Bromodomains are a class of epigenetic proteins that play a role in the regulation of heritable phenotypes that are DNA independent. The bromodomain structural motif is implicated in many types of cancer. Consequently, isoform selective inhibitors for use as chemical probes are needed for elucidating the biological mechanisms of individual bromodomains and developing therapeutics. Screening compounds which are low in complexity and molecular weight, i.e. fragments, is a validated technique for identifying scaffolds with an affinity for proteins of interest. Conventional fragment libraries are comprised of flat, two-dimensional (2D) compounds. 2D-fragment screens often result in many promiscuous hits that are not isoform selective. Drug-like compounds have more 3D-character in the form of sp³ carbons, stereocenters and fewer aromatic rings. However, fragment libraries enriched with 3D-scaffolds are underexplored. The primary goal of this research is the development of isoform selective small molecule chemical probes for bromodomains while assessing the utility of 3D-enriched fragments. The effectiveness of 3D-fragments is evaluated on 4 different factors: hit rate, potency, isoform selectivity and binding pocket filling ability. A library of 500 3D-enriched fragments from Life Chemicals was screened using ¹H CPMG NMR against BRD4(BD1). A similar screen using a library highly enriched for 2D-fragments was done against the same protein previously. A full characterization and comparison of the highly 2D-enriched and 3D-enriched total library and hits was done. Protein observed fluorine (PrOF) NMR is used as an orthogonal assay to verify hits, determine hit selective, and ascertain dissociation constants. Docking studies and crystallography will be used to assess the pocket filling ability of select hit fragments. Through this case study we expect to inform the bromodomain and fragment community about the usefulness of 3D-enriched fragment screening to target bromodomains.