Synthesis of Isoxazoles by Hypervalent Iodine-induced Cycloaddition of Nitrile Oxides to Alkynes

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Supplementary Information

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1H and 13C NMR spectra of oximes

1H and 13C NMR spectra of isoxazoles
General Methods

Reagents. Unless otherwise stated, reactions were carried out in a small glass tube at room temp, no special conditions/atmosphere were needed. Chemicals were purchased from Sigma-Aldrich and used without further purification. Solvents CH₂Cl₂, acetonitrile, THF, Et₂O and toluene were obtained dry from a MBRAUN SPS-800 solvent purification system, CH₃OH was distilled from magnesium and iodine. All other solvents were purchased from standard chemical suppliers and were distilled under N₂-atmosphere from CaH₂. Analytical thin layer chromatography (TLC) was performed on silica gel-coated plates (Merck 60 F254) with the indicated solvent mixture; visualization was done using ultraviolet (UV) irradiation (λ = 260 nm) and/or staining with KMnO₄. Purification by chromatography was carried out using Silicycle silica gel (0.040 – 0.063 mm, and ca. 6 nm pore diameter).

Analytical Methods. All new compounds were characterized by ¹H NMR, ¹³C NMR, ¹⁹F NMR (where applicable), IR spectroscopy and HRMS. ¹H NMR spectra were recorded on a Varian Inova 400 (400 MHz), ¹³C NMR spectra were recorded on a Bruker DMX300 (75 MHz) spectrometer, ¹⁹F NMR spectra was recorded on a Bruker DMX300 (282 MHz) spectrometer. Infrared spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. High resolution mass analyses were performed using Electrospray Ionization on a JEOL AccuTOF. All ¹H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for CHCl₃ (7.27 ppm). All ¹³C NMR spectra were reported in ppm relative to residual CHCl₃ (77 ppm) and were obtained with ¹H decoupling. The yields reported in Table 2 and Schemes 2 and 3 refer to isolated yields and represent an average of at least two independent runs. The pure compounds are estimated to be > 95% pure as determined by ¹H NMR.
**Solvent screening for formation of isoxazole**

![Chemical reaction diagram]

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<td>2</td>
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<td>i-PrOH/H₂O (5:1)</td>
<td>clean reaction (slow)</td>
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General procedure for 3,5-disubstituted isoxazole synthesis (I)

To a solution of alkyne (1 equiv) and oxime (1.5 equiv) in 1.2 mL MeOH/H₂O (5:1), PIFA (1.5 equiv) was added in three portions (3× 0.5 equiv) every two hours. After 7 h stirring, the reaction mixture was diluted with EtOAc (5 mL) and filtered through a small silica plug, which was further washed with EtOAc (10 mL). Combined organic layers were evaporated to dryness and columned by flash chromatography.

Synthesis of 3,5-disubstituted isoxazoles

3,5-Diphenylisoxazole (Table 2, entry 1). Following the general procedure (I), phenyl acetylene (54 mL, 0.49 mmol), benzaldoxime (88.4 mg, 0.727 mmol), and PIFA (315 mg (0.727 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 4:1 → 2:1. White solid; 97 mg (90% yield). IR (ATR): 3113, 2922, 2852, 1488, 762.3, 690.7. ¹H NMR (CDCl₃, 400 MHz): δ 7.87 (m, 4H), 7.48 (m, 6H), 6.84 (s, 1H). ¹³C NMR (CDCl₃, 75 MHz): 170.4, 163.0, 130.2, 130.0, 129.1, 129.0, 128.9, 127.5, 126.8, 125.8, 97.5. HRMS (ESI) m/z calcd for C₁₅H₁₁NO (M+H)⁺: 222.0919, found: 221.0918.

3-Phenyl-5-(pyridin-2-yl)isoxazole (Table 2, entry 2). Following the general procedure (I), 2-ethynylpyridine (50 mg, 0.49 mmol), benzaldoxime (88.4 mg, 0.727 mmol), and PIFA (315 mg (0.727 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. White solid; 86 mg (80% yield). IR (ATR): 3058, 2358, 1701, 1576, 1450, 1139, 763.0, 689.6. ¹H NMR (CDCl₃, 400 MHz): δ 8.74 (m, 1H), 7.99 (dt, J = 8.0 Hz, J = 1.2 Hz, 1H), 7.89 (m, 3H), 7.49 (m, 3H), 7.39 (ddd, J = 1.2 Hz, J = 4.8 Hz, J = 7.6 Hz, 1H), 7.29 (s, 1H). ¹³C NMR (CDCl₃, 75 MHz): 168.9, 162.8, 149.3, 145.9, 137.0, 129.7, 128.5, 128.4, 126.4, 124.1, 120.6, 100.0. HRMS (ESI) m/z calcd for C₁₄H₁₀N₂O (M+H)⁺: 223.0871, found: 223.0881.
5-(4-Methoxyphenyl)-3-phenylisoxazole (Table 2, entry 3). Following the general procedure (I), 1-ethynyl-4-methoxyphenyl acetylene (50 mg, 0.49 mmol), benzaldoxime (88.4 mg, 0.727 mmol), and PIFA (314 mg, 0.727 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. White solid; 77 mg (81% yield). IR (ATR): 3006, 2189, 1614, 1498, 1463, 1251, 1031, 767.4, 689.6. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.86 (m, 2H), 7.78 (m, 2H), 7.47 (m, 3H), 7.00 (m, 2H), 6.71 (s, 1H), 3.88 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 170.4, 162.9, 161.1, 129.9, 129.3, 128.9, 127.4, 126.8, 120.3, 114.4, 96.1, 55.4. HRMS (ESI) $m/z$ calcd for C$_{16}$H$_{13}$NO$_2$ (M+H)$^+$: 252.1025, found: 252.1021.

4-(3-Phenylisoxazol-5-yl)butan-1-ol (Table 2, entry 4). Following the general procedure (I), hex-5-yn-1-ol (90.0 $\mu$L, 0.830 mmol), benzaldoxime (50 mg, 0.413 mmol), and PIFA (177.6 mg, 0.138 mmol) were used. Column chromatography: silica gel, 0 to 5% acetone in CH$_2$Cl$_2$. Colorless oil; 44 mg (49% yield). IR (ATR): 3372, 2933, 2359, 1601, 1471, 767.9, 693.0, 618.8. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.78 (m, 2H), 7.44 (m, 3H), 6.75 (s, 1H), 4.38 (t, $J$ = 5.2 Hz, 1H), 3.39 (dt, $J$ = 5.2 Hz, $J$ = 6.4 Hz, 2H), 2.75 (t, $J$ = 7.3 Hz, 2H), 1.67 (m, 2H), 1.45 (m, 2H). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 173.2, 161.8, 129.3, 129.1, 128.8, 128.4, 128.0, 126.2, 98.5, 61.8, 31.5, 26.1, 23.4. HRMS (ESI) $m/z$ calcd for C$_{13}$H$_{15}$NO$_2$ (M+H)$^+$: 218.1181, found: 218.1190.

5-Phenyl-3-propylisoxazole (Table 2, entry 5). Following general procedure (I), phenyl acetylene (50 mg, 0.49 mmol), butyraldoxime (64 mg, 0.727 mmol), and PIFA (314 mg, 0.727 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 10:1. Colorless oil; 70 mg (76% yield). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.77 (m, 2H), 7.43 (m,
3H), 6.37 (s, 1H), 2.69 (m, 2H), 1.78 (m, 2H), 1.04 (t, J = 7.6 Hz, 3H). 13C NMR (CDCl3, 75 MHz): δ 169.5, 164.5, 129.9, 128.9, 127.7, 125.7, 99.1, 28.1, 21.7, 13.7. HRMS (ESI) m/z calcld for C12H13NO (M+H)+: 188.1075, found: 188.1070.

3-Propyl-5-(pyridin-2-yl)isoxazole (Table 2, entry 6). Following the general procedure (I), 2-ethynylpyridine (50 mg, 0.49 mmol), butyraldoxime (63.3 mg, 0.727 mmol), and PIFA (314 mg (0.727 mmol) were used. Column chromatography: silica gel, 0 to 5% acetone in CH2Cl2. White solid; 82 mg (90% yield). IR (ATR): 3130, 2964, 2359, 1698, 1426, 1183, 791.0. 1H NMR (CDCl3, 400 MHz): δ 8.90 (m, 1H), 8.09 (m, 2H), 7.60 (m, 1H), 7.03 (s, 1H), 2.78 (t, J = 7.2 Hz, 2H), 1.78 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl3, 75 MHz): δ 165.3, 165.2, 147.6, 144.4, 125.3, 122.2, 104.0, 28.0, 21.5, 13.6. HRMS (ESI) m/z calcld for C11H12N2O (M+H)+: 189.1028, found: 189.1020.

5-(4-Methoxyphenyl)-3-propylisoxazole (Table 2, entry 7). Following the general procedure (I), 4-methoxyphenyl acetylene (60 mg, 0.454 mmol), butyraldoxime (59.3 mg, 0.681 mmol), and PIFA (293 mg (0.681 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. White solid; 60 mg (60% yield). IR (ATR): 2960, 2872, 1617, 1513, 1431, 1253, 1176, 836. 1H NMR (CDCl3, 400 MHz): δ 7.70 (m, 2H), 6.96 (m, 2H), 3.86 (s, 3H), 2.67 (m, 2H), 1.74 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H). 13C NMR (CDCl3, 75 MHz): δ 169.4, 164.5, 160.9, 127.3, 120.6, 114.3, 97.7, 55.4, 28.1, 21.7, 13.8. HRMS (ESI) m/z calcld for C13H15NO2 (M+H)+: 218.1181, found: 218.1177.

4-(3-Propylisoxazol-5-yl)butan-1-ol (Table 2, entry 8). Following the general procedure (I), hex-5-yn-1-ol (50 mg, 0.51 mmol), butyraldoxime (67 mg, 0.764 mmol), and PIFA (330 mg (0.764 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. Colorless oil; 9.1 mg (10% yield). 1H NMR (DMSO-d6, 400
MHZ); δ 6.12 (s, 1H), 3.42 (t, J = 6.4 Hz, 1H), 2.71 (t, J = 7.2 Hz, 2H), 2.52 (m, 2H), 1.66 (m, 4H), 1.48 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). 13C NMR (DMSO-d6, 75 MHz): δ 172.7, 163.2, 100.5, 60.1, 31.7, 27.2, 25.6, 23.6, 20.9, 13.5. HRMS (ESI) m/z calcd for C10H17NO2 (M+H)+: 184.1338, found: 184.1331.

(E)-5-Phenyl-3-styrylisoxazole (Table 2, entry 9). Following the general procedure (I), phenyl acetylene (50 mg, 0.49 mmol), (2E)-cinnamaldoxime (108 mg, 0.734 mmol), and PIFA (316 mg (0.734 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. White solid; 96.4 mg (80% yield). IR (ATR): 3032, 2915, 2215, 1714, 1571, 1450, 1204, 957.5, 745.7, 693.9. 1H NMR (CDCl3, 400 MHz): δ 7.84 (m, 2H), 7.55 (m, 2H), 7.48 (m, 3H), 7.39 (m, 3H), 7.27-7.16 (m, 2H), 6.77 (s, 1H). 13C NMR (CDCl3, 75 MHz): δ 169.8, 162.2, 135.9, 134.2, 130.2, 129.0, 128.9, 128.9, 127.4, 127.0, 125.8, 123.5, 116.2, 96.4. HRMS (ESI) m/z calcd for C17H13NO (M+H)+: 248.1075, found: 248.1065.

(E)-5-(Pyridin-2-yl)-3-styrylisoxazole (Table 2, entry 10). Following the general procedure (I), 2-ethynylpyridine (50 mg, 0.49 mmol), (2E)-cinnamaldoxime (107 mg, 0.727 mmol), and PIFA (315 mg (0.727 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. White solid; 87 mg (72% yield). IR (ATR): 3062, 2920, 1731, 1636, 1576, 1424, 1191, 776.0, 698.2. 1H NMR (CDCl3, 400 MHz): δ 8.71 (m, 1H), 7.94 (dt J = 1.1 Hz, J = 7.9 Hz, 1H), 7.85 (td, J = 1.8 Hz, J = 7.7 Hz, 1H), 7.55 (m, 2H), 7.37 (m, 4H), 7.28 (d, J = 16.6 Hz, 1H), 7.19 (d, J = 16.4 Hz, 1H), 7.19 (s, 1H). 13C NMR (CDCl3, 75 MHz): δ 169.1, 162.6, 150.1, 146.5, 137.1, 136.4, 135.8, 129.0, 128.9, 127.1, 124.5, 120.9, 115.9, 99.3. HRMS (ESI) m/z calcd for C11H12N2O (M+H)+: 249.1028, found: 249.1018.
(E)-5-(4-Methoxyphenyl)-3-styrylisoxazole (Table 2, entry 11). Following the general procedure (I), 1-ethynyl-4-methoxybenzene (49 mg, 0.369 mmol), (2E)-cinnamaldoxime (82 mg, 0.556 mmol), and PIFA (210 mg, 0.556 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. Yellow solid; 67 mg (65% yield). IR (ATR): 2924, 1616, 1509, 1438, 1259, 963.8, 835.6, 751.1, 695.6. 1H NMR (CDCl₃, 400 MHz): δ 7.76 (m, 2H), 7.55 (m, 2H), 7.36 (m, 3H), 7.23 (d, J = 16.5 Hz, 1H), 7.16 (d, J = 16.5 Hz, 1H), 7.00 (m, 2H), 6.64 (s, 1H), 3.87 (s, 3H). 13C NMR (CDCl₃, 75 MHz): δ 169.8, 162.2, 161.1, 135.9, 135.7, 128.9, 128.8, 127.4, 127.0, 120.3, 116.3, 114.4, 95.1, 55.4. HRMS (ESI) m/z calcd for C₁₈H₁₅NO₂ (M+H)^+: 278.1181, found: 278.1165.

(E)-4-(3-Styrylisoxazol-5-yl)butan-1-ol (Table 2, entry 12). Following the general procedure (I), hex-5-yn-1-ol (67 mg, 0.679 mmol), (2E)-cinnamaldoxime (50 mg, 0.340 mmol), and PIFA (146 mg, 0.340 mmol) were used. Column chromatography: silica gel, 0 to 10% acetone in CH₂Cl₂. White solid; 50 mg (61% yield). IR (ATR): 3374, 2935, 1597, 1444, 967, 696. 1H NMR (DMSO-d₆, 400 MHz): δ 7.65 (m, 2H), 7.38 (m, 4H), 7.16 (d, J = 16.5 Hz, 1H), 6.64 (s, 1H), 4.40 (t, J = 5.2 Hz, 1H), 3.44 (dt, J = 5.2 Hz, J = 6.4 Hz, 2H), 2.76 (t, J = 7.5 Hz, 2H), 1.70 (m, 2H), 1.48 (m, 2H). 13C NMR (DMSO-d₆, 75 MHz): δ 173.1, 161.4, 135.8, 135.6, 128.7, 126.9, 115.9, 98.2, 60.1, 31.7, 25.6, 23.5. HRMS (ESI) m/z calcd for C₁₅H₁₇NO₂ (M+H)^+: 244.1338, found: 244.1327.

3-(4-Methoxyphenyl)-5-phenylisoxazole (Table 2, entry 13). Following the general procedure (I), phenyl acetylene (50 mg, 0.49 mmol), 4-methoxybenzaldoxime (111 mg,
0.734 mmol, and PIFA (315 mg, 0.734 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. White solid; 87 mg (71% yield). IR (ATR): 2923, 1613, 1448, 1253, 763.9, 686.8. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.82 (m, 4H), 7.47 (m, 3H), 7.00 (m, 2H), 6.78 (s, 1H), 3.87 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 170.1, 162.6, 161.0, 130.1, 129.0, 128.2, 127.6, 125.8, 121.6, 114.3, 97.2, 55.4. HRMS (ESI) $m/z$ calcd for C$_{16}$H$_{13}$NO$_2$ (M+H)$^+$: 252.1025, found: 252.1016.

![Image of 4-(3-(4-Methoxyphenyl)isoxazol-5-yl)butan-1-ol](image)

4-(3-(4-Methoxyphenyl)isoxazol-5-yl)butan-1-ol (Table 2, entry 14). Following the general procedure (I), hex-5-yn-1-ol (65 mg, 0.662 mmol), 4-methoxybenzaldoxime (50 mg, 0.331 mmol), and PIFA (171 mg (0.398 mmol) were used. Column chromatography: silica gel, 0 to 5% methanol in CH$_2$Cl$_2$. White solid; 52 mg (67% yield). IR (ATR): 3365, 2920, 1606, 1524, 1429, 1247, 1027, 836.5. $^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ 7.78 (d, $J = 8.8$ Hz, 2H), 7.04 (d, $J = 8.8$ Hz, 2H), 6.73 (t, $J = 0.8$ Hz, 1H), 4.43 (t, $J = 5.2$ Hz, 1H), 3.80 (s, 3H), 3.43 (dt, $J = 5.2$ Hz, $J = 6.4$ Hz, 2H), 2.79 (t, $J = 7.2$ Hz, 2H), 1.71 (m, 2H), 1.50 (m, 2H). $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 173.7, 161.2, 160.4, 127.8, 121.2, 114.3, 98.9, 60.1, 55.2, 31.7, 25.7, 23.6. HRMS (ESI) $m/z$ calcd for C$_{14}$H$_{17}$NO$_3$ (M+H)$^+$: 248.1287, found: 248.1276.

![Image of 5-Phenyl-3-(p-tolyl)isoxazole](image)

5-Phenyl-3-(p-tolyl)isoxazole (Table 2, entry 15). Following general the procedure (I), phenyl acetylene (50 mg, 0.49 mmol), 4-methylbenzaldoxime (99 mg, 0.734 mmol), and PIFA (316 mg, 0.734 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. White solid; 83 mg (72% yield). IR (ATR): 2921, 2360, 1736, 1615, 1447, 828.5, 756.8, 685.3. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.86 (m, 2H), 7.77 (m, 2H), 7.49 (m, 3H), 7.30 (m, 2H), 6.81 (s, 1H), 2.42 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 170.2, 162.9, 140.1, 130.1, 129.6, 129.0, 127.5, 126.7, 126.3, 125.8, 97.4, 21.4. HRMS (ESI) $m/z$ calcd for C$_{16}$H$_{13}$NO (M+H)$^+$: 236.1075, found: 236.1067.
4-(3-(p-Toly)isoxazol-5-yl)butan-1-ol (Table 2, entry 16). Following the general procedure (I), hex-5-yn-1-ol (50 mg, 0.51 mmol), 4-methylbenzaldoxime (103 mg, 0.764 mmol), and PIFA (331 mg, 0.764 mmol) were used. Column chromatography: silica gel, 0 to 5% acetone in CH$_2$Cl$_2$. Yellow oil. 78 mg (66% yield). IR (ATR): 3392, 2929, 1603, 1432, 1064, 824.4, 621.2. $^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ 7.73 (m, 2H), 7.30 (m, 2H), 6.76 (t, $J = 0.8$ Hz, 1H), 4.43 (t, $J = 5.2$ Hz, 1H), 3.44 (dt, $J = 5.2$ Hz, $J = 6.4$ Hz, 2H), 2.79 (t, $J = 7.2$ Hz, 2H), 2.35 (s, 3H), 1.72 (m, 3H), 1.50 (m, 2H). $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 173.5, 162.3, 139.9, 129.5, 126.6, 126.5, 98.9, 62.3, 32.0, 26.5, 23.9, 21.4. HRMS (ESI) $m/z$ calcd for C$_{14}$H$_{17}$NO$_2$ (M+H)$^+$: 232.1338, found: 232.1337.

4-(3-(p-Toly)isoxazol-5-yl)butan-1-ol (Table 2, entry 16$^b$). Following the general procedure, hex-5-yn-1-ol (50 mg, 0.51 mmol), 4-methylbenzaldoxime (276 mg, 2.04 mmol), and PIFA (881 mg (2.04 mmol) were used. Column chromatography: silica gel, 0 to 5% acetone in CH$_2$Cl$_2$. Yellow oil. 111 mg (94% yield).

3-(4-Nitrophenyl)-5-phenylisoxazole (Table 2, entry 17). Following the general procedure (I), phenyl acetylene (50 mg, 0.49 mmol), 4-nitrobenzaldoxime (122 mg, 0.734 mmol), and PIFA (316 mg, 0.734 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. Yellow solid; 95 mg (73% yield). IR (ATR): 2960, 2853, 2359, 1519, 1345, 1017, 799.1, 611.0. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.36 (m, 2H), 8.06 (m, 2H), 7.86 (m, 2H), 7.52 (m, 3H), 6.90 (s, 1H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 171.5, 161.2, 148.7, 135.2, 130.7, 129.2, 127.7, 126.9, 125.9, 124.2, 97.4, 29.7. HRMS (ESI) $m/z$ calcd for C$_{15}$H$_{10}$N$_2$O$_3$ (M+H)$^+$: 266.0692, found: 266.0693.

4-(3-(4-Nitrophenyl)isoxazol-5-yl)butan-1-ol (Table 2, entry 18). Following the general procedure (I), hex-5-yn-1-ol (65 $\mu$L, 0.602 mmol), 4-nitrobenzaldoxime (50 mg,
0.301 mmol), and PIFA (129 mg, 0.301 mmol) were used. Column chromatography: silica gel, 0 to 5% acetone in CH₂Cl₂. Light yellow solid; 44.3 mg (56 % yield). IR (ATR): 2924, 2320, 1737, 1523, 1348, 1240, 650. ¹H NMR (DMSO-d₆, 400 MHz): δ 8.34 (m, 2H), 8.13 (m, 2H), 7.00 (s, 1H), 4.47 (t, J = 5.2 Hz, 1H), 3.44 (dd, J = 6.3 Hz, J = 11.5 Hz, 2H), 2.84 (t, J = 7.6 Hz, 2H), 1.73 (m, 2H), 1.50 (m, 2H). ¹³C NMR (DMSO-d₆, 75 MHz): δ 175.1, 160.2, 148.1, 134.9, 127.7, 124.2, 99.7, 60.1, 31.6, 25.7, 23.5. HRMS (ESI) m/z calcd for C₁₃H₁₄N₂O₄ (M+H)⁺: 263.1032, found: 263.1029.

3-Cyclohexyl-5-(pyridin-2-yl)isoxazole (Table 2, entry 19). Following the general procedure (I), 2-ethynylpyridine (50 mg, 0.49 mmol), cyclohexanecarbaldoxime (93 mg, 0.727 mmol), and PIFA (313 mg, 0.727 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. White solid; 96 mg (87% yield). IR (ATR): 2924, 2850, 2362, 1714, 1575, 1424, 1264, 987.8, 780.3, 745.7. ¹H NMR (CDCl₃, 400 MHz): δ 8.67 (m, 1H), 7.88 -7.81 (m, 2H), 7.32 (m, 1H), 6.80 (s, 1H), 2.82 (m, 1H), 2.02 (m, 2H), 1.84 (m, 2H), 1.75 (m, 1H), 1.39 (m, 5H). ¹³C NMR (CDCl₃, 75 MHz): δ 169.3, 168.7, 149.9, 146.9, 137.0, 124.2, 120.8, 100.6, 35.9, 32.1, 25.9, 25.9. HRMS (ESI) m/z calcd for C₁₄H₁₆N₂O (M+H)⁺: 229.1341, found: 229.1335.

2-(2-(3-(Perfluorophenyl)isoxazol-5-yl)ethyl)isoindoline-1,3-dione (Table 2, entry 20). Following the general procedure (I), 2-(but-3-ynyl)isoindoline-1,3-dione (50 mg, 0.251 mmol), perfluorobenzaldoxime (106 mg, 0.502 mmol), and PIFA (216 mg, 0.502 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 9:1 → 3:1. White solid; 81.2 mg (80% yield). IR (ATR): 3421, 3123, 1714, 1502, 1398, 1091, 996.5, 823.5, 715.5, 525.3. ¹H NMR (CDCl₃, 400 MHz): δ 7.86 (m, 2H), δ 7.74 (m, 2H), δ 6.47 (m, 1H), 4.12 (t, J = 7.2 Hz, 2H), 3.31 (t, J = 6.8 Hz, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ 170.5, 167.9, 151.5, 146.4, 143.5, 143.1, 140.1, 139.6, 136.2, 134.2, 131.8, 123.4, 105.1, 103.1, 35.5, 25.9. ¹⁹F-NMR (CDCl₃, 300 MHz): δ -62.2 (d, 2F), δ -75.4 (t, 1F), δ -85.0 (q, 2F). HRMS (ESI) m/z calcd for C₁₉H₁₆F₃N₂O₃ (M+H)⁺: 409.0611, found: 409.0603.
**2'-O-((3-Phenylisoxazol-5-yl)methyl)adenosine (Scheme 2, compound 21).** Following the general procedure (I), 2'-O-(propargyl)adenosine (50 mg, 0.164 mmol), benzaldoxime (24 mg, 0.20 mmol), and PIFA (172 mg, 0.40 mmol) were used. Column chromatography: silica gel, CH₂Cl₂/acetone (7:3), CH₂Cl₂/acetone/Methanol (63:7:30). White solid; 63 mg (90% yield). ¹H NMR (DMSO-d₆, 400 MHz): δ 8.38 (s, 1H), 8.10 (s, 1H), 7.73 (m, 2H), 7.50 (m, 3H), 7.37 (s, 2H), 6.72 (s, 1H), 6.09 (d, J = 6.0 Hz, 1H), 5.46 (d, J = 5.2 Hz, 2H), 4.89 (d, J = 13.9 Hz, 1H), 4.76 (d, J = 13.9 Hz, 1H), 4.68 (t, J = 5.2 Hz, 1H), 4.43 (m, 1H), 4.04 (m, 1H), 3.70 (m, 1H), 3.58 (d, 1H). ¹³C NMR (DMSO-d₆, 75 MHz): δ 169.5, 161.5, 156.1, 152.4, 148.8, 139.6, 130.1, 129.0, 128.2, 126.4, 119.2, 101.2, 86.3, 86.0, 80.9, 68.8, 62.3, 61.3. HRMS (ESI) m/z calc'd for C₂₀H₂₀N₆O₅ (M+H)⁺: 425.1573, found: 425.1570.

**2'-O-((3-Cyclohexylisoxazol-5-yl)methyl)adenosine (Scheme 2, compound 22).** Following the general procedure (I), 2'-O-(propargyl)adenosine (40 mg, 0.131 mmol), cyclohexanecarbaldoxime (25 mg, 0.197 mmol), and PIFA (85 mg, 0.197 mmol) were used. Column chromatography: silica gel, 0 to 15% methanol in CH₂Cl₂. Colorless oil; 36.7 mg (65% yield). ¹H NMR (DMSO-d₆, 400 MHz): δ 8.28 (s, 1H), 8.06 (s, 1H), 7.33 (s, 2H), 5.98 (d, J = 6.0 Hz, 2H), 5.43 (m, 1H), 5.35 (d, J = 5.2 Hz, 1H), 4.71 (d, J = 13.9 Hz, 1H), 4.56 (m, 2H), 4.33 (m, 1H), 3.96 (q, J = 3.2 Hz, 1H), 3.63 (m, 1H), 3.51 (m, 1H), 2.50 (m, 1H), 1.62 (m, 4H), 1.20 (m, 6H). ¹³C NMR (DMSO-d₆, 75 MHz): δ 168.1, 167.5, 156.2, 152.4, 148.8, 139.8, 119.3, 105.7, 101.3, 86.5, 86.2, 80.7, 68.8, 62.4, 61.4, 34.9, 31.2, 25.3. HRMS (ESI) m/z calc'd for C₂₀H₂₆N₆O₅ (M+H)⁺: 431.2043, found: 431.2033.
3-N-((3-Phenylisoxazol-5-yl)methyl)thymidine (Scheme 2, compound 23). Following the general procedure (I), 3-N-(propargyl)thymidine (50 mg, 0.178 mmol), benzaldoxime (32.4 mg, 0.268 mmol), and PIFA (115 mg, 0.268 mmol) were used. Column chromatography: silica gel, 0 to 15% methanol in CH₂Cl₂. White solid; 62.7 mg (88% yield). ¹H NMR (DMSO-d₆, 400 MHz): δ 7.89 (d,  J = 1.2 Hz, 1H), 7.84 (m, 2H), 7.49 (m, 3H), 6.94 (s, 1H), 6.22 (t,  J = 6.4 Hz, 1H), 5.26 (d,  J = 4.4 Hz, 1H), 5.18 (s, 2H), 5.07 (t,  J = 5.2 Hz, 1H), 4.26 (m, 1H), 3.80 (q,  J = 3.7 Hz, 1H), 3.60 (m, 2H), 2.15 (m, 2H), 1.87 (s, 3H). ¹³C NMR (DMSO-d₆, 75 MHz): δ 168.5, 162.1, 161.8, 150.0, 135.3, 130.1, 129.0, 128.3, 126.5, 108.4, 100.5, 87.4, 84.9, 70.1, 61.0, 39.6, 3a6.3, 12.8. HRMS (ESI) m/z calcd for C₂₀H₂₁N₃O₆ (M+H)+: 400.1509, found: 400.1521.

3-N-((3-(3-(2'-O-adenosinyl)prop-1-yn-1-yl)phenyl)isoxazol-5-yl)methyl)thymidine (Scheme 2, compound 24). Following the general procedure (I), 3-N-(propargyl)thymidine (26 mg, 0.093 mmol), 4-(3-(2'-O-adenosinyl)prop-1-yn-1-yl)benzaldoxime (59 mg, 0.139 mmol), and PIFA (60 mg, 0.140 mmol) were used. Column chromatography: silica gel, 0 to 15% methanol in CH₂Cl₂. White solid; 62 mg (95% yield). ¹H NMR (DMSO-d₆, 400 MHz): δ 8.40 (s, 1H), 8.10 (s, 1H), 7.89 (d,  J = 1.1 Hz, 1H), 7.81 (d,  J = 8.8 Hz, 2H), 7.38 (s, 2H), 7.33 (d,  J = 8.4 Hz, 2H), 6.98 (s, 1H), 6.22 (t,  J = 6.4 Hz, 1H), 6.06 (d,  J = 6.8 Hz, 1H), 5.62 (m, 1H), 5.40 (d,  J = 4.8 Hz, 1H), 5.28 (d,  J = 4.3 Hz, 1H), 5.17 (s, 2H), 5.10 (t,  J = 5.2 Hz, 1H), 4.88 (dd,  J = 4.9 Hz,  J = 6.7 Hz, 1H), 4.50-4.40 (m, 3H), 4.26 (m, 1H), 4.04 (dd,  J = 3.2 Hz,  J = 5.7 Hz, 1H), 3.79 (q,  J = 3.6 Hz, 1H), 3.70 (m, 1H), 3.60 (m, 3H), 2.14 (m, 2H), 1.87 (s, 3H). ¹³C NMR (DMSO-d₆, 75 MHz): δ 168.8, 162.1, 161.2, 156.1, 152.3, 150.0, 148.9, 139.9, 135.4, 131.7, 128.3, 126.7, 123.2, 119.3, 108.4, 100.6, 87.4, 87.1, 86.8, 86.0, 85.4, 84.9, 79.5, 70.1, 68.8, 61.6, 61.1, 57.5, 39.6, 36.3, 12.8. HRMS (ESI) m/z calcd for C₃₃H₃₄N₈O₁₀ (M+H)+: 703.2476, found: 703.2449.
Isoxazole adduct of benzaldoxime with peptide (Scheme 2, compound 25). Peptide (Gly-Lys-Gly-Ala-Lys-Arg-Leu-Asp) having acetylene on the N-terminal of Asp (MW 923.52) (2.5 mg, 0.027 mmol) was dissolved in water (1.25 mL). To which, a solution of nitrile oxide formed from benzaldoxime (1 mg, 0.0081 mmol) and PIFA (3.5 mg, 0.0081 mmol) in MeOH (0.21 mL) was added at room temperature. Total 6 additions of nitrile oxide were done every two hours thereby using each 18 equiv of oxime and PIFA altogether (concentration of the final solution was 100 μM based on peptide). Reaction was followed by LC-Q, which took 12 h to completion. Solvent evaporated to dryness, dried sample was dissolved in TFA (0.2 mL) and precipitated in ether, centrifugation and decantation gave crude product in 95% purity. Homogeneity of the product was confirmed by HPLC and HRMS (p. 21). HRMS. (ESI) m/z calcd for C_{47}H_{74}N_{14}O_{13} (M+H)^{+}: 1043.5638, found: 1043.5628.
General procedure for 3,4,5-trisubstituted isoxazole synthesis (II)

(1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (BCN) (1 equiv) was added to a solution of oxime (1.2 equiv) and PIFA (1.2 equiv) in 1.2 mL MeOH/H₂O (1:1). The reaction mixture was stirred for 2-5 min at rt, and then extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel.

Synthesis of 3,4,5-disubstituted isoxazoles

((5aS,6S,6aR)-3-phenyl-5,5a,6,6a,7,8-hexahydro-4H-cyclopropa[5,6]cyclocta[1,2-d]isoxazol-6-yl)methanol (Scheme 3, compound 26). Following the general procedure (II), (1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (10 mg, 0.067 mmol), benzaldoxime (9.7 mg, 0.080 mmol), and PIFA (34.4 mg, 0.080 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 0:1 → 1:1. Colorless oil; 17 mg (92% yield). ¹H NMR (CDCl₃, 400 MHz): δ 7.48 (m, 5H), 3.73 (d, J = 7.6 Hz, 2H), 3.15 (m, 1H), 2.93 (m, 1H), 2.75 (m, 1H), 2.52 (m, 1H), 2.21 (m, 2H), 1.68 (m, 1H), 1.55 (m, 2H), 1.22 (m, 1H), 1.07 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ 169.5, 164.0, 130.0, 129.2, 128.7, 128.6, 112.6, 59.8, 26.7, 23.3, 22.5, 21.4, 21.4, 19.6, 19.6. HRMS (ESI) m/z calcd for C₁₇H₁₉NO₂ (M+H)⁺: 270.1494, found: 270.1477.
((5aS,6S,6aR)-3-(4-methoxyphenyl)-5,5a,6,6a,7,8-hexahydro-4H-cyclopropa[5,6]cycloocta[1,2-d]isoxazol-6-yl)methanol (Scheme 3, compound 27). Following the general procedure (II), (1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (10 mg, 0.067 mmol), 4-methoxybenzaldoxime (12.1 mg, 0.080 mmol), and PIFA (34.4 mg, 0.080 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 0:1 → 1:1. Colorless oil; 19 mg (95% yield). 1H NMR (CDCl3, 400 MHz): δ 7.45 (m, 2H), 6.98 (m, 2H), 3.85 (s, 3H), 3.74 (dd, J = 2.6 Hz, J = 7.7 Hz, 2H), 3.12 (m, 1H), 2.92 (m, 1H), 2.76 (m, 1H), 2.55 (m, 1H), 2.23 (m, 2H), 1.66 (m, 3H), 1.20 (m, 1H), 1.07 (m, 2H). 13C NMR (CDCl3, 75 MHz): δ 169.3, 163.6, 160.3, 130.0, 122.2, 114.0, 112.5, 59.8, 55.3, 26.7, 23.3, 22.6, 21.4, 21.3, 19.6, 19.5. HRMS (ESI) m/z calcd for C18H21NO3 (M+H)+: 300.1600, found: 300.1594.

((5aS,6S,6aR)-3-(4-nitrophenyl)-5,5a,6,6a,7,8-hexahydro-4H-cyclopropa[5,6]cycloocta[1,2-d]isoxazol-6-yl)methanol (Scheme 3, compound 28). Following the general procedure (II), (1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (10 mg, 0.067 mmol), 4-nitrobenzaldoxime (13.3 mg, 0.080 mmol), and PIFA (34.4 mg, 0.080 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 0:1 → 1:1. Colorless oil; 19 mg (92% yield). 1H NMR (CDCl3, 400 MHz): δ 8.34 (m, 2H), 7.73 (m, 2H), 3.76 (d, J = 7.6 Hz, 2H), 3.20 (m, 1H), 2.98 (m, 1H), 2.80 (m, 1H), 2.58 (m, 1H), 2.32 (m, 2H), 1.70 (m, 3H), 1.20 (m, 3H). 13C NMR (CDCl3, 75 MHz): δ 170.6, 162.1, 136.5, 129.7, 123.8, 112.7, 106.1, 59.8, 26.7, 23.2, 22.6, 21.4, 21.3, 19.5, 19.5. HRMS (ESI) m/z calcd for C17H18N2O4 (M+H)+: 315.1345, found: 315.1340.
((5aS,6S,6aR)-3-propyl-5,5a,6,6a,7,8-hexahydro-4H-cyclopropa[5,6]cycloocta[1,2-d]isoxazol-6-yl)methanol (Scheme 3, compound 29). Following the general procedure (II), (1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (10 mg, 0.067 mmol), butyraldoxime (11.6 mg, 0.133 mmol), and PIFA (42.9 mg, 0.100 mmol) were used. Column chromatography: silica gel, 0 to 5% acetone in CH$_2$Cl$_2$. Colorless oil; 14.3 mg (91% yield). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.76 (d, $J$ = 8.0 Hz, 2H), 3.07 (m, 1H), 2.85 (m, 1H), 2.62 (m, 1H), 2.52 (m, 2H), 2.42 (m, 1H), 2.18 (m, 2H), 1.65 (m, 3H), 1.55 (m, 2H), 1.20 (m, 1H), 1.05 (m, 5H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 167.8, 164.0, 112.2, 59.9, 27.2, 26.8, 22.7, 22.4, 21.2, 21.1, 20.8, 19.5, 19.3, 14.0. HRMS (ESI) m/z calcd for C$_{14}$H$_{21}$NO$_2$ (M+H)$^+$: 236.1651, found: 236.1647.

((5aS,6S,6aR)-3-(perfluorophenyl)-5,5a,6,6a,7,8-hexahydro-4H-cyclopropa[5,6]cycloocta[1,2-d]isoxazol-6-yl)methanol (Scheme 3, compound 30). Following the general procedure (II), (1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (10 mg, 0.067 mmol), perfluorobenzaldoxime (16.9 mg, 0.080 mmol), and PIFA (34.4 mg, 0.080 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 1:1 $\rightarrow$ 2:1. Colorless oil; 22 mg (92% yield). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.76 (d, $J$ = 7.6 Hz, 2H), 3.21 (m, 1H), 2.98 (m, 1H), 2.43 (m, 2H), 2.27 (m, 1H), 2.15 (m, 1H), 1.69 (m, 1H), 1.52 (m, 1H), 1.15 (m, 4H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 170.0, 114.0, 59.3, 26.4, 22.3, 21.9, 21.0, 20.6, 19.2, 19.1. $^{19}$F-NMR (CDCl$_3$, 300 MHz): $\delta$ -62.6 (q, 2F), $\delta$ -75.1 (t, 1F), $\delta$ -84.8 (q, 2F). HRMS (ESI) m/z calcd for C$_{17}$H$_{14}$NO$_2$F$_5$ (M+H)$^+$: 360.1023, found: 360.1021.
Following the general procedure (II), (1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (10 mg, 0.067 mmol), (2E)-cinnamaldoxime (11.8 mg, 0.080 mmol), and PIFA (34.4 mg, 0.080 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 1:1 → 2:1. Colorless oil; 16.5 mg (84% yield). 1H NMR (CDCl₃, 400 MHz): δ 7.53 (m, 2H), 7.33 (m, 4H), 6.88 (d, J = 16.4 Hz, 1H), 3.76 (d, J = 7.6 Hz, 2H), 3.12 (m, 1H), 2.95 (m, 1H), 2.82 (m, 1H), 2.60 (m, 1H), 2.22 (m, 2H), 1.66 (m, 3H), 1.23 (m, 1H), 1.05 (m, 2H). 13C NMR (CDCl₃, 75 MHz): δ 168.5, 160.7, 136.3, 135.0, 128.7, 128.6, 126.9, 114.7, 112.3, 59.8, 26.8, 22.7, 22.5, 21.1, 20.7, 19.2, 19.0. HRMS (ESI) m/z calcd for C₁₉H₂₁NO₂ (M+H)+: 296.1651, found: 296.1646.

((5aS,6S,6aR)-3-((E)-styryl)-5,5a,6,6a,7,8-hexahydro-4H-cyclopropa[5,6]cycloocta[1,2-d]isoxazol-6-yl)methanol (Scheme 3, compound 31). Following the general procedure (II), (1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (10 mg, 0.067 mmol), (2E)-cinnamaldoxime (11.8 mg, 0.080 mmol), and PIFA (34.4 mg, 0.080 mmol) were used. Column chromatography: silica gel, EtOAc/heptane 1:1 → 2:1. Colorless oil; 16.5 mg (84% yield). 1H NMR (CDCl₃, 400 MHz): δ 7.53 (m, 2H), 7.33 (m, 4H), 6.88 (d, J = 16.4 Hz, 1H), 3.76 (d, J = 7.6 Hz, 2H), 3.12 (m, 1H), 2.95 (m, 1H), 2.82 (m, 1H), 2.60 (m, 1H), 2.22 (m, 2H), 1.66 (m, 3H), 1.23 (m, 1H), 1.05 (m, 2H). 13C NMR (CDCl₃, 75 MHz): δ 168.5, 160.7, 136.3, 135.0, 128.7, 128.6, 126.9, 114.7, 112.3, 59.8, 26.8, 22.7, 22.5, 21.1, 20.7, 19.2, 19.0. HRMS (ESI) m/z calcd for C₁₉H₂₁NO₂ (M+H)+: 296.1651, found: 296.1646.
7.51 (m, 2H), 7.36 (m, 2H), 6.08 (d, J = 6.4 Hz, 1H), 4.85 (dd, J = 4.8 Hz, J = 6.8 Hz, 1H), 4.51-4.41 (m, 3H), 4.05 (m, 1H), 3.70-3.49 (m, 6H), 3.17 (s, 2H), 3.09 (m, 1H), 2.90 (m, 1H), 2.71 (m, 1H), 2.45 (m, 1H), 2.08 (m, 2H), 1.69 (m, 2H), 0.92 (m, 3H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 169.5, 162.6, 156.0, 152.2, 140.0, 131.5, 129.7, 128.6, 122.5, 112.3, 86.9, 86.8, 86.1, 85.5, 79.7, 68.9, 61.6, 57.6, 57.3, 26.1, 26.1, 22.0, 20.8, 20.3, 18.2, 18.2, 18.1, 18.1. HRMS (ESI) $m/z$ calcld for C$_{30}$H$_{32}$N$_6$O$_6$ (M+H)$^+$: 573.2462, found: 573.2467.

$^{(5aS,5a'S,6S,6a'R,6'S,6a'R)}$-3,3'-(1,3-phenylene)bis($5,5a,6,6a,7,8$-hexahydro-$4H$-cyclopropa[5,6]cycloocta[1,2-d]isoxazole-6,3-diyl)dimethanol (Scheme 3, compound 33). Following the general procedure (II), (1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (20.1 mg, 0.134 mmol), 3-((hydroxyimino)methyl)benzaldoxime (10 mg, 0.061 mmol) and PIFA (31.4 mg, 0.073 mmol) were used. Column chromatography: silica gel, 0 to 5% Methanol in CH$_2$Cl$_2$. Colorless oil; 26 mg (93% yield). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.64 (m, 4H), 3.75 (m, 4H), 3.18 (m, 2H), 2.95 (m, 2H), 2.79 (m, 2H), 2.55 (m, 2H), 2.30 (m, 4H), 1.22 (m, 2H), 1.09 (m, 4H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 169.9, 163.5, 130.4, 129.5, 129.0, 128.9, 112.7, 59.8, 26.7, 23.4, 22.5, 22.5, 21.5, 21.5, 19.7, 19.6, 19.6. HRMS (ESI) $m/z$ calcld for C$_{28}$H$_{32}$N$_2$O$_4$ (M+H)$^+$: 461.2440, found: 461.2433.

$7-^{(5aS,6S,6aR)}$-6-(hydroxymethyl)-$5,5a,6,6a,7,8$-hexahydro-$4H$-cyclopropa[5,6]cycloocta[1,2-d]isoxazol-3-yl4-methylcoumarin (Scheme 3, compound 34). Following general procedure (II), (1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (10 mg, 0.067 mmol), 4-methyl coumarin-6-formadoxime (815 mg, 0.074 mmol), and PIFA (315 mg, 0.074 mmol) were used. Column chromatography: silica gel,
EtOAc/heptane 10% acetone in CH$_2$Cl$_2$. White solid; 20 mg (86% yield). $^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ 7.91 (m, 1H), 7.54 (dd, $J = 1.6$ Hz, $J = 6.1$ Hz, 2H), 6.49 (s, 1H), 4.34 (t, $J = 5.1$ Hz, 1H), 3.50 (dd, $J = 5.1$ Hz, $J = 7.2$ Hz, 2H), 3.11 (m, 1H), 2.92 (m, 1H), 2.76 (m, 1H), 2.50 (m, 1H), 2.48 (m, 3H), 2.08 (m, 2H), 1.67 (m, 2H), 0.91 (m, 3H). $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 169.7, 162.0, 159.4, 152.8, 152.7, 132.8, 125.9, 124.3, 120.2, 116.1, 115.1, 112.4, 57.2, 26.1, 22.0, 21.9, 20.7, 20.2, 18.1, 18.1, 17.9. HRMS (ESI) $m/z$ calcd for C$_{21}$H$_{21}$NO$_4$ (M+H)$^+$: 352.1549, found: 352.1542.
General procedure for oxime synthesis (III)

To a solution of aldehyde (1 equiv) in 40 mL MeOH/H₂O (1:1), hydroxylamine hydrochloride (1.05 equiv) and NaOH (1.05 equiv) were added at rt. After 30 min stirring, the methanol was evaporated and the resulting residue was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na₂SO₄), evaporated and columned by flash chromatography.

Synthesis of oximes and some precursors

Benzaldoxime
Following the general procedure (III), benzaldehyde (2.0 g, 18.85 mmol), hydroxylamine hydrochloride (1.37 g, 19.97 mmol), NaOH (792 mg, 19.97 mmol), MeOH/H₂O (1:1) (40 mL). Yield: Colorless oil, 2.10 g (92%). ¹H NMR (CDCl₃, 400 MHz): δ 8.29 (s, 1H), 8.17 (s, 1H), 7.59 (m, 1H), 7.40 (m, 1H).

Butyraldoxime
Commercially available compound

(2E)-cinnamaldoxime
Following the general procedure (III), Cinnamaldehyde (2.20 g, 16.68 mmol), hydroxylamine hydrochloride (1.10 g, 15.89 mmol), NaOH (636 mg, 15.89 mmol), MeOH/H₂O (1:1) (40 mL). Yield: White solid. 2.22 g (90%). ¹H NMR (CDCl₃, 400 MHz): δ 8.73 (s, 1H), 7.52 (dd, J =1.3 Hz, J = 7.9 Hz, 2H), 7.35 (m, 5H), 6.87 (d, J = 16.4 Hz, 1H).
4-Methoxybenzaldoxime
Following general procedure (III), 4-methoxybenzaldehyde (1.12 g, 8.23 mmol), hydroxylamine hydrochloride (600 mg, 8.64 mmol), NaOH (345 mg, 8.64 mmol), MeOH/H₂O (1:1) (20 mL). Yield: White Solid. 1.17 g (94%). ¹H NMR (CDCl₃, 400 MHz): δ 8.41 (s, 1H), 8.14 (s, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H).

4-Methylbenzaldoxime
Following the general procedure (III), 4-methylbenzaldehyde (2.00 g, 16.64 mmol), hydroxylamine hydrochloride (1.21 g, 17.48 mmol), NaOH (700 mg, 17.48 mmol), MeOH/H₂O (1:1) (40 mL). Yield: White Solid. 2.03 g (90%). ¹H NMR (CDCl₃, 400 MHz): δ 8.42 (s, 1H), 8.14 (s, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H).

4-Nitrobenzaldoxime
Following the general procedure (III), 4-nitrobenzaldehyde (1.00 g, 6.62 mmol), hydroxylamine hydrochloride (483 mg, 6.95 mmol), NaOH (278 mg, 6.95 mmol), MeOH/H₂O (1:1) (20 mL). Yield: White Solid. 1.02 g, (93%). ¹H NMR (CDCl₃, 400 MHz): δ 8.25 (m, 2H), 8.20 (s, 1H), 7.88 (s, 1H), 7.75 (m, 2H).

Cyclohexanecarbaldoxime
Following the general procedure (III), cyclohexanecarbaldehyde (2.00 g, 17.83 mmol), hydroxylamine hydrochloride (1.30 g, 18.72 mmol), NaOH (750 mg, 18.72 mmol),
MeOH/H₂O (1:1) (40 mL). Yield: Colorless oil. 1.80 g (79%). ¹H NMR (CDCl₃, 400 MHz): 7.77 (s, 1H), 7.35 (d, J = 6.0 Hz, 1H), 2.22 (m, 1H), 1.80-1.26 (m, 10H).

**Perfluorobenzaldoxime**

Following the general procedure (III), pentafluorobenzaldehyde (2.00 g, 10.21 mmol), hydroxylamine hydrochloride (701 mg, 10.71 mmol), NaOH (410 mg, 10.71 mmol), MeOH/H₂O (1:1) (40 mL). Yield: White solid. 2.04 g (94%). ¹H NMR (CDCl₃, 400 MHz): δ 8.87 (s, 1H), 8.24 (s, 1H).

**3-((Hydroxyimino)methyl)benzaldoxime**

Following the general procedure (III), 3-((hydroxyimino)methyl)benzaldehyde (409 mg, 3.05 mmol), hydroxylamine hydrochloride (434 mg, 6.24 mmol), NaOH (239 mg, 6.24 mmol), MeOH/H₂O (1:1) (10 mL). Yield: White solid. 370 mg (74%). ¹H NMR (DMSO-d₆, 400 MHz): δ 11.25 (s, 2H), 8.11 (s, 2H), 7.75 (q, J = 1.3 Hz, 1H), 7.54 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H).

**4-(3-(2'-O-adenosinyl)prop-1-yn-1-yl)benzaldoxime**

Following the general procedure (III), 4-(3-(2'-O-adenosinyl)prop-1-yn-1-yl)benzaldehyde (500 mg, 1.221 mmol), hydroxylamine hydrochloride (89 mg, 1.282 mmol), NaOH (51 mg, 1.282 mmol), MeOH/H₂O (1:1) (7 mL). Yield: White solid. 430 mg (83%). ¹H NMR (DMSO-d₆, 400 MHz): δ 11.35 (s, 1H), 8.35 (s, 1H), 8.07 (d, J = 12.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.31 (s, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.01 (d, J = 6.8 Hz, 1H), 5.53 (dd, J = 4.4 Hz, J = 7.4 Hz, 1H), 5.33 (d, J = 5.2 Hz, 1H), 4.80 (dd, J = 4.9 Hz, J = 6.6 Hz, 1H), 4.43 (m, 2H), 4.34 (m, 1H), 3.99 (m, 1H), 3.65 (m, 1H), 3.53 (m, 1H). ¹³C NMR (DMSO-d₆, 75 MHz): δ 156.1, 152.3, 148.8, 147.4, 139.8, 133.2, 131.4,
126.3, 122.1, 119.3, 86.8, 86.7, 86.0, 85.7, 79.5, 68.8, 61.6, 57.5. HRMS (ESI) \textit{m/z} calcd for \textit{C}_{20}\textit{H}_{20}\textit{N}_{6}\textit{O}_{5} (M+H)^+: 425.1573, found: 425.1581.

(4-Methylcoumarin-7-yl)carbaldoxime

Following the general procedure (III), 4-methylcoumarin-7-yl)carbaldehyde\textsuperscript{[1]} (200 mg, 1.063 mmol), hydroxylamine hydrochloride (82 mg, 1.180 mmol), NaOH (47 mg, 1.180 mmol), MeOH/H$_2$O (1:1) (12 mL). Yield: White solid. 215 mg (95 %). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 11.64 (s, 1H), 8.24 (s, 1H), 7.78 (d, $J = 8.4$ Hz, 1H), 7.61 (m, 1H), 7.53 (d, $J = 1.5$ Hz, 1H), 6.41 (d, $J = 1.2$ Hz, 1H), 2.43 (d, $J = 1.2$ Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 159.5, 153.0, 152.7, 147.0, 136.5, 125.7, 121.8, 120.0, 114.5, 113.9, 17.9. HRMS (ESI) \textit{m/z} calcd for \textit{C}_{11}\textit{H}_{9}\textit{NO}_{3} (M+H)$^+$: 204.0661, found: 204.0658.

4-(3-(2'-O-adenosinyl)prop-1-yn-1-yl)benzaldehyde

2'-O-(1-propyn-3-yl)adenosine\textsuperscript{[2]} (200 mg, 0.66 mmol), 4-bromobenzaldehyde (182 mg, 0.99 mmol), PdCl$_2$(PPh$_3$)$_2$ (23 mg, 0.032 mmol), Cul (16 mg, 0.084 mmol) in triethylamine and DMF (3 mL, 1:1) was stirred in a microwave at 55 °C (60 W) for 30 min, solvent evaporated and columned. Flash chromatography (CH$_2$Cl$_2$/MeOH, 9:1), furnished a coupled product (265 mg, 95 %) as a colorless powder. $^1$H NMR (400 MHz, DMSO-d$_6$, 400 MHz): $\delta$ 9.95 (s, 1H), 8.35 (s, 1H), 8.05 (s, 1H), 7.81 (d, $J = 8.0$ Hz, 2H), 7.34 (m, 4H), 6.01 (d, $J = 6.7$ Hz, 1H), 5.56 (s, 1H), 5.35 (d, $J = 4.7$ Hz, 1H), 4.82 (dd, $J = 5.0$ Hz, $J = 6.4$ Hz, 1H), 4.47 (dd, $J = 16.5$ Hz, $J = 40.8$ Hz, 2H), 4.35 (dd, $J = 4.9$ Hz, $J = 6.9$ Hz, 1H), 3.99 (dd, $J = 3.3$ Hz, $J = 5.8$ Hz, 1H), 3.65 (d, $J = 12.1$ Hz, 1H), 3.53 (m, 1H). $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 192.3, 156.1, 152.3, 148.8, 139.9, 135.5, 131.7, 129.4, 127.3, 119.3, 89.2, 86.8, 86.0, 85.1, 79.6, 68.8, 61.6, 57.5. HRMS (ESI) \textit{m/z} calcd for \textit{C}_{20}\textit{H}_{19}\textit{N}_{5}\textit{O}_{5} (M+H)$^+$: 410.1464, found: 410.1456.
A solution of propargyl bromide (0.55 ml, 6.19 mmol) was added to a solution of thymidine (1.00 g, 4.13 mmol) and K₂CO₃ (1.71 g, 12.38 mmol) in 25 ml DMF/acetone 1:1, and the reaction was stirred at 50 8C for 3 days. The reaction mixture was filtered and dried in vacuo. Distilled water (40 mL) was added to the residue, and the solution was extracted with CH₂Cl₂ (40 mL). The organic layer was washed with brine (50 mL), dried over Na₂SO₄. Combined organic layers were evaporated to dryness and columned by flash chromatography: silica gel, CH₂Cl₂/MeOH (9:1). Colourless foam. 845 mg (73%). ¹H NMR (DMSO-d₆, 400 MHz): δ 7.77 (d, J = 1.2 Hz, 1H), 6.18 (t, J = 6.8 Hz, 1H), 5.21 (d, J = 4.4 Hz, 1H), 5.01 (t, J = 5.2 Hz, 1H), 4.48 (m, 2H), 4.20 (m, 1H), 3.75 (q, J = 3.7 Hz, 1H), 3.53 (m, 2H), 3.05 (t, J = 2.4 Hz, 1H), 2.08 (m, 2H), 1.79 (d, J = 1.2 Hz, 3H). ¹³C NMR (DMSO-d₆, 75 MHz): δ 161.7, 149.6, 135.1, 108.4, 87.4, 84.8, 79.0, 72.8, 70.2, 61.1, 39.5, 29.9, 12.7. HRMS (ESI) m/z calcd for C₁₃H₁₆N₂O₅ (M+H)⁺: 281.1138, found: 281.1134.
References


$^1$H NMR spectrum of $p$-methylbenzaldoxime. Top: full spectrum, bottom: expansion of aromatic region.
$^1$H NMR spectrum of iodobenzene. Top: full spectrum, bottom: expansion of aromatic region.
**Figure S1.** $^1$H NMR spectrum of $p$-methylbenzaldoxime + PIFA after 1 min. Top: full spectrum, bottom: aromatic region.

- $^*$ = oxime
- $\circ$ = iodobenzene
- $+$ = nitrile oxide
Figure S2. $^1$H NMR spectrum of $p$-methylbenzaldoxime + DIB after 1 min, 15 min and 60 min. Only the aromatic region is depicted.
Figure S3 A) 2'-O-(propargyl)adenosine. B) benzaldoxime. C) reaction mixture 2 h later. D) reaction mixture 7 h later. RP-HPLC [5% MeCN (2 min), 5-20% MeCN (13 min). All peaks are independent of reaction concentration.
Figure S4 a) peptide before reaction b) peptide isoxazole product. RP-HPLC [5% MeCN (5 min), 5-100% MeCN (50 min), 100% MeCN (55 min), 5% MeCN (60 min), 5% MeCN (65 min).
Experimental procedures and NMR spectra for determination of reaction rate constants with BCN

Determination of reaction rate constant of BCN and benzyl azide

\[ \text{\textsuperscript{1}H NMR monitoring of cycloaddition of BCN with benzyl azide was performed by rapid mixing (t=0) of stock solutions A and B (0.3 mL each) in an NMR tube and immediate insertion into a 400 MHz NMR spectrometer. NMR spectra were measured at preset time-intervals. Each experiment was performed in duplo.} \]

Stock solution A: BCN was dissolved in a mixture of CD\textsubscript{3}OD and D\textsubscript{2}O (ratio 1:1, 10 mL) to give a 36 mM solution.

Stock solution B: Benzyl azide was dissolved in a mixture of CD\textsubscript{3}OD and D\textsubscript{2}O (ratio 1:1, 10 mL) to give a 54 mM solution.

Kinetics of the reaction of BCN with benzyl azide was determined by measuring the decrease of the integral of the signal caused by benzyl azide methylene protons, with the integral of the CD\textsubscript{3}OD solvent-peak as internal standard. Due to the fact that cycloaddition had already proceeded significantly by the time of the first measurement, a starting value for the integral of benzyl azide methylene signals was estimated based on the average of the summation of signals of benzyl azide and triazole product.

From the conversion plots thus obtained, the second order rate plots were calculated according to equation:

\[ kt = \frac{1}{[B]_0 - [A]_0} \times \ln \frac{[A]_0 ([B]_0 - [P])}{([A]_0 - [P])[B]_0} \]

with \( k = \text{2\textsuperscript{nd} order rate constant (M}^{-1}\text{s}^{-1}), t = \text{reaction time (s)}, [A]_0 = \text{the initial concentration of substrate A (mmol/mL)}, [B]_0 = \text{the initial concentration of substrate B (mmol/mL) and [P] = the concentration of product (mmol/mL).} \]
Rate plots:

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Based on disappearance of BnN$_3$</th>
<th>Based on formation of triazole</th>
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<tr>
<td>I</td>
<td><img src="image1" alt="Graph I" /></td>
<td><img src="image2" alt="Graph I" /></td>
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<tr>
<td>II</td>
<td><img src="image3" alt="Graph II" /></td>
<td><img src="image4" alt="Graph II" /></td>
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</table>

Exp. I:
- For disappearance of BnN$_3$: \( y = 181.3x \), \( R^2 = 0.9993 \)
- For formation of triazole: \( y = 0.1711x \), \( R^2 = 0.9999 \)

Exp. II:
- For disappearance of BnN$_3$: \( y = 3.1775x \), \( R^2 = 0.9972 \)
- For formation of triazole: \( y = 8.3957x \), \( R^2 = 0.9999 \)
Competition experiments between benzyl azide and benzonitrile-N-oxide

1:1 ratio of benzyl azide and nitrile oxide

Benzyl azide (0.033 mL, 0.25 mmoL) and benzaldoxime (26.53 mg, 0.25 mmoL) were dissolved in CD$_3$OD/D$_2$O (1:1, 6 mL) and $^1$H NMR was taken. To this mixture, PIFA (97 mg, 0.23 mmoL) was added, after 1 minute followed by BCN (3.8 mg, 0.025 mmoL). Reaction mixture was allowed to stir for 10 min, when TLC and LC-Q confirmed completion of reaction.

The solvent mixture was evaporated to remove excess benzyl azide and redissolved in CD$_3$OD/D$_2$O. $^1$H NMR analysis was used to determine the ratio of the methylene peaks of triazole and isoxazole.
$^1$H NMR spectrum of 1:1 mixture of benzyl azide and benzaldoxime before PIFA addition
$^1$H NMR spectrum of 1:1 mixture of BnN$_3$ and benzaldoxime + BCN (full)

$^1$H NMR spectrum of 1:1 mixture of BnN$_3$ and benzaldoxime + BCN (methylene area)
5:1 ratio of benzyl azide and nitrile oxide
The same procedure as above was applied, but now starting with 0.165 mL benzyl azide.

$^1$H NMR spectrum of 1:1 mixture of benzyl azide and benzaldoxime + BCN (full)
$^1$H NMR spectrum of 1:1 mixture of benzyl azide and benzaldoxime + BCN (methylene area)
$^{1}\text{H}$ and $^{13}\text{C}$ NMR spectra of oximes
$^1$H NMR and $^{13}$C NMR spectra of isoxazoles