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# Synthesis of sterically hindered 3,5,5-trimethyl 2,6-dioxo tetrahydro pyrimidine as HCV protease inhibitors

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ABSTRACT

An efficient route for the synthesis of sterically hindered substituted and unsubstituted 2,6-dioxo tetrahydropyrimidines from amine **1** is described. These analogs are active against HCV NS3 serine protease. The biological data for some of the representative examples are also reported.



Although the hydantoins and their analogs are well documented in the literature,[1–6] the corresponding six-membered heterocyclic analogs viz., tetrahydropyrimidines, are still to be explored. It has been recognized that tetrahydropyrimidines are important intermediates in the catabolism of pyrimidines and their derivatives are assumed to play an important role in the nucleic acid synthesis.[7] A survey of literature revealed that relatively little attention has been focused on tetrahydropyrimidine, except a few early reports and patents. The known methods for the synthesis of dihydropyrimidines include the condensation of α,β-unsaturated acids with urea to afford the dihydrouracil in low yield,[8] the dethiation of 5,5-dialkyl-substituted 6-thio 5,6 dihydrouracils using Raney Nickel,[9] and another protocol with unreported yields.[10] Synthesis and the biological importance of substituted uracils and thio uracils are also known.[11–13] Reduction of barbiturates to the corresponding dihydro dioxo pyrimidine[14] and synthesis of dihydropyrimidine 2,4-dione from acrylic acid and urea are reported in 1960s.[15]

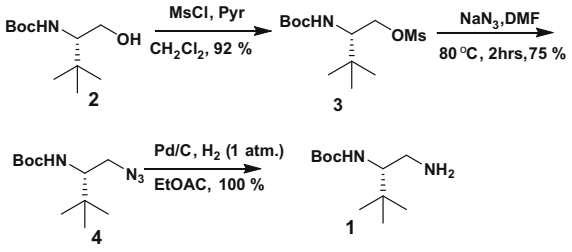
In our SAR studies on the P3 cap area of the HCV NS3 protease inhibitor,[16] we were interested in hydantoins and their six-membered analogs. To our knowledge there is no report on the synthesis of N-linked dihydro dioxo pyrimidines (dihydro uracils) from amines or alcohols and herein we report the synthesis of the unsubstituted and trimethyl-substituted dihydro dioxo pyrimidines **6** and **15** from amine **1** and the biological activity of their analogs.

Amine **1** was synthesized from the commercially available *tert*-leucinol via mesylation, and azide displacement followed by reduction (Scheme 1).[17]

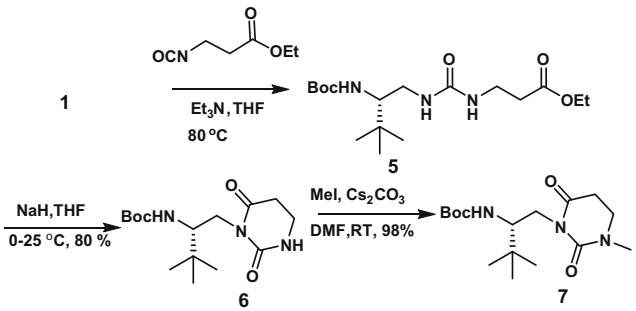
Amine **1** was treated with the ethyl isocyanato propionate and triethyl amine in THF under reflux conditions to afford the urea **5**. The urea **5** was cyclized to the desired product **6** by treating with NaH in THF at ambient temperature in excellent yields along with traces of (<5%) five-membered cyclized urea **12a**. Compound **6** was converted to the *N*-methyl derivative **7** with $Cs_2CO_3$ and MeI in DMF (Scheme 2).[18]

Attempts to convert **1** to **6** via a one-pot cyclization of urea **5** with triethyl amine in THF were unsuccessful even at elevated temperatures (80–150 °C) and with a longer reaction time.

Previous structure–activity relationship studies (SAR) in the HCV protease inhibitor program have shown that when the hydantoins[16] and lactams[19] were substituted with gem-dimethyls, the




**Scheme 1.**




**Scheme 2.**

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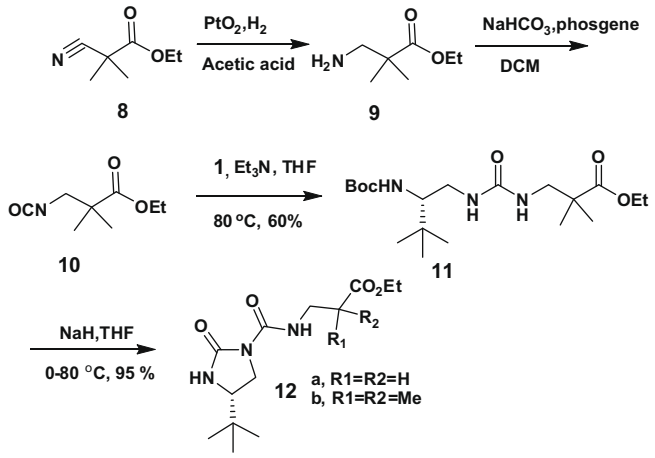



Scheme 3.

inhibitor had a profound effect on in vitro and in vivo profiles. Hence our next approach was to synthesize the dimethyl and trimethyl tetrahydro pyrimidine dione analogs for our SAR study.

Synthesis of the trimethyl derivative started with the nitrile **8**. Conversion of nitrile to the isocyanate **10** was achieved via reduction followed by treatment of the resulting amine **9** with phosgene (Scheme 3). Urea **11** was synthesized via the reaction of isocyanate **10** with the amine **1** under basic conditions. Attempts to synthesize the 5,5-dimethyl-substituted tetrahydrodioxo pyrimidine via the cyclization of the urea **11** resulted in exclusive formation of the five-membered cyclic urea derivative **12b** (Scheme 3). This may be attributed to the geometry of the intermediate in which the gem-dimethyl groups block the attack of the amide nitrogen to the ester carbonyl (Fig 2). According to the minimum energy calculations, steric energy for **11** (Fig 2) is 30.22 kcal/mol whereas that for **5** (Fig 1) is only 20.02 kcal/mol.

The urea **11** was then N-deprotected and re-protected with benzyl groups to avoid the side product resulting from the reaction with the *tert*-butoxy carbonyl group. Urea **13** was treated with NaH at 100 °C to afford the desired product **14** in 90% yield (Scheme 4). The trimethyl derivative **15** was generated via the methylation procedure described earlier.[18]

Alternatively, **15** can be constructed from urea **5**. One-pot, two-step addition of sodium hydride followed by sodium hydride and methyl iodide to urea **17** afforded **15** in 61% yield in two steps (Scheme 5).

Surprisingly, deprotection of the *N*-benzyl group under hydrogenation conditions (Pd/C, $H_2$ or Pd(OH), $H_2$) resulted in the formation of dihydroimidazole **18** as the sole product**.** However, reaction of the hydrochloride salt of **15** with Pearlman's catalyst under acidic conditions afforded the desired amine **19** ready for further transformations. The amine hydrochloride **19** was transformed to the isocyanate under standard conditions with phosgene (Scheme 6).

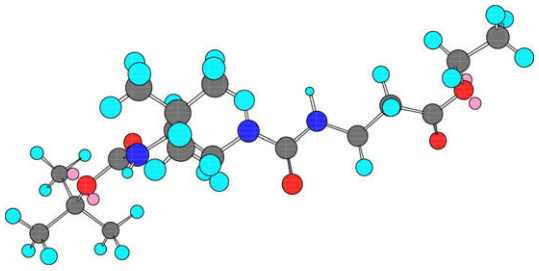


**Figure 1.** Minimum energy configuration of **5**.

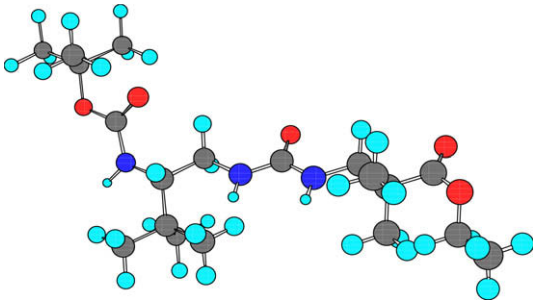
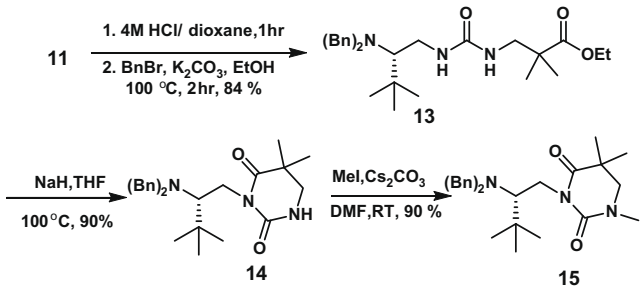
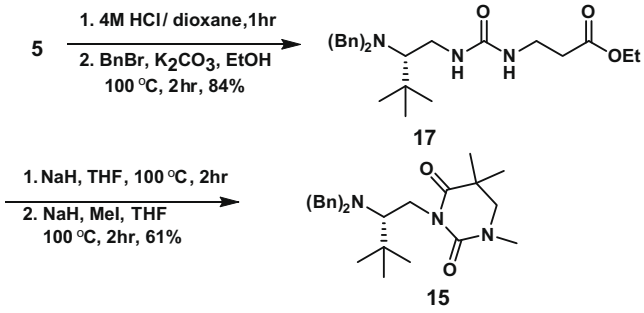


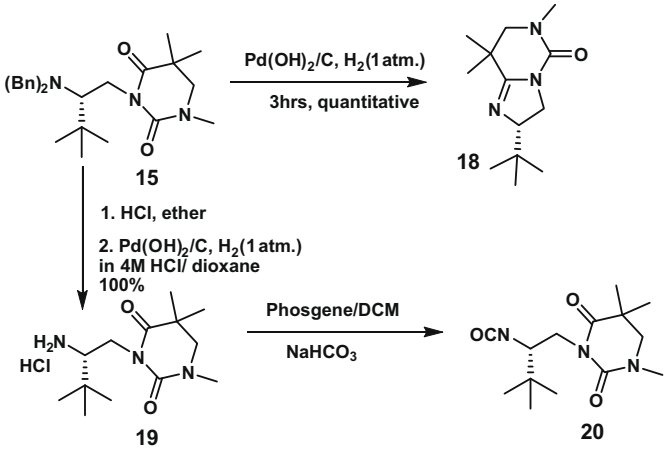
**Figure 2.** Minimum energy configuration of **11**.




Scheme 4.

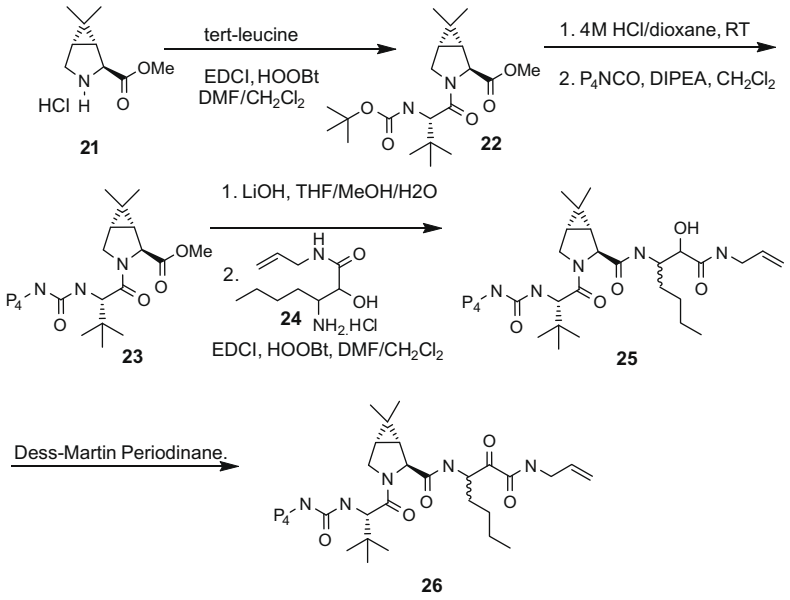



Scheme 5.



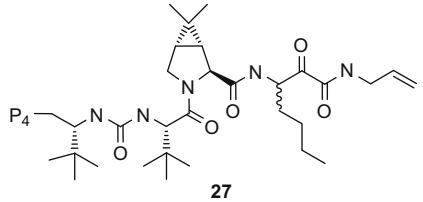

Scheme 6.

Compounds bearing these moieties were active against the HCN NS3 Serine protease. Biological activities of representative examples are given in Table 1.




**Scheme 7.** Synthesis of the P3-capped tetrahydrodioxo pyrimidines.

**Table 1**
Dioxo tetrahydro pyrimidine analogs as HCV NS3 protease inhibitors



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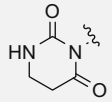
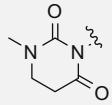
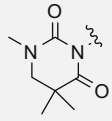
| Compound | P4 | $K_i^*$ (nM) | $IC_{90}$ (nM) | HNE/HCV |
|---|---|---|---|---|
| **28** |  | 4 | 150 | 4300 |
| **29** |  | 7 | 60 | 1400 |
| **30** |  | 92 | NA | 180 |

Inhibitors **28**, **29**, and **30** were synthesized according to the general Scheme 7. The gem-dimethyl proline derivative **21** was prepared by a modified published procedure.[20] **21** was coupled to the P3N-Boc *tert*-leucine[21,22] followed by acidic deprotection of the Boc and subsequent coupling with the P4 isocyanate to afford the P4 methyl ester **23**. Hydrolysis of the methyl ester **23** with LiOH to the corresponding acid followed by coupling to the norleucine allyl amide derivative **24** under EDCI, HOOBt conditions gave the hydroxy allyl amide intermediate **25**. This upon oxidation with Dess–Martin Periodinane afforded the keto amide of type **26**.

All inhibitors were tested in the HCV continuous enzymatic assay[23] using the NS4A-tethered single chain NS3 serine protease.[24] The $K_i^*$ values reflected the equilibrium constant determined by the reversible covalent bond formed between the ketone and serine and other interactions between the inhibitors and the enzyme.[25] The concentration required for inhibition of 90% of virus replication, $EC_{90}$, was obtained as a measure of replicon cellular potency.[26] Inhibitors were tested for the activity against one of the most structurally closely related serine protease, human neutrophil elastase (HNE) to determine the selectivity between HCV and HNE.

In conclusion we have developed a convenient and efficient way to synthesize sterically hindered substituted dioxo tetrahydro pyrimidines from amines. In our efforts toward the backup of our clinical candidate[22] (Boceprevir) in the HCV therapeutic area, we have identified a novel class of compounds with dioxo tetrahydro pyrimidines at the P4 area. Most of these analogs showed four to sixfold improvement in the in vitro potency.

## Acknowledgments

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18. *Experimentals and NMR for* **6** *and* **7**: To the amine (1 g, 4.6 mmol) dissolved in THF (20 mL) were added the ethyl isocyanato acetate (987 mg, 6.9 mmol) and triethyl amine(2.78 g, 27.6 mmol) at room temperature and then heated at 80 °C for overnight. The solvent and the volatiles were evaporated off and the crude product (urea **5**) was used for next step without purification. The urea **5** was dissolved in THF (10 mL) and NaH was added (3.68 g, 9.2 mmol, 60% in mineral oil) at room temperature under nitrogen atmosphere and stirred for 5 h at the same temperature. The reaction mixture was quenched with cold water, extracted with ethyl acetate, washed with brine, and dried over anhyd sodium sulfate. The solvent was filtered and evaporated off. The crude product was purified via flash column (10–40% ethyl acetate–hexane) to isolate **6** (1.16 g, 3.7 mmol) as an amorphous white solid.: $^1$H NMR (300 MHz, $CDCl_3$-$d_6$) $\delta$ 5.86 (br s, 1H), 4.56 (d, $J$ = 10.98 Hz, 1H), 3.89–3.84 (m, 2H), 3.73–3.63 (m, 1H), 3.36–3.32 (m, 2H), 2.72–2.64 (m, 2H), 1.38 (s, 9H), 0.95 (s, 9H).;$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 169.48, 156.21, 154.91, 78.59, 57.62, 40.33, 35.43, 33.89, 31.75, 28.44, 26.47. Compound **6** (790 mg, 2.52 mmol) was dissolved in DMF(5 ml) and Cesium carbonate(1.23 g, 3.78 mmol) was added to it at room temperature under nitrogen atmosphere. The mixture was cooled down to ice temperature and MeI (0.784 mL, 12.6 mmol) was syringed out to this. It was stirred for overnight allowing the temperature to rise to room temperature. The mixture was diluted with ethyl acetate (100 mL), washed with water (25 mL × 3) and with brine (20 mL × 2), and dried over anhyd sodium sulfate. The solvent was filtered and evaporated off. The crude product was purified via flash column (10–40% ethyl acetate–hexane) to isolate **7** (808 mg, 98%) as a white solid.: $^1$H NMR (300 MHz, $CDCl_3$-$d_6$) $\delta$ 4.62 (d, $J$ = 10.98 Hz, 1H), 3.87–3.83 (m, 1H), 3.62–3.60 (m, 1H), 3.59–3.57 (m, 1H), 3.28–2.26 (m, 2H), 3.00 (s, 3H), 2.66–2.64 (m, 2H), 1.38 (s, 9H), 0.98 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.99, 162.19, 156.11, 78.39, 57.69, 42.94, 41.12, 36.48, 35.91, 35.37, 33.79, 31.59, 31.42, 28.41, 26.38, 26.18.
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