Tetrahedron Letters 60 (2019) 151333

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Practical synthesis of Vistusertib (AZD2014), an ATP competitive mTOR inhibitor

Guobing Shen [a], Miaoqing Liu [a], Jianjun Lu [a,*], Tao Meng [b,*]

[a] Key Laboratory of Coal Science and Technology of Ministry of Education and Shanxi Province, Taiyuan University of Technology, Taiyuan 030024, PR China
[b] Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, PR China

ARTICLE INFO

Article history:
Received 18 September 2019
Revised 22 October 2019
Accepted 25 October 2019
Available online 5 November 2019

Keywords:
Vistusertib
AZD2014
mTOR inhibitor
3-Acetylbenzoic acid

ABSTRACT

Vistusertib (AZD2014) is a potent, selective inhibitor of mTOR kinase. Prompted by its fascinating biological activity, an efficient and practical synthesis of Vistusertib has been developed from 3-acetylbenzoic acid through six steps in 48% overall yield.

Introduction

The mechanistic target of rapamycin (mTOR) is a serine/threonine kinase plays an integral role in the coordination of protein synthesis, cell growth and proliferation, autophagy, cell metabolism. Dysregulation of mTOR signal pathway is closely related to many human diseases, including cancer. The limitations of rapamycin-based therapies have led to the development of a second generation of mTOR inhibitors known as ATP-competitive mTOR kinase inhibitors [1]. Among those, Vistusertib (AZD2014) is a novel ATP-competitive selective inhibitor of mTOR shows very good antitumor activity in vivo, good pharmacokinetic and safety properties [2], which is currently in clinical trials for a wide variety of cancers [2b,3] (Fig. 1).

The method for preparation AZD2014 described in the prior art is shown in Scheme 1 [2a]. Reaction of 2,6-dichloronicotinic acid with liquid ammonia at elevated temperature and pressure results in the selective introduction of an amino group into the C2 position and subsequent conversion of the carboxylic acid to the primary amide, which then cyclized with oxalyl chloride to afford the pyridopyrimidine scaffold. Chlorination with phosphorous oxychloride results in the 2,4,7-trichloropyrido[2,3-*d*]pyrimidine, the introduction first of a morpholino substituent at position C-4, followed by C-2 substitution of the second morpholine ring. Then reaction of 4-aminophenylboronic acid in the presence of $Pd(PPh_3)_4$ at position C-7 afforded compound VI (AZD2014) in about 10% overall yield. Owing to the strict condition, high cost and difficulties on large-scale preparation, an efficient and practical synthetic method for AZD2014 is desirable.

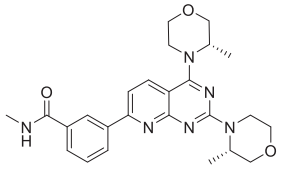


Fig. 1. The chemical structure of Vistusertib (AZD2014).

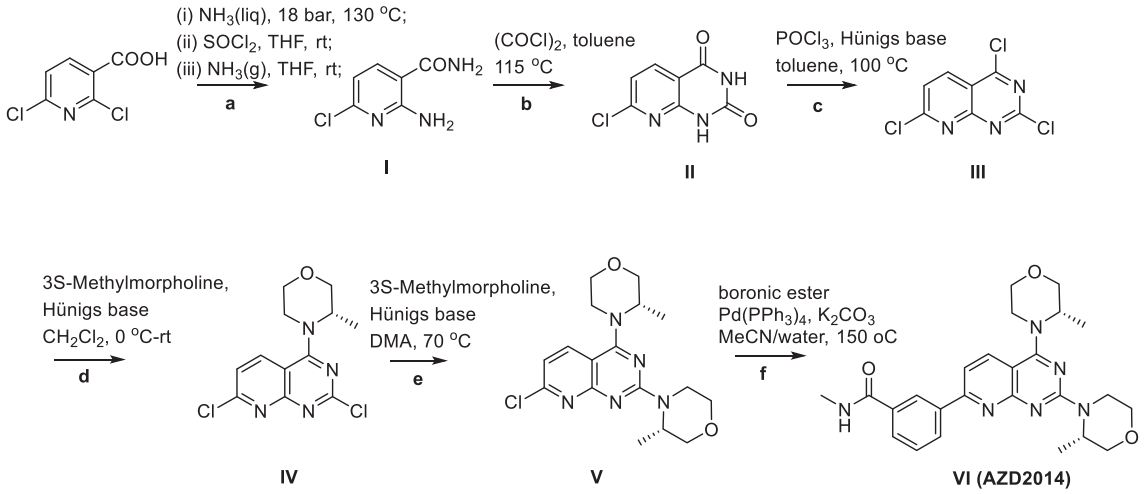
We have recently developed a synthetic process of low cost, high purity and suitable for industrial production of this compound, and also suitable for its analogues synthesis [4]. Herein, we wish to report the details of this improved synthetic procedure (shown in Scheme 2).

Result and discussion

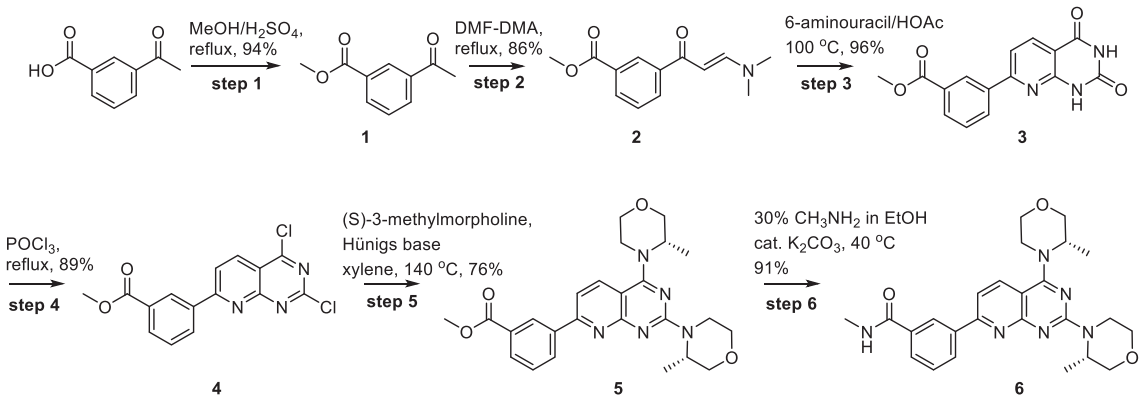
It is found that AZD2014 contains a methylbenzamide structural fragment, which brought significant improvement to the pharmacokinetic properties [2a]. However, Suzuki coupling was used in the final step to introduce this group in the original synthetic route, which increases the cost of removing palladium from Active Pharmaceutical Ingredient (API). We envisioned that

* Corresponding authors.
E-mail addresses: lujianjunktz@tyut.edu.cn (J. Lu), tmeng@sibs.ac.cn (T. Meng).

https://doi.org/10.1016/j.tetlet.2019.151333
0040-4039/



Scheme 1. Discovery route to Vistusertib.



Scheme 2. Improved synthetic route to Vistusertib.

this group could be introduced from the starting material or from introducing potential groups to convert to amides. The synthesis began with the commercially available intermediate 3-acetylbenzoic acid, which was converted to methyl ester (**1**), followed by reaction with dimethylformamide dimethylacetal (DMF-DMA) to give the enaminone (**2**). The heteroannulation reaction of enaminone with 6-aminouracil was carried out under acidic condition to afford the pyrido[2,3-*d*]pyrimidine (**3**), this motif is a common pharmacophore, which is found in a wide range of pharmaceutically active compounds [5]. Compound **3** was subjected to chlorination using phosphorus oxychloride to give the 2,4-dichloropyrido[2,3-*d*]pyrimidine (**4**). Instead of two-step reaction of (S)-3-methylmorpholine with intermediate **4** (C-4 substitution then C-2 substitution), we found out xylene is the optimal solvent for the substitution reaction, and compound **5** was obtained in 76% yield in one-step synthesis. Aminolysis of intermediate **5** in 30% methylamine alcohol solution to afford the final product using potassium carbonate as the reaction promoter (Scheme 2). The final product obtained by this method was identified by ^{1}H NMR, ^{13}C NMR and HRMS, and was consistent with the theoretical values.

Conclusion

In summary, we described a facile, efficient, and commercially viable synthesis of Vistusertib in six steps in 48% overall yield. In addition, a new approach for the synthesis of Vistusertib by introducing the methyl ester group in the starting material, which could be converted to methylbenzamide in the final step. This present synthetic approach has the following advantages over the previous reported preparations: (i) avoids palladium catalyst; (ii) without the need for purification by chromatography and expensive reagents. These modifications make the whole synthesis cost-effective, production-friendly, greener, and practical. In this perspective, we have developed an improved and scalable synthesis of Vistusertib with over 99% chromatographic purity.

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.

Acknowledgement

This work was supported by the National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program", China (grant no.: 2014ZX09508001).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151333.

References

[1] (a) Y.-J. Zhang, Y. Duan, X.-F.S. Zheng, Drug Discovery Today 16 (2011) 325–331;
(b) A. Zask, J.-C. Verheijen, D.-J. Richard, Expert. Opin. Ther. Pat. 21 (2011) 1109–1127.

[2] (a) K.-G. Pike, K. Malagu, M.-G. Hummersone, K.-A. Menear, H.-M. Duggan, S. Gomez, N.-M. Martin, L. Ruston, S.-L. Pass, M. Pass, Bioorg. Med. Chem. Lett. 23 (2013) 1212–1216;
(b) B. Basu, E. Dean, M. Puglisi, A. Greystoke, M. Ong, W. Burke, M. Cavallin, G. Bigley, C. Womack, E.-A. Harrington, S. Green, E. Oelmann, J.-S. de Bono, M. Ranson, U. Banerji, Clin. Cancer Res. 21 (2015) 3412–3419;
(c) B. Zheng, J.-H. Mao, L. Qian, H. Zhu, D.-H. Gu, X.-D. Pan, F. Yi, D.-M. Ji, Cancer Lett. 357 (2015) 468–475;
(d) S.-M. Guichard, J. Curwen, T. Bihani, C.-M. D'Cruz, J.-W. Yates, M. Grondine, Z. Howard, B.-R. Davies, G. Bigley, T. Klinowska, K.-G. Pike, M. Pass, C.-M. Chresta, U.-M. Polanska, R. McEwen, O. Delpuech, S. Green, S.-C. Cosulich, Mol. Cancer Ther. 14 (2015) 2508–2518.

[3] (a) A. MacDonald, G. Scarfe, D. Magirr, T. Sarvotham, J. Charlton, W. Brugger, E. Dean, Cancer Chemother. Pharmacol. 83 (2019) 787–795;
(b) T. Powles, M. Wheater, O. Din, T. Geldart, E. Boleti, A. Stockdale, S. Sundar, A. Robinson, I. Ahmed, A. Wimalasingham, W. Burke, S.-J. Sarker, S. Hussain, C. Ralph, Eur. Urol. 69 (2016) 450–456.

[4] J.-K. Shen, T. Meng, T. Yu, L.-P.Ma, X. Wang, L. Chen, 2018, US2018/79749 A1.

[5] (a) A. Ghaedi, G.-R. Bardajee, A. Mirshokrayi, M. Mahdavi, T. Akbarzadeh, Mol. Divers 23 (2019) 333–340;
(b) B. Veeraswamy, D. Madhu, G. Jitender Dev, Y. Poornachandra, G. Shravan Kumar, C. Ganesh Kumar, B. Narsaiah, Bioorg. Med. Chem. Lett. 28 (2018) 1670–1675;
(c) A.-M. El-Naggar, A.-K. Khalil, H.-M. Zeidan, W.-M. El-Sayed, Anticancer Agents Med. Chem. 17 (2017) 1644–1651;
(d) D.-A. DeGoey, D.-A. Betebenner, D.-J. Grampovnik, D. Liu, J.-K. Pratt, M.-D. Tufano, W. He, P. Krishnan, T.-J. Pilot-Matias, K.-C. Marsh, A. Molla, D.-J. Kempf, C.-J. Maring, Bioorg. Med. Chem. Lett. 23 (2013) 3627–3630.