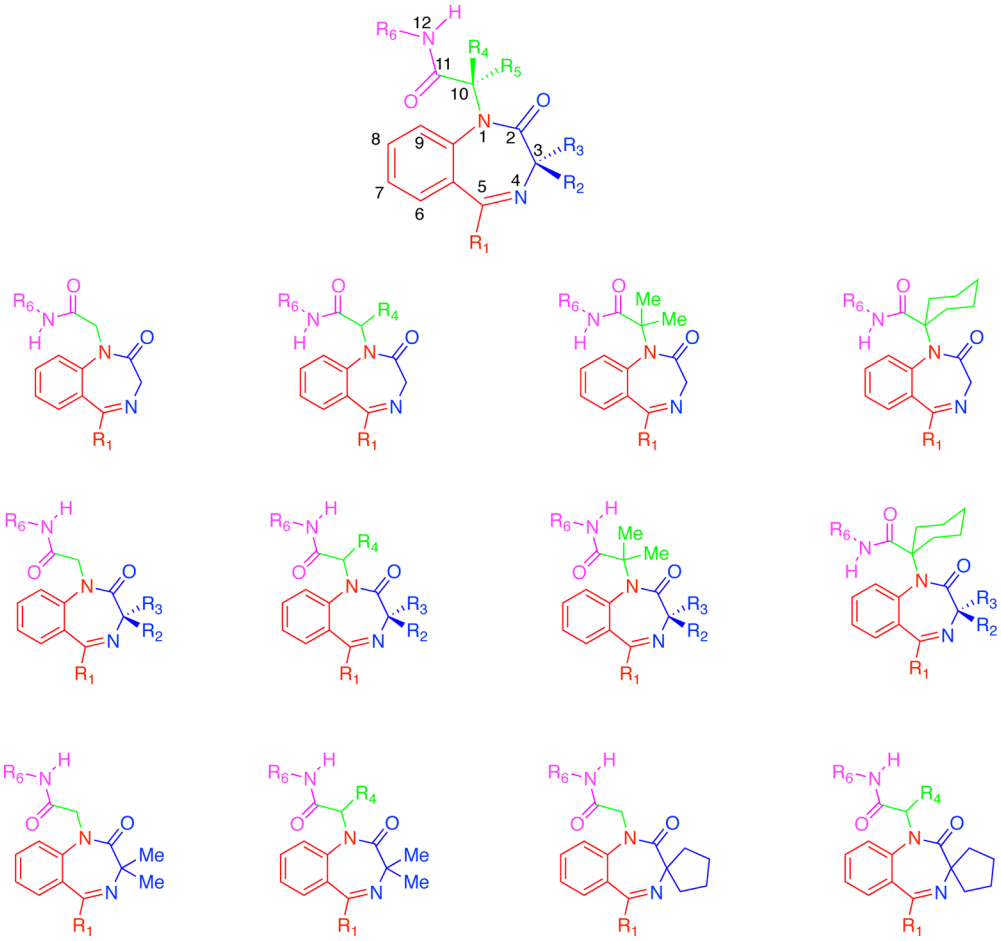

Figure 3. Structure and numbering of 1,4-benzodiazepin-2-one chemotypes **6**–**9** assembled through the Ugi-based approach described herein.

notwithstanding, strongly limited by the scarce availability of functionally and stereochemically diverse 2-azidopropanoic acids and its atom economy. This paper inspired the design of the pathway documented herein (Scheme 1). As observed, it follows the Ugi–deprotect–cyclize (UDC) strategy and capitalizes on the functional and stereochemical diversity of the available *N*-Boc-protected amino acids (**2**). During the practical implementation of our study, a communication[15] described several novel U-4CR approaches to 1,4-benzodiazepine scaffolds, one of them briefly exploring the approach documented herein. Since our exhaustive examination of the transformation not only reveals novel reactivity facets and expanded scope of the method but also provides 1,4-benzodiazepin-2-one chemotypes featuring unexplored functional, skeletal, and stereochemical substitution patterns (Figure 3), we decided to present our results.

As a proof of concept (Scheme 2) 2-aminobenzophenone (**1a**) and 2-aminoacetophenone (**1b**) were selected as model amine substrates for the Ugi reaction, in combination with glycine Boc (**2a**) and benzyl isocyanide (**3a**). With the aim of exhaustively evaluating the chemoselectivity profile of the transformation, and consequentially its robustness and potential contribution in terms of chemical diversity, not only aldehydes (e.g., formaldehyde (**4a**), butyraldehyde (**4b**), and benzaldehyde (**4c**)) but also ketones (e.g., propanone (**4d**) and cyclohexanone (**4e**)) were employed as reactive inputs (Scheme 2). The selected substrates were submitted to the standard conditions of the Ugi condensation in methanol (Scheme 2). Analysis of the reaction behavior for model substrates revealed that transformations are successful regardless of the steric hindrance present at either the amine (**1**) or the carbonylic partners (**4**), with more than 85% of **1** consumed after 36 h in most experiments (independent of the use of aldehyde or ketone). The intermediacy of the *α*-acylamino amides **5** was unequivocally confirmed by spectroscopic methods. It was gratifying to find that, upon reaction quenching and subsequent cleavage of the protecting group, Ugi adducts are readily transformed;, triggering BZDs **6** in a two-step one-pot fashion with overall yields ranging between 46 and 77% (Scheme 2). Among a variety of tested reagents to remove the Boc group, 20% TFA in DCE at 60 °C provided an efficient cleavage while simultaneously promoting mild cyclization in short reaction times (0.5–1 h). With the aim of evaluating the robustness of the method, the reactivity of other isocyanides (e.g., cyclohexyl (**3b**) or *tert*-butyl (**3c**)) was preliminarily tested, thus generating the 1,4-benzodiazepin-2-ones **6k**–**t**. In accord with previous observations,[16] the use of polystyrene-supported *p*-toluenesulfonic acid once the U-4CR is finished, in addition to remove traces of the remaining isocyanide, simultaneously scavenges the unreacted amine **1**, thus simplifying the purification stage.

As observed (Scheme 2), both aldehydes (aliphatic or aromatic) and ketones (acyclic and cyclic) were found to be good substrates, with the transformation exhibiting complete chemoselectivity. It should be highlighted that the strategy documented herein enables the straightforward introduction of

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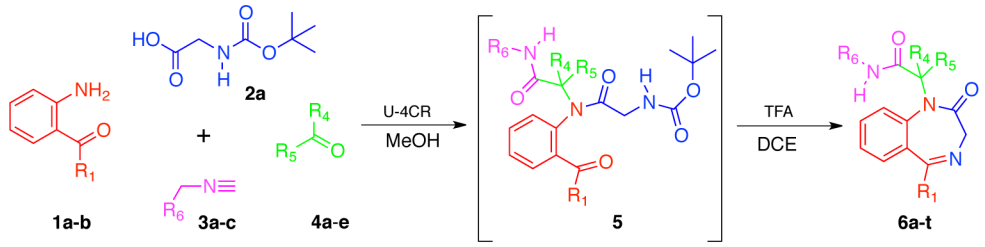
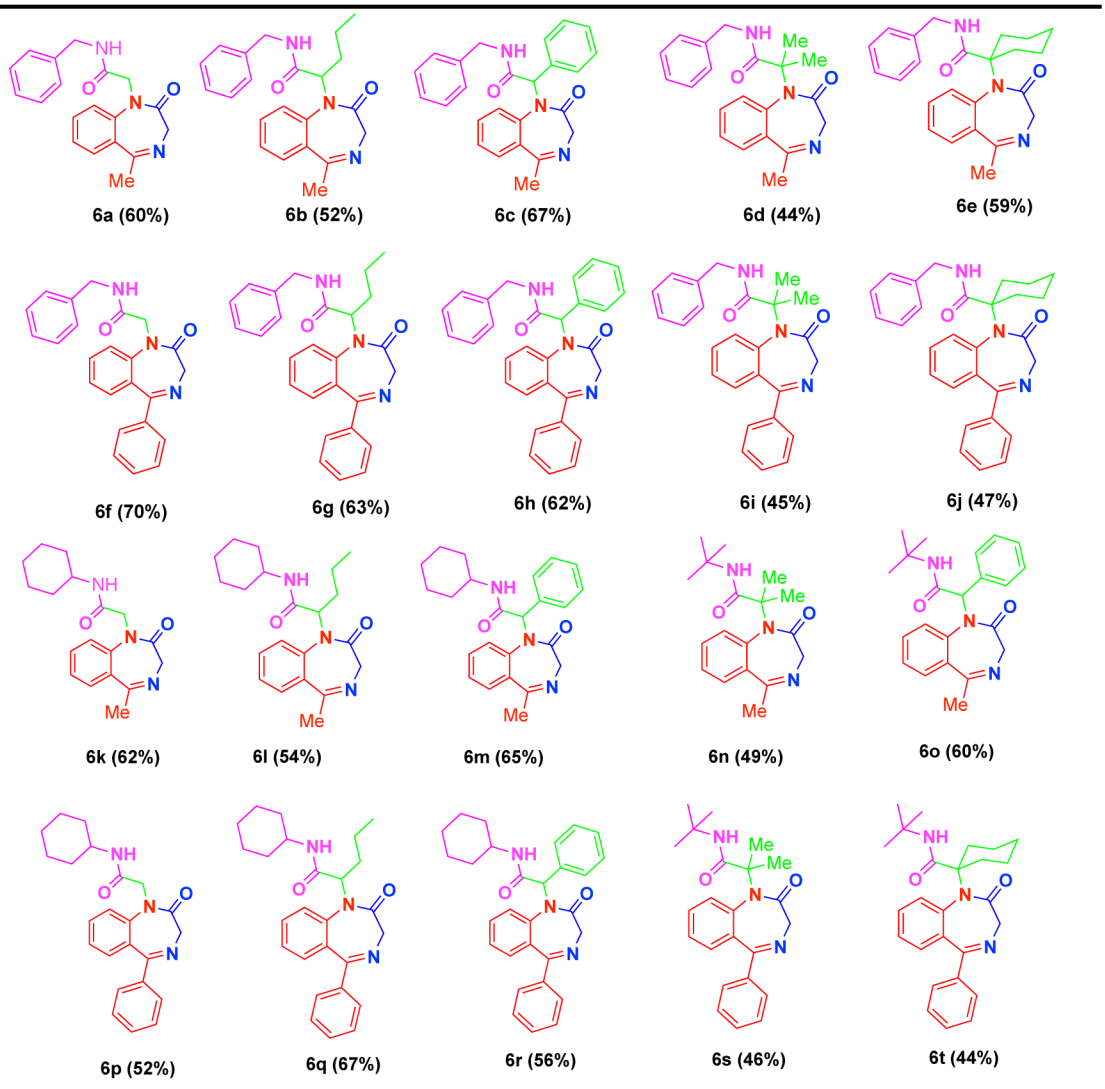
Scheme 2. Ugi-Based Assembly of 1,4-Benzodiazepin-2-ones 6





challenging residues on the exocyclic acetamide linkage under neutral conditions, as represented for 2,2-dimethyl derivatives (**6d**,**i**,**n**,**s**) and particularly for the cyclohexyl analogues (**6e**,**j**,**t**). In addition, to validate the feasibility of the proposed pathway, the results included in Scheme 2 provide a preliminary assessment of the exploratory power of this conceptually and experimentally simple strategy. It should be noted that the strategy documented herein assembles BZDs **6** in a one-pot procedure that involves the formation of six new bonds, thus exhibiting outstanding bond-forming efficiency and step economy.

Analysis of the NMR spectra of compounds **6a**−**t** enables us to observe that exchange between the two boat enantiomeric conformations *P* and *M* is slow on the NMR chemical shift time scale, as previously observed for BZDs with bulky substituents on N1.[7] This is assessed by observing the H3 proton resonances in the ^{1}H NMR spectrum. At room temperature the H3 protons are observed as two well-separated doublets ($\delta(H_{ax})$ ~3.5 ppm vs $\delta(H_{eq})$ ~4.5 ppm, $|^2J_{HH}|$ = 10.5−12.5 Hz). The strong shielding of the pseudoaxial proton H_{ax} is caused by the phenyl ring of the BZD skeleton. When prochiral aldehydes were used in the Ugi reaction (e.g., **4b**,**c**), a new stereocenter is introduced in the side chain at position 1′ and the *P* and *M* boat conformations become diastereomeric (Figure 4). In the ^{1}H NMR spectra of these compounds (**6b**,**c**,**g**,**h**,**l**,**m**,**o**,**q**,**r**), resonances corresponding to each diaster-

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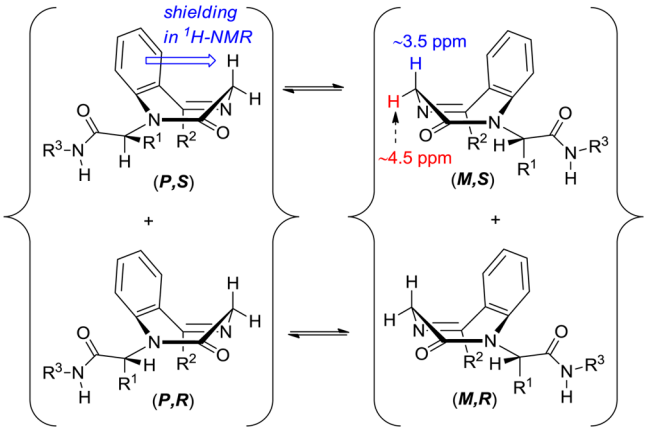

Figure 4. Diastereomeric 1,4-benzodiazepin-2-one chemotypes assembled.

eomeric pair of enantiomers—*P*,*S*/*M*,*R* vs *P*,*R*/*M*,*S*—can be seen, with diastereomeric ratios ranging from 1:2 to 1:5.

Once the feasibility of the proposed method was established for glycine Boc (Scheme 2), and having identified optimal experimental conditions to perform the Ugi−deprotect−cyclize (UDC) sequence, we assessed the robustness and scope of the developed methodology substituting glycine-Boc (**2a**) by a set of assorted protected amino acids (**2b−g**) as key reactive precursors (Scheme 3). The study capitalizes on the excellent commercial availability of enantiopure Boc-protected amino acids **2** to introduce functional and stereochemical diversity at position 3 of the heterocyclic framework. First we focused on the generation of collections of BZDs bearing a stereocenter at C3 (compounds **7**, Scheme 3). With this aim, amines **1a**,**b**, assorted isocyanides **3**, and either formaldehyde **4a** or a symmetric ketone **4d**,**e** were combined in the Ugi reaction with a set of structural and stereochemically diverse enantiopure Boc-protected amino acids **2b−g**. We were pleased to observe that only slight modifications of the previously optimized experimental protocol (Scheme 3) were required to verify the transformation of reactive partners of the U-4CR in the α-acylamino amides **5**. A slight excess (1.3 equiv) of the amine input (**1**) and longer reaction times (48−72 h) were required to achieve similar conversion ratios during the U-4CR, while maintaining mild experimental conditions.

As for previous series, smooth cleavage of the protecting group on the Ugi adducts **5** employing TFA (DCE/60 °C) afforded BZDs **7** in satisfactory overall yields (44−71%). Chiral-stationary HPLC analysis enabled us to verify that during the synthesis no racemization occurs at the stereocenter (ee > 99%; see the Supporting Information). Inspection of Scheme 3 provides a preliminary assessment of the reaction scope, which generates 1,4-benzodiazepin-2-one collections incorporating four points of diversity. As is observed, this scope encompasses the use of aliphatic as well as aromatic inputs of all variable components, not being influenced by the electronic and steric variations of the reacting substrates. Significant structural and stereochemical diversity is successfully provided by the amino acid partner **2**, as exemplified by a range of diverse amino acids (including proteinogenic or synthetic ones), some of them bearing challenging residues (e.g., compounds **7i**,**j**). The NMR data of this series reveal that, for steric reasons, the substituent at C3 is placed preferentially at the pseudoequatorial position (Figure 5). Hence, the 3*S* and 3*R* enantiomers will be locked in the *M* and *P* conformations, respectively. Indeed, the ^{1}H NMR spectra of all compounds **7** showed the resonances of a single diastereoisomer, with the H3 resonance around 3.5 ppm, which is a clear indication of its pseudoaxial position. Since a single set of signals is observed in the ^{1}H NMR spectrum, this means that only *M*,3*S* or *P*,3*R* isomers were obtained.

The structural assignment within the series was complemented by X-ray crystallography data obtained on monocrystals of two representative compounds (compounds **7p**,**u**; see the Supporting Information).[17]

The success achieved in previous series led us to evaluate the utilization of prochiral carbonyl components **4b**,**c**, which will engender the exocyclic stereocenter formed during the U-4CR (Scheme 4). Butyraldehyde (**4b**) and benzaldehyde (**4c**) were employed in combination with enantiopure N-Boc -protected amino acids **2b−g** and the other reactive partners (Scheme 4). These substrates were submitted to stirring at room temperature in methanol, affording the corresponding diastereomeric Ugi adducts (**5**) that were directly transformed into BZDs **8** following the Boc-cleavage−cyclization sequence induced by TFA (Scheme 4). The obtained compounds were purified (by either recrystallization or chromatography) and characterized by spectroscopic and analytical techniques, thus verifying the isolation of the desired BZDs **8** as 1:1 diastereomeric mixtures. Gratifyingly, the exhaustive scrutiny of solvent mixtures enabled us to separate a set of representative diastereomeric pairs **8a−g**, employing conventional chromatographic methods. Comparative chiral HPLC analysis of pure samples of the diastereomeric mixture and the optically pure diastereoisomers confirmed the optical purity of both pairs.

Due to the difficulties in assigning the configuration of the BZDs of the series **8**, and taking into account that important changes in chemical shifts were observed between the diasteroisomeric pairs, we decided to resort to DFT computations as a procedure for the assignment of the relative configurations of the obtained diasteroisomers **8**. In the past decade DFT ab initio chemical shift computations[18] have gradually gained importance in the toolbox used by organic chemists for configurational and conformational analysis through NMR in solution. These studies can be carried out at very affordable computer times and, with enough accuracy, can be successfully employed to distinguish diastereoisomeric structures, even in the presence of conformational flexibility.[19] In the case of flexible molecules, such as the ones treated herein, the determination of the configuration is commonly coupled to the determination of the preferred conformational state. We have therefore explored the conformational space of four representative stereoisomers (**8b1**,**b2** and **8d1**,**d2**) by means of molecular mechanics Monte Carlo calculations. The obtained molecular mechanics structures were refined at the DFT RI-OPBE level (see the Experimental Section for detailed computational procedures). In accordance with NMR observations the BZD ring is conformationally locked into the boat conformation, where the alkyl group at C3 is placed at the equatorial position. Computations show that the conformation of the N1 side chain is dictated by the formation of an intramolecular hydrogen bond between the azepine carbonyl group at C2 and the NH group, which builds a new seven-membered ring. The two rings adopt a convex−concave disposition as the lowest energy form. Thus, the basal conformation for the 3*S*,10*R* isomer corresponds to a pseudoaxial disposition of the side-chain phenyl group but a pseudoequatorial disposition in the case of the 3*S*,10*S* form

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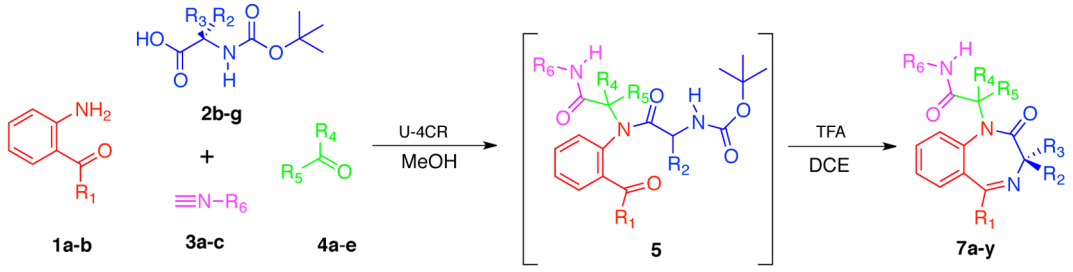
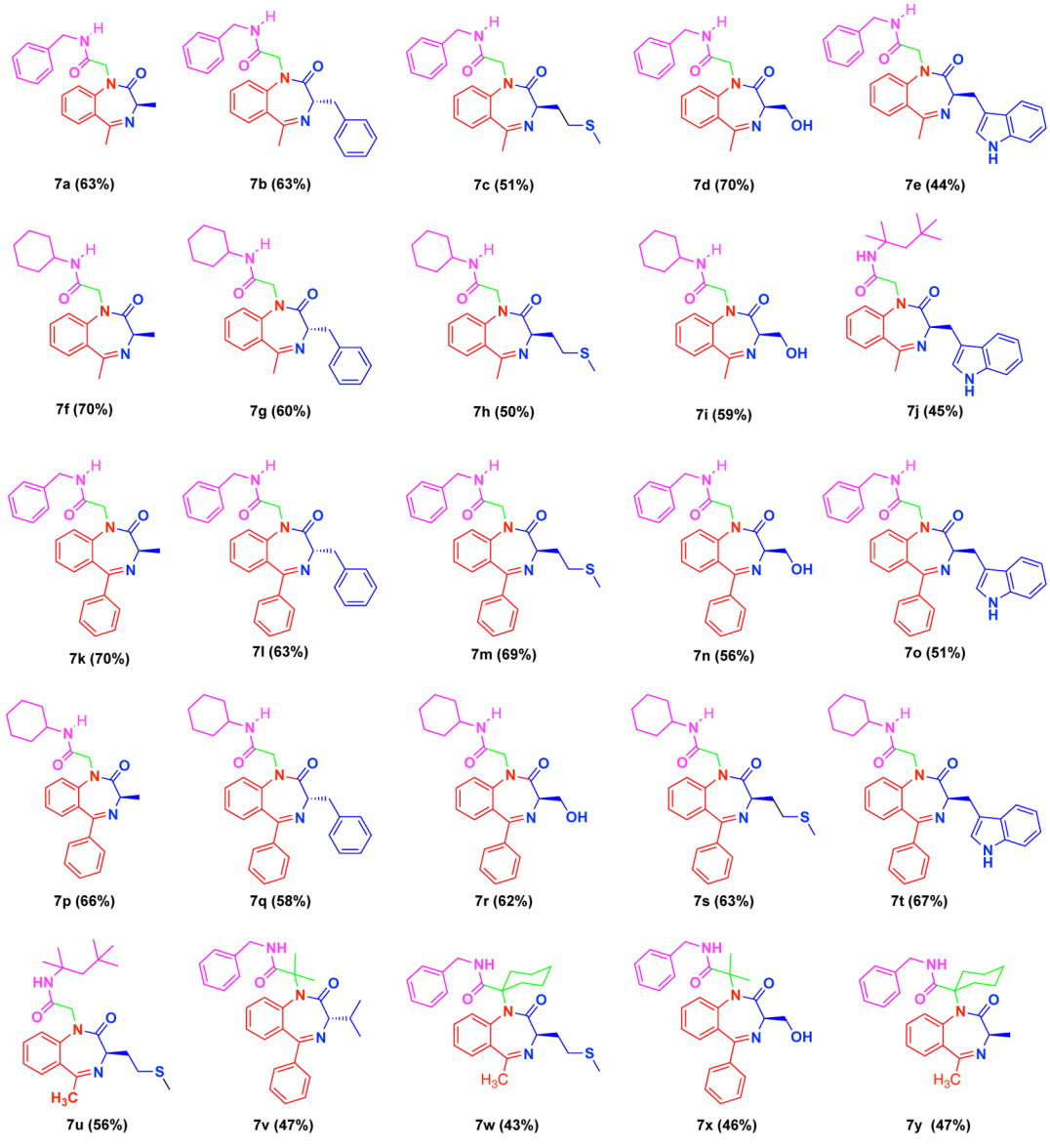
Scheme 3. U-4CR-Based Assembly of Enantiopure BZDs Incorporating Functional and Stereochemically Diverse Groups at Position 3





(Figure 6). The presence of an intramolecular hydrogen bond between the NH and carbonyl C2 was confirmed experimentally by variable-temperature ^{1}H NMR in $CDCl_3$ solution, which yielded temperature coefficients of −1.4 ppb/K for compounds **8d1**,**d2**. Typically, values more positive than −4.5 ppb/K are considered to support an intramolecular H bond.[20]

^{1}H chemical shieldings were computed at the DFT/IGLO OPBE/pcS-1 level for the lowest energy DFT optimized conformation of each diastereoisomer. The computed shieldings were transformed into chemical shifts by computing shieldings for the tetramethylsilane molecule at the same level of theory. The most remarkable difference between the

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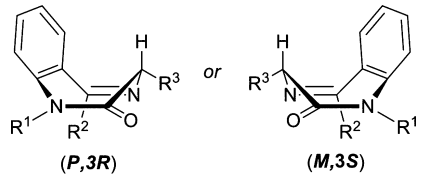
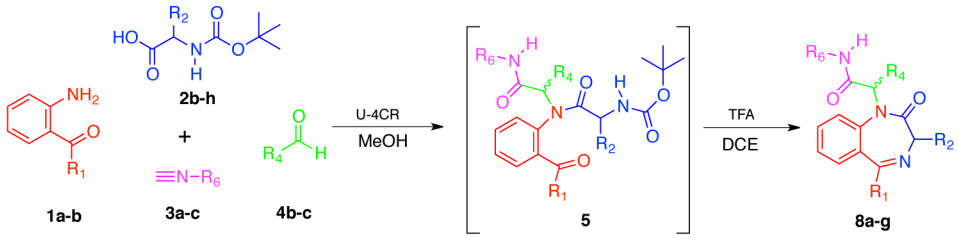
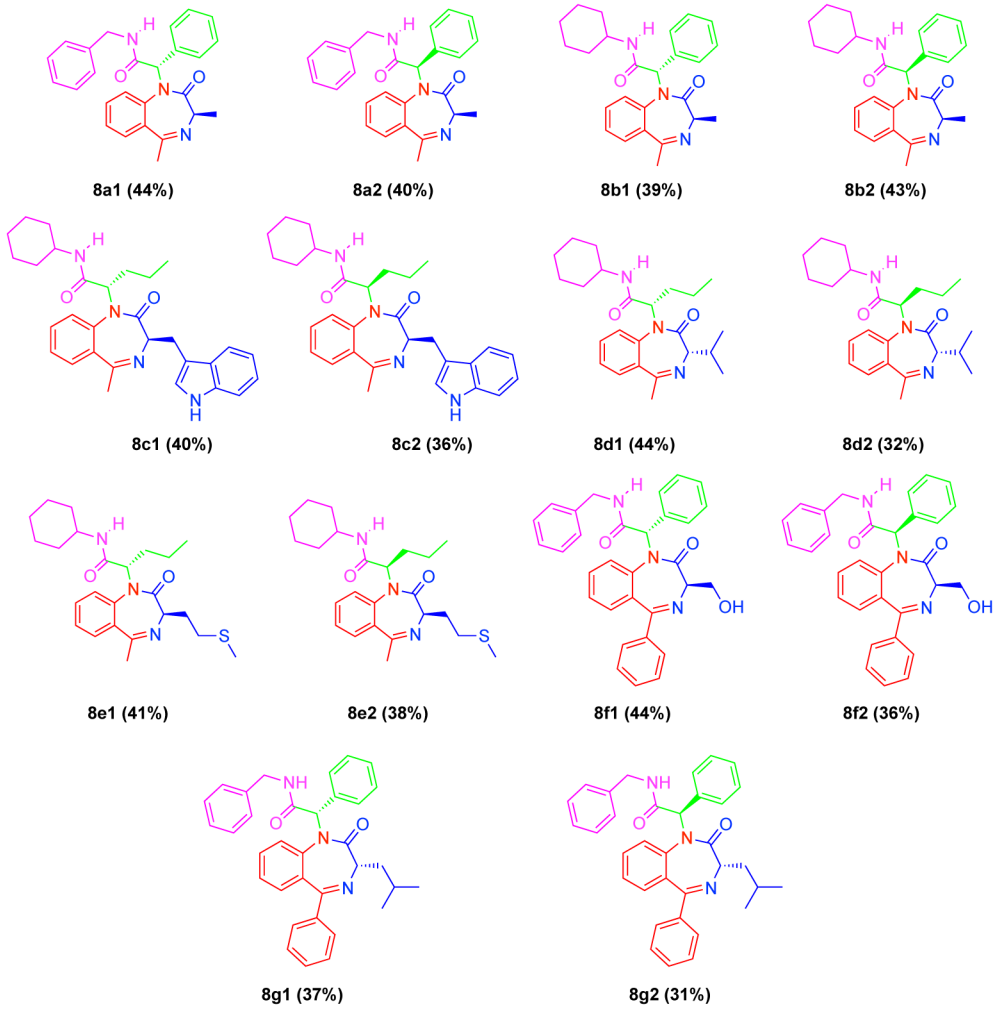


Figure 5. Preferred conformations of *P*,3*R* and *M*,3*S* enantiomers of 3-substituted benzodiazepines.

diastereoisomers is a strong change of the H10 resonance ($\Delta\delta$ = 0.38 and 0.88 ppm in **8b**,**d**, respectively) in the ^{1}H NMR spectra. This agrees with the DFT computations, which predicted the deshielding values $\Delta\delta$ = 0.39 ppm for (P,3*R*10*S*)-**8b1** vs (*P*,3*R*,10*R*)-**8b2** and $\Delta\delta$ = 1.00 ppm for (*M*,3*S*,10*R*)-**8d2** vs (*M*,3*S*,10*S*)-**8d1**. The NMR structural assignment within the series was corroborated by X-ray crystallography data obtained on a monocrystal of the diastereoisomer **8d2**.[21] Note that in the crystal the intramolecular hydrogen bond is no longer present and intermolecular H-bond contacts appear instead. As previously mentioned, the substituent at C3 is preferentially located on the pseudoequatorial position, fixing the BZD core at either the *M*,3*S* or the *P*,3*R* conformation. The isopropyl group adopts an antiperiplanar conformation around the H−C−C−H torsion angle. This is also the case in solution, as evidenced by a vicinal

Scheme 4. Ugi-Based Assembly of Diastereoisomeric BZDs 8





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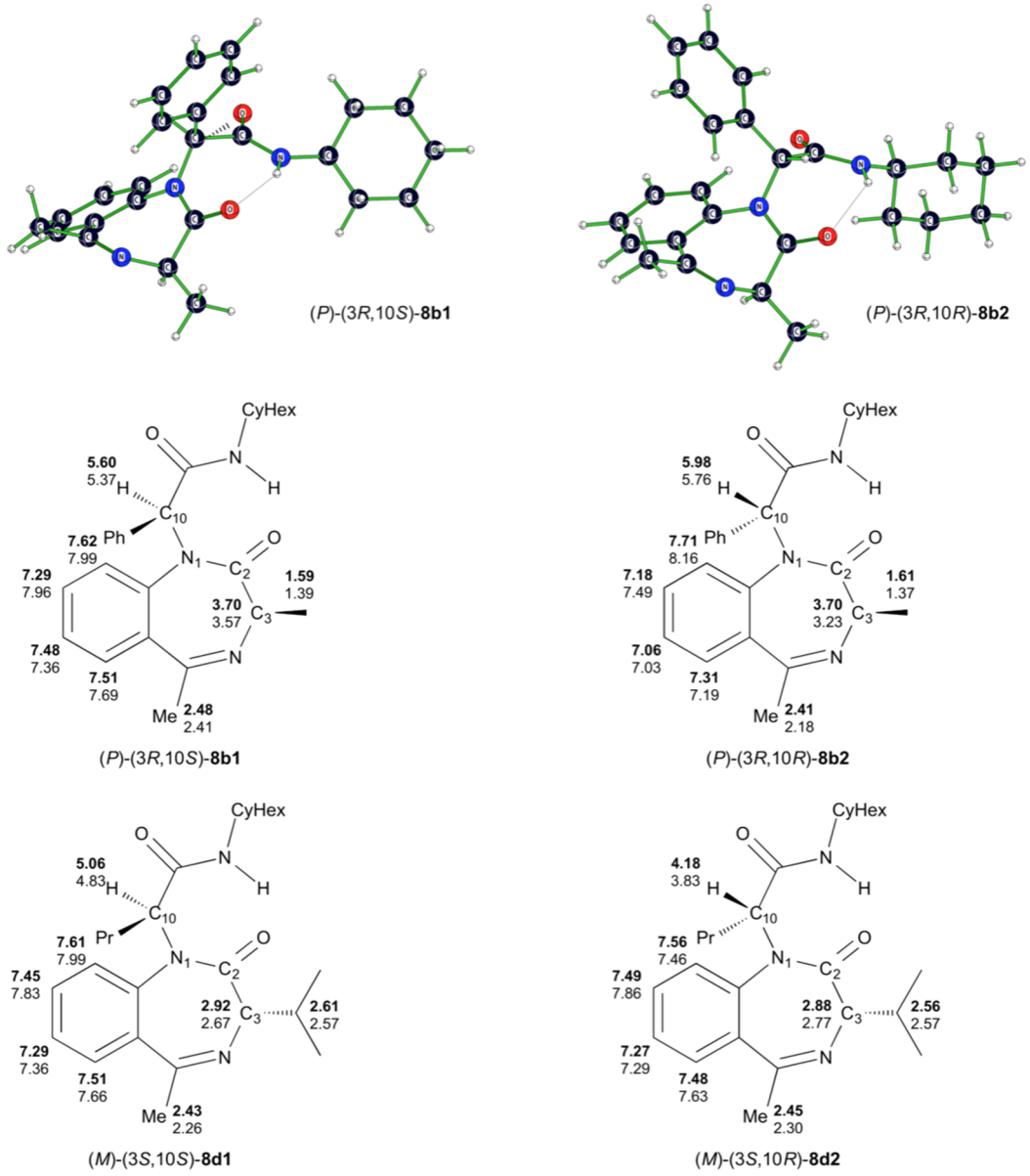

Figure 6. DFT-computed lowest energy conformations (top) for (*P*,3*R*,10*S*)-**8b1** and (*P*,3*S*,10*R*)-**8b2**. Selected experimental (in boldface type) vs computed (in Roman type) ^{1}H chemical shifts of compounds **8b** (middle) and **8d** (bottom).

coupling between H3 and the isopropyl methine proton of ∼10 Hz in both isomers **8d1** and **8d2**.

As significant differences in the deshielding of the H10 resonance are features common to all diastereomeric pairs synthesized herein, we used this diagnostic signal to assign the configuration at C10 for compounds **8**. Supported by the DFT calculations performed (for **8b1**,**b2**,**d1**,**d2**), as well as by the X-ray diffraction analysis of **8d2**, we assumed that the signal for H10 is more deshielded for the *P*,3*R*,10*R* or *M*,3*S*,10*S* compound than for the corresponding *P*,3*R*,10*S* or *M*,3*S*,10*R* diastereoisomer. The assignment of the relative configuration at C10 of compounds **8** is presented in Table 1.

To further challenge the robustness and versatility of the herein documented U-4CR-based strategy, the assembly of BZDs exhibiting challenging substitution patterns at position 3 of the heterocyclic backbone was briefly explored (Scheme 5). It should be noted that, although large and diverse BZD libraries are available, 1,4-benzodiazepin-2-ones featuring quaternary centers at position 3, particularly spiranic compounds derived from this heterocyclic core, have been only rarely described.[5,6] To the best of our knowledge, there are no precedents of 1,4-benzodiazepin-2-ones featuring the substitu-

Table 1. Assignment of C10 Configuration on Compounds 8 on the Basis of Chemical Shifts of H10

δ(H10), ppm/configuration	
diastereoisomer 1	diastereoisomer 2
5.68/(*P*,3*R*,10*S*)-**8a1**	6.12/(*P*,3*R*,10*R*)-**8a2**
5.58/(*P*,3*R*,10*S*)-**8b1**[a]	6.00/(*P*,3*R*,10*R*)-**8b2**[a]
4.16/(*P*,3*R*,10*S*)-**8c1**	5.09/(*P*,3*R*,10*R*)-**8c2**
5.05/(*M*,3*S*,10*S*)-**8d1**[a]	4.17/(*M*,3*S*,10*R*)-**8d2**[a,b]
4.18/(*P*,3*R*,10*S*)-**8e1**	4.99/(*P*,3*R*,10*R*)-**8e2**
5.80/(*P*,3*R*,10*S*)-**8f1**	6.16/(*P*,3*R*,10*R*)-**8f2**
6.27/(*M*,3*S*,10*S*)-**8g1**	5.79/(*M*,3*S*,10*R*)-**8g2**

[a]Predicted by DFT calculations. [b]Confirmed by XRD.

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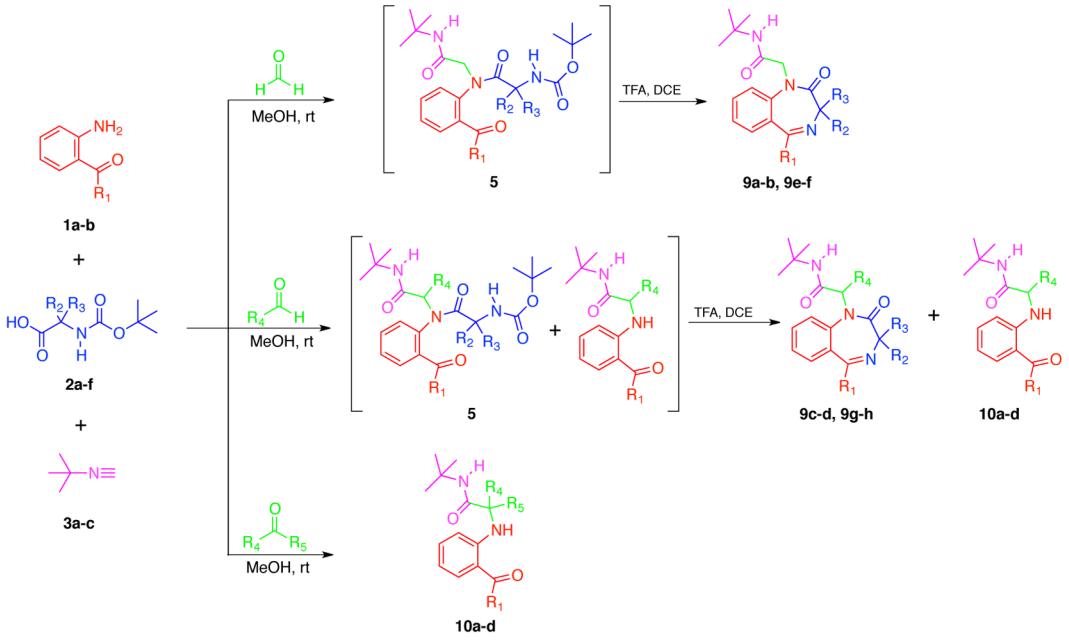
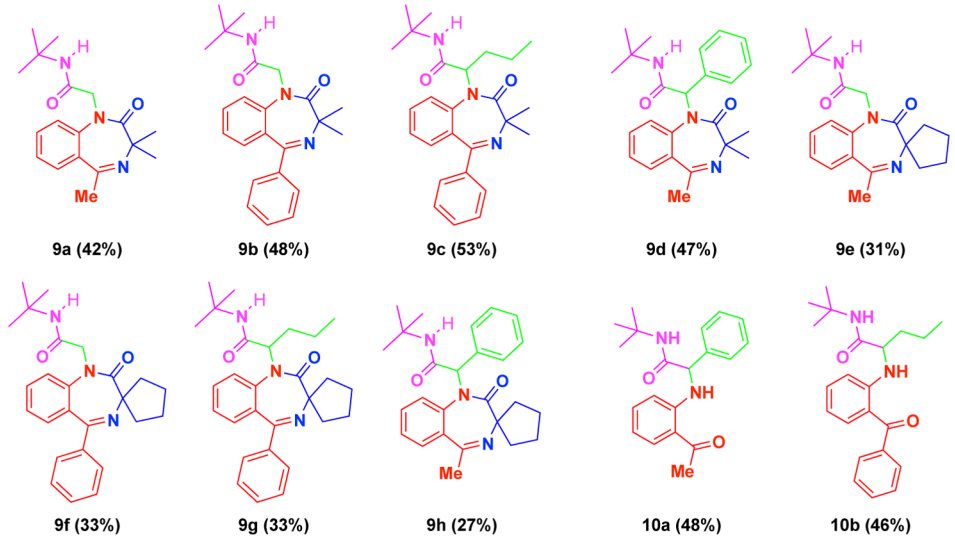
Scheme 5. Ugi-Based Assembly of 1,4-Benzodiazepin-2-ones Featuring Quaternary Centers at C3





tion patterns documented herein (e.g., 3,3-disubstituted and functionalized at position 1, compounds **9**), with close analogues requiring linear multistep synthetic strategies that require harsh experimental conditions not compatible with functionalized frameworks.[5,6] Since the introduction of these substitution patterns is expected to profoundly modify the structural features of the heterocyclic core, and accordingly its pharmacological profile, novel methods providing a rapid and experimentally simple entry to these chemotypes remain a highly pursued methodological challenge.

Two sterically hindering *N*-Boc-protected carboxylic acids (e.g., 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid (**2i**) and 1-((*tert*-butoxycarbonyl)amino)-cyclopentanecarboxylic acid (**2j**)) were selected as model substrates to study the proposed U-4CR sequence (Scheme 5), in combination with the precursors employed along this study (e.g., amines **1a,b**, *tert*-butyl isocyanide **3c**, and the four carbonyl components **4a,d**). The information contained in Scheme 5 reveals novel reactivity facets of the Ugi-based BZD assembly described herein, while exemplifying its contribution in terms of rapid access to complex and hitherto unexplored diversity spaces. The preliminary screening of the transformation revealed a significant decrease in the reactivity profile and scope of the previous respective series (Schemes 2−4), with the reaction behavior being highly dependent on the starting carbonyl compound (Scheme 5). Thus, the aldehydes evaluated (formaldehyde, butyraldehyde, and benzaldehyde) smoothly underwent the U-4CR, albeit with a reduced efficiency with respect to previous series, affording the corresponding Ugi adducts that were subsequently cyclized (Scheme 5). It should be noted that isolated yields of BZDs **9** range from moderate to satisfactory (35−52%), clearly

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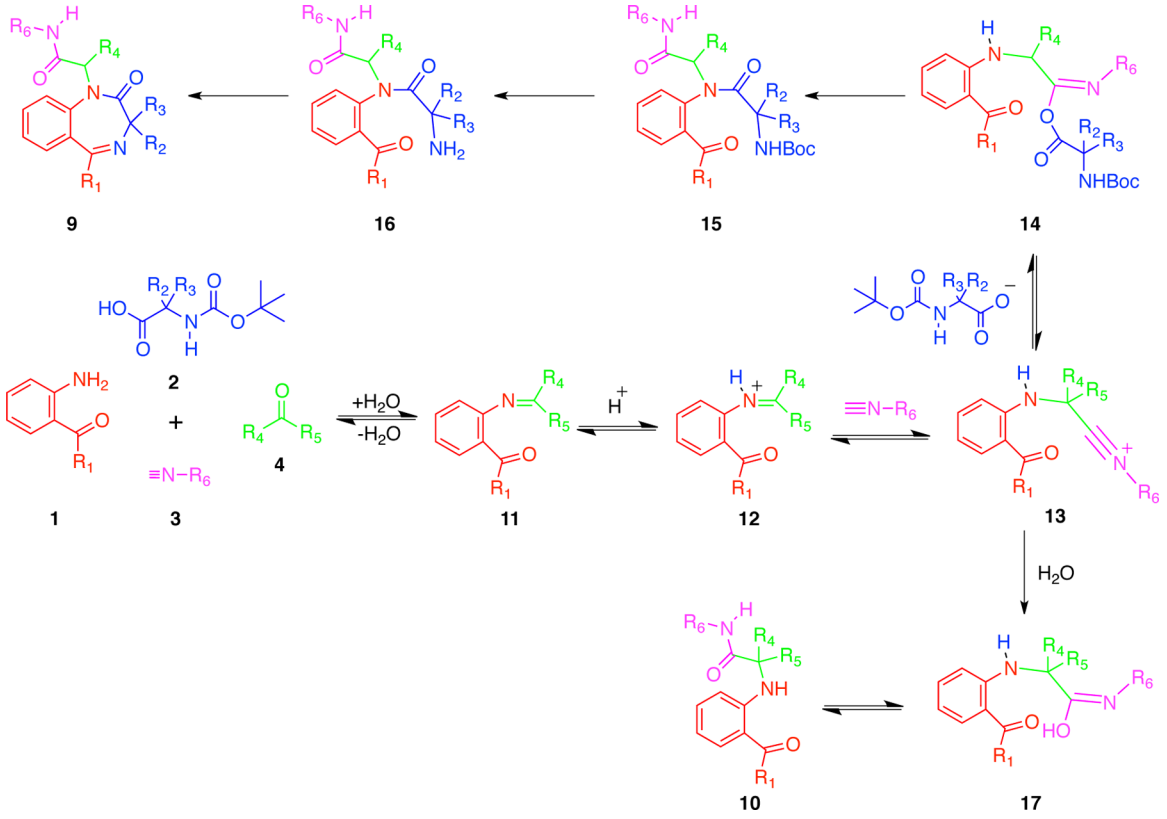
Scheme 6. Mechanistic Proposal for the Ugi-Based Assembly of 3,3-Substituted 1,4-Benzodiazepin-2-ones



correlating with the steric hindrance within the starting aldehyde (Scheme 5). In clear contrast, the U-4CR employing ketones (propanone and cyclohexanone) failed to provide the desired Ugi adducts (Scheme 5), exclusively affording keto aminoacetamides **10** (43−66%) and variable amounts of the unreacted precursors. All attempts to improve these results, by varying the reagent ratio, solvents (EtOH, CF_3CH_2OH, toluene, DCM), and temperatures (45, 60 °C), did not modify the reaction outcome. With the exception of U-4CR that employed formaldehyde as the carbonyl component, all transformations employing **2i,j** afforded variable amounts of substituted keto aminoacetamides **10**, which becomes the only isolated reaction product when employing ketones. Such an experimental outcome, not observed for the less congested amino acids (Schemes 2−5), clearly reflects the attack of the substituted carboxylic acid (carboxylate to be more precise) at the sterically hindered nitrilium ion intermediates to be impossible. It should also be noted that the steric factors of the starting amine (R_1 = Me, Ph) do not affect significantly the viability of the reaction (Scheme 5).

Although it is premature to propose a detailed mechanism at this stage, a plausible mechanistic proposal, consistent with the experimental results described above, is presented in Scheme 6. The overall transformation would start with formation of imine **11** and its subsequent protonation, thus generating the iminium ion **12**, which rapidly undergoes nucleophilic addition of the isocyanide to generate the highly reactive nitrilium **13**. At this point of the transformation the steric hindrance on the nitrilium ion intermediate **13** governs the reaction outcome. Thus, less congested nitrilium adducts (R_4 = R_5 = H) follow the normal course of the U-4CR (e.g., carboxylate insertion to give **14** and then Mumm rearrangement) to afford the expected Ugi adducts **15**, which upon acid-mediated cleavage generate the targeted BZDs **9**. In contrast, for nitrilium ions **13** derived of butyraldehyde, benzaldehyde or ketones the reaction behavior heavily depends of its substitution pattern at the acetamide linkage. The superior steric hindrance in these intermediates prevents the nucleophilc addition of the carboxylate ion (mainly in those derived from ketones); accordingly, a molecule of water could intercept the reactive nitrilium intermediate **17** to afford the isolated keto aminoacetamides **10**.

In summary, we have documented a convergent approach that enables the straightforward assembly of 1,4-benzodiazepin-2-ones exhibiting high skeletal, functional, and stereochemical diversity. This versatile integrated U-4CR-based strategy, which exhibits high bond-forming efficiency as well as structure and step economies, does not require advanced intermediates, anhydrous solvents, or transition-metal catalysts, thus exemplifying the reconciliation of molecular complexity and functional diversity with experimental simplicity. Further work is in progress in our laboratories to apply this method to the synthesis of novel BZD derivatives and complete the pharmacological evaluation of the library documented herein.

EXPERIMENTAL SECTION

Commercially available starting materials and reagents were purchased and used without further purification from freshly opened containers. All solvents were purified and dried by standard methods. Organic extracts were dried with anhydrous sodium sulfate. The reactions were monitored by TLC and, unless stated otherwise, UV light and/or iodine vapor were used for the detection of compounds. The synthesis and purification of all compounds were accomplished using the equipment routinely available in organic chemistry laboratories. Most of the preparative experiments were performed in coated vials on an organic synthesizer with orbital stirring. Purification of isolated products was carried out by recrystallization or chromatographic methods. Reported yields correspond to the mean of two synthetic

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experiments. Compounds were routinely characterized by spectroscopic and analytical methods. Melting points were determined on a melting point apparatus and are uncorrected. The chemical structures of the obtained compounds were characterized by nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C) and high-resolution mass spectra (ESI-TOF). Unless otherwise quoted, NMR spectra were recorded in $CDCl_3$. Chemical shifts are given as δ values against tetramethylsilane as internal standard, and J values are given in Hz. All NMR experiments were carried out at 298 K on a spectrometer operating at 600.13 MHz for ^{1}H, 150.90 MHz for ^{13}C, and 90.56 MHz for ^{2}H, equipped with a triple resonance inverse (TXI) room-temperature probe with Z-only gradients. ^{1}H and ^{13}C resonances of (*R*,*S*)-**8b1**, (*R*,*R*)-**8b2**, (*S*,*S*)-**8d1**, and (*S*,*R*)-**8d2** were assigned from ge-HSQC, ge-HMBC, and ge-COSY experiments recorded at 298 K on a spectrometer operating at 600.13 MHz for 1H, and 150.90 MHz for ^{13}C, equipped with a triple resonance inverse (TXI) room-temperature probe with Z-only gradients. Shifts were referenced to the corresponding $CDCl_3$ (7.26 ppm) and $CDCl_3$ peaks (77.0 ppm). The enantiomeric (or diastereomeric) excesses were determined by chiral-stationary phase HPLC, employing variable mixtures (90/10, 80/20, or 70/30) of *n*-hexane and isopropyl alcohol. The temperature of the column was maintained at 20 °C with flow rates of 0.5−0.8 mL min^{-1}. The eluent was monitored at a wavelength of 200−300 nm. The conformational spaces of the diastereoiosomers were explored using the Monte Carlo torsional procedure as implemented in the Macromodel 9.1 software package using the MMFF94 force field. The lowest MMFF94 energy structures were refined at the RI[22]-DFT BP86 level using the defbas-1 basis set[23] (QuickOpt option in the ORCA package) and the def2-TZV auxiliary basis set.[24] Chemical shifts were computed at the IGLO[25] RI-OPBE[26]/pcS-1[27] level for the lowest energy DFT optimized conformation of each diastereoisomer. The SV/J auxiliary basis set was employed for density fitting. Solvation was taken into account using the COSMO model.[28] The computed shieldings were transformed into chemical shifts by computing shieldings for the tetramethysilane and benzene molecules at the same level of theory. The benzodiazepine aromatic protons were referenced according to benzene shielding, whereas the rest of protons were referenced to TMS. The shifts were computed according to the relationship

$$\delta_{calcd} = \frac{\sigma_{ref} - \sigma_{calcd}}{1 - \sigma_{ref}}$$

where σ_{ref} and σ_{calcd} are the shieldings computed for the reference proton nuclei and the proton of interest in the benzodiazepine. All computations were performed using the Orca 2.9 software package.[29]

General Procedure for the One-Pot Synthesis of 1,4-Benzodiazepin-2-ones 6−9. A mixture of the carbonyl compound (1.0 mmol), the amine (1.3 mmol), the isocyanide (1.0 mmol), and the protected amino acid (1.0 mmol) in MeOH (3 mL) was submitted to orbital stirring at room temperature for 48−72 h. After completion of the reaction, CH_2Cl_2 (3 mL) and PS-*p*-TsOH (2.0 mmol) were added. The reaction mixture was submitted to orbital stirring at room temperature until complete consumption of the unreacted isocyanide (30−60 min). The polymeric reagent was filtered off and successively washed (two times (4 mL)) with MeOH, AcOEt, and CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a residue, which was treated with 20% TFA in DCE (and heated to 60 °C for 1 h). The obtained solution was then treated with saturated $NaHCO_3$. After extraction with ethyl acetate, the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to afford an oily residue that was purified by chromatographic methods on silica gel using hexane/AcOEt mixtures.

*N-Benzyl-2-(5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)acetamide (**6a**):* 193 mg, 60% yield; mp 159−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.63−7.54 (m, 1H), 7.54−7.45 (m, 2H), 7.41−7.10 (m, 7H), 6.77 (d, J = 6.1 Hz, 1H), 4.64 (d, J = 15.5 Hz, 1H), 4.57−4.43 (m, 2H), 4.36 (dd, J = 14.8, 5.4 Hz, 1H), 4.15 (d, J = 15.5 Hz, 1H), 3.66 (d, J = 12.0 Hz, 1H), 2.39 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.2, 170.1, 168.4, 141.1, 137.8, 131.6, 130.2, 128.7, 127.6, 127.6, 127.5, 125.3, 122.3, 55.9, 52.4, 43.6, 25.5; HRMS (ESI) m/z calcd for $C_{19}H_{20}N_3O_2$ $[M + H]^+$ 322.1550, found 322.1552.

*(±)-N-Benzyl-2-(5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-il)pentanamide (**6b**):* 189 mg, 52% yield; mp 127−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.71−7.09 (m, 9H), 5.02 (dd, J = 9.2, 6.4 Hz, 1H), 4.70−4.29 (m, 4H), 3.63 (dd, J = 11.2 Hz, 1H), 2.44 (d, J = 1.5 Hz, 3H), 1.80 (ddt, J = 14.2, 9.8, 6.3 Hz, 1H), 1.35 (dtd, J = 14.2, 9.4, 4.9 Hz, 1H), 1.15−0.78 (m, 2H), 0.71 (q, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.6, 171.4, 170.2, 138.1, 137.5, 130.6, 128.6, 127.5, 127.4, 127.2, 125.9, 124.4, 57.5, 56.3, 43.6, 29.5, 25.2, 18.9, 13.5; HRMS (ESI) m/z calcd for $C_{22}H_{26}N_3O_2$ $[M + H]^+$ 364.2020, found 364.2020.

*(±)-N-Benzyl-2-(5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)-2-phenylacetamide (**6c**):* 266 mg, 67% yield; mp 167−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$, conformers are present) δ (ppm) 7.82−6.91 (m, 14H), 6.84 (t, J = 5.8 Hz, 0.38H), 6.56 (t, J = 5.7 Hz, 0.74H), 6.03 (s, 0.54H), 5.67 (s, 0.35 H), 4.70−4.36 (m, 3H), 3.72 (d, J = 11.0, 1H), 2.42 (dd, J = 7.4, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.78, 170.47, 170.41, 170.12, 169.40, 169.17, 141.65, 139.01, 137.79, 134.39, 134.10, 131.88, 131.32, 130.20, 129.10, 128.77, 128.69, 128.62, 128.55, 128.45, 128.22, 128.16, 127.66, 127.60, 127.56, 127.53, 127.46, 127.34, 127.26, 126.95, 126.58, 126.52, 125.77, 125.48, 125.43, 123.81, 69.52, 65.26, 56.65, 56.30, 43.94, 43.86, 25.20; HRMS (ESI) m/z calcd for $C_{25}H_{24}N_3O_2$ $[M + H]^+$ 398.1863, found 398.1855.

*N-Benzyl-2-methyl-2-(5-methyl-2-oxo-2,3-dihydro-1H-benzo[e]-[1,4]diazepin-1-yl)propanamide (**6d**):* 154 mg, 44% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.59−7.11 (m, 9H), 6.73−6.32 (m, 1H), 4.64−4.16 (m, 3H), 3.56 (d, J = 11.6, 1.6 Hz, 1H), 2.37 (d, J = 1.6 Hz, 3H), 1.54 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)174.2, 173.2, 169.9, 138.5, 138.2, 133.3, 129.8, 128.6, 127.8, 127.4, 126.6, 126.4, 126.2, 63.9, 57.5, 44.1, 26.8, 25.9, 24.8; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3O_2$ $[M + H]^+$: 350.1863, found 350.1863.

*N-Benzyl-1-(5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)cyclohexanecarboxamide (**6e**):* 230 mg, 59% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.24−7.79 (m, 1H), 7.58−7.09 (m, 9H), 4.4.56 (dd, J = 14.9, 6.1 Hz, 1H), 4.45 (dd J = 14.9, 5.4 Hz, 1H), 4.37 (d, J = 12.8 Hz, 1H), 3.64 (d, J = 12.8 Hz, 1H), 3.32−2.93 (m, 1H), 2.48 (s, 3H), 1.85−0.99 (m, 8H), 0.82−0.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 177.3, 175.2, 170.3, 139.2, 138.4, 133.3, 129.9, 128.6, 127.5, 127.2, 126.5, 126.4, 126.0, 66.9, 58.2, 43.7, 32.7, 32.4, 25.0, 24.8, 21.7, 20.7; HRMS (ESI) m/z calcd for $C_{24}H_{28}N_3O_2$ $[M + H]^+$ 390.2176, found 390.2170.

*N-Benzyl-2-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)acetamide (**6f**):* 268 mg, 70% yield; mp 217−219 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69 (dd, J = 8.4, 1.1 Hz, 1H), 7.63−7.48 (m, 3H), 7.49−7.03 (m, 10H), 6.82−6.57 (m, 1H), 4.82 (d, J = 10.7 Hz, 1H), 4.64 (d, J = 15.5 Hz, 1H), 4.55−4.21 (m, 3H), 3.85 (d, J = 10.6 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.7, 170.3, 168.4, 142.8, 138.6, 137.7, 131.9, 130.5, 130.5, 129.5, 128.9, 128.6, 128.3, 127.5, 127.4, 124.8, 122.1, 56.6, 52.2, 43.5; HRMS (ESI) m/z calcd for $C_{24}H_{22}N_3O_2$ $[M + H]^+$ 384.1707, found 384.1713.

*(±)-N-Benzyl-2-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)pentanamide (**6g**):* 268 mg, 63% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.85−7.05 (m, 14H), 5.04 (dd, J = 9.2, 6.3 Hz, 1H), 4.78 (dd, J = 10.9, 0.6 Hz, 1H), 4.71−4.27 (m, 3H), 3.80 (dd, J = 10.9, 7.5 Hz, 1H), 2.02−1.72 (m, 1H), 1.63−1.27 (m, 1H), 1.17−0.82 (m, 2H), 0.67 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.7, 171.5, 170.4, 139.5, 138.2, 138.1, 131.0, 130.7, 130.7, 130.1, 129.4, 129.3, 128.6, 128.4, 128.3, 127.5, 127.4, 127.3, 125.4, 124.4, 57.7, 57.0, 43.6, 29.8, 19.1, 13.6; HRMS (ESI) m/z calcd for $C_{27}H_{28}N_3O_2$ $[M + H]^+$ 426.2176, found 426.2165.

*(±)-N-Benzyl-2-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)-2-phenylacetamide (**6h**):* 285 mg, 62% yield; mp 203−204 °C; ^{1}H NMR (300 MHz, $CDCl_3$, conformers are present) δ (ppm) 7.75 (dd, J = 8.3, 1.2 Hz, 1H), 7.42−6.74 (m, 18H), 6.68 (t, J = 5.9 Hz, 0.25 H), 6.61−6.42 (m, 0.81H), 6.02 (d, J = 2.1 Hz, 0.74H), 5.60 (d, J = 2.0 Hz, 0.22 H), 4.61 (dd, J = 10.7, 6.4 Hz, 1H), 4.53−4.15 (m, 2H), 3.71 (dd, J = 10.7, 1.9 Hz, 1H); ^{13}C NMR (300 MHz,

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$CDCl_3$) δ (ppm) 171.0, 170.5, 169.3, 140.0, 138.4, 137.6, 134.1, 130.3, 130.2, 129.4, 129.4, 129.2, 129.1, 128.7, 128.6, 128.5, 128.2, 128.2, 128.1, 128.0, 127.6, 127.4, 127.3, 127.2, 127.0, 125.9, 124.8, 64.1, 56.9, 43.8; HRMS (EI) m/z calcd for $C_{30}H_{25}N_3O_2$ $[M]^+$ 459.1947, found 459.1950.

*N-Benzyl-2-methyl-2-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)propanamide (**6i**):* 185 mg, 45% yield; mp 213−215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.81−7.57 (m, 2H), 7.56−7.00 (m, 12H), 6.84−6.54 (m, 1H), 4.66 (d, J = 11.4 Hz, 1H), 4.44 (dd, J = 14.7, 6.1 Hz, 1H), 4.28 (dd, J = 14.7, 5.1 Hz, 1H), 3.76 (d, J = 11.5 Hz, 1H), 1.56 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.2, 173.6, 167.0, 140.6, 138.0, 137.8, 132.0, 130.7, 130.1, 129.0, 128.5, 127.6, 127.2, 126.2, 63.9, 58.4, 43.9, 26.8, 26.2; HRMS (ESI) m/z calcd for $C_{26}H_{26}N_3O_2$ $[M + H]^+$ 412.2020, found 412.2031.

*N-Benzyl-1-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)cyclohexanecarboxamide (**6j**):* 212 mg, 47% yield; mp 225−226 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.81 (t, J = 6.0 Hz, 1H), 7.77−7.66 (m, 2H), 7.65−7.38 (m, 5H), 7.38−7.17 (m, 7H), 4.77−4.53 (m, 2H), 4.46 (dd, J = 14.9, 5.5 Hz, 1H), 3.80 (d, J = 12.3 Hz, 1H), 2.96 (d, J = 13.1 Hz, 1H), 2.14−1.04 (m, 8H), 1.00−0.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 176.72, 175.09, 169.94, 141.23, 138.44, 137.38, 131.74, 130.74, 130.11, 129.20, 128.95, 128.64, 128.42, 127.54, 127.27, 126.72, 125.94, 66.85, 58.84, 43.73, 32.43, 29.69, 24.85, 21.85, 21.14; HRMS (CI) m/z calcd for $C_{29}H_{30}N_3O_2$ $[M + H]^+$ 452.2338, found 452.2344.

*N-Cyclohexyl-2-(5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)acetamide (**6k**):* 194 mg, 62% yield; mp 202−203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.97−7.36 (m, 3H), 7.26 (t, J = 7.5 Hz, 1H), 6.30 (d, J = 8.3 Hz, 1H), 4.76−4.35 (m, 2H), 4.07 (d, J = 15.3 Hz, 1H), 3.90−3.53 (m, 2H), 2.48 (s, 3H), 2.20−0.82 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.1, 170.1, 167.5, 141.2, 131.6, 130.2, 127.5, 125.3, 122.4, 56.0, 52.7, 48.4, 32.8, 25.6, 25.4, 24.7; HRMS (CI) m/z calcd for $C_{18}H_{24}N_3O_2$ $[M + H]^+$ 314.1869, found 314.1864.

*(±)-N-Cyclohexyl-2-(5-methyl-2-oxo-2,3-dihydro-1H-benzo[e]-[1,4]diazepin-1-yl)pentanamide (**6l**):* 192 mg, 54% yield; mp 128−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69−7.52 (m, 1H), 7.53−7.38 (m, 2H), 7.34−7.23 (m, 1H), 6.85 (d, J = 8.1 Hz, 1H), 4.92 (dd, J = 9.2, 6.4 Hz, 1H), 4.52 (d, J = 11.2 Hz, 1H), 3.78 (m, 1H), 3.64 (d, J = 11.2, 1H), 2.44 (s, 3H), 2.07−1.46 (m, 5H), 1.46−0.81 (m, 9H), 0.70 (q, J = 7.7, 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.9, 170.7, 170.3, 137.9, 132.3, 130.8, 127.3, 126.0, 124.6, 57.8, 56.6, 48.4, 32.9, 29.6, 25.7, 25.5, 24.8, 19.1, 13.7; HRMS (CI) m/z calcd for $C_{21}H_{30}N_3O_2$ $[M + H]^+$ 356.2338, found 356.2337.

*(±)-N-(Cyclohexyl)-2-(5-methyl-2-oxo-2,3-dihydro-1H-benzo[e]-[1,4]diazepin-1-yl)-2-phenylacetamide (**6m**):* 248 mg, 65% yield; mp 187−189 °C, ^{1}H NMR (300 MHz, $CDCl_3$, conformers are present) δ (ppm) 7.80−7.52 (m, 1H), 7.53−7.37 (m, 1H), 7.37−6.94 (m, 7H), 6.47 (d, J = 8.1 Hz, 0.34 H), 6.10 (d, J = 8.0 Hz, 0.61H), 5.95 (s, 0.56H), 5.58 (s, 0.37H), 4.49 (t, J = 11.3 Hz, 1H), 4.12−3.52 (m, 2H), 2.44 (dd, J = 25.4, 1.5 Hz, 3H), 2.04−1.46 (m, 5H), 1.47−0.89 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.72, 170.51, 170.39, 170.10, 168.43, 168.14, 141.80, 139.04, 134.69, 134.45, 131.85, 131.27, 130.16, 129.01, 128.86, 128.65, 128.54, 128.37, 128.20, 128.03, 128.00, 127.05, 126.89, 126.44, 125.71, 125.54, 125.39, 123.81, 69.65, 65.23, 56.69, 56.32, 48.91, 48.66, 32.79, 32.70, 32.55, 32.48, 25.47, 25.25, 25.18, 24.74, 24.63; HRMS (CI) m/z calcd for $C_{24}H_{28}N_3O_2$ $[M + H]^+$ 390.2182, found 390.2186.

*N-(tert-Butyl)-2-methyl-2-(5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)propanamide (**6n**):* 154 mg, 49% yield; mp 166−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.56−7.38 (m, 2H), 7.36−7.29 (m, 2H), 5.99 (brs, 1H), 4.42 (d, J = 11.7 Hz, 1H), 3.58 (d, J = 11.7, 1H), 2.52 (s, 3H), 1.54 (s, 3H), 1.36 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.43, 173.17, 169.87, 138.79, 133.09, 129.95, 126.43, 126.40, 125.83, 64.31, 57.77, 51.01, 28.39, 27.33, 25.24, 25.13; HRMS (CI) m/z calcd for $C_{18}H_{26}N_3O_2$ $[M + H]^+$ 316.2025, found 316.2036.

*(±)-N-(tert-Butyl)-2-(5-methyl-2-oxo-2,3-dihydro-1H-benzo[e]-[1,4]diazepin-1-yl)-2-phenylacetamide (**6o**):* 218 mg, 60% yield; mp 196−198 °C; ^{1}H NMR (300 MHz, $CDCl_3$, conformers are present) δ (ppm) ^{1}H NMR (300 MHz,) δ (ppm) 7.66 (dd, J = 8.1, 1.2 Hz, 1H), 7.51−7.42 (m, 1H), 7.33−7.26 (m, 2H), 7.22−7.02 (m, 7H), 6.41−6.29 (m, 0.38H), 5.94 (s, 0.69H), 5.90 (s, 0.69H), 5.51 (s, 0.38H), 4.53 (dd, J = 11.0, 8.9 Hz, 1H), 3.73 (ddd, J = 10.9, 3.0, 1.6 Hz, 1H), 2.49 (d, J = 1.5 Hz, 1H), 2.41 (d, J = 1.5 Hz, 2H), 1.42 (s, 6H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, conformers are present) δ (ppm) 170.81, 170.46, 170.34, 170.09, 168.49, 141.82, 138.76, 134.75, 134.52, 131.87, 131.31, 131.21, 130.09, 129.04, 128.63, 128.45, 128.33, 127.94, 126.99, 126.87, 126.34, 125.85, 125.69, 125.34, 123.85, 70.24, 65.84, 65.54, 56.75, 56.39, 51.90, 51.54, 28.61, 28.44, 25.28, 25.23, 15.26; HRMS (CI) m/z calcd for $C_{22}H_{26}N_3O_2$ $[M + H]^+$ 364.2025, found 364.2021.

*N-Cyclohexyl-2-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)acetamide (**6p**):* 195 mg, 52% yield; mp 228−230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.66−6.89 (m, 9H), 6.07 (d, J = 8.2 Hz, 1H), 4.64 (d, J = 10.6 Hz, 1H), 4.37 (d, J = 15.5 Hz, 1H), 4.08 (d, J = 15.4 Hz, 1H), 3.67 (d, J = 10.6 Hz, 1H), 3.61−3.36 (m, 1H), 1.80−0.58 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.5, 170.1, 167.2, 142.8, 138.4, 131.7, 130.5, 130.2, 129.5 128.7, 128.1, 124.6, 122.2, 56.6, 52.3, 48.3, 32.4, 25.2, 24.5; HRMS (CI) m/z calcd for $C_{23}H_{26}N_3O_2$ $[M + H]^+$ 376.2025, found 376.2025.

*(±)-N-Cyclohexyl-2-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e]-[1,4]diazepin-1-yl)pentanamide (**6q**):* 280 mg, 67% yield; mp 153−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.91−7.30 (m, 7H), 7.30−7.11 (m, 2H), 6.88 (d, J = 8.1 Hz, 1H), 4.91 (dd, J = 9.1, 6.3 Hz, 1H), 4.77 (d, J = 10.9 Hz, 1H), 3.78 (dd, J = 10.9, 8.6 Hz, 2H), 2.06−0.76 (m, 14H), 0.64 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.68, 171.39, 170.54, 170.47, 170.42, 145.08, 139.61, 138.44, 138.23, 131.82, 130.95, 130.62, 130.50, 130.01, 129.74, 129.33, 129.13, 128.32, 128.27, 125.26, 125.03, 124.33, 123.48, 68.68, 57.92, 57.77, 56.99, 48.43, 48.24, 32.75, 32.69, 31.04, 29.69, 25.54, 25.49, 24.70, 24.66, 24.62, 19.48, 19.09, 13.56, 13.41; HRMS (CI) m/z calcd for $C_{26}H_{32}N_3O_2$ $[M + H]^+$ 418.2495, found 418.2491.

*(±)-N-Cyclohexyl-2-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e]-[1,4]diazepin-1-yl)-2-phenylacetamide (**6r**):* 253 mg, 56% yield; mp 207−209 °C; ^{1}H NMR (300 MHz, $CDCl_3$, conformers are present) δ (ppm) 7.95 (d, J = 8.3 Hz, 1H), 7.73−7.29 (m, 5H), 7.29−6.82 (m, 8H), 6.50 (d, J = 8.1 Hz, 0.24H), 6.24 (d, J = 8.0 Hz, 0.87H), 6.10 (s, 0.83H), 5.65 (s, 0.24H), 4.76 (d, J = 10.6 Hz, 1H), 4.09−3.64 (m, 2H), 2.22−0.88 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.99, 170.59, 170.41, 168.36, 143.69, 140.26, 138.69, 138.59, 134.61, 134.49, 131.55, 130.92, 130.41, 130.28, 130.04, 129.73, 129.49, 129.35, 129.28, 129.11, 128.68, 128.47, 128.29, 128.18, 127.97, 126.96, 126.15, 125.20, 124.82, 123.76, 69.76, 64.26, 57.42, 57.02, 49.03, 48.72, 32.82, 32.72, 32.51, 25.48, 24.80, 24.66; HRMS (CI) m/z calcd for $C_{29}H_{30}N_3O_2$ $[M + H]^+$ 452.2338, found 452.2334.

*N-(tert-Butyl)-2-methyl-2-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)propanamide (**6s**):* 174 mg, 46% yield; mp 231−233 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.67 (dd, J = 8.3, 1.5 Hz, 2H), 7.56−7.35 (m, 5H), 7.30 (dt, J = 4.6, 0.8 Hz, 2H), 5.76 (s, 1H), 4.67 (dd, J = 11.2, 0.7 Hz, 1H), 3.75 (dd, J = 11.2, 0.7 Hz, 1H), 1.64 (s, 3H), 1.33 (s, 3H), 1.02 (d, J = 0.8 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)173.33, 172.81, 170.06, 140.52, 137.93, 131.89, 130.96, 130.28, 129.05, 129.00, 128.54, 126.18, 125.73, 64.12, 58.47, 50.85, 27.96, 27.90, 24.74; HRMS (ESI) m/z calcd for $C_{23}H_{28}N_3O_2$ $[M + H]^+$ 378.2176, found 378.2174.

*N-(tert-Butyl)-1-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)cyclohexanecarboxamide (**6t**).* 184 mg, 44% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.81−7.65 (m, 2H), 7.57 (dd, J = 8.0, 0.9 Hz, 1H), 7.51−7.34 (m, 5H), 7.32−7.18 (m, 2H), 4.64 (d, J = 12.4 Hz, 1H), 3.80 (d, J = 12.3 Hz, 1H), 2.98−2.73 (m, 1H), 1.84−1.63 (m, 3H), 1.50−1.22 (m, 11H), 1.21−1.01 (m, 3H), 0.99−0.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 176.7, 174.2, 169.9, 141.4, 137.4, 131.7, 130.7, 130.2, 129.2, 129.0, 128.4, 126.5, 125.8, 67.5, 59.0, 51.0, 33.1, 32.9, 28.6, 24.9, 22.0, 21.3; HRMS (EI) m/z calcd for $C_{26}H_{31}N_3O_2$ $[M + H]^+$ 417.2416, found 417.2404.

*(R)-N-Benzyl-2-(3,5-dimethyl-2-oxo-2,3-dihydro-1H-benzo[e]-[1,4]diazepin-1-yl)acetamide (**7a**):* 224 mg, 63% yield; mp 211−213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.57−7.23 (m, 3H), 7.20−

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6.89 (m, 6H), 5.41 (brs, 1H), 4.45 (d, J = 15.7 Hz, 1H), 4.31 (dd, J = 14.9, 6.2 Hz, 1H), 4.13 (dd, J = 14.9, 5.4 Hz, 1H), 4.00 (d, J = 15.7 Hz, 1H), 3.45 (qd, J = 6.6, 1.7 Hz, 1H), 2.23 (s, 3H), 1.34 (d, J = 6.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 170.8, 169.6, 168.2, 140.9, 137.8, 132.1, 130.0, 128.5, 127.5, 127.4, 127.2, 125.2, 122.5, 57.2, 52.4, 43.4, 24.8, 16.3; HRMS (EI) m/z calcd for $C_{20}H_{21}N_3O_2$ $[M]^+$ 335.1634, found 335.1635.

*(S)-N-Benzyl-2-(3-benzyl-5-methyl-2-oxo-2,3-dihydro-1H-benzo-[e][1,4]diazepin-1-yl)acetamide (**7b**):* 259 mg, 63% yield; mp 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.55−7.29 (m, 3H), 7.27−6.91 (m, 12H), 6.62 (t, J = 5.5 Hz,1H), 4.58 (d, J = 15.5 Hz, 1H), 4.38 (dd, J = 14.9, 6.3 Hz, 1H), 4.28−3.98 (m, 2H), 3.76−3.36 (m, 2H), 3.24 (dd, J = 13.9, 6.7 Hz, 1H), 2.28 (d, J = 1.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 170.0, 168.3, 168.1, 140.5, 138.7, 137.7, 131.5, 130.6, 129.5, 128.6, 128.1, 127.5, 127.4, 127.3, 126.1, 125.2, 122.3, 64.2, 52.4, 43.4, 37.5, 25.3; HRMS (CI) m/z calcd for $C_{26}H_{26}N_3O_2$ $[M + H]^+$ 412.2025, found 412.2026.

*(R)-N-Benzyl-2-(5-methyl-3-(2-(methylthio)ethyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)acetamide (**7c**):* 202 mg, 51% yield; mp 185−186 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.82−7.42 (m, 4H), 7.41−7.04 (m, 5H), 6.70 (s, 1H), 4.71 (d, J = 15.2 Hz, 1H), 4.51 (dd, J = 14.9, 5.7 Hz, 1H), 4.39 (dd, J = 14.4, 4.9 Hz, 1H), 4.17 (d, J = 15.1 Hz, 1H), 3.63 (t, J = 6.4 Hz, 1H), 2.76−2.21 (m, 7H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.3, 168.6, 168.6, 140.7, 137.7, 131.7, 130.6, 128.7, 127.6, 127.5, 127.4, 125.3, 122.4, 61.3, 52.6, 43.6, 30.6, 30.4, 25.4, 15.3; HRMS (CI) m/z calcd for $C_{22}H_{26}N_3O_2S$ $[M + H]^+$ 396.1746, found 396.1747.

*(R)-N-Benzyl-2-(3-(hydroxymethyl)-5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)acetamide (**7d**):* 246 mg, 70% yield; mp 236−238 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.73−7.43 (m, 4H), 7.43−7.10 (m, 5H), 6.56 (d, J = 6.1 Hz, 1H), 4.65 (d, J = 15.4 Hz, 1H), 4.54 (dd, J = 14.9, 5.7 Hz, 1H), 4.38 (dd, J = 14.8, 5.0 Hz, 1H), 4.29−4.16 (m, 2H), 4.11 (dd, J = 11.5, 5.6 Hz, 1H), 3.66 (t, J = 6.0 Hz, 1H), 2.40 (d, J = 5.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.9, 169.6, 168.0, 140.4, 137.6, 131.8, 130.8, 128.7, 127.6, 127.4, 125.5, 122.5, 63.1, 62.7, 52.4, 43.7, 25.4; HRMS (CI) m/z calcd for $C_{20}H_{22}N_3O_3$ $[M + H]^+$ 352.1661, found 352.1665.

*(R)-2-(3-((1H-Indol-3-yl)methyl)-5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-dia-zepin-1-yl)-N-benzylacetamide (**7e**):* 198 mg, 44% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47−7.25 (m, 5H), 7.22−6.79 (m, 9H), 6.74 (s, 1H), 6.39 (s, 1H), 4.64 (d, J = 15.5 Hz, 1H), 4.33 (dd, J = 14.9, 6.3 Hz, 1H), 4.10 (dd, J = 14.9, 5.4 Hz, 1H), 3.96 (d, J = 15.4 Hz, 1H), 3.73−3.45 (m, 2H), 3.22 (dd, J = 13.6, 4.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.36, 168.62, 168.07, 140.59, 137.89, 135.77, 131.63, 130.58, 128.72, 127.75, 127.54, 127.48, 127.33, 125.26, 123.37, 122.28, 121.70, 119.07, 118.72, 112.45, 110.93, 63.87, 52.81, 43.54, 27.01, 25.39; HRMS (CI) m/z calcd for $C_{28}H_{27}N_4O_2$ $[M + H]^+$ 451.2134, found 451.2133.

*(R)-N-Cyclohexyl-2-(3,5-dimethyl-2-oxo-2,3-dihydro-1H-benzo-[e][1,4]diazepin-1-yl)acetamide (**7f**):* 229 mg, 70% yield; mp 242−244 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.82−7.37 (m, 2H), 7.26 (dd, J = 9.2, 5.8 Hz, 1H), 6.27 (d, J = 8.4 Hz, 1H), 4.57 (d, J = 15.3 Hz, 1H), 4.12 (d, J = 15.3 Hz, 1H), 3.89−3.38 (m, 2H), 2.47 (s, 3H), 2.12−0.93 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.5, 167.9, 167.5, 140.8, 131.5, 130.8, 127.2, 125.1, 122.5, 57.8, 52.8, 48.4, 32.8, 32.7, 25.5, 25.4, 24.6, 17.1; HRMS (ESI) m/z calcd for $C_{19}H_{26}N_3O_2$ $[M + H]^+$ 328.2020, found 328.2021.

*(S)-2-(3-Benzyl-5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)-N-cyclohexylacetamide (**7g**):* 242 mg, 60% yield; mp 160−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.50 (dq, J = 8.2, 6.8 Hz, 3H), 7.34−7.04 (m, 6H), 6.23 (d, J = 8.2 Hz, 1H), 4.66 (d, J = 15.2 Hz, 1H), 4.01 (d, J = 15.2 Hz, 1H), 3.81−3.53 (m, 3H), 3.30 (dd, J = 11.8, 3.7 Hz, 1H), 2.48 (s, 3H), 1.93−0.75 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 169.9, 168.2, 167.6, 140.7, 138.8, 131.6, 130.5, 129.6, 128.2, 127.4, 126.1, 125.2, 122.4, 64.5, 53.1, 48.3, 37.8, 32.7, 32.6, 25.5, 25.4, 24.7, 24.7; HRMS (ESI) m/z calcd for $C_{25}H_{30}N_3O_2$ $[M + H]^+$ 404.2333, found 404.2335.

*(R)-N-Cyclohexyl-2-(5-methyl-3-(2-(methylthio)ethyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)acetamide (**7h**):* 194 mg, 50% yield; mp 179−181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.65−7.39 (m, 3H), 7.37−7.18 (m, 1H), 6.23 (d, J = 8.2 Hz, 1H), 4.62 (d, J = 15.3 Hz, 1H), 4.07 (d, J = 15.3 Hz, 1H), 3.85−3.58 (m, 2H), 2.76−2.28 (m, 7H), 2.04 (s, 3H), 1.96−0.92 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.3, 168.5, 167.5, 140.7, 131.6, 130.6, 127.3, 125.3, 122.4, 61.2, 52.9, 48.3, 32.8, 32.8, 30.6, 30.5, 25.5, 25.5, 25.4, 24.6, 15.4; HRMS (CI) m/z calcd for $C_{21}H_{30}N_3O_2S$ $[M + H]^+$ 388.2059, found 388.2062.

*(R)-N-Cyclohexyl-2-(3-(hydroxymethyl)-5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)acetamide (**7i**):* 202 mg, 59% yield; mp 193−195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.93−7.40 (m, 3H), 7.40−7.08 (m, 1H), 6.39−5.86 (m, 1H), 4.56 (d, J = 15.3 Hz, 1H), 4.39−3.92 (m, 3H), 3.92−3.46 (m, 2H), 2.51 (s, 3H), 2.19−0.97 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.76, 169.81, 167.08, 140.48, 131.83, 130.65, 127.39, 125.47, 122.58, 63.13, 62.59, 52.53, 48.44, 32.80, 32.77, 25.47, 25.40, 24.64; HRMS (CI) m/z calcd for $C_{19}H_{26}N_3O_3$ $[M + H]^+$ 344.1974, found 344.1985.

*(R)-2-(3-((1H-Indol-3-yl)methyl)-5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)-N-(2,4,4-trimethylpentan-2-yl)-acetamide (**7j**):* 213 mg, 45% yield; mp 215−216 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.10 (s, 1H), 7.60−7.32 (m, 4H), 7.30−6.83 (m, 5H), 6.23 (s, 1H), 4.88−4.37 (m, 1H), 4.01−3.53 (m, 2H), 3.53−3.19 (m, 2H), 2.44 (s, 3H), 1.85−1.45 (m, 2H), 1.43−1.08 (m, 6H), 0.90−0.71 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.47, 168.04, 167.59, 140.85, 136.02, 131.60, 130.47, 127.71, 127.37, 125.17, 123.29, 122.47, 122.42, 121.63, 119.05, 118.82, 112.51, 111.06, 63.71, 55.26, 54.23, 50.88, 31.41, 31.21, 31.10, 29.18, 29.04, 29.00, 27.34, 25.55; HRMS (CI) m/z calcd for $C_{29}H_{37}N_4O_2$ $[M + H]^+$ 473.2917, found 473.2916.

*(R)-N-Benzyl-2-(3-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo-[e][1,4]diazepin-1-yl)acetamide (**7k**):* 278 mg, 70% yield; mp 183−184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.70 (dd, J = 8.3, 1.1 Hz, 1H), 7.64−7.48 (m, 3H), 7.48−7.06 (m, 10H), 6.65 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 15.5 Hz, 1H), 4.55−4.24 (m, 3H), 3.82 (q, J = 6.4 Hz, 1H), 1.72 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.0, 168.9, 168.7, 142.7, 138.7, 137.9, 132.1, 130.6, 130.4, 129.8, 129.7, 128.8, 128.5, 127.7, 127.6, 124.9, 122.5, 58.9, 52.7, 43.7, 17.6; HRMS (CI) m/z calcd for $C_{25}H_{24}N_3O_2$ $[M + H]^+$ 398.1869, found 398.1869.

*(R)-N-Benzyl-2-(3-benzyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo-[e][1,4]diazepin-1-yl)acetamide (**7l**):* 298 mg, 63% yield; mp 156−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.57−7.45 (m, 1H), 7.43−7.22 (m, 4H), 7.22−6.91 (m, 14H), 6.64 (t, J = 5.9 Hz, 1H), 4.51 (d, J = 15.6 Hz, 1H), 4.39−4.00 (m, 3H), 3.73 (dd, J = 7.6, 6.0 Hz, 1H), 3.57−3.28 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 170.5, 168.8, 168.3, 142.3, 138.9, 138.5, 137.7, 131.9, 130.4, 130.2, 129.7, 129.6, 129.1, 128.5, 128.2, 128.1, 127.4, 127.3, 126.1, 124.6, 122.2, 64.7, 52.3, 43.4, 37.7; HRMS (ESI) m/z calcd for $C_{31}H_{28}N_3O_2$ $[M + H]^+$ 474.2176, found 474.2173.

*(R)-N-Benzyl-2-(3-(2-(methylthio)ethyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)acetamide (**7m**):* 315 mg, 69% yield; mp 141−143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.68 (dt, J = 8.3, 1.0 Hz, 1H), 7.63−7.48 (m, 3H), 7.48−7.06 (m, 10H), 6.81 (t, J = 6.0 Hz, 1H), 4.67 (dd, J = 15.7, 0.9 Hz, 1H), 4.44 (dd, J = 14.9, 6.1 Hz, 1H), 4.38−4.25 (m, 2H), 3.86−3.77 (m, 1H), 2.81−2.37 (m, 4H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.6, 169.2, 168.4, 142.5, 138.5, 137.8, 132.0, 130.5, 130.3, 129.6, 129.3, 128.6, 128.3, 127.5, 127.4, 124.8, 122.3, 61.9, 52.4, 43.5, 30.8, 30.7, 15.5; HRMS (ESI) m/z calcd for $C_{27}H_{28}N_3O_2S$ $[M + H]^+$ 458.1897, found 458.1905.

*(R)-N-Benzyl-2-(3-(hydroxymethyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)acetamide (**7n**):* 231 mg, 56% yield; mp 174−176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.75−7.47 (m, 4H), 7.46−7.04 (m, 10H), 6.95 (t, J = 5.9 Hz, 1H), 4.54 (d, J = 15.8 Hz, 1H), 4.48−4.21 (m, 4H), 4.15 (dd, J = 11.4, 5.5 Hz, 1H), 3.78 (dd, J = 6.8, 5.5 Hz, 1H), 3.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.75, 169.98, 168.11, 142.25, 138.27, 137.88, 132.03, 130.66, 130.29, 129.69, 129.36, 128.57, 128.29, 127.48, 127.34, 124.81, 122.33, 63.95, 62.74, 51.87, 43.47; HRMS (EI) m/z calcd for $C_{25}H_{23}N_3O_3$ $[M]^+$ 413.1739, found 413.1735.

*(R)-2-(3-((1H-Indol-3-yl)methyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)-N-benzylacetamide (**7o**):* 261 mg, 51%

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yield; mp 215−216 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.14 (d, J = 2.7 Hz, 1H), 7.83−6.96 (m, 19H), 6.82 (t, J = 5.9 Hz, 1H), 4.69 (d, J = 15.7 Hz, 1H), 4.52−4.17 (m, 3H), 3.94 (t, J = 6.9 Hz, 1H), 3.79 (dd, J = 14.7, 6.8 Hz, 1H), 3.65 (dd, J = 14.7, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.59, 169.31, 168.56, 142.51, 138.18, 137.89, 135.96, 132.17, 130.71, 130.56, 129.88, 129.01, 128.62, 128.40, 128.31, 128.06, 127.68, 127.57, 127.37, 127.36, 124.72, 123.45, 122.20, 121.70, 119.03, 118.88, 112.34, 111.10, 64.18, 52.41, 43.50, 27.06; HRMS (CI) m/z calcd for $C_{33}H_{29}N_4O_2$ $[M + H]^+$ 513.2291, found 513.2292.

*(R)-N-Cyclohexyl-2-(3-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)acetamide (**7p**):* 257 mg, 66% yield; mp 213−214 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.94−7.54 (m, 4H), 7.55−7.06 (m, 5H), 6.37−5.99 (m, 1H), 4.75−4.23 (m, 2H), 3.87 (q, J = 6.5 Hz, 1H), 3.74−3.59 (m, 1H), 2.07−1.40 (m, 8H), 1.40−0.75 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.98, 168.82, 167.70, 142.73, 138.65, 132.08, 130.75, 130.28, 129.91, 128.51, 124.92, 122.63, 58.97, 52.89, 48.61, 32.80, 32.75, 25.61, 24.82, 17.57; HRMS (CI) m/z calcd for $C_{24}H_{28}N_3O_2$ $[M + H]^+$ 390.2182, found 390.2182.

*(S)-2-(3-Benzyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)-N-cyclohexylacetamide (**7q**):* 270 mg, 58% yield; mp 173−175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.79−7.06 (m, 14H), 6.20 (d, J = 8.1 Hz, 1H), 4.62 (d, J = 15.4 Hz, 1H), 4.25 (d, J = 15.3 Hz, 1H), 3.90 (t, J = 6.9 Hz, 1H), 3.78−3.39 (m, 3H), 1.87−1.41 (m, 5H), 1.40−0.70 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)170.4, 168.8, 167.5, 142.5, 139.0, 138.5, 131.9, 130.6, 130.2, 129.8, 129.7, 129.2, 128.3, 128.2, 126.2, 124.7, 122.4, 65.1, 52.9, 48.4, 38.0, 32.6, 25.4, 24.6; HRMS (CI) m/z calcd for $C_{30}H_{32}N_3O_2$ $[M + H]^+$ 466.2495, found 466.2495.

*(R)-N-Cyclohexyl-2-(3-(hydroxymethyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)acetamide (**7r**):* 251 mg, 62% yield; mp 121−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.80−7.50 (m, 4H), 7.50−7.11 (m, 5H), 6.17 (d, J = 8.1 Hz, 1H), 4.51 (d, J = 15.6 Hz, 1H), 4.43−4.13 (m, 3H), 3.85 (dd, J = 6.8, 5.8 Hz, 1H), 3.77−3.53 (m, 1H), 3.43−3.14 (m, 1H), 1.93−0.71 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.0, 170.6, 167.2, 142.5, 138.0, 132.5, 131.2, 130.6, 130.1, 129.4, 128.5, 125.2, 122.7, 64.1, 62.8, 52.5, 48.7, 32.9, 32.8, 25.6, 24.8; HRMS (CI) m/z calcd for $C_{24}H_{28}N_3O_2$ $[M + H]^+$ 406.2131, found 406.2137.

*(R)-N-Cyclohexyl-2-(3-(2-(methylthio)ethyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)acetamide (**7s**):* 283 mg, 63% yield; mp 169−171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.76−7.50 (m, 4H), 7.50−7.14 (m, 5H), 6.18 (d, J = 8.1 Hz, 1H), 4.57 (d, J = 15.5 Hz, 1H), 4.29 (d, J = 15.4 Hz, 1H), 3.84 (dd, J = 7.7, 5.9 Hz, 1H), 3.75−3.56 (m, 1H), 2.90−2.67 (m, 2H), 2.58−2.39 (m, 2H), 2.08 (s, 3H), 1.95−0.72 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.7, 169.8, 167.6, 142.7, 138.3, 132.4, 131.0, 130.5, 130.0, 129.4, 128.5, 125.1, 122.7, 62.0, 52.9, 48.7, 32.8, 30.9, 30.9, 25.6, 24.8, 15.8; HRMS (CI) m/z calcd for $C_{26}H_{32}N_3O_2S$ $[M + H]^+$ 450.2215, found 450.2210.

*(R)-2-(3-((1H-Indol-3-yl)methyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]dia-zepin-1-yl)-N-cyclohexylacetamide (**7t**):* 338 mg, 67% yield; mp 221−223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.27 (s, 1H), 7.80−6.93 (m, 14H), 6.20 (d, J = 8.0 Hz, 1H), 4.60 (d, J = 15.4 Hz, 1H), 4.30 (d, J = 15.4 Hz, 1H), 3.95 (t, J = 6.8 Hz, 1H), 3.89−3.75 (m, 1H), 3.75−3.55 (m, 2H), 1.94−0.63 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.6, 169.1, 167.5, 142.5, 138.1, 136.0, 132.1, 130.8, 130.4, 129.9, 129.0, 128.3, 127.7, 124.7, 123.4, 122.4, 121.7, 119.1, 119.0, 112.6, 111.0, 64.3, 52.7, 48.4, 32.5, 32.4, 27.1, 25.3, 24.7, 24.6; HRMS (ESI) m/z calcd for $C_{32}H_{33}N_4O_2$ $[M + H]^+$ 505.2598, found 505.2601.

*(R)-2-(5-Methyl-3-(2-(methylthio)ethyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diaze-pin-1-yl)-N-(2,4,4-trimethylpentan-2-yl)-acetamide (**7u**):* 234 mg, 56% yield; mp 128−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.52−7.39 (m, 1H), 7.39−7.26 (m, 2H), 7.09 (ddt, J = 7.8, 6.1, 1.2 Hz, 1H), 6.14 (s, 1H), 4.44 (dd, J = 15.0, 1.5 Hz, 1H), 3.68 (d, J = 15.0 Hz, 1H), 3.43 (td, J = 7.0, 1.4 Hz, 1H), 2.57−2.32 (m, 2H), 2.32−2.09 (m, 5H), 1.84 (s, 3H), 1.73−1.27 (m, 2H), 1.27−1.09 (m, 6H), 0.75 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 170.3, 168.4, 167.3, 140.7, 131.5, 130.4, 127.2, 125.1, 122.3, 60.9, 55.2, 54.1, 51.1, 31.4, 31.2, 30.5, 30.4, 29.0, 25.4, 15.2; HRMS (CI) m/z calcd for $C_{23}H_{36}N_3O_2S$ $[M + H]^+$ 418.2526, found 418.2544.

*(S)-N-Benzyl-2-(3-isopropyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)-2-methylpropanamide (**7v**):* 213 mg, 47% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69−7.56 (m, 2H), 7.56−7.25 (m, 7H), 7.21−7.10 (m, 3H), 7.10−6.98 (m, 2H), 6.19 (t, J = 5.7 Hz, 1H), 4.34 (dd, J = 14.7, 5.9 Hz, 1H), 4.21 (dd, J = 14.7, 5.4 Hz, 1H), 3.09 (d, J = 9.3 Hz, 1H), 2.68 (dt, J = 9.3, 6.6 Hz, 1H), 1.37 (s, 3H), 1.19 (d, J = 6.1 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.1, 172.1, 167.6, 140.0, 138.1, 137.8, 132.6, 130.5, 129.9, 129.0, 128.8, 128.4, 128.4, 127.6, 127.0, 126.4, 126.2, 63.9, 43.8, 29.1, 26.8, 26.1, 25.3, 20.2, 19.1; HRMS (CI) m/z calcd for $C_{29}H_{32}N_3O_2$ $[M + H]^+$ 454.2495, found 454.2494.

*(R)-N-Benzyl-1-(5-methyl-3-(2-(methylthio)ethyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)cyclohexanecarboxamide (**7w**):* 199 mg, 43% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.49−7.21 (m, 7H), 7.21−7.02 (m, 3H), 6.94−6.78 (m, 1H), 5.03 (d, J = 16.0 Hz, 1H), 4.27 (d, J = 15.9 Hz, 1H), 3.39 (dd, J = 9.8, 3.9 Hz, 1H), 2.55−1.23 (m, 17H), 1.20 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 176.2, 138.4, 137.6, 131.3, 128.9, 128.7, 127.9, 127.5, 127.2, 123.8, 120.3, 117.5, 105.9, 92.1, 63.0, 61.5, 42.5, 37.1, 32.0, 31.0, 29.9, 25.3, 25.0, 22.5, 22.2, 21.8, 15.1; HRMS (CI) m/z calcd for $C_{27}H_{34}N_3O_2S$ $[M + H]^+$ 464.2372, found 464.2368.

*(R)-N-Benzyl-2-(3-(hydroxymethyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)-2-methylpropanamide (**7x**):* 203 mg, 46% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.647−7.58 (m, 2H), 7.54−7.14 (m, 10H), 7.10−7.03 (m, 2H), 6.27 (t, J = 5.6 Hz, 1H), 4.42−4.22 (m, 3H), 4.09 (dd, J = 11.4, 5.5 Hz, 1H), 3.80−3.67 (m, 1H), 2.48 (brs, 1H), 1.63 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.9, 173.4, 169.3, 139.4, 137.9, 137.4, 132.7, 130.9, 130.2, 129.1, 129.0, 128.5, 128.5, 127.6, 127.2, 126.5, 126.4, 65.2, 64.0, 62.7, 43.9, 26.8, 26.0; HRMS (CI) m/z calcd for $C_{27}H_{28}N_3O_3$ $[M + H]^+$ 442.2131, found 442.2131.

*(S)-N-Benzyl-1-(3-isopropyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)cyclohexanecarboxamide (**7y**):* 190 mg, 47% yield; mp 143−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.83 (t, J = 5.8 Hz, 1H), 7.55−7.16 (m, 9H), 4.62 (dd, J = 15.0, 6.3 Hz, 1H), 4.43 (dd, J = 15.0, 5.3 Hz, 1H), 3.64−3.51 (m, 1H), 3.08 (d, J = 11.4 Hz, 1H), 2.48 (s, 3H), 2.00−1.08 (m, 15H), 0.73−0.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 177.8, 175.2, 168.4, 139.0, 138.5, 134.2, 129.7, 128.6, 127.4, 127.2, 126.5, 126.3, 125.6, 66.9, 59.7, 43.6, 33.3, 32.5, 25.0, 24.7, 21.8, 20.8, 17.1; HRMS (CI) m/z calcd for $C_{25}H_{30}N_3O_2$ $[M + H]^+$ 404.2338, found 404.2334.

*N-Benzyl-2-((R)-3,5-dimethyl-2-oxo-2,3-dihydro-1H-benzo[e]-[1,4]diazepin-1-yl)-2-phenylacetamide (**8a1**):* 181 mg, 44% yield; mp 114−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.66 (d, J = 8.2 Hz, 1H), 7.55−7.44 (m, 2H), 7.38−7.21 (m, 9H), 7.22−7.12 (m, 2H), 6.75 (t, J = 5.1 Hz, 1H), 5.68 (s, 1H), 4.64 (dd, J = 15.0, 6.3 Hz, 1H), 4.44 (dd, J = 15.0, 5.4 Hz, 1H), 3.80−3.65 (m, 1H), 2.44 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.64, 169.50, 168.33, 141.35, 137.96, 134.18, 132.06, 131.33, 128.78, 128.62, 128.23, 127.56, 127.35, 127.27, 126.67, 125.68, 123.94, 69.96, 58.41, 43.90, 25.08, 16.87; HRMS (EI) m/z calcd for $C_{26}H_{25}N_3O_2$ $[M]^+$ 411.1947, found 411.1944.

*N-Benzyl-2-((R)-3,5-dimethyl-2-oxo-2,3-dihydro-1H-benzo[e]-[1,4]diazepin-1-yl)-2-phenylacetamide (**8a2**):* 164 mg, 40% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.72 (dd, J = 8.3, 1.2 Hz, 1H), 7.43−7.01 (m, 13H), 6.58 (t, J = 5.8 Hz, 1H), 6.12 (s, 1H), 4.58 (qd, J = 14.9, 5.8 Hz, 2H), 3.80−3.66 (m, 1H), 2.41 (s, 3H), 1.71−1.43 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.29, 169.38, 168.02, 138.52, 137.84, 134.46, 132.61, 130.15, 129.16, 128.68, 128.40, 128.09, 127.70, 127.46, 126.22, 125.64, 125.40, 65.26, 58.14, 43.96, 25.11, 16.99; HRMS (EI) m/z calcd for $C_{26}H_{25}N_3O_2$ $[M]^+$ 411.1947, found 411.1943.

*N-Cyclohexyl-2-((R)-3,5-dimethyl-2-oxo-2,3-dihydro-1H-benzo-[e][1,4]diazepin-1-yl)-2-phenylacetamide (**8b1**):* 157 mg, 39% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69−7.54 (m, 1H), 7.54−7.38

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(m, 2H), 7.37−7.21 (m, 4H), 7.21−7.08 (m, 2H), 6.39 (d, J = 8.1 Hz, 1H), 5.58 (s, 1H), 3.91−3.75 (m, 1H), 3.75−3.62 (m, 1H), 2.48 (s, 3H), 1.88 (dt, J = 12.4, 4.3 Hz, 2H), 1.74−1.45 (m, 5H), 1.44−0.95 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.7, 168.5, 168.2, 141.6, 134.5, 131.9, 131.2, 128.6, 128.0, 127.0, 126.6, 125.6, 123.9, 70.1, 58.4, 48.6, 32.5, 25.5, 25.1, 24.6, 16.9; HRMS (CI) m/z calcd for $C_{25}H_{30}N_3O_2$ $[M + H]^+$ 404.2338, found 404.2357.

*N-Cyclohexyl-2-((R)-3,5-dimethyl-2-oxo-2,3-dihydro-1H-benzo-[e][1,4]diazepin-1-yl)-2-phenylacetamide (**8b2**):* 173 mg, 43% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.72 (dd, J = 8.3, 1.2 Hz, 1H), 7.32 (dd, J = 7.7, 1.7 Hz, 1H), 7.24−7.01 (m, 7H), 6.00 (s, 1H), 5.94 (d, J = 8.1 Hz, 1H), 4.00−3.81 (m, 1H), 3.80−3.56 (m, 1H), 2.40 (s, 3H), 2.08−1.88 (m, 2H), 1.83−1.49 (m, 5H), 1.49−1.06 (m,6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.2, 168.3, 168.0, 138.6, 134.7, 132.6, 130.1, 129.0, 128.3, 128.0, 126.1, 125.6, 125.3, 65.4, 58.1, 48.9, 32.9, 32.7, 25.5, 25.1, 24.7, 24.7, 17.0; HRMS (CI) m/z calcd for $C_{25}H_{30}N_3O_2$ $[M + H]^+$ 404.2338, found 404.2348.

*2-((R)-3-((1H-Indol-3-yl)methyl)-5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)-N-cyclohexylpentanamide (**8c1**):* 194 mg, 40% yield; mp 216−218 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)7.98 (s, 1H), 7.58 (ddt, J = 7.8, 1.4, 0.7 Hz, 1H), 7.53−7.37 (m, 3H), 7.36−6.95 (m, 5H), 4.16 (dd, J = 10.3, 5.8 Hz, 1H), 3.90−3.57 (m, 3H), 3.37 (ddd, J = 13.8, 5.0, 0.9 Hz, 1H), 2.57−2.32 (m, 4H), 2.02−1.47 (m, 6H), 1.46−0.86 (m, 8H), 0.75 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.7, 170.8, 168.2 143.0, 136.1, 131.8, 131.2, 127.9, 127.0, 125.7, 123.8, 123.4, 122.0, 119.4, 119.1, 113.1, 111.1, 69.6, 64.9, 48.5, 32.9, 31.7, 27.2, 25.8, 25.3, 24.9, 24.9, 19.8, 13.7; HRMS (CI) m/z calcd for $C_{30}H_{37}N_4O_2$ $[M + H]^+$ 485.2917, found 485.2913.

*2-((R)-3-((1H-Indol-3-yl)methyl)-5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)-N-cyclohexylpentanamide (**8c2**):* 174 mg, 36% yield; mp 221−223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)8.50 (s, 1H), 7.60 (ddd, J = 7.6, 1.4, 0.7 Hz, 1H), 7.56−7.32 (m, 3H), 7.32−7.17 (m, 2H), 7.16−6.94 (m, 3H), 6.67 (d, J = 8.1 Hz, 1H), 5.09 (dd, J = 9.3, 6.3 Hz, 1H), 3.93−3.57 (m, 3H), 3.50−3.33 (m, 1H), 2.46 (S, 3H), 1.93−1.41 (m, 6H), 1.42−0.73 (m, 8H), 0.69 (td, J = 7.5, 0.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.6, 170.6, 168.2, 137.2, 136.0, 132.4, 130.6, 127.6, 127.0, 125.7, 124.3, 123.2, 121.6, 119.0, 118.9, 112.6, 111.0, 64.4, 57.4, 48.1, 32.6, 32.6, 32.3, 29.3, 27.2, 25.3, 25.1, 24.6, 18.9, 13.5; HRMS (CI) m/z calcd for $C_{30}H_{37}N_4O_2$ $[M + H]^+$ 485.2917, found 485.2919.

*(S)-N-Cyclohexyl-2-((S)-3-isopropyl-5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)pentanamide (**8d1**):* 175 mg, 44% yield; mp 99−101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)7.61 (dd, J = 8.2, 1.1 Hz, 1H), 7.55−7.37 (m, 2H), 7.36−7.16 (m, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.05 (dd, J = 9.2, 6.5 Hz, 1H), 3.78 (dtt, J = 10.8, 8.5, 4.2 Hz, 1H), 2.92 (dq, J = 10.1, 1.3 Hz, 1H), 2.72−2.51 (m, 1H), 2.42 (s, 3H), 2.00−1.46 (m, 5H), 1.44−1.08 (m, 7H), 1.03−0.79 (m, 8H), 0.75−0.58 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.9, 170.7, 167.5, 137.4, 132.5, 130.4, 126.9, 125.6, 124.2, 69.6, 56.9, 48.0, 32.8, 32.7, 29.2, 29.1, 25.5, 25.3, 25.0, 24.5, 20.0, 19.0, 18.8, 13.4; HRMS (CI) m/z calcd for $C_{24}H_{36}N_3O_2$ $[M + H]^+$ 398.2808, found 398.2820.

*(R)-N-Cyclohexyl-2-((S)-3-isopropyl-5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)pentanamide (**8d2**):* 127 mg, 32% yield; mp 115−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)7.62−7.42 (m, 3H), 7.26 (ddd, J = 8.0, 7.2, 1.3 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 4.17 (dd, J = 10.3, 5.8 Hz, 1H), 3.85−3.67 (m, 1H), 2.87 (dq, J = 10.1, 1.2 Hz, 1H), 2.68−2.28 (m, 5H), 1.99−1.46 (m, 5H), 1.44−0.98 (m, 8H), 0.94 (t, J = 6.6 Hz, 6H), 0.72 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.9, 170.7, 167.4, 142.9, 131.4, 131.0, 126.6, 125.4, 123.4, 70.1, 69.4, 48.1, 32.7, 32.7, 31.6, 28.9, 25.5, 24.9, 24.6, 24.6, 19.9, 19.5, 18.9, 13.4; HRMS (CI) m/z calcd for $C_{24}H_{36}N_3O_2$ $[M + H]^+$ 398.2808, found 398.2817.

*N-Cyclohexyl-2-((R)-5-methyl-3-(2-(methylthio)ethyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)pentanamide (**8e1**):* 176 mg, 44% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.62−7.56 (m, 1H), 7.51 (td, J = 7.3, 1.5 Hz, 2H), 7.33−7.26 (m, 1H), 7.02 (d, J = 8.1 Hz, 1H), 4.18 (dd, J = 10.3, 5.7 Hz, 1H), 3.88−3.70 (m, 1H), 3.59 (t, J = 7.1 Hz, 1H), 2.71−2.51 (m, 2H), 2.47 (d, J = 1.3 Hz, 3H), 2.45−2.25 (m, 3H), 2.05 (s, 3H), 1.96−1.78 (m, 4H), 1.64 (ddt, J = 50.0, 13.3, 4.5 Hz, 3H), 1.45−0.96 (m, 6H), 0.75 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.52, 170.45, 168.51, 142.73, 131.62, 131.06, 126.71, 125.59, 123.55, 69.08, 62.11, 48.27, 32.78, 32.70, 31.39, 30.59, 30.56, 25.56, 25.08, 24.66, 24.62, 19.54, 15.49, 13.44; HRMS (CI) m/z calcd for $C_{24}H_{36}N_3O_2S$ $[M + H]^+$ 430.2528, found 430.2519.

*N-Cyclohexyl-2-((R)-5-methyl-3-(2-(methylthio)ethyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)pentanamide (**8e2**):* 163 mg, 38% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.61 (dq, J = 8.3, 1.1 Hz, 1H), 7.50 (dq, J = 8.1, 1.1 Hz, 1H), 7.46−7.39 (m, 1H), 7.31−7.24 (m, 1H), 6.79 (d, J = 8.2 Hz, 1H), 4.99 (t, J = 7.4 Hz, 1H), 3.84−3.71 (m, 1H), 3.59 (td, J = 7.0, 2.6 Hz, 1H), 2.70−2.51 (m, 2H), 2.51−2.38 (m, 4H), 2.37−2.26 (m, 1H), 2.01 (dt, J = 2.4, 1.2 Hz, 3H), 1.94−1.47 (m, 6H), 1.43−1.07 (m, 6H), 1.05−0.76 (m, 2H), 0.72−0.58 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.58, 170.48, 168.48, 137.22, 132.49, 130.64, 126.94, 125.78, 124.36, 61.66, 57.56, 48.10, 32.70, 32.67, 30.73, 30.64, 29.39, 25.49, 25.09, 24.54, 18.88, 15.41, 13.45; HRMS (CI) m/z calcd for $C_{24}H_{36}N_3O_2S$ $[M + H]^+$ 430.2528, found 430.2528.

*N-Benzyl-2-((S)-3-(hydroxymethyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)-2-phenylacetamide (**8f1**):* 215 mg, 44% yield; mp 182−185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)7.75−7.64 (m, 1H), 7.61−7.41 (m, 4H), 7.41−7.13 (m, 14H), 6.69 (t, J = 5.8 Hz, 1H), 5.80 (s, 1H), 4.64−4.31 (m, 3H), 4.21 (dd, J = 11.5, 5.6 Hz, 1H), 3.90 (dd, J = 7.0, 5.5 Hz, 1H), 2.60 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.0, 170.4, 168.9, 142.6, 138.3, 137.8, 133.9, 131.8, 130.8, 130.6, 129.8, 129.4, 128.9, 128.6, 128.3, 127.6, 127.4, 127.2, 125.4, 123.9, 69.5, 64.4, 62.8, 43.9; HRMS (ESI) m/z calcd for $C_{31}H_{28}N_3O_3$ $[M + H]^+$ 490.2131, found 490.2142.

*N-Benzyl-2-((R)-3-(hydroxymethyl)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)-2-phenylacetamide (**8f2**).* 176 mg, 36% yield; mp 179−181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)7.92 (d, J = 8.3 Hz, 1H), 7.60−7.20 (m, 11H), 7.19−6.94 (m, 7H), 6.64 (t, J = 5.8 Hz, 1H), 6.16 (s, 1H), 4.74−4.49 (m, 2H), 4.37 (dd, J = 11.4, 6.7 Hz, 1H), 4.23 (dd, J = 11.4, 5.4 Hz, 1H), 3.89 (dd, J = 6.6, 5.5 Hz, 1H), 2.57 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.0, 169.9, 169.2, 139.4, 138.2, 137.7, 134.0, 131.5, 130.6, 130.5, 129.6, 129.6, 129.1, 128.7, 128.4, 128.3, 128.2, 127.8, 127.7, 127.5, 126.2, 125.1, 64.5, 64.2, 62.9, 44.0; HRMS (CI) m/z calcd for $C_{31}H_{28}N_3O_3$ $[M + H]^+$ 490.2131, found 490.2127.

*N-Benzyl-2-((S)-3-isobutyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)-2-phenylacetamide (**8g1**):* 191 mg, 37% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.98 (dd, J = 8.4, 1.1 Hz, 1H), 7.53−7.21 (m, 11H), 7.20−7.07 (m, 6H), 7.06−7.00 (m, 1H), 6.75 (t, J = 5.7 Hz, 1H), 6.27 (s, 1H), 4.67 (dd, J = 14.8, 6.0 Hz, 1H), 4.56 (dd, J = 14.8, 5.5 Hz, 1H), 3.77 (dd, J = 9.3, 4.3 Hz, 1H), 2.43−2.24 (m, 1H), 2.05−1.86 (m, 2H), 1.11−0.93 (m, 3H), 0.86−0.73 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.2, 169.7, 168.7, 139.9, 138.6, 137.8, 134.4, 131.5, 130.3, 129.6, 128.9, 128.7, 128.3, 128.2, 128.0, 127.7, 127.4, 126.1, 124.9, 64.2, 61.8, 44.0, 39.9, 24.7, 23.5, 21.9; HRMS (CI) m/z calcd for $C_{34}H_{34}N_3O_2$ $[M + H]^+$ 516.2651, found 516.2668.

*N-Benzyl-2-((S)-3-isobutyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)-2-phenylacetamide (**8g2**):* 160 mg, 31% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.78 (dd, J = 8.3, 1.0 Hz, 1H), 7.67−7.08 (m, 18H), 6.87 (t, J = 5.8 Hz, 1H), 5.79 (s, 1H), 4.61 (dd, J = 15.0, 6.1 Hz, 1H), 4.48 (dd, J = 15.0, 5.8 Hz, 1H), 3.78 (dd, J = 9.0, 4.8 Hz, 1H), 2.36−2.21 (m, 1H), 2.12−1.86 (m, 2H), 1.01 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.90, 169.51, 169.32, 143.30, 138.80, 138.04, 134.22, 131.72, 130.64, 130.32, 129.63, 129.42, 129.26, 128.77, 128.61, 128.31, 128.13, 128.08, 127.61, 127.54, 127.34, 127.07, 125.25, 123.76, 70.10, 62.16, 43.91, 39.85, 24.73, 23.47, 22.03; HRMS (CI) m/z calcd for $C_{34}H_{34}N_3O_2$ $[M + H]^+$ 516.2651, found 516.2650.

*N-(tert-Butyl)-2-(3,3,5-trimethyl-2-oxo-2,3-dihydro-1H-benzo[e]-[1,4]diazepin-1-yl)acetamide (**9a**):* 132 mg, 42% yield; mp 196−197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.78−7.34 (m, 3H), 7.34−7.07 (m, 1H), 6.06 (s, 1H), 4.62 (d, J = 15.3 Hz, 1H), 3.97 (d, J = 15.3 Hz, 1H), 2.49 (s, 3H), 1.72 (s, 3H), 1.33 (s, 9H), 0.87 (s, 3H); ^{13}C

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NMR (75 MHz, $CDCl_3$) δ (ppm) 174.1, 168.3, 166.3, 141.1, 131.8, 131.7, 127.2, 124.8, 122.0, 62.8, 55.5, 51.6, 31.3, 28.9, 27.2, 20.2; HRMS (ESI) m/z calcd for $C_{18}H_{26}N_3O_2$ $[M + H]^+$ 316.2020, found 316.2024.

*N-(tert-Butyl)-2-(3,3-dimethyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-1-yl)acetamide (**9b**):* 181 mg, 48% yield; mp 193−195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.94−6.84 (m, 9H), 6.09 (s, 1H), 4.60 (d, J = 15.3 Hz, 1H), 4.11 (d, J = 15.3 Hz, 1H), 1.84 (s, 3H), 1.29 (s, 9H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.1, 168.0, 166.9, 142.8, 140.1, 131.9, 130.1, 130.1, 129.6, 128.1, 124.0, 121.8, 63.2, 55.1, 51.4, 31.3, 28.6, 19.8; HRMS (ESI) m/z calcd for $C_{23}H_{28}N_3O_2$ $[M + H]^+$ 378.2176, found 378.2179.

*(±)-N-(tert-Butyl)-2-(3,3-dimethyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)pentanamide (**9c**):* 189 mg, 53% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.75−7.31 (m, 8H), 7.30−7.09 (m, 1H), 7.00 (s, 1H), 5.00 (dd, J = 9.3, 6.1 Hz, 1H), 1.85 (s, 3H), 1.56−1.23 (m, 11H), 1.22−0.88 (m, 2H), 0.84 (d, J = 4.6 Hz, 3H), 0.69 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 177.1, 171.3, 166.8, 139.7, 139.1, 132.2, 131.1, 130.2, 129.9, 129.3, 128.2, 124.8, 123.8, 63.4, 59.5, 51.0, 31.7, 29.5, 28.7, 20.1, 19.2, 13.6; HRMS (CI) m/z calcd for $C_{26}H_{34}N_3O_2$ $[M + H]^+$ 420.2651, found 420.2640.

*(±)-N-(tert-Butyl)-2-phenyl-2-(3,3,5-trimethyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-1-yl)acetamide (**9d**):* 184 mg, 47% yield; mp 178−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.74−6.83 (m, 9H), 6.29 (s, 0.37H), 5.83 (d, J = 5.3 Hz, 1H), 5.63 (s, 0.37H), 2.48 (d, J = 20.5 Hz, 3H), 1.71 (d, J = 19.9 Hz, 3H), 1.50−1.14 (m, 9H), 0.87 (d, J = 8.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.69, 174.24, 168.58, 166.49, 163.50, 141.15, 138.54, 135.01, 134.79, 133.28, 132.52, 131.43, 130.19, 129.06, 128.91, 128.77, 128.50, 128.42, 128.33, 128.14, 127.79, 127.71, 127.39, 126.92, 126.56, 125.99, 125.20, 125.12, 124.81, 123.26, 71.28, 67.57, 62.95, 62.88, 51.78, 31.25, 28.64, 28.48, 26.55, 26.45, 20.36, 20.14; HRMS (CI) m/z calcd for $C_{24}H_{30}N_3O_2$ $[M + H]^+$ 392.2338, found 392.2338.

*N-(tert-Butyl)-2-(5-methyl-2-oxospiro[benzo[e][1,4]diazepin-3,1′-cyclopentan]-1(2H)-yl)acetamide (**9e**):* 106 mg, 31% yield; mp 189−191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.71−7.37 (m, 3H), 7.37−7.02 (m, 1H), 6.21 (s, 1H), 4.64 (d, J = 15.2 Hz, 1H), 3.95 (d, J = 15.2 Hz, 1H), 2.82 (dt, J = 13.0, 6.5 Hz, 1H), 2.63−2.25 (m, 4H), 2.22−2.04 (m, 1H), 2.01−1.19 (m, 13H), 1.12−0.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.30, 168.22, 166.68, 140.91, 132.42, 131.52, 126.95, 124.55, 122.02, 54.87, 51.27, 41.25, 40.02, 38.35, 33.68, 28.62, 26.91, 26.34, 25.07, 23.65; HRMS (CI) m/z calcd for $C_{20}H_{28}N_3O_2$ $[M + H]^+$ 342.2182, found 342.2182.

*N-(tert-Butyl)-2-(2-oxo-5-phenylspiro[benzo[e][1,4]diazepine-3,1′-cyclopentan]-1(2H)-yl)acetamide (**9f**):* 133 mg, 33% yield; mp 204−206 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.91−6.94 (m, 9H), 6.14 (s, 1H), 4.63 (d, J = 15.2 Hz, 1H), 4.12 (d, J = 15.2 Hz, 1H), 2.90 (dt, J = 12.7, 7.0 Hz, 1H), 2.33 (dt, J = 13.0, 6.8 Hz, 1H), 1.96−1.37 (m, 5H), 1.27 (s, 9H), 1.18−0.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.6, 168.2, 167.4, 142.7, 139.7, 131.8, 131.0, 130.2, 130.0, 129.5, 128.1, 124.1, 122.1, 74.3, 54.9, 51.3, 40.3, 33.4, 28.5, 25.1, 23.8; HRMS (ESI) m/z calcd for $C_{25}H_{30}N_3O_2$ $[M + H]^+$ 404.2333, found 404.2339.

*(±)-N-(tert-Butyl)-2-(2-oxo-5-phenylspiro[benzo[e][1,4]-diazepine-3,1′-cyclopentan]-1(2H)-yl)pentanamide (**9g**):* 147 mg, 33% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.80−7.30 (m, 7H), 7.31−7.09 (m, 2H), 6.97 (s, 1H), 5.04 (dd, J = 9.3, 6.1 Hz, 1H), 2.94 (dt, J = 13.2, 6.8 Hz, 1H), 2.32 (dt, J = 12.7, 7.0 Hz, 1H), 1.99−1.17 (m, 16H), 1.17−0.79 (m, 3H), 0.76−0.61 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 176.3, 171.4, 167.3, 139.3, 139.2, 133.0, 131.0, 130.3, 129.9, 129.3, 128.2, 124.7, 123.9, 74.3, 59.0, 51.0, 40.6, 33.4, 29.3, 28.7, 25.0, 23.7, 19.2, 13.6; HRMS (ESI) m/z calcd for $C_{28}H_{36}N_3O_2$ $[M + H]^+$ 446.2802, found 446.2813.

*(±)-N-(tert-Butyl)-2-(5-methyl-2-oxospiro[benzo[e][1,4]-diazepine-3,1′-cyclopentan]-1(2H)-yl)-2-phenylacetamide (**9h**):* 113 mg, 27% yield; mp 175−177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.72−7.54 (m, 1H), 7.53−6.89 (m, 8H), 6.42 (s, 0.36H), 5.90 (d, J = 11.4 Hz, 1H), 5.58 (s, 0.37H), 2.95−2.65 (m, 1H), 2.45 (d, J = 26.9 Hz, 3H), 2.29−1.96 (m, 1H), 1.94−1.12 (m, 14H), 1.14−0.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.21, 173.70, 168.89, 168.71, 166.99, 166.89, 141.37, 138.46, 135.03, 134.86, 134.46, 133.54, 131.37, 130.07, 129.18, 129.06, 128.92, 128.77, 128.51, 128.34, 128.27, 127.86, 127.75, 127.67, 127.38, 126.75, 126.54, 125.95, 125.56, 125.07, 124.76, 123.48, 74.02, 73.91, 71.46, 66.85, 40.25, 40.08, 33.98, 33.63, 28.65, 28.47, 28.32, 26.02, 25.89, 25.39, 25.13, 23.88, 23.57; HRMS (CI) m/z calcd for $C_{26}H_{31}N_3O_2$ $[M + H]^+$ 418.2495, found 418.2484.

*2-((2-Acetylphenyl)amino)-N-(tert-butyl)-2-phenylacetamide (**10a**):* 156 mg, 48% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.70−9.27 (m, 1H), 7.81 (dd, J = 8.1, 1.6 Hz, 1H), 7.59−7.15 (m, 6H), 6.75 (t, J = 7.6 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 6.32 (s, 1H), 4.76 (d, J = 4.1 Hz, 1H), 2.60 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 201.3, 170.1, 149.4, 138.2, 135.2, 132.6, 129.1, 128.3, 127.0, 118.9, 116.3, 113.0, 64.0, 51.2, 28.5, 28.0; HRMS (ESI) m/z calcd for $C_{20}H_{25}N_2O_2$ $[M + H]^+$ 325.1916, found 325.1917.

*2-((2-Benzoylphenyl)amino)-N-(tert-butyl)pentanamide (**10b**):* 162 mg, 46% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.61 (d, J = 4.4 Hz, 1H), 7.67−7.54 (m, 2H), 7.54−7.28 (m, 5H), 6.72−6.52 (m, 2H), 6.33 (s, 1H), 3.69 (dt, J = 8.7, 4.4 Hz, 1H), 1.92 (dtd, J = 14.3, 7.1, 6.5, 4.3 Hz, 1H), 1.78 (dddd, J = 13.6, 10.1, 8.4, 5.0 Hz, 1H), 1.66−1.37 (m, 2H), 1.25 (s, 9H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 199.7, 172.4, 150.7, 139.9, 135.2, 135.1, 131.2, 129.1, 128.1, 118.4, 115.8, 112.9, 59.8, 50.8, 35.5, 28.5, 19.3, 13.8; HRMS (CI) m/z calcd for $C_{22}H_{29}N_2O_2$ $[M + H]^+$ 353.2229, found 353.2230.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures, a table, and CIF files giving NMR and HRMS spectra for described compounds, crystallographic structures, and chiral HPLC analysis of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kleemann, A., Engel, J., Kutscher, B., Reichert, D. *Pharmaceutical Substances: Synthesis, Patents, Applications*, 5th ed., Thieme: Stuttgart, Germany, 2008.

(2) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235−2246.

(3) Bateson, A. N. *Sleep Med.* **2004**, S9−S15 (suppl. 1).

(4) (a) Bolli, M. H.; Marfurt, J.; Grisostomi, C.; Boss, C.; Binkert, C.; Hess, P.; Treiber, A.; Thorin, E.; Morrison, K.; Buchmann, S.; Bur, D.; Ramuz, H.; Clozel, M.; Fischli, W.; Weller, T. *J. Med. Chem.* **2004**, *47*, 2776−2795. (b) De Clerq, E. *Antiviral Res.* **1998**, *38*, 153−179. (c) Dourlat, J.; Liu, W.; Gresh, N.; Garbay, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2527−2530. (d) Micale, N.; Vairagoundar, R.; Yakovlev, A. G.; Kozikowski, A. P. *J. Med. Chem.* **2004**, *47*, 6455−6458. (e) Ettari,

DOI: 10.1021/jo502382q
J. Org. Chem. 2015, 80, 1533−1549

R.; Micale, N.; Schirmeister, T.; Gelhaus, C.; Leippe, M.; Nizi, E.; Di Francesco, M. E.; Grasso, S.; Zappalà. *J. Med. Chem.* **2009**, *52*, 2157−2160.
(5) The helical descriptors *M* and *P* are based on the sign of the τ_{2345} torsional angle. For recent studies on this conformational inversion, see: (a) Hsu, D. C.; Lam, P. C.-H.; Slebodnick, C.; Carlier, P. R. *J. Am. Chem. Soc.* **2009**, *131*, 18168−18176. (b) Carlier, P. R.; Sun, Y. S.; Hsu, D. C.; Chen, Q. H. *J. Org. Chem.* **2010**, *75*, 6588−6594.
(6) (a) Linscheid, P.; Lehn, J-M. E. *Bull. Soc. Chim. Fr.* **1967**, 992−997. (b) Carlier, P. R.; Zhao, H.; Mac-Quarrie-Hunter, S. L.; DeGuzman, J. C.; Hsu, D. C. *J. Am. Chem. Soc.* **2006**, *128*, 15215−15220.
(7) (a) Gilman, N. G.; Rosen, P.; Earley, J. V.; Cook, C.; Todaro, L. J. *J. Am. Chem. Soc.* **1990**, *112*, 3969−3978. (b) Lam, P. C. H.; Carlier, P. R. *J. Org. Chem.* **2005**, *70*, 1530−1538.
(8) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.
(9) (a) Yang, S. K. *Chirality* **1994**, *6*, 175−184. (b) Atkins, R. J.; Banks, A.; Bellingham, R. K.; Breen, G. F.; Carey, J. S.; Etridge, S. K.; Hayes, J. F.; Hussain, N.; Morgan, D. O.; Oxley, P.; Passey, S. C.; Walsgrove, T. C.; Wells, A. S. *Org. Process Res. Dev.* **2003**, *7*, 663−675.
(10) (a) *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds., Wiley-VCH: Weinheim, Germany, 2005. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89. (c) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131.
(11) For representative examples see: (a) Shaabani, A.; Rezayan, A. H.; Keshipour, S.; Sarvary, A.; Ng, S. W. *Org. Lett.* **2009**, *11*, 3342−3345. (b) Guggenhem, K. G.; Toru, H.; Kurt, M. J. *Org. Lett.* **2012**, *14*, 3732−3735. (c) Donald, J. R.; Wood, R. R.; Martin, S. F. *ACS Comb. Sci.* **2012**, *14*, 135−143. (d) Xu, J.; Wei, J.; Bian, L.; Zhang, J.; Chen, J.; Deng, H.; Wu, X.; Zhang, H.; Cao, W. *Chem. Commun.* **2011**, *47*, 3607−3609.
(12) For representative examples see: (a) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8935−8939. (b) De Silva, R. A.; Santra, S.; Andreana, P. R. *Org. Lett.* **2008**, *10*, 4541−4544. (c) Marcaccini, S.; Miliciani, M.; Pepino, R. *Tetrahedron Lett.* **2005**, *46*, 711−713. (d) Tempest, P.; Pettus, L.; Gore, V.; Hulme, C. *Tetrahedron Lett.* **2003**, *44*, 1947−1950. (e) Shaabani, A.; Rezayan, A. H.; Keshipour, S.; Sarvary, A.; Weng, S. *Org. Lett.* **2009**, *11*, 3342−3345. (f) Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475−14484. (g) Sañudo, M.; García-Valverde, M.; Marcaccini, S.; Delgado, J. J.; Rojo, J.; Torroba, T. *J. Org. Chem.* **2009**, *74*, 2189−2192.
(13) (a) Gordon, C. P.; Young, K. A.; Hizartzidis, L.; Deane, F. M.; McCluskey, A. *Org. Biomol. Chem.* **2011**, *9*, 1419−1428. (b) He, P.; Nie, Y.; Wu, J.; Ding, M. W. *Org. Biomol. Chem.* **2011**, *9*, 1429−1436. (c) Marcaccini, S.; Pepino, R.; Pozo, M. C.; Basurto, S.; García-Valverde, M.; Torroba, T. *Tetrahedron Lett.* **2004**, *45*, 3999−4001.
(14) Lecinska, P.; Corres, N.; Moreno, D.; García-Valverde, M.; Marcaccini, S.; Torroba, T. *Tetrahedron* **2010**, *66*, 6783−6788.
(15) Huang, Y.; Khoury, K.; Chanas, T.; Dömling, A. *Org. Lett.* **2012**, *14*, 5916−5919.
(16) Azuaje, A.; Coelho, A.; El Maatougui, A.; Blanco, J. M.; Sotelo, E. *ACS Comb. Sci.* **2011**, *13*, 89−95.
(17) The Supporting Information contains crystallographic information files (CIFs) of compounds **7p**,**u**. Additional information can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC 915940 and CCDC 915941).
(18) (a) Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. *Chem. Rev.* **2012**, *112*, 1839−1862. (b) Petrovich, A. G.; Navarro-Vázquez, A.; Alonso-Gómez, J. L. *Curr. Org. Chem.* **2010**, *14*, 1612−1628.
(19) (a) Smith, S. G.; Goodman, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 12946−12959. (b) Smith, S. G.; Goodman, J. M. *J. Org. Chem.* **2009**, *74*, 4597−4607.
(20) Belvisi, L.; Gennari, C.; Mielgo, A.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **1999**, *1999*, 389−400.
(21) The Supporting Information contains the crystallographic information file (CIF) of compound **8d2**. Additional information can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC 915942).
(22) (a) Baerends, E. J.; Ellis, D. E.; Ros, P. *Chem. Phys.* **1973**, *2*, 41−51. (b) Eichkorn, K.; Weigend, K.; Treutler, F.; Ahlrichs, R. O. *Theor. Chem. Acc.* **1997**, *97*, 119−124.
(23) Schaefer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571−2577.
(24) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297−3305.
(25) Kutzelnigg, W., Fleischer, U., Schindler. M. *The IGLO-Method: Ab Initio Calculation and Interpretation of NMR Chemical Shifts and Magnetic Susceptibilities*; Springer-Verlag: Berlin, 1990; Vol. *23*.
(26) Zhang, Y.; Wu, A.; Xu, X.; Yan. *Chem. Phys. Lett.* **2006**, *421*, 383−388.
(27) Jensen, F. *J. Chem. Theory Comput.* **2008**, *4*, 719−727.
(28) Sinnecker, S.; Rajendran, A.; Klamt, A.; Diedenhofen, M.; Neese, F. *J. Phys. Chem. A* **2006**, *110*, 2235−2245.
(29) Neese, F. *WIREs Comput. Mol. Sci.* **2012**, *2*, 73−78.

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J. Org. Chem. 2015, 80, 1533−1549