



XXIV Российский национальный конгресс «Человек и лекарство»

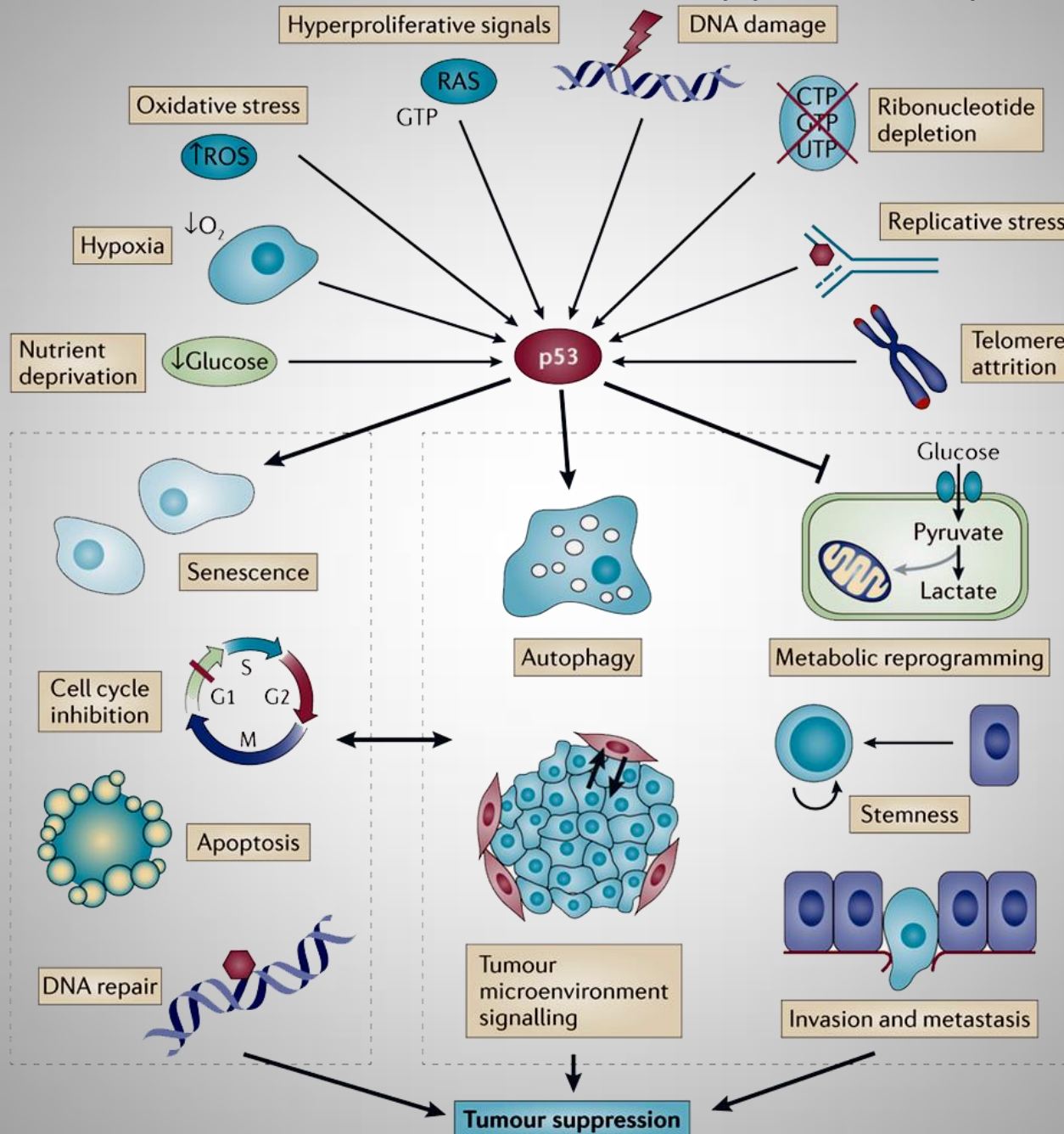
Создание ингибиторов белок-белкового взаимодействия на основе моделирования подвижности N-концевого домена белка MDM2

В.Г. Трибулович

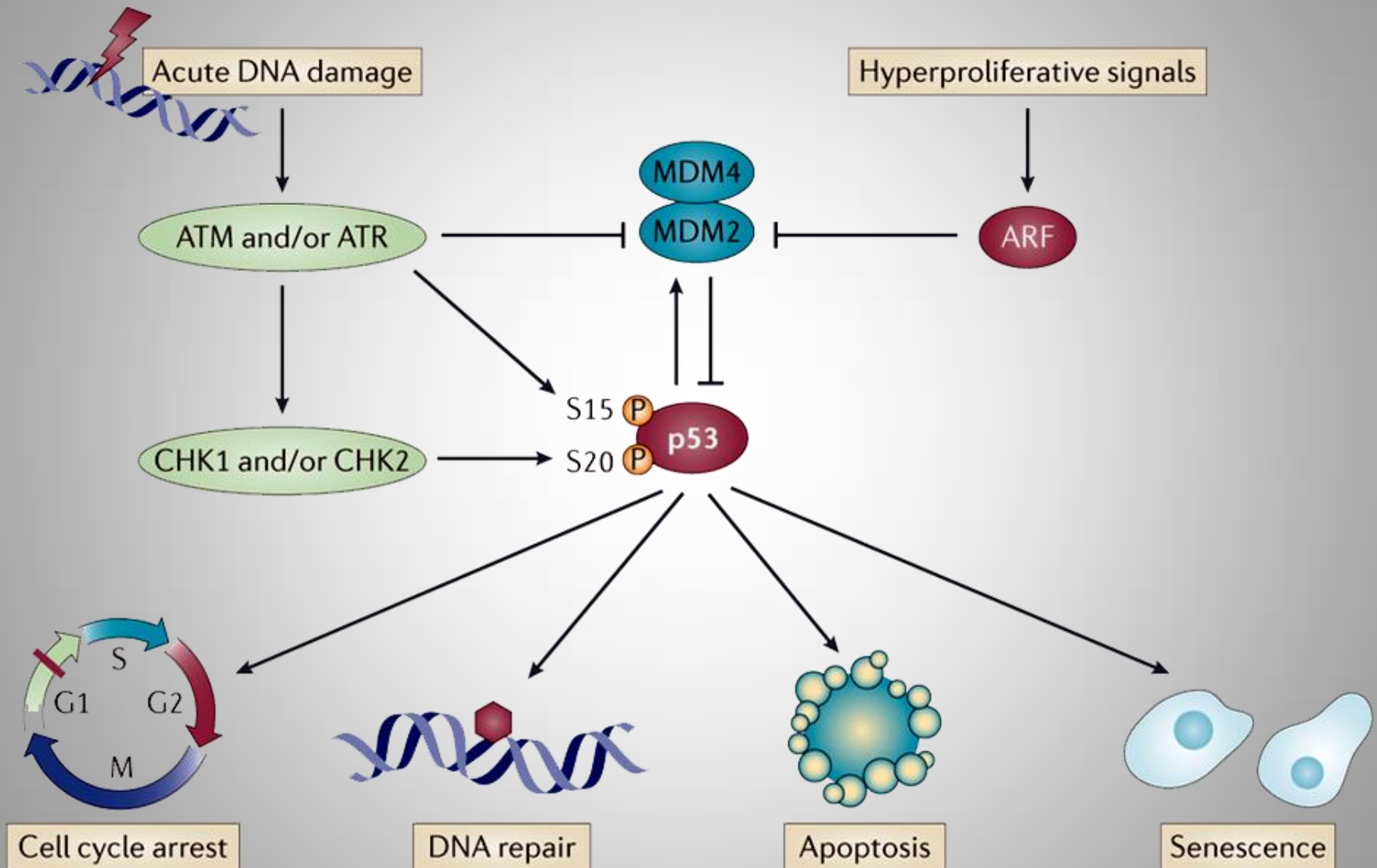
Санкт-Петербургский государственный технологический институт
(технический университет), НИЛ «Молекулярная фармакология»

Апрель 2017

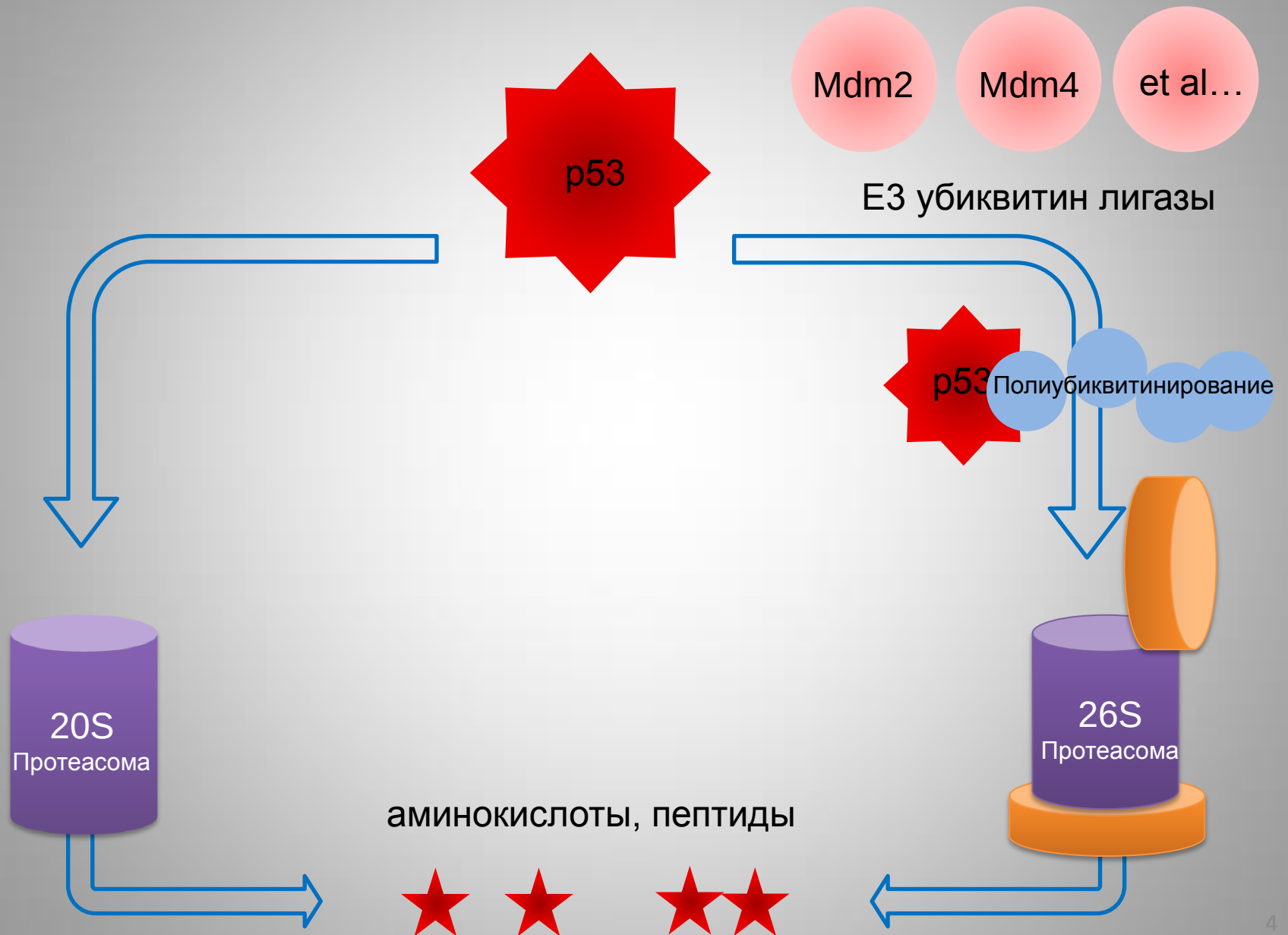
Классический взгляд на функцию p53



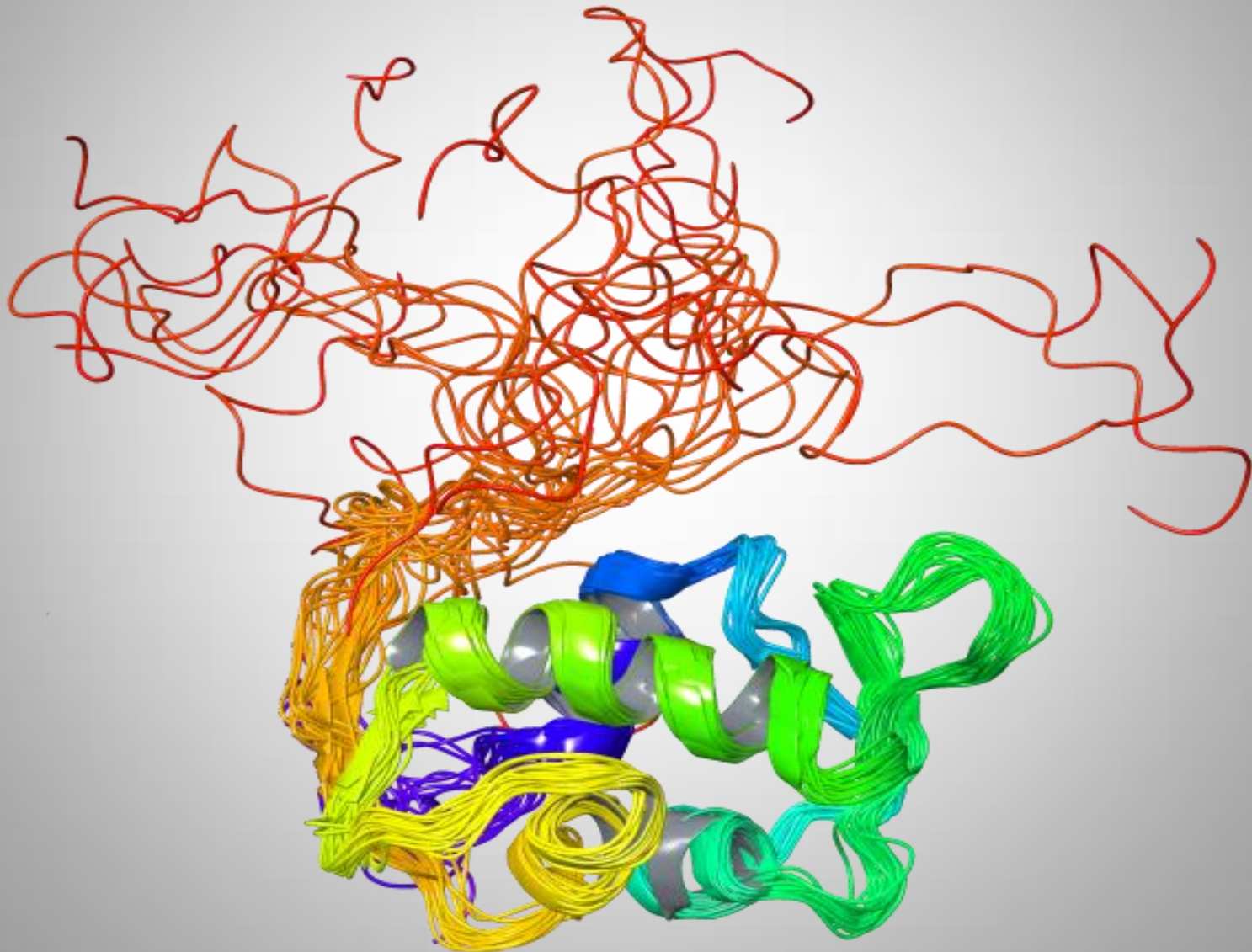
Регуляция p53



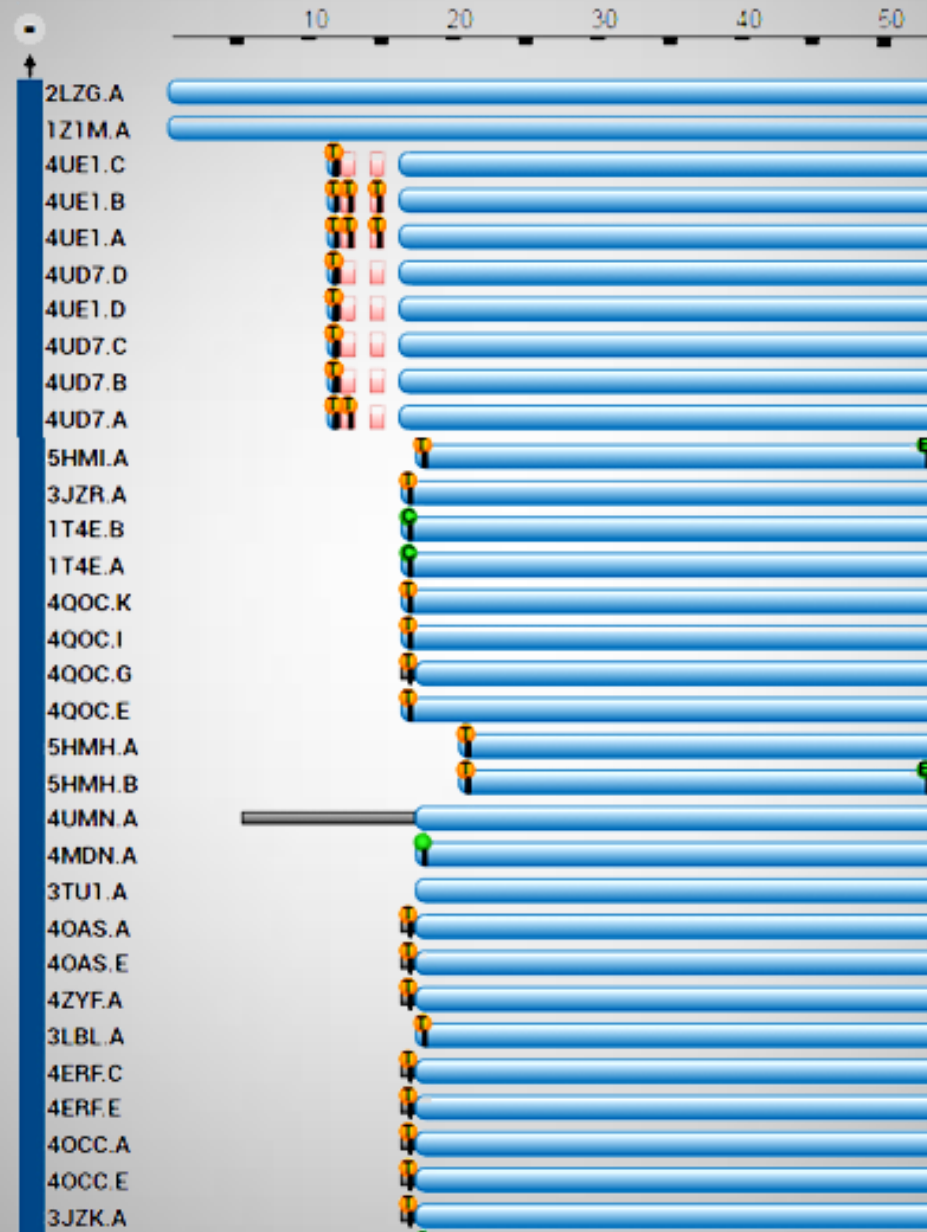
Функция E3 лигаз семейства MDM



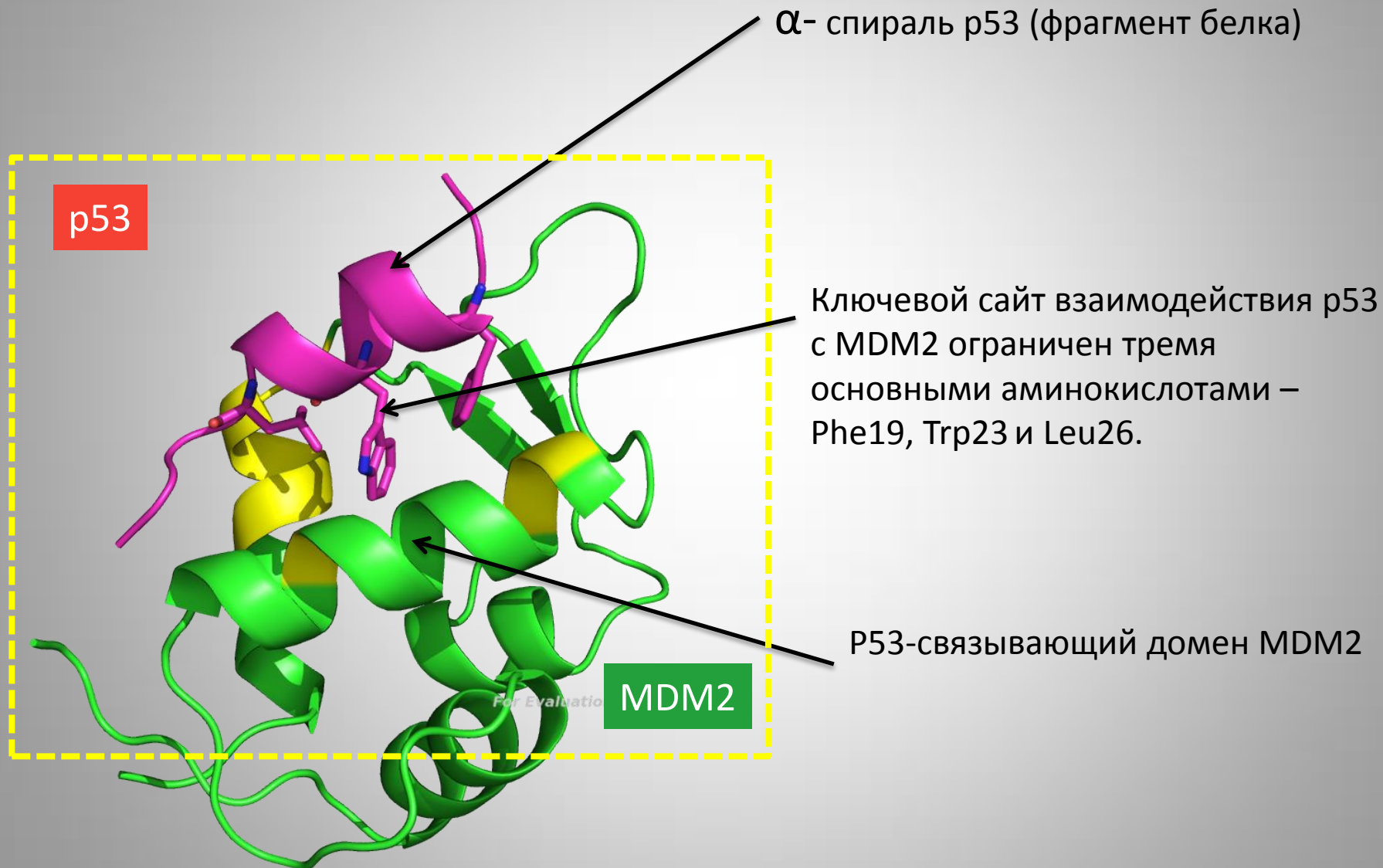
Структура MDM2



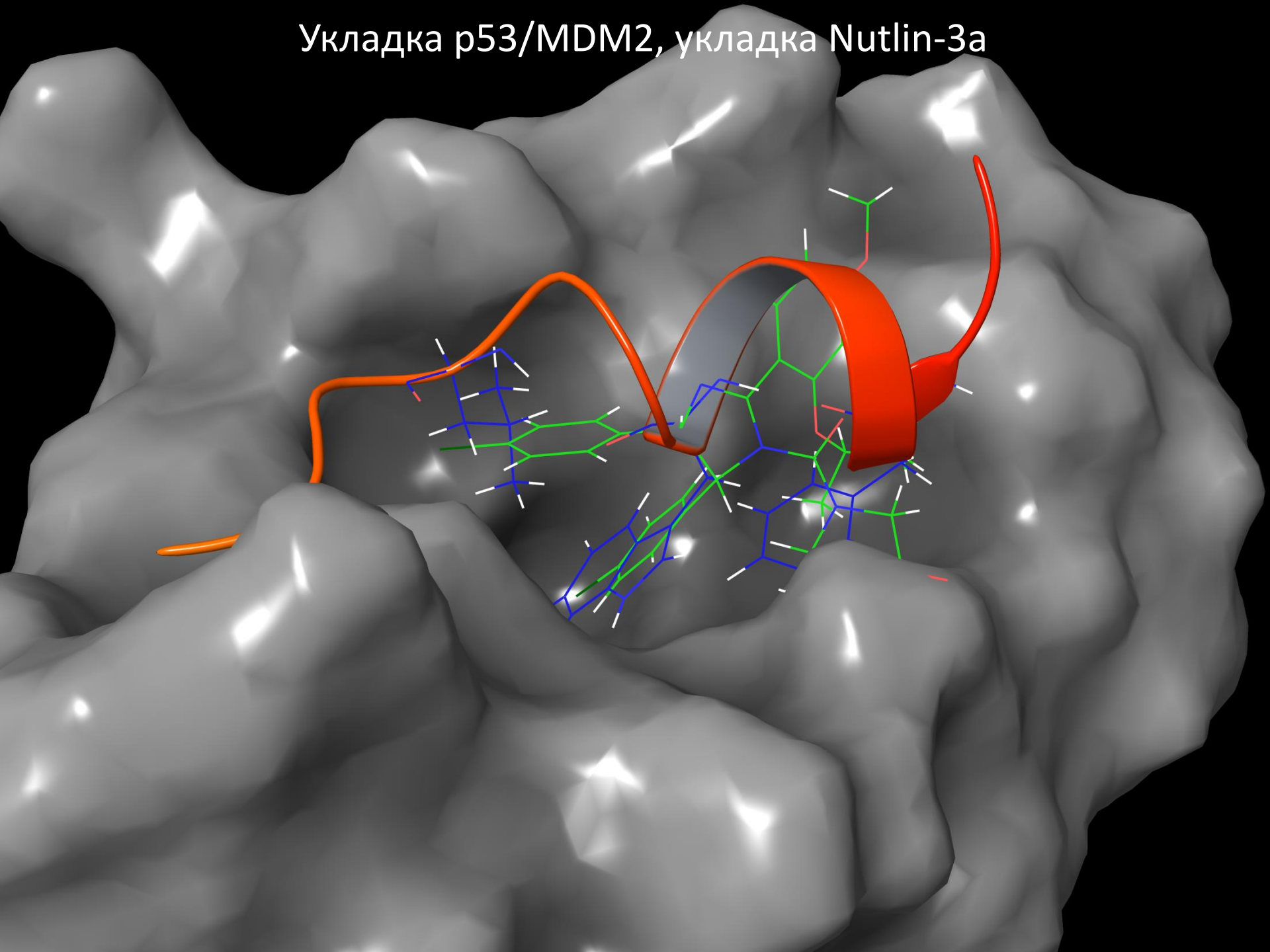
Структуры, представленные в PDB



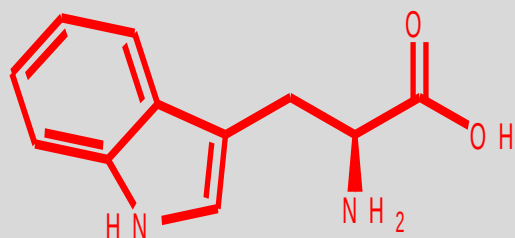
Сайт взаимодействия p53 с MDM2



Укладка p53/MDM2, укладка Nutlin-3a

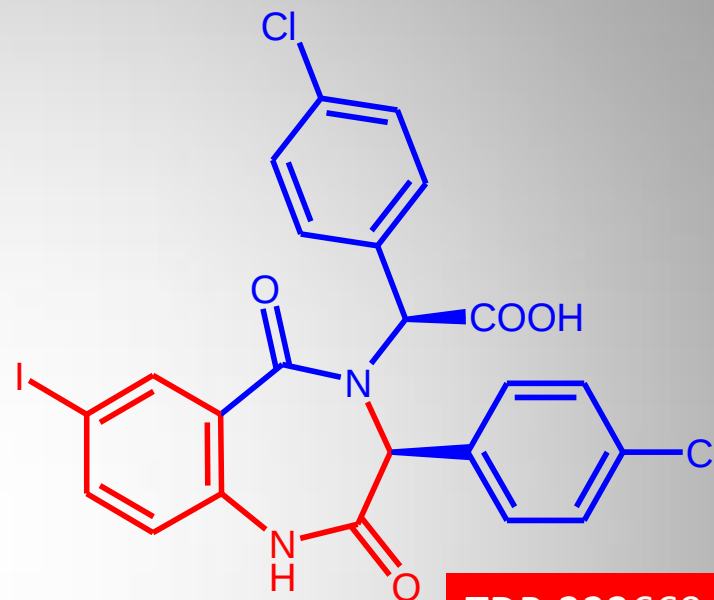


Триптофановый мотив в синтетических ингибиторах MDM2

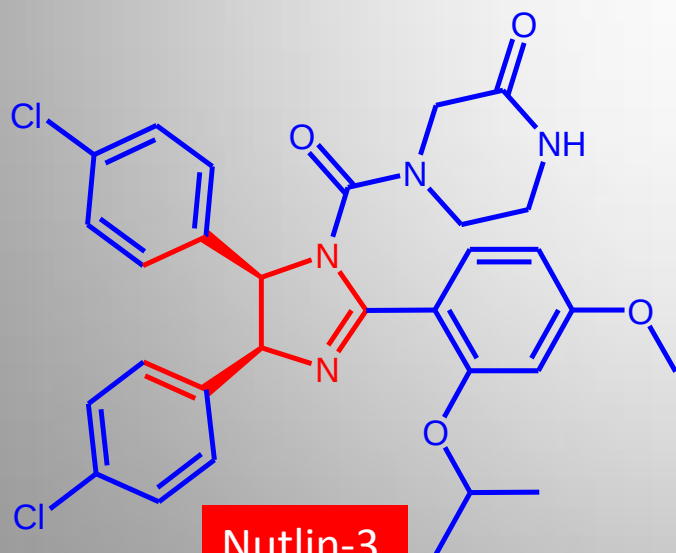


Trp23

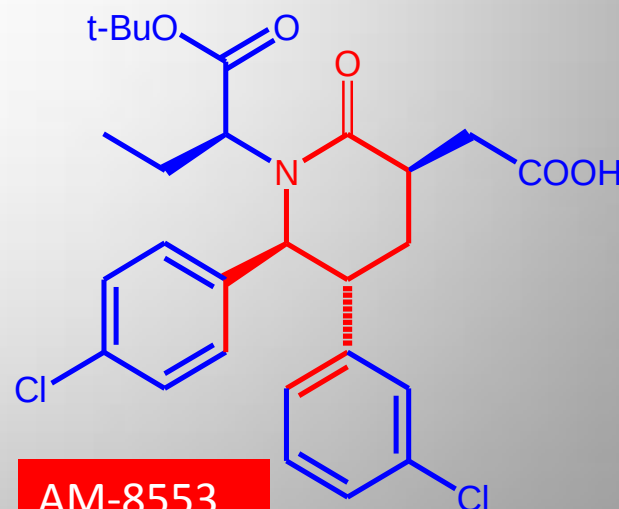
Липофильная
аминокислота



TDP-222669

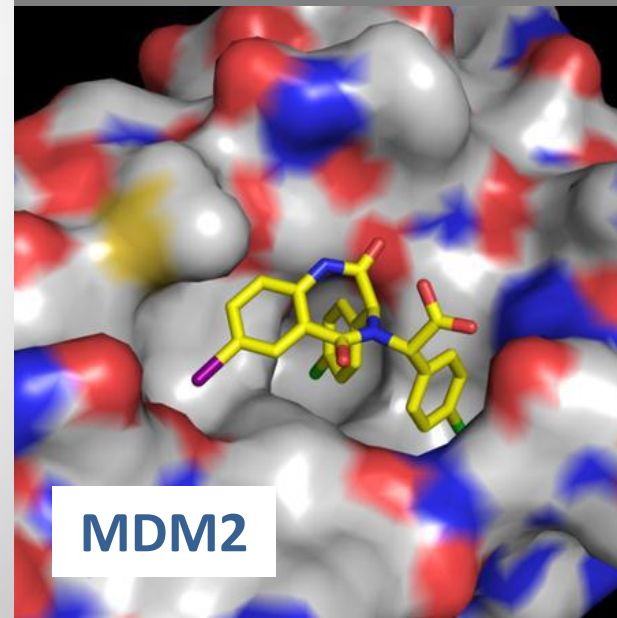
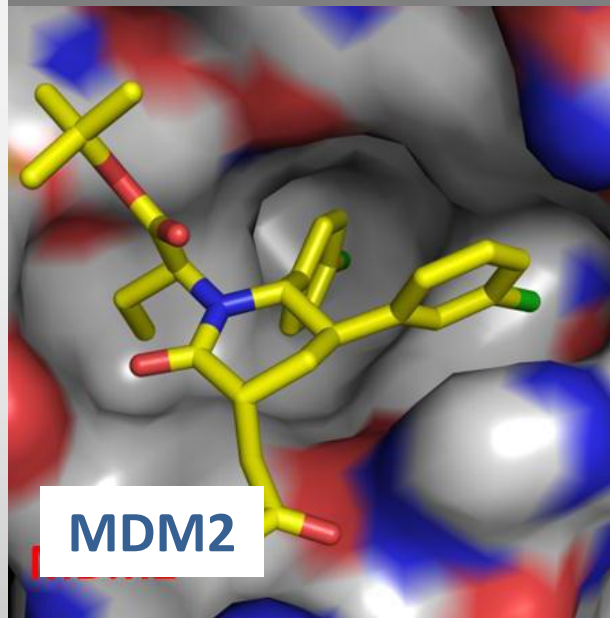
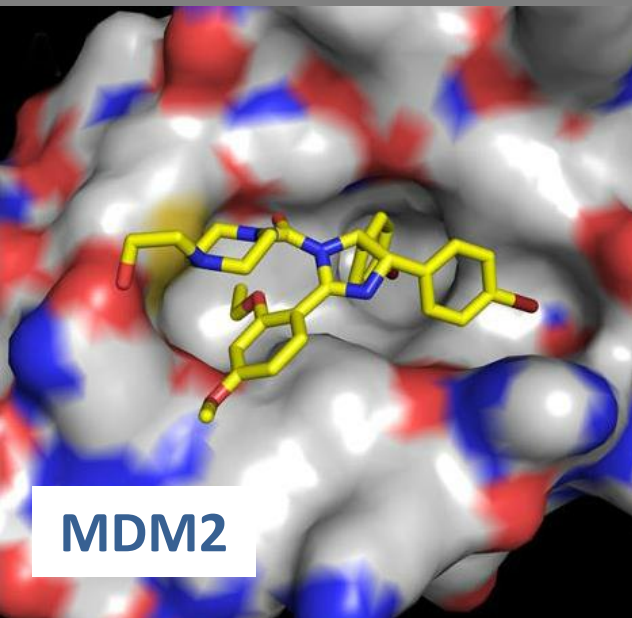
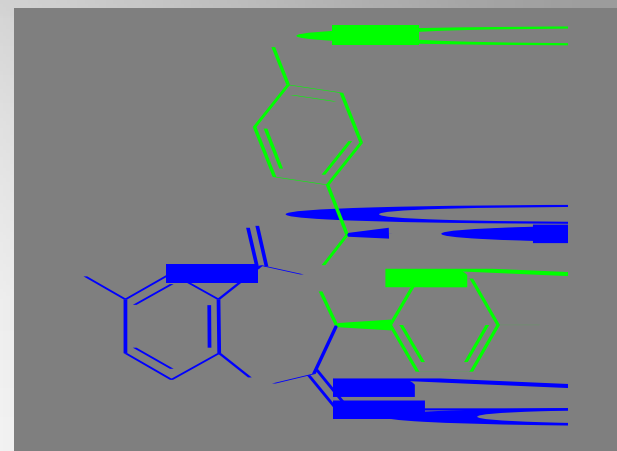
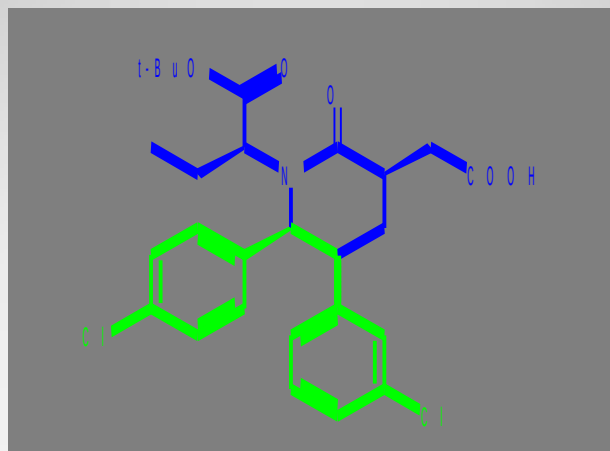
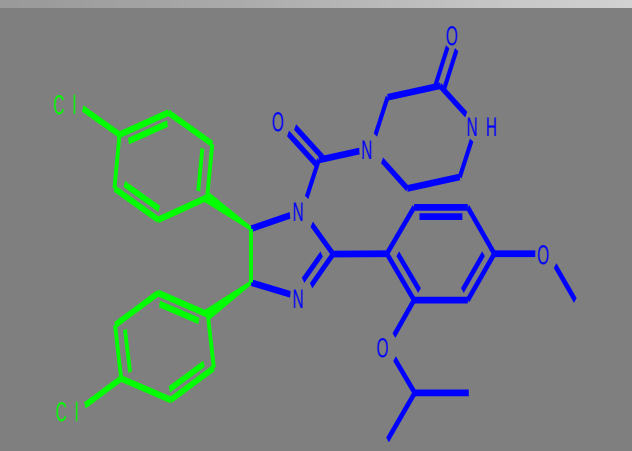


Nutlin-3

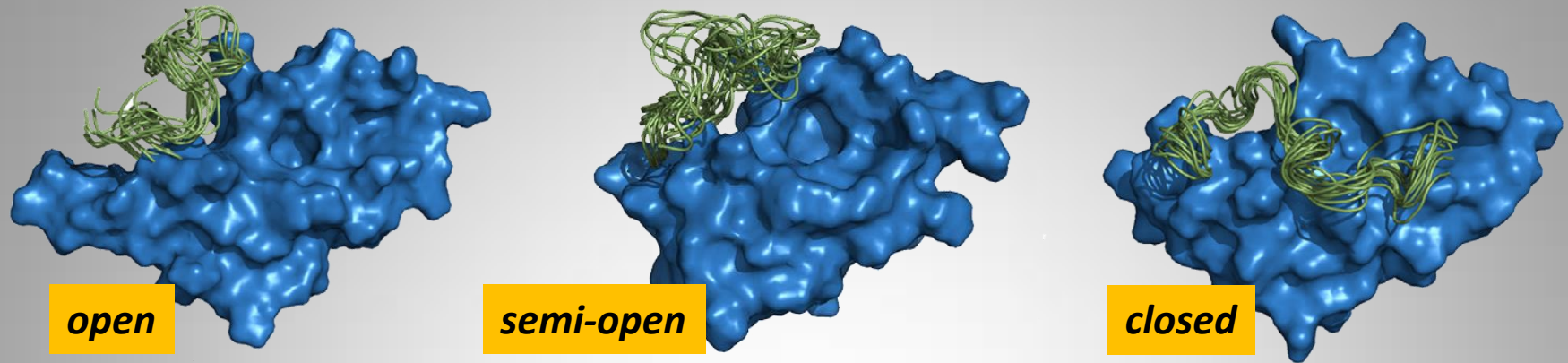


AM-8553

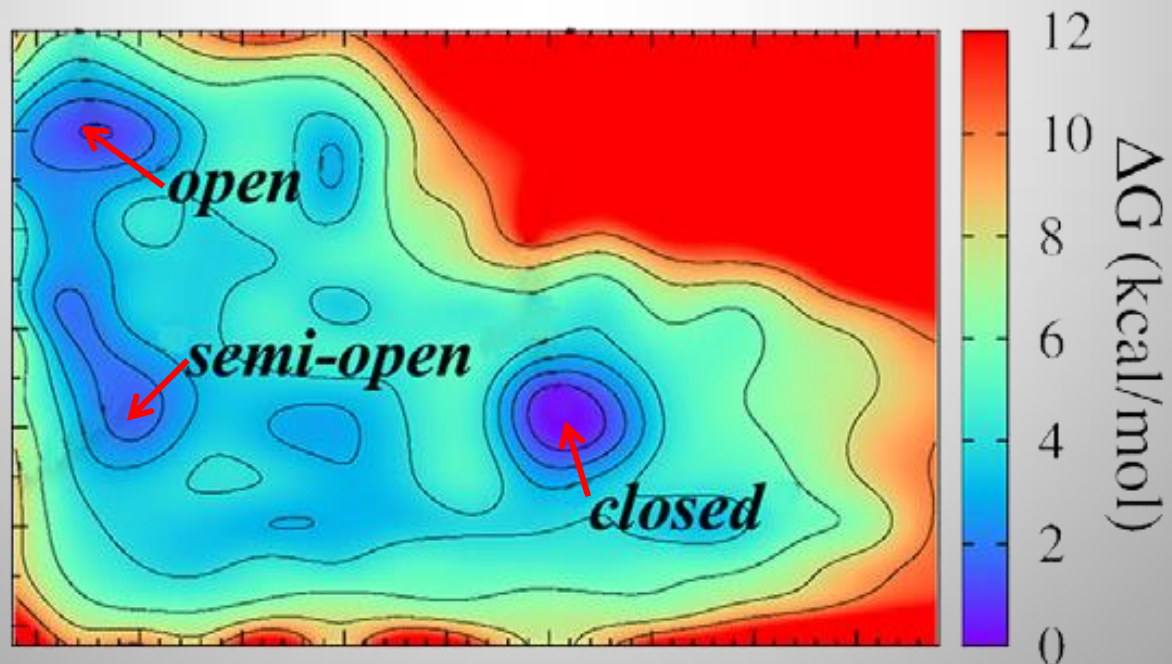
Сайт связывания синтетических ингибиторов MDM2



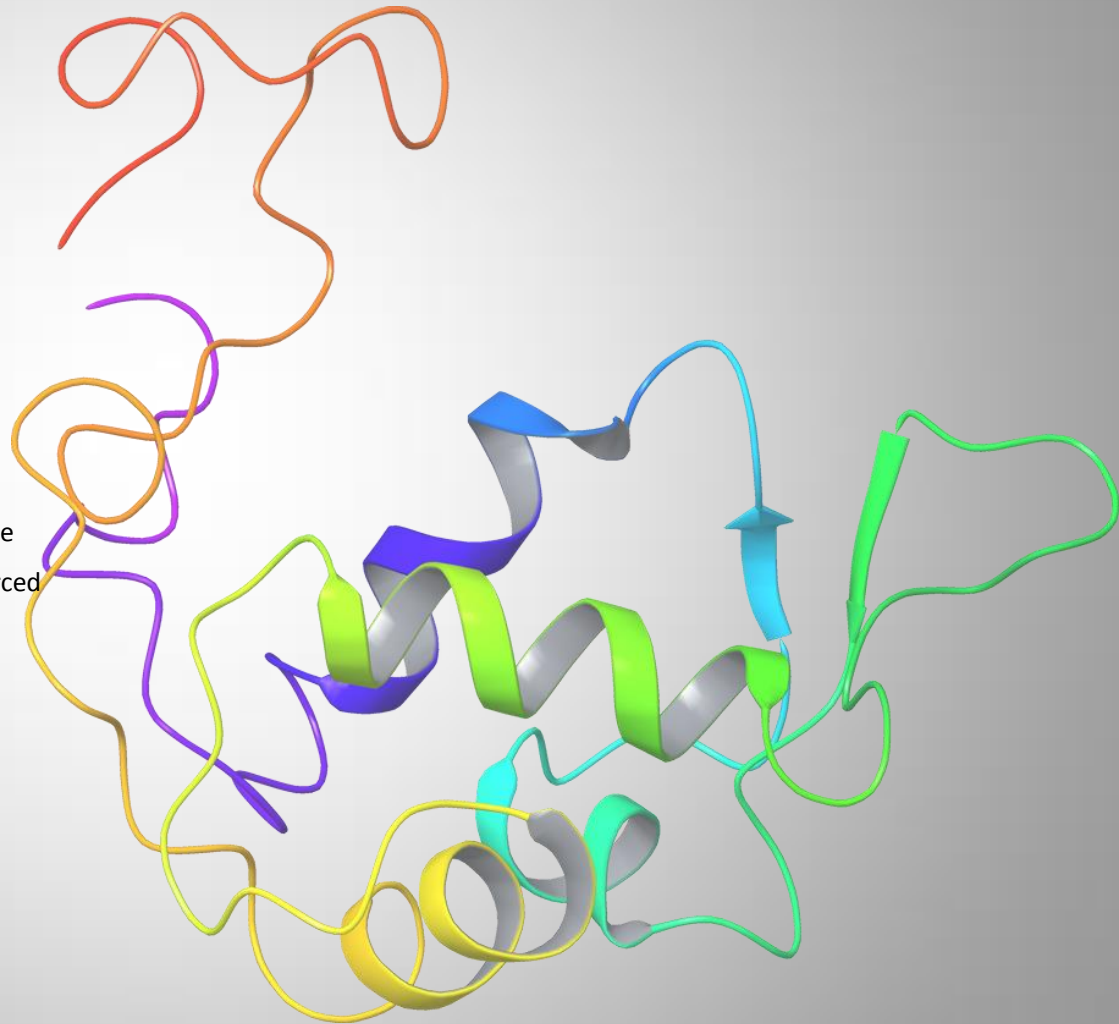
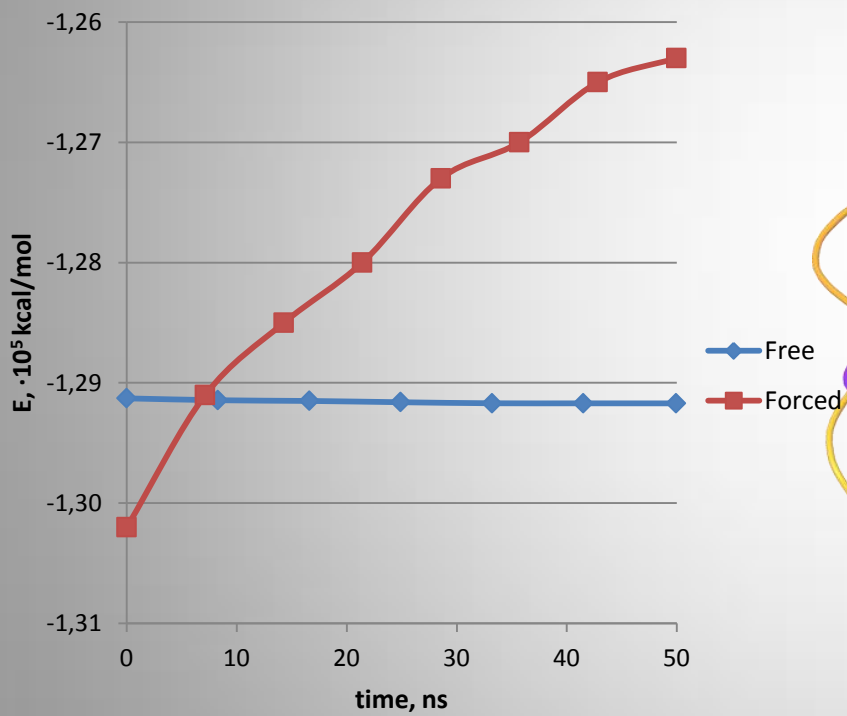
Сравнение энергии конформаций MDM2



Elucidation of Ligand-Dependent Modulation of Disorder-Order Transitions in the Oncoprotein MDM2



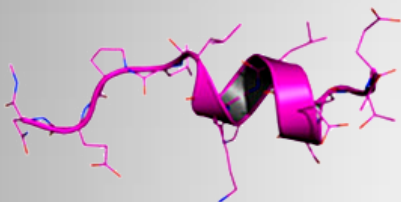
Моделирование динамики N-концевого домена MDM2



Калориметрическое определение констант диссоциации

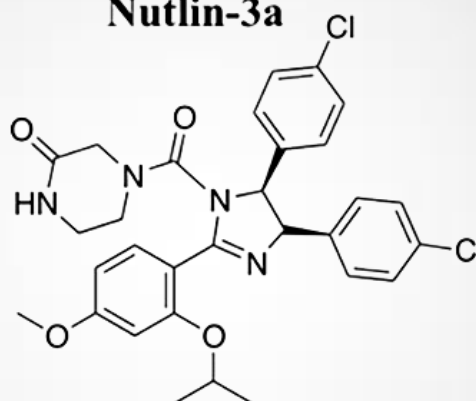
Ordering of the N-Terminus of Human MDM2 by Small Molecule Inhibitors

p53 TAD

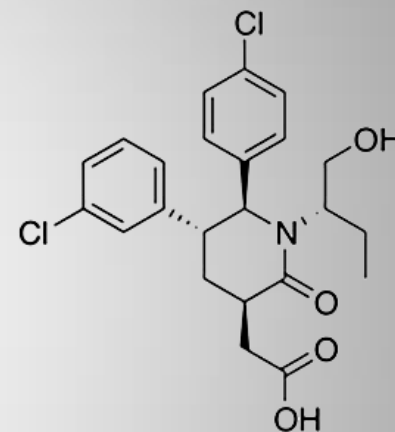


$$\frac{K_d(17-125)}{K_d(2-118)} = 1.0$$

Nutlin-3a

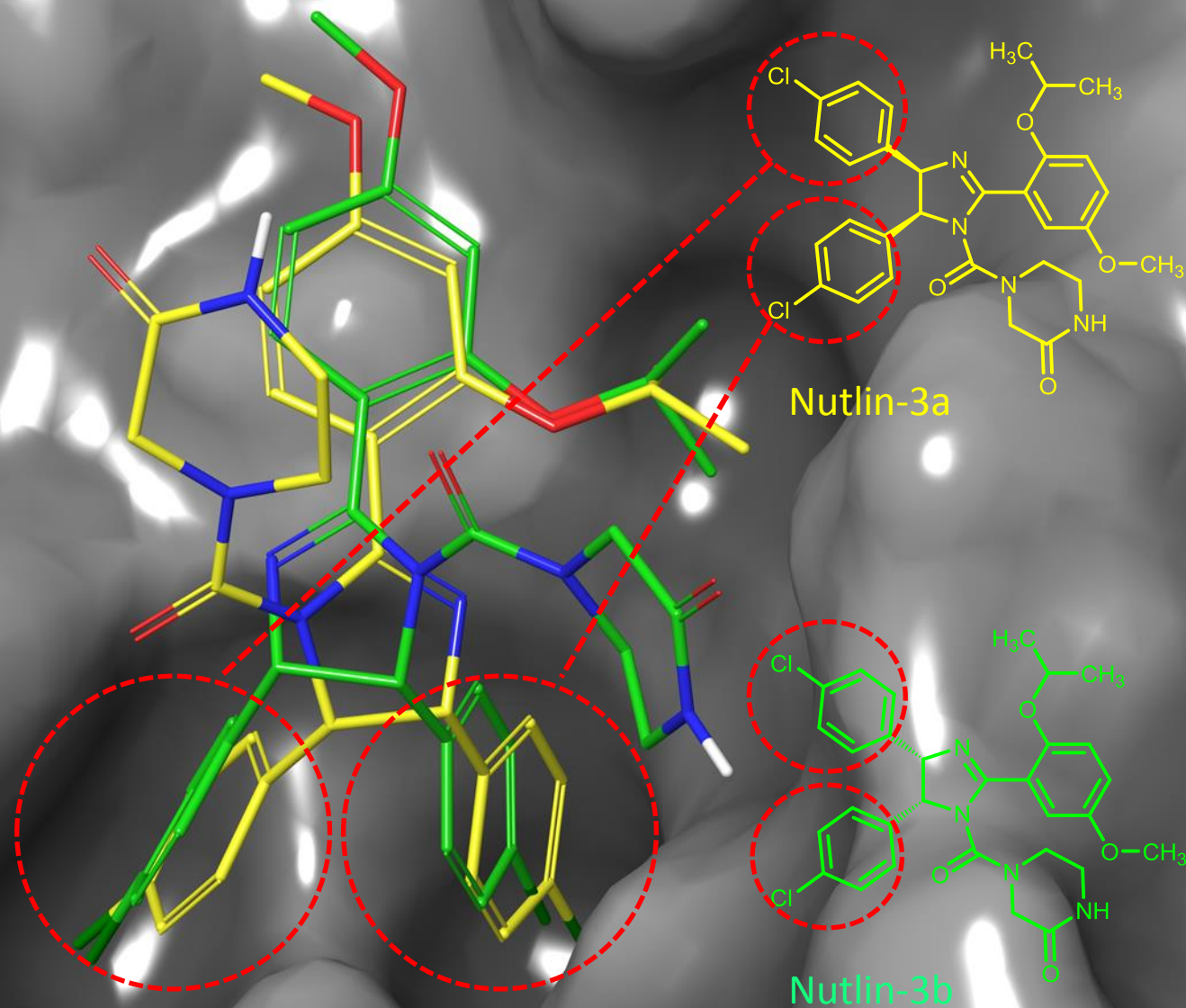


$$\frac{K_d(17-125)}{K_d(2-118)} = 1.3$$



$$\frac{K_d(17-125)}{K_d(2-118)} = 25$$

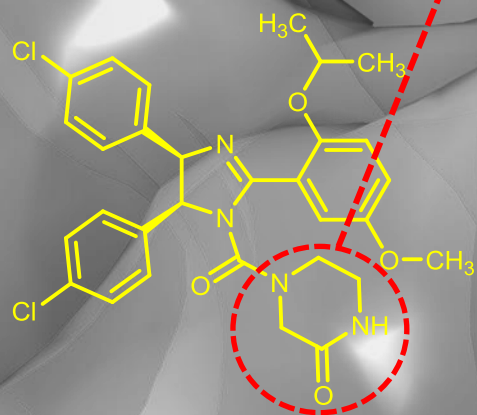
Сходство укладки Nutlin-3a и Nutlin-3b в полости MDM2



Различия укладки Nutlin-3a и Nutlin-3b в полости MDM2

Nutlin-3a Goldscore 61

Nutlin-3b Goldscore 63

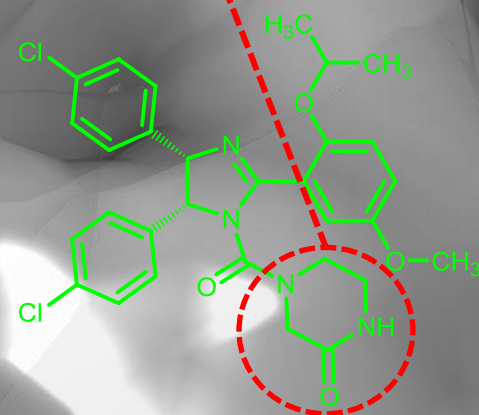


Nutlin-3a

Nutlin-3b EC_{50}

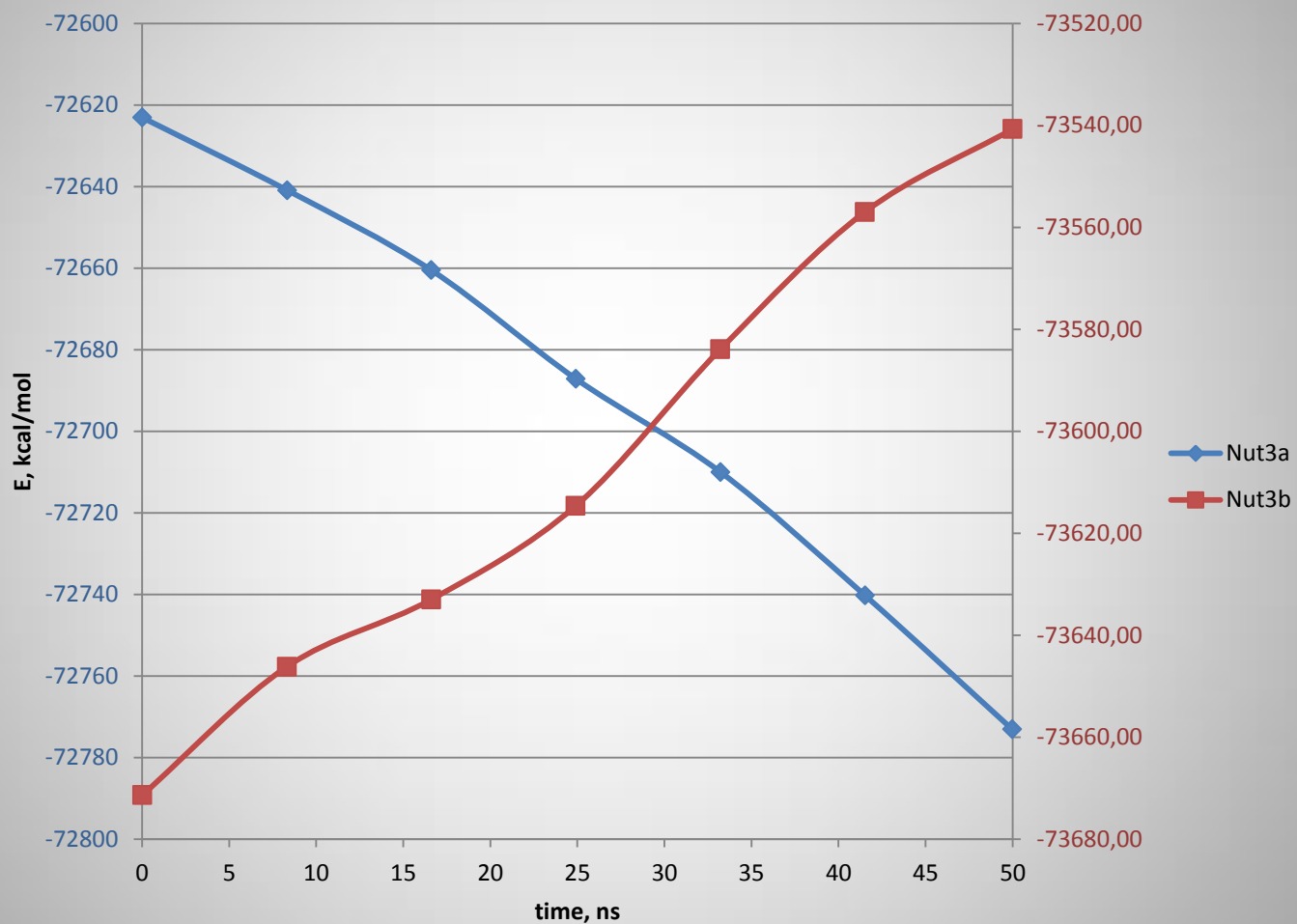
Nutlin-3a EC_{50}

~ 150



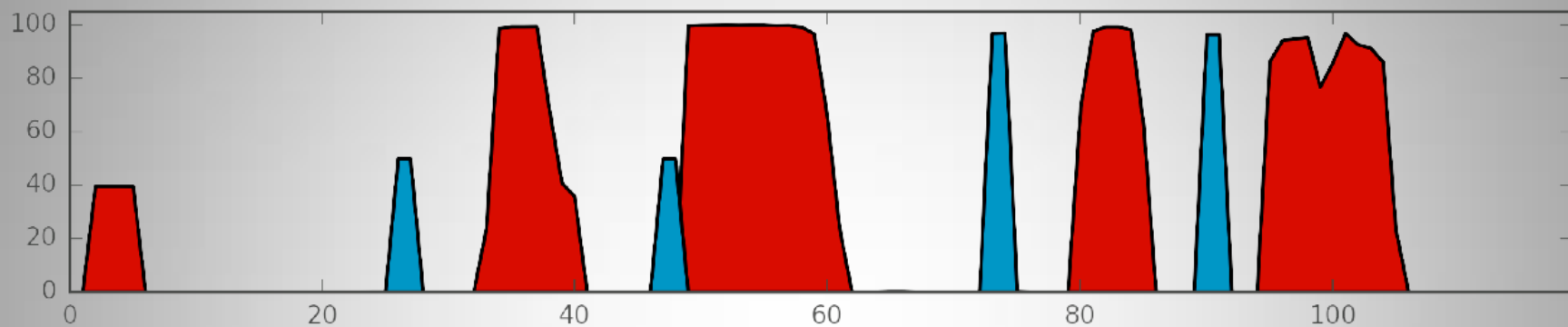
Nutlin-3b

Энергия системы лиганд-белок (Nutlin-3a/b – MDM2)

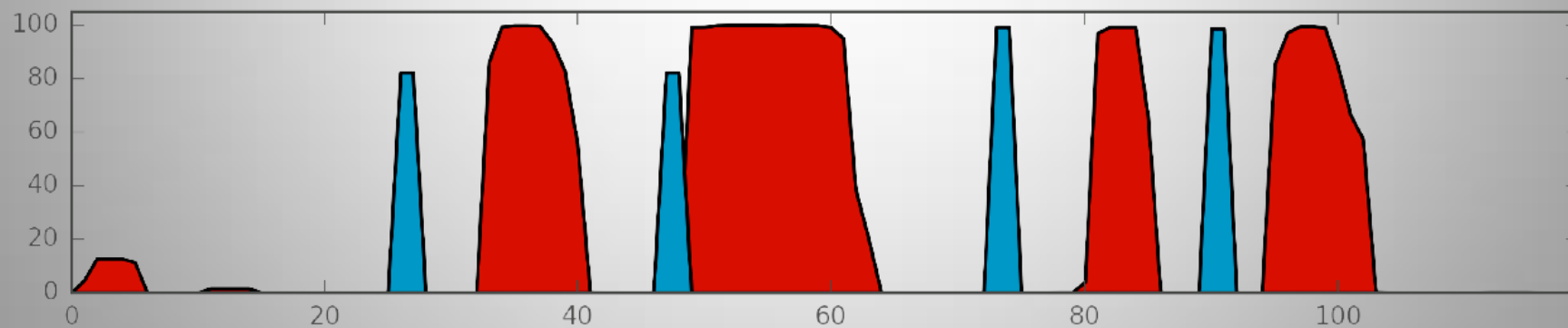


Упорядочение структуры MDM2

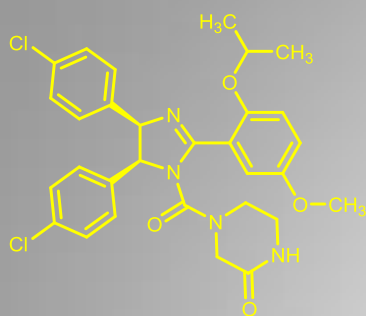
Без лиганда



В присутствии Nutlin-3a

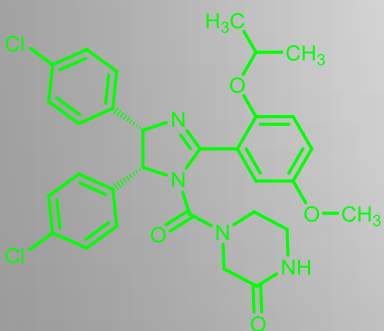
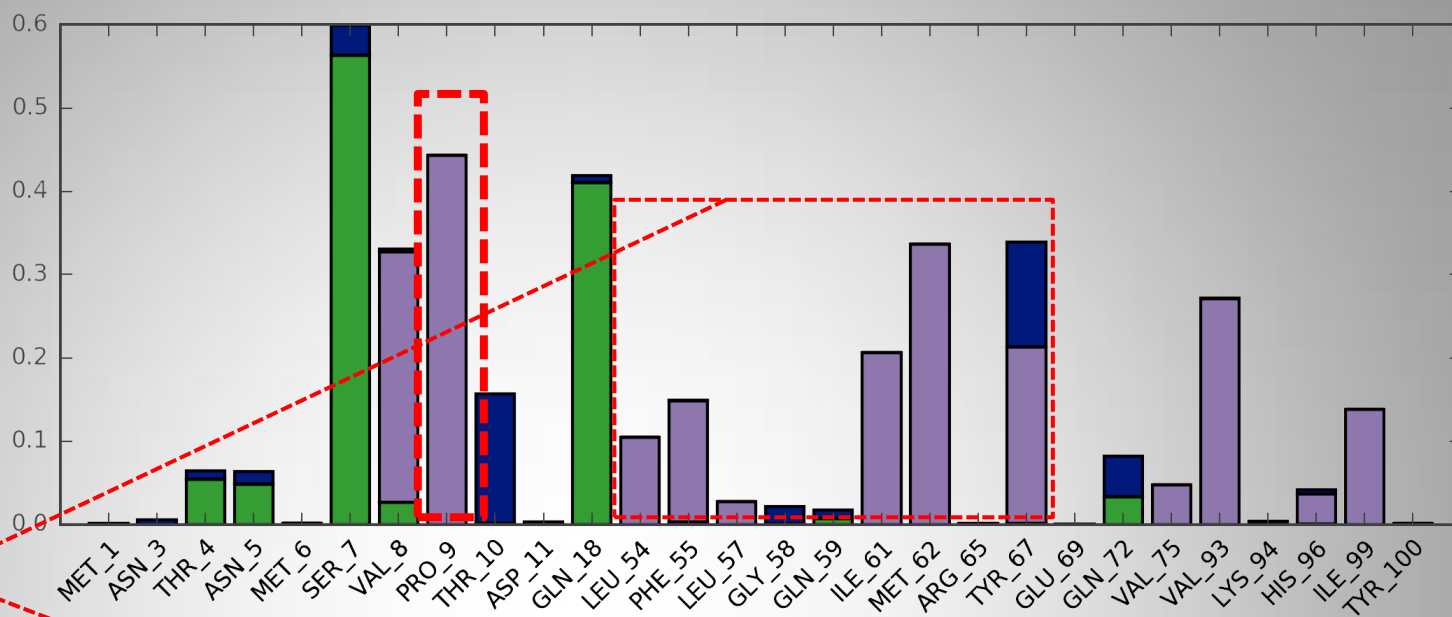


Аминокислоты MDM2 взаимодействующие с лигандом

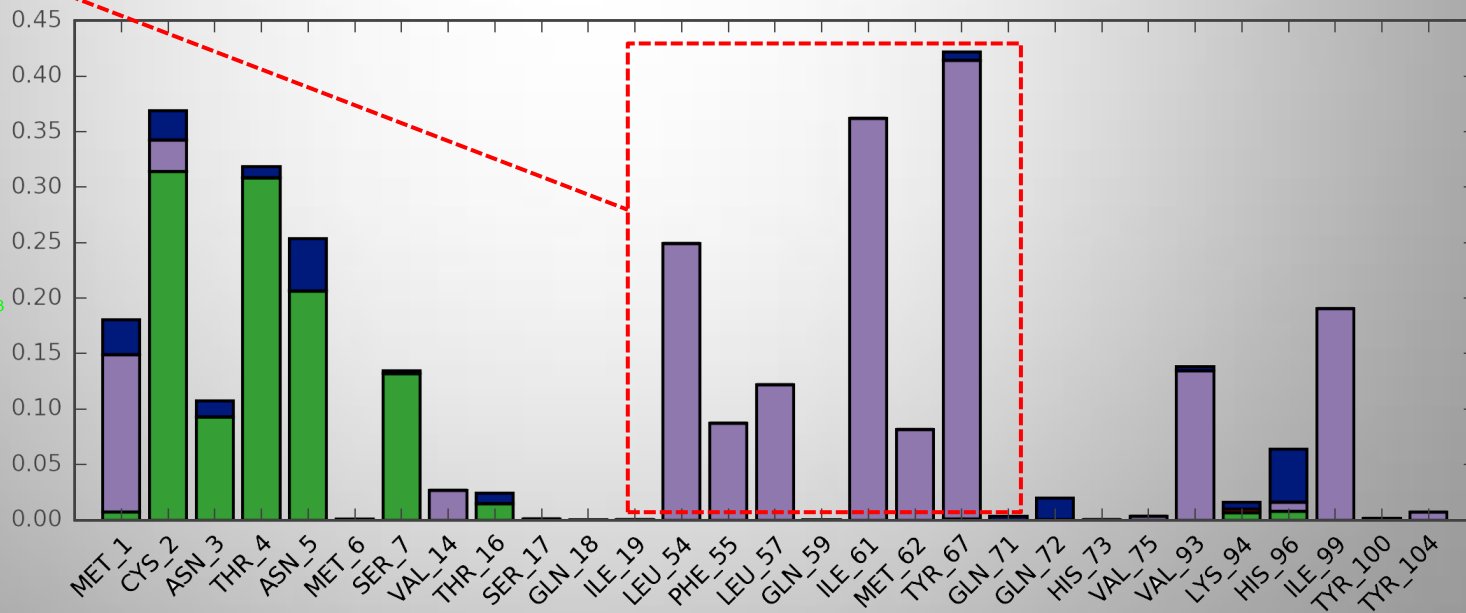


Nutlin-3a

Область
связывания
TAD p53

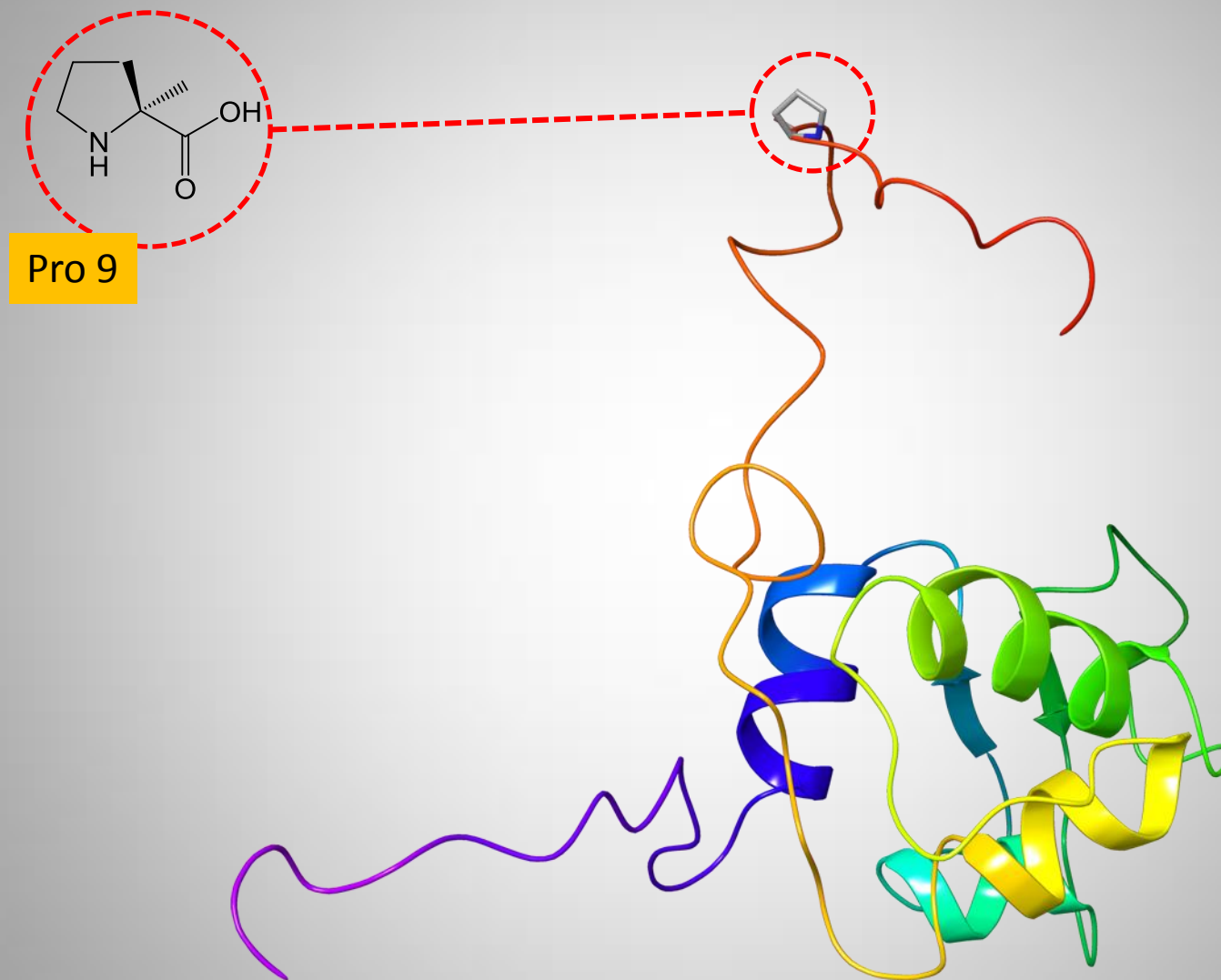


Nutlin-3b

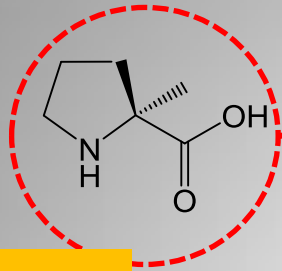


H-bonds Hydrophobic Ionic Water bridges

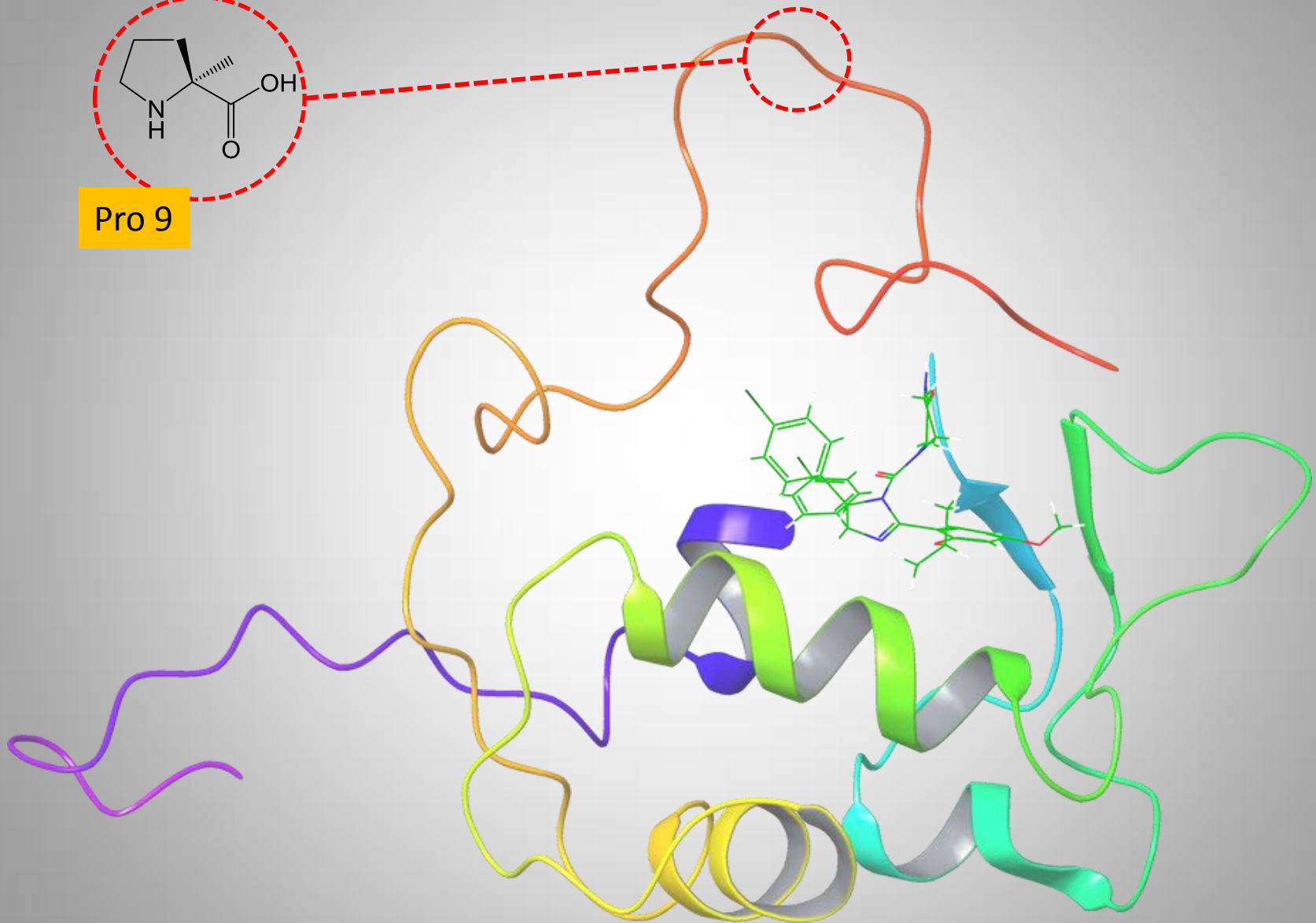
Расположение пролина 9 в N-концевом домене MDM2



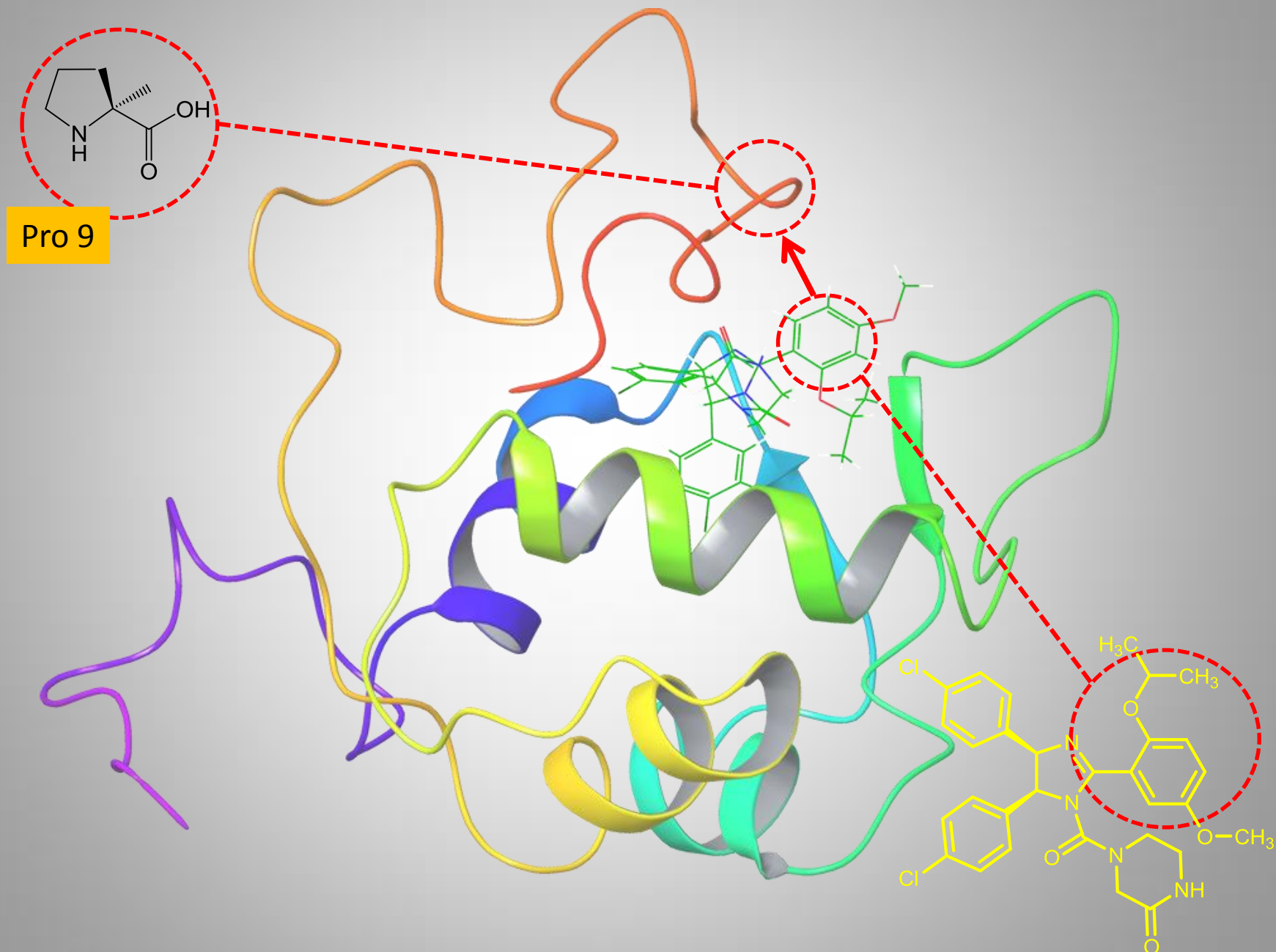
Финальное положение MDM2 – Nutlin-3b



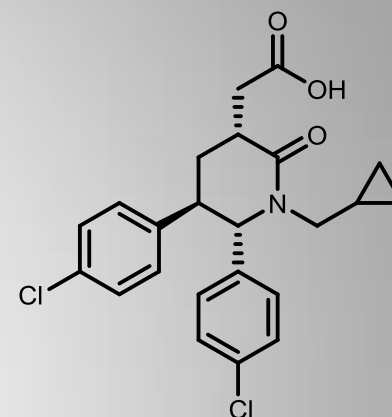
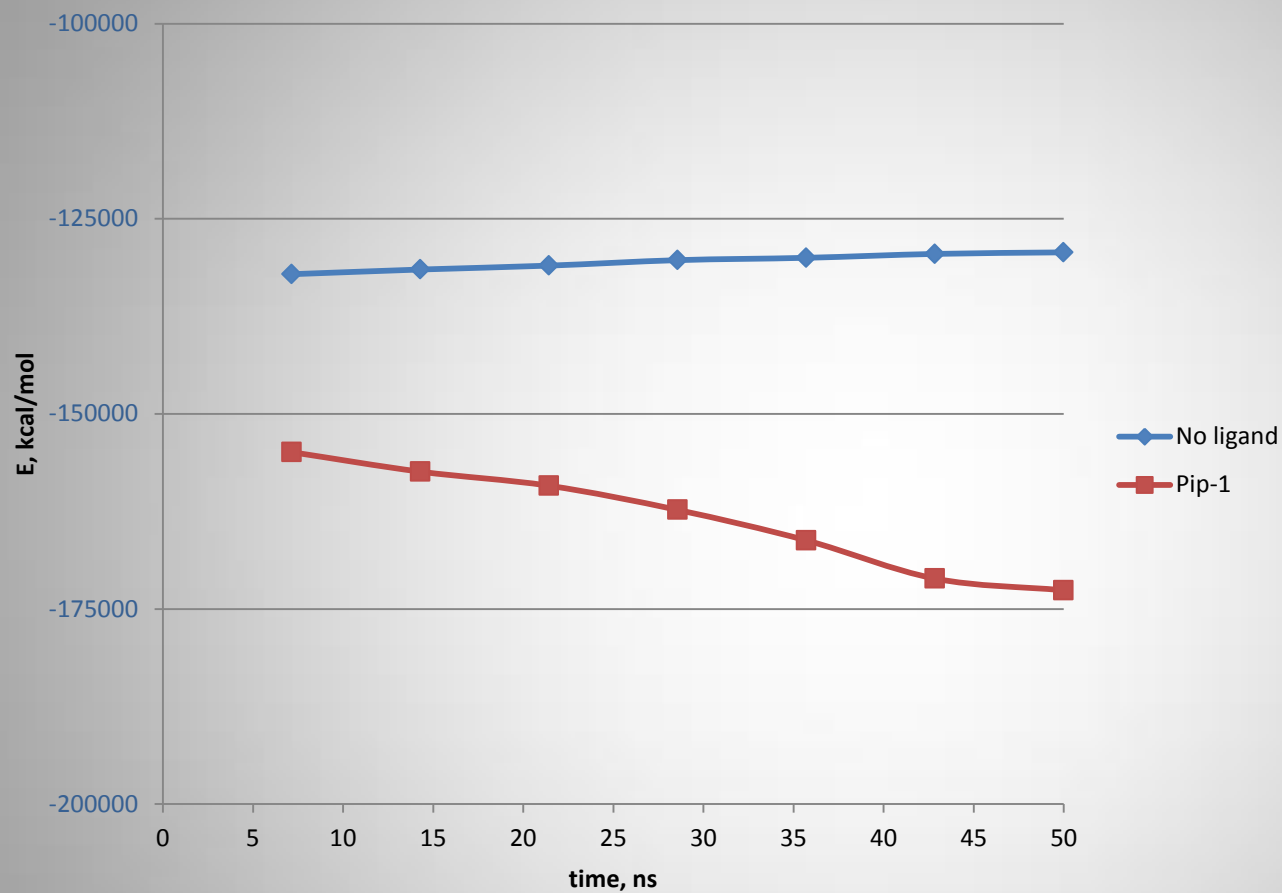
Pro 9



Финальное положение MDM2 – Nutlin-3a



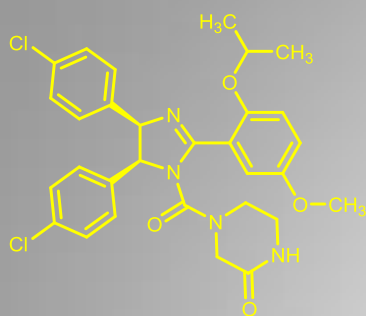
Энергия системы лиганд-белок (Pip-1 – MDM2)



Pip-1

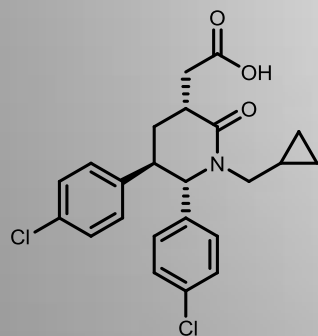
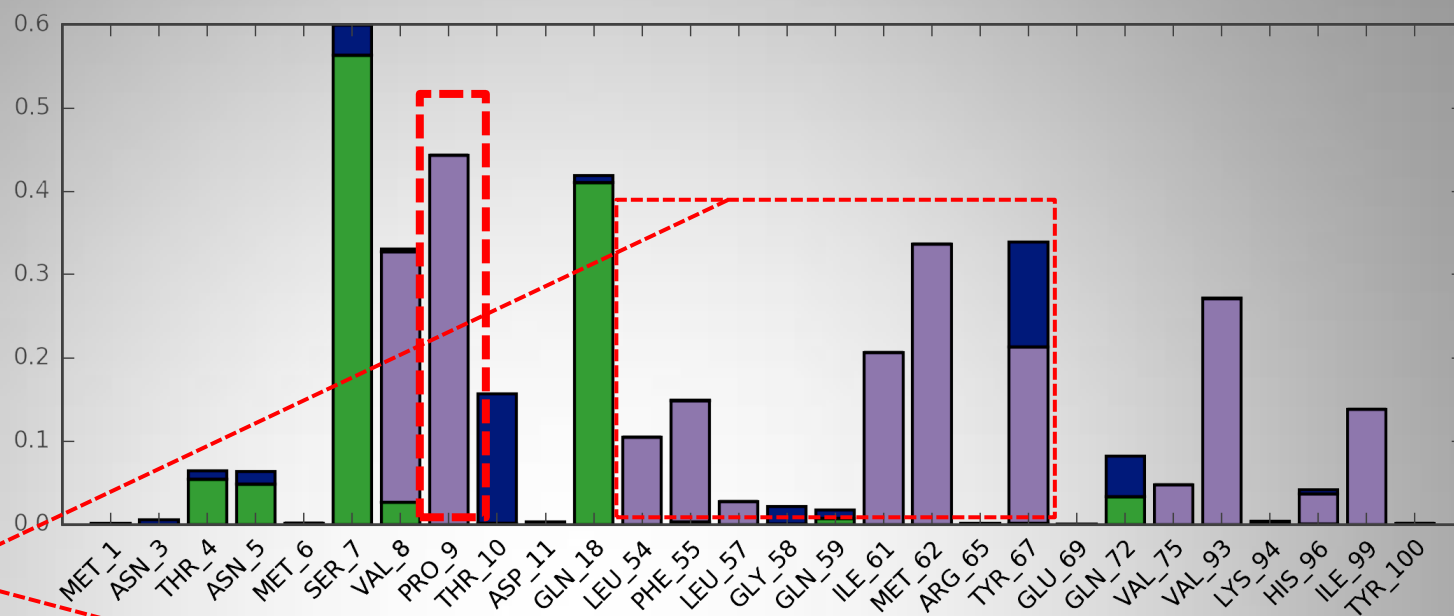
$$\frac{\text{Nutlin-3a } EC_{50}}{\text{Pip-1 } EC_{50}} \sim 15$$

Аминокислоты MDM2 взаимодействующие с лигандом

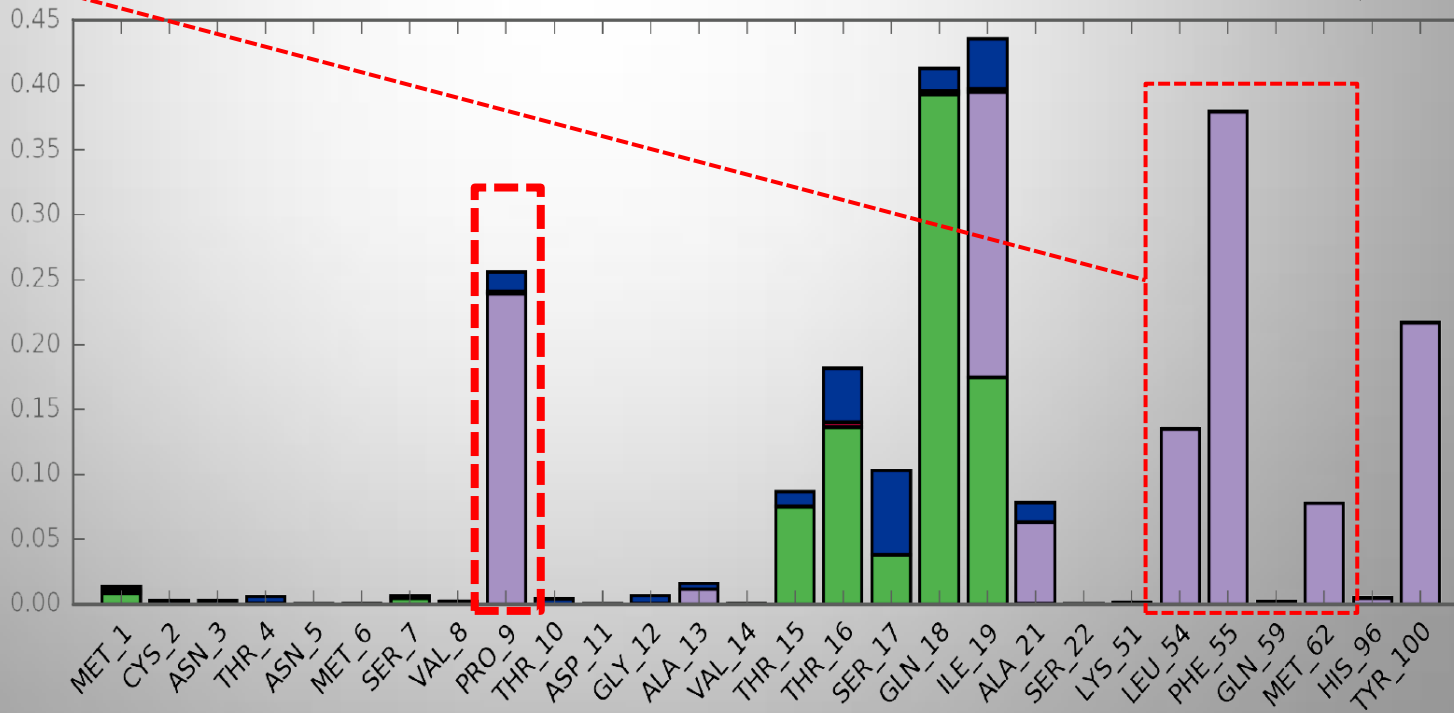


Nutlin-3a

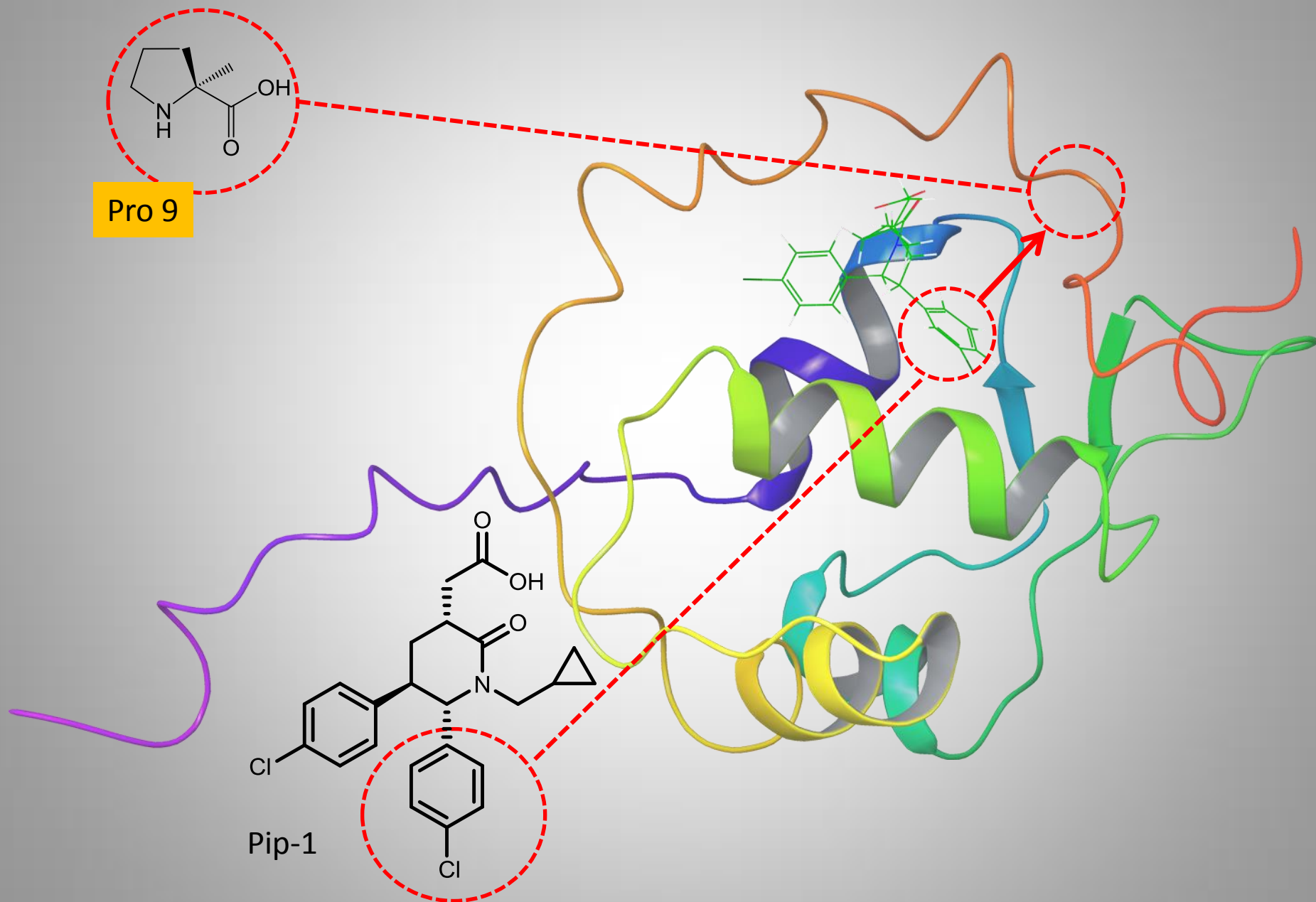
Область
связывания
TAD p53



Pip-1



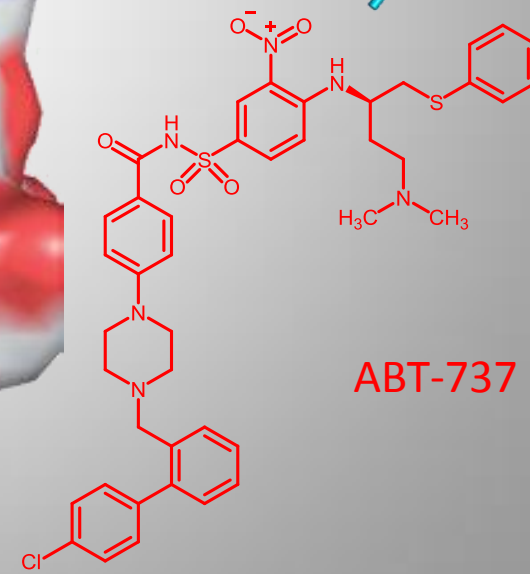
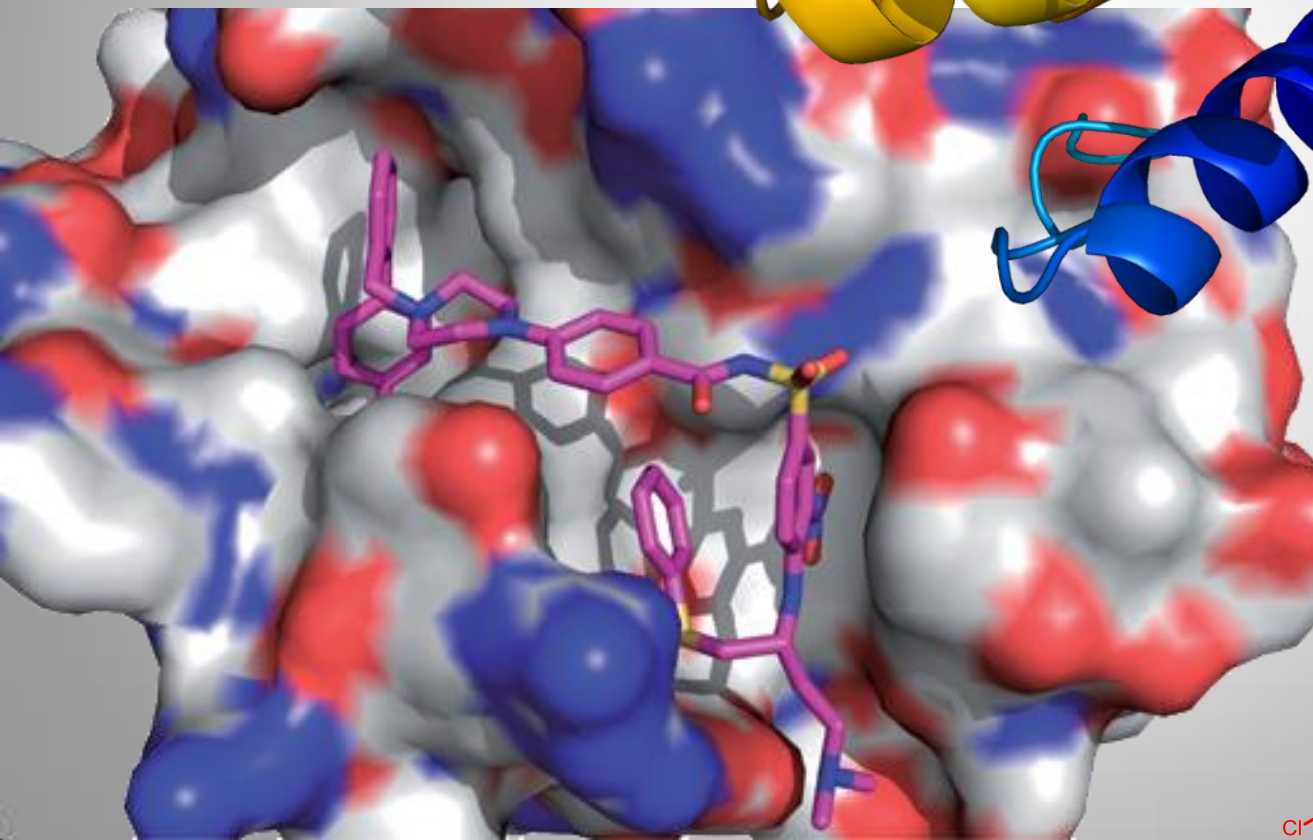
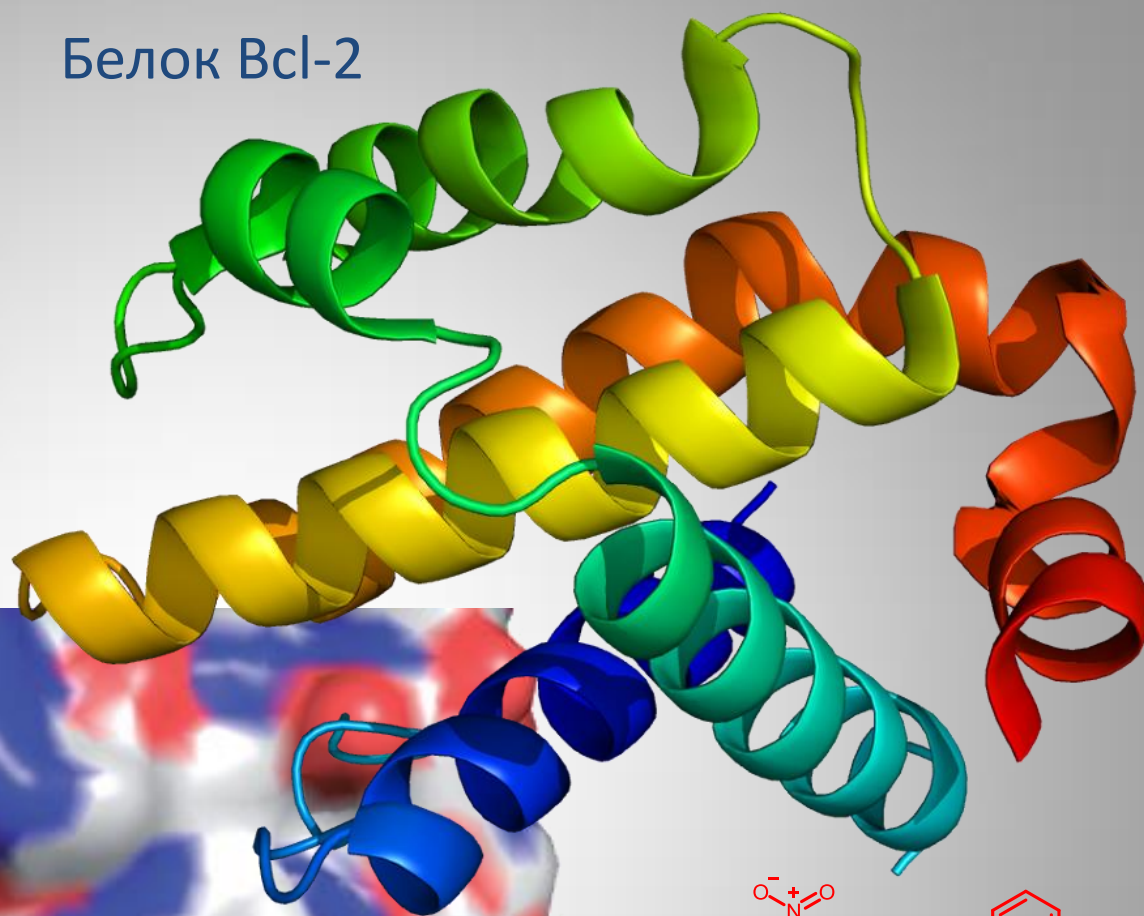
Финальное положение MDM2 – Pip-1



Белок Bcl-2

ABT-737

Эффективен в pM
концентрациях



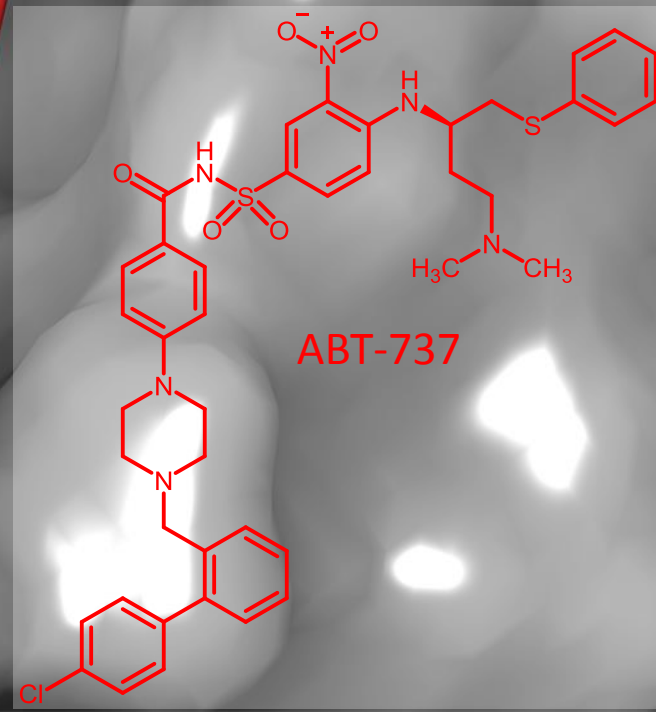
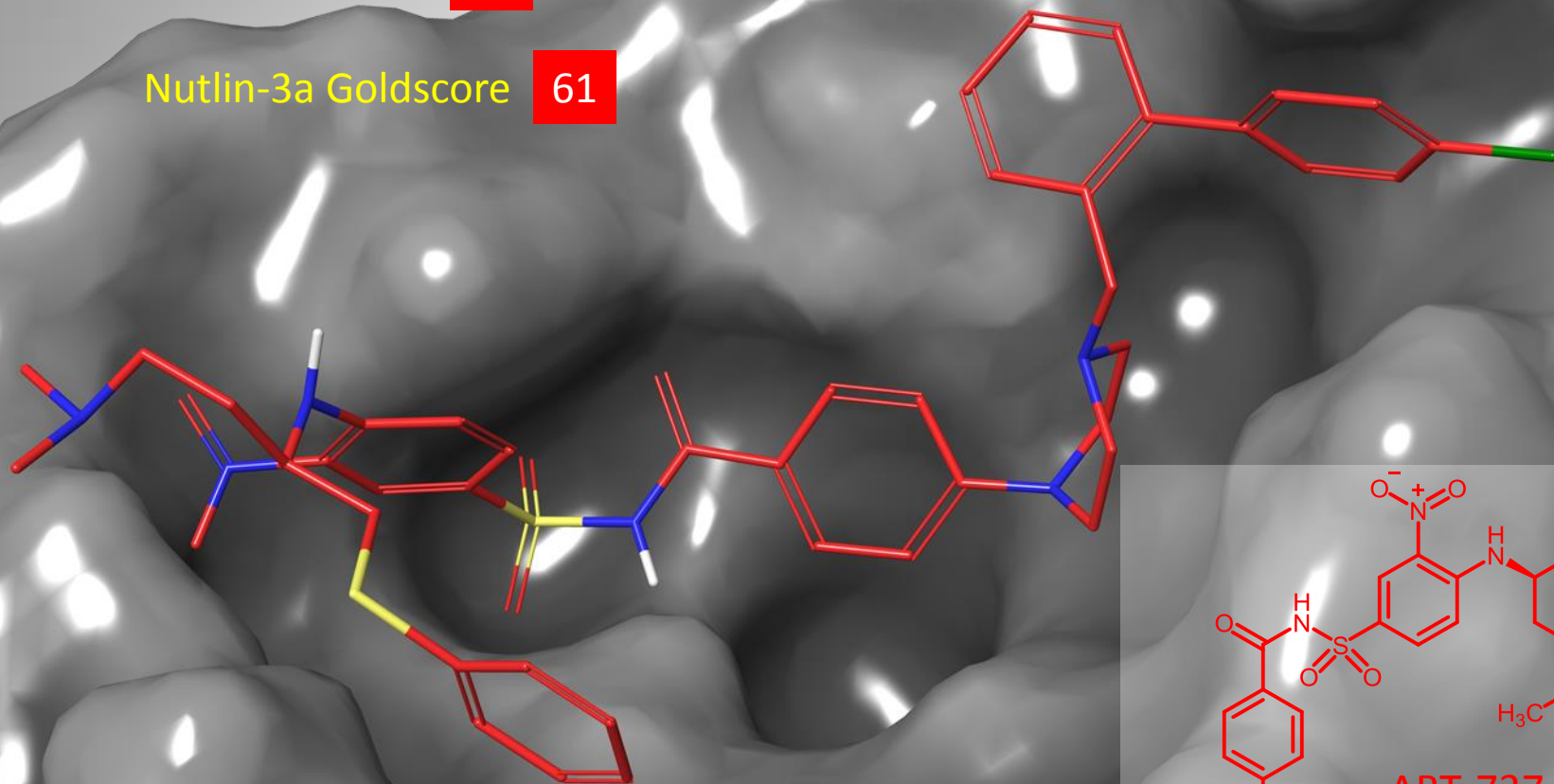
Укладка ABT-737 в p53-связывающей полости MDM2

ABT-737 Goldscore

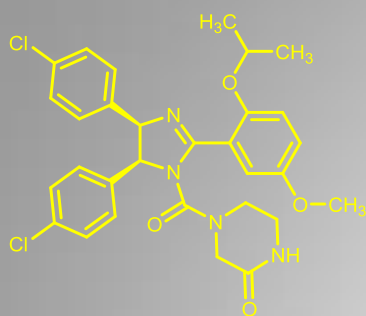
76

Nutlin-3a Goldscore

61

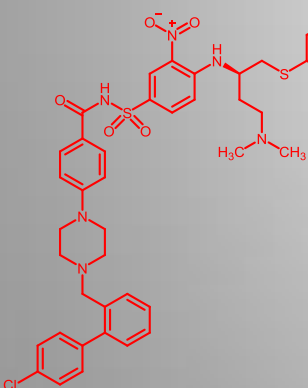
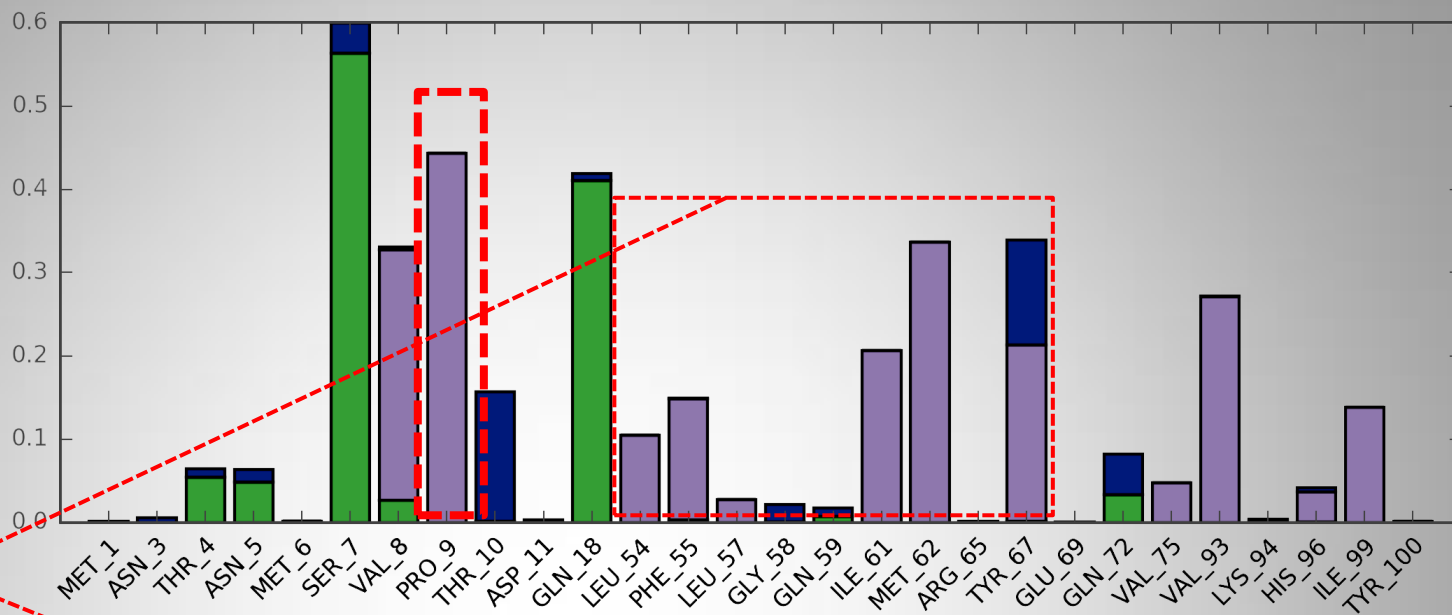


Аминокислоты MDM2 взаимодействующие с лигандом

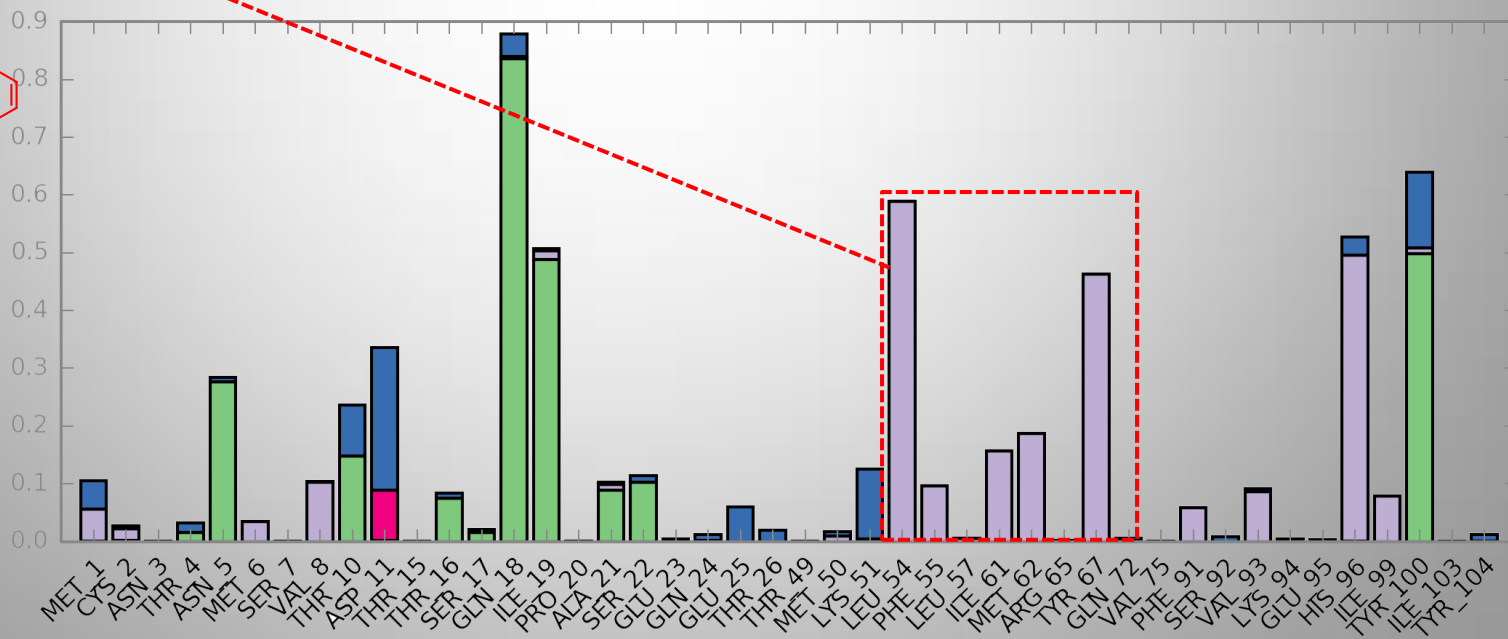


Nutlin-3a

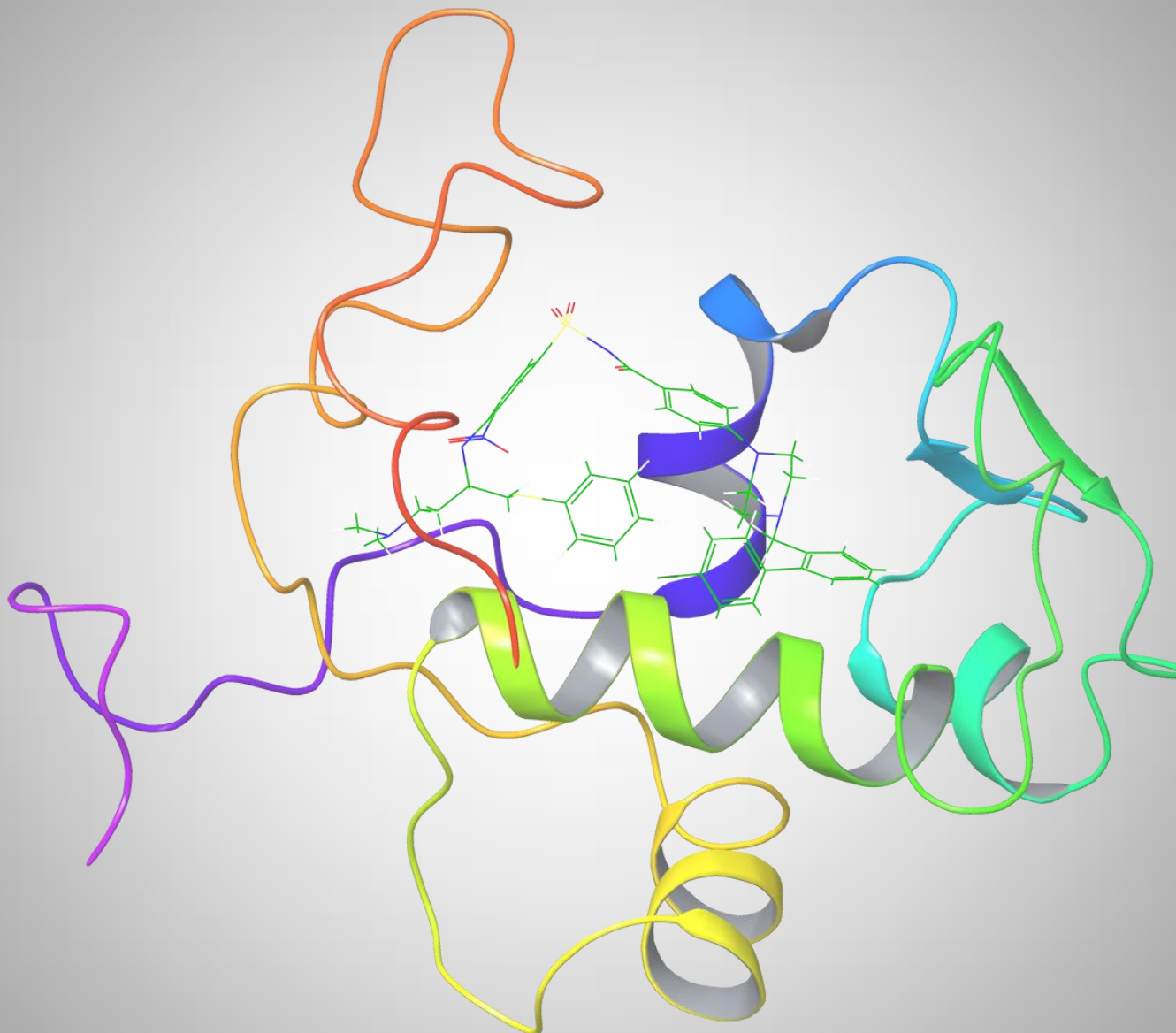
Область
связывания
TAD p53



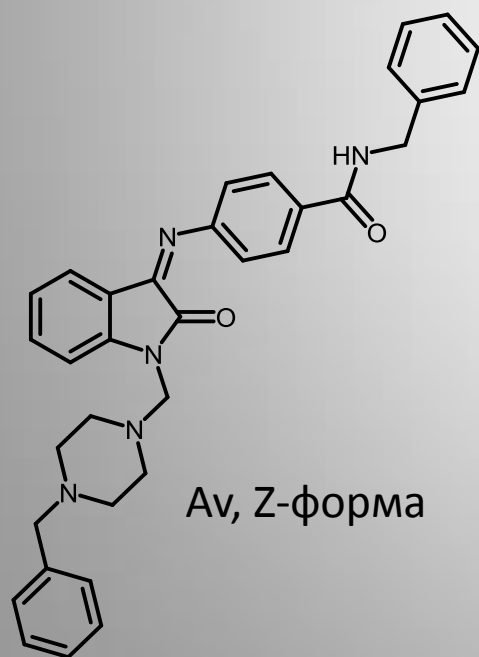
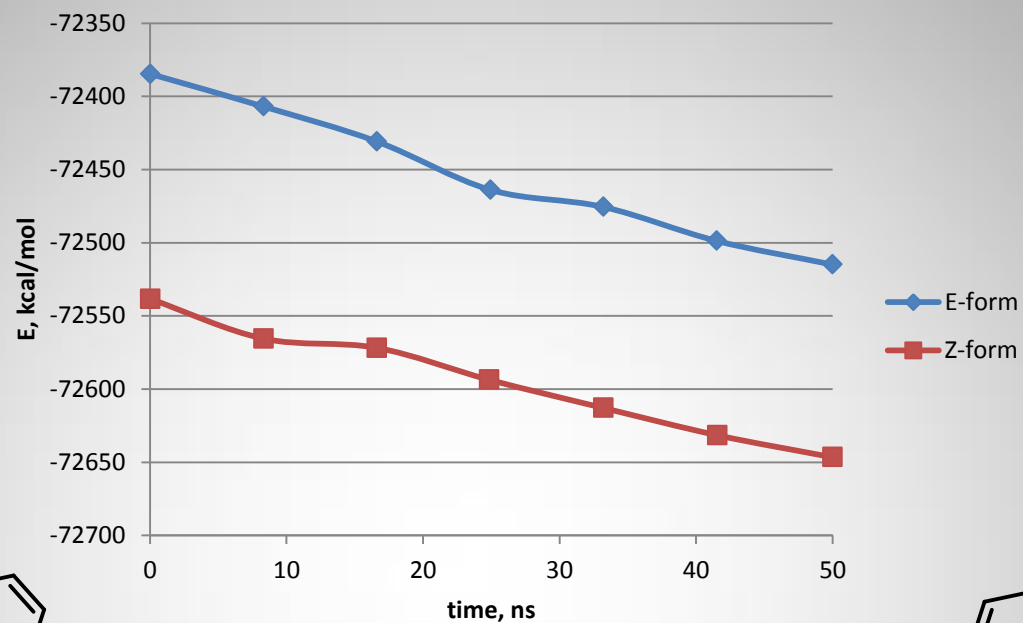
ABT-737



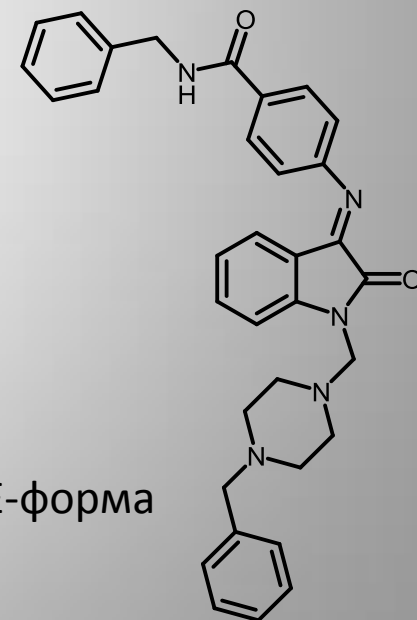
Финальное положение MDM2 – ABT-737



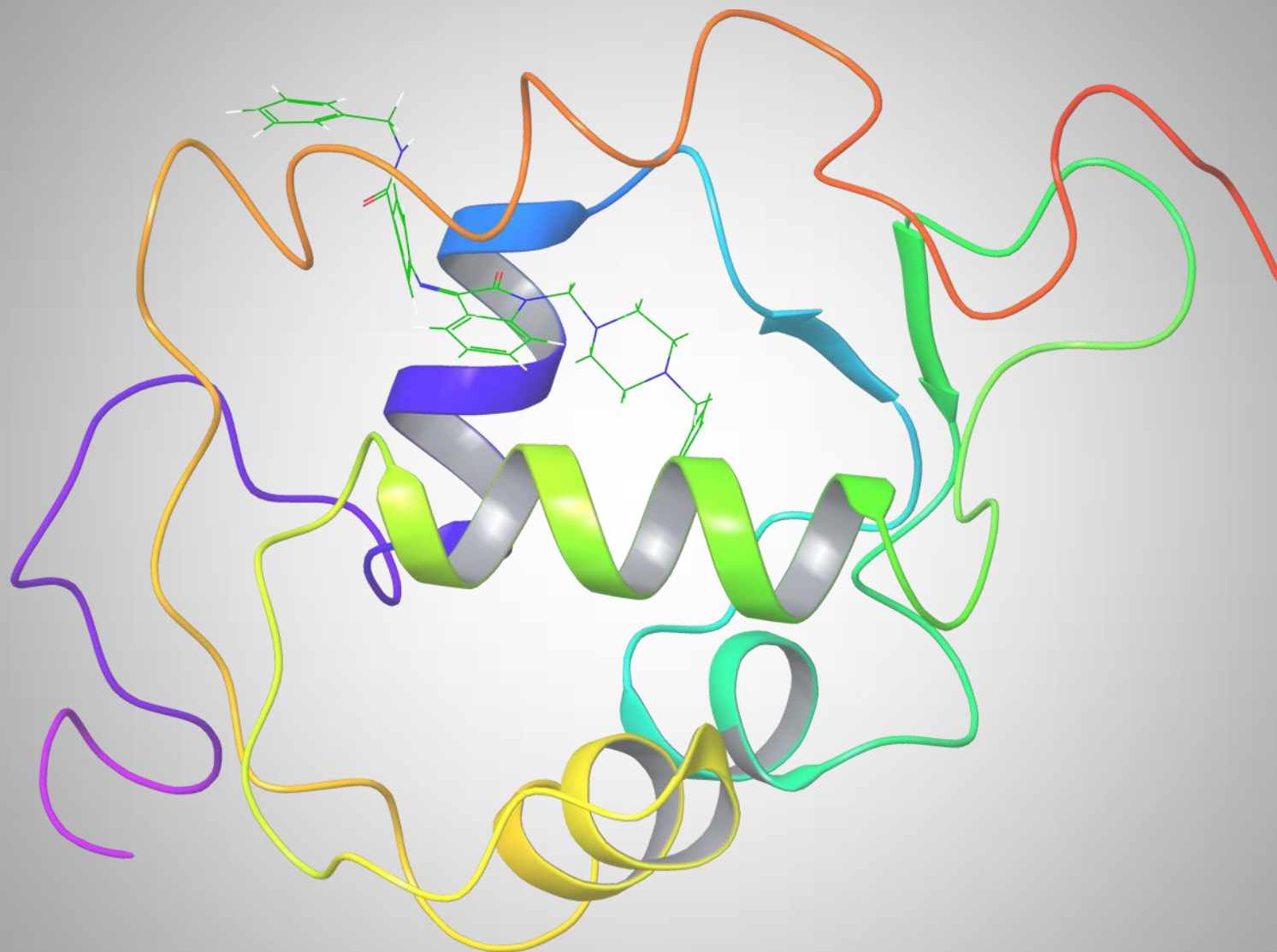
Энергия системы лиганд-белок (Av – MDM2)



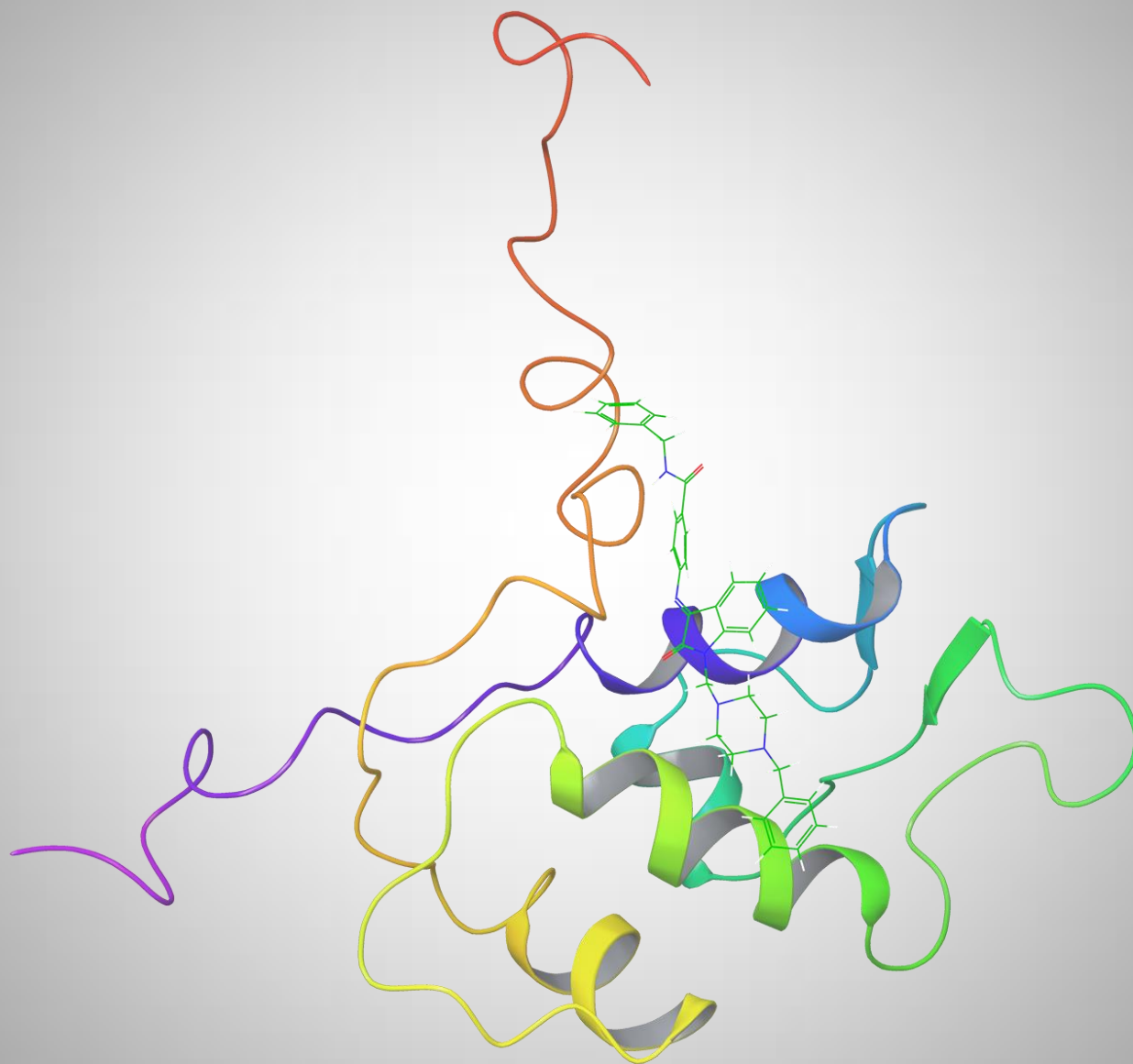
$$\frac{\text{Nutlin-3a } EC_{50}}{\text{Av } EC_{50}} \sim 7$$



Финальное положение MDM2 – Av, Z-форма



Финальное положение MDM2 – Ав, Е-форма



Клинические испытания активаторов p53

Compound	Mechanism of action	Status	ClinicalTrials.gov identifiers	Company
RG7112 (also known as RO5045337)	Small-molecule MDM2 antagonist	Phase I trial in advanced solid tumours, solid tumours, haematological neoplasms and liposarcomas (all completed)	NCT00559533 NCT01164033 NCT00623870 NCT01143740	Roche
RG7112 (also known as RO5045337) with cytarabine	Small-molecule MDM2 antagonist	Phase I in AML (completed)	NCT01635296	Roche
RG7112 (also known as RO5045337) with doxorubicin	Small-molecule MDM2 antagonist	Phase I in soft tissue sarcoma (completed)	NCT01605526	Roche
RO5503781	Small-molecule MDM2 antagonist	Phase I in advanced malignancies (recruiting)	NCT01462175	Roche
RO5503781 with cytarabine	Small-molecule MDM2 antagonist	Phase I in AML (recruiting)	NCT01773408	Roche
MI-773 (also known as SAR405838)	Small-molecule MDM2 antagonist	Phase I in malignant neoplasms (recruiting)	NCT01636479	Sanofi
DS-3032b	Small-molecule MDM2 antagonist	Phase I in advanced solid tumour lymphoma (recruiting)	NCT01877382	Daiichi Sankyo
PRIMA-1 ^{MET} (also known as APR-246)	Reactivation of mutant p53	Phase I in haematological and prostatic neoplasms (completed)	NCT00900614	Aprea

Первые 30 лет исследований

There are more than 65,000 papers published on p53, but these do not yet provide an unequivocal prediction as to which human tumours are most likely to respond to these therapies with the best therapeutic index

Спасибо за внимание