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Photoactivated Colibactin Probes Induce Cellular DNA Damage

Lindon W. K. Moodie,* Madlen Hubert, Xin Zhou, Michael F. Albers, Richard Lundmark, Sjoerd Wanrooij and Christian Hedberg*

Abstract: Colibactin is a small molecule produced by certain bacterial species of the human microbiota that harbour the *pks* genomic island. *Pks*$^+$ bacteria induce a genotoxic phenotype in eukaryotic cells and have been linked with colorectal cancer progression. Colibactin is produced in a benign prodrug form which, prior to export, is enzymatically matured by the producing bacteria to its active form. Although the complete structure of colibactin has not been determined, key structural features have been described including an electrophilic cyclopropane motif, which is believed to alkylate DNA. To investigate the influence of the putative "warhead" and the prodrug strategy on genotoxicity, we prepared a series of photolabile colibactin probes that upon irradiation induced a *pks*$^+$ like phenotype in HeLa cells. Furthermore, results from DNA cross-linking and imaging studies of clickable analogues enforce the hypothesis that colibactin effects its genotoxicity by directly targeting DNA.

Whilst co-evolution between humans and their resident microbes has yielded beneficial relationships, shifts in commensal microbial populations are linked with a number of disease states.[1] However, these correlations are not necessarily indicative of causation and it is important to understand the interactions driving these phenotypes at the molecular level.[2] In 2006, Nougayréde et al reported that certain commensal species of *Escherichia coli* and *Enterobacteriaceae* induced DNA damage and genomic instability during infection of eukaryotic cells.[3] This phenotype was attributed to the *pks* genomic island that produces the small molecule colibactin. Carriage of *pks* containing *E. coli* strains is overrepresented in biopsies from patients suffering colorectal cancer (CRC), inflammatory bowel disease and familial adenomatous polyposis.[4] Furthermore, *pks*$^+$ *E. coli* enhance in vivo tumour growth in mice that are predisposed to CRC.[4a, 5] Colibactin is produced in the bacterial cytoplasm in an inactive prodrug-like form (precolibactin) (Figure 1A). After export into the periplasmic space,[6] the precolibactin is cleaved by the peptidase ClbP to yield the benign *N*-myristoyl-D-asparagine[7] and the active genotoxic colibactin "warhead". It has been proposed that this prodrug mechanism, in combination with the production of the protective protein ClbS,[8] reduces autotoxicity. Given these factors, colibactin has been the subject of several reviews.[9]

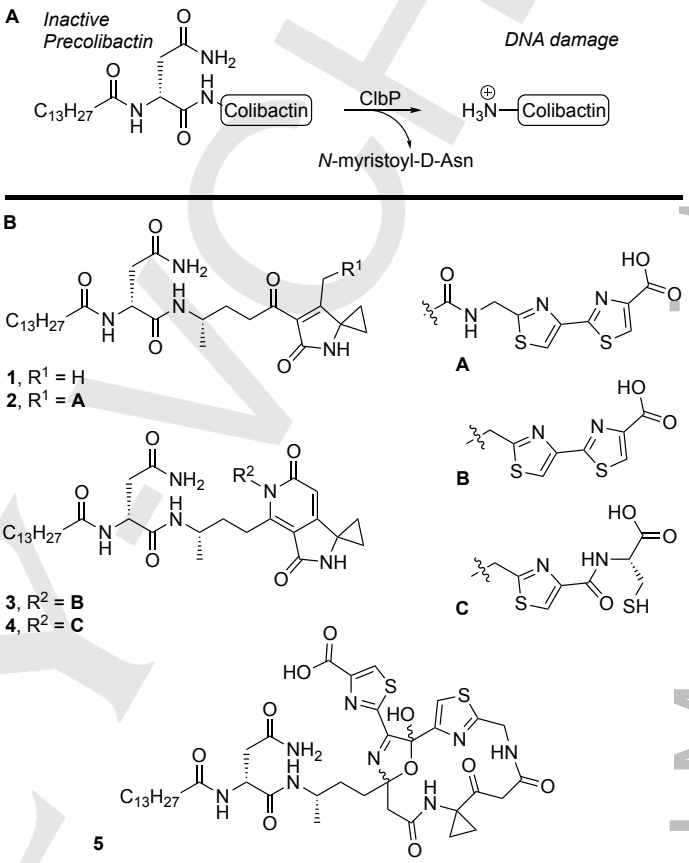

Figure 1. (A) Enzymatic prodrug mechanism of colibactin genotoxicity. (B) Precolibactins of the lactam (**1**-**2**), pyridone (**3**-**4**) and macrocycle (**5**) classes.

To date, the isolation of a colibactin metabolite produced by the full complement of biosynthetic genes required for in vivo genotoxicity has proven elusive. Furthermore, no de-acylated active colibactins have been isolated, presumably due to low production and instability. *ClbP* mutant *E. coli* strains have allowed the isolation of more stable pre-colibactins. However, evidence suggests that ClbP deletion alters the metabolite profile.[10] Three classes of precolibactins have been reported: lactams (**1**,**2**),[11] pyridones (**3**,**4**)[12] and the macrocycle **5** (Figure 1B).[13] The lactam type class is of significant interest due to their spirocyclopropane containing heterocycle, a motif reminiscent of known DNA and protein alkylating molecules.[14] As precolibactins are not genotoxic, it has been proposed that, after deacylation by ClbP and cyclization to form an α,β-unsaturated iminium species, the electrophilic cyclopropane is activated towards an endogenous nucleophile to affect its genotoxicity (Figure 2A).[11a, 11b] Recent studies have shown that precolibactin **1**[11a] and synthetic colibactin analogues[15] can crosslink (to some extent) and alkylate purified DNA, and nucleobase-colibactin adducts have been identified by mass spectrometry.[16] However, although the *pks* gene cluster has been investigated in infection models, studies of homogenous, activated colibactins

Dr. L. W. K. Moodie, Dr. M. F. Albers, Prof. Dr. C. Hedberg
Department of Chemistry
Umeå University
90187 Umeå, Sweden
E-mail: Lindon.moodie@umu.se
E-mail: Christian.hedberg@umu.se
Dr. M. Hubert, Prof. Dr. R. Lundmark
Integrative Medical Biology
Umeå University
90187 Umeå, Sweden
Dr. X. Zhou, Prof. Dr. S. Wanrooij, Prof. Dr. R. Lundmark
Medical Biochemistry and Biophysics
Umeå University
90187 Umeå, Sweden

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10.1002/anie.201812326

(isolated or synthetic) in a cellular context have not been reported. Accordingly, we aimed to determine if an active colibactin analogue featuring the putative cyclopropane-containing warhead, such as **6**, could induce a cellular phenotype similar to that reported for *pks*$^+$ bacterial infection. Given the suspected instability of colibactins towards isolation, we opted to use probes where the *N*-terminal amine is masked by a photolabile group (nitroveratryloxycarbonyl, NVOC) (Figure 2).[17] Analogous to the work of Tietze et al,[18] probes could be activated via photolysis and then added to the relevant biological system for evaluation. This approach would avoid the enzymatic maturation strategy used by the producing bacteria and, importantly, provide proof of concept that genotoxicity can be affected conditionally by alternate means of activation. During the progress of our studies, the synthesis of cyclized colibactin analogues was reported.[15a] However, compound **6** has yet to be synthesised, or isolated via cleavage of its corresponding precolibactin **1** using recombinant enzymes.[10, 11b] Accordingly, probes **7** and **8** were synthesised (See SI), allowing comparison of colibactin and precolibactin type motifs depending on if photolysis is employed before treatment of cells. In addition, the geminal dimethyl group of **8** allows us to elucidate the influence of the cyclopropane motif.

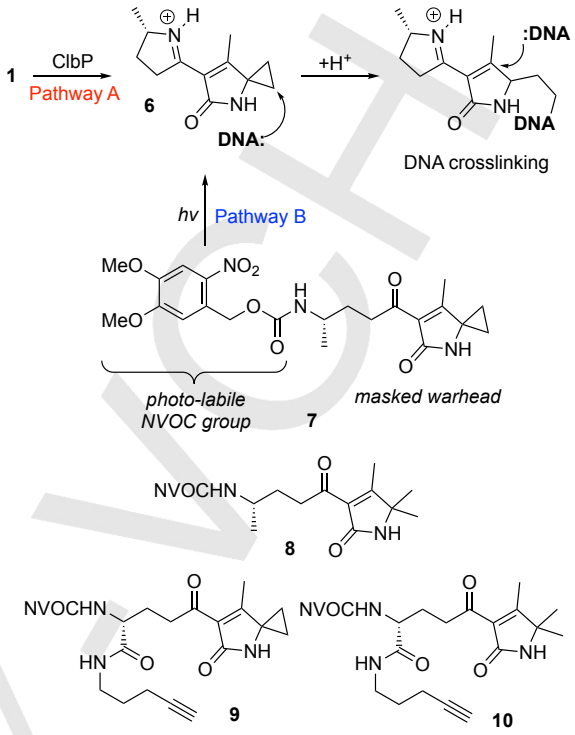

Figure 2. Proposed mechanism of DNA crosslinking.[11a, 19] Probes **7**-**10** featuring the photolabile NVOC group, *hv* indicates irradiation.

To investigate the behavior of **7** and **8** in cell culture, we examined three phenotypes that have been reported in *pks*$^+$ *E. coli* infection of HeLa cells: megalocytosis, cell cycle arrest at the G_2/M transition and histone H2AX phosphorylation.[3] Probes **7** and **8** (50 μM) were activated by irradiation at 365 nm (activated and non-activated compounds denoted as +*hv* and –*hv*, respectively) and then added to HeLa cells. Cell morphology evaluation revealed that cells treated with **7**(+*hv*) for 24 h displayed the megalocytosis phenotype: cellular and nuclear enlargement and the absence of mitosis (Figure 3A). Megalocytosis was not observed for NVOC protected amines **7**(-*hv*) and **8**(-*hv*), and **8**(+*hv*), even after extended incubation (Figure S2). Flow cytometry was used to monitor the effect of **7** and **8** on the cell cycle. After 72 h, only unsynchronized cells treated with **7**(+*hv*) arrested at the G_2/M transition (4n DNA content and negligible cell division) (Figure 3B). Cells synchronized in the G_1/S phase and treated with **7** and **8** (both +/-*hv*) were monitored over 48 h. Cells dosed with **7**(+*hv*) lagged in the S phase (6 and 10 h) before halting at the G_2/M transition. 7(-*hv*) also induced cell cycle delay (6 h), however the normal cell cycle was restored after 10 h. Cells were also monitored for H2AX phosphorylation, a sensitive marker for DNA double strand breaks,[20] via immunostaining and fluorescence microscopy. Only cells treated with **7**(+*hv*) exhibited an increase in γH2AX foci after 24 h (Figure 3C,S4). Consistent with cell cycle studies, non-irradiated **7** induced H2AX activation after 6 h, which returned to background levels after 24 h (Figure S4). These results show for the first time that an activated synthetic

10.1002/anie.201812326

colibactin analogue containing the putative warhead can induce these phenotypic responses observed during *pks*$^+$ bacterial infection. Precolibactin type structure, **7**(-*hv*), elicited only a transient response in terms of delaying cell cycle progression and inducing γH2AX foci. Although this effect could be attributed to NVOC hydrolysis, the stability of this group in cellular environments has been noted.[21] The attenuated activity of **7**(-*hv*), along with the lack of observed genotoxicity of **7**(+*hv*) at low concentrations, suggests that cellular DNA repair mechanisms can manage low-levels of colibactin induced DNA damage; consistent with findings that low doses of *pks*$^+$ *E. coli* induce reversible activation of the DNA damage response in CHO cells, and that cell lines deficient in the nonhomologous end-joining DNA repair pathway were highly susceptible to cell death.[22] These results, and the benign nature of dimethyl analogue **8**, support the hypotheses that colibactin genotoxicity is augmented by enzymatic *N*-deacylation, and the cyclopropane group is vital for genotoxicity. Whilst our work was under review, it was reported that synthetic colibactin analogues induced γH2AX foci but not 53BP1 activation in cell culture; implying that while model colibactins are a valuable tool they do not fully recapitulate the phenotype of *pks*$^+$ *E. coli* infection.[15b]

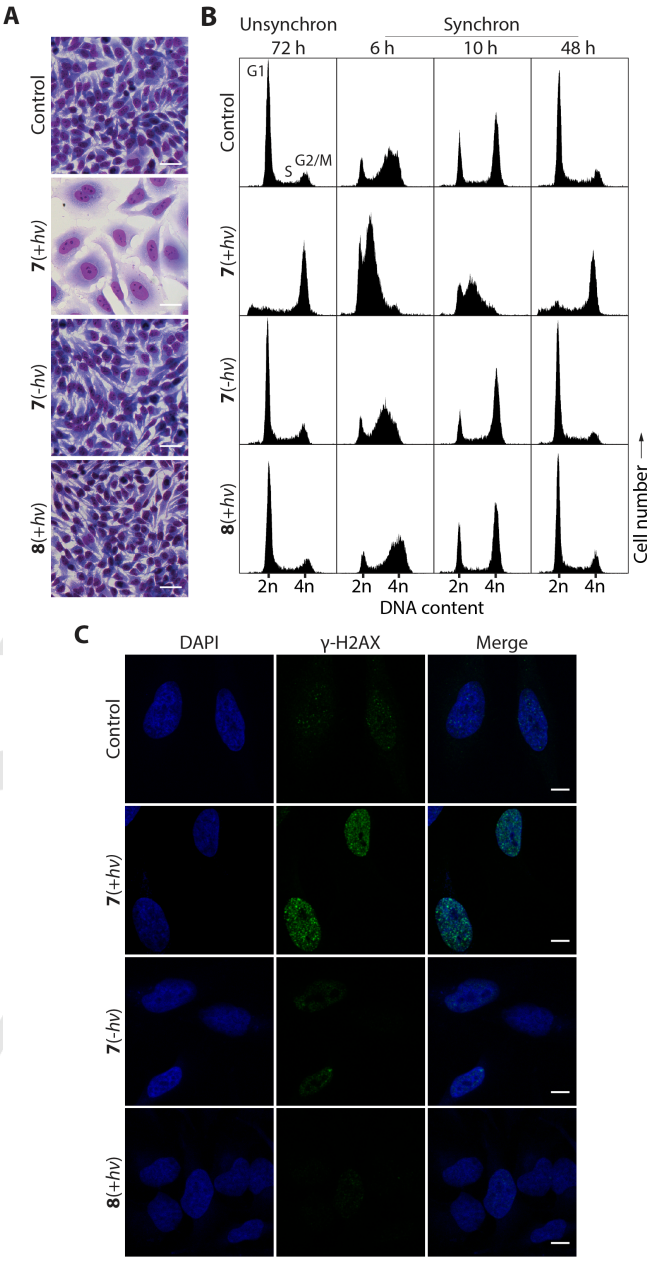

Figure 3. (A) Megalocytosis phenotype. Cells incubated with **7** or **8** (both +/-*hv*) (Giemsa stain). Scale bar, 40 μm (B) Cell cycle progression. Cells were either synchronized in G1/S phase (Synchron) or left unsynchronized (Unsynchron). After incubation with probes, DNA content was analyzed by flow cytometry. (C) Representative confocal images showing immunofluorescence of γ-H2AX and DNA (DAPI). Cells were treated with compounds for 24 h. Scale bar, 10 μm. For A-C: HeLa cells treated with 50 μM of compound, non-treated cells used as negative control. No significant effects observed for **8**(-*hv*) (Figure S3).

We next aimed to validate DNA as a cellular target. Linearized pBR322 plasmid DNA was incubated with either **7** or **8** (pretreated with or without irradiation before DNA incubation: +*hv* and –*hv*, respectively) and DNA crosslinking was evaluated by agarose gel electrophoresis.[15a] After 4 h, only **7**(+*hv*)

induced concentration dependent interstrand crosslinking in vitro (Figure 4A). Increased incubation times led to significant duplex DNA degradation, highlighting the instability of these adducts. Considering that **7**(-*hv*) provoked a mild, reversible *pks*$^+$ phenotype, and **1** is reported to weakly crosslink DNA,[11a] it was surprising that no significant DNA crosslinking was observed for **7**(-*hv*); perhaps due to DNA-adduct instability under the assay conditions. DNA melting curve analysis showed a concentration dependent increase in T_m (temperature where duplex DNA is 50% dissociated) only for DNA incubated with **7**(+*hv*), which is consistent with the cross-linking assays (Fig 4B).

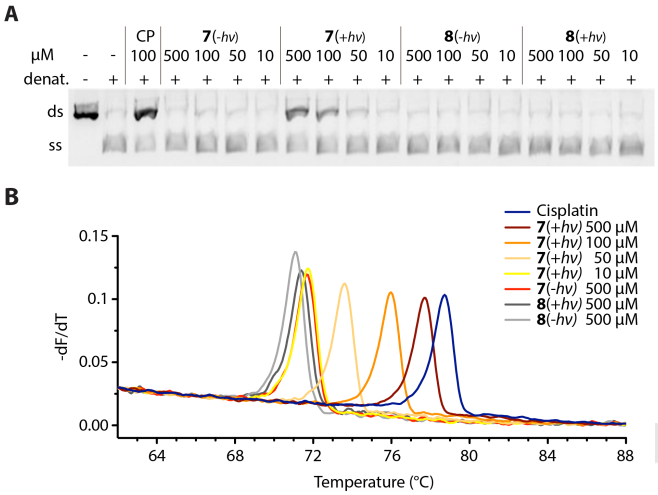

Figure 4. (A) DNA crosslinking assay. Linearized pBR322 plasmid incubated with **7** and **8** (both +/-*hv*) at concentrations shown (4h, 37°C). After NaOH induced strand separation, samples were run on 1% agarose Tris-Borate-EDTA (TBE) gel (75V, 1 h). A non-denatured sample and Cisplatin (CP) were used as positive controls. (B) DNA Melting curve analysis. Probes were incubated with DNA (4h, 37°C). Curves show the negative first derivative of fluorescence (F) with respect to temperature (T).

The ability of **7**(+*hv*) to moderately crosslink DNA in a cyclopropane dependent manner is consistent with the proposed mechanism of genotoxicity where, after cyclopropane opening by DNA, tautomerization leads to a species that behaves as a Michael acceptor for a second nucleophilic attack by DNA (Figure 2).[11a, 11b] This is supported by a recent study showing that infection of cultured human cells with +*pks* bacteria results in cross-linking of genomic DNA and, furthermore, that the addition of extracellular DNA reduced this effect.[23] Healy et al recently reported that colibactin analogues featuring the unsaturated imine found in **6** only alkylated purified DNA.[15a] Subsequent work using optimized assay conditions revealed these compounds are also capable of DNA crosslinking, however the adducts are more labile than those induced by *pks*$^+$ *E. coli*.[15b] It is of note that these compounds were more potent than **7**(+*hv*), which can be attributed to the DNA binding properties of the thiazole and amine containing side chains. Taken together, this suggests that colibactin structure can govern the nature of DNA damage. Determining whether this reactivity is due to differing DNA-colibactin interactions or attenuated reactivity of the warhead towards a second nucleotide 1,4-addition requires further examination.

Inspired by previous work on DNA targeting molecules,[24] we used alkyne-containing analogues **9** and **10** that, after click conjugation with an azide-functionalized fluorophore, are capable of reporting cellular localization. Phenotype and DNA crosslinking studies of these compounds were conducted to verify their suitability as probes (Figures S5-S7). HeLa cells were incubated with either **9** or **10** (+/-*hv*, 50 μM) for 24 h and, after γH2AX immunostaining, were treated with a click cocktail containing $CuSO_4$, TBTA, TCEP and Alexa Fluor 647 azide. The subcellular distribution of the click derived fluorescent signal was examined by confocal fluorescence microscopy. Only cells treated with **9**(+*hv*) showed intense fluorescence, which localized with the γH2AX signal within nuclei (DAPI) (Figure 5). Accumulation in the nucleoli and minor cytoplasmic staining was observed, which has also been noted during studies of platinum based DNA targeting probes.[24d, 24e]

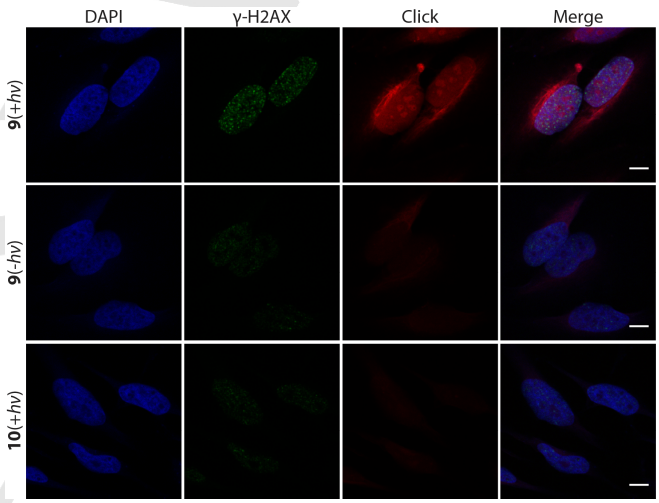

Figure 5. Click labeling of HeLa cells after treatment with **9** or **10** (both +/-*hv*). Cells incubated with probe (50 μM) for 24 h, fixed, permeabilized and immunostained for γ-H2AX. Alexa Fluor 647 azide was conjugated to the alkyne motif via a $CuSO_4$-catalyzed click reaction. DNA stained with DAPI. Scale bar, 10 μm. No significant effects observed for **10**(-*hv*) (Figure S8).

Our crosslinking and cellular localization studies provide strong evidence that activated colibactin molecules **7** and **9** featuring the lactam warhead directly target nuclear DNA. Reactivity with members of the proteome is also possible,[25] and activity based protein-profiling studies will aim to address this. Colibactin represents an enigmatic example of a genotoxic metabolite derived from our resident bacteria that has been linked to both colorectal cancer and inflammatory bowel disease. Our studies with light activated probes **7**-**10** show that colibactin analogues containing the activated warhead motif are capable of inducing phenotypes associated with *pks*$^+$ *E. coli* infection. We note that, given its low potency and lack of more complex structural features resulting from the full complement of biosynthetic genes in the pks cluster, compound **6** is not responsible for genotoxicity induced by +*pks* bacteria. However, our work does link an active colibactin analogue with cellular

genotoxicity. Furthermore, our studies support the hypothesis that colibactins can directly damage DNA via crosslinking.[11a, 15b, 23] Future work will aim at determining the nature of colibactin – DNA interactions using MS and CD-based techniques.[26] The current study is also proof of principle that alternative prodrug activation manifolds can be used to elicit DNA damage. Whilst this work provides a compelling link between molecular structure and cellular genotoxicity, the story of colibactin is far from complete. Unresolved areas of question include the transportation of colibactin between producer and host, the exact mechanism of DNA crosslinking, the role it plays in gastrointestinal disorders and, indeed, the complete structure of colibactin itself. To answer these questions a multidisciplinary approach will be required, where preparative organic chemistry can make a valuable contribution.

Acknowledgements

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Keywords: Colibactin • Microbiome • Photochemistry • DNA Damage • Click Chemistry

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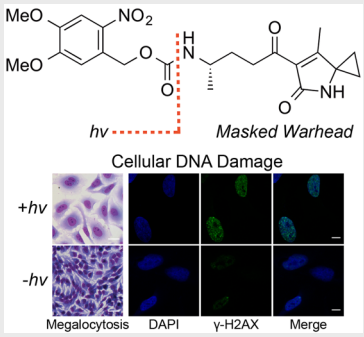

Lindon W. K. Moodie, Madlen Hubert, Xin Zhou, Michael F. Albers, Richard Lundmark, Sjoerd Wanrooij and Christian Hedberg**

Page No. – Page No.

Photoactivated Colibactin Probes Induce Cellular DNA Damage

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Page No. – Page No.

Title