Discovery of a novel allosteric inhibitor scaffold for polyadenosine-diphosphate-ribose polymerase 14 (PARP14) macrodomain 2

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Abstract

The polyadenosine-diphosphate-ribose polymerase 14 (PARP14) has been implicated in DNA damage response pathways for homologous recombination. PARP14 contains three (ADP ribose binding) macrodomains (MD) whose exact contribution to overall PARP14 function in pathology remains unclear. A medium throughput screen led to the identification of N-(2-(-9H-carbazol-1-yl)phenyl)acetamide (GeA-69, 1) as a novel allosteric PARP14 MD2 (second MD of PARP14) inhibitor. We herein report medicinal chemistry around this novel chemotype to afford a sub-micromolar PARP14 MD2 inhibitor. This chemical series provides a novel starting point for further development of PARP14 chemical probes.

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1. Introduction

Poly-(ADP ribose) Polymerases (PARPs) are ADP-ribosyl transferase enzymes which post-translationally modify substrate proteins.1 Of at least 17 human family members of PARPs a sub-set, referred to as mono(ADP-ribosyl)transferase (mARTs), are capable of transferring on a single ADP unit to a given substrate.2 PARP14 (ARTD8) is the largest of the mARTs and contains multiple domains including an ADP ribose transferase domain (ART), a WWE domain, two (RNA binding) RRM repeats and three (ADP-ribose binding) macrodomains.3 PARP14 was found to be highly expressed in B-cell lymphoma and hepatocellular carcinoma and has been associated with poor patient prognosis.4 Furthermore PARP14 has been linked to inhibition of pro-apoptotic kinase JNK1 which activates pyruvate kinase M2 isozform (PKM2) which in turn promotes a higher rate of glycolysis in cancer (Warburg effect)5 shown in some contexts to be regulated by high MYC expression.6 Despite links with cancer pathogenesis5,7 and inflammatory diseases,1b,c,7,8 only a few small molecule PARP14 inhibitors have been reported and many have suffered from a lack of selectivity.9 Most examples of PARP inhibitors have targeted the catalytic domain (ART)10 such as a recent example by Upton and coworkers who identified moderateselective PARP14 inhibitors,10e however to date no PARP14 modulators targeting other domains such as the macrodomains have been reported until recently.11

PARP14 contains three macrodomain modules (MD1, MD2 and MD3); biophysical characterisation of macrodomain:ADP-ribose peptide binding was carried out revealing MD2 as the most potent ADP ribosyl peptide binding domain and therefore the most likely to deliver a functional effect through small molecule inhibition (PARP14 MD1/ADP-ribose peptide KD 137 ± 7 μM, PARP14 MD2/ ADP-ribose peptide KD 6.8 ± 0.1 μM, PARP14 MD3/ADP-ribose peptide KD 15 ± 0.9 μM, Supp. Info Fig. 1 (Fig. 1).
An initial medium throughput screen (~50 k compounds) revealed compound GeA-69 (1) as a sub-micromolar inhibitor of PARP14 MD2 ADP-ribose binding as measured by AlphaScreen™, ITC and BLI. A co-crystal structure of closely related sulfonamide derivative 2 with PARP14 MD2, which was obtained in the course of the project revealed a unique allosteric binding mode for this inhibitor (PDB ID 502D). Overlay of this structure with bound ADP-ribose from a previously published co-crystal structure of PARP14 MD2 (PDB ID 3Q71) showed that compound 2 occupied a novel pocket adjacent to the binding site for ADP-ribose (Fig. 2A). Evaluation of the co-crystal structure of carbazole 2 with PARP14 MD2 also revealed the possibility of extending the methanesulfonamide motif into larger substituents exploring peripheral regions of this newly identified allosteric site.

2. Results

2.1. Systematic SAR studies of screening hit GeA-69 (1)

The screening hit GeA-69 (1) was part of a focused library from the Bracher lab, originally designed for the improvement of kinase inhibitors derived from the 1-(aminopyrimidyl)-β-carboline alkaloid annomontine. The SAR studies on screening hit GeA-69 (1) are described in the following compound library generated as potential PARP14 MD2 inhibitors (Fig. 3). In this library, the β-carboline ring system was replaced by its deaza analogue carbazole, and a number of aromatic and heteroaromatic rings were attached to position 1 (Scheme 1) using Suzuki-Miyaura cross coupling reactions of known 1-bromocarbazole with commercially available or synthesised boronic acids and esters to give compounds 3–12 (Scheme 1).

- Pyridyl compound 13 and 4-pyrimidyl analogue 14 were obtained by regioselective nucleophilic addition of 1,9-dilithiated carbazole (obtained in situ from 1-bromocarbazole and 4 equiv. tert-butyl lithium) to pyridine and pyrimidine, followed by spontaneous rearomatisation during workup. The obtained (hetero)aryl-carbazoles are shown in Fig. 4.

Unfortunately none of these analogues (compounds 3–14) showed any inhibition of PARP14 MD2. Only a few further modifications of the 1-aryl substituent were performed, whereby all new compounds contained the acetylamino moiety, which was recognised as important for activity in this early stage of the project.

The aza analogue 15 was obtained from N-SEM protected 1-bromocarbazole by Masuda borylation at C-1, directly followed by Suzuki-Miyaura cross-coupling with 4-amino-3-bromopyridine, subsequent N-acetylation and SEM deprotection, as previously described. This compound has virtually identical size as the active compound 1, but interestingly was found to be completely inactive at inhibiting PARP14 MD2 presumably due to the differences in electronics of both molecules. Consequently, this compound could serve as a useful negative control in biochemical experiments. The pyridyl-isomers 16 and 17 were obtained in the same manner using 3-amino-2-chloro- and 3-amino-4-chloropyridine in the cross-coupling reaction (Fig. 5). Furthermore, using Suzuki-Miyaura cross-coupling reactions, the acetylaminophenyl residue was attached to position 1 (Scheme 1) of the β-carboline ring system in order to obtain a ring A aza-analogue 18 and to the canthin-4-one 19 and desaza-canthin-4-one 20 ring systems in order to give analogues bearing tetracyclic core structures (Fig. 5).

An analogue of GeA-69 (1) with the acetamido group shifted from the ortho to the meta position at the phenyl ring was prepared by Suzuki-Miyaura cross-coupling of 1-bromocarbazole with 3-aminophenyl boronic acid, followed by N-acetylation. Additionally, the complete acetylaminophenyl residue was shifted from C-1 to N-9, whereby in one example a rigid isomer 22 was obtained.

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Figure 1. Initial hit PARP14 MD2 inhibitor GeA-69 (1) and sulfonamide analogue 2.

Figure 2. (A) Overlay of bound ADPR (Green sticks) (PDB ID 3Q71) superimposed with PARP14 MD2 (cyan sheets and helices, grey loops): compound 2 (yellow sticks) structure (PDB ID 502D). (B) H-Bonding displayed in co-crystal structure of PARP14 MD2 (cyan sticks): compound 2 (yellow sticks) structure (PDB ID 502D).

Figure 3. SAR studies of carbazoles GeA-69 (1) and 2.
and in the other, by means of a methylene spacer, a product 23 in which by appropriate rotation both the phenyl and the acetamido group can adopt positions that are very similar to those these groups have in the lead structure GeA-69 (1). Compound 22 was obtained by N-arylation of carbazole with 2-fluoro-1-nitrobenzene, subsequent reduction of the nitro group, and N-acetylation. N-Benzyl analogue 23 was prepared in an analogous manner via N-alkylation of carbazole with 3-nitrobenzyl chloride (Fig. 6).

As modifications of the central pyrrole ring (ring B) of GeA-69 (1) N-methyl and N-benzyl analogues 24 and 25 were prepared starting from corresponding N-substituted 1-bromocarbazoles via Suzuki-Miyaura cross-coupling with 2-aminophenylboronic acid and subsequent N-acetylation. Dibenzofuran analogue 26 and dibenzothiophene analogue 27 were obtained in a similar manner from commercially available 4-bromodibenzofuran and known 4-iododibenzothiophene (Fig. 7). These experiments were performed before we obtained the crystal structure of PARP14 MD2 with inhibitor 2, which demonstrated the relevance of the pyrrole NH-group (Fig. 2).

In order to replace the NH group of ring B with either an alternative hydrogen bond donor (hydroxy group) or a hydrogen bond acceptor (carbonyl group), known 1-iodofluorenone 19 was coupled
in the established manner to give the 1-arylfluorenone 28, which was easily reduced to the racemic fluorenol 29 with sodium borohydride (Fig. 7).

Controlled mono-acetylation of 2,2'-diaminobiphenyl with equimolar amounts of acetic anhydride gave monoamide 30 in moderate yield. Monoamide 30 was then used to access the seco analogue 31 and the acridone analogue 33. Buchwald-Hartwig arylation of the unsubstituted anilino group with iodobenzene to give biaryl 31 and with methyl 2-iodobenzoate to give biaryl 32, respectively, was accomplished with the BINAP/Pd$_2$(dba)$_3$ catalyst system. Ester 32 was hydrolysed to give the corresponding carboxylic acid, which was converted into the acridone 33 by polyphosphoric acid-mediated intramolecular acylation (Scheme 2).

Further, a series of modifications of ring A was performed. Ring-substituted analogues 37–39 were obtained in two steps from readily available 1,2,3,4-tetrahydrocarbazol-1-ones 34–36 in two steps. Treatment of the ketones with POBr$_3$ in anisole gave the corresponding 1-bromocarbazoles under bromination/dehydrogenation conditions in moderate to poor yields. Subsequent Suzuki-Miyaura cross-coupling gave the desired arylcarbazoles 37–39 (Scheme 3).

8-Aza analogue 43 was obtained by a series of three consecutive Pd-catalyzed coupling reactions. Chemoselective Buchwald-Hartwig amination of 1-bromo-2-iodobenzene with 2-amino-3-bromopyridine 40 using XantPhos as a ligand gave phenylaminopyridine 41, which was cyclised to 8-bromo-α-carboline 42 using CyJohnPhos in an intramolecular Heck coupling. Finally, the acetylamidophenyl residue was introduced in a standard Suzuki-Miyaura cross-coupling (Scheme 4).

Analogue 44 bearing a partially hydrogenated A-ring was obtained from the corresponding brominated tetrahydrocarbazole 23 via Suzuki-Miyaura cross-coupling. A truncated analogue, the 7-aryl-3-isopropylindole 45, in which ring C is replaced by an isopropyl group, was obtained by Suzuki-Miyaura cross-coupling of the respective 7-bromoindole. The 6-aza-5,6,7,8-tetrahydro analogue 47 was prepared in a similar manner from known intermediate 46. Improved yields were obtained, if the secondary amine was protected with the Boc group prior to the cross-coupling reaction (Scheme 5).

Finally, modifications of the acetamido group located at the 1-phenyl substituent (ring D) were performed. Aminophenyl intermediate 48 was further converted into the urea analogue 49 by Pd-catalysed cross-coupling with 2-bromo-3,3,3-trifluoro-1-propene; subsequent reduction with sodium borohydride gave the racemic target compound 51. Treatment with tert-butyl isocyanate (Scheme 6). Since α-trifluoroethylamines are known as bioisosteres of amide groups from peptide chemistry, we also prepared compound 51 for SAR studies. Intermediate 48 was thus converted into 1,1,1-trifluoro-propan-2-imine 50 by Pd-catalysed cross-coupling with 2-bromo-3,3,3-trifluoro-1-propene; subsequent reduction with sodium borohydride gave the racemic target compound 51.

Figure 7. Analogues of GeA-69 (1) bearing substituents at N-9, as well as dibenzofuran (26), dibenzothiophene (27), fluorenone (28), and fluorenol (29) analogues.

Scheme 2. Synthesis of seco analogue 31 and acridone analogue 33.

Scheme 3. Synthesis of analogues of GeA-69 (1) bearing additional substituents at ring A.
Scheme 5. Analogues of GeA-69 (1) with partially hydrogenated or truncated ring A.

Scheme 6. Variations of the acetamide group (thioamide 52, reduced N-ethylamine 53, N-ethyl analogue 54, urea analogue 49). Synthesis of the proposed amide bioisoster 51 from aniline 48.

A screening of the above presented compounds on PARP14 MD2 clearly demonstrated that lead structure GeA-69 (1) is very sensitive to structural modifications. Carbazoles bearing (hetero)aromatic residues different from the acetylaminophenyl residue of GeA-69 (1) (Figure 4) were found to be inactive. Analogues with almost identical shape albeit very different electronically (aza analogues in the rings A, C and D) are completely or virtually (β-carboline 18, IC₅₀ 30 μM) inactive. Any changes in the central pyrrole ring (ring B) eliminated inhibitory activity as well. The NH group was found to be essential, it can not be replaced by another hydrogen bond donor, as demonstrated by the inactive fluorenol analogue, 29. Surprisingly, the dibenzothiophene analogue 27 showed considerable inhibition (IC₅₀ 2.5 μM), whereas the dibenzofuran, 26 and the acidnone, 33 were inactive. The same holds for the (deaza)compounds having tetracyclic canthin-4-one backbones (canthin-4-one 19, deazacanthin-4-one 20). The seco analogue of GeA-69 (1), biaryl 31, was completely inactive, demonstrating that not only the presence of the functional groups of the lead structure, but also their fixation by the carbazole backbone is most important.

The tetrahydro-analogue 44 showed only a slight loss in activity (IC₅₀ 1.1 μM) compared to GeA-69 (1), whereas its 6-aza analogue 47 bearing a polar aliphatic amino group in ring A, was inactive. Lipophilic chlorine substituents at ring A (compounds 37–38) were fairly tolerated (IC₅₀ 1.4 and 3.0 μM), but the 6-methoxyl analogue 39 was inactive. These observations can be rationalised by the hydrophobic environment in the binding region of ring A consisting of residues V1032, V1092, M1108, I111, I1112, F1129, I1132 (Fig. 2).

Removal of the N-acetyl residue from GeA-69 (1), conversion of the acetamide into a tert-amide 54 or into the proposed trifluoroalkyl bioisoster 51, as well as reduction of the amide moiety to an amine 53 resulted in complete loss of activity, the thioamide 52 was an order of magnitude less active (IC₅₀ 10.5 μM) than GeA-69 (1).

In conclusion, these data confirm a very narrow structure–activity relationship for rings A-C (Fig. 3), and for further optimisation of the screening hit GeA-69 (1) only modifications of either the N-acyl residue or ring D were deemed promising.

2.2. SAR studies of ring D and N-acyl residues

Initial construction of the carbazole series was performed using 1-bromo-9H-carbazole and a series of pinacol boronic esters which were coupled under standard Suzuki-Miyaura conditions, furnishing biaryl products in moderate to good yields (Scheme 1). A number of these compounds were then converted to the corresponding acetamides or methanesulfonamides and profiled for their binding activity with PARP14 MD2. Whilst binding activity was not improved, additional substituents on ring D such as methyl, fluoro and cyano were tolerated maintaining single digit μM activity (compounds 55–57, Table 1). As previously observed a comparison of these compounds with the inactive non-acetylated and non-sulfonylated anilines (eg compounds 59–61, Table 1) showed the requirement of this group for binding activity.

Further modification of biaryl-amide 48 to the corresponding amides or sulfonamides (Scheme 7) was carried out. The corresponding amides and sulfonamides 62–108 were then profiled for their PARP14 MD2 binding affinity (Tables 1 and 2).

Compounds were profiled for binding activity with PARP14 MD2 through a competitive (AlphaScreen™) binding assay measuring the displacement of ADP-ribose peptide from PARP14 MD2. Promising compounds were additionally profiled by biophysical assays such as Bio-Layer Interferometry or Isothermal Titration Calorimetry as previously described.²

As previously described the parent carbazole GeA-69 (1) was profiled for its broader selectivity over 12 other human macrodomains, showing exquisite selectivity for MD2 of PARP14.² Furthermore a representative selectivity screen of 46 kinases in a Differential Scanning Calorimetry assay did not reveal any significant activity of carbazole GeA-69 (1) at 10 μM.²

3. Discussion

The binding activities of synthesised PARP14 MD2 inhibitors are summarised in Tables 1 and 2. Despite comprehensive SAR studies of the A-C rings of this carbazole series, no points for the development of more potent ligands were discovered, a number of derivat-
tives were synthesised functionalising ring D (Figure 3). Only small additional substituents to the ring were tolerated (e.g. compounds 55–57, Table 1). Interestingly, elaboration of the sulfonamide in compound 2 into the homologated ethane-, propane- and butane-sulfonamides analogues (compounds 62–64, Table 1) furnished equipotent compounds. Further elaboration of the acetamide in GeA-69 (1) mostly retained single digit μM binding activity (eg compounds 66,67). Interestingly the n-pentanoyl analogue 68 was seemingly inactive, which may be due the entropic penalty associated with longer alkyl substituents or a steric clash with the protein. However, guided by the apparent tolerance of some larger substituents in place of the acetamide in GeA-69 (1) and methanesulfonamide in compound 2, the 2-phenylacetamide and phenylmethanesulfonamide of compounds 78 and 79 (IC50 7.6 ± 0.3 and 3.6 ± 0.3 μM respectively, Table 1) were chosen for further development as they enabled rapid access to diversity and provide a suitable vector for binding pocket exploration. A number of hetero- and substituted- aromatics were appended onto the biaryl core (examples 83–108, Table 2). Moderately flat SAR was observed for both 2- and 4- substituted phenylacetyl and phenylmethanesulfonamide groups. It was found that introduction of a 3-cyano substituent in the phenylmethanesulfonamide series provided a slight improvement in binding activity compared with GeA-69 (1). Carbazole 108 displays sub-micromolar activity for

### Table 1

| R  | R′ | IC50 (μM) | KD (μM) |
|----|----|-----------|---------|
| H  | C  | 0.72 ± 0.04 | 0.86 ± 0.04 |

Table 2

| R/Het | X | IC50 (μM) | KD (μM) |
|-------|---|-----------|---------|
| 3-aza | C | 1.1 | 1.5 |
| 3-aza-4-Me | C | 1.0 | 2.7 |
| 3, 6-aza | C | 2.1 ± 0.1 | 3.9 |
| 4-aza-3-CN | C | 2.4 ± 0.2 | n.d. |
| 3-aza-4-CN | C | 3.5 ± 0.2 | n.d. |
| 3-aza-4-OH | C | 6.4 ± 0.4 | n.d. |
| 2-F | SO | 2.4 ± 0.1 | n.d. |
| 3-OMe | C | 6.6 ± 0.5 | n.d. |
| 4-Me | SO | 8.7 ± 1.2 | n.d. |
| 3-CF3 | SO | 7.1 ± 0.7 |
| 4-CN | SO | 6.2 ± 0.6 | n.d. |

* No error of fit obtained for these KD values. n.d. denotes not determined.
Inhibitory activity can be rationalised through a PARP14 MD2 co-crystal of a similar derivative, sulfonamide 2 (PDB ID 5O2D). Investigation into this carbazole series was then made revealing new opportunities for ligand elaboration. Systematic analysis of SAR demonstrated a very narrow structure activity relationship for rings A–C (carbazole scaffold), and for further optimisation of the screening hit 1 only modifications of either the N-acyl residue or ring D showed promise. A number of carbazole containing compounds were tolerated in this newly identified allosteric site of PARP14 MD2 including a 3–cyano substituted phenylmethanesulfonamide 108. Carbazole 108 displays submicromolar activity binding to PARP14 MD2 by AlphaScreen (IC₅₀ 0.66 μM) which was also confirmed by BLI (Kₒ 0.55 μM). This lead molecule along with others in this series are useful chemical starting points in the development of chemical probes for this poorly understood epigenetic target.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmc.2018.03.020.

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