Category

Innovative Drug Discovery and Development

Key words

SHP2 inhibitor
GDC-1971
allosteric inhibitor
solid tumors
clinical candidate
pyrazolopyrazine

Synfact of the Month

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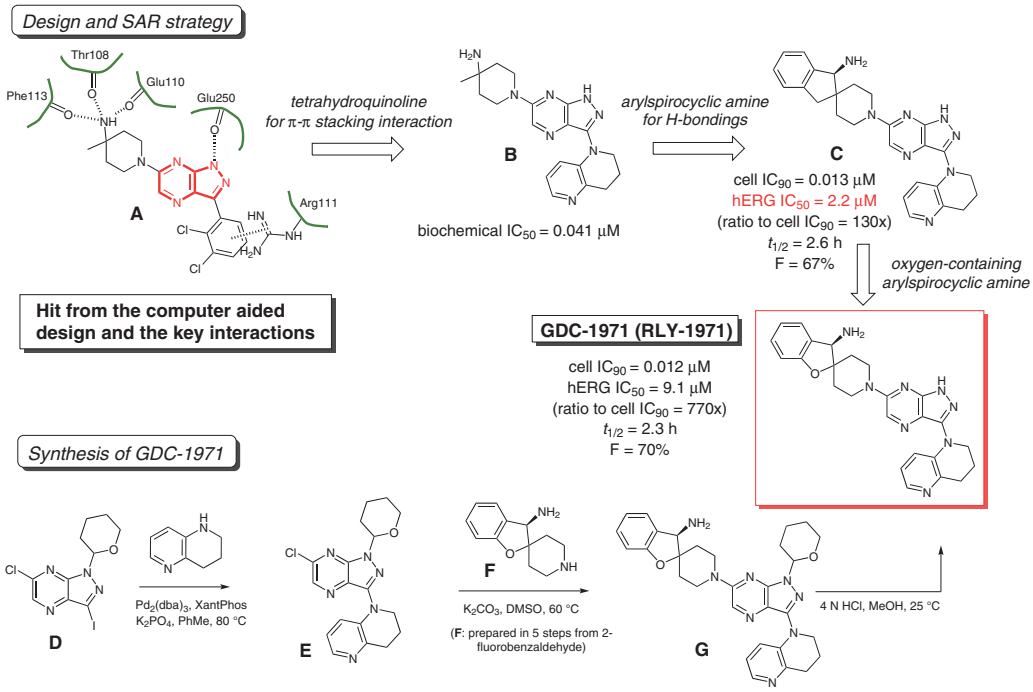
Identification of GDC-1971 (RLY-1971), a SHP2 Inhibitor Designed for the Treatment of Solid Tumors
J. Med. Chem. **2023**, *66*, 13384–13399, DOI: 10.1021/acs.jmedchem.3c00483.

Discovery of SHP2 Inhibitor GDC-1971 (RLY-1971) Containing a Pyrazolopyrazine Core



Significance: SHP2 is a non-receptor protein tyrosine phosphatase and plays an important role in the regulation of multiple signaling cascades, including RAS/MAPK, PI3K/AKT and JAK/STAT pathways. Due to the genetic alterations, SHP2 has been identified in many human cancers. Significant efforts have therefore been made to identify therapeutic molecules with drug-like property for oral delivery leading to the discovery of allosteric inhibitor, **GDC-1971** (RLY-1971). **GDC-1971** is currently undergoing clinical evaluation in metastatic solid tumors in combination with divarasib, a KRAS G12C inhibitor.

Comment: The starting point, compound **A**, was designed by computational methods from the original hit **SHP099** (not shown). Based on the analysis of key binding interactions, a pyrazolopyrazine core was designed and found to be moderately active. The strategy for SAR exploration around the pyazolopyrazine core aimed at improving cellular potency, reducing hERG activity, and optimizing half-life. Through the SAR studies, the tetrahydronaphthyridine motif was identified for π-π interaction with Arg111 (**B**). Further investigation on the H-bonding prone amine moiety led to the spirocyclic derivative **C** with moderate hERG liability. The addition of an oxygen atom to the spirocyclic amine successfully improved the hERG profile to identify **GDC-1971** (RLY-1971). The synthesis of **GDC-1971** began with the key intermediate **D** followed by Pd-catalysed coupling, aromatic substitution, and deprotection.

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Synfacts 2024, 20(01), 0092 Published online: 08.12.2023
DOI: 10.1055/s-0043-1763634; **Reg-No.:** A00424SF