Synthesis of *N*-Fmoc-Protected Amino Alkyl Thiocyanates/Selenocyanates and Their Application in the Preparation of 5-Substituted *S*/*Se*-Linked Tetrazoles

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Abstract: A novel class of *N*-Fmoc-protected amino alkyl thiocyanates/selenocyanates has been prepared by thiocyanation/selenocyanation of the corresponding alkyl iodides. These thiocyanates/selenocyanates undergo a facile [2+3]-cycloaddition reaction with sodium azide to afford novel *N*-Fmoc amino alkyl *S*/*Se*-linked tetrazoles.

Key words: amino acid derivatives, thiocyanates, selenocyanates, [2+3] cycloaddition, *S*/*Se*-linked tetrazoles

Modification of the native structure of amino acids by inserting heterocycles such as tetrazoles, triazoles, thiazoles and isoxazoles through selective carboxy group transformation has been of considerable interest in biochemistry, enzymology and pharmacology.[1] In particular, tetrazoles have been extensively studied in recent years due to their ability to act as a metabolically stable surrogate for the carboxy group,[2] and hence have been used in designing potential anti-inflammatory, central nervous stimulant and hypertensive agents. They are also employed as *cis*-peptide bond mimics and have found numerous applications as catalysts in asymmetric synthesis.[3] Specifically, 5-*S*-linked tetrazoles are an important class of compounds known for their biological and chemical potency. Due to the presence of the alkylthio linkage, they show increased acidity and solubility which makes them powerful activators for DNA and RNA syntheses.[4] On similar lines, 5-*Se*-linked tetrazoles would also represent a useful subclass which has scarcely been addressed in the literature. The recent surge in selenium chemistry,[5] and the discovery of several selenoproteins, prompted us to work on selenium derivatization of amino acids, such as the 5-*Se*-linked tetrazoles.

The most feasible and practical routes for the synthesis of tetrazoles, in general, involve either reaction of a substituted halide with 1*H*-tetrazole or a [2+3]-cycloaddition reaction of a nitrile with an azide ion.[1a,6] Demko and Sharpless have reported an efficient protocol for the synthesis of 5-substituted amino alkyl tetrazoles by the reaction of N^{α}-Z amino nitriles with sodium azide and zinc bromide, followed by removal of the Z group; however, the removal of the protecting group was a challenging task.[1a–c] In this regard, our use of the Fmoc group for N^{α}-protection led to a simple isolation of the free amino tetrazoles.[7] A literature survey on *S*/*Se*-linked tetrazoles resulted in a handful of reports. Dondoni and co-workers synthesized *S*-tetrazoles bearing *C*-glycosyl α-amino acids wherein sugar-derived *C*-alkyl azides were first treated with tosyl cyanide at 100 °C, followed by replacement of the tosyl group with cysteine thiol.[8] Jursic's group reported the synthesis of 5-alkyl- and 5-aryl-*S*-linked tetrazoles from the corresponding thiocyanates.[9] Yildirir and co-workers prepared *Se*-linked tetrazoles by a reaction of aromatic selenocyanates with sodium azide.[10] Though tetrazole derivatives of amino acids have been prepared and employed in varied applications including organic catalysis,[3] the chemistry has not been extended to the preparation of *S*/*Se*-linked tetrazole derivatives from amino acids. Due to the widespread application of *S*/*Se*-linked tetrazolyl compounds, we reasoned that insertion of such moieties in place of the carboxy group of an amino acid would generate novel precursors for the synthesis of peptidic drug candidates, as well as for catalyst applications.[11] In the present study, the synthesis of *S*/*Se*-linked tetrazoles by a [2+3]-cycloaddition reaction of N-protected amino alkyl thiocyanates/selenocyanates with sodium azide is described.

With our previous experience in the synthesis of N^{α}-Fmoc amino tetrazoles from the respective nitriles, we envisaged that N^{α}-Fmoc amino alkyl thiocyanates/selenocyanates would be the ideal intermediates for accessing *S*/*Se*-linked tetrazoles. Thiocyanates/selenocyanates are versatile synthetic intermediates and, owing to their electrophilic nature, they can be engaged as effective dipolarophilic partners of an azide ion. Thiocyanato compounds themselves have been used for the preparation of a few pharmaceuticals.[12] They can also serve as precursors for a plethora of diverse reactions including the synthesis of thio-heterocycles, thiophenols, thiocarbamates, dithiourethanes and sulfonyl cyanides.[13] Likewise, organic selenocyanates are also of interest due to their enhanced cancer chemopreventive activities and utility as starting materials for the synthesis of selenium-containing heterocycles, diselenides and selenoketones.[14]

Several methods are available for the preparation of thiocyanates; most of these involve substitution of a halide with thiocyanic acid or its salt. Some of the other notable protocols make use of thiocyanating agents such as 1-*n*-butyl-3-methylimidazolium thiocyanate ([bmim]SCN),[15] direct nucleophilic substitution of alcohols with the thio-

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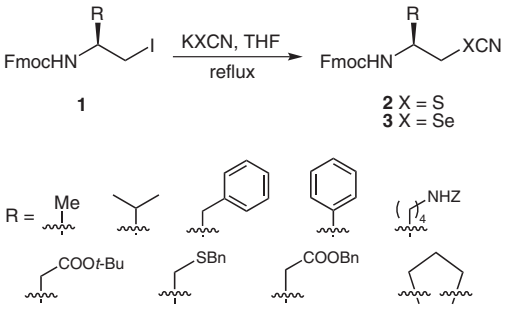
cyanate anion[16] or the Mitsunobu reagent system (Ph_3P–DEAD–NH_4SCN).[17] Similarly, selenocyanates are accessed by nucleophilic substitution of halides with the selenocyanate ion.[18] Kachanov's group reported a one-pot synthesis of selenocyanates using triselenium dicyanide as the selenocyanating agent.[19]

Our interest in designing peptidomimetics and unnatural amino acid derivatives has led to several useful amino acid derived synthons including isocyanates of N^{α}-Fmoc-protected amino acids,[20] *N*-urethane-protected amino alkyl isothiocyanates,[21] N^{α}-Fmoc amino alkyl formamides[22] and *N*-Fmoc β-amino alkyl isonitriles.[23] Though thiocyanate and selenocyanate derivatives have prevailed in various other classes of compounds including carbohydrates,[24] to the best of our knowledge, N-protected amino alkyl thiocyanates and selenocyanates are yet to be reported.

In the present work, the Fmoc group was selected for N-protection[25] and potassium thiocyanate as the thiocyanating agent.[26] The essential precursors, *N*-Fmoc amino alkyl iodides **1a–h** (Scheme 1), were prepared via a reported protocol.[27] In brief, *N*-Fmoc amino acids were reduced to the corresponding β-amino alcohols[28] and then subjected to the Mitsunobu reaction (Ph_3P–imidazole–I_2).[21] In the next step, a solution of the *N*-Fmoc amino alkyl iodide **1** was treated with potassium thiocyanate. Either at room temperature or under reflux, the progress of the reaction was not satisfactory; however, use of a catalytic amount of tetrabutylammonium bromide drove the reaction to completion in a short duration of time. In a typical reaction, a solution of Fmoc-Phe-ψ(CH_2I) (**1c**, R = Bn) in tetrahydrofuran was refluxed along with potassium thiocyanate and catalytic tetrabutylammonium bromide (Scheme 1). After completion of the reaction (TLC analysis), a simple work-up afforded the corresponding thiocyanate **2c** in good yield with a purity of about 91%. HPLC analysis of crude **2c** showed a single major peak and no trace of the corresponding isothiocyanate, which otherwise can be formed due to the ambient nature of the thiocyanate ion, was observed. This was further confirmed by comparing the HPLC chromatograms of Fmoc-Phg-ψ(CH_2NCS) (prepared according to our previous report[21]) with Fmoc-Phg-ψ(CH_2SCN) (**2d**, R = Ph) now in hand.[29]



Scheme 1 Synthesis of *N*-Fmoc-protected amino alkyl thiocyanates/selenocyanates

A single recrystallization using tetrahydrofuran–hexane elevated the purity of the samples to 99% (HPLC analysis). The ^{13}C NMR spectra of these thiocyanates have a prominent signal around 112 ppm, characteristic of SCN, while the IR spectra display a CN stretch at around 2135 cm^{-1}.

To demonstrate the generality of this protocol, a series of *N*-Fmoc amino alkyl iodides was converted into the corresponding thiocyanates **2a–e**, including examples derived from bifunctional amino acids, resulting in Fmoc-Cys(Bn)-ψ(CH_2SCN) (**2f**), Fmoc-Asp(*t*-Bu)-ψ(CH_2SCN) (**2g**) and Fmoc-Lys(Z)-ψ(CH_2SCN) (**2h**) (Table 1). The thiocyanates were stable toward long-time storage at ambient temperature, with no noticeable degradation, as confirmed by HPLC analysis. Further, the thiocyanate moiety was also inserted in place of the side-chain hydroxy group of serine and homoserine (Figure 1; **2i**, **2j**).

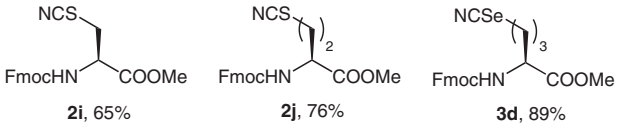
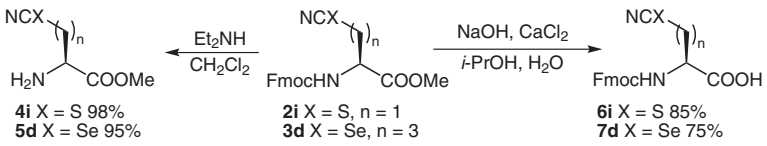


Figure 1

A similar protocol was also employed for the preparation of a few *N*-Fmoc amino alkyl selenocyanates, by reaction of the corresponding alkyl iodides with potassium selenocyanate (Table 1, **3a–c**). The ^{13}C NMR spectrum of **3a** has a characteristic signal at 101.9 ppm and the IR spectrum shows a CN stretch at 2145 cm^{-1}. The selenocyanate moiety was also inserted in the ω-carboxy position of Fmoc-Glu-OMe (Figure 1, **3d**).

Further, treatment of **2i** and **3d** in a separate set of experiments with diethylamine–dichloromethane (1:1) for 45 minutes afforded the corresponding free amino methyl esters **4i** and **5d** in 98% and 95% yield, respectively (Scheme 2). On the other hand, deprotection of the methyl ester in **2i** and **3d** was accomplished following a protocol reported by Pascal and Sola;[30] the free carboxy compounds **6i** and **7d** were isolated in 85% and 75% yield, respectively (Scheme 2). All of these compounds were characterized employing mass and NMR spectroscopy.

In the next set of experiments, we undertook the synthesis of *S*- and *Se*-linked tetrazoles. In a typical study, Fmoc-



Scheme 2

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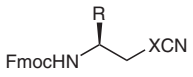
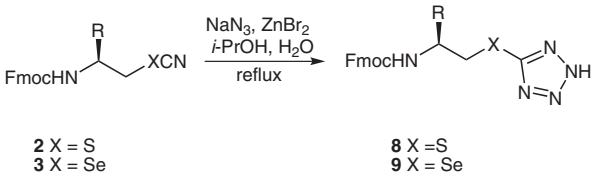
Table 1 List of the Synthesized Thiocyanates/Selenocyanates **2/3**

Entry		R	X	Yield (%)	Mp (°C)	$[\alpha]_D^{29}$ (*c* 0.2, MeOH)	HRMS: $[M + Na]^+$ calcd (found)
1	**2a**	Me	S	92	104–106	+68.0	361.0987 (361.0981)
2	**2b**	*i*-Pr	S	91	107–108	+38.1	389.1300 (389.1294)
3	**2c**	Bn	S	94	105–107	+28.5	432.1746 (432.1742)[a]
4	**2d**	Ph	S	91	gum	–2.2	418.1589 (418.1588)[a]
5	**2e**	-$(CH_2)_3$-[Pro]	S	82	gum	–4.2	387.1143 (387.1146)
6	**2f**	CH_2SBn	S	81	gum	+4.0	483.1177 (483.1171)
7	**2g**	CH_2COO*t*-Bu	S	71	98–99	–2.4	461.1511 (461.1516)
8	**2h**	$(CH_2)_4NHZ$	S	88	106–108	+6.0	547.2379 (547.2373)[a]
9	**3a**	Me	Se	89	102–103	+12.3	409.0431 (409.0438)
10	**3b**	*i*-Pr	Se	88	109–110	+23.5	437.0744 (437.0750)
11	**3c**	*i*-Bu	Se	86	111–113	+28.3	451.0901 (451.0908)

[a] $[M + NH_4]^+$.

Phe-ψ(CH_2SCN) (**2c**, R = Bn) was refluxed along with sodium azide and zinc bromide in a water–2-propanol system (Scheme 3). The reaction was complete in 4.5 hours (TLC analysis). It is worth mentioning that, compared to nitriles,[7] thiocyanates undergo the cycloaddition reaction with sodium azide in a shorter duration of time, which can be attributed to the electron-withdrawing nature of the S atom. A simple workup afforded the desired *S*-linked tetrazole **8c** as a solid in 88% yield. The protocol was extended to the preparation of a series of examples of *N*-Fmoc amino alkyl *S*-linked tetrazoles **8a**–**h**. In a similar way, *Se*-linked tetrazoles **9a**–**c** were prepared by a [2+3]-cycloaddition reaction of the corresponding selenocyanates with sodium azide (Scheme 3, Table 2).

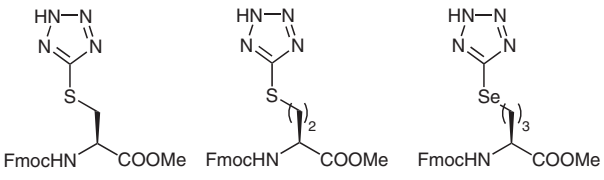


2 X = S
3 X = Se

8 X = S
9 X = Se

Scheme 3 Synthesis of *N*-Fmoc-protected amino alkyl *S*/*Se*-linked tetrazoles

Further, *S*-linked tetrazoles were also incorporated in the side chain of serine and homoserine (Figure 2; **8i**, **8j**). In another example, a *Se*-linked tetrazole was inserted in place of the ω-carboxy group of Fmoc-Glu-OMe (Figure 2, **9d**).



8i, 65% **8j**, 76% **9d**, 79%

Figure 2

Two *S*-linked tetrazoles **8a**, **8e** and a *Se*-linked tetrazole **9b** were treated with diethylamine–dichloromethane (1:1) and the free amino alkyl *S*/*Se*-linked tetrazoles **10a**, **10e** and **11b**, respectively, were isolated as solids (Figure 3). The purity of these free amino derivatives was confirmed by RP-HPLC.[31]

In summary, the preparation of *N*-Fmoc amino alkyl thiocyanates/selenocyanates by reaction of the corresponding

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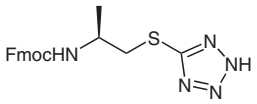
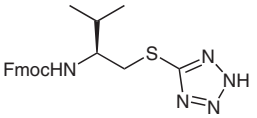
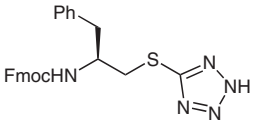
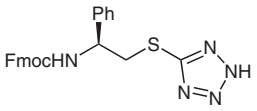
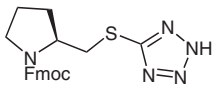
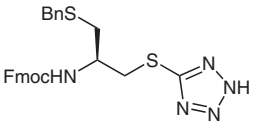
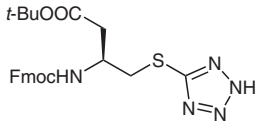
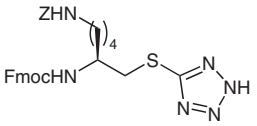
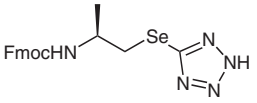
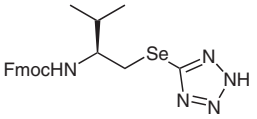
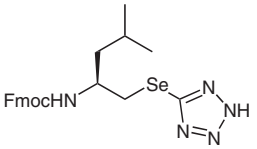
Table 2 List of the Synthesized *S*/*Se*-Linked Tetrazoles **8/9**

Entry	Tetrazole		Yield (%)	Mp (°C)	$[\alpha]_D^{29}$ (*c* 0.2, THF)	HRMS: $[M + Na]^+$ calcd (found)
1	**8a**		92	92–94	–21.0	382.13 (382.05)[a,b]
2	**8b**		87	gum	+12.0	410.1651 (410.1646)[b]
3	**8c**		88	141–142	+9.0	480.1470 (480.1465)
4	**8d**		88	151–152	+8.4	444.1494 (444.1498)[b]
5	**8e**		85	gum	–13.5	408.1494 (408.1495)[b]
6	**8f**		85	142–143	+16.7	521.1793 (521.1785)[c]
7	**8g**		78	78–80	+11.9	504.1681 (504.1686)
8	**8h**		78	148–150	+18.6	573.2284 (573.2287)[b]
9	**9a**		89	136–139	+3.5	430.0782 (430.0790)[b]
10	**9b**		86	gum	+1.6	480.0915 (480.0923)
11	**9c**		85	gum	+5.6	472.1252 (472.1260)[b]

[a] ESI-MS.
[b] $[M + H]^+$.
[c] $[M + NH_4]^+$.

alkyl iodides with potassium thiocyanate or selenocyanate in the presence of tetrabutylammonium bromide is reported. The synthetic utility of these thiocyanates/selenocyanates has been demonstrated by the preparation of a hitherto unreported class of 5-substituted *S*/*Se*-linked tetrazoles via a [2+3]-cycloaddition reaction with sodium azide. Side-chain modification of a few bifunctional amino acids is also reported. Free α-amino alkyl *S*/*Se*-linked tetrazoles were isolated upon removal of the Fmoc group. Keeping in mind the advantages of tetrazole analogues of amino acids, the *S*,*Se*-linked tetrazole derivatives are also expected to deliver interesting properties.

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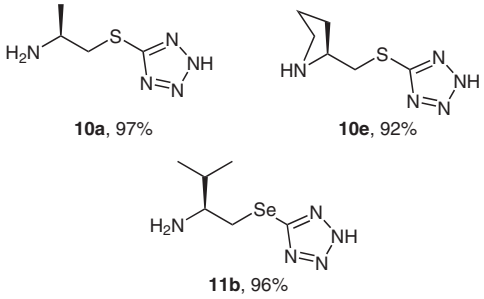

Figure 3

All solvents were distilled prior to use and reagents were used as received from Sigma-Aldrich. Melting points were determined on a Büchi model 150 melting point apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Nicolet Impact 400D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution). ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 (400 MHz) spectrometer. High-resolution mass spectra (HRMS) were recorded on a Micromass Q-Tof mass spectrometer. HPLC analysis was carried out using an Agilent 1100 series G1311A VWD system at λ = 254 nm (flow: 0.5 mL/min, column: C18, 5 μm pore size, 4.6 × 250 mm).

N-Fmoc Amino Alkyl Thiocyanates/Selenocyanates 2/3; General Procedure

To a soln of a *N*-Fmoc amino alkyl iodide **1** (1 mmol) in THF (15 mL) were added KSCN or KSeCN (1.5 mmol) and TBAB (0.1 mmol), and the mixture was refluxed for about 3 h. After completion of the reaction (TLC), the solvent was evaporated under reduced pressure. The residue was diluted with EtOAc (12 mL); this solution was washed with H_2O (2 × 10 mL) and brine (10 mL), and dried (anhyd Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was recrystallized (EtOAc–hexane) to obtain the product **2/3** as analytically pure material.

(9*H*-Fluoren-9-yl)methyl (*S*)-1-Thiocyanatopropan-2-ylcarbamate [Fmoc-Ala-ψ(CH_2SCN), 2a]

Yield: 311 mg (92%); white solid; mp 104–106 °C; R_f = 0.3 (*n*-hexane–EtOAc, 9:1).

IR (KBr): 1713, 2138 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 4.8 Hz, 3 H), 3.02–3.08 (m, 2 H), 3.96 (m, 1 H), 4.11–4.20 (m, 2 H), 4.21 (t, *J* = 3.0 Hz, 1 H), 4.99 (br, 1 H), 7.21–7.68 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 40.2, 47.7, 52.7, 67.2, 113.0, 120.5, 125.6, 127.6, 128.3, 141.8, 144.2, 155.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{18}N_2NaO_2S$: 361.0987; found: 361.0981.

(9*H*-Fluoren-9-yl)methyl (*S*)-3-Methyl-1-thiocyanatobutan-2-ylcarbamate [Fmoc-Val-ψ(CH_2SCN), 2b]

Yield: 333 mg (91%); white solid; mp 107–108 °C; R_f = 0.25 (*n*-hexane–EtOAc, 9:1).

IR (KBr): 1701, 2138 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 4.8 Hz, 6 H), 1.81 (m, 1 H), 3.05 (d, *J* = 6.0 Hz, 2 H), 3.55–3.68 (m, 1 H), 4.05–4.22 (m, 3 H), 4.86 (d, *J* = 6.0 Hz, 1 H), 7.18–7.68 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6, 19.9, 31.4, 37.7, 47.7, 57.0, 67.1, 113.0, 120.5, 125.5, 127.6, 128.2, 141.8, 144.2, 156.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{22}N_2NaO_2S$: 389.1300; found: 389.1294.

(9*H*-Fluoren-9-yl)methyl (*S*)-3-Phenyl-1-thiocyanatopropan-2-ylcarbamate [Fmoc-Phe-ψ(CH_2SCN), 2c]

Yield: 390 mg (94%); white solid; mp 105–107 °C; R_f = 0.35 (*n*-hexane–EtOAc, 9:1).

IR (KBr): 1708, 2135 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.74 (d, *J* = 5.1 Hz, 2 H), 4.07 (d, *J* = 5.7 Hz, 2 H), 4.15 (t, *J* = 5.7 Hz, 1 H), 4.31 (m, 1 H), 4.42 (d, *J* = 6.8 Hz, 2 H), 5.35 (d, *J* = 5.7 Hz, 1 H), 7.16–7.62 (m, 13 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.5, 47.3, 52.3, 53.0, 62.3, 111.9, 120.1, 124.9, 125.1, 127.1, 127.9, 128.1, 129.9, 138.9, 141.4, 143.5, 156.1.

HRMS: *m*/*z* [M + NH_4]$^+$ calcd for $C_{25}H_{26}N_3O_2S$: 432.1746; found: 432.1742.

(9*H*-Fluoren-9-yl)methyl (*S*)-1-Phenyl-2-thiocyanatoethylcarbamate [Fmoc-Phg-ψ(CH_2SCN), 2d]

Yield: 364 mg (91%); gum; R_f = 0.35 (*n*-hexane–EtOAc, 9:1).

IR (CH_2Cl_2): 1703, 2139 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.40 (d, *J* = 6.0 Hz, 2 H), 4.15 (t, *J* = 4.5 Hz, 1 H), 4.21 (m, 1 H), 4.28 (d, *J* = 3.2 Hz, 2 H), 5.98 (m, 1 H), 7.26–7.77 (m, 13 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.1, 47.2, 55.2, 66.9, 111.6, 124.9, 126.4, 127.1, 127.7, 128.5, 128.7, 129.2, 138.1, 141.3, 143.6, 155.5.

HRMS: *m*/*z* [M + NH_4]$^+$ calcd for $C_{24}H_{24}N_3O_2S$: 418.1589; found: 418.1588.

(9*H*-Fluoren-9-yl)methyl (*S*)-2-(Thiocyanatomethyl)pyrrolidine-1-carboxylate [Fmoc-Pro-ψ(CH_2SCN), 2e]

Yield: 299 mg (82%); gum; R_f = 0.25 (*n*-hexane–EtOAc, 9:1).

IR (CH_2Cl_2): 1712, 2137 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.07 (m, 4 H), 3.35 (m, 2 H), 3.59 (m, 2 H), 3.84 (m, 1 H), 4.15 (t, *J* = 6.0 Hz, 1 H), 4.28 (d, *J* = 3.6 Hz, 2 H), 7.26–7.76 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 30.3, 35.0, 47.3, 47.8, 53.6, 67.2, 119.8, 124.2, 125.3, 126.8, 127.4, 141.0, 144.9, 155.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}N_2NaO_2S$: 387.1143; found: 387.1146.

(9*H*-Fluoren-9-yl)methyl (*S*)-1-(Benzylthio)-3-thiocyanatopropan-2-ylcarbamate [Fmoc-Cys(Bn)-ψ(CH_2SCN), 2f]

Yield: 373 mg (81%); gum; R_f = 0.35 (*n*-hexane–EtOAc, 9:1).

IR (CH_2Cl_2): 1699, 2138 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.02 (d, *J* = 6.2 Hz, 2 H), 3.35 (d, *J* = 7.2 Hz, 2 H), 3.68 (s, 2 H), 4.12–4.30 (m, 3 H), 4.42 (br, 1 H), 5.32 (br, 1 H), 7.13–7.82 (m, 13 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.9, 36.5, 36.9, 47.1, 50.6, 66.8, 111.9, 125.0, 127.0, 127.4, 127.7, 128.7, 128.8, 130.1, 137.3, 141.3, 143.6, 155.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{24}N_2NaO_2S_2$: 483.1177; found: 483.1171.

tert-Butyl (*S*)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-4-thiocyanatobutanoate [Fmoc-Asp(*t*-Bu)-ψ(CH_2SCN), 2g]

Yield: 311 mg (71%); white solid; mp 98–99 °C; R_f = 0.30 (*n*-hexane–EtOAc, 9:1).

IR (KBr): 1714, 2134 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9 H), 2.77 (d, *J* = 6.8 Hz, 2 H), 3.21 (d, *J* = 6.2 Hz, 2 H), 3.82 (m, 1 H), 4.14 (t, *J* = 5.6 Hz, 1 H), 4.29 (d, *J* = 4.4 Hz, 2 H), 5.62 (br, 1 H), 7.29–7.38 (m, 8 H).

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^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.5, 37.0, 42.3, 46.2, 48.3, 67.1, 82.5, 111.6, 128.0, 128.2, 128.3, 128.5, 141.1, 143.4, 155.4, 171.1.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{26}N_2NaO_4S$: 461.1511; found: 461.1516.

(9*H*-Fluoren-9-yl)methyl (*S*)-6-{[(Benzyloxy)carbonyl]amino}-1-thiocyanatohexan-2-ylcarbamate [Fmoc-Lys(Z)-ψ(CH_2SCN), 2h]

Yield: 466 mg (88%); white solid; mp 106–108 °C; R_f = 0.30 (*n*-hexane–EtOAc, 9:1).

IR (KBr): 1699, 2140 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32–1.68 (m, 6 H), 3.02 (m, 2 H), 3.56 (d, *J* = 3.8 Hz, 2 H), 3.85 (m, 1 H), 4.12–4.35 (m, 3 H), 5.21 (s, 2 H), 6.43 (br, 2 H), 7.23–7.56 (m, 13 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 29.6, 32.1, 38.6, 40.2, 47.2, 51.2, 62.2, 66.7, 112.3, 124.9, 127.0, 127.7, 128.0, 128.1, 128.5, 128.8, 136.5, 141.3, 143.7, 155.8, 156.6.

HRMS: *m*/*z* [M + NH_4]$^+$ calcd for $C_{30}H_{35}N_4O_4S$: 547.2379; found: 547.2373.

Methyl (*R*)-2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-3-thiocyanatopropanoate [Fmoc-Ser(ψSCN)-OMe, 2i]

Yield: 248 mg (65%); gum; R_f = 0.30 (*n*-hexane–EtOAc, 9:1).

IR (CH_2Cl_2): 1705, 1735, 2135 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (d, *J* = 4.4 Hz, 2 H), 3.82 (s, 3 H), 4.32 (t, *J* = 3.41 Hz, 1 H), 4.56 (d, *J* = 6.3 Hz, 2 H), 4.77 (m, 1 H), 5.97 (br, 1 H), 7.25–7.71 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.7, 47.7, 52.1, 53.1, 67.5, 112.1, 124.5, 125.6, 126.2, 127.1, 142.3, 144.9, 156.7, 171.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{18}N_2NaO_4S$: 405.0885; found: 405.0886.

Methyl (*S*)-2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-4-thiocyanatobutanoate [Fmoc-HSer(ψSCN)-OMe, 2j]

Yield: 301 mg (76%); gum; R_f = 0.30 (*n*-hexane–EtOAc, 9:1).

IR (CH_2Cl_2): 1738, 2139 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98–2.11 (m, 4 H), 3.02 (m, 1 H), 3.85 (s, 3 H), 4.05–4.32 (m, 3 H), 7.07–7.59 (m, 8 H), 7.61 (d, *J* = 4.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 30.2, 47.6, 52.1, 53.0, 67.2, 112.8, 127.6, 127.7, 128.3, 129.4, 141.8, 144.2, 156.1, 171.1.

HRMS: *m*/*z* [M + NH_4]$^+$ calcd for $C_{21}H_{24}N_3O_4S$: 414.1488; found: 414.1484.

(9*H*-Fluoren-9-yl)methyl (*S*)-1-Selenocyanatopropan-2-ylcarbamate [Fmoc-Ala-ψ(CH_2SeCN), 3a]

Yield: 343 mg (89%); white solid; mp 102–103 °C; R_f = 0.35 (*n*-hexane–EtOAc, 9:1).

IR (KBr): 1698, 2145 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 5.2 Hz, 3 H), 3.25 (d, *J* = 4.8 Hz, 2 H), 3.91 (m, 1 H), 4.11 (t, *J* = 4.2 Hz, 1 H), 4.23 (d, *J* = 5.8 Hz, 2 H), 5.99 (d, *J* = 6.2 Hz, 1 H), 7.20–7.69 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 33.8, 47.8, 48.9, 67.8, 101.9, 120.6, 125.6, 127.7, 128.3, 141.9, 144.3, 155.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{18}N_2NaO_2Se$: 409.0431; found: 409.0438.

(9*H*-Fluoren-9-yl)methyl (*S*)-3-Methyl-1-selenocyanatobutan-2-ylcarbamate [Fmoc-Val-ψ(CH_2SeCN), 3b]

Yield: 364 mg (88%); white solid; mp 109–110 °C; R_f = 0.30 (*n*-hexane–EtOAc, 9:1).

IR (KBr): 1699, 2144 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.6 Hz, 6 H), 1.84 (m, 1 H), 3.17 (d, *J* = 4.8 Hz, 2 H), 3.67 (m, 1 H), 4.39 (t, *J* = 4.4 Hz, 1 H), 4.48 (d, *J* = 5.4 Hz, 2 H), 4.85 (d, *J* = 5.6 Hz, 1 H), 7.26–7.73 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 19.9, 32.3, 33.2, 47.8, 57.2, 67.1, 102.6, 120.5, 127.6, 128.3, 141.9, 144.2, 156.7.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{22}N_2NaO_2Se$: 437.0744; found: 437.0750.

(9*H*-Fluoren-9-yl)methyl (*S*)-4-Methyl-1-selenocyanatopentan-2-ylcarbamate [Fmoc-Leu-ψ(CH_2SeCN), 3c]

Yield: 368 mg (86%); white solid; mp 111–113 °C; R_f = 0.30 (*n*-hexane–EtOAc, 9:1).

IR (KBr): 1701, 2141 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (m, 6 H), 1.31 (m, 2 H), 1.93 (m, 1 H), 3.12 (d, *J* = 5.9 Hz, 2 H), 3.95 (m, 1 H), 4.21–4.31 (m, 3 H), 6.53 (br, 1 H), 7.21–7.67 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 22.9, 24.9, 33.5, 43.8, 47.8, 51.0, 67.2, 102.7, 121.0, 125.5, 127.6, 128.4, 141.8, 144.5, 157.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{24}N_2NaO_2Se$: 451.0901; found: 451.0908.

Methyl (*S*)-2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-5-selenocyanatopentanoate (3d)

Yield: 407 mg (89%); gum; R_f = 0.32 (*n*-hexane–EtOAc, 9:1).

IR (CH_2Cl_2): 1712, 1742, 2146 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (m, 2 H), 1.85 (m, 2 H), 2.21 (t, *J* = 3.4 Hz, 2 H), 3.65 (s, 3 H), 4.18 (m, 1 H), 4.38 (t, *J* = 4.2 Hz, 1 H), 4.59 (d, *J* = 4.8 Hz, 2 H), 5.42 (br, 1 H), 7.18–7.72 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 27.6, 34.1, 46.7, 51.6, 55.0, 67.0, 102.1, 122.1, 125.7, 127.7, 128.3, 141.9, 144.3, 156.0, 172.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}N_2NaO_4Se$: 481.0642; found: 481.0649.

Methyl (*R*)-2-Amino-3-thiocyanatopropanoate [H-Ser(ψSCN)-OMe, 4i]

Yield: 57 mg (98% from **2i**); gum.

IR (CH_2Cl_2): 1735, 2135 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.48 (d, *J* = 5.0 Hz, 2 H), 3.82 (s, 3 H), 4.07 (m, 1 H), 5.01 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.8, 52.1, 53.5, 112.1, 171.5.

ESI-MS: *m*/*z* [M – H]$^+$ calcd for $C_5H_7N_2O_2S$: 159.02; found: 159.06.

Methyl (*S*)-2-Amino-5-selenocyanatopentanoate (5d)

Yield: 63 mg (95% from **3d**); gum.

IR (CH_2Cl_2): 1742, 2146 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.22 (m, 2 H), 1.55 (m, 2 H), 2.55 (t, *J* = 3.8 Hz, 2 H), 3.59 (s, 3 H), 3.68 (m, 1 H), 5.21 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.2, 28.5, 33.9, 51.5, 53.5, 102.1, 171.8.

ESI-MS: *m*/*z* [M – H]$^+$ calcd for $C_7H_{11}N_2O_2Se$: 234.99; found: 235.00.

(*R*)-2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-3-thiocyanatopropanoic Acid [Fmoc-Ser(ψSCN)-OH, 6i]

Yield: 57 mg (85% from **2i**); gum; R_f = 0.20 ($CHCl_3$–MeOH, 8:2).

IR (CH_2Cl_2): 1705, 2138 cm^{-1}.

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^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.39 (d, J = 4.6 Hz, 2 H), 4.27 (t, J = 3.8 Hz, 1 H), 4.37 (m, 1 H), 4.66 (d, J = 6.4 Hz, 2 H), 6.12 (br, 1 H), 7.25–7.71 (m, 8 H), 10.98 (br, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.8, 47.5, 53.5, 67.1, 111.9, 124.6, 125.8, 126.6, 127.5, 141.5, 144.5, 155.9, 172.1.

HRMS: m/z [M + Na]$^+$ calcd for $C_{19}H_{16}N_2NaO_4S$: 391.0728; found: 391.0734.

(*S*)-2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-5-selenocyanatopentanoic Acid (7d)

Yield: 68 mg (75% from **3d**); gum; R_f = 0.20 ($CHCl_3$–MeOH, 8:2).

IR (CH_2Cl_2): 1712, 2140 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.32 (m, 2 H), 1.45 (m, 2 H), 2.11 (t, J = 4.0 Hz, 2 H), 3.95 (m, 1 H), 4.38 (t, J = 4.4 Hz, 1 H), 4.59 (d, J = 5.0 Hz, 2 H), 6.82 (br, 1 H), 7.18–7.72 (m, 8 H), 10.99 (br, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.3, 28.1, 33.8, 46.5, 54.8, 67.1, 101.5, 122.3, 125.5, 127.8, 128.5, 141.5, 144.7, 156.5, 172.7.

HRMS: m/z [M + Na]$^+$ calcd for $C_{21}H_{20}N_2NaO_4Se$: 467.0486; found: 467.0481.

***N*-Fmoc Amino Alkyl *S*/*Se*-Linked Tetrazoles 8/9; General Procedure**

A mixture of a *N*-Fmoc amino alkyl thiocyanate/selenocyanate **2/3** (1 mmol), NaN_3 (162 mg, 2.5 mmol) and $ZnBr_2$ (222 mg, 1 mmol) in *i*-PrOH–H_2O (1:1, 30 mL) was heated to reflux for 4–5 h with stirring. After cooling, the reaction mixture was acidified with 10% HCl and diluted with EtOAc (15 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with H_2O (2 × 10 mL) and brine (10 mL), and dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure and the residue was either recrystallized (THF–hexane, 1:4) or column chromatographed.

(9*H*-Fluoren-9-yl)methyl (*S*)-1-(2*H*-Tetrazol-5-ylthio)propan-2-ylcarbamate [Fmoc-Ala-ψ(CH_2SCN_4H), 8a]

Yield: 351 mg (92%); white solid; mp 92–94 °C; R_f = 0.2 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.19 (d, J = 6.4 Hz, 3 H), 3.49 (d, J = 4.6 Hz, 2 H), 3.83 (m, 1 H), 4.18 (t, J = 5.4 Hz, 1 H), 4.27 (d, J = 7.2 Hz, 2 H), 6.70 (br, 1 H), 7.29–7.88 (m, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.8, 37.8, 46.2, 46.7, 66.9, 120.1, 125.1, 126.9, 127.5, 140.7, 143.8, 154.2, 155.5.

ESI-MS: m/z [M + H]$^+$ calcd for $C_{19}H_{20}N_5O_2S$: 382.13; found: 382.05.

(9*H*-Fluoren-9-yl)methyl (*S*)-3-Methyl-1-(2*H*-tetrazol-5-ylthio)butan-2-ylcarbamate [Fmoc-Val-ψ(CH_2SCN_4H), 8b]

Yield: 356 mg (87%); gum; R_f = 0.3 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.87 (d, J = 5.8 Hz, 6 H), 2.32 (m, 1 H), 3.32 (d, J = 4.7 Hz, 2 H), 3.85 (m, 1 H), 3.96 (t, J = 5.2 Hz, 1 H), 4.07 (d, J = 7.1 Hz, 2 H), 6.96 (br, 1 H), 7.32–7.70 (m, 8 H), 7.98 (br, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.0, 18.9, 32.2, 36.9, 46.7, 56.2, 65.2, 120.0, 125.1, 126.9, 127.5, 140.7, 143.7, 154.8, 156.0.

HRMS: m/z [M + H]$^+$ calcd for $C_{21}H_{24}N_5O_2S$: 410.1651; found: 410.1646.

(9*H*-Fluoren-9-yl)methyl (*S*)-3-Phenyl-1-(2*H*-tetrazol-5-ylthio)propan-2-ylcarbamate [Fmoc-Phe-ψ(CH_2SCN_4H), 8c]

Yield: 403 mg (88%); white solid; mp 141–142 °C; R_f = 0.22 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.69 (d, J = 6.2 Hz, 2 H), 3.39 (d, J = 5.7 Hz, 2 H), 4.18 (t, J = 4.3 Hz, 1 H), 4.28 (d, J = 5.0 Hz, 2 H), 4.89 (m, 1 H), 6.48–6.71 (br, 1 H), 7.23–7.49 (m, 13 H), 7.67 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.8, 39.5, 46.7, 51.9, 65.6, 125.2, 126.2, 127.1, 127.6, 128.2, 128.6, 129.2, 138.2, 140.7, 143.8, 155.6, 172.0.

HRMS: m/z [M + Na]$^+$ calcd for $C_{25}H_{23}N_5NaO_2S$: 480.1470; found: 480.1465.

(9*H*-Fluoren-9-yl)methyl (*S*)-1-Phenyl-1-(2*H*-tetrazol-5-ylthio)ethylcarbamate [Fmoc-Phg-ψ(CH_2SCN_4H), 8d]

Yield: 403 mg (88%); white solid; mp 151–152 °C; R_f = 0.20 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.52 (d, J = 4.8 Hz, 2 H), 4.12 (t, J = 3.8 Hz, 1 H), 4.26 (d, J = 6.4 Hz, 2 H), 4.82 (m, 1 H), 5.92 (br, 1 H), 7.26–7.68 (m, 13 H), 8.21 (br, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.7, 46.7, 54.2, 65.4, 120.1, 125.1, 126.3, 127.0, 127.6, 128.5, 140.7, 141.5, 143.7, 155.7, 156.8.

HRMS: m/z [M + H]$^+$ calcd for $C_{24}H_{22}N_5O_2S$: 444.1494; found: 444.1498.

(9*H*-Fluoren-9-yl)methyl (*S*)-2-[(2*H*-Tetrazol-5-ylthio)methyl]pyrrolidine-1-carboxylate [Fmoc-Pro-ψ(CH_2SCN_4H), 8e]

Yield: 346 mg (85%); gum; R_f = 0.20 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.61–1.72 (m, 4 H), 3.31 (m, 2 H), 3.61 (m, 2 H), 3.80 (m, 1 H), 4.11 (t, J = 4.3 Hz, 1 H), 4.32 (d, J = 5.7 Hz, 2 H), 7.30–7.81 (m, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.2, 29.4, 37.5, 45.0, 47.1, 51.6, 66.7, 125.0, 126.1, 127.0, 128.8, 140.3, 143.1, 155.1, 156.2.

HRMS: m/z [M + H]$^+$ calcd for $C_{21}H_{22}N_5O_2S$: 408.1494; found: 408.1495.

(9*H*-Fluoren-9-yl)methyl (*S*)-1-(Benzylthio)-3-(2*H*-tetrazol-5-ylthio)propan-2-ylcarbamate [Fmoc-Cys(Bn)-ψ(CH_2SCN_4H), 8f]

Yield: 428 mg (85%); white solid; mp 142–143 °C; R_f = 0.25 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.13 (d, J = 4.9 Hz, 2 H), 3.35 (d, J = 6.4 Hz, 2 H), 3.75 (s, 2 H), 4.11–4.31 (m, 3 H), 4.45 (m, 1 H), 5.31 (br, 1 H), 7.19–7.80 (m, 14 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.1, 36.0, 41.0, 46.7, 50.0, 65.5, 125.2, 126.9, 127.1, 127.6, 128.4, 128.9, 130.3, 138.3, 140.7, 143.8, 155.1, 156.3.

HRMS: m/z [M + NH_4]$^+$ calcd for $C_{26}H_{29}N_6O_2S_2$: 521.1793; found: 521.1785.

***tert*-Butyl (*S*)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-4-(2*H*-tetrazol-5-ylthio)butanoate [Fmoc-Asp(*t*-Bu)-ψ(CH_2SCN_4H), 8g]**

Yield: 376 mg (78%); white solid; mp 78–80 °C; R_f = 0.20 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.34 (s, 9 H), 2.52 (d, J = 5.2 Hz, 2 H), 3.41 (m, 2 H), 4.11 (m, 1 H), 4.20 (t, J = 4.1 Hz, 1 H), 4.28 (d, J = 5.6 Hz, 2 H), 7.28–7.88 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.6, 36.5, 43.6, 46.6, 47.7, 65.4, 80.1, 120.0, 125.0, 127.0, 127.5, 140.7, 143.7, 155.4, 156.6, 169.3.

HRMS: m/z [M + Na]$^+$ calcd for $C_{24}H_{27}N_5NaO_4S$: 504.1681; found: 504.1686.

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(9*H*-Fluoren-9-yl)methyl (*S*)-6-{[(Benzyloxy)carbonyl]amino}-1-(2*H*-tetrazol-5-ylthio)hexan-2-ylcarbamate [Fmoc-Lys(Z)-ψ(CH_2SCN_4H), 8h]
Yield: 447 mg (78%); white solid; mp 148–150 °C; R_f = 0.20 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.27–1.41 (m, 6 H), 2.66–2.81 (m, 2 H), 2.97 (d, *J* = 4.2 Hz, 2 H), 3.73 (br, 1 H), 4.20–4.31 (m, 3 H), 5.00 (s, 2 H), 7.29–7.51 (m, 13 H), 7.68 (s, 1 H), 7.88 (d, *J* = 5.7 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.7, 29.1, 33.2, 37.1, 42.7, 46.7, 50.3, 65.1, 65.2, 120.0, 125.1, 127.0, 127.6, 127.8, 128.3, 137.2, 140.7, 143.7, 154.3, 155.9, 156.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{33}N_6O_4S$: 573.2284; found: 573.2287.

Methyl (*R*)-2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-3-(2*H*-tetrazol-5-ylthio)propanoate [Fmoc-Ser(ψSCN_4H)-OMe, 8i]
Yield: 276 mg (65%); gum; R_f = 0.30 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.62 (d, *J* = 5.6 Hz, 2 H), 3.84 (s, 3 H), 4.21 (t, *J* = 4.7 Hz, 1 H), 4.42 (d, *J* = 6.4 Hz, 2 H), 4.82 (m, 1 H), 6.92 (br, 1 H), 7.31–7.71 (m, 8 H), 8.01 (br, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.8, 47.5, 52.9, 53.5, 67.5, 123.2, 125.2, 126.4, 127.1, 140.9, 143.1, 154.3, 157.1, 171.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}N_5O_4S$: 426.1236; found: 426.1232.

Methyl (*S*)-2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-4-(2*H*-tetrazol-5-ylthio)butanoate [Fmoc-HSer(ψSCN_4H)-OMe, 8j]
Yield: 334 mg (76%); gum; R_f = 0.25 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.03 (m, 2 H), 3.31 (t, *J* = 3.6 Hz, 2 H), 3.75 (s, 3 H), 4.01 (m, 1 H), 4.15–4.29 (m, 3 H), 6.15 (br, 1 H), 7.12–7.62 (m, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.0, 35.1, 47.3, 52.2, 57.0, 66.9, 125.2, 126.5, 127.1, 128.0, 141.1, 144.3, 154.1, 156.0, 176.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{21}N_5NaO_4S$: 462.1212; found: 462.1217.

(9*H*-Fluoren-9-yl)methyl (*S*)-1-(2*H*-Tetrazol-5-ylselanyl)propan-2-ylcarbamate [Fmoc-Ala-ψ(CH_2SeCN_4H), 9a]
Yield: 381 mg (89%); white solid; mp 136–139 °C; R_f = 0.25 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.27 (d, *J* = 6.7 Hz, 3 H), 3.43 (d, *J* = 6.4 Hz, 2 H), 3.81 (m, 1 H), 4.11 (t, *J* = 3.4 Hz, 1 H), 4.28 (d, *J* = 5.7 Hz, 2 H), 5.08 (br, 1 H), 7.25–7.90 (m, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.3, 34.7, 47.6, 47.8, 66.2, 121.0, 126.1, 127.9, 128.5, 141.6, 144.8, 154.0, 156.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}N_5O_2Se$: 430.0782; found: 430.0790.

(9*H*-Fluoren-9-yl)methyl (*S*)-3-Methyl-1-(2*H*-tetrazol-5-ylselanyl)butan-2-ylcarbamate [Fmoc-Val-ψ(CH_2SeCN_4H), 9b]
Yield: 392 mg (86%); gum; R_f = 0.24 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (d, *J* = 6.5 Hz, 6 H), 1.81 (d, *J* = 5.6 Hz, 1 H), 3.38 (d, *J* = 5.4 Hz, 2 H), 3.93 (m, 1 H), 4.30 (t, *J* = 4.0 Hz, 1 H), 4.42 (d, *J* = 5.5 Hz, 2 H), 5.75 (m, 1 H), 7.31–7.99 (m, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.2, 19.1, 30.5, 32.8, 46.7, 53.1, 66.9, 120.0, 125.1, 126.9, 127.5, 140.6, 143.5, 154.9, 156.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{23}N_5NaO_2Se$: 480.0915; found: 480.0923.

(9*H*-Fluoren-9-yl)methyl (*S*)-4-Methyl-1-(2*H*-tetrazol-5-ylselanyl)pentan-2-ylcarbamate [Fmoc-Leu-ψ(CH_2SeCN_4H), 9c]
Yield: 399 mg (85%); gum; R_f = 0.25 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.82 (m, 6 H), 1.21 (m, 2 H), 1.87 (m, 1 H), 3.41 (d, *J* = 6.4 Hz, 2 H), 3.79 (m, 1 H), 4.11 (t, *J* = 4.4 Hz, 1 H), 4.24 (d, *J* = 5.1 Hz, 2 H), 6.29 (br, 1 H), 7.20–7.98 (m, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.7, 24.0, 25.4, 34.4, 44.2, 47.7, 49.9, 66.0, 121.0, 126.1, 128.0, 128.5, 141.7, 144.8, 156.7, 166.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{26}N_5O_2Se$: 472.1252; found: 472.1260.

Methyl (*S*)-2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-5-(2*H*-tetrazol-5-ylselanyl)pentanoate (9d)
Yield: 395 mg (79%); gum; R_f = 0.25 ($CHCl_3$–MeOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.32 (m, 2 H), 1.71 (m, 2 H), 2.05 (t, *J* = 3.6 Hz, 2 H), 3.55 (s, 3 H), 3.95 (m, 1 H), 4.19 (t, *J* = 4.2 Hz, 1 H), 4.30 (d, *J* = 5.2 Hz, 2 H), 6.20 (br, 1 H), 7.26–7.90 (m, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.5, 29.1, 33.3, 47.5, 51.2, 54.2, 66.5, 124.0, 125.1, 127.0, 128.2, 141.0, 144.1, 154.9, 156.0, 171.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}N_5NaO_4Se$: 524.0813; found: 524.0818.

(*S*)-1-(2*H*-Tetrazol-5-ylthio)propan-2-amine [H-Ala-ψ(CH_2SCN_4H), 10a]
Yield: 54 mg (97% from **8a**); pale yellow solid; mp 178–180 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.22 (d, *J* = 6.2 Hz, 3 H), 3.13 (m, 1 H), 3.31 (d, *J* = 4.4 Hz, 2 H), 5.12 (br, 2 H), 7.54 (br, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.5, 38.5, 47.8, 155.9.

ESI-MS: *m*/*z* [M – H]$^+$ calcd for $C_4H_8N_5S$: 158.05; found: 158.09.

(*S*)-5-[(Pyrrolidin-2-ylmethyl)thio]-2*H*-tetrazole [H-Pro-ψ(CH_2SCN_4H), 10e]
Yield: 61 mg (92% from **8e**); gum.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.50–1.69 (m, 4 H), 2.99 (m, 2 H), 3.20 (m, 1 H), 3.41 (d, *J* = 5.4 Hz, 2 H), 5.01 (m, 1 H), 7.68 (br, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.5, 32.4, 38.2, 45.3, 51.6, 154.9.

ESI-MS: *m*/*z* [M – H]$^+$ calcd for $C_6H_{10}N_5S$: 184.06; found: 184.08.

(*S*)-3-Methyl-1-(2*H*-tetrazol-5-ylselanyl)butan-2-amine [H-Val-ψ(CH_2SeCN_4H), 11b]
Yield: 55 mg (96% from **9b**); pale yellow solid; mp 186–187 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.99 (d, *J* = 6.2 Hz, 6 H), 1.85 (d, *J* = 5.8 Hz, 1 H), 3.88 (d, *J* = 5.6 Hz, 2 H), 4.21 (m, 1 H), 5.91 (br, 2 H), 7.91 (br, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.1, 32.5, 35.9, 53.5, 155.1.

ESI-MS: *m*/*z* [M – H]$^+$ calcd for $C_6H_{12}N_5Se$: 234.02; found: 234.03.

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(31) The RP-HPLC spectrum of H-Ala-ψ(CH_2SCN_4H)(**10a**) had a single peak at t_R 14.2 minutes. The same compound exhibited a distinct methyl group doublet in its ^{1}H NMR spectrum. These two observations confirmed the enantiomeric purity of the free amino tetrazole derivative.

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