Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2021, **31**, 1–3

Mendeleev Communications

6363
February 3, 2021

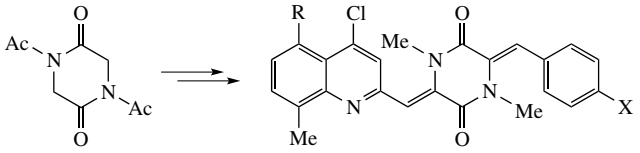
Synthesis and cytotoxic evaluation of novel simplified plinabulin-quinoline derivatives

Pham T. Tham,[a] Pham T. Chinh,*[b] Nguyen V. Tuyen,[c] Duong N. Bang,[b] Dinh T. Van,[b,d] Vu T. Kien,[b] Hoang T. Thanh,[b] Duong H. Quynh,[b,c] Vu D. Cuong,[b,e] Nguyen H. Thanh[b,c] and Alfonso Pérez-Encabo*[f]

[a] *Hanoi University of Industry, Cau Dien, Bac Tu Liem, Hanoi, Vietnam*
[b] *Thai Nguyen University of Science, Tan Thinh, Thai Nguyen, Vietnam. Fax: +84 988 113933; e-mail: chinhpt@tnus.edu.vn*
[c] *Institute of Chemistry, Vietnam Academy of Science and Technology, 18-Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam*
[d] *Thai Nguyen University of Education, Luong Ngoc Quyen, Thai Nguyen, Vietnam*
[e] *Viet Tri University of Industry, Viet Tri, Phu Tho, Vietnam*
[f] *IU CINQUIMA/Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, E-47011 Valladolid, Spain. Fax: +34 831 85867; e-mail: alfonso.perez.encabo@uva.es*

DOI: 10.1016/j.mencom.2021.03.____

A series of new plinabulin-quinoline derivatives and their simplified analogues was obtained from *N,N′*-diacetyl-2,5-diketopiperazines utilizing its aldol condensation with benzaldehydes. One compound showed strong activity related to three (KB, HepG2 and Lu) cancer cell lines while two other compounds demonstrated high potencies against breast carcinoma cell line (MCF-7).



R = NO_2, H; X = OMe, Cl

Keywords: plinabulin, quinoline, piperazine-2,5-diones, anticancer, cytotoxicity.

An important part of eukaryotic cells are microtubules that play a role in various cellular functions such as cell signaling, cell migration and mitosis, making them good candidates when controlling tumor processes becomes urgent. According to this strategy, two types of anticancer drugs have been approved, namely, tubulin depolymerization inhibitors (paclitaxel, docetaxel and sagopilone)[1–5] and tubulin polymerization inhibitors (vincristine, combretastatin and vinblastine).[6] Plinabulin, a synthetic analogue of 2,5-diketopiperazine, has demonstrated induction of apoptosis in cancer cells.[7] Plinabulin derivatives[8] showed high cytotoxicity against different cancer cell lines, for example, benzophenone derivatives were evaluated against human HT-29 colorectal cancer cells while 5-*tert*-butyl-substituted imidazole analogues were not highly active.[9] The benzene ring of the benzoyl group could induce additional π–π interaction, which could be beneficial to antiproleferation.[10,11] Furan-containing derivatives tested against the human lung cancer NCI-H460 cell line exhibited potent cytotoxic activity at the nanomolar level.[12] Of special interest is a novel colchicine-type anti-microtubule: KPU-300, an agent endowed with a 2-pyridyl substituent capable of acting as a potent radiosensitizer.[13] The development of plinabulin derivatives with aryl moieties is a research direction of interest due to the ability of these moieties to significantly alter the hydrophobicity and π–π interaction capacity of the compound.[14] In this study, the moieties of choice were quinoline-2-carbaldehyde ones. The quinoline ring is commonly acknowledged for its antimalarial potency, as the quinine derivative Chloroquine has been the most widely used anti-malarial drug since the 1940s.[15] The versatility of this ring system has enabled the synthesis of a large array of derivatives with diverse biological activities, notably the derivatives of quinoline-2-carbaldehyde.

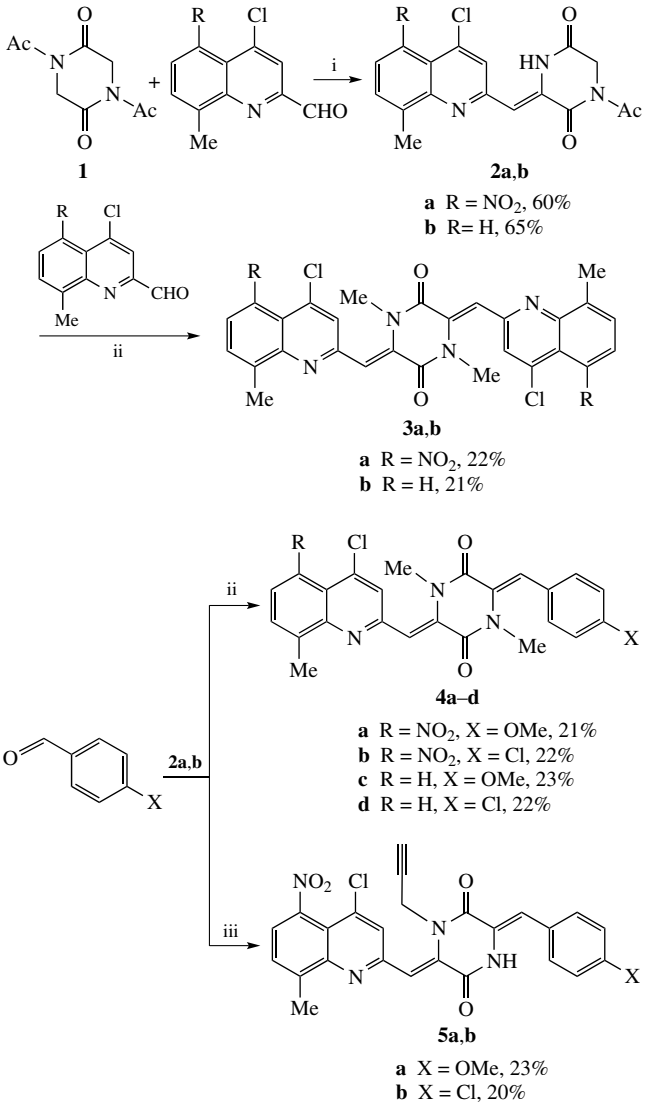
In this study, thirteen new plinabulin derivatives were prepared (Schemes 1 and 2). 3-Monosusbstituted 2,5-diketopiperazines **2a**,**b** were obtained in good yield by the condensation of 4-chloro-8-methylquinoline-2-carbaldehyde derivatives[16,17] with *N,N′*-diacetyl-2,5-ketopiperazine **1** in the presence of potassium carbonate in anhydrous DMF. The condensation proceeds with the hydrolysis of one amide group.[14]

Symmetrical 3,6-bis(arylmethylidiene)-2,5-diketopiperizines **3a**,**b** were obtained by treatment of compounds **2a**,**b** with 4-chloro-8-methylquinoline-2-carbaldehyde derivatives under aldol condensation conditions in the presence of methyl iodide (see Scheme 1). Under these conditions, N,N′-dimethylation of 2,5-diketopiperazine moiety occurs.

The moving from quinolone-2-carbaldehydes to benzaldehydes in the reaction with **2a**,**b** provides non-symmetrical compounds **4a–d**. In this reaction, the hydrolysis of the *N*-acetyl group leads to the parallel N-methylation (see Scheme 1). 3-Monosubstituted 2,5-diketopiperazines **2a**,**b** were also treated with propargyl bromide. The process was carried out in one-pot by reacting **2a**,**b** with propargyl bromide and the benzaldehyde derivatives using K_2CO_3 as condensation base to provide the N-alkylation products **5a**,**b**.

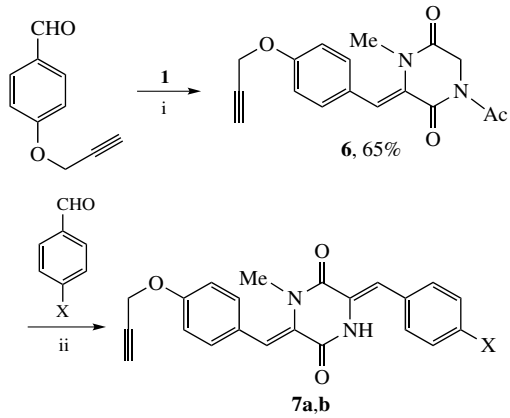
Reaction of 1,4-diacetyl-2,5-diketopiperazine **1** with 4-(prop-2-yn-1-yloxy)benzaldehyde, methyl iodide, potassium carbonate in DMF at room temperature gave product **6** (Scheme 2) in a 65% yield. Finally, compound **6** was reacted with other 4-substituted benzaldehyde derivatives under aldol reaction conditions to provide non-symmetrical diarylidenepiperazines **7a**,**b** in moderate yields.

The cytotoxic activities of the synthesized plinabulin derivatives (Table 1) were evaluated using four human cancer cell lines, including epidermoid carcinoma cell line (KB), hepatoma carcinoma cell line (HepG2), lung cancer cell line



Scheme 1 *Reagents and conditions*: i, K_2CO_3, DMF, room temperature; ii, MeI, K_2CO_3, DMF, 0 → 80 °C; iii, HC≡CCH$_2$Br, K_2CO_3, DMF, 0 → 80 °C.

(Lu) and breast carcinoma cell line (MCF-7) and ellipticine as reference. Compounds **2b**, **3b** and **5a** showed strong cytotoxicity against one (MCF-7) of the three of the cancer cells lines. Compound **5a** also showed strong activity against three cell lines (KB, HepG2, and Lu), and 50% at cytotoxicity compared to ellipticine. The structure–activity relationship between the plinabulin-quinoline substituents and cytotoxic activity was



Scheme 2 *Reagents and conditions*: i, MeI, K_2CO_3, DMF, room temperature; ii, K_2CO_3, DMF, 0 → 80 °C.

Table 1 The cytotoxicity evaluation (IC_{50}) of new simplified plinabulin derivatives.

Compound	Cytotoxicity/μM			
	KB	HepG2	Lu	MCF-7
2a	196.62	172.96	222.64	118.97
2b	44.30	63.28	69.31	5.82
3a	>211	>211	>211	>211
3b	15.50	>248	>248	3.87
4a	220.06	212.63	241.05	260.09
4b	>258	>258	>258	>258
4c	32.20	>286	>286	125.24
4d	>283	>283	>283	>283
5a	5.87	2.66	3.72	>254
5b	15.80	>252	>252	63.23
6	92.91	>410	>410	103.48
7a	82.34	>329	253.07	207.24
7b	>326	>326	219.33	81.61
Ellipticine	1.30	1.30	1.79	2.11

ambiguous because of the higher cytotoxicity showed by compounds **2b**, **3b** (R = H) as compared to that of compounds **2a**, **3a**. However, compound **5a** (R = NO_2) turned to be more active than **5b**. Quinoline-derived compounds have higher cytotoxic activity than benzaldehyde derivatives, however substitution on the quinoline ring has no clear effect on cytotoxicity, therefore further investigations are required.

In conclusion, ten plinabulin-quinoline derivatives and three plinabulin-benzaldehyde derivatives were synthesized from 2,5-diketopiperazine **1**. The plinabulin-quinoline **2b**,**3b** showed higher potencies against breast carcinoma cell line (MCF-7), while compound **5a** exhibited strong cytotoxicity against epidermoid carcinoma (KB), hepatoma carcinoma (HepG2) and lung cancer (Lu) cell lines.

The authors are indebted to the Vietnamese National Foundation for Science and Technology Development (NAFOSTED), code 104.01-2016.18 for financial support.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.___.

References

1 J. A. Silverman and S. R. Deitcher, *Cancer Chemother. Pharmacol.*, 2013, **71**, 555.
2 C. Avendaño and J. C. Menéndez, *Medicinal Chemistry of Anticancer Drugs*, 2nd edn., Elsevier, Oxford, 2015.
3 J. E. Sears and D. L. Boger, *Acc. Chem. Res*., 2015, **48**, 653.
4 C. Dumontet and M. A. Jordan, *Nat. Rev. Drug Discov*., 2010, **9**, 790.
5 H. Guo, X. Li, Y. Guo and L. Zhen, *Med. Chem. Res*., 2019, **28**, 927.
6 M. Ma, L. Sun, H. Lou and M. Ji, *Chem. Cent. J.*, 2013, **7**, 179.
7 (*a*) A. V. Singh, M. Bandi, N. Raje, P. Richardson, M. A. Palladino, D. Chauhan and K. C. Anderson, *Blood*, 2011, **117**, 5692; (*b*) Z. Ding, Y. Hou, S. Wang, T. Sun, M. Ma, H. Guan and W. Li, *Mol. Divers.*, 2017, **21**, 577.
8 S.-R. Liao, X.-C. Qin, Z. Wang, D. Li, L. Xu, J.-S. Li, Z.-C. Tu and Y. Liu, *Eur. J. Med. Chem*., 2016, **121**, 500.
9 Y. Yamazaki, M. Sumikura, Y. Masuda, Y. Hayashi, H. Yasui, Y. Kiso, T. Chinen, T. Usui, F. Yakushiji, B. Potts, S. Neuteboom, M. Palladino, G. K. Lloyd and Y. Hayashi, *Bioorg. Med. Chem.*, 2012, **20**, 4279.
10 (*a*) Y. Yamazaki, K. Tanaka, B. Nicholson, G. Deyanat-Yazdi, B. Potts, T. Yoshida, A. Oda, T. Kitagawa, S. Orikasa, Y. Kiso, H. Yasui, M. Akamatsu, T. Chinen, T. Usui, Y. Shinozaki, F. Yakushiji, B. R. Miller, S. Neuteboom, M. Palladino, K. Kanoh, G. K. Lloyd and Y. Hayasshi, *J. Med. Chem*., 2012, **55**, 1056; (*b*) Z. Fu, Y. Hou, C. Ji, M. Ma, Z. Tian, M. Deng, L. Zhong, Y. Chu and W. Li, *Bioorg. Med. Chem.*, 2018, **26**, 2061.

11 Z. P. Din, M. Ma, C. Zhong, S. Wang, Z. Fu, Y. Hou, Y. Liu, L. Zhong, Y. Chu, F. Li, C. Song, Y. Wang, J. Yang and W. Li, *Bioorg. Med. Chem.*, 2020, **28**, 115186.
12 Z. Ding, F. Li, C. Zhong, F. Li, Y. Liu, S. Wang, J. Zhao and W. Li, *Bioorg. Med. Chem.*, 2020, **28**, 115435.
13 (*a*) Y. Hayashi, H. Takeno, T. Chinen, K. Muguruma, K. Okuyama, A. Taguchi, K. Takayama, F. Yakushiji, M. Miura, T. Usui and Y. Hayashi, *ACS Med. Chem. Lett*., 2014, **5**, 1094; (*b*) K. Okuyama, A. Kaida, Y. Hayashi, Y. Hayashi, K. Harada and M. Miura, *PloS One*, 2015, **10**, e0145995.
14 (*a*) Y. Yamazaki, Y. Kido, K. Hidaka, H. Yasui, Y. Kiso, F. Yakushiji and Y. Hayashi, *Bioorg. Med. Chem.*, 2011, **19**, 595; (*b*) A. Wieczorek, A. Blauz, J. Zakrzewski, B. Rychlik and D. Plazuk, *ACS Med. Chem. Lett*., 2016, **7**, 612; (*c*) F. Yakushiji, K. Muguruma, Y. Hayashi, T. Shirasaka, R. Kawamata, H. Tanaka, Y. Yoshiwaka, A. Taguchi, K. Takayama and Y. Hayashi, *Bioorg. Med. Chem.*, 2017, **25**, 3623.
15 M. Jensen and H. Mehlhorn, *Parasitol. Res*., 2009, **105**, 609.
16 S.-R. Liao, L.-J. Du, X.-C. Qin, L. Xu, J.-F. Wang, X.-F. Zhou, Z.-C. Tu, J. Li and Y.-H. Liu, *Tetrahedron*, 2016, **72**, 1051.
17 P. T. Chinh, P. T. Tham, N. V. Tuyen, D. H. Quynh, D. T. Van, D. N. Bang, V. T. Kien, B. D. Giang, N. T. Thuy, B. T. Nhan and L. T. Giang, *Vietnam J. Chem*., 2020, **58**, 309.

Received: 9th November 2020; Com. 20/6363

Contents entry