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Design, synthesis of schweinfurthin G derivatives and their biological evaluation as potential anticancer agents

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ABSTRACT

Schweinfurthin G, one of the most potent of the schweinfurthins containing a hexahydroxanthene moiety, was found to exhibit strong cytotoxicity against A549 and KB cell lines with the IC_{50} values of 0.8 μM and 0.6 μM, respectively. In this paper, a new series of schweinfurthin G derivatives modified on the isoprenyl side-chain were synthesized from schweinfurthin G using multicomponent reactions. The cytotoxicity of all the synthetic compounds was evaluated against four human cancer cell lines (KB, Hep3B, A549, MCF7) and one non-cancerous cell line (HEK293), which enabled to perform in-depth structure–activity relationships on a still poorly explored part of the molecule.

Introduction

Schweinfurthins and their derivatives/analogues have been reported to be potent and selective inhibitors of cancer cell growth [1–6]. Since the discovery of natural vedelianin, the first example of this family of compounds, several schweinfurthin derivatives have been isolated or synthesized and screened for their biological activities [5,7–12]. Because of their potential *in vitro* and *in vivo* anticancer properties, the synthesis of novel analogues is very attractive and useful. The hexahydroxanthene tricyclic core and a stilbene in *trans* orientation of molecule are essential for biological activities of schweinfurthins [13,14]. Previously reported researches focused on the synthesis/modification of the central stilbene olefin by an amide [15] or a triazole ring [16]; replacement of the D-ring by a coumarin or an indole [17,18] or modifications of both C- and D-rings [19]. Furthermore, it was found that the para position of the D-ring is a site amenable for modifications without significant loss in biological activity (Fig. 1).

Among all the natural derivatives, schweinfurthin G, which was originally isolated from *Macaranga alnifolia* is one of the most potent ones [2]. Schweinfurthin G was found to exhibit strong cytotoxicity, for example against A549 and KB cell lines with IC_{50} values of 0.8 μM and 0.6 μM, respectively [5,20,21]. Nevertheless, articles related to its total synthesis, or its chemical modifications have been limited [19,22]. Thus, our group has focused its interest on the design, synthesis, and biological activity evaluation of a series of new modified schweinfurthin G derivatives which could be more cytotoxic and more stable [5,23]. In order to further improve the activities of schweinfurthin derivatives, we expanded the molecular diversity of schweinfurthin G with various substitution patterns at the D-ring. Our goal was twofold: replacement of the isoprenyl chain with a more polar group like an amide to improve its water solubility while maintaining activity or extension of the isoprenyl chain with a triazole moiety to improve biological activities [24–26]. Multi-component reactions (MCRs) were used to modify the isoprenyl chain as they have used successfully for the preparation of vast libraries of synthetic molecules in medicinal chemistry [27,28].

Results and discussion

Synthesis

Schweinfurthin G was used as starting materials in the synthesis process. This compound was isolated in gram scale after the extraction, isolation, and purification steps from dried fruits of *Macaranga tanarius* with yield of 0.1 %. Details of the procedure was presented in the Supporting information.

In a previous work we disclosed the preparation of alcohol **9** and

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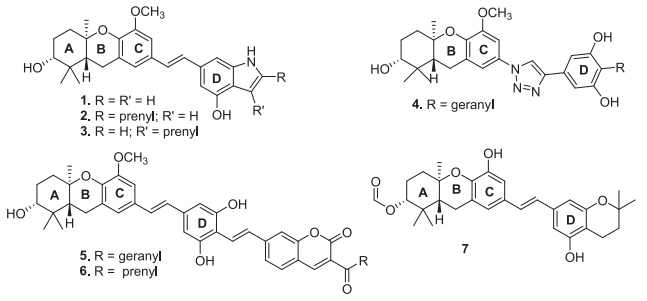
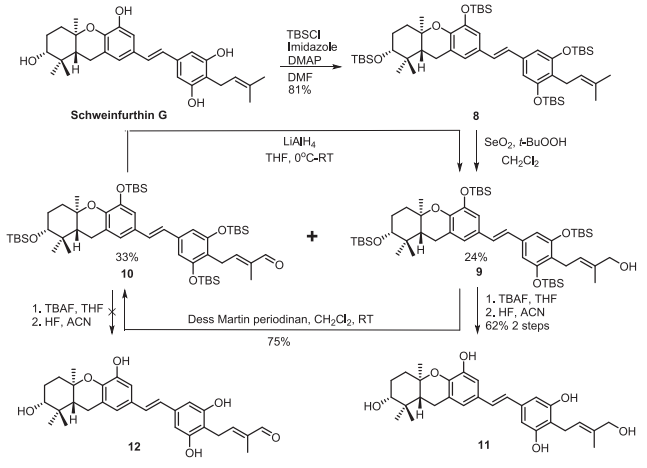


Fig. 1. Selected examples of bioactive synthetic schweinfurthin derivatives/analogues.

aldehyde **10** from schweinfurthin G (Scheme 1) [29]. In this paper, the complete synthesis of schweinfurthin G derivatives and their cytotoxic activity evaluation against a panel of cancer cell lines (KB, Hep3B, A549, MCF7) and non-cancerous HEK293 cell line were reported and discussed.

In this study, the unsaturated aldehyde **10** was converted to carboxylic acid **13** using sodium chlorite ($NaClO_2$) under mild acidic condition following Pinnick oxidation process. The reaction occurred smoothly to yield the desired compound **13** in high yield (80 %). Next, the carboxylic acid **13** was reacted with paraformaldehyde (2 equiv), various amines (R-NH_2, 1.1 equiv) and isonitrile compounds (R′-NC, 1.1 equiv) at room temperature in methanol to give the diamides **14a–g** in moderate to high yields over a period of 12–24 h. With the aim to broaden the reaction scope of Ugi reaction, combination of aliphatic, cyclic or aromatic isocyanides and amines were investigated. After that, deprotection of compounds **14a–g** afforded desired derivatives **15a–g**. Compound **14a** was chosen as a model compound to investigate the deprotection reaction of TBS groups. At first, TBAF in THF was used as reagent in the reaction. Accordingly, the reaction seemed to occur fast and the quick disappearance of the starting material **14a** was observed. However, the analysis of the ^{1}H- NMR spectrum of the obtained compound demontrasted that it was still monoprotected. We thus needed to use HF in acetonitrile to deprotect the remaining TBS group. Other trials consisting of using either TBAF or HF alone or changing the order of deprotection conditions (HF, then TBAF) failed and a decomposition of starting material **14a** was observed. It thus, required two steps for the final deprotection: TBAF in THF first, then HF in MeCN. Following this procedure, we were able to prepare seven original schweinfurthin G derivatives carrying diamide groups on the isoprenyl chain (Scheme 2). Various types of amines and isonitrile compounds were used to afford the new derivatives with higher polarities and chemical diversity



Scheme 1. Previous synthetic work of **9**–**10** and synthesis of **11** and **12**.

(Table 1).

For the second approach, the azide **17** was prepared from alcohol **9**. All our efforts to convert hydroxyl group of alcohol **2** to a better leaving group such as tosyl or mesyl group under several conditions were unsuccessful. Instead, decomposition of alcohol **2** was observed. Given these disappointing results, an alternate route to the azide compound *via* a direct one-pot synthesis of azide from alcohol **2** using diphenyl phosphorazidate (DPPA) was investigated and this proved more successful. The reaction was carried out by dissolving alcohol **2** and DPPA (1.2 equiv), followed by adding a slight excess of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) in anhydrous toluene. After an aqueous workup and quick filtration through silica gel (mixture of *n*-hexane/CH_2Cl_2), azide **17** was isolated and used directly for the next Click reaction (see Scheme 3).

The copper catalysed regioselective cycloaddition of azide **17** and terminal alkynes in the presence of sodium ascorbate at room temperature led to the formation of 1,2,3-triazoles compounds **18a–d** in good yields over two steps (Table 2). The 1,4-disubstituted 1,2,3-triazole moiety was confirmed by the HMBC correlation from the singlet proton of the 1,2,3-triazole rings to the carbon of the methylene group of the isoprenyl chains. Finally, cleavage of the TBS groups with TBAF and HF, respectively provided final products **19a–d** (Table 3).

In addition, protected alcohol **9**, aldehyde **10** and carboxylic acid **13** were also deprotected. Following the same protocol as for the preparation of compounds **15a–g** and **19a–d**, the final products alcohol **11** and carboxylic acid **16** were successfully obtained in 62 % and 56 %, respectively (Scheme 1 and Scheme 2). Unfortunately, we were unable to synthesize aldehyde **12** with these conditions.

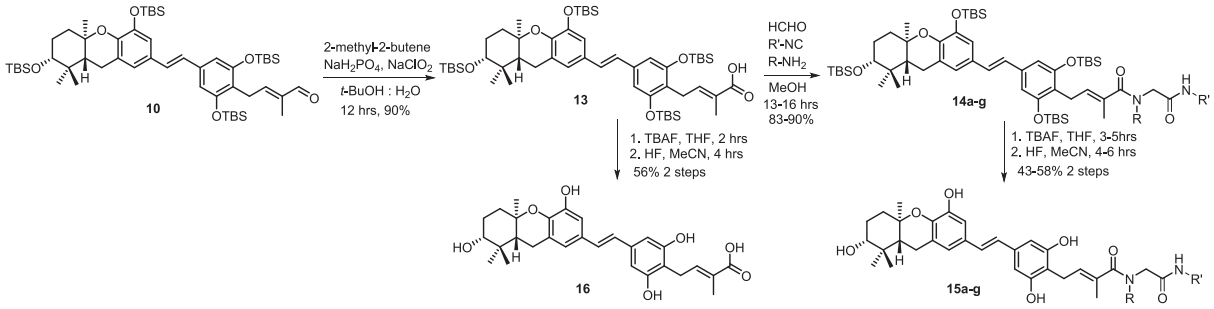
Thus, thirteen derivatives of schweinfurthin G were synthesized and characterized by 1D, 2D NMR spectroscopy and MS spectrometry.

Cytotoxic activity evaluation

The cytotoxic activities of all synthesized derivatives were evaluated *in vitro* against KB, Hep3B, A549, MCF-7 cancer cell lines and the non-cancerous HEK-293 cell line.

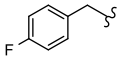
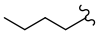
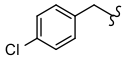
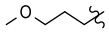
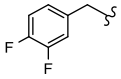
The results of cytotoxic tests showed that ten out of thirteen synthesized derivatives possessed micromolar or submicromolar cytotoxic activity against at least one human cancer cell lines, except compounds **15e, 19d** and **16**, which were inactive. It could be clearly seen that the synthesized derivatives were more cytotoxic against A549 and MCF7, compared with KB and Hep3B cancer cell lines. For example, all synthesized derivatives were less active than schweinfurthin G on KB cell line, with the IC_{50} values ranging from 4 to 195 μM. Meanwhile, seven compounds (**15a–d, 15f–g, 11**) displayed promising cytotoxic activities against Hep3B, A549 and MCF7 cell lines, with IC_{50} values in the same range as the positive control ellipticine and the reference schweinfurthin G, or even much lower.

Compound **11** exhibited one of the highest activities with an IC_{50} value of 0.18 μM on A549 cancer cell line, *i.e.*, four times better than schweinfurthin G (IC_{50} of 0.75 μM) and almost ten times better than ellipticine (IC_{50} of 1.75 μM). Its strong cytotoxic activity seems associated with the addition of the hydroxyl group to the isoprenyl chain. This hypothesis was strengthened by the inactivity of compound **16** carrying a carboxylic function on the isoprenyl chain. That also implied the important role of the additional hydroxyl group of compound **11** to its bioactivity. Notably, compound **11** showed low toxicity on HEK-293 with IC_{50} value of 13.03 μM. Other compounds, such as **15a–g** were also active or more active than schweinfurthin G and ellipticine on the A549 and MCF7 cancer cell lines while they still show less inhibition to the HEK293 cell line (Table 3). Particularly, compounds **15a**, **15b** and **15g** were the most promising ones as they are cytotoxic on a subnanomolar range on three cancer cell lines (Hep3B, A549 and MCF7) while non-toxic on non-cancerous HEK293. Moreover, a decreased cytotoxicity was observed between **15a–g** and **19a–d**, suggesting that diamide groups on the isoprenyl chain of schweinfurthin G is more

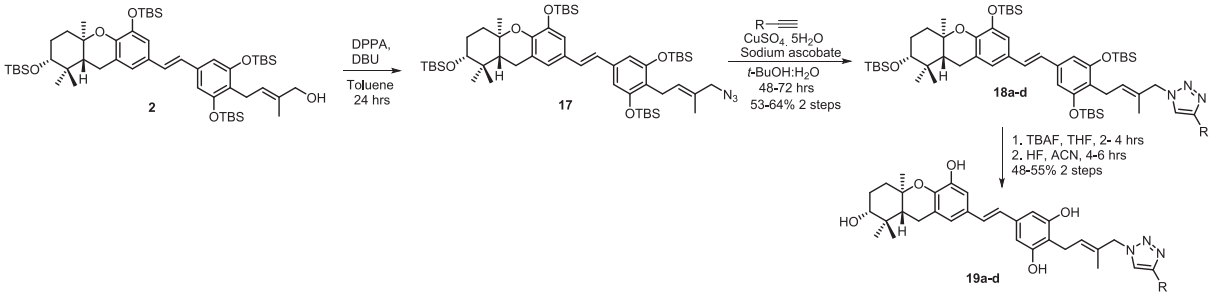


Scheme 2. Synthesis of compounds **15a–g**.

Table 1
Results of synthesis of compounds **14a–g** and **15a–g**.

Entry	R	R′	14a–g		15a–g	
			Compound	Yield[a] (%)	Compound	Yield[b] (%)
1			**14a**	89	**15a**	48
2			**14b**	88	**15b**	45
3			**14c**	89	**15c**	48
4			**14d**	83	**15d**	58
5			**14e**	85	**15e**	43
6			**14f**	87	**15f**	47
7			**14g**	90	**15 g**	53

[a] Isolated yields.
[b] Isolated yields of 2 steps.



Scheme 3. Synthesis of compounds **19a–d**.

effective than a triazole moiety.

Conclusion

In conclusion, we were able to synthesize a new series of novel schweinfurthin G derivatives with the extension of the isoprenyl chain by a diamide chain or a 1,2,3-triazole ring. All the synthetic compounds were evaluated for their cytotoxic activity against four cancer cell lines (KB, Hep3B, A549, MCF-7) and the non-cancerous HEK-293 cell line. The most potent compounds were compounds **11**, **15a**, **15b** and **15g** with sub-nanomolar IC_{50} values on various cancer cell line and almost no cytotoxicity on the non-cancerous HEK293 cell line. Thus, further investigation of these compounds as potential anticancer agents should be necessary.

CRediT authorship contribution statement

Van Cuong Pham: Supervision, Methodology, Formal analysis. **Van**

Table 2
Results of synthesis of compounds **18a–d** and **19a–d**.

Entry	R	18a–d		19a–d	
		Products	Yield (%)[a]	Products	Yield (%)[b]
1		**18a**	61	**19a**	48
2		**18b**	59	**19b**	51
3		**18c**	53	**19c**	46
4		**18d**	64	**19d**	55

[a] Isolated yields of 2 steps.
[b] Isolated yield of 2 steps.

Table 3
Inhibitory concentration (IC_{50}), expressed in μM, of schewinfurthin G derivatives against human mouth epidermal carcinoma (KB), human hepatocellular carcinoma (Hep3B), human lung carcinoma (A549), human breast (MCF7) cancer cell lines and non-cancerous human embryonic kidney (HEK-293) cell line.

Entry	Compound	Cancer cell lines (IC_{50} (μM))				Non-cancerous cell line
		KB	Hep3B	A549	MCF7	HEK293
1	**15a**	5.3 ± 0.5	0.8 ± 0.1	0.5 ± 0.08	0.8 ± 0.03	>128
2	**15b**	9.1 ± 0.7	0.6 ± 0.06	0.5 ± 0.04	0.3 ± 0.04	>128
3	**15c**	6.4 ± 0.5	0.8 ± 0.07	0.6 ± 0.05	0.4 ± 0.04	10.4 ± 0.7
4	**15d**	4.9 ± 0.2	0.7 ± 0.08	0.6 ± 0.05	0.5 ± 0.04	42.3 ± 2.4
5	**15e**	60.6 ± 1.7	89.1 ± 4.3	86.3 ± 1.8	92.2 ± 1.7	80.7 ± 2.4
6	**15f**	7.6 ± 0.9	4.3 ± 0.6	0.5 ± 0.05	34.7 ± 1.1	27.7 ± 2.2
7	**15g**	4.4 ± 0.47	0.9 ± 0.09	0.6 ± 0.05	0.6 ± 0.07	>128
8	**19a**	7.5 ± 0.2	41.2 ± 1.6	12.3 ± 0.4	11.4 ± 0.3	6.7 ± 0.1
9	**19b**	26.2 ± 1.5	10.3 ± 0.2	1.7 ± 0.1	31.4 ± 0.8	10.0 ± 0.9
10	**19c**	29.4 ± 1.9	15.4 ± 0.7	3.6 ± 0.3	45.2 ± 0.6	9.1 ± 0.6
11	**19d**	20.5 ± 0.30	73.8 ± 0.9	72.0 ± 0.7	42.6 ± 2.2	31.5 ± 1.4
12	**11**	39.4 ± 1.2	28.1 ± 2.0	0.2 ± 0.01	37.6 ± 1.7	13.0 ± 0.5
13	**16**	195.4 ± 1.2	198.4 ± 2.0	129.5 ± 0.01	196.5 ± 1.7	131.2 ± 0.5
14	**SWF G**	0.5 ± 0.04	0.7 ± 0.04	0.8 ± 0.04	1.6 ± 0.1	1.4 ± 0.06
15	Ellipticine	1.8 ± 0.08	1.8 ± 0.08	1.8 ± 0.08	1.8 ± 0.08	6.3 ± 0.16

Nam Vu: Methodology, Formal analysis. **Van Hieu Tran:** Methodology, Investigation, Formal analysis. **Thi Dao Phi:** Methodology, Investigation, Formal analysis. **Fanny Roussi:** Writing – review & editing, Methodology. **Marc Litaudon:** Writing – original draft, Methodology. **Thuy Linh Nguyen:** Writing – review & editing, Software, Methodology, Formal analysis. **Thi Mai Huong Doan:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2024.155244.

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