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A Family of “Click” Nucleosides for Metal-Mediated Base Pairing: Unravelling the Principles of Highly Stabilizing Metal-Mediated Base Pairs

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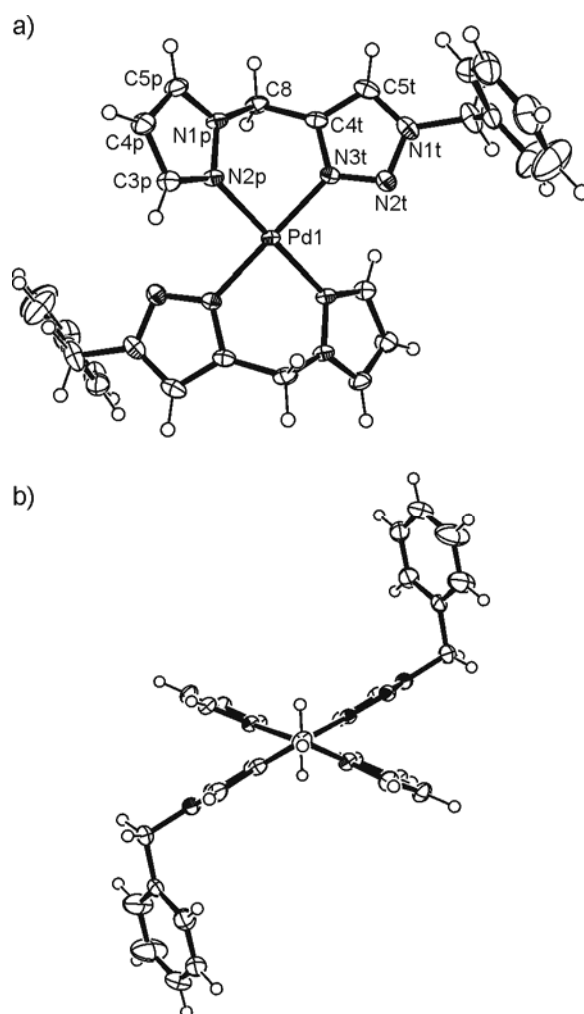


Figure S1: Molecular structure of the cation of $[\text{Pd}(\text{BnTriPyr})_2]\text{Cl}_2 \cdot 2 \text{H}_2\text{O}$ viewed from two different orientations.

Table S1. Melting temperature T_m (°C) of duplex I in the absence of Ag(I).^[a]

	X = Imi	X = TriTri	X = TriPyr	X = TriPy
Y = Imi	29.8	25.4	25.6	33.6
Y = TriTri	25.4	24.3	24.4	31.5
Y = TriPyr	25.4	25.0	24.7	31.8
Y = TriPy	33.9	33.7	32.6	39.0

[a] Conditions: 1 μ M oligonucleotide duplex, 150 mM NaClO₄, 5 mM MOPS (pH 6.8), 1 μ M AgNO₃. The estimated standard deviation of T_m amounts to 1 °C.

Table S2. Melting temperature T_m (°C) of duplex I in the presence of one equivalent of Ag(I).^[a]

	X = Imi	X = TriTri	X = TriPyr	X = TriPy
Y = Imi	39.3	27.6	26.7	46.2
Y = TriTri	31.8	26.4	27.3	33.0
Y = TriPyr	27.9	26.9	27.5	35.9
Y = TriPy	46.5	34.9	40.0	40.4

[a] Conditions: 1 μ M oligonucleotide duplex, 150 mM NaClO₄, 5 mM MOPS (pH 6.8), 1 μ M AgNO₃. The estimated standard deviation of T_m amounts to 1 °C.

Characterization of toluoyl-protected nucleosides

TolTriTri: Yield: 3.34 g, 6.65 mmol, 83%, white solid.

^1H NMR (400 MHz, CDCl_3): δ = 8.14 (s, 1 H, H5*), 7.93 (d, 2 H, H_{meta}(Tol)), 7.90 (s, 1 H, H3*), 7.84 (d, 2 H, H_{meta}(Tol)), 7.82 (s, 1 H, H5), 7.24 (m, 4 H, H_{ortho}(Tol)), 6.45 (t, 1 H, H1'), 5.75 (d, 1 H, H3'), 5.39 (m, 2 H, CH₂), 4.65 (q, 1 H, H4'), 4.61 (dd, 2 H, H5', H5''), 3.19 (dt, 1 H, H2' or H2''), 2.86 (ddd, 1 H, H2' or H2''), 2.43 (s, 3 H, CH₃(Tol)), 2.41 (s, 3 H, CH₃(Tol)) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 166.1 (C=O), 164.9 (C=O), 152.2 (C3*), 144.6 (Tol), 144.2 (Tol), 143.3 (C4), 142.1 (C5*), 129.8 (Tol), 129.7 (Tol), 129.3 (Tol), 126.6 (Tol), 126.3 (Tol), 122.0 (C5), 118.9 (C5), 89.1 (C1'), 83.9 (C4'), 74.7 (C3'), 63.9 (C5'), 44.8 (CH₂), 38.3 (C2'), 21.7 (CH₃(Tol)) ppm.

$\text{C}_{26}\text{H}_{26}\text{N}_6\text{O}_5$ (502.52): calcd. C 62.14, H 5.20, N 16.72; found C 62.17, H 5.21, N 16.47.

Mass (m/z) for (M+Na)⁺: calcd. 525.1862; found 525.1858.

TolTriPyr: 3.06 g, 6.01 mmol, 88%, white solid.

^1H NMR (400 MHz, CDCl_3): δ = 7.92 (d, 2 H, H_{meta}(Tol)), 7.82 (s, 1 H, H5), 7.65 (d, 2 H, H_{ortho}(Tol)), 7.46 (m, 2 H, H5*, H3*), 7.26 (m, 2 H, H_{ortho}(Tol)), 7.19 (m, 2 H, H_{ortho}(Tol)), 6.44 (dd, 1 H, H4*), 6.20 (t, 1 H, H1'), 5.60 (dt, 1 H, H3'), 5.43 (d, 2 H, CH₂), 4.74 (m, 1 H, H4'), 4.59 (dd, 2 H, H5', H5''), 3.15 (m, 1 H, H2' or H2''), 3.00 (m, 1 H, H2' or H2''), 2.42 (s, 3 H, CH₃(Tol)), 2.40 (s, 3 H, CH₃(Tol)) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 166.0 (C=O), 165.8 (C=O), 144.5 (Tol), 144.0 (Tol), 143.9 (C4), 139.8 (C3*), 129.8 (Tol), 129.7 (Tol), 129.3 (C5*), 129.2 (Tol), 126.6 (Tol), 126.3 (Tol), 121.5 (C5), 106.1 (C4*), 88.9 (C1'), 83.7 (C4'), 74.8 (C3'), 63.9 (C5'), 47.3 (CH₂), 38.1 (C2'), 21.7 (CH₃) ppm.

$\text{C}_{27}\text{H}_{27}\text{N}_5\text{O}_5$ (501.54): calcd. C 64.66, H 5.43, N 13.96; found C 64.96, H 5.34, N 13.77.

Mass (m/z) for (M+Na)⁺: calcd. 524.1910; found 524.1911.

TolTriPy: 1.23 g, 2.47 mmol, 74%, white solid.

^1H NMR (400 MHz, CDCl_3): δ = 8.55 (s, 1 H, H2*), 8.40 (d, 1 H, H5), 8.12 (d, 1 H, H5*), 7.96 (d, 2 H, H_{meta}(Tol)), 7.94 (d, 2 H, H_{meta}(Tol)), 7.77 (t, 1 H, H4*), 7.26 (d, 2 H, H_{ortho}(Tol)), 7.23 (d, 1 H, H3*), 7.15 (m, 2 H, H_{ortho}(Tol)), 6.54 (t, 1 H, H1'), 5.80 (m, 1 H, H3'), 4.68 (m, 1 H, H4'), 4.60 (m, 2 H, H5', H5''), 3.25 (m, 1 H, H2' or H2''), 2.89 (ddd, 1 H, H2' or H2''), 2.44 (s, 3 H, CH₃(Tol)), 2.36 (s, 3 H, CH₃(Tol)) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 166.2 (C=O), 165.8 (C=O), 149.9 (C6*), 149.3 (C2*), 148.6 (C4*), 144.5 (Tol), 143.8 (Tol), 136.9 (C4), 129.8 (Tol), 129.7 (Tol), 129.3 (Tol), 129.1 (Tol), 126.6 (Tol), 126.4 (Tol), 122.9 (C5*), 121.0 (C3*), 120.3 (C5), 88.9 (C1'), 83.6 (C4'), 74.7 (C3'), 63.9 (C5'), 38.2 (C2'), 21.7 (CH₃(Tol)) ppm.

$\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_5$ (498.52): calcd. C 67.46, H 5.26, N 11.24; found C 67.78, H 5.32, N 11.11.

Mass (m/z) for (M+Na)⁺: calcd. 521.1801; found 521.1826.

Characterization of free nucleosides

NucTriTri: 1.68 g, 6.29 mmol, 95%, white solid.

^1H NMR (400 MHz, CD_3OD): δ = 8.59 (s, 1 H, H5*), 8.29 (s, 1 H, H3*), 8.01 (s, 1 H, H5), 6.44 (t, 1 H, H1'), 5.60 (s, 2 H, CH_2), 4.56 (q, 1 H, H3'), 4.05 (q, 1 H, H4'), 3.74 (dd, 1 H, H5' or H5''), 3.65 (dd, 1 H, H5' or H5''), 2.79 (m, 1 H, H2' or H2''), 2.54 (m, 1 H, H2' or H2'') ppm.

^{13}C NMR (100 MHz, CD_3OD): δ = 152.5 (C3*), 145.1 (C5*), 130.5 (C4), 124.1 (C5), 90.3 (C1'), 89.7 (C4'), 72.1 (C3'), 63.1 (C5'), 45.4 (CH_2), 41.7 (C2') ppm.

$\text{C}_{10}\text{H}_{14}\text{N}_6\text{O}_3$ (266.26): calcd. for $\text{M} \cdot 0.25 \text{H}_2\text{O}$: C 44.34, H 5.40, N 31.05; found C 44.10, H 5.19, N 30.84.

Mass (m/z) for $(\text{M}+\text{Na})^+$: calcd. 289.1025; found 289.1016.

NucTriPyr: 711 mg, 2.68 mmol, 90%, white solid.

^1H NMR (400 MHz, D_2O , pD 7.1): δ = 8.13 (s, 1 H, H5), 7.75 (s, 1 H, H5*), 7.58 (s, 1 H, H3*), 6.45 (t, 1 H, H1'), 6.38 (dt, 1 H, H4*), 5.46 (s, 2 H, CH_2), 4.59 (q, 1 H, H3'), 4.13 (q, 1 H, H4'), 3.75 (dd, 1 H, H5' or H5''), 3.62 (dd, 1 H, H5' or H5''), 2.83 (m, 1 H, H2' or H2''), 2.60 (m, 1 H, H2' or H2'') ppm.

^{13}C NMR (100 MHz, D_2O , pD 7.1): δ = 143.4 (C5*), 140.3 (C3*), 131.3 (C4), 123.0 (C5), 106.3 (C4*), 88.6 (C1'), 87.5 (C4'), 70.5 (C3'), 61.4 (C5'); 45.9 (CH_2), 39.2 (C2') ppm.

$\text{C}_{11}\text{H}_{15}\text{N}_5\text{O}_3$ (265.27): calcd.: C 49.81, H 5.70, N 26.40; found C 49.70, H 5.50, N 26.36.

Mass (m/z) for $(\text{M}+\text{Na})^+$: calcd. 288.1073; found 288.1067.

NucTriPy: 510 mg, 1.94 mmol, 95%, white solid.

^1H NMR (400 MHz, D_2O , pD 6.6): δ = 8.34 (s, 1 H, H2*), 8.32 (s, 1 H, H5), 7.76 (m, 1 H, H5*), 7.68 (m, 1 H, H4*), 7.27 (m, 1 H, H3*), 6.45 (t, 1 H, H1'), 4.62 (dt, 1 H, H3'), 4.17 (dt, 1 H, H4'), 3.79 (dd, 1 H, H5' or H5''), 3.67 (dd, 1 H, H5' or H5''), 2.84 (ddd, 1 H, H2' or H2''); 2.64 (ddd, 1 H, H2' or H2'') ppm.

^{13}C NMR (100 MHz, D_2O , pD 6.6): δ = 148.8 (C6*), 147.6 (C2*), 147.0 (C4*), 138.3 (C4), 123.9 (C5), 121.4 (C5*), 120.8 (C3*), 88.7 (C1'), 87.8 (C4'), 70.7 (C3'), 61.5 (C5'), 39.4 (C2') ppm.

$\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_3$ (262.26): calcd. for $\text{M} \cdot 1.25 \text{H}_2\text{O}$: C 50.34, H 5.87, N 19.57; found C 50.37, H 5.38, N 19.89.

Mass (m/z) for $(\text{M}+\text{Na})^+$: calcd. 285.0964; found 285.0958.

Characterization of DMT-protected nucleosides

DMTTriTri: 3.14 g, 5.53 mmol, 88%, white foam.

^1H NMR (400 MHz, CDCl_3): δ = 8.03 (s, 1 H, H5), 7.84 (d, 2 H, H3*, H5*), 7.33 (m, 2 H, DMT), 7.25 – 7.19 (m, 7 H, DMT), 6.79 (d, 4 H, DMT), 6.32 (t, 1 H, H1'), 5.27 (d, 2 H, CH_2), 4.63 (m, 1 H, H3'), 4.13 (m, 1 H, H4'), 3.77 (s, 6 H, OCH_3), 3.31 (m, 2 H, H5', H5''), 2.80 (m, 1 H, H2' or H2''), 2.53 (m, 1 H, H2' or H2'') ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 158.5 (DMT), 151.6 (C3*), 144.4 (C5*), 143.0 (DMT), 141.4 (C4), 135.5 (DMT), 135.4 (DMT), 130.0 (DMT), 129.3 (DMT), 128.4 (DMT), 128.1 (DMT), 127.8 (DMT), 126.9 (DMT), 121.9 (C5), 113.1 (DMT), 88.8 (C1'), 86.6 (C4'), 70.8 (C3'), 63.2 (C5'), 55.2 (OCH_3), 44.6 (CH_2), 40.8 (C2') ppm.

$\text{C}_{31}\text{H}_{32}\text{N}_6\text{O}_5$ (568.62): calcd. for $\text{M} \cdot 0.66 \text{ H}_2\text{O}$: C 64.13, H 5.79, N 14.47; found C 64.58, H 5.93, N 14.08.

Mass (m/z) for $(\text{M}+\text{Na})^+$: calcd. 591.2332; found 591.2334.

DMTTriPyr: 1.35 g, 2.37 mmol, 62%, white foam.

^1H NMR (400 MHz, CDCl_3): δ = 8.60 (d, 1 H, H5*), 7.86 (s, 1 H, H5), 7.51 (m, 2 H, DMT), 7.40 (d, 2 H, DMT), 7.29 – 7.18 (m, 5 H, DMT), 6.20 (d, 1 H, H3*), 6.82 (d, 4 H, DMT), 6.35 (d, 1 H, H4*), 6.26 (t, 1 H, H1'), 5.44 (s, 2 H, CH_2), 4.45 (s, 1 H, H3'), 4.35 (s, 1 H, H4'), 3.78 (s, 6 H, OCH_3), 3.30 (dd, 1 H, H5' or H5''), 3.13 (dd, 1 H, H5' or H5''), 2.92 (dt, 1 H, H2' or H2''), 2.34 (m, 1 H, H2' or H2'') ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 158.5 (DMT), 149.7 (DMT), 144.6 (DMT), 143.5 (DMT), 139.8 (DMT), 135.8 (C3*), 135.6 (C5*), 130.0 (C4), 129.4 (DMT), 128.0 (DMT), 127.8 (DMT), 126.8 (DMT), 123.7 (DMT), 122.8 (C5), 113.2 (DMT), 113.1 (DMT), 106.1 (C4*), 89.8 (C1'), 86.3 (C4'), 72.4 (C3'), 63.9 (C5'), 55.2 (OCH_3), 47.2 (CH_2), 41.0 (C2') ppm.

$\text{C}_{32}\text{H}_{33}\text{N}_5\text{O}_5$ (567.63): calcd. C 67.71, H 5.86, N 12.34; found C 67.57, H 5.72, N 12.27.

Mass (m/z) for $(\text{M}+\text{Na})^+$: calcd. 590.2379; found 590.2379.

DMTTriPy: 321 mg, 0.57 mmol, 26%, white foam.

^1H NMR (400 MHz, CDCl_3): δ = 8.53 (ddd, 1 H, H2*), 8.31 (s, 1 H, H5), 8.03 (dt, 1 H, H5*), 7.71 (td, 1 H, H4*), 7.36 (m, 2 H, DMT), 7.25 – 7.19 (m, 7 H, DMT), 7.13 (m, 1 H, H3*), 6.74 (d, 4 H, DMT), 6.38 (t, 1 H, H1'), 5.27 (d, 2 H, H6*), 4.58 (m, 1 H, H3'), 4.15 (m, 1 H, H4'), 3.69 (s, 6 H, OCH_3), 3.30 (m, 1 H, H5' or H5''); 3.23 (m, 1 H, H5' or H5''), 2.85 (m, 2 H, H2', H2'') ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 158.4 (DMT), 150.1 (C6*), 149.4 (C2*), 148.3 (DMT), 144.5 (C4*), 136.7 (DMT), 135.8 (DMT), 135.7 (C4), 129.9 (DMT), 128.1 (DMT), 127.8 (DMT), 126.7 (DMT), 122.7 (C5), 121.0 (C5*), 120.1 (C3*), 113.1 (DMT), 88.6 (DMT), 86.6 (C1'), 86.3 (C4'), 71.2 (C3'), 63.9 (C5'), 55.1 (OCH_3), 40.6 (C2') ppm.

$\text{C}_{33}\text{H}_{32}\text{N}_4\text{O}_5$ (567.63): calcd. for $\text{M} \cdot \text{H}_2\text{O} \cdot 0.5 \text{ NEt}_3$: C 68.28, H 6.61, N 9.95; found C 68.40, H 6.57, N 10.03.

Mass (m/z) for $(\text{M}+\text{Na})^+$: calcd. 587.2270; found 587.2265.

Characterization of orthogonal protected nucleosides

PhosTriTri: 887 mg, 1.15 mmol, 90%, pale yellowish oil.

^1H NMR (400 MHz, CDCl_3): δ = 7.96 (s, 1 H, H5), 7.79 (s, 2 H, H5*, H3*), 7.27 (m, 2 H, DMT), 7.20 – 7.12 (m, 7 H, DMT), 6.72 (m, 4 H, DMT), 6.28 (t, 1 H, H1'), 5.22 (m, 2 H, CH_2), 4.67 (m, 1 H, H3'), 4.16 (m, 1 H, H4'), 3.79 – 3.63 (m, 8 H, OCH_3 , $\text{CH}(\text{CH}_3)_2$), 3.49 (m, 2 H, CH_2CN), 3.23 (m, 2 H, H5', H5''), 2.78 (m, 1 H, H2' or H2''), 2.61 (m, 1 H, H2' or H2''), 2.53 (t, 2 H, OCH_2), 1.10 – 1.00 (m, 12 H, $\text{CH}(\text{CH}_3)_2$) ppm.

^{31}P NMR (162 MHz, CDCl_3): δ = 149.4; 149.1 ppm.

Mass (m/z) for $(\text{M}+\text{Na})^+$: calcd. 791.3410; found 791.3405.

PhosTriPyr: 924 mg, 1.23 mmol, 99%, colourless oil.

^1H NMR (400 MHz, CDCl_3): δ = 8.00 (s, 1 H, H5), 7.51 (m, 2 H, H5*, H3*), 7.41 (m, 2 H, DMT), 7.32 – 7.20 (m, 7 H, DMT), 6.84 (m, 4 H, DMT), 6.56 (dd, 1 H, H4*), 6.25 (t, 1 H, H1'), 5.44 (m, 2 H, CH_2), 4.54 (m, 2 H, H3', H4'), 3.79 (m, 6 H, OCH_3), 3.59 (m, 2 H, $\text{CH}(\text{CH}_3)_2$), 3.46 (m, 2 H, CH_2CN), 3.38 (m, 1 H, H5' or H5''), 3.11 (m, 1 H, H5' or H5''), 2.98 (m, 1 H, H2' or H2''), 2.58 (m, 1 H, H2' or H2''), 2.40 (t, 2 H, OCH_2), 1.10 – 1.00 (m, 12 H, $\text{CH}(\text{CH}_3)_2$) ppm.

^{31}P NMR (162 MHz, CDCl_3): δ = 148.9; 148.8 ppm.

Mass (m/z) for $(\text{M}+\text{Na})^+$: calcd. 791.3410; found 791.3405.

PhosTriPy: 459 mg, 0.58 mmol, 87%, colourless oil.

^1H NMR (400 MHz, CDCl_3): δ = 8.55 (m, 1 H, H2*), 8.36 (s, 1 H, H5), 8.06 (dt, 1 H, H5*), 7.72 (td, 1 H, H4*), 7.38 (m, 2 H, DMT), 7.30 – 7.12 (m, 8 H, DMT, H3*), 6.77 (m, 4 H, DMT), 6.40 (t, 1 H, H1'), 4.74 (m, 1 H, H3'), 4.31 (m, 1 H, H4'), 3.72 (m, 6 H, OCH_3), 3.68 – 3.58 (m, 4 H, $\text{CH}(\text{CH}_3)_2$, CH_2CN), 3.29 (m, 2 H, H5', H5''), 2.95 (m, 1 H, H2' or H2''), 2.65 (m, 1 H, H2' or H2''), 2.44 (t, 2 H, OCH_2), 1.20 – 1.15 (m, 12 H, $\text{CH}(\text{CH}_3)_2$) ppm.

^{31}P NMR (162 MHz, CDCl_3): δ = 149.4; 149.1 ppm.

Mass (m/z) for $(\text{M}+\text{Na})^+$: calcd. 787.3349; found 787.3344.

Characterization of the metal complexes

[Cu(BnTriPyr)₂](NO₃)₂ · 2 CH₃OH: 238 mg, 0.36 mmol, 74%, blue crystals.

Metal salt used during synthesis: Cu(NO₃)₂ · 3 H₂O

No NMR spectra were recorded due to the paramagnetic behaviour of the complex.

C₂₆H₂₆N₁₂O₆Cu (666.11): calcd. for [Cu(**BnTriPyr**)₂](NO₃)₂: C 46.88, H 3.93, N 25.23; found C 46.84, H 3.80, N 25.19.

Mass (m/z) for {[Cu(**BnTriPyr**)₂](NO₃)⁺}: calcd. 603.1516; found 603.1519.

[Pd(BnTriPyr)₂]Cl₂ · 2 H₂O: 268 mg, yellow crystals.

Metal precursor complex used during synthesis: [PdCl₂(cod)]

¹H NMR (400 MHz, CDCl₃): δ = 8.51 (s, 1 H, H5p), 8.12 (s, 1 H, H5t), 7.88 (s, 1 H, H3p), 7.36 (m, 5 H, H2, H3, H4, H5, H6), 6.48 (s, 1 H, H4p), 5.78 (s, 2 H, H7), 5.71 (s, 2 H, H8) ppm.

C₂₆H₃₀N₁₀O₂Cl₂Pd (691.91): calcd. for [Pd(**BnTriPyr**)₂]Cl₂ · 2 H₂O: C 45.13, H 4.37, N 20.24; found C 45.40, H 4.24, N 20.33.

Mass (m/z) for {[Pd(**BnTriPyr**)₂]Cl⁺}: calcd. 619.1065; found 619.066.

Molecular masses of the oligonucleotides as determined by mass spectrometry.

Sequence	Mass (calcd.) / Da	Mass (found) / Da	X/Y	
AGA-AAG-XGA-GGG-A	4038	4040	Imi	duplex I
AGA-AAG-XGA-GGG-A	4120	4121	TriTri	duplex I
AGA-AAG-XGA-GGG-A	4119	4122	TriPyr	duplex I
AGA-AAG-XGA-GGG-A	4117	4118	TriPy	duplex I
TCC-CTC-YCT-TTC-T	3744	3747	Imi	duplex I
TCC-CTC-YCT-TTC-T	3826	3829	TriTri	duplex I
TCC-CTC-YCT-TTC-T	3825	3826	TriPyr	duplex I
TCC-CTC-YCT-TTC-T	3823	3823	TriPy	duplex I
GAG-GGA-XAG-AAA-G	4038	4039	Imi	duplex II
GAG-GGA-XAG-AAA-G	4120	4122	TriTri	duplex II
GAG-GGA-XAG-AAA-G	4119	4121	TriPyr	duplex II
GAG-GGA-XAG-AAA-G	4117	4118	TriPy	duplex II
CTT-TCT-YTC-CCT-C	3744	3746	Imi	duplex II