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Dithiol-Activated Bioorthogonal Chemistry for Endoplasmic Reticulum-Targeted Synergistic Chemophototherapy
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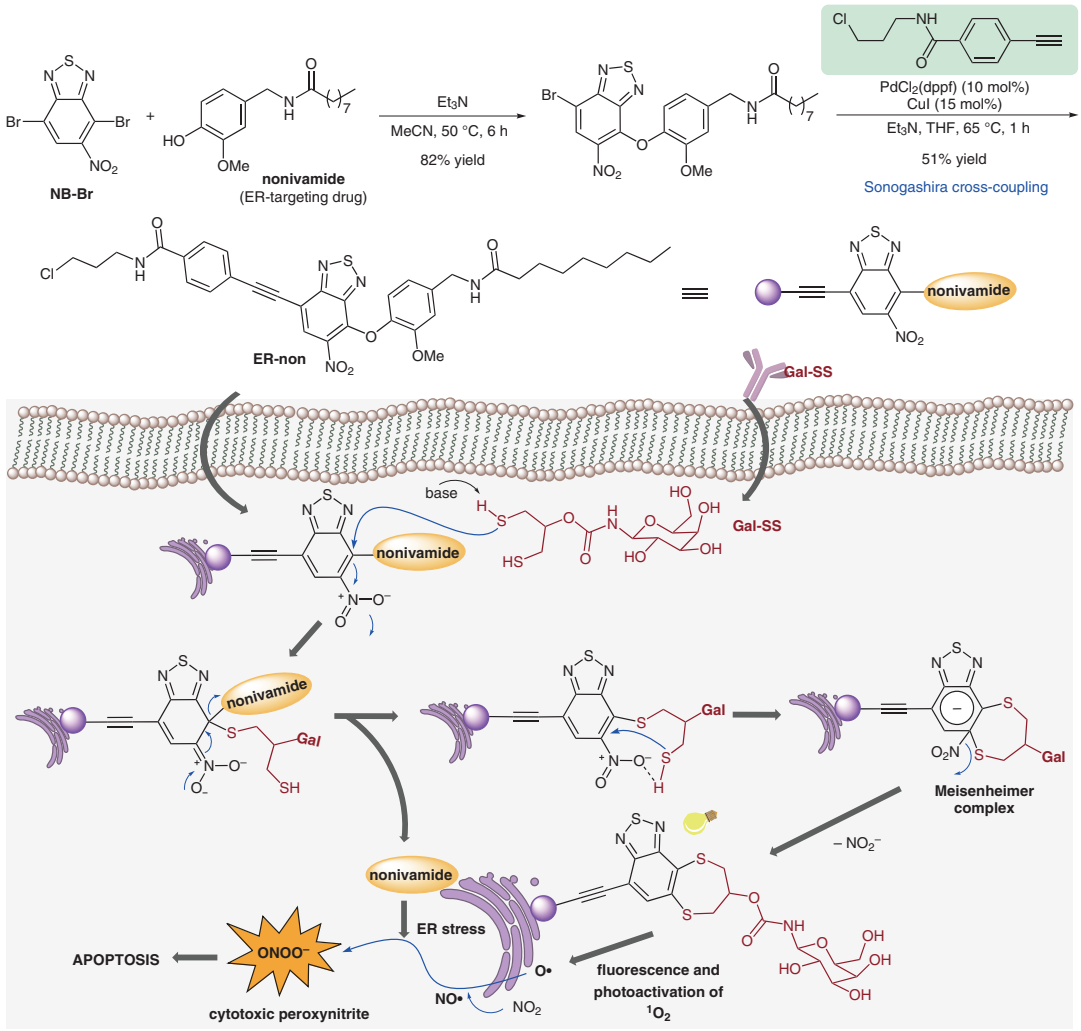
"Click-to-Release" Biorthogonal Chemophototherapy



Significance: Intracellular nitrite release from organic nitrite donors is an emerging approach for inducing apoptosis via reactive nitrogen species (RNS) formation. RNS are known to form cytotoxic peroxynitrite ($OONO^-$) by reacting with intracellular ROS. Here, the authors present a synergistic biorthogonal approach using 5-nitro benzothiadiazole (BTD) as the nitrite donor tethered to the endoplasmic reticulum (ER)-targeting drug nonivamide.

Comment: This biorthogonal 'click-to-release' approach involves an S_NAr reaction by a thiol group of the dithiol **Gal-SS** to release nonivamide, which causes ER stress. Another subsequent S_NAr releases the nitrite through a stabilized Meisenheimer complex, which unmasks the fluorescence of BTD. Upon irradiation, BTD sensitizes singlet oxygen to generate ROS and synergistically causes apoptosis in liver cancer cells (HepG2).

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Synfact of the Month

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