Molecular Structural Requirements for the Dual Inhibition of Mdm2 and Mdm4 for Discovery of Novel Anticancer Agents

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INTRODUCTION

Mdm2 belonging to the E3 ubiqitin family degrades the p53 protein which is a natural tumor suppressor whereas Mdm4, being highly homologous to Mmd2, inhibit the transcriptional activity of p53.High dose of non selective and genotoxic drugs may induce p53 independent pathways and thus cause severe toxicities in normal tissues. As a result, dual inhibitors of Mdm2/ Mdm4 will result in the formation of selective and non-genotoxic agent.

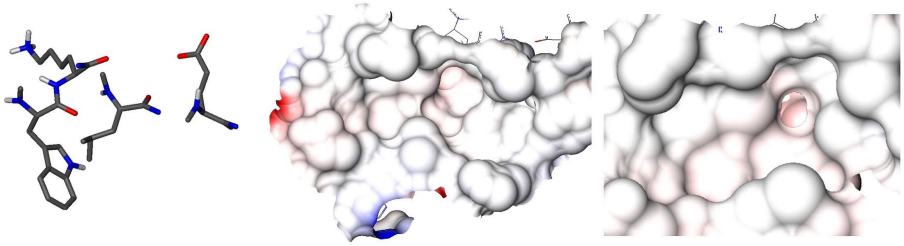


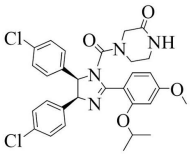
Figure 1: Structure of p53, Mdm2 (PDB id 1YCR) and Mdm4 (PDB id 3DAB).

OBJECTIVES

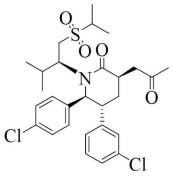
Mdm2/X pharmacological inhibitors to activate the p53 pathway and challenge cancer is an appealing and fruitful therapeutic strategy. The main aim of the study is to identify the structural characteristics of a lead molecule for dual inhibition of Mdm2 and Mdm4.

SUBSTITUENT FOR DUAL INHIBITION

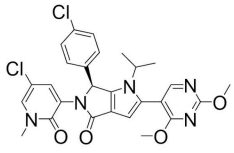
Mdm2 Inhibitors



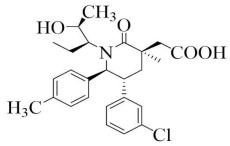
Nutlin 3a(IC_{50}-90nM)



HDM201(IC_{50}-90nM)

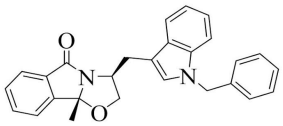


AM 8553 (IC_{50}-1.1nM)



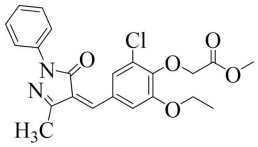
AMG232(IC_{50}-9.1nM)

Dual Inhibitors

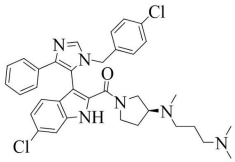


DIMP53-1

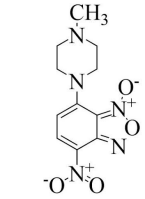
Mdm4 Inhibitors



SJ-17750(IC_{50}~5μM)



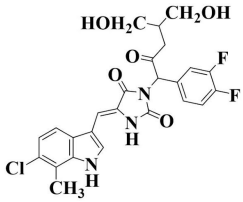
WK-298(IC_{50}-19.7±3.8μM)



XI-006(IC_{50}-2.5μM)

Functional groups of Dual inhibitors

- Phenyl ring
- Pyrrole
- Ethanol



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Mdm2 Inhibitors-Functional Groups		Mdm4 Inhibitors- Functional Groups	
Nutlin 3a	Phenyl ring, Chlorobenzyl, Imidazole, Piperazine	SJ-17750	Phenyl ring, Chlorobenzyl Carboxyl group
HDM201	Cholorobenzyl, Piperidine , Butanone	WK-298	Phenyl ring, Chlorobenzyl Pyrazole, Pyrrole Pyrrolidone
AM8553	Chlorobenzyl , Two fused pyrrole ring, 5-chloropyridin-2-one		
AMG232	Chlorobenzyl, Toulene, Piperidine, Carboxylic group	XI-006	Piperidine Phenyl ring Nitrogen dioxide

CHARACTERISTICS OF DUAL INHIBITORS

- Phenyl ring
- Pyrrole ring

CONCLUSION

Mdm2/X are two key regulators of the tumor suppressor p53 whose over expression disables p53 and causes cancer. Therefore to get the better therapeutic activity simultaneous inhibition is proposed.

SELECTED REFERENCES

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4. Sores J. et al., DIMP53-1 : A novel small molecule dual inhibitor of p53-Mdm2/X interaction with multifunctional p53 dependent anticancer properties, Molecular Oncology, 2017, 11(6), 612-627