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trans-(3*S*,4*S*)-Disubstituted pyrrolidines as inhibitors of the human aspartyl protease renin. Part I: Prime site exploration using an amino linker

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ABSTRACT

Recently, we reported on the discovery of (3*S*,4*S*)-disubstituted pyrrolidines (e.g., **2**) as inhibitors of the human aspartyl protease renin. In our effort to further expand the scope of this novel class of direct renin inhibitors, a new sub-series was designed in which the prime site substituents are linked to the pyrrolidine core by a (3*S*)-amino functional group. In particular, analogs bearing the corresponding sulfonamide spacer (**50**, **51** and **54a**) demonstrated a pronounced increase in in vitro potency compared to compound **2**.

Chronic elevation of systemic blood pressure increases the risk for cardiovascular diseases, such as congestive heart failure, stroke and myocardial infarction. Moreover, hypertension is the most important cause of death in the Western world.[1] The Renin–Angiotensin–Aldosterone-System (RAAS)[2,3] has been recognized as a key pathway in the regulation of blood pressure. Specific inhibition of the aspartyl protease renin[4,5] which catalyzes the first and rate limiting step of the RAAS by cleaving angiotensinogen to angiotensin-1 may offer a beneficial therapeutic profile[6–9] as compared to previously marketed RAAS hypertension therapies.[10] This notion has triggered vast efforts at a number of pharmaceutical companies to identify low molecular weight direct renin inhibitors (DRI)[11,12] suitable for clinical development. Aliskiren[13,14] (**1**, Tekturna/Rasilez®, Fig. 1) demonstrated efficacious reduction in mean arterial blood pressure over 24 h after once-daily oral dosing with a placebo like safety and tolerability profile and has been approved (2007) as the first and only marketed DRI for the treatment of hypertension.

We have recently reported on the discovery of a novel class of DRI related to the 3,4-disubstituted pyrrolidine structure **2** (Fig. 1).[15,16] This highly selective and orally bioavailable renin inhibitor with moderate on-target activity was considered a reasonable starting point for further lead optimization.

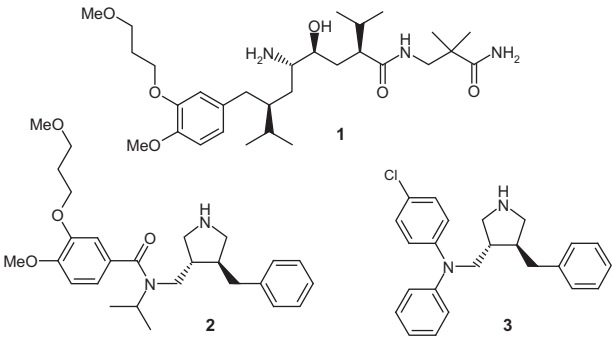

Figure 1. Structures of aliskiren (**1**), the pyrrolidine-based lead inhibitor **2** and the in silico pharmacophore search hit **3**.

Inhibitor **2** (recombinant human (rh)-renin IC_{50} = 0.17 μM) was designed by combining the central basic scaffold of the in silico pharmacophore search hit **3** (IC_{50} = 7.6 μM) with an optimized P1–P3–P3sp motif derived from **1**.[17] However, historical knowledge related to ligand/renin interactions indicated that the benzyl motif is likely suboptimal to be accommodated in the S1′ pocket.[17b]

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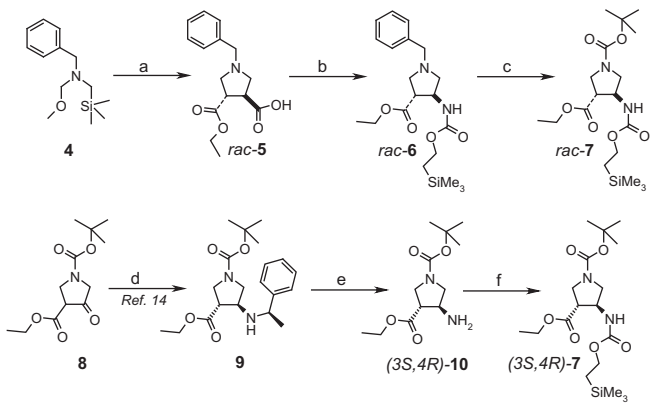
Moreover, inhibitor **2** is not addressing the S2′ binding region of the renin active site which is recognized as important for potency. Hence, our attention focused on the replacement of the benzyl portion of **2** and the identification of a suitable linker allowing rapid derivatization and renin prime site interrogation. Modeling experiments indicated that a 3-amino-linker[18] potentially forming an H-bond with catalytic Asp_{215} could serve this purpose. Herein we report our progress toward the identification of potent 3-amino pyrrolidine-type renin inhibitors by prime site optimization of the lead compound **2**.

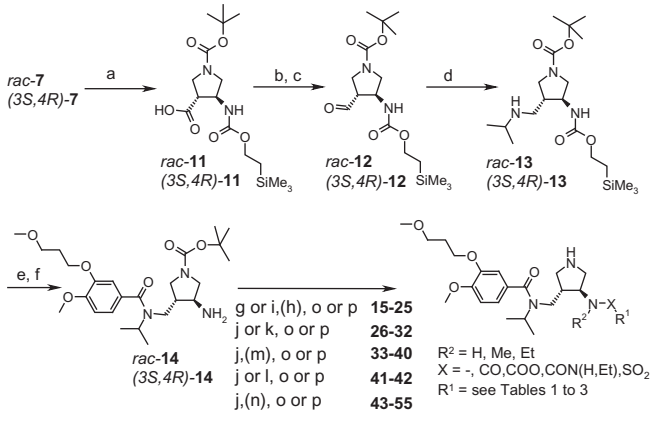
Efficient synthesis[19] of the target compounds via the key double-protected racemic or enantiomerically pure pyrrolidine intermediates (*rac*)-**13** and (3*S*,4*R*)-**13** providing flexible access to various prime and non-prime site modifications were established, as outlined in Schemes 1 and 2.

The synthesis of (*rac*)-**13** started with the assembly of the *trans*-configured pyrrolidine scaffold by 1,3-dipolar cycloaddition[20] of commercial *N*-benzyl-*N*-(methoxymethyl)-trimethyl silyl methyl amine (**4**) and ethyl fumarate in the presence of TFA, followed by Curtius rearrangement of the carboxylic acid (*rac*)-**5** and in situ trapping of the isocyanate intermediate with trimethylsilylethanol to afford the Teoc-protected 3-amino-pyrrolidine derivative (*rac*)-**6**. Reductive debenzylation and concomitant *N*-Boc protection furnished intermediate (*rac*)-**7**. Enantiomerically pure (3*S*,4*R*)-**7** was prepared in three steps from known racemic β-ketoester **8**[21] by diastereoselective reductive amination to (3*S*,4*R*)-**9**[22] using the procedure described by Gellman.[23] This was followed by hydrogenolytic removal of the α-methyl benzyl chiral auxiliary and Teoc protection of the resulting 3-amino group (Scheme 1).



Scheme 1. Reagents and conditions: (a) Mono ethyl fumarate, TFA, CH_2Cl_2, RT, quant.; (b) DPPA, Et_3N, $HOCH_2CH_2SiMe_3$, dioxane, reflux 48 h, 48%; (c) H_2, $Pd(OH_2)$, $(Boc)_2O$, EtOH, 5 h, 71%; (d) (1) (*R*)-(+)-alpha-methylbenzylamine, AcOH, EtOH, RT, then $NaBH_3CN$, 75 °C, 15 h, (2) recrystallization of the HCl salt from CH_3CN, 20%; (e) H_2, Pd/C 10%, EtOH; (f) Teoc-Osuc, Et_3N, dioxane, 95% for 2 steps.

Intermediates (3*S*,4*R*)-**7** and (*rac*)-**7** were further elaborated to the final inhibitor compounds (Tables 1–3) according to the sequence described in Scheme 2. The ester function of (3*S*,4*R*)-**7** and (*rac*)-**7** was saponified and the resulting acid intermediates (*rac*)-**11** and (3*S*,4*R*)-**11** were reduced with borane dimethyl sulfide complex to the corresponding alcohols, followed by Dess–Martin periodinane oxidation to the aldehydes (3*S*,4*R*)-**12** and (*rac*)-**12**. Reductive amination using isopropylamine yielded the key intermediates (*rac*)-**13** and (3*S*,4*R*)-**13**, which were subsequently coupled with the appropriate acids[19] to afford after Teoc deprotection the corresponding 3-amino pyrrolidine intermediates (*rac*)-**14** and (3*S*,4*R*)-**14**. The various prime site linker functionalities including a *N*-alkyl, carboxamide, carbamate, urea, and a sulfonamide spacer group, were introduced by using standard reaction protocols. For example, *N*-alkyl pyrrolidine derivatives (**15**–**19**, **21**, **22**, **24** and **25**) were prepared from (*rac*)-**14** and (3*S*,4*R*)-**14** by reductive amination using the respective aldehyde or ketone, followed by Boc-deprotection under acidic conditions. In the case of **24** and **25**, the syntheses of the aldehyde precursors have been reported previously.[19] Compound **20** was derived from the *N*-Boc protected precursor of **19** by reductive amination with formaldehyde followed by Boc-deprotection. **23** was prepared by alkylation of (*rac*)-**14** with 2-bromomethyl naphthalene. Amides **26**–**32** were obtained by coupling reaction of amine **14** with the appropriate acid or acid chloride, and carbamates **33**–**37**, **39**, **40** were prepared by reaction with the desired chloroformate and subsequent Boc-deprotection. The *N*-methylbenzyl carbamate analog **38** was derived from the corresponding Boc-protected precursor of **37** by alkylation with methyl iodide using sodium hydride as a base. Ureas **41** and **42** were generated by reaction with benzylisocyanate or *N*-ethylbenzyl carbamoylchloride and subsequent Boc removal. Finally, the 3-amino sulfonamide derivatives **43**–**55** (Table 3) were readily prepared by reaction of amine **14** with the appropriate commercially available sulfonyl chloride, followed in one case by an alkylation step (**55**), and final removal of the Boc-protecting group. All inhibitors were assayed as their corresponding HCl salts against purified rh-renin using a FRET assay format.[15]



Scheme 2. Reagents and conditions: (a) LiOH 1 N, MeOH; (b) BH_3Me_2S, THF, −10 °C to RT, 52% (2 steps); (c) Dess–Martin periodinane, wet CH_2Cl_2, 70%; (d) diisopropylamine, $NaBH(OAc)_3$, 1,2-dichloroethane, RT, 91%; (e) 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid, BOP-Cl, NEt_3, CH_2Cl_2, RT, 98%; (f) Et_4NF, CH_3CN, reflux 4 h, 68%; (g) R^1CHO or R^1R^2CO, $NaBH(OAc)_3$, 1,2-dichloroethane, RT; (h) HCHO, $NaBH(OAc)_3$, 1,2-dichloroethane, RT, 86%; (i) (2-bromomethyl)naphthalene, Na_2CO_3, DMF, RT; (j) R^1SO_2Cl, R^1COCl, R^1OCOCl or $R^1N(Et)COCl$, Et_3N, CH_2Cl_2, RT; (k) R^1COOH, HOBt, EDCI, CH_2Cl_2, RT; (l) $PhCH_2NCO$, CH_2Cl_2, RT; (m) MeI, NaH, THF, RT, 82%; (n) MeI, K_2CO_3, DMF, 80 °C, 52%. (o) 4 N HCl/dioxane, RT; (p) TFA, CH_2Cl_2, RT.

The in vitro IC_{50} results for the prime site alkylamine analogs **15**–**25** are summarized in Table 1. Compounds **15**–**23** were tested as racemic mixtures and **2**, **23a**, **23b**, **24** and **25** were tested as single enantiomers. Compound **15** bearing an isopropyl substituent was found to be slightly less active than **2**, while analogs bearing larger cycloalkyl (**16**, **17**), methylene cycloalkyl (**18**) and benzyl (**19**) prime site motifs displayed potency comparable to **2**. These findings were considered to validate our strategy of introducing a basic 3-amino linker to the pyrrolidine scaffold in order to extend into the renin prime site. The predicted binding mode for compound **19** placed the benzyl motif in the S2′ pocket suggesting that introduction of a methyl substituent at the nitrogen atom (**20**) or in the benzylic position (**21**) would fill the S1′ pocket. Unfortunately, the potency of **20** and **21** was significantly lower compared to the unsubstituted analog (**19**). Replacing the benzyl by a phenethyl group (**22**) retained the in vitro potency, and introduction of a 2-naphthylmethyl group (**23**) designed to penetrate deeper into S2′ led to a significant 5-fold improvement in potency. The two