A Simple Approach for the Synthesis of Thio-, Dithio- and Selenothiocarbamate-Tethered Peptidomimetics

H. S. Lalithamba, T. M. Vishwanatha, M. Samarasimha Reddy, Vommina V. Sureshbabu*

#109, Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University, Dr. B. R. Ambedkar Veedhi, Bangalore 560001, India
E-mail: hariccb@hotmail.com; E-mail: hariccb@gmail.com

Received: 23.02.2012; Accepted after revision: 09.04.2012

Abstract: A simple and efficient method is described for the synthesis of thio-, dithio- and selenothiocarbamate-linked peptidomimetics. The nucleophilic addition of enantiopure N^{α}-protected amino alkyl thiols to isocyanates, isothiocyanates or isoselenocyanates obtained from amino acid esters proceeds smoothly in the presence of catalytic amount of DMAP. The protocol was further extended for the synthesis of *N*,*N*′-orthogonally protected thio-, dithio- and selenothiocarbamate-linked peptidomimetics. The reaction is mild, free from racemization, and the products were obtained in good yield.

Key words: peptidomimetics, isocyanates, isothiocyanates and isoselenocyanates, amino alkyl thiols, thiocarbamates, dithiocarbamates, selenothiocarbamates

Peptidomimetics are designed to circumvent some of the problems associated with several natural peptides like stability against proteolysis and poor bioavailability.[1] Certain other properties such as receptor selectivity or potency can be substantially improved.[2] Hence mimics have enormous potential in drug discovery. Therefore, several studies have been carried out over the years to ameliorate the disadvantages of peptide characteristics and thus generate viable pharmaceutical therapies that have focused on the creation of unnatural carbamate-linked peptide mimetics. The carbamate-tethered peptide oligomers have been synthesized by Cho and Liskamp groups.[3] They play a major role in various applications including medicine, agrochemicals, polymers and drugs.[4] They are also present in several natural products. Importantly they serve as potential inhibitors of serine, thrombin and HIV proteases.[5] The amide bond isosteres and/or modification of the native peptide backbone containing sulfur or selenium have been the subject of interest. Indeed, several sulfur-possessing peptidomimetics were designed which show their increased bioavailability and in vivo stability of a peptide without significantly reducing the biological activity of the oxygen counterpart. Consequently, the oxygen of the carbamate may be replaced with sulfur or selenium leading to new mimetics which may find use as drug candidates for pharmaceutical chemistry, e.g., in developing the treatment of infectious diseases and for several protease inhibitors.[6]

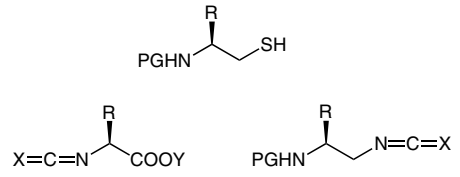
The compounds possessing thio-, dithio- or selenothiocarbamate functionality have been known for their interesting anticancer, antibacterial and anthelmintic, fungicidal and growth depressant properties.[7,8] Dithiocarbamates have been developed as HIV-I NCp7 inhibitors[9] which are also used as linkers in solid-phase organic synthesis.[10] Thiocarbamates are mostly known for their use as commercial herbicides. Selenothiocarbamates are less mentioned in the literature, although considering the important biomedical applications of organoselenium compounds, these compounds may exhibit interesting reactivities towards various inhibitors and in several other functional group transformations.[11,12]

Handful of reports are available on the preparation of S/Se analogues of carbamates.[13] Generally, nucleophilic addition of thiols to isocyanates, isothiocynates or isoselenocyanates has been the frequently employed protocol for the synthesis of title carabamates.[14] Additionally, several carbonylating agents (CDI or thio-CDI) were also used as carbonyl/thiocarbonyl donors.[15] Usually these reagents were treated with amines and thiols or alcohols to afford thiocarbamates or carbamates, respectively. Dithiocarbamates can also be prepared by the reaction of an amine with thiophosgene or CS_2.[16] The only report available on the preparation of selenothiocarbamates was from Koketsu et al., through a reaction of *N*,*N*-dimethylselenocarbamoyl chloride with lithium alkylthiolate.[17] We have reported a new class of peptidomimetics containing the dithiocarbamate linkages at the peptide backbone.[18] This one-pot reaction involving carbon disulfide, amino alkyl iodide and amino acid ester was accessed via in situ generated dithiocarbamic salt. However, the same chemistry cannot be applied for the synthesis of thiocarbamates and selenothiocarbamates which otherwise requires the use of carbon monoxide or toxic carbon diselenide. With the intension to develop a general protocol for the synthesis of chalcogeno derivatives of carbamates at the peptide backbone, we herein describe a simple approach for the synthesis of sulfur- and selenium-containing carbamate peptidomimetics. The protocol involves the reaction of stable N-protected amino alkyl thiol with optically pure isocyanato-, isothiocyanato- and isoselenocyanato esters in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP). Extension of this protocol is also compatible for the synthesis of N,N′-orthogonally protected thio-, dithio- and selenothiocarbamate-linked dipeptidomimetics.

SYNLETT 2012, 23, 1516–1522
Advanced online publication: 25.05.2012
DOI: 10.1055/s-0031-1290683; Art ID: ST-2012-D163-L
© Georg Thieme Verlag Stuttgart · New York

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Over the course of many years, our group and others have registered a series of detailed synthetic approaches for various unnatural amino acids and showed their viability in the construction of novel peptidomimetics. Thus, enantiopure isocyano esters and N^{α}-urethane-protected amino alkyl isocyanates, isothiocyanates and isoselenocyanates have been prepared (Figure 1) and effectively used as substrates to synthesize isonitriles,[19] ureas,[20] thioureas[21] and selenoureido peptidomimetics.[22] We now focused our interest on the application of isocyanates, isothiocyanates and isoselenocyanates in the synthesis of respective carbamates.



X = O, S, Se; Y = Me, Et, Bn; PG = Fmoc, Boc, Z group

Figure 1 Substrate used for the present work

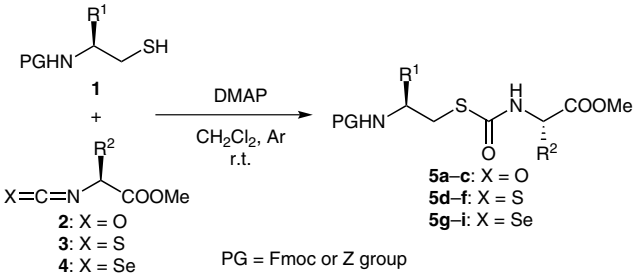
The retrosynthetic analysis of the title sulfur- or selenium-bearing carbamates reveals that the most feasible path to synthesize them is the reaction between N-protected amino alkyl thiols with isocyanato derivatives. The required N-protected amino alkyl thiols **1** were made through reported procedures. Briefly, N-protected amino alkyl iodides were prepared under Mitsunobu condition, which were then treated with thiourea followed by mild hydrolysis with $Na_2S_2O_5$.[23] To prepare dipeptidomimetics of the type **5a**–**c** (Scheme 1), reaction of methyl isocyano valinate **2a** with equimolar amount of *N*-Fmoc-Ala-ψ-[CH_2SH] **1a** without using any base was carried out in CH_2Cl_2. Interestingly, thiocarbamate **5a** was obtained in 68% yield when the reaction was stirred at room temperature for five hours (Table 1, entry 1) and in 72% yield when the reaction was performed at 65 ºC for three hours (Table 1, entry 2).

In order to increase the reaction rate as well as yield, addition of catalytic amount of a base was explored. Our trial experiment employing 0.2 equivalent of DMAP led to good yield of **5a** at room temperature in 30 minutes (Table 1, entry 5). In contrast, screening of other bases, NMM, Et_3N and DBU (Table 1, entries 3, 4 and 6), did not lead to an improvement in the yield (Table 1).

To explore the scope of the present methodology, various side chain functionalized *N*-Fmoc/Z-amino alkyl thiols and isocyano esters were employed. In all the cases reactions were clean with excellent yields in less duration of time. The completion of the reaction was monitored through TLC as well as IR analysis of the reaction mixture at regular intervals (the disappearance of distinct IR peak for isocyanate at 2196 cm^{-1} and appearance of a new peak at 1814 cm^{-1} corresponding to the thiocarbamate). After the complete consumption of the reactants, a simple work-up followed by column chromatographic purification yielded the pure N-protected thiocarbamate-linked dipeptidomimetics **5a**–**c** (Table 2). We then undertook the synthesis of dithiocarbamates **5d**–**f**. Interestingly, isothiocyanato esters **3** were also effectively reacted with thiols **1** in the presence of DMAP. However, the reaction rate was slightly lower and hence longer duration of time was required to obtain good yield of the products **5d**–**f** (Table 2). The reactions were complete in about 50 minutes as monitored by TLC. Further, the reaction of thiols with isoselenocyanates derived from amino acid esters was found to be more or less similar to that of the former isothiocyanates (Table 2, 5g–i).

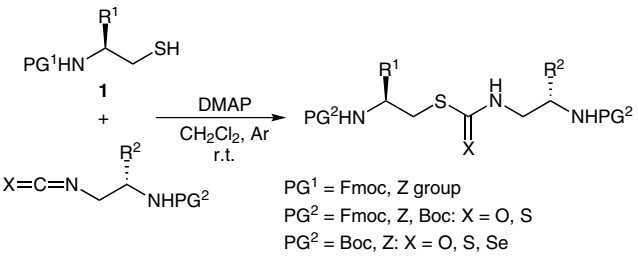
Table 1 Optimization of the Reaction Conditions for the Synthesis of **5a**

Entry	Base catalyst	Temp (ºC)	Time	Yield (%)
1	none	25	5 h	68
2	none	65	3 h	72
3	NMM (0.5 equiv)	35	2 h	75
4	Et_3N (0.5 equiv)	50	2 h	79
5	DMAP (0.2 equiv)	25	30 min	92
6	DBU (0.3 equiv)	25	50 min	80



Scheme 1 Synthesis of N- and C-terminal protected thio-, dithio- and selenothiocarbamate-linked peptidomimetics

The method is also useful for the synthesis of N,N′-orthogonally protected carbamate derivatives **7**. *N*-Urethane-protected amino alkyl isocynato derivatives were synthesized by following published protocols.[14,16,17] The thiols **1** reacted smoothly with the N-protected amino alkyl isocyanate, isothiocyanate and isoselenocyanate **6** in the presence of 0.2 equivalent of DMAP to provide the desired carbamates **7** (Scheme 2, Table 3).

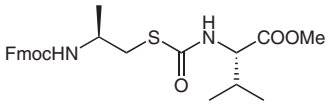
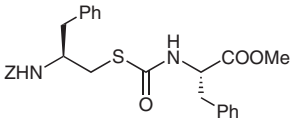
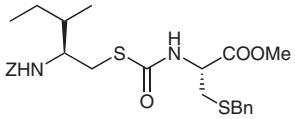
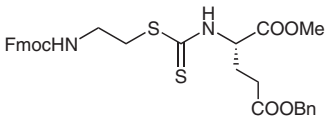
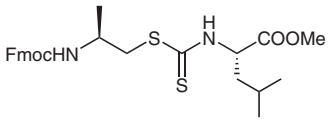
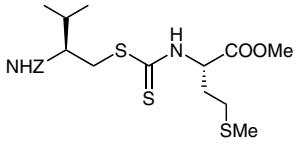
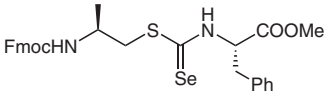
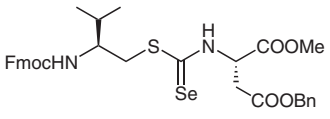
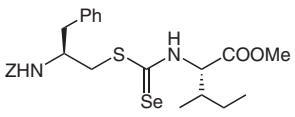


Scheme 2 Synthesis of N,N′-orthogonally protected thio-, dithio- and selenothiocarbamate-linked dipeptidomimetics

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

It has been observed that isocyanates were found to be more reactive with thiols compared to isothiocynates or isoselenocynates. Some of the thiocarbamates have been isolated as pure compounds by recrystallization after the workup or by triturating with diethyl ether. However, during the synthesis of dithio- and selenothiocarbamates even after the reaction mixture being stirred for about five hours at room temperature, about 5% of isothiocynates or isoselenocynates remained unreacted. As a result, the di-

Table 2 List of Thio-, Dithio- and Selenothiocarbamate-Linked Dipeptidomimetics **5**

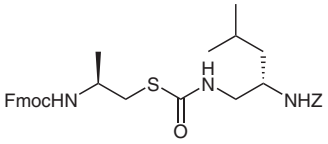
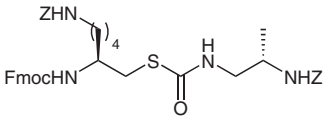
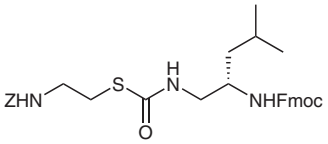
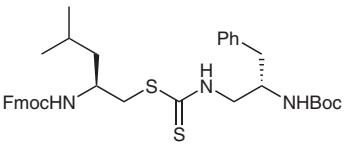
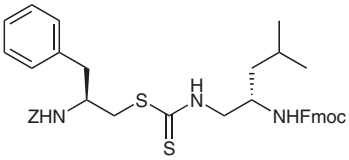
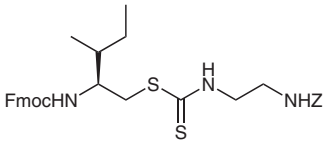
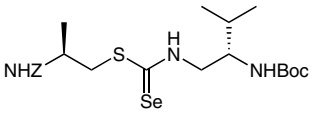
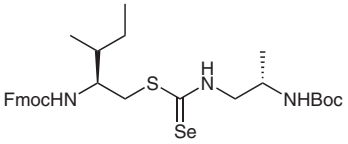
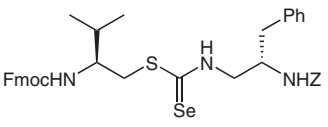
Product **5**	$[\alpha]_D^{25}$ (c = 1, $CHCl_3$)	Yield (%)	HRMS $[M + Na]^+$ found (calcd)
 **5a**	–35.4	92	493.1775 (493.1773)
 **5b**	–27.9	90	529.1770 (529.1773)
 **5c**	–33.2	89	541.1805 (541.1807)
 **5d**	–43.6	91	615.1595 (615.1599)
 **5e**	–51.9	90[a]	523.1705 (523.1701)
 **5f**	–38.9	88	481.1261 (481.1265)
 **5g**	–42.5	85	605.0984 (605.0989)
 **5h**	–33.9	90	691.1352 (691.1357)
 **5i**	–29.9	89	559.1149 (559.1146)

[a] See ref. 18.

 © Georg Thieme Verlag Stuttgart · New York

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Table 3 List of N,N′-Orthogonally Protected S- and Se-Possessing Carbamate-Linked Dipeptidomimetics **7**

Product **7**	$[\alpha]_D^{25}$ (c = 1, $CHCl_3$)	Yield (%)	HRMS $[M + Na]^+$ found (calcd)
 **7a**	–19.3	88	612.2505 (612.2508)
 **7b**	–23.7	90	761.2980 (761.2985)
 **7c**	–29.5	86	598.2350 (598.2352)
 **7d**	–46.9	89[a]	670.2745 (670.2749)
 **7e**	–20.6	91	704.2595 (704.2593)
 **7f**	–27.8	90[a]	614.2126 (614.2123)
 **7g**	–43.4	87	540.1416 (540.1411)
 **7h**	–20.9	85	642.1886 (642.1881)
 **7i**	–19.2	87	738.1884 (738.1881)

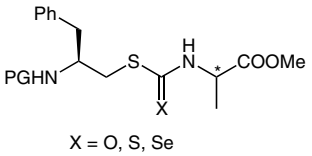
[a] See ref. 18.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

thio- and selenothiocarbamate derivatives have been isolated through column chromatographic purification.

Both ^{13}C NMR as well as ^{77}Se NMR were utilized to confirm the products. A ^{13}C NMR signal corresponding to the carbonyl carbon of the carbamate (OC*O*NH) was reported to resonate in the region δ = 155–157 ppm.[3] As expected, compared to carbamates a downfield shift at around δ = 161–165 ppm was observed in ^{13}C NMR signal pertaining to the carbonyl group of thiocarbamate (SCONH). Similarly, due to more delocalized electrons on sulfur, the thiocarbonyl group of dithiocarbamates (SC*S*NH) appeared further downfield in the range δ = 195–200 ppm.

Table 4 Racemization Studies



Product	$[\alpha]_D^{25}$ (c = 0.1 $CHCl_3$)		HPLC[a] t_R	
	D	L	D	L
thiocarbamate	+16.6	–25.3	12.1	12.6
dithiocarbamate	+32.2	– 8.5	14.3	14.0
selenothiocarbamate	+ 5.8	–16.9	16.9	17.1

[a] HPLC particulars: Agilent 1100 series having G1311A VWD at λ = 254 nm, flow rate: 0.50 mL/min, Column: Agilent Eclipse XDB-C18, pore size 5 μm, diameter × length = 4.6 × 150 mm; gradient elution: H_2O–MeCN–TFA (30:70:0.1); 0.5 mL/min.

On the other hand, selenothiocarbamates (SCSeNH) can be identified by both ^{13}C NMR and ^{77}Se NMR. In ^{13}C NMR spectrum, the carbonyl group of selenothiocarbamates showed a single resonance in the region at around δ = 200–206 ppm which was found to be downfield compared to thiocarbamates. Additionally, ^{77}Se NMR analysis of the selenothiocarbamates was also carried out to find the nature of the selenium nucleus attached to carbon. Thus, a sharp signal resonance in the range δ = 323–353 ppm was detected for selenothiocarbamates which is in agreement with the reported values.[17]

To investigate the stereospecificity of the peptide carbamate analogues synthesized through the present protocol, we undertook the synthesis of three sets of model compounds by the reaction of N^{α}-Fmoc-Phe-ψ-[CH_2SH] with isocyanato esters (**2**, **3** and **4**) derived from L- and D-Ala-OMe (Table 4). The resulting crude products were submitted to HPLC and ^1H NMR analysis. In each case ^1H NMR of the particular epimer contained a single distinct methyl group doublet; also the HPLC chromatograms and optical rotations for the particular epimer had separate and distinct values. Thus the above study inferred that compounds prepared in this communication retain their optical integrity.

In conclusion, new classes of both N- and C-terminal-protected as well as N,N′-orthogonally protected thio-, dithio- and selenothiocarbamate-linked peptidomimetics have been synthesized by reacting N-protected amino alkyl thiols with amino acid derived isocyanate, isothiocyanate and isoselenocyanates.[24] Catalytic amount of DMAP facilitates the rapid reaction and high yield of the products.

Acknowledgment

The authors thank the Board of Research in Nuclear Sciences, the Department of Atomic Energy (grant No. 2011/37/C/35/BRNS), Govt. of India for financial support. H.S.L. thanks the Siddaganga Institute of Technology, Tumkur for a research leave.

References

(1) (a) Conradi, R. A.; Hilgers, A. R.; Ho, N. F. H.; Burton, P. S. *Pharm. Res.* **1992**, *9*, 435. (b) *Pseudo-Peptides in Drug Discovery*; Nielsen, P. E., Ed.; Wiley-VCH: Weinheim, **2004**. (c) *Peptides: Chemistry and Biology*; Sewald, N.; Jakubke, H.-D., Eds.; Wiley-VCH: Weinheim, **2002**, 354.

(2) (a) *Synthesis of Peptides and Peptidomimetics (Houben-Weyl)*; Vol. E22c; Goodman, M.; Felix, A.; Moroder, L.; Toniolo, C., Eds.; Georg Thieme: Stuttgart, **2003**, ; and references cited therein. (b) Boeijen, A.; van Ameijde, J.; Liskamp, R. M. J. *J. Org. Chem.* **2001**, *66*, 8454.

(3) (a) Cho, C. Y.; Moran, E. J.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science* **1993**, *261*, 1303. (b) Liskamp, R. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 633.

(4) (a) Cho, C. Y.; Liu, C. W.; Wemmer, D. E.; Schultz, P. G. *Bioorg. Med. Chem. Lett.* **1999**, *7*, 1171. (b) Warrass, R.; Walden, P.; Wiesmuller, K.-H.; Jung, G. *Lett. Pept. Sci.* **1998**, *5*, 125.

(5) Wang, X.; Huq, I.; Rana, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 6444.

(6) (a) Sharma, A. K.; Sharma, A.; Desai, D.; Madhunapantula, S. V.; Huh, S. J.; Robertson, G. P.; Amin, S. *J. Med. Chem.* **2008**, *51*, 7820. (b) Zheng, G.-Q.; Kenney, P. M.; Lam, L. K. T. *J. Med. Chem.* **1992**, *35*, 185. (c) Bardajee, G. R.; Sadraei, S.; Taimoory, S.; Abtin, E. *Asian J. Biochem Pharma. Res.* **2011**, *1*, 2331. (d) Ronconi, L.; Marzano, C.; Zanello, P.; Corsini, M.; Miolo, G.; Macca, C.; Trevisan, A.; Fregona, D. *J. Med. Chem.* **2006**, *49*, 1648. (e) Elgemeie, G. H.; Sayed, S. H. *Synthesis* **2001**, 1747.

(7) Hou, X.; Ge, Z.; Wang, T.; Guo, W.; Cui, J.; Cheng, T.; Lai, C.; Li, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4214.

(8) (a) Ronconi, L.; Marzano, C.; Zanello, P.; Corsini, M.; Miolo, G.; Macca, C.; Trevisan, A.; Fregona, D. *J. Med. Chem.* **2006**, *49*, 1648. (b) Len, C.; Postel, D.; Ronco, G.; Villa, P.; Goubert, C.; Jeufrault, E.; Mathon, B.; Simon, H. *J. Agric. Food. Chem.* **1997**, *45*, 3. (c) Cao, S.-L.; Feng, Y.-P.; Jiang, Y.-Y.; Liu, S.-Y.; Ding, G.-Y.; Li, R.-T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1915. (d) Nogueira, C. W.; Zeni, G.; Rocha, J. B.T. *Chem. Rev.* **2004**, *104*, 6255. (e) Klayman, D. L.; Gunther, W. H. H. In *Organic Selenium Compounds: Their Chemistry and Biology*; Wiley: New York, **1973**, 30. (f) Nicolaou, K. C.; Petasis, N. A. In *Selenium in Natural Products Synthesis*; CIS Inc: Philadelphia, **1984**, Chap. 3.

(9) Goel, A.; Mazur, S. J.; Fattah, R. J.; Hartman, T. L.; Turpin, J. A.; Huang, M.; Rice, W. G.; Appella, E.; Inman, J. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 767.

 © Georg Thieme Verlag Stuttgart · New York

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

(10) (a) Morf, P.; Raimondi, F.; Nothofer, H.-G.; Schnyder, B.; Yasuda, A.; Wessels, J. M.; Jung, T. A. *Langmuir* **2006**, *22*, 658. (b) Bongar, B. P.; Sadavarte, V. S.; Uppalla, L. S. *J. Chem. Res.* **2004**, *9*, 450. (c) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed; Wiley: New York, **1999**, 484–486.

(11) Mugesh, G.; du Mont, W.-W.; Helmut, S. *Chem. Rev.* **2001**, *101*, 2125.

(12) *Organoselenium Chemistry: A Practical Approach*; Liotta, D., Ed.; Oxford University Press: Oxford, **1999**.

(13) (a) Mizuno, T.; Nishiguchi, I.; Sonoda, N. *Tetrahedron* **1994**, *50*, 5669. (b) Tilles, H. *J. Am. Chem. Soc.* **1959**, *81*, 714. (c) Mizuno, T.; Nishiguchi, I.; Okushi, T.; Hireashima, T. *Tetrahedron Lett.* **1991**, *32*, 6867. (d) Copeland, C. M.; Ghosh, J.; McAdam, D. P.; Skelto, B. W.; Stick, R. V.; White, A. H. *Aust. J. Chem.* **1988**, *41*, 549. (e) Koketsu, M.; Fukuta, Y.; Ishihara, H. *J. Org. Chem.* **2002**, *67*, 1008. (f) Azizi, N.; Aryanasab, F.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 5275. (g) Watkins, B. E.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 4471.

(14) (a) Yamaguchi, T.; Harada, N.; Ozaki, K.; Hayashi, M.; Arakawa, H.; Hashiyama, T. *Tetrahedron* **1999**, *55*, 1005. (b) McCarthy, W. C.; Foss, L. E. *J. Org. Chem.* **1977**, *42*, 1508. (c) Vermeulen, M.; Zwanenburg, B.; Chittenden, G. J. F.; Verhagen, H. *Eur. J. Med. Chem.* **2003**, *38*, 729.

(15) Wood, M. R.; Duncalf, D. J.; Rannard, S. P.; Perrier, S. *Org. Lett.* **2006**, *8*, 553; and references cited therein.

(16) (a) Walter, W.; Bode, K. D. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 281. (b) Garin, J.; Melandz, E.; Merchain, F. L.; Tejero, T.; Urid, S.; Ayestaron, J. *Synthesis* **1991**, 147. (c) Xia, S.; Wang, X.; Ge, Z.-M.; Cheng, T.-M.; Li, R.-T. *Tetrahedron* **2009**, *65*, 1005. (d) Ranu, B. C.; Saha, A.; Banerjee, S. *Eur. J. Org. Chem.* **2008**, 519. (e) Len, C.; Boulogne-Merlot, A.-S.; Postel, D.; Ronco, G.; Villa, P. *J. Agric. Food Chem.* **1996**, *44*, 2856.

(17) (a) Koketsu, M.; Fukuta, Y.; Ishihara, H. *J. Org. Chem.* **2002**, *67*, 1008. (b) Koketsu, M.; Otsuka, T.; Ishihara, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *178*, 443.

(18) Hemantha, H. P.; Sureshbabu, V. V. *Tetrahedron Lett.* **2009**, *50*, 7062.

(19) Sureshbabu, V. V.; Narendra, N.; Nagendra, G. *J. Org. Chem.* **2009**, *74*, 153.

(20) (a) Patil, B. S.; Vasanthakumar, G. R.; Sureshbabu, V. V. *J. Org. Chem.* **2003**, *68*, 7274. (b) Sureshbabu, V. V.; Patil, B. S.; Ramanarao, R. V. *J. Org. Chem.* **2006**, *71*, 7697.

(21) Sureshbabu, V. V.; Naik, S. A.; Hemantha, H. P.; Narendra, N.; Das, U.; Guru Row, T. N. *J. Org. Chem.* **2009**, *74*, 5260.

(22) (a) Hemantha, H. P.; Sureshbabu, V. V. *J. Pept. Sci.* **2010**, *16*, 644. (b) Chennakrishnareddy, G.; Nagendra, G.; Hemantha, H. P.; Das, U.; Guru Row, T. N.; Sureshbabu, V. V. *Tetrahedron* **2010**, *66*, 6718.

(23) Sureshbabu, V. V.; Vishwanatha, T. M.; Vasantha, B. *Synlett* **2010**, 1037.

(24) **General Procedure for the Synthesis of Thio-, Dithio- and Selenothiocarbamate-Linked Peptidomimetics**: To a solution of PgNH-CHR-ψ-[CH_2SH] (10.0 mmol) in anhyd CH_2Cl_2 (10.0 mL), isocyanato derivatives (10.0 mmol) and DMAP (0.2 equiv) were added. The reaction mixture was stirred for 30–50 min at r.t. After the completion of the reaction (TLC), the organic layer was washed with H_2O (10 mL), brine (10 mL) and dried over Na_2SO_4. The organic phase was evaporated under vacuo and the crude was recrystallized (Et_2O–THF) or purified through column chromatography using EtOAc–*n*-hexane (20:80) as eluent.
Spectral data for compounds:
Compound **5a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, 6 H, *J* = 6.1 Hz), 1.59 (d, 3 H, *J* = 5.5 Hz), 2.90–3.11 (m, 3 H), 3.60 (s, 3 H), 3.91 (m, 1 H), 4.28 (m, 1 H), 4.20 (t, 1 H, *J* = 4.6 Hz), 5.01 (d, 2 H, *J* = 5.1 Hz), 5.16 (br, 2 H), 7.22–7.77 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 20.1, 30.9, 37.4, 45.7, 47.1, 51.9, 58.3, 66.6, 126.8, 127.3, 128.2, 128.9, 141.4, 143.2, 155.7, 164.5, 171.8. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{25}H_{30}N_2O_5S$: 493.1773; found: 493.1775.
Compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.70–3.02 (m, 2 H), 3.21–3.30 (m, 4 H), 3.62 (s, 3 H), 4.20 (m, 1 H), 4.83 (m, 1 H), 5.16 (br, 2 H), 5.32 (s, 2 H), 7.19–7.25 (m, 15 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.1, 36.2, 43.3, 52.3, 53.1, 56.5, 64.3, 126.1, 126.3, 126.8, 127.0, 127.2, 127.4, 127.8, 128.2, 129.0, 138.1, 139.0, 140.1, 155.2, 164.2, 171.7. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{28}H_{30}N_2O_5S$: 529.1773; found: 529.1770.
Compound **5c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, 3 H, *J* = 6.0 Hz), 1.02 (d, 3 H, *J* = 5.7 Hz), 1.22 (m, 2 H), 2.24 (m, 1 H), 2.92–3.24 (m, 4 H), 3.61 (s, 3 H), 3.75 (m, 2 H), 3.78 (m, 1 H), 4.81 (m, 1 H), 5.18 (br, 2 H), 5.32 (s, 2 H), 7.18–7.20 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 15.0, 24.1, 32.2, 33.3, 39.0, 40.0, 52.1, 53.9, 55.7, 65.4, 126.4, 127.2, 128.1, 128.3, 128.5, 128.9, 137.4, 141.3, 155.8, 165.2, 171.8. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{26}H_{34}N_2O_5S_2$: 541.1807; found: 541.1805.
Compound **5d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20–2.30 (m, 4 H), 3.13 (d, 2 H, *J* = 5.2 Hz), 3.43–3.60 (m, 3 H), 3.63 (s, 3 H), 4.20 (t, 1 H, *J* = 3.5 Hz), 4.91 (d, 2 H, *J* = 5.8 Hz), 5.15 (br, 2 H), 5.21 (s, 2 H), 7.19–7.72 (m, 13 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 28.3, 37.4, 40.6, 47.2, 51.8, 55.2, 68.1, 68.9, 126.2, 126.9, 127.5, 128.0, 128.4, 128.6, 129.0, 141.2, 143.2, 157.0, 171.1, 173.2, 196.2. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{31}H_{32}N_2O_6S_2$: 615.1599; found: 615.1595.
Compound **5e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, 6 H, *J* = 6.3 Hz), 1.25 (d, 3 H, *J* = 5.8 Hz), 1.70–1.75 (m, 3 H), 2.12–3.20 (m, 2 H), 3.63 (s, 3 H), 3.66 (m, 1 H), 3.85 (m, 1 H), 4.28 (t, 1 H, *J* = 4.8 Hz), 4.91 (d, 2 H, *J* = 6.7 Hz), 5.15 (br, 2 H), 7.26–7.78 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 19.6, 20.7, 40.5, 43.8, 47.0, 47.5, 50.9, 52.4, 66.0, 126.7, 127.5, 128.0, 128.6, 141.4, 143.2, 154.7, 173.2, 195.7. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{26}H_{32}N_2O_4S_2$: 523.1701; found: 523.1705.
Compound **5f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, 6 H, *J* = 5.2 Hz), 2.15 (s, 3 H), 2.23–2.47 (m, 5 H), 2.95 (d, 2 H, *J* = 5.8 Hz), 3.45 (m, 1 H), 3.62 (s, 3 H), 3.86 (m, 1 H), 5.17 (br, 2 H), 5.22 (s, 2 H), 7.19–7.22 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2, 17.3, 17.5, 29.0, 31.1, 33.2, 36.5, 52.1, 56.2, 58.4, 65.4, 126.1, 127.6, 128.3, 142.1, 155.7, 171.2, 197.0. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{30}N_2O_4S_3$: 481.1265; found: 481.1261.
Compound **5g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, 3 H, *J* = 4.6 Hz), 2.96–3.02 (m, 2 H), 3.04–3.31 (m, 2 H), 3.50 (s, 3 H), 3.81 (m, 1 H), 4.10 (m, 1 H), 4.12 (t, 1 H, *J* = 4.9 Hz), 4.99 (d, 2 H, *J* = 6.4 Hz), 5.22 (br, 2 H), 7.12–7.81 (m, 13 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 36.2, 37.1, 47.2, 48.2, 52.0, 58.7, 67.2, 125.1, 126.7, 127.5, 127.9, 128.0, 128.2, 128.6, 139.0, 141.1, 143.4, 155.7, 171.2, 205.7. ^{77}Se NMR (76 MHz, Me_2Se–$CDCl_3$): δ = 322.0. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{29}H_{30}N_2O_4SSe$: 605.0989; found: 605.0984.
Compound **5h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, 6 H, *J* = 5.6 Hz), 2.30 (m, 1 H), 2.73–2.95 (m, 2 H), 2.98–3.21 (m, 2 H), 3.61 (s, 3 H), 3.80 (m, 1 H), 4.10 (m, 1 H), 4.21 (t, 1 H, *J* = 4.2 Hz), 4.80 (d, 2 H, *J* = 6.4 Hz), 5.21 (br, 2 H), 5.30 (s, 2 H), 7.12–7.81 (m, 13 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 17.4, 32.9, 34.3, 37.4, 47.2, 51.8, 52.1, 58.3, 67.1, 69.2, 125.3, 126.2, 127.2, 127.3, 128.0, 128.3, 128.6, 141.3, 142.1, 143.7, 155.1, 171.2, 173.2, 203.4. ^{77}Se

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

NMR (76 MHz, Me_2Se–$CDCl_3$): δ = 322.0. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{33}H_{36}N_2O_6SSe$: 691.1357; found: 691.1352.

Compound **5i**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, 3 H, *J* = 5.8 Hz), 1.01 (d, 3 H, *J* = 6.1 Hz), 1.37 (m, 2 H), 2.51 (m, 1 H), 2.60–2.81 (m, 2 H), 2.94–3.23 (m, 2 H), 3.41 (m, 1 H), 3.59 (s, 3 H), 4.21 (m, 1 H), 5.19 (br, 2 H), 5.29 (s, 2 H), 7.12–7.20 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2, 15.2, 36.2, 37.1, 42.2, 51.2, 55.3, 58.9, 66.3, 125.4, 126.5, 127.4, 128.0, 128.3, 128.7, 139.1, 141.4, 155.2, 171.3, 202.4. ^{77}Se NMR (76 MHz, Me_2Se–$CDCl_3$): δ = 322.0. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{25}H_{32}N_2O_4SSe$: 559.1146; found: 559.1149.

Compound **7a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, 6 H, *J* = 6.0 Hz), 1.31 (d, 3 H, *J* = 5.4 Hz), 1.43 (m, 2 H), 1.76 (m, 1 H), 2.90–3.21 (m, 2 H), 3.01–3.35 (m, 2 H), 4.01–4.21 (m, 2 H), 4.25 (t, 1 H, *J* = 4.0 Hz), 5.01 (d, 2 H, *J* = 7.2 Hz), 5.31 (s, 2 H), 5.88 (br, 3 H), 7.19–7.82 (m, 13 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2, 22.1, 23.4, 37.5, 42.2, 45.2, 47.0, 47.8, 48.9, 65.2, 67.2, 127.2, 127.4, 127.8, 128.1, 128.5, 128.8, 129.4, 141.2, 141.5, 143.1, 155.7, 163.1. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{33}H_{39}N_3O_5S$: 612.2508; found: 612.2505.

Compound **7b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, 3 H, *J* = 6.6 Hz), 1.25–1.60 (m, 6 H), 2.90–3.20 (m, 4 H), 3.25–3.45 (m, 2 H), 3.75 (m, 1 H), 5.01 (m, 1 H), 4.23 (t, 1 H, *J* = 4.5 Hz), 5.21 (d, 2 H, *J* = 6.1 Hz), 5.32 (s, 4 H), 5.81 (br, 4 H), 7.16–7.79 (m, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 22.4, 29.2, 33.8, 35.0, 47.1, 47.4, 49.2, 49.4, 49.8, 67.4, 68.2, 68.5, 126.1, 126.3, 126.9, 127.2, 127.4, 127.7, 128.2, 128.6, 128.9, 129.4, 141.1, 141.4, 141.8, 143.4, 155.3, 155.7, 156.2, 167.5. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{41}H_{46}N_4O_7S$: 761.2985; found: 761.2980.

Compound **7c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, 6 H, *J* = 5.2 Hz), 1.49 (m, 2 H), 1.81 (m, 1 H), 3.01–3.32 (m, 4 H), 3.69 (m, 2 H), 4.32 (m, 1 H), 4.31 (t, 1 H, *J* = 5.2 Hz), 4.83 (d, 2 H, *J* = 6.2 Hz), 5.32 (s, 2 H), 5.80 (br, 3 H), 7.19–7.81 (m, 13 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 22.4, 23.3, 32.5, 39.0, 41.7, 46.3, 47.2, 47.5, 64.2, 68.2, 126.2, 127.6, 127.3, 128.2, 128.7, 128.9, 129.4, 141.3, 141.8, 143.5, 155.2, 156.3, 169.1. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{32}H_{37}N_3O_5S$: 598.2352; found: 598.2350.

Compound **7d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, 6 H, *J* = 5.6 Hz), 1.20 (s, 9 H), 1.72 (m, 3 H), 2.40–2.49 (m, 4 H), 2.51 (d, 2 H, *J* = 4.9 Hz), 3.48 (m, 1 H), 3.99 (m, 1 H), 4.22 (t, 1 H, *J* = 4.2 Hz), 4.91 (d, 2 H, *J* = 6.7 Hz), 5.92 (br, 3 H), 7.21–7.78 (m, 13 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 22.9, 27.7, 38.4, 40.1, 41.6, 46.9, 47.8, 49.1, 51.5, 65.7, 82.3, 127.5, 127.8, 127.9, 128.2, 128.6, 128.9, 129.5, 141.7, 142.3, 143.4, 155.6, 156.3, 194.5. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{36}H_{45}N_3O_4S_2$: 670.2749; found: 670.2745.

Compound **7e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, 6 H, *J* = 5.6 Hz), 1.40 (m, 2 H), 1.80 (m, 1 H), 2.74–3.10 (m, 6 H), 3.80 (m, 1 H), 4.19 (m, 1 H), 4.35 (t, 1 H, *J* = 4.2 Hz), 4.87 (d, 2 H, *J* = 6.7 Hz), 5.33 (s, 2 H), 5.82 (br, 3 H), 7.23–7.81 (m, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 23.1, 23.3, 39.4, 41.9, 42.3, 47.0, 47.8, 49.5, 55.5, 65.1, 67.4, 126.5, 126.8, 127.1, 127.5, 127.9, 128.2, 128.5, 128.7, 129.5, 139.2, 141.2, 143.3, 155.2, 155.8, 198.4. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{39}H_{43}N_3O_4S_2$: 704.2593; found: 704.2595.

Compound **7f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, *J* = 5.6 Hz), 1.08 (d, 3 H, *J* = 5.1 Hz), 1.32 (m, 2 H), 2.23 (m, 1 H), 2.81–3.32 (m, 6 H), 3.80 (m, 1 H), 4.37 (t, 1 H, *J* = 5.2 Hz), 4.99 (d, 2 H, *J* = 6.7 Hz), 5.30 (s, 2 H), 5.82 (br, 3 H), 7.20–7.78 (m, 13 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2, 16.1, 25.5, 35.3, 40.2, 41.0, 43.2, 47.1, 54.2, 66.1, 68.4, 126.6, 127.4, 127.8, 128.5, 128.7, 129.0, 129.5, 141.0, 141.5, 144.3, 155.6, 156.0, 198.4. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{32}H_{37}N_3O_4S_2$: 614.2123; found: 614.2126.

Compound **7g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, 6 H, *J* = 5.4 Hz), 1.31 (d, 3 H, *J* = 5.8 Hz), 1.12 (s, 9 H), 2.40 (m, 1 H), 2.74–2.99 (m, 2 H), 3.04–3.22 (m, 2 H), 3.81–4.01 (m, 2 H), 5.01 (s, 2 H), 6.02 (br, 3 H), 7.10–7.26 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 19.2, 29.0, 31.2, 39.1, 47.2, 48.2, 59.1, 65.2, 79.2, 127.5, 127.8, 128.2, 141.2, 155.7, 204.2. ^{77}Se NMR (76 MHz, Me_2Se–$CDCl_3$): δ = 320.0. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{22}H_{35}N_3O_4SSe$: 540.1411; found: 540.1416.

Compound **7h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, 3 H, *J* = 5.5 Hz), 0.99 (d, 3 H, *J* = 5.6 Hz), 1.10 (s, 9 H), 1.25 (m, 2 H), 1.32 (d, 3 H, *J* = 5.2 Hz), 2.12–3.32 (m, 5 H), 3.90 (m, 2 H), 4.30 (t, 1 H, *J* = 4.2 Hz), 4.92 (d, 2 H, *J* = 5.5 Hz), 5.69 (br, 3 H), 7.21–7.76 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 14.3, 18.8, 26.5, 28.6, 32.1, 40.2, 48.1, 49.1, 52.3, 57.5, 68.2, 80.4, 126.0, 127.1, 127.8, 128.3, 141.3, 143.7, 155.1, 155.7, 202.3. ^{77}Se NMR (76 MHz, Me_2Se–$CDCl_3$): δ = 320.0. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{30}H_{41}N_3O_4SSe$: 642.1881; found: 642.1884.

Compound **7i**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, 6 H, *J* = 6.5 Hz), 2.40 (m, 1 H), 2.60–3.22 (m, 6 H), 3.87 (m, 1 H), 4.30 (m, 1 H), 4.33 (t, 1 H, *J* = 4.3 Hz), 4.92 (d, 2 H, *J* = 6.6 Hz), 5.33 (s, 2 H), 5.99 (br, 3 H), 7.21–7.76 (m, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9, 32.8, 34.5, 40.9, 47.5, 49.6, 53.2, 59.9, 64.3, 68.4, 126.3, 126.8, 126.9, 127.0, 127.3, 127.9, 128.1, 128.3, 128.7, 129.0, 139.2, 140.3, 141.3, 143.9, 155.2, 155.9, 201.5. ^{77}Se NMR (76 MHz, Me_2Se–$CDCl_3$): δ = 320.0. HRMS: *m/z* [M + Na]$^+$ calcd for $C_{38}H_{41}N_3O_4SSe$: 738.1881; found: 738.1884.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

 © Georg Thieme Verlag Stuttgart · New York

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.