Structural analysis of C-terminal bromodomain from the human BRD2 in complex with bromo and extra terminal domain (BET) inhibitor

Swetha V. Marothu and Ravikiran S. Yedidi*

The Center for Advanced-Applied Biological Sciences & Entrepreneurship (TCABS-E), Visakhapatnam, Andhra Pradesh, India. 530002.

*Correspondence to RSY: tcabse.india@gmail.com

INTRODUCTION

Bromodomain-containing protein 2 (BRD2) is a protien that in humans is encoded by the *BRD2* gene. BRD2 is part of the Bromodomain and Extra-Terminal motif (BET) protein family that also contains BRD3, BRD4, and BRDT in mammals. This protien associates with transcription complexes and with acetylated chromatin during mitosis, and it selectively binds to the acetylated lysine-12 residue of the histone H4 via its two bromodomains. BRD2 have a major role in inducing cancer due to its ability to bind with the acetylated lysine regions of DNA and induce transcription more often then reqired. Single bromodomain is present in many histone acetyltransferase(HATs) and chromatin remodeling enzymes that regulates transcription and mediate association of these protein with acetylated nucleosoomes. BRD2 may also play role in spermatogenesis or folliculogenesis BRD2 may have functional overlap with close homolg BRD3, BRD2 function can be blocked by Bromo and Extra Terminal Domain(BET) Inhibitors.

The therapuetic potential of a BET inhibitors are binding equipotently to their eight bromodomain family, has now been extensively reported in oncology and immunoinflammation. These iBET are now playing key role in clinical oncology, cancer treatment and brain tumors illustrating tremendous potential of this epigenetic reader family as a therapeutic targets. the BD1 and BD2- baised inhibitors binding to either the four BD1 or the four BD2 domain of the BET protiens have been published as the structures are shown in Figure 2 with the acetylated lysine mimetics highlighted in blue.

There has been lots of studies detailing different results regaring chromatin binding the BD1 and BD2 domains. The multivalent interaction between the BET family and chromatin or other binding partners is complex and context-dependent and remains poorly understood. It is difficult to predict what different efficacy or inhibitors. In future we can hope that there will be highly selective BD1 and BD2 domain selective BET inhibitors will enable advances in our biological understanding.

EXPERIMENTALS

The following filters have been used:refinement name of source organism(Homo sapiens), experimental method(X-Ray diffraction), refinement resolution(1.5-0.2), release date(2020-2024) PDB ID is 6ZB0 and title is C-terminal Bromodomain of human BRD2 with 1-benzyl-N-methyl-1,2-dihydropyridine-3-carboxamid e(Figure 1).

We have conducted two tests to determine the quality of the protien: (1) We calculated whether the R-Work value is close enough to the 1/10th value of its resolution or not, (2) We calculated the difference between the R-Work Vlalue and the R-Free Value.

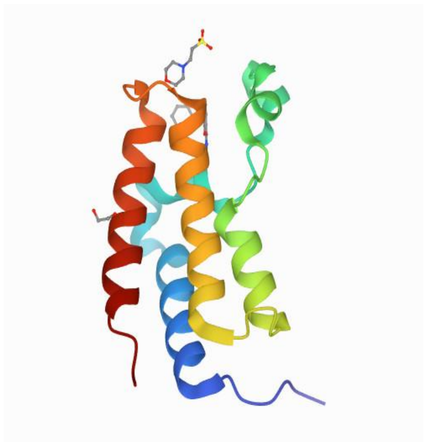

Figure-1.6ZB0 C-Terminal Bromodomain of human BRD2 with 1-benzyl-N-methyl-,1,2-dihydropyridine-3-carboxamide

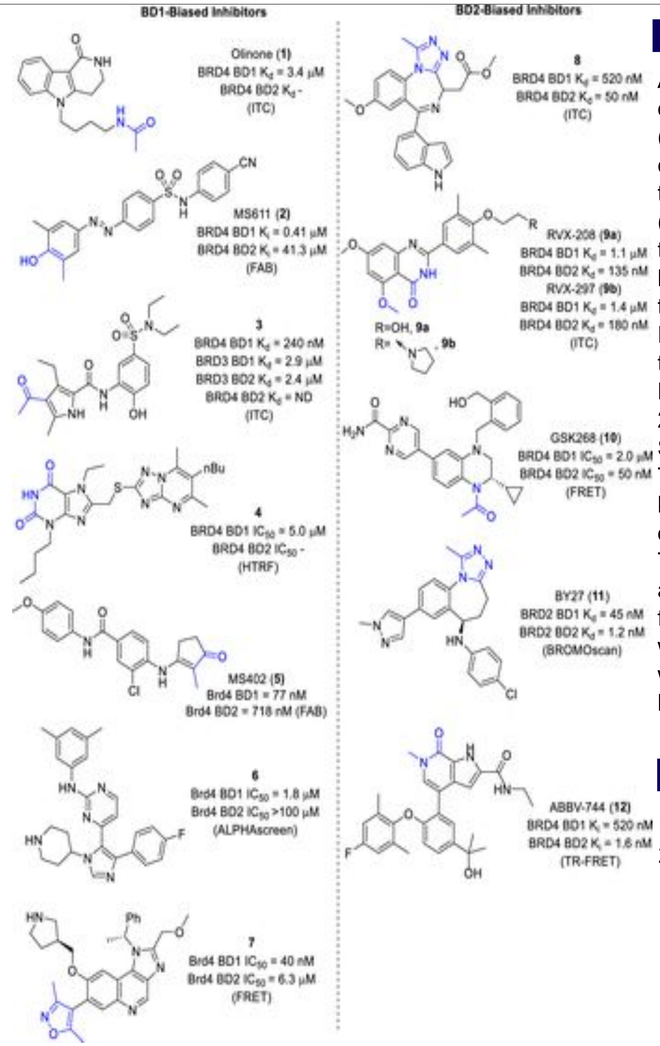

Figure-2. Published domain selective BET bromodomain inhibitors and their literature potencies/affinities to the BD1 and BD2 bromodomain of BRD4 with the acetylated lysine mimetic colored blue

RESULTS & DISCUSSION

As we have conducted the tests for determination of quality of protein:

(1) 0.161Å is the result for this test, from which we can conclude that the R-Work Value is almost equal tp the 1/10th value of its Resolution Value.

(2) 0.0387 is the result that we have obtained from this test, from wihch it is clear that the differance between the R-Work Vlalue and R-Free Value is less than 5%.

From the above two test results we can conclude that the protein is of good quality.

Macromolecule is Bromodomain-conataing protien 2(BRD2) and chain AAA with sequence length 115. Smalll molecules are QCW, MES, EDO.

The protien has six alpha helix stuctures with zero beta sheets and this protien has pretty good strength of hydrogen bonds with individual small molecules. The smalll molcule QCW forms 3H bonds one with arginine and remianing two with water molecule, MES forms 6H bonds where all hydogen bonds are formed with water molecules and EDO forms 6H bonds in which 3H bonds formed with aspartic acid and 3H bonds with watermlecule

REFERENCES

1. RCSB PDB, 6ZB0, Chung C, 2020-08-05.
2. Jonathan T. Seal *et al,* the Optimization of a Novel, Weak Bromo and Extra Terminal Domain (BET) Bromodomain Fragment Ligand to a Potent and Selective Second Bromodomain (BD2) Inhibitor, J. Med. Chem. 2020, 63, 17, 9093–9126, Publication Date:July 23, 2020

e-poster presented online at the ABFR-2020.