One-Pot Synthesis of New Fused 4,5-Bridged 1,2,5-Triazepine-3,6-diones, 1,2,5-Triazepine-3,7-diones Heterocycles by Petasis Reaction

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The one pot synthesis of a new fused 1,2,5-triazepine-3,6-diones, 1,2,5-triazepine-3,7-diones heterocyles has been described via Petasis reactions. These heterocycles might be suitable for elaboration into larger peptides at amino termini. The scope and limitations of this method have been examined.

Introduction

With the recent emergence of combinatorial chemistry and high speed parallel synthesis in the lead discovery arena, the multicomponent reaction (MCR) has witnessed a resurgence of interest.[1] Easily automated one-pot reactions, such as Ugi,[2] Passerini,[3] Petasis[4] reactions are powerful tools for producing diverse arrays of compounds, often in one step and high yield. The Petasis Boronic Acid-Mannich reaction which provides a powerful and convenient method for the preparation of α-amino acids[4] is also quite useful for the synthesis of combinatorial libraries. In earlier studies, it was shown that hydrazine can participate in the Petasis Boronic Acid-Mannich reaction to afford various α-hydrazinocarboxylic acids.[5] Because of our interests in the synthesis of combinatorial libraries of heterocycles for drug discovery,[6,7] we have investigated further the scope and limitations of using substituted hydrazines in the Petasis Boronic Acid-Mannich reaction. Within this context, we wished to apply the strategy more broadly to the preparation of heterocycles, that is, drug like chemical collections, for high throughput biological screening. Herein, we report a practical method for the synthesis of 4,5-bridged 1,2,5-triazepine-3,6-diones, 1,2,5-triazepine 3,7-diones heterocyles via multicomponent condensation reactions in one pot. However, there is no literature report available for the synthesis of 1,2,5-triazepine-3,6-diones **2**, **6** and 1,2,5-triazepine-3,7-diones **4** via Petasis reaction.

Unlike the other 19 common amino acids, which predominantly assume *trans*-amide conformations when incorporated into peptides and proteins, proline amides display an equal tendency to assume both the *cis*- (**I**) and *trans*-amide (**II**) conformation.[8] Because only proline amides possess this conformational flexibility, it has been speculated that *cis-trans* proline isomerization plays many important biochemical roles, including controlling the rate of protein folding,[9] triggering receptor-mediated transmembrane signaling,[10] providing a recognition element in peptide antigens,[11] and regulating both the activation and breakdown of peptide hormones.[12] Proline is unique among proteogenic amino acids in possessing a secondary amino group. Acyl prolines possess no amide hydrogen atoms and, therefore, the energies of the *cis*- and *trans*-isomeric forms are similar.[13] In nature, the Xaa- Pro peptide (Xaa = any proteinogenic amino acid) bond can exist in both stable conformations, structure **I** and **II**, and both forms occur in proteins as in ribonuclease,[14] and in bioactive peptides, such as bradykinin.[15a]

It was reported that some proline-containing bioactive peptides including angiotensin and thyroliberin are believed to bind to their receptor with the Pro residue fixed in the *cis*-form.[15b]

Robinson et. al reported the synthesis of dipeptide *cis*-Gly-Pro (**III**)[16] which is expected to mimic **VI** turn.

Curran et. al reported the synthesis of bicyclic dipeptides having constrained *cis*-proline amides (**IV**).[17]

Gani et al. reported the synthesis of new fused 1,2,5-triazepine-1,5-dione heterocycles (**V** and **VI**)[18a,b] which is expected to mimic structural features of *cis*-peptidyl prolinamides which might be used as reverse turn mimetic in the design of biologically active molecules that need to emulate features of the common β-turn motifs (e.g., type **I**, **II**, **IV**).

β-Turns are not only important structural features in protein secondary structures but are implicated in the receptor bound conformations of many bioactive peptides.[15a,18−20] Work on the synthesis of systems designed to mimic the various types of β-turns include indole derivatives,[21] α-alkylated aspartic and glutamic acids,[22] azanorbornane derivatives,[23] and acetylenes.[24,25]

It is also well-known that benzodiazepine diones (compound **VII**) constitute an important class of bioactive compounds. Members of this class have been identified as platelet aggregation inhibiting mimics of the argentine-glycine-aspartic acid (RGD) peptide sequence, as anticonvulsant agents, as anxiolytic agents, and as antitumor compounds.[26]

Because of a lack of a general synthetic method may have precluded a comprehensive biological evaluation of this

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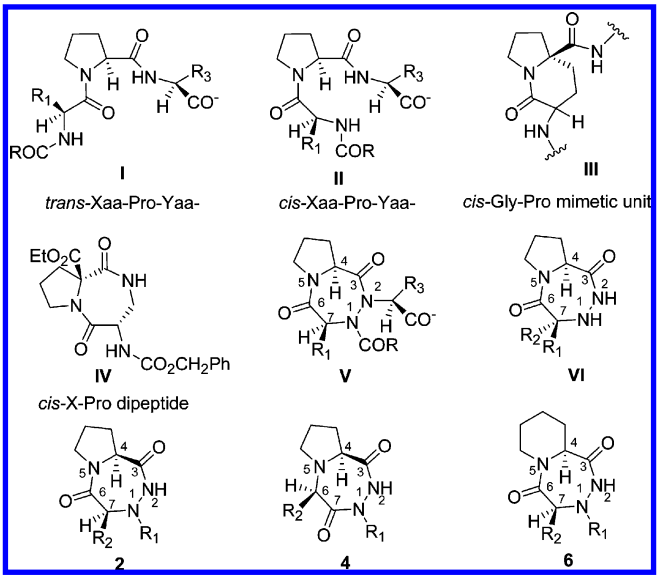
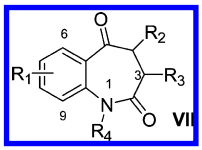




interesting structural class of compounds for these new fused 1,2,5-triazepine-3,6-diones, 1,2,5-triazepine-3,7-diones derivatives, herein, we report an efficient synthesis of 4,5-bridged 1,2,5-triazepine-3,6-diones, and 4,5-bridged 1,2,5-triazepine-3,7-diones derivatives via multicomponent condensation reactions in one pot (Tables 1, 2, and 3).

Result and Discussion

A variety of N-1-Boc-N-2-(alkyl)-hydrazines[5] (Figure 1) were subjected to Petasis three component condensation reaction in the presence of glyoxylic acid monohydrate and a variety of boronic acids (Figure 2) in dichloromethane (DCM) for 24 h, coupling with L-proline methyl ester hydrochloride in the presence of HBTU/DIEA, Boc deprotection using 4 M HCl in 1,4-dioaxne and upon evaporation of the crude reaction mixture which was then cyclized in presence of toluene/HOAc/reflux overnight (Table 1).

Similarly, L-proline methylesterhydrochloride was subjected to Petasis, coupling with a variety of N-1-Boc-N-2-(alkyl)-hydrazines, de-Boc and cyclization conditions (Table 2).

Also, N-1-Boc-N-2-benzyl hydrazine was subjected to Petasis, coupling with pipecolic acid methyl ester hydrochloride, de-Boc and cyclization conditions (Table 3).

In Table 1; when R_1 = Bn and R_2 = aryl (**2a**-**2c**), these reactions proceeded in moderate yields affording 42−50% of the corresponding 4,5-bridged 1,2,5-triazepine-3,6-diones after purification by high-performance liquid chromatography (HPLC). It is also interesting that when R_2 = heterocyclic (**2d**), the reaction afforded 36% yield of the desired product after purification. When R_1 = cyclohexyl and R_2 = aryl (**2e**-**2f**), these reactions proceeded in moderate yields affording 43−48% of the corresponding 4,5-bridged 1,2,5-triazepine-3,6-diones after purification by HPLC. It is to be noted that when R_1 = CH_2CO_2Me, and R_2 = naphthyl (**2g**), this reaction afforded 45% yield of the desired product after purification. When R_1 = substituted phenyl and Bn and R_2 = substituted aryl (**2h**-**2m**), these reactions proceeded in moderate yields affording 39−54% of the corresponding 4,5-bridged 1,2,5-triazepine-3,6-diones after purification by HPLC. As expected, the product consisted of a 50:50 mixture of racemic diastereomers (liquid chromatography mass spectroscopy, LCMS). In the example **2a**, the racemic diastereomers (1:1) were separated by preparative HPLC and characterized by LCMS, ^{1}H NMR, ^{13}C NMR, and high resolution mass spectrometry (HRMS) [**2a(A)** and **2a(B)**]. In the example **2m** also, the racemic diastereomers (1:1) were separated by preparative HPLC and characterized by LCMS, ^{1}H NMR, ^{13}C NMR, and CHN [**2 m(A)** and **2 m(B)**]. It is noteworthy that the reactions proceed through the Petasis, coupling, de-Boc, and cyclization in one pot without purification until the final product (**2**) is isolated. (Table 1; Figure 3).

In Table 2; when R_1 = Bn, and R_2 = naphthyl, aryl (**4a**-**4b**), these reactions proceeded in moderate yields ranging from 34−48% of the corresponding 4,5-bridged 1,2,5-triazepine-3,7-diones after purification by HPLC. When R_1 = cyclohexyl, and R_2 = aryl, (**4c**-**4d**), these reactions proceeded in 32% yields of the desired product after purification. As expected, the product consisted of a 50:50 mixture of racemic diastereomers (LCMS). In the example **4a**, the racemic diastereomers (1:1) were separated by preparative HPLC and characterized by LCMS, ^{1}H NMR, ^{13}C NMR, and HRMS/CHN [**4a(A)** and **4a(B)**]. Similar to the above reaction, the reactions proceed through the Petasis, coupling, de-Boc, and cyclization in one pot without purification until the final product (**4**) is isolated (Table 2; Figure 3).

In Table 3; when R_1 = Bn, and R_2 = aryl (**6a**-**6e**), these reactions proceeded in poor yields in one pot ranging from 25%−35% of the corresponding 4,5-bridged 1,2,5-triazepine-3,6-diones after purification by HPLC. The reactions proceed through the Petasis, coupling, de-Boc, and cyclization in one pot without purification until the final product (**6**) is isolated (Table 3; Figure 3).

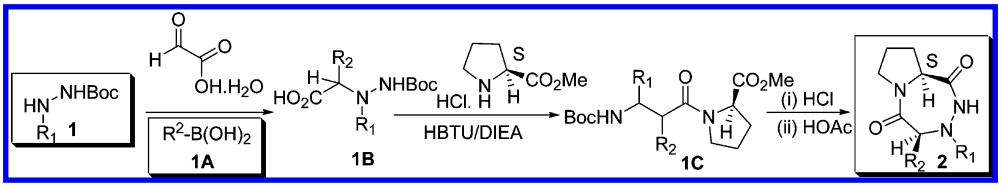
Conclusion

In summary, we have demonstrated that an efficient synthesis of 4,5-bridged 1,2,5-triazepine-3,6-diones, and 4,5-bridged 1,2,5-triazepine-3,7-diones heterocycles have been developed from N-1-Boc-N-2-(alkyl/phenyl substituted)-hydrazines utilizing multicomponent condensation reactions in one pot. All these compounds are having two/three points of diversity, and these heterocycles might be further suitable for elaboration into larger peptides at amino termini. To the best of our knowledge these compounds have not been synthesized previously.

Experimental Section

General Procedure for the Synthesis of 4,5-Bridged 1,2,5-Triazepine-3,6-diones 2 (Table 1). To a stirred mixture of glyoxylic acid monohydrate (184 mg, 2 mmol) in DCM (5 mL) was added N-1-Boc-N-2-(benzyl)-hydrazine (446 mg, 2 mmol) followed by *p*-methoxyphenyl boronic acid (304 mg, 2 mmol). The resulting mixture was stirred at

Table 1. Synthesis of 4,5-Bridged 1,2,5-Triazepine-3,6-diones



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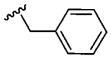
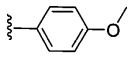
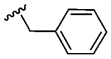
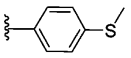
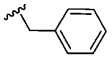
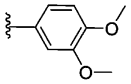
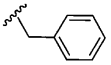
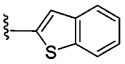
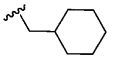
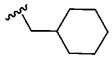
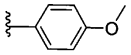
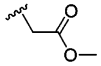
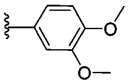
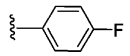
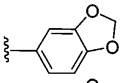
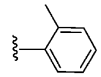
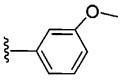
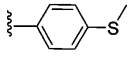
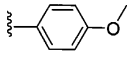
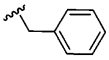
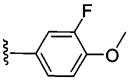
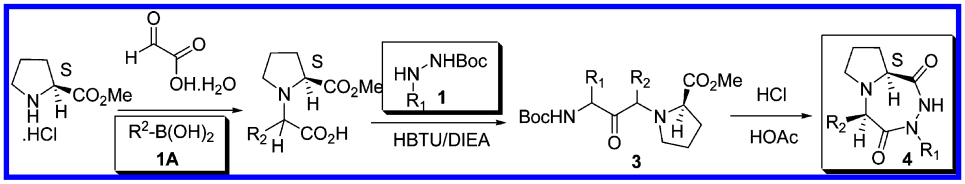
2a			42
2b			50
2c			45
2d			36
2e			48
2f			43
2g			45
2h			40
2i			46
2j			44
2k			39
2l			43
2m			54

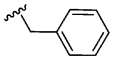
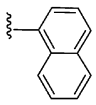
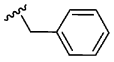
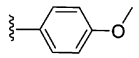
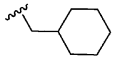
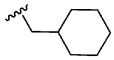
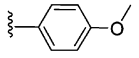
[a] All yields refer to pure, isolated products; the reactions proceed through the Petasis, coupling, de-Boc, and cyclization in one pot without purification until the final product (**2**) is isolated. All compounds have been characterized by LC-MS, ^{1}H NMR, ^{13}C NMR, and HRMS.

ambient temperature for 24 h, and to this solution were added L-proline methyl ester hydrochloride (331 mg, 2 mmol), HBTU (759 mg, 2 mmol), DIEA (774 mg, 6 mmol); the reaction mixture was stirred at ambient temperature for 4 h, and after this time, the solvent was removed and dried under reduced pressure. To this reaction mixture was added 4.0 M HCl (4 mL) in dioxane. The resulting mixture was stirred at ambient temperature for 3 h. The solvent was evaporated and dried under reduced pressure. To a solution of this reaction mixture in toluene (20 mL) was added HOAc (0.20 mL) and refluxed for overnight. The solvent was removed and the crude product was purified by HPLC to afford 310 mg (42%) of **2a** as a white solid. The diastereomers (**A** and **B**) have been separated by preparative HPLC; [Polaris C18 column (250 × 500 mm, 10 μm particle size), mobile phase 0.1% aqueous TFA/CH_3CN linear gradient over 55 min, 6.0 mL/min]; analytical HPLC: Polaris C18 column (4.6 × 250 mm, 3 μm particle size), mobile phase 0.1% aqueous phosphoric acid/CH3CN linear gradient over 30 min, 1 mL/min, one peak detected by ELS and UV at 220 nm, t_R = 5.64 (**A**) and another peak detected by ELS and UV at 220 nm, t_R = 7.66 (**B**).

2a(A). White solid, m.p (Met-TempII): 108°−109 °C (uncorrected); $[\alpha]_D$ −30.90 (c = 0.488, $CHCl_3$, at 20 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.86−2.14 (m, 3H), 2.63 (m, 1H), 3.42 (m, 1H), 3.53 (d, J = 14.1 Hz, 1H), 3.75 (m, 1H), 3.84 (s, 3H), 3.98 (d, J = 14.4 Hz, 1H), 4.56 (s, 1H), 5.46 (m, 1H), 6.80 (br. s, 1H), 6.99 (d, J = 8.7 Hz, 2H), 7.21 (m, 2H), 7.34 (m, 3H), 7.53 (d, J = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.88, 29.23, 48.55, 55.73, 57.32, 75.96, 115.11, 128.45, 129.17, 129.83, 130.19, 131.39, 135.36, 160.38, 169.79, 172.57; LCMS (ELSD): 366.1

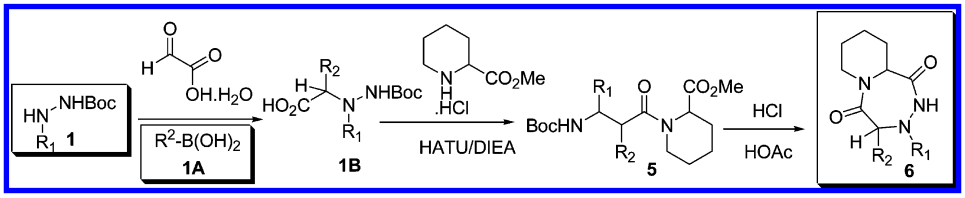
Table 2. Synthesis of 4,5-Bridged 1,2,5-Triazepine-3,7-diones

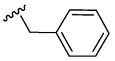
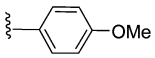
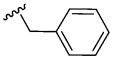
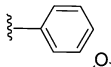
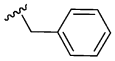
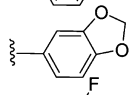
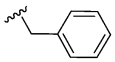
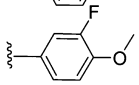
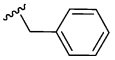
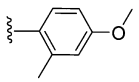


Product	R_1	R_2	Yield(%)[a]
4a			48
4b			34
4c			32
4d			32

[a] All yields refer to pure, isolated products; the reactions proceed through the Petasis, coupling, de-Boc, and cyclization in one pot without purification until the final product (**4**) is isolated. All compounds have been characterized by LC-MS, ^{1}H NMR, ^{13}C NMR, and HRMS.

Table 3. Synthesis of 4,5-Bridged 1,2,5-Triazepine-3,6-diones



Product	R_1	R_2	Yield(%)[a]
6a			26
6b			25
6c			35
6d			32
6e			27

[a] All yields refer to pure, isolated products; the reactions proceed through the Petasis, coupling, de-Boc, and cyclization in one pot without purification until the final product (**6**) is isolated. All compounds have been characterized by LC-MS, ^{1}H NMR, and ^{13}C NMR.

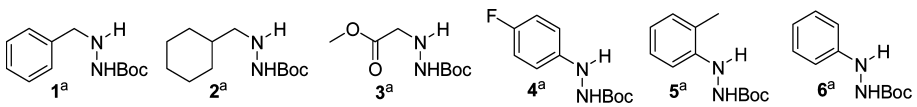


Figure 1. Diversity reagents **1**.

(M+H$^+$); HRMS: 366.180917 [Calcd for $C_{21}H_{24}N_3O_3$ 366.181767 (M+H)$^+$].

2a(B). White solid, m.p (Met-TempII): 179°−180 °C (uncorrected); $[\alpha]_D$ −29.959 (c = 0.484, $CHCl_3$, at 20 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.92−2.2 (m, 3H), 2.64 (m, 1H), 3.67 (m, 1H), 3.72 (d, J = 13.2 Hz, 1H), 3.77 (m, 1H), 3.85 (s, 3H), 3.93 (d, J = 12.9 Hz, 1H), 4.79 (s, 1H), 5.14 (m, 1H), 6.13 (br. s, 1H), 6.96 (d, J = 9 Hz, 2H), 7.04 (d, J = 9 Hz, 2H), 7.29−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.80, 27.83, 48.95, 55.72, 58.60, 58.97, 70.91, 114.65, 124.34, 128.62, 129.29, 129.32, 131.07, 132.97, 160.20, 169.09, 171.49; LCMS (ELSD): 366.1 (M+H$^+$); HRMS: 366.180545 [Calcd for $C_{21}H_{24}N_3O_3$ 366.181767 (M+H)$^+$].

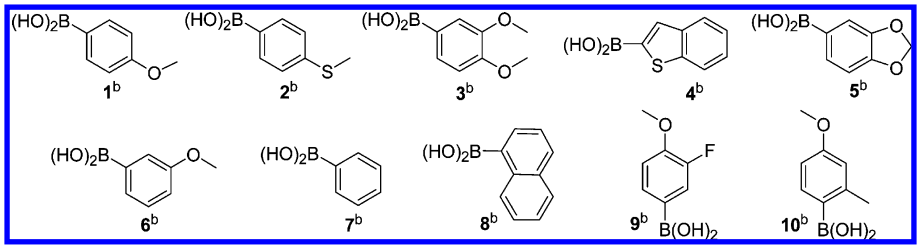


Figure 2. Diversity reagents **1A**.

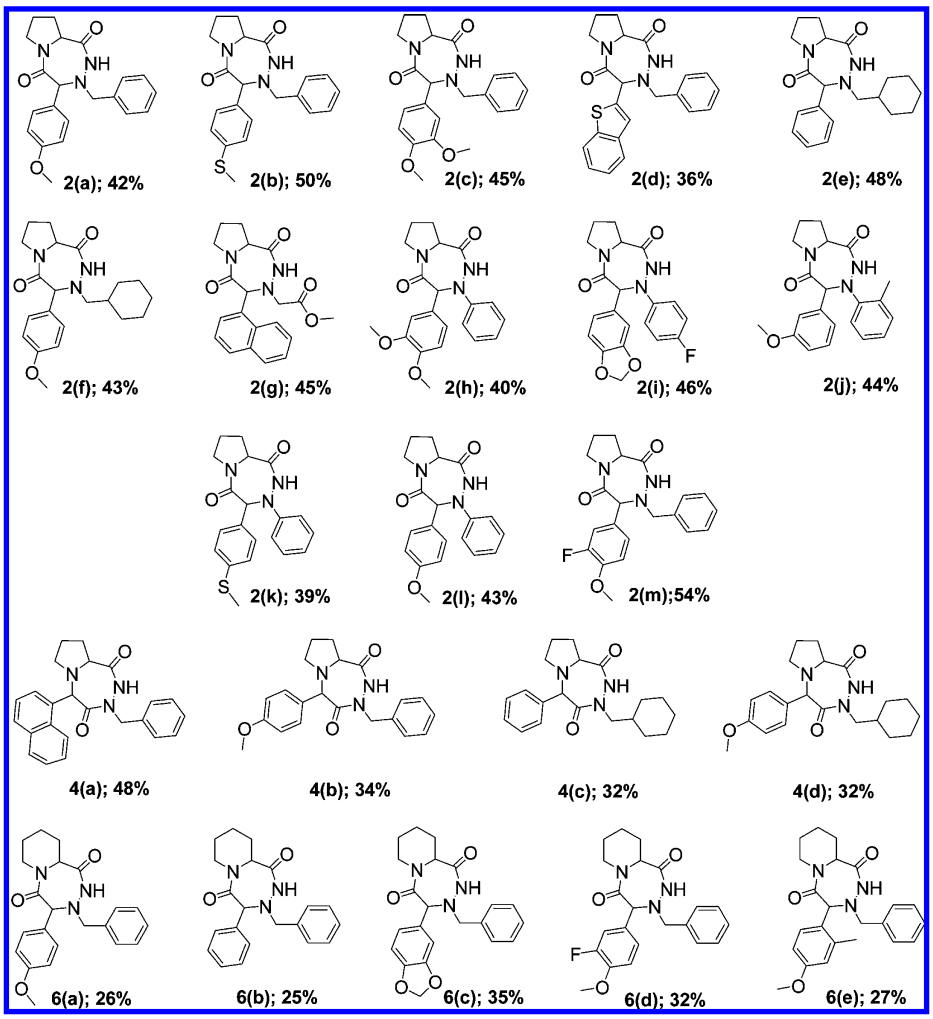


Figure 3. New fused 4,5-bridged 1,2,5-triazepine-3,6-diones, 1,2,5-triazepine-3,7-diones heterocycles.

2b. White Solid; m.p (Met-Temp): 178°−179 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.87−1.93 (m, 3H), 2.52 (s, 3H), 2.55 (m, 1H), 3.44 (m, 1H), 3.54 (d, J = 14.1 Hz, 1H), 3.73 (m, 1H), 3.99 (d, J = 14.1 Hz, 1H), 4.57 (s, 1H), 5.45−5.48 (m, 1H), 6.63 (br. s, 1H), 7.19−7.22 (m, 2H), 7.3−7.35 (m, 5H); 7.53 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 15.98, 22.88, 26.9, 48.53, 57.3, 57.46, 76.13, 127.47, 128.52, 129.04, 129.19, 134.76, 135.09, 140.05, 169.2, 172.5; LCMS (ELSD): 381.9 ($M+H^+$); HRMS: 382.1581 [Calculated for $C_{21}H_{24}N_3O_2S$ 382.1589 $(M+H)^+$].

2c. White Solid; m.p (Met-Temp): 85°− 86 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.88−1.96 (m, 2H), 2.09−2.16 (m, 1H), 2.64 (m, 1H), 3.46 (m, 1H), 3.53 (d, J = 14.1 Hz, 1H), 3.77 (m, 1H), 3.93 (s, 3H), 3.96 (s, 3H), 4.02 (d, J = 14.1 Hz, 1H), 4.56 (s, 1H), 5.43−5.48 (m, 1H), 6.94−6.96 (m, 1H), 7.08 (s, 1H), 7.17−7.23 (m, 3H); 7.30−7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.89, 27.78, 49.02, 56.34, 56.46, 57.32, 57.44, 112.18, 117.61, 120.91, 121.22, 125.13, 128.43, 128.94, 129.09, 135.50, 149.92, 169.73, 172.85; LCMS (ESI): 396.1 ($M+H^+$); HRMS: 396.1921 [Calculated for $C_{22}H_{26}N_3O_4$ 396.1923 $(M+H)^+$].

2d. White Solid; m.p (Met-Temp): 223°−224 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.88−1.96 (m, 2H), 2.1−2.17 (m, 1H), 2.61 (m, 1H), 3.40−3.44 (m, 1H), 3.67−3.78 (m, 2H), 4.22 (d, J = 14.1 Hz, 1H), 5.06 (s, 1H), 5.44−5.48 (m, 1H), 6.88 (br. s, 1H), 7.29−7.41 (m, 7H), 7.60 (s, 1H), 7.80−7.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.89, 26.80, 48.58, 57.24, 57.66, 72.72, 122.85, 125.06, 125.23, 125.42, 125.58, 128.90, 129.01, 129.33, 134.77, 139.47, 140.13, 140.73, 168.5, 172.8; LCMS (ELSD): 392.1 ($M+H^+$); HRMS: 392.148332 [Calculated for $C_{22}H_{22}N_3O_2S$ 392.148874 $(M+H)^+$].

2e. White Solid; m.p (Met-Temp): 185°− 186 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.72 (m, 2H), 1.20−1.23 (m, 3H), 1.62−1.66 (m, 4H), 1.84−2.04 (m, 3H), 2.13−2.41 (m, 4H), 2.68 (m, 1H), 3.39−3.43 (m, 1H), 3.75−3.79 (m, 1H), 4.39 (s, 1H), 5.45−5.5 (m, 1H), 6.65 (br. s, 1H), 7.3−7.46 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 MHz): 22.91, 25.93, 26.03, 26.74, 26.91, 31.34, 31.43, 34.94, 46.09, 48.42, 57.14, 60.37, 126, 128.66, 129.07, 129.36, 129.59, 138.32, 169.68, 172.73; LCMS (ESI): 342.2 ($M+H^+$); HRMS: 342.2172 [Calculated for $C_{20}H_{28}N_3O_2$ 342.2182 $(M+H)^+$].

2f. White Solid; m.p (Met-Temp): 90°−91 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.66−0.78 (m, 2H), 1.05−1.23 (m, 3H),1.45−1.50 (m, 2H), 1.57−1.66 (m, 2H), 1.83−1.99 (m, 3H), 2.12−2.23 (m, 2H), 2.36−2.44 (m, 2H), 2.65−2.71 (m, 1H), 3.37−3.45 (m, 1H), 3.71−3.79 (m, 1H), 3.83 (s, 3H), 4.34 (s, 1H), 5.42−5.47 (m, 1H), 6.45 (br. s, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$,75 MHz): 22.91, 25.71, 25.95, 26.75, 26.92, 31.37, 31.48, 34.95, 48.42, 55.67, 57.15, 55.98, 60.35, 114.77, 129.74, 130.40, 133.21, 160.15, 169.96, 172.73: LCMS (ELSD): 372.1 ($M+H^+$); HRMS: 372.228179 [Calculated for $C_{21}H_{30}N_3O_3$ 372.228717 $(M+H)^+$].

2g. White Solid; m.p (Met-Temp): 181°−182 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.85−2.37 (m, 3H), 2.6−2.8 (m, 1H), 3.31(s, 3H), 3.55−3.61 (m, 1H), 3.79−3.91 (m, 3H), 5.25−5.45 (m, 1H), 5.75−5.98 (m, 1H), 7.01 (br s., 1H), 7.15 (m, 1H), 7.48−7.58 (m, 3H), 7.89−7.94 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.85, 27.87, 49.33, 52.25, 56.71, 58.68, 67.03, 122.61, 125.7, 126.25, 127.27, 127.81, 129.64, 129.85, 129.99, 132.79, 134.47, 169.80, 172.41; LCMS (ELSD): 368.1 ($M+H^+$); HRMS: 368.1604 [Calculated for $C_{20}H_{22}N_3O_4$ 368.1610 $(M+H)^+$].

2h. White solid; m.p (Met-Temp): 73°−74 °C (uncorrected); $_1$H NMR ($CDCl_3$, 400 MHz): δ = 1.75 (m, 1H), 1.99−2.08 (m, 2H), 2.55−2.60 (m, 1H), 3.70−3.74 (m, 1H), 3.75 (s, 3H), 3.82 (s, 3H), 3.87−3.94 (m, 1H), 4.39−4.44 (m, 1H), 5.87 (s, 1H), 6.63 (s, 1H), 6.67−6.69 (d, J =8.2, 1H), 6.79−6.81 (d, J =8.28, 1H), 6.96−7.03 (m, 4H), 7.33−7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.07, 27.87, 48.71, 55.77, 57.83, 66.42, 111.19, 111.54, 112.76, 120.92, 121.17, 126.79, 129.92, 145.88, 149.12, 149.27, 168.89, 172.55; LCMS (UV): 382.1 ($M+H^+$). Anal. Calcd For $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found: C, 66.22; H, 6.12; N, 11.11.

2i. White solid; m.p (Met-Temp): 95°−96 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.86 (m, 1H), 2.02−2.11 (m, 2H), 2.57 (m, 1H), 3.70−3.75 (m, 1H), 3.81−3.84 (m, 1H), 4.47−4.51 (m, 1H), 5.81 (s, 1H), 5.95 (s, 2H), 6.57−6.59 (m, 2H), 6.74−6.76 (d, J = 8.44, 1H), 6.93−6.96 (m, 2H), 7.03−7.08 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.09, 27.82, 48.69, 57.80, 67.20, 101.33, 108.62, 108.74, 114.31, 116.35, 116.58, 122.16, 127.90, 142.11, 147.91, 148.10, 156.44, 158.84, 168.28, 172.50; LCMS (UV): 384.2 ($M+H^+$). Anal. Calcd for $C_{20}H_{18}FN_3O_4$: C, 62.66; H, 4.73; N, 10.96. Found: C, 62.73; H, 4.81; N, 10.89.

2j. White solid; m.p (Met-Temp): 78°−79 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.93 (m, 1H), 2.06−2.13 (m, 2H), 2.39 (s, 3H), 2.61 (m, 1H), 3.69 (s, 3H), 3.76−3.81 (m, 1H), 3.92−3.97 (m, 1H), 4.93−4.97 (m, 1H), 5.16 (s, 1H), 6.44 (s, 1H), 6.53−6.55 (d, J = 7.56, 1H), 6.61−6.63 (d, J = 7.6, 1H), 6.86−6.88 (d, J = 8.24, 1H), 7.10−7.15 (m, 2H), 7.22−7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 19.16, 22.38, 27.81, 48.69, 55.20, 58.34, 71.87, 114.22, 114.88, 119.75, 121.33, 125.22, 126.72, 129.85, 130.09, 132.10, 134.76, 145.43, 159.69, 168.60, 172.36; LCMS (UV): 366.2 ($M+H^+$). Anal. Calcd for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.14; H, 6.40; N, 11.55.

2k. White solid; m.p (Met-Temp): 189°−190 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.82−1.85 (m, 1H), 1.99−2.11 (m, 2H), 2.45 (s, 3H), 2.54−2.58 (m, 1H), 3.71−3.75 (m, 1H), 3.81−3.84 (m, 1H), 4.43−4.47 (m, 1H), 5.91 (s, 1H), 6.93 (s, 1H), 6.97−7.02 (m, 3H), 7.06−7.08 (d, J =8.32, 2H), 7.19−7.21 (d, J = 8.32, 2H), 7.33−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 17.94, 24.59, 30.36, 50.99, 60.02, 68.68, 115.11, 123.54, 129.16, 131.34, 132.38, 134.05, 141.79, 148.42, 170.31, 175.06; LCMS (UV): 368.2 ($M+H^+$). Anal. Calcd for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.44. Found: C, 65.32; H, 5.81; N, 11.38.

2l. White solid; m.p (Met-Temp): 69°−70 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.84−1.87 (m, 1H), 2.01−2.12 (m, 2H), 2.58−2.63 (m, 1H), 3.73−3.75 (m, 1H), 3.80 (s, 3H), 3.81−3.87 (m, 1H), 4.49−4.53 (m, 1H), 5.99 (s, 1H), 6.84 (s, 1H), 6.85−6.87 (m, 3H), 6.98−7.08 (m, 5H), 7.35−7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.16, 27.96, 48.57, 55.31, 57.67, 66.22, 112.71, 114.43, 121.03, 127.03, 129.74, 129.94, 146.08, 159.69, 168.31, 172.70; LCMS (UV): 352.2 ($M+H^+$). Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.23; H, 6.09; N, 11.88.

2m(A). White solid; m.p (Met-Temp): 85°−87 °C (uncorrected); $[\alpha]_D$ −18.52 (c = 0.866, CH_2Cl_2, at 20 °C); ^{1}HNMR ($CDCl_3$, 400 MHz): δ = 1.85−1.94 (m, 2H), 2.07−2.12 (m, 1H), 2.56−2.61 (m, 1H), 3.39−3.44 (m, 1H), 3.49−3.52 (m, 1H), 3.70−3.74 (m, 1H), 3.87 (s, 3H), 3.91−3.95 (m, 1H), 4.54 (s, 1H), 5.38−5.42 (m, 1H), 6.98−7.03 (m, 1H), 7.09 (s, 1H), 7.15−7.17 (d, J = 7.64, 2H), 7.26−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.44, 26.46, 48.26, 56.30, 56.92, 57.08, 75.17, 113.90, 124.83, 128.23, 128.77, 128.87, 130.18, 134.49, 148.19, 148.30, 151.42, 153.88, 168.86, 172.14; LCMS (UV): 384.2 ($M+H^+$). Anal. Calcd for $C_{21}H_{22}FN_3O_3$: C, 65.78; H, 5.78; N, 10.96. Found: C, 65.69; H, 5.75; N, 10.83.

2m(B). White solid; m.p (Met-Temp): 80°−82 °C (uncorrected); $[\alpha]_D$ −49.25 (c = 0.944, $CHCl_3$, at 20 °C); ^{1}HNMR ($CDCl_3$, 400 MHz): δ = 1.89−1.93 (m, 1H), 1.99−2.02 (m, 1H), 2.08−2.13 (m, 1H), 2.53−2.58 (m, 1H), 3.66−3.77 (m, 3H), 3.88 (s, 3H), 3.90−3.91 (m, 1H), 4.78 (s, 1H), 5.08−5.12 (m, 1H), 6.74 (s, 1H), 6.78−6.86 (m, 2H), 6.97−7.01 (m, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.38, 27.37, 48.59, 56.30, 58.14, 58.48, 70.10, 113.90, 117.54, 124.89, 125.88, 128.32, 128.91, 128.95, 135.07, 147.90, 148.01, 150.91, 153.38, 168.07, 171.03; LCMS (UV): 384.2 ($M+H^+$). Anal. Calcd for $C_{21}H_{22}FN_3O_3$: C, 65.78; H, 5.78; N, 10.96. Found: C, 65.74; H, 5.81; N, 10.99.

General Procedure for the Synthesis of 4,5-Bridged 1,2,5-Triazepine-3,7-diones 4 (Table 2). To a stirred

mixture of glyoxylic acid monohydrate (184 mg, 2 mmol) in DCM (5 mL) was added L-proline methyl esterhydrochloride (331 mg, 2 mmol) followed by *p*-methoxyphenyl boronic acid (304 mg, 2 mmol). The resulting mixture was stirred at ambient temperature for 24 h, and to this solution were added N-1-Boc-N-2-(benzyl)-hydrazine (446 mg, 2 mmol), HBTU (759 mg, 2 mmol), and DIEA (774 mg, 6 mmol). The reaction mixture was stirred at ambient temperature for 4 h, and after this time, the solvent was removed and dried under reduced pressure. To this reaction mixture was added 4.0 M HCl (4 mL) in dioxane. The resulting mixture was stirred at ambient temperature for 4 h. The solvent was evaporated and dried under reduced pressure. To a solution of this reaction mixture in toluene (20 mL) was added HOAc (0.20 mL) and refluxed for overnight. The solvent was removed, and the crude product was purified by HPLC to afford 251 mg (34%) of **4b** as a white solid.

4a(A). White solid; m.p (Met-Temp): 210°−211 °C (uncorrected); $[\alpha]_D$ +84.607 (c = 0.890, $CHCl_3$, at 20 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.78−2.14 (m, 3H), 2.36−2.41 (m, 1H), 2.91−2.99 (m, 1H), 3.18−3.24 (m, 1H), 3.41−3.45 (m, 1H), 4.58−4.72 (m, 2H), 5.65 (s, 1H), 6.62 (br s, 1H), 7.10−7.13 (m, 2H), 7.20−7.29 (m, 3H), 7.46−7.64 (m, 3H), 7.82 (d, J = 7.82 Hz, 2H), 7.91 (d, J = 9.3 Hz, 1H), 8.46 (d, J = 8.46 Hz, 1H); ^{13}C NMR($CDCl_3$, 75 MHz): 22.40, 23.06, 52.39, 52.44, 59.97, 61.47, 121.22, 125.46, 125.78, 126.51, 127.32, 128.78, 128.93, 129.13, 129.37, 129.44, 130.11, 131.31, 133.51; 133.71, 168.23, 169.82; LCMS (ELSD): 386 ($M+H^+$); HRMS: 386.185503 [Calculated for $C_{24}H_{24}N_3O_2$ 386.186852 $(M+H)^+$].

4a(B). White solid; m.p (Met-Temp): 215°−216 °C (uncorrected) $[\alpha]_D$ +93.171 (c = 0.946, $CHCl_3$, at 20 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.77−2.14 (m, 3H), 2.31−2.36 (m, 1H), 2.91−2.93 (m, 1H), 3.16−3.18 (m, 1H), 3.37−3.40 (m, 1H), 4.54−4.57 (m, 1H), 4.66−4.70 (m, 1H), 5.62 (s, 1H), 6.66 (br s, 1H), 7.10−7.11 (m, 2H), 7.19−7.27 (m, 3H), 7.44−7.61 (m, 3H), 7.77−7.83 (m, 2H), 7.88−7.90 (d, J = 7.92 Hz, 1H), 8.43−8.45 (d, J = 8.48 Hz, 1H); ^{13}C NMR($CDCl_3$, 100 MHz): 22.94, 24.42, 52.97, 54.03, 58.55, 68.23, 123.55, 124.51, 125.44, 125.66, 126.54, 128.41, 128.43, 128.48, 128.77, 128.87, 129.18, 130.85, 132.61, 133.75; 133.80, 169.84, 171.62; LCMS (ELSD): 386.2 ($M+H^+$); Anal. Calcd for $C_{24}H_{23}N_3O_2$: C, 74.78; H, 6.01; N, 10.90. Found: C, 74.69; H, 6.05; N, 10.92.

4b. White solid, m.p (Met-TempII): 64°−65 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.02 (m, 3H), 2.55 (m, 2H), 3.10 (m, 1H), 3.86 (s, 3H), 4.66 (m, 2H), 4.78 (m, 1H), 5.02 (d, J = 14.1 Hz, 1H), 6.99 (d, J = 7.5 Hz, 2H), 7.49 (m, 5H), 7.52 (d, J = 7.2 Hz, 2H), 8.21 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.35, 23.26, 52.18, 52.95, 55.29, 59.92, 65.45, 114.08, 125.04, 128.76, 129.13, 129.37; 131.08, 133.51, 160.41, 166.95, 168.31; LCMS (ELSD): 366 ($M+H^+$); HRMS: 366.181249 [Calcd for $C_{21}H_{24}N_3O_3$ 366.181767 $(M+H)^+$].

4c. Liquid; ^{1}H NMR ($CDCl_3$, 300 MHz):δ = 0.96−1.28 (m, 5H), 1.65−1.77 (m, 6H), 1.95−2.14 (m, 3H), 2.45 (m, 1H), 2.61 (m, 1H), 3.06 (m, 1H), 3.27 (m, 1H), 3.87 (m, 1H), 4.68 (s, 1H), 4.75 (m, 1H), 7.43−7.51 (m, 5H), 8.45 (br. s, 1H); ^{13}C NMR($CDCl_3$, 75 MHz): 22.56, 23.31, 25.48, 25.61, 26.07, 30.59, 31.04, 35.39, 52.94, 55.48, 60.15, 66.29, 116.59, 128.59, 129.29, 129.74, 133.71, 160.70; 167.39, 168.92; LCMS (ELSD): 342.2 ($M+H^+$);HRMS: 342.2167 [Calculated for $C_{20}H_{28}N_3O_2$ 342.2182 $(M+H)^+$].

4d. White Solid; m.p (Met-Temp): 89°−90 °C (uncorrected); ^{1}H NMR($CDCl_3$, 300 MHz):δ = 0.93−1.22 (m, 5H), 1.7−1.74 (m, 6H), 1.85−2.21 (m, 3H), 2.45 (m, 1H), 2.60 (m, 1H), 3.1(m, 1H), 3.21(m, 1H), 3.83 (s, 3H), 3.84 (m,1H), 4.61 (m, 1H), 4.72 (m, 1H), 6.95 (d, J = 9 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 8.4 (br. s, 1H); ^{13}CNMR($CDCl_3$, 75 MHz): 22.91, 23.76, 25.89, 26.03, 26.48, 30.98, 31.44, 35.81, 53.32, 55.7, 55.9, 60.42, 66.04, 114.43, 125.84, 131.44, 160.74, 167.84, 169.16; LCMS (ELSD): 372.1 ($M+H^+$); HRMS: 372.229450 [Calculated for $C_{21}H_{30}N_3O_3$ 372.228717 $(M+H)^+$].

General Procedure for the Synthesis of 4,5-Bridged 1,2,5-Triazepine-3,6-diones 6 (Table 3). To a stirred mixture of glyoxylic acid monohydrate (184 mg, 2 mmol) in DCM (5 mL) was added N-1-Boc-N-2-(benzyl)- hydrazine (446 mg, 2 mmol), followed by *p*-methoxyphenyl boronic acid (304 mg, 2 mmol). The resulting mixture was stirred at ambient temperature for 24 h, and to this solution were added pipecolic acid methyl ester hydrochloride (359 mg, 2 mmol), HATU (761 mg, 2 mmol), and DIEA (774 mg, 6 mmol). The reaction mixture was stirred at ambient temperature for 4 h, and after this time, the solvent was removed and dried under reduced pressure. To this reaction mixture was added 4.0 M HCl (6 mL) in dioxane. The resulting mixture was stirred at ambient temperature for 4 h. The solvent was evaporated and dried under reduced pressure. To a solution of this reaction mixture in toluene (20 mL) was added HOAc (0.20 mL) and refluxed for overnight. The solvent was removed and the crude product was purified by HPLC to afford 197 mg (26%) of **6a** as a white solid.

6a. White solid; m.p (Met-Temp): 220°−221 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.64−1.75 (m, 3H), 1.82−1.90 (m, 2H), 2.01−2.05 (m, 1H), 2.26−2.29 (m, 1H), 3.20−3.24 (m, 1H), 3.81 (s, 3H), 3.86−3.87 (m, 1H), 3.94 (m, 1H), 4.23 (m, 1H), 4.83 (m, 1H), 6.47 (br. s, 1H), 6.92 (d, J = 8.68 Hz, 2H), 7.23−7.27 (m, 2H), 7.30−7.36 (m, 5H); ^{13}C NMR($CDCl_3$, 100 MHz): 22.75, 24.58, 26.75, 44.02, 55.32, 58.32, 73.98, 74.03, 114.51, 128.18, 128.26, 128.87, 128.91, 129.02, 130.28, 159.89, 170.01, 172.06; LCMS (UV): 380.5 ($M+H^+$). Anal. Calcd for$C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.73; H, 6.69, N, 11.19.

6b. White solid; m.p (Met-Temp): 167°−168 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.70−1.76 (m, 3H), 1.82−1.84 (m, 2H), 1.87−1.91 (m, 1H), 2.29 (m, 1H), 3.22 (m, 1H), 3.85−3.88 (m, 1H), 3.96−3.99 (m, 1H), 4.23−4.25 (m, 1H), 4.89−4.92 (m, 1H), 6.53 (br. s, 1H), 7.3−7.43 (m, 10H); ^{13}C NMR($CDCl_3$, 100 MHz): 22.53, 24.42, 26.65, 43.81, 58.41, 62.01, 74.65, 128.20, 128.76, 128.79, 128.93, 128.96, 129.03, 134.47, 134.85, 169.73, 172.18; LCMS (UV): 350.2 ($M+H^+$). Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.15; H, 6.7, N, 12.11.

6c. White solid; m.p: (Met-Temp): 61°−62 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.68−1.77 (m,

3H), 1.85−1.89 (m, 1H), 2.03−2.05 (m, 1H), 2.24 (m, 1H), 3.26−3.28 (m, 1H), 3.81−3.88 (m, 1H), 3.96−3.99 (m, 1H), 4.17 (m, 1H), 4.67−4.78 (m, 1H), 4.86 (s, 1H), 5.98 (s, 2H), 6.68−6.85 (m, 3H), 7.17 (m, 1H), 7.27−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.35, 24.31, 26.47, 43.86, 58.19, 61.88, 74.27, 101.35, 108.42, 108.69, 122.78, 128.20, 128.26, 128.37, 128.67, 134.74, 148.09, 148.25, 169.96,172.30; LCMS (UV): 394.2 ($M+H^+$). Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 67.22; H, 5.85; N, 10.59.

6d. White solid; m.p: (Met-Temp): 80°−81 °C (uncorrected); $_1$H NMR ($CDCl_3$, 400 MHz): δ = 1.69−1.75 (m, 3H), 1.85−1.89 (m, 1H), 2.02−2.03 (m, 1H), 2.23−2.25 (m, 1H), 3.23−3.26 (m, 1H), 3.82−3.91 (m, 4H), 3.95−3.99 (m, 1H), 4.17−4.19 (m, 1H), 4.65−4.67 (m, 1H), 4.80 (s, 1H), 6.91−6.95 (m, 1H), 6.98−7.02 (m, 1H), 7.08−7.11 (m, 1H), 7.27−7.39 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.35, 24.32, 26.41, 43.97, 56.18, 58.23, 61.84, 73.73, 113.62, 116.42, 116.61, 125.07, 126.95, 128.32, 128.85, 128.95, 134.63, 148.04, 148.15, 151.10, 153.57, 169.65, 172.27; LCMS (UV): 398.2 ($M+H^+$). Anal. Calcd for $C_{22}H_{24}FN_3O_3$: C, 66.48; H, 6.09; N, 10.57. Found: C, 66.59; H, 6.15; N, 10.55.

6e. White solid; m.p (Met-Temp): 60°−61 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.61−1.74 (m, 3H), 2.04−2.06 (m, 1H), 2.46 (s, 3H), 2.49−2.55 (m, 2H), 3.68−3.3.70 (s, 1H), 3.77−3.80 (m, 4H), 3.96−4.02 (m, 2H), 4.61−4.62 (m, 1H), 5.19 (s, 1H), 6.72−6.78 (m, 3H), 6.93−6.95 (m, 1H), 7.22−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 20.05, 24.39, 24.54, 31.73, 42.42, 53.99, 55.19, 59.07, 62.46, 111.86, 116.55, 127.85, 128.45, 128.54, 128.70, 128.89, 136.85, 139.30, 159.24, 163.39, 165.86, 170.85, 173.18; LCMS (UV): 394.2 ($M+H^+$). Anal. Calcd for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.68. Found: C, 70.30; H, 6.89; N, 10.66.

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Supporting Information Available. Detailed experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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