An Alkyne Linchpin Strategy for Drug: Pharmacophore Conjugation: Experimental and Computational Realization of a meta-selective Inverse Sonogashira Coupling[1]

The late-stage functionalization (LSF) of pharmaceutical and agrochemical compounds by the site-selective activation of C−H bonds provides access to diverse structural analogs and expands synthetically-accessible chemical space.[2] In this work, we have reported a C−H functionalization LSF strategy that hinges on the use of an alkyne linchpin to assemble conjugates of sp^2 -rich marketed pharmaceuticals and agrochemicals with sp^3 -rich 3D fragments and natural products. This is accomplished through a template-assisted inverse Sonogashira reaction that displays high levels of selectivity for the *meta*-position. This protocol is also amenable to distal structural modifications of α-amino acids. The transformation of alkyne functionality to other functional groups further highlights the applicative potential. Computational and experimental mechanistic studies shed light on the detailed mechanism. It was found that a heterobimetallic Pd−Ag transition structure is essential for product formation in the β-bromide elimination step.

The protocols' robustness was demonstrated using phenyl acetic acids and benzyl silyl ethers as substrates. In all cases, a range of substituents with varying electronic and steric properties was compatible. Androstanediol, a potent GABAA receptor, could also be conjugated selectively at the *meta* position regardless of the steric hindrance exerted by the bulky steroid. The (protected) diol product contains the ethynylandrostane diol fragment, an orally active analogue of 17-substituted androstanediol used to treat cancer. Pharmaceutical and agrochemical LSF was then examined using this newly developed protocol. To this aim, marketed nonsteroidal anti-inflammatory drugs such as ketoprofen, ibuprofen, naproxen, and baclophen were transformed to their meta-alkynylated derivatives in excellent selectivity with triisopropylsilyl acetylene bromide. Phenoxy-based agrochemicals and drugs such as dichlorprop (herbicide) clofibric acid (lipid lowering agent), and MCPA (herbicide) were similarly functionalized. Further structural diversification of marketed sp^2 -rich aromatic drugs was achieved through conjugation with sp^3 - rich 3D fragments. Both ketoprofen and ibuprofen afforded *meta* products conjugated with menthol in excellent yields and *meta* selectivity. Ethinylestradiol, an orally active derivative of estradiol used as estrogen medication, could selectively be introduced to the meta position of ketoprofen in a preparatively useful yield. The conjugation with aliphatic fragments provides access to an expanded chemical space, escaping the "flatland" of aromatic drugs. In principle, this approach could be used to modulate the bioactivity of either parent molecule.

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3. Imine as a linchpin approach for meta-C–H functionalization. Bag, S.; Jana, S.; Pradhan, S.; Bhowmick, S.; Goswami, N.; Sinha, S. K.; **Maiti, D**. *Nat. Commun*. **2021**, *12*, 1393.

This research work under reference has not been given any award in the past.

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