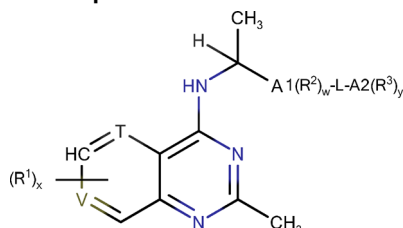


Novel Methyl-aza-quinazolines as Inhibitors of the RAS-SOS Interaction

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Important Compound Classes.



Title. 2-METHYL-AZA-QUINAZOLINES

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Disease Area. Cancer, hyperproliferative diseases

Biological Target. RAS

Summary. The present application describes 2-methyl-aza-quinazoline derivatives as effective and selective inhibitors of the RAS–SOS interaction. This class of compounds is claimed

to not significantly target the EGFR receptor. The RAS–SOS inhibitors described in this application are potentially useful in the treatment of hyperproliferative disorders and in particular cancer.

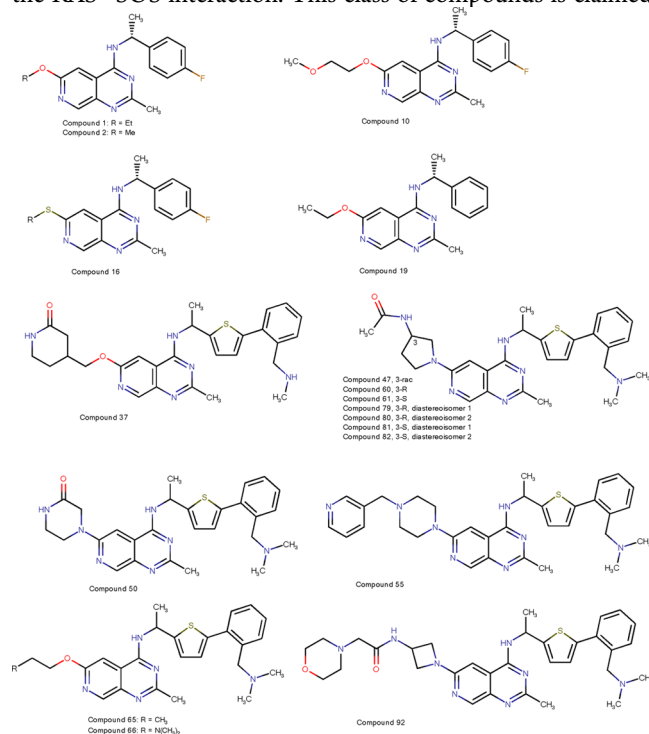
Key Structures.

Biological Assay. K-Ras is a small GTPase that can bind GDP and GTP. SOS1 is a nucleotide exchange factor that binds to K-Ras-GDP and catalyzes the activation of K-Ras by promoting opening the GDP-binding pocket to facilitate the exchange of GDP to GTP. Rebinding of excess nucleotide leads to dissociation of the K-Ras-SOS1. The compounds described here were characterized in a series of biochemical assays

Assay 1: The equilibrium interaction of human SOS1 (hSOS1) with human KRasG12C (hK-RasG12C) was measured using HTRF. **Assay 2:** The activation assay of hK-RasG12C by hSOS1 at high GTP concentration was used to quantify human SOS1-mediated nucleotide exchange of human K-RasG12C (hKRasG1). **Assay 3:** This assay was used to quantify hSOS1-mediated loading of human K-RasG12C-GDP with a fluorescent GTP-analog. **Assay 4:** The phosphorylation of EGFR (in-cell Western) was measured in Hela Cells.

Biological Data.

Compound	Assay 1 IC ₅₀ , μM	Assay 2 IC ₅₀ , μM	Assay 3 IC ₅₀ , μM	EGFR IC ₅₀ , μM
1	1.07	9.30	6.36	>20
2	2.46	2.51	>20	>20
10	1.14	0.934	8.35	>20
16	0.93	0.901	4.34	>20
19	2.06	-	12.5	>20
37	0.090	0.130	0.109	>20
47	0.023	0.036	0.036	>20
50	0.028	0.048	0.054	>20
55	0.044	0.085	0.072	>20
60	0.028	0.023	0.039	>20
61	0.036	0.021	0.040	>20
65	0.042	0.038	0.055	>20
66	0.030	0.027	0.043	>20
79	0.021	0.015	0.024	>20
80	2.820	1.250	1.850	>20
81	0.026	0.035	0.031	>20
82	0.543	0.615	0.594	>20
92	0.045	0.116	0.155	>20



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Notes: One-hundred (100) examples are provided. The Complex formation and Crystallization of hSOS1_12 and Example 81 are described.

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Notes

The author declares no competing financial interest.