

## Small molecule inhibitors in pancreatic cancer

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Electronic Supporting Information

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Table S1      Origin of compound, natural or synthetic

**Table S1.** Origin of compounds, natural versus synthetic, evaluated in clinical trials against pancreatic cancer

<b>Compounds</b>	<b>Origin</b>	<b>Compounds</b>	<b>Origin</b>
Gemcitabine (1)	synthetic	PD173074 (42)	synthetic
5-FU (2)	natural	PKC412 (43)	synthetic
Nab-paclitaxel (3)	semisynthetic	BGB324 (44)	synthetic
leucovorin (4)	synthetic	GSK2256098 (45)	synthetic
irinotecan (5)	semisynthetic	PF573228 (46)	synthetic
oxaliplatin (6)	synthetic	Binimetinib (MEK162) (47)	synthetic
PF-562271 (7)	synthetic	Cobimetinib (48)	synthetic
LB-100 (8)	synthetic	GSK2656157 (49)	synthetic
C4 (9)	synthetic	3-(2,5-dimethoxyphenyl)-N-((4-(5-(4-fluorophenyl)-2-(methylthio)-1H-imidazol-4-yl)pyridin-2-yl)carbamoyl)-propanamide (50)	synthetic
CI-1040 (10)	synthetic	SCH727965 (dinaciclib) (51)	synthetic
Marizomib (11)	synthetic	AZD6738 (52)	synthetic
Salirasib (12)	synthetic	L61H46 (53)	synthetic
Vorinostat (13)	synthetic	PG-53-001 (54)	synthetic
Pimasertib (14)	synthetic	HJC0416 (55)	synthetic
AZD1775 (15)	synthetic	XZH-5 (56)	synthetic
Saridegib (16)	synthetic	methyl N $\alpha$ -(((3,5-bis(trifluoromethyl)phenyl)-carbamoyl)isoleucyl)-N $\tau$ -methyl-L-histidinate (57)	synthetic
capecitabine (17)	synthetic	Cryptotanshinone (58)	natural
Pazopanib (18)	synthetic	JQ1 (59)	synthetic
Vatalanib (19)	synthetic	I-BET 762 (60)	synthetic
Galunisertib (20)	synthetic	ST-3595 (61)	synthetic
Hydroxychloroquine (21)	synthetic	CG200745 (62)	synthetic
Lapatinib (22)	synthetic	MGCD0103 (63)	synthetic
Vandetanib (23)	synthetic	Belinostat (64)	synthetic
Sorafenib (24)	synthetic	Panobinostat (65)	synthetic
erlotinib (25)	synthetic	UMI-77 (66)	synthetic
Dasatinib (26)	synthetic	4-((6-nitroquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl benzamide (67)	synthetic
Saracatinib (27)	synthetic	2,3,4,6-tetrahydroxy-5H-benzo[7]annulen-5-one (68)	synthetic
Imatinib (28)	synthetic	TW-37 (69)	synthetic
Vismodegib (29)	synthetic	ABT737 (70)	synthetic
Dactolisib (30)	synthetic	BMS-754807 (71)	synthetic
Everolimus (31)	synthetic	P1608K04 (72)	synthetic
PX-12 (32)	synthetic	MI-319 (73)	synthetic
Veliparib (33)	synthetic	NPC-26 (74)	synthetic
Trametinib (34)	synthetic	Spongiatriol (75)	natural
Selumetinib (35)	synthetic	SW IV-134 (76)	synthetic
Rigosertib (36)	synthetic	BAY ACC002 (77)	synthetic
Olaparib (37)	synthetic	ICG-001 (78)	synthetic
Axitinib (38)	synthetic	IPI-269609 (79)	synthetic
cisplatin (39)	synthetic	MRK-003 (80)	synthetic
Mitomycin C (40)	natural	MDC-1016 (81)	synthetic
Sunitinib (41)	synthetic	TIC10/ONC201 (82)	synthetic

<b>Table S2.</b> Compound, pancreatic cancer IC <sub>50</sub> and protein target(s)		
<b>Compound</b>	<b>IC<sub>50</sub> (μM)</b>	<b>Target</b>
Gemcitabine (1)	0.0035-0.524 (AsPC-1, BxPC-3, Capan-1, Capan-2, CFPAC1,H48N, Hs766T, KP-1N, KP-2, KP-3, MIA PaCa-2, NOR-P1, Panc1, SUIT-2, SW1990)	Thymidylate synthase and dihydrofolate reductase
5-FU (2)	0.93-6.29 (AsPC-1, BxPC-3, Capan-1, Capan-2, CFPAC1,H48N, Hs766T, KP-1N, KP-2, KP-3, MIA PaCa-2, NOR-P1, Panc1, SUIT-2, SW1990)	Thymidylate synthase
Nab-paclitaxel (3)	0.243-4.9 (AsPC-1, BxPC-3, MiaPaCa-2 and Panc-1)	Microtubulin
leucovorin (4)	NA*	No target
irinotecan (5)	0.426, 0.491, 0.68, 0.26 (pa01c, pa02c, MiaPaCa-2, Panc-1)	Topoisomerase I
oxaliplatin (6)	< 0.025 ( COLO-357, MiaPaCa-2)	Deoxyribonucleic Acid (DNA)
PF-562271 (7)	NA*	Focal adhesion kinase and pyruvate kinase 2
LB-100 (8)	3.98, 0.85 (panc-1, BxPC-3)	Protein phosphatase 2A
C4 (9)	NA*	Focal adhesion kinase
CI-1040 (10)	NA*	Mitogen-activated protein kinase
Marizomib (11)	NA*	Proteasome
Salirasib (12)	NA*	RAS signalling pathway
Vorinostat (13)	1.6 (MiaPaCa-2)	Histone deacetylase (HDAC)
Pimasertib (14)	NA*	Mitogen-activated protein kinase 1/2
AZD1775 (15)	0.5-2.1 (AsPC-1, Capan-1, Capan-2, MIA PaCa-2, PANC-1, SNU213, SNU324, and SNU410)	Wee1 kinase
Saridegib (16)	NA*	Hedgehog signalling pathway
capecitabine (17)	NA*	Deoxyribonucleic Acid (DNA)
Pazopanib (18)	NA*	VEGF tyrosine kinase receptors 1, 2, and 3
Vatalanib (19)	NA*	Polytyrosine kinase
Galunisertib (20)	NA*	Amtransforming growth factor-beta receptor serine/threonine kinase
Hydroxychloroquine (21)	33 (BxPC-3)	Autophagy
Lapatinib (22)	< 2 μM (BxPc-3,HPAC)	HER2/neu and EGF receptor tyrosine kinase
Vandetanib (23)	18 (ASPC-1)	VEGFR2, RET, and EGFR tyrosine kinase
Sorafenib (24)	6.07 (HEK293T with KARS mutation)	VEGF receptor tyrosine kinase
erlotinib (25)	1.6 (ASPC-1)	EGFR Tyrosine kinase
Dasatinib (26)	0.02-0.25 (HPAC1, Panc0403, Panc0504, Panc1005, Panc0813, CaPan2)	SRC (a non-receptor tyrosine kinase protein) and ABL receptor tyrosine kinases
Saracatinib (27)	NA*	SRC receptor tyrosine kinases
Imatinib (28)	15, 17, 19, 30 (BxPC-3, HPAC, MiaPaCa-2, and Panc-1)	PDGFRs tyrosine kinase
Vismodegib (29)	6.3 (MiaPaCa-2)	Hedgehog signalling pathway
Dactolisib (30)	NA*	Phosphatidylinositol 3-kinase and the mammalian target of rapamycin
Everolimus (31)	NA*	Mammalian target of rapamycin
PX-12 (32)	NA*	Proto-oncogene thioredoxin
Veliparib (33)	12 (MiaPaCa-2) <sup>16</sup>	Poly (ADP ribose) polymerase
Trametinib (34)	0.0384, >5 (BxPC-3, panc-1)	Mitogen-activated protein kinase
Selumetinib (35)	NA*	Mitogen-activated protein kinase 1/2
Rigosertib (36)	NA*	Polo-like kinase 1 and phosphoinositide 3-kinase
Olaparib (37)	9 (MiaPaCa-2)	Poly (ADP ribose) polymerase
Axitinib (38)	NA*	Receptor tyrosine kinase of VEGFR
cisplatin (39)	0.215, 0.507, 0.186,0.952 (Pa01c, pa02c, pa03c, pa04c)	Deoxyribonucleic Acid (DNA)
Mitomycin C (40)	0.00476, 0.054, 0.00474,0.00634 (Pa01c, pa02c, pa03c, pa04c) <sup>3</sup>	Deoxyribonucleic Acid (DNA)
Sunitinib (41)	NA*	VEGFR and PDGFR tyrosine kinase

PD173074 (42)	2.5 to 15 (AsPC-1, Capan-1, HPAF-II, MiaPaCa-2, and Panc 1)	FGFR1 tyrosine kinase; VEGFR2
PKC412 (43)	0.25 to 20 (16 pancreatic cancer cell lines)	Ser/Thr and tyrosine kinases, including fms-like tyrosine kinases, protein kinase C, VEGFR2, tyrosine-protein kinase Kit, PDGFR $\alpha$ , and PDGFR $\beta$
BGB324 (44) + gemcitabine (1)	0.016, 0.0069 (AsPC-1, MiaPaCa-2)	Receptor tyrosine kinase Axl
GSK2256098 (45)	25, 29 (L3.6P1, Panc-1)	Focal adhesion kinase
PF573228 (46)	NA*	Focal adhesion kinase
Binimetinib (MEK162) (47)	0.092, 0.28 and 0.316 (MiaPaCa-2, AsPC-1, and CAPAN-2)	Mitogen-activated protein kinase kinase
Cobimetinib (48)	NA	Mitogen-activated protein kinase kinase
GSK2656157 (49)	NA*	Protein kinase R (PKR)-like endoplasmic reticulum kinase
3-(2,5-dimethoxyphenyl)-N-((4-(5-(4-fluorophenyl)-2-(methylthio)-1H-imidazol-4-yl)pyridin-2-yl)carbamoyl)-propanamide (50)	EC <sub>50</sub> : 3.5, 1.5 (Colo357, Panc89)	Protein kinase CK1 $\delta$
SCH727965 (dinaciclib) (51)	GI <sub>50</sub> : 0.01, 0.02 (MiaPaCa-2, Pa20C)	Cyclin-dependent kinase (CDK) inhibitor for CDK2, CDK5, CDK1 and CDK9
AZD6738 (52)	GR <sub>50</sub> : 0.9 $\mu$ M, 1.57, 1.98, 3.2, 4.8, 9.8, 32.3 (SW1990, Capan-1, AsPC-1, HPAF-II, Capan-2, MiaPaCa-2, and Panc-1)	Ataxia telangiectasia and Rad3-related protein
L61H46 (53)	0.86, 2.83 (BxPC-3, Panc-1)	Signal transducer and activator of transcription3
PG-S3-001 (54)	ED <sub>50</sub> : 2.4 (Panc10.05)	Signal transducer and activator of transcription3
HJC0416 (55)	0.04, 1.88 (AsPC-1, Panc-1)	Signal transducer and activator of transcription3
XZH-5 (56)	24.7, 17.4 and 17.9 (Panc-1, HPAC, and SW1990)	Signal transducer and activator of transcription3
methyl N $\alpha$ -(((3,5-bis(trifluoromethyl)phenyl)-carbamoyl)isoleucyl)-N $\tau$ -methyl-L-histidinate (57)	10.1, 7.6, 8.3 (Panc-1, HPAC, and SW1990)	Signal transducer and activator of transcription3
Cryptotanshinone (58)	NA*	Signal transducer and activator of transcription3
JQ1 (59)	0.037, 0.72 and 0.19 (AsPC-1, Panc-1, and CAPAN-1)	Bromodomain and extra terminal proteins: BRD2, BRD3 and BRD4
I-BET 762 (60)	0.231, 2.55 and 0.99 (AsPC-1, Panc-1, and CAPAN-1)	Bromodomain and extra terminal proteins: BRD2, BRD3 and BRD4
BMS-754807 (71) + gemcitabine (1)	0.075, 0.070, 0.016, 0.016 (AsPC, Panc-1, MiaPaCa-2, and BxPC-3)	IGF-1R and insulin receptor (IR) family kinases
P1608K04 (72)	8.5, 14, and 20 (Panc-1, MiaPaCa-2, and AsPC1)	Protein arginine methyltransferases
MI-319 (73)	NA*	Murine double minute 2 protein
NPC-26 (74)	NA*	Mitochondrion interfering
Songiatriol (75)	13, 8, 6 and 13 (AsPC-1, BxPC-3, MiaPaCa-2 and Panc-1)	Nuclear factor kappa B
UMI-77 (66)	3.4, 4.4 and 5.5 (AsPC-1, BxPC-3, and Capan-2)	Bcl-2 family proteins
4-((6-nitroquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl benzamide (67)	15.1 (BxPC-3)	Bcl-2 family proteins
2,3,4,6-tetrahydroxy-5H-benzo[7]annulen-5-one (68)	17.6 (MiaPaCa-2)	Bcl-2 family proteins
TW-37 (69)	NA*	Bcl-2 family proteins
ABT737 (70)	NA*	Bcl-2 family proteins
ST-3595 (61)	NA*	Histone deacetylases
CG200745 (62)	2.4, 10.7 and 7.4 (BxPC3, CFPAC1 and HPAC)	Histone deacetylases
MGCD0103 (63)	3.9, 1.1, 0.6 and 1.8 (AsPC-1, BxPC-3, MiaPaca-2, and Panc-1)	Histone deacetylases
Belinostat (64)	EC <sub>50</sub> : 0.3, 0.7, 0.5, 1.1, 1.1 and 0.7	Histone deacetylases

	(AsPC1, BxPC3, Panc0327, Panc0403, and Panc1005, MiaPaCa-2)	
Panobinostat ( <b>65</b> )	0.284, 0.00046, 0.0077, 0.261, 0.013 (BxPC3, Panc0327, Panc0403, Panc1005, and MiaPaCa-2)	Histone deacetylases
SW IV-134 ( <b>76</b> )	7.4, 6.8, 6.3 and 7.8 (CFPAC-1, BxPC-3, AsPC-1, Panc-1 and MiaPaCa-2)	Sigma-2 receptor
BAY ACC002 ( <b>77</b> )	NA*	Acetyl-CoA carboxylase 1 and 2; Hedgehog signalling pathway
ICG-001 ( <b>78</b> )	5.48, 14.07, 3.43 and 3.31 (AsPC-1, L3.6pl, Panc-1 and MiaPaCa-2)	CREB-binding protein
IPI-269609 ( <b>79</b> )	NA*	Hedgehog signalling pathway
MRK-003 ( <b>80</b> )	NA*	Gamma secretase
MDC-1016 ( <b>81</b> )	NA*	RAS inhibitor
TIC10/ONC201 ( <b>82</b> )	NA*	Tumour necrosis (TNF)-related apoptosis-inducing ligand

\*NA: The IC<sub>50</sub> value is not available in the related literature.