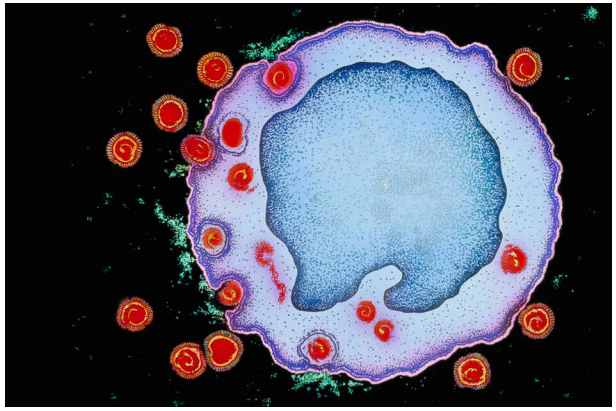
Investigation of novel HIV-1 Integrase Strand Transfer Inhibitors via *Ab initio* Computational Methods



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CH 669
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Evolution of HIV-1 Resistance to Current HAART Regimens

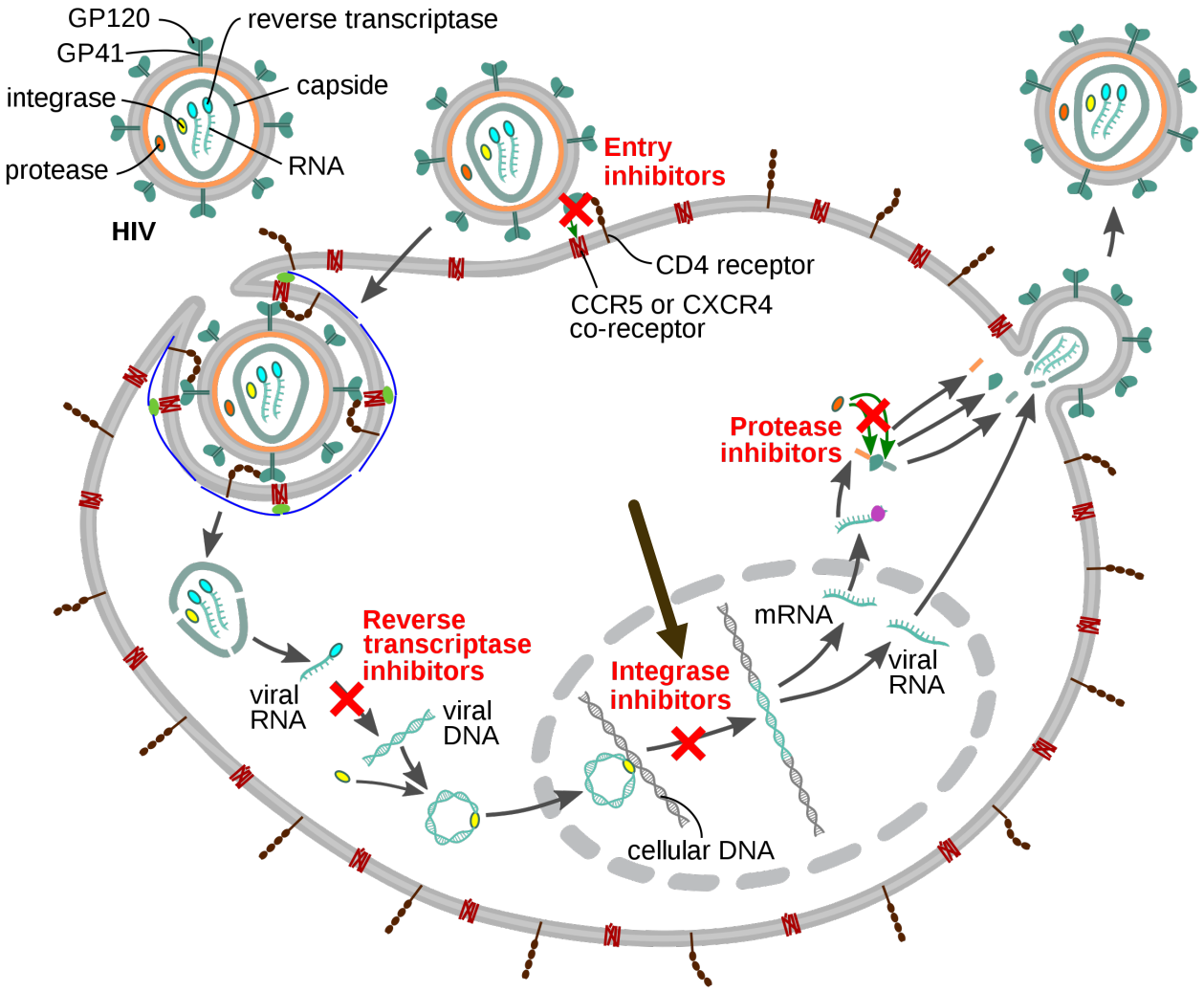
- Highly Active Antiretrovial Therapy has reduced mortality among HIV patients for decades
- However, new mutations in the HIV genome are leading to reduced efficacy of a number of medications
- The diagram to the right outlines the 4 major classes of antiretroviral medications

I. Entry Inhibitors

II. Reverse Transcriptase Inhibitors

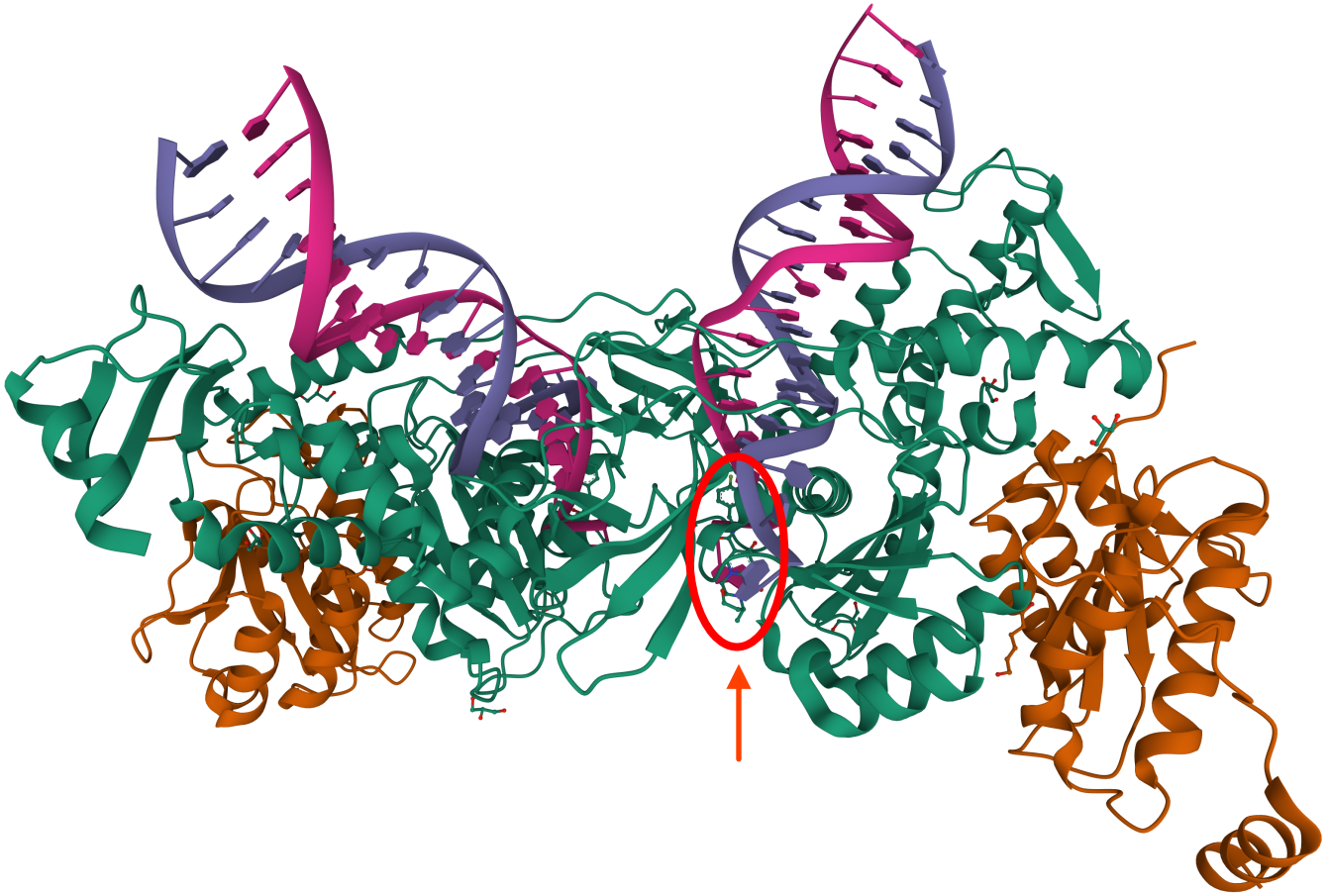
III. **Integrase Inhibitors**

IV. Protease Inhibitors

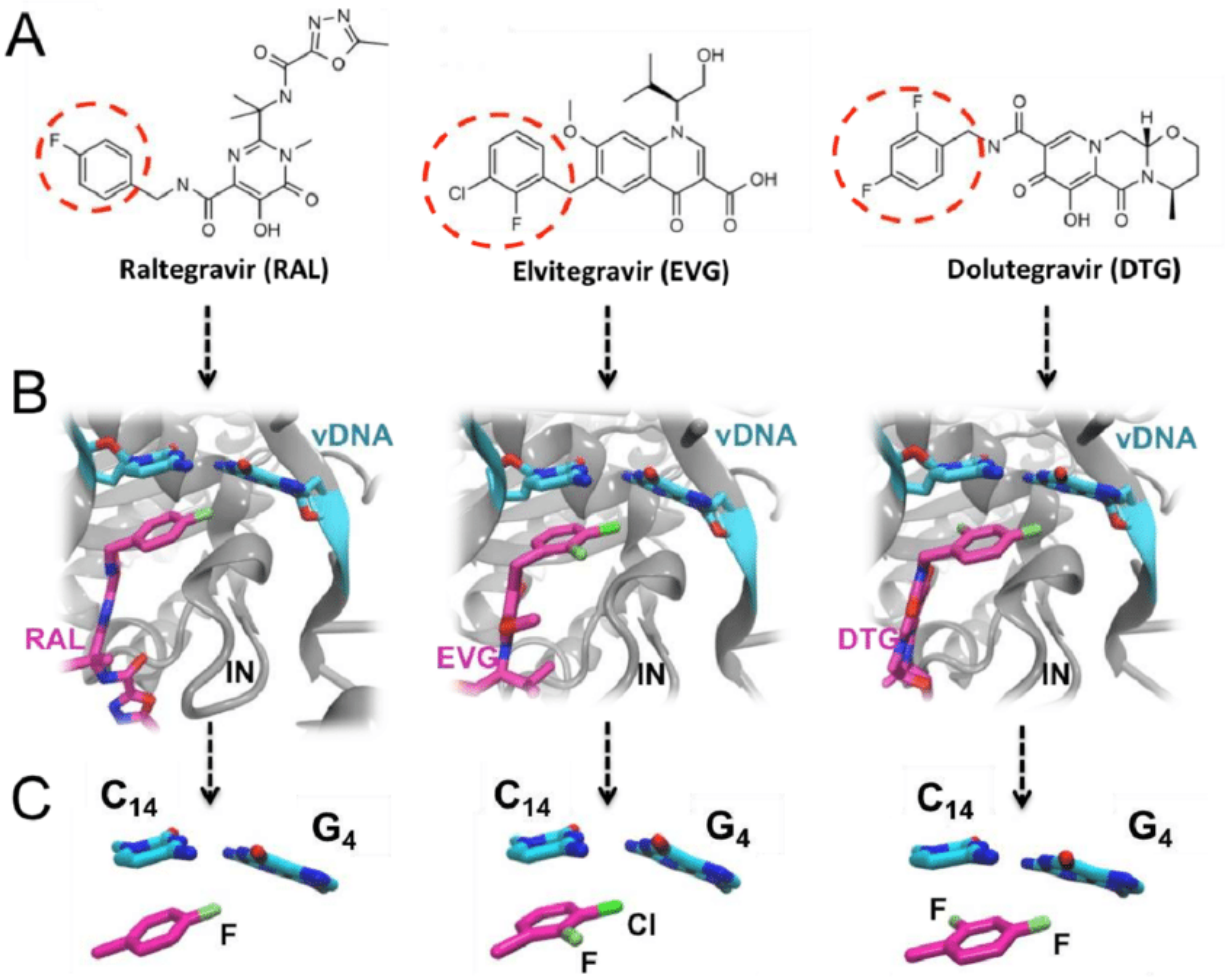


The HIV-1 Integrase in Complex with Host DNA

- INSTIs are the third line of defense against HIV infection
- Even after viral entry and reverse transcription occur, HIV cannot replicate without incorporation into host DNA
- By blocking the site in the integrase where viral and host DNA meet, inhibitors can end the Lytic Cycle
- To the right, the INSTI **Dolutegravir** is seen in the complex, obtained by X-Ray Crystallography



INSTIs Approved by the FDA



A.

The structure of the molecules are provided to the left. A crucial aspect of their design is the circled region – a **halobenzene ring**

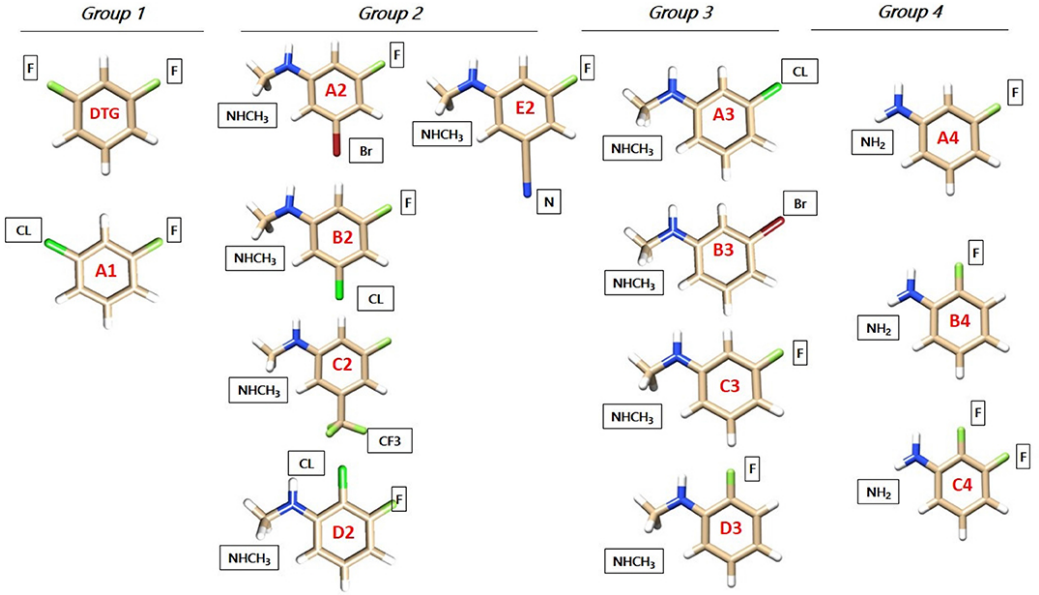
B.

This motif has been shown to interact directly with viral DNA. The backbone of the molecules bind to specific amino acid residues in the integrase

C.

2 Nucleotides near the junction between the integrase and DNA stands are integral to the binding profiles of the drugs. Therefore, design and development of new INSTIs focus heavily on this region

Modification of the Halobenzene Ring impacts overall Drug Affinity and Binding Energies



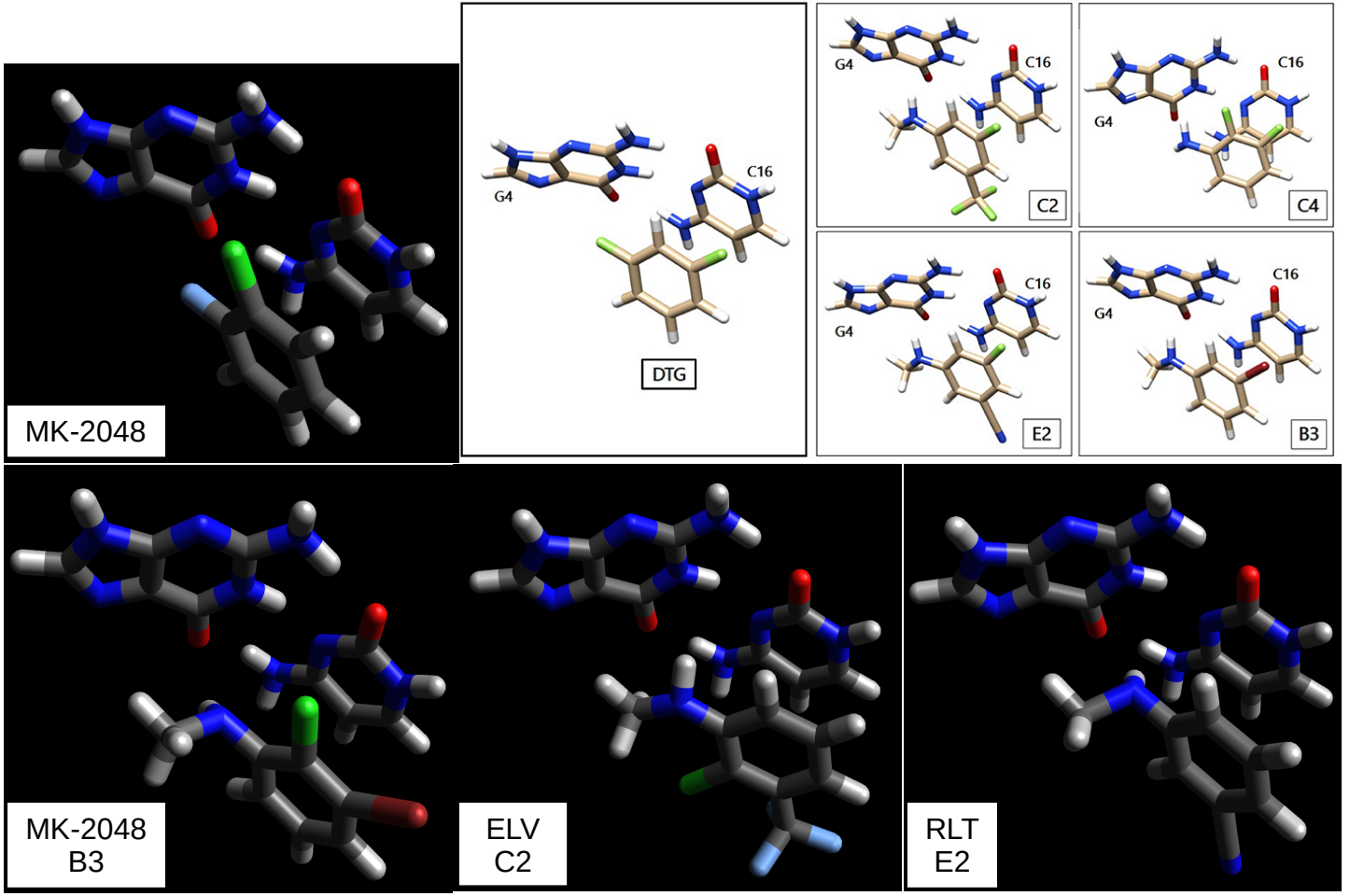
Compounds	ΔE B97-D3 (raw value/BSSE corrected)	ΔE B3LYP-D3 (raw value/BSSE corrected)	ΔE ALMOEDA (B97D3)	ΔE ALMOEDA (ω-B97D)	SIBFA	ΔG solv	Total interaction energy (ΔE B97-D3 -ΔG solv) (raw value/BSSE corrected)
DTG	**−37.4/−33.2**	**−40.6/−36.5**	**−33.2**	**−35.9**	**−39.6**	**−6.1**	**−31.3/−27.1**
A1	−37.5/−33.8	−40.6/−37.0	−33.8	−35.8	−38.4	−5.9	−31.6/−27.9
A2	**−45.1/−40.7**	**−48.1/−43.7**	**−40.6**	**−43.3**	**−45.9**	**−9.7**	**−35.4/−31.0**
B2	**−44.9/−40.5**	**−47.9/−43.5**	**−40.4**	**−43.1**	**−46.6**	**−9.5**	**−35.4/−31.0**
C2	**−46.0/−41.3**	**−49.1/−44.5**	**−41.2**	**−44.1**	**−47.3**	**−10.1**	**−35.9/−31.2**
D2	−43.0/−38.6	−46.3/−41.9	−38.5	−41.0	−45.2	−7.8	−35.2/−30.8
E2	**−45.3/−40.9**	**−48.2/−43.9**	**−40.6**	**−43.4**	**−47.7**	**−7.8**	**−37.5/−33.1**
A3	−44.7/−40.4	−47.6/−43.4	−40.3	−42.7	−44.6	−9.4	−35.3/−31.0
B3	**−44.9/−40.7**	**−47.9/−43.7**	**−40.6**	**−43.1**	**−46.9**	**−9.5**	**−35.4/−31.2**
C3	−44.1/−39.6	−47.0/−42.6	−38.8	−41.5	−45.2	−9.7	−34.3/−29.9
D3	−42.6/−37.8	−45.7/−41.1	−38.4	−41.2	−44.0	−7.8	−34.8/−30.0
A4	−42.5/−38.2	−45.2/−40.9	−38.0	−40.6	−43.7	−11.2	−31.3/−27.0
B4	−41.5/−37.0	−44.2/−39.7	−37.4	−39.7	−41.1	−9.7	−31.8/−27.3
C4	−42.1/−37.5	−45.0/−40.4	−41.2/	−41.0	−42.6	−10.3	−31.9/−27.2

DTG as well as the compounds displaying the best energetic values are highlighted in red.

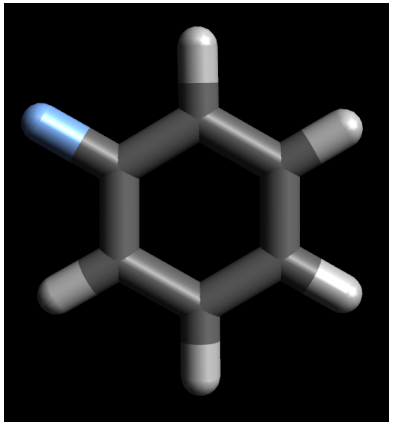
- In a recently published article (Darazi et al., June 2020), the relationship between **R-Group** of the Halobenzene Ring and binding affinity to the **G_4/C_{16} base pair** was expanded upon
- Using Quantum Chemistry Methods (Energy Decomposition Analysis), the group demonstrated that certain configurations of side chains and Halogens on the Benzene ring had stronger interaction energies
- These results served as the basis of my research project – further alterations of the Halobenzene ring could lead to even more favorable properties

Focused Analysis of the Halobenzene Ring – G_4/C_{16} Complex allows for rapid Characterization

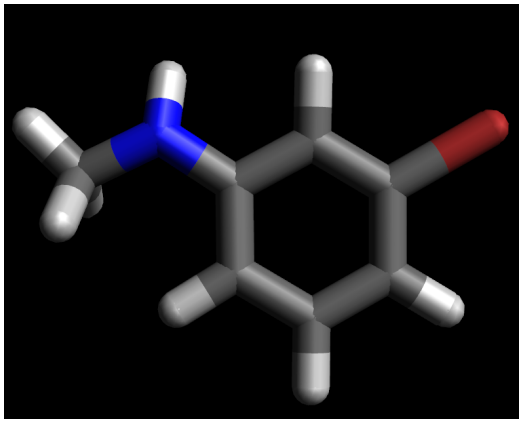
- The figure with the white background is from Darazi et al. 4 of the ring modifications are shown along with the base structure
- The other models are designs that I prepared, using the same side groups in the paper
- However, the alterations performed had significant impact on the stability of the ring – nucleotide complex
- Many more models were created, but not shown



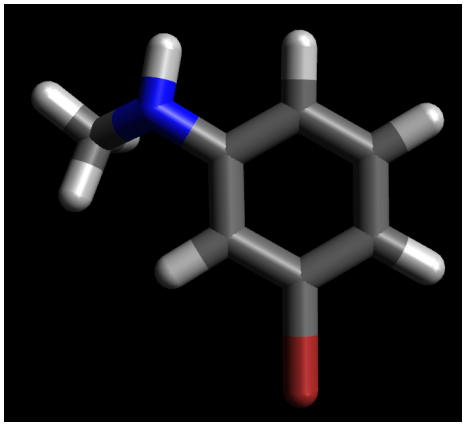
Examples of Halobenzene Ring Derivatives



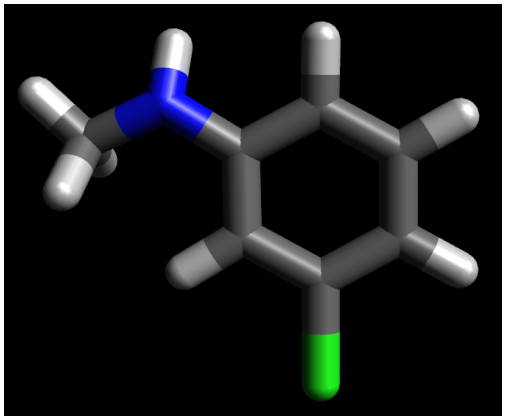
Raltegravir



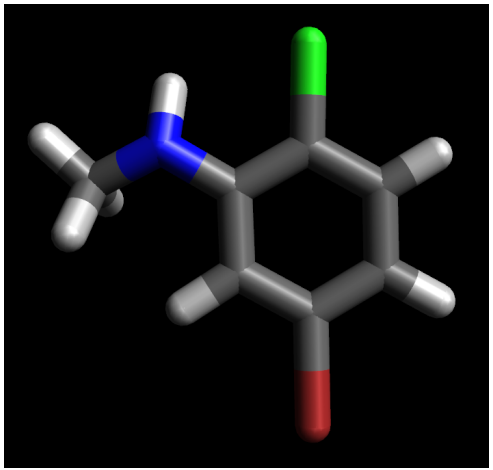
Raltegravir – B3



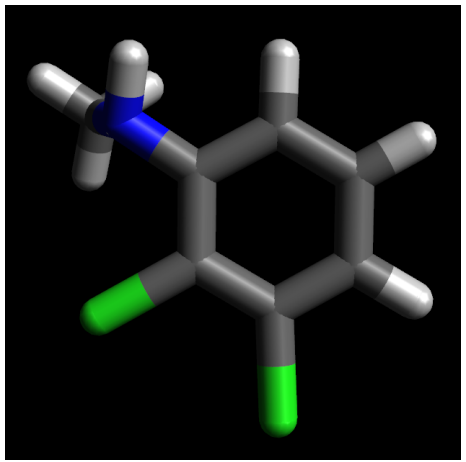
Raltegravir – A2



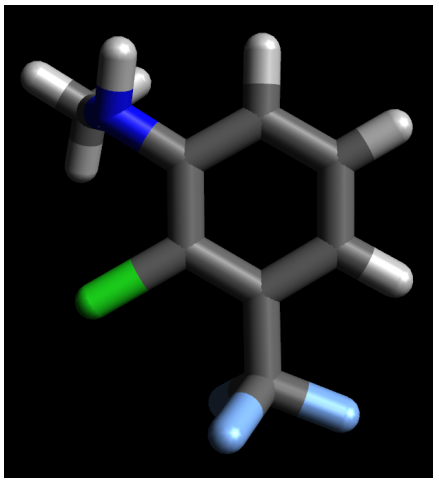
Raltegravir – B2



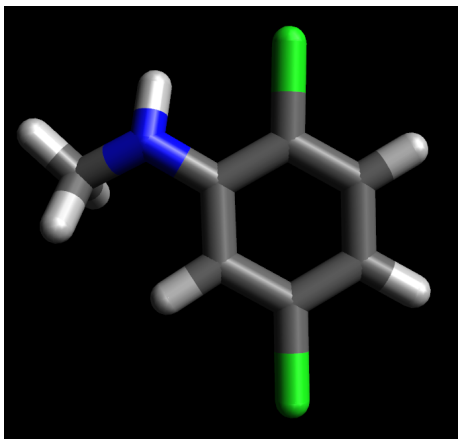
MK-2048 – A2



Raltegravir – B2



Elvitegravir – C2



MK-2048 – B2

Single Point Energy Calculation Results

STRUCTURE	TOTAL ENERGY
DLU – WT	-1367.50
DLU – C2	-1699.81
DLU – E2	-1455.09
DLU – B3	-3836.85
DLU – B2	-1822.44
DLU – A2	-3936.05
ELV – WT	-1727.83
ELV – C2	-2060.13
ELV – E2	-1815.43
ELV – B3	-4296.37
ELV – B2	-2182.75
ELV – A2	-4296.36
RLT – WT	-1268.30
RLT – C2	-1600.60
RLT – E2	-1355.89
RLT – B2	-1723.23
RLT – A2	-3836.84
ZZX – WT	-1727.83
ZZX – C2	-2060.14
ZZX – E2	-1815.42
ZZX – B3	-4296.37
ZZX – B2	-2182.76
ZZX – A2	-4296.37

- As time and computational resources were limited, the methodology used for evaluating structures focused on Single Point Energy

- Energy values are conditionally formatted as follows:
  - **Green → Lowest** (most negative)
  - **Yellow / Orange → Mid-Range**
  - **Red → Highest** (least negative)

- The relative stability of the Halobenzene Ring – G_4/C_{16} Complex can be ascertained from the Single Point Energy
- The **B3** and **A2** R-Groups were significantly more stable (and ostensibly, tighter binding) than the other side chains
- Rationale behind this → the **Bromine** atom

STRUCTURE	TOTAL ENERGY
ELV – B3	-4296.37
ZZX – B3	-4296.37
ZZX – A2	-4296.37
ELV – A2	-4296.36
DLU – A2	-3936.05
DLU – B3	-3836.85
RLT – A2	-3836.84
ZZX – B2	-2182.76
ELV – B2	-2182.75
ZZX – C2	-2060.14
ELV – C2	-2060.13
DLU – B2	-1822.44
ELV – E2	-1815.43
ZZX – E2	-1815.42
ELV – WT	-1727.83
ZZX – WT	-1727.83
RLT – B2	-1723.23
DLU – C2	-1699.81
RLT – C2	-1600.60
DLU – E2	-1455.09
DLU – WT	-1367.50
RLT – E2	-1355.89
RLT – WT	-1268.30

Additional Single Point Energy Results

Molecule	TOTAL ENERGY
Raltegravir	-1578.35
Dolutegravir	-1512.81
Elvitegravir	-1880.31
Bictegravir	-1650.08
L-870810	-1790.60
MK-2048	-1946.68

Density Function Theory Method: **B3LYP**

Molecule	TOTAL ENERGY
MK-2048	-1946.68
Elvitegravir	-1880.31
L-870810	-1790.60
Bictegravir	-1650.08
Raltegravir	-1578.35
Dolutegravir	-1512.81

- To obtain a general baseline of the energy/stability of the source molecules for the Halobenzene Ring derivatives, two sets of runs were performed
- First, the results to the left indicate that for the drugs alone, the experimental compound **MK-2048** is the most intrinsically stable
- Second, the results to the right demonstrate that the complex formed between drug and nucleotides is more stable than drug alone – and follows an identical pattern

Complex	TOTAL ENERGY
Raltegravir	-2515.25
Dolutegravir	-2449.71
Elvitegravir	-2817.07
Bictegravir	-2587.03
L-870810	-2727.59
MK-2048	-2883.55

Basis Set: **6-31g(d)**

Complex	TOTAL ENERGY
MK-2048	-2883.55
Elvitegravir	-2817.07
L-870810	-2727.59
Bictegravir	-2587.03
Raltegravir	-2515.25
Dolutegravir	-2449.71

Conclusion – *Ab initio* Quantum Chemistry Methods Rapidly Accelerate Drug Design

- A significant amount of research has been conducted to develop new antiretroviral drugs to combat resistant HIV-1 subtypes
- Currently available INSTIs include: Raltegravir, Elvitegravir, Dolutegravir – and newer generation molecules – Bictegravir & Cabotegravir
- MK-2048 is still in the pre-clinical stage at Merck
- While basic energy results have limited scope, this project has endeavored to demonstrate the vast potential of computational chemistry – that is successfully being utilized in groundbreaking research

GAMESS