SOS1 Activator | VUBI1

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Summary

VUBI1 is a very potent Son of Sevenless homologue 1 (SOS1) agonist, which acts as a biological control protein for the KRAS pathway. Previously reported as compound **64**, it binds directly to SOS1 with low double-digit nanomolar affinity. VUBI1, along with its control BI9930, offers a unique ability to activate the SOS1/KRAS axis in a controlled, reversible fashion, enabling new ways to study cellular signaling networks.

Chemical Structure

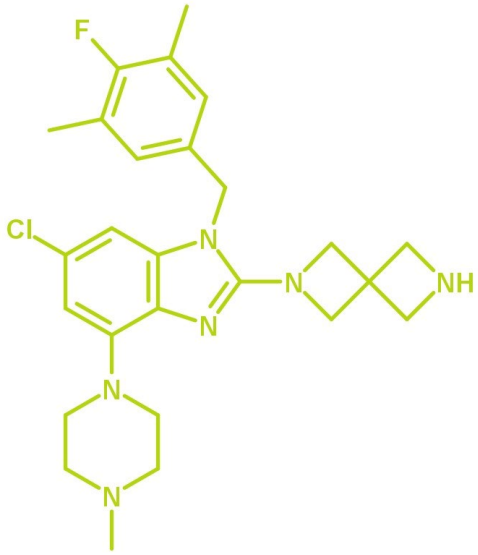

Figure 1: 2-D structure of VUBI1 a SOS1 activator

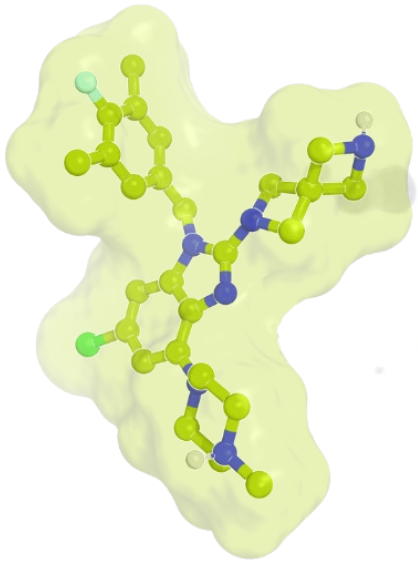

Figure 2: VUBI1, 3D conformation

Highlights

VUBI1 is a potent activator of SOS1 with unique effects on the KRAS pathway. Son of Sevenless homologue 1 (SOS1) is a guanine exchange factor that acts as biological control protein for KRAS, one of the most important cellular signaling nodes. VUBI1, previously reported as compound **64**,[1] is a first-in-class compound that binds directly to SOS1 and agonizes its activity. BI-9930 is provided as a negative control.

Target information

Aberrant activation of Kirsten rat sarcoma viral oncogene homolog (KRAS) by deregulated upstream signaling, loss of GTPase-activating protein function, or oncogenic mutations results in increased GTP-bound KRAS and persistent signaling through downstream effector pathways in cancer.[2,3] KRAS is the most frequently mutated oncogene in three of the deadliest cancers, as it occurs in approximately 90% of pancreatic cancer, 40% of colorectal cancer and 20% of non-small cell lung cancer cases (Data from cBioPortal TCGA Provisional accessed 2017-10-19).

RAS family small GTP/GDP binding proteins, such as KRAS, have a weak intrinsic GTPase activity and slow nucleotide exchange rates. Two classes of enzymes have evolved to facilitate cycling between the active GTP-bound state and the inactive GDP-bound form. GTPase Activating Proteins (GAPs) increase the intrinsic GTPase activity of RAS family proteins, leading to the formation of GDP bound RAS (e.g. NF1), whereas guanine nucleotide exchange factors (GEFs), such as Son of Sevenless 1 (SOS1), directly interact with KRAS and release GDP, enabling GTP binding and re-activation. Cancer-associated mutations in KRAS further suppress the intrinsic and GAP-induced GTPase activity leading to an increased population of signaling competent GTP loaded KRAS molecules.[3-6]

VUBI1 is a first in class potent activator of SOS1. This agonism leads directly to a rapid and dose-responsive increase in GDP-to-GTP nucleotide exchange on KRAS, which leads to higher levels of activated KRAS in cells.[7] However, due to the presence of intracellular feedback mechanisms,[8] a biphasic effect resulting in lower levels of activated ERK downstream of KRAS at higher doses of VUBI1 is observed. Further, decreases in phospho-AKT levels are seen.[9] This compound, along with its control, offers a unique ability to activate the SOS1/KRAS axis in a controlled, reversible fashion, enabling new ways to study cellular signaling networks.

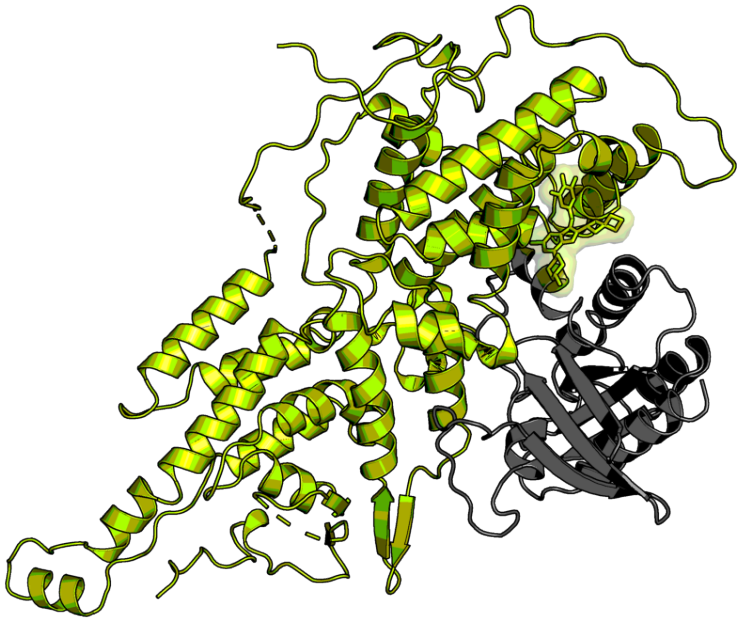

Figure 3: Xray crystal structure of a complex including HRAS, SOS1, and VUBI1 (PDB code: 6D55)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	VUBI1	BI-9930
MW [Da]	483.0	483.0
SOS1 Fluorescence Polarization Anisotropy (FPA) competition binding assay (K_i) [nM][a]	44	> 5000
HRAS Nucleotide Exchange (EC_{50}) [nM][a]	94	n.d.
p-ERK In Cell Western, HeLa cells (EC_{50}) [nM][a]	5900	n.d.
p-ERK In Cell Western, H727 cells (EC_{50}) [nM][a]	10,000	n.d.

[a] assay conditions described in Hodges, Fesik et. al. *J. Medicinal Chemistry* (2018) *61*, 8875-8894

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	VUBI1	BI-9930
logP logD (@ph2, 11)	n.d. 0.56, 5.10	n.d. -0.33, 3.71
Solubility @ pH 6.8 [µg/ml]	>110	tbd
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	1.8	1.0
CACO efflux ratio	17.1	33
Microsomal stability (human/mouse/rat) [% Q_H]	<24/<24/<23	33/<23/39
Hepatocyte stability (human/mouse/rat) [% Q_H]	16/15/24	8/33/6
Plasma protein binding (human/mouse/rat) [%]	99.7/>99.8/>99.8	99.5/98.3/98.3
hERG [inh. % @ 10 µM, 1µM]	42.6, 7.1	38.2, 5
hERG [IC_{50} (µM)]	>10	12.9
CYP 3A4 (IC_{50}) [µM]	7.3	0.9
CYP 2C8 (IC_{50}) [µM]	15.3	28.1
CYP 2C9 (IC_{50}) [µM]	8.1	41.5
CYP 2C19 (IC_{50}) [µM]	>50	>50
CYP 2D6 (IC_{50}) [µM]	>50	>50

Negative control

BI-9930 is a regioisomer of VUBI1 which is inactive against SOS1 and therefore can be used as negative control.

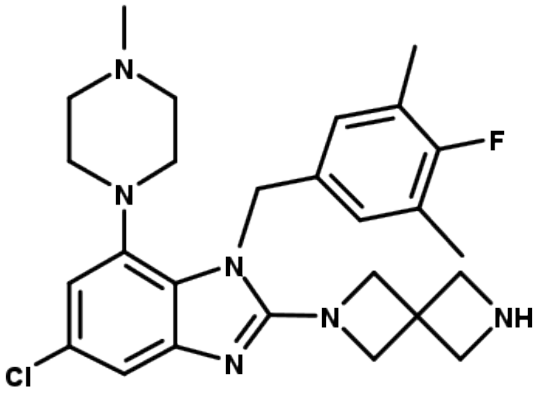

Figure 4: BI-9930 which serves as a negative control

Selectivity

SELECTIVITY DATA AVAILABLE	VUBI1	BI-9930
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Co-crystal structure of the Boehringer Ingelheim probe compound and the target protein.

The Xray crystal structure of a complex including HRAS, SOS1, and VUBI1 is available (PDB code: 6D55)[1].

Supplementary data

2-D structure files can be downloaded free of charge from opnMe.

References

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Additional chemical templates that lead to SOS1 agonism have also been reported:

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