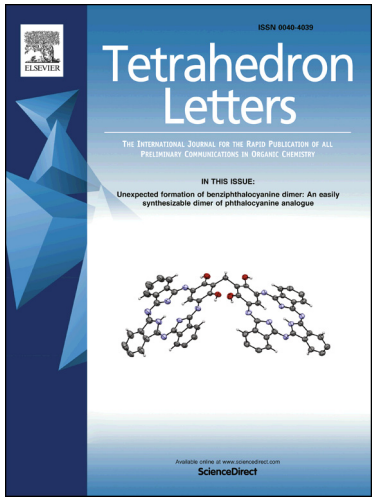


Synthesis and Antiproliferative activity of Novel A-Homo-B-Norsteroid Thiadiazole Derivatives

Yanmin Huang, Chunhui Yang, Junyan Zhan, Chunfang Gan, Zhiping Liu, Chunling Pang, Haifeng Chen, Jianguo Cui

PII: S0040-4039(17)30772-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.06.041
Reference: TETL 49033

To appear in: *Tetrahedron Letters*

Received Date: 23 May 2017
Revised Date: 11 June 2017
Accepted Date: 13 June 2017

Please cite this article as: Huang, Y., Yang, C., Zhan, J., Gan, C., Liu, Z., Pang, C., Chen, H., Cui, J., Synthesis and Antiproliferative activity of Novel A-Homo-B-Norsteroid Thiadiazole Derivatives, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.06.041

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis and Antiproliferative activity of Novel A-Homo-B-Norsteroid Thiadiazole Derivatives

Yanmin Huang[a] Chunhui Yang[a] Junyan Zhan[a] Chunfang Gan[a] Zhiping Liu[a]
Chunling Pang[a] Haifeng Chen[b] Jianguo Cui[a,b*]

[a] College of Chemistry and Material Science, Guangxi Teachers Education University, Nanning, 530001, PR China
[b] Guangxi Colleges and University Key Laboratory of Beibu Gulf Oil and Natural Gas Resource Effective Utilization, Qizhou University, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
cholesterol
B-norsteroid
A-homosteroids
A-Homo-B-Nor-steroidal derivatives
steroidal thiosemicarbazone

ABSTRACT

Using cholesterol as a starting material, two novel steroidal thiadiazole derivatives possessing a structure of A-homo lactam and a B-nor steroidal skeleton were designed and synthesized by six steps of reactions, and their antiproliferative activities were assayed against various cancer cell lines. The result shows that compound **7b** displays an excellent selective inhibition to A-549 (human lung carcinoma) cancer cell lines with an IC_{50} value of 8.0 μM.

It is well known that steroids play an important biological role in the life. However, the applications of natural steroids were greatly restricted because of their limited amount and low content in nature. So introducing specified functional groups into the steroidal skeleton or changing the structure of natural steroids to get new compounds with higher bioactivity and some special biofunction has become a focus of research on the steroidal chemistry in recent years [1-4].

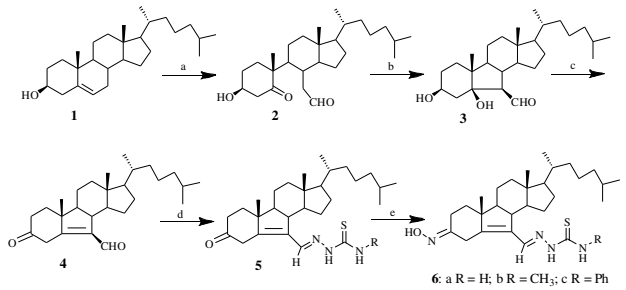
Aza-homosteroids are a class of steroid compounds which are synthesized and modified in order to increase biological activity of steroids. These compounds have been tested successfully as anti-cancer [5-9], antileukemic[10] agents. In order to find novel and effective anti-tumor agents, we synthesized a series of aza-homosteroids with aza-substitution on various position of the steroidal skeleton, and determined the antiproliferative activity of the compounds against various cancer cell lines. The results proved that these compounds showed a high antiproliferative acitivity to some tumor cell line in vitro [11-15]. Our research results showed also that aza-homosteroids with aza-A-homo- and aza-B-homo-configuration possessed a better cytotoxicity to tested tumor cell line [16-17].

B-norsteroid is a kind of novel steroidal compound possessing a special skeleton of [6-5-6-5] fused rings. These compounds were discovered in marine organism [18-19] and land plant [20]. The results of bioactivity assay had shown that these kinds of compounds displayed an excellent antiproliferative activity and good inhibitory activity against *Mycobacterium tuberculosis* [21]. In our previous studies, we synthesized some novel B-norsteroids and investigated their cytotoxic activity against different types of cancer cells [22-25]. The results demonstrated that B-norsteroids with a cholesteric side-chain and a 6-hydroximino, 6-thiosemicarbazone or 6-benzimidazole group displayed good antiproliferative activity against some cancer cells through inducing cancer cell apoptosis.

Basing on the results of our previous work, in order to investigate the bioactivity of new steroidal derivatives as new anticancer drugs, two novel steroidal compounds possessing both a structure of A-homo lactam and a B-nor steroidal skeleton were designed and synthesized by combining the structure of A-homosteroid with B-norsteroid in the present study, and their antiproliferative activities were assayed against various cancer cell lines.

The synthetic route and the structure of target compounds **7a**-**b** are outlined in Scheme **1**. First, cholesterol (**1**) was ozonolyed in a mixture of CH_2Cl_2 and MeOH (CH_2Cl_2/MeOH = 4:1) at -78°C. Then, adding Me_2S to decompose the produced ozonide, the compound **2** was obtained. The **2** was subjected to neutral alumina to realize the intramolecular aldol condensation affording compound **3** [22]. Next, compound **4** was obtained by the oxidation of **3** using Jone's reagent as oxidative agent. The compound **4** was converted to the compound **5** by the reaction of **4** with thiosemicarbazide. Furthermore, an oximation of 3-carbonyl group in compound **5** gave compound **6**. The structure

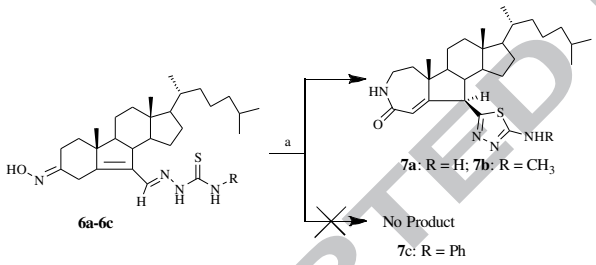
of all synthesized compounds were confirmed by their spectral data.



Reagents and conditions: a: $O_3/(CH_3)_2S$; b: Al_2O_3/Ph; c: Jones reagent; d: $NH_2NHCSNH_2$, 80°C; e: $NH_2OH.HCl$/AcONa.

Scheme **1**

Last, Beckman rearrangement of hydroxyimino group of compound **6a-6b** in $SOCl_2$/THF gave A-homo-lactame ring. During the process of the reaction, 6-thiosemicarbazone group was converted to thiadiazole ring to obtain target products **7a**-**7b**. In the ^{1}H NMR of **7a**, the chemical shift of C_7-H at 2.89 ppm appears as a dd-peak with a coupling constant of 17.7 and 4.5 ppm which illustrate that the C7-H and C8-H are located on an anti-form position of *a*-bond. This result shows that the stereochemistry of C-7 is the β-configuration. On the other side, compound **6c** couldn't be transformed into compound **7c** because there is a larger benzene ring in the structure of its 6-substituted group



Reagents and conditions: a: $SOCl_2$/THF.

Scheme **1**

The cytotoxic activity of compounds **4**-**7** was determined in vitro on HeLa (human cervical carcinoma), CNE-2 (nasopharyngeal carcinoma), HEPG2 (human liver carcinoma), A-549 (human lung carcinoma) cancer cell lines and HEK293T (Normal Kidney Epithelial Cells) cell lines. The MTT method was used to analyze the antiproliferative activity. The results are summarized as IC_{50} values in μmol/L in Table **1**.

Table 1. Antiproliferative activity of compounds **4**-**7** (IC_{50} in μM)（MTT method）

Comp.	HeLa	CNE-2	HEPG2	A-549	HEK293T
4	>80	>80	>80	>80	>80
5a	>80	>80	>80	>80	>80
5b	>80	>80	>80	>80	>80
5c	>80	>80	>80	>80	>80
6a	>80	16.5	>80	>80	>80
6b	>80	>80	>80	>80	>80
6c	18.7	>80	33	7.8	>80
7a	>80	20.5	>80	>80	>80
7b	28.5	>80	30	8.0	>80
Cisplatin	15	10	10	20.8	11

From the data shown in Table 1, compound **6c** with 6-(N-phenyl)thiosemicarbazone group and **7b** with 6-(5'-methylamino)thiadiazole ring show a better selective cytotoxicity on A-549 cells with IC_{50} value of 7.8 and 8.0μM, and are almost inactive on HEK293T cells. Both compounds display a better antiproliferative activities than a positive control cisplatin (20.8μM), and deserve further study.

Acknowledgments

The authors acknowledge the financial support of the National Natural Science Foundation of China (No: 21462009), the Natural Science Foundation of Guangxi Province (No: 2014GXNSFAA118052) and the Guangxi Colleges and University Key Laboratory Foundation of Beibu Gulf Oil and Natural Gas Resource Effective Utilization (No: 2016KLOG10).

Conflict of Interest

The authors declare no conflict of interest.

References and notes

1. Bansal R.; Acharya P. C. Chem. Rev., **2014**, 114 (14), 6986.
2. Chunfang G.; Haibin S.; Binbin Q.; Lei Y.; Dandan Z.; Yanmin H.; Jianguo C. *Chin. J. Org. Chem.*, **2014**, 34, 1730. (in Chinese)
3. Singh H.; Kapoor V. K.; Paul D. Heterosteroids and drug research. In: Progress in Medicinal Chemistry, Vol. 16; Ellis GP, West GB. Eds.; Springer: Amsterdam, **1979**, pp 35–150.
4. Huang Y. M.; Cui J. G.; Gan C, F.; Yao Q. C.; Jia L. Y. *Progress in Chem.*, **2012**, 24(1), 61. (in Chinese).
5. Venetia K.; Eleftheria M.; Zafiroula I.; Dionysios M.; Manolis F.; Anna K.; Evaggelia A.; Sotiris N. *Mutation Research*, **2003**, 535, 79.
6. Dimitrios T. P. T. *Cancer Lett.*, **2006**, 243, 202.
7. Natalija M. K.; Mira S. B.; Željko Ž.; Mirjana D. P.; Zorica D. J.; Vladimir D. P. *Steroids,* **2007**, 72, 406.
8. Anna I. K.; Manolis A. F.; Evagelia S. A.; Athanasios P.; George N. P.; Sotiris S. N. *Bioorg. Med. Chem.*, **2008**, 16, 5207.
9. Dimitrios T. P. T.; George D. G.; Catherine K.; Athanasios P.; Panayiotis K.; Charalambos C. *Breast Can. Res. Treat.*, **2006**, 97, 17.
10. Dimitrios T.; Elena G.; Panagiotis D.; Nikolaos N.; Vasiliki S. *Steroids*, **2016**, 115, 1.
11. Huang Y. M.; Cui J. G.; Zhong Z. G.; Gan C. F.; Zhang W. Y.; Song H. C. *Bioorg. Med. Chem. Lett*. **2011**, 21, 3641.
12. Huang Y. M.; Cui J. G.; Chen S. J.; Gan C. F.; Zhou A. M. *Steroids*, **2011**, 76, 1346.
13. Huang Y. M.; Chen S. J.; Cui J. G.; Gan C. F.; Liu Z. P.; Wei Y. L.; Song H. C. *Steroids*, **2011**, 76, 690.
14. Huang Y. M.; Cui J. G.; Chen S. J.; Gan C. F.; Yao Q. C.; Lin Q. F. *Bioorg. Med. Chem. Lett*., **2013**, 23, 2265.
15. Cui J. G.; Lin Q. F.; Gan C. F.; Yao Q. C.; Su W.; Huang Y. M. *Steroids*, **2014**, 79, 14.
16. Huang Y. M.; Cui J. G.; Zeng Q. X.; Zeng C.; Chen Q.; Zhou A. M. *Steroids*, **2012**, 77, 829.
17. Huang Y. M.; Cui J. G.; Chen S. J.; Lin Q. f.; Song H. C.; Gan C. F.; Su B.; Zhou A. M. *Mar. Drugs*, **2014**, 12, 1715.

18. Miyamoto T.; Kodama K.; Aramaki H. Y. R.; Van Soest R. W. M. *Tetrahedron Lett*., **2001,** 42, 6349.
19. Wei X.; Rodríguez A. D.; Wang Y.; Franzblau S. G. *Tetrahedron Lett*., **2007**, 48, 8851.
20. Lin W. H.; Fang J. M.; Cheng Y. S. *Phytochemistry*, **1998**, 48, 1391.
21. Wei X.; Rodríguez A. D.; Wang Y.; Franzblau S. G. *Bioorg. Med. Chem. Lett*., **2008**, 18, 5448.
22. Gan C. F.; Fan L. F.; Cui J. G.; Huang Y. M.; Jiao Y. X.; Wei W. X. *Steroids*, **2012**, 77, 1061.
23. Gan C. F.; Fan L. F.; Huang Y. M.; Liu Z. P.; Cui J. G. *Med. Chem*., **2013**, 9, 846.
24. Gan C. F.; Lin Q. F.; Cui J. G.; Feng J. D.; Guo J. N.; Liao H. Y.; Huang Y. M. *Steroids*, **2014,** 79, 37.
25. Cui J. G.; Qi B. B.; Gan C. F.; Liu Z. P.; Huang H.; Lin Q. F.; Zhao D. D.; Huang Y. M. Mar. *Drugs*, **2015**, 13, 2488.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Click here to remove instruction text...

Highlights

1. Two novel steroidal derivatives possessing both a A-homo lactam and a B-nor structure were designed and synthesized.
2. Synthesis starting from very cheap cholesterol.
3. Their antiproliferative activities were assayed.
4. Compounds **6c** and **7b** displayed an excellent inhibited selectivity to A-549 cancer cells.
5. The studied result may be useful for the design of novel chemotherapeutic drugs.