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Original article

Synthesis and antimalarial activity of pyrazolo and pyrimido benzothiazine dioxide derivatives

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ABSTRACT

A series of phenylsubstituted pyrazolo and pyrimido benzothiazine dioxide derivatives were synthesized and investigated for their abilities to inhibit β-hematin formation, hemoglobin hydrolysis and *in vivo* for their antimalarial efficacy in rodent *Plasmodium berghei*. Compounds 3-amino-7-chloro-9-(2′-methylpheyl)-1,9-dihydro-pyrazolo-[4,3-*b*]benzothiazine 4,4-dioxide **2b** and 2,4-diamino-8-chloro-10*H*-phenyl-pyrimido-[5,4-*b*]benzothiazine 5,5-dioxide **3a** were the most promising as inhibitors of hemoglobin hydrolysis, however, their effect as inhibitors of β-hematin formation was marginal, except for compound 3-amino-7-chloro-9-(3′-chlorophenyl)-1,9dihydro-pyrazolo-[4,3-*b*]benzothiazine 4,4-dioxide **2g**. The most active compound to emerge from the *in vitro* and *in vivo* murine studies was **2b**, suggesting an antimalarial activity via inhibition of hemoglobin hydrolysis, however, not as efficient as chloroquine.
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1. Introduction

Malaria, a major tropical infectious disease caused primarily by the protozoan parasite *Plasmodium falciparum*, is one of the most serious health problems worldwide and is responsible for the death of over 1 million individuals every year with more than 40% of the global population at risk [1]. Since resistance to currently used antimalarials is spreading rapidly, there is a great need for new drugs. Thus, there is a compelling and urgent necessity for new antimalarials, with mechanisms of action different from the existing ones, and to identify new drug targets [2]. Chloroquine has recently been shown to inhibit hemozoin formation within the parasite food vacuole [3]. This process is also thought to be the molecular target of other quinoline antimalarials [4]. Hemozoin was originally considered to be formed by the polymerization of heme, but it has now been demonstrated to be a crystalline cyclic dimer of ferriprotoporphyrin IX [5–8]. Thus, hemozoin synthesis, a process unique to the malaria parasite, offers a logical and valuable potential target for new antimalarial drug development. New drugs that attack the same vital target of chloroquine but that are not subject to the same resistance mechanism would be highly desirable. Fluoroquinolones are widely used clinically. Some of these quinolones such as ciprofloxacin, gatifloxacin, moxifloxacin and trovafloxacin, display a diverse array of biological activities including antiplasmodial efficacy [9]. We have recently described the preparation and antimalarial activities of several tricyclic quinolone and benzothiazine analogs [10–12]. In continuation of our studies directed toward synthesis of quinolones and benzothiazines annelated with various five- and six-member heterocycles, we reported here the synthesis of 3-amino-6 or 7-chloro-9-(phenylsubstituted)-1,9-dihydro-pyrazolo-[4,3-*b*]benzothiazine 4,4-dioxide **2a–t** and 2,4-diamino-7 or 8-chloro-10-(phenylsubstituted)-10*H*-pyrimido-[5,4-*b*]benzothiazine 5,5-dioxide **3a–t**, their *in vitro* abilities to inhibit β-hematin formation and hemoglobin hydrolysis and their *in vivo* efficacy against rodent *Plasmodium berghei*.

2. Chemistry

2,3-Substituted 6 or 7 chloro-*N*-phenylbenzothiazine **1a–t** were obtained following the method previously reported [10–12]. Products **2a–t** and **3a–t** were obtained when **1a–t** were reacted

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with hydrazine hydrate or guanidine hydrochloride, dry pyridine or DMF under an inert atmosphere of nitrogen, respectively, (Scheme 1).

It is important to mention that in the ^{1}H NMR spectra of these compounds, protons at positions 8 and 9 from derivatives **2a–t** and **3a–t** appeared as doublets around 6.0 ppm with coupling constants ranging between 0.9–2.5 and 7.0–8.0 Hz, clearly indicating the smaller chemical shift of the proton on these positions by the effect of the phenyl group on position 9 or 10, respectively. Additional supports for these structures were obtained from ^{13}C NMR.

The molecular structure of **3p** was confirmed by X-ray crystallography (Fig. 1). The X-ray crystal structure analysis showed that all the bond distances are within expected values [13]. In the tricyclic system, the central ring displays an approximate sofa conformation, with S1 out of the plane [0.600(2) Å], and O1 and O2 in equatorial and axial positions, respectively. The N-bonded phenyl ring is approximately perpendicular to the tricyclic system [dihedral angle between mean planes: 84.83(5)°]. The molecule forms an N–H···O (sulfonyl) intramolecular hydrogen bond. In addition, in the crystal structure there are a number of intermolecular hydrogen bonds of the types N–H···O(sulfonyl), N–H···O(methoxy), N–H···Cl, N–H···S, C–H···O(sulfonyl), C–H···O(methoxy), C–H···N(amino) and C–H···N(pyrimidine, N4) which link the molecules to form a three dimensional network (see CIF file for details).

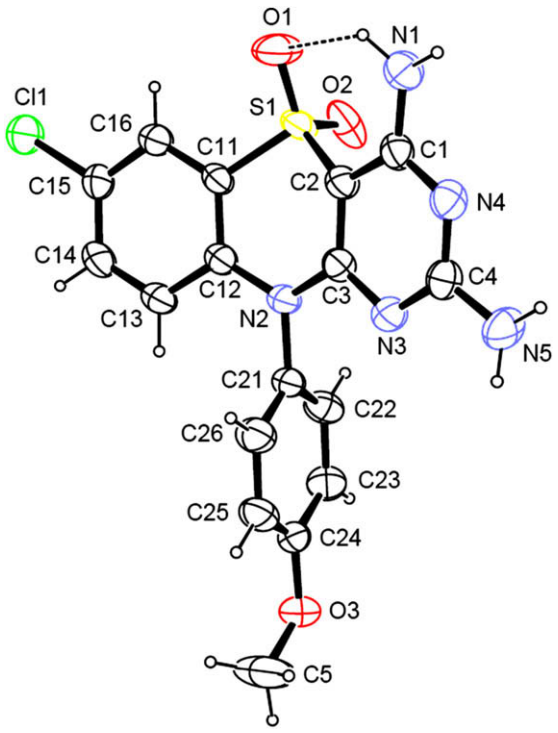
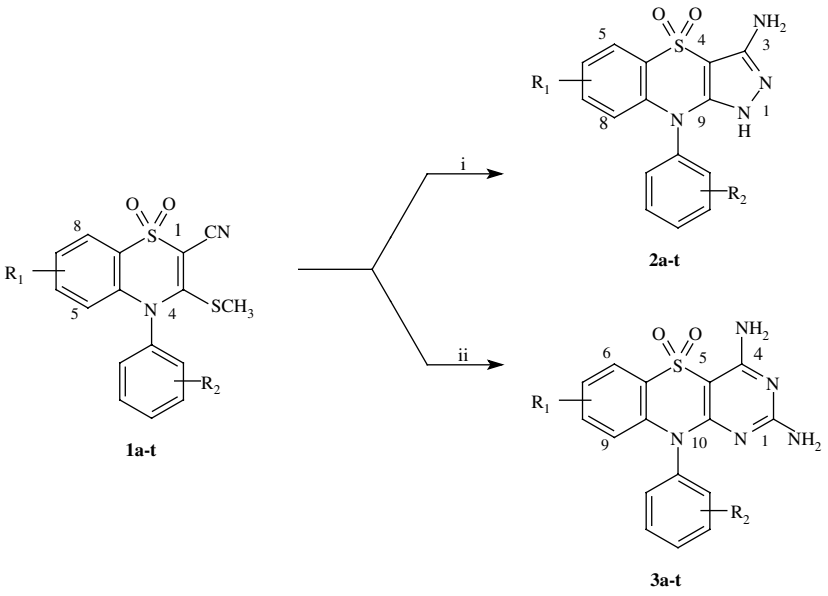


Fig. 1. Molecular structure of compound **3p** showing the atomic numbering. The displacement ellipsoids are drawn at 50% probability. A dashed line indicates an intramolecular hydrogen bond.

3. Biological results and discussion

Previous reports showed that tricyclic benzothiazines exhibited antimalarial activities [10,12]. All analogs of those derivatives were tested *in vitro* for their effects as inhibitors of β-hematin formation, and inhibition of hemoglobin hydrolysis (Table 1). Only **2a**, **2g**, **3a** derivatives were tested *in vivo* for their efficacy in a murine model (Table 3). The first mentioned *in vitro* assay was used to assess the abilities of the *N*-phenylpyrazolo[4,3-*b*]benzothiazine and *N*-phenylpyrimido[5,4-*b*]benzothiazine *S*,*S*-dioxide derivatives to inhibit β-hematin formation, where hemin was allowed to form β-hematin under acidic conditions. Among the 40 compounds tested, only one **2g** showed a measurable activity (85.42 ± 6.14%) compared to chloroquine (86.6 ± 2.75%).

Compounds **2a–t** and **3a–t** were also tested for the inhibition of globin proteolysis using *in vitro* assays which used rich extracts of trophozoites to digest the native hemoglobin of mice. Electrophoretic analyses indicated that compounds **2a–j** and **3a–j** were effective as inhibitors of hemoglobin degradation; however, compounds **2b** and **3a** were the most effectives (92.32 ± 1.1 and 83.72 ± 2.13%) compared to leupeptin and pepstatin (89.06 ± 0.69 and 92.94 ± 0.67), respectively (Table 1).



Scheme 1. Synthesis of pyrazolo and pyrimido benzothiazine dioxide derivatives **2a–t**, **3a–t**. (i) N_2H_4 hydrate, pyridine, Δ. (ii) Guanidine hydrochloride, potassium carbonate, DMF, Δ. R_1: Cl; R_2: H, CH_3, OCH_3, Cl, Br.

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