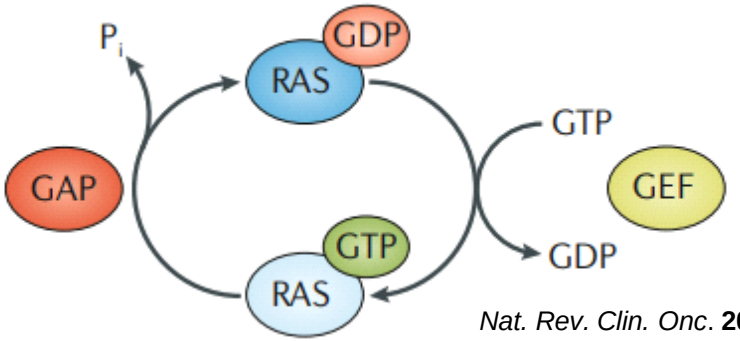
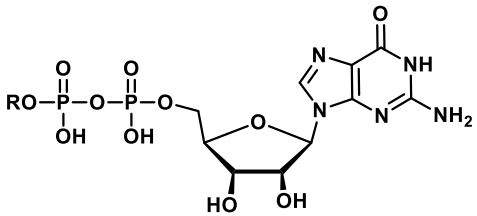
DOTW: AMG 510

RAS:



Nat. Rev. Clin. Onc. **2018**, *15*, 709.



R = PO_3H_2: **GTP**
R = H: **GDP**

RAS oncogene has been known for 30 years, but was thought to be undruggable

KRAS is a GTPase and essential mediator of intracellular signalling pathways

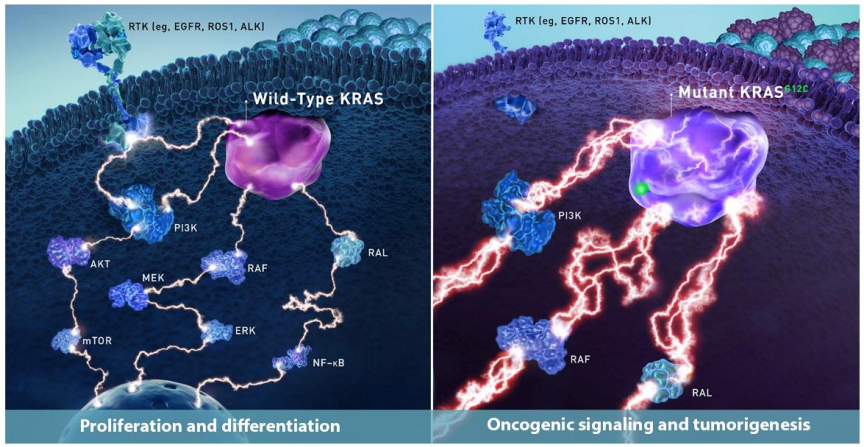
KRAS is a molecular switch, alternating between inactive GDP-bound and active GTP-bound states

Switching between these two states is controlled by two things, guanine nucleotide exchange factor which loads GTP, and GTPase activating proteins (GAP)

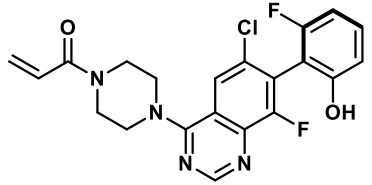
KRAS^{G12C}:

A hallmark of cancer is mutations in KRAS (KRAS^{G12C}) which prevent the binding GTP-ase activating proteins, enhancing KRAS signalling

Responsible for 30% of human tumors.



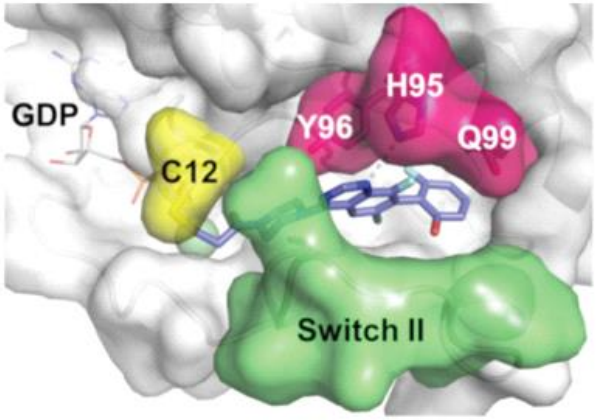
Initial in vivo hit:



ARS-1620

Cell **2018,** *172*, 578.

C-12 allele specific targeting:



p-ERK IC_{50} = 0.831 μM

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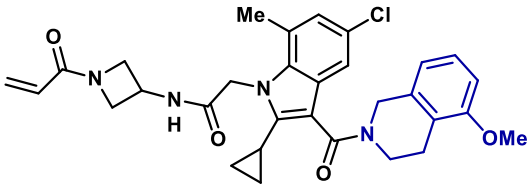
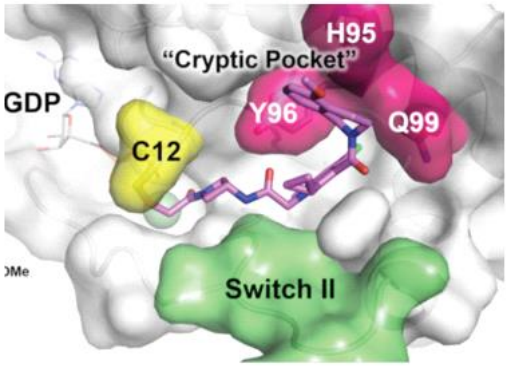
indole lead 1 (Amgen):



tetrohydroisoquinoline engages cryptic pocket



p-ERK IC_{50} = 0.220 μM

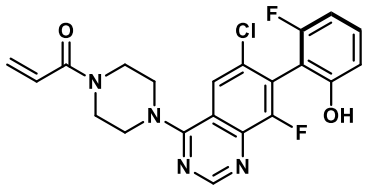
multifold enhancement in potency

low bioavailability and rapid clearance

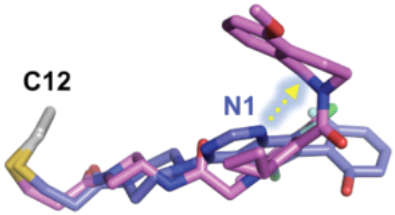
AMGEN

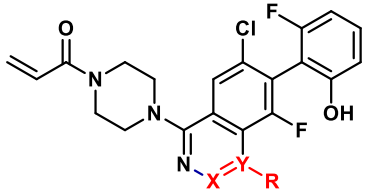
CARMOT

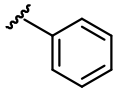
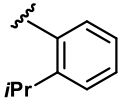
ARS-1620

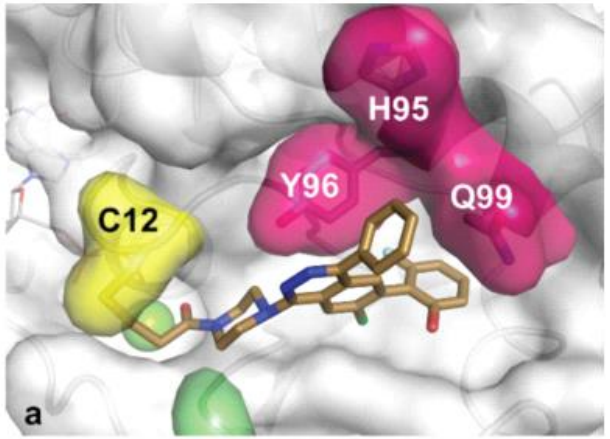


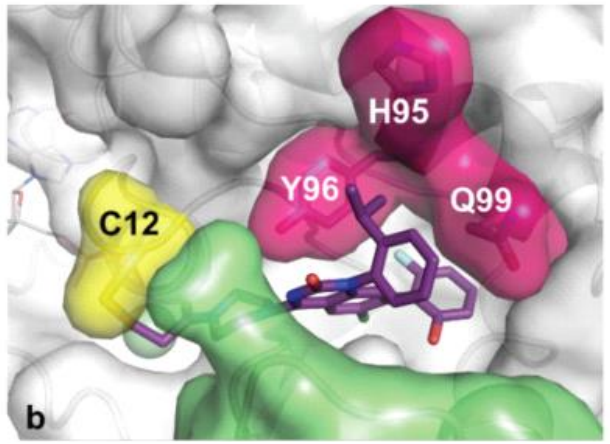
overlay of GDP-KRAS^{G12C} bound confimations of ARS-1620 (blue) and indole lead 1 (pink)





	X	Y	R
a	N	C	
b	CO	N	





"b" found to have 3-9 times the potency of ARS-1620 (but existed as a mixture of atropisomers around the biaryl C-N bond)

Only the R-atropisomer of b showed significant occupancy of the pocket crystallographically

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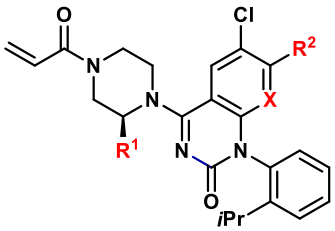
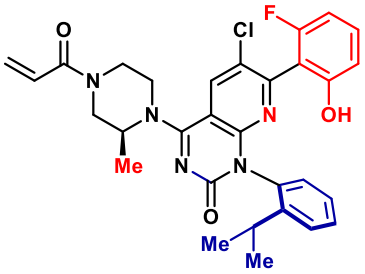
DOTW: AMG 510

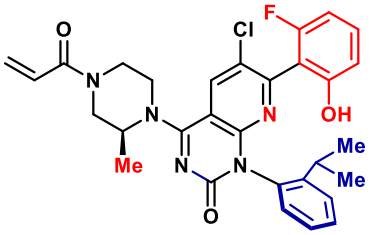


SAR

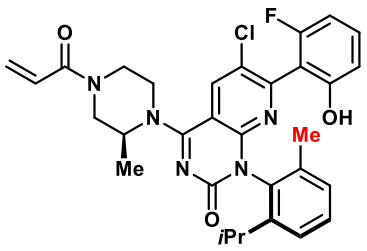


IC_{50} = 0.005 μM

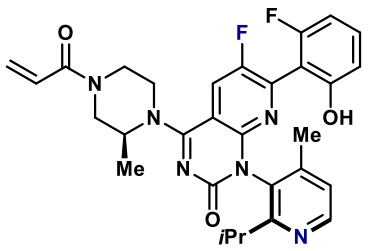
ΔG = 26 kcal/mol
$t_1/_2$ = 8 days



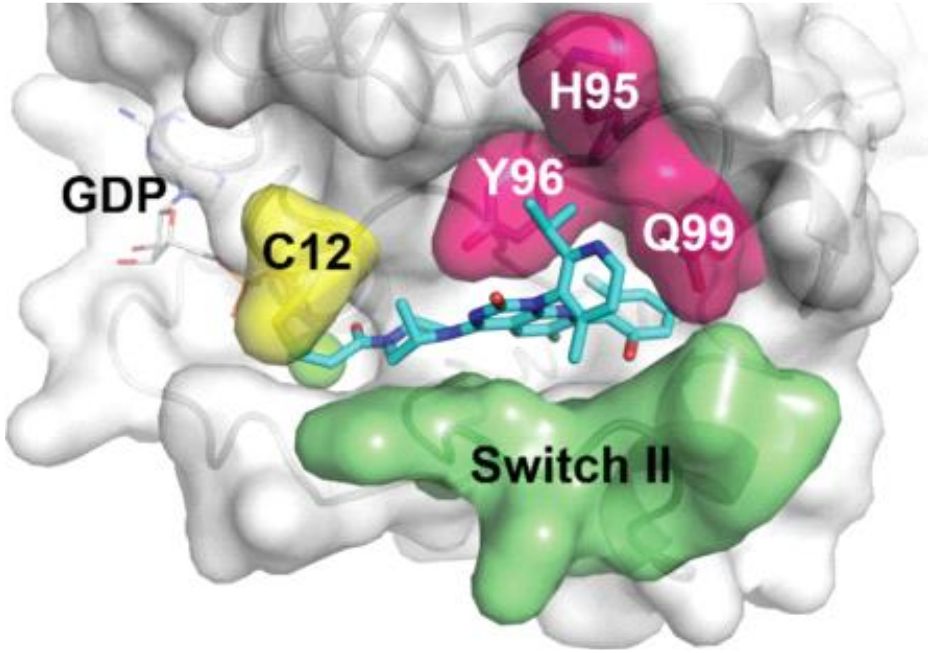
IC_{50} = 0.045 μM



iversion barrier > 30 kcal/mol



bioavailability increased
(AMG-510)



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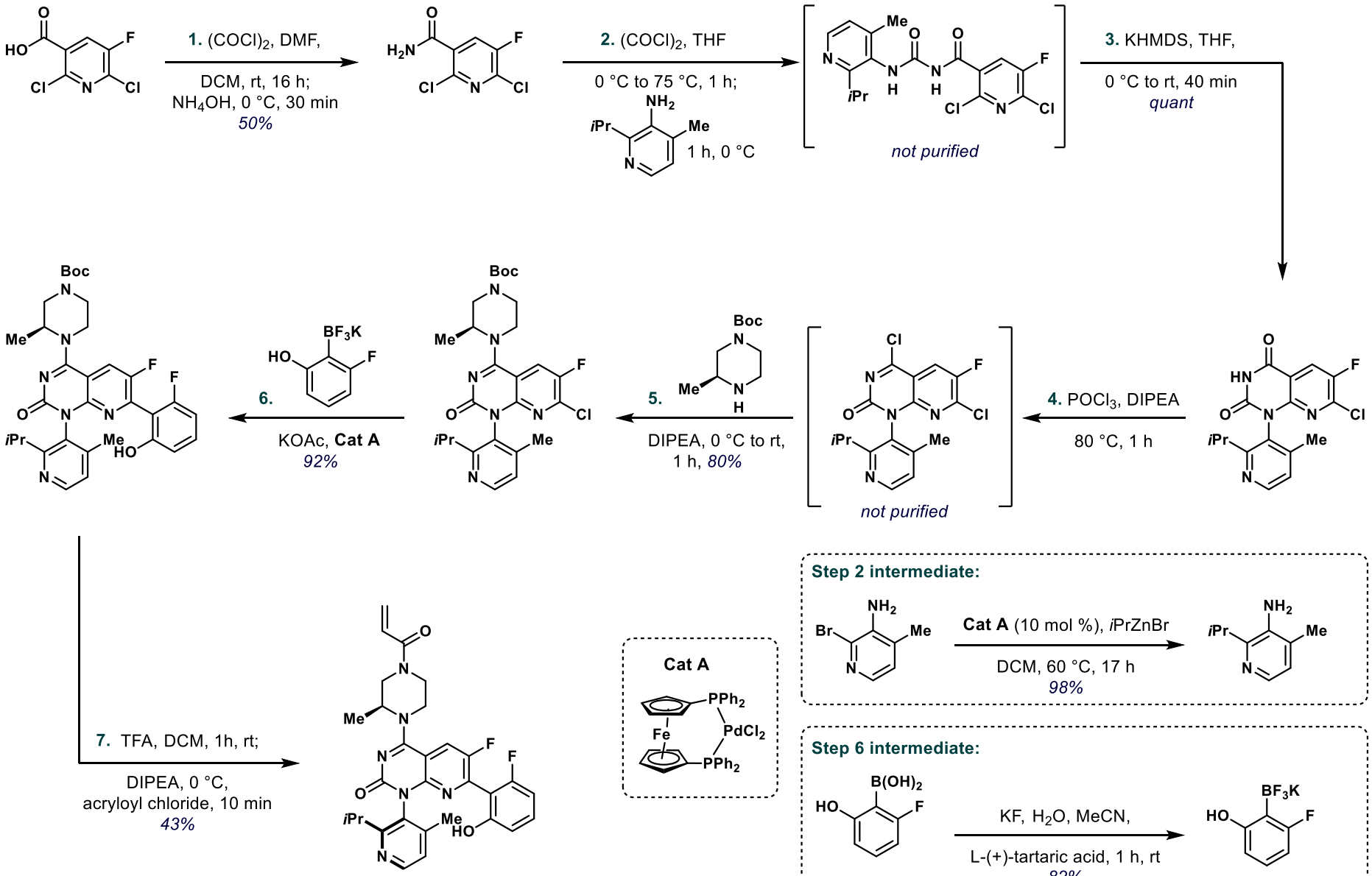
DOTW: AMG 510



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