

Drug Design Teaching

Answers to questions of Session6 (Bioisostere)

🔊 Display all lines by setting “**All**” in the number of **entries to show** on the upper left corner of the result table. Let’s try to answer the following questions:

- *Overall, how many times this specific replacement was found in the literature?*

64 occurrences.

- *Generally speaking, what is the trend: increasing or decreasing the biological activity?*

Decreasing on average, but with most cases of equally potent molecules in vitro (colored in orange, in the delta Bioactivity column and in the pie charts).

- *In what biological context this replacement was mainly tried?*

Mainly in kinases (49 occurrences), then GPCR and finally unclassified enzyme.

- *How many times this replacement was found for compounds tested on our target of interest (erbB1)?*

27 occurrences.

- *What is the trend for activity on this specific protein?*

Increase of in vitro potency, on average. But with most cases of equally potent molecules

- *Can you find the entry corresponding to our case (CHEMBL2087361 to CHEMBL2087355)? Expand the corresponding entries to see the molecules.*

- *Which molecules is the most potent on erbB1 between CHEMBL2087361 and CHEMBL2087355? Note that the activity is given as pIC50.*

The bromo compounds (CHEMBL2087355) is slightly less potent than the ethynyl compound (CHEMBL2087361). This appears in two occurrences.

- *Any idea why is the entry seems duplicated? Click on the PubMed link to get more info from the abstract.*

These data come from the same article (PubMed ID: [22959248](#)) in which they tested this series of molecules on EGFR in two different assays (an in vitro EGFR kinase assay, as well as a EGFR-mediated intracellular tyrosine phosphorylation assay). Both assays qualify for being included in SwissBioisostere.

🔊 With that results let's try to answer the following questions:

- *Can you find the replacement that we studied in details in the previous section (CHEMBL2087361 to CHEMBL2087355)?*

Yes. *m*-bromophenyl fragment is ranked #2 by frequency (64 occurrences).

- *Propose two other sensible replacements for *m*-ethynylbenzene in our biological/chemical contexts and explain how you went to that.*

Choose what fits your needs! A criterion could be simply frequency, or general increase of activity, or increase of activity in a given chemical or biological context. You may also want to tune parameters like log P, size or TPSA to improve say bioavailability or other properties.