Indian Journal of Chemistry
Vol. 61, October 2022, pp. 1039-1045
DOI: 10.56042/ijc.v61i10.64005

Synthesis of glycoprotein inhibitory agents sinuxylamide A-E

K Annapurna[a], K Srinivasa Rao[a] & A Venkat Narsaiah[a,b,*]

[a] Organic Synthesis Laboratory, Fluoro-Agrochemicals Department,
CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, Telangana, India

[b] Academy of Scientific and Innovative Research (AcSIR), CSIR-HRDC Campus, Postal Staff College Area
Sector 19, Kamla Nehru Nagar, Ghaziabad 201 002, Uttar Pradesh, India

*E-mail: vnakkirala@iict.res.in, vnakkirala2001@yahoo.com

Received 27 June 2022; accepted (revised) 3 August 2022

Synthesis of naturally occurring Sinuxylamides A-E has been accomplished. Synthesis started from commercially available L-tyrosine. The key reactions involved in this synthesis are amide formation, Mitsunobu etherification and ester hydrolysis.

Keywords: L-Tyrosine, Amide, Etherification, Glycoprotein, Marine products

Marine organisms are the most abundant source for biologically active molecules. Algae, fungi, sponges, cnidarians, bryozoans, tunicates, echinoderms, mangroves or microorganisms and thousands of compounds are isolating from these sources[1,2]. Recently, Cao group isolated, secondary metabolites from a fungal strain of *Xylaria sp.FM1005*, which shows glycoprotein (IIb /IIIa) inhibitory activity[3-5]. As part of our regular research program, in the synthesis of biologically active natural and synthetic molecules[6-11], herein, we report the synthesis of tyrosine derivatives Sinuxylamides A-E (Fig. 1).

As shown in the retrosynthetic analysis (Scheme 1), the target molecules Sinuxylamide A, could be achieved from compound **3** and Sinuxylamide B, could be from Sinuxylamide A, by ester hydrolysis. Sinuxylamide C, could be derived from the intermediate **4** and Sinuxylamide D, could be obtained from **6**. The Sinuxylamide E, would be from the compound **3**. Fragment **X** could be accomplished from commercially available, L-tyrosine (**1**).

Results and Discussion

As per the plan, synthesis of all target molecules, started from readily available natural amino acid, L-tyrosine (**1**), which on esterfication with methanol in presence of $SOCl_2$, gave (*S*)-methyl-2-amino-3-(4-hydroxyphenyl)propanoate (**2**) in very good yields. The compound **2** was reacted with *n*-hexanoic acid, in presence of EDC.HCl and HOBt in CH_2Cl_2 at RT to afford[12], (*S*)-methyl-2-hexanamido-3-(4-hydroxyphenyl)propanoate (**3**) in 87% yields. The compound **3**, was subjected to etherification with 2-butyn-1-ol, using Mitsunobu conditions[13,14] to obtain the natural product, Sinuxylamide A, in very good yields. Thus obtained, Sinuxylamide A, was subjected to ester hydrolysis under mild conditions with LiOH in THF/MeOH/H_2O mixture at 0°C to yield[15], Sinuxylamide B as shown in the Scheme 2.

The compound **2** was reacted with *n*-pentanoic acid, in presence of EDC.HCl and HOBt in CH_2Cl_2 at RT to obtain, (*S*)-methyl-3-(4-hydroxyphenyl)-2-pentanamidopropa noate (**4**) in 84% yield and the product was confirmed by its spectral data. The compound **4** was subjected to etherification with 2-butyn-1-ol, using Mitsunobu protocol to afford, (*S*)-methyl-3-(4-(but-2-yn-1-yloxy)phenyl-2-pentanamidopropanoate (**5**) in very good yields. The product **5**, was treated with LiOH in THF/MeOH/H_2O solvent mixture to yield Sinuxylamide C, in 84% yields, as shown in the Scheme 3.

The compound **2** and *n*-butanoic acid were reacted in presence of EDC.HCl and HOBt in CH_2Cl_2 at RT to yield, (*S*)-methyl-2-butyramido-3-(4-hydroxyphenyl) propanoate (**6**). The compound **6** was subjected to etherification with 2-butyn-1-ol, using Mitsunobu protocol to afford, (*S*)-methyl-3-(4-(but-2-yn-1-yloxy)phenyl)-2-butyramidopropanoate (**7**) in 80%

IICT Communication No: IICT/Pubs./2021/366.

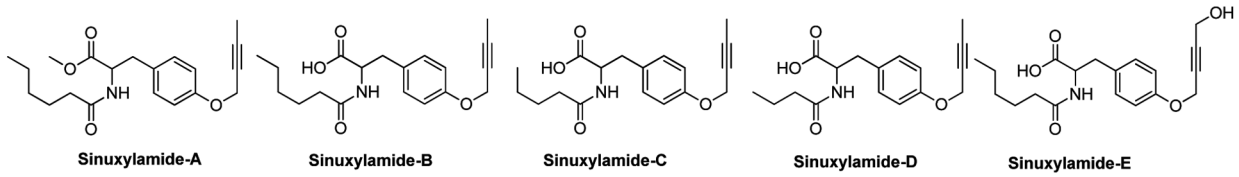
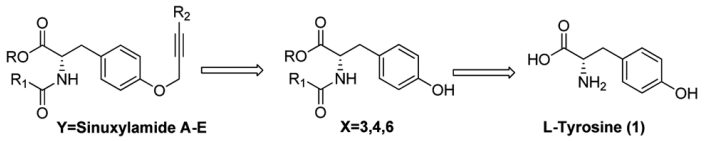
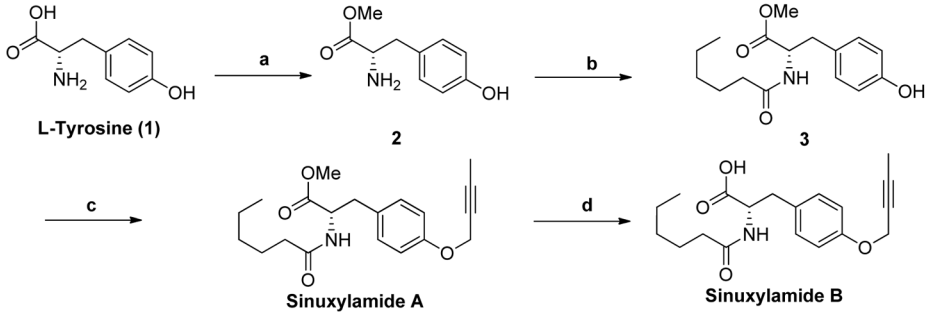


Fig. 1

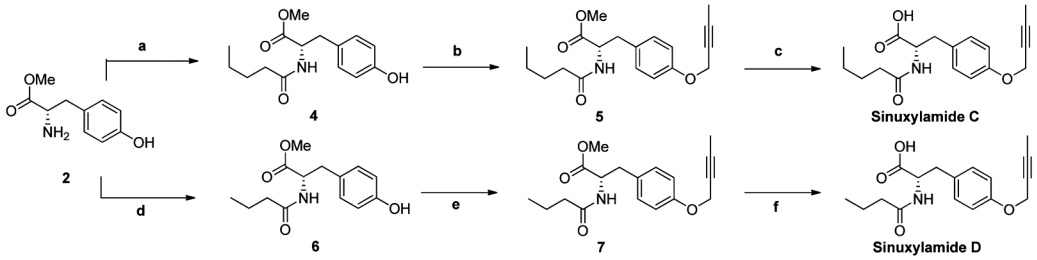


Scheme 1



Reagents and conditions: (a) $SOCl_2$, MeOH, RT, 12 h, 85%; (b) Hexanoic acid, EDC.HCl, HOBt, CH_2Cl_2, RT, 12 h, 87%; (c) 2-Butyn-1-ol, TPP-DEAD, THF, RT, 12 h, 87%; (d) THF/MeOH/H_2O, LiOH, 0°C, 1 h, 84%.

Scheme 2 — Synthesis of Sinuxylamide A and Sinuxylamide B



Reagents and conditions: (a) Pentanoic acid, EDC.HCl, HOBt, CH_2Cl_2, RT, 12 h, 84%; (b) 2-Butyn-1-ol, TPP, DEAD, THF, RT, 12 h, 83%; (c) THF / MeOH /H_2O, LiOH, 0°C, 1 h, 84%; (d) Butanoic acid, EDC.HCl, HOBt, CH_2Cl_2, RT, 12 h, 86%; (e) 2-Butyn-1-ol, TPP-DEAD, THF, RT, 12 h, 80%; (f) THF/MeOH/H_2O, LiOH, 0°C, 1 h, 89%.

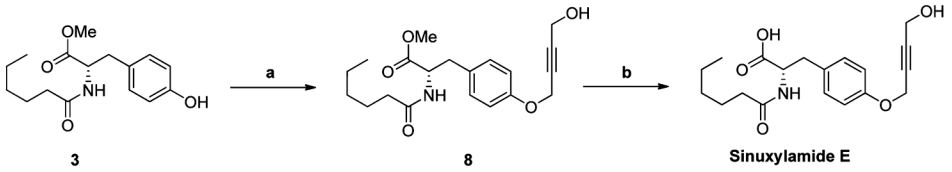
Scheme 3 — Synthesis of Sinuxylamide C and Sinuxylamide D

yields. Sinuxylamide D was obtained by ester hydrolysis of compound **7**, with LiOH, as shown in the Scheme 3.

The compound **3** and but-2-yne-1,4-diol were subjected for etherification, under Mitsunobu conditions to afford, (*S*)-methyl-2-hexanamido-3-(4-[(4-hydroxybut-2-yn-1-yl)oxy]phenyl)propa noate (**8**) in 74% yields. The ester group of compound **8** was hydrolyzed with LiOH as shown in the Scheme 4, to achieve the target molecule Sinuxylamide E, in 79% yields.

All the products were characterized by their ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy analysis and also compared with the literature reports.

In conclusion, we have demonstrated the synthesis of naturally occurring glycoprotein inhibitory agents



Reagents and conditions: (a) But-2-yne-1-4-diol, TPP-DEAD, THF, RT, 12 h, 75%; (b) THF /MeOH/ H_2O, LiOH, 0°C, 1 h, 79%.

Scheme 4 — Synthesis of Sinuxylamide E

Sinuxylamide A-E, in very good yields. The synthesis started from L-tyrosine and ended as its derivatives. The reactions involved in the synthesis are amide formation, etherification and ester hydrolysis.

Experimental Section

All air and moisture sensitive reactions were carried out under nitrogen atmosphere. Oven-dried glass apparatus were used to perform all the reactions. Freshly distilled solvents were used for air and moisture sensitive reactions and commercially available reagents were used as such. Purification of compounds was carried out *via* column chromatography by using silica gel (60-120 mesh) packed in glass columns. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ and CD_3OD solvents on 400 MHz and 500 MHz spectrometers at ambient temperature, using TMS as an internal standard. FT-IR spectra were recorded on a Perkin-Elmer 683 infrared spectrophotometer, neat or as thin films in KBr. High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer. Melting points were obtained using Optics Technology. Optical rotations were measured in MeOH.

Methyl-L-tyrosinate, 2: To a stirred mixture of L-tyrosine (10 g, 55.2 mmol) in MeOH (200 mL) was added thionyl chloride ($SOCl_2$) (8 mL, 110.4 mmol) slowly at 0°C and the reaction mixture was allowed to stir at RT for 12 h. After completion of reaction, as indicated by TLC, the methanol was removed under reduced pressure. Thus obtained white solid was dissolved in H_2O (20 mL) and cooled to 0°C and neutralized with sat.$NaHCO_3$ (50 mL) by adding drop-wise over a period of 10 min, until the solution pH = 10. The reaction mixture was allowed to stir for 30 min at RT, and extracted with CH_2Cl_2 (3×25 mL), followed by the removal of solvent under reduced pressure, the crude product **2** was obtained, in 9.15 g (85% yield), as a white solid. m.p. 135-136°C. Optical rotation, $[\alpha]_D^{20}$ = + 26° (c = 1, MeOH); IR (KBr): 3355, 3300, 29 33, 1744, 1597, 1514, 1480, 1260, 1176, 1020, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, 2H, *J* = 8.4 Hz), 6.72 (d, 2H, *J* = 8.4 Hz), 3.73 (s, 3H), 3.72 - 3.69 (m, 1H), 3.03 (dd, 1H, *J* = 13.7, 5.1 Hz), 2.81 (dd, 1H, *J* = 13.7, 7.7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.6, 154.9, 130.5, 128.8, 115.7, 55.9, 52.2, 40.1; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{10}H_{14}NO_3$: 196.0974. Found: 196.0965.

Methyl-*N*-hexanoyl-L-tyrosinate, 3: To a stirred mixture of hexanioc acid (0.72g, 6.16 mmol), in CH_2Cl_2 (50 mL) were added EDC.HCl (1.18g, 6.16 mmol) and HOBt (1.04g, 7.7 m mol) at 0°C and stirred for 20 min. Then added methyl-L-tyrosinate (1g, 5.13 mmol) and the mixture was stirred at RT, for 12 h. After completion of the reaction (monitored by TLC), quenched with sat.$NaHCO_3$ and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography by eluting with EtOAc-hexane (1:1) mixture to give **3**, in 1.3 g (87% yield), as a white solid. m.p. 88-89°C. Optical rotation, $[\alpha]_D^{20}$ = +11° (c = 1, MeOH); IR (KBr): 3329, 2957, 2928, 1725, 165 6, 1517, 1436, 1271, 1224, 829 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (d, 2H, *J* = 8.5 Hz), 6.74 (d, 2H, *J* = 8.5 Hz), 6.04 (d, 1H, *J* = 8.0 Hz), 4.88 (dt, 1H, *J* = 8.0, 6.0 Hz), 3.73 (s, 3H), 3.08 (dd, 1H, *J* = 14.1, 5.6 Hz), 2.97 (dd, 1H, *J* = 14.1, 6.3 Hz), 2.18 (t, 2H, *J* = 7.6 Hz), 1.61 - 1.54 (m, 2H), 1.33 - 1.19 (m, 4H), 0.86 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 172.5, 155.8, 130.3, 126.8, 115.7, 53.3, 52.5, 37.3, 36.5, 31.3, 25.3, 22.4, 13.9; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{16}H_{24}NO_4$: 294.1705. Found: 294.1699.

Sinuxylamide A: To a stirred mixture of methyl-*N*-hexanoyl-L-tyrosinate (0.5 g, 1.71 mmol), in THF (15 mL) were added triphenylphosphine (TPP) (0.45 g,

1.71 mmol) and 2-butyn-1-ol (0.13 mL, 1.71 mmol), then added diethylazodicarboxylate (DEAD) (0.27 mL, 1.71 mmol) drop-wise at 0°C and stirred at RT, for 12 h. Then completion of reaction was confirmed by TLC and mixture was concentrated *in vacuo* to give a crude oil, which was purified by column chromatography, by eluting with EtOAc-hexane (1:4) mixture over silica-gel (60-120 mesh) to give Sinuxylamide A, in 0.52 g (87%) yield, as a white solid. m.p. 64-65°C. Optical rotation, $[\alpha]_D^{20}$ = +10.5° (c = 1, MeOH); IR (KBr): 3386, 2951, 2864, 2229, 1739, 1649, 1511, 1448, 1220, 1026 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.11 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.7 Hz), 4.66 - 4.57 (m, 3H), 3.69 (s, 3H), 3.10 (dd, 1H, *J* = 14.0, 5.5 Hz), 2.88 (dd, 1H, *J* = 14.0, 9.3 Hz), 2.15 (t, 2H, *J* = 7.4 Hz), 1.81 (t, 3H, *J* = 2.3 Hz), 1.56 - 1.46 (m, 2H), 1.34 - 1.14 (m, 4H), 0.88 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 176.2, 173.7, 158.3, 131.1, 130.7, 115.9, 84.0, 75.3, 57.1, 55.2, 52.6, 37.5, 36.6, 32.3, 26.5, 23.4, 14.3, 3.1; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{20}H_{28}NO_4$: 346.201 8. Found: 346.2012.

Sinuxylamide B: To a stirred mixture of Sinuxylamide A (0.2 g, 0.58 mmol) in THF/ MeOH/ H_2O (3:1:1, 5 mL) was added LiOH (26 mg, 1.16 mmol) at 0°C, and the reaction mixture was stirred for 1 h. After completion of the reaction (monitored by TLC), the organic solvents were removed *in vacuo*, then added water (3 mL) and the reaction mixture was acidified with dil.HCl to pH = 3. Then, mixture was extracted with EtOAc (2×10 mL), the combined organic layers, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography by eluting with EtOAc-hexane (1:6) mixture to afford, Sinuxylamide B, in 0.16 g (84% yield), as a white solid. m.p. 101-102°C. Optical rotation, $[\alpha]_D^{20}$ = + 17.1° (*c* = 1, MeOH); IR (neat): 3357, 2944, 2833, 2228, 1654, 1451, 1114, 1029 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.14 (d, 2H, *J* = 8.7 Hz), 6.86 (d, 2H, *J* = 8.7 Hz), 4.64 (dd, 1H, *J* = 9.4, 5.0 Hz), 4.61 (q, 2H, *J* = 2.3 Hz), 3.15 (dd, 1H, *J* = 14.0, 4.9 Hz), 2.87 (dd, 1H, *J* = 14.0, 9.4 Hz), 2.15 (t, 2H, *J* = 7.4 Hz), 1.81 (t, 3H, *J* = 2.3 Hz), 1.56 - 1.46 (m, 2H), 1.32 - 1.11 (m, 4H), 0.87 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 176.1, 174.9, 158.2, 131.1, 130.9, 115.8, 83.9, 75.3, 57.1, 54.9, 37.6, 36.7, 32.3, 26.6, 23.4, 14.3, 3.1; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{19}H_{26}NO_4$: 33 2.1862. Found: 332.1856.

Methyl-*N*-pentanoyl-L-tyrosinate, 4: To a stirred mixture of pentanioc acid (0.63 g, 6.16 mmol), in CH_2Cl_2 (50 mL) were added EDC.HCl (1.18 g, 6.16 mmol) and HOBt (1.04 g, 7.7 mmol) at 0°C and stirred for 20 min. Then methyl-L-tyrosinate (1 g, 5.13 mmol) was added and the mixture was stirred at RT for 12 h. After completion (monitored by TLC), the reaction mixture was quenched with sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography by eluting with EtOAc-hexane (1:1) mixture to give compound **4**, in 1.2 g (84% yield), as a white solid. m.p. 70-71°C. Optical rotation, $[\alpha]_D^{20}$= +13° (c = 1, MeOH); IR (KBr): 3329, 2957, 2927, 1727, 1655, 1517, 1452, 1273, 1223, 828 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.93 (d, 2H, *J* = 8.4 Hz), 6.74 (d, 2H, *J* = 8.5 Hz), 6.04 (d, 1H, *J* = 7.3 Hz), 4.92 - 4.85 (m, 1H), 3.74 (s, 3H), 3.08 (dd, 1H, *J* = 14.1, 5.6 Hz), 2.97 (dd, 1H, *J* = 14.1, 6.4 Hz), 2.19 (t, 2H, *J* = 7.5 Hz), 1.60 - 1.52 (m, 2H), 1.33 - 1.23 (m, 2H), 0.87 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.5, 172.6, 155.7, 130.4, 127.1, 115.7, 53.3, 52.6, 37.4, 36.4, 27.7, 22.4, 13.8; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{15}H_{22}NO_4$: 280.1549. Found: 280.1543.

Methyl-(*S*)-3-[4-(but-2-yn-1-yloxy)phenyl]-2-pentanamidopropanoate, 5: To a stirred solution of methyl-*N*-pentanoyl-L-tyrosinate (0.5 g, 1.79 mmol), in THF (10 mL) were added TPP (0.47 g, 1.79 mmol) and 2-butyn-1-ol (0.13 mL,1.79 mmol), then added DEAD (0.27 mL,1.79 mmol) slowly at 0°C. After stirring at RT for 12 h, the reaction mixture was concentrated *in vacuo* to give a crude product, which was purified by column chromatography over silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:4) mixture to afford, product **5** in 0.5 g (83% yield), as white solid. m.p. 52-53°C. Optical rotation, $[\alpha]_D^{20}$= +10.3° (c = 1, MeOH); IR (KBr): 3315, 2926, 2858, 2243, 1753, 1644, 1540, 1434, 1218, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, 2H, *J* = 8.7 Hz), 6.88 (d, 2H, *J* = 8.7 Hz), 5.89 (d, 1H, *J* = 7.7 Hz), 4.86 (dt, 1H, *J* = 7.8, 5.8 Hz), 4.62 (q, 2H, *J* = 2.3 Hz), 3.73 (s, 3H), 3.09 (dd, 1H, *J* = 14.0, 5.8 Hz), 3.03 (dd, 1H, *J* = 14.0, 5.7 Hz), 2.20 - 2.15 (m, 2H), 1.86 (t, 3H, *J* = 2.3 Hz), 1.63 - 1.53 (m, 2H), 1.36 - 1.26 (m, 2H), 0.90 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 172.4, 157.1, 130.3, 128.5,

115.0, 83.9, 74.1, 56.6, 53.1, 52.4, 37.2, 36.4, 27.7, 22.4, 13.9, 3.8; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{19}H_{26}NO_4$: 332.1862. Found: 332.1856.

Sinuxylamide C: To a stirred mixture of methyl-(*S*)-3-[4-(but-2-yn-1-yloxy)phenyl]-2-pentanamidopropanoate (0.2 g, 0.6 mmol), in THF/MeOH/H_2O (3:1:1, 5 mL) was added LiOH (27 mg, 1.2 mmol) at 0°C and the reaction mixture was stirred at this temperature for 1 h. After completion of the reaction (monitored by TLC), the organic solvents were removed *in vacuo*, then water (3 mL) was added, and the reaction mixture was acidified with dil.HCl to *p*H = 3 and then extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:6) mixture to give Sinuxylamide C, in 0.16 g (84% yield), as a white solid. m.p. 116-117°C. Optical rotation, $[\alpha]_D^{20}$ = +27.3° (*c* = 1, MeOH); IR (KBr): 3290, 3075, 2955, 2863, 2242, 1705, 1609, 1512, 1452, 1239, 1113, 1024 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.14 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 4.66 - 4.58 (m, 3H), 3.15 (dd, 1H, *J* = 14.0, 4.8 Hz), 2.87 (dd,1H, *J* = 14.0, 9.5 Hz), 2.16 (t, 2H, *J* = 7.4 Hz), 1.81 (s, 3H), 1.53 - 1.44 (m, 2H), 1.26 - 1.16 (m, 2H), 0.86 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 176.1, 174.9, 158.3, 131.2, 131.0, 115.8, 83.9, 75.3, 57.1, 55.0, 37.6, 36.5, 29.0, 23.2, 14.1, 3.1; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{18}H_{24}O_4$: 318.1705. Found: 318.1699.

Methyl-*N*-butyryl-L-tyrosinate, 6: To a stirred mixture of butanioc acid (0.54 g, 6.16 mmol), in CH_2Cl_2 (50 mL) were added EDC.HCl (1.18 g, 6.16 mmol) and HOBt (1.04 g, 7.7 mmol) at 0°C and stirred for 20 min. Then methyl-L-tyrosinate (1 g, 5.13 mmol) was added and the mixture was stirred at RT for 12 h. After completion, (monitored by TLC), the reaction was quenched with sat.$NaHCO_3$ and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers, washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:1) mixture to give compound **6**, in 1.17 g (86% yield), as a colourless syrup. Optical rotation, $[\alpha]_D^{20}$ = +14.5° (c = 1, MeOH); IR (neat): 3304, 2962, 2930, 1739, 1649, 1516, 1443, 1225, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (brs, 1H), 6.91 (d, 2H, *J* = 8.4 Hz), 6.73 (d, 2H, *J* = 8.4 Hz), 6.22 (d, 1H, *J* = 7.9 Hz), 4.89 - 4.81 (m, 1H), 3.70 (s, 3H), 3.05 (dd, 1H, *J* = 14.0, 5.6 Hz), 2.95 (dd, 1H, *J* = 14.1, 6.4 Hz), 2.15 (t, 2H, *J* = 7.5 Hz), 1.65 - 1.52 (m, 2H), 0.86 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 172.5, 155.9, 130.2, 126.7, 115.7, 53.4, 52.5, 38.4, 37.2, 19.1, 13.6; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{14}H_{20}NO_4$: 266.1392. Found: 266.1386.

Methyl-(*S*)-3-[4(but-2-yn-1-yloxy)phenyl]-2-butyramidopropanoate, 7: To a stirred solution of methyl-*N*-butyryl-L-tyrosinate (0.5 g, 1.9 mmol), in THF (10 mL) were added TPP (0.49 g, 1.9 mmol) and 2-butyn-1-ol (0.14 mL, 1.9 mmol), then added DEAD (0.3 mL, 1.9 mmol) slowly at 0°C. After stirring at RT for 12 h, the reaction mixture was concentrated *in vacuo* to give a crude product, which was purified by column chromatography over silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:4) mixture to afford product **7** in 0.48 g (80% yield), as a white solid. m.p. 47-49°C. Optical rotation, $[\alpha]_D^{20}$ = +10.9° (c = 1, MeOH); IR (KBr): 3307, 2964, 2870, 2244, 1753, 1644, 1540, 1438, 1220, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.0 (d, 2H, *J* = 8.7 Hz), 6.88 (d, 2H, *J* = 8.7 Hz), 6.02 (d, 1H, *J* = 7.6 Hz), 4.86 (dt, 1H, *J* = 7.8, 5.7 Hz), 4.61 (dd, 2H, *J* = 4.4, 2.1 Hz), 3.72 (s, 3H), 3.09 (dd, 1H, *J* = 14.0, 5.7 Hz), 3.04 (dd, 1H, *J* = 14.0, 5.7 Hz), 2.19 - 2.12 (m, 2H), 1.86 (t, 3H, *J* = 2.3 Hz), 1.67 - 1.58 (m, 2H), 0.92 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.6, 172.4, 157.1, 130.4, 128.5, 115.1, 83.9, 74.1, 56.6, 53.1, 52.4, 38.6, 37.2, 19.1, 13.8, 3.8; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{18}H_{24}NO_4$: 318.1705. Found: 332.1699.

Sinuxylamide D: To a stirred mixture of methyl-(*S*)-3[4(but-2-yn-1-yloxy)phenyl]-2-butyramidopropanoate (0.2 g, 0.63 mmol), in THF/MeOH/H_2O (3:1:1, 5 mL) was added LiOH (28 mg, 1.26 mmol) at 0ºC, and the reaction mixture was stirred at this temperature for 1 h. After completion of the reaction (monitored by TLC), the organic solvents were removed in *vacuo*, then water (3 mL) was added, and the reaction mixture was acidified with dil.HCl to *p*H = 3. Then, mixture was extracted with EtOAc (2×10 mL) and the combined organic layer was washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude

product was purified by column chromatography by eluting with EtOAc-hexane (4:6) mixture to give the target molecule Sinuxylamide D, in 0.17 g (89%) yield, as a white solid. m.p. 125-127°C. Optical rotation, $[\alpha]_D^{20}$ = +36.3° (*c* = 1, MeOH); IR (KBr): 3298, 2968, 2872, 2223, 1706, 1610, 1510, 1450, 1221, 1017 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.14 (d, 2H, *J* = 8.7 Hz), 6.87(d, 2H, *J* = 8.7 Hz), 4.66 - 4.60 (m, 3H), 3.15 (dd, 1H, *J* = 14.0, 5.0 Hz), 2.88 (dd, 1H, *J* = 14.0, 9.3 Hz), 2.14 (t, 2H, *J* = 7.2 Hz), 1.81 (t, 3H, *J* = 2.3 Hz), 1.59 - 1.49 (m, 2H), 0.84 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (126 MHz, CD_3OD): δ 175.9, 174.9, 158.2, 131.1, 130.9, 115.8, 83.9, 75.3, 57.1, 55.0, 38.6, 37.6, 20.3, 13.8, 3.1; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{17}H_{22}O_4$: 304.1549. Found: 304.1543.

Methyl-(*S*)-2-hexanamido-3-{4[(4-hydroxybut-2-yn-1-yl)oxy]phenyl}propanoate, 8: To a stirred mixture of methyl-*N*-hexanoyl-L-tyrosinate (0.5 g, 1.71 mmol), in THF (15 mL) was added TPP (0.45 g, 1.71 mmol) and 2-butyne-1,4-diol (0.3 g, 3.42 mmol), then added DEAD (0.27 mL, 1.71 mmol) drop-wise at 0 ºC. After stirring at RT, for 12 h, the mixture was concen trated *in vacuo* to give a crude oil, which was purified by column chromatography, using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:1) mixture to give, compound **8**, in 0.46 g (74.6%) yield, as a colorless syrup. Optical rotation, $[\alpha]_D^{20}$ = +9.7° (c = 1, MeOH); IR (neat): 33 02, 2929, 2862, 1742, 1650, 1511, 1440, 1219, 1012 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.02 (d, 2H, *J* = 8.7 Hz), 6.88 (d, 2H, *J* = 8.7 Hz), 5.98 (d, 1H, *J* = 7.8 Hz), 4.86 (dt, 1H, *J* = 7.9, 5.8 Hz), 4.70 (t, 2H, *J* = 1.8 Hz), 4.29 (s, 2H), 3.73 (s, 3H), 3.10 (dd, 1H, *J* = 14.0, 5.7 Hz), 3.01 (dd, 1H, *J* = 14.0, 6.0 Hz), 2.19 - 2.14 (m, 2H), 1.62 - 1.55 (m, 2H), 1.32 - 1.24 (m, 4H), 0.88 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 172.4, 156.8, 130.4, 128.9, 115.1, 86.0, 80.3, 56.2, 53.2, 52.5, 50.9, 37.3, 36.6, 31.4, 25.3, 22.5, 14.0; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{20}H_{28}NO_5$: 362.1967. Found: 362.1962.

Sinuxylamide E: To a stirring mixture of methyl-(*S*)-2-hexanamido-3-{4-[(4-hydroxybut-2-yn-1-yl)oxy]-phenyl}propanoate (0.2 g, 0.55 mmol), in THF/MeOH/H_2O (3:1:1, 5 mL) was added LiOH (25 mg, 1.1 mmol) at 0°C, and the reaction mixture was stirred at this temperature for 1 h. After completion of the reaction (monitored by TLC), the organic solvents were removed in *vacuo*, then added water (3 mL) and the mixture was acidified with dil.HCl to *p*H=3. The mixture was extracted with EtOAc (2×10 mL) and the combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with hexane-EtOAc (1:1) mixture to give Sinuxylamide E, in 0.15 g (78.9%) yield, as colourless liquid. Optical rotation, $[\alpha]_D^{20}$ = +15.5° (*c* = 1, MeOH); IR (KBr): 3317, 2957, 2864, 1728, 1647, 1512, 1445, 1219, 1012 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.15 (d, 2H, *J* = 8.7 Hz), 6.88 (d, 2H, *J* = 8.7 Hz), 4.71 (t, 2H, *J* = 1.8 Hz), 4.63 (dd, 1H, *J* = 9.4, 5.0 Hz), 4.20 (t, 2H, *J* = 1.8 Hz), 3.15 (dd, 1H, *J* = 14.0, 5.0 Hz), 2.88 (dd, 1H, *J* = 14.0, 9.4 Hz), 2.15 (t, 2H, *J* = 7.4 Hz), 1.56 - 1.45 (m, 2H), 1.34 - 1.14 (m, 4H), 0.87 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 176.1, 174.8, 158.1, 131.2, 115.8, 86.7, 80.8, 56.8, 54.9, 50.7, 37.6, 36.7, 32.3, 26.6, 23.4, 14.3; HR-MS: *m/z* $[M+H]^+$ Calcd for $C_{19}H_{26}NO_5$: 348.1811. Found: 348.1805.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Conflict of Interest

The authors declare that there is no conflict of interest.

Funding Information

This research was supported by Science and Engineering Research Board, grant No: EEQ/2018/001311, Department of Science and Technology, Govt. of India.

Acknowledgements

Authors KA is thankful to CSIR-New Delhi for providing fellowship and KSR is thankful to Director CSIR-IICT for providing Fellowship.

References

1 *Handbook of Marine Natural Products*, Vol. 1, edited by Blunt J W, Buckingham J, Munro M, Fattorusso E, Gerwick W H & Scafati T O (Springer, New York), (2013).pp.3
2 Voser T M, Campbell M D & Carroll, A R, *Nat Prod Rep*, 39 (2021) 7.
3 Zaman K H A U, Park J H, Devine L, Hu Z, Wu X, Kim H S & Cao S, *J Nat Prod*, 84 (2021) 466.
4 Newman D J & Cragg G M, *J Nat Prod*, 83 (2020) 770.
5 Fenical W & Jensen P R, *Nat Chem Biol*, 2 (2006) 666.

6 Ranganath P L N, Annapurna K, Anil T & Narsaiah A V, *Arkivoc*, v, 114 (2022).
7 Rohith C S, Anil T, Karunakar B & Narsaiah A V, *Indian J Chem*, 61 (2022) 508.
8 Nagalatha G, Ganesh N S & Narsaiah A V, *Tetrahedron Lett*, 82 (2021) 153410.
9 Ganesh N S, Nagalatha G & Narsaiah A V, *Nat Prod Res*, 33 (2020) 2173.
10 Anil T, Karunakar B & Narsaiah A V, *SynOpen*, 3 (2019) 49.
11 Karunakar B, Anil T & Narsaiah A V, *ChemistrySelect*, 4 (2019) 5531.
12 Srikanth V, Prasad R B N, Purnachandra Y, Kumar C G, Anjaneyulu E, Sirisha K & Reddy J R C, *J Chem Sci*, 129 (2017) 663.
13 Mitsunobu O & Yamada M, *Bull Chem Soc Jpn*, 40 (1967) 2380.
14 Mitsunobu O, *Synthesis*, 1 (1980).
15 Liu N N, Zhao SM, Zhao J F, Zeng G Z, Tan N H & Liu J P, *Tetrahedron*, 70 (2014) 6630.