Tetrahedron Letters 55 (2014) 6831–6835

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot synthesis of orthogonally protected dipeptide selenazoles employing N^{α}-amino selenocarboxamides and α-bromomethyl ketones

Chilakapati Madhu [a], Nageswara Rao Panguluri [a], N. Narendra [b], V. Panduranga [a], Vommina V. Sureshbabu [a,*]

[a] #109, Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University, Dr. B.R. Ambedkar Veedhi, Bangalore 560 001, India
[b] Department of Chemistry, Government Science College, Tumkur University, B.H. Road, Tumkur 572 103, India

ARTICLE INFO

Article history:
Received 30 May 2014
Revised 13 October 2014
Accepted 14 October 2014
Available online 22 October 2014

Keywords:
Amino nitrile
Phosphorus pentaselenide
N^{α}-Amino selenocarboxamide
α-Bromomethyl ketone
Selenazole

ABSTRACT

A simple and efficient protocol for the synthesis of selenazole containing dipeptidomimetics using N^{α}-amino selenocarboxamides and α-bromomethyl ketones is described. All the compounds made were isolated in good yields and fully characterized.

Selenium is an essential trace element for higher organisms and the enzymes which contain selenium such as glutathione peroxidase (GPX), 5-deiodase type-1 play an important role in human physiology.[1] In recent years organoselenium derivatives have shown marked biological and enzyme inhibitory activities.[2,3] Notably, selenazole derivatives are one of the significant groups of organoselenium compounds due to their pharmacological relevance and are of interest in the field of material science.[4] Molecules containing this functional group possess strong inhibitory activity against inducible nitric oxide synthase.[5] The prominent examples are selenazofurin, a potent known antiviral agent, 2-piperidinoselenazole and 4-phenyl-2-piperidinoselenazole, which exhibit superoxide anion-scavenging activity.[6]

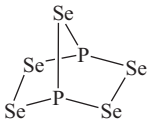
Selenocarboxamides are a class of reactive intermediates, similar to their oxygen and sulfur analogs. They are important precursors for the synthesis of biologically active heterocycles like 1,3-selenazoles[7] and 1,3-selenazines.[8] The reported methods for the synthesis of selenocarboxamides include the reaction of nitrile with hydrogen selenide[9] (H_2Se), sodium hydrogen selenide[10] (NaSeH), monoselenophosphate[11a], and bis(trimethylsilyl)selenide.[11b] Geisler et al., reported an efficient protocol for the synthesis of selenocarboxamides from the corresponding nitriles using phosphorous pentaselenide[12] (P_2Se_5). P_2Se_5 is a more reliable reagent because of its ease of preparation, less toxic than NaSeH or H_2Se, and moreover the ability of P_2Se_5 circumvents the addition of NEt_3/pyridine[10] and borontrifluoride diethyletherate.[11b] This prompted us to opt for P_2Se_5 toward the synthesis of selenocarboxamides from the corresponding N^{α}-protected amino nitriles (Fig. 1).

Recently our group has reported the synthesis of selenoxopeptides,[13] N^{β}-protected amino alkyl isoselenocyanate,[14] selenourea,[15] selenohydantoin,[16] selenocarbamate, and selenazole containing peptidomimetics.[17] The utility of both carboxamides, as well as thiocarboxamide derived from N^{α}-protected amino acids[18] as building blocks for the construction of oxazole/thiazole peptidomimetics has been well documented.[19] In continuation of our interest on organoselenium compounds, herein we report the one-pot synthesis of orthogonally protected selenazole dipeptidomimetics employing N^{α}-Fmoc/Boc/Z protected amino selenocarboxamides and α-bromomethyl ketone which involves the following retrosynthetic pathway (Fig. 2).

Initially, the preparation of N^{α}-protected amino nitrile was undertaken. N^{α}-Protected amino acid was converted to the corresponding carboxamide via its mixed anhydride and then treated with aqueous ammonia. The resulting amide was subjected with

* Corresponding author. Tel.: +91 80 22961339/8147757961.
E-mail addresses: narendrachem@gmail.com (N. Narendra), sureshbabuvommina@rediffmail.com, hariccb@hotmail.com, hariccb@gmail.com (V.V. Sureshbabu).

http://dx.doi.org/10.1016/j.tetlet.2014.10.085
0040-4039/



P_2Se_5

Figure 1. Structure of P_2Se_5.

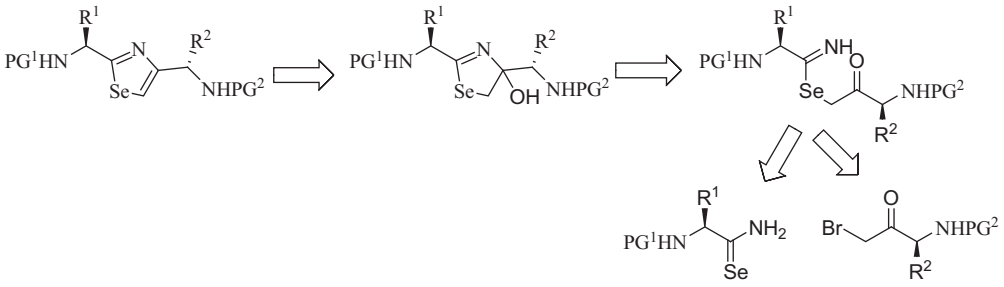


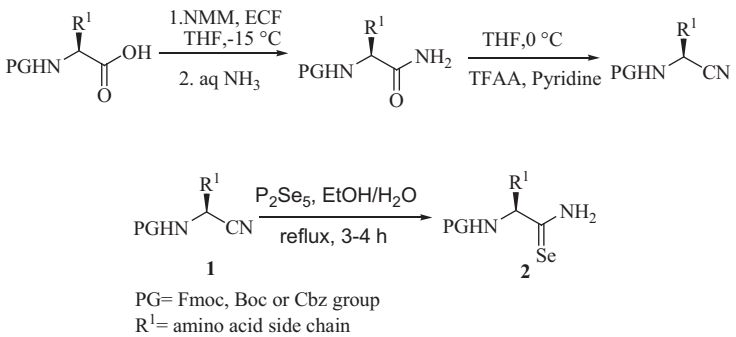
Figure 2. Retro-synthetic analysis of orthogonally protected selenazole dipeptidomimetics.

trifluoroacetic anhydride (TFAA)/pyridine (py) at 0 °C in THF to obtain the nitrile (Scheme 1). Later, elemental Se was heated with red phosphorus under electric Bunsen burner till the mixture became glassy black purple solid indicating the formation of P_2Se_5. Then it was cooled to rt and powdered thoroughly.

In the next step, the synthesis of N^{α}-protected amino selenocarboxamide **2** was carried out (Scheme 1). In a typical procedure Fmoc-Lue-ψ[CN] (1.0 equiv) **1b** was dissolved in EtOH and freshly prepared P_2Se_5 (2.0 equiv) was added. The reaction mixture was heated to reflux and then a few drops of water were added to generate H_2Se, which reacts with nitrile **1b** for the formation of the corresponding selenocarboxamide **2b**. After completion of the reaction, the reaction mixture was filtered and washed with EtOH to obtain Fmoc-Leu-ψ[C(=Se)NH_2] **2b**. The crude residue was purified by column chromatography and the isolated pure compound **2b** was characterized by Mass, ^{1}H, ^{13}C and ^{77}Se NMR spectroscopy. The ^{77}Se NMR shows a characteristic single peak at around δ 529.9 for the selenocarbonyl group. The adoptability and efficacy of the protocol were further demonstrated by synthesizing a series of N^{α}-Fmoc/Boc/Cbz selenocarboxamides **2** from the corresponding nitriles **1** (Table 1).

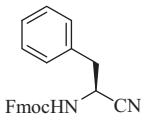
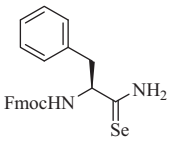
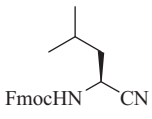
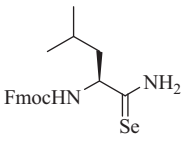
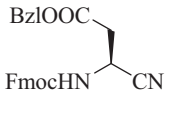
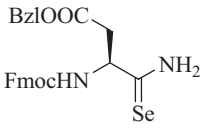
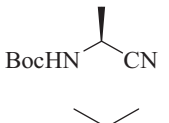
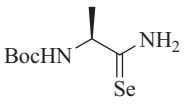
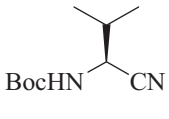
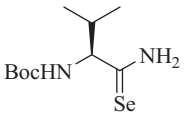
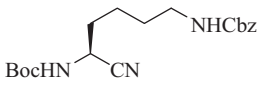
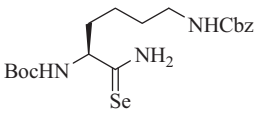
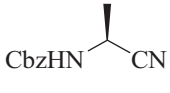
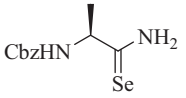
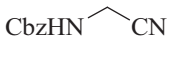
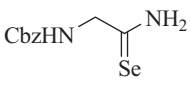
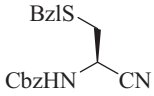
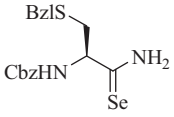
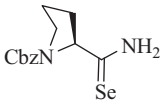
Heterocyclic amino acids such as oxazoles and thiazoles are substructures comprising numerous macrolactam natural products having biological activities including cytotoxicity, *p*-glycoprotein pump inhibition, and metal binding properties.[20] Oxazole containing amino acids are suitable building blocks for the preparation of model systems with well defined secondary structures. Peptides containing thiazole subunits are characterized by reduction of multi drug resistance of certain types of lymphoblasts, antifungal, antibacterial, antimicrobial, and antitubercular activities.[21] The structure of fascinating selenazole resembles with oxazole/thiazole. Different protocols have been reported for the synthesis of selenazoles by using selenoamide[22] or selenourea[23] as the starting material. Selenoureas are inconvenient due to their high cost and low stability to air and light. In particular Zhang et al., have synthesized selenazole containing cyclic peptides (QZ59Se-SSS and QZ59Se-RRR) for crystallization with *p*-glycoprotein (pgp) but this protocol is limited to the preparation of Boc-amino selenocarboxamides.[24] Thus, the limited applicability with the available literature prompted us to prepare orthogonally protected dipeptide selenazoles from the corresponding N^{α}-amino selenocarboxamides.

In the next part of our study, the synthesis of N^{α}-urethane orthogonally protected selenazole linked dipeptidomimetics was carried out (Scheme 2). In a typical procedure, Fmoc-Leu-ψ[C(=Se)NH_2] (**2b**) was refluxed with Boc-Phe-ψ[C(=O)CH_2Br][25] (**3b**) in acetone to obtain selenazole linked dipeptidomimetic **4b**. The reaction was found to be complete within 30 min, as observed by TLC analysis. It was also evident by the disappearance of bromomethyl ketone peak at around 1735 cm^{-1} in the IR spectrum. The isolated crude selenazole dipeptidomimetic **4b** was purified through column chromatography (hexane/EtOAc 9:1%) and characterized by NMR and mass spectrometry. The generality of

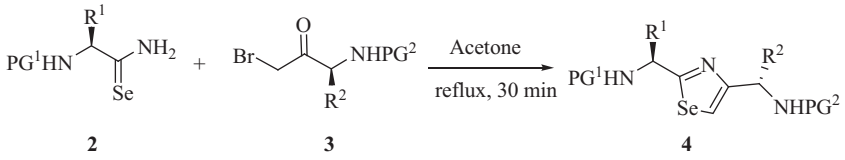


Scheme 1. Synthesis of N^{α}-protected amino selenocarboxamides.

Table 1
List of N^{α}-protected amino selenocarboxamides **2**

Entry	Nitrile **1**	Selenocarboxamide **2**	Yield (%)	HRMS Obsd. (Calcd)*
a			88	473.0744 (473.0735)
b			82	439.0901 (439.1012)
c			78	531.0799 (531.0682)
d			68	275.0275 (275.0315)
e			79	303.0588 (303.0617)
f			64	466.1221 (466.0982)
g			78	309.0118 (309.0109)
h			88	294.9962 (294.1084)
i			73	431.0308 (431.0314)
j			69	335.0275 (335.0186)

* $[M+Na]^+$.



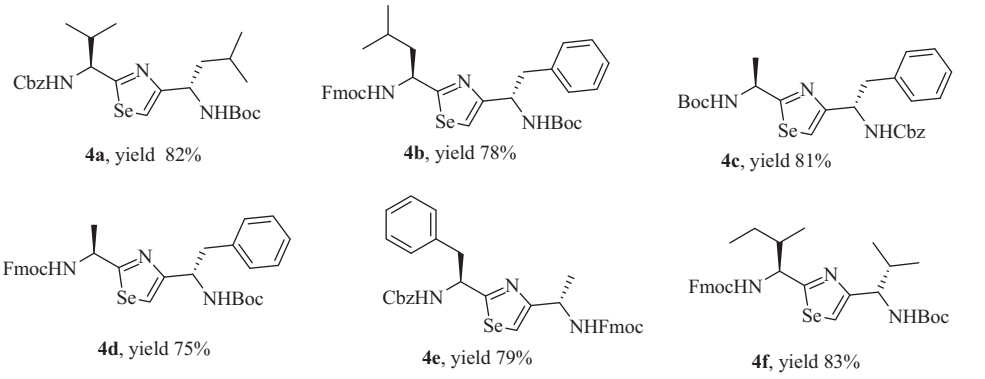
Scheme 2. Synthesis of orthogonally protected dipeptide selenazoles.

the protocol was demonstrated for the synthesis of a series of orthogonally protected dipeptide selenazoles (Table 2).

Using chiral HPLC, the racemization study of the prepared diastereomeric dipeptide selenazoles **4d** and **4d*** were analyzed. They showed peaks at R_t = 13.53 min (**4d**) and R_t = 18.42 min (**4d***), respectively. Also intentionally prepared equimolar mixture of **4d** and **4d*** showed distinct peaks at R_t = 13.62 and R_t = 18.60 min. These observations inferred that the present protocol was free from racemization.

In conclusion we have developed a simple protocol for the synthesis of selenazole linked *N*-orthogonally protected dipeptidomimetics by the condensation of N^{α}-amino selenocarboxamides with α-bromomethyl ketones. Various N^{α}-protected selenocarboxamides have also been synthesized.

Table 2
List of orthogonally protected selenazole dipeptidomimetics prepared



Acknowledgments

We thank the Board of Research in Nuclear Sciences (BRNS), Mumbai (No. 2011/37C/35/BRNS) for the financial assistance. Madhu is thankful to UGC for SRF fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.085.

References and notes

1. (a) Mugesh, G.; Singh, H. B. *Chem. Soc. Rev.* **2000**, *29*, 347; (b) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255; (c) Rappoport, Z. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Wiley, 2014; Vol. 4,
2. Mugesh, G.; du Mont, W. W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125.
3. Muttenthaler, M.; Alewood, P. F. *J. Pept. Sci.* **2008**, *14*, 1223.
4. (a) Hak, J. A.; Koketsu, M.; Eun, M. Y. E.; Yong, M. K.; Ishihara, H.; Hyun, O. Y. *J. Cell. Biochem.* **2009**, *99*, 807; (b) Choi, S. Y.; Jo, Y. O.; Koketsu, M.; Ishihara, H.; Kim, S. H.; Kim, S. Y. J. *Korean Soc. App. Biol. Chem.* **2009**, *52*, 371; (c) Nam, K. N.; Koketsu, M.; Lee, E. H. *Eur. J. Pharmacol.* **2008**, *589*, 53.
5. (a) Ueda, S.; Terauchi, H.; Suzuki, K.; Yano, A.; Matsumoto, M.; Kubo, T.; Minato, H.; Arai, Y.; Tsuji, J.; Watanabe, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 136; (b) Park, Y. J.; Koketsu, M.; Kim, J. M.; Yeo, J. H.; Ishihara, H.; Lee, K. G.; Kim, S. Y.; Kim, C. K. *Biol. Pharm. Bull.* **2003**, *26*, 1657.
6. (a) Goldstein, B. M.; Kennedy, S. D.; Hennen, W. J. *J. Am. Chem. Soc.* **1990**, *112*, 8265; (b) Sekiguchi, A.; Nishina, A.; Kimura, H.; Fukumoto, R. H.; Kanoh, K.; Ishihara, H.; Koketsu, M. *Chem. Pharm. Bull.* **2005**, *53*, 1439.
7. (a) Larsen, R.; Shinkai, I. In *Comprehensive Heterocyclic Chemistry II*; Elsevier Science: Oxford, 1996; Vol. 3, Chapter 8; (b) Koketsu, M.; Nada, F.; Ishihara, H. *Synthesis* **2002**, 195; (c) Wirth, T. *Organo Selenium Chemistry Modern Developments in Organic Synthesis*; Springer: Berlin, 2000; (d) Geisler, K.; Pfeiffer, W. D.; Muller, C.; Nobst, E.; Bulka, E.; Langer, P. *Synthesis* **2003**, 1215.
8. (a) Koketsu, M.; Takenaka, Y.; Ishihara, H. J. *Heteroat. Chem.* **2003**, *14*, 106; (b) Sommen, G. L.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2007**, *90*, 472.
9. (a) Dell, C. P.; Moody, C. J. In *Comprehensive Organic Functional Group Transformation*; Elsevier: Oxford, 1995; Vol. 5, p 565; (b) Ogawa, A.; Miyake, J.; Karasaki, Y.; Murai, S.; Sonoda, N. *J. Org. Chem.* **1985**, *50*, 384; (c) Cohen, V. I. *Synthesis* **1978**, 668.
10. (a) Lai, L. L.; Reid, D. H. *Synthesis* **1993**, 870; (b) Zhao, X. R.; Ruan, M. D.; Fan, W. Q.; Zhao, X. J. *Synth. Commun.* **1994**, *24*, 1761.
11. (a) Kaminski, R.; Glass, R. S.; Skowronska, A. *Synthesis* **2001**, 1308; (b) Shimada, K.; Hikage, S.; Takeishi, Y.; Takikawa, Y. *Chem. Lett.* **1990**, 1403.
12. Geisler, K.; Jacobs, A.; Kunzler, A.; Mathes, M.; Girrleit, I.; Zimmermann, B.; Bulka, E.; Pfeiffer, W. D.; Langer, P. *Synlett* **2002**, 1983.
13. Vishwanatha, T. M.; Narendra, N.; Chattopadhyay, B.; Mukherjee, M.; Sureshbabu, V. V. *J. Org. Chem.* **2012**, *77*, 2689.
14. Chennakrishna Reddy, G.; Nagendra, G.; Hemantha, H. P.; Das, Ushati; Guru Row, T. N.; Sureshbabu, V. V. *Tetrahedron* **2010**, *66*, 6718.
15. Sureshbabu, V. V.; Vasantha, B.; Madhu, C. *Indian J. Chem.* **2013**, *52B*, 895.
16. Hemantha, H. P.; Sureshbabu, V. V. *J. Pept. Sci.* **2010**, *16*, 644.
17. Lalithamba, H. S.; Narendra, N.; Naik, S. A.; Sureshbabu, V. V. *ARKIVOC* **2010**, *xi*, 77.
18. (a) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061; (b) Nuijens, T.; Piva, E.; Kruijtzer, J. A. W.; Rijkers, D. T. S.; Liskamp, R. M. J.; Quaedflieg, P. J. L. M. *Tetrahedron Lett.* **2012**, *53*, 377; (c) Pozdnev, V. F. *Tetrahedron Lett.* **1995**, *36*, 7115; (d) Sureshbabu, V. V.; Nagendra, G.; Venkataramanarao, R. *Ultrason. Sonochem.* **2008**, *15*, 92.
19. (a) Boden, C. D.; Pattenden, G. *J. Chem. Soc., Perkin. Trans. 1* **2000**, 875; (b) Gordon, T.; Hansen, B.; Morgan, J.; Singh, E.; Baizman, E.; Ward, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 915; (c) Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 15644; (d) Liskamp, R. M. J. *Recl. Trav. Chim. Pays-Bas* **1994**, 113.
20. (a) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195; (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1991**, *32*, 2593; (c) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; Mc Caffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354.
21. (a) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771; (b) Latif, H.; Muhammad, Z.; Rehman, U. R.; Naveed, A.; William, W. G.; David, P. L. *Chem. Pharm. Bull.* **2007**, *55*, 1014.
22. (a) Geisler, K.; Künzler, A.; Below, H.; Bulka, E.; Pfeiffer, W. D.; Langer, P. *Synthesis* **2004**, 97; (b) Koketsu, M.; Takenaka, Y.; Ishihara, H. *Synthesis* **2001**, 731; (c) Zhang, P. F.; Chen, Z. C. *Synthesis* **2000**, 1219; (d) Shafiee, A.; Shafaati, A.; Habibi-Khameneh, B. *J. Heterocycl. Chem.* **1989**, *26*, 709; (e) Cohen, V. I. *Synthesis* **1979**, 66.
23. (a) Moriarty, R. M.; Vaid, B. K.; Duncan, M. P.; Levy, S. G.; Prakash, O.; Goyal, S. *Synthesis* **1992**, 845; (b) Comrie, A. M.; Dingwall, D.; Stenlake, J. B. *J. Chem. Soc.* **1963**, 5713.
24. Tao, H.; Weng, Y.; Zhuo, R.; Chang, G.; Urbatsch, I. L.; Zhang, Q. *Chem. Biochem.* **2011**, *12*, 868.
25. Narendra, N.; Vishwanatha, T. M.; Sudarshan, N. S.; Sureshbabu, V. V. *Protein Pept. Lett.* **2009**, *16*, 1029.

Further reading

26. *(a) General procedure for the preparation of P_2Se_5*
Red phosphorus was washed with anhydrous ether (10 mL) then dried. It (10 mmol) was taken into glass vial and greyish elemental selenium powder (25 mmol) was added. The resulting mixture was heated under electric Bunsen until it turned to glassy black-purple solid and then cooled to rt and grained.
(b) General procedure for the synthesis of N^{α}-protected amino selenocarboxamides **2a–j**.
To a solution of N^{α}-protected amino nitrile (10 mmol) in EtOH (10 mL), freshly prepared glassy black powdered P_2Se_5 (20 mmol) was added. The reaction mixture was refluxed followed by the addition of a few drops of water. After complete consumption of the starting material (TLC analysis; 3–4 h), the reaction mixture was filtered. The solvent was removed in vacuo and the crude residue was purified by column chromatography (hexane/EtOAc 8:2%).
(c) General procedure for the synthesis of orthogonally protected dipeptide selenazoles **4a–f**
To a solution of N^{α}-protected amino selenocarboxamide (10 mmol) in dry acetone (10 mL), N^{α}-protected amino acid derived bromomethylketone (10 mmol) was added. The reaction mixture was refluxed for about 30 min. After completion of the reaction, the solvent was removed in vacuo and the crude residue was purified by column chromatography (hexane/EtOAc 9:1%) to obtain the pure dipeptide selenazole in good yield.
27. *Characterization data for selected compounds*
Compound **2a**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.91 (d, 2H, J = 6.8 Hz), 3.94 (t, 1H, J = 5.4 Hz), 4.36 (t, 1H, J = 4.8 Hz), 4.59 (d, 2H, J = 4.8 Hz), 6.12 (br, 1H), 7.12–7.55 (m, 13H), 9.83 (br s, 1H), 10.26 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 40.1, 48.3, 51.7, 66.9, 122.6, 125.2, 126.2, 127.7, 128.0, 128.3, 128.7, 139.3, 141.0, 143.5, 152.4, 196.1; ^{77}Se NMR (75 MHz, DMSO-d_6): δ 490.5; HRMS (m/z) calcd for: $C_{24}H_{22}N_2O_2SeNa$ 473.0744; found: 473.0735 [M+Na]$^+$.
Compound **2f**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.22–1.25 (m, 2H), 1.37 (s, 9H),

1.38–1.41 (m, 2H), 1.50–1.53 (m, 2H), 2.85 (t, 2H, J = 4.8 Hz), 3.72 (t, 1H, J = 4.2 Hz), 5.18 (s, 2H), 6.88 (br, 1H), 7.10 (br, 1H), 7.12–7.16 (m, 5H), 9.56 (br s, 1H), 9.92 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 21.9, 27.9, 31.2, 33.5, 40.8, 50.3, 66.1, 78.5, 127.2, 127.6, 129.8, 140.9, 151.9, 153.3, 197.1; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 517.1; HRMS (m/z) calcd for: $C_{19}H_{29}N_3O_4SeNa$ 466.1221; found: 466.0982 $[M+Na]^+$.

Compound **2i**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.72 (d, 2H, J = 6.6 Hz), 3.61 (s, 2H), 3.81 (t, 1H, J = 3.8 Hz), 5.37 (s, 2H), 7.05 (br, 1H), 7.12–7.19 (m, 10H), 9.88 (br s, 1H), 10.07 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 35.5, 39.5, 53.2, 65.9, 127.2, 127.6, 127.9, 128.2, 128.6, 128.8, 137.2, 141.3, 152.2, 196.7; ^{77}Se NMR (75 MHz, DMSO-d_6): δ 497.8; HRMS (m/z) calcd for: $C_{18}H_{20}N_2O_2SSeNa$ 431.0308; found: 431.0314 $[M+Na]^+$.

Compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, 6H, J = 6.2 Hz), 1.17 (d, 6H, J = 6.4 Hz), 1.38 (s, 9H), 1.52–1.57 (m, 2H), 1.71–1.74 (m, 1H), 2.33–2.37 (m, 1H), 3.25 (d, 1H, J = 6.8 Hz), 4.21 (t, 1H, J = 5.2 Hz), 5.15 (s, 1H), 5.31 (s, 2H), 5.75 (br, 1H), 6.62 (br, 1H), 7.15–7.19 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 17.8, 21.2, 24.5, 29.3, 32.7, 41.4, 49.8, 56.9, 65.7, 81.1, 114.5, 127.1, 127.6, 128.5, 141.4, 149.8, 155.7, 156.5, 174.5; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 656.3; HRMS (m/z) calcd for: $C_{25}H_{37}N_3O_4SeNa$ 546.1847; found: 546.1884 $[M+Na]^+$.

Compound **4b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (d, 6H, J = 7.4 Hz), 1.35 (s, 9H), 1.67–1.93 (m, 3H), 2.63 (d, 2H, J = 5.6 Hz), 3.41 (t, 1H, J = 4.8 Hz), 4.16 (t, 1H, J = 5.2 Hz), 4.41 (t, 1H, J = 7.0 Hz), 4.68 (d, 2H, J = 7.0 Hz), 5.17 (s, 1H), 6.15 (br, 1H), 6.92 (br, 1H), 7.13–7.78 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$): 23.5, 24.7, 29.1, 35.2, 38.7 41.1, 47.4, 55.2, 67.7, 80.4, 115.9, 126.1, 126.6, 127.7, 128.1, 128.5, 128.7, 129.2, 138.8, 141.5, 143.2, 151.5, 156.3, 157.2, 175.4; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 681.7; HRMS (m/z) calcd for: $C_{36}H_{41}N_3O_4SeNa$ 682.2160; found: 682.2195 $[M+Na]^+$.

Compound **4e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (d, 3H, J = 7.2 Hz), 2.51 (d, 2H, J = 6.8 Hz), 3.85 (t, 1H, J = 4.6 Hz),), 4.32 (t, 1H, J = 6.2 Hz), 4.42–4.47 (m, 1H), 4.78 (d, 2H, J = 6.2 Hz), 5.12 (s, 1H), 5.28 (s, 2H), 6.31 (br, 1H), 6.92 (br, 1H), 7.15–7.71 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): 17.6, 35.4, 45.1, 47.3, 54.0, 65.7, 68.2, 110.9, 126.4, 126.8, 127.3, 127.6, 127.8, 128.3, 128.5, 128.7, 128.9, 129.2, 139.2, 140.8, 141.5, 143.2, 152.1, 156.2, 157.5, 171.8; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 681.1; HRMS (m/z) calcd for: $C_{36}H_{33}N_3O_4SeNa$ 674.1534; found: 674.1527 $[M+Na]^+$.