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Communication

Discovery of 1,3,5-triazine-based LSD1 inhibitors to activate immune response in gastric cancer

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ABSTRACT

Lysine-specific demethylase 1 (LSD1), the first identified histone lysine-specific demethylase, plays a crucial role in mediating immune responses in gastric cancer. Most LSD1 inhibitors undergoing clinical trials are irreversible, which has driven significant interest in developing structurally diverse reversible inhibitors. In this study, we present a potent 1,3,5-triazine-based LSD1 inhibitor, XP-2, discovered through high-throughput screening (HTS) of our in-house compound library and subsequent structure-activity relationship (SAR) studies, exhibiting a half maximal inhibitory concentration (IC_{50}) of 0.116 μmol/L. XP-2 enhanced the susceptibility of gastric cancer cells to T cell-mediated cytotoxicity by downregulating programmed cell death ligand 1 (PD-L1) expression, thereby disrupting the programmed cell death protein 1 (PD-1)/PD-L1 interaction. Furthermore, XP-2 significantly inhibited the proliferation of gastric cancer cells without inducing notable toxicity. Pharmacokinetic evaluation revealed favorable oral exposure and a moderate half-life in mice. In conclusion, this study provided a promising LSD1 inhibitor with a novel scaffold and promising pharmacokinetic properties, supporting its further development as an immunomodulator for gastric cancer treatment.

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Gastric cancer remains one of the most common and lethal malignancies worldwide, with a particularly high incidence in Asia [1]. Despite recent advancements in targeted therapies and immune checkpoint inhibitors (ICIs), current treatment options are still limited by modest response rates, rapid development of drug resistance, and insufficient survival benefits for most patients [2], which highlights the urgent need to expand the repertoire of druggable targets and develop structurally innovative small molecules. In recent years, targeting epigenetic regulation has emerged as a highly promising anticancer strategy. As one of the core journals in this field, Chinese Chemical Letters has recently reported explorations of various novel epigenetic-targeting agents in tumor therapy [3,4]. Among these, lysine-specific demethylase 1 (LSD1, also known as KDM1A), as a key epigenetic regulator, has attracted growing attention for the unique potential of its inhibitors to reverse the tumor immunosuppressive microenvironment.

As the first identified histone demethylase, LSD1 demethylates H3K4/9me1/2 through a flavin adenine dinucleotide (FAD)-dependent catalytic mechanism, thereby influencing gene transcription in a context-dependent manner [5,6]. LSD1 is aberrantly overexpressed in several cancers, including gastric cancer, and contributes to tumor proliferation, invasion, and metastatic progression. Small-molecule inhibition or genetic ablation of LSD1 consistently suppresses tumor growth, supporting LSD1 as an attractive drug target. Beyond its canonical chromatin-regulating function, LSD1 has recently been recognized as a key epigenetic regulator of tumor immunity [7,8]. Targeting LSD1 also could activate T cells and increase sensitivity of melanoma cells to programmed cell death protein 1 (PD-1) immune checkpoint blockade [9]. Similar results also were observed in triple-negative breast cancer (TNBC) and cervical cancer [10,11]. Our group previously demonstrated that LSD1 deletion could decrease exosomal programmed cell death ligand 1 (PD-L1) levels and promote the response of gastric cancer to T cell therapy [12,13], and also indicated that LSD1 inhibitors can downregulate PD-L1 expression, facilitating T cell-mediated elimination of gastric cancer cells [14-17].

Over the past decade, extensive medicinal chemistry efforts have led to a diverse range of LSD1 inhibitors with high enzymatic potency, and more than ten LSD1 inhibitors are currently in phase I/II clinical trials for conditions such as non-small cell lung cancer, acute myeloid leukemia and Ewing's sarcoma, including eight irreversible inhibitors (TCP, ORY-1001, GSK2879552, INCB059872, IMG-7289, ORY-2001, TAK-418, LH-1802), two reversible inhibitors (CC-90011, SP-2577), and two dual LSD1/histone deacetylases (HDACs) inhibitors (4SC-202, JBI-802) [6,18]. Notably, clinical trials for several irreversible inhibitors (GSK2879552, INCB059872, TAK-418) have been halted due to hematological adverse effects. Reversible LSD1 inhibitors may offer superior safety profiles and phenotypic advantages, underscoring the urgent need to discover more novel potent reversible LSD1 inhibitors with new chemical structures. In this study, we aim to explore new scaffolds such as 1,3,5-triazine through systematic structural optimization and biological evaluation to identify reversible LSD1 inhibitors with enhanced therapeutic potential. Moreover, we will investigate their molecular mechanisms in modulating PD-L1 expression and promoting T-cell–mediated anti-tumor immunity in gastric cancer.

A high-throughput screening (HTS) of our in-house compound library (3182 small compounds) using horseradish peroxidase (HRP)/Amplex Red assay [14-17] identified XP-1 (compound **1**), featuring a 1,3,5-triazine scaffold, which showed promising LSD1 inhibitory activity (37.5 % inhibition at 10 μmol/L) (Fig. 1). Subsequent structure-activity relationship (SAR) studies were conducted to optimize the potency of XP-1. The synthetic routes for 1,3,5-triazine derivatives are outlined in Scheme S1 (Supporting information). Route A was used to synthesize compounds **1-45**. Intermediates **C1-C26** were prepared *via* Suzuki coupling between commercially available 2,4-dichloro-6-phenyl-1,3,5-triazine (**B1**) and $R_2B(OH)_2$. Subsequent nucleophilic aromatic substitution of **C1-C26** with R_1XH yielded the target compounds **1-45**. Route B was employed for compounds **46-50**, involving a Grignard reaction between 2,4,6-trichloro-1,3,5-triazine and R_3MgBr to afford intermediates **B2-B6**. The intermediates **B2-B6** then underwent nucleophilic aromatic substitution with *N*,*N*-diethyl-*p*-phenylenediamine to give intermediates **D1-D5**, which were subsequently subjected to Suzuki coupling to yield the final compounds **46-50**.

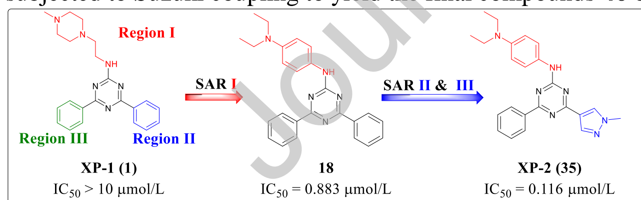

Fig. 1. Discovery of 1,3,5-triazine-based LSD1 inhibitors.

Fifty novel compounds were designed and synthesized by varying the substituents on the 2-, 4- and 6- positions of the triazine core (Tables S1-S3 in Supporting information). Initial exploration focused on the R_1 group (Table S1). Replacing the R_1 group of XP-1 with straight-chain *N*-dimethylethylenediamine or cyclic secondary amines (piperidine, morpholine, and *N*-methylpiperazine) resulted in slightly decreased activity (compounds **1-6**). Modification at the triazine 2-position with various 4-substituted anilines revealed that compound **12**, bearing an unsubstituted aniline, showed considerable potency (the half maximal inhibitory concentration (IC_{50}) = 4.373 μmol/L). Replacing the NH group with O or S atoms (compounds **13** and **14**) led to slightly reduced activity. Compound **15**, with a free amine group at the *meta*-position of benzene ring, was virtually inactive. Substitution with aminotriazole (compound **16**) also significantly diminished activity. Introduction of methyl or ethyl groups onto the free amino group of compound **12** enhanced activity, yielding compounds **17** (IC_{50} = 2.750 μmol/L) and **18** (IC_{50} = 0.883 μmol/L). Surprisingly, replacing the diethylamino group with cyclic piperazine or morpholine (compounds **19** and **20**) reduced activity. Consequently, *N*,*N*-diethyl-*p*-phenylenediamine was identified as the optimal substituent at the triazine 2-position.

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Subsequent structural modifications focused on the R_2 group (Table S2). Based on compound **18**, introducing various substituents (methyl, isopropyl, methoxy, hydroxy, amino, methylsulfonyl) at the *para*-position of the benzene ring improved activity to varying degrees (compounds **21**-**26**). The position of substituents on the benzene ring significantly influenced activity; for instance, compound **27** with an *ortho*-isopropyl group was significantly less active than its *para*-substituted analogue **22**. Introducing fluorine or acetyl groups at the *meta*-position decreased activity, while an acetamido group enhanced it (compounds **28**-**30**). Di- or multi-substitution on the benzene ring generally reduced activity compared to compound **18**. Replacement of the benzene ring with aromatic heterocycles (thiophene, oxazole, pyridine, naphthalene, dibenzodioxin, indole, dibenzothiophene) was explored. Compound **35** (XP-2), bearing a 2-methylpyridyl group, exhibited the highest potency (IC_{50} = 0.116 μmol/L). Although the oxazole group showed promise, further optimization of its substituents (compounds **41**-**45**) did not yield activities superior to XP-2.

Finally, SAR studies on the R_3 group were conducted based on compound **35** (Table S3). Introducing either electron-donating (methyl, methoxy) or electron-withdrawing (chloro, fluoro) substituents at the *para*-position of the terminal benzene ring markedly reduced activity (compounds **46**-**49**). Introducing a fluorine at the *meta*-position (compound **50**) did not improve activity.

SAR studies revealed that the *N*,*N*-diethyl-*p*-phenylenediamine moiety at the 2-position of the 1,3,5-triazine core was optimal for inhibiting LSD1 (Fig. S1 in Supporting information). Replacement of the NH group at this position with O or S atoms (compounds **13** and **14**) resulted in a moderate decrease in activity. Further optimization at the 4-position showed that substituting the original phenyl ring with a 2-methylpyridyl group was critical for enhancing potency. In contrast, modifications at the 6-position were poorly tolerated; introduction of any substituent on the terminal phenyl ring led to a marked reduction in activity.

To elucidate the structural basis for the potent inhibitory activity of XP-2, molecular docking was performed using MOE 2019 software [19] with the LSD1 crystal structure (PDB: 5YJB). The resulting top-ranked pose was visualized with PyMOL 2.6. Analysis revealed that all four aryl rings of XP-2 (triazine, pyrazole, and two phenyl rings) engage in *π*-H interactions with residues Ala331, Tyr761, Thr810, and Val288, respectively (Fig. S2A in Supporting information). Superimposition of docked XP-2 with the co-crystallized FAD molecule showed significant overlap (Fig. S2B in Supporting information), indicating that XP-2 effectively occupies the FAD-binding pocket, likely stabilizing its binding by mimicking key interactions of the native cofactor.

Molecular dynamics (MD) simulations of the LSD1-XP-2 complex over 100 ns were conducted to assess binding stability. As shown in Fig. S3 (Supporting information), the root-mean-square deviation (RMSD) of the complex backbone remained around 8 Å after equilibration, with minor fluctuations reflecting a stable conformational state (Fig. S3A). The radius of gyration (Rg) profile showed only slight variations (Fig. S3B), indicating that XP-2 binding induces moderate structural adjustments without compromising the overall compactness of LSD1. The solvent-accessible surface area (SASA) exhibited minimal changes (Fig. S3C), supporting the notion that the complex remains structurally consolidated throughout the simulation. Hydrogen-bond analysis confirmed the stability of the LSD1–XP-2 interaction, with an average of three hydrogen bonds maintained during the simulation (range: 0–6; Fig. S3D). Root-mean-square fluctuation (RMSF) calculations revealed low backbone flexibility across most residues (mostly below 6 Å; Fig. S3E), indicating enhanced conformational restraint upon ligand binding.

Given the promising LSD1 inhibitory activity of compound XP-2, we next evaluated its selectivity against homologous FAD-dependent amine oxidases. LSD1, LSD2, monoamine oxidase A (MAO-A) and MAO-B all belong to the FAD-dependent amine oxidase family, and their catalytic mechanisms depend on FAD. Their domains are highly conserved and form the core of their catalytic function. Therefore, we further evaluated the biochemical activity of compound XP-2 against LSD2, MAO-A, and MAO-B. As shown in Table S4 (Supporting information), XP-2 exhibited no significant inhibitory activity toward these homologous proteins of LSD1. Furthermore, in Table S5 (Supporting information), XP-2 also showed no detectable inhibitory activity against other key epigenetic proteins, including HDACs. These data confirmed the selectivity of XP-2 to LSD1. A dilution assay was performed to assess the reversibility of XP-2. After 50-fold dilution, LSD1 activity was restored, suggesting a noncovalent interaction. In contrast, LSD1 activity could not be recovered after dilution in the presence of the covalent inhibitor 2-PCPA (Fig. S4 in Supporting information), indicating that XP-2 is a reversible inhibitor.

Based on the IC_{50} value of compound XP-2 against recombinant LSD1 protein (0.116 μmol/L, Fig. 2A), a cellular thermal shift assay (CETSA) was conducted to evaluate the binding efficiency between XP-2 and LSD1. As anticipated, the presence of XP-2 led to a pronounced increase in the thermal stability of LSD1 (Fig. 2B). These results indicate that compound XP-2 can stably bind to LSD1 at the cellular level. As a histone demethylase, LSD1 specifically catalyzes the demethylation of H3K4me1/2. To assess whether compound XP-2 exhibits selective inhibitory activity toward LSD1, it was applied to the LSD1 overexpressed gastric cancer cell line MKN-45 and its LSD1 knockout counterpart, MKN-45 LSD1 knock out (KO) cells (Figs. 2C and D). The results demonstrated that compound XP-2 inhibited LSD1 activity in a dose-dependent manner, thereby preventing the demethylation of H3K4me1/2 (Figs. 2D and E). Moreover, compound XP-2 has no effect on the expression level of LSD1 protein in cells. Taken together, the data suggest that compound XP-2 can be considered as a selective and cell-active LSD1 inhibitor.

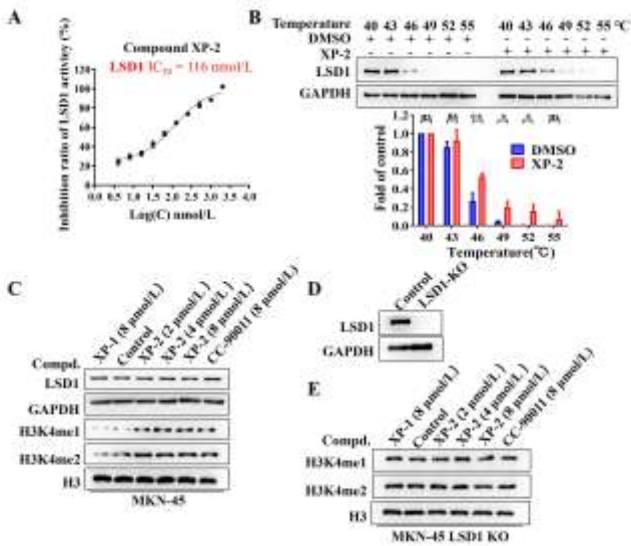

Fig. 2. Compound XP-2 can bind LSD1 and inhibit its enzymatic activity in the cellular level. (A) Inhibition curve of compound XP-2 on LSD1 recombinant. (B) Target engagement of compound XP-2 with LSD1 was evaluated by CETSA and subsequent quantitative analysis. (C) The protein levels of LSD1 and its substrates H3K4me1/2 were detected after treatment of XP-2 in MKN-45 cells. (D) LSD1 was completely knockout in MKN-45 LSD1 KO cells. (E) The protein levels of LSD1's substrates H3K4me1/2 were also detected after treatment of XP-2 in MKN-45 LSD1 KO cells. Compounds XP-1 and CC-90011 were used as negative control and positive control respectively. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and H3 served as a loading control. Dates are mean ± SD (n = 3). ns, no significance. *$P < 0.05$, **$P < 0.01$ *vs*. the control.

To explore whether compound XP-2 could regulate the immune response of gastric cancer cells by affecting the expression of PD-L1, we first detected the expression of PD-L1 after treatment of XP-2 in MKN-45 and MKN-45 LSD1 KO cells. In addition, MFC cell line, derived from 615 mice, was used for *in vivo* efficacy assessment, and the impact of the compound on PD-L1 expression in these cells was also examined. The results showed that treatment with compound XP-2 led to a dose-dependent reduction in PD-L1 expression in MKN-45 cells (Fig. 3A and Fig. S5 in Supporting information) and MFC cells (Fig. S6A in Supporting information). And the result of flow cytometry further revealed a consistent trend with the previous results (Fig. 3B). To further verify whether compound XP-2 downregulates PD-L1 expression through LSD1, MKN-45 LSD1 KO cells (Fig. 3C) and MFC LSD1 KO cells (Fig. S6B in Supporting information) were treated in the same manner as MKN-45 cells and MFC cells. The results showed no significant change in PD-L1 expression, suggesting that LSD1 may play a critical role in mediating the PD-L1 downregulation induced by XP-2.

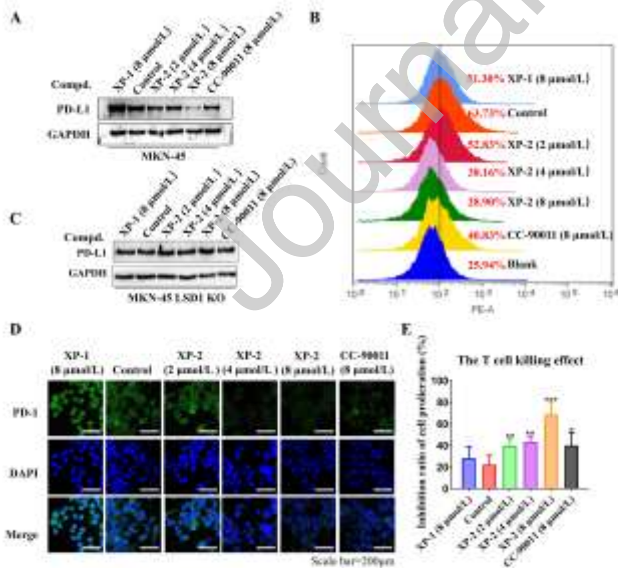

Fig. 3. Compound XP-2 enhanced T cell-mediated cytotoxic responses by downregulating the expression of PD-L1 in gastric cancer cells. (A) Expression level of PD-L1 in MKN-45 cells after treatment of XP-2. (B) Expression of PD-L1 was analyzed by flow cytometry after the treatment of compound XP-2 in MKN-45 cells. (C) Protein levels of PD-L1 in MKN-45 LSD1 KO cells treated as indicated were detected by Western blot. (D) PD-1 binding on the membrane of MKN-45 cells with compound treatment. (E) T-cell killing response of MKN-45 cells with indicated treatment. Dates are mean ± SD (n = 3). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ *vs*. the control.

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PD-L1 expressed on the surface of tumor cells serves as the primary ligand for PD-1 on T cells. Their interaction suppresses T cell immune function, ultimately contributing to tumor immune evasion. Since it has been proved that compound XP-2 can reduce the expression of PD-L1 through LSD1, we hypothesized that compound XP-2 could activate the killing ability of T cells, but further verification is needed. Based on this, the effect of compound XP-2 treatment on the interaction between PD-L1 and PD-1 was further detected. The results showed that compound XP-2 reduced the binding of PD-1 to the cell membrane of MKN-45 in a dose-dependent manner (Fig. 3D). Moreover, results from the T cell-mediated cytotoxicity assay, as shown in Fig. 3E, indicated that compound XP-2 enhanced the susceptibility of MKN-45 cells to T cell killing in a dose-dependent manner. These findings suggest that compound XP-2 promotes the responsiveness of MKN-45 cells to T cell-mediated killing by downregulating PD-L1 expression and subsequently reducing the PD-1/PD-L1 interaction.

Inspired by the potent LSD1 inhibitory activity and immunomodulatory effects of compound XP-2 in gastric cancer cells, its antitumor efficacy *in vivo* was further evaluated using a syngeneic mouse model bearing MFC cell-derived tumors in immunocompetent mice. All animal experiments were performed following the protocols evaluated and approved by the Animal Care and Use Committee (ACUC) of Zhengzhou University (ethics approval No. 23-IACUC-Y146). The study was conducted in accordance with the guidelines established by the committee. After treatment with compound XP-2, the growth of MFC cells was blocked, especially in the higher-dose group (Fig. 4A). Tumor volume (Fig. 4B) and weight (Fig. 4C) measured from excised tumors exhibited consistent results, further confirming the potent *in vivo* anti-proliferative effect of compound XP-2. Additionally, no significant change in body weight and major organs (including the heart, liver, spleen, lungs, kidneys) were observed among the treatment groups (Figs. 4D and E), indicating that XP-2 induced no apparent toxicity. Immunohistochemical staining in Fig. 4F demonstrated that compound XP-2 treatment led to a marked decrease in PD-L1 expression and enhanced $CD8^+$ T-cell infiltration within tumor tissues, consistent with the results observed *in vitro*. Collectively, these results confirm that the LSD1 inhibitor compound XP-2 significantly suppresses gastric cancer cell growth *in vivo* and enhances T cell-mediated immune responses.

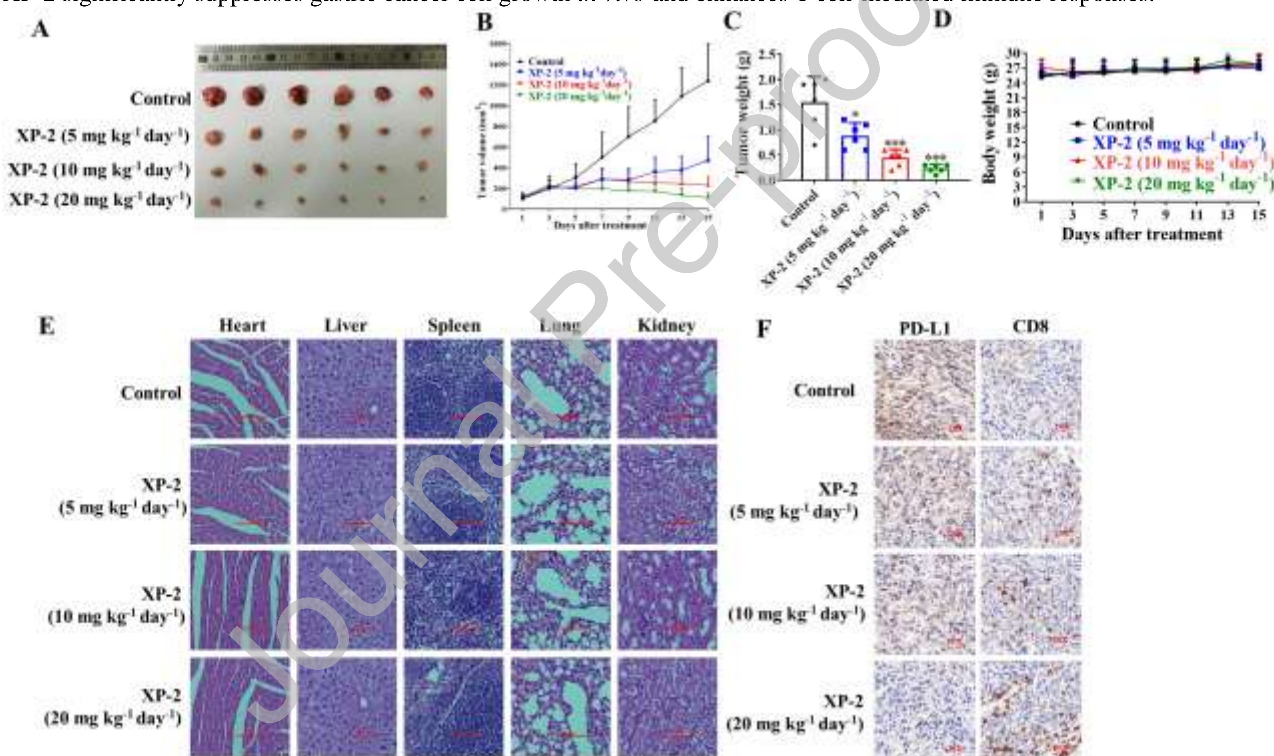

Fig. 4. Compound XP-2 inhibited the growth of gastric cancer cells *in vivo*. MFC cells were transplanted subcutaneously to the 615 mice, and the mice were administrated compound XP-2 (5, 10, and 20 mg/kg) for 14 days, respectively. (A) Images of the stripped tumors from the mice after treatment. (B) Tumor volume was measured every 2 days. (C) Tumor weight of the stripped tumors. (D) The body weight of the mice with compound treatment. (E) Hematoxylin and eosin staining (HE) staining of the heart, liver, spleen, lungs, and kidneys of mice. Scale bar: 600 μm. (F) PD-L1 and CD8 expression were analyzed by immunohistochemistry assay. Dates are mean ± SD ($n = 3$). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ *vs*. the control.

Furthermore, we also evaluated the oral exposure in mice for compound XP-2 with the detailed data summarized in Table S6 (Supporting information), demonstrating that XP-2 achieved good systemic exposure after a 20 mg/kg oral dose. We next assessed its pharmacokinetic profile in mice. As shown in Table S7 (Supporting information), XP-2 exhibited rapid absorption (T_{max} = 0.25 h), a moderate half-life ($T_{1/2}$ = 5.43 h), and favorable oral exposure (C_{max} = 2057 ng/mL, AUC_{0-inf} = 13,501 h ng mL^{-1}). These results indicate that XP-2 possesses promising drug-like properties suitable for further development.

In this study, a series of 1,3,5-triazine derivatives was identified as novel potent LSD1 inhibitors. Among them, compound XP-2 exhibited the most potent inhibitory activity (IC_{50} = 0.116 μmol/L), potentially by occupying the FAD-binding pocket of LSD1, as

suggested by molecular docking. CETSA confirmed direct target engagement of XP-2 with intracellular LSD1. Mechanistic investigations revealed that XP-2 enhances the susceptibility of gastric cancer cells to T cell-mediated cytotoxicity by downregulating PD-L1 expression and disrupting the PD-1/PD-L1 axis. In immune-competent mouse models, XP-2 demonstrated pronounced *in vivo* antitumor efficacy without apparent systemic toxicity. Pharmacokinetic studies further revealed that XP-2 possesses favorable drug-like properties, including rapid oral absorption, moderate half-life, and good systemic exposure. Overall, XP-2 represents a potent, cell-active LSD1 inhibitor with promising immunomodulatory and anti-tumor activities, coupled with acceptable pharmacokinetic profiles, warranting further development as a candidate for cancer immunotherapy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated to this article can be found, in the online version, at doi:.

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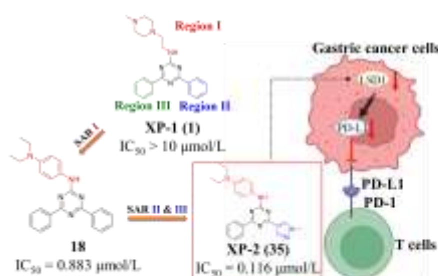
Graphical abstract



In this study, we present a potent 1,3,5-triazine-based LSD1 inhibitor, XP-2, which enhanced the susceptibility of gastric cancer cells to T cell-mediated cytotoxicity by downregulating PD-L1 expression, thereby disrupting the PD-1/PD-L1 interaction. Furthermore, XP-2 significantly inhibited the proliferation of gastric cancer cells without inducing notable toxicity.

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