PROFESSOR HENOK KINFE (Orcid ID : 0000-0002-4958-2836)

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# Design, synthesis and antiplasmodial evaluation of a series of novel sulfoximine analogues of carbohydrate–based thiochromans

Munashe Chizema,[1] Tommy F Mabasa,[1] Heinrich C Hoppe[2] and Henok H Kinfe[1]*

[1]*Center of Synthesis and Catalysis, Department of Chemistry, University of Johannesburg–Kingsway Campus, Auckland Park 2006, Johannesburg, South Africa*
[2]*Department of Biochemistry and Microbiology, Rhodes University, Grahamstown 6140, South Africa*

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**Abstract**

Sulfone/sulfoxide–containing carbohydrate derived thiochromans were found to be highly active antiplasmodial agents. However, the inability of the sulfone/sulfoxide functional groups for further derivatization and manipulation limited the potential for further exploration. In this study, based on the interesting and important physicochemical properties, as well as amenability of sulfoximines (isosters of sulfones) for further derivatization, a series of novel sulfoximine–type carbohydrate–derived thiochroman derivatives have been successfully synthesized, characterised and evaluated for their antiplasmodial activity. Although the replacement of the sulfone functional group with a sulfoximine unit improved the antiplasmodial activity of the scaffolds, the activity was highly dependent on the configuration of the stereogenic centre at the sulfur atom. Moreover, analysis of the crystal structures of the sulfoximine analogues revealed that the bond between the sulfur and nitrogen atoms of the sulfoximine functional group is not a true double bond but rather a polarized single bond.

* Corresponding author. Tel.: +27-011 559 3918; fax: +27-011-559-2819; e-mail: hhkinfe@uj.ac.za

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## Introduction

Malaria is one of the leading causes of death globally especially in poor communities and in children under the age of five.[1–5] Protozoan parasites of the genus *Plasmodium* are the causative agents of malaria that are transmitted by the bite of the female *Anopheles* mosquito.[6] There are six species of *Plasmodium* that cause malaria in humans, namely: *P. falciparum*, *P. vivax*, *P. ovale curtisi*, *P. ovale wallikeri*, *P. malariae* and *P. knowlesi*.[6,7] Among them, *P. falciparum* and *P. vivax* are the most deadly species and responsible for the main burden of malaria in sub–Saharan Africa and the rest of the world, respectively.[7] According to the 2017 WHO report half of the world's population was at risk of malaria and malaria cases and malaria deaths stood at 216 000 000 and 445 000, respectively, of which sub–Saharan countries accounted for almost 90% of these cases.[7]

Preventative and curative measures for this significant health challenge have been implemented predominantly using antimalarial drugs. Currently, the use of a combination of two or more drugs possessing different modes of action, such as ACT (artemisinin–based combination therapy that involves the use of artemisinin along with companion drugs: lumefantrine, mefloquine, amodiaquine, sulfadoxine/pyrimethamine, piperaquine and chlorproguanil/dapsone), is the WHO recommended treatment of malaria.[7–11] However, tolerance, which may lead to resistance against this class of drugs, has been reported. The emergence of these drug resistant strains of malaria necessitates the discovery of new drugs, paying particular attention to new chemotypes, cellular targets or pivotal characteristics that could retard the emergence of resistance.[7,12–14]

Sulfur–containing compounds in the form of sulfides, sulfoxides and sulfones are known to possess interesting biological activities as exemplified by the famous drug compounds, Penicillin **1**,[15,16] Esomeprazole **2**,[17] Dapsone **3a**[18] and Prontosil **3b**[15,16] (Figure 1).[7]

However, sulfoximine (an isostere of sulfone)–containing compounds are less explored for their therapeutic use, despite being discovered over six decades ago. It is only in the last ten years that the synthesis of bioactive sulfoximine derivatives started to pick up momentum due to their favorable physicochemical properties,[19-21] hydrogen–bond acceptor/donor functionalities,[20,21c] relatively higher metabolic stability[21a,21b] and solubility[21] than the corresponding analogues. The presence of a stereogenic centre at the sulfur atom and amenability for further derivatization are additional attractive features of sulfoximines in medicinal chemistry. For instance, sulfoximine containing compounds have been reported to exhibit various biological activities such as antiviral **4a**,[22] anticancer **4b**[23] and antidepression **4c**[24] (Figure 1).

In our efforts in the development of new antimalarial agents, we have recently reported the synthesis and antiplasmodial activity of novel carbohydrate–derived thiochromans.[25,26] Although compound **5** (Figure 3) from the series of the tested compounds exhibited promising activity against both chloroquine–sensitive (3D7) and chloroquine–resistant (FCR3) strains with $IC_{50}$ values of 0.3–0.4 μM, however, the inability of the sulfone functional group to undergo further diversification and manipulation limited the potential to explore the possibility of improving the $IC_{50}$ values of these scaffolds to nanomolar concentrations.

Derivatization at the α–carbon of the sulfone led to epimerization at the anomeric centre of the sugar moiety resulting in products which were found to be less potent against the *Plasmodium* strains.[25] These limitations, coupled with the special features endowed to sulfoximines, prompted us to synthesise sulfoximine analogue **6** (Figure 2) of the most active carbohydrate derived thiochroman **5**, in the hope of improving the antiplasmodial activity of these scaffolds. Herein, we report the synthesis, antiplasmodial activity results and the structural activity relationship (SAR) studies of novel sulfoximine derivatives of the carbohydrate derived thiochroman scaffolds.

## Methods and Materials

### *Chemistry*

The solvents were dried by appropriate techniques reported in the Purification of Laboratory Chemicals by Perrin and Armarego.[27] All reactions were monitored by thin layer chromatography (TLC) on aluminum–backed silica gel 60 $F_{254}$ plates using an ascending technique. The plates were visualized under UV–light. Gravity column chromatography was done on silica gel 60 (70–230 mesh). Melting points were determined using a hot–stage and are uncorrected. All $^{1}H$ and $^{13}C$ nuclear magnetic resonance spectra were recorded as deuteriochloroform solutions using tetramethylsilane as an internal standard. All chemical shifts are reported in ppm. The carbohydrate-based thiochroman **7** and the corresponding sulfone **5** and sulfoxide derivatives **8a** and **8b** were synthesized according to literature methods previously reported and their experimental data were in agreement with the literature.[25, 28, 32] The experimental procedures, NMR and IR spectroscopic as well as HRMS data for all new compounds is provided in the Supporting Information.

### Antiplasmodial assay

*Plasmodium falciparum* (strain 3D7) parasites were maintained in culture medium consisting of RPMI 1640 supplemented with 25 mM HEPES, 0.5% (w/v) Albumax II, 22 mM glucose, 0.65 mM hypoxanthine and antibiotics (20 µg/ml gentamicin). The cultures contained human erythrocytes (2 – 4% haematocrit) and were incubated at 37 $^{o}C$ under an atmosphere of 5% $CO_2$, 5% $O_2$, and 90% $N_2$. To assess compound activity, a parasite culture containing predominantly mature stage parasites was distributed into 96–well plates, compounds added to a final concentration of 20 µM (from 10 mM stocks in DMSO; final culture parasitemia 2%, haematocrit 1%) and incubation continued for 48 hours. Twenty µl of resuspended culture was removed from each well and used to perform a parasite lactate dehydrogenase (pLDH) colorimetric enzyme assay.[29] After subtracting background readings from wells containing uninfected erythrocytes, the absorbance values were converted to % parasite viability relative to wells containing untreated control parasite cultures. Dose–response $IC_{50}$ assays were performed as described above, except that parasites were incubated with 3–fold serial dilutions of the test compounds. Plots of % parasite viability *vs.* log[compound] were used to determine IC50 values by non–linear regression analysis using GraphPad Prism software.

**Cytotixicity assay**

HeLa cells were cultured in DMEM medium containing 10% fetal calf serum and penicillin/streptomycin/amphotericin B at 37 $^{o}$C in a 5% $CO_2$ incubator. Twenty–four hours prior to compound addition, cells were plated into 96–well plates at a density of 2 x $10^4$ cells per well. Compounds were added to a final concentration of 20 µM and incubation continued for 48 h. To assess cell viability, 20 µl resazurin reagent (0.5 mM resazurin in phosphate–buffered saline) was added to each well, incubation continued for 4 hours and fluorescence ($Ex_{560}/Em_{590}$) measured in a plate reader. After subtracting background reading obtained from empty wells, the fluorescence readings were converted to % cell viability relative to wells containing untreated control HeLa cells.

## Result and discussion

### Chemistry

*Synthesis of sulfoximine analogues of the sulfone–derived thiochroman.*

In order to investigate whether replacing the sulfone moiety with a sulfoximine improves the antiplasmodial activity of the thiochroman scaffolds, sulfoximines **6a** and **6b** were prepared as shown in Scheme 1 using the protocol reported by Zenzola *et al*.[30,31] Accordingly thiochroman **7**, prepared according to our previously reported protocol,[32] was oxidized using 1.2 equiv. of oxone® to afford sulfoxides **8a** and **8b** as a separable mixture in 1:3 diastereoisomeric ratio, while oxidation with excess oxone® led to the formation of sulfone **5** in reasonable yields (Scheme 1).[30] Imidation of sulfoxide **8a** upon treatment with a mixture of (diacetoxyiodo)benzene (DIB) and $NH_2COONH_4$ provided the desired sulfoximine **6a** in 90% yield with retention of stereochemistry at the sulfur atom. The stretching frequency of the quasi–broad N–H band at 3250 $cm^{-1}$ and also the appearance of the singlet signal at $\delta_H$ 3.00 confirmed the presence of the NH moiety in sulfoximine **6a**. Likewise, sulfoximine **6b** was successfully synthesized and characterized (Scheme 1).

Furthermore, the absolute stereochemistry of the stereogenic centre at the sulfur atom was confirmed by X–ray crystallography (Figure 3). As expected, the fused pyran and thiopyran rings adopted a chair and an envelope conformation, respectively, with the NH–group in the *pseudo*–axial position.[33] To find out the bonding nature around the sulfoximine functional group, the presence or absence of double bonds between the sulfur and oxygen atoms, as well as between sulfur and nitrogen atoms of the sulfoximine **6a** were analyzed on the X–ray crystal structure. Interestingly, using OLEX2 (structural refinement program), no double bond was observed about the expected S=N bond. Thus it is reasonable to conclude that the bonding between the sulfur and nitrogen atoms of the sulfoximine functional group is of a polar nature and can be represented with a single bond as opposed to the expected double bond. This is in agreement with previous reports which indicated that, π–bonding between *3p* orbitals of sulfur and *2p* orbitals of another atom such as carbon and nitrogen, are less effective than π–bonds formed *via* overlap of *2p* orbitals only.[34–36]

After the successful synthesis of sulfoximine **6**, **v**arious sulfoximine derivatives were synthesized for structural activity relationship studies and are discussed below.

*Sulfonamide derivatives of sulfoximine **6a***

The sulfonamide group is a well–known structural unit found in a number of drugs that are used to treat a wide spectrum of diseases including malaria, as exemplified by sulfadoxine and sulfamethoxypyridazine.[37] Hence a nosyl unit was incorporated into the sulfoximine **6a** as shown in

Scheme 2. Since treatment of sulfoxide **8a** with an *in situ* generated nitrene source (PhINNs) from the reaction of nosyl amide and DIB led to the formation of the sulfonamide **10** in low yields, the desired product **10** was synthesized *via* a two–pot synthesis, whereby the nitrogen source **9** was prepared by treating nosyl amide with DIB in the presence of KOH.[38,39] The isolated compound was then reacted with sulfoxide **8a** in the presence of $Cu(OTf)_2$ to provide sulfonamide **10** in reasonable yield as shown in Scheme 2.[40] Among others, the appearance of the characteristic two doublets of the *para*–substituted benzene ring at $\delta_H$ 8.25 and 8.13 confirmed the formation of the desired product.

*Alkylation of sulfoximine **6a***

By exploiting the acidity of the NH group of sulfoximine **6a**, alkylated derivatives **11a–i** were successfully synthesized according to Scheme 3. The reaction involved treatment of sulfoximine **6a** with KOH in DMSO, followed by addition of alkyl halides to provide a series of alkylated derivatives upon column chromatography–mediated purification using trimethylamine–doped silica gel. A variety of alkylated sulfoximines **11a–i** were synthesized possessing short, medium and long chain aliphatic alkyl moieties and the results are summarized in Scheme 3. Interestingly, of all the alkylated sulfoximines synthesized, the sulfoximine **11d** with the branched alkyl group underwent epimerization at the anomeric centre of the sugar moiety. This could be due to the high steric demand of the branched alkyl group and hence the competitive abstraction of the acidic anomeric proton to form the more stable β–arylglycoside might have taken place prior to alkylation at the NH group. A similar phenomenon was observed when sulfone **5** was treated with a base in our previous study.[28] The epimerization was confirmed by an upfield shift of the anomeric proton signal from around $\delta_H$ 5.23 of the starting material **8a** to $\delta_H$ 4.57, as well as an increase in the coupling constant of the anomeric proton to $J$ = 10.5 Hz from $J$ = 4.4 Hz, indicating a *trans*–diaxial relationship with the adjacent proton (H–2 of the sugar moiety).

In a similar fashion, the minor sulfoximine **6b** was alkylated to provide sulfoximines **12–17** and the results are summarized in Scheme 4. Unlike in the case of the alkylation of sulfoximine **6a**, alkylation of sulfoximine **6b** led to a concomitant epimerization at the anomeric centre in most cases and provided separable diastereomeric mixtures.

*N–S coupling reaction*

In addition, separable diastereomeric mixtures of **18a** and **18b** were obtained *via* a simple substitution reaction of sulfoximine **6a** with 3–nitro–2–pyridinesulfenyl chloride (Npys–Cl) under basic condition as shown in Scheme 5.

Though this protocol is simple, the unavailability of various commercial sulfenyl halides limited its scope. Thus we opted to use a general N–S coupling methodology to synthesize N–S–coupled sulfoximine derivatives. Following the methodology reported by Zhu *et al*,[39–41] a solution of sulfoximine **6a** in DMSO was treated with a disulfide and sodium acetate in the presence of CuI as a catalyst, to provide the N–S coupled sulfoximines **18c–g** in quantitative yields, the results are summarized in Scheme 6. The structures of the products were established using NMR and HRMS spectroscopy. The disappearance of the NH signals and the increase of the integration of the aromatic protons were a clear indication of the successful synthesis of this class of compounds.

**Antiplasmodial activity**

Encouraged by the excellent antiplasmodial activity of the sulfone **5**, we synthesized the sulfoximine **6** analogues (Scheme 1), motivated by the notion that replacing the sulfone moiety with the sulfoximine could potentially enhances physicochemical properties. Since the compounds previously

tested showed almost similar activities against both strains of the chloroquine–sensitive (3D7) and chloroquine–resistant (FCR3) *P. falciparum*, the sulfoximine derivatives in the current study were evaluated for their activity against the 3D7 strain only. Determination of the parasite viability using a single 20 μM concentration of each of the sulfoximines (**6a** and **6b**) and sulfone **5** resulted in a reduction of parasite viability to 6.2%, 8.0% and 3.7% of untreated controls (Table 1), respectively that warranted the determination of their respective $IC_{50}$ values. Interestingly while the minor isomer, sulfoximine **6b**, displayed a ~20% improvement in activity with an $IC_{50}$ value of 0.8 μM (vs 1.0 μM of the sulfone **5**),[42] the major isomer, sulfoximine **6a**, was found to be inactive. Although replacing the sulfone with the sulfoximine indeed improved the antiplasmodial activity as anticipated, the activity was highly dependent on the absolute configuration of the sulfoximine stereogenic centre. The fact that both the sulfone **5** and sulfoximine **6b** were found to be active thus suggests the active site of the host prefers a hydrogen bond–acceptor on the *endo*–face of the fused ring of the thiochroman scaffold.

With this finding in hand, we decided to convert the major sulfoximine **6a** to its alkylated derivatives, thereby transforming it from being a hydrogen–bond donor to an accepter. Accordingly, a series of alkylated sulfoximine derivatives **11a**–**i** were successfully prepared and evaluated for their antiplasmodial activities. As expected, the alkylation sulfoximine **6a** resulted in compounds with improved activity; from being inactive to highly active (Table 1, **6a** Vs **11a–i** except **11f**). This further proves that the endo face of the thiochroman scaffolds indeed requires a hydrogen–bond acceptor not a donor. However, the activity was found to be dependent on the chain length of the alkyl group with the methyl group exhibiting the highest activity (Table 1, **11a** *vs*. **11f**). With increase in the chain length of the alkyl substituents, the activity diminished and this might be attributed to the increased hydrophobicity and steric hindrance. Transforming sulfoximine **6b** from being a hydrogen–bond donor to an acceptor reduced the activity (Table 1, **6b** *vs*. **12**, **13**, **14a** and **16a**). The multiple bond possessing alkyl substituents also displayed similar activities (Table 1, **11g–i**) with the π–bonds exhibiting no influence on the possible guest–host interaction. In agreement with our previous report,[25] the activity of the sulfoximine derivatives was also dependent on the stereochemistry of the anomeric centre of the sugar moiety. A *β*–glycosidic bond led generally to inferior activity when compared with the corresponding *α*–glycosylated sulfoximines (Table 1, **14a** and **16a** *vs*. **14b** and **16b**, respectively). A cytotoxicity study of all the active compounds was investigated and they were all found to be non–toxic at 20 μM against the human HeLa cell line (Table 1).

Since sulfur has high enzyme binding affinity,[43] the hydrogen–bond donor sulfoximine **6a** was transformed into a hydrogen bond–acceptor *via* N–S coupling reactions, as well as by $S_N2$ reactions, in the hope of improving the potency of these thiochroman derivatives. Accordingly, sulfoximine derivatives **18a–g** were successfully prepared as described in the experimental section and evaluated for their antiplasmodial activities. Unfortunately, all of them exhibited above 25% parasite viability and were not considered further for $IC_{50}$ value determination. The poor activity of these N–S coupled products could perhaps be attributed to the weak N–S bond, which probably dissociates in the bioassay medium to give the inactive free sulfoximine **6a**.[33] Similarly, the sulfonamide derived analogue was also found to be inactive (Table 1, entry **18a–b**).

## Conclusion

The main objective of the current study was to evaluate the effect of replacing the sulfone functional group of the antiplasmodial thiochroman scaffolds with a sulfoximine moiety. Various novel sulfoximine derivatives were successfully synthesized, characterized, and evaluated for their antiplasmodial activity. The *in vitro* antiplasmodial activity results confirmed that the presence of the free–sulfoximine unit enhanced the activity, but this effect was highly dependent on the configuration of the stereogenic centre at the sulfur atom. These results demonstrate the importance of the stereogenicity of the sulfoximine unit that is commonly overlooked in the literature reports. Better

activity was exhibited with the presence of the hydrogen–bond donor NH on the *exo*–face of the molecule, while a hydrogen–bond donor on the *endo*–face of the molecule completely suppressed the activity. Encouragingly, transforming the *endo*–NH from being a hydrogen–bond donor into an acceptor *via* simple alkylation reactions forming a strong bond with the nitrogen atom, improved the activity significantly, suggesting exploration of further derivatization might lead to better activity.

Although there is a growing interest in the development of methodologies for the synthesis of sulfoximines and their use in medicinal chemistry, to the best of our knowledge, there is no report on the bonding nature of sulfoximines. On the basis of the crystal structure of sulfoximine **6a**, we suggest that the bond between the sulfur and nitrogen atoms is not a true double bond but rather a polarized single bond. Computational studies on simple sulfoximine derivatives is currently underway in our group to fully understand the properties of bonding between the sulfur and nitrogen atoms.

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**Figure 1.** Examples of sulfur–containing drugs and biologically active sulfoximines.

**Figure 2.** Sulfone **5** and the proposed sulfoximine **6** analogue of the thiochroman scaffold.

**Scheme 1.** Synthesis of sulfoxide **8**, sulfone **5** and sulfoximine **6**. i. Wet $Al_2O_3$, oxone®, DCM, 3 h, rt, 63% (3:1, **8a**:**8b**); ii. Wet $Al_2O_3$, excess oxone®, DCM, 4 h, 80%; iii. DIB, $NH_2CO_2NH_4$, MeOH, 30 min, rt, **6a** (90%) and **6b** (84%).

**Figure 3**. ORTEP diagram of sulfoximine **6a** with ellipsoids drawn at 50% probability. **Crystal Data** for $C_{38}H_{43}NO_5S$ ($M$ =625.79 g/mol): monoclinic, space group $P2_1$ (no. 4), $a$ = 16.253(3) Å, $b$ = 6.0345(10) Å, $c$ = 17.334(3) Å, $\beta$ = 105.345(5) °, $V$ = 1639.5(5) Å$^3$, $Z$ = 2, $T$ = 99.98 K, μ(MoK$\alpha$) = 0.144 mm$^{-1}$, *Dcalc* = 1.268 g/cm$^3$, 18020 reflections measured (4.006° ≤ 2Θ ≤ 56.544°), 7709 unique ($R_{int}$ = 0.0771, $R_{sigma}$ = 0.1171) which were used in all calculations. The final $R_1$ was 0.0594 (I > 2σ(I)) and $wR_2$ was 0.1353.

**Scheme 2.** Synthesis of sulfonamide **10**: $Cu(OTf)_2$ (10 mol%), $CH_3CN$, 30 min, rt, 70%.

**Scheme 3.** Alkylation of sulfoximine **6a**: i) a. KOH, DMSO, 5 min, rt; b. RX, 6 h, rt.

**Scheme 4.** Synthesis alkylated–sulfoximine **12**–**17** using the minor sulfoximine **6b** as the precursor. i) a. KOH, DMSO, 5 min, rt; b. RX, 30 min (with 4 equiv. of RX), rt,

**Scheme 5.** Sulfonamide **18** synthesis. Npys–Cl, KOH, DMSO, 6 h, rt.

**Scheme 6.** Thioetherification of sulfoximine **6a**. ArS–SAr, NaOAc, CuI (10 mol %), DMSO.

**Table 1.** Antiplasmodial and cytotoxicity assay of sulfone **5** and the sulfoximine derivatives.[a]

Note: The authors declare no competing financial interest.

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42. The difference between the current and our previously reported Ref 11 and 12 could be as a result of the set up used for the bioassay study. The previous study was conducted at Council

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**Table 1.** Antiplasmodial and cytotoxicity assay of sulfone **5** and the sulfoximine derivatives.[a]

| Compound at 20 µM | Parasite % viability | $IC_{50}$ value µM | HeLa cell % viability |
|---|---|---|---|
| **5** | 3.7 ± 0.2 | 1.0 ± 0.6 | 100.9 ± 3.2 |
| **6a** | 89.4 ± 11.1 | N/A | 89.4 ± 11.1 |
| **6b** | 8.0 ± 1.7 | 0.8 ± 0.3 | 80.5 ± 0.8 |
| **10** | 59.6 ± 2.0 | N/A | 98.3 ± 8.8 |
| **11a** | 6.5 ± 3.6 | 0.9 ± 0.4 | 62.6 ± 5.0 |
| **11c** | 9.4 ± 0.0 | 2.8 ± 0.6 | 98.3 ± 2.7 |
| **11d** | 8.1 ± 2.7 | 17.0 ± 11.0 | 91.0 ± 0.7 |
| **11e** | 11.9 ± 5.3 | 3.0 ± 1.1 | 98.2 ± 5.5 |
| **11f** | 107.3 ± 0.7 | N/A | 83.6 ± 7.0 |
| **11g** | 11.3 ± 0.8 | 4.6 ± 0.7 | 103.3 ± 8.8 |
| **11h** | 14.4 ± 0.6 | 7.3 ± 3.5 | 101.7 ± 1.7 |
| **11i** | 6.9 ± 1.9 | 0.9 ± 1.0 | 52.5 ± 1.5 |
| **12** | 10.9 ± 0.7 | 2.8 | 96.3 ± 25.0 |
| **13** | 13.9 ± 8.1 | 3.1 ± 1.7 | 111.8 ± 4.5 |
| **14a** | 22.6 ± 8.1 | 1.7 ± 1.4 | 111.8 ± 4.5 |
| **14b** | 64.5 ± 12.6 | NA | 111.5 ± 8.9 |
| **15b** | 36.0 ± 6.3 | 6.4 ± 0.6 | 99.3 ± 26.2 |
| **16a** | 15.1 ± 1.2 | 2.6 ± 0.5 | 101.5 ± 8.4 |
| **16b** | 8.4 ± 4.1 | 3.3 ± 1.1 | 65.3 ± 2.2 |
| **17a** | 32.4 ± 0.4 | 20.0 ± 5.9 | 55.1 ± 1.5 |
| **17b** | 46.4 ± 0.9 | 16.7 ± 3.8 | 66.2 ± 5.4 |
| **18a** | 37.9 ± 0.6 | N/A | 98.0 ± 4.8 |
| **18b** | 58.3 ± 11.6 | N/A | 53.9 ± 0.1 |
| **18c** | 103.4 ± 4.2 | N/A | 108.5 ± 13.0 |
| **18d** | 72.8 ± 3.5 | N/A | 83.3 ± 11.6 |
| **18e** | 111.7 ± 4.8 | N/A | 71.1 ± 1.6 |
| **18f** | 80.4 ± 1.6 | N/A | 116.8 ± 0.4 |
| **18g** | 112.6 ± 0.4 | N/A | 105.9 ± 5.7 |
| **Chloroquine** | N/A | 0.019 µM | N/A |

[a] Compounds were incubated with *P. falciparum* (3D7) parasites and HeLa cells at 20 µM for 48 h. Following the incubation, percentage parasite and HeLa cell viability was calculated relative to untreated control samples. $IC_{50}$ values against *P. falciparum* are also shown.

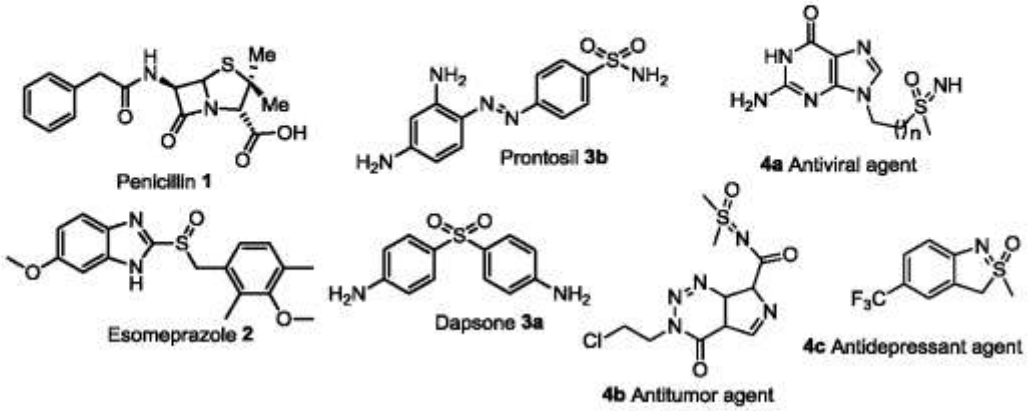



**Figure 1.** Examples of sulfur–containing drugs and biologically active sulfoximines.

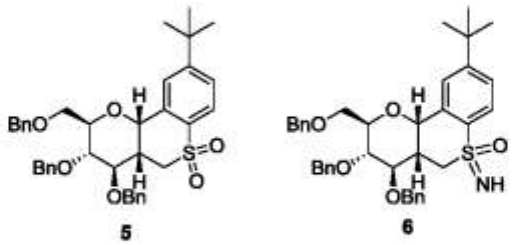



**Figure 2**. Sulfone **5** and the proposed sulfoximine **6** analogue of the thiochroman scaffold.

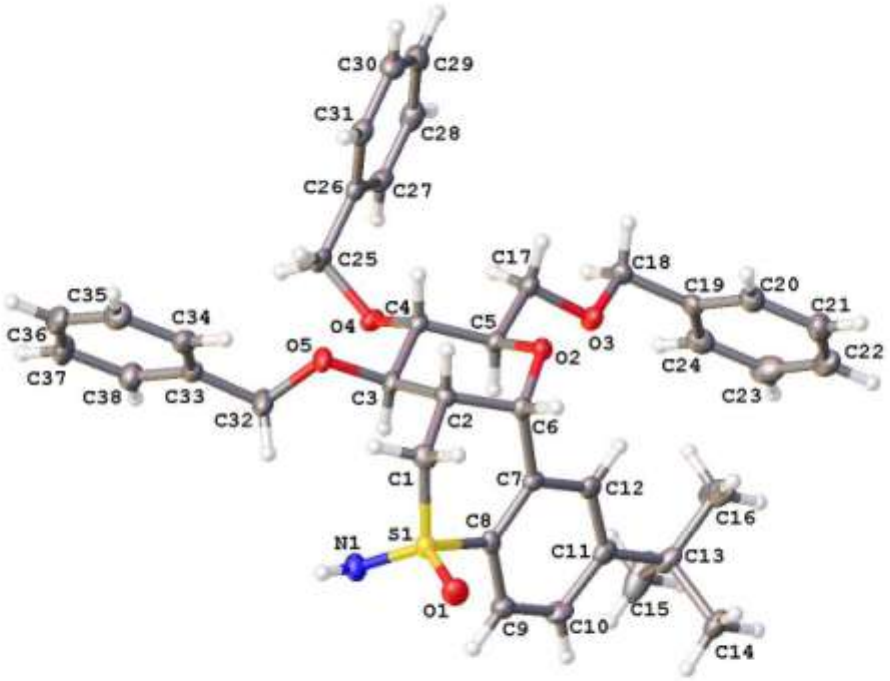
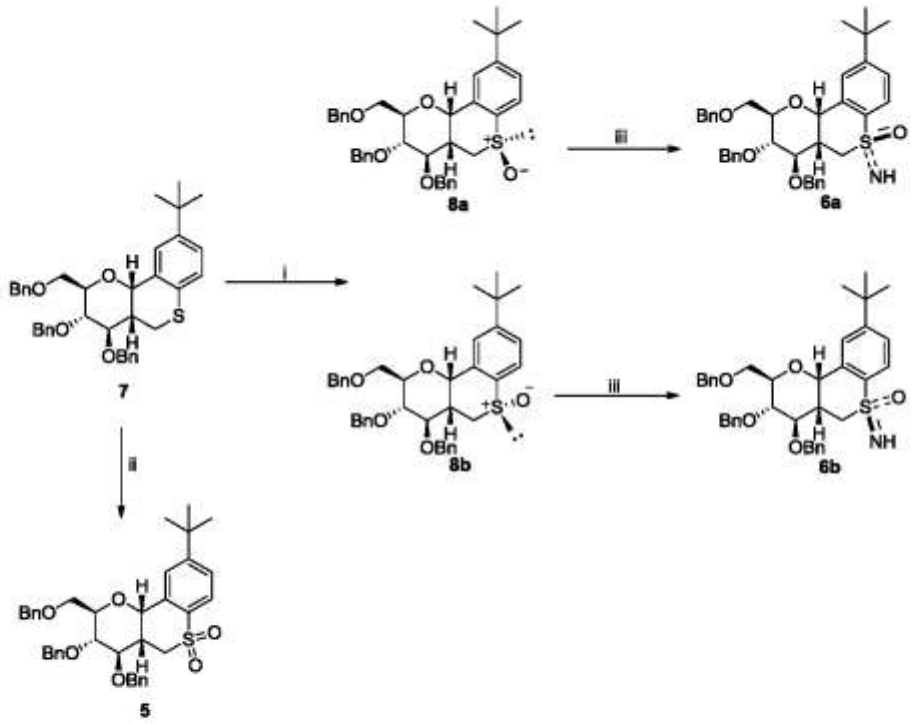
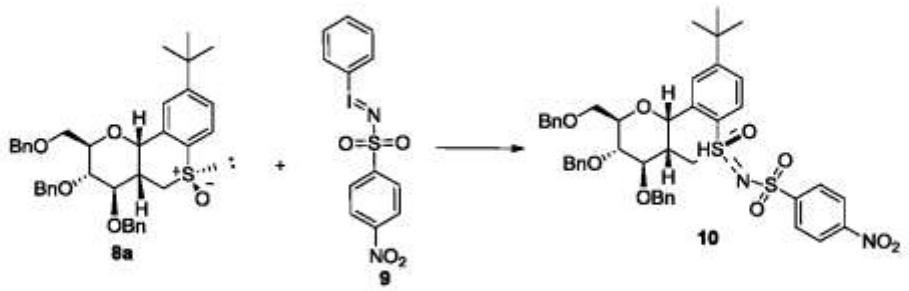


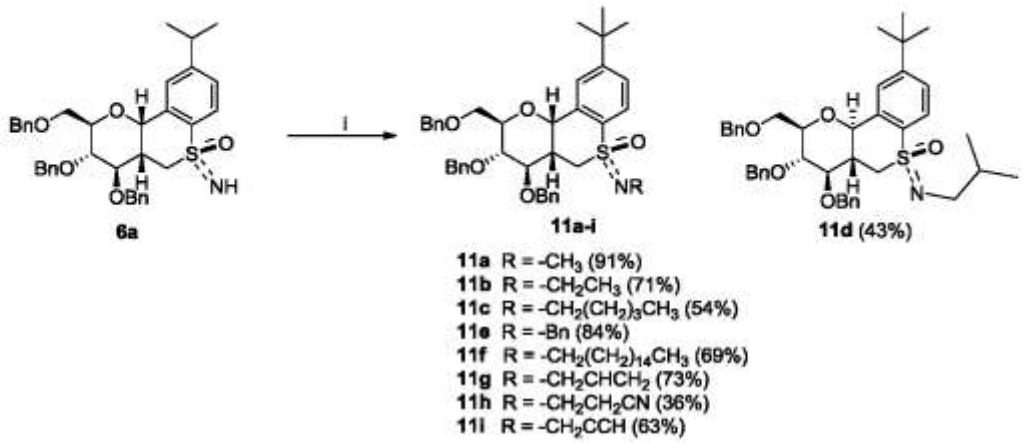

**Figure 3**. ORTEP diagram of sulfoximine **6a** with ellipsoids drawn at 50% probability. **Crystal Data** for $C_{38}H_{43}NO_5S$ ($M$ =625.79 g/mol): monoclinic, space group $P2_1$ (no. 4), $a$ = 16.253(3) Å, $b$ = 6.0345(10) Å, $c$ = 17.334(3) Å, $\beta$ = 105.345(5) °, $V$ = 1639.5(5) Å$^3$, $Z$ = 2, $T$ = 99.98 K, μ(MoKα) = 0.144 mm$^{-1}$, *Dcalc* = 1.268 g/cm$^3$, 18020 reflections measured (4.006° ≤ 2Θ ≤ 56.544°), 7709 unique ($R_{int}$ = 0.0771, $R_{sigma}$ = 0.1171) which were used in all calculations. The final $R_1$ was 0.0594 (I > 2σ(I)) and $wR_2$ was 0.1353.




**Scheme 1**. Synthesis of sulfoxide **8**, sulfone **5** and sulfoximine **6**. i. Wet $Al_2O_3$, oxone®, DCM, 3 h, rt, 63% (3:1, **8a**:**8b**); ii. Wet $Al_2O_3$, excess oxone®, DCM, 4 h, 80%; iii. DIB, $NH_2CO_2NH_4$, MeOH, 30 min, rt, **6a** (90%) and **6b** (84%).

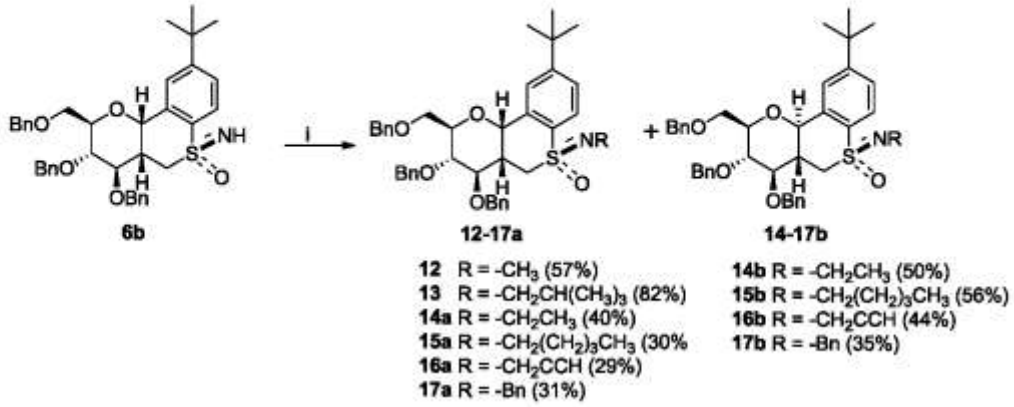



**Scheme 2**. Synthesis of sulfonamide **10**: $Cu(OTf)_2$ (10 mol%), $CH_3CN$, 30 min, rt, 70%.

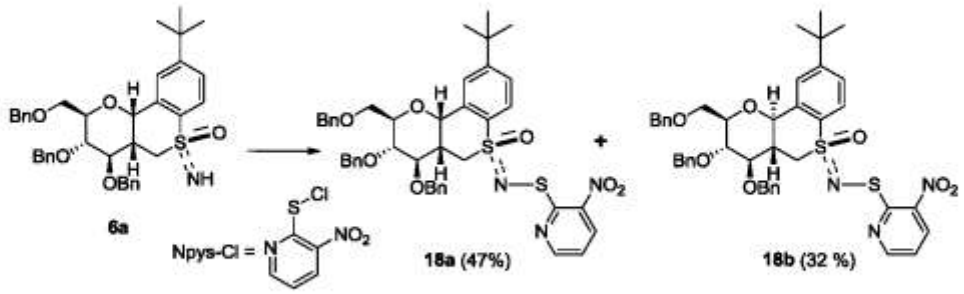



**11a** R = $-CH_3$ (91%)
**11b** R = $-CH_2CH_3$ (71%)
**11c** R = $-CH_2(CH_2)_3CH_3$ (54%)
**11e** R = -Bn (84%)
**11f** R = $-CH_2(CH_2)_{14}CH_3$ (69%)
**11g** R = $-CH_2CHCH_2$ (73%)
**11h** R = $-CH_2CH_2CN$ (36%)
**11i** R = $-CH_2CCH$ (63%)

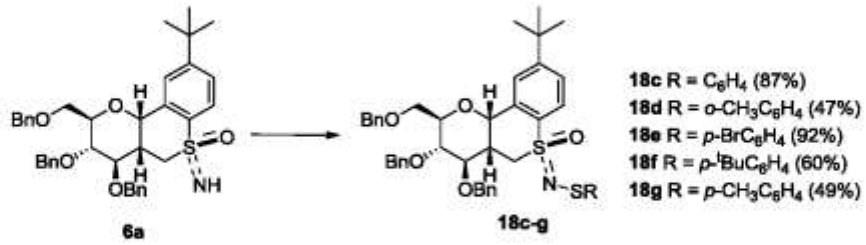
**Scheme 3**. Alkylation of sulfoximine **6a**: i) a. KOH, DMSO, 5 min, rt; b. RX, 6 h, rt.




**Scheme 4**. Synthesis alkylated–sulfoximine **12**–**17** using the minor sulfoximine **6b** as the precursor. i) a. KOH, DMSO, 5 min, rt; b. RX, 30 min (with 4 equiv. of RX), rt,




**Scheme 5.** Sulfonamide **18** synthesis. Npys–Cl, KOH, DMSO, 6 h, rt.




**Scheme 6.** Thioetherification of sulfoximine 6a. ArS–SAr, NaOAc, CuI (10 mol %), DMSO.