(2R,1'S,2'R)- and (2S,1'S,2'R)-3-[2-Mono(di,tri)fluoromethyl-cyclopropyl]alanines and their incorporation into hormaomycin analogues

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Abstract
Efficient and scalable syntheses of enantiomerically pure (2R,1'S,2'R)- and (2S,1'S,2'R)-3-[2-mono(di,tri)fluoromethyl-cyclopropyl]alanines 9a–c, as well as allo-D-threonine (4) and (2S,3'R)-β-methylphenylalanine (3), using the Belokon' approach with (S)- and (R)-2-[(N-benzylprolyl)amino]benzophenone [(S)- and (R)-10] as reusable chiral auxiliaries have been developed. Three new fluoromethyl analogues of the naturally occurring octadepsipeptide hormaomycin (1) with (fluoromethyl-cyclopropyl)alanine moieties have been synthesized and subjected to preliminary tests of their antibiotic activity.

Introduction
The intermolecular signal metabolite hormaomycin (1, Figure 1) was first isolated from a Streptomyces griseoflavus (strain W-384) fermentation broth by Zähner et al. in Tübingen, Germany and structurally identified by Zeek et al. in Göttingen, Germany in 1989–1990 [3,4]. Once the absolute configuration of all the previously unassigned stereogenic
centers in the octapeptidolactone had been established [5,6] and feasible enantioselective syntheses of all the amino acid building blocks had been developed [7,8], a total synthesis of 1 could be embarked on and eventually completed [9]. Several precursor-induced biosyntheses [10,11] and chemical syntheses [11,12] have provided close to 20 hormaomycin analogues that have contributed to an understanding of the biosynthetic pathways, the conformational behavior in solution and the structure–activity relationship.

After the initial observation that hormaomycin (1) has a marked influence on the secondary metabolite production of various streptomycetes including the producing strain itself, and an exceptionally selective inhibitory effect on coryneform bacteria [3,4], an interesting antimalarial activity was discovered [13]. It was this property that led us to consider the synthesis of even more analogues of 1. Bearing in mind that tri(di,mono)fluoromethyl substituents often enhance the activity of pharmacologically relevant compounds [14-17], we embarked on the project to synthesize analogues 8 of hormaomycin (1), in which the (2-nitrocyclopropyl)alanine moieties would be replaced by [2-tri(di,mono)fluoromethylcyclopropyl]alanine residues (Figure 1).

**Results and Discussion**

As prerequisites for the hormaomycin analogues 8a–c, the correctly configured two diastereomers each of the [2-tri(di,mono)fluoromethylcyclopropyl]alanines 9a–c had to be synthesized in enantiomerically pure form. In view of the successful employment of the enantiomeric nickel(II) complexes (R)-10 and (S)-10 [18-20] in the synthesis of (2R,1'R,2'R)- and (2S,1'R,2'R)-3-(2-nitrocyclopropyl)alanine (5) for the native hormaomycin (1) [7,9], a completely analogous route was chosen towards (2R,1'S,2'R)- and (2S,1'S,2'R)-9a–c. This required the racemic trans-(2-fluoromethylcyclopropyl) iodides 11a–c as alkylating agents for the enolates of (R)-10 and (S)-10 (Figure 2).

The initially intended preparations of the three precursors 14a–c to the iodides 11a–c all starting from the known dimethyl trans-cyclopropane-1,2-dicarboxylate (12) [21] through the monomethyl ester 13 [22], the hydroxymethyl 15 [22] and the formyl derivative 16 [23,24] as outlined in Scheme 1, were only partially successful.

As expected, the hydroxymethyl (15) and formyl derivative 16 underwent smooth conversion into the monofluoro- and difluor-
romethyl derivatives 14c and 14b, respectively upon treatment with a solution of Deoxo-Fluor in toluene at ambient temperature. Unfortunately, conducting the reaction with carboxylic acid 13 under the same conditions only provided the acid fluoride and not the trifluormethylated compound 14a.

Therefore, an alternative approach to trans-(2-trifluoromethyl)cyclopropanecarboxylic acid 23 by way of the Claisen condensation product of ethyl trifluoroacetate (17) with diethyl succinate (18) [25] was used. The conditions for two of the known further steps [26,27] (Scheme 2) had to be modified to achieve acceptable yields. The reduction of the ketoester 20 to the hydroxyster 21 under the previously described conditions (H2/PtO2) proceeded very slowly, and in several runs (2 h, 24 h, 72 h) the yield of 21 was never better than 60% with up to 25% recovered ketoester 20. However, with powdered sodium borohydride in diethyl ether, the conversion of 20 was quantitative, and the yield of 21 was excellent (98%). In the final step, the attempted 1,3-dehydrotrosylation of 22 with potassium tert-butoxide, when carried out in dimethyl sulfoxide as reported [26,27], compound 23 as an intermolecular condensation product of the expected ethyl trans-(2-trifluoromethyl)cyclo-
propanecarboxylate with DMSO was obtained in 74% yield. Among several other base/solvent combinations tested – \( \text{NaOEt/EtOH, NaOMe/MeOH, } t\text{-BuOK/t-BuOH, NaH/THF, } t\text{-BuOK/THF under reflux} \) – the last one gave the best results with up to 47% yield of the \( \text{trans} \)-(2-trifluoromethyl)cyclopropanecarboxylic acid \( \text{24} \).

The conversion of the carboxylic acid \( \text{24} \) and esters \( \text{14b-c} \) to the corresponding cyclopropylmethyl alcohols was attempted according to the standard protocol by adding the respective substrate to a twofold excess of \( \text{LiAlH}_4 \) in diethyl ether under reflux. \( \text{(2-Trifluoromethyl)cyclopropyl)methanol} \ (\text{25a}) \) thus was obtained in excellent yield (88%), but the difluoromethyl- \( \text{(25b)} \) and especially monofluoromethylcyclopropylmethanol \( \text{25c} \), respectively, were obtained from the corresponding methyl cyclopropanecarboxylates \( \text{14b-c} \), in very poor yields (3% and 4%, respectively). In the case of monofluoro derivative \( \text{14c} \) the main product (38%) was \( \text{trans} \)-(2-methylcyclopropyl)methanol. In the case of the difluoro compound \( \text{14b} \), a mixture of the mono- \( \text{(25c)} \) and difluoromethylcyclopropylmethanol \( \text{25b} \) along with the non-fluorinated alcohol was obtained in a ratio of approximately 1:1:1.

To avoid this overreduction, inverse addition of 1.1 equiv of \( \text{LiAlH}_4 \) in diethyl ether solution (ca. 1 M) to a solution of the acid \( \text{24} \) or the respective ester \( \text{14b-c} \) in diethyl ether (ca. 1 M) was practiced. This way, the desired alcohols \( \text{25a-c} \) were obtained in good yields (88, 82 and 76%, respectively). Upon treatment with the iodine/triphenylphosphine reagent in the presence of imidazole, the racemic \( \text{trans} \)-(2-fluoromethylcyclopropyl)methanols \( \text{25a-c} \) were smoothly converted to the corresponding iodides \( \text{11a-c} \) in very good yields (Scheme 3).

Alkylation of the glycine equivalent enolates derived from \( \text{(S)}\)- and \( \text{(R)}\)-\(2\text{-[}(N\text{-benzylprolyl)}\text{amino}][\text{benzophenone}] \( \text{10} \) as reusable chiral auxiliaries with the racemic iodides \( \text{11a-c} \), employing the protocol of Larionov and de Meijere [7], in each case led to a mixture of diastereomeric products, which were separated by column chromatography. Unfortunately, the diastereomers could not be separated by fractional crystallization as easily as was previously reported for the corresponding \( \text{3-(trans}-2\text{-nitrocyclopropyl})\text{alanines} \) [7]. The absolute configuration of the arbitrarily selected nickel(II) complexes \( \text{(2S,1'R,2'S)}, \text{(2S,1'R,2'S)}, \text{(2R,1'R,2'S)}-\text{26a-c} \) and \( \text{(2R,1'S,2'R)}-\text{26b} \) were determined by a single crystal X-ray structure analysis (see Figure 3 and Supporting Information File 1) [28].

The isolated nickel complexes \( \text{26a-c} \) were decomposed by treatment with refluxing aqueous methanolic hydrogen chloride to give, after ion-exchange chromatography, the corresponding \( \text{2S,1'S,2'R)} \)- [see Scheme 3, derived from \( \text{(S)}\)-\text{10} \) and \( \text{(2R,1'S,2'R)}-\text{26b} \) derived from \( \text{(R)}\)-\text{10} \) in good to excellent yields. The chiral auxiliary was recovered as the hydrochloride of \( \text{2-[(N-benzylprolyl)amino}][\text{benzophenone}} \) (~95%).

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**Scheme 2:** Synthesis of \( \text{trans} \)-(2-trifluoromethyl)cyclopropanecarboxylic acid \( \text{24} \).
Scheme 3: Preparation of racemic trans-2-(fluoromethyl)cyclopropylmethyl iodides 11a–c and their conversion to (2S,1'S,2'R)- and (2R,1'S,2'R)-3-(trans-2'-fluoromethylcyclopropyl)alanines 9a–c (only (2S)-enantiomers are shown in the Scheme). Compounds (S)-10 and (R)-10 are shown in Figure 2. For details see Table 1.

Table 1: Alkylation of the enolates of the Belokon'-type glycine equivalents (S)- and (R)-10 with the racemic trans-2-(fluoromethyl)cyclopropylmethyl iodides rac-11a–c (see Scheme 3). Yields in % based on converted (S)- and (R)-10.

| Iodide from (S)-10 | from (R)-10 |
|-------------------|-------------|
| 2S,1'S,2'R        | 2S,1'R,2'S  |
| rac-11a           | 46          | 2S,1'S,2'R    | 44          |
| rac-11b           | 45          | 2R,1'S,2'R    | 47          |
| rac-11c           | 44          | 2R,1'R,2'S    | 47          |

(R)-allo-Threonine (4) is commercially available, but extremely expensive (from 77.80 € for 250 mg to 60.80 € for 25 mg). Therefore a simple and inexpensive access to (R)-allo-threonine was desirable.

The synthesis of 4 from (R)-threonine as a chiral precursor was performed according to the known protocol reported by Tanner et al [29]. Although (R)-threonine is less expensive (21–37 € for 5 g) than the target amino acid, the conversion requires five steps, and the overall yield is not better than 72%.

The Belokon’ protocols are among the best to access enantiomerically pure non-proteogenic amino acids. Nickel(II) or copper(II) complexes of Schiff bases derived from glycine and (S)- or (R)-2-N-(benzylprolyl)aminobenzophenone (BPB) [30,31], aminoacetophenone (BPA) [32] or aminobenzaldehyde...
Figure 3: Structure and absolute configurations of the nickel(II) complexes $(2S,1'R,2'S)$-26a, $(2S,1'R,2'S)$-26b and $(2R,1'R,2'S)$-26b in the crystals. Less important hydrogen atoms are omitted for clarity.

(BPH) [33] can be used as chiral nucleophilic glycine equivalents in reactions with alkyl halides or carbonyl compounds. The most versatile one is the nickel(II) aminobenzophenone derivative.

It is interesting that nickel(II) complexes of Schiff bases derived from 2-bromoglycine and $(S)$-BPB can be used as electrophilic glycine equivalents [34]. Alkylation of the nickel(II) complexes of Schiff bases derived from glycine and $(S)$- or $(R)$-BPB with alkyl halides virtually yield single stereoisomers, in which the configuration of the newly formed stereogenic center at C-2 of the amino acid moiety is the same as that in the proline moiety of the chiral auxiliary in the starting material.

In reactions of the enolate of this chiral glycine equivalent with aldehydes the situation is more complicated. The reaction of $(S)$-10 with acetaldehyde under strongly basic conditions led to the $(R)$-threonine complex 29 (inverse configuration relative to that of the proline moiety of $(S)$-10 due to epimerization on C-2), but when a weaker base such as triethylamine was employed, a mixture of $(R)$-threonine 29 and $(S)$-allo-threonine 31 complexes [35] was obtained.

The hypothesis, that the reaction of the Belokon' glycine complex (BGC) 10 with aldehydes under strongly basic conditions proceeds in two steps and is thermodynamically controlled, was corroborated by experimental tests [36]. The initially formed main product $(R,R,R)$-28 in the aldol reaction of acetaldehyde with 10 had the same configuration at C-2 as the proline unit in 10. The absolute configuration of this nickel(II) complex was determined by a single crystal X-ray structure analysis (see Figure 4 and Supporting Information File 1) [28]. However, the product ratio changed in time from 95:5 after 30 s through 70:18 after 10 min to 5:95 after 24 h at ambient temperature.
This epimerization comes along with a possible rearrangement in the Ni complex. The newly formed hydroxide group of the product 28 can coordinate the Ni atom liberating the carboxylate moiety and thus making the proton at C-2 accessible to base attack (Scheme 4). In order to obtain (R)-allo-threonine (4), it is necessary to carry out the aldol reaction of (R)-10 with an excess of acetaldehyde under strongly basic conditions at low temperature and to quench the reaction after a short time to avoid epimerization of 28.

This modified protocol indeed gave the (R)-allo-threonine (4) in relatively poor yield [7.5% for the Ni complex, 91% (7% overall) for the amino acid], but with high enantiomeric purity in two steps. Bearing in mind that the starting materials are inexpensive and the chiral auxiliary is reusable (≥95% recovery), this protocol represents one of the best routes to the rather expensive (R)-allo-threonine (4).

It is also possible to obtain (R)-allo-threonine starting from (R)-10 and acetaldehyde under thermodynamic control (Et₃N as the base, (S)-threonine:(R)-allo-threonine = 1:7), but it is necessary to leave the reaction mixture for two months for the reaction to go to completion [37].

(2S,3R)-3-Methylphenylalanine (L-β-methylphenylalanine, (β-Me)Phe, MeF, 3) also is a constituent of the peptidolactone...
hormaomycin (1) and is contained in the molecule twice. Thus it is required for the synthesis of hormaomycin and the analogues envisaged here. In addition, a versatile protocol for the preparation of other β-alkylarylalanines for incorporation into hormaomycin analogues as well as into other peptides would be desirable as the incorporation of conformationally constrained α-amino acids such as 3 into peptides is frequently used to study structure–activity relationships [38-40].

Several methods have been developed for the preparation of analogues of β-methylphenylalanine in enantiopure form. These include classical resolution [41], enzymatic resolution in conjunction with HPLC [42], or HPLC separation of derived peptides [43], preparative HPLC separation on a chiral phase column [44], asymmetric synthesis from chiral precursors [45,46] including the stereoselective alkylation of aromatic compounds with triflates of threonine stereoisomers [47], the chiral auxiliary approach [48-51] and enantioselective hydrogenation over a chiral catalyst [52,53]. All these approaches ought to be applicable to prepare unsubstituted β-methylphenylalanine, but most if not all of them have severe drawbacks. Among the chiral auxiliary approaches to β-branched arylationanes, including all four stereoisomers of β-methylphenylalanine, the one employing the “Evans amide” method with a 4-benzyl- or 4-phenyl-2-oxazolidinone moiety, has been used most frequently. Along this route, which requires eight procedural steps (including a transmetallation), the (2S,3R)-3-methyl-3-phenylalanine required for hormaomycin and its analogues, has previously been utilized [9,54,55].

In view of the good performance of the Belokoń protocol for various electrophilic reagents it appeared attractive to apply it for the synthesis of β-methylphenylalanines as well (Scheme 5). Towards this, the (S)-configured glycine nickel(II) complex (S)-10 was alkylated with 1-phenylethyl iodide and some analogues with substituents in the aryl moiety, all in racemic form. The diastereomeric product Ni(II) complexes obtained in each case, could be separated by column chromatography. The pure

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**Scheme 5**: A new general approach to (2S,3R)-β-methylarylalanines 3 by alkylation of the glycine nickel(II) complex (S)-10 with 1-arylethyl iodides 35. For details see Table 2.
diastereomers with (2S,3R) configuration were decomposed with an aqueous methanolic HCl solution to furnish the target amino acids, which were purified by ion-exchange chromatography, in good yields (Table 2). (2S,3R)-β-Methylphenylalanine was thus prepared from acetophenone in only four steps in an overall yield of 30%.

A similar protocol for the synthesis of 3-alkylphenylalanines was independently developed by Soloshonok et al. [56]. These authors used sodium hydroxide for the deprotonation of 10 and 1-phenylalkyl bromides for the alkylation of the enolate.

Once sufficient quantities of (2S,1'S,2'R)-9a–c and (2R,1'R,2'R)-9a–c (FmcpA), as well as the N-Boc-protected (2S,4R)-4-(Z)-propenylproline [(4-Pe)Pro, 6] [8], the O-MOM-protected 5-chloro-1-hydroxypyrrole-2-carboxylic acid (Chpca, 7) [8], (R)-allo-threonine (allo-Thr, 4) and (2S, 3R)-β-methylphenylalanine ([β-Me]Phe, 3) had been prepared. The assembly of the hormaomycin analogues 8a–c with 3-(2'-fluoromethylcyclopropyl)alanine residues was initiated, employing the same sequence as developed by Zlatopoliskiy for the synthesis of hormaomycin I [9] and its aza-analogue [12]. To start with, the dicyclopropylmethyl (DCPM) ester of N-Fmoc-protected Ile 37, was condensed with N-Z-protected (βMe)Phe-OH 39. After removal of the Z group from the N-terminus of the resulting dipeptide 42 by catalytic hydrogenation, the product was coupled with N-Fmoc-protected (2R,1'R,2'R)-[3-(mono-, di- or tri-)fluoromethylcyclopropyl]alanines 41a–c to yield tripeptides 47a–c, which, in turn, after deprotection with Et₂NH/THF, were coupled with N-Fmoc-protected (βMe)Phe-OH 46 to give N,C-protected tetrapeptides 49a–c.

The N-Boc-protected (4-Pe)Pro-OH 43 and N,C-protected allo-Thr 40 were condensed under 4-pyrrolidinopyridine catalysis to give the ester 45, which, after deallylation under palladium catalysis, was coupled with the tetrapeptides employing the HATU reagent in the presence of HOAt to give the corresponding hexadepsipeptides 51a–c.

From the latter, the DCPM and Boc groups were cleaved off from both termini, leaving the MeZ group intact as proved by an ESIMS spectrum, and the cyclizing peptide condensation was achieved under high dilution conditions with the HATU reagent. The cyclohexadepsipeptides 52a–c were obtained in 54, 60 and 53%, respectively, yield over 8 steps, after HPLC purification (Scheme 6).

The assemblies of the corresponding hormaomycin analogues were completed after removal of the N-MeZ groups from the cyclic intermediates 52a–c, subsequent coupling with the corresponding N-Teoc-protected (2S,1'R,2'R)-[3-(mono-, di- or tri-)fluoromethylcyclopropyl]alanines 53a–c and, after removal of the Teoc groups, the intermediates 56a–c were in turn coupled with the 1-O-MOM-protected 5-chloro-1-hydroxypyrrole-2-carboxylic acid 54. Eventually, the MOM group was

![Structure and absolute configuration of nickel(II) complex (2S,3S)-32 in the crystal. Hydrogen atoms are omitted for clarity.](Image)

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Table 2: Substituted β-methylphenylalanines by alkylation of the glycine nickel(II) complex (S)-10 with 1-arylethyl iodides (yields based on converted 10, d.e. ≥98%). See Scheme 5. The yields of the liberated amino acids 3 based on the respective Ni complexes 32 are in parentheses.

| X   | Product        | Yield (%) | Product        | Yield (%) |
|-----|----------------|-----------|----------------|-----------|
| H   | (2S,3S)-32a    | 35        | (2S,3R)-32     | 38 (59)   |
| o-Cl| (2S,3S)-32-o-Cl| 38        | (2S,3R)-32-o-Cl| 42        |
| m-Cl| (2S,3S)-32-m-Cl| 37        | (2S,3R)-32-m-Cl| 42 (96)   |
| p-Cl| (2S,3S)-32-p-Cl| 42        | (2S,3R)-32-p-Cl| 40 (89)   |
| p-F | (2S,3S)-32-p-F | 46        | (2S,3R)-32-p-F | 43        |

*The absolute configurations of the arbitrarily selected nickel(II) complexes (2S,3S)-32, (2S,3R)-32-m-Cl and (2S,3R)-32-p-F were determined by single crystal X-ray structure analyses (see Figure 5 and CCDC-deposited material) [28].
cleaved off by treatment with MgBr$_2$•Et$_2$O and EtSH in dichloromethane to give, after HPLC purification, the target compounds 8a–c in 72, 82 and 84% yield, respectively (Scheme 7).

Since the MeZ-protected cyclohexadepsipeptide core of the native hormaomycin was found to have a significant antiparasitic activity, N-acetylated 58 and N-trifluoroacetylated 59 derivatives were prepared by coupling the deprotected cyclic intermediate 52a with acetic and trifluoroacetic acid (Figure 6).

Some antiparasitic activities of hormaomycin, its all-peptide analogue and the new analogues

The syntheses of hormaomycin (1) itself and of its all-peptide aza-analogues 60 and 61 (Figure 6) as developed by Zlatopolskiy et al. [9,12], were reproduced in order to provide large enough quantities for biological tests of their antimalarial activities. Results of the in vitro tests of the antiparasitic activities of hormaomycin (1) [57], its analogues 8a, 52a, 58 and 59, as well as the aza-analogues 60 and 61 are presented in Table 3.

All the newly prepared and tested hormaomycin analogues and the native hormaomycin (1) [57] showed good and selective antimalarial activities. However, the activities of the (trifluoromethylcyclopropyl)alanine-containing hormaomycin analogue 8a against L. donovani and P. falciparum were 37 and 45% lower than those of hormaomycin (1) itself. Further exploration of structure–activity relationships of the hormaomycins would be required to prepare new antiparasitic lead compounds.
Conclusion

At first sight, the oligopeptide assembly leading to hormaomycin does not appear to be a very complicated problem. "State of the art" peptide coupling methodology [59,60] allows one to prepare almost any peptides, that do not contain extremely sterically congested fragments such as $a,a$-dialkyl-substituted amino acids, $N$-alkyl amino acids or even the more challenging $N$-aryl amino acids. With a proper choice of the coupling reagent, solvent and other experimental conditions, the oligopeptides in this study were obtained in high yields and with high optical purities. As almost all amino acids, which comprise hormaomycin (1) itself and its anticipated analogues, are $\beta$-branched with the exception of 3-(2'-nitrocyclopropyl)alanine and the 3-(2'-fluoromethylcyclopropyl)alanines, HATU as well as the combination of EDC and 7-aza-1-hydroxybenzotriazole (HOAt) [61] were used for each condensation step to ensure high yields. The most unusual fragment in hormaomycin (1) and its analogues is the ester bond between the secondary (4-Pe)Pro moiety and the hydroxy group of allo-Thr. Among several methods described in the literature for the creation of such bonds, the dialkylaminopyridine-promoted carbodiimide-mediated esterification was successfully employed here [62].
Table 3: In vitro activities of some hormaomycin-derived compounds [58] and established reference drugs against \( L. \) donovani (axenic amastigotes), \( P. \) falciparum and L6 cells (IC\(_{50}\), concentration in \( \mu \)g/mL).

| Compound   | \( Leishmania \) donovani strain MHOM-ET-67/L82 | \( Plasmodium \) falciparum strain K1 | L6 cells |
|------------|-----------------------------------------------|--------------------------------------|----------|
| Miltefosine| 0.143                                         | –                                    | –        |
| Chloroquine| –                                             | 0.089                                | –        |
| Podophyllotoxin| –                                    | 0.006                                | –        |
| 1          | 0.15                                          | 0.129                                | 17.20    |
| 52a        | 2.13                                          | 0.042                                | >90      |
| 58         | 1.73                                          | 0.151                                | >90      |
| 8a         | 0.205                                         | 0.183                                | 40       |
| 59         | 2.37                                          | 0.265                                | >90      |
| 60         | 4.8                                           | 0.023                                | 40       |
| 61         | –                                             | 0.061                                | >90      |

\(^{a}\)IC\(_{50}\) values reported are the averages of two independent assays which varied less than ±50%.

As far as the biological activities against \( L. \) donovani and \( P. \) falciparum are concerned, a certain degree of lowering was observed, but by far no complete loss. Thus, further modifications would be desirable to eventually arrive at a new lead compound.

Experimental

For detailed experimental procedures of all the described syntheses see the Supporting Information File 1.

In vitro antiprotozoal activity assays: The in vitro activities against the protozoan parasites \( L. \) donovani and \( P. \) falciparum as well as cytotoxicity assessments against L6 cells were determined as reported elsewhere [58]. The following strains, parasite forms and positive controls were used: \( L. \) donovani, MHOM/ET/67/L82, axenic amastigote forms, miltefosine, IC\(_{50}\) of 0.143 \( \mu \)g/mL; \( P. \) falciparum, K1 (chloroquine and pyrimethamine resistant), erythrocytic stages, chloroquine, IC\(_{50}\) of 0.089 \( \mu \)g/mL and L6 cells, rat skeletal myoblasts, podophyllotoxin, IC\(_{50}\) of 0.006 \( \mu \)g/mL.

Supporting Information

Supporting Information File 1

Experimental procedures and analytical data. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-302-S1.pdf]

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