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Facile Entry to 4,5,6,7-Tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-6-ones from Amines and Amino Acids

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Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

Keywords: Triazoles / Alkynes / Cycloaddition / Nitrogen heterocycles / Amino acids

A practical and high-yielding regioselective synthesis of several enantiopure 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]-pyrazin-6-ones is described starting from primary amines and α-amino acid derivatives in a three-step reaction sequence by employing a constrained intramolecular "click" reaction as the key step. The method obviates chromatographic purification of products.

Introduction

Huisgen 1,3-dipolar cycloaddition of an azide and an alkyne to afford the 1,2,3-triazole ring system has been widely used in organic synthesis.[1] Several compounds containing the 1,2,3-triazole structural motif possess a broad spectrum of biological properties like anti-HIV,[2a] antibacterial,[2b] antiallergic,[2c] herbicidal, fungicidal,[2d] and antihistamine activity.[3] With careful choice of appropriate building blocks, "click chemistry" can provide derivatives or mimics of traditional drugs, pharmacophores, and natural products.[4] Its ability lies in the generation of novel structures that might not necessarily resemble known pharmacophores. The Cu^{I}-catalyzed formation of 1,2,3-triazoles from azides and terminal acetylenes is a particularly powerful linking reaction because of its high degree of dependability and complete specificity, which generates regioselectively the 1,4-substituted ring system; this system is extensively used in an intermolecular[5] fashion for the synthesis of various conjugates[6a–6h] and in an intramolecular fashion for the synthesis of triazole-containing small peptides.[6i–6k] Ideally, an intramolecular reaction should provide a powerful method for the synthesis of structurally diversified analogs difficult to obtain by an intermolecular version, particularly to generate fused polycyclic triazole derivatives that should be of interest to medicinal chemists. Because of the emergence of combinatorial chemistry and high-speed parallel synthesis, the development of synthetic procedures that can be used to generate a library of compounds, especially the synthesis of target heterocycles in an enantiomerically pure form, is challenging. Ring-constrained intramolecular Huisgen cycloaddition has been used by many research groups to synthesize several bicyclic, as well as polycyclic, triazole-fused nitrogen-containing heterocycles, especially triazole-fused piperazine, pyrazine, and pyrazinone[7] derivatives and also in the synthesis of triazole-fused oxygen-rich heterocycles.[8]

Literature reports on 4,5,6,7-tetrahydro[1,2,3]triazolo-[1,5-*a*]pyrazin-6-ones are scarce[7a–7e] and these scaffolds remain relatively under-explored. Rohr et al. studied the herbicidal activity of a few triazole-fused pyrazinones.[7d] Recently, Pokorski et al. synthesized a 1,5-triazole-substituted amino acid (Tzl) by hydrolysis of triazole-fused tetrahydropyrazinone derived from bromoacetamide of propargylamine.[7e] Their focus was to study its effects upon the secondary structure of short peptoids. The significant biological profiles of 1,2,3-triazoles coupled with our interest in the development of short and versatile routes to a variety of novel heterocyclic structures, as well as the paucity of the literature for the synthesis of 4,5,6,7-tetrahydro[1,2,3]-triazolo[1,5-*a*]pyrazin-6-ones, stimulated us to develop a synthetic protocol that would generate a library of enantiopure, triazole-fused bicyclic compounds from easily available starting materials. Herein, we report a simple synthesis method involving a three-step protocol starting from primary amines, that is, sequential alkylation, acylation and one-pot substitution/cycloaddition (Scheme 1) for the preparation of triazole-fused tetrahydropyrazinones.

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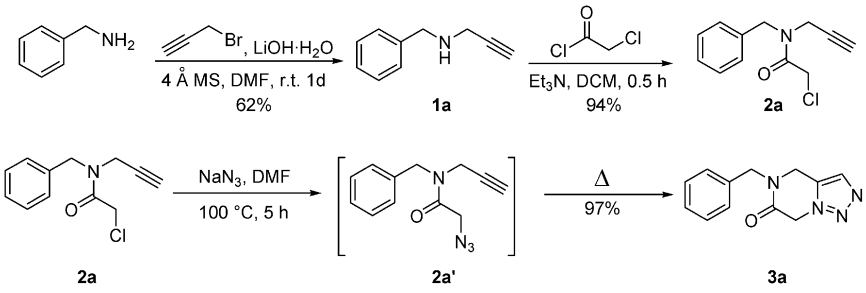


Scheme 1. Synthesis of bicyclic triazole 3a from benzylamine.

Results and Discussion

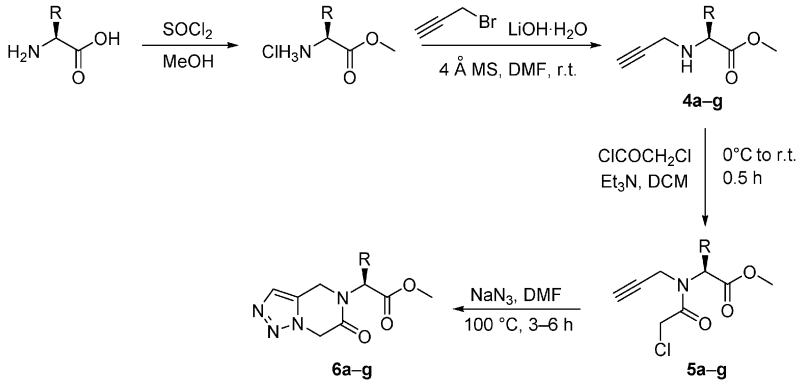
Our initial efforts were devoted to the synthesis of compound **3a** from benzylamine. *N*-benzyl propargylamine (**1a**) was synthesized from benzylamine and propargyl bromide in DMF by employing $LiOH·H_2O$ as the base. This was then treated with chloroacetyl chloride in the presence of triethylamine to give chloroacetylated alkyne **2a** in excellent yield (Scheme 1). The reaction of **2a** with an excess amount of sodium azide (5 equiv.) in DMF at 100 °C for 1 h resulted in the formation of azide **2a′**. Without isolating azide **2a′**, the reaction mixture was further heated for 4 h, where the latter underwent constrained intramolecular cycloaddition with the alkyne moiety to furnish regioselectively the desired bicyclic compound **3a** in 97% yield as the only product. This result encouraged us to synthesize other chloroacetylated alkynes derived from primary amines by employing the same set of reaction conditions as those described for the synthesis of **2a**. Accordingly, compounds **2b**–**e** were synthesized from 1-phenylethylamine, 2-phenylethylamine, (*S*)-α-naphthylethylamine, and 2-furfurylamine, respectively. These compounds existed as rotameric mixtures,[9] as exemplified by their ^1H and ^{13}C NMR spectra. Compounds **2b**–**e** were then treated with sodium azide under identical conditions as those described earlier, and the results are summarized in Table 1. The reactions proceeded smoothly (3–6 h) to afford 1,2,3-triazole-fused 4,5,6,7-tetrahydropyrazin-6-ones **3b**–**e** as the only product in excellent yields.

Table 1. Ring-constrained cycloaddition of chloroacetylated alkynes **2b**–**e** derived from alkylamines.[a]

Substrate	Product	Time [h]	Yield [%]
2b	**3b**	5	96
2c	**3c**	6	95
2d	**3d**	3	99
2e	**3e**	5	95

[a] Conditions: NaN_3 (5 equiv.), DMF, 100 °C.

Characteristic resonances were observed around δ = 127 and 129 ppm in the ^{13}C NMR spectra for compounds **3a**–**e**, which correspond to the olefinic carbon atoms of the tri-

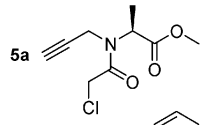
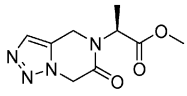
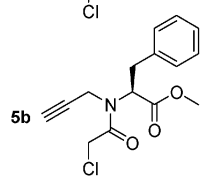
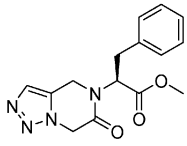
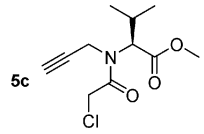
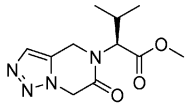
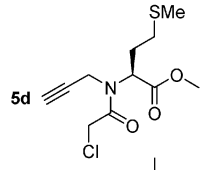
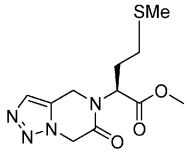
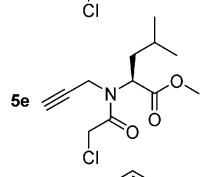
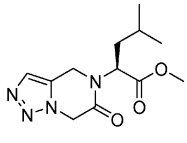
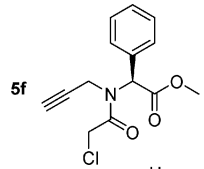
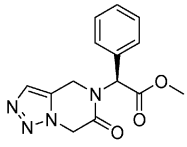
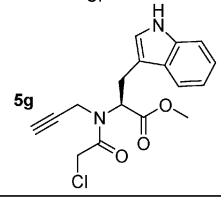
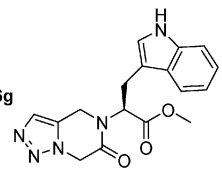


Scheme 2. General scheme for the synthesis of enantiopure fused triazoles from L-amino acids.

azole ring. We felt that this methodology could then be extended to synthesize enantiopure 4,5,6,7-tetrahydro[1,2,3]-triazolo[1,5-*a*]pyrazin-6-ones from chloroacetylated alkynes derived from α-amino acids.

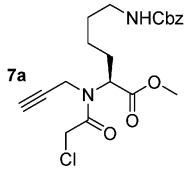
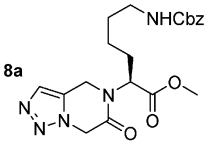
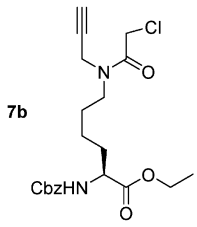
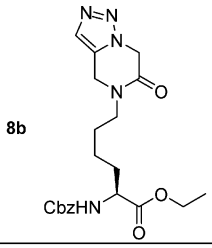
In this context, we synthesized chloroacetylated alkynes **5a**–**g** from the naturally abundant L-amino acids alanine, phenylalanine, valine, methionine, leucine, phenylglycine and tryptophan, respectively, according to the general scheme (Scheme 2). $LiOH·H_2O$ mediated N-alkylation of amino acid esters with propargyl bromide in DMF was performed by using a literature procedure[10] to furnish *N*-propargylated amino acids **4a**–**g** in good yield (70–80%). These *N*-propargyl amino acid esters were then treated with chloroacetyl chloride (1.2 equiv.) and triethylamine (2 equiv.) at 0 °C in CH_2Cl_2 to afford compounds **5a**–**g** in excellent yield (80–90%). All chloroacetylated alkynes **5a**–**g** existed as rotameric mixtures, and the rotamer ratio varied with each substrate. Enantiopure chloroacetylated alkynes **5a**–**g** were then heated in the presence with an excess amount of sodium azide (5 equiv.) in DMF at 100 °C. At this temperature, the azides formed in situ underwent constrained intramolecular cycloaddition in a facile manner (3–6 h) to furnish optically pure triazole-fused bicyclic compounds **6a**–**g** as the sole products in excellent yield (92–97%) (Table 2). The methodology was then extended to suitably protected L-lysine-derived chloroacetylated alkynes **7a** and **7b** synthesized from H-Lys(*Z*)-OMe·HCl and Z-Lys-OEt, respectively. They underwent facile cycloaddition to furnish **8a** and **8b**, respectively, in excellent yield (Table 3). These two compounds can be viewed as novel, protected amino acids incorporating a heterocyclic backbone. In general, cycloaddition of chloroacetylated alkynes containing a bulkier side chain (**2d** and **5g**) was faster than the less bulky substrates.

Table 2. Intramolecular cycloaddition of chloroacetylated alkynes **5a**–**g** derived from amino acids.[a]

Substrate	Product	Time [h]	Yield [%]
5a 	**6a** 	6	96
5b 	**6b** 	5	95
5c 	**6c** 	4	95
5d 	**6d** 	5	94
5e 	**6e** 	5	95
5f 	**6f** 	6	92
5g 	**6g** 	3	97

[a] Conditions: NaN_3 (5 equiv.), DMF, 100 °C.

Table 3. Novel protected amino acids derived from L-lysine.[a]

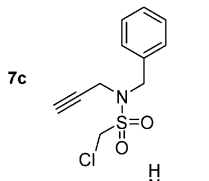
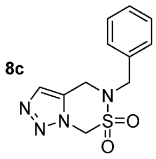
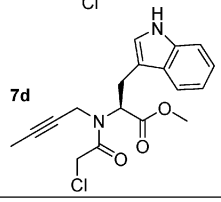
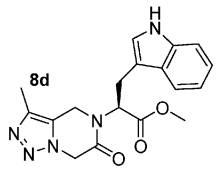
Substrate	Product	Time [h]	Yield [%]
7a 	**8a** 	5	96
7b 	**8b** 	6	94

[a] Conditions: NaN_3 (5 equiv.), DMF, 100 °C.

This may be attributed to the spatial proximity of the azide and alkyne substituents enforced by the bulky side chain. After successfully synthesizing amino acid derived fused triazoles **6a**–**g**, **8a**, and **8b**, we decided to extend the scope of this methodology by varying the alkyl, as well as the acyl components, which may furnish other triazole-fused heterocycles. Accordingly, compound **1a** was treated with chloromethane sulfonyl chloride in the presence of triethylamine to furnish chlorosulfonamide derivative **7c** in moderate yield (60%). Compound **7c** was then treated with an excess amount of sodium azide in DMF at 100 °C.

Because the cycloaddition was sluggish under these conditions, the temperature was increased to 120 °C and the cycloaddition took place to furnish **8c** in moderate yield (35%) in 9 h. It is worth noting that **8c** has a substructure hitherto unknown in the literature. Similarly, alkylating L-tryptophan methyl ester with 1-bromo-2-butyne followed by chloroacetylation in CH_2Cl_2 furnished compound **7d** in good yield (70% over 2 steps). When **7d** was treated with NaN_3 (DMF, 100 °C, 9 h) compound **8d** could be isolated in moderate yield (50%) (Table 4).

Table 4. Cycloaddition of a few other substrates.[a]

Substrate	Product	Time [h]	Yield [%]
		9	35
		9	50

[a] Conditions: NaN_3 (5 equiv.), DMF, 100 °C.

Conclusions

We disclosed an access to achiral, as well as enantiopure, 1,2,3-triazole-fused 4,5,6,7-tetrahydropyrazin-6-ones in excellent yields from several primary amines and amino acids in a three-step protocol (alkylation, acylation, one-pot substitution/cycloaddition) involving constrained intramolecular cycloaddition as the key step. The methodology in general obviates chromatographic purification of products.

Experimental Section

Physical Properties and Spectral Measurements: All glassware was oven dried before starting a reaction. Propargyl bromide was purchased from Sigma–Aldrich and used as such. Solvents like DMF, CH_2Cl_2, and MeOH were purified as mentioned in "Purification of Laboratory Chemicals" by Perrin & Armarego, Pergamon Press, Third Edition, 1988. Analytical TLC was performed on commercial plates coated with silica gel GF254 (0.25 mm). Silica gel (230–400 mesh) was used for column chromatography. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded with 300 MHz (300 MHz, ^1H and 75 MHz, ^{13}C) or 400 MHz (400 MHz, ^1H and 100 MHz, ^{13}C) spectrometers. Chemical shifts are reported in parts per million downfield from the internal reference tetramethylsilane for ^1H and $CDCl_3$ for ^{13}C NMR. The following abbreviations explain the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. s = broad singlet, and dd = doublet of doublets. IR spectra were recorded with an FTIR spectrometer. High-resolution mass spectra (HRMS) were recorded with a Micromass Q-TOF mass spectrometer. All propargylamines were synthesized according to a literature procedure.[10]

General Procedure for the Synthesis of Chloroacetylated Alkynes: To a solution of propargylamine (1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethylamine (2 mmol) followed by chloroacetyl chloride (1.2 mmol) under an atmosphere of nitrogen. After 0.5 h, the reaction mixture was washed with water (2 × 10 mL) followed by brine (10 mL) and dried with anhydrous Na_2SO_4. The filtrate was concentrated, and the crude product was purified by flash chromatography on silica gel (230–400 mesh) by using ethyl acetate and petroleum ether to obtain the corresponding chloroacetylated alkynes.

***N*-Benzyl-*N*-(2-propynyl)-2-chloroacetamide (2a):** R_f = 0.5 (hexane/EtOAc, 7:3). Yield: 229 mg (94%). Pale-yellow oil. IR (neat): $\tilde{\nu}$ = 3292, 2120, 1661, 1448, 1212, 956, 795, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.38–7.24 (m, 5 H), 4.73, 4.71 (2 s, 2 H), 4.25–4.0 (m, 4 H), 2.37, 2.26 (2 t, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ = 166.3, 135.7, 128.8, 128, 126.7, 77.4, 73.3, 50.3, 41.1, 36.3 ppm. HRMS: calcd. for $C_{12}H_{12}ClNO$ $[M + Na]^+$ 244.0505; found 244.0501.

***N*-(1-Phenylethyl)-*N*-(2-propynyl)-2-chloroacetamide (2b):** R_f = 0.40 (hexane/EtOAc, 7:3). Yield: 232 mg (90%). Pale-yellow oil. IR (neat): $\tilde{\nu}$ = 3293, 2980, 2119, 1658, 1448, 1413, 1173, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.36–7.27 (m, 5 H), 6.0, 5.24 (2 br. s, 1 H), 4.36–4.21 (m, 2 H), 3.93 (d, J = 18.9 Hz, 1 H), 3.69–3.49 (m, 1 H), 2.28–2.15 (m, 1 H), 1.89–1.42 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 166.7, 139.2, 128.6, 127.8, 127.3, 79.4, 72.8, 52.1, 41.7, 32.4, 16.1 ppm. HRMS: calcd. for $C_{13}H_{14}ClNO$ $[M + Na]^+$ 258.0662; found 258.0662.

***N*-Phenylethyl-*N*-(2-propynyl)-2-chloroacetamide (2c):** R_f = 0.40 (hexanes/EtOAc, 7:3). Yield: 219 mg (85%). Pale-yellow oil. IR (neat): $\tilde{\nu}$ = 3292, 2944, 2120, 1659, 1454, 1426, 1137, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.36–7.12 (m, 5 H), 4.26, 3.93 (2 d, J = 2.1 Hz, 2 H), 4.14 (s, 1 H), 3.73–3.65 (m, 3 H), 2.98–2.89 (m, 2 H), 2.35–2.30 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 166.2, 137.7, 128.9, 128.7, 126.9, 78.2, 72.6, 49.3, 40.5, 34.7, 33.6 ppm. HRMS: calcd. for $C_{13}H_{14}ClNO$ $[M + Na]^+$258.0662; found 258.0659.

***N*-[(1*S*)-1-(1-Naphthyl)ethyl]-*N*-(2-propynyl)-2-chloroacetamide (2d):** R_f = 0.40 (hexanes/EtOAc, 6:4). Yield: 265 mg (86%). Pale-yellow solid. M.p. 101 °C. IR (neat): $\tilde{\nu}$ = 3292, 2979, 2119, 1654, 1446, 1414, 1177, 805, 782 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.90–7.83 (m, 3 H), 7.62–7.46 (m, 4 H), 6.58 (q, J = 6.3 Hz, 1 H), 4.29 (d, J = 12.6 Hz, 1 H), 4.23 (d, J = 12.9 Hz, 1 H), 3.71 (dd, J_1 = 19.5 Hz, J_2 = 2.1 Hz, 1 H), 3.56 (dd, J_1 = 19.2 Hz, J_2 = 2.1 Hz, 1 H), 2.11 (t, J = 2.4 Hz, 1 H), 1.75 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 166.2, 134.5, 133.8, 131.9, 129.3, 128.6, 126.9, 126.1, 125.2, 124.8, 123.6, 79.4, 72.5, 49.8, 41.9, 31.9, 16.6 ppm. $[a]_D^{23}$ = –88.3 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{17}H_{16}ClNO$ $[M + Na]^+$ 308.0818; found 308.0832.

***N*-(2-Furylmethyl)-*N*-(2-propynyl)-2-chloroacetamide (2e):** R_f = 0.40 (hexanes/EtOAc, 7:3). Yield: 196 mg (84%). Pale-yellow oil. IR (neat): $\tilde{\nu}$ = 3292, 2121, 1662, 1451, 1353, 1198, 1012, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.4 (s, 1 H), 6.33 (s, 2 H), 4.67 (s, 2 H), 4.28–4.12 (m, 4 H), 2.34, 2.27 (2 br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ = 166.0, 148.6, 143.0, 110.4, 109.2, 77.8, 72.6, 43.4, 41.1, 34.5 ppm. HRMS: calcd. for $C_{10}H_{10}ClNO_2$ $[M + Na]^+$ 234.0298; found 234.0294.

Methyl (2*S*)-2-[(2-Chloroacetyl)(2-propynyl)amino]propanoate (5a): R_f = 0.30 (hexanes/EtOAc, 7:3). Yield: 204 mg (85%). Pale-yellow oil. IR (neat): $\tilde{\nu}$ = 3287, 2953, 2120, 1742, 1666, 1454, 1222, 1197, 801, 676 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 5.04 (q, J = 7.2 Hz, 1 H), 4.34–4.08 (m, 4 H), 3.76, 3.72 (2 s, 3 H), 2.43 (t, J = 2.7 Hz, 1 H), 1.65, 1.54 (2 d, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ = 171.4, 166.4, 78.3, 73.4, 53.4, 52.2, 41.3, 35.2, 14.6 ppm. $[a]_D^{23}$ = –57.1 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_9H_{12}ClNO_3$ $[M + Na]^+$ 240.0403; found 240.0406.

Methyl (2*S*)-2-[(2-Chloroacetyl)(2-propynyl)amino]-3phenylpropanoate: (5b): R_f = 0.40 (hexanes/EtOAc, 7:3). Yield: 272 mg (86%). Pale-yellow oil. IR (neat): $\tilde{\nu}$ = 3286, 2952, 2122, 1742, 1666, 1450,

1222, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.29–7.21 (m, 5 H), 4.90 (dd, J_1 = 6.0 Hz, J_2 = 9.6 Hz, 1 H), 4.23–4.05 (m, 3 H), 3.85–3.80 (m, 1 H), 3.74–3.72 (m, 3 H), 3.4 (dd, J_1 = 5.7 Hz, J_2 = 14.4 Hz, 1 H), 3.19 (dd, J_1 = 9.6 Hz, J_2 = 14.4 Hz, 1 H), 2.3 (t, J = 2.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 170.3, 166.5, 136.7, 129.0, 128.5, 126.8, 77.4, 73.7, 60.1, 52.3, 41.1, 36.9, 34.7 ppm. $[\alpha]_D^{23}$ = –111.3 (c = 1.0, $CHCl_3$) HRMS: calcd. for $C_{15}H_{16}ClNO_3$ [M + Na]$^+$ 316.0716; found 316.0708.

Methyl (2*S*)-2-[(2-Chloroacetyl)(2-propynyl)amino]-3-methylbutanoate (5c): R_f = 0.70 (hexanes/EtOAc, 7:3). Yield: 241 mg (90%). Pale-yellow oil. IR (neat): $\tilde{\nu}$ = 3288, 2967, 2122, 1740, 1670, 1445, 1212, 1170, 1008, 668 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 4.91 (d, J = 10.2 Hz, 1 H), 4.44–3.98 (m, 4 H), 3.75, 3.72 (2 s, 3 H), 2.49–2.19 (m, 2 H), 1.07–0.95 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 170.9, 167.4, 78.5, 73.4, 61.6, 51.9, 41.4, 33.9, 28.0, 19.4, 18.9 ppm. $[\alpha]_D^{22}$ = –141.4 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{11}H_{16}ClNO_3$ [M + Na]$^+$ 268.0716; found 268.0713.

Methyl (2*S*)-2-[(2-Chloroacetyl)(2-propynyl)amino]-4-(methylsulfanyl)butanoate (5d): R_f = 0.40 (hexanes/EtOAc, 7:3). Yield: 246 mg (82%). Pale-yellow oil. IR (neat): $\tilde{\nu}$ = 3276, 2953, 2120, 1739, 1666, 1436, 1220, 1198, 798 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 5.08, 4.79 (2 dd, J_1 = 9.3 Hz, J_2 = 4.8 Hz, 1 H), 4.40–4.07 (m, 4 H), 3.79–3.73 (m, 3 H), 2.76–2.12 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 170.7, 167.1, 78.1, 73.9, 57.4, 52.4, 41.3, 36.3, 30.7, 28.5, 15.3 ppm. $[\alpha]_D^{23}$ = 63.4 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{11}H_{16}ClNO_3S$ [M + Na]$^+$ 300.0437; found 300.0431.

Methyl (2S)-2-[(2-Chloroacetyl)(2-propynyl)amino]-4-methylpentanoate (5e): R_f = 0.40 (hexanes/EtOAc, 7:3). Yield: 234 mg (83%). Pale-yellow oil. IR (neat): $\tilde{\nu}$ = 3372, 2958, 2872, 2120, 1741, 1668, 1446, 1178, 672 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 5.3 (dd, J_1 = 9.9 Hz, J_2 = 4.8 Hz, 1 H), 4.38–4.07 (m, 4 H), 3.71 (s, 3 H), 2.40 (t, J = 2.7 Hz, 1 H), 1.86–1.65 (m, 3 H), 1.01–0.93 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ = 171.8, 167.2, 78.5, 73.4, 55.3, 52.2, 41.4, 37.8, 34.4, 24.8, 22.8, 21.5 ppm. $[\alpha]_D^{23}$ = –40.6 (c = 2.0, $CHCl_3$). HRMS: calcd. for $C_{12}H_{18}ClNO_3$ [M + Na]$^+$ 282.0873; found 282.0865.

Methyl (2*S*)-2-[(2-Chloroacetyl)(2-propynyl)amino]-2-phenylethanoate: (5f): R_f = 0.40 (hexanes/EtOAc, 7:3). Yield: 241 mg (80%). Pale-yellow oil. IR (neat): $\tilde{\nu}$ = 3289, 2954, 2122, 1747, 1668, 1446, 1173, 1003, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.40–7.30 (m, 5 H), 6.28 (s, 1 H), 4.36 (s, 2 H), 4.14–3.97 (m, 2 H), 3.78 (s, 3 H), 2.15 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 170.3, 167.5, 132.9, 129.3, 129.1 129.0, 78.3, 72.6, 60.9, 52.5, 41.6, 34.7 ppm. $[\alpha]_D^{23}$ = 140.3 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{15}H_{18}ClNO_3$ [M + Na]$^+$ 302.0560; found 302.0561.

Methyl (2*S*)-2-[(2-Chloroacetyl)(2-propynyl)amino]-3-(1*H*-3-indolyl)propanoate (5g): R_f = 0.30 (hexanes/EtOAc, 6:4). Yield: 291 mg (82%). Light-brown oil. IR (neat): $\tilde{\nu}$ = 3292, 2952, 2122, 1738, 1731, 1660, 1456, 1342, 1246, 1045, 746 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 8.30, 8.19 (2 br. s, 1 H), 7.62 (d, J = 7.2 Hz, 1 H), 7.40–7.45 (m, 4 H), 5.06, 4.72 (2 dd, J_1 = 9.6 Hz, J_2 = 6 Hz, 1 H), 4.34–3.35 (m, 9 H), 2.20 (t, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 170.7, 166.7, 136.2, 127.3, 122.9, 122.1, 119.6, 118.4, 111.2, 110.8, 77.3, 73.5, 59.1, 52.4, 41.4, 36.8, 24.7 ppm. $[\alpha]_D^{23}$ = –162 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{17}H_{17}ClN_2O_3$ [M + Na]$^+$ 355.0825; found 355.0818.

Methyl (2*S*)-6-[(Benzyloxy)carbonyl]amino-2-[(2-chloroacetyl)(2-propynyl)amino]hexanoate (7a): R_f = 0.40 (hexanes/EtOAc, 6:4). Yield: 345 mg (80%). Colorless oil. IR (neat): $\tilde{\nu}$ = 3292, 2951, 2120, 1714, 1667, 1531, 1454, 1248, 1018, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.36–7.32 (m, 5 H), 5.14–5.08 (m, 3 H), 4.87 (br. s, 1 H), 4.41–4.10 (m, 4 H), 3.74–3.68 (m, 3 H), 3.21–3.15 (m, 2 H), 2.38 (t, J = 2.4 Hz, 1 H), 2.09–1.77 (m, 2 H), 1.58–1.34 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ = 171.1, 167.4, 156.3, 136.6, 128.5, 128.4, 128.0, 78.3, 73.7, 66.5, 57.0, 52.3, 41.3, 40.6, 34.8, 29.3, 28.5, 23.2 ppm. $[\alpha]_D^{22}$ = –27.3 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{20}H_{25}ClN_2O_5$ [M + Na]$^+$ 431.1350; found 431.1352.

Ethyl (2*S*)-2-[(Benzyloxy)carbonyl]amino-6-[(2-chloroacetyl)(2-propynyl)amino]hexanoate (7b): R_f = 0.30 (hexanes/EtOAc, 6:4). Yield: 356 mg (80%). Colorless oil. IR (neat): $\tilde{\nu}$ = 3297, 2943, 2120, 1719, 1659, 1533, 1454, 1251, 1026, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.36 (br. s, 5 H), 5.38 (d, J = 7.8 Hz, 1 H), 5.11 (s, 2 H), 4.38–4.08 (m, 7 H), 3.42 (br. s, 2 H), 2.34, 2.23 (2 br. s, 1 H), 1.86–1.58 (m, 4 H), 1.41–1.34 (m, 2 H), 1.27 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ = 172.1, 166.4, 155.8, 136.3, 128.5, 128.1 (2 C), 78.0, 66.9, 61.4, 53.7, 47.4, 41.2, 37.6, 34.7, 32.5, 27.9, 22.2, 14.1 ppm. $[\alpha]_D^{22}$ = +11.3 (c = 2.0, $CHCl_3$). HRMS: calcd. for $C_{21}H_{27}ClN_2O_5$ [M + Na]$^+$ 445.1506; found 445.1505.

***N*-Benzyl-*N*-(2-propynyl)chloromethanesulfonamide (7c):** R_f = 0.50 (hexanes/EtOAc, 6:4). Yield: 168 mg (60%). Colorless oil. IR (neat): $\tilde{\nu}$ = 3285, 3017, 2121, 1495, 1356, 1244, 1161, 1064, 899 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 5 H), 4.67 (s, 2 H), 4.66 (s, 2 H), 3.94 (d, J = 2.7 Hz, 2 H), 2.45 (t, J = 2.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.7, 128.8, 128.5, 128.3, 76.6, 74.4, 55.7, 51.6, 35.7 ppm. HRMS: calcd. for $C_{11}H_{12}ClNO_2S$ [M + Na]$^+$ 280.0175; found 280.0164.

Methyl (2*S*)-2-[2-Butynyl(2-chloroacetyl)amino]-3-(1*H*-3-indolyl)propanoate (7d): R_f = 0.40 (hexanes/EtOAc, 6:4). Yield: 295 mg (80%). Light-brown oil. IR (neat): $\tilde{\nu}$ = 3404, 2231, 1735, 1652, 1457, 1433, 1346, 1215, 1170, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 8.19 (s, 1 H), 7.63 (d, J = 7.5 Hz, 1 H), 7.35 (d, J = 8.1 Hz, 1 H), 7.20–7.05 (m, 3 H), 5.14 (dd, J_1 = 9.3 Hz, J_2 = 5.7 Hz, 1 H), 4.24–3.59 (m, 7 H), 3.52 (dd, J_1 = 15.3 Hz, J_2 = 6 Hz, 1 H), 3.38 (dd, J_1 = 15.3 Hz, J_2 = 9.6 Hz, 1 H), 1.80, 1.72 (2 br. s, 1 H), 1.57 (t, J = 2.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ = 170.9, 166.8, 136.2, 127.4, 122.8, 122, 119.5, 118.5, 111.1 (2 C), 81.6, 73.0, 58.6, 52.2, 41.6, 37.0, 24.7, 3.23 ppm. $[\alpha]_D^{23}$ = –56.7 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{18}H_{19}ClN_2O_3$ [M + Na]$^+$ 369.0982; found 369.0992.

General Procedure for the Synthesis of Triazole-Fused Tetrahydropyrazin-6-ones: To a solution of chloroacetylated alkyne (1 mmol) in DMF (5 mL) was added NaN_3 (5 mmol). The mixture was heated to 100 °C for appropriate time. After the reaction was complete (monitored by TLC) DMF was evaporated under vacuum, and the compound was extracted from the reaction mixture with CH_2Cl_2 (25 mL). The combined organic layer was then dried with anhydrous Na_2SO_4, filtered, and concentrated to obtain the corresponding triazole-fused tetrahydropyrazin-6-ones.

5-Benzyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-6-one (3a): R_f = 0.30 (hexanes/EtOAc, 4:6). Yield: 222 mg (97%). White solid. M.p. 147 °C. IR (neat): $\tilde{\nu}$ = 2936, 1659, 1489, 1349, 1255, 991, 836 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, 1 H), 7.37–7.28 (m, 5 H), 5.11 (s, 2 H), 4.77 (s, 2 H), 4.57 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 134.8, 129.1, 129, 128.4, 128.3, 127.2, 50.2, 48.6, 41.4 ppm. HRMS: calcd. for $C_{12}H_{12}N_4O$ [M + H]$^+$ 229.1089; found 229.1085.

5-(1-Phenylethyl)-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-6-one: (3b): R_f = 0.30 (hexanes/EtOAc, 4:6). Yield: 254 mg (96%). Colorless viscous oil. IR (neat): $\tilde{\nu}$ = 2980, 1656, 1472, 1346, 990, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1 H), 7.37–7.31 (m, 5 H), 6.21 (q, J = 6.9 Hz, 1 H), 5.12 (s, 1 H), 5.11 (s, 1 H), 4.51 (d, J = 16.2 Hz, 1 H), 4.14 (d, J = 16.2 Hz, 1 H), 1.64 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 137.9, 129.1, 128.7, 128.1, 127.5, 127.3, 50.8, 48.7, 36.3, 14.9 ppm. HRMS: calcd. for $C_{13}H_{14}N_4O$ $[M + Na]^+$ 265.1065; found 265.1066.

5-Phenethyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-6-one (3c): R_f = 0.40 (hexanes/EtOAc, 4:6). Yield: 252 mg (95%). White solid. M.p. 158 °C. IR (neat): $\tilde{\nu}$ = 2925, 1652, 1489, 1347, 1169, 991, 836, 750, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52 (s, 1 H), 7.33–7.20 (m, 5 H), 5.08 (s, 2 H), 4.43 (s, 2 H), 3.8 (t, J = 7.2 Hz, 2 H), 2.98 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 137.9, 129.0, 128.9, 128.7, 127.2, 126.9, 49.4, 48.7, 43.1, 33.4 ppm. HRMS: calcd. for $C_{13}H_{14}N_4O$ $[M + Na]^+$ 265.1065; found 265.1059.

5-[(1*S*)-1-(1-Naphthyl)ethyl]-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]-pyrazin-6-one (3d): R_f = 0.30 (hexanes/EtOAc, 5:5). Yield: 311 mg (99%). White solid. M.p. 94 °C. IR (neat): $\tilde{\nu}$ = 3052, 2980, 1651, 144, 1346, 784 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.85 (m, 3 H), 7.66–7.46 (m, 4 H), 7.37 (s, 1 H), 6.79 (q, J = 6.9 Hz, 1 H), 5.19 (d, J = 17.7 Hz, 1 H), 5.09 (d, J = 18 Hz, 1 H), 4.39 (d, J = 16.2 Hz, 1 H), 3.67 (d, J = 16.5 Hz, 1 H), 1.75 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 133.7, 133, 131.4, 129.4, 129.1, 128.8, 127.4, 127.1, 126.1, 125.2, 124.7, 122.7, 48.5, 48.2, 36.6, 15.3 ppm. $[a]_D^{22}$ = –121.8 (c = 2.0, $CHCl_3$). HRMS: calcd. for $C_{17}H_{16}N_4O$ $[M + Na]^+$ 315.1220; found 315.1230.

5-(2-Furylmethyl)-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-6-one (3e): R_f = 0.40 (hexanes/EtOAc, 5:5). Yield: 229 mg (95%). Colorless oil. IR (neat): $\tilde{\nu}$ = 3511, 2986, 1665, 1485, 1424, 1347, 1011, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (s, 1 H), 7.59 (s, 1 H), 6.40 (d, J = 3.3 Hz, 1 H), 6.36 (t, J = 2.1 Hz, 1 H), 5.1 (s, 2 H), 4.77 (s, 2 H), 4.72 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.4, 148.4, 142.8, 128.9, 127.2, 110.4, 109.8, 48.3, 42.5, 41.7 ppm. HRMS: calcd. for $C_{10}H_{10}N_4O_2$ $[M + Na]^+$ 241.0701; found 241.0706.

Methyl (2*S*)-2-(6-Oxo-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)propanoate (6a): R_f = 0.30 (hexanes/EtOAc, 4:6). Yield: 216 mg (96%). Colorless gummy liquid. IR (neat): $\tilde{\nu}$ = 2953, 1742, 1692, 1666, 1556, 1350, 1201, 991, 735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 5.31 (q, J = 7.5 Hz, 1 H), 5.15 (s, 2 H), 4.79 (d, J = 15.3 Hz, 1 H), 4.71 (d, J = 15.6 Hz, 1 H), 3.76 (s, 3 H), 1.57 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 162.5, 129.3, 127.4, 52.6, 52.0, 48.7, 38.6, 14.1 ppm. $[a]_D^{22}$ = –4 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_9H_{12}N_4O_3$ $[M + Na]^+$ 225.0988; found 225.0981.

Methyl (2S)-2-(6-Oxo-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)-3-phenylpropanoate (6b): R_f = 0.30 (hexanes/EtOAc, 4:6). Yield: 286 mg (95%). Colorless gummy liquid. IR (neat): $\tilde{\nu}$ = 2953, 1741, 1666, 1474, 1435, 1200, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, 1 H), 7.27–7.14 (m, 5 H), 5.28 (dd, J_1 = 10.8 Hz, J_2 = 5.7 Hz, 1 H), 5.05 (d, J = 18 Hz, 1 H), 4.91 (d, J = 18 Hz, 1 H), 4.59 (d, J = 16 Hz, 1 H), 4.49 (d, J = 16 Hz, 1 H), 3.76 (s, 3 H), 3.49 (dd, J_1 = 14.7 Hz, J_2 = 5.4 Hz, 1 H), 3.2 (dd, J_1 = 14.7 Hz, J_2 = 11.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 162.5, 135.6, 128.9, 128.7, 128.5, 128.3, 127.2, 58.3, 52.6, 48.5, 40.3, 34.0 ppm. $[a]_D^{23}$ = –5.8 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{15}H_{16}N_4O_3$ $[M + H]^+$ 301.1300; found 301.1302.

Methyl (2*S*)-3-Methyl-2-(6-oxo-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)butanoate (6c): R_f = 0.50 (hexanes/EtOAc, 4:6). Yield: 240 mg (95%). Colorless gummy liquid. IR (neat): $\tilde{\nu}$ = 2966, 1740, 1691, 1555, 1210, 992, 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 5.16 (s, 2 H), 5.03 (d, J = 10.8 Hz, 1 H), 4.97 (d, J = 16.2 Hz, 1 H), 4.66 (d, J = 16.2 Hz, 1 H), 3.75 (s, 3 H), 2.39–2.27 (m, 1 H), 1.07 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 162.9, 129.3, 127.7, 61.2, 52.3, 48.9, 38.3, 27.2, 19.5, 18.9 ppm. $[a]_D^{22}$ = –17.8 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{11}H_{16}N_4O_3$ $[M + H]^+$ 253.1300; found 253.1301.

Methyl (2*S*)-4-(Methylsulfanyl)-2-(6-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)butanoate (6d): R_f = 0.30 (hexanes/EtOAc, 1:1). Yield: 288 mg (94%). Colorless gummy liquid. IR (neat): $\tilde{\nu}$ = 3474, 2921, 1740, 1665, 1475, 1430, 1199, 991 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 5.18–5.14 (m, 3 H), 4.84 (d, J = 15.6 Hz, 1 H), 4.72 (d, J = 15.9 Hz, 1 H), 3.77 (s, 3 H), 2.60–2.40 (m, 3 H), 2.27–2.10 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 162.9, 129.2, 127.4, 56.5, 52.6, 48.7, 40.2, 30.5, 27.3, 15.3 ppm. $[a]_D^{23}$ = –2 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{11}H_{16}N_4O_3S$ $[M + Na]^+$ 307.0841; found 307.0836.

Methyl (2*S*)-4-Methyl-2-(6-oxo-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)pentanoate (6e): R_f = 0.40 (hexanes/EtOAc, 4:6). Yield: 253 mg (95%). Colorless gummy liquid. IR (neat): $\tilde{\nu}$ = 3475, 2957, 2875, 1740, 1667, 1471, 1349, 1185, 990 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (s, 1 H), 5.42 (dd, J_1 = 10.2 Hz, J_2 = 5.7 Hz, 1 H), 5.15 (s, 2 H), 4.81 (d, J = 15.6 Hz, 1 H), 4.6 (d, J = 15.6 Hz, 1 H), 3.75 (s, 3 H), 1.94–1.77 (m, 2 H), 1.51–1.40 (m, 1 H), 0.96 (t, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 163, 129.3, 127.5, 54.1, 52.5, 48.8, 38.3, 36.6, 24.9, 23, 21.2 ppm. $[a]_D^{22}$ = –9.2 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{12}H_{18}N_4O_3$ $[M + H]^+$ 267.1457; found 267.1456.

Methyl (2*S*)-2-(6-Oxo-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)-2-phenylethanoate (6f): R_f = 0.30 (hexanes/EtOAc, 5:5). Yield: 284 mg (92%). Pale-yellow gummy liquid. IR (neat): $\tilde{\nu}$ = 2926, 1740, 1647, 1441, 1347, 1201, 986, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.46–7.44 (m, 3 H), 7.30–7.26 (m, 2 H), 6.53 (s, 1 H), 5.18 (s, 2 H), 4.84 (d, J = 15 Hz, 1 H), 4.12 (d, J = 15 Hz, 1 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 162.9, 131.8, 129.4, 129.3 (2 C), 129.2, 127.6, 59.9, 52.7, 48.7, 38.9 ppm. $[a]_D^{23}$ = 9.5 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{14}H_{14}N_4O_3$ $[M + H]^+$ 309.0964; found 309.0964.

Methyl (2*S*)-3-(1*H*-3-Indolyl)-2-(6-oxo-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)propanoate (6g): R_f = 0.30 (hexanes/EtOAc, 5:5). Yield: 351 mg (97%). Pale-yellow gummy liquid. IR (neat): $\tilde{\nu}$ = 3397, 2950, 1740, 1664, 1432, 1349, 1099, 833, 744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (s, 1 H), 7.55 (d, J = 7.8 Hz, 1 H), 7.37 (s, 1 H), 7.33–7.06 (m, 4 H), 6.95 (d, J = 2.1 Hz, 1 H), 5.31 (dd, J_1 = 11.1 Hz, J_2 = 5.1 Hz, 1 H), 5.04 (d, J = 17.7 Hz, 1 H), 4.92 (d, J = 18 Hz, 1 H), 4.52 (d, J = 15.6 Hz, 1 H), 4.43 (d, J = 15.9 Hz, 1 H), 3.78 (s, 3 H), 3.57 (dd, J_1 = 15.9 Hz, J_2 = 5.1 Hz, 1 H), 3.42 (dd, J_1 = 15.3 Hz, J_2 = 10.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 162.8, 136.3, 129.1, 127.6, 126.9, 122.5 (2 C), 119.8, 117.9, 111.7, 109.9, 58.1, 52.8, 48.8, 40.5, 24.2 ppm. $[a]_D^{23}$ = –29.4 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{17}H_{17}N_5O_3$ $[M + Na]^+$ 362.1229; found 362.1223.

Methyl (2*S*)-6-[(Benzyloxy)carbonyl]amino-2-(6-oxo-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)hexanoate (8a): R_f = 0.40 (hexanes/EtOAc, 4:6). Yield: 420 mg (96%). Colorless gummy liquid. IR (neat): $\tilde{\nu}$ = 3338, 2938, 2867, 1715, 1666, 1534, 1457, 1251, 743, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63 (s, 1 H), 7.34–7.32 (m, 5 H), 5.27 (dd, J_1 = 10.5 Hz, J_2 = 5.1 Hz, 1 H), 5.13

(br. s, 2 H), 5.05 (s, 2 H), 4.84 (br. s, 1 H), 4.75 (d, J = 15.9 Hz, 1 H), 4.59 (d, J = 16.2 Hz, 1 H), 3.74 (s, 3 H), 3.23–3.15 (m, 2 H), 2.21–2.05 (m, 1 H), 1.96–1.25 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 163.2, 156.5, 136.5, 129.4, 128.5, 128.1, 128, 127.5, 66.7, 55.9, 52.6, 48.8, 40.3, 38.6, 29.4, 27.5, 23.0 ppm. $[\alpha]_D^{22}$ = 2.8 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{20}H_{25}N_5O_5$ [M + Na]$^+$ 438.1753; found 438.1752.

Ethyl (2*S*)-2-[(Benzyloxy)carbonyl]amino-6-(6-oxo-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)hexanoate (8b): R_f = 0.40 (hexanes/EtOAc, 4:6). Yield: 425 mg (94%). Colorless gummy liquid. IR (neat): $\tilde{\nu}$ = 3313, 2939, 1720, 1661, 1532, 1346, 1256, 1213, 1026, 737 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (s, 1 H), 7.30 (br. s, 5 H), 5.51 (d, J = 8.1 Hz, 1 H), 5.07 (s, 2 H), 5.04 (s, 2 H), 4.63 (s, 2 H), 4.34 (dd, J_1 = 12.6 Hz, J_2 = 7.5 Hz, 1 H), 4.19 (q, J = 6.9 Hz, 2 H), 3.55 (t, J = 6.3 Hz, 2 H), 2.04–1.56 (m, 4 H), 1.42–1.39 (m, 2 H), 1.26 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 161.7, 155.9, 136.2, 129.1, 128.4, 128.1, 127.9, 127.2, 66.9, 61.5, 53.5, 48.5, 46.8, 42.1, 32.1, 26.0, 22.2, 14.1 ppm. $[\alpha]_D^{23}$ = 6.3 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{21}H_{27}N_5O_3$ [M + Na]$^+$ 452.1910; found 452.1905.

5-Benzyl-4,5,6,7-tetrahydro-6λ^6-[1,2,3]triazolo[5,1-*d*][1,2,5]thiadiazine-6,6-dione (8c): R_f = 0.40 (hexanes/EtOAc, 5:5). Yield: 100 mg (35%). White solid. M.p. 110 °C. IR (neat): $\tilde{\nu}$ = 2993, 2941, 1455, 1371, 1302, 1188, 1161, 903, 736 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (s, 1 H), 7.55–7.27 (m, 5 H), 5.53 (s, 2 H), 4.54 (s, 2 H), 4.38 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.2, 130.2, 129.2, 128.9, 128.6, 126.8, 61.6, 52.8, 42.6 ppm. HRMS: calcd. for $C_{11}H_{12}N_4O_2S$ [M + Na]$^+$ 287.0579; found 287.0754.

Methyl (2*S*)-3-(1*H*-3-Indolyl)-2-(3-methyl-6-oxo-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-5-yl)propanoate (8d): R_f = 0.40 (hexanes/EtOAc, 5:5). Yield: 188 mg (50%). Pale-yellow gummy liquid. IR (neat): $\tilde{\nu}$ = 3336, 2928, 1741, 1665, 1435, 1344, 1234, 745 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 7.56 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 8.1 Hz, 1 H), 7.26 (s, 1 H), 7.22–7.09 (m, 2 H), 6.97 (d, J = 2.1 Hz, 1 H), 5.34 (dd, J_1 = 10.8 Hz, J_2 = 5.4 Hz, 1 H), 5.04 (d, J = 17.7 Hz, 1 H), 4.93 (d, J = 18 Hz, 1 H), 4.41 (d, J = 15.9 Hz, 1 H), 4.32 (d, J = 15.3 Hz, 1 H), 3.81 (s, 3 H), 3.58 (dd, J_1 = 15.9 Hz, J_2 = 5.7 Hz, 1 H), 3.46 (dd, J_1 = 15.3 Hz, J_2 = 10.5 Hz, 1 H), 2.09 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 162.9, 138.0, 136.2, 126.9, 124.1, 122.6, 122.2, 119.9, 117.9, 111.5, 110.1, 58.1, 52.7, 48.9, 40.2, 24.2, 9.8 ppm. $[\alpha]_D^{23}$ = 4.4 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{18}H_{19}N_5O_3$ [M + Na]$^+$ 376.1386; found 376.1381.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all new compounds.

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