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## Design and synthesis of potent and selective inhibitors of BRD7 and BRD9 bromodomains†

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Emerging evidence suggests bromodomain-containing proteins 7 and 9 (BRD7 and BRD9) have roles in the regulation of human transcription and disease including cancer. We describe potent and selective inhibitors of the BRD7 and BRD9 bromodomains intended for use as tools to elucidate the biological roles of BRD7 and BRD9 in healthy and diseased cells.

Compared to other bromodomain- (BRD-) containing proteins, such as bromodomain and extra terminal (BET) family members very little is known about the biological function of BRD-containing protein 9 (BRD9). BRD9 has 598 residues and its BRD is the only functional domain that has been assigned to date.<sup>1</sup> Proteomic analysis implies that BRD9 is associated with human BAF-type (BRG1/BRM-associated factors) SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin remodeling complexes.<sup>2</sup> Recently, it has been reported that BRD9 is a core sub-unit of SWI/SNF complexes.<sup>3</sup> The BRD9 paralog bromodomain-containing protein 7 (BRD7) is a subunit of PBAF (poly-bromo-associated BAF) SWI/SNF complexes.<sup>2,4,5</sup> It is proposed that BRD7 regulates transcription through binding of its BRD to the acetylated form of Lys-14 of histone H3 (H3K14Ac).<sup>6</sup> BRD7 and BRD9 are only 36% similar at in terms of their overall residues, but the similarity of their BRDs is much higher (72%).

Evidence is emerging which indicates that BRD9 and BRD7 have roles in oncology and are consequently potential drug targets. BRD9 has been identified as part of a group of genes with copy number variations in non-small cell lung cancer (NSCLC) tumour samples, implying that a chromosomal imbalance in BRD9 could be involved in tumorigenesis.<sup>7</sup> Similar analysis of cervical cancer tumour samples also found copy number increases in BRD9.<sup>8</sup> The links of BRD7 to oncology are even more compelling. It has been suggested

that BRD7 is a possible tumour-suppressor gene, which inhibits G1-S progression by blocking the translocation of  $\beta$ -catenin from the cytoplasm to the cell nucleus and negatively regulating the extracellular signal-regulated kinases (ERK) 1/2 pathway.<sup>9,10</sup> Additionally, BRD7 is reported to be a critical regulator of the tumour suppressor protein p53.<sup>11–13</sup> BRD7 also regulates estrogen receptor  $\alpha$  (ER $\alpha$ ) expression through BRCA1 recruitment.<sup>14</sup> Analysis of tumour biopsies shows that BRD7 is down-regulated in nasopharyngeal carcinoma, colorectal cancer and epithelial ovarian cancers.<sup>9,15,16</sup> In colorectal cancer, BRD7 expression is also negatively correlated with survival time.<sup>15</sup> The BRD7 locus is frequently deleted in breast cancer tumours.<sup>12</sup> However, it was found that BRD7 mutations represent rare polymorphisms in breast cancer, with no pathogenic effect.<sup>17</sup> MicroRNA-200c (miR-200c), which is over-expressed in endometrial carcinoma, inhibits BRD7 expression.<sup>18</sup>

With little known about the molecular function of BRD7, and even less in the case of BRD9, potent and selective small molecule inhibitors would be valuable tools to study the roles of these proteins in transcription, elucidate their roles in oncology and other human diseases, and to test them as drug targets. Non-selective BRD9 inhibitors have been reported, but their potent BET inhibition makes them unsuitable to

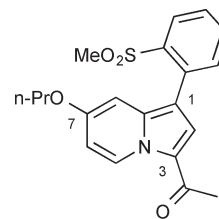
BAZ2A  $K_d$  0.26  $\mu$ MBAZ2B  $K_d$  0.14  $\mu$ M

Fig. 1 GSK2801 1, a BAZ2A/BAZ2B chemical probe.

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‡ These authors contributed equally to this work.



Table 1 Potency and selectivity of indolizine inhibitors of BRD9 bromodomain

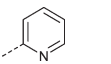

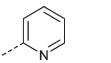

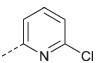
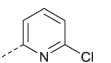

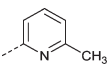

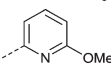

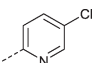

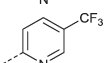

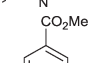
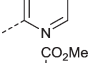

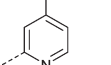

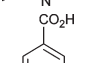

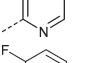

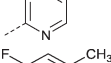

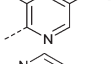

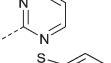

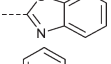

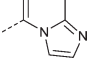

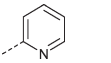

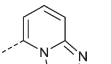

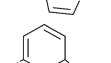

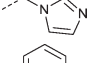

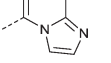
Cmpd	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	c log P <sup>a</sup>	BRD9 ΔT <sub>m</sub> (°C) <sup>b</sup> pIC <sub>50</sub> 5.6 ± 0.12 (2) <sup>c</sup>	BRD4(1) ΔT <sub>m</sub> (°C) <sup>b</sup>	BRPF1B ΔT <sub>m</sub> (°C) <sup>b</sup>	BAZ2B pIC <sub>50</sub> <sup>c</sup>
2	<i>n</i> PrO-		-CH <sub>3</sub>	2.6	1.1 ± 0.40 (2) pIC <sub>50</sub> 5.6 ± 0.12 (2) <sup>c</sup>	-0.35 ± 0.11 (2)	0.32 ± 0.19 (2)	5.6 ± 0.12 (2)
3			-CH <sub>3</sub>	1.8	5.7 ± 0.071 (2) pIC <sub>50</sub> 6.3 ± 0.066 (2) <sup>c</sup>	1.9 ± 0.27 (2)	1.3 ± 0.25	5.5 ± 0.033 (2)
15			-CH <sub>3</sub>	2.6	0.81 ± 0.39 (2)	0.28 ± 0.28 (2)	0.34 ± 0.046 (2)	ND <sup>e</sup>
16	<i>n</i> PrO-		-CH <sub>3</sub>	3.5	0.085 ± 0.60 (2)	-0.60 ± 0.042 (2)	-0.18 ± 0.24 (2)	ND
17			-CH <sub>3</sub>	1.9	4.2 ± 0.0 (2) pIC <sub>50</sub> 6.3 ± 0.12 (2) <sup>c</sup>	1.2 ± 0.057 (2)	0.65 ± 0.060 (2)	4.8 ± 0.10 (2)
18			-CH <sub>3</sub>	2.2	1.3 ± 0.11 (2)	0.82 ± 0.071 (2)	0.53 ± 0.035 (2)	ND
19			-CH <sub>3</sub>	2.4	-0.23 ± 0.067 (2)	-0.39 ± 0.0035 (2)	-0.22 ± 0.053 (2)	ND
20			-CH <sub>3</sub>	2.7	-1.1 ± 0.21 (2)	-4.0 ± 0.47 (2)	-2.5 ± 0.12 (2)	ND
21			-CH <sub>3</sub>	1.8	0.35 ± 0.046 (2)	0.075 ± 0.13 (2)	-0.040 ± 0.099 (2)	ND
22	<i>n</i> PrO-		-CH <sub>3</sub>	2.6	-0.030 ± 0.37 (2)	-0.24 ± 0.17 (2)	-0.090 ± 0.021 (2)	ND
23			-CH <sub>3</sub>	1.5	-0.060 ± 0.11 (2)	-0.24 ± 0.11 (2)	0.010 ± 0.12 (2)	ND
24			-CH <sub>3</sub>	1.9	1.3 ± 0.27 (2)	0.41 ± 0.23 (2)	0.71 ± 0.32 (2)	ND
25			-CH <sub>3</sub>	2.5	-0.28 ± 0.039 (2)	-0.42 ± 0.15 (2)	-0.48 ± 0.11 (2)	ND
26			-CH <sub>3</sub>	1.5	0.035 ± 0.053 (2)	0.43 ± 0.092 (2)	0.29 ± 0.11 (2)	ND
27			-CH <sub>3</sub>	3.1	-0.30 ± 0.12 (2)	0.55 ± 0.088 (2)	0.040 ± 0.13 (2)	ND
28			-CH <sub>3</sub>	1.3	4.5 ± 0.19 (2) pIC <sub>50</sub> 6.9 ± 0.065 (2) <sup>c</sup> K <sub>d</sub> 0.068 ± 0.0049 μM <sup>d</sup>	1.3 ± 0.11 (2)	1.7 ± 0.11 (2)	<4.0 (2)
29			-CH <sub>3</sub>	1.5	5.7 ± 0.20 (2)	4.0 ± 0.095 (2)	1.7 ± 0.52 (2)	ND
30			-CH <sub>3</sub>	1.0	5.1 ± 0.064 (2)	2.6 ± 0.17 (2)	2.3 ± 0.30 (2)	ND
31			-CH <sub>3</sub>	1.4	7.5 ± 0.16 (2)	4.1 ± 0.24 (2)	3.5 ± 0.47 (2)	ND
32			-Et	2.0	3.0 ± 0.14 (2)	0.98 ± 0.14 (2)	0.20 ± 0.12 (2)	ND
33			-CF <sub>3</sub>	2.5	0.26 ± 0.099 (2)	-0.40 ± 0.17 (2)	0.20 ± 0.35 (2)	ND
34			-Et	2.1	1.2 ± 0.035 (2)	0.51 ± 0.35 (2)	-0.15 ± 0.19 (2)	ND
35			- <i>i</i> Pr	2.6	1.0 ± 0.19 (2)	0.19 ± 0.70 (2)	0.71 ± 0.24 (2)	ND



Table 1 (continued)

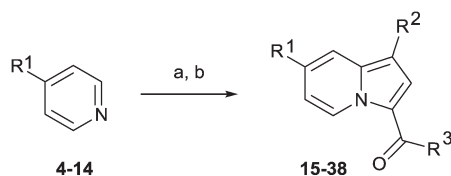
Cmpd	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	c log P <sup>a</sup>	BRD9 ΔT <sub>m</sub> (°C) <sup>b</sup>	BRD4(1) ΔT <sub>m</sub> (°C) <sup>b</sup>	BRPF1B ΔT <sub>m</sub> (°C) <sup>b</sup>	BAZ2B pIC <sub>50</sub> <sup>c</sup>
36			-cPr	2.2	0.76 ± 0.98 (2)	-0.65 ± 0.16 (2)	-0.085 ± 0.081 (2)	ND
37			-nBu	3.0	0.27 ± 0.095 (2)	-0.78 ± 0.19 (2)	-0.50 ± 0.067 (2)	ND
38			-CF <sub>3</sub>	2.5	0.30 ± 0.028 (2)	-0.70 ± 0.31 (2)	-0.26 ± 0.025 (2)	ND

<sup>a</sup> Calculated using ChemAxon.<sup>31</sup> <sup>b</sup> Mean ΔT<sub>m</sub> ± SEM (number of measurements). <sup>c</sup> Mean pIC<sub>50</sub> ± SEM (number of measurements) determined by AlphaScreen. <sup>d</sup> K<sub>d</sub> determined by ITC. <sup>e</sup> Not determined.

study the function of BRD9 in isolation.<sup>19,20</sup> Potent and selective small molecule inhibitors of BRD7 and BRD9 are presently limited with the first selective BRD7/9 inhibitors LP99 and I-BRD9 having just been reported.<sup>21</sup> The availability of inhibitors with similar pharmacology but orthogonal chemotypes lends confidence to the interpretation of results obtained using chemical tools in target discovery; therefore, we sought to develop BRD7/9 inhibitors in a new chemical series.<sup>22</sup> Here, we describe the design and synthesis of potent and selective inhibitors of the BRD7 and BRD9 BRDs, based on a series of C-3 keto-indolizines.<sup>23</sup>

Compound 1 (GSK2801) is a chemical probe for the bromodomain adjacent zinc finger (BAZ) 2A and BAZ2B BRDs (Fig. 1).<sup>24</sup> We noted that pyridine-containing analogues of compound 1 inhibited the BRD9 BRD; thus, compounds 2 and 3 were relatively potent inhibitors of BRD9 in a peptide displacement AlphaScreen (amplified luminescent proximity homogeneous assay screen) assay (pIC<sub>50</sub> 5.6 and 6.3, respectively) (Table 1).<sup>25</sup> Notably, we observed that compound 3 was more than 5-fold selective for BRD9 over BAZ2B. The low lipophilicity of these compounds (c log P 2.6, 1.8) made them attractive for further development of a BRD9 chemical probe. Our aim was to investigate the effects of varying the substituents on positions C-1, 3 and 7 of the indolizine ring in variants of compound 3 on BRD9 potency and selectivity while keeping the lipophilicities moderate (c log P 1–3) to ensure good drug-like properties.

The indolizine target compounds (15–38) were synthesized by quaternisation of substituted pyridines 4–14 followed by base-promoted [3 + 2] cycloaddition of the pyridinium salts



**Scheme 1** Synthesis of indolizine analogues. Reagents and conditions: (a) R<sup>3</sup>COCH<sub>2</sub>X (X = Cl, Br), THF or acetone (15–91%); (b) alkyne (R<sup>2</sup>CCH), K<sub>2</sub>CO<sub>3</sub>, DMF, 90 °C (2.3–40%).

with alkynes (Scheme 1).<sup>26,27</sup> The analogues (15–38) were screened for binding to bromodomain proteins by differential scanning fluorimetry (DSF, ΔT<sub>m</sub>) (Table 1).<sup>28</sup> In order to obtain an initial idea of potency and selectivity the analogues were initially screened against BRD9, BRD4(1) and bromodomain and PHD finger containing (BRPF) 1B. Propoxy analogues 16 and 22 showed significantly less affinity against BRD9 than the corresponding morpholino analogues 15 and 21 in the DSF assay, indicating that the morpholine ring promotes affinity for BRD9. The introduction of substituents onto the 3-, 4-, 5- and 6-positions of the pyridine ring, as in compounds 15, 17–21 and 23–25, generally led to a significant drop in BRD9 potency compared to compound 3. Out of the substituted pyridine analogues tested, compound 17 had the highest affinity for BRD9 (ΔT<sub>m</sub> 4.2 °C). Analogues were then prepared which replaced the pyridine ring with an alternative heterocycle (26, 27 and 28). The best tolerated of these was the imidazopyridine compound 28 (BRD9 ΔT<sub>m</sub> 4.5 °C).

The SAR at the R<sup>1</sup> position of the indolizine scaffold was further examined; the C-7 piperazine analogues were highly potent against BRD9, but were not very selective with respect to BRD4. For example, compound 31 was potent against BRD9 (ΔT<sub>m</sub> 7.5 °C), but was also relatively potent against BRD4(1) (ΔT<sub>m</sub> 4.1 °C) and BRPF1B (ΔT<sub>m</sub> 3.5 °C). The T<sub>m</sub> shifts for BRD4(1) and BRPF1B would correspond to AlphaScreen IC<sub>50</sub> ≤ 1 μM based on benchmarking with similar published compounds such as compound 28a in Hay, *et al.* (BRD4(1) IC<sub>50</sub> 0.20 μM, T<sub>m</sub> 3.2)<sup>29</sup> and compound 34 in Bennett, *et al.* (BRPF1B IC<sub>50</sub> 0.34 μM, T<sub>m</sub> 6.2).<sup>30</sup>

The C-3 ketone analogues (32–38) with modifications at R3 generally showed a drop in BRD9 potency with respect to the methyl ketone analogues (*e.g.* compound 28). Compound 32 was the most encouraging of the larger ketones, which manifested moderate BRD9 affinity (ΔT<sub>m</sub> 3.0 °C), but no appreciable potency against BRD4(1) or BRPF1B (ΔT<sub>m</sub> < 1 °C). The pIC<sub>50</sub> was determined for the most potent and selective compounds using the AlphaScreen assay (Table 1). Compound 17 was of similar potency to compound 3, with pIC<sub>50</sub> 6.3. Additionally, compound 17 was ~30-fold selective over BAZ2B in the AlphaScreen assay and showed a weak affinity







BRD9 inhibitors LP99 and I-BRD9, compound 28 will serve as a useful chemical probe to elucidate the biological roles of BRD7 and BRD9 in transcription and pathogenesis.

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