GSK6853, a Chemical Probe for Inhibition of the BRPF1 Bromodomain

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ABSTRACT: The BRPF (Bromodomain and PHD Finger-containing) protein family are important scaffolding proteins for assembly of MYST histone acetyltransferase complexes. A selective benzimidazolone BRPF1 inhibitor showing micromolar activity in a cellular target engagement assay was recently described. Herein, we report the optimization of this series leading to the identification of a superior BRPF1 inhibitor suitable for in vivo studies.

KEYWORDS: BRPF1, BRPF2, BRD1, BRPF3, BET, bromodomain, epigenetics, chemical probe, inhibitor

There are at least 56 bromodomain modules contained within 42 human chromatin-regulator proteins. Of these, the eight bromodomains of the BET (Bromodomain and Extra Terminal) subfamily (BRD2/3/4/T) have received most attention following the discovery that small-molecule inhibitors found during cellular screening campaigns bind to these targets because of the multidomain architecture and scaffolding function of these proteins the precise role of the bromodomain is often uncertain. For example, the BRPF (Bromodomain and PHD Finger-containing) family of BRPF1, BRPF2/BRD1, and BRPF3 (Figure S1, Supporting Information) act to facilitate the assembly of MYST-family histone acetyltransferase complexes. In addition to the bromodomain, which binds acetylated histones, the proteins contain other histone-binding domains (PZP and PWWP). The availability of potent and selective chemical probes for BRPF bromodomains would significantly enhance our ability to dissect their biological role and better understand the therapeutic opportunities. We recently reported the discovery of the BRPF1 bromodomain inhibitor I (GSK5959) (Table 1). In the BROMOscan panel of 34 bromodomain binding assays, it showed 10 nM BRPF1 inhibition, 90-fold selectivity over BRPF2, and over 500-fold selectivity over all members of the BET family. Others have independently found related BRPF1 inhibitors with similar properties. Although the qualities of I made it an excellent probe to further elucidate the role of the BRPF1 bromodomain in many situations, its physicochemical properties and solubility are suboptimal. As part of our ongoing efforts to develop bromodomain probe molecules we sought to obtain an inhibitor with lower logD, solubility >100 μg/mL, and cellular activity < 100 nM.

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Expansion of the SAR was carried out via analogue searches within the GSK collection, and bespoke syntheses (Scheme S1). The piperidine of 1 could be truncated to deliver the more potent and ligand efficient inhibitor 2, albeit at the expense of increased inhibition of BRD4 BD1 (Table 2). Further reduction in the size of the 6-substituent (3) was detrimental. However, with the ether-linked analogues an increase in potency and selectivity was observed on moving from 6-methoxy 4 to isopropoxy 5, while ligand efficiency (LE) was retained. Although the discovery of 5 represented a step toward an improved probe in terms of potency, LE, and logD, solubility still remained to be addressed.

The X-ray complex of BRPF1 with 1 (Figure 1) suggested that the 3- and 4-positions on the benzamide provided vectors suitable for projecting a solubilizing group directly out into solvent, but presented no prospect of gaining interactions with the protein. In contrast, elaboration of the phenyl 2-methoxy also offered the potential to interact with residues of the ZA loop, such as Glu655, while retaining the intramolecular hydrogen-bond seen between the 2-methoxy and the amide NH of 1. Compounds 6–12 were accessed via amide coupling of the appropriate benzoic acids with the aromatic amine (Scheme S1).

While introduction of these groups generally improved solubility relative to 5, they all resulted in weaker inhibition of BRPF1 (Table 3). This observation was particularly disappointing for side-chains containing hydrogen-bond donors (6 and 7), which were no more potent than close analogues without this functionality (10, 11), hydrogen bond acceptors (9), or basic groups (8 and 12). These results suggest that introduction of substituents larger than a methyl may give rise to steric clashes with the residues of the ZA loop and suboptimal binding conformations.

With the goals of expanding the diversity of substituents on the 5-position of the benzimidazolone core, improving solubility by lowering logD, and exploring alternatives to the intramolecular methoxy/amide hydrogen-bond, further 5-position analogues were synthesized (Schemes S1 and S2; Table 4). All substituents showed improved solubility relative to 5, but aliphatic groups, whether linear (14 and 15) or cyclic

**Table 1. Summary of the Properties of GSK5959**

| Compound | TR-FRET pIC50 | BROMOscan pKd | NanoBRET pIC50 | BRPF 2/3 TR-FRET pIC50 | BRD4 BD1/2 TR-FRET pIC50 | Selectivity | Chrom logDpH5.4 | CLND solubility (μg/mL) |
|----------|---------------|---------------|---------------|----------------------|-------------------------|------------|----------------|---------------------|
| BRPF1    | 7.1           | 8.0           | 6.0           | 5.2/4.5              | <4.3/<4.3               | >90-fold   | 6.0            | 8                   |

**Table 2. SAR at the Benzimidazolone 6-Position**

| R1 | # | BRPF1 pIC50 | LE | Chrom logDpH7.4 | Solubility | BRD4 BD1 pIC50 |
|----|---|-------------|----|----------------|------------|----------------|
| N  | 1 | 7.1         | 0.34 | 6.0          | 8          | <4.3          |
| N  | 2 | 7.3         | 0.38 | 4.6          | 115        | 5.0           |
| Me | 3 | 5.8         | 0.33 | 3.9          | 110        | <4.3          |
| O  | 4 | 6.9         | 0.38 | 4.1          | 11         | 5.0*          |
| O  | 5 | 7.5         | 0.38 | 5.0          | 9          | <4.3*         |

**Table 3. Benzamide ortho-Position SAR**

| R   | # | BRPF1 pIC50 | Solubility | R   | # | BRPF1 pIC50 | Solubility |
|-----|---|-------------|------------|-----|---|-------------|------------|
| Me  | 5 | 7.5         | 9          | N   | 9 | 6.8         | 3          |
| O   | 6 | 6.9         | 156        | O   | 10| 7.0         | 174        |
| O   | 7 | 7.0         | 19         | N   | 11| 7.0         | 163        |
| O   | 8 | 6.5         | 164        | N   | 12| 6.5         | 187        |

**Table 4. Summary of the Properties of GSK5959**

| Compound | TR-FRET pIC50 | BROMOscan pKd | NanoBRET pIC50 | BRPF 2/3 TR-FRET pIC50 | BRD4 BD1/2 TR-FRET pIC50 | Selectivity | Chrom logDpH5.4 | CLND solubility (μg/mL) |
|----------|---------------|---------------|---------------|----------------------|-------------------------|------------|----------------|---------------------|
| BRPF1    | 7.1           | 8.0           | 6.0           | 5.2/4.5              | <4.3/<4.3               | >90-fold   | 6.0            | 8                   |

**See also Table S1, Supporting Information.**

**See also Table S1, Supporting Information.**

**See also Table S1, Supporting Information.**
The compounds in Table 4 all met the objective for increased solubility relative to 5. However, it was disappointing that the best balance between BRPF1 potency and selectivity over BRD4 BD1 was achieved with the poorly soluble 2-methoxypyridyl 5. Unable to improve upon the 2-methoxybenzamide in the 5-position, we switched our efforts to the benzimidazolone core itself. Inspection of the structure of 1 bound to BRPF1 (Figure 1) suggested it may be possible for a chain possessing a solubilizing group to pass through the channel between Phe714, Asn708, and Tyr707, although the space for such a group was very limited. Extension of the 3-Me to a hydroxethyl (Scheme S3) (26) gave a substantial increase in solubility, but with an unacceptable 40-fold drop in BRPF1 inhibition (Table 5).

As the 3- and 5- positions seemed unproductive we returned to the 6-position of the benzimidazolone. The crystal structure of 1 in complex with BRPF1 (Figure 1) showed the proximity of the backbone carbonyl of Asn651 to the C4 carbon of the piperidine. It was postulated that introduction of a basic nitrogen in this position could pick up an additional hydrogen bond to this carbonyl, while also improving solubility.

To test this hypothesis, compounds 28−31 were synthesized via S_NAr reaction or Suzuki chemistry on an appropriately substituted core (Schemes S4 and S5). The piperazine 28 was well tolerated, delivering the desired improvement in physicochemical properties while maintaining potency at BRPF1 (Table 6). Methylation of the piperazine to give 4-methylpiperazine 29 was slightly detrimental. The C-linked piperidine 30 and 1,2,3,6-tetrahydropyridine 31, however, were significantly less potent, with the sp^3 hybridized carbon being more deleterious than the sp^2. This is in accordance with our previous observation that the 6-H and 6-Me (4) analogues were ~10-fold less active than the 6-OMe (5). Collectively, the results for compounds 1−5, 28, and 30−31 rule out steric demands as the explanation for the reduced inhibition of carbon-linked 6-substituents. Instead, they provide support for the hypothesis put forward in our previous paper that linking hydrophobic groups is detrimental to activity (compare 24 to 4), probably as a result of electrostatic repulsion between the lone pair of the pyridyl nitrogen and the amide carbonyl. This effect would be greater with the 6-OMe (25), explaining the further drop in potency.

Table 4. Modifications at the 5-Position

| R   | # | BRPF1 pIC_{50} | BRD4 BD1 pIC_{50} | Sol | R   | # | BRPF1 pIC_{50} | BRD4 BD1 pIC_{50} | Sol |
|-----|---|----------------|--------------------|-----|-----|---|----------------|--------------------|-----|
| H   | 13| 5.8            | 4.4                | 114 | 19  | 7.2          | 5.0                | 126 |
| N   | 14| 6.0            | <4.3               | 123 | 20  | 5.9          | <4.3               | 154 |
| O   | 15| 5.9            | <4.3               | 145 | 21  | 6.1          | <4.3               | 157 |
| NH  | 16| 6.1            | <4.3               | 135 | 22  | 6.9          | 4.6                | 82  |
| N   | 17| 5.8            | <4.3               | 141 | 23  | 7.5          | 5.1                | 130 |
| OH  | 18| 6.3            | <4.3               | 164 | 24  | 7.0          | 4.4               | 167 |
| O   | 25| 5.7            | <4.3               | 9   | 25  | 5.7          | <4.3               | 167 |

See also Table S1, Supporting Information.

Table 5. Modifications at the N3-Position

| R   | # | BRPF1 pIC_{50} | Solubility (μg/mL) |
|-----|---|----------------|--------------------|
| Me  | 5 | 7.5            | 9                  |
| O   | 26| 5.9            | 187                |

See also Table S1, Supporting Information.
The largest selectivity window over BRPF2 is therefore approximately 160-fold (27 and 28).

Having achieved with 28 acceptable solubility, while maintaining significant BRPF1 inhibition, we next sought to investigate whether improved potency and selectivity was readily achievable. Interrogating the crystal structure of 1 in complex with BRPF1, it was intriguing to note that the 2-position of the piperidine presented a vector toward Pro658 (Figure 2A). This residue is one of the few that are not conserved across the BRPF subfamily, being substituted for Ser592 in BRPF2 or Asn619 in BRPF3. Analysis of the BRPF1 site using GRID probes suggested the potential for favorable interaction with a methyl group in the small indentation in the surface near Pro658 (Figure 2A).20 This hypothesis was first explored with the 2-methyl pyrrolidines 32 and 33. Indeed, a significant increase in BRPF1 inhibition was observed, especially with the (R)-enantiomer, with minimal effect on the inhibition of BRPF2 (Table S1, compare 32 with 27), BRPF3, and BRD4 (Table 6).

Transferring these findings to the more soluble piperazines (34−35) again showed the (R)-enantiomer 34 to be the most potent. The comparatively weaker inhibition with the 2-(S)-enantiomer 35, and 3-methyl enantiomers (36−37), confirm the specificity of this interaction.

Shortly afterward a 2.0 Å crystal structure of the BRPF1 bromodomain in complex with 34 was obtained (Figure 2B). This showed that 34 binds to BRPF1 in a very similar way to 1. As expected, the 2-methylpiperidine occupies the pocket close to Pro658, and the piperazine 4-NH makes a direct hydrogen bond to the backbone carbonyl of Asn651. Overlaying the apo structure of BRPF2 highlights the structural differences between the isoforms, which the 2-methyl substituent is able to exploit.

To facilitate interpretation of phenotypic assays we designed a less active analogue of 34 in which the 5-amide was alkylated, 38 (Scheme S5, GSK9311). We reasoned that this would prevent the 5-aryl group from adopting the conformation observed in the structures of 1 and 34 because of the loss of all internal hydrogen-bonding interactions, and steric clashes between the amide N-alkyl group and both the piperazine and the o-methoxy substituents. Usefully, this change resulted in a 100-fold drop in BRPF1 inhibition. This result can be rationalized by a crystal structure of 38 in BRPF1 in which the benzamide group packs poorly against P658 and E661 (Figure 3).

### Table 6. Modifications at the 6-Position

| R   | pIC₅₀ | Solb | R   | pIC₅₀ | Solb |
|-----|-------|------|-----|-------|------|
|     | BRPF1| BRD4| BD1|     | BRPF1| BRD4| BD1|
| 27  | 7.3   | <4.3 | 72  | 1     | 7.1  | <4.3 | 8   |
| 28  | 7.1   | <4.3 | 135 | 29    | 6.7  | <4.3 | 149 |
| 30  | 5.5   | <4.3 | 107 | 31    | 5.9  | <4.3 | 110 |
| 32  | 8.3   | 5.0  | 4   | 33    | 7.8  | 4.9  | 3   |
| 34  | 8.1   | 4.7  | 140 | 35    | 6.9  | <4.3 | 134 |
| 36  | 7.1   | <4.3 | 141 | 37    | 6.9  | 4.7  | 139 |

aSee also Table S1, Supporting Information. bCLND (μg/mL).

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(Branch S1). The largest selectivity window over BRPF2 is therefore approximately 160-fold (27 and 28).

![Figure 2. (A) GRID map analysis using the BRPF1 structure of compound 1 (PDB 4UYE). Methyl probe is shown in orange mesh. (B). X-ray structure of BRPF1 (cyan, PDB 5G4R) with 34, overlaid with BRPF2 apo (magenta, PDB 3RCW).](image)

![Figure 3. X-ray structures of BRPF1 with 34 (cyan, PDB 5G4R) and 38 (magenta, PDB 5G4S).](image)
Compound 34 was tested in the BROMOscan panel of bromodomain binding assays (DiscoveRx). Consistent with the data above, it showed excellent BRPF1 potency (pIC\textsubscript{50} 9.5) and greater than 1600-fold selectivity over all other bromodomains tested (Table S2). To our knowledge this is the most potent and selective inhibitor of any single bromodomain reported to date.

All biochemical data presented thus far was determined using recombinant, truncated bromodomains. Potent binding to full-length endogenous BRPF1 (pIC\textsubscript{50} 8.6) was confirmed in a chemoproteomic competition binding assay using pull-down of lysate from HuT-78 cells followed by immuno readout (Figure S4). Selectivity over endogenous BRD3 was also shown.

![Figure 4. Potency for endogenous cellular BRPF1. pIC\textsubscript{50} of 34 for BRPF1 and BRD3 measured in a chemoproteomic competition binding assay (Supplementary Methods, Supporting Information).](image)

Table 7. Summary of Properties of Compound 34a

| Compound   | TR-FRET pIC\textsubscript{50} | BROMOscan pIC\textsubscript{50} | NanoBRET pIC\textsubscript{50} |
|------------|-------------------------------|-------------------------------|-------------------------------|
| BRPF1      | 8.1                           | 9.5                           | 7.7                           |
| BRPF 2/3   | 5.1/4.8                       |                               |                               |
| BRD4 BD1/2 | 4.7/4.3                       |                               |                               |
| selectivity | BROMOscan                     |                               |                               |
|            | >1600-fold                     |                               |                               |

Chrom logD\textsubscript{pH 7.4} 2.0
CLND solubility (μg/mL) 140
iv Clb (mL/min/kg)/t\textsubscript{1/2} (h) 107/1.7
F% ip/po (3 mg/kg) 85/22

aSee also Table S1, Supporting Information. bPromega Corp., Figure S5. cDiscoveRx Corp., Table S2.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00092.

Synthetic procedures, analytical data, methods, Figures S1–S7, and Tables S1–S3 (PDF)

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Notes
The authors declare no competing financial interest.

Biographies
Armelle Le Gall gained her MSc in Chemoinformatics from the University of Sheffield, U.K. After graduating, she joined GSK, where she is currently an Investigator in the Molecular Design department. She has been mainly involved in medicinal chemistry projects in the Respiratory and Immuno-Inflammation Therapeutic areas. Most recently, her research has focused on structure-based drug design, in particular, including protein flexibility, and also high throughput screening data analysis.

Robert J. Sheppard graduated with a degree in Chemistry from the University of Oxford in 1997. After joining SmithKline Beecham he worked on the design and synthesis of novel antibacterial agents targeting tRNA synthetases, bacterial topoisomerase, and the ribosome. In 2009 he moved to GSK’s Epinova Discovery Performance Unit as a team leader focused on developing inhibitors of epigenetic proteins including demethylases, deiminases, and bromodomains. Robert moved to AstraZeneca’s Oncology iMED in 2015 where he maintains a strong interest in the role of epigenetics in cancer and immuno-oncology. He represents AstraZeneca in the Kinetics for Drug Discovery Innovative Medicines Initiative.

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**ABBREVIATIONS**

CLND, ChemiLuminescent Nitrogen Detection; LE, ligand efficiency; KAc, acetyl-lysine; Sol, solubility

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