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Original Research Article

A New Survey on SOS1 Inhibitors as Promising Therapeutic Molecules

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ABSTRACT

SOS1 (Son of Sevenless 1) is a guanine nucleotide exchange factor that plays a crucial role in the activation of the RAS signaling pathway, making it a significant target for therapeutic intervention in various cancers. Recent developments in the field of medicinal chemistry have led to the identification and optimization of SOS1 inhibitors, which exhibit diverse chemical structures that impact their biological activity. This abstract discusses the chemical scaffolds of SOS1 inhibitors, highlighting key structural features that contribute to their potency and selectivity. Structure-activity relationship (SAR) studies reveal that modifications in functional groups, ring systems, and stereochemistry can significantly influence the binding affinity to the SOS1 protein and downstream effects on RAS activation. By analyzing various classes of SOS1 inhibitors, including small molecules and peptidomimetics, this work elucidates the interplay between chemical structure and biological function. The findings underscore the importance of rational design in the development of effective SOS1 inhibitors, paving the way for novel therapeutic strategies against RAS-driven malignancies.

Keywords: SOS1, Enzyme inhibitors, Docking, Structure-activity relationship

Introduction

SOS1 (Son of Sevenless Homolog 1) is a guanine nucleotide exchange factor (GEF) that plays a crucial role in cellular signaling pathways [1]. It is a key regulator of the RAS signaling pathway,

which is involved in cell proliferation, survival, and differentiation. SOS1 facilitates the activation of RAS proteins by catalyzing the exchange of GDP (guanosine diphosphate) for GTP (guanosine triphosphate) on RAS [2]. Once activated, RAS triggers downstream signaling cascades, including the MAPK/ERK and PI3K/AKT pathways, which are critical for normal cell functions and cancer development [3]. Dysregulation of SOS1 or RAS signaling is implicated in many cancers, as RAS mutations are some of the most common oncogenic drivers. Even in cancers without direct RAS mutations, SOS1 can amplify aberrant signaling, making it a therapeutic target [4]. SOS1 inhibitors are designed to block the interaction between SOS1 and RAS, thereby preventing RAS activation. These inhibitors have the potential to disrupt downstream oncogenic signaling and are being explored in preclinical and clinical studies [5].

Crystal Structure of SOS1

The structure of SOS1 is complex and designed to regulate its function as a GEF for RAS [6]. SOS1's structure enables it to interact with various components in the cell to activate RAS, thereby triggering downstream signaling pathways that affect cell growth, differentiation, and survival [7]. The full-length SOS1 protein consists of several distinct domains that work together to facilitate its function. The N-terminal region (proline-rich domain) of SOS1 is rich in proline residues and is responsible for interacting with adaptor proteins such as GRB2 (Growth Factor Receptor-Bound Protein 2) [8]. The SH3 domains of GRB2 bind to the proline-rich region of SOS1, which brings SOS1 to the membrane, specifically to the site where RAS is localized (the inner side of the plasma membrane). This membrane association is important for SOS1 to efficiently activate RAS [9]. The DH domain is a conserved domain found in GEFs like SOS1 and is typically around 200 amino acids in length. The DH domain is responsible for the

exchange of GDP for GTP on RAS. It binds to the RAS protein in its inactive GDP-bound state and facilitates the release of GDP, allowing GTP to bind in its place, thereby activating RAS.The DH domain interacts with RAS in a highly specific manner, inducing a conformational change in RAS that enables it to bind GTP. This is a crucial step in the activation of the RAS signaling pathway [10].

The Pleckstrin Homology PH domain is adjacent to the DH domain and is typically around 100 amino acids in length.The PH domain is involved in membrane localization by binding phosphoinositides, particularly PIP2 (phosphatidylinositol 4,5-bisphosphate), found on the inner membrane of the plasma membrane[11]. This interaction helps anchor SOS1 to the membrane, positioning it in close proximity to RAS, thereby facilitating efficient RAS activation. The PH domain facilitates SOS1's binding to membrane lipids (especially PIP2), which helps bring it to the plasma membrane where RAS is localized. This membrane association is critical for the function of SOS1[11].

The C-terminal domain (Cdc25-like domain) of SOS1 shares structural similarities with the Cdc25 protein, a well-known GEF that activates RAS [12]. This domain may also contribute to the regulation and specificity of RAS activation by stabilizing SOS1 in its active conformation [13]. While not as functionally distinct as the DH and PH domains, the C-terminal region is involved in SOS1’s overall stability and interaction with other factors. As mentioned, SOS1 interacts with SH3 domain-containing proteins (like GRB2) via its proline-rich region [14]. These interactions help modulate SOS1's activation and recruitment to specific membrane regions in response to cellular signals [15].

Functionality of SOS1

SOS1's activity is tightly regulated by its conformation. In an inactive state, SOS1 is partially autoinhibited by interactions between its domains, particularly the DH and PH domains [16]. When SOS1 is recruited to the plasma membrane, the autoinhibition is relieved, and it becomes active. The functionality of SOS1 revolves around its role as a GEF for RAS, which is a small GTPase that regulates critical cellular processes such as proliferation, survival, differentiation, and migration. SOS1 is a key player in the RAS signaling pathway, and its primary function is to activate RAS by promoting the exchange of GDP (inactive form) for GTP (active form) on RAS [17].

The primary role of SOS1 is to activate RAS by catalyzing the exchange of GDP for GTP on RAS. In its inactive state, RAS is bound to GDP, but upon binding with SOS1, RAS undergoes a conformational change that allows GDP to dissociate and be replaced by GTP [18]. This transformation activates RAS, turning it into the GTP-bound form, which is essential for initiating downstream signaling pathways. SOS1's DH (Dbl-homology) domain is directly responsible for this nucleotide exchange [19]. It binds to RAS, facilitating the release of GDP, and the GTP binding is a spontaneous process once GDP is removed. Once activated, RAS-GTP interacts with a variety of downstream effectors, leading to the activation of key signaling pathways, such as MAPK/ERK, PI3K/AKT, and RalGEF pathways [20]. These pathways are crucial in cellular processes such as proliferation, survival, and differentiation, and their dysregulation is often associated with cancer and other diseases [21].

SOS1 is regulated through an autoinhibitory mechanism. In the absence of signaling, the protein exists in an inactive state, where interactions between its different domains (such as between the

DH and PH domains) block its ability to activate RAS. When cell surface receptors (such as receptor tyrosine kinases (RTKs)) are activated by external signals (like growth factors), they recruit GRB2 (an adaptor protein) to the membrane [22]. GRB2 binds to the proline-rich region of SOS1, relieving its autoinhibition and enabling SOS1 to activate RAS. GRB2 binds to the proline-rich region of SOS1 and helps recruit SOS1 to activated RTKs at the membrane [23]. The interaction between GRB2 and SOS1 is key to SOS1's role in signal transduction from cell surface receptors to intracellular signaling pathways. SOS1 also interacts with other scaffolding and regulatory proteins that help control its localization and activity, ensuring that it is only active when and where it is needed.

The Role of SOS1 in Pathophysiology of Cancer

Due to its critical role in activating RAS, SOS1 inhibitors are being investigated as potential therapeutic agents for cancers that are driven by RAS mutations or dysregulated RAS signaling [24]. By inhibiting SOS1, these therapies aim to block RAS activation and downstream oncogenic signaling. In response to signaling cues, SOS1 undergoes conformational changes that allow it to transition from an inactive, autoinhibited state to an active state [25]. When this occurs, the DH domain is exposed and capable of interacting with RAS, while the PH domain anchors SOS1 to the membrane. These structural changes are central to SOS1's functionality. The activity of SOS1 is spatially controlled, as it needs to be recruited to the plasma membrane where RAS is active. This spatial localization ensures that SOS1 activates RAS only in the appropriate cellular context.

Development of SOS1 Inhibitors as Potential Cancer Chemopreventive Agents

SOS1 inhibitors are a class of compounds designed to block the function of SOS1. By inhibiting SOS1, these compounds aim to disrupt the activation of RAS, thereby interfering with downstream signaling that contributes to oncogenesis, tumor progression, and therapeutic resistance. Mutations in RAS genes (HRAS, KRAS, and NRAS) are common in various cancers, making RAS signaling one of the most important targets in oncology. However, directly inhibiting RAS has proven difficult because RAS lacks suitable binding sites for small molecules. SOS1 is a key upstream regulator of RAS activation. It facilitates the exchange of GDP for GTP on RAS, which is the first step in RAS activation. Therefore, SOS1 inhibition offers an alternative strategy to block RAS signaling without directly targeting RAS itself, which is often mutated and hyperactive in cancers.

1. Chemical Classes of SOS1 Inhibitors

Several types of small molecule inhibitors have been developed to target SOS1 and inhibit its function. These inhibitors can be grouped into different chemical classes based on their structure and mode of action:

1.1. Peptoid and Peptide-based Inhibitors

These are peptide mimetics that have a backbone similar to peptides but with side chains attached to nitrogen rather than carbon. Some peptoids have been identified as inhibitors of SOS1 by blocking its interaction with RAS [26]. They often work by disrupting protein-protein interactions, preventing SOS1 from binding to RAS or other key regulatory proteins. Synthetic peptides that mimic portions of SOS1's structure can inhibit its function by preventing its

interaction with GRB2, a protein necessary for SOS1 recruitment to the plasma membrane. These peptides can disrupt the autoinhibition and activation of SOS1, thus blocking RAS activation.

Small Organic Compounds

These compounds typically consist of small organic molecules that can fit into the binding sites of SOS1, blocking its interaction with RAS or other proteins required for its activation. A class of small molecule inhibitors has been developed to target the DH domain of SOS1, which is responsible for the GDP-GTP exchange on RAS. These inhibitors typically bind to the active site of SOS1 and prevent it from interacting with RAS, effectively blocking RAS activation. Small organic molecules that target the PH domain of SOS1 can also disrupt its membrane localization. This prevents SOS1 from being recruited to the plasma membrane, where RAS activation occurs, thereby inhibiting the SOS1-RAS interaction.

Allosteric Inhibitors

Allosteric inhibitors are small molecules that bind to an allosteric site on SOS1, which is distinct from the active site involved in RAS activation. These inhibitors induce conformational changes that prevent SOS1 from adopting the necessary structure for RAS binding or membrane association. By binding to allosteric sites, these inhibitors can modulate the activity of SOS1 without directly competing for the active site. This can provide a more specific and reversible way to inhibit SOS1 compared to traditional active site-directed inhibitors [27].

Macrocyclic Compounds

Macrocyclic compounds are large, cyclic molecules that are designed to bind with high specificity to SOS1, often in a manner that mimics the interaction between SOS1 and other binding partners like GRB2 or RAS. These compounds can be highly selective, offering the advantage of targeted inhibition. They can inhibit SOS1 by blocking the protein-protein interactions necessary for its function, such as the interaction with GRB2 or the membrane-bound RAS [28].

Ras-SOS1 Interaction Disruptors

This class of inhibitors targets the interaction between SOS1 and RAS itself. By blocking the binding interface, these inhibitors prevent the activation of RAS through the exchange of GDP for GTP. The inhibitors either disrupt the RAS-binding site on SOS1 or interfere with the induced conformational changes that are required for RAS activation. The disruption of this critical interaction has the potential to attenuate oncogenic signaling driven by mutated RAS.

Strategies for Developing SOS1 Inhibitors

Screening for Inhibitors

High-throughput screening (HTS) techniques are used to identify small molecules that can bind to SOS1 and block its activity. These compounds can then be further optimized for higher specificity and efficacy.

Structure-Based Drug Design

X-ray crystallography and NMR spectroscopy can provide detailed structural information about SOS1's domains and its interactions with RAS. This structural data allows for structure-based

drug design, where potential inhibitors are designed to specifically block the RAS-binding domain or other key regions of SOS1.

Targeting Specific Domains

SOS1 contains multiple functional domains that interact with other proteins to regulate its activity. Targeting specific domains, such as the DH domain (responsible for RAS activation) or the PH domain (involved in membrane localization), provides a more targeted approach to inhibit SOS1's function.

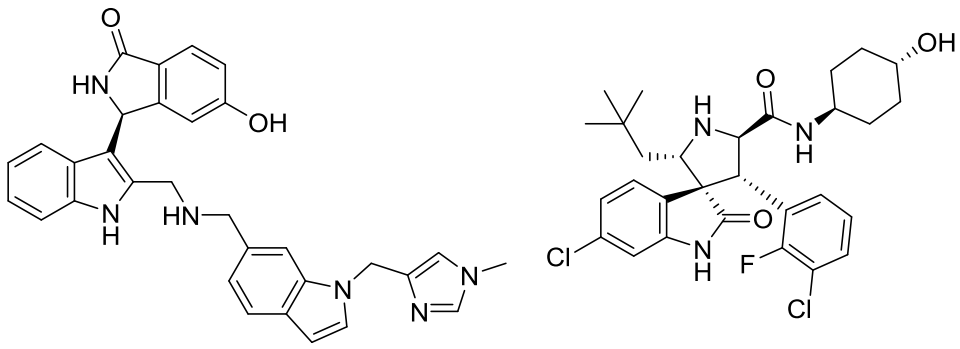
Challenges in Developing SOS1 Inhibitors

Since SOS1 shares structural similarities with other GEFs, it can be challenging to design inhibitors that specifically target SOS1 without affecting other GEFs. The requirement for SOS1 to localize to the plasma membrane complicates the design of inhibitors that can effectively prevent this process. In cancers with KRAS or NRAS mutations, which are often hyperactivated, directly inhibiting RAS can be difficult. Thus, SOS1 inhibitors offer a promising alternative, but finding compounds that are effective in the presence of mutant RAS remains a challenge. Just like with other targeted therapies, there is a risk of resistance developing over time, especially if cancer cells find alternative pathways to activate RAS signaling.

Current Status and Clinical Development

While SOS1 inhibitors are still in the early stages of development, preclinical studies have shown promise in using SOS1 inhibition to block RAS-driven cancers, especially in tumors where RAS mutations are involved. Some compounds have shown the ability to inhibit tumor growth and sensitize cancer cells to other therapies. Some early-phase clinical trials have been

launched to test the safety and efficacy of SOS1 inhibitors in treating RAS-mutant cancers, but these agents are still under investigation. BI-2852 **(Fig. 1)** is one of the leading SOS1 inhibitors that has shown promise in preclinical studies. It works by binding to the SOS1-RAS interface, preventing RAS activation and thus inhibiting downstream oncogenic signaling[25]. SAR405838 or (2'S,3R,4'S,5'R)-6-Chloro-4'-(3-chloro-2-fluorophenyl)-2'-(2,2-dimethylpropyl)-N-(trans-4-hydroxycyclohexyl)-2-oxo-1,2-dihydrospiro(indole-3,3'-pyrrolidine)-5'-carboxamide **(Fig. 1)** is another example of a small molecule that targets the interaction between SOS1 and RAS, this compound has been evaluated for its ability to reduce RAS activation in cancer models.



BI-2852 SAR405838

Figure 1. Two well-known examples of SOS1 inhibitors

Conclusion

SOS1 inhibitors are a promising class of compounds aimed at blocking RAS activation in cancer and other diseases driven by RAS signaling. They work by targeting SOS1's interaction with RAS or by preventing SOS1's membrane localization. These inhibitors come from several

chemical classes, including small organic molecules, peptides, allosteric inhibitors, and macrocyclic compounds. While they offer an exciting therapeutic strategy, challenges remain in terms of specificity, resistance, and clinical development. However, ongoing research continues to refine these compounds for use in treating RAS-driven cancers.

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