Solid-Phase Preparation of a Pilot Library Derived from the 2,3,4,5-Tetrahydro-1*H*-benzo[b]azepin-5-amine Scaffold

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A convenient and reliable solid-phase strategy for the synthesis of di- and trisubstituted benzazepine derivatives was developed. 5-Amino-1-*tert*-butoxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine and 5-amino-1-*tert*-butoxycarbonyl-7-bromo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine G-protein coupled receptor-targeted (GPCR-targeted) scaffolds were efficiently synthesized in a six-step solution-phase process, immobilized on the acid-labile FMPB-AM resin, and further functionalized through acylation, sulfonation, reductive amination, alkylation, and Suzuki or Buchwald−Hartwig cross-coupling reactions. The efficacy of this strategy was exemplified by the preparation of an original pilot library of di- and trisubstituted benzazepines obtained in high purity as assessed by both ^{1}H NMR and liquid chromatography/mass spectrometry (LC/MS) analysis.

Introduction

Benzannulated nitrogen heterocycles are a well-known class of biologically active compounds displaying a wide range of pharmacological activities. Among this class of molecules, benzodiazepinones, -thiazepines, or -oxazepines have been extensively studied and proved to be highly valuable templates for drug discovery. As a result, great efforts have been made this past decade to develop efficient strategies to produce large sets of diversity-oriented chemical libraries of these molecules for lead discovery programs.[1−11] In contrast, the 2,3,4,5-tetrahydro-1*H*-benzo[b]azepine (1-benzazepine) scaffold has received much less attention despite its promising biological activities toward various targets such as enzymes,[12−16] ion channels,[17−20] and G-protein coupled receptors (GPCRs) (Figure 1).[21−27] In particular, the 1-benzazepine core was found to be a useful platform to design new ligands of arginine−vasopressin (AVP) and oxytocin (OT) receptors, two GPCRs extensively studied in our group.[28] Hence, as part of our program aimed at discovering novel, nonpeptide oxytocin agonists with potential applications as pharmacological tools, we developed a convenient method to rapidly access structurally diverse collections of 1-benzazepine derivatives.

In this paper, we report the synthesis of 1-benzazepine derivatives, featuring two and three points of diversity. Two benzazepine scaffolds were prepared in solution and then anchored to a 4-(4-formyl-3-methoxyphenoxy)butyrylaminomethylated polystyrene (FMPB-AM) resin. The scope and limitation of reactions feasible on such resin-bound 1-benzazepine templates were carefully studied to extend the structural diversity accessible in a future library focused on the OT receptor.

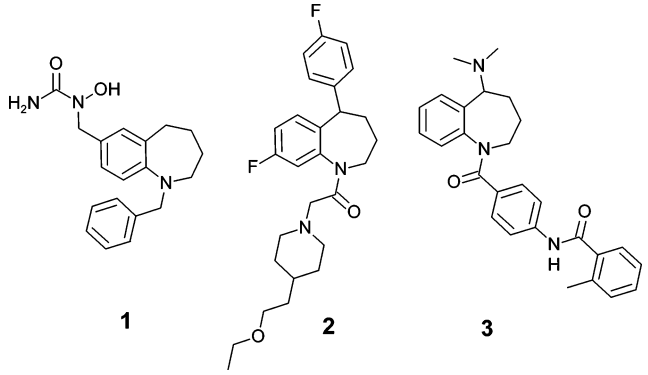

Figure 1. Representative 1-benzazepine-based biologically active compounds and their respective targets: (compound **1**) 5-lipoxygenase inhibitor;[13] (compound **2**) inhibitor of *N*-type calcium channels;[20] (compound **3**) V_2 receptor antagonist, OPC-31260.[21]

Results and Discussion

Solution-Phase Synthesis of the 2,3,4,5-Tetrahydro-1*H*-benzo[b]azepin-5-amine Scaffold and Its Immobilization on the FMPB-AM Resin. Our efforts were primarily focused on developing an efficient solution-phase synthesis of a conveniently protected 1-benzazepine building block that would be easily immobilized and functionalized on solid-support. As depicted in Scheme 1, the 1-benzazepine framework was obtained from methyl-2-aminobenzoate using a successive four-step reaction sequence that involves sulfonation of methyl-2-aminobenzoate to give tosylamide **4**, alkylation with ethyl γ-bromobutyrate,[29] and intramolecular Dieckmann cyclization to yield an intermediate cyclic β-ketoester that was hydrolyzed and decarboxylated to afford the protected benzazepinone **6**.[30] It was noteworthy that the use of microwave irradiation in the hydrolysis/decarboxy-

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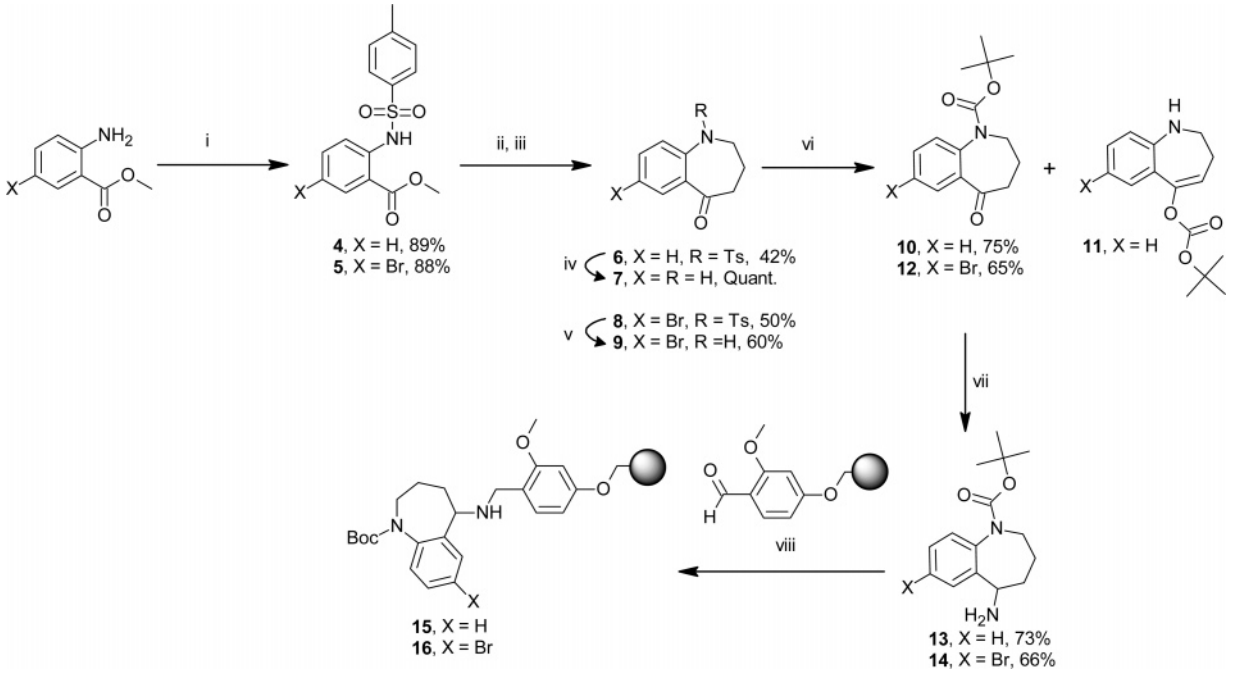
Scheme 1. Solution-Phase Synthesis of 1-Benzazepine Scaffold and Its Immobilization onto FMPB-AM Resin[a]



[a] Reagents and conditions: (i) TsCl (1.1 equiv), Py, 1 h, 0 °C; (ii) NaH (1.2 equiv), $Br(CH_2)_2COOEt$ (1.1 equiv), DMF, 90 °C, 10 h then NaH (1.2 equiv), toluene/MeOH, room temperature (rt); (iii) EtOH/AcOH/HCl conc/H_2O 2/6/1/1 (v/v), microwave irradiation, 10 min, 160 °C; (iv) polyphosphoric acid, 2 h, 110 °C; (v) EtOH/AcOH/HCl conc 1/3/6 (v/v), microwave irradiation, 30 min, 140 °C; (vi) Boc_2O (2.0 equiv), 4-DMAP (0.1 equiv), THF, 16 h, reflux; (vii) NH_4OAc (50 equiv), $NaBH_3CN$ (5 equiv), MeOH, 3 h, reflux; (viii) 1 equiv of FMPB-AM resin, 3 equiv of **13** or **14**, $NaBH_3CN$, 4 equiv DMF/AcOH (100/1, v/v), 80 °C, 3 h, quantitative loading as observed by a negative DNPH test.[46]

lation step was valuable because it shortened the reaction time from 10 h to 10 min and improved the overall yield from 20% to 37% when compared to the conventional heating procedure. Protected benzazepinone **6** was then treated with polyphophosphoric acid at 110 °C for 2 h to quantitatively remove the tosyl group.[31] To allow a subsequent immobilization on the FMPB-AM resin, 1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one **7** had to be conveniently protected and functionalized. We envisaged the protection of the secondary amine by a *tert*-butoxy-carbonyl (Boc) group[32] followed by the conversion of the ketone to a primary amine. Initial attempts to protect compound **7** with a Boc group under similar conditions used to protect 2,3-dihydroquinolin-4(1*H*)-one[33] or 1,2-dihydro-3*H*-indol-3-one derivatives,[34] i.e., di-*t*-butyl-dicarbonate (Boc_2O) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in THF or CH_3CN at room temperature, furnished only carbonate derivative **11** in 19% yield. By heating at reflux in THF, the regioselectivity of acylation could be tuned and the reactivity of 1-benzazepin-5-one nitrogen increased to allow isolation of Boc-protected benzazepin-5-one derivative **10** in 75% yield.

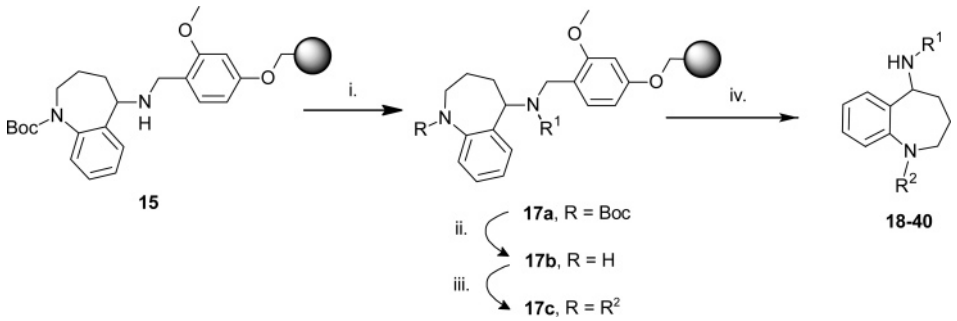
Conversion of ketone **10** into amine **13** was then achieved by treatment with excess of ammonium acetate and sodium cyanoborohydride under dilute conditions in refluxing MeOH.[35] Scaffold **13** was thus obtained in 21% overall yield in a convenient six-step synthesis that was amenable to gramme-scale production.

The synthesis of the bromo analog **14** was also investigated to provide an additional point of diversity through Pd-catalyzed reactions. This compound was prepared from methyl 2-amino-5-bromobenzoate with a 12% overall yield in a similar manner to its hydrogenated counterpart **13** with the exception of the tosyl removal conditions. Indeed, treatment of compound **8** with polyphosphoric acid failed to afford the deprotected compound **9**. However, its treatment with a mixture of EtOH, acetic acid, and concentrated HCl (1/3/6 v/v/v) advantageously combined with microwave irradiation delivered 7-bromo-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (**9**) in 60% yield.

With 5-amino-1-*tert*-butoxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine (**13**) and the bromo analog **14** in hand, we next examined the immobilization onto a polymeric solid support to enable their subsequent chemical derivatizations. A variety of linkers have been devised to anchor primary or secondary amines on solid-support for preparation of peptide or heterocyclic compounds: REM,[36] triazene,[37] trityl,[38] activated carbonate modified Wang,[39] or backbone amide linker (BAL).[40] In light of the good chemical stability of BAL toward a large range of reagents and of the various functionalities accessible with this type of linker upon acidic cleavage (carboxamide,[41] sulfonamide,[42] urea,[43] amine,[3,44] or guanidine[45]), we selected the commercially available FMPB-AM resin to prepare a 1-benzazepine pilot library. 2,3,4,5-Tetrahydro-1*H*-1-benzo[b]azepin-5-amino (**13**) and bromo analog **14** were loaded onto FMPB-AM resin by reductive amination in nearly quantitative yield, as monitored by the negative 2,4-dinitrophenyl hydrazide (DNPH) test.[46] Unreacted building block **13** or **14** was readily recovered by concentration of filtrate and purification on a short pad of silica gel.

Functionalization of Resin-Bound 1-Benzazepine 15: Access to Disubstituted 1-Benzazepine Derivatives. As depicted in Scheme 2, general access to disubstituted

Scheme 2. General Synthetic Scheme Used to Access Disubstituted 1-Benzazepines **18**−**40**[a]



[a] Reagents and conditions: (i) Reaction 1, acylation or sulfonation; (ii) TMSOTf (3 equiv, 0.2M), Et_3N (1.5 equiv), DCM, 15 min, rt; (iii) Reaction 2, acylation, sulfonation, alkylation, reductive amination, or *N*-arylation reaction; (iv) TFA, 3−12 h.

1-benzazepine derivatives involved the following successively: (1) acylation/sulfonylation of resin-bound secondary amine **15**, (2) selective Boc deprotection, (3) treatment of resulting resin-bound benzazepine **17b** with various electrophiles, and (4) final acidic cleavage. This strategy was first validated by the synthesis of model compound **18** (R^1 = butyryl, R^2 = benzoyl). Resin **15** was treated with a 5-fold excess of butyryl chloride in the presence of Hünig's base in CH_2Cl_2 at room temperature. Complete acylation was achieved within 1 h as shown by a negative chloranil/acetaldehyde test.[47]

Prior to the introduction of a second diversity center R^2, the Boc group must be selectively removed from resin-bound benzazepine **17a** without premature cleavage of substrate from its solid-support. Recent publications have described such a deprotection on related acid-labile Rink[48] or Wang[49] resins using a trimethylsilyltriflate-based cocktail (TMSOTf). This protocol was adapted to FMPB-AM resin-bound substrate **17a** by changing both the TMSOTf amount and time of reaction. Treatment of resin **17a** with a TMSOTf/Et_3N (3/1.5 equiv) solution in CH_2Cl_2 for 15 min followed by MeOH washings enabled full removal of the Boc group with a minimum loss of material from the resin. Indeed, subsequent acylation with benzoyl chloride followed by trifluoroacetic acid (TFA) mediated cleavage delivered disubstituted benzazepine **18** in 61% overall yield and in >95% purity as assessed by both reversed-phase high performance liquid chromatography (RP-HPLC) (UV detection at 254 nm) and ^1H NMR analysis.

Having a robust and reliable method to selectively remove the Boc group, the scope of our methodology was demonstrated by the synthesis of a small disubstituted 1-benzazepine-based library (Table 1).

The R^1 group was introduced using acid chlorides and sulfonyl chloride, either commercially available or obtained by custom synthesis. Aliphatic acyclic and cyclic (entries 1, 3, and 7−8), aromatic (entries 2, 6, and 10−23), and aminoacyl (entries 3−5) groups were easily incorporated as shown by a negative chloranil test.

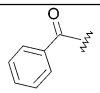
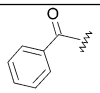
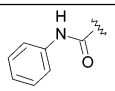
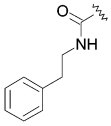
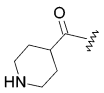
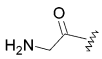
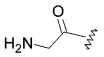
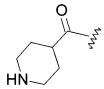
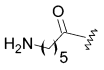
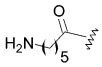
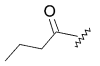
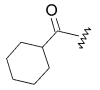
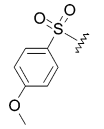
In a second diversification step (R^2 group), functionalization of the endocyclic nitrogen of resin-bound benzazepine **17b** was promoted by reaction with various electrophiles, including acid chlorides (entries 1−11 and 15−17), a sulfonyl chloride (entry 12), an isocyanate (entry 13), aldehydes (entries 19−21), a ketone (entry 22), and alkyl (entry 18) or aromatic (entry 23) halides leading to the generation of the corresponding amide, sulfonamide, urea, or tertiary amine benzazepine derivatives, respectively. Completion of all reactions was also conveniently monitored using a chloranil/acetaldehyde test.

Whereas acylation of resin-bound benzazepine **17b** by butyryl chloride (entries 6−9), benzoyl chloride (entries 1−5), or cyclohexane carbonyl chloride (entry 10) using 5 equiv of reagent in the presence of Hünig's base in CH_2Cl_2 was achieved within 1 h, complete acylation with less reactive homemade acid chlorides[50] (entries 11 and 15−17) required a second cycle of acylation. The glycinyl moiety (entry 15) was best introduced by treatment of resin **17b** in THF with a 5-fold excess of Fmoc−Gly−Cl, generated in situ from Fmoc−Gly−OH, bis(trichloromethyl)carbonate (BTC), and 2,4,6-collidine.[51]

The R^2 groups of tertiary amine benzazepines **36**, **37**, **38**, and **39** were introduced under reductive amination conditions respectively from phenylacetaldehyde, isovaleraldehyde, cyclohexanecarboxaldehyde, and cyclohexanone, whereas the benzyl group of benzazepine **35** was best introduced under alkylation conditions with benzyl bromide as electrophile. The phenyl group of compound **40** was introduced through a Buchwald−Hartwig cross-coupling reaction between resin-bound benzazepine **17b** (R^1 = PhCO−) and bromobenzene using Pd_2dba_3 as the catalyst, NaOtBu as the base, and P(*t*Bu)$_3$ as the ligand.

Resin **17b** was also successfully reacted with phenylisocyanate (10 equiv) in the presence of pyridine (20 equiv) in CH_2Cl_2 to provide the urea derivative **30** (entry 13). An alternative route to install the urea moiety was investigated that avoids the reliance on isocyanates in favor of more accessible amine building blocks. It relies on the displacement of an activated resin-bound *p*-nitrophenylcarbamate intermediate **31a** with various amines[52] (see Scheme 3). Surprisingly, this intermediate was found to be highly stable toward aliphatic amines such as phenylethylamine. Conventional or microwave irradiation-assisted heating or the use of a large excess of amine all resulted in a low consumption of starting material and lead to the formation of several unidentified byproducts. Then, we turned our attention to the formation of the more reactive intermediate resin-bound benzazepine-1-carbonyl chloride **31b** that was obtained by treatment of resin **17b** (R^1 = PhCO−) with BTC in presence

Table 1. RP-HPLC Purities and Overall Yields of the Disubstituted 1-Benzazepines Synthesized (**18**−**40**)

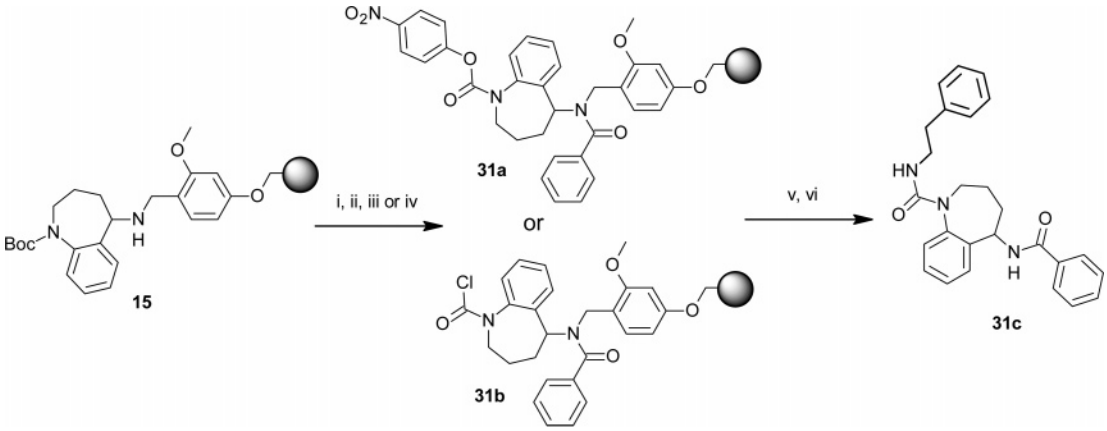
entry	compd.	R^1	R^2	RP-HPLC purity[a] %	yield %	entry	compd.	R^1	R^2	RP-HPLC purity[a] %	yield %
1	**18**			>95	61[b]	13	**30**			95	67[b]
2	**19**			>95	85[b]	14	**31c**			89	86[b]
3	**20**			90	56[b,d]	15	**32**			>95	36[b,d]
4	**21**			>95	12[b,d]	16	**33**			81	40[b,d]
5	**22**			>95	32[b,d]	17	**34**			84	40[b,d]
6	**23**			>95	71[b]	18	**35**			>95	57[b]
7	**24**			>95	51[b]	19	**36**			>95	68[b]
8	**25**			>95	32[b]	20	**37**			>95	52[b]
9	**26**			>95	22[b]	21	**38**			>95	35[b]
10	**27**			95	81[b]	22	**39**			64	30[b]
11	**28**			>95	49[b]	23	**40**			>95	38[c]
12	**29**			>95	77[b]						

[a] Determined by RP-HPLC analysis of the crude product at 254 nm. [b] Determined by weight of the crude products (TFA salts if any) based on the initial BAL resin loading. [c] Determined by the weight of the purified products based on the initial BAL resin loading. [d] Compounds obtained with an additional Fmoc deprotection step prior to final acidic cleavage from the resin.

of 2,4,6-collidine. Treatment of the resulting resin **31b** with phenylethylamine enabled clean formation of the urea moiety and delivered compound **31c** in good purity and yield upon acidic cleavage (entry 14).

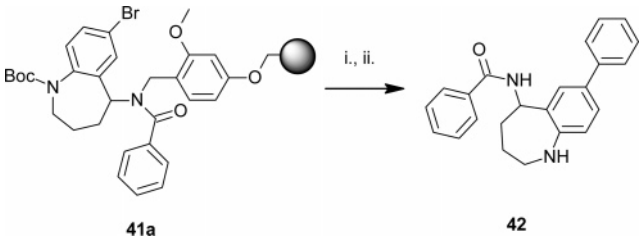
Notwithstanding, most compounds of this pilot library were obtained in good to excellent purity; crude yields, however, were found to be very substrate dependent. In particular, low overall yields were observed for compounds which contain a protonation site close to the amide backbone linker. This could be ascribed to the difficulty in oxygen protonation of the amide linker which renders a sluggish final acid cleavage of some 1-benzazepine derivatives. Nevertheless, this strategy was found to be a convenient and versatile entry to disubstituted 1-benzazepines. The R^2 group could be introduced through various chemical linkages (amide, sulfonamide, urea, alkyl, and aryl amine) leading to different

Scheme 3. Preparation of Urea Derivative **31c** Using Carbonyl Activating Reagent[a]



[a] Reagents and conditions: (i) PhCOCl (5 equiv), DCM, DIEA (6 equiv), 30 min, rt; (ii) TMSOTf (3 equiv, 0.2 M), Et_3N (1.5 equiv), DCM, 15 min, rt; (iii) *p*-nitrophenyl chloroformate (10 equiv), Py (200 equiv), DCM, 1 h, rt; (iv) bis(trichloromethyl)carbonate (1 equiv), 2,4,6-collidine (10 equiv), THF, rt, 30 min; (v) phenylethylamine (20 equiv), DIEA (10 equiv), DCM, rt, 3 h; (vi) TFA/DCM (1/1 v/v), 3−9 h.

Scheme 4. Suzuki Cross-Coupling Optimization[a]



[a] Reagents and conditions: (i) $Pd(PPh_3)_4$ (0.1 equiv), $PhB(OH)_2$ (5 equiv), K_3PO_4 (5 equiv), DMF/H_2O (90/10 v/v), 12 h and 90 °C or 15 min and 140 °C, microwave irradiation; (ii) TFA/DCM (1/1 v/v) 3−9 h. The crude yield and RP-HPLC purity of crude product **42** at 214 nm was found in 66% yield with >95% purity using the conventional heating procedure and in 78% yield with 88% purity using the microwave irradiation heating procedure.

functional group arrangements in space and thus increasing the likelihood of the molecule to selectively bind to receptors.

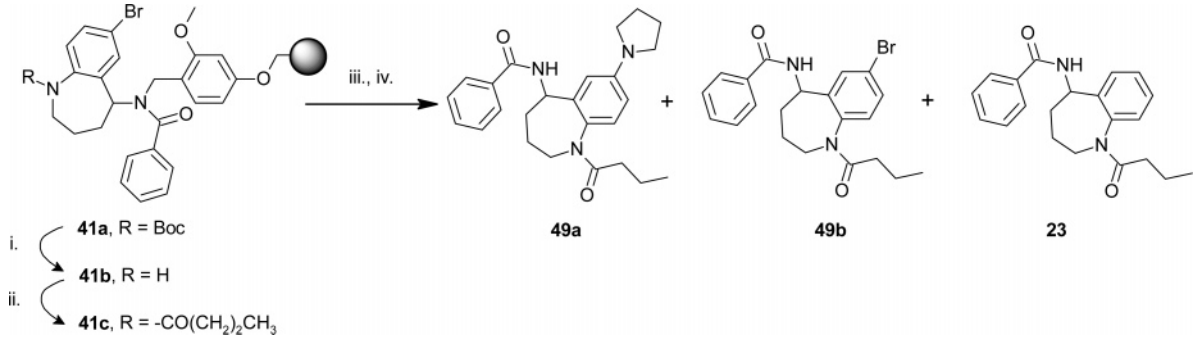
Functionalization of Resin-Bound 1-Benzazepine 16: Access to Trisubstituted 1-Benzazepine Derivatives. To further extend the chemical space accessible around the 1-benzazepine platform, an additional diversity point was introduced through Suzuki and Buchwald−Hartwig cross-coupling reactions using resin-bound bromobenzazepine **16** as the starting material.[53]

Suzuki Cross-Coupling Reaction. Experimental conditions were first optimized using a model reaction (Scheme 4). Hence, the resin-bound bromobenzazepine **41a** was reacted with phenylboronic acid and the resulting resin was treated in acidic conditions to provide benzazepine **42**. The best results were obtained when the reaction was conducted in a DMF/H_2O (90/10, v/v) mixture using a 5-fold excess of phenylboronic acid, K_3PO_4 (5 equiv) as the base, and $Pd(PPh_3)_4$ (0.1 equiv) as the catalyst at 90 °C for 12 h. Compound **42** was obtained in a 66% overall yield and a >95% purity as assessed by RP-HPLC and NMR analysis of the crude product. It was of particular note that microwave irradiation mediated cross-coupling reaction at 140 °C for 15 min afforded compound **42** in an appreciably reduced time with similar overall crude yield (78%), albeit with slightly lower but acceptable purity (88%).

Buchwald−Hartwig Cross-Coupling Reaction. To extend the accessible molecular diversity, we studied the palladium-catalyzed Buchwald−Hartwig cross-coupling reaction between resin-bound aryl halides and various readily commercially available amines. In recent years, the Buchwald−Hartwig reaction has emerged as a straightforward and rapid method to prepare alkyl and aryl amines in both solution and solid phase.[55−57] The scope and limitations of the reaction were evaluated on the resin-bound bromobenzazepine substrate **41c**, obtained in three steps from resin-bound benzazepine **16** as described above. Resin **41c** was then reacted with pyrrolidine, its amine reaction partner (Scheme 5). The influence of the nature and amount of catalyst and of the temperature on RP-HPLC purity (UV detection at 254 nm) was carefully examined (Table 2). A large excess of NaOtBu (10 equiv) was used for reproducibility,[56] and toluene was selected as the reaction solvent in all experiments. On the basis of the literature, three Pd-based catalytic systems were evaluated: (1) a mixture of Pd_2dba_3 and a bulky and electron-rich monophosphine ligand P(*t*-Bu)$_3$;[58] (2) Pd_2dba_3 associated with bisphosphine ligand BINAP;[59] and (3) the newly reported carbene-based Pd catalyst: [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]-(3-chloropyridyl)palladium(II) dichloride (or PEPPSI-IPr for pyridine enhanced precatalyst preparation stabilization and initiation).[60] Reactions performed at room-temperature failed to provide the expected products regardless of the catalytic system. Final cleavage only provided a mixture of unreacted bromobenzazepine **49b** contaminated with a small amount of reduced, debrominated benzazepine **23** (Table 2, entries 1, 3, and 5). Heating at 90 °C dramatically improved the catalyst activity, where the best conversion was obtained with the Pd_2dba_3/BINAP system in toluene (Table 2, entry 4). In these conditions, compound **49a** was obtained in good overall yield (83%, 6 steps) and >85% purity while minimizing the amount of reduced benzazepine **23** (<5%). In our hands, the PEPPSI-IPr catalyst did not further improve the **49a**/**49b**/**23** ratio.

Synthesis of the Trisubstituted Benzazepines Pilot Library. The scope of our methodology was demonstrated by the synthesis of a small library on solid phase by using both Suzuki and Buchwald−Hartwig pathways (Scheme 6).

Scheme 5. Buchwald−Hartwig Cross-Coupling Optimization[a]



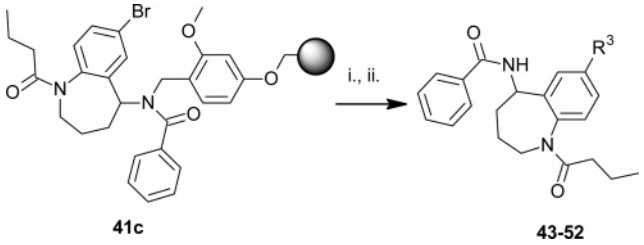
[a] Reagents and conditions: (i) TMSOTf (3 equiv, 0.2 M), Et_3N (1.5 equiv), DCM, 30 min, rt; (ii) $CH_3(CH_2)_2COCl$ (5 equiv), DCM, DIEA (6 equiv), 30 min, rt; (iii) Buchwald−Hartwig cross-coupling, see Table 2; (iv) TFA, 9 h.

Table 2. Buchwald−Hartwig Cross-Coupling Optimization

entry	catalyst	temp (°C)	time (h)	**49a**/**49b**/**23**[a] (%)
1	$Pd_2(dba)_3$ (0.05 equiv), $P(tBu)_3$ (0.4 equiv), NaOtBu (10 equiv)	25	12	0/83/5
2	$Pd_2(dba)_3$ (0.05 equiv), $P(tBu)_3$ (0.4 equiv), NaOtBu (10 equiv)	90	12	70/0/25
3	$Pd_2(dba)_3$ (0.05 equiv), BINAP (0.4 equiv), NaOtBu (10 equiv)	25	12	0/94/3
4	$Pd_2(dba)_3$ (0.05 equiv), BINAP (0.4 equiv), NaOtBu (10 equiv)	90	12	87/0/5
5	PEPPSI-Ipr (0.1 equiv), NaOtBu (10 equiv)	25	12	0/96/3
6	PEPPSI-Ipr (0.1 equiv), NaOtBu (10 equiv)	90	12	83/3/12

[a] Ratio determined by RP-HPLC analysis of the crude product with UV detection at 254 nm.

Scheme 6. Pilot Library of Trisubstituted 1-Benzazepines **43**−**52**[a]



[a] Reagents and conditions: (i) Suzuki cross-coupling, $Pd(PPh_3)_4$ (0.1 equiv), R^3-$B(OH)_2$ (5 equiv), K_3PO_4 (5 equiv), DMF/H_2O (90/10 v/v), 12 h, 90 °C or Buchwald−Hartwig cross coupling, $Pd_2(dba)_3$ (0.05 equiv), NaOtBu (10 equiv), BINAP (0.4 equiv), amine (5 equiv), toluene, 12 h, 90 °C; (ii) TFA, 9 h.

Resin-bound benzazepine **41c** was reacted with different aryl boronic acids, being substituted or unsubstituted, possessing electron-donating or withdrawing groups, as well as a vinyl boronic acid. In all cases, the expected trisubstituted benzazepine derivatives **43**−**47** were obtained with an HPLC purity and a crude yield ranging from 85% to 96% and 28% to 79%, respectively (Table 3). However, an attempt to perform the reaction with isopropylboronic acid failed to generate compound **48** in satisfactory purity (entry 6, Table 3).

In addition to pyrolidine, Buchwald−Hartwig optimized conditions were also successfully applied to aniline (Table 3, entry 8) and isopropylamine (Table 3, entry 10) allowing access to trisubstituted benzazepines **50** and **52** in reasonable overall yields (>41%) and good purity (>71%). Nevertheless, reaction with *N*,*N*-diethylamine did not provide the expected product with satisfactory purity and yield (Table 3, entry 9).

All the library members herein described have been obtained with a racemic carbon center at the 5-position of the benzazepine ring. It is noteworthy that the enzymatic resolution of potential hits arising from the future library screening could be envisaged using the previously described lipase-catalysis method giving access to optically active benzazepines.[61]

Conclusion

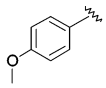
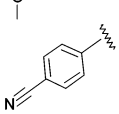
In summary, we have developed a rapid and convenient solid-phase approach for the parallel synthesis of benzazepine derivatives in high purity. Two or three points can be funtionnalized via diverse coupling systems opening access to a high diversity, benzazepine library. An expanded library is currently underway. It will be evaluated on various GPCRs which include the AVP and OT receptors. We anticipate that this method may have interesting applications in the field of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

Experimental Section

General Methods. 4-(4-Formyl-3-methoxyphenoxy)butyryl aminomethylated polystyrene resin (FMPB-AM, 50−100 mesh) (BAL type resin) was purchased from Novabiochem, and the manufacturer's reported loading of the resin (0.74 mmol/g) was used in the calculation of the yields for the final products. Solid-phase reactions conducted at room temperature were performed in polypropylene tubes equipped with polyethylene frits and polypropylene caps using an orbital agitator shaking device. Solid-phase reactions at 80−100 °C were conducted in sealed glassware tubes using the Chemflex rotating oven from Robbins Scientific as the shaking device.

^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ or DMSO as the solvent containing an internal reference. Chemical shifts are reported in parts per million (ppm), coupling constants (*J*) are reported in hertz (Hz). Melting points are uncorrected. LC/MS spectra were obtained on a ZQ (Z quadripole) Waters/Micromass spectrometer equipped with an X-Terra C18 column (4.6 ×

Table 3. RP-HPLC Purities and Overall Yields of Synthesized Trisubstituted 1-Benzazepines **43**−**52**

Entry	Compds	R^3	Purity[a] %	yield[b] %	Entry	Compds	R^3	Purity[a] %	yield[b] %
1[c]	**43**		95	79	6[c]	**48**		10	N.D.
2[c]	**44**		96	72	7[d]	**49**		79	83[b]
3[c]	**45**		85	28	8[d]	**50**		76	41[b]
4[c]	**46**		90	44	9[d]	**51**		29	N.D.
5[c]	**47**		88	65	10[d]	**52**		75	69[b]

[a] Determined by RP-HPLC analysis of the crude product (UV detection at 254 nm). [b] Determined by weight of the crude products (TFA salts if any) based on the initial BAL resin loading. [c] Suzuki reaction product of corresponding boronic acid and bromobenzazepine **41c**. [d] Buchwald−Hartwig reaction product of corresponding amine and bromobenzazepine **41c**.

50 mm, 3.5 μm) using electrospray ionization (ESI) mode. HRMS spectra were obtained on a MicroTof mass spectrometer from Bruker using electrospray ionization (ESI) mode and a time-of-flight (TOF) analyzer. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from Merck. Flash chromatography was performed on silica gel 60 (230−400 mesh ASTM) from Merck. Analytical HPLC analyses were performed on a Chromolith SpeedROD column (50 × 4.6 mm, C_{18}) from Merck with a flow rate of 7 mL/min using a 5 min linear gradient from water (0.1% TFA) to CH_3CN (0.1% TFA). Retention times (t_R) from analytical RP-HPLC are reported in minutes.

Methyl 2-{[(4-Methylphenyl)sulfonyl]amino}benzoate (4). To a solution of tosyl chloride (27.75 g, 145.5 mmol, 1.1 equiv) in anhydrous pyridine (50 mL) at 0 °C was added dropwise, under argon, methyl 2-aminobenzoate (20 g, 132.3 mmol, 1 equiv). After 1 h at 0 °C, the reaction mixture was filtered, and the white solid obtained was washed with cold MeOH and then recristalised from MeOH to yield the title compound (35.96 g, 89%). $C_{15}H_{15}NO_4S$, F.W. = 305.35 g/mol, R_f = 0.25 (30% EtOAc in heptane), white solid, mp = 115−116 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 300 K) δ = 2.36 (s, 3H); 3.88 (s, 3H); 7.03 (t, J = 7.2 Hz, 1H); 7.21 (d, J = 8.4 Hz, 2H); 7.44 (td, J = 7.5 Hz, 1.8 Hz, 1H); 7.69 (d, J = 8.1 Hz, 1H); 7.74 (d, J = 8.1 Hz, 2H); 7.91 (dd, J = 8.1 Hz, 1.8 Hz, 1H); 10.64 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K) δ = 22.0; 52.9; 116.2 (Cq); 119.4; 123.2; 127.7 (2C); 130.1 (2C); 131.6; 134.9; 136.8 (Cq); 140.9 (Cq); 144.3 (Cq); 168.7 (Cq). HRMS (ESI) m/z for $C_{15}H_{15}NO_4SNa$ $(M+Na)^+$, calcd 328.0614, found 328.0634.

Methyl 5-Bromo-2-{[(4-methylphenyl)sulfonyl]amino}-benzoate (5). To a solution of tosyl chloride (4.56 g, 23.90 mmol, 1.1 equiv) in anhydrous pyridine (14.5 mL) at 0 °C was added, under argon, methyl 2-amino-5-bromobenzoate (5 g, 21.73 mmol, 1 equiv). After 1 h at 0 °C, 200 mL of EtOAc was added, the organic layer was washed with a 1M $KHSO_4$ aqueous solution, brine, dried over Na_2SO_4, and evaporated to a solid which was recristalised from MeOH (7.37 g, 88%). $C_{15}H_{14}BrNO_4S$, F.W. = 384.24 g/mol, white solid, R_f = 0.53 (30% EtOAc in heptane), mp = 122 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 300 K) δ = 2.38 (s, 3H); 3.89 (s, 3H); 7.24 (d, J = 8.4 Hz, 2H); 7.53 (dd, J = 9.0 Hz, 2.1 Hz, 1H); 7.61 (d, J = 9.0 Hz, 1H); 7.73 (d, J = 8.1 Hz, 2H); 8.03 (d, J = 2.4 Hz, 1H); 10.52 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K) δ = 22.0; 53.2; 115.9 (Cq); 117.7 (Cq); 121.1; 127.7 (2C); 130.2 (2C); 134.1; 136.5 (Cq); 137.7; 140.0 (Cq); 144.6 (Cq); 167.5 (Cq). HRMS (ESI) m/z for $C_{15}H_{14}BrNO_4SK$ $(M+K)^+$, calcd 421.9458, found 421.9473.

1-[(4-Methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-benzo[b]azepin-5-one (6). A stirred solution of methyl 2-{[(4-methylphenyl)sulfonyl]amino}benzoate **(4)** (7.20 g, 23.6 mmol) in anhydrous DMF (31 mL) at 0 °C was treated with successive small portions of NaH 60% (1113 mg, 27.8 mmol, 1.2 equiv) added over 5 min, stirred over 1.5 h at 0 °C, and treated dropwise with ethyl-4-bromobutanoate (3.68 mL, 25.7 mmol, 1.1 equiv). After 30 min, the reaction mixture was heated at 90 °C for 10 h, treated successively with small portions of NaH 60% (1113 mg, 27.8 mmol, 1.2 equiv) at 0 °C followed by a solution of anhydrous toluene (2.2 mL) and MeOH (56 μL). After 10 h at room temperature, the reaction mixture was concentrated in vacuo to yield a residue that was quenched with an aqueous $KHSO_4$ solution (1 M) and then extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. In succession, the crude residue was dissolved in 31 mL of EtOH/AcOH/HCl conc/H_2O (2/6/1/1 v/v) solution, placed in a microwave reactor, heated under microwave irradiation at 160 °C for 10 min, basified using an aqueous NaOH solution, and extracted twice with $CHCl_3$. Combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield a residue that was triturated at 0 °C with an EtOAc/heptane (4/6, v/v) solution. The precipitate was filtered, washed with heptane, and dried in vacuo to yield benzazepinone **(6)** as a white solid (3.12 g, 42%). $C_{17}H_{17}NO_3S$, F.W. = 315.39 g/mol, R_f = 0.31 (30% EtOAc in heptane), white solid, mp = 120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 300 K) δ = 1.96 (m, 2H); 2.36−2.46

(m, 5H); 3.86 (t, J = 6.6 Hz, 2H); 7.27 (d, J = 3 Hz, 1H); 7.29 (s, 1H); 7.39 (td, J = 7.2 Hz, 1.5 Hz, 1H); 7.49 (td, J = 6 Hz, 1.5 Hz, 1H); 7.54 (dd, J = 8.1 Hz, 1.5 Hz, 1H); 7.60 (d, J = 8.4 Hz, 2H); 7.71 (dd, J = 7.8 Hz, 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K) δ = 22.0; 24.0; 39.7; 50.2; 127.4 (2C); 128.5; 129.6; 130.0; 130.3 (2C); 133.6; 136.5 (Cq); 137.8 (Cq); 138.8 (Cq); 144.4 (Cq); 202.6 (Cq). HRMS (ESI) *m/z* for $C_{17}H_{17}NO_3SK$ $(M+K)^+$, calcd 354.0561, found 354.0579.

7-Bromo-1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-benzo[b]azepin-5-one (8). A stirred solution of methyl 5-bromo-2-{[(4-methylphenyl)sulfonyl]amino}benzoate **(5)** (14 g, 36.4 mmol) in anhydrous DMF (52 mL) at 0 °C was treated with successive small portions of NaH 60% (1749 mg, 43.7 mmol, 1.2 equiv) added over 5 min, stirred during 1.5 h at 0 °C and treated dropwise with ethyl-4-bromobutanoate (6.72 mL, 40.1 mmol, 1.1 equiv). After 30 min, the reaction mixture was heated at 90 °C for 10 h and treated successively with small portions of NaH 60% (1749 mg, 43.7 mmol, 1.2 equiv) at 0 °C followed by a solution of anhydrous toluene (3.7 mL) and MeOH (97 μL). After 10 h at room temperature, the reaction mixture was concentrated in vacuo to yield residue that was quenched with an aqueous $KHSO_4$ solution (1 M) and then extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. In succession, the crude residue was dissolved in 52 mL of EtOH/AcOH/HCl conc/H_2O (2/6/1/1 v/v) solution that was successively placed in a microwave reactor, heated under microwave irradiation at 160 °C for 8 min, basified using an aqueous NaOH solution, and extracted twice with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield a residue that was triturated at 0 °C with a EtOAc/heptane (4/6, v/v) solution. The precipitate was filtered, washed with heptane, and dried in vacuo to yield bromobenzazepinone **(8)** as a white solid (7.2 g, 50%). $C_{17}H_{16}BrNO_3S$, F.W. = 394.28 g/mol, R_f = 0.19 (20% EtOAc in heptane), white solid, mp = 140 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 300 K) δ = 1.97 (m, 2H); 2.39 (m, 2H); 2.43 (s, 3H); 3.83 (t, J = 6.6 Hz, 2H); 7.28 (d, J = 7.8 Hz, 2H); 7.36 (d, J = 8.4 Hz, 1H); 7.57 (s, 1H); 7.60 (s, 1H); 7.61 (d, J = 2.7 Hz, 1H); 7.64 (d, J = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K) δ = 21.9; 23.8; 39.3; 50.0; 122.5 (Cq); 127.2 (2C); 130.5 (2C); 131.5; 132.7; 136.5; 137.6 (Cq); 137.8 (Cq); 138.0 (Cq); 144.7 (Cq); 201.2 (Cq). LRMS (ESI) 394.0 $(M+H)^+$, 396.0 $(M+H)^+$, 416.0 $(M+Na)^+$, 418.0 $(M+Na)^+$, 789.0 $(2M+H)^+$, 811.0 $(2M+Na)^+$. HRMS (ESI) *m/z* for $C_{17}H_{16}BrNO_4SK$ $(M+K)^+$, calcd 431.9666, found 431.9675.

1-*tert*-Butoxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[b]-azepin-5-one (10). To a preheated (110 °C) polyphosphoric acid (20 g) was added 1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one **(6)** (2 g, 6.34 mmol). The reaction mixture was stirred and heated for 2 h at 110 °C, quenched with a mixture of ice and water, basified with an aqueous NaOH (1 M) solution, and extracted twice with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, dried overnight to yield 1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (**7**) as a dark oil. $C_{10}H_{11}NO$, F.W. = 161.20 g/mol, R_f = 0.31 (30% EtOAc in heptane). ^{1}H NMR ($CDCl_3$, 300 MHz, 300 K) δ = 2.16 (quint, J = 6.9 Hz, 2H); 2.83 (t, J = 7.2 Hz, 2H); 3.24 (t, J = 6.9 Hz, 2H); 6.75 (d, J = 8.1 Hz, 1H); 6.80 (td, J = 7.8 Hz, 0.9 Hz, 1H); 7.23 (d, J = 8.1 Hz, 1H); 7.72 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K) δ = 31.9; 41.7; 48.3; 118.1; 119.1; 125.7 (Cq); 129.9; 132.8; 154.0 (Cq); 203.3 (Cq). 1,2,3,4-Tetrahydro-5*H*-1-benzazepin-5-one (**7**) was dissolved in anhydrous THF (35 mL) that was treated successively under argon with 4-DMAP (77.4 mg, 0.634 mmol, 0.1 equiv) and Boc_2O (2.77 g, 12.68 mmol, 2 equiv) at 0 °C. After 5 min at 0 °C, the cooling bath was removed and the reaction mixture was heated to reflux under argon for 18 h and then concentrated in vacuo to yield a residue. *tert*-Butyl 5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-carboxylate (**10**) was isolated as a brown solid (1.25 g, 75%) by flash chromatography using a EtOAc/heptane 1/9 (v/v) solution as eluant. $C_{15}H_{19}NO_3$, F.W. = 261.32 g/mol, R_f = 0.52 (30% EtOAc in heptane), brown solid, mp = 100−101 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, 360 K) δ = 1.41 (s, 9H); 2.00 (quint, J = 5.1 Hz, 2H); 2.62 (t, J = 6.9 Hz, 2H); 3.67 (t, J = 6.9 Hz, 2H); 7.33 (t, J = 7.5 Hz, 1H); 7.41 (d, J = 8.1 Hz, 1H); 7.56 (t, J = 7.2 Hz, 1H); 7.71 (d, J = 7.8 Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz, 360 K) δ = 24.5; 28.8 (3C); 40.4; 48.9; 81.2; 127.0; 129.1; 129.3; 133.2; 134.2 (Cq); 144.0 (Cq); 154.2 (Cq); 201.4 (Cq). HRMS (ESI) *m/z* for $C_{15}H_{19}NO_3Na$ $(M+Na)^+$, calcd 284.1257, found 284.1262.

1-*tert*-Butoxycarbonyl-2,3-dihydro-1*H*-benzo[b]azepin-5-yl (11). $C_{15}H_{19}NO_3$, F.W. = 261.32 g/mol, R_f = 0.40 (30% EtOAc in heptane), brown solid, mp = 72−73 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 300 K) δ = 1.47−1.51 (m, 9H); 2.59 (m, 2H); 3.44 (t, J = 5.3 Hz, 2H); 5.93 (t, J = 5.3 Hz, 1H); 6.97 (m, 2H); 7.14 (t, J = 7.9 Hz, 1H); 7.25 (m, 1H); 7.35−7.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz, 300 K) δ = 27.7 (3C); 30.3; 45.5; 82.9 (Cq); 118.7; 120.2; 120.6; 121.0; 126.7; 128.6; 144.5 (Cq); 147.5 (Cq); 152.6 (Cq). LRMS (ESI) *m/z* 262.2 $(M+H)^+$, 284.2 $(M+Na)^+$, 523.3 $(2M+H)^+$, 545.3 $(2M+Na)^+$. HRMS (ESI) *m/z* for $C_{15}H_{20}NO_3$ $(M+H)^+$, calcd 262.1438, found 284.1428.

1-*tert*-Butoxycarbonyl-7-bromo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-5-one (12). A supension of 7-bromo-1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (**8**) (400 mg, 1.01 mmol) in 10 mL of a HCl conc/AcOH/EtOH (6/3/1, v/v/v) solution was successively heated under microwave irradiation for 30 min at 140 °C, basified with an aqueous NaOH (1 M) solution, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to a residue. 7-Bromo-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (**9**) was isolated as a brown oil (146.5 mg, 60%) by flash chromatography using an EtOAc/heptane 3/7 (v/v) solution as eluant. $C_{10}H_{10}BrNO$, F.W. = 240.10 g/mol, R_f = 0.28 (30% EtOAc in heptane), brown oil. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 2.07 (quint, J = 6.9 Hz, 2H); 2.63 (t, J = 7.2 Hz, 2H); 3.07 (bs, 2H); 6.87 (d, J = 8.7 Hz, 1H); 7.02 (bs, 1H); 7.33 (dd, J = 8.7 Hz, 2.1 Hz, 1H); 7.51 (d, J = 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K) δ =

32.47; 41.9; 47.6; 109.0 (Cq); 121.0; 126.1; 131.3; 135.2; 154.4 (Cq); 201.4 (Cq). LRMS (ESI) 240.0 $(M+H)^+$, 242.0 $(M+H)^+$.

A stirred solution of 7-bromo-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (**9**) (146.5 mg, 0.61 mmol) in anhydrous THF was treated successively at 0 °C with 4-DMAP (8 mg, 0.06 mmol, 0.1 equiv) and Boc_2O (266.4 mg, 1.22 mmol, 2 equiv), heated under argon to reflux for 18 h and concentrated in vacuo to a residue. *tert*-Butyl 7-bromo-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-carboxylate (**12**) was isolated as an oil (135 mg, 65%) by flash chromatography using an EtOAc/heptane solution 1/9 (v/v) as eluant. $C_{15}H_{18}BrNO_3$, F.W. = 340.21 g/mol, R_f = 0.22 (10% EtOAc in heptane), slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 360 K) δ = 1.47 (s, 9H); 2.13 (quint, J = 6.6 Hz, 2H); 2.73 (t, J = 6.9 Hz, 2H); 3.71 (t, J = 6 Hz, 2H); 7.33 (bs, 1H); 7.54 (dd, J = 8.4 Hz, 2.4 Hz, 1H); 7.95 (d, J = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 360 K) δ = 25.0; 28.7 (3C); 40.4; 49.2; 82.0 (Cq); 119.7 (Cq); 130.1; 132.1; 134.8 (Cq); 135.4; 143.7 (Cq); 153.9 (Cq); 199.9 (Cq). HRMS (ESI) *m*/*z* for $C_{15}H_{18}BrNO_3Na$ $(M+Na)^+$, calcd 362.0362, found 362.0383.

(±)-5-Amino-1-*tert*-butoxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine (13). A stirred solution of *tert*-butyl 5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-carboxylate (**10**) (2.85 g, 10.9 mmol) in MeOH (220 mL) was treated in succession with NH_4OAc (50.4 g, 0.65 mol, 60 equiv) and $NaBH_3CN$ (3.4 g, 54.5 mmol, 5 equiv), heated to reflux for 3 h, concentrated in vacuo to a residue that was redissolved in EtOAc. The organic layer was washed twice with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4, and concentrated *in* vacuo to yield a residue. *tert*-Butyl 5-amino-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-carboxylate (**13**) was isolated as a colorless oil (2.09 g, 73%) by flash chromatography using an EtOAc/heptane 1/1 (v/v) solution and an EtOAc/MeOH 9/1 v/v solution containing 2% of Et_3N solution as eluants. $C_{15}H_{22}N_2O_2$, F.W. = 262.35 g/mol, R_f = 0.22 (95/5/2 v/v/v EtOAc/MeOH/Et_3N), colorless oil. ^{1}H NMR (DMSO-d_6, 300 MHz, 360 K) δ = 1.08−2.00 (m, 15H); 3.94 (d, J = 9.3 Hz, 1H); 7.07 (dd, J = 7.2, 1.8 Hz, 1H); 7.14−7.27 (m, 2H); 7.51 (bs, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz, 360 K) δ = 26.6; 29.0 (3C); 36.2; 48.5; 53.5; 79.9 (Cq); 127.2; 127.3 (2C); 129.0; 141.5 (Cq); 143.8 (Cq); 154.2 (Cq). LRMS (ESI) 207.2 $(M+H-56)^+$, 263.2 $(M+H)^+$, 525.4 $(2M+H)^+$. HRMS (ESI) *m*/*z* for $C_{15}H_{23}N_2O_2$ $(M+H)^+$, calcd 263.1754, found 263.1750.

(±)-5-Amino-1-*tert*-butoxycarbonyl-7-bromo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine (14). A stirred solution of *tert*-butyl 7-bromo-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-carboxylate (**12**) (135 mg, 0.397 mmol) in MeOH (8 mL) was treated in succession with NH_4OAc (1.53 g, 19.8 mmol, 50 equiv) and $NaBH_3CN$ (125 mg, 1.98 mmol, 5 equiv), heated to reflux for 3 h, and concentrated in vacuo to a residue that was redissolved with EtOAc. The organic layer was washed twice with a saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, and concentrated in vacuo to yield a residue. *tert*-Butyl 5-amino-7-bromo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-carboxylate (**14**) was isolated as a colorless oil (89.2 mg, 66%) by flash chromatography using an EtOAc/heptane 1/1 (v/v) solution and an EtOAc/MeOH 9/1 v/v solution containing 2% of Et_3N solution as eluants. $C_{15}H_{21}BrN_2O_2$, F.W. = 341.24 g/mol, R_f = 0.52 (80/20/2 v/v/v EtOAc/MeOH/Et_3N), colorless oil. ^{1}H NMR (DMSO-d_6, 300 MHz, 360 K) δ = 1.15−1.64 (m, 11H); 1.82 (bs, 2H); 2.25 (bs, 2H); 3.89 (d, J = 9.6 Hz, 1H); 7.03 (d, J = 8.4 Hz, 1H); 7.35 (dd, J = 8.4 Hz, 2.4 Hz, 1H); 7.69 (bs, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz, 360 K) δ = 26.4; 28.9 (3C); 35.7; 48.2; 53.2; 80.3 (Cq); 120.4 (Cq); 129.8; 130.0; 131.2; 140.7 (Cq); 146.5 (Cq); 153.9 (Cq). LRMS (ESI) 285.1 $(M+Na-100)^+$, 287.1 $(M+Na-100)^+$, 341.2 $(M+H)^+$, 343.2 $(M+H)^+$. HRMS (ESI) *m*/*z* for $C_{15}H_{22}BrN_2O_2$ $(M+H)^+$, calcd 341.0859, found 341.0874.

Procedure for the Loading of (±)-5-Amino-1-*tert*-butoxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine (13) or (±)-5-Amino-1-*tert*-butoxycarbonyl-7-bromo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine (14) onto 4-(4-Formyl-3-methoxyphenoxy)butyryl Aminomethylated Polystyrene Resin. To 1 g of FMPB-AM resin (0.74 g/mol, 0.74 mmol) was added a solution of 583 mg of **13** or 756 mg of **14** (2.22 mmol, 3 equiv) in 4 mL of a DMF/AcOH (99/1, v/v) followed by 186.l mg (2.96 mmol, 4 equiv) of $NaBH_3CN$. The reaction mixture was heated at 80 °C for 3 h, allowed to cool to room temperature, and filtered. Excess benzazepine reagent **13** or **14** was recovered in the filtrate and reused for a subsequent loading experiment after a short purification step. The resin was washed with DMF (three times), MeOH (three times), and DCM(three times) and dried in vacuo. Complete loading of benzazepine scaffold onto FMPB-AM resin was verified by a negative DNPH test. Dried resin-bound benzazepine **15** or **16** was divided into equal portions (37 μmol each) and used for all subsequent experiments.

General Procedure for Introduction of the R^1 Diversity Center onto Resin-Bound Benzazepine 15 or 16 by Acylation or Sulfonation. To resin-bound benzazepine **15** or **16** (37 μmol) preswollen in anhydrous DCM was added a solution of acyl chloride or sulfonyl chloride (185 μmol, 5 equiv) and DIEA (39 μL, 222 μmol, 6 equiv) in DCM (300 μL). The reaction mixture was shaken for 1 h at room temperature after which the resin was filtered, washed with DCM (three times), MeOH (three times), and DCM again. In certain cases, the acylation/sulfonation reaction was repeated to ensure complete conversion as monitored by a negative chloranil/acetaldehyde test.

General Procedure for Selective 1-Benzazepine Boc Deprotection on Acid-Labile BAL Resin. To the resin-bound *N*-Boc benzazepine **17a** (37 μmol) preswollen in anhydrous DCM was added a freshly prepared solution of TMSOTf (20.4 μL, 111 μmol, 3 equiv) and Et_3N (7.7 μL, 55.5 μmol, 1.5 equiv) in anhydrous DCM (0.8 mL). The reaction mixture was shaken at room temperature for 15 min, filtered, and washed in DCM (three times), MeOH (three times), and DCM again.

General Procedure for the Introduction of the R^2 Diversity Center onto Resin-Bound Benzazepine by Acylation, Sulfonation, Alkylation, Reductive Amination, Urea Formation, or Buchwald−Hartwig Cross-Coupling Reaction. Acylation Reaction. To a resin-bound benzazepine (**17b**) (37 μmol) preswollen in anhydrous DCM was added a solution of acyl chloride (185 μmol, 5 equiv) and

DIEA (39 μL, 222 μmol, 6 equiv) in anhydrous DCM (300 μL). The reaction mixture was shaken for 1 h at room temperature after which the resin was filtered and washed with DCM (three times) and MeOH (three times), and a final DCM wash was completed. In certain cases, the acylation reaction was repeated to ensure complete conversion as monitored by a negative chloranil/acetaldehyde test.

Sulfonation Reaction. To a resin-bound benzazepine (**17b**) (37 μmol) preswollen in anhydrous DCM was added a solution of sulfonyl chloride (370 μmol, 10 equiv) and pyridine (60 μL, 740 μmol, 20 equiv) in anhydrous DCM (300 μL). The reaction mixture was shaken for 1 h at room temperature after which the resin was filtered, washed with DCM (three times) and MeOH (three times), and a final DCM wash was completed. In certain cases, the sulfonation reaction was repeated to ensure complete conversion as monitored by a negative chloranil/acetaldehyde test.

Reductive Amination Reaction. To a resin-bound benzazepine (**17b**) (37 μmol) preswollen in DMF was added 400 μL of a solution of DMF/AcOH (99/1 v/v) followed by 23.3 mg of $NaBH_3CN$ (370 μmol, 10 equiv) and 10 equiv of the aldehyde or ketone diversity reagent. The reaction mixture was shaken for 24 h at room temperature after which the resin was filtered and washed with DCM (three times), MeOH (three times), and DCM again. The reductive amination reaction was repeated to ensure complete conversion as monitored by a negative chloranil/acetaldehyde test.

Alkylation Reaction. To a resin-bound benzazepine (**17b**) (37 μmol) preswollen in DMF was added 300 μL of DMF followed by 44 μL of BnBr (370 μmol, 10 equiv) and 129 μL of DIEA (740 μmol, 20 equiv). The reaction mixture was shaken for 24 h at room temperature after which the resin was filtered, and washed with DMF (three times), MeOH (three times), and DCM (three times). The alkylation reaction was repeated to ensure complete conversion as monitored by a negative chloranil/acetaldehyde test.

Preparation of Urea Derivative 31c Using a Carbonyl Activating Reagent. To a resin-bound benzazepine (**17b**) (37 μmol) preswollen in dry THF was added the suspension obtained from slow addition of 47 μL of 2,4,6-collidine (370 μmol, 10 equiv) in 500 μL of anhydrous THF solution containing 11.0 mg of bis(trichloromethyl)carbonate (37 μmol, 10 equiv). The reaction mixture was shaken for 30 min at room temperature after which the resin was filtered and washed with anhydrous THF (one time) followed by anhydrous DCM (three times). The above was treated with a solution of 9 μL of phenylethylamine (740 μmol, 20 equiv) and 65 μL of DIEA (370 μmol, 10 equiv) in 400 μL of anhydrous DCM. The reaction mixture was shaken for 3 h at room temperature after which the resin was filtered and washed with DMF (three times), MeOH (three times), and DCM (three times).

Buchwald−Hartwig Cross-Coupling Reaction. To a resin-bound benzazepine (**17b**) (37 μmol) was added in succession 35.5 mg of NaO*t*Bu (370 μmol, 10 equiv), 6.8 mg of $Pd_2(dba)_3$ (7.4 μmol, 0.2 equiv), 300 μL of anhydrous 1,4-dioxane, 20 μL of bromobenzene (185 μmol, 5 equiv) and 7.3 μL of P(*t*Bu)$_3$ (30 μmol, 0.8 equiv). The reaction mixture was flushed with argon and shaken for 12 h at 90 °C after which the resin was filtered and washed with DMF (three times), H_2O (three times), MeOH (three times), and DCM (three times).

General Procedure for the Introduction of the R^3 Diversity Center by Suzuki Cross-Coupling Reaction. To a resin-bound *N*-Boc bromo-benzazepine (**41c**) (37 μmol) was successively added 39 mg (185 μmol, 5 equiv) of K_3PO_4, 5 equiv of boronic acid $R^3B(OH)_2$, 5 mg of $Pd(PPh_3)_4$ (3.7 μmol, 0.1 equiv), 400 μL of DMF, and 40 μL of H_20. The reaction mixture was flushed with argon and shaken at 90 °C for 12 h, filtered, and washed with DMF (three times), H_20 (three times), MeOH (three times), and DCM (three times).

General Procedure for Introduction of the R^3 Diversity Center by Buchwald−Hartwig Cross-Coupling Reaction. To a resin-bound *N*-Boc bromo-benzazepine (**41c**) (37 μmol) was successively added 35.6 mg (370 μmol, 10 equiv) of NaO*t*Bu, 5 equiv of amine R^3NH_2, 1.7 mg of $Pd_2(dba)_3$ (1.85 μmol, 0.05 equiv), 9.2 mg of BINAP (148 μmol, 0.4 equiv), and 300 μL of anhydrous toluene. The reaction mixture was flushed with argon and shaken at 90 °C for 12 h, filtered, and washed with DMF (three times), H_2O (three times), MeOH (three times), and DCM (three times).

General Procedure for Cleavage of Functionalized 1-Benzazepine from its Support. To a resin-bound functionalized 1-benzazepine (37 μmol) preswollen in DCM was added 1.5 mL of TFA. The reaction mixture was shaken for 12 h at room temperature after which the resin was filtered, washed with DCM (two times) and MeOH (two times). The combined filtrates were mixed and evaporated to dryness in a genevac evaporator to yield the 1-benzazepine residue that was dissolved in acetonitrile/H_2O (1/1 v/v) and lyophilized.

***N*-(1-Benzoyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-butanamide (18).** $C_{21}H_{24}N_2O_2$, F.W. = 336.4 g/mol, T_r = 1.720 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 0.94 (t, J = 7.2 Hz, 3H); 1.44−1.75 (m, 4H); 1.82−2.12 (m, 2H); 2.26 (t, J = 7.5 Hz, 2H); 2.97 (broad t, J = 10.2 Hz, 1H); 1.48 (m, 1H); 5.23 (m, 1H); 6.64 (d, J = 7.5 Hz, 1H); 6.96 (t, J = 7.2 Hz, 1H); 7.05−7.50 (m, 7H); 8.52 (1H, d, J = 7.2 Hz). LC/MS (ESI) 337.2 $(M+H)^+$, 359.2 $(M+Na)^+$.

***N*-(1-Benzoyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-benzamide (19).** $C_{24}H_{22}N_2O_2$, F.W. = 370.4 g/mol, T_r = 2.122 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.64 (m, 1H); 1.83 (m, 1H); 1.96 (m, 1H); 2.10 (m, 1H); 2.99 (m, 1H); 4.53 (m, 1H); 5.48 (m, 1H); 6.67 (d, J = 7.5 Hz, 1H); 6.95 (t, J = 7.2 Hz, 1H); 7.09−7.34 (m, 5H); 7.39 (m, 2H); 7.48−7.63 (m, 3H); 8.02 (d, J = 6.6 Hz, 2H); 9.10 (d, J = 7.8 Hz, 1H). LC/MS (ESI) 371.2 $(M+H)^+$, 393.2 $(M+Na)^+$.

***N*-(1-Benzoyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-piperidine-4-carboxamide (20).** $C_{23}H_{27}N_3O_2$, CF_3COOH, F.W. = 377.5 g/mol, T_r = 1.270 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.40−2.15 (m, 8H); 2.65 (m, 1H); 2.83−3.10 (m, 3H); 3.20−3.47 (m, 2H); 4.47 (m, 1H); 5.18 (m, 1H); 6.65 (d, J = 7.5 Hz, 1H); 6.94 (t, J = 7.2 Hz, 1H); 7.07−7.42 (m, 7H); 8.37 (d, J = 9.3 Hz, 1H); 8.68 (d, J = 7.5 Hz, 1H); 8.76 (d, J = 9.5 Hz, 1H). LC/MS (ESI) 378.2 $(M+H)^+$.

2-Amino-*N*-(1-benzoyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)acetamide (21). $C_{19}H_{21}N_3O_2$, CF_3COOH, F.W. = 323.4 g/mol, T_r = 1.234 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.52−1.72 (m, 2H); 1.85−2.13 (m, 2H); 2.98 (m, 1H); 3.78 (m, 2H); 4.48 (m, 1H); 5.24 (m, 1H); 6.68 (d, J = 7.5 Hz, 1H); 6.97 (t, J = 7.2 Hz, 1H); 7.05−7.38 (m, 7H); 8.08 (bs, 2H); 9.09 (d, J = 7.8 Hz, 1H). LC/MS (ESI) 324.3 $(M+H)^+$, 346.3 $(M+Na)^+$.

6-Amino-*N*-(1-benzoyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)hexanamide (22). $C_{23}H_{29}N_3O_2$, CF_3COOH, F.W. = 379.5 g/mol, T_r = 1.332 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.35 (m, 2H); 1.43−1.71 (m, 6H); 1.83−2.05 (m, 2H); 2.28 (d, J = 7.5 Hz, 2H); 2.68−2.87 (m, 2H); 2.96 (t, J = 10.2 Hz, 1H); 4.46 (m, 1H); 5.21 (m, 1H); 6.64 (d, J = 7.5 Hz, 1H); 6.94 (t, J = 8.2 Hz, 1H); 7.04−7.43 (m, 7H); 7.72 (bs, 2H); 8.54 (d, J = 7.5 Hz, 1H). LC/MS (ESI) 371.2 $(M+H)^+$, 393.2 $(M+Na)^+$. LC/MS (ESI) 380.4 $(M+H)^+$, 402.3 $(M+Na)^+$.

***N*-(1-Butyryl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-benzamide (23).** $C_{21}H_{24}N_2O_2$, F.W. = 336.4 g/mol, T_r = 1.961 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 0.81 (t, J = 7.5 Hz, 3H); 1.51 (m, 2H); 1.56−1.79 (m, 2H); 1.81−2.04 (m, 3H); 2.16 (m, 1H); 2.61 (m, 1H); 4.45 (dt, J = 13.2 Hz, 3.9 Hz, 1H); 5.10 (m, 1H); 7.20−7.37 (m, 4H); 7.45−7.61 (m, 3H); 7.96 (d, J = 6.6 Hz, 2H); 8.99 (d, J = 8.1 Hz, 1H). LC/MS (ESI) 337.2 $(M+H)^+$, 359.2 $(M+Na)^+$.

***N*-(1-Butyryl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-butanamide (24).** $C_{18}H_{26}N_2O_2$, F.W. = 302.4 g/mol, T_r = 1.559 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 0.77 (t, J = 7.2 Hz, 3H); 0.89 (t, J = 7.2 Hz, 3H); 1.36−1.66 (m, 6H); 1.72−1.92 (m, 3H); 2.04−2.31 (m, 3H); 2.40−2.67 (m, 1H under DMSO); 4.40 (d, J = 13.2 Hz, 1H); 4.85 (t, J = 8.4 Hz, 1H); 7.10−7.47 (m, 4H); 8.40 (d, J = 8.1 Hz, 1H). LC/MS (ESI) 303.2 $(M+H)^+$, 325.2 $(M+Na)^+$.

***N*-(1-Butyryl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-cyclohexanecarboxamide (25).** $C_{21}H_{30}N_2O_2$, F.W. = 342.45 g/mol, T_r = 2.020 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 0.77 (t, J = 7.5 Hz, 3H); 1.04−1.93 (m, 17H); 2.11 (m, 1H); 2.27 (m, 1H); 2.55 (m, 1H); 4.40 (d, J = 12.9 Hz, 1H); 4.79 (t, J = 7.8 Hz, 1H); 7.06−7.51 (m, 4H); 8.31 (d, J = 7.8 Hz, 1H). LC/MS (ESI) 343.2 $(M+H)^+$, 365.2 $(M+Na)^+$.

4-Methoxy-*N*-(1-butyryl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)benzenesulfonamide (26). $C_{21}H_{26}N_2O_4S$, F.W. = 402.5 g/mol, T_r = 1.997 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 0.76 (t, J = 7.8 Hz, 3H); 1.31−1.66 (m, 6H); 1.73 (m, 1H); 2.05 (m, 1H); 2.40−2.60 (m, 1H under DMSO); 3.78−3.88 (m, 4H); 4.21 (m, 1H); 7.05 (d, J = 6.6 Hz, 1H); 7.09−7.36 (m, 5H); 7.42−7.52 (m, 1H); 7.64 (m, 6.9 Hz, 1H); 8.34 (d, J = 7.8 Hz, 1H). LC/MS (ESI) 403.2 $(M+H)^+$, 426.2 $(M+Na)^+$.

***N*-[1-(Cyclohexylcarbonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]benzamide (27).** $C_{24}H_{28}N_2O_2$, F.W. = 376.5 g/mol, T_r = 2.338 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 0.70−2.06 (m, 14H); 2.24 (tt, J = 11.4 Hz, 3.3 Hz, 1H); 2.60 (t, J = 10.8 Hz, 1H); 4.41 (dt, J = 13.2 Hz, 3.6 Hz, 1H); 5.16 (m, 1H); 7.18−7.40 (m, 4H); 7.44−7.64 (m, 3H); 7.96 (d, J = 6.6 Hz, 2H); 8.99 (d, J = 8.1 Hz, 1H). LC/MS (ESI) 377.3 $(M+H)^+$, 399.3 $(M+Na)^+$.

***N*-[1-(Biphenyl-4-ylcarbonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]benzamide (28).** $C_{30}H_{26}N_2O_2$, F.W. = 446.5 g/mol, T_r = 2.519 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.65 (m, 1H); 1.86 (m, 1H); 1.98 (m, 1H); 2.13 (m, 1H); 3.02 (m, 1H); 4.55 (m, 1H); 5.52 (m, 1H); 6.74 (d, J = 7.5 Hz, 1H); 6.99 (t, J = 6.9 Hz, 1H); 7.18 (t, J = 7.5 Hz, 1H); 7.27−7.72 (m, 13H); 8.04 (d, J = 7.2 Hz, 2H); 9.08 (d, J = 7.5 Hz, 1H). LC/MS (ESI) 447.3. $(M+H)^+$, 369.3 $(M+Na)^+$.

***N*-{1-[(4-Methoxyphenyl)sulfonyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl}benzamide (29).** $C_{24}H_{24}N_2O_4S$, F.W. = 436.5 g/mol, T_r = 2.240 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.58−1.99 (m, 4H); 3.11 (m, 1H); 3.86 (s, 3H); 3.91 (m, 1H); 5.21 (t, J = 9.3 Hz, 1H); 7.05 (d, J = 7.5 Hz, 1H); 7.11−7.38 (m, 5H); 7.45−7.61 (m, 3H); 7.84 (d, J = 8.7 Hz, 2H); 7.94 (d, J = 6.6 Hz, 2H); 8.76 (bs). LC/MS (ESI) 437.2 $(M+H)^+$, 459.2 $(M+Na)^+$.

5-(Benzoylamino)-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-carboxamide (30). $C_{24}H_{23}N_3O_2$, F.W. = 385.4 g/mol, T_r = 2.240 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.43−2.14 (m, 4H); 2.85 (bs, 1H); 4.36 (bs, 1H); 5.25 (bs, 1H); 6.96 (t, J = 7.2 Hz, 1H); 7.14−7.62 (m, 11H); 7.69−8.09 (bs, 3H); 8.98 (bs, 1H). LC/MS (ESI) 386.2 $(M+H)^+$, 408.2 $(M+Na)^+$.

5-(Benzoylamino)-*N*-(2-phenylethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-carboxamide (31c). $C_{26}H_{27}N_3O_2$, F.W. = 413.5 g/mol, T_r = 2.238 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.41−2.14 (m, 4H); 2.60−2.92 (m, 3H); 3.27 (m, 2H); 4.28 (bs, 1H); 5.17 (bs, 1H); 6.92−7.72 (m, 12H); 7.73−8.15 (m, 3H); 8.97 (bs, 1H). LC/MS (ESI) 414.3 $(M+H)^+$, 436.2 $(M+Na)^+$.

***N*-[1-(2-Aminoacetyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]benzamide (32).** $C_{19}H_{21}N_3O_2$, CF_3COOH, F.W. = 323.4 g/mol, T_r = 1.121 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.55−2.14 (m, 4H); 2.79 (t, J = 10.8 Hz, 1H); 3.02 (d, J = 16.5 Hz, 1H); 3.83 (d, J = 16.5 Hz, 1H); 4.45 (m, 1H); 5.13 (m, 1H); 7.25−7.67 (m, 7H); 7.97 (m, J = 6.9 Hz); 8.13 (bs, 2H); 9.10 (d, J = 8.1 Hz). LC/MS (ESI) 324.3 $(M+H)^+$, 346.3 $(M+Na)^+$.

***N*-[1-(Piperidin-4-ylcarbonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]benzamide (33).** $C_{23}H_{27}N_3O_2$, CF_3COOH, F.W. = 377.5 g/mol, T_r = 1.168 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.46−2.12 (m, 9H); 2.56−2.85 (m, 3H); 3.19 (d, J = 12.9 Hz, 1H); 3.28 (d, J = 12.3 Hz, 1H); 4.41 (m, 1H); 5.11 (m, 1H); 7.27−7.61 (m, 7H); 7.91−8.00 (m, 2H); 8.30 (bs, 1H); 8.55 (bs, 1H); 9.04 (d, J = 7.8 Hz, 1H). LC/MS (ESI) 378.3 $(M+H)^+$.

***N*-[1-(6-Aminohexanoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]benzamide (34).** $C_{23}H_{29}N_3O_2$, CF_3COOH, F.W. = 379.5 g/mol, T_r = 1.278 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.12−1.33 (m, 2H); 1.37−2.07 (m, 9H); 2.20 (m, 1H); 2.63 (m, 1H); 2.69−2.84 (m, 2H); 4.45 (m, 1H); 5.11 (m, 1H); 7.20−7.39 (m, 4H); 7.45−7.62 (m, 3H); 7.65 (bs, 3H); 7.90−8.01 (m, 2H); 9.09 (d, J = 8.1 Hz, 1H). LC/MS (ESI) 380.3 $(M+H)^+$.

***N*-(1-Benzyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-benzamide (35).** $C_{24}H_{24}N_2O$, CF_3COOH, F.W. = 356.5 g/mol, T_r = 2.533 min. ^{1}H NMR (DMSO-d_6, 300 MHz, 300 K) δ = 1.46 (m, 1H); 1.58−1.81 (m, 2H); 1.88 (m, 1H);

2.65 (m, 1H); 3.08 (m, 1H); 4.22 (d, $J = 14.0$ Hz, 1H); 4.45 (d, $J = 14.0$ Hz, 1H); 5.55 (m, 1H); 6.92 (t, $J = 7.2$ Hz, 1H); 7.02 (d, $J = 7.8$ Hz, 1H); 7.14 (m, 1H); 7.18−7.29 (m, 2H); 7.29−7.38 (m, 2H); 7.40−7.62 (m, 5H); 7.95 (m, 2H); 8.79 (d, $J = 8.4$ Hz, 1H). LC/MS (ESI) 357.2 $(M+H)^+$, 379.2 $(M+Na)^+$.

***N*-[1-(2-Phenylethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]benzamide (36).** $C_{25}H_{26}N_2O$, CF_3COOH, F.W. = 370.5 g/mol, $T_r = 2.411$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 1.53$ (m, 1H); 1.73 (m, 2H); 1.90 (m, 1H); 2.72 (m, 1H); 2.86 (m, 2H); 3.28 (m, 2H); 3.48 (m, 1H); 5.42 (m, 1H); 6.94 (m, 1H); 7.05 (m, 1H); 7.12−7.35 (m, 6H); 7.44−7.60 (m, 4H); 7.93 (d, $J = 7.2$ Hz, 2H); 8.75 (bs, 1H). LC/MS (ESI) 371.2 $(M+H)^+$, 393.2 $(M+Na)^+$.

***N*-[1-(3-Methylbutyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]benzamide (37).** $C_{22}H_{28}N_2O$, CF_3COOH, F.W. = 336.5 g/mol, $T_r = 2.056$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.88$ (d, $J = 6.6$ Hz, 3H); 0.92 (d, $J = 6.6$ Hz, 3H); 1.46 (m, 3H); 1.71 (m, 3H); 1.89 (m, 1H); 2.64 (m, 1H); 3.04 (m, 1H); 3.20 (m, 2H); 5.40 (m, 1H); 6.80−7.08 (m, 2H); 7.10−7.30 (m, 2H); 7.37−7.66 (m, 3H); 7.91 (d, $J = 6.6$ Hz, 2H); 8.72 (d, $J = 6.9$ Hz, 1H). LC/MS (ESI) 337.3 $(M+H)^+$.

***N*-(1-Cyclohexylmethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)benzamide (38).** $C_{24}H_{30}N_2O$, CF_3COOH, F.W. = 362.5 g/mol, $T_r = 2.463$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.76-1.04$ (m, 2H); 1.05−1.34 (m, 3H); 1.37−2.12 (m, 10H); 2.62 (m, 1H); 2.81 (dd, $J = 12.3$ Hz, 6.0 Hz, 1H); 3.05 (dd, $J = 12.3$ Hz, 7.2 Hz, 1H); 3.16 (m, 1H); 5.46 (m, 1H); 6.83−7.05 (m, 2H); 7.08−7.28 (m, 2H); 7.41−7.62 (m, 3H); 7.85−8.00 (m, 2H); 8.70 (d, $J = 8.4$ Hz, 1H). LC/MS (ESI) 363.3 $(M+H)^+$.

***N*-(1-Cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)benzamide (39).** $C_{23}H_{28}N_2O$, CF_3COOH, F.W. = 348.5 g/mol, $T_r = 1.582$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.76-1.04$ (m, 2H); 1.05−1.34 (m, 3H); 1.37−2.12 (m, 10H); 2.62 (m, 1H); 2.81 (dd, $J = 12.3$ Hz, 6.0 Hz, 1H); 3.05 (dd, $J = 12.3$ Hz, 7.2 Hz, 1H); 3.16 (m, 1H); 5.46 (m, 1H); 6.83−7.05 (m, 2H); 7.08−7.28 (m, 2H); 7.41−7.62 (m, 3H); 7.85−8.00 (m, 2H); 8.70 (d, $J = 8.4$ Hz, 1H). LC/MS (ESI) 349.3 $(M+H)^+$, 371.3 $(M+Na)^+$.

***N*-(1-Phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-benzamide (40).** $C_{23}H_{22}N_2O$, CF_3COOH, F.W. = 342.4 g/mol, $T_r = 2.828$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 1.56$ (m, 1H); 1.71−2.13 (m, 3H); 3.39 (1H under DMSO); 3.78 (t, $J = 9.9$ Hz, 1H); 5.18 (m, 1H); 6.60−6.85 (m, 3H); 7.08−7.65 (m, 9H); 7.80 (d, $J = 7.2$ Hz, 2H); 8.61 (bs, 1H). LC/MS (ESI) 343.2 $(M+H)^+$.

***N*-(7-Phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-benzamide (42).** $C_{23}H_{22}N_2O$, CF_3COOH, F.W. = 342.4 g/mol, $T_r = 1.713$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 1.72-2.17$ (m, 4H); 2.98 (m, 1H); 3.46 (d, $J = 12.6$ Hz, 1H); 5.43 (t, $J = 8.1$ Hz, 1H); 7.21−7.35 (m, 2H); 7.41 (t, $J = 7.8$ Hz, 2H); 7.46−7.61 (m, 7H); 7.90−7.97 (m, 2H); 8.95 (d, $J = 8.1$ Hz, 1H). LC/MS (ESI) 343.3 $(M+H)^+$.

***N*-(1-Butyryl-7-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)benzamide (43).** $C_{27}H_{28}N_2O_2$, F.W. = 412.5 g/mol, $T_r = 2.445$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.84$ (t, $J = 7.2$ Hz, 3H); 1.54 (m, 2H); 1.60−2.10 (m, 5H); 2.24 (m, 1H); 2.66 (t, $J = 11.4$ Hz, 1H); 4.48 (m, 1H); 5.16 (t, $J = 8.4$ Hz, 1H); 7.26−7.67 (m, 11H); 7.96 (m, 2H); 9.06 (d, $J = 8.1$ Hz, 1H). LC/MS (ESI) 413.4 $(M+H)^+$, 435.4 $(M+Na)^+$.

***N*-[1-Butyryl-7-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]benzamide (44).** $C_{28}H_{30}N_2O_3$, F.W. = 442.5 g/mol, $T_r = 2.449$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.84$ (t, $J = 7.5$ Hz, 3H); 1.54 (m, 2H); 1.42−2.11 (m, 5H); 2.23 (m, 1H); 2.65 (t, $J = 10.8$ Hz, 1H); 3.76 (s, 3H); 4.48 (m, 1H); 5.14 (t, $J = 8.1$ Hz, 1H); 7.00 (d, $J = 8.4$ Hz, 2H); 7.32 (d, $J = 8.7$ Hz, 1H); 7.41−7.62 (m, 7H); 7.96 (d, $J = 6.9$ Hz, 2H); 9.05 (d, $J = 8.1$ Hz, 1H). LC/MS (ESI) 443.2 $(M+H)^+$.

***N*-[1-Butyryl-7-(4-cyanophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]benzamide (45).** $C_{28}H_{27}N_3O_2$, F.W. = 437.5 g/mol, $T_r = 2.341$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.84$ (t, $J = 7.5$ Hz, 3H); 1.54 (m, 2H); 1.60−2.10 (m, 5H); 2.25 (m, 1H); 2.67 (t, $J = 11.2$, Hz, 1H); 4.47 (m, 1H); 5.14 (t, $J = 9.3$ Hz, 1H); 7.40−7.61 (m, 5H); 7.62−7.75 (m, 2H); 7.76−7.83 (m, 2H); 7.90 − 8.00 (m, 3H); 9.05 (d, $J = 8.4$ Hz, 1H). LC/MS (ESI) 438.2 $(M+H)^+$, 460.2 $(M+Na)^+$.

***N*-[1-Butyryl-7-(2-thienyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]benzamide (46).** $C_{25}H_{26}N_2O_2S$, F.W. = 418.6 g/mol, $T_r = 2.359$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.83$ (t, $J = 7.2$ Hz, 3H); 1.45−2.08 (m, 7H); 2.21 (m, 1H); 2.66 (t, $J = 11.4$ Hz, 1H); 4.46 (d, $J = 13.2$ Hz, 1H); 5.11 (t, $J = 8.7$ Hz, 1H); 7.11 (t, $J = 3.9$ Hz, 1H); 7.32 (d, $J = 8.1$ Hz, 1H); 7.42 (d, $J = 3.6$ Hz, 1H); 7.46−7.66 (m, 8H); 7.94−8.00 (m, 2H); 9.04 (d, $J = 7.8$ Hz, 1H). LC/MS (ESI) 419.2 $(M+H)^+$, 441.2 $(M+Na)^+$.

***N*-{1-Butyryl-7-[(*E*)-2-phenylvinyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl}benzamide (47).** $C_{29}H_{30}N_2O_2$, F.W. = 438.6 g/mol, $T_r = 2.645$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.83$ (t, $J = 7.2$ Hz, 3H); 1.43−2.09 (m, 7H); 2.20 (m, 1H); 2.66 (t, $J = 10.8$ Hz, 1H); 4.45 (d, $J = 12.9$ Hz, 1H); 5.13 (t, $J = 9.3$ Hz, 1H); 7.06−7.69 (m, 13 H); 7.96−8.04 (m, 2 H); 8.98 (d, $J = 8.1$ Hz, 1 H). LC/MS (ESI) 439.3 $(M+H)^+$, 461.3 $(M+Na)^+$.

***N*-(1-Butyryl-7-isobutyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)benzamide (48).** $C_{25}H_{32}N_2O_2$, F.W. = 392.5 g/mol, $T_r = 2.483$ min. LC/MS (ESI) 393.3 $(M+H)^+$, 415.2 $(M+Na)^+$.

***N*-(1-Butyryl-7-pyrrolidin-1-yl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)benzamide (49a).** $C_{25}H_{31}N_3O_2$, CF_3-$COOH$, F.W. = 405.5 g/mol, $T_r = 1.950$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.81$ (t, $J = 7.2$ Hz, 3H); 1.40−1.77 (m, 4H); 1.78−2.03 (m, 7H); 2.13 (m, 1H); 2.53 (m, 1H under DMSO); 3.15 (m, 4H); 4.41 (d, $J = 13.2$ Hz, 1H); 5.01 (t, $J = 8.4$ Hz, 1H); 6.40 (d, $J = 8.4$ Hz, 1H); 6.46 (s, 1H); 6.99 (d, $J = 8.4$ Hz, 1H); 7.42−7.63 (m, 3H); 7.92 (d, $J = 7.8$ Hz, 2H); 8.92 (d, $J = 7.8$ Hz, 1H). LC/MS (ESI) 406.2 $(M+H)^+$, 428.2 $(M+Na)^+$.

***N*-(7-Bromo-1-butyryl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)benzamide (49b).** $C_{21}H_{23}BrN_2O_2$, F.W. = 415.3 g/mol, $T_r = 2.228$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.84$ (t, $J = 7.5$ Hz, 3H); 1.43−1.81 (m, $J = 4$H); 1.81−2.08 (m, 3H); 2.19 (m, 1H); 2.64 (t, $J = 12.3$ Hz, 1H); 4.43 (d, $J = 13.5$ Hz, 1H); 5.07 (d, $J = 9.6$ Hz, 1H); 7.29

(d, $J = 8.1$ Hz, 1H); 7.41 (s, 1H); 7.48−7.67 (m, 4H); 7.96 (d, $J = 7.5$ Hz, 2H); 9.02 (d, $J = 7.2$ Hz, 1H). LC/MS (ESI) 417.1 $(M+H)^+$, 439.1 $(M+Na)^+$.

***N*-(1-Butyryl-7-anilino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)benzamide (50).** $C_{27}H_{29}N_3O_2$, CF_3COOH, F.W. = 427.5 g/mol, $T_r = 2.264$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.84$ (t, $J = 7.2$ Hz, 3H); 1.42−2.08 (m, 7H); 2.17 (m, 1H); 2.57 (m, 1H, under DMSO); 4.44 (m, 1H); 5.00 (t, $J = 8.7$ Hz, 1H); 6.77 (t, $J = 6.9$ Hz, 1H); 6.90 (dd, $J = 8.4$ Hz, 2.4 Hz, 1H); 6.99−7.18 (m, 6H); 7.44−7.60 (m, 3H); 7.90−8.00 (m, 2H); 8.33 (m, 1H); 8.91 (d, $J = 8.1$ Hz, 1H). LC/MS (ESI) 428.3 $(M+H)^+$, 450.3 $(M+Na)^+$.

***N*-(1-Butyryl-7-(diethylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)benzamide (51).** $C_{25}H_{33}N_3O_2$, CF_3COOH, F.W. = 407.5 g/mol, $T_r = 1.290$ min. LC/MS (ESI) 408.3 $(M+H)^+$.

***N*-(1-Butyryl-7-(isobutylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)benzamide (52).** $C_{25}H_{33}N_3O_2$, CF_3COOH, F.W. = 407.6 g/mol, $T_r = 1.803$ min. ^1H NMR (DMSO-d_6, 300 MHz, 300 K) $\delta = 0.69$−1.00 (9H, m); 1.38−2.05 (m, 8H); 2.12 (m, 1H); 2.53 (m, 1H under DMSO); 2.75 (t, $J = 5.4$ Hz, 2H); 4.40 (d, $J = 12.9$ Hz, 1H); 4.97 (t, $J = 8.7$ Hz, 1H); 6.43 (d, $J = 8.2$ Hz, 1H); 6.55 (s, 1H); 6.91 (d, $J = 8.2$ Hz, 1H); 7.35−7.65 (m, 5H); 7.96 (m, 2H); 8.88 (d, $J = 7.6$ Hz, 1H). LC/MS (ESI) 408.4 $(M+H)^+$.

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Supporting Information Available. ^1H and ^{13}C NMR spectra for compounds **4**−**14** and ^1H NMR spectra and LC/MS profiles for compounds **18**−**52**. This material is available free of charge via the Internet at http://pubs.acs.org.

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