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A rapid entry to amino acid derived diverse 3,4-dihydropyrazines and dihydro[1,2,3]triazolo[1,5-*a*]-pyrazines through 1,3-dipolar cycloaddition†

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An efficient, general and practical synthesis of diverse 3,4-dihydropyrazines, 6,7-dihydro-[1,2,3]triazolo-pyrazines and 7,8-dihydro-[1,2,3]triazolodiazepines through intramolecular 1,3-dipolar cycloaddition from amino acid derived common intermediates with high yields is described. Moreover, one-pot access to optically active 3-aryl substituted 6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazines in the palladium–copper co-catalytic system has also been achieved in this work. The easy substrate availability and operational simplicity make the process suitable for further exploration.

Introduction

Click chemistry is a modular synthetic approach towards the assembly of new molecular entities by efficiently and reliably joining small units together. By applying this concept, it is now possible to produce manmade compounds of enormous diversity than what is currently known or available. The traditional cycloaddition between azides and acetylenes studied by Huisgen[1a–c] in the 1960s led to the development of a straightforward synthesis of 1,4- and 1,5-substituted 1,2,3-triazoles as regioisomeric mixtures. This classical reaction gained enormous importance after its discovery.[1d] The regio-selective synthesis of 1,4-substituted 1,2,3-triazoles through the use of a copper catalyst was established independently by Sharpless[2a] and Meldal[2b] which ensured dramatic acceleration of the reaction rate and lowering of the reaction temperature. The structural and electronic properties of 1,2,3-triazoles are applicable in peptidomimetic chemistry for introducing global and local conformational restrictions.[3] 1,2,3-Triazoles have been used as replacements of backbone peptide bonds[4] or to stabilize turn[5,6] or helical[7] architectures by cyclization between side chain or backbone modified amino acid residues.[8] Several compounds of the 1,2,3-triazole class possess a broad spectrum of biological properties including anti-HIV,[9a] anti-allergic,[9b] anti-bacterial,[9c] and fungicidal activities.[9d] On the other hand, piperazine fused triazole compounds are found in a number of biologically active natural products, synthetic agents, and drugs.

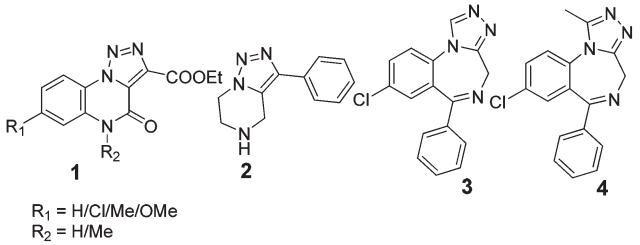

Fig. 1 Some important triazolo-piperazine derivatives.

Besides, 1,2,3-triazolo[1,5-*a*]quinoxaline **1** (Fig. 1) has also shown good affinity toward benzodiazepine and adenosine receptors.[10a,b] In view of the frequent occurrence of 1,2,3-triazoles and piperazines in various biologically active compounds, we envisioned that 4,5,6,7-tetrahydro[1,2,3]triazolo-[1,5-*a*]pyrazines **2** and/or their fused analogues could be novel pharmacophores or important building blocks. Only a few methods are available in the literature for the synthesis of compounds of type **2**[11] and of its 6-keto derivatives.[12] Most of the syntheses used the conventional intramolecular cycloaddition between azides and terminal alkynes, limiting the diversity of substitutions at C-3 and C-4 of the product. Despite the significant interest in these heterocyclic systems in medicinal chemistry,[13] arising from its close structural similarity to benzodiazepine drugs such as Estazolam **3** and Alprazolam **4**, synthetic methods for their preparation are limited,[14,15] and all chiral approaches to these compounds are based on the construction of the molecules on carbohydrate motifs.[16]

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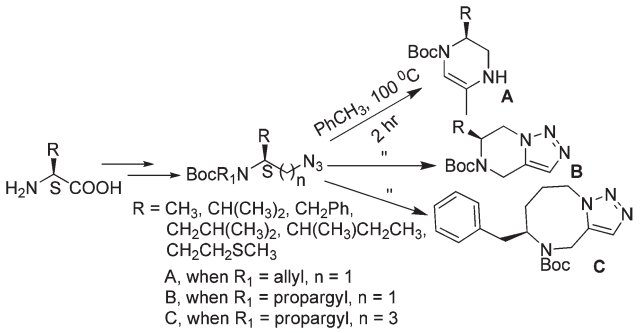
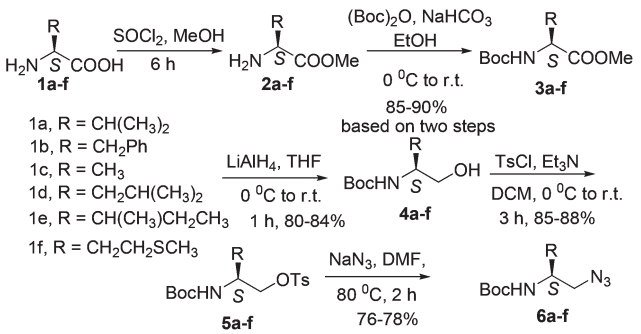


Scheme 1 Synthesis of amino acid derived substituted 5-methyl-3,4-dihydropyrazine and dihydro[1,2,3]triazolo[1,5-*a*]pyrazines.

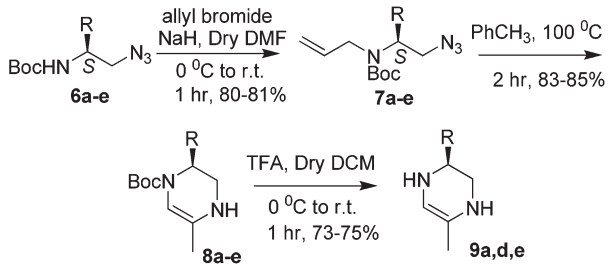
Our work centered on chemical synthesis and properties of *S*-amino acid-derived chiral heterocycles and natural product-like molecules.[17] Recently, we have published a series of amino acid derived benzoxazepines as antitumor agents in breast cancer[17b] and a novel methodology for the synthesis of *trans*-2,5-disubstituted morpholines, piperazines and thiomorpholines through a straightforward and modular pathway involving iodine mediated 6-*exo*-*trig* cyclization.[17e] In conjunction with our continued interest, we hereby report an extremely simple and mild method for the diversity oriented synthesis of amino acid derived substituted dihydro[1,2,3]triazolo [1,5-*a*]-pyrazines and their ring fused analogues (Scheme 1).

Results and discussion

The synthesis of the required substrates for 1,3-dipolar cycloaddition reaction began with *S*-amino acids **1a–f** which were converted to their methyl esters **2a–f** followed by boc protection of primary amines to give **3a–f** (Scheme 2). Ester reduction to **4a–f** proceeded smoothly, followed by tosyl protection of primary alcohols affording **5a–f**. Amino acid-derived azido substrates **6a–f** for intramolecular click reaction were synthesized by an S_N2 displacement of the corresponding tosylates with NaN_3. All of these steps were accomplished in excellent yields and are amenable to easy scale-up. In this letter, we reveal an effective integration of click chemistry into amino acid substrates in order to synthesize 1,2,3-triazole-fused bicyclic compounds in high yields.



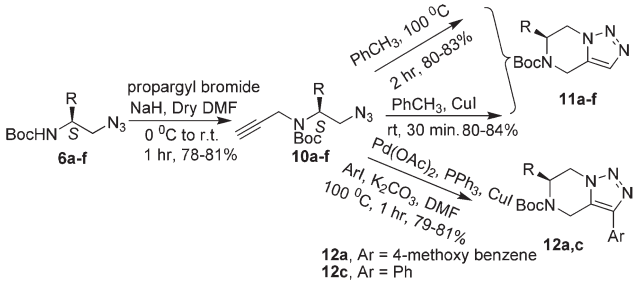
Scheme 2 Synthesis of intermediates **6a–e**.



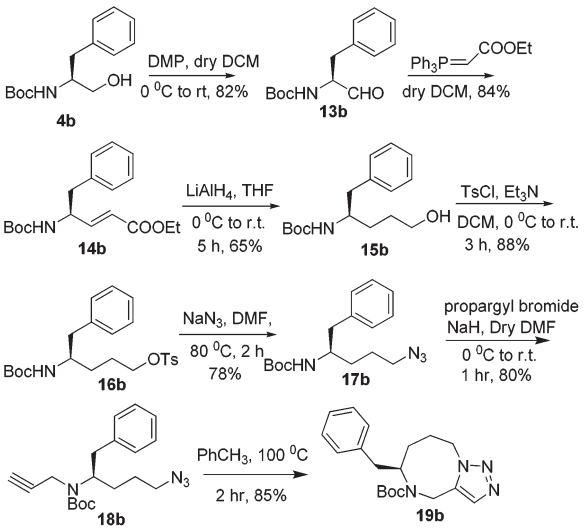
Scheme 3 Synthesis of 5-methyl-3,4-dihydropyrazine.

The derived azido compound **6a–e** reacted smoothly with allylbromide and NaH in the presence of dry DMF at 0 °C to give **7a–e** (Scheme 3). The peak at ν_{max} 2108 cm^{-1} in the IR spectra of the products clearly indicated the presence of the azide functionality. Finally, 1,3-dipolar cycloaddition reaction was carried out under reagent-free conditions by heating a toluene solution of the azido alkene **7a–e** at 100 °C for 2 h to provide 5-methyl-3,4-dihydropyrazine in good yields. In the ^{13}C NMR spectrum of **8a–e**, the presence of carbon signals at δ 162.8, 151.1, 155.2 and 20.7 suggested the presence of amide carbonyl, olefinic quaternary as well as methine carbons. Additionally, the methyl proton signal at δ 2.14 (d, J = 1.8 Hz, allylic coupling) testified the location of a vinylic methyl group. In addition, the Boc protection of **8** can be removed using TFA in dry DCM to afford **9** which provides an additional opportunity for diversity oriented synthesis through derivatization of the resulting secondary amine.

With intermediate azido compounds **6a–f** in hand, synthesis of dihydro [1,2,3]triazolo[1,5-*a*]pyrazines was attempted. Compounds **6a–f** were treated with propargyl bromide and NaH in the presence of dry DMF at 0 °C to furnish azido alkynes **10a–f**. As above, reagent-free conditions by heating a toluene solution of the azidoalkene at 100 °C gave triazolo [1,5-*a*]pyrazines **11a–f** in good yields (Scheme 4). With these optimized conditions, the scope of the reaction with terminal alkynes was investigated. The copper catalyzed 1,3-dipolar cycloaddition reaction proceeds well in both aqueous and organic solvents under very simple experimental conditions. In this case, the starting materials were fully consumed within



Scheme 4 Synthesis of dihydro [1,2,3]triazolo[1,5-*a*]pyrazines under palladium-copper catalysis.

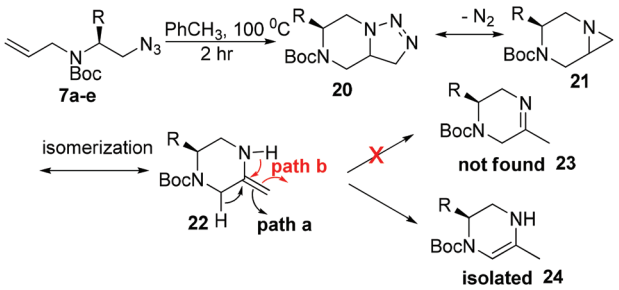


Scheme 5 Synthesis of tetrahydro[1,2,3]triazolo[1,5-*a*][1,4]diazocine.

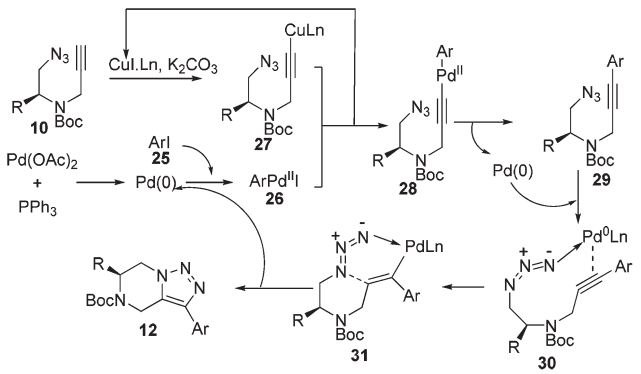
30 min as monitored by TLC even at rt. This mild condition instead of an unnecessary requirement of high temperatures radically improves the utility of this reaction. In order to increase the structural diversity, the functionality at the C-3 position of compound **11** was investigated. Thus, employment of $Pd(OAc)_2/PPh_3$ as a catalyst and CuI as a cocatalyst along with K_2CO_3 as a base allowed the reaction to proceed to completion within 1 h, affording exclusively the desired product **12a,c** with a good yield (81%).

Another pathway was adopted for the synthesis of chiral triazolo [1,5-*a*][1,4]diazocine from the common carbinol precursor (Scheme 5). Compound **4b** was oxidized to aldehyde **13b** which was subjected to HWE olefination in dry DCM (ratio of $E:Z$ = 95 : 5) without any further purification furnishing **14b**. The double bond and the ester group were reduced simultaneously using LAH (3 equiv.) to produce **15b**. Tosylation of the primary alcohol **15b** in the presence of *p*-toluenesulphonyl chloride and triethyl amine followed by nucleophilic substitution with sodium azide affords **17b**. The azido compound was treated with propargylbromide and NaH in the presence of dry DMF at 0 °C to give **18b**. Under similar 1,3-dipolar cycloaddition reaction conditions, **18b** provided triazolo[1,5-*a*][1,4]-diazocine **19b** with an excellent yield.

The formation of 5-methyl-3,4-dihydropyrazine may be rationalized by assuming that the 1,3-DAC reaction proceeds through the generation of a triazoline intermediate **20**, which after nitrogen elimination leads to an aziridine intermediate **21** (Scheme 6). This quickly isomerizes to afford the imine–enamine mixture.[18] From the hitherto intermediate two possibilities can arise, either the reaction can follow 'path a' giving rise to 3,4-dihydropyrazine **24**, or the reaction can follow 'path b' yielding compound **23**. Probably due to the greater stability of compound **24** compared to **23** (the double resonance stabilized with both the nitrogen atoms compared to the single resonance stabilized with one nitrogen atom), compound **24** is the sole product obtained.



Scheme 6 Plausible reaction mechanism for the formation of 5-methyl-3,4-dihydropyrazine.



Scheme 7 Plausible reaction mechanism.

A plausible reaction mechanism for the formation of compound **12** could be explained by applying features of palladium chemistry. The oxidative addition of aryl iodide **25** to Pd(0), formed *in situ* through the interaction of palladium acetate and triphenyl phosphine, affords the arylpalladium(II) complex **26** which undergoes transmetalation with copper-acetylide **27** to generate the arylalkynylpalladium complex **28** (Scheme 7). This on reductive elimination of palladium(0) affords the arylated internal alkyne **29**. Palladium(0) then activates the triple bond through a complex **30**, in which palladium is stabilised by the nitrogen in proximity. Insertion of palladium into the triple bond possibly leads to the vinylidene like transition state **31**. The increase of electron density in the dipolarophile due to the palladium insertion accelerates the cycloaddition through a HOMO–LUMO interaction leading to the formation of the desired cycloadduct **12** with regeneration of palladium(0).

Conclusion

In summary, we have described a simple and powerful synthetic route that provides access to chirally pure diverse 5-methyl-3,4-dihydropyrazine, triazolo[1,5-*a*]pyrazines and triazolo[1,5-*a*][1,4]diazocine starting from commercially available *S*-amino acid derived synthetic intermediates. The key step involves 1,3-dipolar cycloaddition under reagent free con-

ditions, giving heterocycles that can be further elaborated in several ways, such as by nucleophilic substitution on the rings as well as incorporation of substituents at the 6-position from amino acid constituents.

Experimental section

General

IR spectra were recorded on a Perkin-Elmer FT-IR RXI spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker DPX-200 (operating at 200 MHz for ^{1}H and 50 MHz for ^{13}C) or DPX-300 (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer using $CDCl_3$ as the solvent. Tetramethylsilane (0.00 ppm) served as the internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) served as the internal standard in ^{13}C NMR. All spectra were recorded at 25 °C. Coupling constants (J values) are given in hertz (Hz). Chemical shifts are expressed in parts per million (ppm). Mass spectra were recorded by electron spray ionization (ESMS). Glycerol or *m*-nitro benzyl alcohol was used as a matrix. Reactions were monitored on silica gel TLC plates (coated with TLC grade silica gel). Detecting agents used (for TLC) were iodine vapors and/or spraying with an aqueous solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Column chromatography was performed over silica gel (100–200 mesh) procured from Qualigens (India) using freshly distilled solvents.

Experimental procedures and characterization data

General experimental procedure for the synthesis of 5a–e. Compounds **4a–e** (1 equiv.) were dissolved in 20 mL dry DCM and then it was cooled at 0 °C, followed by addition of Et_3N (2 equiv.) and *p*-toluene sulfonyl chloride (1.2 equiv.). Then it was stirred for 3 h at RT and diluted with 30 mL water. The aqueous layer was extracted with DCM (2 × 50 mL) and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the crude product was then chromatographed over silica gel with the eluent AcOEt–hexane (1 : 9) to afford the title compounds **5a–e**.

*(S)-2-(tert-Butoxycarbonylamino)-3-methylbutyl-4-methylbenzenesulfonate **5a**.* Colourless oil; yield, 86%; R_f 0.52 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −11.69 (*c* 0.32, $CHCl_3$); IR (neat, cm^{-1}): 3504, 2960, 1729, 1369, 1175, 775; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 2H, J = 8.2 Hz), 7.27 (d, 2H, J = 7.9 Hz), 4.55 (d, 1H, J = 8.4 Hz), 3.99–3.95 (m, 2H), 3.43 (s, 1H), 2.37 (s, 3H), 1.76–1.67 (m, 1H), 1.33 (s, 9H), 0.80 (t, 6H, J = 8.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4, 144.9, 132.5, 129.8, 127.8, 79.4, 70.0, 54.7, 28.8, 28.2, 21.5, 19.1 ppm; MS (ESI): *m*/*z* 358 $[M + H]^+$; Anal. Calcd for $C_{17}H_{27}NO_5S$: C, 57.12; H, 7.61; N, 3.92; O, 22.38; S, 8.97. Found: C, 57.16; H, 7.64; N, 3.89.

*(S)-2-(tert-Butoxycarbonylamino)-3-phenylpropyl-4-methylbenzenesulfonate **5b**.* Colourless oil; yield, 88%; R_f 0.53 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −7.46 (*c* 0.26, $CHCl_3$); IR (neat, cm^{-1}): 3508, 2959, 1716, 1360, 1177, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 2H, J = 8.0 Hz), 7.21 (d, 2H, J = 7.9 Hz), 7.10–6.96 (m, 5H), 4.75 (s, 1H), 4.03–3.80 (m, 3H), 2.73–2.66 (m, 2H), 2.32 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9, 144.9, 136.7, 132.5, 129.9, 129.1, 128.5, 127.9, 126.6, 79.7, 69.9, 50.7, 37.1, 28.2, 21.5 ppm; MS (ESI): *m*/*z* 406 $[M + H]^+$; Anal. Calcd for $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45; O, 19.73; S, 7.91. Found: C, 62.26; H, 6.74; N, 3.49.

*(S)-2-(tert-Butoxycarbonylamino)propyl-4-methylbenzenesulfonate **5c**.* Colourless oil; yield, 85%; R_f 0.51 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −15.8 (*c* 0.25, $CHCl_3$); IR (neat, cm^{-1}): 3393, 2367, 1692, 1355, 1177, 932; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 2H, J = 8.1 Hz), 7.21 (d, 2H, J = 7.9 Hz), 4.98 (s, 1H), 3.84–3.71 (m, 3H), 2.28 (s, 3H), 1.26 (s, 9H), 0.99 (d, 3H, J = 6.5 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 144.6, 139.3, 129.4, 128.4, 125.5, 78.8, 47.8, 27.7, 23.4, 16.4 ppm; MS (ESI): *m*/*z* 330 $[M + H]^+$; Anal. Calcd for $C_{15}H_{23}NO_5S$: C, 54.69; H, 7.04; N, 4.25; O, 24.28; S, 9.73. Found: C, 54.66; H, 7.14; N, 4.29.

*(S)-2-(tert-Butoxycarbonylamino)-4-methylpentyl-4-methylbenzenesulfonate **5d**.* Colourless oil; yield, 87%; R_f 0.50 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −11.34 (*c* 0.22, $CHCl_3$); IR (neat, cm^{-1}): 3500, 2962, 1737, 1364, 1178, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 7.7 Hz), 4.62 (s, 1H), 3.94–3.73 (m, 3H), 2.33 (s, 3H), 1.46 (d, 1H, J = 5.6 Hz), 1.30 (s, 9H), 1.17 (s, 2H), 0.77 (t, 6H, J = 5.4 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9, 144.6, 132.4, 129.6, 127.6, 79.1, 71.7, 47.4, 39.7, 28.0, 24.2, 22.5, 21.3 ppm; MS (ESI): *m*/*z* 372 $[M + H]^+$; Anal. Calcd for $C_{18}H_{29}NO_5S$: C, 58.20; H, 7.87; N, 3.77; O, 21.53; S, 8.63. Found: C, 58.26; H, 7.84; N, 3.70.

*(2S,3R)-2-(tert-Butoxycarbonylamino)-3-methylpentyl-4-methylbenzenesulfonate **5e**.* Colourless oil; yield, 86%; R_f 0.52 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −21.13 (*c* 0.25, $CHCl_3$); IR (neat, cm^{-1}): 3512, 2956, 1721, 1343, 1177, 769; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2H, J = 8.1 Hz), 7.27 (d, 2H, J = 7.9 Hz), 4.56 (d, 1H, J = 8.4 Hz), 3.98 (s, 2H), 3.49 (bs, 1H), 2.37 (s, 3H), 1.47 (s, 2H), 1.33 (s, 9H), 1.06–0.97 (m, 1H), 0.80–0.74 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 144.7, 132.4, 129.7, 127.7, 79.1, 68.0, 56.8, 38.6, 28.0, 23.8, 21.3, 15.0, 10.7 ppm; MS (ESI): *m*/*z* 372 $[M + H]^+$; Anal. Calcd for $C_{15}H_{23}NO_5S$: C, 58.20; H, 7.87; N, 3.77; O, 21.53; S, 8.63. Found: C, 58.26; H, 7.82; N, 3.71.

General experimental procedure for the synthesis of 6a–f. To a stirred solution of compounds **5a–f** (1 equiv.) in anhydrous DMF (10 mL) sodium azide (2 equiv.) was added. The reaction mixture was stirred for 2 h at 80 °C. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane–ethyl acetate, 9.2/0.8) to furnish compounds **6a–f** (78% yield) as colourless oil.

*(S)-tert-Butyl-1-azido-3-methylbutan-2-ylcarbamate **6a**.* Colourless oil; yield, 77%; R_f 0.60 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −31.15 (*c* 0.17, $CHCl_3$); IR (neat, cm^{-1}): 3348, 2971, 2101, 1701, 1507, 1169, 760; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (s, 1H), 3.44 (s, 1H), 3.34 (d, 2H, J = 3.8 Hz), 1.74–1.67 (m, 1H), 1.38 (s, 9H), 0.86 (t, 6H, J = 6.4 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.4, 79.4, 55.5, 53.0, 29.7, 28.3, 19.4 ppm; MS (ESI): *m*/*z* 229

$[M + H]^+$; Anal. Calcd for $C_{10}H_{20}N_4O_2$: C, 52.61; H, 8.83; N, 24.54; O, 14.02. Found: C, 52.64; H, 8.85; N, 24.50.

(S)-tert-Butyl-1-azido-3-phenylpropan-2-ylcarbamate ***6b***. This product was isolated as colourless oil. yield, 78%, R_f 0.61 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30} = -21.67$ (*c* 0.18, $CHCl_3$); IR (neat, cm^{-1}): 3455, 2975, 2110, 1716, 1513, 1162, 763; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.10 (m, 5H), 4.63 (s, 1H), 3.88 (s, 1H), 3.37–3.15 (m, 2H), 2.77–2.66 (m, 2H), 1.34 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 137.0, 129.1, 128.5, 126.6, 79.6, 53.1, 51.3, 38.1, 28.2 ppm; MS (ESI): *m*/z 277 $[M + H]^+$; Anal. Calcd for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.30; N, 20.28; O, 11.58. Found: C, 60.80; H, 7.36; N, 20.23.

(S)-tert-Butyl-1-azidopropan-2-ylcarbamate ***6c***. Colourless oil; yield, 78%; R_f 0.63 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30} = -24.34$ (*c* 0.16, $CHCl_3$); IR (neat, cm^{-1}): 3352, 2965, 2107, 1689, 1512, 1160, 765; ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (s, 1H), 3.77 (s, 1H), 3.30–3.22 (m, 2H), 1.37 (s, 9H), 1.11 (d, 3H, *J* = 6.7 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 79.4, 55.8, 46.1, 28.2, 18.0 ppm; MS (ESI): *m*/*z* 201 $[M + H]^+$; Anal. Calcd for $C_8H_{16}N_4O_2$: C, 47.99; H, 8.05; N, 27.98; O, 15.98. Found: C, 48.04; H, 8.01; N, 27.91.

(S)-tert-Butyl-1-azido-4-methylpentan-2-ylcarbamate ***6d***. Colourless oil; yield, 78%; R_f 0.60 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30} = -22.19$ (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3359, 2977, 2112, 1700, 1523, 1162, 757; ^1H NMR (300 MHz, $CDCl_3$) δ 4.54 (s, 1H), 3.73 (s, 1H), 3.34–3.22 (m, 2H), 1.65–1.53 (m, 1H), 1.37 (s, 9H), 1.31–1.18 (m, 2H), 0.85 (d, 6H, *J* = 4.8 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 79.4, 55.1, 48.5, 45.1, 28.3, 24.7, 22.9, 22.0 ppm; MS (ESI): *m*/*z* 243 $[M + H]^+$; Anal. Calcd for $C_{11}H_{22}N_4O_2$: C, 54.52; H, 9.15; N, 23.12; O, 13.21. Found: C, 54.48; H, 9.19; N, 23.20.

tert-Butyl (2S,3R)-1-azido-3-methylpentan-2-ylcarbamate ***6e***. Colourless oil; yield, 78%; R_f 0.61 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30} = -24.6$ (*c* 0.16, $CHCl_3$); IR (neat, cm^{-1}): 3378, 2963, 2114, 1709, 1521, 1162, 769; ^1H NMR (300 MHz, $CDCl_3$) δ 4.58 (d, 1H, *J* = 8.0 Hz), 3.51 (s, 1H), 3.35 (s, 2H), 1.48–1.44 (m, 2H), 1.38 (s, 9H), 1.17–0.98 (m, 1H), 0.83 (t, 6H, *J* = 6.7 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 79.3, 54.3, 52.7, 36.2, 28.2, 25.0, 15.3, 11.1 ppm; MS (ESI): *m*/*z* 243 $[M + H]^+$; Anal. Calcd for $C_{11}H_{22}N_4O_2$: C, 54.52; H, 9.15; N, 23.12; O, 13.21. Found: C, 54.57; H, 9.20; N, 23.08.

(S)-tert-Butyl-1-azido-4-(methylthio)butan-2-ylcarbamate ***6f***. This product was isolated as colourless oil. Yield, 76%, R_f 0.62 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30} = -39.72$ (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3478, 2977, 2119, 1752, 1518, 1166, 842, 760; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (d, 1H, *J* = 2.9 Hz), 3.36–3.31 (m, 2H), 2.60–2.43 (m, 3H), 2.03 (s, 3H), 1.75–1.64 (m, 1H), 1.38 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 80.9, 57.6, 52.1, 36.1, 32.3, 28.3, 15.4 ppm; MS (ESI): *m*/z 261 $[M + H]^+$; Anal. Calcd for $C_{10}H_{20}N_4O_2S$: C, 46.13; H, 7.74; N, 21.52; O, 12.29; S, 12.32. Found: C, 46.16; H, 7.78; N, 21.54.

General experimental procedure for the synthesis of 7a–e. To a stirred solution of compounds **6a–e** (1 equiv.) in anhydrous DMF (10 mL) NaH (19 mg, 60% suspension in mineral oil) was added at 0 °C. Then the required amount of allylbromide (1 equiv.) was added at 0 °C. The reaction mixture was stirred for 1 h at RT. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane–ethyl acetate, 9.4/0.6) to furnish the disubstituted morpholine **7a–e** (80% yield).

(S)-tert-Butyl allyl(1-azido-3-methylbutan-2-yl)carbamate ***7a***. Colourless oil; yield, 80%; R_f 0.63 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30} = -11.9$ (*c* 0.12, $CHCl_3$); IR (neat, cm^{-1}): 3483, 2109, 1683, 1415, 1168, 766, 700; ^1H NMR (300 MHz, $CDCl_3$): δ 5.87–5.78 (m, 1H), 5.12–5.04 (m, 2H), 3.81–3.52 (m, 3H), 3.33 (d, 2H, *J* = 9.2 Hz), 1.88–1.86 (m, 1H), 1.39 (s, 9H), 0.84 (dd, 6H, J_1 = 6.5 Hz, J_2 = 14.6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 135.4, 116.1, 80.1, 67.7, 58.8, 45.8, 28.3, 28.2, 20.0 ppm; MS (ESI): *m*/*z* 269 $[M + H]^+$; Anal. Calcd for $C_{13}H_{24}N_4O_2$: C, 58.18; H, 9.01; N, 20.88; O, 11.92. Found: C, 58.20; H, 9.05; N, 20.80.

(S)-tert-Butyl allyl(1-azido-3-phenylpropan-2-yl)carbamate ***7b***. Colourless oil; yield, 81%; R_f 0.62 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30} = -8.61$ (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 2977, 2108, 1690, 1411, 1165, 1024, 758; ^1H NMR (300 MHz, $CDCl_3$): δ 7.18–7.07 (m, 5H), 5.59–5.47 (m, 1H), 4.95 (d, 2H, *J* = 13.5 Hz), 3.87–3.45 (m, 4H), 3.17 (d, 1H, *J* = 9.5 Hz), 2.96–2.63 (m, 2H), 1.35 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.4, 136.6, 128.8, 128.6, 128.1, 126.1, 115.9, 79.6, 54.0, 53.5, 45.9, 37.8, 27.7 ppm; MS (ESI): *m*/*z* 317 $[M + H]^+$; Anal. Calcd for $C_{17}H_{24}N_4O_2$: C, 64.53; H, 7.65; N, 17.71; O, 10.11. Found: C, 64.50; H, 7.69; N, 17.78.

(S)-tert-Butyl allyl(1-azidopropan-2-yl)carbamate ***7c***. Colourless oil; yield, 80%; R_f 0.61 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30} = -14.39$ (*c* 0.17, $CHCl_3$); IR (neat, cm^{-1}): 3486, 2112, 1689, 1410, 1167, 765, 700; ^1H NMR (300 MHz, $CDCl_3$): δ 5.76–5.74 (m, 1H), 5.09–5.02 (m, 2H), 4.02–3.68 (m, 3H), 3.44 (s, 1H), 3.12 (q, 1H, *J* = 5.8 Hz), 1.39 (s, 9H), 1.13 (d, 3H, *J* = 6.9 Hz) ppm; MS (ESI): *m*/*z* 241 $[M + H]^+$; Anal. Calcd for $C_{11}H_{20}N_4O_2$: C, 54.98; H, 8.39; N, 23.32; O, 13.32. Found: C, 54.93; H, 8.43; N, 23.38.

(S)-tert-Butyl allyl(1-azido-4-methylpentan-2-yl)carbamate ***7d***. Colourless oil; yield, 81%; R_f 0.60 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30} = -9.72$ (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3488, 2962, 2110, 1683, 1413, 1168, 762; ^1H NMR (300 MHz, $CDCl_3$): δ 5.78 (s, 1H), 5.10–5.01 (m, 2H), 4.04–3.97 (m, 1H), 3.66 (d, 2H, *J* = 13.6 Hz), 3.49–3.26 (m, 1H), 3.13–3.07 (m, 1H), 1.48 (d, 2H, *J* = 9.9 Hz), 1.39 (s, 10H), 0.89 (t, 6H, *J* = 5.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 135.5, 115.9, 80.0, 53.5, 53.2, 50.3, 39.0, 28.2, 24.7, 24.4, 22.0 ppm; MS (ESI): *m*/*z* 283 $[M + H]^+$; Anal. Calcd for $C_{14}H_{26}N_4O_2$: C, 59.55; H, 9.28; N, 19.84; O, 11.33. Found: C, 59.50; H, 9.22; N, 19.79.

tert-Butyl allyl((2S,3R)-1-azido-3-methylpentan-2-yl)carbamate ***7e***. Colourless oil; yield, 80%; R_f 0.62 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30} = -7.6$ (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3388, 2117, 1680, 1423, 1208, 762, 677; ^1H NMR (300 MHz, $CDCl_3$): δ 5.83–5.81 (m, 1H), 5.09–5.02 (m, 2H), 3.73 (bs, 1H), 3.65–3.48 (m, 3H), 3.36 (s, 1H), 1.39 (s, 9H), 1.07–0.94 (m, 3H), 0.83–0.78 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 135.5, 116.0,

80.1, 67.6, 57.5, 56.1, 38.5, 28.3, 24.5, 15.9, 11.6 ppm; MS (ESI): *m/z* 283 $[M + H]^+$; Anal. Calcd for $C_{14}H_{26}N_4O_2$: C, 59.55; H, 9.28; N, 19.84; O, 11.33. Found: C, 59.60; H, 9.23; N, 19.80.

General experimental procedure for the synthesis of 8a–e. Compounds **7a–e** (1 equiv.) were dissolved in 20 mL dry toluene, and then it was heated up to 100 °C and stirred for 2 h. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane–ethyl acetate, 8/2) to furnish **8a–e** (80% yield) as colourless oil.

*(S)-tert-Butyl 2-isopropyl-5-methyl-3,4-dihydropyrazine-1(2H)-carboxylate **8a**.* Colourless oil; yield, 85%; R_f 0.45 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +35.6 (*c* 0.22, $CHCl_3$); IR (neat, cm^{-1}): 2976, 1763, 1681, 1270, 1161, 1221, 778; ^1H NMR (300 MHz, $CDCl_3$): δ 4.20 (s, 1H), 4.08–3.99 (m, 2H), 3.63–3.56 (m, 1H), 2.16 (s, 3H), 1.89–1.77 (m, 1H), 1.48 (s, 9H), 1.39–1.26 (m, 1H), 0.85 (dd, 6H, J_1 = 3.1 Hz, J_2 = 6.7 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 155.6, 151.9, 83.8, 58.1, 49.0, 30.4, 27.9, 20.8, 20.0, 19.4 ppm; MS (ESI): *m/z* 241 $[M + H]^+$; Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.07; N, 11.66; O, 13.31. Found: C, 64.91; H, 10.12; N, 11.60.

*(S)-tert-Butyl 2-benzyl-5-methyl-3,4-dihydropyrazine-1(2H)-carboxylate **8b**.* Colourless oil; yield, 85%; R_f 0.43 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +31.24 (*c* 0.20, $CHCl_3$); IR (neat, cm^{-1}): 3366, 2338, 1717, 1283, 1154, 1024, 762; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20–7.06 (m, 5H), 5.60 (s, 1H), 4.39–4.33 (m, 1H), 3.81–3.75 (m, 1H), 3.50–3.43 (m, 1H), 2.88–2.82 (m, 1H), 2.70–2.62 (m, 1H), 2.14 (d, 3H, *J* = 1.0 Hz), 1.45 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9, 154.8, 150.8, 136.6, 128.9, 128.2, 126.4, 83.5, 54.1, 48.8, 37.4, 27.5, 20.5 ppm; MS (ESI): *m/z* 289 $[M + H]^+$; Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71; O, 11.10. Found: C, 70.86; H, 8.32; N, 9.68.

*(S)-tert-Butyl 2,5-dimethyl-3,4-dihydropyrazine-1(2H)-carboxylate **8c**.* Colourless oil; yield, 85%; R_f 0.44 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +27.69 (*c* 0.19, $CHCl_3$); IR (neat, cm^{-1}): 2948, 1760, 1642, 1279, 1153, 1201, 770; ^1H NMR (300 MHz, $CDCl_3$): δ 4.95 (s, 1H), 4.40–4.32 (m, 1H), 3.75–3.74 (m, 2H), 2.19 (d, 3H, *J* = 1.8 Hz), 1.48 (s, 10H), 1.18 (d, 3H, *J* = 1.6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8, 155.2, 151.1, 83.6, 52.7, 48.9, 27.7, 20.7, 17.7 ppm; MS (ESI): *m/z* 213 $[M + H]^+$; Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20; O, 15.07. Found: C, 62.26; H, 9.56; N, 13.26.

*(S)-tert-Butyl 2-isobutyl-5-methyl-3,4-dihydropyrazine-1(2H)-carboxylate **8d**.* Colourless oil; yield, 85%; R_f 0.45 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +37.19 (*c* 0.18, $CHCl_3$); IR (neat, cm^{-1}): 3440, 1718, 1651, 1286, 1157, 768; ^1H NMR (300 MHz, $CDCl_3$): δ 4.70 (s, 1H), 4.33–4.27 (m, 1H), 3.94–3.88 (m, 1H), 3.65–3.57 (m, 1H), 2.18 (d, 3H, *J* = 2.3 Hz), 1.48 (s, 10H), 1.41 (d, 1H, *J* = 5.3 Hz), 1.35–1.24 (m, 2H), 0.87–0.84 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 155.3, 150.9, 83.6, 51.1, 49.7, 40.1, 27.6, 24.8, 23.0, 21.2, 20.6 ppm; MS (ESI): *m/z* 255 $[M + H]^+$; Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 66.10; H, 10.30; N, 11.01; O, 12.58. Found: C, 66.16; H, 10.25; N, 11.07.

*(S)-tert-Butyl 2-sec-butyl-5-methyl-3,4-dihydropyrazine-1(2H)-carboxylate **8e**.* Colourless oil; yield, 85%; R_f 0.42 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +34.7 (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3471, 2356, 1703, 1370, 1155, 768, 672; ^1H NMR (300 MHz, $CDCl_3$): δ 4.67 (s, 1H), 4.16–4.12 (m, 1H), 4.04–3.98 (m, 1H), 3.63–3.57 (m, 1H), 2.16 (s, 3H), 1.62–1.53 (s, 1H), 1.48 (s, 9H), 1.39–1.27 (m, 2H), 1.14–1.02 (m, 1H), 0.85–0.77 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 155.8, 151.8, 83.8, 56.8, 48.6, 37.2, 27.9, 25.6, 20.8, 16.4, 11.6 ppm; MS (ESI): *m/z* 255 $[M + H]^+$; Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 66.10; H, 10.30; N, 11.01; O, 12.58. Found: C, 66.17; H, 10.36; N, 11.06.

General experimental procedure for the synthesis of 9. To a stirred solution of compounds **8** (1 equiv.) in anhydrous DCM (10 mL) TFA (1 equiv.) was added at 0 °C. The resulting solution was then warmed to RT and it was stirred for 30 min. The aqueous layer was extracted with DCM (3 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane–ethyl acetate, 7.5/2.5) to furnish compound **9**.

*(S)-2-Isopropyl-5-methyl-1,2,3,4-tetrahydropyrazine **9a**.* Colourless oil; yield, 74%; R_f 0.41 (6/4, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +23.12 (*c* 0.14, $CHCl_3$); IR (neat, cm^{-1}): 3721, 2352, 1659, 1237, 1011, 779, 674; ^1H NMR (300 MHz, $CDCl_3$): δ 4.37 (s, 1H), 3.70–3.62 (m, 3H), 2.78 (bs, 1H), 2.11 (s, 3H), 1.79–1.72 (m, 1H), 0.93–0.89 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 126.6, 109.3, 70.6, 48.6, 32.3, 19.8 ppm; MS (ESI): *m/z* 141 $[M + H]^+$; Anal. Calcd for $C_8H_{16}N_2$: C, 68.52; H, 11.50; N, 19.98. Found: C, 68.57; H, 11.47; N, 19.96.

*(S)-2-Isobutyl-5-methyl-1,2,3,4-tetrahydropyrazine **9d**.* Colourless oil; yield, 73%; R_f 0.42 (6/4, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +13.46 (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3709, 2351, 1670, 1222, 1031, 776, 678; ^1H NMR (300 MHz, $CDCl_3$): δ 4.58 (s, 1H), 3.56–3.48 (m, 1H), 3.30–3.19 (m, 2H), 2.76–2.65 (m, 1H), 2.13 (s, 3H), 1.69–1.61 (m, 1H), 1.30–1.20 (m, 2H), 0.88–0.85 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 126.0, 108.0, 59.9, 49.8, 40.3, 25.0, 23.3, 19.5 ppm; MS (ESI): *m/z* 155 $[M + H]^+$; Anal. Calcd for $C_9H_{18}N_2$: C, 70.08; H, 11.76; N, 18.16. Found: C, 70.04; H, 11.78; N, 18.12.

*(S)-2-sec-Butyl-5-methyl-1,2,3,4-tetrahydropyrazine **9e**.* Colourless oil; yield, 75%; R_f 0.40 (6/4, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +19.6 (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3712, 2360, 1638, 1218, 1026, 771, 672; ^1H NMR (300 MHz, $CDCl_3$): δ 4.57 (s, 1H), 3.79–3.69 (m, 1H), 3.38 (d, 2H, *J* = 5.3 Hz), 2.40 (bs, 1H), 2.14 (s, 3H), 1.49–1.36 (m, 3H), 1.18–1.07 (m, 1H), 0.88–0.84 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 125.8, 108.0, 66.4, 48.6, 41.3, 24.8, 19.8, 18.0, 12.0 ppm; MS (ESI): *m/z* 155 $[M + H]^+$; Anal. Calcd for $C_9H_{18}N_2$: C, 70.08; H, 11.76; N, 18.16. Found: C, 70.01; H, 11.79; N, 18.10.

General experimental procedure for the synthesis of 10a–f. To a stirred solution of compounds **6a–e** (1 equiv.) in anhydrous DMF (10 mL), NaH (18 mg, 60% suspension in mineral oil) was added at 0 °C. Then the required amount of propargyl bromide (1 equiv.) was added at 0 °C. The reaction mixture was stirred for 1 h at RT. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted

with ethyl acetate (2 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane–ethyl acetate, 9.6/0.4) to furnish **10a–f** (78–81% yield).

(S)-tert-Butyl 1-azido-3-methylbutan-2-yl(prop-2-ynyl)carbamate ***10a***. Colourless oil; yield, 78%; R_f 0.65 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −41.7 (*c* 0.12, $CHCl_3$); IR (neat, cm^{-1}): 3421, 2123, 2102, 1641, 1166, 793, 741; ^1H NMR (300 MHz, $CDCl_3$): δ 4.69 (d, 1H, *J* = 13.0 Hz), 4.15 (dd, 2H, J_1 = 4.2 Hz, J_2 = 13.4 Hz), 4.09 (s, 1H), 3.33 (d, 1H, *J* = 4.1 Hz), 2.74 (d, 1H, *J* = 2.3 Hz), 2.18–2.12 (m, 1H), 1.42 (s, 9H), 0.86 (t, 6H, *J* = 7.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 80.8, 78.8, 54.1, 52.4, 46.4, 35.9, 27.9, 24.7, 15.0 ppm; MS (ESI): *m*/*z* 267 $[M + H]^+$; Anal. Calcd for $C_{13}H_{22}N_4O_2$: C, 58.62; H, 8.33; N, 21.04; O, 12.01. Found: C, 58.68; H, 8.29; N, 21.10.

(S)-tert-Butyl 1-azido-3-phenylpropan-2-yl(prop-2-ynyl)carbamate ***10b***. Colourless oil; yield, 79%; R_f 0.64 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −38.9 (*c* 0.12, $CHCl_3$); IR (neat, cm^{-1}): 3334, 2137, 2111, 1661, 1472, 1166, 762, 702; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21–7.10 (m, 5H), 4.00–3.59 (m, 3H), 3.26 (d, 1H, *J* = 10.3 Hz), 2.95–2.82 (m, 2H), 1.37 (s, 9H), 1.32 (d, 2H, *J* = 4.5 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8, 137.7, 129.0, 128.9, 128.5, 81.2, 80.0, 72.2, 58.8, 52.0, 31.8, 30.5, 28.2 ppm; MS (ESI): *m*/*z* 315 $[M + H]^+$; Anal. Calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82; O, 10.18. Found: C, 64.90; H, 7.00; N, 17.88.

(S)-tert-Butyl 1-azidopropan-2-yl(prop-2-ynyl)carbamate ***10c***. Colourless oil; yield, 80%; R_f 0.62 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −47.6 (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3473, 2137, 2107, 1446, 1153, 761, 704; ^1H NMR (300 MHz, $CDCl_3$): δ 4.40–4.23 (m, 1H), 4.02–3.88 (m, 3H), 3.48 (t, 1H, *J* = 11.2 Hz), 3.24–3.18 (m, 1H), 1.42 (s, 9H), 1.21 (d, 3H, *J* = 6.7 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8, 81.1, 80.5, 70.6, 50.1, 44.8, 35.9, 28.2, 15.9 ppm; MS (ESI): *m*/*z* 239 $[M + H]^+$; Anal. Calcd for $C_{11}H_{18}N_4O_2$: C, 55.44; H, 7.61; N, 23.51; O, 13.43. Found: C, 55.40; H, 7.65; N, 23.46.

(S)-tert-Butyl 1-azido-4-methylpentan-2-yl(prop-2-ynyl)carbamate ***10d***. Colourless oil; yield, 81%; R_f 0.66 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −42.4 (*c* 0.14, $CHCl_3$); IR (neat, cm^{-1}): 3431, 2132, 2104, 1441, 1161, 782, 704; ^1H NMR (300 MHz, $CDCl_3$): δ 4.58 (d, 1H, *J* = 7.8 Hz), 3.72 (s, 1H), 3.33–3.32 (m, 2H), 1.58–1.56 (m, 1H), 1.42 (s, 2H), 1.37 (s, 9H), 1.29–1.19 (m, 2H), 0.85 (d, 6H, *J* = 6.5 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9, 81.3, 78.1, 72.2, 53.3, 49.3, 38.7, 30.5, 28.2, 24.8, 24.5, 21.6 ppm; MS (ESI): *m*/*z* 281 $[M + H]^+$; Anal. Calcd for $C_{14}H_{24}N_4O_2$: C, 59.98; H, 8.63; N, 19.98; O, 11.41. Found: C, 59.90; H, 8.67; N, 19.90.

tert-Butyl (2S,3R)-1-azido-3-methylpentan-2-yl(prop-2-ynyl)carbamate ***10e***. Colourless oil; yield, 79%; R_f 0.64 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −37.6 (*c* 0.18, $CHCl_3$); IR (neat, cm^{-1}): 3489, 2122, 2105, 1419, 1134, 781, 723; ^1H NMR (300 MHz, $CDCl_3$): δ 4.72–4.62 (m, 1H), 3.92–3.75 (m, 1H), 3.43–3.34 (m, 3H), 1.41 (s, 9H), 1.37 (s, 3H), 1.07–1.02 (s, 1H), 0.84 (d, 6H, *J* = 6.3 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 81.2, 80.0, 72.2, 57.5, 56.1, 38.5, 34.1, 28.3, 24.5, 15.9, 11.6 ppm; MS (ESI): *m*/*z* 281 $[M + H]^+$; Anal. Calcd for $C_{14}H_{24}N_4O_2$: C, 59.98; H, 8.63; N, 19.98; O, 11.41. Found: C, 59.92; H, 8.69; N, 19.92.

(S)-tert-Butyl 1-azido-4-(methylthio)butan-2-yl(prop-2-ynyl)carbamate ***10f***. Colourless oil; yield, 81%; R_f 0.63 (8.5/1.5, hexane–ethyl acetate); $[\alpha]_D^{30}$ = −30.1 (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3411, 2167, 2115, 1420, 1131, 869, 775, 720; ^1H NMR (300 MHz, $CDCl_3$): δ 3.78–3.77 (m, 2H), 3.36–3.31 (m, 2H), 2.60 (s, 1H), 2.49–2.43 (m, 2H), 2.03 (s, 3H), 1.75–1.64 (m, 3H), 1.38 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8, 81.2, 80.0, 72.2, 56.8, 48.6, 37.2, 30.5, 28.2, 16.4 ppm; MS (ESI): *m*/*z* 299 $[M + H]^+$; Anal. Calcd for $C_{13}H_{22}N_4O_2S$: C, 52.32; H, 7.43; N, 18.78; O, 10.72; S, 10.75. Found: C, 52.37; H, 7.40; N, 18.81.

General experimental procedure for the synthesis of 11a–e. The procedure was followed as described for **8a–e**.

(S)-tert-Butyl 6-isopropyl-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazine-5(4H)-carboxylate ***11a***. Colourless oil; yield, 80%; R_f 0.40 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +11.12 (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3312, 1721, 1212, 1067, 783, 656; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 5.06 (bs, 1H), 4.69 (d, 1H, *J* = 12.8 Hz), 4.18–4.12 (m, 3H), 1.53–1.49 (m, 1H), 1.43 (s, 9H), 0.91 (d, 3H, *J* = 6.5 Hz), 0.85 (d, 3H, *J* = 6.6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 154.2, 129.1, 81.1, 54.7, 46.7, 36.7, 28.2, 26.9, 19.8 ppm; MS (ESI): *m*/*z* 267 $[M + H]^+$; Anal. Calcd for $C_{13}H_{22}N_4O_2$: C, 58.62; H, 8.33; N, 21.04; O, 12.01. Found: C, 58.67; H, 8.31; N, 21.10.

(S)-tert-Butyl 6-benzyl-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazine-5(4H)-carboxylate ***11b***. Colourless oil; yield, 81%; R_f 0.41 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +15.4 (*c* 0.13, $CHCl_3$); IR (neat, cm^{-1}): 3245, 3013, 1694, 1398, 1165, 759; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.28–7.17 (m, 3H), 7.08 (d, 2H, *J* = 7.1 Hz), 5.05–5.00 (m, 2H), 4.53 (d, 1H, *J* = 13.2 Hz), 4.43–4.37 (m, 1H), 4.19 (d, 1H, *J* = 10.4 Hz), 2.73–2.66 (m, 1H), 2.57–2.50 (m, 1H), 1.36 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 136.3, 129.2, 129.0, 128.6, 126.9, 81.2, 61.1, 58.0, 47.8, 36.4, 28.1 ppm; MS (ESI): *m*/*z* 315 $[M + H]^+$; Anal. Calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82; O, 10.18. Found: C, 64.90; H, 7.10; N, 17.88.

(S)-tert-Butyl 6-methyl-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazine-5(4H)-carboxylate ***11c***. Colourless oil; yield, 83%; R_f 0.42 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +11.7 (*c* 0.11, $CHCl_3$); IR (neat, cm^{-1}): 3454, 1761, 1243, 1025, 791, 679; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 4.95–4.90 (s, 1H), 4.78 (bs, 1H), 4.32 (d, 1H, *J* = 12.9 Hz), 4.23–4.18 (m, 2H), 1.35 (s, 9H), 1.01 (d, 3H, *J* = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 153.4, 128.8, 80.7, 49.9, 44.5, 35.8, 27.8, 15.5 ppm; MS (ESI): *m*/*z* 239 $[M + H]^+$; Anal. Calcd for $C_{11}H_{18}N_4O_2$: C, 55.44; H, 7.61; N, 23.51; O, 13.43. Found: C, 55.40; H, 7.67; N, 23.58.

(S)-tert-Butyl 6-isobutyl-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazine-5(4H)-carboxylate ***11d***. Colourless oil; yield, 80%; R_f 0.43 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +16.4 (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3468, 2921, 2257, 1781, 1491, 1221, 761; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 5.08 (d, 1H, *J* = 14.2 Hz), 4.74 (bs, 1H), 4.37 (d, 1H, *J* = 12.9 Hz), 4.25 (d, 1H, *J* = 4.4 Hz), 4.20 (d, 1H, *J* = 4.6 Hz), 4.12 (d, 1H, *J* = 15.7 Hz), 1.41 (s, 9H), 0.86 (q, 6H, *J* = 6.4 Hz), 0.77 (d, 3H, *J* = 6.6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 153.5, 128.7, 80.7, 49.0, 38.3, 29.3,

27.8, 24.4, 22.5, 21.7 ppm; MS (ESI): *m/z* 281 $[M + H]^+$; Anal. Calcd for $C_{14}H_{24}N_4O_2$: C, 59.98; H, 8.63; N, 19.98; O, 11.41. Found: C, 59.92; H, 8.61; N, 19.95.

(S)-tert-Butyl 6-sec-butyl-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazine-5(4H)-carboxylate ***11e***. Colourless oil; yield, 81%; R_f 0.41 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +17.6 (*c* 0.14, $CHCl_3$); IR (neat, cm^{-1}): 3435, 2961, 2341, 1768, 1420, 1209, 763; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 5.07 (bs, 1H), 4.70 (d, 1H, *J* = 13.1 Hz), 4.17–4.01 (m, 3H), 1.42 (s, 9H), 1.32 (d, 2H, *J* = 6.0 Hz), 1.12–1.03 (m, 1H), 0.85–0.78 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 153.9, 128.8, 80.9, 63.9, 56.0, 46.5, 32.4, 27.9, 24.6, 15.6, 10.4 ppm; MS (ESI): *m/z* 281 $[M + H]^+$; Anal. Calcd for $C_{14}H_{24}N_4O_2$: C, 59.98; H, 8.63; N, 19.98; O, 11.41. Found: C, 59.90; H, 8.67; N, 19.91.

(S)-tert-Butyl 6-(2-(methylthio)ethyl)-6,7-dihydro-[1,2,3]triazolo-[1,5-a]pyrazine-5(4H)-carboxylate ***11f***. Colourless oil; yield, 83%; R_f 0.40 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +16.21 (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3411, 2918, 2362, 1779, 1431, 1253, 1213, 762; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 2.44–2.42 (m, 5H), 2.11–2.10 (m, 5H), 2.07 (s, 3H), 1.38 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 147.9, 136.6, 79.7, 56.5, 55.1, 40.8, 33.8, 30.9, 28.7, 15.9 ppm; MS (ESI): *m/z* 299 $[M + H]^+$; Anal. Calcd for $C_{13}H_{22}N_4O_2S$: C, 52.32; H, 7.43; N, 18.78; O, 10.72; S, 10.75. Found: C, 52.30; H, 7.46; N, 18.77.

General experimental procedure for the synthesis of 12a, c. A solution of $Pd(OAc)_2$ (7 mol%) and PPh_3 (23 mol%) in dry DMF (2 mL) was stirred at room temperature for 20 min under an argon atmosphere. Aryl iodide (0.9 mmol), K_2CO_3 (1.8 mmol) and tetrabutylammonium bromide (7 mol%) were then added successively and the whole reaction mixture was allowed to stir at room temperature for another 15 min. A solution of azido-acetylene **10a,c** (1 equiv.) in dry DMF (3 mL) was added dropwise, followed by the addition of CuI (15 mol%). The resulting mixture was flushed with argon carefully and stirred for 45 min at room temperature. After disappearance of the starting materials (monitored by TLC), the reaction mixture was allowed to heat at 90 °C for 1 h. The reaction mixture was diluted with water (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane–ethyl acetate, 9/1) to furnish **12c** (81% yield).

(S)-tert-Butyl 6-isopropyl-3-(4-methoxyphenyl)-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazine-5(4H)-carboxylate ***12a***. Colourless oil; yield, 79%; R_f 0.50 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +22.0 (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3467, 1752, 1362, 1290, 1073, 771, 679; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.17 (m, 3H), 7.05 (d, 1H, *J* = 5.5 Hz), 4.52–4.34 (m, 2H), 4.19–4.15 (m, 2H), 3.76 (s, 3H), 2.68–2.65 (m, 1H), 2.53–2.47 (m, 1H), 1.33 (s, 9H), 1.23 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 155.6, 146.9, 143.3, 128.3, 123.0, 114.0, 79.4, 66.6, 56.9, 55.4, 36.4, 28.1, 27.7, 20.6 ppm; MS (ESI): *m/z* 373 $[M + H]^+$; Anal. Calcd for $C_{20}H_{28}N_4O_3$: C, 64.49; H, 7.58; N, 15.04; O, 12.89. Found: C, 64.47; H, 7.61; N, 15.07.

(S)-tert-Butyl 6-methyl-3-phenyl-6,7-dihydro-[1,2,3]triazolo[1,5-a]-pyrazine-5(4H) carboxylate ***12c***. Colourless oil; yield, 81%; R_f 0.52 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +26.9 (*c* 0.13, $CHCl_3$); IR (neat, cm^{-1}): 3437, 1776, 1434, 1265, 1082, 763, 671; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.23 (m, 5H), 4.40–4.10 (m, 3H), 3.59–3.50 (m, 1H), 3.25–3.21 (m, 1H), 1.44 (s, 9H), 1.27 (d, 3H, *J* = 4.7 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 131.6, 128.9, 128.2, 127.8, 126.0, 122.9, 81.7, 60.0, 56.0, 34.6, 28.5, 14.0 ppm; MS (ESI): *m/z* 315 $[M + H]^+$; Anal. Calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82; O, 10.18. Found: C, 64.90; H, 7.10; N, 17.78.

General experimental procedure for the synthesis of 14b. To an ice cooled solution of compound **13b** (1 equiv.) in dry DCM (10 mL), $Ph_3P{=}CHCO_2Et$ (1.3 equiv.) was added. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the solvent was evaporated and the residue was chromatographed over silica gel to furnish **14b** as colourless oil.

(S,E)-Ethyl 4-((tert-butoxycarbonyl) amino)-5-phenylpent-2-enoate ***14b***. Colourless oil; yield, 89%; R_f 0.50 (8/2, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +9.81 (*c* 0.15, $CHCl_3$); IR (neat, cm^{-1}): 3420, 1735, 1680, 1261, 1154, 791, 673; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.15 (m, 3H), 7.09 (d, 2H, *J* = 5.2 Hz), 5.78 (d, 1H, *J* = 12.6 Hz), 4.56 (s, 2H), 4.12–4.07 (m, 2H), 2.85–2.80 (m, 2H), 1.31 (s, 9H), 1.90 (t, 3H, *J* = 5.3 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 154.8, 147.5, 136.3, 129.2, 128.4, 126.7, 120.9, 79.6, 60.3, 52.2, 40.7, 28.1, 14.1 ppm; MS (ESI): *m/z* 320 $[M + H]^+$; Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39; O, 20.04. Found: C, 67.61; H, 7.92; N, 4.32.

General experimental procedure for the synthesis of 15b. To a stirred solution of compound **14b** (1 equiv.) in anhydrous THF (10 mL), $LiAlH_4$ (3 equiv.) was added portion wise. The reaction was cooled to 0 °C and stirred for 3 h. The reaction was quenched by addition of ethyl acetate (30 mL) followed by water (30 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel(eluent = hexane–ethyl acetate, 8/2) to furnish the carbinol **15b**.

(S)-tert-Butyl 5-hydroxy-1-phenylpentan-2-ylcarbamate ***15b***. Colourless oil; yield, 68%; R_f 0.40 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +17.29 (*c* 0.13, $CHCl_3$); IR (neat, cm^{-1}): 3329, 1854, 1351, 1291, 981, 793, 674; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.13 (m, 5H), 4.67 (s, 1H), 3.79 (s, 1H), 3.61–3.57 (m, 1H), 3.50–3.45 (m, 1H), 2.76 (d, 2H, *J* = 5.3 Hz), 1.61 (d, 2H, *J* = 6.0 Hz), 1.35 (s, 9H), 1.18 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 143.1, 138.7, 129.7, 126.9, 80.9, 66.2, 58.8, 46.9, 37.7, 29.7, 28.1 ppm; MS (ESI): *m/z* 280 $[M + H]^+$; Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01; O, 17.18. Found: C, 68.71; H, 9.09; N, 4.96.

General experimental procedure for the synthesis of 19b. The procedure was followed as described for **11a–e**.

(R)-tert-Butyl 6-benzyl-6,7,8,9-tetrahydro-[1,2,3]triazolo[1,5-a]-[1,4]diazocine-5(4H)-carboxylate ***19b***. Colourless oil; yield, 84%; R_f 0.42 (7/3, hexane–ethyl acetate); $[\alpha]_D^{30}$ = +28.41 (*c* 0.11, $CHCl_3$); IR (neat, cm^{-1}): 3278, 3023, 1681, 1391, 1121, 781, 673; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.25–7.17 (m, 3H), 7.06–7.01 (m, 2H), 5.13–4.71 (m, 2H), 4.71 (d, 1H, *J* =

13.1 Hz), 4.36 (d, 1H, J = 12.9 Hz), 4.25–4.16 (m, 2H), 2.75–2.64 (m, 2H), 2.53–2.47 (m, 2H), 2.02–1.96 (m, 1H), 1.33 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 136.4, 131.3, 129.1, 128.8, 128.4, 127.0, 81.4, 58.9, 47.0, 40.2, 36.6, 29.6, 28.1, 22.1 ppm; MS (ESI): m/z 343 $[M + H]^+$; Anal. Calcd for $C_{19}H_{26}N_4O_2$: C, 66.64; H, 7.65; N, 16.36; O, 9.34. Found: C, 66.61; H, 7.71; N, 16.30.

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