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COMMUNICATION

Close the ring to break the cycle: Tandem quinolone-alkyne-cyclisation gives access to tricyclic pyrrolo[1,2-*a*]quinolin-5-ones with potent anti-protozoal activity

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Dávid Szamosvári,[a] Kayla Sylvester,[b] Philipp Schmid,[a] Kuan-Yi Lu,[b] Emily R. Derbyshire *[bc] and Thomas Böttcher *[a]

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Expanding the chemical space of quinolones led to a tandem quinolone-alkyne-cyclisation reaction allowing chemoselective control of the synthesis of tricyclic pyrrolo[1,2-*a*]quinolin-5-ones. Importantly, we discovered anti-protozoal activity against *Plasmodium* and *Toxoplasma* with specific potency of one of the compounds against the liver stage of the malaria parasite in the nanomolar range.

Quinolines and quinolones are privileged structures that are common features in a large variety of medically valuable natural products and artificial drugs.[1-3] Many of them exhibit antibiotic[4, 5] and antiprotozoal activities.[6, 7] While 3-carboxy-4(1*H*)-quinolones inhibit topoisomerases and thus replication, 2-alkyl-4(1*H*)-quinolones (AQs) and their *N*-oxides (AQNOs) are known to target proteins of the electron transport chain in Gram-positive bacteria, mycobacteria and protozoa.[1] We have recently demonstrated that one of the various naturally produced AQNOs of the human pathogen *P. aeruginosa* – a *trans*-unsaturated 2-nonenyl-4-quinolone *N*-oxide (*trans*-Δ^1-NQNO) – is particularly potent against *S. aureus*.[8] While the saturated AQNO congeners were considerably less active or inactive against *S. aureus*,[8] saturated AQNOs such as 2-dodecyl-4-quinolone *N*-oxide (DQNO) are potent anti-protozoal agents with activity against *Plasmodium falciparum* and *Toxoplasma gondii* parasites.[9-12] These 4(1*H*)-quinolones and their *N*-oxides are dual inhibitors of the electron transport chain of protozoa via type II NADH:ubiquinone oxidoreductase (*Pf*NDH2 and *Tg*NDH2) and the cytochrome bc_1 complex.[11-13] In *Mycobacterium tuberculosis* structurally related 4(1*H*)-quinolones inhibited NADH:menaquinone oxidoreductase (Ndh).[14] In addition, ortho- and peri-fused tricyclic quinolines and 4(1*H*)-quinolones have been described as anti-plasmodial agents. These include natural products like aurachine E[15] or furoquinolines[16] as well as the quinolone related, synthetic tricyclic acridinediones and acridones.[17] Hereby the fusion side of the ring on the quinolone seems to be a critical factor for antiplasmodial activity. While ortho-ring fusion *b* sides are common and enable activity, *c* side fused-4(1*H*)-quinolones that lock the 4-position, such as aurachines A and H, were inactive against protozoa.[15] Interestingly, *a* side fused 4(1*H*)-quinolones including position 1 nitrogen have so far not been investigated for their antiprotozoal potential. We thus envisioned a simple synthesis giving access to new tricyclic 4-quinolone compounds to study their activity against protozoal pathogens. Here, we report synthetic access to previously undescribed pyrrolo[1,2-*a*]quinolin-5-ones by a tandem cyclization reaction involving a Camps reaction and the nucleophilic addition on an alkyne moiety. In addition, we show that these tricyclic quinolinones display antiprotozoal activity and are especially potent against the liver stage of *Plasmodium*. Our pyrrolo[1,2-*a*]quinolin-5-ones represent the first examples of antiprotozoan compounds based on this tricyclic core which may be useful for future drug development efforts. In particular new scaffolds with antiplasmodial activity are desirable to address parasite resistance to existing quinolone-based drugs.

We started by comparing the activities of the native saturated and unsaturated AQs and AQNOs of *P. aeruginosa* against the blood and liver stage of the *Plasmodium* parasite that causes malaria, and against *Toxoplasma gondii,* the causative agent of toxoplasmosis. The synthesis of the saturated AQs (**1-4**) and AQNOs (**5-8**) was described previously.[8] At concentrations of 5 µg/mL all tested AQs and AQNOs were highly potent against *Plasmodium* and *Toxoplasma*, demonstrating the general activity of the 4-quinolone scaffold is largely independent of its alkyl side chain length (Fig. 1). Most notably, infection of human red blood cells by *Plasmodium falciparum* was fully abrogated by all compounds at 5 µg/mL.

[a] *Department of Chemistry, Konstanz Research School Chemical Biology, Zukunftskolleg, University of Konstanz, 78457 Konstanz, Germany. E-mail: Thomas.Boettcher@uni-konstanz.de*
[b] *Department of Molecular Genetics and Microbiology, School of Medicine, Duke University, Durham, North Carolina 27708 USA.*
[c] *Department of Chemistry, Duke University, Durham, North Carolina 27708 USA. E-mail: Emily.Derbyshire@duke.edu.*
† Footnotes relating to the title and/or authors should appear here.
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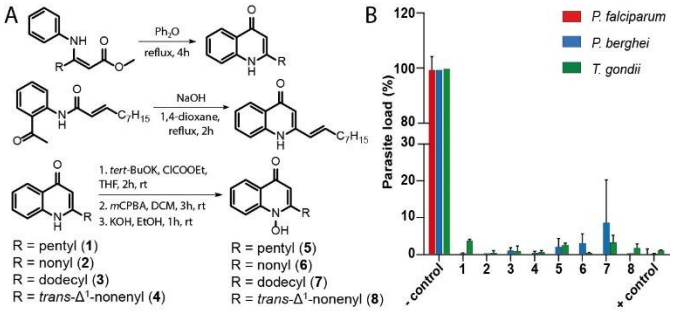
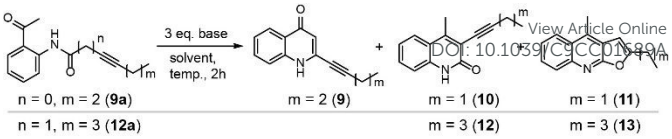


Fig. 1 (A) Synthetic route for the generation of natural saturated and unsaturated AQs (**1**-**4**) and AQNOs (**5**-**8**). (B) Activity of compounds **1**-**8** against protozoa.

Parasite loads of *Plasmodium berghei* in liver HuH7 cells decreased by one to three orders of magnitude and *T. gondii* parasite load decreased by two orders of magnitude. No major differences were found in the activity between AQs and AQNOs, and saturated and unsaturated compounds, in all three protozoan infection models. This result was particularly interesting since AQs were virtually inactive against *S. aureus*, suggesting that a greater diversity of substitutions at the nitrogen could be tolerated for compounds against protozoa. We next aimed to expand the chemical space by the synthesis of novel tricyclic quinolone-derived scaffolds. Since alkynes are known to engage in diverse rearrangement and annulation reactions,[18, 19] we explored if alkynylated 4(1*H*)-quinolones could give access to the corresponding tricycles. We first focused on the synthesis of Δ[1]-2-pentynyl-4(1*H*)-quinolone (**9**) with an alkyne group directly at the position 2. The only method for the synthesis of similar 2-alkynyl-4-quinolone was described by Wube et al.[20] who reacted *N*-alkyl isatoic acid anhydride with 3-alkynyl-2-ones to obtain *N*-alkyl-2-alkynyl-4-quinolones after the procedure of Coppola.[21] This method could not be applied for our non-*N*-alkylated target compound therefore we used previous Camps cyclization conditions for amide **9a** to give the desired compound **9**. Interestingly, we could also isolate the 2-quinolone **10** as the main product of the reaction which required a 1,2 shift of the triple bond. Activation by the electron withdrawing carbonyl of the amide group next to the triple bond likely facilitated deprotonation and thereby induction of an alkyne-zipper reaction that enabled the ring closure to the 3,4-disubstituted-2(1*H*)-quinolone product by Camps cyclization (Scheme S1A). Since the chemoselectivity of this alkyne-zipper-induced Camps cyclization was surprising, we screened different reaction conditions (Table S1). The 4-quinolone product was obtained only in low yields under all conditions and always as byproduct with its 2-quinolone isomer. The ring closure to the 2-quinolone was generally preferred in presence of weak ($CsCO_3$) or bulky base (*tert*-BuOK). These conditions may have favored induction of the alkyne shift over α-deprotonation of the acetophenone. When using *tert*-butanol as solvent instead of 1,4-dioxane with either $CsCO_3$ or *tert*-BuOK under reflux conditions (83°C), we could surprisingly observe the formation of a third product identified as 2-ethyl-4-methylfuro[2,3-*b*]quinoline **11**.



Scheme 1. Synthesis of furo[2,3-*b*]quinolones **11** and **13**.

The more polar solvent *tert*-butanol seemed to facilitate lactam-lactim tautomerization of the 2- quinolone amide group to its 2-hydroxyquinoline that reacts in an intramolecular nucleophilic addition with the sp[1]-carbon of the triple bond to perform a second, consecutive ring closure after the alkyne-zipper-induced Camps cyclization. The reaction mechanism via the 3-alkynyl-2(1*H*)-quinolone was confirmed by base treatment of the isolated 2-quinolone **10** bypassing the alkyne zipper to receive **11** in 64% yield which proofed to be the limiting factor for the synthesis of the furo[2,3-*b*]quinolones during the tandem reaction. When oct-3-ynamide **12a** was used as substrate under the same conditions, yield of the furoquinoline **13** in the tandem reaction could be increased to 32% (Scheme 1). Cyclization reactions of similar 2-quinolones and 2-pyridones that depend on iodide or copper(I) iodide catalysts are known.[22, 23] While our tandem mechanism allows a new rapid synthesis of furo[2,3-*b*]quinolones, this compound class itself is already known for its antiprotozoal activity.[16, 24] We speculated that Δ[2]-2-alkynyl-4(1*H*)-quinolones could give access to new tricyclic cores when the α-position of the amide was blocked and hence obstructed 2-quinolone formation.

We synthesized 2,2-dimethyl-oct-3-ynamide **14d** and subjected it to the same conditions that enabled the tandem reaction leading to furoquinolones. As expected, Camps cyclization to the 2(1*H*)-quinolone product was prevented and the 4(1*H*)-quinolone **14** was isolated as a minor reaction product. The major product was isolated and identified as 1-butyl-3,3-dimethylpyrrolo[1,2-*a*]quinolin-5(3*H*)-one **15**, a tricyclic compound with a previously undescribed scaffold which presumably was formed by addition of the quinolone-nitrogen on the alkyne. To investigate the synthesis of this pyrroloquinolin-5-one structure, we screened the reaction for chemoselectivity under identical reaction conditions as for the furoquinolones.

4(1*H*)-Quinolone (**14**) formation was generally facilitated by strong bases like NaOH and *tert*-BuOK independent of temperature and whether a protic (*tert*-butanol) or aprotic solvent (1,4-dioxane) was used. Only in combination with the more polar solvent *tert*-butanol, $CsCO_3$ induced Camps cyclization in very low yields. In 1,4-dioxane at 75 °C with *tert*-BuOK as base, trace amounts of the endocyclic unsaturated pyrrolo[1,2-*a*]quinolin-5-one (**15**) were observed, while under reflux traces of only an exocyclic unsaturated product, 3,3-dimethyl-2,3-dihydropyrrolo[1,2-*a*]quinolin-5-one (**16**) were obtained. With the protic solvent *tert*-butanol, cyclization of **14** to the endocyclic unsaturated tricycle **15** increased drastically with either NaOH (yield 35%) or tert-BuOK (yield 57%). In order to mechanistically dissect these reactions, we used an up-scaled preparation of 2-alkynyl-4(1*H*)-quinolone **14** which was subsequently investigated in cyclisation reactions to the pyrrolo[1,2-*a*]quinolin-5-ones **15** and **16**. In *tert*-butanol under

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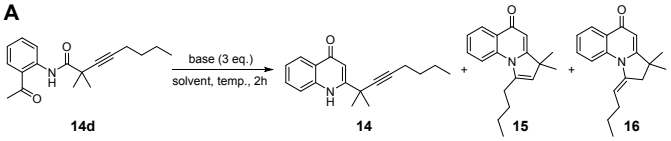
reflux with *tert*-BuOK, **15** was obtained in 55% yield, confirming that the reaction proceeded via the 4(1*H*)-quinolone. However, under these conditions the constitutional isomer **16** was not detectable. This phenomenon suggests that **15** was the kinetic product whereas the thermodynamically more favorable product **16** with lower strain in the fused pyrrolidine ring would form at higher temperature (Table 1A). Motivated by the perspective of chemoselective synthesis of the unprecedented scaffold of **16**, we tested solvents with higher boiling points. While Ph_2O and DMSO gave no product or a complex mixture of products, DMF at 100°C selectively facilitated the cyclization of **14** to **16** in yields of 27% without formation of **15**. Temperature increase or longer reaction times had no or rather adverse effects on the yield of **16** (Table 1B). Interestingly, from the same reaction we could also identify the dienylquinolones **17** and **18** (Scheme S1B), suggesting the formation of **16** via the allene as the initial step of an alkyne-zipper reaction similar to the reaction towards furoquinolines (Scheme S1C). Previously reported syntheses of pyrrolo[1,2-*a*]quinoline-5-ones were dependent on pyrrolidine or pyrrolidine-2-one precursors and therefore contained only fully saturated pyrrolo-units.[25-28] We here provide the first example of chemoselectively synthesized unsaturated pyrrolo[1,2-*a*]quinolin-5-ones **15** and **16** that extend

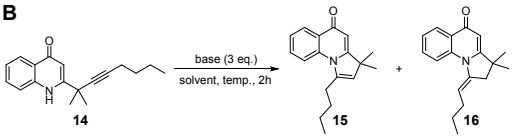
Table 1 Optimization of reaction conditions.

A



base	solvent	temp.	yield **14** (%)[a]	yield **15** (%)[a]	yield **16** (%)[a]
NaOH	1,4-dioxane	75 °C	76	-	-
tert-BuOK	1,4-dioxane	75 °C	68	traces[b]	-
$CsCO_3$	1,4-dioxane	75 °C	-	-	-
NaOH	1,4-dioxane	reflux	72	-	-
tert-BuOK	1,4-dioxane	reflux	60	-	traces[b]
$CsCO_3$	1,4-dioxane	reflux	-	-	-
NaOH	*tert*-BuOH	reflux	64	35	-
tert-BuOK	*tert*-BuOH	reflux	26	57	-
$CsCO_3$	*tert*-BuOH	reflux	8	-	-

B



base	solvent	temp.	time (h)	yield **15** (%)[a]	yield **16** (%)[a]
tert-BuOK	*tert*-BuOH	reflux	4	75	-
tert-BuOK	DMSO	100 °C	2	-	-[c]
tert-BuOK	DMF	100 °C	2	-	27[d]
tert-BuOK	DMF	100 °C	4	-	15[e]
tert-BuOK	DMF	125 °C	o/n	-	-[c]
tert-BuOK	Ph_2O	100 °C	2	-	-[f]

[a]isolated yields. [b]identification based on NMR from impure chromatography fractions. [c]complex mixture of products. [d]48% of **14** was recovered. [e]35% of **14** was recovered. [f]93% of **14** was recovered.

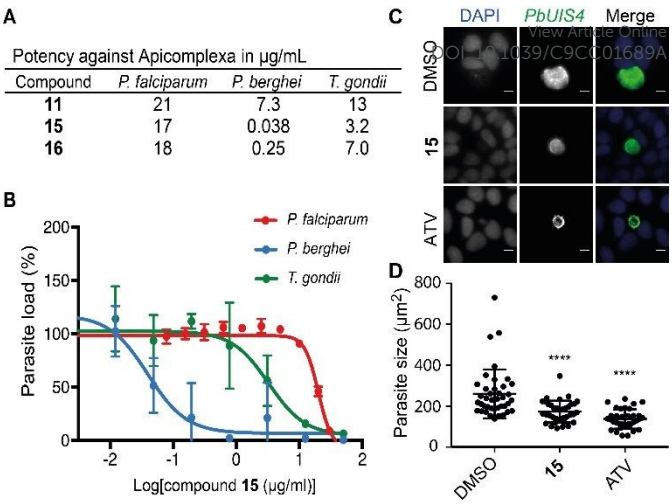


Fig. 2 (A) Activity of tricyclic compounds **11**, **15** and **16** against protozoa. Potency reported as IC_{50}s in µg/mL. *P. berghei* and *T. gondii* loads were evaluated in human liver HuH7 cells while *P. falciparum* load was evaluated in human red blood cells. (B) Dose-dependent activity of **15** against various parasites. (C) Visualization of *P. berghei* growth in liver HuH7 cells in the presence of **15** (0.37 µM) and atovaquone (1 nM). Representative images were shown. Scale bar is 10 µm. (D) Quantification of parasite size in the presence of **15** and atovaquone (ATV). *p*-value <0.0001 (****).

the chemical space of this so far rather unexplored class of pyrrolo[1,2-*a*]quinolin-5-ones. To determine if these new scaffolds have biological activities similar to quinolines and quinolones, their antiparasitic activity was profiled.

We hereby investigated the anti-protozoal activity of novel tricyclic compounds. All compounds exhibited only moderate activity against the blood stage of *P. falciparum* (Fig. 2A). While the furo[2,3-*b*]quinolone was generally the least active compound, the pyrrolo[1,2-*a*]quinolin-5-ones **15** and **16** gave IC_{50} values of 3.2 µg/mL and 7.0 µg/mL against *T. gondii*. The compounds were particularly active against the liver stage of *P. berghei*. Here, **15** and **16** exhibited IC_{50} values of 0.038 µg/mL and 0.25 µg/mL corresponding to activity in the nanomolar range (142 nM and 935 nM, respectively). Importantly, **15** did not affect human liver cell (HuH7) viability up to 50 µg/mL, indicating a favorable selectivity index (Fig. 2B, Fig S3). While the scaffold structure of **15** and **16** differs only in the endo- and exocyclic double bond of the fused pyrrole-unit, it caused a pronounced difference in activity with **15** being over six-times more active than **16** against the liver stage of *P. berghei*. This strict dependence on the position of just one double bond indicates that even minor structural modification of the pyrrolo[1,2-*a*]quinolin-5-one scaffold may be exploited to customize anti-protozoal activity. Compound **15** reduced *P. berghei* parasite size similar to the atovaquone positive control (Fig. 2C, 2D), further demonstrating the anti-*Plasmodium* activity of the compound. Yet unlike atovaquone and other cytochrome bc_1 complex inhibitors,[29-31] **15** exhibits greater inhibition of liver stage *Plasmodium* parasites when compared to the blood stage (Table S2, Fig. S4). This unique selectivity profile suggests that **15** reduces parasite load by a mechanism

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distinct from well-characterized electron transport chain disruption. While currently unknown, this additional mode(s) of action makes the scaffold desirable for further development to target drug resistant *Plasmodium* parasites.

Access to new structural diversity is one of the most promising strategies against the uprising of drug resistance in protozoan pathogens like *Plasmodium* or *Toxoplasma*. Besides modification of already existing scaffolds, the innovation of skeletal diversity is arguably the most important principle for generating biological activity.[32, 33] Naturally produced 2-alkyl-4-quinolone and their *N*-oxides comprise general activity against protozoa with position 1 and 2 as convenient and flexible modification sites. Using a catalyst-free, tandem cyclization reaction we optimized the chemoselective synthetic accessibility of novel tricyclic pyrrolo[1,2-*a*]quinolin-5-one scaffolds that exhibit promising new skeletal features for drug development.

Conflicts of interest

There are no conflicts to declare.

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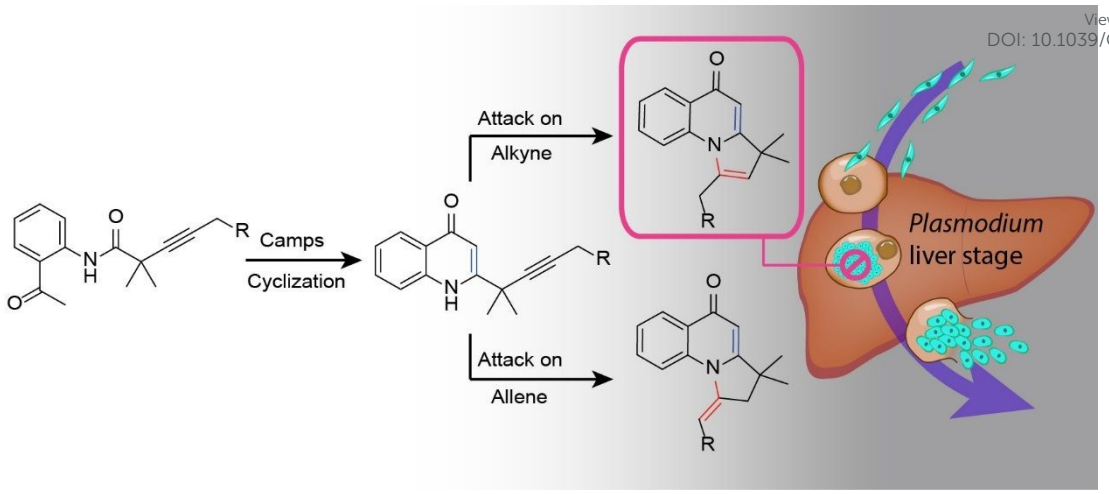

We describe a tandem reaction leading to tricyclic pyrrolo[1,2-*a*]quinolin-5-ones with unique selectivity against the liver stage of the malaria parasite.

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