Lipophilic Salirasib analogs with enhanced antiproliferative activity against human solid tumor cell lines.

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Abstract:

Aim: We proposed to determine the antiproliferative activity of a series of synthetic salirasib analogs, presenting or not a 1,2,3-triazole linker, against five different cancer cell lines. Results: Bioassay, cheminformatic, and in silico ADME-Tox allowed the identification of new potent analogs. SAR analysis allowed the identification of structural and physicochemical features that benefit the antiproliferative activity. Conclusion: Isoprenyl R chains with three or more isoprene units, or long aliphatic R chains are the preferred ones within the active compounds. Likewise, we have identified three compounds with better activity profiles than salirasib against all the cell lines tested.

Graphical abstract:

Keywords: Salirasib; 1,2,3-triazoles; Cancer; SAR studies; Cheminformatics.
Introduction

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, and is the second leading cause of death globally [1]. Guanine binding proteins (G proteins) such as Ras, Rap, Rho, and Rab enclose the largest group of isoprenylated proteins. Among these, Ras proteins have attracted particular attention because of the important role they play in carcinogenesis [2]. These proteins are engaged in signal transduction pathways, crucial for cell growing and differentiation. Specific mutations in Ras proteins turn them into oncogenic and they are found in around 30% of all human tumors, including near 90% of pancreatic cancers and 50% of colon cancers [3].

Ras proteins undergo prenylation in a three-step post-translational process that facilitates membrane association to Ras, a crucial step to trigger its oncogenic activity [4]. In the first step of prenylation, which occurs in the cytoplasm, an isoprenyl transferase (Farnesyl Transferase, FTase, or Geranylgeranyl Transferase, GGTase) recognizes a carboxyl terminus CAAX motif of Ras (C: Cysteine, AA: two aliphatic amino acids, X: a final varied amino acid), and a farnesyl (FTase) or geranylgeranyl (GGTase) group is transferred to the cysteine of CAAX, forming a thioether bond with the corresponding sulphhydryl group. After prenylation, the protein can migrate to the endoplasmic reticulum, where a Ras Converting CAAX Endopeptidase 1 (RCE-1) cleaves the -AAX tail, leaving the C-terminus with an isoprenylcysteine. This motif is recognized by Isoprenylcysteine Carboxymethyl Transferase (ICMT), which catalyzes the transfer of a methyl group from an S-adenosyl-L-methionine to the isoprenylated Ras terminus carboxylate to form an ester, allowing the membrane anchoring of Ras [2,5].

The development of anticancer agents through a Ras-related mechanism has been approached by different strategies. One alternative is to directly prepare Ras inhibitors, such as DABP-GTP [6] (Fig. 1), a GTP analog, or by an anti-sense RNA like ISIS 2503 [7], which has undergone clinical trials in various cancer types. A strategy that has gained relevance over the years is the development of inhibitors for the post-translational prenylation process at any of its three stages. FTase inhibitors have been successful in pre-clinical studies [8,9], but many of them failed in phase III of clinical trials, because many Ras mutants (e.g, KRAS, NRAS, etc.) proved to be good GGTase substrates when FTase is inhibited [4,10]. However, FTase inhibitor clinical trials for Ras mutants.
that did not show this effect are promising [11,12]. Inhibition of RCE-1 was also studied [13–15], but experiments in mice have thrown discouraging results [16,17], and this target was set aside. ICMT inhibitors have gained relevance among the Ras-dependent anti-cancer agents [5]. Amid ICMT inhibitors, the most relevant are the indole cysmethynil [18] and the substrate analog salirasib [19,20] (Fig. 1).

![Chemical structures of RAS-related anti-cancer agents.](image)

**Fig. 1.** RAS-related anti-cancer agents.

Salirasib, or farnesylthiosalicylic acid (FTS), is a salicylic acid derivative with antineoplastic activity. It was designed as a competitor of S-farnesyl cysteine on Ras [21–23], and it acts as a potent competitive inhibitor of ICMT. In consequence, salirasib selectively disrupts the association of activated Ras proteins to the plasma membrane [24,25]. This compound is usually indicated for the treatment of a wide range of cancers, such as
pancreas, lung, and colon, among others. Preclinical and phase I clinical trials in Ras-positive cancer patients showed that salirasib could be well tolerated, with no significant side effects and with the predicted levels of absorption [26–28]. There is still little information about phase II clinical trials, which at least required dosage increments to improve results [29]. Hence, the scientific community is still working on salirasib structural optimization that could lead to improve the late stages of clinical trials [30–34].

We have previously reported the synthesis and antimalarial activity of salirasib analogs as a mean of drug repurposing [35]. The compounds collection consists on thiosalicylic acid (TSA) derivatives, S-substituted with alkyl, propargyl, ester, aryl or isoprenyl chains (1 - 13), or with a triazole linker inserted between the TSA and the R substituent (14 - 25) (Fig. 2). In this opportunity, we present the results of the salirasib analogs as antiproliferative agents, along with their SAR and predicted ADME-Tox analysis.

![Fig. 2. Salirasib analogs studied in this work.](image)

**Materials and Methods**

**General method for the preparation of S-alkylated thiosalicylic acid compounds**

Thiosalicylic acid (1 equivalent) was dissolved in anhydrous acetone (10 mL/eq), under constant stirring and inert atmosphere. Next, guanidinium carbonate (1 equivalent) and organobromide compound (1 equivalent) were added. The reaction mixture was brought to reflux for 8 hours. To finish the reaction, a solution of 1M HCl was added, continuing to extract the compound of interest with ethyl ether (3 x 25 mL). Combined organic extracts were dried with sodium sulfate and evaporated. Products 1 - 13 were purified by column chromatography in silica gel with increasing hexanes/ethyl acetate gradients.
General procedure for the Cu(I) mediated 1,3-dipolar cycloaddition (CuAAC)

Alkyne 1 (1 equivalent) and azide (1.5 equivalent) were suspended in 10 mL/eq of tBuOH:H₂O (1:1). Then, 1 M CuSO₄ solution (0.05 equivalents) and 1 M sodium ascorbate solution (0.2 equivalents) were added, and the mixture stirred overnight at room temperature. Brine (30 mL) was added and the solution was extracted with dichloromethane (3 x 25 mL). Combined organic extracts were dried over sodium sulfate and evaporated. Products 14 – 25 were purified by column chromatography in silica gel with increasing hexane/ethyl acetate gradients.

General procedure for in vitro antiproliferative activity

The in vitro antiproliferative activity of investigated compounds was evaluated using the protocol of the National Cancer Institute of the United States [36]. A panel of five human solid tumor cell lines was used:

- **A549**: adenocarcinomic human alveolar basal epithelial cells, extracted from cancerous lung tissue in the explanted tumor of a 58 years old caucasian male (non-small cell lung cancer);
- **SW1573**: alveolar cell carcinoma extracted from a 44 years old white female (non-small cell lung cancer);
- **HeLa**: cervical cancer cells extracted from Henrietta Lacks, a 31 years old African-American female (cervix cancer);
- **HBL-100**: extracted from the milk of a 27 years old caucasian nursing mother and obtained 3 days after delivery (breast cancer);
- **T-47D**: isolated from a pleural effusion obtained from a 54 years old female patient with an infiltrating ductal carcinoma of the breast (breast cancer).

Cells were maintained in 25 cm² culture flasks in RPMI 1640 supplemented with 5% heat-inactivated fetal calf serum, and 2 mM L-glutamine in a 37 °C, 5% CO₂, 95% humidified air incubator. Exponentially growing cells were trypsinized and re-suspended in antibiotic-containing medium (100 units penicillin G and 0.1 mg of streptomycin per mL). Single-cell suspensions displaying > 97% viability by trypan blue dye exclusion were subsequently counted. After counting, dilutions were made to give the appropriate cell densities for inoculation onto 96-well microtiter plates. Cells were inoculated in a volume of 100 µL per well at densities of 3920 (A549,
HBL-100, HeLa and SW1573) or 5000 (T-47D) cells per well, based on their doubling times. Compounds to be tested were dissolved in DMSO at an initial concentration of 40 mM. Control cells were exposed to an equivalent concentration of DMSO (0.25% v/v, negative control). Each compound was tested in triplicate at different dilutions in the range 1–100 µM. The drug treatment was started on day 1 after plating. Drug incubation times were 48 h, after which time cells were precipitated with 25 µL ice-cold TCA (50% w/v) and fixed for 60 min at 4 ºC. Then the sulforhodamine B (SRB) assay was performed [37]. The optical density (OD) of each well was measured at 530 nm, using BioTek’s PowerWave XS Absorbance Microplate Reader. Values were corrected for background OD from wells only containing medium. Antiproliferative activity of the compounds was expressed as GI₅₀, that is, the concentration of the compound that inhibits 50% of the culture growth.

**Physicochemical properties prediction**

Using Osiris DataWarrior platform [38], a search in ChemBL database [39,40] was made. Filters on target (ICMT), Organism (*Homo sapiens*), and inhibitory activity (< 100 µM) were applied. This search thrown a total on 467 reported HsICMT inhibitors. On the same platform, relevant properties were predicted (Total Molweight, cLogP, cLogS, and Total Surface Area). Also on Osiris DataWarrior platform, SMILES of the 25 farnesylthiosalicylic acid (FTS) analogues were introduced, and the same properties were predicted. For the FTS analogues, LogD was also predicted, using the online ChemAxon LogD predictor [41].

**ADMETox predictions**

Computational modelling to estimate the bioavailability, aqueous solubility, human intestinal absorption, metabolism, mutagenicity, toxicity, etc. for the compounds was performed using the SwissADME [42], pkCSM [43] and Biotransformer [44] platforms.

**SwissADME**: The SMILES of compounds 1 - 25 were uploaded to SwissADME (http://www.swissadme.ch/), pasting the list of smiles on the designated window. The following parameters were calculated: **Physicochemical Properties** (Formula, MW, Num. heavy atoms, Num. arom. heavy atoms, Fraction Csp3, Num. rotatable bonds, Num. H-bond acceptors, Num. H-bond donors, Molar Refractivity and TPSA); **Lipophilicity** (Log Po/w (iLOGP), Log Po/w (XLOGP3), Log Po/w (WLOGP), Log Po/w (MLOGP), Log Po/w (SILICOS-IT) and Consensus Log Po/w); **Water Solubility** (Log S (ESOL), Solubility, Class, Log S (Ali), Solubility, Class, Log S (SILICOS-IT),
Solubility and Class; Pharmacokinetics (GI absorption, BBB permeant, P-gp substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor and Log Kp -skin permeation-); Druglikeness (Lipinski, Ghose, Veber, Egan, Muegge and Bioavailability Score); Medicinal Chemistry (PAINS, Brenk, Lead likeness and Synthetic accessibility).

pkCSM: The SMILES of compounds 1 - 25 were uploaded to pkCSM (http://biosig.unimelb.edu.au/pkcsmprediction), through a *.txt SMILE file. The following parameters were calculated: Absorption (Water solubility, Caco2 permeability, Intestinal absorption (human), Skin Permeability, P-glycoprotein substrate, P-glycoprotein I inhibitor, P-glycoprotein II inhibitor); Distribution (VDss (human), Fraction unbound (human), BBB permeability, CNS permeability); Metabolism (CYP2D6 substrate, CYP3A4 substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibition); Excretion (Total Clearance, Renal OCT2 substrate); Toxicity (AMES toxicity, Max. tolerated dose (human), hERG I inhibitor, hERG II inhibitor, Oral Rat Acute Toxicity (LD50), Oral Rat Chronic Toxicity (LOAEL), Hepatotoxicity, Skin Sensitisation, T.Pyriformis toxicity, Minnow toxicity).

Biotransformer: The SMILES of compounds 9, 12, 13, 14, 15, 22 and 25 were uploaded to Biotransformer (http://biotransformer.ca/). The metabolites prediction was performed for one-step CYP450 catalyzed reactions.

Results and discussion

The salirasib analogs 1 - 13 were easily obtained from thiosalicylic acid and the proper halide in the presence of guanidinium carbonate in refluxing acetone, and compounds 14 – 25 were obtained through Click chemistry between propargyl thiosalicylic acid 1 and the proper azide, as we have previously reported [35]. The different R substituents were chosen in order to fill a wide place in chemical space, producing compounds with structural diversity and with an appropriate physicochemical properties distribution.

Since our compounds were inspired in salirasib, an ICMT inhibitor, we decided to compare the physicochemical properties of our compound collection with reported ICMT inhibitors. A search in ChemBL database [39,40] afforded a total of 467 reported HsICMT inhibitors. Using Osiris DataWarrior platform [38], we calculated the physicochemical properties of the ChemBL database and our collection. Normalized histograms are shown in Fig. 3, where molecular weight (MW), total surface area, cLogP and cLogS are presented,
comparing the distribution of the different properties among compounds belonging to the ChemBL database and our set of salirasib analogs. We can observe that the property distributions are very similar between both sets. For the ChemBL database, the maximum compound counts were at MW = 350 – 400 Da, total surface area = 250 – 300 Å², cLogP = 4.5 – 5, and cLogS = -5 – (-4.5). Instead, for our set of compounds, maximum counts were at MW = 250 - 350 Da, total surface area = 200 – 250 Å², cLogP = 3 – 3.5, and cLogS = -4.5 – (-4). The most frequent values for each property were a bit lower for our salirasib analogs library, but overall our collection covers a wide range of desirable properties to afford a good antiproliferative activity against cancer cell lines.

**Fig. 3.** Normalized physicochemical properties distribution for ChemBL dataset (ChemBL, green bars) and Salirasib analogs dataset (This Work, violet bars). Distributions were fitted to Kernel Smooth function (green and violet lines for ChemBL and This Work datasets, respectively). A) MW; B) Total Surface Area; C) cLogP; D) cLogS.

The in vitro antiproliferative activity of compounds 1 - 25 were tested against a panel of five human solid tumor cell lines: A549 (non-small cell lung), HeLa (cervix), SW1573 (non-small cell lung), T-47D (breast), and HBL-100 (breast) [45]. The measurement of the corresponding GI₅₀ was carried out, and results are shown in **Table 1**.
GI\textsubscript{50} is defined as the half maximal inhibitory concentration. The compounds were tested at a maximum concentration of 100 μM. Seven of the twenty-five compounds assayed were active against the five cell lines (GI\textsubscript{50} < 100 μM), and showed a similar trend against all of them. The detailed analysis of the Table 1, excluding Salirasib that is considered the positive control, showed only six compounds have GI\textsubscript{50} below 100 mM. The GI\textsubscript{50} of the active analogs are around 40 μM for the less potent, to below 5 μM for the most effective, without substantial differences between the cell lines.

Table 1. Antiproliferative activity of salirasib and its analogs (GI\textsubscript{50} < 100 μM).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Family</th>
<th>R</th>
<th>GI\textsubscript{50} (µM)</th>
<th>GI\textsubscript{50} range plot</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>A549</td>
<td>HeLa</td>
</tr>
<tr>
<td>9</td>
<td>S-R</td>
<td>Phytyl</td>
<td>14 ± 2.4</td>
<td>12 ± 2.4</td>
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<tr>
<td>12</td>
<td>S-R</td>
<td>Farnesyl (Salirasib)</td>
<td>34 ± 7.0</td>
<td>34 ± 5.1</td>
</tr>
<tr>
<td>13</td>
<td>S-R</td>
<td>Geranylgeranyl</td>
<td>38 ± 6.1</td>
<td>29 ± 2.9</td>
</tr>
<tr>
<td>14</td>
<td>S-triazolyl-R</td>
<td>Octyl</td>
<td>61 ± 3.4</td>
<td>39 ± 6.5</td>
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<tr>
<td>15</td>
<td>S-triazolyl-R</td>
<td>Cetyl</td>
<td>9.2 ± 0.7</td>
<td>6.9 ± 0.04</td>
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<tr>
<td>22</td>
<td>S-triazolyl-R</td>
<td>Phytyl</td>
<td>5.4 ± 0.7</td>
<td>4.3 ± 1.3</td>
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<tr>
<td>25</td>
<td>S-triazolyl-R</td>
<td>Farnesyl</td>
<td>40 ± 9.9</td>
<td>33 ± 3.3</td>
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</tbody>
</table>

Values are mean ± standard deviation of two to three independent experiments.

All the active compounds have in common that the sulphur is bound to an electron deficient carbon. So, the presence of an allyl or 4-triazolyl methylene next to the sulphur could be playing an important role in the recurrence of antiproliferative activity, but it would not be the only requirement. It was also very interesting to note that all the active analogs present long lipophilic chain substitutions, with or without a triazole linker, of at least eight carbon atoms. The most preferred R chains are farnesyl, geranylgeranyl, phytyl and cetyl. Interestingly, phytyl (9, 22) and cetyl (15) analogs, are both 16 carbons long, were more active than salirasib (12), as deduced from the GI\textsubscript{50} range plot (Table 1). This indicates that the R chain would be occupying the farnesyl pocket in the ICMT. Probably, the more flexible cetyl and phytyl chains could accommodate better in the lipophilic cavity, producing an activity increment.

In particular, compound 22 is the hit of this collection and has been shown to have better antiproliferative activity in all cell lines tested: it is 6.3 times more active in A549, 8 times more active in HeLa, 7 times more active in SW1573, 4.4 times more active in T-47D, and 2.2 more active in HBL-100 compared with salirasib. **Fig. 4** shows the activity profile of all active compounds, and their comparison with salirasib. It results interesting that
the thiosalicylic acid S-substituted with a triazolyl phytaly group presented the best performance. Phytaly S-substitution was previously studied in cysteine analogs, achieving interesting results as non steroidal anti-inflammatory agents targeting ICMT [46–49]. Also, in our previous study of salirasib analogs as antimalarial agents, phytaly substituted compounds, both with or without the triazole linker, were the most active compounds of the series, and presented similar potencies as the observed on the tumor cell lines (9, IC\textsubscript{50} (P. falciparum) = 13.40 ± 1.53 µM; 22, IC\textsubscript{50} (P. falciparum) = 9.75 ± 1.97 µM) [35]. This reinforces our hypothesis, where the triazolyl-phytaly group could be considered as a privileged structure for ICMT inhibitors, enhancing the thiosalicylic acid interaction with the active site. To our knowledge, the triazolyl-isoprenyl S-substitution of cysteine analogs was not previously studied as antiproliferative agents.

<table>
<thead>
<tr>
<th></th>
<th>A549</th>
<th>HeLa</th>
<th>SW1573</th>
<th>T-47D</th>
<th>HBL-100</th>
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<tr>
<td>9</td>
<td>2.43</td>
<td>2.83</td>
<td>2.73</td>
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<td>1.00</td>
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<td>7.07</td>
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<td>25</td>
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<td>1.03</td>
<td>1.03</td>
<td>0.81</td>
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</tr>
</tbody>
</table>

Fig 4. Trend map of active compounds against tumor cell lines (A549, HeLa, SW1573, T-47D, HBL-100). The green triangles show an improvement in biological activity compared to salirasib, while the red triangles show a loss of activity. The numbers reflect the improvement or loss of activity (= GI\textsubscript{50}salirasib / GI\textsubscript{50}product).

In order to have a deeper insight of the physicochemical properties required for this collection (and its biological response), we graphed different properties vs GI\textsubscript{50} for each cell line: MW, total surface area, LogD, and cLogS. Similar trends were observed for all the cell lines, so SAR graphs for A549 cell line were chosen to represent the panel (Fig. 5), while graphs for the rest can be found in the Supporting Information. Since our compounds collection have ionizable groups that are charged at physiological pH, LogD (pH = 7) [41] results a better lipophilicity descriptor than cLogP, and the former was used in the SAR analysis. It can be observed that there is a clear “high activity” zone for each property. In fact, there is a preference for active compounds that present a MW > 350 Daltons, total surface area > 300 Å\textsuperscript{2}, LogD > 3, and cLogS < -5.
Fig. 5. Correlation between antiproliferative activity against A549 cell line and physicochemical properties.

A) MW; B) Total Surface Area; C) LogD; D) cLogS.

Additionally, looking to predict the potential of the compounds as leads and their ADME-Tox properties, the selected candidates were evaluated using the web-based software SwissADME [42], Biotransformer [44] and pkCSM [43] (See Supporting Information). The SwissADME analysis on the active compounds (9, 12, 13, 14, 15, 22 and 25) thrown that they did not present PAINS alerts, although they did not fulfill the leadlikeness parameters for oral dosage, presenting 1 to 3 alerts. Only 25 did not present any violation regarding Lipinski, Ghose, Veber, Egan, and Muegge parameters. Unfortunately, the most active compounds 9, 15 and 22 were the ones that presented more druglikeness violations. In particular, 22 did not fulfill the minimum requirements to be considered as “druglike”, and was the one with more alerts of the series, despite it was the most active compound.

Regarding the metabolism process, the Biotransformer analysis thrown that these compounds could be metabolized by the CYP450 complex. The compounds could be substrates of CYP1A2, CYP2B6, CYP2C8,
CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and they could go under aliphatic, allylic or aromatic hydroxylations, thioether oxidation, arene epoxidation or terminal desaturation. The generation of more polar and soluble metabolites could allow a more effective elimination than expected for their parent compounds.

According to pkCSM prediction, all the active compounds present fairly good ADME-Tox properties. From the absorption estimation, we could expect a reduced colorectal permeability for 14, 15, 22, and 25, but all active compounds were predicted to have an excellent intestinal absorption. The volumes of distribution (VDss) are rather low, and it is most likely that the compounds remain bound to serum proteins, as we could expect from their solubility parameters, which could difficult the distribution process. Regarding excretion, clearance parameters were predicted to improve respect to salirasib (12), with the sole exception of 13. Also, the compounds did not present signs of being mutagenic, and only 14, 15, and 25 presented hepatotoxicity alerts.

Although druglikeness guidelines, such as Lipinski’s rule of 5 [50], establish a base of desirable parameters values that an active compound should have, in this case it seems to be “counterintuitive”, since the best compounds are the heaviest, largest, more non-polar and least soluble, which translates into a low oral bioavailability, and limiting the dosage mode. These types of compounds are more likely to require a formulation process, such as liposomes, to achieve a good \textit{in vivo} biological effect. This does not represent any disadvantage, since this type of formulations is widely used in cancer chemotherapies. For example, Doxorubicin and Daunorubicin may be given via liposomes.

**Conclusion**

In summary, we were able to validate our design of salirasib analogs, obtaining compounds that resulted to be better antiproliferative agents than salirasib, namely 9, 15 and 22 (Fig. 6). Also, our collection of salirasib analogs contributed to get a deeper insight of the physicochemical requirements (Fig. 7) that this kind of compounds need in order to achieve a proper anti-tumor activity. We could determine that all active compounds presented an electron deficient carbon alpha to the sulphur, being bound to an allyl or triazolyl group, which could mean that this electron density may be important in order to achieve a good interaction with the target. Furthermore, the most active compounds 9, 15 and 22 were characterized for having a 16 carbons long, flexible
aliphatic chain, which could be related to an improved lipophilic interaction with the enzyme. Although their physicochemical parameters are not optimal for oral dosage, other dosage forms, such as IV, could be explored.

![Structures](https://via.placeholder.com/150)

<table>
<thead>
<tr>
<th>Cell line</th>
<th>9</th>
<th>15</th>
<th>22</th>
</tr>
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<tbody>
<tr>
<td>A549</td>
<td>14 ± 2.4</td>
<td>9.2 ± 0.7</td>
<td>5.4 ± 0.7</td>
</tr>
<tr>
<td>HeLa</td>
<td>12 ± 2.4</td>
<td>6.9 ± 0.04</td>
<td>4.3 ± 1.3</td>
</tr>
<tr>
<td>SW1573</td>
<td>15 ± 3.3</td>
<td>9.3 ± 0.03</td>
<td>5.8 ± 0.6</td>
</tr>
<tr>
<td>T47D</td>
<td>18 ± 1.3</td>
<td>20 ± 5.9</td>
<td>9.6 ± 1.3</td>
</tr>
<tr>
<td>HBL-100</td>
<td>14 ± 1.9</td>
<td>14 ± 1.2</td>
<td>10 ± 1.1</td>
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</tbody>
</table>

**Fig. 6.** Selected most promising TSA derivatives.

![Graph](https://via.placeholder.com/150)

**Fig 7.** Structure-activity relationship of our library as antiproliferative agents.

Optimal physicochemical properties:
MW > 350 Da; TSA > 300 Å2; LogD > 3; cLogS < -5
Acknowledgements

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References


* The general protein prenylation process is established and different inhibition strategies are summarized.


* This review summarizes some of the most relevant ICMT inhibitors.


* This is the first report on salirasib.


** This article reports the synthesis of salirasib analogs under study in this work.


