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Synthesis of Symmetric Bis(imidazole-4,5-dicarboxamides) Substituted with Amino Acids

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Abstract: A series of symmetric bis(imidazole-4,5-dicarboxamides) (bis-I45DCs) were prepared with amino acid esters and a variety of linker groups. The critical pyrazine intermediates, substituted with amino acid esters, were synthesized by stoichiometric control of the amino acid ester, even though primary alkanamines, in comparison, generally offer less selectivity for this reaction. Diamines are added to subsequently react with and open the remaining acyl imidazole bonds in the pyrazine intermediates and thereby yield the bis-I45DCs.

There is a current need for small molecules capable of inhibiting protein−protein interactions of biological significance to be used as both biochemical tools and as potential clinical candidates for treating disease. We herein report on a series of symmetrically disubstituted bis(imidazole-4,5-dicarboxamides) (bis-I45DCs) bearing amino acid esters as part of a continuing effort to illustrate the utility of the imidazole-4,5-dicarboxylic acid as a scaffold for the synthesis of new chemical entities. These compounds were designed to present amino acid side chains in relative 3-dimensional space in order to yield functional mimics of the surface of an α-helix found in the large extracellular loop of tetraspanin CD81,[1] the putative receptor of the hepatitis C virus.[2] Disrupting protein−protein interactions with small molecules is a difficult task, yet this remains an important goal for the discovery of new therapeutic agents.[3−9]

The relative presentation of substituent groups off of a terphenyl scaffold,[10−12] an oligoamide-foldamer,[13] or a β-hairpin[14] have all been previously used to identify bioactive α-helix mimics for interacting with a variety of protein−protein interactions. The combination of conformational and structural features along with their synthetic accessibility makes the bis-I45DCs a useful scaffold. A series of bis-heterocyclic compounds have been recently synthesized from resin-bound amino acids,[15−17] further illustrating the interest in such compounds for the discovery of new chemical entities.

The bis-I45DC compounds can form intramolecular hydrogen bonds that are favored even in water.[18] Hydrogen bonds have shallow energy potentials in comparison with covalent bonds, and we think this represents an advantage of the bis-I45DCs over structurally complex and covalently bound scaffolds in the discovery of small molecule proteomimetics, as protein−protein interactions require a high degree of shape complementarity.[19] A symmetric bis-I45DC (**24**) was identified as an inhibitor of the CD81 binding interaction with the hepatitis C virus glycoprotein E2 having an EC_{50} of 38 μM.[1]

The preparation of the bis-I45DCs in this study begins with a symmetric pyrazine derivative (**1**) bearing reactive acid chloride and acyl imidazole functionalities (Scheme 1). A modified preparation of **1** has been previously reported.[20] Amino acid ester hydrochlorides or tosylate salts are capable of reacting with both functionalities in THF to thereby produce the symmetrically disubstituted I45DCs (**2**−**8**) summarized in Table 1. Dissymmetrically disubstituted I45DCs produced by two subsequent primary amine additions to **1** results in the desired product contaminated by substantial amounts of symmetrically disubstituted products. Thus, an alternate procedure to produce dissymmetrically disubstituted I45DCs in high purity was developed.[20] In contrast to the reactivity and poor selectivity of primary amines with **1**, we observed that modest yields of the symmetric amino acid ester-substituted pyrazines **9**−**14** could be obtained by addition of 2 equiv of an amino acid salt along with a base to scavenge the acid in this reaction (Table 2). The amino acid ester-substituted pyrazines are then readily opened by diamines leading to the bis-I45DCs **15**−**25** (Table 3). Compound **26** (Table 3) was prepared by catalytic hydrogenation of **25**. It is also possible to open the acyl imidazole bonds with alcohols as shown by the reaction

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(18) *N*,*N*′-Dimethylimidazole-4,5-dicarboxamide in H_2O shows two broad amide NH resonances (8.1 and 10.8 ppm) above pH ∼5.4. Below this pH value the imidazole ring is protonated part of the time, thereby disrupting the intramolecular hydrogen bond and leading to a coalesced amide NH signal. A figure of these amide chemical shifts as a function of pH is shown in the Supporting Information.
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SCHEME 1

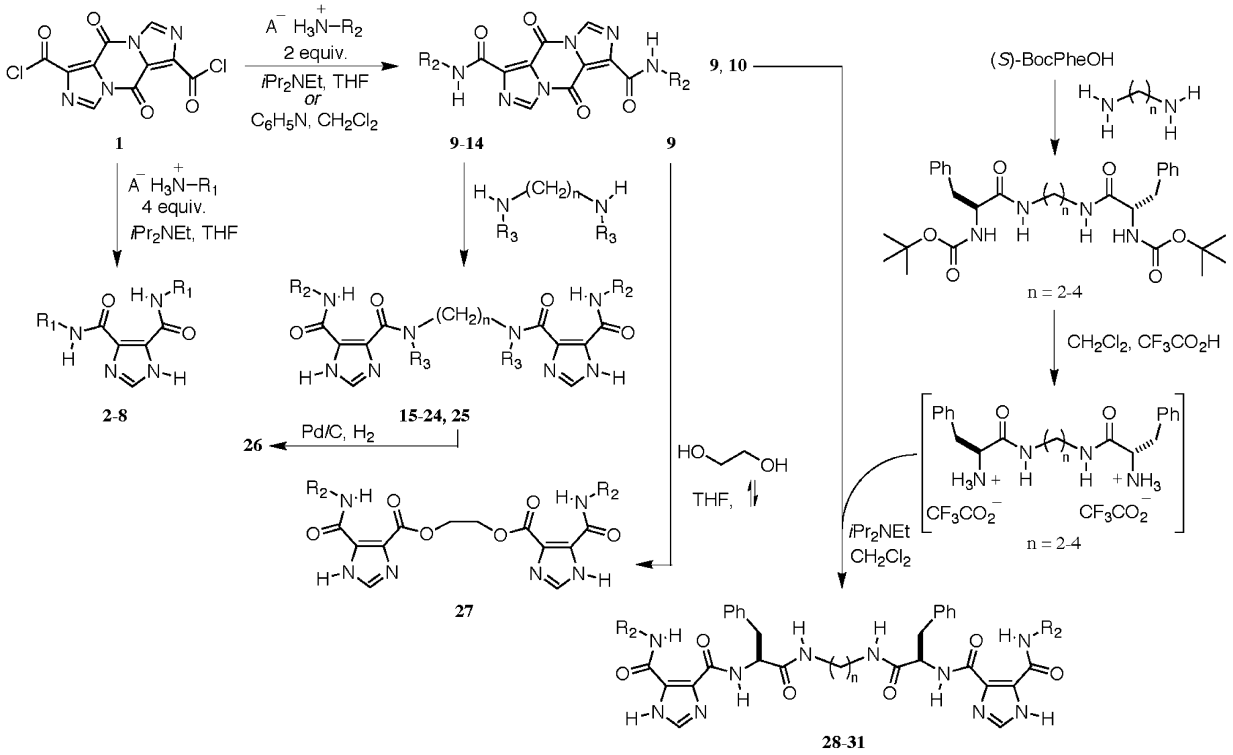

TABLE 1. Substituents and Isolated Yields of Amino Acid Ester Symmetrically Disubstituted I45DCs 2−8

compd	substitution, R_1 =	yield (%)
2	(*S*)-PheO*t*Bu	89
3	(*S*)-PheOMe	94
4	(*S*)-LeuOMe	93
5	(*S*)-ValOMe	99
6	(*S*)-AlaOMe	94
7	GlyOEt	33
8	GlyO*t*Bu	89

TABLE 2. Substituents and Isolated Yields of Amino Acid Ester Substituted Pyrazines 9−14

compd	substitution, R_2 =	yield (%)
9	(*S*)-PheO*t*Bu	40
10	(*S*)-IleO*t*Bu	59
11	(*S*)-ValOBzl	69
12	(*S*)-ValOEt	77
13	(*S*)-ValO*t*Bu	80
14	(*S*)-LeuOBzl	54

TABLE 3. Substituents and Isolated Yields of the Bis-I45DCs 15−27

compd	substitution	n	R_3	yield (%)
15	R_2 = (*S*)-ValOBzl	2	H	47
16	R_2 = (*S*)-ValOBzl	3	H	69
17	R_2 = (*S*)-ValOBzl	4	H	71
18	R_2 = (*S*)-ValOBzl	6	H	67
19	R_2 = (*S*)-PheO*t*Bu	6	H	73
20	R_2 = (*S*)-ValOBzl	6	Bu	49
21	R_2 = (*S*)-ValOBzl	2	Et	49
22	R_2 = (*S*)-ValO*t*Bu	2	Et	42
23	R_2 = (*S*)-ValOEt	2	Et	28
24	R_2 = (*S*)-ValOBzl	2	$-(CH_2)_2-$	85
25	R_2 = (*S*)-LeuOBzl	2	Et	59
26	R_2 = (*S*)-LeuOH	2	Et	100
27	R_2 = (*S*)-ValOBzl			49

TABLE 4. Substituents and Isolated Yields of the Bis-I45DCs 28−31

compd	substitution	n	yield (%)
28	R_2 = (*S*)-PheO*t*Bu	2	47
29	R_2 = (*S*)-PheO*t*Bu	3	69
30	R_2 = (*S*)-IleO*t*Bu	2	71
31	R_2 = (*S*)-IleO*t*Bu	4	67

of **9** with ethylene glycol to produce **27** (Table 3), although this reaction is slow even at elevated temperatures. The bis-I45DCs **15**−**27** contain only two amino acid side chains. In select examples there are alkyl groups substituted off the nitrogens of the diamine that can, at least in part, substitute for an amino acid side chain. Representative bis-I45DCs **28**−**31** contain four amino acids and were prepared by linking (*S*)-Boc-PheOH with alkyldiamines, removal of the Boc group with TFA, and addition of the resulting diamine salts in the presence of a base to an amino acid ester-substituted pyrazine (Table 4).

The bis-I45DCs can adopt conformations that are, at least in part, dependent upon whether the diamine linker bears an *N*-alkyl substituent. The conformational behavior of bis-I45DCs having *N*-methyl imidazole rings has been described,[21] and we expect the bis-I45DCs in this study to be similar. We note that many of the bis-I45DCs show evidence of multiple conformations in both their ^1H and ^{13}C NMR spectra at room temperature.

This work illustrates how readily the I45DC scaffold is derivatized with amino acids to provide structurally

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diverse new chemical entities that are useful in discovering inhibitors of protein−protein interactions.

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Supporting Information Available: Experimental section and data, ^{1}H and ^{13}C NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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