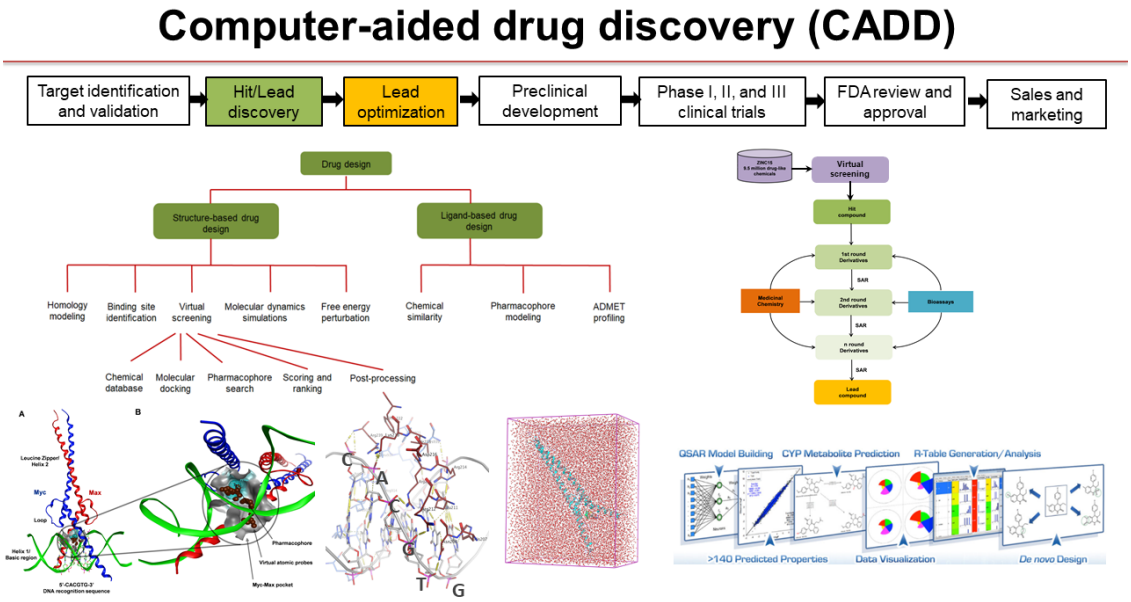
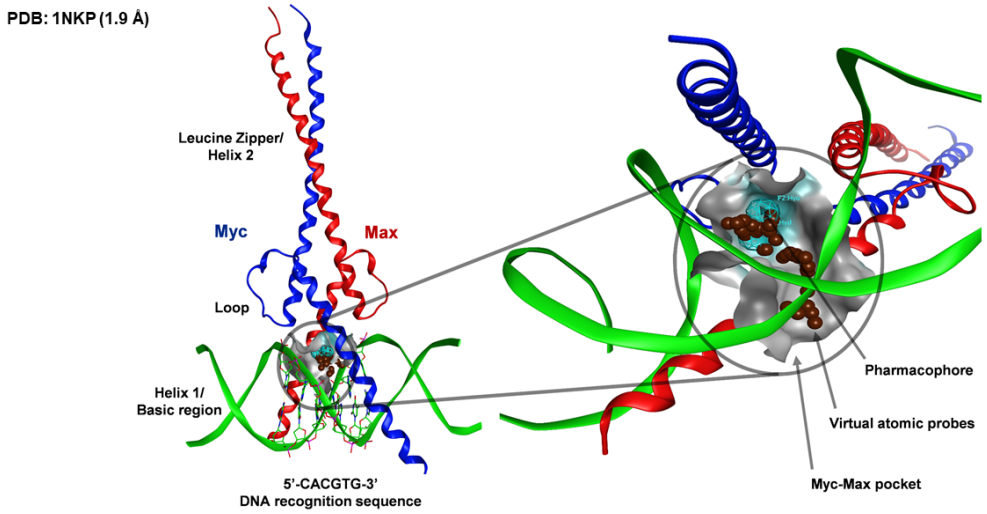
Myc-Max_70551_lead_inhibitor_development

April 8, 2022

1 Computational Drug Discovery Pipeline for c-Myc-Max and N-Myc-Max inhibitors of DNA binding and transcriptional activity



Myc-Max DNA Binding Site

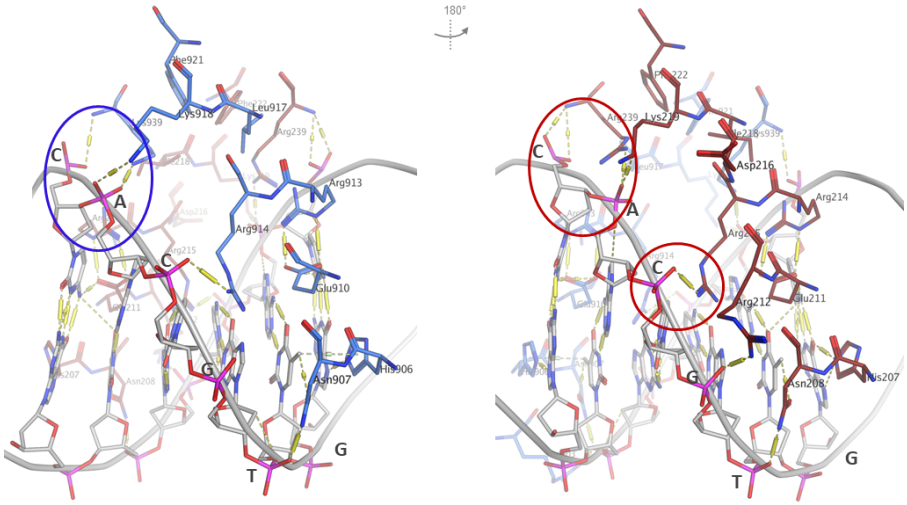


Carabet LA et al. *Computer-aided drug discovery of Myc-Max inhibitors as potential therapeutics for prostate cancer. Eur J Med Chem 2018, 160, 108-119*

Myc-Max/DNA 5'-CACGTG-3' interactions

Myc

Leu917
Phe921
Lys939



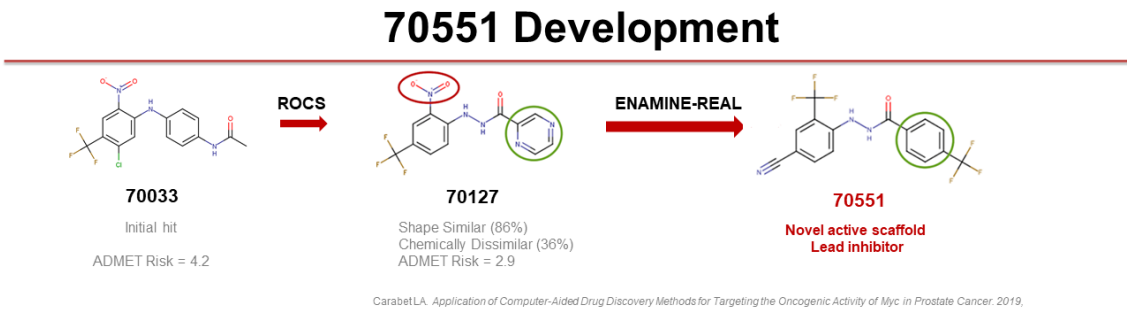
Max

Ile218
Phe222
Arg212
Arg215
Asp216
Arg239

Inhibitors targeting Myc-Max DBD are expected to disrupt these contacts.

2 Development of 70551 Lead Myc-Max Inhibitor

2.1 Optimization Pathway 70033 -> 70127 -> 70551



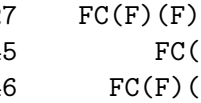
[1]:
```
import os
import pandas as pd                 # Dealing with data in tables
import numpy as np
from rdkit import Chem              # RDKit libraries for chemistry functions
from rdkit.Chem import Draw         # Drawing chemical structures
from rdkit.Chem import PandasTools  # Manipulating chemical data
from rdkit.Chem.Scaffolds import MurckoScaffold

#load dataset
dataset_file = os.path.join('.', 'myc_compounds.csv')
df = pd.read_csv(dataset_file)
```

[2]:
```
PandasTools.AddMoleculeColumnToFrame(df, 'smiles', 'Mol')
df_opt = df.loc[df['id'].isin([70033, 70127, 70545, 70546, 70551])]
df_opt = df_opt.reset_index(drop=True)

mol_list = df_opt["Mol"]
core_smiles = [Chem.MolToSmiles(MurckoScaffold.GetScaffoldForMol(m)) for m in␣
 ↪mol_list]
df_opt['core_smiles'] = core_smiles
PandasTools.AddMoleculeColumnToFrame(df_opt, 'core_smiles', 'Scaffold')
df_opt.loc[:, 'IC50 (μM)'] = [10, 1, '', '', 4]
df_opt
```

[2]:

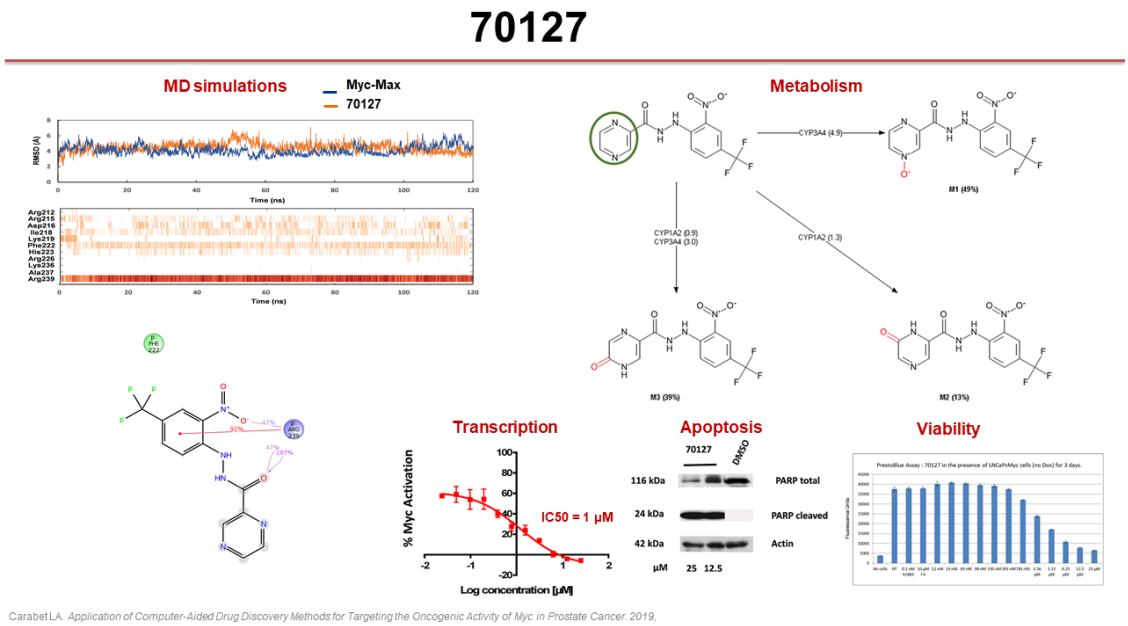
	id	smiles	Mol	core_smiles
0	70033	Clc1c(C(F)(F)F)cc([N+](=O)[O-])c(Nc2ccc(NC(=O)…		c1ccc(Nc2ccccc2)cc1
1	70127	FC(F)(F)c1cc([N+](=O)[O-])c(NNC(=O)c2nccnc2)cc1		
2	70545	FC(F)(F)c1cc(C(=O)NNc2c(F)c(F)c(F)cc2)ccc1		
3	70546	FC(F)(F)c1c(NNC(=O)c2ccc(C(=O)N(C)C)cc2)cccc1		
4	70551	FC(F)(F)c1c(NNC(=O)c2ccc(C(F)(F)F)cc2)ccc(C#N)c1		

1	<img data-content="rdkit/molecule" src="data:i…	O=C(NNc1ccccc1)c1cnccn1
2	<img data-content="rdkit/molecule" src="data:i…	O=C(NNc1ccccc1)c1ccccc1
3	<img data-content="rdkit/molecule" src="data:i…	O=C(NNc1ccccc1)c1ccccc1
4	<img data-content="rdkit/molecule" src="data:i…	O=C(NNc1ccccc1)c1ccccc1

		Scaffold IC50 (µM)
0	<img data-content="rdkit/molecule" src="data:i…	10
1	<img data-content="rdkit/molecule" src="data:i…	1
2	<img data-content="rdkit/molecule" src="data:i…	
3	<img data-content="rdkit/molecule" src="data:i…	
4	<img data-content="rdkit/molecule" src="data:i…	4

2.1.1 70127 structural analysis, predicted metabolism, and biological profile

70127 distant analog of initial hit 70033 with an novel chemical scaffold resulting from ROCS ligand-based chemical similarity searches

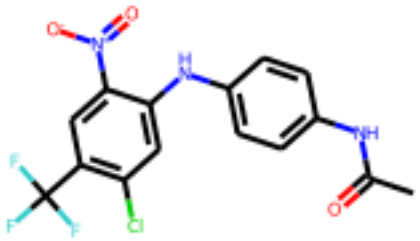


Carabet LA. *Application of Computer-Aided Drug Discovery Methods for Targeting the Oncogenic Activity of Myc in Prostate Cancer*. 2019.

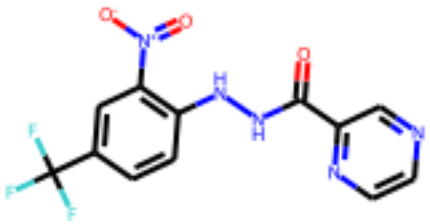
2.1.2 Derivatives of 70127

[3]:
```
ids = df_opt["id"].astype({'id': 'string'}).tolist()
common_scaffold = Chem.MolFromSmiles('O=C(NNC1=CC=CC=C1)C1=CC=CC=C1')
match_list = [mol.GetSubstructMatch(common_scaffold) for mol in mol_list]
Draw.MolsToGridImage(mols=mol_list, molsPerRow=2,␣
↪highlightAtomLists=match_list, legends=ids)
```

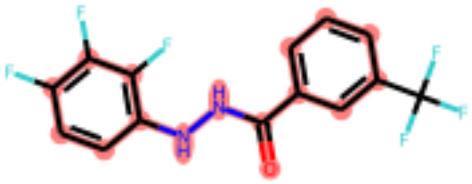
[3]:



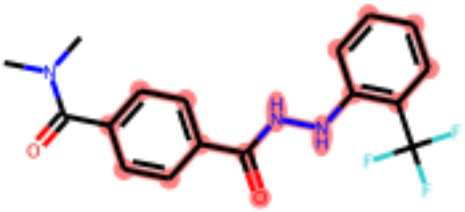
70033



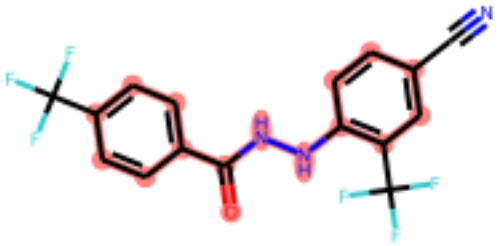
70127



70545



70546



70551

2.1.3 Some evidence of SAR for the derivatives of 70127 resulting from substructure searches without the reactive nitro group and replacement of the metabolically vulnerable pyrazine ring

The activities of the three analogs positively correlate with the pharmacophore RMSD values. The lower the RMSD, the higher the activity. 70551 shows best inhibition of Myc-Max transcriptional activity.

[4]:
```
df_sar = pd.DataFrame({'id':[70551, 70545, 70546],
                       '% Inhibition transcriptional activity (@12.5 µM)':[98,␣
 ↪66, 58],
                       'RMSD pharmacophore (Å)':[0.60, 0.98, 1.23]})
df_sar
```

[4]:
```
      id  % Inhibition transcriptional activity (@12.5 µM)  \
0  70551                                                98
1  70545                                                66
2  70546                                                58

   RMSD pharmacophore (Å)
0                    0.60
1                    0.98
2                    1.23
```

2.1.4 Potency, specificity and number of predicted metabolites comparison between 70127 and 70551

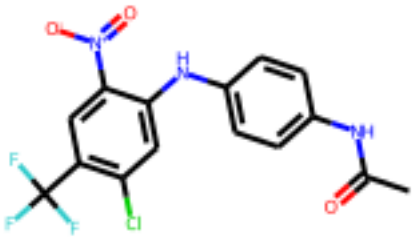
[5]:
```
df_activ = pd.DataFrame({'id':[70127, 70551],
                         '% Non-specific cytotoxicity':[19, 10],
                         '# Predicted metabolites':[3, 0]})
df_activ
```

[5]:
```
      id  % Non-specific cytotoxicity  # Predicted metabolites
0  70127                           19                        3
1  70551                           10                        0
```

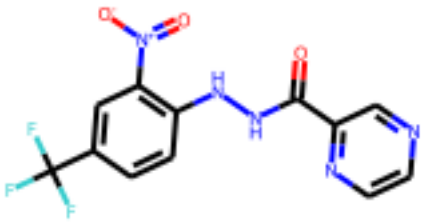
2.1.5 70551 lead novel active scaffold

[6]:
```
lead_active_scaffold = Chem.
 ↪MolFromSmiles('FC(F)(F)C1=C(NNC(=O)C2=CC=CC=C2)C=CC(=C1)C#N')
match_list = [mol.GetSubstructMatch(lead_active_scaffold) for mol in mol_list]
Draw.MolsToGridImage(mols=mol_list, molsPerRow=2,␣
 ↪highlightAtomLists=match_list, legends=ids)
```

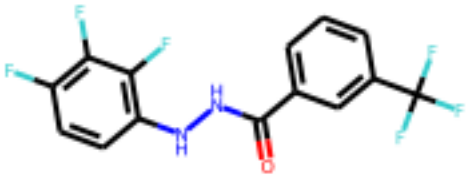
[6]:



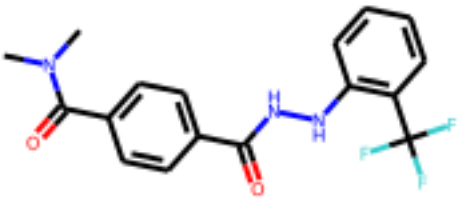
70033



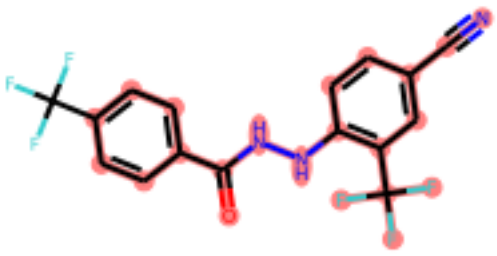
70127



70545

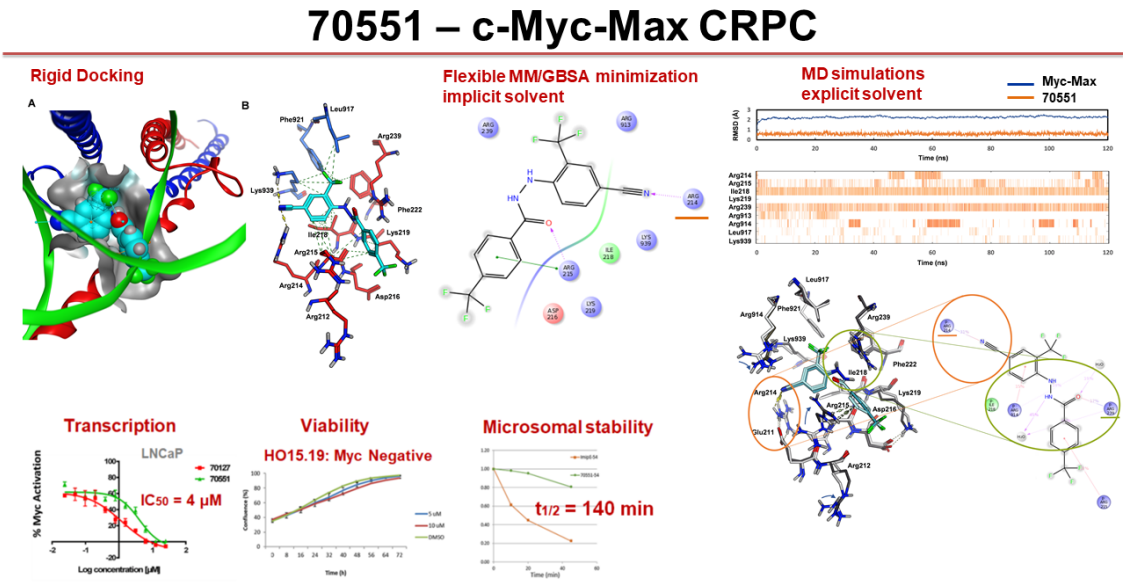


70546



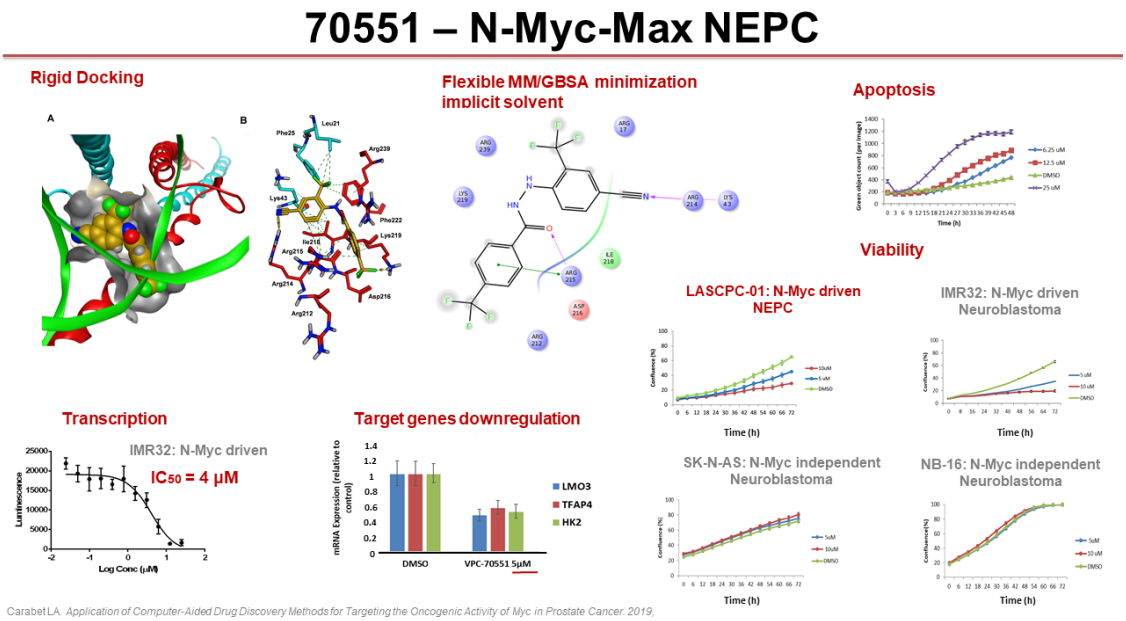
70551

2.2 Structural determinants of 70551 binding affinity for c-Myc-Max site at the DNA interface and activity in models of castration-resistant prostate cancer (CRPC)



Carabet LA. *Application of Computer-Aided Drug Discovery Methods for Targeting the Oncogenic Activity of Myc in Prostate Cancer.* 2019.

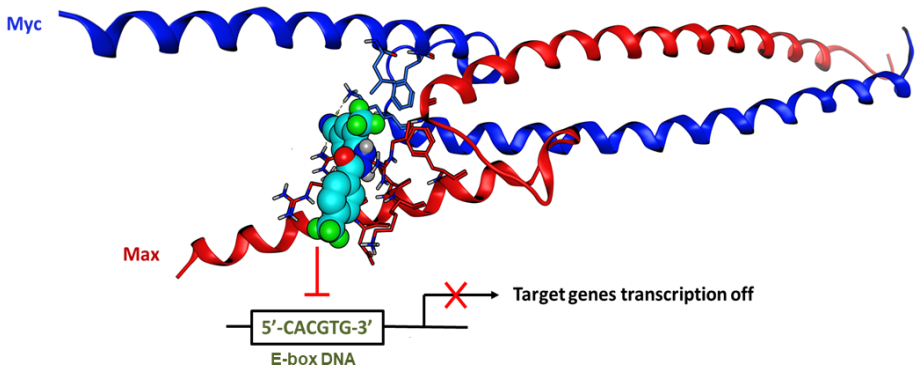
2.3 70551 identical binding affinity for the equivalent N-Myc-Max site at the DNA interface and same activity in models of neuroendocrine prostate cancer (NEPC)



Carabet LA. *Application of Computer-Aided Drug Discovery Methods for Targeting the Oncogenic Activity of Myc in Prostate Cancer.* 2019.

2.4 70551 - moderately potent, specific and metabolically stable, with some evidence of SAR

70551 Lead Inhibitor



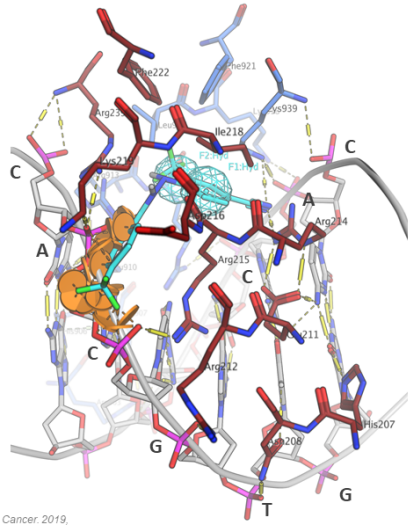
Carabet LA. *Application of Computer-Aided Drug Discovery Methods for Targeting the Oncogenic Activity of Myc in Prostate Cancer*. 2019.

2.5 70551 competes with DNA for binding to Myc-Max dimer by mimicking DNA interactions with specific residues, mutations of which abrogate Myc-Max binding to DNA, matches the pharmacophore/hydrophobic core of the binding site and clashes with DNA

70551 versus DNA 5'-CACGTG-3'

NOVEL ACTIVE SCAFFOLD

N'-[4-cyano-2-(trifluoromethyl)phenyl]benzohydrazide



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[ ]: