

Supporting Information: Previous studies that reported the relationship between cancers/tumors and top most feasible drug candidate compounds selected for ALK, ELGN3 and NUAk1

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Citations/reports that related drug candidate compounds to cancers

Each compound listed to target each gene was shown below in the descending-order of FPAScores averaged over three trials. Compound IDs were taken from DrugBank.

ALK

7-Hydroxystaurosporine (DB01933)

This compound was reported to target 3-phosphoinositide dependent protein kinase-1 (PDK1 or PDK1) [1,2]. PDK1 was reported to be cancer-related therapeutic target gene [3]. This compound was also included in National Cancer Institute Drug Dictionary (NCIDD) that says "A synthetic derivative of staurosporine with antineoplastic activity. 7-hydroxystaurosporine inhibits many phosphokinases, including the serine/threonine kinase AKT, calcium-dependent protein kinase C, and cyclin-dependent kinases. This agent arrests tumor cells in the G1/S of the cell cycle and prevents nucleotide excision repair by inhibiting the G2 checkpoint kinase chk1, resulting in apoptosis."

3-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-yl-1H-pyrazol-4-yl)pyridin-2-amine (DB08700)

this compound was reported to target ALK, LCK, c-MET, TRKA, TRKB, TIE2 and ABL [4]. Hepatocyte growth factor receptor (c-MET) was also reported to be targeted by this compound in an additional report [5]. c-MET was reported to be cancer-related therapeutic target gene [6]. LCK [4] that was reported to a tumor antigen [7]. TRKA and TRKB are receptors of Trk kinase whose inhibition was reported to be as new treatments for cancer and pain [8]. Targeting the TIE2 was reported to inhibit tumor growth and metastasis [9]. Activation of Abl Tyrosine Kinases was reported to promote invasion of aggressive breast cancer cells [10].

BIOTINOL-5-AMP (DB04651)

There were no reports that suggest tight relationship with cancers.

4-[4-(1-Amino-1-Methylethyl)Phenyl]-5-Chloro-N-[4-(2-Morpholin-4-Ylethyl)Phenyl] Pyrimidin-2-Amine (DB02491)

This compound was reported to target FGFR-2 [1,2] that was reported to be related to be cancers [11].

9-HYDROXY-6-(3-HYDROXYPROPYL)-4-(2-METHOXYPHENYL)PYRROLO[3,4-C]CARBAZOLE-1,3(2H,6H)-DIONE (DB07006)

This compound was reported to target WEE1 [5] that was reported to be targeted to treat cancer [12].

Staurosporine (DB02010)

This compound was reported to target LCK, PIM1, ITK, SYK, MAPKAPK2, GSK3B, CSK, CDK2, PIK3CG, PDPK1, ZAP70 [1, 2]. LCK and PDPK1 were reported to be related to cancers in the above. PIM1 was reported to be a therapeutic target gene for cancers [13]. ITK was reported to be a therapeutic target gene for cancers [14]. SYK was reported to suppress malignant growth of human breast cancer cells. [15]. A functional copy-number variation in MAPKAPK2 predicts risk and prognosis of lung cancer [16]. Inhibition of GSK3 activity was reported to trigger an apoptotic response in pancreatic cancer cells through JNK-dependent mechanisms [17]. Overexpression of the CSK gene was reported to suppress tumor metastasis in vivo [18]. CDK was well-known therapeutic target gene by inhibition [19]. PIK3CG was reported to be down-regulated by CpG hypermethylation in human colorectal carcinoma [20]. ZAP-70 expression was reported to identify a chronic lymphocytic leukemia subtype [21].

6-Hydroxy-Flavin-Adenine Dinucleotide (DB02654)

There were no reports that suggest tight relationship with cancers.

2-({5-CHLORO-2-[(2-METHOXY-4-MORPHOLIN-4-YLPHENYL)AMINO]PYRIMIDIN-4-YL}AMINO)-N-METHYLBENZAMIDE (DB07460)

This compound was reported to target PTK2 [5] and ALK [22]. Molecular characterization of the role of PTK2 amplification in oral squamous cell carcinoma was investigated [23].

4-(4-METHYLPIPERAZIN-1-YL)-N-[5-(2-THIENYLACETYL)-1,5-DIHYDROPYRROLO[3,4-C]PYRAZOL-3-YL]BENZAMIDE (DB07186)

This compound was reported to target AURKA and PLK1 [5]. AURKA was reported to be related to breast cancer [24]. Inhibition of PLK1 was reported to suppress cancer cell [25].

Riboflavin Monophosphate (DB03247)

This compound was reported to target 55 genes in DrugBank. However, targeted human genes were limited and were RPS6KA4, HAO2, POR, PPCDC, SGK1 [5], BLVRB [1, 2], HAO1, PNPO, RFK, NOS1, DPYD, and DHODH [1, 2, 5]. Not all, but some of them were reported to be related to cancers. NF- κ B induction of RPS6KA4 was reported to block p53 degradation in colon cancer cell [26]. POR, also termed as P450, was suggested to related to cancers [27]. Elevated SGK1 was reported to predict resistance of breast cancer cells to Akt inhibitors [28]. Loss of NOS1 expression in high-grade renal cell carcinoma was reported to be associated with a shift of no signalling [29]. Absence of large intragenic rearrangements in the DPYD gene was reported in a large cohort of colorectal cancer patients treated with 5-FU-based chemotherapy [30]. DHODH inhibition was proposed as a candidate of cancer treatment [31].

EGLN3 (with Fe)

2-[4-[[[(S)-1-[[[(S)-2-[[[(Rs)-3,3,3-Trifluoro-1-Isopropyl-2-Oxopropyl]Aminocarbonyl]Pyrrolidin-1-Yl-]Carbonyl]-2-Methylpropyl]Aminocarbonyl]Benzoylamino]Acetic Acid (DB03702)

This compound was reported to target CELA1 [1, 2, 5] that was reported to be upregulated in pancreatic tumor cell [32].

PYRIMIDINE-4,6-DICARBOXYLIC ACID BIS-[(PYRIDIN-3-YLMETHYL)-AMIDE] (DB04761)

This compound was reported to target MMP13 [5] that was reported to promote tumor angiogenesis directly and indirectly [33].

N-[(1-CHLORO-4-HYDROXYISOQUINOLIN-3-YL)CARBONYL]GLYCINE (DB08687)

This compound was reported to inhibit EGLN1 [34] that was reported to be differentially expressed in cancer-associated fibroblasts [35]. This compound was also reported to inhibit PHD2 [36] that was reported to improve tumor response to chemotherapy and to prevent side-toxicity when targeted [37].

2-{4-[2-(2-AMINO-4-OXO-4,7-DIHYDRO-3H-PYRROLO[2,3-D]PYRIMIDIN-5-YL)-ETHYL]-BENZOYLAMINO}-3-METHYL-BUTYRIC ACID (DB08131)

This compound was reported to target thyA [5] that was reported to be a critical target for cancer chemotherapy [38].

5-Formyl-6-Hydrofolic Acid (DB02718)

There were no reports that suggest tight relationship with cancers.

Dihydrofolic Acid (DB02015)

There were no reports that suggest tight relationship with cancers.

(6s)-5,6,7,8-Tetrahydrofolate (DB02031)

This compound was reported to target nos and thyA [1, 2]. Although these two are bacterial proteins, NOS1, which is human homolog to nos1, and thyA were reported to be related to cancers in the above.

PYRIMIDINE-4,6-DICARBOXYLIC ACID BIS-(4-FLUORO-3-METHYL-BENZYLAMIDE) (DB04760)

This compound was reported to target MMP13 [5] that was reported to be related to cancers in the above.

PYRIMIDINE-4,6-DICARBOXYLIC ACID BIS-(3-METHYL-BENZYLAMIDE) (DB04759)

This compound was reported to inhibit MMP13 [39] that was reported to be related to cancers in the above.

N-[(4-HYDROXY-8-iodoisoquinolin-3-yl)carbonyl]glycine (DB07112)

This compound was reported to target EGLN1 [5] and to inhibit PHD2 [40]. EGLN1 and PHD2 were reported to be related to cancers in the above.

EGLN3 (without Fe)**N-[(1-CHLORO-4-HYDROXYISOQUINOLIN-3-YL)CARBONYL]GLYCINE (DB08687)**

This compound was reported to inhibit EGLN1 [34], PHD2 [36] and HIF1A [5]. EGLN1 and PHD2 were reported to be related to cancers in the above. HIF1 was known to be target for cancer therapy [41].

2-[4-[[[(S)-1-[[[(S)-2-[[[(Rs)-3,3,3-Trifluoro-1-Isopropyl-2-Oxopropyl]Aminocarbonyl]Pyrrolidin-1-Yl]-]Carbonyl]-2-Methylpropyl]Aminocarbonyl]Benzoylamino]Acetic Acid (DB03702)

This compound was reported in the above.

PYRIMIDINE-4,6-DICARBOXYLIC ACID BIS-(3-METHYL-BENZYLAMIDE) (DB04759)

This compound was reported in the above.

5,10-Dideazatetrahydrofolic Acid (DB03625)

This compound was reported to inhibit mouse recombinant GARFTase [42]. Some compounds that inhibit GARFTase were proposed to be therapeutic targeting malignant mesothelioma [43].

PYRIMIDINE-4,6-DICARBOXYLIC ACID BIS-(4-FLUORO-3-METHYL-BENZYLAMIDE) (DB04760)

This compound was reported in the above.

N-[(4-HYDROXY-8-iodoisoquinolin-3-yl)carbonyl]glycine (DB07112)

This compound was reported in the above.

Dihydrofolic Acid (DB02015)

This compound was reported in the above.

10-Propargyl-5,8-Dideazafolic Acid (DB03541)

This compound was reported to inhibit TYMS [44] and DHFR [45]. TYMS [46] and DHFR [47] were reported to be related to cancers, respectively.

Folic Acid (DB00158)

Folic acid were not proven to be related to cancers.

PYRIMIDINE-4,6-DICARBOXYLIC ACID BIS-[(PYRIDIN-3-YLMETHYL)-AMIDE] (DB04761)

This compound was reported in the above.

NUAK1**1-cyclobutyl-3-(3,4-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (DB08053)**

This compound was reported to inhibit numerous target genes (more than a hundred reported in ChEMBL under the chemblid:CHEMBL1233881). For example, this compound was reported to inhibit CSF1R that was reported to improve the efficacy of radiotherapy in prostate Cancer if its signaling is blocked [48]. For more genes inhibited by this compound, see ChEMBL directly.

1-cyclopentyl-3-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (DB08052)

This compound was reported to inhibit numerous target genes (more than a hundred reported in ChEMBL under the chemblid:CHEMBL1081312). For example, this compound was also reported to inhibit CSF1R. For more genes inhibited by this compound, see ChEMBL directly.

1-(1-methylethyl)-3-quinolin-6-yl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (DB08054)

This compound was reported to inhibit numerous target genes (more than a hundred reported in ChEMBL under the chemblid:CHEMBL1233882). For example, this compound was also reported to inhibit CSF1R. For more genes inhibited by this compound, see ChEMBL directly.

1-{7-cyclohexyl-6-[4-(4-methylpiperazin-1-yl)benzyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}methanamine (DB07563)

This compound was reported to target Cathepsin K (CTSK) [5] that was reported to be expressed in prostate cancer progression [49].

1-TERT-BUTYL-3-(2,5-DIMETHYLBENZYL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-4-AMINE (DB08035)

This compound was reported to target AR [50] that was reported to promote prostate cancer epithelial cell growth and invasion in human prostate cancer-associated fibroblasts [51].

3-(4-Amino-1-Tert-Butyl-1h-Pyrazolo[3,4-D]Pyrimidin-3-YI)Phenol (DB04463)

This compound was reported to target Carbonyl reductase 1 (CBR1) [5] that was reported to promote malignant behaviours when its expression decrease [52].

1-methyl-3-naphthalen-2-yl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (DB08300)

This compound was reported to inhibit numerous target genes (more than a hundred reported in ChEMBL under the chemblid:CHEMBL1234815). For example, this compound was also reported to inhibit CSF1R. For more genes inhibited by this compound, see ChEMBL directly.

1-Ter-Butyl-3-P-Tolyl-1h-Pyrazolo[3,4-D]Pyrimidin-4-Ylamine (DB01809)

This compound was reported to inhibit numerous target genes (more than half a hundred reported in ChEMBL under the chemblid:CHEMBL306380). For example, this compound was reported to inhibit PKD1 that was reported to inhibit cancer cells migration and invasion via Wnt signaling pathway in vitro [53]. For more genes inhibited by this compound, see ChEMBL directly.

3-[(4-AMINO-1-TERT-BUTYL-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)METHYL]PHENOL (DB08461)

This compound was reported to target AR [50] that was reported in the above.

1-tert-butyl-3-(3-methylbenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (DB08699)

This compound was reported to target CAMK2G [5] that was reported to be differentially expressed between colon and rectal cancer [54].

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