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A Single-Step Synthesis of Azetidine-3-amines

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ABSTRACT: The azetidine group is frequently encountered within contemporary medicinal chemistry. However, the introduction of an azetidine can be synthetically challenging. Herein, a straight-forward synthesis of azetidine-3-amines, starting from a bench stable, commercial material is presented. The reaction tolerates common functionality, and proceeds in moderate-to-high yield with secondary amines, and moderate-to-low yield with primary amines. The methodology compares favorably to alternative procedures and can be utilized in "any-stage" functionalization, including late-stage azetidinylation of approved drugs and other compounds with pharmacological activity.

The azetidine motif is one of the most important substructures in pharmaceuticals and is present in a number of approved drugs such as antibiotics,[1] kinases[2] (*e.g.* baricitinib, cobimetinib, itacitinib), and other compound classes[3] (*e.g.* thrombin inhibitor, ximelagatran/melagatran; Ca-channel blocker, azelnidipine). The azetidine group is also attractive since it can restrict the conformation of an acyclic counterpart (rigidification),[4] and lead to compounds with an improved pharmacokinetic or toxicity profile.[5] Azetidine-3-amines (3-aminoazetidines, or azaazetidines) are a less well developed subset of azetidines, that nonetheless have found important applications in medicinal chemistry, being a substructure of JNJ-41443532 (a CCR2 antagonist),[6] macrolide antibiotics,[7] triple reuptake inhibitors[8] and kinase inhibitors,[9] amongst others (Figure 1).[10] Recently, there has been a renewed interest in the synthesis of azetidine-3-amines, by modifying ring-opening conditions of azabicyclobutane (ABB) with amine nucleophiles in a strain-release reaction.[11,12] Other approaches to azetidine-3-amines are based upon reductive amination.[8,13] Yet another synthesis of azetidine-3-amines, which has been used sporadically, is the direct displacement of an azetidine electrophile with an amine nucleophile.[14] This approach is more frequently encountered in the patent literature,[15] with a direct displacement of 1-benzhydrylazetidin-3-yl methanesulfonate **1** being the most frequently encountered azetidine electrophile.[14,15] The resulting 1-benzhydrylazetidinazetidine-3-amine products can be easily deprotected to the parent azetidine.[16,17] In other cases, it is also possible to transform the 1-benzyhydryl protecting group directly to a carbamoyl chloride.[18] One of us has prior experience of the amine displacement reaction with compound **1**,[19] and also has an interest in the azetidine group within drug discovery.[20] In this paper we undertake a detailed study of the reaction of compound **1** with amines to afford azetidine-3-amine products. We found a simple "mix-and-heat" approach could be used at any stage of a synthesis, including the late-stage functionalization of approved drugs and other substances with pharmacological activity. In addition, this simple displacement approach seems to compare favorably to related strain-release methodology, particularly in-terms of experimental setup, yield and scope of substrate that can be employed.

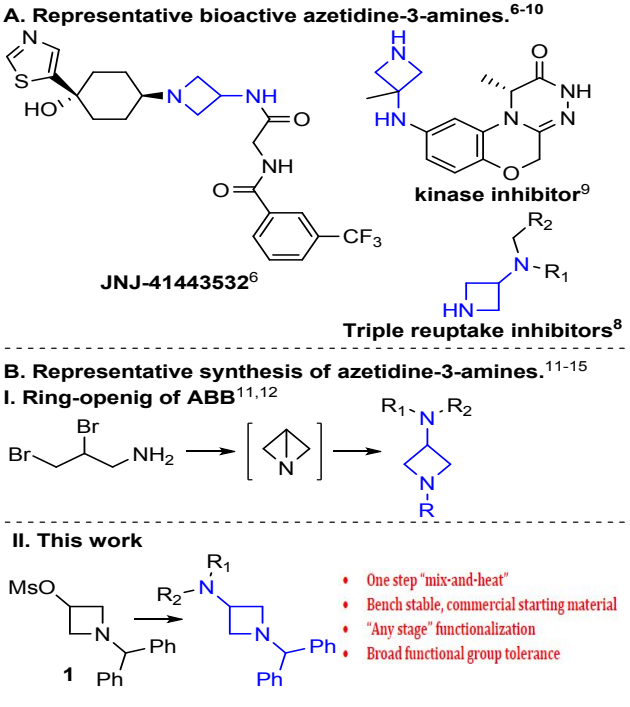


Figure 1. (A) Representative bioactive azetidine-3-amines. (B) Representative synthesis of azetidine-3-amines.

We initiated our studies by examining the displacement of 1-benzhydrylazetidin-3-yl methanesulfonate **1** with simple amines. Compound **1** is a well-known,[21] commercially available intermediate, although for our studies, we prepared the material in a single batch starting from 1-benzyhydryl-3-azetidinol. In our hands, **1** was stable at ambient (room) temperature for at least nine (9) months. Compound **1** was reacted with 1 equiv piperidine and 1 equiv of Hunig's base (^{i}Pr$_2$NEt) in acetonitrile (MeCN) at 80 °C to give a 33% yield of the desired displacement product **2**. A large improvement to the yield could be realized by using 2 equiv of piperidine and omitting Hunig's base altogether. This afforded the desired product **2** in 72% isolated yield after purification by column chromatography (Scheme 1). The yield compares favorably to that reported when using strain-release methodology (56% yield, reported in brackets in Scheme 1).[11] Except for examples giving compounds **3** and **4**, we employed 2 equiv of amine for all subsequent reactions. As can be seen in Scheme 1, simple cyclic amines afforded fine isolated yields of products **2** to **8**. A more complex spirocyclic amine gave a lower 21% yield of product **9**. Significantly, we could also utilize anilines in the displacement reaction, something that was not reported for the recently-reported strain-release technique.[11,22] Thus, compound **10** was produced in 34% isolated yield when 1,2,3,4-tetrahydroquinoline was used as a nucleophile. We also used acyclic secondary amines in the displacement. Again, good yields were obtained. For example, *N*-methylbenzylamine gave **11** in 69% isolated yield (*cf*. 46% using strain-release). Even the use of diisopropylamine, a very hindered secondary amine most commonly encountered in non-nucleophilic bases (*e.g.* diisopropylamide, LDA), but also a substructure of the herbicides diallate and triallate, afforded a 49% isolated yield of product **12**. Late-stage azetidinylation of pharmacologically-active drug substances could also be undertaken in high-to-moderate yield. Thus, the 5-HT$_{2C}$ agonist, 1-(3-trifluoromethylphenyl) piperazine (TFMPP), and the selective serotonin reuptake inhibitors, fluoxetine and sertraline, gave products **13** (87%), **14** (79%) and **15** (59% *cf*. 45% using strain-release).

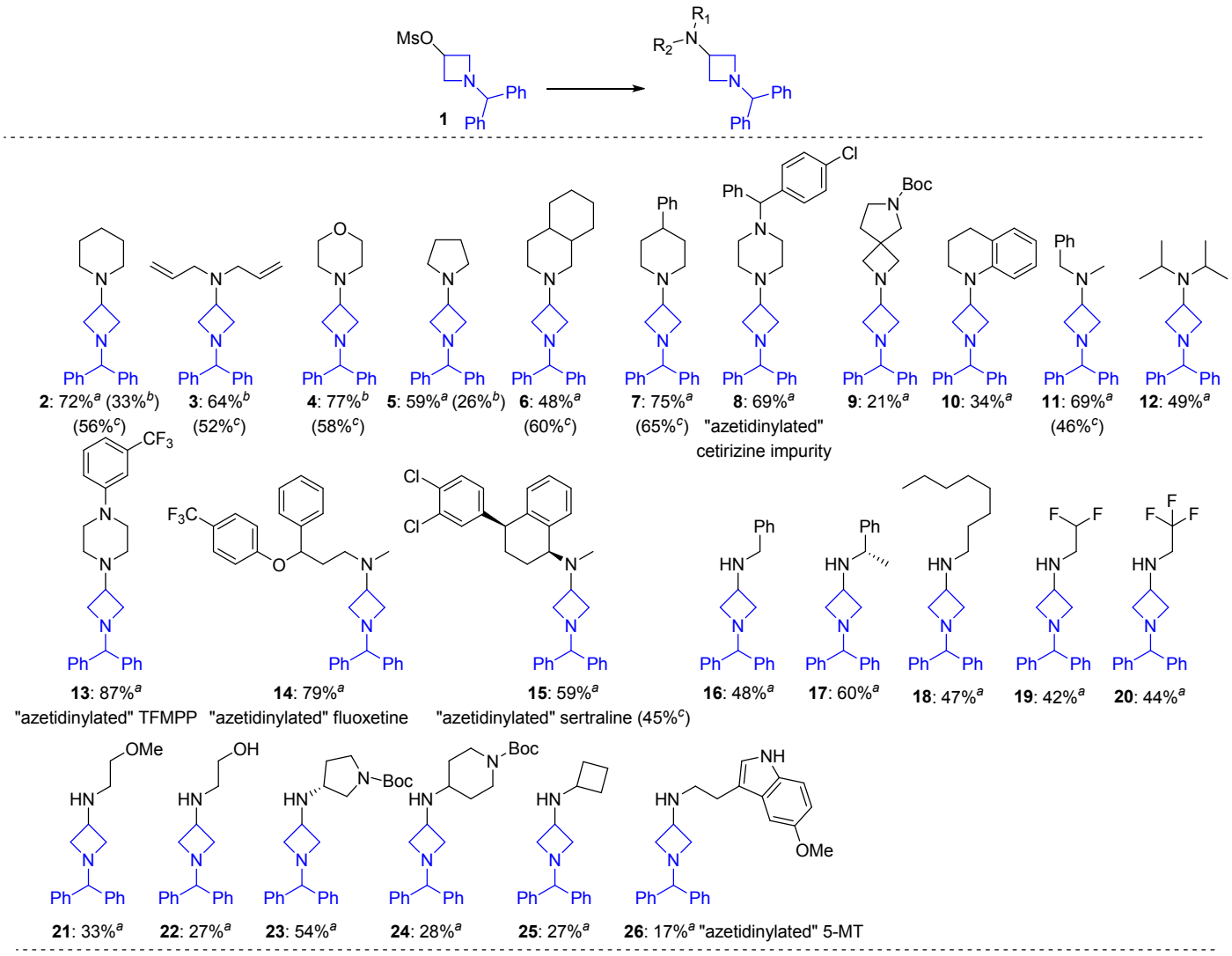
Next, we sought to extend the methodology to the use of primary amines, since these could not be utilized in analogous strain-release methodology.[23] The use of simple chain amines such as benzylamine, alpha-methylbenzylamine, or octylamine gave good yields of products **16** (48%), **17** (60%) and **18** (47%). We then extended the methodology to the use of functionalized amines. Significantly, the reaction tolerated common functionality found in medicinal chemistry, such as difluoromethyl (**19**; 42%), trifluoromethyl (**20**; 44%), methoxy (**21**; 33%) and even a free hydroxyl group (**22**; 27%). The use of primary amines appended to a cyclic system were also successful giving products **23** (54%), **24** (28%) and **25** (27%) in moderate-to-low yield. In the case of products **23** and **24** a Boc-protected amine was unaffected in the reaction. Finally, we undertook a late-stage azetidinylation of 5-methoxytryptamine (5-MT; aka, mexamine), which contains an unprotected indole nitrogen, to give **26** in 17% isolated yield.

The overall versatility and success of this straight-forward displacement reaction deserves some comment, especially in relation to complementary methodology such as the recently-reported strain-release approach to azetidinylation.[11] The direct displacement described in this paper uses mild and very simple reaction conditions (mixing of two substances in reagent grade MeCN and heating to 80 °C), with equipment that does not have to be flame-dried prior to use. In comparison, azetidinylation using strain-release methodology requires the use of PhLi, added dropwise and slowly,[23] at -78 °C to form azabicyclobutane (ABB), in preparation for a "spring-loaded" ring-opening. In a separate flame-dried flask, an amine nucleophile also needs to be activated with a turbo-Grignard (*i*PrMgCl.LiCl), with evolution of gas.[23] After 2h, the "turbo-amide" is added dropwise to the pre-formed solution of ABB at -78 °C. It should be noted that the reaction is sensitive to the time used to form ABB, with 2 h reaction time being optimal for maximal yield,[23] so timings have to be quite well-controlled. The strain-release reaction seems to occur uneventfully overnight from -78 °C to room temperature. However, quenching to give a Boc-azetidine product occurs at 0 °C and requires the slow addition of di-*tert*-butyl dicarbonate (Boc$_2$O) in dry THF.[23] Unfortunately, carbamates and free alcohols are incompatible with the strain-release technique,[23] whereas free alcohols, carbamates and an unprotected heterocyclic nitrogen (*e.g.* indole of 5-MT) are all tolerated in the direct displacement reaction described in this paper. We did not evaluate the use of amines containing a ketone group, sulfide, or amide functionality, which are also incompatible with strain-release methodology.[23] Future work can ascertain whether such functionality is unaffected with the direct displacement reaction. The isolated yields obtained with a direct displacement appear to be slightly higher than an analogous reaction using strain-release methodology (*e.g.* isolated yields for **2**, **3**, **4**, **7**, **11** and **15**; the yield for compound **6** was slightly lower than the strain-release approach). The higher yields may be reflective of the multi-operational nature of experiments using strain-release methodology, as compared to a simple "mix-and-heat" approach for displacement methodology. Perhaps, the biggest difference between the displacement and strain-release techniques, concerns the participation of primary amines. The use of primary amines in the displacement reaction was successful, giving moderate-to-low yields of product, whereas primary amines are incompatible with the strain-release method.[23] Considering the above, we conclude that the direct displacement may offer advantages over strain-release methodology, especially in-terms of operational simplicity, scope of substrate and isolated yield. The facile nature of the displacement reaction, even for late-stage functionalization of unprotected starting materials, may appeal to those working in an industrial environment, where complexity (time) considerations are important.

In summary, this paper describes a simple one-step synthesis of azetidine-3-amines from a bench-stable commercial starting material. Both secondary and primary amines can successfully participate in the reaction, and the procedure tolerates common functionality such as ether, halide, difluoromethyl, trifluoromethyl, carbamate,

unprotected heterocyle and even free hydroxyl groups. The methodology can be used for the late-stage functionalization of substances with pharmacological activity and compares favorably to complementary techniques such as strain-release azetidinylation. It is anticipated that the methodology described in this paper will find application in medicinal, biochemical, materials, polymer and agrochemical disciplines, where the azetidine group has shown to be a very useful and desirable motif.

Scheme 1. Scope of azetidinylation upon reaction of 1-benzhydrylazetidin-3-yl methanesulfonate 1 with amines.



[a]Isolated yield from reaction of **1** with 2.0 equiv R_1R_2NH,or R_1NH_2, MeCN, 80 °C; [b]Isolated yield from reaction of **1** with 1.0 equiv of R_1R_2NH, 1.0 equiv of $^iPr_2NEt$, MeCN, 80 °C; [c]Yield of an analogous reaction using "strain-release" methodology to give an *N*-Boc azetidine

EXPERIMENTAL SECTION

General. All reagents were purchased from commercial sources and used without further purification. All solvents were reagent, or HPLC grade. Heating was undertaken using a heating block. EtOAc refers to ethyl acetate, MeOH refers to methanol, and Et_3N refers to triethylamine. Analytical TLC was performed on silica gel 60 F254 plates and visualized by UV if possible, or by staining with $KMnO_4$ dip, or phosphomolybdic acid in ethanol dip. Flash chromatography was carried out using an automated system with pre-packed silica columns.. Yields refer to isolated yields of pure compounds. ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer at ambient temperature. Chemical shifts are reported in parts per million (ppm) relative to deuterated solvent, or a TMS internal standard. Multiplicities are reported as follows: s = singlet; d = doublet, t = triplet; dd = doublet of doublets;

dt = doublet of triplets; m = multiplet; br = broad; f = fine. High-resolution mass spectrometry was obtained on a Waters Xevo G2-XS QToF.

*1-benzhydrylazetidin-3-yl methanesulfonate (**1**)*.[21,24] MsCl (3.9 mL, 50 mmol) was added dropwise to a solution of 1-benzyhydryl-3-azetidinol (10 g, 42 mmol) and Et_3N (8.2 mL, 59 mmol) in DCM (125 mL) at 0 °C (ice-water bath), and the mixture was stirred at 0 °C (ice-water bath), for 1 h. Saturated aqueous $NaHCO_3$ was added. The phases were separated, and the aqueous layer was extracted with DCM (3 x 125 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the product as a solid (14.2 g, 100%). LC-MS: 317.88 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.38 (m, 4H), 7.30-7.25 (m, 4H), 7.22-7.17 (m, 2H), 5.10 (m, 1H), 4.41 (s, 1H), 3.67-3.62 (m, 2H), 3.23-3.18 (m, 2H), 2.98 (s, 3H).

General procedure for the synthesis of azetidine-3-amines using 1 equiv of amine. A solution of **1** (630 mg, 2 mmol) in MeCN (9.5 mL) was treated with $^iPr_2NEt$ (0.35 mL, 2 mmol) and amine (2 mmol). The reaction mixture was sealed and stirred at 80 °C overnight. The mixture was concentrated, and the residue was dissolved in 1:1 EtOAc / hexanes (30 mL). The organic layer was washed with 1:1 H_2O / brine (30 mL), brine (30 mL), dried over $MgSO_4$, filtered, concentrated and purified by silica gel column chromatography to give the product.

*N,N-diallyl-1-benzhydrylazetidin-3-amine (**3**)*. Purified using 0:1 to 3:7 EtOAc / hexanes as eluent to give a solid (408 mg, 64% yield). LC-MS: *m/z* = 319.34 $[M+H]^+$; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.42-7.38 (m, 4H), 7.29-7.24 (m, 4H), 7.20-7.15 (m, 2H), 5.88-5.74 (m, 2H), 5.15-5.08 (m, 4H), 4.38 (s, 1H), 3.43-3.27 (m, 3H), 3.01 (d, *J* = 6.4 Hz, 4H), 2.88-2.83 (m, 2H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.3, 134.7, 128.5, 127.6, 127.2, 118.2, 78.5, 59.8, 54.3, 52.9; HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{27}N_2$ *m/z* 319.2174; found, 319.2171.

*4-(1-Benzhydrylazetidin-3-yl)morpholine (**4**)*. Purified using 0:1 to 1:1 EtOAc / hexanes as eluent to give an oil (239 mg, 77% yield). LC-MS: *m/z* = 309.29 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42-7.40 (m, 4H), 7.28-7.24 (m, 4H), 7.20-7.15 (m, 2H), 4.51 (s, 1H), 3.42-3.39 (m, 2H), 3.17 (m, 3H), 2.63 (m, 4H), 1.88 (m, 4H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.2, 128.5, 127.6, 127.2, 78.3, 66.7, 58.0, 55.0, 50.3; HRMS (ESI): $[M+H]^+$ calcd for $C_{20}H_{25}N_2O$ *m/z* 309.1967; found 309.1968.

General procedure for the synthesis of azetidine-3-amines using 2 equiv of amine. A solution of **1** (317 mg, 1 mmol) in MeCN (5 mL) was treated with amine (2 mmol). The reaction mixture was sealed and stirred at 80 °C overnight. The mixture was concentrated, and the residue was dissolved in 1:1 EtOAc / hexanes (30 mL). The organic layer was washed with 1:1 H_2O / brine (30 mL), brine (30 mL), dried over $MgSO_4$, filtered, concentrated and purified by silica gel column chromatography.

*1-(1-Benzhydrylazetidin-3-yl)piperidine (**2**)*. Purified using 0:1 to 1:4 EtOAc / hexanes as eluent to give a solid (221 mg, 72% yield). LC-MS: *m/z* = 307.36 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.38 (m, 4H), 7.27-7.22 (m, 4H), 7.17-7.13 (m, 2H), 4.42 (s, 1H), 3.39 (m, 2H), 2.88 (m, 3H), 2.17 (m, 4H), 1.55-1.52 (m, 4H), 1.41-1.40 (m, 2H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.3, 128.4, 127.6, 127.1, 78.1, 58.7, 55.4, 51.1, 25.4, 24.2; HRMS (ESI): $[M+H]^+$ calcd for $C_{21}H_{27}N_2$ *m/z* 307.2174; found 307.2177.

*1-(1-Benzhydrylazetidin-3-yl)pyrrolidine (**5**)*. Purified using 0:1 to 5:95 MeOH / DCM as eluent to give an oil (174 mg, 59% yield). LC-MS: *m/z* = 293.27 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43-7.41 (m, 4H), 7.34-7.24 (m, 4H), 7.20-7.15 (m, 2H), 4.43 (s, 1H), 3.42-3.37 (m, 2H), 3.11-2.95 (m, 3H), 2.40-2.38 (m, 4H), 1.83-1.73 (m, 4H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.3, 128.5, 127.6, 127.1, 78.3, 59.0, 53.9, 51.5, 23.5; HRMS (ESI): $[M+H]^+$ calcd for $C_{20}H_{25}N_2$ *m/z* 293.2018; found 293.2023.

*2-(1-benzhydrylazetidin-3-yl)decahydroisoquinoline (**6**)*. After stirring at 80 °C overnight, the mixture was placed in a -20 °C freezer for 16 h, giving crystals. These were collected by filtration and rinsed with cold MeCN to give a crude solid, which was recrystallized from MeCN (x 2) to give a solid (173 mg, 48% yield). LC-MS: *m/z* = 361.14 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42-7.40 (m, 4H), 7.29-7.24 (m, 4H), 7.21-7.15 (m, 2H), 4.43 (s, 1H), 3.44-3.38 (m, 2H), 2.88-2.84 (m, 3H), 2.22-2.05 (m, 4H), 1.67-1.34 (m, 10H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.4, 128.5, 127.6, 127.1, 78.3, 59.0, 58.8, 55.3, 33.9; HRMS (ESI): $[M+H]^+$ calcd for $C_{25}H_{33}N_2$ *m/z* 361.2644; found 361.2643.

*1-(1-benzhydrylazetidin-3-yl)-4-phenylpiperidine (**7**)*. After stirring at 80 °C overnight, the mixture was placed in a -20 °C freezer for 16 h, giving crystals. The solid was purified by silica gel column chromatography using 0:1 to 1:4 EtOAc / hexanes to give a solid (288 mg, 75% yield). LC-MS: *m/z* = 383.14 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.43 (m, 4H), 7.34-7.17 (m, 11H), 4.48 (s, 1H), 3.49-3.45 (m, 2H), 3.05-2.85 (m, 5H), 2.55-2.44 (m, 1H), 1.93-1.71 (m, 6H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 146.3, 142.3, 128.5, 127.6, 127.2, 126.9, 126.3, 78.1, 58.8, 55.3, 51.1, 42.6, 32.9; HRMS (ESI): $[M+H]^+$ calcd for $C_{27}H_{31}N_2$ *m/z* 383.2487; found 383.2475.

*1-(1-Benzhydrylazetidin-3-yl)-4-((4-chlorophenyl)(phenyl)methyl)piperazine (**8**)*. Purified using 5:95 to 45:55 EtOAc / hexanes as eluent to give a solid (355 mg, 69% yield). LC-MS: *m/z* = 508.07 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.31 (m, 8H), 7.28-7.15 (m, 11H), 4.40 (s, 1H), 4.21 (s, 1H), 3.41-3.37 (m, 2H), 3.01-2.95 (m, 1H), 2.89-2.85 (m, 2H), 2.32 (m, 8H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.2, 142.1, 141.3, 132.6, 129.3, 128.7, 128.69, 128.5, 127.9, 127.6, 127.3, 127.2, 78.2, 75.4, 58.3, 55.0, 51.3, 50.2; HRMS (ESI): $[M+H]^+$ calcd for $C_{33}H_{35}ClN_3$ *m/z* 508.2519; found 508.2522.

*Tert-butyl 2-(1-benzhydrylazetidin-3-yl)-2,6-diazaspiro[3.4]octane-6-carboxylate (**9**)*. Purified using 1:1 to 1:0 EtOAc / hexanes as eluent to give an oil (94 mg, 21% yield). LC-MS: *m/z* = 434.10 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.38 (m, 4H), 7.28-7.24 (m, 4H), 7.19-7.15 (m, 2H), 4.35 (s, 1H), 3.41 (s, 2H), 3.37-3.22 (m, 5H), 3.16-3.12 (m, 4H), 2.93-2.89 (m, 2H), 2.06-1.95 (m, 2H), 1.45 (s, 9H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 154.6, 142.3, 128.5, 127.5, 127.2, 79.4, 78.2, 60.4, 60.2, 56.7, 55.9, 55.2, 54.6, 44.9, 44.4, 40.6, 39.7, 36.3, 35.4, 28.6; HRMS (ESI): $[M+H]^+$ calcd for $C_{27}H_{36}N_3O_2$ *m/z* 434.2808; found 434.2793.

*1-(1-benzhydrylazetidin-3-yl)-1,2,3,4-tetrahydroquinoline (**10**)*. After stirring at 80 °C overnight, the mixture was placed in a 0-5 °C fridge for 16 h, giving crystals. The solid was purified by silica gel column chromatography using 0:1 to 1:9 EtOAc +1% Et_3N / hexanes +1% Et_3N as eluent to give a solid (121 mg, 34% yield). LC-MS: *m/z* = 355.05 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.42 (m, 4H), 7.31-7.26 (m, 4H), 7.22-7.16 (m, 2H), 7.00-6.95 (m, 2H), 6.64 (t, *J* = 7.3 Hz, 1H), 6.34 (d, *J* = 8.2 Hz, 1H), 4.36 (s, 1H), 4.05 (m, 1H), 3.67 (t, *J* = 7.3 Hz, 2H), 3.03 (m, 4H), 2.74 (t, *J* = 6.4 Hz, 2H), 1.94 (m, 2H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 145.9, 142.1, 128.9, 128.6, 127.6, 127.3, 126.9, 124.7, 117.4, 112.0, 78.6, 59.7, 49.7, 44.5, 27.7, 22.9; HRMS (ESI): $[M+H]^+$ calcd for $C_{25}H_{27}N_2$ *m/z* 355.2174; found 355.2176.

*1-Benzhydryl-N-benzyl-N-methylazetidin-3-amine (**11**)*. After stirring at 80 °C overnight, the mixture was placed in a -20 °C freezer for 16 h, giving crystals. These were collected by filtration and carefully rinsed with a small amount of cold MeCN to give a solid (239 mg, 69% yield). LC-MS: *m/z* = 343.02 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.41 (m, 4H), 7.33-7.16 (m, 11H), 4.42 (s, 1H), 3.45 (t, *J* = 6.7 Hz, 2H), 3.33 (s, 2H), 3.11 (m, 1H), 2.91 (t, *J* = 7.0 Hz, 2H), 1.97 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.3, 137.7, 129.5, 128.5, 128.3, 127.6, 127.24, 127.21, 78.5, 59.2, 59.0, 54.7, 38.3; HRMS (ESI): $[M+H]^+$ calcd for $C_{24}H_{27}N_2$ *m/z* 343.2174; found 343.2172.

*1-Benzhydryl-N,N-diisopropylazetidin-3-amine (**12**)*. After stirring at 80 °C overnight, the mixture was placed in a 0-5 °C fridge for 16 h, giving crystals, which were washed with cold MeCN to give a solid (158 mg, 49% yield). LC-MS: *m/z* = 323.09 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43-7.40 (m, 4H), 7.29-7.24 (m, 4H), 7.21-7.16 (m, 2H), 4.37 (s, 1H), 3.71 (m, 1H), 3.42-3.37 (m, 2H), 2.94 (m, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 0.96 (d, *J* = 6.5 Hz, 12H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.4, 128.5, 127.6, 127.1, 78.4, 61.3, 47.0, 46.5, 21.3; HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{31}N_2$ *m/z* 323.2487; found 323.2488.

*1-(1-Benzhydrylazetidin-3-yl)-4-(3-(trifluoromethyl)phenyl)piperazine (**13**)*. After stirring at 80 °C overnight, the mixture was cooled and treated with EtOAc (10 mL), giving a solid, which was collected by filtration. The filtrate was concentrated, and the residue was purified by silica gel column chromatography using 5:95 to 3:7 EtOAc / hexanes as eluent to give a solid (397 mg, 87% yield). LC-MS: *m/z* = 452.10 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.41 (m, 4H), 7.36-7.26 (m, 5H), 7.22-7.17 (m, 2H), 7.08-7.02 (m, 3H), 4.44 (s, 1H), 3.45 (m, 2H), 3.25-3.22 (t, *J* = 5.0 Hz, 4H), 3.04-2.95 (m, 3H), 2.47-2.44 (t, *J* = 5.0 Hz, 4H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 151.4, 142.1, 131.5 (q, *J* = 32 Hz, 1C), 129.7, 128.6, 127.6, 127.3, 124.4 (q, *J* = 272 Hz, 1C), 118.8, 116.0 (q, *J* = 3 Hz, 1C), 112.3 (q, *J* = 4 Hz, 1C), 78.3, 58.2, 54.8, 49.8, 48.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ -62.7; HRMS (ESI): $[M+H]^+$ calcd for $C_{27}H_{29}F_3N_3$ *m/z* 452.2314; found 452.2302.

*1-Benzhydryl-N-methyl-N-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)azetidin-3-amine (**14**)*. Purified using 5:95 to 3:7 EtOAc / hexanes as eluent to give an oil (423 mg, 79% yield). LC-MS: *m/z* = 531.10 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.16 (m, 17H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.29-5.25 (m, 1H), 4.22 (s, 1H), 3.38-3.36 (m, 2H), 3.03-2.99 (m, 1H), 2.79-2.71 (m, 2H), 2.47-2.38 (m, 1H), 2.32-2.24 (m, 1H), 2.15-2.03 (m, 4H), 1.99-1.90 (m, 1H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 160.8, 142.2, 142.2, 141.2, 128.9, 128.5, 128.5, 127.9, 127.6, 127.2, 126.9 (q, *J* = 4 Hz, 2C), 125.9, 124.5 (q, *J* = 271 Hz, 1C), 122.8 (q, *J* = 33 Hz, 1C), 115.9, 78.6, 78.3, 59.22, 59.16, 55.2, 50.7, 38.5, 36.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ -61.5; HRMS (ESI): $[M+H]^+$ calcd for $C_{33}H_{34}F_3N_2O$ *m/z* 531.2623; found 531.2625.

*1-Benzhydryl-N-((1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-N-methylazetidin-3-amine (**15**)*. Purified using 0:1 to 1:4 EtOAc / hexanes as eluent to give a solid (313 mg, 59% yield). LC-MS: *m/z* = 527.17 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.6 H, 1H), 7.45-7.42 (m, 4H), 7.31-7.25 (m, 6H), 7.22-7.11 (m, 3H), 7.07 (s, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 6.4 Hz, 1H), 4.38 (s, 1H), 4.12-4.08 (m, 1H), 3.76 (t, *J* = 7.9 Hz, 1H), 3.57-3.51 (m, 1H), 3.43-3.41 (m, 2H), 2.89-2.88 (m, 2H), 2.12-1.90 (m, 5H), 1.59-1.52 (m, 2H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 147.5, 142.3, 139.0, 138.2, 132.2, 130.8, 130.3, 130.0, 130.0, 128.5, 128.3, 127.6, 127.2, 127.1, 126.9, 78.7, 59.6, 59.0, 58.3, 51.6, 43.6, 32.5, 30.2, 15.8; HRMS (ESI): $[M+H]^+$ calcd for $C_{33}H_{33}Cl_2N_2$ *m/z* 527.2021; found 527.2021.

*1-Benzhydryl-N-benzylazetidin-3-amine (**16**)*. Purified using 1:9 to 1:0 EtOAc +1% Et_3N / hexanes +1% Et_3N as eluent to give a solid (159 mg, 48% yield). LC-MS: *m/z* = 329.21 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43-7.17 (m, 15H), 4.34 (s, 1H), 3.71 (s, 2H), 3.57-3.49 (m, 3H), 2.78-2.75 (m, 2H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.3, 140.0, 128.6, 128.5, 128.3, 127.5, 127.2, 78.6, 61.9, 51.7, 48.4; HRMS (ESI): [M+H]+ calcd for $C_{23}H_{25}N_2$ *m/z* 329.2018; found 329.2015.

*(S)-1-benzhydryl-N-(1-phenylethyl)azetidin-3-amine (**17**)*. Purified using 0:1 to 3:7 EtOAc / hexanes as eluent to give an oil (208 mg, 60% yield). LC-MS: *m/z* = 343.06 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.36 (m, 4H), 7.33-7.15 (m, 11H), 4.29 (s, 1H), 3.73 (q, *J* = 6.4 Hz, 1H), 3.50-3.31 (m, 3H), 2.72 (t, *J* = 6.4 Hz, 1H), 2.62 (t, *J* = 6.4 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 145.2, 142.3, 128.6, 128.5, 127.5, 127.5, 127.2, 127.1, 127.1, 126.7, 78.6, 62.3, 62.3, 56.5, 47.0, 24.0; HRMS (ESI): $[M+H]^+$ calcd for $C_{24}H_{27}N_2$ *m/z* 343.2174; found 343.2173.

*1-Benzhydryl-N-octylazetidin-3-amine (**18**)*. After stirring at 80 °C overnight, the mixture was placed in a 0-5 °C fridge for 16 h, giving crystals. The filtrate was purified by silica gel column chromatography using 1:4 to 3:7 EtOAc / hexanes as eluent to give a solid (165 mg, 47% yield). LC-MS: *m/z* = 351.14 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42-7.38 (m, 4H), 7.29-7.24 (m, 4H), 7.21-7.15 (m, 2H), 4.32 (s, 1H), 3.54-3.42 (m, 3H), 2.74-2.70 (m, 2H), 2.50 (t, *J* = 7.3 Hz, 2H), 1.45-1.41 (m, 3H), 1.32-1.20 (m, 10H), 0.88 (t, *J* = 6.7 Hz, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.3, 128.5, 127.6, 127.2, 78.7, 62.1, 48.9, 47.7, 31.9, 30.4, 29.6, 29.4, 27.5, 22.8, 14.2; HRMS (ESI): $[M+H]^+$ calcd for $C_{24}H_{35}N_2$ *m/z* 351.2800; found 351.2794.

*1-Benzhydryl-N-(2,2-difluoroethyl)azetidin-3-amine (**19**)*. After stirring at 80 °C overnight, the mixture was placed in a 0-5 °C fridge for 16 h, giving crystals. The filtrate was purified by silica gel column chromatography using 0:1 to 1:9 MeOH/ DCM as eluent to give an oil (128 mg, 42% yield). LC-MS: *m/z* = 302.99 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.37 (m, 4H), 7.29-7.25 (m, 4H), 7.21-7.16

(m, 2H), 5.98-5.57 (m, 1H), 4.31 (s, 1H), 3.51-3.46 (m, 3H), 2.97-2.85 (m, 2H), 2.77-2.70 (m, 2H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.1, 128.6, 127.5, 127.2, 115.7 (t, *J* = 241 Hz, 1C), 78.5, 61.7, 49.7 (t, *J* = 24 Hz, 1C), 49.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ -122.1 (dt, *J* = 56, 15 Hz, 2F); HRMS (ESI): $[M+H]^+$ calcd for $C_{18}H_{21}F_2N_2$ *m/z* 303.1673; found 303.1673.

*1-Benzhydryl-N-(2,2,2-trifluoroethyl)azetidin-3-amine (**20**)*. Purified using 0:1 to 5:95 MeOH / DCM as eluent to afford a crude solid, which was purified again using 0:1 to 3:7 EtOAc +1% Et_3N / hexanes +1% Et_3N as eluent to give a solid (141 mg, 44% yield); LC-MS: *m/z* = 320.95 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.38 (m, 4H), 7.30-7.25 (m, 4H), 7.21-7.16 (m, 2H), 4.30 (s, 1H), 3.52-3.51 (m, 3H), 3.14 (q, *J* = 9.4 Hz, 2H), 2.74 (m, 2H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.1, 128.6, 127.5, 127.3, 125.3 (q, *J* = 279 Hz, 1C), 78.5, 62.0, 49.1 (q, *J* = 31 Hz, 1C), 49.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ -72.2 (t, *J* = 9 Hz, 3F); HRMS (ESI): $[M+H]^+$ calcd for $C_{18}H_{20}F_3N_2$ *m/z* 321.1579; found 321.1578.

*1-Benzhydryl-N-(2-methoxyethyl)azetidin-3-amine (**21**)*. Purified using 0:1 to 5:95 MeOH / DCM +1% Et_3N as eluent to give an oil, which after cooling at -20 °C solidified to a solid (99 mg, 33% yield). LC-MS: *m/z* = 297.04 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.37 (m, 4H), 7.29-7.23 (m, 4H), 7.20-7.15 (m, 2H), 4.32 (s, 1H), 3.54-3.48 (m, 3H), 3.44 (t, *J* = 5.3 Hz, 2H), 3.34 (s, 3H), 2.76-2.68 (m, 4H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.3, 128.5, 127.5, 127.1, 78.6, 72.1, 61.9, 58.9, 48.8, 47.0; HRMS (ESI): $[M+H]^+$ calcd for $C_{19}H_{25}N_2O$ *m/z* 297.1967; found 297.1972.

*2-((1-Benzhydrylazetidin-3-yl)amino)ethanol (**22**)*. Purified using 1:9 to 1:0 EtOAc +1% Et_3N / hexanes +1% Et_3N as eluent to give a solid (78 mg, 27% yield); LC-MS: *m/z* = 282.96 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.38 (m, 4H), 7.30-7.24 (m, 4H), 7.21-7.18 (m, 2H), 4.33 (s, 1H), 3.62 (t, *J* = 5.0 Hz, 2H), 3.50-3.49 (m, 3H), 2.80-2.79 (m, 2H), 2.70 (t, *J* = 5.0 Hz, 2H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.0, 128.5, 127.5, 127.2, 78.5, 61.3, 60.9, 48.8, 48.4; HRMS (ESI): $[M+H]^+$ calcd for $C_{18}H_{23}N_2O$ *m/z* 283.1811; found 283.1811.

*(R)-tert-butyl 3-((1-benzhydrylazetidin-3-yl)amino)pyrrolidine-1-carboxylate (**23**)*. After stirring at 80 °C overnight, the mixture was placed in a -20 °C freezer for 16 h, giving crystals. The filtrate was purified by silica gel column chromatography using 0:1 to 9:1 EtOAc / hexanes as eluent to give a solid (221 mg, 54% yield). LC-MS: *m/z* = 408.10 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.38 (m, 4H), 7.31-7.24 (m, 4H), 7.20-7.15 (m, 2H), 4.30 (s, 1H), 3.53-3.34 (m, 5H), 3.31-3.25 (m, 2H), 3.02-2.96 (m, 1H), 2.69 (m, 2H), 2.02-1.93 (m, 1H), 1.66-1.55 (m, 2H), 1.43-1.42 (m, 9H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 154.6, 142.1, 128.6, 127.5, 127.2, 79.3, 78.6, 62.7, 62.4, 56.5, 55.7, 52.0, 51.7, 47.8, 44.4, 44.0, 32.4, 31.7, 28.6; HRMS (ESI): $[M+H]^+$ calcd for $C_{25}H_{34}N_3O_2$ *m/z* 408.2651; found 408.2638.

*Tert-butyl 4-((1-benzhydrylazetidin-3-yl)amino)piperidine-1-carboxylate (**24**)*. After stirring at 80 °C overnight, the mixture was placed in a 0-5 °C fridge for 16 h, giving crystals. The filtrate was concentrated, and the residue was purified by silica gel column chromatography using 1:9 to 1:0 EtOAc / hexanes as eluent to give a solid (122 mg, 28% yield). LC-MS: *m/z* = 422.13 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.37 (m, 4H), 7.29-7.24 (m, 4H), 7.20-7.15 (m, 2H), 4.30 (s, 1H), 3.98 (m, 2H), 3.57-3.51 (m, 3H), 2.75-2.66 (m, 4H), 2.62-2.52 (m, 1H), 1.73-1.70 (m, 2H), 1.43 (s, 9H), 1.28-1.14 (m, 2H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 154.8, 142.2, 128.5, 127.5, 127.2, 79.5, 78.6, 63.0, 54.1, 46.8, 33.0, 28.5; HRMS (ESI): $[M+H]^+$ calcd for $C_{26}H_{36}N_3O_2$ *m/z* 422.2808; found 422.2791.

*1-Benzhydryl-N-cyclobutylazetidin-3-amine (**25**)*. After stirring at 80 °C overnight, the mixture was placed in a 0-5 °C fridge for 16 h, giving crystals. The filtrate was concentrated, and the residue was purified by silica gel column chromatography using 0:1 to 1:9 MeOH / DCM, then again using 1:4 to 1:1 EtOAc +1% Et_3N / hexanes +1% Et_3N as eluent to give an oil (80 mg, 27% yield). LC-MS: *m/z* = 293.00 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.39 (m, 4H), 7.29-7.24 (m, 4H), 7.20-7.16 (m, 2H), 4.30 (s, 1H), 3.52-3.42 (m, 3H), 3.23-3.16 (m, 1H), 2.75-2.67 (m, 2H), 2.16-2.07 (m, 2H), 1.74-1.54 (m, 5H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.3, 128.5, 127.5, 127.2, 78.7, 62.5, 52.9, 47.1, 31.7, 15.1; HRMS (ESI): $[M+H]^+$ calcd for $C_{20}H_{25}N_2$ *m/z* 293.2018; found 293.2018.

*1-Benzhydryl-N-(2-(5-methoxy-1H-indol-3-yl)ethyl)azetidin-3-amine (**26**)*. After stirring at 80 °C overnight, the mixture was placed in a -20 °C freezer for 16 h, giving crystals. The filtrate was concentrated, and the residue was purified by silica gel column chromatography using 5:95 to 1:0 EtOAc +1% Et_3N/ hexanes +1% Et_3N as eluent, then 1:99 to 5:95 MeOH / DCM as eluent to give a solid (71 mg, 17% yield). LC-MS: *m/z* = 412.10 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.39-7.36 (m, 4H), 7.32-7.23 (m, 5H), 7.19-7.15 (m, 2H), 7.00 (dd, *J* = 8.8, 2.4 Hz, 2H), 6.86 (dd, *J* = 8.8, 2.3 Hz, 1H), 4.30 (s, 1H), 3.83 (s, 3H), 3.56-3.47 (m, 3H), 2.94-2.83 (m, 4H), 2.74-2.71 (m, 2H), 1.75 (s, 1H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$): δ 154.0, 142.2, 131.6, 128.5, 127.8, 127.5, 127.2, 122.9, 113.5, 112.4, 112.0, 100.7, 78.5, 61.7, 56.0, 48.8, 47.6, 26.1; HRMS (ESI): $[M+H]^+$ calcd for $C_{27}H_{30}N_3O$ *m/z* 412.2389; found 412.2379.

ASSOCIATED CONTENT

Supporting Information. FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds 2-26. Graphical representation of a 1 mmol scale reaction. Analytical data (^1H, ^{13}C, ^{19}F NMR, HPLC) for all new compounds (PDF). The Supporting Information is available free of charge on the Internet at http://pubs.acs.org.

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing conflicts.

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