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The synthesis and conformational analysis of amino acid–tetrahydroanthranilic acid hybrids

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ABSTRACT

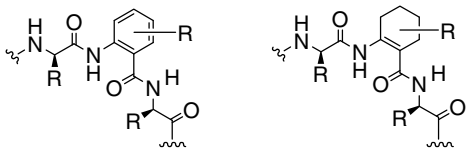
The optimization of a palladium-catalyzed amidation reaction providing a new class of amino acid–tetrahydroanthranilic acid derivatives has been achieved. The scope of the reaction and preliminary conformational analysis of the resulting series of molecules is discussed.

With distinct advantages over peptide-based therapeutics, anthranilic acid containing peptides (**1**) have found general utility as biologically active molecules in a number of drug discovery programs.[1]

Despite the broad interest in peptides containing an anthranilic acid moeity, the functionally similar tetrahydroanthranilic acid (THA)–peptide hybrids (**2**) have received no attention. Previously, we have described the design and discovery of tetrahydroanthranilic acid (THA) as a bioisosteric replacement of anthranilic acid within a series of GPR109A niacin receptor agonists.[2] As part of an effort to identify new classes of peptidomimetics that might enable drug discovery, we became interested in exploring the potential of THA-containing peptides as surrogates to the ubiquitious anthranilic acid embedded peptides. Most notably, we were interested in determining whether the hydrogen bond central to the chemical stability and conformational rigidity of anthranilic acid embedded peptides was also present in the THA-containing derivatives (Fig. 1).

With this goal in mind, we searched for a proficient synthetic route toward this class of molecules. Surprisingly, we found that traditional amide coupling techniques provided low yields of the desired THA-derived peptide products and required long reaction time periods.[3]

Recent advances in palladium-catalyzed amidation reactions have provided alternative methods for the construction of amide bonds.[4] Despite a considerable amount of work in this area, the use of an amino acid-derived amide as a coupling partner has not been explored. With only modest success employing traditional amide coupling methods, we became interested in constructing our THA–amino acid hybrids using a palladium-catalyzed amidation reaction. Our initial efforts, employing conditions developed by Klapars and coworkers, were quite promising. The



1 **2**

Figure 1. Anthranilic acid (**1**) and THA (**2**) containing peptides.

reaction of commercially available *N*-Boc protected alanine **3** with vinyl triflate **4**, in the presence of $Pd_2(dba)_3$, xantphos,[5] and Cs_2CO_3 provided the desired tetrahydroanthranilic ester **5** in 63% isolated yield in 4 h (Table 1, entry 1).

Optimization of the reaction conditions, employing 2 equiv of triflate and 1 equiv of the amide, provided the desired product **5** in an improved 97% isolated yield (Table 1, entry 3).[6] Further investigations showed that lower catalyst loadings and lower temperatures could be accommodated, albeit with slightly lower yields (Table 1, entries 4–7). Finally, control experiments showed that both the palladium catalyst and the xantphos ligand are required for the reaction to occur (Table 1, entries 8–10).

Using our optimized reaction conditions, we began exploring the scope of the reaction by modifying the nitrogen protecting group on the amino amide coupling partner. As shown in Table 2, synthetically useful yields of the coupled products were obtained using a variety of traditional N-protected amino amides: *N*-Cbz (**19**, 90%), *N*-Ac (**20**, 47%), and *N*-Fmoc (**21**, 66%).

The functional group tolerance of the coupling reaction was investigated by screening a series of Boc-protected amino amides. The use of phenyl and naphthyl-substituted amino amides **9** and **10** resulted in formation of the desired products in high yields, 90% and 83%, respectively. Whereas the coupling of the more sterically encumbered biphenyl derivative **11** afforded the product **24** in a slightly lower yield (68%). Heteroaromatic amino amides

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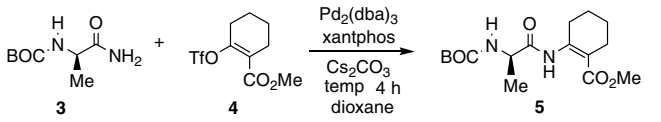
Table 1
The palladium-catalyzed amidation of amino amides



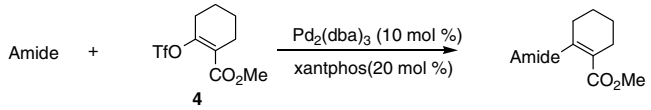
Entry	**3** (equiv)	**4** (equiv)	Temp (°C)	$Pd_2(dba)_3$[a]	Xantphos[a]	**5** Yield[b] (%)
1	1	1	80	10	20	63
2	2	1	80	10	20	76
3	**1**	**2**	**80**	**10**	**20**	**97**
4	1	2	80	5	10	83
5	1	2	80	2	5	72
6	1	2	50	10	20	78
7	1	2	rt	10	20	65
8	1	2	80	—	20	—
9	1	2	80	10	—	—
10	1	2	80	—	—	—

[a] mol %.
[b] Isolated yields after chromatography.

12 and **13** were proficient coupling partners under our conditions, providing good yields of the desired products, 87% and 78%. In contrast, the coupling with tryptophan derivative **14**, containing an unprotected indole moeity, afforded only 31% of the desired product **27**.[7] A free carboxylic acid was also tolerated under the reaction conditions. The palladium-catalyzed coupling of triflate **4** to glutamic acid derivative **15** provided the desired product **28** in 54% isolated yield.

Having discovered a general and functional group- tolerant method for the synthesis of THA-containing amino acid derivatives, we became interested in extending this methodology toward the synthesis of THA-embedded peptide molecules. With this goal in mind, we investigated the utility of the palladium-catalyzed amidation reaction in coupling larger peptide-based amide fragments. The coupling of dipeptide **16** in the presence of vinyl triflate **4** afforded the corresponding peptide–THA hybrid **29** in 77% yield. Under the same reaction conditions, tripeptide **17** coupled to give the desired product **30** in 71% yield. We were pleased to see that neither the size of the peptide nor the dense functionality seemed

Table 2
Coupling of amino amides and enol-triflates[a]



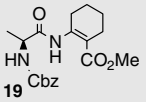
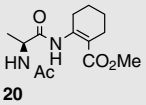
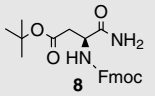
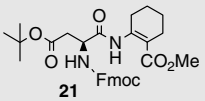
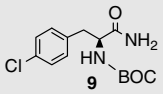
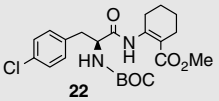
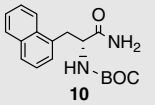
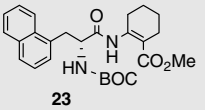
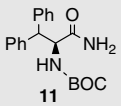
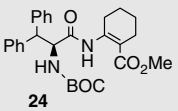
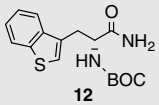
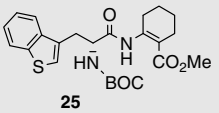
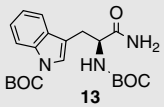
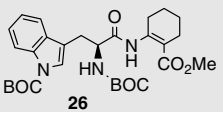
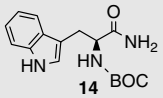
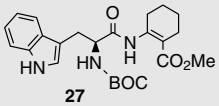
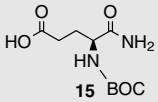
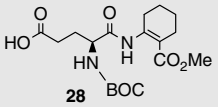
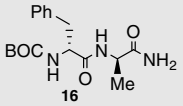
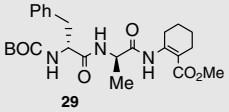
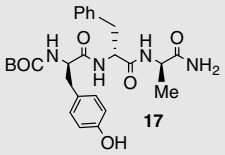
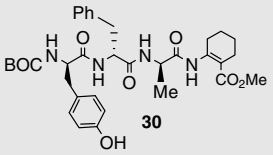
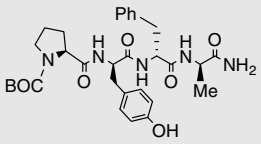
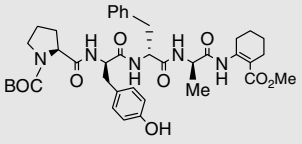
Entry	Amide	Product	Yield[b] (%)
1	 **6**	 **19**	90
2	 **7**	 **20**	47
3	 **8**	 **21**	66
4	 **9**	 **22**	90
5	 **10**	 **23**	83
6	 **11**	 **24**	68
7	 **12**	 **25**	87
8	 **13**	 **26**	78

Table 2 (*continued*)

Entry	Amide	Product	Yield[b] (%)
9	 **14**	 **27**	31
10	 **15**	 **28**	54
11	 **16**	 **29**	77
12	 **17**	 **30**	71
13	 **18**	 **31**	75

[a] Reagents and conditions: enol triflate 2.0 equiv, amide 1.0 equiv, Cs_2CO_3 2 equiv, 1 M in dioxane, at 80 °C for 4 h.
[b] Isolated yields after chromatography.

to effect the efficiency of the reaction. Finally, tetrapeptide **18**, the largest and most functionally diverse coupling partner employed in this reaction, effectively coupled to vinyl triflate **4**, affording the desired product **31** in a 75% isolated yield.

With access to a variety of stereochemically and functionally diverse amino acid and peptide-based THA-containing molecules, we sought to establish whether these compounds pre-organize into conformations similar to those observed with the corresponding anthranilic acid derivatives.[1] Most importantly, we hoped to verify that the backbone hydrogen bond observed in peptide anthranilic acid peptidomimetics was also present in the THA-containing amino acid derivatives.[8]

Toward this end, we obtained an X-ray crystal structure of compound **5**. As shown in Figure 2, the 1.9 Å bond distance between O(4) and N(1)H suggests that the preferred conformation of the amino acid–THA hybrid does indeed conserve this distinct hydrogen bond, similar to that observed with the anthranilic acid moeity.[9]

Further analysis of **5** in solution provided additional support for the presence of the backbone hydrogen bond. At ambient temperature, the ^{1}H NMR spectrum exists as a sharp set of unique resonances in C_6D_6. Titrating a solution of alanine derivative **5** in C_6D_6 with increasing equivalents of DMSO-d_6 causes a characteristic downfield shift of the free BOC NH_a proton. In contrast, the amide NH_b resonance is unaffected by increasing DMSO-d_6 concentrations. These chemical shift data support a solution structure for **5** in which the amide proton is involved in an intramolecular hydrogen bond[10] (Fig. 3).

In summary, we have developed a palladium-catalyzed amidation reaction employing amino acid-derived amides that allows for the construction of amino acid THA hybrid molecules. We have shown that the optimized reaction conditions are generally efficient with respect to a number of protected and unprotected amino acid-derived amides. In addition, we have showcased the functional group tolerance and convergent nature of the coupling by employing amide-terminating di-, tri-, and tetrapeptides to provide direct access to a class of THA-based peptidomimetics. Finally, preliminary studies have revealed that molecules of type **5**, both in crystalline form and in solution, contain an intramolecular hydrogen bond reminiscent of the related anthranilic acid peptidomimetics. Future investigations in this effort will continue to focus on the conformational analysis of both the amino acid and peptide-based THA hybrid molecules.

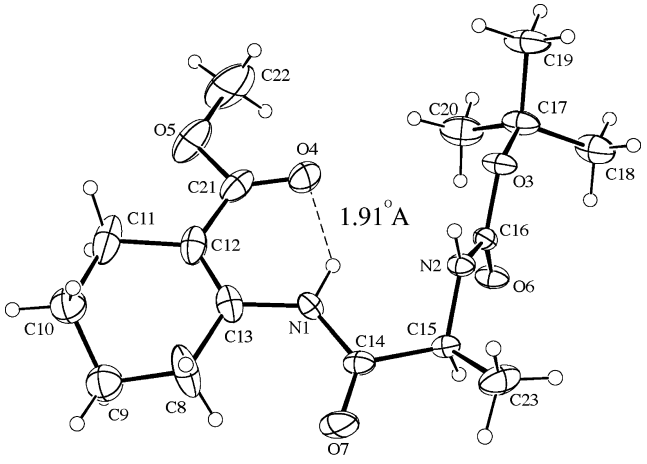
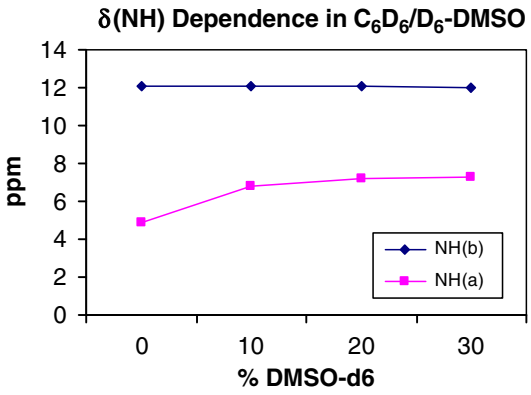
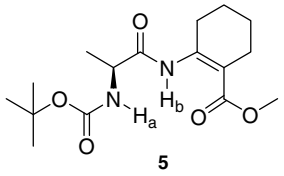


Figure 2. X-ray crystal structure of **5**.





5

Figure 3. Chemical shift data for THA **5** as a function of solvent composition (% DMSO-d_6 in C_6D_6).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.148.

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3. Standard diimide coupling employing DCC and HOBT in the presence of BOC-alanine and methyl 2-amino-1-cyclohexen-1-carboxylate provided a 32% isloated yield over a 24 h time period. Standard mixed anhydride conditions of isobutylchloroformate and NMM provided 27% yield of product over a 28 h time period.
4. (a) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104; (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048; (c) Wallace, D. J.; Klauber, D. J.; Chen, C.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749–4752; (d) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, *6*, 2433–2435; (e) Dallas, A. S.; Gotheif, K. V. *J. Org. Chem.* **2005**, *70*, 3321–3323; (f) Klapars, A.; Campos, K. R.; Chen, C.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185–1188; (g) Ganton, M. D.; Kerr, M. *Org. Lett.* **2005**, *7*, 4777–4779; (h) Van den Hoogenband, A.; Lange, J. H. M.; Iwema-Bakker, W.; den Hatrog, J.; van Schaik, J.; Feenstra, R.; Terpstra, J. W. *Tetrahedron Lett.* **2006**, *47*, 4361–4364.
5. Kamer, P. C.; van Leeuwen, P. W. N. M.; Reek, J. N. *Acc. Chem. Res.* **2001**, *34*, 895–904.
6. General procedure for the palladium-catalyzed amidation reaction: Synthesis of THA **5**. To a degassed solution of Boc-D-alanine-amide **3** (0.049 g, 0.26 mmol) in anhydrous dioxane, under nitrogen, was added triflate **4** (0.150 g, 0.52 mmol), 9,9-dimethyl-4,5-bis(di-tert-butylphosphino)xanthene (0.030 g, 0.052 mmol), cesium carbonate (0.170 g, 0.52 mmol), and tris(dibenzylideneacetone)dipalladium (0.024 g, 0.026 mmol) at room temperature. The reaction mixture was then heated to 80 °C, for 4 h. The reaction was then allowed to cool to room temperature, filtered through silica gel, and concentrated in vacuo. The residue was purified by flash chromatography (Biotage, Horizon) using (20% EtOAc/hexane) to give the desired product **5** (0.083 g, 0.54 mmol, 97%) as a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.97 (s, 1H), 5.08 (s, 1H), 4.25 (s, 1H),3.75 (s, 3H), 2.99 (m, 2H), 2.33 (m, 2H), 1.65 (m, 4H), 1.49 (s, 9H), 1.45 (d, J = 7.0 Hz, 3H);13C (125 MHz, $CDCl_3$): δ 171.8, 170.3, 155.4, 151.8, 150.6, 80.2, 51.8, 51.7, 28.7, 28.6, 24.5, 22.0, 21.8, 19.2. $[\alpha]_D^{22}$ +86.2 (*c* 1.00, HOAc). LCMS [M+Na]: *m*/*z* calcd for $C_{16}H_{26}N_2NaO_5$ 349.17, obsd 349.20.
7. The product resulting from coupling of the triflate to both the amide and the indole nitrogens was also isolated in 34% yield.
8. (a) Rae, I. D. *Can. J. Chem.* **1968**, *46*, 2589–2592; (b) Zanger, M.; Simons, W. W.; Gennaro, A. R. *J. Org. Chem.* **1968**, *33*, 3673–3675; (c) Etter, M. C. *J. Am. Chem. Soc.* **1982**, *104*, 1095–1096; (d) Mascarenhas, Y. P.; DeAlmeida, V. N.; Lechat, J. R.; Barelli, N. *Acta Crystallogr., Sect. B* **1980**, 502–504; (e) Mascarenhas, Y. P.; DeAlmeida, V. N.; Lechat, J. R.; Barelli, N. *Acta Crystallogr., Sect. B* **1980**, 502–504.
9. The crystallographic data for compound **5** have been deposited in the Cambridge Crystallographic Data Base.
10. For a discussion of the interpretation of these titration experiments, see: Venkatachalapathi, Y. V.; Venkataram Prasad, B. V.; Balaram, P. *Biochemistry* **1982**, *21*, 5502–5509.