Solution-Phase Parallel Synthesis of Spirohydantoins

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Spirohydantoins are considered privileged structures, making them attractive for the preparation of compound libraries with the potential for diverse biological activity. However, very few modifications of this scaffold have been reported to date. The spirohydantoin template was elaborated into a library of 168 compounds through a two-step solution-phase parallel synthesis starting from various N-substituted piperidinones. The Strecker reaction was employed to generate α-amino nitriles from aniline and TMSCN (or KCN). Subsequent reaction of the anilido nitrogen with a diverse set of isocyanates, followed by refluxing under acidic conditions, afforded the title library in high yield and purity.

Introduction

Parallel synthesis methodology and related multiple synthesis technologies toward the preparation of small-molecular-weight compound libraries have been widely utilized in modern drug discovery, especially in the lead generation and lead optimization stages. The combination of rational drug design and parallel synthesis has accelerated the process of lead generation and optimization. Our laboratory is primarily interested in analogues of opioid analgesics based on the 4-anilido piperidine privileged scaffold (i.e., lofentanyl, Figure 1).[1,2] We are also significantly interested in developing compounds that may serve as antiparasitic agents for such diseases as malaria. To medicinal chemists, privileged scaffolds are attractive from a drug design standpoint, especially in the lead generation stages. On the basis of one core scaffold, a library can be designed, synthesized, and screened against a variety of different biological targets, potentially yielding several active compounds.[3]

During a literature search for synthetic methodologies toward a related project in our laboratory, we identified a relatively unexplored spirohydantoin template.[2] Due to the wide array of biological activity associated with the hydantoin moiety as well as the piperidine moiety, we embarked on a project to investigate possible bioactive molecules based on this hybrid template.[4−8] Herein, we report a facile solution-phase parallel synthetic route to diversify the spirohydantoin scaffold in three different positions.

Chemistry

The spirohydantoin library was efficiently synthesized using the approach outlined in Scheme 1. The present sequence of reactions was proposed in such a way that the resultant core scaffold could be diversified in up to three different positions (Figure 1). In general terms, the synthesis first utilized the Strecker reaction, followed by condensation of the anilido nitrogen with the corresponding isocyanate derivative to give the intermediate compound (**7**, **8**, or **9**), which was subsequently cyclized upon addition of concentrated HCl (and heat) to give the desired product (**10**, **11**, or **12**) with diversity in two positions. The current study utilized aniline in the Strecker reaction as proof of concept. The employment of substituted anilines or amines (not used in the present work) would afford a third position of diversity.

Results and Discussion

The Strecker reaction offers one of the most direct and viable methods for the asymmetric synthesis of α-amino acid derivatives. In this case, it was used to obtain the α-amino nitriles as shown in Scheme 1.[9,10] Reaction of *N*-phenethyl-4-piperidinone (**1**, R = phenethyl) with aniline and potassium cyanide in aqueous acetic acid (method A) yielded 21% of **4.** To improve the yield, an anhydrous modification of the Strecker reaction was employed using trimethylsilyl cyanide (TMSCN)[2] in place of KCN. The solvent was changed to glacial acetic acid (method B), affording **4** with an improved yield of 76% and significantly decreased reaction time. The use of TMSCN with Lewis acids to effect addition of cyanide to imines is precedent; however, we found it more efficient and convenient to use the one-pot anhydrous procedure as described.[2] Due to the results obtained using the modified Strecker reaction, the use of KCN was not explored further.

The reaction of primary and secondary amines with isocyanates is well-known and serves as an excellent method to prepare substituted hydantoins.[11−15] Initial experiments in our laboratory used dichloromethane (DCM) as a solvent; the results obtained demonstrated poor (<50% yield) to no reactivity of aliphatic isocyanates. This led us to investigate 1,2-dichloroethane (DCE) as a substitute for DCM. To our satisfaction, DCE afforded high yields in each case that an aliphatic isocyanate was utilized.

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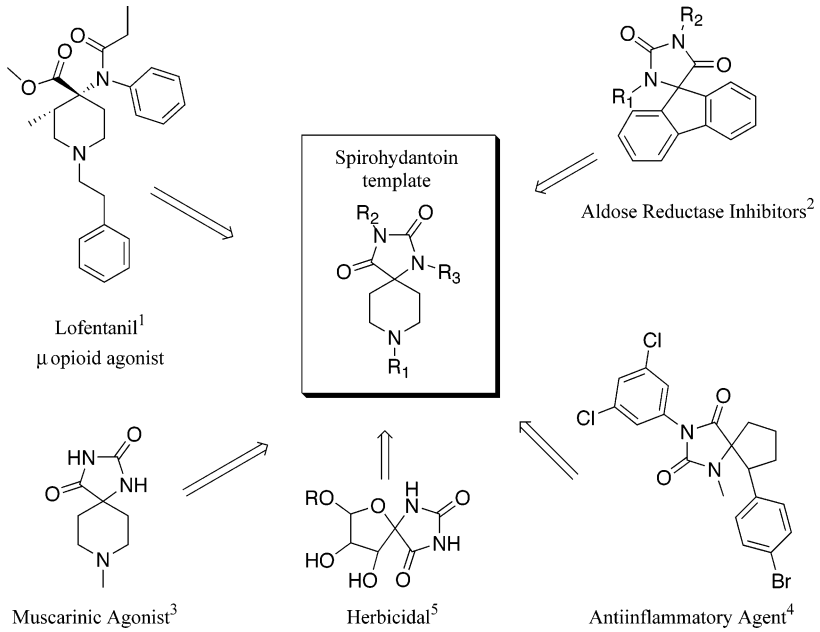
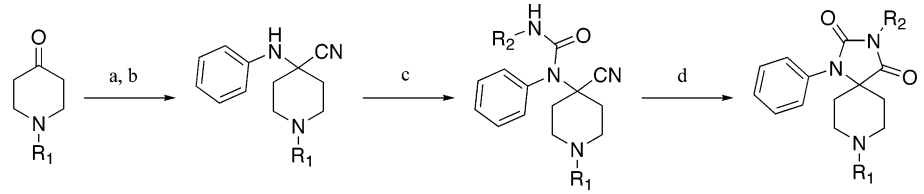


Figure 1. Design rationale of the spirohydantoin library.

Scheme 1[a]



1. R_1 = Phenethyl	**4.** R_1 = Phenethyl	**7.** R_1 = Phenethyl	**10.** R_1 = Phenethyl
2. R_1 = Benzyl	**5.** R_1 = Benzyl	**8.** R_1 = Benzyl	**11.** R_1 = Benzyl
3. R_1 = Methyl	**6.** R_1 = Methyl	**9.** R_1 = Methyl	**12.** R_1 = Methyl

[a] (a) Aniline, glacial acetic acid; (b) TMSCN; (c) DCE, R_2NCO, 80 °C for 2 h, rt overnight; (d) HCl, 80 °C, 1 h, rt 2 h.

The intramolecular cyclization step was accomplished by treatment with HCl at 80 °C.[16] The crude material from the isocyanate addition and subsequent cyclization was filtered, and the reaction vessels were washed with DCE (2 × 3 mL) and DCM (2 × 3 mL). Figure 2 shows the structures of the 168 spirohydantoin prepared. An aliquot of the crude reaction was injected directly onto either a HPLC or a LC/MS instrument to determine the yield and purity.[17] The entire library was characterized by LC/MS analysis, indicating the presence of all compounds with a purity range, determined by HPLC analysis, from 30 to 100%. Table 1 shows the crude analysis result for 30 members of the library, and the average purity of the complete set shown in Figure 2 was 72% for the crude product. More than 80% of compounds have a purity of more than 80%. Overall, the average yield of the library was 83% and more than 70% of the reactions produced a yield higher than 80%.

Conclusions

A practical solution-phase synthesis of spirohydantoins was successfully developed and optimized. The synthetic route performed provided facile access to a library of spirohydantoins with diversification in two different positions. The next exploration in this project will employ a variety of substituted anilines in order to fully investigate the current template for biological activity. Biological testing is currently underway and the results will be published in a later paper.

Experimental Section

Materials and General Methods. All the solvents and reagents were obtained commercially and were used as received unless noted otherwise. Dichloromethane (DCM) was dried by refluxing over CaH, Dichloroethane (DCE) was dried over molecular sieves. NMR spectra were recorded in 3-mm tubes on a Bruker 400 MHz spectrometer (^{1}H at 400 MHz and ^{13}C at 100 MHz) in $CDCl_3$ unless otherwise stated. HPLC/MS spectra were recorded on a Waters Alliance LC/MS System, consisting of a Waters ZQ mass detector, photodiode array detector, and an Alliance HPLC system, equipped with a XTerra column (C-8, 2.1 × 5 mm). The reaction steps were performed in parallel using a Quest 210 from Argonaut Technologies. A Speedvac SC250DDA (Thermo Savant) was used for parallel concentration. Flash chromatography was performed on a Combiflash from ISCO, Inc. using a gradient of ethyl acetate (0−50%) in hexane unless otherwise noted.

General Procedure for the Strecker reaction. 1. Method A. A mixture of *N*-phenethyl-4-piperidone (0.1 mmol), aniline (0.15 mmol), glacial acetic acid (130 mL), water (20 mL), and KCN (0.25 mmol) was stirred at 45 °C for 45 h.

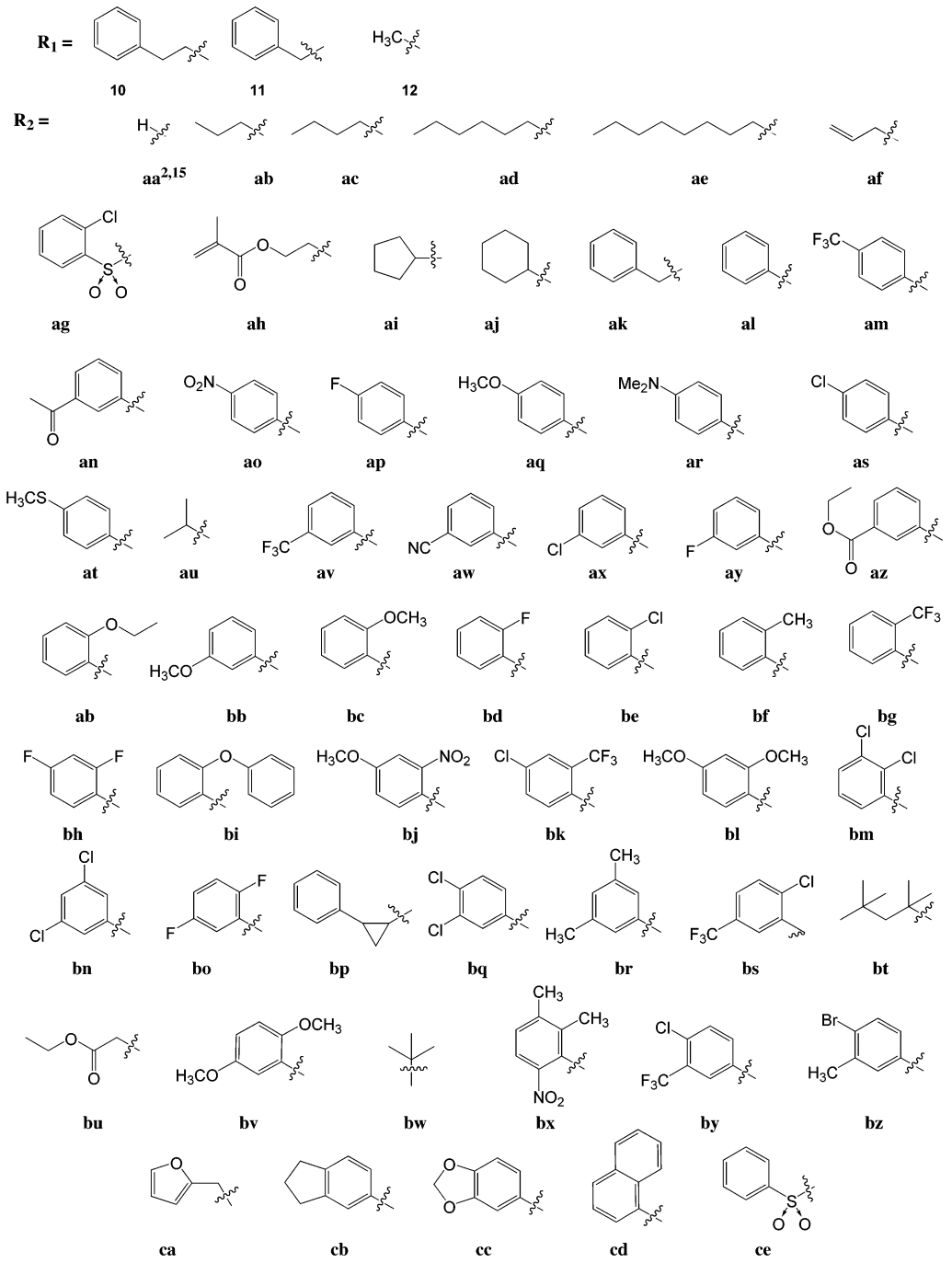


Figure 2. Structural diversity of the spirohydantoin library.

The reaction mixture was then poured into a cold ammonium hydroxide mixture (50 mL of concentrated NH_4OH, 50 g of crushed ice). Additional concentrated ammonium hydroxide was slowly added until pH 10 was reached. The resultant mixture was extracted with DCM (3 × 100 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to a yellow solid. The solid was washed with ether (50 mL), resulting in a white solid that was filtered and washed with cold ether and then dried to give the desired product as a white solid.

2. Method B. To a stirred solution of N-substituted 4-piperidone (0.1 mol) and aniline (0.11 mol) in glacial acetic acid (100 mL) was added trimethylsilyl cyanide (0.1 mol) dropwise over a 10-min period, maintaining the temperature below 40 °C using a cold-water bath. The solution was stirred an additional 30 min and then poured into a cold ammonium hydroxide mixture (100 mL of concentrated NH_4OH, 100 g of crushed ice). Additional concentrated ammonium hydroxide was slowly added until pH 10 was reached. The resultant mixture was extracted with $CHCl_3$ (3 × 100 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to a yellow solid, which was washed with ether (70 mL). The resulting white solid was filtered and washed with cold ether and then dried to give the desired product as a white solid.

General Procedure for the Acylation with Isocyanates and Further Cyclization. The addition of isocyanates to the α-amino nitriles was run in parallel fashion in Quest 210

Table 1. Crude Yield and Purity of Selected Library Members

cmpd	purity %	yield %	MW	MS $[M + H]^+$	cmpd	purity %	yield %	MW	MS $[M + H]^+$
10ae	86.0	98.4	461.30	462.34	**11bb**	84.7	98.4	441.21	442.14
10ah	87.0	100.0	461.23	462.34	**11bn**	74.2	100.0	479.12	480.02
10ar	93.0	87.6	468.25	469.40	**11bw**	83.4	95.5	391.23	392.06
10bd	82.0	98.4	443.20	444.33	**11ce**	87.7	97.6	475.16	476.12
10bk	74.0	100.0	527.16	528.22	**12aa**	99.0	93.8	357.06	358.15
10bp	74.0	100.0	465.24	466.37	**12ab**	85.0	89.4	301.18	302.10
10bq	94.0	84.9	493.13	494.21	**12ac**	94.0	83.4	315.20	316.15
10bz	99.0	99.1	517.14/519.21	518.21/520.23	**12al**	82.0	100.0	335.16	336.14
10cc	100.0	89.8	469.20	470.28	**12au**	93.0	100.0	301.18	302.04
11aa	79.9	97.5	433.09	434.02	**12aw**	88.0	97.2	360.16	361.08
11ad	77.3	82.7	419.26	420.17	**12az**	91.0	100.0	407.18	408.35
11ag	81.9	100.0	509.12	510.05	**12bf**	91.0	88.0	349.18	350.13
11ai	71.9	97.9	403.23	404.13	**12bi**	90.0	88.8	427.19	427.91
11aq	76.3	87.5	441.21	442.14	**12bl**	94.0	100.0	395.18	396.05
11aw	77.9	100.0	436.19	437.12	**12ca**	97.0	100.0	339.16	340.04

5-mL reaction vessels at a 0.3-mmol scale, in 1,2-dichloroethane (DCE) or dichloromethane (DCM). The mixture was heated at 80 °C for 2 h and then stirred at ambient temperature for 24 h. Concentrated HCl (100 μL) was added to the reaction vessels, and the temperature was raised to 80 °C for 1 h, when it was allowed to return to ambient and stirred for another 2 h. The resulting mixture was filtered, dried, and analyzed. The purification of the library by flash chromatography was performed after neutralization of the mixture. The characterization was done by LC/MS and NMR (^{1}H and ^{13}C).

***N*-Phenethyl-4-aniliono-4-cyanopiperidine (4). 1. Method A.** *N*-Phenethyl-4-piperidone (5.00 g, 24.6 mmol), aniline (3.43 g, 36.9 mmol), glacial acetic acid (130 mL), water (20 mL), and KCN (4.00 g, 61.50 mmol) gave 1.58 g (5.16 mmol, 21%) of the desired product as a white solid.

2. Method B. To a solution of *N*-phenethyl-4-piperidone (10.00 g, 49.20 mmol) and aniline (4.14 mL, 54.12 mmol) in glacial acetic acid (50 mL) was added dropwise trimethylsilyl cyanide (6.5 mL, 49.20 mmol) over a 10-min period to give 11.54 g (37.7 mmol, 76.6%) of the desired product as a white solid. mp: 121−122 °C. ^{1}H NMR ($CDCl_3$), δ :7.31−7.20 (m, 6H), 6.95−6.92 (m, 4H), 3.72 (s, 1H), 3.02−2.62 (m, 8H), 2.42−2.39 (d, 2H), 2.06−2.05 (bd, 2H). ^{13}CNMR ($CDCl_3$) δ: 175.28, 143.29, 139.55, 128.73, 126.36, 121.08, 120.88, 117.88, 59.60, 49.10, 35.53, 33.10, 21.85. MS *m*/*z* $[M + H]^+$ 306; calcd, 305.

***N*-Benzyl-4-anilino-4cyanopiperidine (5). Method B.** To a solution of *N*-benzyl-4-piperidone (10.00 g, 52.83 mmol) and aniline (5.41 g, 58.11 mmol) in glacial acetic acid (50 mL) was added dropwise trimethylsilyl cyanide (7.04 mL, 52.83 mol) over a 10-min period, to give 11.73 g (40.28 mmol, 76.25%) of the desired product as a white solid. mp: 143−145 °C. ^{1}H NMR ($CDCl_3$) δ: 7.34−7.23 (m, 7H), 6.90−6.94 (m, 3H), 3.64 (s, 1H), 3.56 (s, 2H), 2.83−2.80 (bd, 2H), 2.50−2.44 (t, 2H), 2.35−2.32 (d, 2H), 1.95−1.90 (t, 3H). ^{13}CNMR ($CDCl_3$) δ: 143.4, 138.1, 129.4, 129.1, 128.4, 127.4, 120.9, 117.8, 62.66, 53.1, 49.4, 36.2. LC/MS: 292.01 $[M + H]^+$; calcd mass, 291.17.

***N*-Methyl-4-anilino-4-cyanopiperidine (6). Method B.** To a solution of *N*-methyl-4-piperidone (11.89 g, 0.1051 mol) and aniline (10.55 mL, 0.1156 mol) in glacial acetic acid (100 mL) was added dropwise trimethylsilyl cyanide (14 mL, 0.1051 mol) to give 21.80 g (96.4%) of the desired product as a white solid. mp: 88−90 °C. ^{1}H NMR ($CDCl_3$) δ: 7.24−7.28 (d, 2H), 6.92−6.94 (d, 3H), 2.90−2.92 (d, 2H), 2.50−2.55 (d, 2H), 2.38 (s, 3H), 1.99−2.03 (bd, 4H). ^{13}C NMR ($CDCl_3$) δ: 175.37, 143.25, 139.27, 129.34, 121.03, 120.43, 117.84, 52.33, 51.01, 50.96, 45.14, 35.55, 35.83, 21.50. LC/MS: 216.22 $[M + H]^+$; calcd mass, 215.14.

1-Phenyl-3-butyl-8-methyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (12ac). ^{1}HNMR ($CDCl_3$) δ: 7.42−7.40 (m, 3H), 7.19−7.17 (bd, 2H), 4.30−4.20 (m, 2H), 3.96−3.93 (m, 2H), 2.77−2.68 (m, 4H), 2.29 (s, 3H), 2.00−1.92 (m, 4H), 1.30−1.25 (t, 3H). ^{13}CNMR ($CDCl_3$) δ: 170.73, 157.01, 137.83, 134.91, 130.66, 129.68, 129.35, 128.65, 62.73, 50.37, 45.58, 39.29, 33.07, 31.95, 23.70, 23.28. LC/MS = 316.02 $[M + H]^+$; calcd 315.19. Purity$_{UV220}$ = 94%; yield = 83.4%.

2-(1-Phenyl-8-benzyl-1,3,8-triazaspiro[4,5]decane-2,4-dione-3-yl)-ethyl Methacrylate (11ah). ^{1}HNMR ($CDCl_3$) δ: 8.01−7.92 (m, 2H), 7.54−7.39 (m, 8H), 6.12 (s, 1H), 5.58 (s, 1H), 4.43−3.98 (m, 4H), 3.83−3.60 (m, 3H), 3.49−3.32 (m, 2H), 2.94−2.93 (m, 2H), 2.62−2.49 (m, 2H), 1.98−1.88 (m, 2H). LC/MS = 447.8 $[M + H]^+$; calcd, 447.2. Purity = 82.4%; yield = 100%.

2-(1-Phenyl-8-methyl-1,3,8-triazaspiro[4,5]decane-2,4-dione-3-yl)-ethyl Methacrylate (12ah). ^{1}HNMR ($CDCl_3$) δ: 7.43−7.40 (m, 3H), 7.18−7.16 (m, 2H), 6.13 (s, 1H), 5.74 (s, 1H), 4.43−4.41 (t, 2H), 3.92−3.89 (t, 2H), 2.81−2.70 (m, 4H), 2.31 (s, 3H), 1.98−1.88 (m, 4H). LC/MS = 372.03 $[M + H]^+$; calcd, 371.18. Purity$_{UV220}$ = 85.0%; yield = 100.0%.

1-Phenyl-3-benzyl-8-methyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (12ak). ^{1}HNMR ($CDCl_3$) δ: 7.43−7.32 (m, 8H), 7.17−7.14 (m, 2H), 4.72 (s, 2H), 2.81−2.76 (m, 2H), 2.69−2.66 (m, 2H), 2.29 (s, 3H), 2.00−1.93 (m, 2H), 1.84−1.80 (bd, 2H). ^{13}CNMR ($CDCl_3$) δ: 175.07, 153.00, 136.21, 132.83, 130.76, 129.53, 129.01, 128.70, 128.61, 127.85, 62.25, 50.60, 45.68, 42.26, 30.04. LC/MS: 350.1 $[M + H]^+$; calcd, 349.2. Purity$_{UV220}$ = 85.0%; yield = 88.6%

1-Phenyl-3-(3-acetyl)phenyl-8-benzyl-1,3,8-triazaspiro-[4,5]decane-2,4-dione (11an). ^{1}HNMR ($CDCl_3$) δ: 8.79 (s, 1H), 7.91−7.87 (m, 2H), 7.61−7.54 (m, 3H), 7.42−7.20 (m, 6H), 6.95−6.85 (m, 1H), 4.30−4.20 (m, 2H), 3.78−3.68 (m, 2H), 3.12−2.88 (m, 4H), 2.57 (s, 3H), 2.10−2.00 (m, 4H),

1.30−1.25 (t, 3H). ^{13}CNMR ($CDCl_3$) δ: 174.97, 167.19, 132.68, 130.77, 129.60, 129.15, 62.73, 61.91, 50.61, 45.68, 42.18, 39.38, 31.96, 14.11. LC/MS = 454.15 $[M + H]^+$; calcd, 453.21. $Purity_{UV220}$ = 66.8%; yield = 100.0%.

1-Phenyl-3-*p*-nitrophenyl-8-benzyl-1,3,8-triazaspiro-[4,5]decane-2,4-dione (11ao). ^{1}HNMR ($CDCl_3$) δ: 8.31−8.28 (d, 2H), 8.05−8.00 (m, 1H), 7.76−7.74 (d, 2H), 7.59−7.18 (m, 8H), 6.95−6.90 (m, 1H), 4.17 (s, 2H), 3.61−3.36 (m, 4H), 2.90−2.85 (m, 2H), 2.21−2.17 (m, 2H). LC/MS = 457.12 $[M + H]^+$; calcd, 456.18. $Purity_{UV220}$ = 42.5%; yield = 87.7%.

1-Phenyl-3-*p*-nitrophenyl-8-methyl-1,3,8-triazaspiro-[4,5]decane-2,4-dione (12ao). ^{1}HNMR ($CDCl_3$) δ: 8.34−8.32 (d, 2H), 8.21−8.08 (m, 2H), 7.84−7.82 (d, 2H), 7.70−7.68 (d, 1H), 7.51−7.46 (m, 2H), 2.87−2.75 (m, 2H), 2.33 (s, 3H), 2.14−2.08 (m, 2H), 1.66−1.60 (m, 2H). LC/MS = 381.07 $[M + H]^+$; calcd, 380.15. $Purity_{UV220}$ = 71.0%; yield = 100.0%.

1-Phenyl-3-isopropyl-8-benzyl-1,3,8-triazaspiro[4,5]-decane-2,4-dione (11au). ^{1}HNMR (CDCl3) δ: 7.35−7.24 (m, 8H), 6.92−6.88 (m, 2H), 3.68−3.54 (m, 3H), 2.82−2.74 (m, 5H), 2.48−2.33 (m, 7H), 1.94−1.89 (m, 4H). ^{13}-CNMR (CDCl3) δ: 175.07, 154.94, 143.31, 137.95, 129.26, 128.98, 128.89, 128.32, 127.29, 127.21, 120.85, 120.69, 117.72, 62.62, 61.94, 52.89, 49.26, 41.28, 36.06. LC/MS: 378.21 $[M + H]^+$; calcd 377.21. Purity = 71.5%; yield = 100.0%.

1-Phenyl-3-trifluoro-*m*-tolyl-8-benzyl-1,3,8-triazaspiro-[4,5]decane-2,4-dione (11av). ^{1}HNMR ($CDCl_3$) δ: 7.83 (s, 1H), 7.74−7.72 (d, 1H), 7.61−7.58 (m, 3H), 7.49−7.40 (m, 4H), 7.32−7.21 (m, 4H), 3.55 (s, 2H), 2.89−2.79 (m, 4H), 2.07−2.00 (m, 4H). ^{13}CNMR ($CDCl_3$) δ: 175.07, 153.00, 130.72, 129.82, 129.57, 129.53, 129.32, 129.13, 128.29, 127.21, 62.62, 48.28, 32.32. LC/MS: 480.15 $[M + H]^+$; calcd, 479.18. $Purity_{UV220}$ = 79.6%; yield = 100.0%.

1-Phenyl-3-(3-chlorophenyl)-8-methyl-1,3,8-triazaspiro-[4,5]decane-2,4-dione (12ax). ^{1}HNMR ($CDCl_3$) δ: 7.55−6.97 (m, 9H), 3.75−3.52 (m, 4H), 2.91−2.81 (m, 3H), 2.21−2.07 (m, 4H). LC/MS: 370.02 $[M + H]^+$; calcd 369.12. Purity = 84.0%; yield = 39.9%.

1-Phenyl-3-(2,4-difluorophenyl)-8-phenethyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (10bh). ^{1}HNMR ($CDCl_3$) δ: 7.87−7.85 (m, 3H), 7.29−7.19 (m, 5H), 6.94−6.91 (d, 2H), 6.79 (s, 1H), 6.49−6.46 (m, 3H), 3.83−3.70 (m, 4H), 2.90−2.50 (m, 6H), 2.47−2.15 (m, 2H). ^{13}CNMR ($CDCl_3$) δ: 175.07, 156.33, 153.55, 150.36, 140.00, 129.31, 128.66, 128.43, 126.15, 121.75, 121.29, 117.77, 103.98, 98.88, 59.91, 55.66, 53.08, 49.35, 41.24, 36.10, 33.72. LC/MS: 462.34 $[M + H]^+$; calcd, 461.19. Purity = 74.0%; yield = 45.5%.

1-Phenyl-3-(2-phenoxyphenyl)-8-benzyl-1,3,8-triazaspiro-[4,5]decane-2,4-dione (11bi). ^{1}HNMR ($CDCl_3$) δ: 8.18−8.16 (d, 2H), 7.33−7.29 (m, 4H), 7.15−7.07 (m, 6H), 6.98−6.95 (m, 5H), 6.85−6.82 (d, 2H), 3.75 (s, 2H), 2.78−2.58 (m, 2H), 1.58−1.26 (m, 6H). LC/MS: 503.93 $[M + H]^+$; calcd, 503.22. $Purity_{UV220}$ = 73.0%; yield = 45.7%.

1-Phenyl-3-[4-chloro-2-(trifluoromethyl)phenyl]-8-phenethyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (10bk). ^{1}-HNMR ($CDCl_3$) δ: 7.82 (s, 1H), 7.72−7.70 (d, 1H), 7.53−7.50 (m, 3H), 7.40−7.38 (bd, 1H), 7.32−7.20 (m, 7H), 3.64−3.51 (m, 4H), 2.42−2.39 (d, 4H), 2.23−2.08 (bd, 4H). LC/MS: 528.22 $[M + H]^+$; calcd 527.16. $Purity_{UV220}$ = 74.0%; yield = 100.0%.

1-Phenyl-3-(2,4-dimethoxyphenyl)-8-phenethyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (10bl). ^{1}HNMR ($CDCl_3$) δ: 7.46−6.90 (m, 13H), 3.80−3.20 (m, 5H), 2.96−2.00 (m, 13H). ^{13}CNMR ($CDCl_3$) δ: 180.96, 162.44, 158.47, 143.18, 131.25, 129.33, 128.66, 128.49, 126.27, 121.06, 117.85, 112.33, 59.72, 53.54, 52.98, 49.23, 41.66, 41.08, 35.73, 33.33, 27.69. LC/MS: 486.34 $[M + H]^+$; calcd, 485.23. Purity = 65.0%; yield = 98.5%.

1-Phenyl-3-(2,5-difluorophenyl)-8-methyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (12bo). ^{1}HNMR ($CDCl_3$) δ: 7.44−6.58 (m, 8H), 3.71−3.50 (m, 4H), 2.77 (s, 3H), 2.51−2.00 (m, 4H). LC/MS: 372.03 $[M + H]^+$; calcd, 371.14. Purity = 80.3%; yield = 100.0%.

1-Phenyl-3-(*trans*-2-phenylcyclopropyl)-8-methyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (12bp). ^{1}HNMR ($CDCl_3$) δ: 7.47−7.44 (m, 2H), 7.30−7.07 (m, 8H), 3.72−3.39 (m, 3H), 2.80−2.58 (m, 4H), 2.02−1.99 (m, 2H), 1.70−1.51 (m, 2H), 1.30−1.15 (m, 2H). LC/MS: 376.12 $[M + H]^+$; calcd, 375.19. Purity = 84.0%; yield = 99.0%.

1-Phenyl-3-(ethyl-2-acetate)-8-benzyl-1,3,8-triazaspiro-[4,5]decane-2,4-dione (11bu). ^{1}HNMR ($CDCl_3$) δ: 7.59−6.67 (m, 10H), 4.30−4.00 (m, 4H), 3.15−2.55 (m, 9H), 1.30−1.25 (m, 3H). LC/MS: 422.90 $[M + H]^+$; calcd, 421.20. $Purity_{UV220}$ = 72.0%; yield = 54.1%.

1-Phenyl-3-(ethyl-2-acetate)-8-methyl-1,3,8-triazaspiro-[4,5]decane-2,4-dione (12bu). ^{1}HNMR ($CDCl_3$) δ: 7.42−7.40 (m, 3H), 7.19−7.17 (bd, 2H), 4.30−4.20 (m, 2H), 3.96−3.93 (m, 2H), 2.77−2.68 (m, 4H), 2.29 (s, 3H), 2.00−1.92 (m, 4H), 1.30−1.25 (t, 3H). ^{13}CNMR ($CDCl_3$) δ: 174.97, 167.19, 132.68, 130.77, 129.60, 129.15, 62.73, 61.91, 50.61, 45.68, 42.18, 39.38, 31.96, 14.11. LC/MS: 346.04 $[M + H]^+$; calcd 345.17. $Purity_{UV220}$ = 90.0%; yield = 87.2%.

1-Phenyl-3-(4-chloro-3-(trifluoromethyl)phenyl)-8-benzyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (11by). ^{1}HNMR ($CDCl_3$) δ: 7.61−7.50 (m, 2H), 7.37−7.32 (m, 3H), 7.24 (s, 1H), 7.22 (s, 1H), 6.97−6.93 (m, 3H), 6.75−6.72 (m, 2H), 3.85 (s, 2H), 2.29−2.27 (m, 2H), 1.58−1.56 (m, 2H). LC/MS: 514.14 $[M + H]^+$; calcd, 513.14. $Purity_{UV220}$ = 83.1%; yield = 100.0%.

1-Phenyl-3-(4-bromo-3-methylphenyl)-8-phenethyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (10bz). ^{1}HNMR ($CDCl_3$) δ: 7.65−7.63 (d, 2H), 7.51−7.00 (m, 11H), 3.50−3.39 (m, 4H), 2.67−2.66 (m, 4H), 2.43 (s, 3H), 2.35−2.14 (m, 4H). LC/MS: 518.21/520.23 $[M + H]^+$; calcd, 517.14/519.21. $Purity_{UV220}$ = 99.0%; yield = 99.1%.

1-Phenyl-3-furfuryl-8-benzyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (11ca). ^{1}HNMR ($CDCl_3$) δ: 8.18−8.16 (d, 2H), 7.34−7.30 (m, 3H), 7.25 (s, 1H), 7.13−7.10 (m, 3H), 6.98−6.95 (m, 3H), 6.85−6.82 (d, 1H), 5.30 (s, 2H), 3.65 (s, 2H), 2.22 (m, 2H), 1.58−1.26 (m, 6H). LC/MS: 415.97 $[M + H]^+$; calcd, 415.19. $Purity_{UV220}$ = 89.0%; yield = 100.0%.

1-Phenyl-3-(5-indanyl)-8-benzyl-1,3,8-triazaspiro[4,5]-decane-2,4-dione (11cb). ^{1}HNMR ($CDCl_3$) δ: 7.34−7.03

(m, 10H), 6.41 (m, 3H), 2.90−2.85 (m, 6H), 2.09−2.07 (m, 4H), 1.57−1.25 (m, 6H). LC/MS: 452.00 $[M + H]^+$; calcd, 451.23. Purity = 99.0%; yield = 78.5%.

1-Phenyl-3-[3,4-(methylenedioxy)phenyl]-8-benzyl-1,3,8-triazaspiro[4,5]decane-2,4-dione (11cc). ^{1}HNMR ($CDCl_3$) δ: 7.34−7.25 (m, 10H), 6.92−6.89 (m, 3H), 5.88 (s, 2H), 3.55 (s, 2H), 2.83−2.75 (m, 2H), 2.50−2.35 (m, 4H), 1.96−1.71 (m, 2H). ^{13}CNMR ($CDCl_3$) δ: 175.07, 153.00, 144.85, 129.29, 129.00, 128.38, 127.25, 120.94, 117.80, 62.61, 49.29, 36.11. LC/MS: 456.13 $[M + H]^+$; calcd, 455.18. $Purity_{UV220}$ = 82.5%; yield = 100.0%.

1-Phenyl-3-(1-naphthyl)-8-benzyl-1,3,8-triazaspiro[4,5]-decane-2,4-dione (11cd). ^{1}HNMR ($CDCl_3$) δ: 8.21−7.70 (m, 2H), 7.60−7.14 (m, 12H), 6.93−6.81 (m, 3H), 4.19 (s, 2H), 3.52−2.00 (m, 8H). LC/MS: 462.13 $[M + H]^+$; calcd, 461.21. Purity = 64.8%; yield = 52.7%.

1-Phenyl-3-benzenesulfonyl-8-benzyl-1,3,8-triazaspiro-[4,5]decane-2,4-dione (11ce). ^{1}HNMR ($CDCl_3$) δ: 8.16−8.14 (d, 2H), 7.90−7.88 (d, 2H), 7.73−7.71 (m, 1H), 7.64−7.32 (m, 8H), 7.09−7.05 (m, 2H), 4.11 (s, 2H), 3.40−3.36 (m, 4H), 2.52−2.50 (m, 2H), 2.03−2.00 (d, 2H). ^{13}CNMR ($CDCl_3$) δ: 175.00, 134.99, 130.60, 129.75, 129.40, 128.90, 128.68, 62.07, 50.30, 45.30, 31.59. LC/MS: 476.12 $[M + H]^+$; calcd, 475.16. $Purity_{UV220}$ = 87.7%; yield = 97.6%.

1-Phenyl-3-benzenesulfonyl-8-methyl-1,3,8-triazaspiro-[4,5]decane-2,4-dione (12ce). ^{1}HNMR ($CDCl_3$) δ: 8.20−8.18 (d, 2H), 7.98−7.96 (d, 1H), 7.75−7.71 (m, 1H), 7.62−7.58 (m, 3H), 7.52−7.49 (m, 1H), 7.43−7.40 (m, 3H), 7.12−7.10 (m, 2H), 2.83−2.81 (d, 2H), 2.35 (s, 3H), 2.03−1.87 (m, 6H). ^{13}CNMR ($CDCl_3$) δ: 175.00, 134.99, 130.60, 129.75, 129.40, 128.90, 128.68, 62.07, 50.30, 45.30, 31.59. LC/MS: 400.07 $[M + H]^+$; calcd, 399.13. $Purity_{UV220}$ = 93.0%; yield = 78.5%.

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Supporting Information Available. NMR and mass spectral data. This material is available free of charge via the Web at http://pubs.acs.org.

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