Chemical Tools to Enable Drug Discovery: The Development of I-BRD9

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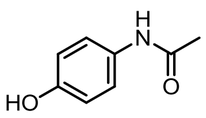
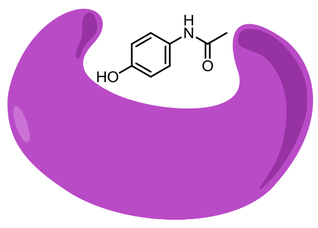
Biologically active molecules interact with proteins

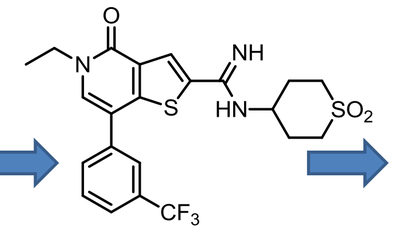


Paracetamol



Paracetamol interacts with the COX2 protein

pain relief



I-BRD9

I-BRD9 interacts with the BRD9 protein

?

Chemical probes used to investigate protein biology

- Chemical probes are small molecules, which inhibit selected proteins.
- Prevent the protein participating in it's usual biological role.
- Help to determine whether or not a protein is worthwhile target for drug discovery.

Strong interaction with target protein → Excellent selectivity for target protein → Biological activity

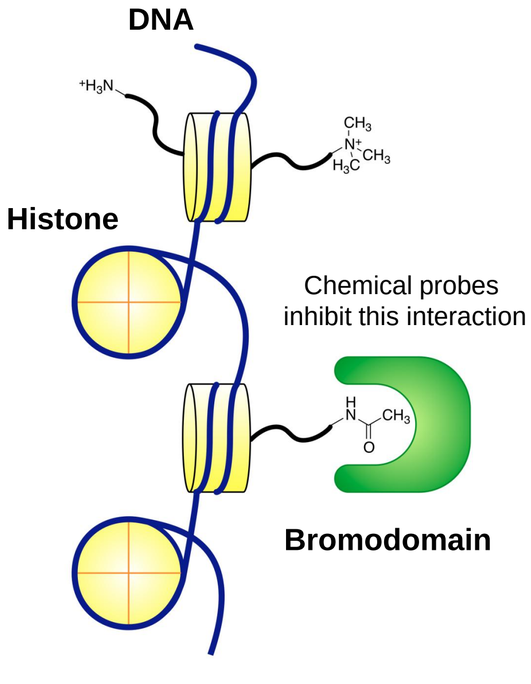
Epigenetic proteins are targets for drug discovery

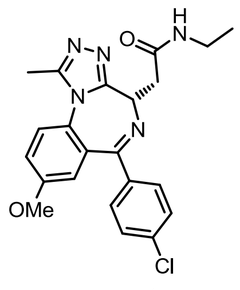
- **Genetically identical**
- **Epigenetically different**

- Epigenetics controls which genes are expressed.
- Epigenetic drugs have been approved for the treatment of cancer.

Bromodomain proteins have been implicated in disease

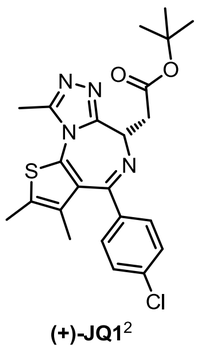
- Bromodomains are epigenetic proteins, which regulate gene expression.



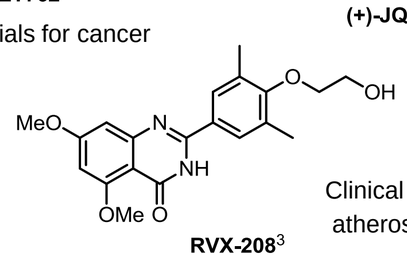


I-BET762[1]

Clinical trials for cancer

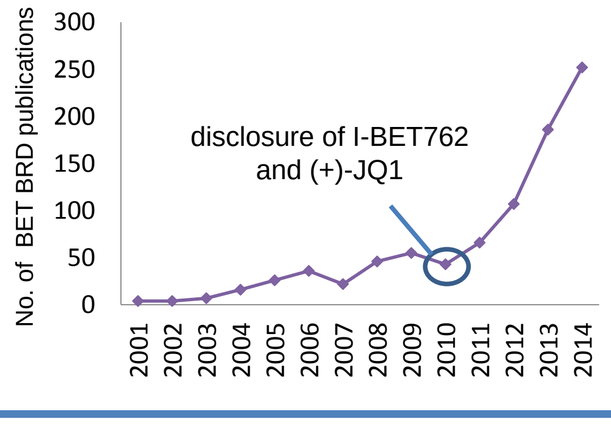


(+)-JQ1[2]



RVX-208[3]

Clinical trials for atherosclerosis



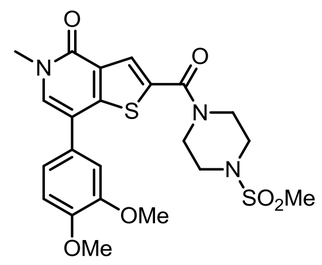
- Bromodomains have been implicated in various disease pathways.
- Chemical probes for the BET family of bromodomains show profound anti-cancer and anti-inflammatory properties.

I-BRD9 is the first chemical probe for BRD9

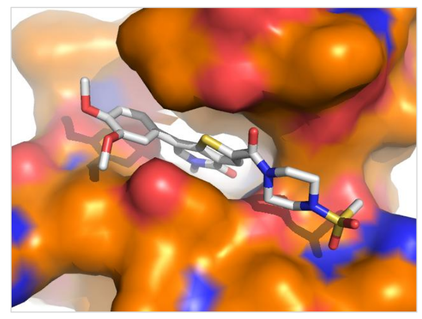
- BRD9 is a bromodomain for which the biological role is currently unknown.
- In order to investigate the therapeutic potential of BRD9, a chemical probe has been developed.

start point

✓ Good activity
✘ Poor selectivity



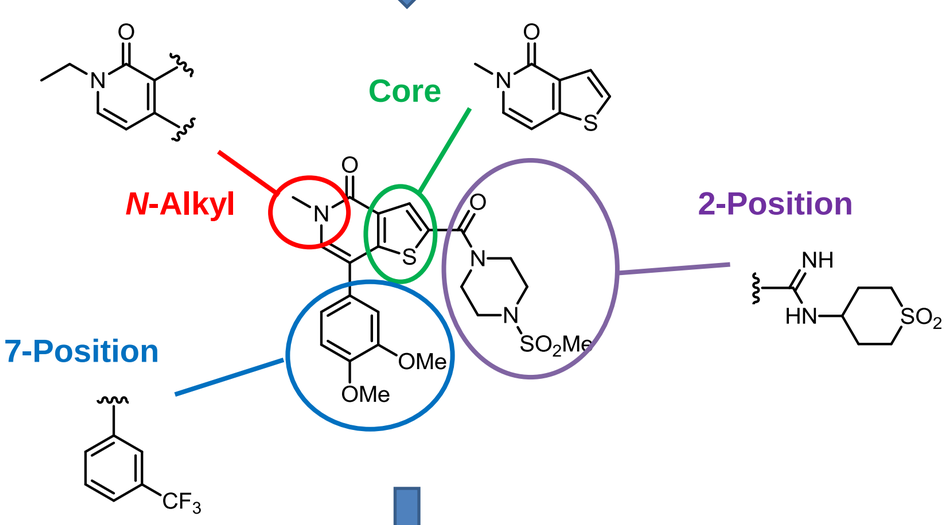
Compound 1



Compound 1 interacts with BRD9

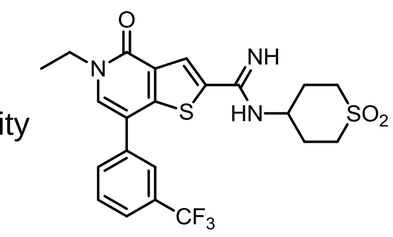
~400 compounds made

optimisation using medicinal chemistry

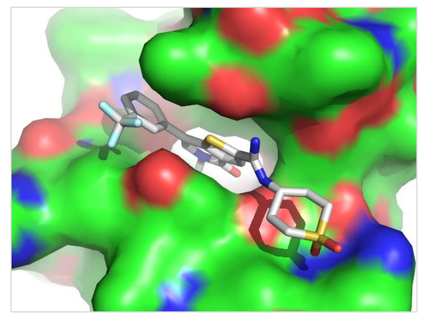


optimisation using medicinal chemistry

✓ Excellent activity
✓ Excellent selectivity
✓ Biological activity



I-BRD9

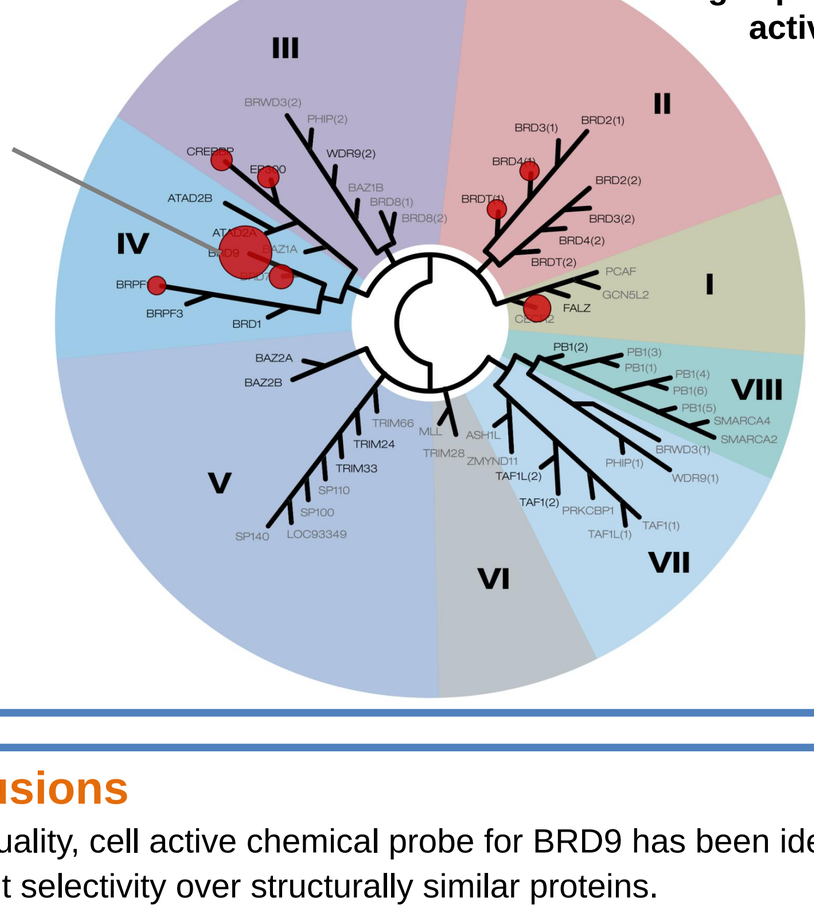


I-BRD9 interacts with BRD9

- I-BRD9 is the first potent, cell active and highly selective chemical probe for BRD9.
- 70 times more active in BRD9 than any other bromodomain tested.
- I-BRD9 will allow the biological role of the BRD9 bromodomain to be investigated for the first time.

large spot = high activity

BRD9 activity



Conclusions

- A high quality, cell active chemical probe for BRD9 has been identified.
- Excellent selectivity over structurally similar proteins.
- The biological role of BRD9 can be investigated for the first time.
- Discovery of I-BRD9 submitted for publication.

1. *Nature* **2010**, *468*, 1119–1123; 2; *Nature* **2010**, *468*, 1067–1073; 3. *PLoS. One.* **2013,** *8,* (12) e83190.