

## Bromodomain inhibitors and cancer therapy: From structures to applications

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### ABSTRACT

Aberrations in the epigenetic landscape are a hallmark of cancer. Alterations in enzymes that are “writers,” “erasers,” or “readers” of histone modification marks are common. Bromodomains are “readers” that bind acetylated lysines in histone tails. Their most important function is the regulation of gene transcription by the recruitment of different molecular partners. Moreover, proteins containing bromodomains are also epigenetic regulators, although little is known about the specific function of these domains. In recent years, there has been increasing interest in developing small molecules that can target specific bromodomains. First, this has helped clarify biological functions of bromodomain-containing proteins. Secondly, it opens a new front for combatting cancer. In this review we will describe the structures and mechanisms associated with Bromodomain and Extra-Terminal motif (BET) inhibitors and non-BET inhibitors, their current status of development, and their promising role as anti-cancer agents.

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### Introduction

The different cells of an organism contain the same DNA sequence but they are able to differentiate and maintain different phenotypes that express different biological functions. These processes are possible due to epigenetics. The term “epigenetics” was coined by C.H. Waddington in 1939<sup>1</sup> and later defined as heritable changes in gene expression that are not due to any alteration in the DNA sequence.<sup>2</sup> Aberrancies in epigenetic regulation are frequent in cancer, the best known epigenetic mark being DNA methylation. In general terms, cancer cells undergo global hypomethylation of their DNA, and localized hypermethylation of some gene promoters, specifically in tumor-suppressor genes.<sup>3</sup>

Apart from changes in DNA methylation, covalent modification of histones is an important mechanism in the epigenetic landscape. Histones can undergo several types of modification, the most common being phosphorylation, acetylation, methylation, ubiquitination, and sumoylation.<sup>4</sup> Disruption of normal histone modification patterns is common in cancer, as are mutation and deregulation of the enzymes responsible for adding, removing, or recognizing these histone marks.<sup>5</sup>

Lysine acetylation is one of the main modifications occurring in histone tails and it has been widely studied in the context of the histone code. Acetylation of chromatin has generally been associated with its open state and transcriptional activation, although more recent studies have found some acetylation marks to be responsible for the compaction of chromatin,<sup>6</sup> protein stability,<sup>4</sup> and the regulation of protein-protein interactions.

$\epsilon$ -N-acetylation of lysine residues on the amino-terminal tails of histones is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). The former act as “writers,” adding acetyl groups, the latter are “erasers,” which remove these acetyl marks. These enzymes are often aberrantly expressed in cancer, suffering mutations and being subjected to other deregulation mechanisms. For example, in the HAT group, we can find inactivating mutations in *CBP* (*KAT3A*) and *p300* (*KAT3B*) of B cell lymphomas,<sup>7</sup> monoallelic loss of *KAT5* in human lymphomas, breast and head and neck cancers,<sup>8</sup> and homozygous deletion of *KAT6B* in small cell lung cancer.<sup>9</sup> Additionally, HDAC deregulation results in the silencing of tumor-suppressor genes or overexpression of oncogenes. For example, HDAC1, HDAC3 and HDAC6 are overexpressed in tumors.<sup>10</sup> These studies have provided the basis for the development of HAT<sup>11</sup> and HDAC inhibitors, some of which had already proved successful in clinical oncology.<sup>10</sup> However, they have two common weaknesses: a lack of efficacy and a lack of specificity.

Bromodomains (BRDs) are “readers” of acetyl marks in histone tails, targeting chromatin-modifying enzymes and other protein machinery to specific sites in the chromatin, thus regulating gene transcription. They appear to be a potential druggable epigenetic target, which has encouraged the discovery and development of several small-molecule inhibitors in recent years.

In this review we will summarize the bromodomain inhibitors discovered so far, focusing on their molecular mechanisms in cancer and their developmental status. For convenience, we will classify them as BET and non-BET inhibitors.

## Bromodomains

Bromodomains are a family of evolutionarily conserved motifs identified for the first time in the early 1990s in the *brahma* gene of *Drosophila melanogaster*.<sup>12</sup> BRDs bind the acetylated lysines in histone tails, the recognition of the acetyl group being decisive for the recruitment of other chromatin factors and transcriptional machinery, and thereby the regulation of gene transcription (Fig. 1).

A total of 61 bromodomains were found in 46 different proteins of the human proteome.<sup>13</sup> They are classified into eight subfamilies on the basis of their structure (Fig. 2). They share a highly conserved structure consisting of a left-handed bundle of four  $\alpha$ -helices ( $\alpha$ Z,  $\alpha$ A,  $\alpha$ B,  $\alpha$ C), linked by flexible loop regions known as ZA and BC loops, which are variable in sequence and charge and which form the acetyl binding site. Despite the variations in the loop regions of the various bromodomains, the amino acid residues responsible for the recognition of the acetyl lysine are highly conserved, asparagine (Asn) and tyrosine (Tyr) residues being present where a specific hydrogen bond and water-mediated interactions, respectively, occur with the acetyl group.<sup>14</sup> The cooperative binding of two acetyl groups by a single bromodomain has also been reported in BRD3, BRD4<sup>13</sup> and BRDT.<sup>15</sup> Some structural studies<sup>16</sup> suggest the possibility of binding di-acetylated peptides by two bromodomains in tandem, such as in the transcription-initiation factors TAF1 and TAF1L, in which two bromodomains are separated by sequences of fewer than 20 residues.<sup>13</sup>

The hydrophobic nature of the acetylated lysine-binding pocket of the bromodomain, which is optimal for the interaction of the charge-neutralized acetylated lysine, and the fact that the strength of this protein-protein interaction is comparatively low, make these domains particularly targetable by small molecules that interfere with this interaction.<sup>17</sup> In recent years, numerous discoveries about the potential of new bromodomain inhibitors have been published.

## BET bromodomains

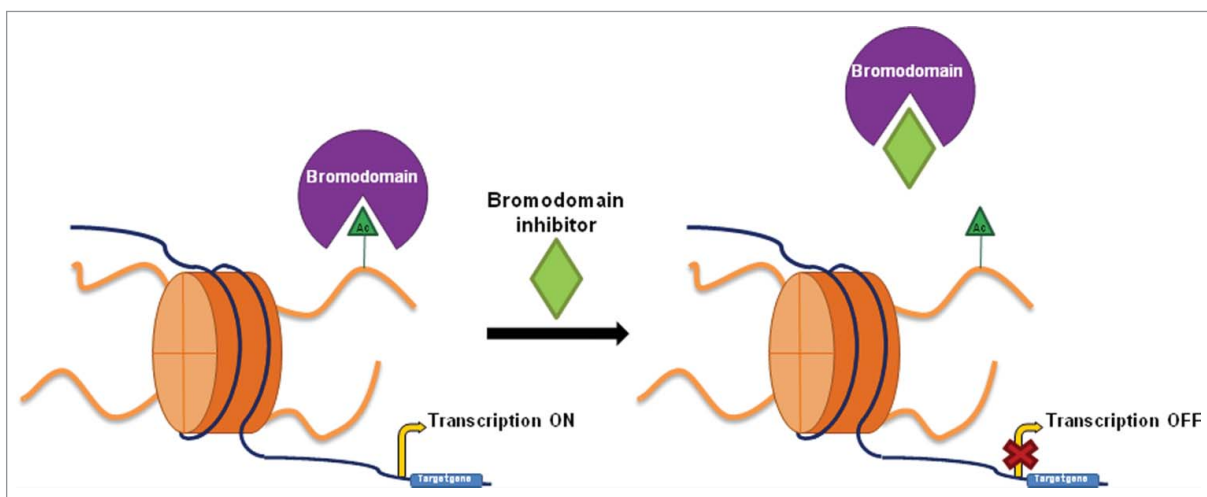
The bromodomain and extra terminal (BET) family has been thoroughly investigated. It is made up of BRD2, BRD3, BRD4, and BRDT, all of which are ubiquitously expressed, except for BRDT, which is only expressed in testis. Their main features are two bromodomains in tandem (BD1 and BD2) in the N-terminal and a C-terminal extra-terminal (ET) domain.

BRD4 and BRD2 play an important role in transcription elongation by recruiting the positive transcription elongation factor complex (P-TEFb) through its BRDs to acetylated chromatin.<sup>18</sup> P-TEFb is composed of cyclin-dependent kinase-9 (CDK9) and its activator, cyclin T. Efficient transcription requires the phosphorylation of the C-terminal repeat domain (CTD) of RNA polymerase II (RNAP II). It has been reported that BRD4 recruits P-TEFb to acetylated chromatin and plays a role in activating the CDK9 kinase subunit, whereby it acts as an important transcription regulator. In addition, BRD4 controls the release of active P-TEFb from its inactive complex with HEXIM1 protein and 7S snRNA. Recruitment of P-TEFb by BRD4 is crucial for transcriptional initiation and elongation, and for the expression of genes controlling cell proliferation.<sup>18</sup>

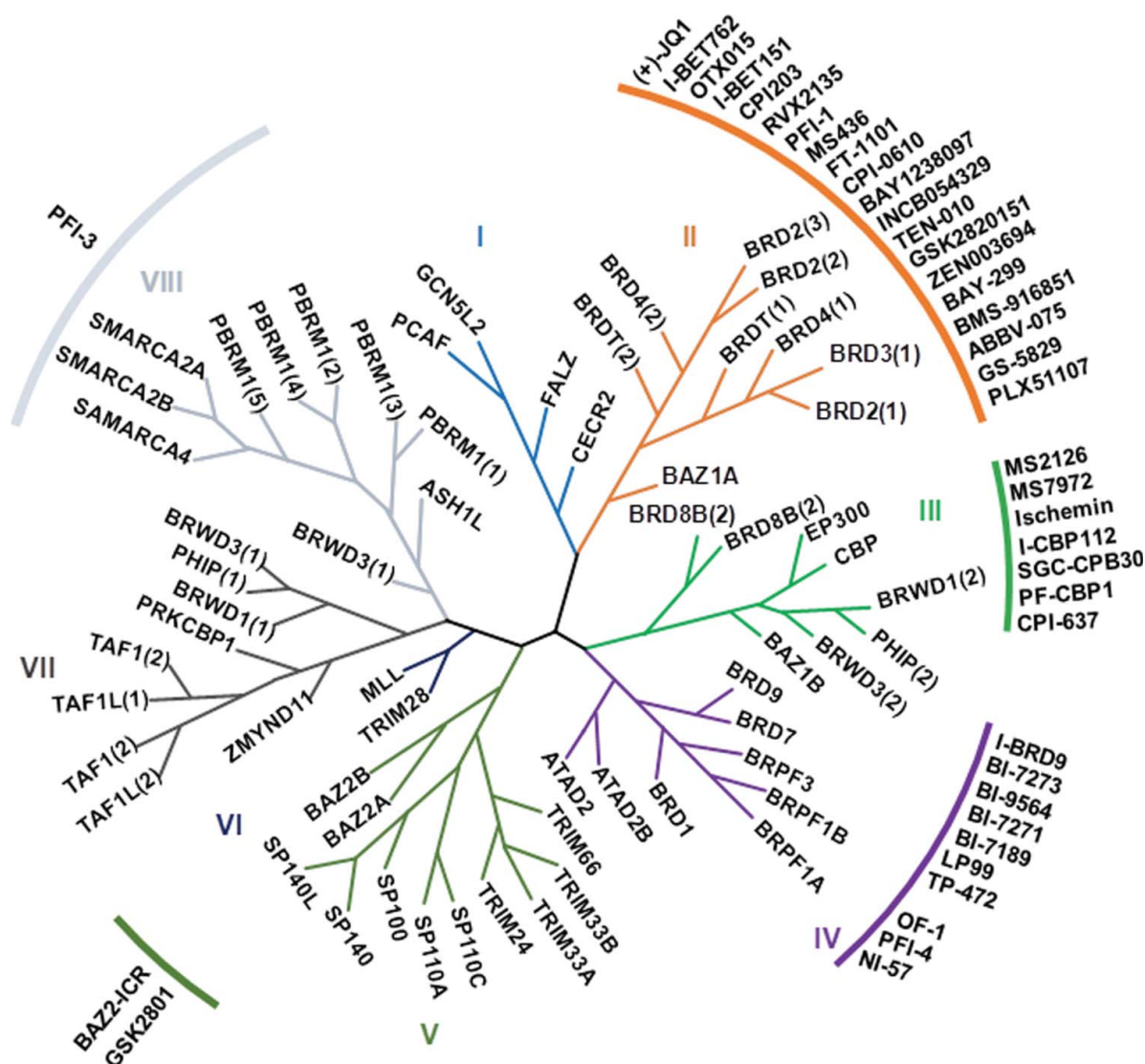
BET proteins are highly involved in cancer, directly regulating the expression of certain cancer-related genes, such as *c-MYC*. Avoiding the binding of BET proteins at the *MYC* locus with BET inhibitors leads to a reduction in cell proliferation.<sup>19</sup>

BRD4 regulates *NF- $\kappa$ B*-dependent genes, preventing degradation of Rel A, which maintains *NF- $\kappa$ B* activity, and so plays an important role in *NF- $\kappa$ B*-driven cancers.<sup>20</sup> In breast cancer, BRD3/4 interacts with WHSC1, promoting *ESR1* transcription and thereby contributing to tamoxifen resistance in ER-positive breast cancer.<sup>21</sup>

The BET family also functions as cell cycle regulators. BRD4 is important in regulating the expression of genes required for M to early G1 phase transition,<sup>18,22</sup> while BRD2 provides a scaffold on the chromatin for recruiting the key transcriptional cell cycle-regulatory genes *E2F1* and *E2F2*. BRD2 can also interact



**Figure 1.** Overview of bromodomain inhibition. Bromodomains recognize acetylation marks in histone tails and recruit transcriptional machinery promoting target gene transcription, such as in the case of *c-MYC*. Bromodomain inhibitors prevent interaction between the bromodomain and the acetyl group, causing the downregulation of certain genes. Bromodomains play a key role in gene transcription regulation.



**Figure 2.** Structure-based phylogeny of the human bromodomains and their inhibitors. There are 61 bromodomains in 46 bromodomain-containing proteins. Roman numerals indicate the eight major structural classes. The phylogenetic tree is derived from data obtained Filipakouopoulos et al. (ref 17). The specific inhibitors described in this review are indicated next to the corresponding bromodomain.

with the SWI/SNF complex, regulating the expression of genes such as cyclin D1 (*CCND1*).

BRD4 is a global regulator of gene transcription, so its inhibition would be expected to cause the global downregulation of gene activity. However, BRD4 inhibition only downregulates few hundred genes, most of which are very important in tumorigenesis. The molecular basis of this selectivity can be explained by the fact that BRD4, in addition to occupying gene promoters, has a strong preference for enhancers and super-enhancers, the latter frequently being present in key genes of hematological and solid tumors, such as *MYC*.<sup>23</sup>

### Other bromodomains

As well as BET bromodomains, BRDs are present in other proteins that play important roles in the epigenetic landscape and in cancer development.

Histone methyltransferase *ASH1L* and the mixed-lineage leukemia (*MLL*) gene product contain one BRD. Both are

associated with actively transcribed genes.<sup>24</sup> The BRPF (bromodomain and PHD finger-containing) family consist of BRPF1, BRPF2 and BRPF3, which function as scaffolds for assembling HAT complexes of the MOZ/MORF family. Bromodomains are also present in transcriptional coactivators like tripartite motif-containing proteins (TRIMs) and TBP-associated factors (TAFs).<sup>17</sup>

ATPase family, AAA domain containing 2 (*ATAD2*) contains an ATPase region and a bromodomain located in the C-terminal. *ATAD2* is overexpressed in a wide variety of cancers, such as colorectal,<sup>25</sup> gastric,<sup>26</sup> endometrial,<sup>27</sup> cervical,<sup>28</sup> and ovarian<sup>29</sup> cancers, in which it increases cell proliferation. Its overexpression is already used as a poor prognosis marker. *ATAD2* is an E2F target regulated by the pRb-E2F pathway, and is important for access to the S phase of the cell cycle. *ATAD2* is localized in the same chromosome arm as *MYC*, and is co-amplified with it in several tumors. In fact, it contributes to tumor development by binding the *MYC* oncogene and stimulating its transcriptional activity.<sup>30</sup> *ATAD2* is also associated

with other oncogenic transcription factors, like the androgen receptor (AR)<sup>31</sup> and estrogen receptors (ER).<sup>32</sup> ATAD2 expression is itself stimulated by androgens and estrogens and simultaneously works as a coactivator of AR and ER, contributing to carcinogenesis in prostate and breast cancers.<sup>31,32</sup> Little is known about the specific function of the ATAD2 bromodomain, but its importance in cancer development means there is increasing interest in finding bromodomain inhibitors for it. This can help elucidate its function and establish it as a novel target for anti-cancer drug development.

BAZ2A and BAZ2B are members of the BAZ protein family. They contain a PHD finger located near a homologous bromodomain in the C-terminal part of the protein.<sup>33</sup> BAZ2A (also known as TIP5) is a component of the NoRC nuclear remodeling complex, which is essential for rRNA silencing.<sup>34</sup> Additionally, BAZ2A is overexpressed in prostate cancer and is important for maintaining cell growth. BAZ2A directly interacts with EZH2 to epigenetically silence genes repressed in metastasis, playing a different role that is independent of rRNA.<sup>35</sup> Very little is known about the function of BAZ2B, apart from the recently published histone binding preferences of its bromodomain.<sup>36</sup>

Several HATs also contain bromodomains that are simultaneously “writers” and “readers” of acetyl groups. The p300/CBP-associated factor PCAF (also known as KAT2B) acetylates histones H3 and H4,<sup>37</sup> regulating the expression of several genes, like insulin, and several transcription factors, including p53,<sup>38</sup> FOX1,<sup>39</sup> and p27,<sup>40</sup> that alter various important molecular pathways in cancers such as glioblastoma and medulloblastoma.<sup>41</sup> However, little is known about the specific function of the PCAF bromodomain. There is heightened interest in finding specific inhibitors against it, because it will probably cause the loss of PCAF acetylation function. In fact, PCAF bromodomain inhibitors have already been developed for the treatment of HIV. They work by preventing the interaction between the PCAF bromodomain and acetylated HIV Tat protein<sup>42</sup> which is a potent inhibitor of HIV replication.<sup>43</sup> In the context of cancer, several molecules targeting PCAF bromodomain are being developed,<sup>43,44</sup> but they have not been clinically tested yet.

CREBBP (also known as CBP and KAT3A), the cAMP response binding protein, and its highly homologous EP300 (also known as p300 or KAT3B), adenoviral E1 binding protein, are two HATs that, in addition to the HAT domain, contain a CREB binding domain, several zinc finger domains, a plant homology domain (PHD) and a bromodomain. These bromodomains bind the acetylated lysine 382 of p53. This interaction is required for p53 recruitment of CREBBP after DNA damage, a step which is crucial for p53 transcriptional activation of p21 in cell cycle arrest.<sup>45</sup> CPB/p300 is a transcriptional coactivator that binds to several transcription factors and acetylates specific sites in chromatin (reviewed by Dancy et al.<sup>46</sup>), causing its relaxation and subsequent transcriptional activation.<sup>47</sup> These proteins also acetylate some transcription factors, modulating their activity. Besides that, CBP and EP300 play a key role in the development of many human cancers (reviewed by Iyer et al.<sup>48</sup>). Acetyltransferase activity is critical for the function of CBP/EP300, so some inhibitors are known to disrupt their catalytic domain.<sup>49</sup> There is now great interest in the development of specific bromodomain inhibitors for CBP/EP300.

Bromodomain-containing protein 9 (BRD9) is a known component of the chromatin-remodeling BAF SNF/SWI complex. Little is known about its function but a role in cancer has been described. A recent study reported that AML cells require BRD9 to sustain *MYC* transcription and thereby increase proliferation.<sup>50</sup> Bromodomain-containing protein 7 (BRD7) is very similar to BRD9 and is a subunit of PBAF SWI/SNF. Several studies have described *BRD7* as a tumor suppressor gene,<sup>51</sup> whose expression is partially or completely suppressed in several types of cancer, such as colorectal cancer,<sup>52</sup> ovarian cancer,<sup>53</sup> hepatocellular carcinoma,<sup>54</sup> small-cell lung cancer,<sup>55</sup> endometrial carcinoma,<sup>56</sup> and breast cancer, in which it acts as a partner of *BRCA1*.<sup>57</sup> Due to the close homology between the BRD9 and BRD7 bromodomains, co-inhibitors exist.

## Bromodomain inhibitors

### BET inhibitors

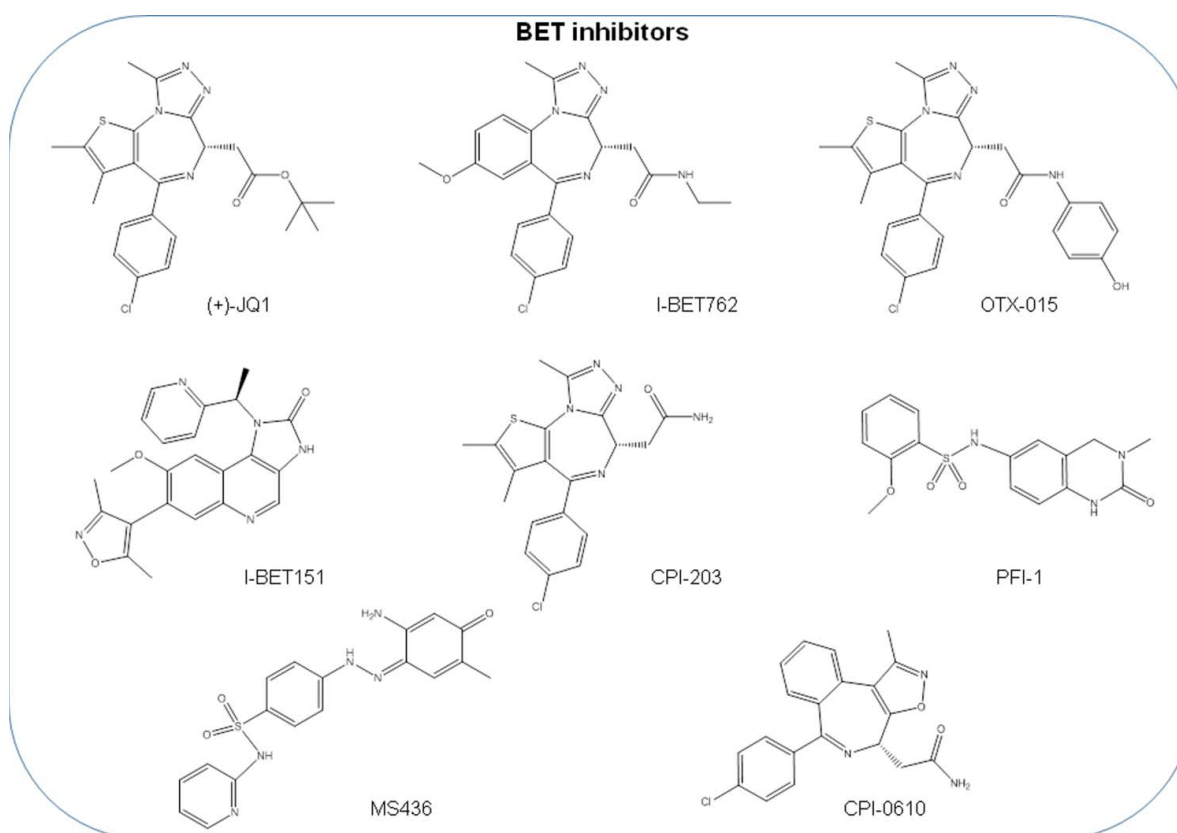
The first known inhibitors of the BET bromodomain family were (+)-JQ1, reported by the Structural Genomics Consortium (SGC) and the Dana-Faber Cancer Institute,<sup>58</sup> and I-BET762, reported by GlaxoSmithKline (GSK).<sup>59,60</sup>

When thieno-triazolo-1,4-diazepine (JQ1) (Fig. 3) was first reported, it was tested in NUT midline carcinoma (NMC).<sup>58</sup> BRD4 forms a fusion protein with nuclear protein in testis (NUT) protein, BRD4-NUT oncoprotein, which plays a key role in the differentiation and proliferation of this aggressive squamous cell carcinoma.<sup>61</sup> JQ1 binds competitively to acetyl-lysine binding motifs and displaces the BRD4 fusion oncoprotein from chromatin, producing squamous differentiation and specific anti-proliferative effects in xenograft models and cell lines of NMC.<sup>58</sup>

After the first report, a large number of studies were published showing the efficacy of JQ1 in hematological malignancies<sup>62-66</sup> and in a variety of solid tumors such as glioblastoma,<sup>67,68</sup> medulloblastoma,<sup>69-71</sup> hepatocellular carcinoma,<sup>72,73</sup> colon cancer,<sup>74,75</sup> pancreatic cancer,<sup>76-78</sup> prostate cancer,<sup>79-82</sup> lung cancer,<sup>83-87</sup> and breast cancer.<sup>21,88-94</sup>

The *MYC* oncoprotein regulates transcription and alters cell proliferation in acute myeloid leukemia,<sup>62</sup> Burkitt's lymphoma,<sup>63</sup> multiple myeloma,<sup>64</sup> and B cell acute lymphoblastic leukemia,<sup>65</sup> diffuse large B cell lymphoma.<sup>66</sup> In these hematological cancers, BET inhibition by JQ1 downregulates *MYC* transcription and genome-wide *MYC*-dependent target genes, promoting cell cycle arrest and cellular senescence. Even though *MYC* downregulation is the most common and important effect of BET bromodomain inhibition in hematological malignancies, other genes and mechanisms are also affected. For example, in acute lymphoblastic leukemia, JQ1 causes a significant deletion of interleukin 7 receptor gene (*IL7R*),<sup>65</sup> and in diffuse large B cell lymphoma it leads to the significant downregulation of *MYC* and *E2F1* target genes<sup>66</sup> and an alteration of others such as *POU2AF1* (which encodes the OCA-B transcriptional coactivator protein), *BCL6*, *IRF8*, and *PAX5*.<sup>66</sup>

In the case of solid tumors, the treatment of a panel of a group of genetically heterogeneous glioblastoma (GBM) samples with JQ1-induced G1 cell cycle arrest and apoptosis and produces expression changes in key genes such as *c-MYC*, *p21*, *hTERT*, *BCL-2*, and *BCL-XL*.<sup>67</sup> Moreover, the common mutation,



**Figure 3.** BET bromodomain inhibitor molecules. (+)-JQ1, I-BET762, OTX015, I-BET151, CPI203, PFI-1, MS436, CPI-0610 chemical structures are shown. RVX2135, FT-1101, BAY1238097, INCB054329, TEN-010, GSK2820151, ZEN003694, BAY-299, BMS-986158, ABBV-075, GS-5829, and PLX51107 are BET bromodomain inhibitors that are under clinical trial and whose structure has not been disclosed.

EGFRvIII, of the epidermal growth factor receptor (*EGFR*) sensitizes GBM cells to this drug. EGFRvIII regulates c-MYC levels through SOX9- and FOXG1-mediated regulation of BRD4.<sup>68</sup> In *MYC*-amplified medulloblastoma, JQ1 reduced cell viability and downregulated its expression, causing inhibition of *MYC*-associated transcriptional targets.<sup>69</sup> The treatment also altered the expression of cell cycle genes and p53 signaling.<sup>70</sup> Additionally, JQ1 promoted senescence in medulloblastoma cells by activating cell cycle kinase inhibitors and reducing E2F activity. JQ1 also attenuated stem cell signaling in *MYC*-driven medulloblastoma.<sup>71</sup>

BRD4 is overexpressed in hepatocellular carcinoma (HCC). Treatment with JQ1 induced G1 cell cycle arrest by repressing *MYC* expression and caused the upregulation of *p27* and the pro-apoptotic gene *BIM*.<sup>72</sup> Furthermore, inhibition of BRD4 by JQ1 in liver cancer repressed E2F2 cell cycle regulation, E2F2 overexpression being a marker of poor prognosis in HCC patients.<sup>73</sup>

A recent study in colon cancer stated that BRD4 plays a key role in proliferation, JQ1 having an anti-growth effect, especially in tumors characterized as having the CpG island methylator phenotype (CIMP).<sup>74</sup> This is due to the presence of a CIMP-associated super-enhancer that regulates *MYC* transcription and from which CCAT1, a long noncoding RNA colon cancer-associated transcript 1, is transcribed, which significantly increases sensitivity to JQ1.<sup>74</sup> Another study reported that combination of JQ1 with arsenic sulfide ( $As_4S_4$ ) in gastric and colon cancer cells inhibited BRD4 and c-MYC, synergistically activating p53.<sup>75</sup>

In pancreatic ductal adenocarcinoma (PDAC), JQ1 inhibited tumor progression in patient-derived xenograft models, reducing CDC25B expression, a regulator of cell cycle progression, independently of *MYC*.<sup>76</sup> By contrast, a study in PDAC mouse models<sup>77</sup> found that tumor reduction by JQ1 was due to *MYC* activity inhibition together with inflammatory signals. Additionally, combination of the HDAC inhibitor SAHA and JQ1 produced upregulation of *p57*, a pro-apoptotic gene whose transcription is repressed by *MYC* and usually silenced in PDAC.<sup>77</sup> Resistance to JQ1 has also been studied in pancreatic cancer cells.<sup>78</sup> The main mechanism was the increased expression of JQ1 target genes that remain dependent on *MYC*, which, in turn, was co-regulated by GLI2.<sup>78</sup>

Androgen receptor (AR) is a key element in castration-resistant prostate cancer (CRPC) progression, partly due to its overexpression.<sup>79</sup> Therapies targeting AR signaling have shown limitations creating a need for identifying new therapies. In 2014, Asangani et al. reported JQ1 potential activity in CRPC<sup>80</sup> showing that JQ1 reduces the levels of AR target gene transcription in AR-positive cells, inhibiting BRD4 localization in AR target loci. Prostate tumor xenograft mice treated with JQ1 also showed significant tumor reduction.<sup>80</sup> JQ1 has been broadly studied in an attempt to find a means of overcoming resistance to endocrine-based therapies in prostate cancer (PCa).<sup>81</sup> The expression of androgen receptor variants (AR-Vs) is associated with resistance to AR-targeting endocrine therapies. JQ1 downregulates AR-V transcription and protein expression, inhibiting

Table 1. BET inhibitors

Compound	Tumor type	Status	References/Clinical Trials Identifier
(+)–JQ1	Hematologic Malignancies	Preclinical	62–66
	Lung cancer	Preclinical	83–87
	Breast cancer	Preclinical	21,88–94
	Prostate cancer	Preclinical	79–82
	Pancreatic cancer	Preclinical	76–78
	Colon cancer	Preclinical	74,75
	Hepatocellular cancer	Preclinical	72,73
	Glioblastoma	Preclinical	67,68
	Medulloblastoma	Preclinical	69–71
I-BET762 (GSK525762)	Hematologic Malignancies	Clinical trials	NCT01943851
	NUT Midline Carcinoma	Clinical trials	NCT01587703
	Small cell lung cancer		
	Non-small cell lung cancer		
	Colorectal cancer		
	Neuroblastoma		
	Castration resistant prostate cancer		
	Triple negative breast cancer		
	Estrogen receptor positive (ER positive)breast cancer		
	MYCN driven solid tumor subjects		
	Healthy females subjets in combination with Itraconazole and Rifampicin	Clinical trials	NCT02706535
Multiple myeloma		Preclinical	96
	Prostate cancer	Preclinical	97
OTX015(MK-8628)	NUT Midline Carcinoma	Clinical trials	NCT02698176
	Triple Negative Breast Cancer		
	Non-small Cell Lung Cancer		
	Castration-resistant Prostate Cancer		
	Pancreatic Ductal Adenocarcinoma		
	Acute Myeloid Leukemia	Clinical trials	NCT02698189
	Diffuse Large B-cell Lymphoma		NCT01713582
	Acute Lymphoblastic Leukemia		99
	Multiple Myeloma		
	Acute Myeloid Leukemia (in combination with Azacitidine)	Clinical trials	NCT02303782
Glioblastoma multiforme	Preclinical/Clinical trials	98	
I-BET151 (GSK1210151A)	Mixed lineage leukemia	Preclinical	NCT02296476
	Myeloma	Preclinical	100
	Glioblastoma	Preclinical	96
	Acute myeloid leukemia	Preclinical	102
	Melanoma	Preclinical	103
CPI203	Mutiple myeloma (resistant to bortezomib and melphalan)	Preclinical	104,105
	Pancreatic neuroendocrine tumors (PanNET)	Preclinical	106
	Mantle cell lymphoma (bortezomib resistant)	Preclinical	107
RVX2135	Myc-induced murine lymphoma	Preclinical	108
	Leukemia	Preclinical	109
PFI-1	Compound report	Compound discovery	110
MS436	Compound report	Compound discovery	111
FT-1101	Acute Myeloid Leukemia	Clinical trials	NCT02543879
	Acute Myelogenous Leukemia		112
	Myelodysplastic Syndrome		
CPI-0610	Lymphoma	Clinical trials	NCT01949883
	Multiple Myeloma	Clinical trials	NCT02157636
	Acute Leukemia	Clinical trials	NCT02158858
	Myelodysplastic Syndrome		113
	Myelodysplastic/Myeloproliferative Neoplasm		
BAY1238097	Myelofibrosis		
	Hepatocellular carcinoma	Clinical trials	NCT02369029
	Lung cancer		114
	NUT midline carcinoma		
Melanoma			
	Lymphoma		
INCB054329	Advanced solid tumor	Clinical trials	NCT02431260
	Hematologic malignancies		115
TEN-010	Advances solid malignancies	Cliniacal trials	NCT01987362
GSK2820151	NUT Midline Carcinoma		116
	Solid tumors	Clinical trials	NCT02630251
ZEN003694	Metastatic Castration-Resistant Prostate Cancer	Clinical trials	NCT02705469
	In combination with Enzalutamide		NCT02711956

(Continued on the next page)

Table 1. (Continued)

Compound	Tumor type	Status	References/Clinical Trials Identifier
BAY-299	Compound report	Compound discovery	117
BMS-986158	Advanced solid tumors	Clinical trials	NCT02419417
ABBV-075	Advanced Cancer Breast Cancer Non-Small Cell Lung Cancer Acute Myeloid Leukemia Multiple Myeloma	Clinical trials	NCT02391480
GS-5829	Metastatic Castrate-Resistant Prostate Cancer (and in combination with Enzalutamide)	Clinical trials	NCT02607228
	Solid Tumors and Lymphomas (in combination with exemestane)	Clinical trials	NCT02392611
	ER+breast cancer (in combination with fulvestrant)		
PLX51107	Solid Tumors	Clinical trials	NCT02683395
	Acute Myeloid Leukemia		
	Myelodysplastic Syndrome		

Clinical trials from <https://clinicaltrials.gov/> (accessed 2016, September 20).

cell growth driven by AR-Vs *in vitro* and *in vivo*.<sup>81</sup> Another study revealed that JQ1 inhibits the interaction between BRD4 and ERG, a transcription factor aberrantly upregulated in prostate cancer. This interaction seems to be essential for ERG-mediated cell invasion in this type of cancer.<sup>82</sup> All these studies support the potential activity of BET inhibitors in prostate cancer. In fact, clinical trials with I-BET762, GSK525762, ZEN003694, GS-5829, and OTX015 to treat castration-resistant prostate cancer are currently underway (Table 1).

In non-small cell lung cancer (NSCLC), JQ1 was found to be effective in several lung adenocarcinoma cell lines due to its suppression of the oncogenic transcription factor *FOSL1* and its targets.<sup>83</sup> JQ1 treatment also produced tumor regression in NSCLC KRAS mutant mice by inhibiting MYC function. However, KRAS and, simultaneously, liver kinase B1- (*LKB1*-) mutated mice were not sensitive to JQ1.<sup>84</sup> Nevertheless, human lung adenocarcinoma tumors with loss of wild type LKB1 have poor outcome and high invasiveness mediated by upregulation of MYC via an increase in MZF1 expression and can be overcome by treatment with JQ1.<sup>85</sup> Small cell lung cancer (SCLC) cell lines are especially sensitive to growth inhibition by JQ1, not due to changes in MYC expression, but because of the downregulation of the lineage-specific transcription factor achaete-scute homolog-1 (*ASCL1*), which is overexpressed in more than 50% of SCLC patients.<sup>86</sup> JQ1 disrupts the interaction between BRD4 and *ASCL1* enhancer.<sup>87</sup>

Several studies were made concerning JQ1 treatment in standard therapy-resistant breast cancer models. For example, in tamoxifen-resistant breast cancer, JQ1 demonstrated anti-tumor activity in mouse models and a synergistic activity with fulvestrant, an ER degrader.<sup>21</sup> Tamoxifen has been the first-line treatment for estrogen receptor alpha ( $ER\alpha$ )-positive breast tumors, although resistance to this drug is very common.<sup>88</sup> JQ1 effect stems from its capacity to suppress the classic  $ER\alpha$  signaling pathway. WHSC1, a histone H3K36 methyltransferase, is a positive regulator of  $ER\alpha$  signaling in breast cancer that is recruited to the *ER\alpha* gene by BRD3/4. JQ1 inhibits this interaction, slowing the rate of cell growth in tamoxifen-resistant breast cancer cells.<sup>21</sup>

Another study reported that JQ1 blocks the transition of RNA polymerase II from initiation to elongation induced by

estrogen ( $E_2$ ), establishing that BET proteins are mediators of  $E_2$ -induced transcriptional activation.<sup>89</sup> Upregulation of MYC driven by BRD4 was observed in everolimus-resistant ER+ breast cancers. Depletion of MYC resensitized cells to everolimus, and JQ1 in combination with this drug decreased tumor growth in xenograft models.<sup>90</sup> Moreover, the combination of JQ1 with HDAC inhibitors such as mocetinostat resulted in a greater reduction in cell viability for triple-negative and ER+ breast cancer cells.<sup>91</sup> This synergistic effect was associated with the decreased expression of genes that play a key role in cell cycle progression and a significant increase in the expression of genes from the ubiquitin-specific protease (USP17) family, which were able to diminish the activity of the RAS/MAPK pathway, resulting in reduced cell viability.<sup>91</sup> *In vitro* and *in vivo* triple-negative breast cancer (TNBC) models were found to be more highly sensitive to BET inhibitors than to more resistant luminal lines. JQ1 treatment results in growth inhibition by cell cycle arrest in G1 and apoptosis. Similar results were obtained treating TNBC xenografts.<sup>92</sup> Data show that JQ1 selective disruption of super-enhancer-associated genes alters transcriptional pathways involved in cell proliferation, tumor invasion and survival.<sup>92</sup> Another study in TNBC reported that treatment with JQ1 resulted in a reduction of transcription factors like the DEP domain containing 1 (*DEPDC*), Forkhead box M1 (*FOXM1*), and Lim domain only 4 (*LMO4*). It also suggests that BET inhibitors could be a new targeted therapy for TNBC, the most aggressive form of breast cancer, for which treatment is currently limited to chemotherapy.<sup>93</sup> Moreover, TNBC is the breast cancer subtype most frequently associated with hypoxia.<sup>95</sup> JQ1 modulated 44% of hypoxia-responsive genes,<sup>94</sup> most of which were downregulated, including carbonic anhydrase 9 (*CA9*) and vascular endothelial growth factor A (*VEGF-A*). This study concluded that BET inhibitors jointly target angiogenesis and the hypoxic response, making it an effective anti-tumor combination.<sup>94</sup>

At the same time as the apparition of JQ1, another diazepine-based compound, I-BET762 (GSK525762) (Fig. 3), was independently reported by GSK.<sup>60</sup> I-BET762, like JQ1, arrests the growth of NMC-malignant cells. GSK started clinical trials for the treatment of this malignancy that were subsequently extended to other types of cancer, such as small cell lung cancer, non-small

cell lung cancer, colorectal cancer, neuroblastoma, castration-resistant prostate cancer, triple-negative breast cancer, estrogen receptor-positive breast cancer, and MYCN driven solid tumor subjects (Table 1). I-BET762 has also been reported to exert anti-proliferative effects and to induce apoptosis in multiple myeloma *in vitro* and *in vivo*.<sup>96</sup> It is also effective in prostate cancer, whereby tumor growth is reduced by inhibiting MYC.<sup>97</sup>

OTX015 (MK-8628) (Fig. 3) is a BRD2/3/4 inhibitor under evaluation in dose-finding studies for solid tumors as glioblastoma multiform. OTX015 showed a stronger anti-proliferative effect than JQ1, and a significant anti-tumoral effect in GBM mouse models has recently been reported.<sup>98</sup> Treatment with OTX015 leads to cell growth inhibition, cell cycle arrest and apoptosis in acute leukemia cell lines, indicating that OTX015 and JQ1 have similar effects in leukemic cells.<sup>99</sup> There are currently six clinical trials underway with OTX015 in GBM, hematological malignancies and several other solid tumors like NUT midline carcinoma, TNBC, castration-resistant prostate cancer and pancreatic ductal carcinoma (Table 1).

I-BET151 (GSK1210151A) (Fig. 3) was reported in 2011 as being a novel BET bromodomain inhibitor that had proved its efficacy in mixed-lineage leukemia (MLL) cell lines at inducing apoptosis and cell cycle arrest, due in part to a decrease in the *BCL-2*, *MYC*, and *CDK6* genes through the inhibition of BRD3/BRD4.<sup>100</sup> It also exhibits potent anti-myeloma activity through transcriptional repression of *MYC* by avoiding *P-TEFb* chromatin occupation, and upregulation of *HEXIM1*, which is an inhibitor of P-TEFb.<sup>96</sup> I-BET151 was reported to be an alternative treatment for myeloproliferative neoplasms driven by constitutively active JAK2 kinase<sup>101</sup> and glioblastoma, in which it inhibits proliferation by arresting cell cycle progression.<sup>102</sup> It was also found to be effective for treating *NPM1*-mutated acute myeloid leukemia.<sup>103</sup> In melanoma cells, on the one hand, I-BET151 induces BIM-dependent apoptosis and cell cycle arrest,<sup>104</sup> while, on the other controlling NF- $\kappa$ B activity.<sup>105</sup>

CPI203 (Fig. 3) is a BET bromodomain inhibitor that has shown synergistic activity with drugs that have already been clinically approved for cancer treatment. Multiple myeloma cells resistant to bortezomib and melphalan treated with CPI203 plus bortezomib increased the apoptosis level and decreased the proliferation rate.<sup>106</sup> Furthermore, CPI203 demonstrated its efficacy in pancreatic neuroendocrine tumors (PanNET) by downregulating *MYC* expression, producing G1 cell cycle arrest and almost completely inhibiting cell proliferation. It also enhanced the antitumor effects of rapamycin in PanNET, attenuating rapamycin-induced AKT activation, which is a major limitation of rapamycin therapy.<sup>107</sup> CPI203 synergistic antitumor activity with lenalidomide, reported in bortezomib-resistant mantle cell lymphoma, caused simultaneous *MYC* and *IRF4* downregulation and apoptosis induction.<sup>108</sup>

RVX2135 inhibits proliferation and induces apoptosis in Myc-induced murine lymphoma, affecting many transcription factor networks.<sup>109</sup>

PFI-1 (Fig. 3) was reported as being a BET inhibitor for BRD2 and BRD4 that showed anti-proliferative efficiency in leukemic cell lines. Treatment with PFI-1 produced cell cycle arrest in G1, downregulation of *MYC* expression and induction of apoptosis. Unlike other BET inhibitors, PFI-1 caused significant downregulation of *Aurora B kinase*, suggesting a

potential synergism between *MYC* and *Aurora B*, two potent oncogenes that could be targeted simultaneously with this inhibitor.<sup>110</sup>

MS436 (Fig. 3) is another BRD4 inhibitor that was reported to inhibit NF- $\kappa$ B-directed production of nitric oxide and pro-inflammatory cytokine interleukin-6 in murine macrophages.<sup>111</sup> However, since first being reported in 2013, no further studies have been published concerning this molecule.

FT-1101,<sup>112</sup> CPI-0610<sup>113</sup> (Fig. 3) are novel BET inhibitors that were reported recently and are undergoing clinical trials in hematological cancers. BAY 1238097<sup>114</sup> and INCB054329<sup>115</sup> are being clinically trialed for several solid tumors and hematological malignancies. Also currently the subject of clinical trials are TEN-010,<sup>116</sup> for NUT-midline carcinoma and advanced solid tumors, GSK2820151, for subjects with advanced or recurrent solid tumors, ZEN003694, which is for metastatic castration-resistant prostate cancer, and BMS-986158, ABBV-075, GS-5829, and PLX51107, for several types of cancer (Table 1).

Finally, BAY-299 is an inhibitor of BRD1 and the second bromodomain of TAF1 reported on the SGC webpage, as a collaboration with Bayer.<sup>117</sup>

### Non-BET inhibitors

BET-family inhibitors have been extensively studied in recent years, but far less attention has been paid to the other bromodomains. Given that the latter are frequently in proteins with other epigenetic functions, such as HAT activity, finding non-BET inhibitors will allow a better understanding of them. This will also help identify new druggable targets for treating diseases like cancer (Table 2).

In this context, Bromosporine<sup>118</sup> (Fig. 4) is a multi-bromodomain inhibitor, which has been made available by the SGC. It acts as a broad-spectrum bromodomain inhibitor and can be useful for studying biological functions.

The ATAD2 bromodomain is known to be difficult to drug.<sup>119</sup> GSK reported the first micromolar inhibitor of ATAD2, but it was not selective for the BET family.<sup>120</sup> This compound was then optimized to improve its activity to subnanomolar and 100-fold BET selectivity.<sup>121</sup> Studies to improve this compound are being conducted but have not yet been published.

Although the homologous bromodomains BAZ2A and BAZ2B also have low predicted druggability,<sup>119</sup> to date, two structurally distinct selective inhibitors have been reported, BAZ2-ICR and GSK2801 (Fig. 4).<sup>122,123</sup>

BAZ2-ICR<sup>122</sup> was published in 2015 by the Institute of Cancer Research. It is suitable for use *in vitro* and *in vivo* and is available to the scientific community for the purpose of further investigating the biological role of BAZ2A/B. GSK2801<sup>123</sup> was investigated as a collaboration between GSK and SGC as found to be a potent, selective bromodomain inhibitor of BAZ2A and BAZ2B that acts in a competitive binding model with acetyllysines. It is also suitable for treatments *in vitro* and in animal models.<sup>123</sup>

BRD9 is a component of the chromatin remodeling complex SNF/SWI BAF but its biological function has not yet been fully elucidated.<sup>124</sup> Its potential role in disease has encouraged research on inhibitors, and several BRD9 chemical probes have



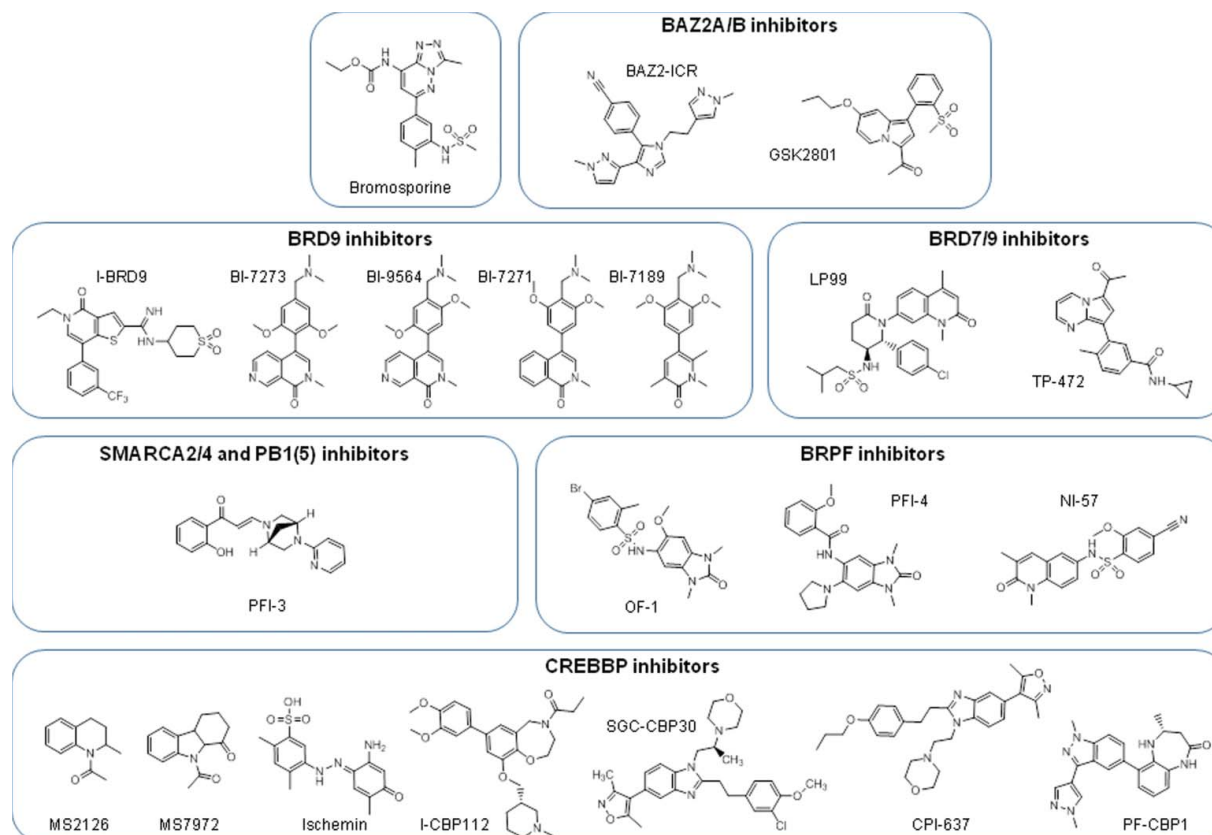
**Table 2.** Non-BET inhibitors

Target	Ligand	Tumor type	References
Multi-bromodomain	Bromosporine	NT	118
BAZ2A/B	BAZ2-ICR	NT	122
	GSK2801	NT	123
BRD9	I-BRD9	Leukemia	126
	BI-7273/BI-9564	Acute Myeloid Leukemia (AML)	128
	BI-7271/BI-7273/BI-7189	Acute Myeloid Leukemia (AML)	50
BRD9/BRD7	LP99	NT	127
	TP-472	NT	129
BRPF family	OF-1	NT	131
	PFI-4	NT	132
	NI-57	NT	133
SMARCA2/4 and PB1(5)	PFI-3	Lunc cancer, synovial sarcoma, rhabdoid cancer, AML	138,139
CREBBP	MS2126/MS7972	Osteosarcoma	142
	Ischemin	NT	143
	I-CBP112	Leukemia and prostate cancer	144
	SGC-CBP30	Multiple myeloma	146–148
	PF-CBP1	NT	149
	CPI-637	NT	150

NT = Not tested in cancer

been reported so far. Filippakopoulos and colleagues described the 9-H purine scaffold as a template to be used for further studies involving inhibition of BRD9.<sup>125</sup> Subsequently, GSK in collaboration with the University of Strathclyde reported I-BRD9<sup>126</sup> (Fig. 4), a selective BRD9 inhibitor with more than 700-fold selectivity over the BET family and 200-fold selectivity over the highly homologous BRD7.<sup>126</sup> The SGC and the

University of Oxford published LP99 (Fig. 4), a potent and selective inhibitor for both BRD9 and BRD7 bromodomains, which plays a role in regulating pro-inflammatory cytokine secretion.<sup>127</sup> Two other BRD9 inhibitors, BI-7273 and BI-9564, were described by Boehringer Ingelheim and the SGC (Fig. 4).<sup>128</sup> These compounds exert antitumor activity in an AML xenograft model.<sup>128</sup> Moreover, BI-7271, BI-7273, and BI-



**Figure 4.** Non-BET bromodomain inhibitor molecules. Chemical structures of non-BET inhibitors, clustered according to the specific bromodomains in which they act. Bromosporine is a multibromodomain inhibitor.

7189 BRD9 inhibitors (Fig. 4) suppressed the proliferation of AML cells.<sup>50</sup> The SGC website has recently added TP-472 (Fig. 4), a new inhibitor of the BRD9/7 bromodomain that is also suitable for *in vivo* treatments.<sup>129</sup>

Inhibitors of BRPF family bromodomains are also being investigated in order to elucidate their biological role and druggability. In 2014, GSK reported a series of selective drugs for the BRPF1 bromodomain. These are benzimidazolone compounds that showed 100- and >1000-fold selectivity over BRPF2 and BRPF3, respectively.<sup>130</sup> The SGC disclosed OF-1 on its website (Fig. 4), describing that it inhibits BRPF1B/2/3 bromodomains, and has good selectivity against other bromodomains, although the closest off target is BRD4 (39-fold selectivity).<sup>131</sup> The SGC in collaboration with Pfizer has reported PFI-4 (Fig. 4), a selective BRPF1B bromodomain inhibitor, and an isoform of BRPF1 that binds to acetylated histones in the opposite manner to isoform BRPF1B.<sup>132</sup> NI-57 (Fig. 4) is another compound listed on the SGC webpage that was discovered by them in collaboration with University College London, and which selectively inhibits all members of the BRPF family. The closest off target is BRD9 (32-fold selectivity), but is very selective against other bromodomains, including those of the BET family.<sup>133</sup> Recently, a dual inhibitor of BRPF1 and TRIM24 was reported, which exerts good selectivity over other bromodomains.<sup>134</sup>

SMARCA4 (BRG1), SMARCA2, and PB1 are bromodomain-containing proteins that are also members of the SWI/SNF chromatin-remodeling complexes. Loss of function of SMARCA4<sup>135</sup> and other alterations in components of the SWI/SNF complex are associated with cancer development. PB1 (BAF180) contains six bromodomains that are frequently mutated in cancer.<sup>136</sup> The SMARCA4 bromodomain is involved in DNA damage repair.<sup>137</sup> The SGC reported the development of PFI-3 (Fig. 4), a bromodomain inhibitor of SMARCA2/4 and PB1(5),<sup>138,139</sup> which showed high selectivity over other bromodomains. However, subsequent studies with PFI-3 determined that the ATPase catalytic domain of SMARCA2/4 has an indispensable role in cancer growth, whereas bromodomain inhibition is not crucial for the process, thereby highlighting the importance of the ATPase domain in these proteins as a significant therapeutic target.<sup>140</sup> A recent study reported the optimization of a compound inhibiting the second and fifth bromodomains of PB1 more selectively than SMARCA2/4, and another one inhibiting PB1(5).<sup>141</sup>

CREBBP bromodomain inhibitors are the second most thoroughly studied group, after the BET family inhibitors. The first attempts to do so involved inhibiting the CREBBP-p53 interaction using the compounds MS2126 and MS7972 (Fig. 4).<sup>142</sup> Treatment of U2OS cells with previously stimulated DNA damage resulted in a dramatic decrease in p53 levels.<sup>142</sup> Ischemin (Fig. 4) was reported by the same group<sup>143</sup> to be a bromodomain inhibitor of CREBBP that is also able to inhibit this interaction and consequently alter the expression of p53 target genes involved in apoptosis and DNA damage repair.<sup>143</sup> I-CBP112 (Fig. 4) was reported by SGC and GSK as being a novel compound for CREBBP and P300 bromodomains with nanomolar activity and good selectivity.<sup>144</sup> This compound impaired the disease-initiating self-renewal leukemic cells *in vitro* and *in vivo*.<sup>144</sup> A recent study of I-CBP112<sup>145</sup> reported

that this compound stimulates acetylation activity by CREBBP/P300 acting as an activator of these HATs, contributing to its anti-proliferative effect in cancer. It is also suggested that activation activity of I-CBP112 could help restore the balance of acetylation levels in tumors that experience CREBBP/P300 loss of function due to mutations, although the mechanism and networks involved in tumors affected by this activation are not yet fully understood.<sup>145</sup> SGC-CBP30 (Fig. 4) was reported by the SGC and the University of Oxford.<sup>146</sup> This compound is selective for CREBBP/P300 bromodomains but is not suitable for use *in vivo* because it is metabolized so quickly. SGC-CBP30 was reported to suppress the Th17 response that is critical to a variety of human autoimmune diseases.<sup>147</sup> Moreover, I-CBP112 and SGC-CBP30 suppress the lymphocyte-specific transcription factor IRF4, which is crucial for the viability of myeloma cells, and consequently targets c-MYC.<sup>148</sup> PF-CBP1 (Fig. 4) is another selective inhibitor of the CREBBP/P300 bromodomain, which downregulates a number of inflammatory genes in macrophages and the RSG4 gene in neurons.<sup>149</sup> Finally, another CREBBP/P300 bromodomain inhibitor, CPI-637 (Fig. 4),<sup>150</sup> was recently reported to have high potency *in vitro* and selectivity over other bromodomains.

### Targeting protein acetylation beyond bromodomain inhibition and cancer: HAT activation and other human diseases

Apart from cancer, bromodomains are key transcriptional regulators in diabetes, inflammation and cardiovascular diseases (reviewed by Denis<sup>151</sup> and Nicholas DA et al.<sup>152</sup>), and are considered potentially druggable to treat these disorders.

RVX-208 (RVX000222; apabelaton) was developed by Resverlogix Corporation to treat atherosclerotic cardiovascular diseases.<sup>153</sup> Its use is currently being investigated in several clinical trials for atherosclerosis, coronary syndromes and Alzheimer disease.<sup>154,155</sup> RVX-208 is an orally available BET bromodomain inhibitor which selectively inhibits BRD2.<sup>156</sup> It increases apolipoprotein AI (ApoA-I) gene transcription and leads to production of high density lipoprotein (HDL) cholesterol levels *in vitro* and *in vivo*,<sup>157</sup> resulting in the stimulation of reverse cholesterol transport. It also represses inflammatory and atherosclerotic pathways that contribute directly to cardiovascular risk.<sup>158</sup> RVX-208 is also being tested in patients with pre-diabetes, demonstrating effects in HDL lipidome and glucose metabolism that may protect against the development of type 2 diabetes.<sup>159</sup>

Furthermore, some of the bromodomain inhibitors studied for cancer therapies have also been tested in diabetes and inflammatory diseases. For example, I-BET151 suppressed the development of type 1 diabetes in mice.<sup>160</sup> Another study suggests that BET inhibitors may be useful to treat diabetic patients resistant to insulin because it was observed that JQ1 increases insulin secretion *in vitro* and decreased intracellular triglyceride stores in cells.<sup>161</sup> In inflammation, JQ1 was reported to suppress psoriasis-like skin inflammation in mice by modulating RORC/IL-17A pathway.<sup>162</sup> In addition, JQ1<sup>163</sup> and I-BET151<sup>164</sup> prevented synovial inflammation in rheumatoid arthritis synovial fibroblasts. I-BET151 also regulates IL-6 production, decreasing the early symptoms in a multiple sclerosis mouse model.<sup>165</sup> I-BET762 was also reported to have high anti-

inflammatory potential by regulating the expression of key inflammatory genes.<sup>59</sup> Moreover, a recent study described that inhibition of BET bromodomain also suppresses vascular inflammation by inhibiting NF- $\kappa$ B and MAPK activation.<sup>166</sup>

Aberrant protein acetylation is common in cancer as well as in other disorders such as neurological and cardiac disease. Besides bromodomain inhibition, HAT activation emerged as other potential strategy in treating diseases through modulation of protein acetylation levels and consequent gene expression regulation. Several positive modulators of HATs have been identified in the last few years. CTPB, an anacardic acid derivative, was reported as a selective activator of p300 (KAT3B) HAT activity but not PCAF (KAT2B), which enhanced HAT-dependent transcriptional activation.<sup>167</sup> Posterior studies reported long chain alkylidenemalonates (LoCAMs) as a novel class of HAT modulators with a powerful apoptotic effect.<sup>168</sup> Important to highlight in this family of compounds are the unique properties of pentadecylidenemalonate 1b (SPV106), that leads to PCAF (KAT2B) acetylation activity increase, together with its inhibitory properties against CBP (KAT3A) and p300 (KAT3B).<sup>168,169</sup> This inspired the synthesis of SVP106 analogs that feature different levels of activity modulation for KAT2B and KAT3B simultaneously.<sup>170</sup> SPV106 has been successfully used in neurological<sup>171</sup> and cardiological<sup>172,173</sup> studies where the acetylation activity of KAT2B was investigated. Moreover, in cardiac mesenchymal cells, SPV106 recovered differentiation and proliferation in patients with diabetes.<sup>174</sup> Additionally, TTK21 was reported as an activator of CBP (KAT3A) and p300 (KAT3B), which was able to promote neurogenesis and increased long-term memory in adult mice.<sup>175</sup> These HAT positive modulators may be useful for a better understanding the biology of HATs and also may open new treatment strategies for cancer as well as for other diseases frequent in developed societies like cardiac and brain disease.

## Concluding remarks

Since the discovery of the high potency of (+)-JQ1 and I-BET762 in NMC and subsequently in other types of cancer, a large number of bromodomain inhibitors have been developed. Currently, several clinical trials of BET inhibitors, representing a new family of compounds for cancer-targeted therapy, are underway. Discovery of non-BET inhibitors will also help elucidate the possible role (s) of bromodomain-containing proteins in cancer, and reveal new druggable targets for combating this disease. The problems of specificity should be overcome in the near future, but bromodomain inhibitors already show great potential as new drugs in cancer therapy. Progress in this field of research should reveal new molecular targetable pathways, and even novel biomarkers that predict bromodomain-inhibitor sensitivity, which would represent a significant step toward personalized medicine.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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