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Rapid access to multi-substituted pyrimido[4,5-*b*][1,4]diazepine-2,4,6-trione and pyrimido[4,5-*b*][1,4]diazepine-2,4-dione as novel and versatile scaffolds for drug discovery

Gong Li, Xiaowei Wang *, Chao Tian, Tongbo Zhang, Zhili Zhang, Junyi Liu *

The State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100191, China
Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China

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ABSTRACT

A novel pyrimido[4,5-*b*][1,4]diazepine-2,4,6-trione was synthesized with an efficient strategy. Especially, the key intermediate 2,4-dimethoxypyrimido[4,5-*b*][1,4]diazepin-6-one was promoted by one pot tandem reduction–cyclization with $Na_2S_2O_4$. Subsequently, reduction of lactams **6** with $LiAlH_4$ afforded a more flexible scaffold of pyrimidodiazepines. The synthetic strategy was versatile since it facilitated the sequential functionalization on the pyrimidodiazepine at three positions. Thus a convenient and effective method for the rapid preparing of multi-substituted pyrimido[4,5-*b*][1,4]diazepines was developed.

At present, an effective approach for identification of new lead compounds in drug discovery involves screening of chemical libraries based upon privileged structure.[1,2] These frameworks could address multiple biological targets by varying the nature of peripheral substituents. Benzodiazepines are the prototypical privileged structures, among them, 1,5-benzodiazepine-2-ones exhibit a range of biological activities.[3–5] Since pyrimidines are often incorporated into drugs designed for cancer and anti-viral treatment due to their wide range of biological activities, best known as the heterocyclic core of the nucleic acid bases.[6] We suppose that if the bioisosteric replacement of archetypal benzene ring by pyrimidine on the 1,5-benzodiazepine-2-one could give us an unique handle toward developing druggable molecules against cancer and virus. And it is also believed that the corresponding pyrimido[4,5-*b*][1,4]diazepine scaffolds comprising part of the privileged structure should share the good physico-chemical and pharmacokinetic properties of benzodiazepine.

Intrigued by this idea, we would like to hybridize the 1,5-benzodiazepine-2-one skeleton with compound **I** (Fig. 1) which was previously reported as a potent HIV-1 RT inhibitor[7] to achieve the pyrimido[4,5-*b*][1,4]diazepine-2,4,6-trione scaffold (Fig. 1). As far as we know the pyrimidodiazepine scaffolds had never been studied as the inhibitors of HIV-1 RT, though a number of unique approaches in regard to pyrimidodiazepine have been explored due to its important potential biological properties.[8] Moreover, as a special interest in developing flexible scaffold of HIV-1 RT inhibitors,[7] we performed the reduction of lactam **6** which provided the pyrimido[4,5-*b*][1,4]diazepine-2,4-dione scaffold (Fig. 1).

From the structural perspective, pyrimido[4,5-*b*][1,4]diazepine represents a versatile intermediate for bearing three orthogonal groups with R_1, R_2 and R_3. Therefore, a library of pyrimidodiazepine compounds could provide the structure–activity relationship (SAR) study based on privileged structure. However, there is no example for synthesizing skeleton of target compounds with a combination of privileged structure and **I**.

The reported synthetic strategies, in which 5,6-diaminouracils were usually adopted to undergo an intermolecular condensation with ether chalcones or β-dicarbonyl compounds to afford the pyrimido[4,5-*b*][1,4]diazepine skeleton,[9] were not efficient for the preparation of highly substituted pyrimido[4,5-*b*][1,4]diazepine-2,4,6-triones (Fig. 1). The first reason is that diaminopyrimidines are usually expensive and difficult for preservation. Another one is that though the presence of non-equivalent amino groups, the desired cyclization manner could not be exclusive. The cyclization products, formed as a mixture of two regioisomers, are difficult for isolation and identification from each other due to their similar physico-chemical properties. Concerning the above disadvantages, we make efforts to develop a novel strategy that permits the rapid and efficient synthesis of multi-substituted pyrimido[4,5-*b*][1,4]diazepine-2,4,6-triones.

In our synthetic strategy, the fused bicyclic core was obtained in two steps as illustrated in Scheme 1 from the easily prepared

* Corresponding authors.
E-mail addresses: xiaoweiwang@bjmu.edu.cn (X. Wang), jyliu@bjmu.edu.cn (J. Liu).

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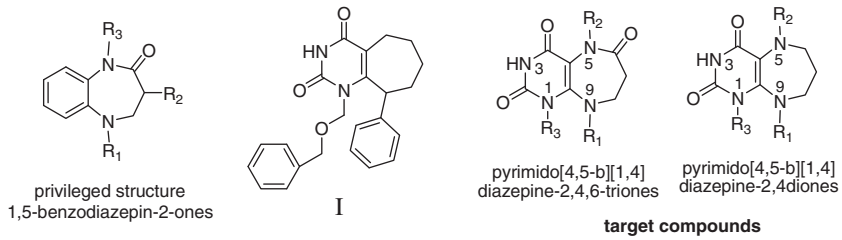
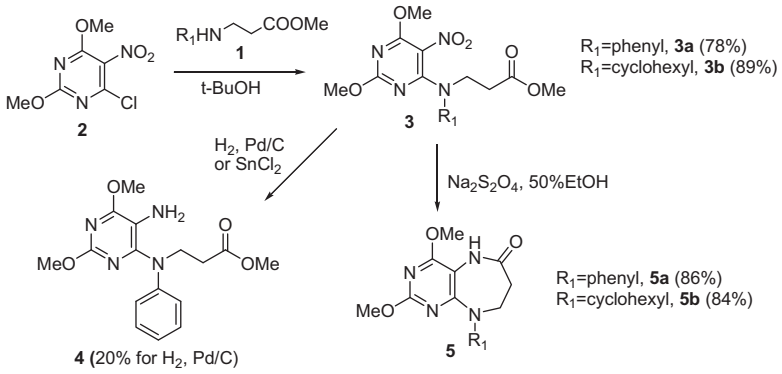


Figure 1. Structures of privileged skeleton, **I** and target compounds.



Scheme 1. Synthesis of pyrimido[4,5-*b*][1,4]diazepines from 2,4-dimethoxyl-6-chloro-5-nitro-pyrimidine and β-aminopropanoates.

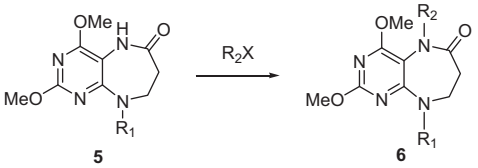
intermediate **2**.[10] First, nucleophilic substitution of 2,4-dimethoxyl-6-chloro-5-nitropyrimidine **2** with β-aminopropanoates **1** afforded intermediates **3** in good yields. Obviously, a free amino group was necessary for the coming intramolecular cyclization. Therefore, three reagents were examined for the reduction of **3a**. First, **3a** was treated with hydrogen in the presence of a catalytic amount of 10% palladium on carbon to give the aminopyrimidine **4** in an unacceptable yield. Second, $SnCl_2$[11] was used as reduction agent which could afford the cyclization product **5a,** but in rather low yield. Finally, we found that the reduction of nitro compounds **3** took place along with an intramolecular cyclization when 10 equiv of $Na_2S_2O_4$[12] was used in the circumstance of 50% alcohol at refluxing for 6 h to give lactam **5** in excellent yields (84–86%). The analytical data showed that no amino compounds **4** were isolated, which meant that treatment of nitro compounds **3** with excess $Na_2S_2O_4$ gave the amino compounds, and then immediately carried out an intramolecular nucleophilic attack by amino on ester to give the seven-membered ring compounds **5**. It had to be noted here that $Na_2S_2O_4$ also showed purification advantage that crude cyclization product collected from the extraction of reaction mixture could be used directly for the next step without further purification. It was evident that the present methodology shortened the synthesis steps and increased the reaction yields.

Subsequent N5-alkylation of lactams **5** occurred smoothly on treatment with different alkyl halides (CH_3I, BnBr) in the presence of NaH to give **6a**, **6c,** and **6d** in good yields (Scheme 2). However, we did not reach an acceptable yield when introducing the isopropyl group by using NaH as base. Alternatively, the phase-transfer catalysis method in which the two substrates were refluxing with KOH/TBAB for 5 h in CH_3CN facilitated the isopropylated products **6b** and **6e** in high yields (Table 1).

Deblocking of the 2,4-dimethoxypyrimidine ring of **6** to uracil **7** was achieved under a relatively mild condition with TMSCl and NaI as deprotection agents to give compound **7a** and **7b**, while **7c** was achieved by an alternative HCl/THF hydrolysis method (Scheme 3). The results indicated that the lactam was tolerated to HCl/THF condition. Treatment of **7** with *N,O*-bis(trimethylsilyl)acetamide (BSA) and alkyl chloromethyl ether in $CHCl_3$ at room temperature gave the N1 substituted uracils **8** in good yields (Scheme 3).[7] Moreover, the N3 substituted compounds **9a** and **9b** were also isolated and identified as byproducts in 40% and 33% yields respectively (Scheme 3).

The reduction of lactams **6** with $LiAlH_4$ afforded a more flexible scaffold of pyrimidodiazepine **10** (Scheme 3), which was characterized by ^1H NMR, and MS. However, the N1 and N3 regioisomers showed very similar physical and chemical properties. Therefore, it would be difficult to distinguish between the N1 and N3 alkylation products with ^1H NMR only. To facilitate more exact structural information of the N1[13] and N3 regioisomers, the X-ray structural analyses of **11a** and **12a** were shown in Figure 2.

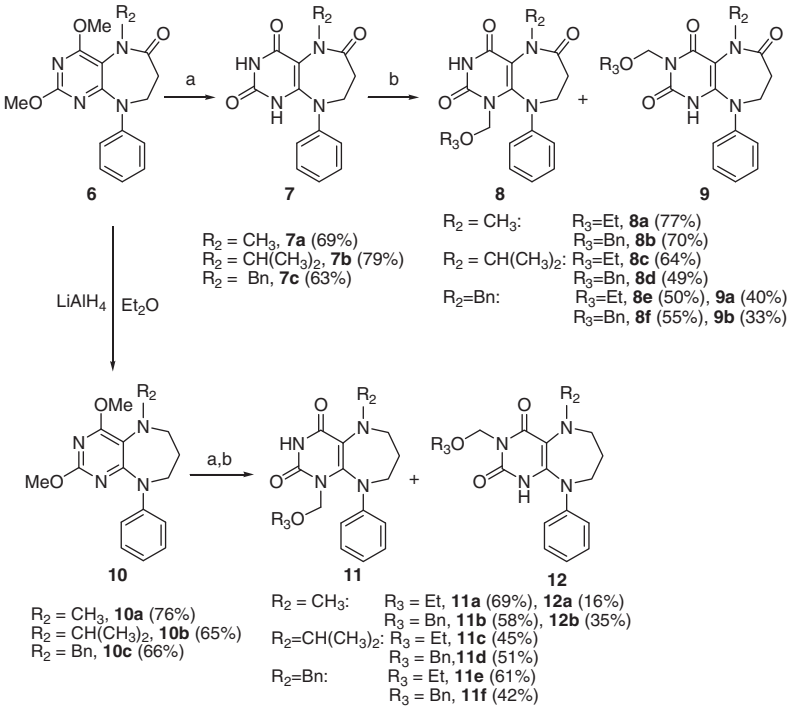
In conclusion, we have developed an effective synthesis strategy that permits the rapid access to the pyrimido[4,5-*b*][1,4]diazepine-2,4,6-triones and pyrimido[4,5-*b*][1,4]diazepine-2,4-diones



Scheme 2. Reaction conditions: NaH (60% dispersion in mineral oil) THF, rt; KOH/TBAB, acetonitrile, refluxing.

Table 1
N5-alkylation on lactams **5**

Entry	**6**	R_1	R_2X	Base	Yield (%)
1	**6a**	Ph	CH_3I	NaH	92
2	**6b**	Ph	$CH(CH_3)_2Br$	KOH	96
3	**6c**	Ph	BnBr	NaH	99
4	**6d**	Cyclohexyl	CH_3I	NaH	88
5	**6e**	Cyclohexyl	$CH(CH_3)_2Br$	KOH	98



Scheme 3. Reagents and conditions: (a) TMSCl/NaI or HCl/THF; (b) BSA, R_3OCH_2Cl.

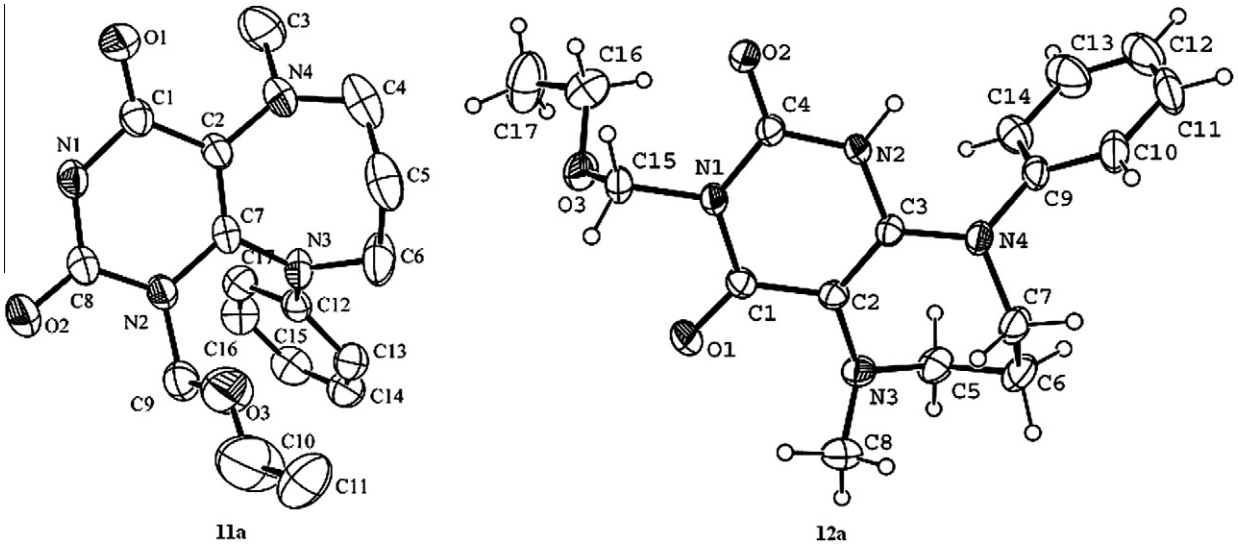


Figure 2. X-ray crystal structure of **11a** and **12a**.

from the readily available 2,4-dimethoxyl-6-chloro-5-nitropyrimidine and β-aminopropanoates. The overall yield is acceptable and the purification of intermediates is trouble-free. The synthetic strategy is versatile for the sequential functionalization on the pyrimidodiazepine which are of great interest in drug discovery based on privileged structure. More detailed SAR studies are underway with a focus on exploring the important role of this unique structural feature.

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Supplementary data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication 782159 CCDC.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.143.

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