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Parallel Synthesis of An Oligomeric Imidazole-4,5-dicarboxamide Library

Zhigang Xu[1], **John C. DiCesare**[2], and **Paul W. Baures**[*,1]

[1]Department of Chemistry and Biochemistry, The University of Tulsa, 800 South Tucker Drive, Tulsa, OK 74104

[2]Department of Chemistry, Georgia Southern University, P.O. Box 8064, Statesboro, GA 30460

Abstract

A library of oligomeric compounds was synthesized based on the imidazole-4,5-dicarboxylic acid scaffold along with amino acid esters and chiral diamines derived from amino acids. The final compounds incorporate non-polar amino acids (Leu, Phe, Trp), polar amino acids (Ser, Asp, Arg), and neutral amino acids (Gly, Ala), and where designed to be useful in screening for inhibitors of protein-protein interactions. Many of the protected and deprotected oligomers show evidence of conformational isomers persistent at room temperature in aqueous solution. A total of 317 final oligomers, out of 441 targeted compounds, were obtained in high analytical purity and of sufficient quantity in order to submit them for high-throughput screening as part of the NIH Roadmap.

Introduction

The design and preparation of compound libraries for application in high-throughput screening is a well-known approach to hit identification in drug discovery research.[1,2] The library design criteria are generally target dependent, with the choice of scaffold or building blocks determined by considering known bioactive compounds or hypothesis or both.[3-5]

Protein-protein interactions (PPI) are significant events in signaling within and between cells, and as such are potential targets for intervention by small molecules in order to modulate or treat diseases related to these signals.[6-10] The design of inhibitors for PPIs has, in the past, been considered intractable due to the size and flatness of the associating surfaces. Yet, most buried interfaces rely on “hot spots” that require relatively few residues in order to obtain the majority of the thermodynamic driving force for the PPI.[11,12] Thus, targeting a PPI “hot spot” is a practical approach to reduce the overall size and molecular weight of a potential PPI inhibitor.

Good progress toward the design and discovery of inhibitors of PPIs has been reported in recent years by generating a suitable mimic of one of the two protein surfaces.[13-18] In general these inhibitors mimic secondary structures, such as β-turns,[3,10] β-strands,[19] or an α-helix,[9,10,20] in order to accurately display important residues or “hot spots” of the PPI in a proper orientation.

paul-baures@utulsa.edu .

Supporting Information Available. General Methods, synthetic procedures and characterization data for intermediates and final oligomers, tables of data for intermediates and final oligomers, LC-MS and ^{1}H NMR spectra for 53 protected oligomers in chemset **22**, LC-MS data for 51 deprotected final compounds in chemset **23**, variable temperature LC-MS data for four conformationally promiscuous final products in chemset **23**, as well as VT-NMR data in DMSO-d_6 for two protected oligomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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This approach can yield compounds with drug-like or nearly drug-like features;[21,22] therefore, the use of inhibitors of PPIs as therapeutic agents is anticipated.[23]

We have previously employed the imidazole-4,5-dicarboxylic acid scaffold in the design of CD81 proteomimetics that were based on the comparable distance between carbon atoms of the imidazole-4,5-dicarboxamide (I45DC) substituents with the spacing of side chains in a critical α-helix within the PPI.[24,25] These first-generation oligomeric I45DCs were symmetric and utilized two L-amino acids as well as a *N*,*N*′-dialkylalkanamine in their design and synthesis.[26] Selected oligomers were effective as inhibitors of the CD81-hepatitis C glycoprotein E2 interaction, thereby supporting our design hypothesis.[24]

The second-generation oligomeric I45DCs in this project likewise anticipate the distance between substituents on each I45DC to match the distance between side chains found along the length of an α-helix or adjacent along one side of a β-strand.[25] The total of four amino acid side chains per oligomer in this design is expected to be a significant improvement and doubles the number of pharmacophoric side chains as compared with the first-generation oligomers. Although only a few amino acids are often involved in a PPI hot spot,[11,12] we nonetheless reason the oligomers in this project have greatly improved odds of yielding inhibitors of PPIs when employed in high-throughput screening.

The number and type of amino acid building blocks that we employed for these oligomeric I45DCs was based on a compromise between those amino acids expected to be important in PPI hot spots and the number of compounds we could reasonably synthesize, purify, and characterize in parallel. Also guiding our selection was the knowledge that aromatic, polar, and ionic amino acid side chains were of equal or greater significance to hydrophobic interactions in many PPIs, such as those in antibody-antigen or enzyme-protein inhibitor interactions.27,[28] The oligomeric design uses combinations of two ethylenediamines along with two L-amino acids. Two of the three ethylenediamines used are chiral with Ala and Leu side chains, and were synthesized from their L-amino acids. The seven L-amino acids we chose included two aromatic residues (Tp and Phe), two hydrophobic residues (Leu and Ala), two charged residues (Asp and Arg) and one polar residue (Ser). The monomeric I45DCs were also differentially protected in order to allow selective deprotection of the amino and carboxylic acid termini before coupling in parallel to create a maximum of 441 unique oligomeric I45DCs. A total of 317 of these pure oligomeric I45DCs have been characterized and were obtained in sufficient quantity for submission to the Molecular Library Small Molecule Repository (MLSMR) for use in high-throughput screening as part of the NIH Roadmap.

Results and Discussion

Ethylenediamine was mono-protected to yield **12**{*1*}, as shown in Scheme 1, by following a literature procedure.[29] This compound was further protected with a known procedure[30] to give **11**{*1*} and then selectively deprotected to give **6**{*1*} as the free amine, thereby providing the two differentially monoprotected ethylenediamines, **6**{*1*} and **12**{*1*} needed for oligomer synthesis. The other chiral diamines used in this project were synthesized from L-amino acids bearing either *N*-Boc or *N*-Cbz protecting groups as shown in Table 1. Boc-L-amino acids, **1**{*2-3*}, were the starting materials for the chiral diamines **6**{*2-3*} as shown in Scheme 2. The amino acids **1**{*2-3*} were converted to their respective methyl esters, **2**{*2-3*}, by slight modification of a known procedure,[31] converted to amides **3**{*2-3*} with an NH_4OH solution,[32] and subsequently reduced to the chiral diamines **4**{*2-3*} with $BH_3{\cdot}S(CH_3)_2$ in THF.[33] These intermediates were not purified, but first protected with Cbz-Cl to give **5**{*2-3*} following purification.[30] Deprotection of the Boc group in **5**{*2-3*} with CF_3CO_2H in CH_2Cl_2 yielded **6**{*2-3*}. Likewise, Cbz-L-amino acids, **7**{*2-3*}, were starting materials for the chiral diamines **12**{*2-3*} as shown in Scheme 3. The synthesis again proceeded through methyl esters **8**{*2-3*},

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amides **9**{*2-3*}, reduced intermediates **10**{*2-3*}, and the differentially-protected chiral diamines **11**{*2-3*}. Hydrogenation then produced the final chiral diamines **12**{*2-3*} needed for oligomer synthesis.

The oligomeric design uses the two chiral, mono-protected diamine chemsets **6** and **12** that were synthesized from amino acid amides, along with the two L-amino acid chemsets **14** and **18**. The two halves of the oligomers come from chemsets **16** and **20** that are independently synthesized with orthogonal protecting groups in order to allow selective deprotection of these monomeric building blocks (Scheme 4).

Synthesis of the monomeric building blocks begins with the pyrazine diacid chloride, **13**, which is prepared from imidazole-4,5-dicarboxylic acid as previously reported.[34] The amino acid ester-substituted pyrazine chemsets **15** and **19** were likewise prepared by following methods previously reported, generally giving good to excellent yields of product (Table 3).[26,35]

The monomeric building blocks with a Cbz-protected amino group, chemset **16**, were prepared by reacting pyrazine chemset **15** with the Cbz-protected diamine chemset **6** in CH_2Cl_2 at room temperature from 5-120 hours. These products were purified by column chromatography with EtOAc/hexanes as the eluant. Product was not obtained for **16**{*2,7*} and **16**{*3,7*}. The reason for reagent failure as well as identification of the reaction product(s) for these two reactions was not done. These reactions were attempted more than once with the same results. Reaction yields for the remaining chemset compounds of **16** ranged from 30-80% and averaged 58%.

Likewise, monomeric building blocks with a benzyl ester-protecting group, chemset **20**, were prepared by reacting pyrazine chemset **19** with the *N*-Boc protected diamine chemset **12** in CH_2Cl_2 at room temperature from 1-72 hours. These products were likewise purified by column chromatography with EtOAc/hexanes as the eluant. Product was not obtained for **20** {*3,5*} and the reason for this was not further investigated. Reaction yields for the remaining chemset compounds of **20** ranged from 25-89% and averaged 66%.

The Cbz and benzyl ester, respectively, for isolated chemset intermediates **16** and **20** were deprotected with 1 atm. H_2 and 5% Pd/C in MeOH. The reactions were stirred at room temperature from 4.5-29 h for chemset **16** and 11-30 h for chemset **20**, at which point the reaction was complete as determined by TLC analysis. The reaction mixture was filtered through celite and the solvent removed under vacuum to afford chemsets **17** and **21**, respectively, from chemsets **16** and **20**, minus members **17**{*2,7*}, **17**{*3,7*}, and **21**{*3,5*} for which starting materials were unavailable. The yields for chemset **17** ranged from 84-99% and averaged 94%, whereas the yields for chemset **21** ranged from 65-100% and averaged 89%. All of the products were suitable for use without further purification.

The protected oligomer chemset **22**, excluding those examples where monomeric intermediates **17**{*2,7*}, **17**{*3,7*}, and **21**{*3,5*} were unavailable, were prepared in CH_2Cl_2 at room temperature over 20 h by coupling chemsets **17** and **21** with the water-soluble carbodiimide, EDC·HCl, and dimethylaminopyridine.[36] The reaction mixtures were concentrated under vacuum and the product purified by column chromatography with a gradient ranging from EtOAc/hexanes to EtOAc/MeOH as the eluents, affording chemset **22**.

Out of the 361 possible combinations for which monomeric chemset intermediates **17** and **21** were available, a total of 323 products were purified and yields determined, which were generally good (Table 4). The compounds of the protected oligomer chemset **22** were characterized by combined LC-MS and ^{1}H NMR spectroscopy (see supporting information). In a few cases a library member was identified by LC-MS, but was not completely characterized or carried forward due to insufficient amounts of material or contamination with impurities.

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Quantitative deprotection of products of chemset **22** was done with 25% CF_3CO_2H in CH_2Cl_2 at room temperature over 2-18 h, using LC-MS analysis to determine when the reaction was complete.

Following removal of the solvents, the trifluoroacetate salt was exchanged for chloride by dissolving the deprotected oligomer chemset **23** in 0.90 mL of 10% aqueous MeOH with gentle heat as needed for solubilization and adding 100 μL of 1 M HCl. The solutions were immediately frozen in liquid N_2 before lyophilizing to dryness.

Interestingly, we observed two significant signals in the LC-MS analysis of 45 of the protected oligomer library compounds. In all cases both signals have an identical MS spectra that is consistent with the proposed structure. We hypothesize that this is evidence of two conformers that are stable under the conditions of the analysis. Indeed, conformational isomers have been reported for comparable oligomers containing two *N*-methylimidazole-4,5-dicarboxylic acid rings.[37] A majority of the hypothesized conformational isomers that are observed have hydrophobic amino acid side chains located in both substituent amides of chemset, such as combinations of leucine or phenylalanine (see supporting information). However, we do not observe such conformational isomers in the protected oligomers containing tryptophan in chemset **21**. It is possible that this is due to a preference for one conformer with the larger tryptophan substituent as compared with leucine or phenylalanine, or that these conformational isomers simply do not resolve in the LC-MS for those examples.

Our hypothesis of conformational isomers in protected oligomer chemset **22** is further supported by the fact that many compounds show broad and poorly defined ^{1}H NMR spectra, whereas others have comparably well defined signals. Figure 1 compares part of the LC-MS and ^{1}H NMR spectra for **22**{*2,1,2,2*} with **22**{*2,1,3,2*}. Oligomer **22**{*2,1,2,2*} showed only a single peak in the LC-MS analysis while **22**{*2,1,3,2*} shows two peaks hypothesized to be the conformational isomers. The ^{1}H NMR spectra in the aliphatic region for **22**{*2,1,2,2*} is considerably more defined than the comparable region for **22**{*2,1,3,2*}. The broadness of the ^{1}H NMR spectra for **22**{*2,1,3,2*} is therefore hypothesized to result from the presence of conformational isomers having overlap in their ^{1}H NMR chemical shifts or the relative dynamics of the compound on the NMR time scale or both. It is noted, however, that a broad ^{1}H NMR spectrum did not necessarily mean that the oligomer showed two peaks in the LC-MS analysis, since there are examples of this behavior also. Among the potential explanations for this differing behavior include overlap in the retention time of persistent conformers in the LC conditions or that the change in solvent from aqueous CH_3CN (LC-MS) versus $CDCl_3$ (^{1}H NMR) alters the conformational behavior between the analyses.

One concern was that the two signals in the LC-MS analysis represent diasteromeric oligomers resulting from epimerization of a stereocenter under the coupling conditions. We did not expect the coupling conditions to cause in significant epimerization, and note that we observe two signals only in select cases for any given set of hydrophobic amino acids. This variability in behavior is strong evidence against epimerization as the explanation for our results.

As with the protected oligomers, two significant LC-MS signals were observed in 54 of final compounds of chemset **23**. Again, the general trend appears to be related to the presence of two hydrophobic amino acids in chemset **21**, although there are exceptions in the deprotected oligomers just as there were for the protected oligomers. Importantly, some protected oligomers with two conformers did not show two conformers when deprotected (*e.g.*, **23**{*2,2,3,2*} and **23**{*2,2,3,3*}), while others did not show two conformers until the oligomer was deprotected (*e.g.*, **23**{*1,2,3,4*} and **23**{*1,3,3,4*}). This is yet further evidence against the formation of diasteromers in the coupling reactions, as diastereomeric compounds of chemset **22** would yield diastereomeric compounds of chemset **23**.

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As additional evidence in support of the conformational hypothesis, we performed variable-temperature LC-MS on four deprotected oligomers (**23**{*1,2,3,3*}, **23**{*1,3,3,4*}, **23**{*2,5,3,3*}, and **23**{*1,6,3,3*}) that show evidence of two peaks in the LC-MS analysis (see supporting information). The analysis was run from 25 °C to 65 °C, and showed a steady decline in the relative amounts of the lesser conformer as compared to the major conformer. While we did not observe coalescence of the two conformers at 65 °C, it is possible that hydrophobic interactions could continually stabilize the conformation(s) in an aqueous environment. Nonetheless, the differing relative amounts of the two peaks support our hypothesis that these are conformational isomers rather than diastereomers.

It is commonplace to use VT-NMR spectroscopy in order to examine conformational isomerism in solution. We know from our previous experience with monomeric derivatives that self-association occurs at or above 1 mM in $CDCl_3$ and above 10 mM in DMSO-d_6.[39] Thus, VT-NMR was performed from 30 °C to 70 °C in DMSO-d_6 for **22**{*2,1,2,2*} and **22**{*2,1,3,2*} at 3 mM (see supporting information), resulting in similar ^{1}H NMR spectra observed for both compounds across the range of temperatures. We are unable to assign specific NHs to observed signals, but can nonetheless identify the two imidazole NHs as those signals around 13 ppm, the two amide NHs involved in intramolecular hydrogen bonding as the signals around 11 ppm, the three remaining amide NHs between 8-9 ppm, and the carbamate NH near 7 ppm, as shown in Figure 2 for **22**{*2,1,3,2*}. From inspection it is then clear that there are conformational isomers present in the solution. For example, there are four signals for the two intramolecular hydrogen bonded hydrogens (b). An increase in temperature yields only modest changes on the chemical shifts of the NHs over this entire region. This has previously been reported for oligomeric I45DCs that form conformation isomers observable in DMSO-d_6 even at 100 °C.[37] Cooling the NMR sample of **22**{*2,1,3,2*} to 30 °C from 70 °C yields the same spectrum as first recorded at 30 °C, indicating the stability of the compounds in a polar solvent at high temperatures.

We suggest that the conformational isomers may result from differing intramolecular hydrogen bonding interactions, particularly around the I45DC from chemset **21**, and perhaps supported by the presence of hydrophobic interactions that protect the hydrogen bond from fast exchange during the LC-MS analysis and on the ^{1}H NMR time scale. We have previously observed two intramolecularly hydrogen bonded conformations in dissymmetrically-disubstituted I45DCs and provided evidence that the favored hydrogen bond donor arose from increasing substitution adjacent the amide nitrogen.[38] Moreover, we have shown in model I45DCs that the intramolecular hydrogen bond is relatively strong and worth least 14±1 kcal/mol, as well as observed in an aqueous environment.[39] The two conformations for **22**{*2,1,3,2*} shown in Figure 2 are therefore real possibilities for explaining the observed behavior in both the LC-MS analysis and ^{1}H NMR spectra. It is reasonable that **22**{*2,1,2,2*} would also adopt analogous intramolecularly hydrogen bonded conformations, and the lack of a second hydrophobic side chain may increase the dynamics of the conformational exchange.

The expected intramolecular hydrogen bonding conformations were a valuable design criteria as they fix the distance between amide substituents in order to approximate the separation of nearby side chains in α-helices and β-strands.[24,25] The two different conformers would not affect that separation, but do alter the possible hydrogen bonding interactions with the imidazole ring, as hydrogen bond donor and acceptor groups on the ring have their relative positions switched. One conformation about a single I45DC of the oligomer, relative to the other I45DC conformer, may also be valuable as the oligomers optimize binding interactions at protein interfaces. In this way the conformational isomers could be of added value in the use of these oligomers in screening for inhibitors of protein-protein interactions.

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Conclusion

A total of 317 final products in chemset **23** that were both analytically pure and of sufficient quantity were submitted as HCl salts to the Molecular Library Small Molecule Repository (MLSMR) for high-throughput screening by the as part of the NIH Roadmap. A total of 37 protected intermediates from chemset **22** where likewise submitted to the MLSMR. Chemical and biological data for the oligomers will be accessible free of charge at PubChem (http://pubchem.ncbi.nlm.nih.gov) as the compounds are incorporated into the database and subsequently screened by the Molecular Libraries Probes Production Centers Network (MLPCN). It is reasonably hypothesized that these oligomers will be valuable in the discovery of inhibitors against protein-protein interactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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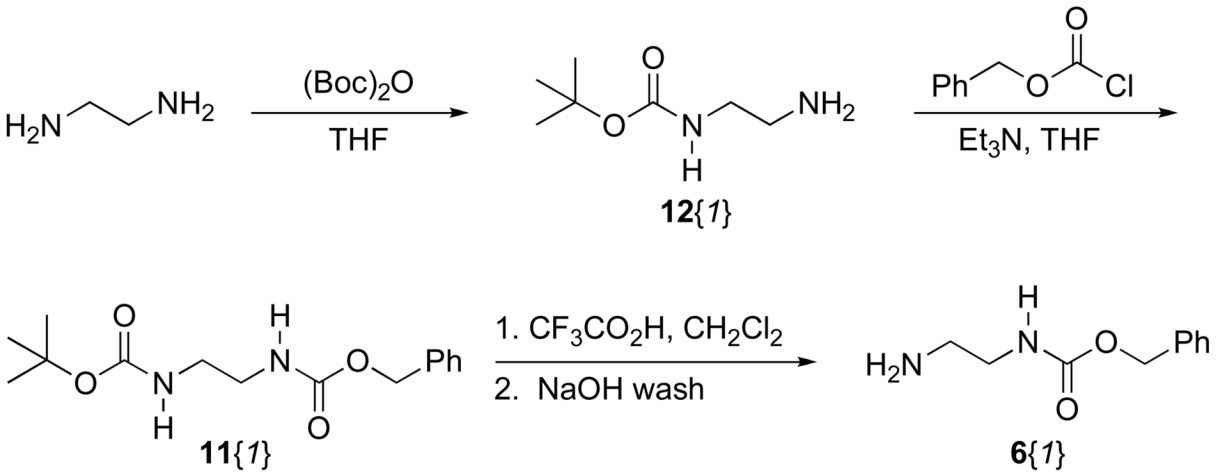

Scheme 1.

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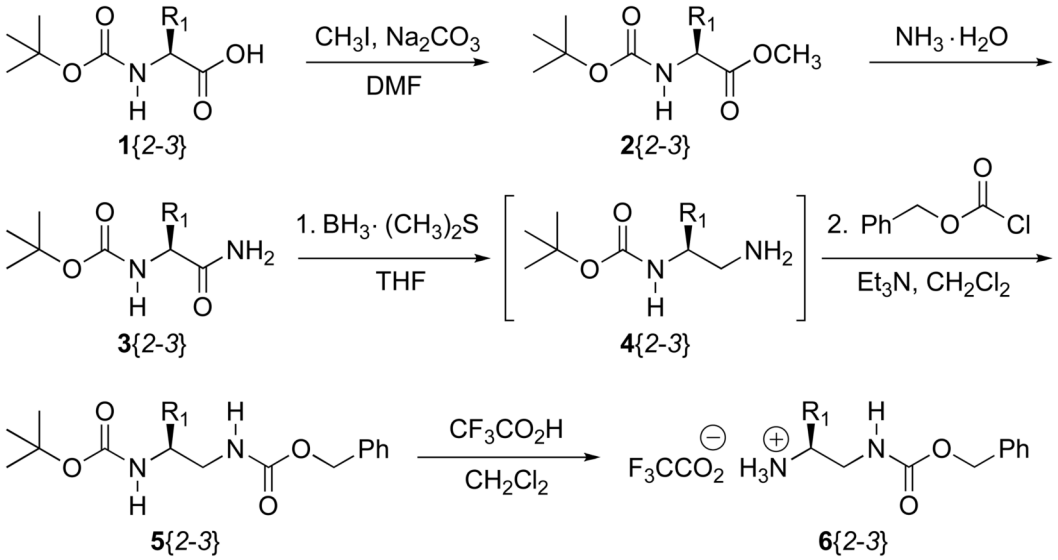

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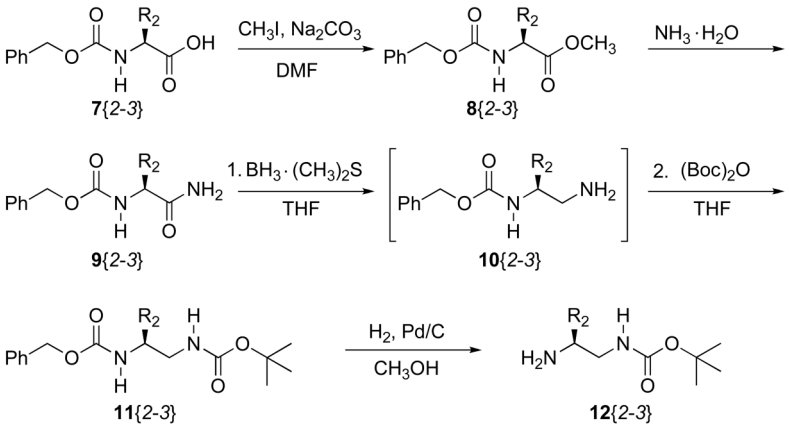

Scheme 3.

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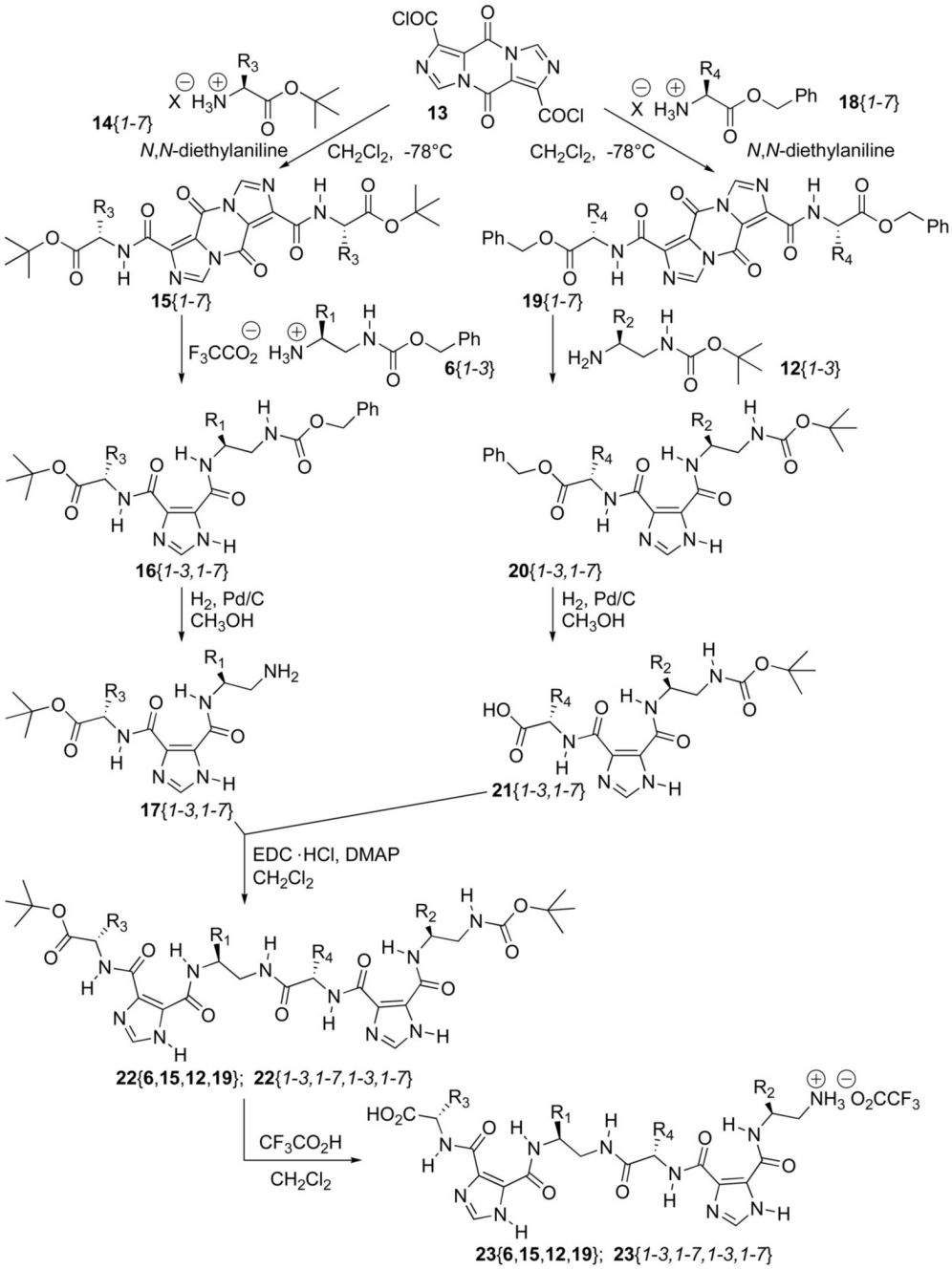

Scheme 4.

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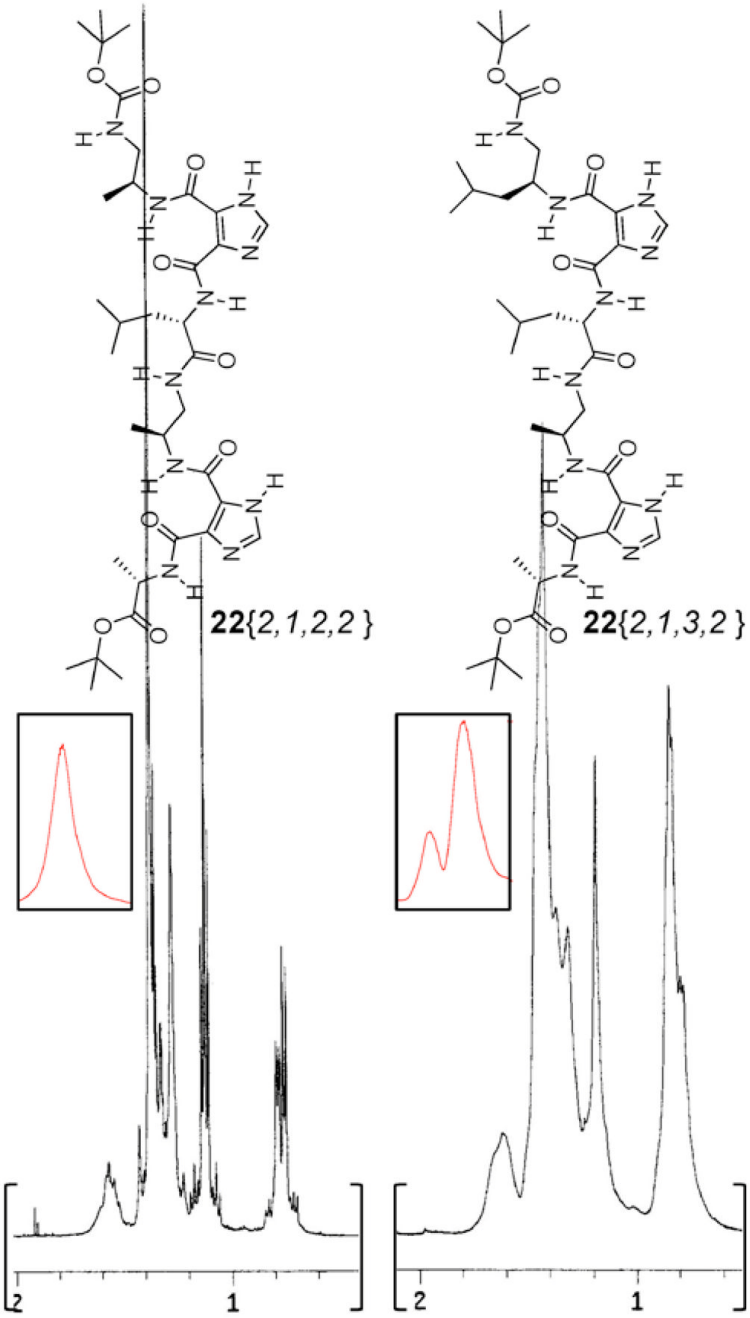

Figure 1.

Comparison of the LC-MS trace (boxed) and aliphatic region in the ^{1}H NMR spectra of **22** {*2,1,2,2*} (left) with **22**{*2,1,3,2*} (right).

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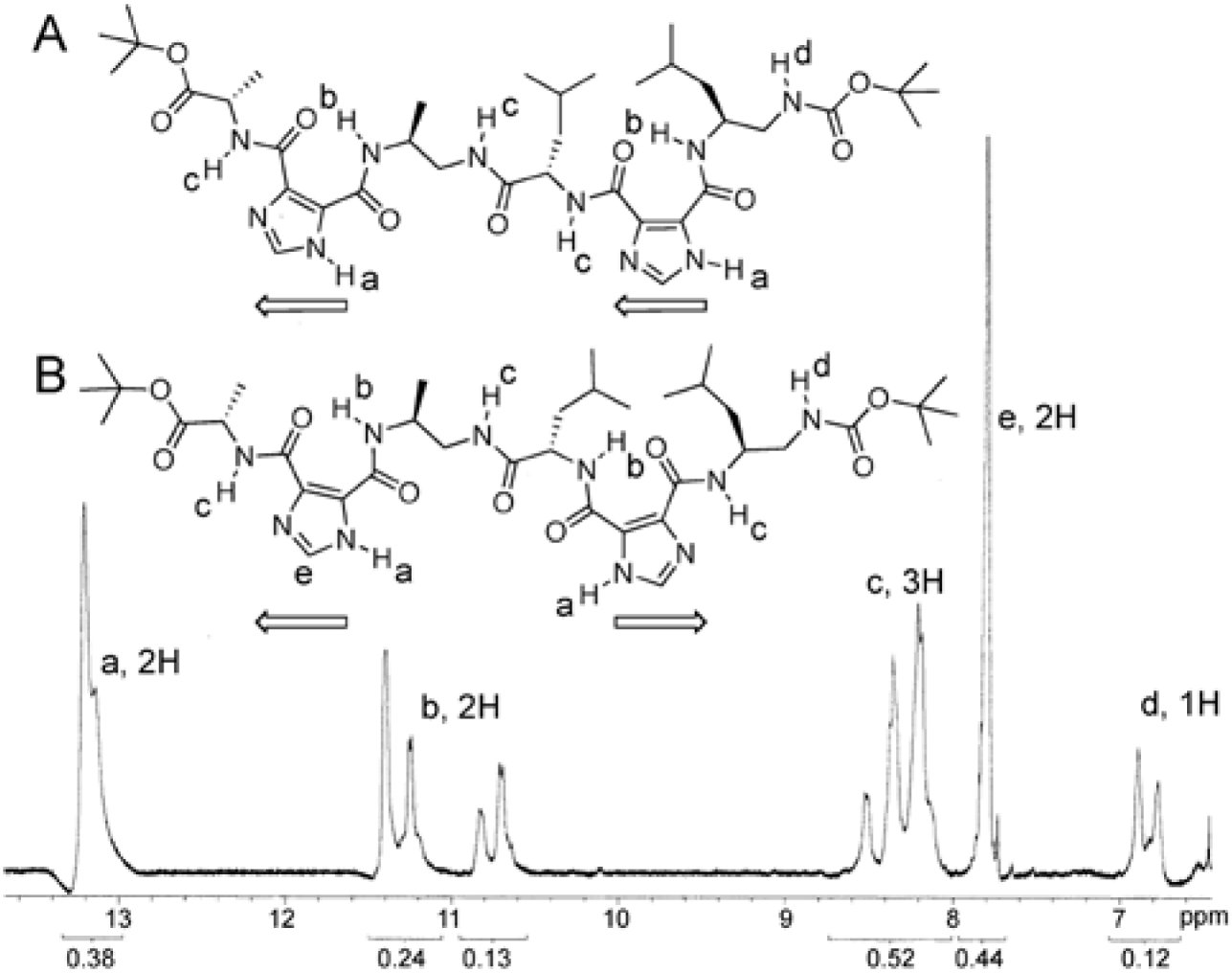

Figure 2.

A partial ^{1}H NMR spectrum of **22**{*2,1,3,2*} recorded at 3 mM in DMSO-d_6 at 30 °C. The imidazole NHs, amide NHs (intramolecular hydrogen bonded as well as free amide) and carbamate NH are labeled and indicate the presence of conformational isomers. Also shown in the 2-CH of the imidazole (e) at 7.8 ppm. Two intramolecularly hydrogen bonded conformations of **22**{*2,1,3,2*} that differ about the I45DC acquired from chemset **21** are also shown (A and B). The arrows underneath each imidazole indicate the direction of the intramolecular hydrogen bond from donor to acceptor for that ring. The top conformer has the same direction for each hydrogen bond and the bottom conformer has opposing directions.

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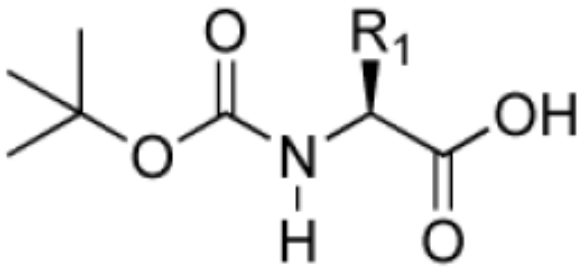
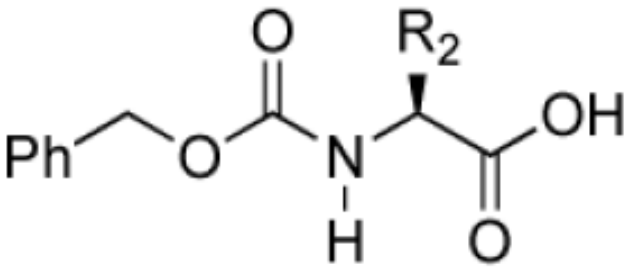
Table 1

N-Boc and Cbz protected amino acids, **1**{*2-3*} and **7**{*2-3*}, respectively, used in library synthesis.



1{*2-3*}



7{*2-3*}

Cmpd	R_1	Cmpd	R_2
1{*2*}	CH_3	**7**{*2*}	CH_3
1{*3*}	$CH_2CH(CH_3)_2$	**7**{*3*}	$CH_2CH(CH_3)_2$

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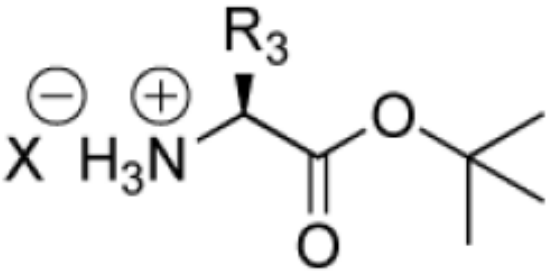
Table 2

Protected amino acids, **14**{*1-7*} and **18**{*1-7*}, respectively, used in library synthesis.



14{*1-7*}

Cmpd	R_3	Cmpd
14{*1*}		**18**{*1*}

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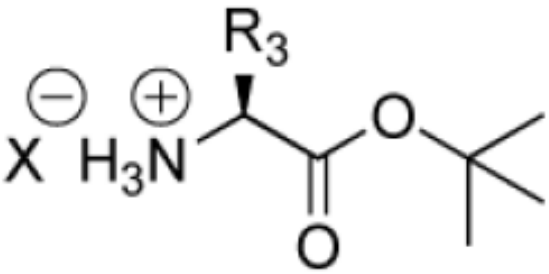
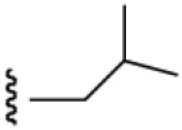


14{*1-7*}

Cmpd	R_3	Cmpd
14{*2*}		**18**{*2*}

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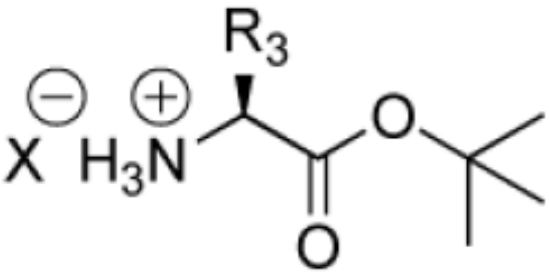
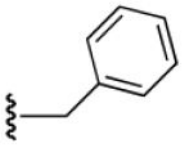


14{*1-7*}

Cmpd	R_3	Cmpd
14{*3*}		**18**{*3*}

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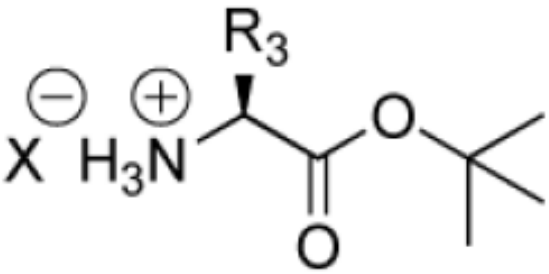
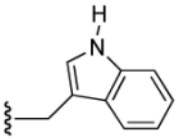
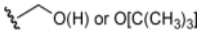


14{*1-7*}

Cmpd	R_3	Cmpd
14{*4*}		**18**{*4*}
14{*5*}		**18**{*5*}

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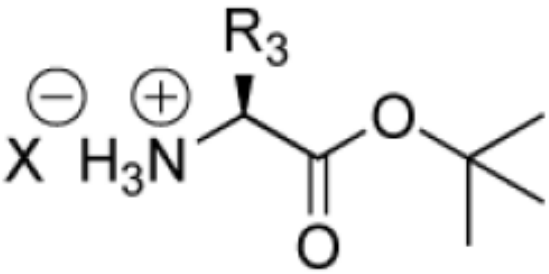
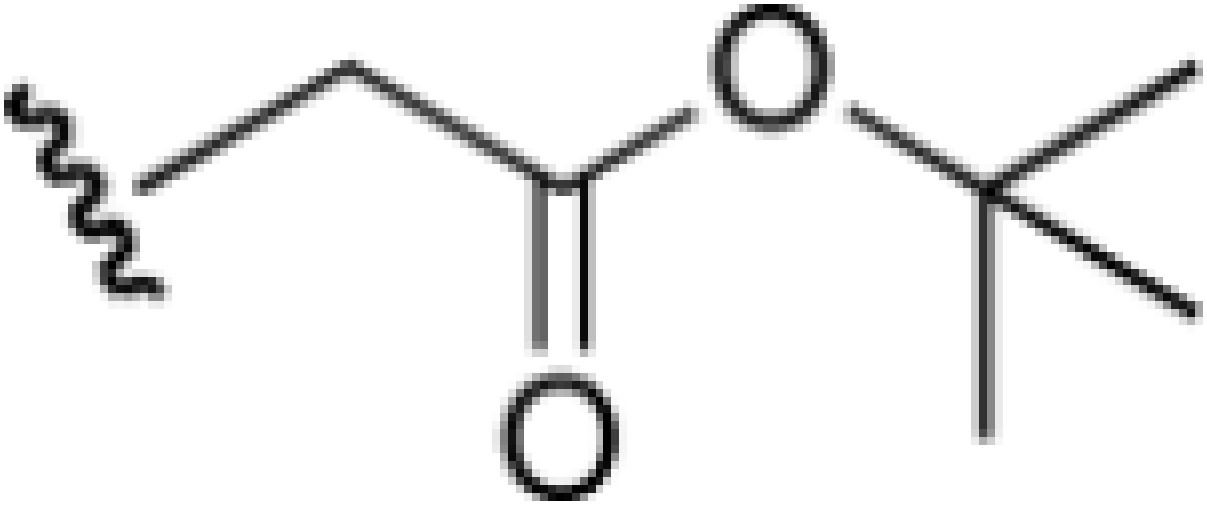


14{*1-7*}

Cmpd	R_3	Cmpd
14{*6*}		**18**{*6*}

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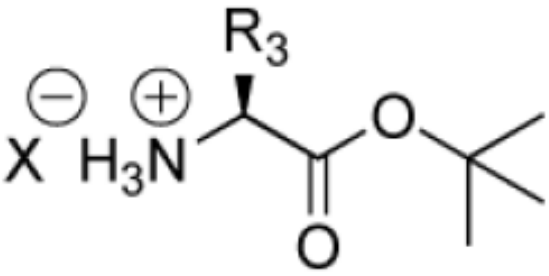
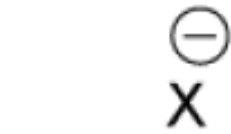


14{*1-7*}



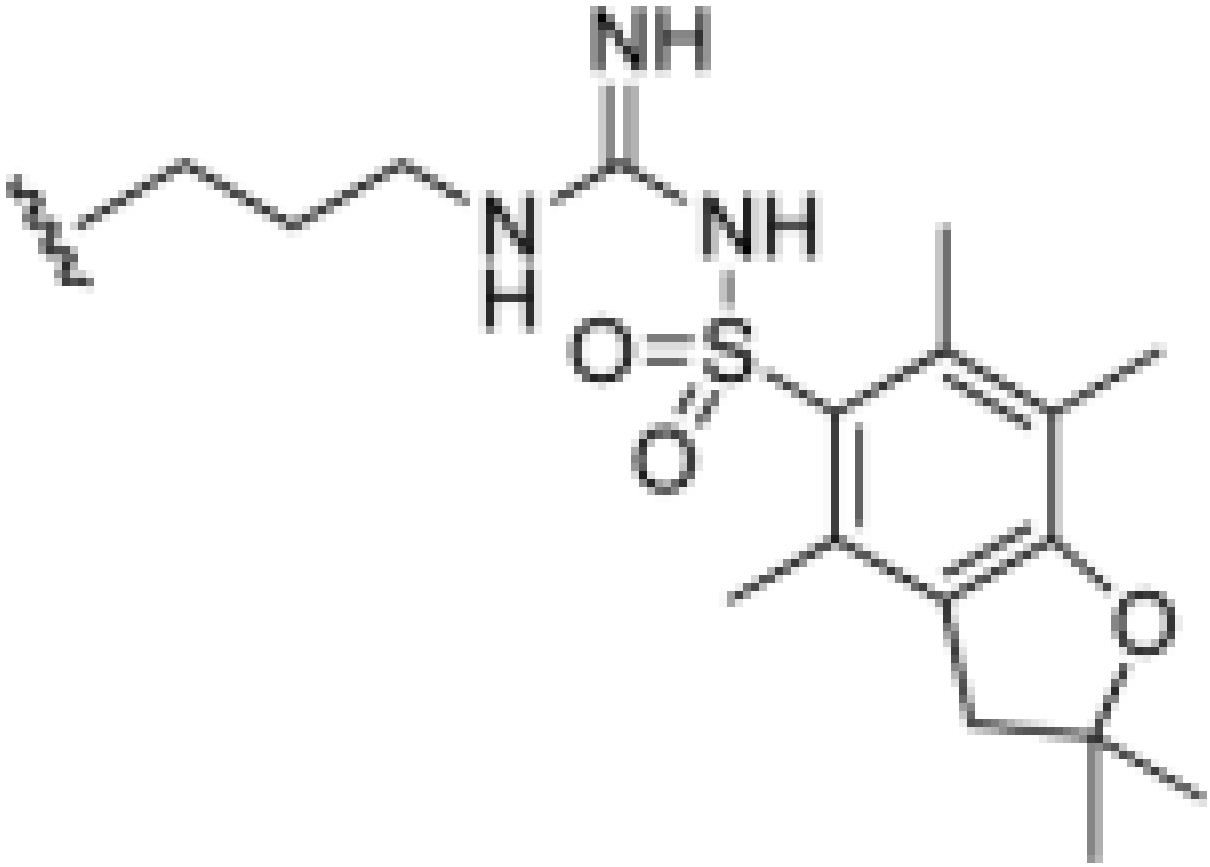
Cmpd	R_3	Cmpd
14{*7*}		**18**{*7*}

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Table 3

Pyrazines substituted with amino acid esters.

compound	amino acid ester	yield (%)	compound	amino acid ester	yield (%)
15{*1*}	**14{***1*}	76	**19**{*1*}	**18{***1*}	71
15{*2*}	**14{***2*}	72	**19**{*2*}	**18{***2*}	84
15{*3*}	**14{***3*}	85	**19**{*3*}	**18{***3*}	84
15{*4*}	**14{***4*}	99	**19**{*4*}	**18{***4*}	98
15{*5*}	**14{***5*}	70	**19**{*5*}	**18{***5*}	67
15{*6*}	**14{***6*}	64	**19**{*6*}	**18{***6*}	34
15{*7*}	**14{***7*}	89	**19**{7}	**18{***7*}	ND

ND; Yield was not determined and the member was used without purification

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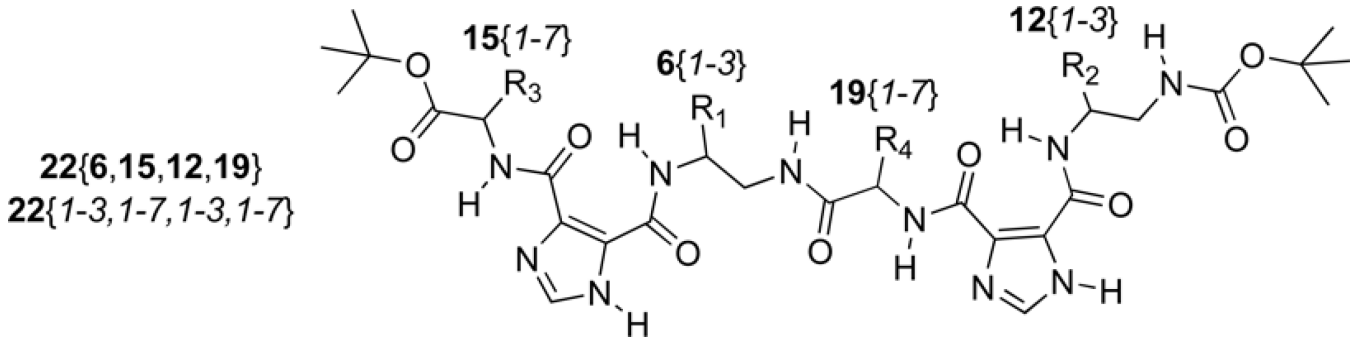
Table 4

Yields of protected oligomer chemset **22**.



17 \ 21	{1,1}	{2,1}	{3,1}	{1,2}	{2,2}	{3,2}	{1,3}	{2,3}	{3,3}	{1,4}	{2,4}	{3,4}	{1,5}	{2,5}	{3,5}	{1,6}	{2,6}	{3,6}	{1,7}	{2,7}	{3,7}
{1,1}	51	53	71	58	48	58	63	61	76	61	52	38	83			70	65	47	67		84
{2,1}	50	56	51	44	50	51	47	69	53	47	48	41	51			46	39	43	66		45
{3,1}	36	24	41	44	25	42	51	29	33	37	36	53				51	35	40			76
{1,2}	84	56	53	42	62	69	60	66	73	58	53	44	60			58	50	56	68		68
{2,2}	70	46	57	64	49	44	68	78	58	51	34	36	39			63	37	46	56		56
{3,2}	58	49		60	59	67	66	68	65	51	63	60	47			54	63	73	69		79
{1,3}	53	51	67	71	96	47	70	68	74	67	60	36	53			52	65	64	66		81
{2,3}	60	53	43	59	46	55	66	71	49	49	39	49	38			61	42	41	68		62
{3,3}	64	47	62	58	61	52	63	62	43	45	52	44				55	65	48	56		76
{1,4}	63	40	53	57	51	63	64	60	51	76	52	46	51			71	56	45	50		74
{2,4}	87	59	75	73	85	83	78	74	77	61	63	68				63	64	90			30
{3,4}	86	79	60	77	65	57	90	60	57	78	64	51				77	62	63			77
{1,5}	82	66	78	74	60	63	72	82	68	73	49	38	61			70	47	56	81		70
{2,5}	62	66	69	67	75	80	74	75	82	66	63	60	44			57	73	70	56		66
{3,5}	63	50	42	66	51	40	47	47	35	55	42	35	35			58		41	84		54
{1,6}	62	33	69	57	70	67	68	74	70	56	61	37	48			68	67	62	67		70
{2,6}	38	49	52	58	52	44	49	66	58	27	47	43	41			37	46	58	52		56
{3,6}	49	48	39	48	54	34	53	42	31	42	53	29				61	58	36			
{1,7}	69	49		60	37		65	32			52						49		50		

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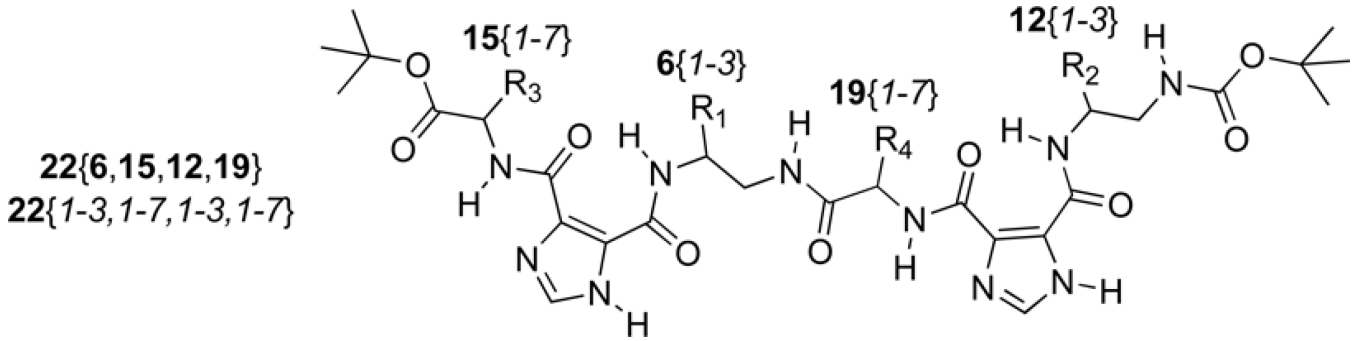

17	21	{1,1}	{2,1}	{3,1}	{1,2}	{2,2}	{3,2}	{1,3}	{2,3}	{3,3}	{1,4}	{2,4}	{3,4}	{1,5}	{2,5}	{3,5}	{1,6}	{2,6}	{3,6}	{1,7}	{2,7}	{3,7}
	{2,7}																					
	{3,7}																					

Areas shaded in gray indicate regions of chemset space for which intermediates were not obtained.