Peptoids on Steroids: Precise Multivalent Estradiol-Peptidomimetic Conjugates Generated via Azide-Alkyne [3+2] Cycloaddition Reactions

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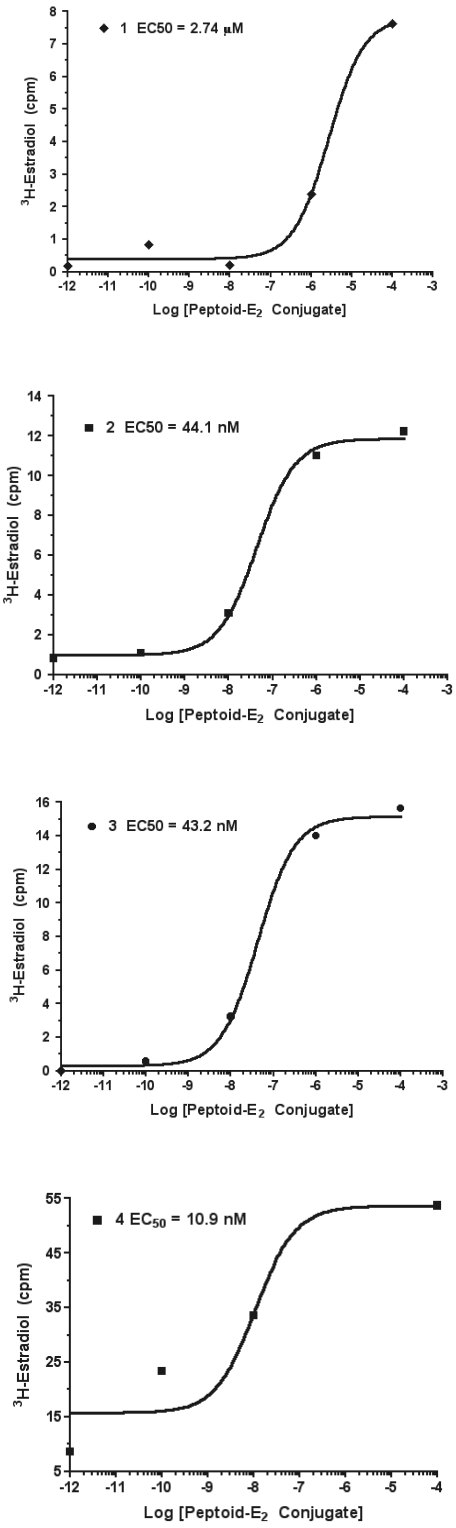
Supplemental Information

Synthesis of Ethisterone-Peptidomimetic Conjugates: Using a modification of previously described solid-phase peptoid synthesis procedures[1], peptoid scaffolds containing one, two or three site-specifically positioned azidopropyl sidechains were synthesized with high efficiency. Following characterization of the linear peptoid scaffolds, resin-bound oligomers were taken up in 20 ml 2-butanol:DMF:pyridine (5:3:2 v/v/v) and reacted with Ethisterone (Sigma), CuI, ascorbic acid and *N,N*-diisopropylethylamine (DIPEA) in a 20 ml scintillation vial (see Table **S1** for reactant concentrations). The vessel was purged with gaseous nitrogen, tightly capped, sealed with paraffin film and shaken at 45 deg C for 18 hrs. Following completion of the reaction, the resin was washed with DMF (7 x 3 mL), Cu scavenger cocktail (DMF/pyridine 6/5 v/v, ascorbic acid 0.02 g mL^{-1}) (7 x 3 mL) and DCM (7 x 3 mL). The resin was then dried under nitrogen gas flow and approximately 3 mg resin was removed for characterization. Mass data: Compound **5**, calc. 700.88, obs. 700.30; Compound **6**, calc. 1382.73, obs. 1382.61; Compound **7**, calc. 2065.58, obs. 2065.88.

Entry	Compound	Valency (n)	[Ethist.][a]	[CuI]	[AA][b]	[DIPEA]	Purity[c]
1	**5**	1	0.05 M	0.10 M	0.05 M	0.12 M	81%
2	**6**	2	0.125 M	0.24 M	0.125 M	0.30 M	35%
3	**7**	3	0.15 M	0.29 M	0.15 M	0.36 M	30%

Table S1. Reactant concentrations for Ethisterone-Peptidomimetic Conjugate synthesis. [a] Ethisterone. [b] Ascorbic acid. [c] Crude purity as determined by RP-HPLC product peak integration monitored at λ = 214 nm.

Figure S1. Binding curves of estradiol-peptidomimetic conjugates. Binding curves are representative of three separate competitive binding assays performed on MCF-7 whole cell lysate.



References

1. R. N. Zuckermann, J. M. Kerr, S. B. H. Kent, W. H. Moos. *J. Am. Chem. Soc.,* **1992**, *114,* 10646.