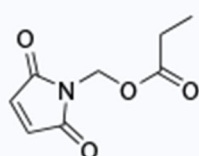


**Building Blocks / Pharmaceutical Intermediates / Catalysts & Ligands**

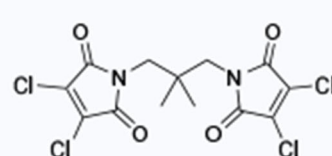
www.ChemScene.com



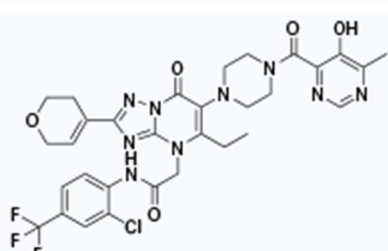
Werner syndrome helicase (WRN) is a member of the RecQ DNA helicase subfamily<sup>[1]</sup>. RecQ helicases are involved in multiple DNA processing steps including DNA replication, double-strand break repair, transcription and telomere maintenance and are therefore considered to serve as 'genome caretakers'. Recent studies have shown that WRN helicase is a synthetic lethal target for cancer cells with microsatellite instability (MSI), a form of genetic hypermutability that arises from impaired mismatch repair. MSI is associated with a high mutational load and occurs in more than 20 tumours types and is frequent in colon, ovarian, endometrial and gastric cancers. Depletion of WRN induces widespread DNA double-strand breaks in MSI cells, leading to cell cycle arrest and/or apoptosis. Thus, inhibiting the WRN helicase is an attractive strategy for the treatment of mismatch repair defective cancers. To date, no WRN inhibitors have entered clinical trials, and most of them are in the preclinical and drug discovery stages<sup>[2-8]</sup>.



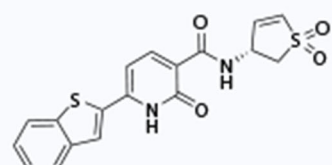
**NSC 19630**  
WRN inhibitor



**NSC 617145**  
WRN inhibitor



**Example 42 (WO2022249060A1)**  
WRN inhibitor



**Example 46 (WO2023062575A1)**  
WRN inhibitor

A series of building blocks will be used as molecular fragments in the design of WRN inhibitors.

[1] Cancer Discovery (2021), 11, 8, 1923–1937.

[2] Nature (2019), 568, 511–516.

[3] Nature (2019), 568, 551–556.

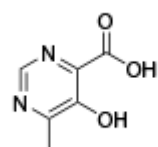
[4] Nature (2020), 586, 292–298.

[5] iScience (2019), 13, 488–497.

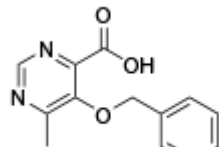
[6] WO2019241802A2.

[7] WO2022249060A1.

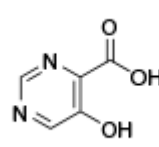
[8] WO2023062575A1.



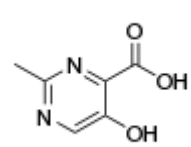
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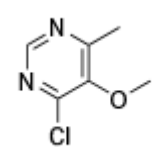
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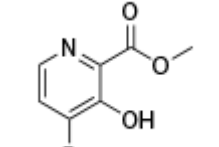
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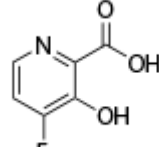
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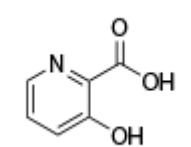
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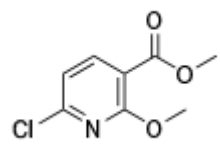
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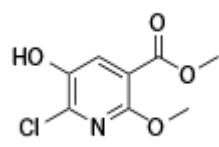
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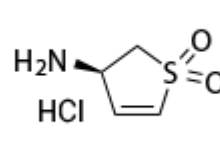
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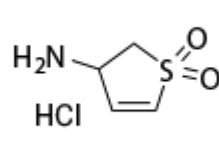
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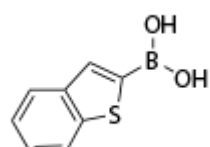
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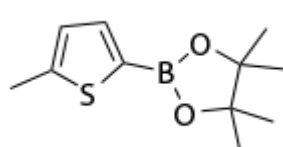
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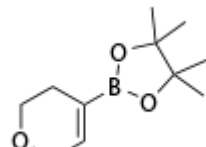
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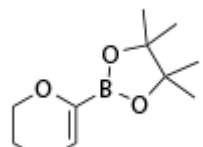
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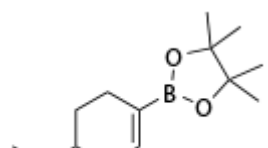
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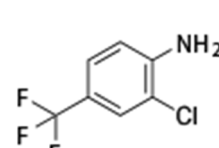
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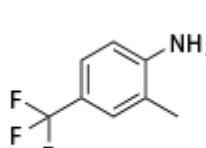
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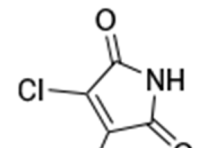
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