Supporting Information for
**Concise Approach to Novel Isothiazolidinone (IZD) Phosphotyrosine Mimetics:
Microwave-Assisted Addition of Bisulfite to Activated Olefins**

Matthew L. Crawley,* Erin McLaughlin, Wenyu Zhu, and Andrew P. Combs

Discovery Chemistry, Experimental Station, Incyte Corporation, Route 141 and Henry Clay
Road, Wilmington, Delaware 19880

General Information

All glassware used in anhydrous reactions was dried overnight under nitrogen. Moisture or oxygen sensitive reactions were performed under an atmosphere of nitrogen gas. All solvents were used without further purification from commercial sources. ¹H NMR spectra were obtained using either a Varian Mercury-300, Mercury 400, or Inova-500 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the standard. The LCMS method utilized a Waters SunFire column (19 x 100 mm, 5 μM particle size), with a water / 0.1% TFA and acetonitrile / 0.1% TFA gradient at a flow rate of 30 mL / min over a total run time of 5 minutes. All products were characterized by ¹H NMR and LCMS methods.

Purifications by flash chromatography were performed on RediSep columns using an Isco CombiFlash SG100c. Preparative LCMS purifications were performed on a Waters FractionLynx system using mass directed fractionation and compound-specific method optimization.¹ Microwave reactions were performed in a Personal Chemistry Emrys Optimizer.

Experimental Conditions

General procedure for the addition of sodium bisulfite to activated olefins (Method A): To a solution of the appropriate olefin **5a-5l** (1.0 mmol) in ethanol (0.5 mL) was added a solution of sodium bisulfite (208 mg, 2.0 mmol) in water (0.5 mL). The mixture was placed in a 10 mL microwave tube, sealed, and irradiated at 165 °C for 0.5 h. The crude sample was filtered

¹ Blom, K. F.; Glass, B.; Sparks, R.; Combs, A. P. *J. Comb. Chem.* **2004**, 6, 874.

and purified by direct injection on preparative LCMS to provide the desired products **6a-6l** in 53-92% yield.

General procedure for the addition of sodium bisulfite to activated olefins (Method B): To a solution of the appropriate olefin **5a-5d**, **5i-5j** (3.0 mmol) in ethanol (2.0 mL) was added a solution of sodium bisulfite (624 mg, 6.0 mmol) in water (2.0 mL). The mixture was placed in a 20 mL microwave tube, sealed, and irradiated at 165 °C for 0.5 h. The crude sample was concentrated *in vacuo* and dissolved in a 10% methanol: methylene chloride mixture (50 mL). The solids were removed by filtration and the solution concentrated. The crude solid were triterated with diethyl ether (50 mL) to produce crystalline solid. The products **6a-6d**, **6i-6j** were collected by filtration in 53-92% yield.

Compound **6a**. ^1H NMR (500 MHz, CD_3OD): δ 7.47-7.43 (m, 2H), 7.34-7.26 (m, 3H), 4.42 (dd, J = 10.7, 5.1 Hz, 1H), 4.02 (q, J = 7.2 Hz, 2H), 3.35 (dd, J = 16.2, 5.1 Hz, 1H), 3.08 (dd, J = 16.1, 10.7 Hz, 1H), 1.10 (t, J = 7.2 Hz, 3H); MS for $\text{C}_{11}\text{H}_{15}\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$: m/z = 259.

Compound **6b**. ^1H NMR (500 MHz, CD_3OD): δ 7.79 (s, 1H), 7.72-7.68 (m, 2H), 7.51-7.36 (m, 5H), 7.32-7.28 (m, 2H), 7.15 (dd, 8.8, 2.6 Hz, 1H), 5.19 (s, 2H), 4.53 (dd, J = 10.1, 4.6 Hz, 1H), 3.40 (dd, J = 16.2, 4.6 Hz, 1H), 3.17 (dd, J = 16.2, 10.1 Hz, 1H); MS for $\text{C}_{21}\text{H}_{21}\text{O}_6\text{S}$ $[\text{M} + \text{H}]^+$: m/z = 401.

Compound **6c**. ^1H NMR (400 MHz, CD_3OD): δ 7.94 (dd, $J = 8.7, 1.8$ Hz, 2H), 7.55 (dd, $J = 6.8, 1.8$ Hz, 2H), 4.40 (dd, $J = 10.5, 4.7$ Hz, 1H), 4.00 (q, $J = 7.2$ Hz, 2H), 3.88 (s, 3H), 3.37-3.32 (dd, $J = 16.2, 5.7$ Hz, 1H), 3.08 (dd, $J = 16.2, 10.6$ Hz, 1H) 1.08 (t, $J = 7.2$ Hz, 1H); MS (ES-) for $\text{C}_{13}\text{H}_{15}\text{O}_7\text{S}$ $[\text{M} - \text{H}]^+$: $m/z = 315$.

Compound **6d**. ^1H NMR (400 MHz, CD_3OD): δ 8.19 (d, $J = 2.5$ Hz, 1H), 7.92 (dd, $J = 8.2, 1.8$ Hz, 2H), 7.73 (d, $J = 8.2$ Hz, 1H), 5.18 (dd, $J = 9.8, 5.1$ Hz, 1H), 3.88 (s, 3H), 3.56 (s, 3H), 3.37-3.31 (m, 1H), 3.08 (dd, $J = 16.5, 9.8$ Hz, 1H); MS (ES-) for $\text{C}_{12}\text{H}_{12}\text{BrO}_7\text{S}$ $[\text{M} - \text{H}]^-$: $m/z = 379 / 381$.

Compound **6d**. ^1H NMR (500 MHz, CD_3OD): δ 7.98 (brs, 1H), 7.62-7.58 (m, 2H), 7.29 (dd, $J = 7.8, 1.5$ Hz, 1H), 5.12 (dd, $J = 10.1, 4.9$ Hz, 1H), 4.56 (s, 2H), 3.58 (s, 3H), 3.32 (dd, $J = 16.1, 4.9$ Hz, 1H), 3.03 (dd, $J = 16.1, 10.1$ Hz, 1H); MS for $\text{C}_{11}\text{H}_{14}\text{BrO}_6\text{S}$ $[\text{M} + \text{H}]^+$: $m/z = 353 / 355$.

Compound **6f**. ^1H NMR (400 MHz, CD_3OD): δ 7.47-7.43 (m, 2H), 7.31-7.24 (m, 3H), 4.41 (dd, $J = 10.9, 4.6$ Hz, 1H), 3.27 (dd, $J = 14.7, 4.6$ Hz, 1H), 3.05 (dd, $J = 14.7, 10.9$ Hz, 1H); MS for $\text{C}_9\text{H}_{10}\text{NO}_4\text{S}$ $[\text{M} + \text{H}]^+$: $m/z = 228$.

Compound **6g**. ^1H NMR (300 MHz, CD_3OD): δ 4.11 (q, $J = 7.2$ Hz, 2H), 2.72 (s, 2H), 1.41 (s, 6H), 1.24 (t, $J = 7.2$ Hz, 3H); MS for $\text{C}_7\text{H}_{15}\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$: $m/z = 211$.

Compound **6h**. ^1H NMR (300 MHz, CD_3OD): δ 6.31 (s, 1H), 5.24 (s, 2H), 4.80 (s, 2H); MS for $\text{C}_4\text{H}_7\text{O}_6\text{S}$ $[\text{M} + \text{H}]^+$: $m/z = 183$.

Compound **6i**. ^1H NMR (500 MHz, CD_3OD): δ 7.29-7.25 (m, 5H), 3.95 (q, $J = 6.9$ Hz, 2H), 3.61-3.58 (m, 1H), 3.48 (dd, $J = 13.5, 3.8$ Hz, 1H), 2.85 (dd, $J = 16.2, 6.8$ Hz, 1H), 2.71 (dd, $J = 15.2, 11.6$ Hz, 1H), 2.40 (dd, $J = 16.2, 5.8$ Hz, 1H), 1.13 (t, $J = 6.9$ Hz, 3H); MS for $\text{C}_{12}\text{H}_{17}\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$: $m/z = 273$.

Compound **6j**. ^1H NMR (400 MHz, CD_3OD): δ 7.92 (d, $J = 8.2$ Hz, 2H), 7.38 (d, $J = 8.2$ Hz, 2H), 3.88 (s, 3H), 3.84 (q, $J = 7.0$ Hz, 2H), 3.56-3.48 (m, 2H), 2.87-2.77 (m, 2H), 2.41 (dd, $J = 16.2, 5.9$ Hz, 1H), 1.10 (t, $J = 7.0$ Hz, 3H); MS for $\text{C}_{14}\text{H}_{18}\text{O}_7\text{S}$ $[\text{M} + \text{H}]^+$: $m/z = 331$.

Compound **6k**. ^1H NMR (300 MHz, CD_3OD): δ 7.94 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 3.88 (s, 3H), 3.13-3.08 (m, 4H); ^1H NMR (300 MHz, $\text{d}_6\text{-DMSO}$): δ 7.83 (dd, $J = 8.4, 1.7$ Hz, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 3.81 (s, 3H), 2.96-2.91 (m, 2H), 2.69-2.66 (m, 2H); MS for $\text{C}_{10}\text{H}_{13}\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$: $m/z = 245$.

Compound **6l**. ^1H NMR (300 MHz, CD_3OD): δ 7.71 (dd, J = 6.4, 1.8 Hz, 2H), 7.43 (d, J = 6.4 Hz, 2H), 2.97-2.92 (m, 2H), 2.72-2.68 (m, 2H); MS for $\text{C}_9\text{H}_{10}\text{NO}_3\text{S}$ $[\text{M} + \text{H}]^+$: m/z = 212.

General procedure for the preparation of isothiazolidinone (IZD) adducts: To a solution of sulfonic acid **6a-6d**, **6i-6j** (0.5 mmol) in methylene chloride (2.0 mL) was added phosphorus pentachloride (208 mg, 1.0 mmol). The solution was stirred at rt for 16 h. To the solution at 0 °C was added aqueous ammonium hydroxide solution (2.0 mL) over 15 minutes. The reaction was diluted with methylene chloride (10 mL) and water (10 mL) and the organic layer separated. The aqueous layer was extracted with methylene chloride (10 mL) and the combined organic layer was dried over sodium sulfate and concentrated. The residue was dissolved in methanol (2.00 mL) and sodium methoxide in methanol (25% wt. sol., 0.2 mL) was added. After 1 h of stirring at rt the reaction mixture was purified by direct injection on preparative LCMS to afford the desired products **7a-7d**, **7i-7j** as white solids.

Compound **7a**. ^1H NMR (500 MHz, CD_3OD): δ 7.52-7.49 (m, 2H), 7.48-7.45 (m, 3H), 5.14 (t, J = 9.4 Hz, 1H), 3.58-3.44 (m, 2H); MS (ES-) for $\text{C}_9\text{H}_8\text{NO}_3\text{S}$ $[\text{M} - \text{H}]^-$: m/z = 210.

Compound **7c**. ^1H NMR (400 MHz, CD_3OD): δ 8.08 (dd, J = 6.6, 1.8 Hz, 2H), 7.62 (dd, J = 6.6, 1.8 Hz, 2H), 5.21 (t, J = 8.6 Hz, 1H), 3.91 (s, 3H), 3.36-3.30 (m, 2H); MS for $\text{C}_{11}\text{H}_{11}\text{NO}_5\text{S}$ $[\text{M} + \text{H}]^+$: m/z = 270.

Compound **7d**. ^1H NMR (400 MHz, CD_3OD): δ 8.30 (d, $J = 1.6$ Hz, 1H), 8.07 (dd, $J = 8.1, 1.6$ Hz, 1H), 7.67 (d, $J = 8.1$, 1H), 5.71 (dd, $J = 8.3, 6.8$ Hz, 1H), 3.93 (s, 3H), 3.50 (dd, $J = 17.6, 8.3$ Hz, 1H), 3.29 (dd, $J = 17.5, 6.8$ Hz, 1H); MS (ES $^-$) for $\text{C}_{11}\text{H}_{11}\text{BrO}_5\text{NaS}$ [$\text{M} + \text{Na}$] $^+$: $m/z = 370 / 372$.

Compound **7e**. ^1H NMR (400 MHz, CD_3OD): δ 7.73 (d, $J = 1.8$ Hz, 1H), 7.55 (d, $J = 8.2$ Hz, 1H), 7.46 (dd, $J = 8.2, 1.8$ Hz, 1H), 5.66 (dd, $J = 8.2, 7.0$ Hz, 1H), 5.11 (s, 2H), 3.47 (dd, $J = 17.5, 8.2$ Hz, 1H), 3.27 (dd, $J = 17.5, 7.0$ Hz, 1H), 2.11 (s, 3H); MS (ES $^-$) for $\text{C}_{12}\text{H}_{11}\text{BrO}_5\text{S}$ [$\text{M} - \text{H}$] $^-$: $m/z = 360 / 362$.

Compound **7i**. ^1H NMR (500 MHz, CD_3OD): δ 7.35-7.33 (m, 4H), 7.29-7.27 (m, 1H), 4.19-4.14 (m, 1H), 3.39-3.35 (m, 1H), 3.03-2.95 (m, 1H), 2.79 (dd, $J = 17.4, 8.3$ Hz, 1H); MS (ES $^-$) for $\text{C}_{10}\text{H}_{10}\text{NO}_3\text{S}$ [$\text{M} - \text{H}$] $^-$: $m/z = 225$

Compound **7j**. ^1H NMR (400 MHz, CD_3OD): δ 7.98 (d, $J = 8.5$ Hz, 2H), 7.46 (d, $J = 8.5$ Hz, 2H), 4.23-4.18 (m, 1H), 4.20 (s, 3H), 3.42-3.35 (m, 1H), 3.11-3.07 (m, 1H), 2.99 (dd, $J = 17.2, 8.3$ Hz, 1H), 2.79 (dd, $J = 17.2, 8.4$ Hz, 1H); MS (ES $^-$) for $\text{C}_{12}\text{H}_{12}\text{NO}_5\text{S}$ [$\text{M} - \text{H}$] $^-$: $m/z = 282$