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An Efficient Approach to Chiral C8/C9-Piperazino-Substituted 1,4-Benzodiazepin-2-ones as Peptidomimetic Scaffolds

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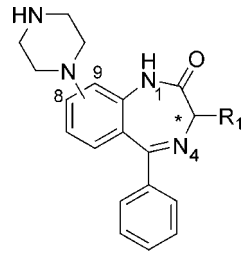

A promising way to interfere with biological processes is through the modulation of protein−protein interactions by means of small molecules acting as peptidomimetics. The 1,4-benzodiazepine scaffold has been widely reported as a peptide-mimicking, pharmacogenic system. While several synthetic pathways to C6−8 substituted benzodiazepines have been disclosed, few 1,4-benzodiazepines substituted at C9 have been reported. Herein, we describe a versatile approach to introduce cyclic, protonatable functionality at C8/C9. Introduction of the piperazine system at C8 and C9 gave access to a unique functionalization of the versatile benzodiazepine skeleton, broadening tailoring options on the benzofused side of the molecule, and the possibility of discovering novel peptidomimetics potentially able to modulate protein−protein interactions. Coupling of activated amino acids with poorly reactive anilines under mild conditions, while avoiding racemization, gave easy access to these compounds. Efficient amino acid activation was obtained by exploiting the rapid formation of acid chlorides under low temperature and acid/base free conditions, using triphenylphosphine and hexachloroacetone. This procedure successfully resulted in high reaction yields, did not produce racemization (ee > 98%, as demonstrated by using chiral solvating agents), and was compatible with the acid sensitive protecting groups present in the substrates.

Introduction

Many proteins exert their biological roles as components of complexes, and their functions are often determined by specific protein−protein interactions (PPIs). Because of their central role in cellular processes, the ability to interfere with such specific interactions provides a powerful means of influencing the function of selected proteins within the cell.

A minor fraction of the protein−protein interface residues can account for the majority of the free energy of binding between proteins.[1] Such "hot spots" are common at protein−protein interfaces[2] and have been identified by combining X-ray crystallography with site-directed mutagenesis.[3,4] Thus, from a pharmaceutical standpoint, cell-permeable small organic modu-

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lators of PPIs are highly desirable tools for both the study of physiological cellular processes and the treatment of a number of diseased states in which aberrant or inappropriate PPIs occur. A molecular recognition event depends upon electrostatic and steric complementarities at the ligand/receptor interface. For small molecules this recognition surface is dictated by the geometry of appended functional groups on a suitable scaffold, matching protein surface features where shape and electrostatic potential, hydrophobic patches,[3b,5−8] and about 76% of all hydrogen bonds in protein complexes[5,9] are mainly associated with side chains as key recognition elements in PPIs.[10]

β-Turns are often conserved during evolution, they represent an important recognition element of peptides and proteins, and are considered as initiation sites for protein folding. Consequently, a great deal of scientific effort has been devoted to classifying, designing, and synthesizing β-turn mimetics.[11] Three classes of peptidomimetics were defined:[12] (i) class I mimetics that often match the amide bond backbone, (ii) class II mimetics that do not necessarily mimic the structure of the parent peptide, and (iii) class III compounds based on replacing the amide backbone of peptides by other templates or scaffolds. The benzodiazepine (BDZ) scaffold represents a classic example of class III peptidomimetics and is considered a protypical privileged substructure.[13] The term "privileged structure" was first applied by Evans et al. to 1,4-benzodiazepine-2-ones able to bind cholecystokinin, gastrin, and central BDZ receptor.[14,15] There is a plethora of literature indicating the "pharmacogenicity" of the BDZ scaffold and its therapeutic utility. Besides the well-known anxiolytic,[16] sedative,[17] and anticonvulsant[18] activities of the classic BDZs (e.g., diazepam, triazolam, or midazolam), several 1,4-benzodiazepine derivatives demonstrated activity as antitumor antibiotics,[19] anti-HIV agents,[20] and antiarrhythmics.[21] Furthermore, diverse 1,4-benzodiazepine derivatives were also used as constrained dipeptide mimics or nonpeptide scaffolds in the search for peptidomimetics either as enzyme inhibitors[22] or as ligands of G-protein coupled receptors.[23] More recently, the 1,4-benzodiazepine-2,5-dione scaffold was also used as a PPI modulator.[24]

Given the importance of PPIs, the utility of peptidomimetics, and the pharmacogenic profile of 1,4-benzodiazepin-2-ones, we decided to further explore this scaffold with the aim of identifying new molecular entities that match PPI motifs. In particular, we focused our attention on fuctionalizing the BDZ C8 and C9 positions with a piperazine ring. The distal piperazine nitrogen atom represents an interaction point that in combination with the BDZ scaffold could allow the reproduction of protein secondary structures and/or hot-spots (PPI domains). In fact, the piperazine ring is a common pharmacophore found in a large number of drugs, it is regarded as a privileged structural element for the enhancement of "drug-like" properties, and has been used in the construction of peptidomimetic compounds and PPI inhibitors.[24c,25]

Most of the BDZs described to date present either an unsubstituted or C6/C7-substituted benzofused ring system due, in part, to the facile incorporation of functionality at these positions. On the contrary, examples of C8/C9-substituted 1,4-benzodiazepines are scarce and an even smaller subset of these examples bear groups that can be functionalized to generate chemical diversity[13] (e.g., amine, carboxylic functions, etc.), although few examples are reported of chemical routes leading

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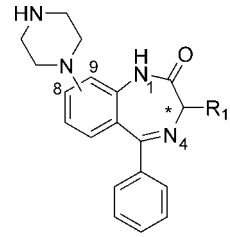
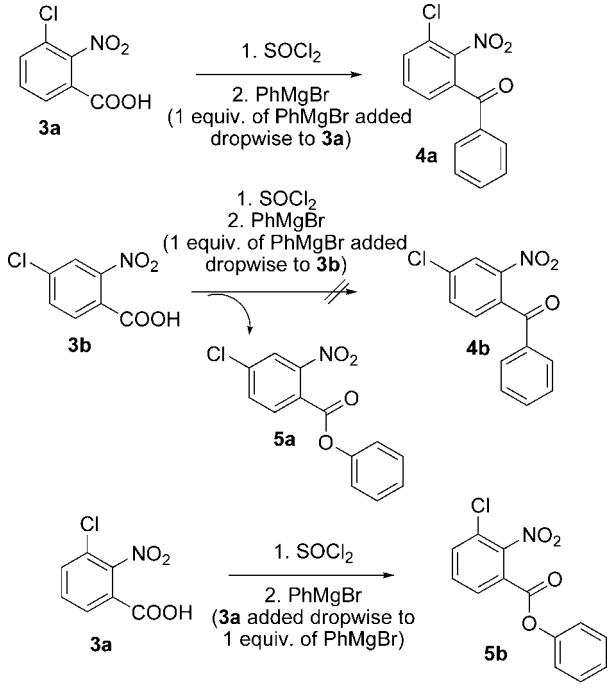
CHART 1. C8/C9-Substituted 1,4-Benzodiazepin-2-ones 1a−i and 2a−c (R_1 as defined in Tables 1 and 2)



1a-i, C9-piperazyn-1-yl
2a-c, C8-piperazyn-1-yl

SCHEME 1. Synthesis of Benzophenone 4a and Esters 5a,b



to nitro-[26] or azido-derivatives[27] that can be reduced to the corresponding amino functionality.

For the synthesis of the C8 and C9 piperazin-1-yl-substituted 1,4-benzodiazepine-2-ones **1a−i** and **2a−c** (Chart 1) presented herein, a standard approach to the BDZ system was applied. Specifically, *N*-acylation of an *o*-aminobenzophenone (**7a**,**c**, **10a**,**c**, Schemes 1−5) with an activated L- or D-α-amino acid derivative, followed by a ring closure event to form the BDZ N4/C5 bond.

The coupling of amino acids with poorly reactive anilines under mild conditions, while avoiding racemization, represented the critical step of this synthetic method. To address this issue, efficient amino acid activation was pursued exploiting the rapid formation of acid chlorides, under low temperature and acid/base free conditions, using triphenylphosphine and hexachloroacetone. This procedure resulted in high reaction yields, did not produce racemization, and was compatible with the acid-sensitive protecting group in the reaction substrates. The enantiomeric purity of the synthesized BDZs was assessed by NMR spectroscopy with use of chiral solvating agents (CSA).

Results and Discussion

The synthesis of the target BDZs **1a−i** and **2a−c** (Chart 1) and of their intermediates (and byproducts) is described in Schemes 1−5. The key intermediates for the synthesis of C8- or C9-substituted BDZs (**1a−i** and **2a−c**) were aminobenzophenones **7a−c** and **10a−c**, respectively. Commercially available benzoic acids **3a**,**b** were chosen as suitable starting materials to give access to these key intermediates. Accordingly, as outlined in Scheme 1, compound **3a** was transformed into the corresponding benzoyl chloride[28] and then reacted with phenylmagnesium bromide to afford nitrobenzophenone **4a** in 50% overall yield. However, treatment of **3b** under the same reaction conditions did not afford the expected product **4b**, but resulted in the formation of the benzoic ester **5a**, whose structure was confirmed by X-ray analysis (Figure 1, SI).

These data encouraged us to speculate about the reaction mechanism leading to the formation of **5a** from **3b**. Accordingly, we propose a multistep mechanism (Scheme 2) based on a previously described single electron transfer (SET) reaction[29] between nitroarenes and Grignard reagents as the initiating step. Initially, the reaction between the acid chloride of **3b** and the Grignard reagent (Scheme 2, Step A) could generate a nitroarene radical anion (**A**) and a phenyl radical through the SET reaction. In the next step, the phenyl radical attacks the oxygen atom of the nitro group, forming a reactive intermediate (**B**) that by loss of magnesium bromide phenolate (Step C) evolves to 4-chloro-2-nitrosobenzoyl chloride (**C**).[29] At this point we hypothesized that the phenoxide anion formed in Step C could react with the acid chloride functionality to form the phenylbenzoic ester (**D**). However, we cannot rule out a concerted mechanism directly leading to intermediate **D** from **B** involving an intramolecular nucleophilic attack of the phenoxy-functionality of **B** on the acyl chloride thus forming **D**.

Although Steps A−D are all plausible, the oxidation of the nitroso group (Step E) remains speculative.

Phenyl 3-chloro-2-nitrobenzoate (**5b**) was formed starting from 3-chloro-2-nitrobenzoyl chloride (Scheme 1) only when this latter was added to a solution of the Grignard reagent (an excess of phenylmagnesium bromide was consequently present). On the contrary, compound **5a** was formed from 4-chloro-2-nitrobenzoyl chloride even if the presence of an excess of phenylmagnesium bromide was carefully avoided. Although we do not have an exact explanation for the different reactivity of the acid chlorides of compounds **3a** and **3b** toward phenylmagnesium bromide, the electronic and steric differences of the two compounds are likely to play a pivotal role in the SET reaction.

In the following step of the synthetic pathway, the aforementioned nitrobenzophenone **4a** was used as the starting material for the synthesis of key intermediates **7a−c** (Scheme 3), while compounds **10a−c**, necessary for the preparation of benzodiazepines **2a−c**, were synthesized following an alternative synthetic strategy (Scheme 4).

Benzophenone **4a** was subjected to a nucleophilic aromatic substitution reaction with *N*-protected piperazines at 100 °C in a sealed tube for 24 h to obtain derivatives **6a−c** (Scheme 3).

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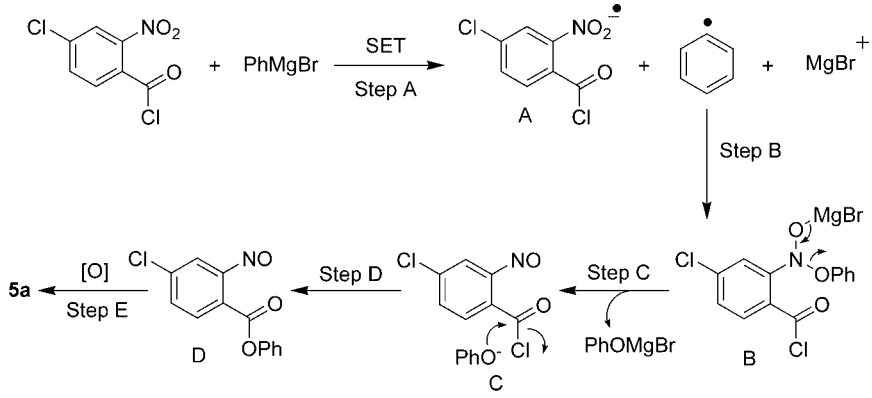
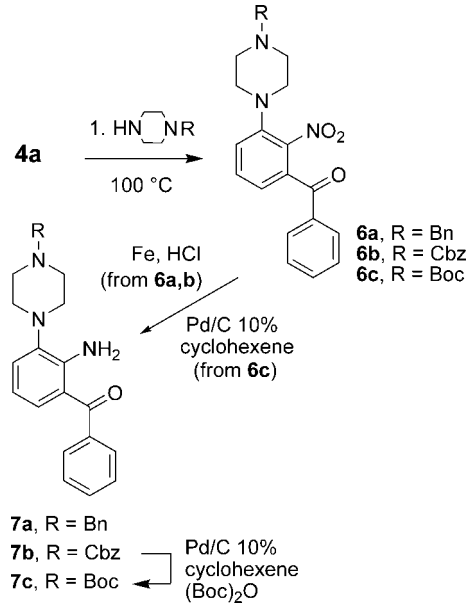
SCHEME 2. Hypothesized Reaction Mechanism Leading to the Formation of 5a from 3b



SCHEME 3. Synthesis of Compounds 7a−c



The reduction of the nitro group of **6a−c** was then performed by using different methods depending upon the nature of the piperazine protecting groups which had been chosen according to the orthogonal protection strategy employed.

Reaction of **6a**,**b** with tin(II) chloride in ethanol to obtain **7a**,**b** failed, while successful reduction was achieved by using Fe(0) in acidic ethanol, leading to the desired anilines **7a**,**b** in good yield. On the other hand, the reduction of compound **6c** to aniline **7c** was performed by catalytic transfer hydrogenation (Pd/C and cyclohexene). Boc-protected derivative **7c** was also accessed from the less expensive intermediate **7b**, using Pd/C and cyclohexene in the presence of $(Boc)_2O$. Reduction of the aromatic nitro group and simultaneous hydrogenolytic cleavage of the Cbz group afforded the free piperazine, which was trapped in situ with $(Boc)_2O$.

Due to the undesired formation of the benzoic ester **5a** previously discussed (Scheme 2), a different synthetic strategy was undertaken for the synthesis of 4-piperazinebenzophenones **10a−c** (Scheme 4). An ortho-benzoylation of 3-bromoaniline **8** was effected with benzonitrile in the presence of boron trichloride and aluminum trichloride[30] affording benzophenone **9a**, which was substituted with *N*-Boc-piperazine and *N*-Cbz-piperazine to afford intermediates **10a** and**10b**, respectively, each in 10% yield over two steps.

Attempts to improve the yield by varying reaction conditions (e.g., temperature, solvents, or using microwave irradiation) failed to convey a substantial improvement. Probably, the low reactivity of the benzophenone C4 halo substituents toward the aromatic nucleophilic displacement could rely on the electron-donating effect of the *m*-amino group. Consequently, we decided to optimize the formation of the benzophenone **9** through an alternative and less expensive procedure. Accordingly, benzonitrile **11** was selected as the starting material and when treated sequentially with phenylmagnesium bromide (2 equiv) and aqueous acid provided the corresponding chloroaminobenzophenone **9b** in 80% yield. Reaction of *N*-Bn-piperazine with **9b** furnished **10c** in 35% yield. Starting from **10b** and **10c** the Boc-derivative **10a** was obtained as previously described.

Scheme 5 describes the synthesis of target compounds **1a−i** and **2a−c**. Attempts to directly couple Cbz-α-amino acids with di-*o*-substituted anilines **7a**,**c** by using a variety of peptide coupling reagents failed due to a combination of the inherently poor nucleophilicity and steric inaccessability of this aminobenzophenone nitrogen atom. Preprepared activated esters (e.g., *p*-nitrophenyl and hexafluorophenyl) of the aforementioned Cbz-α-amino acids similarly failed to react with compound **7c**. Activation of a carboxylic acid can also be achieved through conversion to the corresponding acyl chloride and several methods are available for such reaction.[31] However, the use of protected α-amino acid chlorides has been limited as they tend to undergo racemization (either during synthesis or subsequent coupling) via azalactone-type intermediates and cleavage of protecting groups can occur.[31,32] Consequently, we turned our attention to developing a method for the formation of Cbz-α-amino acid chlorides in situ under mild conditions. Once formed, these highly reactive intermediates would certainly react with the sterically encumbered amines **7a**,**c**.

It is known that rapid formation of acid chlorides under low temperature and acid/base free conditions could be conveniently achieved by using triphenylphosphine and a source of chloride like carbon tetrachloride or hexachloroacetone[33] and in a few examples similar methodologies were applied to the formation

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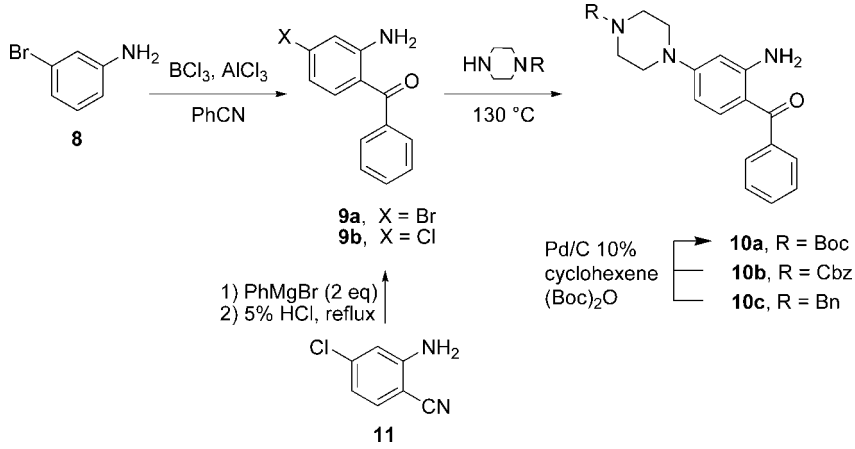
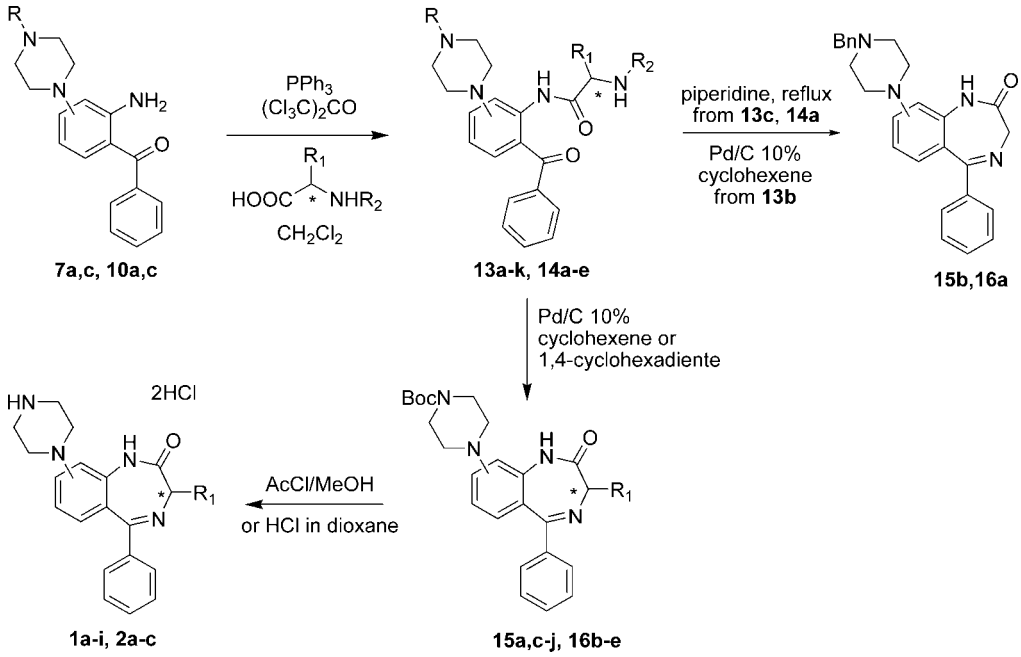
SCHEME 4. Synthesis of Compounds 10a−c



SCHEME 5. Synthesis of 1,4-Benzodiazepines 1a−i and 2a−c[a]



[a] For R, R_1, and R_2 see Tables 1 and 2.

of amino acid chlorides.[34] Gratifyingly, under these conditions, compounds **7a**,**c** and **10a**,**b** were converted into **13a−k** and **14a−e**. Optimal reaction conditions required the use of 3 equiv of triphenylphosphine, 0.75 equiv of hexachloroacetone, and 1.5 equiv of *N*-protected amino acid in dichloromethane at 25 °C. Reaction yields are listed in Tables 1 and 2, and with few exceptions they were higher than 90% for compounds of type **13** and **14**. Moreover, enantiomeric excess (ee), determined for the target compounds (see below and the Supporting Information), indicated that no amino acid racemization occurred under the above-described reaction conditions. This methodology offers a valid alternative to the use of protected amino acid fluorides which are needed to perform similar transformations.[31,35]

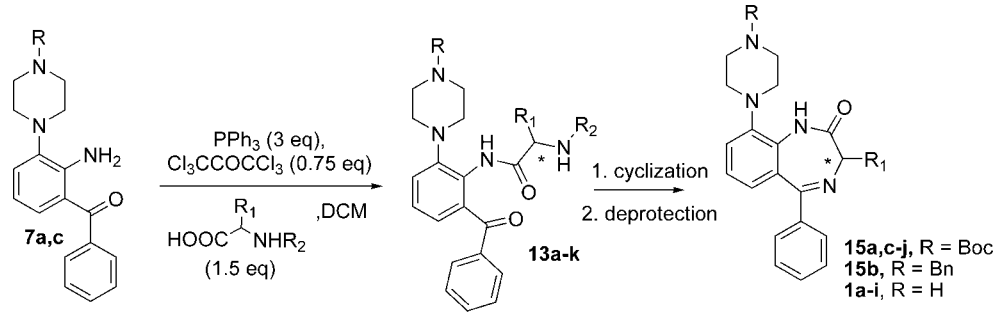
In the next steps of the synthetic pathway, deprotection of Cbz-protected amino groups of **13a**,**b**,**d−k** and **14b−e** was accomplished by hydrogenolysis, using cyclohexene and 10% Pd/C in ethanol under reflux. During the hydrogenation step, a simultaneous cyclization reaction produced the corresponding Boc-protected benzodiazepines **15a**,**c−j** and **16b−e** and the Bn-protected derivative **15b** with yields ranging from 78% to 80%.

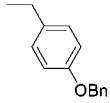
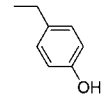
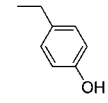
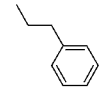
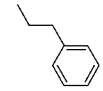
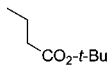
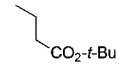
Starting from compounds **13c** and **14a**, deprotection of the Fmoc group in refluxing piperidine occurred with in situ cyclization to afford **15b** and **16a**, respectively. For compounds **13h**,**j** and **14c**, which presented an additional benzyl group for protection of the primary alcohol (Ser) or the phenolic hydroxyl (Tyr) function, longer reaction times were required for complete deprotection, which resulted in partial decomposition and a lowering of the overall yield. Replacement of cyclohexene with cyclohexadiene as the hydrogen donor shortened the reaction time (12 h) but did not lead to improved yields. In the last step of the synthesis, quantitative *N*-Boc-deprotection of **15a**,**c−j** and **16b−d** was achieved by treatment with a freshly prepared dry solution of 5% hydrochloric acid in methanol. This method

(34) (a) Lorca, M.; Kurosu, M. *Synth. Commun.* **2001**, *31*, 469–473. (b) Miller, M. C.; Sood, A.; Spielvogel, B. F.; Hall, I. H. *Anticancer Res.* **1997**, *17*, 3299–3306.

(35) (a) Dourlat, J.; Liu, W.-Q.; Gresh, N.; Garbay, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2527–2530. (b) Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M. *Acc. Chem. Res.* **1996**, *29*, 268–274.

TABLE 1. Coupling of *N*-Protected Amino Acids with Aminobenzophenones 7a,c Affording Amides 13a−k, Cyclization Products 15a−j, and Deprotected 1,4-Benzodiazepines 1a−i As Described in Scheme 5



Amides	R	R_1	R_2	Yield (%)	Cyclization products	R_1	Piperazine-deprotected compounds	R_1
13a	Boc	-H	Cbz	86	**15a**	-H	**1a**	-H
13b	Bn	-H	Cbz	45	**15b**	-H	-	-
13c	Bn	-H	Fmoc	75	**15b**	-H	-	-
(*R*)-**13d** (*S*)-**13d**	Boc	-Me	Cbz	94 97	(*R*)-**15c** (*S*)-**15c**	-Me	(*R*)-**1b** (*S*)-**1b**	-Me
(*R*)-**13e** (*S*)-**13e**	Boc		Cbz	65 80	(*R*)-**15d** (*S*)-**15d**		(*R*)-**1c** (*S*)-**1c**	
(*R*)-**13f** (*S*)-**13f**	Boc		Cbz	98 90	(*R*)-**15e** (*S*)-**15e**		(*R*)-**1d** (*S*)-**1d**	
(*R*)-**13g** (*S*)-**13g**	Boc		Cbz	92 90	(*R*)-**15f** (*S*)-**15f**		(*R*)-**1e** (*S*)-**1e**	
(*R*)-**13h** (*S*)-**13h**	Boc		Cbz	96 70	(*R*)-**15g** (*S*)-**15g**		(*R*)-**1f** (*S*)-**1f**	
(*R*)-**13i** (*S*)-**13i**	Boc		Cbz	98 74	(*R*)-**15h** (*S*)-**15h**		(*R*)-**1g** (*S*)-**1g**	
(*R*)-**13j** (*S*)-**13j**	Boc		Cbz	96 93	(*R*)-**15i** (*S*)-**15i**		(*R*)-**1h** (*S*)-**1h**	
(*R*)-**13k** (*S*)-**13k**	Boc		Cbz	98 90	(*R*)-**15j** (*S*)-**15j**		(*R*)-**1i** (*S*)-**1i**	

cleanly afforded the corresponding target compounds **1a−i** and **2a−c** as the hydrochloride salts.

The ee of *N*-Boc protected benzodiazepines **15c−j** and **16c−e** was determined by NMR spectroscopy by using Pirkle alcohol (*R*)-trifluorobenzyl alcohol as the chiral solvating agent. Applying this methodology, the ee determined for compounds **15c−j** and **16c−e** proved to be ≥98%, thus confirming that no racemization occurred during the synthetic process (further details are given as Supporting Information).

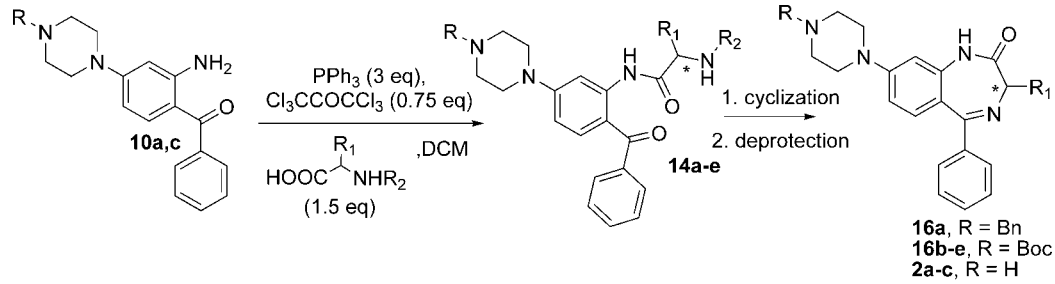
Conclusions

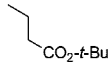
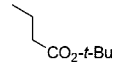
This work provides a new, mild, and efficient method for the synthesis of C8/C9-piperazino-substituted 1,4-benzodiazepine peptidomimetic scaffolds potentially useful for the synthesis of small-molecule PPI modulators. The synthetic strategy herein discussed is based on a mild chlorination procedure applied to the synthesis of enantiopure amino acid chlorides. By using this methodology, these highly reactive intermediates could be prepared and coupled with poorly reactive and hindered anilines, thus giving access to anilides which were otherwise inaccessible. Moreoever, this coupling took place without racemization as evidenced by the high ee (≥98%) determined for the BDZ products. The ee was evaluated by means of an NMR method based on the use of CSAs.

Experimental Procedure

(3-Chloro-2-nitrophenyl)phenylmethanone (4a). 3-Chloro-2-nitrobenzoic acid (**3a**) (3.04 g, 15.08 mmol) was converted into the corresponding 3-chloro-2-nitrobenzoyl chloride as described in

TABLE 2. Coupling of *N*-Protected Amino Acids with Aminobenzophenones 10a,c Affording Amides14a−e, Cyclization Products 16a−e, and Deprotected 1,4-Benzodiazepines 2a−c As Described in Scheme 5



Amides	R	R_1	R_2	Yield (%)	Cyclization products	R_1	Piperazine-deprotected compounds	R_1
14a	Bn	-H	Fmoc	91	**16a**	-H	-	-
14b	Boc	-H	Cbz	89	**16b**	-H	**2a**	-H
(*R*)-**14c**	Boc		Cbz	45	(*R*)-**16c**		(*R*)-**2b**	
(*S*)-**14c**				66	(*S*)-**16c**		(*S*)-**2b**	
(*R*)-**14d**	Boc		Cbz	72	(*R*)-**16d**		(*R*)-**2c**	
(*S*)-**14d**				82	(*S*)-**16d**		(*S*)-**2c**	
(*R*)-**14e**	Boc		Cbz	88	(*R*)-**16e**		-	-
(*S*)-**14e**				74	(*S*)-**16e**			

the literature,[36] and this latter was dissolved in THF (100 mL) and cooled to −10 °C. A solution of phenylmagnesium bromide (1 M solution in THF, 15.08 mmol, 15.1 mL) was added dropwise over a period of 10 min. The reaction mixture was stirred at 23 °C for 16 h; afterward it was poured into a 5% solution of HCl (100 mL) and the aqueous phase was extracted with EtOAc (5 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried (Na_2SO_4) then the solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 11:1) to afford, after recrystallization, the title compound as light orange prisms (1.98 g, 50%). Mp (*n*-hexane) 65−67 °C [lit.[37] mp (isopropanol) 67−69 °C]. Anal. ($C_{13}H_8ClNO_3$) C, H, N.

4-Chloro-2-nitrobenzoic Acid Phenyl Ester (5a). 4-Chloro-2-nitrobenzoyl chloride (5.0 g, 2 mmol), prepared from 2-nitro-4-chlorobenzoic acid (**3b**) as described in the literature,[36] was dissolved in THF (20 mL) and cooled to −10 °C. A solution of phenylmagnesium bromide (1 equiv, 3 M in THF) was added dropwise over a period of 10 min. The reaction mixture was stirred at 23 °C for 5 h; afterward it was poured into a 5% solution of HCl (100 mL) and extracted with EtOAc (5 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried then the solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 11:1) to afford, after recrystallization, the title compound as orange prisms (2.3 g, 42%). Mp (*n*-hexane) 81−82 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20 (m, 3H), 7.37 (m, 2H), 7.68 (dd, 1H, J = 7.7, 1.8 Hz), 7.84−7.00 (d, 1H, J = 8.4 Hz), 7.94 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 121.0, 124.2, 125.0, 126.4, 129.5, 131.3, 133.0, 138.3, 150.2, 162.8; ESI MS *m*/*z* 300 (M + Na)$^+$. Anal. ($C_{13}H_8ClNO_4$) C, H, N.

3-Chloro-2-nitrobenzoic Acid Phenyl Ester (5b). To a solution of phenylmagnesium bromide (1 equiv, 3 M in THF) was added 3-chloro-2-nitrobenzoyl chloride (846 mg, 3.44 mmol), prepared from 2-nitro-3-chlorobenzoic acid (**3a**) as described in the literature,[36] over a period of 10 min. The reaction mixture was stirred at room temperature for 6 h then poured into a 5% solution of HCl (10 mL) and extracted with EtOAc (5 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried then the solvent was removed in vacuo. The residue was purified by column chromatography (4:1, *n*-hexane/EtOAc; R_f 0.42) to afford the title compound as an orange oil (300 mg, 27%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.16−7.68 (m, 5H), 8.03 (m, 2H), 8.17 (d, J = 8.1 Hz, 1H). MS *m*/*z* 300 (M + Na)$^+$. Anal. ($C_{13}H_8ClNO_4$) C, H, N.

[3-(4-Benzylpiperazin-1-yl)-2-nitrophenyl]phenylmethanone (6a). 3-Chloro-2-nitrobenzophenone (**4a**) (234 mg, 0.89 mmol) was dissolved in 1-benzylpiperazine (1 mL, 5.75 mmol) and the resulting mixture was stirred at 100 °C in a sealed tube for 48 h. After cooling to 23 °C, the mixture was partitioned between EtOAc (10 mL) and water (5 mL). The organic phase was separated and dried then the solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 1:1; R_f 0.23) to afford, after recrystallization, the title compound as yellow prisms (200 mg, 56%) and the unreacted starting material was recovered. Mp (*n*-hexane) 122−124 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.56−2.60 (m, 4H), 3.06−3.11 (m, 4H), 3.55 (s, 2H), 7.11 (d, 1H, J = 7.0 Hz), 7.27−7.37 (m, 6H), 7.41−7.52 (m, 3H), 7.60 (m, 1H), 7.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.4, 53.3, 63.2, 123.4, 124.5, 127.4, 128.5, 128.8, 129.4, 130.2, 131.4, 134.0, 134.9, 136.0, 138.1, 144.8, 146.0, 193.3; ESI-MS *m*/*z* 424 (M + Na)$^+$, 402 (M + H)$^+$. Anal. ($C_{24}H_{23}N_3O_3$) C, H, N.

[3-(4-Benzyloxycarbonylpiperazin-1-yl)-2-nitrophenyl]phenylmethanone (6b). 3-Chloro-2-nitrobenzophenone (**3a**) (3.26 g, 12.47 mmol) was dissolved in 1-benzyloxycarbonylpiperazine (10 mL, 39.75 mmol) and the resulting mixture was stirred at 100 °C in a sealed tube for 48 h. After cooling, the mixture was partitioned between EtOAc (100 mL) and water (50 mL). The organic phase was separated and dried then the solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 1:1; R_f 0.33) to afford the title compound as yellow prisms

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(37) Walsh, D. A.; Moran, H. W.; Shamblee, D. A.; Welstead, W. J. J.; Nolan, J. C.; Sancilio, L. F.; Graff, G. *J. Med. Chem.* **1990**, *33*, 2296–2304.

(2.80 g, 50%) and the unreacted starting material was recovered. Mp (*n*-hexane) 126−128 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.02 (m, 4H), 3.62 (m, 4H), 5.15 (s, 2H), 7.18−7.25 (m, 1H), 7.30−7.41 (m, 6H), 7.42−7.52 (m, 3H), 7.59 (m, 1H), 7.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.3, 52.6, 67.6, 124.8, 125.1, 128.2, 128.4, 128.8, 128.9, 130.3, 131.5, 134.2, 134.8, 135.9, 136.8, 145.7, 155.4 (2C), 193.1; ESI-MS *m*/*z* 468 $(M + Na)^+$. HRMS calcd for $[(C_{25}H_{23}N_3O_5) + Na]^+$ 468.1530, found 468.1529. Anal. ($C_{25}H_{23}N_3O_5$) C, H, N.

[3-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-2-nitrophenyl]phenylmethanone (6c). A mixture of 3-chloro-2-nitrobenzophenone (**4a**) (1.40 g, 5.35 mmol) and 1-*tert*-butoxycarbonylpiperazine (2.80 g, 15.03 mmol) was heated to 100 °C in a sealed tube for 48 h. After cooling to 23 °C, the mixture was partitioned between EtOAc (50 mL) and water (30 mL). The organic phase was separated and dried then the solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 3:1; R_f 0.17) to afford the title compound as a bright orange oil (1.46 g, 66%) and the unreacted starting material was recovered. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.98 (m, 4H), 3.52 (m, 4H), 7.16 (d, 1H, J = 8.0 Hz), 7.33−7.58 (m, 5H), 7.77 (d, 2H, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 44.2, 52.5, 80.2, 124.5, 125.0, 128.8, 130.3, 131.5, 134.1, 134.8, 135.9, 145.5, 145.8, 154.9, 193.2; ESI-MS *m*/*z* 450 $(M + K)^+$, 434 $(M + Na)^+$. Anal. ($C_{22}H_{25}N_3O_5$) C, H, N.

[3-(4-Benzylpiperazin-1-yl)-2-aminophenyl]phenylmethanone (7a). To a solution of 3-(4-benzylpiperazinyl)-2-nitrobenzophenone (**6a**) (763 mg, 1.901 mmol) in ethanol (5 mL), glacial acetic acid (5 mL), water (1 mL) and 6 M HCl (0.1 mL) was added iron powder (740 mg, 13.25 mmol). The resulting heterogeneous mixture was heated under reflux for 30 min, poured into water (20 mL), and filtered through a bed of Celite, which was subsequently washed with dichloromethane (10 mL). The aqueous filtrate was extracted with dichloromethane (5 × 10 mL) and the organic phases were combined, washed with 10% $NaHCO_3$ solution (10 mL), water (10 mL), and brine (10 mL) and dried. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane /EtOAc 1:1; R_f 0.60) to afford, after recrystallization, the title compound as bright yellow prisms (693 mg, 98%). Mp (*n*-hexane) 115−116 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.63 (br, 4H), 2.95 (m, 4H), 3.61 (s, 2H), 6.59 (t, 1H, J = 8.0 Hz), 6.65 (br, 2H), 7.15−7.51 (m, 10H), 7.60−7.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.6, 54.1, 63.4, 114.6, 118.1, 124.9, 127.4, 128.2, 128.5, 129.3, 129.5, 130.4, 131.1, 138.2, 140.2, 140.6, 147.1, 199.5; ESI-MS *m*/*z* 394 $(M + Na)^+$, 372 $(M + H)^+$. HRMS calcd for $[(C_{24}H_{25}N_3O) + Na]^+$ 394.1890, found 394.1893. Anal. ($C_{24}H_{25}N_3O$) C, H, N.

[3-(4-Benzyloxycarbonylpiperazin-1-yl)-2-aminophenyl]phenylmethanone (7b). Starting from **6b** (1.11 g, 2.49 mmol), the title compound was obtained as described for **7a**. After purification by column chromatography (*n*-hexane/EtOAc 2:1; R_f 0.37) and recrystallization the title compound was obtained as bright yellow prisms (774 mg, 75%). Mp (*n*-hexane) 122−123 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.02 (br, 6H), 4.20 (br, 2H), 5.19 (s, 2H), 6.56 (t, 1H, J = 8.0 Hz), 6.66 (br, 2H), 7.12 (d, 1H, J = 8.0 Hz), 7.27 (d, 1H, J = 8.0 Hz), 7.30−7.51 (m, 8H), 7.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.8, 51.5, 67.5, 114.7, 118.4, 124.9, 128.2, 128.3, 128.3, 128.8, 129.3, 130.9, 131.2, 136.9, 139.6, 140.4, 155.5, 199.5. ESI-MS *m*/*z* 454 $(M + K)^+$, 438 $(M + Na)^+$, 416 $(M + H)^+$. HRMS calcd for $[(C_{25}H_{25}N_3O_3) + Na]^+$ 438.1788, found 438.1792. Anal. ($C_{25}H_{25}N_3O_3$) C, H, N.

[3-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-2-aminophenyl]phenylmethanone (7c). From 6c: To a solution of 3-(4-*tert*-butoxycarbonylpiperazin-1-yl)-2-nitrobenzophenone (**6c**) (1.46 g, 3.55 mmol) in ethanol (20 mL) and cyclohexene (10 mL) was added 10% palladium on carbon. The resulting suspension was heated under reflux under an argon atmosphere for 16 h, cooled, and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/EtOAc 3:1; R_f 0.43) to afford, after recrystallization, the title compound in 84% yield (1.14 g).

From 6b: To a suspension of 3-(4-benzyloxycarbonylpiperazin-1-yl)-2-nitrobenzophenone (**6b**) (2.84 g, 6.38 mmol) in ethanol (60 mL) were added cyclohexene (20 mL), di-*tert*-butyldicarbonate (2.09 g, 9.58 mmol), and 10% palladium on carbon (250 mg). The reaction mixture was heated under reflux under an argon atmosphere for 48 h, cooled, and filtered then the solvent was removed in vacuo. The residue was purified as described above to afford the title compound (2.28 g, 92%) as yellow prisms. Mp (*n*-hexane) 117−119 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.90 (br, 6H), 4.08 (br, 2H), 6.49 (t, 1H, J = 8.0 Hz), 6.63 (br, 2H), 7.07 (d, 1H, J = 8.0 Hz), 7.20 (d, 1H, J = 8.0 Hz), 7.33−7.47 (m, 3H), 7.55−7.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 48.6, 51.6, 80.1, 114.7, 118.3, 124.9, 128.3, 129.3, 130.8, 131.2, 139.8, 140.5, 146.9, 155.0, 199.4; ESI-MS *m*/*z* 420 $(M + K)^+$, 404 $(M + Na)^+$, 382 $(M + H)^+$. Anal. ($C_{22}H_{27}N_3O_3$) C, H, N.

(4-Bromo-2-aminophenyl)phenylmethanone (9a). To a stirred solution of boron trichloride (1 M solution in THF, 5.8 mmol, 5.8 mL) in dichloroethane was added a solution of 2-bromoaniline (0.63 mL, 5.8 mmol) dropwise under ice cooling. To the resulting solution were added benzonitrile (1.18 mL, 11.6 mmol) and aluminum trichloride (770 mg, 6.38 mmol) and within 20 min of stirring at 23 °C, the aluminum trichloride was completely dissolved. Subsequently, the solution was heated under reflux for 6 h, then cooled in ice and 2 N HCl was added dropwise under stirring. The resulting mixure was warmed to 80 °C for 1 h, then cooled to 23 °C and extracted with dichloromethane (5 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried then the solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 10:1; R_f 0.53) to afford the title compound (5.5 g, 34%) as a brownish solid. Mp (*n*-hexane) 90−92 °C [lit.[38] mp (diluted alcohol) 88−90 °C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (br, 2H), 6.72 (d, 1H, J = 7.3 Hz), 6.93 (s, 1H), 7.29 (d, 1H, J = 7.0 Hz), 7.43−7.62 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.1, 119.2, 119.4, 128.1, 128.7, 131.0, 138.3, 139.9, 154.4 (2C), 199.6; ESI-MS *m*/*z* 276 $(M + H)^+$. HRMS calcd for $[(C_{13}H_{10}BrNO) + H]^+$ 276.0019, found 276.0018. Anal. ($C_{13}H_{10}BrNO$) C, H, N.

(4-Chloro-2-aminophenyl)phenylmethanone (9b). To a stirred solution of 2-amino-4-chlorobenzonitrile (1.55 g, 1.01 mmol) in THF (30 mL) was added a solution of phenylmagnesium bromide (2.5 equiv, 3 M in THF) dropwise over a period of 10 min. The reaction mixture was stirred at 23 °C for 16 h; afterward it was poured into a 5% solution of HCl (100 mL) and the resulting mixture was heated under reflux for 3 h. The phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried then the solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 5:1) to afford the title compound (1.79 g, 80%). Analytical data were identical to those reported in the literature.[39]

[4-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-2-aminophenyl]phenylmethanone (10a). From 9a: A mixture of 4-bromo-2-aminobenzophenone (**9a**) (225 mg, 0.81 mmol) and 1-*tert*-butoxycarbonylpiperazine (761 mg, 4 mmol) was heated to 130 °C in a sealed tube for 48 h. After cooling to 23 °C, the mixture was partitioned between EtOAc (50 mL) and H_2O (30 mL). The organic phase was separated and dried then the solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 2:1; R_f 0.32) to afford the title compound as a bright orange oil (91 mg, 30%) and the unreacted starting material was recovered.

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(39) Carter, M. C.; Alber, D. G.; Baxter, R. C.; Bithell, S. K.; Budworth, J.; Chubb, A.; Cockerill, G. S.; Dowdell, V. C. L.; Henderson, E. A.; Keegan, S. J.; Kelsey, R. D.; Lockyer, M. J.; Stables, J. N.; Wilson, L. J.; Powell, K. L. *J. Med. Chem.* **2006**, *49*, 2311–2319.

From 10b: To a suspension of [4-(4-benzyloxycarbonylpiperazin-1-yl)-2-aminophenyl]phenylmethanone (**10b**) (1.6 g, 3.85 mmol) in ethanol (50 mL) was added cyclohexene (20 mL), di-*tert*-butyldicarbonate (1.26 g, 5.57 mmol), and 10% palladium on carbon (250 mg). The reaction was heated under reflux under argon for 48 h, cooled, and filtered then the solvent was removed in vacuo. The residue was purified as described above to afford the title compound (1.3 g, 88%).

From 10c: To a suspension of [4-(4-benzylpiperazin-1-yl)-2-aminophenyl]phenylmethanone (**10c**) (510 mg, 1.37 mmol) in ethanol (20 mL) were added cyclohexene (20 mL) and 10% palladium on carbon (50 mg). The reaction was heated under reflux under argon for 16 h, cooled, and filtered, then di-*tert*-butyldicarbonate (382 mg, 2.02 mmol) was added and the solution was heated under reflux for an additional 3 h. The solvent was removed in vacuo, the residue was purified as described above to afford the title compound (396 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 3.30 (m, 4H), 3.50 (m, 4H), 6.02 (d, 1H, J = 2.3 Hz), 6.15 (dd, 1H, J = 9.1, 2.3 Hz), 6.30 (br, 2H), 7.33 (d, 1H, J = 9.1 Hz), 7.39−7.48 (m, 3H), 7.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 43.1, 47.2, 80.4, 99.6, 103.9, 111.0, 128.2, 128.9, 130.4, 136.9, 141.2, 153.6, 154.8, 154.9, 197.2; ESI-MS m/z 420 (M + K)$^+$, 404 (M + Na)$^+$, 382 (M + H)$^+$. Anal. ($C_{22}H_{27}N_3O_3$) C, H, N.

[4-(4-Benzyloxycarbonylpiperazin-1-yl)-2-aminophenyl]phenylmethanone (10b). A mixture of 4-bromo-2-aminobenzophenone (**9a**) (2.5 g, 9.1 mmol) and 1-benzyloxycarbonylpiperazine (8.7 mL, 45.4 mmol) was stirred at 130 °C in a sealed tube for 48 h. After cooling, the mixture was partitioned between EtOAc (100 mL) and water (50 mL). The organic phase was separated and dried then the solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 2:1; R_f 0.21) to afford the title compound as a thick yellow oil (1.1 g, 33%) and the unreacted starting material was recovered. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (m, 4H), 3.63 (m, 4H), 5.16 (s, 2H), 6.01 (d, 1H, J = 2.3 Hz), 6.12 (dd, 1H, J = 8.5, 2.3 Hz), 6.31 (br, 2H), 7.30−7.46 (m, 9H), 7.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.6, 47.2, 67.2, 99.8, 104.0, 111.1, 128.2 (2C), 128.4, 128.8, 128.9, 130.5, 136.7, 136.9, 141.2, 153.5, 154.8, 155.4, 197.3; ESI-MS m/z 454 (M + K)$^+$, 438 (M + Na)$^+$, 416 (M + H)$^+$. Anal. ($C_{25}H_{25}N_3O_3$) C, H, N.

[4-(4-Benzylpiperazin-1-yl)-2-aminophenyl]phenylmethanone (10c). 4-Chloro-2-aminobenzophenone (**9b**) (1.41 g, 6.1 mmol) was dissolved in 1-benzylpiperazine (5.7 mL, 30 mmol) and the resulting mixture was stirred at 130 °C in a sealed tube for 48 h. After cooling, the mixture was partitioned between EtOAc (100 mL) and water (50 mL). The organic phase was separated and dried then the solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc 3:1) to afford the title compound as a yellow low-melting solid (0.77 g, 33%) and the unreacted starting material was recovered. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (m, 4H), 3.33 (m, 4H), 3.55 (s, 2H), 6.01 (d, 1H, J = 2.3 Hz), 6.14 (dd, 1H, J = 8.3, 2.3 Hz), 6.19 (br, 2H), 7.16−7.46 (m, 9H), 7.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.2, 53.0, 63.3, 99.3, 103.8, 110.6, 127.5, 128.2, 128.6, 128.9, 129.4, 130.3, 136.9, 138.1, 141.4, 153.7, 155.2, 197.1; ESI-MS m/z 394 (M + Na)$^+$, 372 (M + H)$^+$. Anal. ($C_{24}H_{25}N_3O$) C, H, N.

General Procedure for Preparation of compounds 13a−k and 14a−e. A stirred solution of protected amino acid (0.94 mmol) and triphenylphosphine (1.88 mmol) in dry dichloromethane (10 mL) was cooled to −10 °C and hexachloroacetone (0.75 equiv) was added dropwise. After 15 min, a solution of the appropriate protected benzophenones (0.63 mmol) in dichloromethane (2 mL) was added. The reaction mixture was stirred at −10 °C for 30 min, warmed to 23 °C, and washed with 10% $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with dichloromethane (2 × 5 mL), the organic extracts were combined and dried, then the solvent was removed in vacuo. The residue was purified by column chromatography, using a mixture of *n*-hexane/EtOAc as the eluent.

2-(Benzyloxycarbonylamino)-*N*-[2-benzoyl-6-(4-*tert*-butoxycarbonylpiperazin-1-yl)phenyl]acetamide (13a). Compound **13a** was prepared following the above-described general procedure and after purification by column chromatography (*n*-hexane /EtOAc 2:1; R_f 0.59) was obtained as a colorless oil (343 mg, 86%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.77 (br, 4H), 3.53 (br, 4H), 3.82 (d, 2H, J = 5.9 Hz), 5.09 (s, 2H), 5.48 (m, 1H), 7.08−7.49 (m, 10H), 7.53 (m, 1H), 7.87 (d, 2H, J = 7.2 Hz), 8.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 44.5, 45.4, 52.0, 67.5, 80.2, 122.9, 125.2, 125.6, 128.4, 128.5 (2C), 128.8, 129.4, 130.6, 133.0, 133.7, 136.2, 137.0, 145.4, 154.9, 156.9, 167.9, 195.6; ESI-MS m/z 1167 (2 M + Na)$^+$, 611 (M + K)$^+$, 595 (M + Na)$^+$, 573 (M + H)$^+$. Anal. ($C_{32}H_{36}N_4O_6$) C, H, N.

2-(Benzyloxycarbonylamino)-*N*-[2-benzoyl-6-(4-benzylpiperazin-1-yl)phenyl]acetamide (13b). The title compound was prepared following the above-described general procedure and after purification by column chromatography (*n*-hexane/EtOAc 1:1) was obtained as a colorless oil (320 mg, 45%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.63 (br, 4H), 2.89 (br, 4H), 3.54 (s, 2H), 3.87 (d, 2H, J = 5.8 Hz), 5.13 (s, 2H), 5.49 (m, 1H), 7.10−7.54 (m, 16H), 7.88 (d, 2H, J = 7.1 Hz), 8.65 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.3, 52.1, 53.8, 63.3, 67.4, 122.9, 125.2, 125.4, 127.4, 128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 129.3, 129.4, 130.5, 133.3, 136.3, 137.2, 138.2, 145.5, 156.6, 167.3, 195.4; ESI-MS m/z 601 (M + K)$^+$, 585 (M + Na)$^+$, 563 (M + H)$^+$. Anal. ($C_{34}H_{34}N_4O_4$) C, H, N.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-*N*-[2-benzoyl-6-(4-benzylpiperazin-1-yl)phenyl]acetamide (13c). The title compound was prepared following the above-described general procedure and after purification by column chromatography (*n*-hexane/EtOAc 1:1; R_f 0.30) was obtained as a colorless oil (308 mg, 75%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.54 (br, 4H), 2.85 (br, 4H), 3.42 (s, 2H), 3.96 (d, 2H, J = 5.5 Hz), 4.23 (m, 1H), 4.40 (m, 2H), 5.90 (m, 1H), 7.08−7.62 (m, 17H), 7.77 (d, 2H, J = 7.4 Hz), 7.98 (d, 2H, J = 7.4 Hz), 8.87 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.3, 47.3, 52.2, 53.8, 63.2, 67.8, 120.3, 123.0, 125.2, 125.4, 127.3, 128.0, 128.4, 128.5, 129.3, 130.6, 132.9, 133.4, 137.2, 138.1, 141.5, 144.0, 145.5, 156.7, 167.3, 195.5; ESI-MS m/z 689 (M + K)$^+$, 673 (M + Na)$^+$, 651 (M + H)$^+$. Anal. ($C_{41}H_{38}N_4O_4$) C, H, N.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-*N*-[2-benzoyl-5-(4-benzylpiperazin-1-yl)phenyl]acetamide (14a). Compound **14a** was prepared following the above-described general procedure and after purification by column chromatography (*n*-hexane/EtOAc 2:1; R_f 0.38) was obtained as a waxy yellow solid (381 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (br, 2H), 3.48 (br, 2H), 3.89 (br, 4H), 4.05−4.41 (m, 7H), 5.83 (br, 1H), 6.43 (br, 1H), 7.22−7.74 (m, 18H), 8.28 (s, 1H), 12.10 (br, 1H), 13.00 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.5, 46.0, 47.4, 51.0, 61.2, 67.8, 106.0, 108.0, 114.7, 120.1, 125.5, 127.3, 127.7, 127.9, 128.4, 129.5, 129.7, 130.6, 131.8 (2C), 136.9, 139.4, 141.5, 143.1, 144.1, 153.3, 157.0, 169.2, 198.4; ESI-MS m/z 689 (M + K)$^+$, 673 (M + Na)$^+$, 651 (M + H)$^+$. HRMS calcd for [($C_{41}H_{38}N_4O_4$) + H]$^+$ 651.2966, found 651.2964. Anal. ($C_{41}H_{38}N_4O_4$) C, H, N.

2-(Benzyloxycarbonylamino)-*N*-[2-benzoyl-5-(4-*tert*-butoxycarbonylpiperazin-1-yl)phenyl]acetamide (14b). Compound **14b** was prepared following the above-described general procedure and after purification by column chromatography (*n*-hexane/EtOAc 2:1; R_f 0.20) was obtained as a colorless oil (400 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 3.38 (m, 4H), 3.55 (m, 4H), 4.09 (d, 2H, J = 5.4 Hz), 5.14 (s, 2H), 5.75 (br, 1H), 6.44 (d, 1H, J = 9.1 Hz), 7.27−7.56 (m, 11H), 8.33 (s, 1H), 12.2 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 43.4, 45.9, 46.9, 67.5, 80.5, 104.8, 107.3, 113.2, 128.3, 128.4, 128.7, 129.4, 129.9, 131.5, 136.5, 136.9, 140.0, 143.4, 154.8, 154.9, 156.8, 168.9, 198.3;.ESI-MS m/z 595 (M + Na)$^+$, 573 (M + H)$^+$. Anal. ($C_{32}H_{36}N_4O_6$) C, H, N.

The characterization data of compounds **13d−k** and**14c−e** are available as Supporting Information.

General Procedure for Preparation of Compounds 15a−j and 16a−e. To a degassed solution of Cbz-derivatives **13** or **14**

(0.48 mmol) and cyclohexene or 1,4-cyclohexadiene (10 mL) in ethanol (10 mL) was added 10% palladium on carbon (30 mg). The reaction mixture was heated under reflux until the reaction was complete (the reaction was monitored by TLC or ESI-MS and was typically complete within 24−48 h). The catalyst was removed by filtration through a bed of Celite and the solvent was removed in vacuo.

9-(4-*tert*-Butoxycarbonylpiperazinyl)-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (15a). Compound **15a** was prepared following the above-described general procedure and after purification by column chromatography (*n*-hexane/EtOAc 2:1; R_f 0.44) and recrystallization the title compound was obtained as colorless prisms (126 mg, 53%). Mp (*n*-hexane) 216−218 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.87 (br, 4H), 3.46−3.73 (m, 4H), 4.32 (br, 2H), 7.10 (m, 2H), 7.25−7.43 (m, 4H), 7.50 (m, 2H), 8.24 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 44.3, 52.2, 57.4, 80.4, 123.0, 123.6, 127.6, 127.8, 128.4, 130.0, 130.5, 134.0, 139.8, 142.9, 154.9, 170.9 (2C); ESI-MS *m*/*z* 863 (2 M + Na)$^+$, 459 (M + K)$^+$, 443 (M + Na)$^+$, 421 (M + H)$^+$. Anal. ($C_{24}H_{28}N_4O_3$) C, H, N.

9-(4-Benzylpiperazinyl)-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (15b). From 13b: Compound **15b** was prepared following the above-described general procedure and after purification by column chromatography (*n*-hexane/EtOAc 4:1) was obtained in 75% yield (180 mg).

From 13c: To a solution of *N*-Fmoc protected anilide **13c** (488 mg, 0.75 mmol) in dichloromethane (10 mL) was added piperidine (1 mL). The reaction mixture was stirred under reflux for 24 h. After this time the solvent was removed in vacuo and the residue was purified by column chromatography (*n*-hexane/EtOAc 4:1) and recrystallization to afford the title compound as colorless prisms (58 mg, 30%). Mp (*n*-hexane) 216−218 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.68 (br, 4H), 2.96 (m, 4H), 3.60 (s, 2H), 4.31 (s, 2H), 7.08 (m, 2H), 7.25−7.43 (m, 9H), 7.51 (m, 2H), 8.24 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 53.4, 57.3,. 63.1, 122.7, 123.2, 127.1, 127.2, 127.3, 128.1, 128.3, 129.3, 129.7, 130.2, 133.9, 137.8, 139.7, 143.0, 170.6, 170.7; ESI-MS *m*/*z* 433 (M + Na)$^+$, 411 (M + H)$^+$. Anal. ($C_{26}H_{26}N_4O$) C, H, N.

3-Methyl-5-phenyl-9-(4-*tert*-butoxycarbonylpiperazin-1-yl)-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (15c). Compound (*R*)-(−)-**15c** was prepared following the above-described general procedure and after purification by column chromatography (*n*-hexane/EtOAc 1:1; R_f 0.39) and recrystallization was obtained as yellow prisms (182 mg, 62%). Mp (*n*-hexane) 115−117 °C dec; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.76 (d, 3H, J = 7.0 Hz), 2.75 (br, 2H), 3.02 (m, 2H), 3.46−3.74 (m, 5H), 7.10 (m, 2H), 7.26 (m, 1H), 7.31−7.42 (m, 3H), 7.50 (m, 2H), 8.26 (br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.2, 28.4, 43.9, 51.9, 59.3, 80.1, 122.5, 123.1, 127.1, 127.7, 128.1, 129.8, 130.1, 133.5, 139.5, 142.6, 154.6, 168.1, 171.6; ESI-MS *m*/*z* 891 (2 M + Na)$^+$, 473 (M + K)$^+$, 457 (M + Na)$^+$, 435 (M + H)$^+$; $[\alpha]^{20}_D$ −47.6 (*c* 0.9, CH_3OH). Anal. ($C_{25}H_{30}N_4O_3$) C, H, N. Following the same procedure, (*S*)-(+)-**15c** was obtained as a colorless oil (182 mg, 63%). $[\alpha]^{20}_D$ +47.7 (*c* 0.2, CH_3OH). ESI-MS, ^{1}H and ^{13}C NMR data of (*S*)-**15c** were identical with those obtained for (*R*)-**15c.**

8-(4-Benzylpiperazin-1-yl)-5-phenyl-1,3-dihydrobenzo[*e*][1,4]-diazepin-2-one (16a). The title compound was prepared following the above-described general procedure and after purification by column chromatography (EtOAc 1:1; R_f 0.36) was obtained as a colorless amorphous solid (78 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (m, 4H), 3.31 (m, 4H), 3.56 (s, 2H), 4.29 (s, 2H), 6.48 (s, 1H), 6.61 (d, 1H, J = 8.8 Hz), 7.11 (d, 1H, J = 8.8.Hz), 7.25−7.41 (m, 10H), 7.53 (d, 1H, J = 7.4 Hz), 9.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.6, 53.0, 57.0, 63.1, 105.2, 110.3, 117.9, 127.5, 128.3, 128.6, 129.5, 130.1, 130.2, 132.9, 137.7, 140.2, 140.5, 153.2, 171.4, 172.0; ESI-MS *m*/*z* 433 (M + Na)$^+$, 411 (M + H)$^+$. Anal. ($C_{26}H_{26}N_4O$) C, H, N.

3-(Hydroxymethyl)-5-phenyl-8-(4-*tert*-butoxycarbonylpiperazin-1-yl)-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (16c). Compound (*R*)-(−)-**16c** was prepared following the above-described general procedure and after purification by column chromatography (*n*-hexane/EtOAc 2:1) was obtained as amorphous white solid (61 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 3.32 (m, 4H), 3.61 (m, 4H), 3.85 (t, 1H, J = 6.9 Hz), 4.26 (m, 1H), 4.43 (m, 1H), 6.46 (d, 1H, J = 2.2 Hz), 6.68 (dd, 1H, J = 8.8, 2.2 Hz), 7.2 (d, 1H, J = 8.8 Hz), 7.36−7.46 (m, 4H), 7.56 (d, 2H, J = 7.3 Hz), 8.38 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 27.3, 43.0, 61.6, 64.6, 80.1, 104.9, 110.5, 118.0, 127.8, 129.7, 130.2, 132.4, 139.3, 140.4, 153.4, 155.0, 170.2, 171.4; ESI-MS *m*/*z* 489 (M + K)$^+$, 451 (M + H)$^+$; $[\alpha]^{20}_D$ −21.9 (*c* 0.2, CH_3OH). Anal. ($C_{25}H_{30}N_4O_4$) C, H, N. From the reaction mixture was also recovered as a byproduct the (+)-(3*R*)-3-(benzyloxymethyl)-5-phenyl-8-(4-*tert*-butoxycarbonylpiperazin-1-yl)-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (40 mg, 21%) as a colorless low-melting solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 3.27 (m, 4H), 3.58 (m, 4H), 3.92 (t, 1H, J = 6.7 Hz), 4.18 (dd, 1H, J = 6.4, 6.1 Hz), 4.46 (dd, 1H, J = 9.3, 7.0 Hz), 4.71 (s, 2H), 6.45 (d, 1H, J = 2.0 Hz), 6.64 (dd, 1H, J = 8.8, 2.0 Hz), 7.15 (d, 1H, J = 8.8 Hz), 7.24−7.44 (m, 8H), 7.54 (m, 2H), 8.48 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 27.5, 44.3, 63.3, 70.2, 73.4, 80.4, 105.1, 110.8, 118.3, 127.5, 127.7, 128.1, 128.2, 129.9, 130.6, 132.6, 138.5, 139.6, 140.6, 153.6, 155.2, 169.9, 171.5; ESI-MS *m*/*z* 563 (M + Na)$^+$, 541 (M + H)$^+$; $[\alpha]^{20}_D$ +15.2 (*c* 0.1, CH_3OH). Anal. ($C_{32}H_{36}N_4O_4$) C, H, N. Following the same procedure, (*S*)-(+)-**16c** was obtained as a colorless oil (50 mg, 46%). $[\alpha]^{20}_D$ +21.5 (*c* 0.3, CH_3OH). Anal. ($C_{25}H_{30}N_4O_4$) C, H, N. From the reaction mixture was also recovered as a byproduct the (−)-(3*S*)-3-(benzyloxymethyl)-5-phenyl-8-(4-*tert*-butoxycarbonylpiperazin-1-yl)-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (20 mg, 31%). $[\alpha]^{20}_D$ −15.8 (*c* 0.2, CH_3OH). ESI-MS, ^{1}H and ^{13}C NMR data of both compounds were identical with those described above. Anal. ($C_{32}H_{36}N_4O_4$) C, H, N.

The characterization data of compounds **15d**−**j** and**16b**,**d**−**e** are available as Supporting Information.

General Procedure for Preparation of Compounds 1a−h and 2a−c. A 0.1 N dry solution of hydrochloric acid in methanol was prepared by carefully adding acetyl chloride (0.3 mmol) to dry methanol (3 mL). The resulting solution was added to Boc-protected derivatives **15** or **16** (0.15 mmol) dissolved in dry methanol (3 mL) and the reaction mixture was placed at the rotavapor and kept at 60 °C until complete removal of the solvent (10 min). Addition and evaporation of the methanolic solution of hydrochloric acid was repeated (usually three times) until complete disappearance of the starting material as monitored by TLC or ESI-MS. The solvent was removed in vacuo to afford the title compounds as their corresponding hydrochloride salts.

9-(Piperazin-1-yl)-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (1a). Following the above-described general procedure, the title compound was obtained in quantitative yield, and as a bright yellow amorphous solid. ^{1}H NMR (200 MHz, CD_3OD) δ 3.30 (br, 4H), 3.50 (br, 4H), 4.50 (br, 2H), 7.25 (d, 1H, J = 8.1, Hz), 7.45 (m, 1H), 7.68 (m, 4H), 7.82−7.91 (m, 2H); ^{13}C NMR (50 MHz, CD_3OD) δ 44.9, 52.6, 126.8, 130.3, 130.7, 132.4, 133.2, 133.5, 136.6, 137.8, 144.8, 168.9, 179.5; ESI-MS *m*/*z* 321 (M + H)$^+$. Anal. ($C_{19}H_{20}N_4O$) C, H, N.

The characterization data of compounds **1b**−**h** are available as Supporting Information.

3-(2-Carboxyethyl)-5-phenyl-9-(piperazin-1-yl)-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (1i). To solution of (*R*)-**15j** (50 mg, 0.1 mmol) in dry 1,4-dioxane (3 mL) was added a 0.1 N solution of HCl in 1,4-dioxane (3 mL). The reaction mixture was stirred on a rotavapor at 60 °C for 10 min, then was monitored by TLC or ESI-MS. The solvent was removed in vacuo to afford the hydrochloride salt of (*R*)-(+)-**1i** as a bright yellow amorphous solid (42.0 mg, 99%). ^{1}H NMR (200 MHz, D_2O) δ 2.42−2.61 (m, 4H), 3.05 (m, 2H), 3.28−3.54 (m, 6H), 4.22 (m, 1H), 7.17 (d, 1H, J = 7.1 Hz), 7.33 (m, 1H), 7.49−7.56 (m, 4H), 7.69−7.76 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 22.4, 30.0, 43.6, 59.7, 123.3, 125.8, 129.3, 129.4, 131.2, 131.9, 132.6, 135.6, 136.6, 143.7, 167.8, 175.1,

178.4; ESI-MS *m*/*z* 393 $(M + H)^+$; $[\alpha]^{20}_D$ +234 (*c* 0.3, CH_3OH). Anal. ($C_{22}H_{24}N_4O_3$) C, H, N. Following the same procedure, (*S*)-(−)-**1i** was obtained in quantitative yield as a bright yellow amorphous solid; $[\alpha]^{20}_D$ −238 (*c* 0.4, CH_3OH). ESI-MS, ^1H and ^{13}C NMR data of (*S*)-**1i** were identical to those obtained for (*R*)-**1i.** HRMS calcd for $[(C_{22}H_{24}N_4O_3) + H]^+$ 393.1921, found 393.1919. Anal. ($C_{22}H_{24}N_4O_3$) C, H, N.

8-(4-Piperazin-1-yl)-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (2a). Following the above-described general procedure, the title compound was obtained in quantitative yield as a bright yellow amorphous solid. ^1H NMR (200 MHz, CD_3OD) δ 3.40 (m, 4H), 3.85 (m, 4H), 4.34 (s, 2H), 6.84 (s, 1H), 7.01 (d, 1H, $J = 8.0$, Hz), 7.25 (d, 1H, $J = 8.0$, Hz), 7.40−7.73 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD) δ. 42.9, 43.6, 50.5, 104.4, 111.3, 111.4, 129.4, 131.8, 132.9, 134.8, 137.5, 144.4, 156.0, 167.8, 175.8; ESI-MS *m*/*z* 321 $(M + H)^+$. Anal. ($C_{19}H_{20}N_4O$) C, H, N.

The characterization data of compounds **2b**,**c** are available as Supporting Information.

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Supporting Information Available: X-ray crystallography; determination of enantiomeric purity by chiral solvating agents; general experimental methods; characterization data of compounds **13d**−**k**, **14c**−**e**, **15d**−**j**, **16b**,**d**,**e**, **1b**−**h**, and **2b**,**c**; copies of ^1H and ^{13}C NMR spectra of new compounds; and elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org. The crystallographic data of compound **5a** was deposited at the Cambridge Crystallographic Data Centre with deposit numbers CCDC 688413. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax (+44) 1223-336-033; or e-mail deposit@ccdc.cam.ac.uk).

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