Design, Synthesis, and Evaluation in Vitro of Quinoline-8-carboxamides, a New Class of Poly(adenosine-diphosphate-ribose)polymerase-1 (PARP-1) Inhibitor

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Poly(ADP-ribose)polymerase-1 is an important target enzyme in drug design; inhibitors have a wide variety of therapeutic activities. A series of quinoline-8-carboxamides was designed to maintain the required pharmacophore conformation through an intramolecular hydrogen bond. 3-Substituted quinoline-8-carboxamides were synthesized by Pd-catalyzed couplings (Suzuki, Sonogashira, Stille) to 3-iodoquinoline-8-carboxamide, an efficient process that introduces diversity in the final step. 2-Substituted quinoline-8-carboxamides were prepared by selective Pd-catalyzed couplings at the 2-position of 2,8-dibromoquinoline, followed by lithium−bromine exchange of the intermediate 2-(alkyl/aryl)-8-bromoquinolines and reaction with trimethylsilyl isocyanate. The intramolecular hydrogen bond was confirmed by X-ray and by NMR. The SAR of the 3-substituted compounds for inhibition of human recombinant PARP-1 activity showed a requirement for a small narrow group. Substituents in the 2-position increased potency, with the most active 2-methylquinoline-8-carboxamide having IC_{50} = 500 nM (IC_{50} = 1.8 μM for 5-aminoisoquinolin-1-one (5-AIQ, a standard water-soluble inhibitor)).

Introduction

Poly(ADP-ribose) polymerase-1 (PARP-1[a]) is a multifunctional enzyme present in eukaryotic cells and is the major isoform of an expanding family of poly(ADP-ribose) polymerases (PARPs).[1−4] The enzyme is predominantly found in the nucleus, where it is tightly bound to the chromatin. PARP-1 is involved in locating and repairing single and double DNA strand breaks. PARP-1, upon activation by a DNA strand break, catalyzes the transfer of ADP-ribose units from its substrate nicotinamide adenine dinucleotide (NAD^+) to nuclear acceptor proteins such as histones, topoisomerases, DNA polymerases, DNA ligases, and PARP-1 itself. Current research has implicated PARP-1 activity in areas such as DNA replication, differentiation, sister chromatid exchange, cellular proliferation, and cell death. DNA damage is the most important element in the regulation of poly(ADP-ribosyl)ation reactions. During PARP-1 automodification, the enzyme progressively becomes more negatively charged, resulting in electrostatic repulsion between DNA and the ADP-ribose polymers linked to the enzyme. This leads to the release of the automodified PARP-1 from the DNA strand break and subsequent inactivation of the enzyme. This exposes the damaged site of DNA to repair processes. When DNA is moderately damaged, PARP-1 participates in DNA repair processes and the cell survives. However, in the case of extensive DNA damage PARP-1 overactivation occurs. This leads to a rapid depletion of NAD^+ and ATP levels. The cell then attempts to resynthesise NAD^+, resulting in energy crisis and, ultimately, cell death by necrosis.[5]

Inhibitors of PARP-1 activity could be predicted to exhibit a wide range of therapeutic activities, and this prediction is borne out in many studies. Inhibition of PARP-1 potentiates radiotherapy of cancer by preventing repair of radiation-induced DNA damage.[6,7] Since many conventional cancer chemotherapeutic drugs act, at least in part, by damaging DNA, inhibition of PARP-1 activity is also effective in potentiating the therapeutic actions of these cytotoxins.[8−12] Moreover, there are recent indications that PARP-1 inhibitors may have activity against cancer as single agents in BRCA-2-deficient tumors.[13,14] PARP-1 inhibitors have also shown beneficial activities in models of a wide range of ischemia−reperfusion disorders and inflammatory diseases, including hemorrhagic shock,[15] myocardial infarction and other heart disease,[16−18] inflammatory lung disorders,[19,20] ischemic kidney disease,[21] colitis,[22] spinal cord trauma,[23] stroke,[24,25] ischemic liver disease,[26] organ transplantation,[27,28] and asthma.[29]

The consensus pharmacophore for inhibition of PARP-1,[2] developed by classical structure−activity relationship (SAR) studies and by modeling using the X-ray crystal structure of the catalytic (NAD^+-binding) domain,[9] is a primary or secondary benzamide, with the amide N−H and carbonyl conformationally constrained relative to the benzene ring (**1**, Figure 1). This pharmacophore makes important hydrogen bonds with Gly863 (N−H to Gly C=O and C=O to Gly N−H) and with Ser904 (C=O to Ser O−H) and π-stacks with Tyr907 and, to some extent, with Tyr896 in the PARP-1 structure. The first selective inhibitor, 3-aminobenzamide,[30] lacked this conformational constraint and thus had only modest potency. Potency is increased by incorporating the amide into a lactam ring, i.e., constraining its conformation by linking back to the benzene ring through covalent bonds. Thus, 2-substituted quinazolin-4-ones,[31] 5-substituted isoquinolin-1-ones **2**[7] (including the highly water-soluble inhibitor **3** (5-AIQ)),[15,16,19−23,32] 5-substituted 3,4-dihydroisoquinolin-1-ones,[7] the 4-benzylphthalazin-1-ones **4**,[33,34] and the tricyclic lactams **5**[8,9] all have IC_{50} values some 10-fold to 1000-fold lower. An alternative approach to constraining the

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[a] Abbreviations: PARP, poly(ADP ribose)polymerase; ADP, adenosine diphosphate ribose; SAR, structure−activity relationship; NAD^+, nicotinamide adenine dinucleotide; DNA, deoxyribonucleic acid; ATP, adenosine triphosphate ribose; BRCA, breast cancer syndrome locus; THF, tetrahydrofuran; DMF, dimethylformamide; NMP, *N*-methylpyrrolidin-2-one; dba, dibenzylideneacetone; S-Phos: 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine; $\Delta\delta$, difference in NMR chemical shift.

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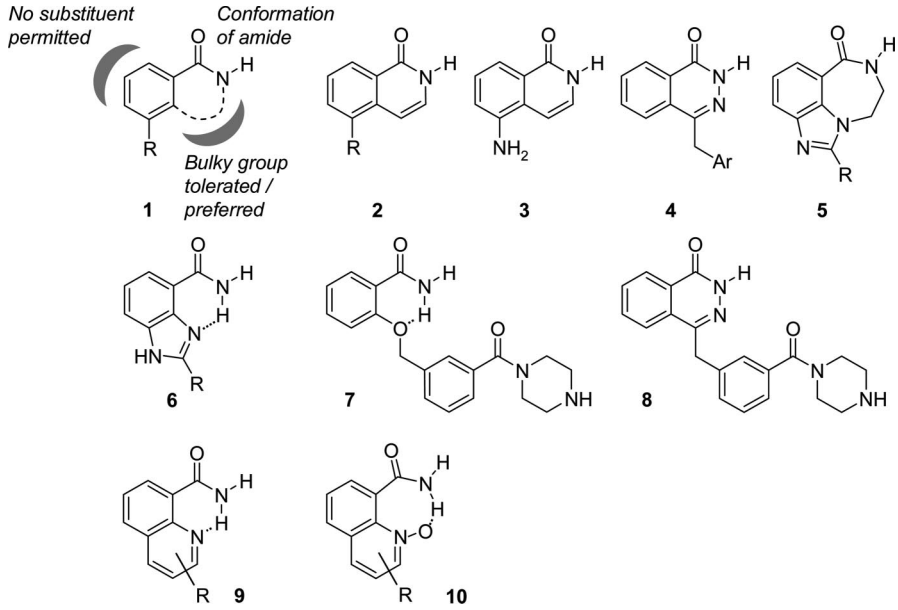
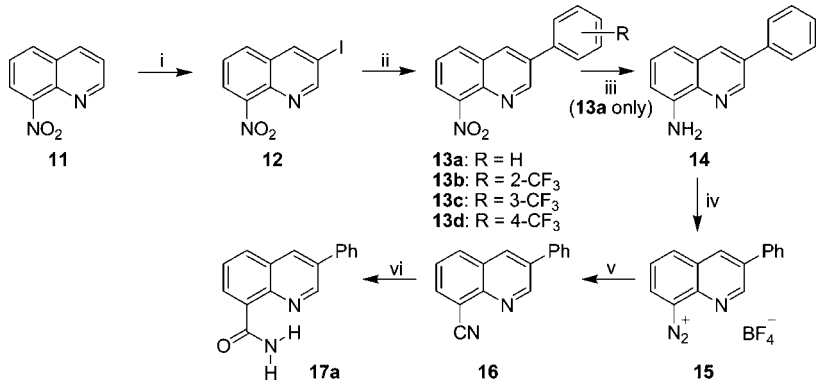


Figure 1. Structures of the consensus pharmacophore for PARP-1 inhibition **1**, of types of potent inhibitor **2**−**8**, and of the designed quinoline-8-carboxamide inhibitors. Compound **3** is the potent water-soluble inhibitor 5-aminoisoquinolin-1-one. The correct conformation of the carboxamide is held in a covalently bonded ring in **2**−**5** and **8** but by intramolecular hydrogen bonding in **6**, **7**, **9**, and **10**.

Scheme 1. Synthetic Approaches to 3-Substituted Quinoline-8-carboxamides via Couplings to 3-Iodo-8-nitroquinoline **12**[a]



[a] Reagents: (i) *N*-iodosuccinimide, AcOH, Δ; (ii) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, PhMe, EtOH, water, Δ; (iii) $SnCl_2$, EtOH; (iv) $NaNO_2$, aqueous HBF_4; (v) CuCN, KCN, water; (vi) NaOH, H_2O_2, EtOH.

amide is to use an intramolecular hydrogen bond to hold one N—H of a primary amide. The 2-substituted benzimidazole-4-carboxamides **6** exploit this approach, using effectively a 6:6:5 ring system.[35] Very recently, the KuDOS group has disclosed[36] the 2-(substituted-benzyl)oxybenzamides as potent inhibitors of PARP-1 activity, in which the intramolecular hydrogen bond is from the amide N—H to the adjacent ether oxygen. These compounds retain much of the potency of the analogous phthalazinones, **7** being only 9-fold less active than **8**. Iwashita et al. disclosed a limited series of quinoxaline-5-carboxamides with some PARP-1 inhibitory activity.[31,37]

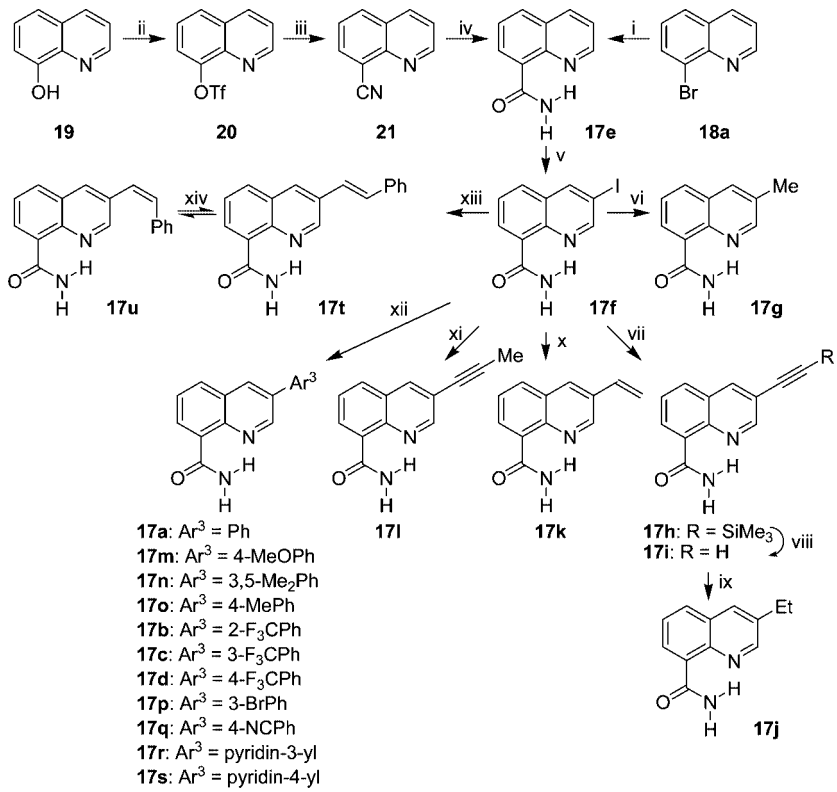
This approach was exploited by us in our design of a new series of inhibitors, the quinoline-8-carboxamides **9** (Figure 1). In this ring system, the lone pair of the heterocyclic nitrogen is perfectly located to form a strong intramolecular hydrogen bond with the primary amide N—H; this lone pair is directed straight toward the hydrogen. Moreover, this hydrogen bond should be particularly strong, as it is located within a completely unstrained 6:6:6 tricyclic system rather than the 6:6:5 system of **6** or the more flexible 6:6 system of **7**. Preliminary rational drug design, using the crystal structure of the catalytic domain of chicken PARP-1,[38] suggested that lipophilic substituents should be placed in the 3-position or the 2-position of the quinoline to interact with a hydrophobic pocket. The *N*-oxide **10** was also designed to test the utility of holding the amide through a hydrogen bond in a seven-membered ring.

Chemical Synthesis

Two series of quinoline-8-carboxamides **9** were designed, carrying alkyl, alkenyl, alkynyl, and aryl substituents at the 2- and 3-positions of the heterocycle. One *N*-oxide **10** was also a target for synthesis. The synthetic strategies for the two series were different, but each relied on introducing the diverse substituents in a late step through palladium-catalyzed couplings to maximize efficiency in the preparation of the candidate inhibitors. Clearly, approaches involving construction of the heterocycle with substituents already in place would be highly inefficient, particularly as many of the known methods for forming quinolines require drastic conditions and are low yielding.[39]

Scheme 1 shows the initial approach to the 3-substituted quinoline-8-carboxamides. In this route, the 3-substituent is introduced by Pd-catalyzed coupling to 3-iodo-8-nitroquinoline **12**. The 8-carboxamide is then incorporated in four steps by

Scheme 2. Synthetic Route to 3-Substituted Quinoline-8-carboxamides, Designed for Introduction of Diversity in the Final Step (Pd-Catalyzed Stille, Sonogashira, and Suzuki Couplings of **17f**)[a]



[a] Reagents: (i) BuLi, THF, −78 °C, then Me_3SiNCO, 20 °C; (ii) Tf_2O, pyridine; (iii) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, Δ; (iv) NaOH, H_2O_2, EtOH, H_2O; (v) *N*-iodosuccinimide, $FeCl_3$, AcOH, Δ; (vi) Me_4Sn, $Pd(PPh_3)_4$, NMP, Δ; (vii) $Me_3SiC{\equiv}CH$, $(PPh_3)_2PdCl_2$, CuI, $^iPr_2NH$, THF; (viii) AgOTf, $CHCl_3$, MeOH, water, Δ; (ix) H_2, Pd/C, DMF, MeOH; (x) $Bu_3SnCH{=}CH_2$, Pd_2dba_3, Ph_3P, CuI, NMP, Δ; (xi) $Bu_3SnC{\equiv}CMe$, $Pd(PPh_3)_4$, NMP, Δ; (xii) $Ar^3B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, PhMe, EtOH, water, Δ or $Ar^3B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, THF, water, Δ or $Ar^3B(OH)_2$, $Pd(OAc)_2$, S-Phos, K_3PO_4, PhMe, Δ; (xiii) *E*-$PhCH{=}CHB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, PhMe, EtOH, water, Δ; (xiv) *hν*, MeOH.

reduction of the nitro group, diazotization, Sandmeyer reaction, and hydration of the resulting 8-cyano group. Iodination of commercially available 8-nitroquinoline **11** with *N*-iodosuccinimide in hot acetic acid gave the important intermediate **12** in satisfactory yield; other electrophilic iodinating systems were less effective, particularly those using the much less expensive molecular iodine. To investigate the potential of this compound for Pd-catalyzed couplings, it was treated with phenylboronic acid and with the three isomeric trifluoromethylphenylboronic acids under conventional Suzuki coupling conditions (tetrakis(triphenylphosphine)palladium, sodium carbonate) in a two-phase solvent system of toluene and water to give the corresponding 3-aryl-8-nitroquinolines **13a**−**d** in very high yields. The 3-phenyl example **13a** was then taken forward in a series of experiments to test the feasibility of and to optimize the replacement of the 8-nitro group with the required carboxamide. The reduction of the nitro group to the amine required the use of tin(II) chloride, and the amine **14** was isolated in 82% yield after some optimization. However, all attempts to introduce the one-carbon unit at the 8-position by one-pot diazotisation/Sandmeyer reaction failed, reflecting the failure reported by Fieser and Herschberg[40] to form 8-cyanoquinoline from quinolin-8-amine. It was necessary to isolate and dry the diazonium compound as its tetrafluoroborate salt **15** before reaction with copper(I) cyanide in a separate step to be able to obtain the required 8-cyano-3-phenylquinoline **16** in modest yield over the two steps. Hydration of the nitrile with the mild hydrogen peroxide/sodium hydroxide system[32] was then straightforward in affording the required 3-phenylquinoline-8-carboxamide **17a**. However, this reaction sequence suffers two drawbacks as a general route for generation of a library of 3-substituted quinoline-8-carboxamides; the diazotisation/Sandmeyer step is difficult and low-yielding, and the 3-substituent is introduced at an early step in the synthesis, which makes the synthesis of the library inefficient.

Responding to these challenges, an alternative sequence was devised in which the diversity of the library is introduced in the final step (Scheme 2). 3-Iodoquinoline-8-carboxamide **17f** is the critical intermediate in this route, as we rationalized that Pd-catalyzed couplings of **17f** would lead directly to a wide range of target 3-substituted quinoline-8-carboxamides in one step. Compound **17f** could be produced by electrophilic iodination of **17e**, by analogy with the route in Scheme 1.

Two approaches were investigated for the synthesis of **17e** to improve on the method of Prijs et al.,[41] who treated methyl quinoline-8-carboxylate with ammonia under forcing conditions. First, lithium−bromine exchange of commercially available 8-bromoquinoline **18a** followed by quench of the 8-lithioquinoline with trimethylsilylisocyanate gave **17e** directly in very high yield after aqueous workup to remove the *N*-silyl group. 8-Bromoquinoline **18a** is too expensive to be used as a general starting material, so an alternative 8-substituted quinoline, quinolin-8-ol **19**, was selected as a starting material that would be more cost-effective, despite the extra steps required. To introduce the one-carbon unit at the 8-position, quinolin-8-ol **19** was converted to the triflate **20**. Palladium-catalyzed displacement of the triflate with cyanide required the use of $Pd(PPh_3)_4$ in boiling DMF, with zinc cyanide as the cyanide source, affording 8-cyanoquinoline **21** in good yield. Simple hydration of the nitrile with hydrogen peroxide/hydroxide ion

Table 1. Iodination of **17e** with *N*-Iodosuccinimide under Brønsted and Lewis Acid Catalyzed Conditions

solvent	catalyst	yield of **17f** (%)
AcOH	none	26
none	TFA	0
MeCN	TFA	0
AcOH	$InCl_3$	31
AcOH	$FeCl_3$	40
AcOH	$AlCl_3$	34

provided quinoline-8-carboxamide **17e**, in good overall yield from **19**. Iodination at the 3-position proved to be a difficult step in the presence of the carboxamide. The conditions that had iodinated **11** to give **12**, NIS in boiling acetic acid, gave only a 26% conversion of **17e** to **17f**. Combination of NIS with a stronger Brønsted acid, trifluoroacetic acid, had been found by Castanet et al.[42] to be a superior iodinating agent but failed completely with **17e**. Finally, Lewis acids were investigated as activators of the electrophilic iodination. As shown in Table 1, the optimum conditions were to use $FeCl_3$ as Lewis acid in boiling acetic acid, which gave 40% conversion of **17e** to **17f**. Interestingly, up to 30% of unreacted **17e** could also be isolated under these optimum conditions, which could then be recycled.

3-Iodoquinoline-8-carboxamide **17f** was thus available as the central intermediate for generation of the target 3-substituted quinoline-8-carboxamides. The simplest substituent, methyl, was introduced through a $Pd(PPh_3)_4$-catalyzed Stille coupling of **17f** with tetramethyltin in hot *N*-methylpyrrolidin-2-one (NMP) to give **17g** in 40% yield. Sonogashira coupling of **17f** with trimethylsilylethyne with $(Ph_3P)_2PdCl_2$/CuI as the catalyst system in a mixture of diisopropylamine and THF attached the two-carbon unit to the 3-position of the quinoline, giving the protected alkyne **17h** in 62% yield. Fluoride ion failed to remove the trimethylsilyl group under a variety of conditions, but the deprotection of **17h** was achieved efficiently with silver(I) triflate in a two-phase reaction in chloroform/water to give 3-ethynylquinoline-8-carboxamide **17i**. The corresponding 3-ethyl compound **17j** was then accessed by hydrogenation of the alkyne. Only the ethenyl group was transferred in a Stille coupling of **17f** with ethenyltributyltin, yielding the third analogue **17k** with a two-carbon substituent at the 3-position, although this coupling required a modified catalyst system (Ph_3P/Pd_2dba_3/CuI) for optimum coupling. Although a Sonogashira coupling had been successful in introducing the 3-trimethylsilyethynyl group in **17h**, this reaction could not be adapted to the synthesis of the 3-(prop-1-ynyl) analogue **17l**, owing to the gaseous nature of propyne. The less volatile coupling synthon (prop-1-ynyl)tributyltin was therefore used in a Stille coupling with **17f** to afford **17l**.

The 3-aryl analogues **17a**−**d**,**m**−**s** were generally prepared by Suzuki couplings of **17f** with a range of arylboronic acids under basic conditions. Coupling of **17f** with phenylboronic acid in a two-phase toluene/water system using $Pd(PPh_3)_4$ gave **17a** in 76% yield, which was improved to 93% with S-Phos[43] as ligand and $Pd(OAc)_2$ as precatalyst (Table 2). Phenylboronic acids carrying electron-donating or electron-neutral substituents coupled in good yields with the $Pd(PPh_3)_4$/toluene/water/Na_2CO_3 system to provide **17m**−**o**. The efficiency of the coupling with 4-methylphenylboronic acid was improved slightly by use of THF/water as the solvent mixture, but as for the synthesis of **17a**, the yield of **17o** was raised markedly to 78% by the use of S-Phos/$Pd(OAc)_2$. As expected, the Suzuki couplings of the electron-poor phenylboronic acids proceeded in lower yields to afford **17b**−**d**,**p**,**q**. The particularly low yield of **17b** (27%) would appear to be due to steric obstruction of the formation of the arene-arene bond by the *o*-trifluoromethyl group. The coupling of **17f** with 3- and 4-pyridylboronic acids using the standard reaction conditions failed, apparently because of the poor solubility of the pyridylboronic acids in toluene. However, changing the solvent to DMF provided the coupled products **17r**,**s** in moderate yields but the analogous reaction with pyrimidine-5-boronic acid failed. In an attempt to provide a function on the phenyl ring that would be available for further elaboration, **17f** was treated with 4-hydroxymethylphenylboronic acid and with 3-hydroxymethylphenylboronic acid but coupling could not be achieved, even using the $Pd(OAc)_2$/S-Phos method. Alkylboronic acids are generally less reactive as coupling partners, and benzylboronic acid was similarly unreactive with **17f** under a variety of conditions. However, the alkenylboronic acid, *E*-2-phenylethenylboronic acid, coupled with **17f** in good yield using the $Pd(PPh_3)_4$/DMF conditions, giving the *E*-isomer **17t** with complete retention of configuration. Interestingly, **17t** readily photoisomerized to the *Z*-isomer **17u** under standard domestic laboratory light.

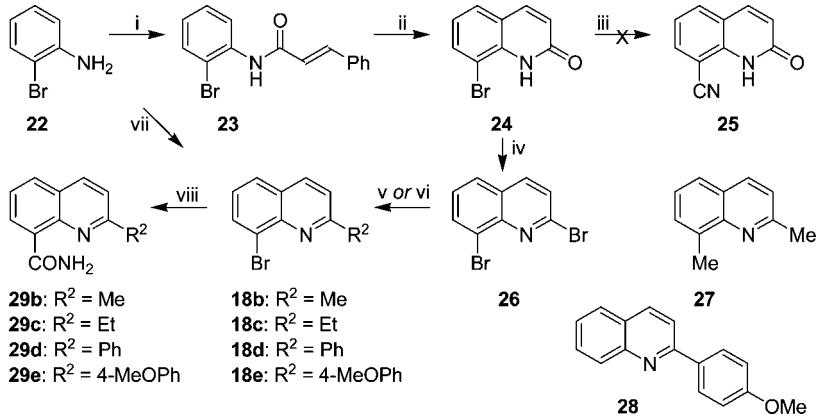
The synthetic approach to the 2-substituted quinoline-8-carboxamides **29b**−**e** is shown in Scheme 3. In this approach, it was not possible to devise a straightforward route where the 2-substituent was introduced at the final step, as it had been for the preparation of the 3-substituted analogues **17**, owing to the difficulty of accessing 2-haloquinoline-8-carboxamides. Initially, it was planned to carry our Pd-catalyzed couplings on a 2-haloquinoline-8-carbonitrile, using the nitrile as a masked form of the carboxamide, and that this material could be accessed from 8-cyanoquinolin-2-one **25**, formed in turn from Pd-catalyzed cyanation of 8-bromoquinolin-2-one **24**. Cottet et al.[44] have developed an ingenious synthesis of the precursor **24** by high-temperature Lewis acid-catalyzed cyclization of the *N*-arylcinnamamide **23** in a reaction that formally generates benzene as a leaving group. Following this route, 2-bromoaniline **22** was acylated with cinnamoyl chloride to afford **23** in high yield. Reaction of **23** with $AlCl_3$ at 125 °C led to a 41% isolated yield of the quinolin-2-one **24**. Unfortunately, no Pd-catalyzed or Cu-catalyzed conditions could be found to displace the bromine of **24** with cyanide to give **25** in more than trace amounts.

Reaction of **24** with $POBr_3$ at 140 °C converted the lactam to the dibromoquinoline **26** in excellent yield. It was expected that the 2-position of this compound should be much more reactive toward Pd-catalyzed couplings than the 8-position, owing to the increased electrophilicity caused by the adjacent ring-nitrogen. Thus, it should be possible to couple the planned 2-substituents selectively at this stage and allow the 8-bromine to be elaborated into the required 8-carboxamide later in the synthesis. Unfortunately, Stille coupling of **26** with tetramethyltin in the presence of $Pd(PPh_3)_4$ led only to an inseparable 2:1 mixture of the required 8-bromo-2-methylquinoline **18b** and 2,8-dimethylquinoline **27**, a product of coupling at both Ar−Br positions. No conditions could be found to achieve full selectivity for this coupling with Me_4Sn. However, repetition of the reaction with the more sterically hindered (and thus less reactive) coupling partner Et_4Sn introduced the ethyl group highly selectively at the 2-position, furnishing **18c** in a satisfactory 50% yield. Suzuki couplings of phenylboronic acid and 4-methoxyphenylboronic acid with **26** were similarly regioselective, forming the 2-phenyl- and 2-(4-methoxyphenyl)-8-bromoquinolines **18d** and **18e**, respectively, in good yields. It was necessary to use an alternative route to the 2-methyl compound **18b**, one that introduced the 2-methyl group unequivocally from an appropriate starting material. A Doebner−Miller

Table 2. Conditions and Yields for Suzuki Couplings of 3-Iodoquinoline-8-carboxamide **17f** with Boronic Acids

boronic acid	reaction conditions	3-substituted quinoline-8-carboxamide product	yield (%)
$PhB(OH)_2$	$Pd(PPh_3)_4$, PhMe, EtOH, H_2O, Na_2CO_3	**17a**	78
$PhB(OH)_2$	$Pd(OAc)_2$, S-Phos, PhMe, K_3PO_4	**17a**	93
4-$MeOC_6H_4B(OH)_2$	$Pd(PPh_3)_4$, PhMe, EtOH, H_2O, Na_2CO_3	**17m**	95
3,5-$Me_2C_6H_3B(OH)_2$	$Pd(PPh_3)_4$, PhMe, EtOH, H_2O, Na_2CO_3	**17n**	65
4-$MeC_6H_4B(OH)_2$	$Pd(PPh_3)_4$, PhMe, EtOH, H_2O, Na_2CO_3	**17o**	41
4-$MeC_6H_4B(OH)_2$	$Pd(PPh_3)_4$, K_2CO_3, THF, H_2O	**17o**	48
4-$MeC_6H_4B(OH)_2$	$Pd(OAc)_2$, S-Phos, PhMe, K_3PO_4	**17o**	78
3-$F_3CC_6H_4B(OH)_2$	$Pd(PPh_3)_4$, PhMe, EtOH, H_2O, Na_2CO_3	**17c**	43
4-$F_3CC_6H_4B(OH)_2$	$Pd(PPh_3)_4$, PhMe, EtOH, H_2O, Na_2CO_3	**17d**	38
2-$F_3CC_6H_4B(OH)_2$	$Pd(PPh_3)_4$, PhMe, EtOH, H_2O, Na_2CO_3	**17b**	27
3-$BrC_6H_4B(OH)_2$	$Pd(PPh_3)_4$, PhMe, EtOH, H_2O, Na_2CO_3	**17p**	31
3-$NCC_6H_4B(OH)_2$	$Pd(PPh_3)_4$, PhMe, EtOH, H_2O, Na_2CO_3	**17q**	41
pyridine-3-boronic acid	$Pd(PPh_3)_4$, THF, H_2O, Na_2CO_3	**17r**	0
pyridine-3-boronic acid	$Pd(PPh_3)_4$, DMF, Na_2CO_3	**17r**	26
pyridine-4-boronic acid	$Pd(PPh_3)_4$, DMF, Na_2CO_3	**17s**	40
pyrimidine-5-boronic acid	$Pd(PPh_3)_4$, DMF, Na_2CO_3		0
4-$HOCH_2C_6H_4B(OH)_2$	$Pd(PPh_3)_4$, K_2CO_3, THF, H_2O		0
4-$HOCH_2C_6H_4B(OH)_2$	$Pd(OAc)_2$, S-Phos, PhMe, K_3PO_4		0
3-$HOCH_2C_6H_4B(OH)_2$	$Pd(PPh_3)_4$, K_2CO_3, THF, H_2O		0
$PhCH_2B(OH)_2$	$Pd(PPh_3)_4$, PhMe, EtOH, H_2O, Na_2CO_3		0
$PhCH_2B(OH)_2$	$Pd(PPh_3)_4$, K_2CO_3, THF, H_2O		0
E-PhCH=CHB$(OH)_2$	$Pd(PPh_3)_4$, DMF, Na_2CO_3	**17t**	52

Scheme 3. Synthesis of 2-Substituted Quinoline-8-carboxamides **29**[a]

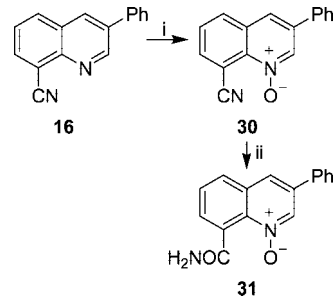


[a] Reagents: (i) *E*-PhCH=CHCOCl, K_2CO_3, water, acetone; (ii) $AlCl_3$, ClPh, Δ; (iii) CuCN or $Zn(CN)_2$, DMF, Δ; (iv) $POBr_3$, Δ; (v) Me_4Sn or Et_4Sn, $Pd(PPh_3)_4$, NMP, Δ; (vi) $PhB(OH)_2$ or 4-$MeOPhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, PhMe, EtOH, water, Δ; (vii) *E*-MeCH=CHCHO, aqueous HCl, Δ; (viii) BuLi, THF, then Me_3SiNCO.

reaction of 2-bromoaniline **22** with but-2-enal provided **18b** in high yield, following the modified procedure of Lier,[45] with isolation through the $ZnCl_2$ complex. With the set of 8-bromoquinolines **18b**−**e** now in place, lithium−halogen exchange and quench of the intermediate aryllithium with trimethylsilyl isocyanate gave the required 2-alkyl and 2-arylquinoline-8-carboxamides **29b**−**e** (Scheme 3), by analogy with the preparation of the parent quinoline-8-carboxamide **17e** from 8-bromoquinoline **18a** (Scheme 2). Interestingly, this process also furnished a significant yield of the debrominated product **28** during the synthesis of **29e**.

The target quinoline *N*-oxide **31**, carrying the 8-carboxamide, could not be accessed by direct oxidation of **17a**, presumably owing to the strong intramolecular hydrogen bond making the ring-nitrogen non-nucleophilic. N-Oxidations of 8-substituted quinolines are known to be problematic, owing to steric effects and electronic deactivation if the 8-substituent is electron-withdrawing.[46,47] However, oxidation of 8-cyano-3-phenylquinoline **16** with the very powerful N-oxidizing reagent urea−hydrogen peroxide complex[49] activated by trifluoroacetic anhydride (presumably generating dry peroxytrifluoroacetic acid in situ)[50] gave the *N*-oxide **30** in modest yield (Scheme 4).

Scheme 4. Synthesis of Quinoline-8-carboxamide *N*-Oxide **31**[a]



[a] Reagents: (i) H_2O_2−urea complex, $(CF_3CO)_2O$, Na_2CO_3, CH_2Cl_2; (ii) NaOH, H_2O_2, EtOH, H_2O.

Hydration of the nitrile to the carboxamide was achieved with hydrogen peroxide under mildly basic conditions,[32] a process that did not adversely affect the *N*-oxide, to provide the target **31**.

Conformational Studies

Since an essential point of the design of the quinoline-8-carboxamides was the prediction that one amide N−H would

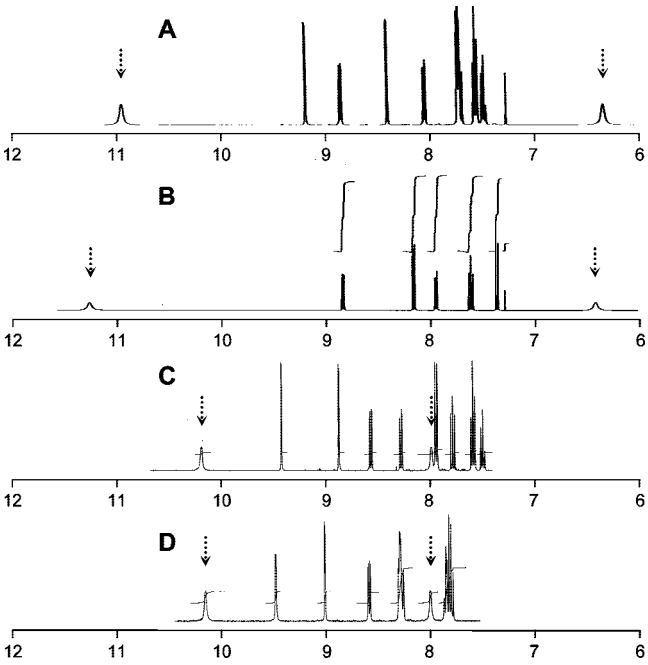


Figure 2. Parts of ^{1}H NMR spectra of **17a**,**c** and **29**, showing signals (dotted arrows) for intramolecularly hydrogen-bonded amide N—H protons and non-hydrogen-bonded amide N—H protons. The scale is in ppm (Δ): (A) **17a** in $CDCl_3$; (B) **29** in $CDCl_3$; (C) **17a** in $(CD_3)_2SO$; (D) **17c** in $(CD_3)_2SO$.

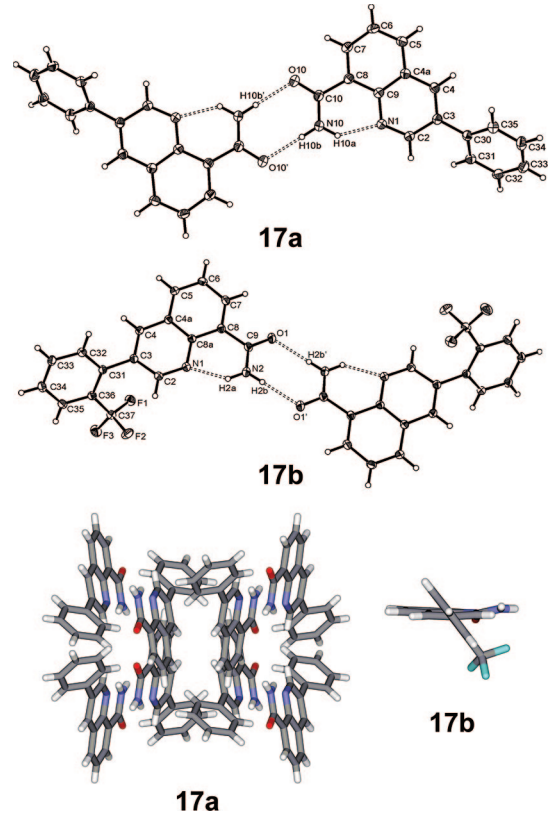


Figure 3. Views of crystal structures of 3-arylquinoline-8-carboxamides **17a** and **17b**, showing intramolecular and intermolecular hydrogen bonding and the dihedral angle between the plane of the quinoline and the plane of the 3-aryl group.

be intramolecularly hydrogen-bonded to the heterocyclic nitrogen, a short series of studies was carried out to confirm this hydrogen bond and to confirm the planar nature of the quinoline-carboxamide unit (excluding the 2- or 3-substituent). First, the ^{1}H NMR spectra of quinoline-8-carboxamides **17** and **29** were examined and compared with that of naphthalene-1-carboxamide,[48] a structurally very similar compound that lacks the ring nitrogen and thus cannot experience intramolecular hydrogen bonding.

In the ^{1}H NMR spectrum of naphthalene-1-carboxamide in $CDCl_3$, one N—H proton signal was observed at δ 7.74 and the other at δ 7.99. In this compound, intramolecular hydrogen-bonding is impossible and the NH_2 proton signals are only separated by ∼0.25 ppm. In the ^{1}H NMR spectrum of **17e** in $CDCl_3$, one N—H proton resonates at δ 6.49 and the other at δ 10.95. Similarly, the signals for the NH_2 protons in **17a** in $CDCl_3$ were observed at δ 6.17 and δ 10.95 (Figure 2A). The difference of $\Delta\delta \simeq 5$ ppm between the signals of the NH_2 protons in both compounds **17a** and **17e** indicates that one proton is in a very strongly intramolecularly hydrogen-bonded environment (giving the downfield signals) while the other proton is not intramolecularly hydrogen-bonded. Interestingly, the ^{1}H−^{1}H COSY spectrum of **17a** in $CDCl_3$ showed a cross-peak between the two N—H signals of the carboxamide group, suggesting that they are in slow exchange and thus can couple to each other. Similar $\Delta\delta$ values were seen for other examples of quinoline-8-carboxamides **17**. The effect in the 2-substituted series **29** was also very similar, with $\Delta\delta$ between the two N—H signals in **29b** being 4.85 ppm in $CDCl_3$ solution (Figure 2B); thus, the presence of the 2-substituent has little effect on the hydrogen bonding. These data are consistent with a strong intramolecular hydrogen bond in solution in the nonpolar and non-hydrogen-bonding solvent chloroform. When ^{1}H NMR spectra were run of samples of **17a** in DMSO, a much more polar and hydrogen-bond-accepting solvent that is a powerful disruptor of hydrogen-bonded systems, a similar effect was seen. One of the N—H signals was evident at δ 7.99, whereas the other was at δ 10.17 (Figure 2C), giving a $\Delta\delta$ of ∼2.2 ppm. A similar $\Delta\delta$ was seen for **17c** in $(CD_3)_2SO$ (Figure 2D). This indicates that intramolecular hydrogen bonding is present even in this potentially powerfully disrupting solvent and points to the maintenance of the hydrogen bonds in aqueous biological media. Thus, the ^{1}H NMR studies indicate that the carboxamides are held in a conformation that is apposite for PARP-1 inhibitory activity.

In the ^{1}H NMR spectrum of *N*-oxide **31** in DMSO, the two N—H signals are again separated, occurring at δ 7.28 and δ 7.48. This $\Delta\delta$ (0.2 ppm) is much smaller than the values for **17** and may reflect weaker intramolecular hydrogen bonding.

X-ray crystal structure determinations were also carried out on two members of the 3-arylquinoline-8-carboxamide series, the 3-phenyl parent **17a**, and the 3-(2-trifluorophenyl) analogue **17b**, which formed suitable crystals. Crystals of **17a** were grown in an EtOAc/hexane system. A single crystal of **17a** was analyzed at 150(2) K using graphite monochromated Mo Kα radiation and a Nonius Kappa CCD diffractometer. The X-ray crystallographic structure is shown in Figure 3. The structure shows the presence of the predicted intramolecular hydrogen bond between the heterocyclic nitrogen and one N—H of the carboxamide, with this hydrogen being located and refined at a distance of 0.89 Å from the parent atom. An additional (intermolecular) hydrogen bond is seen in the crystal between the carbonyl oxygen on one molecule and the "exocyclic" N—H of an adjacent molecule. The upper structure of **17a** in Figure 3 illustrates these interactions between a pair of molecules, whereas the lower structure of **17a** shows the longer range hydrogen-bonding and stacking arrangement of eight molecules. The phenyl group in **17a** is twisted out of the plane of the quinoline ring by 46.9°.

Table 3. IC_{50} Values for Inhibition of PARP-1 Activity by Quinoline-8-carboxamides **17**, **29**, and **31** and by Positive Control 5-AIQ **3**

compd	R^2	R^3	IC_{50} (μM)	log[IC_{50} (μM)][a]
3			1.8	0.26 ± 0.12
17a	H	Ph	15	1.17 ± 0.15
17c	H	3-$F_3CC_6H_4$	52	1.71 ± 0.16
17e	H	H	1.9	0.27 ± 0.11
17g	H	Me	3.4	0.53 ± 0.08
17i	H	HC≡C	2.3	0.36 ± 0.17
17j	H	Et	3.7	0.57 ± 0.05
17k	H	H_2C═CH	5.8	0.76 ± 0.07
17l	H	MeC≡C	2.2	0.34 ± 0.10
17m	H	4-$MeOC_6H_4$	62	1.79 ± 0.15
17o	H	4-MeC_6H_4	43	1.63 ± 0.25
17q	H	4-NCC_6H_4	27	1.43 ± 0.14
29b	Me	H	0.5	−0.30 ± 0.08
29c	Et	H	0.8	−0.09 ± 0.10
29d	Ph	H	0.9	−0.06 ± 0.33
29e	4-$MeOC_6H_4$	H	1.1	0.03 ± 0.13
31 (*N*-oxide)	Ph	H	23	1.36 ± 0.27

[a] Values are the mean of three experiments and are reported as mean ± standard error of the mean (SEM).

Similarly, X-ray crystallography of **17b** provided supporting evidence for the formation of the predicted intramolecular hydrogen bond. As for **17a**, a single crystal of **17b** was analyzed at 150(2) K using graphite monochromated Mo Kα radiation and a Nonius Kappa CCD diffractometer. Again, an intramolecular hydrogen-bond interaction was observed between the heterocyclic nitrogen and one N—H of the carboxamide, as shown in Figure 3 (lower right). The proposed intramolecular hydrogen bond in **17b** is 2.03 Å, with a bond angle (N—H—N) at hydrogen of 134.9°, with this hydrogen being located and refined at a distance of 0.89 Å from the parent atom. The steric bulk of the *o*-CF_3 substituent in **17b** has a marked effect on the conformation in that the trifluoromethylphenyl group is twisted out of the plane of the quinoline ring by 55.8°, a dihedral angle some 9° greater than that in **17a** (Figure 3, lower right). Hydrogen-bonded dimers are again evident in the gross structure.

Biochemical Evaluation

Quinoline-8-carboxamide **17e**, the 3-substituted quinoline-8-carboxamides **17**, the 2-substituted quinoline-8-carboxamides **29**, and the N-oxide **31** were evaluated for inhibition of the catalytic activity of human recombinant PARP-1 using a commercial kit (Trevigen, Inc.). The IC_{50} values for the inhibition are shown in Table 3 for **17a**,**c**,**e**,**g**,**i**−**m**,**o**,**q**, **29a**−**d**, and **31**; **3** was also evaluated as a positive control. 3-Substituted quinoline-8-carboxamides **17b**,**d**,**f**,**h**,**r**−**t** were insufficiently soluble to permit measurement of IC_{50}.

Direct comparison of measures of inhibition of PARP-1 (e.g., IC_{50}) from different laboratories should be undertaken with caution, since values for the same compound can vary, depending on the assay system employed. Suto et al.[7] and Watson et al.,[32] for instance, reported an IC_{50} value of 0.24 μM when **3** was evaluated using an in vitro cell-free preparation of PARP-1 isolated from calf thymus. In contrast, using the Trevigen PARP-1 colorimetric assay, an IC_{50} value of 1.8 μM was obtained in the current work. Thus, IC_{50} values should be used to examine trends within a set of inhibitors using the same assay, with comparison with a well-known standard (**3**, in this case).

The parent ring-unsubstituted quinoline-8-carboxamide **17e** was equipotent with the standard **3**, with IC_{50} = 1.9 μM. White et al.[35] found that introducing a (substituted) phenyl group at the 2-position of the benzimidazole-4-carboxamides **6** increased the inhibitory potency by 10- to 100-fold. However, in the 3-substituted quinoline-8-carboxamide series **17**, where the 3-substituent should lie in a similar region of space to the 2-aryl substituent in **6**, introduction of a phenyl group (in **17a**) causes an 8-fold diminution in activity. Addition of small moderately lipophilic electron-withdrawing (in **17c** and **17q**), electron-donating (in **17m**), and electron-neutral (in **17o**) groups to the 3-phenyl ring caused further loss of activity, again in contrast to similar further substitution in the 2-phenylbenzimidazole-4-carboxamides **6**. Small alkyl substituents were tolerated better in the 3-position of the quinoline-8-carboxamides, the 3-methyl compound **17g** and the 3-ethyl analogue **17j** being approximately 2-fold less active than the parent **17e**. Restoration of potency was achieved by making the 3-substituent sterically very narrow in the 3-ethynylquinoline-8-carboxamide **17i** (IC_{50} = 2.3 μM) and in the 3-prop-1-ynyl analogue **17l** (IC_{50} = 2.2 μM), suggesting that the 3-substituent may be located very close to the side of a binding pocket and pressing closely against this protein surface.

By contrast, substitution at the 2-position enhanced activity. This position can also be considered as analogous to the 2-position of the benzimidazole-4-carboxamides **6**. In the quinoline-8-carboxamide series, small alkyl groups (Me, **29b**, IC_{50} = 500 nM; Et, **29c**, IC_{50} = 800 nM) were very well tolerated. Most interestingly, the two 2-aryl compounds **29d** and **29e** were also more potent than the parent compound **17e**. This suggests that the 2-position may be directed more toward the center of the lipophilic pocket of the enzyme, allowing inclusion of larger substituents.

Interestingly, comparison of the IC_{50} values for 3-phenylquinoline-8-carboxamide **17a** (15 μM) and for its *N*-oxide **31** (23 μM) shows that the *N*-oxide has only a small effect in reducing potency of inhibition of PARP-1. This may be due to formation of a seven-membered hydrogen-bonded ring from the N—H to the oxygen of the *N*-oxide, although this was not clearly demonstrated in the NMR study. This putative conformation of **31** has parallels with the constraint of the amide in a seven-membered covalently bonded ring in the highly potent tricyclic inhibitors **5**, although the latter compounds have a 5:6:7 tricyclic system rather than the 6:6:7 system of **31**. Unfortunately, the *N*-oxides of the more potent quinoline-8-carboxamides **17e**,**g**,**i**−**l** and **29b**−**e** were not synthetically accessible for comparison to develop understanding of the inhibition by **31**.

Conclusions

In this paper, we disclose a new type of inhibitor of the important target enzyme PARP-1, the quinoline-8-carboxamides. We propose that a tight intramolecular hydrogen bond constrains the carboxamide in a conformation apposite for optimum binding to the nicotinamide-binding site of the enzyme. The 3-substituted series of these compounds **17** was readily synthesized by Pd-catalyzed couplings (Sonogahsira, Suzuki, Stille) to the key intermediate 3-iodoquinoline-8-carboxamide. This route allows introduction of diversity at the 3-position in the final synthetic step, to maximize efficiency in preparing the compound library. Such maximal synthetic efficiency was not possible in the preparation of a short series of 2-alkyl and 2-aryl quinoline-8-carboxamides **29**. These target inhibitors were accessed through selective Pd-catalyzed couplings at the 2-position of 2,8-dibromoquinoline. Lithium−bromine exchange at the 8-position was followed by reaction with trimethylsilyisocyanate to afford the target 2-substituted quinoline-8-carboxamides **29**, in a sequence that introduces the diversity of substitution in the penultimate step.

The presence of the critical designed intramolecular hydrogen bonds was confirmed in two X-ray crystal structures (compounds

17a and **17b**) and demonstrated in solution by ^{1}H NMR spectroscopy.

The 3-arylquinoline-8-carboxamides **17a**,**c**,**m**−**q** were markedly less active than the parent unsubstituted quinoline-8-carboxamide **17e**, which was equipotent with the leading water-soluble inhibitor **3**. Activity was restored by the 3-substituent being small and narrow (alkynes), suggesting that the 3-substituent was pressed tightly against the protein surface of a pocket in the enzyme. Substituents were much better tolerated in the 2-position (compounds **29a**−**d**), with 2-alkyl and 2-aryl groups being better accommodated in the pocket and thus increasing potency. The *N*-oxide **31** had activity similar to its nonoxidized congener **17a**, indicating that constraint of the carboxamide in a seven-membered hydrogen-bonded ring may be acceptable in binding to the enzyme. Thus, the quinoline-8-carboxamide core and, possibly, its *N*-oxide are shown to be active leads for further development of inhibitors of the important target enzyme PARP-1.

Experimental Section

NMR spectra were recorded on JEOL/Varian GX270 and EX400 spectrometers of samples in $CDCl_3$, unless otherwise stated. IR spectra were measured as thin films or as KBr disks on a Perkin-Elmer RXI FT-IR spectrometer. The stationary phase for chromatography was silica gel. Solvents were evaporated under reduced pressure. Solutions in organic solvents were dried with $MgSO_4$. Melting points were determined using a Reichert-Jung Thermo Galen instrument and are uncorrected. Details of the syntheses of compounds **12**, **13a**−**d**, **14**−**16**, **17b**−**d**,**m**,**n**,**p**−**u**, **18b**,**d**,**e**, **20**, **23**, **24**, **26**, **27**, **29c**−**e** and of the biochemical evaluation are given in the Supporting Information.

General Coupling Procedure 1. The haloquinoline (1.0 mmol), $Pd(PPh_3)_4$ (0.1 mmol), Na_2CO_3 (1.2 mmol), and the arylboronic acid (1.1 mmol) were heated at reflux for 24 h under N_2 in toluene/EtOH/H_2O (10 mL:1.0 mL:1.0 mL). The evaporation residue, in EtOAc, was washed with water and brine. Drying, evaporation, and chromatography (hexane/EtOAc 10:1) gave the coupled product.

General Coupling Procedure 2. The haloquinoline (1.0 mmol), arylboronic acid (1.6 mmol), and $Pd(PPh_3)_4$ (0.05 mmol) were sequentially added to degassed DMF (1.0 mL), and the mixture was stirred for 30 min. Degassed aqueous Na_2CO_3 (1.0 M, 0.25 mL) was added, and the mixture was heated under N_2 at 80 °C until TLC monitoring showed that the reaction was complete (8−48 h). The evaporation residue, in EtOAc, was washed with water and brine. Drying, evaporation, and chromatography (hexane/EtOAc 3:2) gave the coupled product.

General Coupling Procedure 3. The haloquinoline (1.0 mmol), $Pd(PPh_3)_4$ (0.1 mmol), and the substituted stannane (2.0 mmol) in NMP (5.0 mL) were heated at 80 °C for 24 h under N_2. The mixture was extracted with EtOAc. Drying, evaporation, and chromatography (hexane/EtOAc 3:2) gave the coupled product.

3-Phenylquinoline-8-carboxamide (17a). Method A. Compound **16** (50 mg, 0.2 mmol) in EtOH (1.0 mL) was stirred with aqueous NaOH (0.5 M, 4.3 mL, 2.2 mmol) and aqueous H_2O_2 (35%, 0.2 mL) at 50 °C for 1 h before being neutralized with aqueous H_2SO_4 (10%). The evaporation residue, in CH_2Cl_2, was washed (water, brine). Drying and evaporation gave **17a** (32 mg, 60%) as a pale-yellow solid: mp 130−132 °C.

3-Phenylquinoline-8-carboxamide (17a). Method B. Compound **17f** was treated with $PhB(OH)_2$ by general coupling procedure 1 to give **17a** (76%), with properties as above.

3-Phenylquinoline-8-carboxamide (17a). Method C. A dried flask was charged with $Pd(OAc)_2$ (1.1 mg, 5 μmol), 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine (S-Phos) (4.2 mg, 10 μmol), phenylboronic acid (91 mg, 0.75 mmol), powdered anhydrous K_3PO_4 (212 mg, 1.0 mmol), and **17f** (149 mg, 0.50 mmol). Dry PhMe (2.0 mL) was added, and the mixture was heated at 100 °C for 24 h under Ar. The cooled mixture was diluted with Et_2O and filtered through silica gel. Evaporation, chromatography (hexane/EtOAc 10:1), and recrystallization (hexane/EtOAc) gave **17a** (115 mg, 93%) with properties as above.

Quinoline-8-carboxamide (17e). Method A. BuLi (1.6 M in hexanes, 2.6 mmol) was added to 8-bromoquinoline **18a** (500 mg, 1.2 mmol) in dry THF (2.0 mL) at −78 °C. After 30 min at −78 °C, trimethylsilyl isocyanate (430 mg, 3.7 mmol) was added. The mixture was stirred for 15 min at −78 °C and for 12 h at 20 °C. The evaporation residue in CH_2Cl_2 was washed (water, brine) and filtered. Evaporation and chromatography (CH_2Cl_2/EtOAc 1:2) gave **17e** (200 mg, 97%) as a white solid: mp 170−172 °C (lit.[41] mp 170−173 °C).

Quinoline-8-carboxamide (17e). Method B. Compound **21** (1.00 g, 6.5 mmol) in EtOH (10 mL) was stirred at 50 °C with aqueous NaOH (0.5 M, 12.7 mL, 6.5 mmol) and aqueous H_2O_2 (35%, 2.2 mL, 23 mmol) for 1 h. The mixture was neutralized with aqueous H_2SO_4 (10%). The evaporation residue, in CH_2Cl_2, was washed (water, brine). Drying and evaporation gave **17e** (870 mg, 78%) with properties as above.

3-Iodoquinoline-8-carboxamide (17f). Compound **17e** (700 mg, 4.1 mmol) was boiled under reflux with *N*-iodosuccinimide (910 mg, 4.1 mmol) in AcOH (7.0 mL) for 24 h. The mixture was poured into water and extracted ($CHCl_3$). The extract was washed (aqueous $NaHCO_3$) and dried. Evaporation and chromatography (hexane/EtOAc 3:2) gave **17f** (480 mg, 40%) as a pale-yellow solid: mp 211−214 °C.

3-Methylquinoline-8-carboxamide (17g). Compound **17f** was treated with Me_4Sn by general coupling procedure 3 to give **17g** (40%) as a white solid: mp 144−142 °C.

3-Trimethylsilylethynylquinoline-8-carboxamide (17h). $PdCl_2$ (130 mg, 0.7 mmol) was stirred with Ph_3P (375 mg, 1.4 mmol) in DMF (20 mL) at 80 °C for 24 h. The precipitate was collected and dried to give $(Ph_3P)_2PdCl_2$ (450 mg, 90%) as a yellow powder. Compound **17f** (200 mg, 0.67 mmol) in dry THF (10 mL) was added to a suspension of $(Ph_3P)_2PdCl_2$ (20 mg, 27 μmol) and CuI (27 mg, 140 μmol) in dry ^{i}Pr$_2$NH (2.7 mL), and the mixture was stirred at 45 °C for 30 min under Ar. Trimethylsilylethyne (72 mg, 0.72 mmol) was added during 30 min, and stirring continued at 45 °C for a further 2 h. Filtration (Celite), evaporation, and chromatography (hexane/EtOAc 3:2) gave **17h** (140 mg, 62%) as white crystals: mp 152−155 °C.

3-Ethynylquinoline-8-carboxamide (17i). Compound **17h** (100 mg, 0.34 mmol) was stirred vigorously at reflux with AgOTf (9.5 mg, 37 μmol) in $CHCl_3$ (6.3 mL), MeOH (1.7 mL), and water (12 mL) for 3 days. Aqueous NH_4Cl (saturated) was added, and the mixture was extracted ($CHCl_3$). Washing (water), drying, evaporation, and recrystallization (hexane/EtOAc) gave **17i** (72 mg, 99%) as pale-buff crystals: mp 252−255 °C.

3-Ethylquinoline-8-carboxamide (17j). Compound **17i** (70 mg, 0.36 mmol) was stirred with Pd/C (10%, 50 mg) in DMF (1.5 mL) and MeOH (1.5 mL) under H_2 for 24 h. Filtration (Celite) and recrystallization (EtOAc/hexane) gave **17j** (46 mg, 64%) as pale-buff crystals: mp 121−123 °C.

3-Ethenylquinoline-8-carboxamide (17k). Compound **17f** (100 mg, 0.34 mmol) was stirred with Ph_3P (6.9 mg, 30 μmol), Pd_2dba_3 (3.0 mg, 5 μmol), CuI (3.6 mg, 19 μmol), and tributylvinyltin (108 mg, 0.34 mmol) in degassed NMP (3.0 mL) at 80 °C for 24 h under Ar. The mixture was extracted with EtOAc. The extract was washed (brine) and dried. Evaporation and chromatography (hexane/EtOAc, 10:1) gave **17k** (37 mg, 55%) as a pale-yellow solid: mp 174−176 °C.

3-Prop-1-ynylquinoline-8-carboxamide (17l). Compound **17f** was treated with $Bu_3SnC{\equiv}CMe$ by general coupling procedure 3 to give **17l** (28 mg, 39%) as a pale-buff solid: mp 109−110 °C.

3-(4-Methylphenyl)quinoline-8-carboxamide (17o). Compound **17f** (447 mg, 1.5 mmol) was heated at reflux with 4-methylphenylboronic acid (306 mg, 2.3 mmol), K_2CO_3 (620 mg, 4.5 mmol), and $Pd(PPh_3)_4$ (170 mg, 0.1 mmol) for 24 h under Ar in THF/water (10 mL:1 mL). The evaporation residue, in EtOAc, was washed with water and brine. Drying, evaporation, chromatography

(hexane/EtOAc 10:1), and recrystallization (hexane/EtOAc) gave **17o** (306 mg, 78%) as a white solid: mp 176−177 °C.

8-Bromo-2-ethylquinoline (18c). Compound **26** was treated with Et_4Sn by general coupling procedure 3 to give **18c** (50%) as a pale-brown oil.

8-Cyanoquinoline (21). Compound **20** (3.00 g, 11 mmol) was boiled under reflux with $Zn(CN)_2$ (780 mg, 6.9 mmol) and $(Ph_3P)_4Pd$ (1.28 g, 1.1 mmol) in DMF (30 mL) for 2 h. Water (200 mL) was added, followed by aqueous H_2SO_4 (2 M, 20 mL; CAUTION). The mixture was extracted (EtOAc). Washing (brine), drying, evaporation, and recrystallization (EtOAc/hexane) gave **21** (1.24 g, 73%) as a white solid: mp 86−88 °C (lit.[53] mp 87.5−88.5 °C).

2-Methylquinoline-8-carboxamide (29b). BuLi (1.6 M in hexanes, 0.61 mL, 0.94 mmol) was added to **18b** (50 mg, 0.21 mmol) in dry THF (0.34 mL) at −78 °C. After 30 min, trimethylsilyl isocyanate (162 mg, 1.4 mmol) was added. The mixture was stirred for a further 15 min at −78 °C and for 12 h at 20 °C. The evaporation residue, in CH_2Cl_2, was washed with water and brine and dried. Evaporation and chromatography (CH_2Cl_2/EtOAc, 3:2) gave **29b** (44 mg, 52%) as a pale-yellow solid: mp 170−171 °C (lit.[57] mp 170−171 °C).

8-Cyano-3-phenylquinoline-1-oxide (30). Trifluoroacetic anhydride (315 mg, 1.5 mmol) was added dropwise to a suspension of Na_2CO_3 (280 mg, 2.6 mmol) and urea hydrogen peroxide (280 mg, 3.0 mmol) in dry CH_2Cl_2 (5.0 mL) at 0 °C. The mixture was warmed to 20 °C, and **16** (70 mg, 0.30 mmol) was added. The mixture was stirred for 24 h at 40 °C, then extracted (CH_2Cl_2). The extract was washed (water, brine). Drying, evaporation, and chromatography (hexane/EtOAc, 1:1) gave **30** (10 mg, 14%) as a white solid: mp 212−214 °C.

1-Oxo-3-phenylquinoline-8-carboxamide (31). Compound **30** (283 mg, 1.2 mmol) in EtOH (3.7 mL) was stirred at 50 °C with aqueous NaOH (0.5 M, 0.52 mL, 0.27 mmol) and aqueous H_2O_2 (35%, 0.45 mL, 3.6 mmol) for 1 h before being neutralized with aqueous H_2SO_4 (10%). Evaporation and chromatography (EtOAc/MeOH 5:1) gave **31** (43 mg, 14%) as a white solid: mp 264−265 °C.

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Supporting Information Available: Experimental procedures and analytical data for the synthesis of compounds **12**, **13a**−**d**, **14**−**16**, **17b**−**d**,**m**,**n**,**p**−**u**, **18b**,**d**,**e**, **20**, **23**, **24**, **26**, **27**, **29c**−**e**;[51,52,54−56,58−61] analytical data for **17a**,**e**−**l**,**o**, **18c**, **21**, **29b**, **30**, **31**; X-ray crystallographic data and the procedure for the biochemical evaluation. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for **17a** and **17b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 706648 and CCDC 706648, respectively. Requests for data should be addressed to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.

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