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Synthesis of 1,2,3-Triazole-Methyl-Menadione Derivatives: Evaluation of Electrochemical and Antiparasitic Properties against two Blood-Dwelling Parasites

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This study explores the synthesis and evaluation of novel 1,2,3-triazole-methyl-1,4-naphthoquinone hybrids, focusing on their electrochemical properties and antiparasitic efficacies against two human blood-dwelling parasites *Plasmodium falciparum* and *Schistosoma mansoni*. Using copper-catalyzed azide-alkyne cycloaddition (CuAAC), a well-established tool in click chemistry, two synthetic routes were assessed to develop α - and β -[triazole-methyl]-menadione derivatives. By optimizing the CuAAC reaction conditions, yields were significantly improved, reaching up to 94% for key intermediates and resulting in the formation of a library of approximately 30 compounds. Bio-

logical evaluation of the compounds in antiparasitic drug assays demonstrated notable antischistosomal potencies, while no significant activity was observed for the same series against *P. falciparum* parasites. Electrochemical and 'benzylic' oxidation studies confirmed that the active 'benzoyl' metabolite responsible for the antiplasmodial activity of plasmodione cannot be generated. These findings highlight the potential of triazole-linked menadione hybrids as promising early candidates for antischistosomal drug development, and provides insights into structure-activity relationships crucial for future therapeutic strategies.

Introduction

Malaria is an infectious disease caused by the protozoan parasite *Plasmodium*, which is transmitted by the bite of an infected *Anopheles* mosquito. It is most prevalent in the Sub-Saharan Africa and in tropical and sub-tropical regions. In 2022, there was 249 million cases of malaria – well above the estimated number of cases before the COVID-19 pandemic, and an increase of five million over 2021, killing an estimated 608,000 people in 2022, mainly children under the age of five years in sub-Saharan Africa.^[1] Five major species of the *Plasmodium* parasite – *P. falciparum*, *P. malariae*, *P. vivax*,

P. ovale, *P. knowlesi* – can infect humans; the most severe forms of the disease, leading to cerebral malaria, severe anaemia and ultimately death are largely caused by *P. falciparum*. However, most of the drugs among them chloroquine, atovaquone, or artemisinin available to treat these diseases are subject to resistance, which limit their effectiveness.^[2]

Schistosomiasis is an acute and chronic neglected tropical disease caused by *Schistosoma* trematode worms. There are two major forms of schistosomiasis – intestinal and urogenital – caused by five main species of blood flukes that infect humans: *S. mansoni*, *S. japonicum*, *S. haematobium*, *S. intercalatum* and *S. mekongi*. The intermediate host of the parasite, various species of freshwater snails, transfer human infection through skin contact with infective cercariae.^[3] According to the World Health Organization report published in 2023, 251.4 million people are infected, more than 700 million people are at risk of infection and currently estimated – but likely underestimated – 11,792 deaths globally per year.^[4] The disease is often co-endemic with malaria and is found in most of Africa, Brazil, China, and the Philippines. In addition, urogenital schistosomiasis and genital schistosomiasis caused by *S. haematobium* increases the risk of HIV co-infection and cervical precancer lesions in women with a nearly four-fold higher susceptibility.^[5]

Over the last decade, our team have invested much effort in a potent antiparasitic series of compounds known as 3-benzylmenadione (bMD) that target the redox homeostasis of two blood-feeding parasites, such as *P. falciparum* parasitizing human red blood cells (pRBC)^[6,7] or the *S. mansoni* flatworms.^[8] Most of the research was focused on medicinal chemistry of the antiplasmodial early lead plasmodione (PD)^[9] (Figure 1), in particular on the understanding of its mode of action

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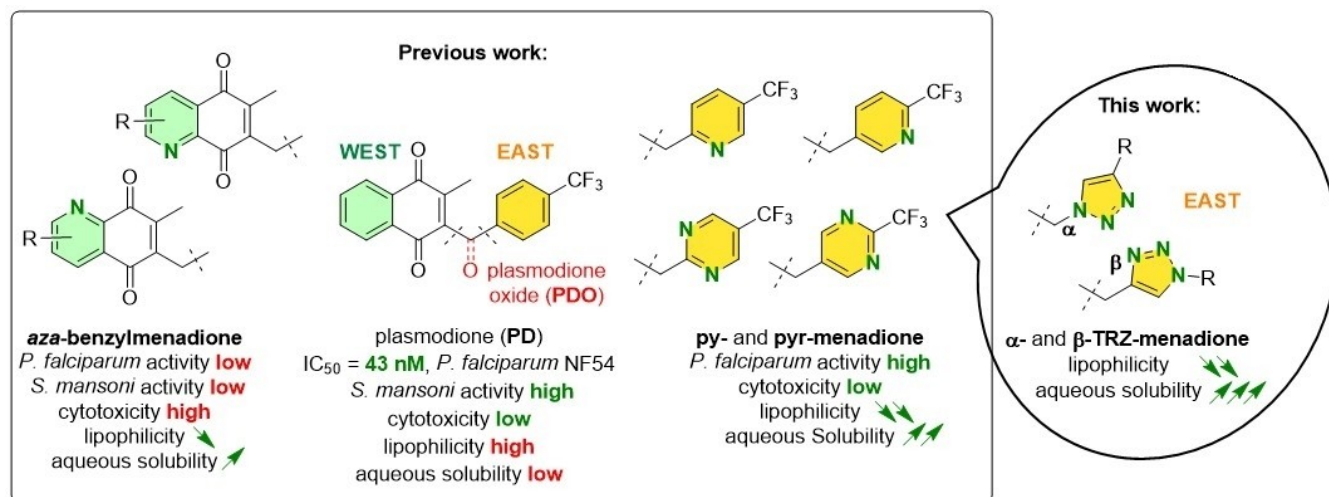


Figure 1. Work progress following introduction of *N*-heteroaromatics in the aromatic rings of 3-benzylmenadiones, from the eastern to the western part.

(MoA)^[10–12] and the optimization of its biological activity and pharmacokinetic (PK) properties.^[13,14] Although its MoA has been partially deciphered in yeast,^[15] we demonstrated that the 3-benzoylmenadione (PDO) (Figure 1) is a key metabolite generated from PD through a bioactivation process.^[12,16] PDO is generated via a two steps sequence: reduction of the 1,4-naphthoquinone electrophore to semi-naphthoquinone^[17] by flavoenzymes that thus enables oxidation of the benzylic position by insertion of O_2 .^[12] The resulting PDO then acts as a subversive substrate in a redox cycle involving an endogenous reductant, oxygen and/or methemoglobin.^[6,10,15] This redox cycle not only slows down the process of methemoglobin catabolism (digestion through proteolysis and hemozoin formation), but also produces other harmful drug metabolites and reactive oxygen species (ROS) that ultimately leads to the death of the parasite.^[10]

One of the main advantages that medicinal chemistry can bring to enhance the potency of a lead molecule is to bring subtle modifications of its physicochemical properties through introduction of chemical diversity in order to improve its PK properties. In particular the enhancement of the aqueous solubility and the decrease of the lipophilicity of derivatives based on a BMD scaffold is one of the target strategies in this work. We have therefore investigated the effect of introducing nitrogen-containing aromatics into the backbone of the lead molecule. A first step towards this goal has been achieved through the development of a series of aza-benzylmenadiones^[8] (Figure 1) which, while improving the solubility properties, also increased the cytotoxicity towards human cells through their effects on electrochemical properties of the aza-menadione core. The chemical modifications on the west side of the molecule were therefore abandoned and efforts focused on the east side of the molecule.

Recently, we have shown that the introduction of various substituted pyridine (py) and pyrimidine (pyr) moieties on the eastern part (Figure 1) led to promising antimalarial activities without generating undesirable side effects (e.g. increased

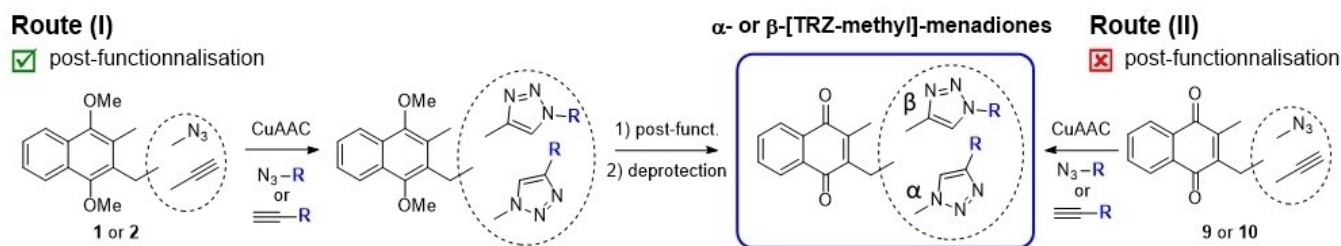
cytotoxicity).^[18] Following this concept, 1,2,3-triazole (TRZ) motifs were thus considered to improve the properties of the pharmacophore. TRZ rings, which are bioisosters of amide and ester functions, have indeed a high stability, dipole moment and hydrogen bonding ability that enhances their pharmacological properties, in particular their influence on target-drug interactions, metabolism and PK properties.^[19] Over the last decade, advances in click chemistry (e.g. Cu-catalyzed azide-alkyne cycloaddition or CuAAC)^[20] have not failed to stimulate interest in antiparasitic TRZs in medicinal chemistry of naphthoquinone moieties.^[21–25] A recent review also describes the many developments in life sciences based on 1,4,5-trisubstituted halo-1,2,3-triazole scaffolds.^[19] Therefore, we hypothesized that the introduction of α - or β -TRZ (Figure 1) could contribute to improve the antischistosomal and antimalarial activities of our substituted menadione series. In this work, we thus evaluated in depth the effect of the introduction of TRZ moieties on the antiparasitic activity against two different parasites and the consequences on the physico-chemical properties.

Results and Discussion

Synthesis of 1,2,3-[TRZ-Methyl]-Menadiones

Two different synthetic routes were initially considered to obtain the α - or β -[TRZ-methyl]-menadione derivatives (Scheme 1). Route (I) involves the use of a protected menadione as starting material, i.e., 1,4-dimethoxy-2-methylnaphthalene, functionalized with azide or alkyne groups to be engaged in a CuAAC reaction.

Since the carbonyls are protected, straightforward post-functionalization can be initiated, followed by deprotection to generate the α - or β -[TRZ-methyl]-menadione in three steps. Route (II) directly involves the unprotected menadione, generating [TRZ-methyl]-menadiones in only one step, but greatly



Scheme 1. Accessibility of α - or β -[TRZ-methyl]-menadione through two different routes with their pros and cons.

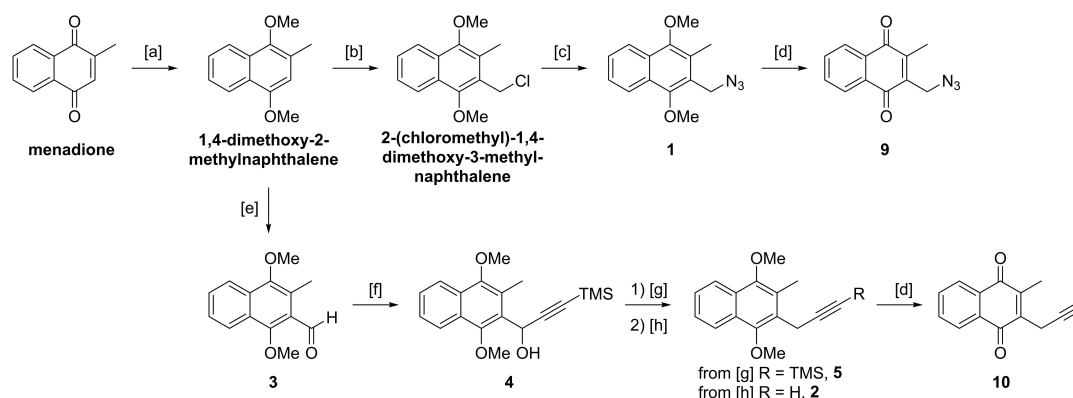
reduces the possibilities of post-functionalization and limits the accessibility to the desired product.

Our initial goal was to avoid limiting steps while introducing structural diversity into the TRZ in order to better understand the structure-activity relationships (SAR). Therefore, we first investigated the synthetic route (I). This route involved the synthesis of two menadione derivatives converted to 2-methyl-1,4-dimethoxynaphthalene homologues, the azide **1** and the alkyne **2** (Scheme 2). The azido derivative was obtained from the commercially available menadione through sequential reduction and protection (via the known intermediate 1,4-dimethoxy-2-methylnaphthalene), followed by chloromethylation (via the intermediate 2-(chloromethyl)-1,4-dimethoxy-3-methyl-naphthalene), and finally nucleophilic substitution with sodium azide producing **1** in three steps with a 74% overall yield. For the alkyne **2**, the synthesis started with the starting intermediate 1,4-dimethoxy-2-methylnaphthalene, followed by formylation to give the 1,4-dimethoxy-3-methyl-2-naphthaldehyde **3**. The latter was then alkylated with acetylene-TMS (trimethylsilylacetylene) to afford the secondary alcohol **4**, which was reduced to **5**. The TMS protecting group was finally removed in the final step to produce the targeted terminal alkyne **2** in a five steps sequence in 53% overall yield.

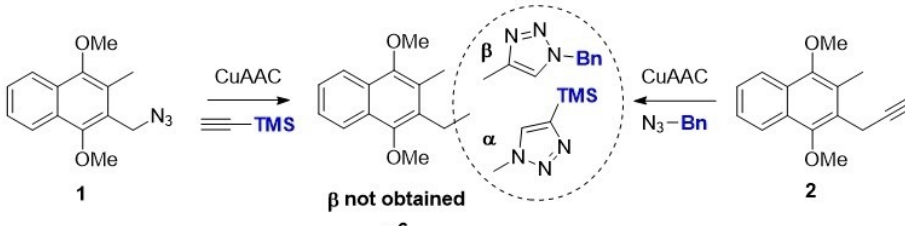
The CuAAC click reaction^[26–28] was then investigated using the azide **1** and a TMS-acetylene model to select the optimal

experimental conditions applicable to different alkynes (Table 1).

As the CuAAC reaction has been very popular since its discovery, a large number of experimental conditions are thus available in the literature. Inspired by the original review by Meldal and Tornøe,^[29] we initially used copper iodide CuI as the catalyst. However, only 5% of the targeted α 6 click product was obtained (Table 1, entry 1). Increasing the amount of catalyst and using DMSO as the solvent and triethylamine TEA as the amine base led to a significant improvement (Table 1, entry 2). In the proposed mechanism, the generation of Cu-acetylide from Cu(I) requires an amine base and/or a high temperature. However, in our case, increasing the temperature and reaction time led to degradation of the starting product (Table 1, entry 3). The use of other more classical conditions, such as a copper sulphate (CuSO₄) catalyst and sodium ascorbate as reductant, resulted in only 4% of the target product (Table 1, entry 4). Finally, we turned to the use of Cu(MeCN)₄BF₄ as the catalyst, as the latter has the advantage of being a source of Cu(I) soluble in organic solvents. These new conditions considerably improved the yield of the CuAAC reaction, giving α 6 in 9% yield (Table 1, entry 5). Following the click reaction, the TMS group of α 6 was deprotected with TBAF to give the compound α 7 in 66% yield (Scheme 3). Finally, an oxidative demethylation reaction with BCl₃/TBAI afforded the first α -[TRZ-methyl]-menadione (α 8) in moderate yield of 40% (Scheme 3).

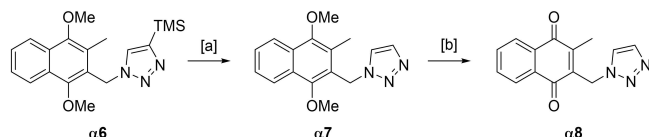


Scheme 2. Access to azido substrates **1**, **9** and alkyne substrates **2**, **10**. Conditions: [a] 1. SnCl₂ (2.5 equiv.), HCl (4 equiv.), EtOH (0.2 M), r.t., 2 h, 2. Me₂SO₄ (5 equiv.), acetone (0.2 M), KOH (5 equiv.), MeOH (1 M), 60 °C, 4 h, 93%. [b] CH₂O (5 equiv.), HCl (0.4 M), 80 °C, 2 h, 81%. [c] NaN₃ (3 equiv.), DMF (0.2 M), 70 °C, 16 h, 98%. [d] CAN (2.2 equiv.), MeCN/H₂O (7/3, 0.06 M), r.t., 1 h, 94% for **9** and 95% for **10**. [e] TiCl₄ (1.1 equiv.), dichloromethyl methyl ether (1.1 equiv.), DCM (0.7 M), 0 °C, 2 h, 100%. [f] trimethylsilylacetylene (1.8 equiv.), *n*-BuLi (1.5 equiv.), THF (0.1 M), 0 °C to r.t., 3 h, 100%. [g] Et₃SiH (1.5 equiv.), BF₃·Et₂O (1.5 equiv.), DCM (0.05 M), 0 °C, 30 min, 89%. [h] K₂CO₃ (5 equiv.), MeOH (0.1 M), r.t., 3 h, 65%.

Table 1. Evaluation of the reactivity of **1** and **2** under different CuAAC reaction conditions.


Entry	Cpnd	Catalyst/reductant or ligand	Solvent	Conditions ^[a]	Yield ^[b] [%]
1	1	CuI (0.3 equiv.)	MeCN (0.6 M)	r.t., 48 h	5 ^[c]
2	1	CuI (0.75 equiv.), TEA	DMSO (0.2 M)	r.t., 48 h	39 ^[c]
3	1	CuI (0.5 equiv.), TEA	DMSO (0.2 M)	50 °C, 72 h	Degradation ^[c]
4	1	CuSO ₄ (0.15 equiv.)/Na ascorbate (0.8 equiv.)	DMF/H ₂ O (9/1) (0.6 M)	r.t., 48 h	4 ^[c]
5	1	Cu(MeCN) ₄ BF ₄ (0.5 equiv.)	MeCN (0.1 M)	50 °C, 72 h	94 ^[c]
6	2	Cu(MeCN) ₄ BF ₄ (0.5 equiv.)	MeCN (0.1 M)	50 °C, 72 h	0 ^[d]
7	2	Cu(MeCN) ₄ BF ₄ (0.5 equiv.)/bathocuproine (0.5 equiv.)	DCM (0.1 M)	r.t., 72 h	0 ^[d]

^[a] Under argon atmosphere. ^[b] Isolated yield. ^[c] 3 equiv. of alkyne used. ^[d] 2 equiv. of azide used.

**Scheme 3.** Synthesis of α -[TRZ-methyl]-menadione ($\alpha 8$). Conditions: [a] TBAF (3 equiv.), THF (0.05 M), r.t., 16 h, 66%. [b] TBAI (2 equiv.), BCl₃ (6 equiv.), DCM (6 mM), -78 °C to r.t., 16 h, 40%.

The total yield for these three steps to afford $\alpha 8$ is about 25% (Scheme 3). Noteworthy is to mention that $\alpha 8$ could only be obtained by route (I), and not by route (II), as it will be discussed below.

The experimental conditions for the CuAAC reaction were then optimized (Table 1, entry 5) and subsequently applied to the alkyne **2** in combination with a model azide, the benzyl azide. However, no reaction occurred, even when a chelator of Cu(I) (i.e. bathocuproine^[30]) was used to stabilize copper in its + I oxidation state, to improve its reactivity and prevent its oxidation (Table 1, entries 6 and 7).

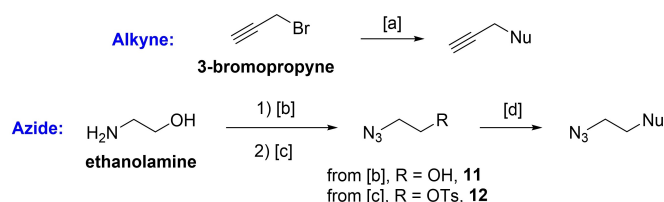
In addition, the optimized condition from entry 5 (Table 1) was tested with three different alkynes. Starting with azido **1** (Table S1 in the SI), the reaction with propargyl bromide only led to the starting material, accompanied with an undetermined by-product, which could correspond to a stable intermediate of the CuAAC catalytic cycle.

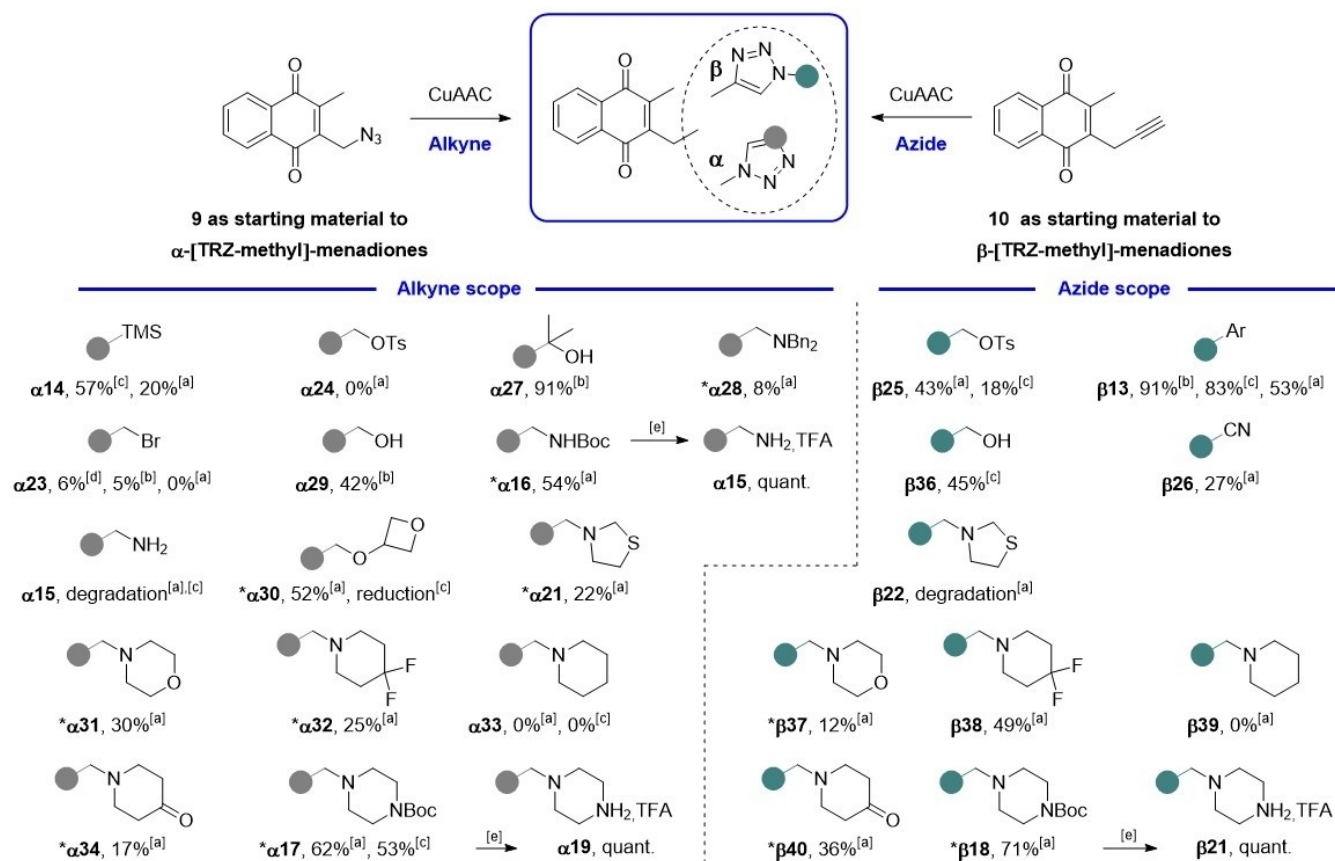
Finally, when propargyl alcohol or 3-methylbutynol was used, the reaction quantitatively reduced the azide function of compound **1** (Table S1 in the SI). Taken together, these results suggest that the CuAAC reaction is highly dependent on the nature of the substrate when using the protected menadiones **1** and **2**.

Following these first results, we then investigated the synthetic route (II). The corresponding alkyne- (**10**) and azido-functionalized (**9**) menadione derivatives were obtained from **1**

and **2** by oxidative demethylation, achieving high yields (i.e. 95% and 94%, respectively). We selected the conditions from Table 1 and tested them to investigate the accessibility to [TRZ-methyl]-menadiones. To introduce substituents compatible with desired physico-chemical properties, we synthesized several non-commercial alkynes and azides. Alkynes were readily obtained by a one-step nucleophilic substitution from propargyl bromide (Scheme 4). As far as azide derivatives are concerned, a three steps sequence starting from ethanolamine allowed their access, first, with a diazo transfer reaction leading to compound **11**, then a tosylation of the alcohol function allowing access to compound **12** and finally a nucleophilic substitution reaction carried out to introduce the desired group (Scheme 4).

The results indicated that the various functional groups were well tolerated under the CuAAC conditions, allowing access to the targeted α - and β -[TRZ-methyl]-menadiones in low to good yields (Scheme 5). Selected side-chains tethered on the alkyne or azide groups were inspired by the structures of antischistosomal drugs, e.g. nitro-, amino-, and methanol groups are found in oxamniquine, the piperidine ring is inspired

**Scheme 4.** Synthesis of alkyne and azide derivatives. Conditions: [a] Nu (2.5 equiv.), DCM (1.7 M), 30 °C, 16 h. [b] 1-(azidosulfonyl)-1H-imidazol-3-ium hydrogen sulfate (**52**) (1.2 equiv.), TEA (7 equiv.), MeOH (0.15 M), r.t., 16 h, 76%. [c] TsCl (2.5 equiv.), NaOH (5 equiv.), THF (1.15 M), H₂O (1.15 M), 0 °C to r.t., 3 h, 63%. [d] Nu (2 equiv.), K₂CO₃ (3 equiv.), MeCN (0.2 M), 80 °C, 20 h.



Scheme 5. Access to [TRZ-methyl]-menadiones from **9** or **10** by CuAAC reaction. Grey balls represents a C (sp^2) atom and green balls represents a CH₂ (sp^3) group. *Products obtained from corresponding alkyne or azide crude mixture (two-steps yield). All yields are isolated yields. [a] 1.2 equiv. of azide or alkyne, CuSO₄ (0.2 equiv.)/Na ascorbate (0.4 equiv.), THF/H₂O (7/3, 0.02 M), r.t., 16 h. [b] 1.5 equiv. of azide or alkyne, Cu(MeCN)₄BF₄ (0.1 equiv.), DCM (0.1 M), 40 °C, 16 h, under argon. [c] 1.5 equiv. of azide or 2 equiv. of alkyne, Cu(MeCN)₄BF₄ (0.4 equiv.)/bathocuproine (0.4 equiv.), DCM (0.1 M), 40 °C, 72 h, under argon. [d] 2 equiv. of alkyne, Cu(MeCN)₄BF₄ (0.1 equiv.)/bathocuproine (0.1 equiv.), MeCN (0.01 M), 80 °C, 72 h, under argon. [e] 32 equiv. of TFA, DCM (0.06 M), r.t., 1 h.

by the quinolyl cycle of oxamniquine, oxopiperidinyl and piperazine cycles as similar to those found in praziquantel, and finally fluorine atoms and cyano groups have been observed in various antischistosomal derivatives described in literature.^[31]

Despite successful synthesis of many [TRZ-methyl]-menadiones, challenges remained with the deprotection of the TRZ-substituted side-chain. We were unable to debenzylate **β 13** either by palladium-catalyzed hydrogenation or under the conditions (*tert*-butoxide/DMSO/O₂) described by Deaton-Rewolinski *et al.*^[32] Similarly, deprotection of **α 14** only led to degradation, using either fluoride or methanolate conditions. This unusual low reactivity could be explained by the fact that the menadione core is an efficient electron acceptor, which, in reduced form, is very sensitive to nucleophiles and/or bases (Michael acceptor). Attempts were thus made to protect the [TRZ-methyl]-menadione under conditions used for 1,4-dimethoxy-2-methylnaphthalene (Scheme 1). However, this only led to the degradation of the starting material, highlighting the limitation of post-modifications in synthetic route (II) to access [TRZ-methyl]-menadione derivatives. As direct introduction of the amine was not tolerated by the CuAAC conditions (potential interaction with Cu(II)), the free amino- α -TRZ **α 15** was therefore obtained by TFA deprotection of the *N*-Boc protected amine

α 16. In contrast, the use of hydroxyl or *O*-oxetanyl groups were well tolerated, affording the targeted products in moderate to excellent yields (Scheme 5). In addition, several six-membered aliphatic heterocycles diversely substituted were introduced without much difficulty, except for unsubstituted piperidine, which was not tolerated to access either α - or β -isomers, likely because of methyl deprotonation of the menadione core.^[33] By TFA deprotection of **α 17** and **α 18**, piperazine derivatives **α 19** and **α 20** were quantitatively obtained, respectively (Scheme 5). For five-membered heterocycles, only thiazolidine was tested, producing **α 21** in 22% yield, while **β 22** was formed in a small amount but degraded after a few hours (yield not quantified). Other functional groups of interest were also considered, e.g. Br or OTs (**α 23**, **α 24**). The bromo- α -TRZ **α 23** was obtained in very low yield. As observed for **1** (Table S1 in the SI) different by-products were generated (not isolated), which could be linked to the competition between the generation of Cu-acetylide, Glaser coupling^[34] and oxidative coupling. The tosyl- β -TRZ **β 25** was obtained in moderate yield, but post-functionalization by nucleophilic substitution with morpholine in mild conditions led to the degradation of the starting material. In contrast, its isomer **α 24** was not obtained. For the electron-withdrawing

substitution, only the cyano group was tested, giving the desired derivative **β26**.

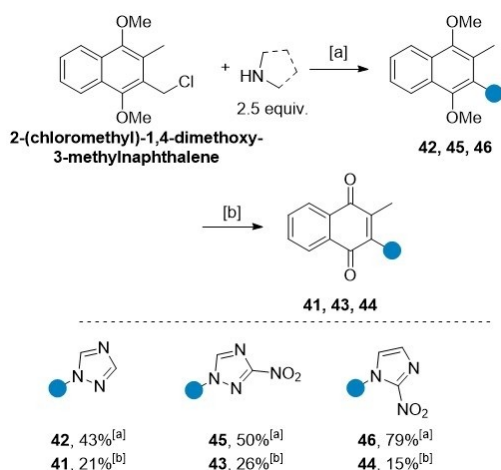
Although successful for a large number of substituents, these results highlight the drawbacks of direct CuAAC click chemistry with unprotected reactive menadiones or for their post-functionalization. Nevertheless, through this proposed methodological approach, we could demonstrate that the synthetic route (II) (Scheme 1) allowed the preparation of a series of [TRZ-methyl]-menadiones in one single step (i.e. without protection/deprotection of the menadione core).

Synthesis of 1,2,4-Triazole-, 3-Nitro-1,2,4-Triazole- and 2-Nitroimidazole-Menadiones

To introduce more compatible structural diversity within the α - and β -[TRZ-methyl]-menadiones, other five-membered *N*-heteroaromatic groups of varying diversity (Scheme 6) were considered. For example, the 1,2,4-TRZ derivative (**41**) was obtained in moderate yield and NMR data was studied in detail. The latter is prepared from intermediate 2-(chloromethyl)-1,4-dimethoxy-3-methylnaphthalene by nucleophilic substitution with the commercially available secondary amine *N*-heteroaromatic followed by an oxidative demethylation of **42**. The importance of a nitro group was also evaluated and the compounds 3-nitro-1,2,4-TRZ (**43**) and 2-nitroimidazole (**44**) were prepared in moderate yields using the same methodology as for other triazoles.

Antiparasitic Activities and Toxicity against Mammalian Cells of [TRZ-Methyl]-Menadiones

All [TRZ-methyl]-menadiones were tested for antimalarial and antischistosomal activities using standard 72 h assays and for cytotoxicity on L6 cells derived from rat skeletal myoblasts (ATCC CRL-1458) (Table 2). Growth inhibition of *P. falciparum*



Scheme 6. Synthesis of menadione derivatives containing a five-membered *N*-heteroaromatic ring. Conditions: [a] 2.5 equiv. of the corresponding secondary amine, 3 equiv. TEA, MeCN (0.05 M), 80 °C, 16 h. [b] 2 equiv. TBAI, 6 equiv. BCl₃, DCM (0.01 M), –78 °C, 16 h.

(NF54 strain) using the [³H]-hypoxanthine incorporation assay^[35] or *in vitro* drug efficacy testing on two different *S. mansoni* life stages (newly transformed schistosomula (NTS)^[36] and adult worms. Assays were conducted as described by Lombardo and colleagues.^[36] IC₅₀ values of the compounds were determined accordingly by measuring the concentration of the inhibitor required to reduce the growth (*P. falciparum*) or the viability (*S. mansoni*) of the parasites by 50%. In addition, the drug effect on the viability of *S. mansoni* NTS was evaluated after a 72 h exposure time, at a concentration of 10 μM for all our compounds. If the compound showed significant activity (>70% drug effect), the same test was performed with a lower concentration of 1 μM (Table 2). Regarding activity against *P. falciparum*, the α -[TRZ-methyl]-menadione series (including the other 5-membered *N*-heteroaromatic isomers, Scheme 6) clearly show no efficacy with IC₅₀ values far above 1 μM. Interestingly, half of the β -[TRZ-methyl]-menadione series showed promising antimalarial activity with IC₅₀ values in the sub-micromole range. In particular, compounds **β38** and **β18** exhibited low IC₅₀ values of 0.332 and 0.465 μM, respectively. Notably, the deprotected form of **β18**, compound **β20**, is inactive, indicating the negative effect of the presence of an ionisable free amine on the antiparasitic activity of the molecule. Comparison of the β -[TRZ-methyl]-menadione series with the pyridine- and pyrimidine-substituted menadiones recently published by our team^[18] clearly showed that the 6-membered *N*-heteroaromatics are generally more potent than their 5-membered congeners, with IC₅₀ values below 1 μM for most of them (Table 2). The data obtained allowed us to demonstrate the absence of antimalarial activity for the α -TRZ and a moderate activity for the β -isomers. These results could be explained by alterations of the redox properties of the naphthoquinone electrophore depending on the type of heteroaromatic introduced and its nature (isomer). It should be noted that 3-benzylmenadiones or their heteroaromatic analogues were proposed to act as prodrugs and are prone to benzylic oxidation within pRBCs, which can significantly alter the reactivity and the electrochemical properties of the generated metabolites, as well as the influence of these substitutions on the menadione moiety (see below).^[17,37,38]

Screening against NTS at 10 μM for 72 h revealed that approximately 80% of the 28 triazoles tested inhibited NTS viability by at least 70%, with IC₅₀ values between 1.89 and 0.81 μM (Table 2). The most potent triazoles were then retested at a tenfold lower concentration. The results showed that **α15**, which bears a free amine, was the most active of the series, with an activity of almost 54% and an IC₅₀ value of 0.81 μM. It is interesting to note that although the series of 5-membered heteroaromatics showed no or only moderate antimalarial activity, almost all these triazoles showed potent antischistosomal activity, with NTS activity in the order of 35–54% at 1 μM. To investigate this further, additional studies were carried out on *S. mansoni* adult worms at a concentration of 10 μM to 25 μM after 72 h exposure (Table 3). At a concentration of 25 μM, 85% of [TRZ-methyl]-menadiones showed an activity of over 50% and were therefore re-tested at a 2.5 times lower concentration. Most have antischistosomal activity in the 40–

Cpnd	Menadione-substituent	NF54 IC ₅₀ (μM)	L6 CC ₅₀ (μM)	si ^[c]	NTS activity ^[b] % (±), 72 h		NTS IC ₅₀ μM, 72 h	si ^[d]
					10 μM	1 μM		
α-1,2,3-triazole								
α8	α-TRZ	> 10	6.24		100 (0)	34 (2)	1.05	5.9
α14	α-TRZ (TMS)	7.20	18.24	2.5	91.72 (2.1)	38 (2)	1.57	11.6
α15	α-TRZ (NH ₂)	> 10	–		100 (0)	54.17 (0)	–	
α16	α-TRZ (NHBoc)	> 10	–		40.26 (5.6)	–	–	
α17	α-TRZ (piperazine-Boc)	1.46	–		75.26 (0.3)	50 (0)	1.50	
α19	α-TRZ (piperazine)	> 10	–		100 (0)	43.75 (2.1)	0.93	
α21	α-TRZ (thiazolidine)	> 10	–		42.35 (7.7)	–	–	
α23	α-TRZ (Br)	5.55	18.23	3.3	89.58 (2.1)	36 (4)	1.02	17.9
α27	α-TRZ (tBuOH)	> 10	7.27		100 (0)	34(4)	1.05	6.9
α28	α-TRZ (NBn ₂)	1.91	–		44.35 (1.5)	–	–	
α29	α-TRZ (OH)	> 10	6.69		100 (0)	34 (6)	1.05	6.4
α30	α-TRZ (O-Oxetane)	> 10	7.10		100 (0)	32 (0)	1.08	6.6
α31	α-TRZ (morpholine)	> 10	–		100 (0)	39.58 (2.1)	0.98	
α32	α-TRZ (difluoropiperidine)	2.84	–		87.5 (12.5)	45.83 (4.2)	1.48	
α34	α-TRZ (4-piperidone)	> 10	–		100 (0)	41.67 (4.2)	0.95	
β-1,2,3-triazole								
β13	β-TRZ (Ar)	0.89	49.16	55.2	58.33 (4.2)	–	–	
β18	β-TRZ (piperazine-Boc)	0.465	–		71.17 (3.8)	33.33 (0)	1.89	
β20	β-TRZ (piperazine)	6.51	–		91.84 (8.2)	33.33 (4.2)	1.67	
β25	β-TRZ (OTs)	0.77	44.41	57.7	41.47 (4.2)	–	–	
β26	β-TRZ (CN)	1.89	–		85.46 (10.5)	43.75 (6.3)	1.54	
β36	β-TRZ (OH)	1.847	17.55	9.5	97.92 (2.1)	36 (4)	1.44	12.2
β37	β-TRZ (morpholine)	5.95	–		50.51	–	–	
β38	β-TRZ (difluoropiperidine)	0.332	–		83.42 (8.4)	41.67 (0)	1.60	
β40	β-TRZ (4-piperidone)	2.07	–		100 (0)	35.42 (2.1)	–	
5-membered-N-heteroaromatic								
41	α-1,3,4-TRZ	7.48	–		100 (0)	45.83 (4.2)	0.90	
43	α-3-nitro-1,2,4-TRZ	> 10	–		100 (0)	50 (0)	0.86	
44	α-2-nitroimidazole	> 10	–		100 (0)	35.42 (2.1)	1.03	
6-membered-N-heteroaromatic (pyridine, pyrimidine) and reference drugs								
47 ^[e]	γ-py-CF ₃	0.078 ± 0.024 ^[e]	50.9	652.6			–	
48 ^[e]	β-py-CF ₃	0.069 ± 0.024 ^[e]	8.82	127.8			–	
49 ^[e]	γ-pyr-CF ₃	0.194 ± 0.125 ^[e]	179.20	923.7			–	
50 ^[e]	β-pyr-CF ₃	0.414 ± 0.293 ^[e]	17.56	42.4			–	
PD ^[f]	benzyl-CF ₃	0.043 ± 0.002 ^[e]	141.70	3295.3	46.43 (0)		11.3	12.5
CQ		0.004 ± 0.00037 μg/ml ^[e]						

^[a] Praziquantel displayed CC₅₀ and IC₅₀ values of 96 μM and 2.2 μM against *S. mansoni* NTS, respectively (data from ref. [44]). ^[b] Effect in percentage in NTS assays after 72 h. ^[c] Selectivity index for the anti-*P. falciparum* NF54 activity: CC₅₀ (L6)/IC₅₀ (NF54). ^[d] Selectivity index for the anti-*S. mansoni* NTS activity: CC₅₀ (L6)/IC₅₀ (NTS). ^[e] from ref. [18]. ^[f] PD displayed an IC₅₀ value of 11.3 μM in the NTS assay (data from ref. [39]). “–” means not tested.

50% mortality range. Two compounds in particular, **β13** and **β36** (IC₅₀ = 7.3 μM, 72 h), stand out with much higher mortality rate at 10 μM of 56.9% and 64.7%, respectively. By comparison, with 54.1% activity at 10 μM, **PD** (Table 3), one of our leading antimalarials, was already shown to be very potent against

adult worms.^[39] With the exception of **43** (Table 3), a compound that is very active on the NTS is not necessarily very active on the adult worms (48.1% at 10 μM, IC₅₀ = 7.3 μM, 72 h), and *vice versa*, as has been demonstrated with our series of compounds here. No clear correlation between α- or β-substituted triazoles

Table 3. Antischistosomal activity against *S. mansoni* adult worms.^[a]

Cpnd	Adult worms ^[b] % (±), 25 μM			Adult worms ^[b] % (±), 10 μM		
	24 h	48 h	72 h	24 h	48 h	72 h
α8	46 (1)	50 (0)	54.9 (2)	41.3 (1)	42.8 (0)	43.8 (5.1)
α14	50.9 (4)	51.05 (9.4)	70.55 (2)	39.37 (1)	39.75 (5.1)	43.8 (5.1)
α15	50.4 (2.5)	50 (0)	52.75 (4.6)	37 (3.7)	44.4 (0)	45.35 (0.9)
α16	54.25 (10.5)	54.55 (0.4)	55.55 (7.4)	–	–	–
α17	43.75 (4.2)	45.45 (0.4)	50.95 (0.9)	41.65 (2.8)	45.35 (0.9)	46.25 (1.9)
α19	43.8 (0)	48.45 (0.6)	62.5 (4.2)	43.55 (8.3)	46.25 (1.9)	46.25 (1.9)
α21	43.5 (2.3)	46.4 (2.6)	51.85 (3.7)	–	–	–
α23	39.95 (1.2)	50 (0)	50 (1)	38.4 (0)	44.85 (2)	44.85 (2)
α27	43.85 (5.1)	44.8 (1)	45.1 (2)	39.37 (1.9)	40.8 (0)	40.8 (0)
α28	45.2 (7.7)	46.45 (0.6)	48.1 (0)	–	–	–
α29	43.95 (1.1)	56.25 (4.2)	57.85 (1)	39.37 (1.9)	39.75 (1)	43.8 (5.1)
α30	47 (0.1)	51.05 (5.2)	52.9 (0)	46.9 (4.1)	47.9 (1)	48.05 (2.9)
α31	45.45 (0.4)	46.45 (0.6)	54.65 (0.9)	29.6 (3.7)	44.4 (0)	47.2 (2.8)
α32	43.15 (2)	44.65 (0.9)	51.85 (1.9)	40.7 (7.4)	40.7 (3.7)	43.5 (2.8)
α34	36.45 (1)	42.75 (1)	50 (0)	35.15 (1.9)	42.55 (1.9)	47.2 (2.8)
β13	53.95 (0.9)	56.3 (0)	58.8 (0)	49.95 (1)	55.1 (0)	56.9 (0)
β18	33.33 (0)	46.9 (3.1)	49.9 (0.9)	29.6 (3.7)	41.65 (2.8)	44.4 (0)
β20	48.35 (4.6)	48.45 (0.6)	50 (5.6)	34.25 (0.9)	50 (5.6)	50 (5.6)
β25	34.05 (4.7)	42.7 (3.1)	48.05 (1)	33.6 (1)	35.65 (1)	43.1 (0)
β26	38.55 (1)	44.8 (1)	46.95 (1.2)	37.95 (4.6)	43.5 (4.6)	45.35 (4.6)
β36	48.05 (2.9)	55.25 (1)	66.7 (0)	44.85 (6.1)	51 (0)	64.7 (0)
β37	40.3 (2.8)	43.5 (2.3)	49.05 (4.6)	–	–	–
β38	41.3 (3.8)	41.45 (0.2)	53.75 (1.9)	37 (3.7)	41.65 (2.8)	44.4 (0)
β40	46.45 (0.6)	47.4 (1.6)	55.55 (1.9)	45.4 (6.5)	47.2 (2.8)	49.05 (0.9)
41	41.7 (0)	45.8 (0)	54.65 (4.6)	40.75 (1.9)	44.4 (0)	50 (0)
43	41.7 (2.1)	45.85 (2.1)	51.85 (1.9)	37.95 (4.6)	40.7 (3.7)	48.15 (1.9)
44	48.55 (1.5)	56.85 (3.9)	71.3 (6.5)	42.55 (1.9)	43.5 (0.9)	44.4 (0)
PD ^[c]	73.95 (0.5)	75 (0)	76.5 (0)	50 (1)	50 (0)	54.15 (4.2)

^[a] Praziquantel displayed an IC₅₀ value of 0.1 μM against adult worms (data from ref. [44]). ^[b] Effect in percentage on adult worms after 24 h, 48 h, and 72 h. ^[c] PD displayed an IC₅₀ value of 8.6 μM in the adult worm assay (data from ref. [39]). “–” means not tested.

and *S. mansoni* antischistosomal activity could be observed. This suggests that [TRZ-methyl]- or 3-benzyl-menadiones have different penetration properties in *S. mansoni* compared to *P. falciparum*, and consequently, possible distinct targets/drug transports mechanisms in these two hemoglobin-feeding parasites. 1,2,3-TRZ are known to allow simultaneous metal coordination and hydrogen bond donation (through dipole–ion interaction), making a synergistic increase of both CH-acidity and *N*-donor strength.^[40] Here, in our study and from others,^[41] 1,2,3-TRZ exert – via their ambivalent character – excellent antischistosomal activities through better PK and penetration properties. Similarly to 1,2,3-triazoles, our previous study on 1,2,3,4-tetrazoles clearly highlighted the bioisosteric character of this heterocycle to mimic the negative charge of carboxylic acids.^[42] Several works also reported the potent antischistosomal activities of carboxylic acids.^[31,43]

Physico-Chemical Properties of the Most Potent [TRZ-Methyl]-Menadiones

While it is essential to optimize the efficacy of our compounds against the target parasites, it is also important to characterize the pharmacological profile of these compounds. By introducing *N*-heteroaromatic groups, in particular triazoles, we aimed to improve the oral bioavailability and the physico-chemical properties of the 3-benzylmenadione series. Therefore, an *in silico* prediction of several key PK parameters was performed using the SwissADME^[45] web tool for compounds **β38**, **β18**, **β13**, **β36** and **47**, **48**, **49**, **50**, **PD** and **CQ** (used as reference) based on their antimalarial and antischistosomal activities. The Lipinski's and Veber's rules,^[46,47] which are the most widely used drug-likeness filters, were used in this work. The physico-chemical properties of the selected compounds, including their molecular weight (MW), number of hydrogen bonds acceptors/donors

(HBA/HBD) and total polar surface area (tPSA) were calculated and are presented in Table 4.

In addition, Table 4 presented their predicted *n*-octanol/water partition coefficient (clog P), their solubility, their number of rotatable bonds and the number of violations of Lipinski's rules. All compounds studied fulfilled Lipinski's five rules and showed interesting predicted bioavailability properties. They also have acceptable tPSA^[48] values below 140 Å², suggesting acceptable solubility values above 0.0001 mg/L. The lead antimalarial molecule, plasmodione PD, has a low aqueous solubility and a relatively high lipophilicity. By introducing *N*-heteroatomic moieties, we have attempted to improve these properties. Clear trends in lipophilicity were observed for the *N*-heteroaromatic series. Each addition of aromatic nitrogen tends to reduce the log P by about one unit, from benzyl to pyridine to pyrimidine and triazole. Compared to benzyl (PD) or pyridine (47, 48) or pyrimidine (49, 50) substitution, the introduction of a triazole significantly improved the aqueous solubility of the molecule. Despite improvements in these physico-chemical properties, there is no correlation with their ability to kill the *P. falciparum* parasite. Compounds with poor aqueous solubility and high lipophilic are most likely the most potent against *P. falciparum* (i.e. PD and neutral CQ). Whereas, for their antischistosomal potencies we can conclude that lipophilicity and aqueous solubility are not necessarily determinant in our case, as shown by the diverse physico-chemical profiles of PD (clog P: 4.4), β13 (clog P: 3.1), and β36 (clog P: 1.3), all of which demonstrate strong efficacy against *S. mansoni* adult worms (54.1%, 56.9% and 64.7%, respectively). While González *et al.*^[49] suggested an optimal lipophilicity (clog P ≤ 2.5) for better aqueous solubility and parasite penetration to enhance antischistosomal potency, our compounds deviate from this trend, with PD and β13 exhibiting higher clog P values. Despite this, they remain highly effective, similar to praziquantel (clog P: 2.4), suggesting that in this case, the relationship between physico-chemical properties and antischistosomal activity may involve

other factors rather than just lipophilicity and aqueous solubility. The introduction of α- or β-TRZ into our pharmacophores has enabled us to make progress towards our goal of identifying more potent compounds with improved PK properties against various parasites of interest.

Redox Properties of [TRZ-Methyl]-Menadiones

To provide a possible explanation for the lack of activity of this series against *P. falciparum* and the contrast that exists between the activities against *S. mansoni* worms and *P. falciparum* parasite, we investigated the redox properties of the menadione electrophore for α- or β-[TRZ-methyl]-menadiones (Figure 2). For the sake of comparison, β-[TRZ-methyl]-menadione β36 and α-[TRZ-methyl]-menadione α29 bearing a hydroxymethyl substituent on the TRZ moiety were studied and compared to PD used as reference (Figure S1–S10 in the SI). The typical electrochemical profile of menadione derivatives, including PD and PDO, has been already described in detail in previous studies.^[17,37,38] It relies on two consecutive one-electron reversible waves, which correspond to the sequential reduction of the 1,4-naphthoquinone core leading to the semi-naphthoquinone and dihydro-naphthoquinone, respectively. In this work, we have not considered anode potentials greater than 0.1 V. The comparison of the redox properties of β36 (β-TRZ, Figure S2 in the SI) with the benzylmenadione PD (Figure S1 in the SI) firstly shows a comparable electrochemical profile (Table 4), except for a third irreversible wave observed at a much more negative value of −1.88 V (vs. Ag/AgCl/3 M KCl), which could be attributed to the reduction of the triazole unit (Figure S3 in the SI).^[50,51] While the methylene bridge is expected to act as an effective electronic insulator, the weak differences observed for the two redox waves can be explained by possible non-covalent interactions (e.g., hydrogen bond^[52]

Table 4. Predicted physico-chemical parameters of the most potent compounds.

Cpnd	MW ^[a]	HBA/HBD ^[b]	Number of rotatable bonds	tPSA ^[c]	clog P ^[d]	Solubility ^[e]	Lipinski violations ^[f]
Ref values	≤ 500	≤ 10/ ≤ 5	≤ 10	≤ 140	≤ 5	> 0.0001	≤ 1
β13	343.38	4/0	4	64.85	3.09	23.0	0
β18	465.54	7/0	8	97.63	2.48	70.9	0
β36	297.31	5/1	4	85.08	1.35	1490	0
β38	400.42	7/0	5	68.09	2.69	43.1	0
47	331.29	6/0	3	47.03	3.79	15.4	0
48	331.29	6/0	3	47.03	3.77	15.4	0
49	332.28	7/0	3	59.92	3.28	39	0
50	332.28	7/0	3	59.92	3.26	39	0
PD	330.30	5/0	3	34.14	4.43	6.89	0
CQ	319.87	2/1	8	28.16	4.15	9.05	0
Praziquantel	312.41	2/0	2	40.62	2.4	94.3	0

^[a] Molecular weight (g/mol). ^[b] Number of hydrogen bond acceptors/number of hydrogen bond donors. ^[c] Total polar surface area (Å²). ^[d] Average of five predicted logarithm of compound's partition coefficient between *n*-octanol and water. ^[e] Solubility (mg/L). ^[f] Number of violations of Lipinski's rules.

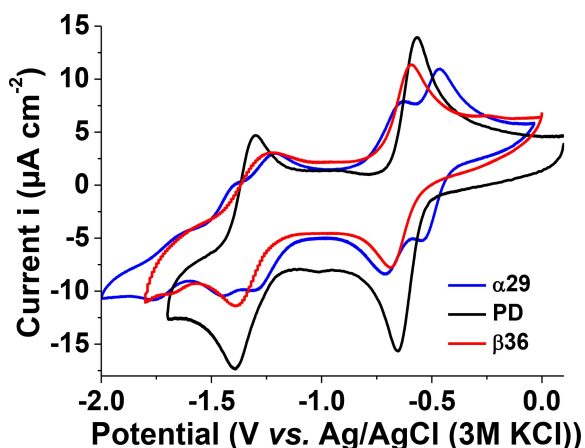


Figure 2. Comparison of the CV spectra recorded for $\alpha 29$ (1.07 mM, blue curve) PD (1.13 mM, black curve) and $\beta 36$ (0.93 mM, red curve). Solvent: DMSO; $I = 0.1$ M $n\text{-Bu}_4\text{NPF}_6$; $v = 200$ mV s^{-1} . Reference electrode = KCl(3 M)/Ag/AgCl; working electrode = glassy carbon disk of 0.07 cm^2 area; auxiliary electrode = Pt wire.

between the triazole and the negatively charged semiquinone,^[53,54] CH- π or dipole-dipole^[37].

The study of the electrochemical properties of the α -[TRZ-methyl]-menadione $\alpha 29$ is much more complex. Although it is characterized by two main redox waves separated by more than 600 mV comparable to $\beta 36$ and PD, each of the main waves is composed of two reversible waves separated by about 170 mV for the first redox process and about 100 mV for the second one (Figure S4 in the SI). Similarly to $\beta 36$, a third irreversible redox wave can be observed at more negative potentials (-1.63 V vs. Ag/AgCl/3 M KCl) that can be assigned to the TRZ unit. It is interesting to note that when the scanning potential is shifted to more negative values (down to -2.5 V, Figure S5 in the SI), a change in the intensity of each of the 2 waves corresponding to each 1-electron transfer process is observed, but without changing the global shape (i.e. position of each redox peaks) of the voltammogram. Regardless of the complexity of the $\alpha 29$ voltammogram, its CV and SWV profiles remain comparable to that of $\beta 36$, with the first redox waves at the same potentials as PD and $\beta 36$ and a second redox wave that is more oxidizing than that measured for PD and comparable to that of $\beta 36$ (Table 5, Figure S6 in the SI). Note that the electronic UV-visible absorption spectra recorded for these three compounds (i.e. PD, $\beta 36$ and $\alpha 29$) are comparable

indicating an unaffected 1,4-naphthoquinone core (π - π^* transitions centered at about 330 nm, Figure S7 in the SI) by the benzyl or TRZ-methyl substitution. The main structural differences between $\beta 36$ and $\alpha 29$ are: *i*) the position of the α - or β -TRZ-methyl relative to the menadione core and *ii*) the position of the substituent on the triazole. To first investigate the possible effect of the hydroxymethyl substituent, we performed the same electrochemical experiment on the unsubstituted α -[TRZ-methyl]-menadione $\alpha 8$ (Figures S8 and S9 in the SI). $\alpha 8$ displays exactly the same profile as $\alpha 29$ (when reduced to -2.0 V or to -2.5 V), implying that only the triazole position (α -TRZ vs. β -TRZ) relative to menadione alters the electrochemical profile without any influence of the hydroxymethyl substituent (Figure S10 in the SI). We therefore hypothesized that for α -[TRZ-methyl]-menadiones a new electroactive product is generated during the electrochemical process,^[55] a product also characterized by two reversible redox waves shifted towards anodic currents of more than 100 mV. This new unidentified species most likely involves the α -[TRZ-methyl] unit, the intensity ratio of each of the redox waves being modified according to the potential window considered.

'Benzylic' Oxidation of [TRZ-Methyl]-Menadiones

Based on our previous work with PD and its analogues^[6,12,16] (i.e. benzyl oxidation to produce a highly active metabolite), the biological activity of [TRZ-methyl]-menadiones in *P. falciparum* could be based on their ability to undergo oxidation at the same carbon position *in vivo* to produce an active metabolite. In the case of [TRZ-methyl]-menadiones, the phenyl group has been indeed replaced by a heteroaromatic fragment and the nitrogen atom substituted to the methylene bridge (oxidation position) could therefore have a significant effect on oxygen insertion and therefore menadione activity. Note that for triazoles in the α -position, oxidation of the methylene group would lead to an amide bond after oxidation, which could significantly alter the redox properties of the naphthoquinone electrophore. [TRZ-methyl]-menadiones have little or no activity against *P. falciparum* (Table 2) and this lack of activity may be related to the inability of these compounds to generate the oxidized metabolite.

To investigate this property further, we used the photo-redox conditions established by our team,^[11,12] which allow the oxidation of 3-benzylmenadione (in the presence of O_2) under

Table 5. Electrochemical data measured using cyclic voltammetry (CV).

Compound	$E_{1/2}^1(\Delta E)^{[a]}/E_{1/2}^{1* [b]}$ [V(mV)] ^[a] /[V] ^[b]	$E_{1/2}^{1*}(\Delta E)^{[a]}/E_{1/2}^{1* [b]}$ [V(mV)] ^[a] /[V] ^[b]	$E_{1/2}^2(\Delta E)^{[a]}/E_{1/2}^{2* [b]}$ [V(mV)] ^[a] /[V] ^[b]	$E_{1/2}^{2*}(\Delta E)^{[a]}/E_{1/2}^{2* [b]}$ [V(mV)] ^[a] /[V] ^[b]	$E_{1/2}^3(\Delta E)^{[a]}/E_{1/2}^{3* [b]}$ [V(mV)] ^[a] /[V] ^[b]
PD ^[c]	-0.63 (84)/-0.59	NA	-1.35 (88)/-1.32	NA	NA
$\beta 36$	-0.64 (90)/-0.61	NA	-1.31 (164)/-1.28	NA	-1.88
$\alpha 29$	-0.67 (86)/-0.65	-0.50 (84)/-0.49	-1.41 (76)/-1.34	-1.26 (102)/-1.23	-1.63
$\alpha 8$	-0.68 (88)/-0.65	-0.52 (64)/-0.48	-1.39/-1.24 ^[d]		-1.62

^[a] and Square Wave Voltammetry (SWV). ^[b] Solvent: DMSO; $I = 0.1$ M $n\text{-Bu}_4\text{NPF}_6$, $v = 200$ mV s^{-1} . NA: not applicable. ^[c] PD data from ref. [12, 37]. ^[d] blended signals.

reducing conditions (photoirradiation with a hydrogen donor). These conditions perfectly mimic the enzymatic catalytic conditions. Menadione is known to be reduced to dihydromenadione via a semi-quinone by photoreduction in isopropanol,^[56] and we have demonstrated that benzylic oxidation is possible by insertion of O₂ from the corresponding reduced species.^[11,12] We therefore subjected two [TRZ-methyl]-menadiones bearing inert substituents to photo-oxidation conditions (UV irradiation for 72 h in an oxygen atmosphere), namely compounds **α14** and **β13** (Scheme 7). These experiments were performed in a dichloromethane/isopropanol (1/1) mixture to avoid solubility issues. As expected, only **β51**, the oxidized form of **β13**, was obtained in 27% yield, while **α14** either remained intact or underwent degradation due to the high-energy excitation conditions. These data are in excellent agreement with the antiplasmodial activities (Table 2), which show that the α-[TRZ-methyl]-menadiones have little or no activity against this pathogen, while the β-analogues are moderately active compared to PD. This also suggests different action or drug transport mechanisms in *S. mansoni*, as we were able to clearly demonstrate that both α- and β-[TRZ-methyl]-menadiones were active on NTS and adult worms.

To go even further, 3-benzylmenadiones can be chemically oxidized to benzoyl derivatives under harsher conditions. Indeed, Baltas *et al.* have described^[57] a method for the preparation of α-keto-1,2,3-triazoles from benzyl-triazoles in the presence of *tert*-butyl hydroperoxide (TBHP) and catalytic amounts of copper iodide (Scheme 7). However, neither α- nor β-[TRZ-methyl]-menadiones were found to be reactive under these experimental conditions. This may be explained by the fact that the 1,4-naphthoquinone is a very electron-deficient group, already highly oxidized and acting as a strong EWG presumably requiring much harsher conditions. Among the numerous systems considered by Baltas *et al.*,^[57] only nitrobenzyl was tested (NO₂ is a potent EWG that can be reduced). In the same report, no oxidation of the *N*-substituted benzyl moiety of the triazole ring was described as possible, confirming our hypothesis that α-[TRZ-methyl]-menadiones cannot be oxidized. We thus confirm that oxidation of β-[TRZ-methyl]-menadiones is possible *in tubo* (27% for **β51**) and that this is similar to the conversion observed for PD (37%) under

comparable experimental conditions.^[58] In the case of α-[TRZ-methyl]-menadiones or the various 5-membered-*N*-heteroaromatic menadiones, the presence of a nitrogen atom in the α-position significantly reduces this possibility, leading to compounds with little or no activity against *P. falciparum*.

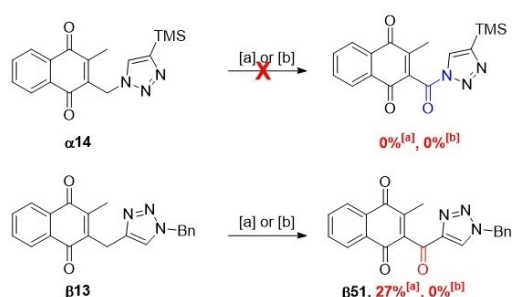
Conclusions

Our goal was to revisit and improve the antiparasitic bMD series with the introduction of a triazole as “MedChem friendly” moiety. In this study, we were able to synthesize a library of about 30 compounds distributed in two series of α- and β-[TRZ-methyl]-menadiones, through one single step using CuAAC click chemistry. This modification led to a clear increase of aqueous solubility while decreasing the lipophilicity of our compounds, which significantly improved their bioavailability. However, their antimalarial evaluation revealed that, 1,2,3-triazoles were not internalized/active in general. By contrast, β-[TRZ-methyl]-menadiones **β13** and **β36** were highly potent against *in vitro* adult *S. mansoni* worms. Therefore, this highlights that the introduction of α- or β-TRZ-methyl resulted in differential antimalarial *versus* antischistosomal activities of compounds. To explain this contrast, we evaluated their electrochemical properties and their ability to undergo benzylic oxidation via a photo-reduction process. We demonstrated that the 1,2,3-triazole moiety does not necessarily affect the redox properties of the menadione core, while the insertion of oxygen in the benzylic position was totally altered, making the generation of the active metabolite in *P. falciparum* impossible for an α-TRZ and not favored for a β-TRZ. This study clearly raises the question that 3-benzylmenadiones or [TRZ-methyl]-menadiones share different MoA/penetration processes in *S. mansoni* worms compared to those in *P. falciparum* parasite. Future studies will aim to continue the development of [TRZ-methyl]-menadione series for a better SAR comprehension as antischistosomal compounds while investigate their MoA and evaluate possible distinct biological targets or drug transport mechanisms.

Experimental Section

General

All reagents and solvents were purchased from commercial sources and used as received, unless otherwise stated. The ¹H, ¹⁹F {¹H} and ¹³C {¹H} NMR spectra were obtained with CDCl₃, MeOD or acetone-*d*₆ as deuterated solvents using a 400 MHz or a 500 MHz spectrometer. Chemical shifts were reported in parts per million (δ). ¹H NMR data were reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz) and integration). Multiplicities are reported as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, quintuplet, or their combinations. High resolution mass spectroscopy (HRMS) spectra were recorded using electron spray ionization (ESI).



Scheme 7. Oxidation of α- or β-[TRZ-methyl]-menadiones via UV-irradiation or chemical conditions. Conditions: [a] DCM/*i*PrOH (1/1, 0.01 M), under O₂ atmosphere and UV-irradiation 350 nm (i.e. a Rayonet photochemical reactor equipped with 16 UV lamps of 14 W), 15 °C, 72 h. [b] described from ref. [57]: TBHP (4 equiv.), CuI (0.1 equiv.), MeCN (0.1 M), r.t., 20 h.

Synthesis of Precursors

Starting chemicals were purchased from commercial sources, such as Fluorochem, Sigma-Aldrich, BLDpharm or Alfa Aesar. 1,4-Dimethoxy-2-methylnaphthalene,^[6] 2-(chloromethyl)-1,4-dimethoxy-3-methylnaphthalene,^[18] 1,4-dimethoxy-3-methyl-2-naphthaldehyde **3**^[59] were synthesized according to previously published methods.

Synthesis of 1,2,3-[TRZ-Methyl]-Menadiones

1-((1,4-Dimethoxy-3-methylnaphthalen-2-yl)methyl)-4-(trimethylsilyl)-1H-1,2,3-triazole (α 6). **1** (50 mg, 0.2 mmol, 1 equiv.) was solubilized in MeCN (2.3 mL). Trimethylsilylacetylene (55 μ L, 0.4 mmol, 2 equiv.) was then added under argon. Finally, Cu(MeCN)₄BF₄ (30.5 mg, 0.1 mmol, 0.5 equiv.) was added and the mixture was stirred at 50 °C under argon for 72 h. The conversion was monitored by TLC (CHX/EtOAc, 7/3, v/v, UV). The crude was then evaporated, extracted three times with ethyl acetate, dried over magnesium sulphate and the solvent was removed under vacuum. The crude was purified by silica gel chromatography (CHX/EtOAc, 7/3 to 0/10, v/v, UV) to afford **1-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)-4-(trimethylsilyl)-1H-1,2,3-triazole (α 6)** as a light yellow oil (65 mg, 94.1%). ¹H NMR (400 MHz, CDCl₃) δ 8.16–8.05 (m, 2H), 7.55 (dq, *J* = 9.7, 6.8, 1.6 Hz, 2H), 7.39 (s, 1H), 5.79 (s, 2H), 3.95 (s, 3H), 3.85 (s, 3H), 2.37 (s, 3H), 0.25 (s, 9H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 151.9, 150.8, 146.7, 129.5, 128.7, 127.2, 126.6, 126.1, 123.5, 122.9, 122.6, 63.2, 61.6, 45.7, 12.3, –1.0. HRMS (ESI+) calcd. for C₁₉H₂₆N₃O₂Si: 356.1789. Found: 356.1794 (M + H⁺).

1-((1,4-Dimethoxy-3-methylnaphthalen-2-yl)methyl)-1H-1,2,3-triazole (α 7). To a solution of **α 6** (63.4 mg, 0.2 mmol, 1 equiv.) in THF (3.5 mL) was added at r.t. a 1 M TBAF solution in THF (0.5 mL, 0.5 mmol, 3 equiv.). The crude mixture was stirred at r.t. for 16 h. The grey mixture was hydrolyzed with saturated aqueous ammonium chloride and extracted three times with ethyl acetate, dried over magnesium sulphate, and the solvent was removed under vacuum. The crude was purified by silica gel chromatography (CHX/EtOAc, 7/3 to 0/10, v/v, UV) to afford **1-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)-1H-1,2,3-triazole (α 7)** as a light yellow solid (33.4 mg, 66.1%). M.p. 111–113 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.14–8.05 (m, 2H), 7.65 (s, 1H), 7.60–7.50 (m, 2H), 7.49 (s, 1H), 5.79 (s, 2H), 3.94 (s, 3H), 3.84 (s, 3H), 2.36 (s, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 151.9, 150.9, 129.6, 127.3, 127.0, 126.4, 126.2, 123.2, 122.9, 122.6, 63.2, 61.6, 46.3, 12.3. HRMS (ESI+) calcd. for C₁₆H₁₈N₃O₂: 284.1393. Found: 284.1395 (M + H⁺).

2-((1H-1,2,3-triazol-1-yl)methyl)-3-methylnaphthalene-1,4-dione (α 8). To a stirred solution of **α 7** (33.4 mg, 0.1 mmol, 1 equiv.) and tetrabutylammonium iodide (87.1 mg, 0.2 mmol, 2 equiv.) in dry DCM (17.4 mL) was added dropwise boron trichloride (0.7 mL, 0.7 mmol, 6 equiv.) at –78 °C. The reaction mixture was then allowed to reach r.t. and stirred for 16 h. The yellow reaction mixture was quenched with water and extracted three times with DCM, dried over magnesium sulphate, and the solvent was removed under vacuum. The crude was purified by silica gel chromatography (DCM, UV) to afford **2-((1H-1,2,3-triazol-1-yl)methyl)-3-methylnaphthalene-1,4-dione (α 8)** as an orange solid (12 mg, 40.2%). M.p. 79–81 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H), 8.22 (d, *J* = 1.4 Hz, 1H), 8.16–8.05 (m, 2H), 7.82–7.77 (m, 2H), 5.77 (s, 2H), 2.51 (s, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 183.89, 183.82, 150.6, 135.7, 134.9, 134.5, 132.1, 131.4, 131.1, 128.5, 127.3, 126.8, 48.4, 13.7. HRMS (ESI+) calcd. for C₁₄H₁₂N₃O₂: 254.0924. Found: 254.0923 (M + H⁺).

General Procedure for CuAAC Click Reaction

Procedure [a]

The azide **9** (1 equiv.) or the alkyne **10** (1 equiv.) was mixed with the corresponding crude of alkyne or azide (1.2 equiv.) in THF (70% of 0.02 M). A solution of sodium ascorbate (0.4 equiv.) and CuSO₄ (0.2 equiv.) prepared in water (30% of 0.02 M) was then added. The mixture was stirred at r.t. for 16 h. The organic solvent was removed under reduced pressure, extracted three times with DCM, washed with water, dried over magnesium sulphate, and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using the appropriate eluent (see below). All the yields are calculated in two steps, since the alkyne or azide are not purified.

2-(4-((3-Methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)-1H-1,2,3-triazol-1-yl)ethyl 4-methylbenzenesulfonate (β 25). With **12**, eluent (CHX/EtOAc, 8/2 to 6/4, v/v, UV), yellow solid, 42.6% yield. M.p. 87–89 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.06 (dt, *J* = 6.2, 3.3 Hz, 2H), 7.71–7.67 (m, 2H), 7.66–7.62 (m, 2H), 7.44 (s, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 4.55 (t, *J* = 5.2 Hz, 2H), 4.35 (t, *J* = 5.2 Hz, 2H), 4.04 (s, 2H), 2.41 (s, 3H), 2.32 (s, 3H). ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 184.1, 183.3, 144.4, 143.9, 143.5, 142.3, 132.6, 132.5, 131.1, 131.0, 130.9, 129.0, 126.8, 125.4, 125.3, 122.1, 66.5, 47.9, 22.5, 20.6, 12.1. HRMS (ESI) calcd. for C₂₃H₂₂N₃O₃S: 452.1314. Found: 452.1275 (M + H⁺).

Tert-Butyl 4-((1-((3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)piperazine-1-carboxylate (α 17). With **63**, eluent (EtOAc/MeOH, 10/0 to 8/2, v/v, UV), orange solid, 61.6% yield. M.p. 97–99 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.13–8.06 (m, 2H), 7.76–7.72 (m, 2H), 7.66 (s, 1H), 5.54 (s, 2H), 3.64 (s, 2H), 3.40 (t, *J* = 5.1 Hz, 4H), 2.45 (s, 3H), 1.42 (s, 9H). ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 184.7, 184.0, 154.8, 148.7, 144.0, 138.2, 134.3, 134.2, 132.2, 131.5, 126.9, 126.7, 123.9, 79.8, 53.3, 52.7, 45.0, 28.5, 13.4. HRMS (ESI) calcd. for C₂₄H₃₀N₅O₄: 452.2292. Found: 452.2305 (M + H⁺).

2-Methyl-3-((4-((oxetan-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (α 30). With **67**, eluent (EtOAc, v/v, UV), yellow solid, 51.7% yield. M.p. 122–124 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.12–8.05 (m, 2H), 7.76–7.71 (m, 3H), 5.55 (s, 2H), 4.73–4.65 (m, 3H), 4.56–4.53 (m, 2H), 4.52 (s, 2H), 2.45 (s, 3H). ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 184.6, 183.9, 148.6, 144.5, 138.1, 134.3, 134.2, 132.1, 131.4, 126.9, 126.6, 123.9, 78.7, 72.3, 62.4, 45.1, 13.3. HRMS (ESI) calcd. for C₁₈H₁₇N₃NaO₄: 362.1111. Found: 362.1106 (M + Na⁺).

2-Methyl-3-((4-(morpholinomethyl)-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (α 31). With **62**, eluent (EtOAc/MeOH, 10/0 to 8/2, v/v, UV), yellow solid, 29.9% yield. M.p. 127–129 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.09 (ddt, *J* = 7.0, 5.5, 3.7 Hz, 2H), 7.74 (dd, *J* = 5.8, 3.3 Hz, 2H), 7.67 (s, 1H), 5.54 (s, 2H), 3.71–3.65 (m, 4H), 3.63 (s, 2H), 2.57–2.46 (m, 4H), 2.44 (s, 3H). ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 184.7, 184.0, 148.6, 143.9, 138.2, 134.3, 134.1, 132.2, 131.5, 126.9, 126.6, 123.9, 66.8, 53.6, 53.4, 44.9, 13.3. HRMS (ESI) calcd. for C₁₉H₂₁N₄O₃: 353.1608. Found: 353.1611 (M + H⁺).

Tert-Butyl ((1-((3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)carbamate (α 16). With **69**, eluent (CHX/EtOAc, 2/8, v/v, UV), orange solid, 54% yield. M.p. 105–107 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.10–8.04 (m, 2H), 7.75–7.69 (m, 2H), 7.66 (s, 1H), 5.52 (s, 2H), 5.13 (s, 1H), 4.33 (d, *J* = 5.8 Hz, 2H), 2.41 (s, 3H), 1.39 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 184.7, 183.8, 155.9, 148.5, 145.5, 138.2, 134.2, 134.1, 132.1, 131.4, 126.8, 126.6, 122.9, 44.9, 36.2, 28.4, 13.3. HRMS (ESI) calcd. for C₂₀H₂₂N₄NaO₄: 405.1533. Found: 405.1533 (M + Na⁺).

2-((4-((Dibenzylamino)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-methylnaphthalene-1,4-dione (α 28). With **70**, eluent (CHX/EtOAc, 7/3, v/v, UV), orange oil, 8.3% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.11–8.05 (m,

2H), 7.75–7.69 (m, 2H), 7.62 (s, 1H), 7.39–7.36 (m, 4H), 7.32–7.27 (m, 4H), 7.22–7.18 (m, 2H), 5.53 (s, 2H), 3.72 (s, 2H), 3.59 (s, 4H), 2.45 (s, 3H). ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 184.7, 183.9, 148.4, 145.4, 139.3, 138.3, 134.2, 134.0, 132.1, 131.5, 128.9, 128.3, 127.0, 126.8, 126.6, 123.8, 57.8, 48.1, 44.9, 13.3. HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{27}\text{N}_4\text{O}_2$: 463.2128. Found: 463.2136 ($\text{M} + \text{H}^+$).

2-(4-((3-Methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)-1H-1,2,3-triazol-1-yl)acetonitrile (β 26). With **60**, eluent (CHX/EtOAc, 6/4, v/v, UV), orange solid, 26.8% yield. M.p. 112–114 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.11–7.96 (m, 2H), 7.70–7.65 (m, 2H), 7.64 (s, 1H), 5.27 (s, 2H), 4.08 (s, 2H), 2.34 (s, 3H). ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 185.1, 184.5, 145.9, 145.4, 142.9, 133.8, 133.7, 132.2, 131.9, 126.6, 126.4, 122.6, 112.7, 37.5, 23.7, 13.3. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_4\text{O}_2$: 293.1033. Found: 293.1036 ($\text{M} + \text{H}^+$).

2-((4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)-3-methylnaphthalene-1,4-dione (α 32). With **64**, eluent (EtOAc/MeOH, 95/5, v/v, UV), orange oil, 25.1% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.09 (td, $J=6.0$, 3.3 Hz, 2H), 7.74 (dd, $J=5.8$, 3.3 Hz, 2H), 7.65 (s, 1H), 5.54 (s, 2H), 3.66 (s, 2H), 2.58 (t, $J=5.8$ Hz, 4H), 2.45 (s, 3H), 2.01–1.90 (m, 4H). ^{19}F { ^1H } NMR (377 MHz, CDCl_3) δ –98.13. ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 184.7, 184.0, 148.6, 144.5, 138.2, 134.3, 134.2, 132.2, 131.5, 126.9, 126.6, 123.8, 52.5, 49.9 (t, $J=5.4$ Hz), 45.0, 33.9 (t, $J=23.1$ Hz), 13.3. HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{O}_2\text{N}_4\text{F}_2$: 387.1627. Found: 387.1635 ($\text{M} + \text{H}^+$).

Tert-Butyl 4-((1-((3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)piperazine-1-carboxylate (α 34). With **65**, eluent (EtOAc/MeOH, 90/10, v/v, UV), orange oil, 16.9% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.14–8.06 (m, 2H), 7.75 (dd, $J=5.8$, 3.3 Hz, 2H), 7.70 (s, 1H), 5.56 (s, 2H), 3.76 (s, 2H), 2.80 (t, $J=6.1$ Hz, 4H), 2.46 (s, 3H), 2.44 (t, $J=6.1$ Hz, 4H). ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 208.8, 184.7, 184.1, 148.7, 144.4, 138.2, 134.3, 134.2, 132.2, 131.5, 126.9, 126.7, 123.9, 52.8, 52.4, 45.1, 41.2, 13.4. HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{O}_3\text{N}_4$: 365.1608. Found: 365.1610 ($\text{M} + \text{H}^+$).

2-Methyl-3-((4-(thiazolidin-3-ylmethyl)-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (α 21). With **66**, eluent (EtOAc/MeOH, 9/1, v/v, UV), orange oil, 21.8% yield, contains a small impurity. ^1H NMR (400 MHz, CDCl_3) δ 8.10 (dt, $J=5.8$, 3.6 Hz, 2H), 7.75 (dd, $J=5.8$, 3.3 Hz, 2H), 7.71 (s, 1H), 5.56 (s, 2H), 4.07 (s, 2H), 3.65 (s, 2H), 3.09 (t, $J=6.6$ Hz, 2H), 2.95 (t, $J=6.5$ Hz, 2H), 2.46 (s, 3H). ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 184.8, 184.0, 148.7, 145.7, 138.2, 134.3, 134.2, 132.2, 131.5, 126.9, 126.7, 123.7, 60.5, 57.5, 48.0, 45.0, 29.5, 13.4. HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_2\text{N}_4\text{S}$: 355.1223. Found: 355.1230 ($\text{M} + \text{H}^+$).

2-Methyl-3-((1-(2-morpholinoethyl)-1H-1,2,3-triazol-4-yl)methyl)naphthalene-1,4-dione (β 37). With **53**, eluent (EtOAc/MeOH, 9/1, v/v, UV), orange oil, 11.9% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.10–8.04 (m, 2H), 7.70 (dd, $J=5.8$, 3.3 Hz, 2H), 7.51 (s, 1H), 4.38 (t, $J=6.4$ Hz, 2H), 4.08 (s, 2H), 3.67–3.60 (t, 4H), 2.77 (t, $J=6.4$ Hz, 2H), 2.47–2.42 (t, 4H), 2.37 (s, 3H). ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 185.3, 184.7, 145.1, 144.3, 143.8, 133.7, 133.6, 132.3, 132.0, 126.6, 126.3, 122.9, 66.9, 57.9, 53.6, 47.5, 23.8, 13.3. HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_3\text{N}_4$: 367.1760. Found: 367.1764 ($\text{M} + \text{H}^+$).

2-Methyl-3-((1-(2-(thiazolidin-3-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)naphthalene-1,4-dione (β 22). With **55**, eluent (EtOAc/MeOH, 9/1, v/v, UV), yellow solid, 5.7% yield, not stable leads to degradation after few hours. ^1H NMR (400 MHz, CDCl_3) δ 8.21–8.16 (m, 2H), 7.55–7.46 (m, 2H), 6.68 (s, 1H), 3.94 (s, 2H), 3.41–3.36 (m, 2H), 2.86–2.83 (m, 2H), 2.80–2.75 (m, 4H), 2.48 (s, 3H).

2-Methyl-3-((1-(2-(4-oxopiperidin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)naphthalene-1,4-dione (β 40). With **56**, eluent (EtOAc/MeOH, 9/1, v/v, UV), orange solid, 35.7% yield. M.p. 109–111 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.08–7.97 (m, 2H), 7.70–7.64 (m, 2H), 7.53 (s, 1H), 4.42 (t, $J=6.3$ Hz, 2H), 4.07 (s, 2H), 2.90 (t, $J=6.3$ Hz, 2H), 2.75 (t, $J=6.0$ Hz, 4H), 2.37 (d, $J=7.0$ Hz, 7H). ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ

208.2, 185.2, 184.6, 145.0, 143.6, 133.7, 133.6, 132.2, 131.9, 126.5, 126.2, 56.5, 53.1, 48.3, 41.2, 23.8, 13.2. HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{22}\text{O}_3\text{N}_4\text{Na}$ 401.1584. Found: 401.1579 ($\text{M} + \text{Na}^+$).

2-((1-(2-(4,4-Difluoropiperidin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methylnaphthalene-1,4-dione (β 38). With **57**, eluent (EtOAc/MeOH, 9/1, v/v, UV), orange solid, 49.1% yield. M.p. 110–112 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.05 (ddd, $J=9.3$, 6.2, 3.3 Hz, 2H), 7.70–7.66 (m, 2H), 7.50 (s, 1H), 4.37 (t, $J=6.3$ Hz, 2H), 4.07 (s, 2H), 2.81 (t, $J=6.2$ Hz, 2H), 2.55 (t, $J=5.7$ Hz, 4H), 2.36 (s, 3H), 1.91 (tt, $J=13.6$, 5.7 Hz, 4H). ^{19}F { ^1H } NMR (377 MHz, CDCl_3) δ –98.08, –98.34. ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 185.3, 184.6, 145.0, 143.7, 133.7, 133.6, 132.2, 131.9, 126.5, 126.3, 56.6, 50.1, 50.1, 50.0, 48.1, 34.2, 34.0, 33.8, 23.8, 13.2. HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{23}\text{F}_2\text{O}_2\text{N}_4$: 401.1779. Found: 401.1783 ($\text{M} + \text{H}^+$).

Tert-Butyl 4-(2-(4-((3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)-1H-1,2,3-triazol-1-yl)ethyl)piperazine-1-carboxylate (β 18). With **58**, eluent (EtOAc/MeOH, 9/1, v/v, UV), orange oil, 71.3% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.11–8.02 (m, 2H), 7.71–7.67 (m, 2H), 7.50 (s, 1H), 4.38 (t, $J=6.4$ Hz, 2H), 4.08 (s, 2H), 3.37 (t, $J=5.1$ Hz, 4H), 2.78 (t, $J=6.4$ Hz, 2H), 2.40 (t, $J=4.9$ Hz, 4H), 2.37 (s, 3H), 1.45 (s, 9H). ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 185.3, 184.7, 154.8, 145.1, 144.3, 143.8, 133.7, 133.6, 132.3, 132.1, 126.6, 126.3, 122.9, 79.9, 57.6, 53.0, 47.8, 28.5, 23.8, 13.3. HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{32}\text{O}_4\text{N}_5$: 466.2440. Found: 466.2449 ($\text{M} + \text{H}^+$).

Procedure [b]

Azide **9** (1 equiv.) or alkyne **10** (1 equiv.) was mixed with the corresponding alkyne or azide (1.5 equiv.) in DCM (0.1 M) under argon. $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (0.4 equiv.) was then added. The mixture was stirred at 40 °C under argon for 16 h. The organic solvent was removed under reduced pressure, extracted three times with DCM, washed with water, dried over magnesium sulphate, and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using the appropriate eluent (see below).

2-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-methylnaphthalene-1,4-dione (β 13). With (azidomethyl)benzene **59**, eluent (CHX/EtOAc, 6/4, v/v, UV), yellow solid, 91% yield. M.p. 115–117 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.09–7.95 (m, 2H), 7.70–7.65 (m, 2H), 7.35–7.31 (m, 3H), 7.24–7.21 (m, 2H), 5.43 (s, 2H), 4.04 (s, 2H), 2.33 (s, 3H). ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 185.2, 184.5, 145.1, 144.8, 143.5, 134.7, 133.6, 133.5, 132.2, 131.9, 129.1, 128.7, 128.1, 126.5, 126.3, 122.0, 54.1, 23.7, 13.2. HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{17}\text{O}_2\text{N}_3\text{Na}$: 366.1213. Found: 366.1191 ($\text{M} + \text{Na}^+$).

2-((4-(2-Hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)methyl)-3-methylnaphthalene-1,4-dione (α 27). With 3-methyl-butynol, eluent (CHX/EtOAc, 8/2 to 0/10, v/v, UV), yellow solid, 91% yield. M.p. 113–115 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.20–8.00 (m, 2H), 7.77–7.69 (m, 2H), 7.62 (s, 1H), 5.53 (s, 2H), 2.45 (s, 3H), 1.59 (s, 6H). ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 184.8, 184.0, 148.7, 138.2, 134.3, 134.1, 132.2, 131.5, 126.9, 126.7, 44.9, 30.5, 13.3. HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_3$: 312.1343. Found: 312.1334 ($\text{M} + \text{H}^+$).

2-((4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)-3-methylnaphthalene-1,4-dione (α 29). With 2-propyn-1-ol, eluent (EtOAc, UV), yellow solid, 42% yield. M.p. 109–111 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.21–8.01 (m, 2H), 7.82–7.62 (m, 3H), 5.56 (s, 2H), 4.75 (s, 2H), 2.46 (s, 3H). ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ 184.6, 183.9, 148.5, 147.6, 138.1, 134.2, 134.1, 132.1, 131.4, 126.8, 126.6, 122.8, 56.6, 44.9, 13.2. HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_3$: 284.1029. Found: 284.1031 ($\text{M} + \text{H}^+$).

Procedure [c]

Azide **9** (1 equiv.) or alkyne **10** (1 equiv.) was mixed with the corresponding alkyne (2 equiv.) or azide respectively (1.5 equiv.) in DCM (0.1 M) under argon. Cu(MeCN)₄BF₄ (0.4 equiv.) and bathocuproine (0.4 equiv.) were then added. The mixture was stirred at 40 °C under argon for 72 h. The organic solvent was removed under reduced pressure, extracted three times with DCM, washed with water, dried over magnesium sulphate, and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using the appropriate eluent (see below).

2-((1-(2-Hydroxyethyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methylnaphthalene-1,4-dione (β36). With **11**, eluent (CHX/EtOAc, 8/2 to 0/10, v/v, UV), yellow solid, 45.5% yield. M.p. 102–104 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.12–8.03 (m, 2H), 7.72–7.67 (m, 2H), 7.50 (s, 1H), 4.46–4.36 (m, 2H), 4.10 (s, 2H), 4.05 (q, J=5.2 Hz, 2H), 2.38 (s, 3H). ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 185.3, 184.7, 145.2, 143.6, 133.8, 133.6, 132.3, 132.1, 126.6, 126.4, 61.4, 52.6, 23.8, 13.3. HRMS (ESI) calcd. for C₁₆H₁₆N₃O₃: 298.1186. Found: 298.1183 (M + H⁺).

2-Methyl-3-((4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (α14). With trimethylsilylacetylene, eluent (CHX/EtOAc, 8/2 to 6/4, v/v, UV), yellow solid, 56.5% yield. M.p. 117–119 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.11–8.05 (m, 2H), 7.75–7.70 (m, 2H), 7.67 (s, 1H), 5.57 (s, 2H), 2.47 (s, 3H), 0.28 (s, 9H). ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 184.8, 184.1, 148.6, 146.8, 138.5, 134.2, 134.1, 132.2, 131.5, 129.9, 126.8, 126.6, 44.3, 13.4, –1.0. HRMS (ESI) calcd. for C₁₇H₂₀N₃O₂Si: 326.1319. Found: 326.1335 (M + H⁺).

Procedure [d]

Azide **9** (1 equiv.) was mixed with the corresponding alkyne (2 equiv.) in MeCN (0.01 M) under argon. Cu(MeCN)₄BF₄ (0.1 equiv.) and bathocuproine (0.1 equiv.) were then added. The mixture was stirred under reflux at 80 °C under argon for 72 h. The organic solvent was removed under reduced pressure, extracted three times with DCM, washed with water, dried over magnesium sulphate, and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using the appropriate eluent (see below).

2-((4-(Bromomethyl)-1H-1,2,3-triazol-1-yl)methyl)-3-methylnaphthalene-1,4-dione (α23). With 3-bromopropyne, eluent (CHX/EtOAc, 8/2 to 3/7, v/v, UV), yellow solid, 6% yield, contains a small impurity. M.p. 93–95 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.14–8.08 (m, 2H), 7.79 (s, 1H), 7.75 (dd, J=5.8, 3.3 Hz, 2H), 5.55 (s, 2H), 4.53 (s, 2H), 2.47 (s, 3H). ¹³C {¹H} NMR (126 MHz, CDCl₃) δ 184.7, 184.1, 148.8, 138.0, 134.4, 134.2, 132.2, 131.5, 126.9, 126.7, 45.2, 21.6, 13.4. HRMS (ESI) calcd. for C₁₅H₁₃BrN₃O₂: 346.0186. Found: 346.0168 (M + H⁺).

General Procedure for TFA Deprotection

The Boc-protected 1,2,3-[TRZ-methyl]-menadione (1 equiv.) was solubilized in DCM (0.03 M) and then TFA was added (32 equiv.). The mixture was stirred at r.t. for 1 h. The organic solvent was removed and the crude was dissolved in MeOH and dried under vacuum. This procedure was repeated three times. The same procedure was then carried out with CHCl₃.

2-Methyl-3-((4-(piperazin-1-ylmethyl)-1H-1,2,3-triazol-1-yl)methyl)naphthalene-1,4-dione (α19). From **α17**, the pure product was obtained quantitatively as a TFA salt, orange solid. M.p. 125–127 °C. ¹H NMR (400 MHz, MeOD) δ 8.20 (s, 1H), 8.08–7.94 (m, 2H), 7.81–7.67 (m, 2H), 5.64 (s, 2H), 4.36 (s, 2H), 3.51–3.45 (m, 4H), 3.41 (dd, J=6.9, 3.8 Hz, 4H), 2.36 (s, 3H). ¹³C {¹H} NMR (101 MHz, MeOD) δ 185.8, 184.9, 149.5, 139.3, 135.2, 135.1, 133.5, 132.9, 127.5, 127.3, 58.3, 46.5,

43.6, 41.7, 18.4, 13.1. HRMS (ESI) calcd. for C₁₉H₂₂N₅O₂: 352.1770. Found: 352.1768 (M + H⁺).

2-((4-(Aminomethyl)-1H-1,2,3-triazol-1-yl)methyl)-3-methylnaphthalene-1,4-dione (α15). From **α16**, the pure product was obtained quantitatively as a TFA salt, brown solid. M.p. 127–129 °C. ¹H NMR (500 MHz, MeOD) δ 8.17 (s, 1H), 7.95 (dq, J=7.1, 4.1 Hz, 2H), 7.72 (dt, J=6.3, 3.0 Hz, 2H), 5.62 (s, 2H), 4.27 (s, 2H), 2.33 (s, 3H). ¹³C {¹H} NMR (126 MHz, MeOD) δ 185.7, 184.7, 149.3, 141.2, 139.2, 135.2, 135.1, 133.2, 132.6, 127.4, 127.2, 126.4, 46.3, 35.4, 13.1. HRMS (ESI) calcd. for C₁₅H₁₅N₄O₂: 283.1189. Found: 283.1196 (M + H⁺).

2-Methyl-3-((1-(2-(piperazin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)naphthalene-1,4-dione (β20). From **β18**, the pure product was obtained quantitatively as a TFA salt, brown solid. M.p. 85–87 °C. ¹H NMR (400 MHz, MeOD) δ 8.07–8.01 (m, 2H), 7.85 (s, 1H), 7.78–7.72 (m, 2H), 4.55 (t, J=6.1 Hz, 2H), 4.07 (s, 2H), 3.25–3.21 (m, 4H), 3.05 (t, J=6.1 Hz, 2H), 2.90–2.82 (m, 4H), 2.24 (s, 3H). ¹³C {¹H} NMR (101 MHz, MeOD) δ 186.2, 185.4, 146.1, 145.6, 144.4, 134.8, 134.8, 133.5, 133.3, 127.2, 127.1, 124.8, 57.6, 50.4, 48.1, 44.4, 24.1, 13.1. HRMS (ESI) calcd. for C₂₀H₂₄O₂N₅: 366.1924. Found: 366.1921 (M + H⁺).

Synthesis of 1,2,4-TRZ-, 3-Nitro-1,2,4-TRZ- and 2-Nitroimidazole-Menadiones**General Procedure for SN₂ with 2-(Chloromethyl)-1,4-Dimethoxy-3-Methylnaphthalene**

2-(chloromethyl)-1,4-dimethoxy-3-methylnaphthalene (1 equiv.) was dissolved in MeCN (0.05 M). Then the nucleophile (2.5 equiv.) with TEA (3 equiv.) was slowly added. The reaction mixture was stirred under reflux at 80 °C for 16 h. The organic solvent was removed under reduced pressure, extracted three times with DCM, washed with water, dried over magnesium sulphate, and solvent was removed under vacuum. The crude was purified by silica gel chromatography using the appropriate eluent (see below).

1-((1,4-Dimethoxy-3-methylnaphthalen-2-yl)methyl)-1H-1,2,4-triazole (42). With 4H-1,2,4-triazole, eluent (CHX/EtOAc, 3/7, v/v, UV), white solid, 39.8% yield. M.p. 115–117 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.19–8.04 (m, 2H), 7.97 (s, 1H), 7.93 (s, 1H), 7.64–7.45 (m, 2H), 5.58 (s, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 2.38 (s, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 152.1, 151.8, 150.9, 129.6, 127.3, 127.1, 126.2, 126.2, 122.9, 122.9, 122.6, 63.2, 61.7, 46.0, 12.4. HRMS (ESI) calcd. for C₁₆H₁₈O₂N₃: 284.1393. Found: 284.1402 (M + H⁺).

1-((1,4-Dimethoxy-3-methylnaphthalen-2-yl)methyl)-3-nitro-1H-1,2,4-triazole (45). With 3-nitro-1,2,4-triazole, eluent (CHX/EtOAc, 8/2 to 4/6, v/v, UV), yellow oil, 50.4% yield. ¹H NMR (400 MHz, MeOD) δ 8.58 (s, 1H), 8.06–7.97 (m, 2H), 7.57–7.40 (m, 2H), 5.68 (s, 2H), 3.93 (s, 3H), 3.80 (s, 3H), 2.41 (s, 3H). ¹³C {¹H} NMR (101 MHz, MeOD) δ 153.6, 151.9, 147.2, 130.8, 128.3, 128.1, 127.3, 127.1, 123.8, 123.5, 123.4, 63.5, 61.9, 48.3, 12.6. HRMS (ESI) calcd. for C₁₆H₁₆O₄N₄Na: 351.1064. Found: 351.1071 (M + Na⁺).

1-((1,4-Dimethoxy-3-methylnaphthalen-2-yl)methyl)-2-nitro-1H-imidazole (46). With 2-nitroimidazole, eluent (CHX/EtOAc, 8/2 to 4/6, v/v, UV), yellow oil, 78.9% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.18–8.01 (m, 2H), 7.60–7.45 (m, 2H), 6.95 (d, J=1.2 Hz, 1H), 6.61 (d, J=1.2 Hz, 1H), 5.79 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.24 (s, 3H). ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 152.3, 150.9, 145.2, 129.6, 128.2, 127.4, 126.9, 126.3, 125.6, 124.2, 122.8, 122.5, 122.0, 63.1, 61.5, 45.9, 11.9. HRMS (ESI) calcd. for C₁₇H₁₇O₄N₃Na: 350.1111. Found: 350.1115 (M + Na⁺).

General Procedure for the Oxidative Demethylation

Boron trichloride (6 equiv.) was added dropwise at -78°C to a stirred solution of the protected substituted menadione and tetrabutylammonium iodide (2 equiv.) in dry DCM (0.007 M). The reaction mixture was then allowed to heat to r.t. and stirred for 16 h. The yellow reaction mixture was quenched with water and the crude was extracted three times with DCM, dried over magnesium sulphate, and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using the appropriate eluent.

2-((1H-1,2,4-Triazol-1-yl)methyl)-3-methylnaphthalene-1,4-dione

(**41**). From **42**, eluent (CHX/EtOAc, 8/2 to 0/10, v/v, UV), orange solid, 20.9% yield. M.p. $129\text{--}131^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 9.33 (s, 1H), 8.55 (s, 1H), 8.19–8.08 (m, 3H), 7.81–7.76 (m, 2H), 5.52 (s, 2H), 2.51 (s, 3H). ^{13}C NMR (^1H) (101 MHz, CDCl_3) δ 184.0, 183.8, 149.8, 145.9, 142.9, 135.5, 134.8, 134.6, 132.1, 131.1, 127.2, 127.1, 47.5, 13.7. HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_2\text{N}_3$: 254.0924. Found: 254.0928 ($\text{M} + \text{H}^+$).

2-Methyl-3-((3-nitro-1H-1,2,4-triazol-1-yl)methyl)naphthalene-1,4-dione

(**43**). From **45**, eluent (CHX/EtOAc, 8/2 to 5/5, v/v, UV), yellow solid, 25.7% yield, very low solubility in deuterated solvent no ^{13}C NMR spectra was obtained. M.p. $132\text{--}134^{\circ}\text{C}$. ^1H NMR (400 MHz, acetone- d_6) δ 8.79 (s, 1H), 8.13–7.99 (m, 2H), 7.92–7.81 (m, 2H), 5.68 (s, 2H), 2.44 (s, 3H). HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{10}\text{O}_4\text{N}_4\text{Na}$: 321.0594. Found: 321.0591 ($\text{M} + \text{Na}^+$).

2-Methyl-3-((2-nitro-1H-imidazol-1-yl)methyl)naphthalene-1,4-dione

(**44**). From **46**, eluent (CHX/EtOAc, 8/2 to 0/10, v/v, UV), orange solid, 14.6% yield. M.p. $132\text{--}134^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 8.16–8.04 (m, 2H), 7.79–7.74 (m, 2H), 7.17 (d, $J = 1.2$ Hz, 1H), 7.12 (d, $J = 1.2$ Hz, 1H), 5.68 (s, 2H), 2.33 (s, 3H). ^{13}C (^1H) NMR (101 MHz, CDCl_3) δ 184.4, 183.8, 148.4, 138.1, 134.4, 134.4, 132.0, 131.6, 128.6, 126.9, 126.8, 126.1, 45.3, 13.4. HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_4\text{N}_3$: 298.0822. Found: 298.0845 ($\text{M} + \text{H}^+$).

Oxidation of 1,2,3-[TRZ-Methyl]-Menadione by UV-Irradiation

Reactions were irradiated with a 350 nm light generated by eight RPR-3500 A lamps of 200 W with a photochemical reactor for 72 h at a distance of 3 cm from the light source.

2-(1-Benzyl-1H-1,2,3-triazole-4-carbonyl)-3-methylnaphthalene-1,4-dione

(**β 51**). In a tube was dissolved in a mixture of propan-2-ol (0.74 mL) and DCM (0.92 mL), followed by **β 13** (55 mg, 0.16 mmol, 1 equiv.). The mixture was bubbled in O_2 for 5 min, then stirred under O_2 pressure at 16°C for 72 h under UV irradiation. The solvent was removed under vacuum and purified by silica gel chromatography (CHX/EtOAc, 8/2, v/v, UV) to afford 2-(1-benzyl-1H-1,2,3-triazole-4-carbonyl)-3-methylnaphthalene-1,4-dione (15.6 mg, 27.2%) as orange solid. M.p. $115\text{--}117^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 8.17–8.11 (m, 2H), 8.08–8.03 (m, 1H), 7.78–7.73 (m, 2H), 7.43 (dd, $J = 5.1, 2.0$ Hz, 2H), 7.35–7.32 (m, 2H), 5.58 (s, 2H), 2.10 (s, 3H). ^{13}C (^1H) NMR (101 MHz, CDCl_3) δ 187.2, 185.1, 183.4, 147.5, 144.2, 143.8, 134.2, 134.1, 133.2, 132.1, 131.8, 129.6, 129.6, 128.8, 126.8, 126.5, 126.4, 54.8, 13.7. HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{16}\text{N}_3\text{O}_3$: 358.1186. Found: 358.1183 ($\text{M} + \text{H}^+$).

Supporting Information Summary

Supporting Information (SI) content: pages S2–S8 (Figures S1–S10) – electrochemistry CV, SWV curves and UV-visible absorption curves; pages S9–S11: synthesis of precursors ; page S12 (Table S1) – CuAAC reaction with **1** using different conditions; pages S13–S15 – By-product and reduction after CuAAC from **1**; pages S16–S17 – synthesis of azido-substrates engaged in the CuAAC reaction

to form b-[TRZ-methyl]-menadione; pages S18–S19 – synthesis of alkyne-substrates engaged in the CuAAC reaction to form a-[TRZ-methyl]-menadione; pages S20–S65 – ^1H , ^{19}F (^1H) and ^{13}C (^1H) NMR spectra of compounds **1**– **β 51**.

The authors have cited additional references within the Supporting Information.^[60–78]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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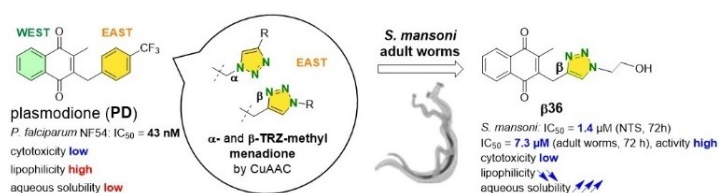
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The present study describes the synthesis and thorough investigation of 1,2,3-triazole-methyl-menadione derivatives with particular emphasis on their electrochemical and physicochemical properties and their antiparasitic activities against *Plasmodium*

falciparum and *Schistosoma mansoni*. Although less effective against *P. falciparum*, several compounds showed potent antischistosomal activity, highlighting their potential to develop more effective candidates for the treatment of schistosomiasis.

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Synthesis of 1,2,3-Triazole-Methyl-Menadione Derivatives: Evaluation of Electrochemical and Antiparasitic Properties against two Blood-Dwelling Parasites

