Drug Design Teaching

Answers to questions of Session6 (Bioisostere)

After a few seconds is displayed in a new tab the SwissBiosisostere output page compiling all examples found in the literature about the replacement of *m*-ethynylbenzene fragment by *m*-bromobenzene.

- 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?*
    Most cases of similarly 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?*
    5 target classes, mainly in kinases (49 occurrences), then GPCR (7 occurrences), epigenetic modulator eraser (5 occurences) and finally one ion channel and two unclassified enzymes.
  - *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?*
    Most cases of similarly potent molecules in vitro

    Can you find the entry corresponding to our case (CHEMBL2087361 to CHEMBL2087355)? 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 two different CHEMBL IDs, which are links to the details of the assays in ChEMBL).

After a few seconds the SwissBiosisostere output page listing all possible replacements of *m*-ethynylbenzene found in the literature is displayed in a new tab.

- 📣 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*, MW or TPSA to improve say bioavailability or other properties.