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ARTICLE TYPE

A rapid entry to amino acids 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]triazolopyrazines and 7,8-dihydro-[1,2,3]triazolodiazepines through intramolecular 1,3-dipolar cycloaddition from amino acids derived common intermediate 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 under 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] during the 1960's 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 importance including anti-HIV,[9a] anti-allergic,[9b] anti-bacterial,[9c] and fungicidal activity.[9d] On the other hand, piperazine fused triazole compounds are found in a number of biologically active natural products, synthetic agents, and drugs.

Besides, 1,2,3-triazolo[1,5-*a*]quinoxaline **1** (Figure **1**) has also been 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

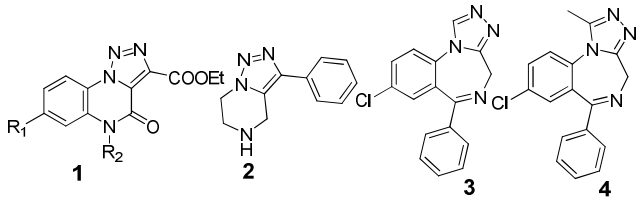
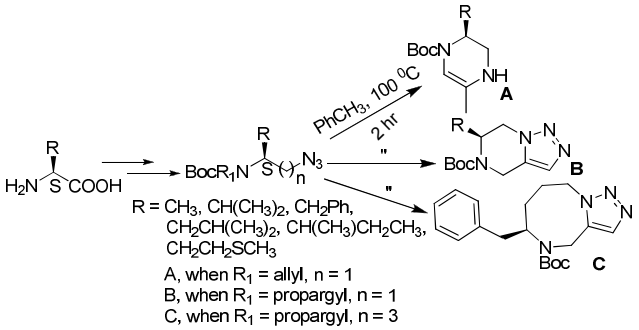


Figure1. Some important triazolo-piperazine derivatives

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 azide and terminal alkyne, limiting the diversity of substitutions at C-3 and C-4 of the product. Despite the significant interest of these heterocyclic systems in medicinal chemistry, [13] arising from its close structural similarity with 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]

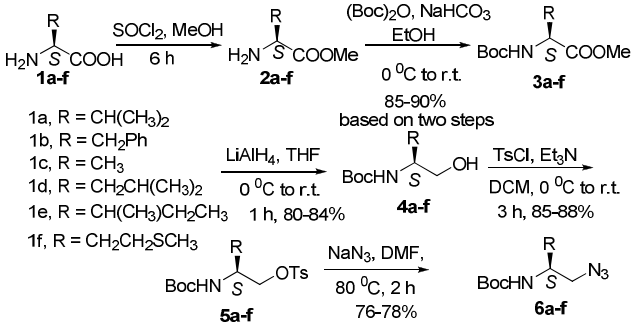
Our work centered on chemical synthesis and properties of *S*-amino acids-derived chiral heterocycles and natural product-like molecules.[17] Recently, we have published a series of amino acids derived benzoxazepines as antitumor agents in breast cancer[17b] and a novel methodology for the synthesis of *trans*-2,5-disubstituted morpholines, piperazines and thiomorpholines through a straight forward 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 acids derived substituted dihydro[1,2,3]triazolo [1,5-a]pyrazines and their ring fused analogues (Scheme **1**).



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

Results and discussion:

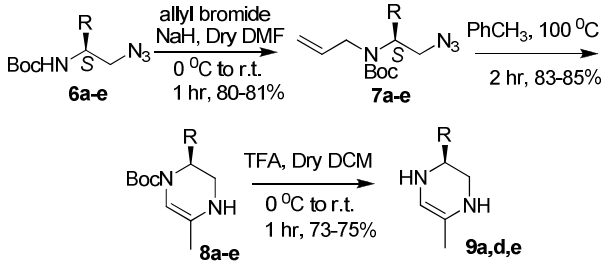
The synthesis of the required substrates for 1,3-dipolar cycloaddition reaction began with S-amino acids **1a-f** which was converted to their methyl esters **2a-f** followed by boc protection of primary amine to give **3a-f** (Scheme **2**). Ester reduction to **4a-f** proceeded smoothly, followed by tosyl protection of primary alcohol affording **5a-f**. Amino acid-derived azido substrates **6a-f** for intramolecular click reaction was synthesized by an S_N2 displacement of the corresponding tosylates with NaN_3. All of these steps were accomplished in excellent yields and are



Scheme 2: Synthesis of intermediates **6a-e**

amenable to easy scale-up. In this letter, we reveal an effective integration of click chemistry onto amino acid substrates in order to synthesize 1,2,3-triazole-fused bicyclic compounds in high yields.

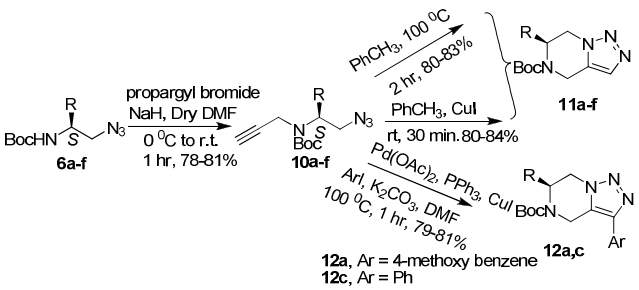
The derived azido compound **6a-e** reacted smoothly with allylbromide and NaH in presence of dry DMF at 0 ^{0}C to give **7a-e** (Scheme **3**). The peak at ν_{max} 2108 cm^{-1} in the IR spectra of the products clearly indicated the presence of azide functionality. Finally, 1,3-dipolar cycloaddition reaction was carried out under reagent-free conditions by heating a toluene solution of the azido alkene **7a-e** at 100 ^{0}C for 2 h to provide 5-methyl-3,4-dihydropyrazine in good yield. 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 additional opportunity for diversity oriented synthesis through derivatization of the resulting secondary amine.



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

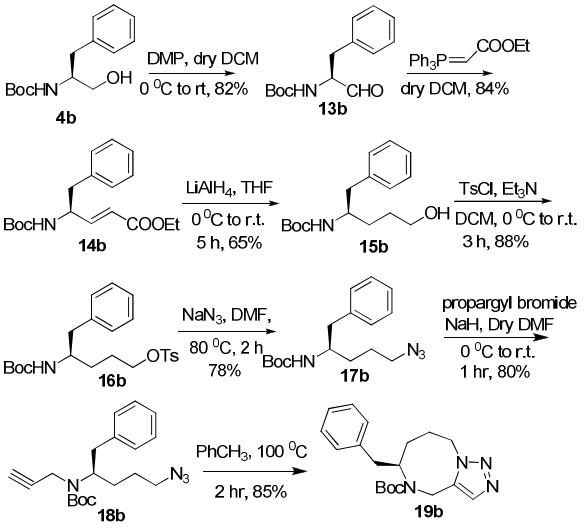
With intermediate azido compound **6a-f** in hand, synthesis of dihydro [1,2,3]triazolo [1,5-a]pyrazines was attempted. Compounds **6a-f** was treated with propargyl bromide and NaH in presence of dry DMF at 0 ^{0}C to furnish azido alkynes **10a-f**. As above, reagent-free conditions by heating a toluene solution of the azidoalkene at 100 ^{0}C gave triazolo [1,5-a]pyrazines **11a-f** in good yield (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 30 min as monitored by TLC even at rt. This mild condition instead of unnecessary requirement of high temperatures radically improves the utility of this reaction. In order to increase the structural diversity, functionality at C-3 position of compound **11** was investigated. Thus, employment of $Pd(OAc)_2/PPh_3$ as catalyst and CuI as cocatalyst along with K_2CO_3 as base allowed the reaction to proceed to completion within 1 hr, affording exclusively the desired product **12a,c** with 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



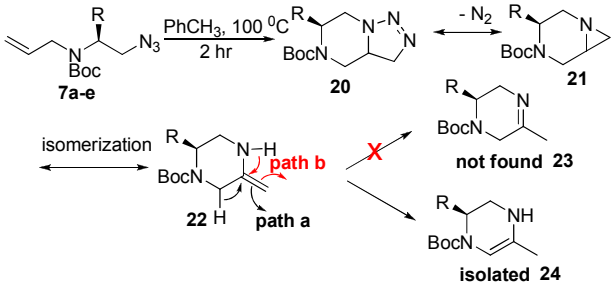
Scheme 4: Synthesis of dihydro [1,2,3]triazolo[1,5-a]pyrazines under palladium-copper catalysis.

13b which was subjected to HWE olefination in dry DCM (ratio of *E:Z* = 95:5) without anyfurther purification furnishing **14b**. Double bond and ester group was 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 presence of dry DMF at 0 ^{0}C to give **18b.** Under similar 1,3-dipolar cycloaddition reaction condition, **18b** provided triazolo[1,5-a][1,4]diazocine **19b** with excellent yield.



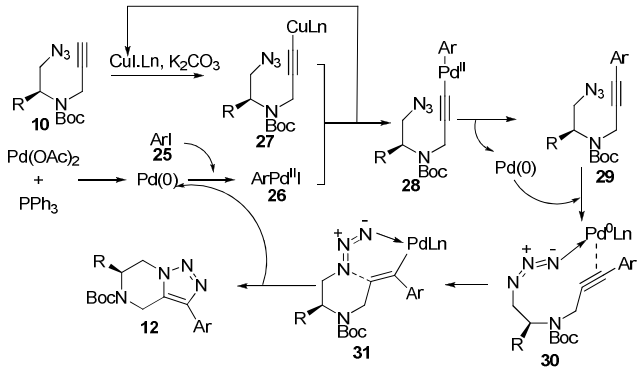
Scheme 5: Synthesis of tetrahydro[1,2,3]triazolo[1,5-a][1,4]diazocine.

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 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 the compound **24** compared to **23** (doubly resonance stabilized with both the nitrogen atoms compared to 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

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 arylpalladium(II) complex **26** which undergoes transmetalation with copper-acetylide **27** to generate arylalkynylpalladium complex **28** (Scheme **7**). This on reductive elimination of palladium (0) affords the arylated internal alkyne **29**. Palladium (0) then activate 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).



Scheme 7: Plausible reaction mechanism

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 acids derived synthetic intermediates. The key step involves 1,3-

dipolar cycloaddition under reagent free condition, giving heterocycles that can be further elaborated in several ways, such as by nucleophilic substitution on the rings as well as incorporation of substituent at 6-position from amino acids 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 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 solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^{1}H NMR and CDCl3 (77.0 ppm) in ^{13}C NMR. All spectra were recorded at 25 ^{0}C. Coupling constants (*J* values) are given in hertz (Hz). Chemical shifts are expressed in parts per million (ppm). Mass spectra were recorded using electron spray ionization (ESMS). Glycerol or *m*-nitro benzyl alcohol was used as 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 ^{0}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: The compound **4a-e** (1equiv) was dissolved in 20 mL dry DCM and then it was cooled at 0 ^{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 X 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 eluent AcOEt-Hexane (1:9) to afford the title compound **5a-e.**

(*S*)-2-(tert-butoxycarbonylamino)-3-methylbutyl4-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-phenylpropyl4-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)propyl4-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-methylpentyl4-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 compound **5a-f** (1 equiv.) in anhydrous DMF (10 mL) sodium azide (2 equiv.) was added. Reaction mixture was stirred for 2 h at 80 ^{0}C. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 X 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 with (eluent = hexane/ethyl acetate, 9.2/0.8) as eluent to furnish the compound **6a-f** (78% yield) as a 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; ^1H 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 compound 6**a-e** (1 equiv.) in anhydrous DMF (10 mL) NaH (19 mg, 60% suspension in mineral oil) was added at 0 ^{0}C. Then required amount of allylbromide (1 equiv.) was added at 0 ^{0}C. 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 X 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 with (eluent = hexane/ethyl acetate, 9.4/0.6) as eluent 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-butylallyl((2*S*,3*R*)-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: The compound **7a-e** (1equiv) was dissolved in 20 mL dry toluene, and then it was heated upto 100 ^0C and stirred for 2 h. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 X 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 with (eluent = hexane/ethyl acetate, 8/2) as eluent to furnish **8a-e** (80% yield) as a 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 or 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 ^0C. The resulting solution was then warmed to RT and it was stirred for 30 min. The aqueous layer was extracted with DCM (3 X 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 the 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 or the synthesis of 10a-f: To a stirred solution of compound 6**a-e** (1 equv.) in anhydrous DMF (10 mL), NaH (18 mg, 60% suspension in mineral oil) was added at 0 ^{0}C. Then required amount of propargyl bromide (1 equiv.) was added at 0 ^{0}C. 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 X 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 with (eluent = hexane/ethyl acetate, 9.6/0.4) as eluent 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 or 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 or the synthesis of 12a,c: To a stirred 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 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 15min. 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 starting materials (monitored by TLC), the reaction mixture was allowed to heat at 90 ^0C for 1 hr. The reaction mixture was diluted with water (20 mL). The aqueous layer was extracted with ethyl acetate (2 X 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 with (eluent = hexane/ethyl acetate, 9/1) as eluent 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-butyl6-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 or 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 2h. 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 or the synthesis of 15b: To a stirred solution of compound **14b** (1 equv.) in anhydrous THF (10 mL), $LiAlH_4$ (3 equiv.) was added portion wise. The reaction was cooled to 0 ^0C and stirred for 3 h. The reaction was quenched by addition of ethyl acetate (30 mL) followed by water (30 mL) at 0 ^0C. The aqueous layer was extracted with ethyl acetate (3 X 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 as 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 or the synthesis of 19b:

The procedure was followed as described for **11a-e**.

(R)-tert-butyl6-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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Notes and references

(1) (a) R. Huisgen, *Proc. Chem. Soc.*, **1961**, 357; (b) R. Huisgen, *Angew.Chem., Int. Ed. Engl.*, **1963**, *2*, 565; (c) R. Huisgen, In *1,3-Dipolar Cycloaddition Chemistry*, Ed. A. Padwa,Wiley, New York, **1984**, pp 1-176 see review article: (d) S. Dedola, S. A. Nepogodiev and R. A. Field, *Org. Biomol. Chem.*, **2007**, *5*, 1006 and other references cited therein.

(2) (a) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, **2002,** *41*, 2596; (b) C.W. Tornoe,C.Christensen and M. Meldal, *J. Org. Chem.*, **2002**, *67*, 3057.

(3) (a) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674–1689. (b) Yoo, B.; Shin, S. B. Y.; Huang, M. L.; Kirshenbaum, K.*Chem.;Eur. J.* **2010**, *16* (19), 5528–5537. (c) Pedersen, D. S.; Abell, A.*Eur. J. Org. Chem.* **2011**, *13*, 2399–2411.

(4) (a) Tam, A.; Arnold, U.; Soellner, M. B.; Raines, R. T. *J. Am. Chem. Soc.* **2007**, *129*, 12670–12671. (b) Horne, W. S.; Yadav, M. K.; Stout, C. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2004**, *126* (47), 15366–15367. (c) van Maarseveen, J. H.; Horne, W. S.; Ghadiri, M. R. *Org. Lett.* **2005**, *7* (20), 4503–4506.

(5) (a) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett*. **2004**, *6* (23), 4223–4225. (b) Oh, K.; Guan, Z. B. *Chem. Commun*. **2006**, *29*, 3069–3071. (c) Holland-Nell, K.; Meldal, M. *Angew. Chem., Int. Ed*. **2011**, *50*, 5204–5206.

(6) Pokorski, J. K.; Jenkins, L. M. M.; Feng, H. Q.; Durell, S. R.; Bai, Y. W.; Appella, D. H. *Org. Lett*. **2007**, *9* (12), 2381–2383.

(7) (a) Cantel, S.; Isaad, A. L. C.; Scrima, M.; Levy, J. J.; DiMarchi, R. D.; Rovero, P.; Halperin, J. A.; D'Ursi, A. M.; Papini, A. M.; Chorev, M. *J. Org. Chem*. **2008**, *73* (15), 5663–5674. (b) Scrima, M.; Le Chevalier-Isaad, A.; Rovero, P.; Papini, A. M.; Chorev, M.; D'Ursi, A. M. Eur. *J. Org. Chem*. **2010**, *3*, 446–457. (c) Ingale, S.; Dawson, P. E. *Org. Lett.* **2011**, *13* (11), 2822–2825.

(8) Pedersen, D. S.; Abell, A.The Huisgen Cycloaddition in Peptidomimetic Chemistry. In Protection Reactions, Medicinal

Chemistry, *Combinatorial Synthesis*; Hughes, A. B., Ed.; Wiley-VCH: Weinheim, **2011**; pp 101-124.

(9) (a) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185–4194; (b) Buckle, D. R.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1986**, *29*, 2269–2277; (c) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stper, D.; Yagi, B. H. *J. Med. Chem*. **2000**, *43*, 953–970; (d) Wamhoff, H. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Rees, C. W., Eds.; *Pergamon: Oxford*, **1984**; *5*, 669–732.

(10) (a) G. Biagi, I. Giorgi, O. Livi, V. Scartoni, L. Betti, G. Giannaccini andM. L. Trincavelli, *Eur. J. Med. Chem.,* **2002**, *37*, 565; (b) L. Bertelli, G. Biagi, I. Giorgi, C. Manera, O. Livi, V. Scartoni, L. Betti, G. Giannaccini, L. Trincavelli and P. L. Barili, *Eur. J. Med. Chem.*, **1998**, *33*, 113.

(11) (a) D. K. Mohapatra, P. K. Maity, R. J. Gonnade, M. S. Chorghade and M. K. Gurjar, *Synlett*, **2007**, 1893; (b) R. Li, D. J. Jansen and A. Datta, *Org. Biomol. Chem.*, **2009**, *7*, 1921; (c) F. Couty, F. Durrat and D. Prim, *Tetrahedron Lett.*, **2004**, *45*, 3725; (d) H.Yanai and T. Taguchi, *Tetrahedron Lett.*, **2005**, *46*, 8639; (e) V. S. Sudhir, N. Y. P. Kumar, R. B. N. Baig and S. Chandrasekaran, *J. Org. Chem.,* **2009**, *74*, 7588.

(12) (a) E. Balducci, L. Bellucci, E. Petricci, M. Taddei and A. Tafi, *J. Org. Chem.*, **2009**, *74*, 1314; (b) V. S. Sudhir, R. B. N. Baig and S. Chandrasekaran, *Eur. J. Org. Chem.*, **2008**, 2423; (c) J. K. Pokorski, L. M. M. Jenkins, H. Feng, S. R. Durell, Y. Bai and D. H. Appella, *Org. Lett.,* **2007**, *9*, 2381; (d) A. N. Semakin, A. Y. Sukhorukov, A. V. Lesiv, Y. A. Khomutova and S. L. Ioffe, *Russ. J. Org. Chem.*, **2007**, *43*,1222; (e) I. Kumar and C. V. Rode, *Chem. Lett.*, **2007**, *36*, 592; (*f*) I. Akritopoulou-Zanze, V. Gracias and S. W. Djuric, *Tetrahedron Lett.*, **2004**, *45*, 8439.

(13) (a) Hein, C. D.; Liu, X. M.; Wang, D. *Pharm. Res.* **2008**, *25*, 2216. (b) Donald, J. R.; Martin, S. F. *Org. Lett.***2011**, *13*, 852.

(14) (a) Padwa, A.; Ku, A.; Ku,H.;Mazzu, A. *J. Org. Chem*. **1978**, *43*, 66. (b) Orlek, B. S.; Sammes, P. G.; Weller, D. J. *Tetrahedron* **1993**, *49*, 8179. (c) Orlek, B. S.; Sammes, P. G.;Weller, D. J. *J. Chem. Soc., Chem. Commun*. **1993**, 607. (d) Garanti, L.; Molteni, G.; Zecchi, G. *Heterocycles* **1994**, *38*, 291. (e) Alajarı´n, M.; Cabrera, J.; Pastor, A.; Villalgordo, J. M. *Tetrahedron Lett*. **2007**, *48*, 3495.

(15) (a) Declerck, V.; Toupet, L.; Martinez, J.; Lamaty, F. *J. Org. Chem*. **2009**, *74*, 2004. (b) Brawn, R. A.; Welzel, M.; Lowe, J. T.; Panek, J. S. *Org. Lett*. **2010**, *12*, 336.

(16) (a) Hotha, S.; Anegundi, R. I.; Natu, A. A. *Tetrahedron Lett*. **2005**, *46*, 4585.(b) Chandrasekhar, S.; Rao,C. L.;Nagesh,C.; Reddy, C. R.; Sridhar, B. *Tetrahedron Lett.* **2007**, *48*, 5869. (c) Anegundi, R. I.; Puranik, V. G.; Hotha, S. *Org. Biomol. Chem*. **2008**, *6*, 779. (d) Jarosz, S.; Lewandowski, B.; Listkowski, A. *Synthesis* **2008**, 913.

(17) (a) Mishra, J. K.; Panda, G. *J. Comb. Chem*. **2007**, *9*, 321. (b) Samanta, K.; Chakravarti, B.; Mishra, J. K.; Dwivedi, S. K. D.; Nayak, L. V.; Choudhry, P.; Bid, H. K.; Konwar, R.; Chattopadhyay, N.; Panda, G. *Bioorg. Med. Chem.Lett*. **2010,** *20*, 283. (c) Mishra, J. K.; Samanta, K.; Jain, M.; Dikshit, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010,** *20,* 244. (d) Samanta, K.; Panda, G. *Chemistry an Asian Journal*, **2011**, 189-197. (e) Bera, S.; Panda, G. *ACS Comb. Sci.***2012**, *14*, 1−4.

(18) Tripathi, S.; Singha, K.; Achari, B.; Mandal, S. *Tetrahedron* **2004**, *60*, 4959.

