Design and Discovery of MRTX0902, a Potent, Selective, Brain-Penetrant, and Orally Bioavailable Inhibitor of the SOS1:KRAS Protein–Protein Interaction

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ABSTRACT: SOS1 is one of the major guanine nucleotide exchange factors that regulates the ability of KRAS to cycle through its “on” and “off” states. Disrupting the SOS1:KRAS<sup>G12C</sup> protein–protein interaction (PPI) can increase the proportion of GDP-loaded KRAS<sup>G12C</sup>, providing a strong mechanistic rationale for combining inhibitors of the SOS1:KRAS complex with inhibitors like MRTX849 that target GDP-loaded KRAS<sup>G12C</sup>. In this report, we detail the design and discovery of MRTX0902—a potent, selective, brain-penetrant, and orally bioavailable SOS1 binder that disrupts the SOS1:KRAS<sup>G12C</sup> PPI. Oral administration of MRTX0902 in combination with MRTX849 results in a significant increase in antitumor activity relative to that of either single agent, including tumor regressions in a subset of animals in the MIA PaCa-2 tumor mouse xenograft model.

INTRODUCTION

Activating mutations of KRAS that lead to aberrant signaling and hyperactivation within the MAPK pathway are among the most common driver mutations in human cancers. These KRAS mutations, a majority of which are single codon mutations (G12, G13, Q61, etc.), show a high occurrence in some of the most aggressive cancer types: non-small-cell lung cancer (NSCLC), colorectal cancer (CRC), and pancreatic cancers. The prevalence of KRAS mutations has made KRAS a prime target for oncology drug discovery programs for several decades. KRAS, however, was thought to be undruggable until the recent clinical success of the KRAS<sup>G12C</sup> inhibitors adagrasib (MRTX849) and sotorasib (AMG510). KRAS is a small GTPase that cycles between the GTP-loaded “on” state and the GDP-loaded “off” state—a process that is crucial for normal cell proliferation and survival. One of the major regulators of this process is the Son of Sevenless (SOS) protein, a guanine nucleotide exchange factor (GEF) that acts as a key activator for KRAS function. The binding between KRAS and SOS proteins helps facilitate the turnover of GDP-loaded KRAS into its GTP-loaded state. While two homologs of SOS exist (SOS1 and SOS2) that impart GEF activity onto KRAS, various studies have demonstrated a dominant role for SOS1 over SOS2. Moreover, SOS1 is the only isoform that is reported to participate in a negative feedback loop within the KRAS pathway. Additionally, functional genomic screens have identified that several cancer cell lines addicted to KRAS signaling are particularly sensitive to genetic perturbation of SOS1. Functionally, KRAS mutations lead to a reduction in GTPase activity, resulting in a higher population of GTP-bound KRAS and increased RAS-pathway signaling. GTP-bound KRAS also binds to an allosteric site on SOS1, leading to an increase in SOS1 GEF activity, thereby ensuring a high population of active KRAS.

Activating mutations of SOS1 are found in ~1% of lung adenocarcinomas and uterine carcinomas and at lower frequencies in other cancer types. Furthermore, these mutations have been reported in other RASopathies such as hereditary gingival fibromatosis (HGF) and Noonan’s syndrome. The catalytic site of SOS1 has a well-defined binding pocket adjacent to the KRAS:SOS1 interface; thus, disrupting the SOS1:KRAS protein–protein interaction (PPI) with an SOS1 binder is a compelling strategy to help treat KRAS-driven cancers.

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The clinical stage KRAS<sup>G12C</sup> inhibitor, adagrasib, has garnered much attention recently based on its promising clinical activity across several cancer types.<sup>3–5</sup> Since adagrasib is an irreversible inhibitor that targets GDP-loaded KRAS<sup>G12C</sup>, we envisioned a combination strategy with an SOS1 binder that could disrupt the KRAS:SOS1 PPI and increase the concentration of adagrasib-susceptible GDP-loaded KRAS<sup>G12C</sup>, potentially leading to an increased response rate and/or more durable clinical responses relative to single agent adagrasib. Additionally, this combination strategy could be leveraged to target other KRAS mutant-driven cancers with the appropriate KRAS<sup>mut</sup> inhibitor combination partner (KRAS<sup>G12D</sup> or KRAS<sup>G12V</sup>, etc.).

While several reports have detailed the discovery of small-molecule agonists of SOS1,<sup>26–33</sup> fewer literature reports have described the use of compounds that disrupt the SOS1:KRAS complex<sup>34–37</sup> or degrade SOS1.<sup>38</sup> However, several patent applications have been published describing the use of SOS1 binders to target KRAS mutant cancers.<sup>39–54</sup> Early SOS1 binders such as BAY-293 (1)<sup>35</sup> and BI-3406 (2)<sup>36,37</sup> were discovered from independent high-throughput screening campaigns and serendipitously share the same quinazoline scaffold (Figure 1), similar to many EGFR inhibitors, such as erlotinib (3, Figure 1). The 2-methyl substituent was installed to preclude binding to the hinge region of EGFR and achieve selectivity for SOS1.<sup>35,55</sup> In these leads, the 6-ether substituents extend beyond the SOS1 binding pocket to block the KRAS:SOS1 PPI and prevent the reactivation of KRAS.

Herein, we report the design of a new class of phthalazine-based SOS1 binders that effectively disrupt the SOS1:KRAS protein–protein interaction (Figure 2). These molecules are highly selective for SOS1 and show no activity against EGFR. Our work has led to the identification of the clinical candidate MRTX0902, a potent and orally bioavailable inhibitor of the SOS1:KRAS complex that exhibits complete tumor regressions in mouse models when administered in combination with sub-maximal doses of our KRAS<sup>G12C</sup> inhibitor adagrasib.

## RESULTS AND DISCUSSION

Initial modeling efforts based on previously reported co-crystal structures<sup>35</sup> of SOS1 suggested that the transposition of the N1-quinazoline nitrogen (4) to form a phthalazine core (5) would be well-tolerated within the binding pocket of SOS1 while also preventing binding to EGFR (Figure 2). We began with a simplified class of 6,7-dimethoxy-substituted phthalazines and screened several benzylic amino substituents to probe the hydrophobic back pocket of SOS1 (6–11, Table 1). The potency of these inhibitors was measured using an HTRF displacement assay (<i>K<sub>i</sub></i>) and an In-Cell Western Assay that quantifies phosphorylated ERK1/2 (pERK) modulation in MKN1 cells (<i>IC<sub>50</sub></i>). Gratifyingly, substitution with a simple (<i>R</i>)-α-methylbenzyl amine resulted in a compound (6) with an SOS1 <i>K<sub>i</sub></i> of 637 nM and no activity against EGFR (<i>IC<sub>50</sub></i> > 10 000 nM). To push deeper into the pocket, the phenyl substituent in 6 was replaced with a naphthyl ring (7), leading to an 8-fold increase in binding potency (<i>K<sub>i</sub></i> = 76 nM). However, we found that simply substituting the phenyl ring in 6 with a 3-CF<sub>3</sub> substituent (8) led to a 12-fold boost in binding affinity (<i>K<sub>i</sub></i> = 52 nM) and measurable cellular potency in the MKN1 cell line (<i>IC<sub>50</sub></i> = 958 nM), while the 2-Me substituent (9) resulted in a 3-fold loss in binding potency (<i>K<sub>i</sub></i> = 2049 nM) when compared with compound 6. Surprisingly, combination of the 2-Me and 3-CF<sub>3</sub> substituents led to a compound (10) with an SOS1 <i>K<sub>i</sub></i> of 13 nM and MKN1 cellular <i>IC<sub>50</sub></i> of 378 nM. Presumably this boost in potency was due to the combined lipophilicity of both substituents pushing into the hydrophobic back pocket. Furthermore, installation of the synthetically more complex 2,4-substituted thiophene (11), inspired by BAY-293 (1),<sup>35</sup> led to a 2–3-fold boost in both SOS1 <i>K<sub>i</sub></i> and cellular potency (<i>K<sub>i</sub></i> = 3.9 nM and MKN1 <i>IC<sub>50</sub></i> = 165 nM) when compared to those of compound 10. The initial structure–activity relationship (SAR) of these phthalazines proved that the phthalazine core provided a new class of highly potent SOS1 binders not previously reported in the literature. With this new scaffold in hand, we then focused on designing a bioavailable compound for in vivo profiling.

Early in vitro ADME profiling revealed that the C4-position of the phthalazine scaffold is highly susceptible to metabolism by aldehyde oxidase (AO) (Table 2).<sup>56,57</sup> When tested in human liver S9 fractions, 11 was rapidly metabolized, leading to a t<sub>1/2</sub> of only 14 min. However, in the presence of the known AO inhibitor raloxifene, the t<sub>1/2</sub> of 11 was dramatically increased to >180 min. Molecular modeling (using MOE software<sup>58</sup>) of 11 in SOS1 (Figure 3a, modeled with PDB SOVI) indicated that the C4-
methyl analog 12 (Figure 3b) should bind to SOS1 effectively; moreover, this C4-methyl may also block AO-mediated oxidation. Gratifyingly, installation of the C4-methyl in 12 increased the SOS1 $K_i$ by 8-fold ($SOS1 K_i = 0.5 \text{nM}$) while effectively blocking AO metabolism ($t_{1/2} > 180 \text{ min} \pm \text{raloxifene, 12, Table 2}$). This increase in metabolic stability was further demonstrated with the simplified ($R$)-1-(2-methyl-3-(trifluoromethyl)phenyl)ethan-1-amine analog 13 without a loss in binding potency when compared to 11, and with cellular potency comparable to that of 11 and 12.

Having resolved the oxidative metabolism liability of the original core, we next focused our efforts on exploring the SAR around the C7-substituent. The ideal C7-substituent should extend from the SOS1 binding pocket into the interface of the KRAS:SOS1 protein−protein interaction between the Arg73 of KRAS and Asn879/Tyr884 of SOS1, thereby disrupting the PPI, while also providing favorable drug-like properties. For synthetic ease and reduction of molecular weight, the simplified C1-substituent ($R$)-1-(2-methyl-3-(trifluoromethyl)phenyl)ethan-1-amine was held constant while probing the C7-vector (Table 3). Further molecular modeling suggested that

![Figure 3. (a) Modeled structure of 11 bound to SOS1 (b) Modeled structure of 12 bound to SOS1 (modeled with PDB 5OVI).](https://doi.org/10.1021/acs.jmedchem.2c00741)

### Table 1. Initial Phthalazine Binders of SOS1

| Cmpd | $R$ | SOS1 Binding $K_i$ (nM) | MKN1 Cell IC$_{50}$ (nM)$^a$ | EGFR IC$_{50}$ (nM) |
|------|-----|------------------------|-------------------------------|-------------------|
| 6    | $^*\text{C}_6$ | 637 | >10000 | >10000 |
| 7    | $^*\text{C}_7$ | 76 | >10000 | >10000 |
| 8    | $^*\text{C}_8$ | 52 | 958 | >10000 |
| 9    | $^*\text{C}_9$ | 2049 | >10000 | >10000 |
| 10   | $^*\text{C}_{10}$ | 13 | 378 | >10000 |
| 11   | $^*\text{C}_{11}$ | 3.9 | 165 | >10000 |

$^a$In-Cell Western Assay measuring pERK.

### Table 2. C4-Methyl Substitution Blocks Aldehyde Oxidase-Mediated Metabolism in Human Liver S9 Fractions

| Cmpd | SOS1 binding $K_i$ (nM) | MKN1 cell IC$_{50}$ (nM) | human liver S9 | human liver S9 + 25 $\mu$M raloxifene |
|------|------------------------|----------------------------|----------------|-------------------------------------|
| 11   | 3.9 | 165 | 14 | >180 |
| 12   | 0.5 | 249 | >180 | >180 |
| 13   | 2.6 | 195 | >180 | >180 |

![Putative AO Metabolite of 11](https://doi.org/10.1021/acs.jmedchem.2c00741)
the C6-substituent would have little effect on the binding of
these phthalazines. Thus, the C6-methoxy substituent was
removed, and a simple dimethylamine group was installed in
the C7-position to provide an inhibitor (14) with high binding
affinity and cellular potency ($K_i = 2.2$ nM, MKN1 IC$_{50} = 57$
(nM)). Furthermore, replacing the dimethylamine with a
piperazine (15) led to a $\sim 7$-fold increase in binding affinity
for SOS1 and similar cellular potency when compared with 14.
However, swapping out the C7-nitrogen linkage with a carbon
to form piperidine 16 was met with a 10-fold loss in binding
potency. This observation indicated that the electronics of the
phthalazine core and the conformation of the C7-substituent
could play significant roles in the SOS1 activity ($vide infra$).

Decreasing the basicity of 15 with piperazinone 17 resulted in
a similar cellular potency when compared with 14. Unfortunately,
while both substituents modeled well in the crystal structure, these changes were met
with a $>100$-fold loss in binding affinity and a complete loss of
cellular potency for compounds 18 and 19. Furthermore,
replacing the C4-methyl with a dimethylamine (20) resulted in
a $>3$-fold loss in both the binding and cellular potency, and
oxidation of the phthalazine scaffold to phthalazinones 21
and 22 also proved detrimental. Sterically, these changes should be
accommodated, thus providing further evidence that the
electronics of the phthalazine core are crucial for SOS1
binding.

Based on the high affinity for SOS1 and ability to modulate
pERK in the MKN1 cellular assay, 15 was dosed in female CD-
1 mice to determine if its pharmacokinetics (PK) profile
supported use of this compound as an in vivo tool for
pharmacodynamics (PD) studies in mice (Table 5). Unfortu-
nately, although the intrinsic clearance in human liver
microsomes was moderate, 15 had a high intravenous (IV)
clearance (Cl = 85 mL/min/kg) and low bioavailability (%F =
11) in mice. To reduce the clearance of 15, the 6-position
carbon on the phthalazine core was replaced with a nitrogen to
lower lipophilicity and form the pyridopyridazine core in
23. Fortunately, the pyridopyridazine 23 was equipotent to
15 and showed moderate clearance (Cl = 52 mL/min/kg) after IV
bolus administration, with a significantly higher oral (PO)
exposure and bioavailability (%F = 44). Furthermore, replacing
the basic C7-piperazine substituent with a neutral morpholine


disruption of the SOS1:KRAS complex. Interestingly, based on
atomic distances in the crystal structure, the nitrogen on the 3-
position of the phthalazine core is clearly protonated and
makes a salt bridge with the carboxylate of Glu902. This is in
stark contrast to the previously reported quinazoline-based
SOS1 binders that require a methyl group in this position and
are unable to utilize this interaction.$^{34-37}$ Finally, the C4-
methyl substituent protrudes into the solvent front, which
indicated that this vector could be used as an additional
opportunity for growth and further tuning of the physico-
chemical properties of our phthalazine scaffold.

To probe the SAR of the C4-position and tune the
electronics of the core structure, we first tested both
electron-withdrawing and electron-donating groups such as
trifluoromethyl and methoxy substituents, 18 and 19,
respectively (Table 4). Unfortunately, while both substituents
modeled well in the crystal structure, these changes were met
with a $>100$-fold loss in binding affinity and a complete loss of
cellular potency for compounds 18 and 19. Furthermore,
replacing the C4-methyl with a dimethylamine (20) resulted in
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bolus administration, with a significantly higher oral (PO)
exposure and bioavailability (%F = 44). Furthermore, replacing
the basic C7-piperazine substituent with a neutral morpholine

Table 3. Initial SAR Data of the C7-Substituent

| Cmpd | R$^6$ | R$^7$ | SOS1 Binding $K_i$ (nM) | MKN1 Cell IC$_{50}$ (nM) |
|-------|-------|-------|-------------------------|-------------------------|
| 13    | MeO$^-$ | MeO$^-$ | 2.6                     | 195                     |
| 14    | H$^+$  | Me$^+$ | 2.2                     | 57                      |
| 15    | H$^+$  | HN$^-$ | 0.33                    | 46                      |
| 16    | H$^+$  | HN$^-$ | 3.1                     | 183                     |
| 17    | H$^+$  | MeO$^-$ | 0.43                    | 74                      |

Figure 4. X-ray co-crystal structure of 15 bound to SOS1 (PDB 7UKS).
substituent (24) significantly decreased the clearance (Cl = 17 mL/min/kg) and provided exceptionally high PO exposure (AUC_{0-last} = 130 318 ng·h/mL) and bioavailability (%F ≈ 100) in mice. This result was somewhat surprising, as studies with human liver microsomes predicted this compound to have high clearance, demonstrating a clear species difference with these compounds and a potential disconnect for in vitro/in vivo results.

Based on the combined potency and mouse PK profile, compound 24 was selected as an exploratory tool for a PD study conducted in the 

KRAS^{G12C} mutant MIA PaCa-2 (human tumor cell line) mouse xenograft model (Figure 5). As a proof of concept for the combination of an SOS1 binder with a 

KRAS^{G12C} inhibitor, a dose of MRTX849 (10 mg/kg, dosed PO) that elicits approximate tumor stasis was administered to better observe the impact of 24 on the RAS/MAPK pathway. After 21 days of dosing, tumor pERK levels were determined 3 h after the last dose of orally administered 24 at 100 mg/kg bid (twice daily), MRTX849 at 10 mg/kg qd (once daily), and the combination of 24 and MRTX849. No modulation was observed with either single agent, whereas the combination showed a 69% reduction in pERK in the MIA PaCa-2 model. These results demonstrate that the combination of a KRAS^{G12C} inhibitor with an SOS1 binder more effectively inhibited the RAS/MAPK pathway and provided early proof of concept for the program.

While 24 served as an acceptable in vivo tool compound, it suffered from CYP3A4 inhibition (IC_{50} = 640 nM) and was not advanced further. To decrease the CYP inhibition of these phthalazine inhibitors, we further focused on designing inhibitors with decreased cLogP compared to the highly lipophilic 24 (cLogP = 4.4). Further modeling using the co-crystal structure of compound 15 suggested that a small hydrophilic hole existed in the back pocket of the protein and incorporation of more polar substituents on the phenyl ring may be tolerated. Simple replacement of the 2-methyl on the phenyl ring with a 2-fluoro substituent (25) was well tolerated for potency; however, this modification only slightly changed the cLogP and increased the human liver microsome Cl_{int} by 2-fold compared to that of 24 (Table 6). Swapping out the 2-fluoro for a nitrogen to form the 6-CF_{3}-pyridyl 26 resulted in a loss in both binding and cellular potency. In hopes to target the buried Met878 and increase the potency for these pyridyl substituents, the 4-amino substituent was installed on pyridyl 27, which resulted in a 3-fold increase in binding potency compared to the parent 26 but showed no improvement in the cellular potency. Transposition of the nitrogen to form the 2-methyl-pyridyl 28 or replacement of the pyridyl ring with 3,4-substituted pyrazoles (29 and 30) resulted in a lower Cl_{int} in human liver microsomes, albeit with a significant loss in potency. Pushing out from the 3-position of the phenyl ring with a bromo substituent was well tolerated for SOS1 binding (31), and further introduction of the 3-cyano substituent resulted in the highly potent inhibitor of the SOS1:KRAS PPI, MRTX0902 (32), with a reduced lipophilicity (cLogP = 3.4). Replacement of the 3-cyano with a methyl sulfone (33, MKN1 IC_{50} = 242 nM) or deletion of the 2-methyl substituent (34, MKN1 IC_{50} = 333 nM) resulted in a significant drop in cellular potency when compared to that of MRTX0902 (32).

A co-crystal structure of MRTX0902 (32) bound to SOS1 (Figure 6, PDB 7UKR) was obtained that showed key interactions similar to those of the previous co-crystal structure of compound 15, including the salt bridge between the phthalazine core and Glu902. Based on the pK_{a} of MRTX0902 (measured pK_{a} = 6.7, ~17% ionized at pH 7.4), the phthalazine is not highly protonated under physiological conditions; however, the local acidic environment of the protein likely helps drive protonation of the phthalazine core.

The structure further revealed that the newly installed 3-cyano substituent on the phenyl ring presumably enhances the edge-to-face interaction with Phe890 due to the electron-withdrawing nature of the 3-cyano substituent. The substituted phenyl ring also provides shape complementary with the back

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Table 4. Evaluation of the C4-Substituent SAR

| Compound | Structure | SOS1 Bind. (ng/K) | MKNI Cell IC_{50} (nM) |
|----------|-----------|------------------|------------------------|
| 15       | ![Structure](image1.png) | 0.33 | 46 |
| 18       | ![Structure](image2.png) | 59 | >10000 |
| 19       | ![Structure](image3.png) | 109 | >10000 |
| 20       | ![Structure](image4.png) | 1.1 | 176 |
| 21       | ![Structure](image5.png) | 11 | 114 |
| 22       | ![Structure](image6.png) | 32 | 881 |
pocket of SOS1, although the cyano substituent creates no discernible interactions with the protein as captured in the static structure. The SAR of the benzyl amine modifications show that the 3-cyano substituent in provided the most effective combination of potency and lipophilicity and led to a nearly 6-fold decrease in CYP3A4 inhibition (IC\textsubscript{50} = 3.6 \mu M) when compared to that of the 3-trifluoromethyl-substituted phenyl. Furthermore, the co-crystal structure of MRTX0902 (32) suggested that the C6-position on the phthalazine could be used to further tune the electronics of the core structure. To this end, several electron-withdrawing substituents (-F, -Cl, -CN, -CF\textsubscript{3}) were installed onto the C6-position of the phthalazine ring; however, all modifications were met with a significant loss in both binding affinity and cellular potency (Table 7, -38). Further in vitro profiling showed that MRTX0902 (32) was highly selective for SOS1 when compared to SOS2 and showed no inhibition of EGFR (Table 8). Additionally, a safety panel comprised of 78 protein targets revealed that MRTX0902 is highly selective for SOS1 (EC/IC\textsubscript{50} > 10 \mu M for 74 targets; see Supporting Information for additional details). The PK properties of MRTX0902 after IV and PO dosing were evaluated in CD-1 mice, Sprague–Dawley rats, and beagle dogs (Table 9). Upon IV administration across species, MRTX0902 displayed a low clearance (4.4–14.6 mL/min/kg), low volume of distribution (0.28–0.48 L/kg), and a short half-life (0.62–1.3 h). PO administration of MRTX0902 as a homogeneous suspension in 0.5% MC (4000 cps)/0.2% Tween80 in water led to moderate to high bioavailability (38–83%F) in mice, rats, and dogs. Disease progression for KRAS mutant-driven cancers can lead to brain metastases; therefore, the concentrations of MRTX0902 (32) were measured in a central nervous system (CNS) mouse PK study. Both the total (mean brain, ng/g) and free (cerebral spinal fluid (CSF), nM) concentrations of MRTX0902 were measured after PO dosing in female CD-1 mice (Table 10), and the results demonstrated full coverage of the MK1 cellular IC\textsubscript{50} (29 nM) and efficacious free C\textsubscript{avg} (25 nM, vide infra) in the CSF for up to 8 h. Importantly, drug exposure in the CSF is commonly used as a surrogate for unbound drug in the brain, and the observed free drug exposure in the brain as well as the efflux ratio in the Caco-2 assay (ER = 1.5; Table 8) appear to support the investigation of MRTX0902 in patients harboring KRAS mutant brain metastases. The brain penetrance, low clearance, and high bioavailability of MRTX0902 (32) across species compelled its advancement to an in vivo antitumor efficacy study in the MIA PaCa-2 mouse model (n = 5 animals/group, Figure 7). Based on the short half-life of the compound in mice (t\textsubscript{1/2} = 1.3 h), bid dosing was selected for these studies. After 25 days of PO dosing as a single agent, MRTX0902 resulted in 41% and 53% tumor growth inhibition (TGI) at 25 and 50 mg/kg bid, respectively. A sub-maximally efficacious dose of the KRAS\textsubscript{G12C} inhibitor MRTX849 (10 mg/kg, qd) demonstrated nearly complete TGI (94%) as a single agent; however, this treatment did not result in tumor regression after 25 days of dosing. The

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**Table 5. Mouse PK Profiles of Compounds 15, 23, and 24**

| Compd | Structure | SOS1 Binding K (nM) | MKN1 Cell IC\textsubscript{50} (nM) | Human liver microsome C\textsubscript{o},\textsubscript{0} (ml/min/kg) | mPK IV\textsuperscript{0} CI (ml/min/kg) | E\textsubscript{a} | mPK PO Dosing AUC\textsubscript{0,\infty} (ng/h/mL) %F |
|-------|-----------|---------------------|------------------------------------|------------------------------------------|--------------------------------|-------------|-----------------------------------|
| 15    | ![Image](15.png) | 0.33                | 46                                 | 20                                       | 85                                 | 0.94        | 1298 / 11%                        |
| 23    | ![Image](23.png) | 0.36                | 30                                 | 27                                       | 52                                 | 0.58        | 9971 / 44%                       |
| 24    | ![Image](24.png) | 0.91                | 26                                 | 114                                      | 17                                 | 0.19        | 150318 / -100%                   |

*IV dosing in CD-1 mice (3 mg/kg, 20% SBE-β-CD/50 mM citric acid pH 5.0).* PO dosing in CD-1 mice (100 mg/kg, 20% SBE-β-CD/50 mM citric acid pH 5.0). PO dosing in CD-1 mice (100 mg/kg, 0.5% MC (4000 cps)/0.2% Tween80 in water).
combination of MRTX849 (10 mg/kg, qd) and MRTX0902 at 25 mg/kg bid resulted in −54% regression, while nearly complete tumor regression (−92%) and two tumor-free animals were observed when MRTX0902 was dosed at 50 mg/kg bid with MRTX849 (10 mg/kg, qd). PD studies following 6 days of dosing demonstrated that the combination MRTX849 and MRTX0902 led to increased pERK modulation in tumors collected 4 h after the last dose. Additionally, the plasma concentration of MRTX849 remained unchanged when dosed in combination with MRTX0902.

Chemistry. The synthesis of compound 32 (MRTX0902, Scheme 1) began with a Heck coupling between 39 and 1-(vinyloxy)butane to form the vinyl ether, followed by direct hydrolysis of the vinyl ether using hydrochloric acid to reveal
We have designed a novel phthalazine series of potent SOS1 binders that disrupt the protein interaction between SOS1 and KRAS. X-ray co-crystal structures of these inhibitors reveal a unique salt bridge between the phthalazine core and Glu902 of SOS1 that has not been reported with previous inhibitors. Further optimization of the physiochemical properties led to the non-obvious introduction of the aryl nitrile and the 6-position of the core increased the bioavailability. These improvements provided the early in vivo tool compound MRTX0902 (32), a potent, selective, brain-penetrant, and orally bioavailable inhibitor of the SOS1:KRAS complex. In combination with our KRASG12C inhibitor MRTX849, MRTX0902 provides enhanced inhibition of the EGFR IC50 of MRTX0902 was calculated from the AUC0−24 of the 50 mg/kg bid dose in combination with MRTX849 in the MIA PaCa-2 PD study after 6 days of dosing (Figure 7).

**CONCLUSIONS**

We have designed a novel phthalazine series of potent SOS1 binders that disrupt the protein–protein interaction between SOS1 and KRAS. X-ray co-crystal structures of these inhibitors reveal a unique salt bridge between the phthalazine core and Glu902 of SOS1 that has not been reported with previous SOS1 binders. Through rational design, the binding affinity (Kd) of our initial lead 6 was increased more than 300-fold. Early ADME screening and molecular modeling efforts led to the introduction of a C4-methyl substituent to block A0-mediated metabolism, and the installation of the nitrogen at the 6-position of the core increased the bioavailability. These improvements provided the early in vivo tool compound 24. Further optimization of the physiochemical properties led to the non-obvious introduction of the aryl nitrite and the discovery of MRTX0902 (32), a potent, selective, brain-penetrant, and orally bioavailable inhibitor of the SOS1:KRAS complex. In combination with our KRASG12C inhibitor MRTX849, MRTX0902 provides enhanced inhibition of the

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**Table 8. In Vitro Profile of MRTX0902 (32)**

| assay                        | activity |
|------------------------------|----------|
| SOS1 binding Kd (nM)         | 2        |
| MKN1 cell IC50 (nM)          | 29       |
| SOS2 KRAS GDP exchange IC50 (nM) | >10,000 |
| EGFR IC50 (nM)               | >10,000  |
| MW/cLogp/PSA                 | 388.5/3.4/86.9 |
| Caco-2 Papp, A-to-B (10−6 cm/s)/efflux ratio | 32.3/1.5 |

*a*Caco-2 membrane permeability at 10 μM substrate concentration and pH 7.4.

**Table 9. PK Parameters for MRTX0902 (32) across Species**

| PK parameters | mouse | rat | dog |
|----------------|-------|-----|-----|
| Cl (mL/min/kg) | 4.4   | 14.6| 7.6 |
| Vdss (L/kg)  | 0.28  | 0.28| 0.48|
| IV t1/2 (h)  | 1.3   | 0.62| 0.86|
| F (%)        | 69    | 83  | 38  |
| dose, IV/PO (mg/kg) | 3/30 | 1/10| 2/10|

**Table 10. CNS Mouse PK Profile of MRTX0902 (32)**

| time (h) | mean free plasma concn (Ceff, μM) | mean brain concn (ng/g) | efficacious free C50 (nM) | CSF:C0 | % influent total HMK |
|----------|-----------------------------------|-------------------------|--------------------------|--------|----------------------|
| 1        | 134                               | 1388                    | 209                      | 1.56   | 25                   |
| 8        | 35                                | 388                     | 36                       | 1.03   |                      |

PO dosing: 100 mg/kg, single dose (n = 3). The efficacious free C50 of MRTX0902 was calculated from the AUC0−24 (MRTX0902) of the 50 mg/kg bid dose in combination with MRTX849 in the MIA PaCa-2 PD study after 6 days of dosing (Figure 7).

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**Figure 7. MRTX0902 (32) in vivo efficacy and PD in the MIA PaCa-2 mouse model.

MAPK pathway and displays complete tumor regression in the MIA PaCa-2 tumor xenograft model. MRTX0902 has completed Investigational New Drug (IND)-enabling studies, and further profiling will be reported in due course.

**EXPERIMENTAL SECTION**

**General Procedures.** All final compounds were purified to ≥95% purity by either high-performance liquid chromatography (HPLC) or supercritical fluid chromatography (SFC). Purity was determined by HPLC, and additional structural characterization was performed by proton NMR, carbon NMR, and high-resolution mass spectrometry (HRMS) as described below. All chemicals were purchased from commercial suppliers and used as received unless otherwise indicated.

Proton nuclear magnetic resonance (1H NMR) spectra were recorded on Bruker Avance 400 MHz spectrometers. Chemical shifts are expressed in δ parts per million (ppm) and are calibrated to the residual solvent peak: proton (e.g., CDCl3, 7.27 ppm). Coupling constants (J), when given, are reported in hertz. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet (range of multiplet is given), br = broad signal, dt = doublet of triplets. Carbon nuclear magnetic resonance (13C NMR) spectra were recorded using a Bruker Avance HD spectrometer at 100 MHz. Chemical shifts are reported in δ ppm and are calibrated to the solvent peak: carbon (CDCl3, 77.23 ppm). The purity of test compounds was determined by HPLC on a Shimadzu LC-20AB instrument. HPLC conditions were as follows: Kinetex EVO C18 3.0×50 mm, 2.6 μm, 10%–80% ACN (0.0375% TFA) in water (0.01875% TFA), 3–10 min run, flow rate 1.2 mL/min, UV detection (A = 220, 215, 254 nm), or...
Scheme 1. Synthesis of MRTX0902 (32)\textsuperscript{a}

\textsuperscript{a}Reagents and conditions: (a) 1-(vinyloxy)butane, P(t-Bu),Pd G2, N,N-dicyclohexylamine, dioxane, 85 °C, 10 h, then 4 N HCl, 40 °C, 2 h; (b) hydrazine monohydrate, EtOH, 70 °C, 10 h, 76% yield (over 2 steps); (c) 12 N HCl, 80 °C, 6 h; (d) POCl\textsubscript{3}, 100 °C, 5 h, 63% yield (over 2 steps); (e) (R)-3-(1-aminomethyl)-2-methylbenzonitrile, CsF, DMSO, 130 °C, 2 h, 43% yield; (f) morpholine, 110 °C, 1 h, 88% yield.

Kinetex C18 LC column 4.6 mm × 50 mm, 5 μm, 10%–80% ACN (0.0375% TFA) in water (0.01875% TFA), 4–10 min runs, flow rate 1.5 mL/min, UV detection (λ = 220, 215, 254 nm), or XBridge C18, 2.1 mm × 50 mm, 5 μm, 10%–80% ACN in water buffered with 0.025% ammonia, 4–10 min runs, flow rate 0.8 mL/min, UV detection (λ = 220, 215, 254 nm). The mass spectra were obtained using liquid chromatography–mass spectrometry (LC-MS) on a Shimadzu LCMS-2020 instrument using electrospray ionization (ESI). LC-MS conditions were as follows: Kinetex EVO C18 30 mm × 2.1 mm, 5 μm, 5%–95% ACN (0.0375% TFA) in water (0.01875% TFA), 1.5 min run, flow rate 1.5 mL/min, UV detection (λ = 220, 254 nm), or Kinetex EVO C18 2.1 mm × 30 mm, 5 μm, 5%–95% ACN in water buffered with 0.025% ammonia, 1.5 min run, flow rate 1.5 mL/min, and UV detection (λ = 220, 254 nm). HRMS measurements were carried out on an Agilent 1290LC and 6530QTOF series instruments with ESI. The SFC purity was determined with a Shimadzu LC-30ADs instrument.

Preparation of Compound 32 (MRTX0902). Methyl 5-Acetyl-2-methoxyisonicotinate (40). To a solution of 39 (300 g, 1.22 mol, 1.0 equiv) in dioxane (2.1 L) were added 1-(vinyloxy)butane (244 g, 2.44 mol, 2.0 equiv), P( t-Bu),PdG2 (9.37 g, 18.3 mmol, 1.5 mol%), and N,N-dicyclohexylamine (262 g, 1.34 mol, 1.1 equiv), and the mixture was stirred at 85 °C for 10 h. After LCMS showed that the reaction was complete, the solution was cooled to room temperature, HCl (4 M in THF, 1.46 mol, 1.2 equiv) was added, and the solution was warmed to 40 °C and stirred for 2 h. The reaction mixture was diluted with H2O (500 mL), the pH of the mixture was adjusted to pH 8 with saturated NaHCO\textsubscript{3} (in water), then the mixture was extracted with dichloromethane (1.0 L × 2). The combined organic layers were washed with brine, dried over Na2SO\textsubscript{4}, filtered, and concentrated under reduced pressure to give 40 (250 g, crude) as a yellow solid which was used without further purification.

7-Methoxy-4-methylpyrido[3,4-d]pyrazin-1(2H)-one (41). To a mixture of 40 (500 g, 2.39 mol, 1 equiv, crude) in EtOH (2.0 L) was added N\textsubscript{2}H\textsubscript{4}H\textsubscript{2}O (169 g, 2.87 mol, 164 mL, 85% purity, 1.2 equiv) in one portion at 25 °C under a nitrogen atmosphere. The mixture was then heated to 70 °C and stirred for 10 h. After this time, the mixture was cooled to 25 °C and filtered, and the filter cake was collected and dried under reduced pressure to give 41 (350 g, 1.77 mol, 76% yield over 2 steps, 100% purity) as a black-brown solid. LCMS [M+1]\textsuperscript{+} = 192.2.

1,7-Dichloro-4-methylpyrido[3,4-d]pyrazidine (42). A mixture of 41 (500 g, 2.62 mol, 1 equiv) in HCl (12 N in water, 2.0 L, 9.2 equiv) was prepared at 20 °C under a nitrogen atmosphere, and then the mixture was stirred at 80 °C for 6 h. The reaction mixture was then cooled to 25 °C and filtered, and the filter cake was concentrated under reduced pressure to give 7-hydroxy-4-methylpyrido[3,4-d]-pyrazin-1(2H)-one (460 g, 2.60 mol, 92% yield, 99.8% purity) as a yellow solid. LCMS [M+1]\textsuperscript{+} = 178.0. \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) \( \delta \) 12.53 (s, 1H), 8.41 (s, 1H), 6.92 (s, 1H), 2.35 (s, 3H). A solution of 7-hydroxy-4-methylpyrido[3,4-d]pyrazin-1(2H)-one (460 g, 2.60 mol, 1 equiv) in POCl\textsubscript{3} (1.99 kg, 13.0 mol, 1.21 L, 5 equiv) was stirred at 100 °C for 5 h. After this time, the volatiles were removed via reduced pressure to give a residue. The residue was dissolved in dichloromethane (2.0 L), and the pH of the mixture was adjusted to pH 8 at 0 °C with saturated NaHCO\textsubscript{3} (in water). The mixture was then filtered, and the filtrate was extracted with dichloromethane (2.0 L × 2). The combined organic layers were washed with brine, dried over Na2SO\textsubscript{4}, filtered, and concentrated under reduced pressure to give 42 (552 g, 1.64 mol, 63% yield, 94.9% purity) as an orange solid. LCMS [M+1]\textsuperscript{+} = 214.1. \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) \( \delta \) 9.37 (s, 1H), 8.19 (s, 1H), 7.01 (s, 1H), 4.43 (s, 1H). (R)-3-((7-Chloro-4-methylpyrido[3,4-d]pyrazin-1-yl)amino)-2-methylbenzonitrile (43). To a solution of (R)-3-(1-aminomethyl)-2-methylbenzonitrile (16.0 g, 99.9 mmol, 1.00 equiv) and 42 (21.4 g, 99.9 mmol, 1.00 equiv) in DMSO (130 mL) was added cesium fluoride (22.8 g, 150 mmol, 5.52 mL, 1.50 equiv), and the mixture was stirred at 130 °C for 2 h. The reaction was cooled to 25 °C and then poured into water (200 mL). The aqueous phase was extracted with ethyl acetate (200 mL × 3). The combined organic phases were washed with brine (100 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Kromasil Eternity XT 250 × 80 mm × 10 μm; mobile phase A: 0.1% TFA in water, mobile phase B: acetonitrile; B%: 25%–55%). To the aqueous phase was added sodium bicarbonate to adjust the pH to 8, and then the suspension was extracted with ethyl acetate (1000 mL × 3). The combined organic phases were washed with brine (100 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 43 (14.5 g, 42.9 mmol, 43% yield) as a yellow solid. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) = 9.19 (d, \( J = 0.4 \) Hz, 1H), 7.74 (s, 1H), 7.63 (d, \( J = 8.0 \) Hz, 1H), 7.50 (dd, \( J = 1.2, 7.6 \) Hz, 1H), 7.23 (t, \( J = 7.6 \) Hz, 1H), 5.72 (quin, \( J = 6.8 \) Hz, 1H), 5.40 (br d, \( J = 6.0 \) Hz, 1H), 2.86 (s, 3H), 2.69 (s, 3H), 1.63 (s, 3H).

MRTX0902, (R)-2-Methyl-3-(1-(4-methyl-7-morpholinopyrido[3,4-d]pyrazin-1-yl)amino)ethyl)benzonitrile (32). A solution of 43 (13.5 g, 40.0 mmol, 1.00 equiv) in morpholine (10.4 g, 120 mmol, 10.6 mL, 3.00 equiv) was stirred at 110 °C for 1 h. The reaction mixture was cooled to 25 °C, poured into water (15.0 mL), and stirred for 5 min. After this time the mixture was filtered, and the filter cake was dried under reduced pressure to give a residue. The residue was washed with water (15.0 mL × 3) to give MRTX0902 (32) (14.0
g. 35.3 mmol, 88% yield, 98.9% purity) as a yellow solid. 1H NMR (400 MHz, DMSO-d$_6$) δ = 8.96 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.63–7.48 (m, 2H), 7.38 (s, 1H), 7.30 (t, J = 8.0 Hz, 1H), 5.54–5.49 (m, 1H), 3.80–3.71 (m, 4H), 3.67–3.65 (m, 4H), 2.62 (s, 3H), 2.54 (s, 3H), 1.52 (d, J = 7.2 Hz, 3H). 13C NMR (101 MHz, DMSO-d$_6$) δ = 159.79, 151.20, 149.42, 147.56, 146.39, 139.20, 131.25, 129.71, 127.41, 125.10, 119.01, 114.44, 112.69, 93.62, 66.30, 47.06, 45.49, 21.86, 18.47, 17.20. HRMS (m/z): [M+H]$^+$ calc for C$_{24}$H$_{28}$N$_2$O, 389.2102; found, 389.2012. HPLC (0.025% NH$_3$ in water): t$_R$ = 11.62 min (98.9% purity).

■ ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c00741.

Synthetic experimental procedures for compounds 6–38; NMR spectra and HPLC trace of final compounds; SOS1 X-ray structures for compounds 15 and 32; biochemical and cellular assay protocols; in vivo PK, PD, and TGI studies (PDF)

Molecular formula strings (CSV)

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■ ABBREVIATIONS USED

bid, bis in die (twice a day); Cmpd, compound; CNS, central nervous system; CSF, cerebral spinal fluid; EGFR, epidermal growth factor receptor; IV, intravenous; KRAS, Kirsten rat sarcoma virus; MC, methyl cellulose; PD, pharmacodynamics; PK, pharmacokinetics; PO, per os (oral); qd, quaque die (once daily); SAR, structure–activity relationship; SFC, supercritical fluid chromatography; SOS1, son of sevenless homolog 1; TGI, tumor growth inhibition; Tween80, polyoxyethylene sorbitan monoleate

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