Bioorganic & Medicinal Chemistry Letters 19 (2009) 4050–4054

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and SAR of novel tricyclic quinoxalinone inhibitors of poly(ADP-ribose)polymerase-1 (PARP-1)

Julie Miyashiro [a,*], Keith W. Woods [a], Chang H. Park [b], Xuesong Liu [a], Yan Shi [a], Eric F. Johnson [a], Jennifer J. Bouska [a], Amanda M. Olson [a], Yan Luo [a], Elizabeth H. Fry [b], Vincent L. Giranda [a], Thomas D. Penning [a]

[a] Cancer Research, GPRD, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064, USA
[b] Structural Biology, GPRD, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064, USA

ARTICLE INFO

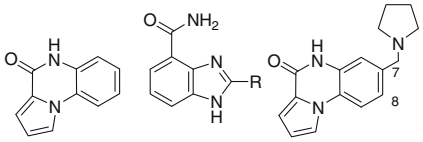
Article history:
Received 21 April 2009
Revised 3 June 2009
Accepted 5 June 2009
Available online 13 June 2009

Keywords:
PARP-1
Poly(ADP-ribose)polymerase
Quinoxalinone
Nuclear enzyme
DNA repair
Programmed cell death
Nicotinamide

ABSTRACT

Based on screening hit **1**, a series of tricyclic quinoxalinones have been designed and evaluated for inhibition of PARP-1. Substitutions at the 7- and 8-positions of the quinoxalinone ring led to a number of compounds with good enzymatic and cellular potency. The tricyclic quinoxalinone class is sensitive to modifications of both the amine substituent and the tricyclic core. The synthesis and structure–activity relationship studies are presented.

Poly(ADP-ribose)polymerases (PARPs) are a family of nuclear enzymes (17 members) involved in the regulation of a number of cellular processes involving DNA repair and programmed cell death. PARP-1, the main isoform, is one of the most abundant proteins in the nucleus and can be activated up to 100-fold by DNA strand breaks. This ubiquitous 116-kDa protein consists of 3 domains: an amino(N)-terminal DNA-binding domain, an automodification domain, and a carboxy(C)-terminal domain. The N-terminal zinc fingers of PARP-1 recognize single and double-stranded DNA breaks. The oxidative stress induced by DNA damage catalyzes the synthesis of poly ADP-ribose polymers on acceptor proteins with NAD^+ as the substrate. This cellular ADP-ribose transfer is an essential component of DNA repair and the maintenance of genomic integrity.[1] PARP-1 is primarily responsible for the catastrophic depletion of NAD^+ and ATP observed under high oxidative stress which culminates in cell dysfunction and death. Since tumor cells often have compromised DNA repair mechanisms, they are more dependent than normal cells on PARP-1 for DNA repair. Thus, using a PARP-1 inhibitor to shut down the DNA repair mechanism has the potential to enhance the therapeutic benefit of DNA-damaging anticancer drugs or ionizing radiation.[2–7]



1 2 9c

A considerable number of novel PARP inhibitors have been described in the literature over the past decade.[8] Many of the recent medicinal chemistry efforts have focused on tricyclic and tetracyclic carboxamide scaffolds. In general, these inhibitors mimic the binding mode of nicotinamide with the carboxamide group forming hydrogen bonds with Gly-863 and Ser-904 in the PARP enzyme.[4–9] Utilizing screening hit **1,** whose core has a potency comparable to the previously described benzimidazole carboxamide core **2** (R = H, PARP-1 K_i = 0.240 μM),[10] a series of tricyclic quinoxalinone analogues were explored leading to the identification of **9c**. This compound displayed excellent enzymatic and cellular potency. As seen in the PARP-1 X-ray co-crystal structure (Fig. 1), the quinoxalinone scaffold accesses a binding region previously not filled by the benzimidazole inhibitors. Access to this new 'northern' binding pocket may provide insights into the activity of **9c** and its analogues.

The synthesis of pyrroloquinoxalinone **9c** and its analogues is shown in Scheme 1. Attempts to arylate methyl pyrrole-2-carbox-

* Corresponding author. Tel.: +1 847 938 3686.
E-mail address: julie.miyashiro@abbott.com (J. Miyashiro).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.06.016

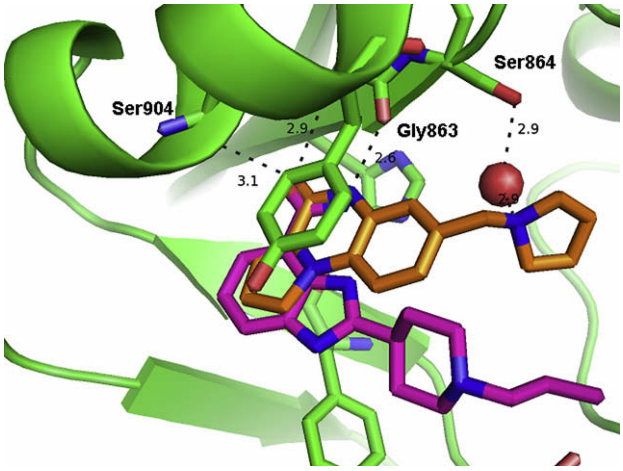
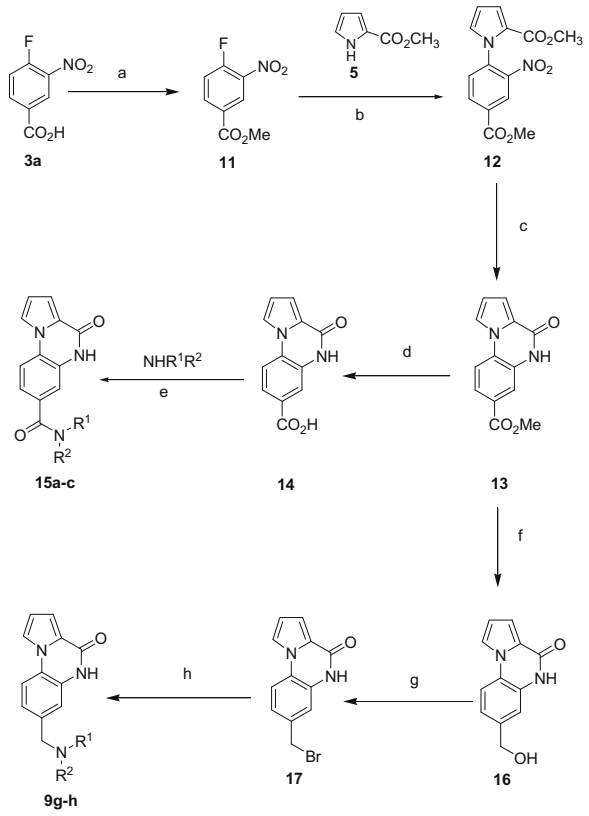


Figure 1. X-ray of **2** (R = 4-(*N*-propylpiperidine), purple) and **9c** (orange) in PARP-1 binding site.[11]

ylate (**5**) with fluoronitrobenzoic acid **3a** or **3b** were unsuccessful. The reaction was facilitated by conversion of the benzoic acid to either the Weinreb amide **4** (Scheme 1) or the methyl ester **11** (Scheme 2). Weinreb amide **4** and methyl pyrrole-2-carboxylate (**5**) were heated under basic conditions to give arylpyrrole **6**. Reduction of the nitro group and subsequent cyclization formed the quinoxalinone core. The Weinreb amide **7** was reduced to aldehyde **8** with lithium aluminum hydride. Introduction of the amine substituents at the 7- and 8-positions was made via reductive aminations of aldehyde **8** with various amines to give compounds 9a–**f** and **10a–c** (Table 1).

Alternatively, compounds **9g–h** were synthesized via bromide **17** shown in Scheme 2. Methyl ester **13** was reduced to alcohol **16** then converted to bromide **17** with PBr_3. Reaction with amines resulted in compounds **9g–h** (Table 1). Saponification of ester **13** to give carboxylic acid **14** followed by amide formation gave the desired amides **15a–c** (Table 1).

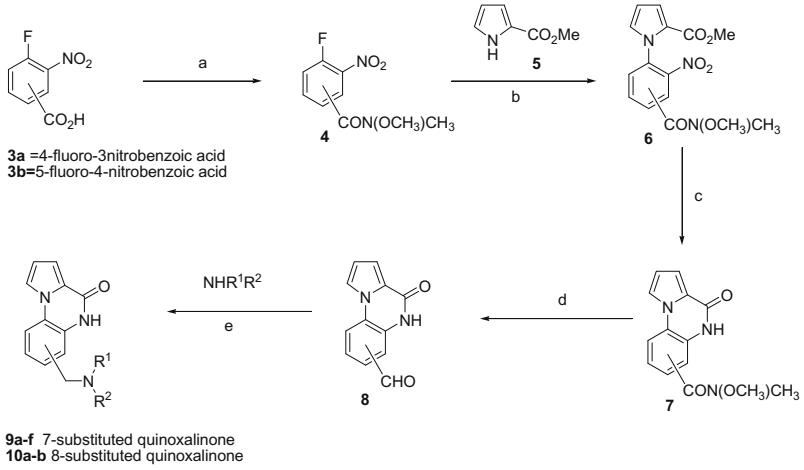
Imidazoquinoxalinones **23a–b** were prepared from N-arylation of ethyl imidazole-2-carboxylate (**18**) with methyl 4-fluoro-3-nitrobenzoate (**11**) as shown in Scheme 3. As in the pyrroloquinoxalinone series, the quinoxalinone core was constructed by reduction of the nitro group followed by cyclization. Reduction of methyl ester **20** followed by reaction with PBr_3 gave bromide **22**



Scheme 2. Reagents and conditions: (a) $SOCl_2$, MeOH; (b) Cs_2CO_3, DMF, 80 °C; (c) 10% Pd/C, EtOH; (d) 5 equiv LiOH, 5:1 THF/MeOH; (e) HATU, DIPEA, DMF; (f) LAH, 0 °C to rt; (g) PBr_3, dioxane, 0 °C to rt; (h) 3 equiv amine, CH_3CN.

which was reacted with various amines to give compounds **23a–b** (Table 1).

Ring expansion of the tricylic core to give the pyrrolodiazepinone scaffold is shown in Scheme 4. The acetal protected fluorocyanobenzaldehyde **25** was heated under basic conditions with pyrrole **6** to give N-arylated pyrrole **26.** The key intermediate **27** was obtained after Raney nickel reduction of the nitrile, cyclization and deprotection of the aldehyde. Reductive amination of aldehyde **27** with the requisite amines gave compounds **28a–b**.



Scheme 1. Reagents and conditions: (a) (1) $(COCl)_2$, CH_2Cl_2; (2) NH(OMe)Me·HCl; (b) Cs_2CO_3, DMF, 80 °C; (c) 10% Pd/C, EtOH; (d) 1 M LAH in THF, 0 °C for 0.5 h; (e) $Na(OAc)_3BH$, HOAc, CH_2Cl_2.