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Novel Spirocyclic Pyrrolidones as P2/P1 Mimetics in Potent Inhibitors of HIV-1 Protease

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Abstract—We have developed concise and efficient syntheses of novel spirocyclic pyrrolidones **1**–**3**, which involve the alkylation of pyrrolidone precursor **13** with 1,5-dibromopentane, **16** and **15**, followed by an in situ lactamization. Conjugates of **1** and **2** with P1′/P2′ hydroxy-indanolamine moiety resulted in novel and potent inhibitors of HIV-1 protease **25** and **26**, suggesting that **1** and **2** are novel P2/P1 HIV-PI mimetics.

Highly Active Antiretroviral Therapy (HAART) employs various cocktails of reverse transcriptase and HIV-1 protease inhibitors (PI). Although several PIs, including Amprenavir[1] and Indinavir[2] have been deployed in HAART, there is a continued need for new entities with improved physical properties, potency, viral resistance, and safety.

Our laboratory has been involved in syntheses of such PIs, and in this Letter we would like to describe novel and potent HIV-protease inhibitors, which are based on an unprecedented spirocyclic pyrrolidone scaffold, exemplified by **1**–**3** (Fig. 1). We have designed this scaffold to incorporate hybrid features of the two other, recently disclosed P2/P1 PI mimetics **4** and **5**.[3–7] The spirocyclic morpholinone **4**, when combined with a sulfonamide P1′/P2′ fragment, yielded a potent HIV-protease inhibitor **6** ($K_i = 1.7$ nM, Fig. 2).[3,6,7] Similarly, the combination of pyrrolidone **5** with a sulfonamide P1′/P2′ fragment as well as with a hydroxy-indane P1′/P2′ fragment yielded potent HIV-1 protease inhibitors **7** ($K_i = 0.8$ nM) and **8** ($K_i = 0.05$ nM, Fig. 2), respectively.[3–5]

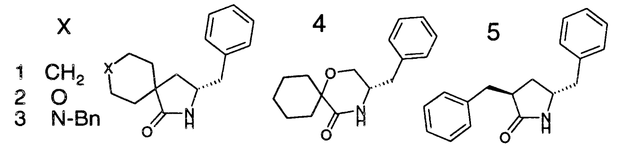

Figure 1. Spirocyclic pyrrolidone P2/P1 mimetics **1**–**5**.

Based on the known monoalkylation of *N*-benzyl-pyrrolidone and bisalkylation of *N*-alkyl pyrrolidone [8,9] we attempted to bis-alkylate the (5*R*)-5-benzylpyrrolidin-2-one with 1,5-dibromopentane, but detected no desired product **1**. We also attempted to synthesize **1**–**3** by alkylating Boc-protected lactam **9**[3] with 1,5-dibromopentane (Fig. 3) under the conditions we successfully developed towards the benzyl-derivative **5**,[4] but the resulting mixture of mostly intractable products contained no desired spirocyclic pyrrolidone **10**.

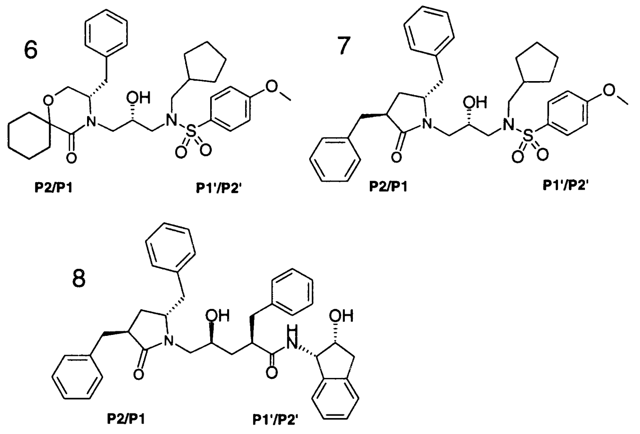

Figure 2. Structures of the sulfonamide- and hydroxy-indane based inhibitors **6**–**8**.

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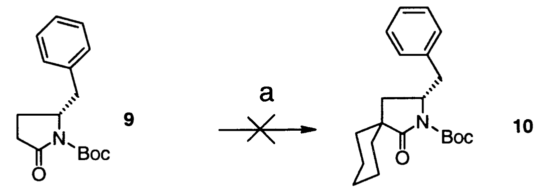

Figure 3. (a) LHMDS −78 °C, 1,5-dibromopentane.

Since bis-alkylation of *N*-acyl pyrrolidones has only been described for reactive benzylic electrophiles,[10] in conjunction with our own results we concluded that more reactive nucleophile was required. We envisioned that the anion of methyl (4*R*)-4-[(*tert*-butoxycarbonyl)amino]-5-phenylpentanoate **11** (Fig. 4) might serve as a highly reactive pyrrolidone precursor. Further chemical plans, following successful bis-alkylation with 1,5-dibromopentane, included the deprotection of Boc group with acids and cyclization of products to target lactam **1** under basic conditions. Accordingly, we synthesized **11** and then generated its lithium anion and subjected it to alkylation with 1,5-dibromopentane. We observed a complete consumption of starting materials, but careful examination of a complex mixture of products revealed formation of only minor amounts (5%) of the target spiro-pyrrolidone **1**. The major product in this reaction was identified as the methyl ester **12** (40% yield, Fig. 4), possibly arising from intramolecular attack of the enolate on the *tert*-butylcarboxy protecting group.[11]

Based on this result, we decided to increase the steric bulk in the hope of favoring the alkylation over cyclization to carboxy-lactam of the type **12**. Using similar chemistry we developed towards **11**, we then designed and synthesized the *tert*-butyl (4*R*)-4-[(*tert*-butoxycarbonyl) amino]-5-phenylpentanoate **13** as substrate for bis-alkylation (Fig. 5).[12] Rewardingly, the alkylation of **13** with the 1,5-dibromopentane resulted in the formation of the desired pyrrolidone **1** in 50% yield (Fig. 5, entry 3), which was consistent with the proposed design rationale. The only other major byproduct identified was the cross-linked bis-lactam **14** (40%).[13]

Encouraged by this result, we subjected **13** to additional alkylations with *N*-benzyl-bis-*N*-(iodoethyl) amine **15** and bis-*O*-(iodoethyl) ether **16** (entries 1 and 2, Fig. 5), in order to synthesize the spirocycles **2** and **3**. These analogues incorporated predictions from molecular modeling, that heteroatoms in the six-membered ring in **2** and **3** might develop additional H-bonding interactions with the S2 pocket of HIV-1 protease, while improving overall solubility. In both cases, significant amounts of the desired spiro-pyrrolidinones **2** and **3** were formed, but we also isolated Boc-protected **17** and **18**, and their uncyclized precursors **19** and **20**. In addition, variable amounts (0–40%) of the cross-linked **21** and **22** were isolated. Products **18** and **20**, obtained from **16**, as well as products **17** and **19**, obtained from **15**, afforded additional quantities of **2** and **3**, respectively, upon workup.[13] The use of diiodopentane (entry 4, Fig. 5) as the alkylating agent met with even greater success, affording a 70% combined yield of the desired spirocycle **1**, after quantitative conversion of **23** into **1**.

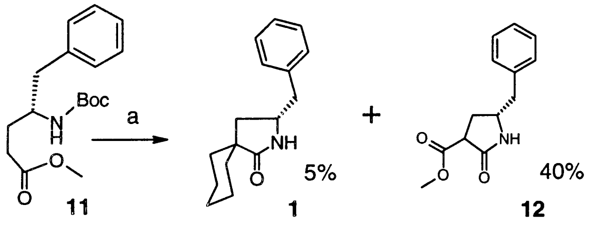

Figure 4. (a) LHMDS, 1 equiv **13** at −78 °C, 45 min. Then continue overnight at ambient temperature.

While further optimization of this chemistry is beyond the scope of this report, yields of the desired products **1**–**3** can in principle be improved by adjusting reaction times and temperatures. Formation of the undesired cross-linked products **14**, **21**, and **22** might be minimized under high dilution or by further increasing the reactivity of electrophile.

In summary, we discovered a novel, one-pot procedure towards the previously unreported spiro-lactams **1**–**3**. When coupled to epoxide-indolamine P1/P2 **24**, both **1** and **2** resulted in potent HIV-1 PIs **25** and **26** ($K_i = 50$ and 23 nM, respectively, Fig. 6).[14] *N*-Benzyl substituted spiro-pyrrolidinone **3** produced a weak inhibitor **27** ($K_i = 2.5$ uM), presumably due to steric interactions of N-Bn with the S2 site in HIV-1 protease. Molecular modeling of these inhibitors docked to HIV-PR active site suggests that P2 moiety in spirolactams **1** and **2** may be further chemically manipulated in order to improve the HIV-1 protease inhibitory potency.

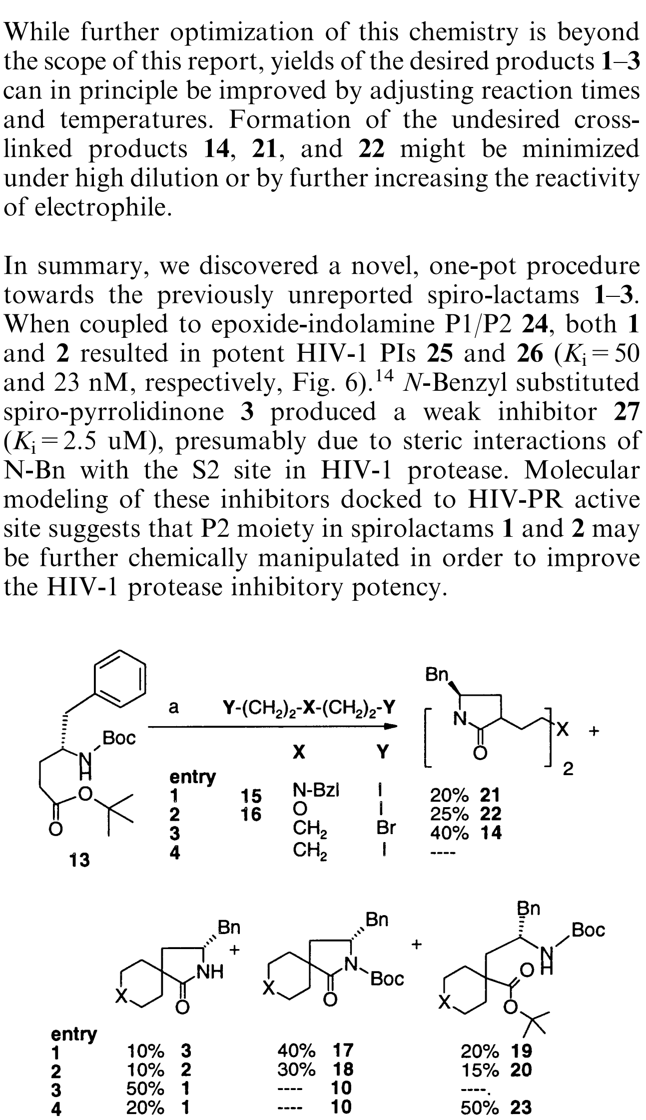

Figure 5. (a) THF, 3 equiv LHMDS −78 °C, 1 equiv alkylating agent 45 min at −78 °C, then 17 h at rt.

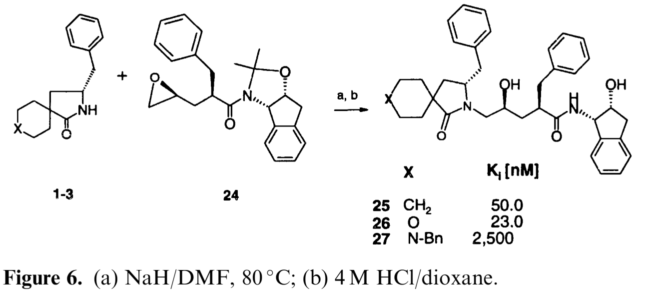

Figure 6. (a) NaH/DMF, 80 °C; (b) 4 M HCl/dioxane.

Acknowledgements

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12. Synthesis of **13**: *tert*-butyl diethylphosphonoacetate (16.9 g, 80.22 mM) in 20 mL of THF was cooled to 0 °C and added NaH (2.11 g, 88.2 mM) portion-wise. After 30 min. at rt, the solution was cooled down to 0 °C and added Boc-Phe(al) (20.0 g, 80.2 mM). The reaction was then continued for 1.5 h at rt, added 200 mL of dioxane and Pd.C (10%, 0.5 g), and hydrogenated for 24 h at 30 psi. ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 5H), 4.42 (m, 1H), 3.79 (m, 1H), 2.79 (m, 2H), 2.24 (t, 2H, $J = 7.4$ Hz), 1.78 (m, 1H), 1.57 (m, 1H), 1.42 (s, 9H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.8, 152.3, 134.8, 126.4, 125.2, 123.2, 77.3, 76.0, 48.6, 38.8, 29.3, 25.9, 25.3, 25.0. MS: m/z 372.2 (M + Na).
13. Synthesis of **1**. Intermediate **13** (1.228 mM, 0.377 g) in THF (8 mL) was added 3 equiv of LHMDS (1 M in THF, 3.68 mM, 3.68 mL) at −78 °C. After 45 min at −78 °C, 1 equiv of 1,5-dibromopentane (1.228 mM, 0.282 g) in THF (5 mL) was added, and the reaction was allowed to proceed at room temperature for 17 h, and then quenched with 10% aqueous citric acid. Aqueous work-up, followed by C_{18} RP-HPLC purification afforded 149 mg of **1** (0.614 mmol, yield 50%). ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 5H), 3.87 (m, 1H), 2.81 (m, 2H), 2.26 (m, 1H), 1.8–1.2 (11H); ^{13}C NMR ($CDCl_3$) δ 184.2, 136.9, 129.0, 128.9, 127.1, 54.2, 46.0, 43.0, 37.7, 33.9, 31.9, 25.2, 22.1, 22.0. MS m/z 244.2 ($M + H^+$).

   Synthesis of **2**. Synthesized as above except that bis-*O*-iodoethyl ether was used (1.26 g, 1 equiv). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.79 (s, 1H), 7.22 (m, 5H), 3.73 (m, 3H), 3.24 (m, 2H), 2.88 (dd, 1H, $J = 4.8$, 13.4 Hz), 2.57 (dd, 1H, $J = 8.4$, 13.4 Hz), 2.03 (m, 1H), 1.76 (m, 1H), 1.55 (m, 2H), 1.22 (m, 1H), 1.01 (m, 1H). MS m/z 246.2 ($M + H^+$).

   Synthesis of **3**. Synthesized as above, except that additional treatment with 1:1 (v/v) DCM/TFA (40 mL) was needed to convert **17** into **3**. *N*-benzyl-*N*-bis-iodoethane (5.5 g, 13.25 mmol) was prepared from the *N*-benzyl-*N*-bis-chloroethane via Finkelstein reaction. ^{1}H NMR ($CDCl_3$, 300 MHz) of **3** (TFA salt) δ 7.30 (m, 10H), 5.85 (m, 1H), 4.16 (m, 2H), 3.86 (m, 1H), 3.68 (m, 1H), 3.36 (m, 3H), 2.88 (dd, 1H), 2.62 (dd, 1H), 1.7–2.2 (m, 6H). MS m/z 335.2 ($M + H^+$).
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