#3249

Design and Synthesis of Imidazopyridine Derivatives as Novel HSP90 Inhibitors for the Treatment of Cancer

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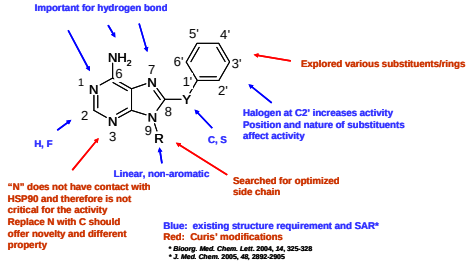
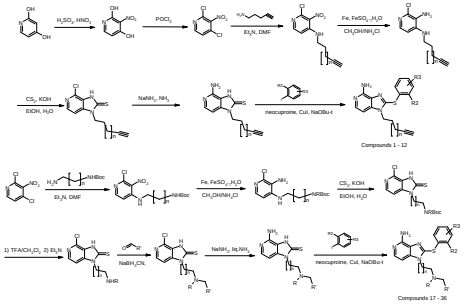
Introduction

The molecular chaperone heat shock protein 90 (HSP90) is involved in folding and stabilization of a wide range of client proteins, including key proteins involved in cancer. Through structure-based design, we synthesized a novel imidazopyridine class of potent HSP90 inhibitors. Extensive SAR study and lead optimization resulted in the identification of the development candidate CUDC-305 (compound 28), later renamed Debio 0932. Debio 0932 demonstrates potent HSP90 inhibition in vitro and high in vivo efficacy in various cancer xenograft models. It is orally bioavailable and has high drug concentrations and a prolonged half-life in tumor tissues. This drug candidate is currently in Phase I clinical trials.

Structure Requirements and Compound Design



Representative Synthesis



SAR of R2 substitution

Cpd #	R2	HSP90α Binding IC_{50} (nM)	Cpd #	R2	HSP90α Binding IC_{50} (nM)
1	Cl	1165	4	Cl	4574
2	Br	347	5	Br	1986
3	I	116	6	I	840

- Modifications on two series indicates that among halogen substitutions at R2, the potency of HSP90 inhibition has an order of I > Br >Cl
- Benzodioxol analogs are more potent that methoxylphenyl analogs

SAR of R3 Substitution

Cpd #	R3	HSP90α Binding IC_{50} (nM)	Cpd #	R3	HSP90α Binding IC_{50} (nM)
3		116	8		>20000
6		840	9		>20000
7		120	10		>20000

- 5-Membered dioxolane (3) and 6-membered dioxane (7) give similar HSP90 inhibitory activity
- C5'-methoxy (6) is less potent than dioxolane (3) and dioxane (7) analogs
- Introduction of additional methoxy at C4' gives a compound (8) with much reduce potency in HSP90 inhibition (IC_{50} > 20 μM)
- Both C4',C5'-diol (9) and C4',C5'-difluoro (10) analogs have very low HSP90 inhibitory activity (IC_{50} > 20 μM)

SAR of R1 Substitution

Cpd #	R1	HSP90α Binding IC_{50} (nM)	Cpd #	R1	HSP90α Binding IC_{50} (nM)
3	$-(CH_2)_3C{\equiv}CH$	116	17	$-(CH_2)_2NH_2$	808
11	$-(CH_2)_2C{\equiv}CH$	501	18	$-(CH_2)_2N(CH_3)_2$	298
12	$-(CH_2)_4C{\equiv}CH$	515	19	$-(CH_2)_2NHCH(CH_3)_2$	237
13	$-(CH_2)_4CH_3$	754	20	$-(CH_2)_2NHCH(CH_2CH_3)_2$	192
14	$-(CH_2)_2C{\equiv}N$	237	21	$-(CH_2)_2NHC(CH_3)_3$	948
15	$-(CH_2)_2OCH(CH_3)_2$	265	22	$-(CH_2)_2NHCH_2C(CH_3)_3$	121
16	$-(CH_2)_3CONH_2$	113	23	$-(CH_2)_3NHCH_2C(CH_3)_3$	562

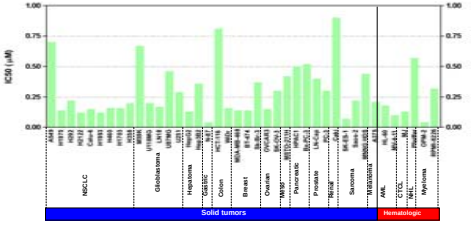
- Within the alkynyl R1 group, potency has the following order: pentynyl (3) > butynyl (11) ~ hexynyl (12)
- Saturation of pentynyl (3) to pentyl (13) results in 6.5-fold decrease in potency
- Replacement of terminal alkynyl (3) with cyano (14) reduces potency
- Ether chain (15) reduces potency while amide (16) is tolerated
- "N" containing chains display various inhibitory activity with neopentyl-aminoethyl (22) being the best (IC_{50} 121 nM) which is comparable to cpd 3

Optimization of Compound 22

Cpd #	R2	HSP90α Binding IC_{50} (nM)	Cpd #	R2	HSP90α Binding IC_{50} (nM)
22	-I	121	30	$-NH_2$	10715
24	$-SCH_3$	208	31	$-NCH_3(CH_2CH_3)$	140
25	$-OCH_3$	267	32		750.8
26	$-CH_3$	2230	33	$-NH(CH_3)$	390
27	-CN	530	34	$-NO_2$	474
28	$-N(CH_3)_2$	100	35	$-COOCH_3$	148
29	$-N(CH_2CH_3)_2$	7030	36	$-SO_2CH_3$	137

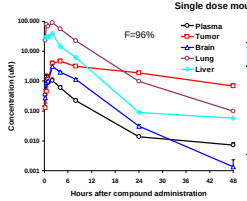
- Kept best R1 and R2, searched for a group to replace iodo
- Electron donating groups (cpds 24, 25, 26) result in reduced potency
- Some electro-withdrawing groups are tolerated (35, 36) but others are not (27, 34)
- Dimethylamino analog (28) displays potent HSP90 inhibition
- The SAR surrounding dimethylamino group is stringent

Debio 0932 Displays Potent Anti-proliferative Activity



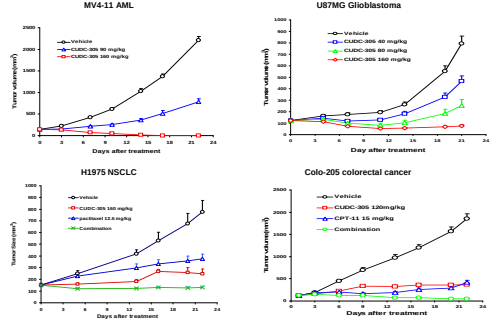
- The median IC_{50} = 220 nM (range 40 to 900 nM)
- All IC50s are well below concentrations achieved in tumor tissue (~4 to 20 uM)

Debio 0932 Has Unique PK Profile



Tissue	Half Life (hour)	Cmax (μM)	AUC (nmol/L*h or μmol/kg*h)
Plasma	7.8	1.3	6.2
Tumor	20.4	4.7	114.9
Brain	4.0	3.1	23.7
Lung	4.6	91.7	623.8
Liver	4.8	38.8	207.6

Debio 0932 is Efficacious in Xenograft Models



Conclusion

- Extensive structure and activity relationship has been investigated
- Debio 0932 has been identified as a potent HSP90 inhibitor with broad range of anti-proliferative activity in vitro and high in vivo efficacy in xenograft models
- Debio 0932 is orally bioavailable and displays a unique PK profile
- Debio 0932 displays good safety and tolerability with the hematological compartment and the intestine as target organs for toxicity
- Cardiovascular effects have been observed, but only at very high in single, but not repeated doses in dogs
- In 4-week repeat toxicology studies, the rat and dog NOAEL (No Observed Adverse Effect Level) of Debio 0932 was 60-100 mg/kg and 20 mg/kg (every other day), respectively, and 10 mg/kg on daily administration in dogs
- Debio 0932 is currently in Phase I clinical trials