

Synthesis of Amino Acid derived 2-Methylene Morpholines and 3,4-dihydro-2H-1,4-Oxazines via Ag (I) promoted Intra-molecular Cyclization of Alkynols

Amit Kumar,^a Sandeep Bhattacharjee,^a and Gautam Panda^{*ab}

^aMedicinal & Process Chemistry Division, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, UP, India

^bAcademy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India

Email: gautam.panda@gmail.com, gautam_panda@cdri.res.in

Dedicated to Professor Sambasivarao Kotha on the occasion of his 65th birthday

Received mm-dd-yyyy

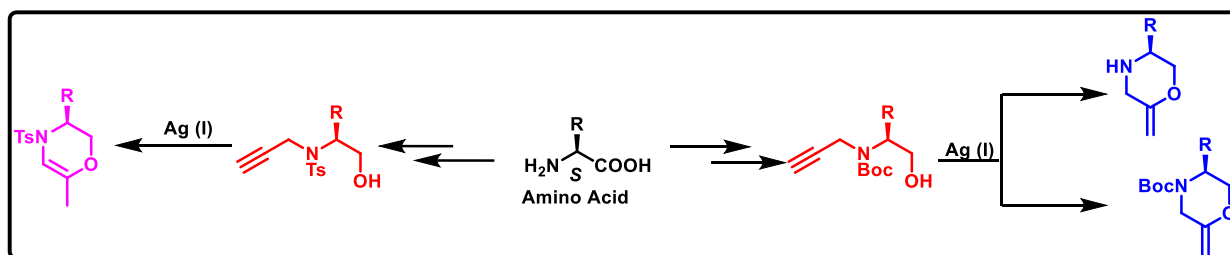
Accepted Manuscript mm-dd-yyyy

Published on line mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

Protecting group dependent change in product formation in Ag (I) promoted intra-molecular cyclization is revealed on amino acid derived alkynols. We herein report that the N-Boc protected amino acid derived alkynols provide kinetically controlled 2-methylene morpholines while N-Tosyl protected amino acid derived alkynols afford thermodynamically controlled 3,4-dihydro-2H-1,4-oxazines via Ag (I) promoted intra-molecular cyclization.



Keywords: 2-Methylene morpholines, 3,4-dihydro-2H-1,4-oxazines, silver (I), alkynols, intramolecular cyclization

Introduction

The strategy towards the synthesis of compounds bearing oxygen and nitrogen in a ring is growing attention because the resulting molecules are present in numerous biologically important compounds.¹⁻⁵ The morpholine moiety has a greater impact on human well-being as it presents in approved CNS drugs such as doxapram,⁶ phendimetrazine,⁷ moclobemide,⁸ aprepitant,⁹⁻¹¹ reboxetine,¹² and antifungal compound fenpropimorph¹³ (**figure 1**). A weakly basic nitrogen atom and oxygen atom at the opposite position gives flexible conformation and peculiar pKa value to the ring thus morpholines are used to modulate pharmacokinetic/pharmacodynamic (PK/PD) properties and to enhance the potency through molecular interactions in CNS active compounds.¹⁴ The addition of OH nucleophile to carbon-carbon (C-C) multiple bonds is one of the well-developed method¹⁵⁻²⁰ and is also useful in the synthesis of heterocycles bearing nitrogen and oxygen atom.²¹ For example, Wang et al²² reported the synthesis of 1,4-oxazines and 1,4-oxazepines via base-promoted *exo* mode cyclization of alkynyl alcohols. However, an efficient intra-molecular hydrofunctionalization reaction remains a challenge till now because of the relatively high bond enthalpies of most OH σ -bonds, the modest reactivity of electron-rich olefins with nucleophiles and poor nucleophilicity of hydroxyl group.

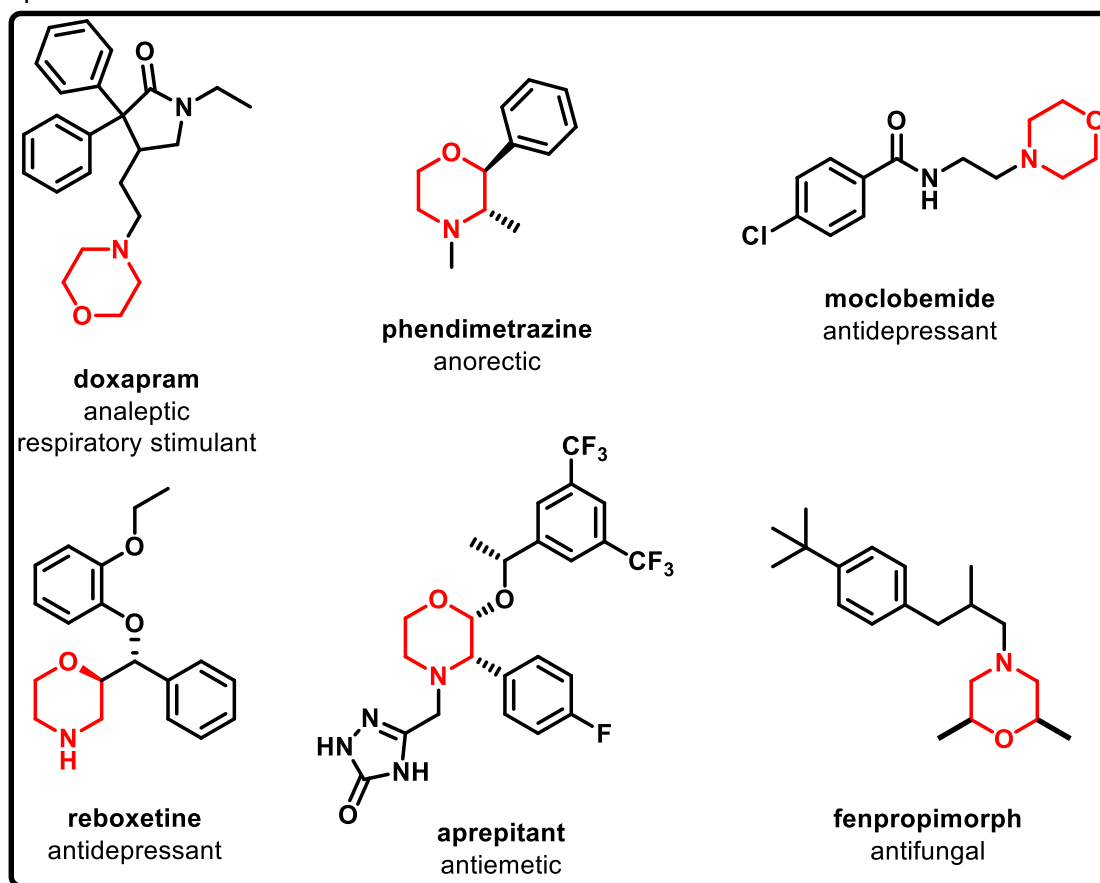
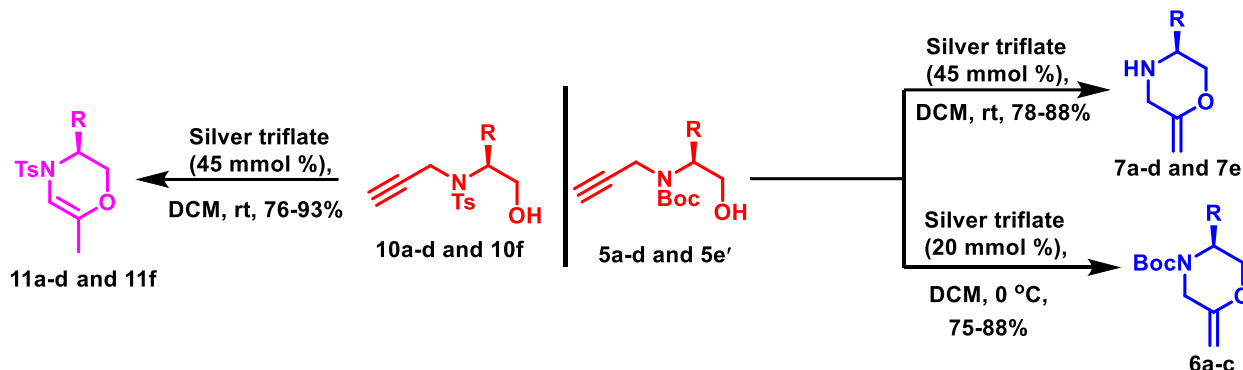


Figure 1. Structures of morpholine ring containing bioactive molecules.

Our group is relentlessly working in the area of synthesis and biology of amino acid-derived chiral heterocycles and natural-product-like molecules.²³⁻²⁶ In this connection, novel methodologies for the synthesis of substituted piperazine²⁷ by regioselective ring-opening of amino acid-derived chiral aziridines and diastereoselective synthesis of amino acid derived *trans*-2,5-disubstituted morpholines, piperazines, and thiomorpholines via I₂-Mediated cyclization²⁸ have been reported. Inspired by these well-developed strategies

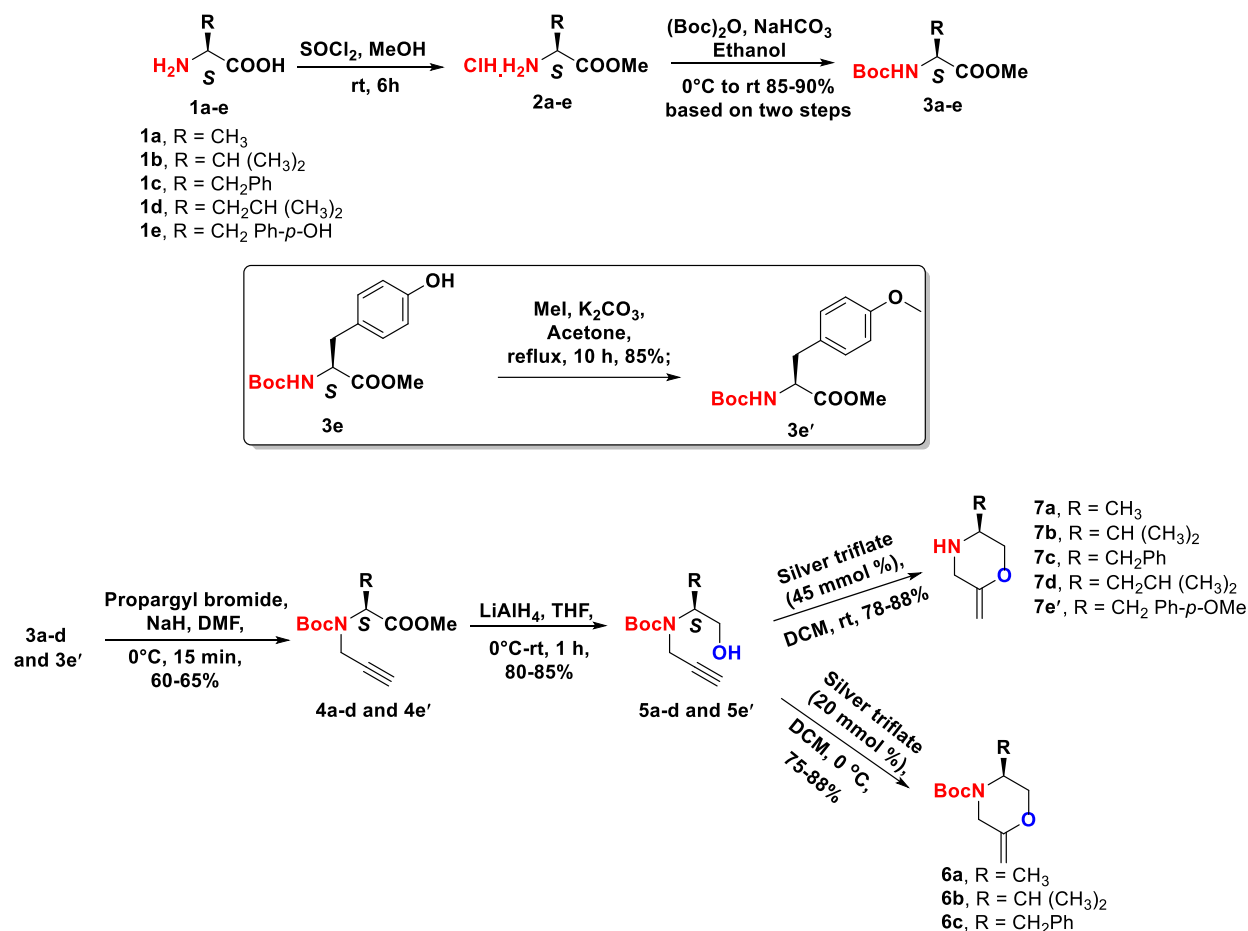
towards the exploration of natural amino acids, we sought to investigate the reactivity of silver salt on amino acid derived alkynols in order to synthesize diverse oxazines like morpholines via intramolecular cyclization. To the best of our knowledge, the use of silver catalyst Ag (I) on amino acid derived alkynols to furnish oxazine derivatives via intramolecular cyclization has not been attempted to date. We herein demonstrate the synthesis of 2-methylene morpholines and 3,4-dihydro-2H-1,4-oxazines from amino acid derived alkynols by Ag (I) catalyzed intra-molecular cyclization (**Scheme 1**).



Scheme 1. Synthesis of Ag (I) promoted 2-methylene morpholines and 3,4-dihydro-2H-1,4-oxazines from amino acid derived alkynol

Results and Discussion

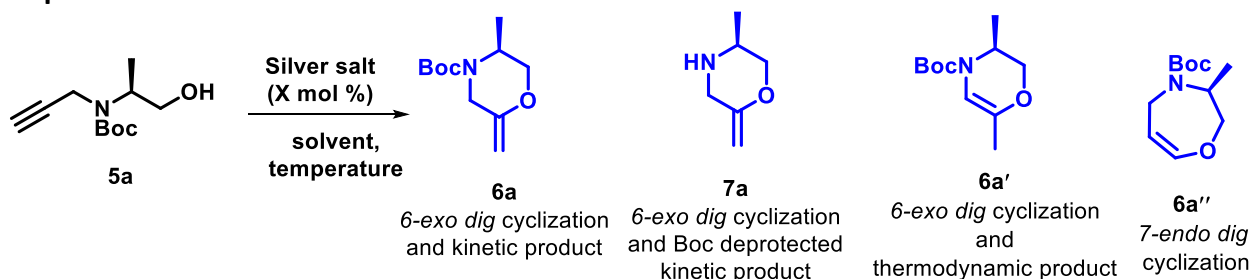
The synthesis of Boc protected amino acid derived alkynols (**5a-d** and **5e'**) for silver promoted intramolecular cyclization reaction began with S-amino acids **1a-e** (**Scheme 2**). S-amino acids **1a-e** reacted with thionyl chloride to furnish their methyl esters **2a-e**^{35,36} which underwent Boc protection of primary amines to give **3a-e**.³⁵ The tyrosine derivative **3e** was reacted with MeI in presence of K₂CO₃ to provide **3e'**.³⁷ Further, **3a-e'** reacted with propargyl bromide to accomplish alkyne derivatives **4a-d** and **4e'**. Ester reduction to **4a-d** and **4e'** using LiAlH₄ proceeded amino acid derived alkynols **5a-d** and **5e'** smoothly (**Scheme 2**). Our investigation on silver promoted intramolecular cyclization was started by selecting alkynol **5a** as the standard substrate. Initially, by the treatment of silver salt on substrate **5a**, we were expecting different products by means of different modes of cyclization (*6-exo-dig* vs. *7-endo-dig* cyclization). Compound **6a** and /or **6a'** was expected from favourable *6-exo-dig* cyclization and **6a''** from unfavourable *7-endo-dig* cyclization according to Baldwin's rule. Here, the formation of thermodynamic product **6a'** was highly expected over kinetic product **6a**. Additionally, compound **7a** was the least expected product in our mind because of lacking suitable reagent for Boc deprotection and product stability. To verify our hypothesis, we treated the silver carbonate (15 mmol%) with **5a** in DCM solvent at room temperature as a suitable reaction condition and monitored for 16 h but no product formation occurred. Similarly, other silver salts like silver acetate, silver sulfate and silver *p*-toluene sulfonate also could not provide fruitful results after screening on substrate **5a**. However, in case of silver triflate (15 mmol%), we observed the formation of two products. Interestingly, the deep NMR studies on the resultant products suggested that compounds **6a** and **7a** in a ratio of 40:60 were formed over the most expected and stable compound **6a'** (entry 5, **Table 1**).



Scheme 2. Synthesis of 2-methylene morpholines

The product formation towards **7a** was drastically increased with the use of 45 mmol% of silver triflate (entry 6, **Table 1**). As the product **7a** was kinetically stabilized product, therefore, we anticipated that thermodynamically stabilized product **6a'** can be synthesized at a higher temperature. Thus, we treated substrate **5a** with 45 mmol% of silver triflate at 80 °C in toluene. However, we observed the formation of **7a** in 80% of yield (entry 7). Further, the product towards Boc protected **6a** was increased when we used 20 mmol% of silver triflate at 0 °C in DCM solvent (entry 8). Moreover, two other silver salts namely silver hexa-antimonate (V) and silver nitrate were also examined for intra-molecular cyclization. The subsequent results suggested that silver hexa-antimonate (V) predominantly was found supportive for the formation of the Boc protected **6a** (entry 9) while silver nitrate was useful for the synthesis of compound **7a** (entry 10). From the optimization table, it was clear that 2-methylene morpholine **7a** can be synthesized by the reaction of amino acid derived Boc alkynol **5a** with silver triflate and controlled use of silver triflate can also provide Boc protected 2-methylene morpholine **6a** in good yield.

Table 1: Optimization of reaction conditions

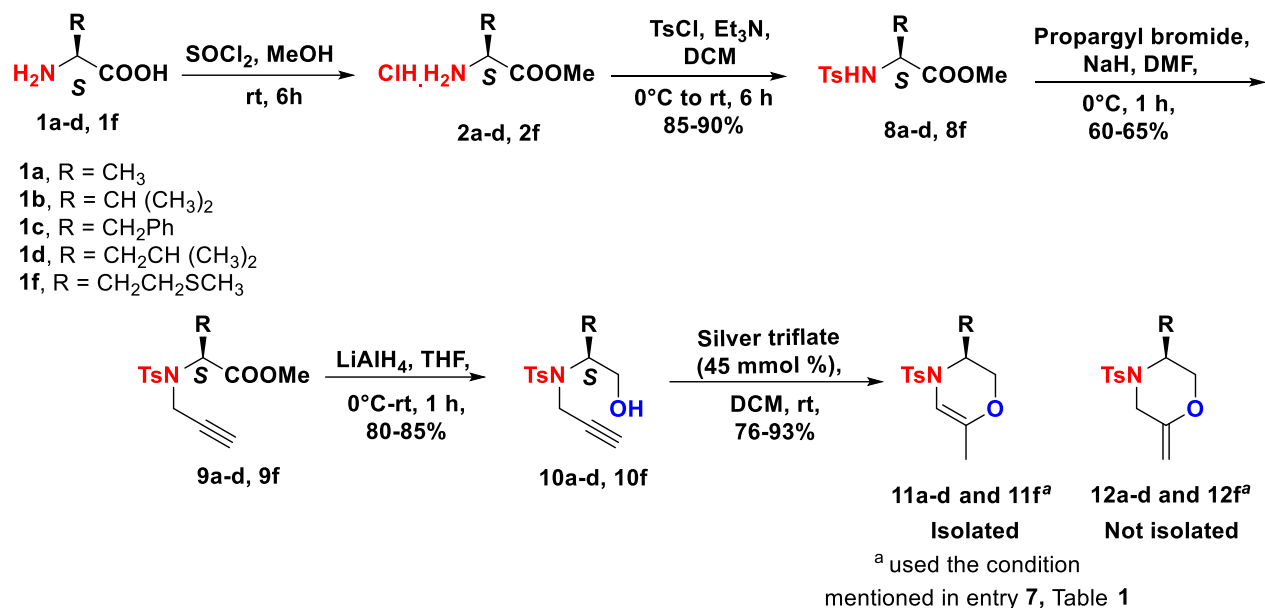


Entry	Silver salt	X	Solvent	Temp	Time	Product yield (6a:7a) ^a
1	Silver carbonate	15	DCM	rt	16 h	nd
2	Silver acetate	15	DCM	rt	16 h	nd
3	Silver sulfate	15	DCM	rt	16 h	nd
4	Silver <i>p</i> -toluene sulfonate	15	DCM	rt	16 h	15:25
5	Silver triflate	15	DCM	rt	3 h	40:60
6	Silver triflate	45	DCM	rt	3 h	15:85
7	Silver triflate	45	Toluene	80 °C	3h	10:80
8	Silver triflate	20	DCM	0 °C	45 min	88:10
9	Silver hexa-antimonate (V)	45	DCM	rt	3 h	65:30
10	Silver nitrate	45	DCM	rt	3 h	10:80

nd = not determined; a = isolated yield

Substrate scope:

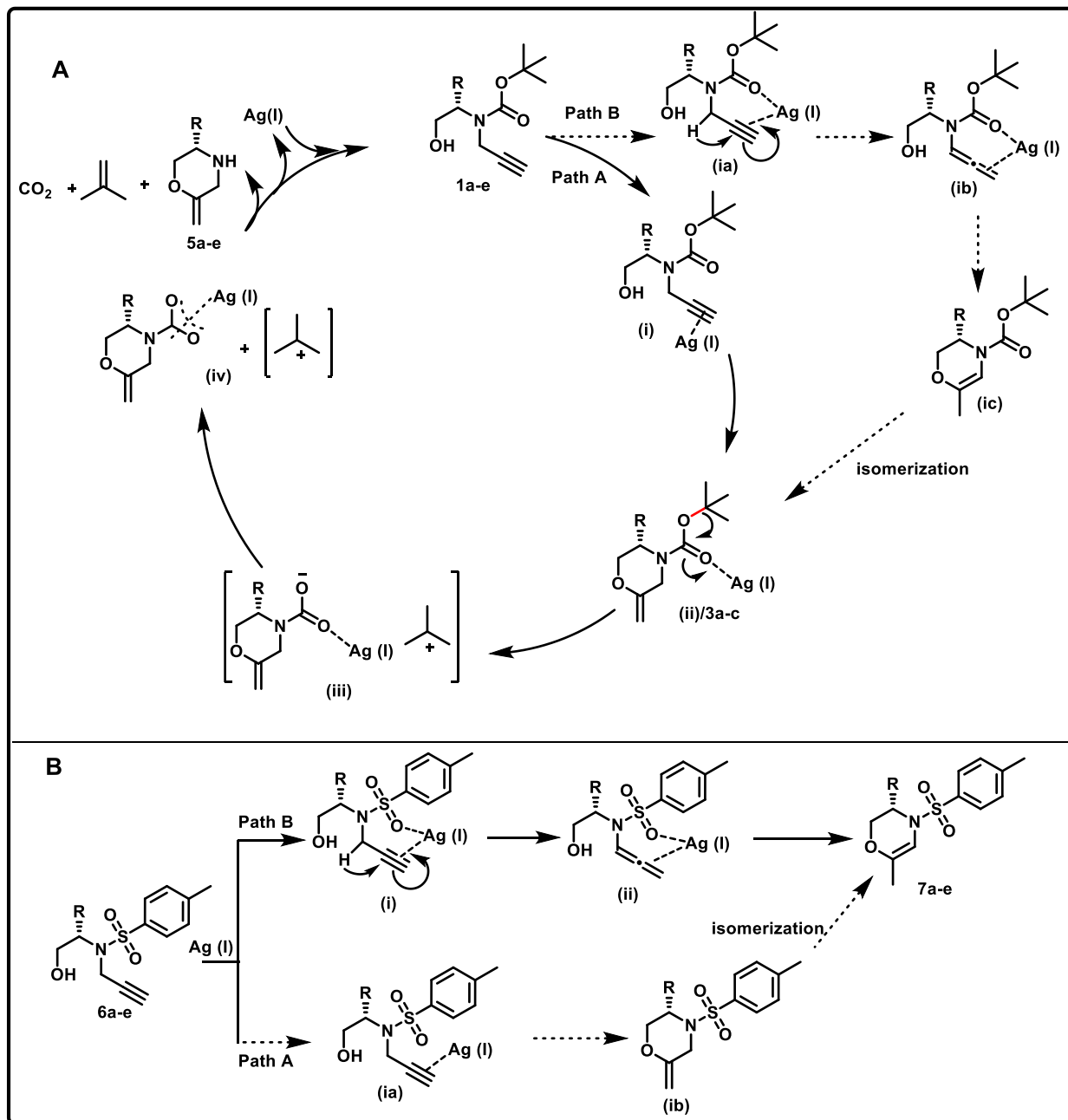
The observed 2-methylene morpholines could be key building blocks for the synthesis of significant bioactive molecules. Thus, after optimizing the reaction conditions, we started to evaluate the substrate scope of this chemical transformation. In this context, some Boc protected alkynols **5a-d** and **5e'** were examined for the synthesis of 2-methylene morpholines (Scheme 2). Firstly, free amine containing 2-methylene morpholines (**7a-d** and **7e'**) were successfully synthesized in good to moderate yield. Moreover, Boc protected 2-methylene morpholines (**6a-c**) were smoothly synthesized by using silver triflate (20 mmol %) in DCM solvent at 0 °C in a short reaction time (Scheme 2). To extend the substrate scope, we synthesized N-tosyl protected amino acid derived alkynols (10a-d, 10f) as illustrated in scheme 3. When the optimized reaction condition was subjected to substrate **10a**, it furnished product formation in good yield. However, we were surprised when the observed product was characterized by NMR studies. Three CH₃ groups were confirmed by NMR studies that suggested the formation of 3,4-dihydro-2H-1,4-oxazine derivative **11a** instead of anticipated **12a**. Moreover, this functional group based change in product formation was also observed in other N-tosyl protected amino acid derived alkynols (**10b-d**, **10f**) leading to products (**11b-d**, **11f**). However, the formation of **11f** was accomplished in 76% yield at 80 °C in toluene solvent (according to entry 7, table 1) instead of room temperature.



Scheme 3. Synthesis of 3,4-dihydro-2H-1,4-oxazines.

Plausible mechanism:

Based on the above experimental results, we believe that the formation of 2-methylene morpholines and 3,4-dihydro-2H-1,4-oxazines from amino acid derived alkynols might proceed *via 6 exo dig* and *6 exo trig (in-situ)* cyclization respectively through two different routes as illustrated in **scheme 4**. For the synthesis of 2-methylene morpholine (**scheme 4A**), the mechanism involving the alkynol (**i**) is considered more likely than alternative allenol (**ib**) on the basis of the hypothesis that the cyclized product (**ic**) which is possible from allenol (**path B, scheme 4A**) is more stable than the product probable from alkynol (**path A, scheme 4A**). Therefore, the product **ic** probably could not isomerize into product **ii/3a-c**. To support this hypothesis, we also performed the reaction in NMR tube and recorded the ¹H NMR. In result, we also could not observe the formation of **ic** in the crude reaction mixture (**figure S49, see supporting information**). Moreover, we also believe that Boc deprotection may also be carried due to the Lewis acid character of silver (Ag). Next, unlike 2-methylene morpholine, for the formation of 3,4-dihydro-2H-1,4-oxazine (**Scheme 4B**), the mechanism involving the sulfonamide supported allenol (**i**) is considered more likely (**path A, scheme 4B**) than alkynol (**path A, scheme 4B**) on the basis of some reported literatures²⁹⁻³¹ and absence of *exo*-methylene intermediate in ¹H NMR of the crude reaction mixture (**figure 50, see supporting information**).



Scheme 4. Plausible mechanism; (A) synthesis of 2-methylene morpholines. (B) synthesis 3,4-dihydro-2H-1,4-oxazines.

Conclusions

We have demonstrated an easy and effective route that affords access to diverse 2-methylene morpholines and 3,4-dihydro-2H-1,4-oxazines starting from *S*-amino acids derived alkynols via Ag (I) promoted intramolecular cyclization. The obtained 2-methylene morpholines can be elaborated as good nucleophile that may create potential bioactive molecules in future. Moreover, some of the 3,4-dihydro-2H-1,4-oxazines can be utilized in several ways such as good lead molecule in the discovery of anti-breast cancer drugs and the alkene oxidation may provide 2-hydroxy morpholine which is part of many bioactive molecules.³²⁻³⁴

Experimental Section

General. Unless otherwise noted, all commercial reagents were used without further purification. Organic solvents were dried by standard methods. The products were characterized by ^1H , ^{13}C , IR, ESMS, and HRMS. Analytical TLC was performed using 2.5×5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254); visualization was accomplished with iodine and under a UV lamp. Column chromatography was performed using silica gel (60-120 and 100-200 mesh). NMR spectra were recorded on Bruker Avance 400 Spectrometers at 400, MHz (^1H) and 100, MHz (^{13}C). Experiments were recorded in CDCl_3 ($\delta = 7.26$ ppm for ^1H and 77.00 ppm for ^{13}C NMR) and DMSO-d_6 ($\delta = 2.50$ ppm for ^1H and 39.52 ppm for ^{13}C NMR) at 25 °C and are referenced to the TMS at 0.00 ppm for proton. *J* values were expressed in hertz (Hz). Multiplicities were given as: s (singlet); brs (broad singlet), d (doublet); t (triplet); q (quartet); dd (doublets of doublet); m (multiplets). Mass spectra were recorded on a JEOL JMS-600H high resolution spectrometer using EI mode at 70 eV.

General procedure for the synthesis of 3a-e.³⁵ To a stirred solution of **2a-f** (1.0 equiv) in ethanol (30 mL), $(\text{Boc})_2\text{O}$ (1.1 equiv.) was added at room temperature followed by addition of NaHCO_3 (2.5 equiv) and then the reaction mixture was stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), ethanol was removed under reduced pressure, diluted with water, extracted with ethyl acetate, washed with brine solution, dried over sodium sulfate, concentrated under reduce pressure to get crude product. Desired product was purified by using manual chromatography to furnish the Boc protected **3a-e** in good yield.

General procedure for the synthesis of 4a-d and 4e'.³⁵ To a stirred solution of compounds **3a-d** and **3e'** (1.0 equiv.) in anhydrous DMF (10 mL), NaH (1.0 equiv, 60% suspension in mineral oil) was added at 0 °C. Then the required amount of propargyl bromide (1.0 equiv) was added at 0 °C. The reaction mixture was stirred for 15-30 min at 0 °C. The reaction mixture was diluted with water. The aqueous layer was extracted with ethyl acetate and the organic layer was dried over anhydrous Na_2SO_4 . After concentration under vacuum, the crude product was chromatographed on silica gel to furnish **4a-d** and **4e'** (60-65% yield).

General procedure for the synthesis of 5a-d and 5e'.³⁵ To a stirred solution of compound **4a-d** and **4e'** (1.0 equiv.) in anhydrous THF (10 mL), LiAlH_4 (1.0 equiv.) was added at 0 °C and stirred for 1 h. After completion of the reaction, the reaction was quenched by addition of ethyl acetate followed by water at 0 °C. The aqueous layer was extracted with ethyl acetate and the organic layer was dried over anhydrous Na_2SO_4 . After concentration under vacuum, the crude product was chromatographed on silica gel to furnish the alkynols **5a-d** and **5e'** with 80-85% of yield.

tert-Butyl (S)-(1-hydroxypropan-2-yl)(prop-2-yn-1-yl)carbamate (5a). Colorless oil, 80% yield, $R_f = 0.50$ (in 20% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 4.61 (1H, s), 3.76 (1H, s), 3.65-3.61 (1H, m), 3.52-3.48 (1H, m), 2.73 (1H, s), 1.83 (1H, s), 1.44 (9H, s), 1.14 (3H, d, *J* 6.86 Hz).

tert-Butyl (S)-(1-hydroxy-3-methylbutan-2-yl)(prop-2-yn-1-yl)carbamate (5b). Colorless oil, 83% yield, $R_f = 0.60$ (in 20% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 4.23-3.77 (4H, m), 3.64-3.55 (1H, m), 2.25 (1H, d, *J* 12.62 Hz), 2.17-1.82 (2H, m), 1.48 (9H, s), 0.98 (3H, d, *J* 6.13 Hz), 0.90 (3H, d, *J* 6.13 Hz). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 156.08, 81.01, 71.16, 70.83, 65.01, 62.20, 61.94, 34.91, 32.85, 28.35, 27.70, 26.84, 20.09, 19.99. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3394, 2968, 1678, 1382, 1253, 1166, 1070, 771.

tert-Butyl (S)-(1-hydroxy-3-phenylpropan-2-yl)(prop-2-yn-1-yl)carbamate (5c). Colorless oil, 85% yield, $R_f = 0.50$ (in 20% EtOAc/Hexane); ^1H NMR (CD_3OD , 400 MHz, ppm): δ 7.17-7.08 (5H, m), 4.09-3.55 (5H, m), 2.89-2.73 (2H, m), 2.44 (1H, d, *J* 8.56), 1.27 (9H, d, *J* 38.77 Hz). ^{13}C $\{^1\text{H}\}$ NMR (CD_3OD , 100 MHz, ppm): δ 154.03, 137.43, 137.18, 127.41, 127.32, 126.53, 124.43, 111.82, 78.87, 78.69, 69.56, 69.56, 69.12, 60.71, 60.37, 59.46, 58.65, 33.87, 33.39, 32.46, 31.26, 27.85, 25.74, 25.66. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3388, 2928, 1679, 1382, 1248, 1164, 1049, 768, 698.

tert-Butyl (S)-(1-hydroxy-4-methylpentan-2-yl)(prop-2-yn-1-yl)carbamate (5d). Colorless oil, 80% yield, $R_f = 0.60$ (in 20% EtOAc/Hexane); ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 4.64-4.61 (1H, m), 4.09-3.75 (3H, m), 3.42-3.41 (2H, m), 2.99 (1H, s), 1.58-1.56 (2H, m), 1.40 (9H, s), 1.23-1.15 (1H, m), 0.88-0.86 (6H, m). ^{13}C $\{^1\text{H}\}$ NMR (DMSO- d_6 , 100 MHz, ppm): δ 155.27, 155.17, 82.32, 79.45, 79.29, 72.85, 72.36, 62.66, 56.68, 55.15, 38.48, 37.94, 32.32, 31.98, 29.87, 29.45, 28.68, 28.49, 28.29, 24.73, 24.58, 23.67, 22.21.

tert-Butyl(S)-(1-hydroxy-3-(4-methoxyphenyl)propan-2-yl)(prop-2-yn-1-yl)carbamate (5e'). Colorless oil, 82% yield, $R_f = 0.40$ (in 20% EtOAc/Hexane); ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 7.12-7.08 (2H, m), 6.88-6.82 (2H, m), 4.77-4.73 (1H, m), 4.09-3.75 (3H, m), 3.70 (3H, s), 3.57-3.50 (2H, m), 3.04 (1H, s), 2.83-2.78 (1H, m), 2.73-2.67 (1H, m), 1.30 (9H, d, J 38.39). ^{13}C $\{^1\text{H}\}$ NMR (DMSO- d_6 , 100 MHz, ppm): δ 158.10, 156.02, 154.84, 131.47, 130.79, 130.38, 115.03, 114.43, 114.10, 82.25, 79.50, 78.44, 75.66, 73.48, 73.00, 66.83, 62.06, 61.58, 60.93, 59.65, 55.86, 55.77, 35.44, 36.50, 34.95, 34.38, 33.02, 32.36, 28.70, 28.45, 28.31.

General procedure for the synthesis of 8a-d and 8f.³⁵ The compound 2a-d and 2f (1.0 equiv.) was dissolved in 5 mL DCM solvent, and then stirred solution was cooled to 0 °C, followed by addition of *p*-toluene sulfonyl chloride (1.5 equiv.) and triethyl amine (2.5 equiv). Then it was continuously stirred for 6 h at room temperature. After completion the reaction, water was added and extracted with DCM solvent, washed with brine solution, dried over sodium sulfate, concentrated under reduced pressure to get crude product. The resulted crude product was then chromatographed over silica gel with eluent AcOEt-Hexane to afford the title compound 8a-d and 8f (85-90% yield)

General procedure for the synthesis of 9a-d and 9f.³⁵ To a stirred solution of compounds 8a-d and 8f (1.0 equiv.) in anhydrous DMF, NaH (1.0 equiv, 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 0 °C. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate and the organic layer was dried over anhydrous Na_2SO_4 . After concentration under vacuum, the crude product was chromatographed on silica gel to furnish 9a-d and 9f (60-65% yield).

General procedure for the synthesis of 10a-d and 10f.³⁵ To a stirred solution of compound 9a-d, 9f (1.0 equiv.) in anhydrous THF, LiAlH_4 (1.0 equiv.) was added at 0 °C and stirred for 1 h. After completion of the reaction, the reaction was quenched by addition of ethyl acetate followed by water at 0 °C. The aqueous layer was extracted with ethyl acetate and the organic layer was dried over anhydrous Na_2SO_4 . After concentration under vacuum, the crude product was chromatographed on silica gel to furnish the alkynols 10a-d and 10f with 80-95% of yield.

(S)-N-(1-Hydroxypropan-2-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (10a). Colorless oil, 88% yield, $R_f = 0.50$ (in 15% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 7.80 (2H, d, J 8.31 Hz), 7.30-7.28 (2H, m), 4.26-4.21 (1H, m), 4.11-4.00 (2H, m), 3.67 (1H, dd, $J_1 = 11.99$ Hz, $J_2 = 8.63$ Hz), 3.55 (1H, dd, $J_1 = 11.99$ Hz, $J_2 = 4.47$ Hz), 2.42 (3H, s), 2.22 (1H, t, J 2.46 Hz), 1.06 (3H, d, J 6.86 Hz). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 143.61, 137.38, 129.57, 127.46, 79.94, 72.62, 64.30, 55.61, 31.88, 21.54, 14.45. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3372, 2922, 1623, 1384, 1328, 1153, 1028, 659, 577.

(S)-N-(1-Hydroxy-3-methylbutan-2-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (10b). Colorless oil, 84% yield, $R_f = 0.50$ (in 15% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 7.81 (2H, d, J 8.25), 7.28 (2H, d, J 8.03), 4.35 (1H, dd, $J_1 = 18.74$, $J_2 = 2.44$ Hz), 3.89 (1H, dd, $J_1 = 18.64$, $J_2 = 2.40$ Hz), 3.78-3.65 (2H, m), 3.64-3.58 (1H, m), 2.41 (3H, s), 2.17 (1H, t, J 2.52 Hz), 1.87-1.78 (2H, m), 0.96 (3H, d, J 6.56 Hz), 0.82 (3H, d, J 6.71 Hz). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 143.49, 137.75, 129.35, 127.76, 79.70, 72.49, 66.26, 61.71, 32.27, 27.32, 21.55, 20.49, 20.08. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3389, 1634, 1383, 1042, 771. HRMS: m/z Calcd for $[\text{C}_{15}\text{H}_{21}\text{NO}_3\text{S}+\text{Na}]^+$: 296.1315, found: 296.1310.

(S)-N-(1-Hydroxy-3-phenylpropan-2-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (10c). Colorless oil, 90% yield, $R_f = 0.50$ (in 15% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 7.71 (2H, d, $J = 8.33$ Hz), 7.25-7.19 (5H, m), 7.08-7.06 (2H, m), 4.28 (1H, dd, $J_1 = 18.64$, $J_2 = 2.45$ Hz), 4.17-4.12 (1H, m), 4.09 (1H, dd, $J_1 = 18.78$, $J_2 = 2.45$ Hz), 3.73 (1H, dd, $J_1 = 12.25$, $J_2 = 8.44$ Hz), 3.62 (1H, dd, $J_1 = 12.25$, $J_2 = 4.08$ Hz), 2.86-2.75 (2H, m), 2.40 (3H, s), 2.26 (1H, t, $J = 2.45$), 1.86 (1H, brs). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 143.61, 137.41, 137.19, 129.54, 129.05, 128.65, 127.57, 126.71, 79.95, 72.83, 62.06, 61.63, 36.09, 32.78, 21.55. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3381, 2923, 1383, 1154, 1061, 770, 662.

(S)-N-(1-Hydroxy-4-methylpentan-2-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (10d). Colorless oil, 81% yield, $R_f = 0.50$ (in 15% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 7.81 (2H, d, $J = 8.25$ Hz), 7.29-7.27 (2H, m), 4.21 (1H, dd, $J_1 = 18.69$, $J_2 = 2.48$ Hz), 4.04-3.95 (2H, m), 3.66-3.56 (2H, m), 2.41 (3H, s), 2.21 (1H, t, $J = 2.52$), 2.12 (1H, brs), 1.51-1.41 (1H, m), 1.39-1.32 (1H, m), 1.27-1.20 (1H, m), 0.82-0.78 (6H, m). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 143.59, 137.43, 129.43, 127.69, 79.90, 72.42, 63, 28, 58.14, 37.95, 31.88, 24.56, 22.67, 22.25, 21.52. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3366, 2948, 1605, 1383, 1331, 1155, 1057, 875, 770, 661, 577.

(S)-N-(1-Hydroxy-4-(methylthio)butan-2-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (10f). Colorless oil, 80% yield, $R_f = 0.50$ (in 20% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 7.82-7.80 (2H, m), 7.30-7.28 (2H, m), 4.23 (1H, dd, $J_1 = 18.70$, $J_2 = 2.49$ Hz), 4.12-4.06 (1H, m), 4.05-4.01 (1H, m), 3.70-3.60 (2H, m), 2.41 (3H, s), 2.40-2.26 (2H, m), 2.22 (1H, t, $J = 2.46$ Hz), 1.99 (3H, s), 1.85-1.69 (2H, m). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 143.72, 137.35, 129.52, 127.62, 79.64, 72.72, 63.09, 59.03, 32.37, 30.74, 28.32, 21.54, 15.33. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3368, 2922, 1607, 1384, 1331, 1155, 1096, 875, 770, 660, 576.

General procedure for the synthesis of 6a-c. To a stirred solution of compound 5a-c (1.0 equiv) in dry DCM (10 mL), silver triflate (20 mmol %) was added at 0 °C. Then it was continuously stirred for 30 min at 0 °C. After completion of the reaction, reaction mixture was quenched with water, extracted with DCM, washed with brine solution, dried over sodium sulfate, concentrated under reduced pressure to get crude product. Then, the crude product was chromatographed on silica gel with eluent (hexane/ethyl acetate) to furnish the title product 6a-c (75-88% yield) as colorless oil.

tert-butyl (S)-5-methyl-2-methylenemorpholine-4-carboxylate (6a). Colorless oil, 75% yield, $R_f = 0.50$ (in 15% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 4.70 (1H, q, $J = 2.74$ Hz), 4.30-4.24 (2H, m), 4.21-4.16 (1H, m), 4.08-4.00 (1H, m), 3.48 (1H, dd, $J_1 = 9.40$ Hz, $J_2 = 4.06$ Hz), 3.37 (1H, dd, $J_1 = 9.40$ Hz, $J_2 = 5.56$ Hz), 1.22 (3H, d, $J = 7.10$ Hz), 1.16 (9H, s). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 155.27, 150.04, 85.80, 73.09, 63.68, 49.26, 45.78, 27.40, 14.50. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3387, 2923, 1778, 1383, 1062. HRMS: m/z Calcd for $[\text{C}_{11}\text{H}_{19}\text{NO}_3 + \text{Na}]^+$: 236.1257, found: 236.1261.

tert-Butyl (S)-5-isopropyl-2-methylenemorpholine-4-carboxylate (6b). Colorless oil, 80% yield, $R_f = 0.50$ (in 15% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 4.70 (1H, q, $J = 2.75$ Hz), 4.36 (1H, dt, $J_1 = 14.79$ Hz, $J_2 = 2.45$ Hz), 4.25 (1H, q, $J = 2.87$ Hz), 4.14 (1H, dt, $J_1 = 14.77$ Hz, $J_2 = 2.35$ Hz), 3.58-3.47 (3H, m), 2.07-1.98 (1H, m), 1.16 (9H, s), 0.97 (3H, d, $J = 6.62$ Hz), 0.91 (3H, d, $J = 6.70$ Hz). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 156.01, 150.20, 85.57, 72.94, 60.91, 59.87, 46.47, 27.39, 26.41, 19.89, 19.41. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3385, 2941, 1779, 1683, 1383, 1058. HRMS: m/z Calcd for $[\text{C}_{13}\text{H}_{23}\text{NO}_3 + \text{Na}]^+$: 236.1257, found: 236.1261.

tert-Butyl (S)-5-benzyl-2-methylenemorpholine-4-carboxylate (6c). Colorless oil, 88% yield, $R_f = 0.50$ (in 15% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 7.31-7.27 (2H, m), 7.23-7.21 (3H, m), 4.66 (1H, q, $J = 2.71$ Hz), 4.26-4.21 (1H, m), 4.20-4.16 (2H, m), 4.15-4.10 (1H, m), 3.51 (1H, dd, $J_1 = 9.56$ Hz, $J_2 = 3.69$ Hz), 3.45 (1H, dd, $J_1 = 9.56$ Hz, $J_2 = 3.51$ Hz), 3.01-2.90 (2H, m), 1.16 (9H, s). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 155.32, 149.96, 137.48, 128.91, 128.62, 126.71, 85.75, 73.26, 61.83, 55.06, 47.07, 34.73, 27.44. HRMS: m/z Calcd for $[\text{C}_{17}\text{H}_{23}\text{NO}_3 + \text{Na}]^+$: 264.1570, found: 264.5.

General procedure for the synthesis of 7a-d and 7e.' To a stirred solution of compound 5a-d and 5e' (1.0 equiv) in dry DCM, silver triflate (45 mmol %) was added at room temperature. Then, it was continuously stirred for 2-3 h at room temperature. After completion of the reaction, reaction mixture was quenched with water, extracted with DCM, washed with brine solution, dried over sodium sulfate, concentrated under reduced pressure to get crude product. Then, the crude product was chromatographed on silica gel with eluent (hexane/ethyl acetate, to furnish the title product **7a-d** and **7e'** (78-88% yield) as colorless oil.

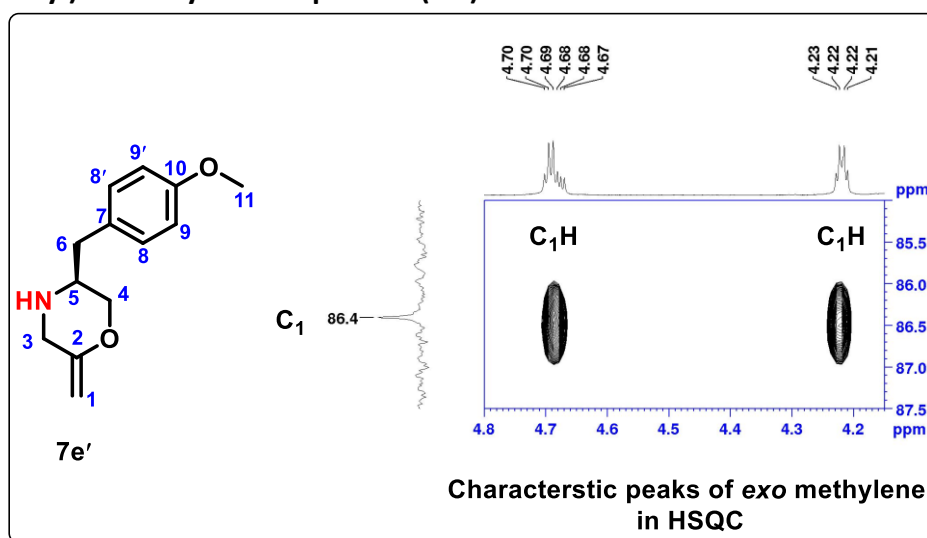
(S)-5-Methyl-2-methylenemorfoline (7a). Colorless oil, 88% yield, $R_f = 0.30$ (in 20% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 4.75(1H, q, J 2.69 Hz), 4.30-4.24 (2H, m), 4.20-4.15 (1H, m), 4.06-3.98 (1H, m), 3.76 (1H, dd, $J_1 = 11.59$ Hz, $J_2 = 4.04$ Hz), 3.62 (1H, dd, $J_1 = 11.64$ Hz, $J_2 = 7.76$ Hz), 1.21 (3H, d, J 6.97 Hz). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 155.93, 149.49, 86.55, 64.20, 51.01, 44.97, 13.97. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3387, 2921, 1658, 1383, 1061, 771.

(S)-5-Isopropyl-2-methylenemorfoline (7b). Colorless oil, 75% yield, $R_f = 0.30$ (in 20% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 4.74 (1H, q, $J = 2.75$ Hz), 4.33 (1H, dt, $J_1 = 14.14$ Hz, $J_2 = 2.49$ Hz), 4.29 (1H, q, J 2.36 Hz), 4.13 (1H, dt, $J_1 = 14.14$ Hz, $J_2 = 2.31$ Hz), 3.90 (1H, dd, $J_1 = 11.78$ Hz, $J_2 = 3.49$ Hz), 3.73 (1H, dd, $J_1 = 11.53$ Hz, $J_2 = 7.96$ Hz), 3.54-3.49 (1H, m), 1.96-1.86 (1H, m), 1.00 (3H, d, J 6.78 Hz), 0.95 (3H, d, J 6.63 Hz). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 156.71, 149.63, 86.33, 61.45, 61.40, 45.65, 27.22, 19.87, 19.53.

(S)-5-Benzyl-2-methylenemorfoline (7c). Colorless oil, 88% yield, $R_f = 0.30$ (in 20% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 7.33-7.29 (2H, m), 7.24-7.20 (3H, m), 4.69 (1H, q, J 2.95 Hz), 4.22-4.20 (1H, m), 4.11 (2H, q, J 2.23 Hz), 4.09-4.02 (1H, m), 3.84 (1H, dd, $J_1 = 11.59$ Hz, $J_2 = 3.72$ Hz), 3.76 (1H, dd, $J_1 = 11.59$ Hz, $J_2 = 7.14$ Hz), 2.94 (2H, d, J 7.73 Hz). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 154.88, 148.41, 135.97, 127.82, 127.78, 125.92, 85.42, 61.70, 56.01, 45.64, 33.55. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3385, 1383, 1059, 771.

(S)-5-Isobutyl-2-methylenemorfoline (7d). ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 4.75 (1H, q, J 2.94 Hz), 4.30-4.28 (1H, m), 4.27-4.22 (1H, m), 4.13-4.08 (1H, m), 4.04-3.97 (1H, m), 3.75 (1H, dd, $J_1 = 11.62$ Hz, $J_2 = 4.09$ Hz), 3.60 (1H, dd, $J_1 = 11.56$ Hz, $J_2 = 8.11$ Hz), 2.12 (1H, brs), 1.62-1.53 (1H, m), 1.52-1.44 (1H, m), 1.31-1.28 (1H, m), 0.96 (3H, d, J 2.64 Hz), 0.94 (3H, d, J 2.77 Hz). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 156.31, 149.53, 86.46, 63.39, 53.38, 44.73, 36.96, 24.79, 23.09, 21.92. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3386, 2925, 1763, 1383, 1067.

(S)-5-(4-Methoxybenzyl)-2-methylenemorfoline (7e').



Colorless oil, 80% yield, $R_f = 0.30$ (in 20% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 7.15-7.10 (2H, m, H-9 and H-9'), 6.86-6.82 (2H, m, H-8 and H-8'), 4.70-4.67 (1H, m, H-1), 4.22-4.20 (1H, m, H-1), 4.11 (2H, t, J 2.37 Hz, H-4), 4.04 (1H, m, H-5), 3.83 (1H, dd, $J_1 = 11.57$ Hz, $J_2 = 3.65$ Hz, H-6), 3.78 (3H, s, H-11), 3.74 (1H, dd, $J_1 = 11.53$ Hz, $J_2 = 7.17$ Hz, H-6), 2.89 (2H, m, H-3). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 158.54 (C-2), 155.93 (C-

10), 149.48, 129.76 (C-9/9'), 128.89 (C-7), 115.31, 114.26 (C-8/8'), 86.40 (C-1), 62.69 (C-6), 57.16 (C-5), 55.26 (C-11), 46.61 (C-4), 33.68 (C-3). DEPT-90 NMR (CDCl₃, 100 MHz, ppm): δ 129.76 (C-9/9'), 114.26 (C-8/8'), 57.16 (C-5). DEPT-135 NMR (CDCl₃, 100 MHz, ppm): δ 129.76 (C-9/9'), 114.26 (C-8/8'), 86.40 (C-1), 62.69 (C-6), 57.16 (C-5), 55.26 (C-11), 46.61 (C-4), 33.68 (C-3). IR (in CHCl₃, ν_{max} in cm⁻¹): 3386, 2921, 1383, 1054.

General procedure for the synthesis of 11a-d. To a stirred solution of compound 10a-d (1.0 equiv) in dry DCM, silver triflate (45 mmol %) was added at room temperature. Then it was continuously stirred for 2-3 h at room temperature. After completion of the reaction, reaction mixture was quenched with water, extracted with DCM, washed with brine solution, dried over sodium sulfate, concentrated under reduced pressure to get crude product. Then, the crude product was chromatographed on silica gel with eluent (hexane/ethyl acetate, to furnish the title product **11a-d** (76-93% yield) as colorless oil.

(S)-3,6-Dimethyl-4-tosyl-3,4-dihydro-2H-1,4-oxazine (11a). Colorless oil, 90% yield, R_f = 0.40 (in 20% EtOAc/Hexane); ¹H NMR (CDCl₃, 400 MHz, ppm): δ 7.64-7.62 (2H, m), 7.31-7.29 (2H, m), 5.77 (1H, s), 3.94-3.87 (1H, m), 3.64 (1H, dd, J_1 = 10.73 Hz, J_2 = 1.36 Hz), 2.80 (1H, dd, J_1 = 10.76 Hz, J_2 = 2.23 Hz), 2.42 (3H, s), 1.76 (3H, d, J 0.88 Hz), 1.19 (3H, d, J 6.71 Hz). ¹³C {¹H} NMR (CDCl₃, 100 MHz, ppm): δ 143.64, 139.52, 134.21, 129.74, 127.39, 98.10, 66.44, 47.48, 21.55, 17.67, 16.76. IR (in CHCl₃, ν_{max} in cm⁻¹): 3389, 2925, 1612, 1382, 1349, 1304, 1212, 1163, 1036, 771, 677, 573, 544. HRMS: m/z Calcd for [C₁₃H₁₇NO₃S+H]⁺: 268.1002, found: 268.0999.

(S)-3-Isopropyl-6-methyl-4-tosyl-3,4-dihydro-2H-1,4-oxazine (11b). Colorless oil, 76% yield, R_f = 0.40 (in 20% EtOAc/Hexane); ¹H NMR (CDCl₃, 400 MHz, ppm): δ 7.62-7.60 (2H, m), 7.29 (2H, d, J 7.84 Hz), 5.74 (1H, s), 3.94 (1H, dd, J_1 = 11.14 Hz, J_2 = 1.25 Hz), 3.29-3.26 (1H, m), 2.59 (1H, dd, J_1 = 11.23 Hz, J_2 = 2.49 Hz), 2.41 (3H, s), 1.81-1.73 (1H, m), 1.72 (3H, d, J 0.91 Hz), 1.06 (3H, d, J 6.81 Hz), 0.94 (3H, d, J 6.73). ¹³C {¹H} NMR (CDCl₃, 100 MHz, ppm): δ 143.59, 140.98, 134.06, 129.70, 127.53, 98.41, 62.75, 57.93, 26.93, 21.54, 19.92, 19.19, 17.64. IR (in CHCl₃, ν_{max} in cm⁻¹): 3385, 2922, 1383, 1161, 1031, 771, 683.

(S)-3-Benzyl-6-methyl-4-tosyl-3,4-dihydro-2H-1,4-oxazine (11c). Colorless oil, 93% yield, R_f = 0.40 (in 20% EtOAc/Hexane); ¹H NMR (CDCl₃, 400 MHz, ppm): δ 7.60 (2H, d, J 8.26 Hz), 7.31-7.21 (3H, m), 7.25-7.20 (4H, m), 5.84 (1H, s), 3.90-3.86 (1H, m), 3.66 (1H, dd, J_1 = 10.97 Hz, J_2 = 1.12 Hz), 2.88 (1H, dd, J_1 = 13.38 Hz, J_2 = 5.47 Hz), 2.76 (1H, dd, J_1 = 13.26 Hz, J_2 = 10.12 Hz), 2.68-2.65 (1H, m), 2.39 (3H, s), 1.80 (3H, d, 3H, d, J 0.81 Hz). ¹³C {¹H} NMR (CDCl₃, 100 MHz, ppm): δ 143.70, 140.05, 137.35, 134.18, 129.75, 129.70, 128.59, 127.43, 126.74, 98.36, 62.81, 53.28, 36.66, 21.54, 17.74. IR (in CHCl₃, ν_{max} in cm⁻¹): 3387, 2923, 1383, 1162, 1066, 771, 680, 572. HRMS: m/z Calcd for [C₁₉H₂₁NO₃S+H]⁺: 344.1315, found: 344.1312.

(S)-3-Isobutyl-6-methyl-4-tosyl-3,4-dihydro-2H-1,4-oxazine (11d). Colorless oil, 85% yield, R_f = 0.40 (in 20% EtOAc/Hexane); ¹H NMR (CDCl₃, 400 MHz, ppm): δ 7.64-7.62 (2H, m), 7.30 (2H, m), 5.72 (1H, s), 3.80-3.76 (1H, m), 3.66 (1H, dd, J_1 = 10.81 Hz, J_2 = 1.25 Hz), 2.72 (1H, dd, J_1 = 10.85 Hz, J_2 = 2.56 Hz), 2.42 (3H, s), 1.84-1.76 (1H, m), 1.74 (3H, d, J 0.92), 1.53-1.46 (1H, m), 1.15-1.09 (1H, m), 0.98 (3H, d, J 6.65 Hz), 0.93 (3H, d, J 6.78 Hz). ¹³C {¹H} NMR (CDCl₃, 100 MHz, ppm): δ 143.62, 140.30, 134.09, 129.71, 127.55, 98.09, 65.46, 50.03, 39.05, 24.21, 22.99, 22.14, 21.55, 17.69. IR (in CHCl₃, ν_{max} in cm⁻¹): 3386, 2928, 1382, 1163, 1057, 770, 679, 578.

General procedure for the synthesis of 11f. To a stirred solution of compound 10f (1.0 equiv) in dry toluene, silver triflate (45 mmol %) was added at room temperature. Then, the reaction mixture was heated at 80 °C for 1 h. After completion of the reaction, reaction mixture was quenched with water, extracted with ethyl acetate, washed with brine solution, dried over sodium sulfate, concentrated under reduced pressure to get crude product. Then, the crude product was chromatographed on silica gel with eluent hexane/ethyl acetate to furnish the title product **11f** (76 % yield) as colorless oil.

(S)-6-Methyl-3-(2-(methylthio)ethyl)-4-tosyl-3,4-dihydro-2H-1,4-oxazine (11f). Colorless oil, 76% yield, $R_f = 0.40$ (in 20% EtOAc/Hexane); ^1H NMR (CDCl_3 , 400 MHz, ppm): δ 7.65-7.63 (2H, m), 7.31 (2H, d, $J = 8.10$ Hz), 5.75 (1H, s), 3.92-3.88 (1H, m), 3.72 (1H, dd, $J_1 = 10.96$ Hz, $J_2 = 1.19$ Hz), 2.73 (1H, dd, $J_1 = 10.96$ Hz, $J_2 = 2.51$ Hz), 2.65 (2H, t, $J = 7.40$ Hz), 2.42 (3H, s), 2.12 (3H, s), 1.91-1.81 (1H, m), 1.74 (3H, d, $J = 0.88$ Hz), 1.62-1.57 (1H, m). ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz, ppm): δ 143.80, 140.34, 133.87, 129.78, 127.54, 98.06, 65.13, 50.78, 30.45, 29.41, 21.57, 17.69, 15.45. IR (in CHCl_3 , ν_{max} in cm^{-1}): 3383, 1383, 1063. HRMS: m/z Calcd for $[\text{C}_{15}\text{H}_{21}\text{NO}_3\text{S}_2+\text{Na}]^+$: 350.0855, found: 350.0854.

Acknowledgements

Fellowship support to A. K. and S. B. from CSIR and DST respectively is acknowledged. A. K. also acknowledge JNU, New Delhi. Financial support from Department of Science & Technology (DST; CRG/2019/000489) is highly appreciated. This article bears the CDRI communication number----

Supplementary Material

Electronic supplementary information (ESI) available: copies of NMR spectra of compounds **5a-d**, **5e'**, **10a-d**, **10f**, **7a-d**, **7e'**, **11a-d** and **11f**. This material can be found via the "Supplementary Content" section of this article's webpage.

References

1. Shimizu, Y. *Marine Natural Products*; Academic Press: New York, 1978; Vol. 1.
<https://doi.org/10.1016/B978-0-12-624001-6.50006-0>
2. Moore, R. E. *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 2.
3. Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1.
<https://doi.org/10.1039/np9860300001>
4. Yasumoto, T.; Murata, M. *Chem. Rev.* 1993, *93*, 1897.
5. <https://doi.org/10.1021/cr00021a011>Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75.
<https://doi.org/10.1039/np9961300075>
6. Cotten, J. F., Keshavaprasad, B., Laster, M. J., Eger, E. I., and Yost, C S. *Anesth. Analg.* **2006**, *102*, 779-785.
<https://doi.org/10.1213/01.ane.0000194289.34345.63>
7. Stoops, W. W., Strickland, J. C., Alcorn, J. L., Hays, L. R., Rayapati, A. O., Lile, J. A., and Rush, C. R. *Psychopharmacology*, **2019**, *236*, 2569-2577.
<https://doi.org/10.1007/s00213-019-05227-x>
8. Bonnet, U. *CNS Drug Rev.* **2003**, *9*, 97-140.
<https://doi.org/10.1111/j.1527-3458.2003.tb00245.x>
9. Walsh, S. L., Heilig, M., Nuzzo, P. A., Henderson, P., and Lofwall, M. R. *Addict. Biol.* **2013**, *18*, 332-343.
10. Hale, J. J., Mills, S. G., MacCoss, M., Finke, P. E., Cascieri, M. A., Sadowski, S., Ber, E., Chicchi, G. G., Kurtz, M., Metzger, J., et al. *J. Med. Chem.* **1998**, *41*, 4607-4614.
11. Hargreaves, R., Arjona Ferreira, J. C., Hughes, D., Brands, J., Hale, J., Mattson, B., and Mills, S. *Ann. N. Y. Acad. Sci.* **2011**, *1222*, 40-48.

- <https://doi.org/10.1111/j.1749-6632.2011.05961.x>
12. Naidu, C., and Kulkarni, J. *Aust. N. Z. J. Psychiatry*, **2019**, *53*, 1227-1228.
<https://doi.org/10.1177/0004867419865612>
13. Dieckmann, H.; Stockmaier, M.; Kreuzig, R.; Bahadir, M. *Fresenius' J. Anal. Chem.* 1993, *345*, 784.
<https://doi.org/10.1007/BF00323011>
14. Lenci, E., Calugi, L. and Trabocchi, A. *ACS Chem. Neurosci.* **2021**, *12*, 378-390.
<https://doi.org/10.1021/acschemneuro.0c00729>
15. Sordo, T.; Campomanes, P.; Die'guez, A.; Rodr'iguez, F. and Fañanás, F. J. *J. Am. Chem. Soc.* 2005, *127*, 944-952.
<https://doi.org/10.1021/ja045567k>
16. Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S. and Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744-8754.
<https://doi.org/10.1021/ja048693x>
17. Fukudome, Y.; Naito, H.; Hata, T. and Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820-1821.
<https://doi.org/10.1021/ja078163b>
18. Pale, P. and Chucho, J. *Eur. J. Org. Chem.* **2000**, 1019-1025.
[https://doi.org/10.1002/\(SICI\)1099-0690\(200003\)2000:6<1019::AID-EJOC1019>3.0.CO;2-4](https://doi.org/10.1002/(SICI)1099-0690(200003)2000:6<1019::AID-EJOC1019>3.0.CO;2-4)
19. Kadota, I.; Lutete, L. M.; Shibuya, A. and Yamamoto, Y. *Tetrahedron Lett.*, 2001, *42*, 6207-6210.
[https://doi.org/10.1016/S0040-4039\(01\)01207-2](https://doi.org/10.1016/S0040-4039(01)01207-2)
20. Dalla V. and Pale P. *New J. Chem.*, **1999**, *23*, 803-805.
<https://doi.org/10.1039/a903587g>
21. Dai, L-Z.; Qi, M-J.; Shi, Y-L.; Liu, X-G. and Shi, M. *Org. Lett.* **2007**, *9*, 3191-3194.
<https://doi.org/10.1021/ol0713640>
22. Vandavasi, J. K.; Hu, W-P.; Chen, H-Y.; Senadi, G. C.; Chen, C-Y.; and Wang, J-J. *Org. Lett.*, **2012**, *14*, 3134-3137.
<https://doi.org/10.1021/ol301219c>
23. Mishra, J. K.; Panda, G. *J. Comb. Chem.* **2007**, *9*, 321.
<https://doi.org/10.1021/cc0601480>
24. 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.
<https://doi.org/10.1016/j.bmcl.2009.10.115>
25. Mishra, J. K.; Samanta, K.; Jain, M.; Dikshit, M.; Panda, G. *Bioorg. Med. Chem. Lett.* 2010, *20*, 244.
<https://doi.org/10.1016/j.bmcl.2009.10.126>
26. Jana, A. K.; Singh, J.; Ganesh, A.; Kumar, A.; Banerjee, A.; Kumar, D.; Verma, S. K.; Sharma, A. K.; Bhatta, R. S.; Konwar, R. and Panda, G. *J. Med. Chem.* **2021**, *64*, 16293-16316.
<https://doi.org/10.1021/acs.jmedchem.1c01624>
27. Samanta, K.; Panda, G. *Chem.-Asian J.* **2011**, 189-197.
<https://doi.org/10.1002/asia.201000554>
28. Bera, S. and Panda, G. *ACS Comb. Sci.* **2012**, *14*, 1-4.
<https://doi.org/10.1021/co200129t>
29. Mageswara, M.; Lee, Y. Y.; Kang, E. J. *Synlett* **2012**, *23*, 2481-2484.
<https://doi.org/10.1055/s-0031-1290466>
30. Wang, Z.; Lin, X.; Luck, R. L. Gibbons, G.; Fang S. *Tetrahedron*, **2009**, *65*, 2643-2648.
<https://doi.org/10.1016/j.tet.2009.01.065>

31. Barluenga, J., Fernandez, A., Satrustegui, A., Diéguez, A., Rodríguez, F. and Fañanás, F.J., *Chem. Eur. J.* **2008**, *14*, 4153-4156.
<https://doi.org/10.1002/chem.200800312>
32. Azumi, M.; Ogawa, K.; Fujita, T.; Takeshita, M.; Yoshida, R.; Furumai, T.; Igarashi, Y. *Tetrahedron*, **2008**, *64*, 6420-6425.
<https://doi.org/10.1016/j.tet.2008.04.076>
33. Viswanadha, S.; McGilliard, M. L.; Gandour, R. D.; Herbein, J. H. *Eur. J. Lipid Sci. Technol.* **2008**, *110*, 16-22.
<https://doi.org/10.1002/ejlt.200600284>
34. Monge, A.; Aldana, I.; Cerecetto, H.; Rivero, A.; Delbarrio, A.; Perez, R.; Portillo, M.; Martinez, A. *Pharmazie*, **1995**, *50*, 768-769.
35. Bera, S. and Panda, G. *Org. Biomol. Chem.* **2014**, *12*, 3976-3985.
<https://doi.org/10.1039/C4OB00639A>
36. Fanter, L.; Müller, C.; Schepmann, D.; Bracher, F.; Wünsch, B. *Bioorg. Med. Chem.* **2017**, *25*, 4778–4799.
<https://doi.org/10.1039/C4OB00639A>
37. Zůrek, J.; Svobodová, E.; Šturala, J.; Dvořáková, H.; Svoboda, J.; Cibulka, R. *Tetrahedron Asymmetry* **2017**, *28*, 1780–1791.
<https://doi.org/10.1016/j.tetasy.2017.10.029>

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>)