

Supporting Information

Design and synthesis of pyrrole-5-(2,6-dichlorobenzyl)sulfonylindolin-2-ones with C-3' side chains as potent Met kinase inhibitors

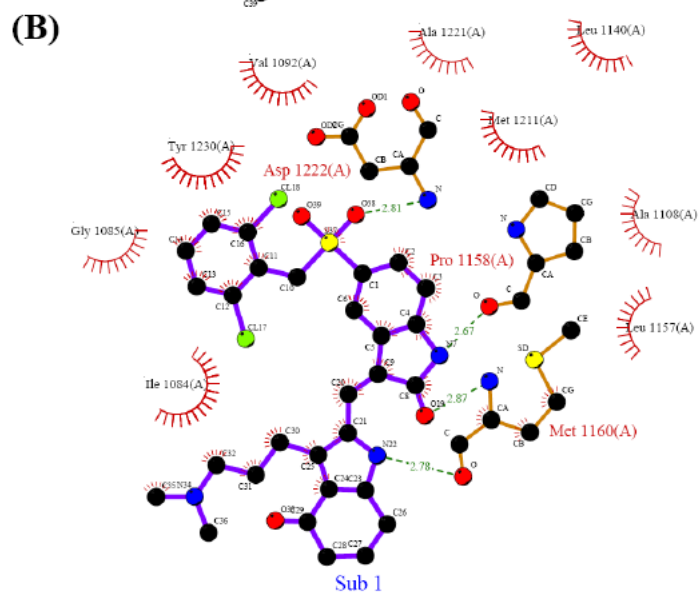
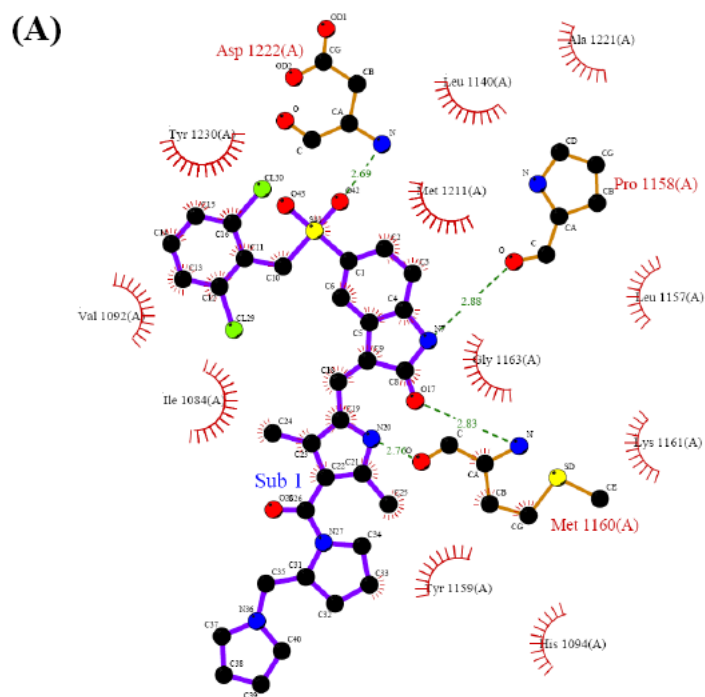
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Key

- Ligand bond
- Non-ligand bond
- Hydrogen bond and its length
- His 53 Non-ligand residues involved in hydrophobic contact(s)
- Corresponding atoms involved in hydrophobic contact(s)

Supporting Figure. Ligplot diagrams¹ of the ATP binding site of Met complexed with compounds **2** and **20**: (A) Met with **2**, and (B) Met with **20**.

Supporting Table. Kinase profiling data of 20.

Ambit KinomeScan Kinase Profiling (1.0 μ M test concentration):

| Ambit Gene Symbol | Percentage of control (%) |
|-------------------------------|---------------------------|
| | 20 |
| AAK1 | 68 |
| ABL1(E255K)-phosphorylated | 85 |
| ABL1(F317I)-nonphosphorylated | 78 |
| ABL1(F317I)-phosphorylated | 65 |
| ABL1(F317L)-nonphosphorylated | 76 |
| ABL1(F317L)-phosphorylated | 100 |
| ABL1(H396P)-nonphosphorylated | 65 |
| ABL1(H396P)-phosphorylated | 72 |
| ABL1(M351T)-phosphorylated | 83 |
| ABL1(Q252H)-nonphosphorylated | 64 |
| ABL1(Q252H)-phosphorylated | 73 |
| ABL1(T315I)-nonphosphorylated | 74 |
| ABL1(T315I)-phosphorylated | 95 |
| ABL1(Y253F)-phosphorylated | 75 |
| ABL1-nonphosphorylated | 73 |
| ABL1-phosphorylated | 75 |
| ABL2 | 78 |
| ACVR1 | 100 |
| ACVR1B | 74 |
| ACVR2A | 95 |
| ACVR2B | 79 |
| ACVRL1 | 100 |
| ADCK3 | 81 |
| ADCK4 | 86 |
| AKT1 | 100 |
| AKT2 | 100 |
| AKT3 | 100 |
| ALK | 70 |
| AMPK-alpha1 | 11 |
| AMPK-alpha2 | 34 |
| ANKK1 | 60 |

| Ambit Gene Symbol | Percentage of control (%) |
|-------------------|---------------------------|
| | 20 |
| ARK5 | 27 |
| ASK1 | 100 |
| ASK2 | 67 |
| AURKA | 49 |
| AURKB | 74 |
| AURKC | 24 |
| AXL | 27 |
| BIKE | 53 |
| BLK | 72 |
| BMPR1A | 76 |
| BMPR1B | 64 |
| BMPR2 | 85 |
| BMX | 81 |
| BRAF | 89 |
| BRAF(V600E) | 98 |
| BRK | 87 |
| BRSK1 | 65 |
| BRSK2 | 72 |
| BTK | 100 |
| BUB1 | 64 |
| CAMK1 | 50 |
| CAMK1D | 67 |
| CAMK1G | 64 |
| CAMK2A | 91 |
| CAMK2B | 79 |
| CAMK2D | 87 |
| CAMK2G | 86 |
| CAMK4 | 100 |
| CAMKK1 | 7.2 |
| CAMKK2 | 15 |
| CASK | 63 |

| Ambit Gene Symbol | Percentage of control (%) |
|---------------------|---------------------------|
| | 20 |
| CDC2L1 | 100 |
| CDC2L2 | 95 |
| CDC2L5 | 71 |
| CDK11 | 84 |
| CDK2 | 73 |
| CDK3 | 95 |
| CDK4-cyclinD1 | 42 |
| CDK4-cyclinD3 | 46 |
| CDK5 | 75 |
| CDK7 | 11 |
| CDK8 | 87 |
| CDK9 | 55 |
| CDKL1 | 68 |
| CDKL2 | 9.7 |
| CDKL3 | 78 |
| CDKL5 | 96 |
| CHEK1 | 100 |
| CHEK2 | 100 |
| CIT | 100 |
| CLK1 | 49 |
| CLK2 | 32 |
| CLK3 | 67 |
| CLK4 | 79 |
| CSF1R | 6.8 |
| CSF1R-autoinhibited | 71 |
| CSK | 79 |
| CSNK1A1 | 51 |
| CSNK1A1L | 83 |
| CSNK1D | 32 |
| CSNK1E | 16 |
| CSNK1G1 | 89 |
| CSNK1G2 | 88 |
| CSNK1G3 | 66 |
| CSNK2A1 | 41 |
| CSNK2A2 | 25 |

| Ambit Gene Symbol | Percentage of control (%) |
|---------------------------|---------------------------|
| | 20 |
| CTK | 50 |
| DAPK1 | 58 |
| DAPK2 | 86 |
| DAPK3 | 36 |
| DCAMKL1 | 32 |
| DCAMKL2 | 18 |
| DCAMKL3 | 9.8 |
| DDR1 | 17 |
| DDR2 | 30 |
| DLK | 67 |
| DMPK | 100 |
| DMPK2 | 71 |
| DRAK1 | 100 |
| DRAK2 | 54 |
| DYRK1A | 100 |
| DYRK1B | 67 |
| DYRK2 | 62 |
| EGFR | 100 |
| EGFR(E746-A750del) | 100 |
| EGFR(G719C) | 64 |
| EGFR(G719S) | 67 |
| EGFR(L747-E749del, A750P) | 100 |
| EGFR(L747-S752del, P753S) | 100 |
| EGFR(L747-T751del,Sins) | 67 |
| EGFR(L858R) | 94 |
| EGFR(L858R,T790M) | 83 |
| EGFR(L861Q) | 57 |
| EGFR(S752-I759del) | 70 |
| EGFR(T790M) | 57 |
| EIF2AK1 | 85 |
| EPHA1 | 82 |
| EPHA2 | 90 |
| EPHA3 | 67 |
| EPHA4 | 82 |
| EPHA5 | 76 |

| Ambit Gene Symbol | Percentage of control (%) |
|-------------------|---------------------------|
| | 20 |
| EPHA6 | 83 |
| EPHA7 | 70 |
| EPHA8 | 66 |
| EPHB1 | 79 |
| EPHB2 | 96 |
| EPHB3 | 97 |
| EPHB4 | 100 |
| EPHB6 | 91 |
| ERBB2 | 73 |
| ERBB3 | 86 |
| ERBB4 | 78 |
| ERK1 | 85 |
| ERK2 | 80 |
| ERK3 | 90 |
| ERK4 | 100 |
| ERK5 | 50 |
| ERK8 | 38 |
| ERN1 | 57 |
| FAK | 58 |
| FER | 100 |
| FES | 100 |
| FGFR1 | 87 |
| FGFR2 | 89 |
| FGFR3 | 86 |
| FGFR3(G697C) | 64 |
| FGFR4 | 83 |
| FGR | 63 |
| FLT1 | 100 |
| FLT3 | 40 |
| FLT3(D835H) | 18 |
| FLT3(D835Y) | 9.8 |
| FLT3(ITD) | 9 |
| FLT3(K663Q) | 29 |
| FLT3(N841I) | 15 |
| FLT3(R834Q) | 54 |

| Ambit Gene Symbol | Percentage of control (%) |
|------------------------------|---------------------------|
| | 20 |
| FLT3-autoinhibited | 86 |
| FLT4 | 100 |
| FRK | 96 |
| FYN | 78 |
| GAK | 74 |
| GCN2(Kin.Dom.2,S808G) | 76 |
| GRK1 | 2 |
| GRK4 | 71 |
| GRK7 | 3 |
| GSK3A | 81 |
| GSK3B | 70 |
| HASPIN | 87 |
| HCK | 88 |
| HIPK1 | 60 |
| HIPK2 | 37 |
| HIPK3 | 41 |
| HIPK4 | 74 |
| HPK1 | 30 |
| HUNK | 50 |
| ICK | 49 |
| IGF1R | 87 |
| IKK-alpha | 70 |
| IKK-beta | 85 |
| IKK-epsilon | 65 |
| INSR | 56 |
| INSRR | 100 |
| IRAK1 | 13 |
| IRAK3 | 45 |
| IRAK4 | 4.2 |
| ITK | 81 |
| JAK1(JH1domain-catalytic) | 69 |
| JAK1(JH2domain-pseudokinase) | 82 |
| JAK2(JH1domain-catalytic) | 3.6 |
| JAK3(JH1domain-catalytic) | 12 |
| JNK1 | 100 |

| Ambit Gene Symbol | Percentage of control (%) |
|-------------------|---------------------------|
| | 20 |
| JNK2 | 100 |
| JNK3 | 100 |
| KIT | 47 |
| KIT(A829P) | 45 |
| KIT(D816H) | 64 |
| KIT(D816V) | 49 |
| KIT(L576P) | 20 |
| KIT(V559D) | 45 |
| KIT(V559D,T670I) | 54 |
| KIT(V559D,V654A) | 53 |
| KIT-autoinhibited | 100 |
| LATS1 | 84 |
| LATS2 | 83 |
| LCK | 46 |
| LIMK1 | 94 |
| LIMK2 | 100 |
| LKB1 | 100 |
| LOK | 32 |
| LRRK2 | 55 |
| LRRK2(G2019S) | 70 |
| LTK | 100 |
| LYN | 65 |
| LZK | 68 |
| MAK | 43 |
| MAP3K1 | 73 |
| MAP3K15 | 47 |
| MAP3K2 | 74 |
| MAP3K3 | 61 |
| MAP3K4 | 45 |
| MAP4K2 | 1.8 |
| MAP4K3 | 1.2 |
| MAP4K4 | 3.7 |
| MAP4K5 | 0.45 |
| MAPKAPK2 | 100 |
| MAPKAPK5 | 88 |

| Ambit Gene Symbol | Percentage of control (%) |
|-------------------|---------------------------|
| | 20 |
| MARK1 | 72 |
| MARK2 | 55 |
| MARK3 | 51 |
| MARK4 | 100 |
| MAST1 | 72 |
| MEK1 | 58 |
| MEK2 | 29 |
| MEK3 | 93 |
| MEK4 | 97 |
| MEK5 | 16 |
| MEK6 | 58 |
| MELK | 73 |
| MERTK | 33 |
| MET | 3.2 |
| MET(M1250T) | 5.7 |
| MET(Y1235D) | 1.2 |
| MINK | 11 |
| MKK7 | 63 |
| MKNK1 | 100 |
| MKNK2 | 88 |
| MLCK | 100 |
| MLK1 | 94 |
| MLK2 | 90 |
| MLK3 | 100 |
| MRCKA | 83 |
| MRCKB | 98 |
| MST1 | 60 |
| MST1R | 62 |
| MST2 | 3.5 |
| MST3 | 57 |
| MST4 | 78 |
| MTOR | 99 |
| MUSK | 96 |
| MYLK | 80 |
| MYLK2 | 37 |

| Ambit Gene Symbol | Percentage of control (%) |
|-----------------------|---------------------------|
| | 20 |
| MYLK4 | 71 |
| MYO3A | 85 |
| MYO3B | 89 |
| NDR1 | 70 |
| NDR2 | 84 |
| NEK1 | 36 |
| NEK11 | 56 |
| NEK2 | 25 |
| NEK3 | 91 |
| NEK4 | 58 |
| NEK5 | 62 |
| NEK6 | 83 |
| NEK7 | 77 |
| NEK9 | 88 |
| NIM1 | 71 |
| NLK | 86 |
| OSR1 | 55 |
| p38-alpha | 64 |
| p38-beta | 87 |
| p38-delta | 89 |
| p38-gamma | 74 |
| PAK1 | 78 |
| PAK2 | 71 |
| PAK3 | 34 |
| PAK4 | 100 |
| PAK6 | 75 |
| PAK7 | 78 |
| PCTK1 | 100 |
| PCTK2 | 89 |
| PCTK3 | 99 |
| PDGFRA | 76 |
| PDGFRB | 2.7 |
| PDPK1 | 100 |
| PFCDPK1(P.falciparum) | 67 |
| PFPK5(P.falciparum) | 82 |

| Ambit Gene Symbol | Percentage of control (%) |
|----------------------|---------------------------|
| | 20 |
| PFTAIRE2 | 65 |
| PFTK1 | 92 |
| PHKG1 | 66 |
| PHKG2 | 50 |
| PIK3C2B | 67 |
| PIK3C2G | 100 |
| PIK3CA | 96 |
| PIK3CA(C420R) | 74 |
| PIK3CA(E542K) | 59 |
| PIK3CA(E545A) | 72 |
| PIK3CA(E545K) | 42 |
| PIK3CA(H1047L) | 89 |
| PIK3CA(H1047Y) | 100 |
| PIK3CA(I800L) | 100 |
| PIK3CA(M1043I) | 100 |
| PIK3CA(Q546K) | 100 |
| PIK3CB | 84 |
| PIK3CD | 100 |
| PIK3CG | 99 |
| PIK4CB | 88 |
| PIM1 | 74 |
| PIM2 | 100 |
| PIM3 | 97 |
| PIP5K1A | 51 |
| PIP5K1C | 83 |
| PIP5K2B | 62 |
| PIP5K2C | 66 |
| PKAC-alpha | 100 |
| PKAC-beta | 100 |
| PKMYT1 | 100 |
| PKN1 | 64 |
| PKN2 | 58 |
| PKNB(M.tuberculosis) | 84 |
| PLK1 | 100 |
| PLK2 | 77 |

| Ambit Gene Symbol | Percentage of control (%) |
|-------------------------------|---------------------------|
| | 20 |
| PLK3 | 76 |
| PLK4 | 41 |
| PRKCD | 93 |
| PRKCE | 60 |
| PRKCH | 100 |
| PRKCI | 70 |
| PRKCQ | 61 |
| PRKD1 | 78 |
| PRKD2 | 81 |
| PRKD3 | 100 |
| PRKG1 | 100 |
| PRKG2 | 98 |
| PRKR | 72 |
| PRKX | 80 |
| PRP4 | 79 |
| PYK2 | 49 |
| QSK | 73 |
| RAF1 | 100 |
| RET | 70 |
| RET(M918T) | 54 |
| RET(V804L) | 49 |
| RET(V804M) | 55 |
| RIOK1 | 43 |
| RIOK2 | 70 |
| RIOK3 | 39 |
| RIPK1 | 100 |
| RIPK2 | 90 |
| RIPK4 | 97 |
| RIPK5 | 76 |
| ROCK1 | 48 |
| ROCK2 | 54 |
| ROS1 | 36 |
| RPS6KA4(Kin.Dom.1-N-terminal) | 100 |
| RPS6KA4(Kin.Dom.2-C-terminal) | 87 |
| RPS6KA5(Kin.Dom.1-N-terminal) | 100 |

| Ambit Gene Symbol | Percentage of control (%) |
|-------------------------------|---------------------------|
| | 20 |
| RPS6KA5(Kin.Dom.2-C-terminal) | 53 |
| RSK1(Kin.Dom.1-N-terminal) | 53 |
| RSK1(Kin.Dom.2-C-terminal) | 62 |
| RSK2(Kin.Dom.1-N-terminal) | 51 |
| RSK2(Kin.Dom.2-C-terminal) | 100 |
| RSK3(Kin.Dom.1-N-terminal) | 3.6 |
| RSK3(Kin.Dom.2-C-terminal) | 73 |
| RSK4(Kin.Dom.1-N-terminal) | 55 |
| RSK4(Kin.Dom.2-C-terminal) | 75 |
| S6K1 | 25 |
| SBK1 | 74 |
| SGK | 42 |
| SgK110 | 44 |
| SGK3 | 50 |
| SIK | 71 |
| SIK2 | 62 |
| SLK | 40 |
| SNARK | 12 |
| SNRK | 80 |
| SRC | 98 |
| SRMS | 55 |
| SRPK1 | 55 |
| SRPK2 | 76 |
| SRPK3 | 67 |
| STK16 | 64 |
| STK33 | 12 |
| STK35 | 73 |
| STK36 | 94 |
| STK39 | 87 |
| SYK | 100 |
| TAK1 | 79 |
| TAOK1 | 4.2 |
| TAOK2 | 4.8 |
| TAOK3 | 0.45 |
| TBK1 | 44 |

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References

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