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Skeletal Diversification via Heteroatom Linkage Control: Preparation of Bicyclic and Spirocyclic Scaffolds from N-Substituted Homopropargyl Alcohols

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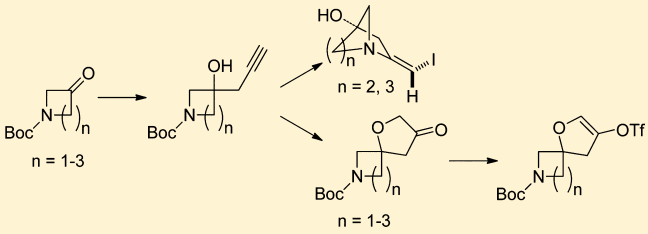
Supporting Information

ABSTRACT: The discovery and application of a new branching pathway synthesis strategy that rapidly produces skeletally diverse scaffolds is described. Two different scaffold types, one a bicyclic iodo-vinylidene tertiary amine/tertiary alcohol and the other, a spirocyclic 3-furanone, are each obtained using a two-step sequence featuring a common first step. Both scaffold types lead to intermediates that can be orthogonally diversified using the same final components. One of the scaffold types was obtained in sufficiently high yield that it was immediately used to produce a 97-compound library.



INTRODUCTION

In recent years, high-throughput organic synthesis has gained an increasingly prominent role for lead generation in the service of drug discovery. The accelerated creation of innovative compound collections with high degrees of structural diversity is now seen as a necessary component of the larger biomedical research landscape. Coupled with increasingly efficient high throughput screening and assay models that seek to be more relevant to biological reality the impetus for developing versatile methods to create chemical diversity continues to increase. Skeletal diversification represents one of the most versatile concepts in high throughput organic synthesis.[1] One manifestation of this concept is the derivation of profoundly different molecular scaffolds from a common precursor by employing different reagents, sometimes referred to as the "branching pathway" strategy.[2]

Our laboratory's mission involves the development of innovative chemistry with the goal of using it to produce unique compound libraries by high-throughput synthesis. Deriving more than one scaffold from the same substrate is clearly advantageous in terms of both compound diversity and productivity. This report deals with the preparation of two distinct families of scaffolds so derived.

RESULTS AND DISCUSSION

Our interest in exploring chemical space by creating structural diversity led us to survey the literature to find under-represented compound types. One such substructure search centered on diversifiable spirocycles. Spirocyclic scaffolds offer an opportunity to create chemical diversity by combining structural complexity with rigidity. Substituents can be moved around the scaffold in discrete, predictable increments thus enabling the controlled exploration of the surrounding space.[3] These and other characteristics of spirocycles have been exploited in recent reports.[4] Surveying the number of highly saturated spirocycles derived from diversifiable ketones like 4-piperidone with the corresponding ones derived from 3-piperidone revealed that the latter structural class contained comparatively few members. We therefore initiated studies to discover a methodology that affords rapid access to spirocyclic scaffolds from 3-piperidone.

As part of a larger spirocycle synthesis effort, we started by noting the precedents of Larock and others who used electrophilic iodoetherification for the efficient preparation of benzofurans from *o*-alkyne-substituted anisoles.[5] We sought to use iodoetherification to obtain spirocycles bearing a dihydrofuran that is not fused to an aromatic ring. We imagined that treatment of homopropargyl tertiary alcohol **3** with iodine monochloride (ICl) would affect electrophilic cyclization to afford the previously unreported spirocyclic *β*-iodo-enol ether **4** with possible concomitant loss of the Boc group (Scheme 1). Loss of the protecting group would facilitate isolation of **4** as it could be extracted into 0.1 N HCl and lyophilized to afford its salt. This substrate would be ready for orthogonal diversification via the unprotected amine and the vinyl iodide.

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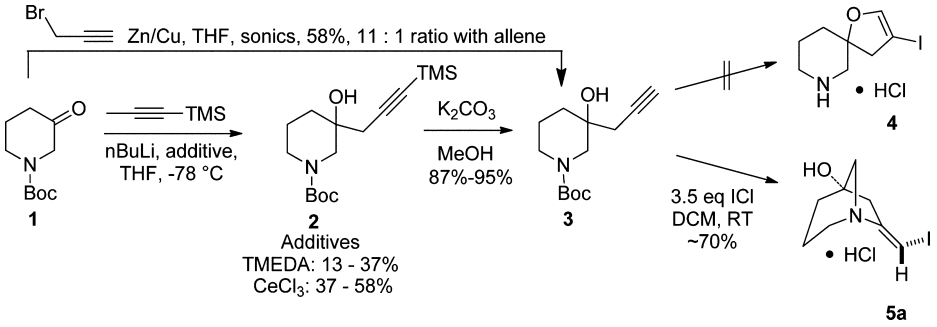
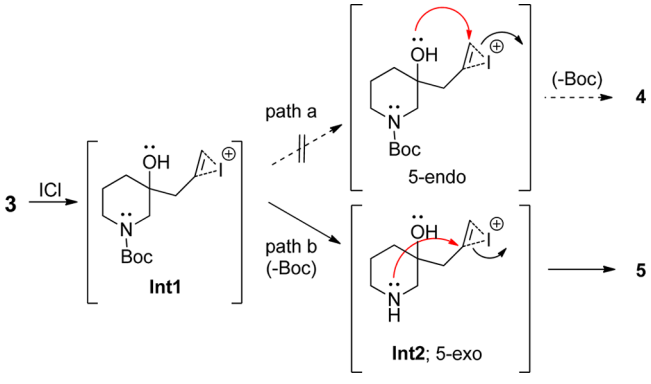
Scheme 1. Synthesis of Bicyclo[3.2.1]-*β*-iodo Enamines from Homopropargyl Tertiary Alcohols Derived from *N*-Boc-3-piperidone



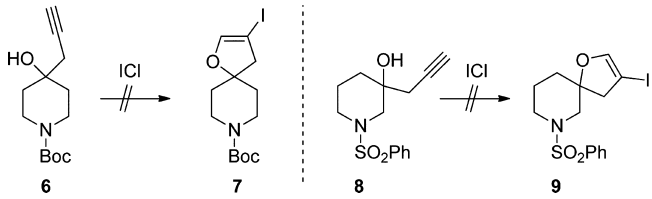
Synthesis of compound **3** was envisioned as a two-step sequence starting from *N*-Boc-3-piperidone **1**. Addition of lithiated 1-TMS-1-propyne to **1** using TMEDA as additive afforded **2** in poor to modest yields that diminished on larger scale.[6] Modification of the organolithium with $CeCl_3$ gave **2** in a range of yields that was higher.[7] Basic hydrolysis of **2** afforded the cyclization precursor **3** in generally excellent yields and purity. A more direct method using **1**, propargyl bromide, and Zn/Cu couple with sonication afforded **3** accompanied by a minor amount of its inseparable allene isomer (not shown).[8] The allene byproduct did not introduce any apparent complications in the subsequent steps. Treatment of **3** with ICl afforded, not the anticipated **4**, but the bicyclic [3.2.1] *β*-iodo-enamine HCl salt **5a** after extraction and lyophilization. *β*-Iodo-enamine HCl salt **5a** was accompanied by a minor amount (~10 A% by HPLC) of a diiodo species which could be separated by pHPLC. Compound **5a** was elaborated to the more complex derivative **10*{10,1}*** as described below (Scheme 4). X-ray crystallography of **10*{10,1}*** confirmed the depicted bicyclic core structure of its precursor **5a**. The presence of the diiodo species did not affect subsequent steps. Enamine **5a** was stable and could be handled using standard techniques presumably because the bridgehead position of the nitrogen precludes interaction between it and the olefin.

The conversion of **3** to **5a** is envisioned as proceeding via an unsaturated iodonium intermediate **Int1** (Scheme 2). Instead of the iodonium being attacked by the free tertiary alcohol via a 5-endo cyclization (path a) and leading to **4** it is captured by the nitrogen via a 5-exo mechanism (path b, **Int2**).[9] This latter mode of cyclization is precedented for unsubstituted terminal alkynes although not in the presence of a well-positioned free hydroxyl.[10] In addition, *β*-iodoenamines contained within a bicyclic structure have been previously reported.[11] We were curious about whether removing the possibility of participation by the piperidine nitrogen would lead to the desired cyclization. To test this hypothesis, we prepared tertiary alcohols **6** and **8** from 1-Boc-4-piperidone and 1-PhSO$_2$-3-piperidone, respectively (Scheme 3). In the case of **6** we predicted that nitrogen would be unable to participate due to distance and/or unfavorable conformation. In the case of **8**, we expected the protecting group to survive the reaction conditions and prevent nitrogen unmasking. This would demonstrate that the loss of the Boc group is required for iodoamination to occur. In the event, treatment of **6** and **8** with ICl gave only complex mixtures with no detectable formation of **7** or **9**.

Scheme 2. Alternative Mechanisms for Cyclization of the Iodonium Derived from 3



Scheme 3. Attempted Iodoetherification of Homopropargyl Tertiary Alcohols



We then performed the originally desired spirocyclization using the precedent of Zhang (Scheme 4).[12] Thus, exposure of **3** to catalytic Au(PPh$_3$)(NTf$_2$) in the presence of a substituted pyridine *N*-oxide as co-oxidant under acidic conditions gave the spirocyclic 3-furanone **11**.[13] Moving further, we prepared a pair of potential final library compounds featuring the same peripheral substituents. Salt **5a** was neutralized, and the free amine **5b** was treated with *p*-Cl-benzoyl chloride/TEA in the presence of DMAP. This method afforded the intermediate ester (not shown) which was subjected to Suzuki coupling to give the orthogonally diversified derivative **10*{10,1}***, confirmed by X-ray crystallography (see the Supporting Information, Figure S1). Moving in the other direction, spirocycle **11** was converted to its enol triflate **12**.[14] Enol triflate **12** was subjected to Suzuki coupling followed by deprotection and amide coupling with *p*-Cl-benzoyl chloride/TEA/DMAP. This alternate sequence gave the skeletally divergent derivative **13**.

We deferred further optimizing the spirocycle route and instead elected to first use the [3.2.1] scaffold **5** for library production. Compounds like **10**, having both the bridgehead ester and an exoarylenamine, are previously unreported and so we used this serendipitous discovery to prepare a novel compound library. A 14 × 10 diversity component library of

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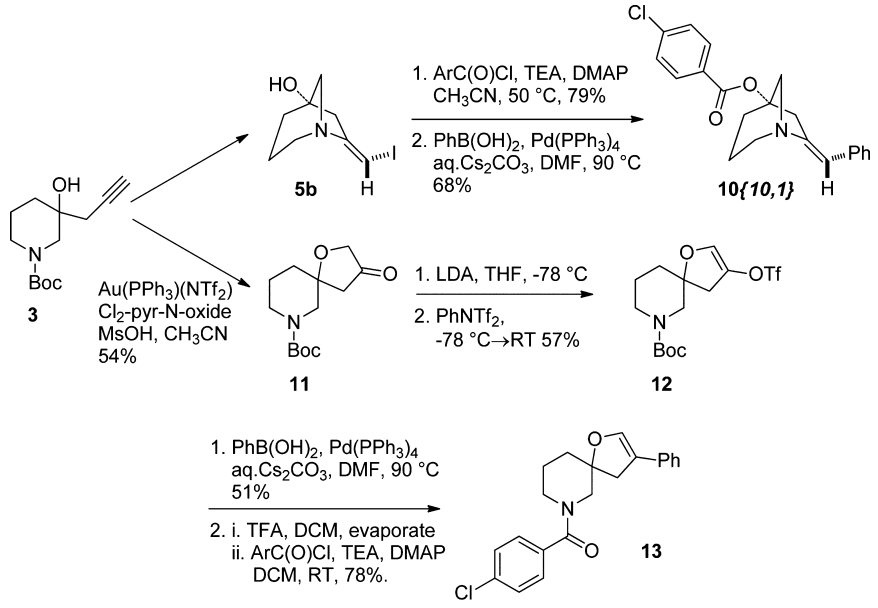
Scheme 4. Skeletal Diversification Including Introduction of Peripheral Substituents



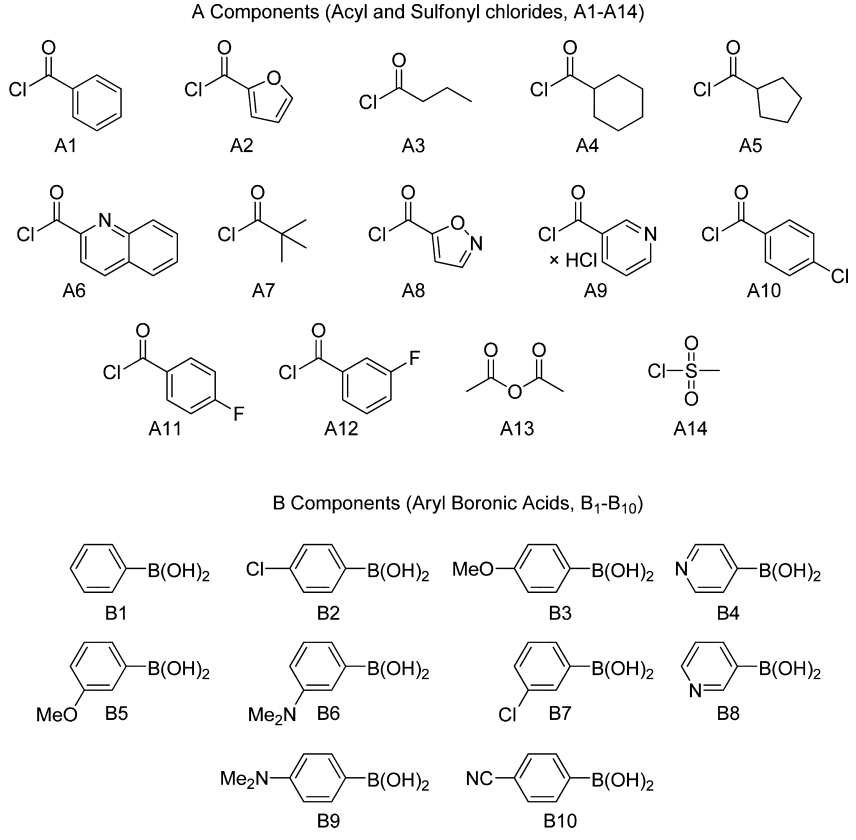


Figure 1. Components for the proposed 140-member library from scaffold **5**.

140 members was designed (Figure 1). As a matter of routine, component subsets were used to validate the methodology and the synthesis platform. Components A6 and B9 were poor performers and thus removed. The remaining 117 compounds were prepared using miniblocks.

Some of the compounds were obtained by an alternative sequence as shown in Scheme 5. Treatment of free amine **5b** with Boc_2/TEA in the presence of DMAP gave the O-protected vinyl iodide **14**. At this stage, any diiodo species present could be readily removed by silica gel chromatography. Suzuki coupling, deprotection, and acylation gave the library compounds.

Table 1 shows the isolated yields of the compounds. Of the 117 compounds proposed, 97 were obtained in our target purities of ≥90%.

Finally, we explored the limits of the both the iodoamination and spirocyclization. For this purpose, we employed homopropargyl alcohols **16a** and **16b** (Scheme 6). Both of these

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Scheme 5. Alternate Sequence for Library Compounds

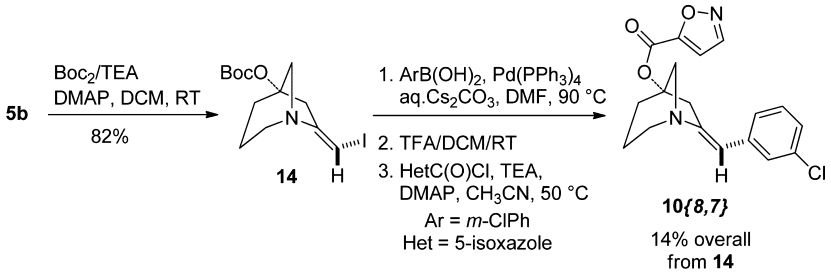
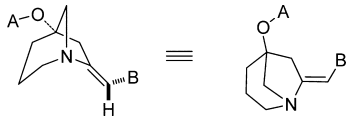


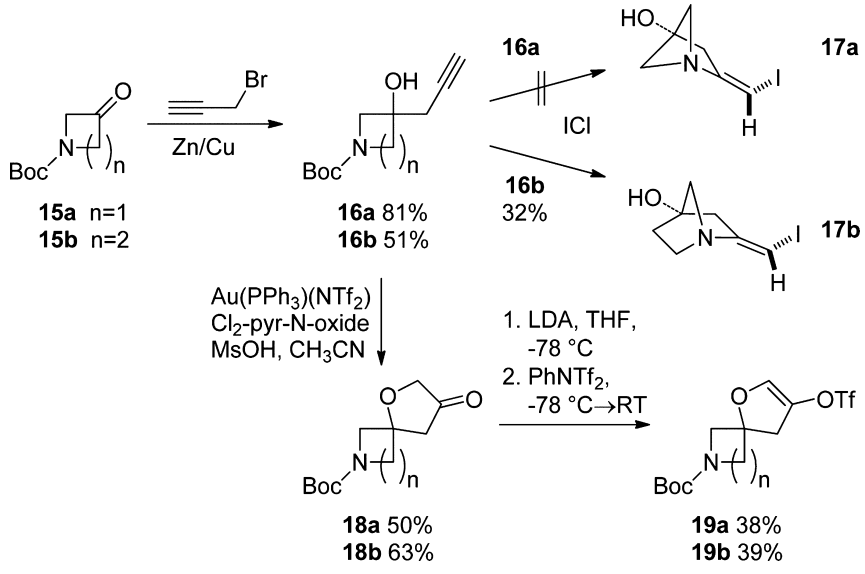
Table 1. Yields of Library Compounds 10 after Reversed-Phase Preparative Mass Directed Fractionation (MDF)



		boronic acids								
		B1	B2	B3	B4	B5	B6[a]	B7	B8	B10
acid chlorides	A1	30	36	34	19	13	14	31	28	24
	A2	37	35	33	25	32	18	39	38	26
	A3	11	13	13		6	10	14		14
	A4	41	32	40	32	41	23	41	46	43
	A5	34	27	35	29	35	15	34	41	42
	A7	19	16		13	17	9	23	14	19
	A8		10		7			14		
	A9	4		1	1	4			4	
	A10	35	34	26	31	28	23	30	20	32
	A11	28	21	23	19	32	15	23	21	26
	A12	31	28	22	34	27	10	37	31	20
	A13	32	43	42	31	36	26	47	42	50
	A14	30	14							

[a]Compounds incorporating B6 were reprocessed by normal-phase preparative TLC after MDF to attain 90% purity by HPLC.

Scheme 6. Skeletal Diversification of Lower Homologues of 3



substrates were obtained from the precursor ketones **15a** and **15b** by the action of propargyl bromide and Zn/Cu couple. Treatment of **16a** with ICl afforded no detectable **17a**. In contrast, **16b** gave the corresponding bicyclic [2.2.1] amine **17b** in reduced yield. We surmise that the diminished yields obtained in these systems largely arise from increased ring strain.

Using catalytic $Au(PPh_3)(NTf_2)$, both **16a** and **16b** were successfully employed in spirocyclization. Thus both substrates afforded spiro-3-furanones **18a** and **18b**.[13] These products were

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advanced to the enol triflates **19a** and **19b** by LDA-promoted enolization and trapping on oxygen.

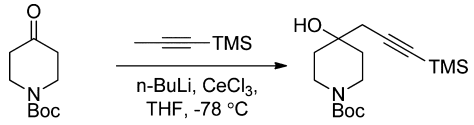
CONCLUSION

We have developed a divergent synthetic strategy that, from *N*-Boc-3-piperidone, rapidly affords two profoundly different scaffolds, exemplified by compounds **5** and **12**, each of which was shown to be orthogonally diversifiable using the same diversity components. The previously unreported scaffold **5** was formed via an unanticipated iodoamination reaction. Compound **5** was used to produce an innovative 97 member library. Work continues to further optimize the preparation and use of spirocyclic scaffold **12** with the goal of using it for production of other libraries of compounds.

EXPERIMENTAL SECTION

General Methods. All air- and moisture-sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gastight syringes, cannula, and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH_2Cl_2 was purified by passage through a purification system employing activated Al_2O_3. Flash column chromatography was performed with SiO_2 from Sorbent Technology (30930M-25, silica gel 60A, 40−63 μm) or by using an automated chromatography instrument with an appropriately sized column. Thin-layer chromatography was performed on silica gel 60F254 plates (EM-5717). Deuterated solvents were purchased from commercial sources. ^{1}H and ^{13}C NMR spectra were recorded on instruments operating at 400 or 500 MHz and 100 or 125 MHz respectively. High-resolution mass spectrometry (HRMS) spectra were obtained on a spectrometer operating on ESI. Library synthesis was carried out on a mini-block platform in 17 × 100 mm tubes with parallel evaporation. Automated preparative reversed-phase HPLC purification was performed using a mass-directed fractionation system with UV-DAD detection and a quadrapole spectrometer using a C18 column (19 × 150 mm, 5 μm, w/19 × 10 mm guard column). Samples were diluted in DMSO and purified utilizing an elution of water (modified to pH 9.8 through addition of NH_4OH) and CH_3CN, with a gradient increasing by 20% in CH_3CN over 4 min at a flow rate of 20 mL/min. The starting and ending points of the corresponding preparative CH_3CN/water gradient, triggering thresholds, and UV wavelength were selected on the basis of the HPLC analysis of each crude sample. Analytical analysis of each sample after purification employed an HPLC system with UV and mass detection using an ESI-TOF mass spectrometer. The analytical method utilized a Waters Aquity BEH C18 column (2.1 × 50 mm, 1.7 μm) eluting with a linear gradient of 95% water (modified to pH 9.8 through addition of NH_4OH) to 100% CH_3CN at 0.6 mL/min flow rate where purity was determined using UV peak area at 214 nm. Melting points were determined using an automated apparatus with digital imaging capability. Alkyllithiums were titrated using *N*-benzylbenzamide.[15]

***tert*-Butyl 3-Hydroxy-3-(3-(trimethylsilyl)prop-2-yn-1-yl)-piperidine-1-carboxylate (2).** Using a procedure similar to that of Imamoto,[7] a three-necked, 5 L flask equipped with an overhead stirrer and nitrogen inlet was purged with nitrogen for 40 min. Anhydrous cerium(III) chloride (100.0g, 405.6 mmol) pellets were added to the flask and suspended in anhydrous THF (810 mL). The mixture was stirred for 20 h at 120 rpm under nitrogen resulting in a thick white suspension. A second, 3 L, three-necked flask equipped with an overhead stirrer, nitrogen inlet, and addition funnel was purged with nitrogen for 40 min. 1-(Trimethylsilyl)-1-propyne (45.52 g, 405.6 mmol) was added to this flask and dissolved in THF (810 mL). This solution was cooled to −78 °C, and *n*-BuLi (181.0 mL of a 2.24 M solution in hexanes, 405.6 mmol) was added via the addition funnel over 15 m. This solution was stirred for 1 h. The initial $CeCl_3$ mixture was cooled to −78 °C, and the solution from the second three-necked flask was added to it via cannula over 1.5 h. The new combined mixture was stirred for 1 h, and a solution of *N*-Boc-3-piperidone **1** (40.40 g, 202.8 mmol) in THF (290 mL) was added via addition funnel over 25 m. The final reaction mixture was stirred for 2 h, and then satd aq NH_4Cl (1 L) was added. The cold bath was removed and the reaction mixture warmed to rt overnight. The mixture was diluted with 1 M HCl (500 mL) and MTBE (800 mL). The mixture was drawn in portions from the flask by suction through a polypropylene tube and filtered through Celite to remove flocculent salts. The two-phase filtrate was returned to the reaction flask and partitioned by siphoning the aqueous via a suction tube. The combined organics were dried over $MgSO_4$, filtered, and concentrated under vacuum using a continuous-feed rotovapor. The crude material (59.00 g) was chromatographed on silica gel (15 to 30% EtOAc in hexanes) to afford the product as a white waxy solid (24.30 g, 38%). A yield of 58% was obtained using 1.350 g (6.760 mmol) of *N*-Boc-3-piperidone (**1**): ^{1}H NMR (DMSO-d_6, 400 MHz 85 °C) δ 4.15 (s, 1H), 3.46 (m, 1H), 3.38 (d, *J* = 13.1 Hz, 1H), 3.16 (d, *J* = 13.1 Hz, 1H), 3.05 (m, 1H), 2.37 (d, *J* = 17.1 Hz, 1H), 2.32 (d, *J* = 17.1 Hz, 1H), 1.69 (m, 2H), 1.55 (m, 1H), 1.42 (s, 9H), 1.37 (m, 1H), 0.14 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz, 85 °C) δ 153.9, 103.9, 86.1, 77.9, 67.7, 52.2, 42.8, 34.3, 30.3, 27.7, 20.6, −0.39; IR 3426, 2954, 2176, 1669 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for (M + H−Boc)$^+$ $(C_{11}H_{22}NOSi)^+$ 212.1471, found 212.1492.



20

***tert*-Butyl 4-Hydroxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)-piperidine-1-carboxylate (20).** Following the procedure for the synthesis of compound **2**, *N*-Boc-4-piperidone (1.000 g, 5.020 mmol) was reacted with cerium trichloride (3.710 g, 15.06 mmol), *n*-butyllithium (6.350 mL of a 2.37 M solution in hexanes, 15.06 mmol), and 1-(trimethylsilyl)-1-propyne (1.700 g, 15.15 mmol) to afford the product **20** (0.966 g, 62%) as a white granular solid: mp = 98.8−102.4 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, 85 °C) δ 4.28 (s, 1H), 3.78−3.58 (m, 2H), 3.09 (td, *J* = 13.2, 2.9 Hz, 2H), 2.42−2.32 (m, 2H), 1.62 (td, *J* = 12.7, 4.7 Hz, 2H), 1.52−1.37 (m, 11H), 0.14 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz, 85 °C) δ 153.6, 104.3, 86.0, 77.9, 67.6, 34.9, 33.7, 27.7, 27.6, −0.4; IR 3428, 2960, 2175, 1664 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for (M + M + H)$^+$ $(C_{32}H_{59}N_2O_6Si_2)^+$ 623.3912, found 623.3908.

***tert*-Butyl 3-Hydroxy-3-(prop-2-yn-1-yl)piperidine-1-carboxylate (3).** To a 3-L, three-necked flask equipped with an overhead stirrer were added *tert*-butyl 3-hydroxy-3-(3-(trimethylsilyl)prop-2-yn-1-yl)piperidine-1-carboxylate (**2**) (24.30 g, 78.01 mmol), methanol (780 mL), and K_2CO_3 (12.90 g). The mixture was stirred at rt for 2.5 h, drawn from the flask via suction, concentrated under vacuum, redissolved in MTBE (300 mL), and adsorbed onto silica gel (80 g) by evaporation. The dried silica gel was put over Celite in a fritted funnel and eluted with MTBE (1500 mL). The filtrate was concentrated under vacuum to give the product (16.70 g, 89%) as a granular white solid which was used without further purification: mp = 63.6−67.0 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, 85 °C) δ 4.22 (s, 1H), 3.39 (m, 1H), 3.32 (d, *J* = 13.1 Hz, 1H), 3.22 (d, *J* = 13.1 Hz, 1H), 3.13 (m, 1H), 2.62 (t, *J* = 2.5 Hz, 1H), 2.30 (m, 2H), 1.78−1.62 (m, 2H), 1.55 (m, 1H), 1.41 (s, 9H), 1.36 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz, 85 °C) δ 153.9, 80.6, 78.0, 72.0, 67.6, 52.2, 42.8, 34.2, 28.8, 27.7, 20.7; IR 3427, 2934, 2119, 1670 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for (M + NH_4)$^+$ $(C_{13}H_{25}N_2O_3)^+$ 257.1865, found 257.1877.

***tert*-Butyl 4-Hydroxy-4-(prop-2-yn-1-yl)piperidine-1-carboxylate (6).** Using the above K_2CO_3 hydrolysis procedure for compound **3**, *tert*-butyl 4-hydroxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)piperidine-1-carboxylate (**20**) (0.913 g, 2.93 mmol) was reacted with K_2CO_3 (0.486g, 3.520 mmol). The crude material was chromatographed on silica gel (5 to 30% EtOAc in hexanes) to afford the product **6** (0.530 g, 76%) as a powdered white solid: mp = 41.9−45.1 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, 85 °C) δ 4.29 (s, 1H), 3.67 (dt, *J* = 13.0, 3.6 Hz, 2H), 3.11 (m, 2H), 2.62 (t, *J* = 2.5 Hz, 1H), 2.32 (d, *J* = 2.5 Hz, 2H), 1.59 (m, 2H), 1.50 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz, 85 °C) δ 153.7, 80.9, 78.0, 72.0, 67.4, 35.0, 32.2, 27.7; IR

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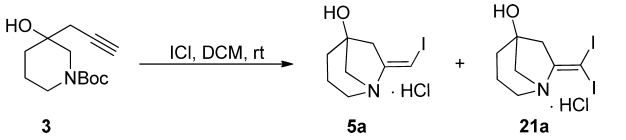
3418, 2934, 2119, 1662 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{13}H_{22}NO_3)^+$ 240.1600, found 240.1587.

***tert*-Butyl 3-Hydroxy-3-(prop-2-yn-1-yl)piperidine-1-carboxylate (3).** Compound **3** was prepared directly from *N*-Boc-3-piperidone (**1**). (CAUTION: This reaction can be accompanied by a vigorous exotherm and should be properly cooled and vented.) Using a procedure modified from that of Wang,[8] to a solution of *N*-Boc-3-piperidone (10.13 g, 50.80 mmol) and propargyl bromide (8.49 mL of an 80 wt % solution in toluene, 76.00 mmol) in THF (10.2 mL) at 0 °C was added Zn/Cu couple (4.550 g, 55.90 mmol). The mixture was sonicated for 10 min and then diluted with sat' aq NH_4Cl and ethyl acetate. (On a scale >1 g of ketone filtration of the mixture through paper at this point facilitates isolation.) The layers were separated, and the aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was chromatographed on silica gel (5−30% EtOAc in hexanes) to afford the product (7.100 g, 58%) as a white solid. The product contains an inseparable but small amount of the allene isomer (~10:1, alkyne/allene as observed by ^1H NMR). This causes no perceivable issues in subsequent reactions. Spectral data is reported above.

1-(Phenylsulfonyl)-3-(prop-2-yn-1-yl)piperidin-3-ol (8). Using the above Zn/Cu/propargyl bromide procedure for compound **3**, *N*-benzensulfonyl-3-piperidone (1.024 g, 4.280 mmol) was reacted with propargyl bromide (0.715 mL, 6.420 mmol) and Zn/Cu couple (0.383 g, 4.710 mmol) under sonication for 50 min to afford the product **8** (0.610 g, 51%) as a viscous, orange oil. The product contains an inseparable, but small amount of the allene isomer (~8.3:1, alkyne/allene as observed by ^1H NMR): ^1H NMR (DMSO-d_6, 400 MHz, 85 °C) δ 7.75 (m, 2H), 7.66 (m, 3H), 3.04 (m, 1H), 2.95 (d, J = 11.6 Hz, 1H), 2.87 (d, J = 11.5 Hz, 1H), 2.80 (m, 1H), 2.63 (t, J = 2.6 Hz, 1H), 2.41 (dd, J = 16.9, 2.6 Hz, 1H), 2.34 (dd, J = 16.9, 2.6 Hz, 1H), 1.79 (m, 1H), 1.61 (m, 1H), 1.56−1.43 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz, 85 °C) δ 136.4, 132.3, 128.7, 126.7, 80.2, 72.3, 67.4, 54.0, 45.3, 33.4, 28.8, 20.5; IR 3497, 2940, 2115, 1446, 1334 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(C_{14}H_{18}NO_3S)^+$ $(M + H)^+$, 280.1007 found 280.1021.

***tert*-Butyl 3-Hydroxy-3-(prop-2-yn-1-yl)azetidine-1-carboxylate (16a).** Using the above Zn/Cu/propargyl bromide procedure for compound **3**, *N*-Boc-3-azetidinone (1.673 g, 9.77 mmol) was reacted with propargyl bromide (1.633 mL, 14.66 mmol) and Zn/Cu couple (0.875 g, 10.75 mmol) under sonication for 30 min to afford the product **16a** (1.674 g, 81%) as a white solid. The product contains an inseparable but small amount of the allene isomer (~8.3:1, alkyne/allene as observed by ^1H NMR. This causes no perceivable issues in subsequent reactions): mp = 83.8−90.0 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.92 (d, J = 9.6 Hz, 2H), 3.87 (d, J = 9.6 Hz, 2H), 3.53 (s, 1H), 2.62 (d, J = 2.6 Hz, 2H), 2.06 (t, J = 2.6 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4, 79.9, 79.0, 71.1, 68.9, 61.0, 29.4, 28.3; IR 3384, 2977, 1669 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(C_{11}H_{18}NO_3)^+$ $(M + H)^+$ 212.1287, found 212.1287.

***tert*-Butyl 3-Hydroxy-3-(prop-2-yn-1-yl)pyrrolidine-1-carboxylate (16b).** Using the above Zn/Cu/propargyl bromide procedure for compound **3**, *N*-Boc-3-pyrrolidinone (**15b**) (4.062 g, 21.93 mmol) was reacted with propargyl bromide (3.660 mL, 32.90 mmol) and Zn/Cu couple (1.964 g, 24.12 mmol) under sonication for 45 min to afford the product **16b** (2.535 g, 51%) as a white solid. The product contains an inseparable, but small amount of the allene isomer (~8:1, alkyne/allene as observed by ^1H NMR. This causes no perceivable issues in subsequent reactions): mp = 75.3−79.8 °C; ^1H NMR (DMSO-d_6, 500 MHz, 90 °C) δ 4.54 (s, 1H), 3.45−3.36 (m, 2H), 3.32 (m, 1H), 3.27 (d, J = 11.2 Hz, 1H), 2.54 (s, 1H), 2.49 (m, 2H), 1.96 (m, 1H), 1.84 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz, 90 °C) δ 153.2, 80.6, 77.5, 76.2, 70.9, 56.1, 43.9, 35.9, 28.0, 27.6; IR 3379, 2978, 2109, 1658 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{12}H_{20}NO_3)^+$ 226.1443, found 226.1452.



3 **5a** **21a**

***(E)*-7-(Iodomethylene)-1-azabicyclo[3.2.1]octan-5-ol (HCl Salt) (5a).** To a 5 L, three-necked flask equipped with an overhead stirrer were added *tert*-butyl 3-hydroxy-3-(prop-2-yn-1-yl)piperidine-1-carboxylate (**3**) (16.70 g, 69.78 mmol) and dichloromethane (DCM, 700 mL). To this was added a solution of iodine monochloride (34.00 g, 209.3 mmol) in DCM (700 mL) over 30 min via addition funnel. The reaction mixture was stirred for 22 h, quenched with satd aq Na_2SO_3 (1000 mL), and made basic (pH paper checking) with satd aq $NaHCO_3$ (1000 mL). The aqueous layer was removed via siphon and the organic layer washed in this fashion with deionized water (300 mL × 2). Approximately 250 mL of deionized water was added to the organic layer and the mixture acidified to pH 2 with 1 M HCl as determined by pH meter. The layers were separated, and the aqueous layer was lyophilized to afford the amine salt **5a** (15.80 g, ~75%) as a yellow powder which was used without further purification. In all cases, and as determined by LC−MS, the product contains the diiodo species **21a** as a 10 area % impurity: mp (HCl salt **5a** as mixture with **21a**) = 175.7−177.4 °C dec. The two products could be separated via reversed-phase HPLC as their free bases. The stationary phase was a Waters Sunfire C18-OBD 5 μM 30 × 150 mm column. The mobile phase was an CH_3CN/water (0.02% TFA) gradient starting at 0% CH_3CN and ending at 100% CH_3CN over 13 min. Both products were obtained as viscous brown oils. Remaining data provided for free base **5b**: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.96 (t, J = 2.5 Hz, 1H), 3.55 (d, J = 10.2 Hz, 1H), 3.35 (dd, J = 12.4, 4.8 Hz, 1H), 3.25−3.11 (m, 2H), 2.66 (d, J = 18.0 Hz, 1H), 2.61 (dd, J = 18.0, 2.7 Hz, 1H), 2.08−1.85 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.1, 75.0, 73.2, 62.8, 55.6, 43.3, 35.2, 18.1; HRMS (ESI-TOF) m/z calcd for $(C_8H_{13}INO)^+$ $(M + H)^+$ 266.0042, found 266.0054. Data provided for free base **21b**: ^1H NMR (DMSO-d_6, 500 MHz) δ 3.20 (dd, J = 12.8, 5.7 Hz, 1H), 2.99 (d, J = 10.0 Hz, 1H), 2.85 (d, J = 9.5 Hz, 1H), 2.70 (m, 1H), 2.44−2.35 (m, 2H), 2.19 (d, J = 16.8 Hz, 1H), 1.69−1.54 (m, 3H), 1.47 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 155.7, 75.9, 65.2, 52.0, 48.8, 35.9, 20.5, 10.1; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_8H_{12}I_2NO)^+$ 391.9008, found 391.9029.

***(E)*-2-(Iodomethylene)-1-azabicyclo[2.2.1]heptan-4-ol (HCl Salt) (17b).** Following the above procedure for compound **5a**, *tert*-butyl 3-hydroxy-3-(prop-2-yn-1-yl)pyrrolidine-1-carboxylate (**16b**) (0.530 g, 2.353 mmol) was reacted with iodine monochloride (1.146 g, 7.060 mmol) to afford **17b** (0.217 g, 32%) as a yellow powder: mp = 155.9−159.1 °C dec; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.63 (s, 1H), 6.97 (s, 1H), 6.41 (s, 1H), 3.72 (td, J = 11.1, 6.2 Hz, 1H), 3.34−3.22 (m, 2H), 3.19 (d, J = 8.1 Hz, 1H), 2.48 (m, 2H), 1.99 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 146.7, 78.4, 74.6, 60.5, 54.4, 42.5, 31.3; IR 3247, 2824, 2503, 1356 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_7H_{11}INO)^+$ 251.9885, found 251.9906.

***(E)*-7-(Iodomethylene)-1-azabicyclo[3.2.1]octan-5-ol (5b) by Neutralization of 5a.** A solution of salt **5a** (5.008 g, 16.61 mmol) in water (150 mL) was made basic to pH > 7 (pH paper) using satd aq sodium bicarbonate. The solution was extracted into ethyl acetate (×6), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to give the free base as a viscous, brown oil (3.900 g, 89%).

***(E)*-7-Benzylidene-1-azabicyclo[3.2.1]octan-5-yl 4-Chlorobenzoate (10*{10,1}*).** To a solution of (*E*)-7-(iodomethylene)-1-azabicyclo[3.2.1]octan-5-ol (**5b**) (0.064 mg, 0.242 mmol), triethylamine (0.200 mL, 1.45 mmol), and dimethylaminopyridine (0.015 g, 0.121 mmol) in CH_3CN (1.00 mL) was added 4-chlorobenzoyl chloride (0.16 mL, 1.21 mmol). The reaction mixture was heated to 50 °C for 22 h. The reaction mixture was diluted with diethyl ether, filtered through Celite, and concentrated under vacuum. The crude residue was chromatographed on silica gel (15 to 30% EtOAc in hexanes) to give the purified intermediate (*E*)-7-(iodomethylene)-1-azabicyclo[3.2.1]octan-5-yl 4-chlorobenzoate (0.078 g, 79%). This was taken directly on to the next step.

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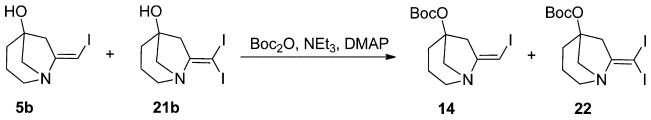
A solution of (*E*)-7-(iodomethylene)-1-azabicyclo[3.2.1]octan-5-yl 4-chlorobenzoate (0.046 g, 0.110 mmol), cesium carbonate (0.22 mL of a 2 M aqueous solution, 0.440 mmol), phenylboronic acid (0.015 g, 0.120 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.008 g, 0.007 mmol) in DMF (1.10 mL) was heated to 90 °C for 90 min. The reaction mixture was diluted with EtOAc and filtered through a 1 g silica gel solid-phase extraction column (SPE). The filtrate was concentrated under vacuum and the residue chromatographed on reversed-phase C18 (10 to 100% CH_3CN in water) to give the product **10*{10,1}*** (0.026 mg, 68%) as a brown solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (m, 2H), 7.43 (m, 2H), 7.38−7.31 (m, 4H), 7.21 (m, 1H), 6.34 (t, J = 2.3 Hz, 1H), 3.49 (dt, J = 16.8, 2.1 Hz, 1H), 3.29 (dd, J = 10.7, 2.1 Hz, 1H), 3.21 (dd, J = 10.7, 3.2 Hz, 1H), 3.16 (dd, J = 13.4, 6.0 Hz, 1H), 3.12−2.99 (m, 2H), 2.39 (m, 1H), 2.22 (tdd, J = 12.4, 5.8, 1.3 Hz, 1H), 2.02 (m, 1H), 1.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.8, 149.5, 139.5, 136.6, 131.0, 128.9, 128.7, 128.5, 127.8, 126.2, 117.1, 84.1, 62.7, 58.1, 42.2, 33.2, 21.5; IR 2942, 1718 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{21}H_{21}ClNO_2)^+$ 354.1261, found 354.1254.



(*E*)-*tert*-Butyl (7-(Iodomethylene)-1-azabicyclo[3.2.1]octan-5-yl)carbonate (14) and *tert*-Butyl (7-(Diiodomethylene)-1-azabicyclo[3.2.1]octan-5-yl)carbonate (22). To a solution of the alcohol mixture **5b** (3.538 g, 13.35 mmol) and **21b** (579 mg, 1.48 mmol) in DCM (62 mL) were added *N*,*N*-dimethylaminopyridine (DMAP, 0.379 g, 3.110 mmol), triethylamine (TEA, 4.330 mL, 31.10 mmol), and di-*tert*-butyl dicarbonate (Boc_2O, 4.070 g, 18.64 mmol). The reaction mixture was stirred for 3 h and then diluted with water and DCM, and the layers were separated. The aqueous layer was extracted with DCM (2×), and the combined organic layers were washed with 10% aqueous citric acid (1×) and brine (1×), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was chromatographed on silica gel (5 to 30% EtOAc in hexanes) to give the separated final products: **(*E*)-*tert*-butyl (7-(iodomethylene)-1-azabicyclo[3.2.1]octan-5-yl)carbonate (14)** as a light brown powder (4.131 g, 11.31 mmol) and **tert-butyl (7-(diiodomethylene)-1-azabicyclo[3.2.1]octan-5-yl)carbonate (22)** as a granular brown solid (0.393 g, 0.80 mmol). Overall amount: 12.11 mmol, 82%. **Monoiodide 14**: mp = 61.1−64.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (m, 1H), 3.14 (dd, J = 11.0, 2.3 Hz, 1H), 3.10 (dd, J = 11.0, 3.0 Hz, 1H), 3.07−2.94 (m, 2H), 2.84 (td, J = 13.1, 4.5 Hz, 1H), 2.56 (ddd, J = 17.2, 2.5, 1.9 Hz, 1H), 2.31−2.21 (m, 1H), 2.05 (tdd, J = 12.3, 5.9, 1.6 Hz, 1H), 1.86 (m, 1H), 1.64 (m, 1H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.1, 151.9, 83.4, 82.3, 64.9, 64.3, 57.7, 45.0, 32.9, 27.7, 21.5; IR 2940, 1738 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(C_{13}H_{21}INO_3)^+$ $(M + H)^+$ 366.0566, found 366.0596. **Diiodide 22**: mp = 98.2−137.7 °C (slowly decomposes over reported range); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.45−3.32 (m, 1H), 3.27−2.96 (m, 3H), 2.69 (m, 1H), 2.60 (dd, J = 17.2, 1.6 Hz, 1H), 2.28 (dd, J = 11.2, 1.6 Hz, 1H), 2.05 (m, 1H), 1.73 (m, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5, 151.7, 85.2, 82.4, 64.4, 52.5, 47.4, 32.6, 27.7, 22.1, 0.6; IR 2977, 1737 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(C_{13}H_{20}I_2NO_3)^+$ $(M + H)^+$ 491.9533, found 491.9532.

***tert*-Butyl 3-Oxo-1-oxa-7-azaspiro[4.5]decane-7-carboxylate (11).** Using the method of Zhang,[12] to a solution of *tert*-butyl 3-hydroxy-3-(prop-2-yn-1-yl)piperidine-1-carboxylate (**3**) (0.927 g, 3.870 mmol) in DCE (31.0 mL) were added 3,5-dichloropyridine *N*-oxide (1.270 g, 7.750 mmol) and methanesulfonic acid (0.302 mL, 4.650 mmol). In a separate flask, triphenylphosphinegold(I) bis(trifluoromethanesulfonyl)imidate (0.143 g, 0.194 mmol, 5 mol %) was weighed in a glovebox. The gold catalyst was placed under argon, removed from the glovebox and dissolved in DCE (46.50 mL). The contents of the first reaction flask were added to the gold catalyst-containing flask via cannula and the reaction mixture stirred for 4 h. The reaction mixture was concentrated under vacuum and chromatographed on silica gel (5 to 30% EtOAc in hexanes) to give the product **11** (0.511 g, 52%) as a colorless oil: ^{1}H NMR (DMSO-d_6, 500 MHz, 90 °C) δ 4.02 (d, J = 17.0 Hz, 1H), 3.96 (d, J = 17.0 Hz, 1H), 3.51−3.39 (m, 2H), 3.38−3.23 (m, 2H), 2.38 (d, J = 18.2 Hz, 1H), 2.34 (d, J = 18.1 Hz, 1H), 1.89−1.69 (m, 3H), 1.49−1.36 (m, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz, 90 °C) δ 212.7, 153.5, 78.5, 78.2, 68.7, 50.0, 44.6, 42.6, 34.1, 27.4, 21.0; IR 2936, 1760, 1687 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M-Boc + H)^+$ $(C_8H_{14}NO_2)^+$ 156.1025, found 156.1053.

***tert*-Butyl 7-Oxo-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (18a).** Following the above procedure for compound **11**, *tert*-butyl 3-hydroxy-3-(prop-2-yn-1-yl)azetidine-1-carboxylate (**16a**) (1.138 g, 5.39 mmol) was reacted with 3,5-dichloropyridine *N*-oxide (1.767 g, 10.77 mmol), methanesulfonic acid (0.419 mL, 6.460 mmol), and triphenylphosphinegold(I) bis(trifluoromethanesulfonyl)imidate (0.199 g, 0.269 mmol) to afford the product **18a** (0.606 g, 50%) as a granular white solid: mp = 70.6−80.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.10 (d, J = 9.4 Hz, 2H), 4.00−3.97 (t, J = 5.9 Hz, 4H), 2.70 (s, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.2, 156.1, 80.0, 77.3, 70.8, 61.0, 45.5, 28.2; IR 2978, 1765, 1694 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(C_{11}H_{16}NO_4)^-$ $(M-H)^-$, 226.1085 found 226.1062.

***tert*-Butyl 3-Oxo-1-oxa-7-azaspiro[4.4]nonane-7-carboxylate (18b).** Following the above procedure for compound **11**, *tert*-butyl 3-hydroxy-3-(prop-2-yn-1-yl)pyrrolidine-1-carboxylate (**16b**) (2.470 g, 10.96 mmol) was reacted with 3,5-dichloropyridine *N*-oxide (3.600 g, 21.93 mmol), methanesulfonic acid (0.854 mL, 13.16 mmol), and triphenylphosphinegold(I) bis(trifluoromethanesulfonyl)imidate (0.405 g, 0.548 mmol) to afford the product **18b** (1.653 g, 63%) as a granular pale yellow solid: mp = 70.8−76.2 °C; ^{1}H NMR (DMSO-d_6, 500 MHz, 90 °C) δ 4.01 (m, 2H), 3.54 (d, J = 11.7 Hz, 1H), 3.48−3.40 (m, 2H), 3.36 (d, J = 11.7 Hz, 1H), 2.66 (d, J = 18.1 Hz, 1H), 2.57 (d, J = 18.1 Hz, 1H), 2.19−2.08 (m, 1H), 1.99 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz, 90 °C) δ 212.4, 153.1, 85.8, 77.9, 69.2, 54.6, 43.8, 42.9, 34.8, 27.6; IR 2975, 1762, 1688 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{12}H_{20}NO_4)^+$ 242.1392, found 242.1374.

***tert*-Butyl 3-(((Trifluoromethyl)sulfonyl)oxy)-1-oxa-7-azaspiro[4.5]dec-2-ene-7-carboxylate (12).** To a solution of diisopropylamine (0.373 mL, 2.660 mmol) in THF (8.87 mL) at −78 °C was added *n*-butyllithium (1.142 mL of a 2.330 M solution in hexanes). The reaction mixture was warmed to 0 °C, stirred for 30 min, and then cooled to −78 °C. A solution of *tert*-butyl 3-oxo-1-oxa-7-azaspiro[4.5]decane-7-carboxylate (**11**) (0.227 g, 0.887 mmol) in THF (4.44 mL) was then added via cannula and the mixture stirred for 30 min. A solution of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (0.634 g, 1.775 mmol) in THF (7.10 mL) was then added via cannula and the solution allowed to warm to rt and stirred overnight for 18 h. The reaction mixture was quenched with satd aq NH_4Cl and diluted with water and MTBE, and the layers were separated. The aqueous layer was extracted with MTBE (3×), and the combined organic layers were dried over $MgSO_4$, filtered through a pad of silica gel, and concentrated under vacuum. The crude residue was chromatographed on reversed-phase C18 (0 to 100% CH_3CN in pH 9.4 ammonia/water) to give the product **12** (0.196 g, 57%) as an orange/brown oil: ^{1}H NMR (DMSO-d_6, 500 MHz, 85 °C) δ 6.09 (t, J = 1.9 Hz, 1H), 4.64 (m, 2H), 3.43−3.36 (m, 2H), 3.37 (d, J = 13.3 Hz, 1H), 3.23 (m, 1H), 1.82 (m, 1H), 1.73 (m, 2H), 1.52 (m, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz, 85 °C) δ 153.5, 144.2, 117.8, 117.6 (q, J_{C-F} = 322.12 Hz), 85.1, 78.2, 67.7, 50.7, 42.3, 33.9, 27.4, 20.7; IR 2938, 1692 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M-Boc + H)^+$ $(C_9H_{13}F_3NO_4S)^+$ 288.0517, found 288.0532.

***tert*-Butyl 7-(((Trifluoromethyl)sulfonyl)oxy)-5-oxa-2-azaspiro[3.4]oct-6-ene-2-carboxylate (19a).** Following the above procedure for compound **12**, *tert*-butyl 7-oxo-5-oxa-2-azaspiro[3.4]-octane-2-carboxylate (**18a**) (0.125 g, 0.550 mmol) was reacted with LDA (0.231 mL, 1.650 mmol of diisopropylamine with 0.743 mL, 1.650 mmol of a 2.220 M solution of butyllithium in hexanes) and *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*-((trifluoromethyl)sulfonyl)-methanesulfonamide (Comins' reagent, 0.432 g, 1.100 mmol) in place of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methane-

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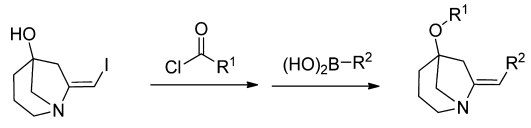
sulfonamide. The reaction was quenched with 5 M aqueous NH_4OH saturated with NH_4Cl and washed again (1×) with this solution after dilution with MTBE. The workup then proceeded as for compound **12**. Chromatography on silica gel (0−25% EtOAc in hexanes) afforded the product **19a** (0.075 g, 38%) as a granular off-white solid: mp = 46.2−52.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.98 (s, 1H), 4.66 (d, J = 2.1 Hz, 2H), 4.20−4.09 (m, 2H), 4.07−3.96 (m, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.0, 145.8, 118.4 (q, J_{C-F} = 321.1 Hz), 114.4, 83.8, 80.0, 70.2, 62.0, 28.3; IR 2978, 1702, 1667 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(C_{24}H_{33}F_6N_2O_{12}S_2)^+$ $(M + M + H)^+$ 719.1379, found 719.1380.

***tert*-Butyl 3-(((Trifluoromethyl)sulfonyl)oxy)-1-oxa-7-azaspiro[4.4]non-2-ene-7-carboxylate (19b).** Following the above procedure for compound **12**, *tert*-butyl 3-oxo-1-oxa-7-azaspiro[4.4]nonane-7-carboxylate (**18b**) (0.186 g, 0.771 mmol) was reacted with LDA (0.324 mL, 2.313 mmol of diisopropylamine with 1.042 mL, 2.313 mmol of a 2.220 M solution of butyllithium in hexanes) and 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)-methanesulfonamide (0.551 g, 1.542 mmol). In this case, chromatography on silica gel (0 to 25% EtOAc in hexanes) afforded the product **19b** (0.112 g, 39%) as an orange/brown oil: ^{1}H NMR (DMSO-d_6, 500 MHz, 90 °C) δ 6.15 (s, 1H), 4.65 (m, 2H), 3.48 (m, 1H), 3.45−3.34 (m, 3H), 2.11 (dt, J = 13.0, 9.1 Hz, 1H), 2.02 (ddd, J = 13.0, 7.1, 3.1 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz, 90 °C) δ 152.9, 144.1, 122.3, 117.6 (q, J_{C-F} = 321.7 Hz), 92.3, 77.9, 67.8, 54.5, 43.7, 35.4, 27.5; IR 2979, 1693, 1671 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{13}H_{19}F_3NO_6S)^+$ 374.0885, found 374.0901.

(4-Chlorophenyl)(3-phenyl-1-oxa-7-azaspiro[4.5]dec-2-en-7-yl)methanone (13). A solution of *tert*-butyl 3-(((trifluoromethyl)-sulfonyl)oxy)-1-oxa-7-azaspiro[4.5]dec-2-ene-7-carboxylate (**12**) (0.044 g, 0.113 mmol), phenylboronic acid (0.015 g, 0.125 mmol), and Cs_2CO_3 (0.227 mL of a 2 M aqueous solution, 0.453 mmol) in DMF (1.11 mL) was purged with argon for 5 min. Tetrakis-(triphenylphosphine)palladium(0) (0.008 g, 0.007 mmol) was added and the reaction mixture heated to 90 °C for 110 min. The reaction mixture was cooled and diluted with ethyl acetate and water, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×), and the combined organic layers were washed with brine (1×), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was chromatographed on silica gel (0 to 10% EtOAc in hexanes) to give the intermediate arylated product, *tert*-butyl 3-phenyl-1-oxa-7-azaspiro[4.5]dec-2-ene-7-carboxylate (0.018 mg, 51%) as a yellow oil. This was taken directly to the next step.

To a solution of *tert*-butyl 3-phenyl-1-oxa-7-azaspiro[4.5]dec-2-ene-7-carboxylate (0.018 g, 0.057 mmol) in DCM (0.300 mL) was added activated 4 Å molecular sieves and trifluoroacetic acid (TFA, 0.300 mL). After 5 min, the reaction mixture was filtered, and the filtrate was diluted with toluene and concentrated under vacuum (flushed) three times to remove TFA. The residue was then dissolved in DCM (1.000 mL). To this solution were added TEA (0.020 mL, 0.143 mmol), DMAP (~1 mg, ~0.006 mmol), and 4-chlorobenzoyl chloride (0.011 mL, 0.086 mmol). The reaction mixture was stirred for 2 h at rt, concentrated under vacuum, and directly chromatographed on silica gel (20 to 40% EtOAc in hexanes) to give the product **13** (0.016 g, 78%) as a white, amorphous solid: ^{1}H NMR (DMSO-d_6, 500 MHz, 90 °C) δ 7.53−7.24 (m, 9H), 6.30 (s, 1H), 4.95 (dd, J = 12.6, 1.8 Hz, 1H), 4.81 (d, J = 12.6 Hz, 1H), 3.82 (m, 1H), 3.54 (d, J = 13.2 Hz, 1H), 3.44 (d, J = 13.2 Hz, 1H), 3.23 (m, 1H), 1.88−1.84 (m, 3H), 1.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz, 90 °C) δ 168.0, 138.6, 135.0, 133.3, 131.5, 128.1, 127.8, 127.6, 127.5, 125.2, 124.8, 87.6, 72.7, 52.4, 43.0, 34.0, 21.0; IR 2941, 1628 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{21}H_{21}ClNO_2)^+$ 354.1261, found 354.1254.

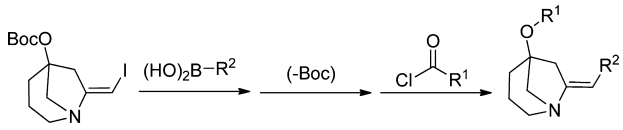


5b **10**

General Procedure for Library Synthesis, Route 1. The following describes the synthesis of a subset of the library consisting of 48 (8 × 6) members. Stock solutions were prepared to accommodate 52 members in order to provide for potential handling losses.

Step 1. Stock solutions were prepared as follows: (1) **(*E*)-7-(Iodomethylene)-1-azabicyclo[3.2.1]octan-5-ol (5b)**: 4.461 g (16.83 mmol) in acetonitrile (CH_3CN, 58.40 mL, 0.288 M). (2) TEA (8.320 mL, 59.69 mmol) and DMAP (572.0 mg, 4.322 mmol) in CH_3CN (7.800 mL). To each of 48 17 × 100 mm tubes equipped with stirring bars on two 24-place mini-block platforms on stirring plates were added 1.000 mL of stock solution **1** (0.288 mmol amine), 0.320 mL of stock solution **2** (1.150 mmol TEA and 0.090 mmol DMAP), and the appropriate volume of each neat acid chloride (0.864 mmol, eight acid chlorides were used six times each in this first step). The reactor blocks were heated to 50 °C, as judged by thermocouple inserted into each block, for 22 h. Each reaction mixture was then diluted with MTBE (10 mL) and filtered into new 17 × 100 mm reaction tubes through a 1 g silica gel SPE using a mini-block filtration platform. The filtrates were concentrated in parallel using a parallelpersonal evaporator. The crude material was taken on to the final step.

Step 2. Using the same mini-block setup described above, to each reaction tube were added dimethylformamide (2.900 mL), cesium carbonate (0.580 mL of a 2 M solution in water, 1.15 mmol), the appropriate amount of each bornic acid (0.320 mmol), and tetrakis(triphenylphosphine)palladium(0) (20.00 mg, 0.017 mmol, added using the mini-block powder dispenser). The reactor blocks were heated to 90 °C, as judged by a thermocouple inserted into each block, for 90 min. Each reaction mixture was then diluted with ethyl acetate (7 mL) and filtered through 1 g of silica gel SPE tubes into bar-coded 16 × 100 mm screw cap tubes. The filtrates were concentrated under vacuum using a parallel evaporator and the crude products purified using high-throughput MDF as described in the general procedures section above.



14 **10**

General Procedure for Library Synthesis, Route 2. The following describes the synthesis of a subset of the library consisting of eighteen (9 × 2) members. Stock solutions were prepared in a 10% excess to provide for potential handling losses.

Step 1. Stock solutions were prepared as follows: (1) (*E*)-*tert*-butyl (7-(iodomethylene)-1-azabicyclo[3.2.1]octan-5-yl)carbonate (**21**) (2.530 g, 6.930 mmol) in DMF (69.30 mL, 0.100 M). Using the same mini-block setup described above to each reaction tube was added 3.5 mL of stock solution **1** (0.350 mmol of **21**), cesium carbonate (0.700 mL of a 2 M solution in water, 1.400 mmol), the appropriate boronic acid (0.385 mmol, nine boronic acids were used twice each in this first step), and tetrakis(triphenylphosphine)-palladium(0) (24.00 mg, 0.021 mmol, added using the mini-block powder dispenser). The reactor blocks were heated to 90 °C, as judged by thermocouple inserted into each block, for 3 h. Each reaction mixture was then diluted with ethyl acetate (8 mL) and filtered into new 17 × 100 mm reaction tubes through a 1 g silica gel SPE using a mini-block filtration platform. The filtrates were concentrated in parallel using a parallel evaporator.

Step 2. A stock solution of 1:1 DCM/TFA (1.80 mL) was added to each of the 18 reaction tubes. The mixtures were stirred for 30 min and then toluene (4.000 mL) was added to each reaction. After removal of the solvent on the parallel personal evaporator, another 4.00 mL of toluene was added to each and once again removed under vacuum in the same manner.

Step 3. A stock solution of TEA and DMAP was prepared: (1) TEA (6.80 mL, 48.79 mmol) and DMAP (260.0 mg, 2.128 mmol) in CH_3CN (35.00 mL). To each reaction tube was added 1.750 mL of CH_3CN, 2.100 mL of stock solution **1**, and the appropriate acid chloride (1.050 mmol). The reactor blocks were either heated to 50 °C, as judged by thermocouple (A8, isoxazole derived acid chloride) for 3 h, or kept at room temperature (A14, mesyl chloride) for 1 h. In

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the case of A8, each reaction mixture was diluted with MTBE (5 mL), while the A14 mixtures were diluted with 1:1, DCM:CH_3CN (5 mL). All reaction mixtures were filtered through 1 g silica gel SPE tubes into bar-coded 16 × 100 mm screw cap tubes. The filtrates were concentrated under vacuum using a parallel evaporator and the crude products purified using high-throughput MDF as described in the general procedures section above.

(*E*)-7-Benzylidene-1-azabicyclo[3.2.1]octan-5-yl 4-chlorobenzoate (10*{10,1}*): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (m, 2H), 7.43 (m, 2H), 7.38−7.31 (m, 4H), 7.21 (m, 1H), 6.34 (t, J = 2.3 Hz, 1H), 3.49 (dt, J = 16.8, 2.1 Hz, 1H), 3.29 (dd, J = 10.7, 2.1 Hz, 1H), 3.21 (dd, J = 10.7, 3.2 Hz, 1H), 3.16 (dd, J = 13.4, 6.0 Hz, 1H), 3.12−2.99 (m, 2H), 2.39 (m, 1H), 2.22 (tdd, J = 12.4, 5.8, 1.3 Hz, 1H), 2.02 (m, 1H), 1.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.8, 149.5, 139.5, 136.6, 131.0, 128.9, 128.7, 128.5, 127.8, 126.2, 117.1, 84.1, 62.7, 58.1, 42.2, 33.2, 21.5; IR 2942, 1718 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{21}H_{21}ClNO_2)^+$ 354.1261, found 354.1254. Crystal structure CIF available (Supporting Information).

(*E*)-7-(4-Cyanobenzylidene)-1-azabicyclo[3.2.1]octan-5-yl furan-2-carboxylate (10*{2,10}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.98 (dd, J = 1.7, 0.8 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.31 (dd, J = 3.5, 0.8 Hz, 1H), 6.70 (dd, J = 3.5, 1.7 Hz, 1H), 6.31 (s, 1H), 3.32 (d, J = 17.0 Hz, 1H), 3.21 (dd, J = 10.6, 2.3 Hz, 1H), 3.11 (d, 17.0 Hz, 1H), 3.05−3.00 (m, 3H), 2.21 (m, 1H), 2.14 (m, 1H), 1.83 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 157.1, 155.2, 147.7, 143.9, 141.7, 132.3, 128.1, 119.2, 118.8, 114.7, 112.4, 107.9, 83.9, 61.7, 57.7, 42.5, 32.6, 21.3; IR 2946, 2223, 1721, 1603, 1301 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{20}H_{19}N_2O_3)^+$ 335.1390, found 335.1369.

(*E*)-7-(3-Chlorobenzylidene)-1-azabicyclo[3.2.1]octan-5-yl cyclopentanecarboxylate (10*{5,7}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.36 (t, J = 7.9 Hz, 1H), 7.32 (t, J = 1.7 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.22 (ddd, J = 7.9, 2.1, 0.9 Hz, 1H), 6.18 (t, J = 2.1 Hz, 1H), 3.20 (dt, J = 16.9, 1.9 Hz, 1H), 3.06 (dd, J = 10.6, 2.3 Hz, 1H), 2.96−2.84 (m, 4H), 2.72 (m, 1H), 2.09 (m, 1H), 2.00 (dt, J = 11.9, 6.0 Hz, 1H), 1.84−1.50 (m, 10H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 175.1, 152.9, 139.0, 133.2, 130.3, 127.0, 125.9, 125.6, 114.4, 82.6, 61.8, 57.6, 43.3, 42.1, 32.5, 29.5, 29.4, 25.4, 21.1; IR 2947, 1730, 1662 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{20}H_{25}ClNO_2)^+$ 346.1568, found 346.1550.

(*E*)-7-(4-Methoxybenzylidene)-1-azabicyclo[3.2.1]octan-5-yl 4-fluorobenzoate (10*{11,3}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.03 (m, 2H), 7.36 (t, J = 9.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.16 (t, J = 2.0 Hz, 1H), 3.74 (s, 3H), 3.28 (d, J = 16.7 Hz, 1H), 3.19 (dd, J = 10.6, 2.1 Hz, 1H), 3.03−2.95 (m, 4H), 2.24 (m, 1H), 2.16 (dt, J = 12.0, 5.8 Hz, 1H), 1.85 (m, 1H), 1.58 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.2 (d, J_{C-F} = 249.9 Hz), 164.1, 157.5, 148.3, 132.2 (d, J_{C-F} = 9.5 Hz), 129.3, 128.7, 126.8 (d, J_{C-F} = 2.8 Hz), 115.9 (d, J_{C-F} = 21.9 Hz), 114.0, 84.0, 61.9, 57.5, 55.1, 41.9, 32.8, 21.3; IR 2941, 1718, 1280 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{22}H_{23}FNO_3)^+$ 368.1656, found 368.1629.

(*E*)-7-(3-(Dimethylamino)benzylidene)-1-azabicyclo[3.2.1]-octan-5-yl furan-2-carboxylate (10*{2,6}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.97 (dd, J = 1.8, 0.9 Hz, 1H), 7.31 (dd, J = 3.6, 0.9 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H), 6.69 (dd, J = 3.6, 1.8 Hz, 1H), 6.64 (d, J = 7.9 Hz, 1H), 6.61 (m, 1H), 6.57 (dd, J = 8.1, 2.2, 1H), 6.15 (t, J = 2.0, 1H), 3.29 (d, J = 16.7 Hz, 1H), 3.16 (dd, J = 10.6, 2.2 Hz, 1H), 3.01−2.94 (m, 4H), 2.88 (s, 6H), 2.22 (m, 1H), 2.14 (dt, J = 12.2, 6.0 Hz, 1H), 1.84 (m, 1H), 1.58 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 157.1, 150.6, 149.9, 147.7, 144.0, 137.2, 128.9, 118.7, 116.7, 115.6, 112.4, 112.0, 110.5, 84.0, 61.8, 57.5, 42.1, 40.2, 32.8, 21.3; IR 2943, 1714, 1298 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{21}H_{25}N_2O_3)^+$ 353.1860, found 353.1866.

(*E*)-7-(3-Chlorobenzylidene)-1-azabicyclo[3.2.1]octan-5-yl isoxazole-5-carboxylate (10*{8,7}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.85 (d, J = 1.9 Hz, 1H), 7.39−7.35 (m, 2H), 7.30−7.28 (m, 2H), 7.25 (ddd, J = 7.9, 2.0, 0.9 Hz, 1H), 6.24 (t, J = 2.1 Hz, 1H), 3.31 (dt, J = 16.9, 1.9 Hz, 1H), 3.21 (dd, J = 10.6, 2.2 Hz, 1H), 3.14 (d, J = 16.9 Hz, 1H), 3.06 (dd, J = 10.6, 3.0 Hz, 1H), 3.00−2.99 (m, 2H), 2.23 (m, 1H), 2.18 (dt, J = 11.8, 6.0 Hz, 1H), 1.86 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.2, 155.4, 152.2, 138.9, 133.3, 130.3, 127.1, 126.0, 125.8, 114.7, 109.9, 85.5, 61.4, 57.5, 41.6, 32.5, 21.3; IR 2946, 1731, 1279 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{18}H_{18}ClN_2O_3)^+$ 345.1000, found 345.0998.

(*E*)-7-(4-Cyanobenzylidene)-1-azabicyclo[3.2.1]octan-5-yl pivalate (10*{7,10}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.78 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4, 2H), 6.29 (t, J = 2.0 Hz, 1H), 3.24 (dt, J = 17.0, 1.9 Hz, 1H), 3.10 (dd, J = 10.6, 2.3 Hz, 1H), 3.02−2.88 (m, 4H), 2.08 (m, 1H), 2.00 (dt, J = 12.2, 5.6 Hz, 1H), 1.77 (m, 1H), 1.54 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 176.9, 155.5, 141.7, 132.4, 128.1, 119.2, 114.7, 107.8, 82.5, 61.8, 57.7, 42.5, 38.5, 32.3, 26.9, 21.2; IR 2961, 2224, 1726 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{20}H_{25}N_2O_2)^+$ 325.1911, found 325.1887.

(*E*)-7-(4-Cyanobenzylidene)-1-azabicyclo[3.2.1]octan-5-yl 4-chlorobenzoate (10*{10,10}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.97 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.49(d, J = 8.4 Hz, 2H), 6.32 (s, 1H), 3.34 (m, 1H), 3.24 (dd, J = 10.6, 2.2 Hz, 1H), 3.16 (d, J = 17.7 Hz, 1H), 3.08 (dd, J = 10.6, 2.8 Hz, 1H), 3.05−3.02 (m, 2H), 2.25−2.15 (m, 2H), 1.84 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 164.2, 155.3, 141.7, 138.4, 132.4, 131.2, 129.0, 128.9, 128.1, 119.2, 114.7, 107.9, 84.0, 61.7, 57.7, 42.5, 32.5, 21.3; IR 2946, 2223, 1717 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{22}H_{20}ClN_2O_2)^+$ 379.1208, found 379.1209.

(*E*)-7-(Pyridin-4-ylmethylene)-1-azabicyclo[3.2.1]octan-5-yl 4-chlorobenzoate (10*{10,4}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.49 (d, J = 6.2 Hz, 2H), 7.97 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 6.2 Hz, 2H), 6.21 (s, 1H), 3.37 (dd, J = 16.6, 1.9 Hz, 1H), 3.25 (dd, J = 10.6, 2.3 Hz, 1H), 3.17 (d, J = 17.0 Hz, 1H), 3.08 (dd, J = 10.6, 2.8 Hz, 1H), 3.05−3.03 (m, 2H), 2.22 (m, 1H), 2.19 (dt, J = 11.7, 5.6 Hz, 1H), 1.85 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 164.2, 156.5, 149.7, 144.0, 138.4, 131.2, 129.0, 128.9, 122.0, 113.6, 83.9, 61.7, 57.8, 42.5, 32.5, 21.3; IR 2944, 1719 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{20}H_{20}ClN_2O_2)^+$ 355.1208, found 355.1197.

(*E*)-7-(4-Chlorobenzylidene)-1-azabicyclo[3.2.1]octan-5-yl 3-fluorobenzoate (10*{12,2}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.81 (dt, J = 7.6, 1.2 Hz, 1H), 7.70 (ddd, J = 9.5, 2.6, 1.6 Hz, 1H), 7.59 (ddd, J = 13.9, 8.2, 5.8 Hz, 1H), 7.53 (ddt, J = 8.7, 2.6, 1.2 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H) 6.22 (t, J = 2.1 Hz, 1H), 3.30 (m, 1H), 3.22 (dd, J = 10.6, 2.2 Hz, 1H), 3.08 − 3.04 (m, 2H), 3.00−2.95 (m, 2H), 2.25−2.15 (m, 2H), 1.89−1.81 (m, 1H), 1.61−1.57 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 163.9 (J_{CF} = 2.5 Hz), 162.0 (d, J_{CF} = 243.8 Hz), 151.7, 135.7, 132.5 (d, J_{CF} = 7.5 Hz), 131.0 (d, J_{CF} = 7.5 Hz); 130.3, 129.2, 128.4, 125.5 (d, J_{CF} = 6.3 Hz), 120.5 (d, J_{CF} = 21.1 Hz), 115.9 (d, J_{CF} = 22.9 Hz), 114.6, 84.2, 61.7, 57.6, 42.0, 32.6, 21.3; IR 2944, 1720 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{21}H_{20}ClFNO_2)^+$ 372.1167, found 372.1146.

(*E*)-7-(3-Methoxybenzylidene)-1-azabicyclo[3.2.1]octan-5-yl acetate (10*{13,5}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.24 (t, J = 7.8 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.82 (m, 1H), 6.76 (m, 1H), 6.15 (t J = 2.2 Hz), 3.75 (s, 3H), 3.20 (dt, J = 16.8, 2.0 Hz, 1H), 3.04 (dd, J = 10.6, 2.3 Hz, 1H), 2.96−2.90 (m, 2H), 2.89−2.82 (m, 2H), 2.16−2.10 (m, 1H), 2.06−1.96 (m, 1H), 2.00 (s, 3H), 1.83−1.71 (m, 1H), 1.58−1.48 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 169.8, 159.3, 151.3, 138.1, 129.4, 119.9, 115.5, 113.1, 111.4, 82.8, 61.9, 57.5, 55.0, 42.1, 32.6, 21.4, 21.2; IR 2942, 1735 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{17}H_{22}NO_3)^+$ 288.1600, found 288.1593.

(*E*)-7-(Pyridin-3-ylmethylene)-1-azabicyclo[3.2.1]octan-5-yl 4-fluorobenzoate (10*{11,8}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.53 (d, J = 2.1 Hz, 1H), 8.37 (dd, J = 4.7, 1.5 Hz, 1H), 8.08−8.00 (m, 2H), 7.74 (dt, J = 8.0, 1.8 Hz, 1H), 7.36 (m, 3H), 6.24 (t, J = 2.0 Hz, 1H), 3.33 (m, 1H), 3.24 (dd, J = 10.6, 2.2 Hz, 1H), 3.15−2.99 (m, 4H), 2.28−2.13 (m, 2H), 1.95−1.76 (m, 1H), 1.67−1.52 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 166.2, 165.2 (d, J_{CF} = 251.5 Hz), 164.1, 153.3, 148.8, 146.7, 133.9, 132.2 (d, J_{CF} = 9.6 Hz), 126.7 (d, J_{CF} = 2.8 Hz), 123.5, 115.9 (d, J_{CF} = 22.1 Hz), 112.2, 83.8, 61.8, 57.6, 42.1, 32.6, 21.2; IR 2947, 1717 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{20}H_{20}FN_2O_2)^+$ 339.1509, found 339.1483.

(*E*)-7-Benzylidene-1-azabicyclo[3.2.1]octan-5-yl acetate (10*{13,1}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.36−7.31 (m, 2H),

7.29 (m, 2H), 7.21−7.14 (m, 1H), 6.18 (t, J = 2.2 Hz, 1H), 3.20 (dt, J = 16.8, 2.1 Hz, 1H), 3.04 (dd, J = 10.6, 2.3 Hz, 1H), 2.97−2.81 (m, 4H), 2.18−2.10 (m, 1H), 2.06−1.96 (m, 1H), 2.00 (s, 3H), 1.84−1.70 (m, 1H), 1.53 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 169.8, 150.9, 136.7, 128.5, 127.5, 125.9, 115.6, 82.8, 61.9, 57.5, 42.0, 32.6, 21.4, 21.2; IR 2942, 1735 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{16}H_{19}NO_2$)$^+$ 258.1494, found 258.1464.

(*E*)-7-(Pyridin-3-ylmethylene)-1-azabicyclo[3.2.1]octan-5-yl 4-chlorobenzoate (10*{10,8}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.53 (d, J = 2.1 Hz, 1H), 8.37 (dd, J = 4.7, 1.5 Hz, 1H), 7.99−7.95 (m, 2H), 7.74 (dt, J = 8.0, 1.8 Hz, 1H), 7.64−7.59 (m, 2H), 7.37 (dd, J = 7.9, 4.7 Hz, 1H), 6.24 (s, 1H), 3.38−3.29 (m, 1H), 3.24 (dd, J = 10.6, 2.2 Hz, 1H), 3.15−2.99 (m, 4H), 2.28−2.14 (m, 2H), 1.94−1.80 (m, 1H), 1.65−1.56 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 164.2, 153.2, 148.8, 146.7, 138.4, 133.9, 132.6, 131.2, 128.9, 123.5, 112.3, 84.0, 61.8, 57.6, 42.1, 32.6, 21.2; IR 2944, 1718 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{20}H_{20}ClN_2O_2$)$^+$ 355.1213, found 355.1216.

(*E*)-7-(3-Chlorobenzylidene)-1-azabicyclo[3.2.1]octan-5-yl cyclohexanecarboxylate (10*{4,7}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.36 (t, J = 7.9 Hz, 1H), 7.32 (t, J = 1.7 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.23 (ddd, J = 7.9, 2.1, 0.9 Hz, 1H), 6.19 (t, J = 2.1 Hz, 1H), 3.20 (dd, J = 10.3, 8.4 Hz, 1H), 3.07 (dd, J = 10.7, 2.2 Hz, 1H), 2.99−2.80 (m, 4H), 2.27 (tt, J = 10.7, 3.6 Hz, 1H), 2.08 (dd, J = 10.3, 5.6 Hz, 1H), 2.00 (td, J = 12.0, 6.1 Hz, 1H), 1.86−1.70 (m, 3H), 1.70−1.61 (m, 2H), 1.55 (m, 2H), 1.41−1.12 (m, 5H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.4, 152.9, 139.0, 133.2, 130.3, 127.0, 125.9, 125.6, 114.4, 82.5, 61.8, 57.6, 42.5, 42.1, 32.5, 28.6, 28.5, 25.3, 24.8, 24.7, 21.1; IR 2934, 1731 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{21}H_{27}ClNO_2$)$^+$ 360.1730, found 360.1711.

(*E*)-7-Benzylidene-1-azabicyclo[3.2.1]octan-5-yl nicotinate (10*{9,1}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.11 (dd, J = 2.2, 0.7 Hz, 1H), 8.82 (dd, J = 4.8, 1.8 Hz, 1H), 8.34−8.28 (m, 1H), 7.60−7.56 (m, 1H), 7.38−7.32 (m, 4H), 7.19 (m, 1H), 6.23 (t, J = 2.2 Hz, 1H), 3.36−3.31 (m, 1H), 3.23 (dd, J = 10.6, 2.2 Hz, 1H), 3.14−3.04 (m, 2H), 3.04−2.97 (m, 2H), 2.30−2.16 (m, 2H), 1.86 (m, 1H), 1.61 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 164.0, 153.7, 150.7, 150.2, 137.0, 136.7, 128.5, 127.5, 126.1, 126.0, 123.9, 115.7, 84.3, 61.7, 57.5, 42.0, 32.69, 21.28; IR 2943, 1718 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{20}H_{21}N_2O_2$)$^+$ 321.1603, found 321.1580.

(*E*)-7-(4-Methoxybenzylidene)-1-azabicyclo[3.2.1]octan-5-yl benzoate (10*{1,3}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.00−7.94 (m, 2H), 7.70−7.63 (m, 1H), 7.56−7.50 (m, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.95−6.89 (m, 2H), 6.16 (t, J = 2.0 Hz, 1H), 3.75 (s, 3H), 3.29 (d, J = 16.7 Hz, 1H), 3.20 (dd, J = 10.5, 2.0 Hz, 1H), 3.07−2.92 (m, 4H), 2.29−2.21 (m, 1H), 2.16 (m, 1H), 1.91−1.78 (m, 1H), 1.58 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.0, 157.5, 148.4, 133.4, 130.2, 129.3, 128.7, 128.7, 115.2, 114.0, 83.8, 61.9, 57.5, 55.1, 41.9, 32.8, 21.3 (one overlap peak in aromatic region); IR 2939, 1714 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{22}H_{24}NO_3$)$^+$ 350.1756, found 350.1738.

(*E*)-7-(Pyridin-4-ylmethylene)-1-azabicyclo[3.2.1]octan-5-yl furan-2-carboxylate (10*{2,4}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.48 (dd, J = 4.6, 1.6 Hz, 2H), 7.98 (dd, J = 1.6, 0.8 Hz, 1H), 7.32 (dd, J = 3.5, 0.8 Hz, 1H), 7.27 (dd, J = 4.6, 1.6 Hz, 2H), 6.70 (dd, J = 3.5, 1.6 Hz, 1H), 6.20 (t, J = 2.0 Hz, 1H), 3.39−3.31 (m, 1H), 3.21 (dd, J = 10.6, 2.3 Hz, 1H), 3.12 (d, J = 17.6 Hz, 1H), 3.04 (m, 3H), 2.25−2.10 (m, 2H), 1.90−1.74 (m, 1H), 1.60−1.56 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 157.1, 156.4, 149.7, 147.7, 143.9, 122.0, 118.8, 113.6, 112.4, 83.9, 61.7, 57.7, 42.5, 32.6, 21.3 (one overlap in aromatic region); IR 2945, 1718 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{18}H_{19}N_2O_3$)$^+$ 311.1396, found 311.1377.

(*E*)-7-(4-Methoxybenzylidene)-1-azabicyclo[3.2.1]octan-5-yl butyrate (10*{3,3}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.22 (d, J = 8.8 Hz, 2H), 6.96−6.84 (m, 2H), 6.12 (t, J = 2.1 Hz, 1H), 3.74 (s, 3H), 3.22−3.10 (m, 1H), 3.03 (dd, J = 10.6, 2.1 Hz, 1H), 2.96−2.81 (m, 3H), 2.77 (m, 1H), 2.26 (t, J = 7.3 Hz, 2H), 2.17−2.08 (m, 1H), 2.00 (td, J = 12.0, 5.7 Hz, 1H), 1.86−1.67 (m, 1H), 1.60−1.45 (m, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.2, 157.5, 148.5, 129.3, 128.7, 115.1, 114.0, 82.8, 62.0, 57.4, 55.1, 41.9, 35.9, 32.7, 21.2, 18.0, 13.4; IR 2958, 1733 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{19}H_{26}NO_3$)$^+$ 316.1913, found 316.1898.

(*E*)-7-(Pyridin-4-ylmethylene)-1-azabicyclo[3.2.1]octan-5-yl cyclohexanecarboxylate (10*{4,4}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.47 (dd, J = 4.6, 1.6 Hz, 2H), 7.24 (dd, J = 4.7, 1.5 Hz, 2H), 6.17 (t, J = 2.0 Hz, 1H), 3.25 (dt, J = 17.0, 2.0 Hz, 1H), 3.09 (dd, J = 10.7, 2.4 Hz, 1H), 3.03−2.84 (m, 4H), 2.27 (tt, J = 10.7, 3.6 Hz, 1H), 2.15−2.04 (m, 1H), 2.04−1.96 (m, 1H), 1.86−1.69 (m, 3H), 1.66 (m, 2H), 1.55 (m, 2H), 1.43−1.08 (m, 5H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.4, 156.7, 149.7, 144.0, 122.0, 113.5, 82.4, 61.8, 57.7, 42.6, 42.4, 32.4, 28.6, 28.5, 25.3, 24.8, 24.7, 21.2; IR 2932, 1731 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{20}H_{27}N_2O_2$)$^+$ 327.2073, found 327.2058.

(*E*)-7-(3-Methoxybenzylidene)-1-azabicyclo[3.2.1]octan-5-yl cyclopentanecarboxylate (10*{5,5}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.25 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.82 (m, 1H), 6.76 (m, 1H), 6.15 (t, J = 2.1 Hz, 1H), 3.74 (s, 3H), 3.22−3.19 (m, 1H), 3.05 (dd, J = 10.6, 2.2 Hz, 1H), 3.00−2.77 (m, 4H), 2.77−2.65 (m, 1H), 2.10 (m, 1H), 1.99 (m, 1H), 1.87−1.73 (m, 3H), 1.73−1.63 (m, 2H), 1.63−1.45 (m, 5H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 175.2, 159.3, 151.3, 138.1, 129.5, 119.8, 115.6, 113.3, 111.3, 82.6, 61.9, 57.6, 55.0, 43.3, 42.2, 32.5, 29.5, 29.4, 25.4, 21.1; IR 2947, 1729 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{21}H_{28}NO_3$)$^+$ 342.2069, found 342.2054.

(*E*)-7-(4-Chlorobenzylidene)-1-azabicyclo[3.2.1]octan-5-yl pivalate (10*{7,2}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.46−7.35 (m, 2H), 7.35−7.25 (m, 2H), 6.19 (t, J = 2.1 Hz, 1H), 3.19 (m, 1H), 3.07 (dd, J = 10.6, 2.2 Hz, 1H), 3.02−2.89 (m, 2H), 2.86 (dd, J = 10.6, 3.1 Hz, 1H), 2.80 (d, J = 16.9 Hz, 1H), 2.08 (m, 1H), 2.00 (m, 1H), 1.77 (m, 1H), 1.53 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 176.9, 151.9, 135.7, 130.2, 129.1, 128.4, 114.5, 82.5, 61.8, 57.5, 42.0, 38.5, 32.3, 26.9, 21.1; IR 2957, 1727 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{19}H_{25}ClNO_2$)$^+$ 334.1574, found 334.1571.

(*E*)-7-(3-Methoxybenzylidene)-1-azabicyclo[3.2.1]octan-5-yl pivalate (10*{7,5}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.26 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.82 (m, 1H), 6.77 (m, 1H), 6.16 (t, J = 2.1 Hz, 1H), 3.75 (s, 3H), 3.21 (m, 1H), 3.06 (dd, J = 10.6, 2.2 Hz, 1H), 2.93 (m, 2H), 2.85 (dd, J = 10.6, 3.1 Hz, 1H), 2.79 (d, J = 16.8 Hz, 1H), 2.09 (m, 1H), 1.99 (m, 1H), 1.77 (m, 1H), 1.53 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 176.9, 159.3, 151.2, 138.1, 129.5, 119.8, 115.6, 113.4, 111.2, 82.5, 61.8, 57.5, 55.0, 42.1, 38.5, 32.4, 26.9, 21.1; IR 2957, 1726 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{20}H_{28}NO_3$)$^+$ 330.2069, found 330.2070.

(*E*)-7-(Pyridin-3-ylmethylene)-1-azabicyclo[3.2.1]octan-5-yl benzoate (10*{1,8}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.53 (d, J = 2.1 Hz, 1H), 8.37 (dd, J = 4.7, 1.5 Hz, 1H), 7.97 (m, 2H), 7.74 (dt, J = 8.0, 1.8 Hz, 1H), 7.66 (m, 1H), 7.53 (m, 2H), 7.36 (dd, J = 8.0, 4.7 Hz, 1H), 6.24 (t, J = 2.0 Hz, 1H), 3.39−3.30 (m, 1H), 3.24 (dd, J = 10.6, 2.2 Hz, 1H), 3.16−2.95 (m, 4H), 2.32−2.12 (m, 2H), 1.87 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.0, 153.4, 148.8, 146.7, 133.8, 133.4, 132.6, 130.1, 129.3, 128.7, 123.5, 112.2, 83.7, 61.9, 57.6, 42.2, 32.6, 21.3; IR 2945, 1716 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{20}H_{21}N_2O_2$)$^+$ 321.1603, found 321.1608.

(*E*)-7-(4-Chlorobenzylidene)-1-azabicyclo[3.2.1]octan-5-yl butyrate (10*{3,2}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.38 (m, 2H), 7.30 (m, 2H), 6.18 (t, J = 2.1 Hz, 1H), 3.19 (dt, J = 16.8, 2.2 Hz, 1H), 3.06 (dd, J = 10.6, 2.2 Hz, 1H), 3.01−2.76 (m, 4H), 2.26 (t, J = 7.3 Hz, 2H), 2.32 (m, 1H), 2.01 (m, 1H), 1.77 (m, 1H), 1.61−1.47 (m, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.2, 152.0, 135.7, 130.2, 129.1, 128.4, 114.5, 82.7, 61.9, 57.5, 42.1, 35.9, 32.6, 21.2, 18.0, 13.4; IR 2939, 1732 cm^{-1}; HRMS (ESI-TOF) m/z calcd for (M + H)$^+$ ($C_{18}H_{23}ClNO_2$)$^+$ 320.1417, found 320.1422.

(*E*)-7-(3-(Dimethylamino)benzylidene)-1-azabicyclo[3.2.1]-octan-5-yl 3-fluorobenzoate (10*{12,6}*): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.81 (dt, J = 7.6, 1.2 Hz, 1H), 7.71 (ddd, J = 9.5, 2.5, 1.5 Hz, 1H), 7.59 (m, 1H), 7.53 (m, 1H), 7.15 (t, J = 7.9 Hz, 1H), 6.66 (d, J = 7.7 Hz, 1H), 6.62 (m, 1H), 6.58 (dd, J = 8.1, 2.3 Hz, 1H), 6.17 (t, J = 2.0 Hz, 1H), 3.32 (m, 1H), 3.21 (dd, J = 10.6, 2.1 Hz, 1H), 3.10−2.93

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(m, 4H), 2.89 (s, 6H), 2.31−2.11 (m, 2H), 1.86 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 163.9 (d, J_{CF} = 3.0 Hz), 162.0 (d, J_{CF} = 245.0 Hz), 150.6, 149.9, 137.2, 132.5 (d, J_{CF} = 7.3 Hz), 131.0 (d, J_{CF} = 8.0 Hz), 128.9, 125.5 (d, J_{CF} = 2.7 Hz), 120.4 (d, J_{CF} = 21.2 Hz), 116.7, 115.9 (d, J_{CF} = 22.9 Hz), 115.5, 112.1, 110.5, 84.2, 61.7, 57.5, 42.0, 40.2, 32.6, 21.3; IR 2943, 1718 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $(M + H)^+$ $(C_{23}H_{26}FN_2O_2)^+$ 381.1978, found 381.1954.

■ ASSOCIATED CONTENT

Supporting Information

X-ray structure of compound **10*{10,1}***, details about library compound yield trend data for individual components, and ^{1}H and ^{13}C NMR spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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