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A new approach to the 2,5-diamino-5,6-dihydro-1*H*-pyrimidine-4-one derivatives: synthesis of TAN-1057A/B and analogs

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Abstract—TAN-1057A/B has shown potent activity against MRSA. A new approach to the 2,5-diamino-5,6-dihydro-1*H*-pyrimidine-4-one derivatives has been developed. TAN-1057A/B and its analogs were efficiently synthesized using this new approach.

TAN-1057A/B, isolated a few years ago from *Flexibacter* in Japan,[1] exhibits potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (Fig. 1). As part of our structure–activity relationship (SAR) study on TAN-1057A/B, methylated analogs **2** and **3** were targeted (Scheme 1).

The total synthesis of TAN-1057A/B has been reported by the groups of Williams and de Meijere.[2] Both syntheses were based on the coupling of an α,β-diamino acid derivative with an *S*-methylisothiourea derivative to construct the 2,5-diamino-5,6-dihydro-1*H*-pyrimidine-4-one scaffold. Recently, construction of the dihydropyrimidinone derivative using a tandem reaction reported by Ganesan et al. is an extension of the above strategy.[3] We also reported a concise construction of this scaffold that allows for synthesis of TAN-1057A/B analogs with alteration at the 2-position.[4] Unfortunately, the existing approaches are not suitable for regioselective synthesis of analogs **2** and/or **3**. Not surprisingly, direct methylation of the Boc-protected heterocycle core **5** ($R_1 = R_2 = H$) (Scheme 1) with iodomethane in the presence of cesium carbonate yielded multiple products, and only a small amount of the N-3 methylated product **5a** could be isolated. In order to synthesize **2** and **3** successfully, a new route needed to be developed for the efficient construction of heterocyclic compound **6**. In this paper, we report a new approach for the construction of the 2,5-diamino-5,6-1*H*-dihydropyrimidine-4-one scaffold and the regioselective syntheses of **2** and **3** using this new approach.

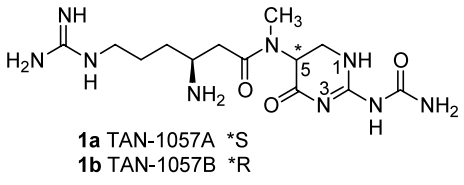
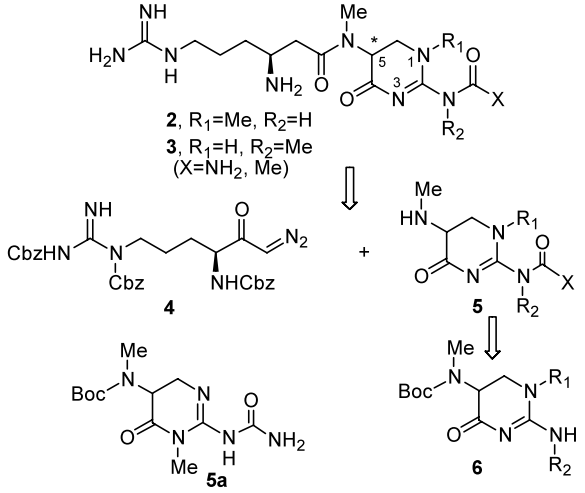


Figure 1.

As shown in Scheme 1, we envisioned that both **2** and **3** could be prepared through the coupling of diazoketone **4** with heterocycle core **5** following the strategy developed by de Meijere group.



Scheme 1.

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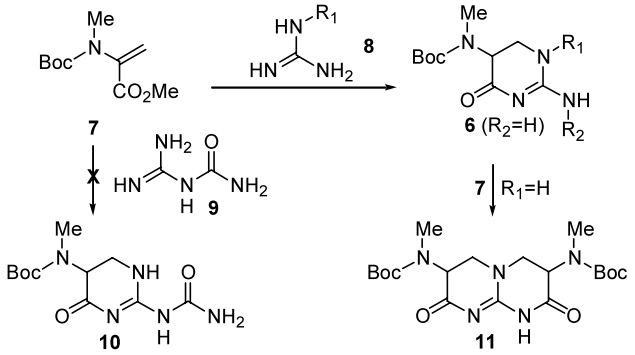
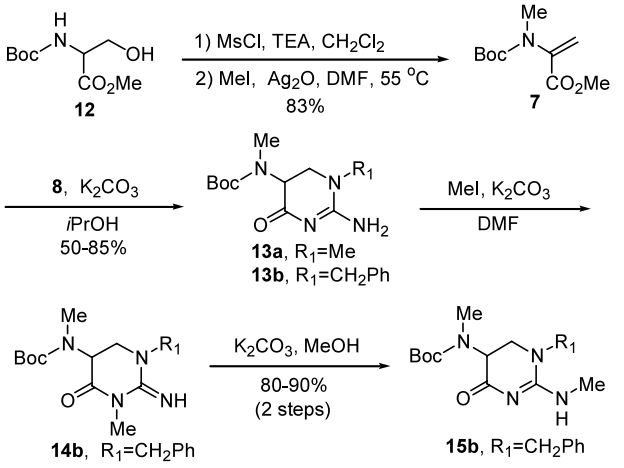


Scheme 2.

It was observed[2b] that *N*-(*tert*-butoxycarbonyl)-*N*-methyldehydroalanine methyl ester **7** failed to react with *N*-guanylurea **9** for the synthesis of heterocycle **10** possibly due to insufficient reactivity of **9** (Scheme 2). On the other hand, reaction of dehydroalanine **7** with guanidine **8** ($R_1=H$) proceeded all the way to the bicycle compound **11** through an ensuing Michael addition of intermediate **6** ($R_1=R_2=H$) with a second molecule of **7** and subsequent cyclization.

We considered that if 1-alkylguanidine **8** ($R_1=$alkyl) was used, compound **6** should be a stable intermediate because it could no longer undergo the second round of Michael addition and subsequent cyclization with **7**. In addition, compound **6** ($R_2=H$) should be formed as a regioselective major product because Michael addition of **8** should favor at the alkylated N-1 position due to the anticipated higher nucliphilicity of the alkylated nitrogen over the other two nitrogens.

Indeed, as outlined in Scheme 3, when 1-methylguanidine hydrochloride **8** ($R_1=Me$) and compound **7**, prepared from serine methyl ester **12**,[5] was treated with potassium carbonate in acetonitrile at room temperature, desired pyrimidone **13a** was isolated in 85% yield. When 1-benzylguanidine **8** ($R_1=CH_2Ph$)[6] was used for the Michael addition–cyclization reaction, desired

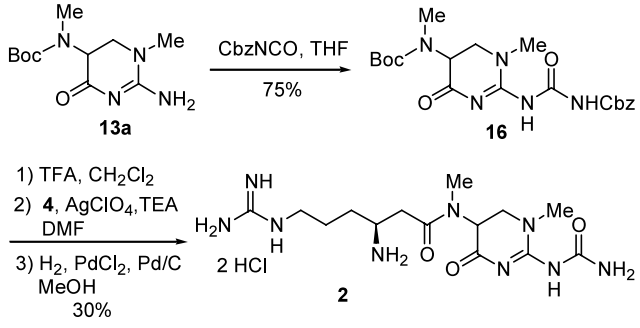


Scheme 3.

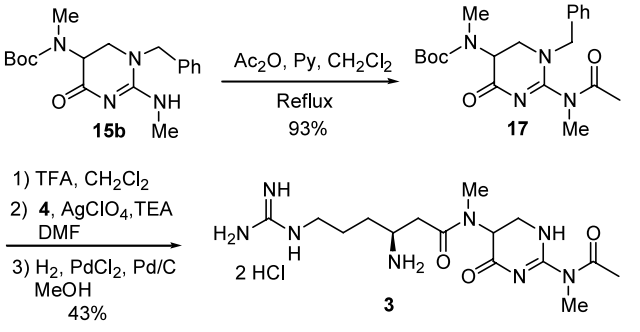
product **13b** was isolated in 50% yield, along with 13% of regioisomer **6** ($R_1=H$, $R_2=CH_2Ph$). The lower regioselectivity compared to the methyl analog may be due to the higher steric hindrance of the benzyl group over the methyl group. Compound **6** ($R_1=R_2=H$), which was not accessible by direct reaction of guanidine with **7**, could be readily obtained by hydrogenation of compound **13b**.

With the key intermediate **13** in hand, we turned our attention to the methylation of 2-amino functional group of **13**. It was reported that direct methylation of compounds resembling **13** favored the amide nitrogen (N-3) over the 2-NH_2 nitrogen.[7] When compound **13b** was treated with iodomethane and potassium carbonate in DMF, the regioisomer **14b** was indeed formed as a major product. However, the desired product **15b** can be obtained in high yield by additional treatment of **14b** with potassium carbonate in methanol. Base treatment of **14b** induced the ring-opening of **14b** followed by a ring-closure to yield the thermodynamicaly more stable isomer.[8]

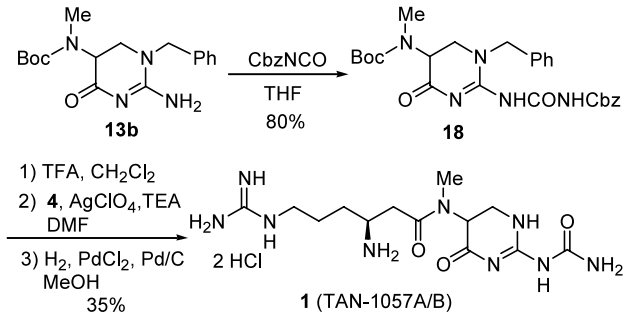
Final steps of syntheses of methylated analogs **2** and **3** are illustrated in Schemes 4 and 5, starting from **13a** and **15b**, respectively. Compound **13a** was treated with benzyloxycarbonyl isocyanate to give compound **16**. Similarly, acetylation of **15b** afforded **17**. TAN-1057 A/B analogs **2** and **3** were thus obtained respectively by deprotection of the Boc group, coupling of the resulting amine with side chain **4**,[2b] and hydrogenolysis removal of the Cbz and benzyl groups.[9]



Scheme 4.



Scheme 5.



Scheme 6.

With the availability of **13b**, an alternative route for the synthesis of TAN-1057A/B can be achieved (Scheme 6). Treatment of **13b** with benzyloxycarbonyl isocyanate provided **18**. TAN-1057A/B was then obtained applying the same protocol as was used for synthesis **2** and **3**. It is worth noting here that TAN-1057A/B is synthesized in 7 steps with 12% overall yield from serine analog **12**. This is an improvement over the existing routes for synthesis of TAN-1057A/B and the method developed here is complimentary to the reported routes.

In summary, based on a Michael addition and subsequent cyclization of 1-alkylguanidine **8** with dehydroalanine methyl ester **7**, a new approach to the 2,5-diamino-5,6-1*H*-dihydropyrimidine-4-one class of compounds was developed. TAN-1057A/B and its methylated analogs **2** and **3** were synthesized in good yield and with a high degree of regioselectivity using this new approach. This method allows for rapid preparation of TAN-1057A/B and its analogs for biological activity evaluation. More detailed SAR studies of this class of compounds will be discussed in future publications.

Acknowledgements

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8. *Experimental procedures for **13b** and **15b***:
   13b: To a solution of **7** (795 mg, 3.7 mmol) and 1-benzylguanidine TFA salt (3.7 mmol) in isopropanol (15 mL) was added potassium carbonate (1380 mg, 10 mmol). After stirred at room temperature for 16 h and at 50°C for 4 h, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluted with 10% MeOH/CH_2Cl_2) to afford desired product **13b** (610 mg, 50%). ^{1}H NMR ($CDCl_3$) δ: 1.4 (two brs (2:1), 9H), 2.8 (brs, 3H), 3.35 (m, 1H), 3.7 (m, 1H), 4.6 (m, 2H), 4.9 (m, 1H), 7.2–7.4 (m, 5H). MS (M+1): 333.
   15b: To a solution of **13b** (300 mg, 0.9 mmol) in DMF (4 mL) was added iodomethane (155 mg, 1.09 mmol) and potassium carbonate (280 mg, 2 mmol). The reaction mixture was stirred at room temperature for 4 h, diluted with ethyl acetate and filtered. The filtrate was concentrated under reduced pressure to give crude product **14b** [^{1}H NMR ($CDCl_3$) δ: 1.4 (two brs (2:1), 9H), 2.8 (two brs, 3H), 3.2 (m, 1H), 3.3 (s, 3H), 3.6 (m, 1H), 4.4–4.9 (m, 3H), 7.2–7.4 (m, 5H). MS (M+1): 347]. The crude product **14b** was dissolved in methanol (20 mL) and potassium carbonate (28 mg) was added. The resulting mixture was stirred at room temperature for 3 h, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel and precipitation from hexane–ethyl acetate to yield compound **15b** (275 mg, 88%). ^{1}H NMR ($CDCl_3$) δ: 1.4 (brs, 9H), 2.8 (brs, 3H), 2.9 (brs, 3H), 3.35 (m, 1H), 3.7 (m, 1H), 4.5 (m, 2H), 5.05 (m, 1H), 7.2–7.4 (m, 5H). MS (M+1): 347.
9. Both analogs **2** and **3** displayed reduced minimal inhibitory concentration (MIC) against Staphylococci, data are listed as follows: MIC, *S. aureus* 29213 (μg/mL): TAN-1057, 8; analog **2**, >256; analog **3**, 64.