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One-pot synthesis of 1,2,4-oxadiazoles from chalcogen amino acid derivatives under microwave irradiation

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ABSTRACT

A series of sulfur- and selenium-bearing, amino acid-derived 1,2,4-oxadiazoles were obtained by a simple procedure. The method consists of EDC-promoted coupling of chalcogen amino acid derivatives with arylamidoximes in acetone, followed by solvent removal and microwave irradiation in water medium. Influence of amidoxime substituents, of the chalcogen atom and of the amino acid side chain is discussed. The results showed this to be a fast, easy and effective method to obtain these compounds, with good functional-group tolerance, potentially favouring future applications in organic synthesis.

1. Introduction

Heterocycles form, by far, the largest of the classical divisions of organic chemistry, having been used successfully in different fields, such as pharmaceutics, agriculture and industry. Most pharmaceutical products that mimic natural products with biological activity are heterocycles. 1,2,4-oxadiazoles are an important class of heterocyclic compounds [1] with a broad biological spectrum of activities, including cytotoxic [2], larvicidal [3], antibiotic [4], antiviral [5], antioxidant [6] and anti-inflammatory [6] activities, and some have also been investigated for their liquid crystal [7] and fluorescent properties [8].

Accordingly, many methods have appeared in the literature for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles [9]. The most efficient and widely used protocol involves the coupling of an amidoxime with an activated carboxyl group [10], leading to the formation of *O*-acyl amidoximes, which then undergo dehydrative cyclization.

On the other hand, the attention gained by organochalcogen compounds has been driven by the potential applications of small molecules containing selenium and sulfur in modern organic synthesis [7a,11] and asymmetric catalysis [11d,12]. Organoselenium compounds perform multiple therapeutic functions [11d,13] of great importance, for example, as antimicrobial [11e,14], anti-inflammatory [15], anticancer [16], antioxidant [15a,17], antithyroid [18], antinociceptive [19], antidepressant [20] and anticonvulsant [21] agents, as well as in a variety of situations where free radicals are involved [22]. The design of new organoselenium compounds and other developments have attracted considerable attention, particularly due to the importance of seleno-amino acid derivatives [23], which have emerged as an exceptional class of structures in recent years, because of their potential biological activity, for example, to protect against neurodegenerative diseases such as Parkinson's and Alzheimer's diseases [17a,24]. Significant attention has also been focused on sulfur-containing groups as model compounds of active sites of both natural enzymes [25] and catalytic metal surfaces [26].

Much effort has been devoted to the synthesis of 1,2,4-oxadiazoles under environmentally friendly procedures. Among them, we can highlight the replacement of hazardous solvents by more sustainable ones in order to minimize the environmental impacts caused by the use of toxic and volatile solvents [27]. To help chemists in the selection of more sustainable practices, many pharmaceutical companies have elaborated solvent selection

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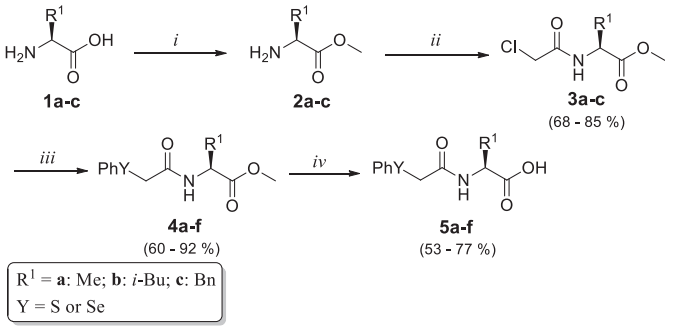
guides [28]. In recent years, numerous reports on the synthesis of heterocyclic compounds under microwave irradiation conditions have appeared in the literature [29]. The introduction of new energy-saving sources, such as microwave irradiation which has dramatically shortened reaction times and access to reaction conditions that are not attainable under conventional thermal heating have been also used for the synthesis of 1,2,4-oxadiazoles [29c,d,30].

Based on our insights about the synthesis of amino acid derivatives containing sulfur and selenium atoms and their applications in biological and asymmetric transformations [12,31] and considering the increasing importance of synthesizing small libraries of compounds with programmed variations of substituents [10c], we present here an easy and short synthetic route for the preparation of a new class of 3,5-disubstituted 1,2,4-oxadiazoles, together with the potential remarkable properties of the chalcogen amino acid derivatives. The synthesis of these compounds proceeded smoothly in the eco-friendly solvents acetone and water, in the absence of an inert atmosphere [32].

2. Results and discussion

According to our objectives and as the starting point for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles we devised an efficient method for preparation of chiral chalcogen amino acid derivatives **5a-f** in a short and high-yielding sequence. To accomplish this task we used some methodologies previously reported in the literature [11c,33]. The synthesis of the chalcogen amino acid derivatives **5a-f** is illustrated in Scheme 1. Amino esters **2a-c** were synthesized using the commercially available L-amino acids, alanine **1a**, leucine **1b** and phenylalanine **1c** as starting materials [33a]. In the next step, the amino esters were then treated with chloroacetyl chloride at 0 °C in the presence of potassium carbonate, followed by a purification step, to afford the compounds **3a-c** in good yields [33a]. We then inserted the organochalcogen moiety into the chloro amides through the nucleophilic attack of chalcogen anions generated by the reaction of diphenyl diselenide with $NaBH_4$ in a mixture of THF [33b] and ethanol or thiophenol with Et_3N in MeCN [11c]. The target compounds were obtained in moderate to good yields; compound **4a** was obtained in 92% yield. Changing the amino acid residue did not produce a pronounced effect on the yield of the products. However, when selenium was employed as a nucleophile, the yields were slightly lower in comparison to the sulfur analogues. In the final step, the hydrolysis of methyl ester was achieved by reaction with aqueous solution of lithium hydroxide 1.0 M, affording the chalcogen α-acetamido acid derivatives **5a-f** in good yields [33c].



Scheme 1. Synthetic strategies to prepare chiral chalcogen amino acid derivatives **5a-f**. Reagents and conditions: (*i*) MeOH, $SOCl_2$, r.t., 12 h; (*ii*) chloroacetyl chloride, H_2O/ethyl acetate (1:3), K_2CO_3, r.t., 12 h (*iii*) PhSeSePh, $NaBH_4$, THF:EtOH (3:1), r.t., 12 h, under argon atmosphere, or PhSH, triethylamine, MeCN, reflux, 12 h, under argon atmosphere. (*iv*) 1.0 M LiOH aqueous solution, THF, r.t., 1 h.

The amidoximes were prepared using classic procedures from the corresponding nitriles through a reaction with hydroxylamine in refluxing ethanol [34].

Due to the efficiency of microwave-promoted synthesis of 1,2,4-oxadiazoles [30], this method was chosen to synthesize the target molecules. To identify the best reaction conditions for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from chalcogen α-acetamido acid derivatives, a set of experiments was carried out employing (*S*)-2-(2-(phenylthio)acetamido)propanoic acid **5a**, benzamidoxime **6a** and *N,N′*-dicyclohexyl-carbodiimide (DCC) as a model system (Table 1). In the first experiment the (*S*)-2-(2-(phenylthio) acetamido)propanoic acid **5a** was allowed to react with DCC in 1,4-dioxane under room temperature for 20 min, to allow the activation of the carboxylic acid moiety. The active intermediate was not isolated and it immediately reacted in the next step with benzamidoxime **6a**, forming the coupled intermediate, and delivering the 3,5-disubstituted 1,2,4-oxadiazole derivative **7aa** after being heated to 100 °C for 15 min under microwave irradiation, in 80% yield after purification. Despite the good initial result, this method invariably produces *N,N′*-dicyclohexylurea (DCU) as a byproduct, which is very difficult to remove from the crude product, even by means of filtering or column chromatography. Thus, another coupling reagent, *N*-(3-(dimethylamino)propyl)-*N′*-ethylcarbodi-imide hydrochloride (EDC) was also tested, as its water-soluble corresponding urea is easily removed during extraction. In an attempt to improve the yield, a series of different solvents was evaluated, including protic polar (H_2O), aprotic polar (1,4-dioxane, CH_3CN, THF, DMF, EtOAc and Acetone) and non-polar (Toluene) solvents (Table 1, entries 1–12) for both DCC and EDC-promoted reactions.

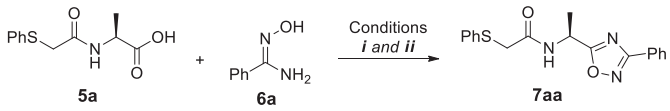
In tetrahydrofuran (entries 3 and 4) and in acetonitrile (entries 7 and 8), product **7aa** was obtained in satisfactory yields (72–87%) when employing either DCC or EDC coupling reagents. A more significant discrepancy was observed with solvents 1,4-dioxane (entries 1 and 2) and toluene (entries 5 and 6), presumably due to low solubility of EDC in these solvents, in which cases DCC was more effective.

Many efforts have been made to substitute hazardous solvents with greener ones [35], which provide better environmental, health and safety profiles. Prat and co-workers have compiled a solvent selection guide [28c,d], which classifies solvents as “recommended”, “problematic”, “hazardous”, and “highly hazardous”. Based on this guide and in order to make our methodology more sustainable for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles, water was chosen as a green solvent for the two steps. Unfortunately, under these conditions, the product was not obtained employing DCC (entry 11), and only slightly more than traces were observed for the EDC-coupled product (entry 12).

Aiming to achieve good yields for the product **7aa** employing a relatively “green” protocol, we attempted to modify the procedure by conducting each of the two steps of the reaction in a different solvent. For this experiment, acetone and water were selected as solvents. The first step involved the reaction of (*S*)-2-(2-(phenylthio)acetamido)propanoic acid with DCC or EDC in acetone for 20 min to obtain the reactive intermediate. After this, benzamidoxime **6a** was added and the mixture was homogenized. Acetone was then removed under vacuum, and water (1.0 mL) was added to the mixture. The tube was sealed and heated under microwave irradiation (100 W) at 100 °C for 15 min (Table 1, entries 13 and 14), furnishing the product in 85 and 83% yields for DCC and EDC-coupling, respectively. Thus, acetone/water was chosen to carry out the following experiments.

Focusing on the influence of the microwave heating conditions,

Table 1
Synthesis of *L*-Chalcogen amino acid-derived 1,2,4-oxadiazoles.



Entry	Coupling reagent	Solvent A/B	Temp/time (°C/min)	Yield (%)[c]
1	DCC	1,4-Dioxane[a]	100/15	80
2	EDC	1,4-Dioxane[a]	100/15	48
3	DCC	THF[a]	100/15	72
4	EDC	THF[a]	100/15	81
5	DCC	Toluene[a]	100/15	70
6	EDC	Toluenea[a]	100/15	55
7	DCC	MeCN[a]	100/15	75
8	EDC	MeCN[a]	100/15	87
9	DCC	Acetone[a]	100/15	50
10	EDC	Acetone[a]	100/15	74
11	DCC	H_2O[a]	100/15	–
12	EDC	H_2O[a]	100/15	2
13	DCC	Acetone/H_2O[b]	100/15	85
14	EDC	Acetone/H_2O[b]	100/15	83
15	DCC	Acetone/H_2O[b]	120/15	71
16	EDC	Acetone/H_2O[b]	120/15	72
17	DCC	Acetone/H_2O[b]	100/10	86
18	EDC	Acetone/H_2O[b]	100/10	90
19	DCC	Acetone/H_2O[b]	100/20	80
20	EDC	Acetone/H_2O[b]	100/20	86

Conditions.
[a] ***i***) Chalcogen amino acid derivative **5a** (1.0 mmol), EDC or DCC (1.2 equiv.), solvent (1.0 mL), r.t., 20 min; then, benzamidoxime **6a**; followed by microwave heating (100 W, 100 °C, 10 min).
[b] ***i***) Chalcogen amino acid derivative **5a** (1.0 mmol), EDC or DCC (1.2 equiv.), acetone (1.0 mL), r.t., 20 min; then, benzamidoxime **6a**. ***ii***) Solvent was then removed under vacuum; water (1.0 mL) was added, followed by microwave heating (100 W, 100 °C, 10 min).
[c] Isolated yields.

we carried out the reaction at different temperatures (100–120 °C) and times (10–20 min). When temperature was increased to 120 °C, the product yield decreased to 71–72% (entries 15 and 16). We also standardized the time conditions, as time influenced product yields, with 10 min being the most appropriate, since the yields of **7aa** increased to 86 and 90% (entries 17 and 18, respectively). Increasing the reaction time to 20 slightly decreased the yields (entries 19 and 20) when compared to the 10 min reactions. Notably, *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) was selected for its overall better performance among the screened coupling reagents, furnishing the desired product in better yields (Table 1), and resulting in an easier purification step (see Scheme S1 in the Supporting Information for the proposed reactions mechanisms).

After optimization of the reaction conditions, the reaction was extended to a broader range of chiral chalcogen amino acid derivatives **5a-f** shown in Scheme 1 and to a set of *C*-aryl-substituted amidoximes **6a-e**. All reactions were carried out in acetone in the first step, beginning with EDC-promoted activation of the carboxylic acid for 20 min at room temperature, followed by addition of the amidoximes **6a-e**. Acetone was then removed under vacuum and water was added. The mixture was heated under microwave conditions (100 W, 100 °C) for 10 min, and monitored by TLC. The results are shown in Table 2.

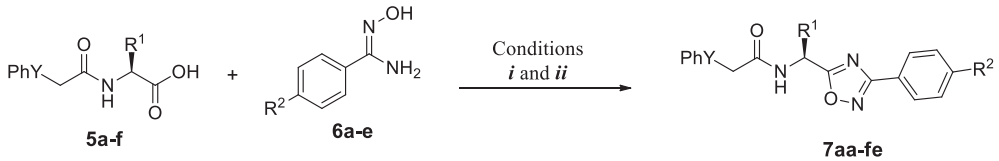
As summarized in Table 2, a series of 3,5-disubstituted 1,2,4-oxadiazoles was obtained in moderate to good yields. The reaction was performed using sulfur- and selenium-bearing chalcogen amino acid derivatives with lipophilic (alanine, phenylalanine and leucine) side chains. The electronic effect of the substituents on the arylamidoximes was also studied. Arylamidoximes bearing the electron-donating groups methyl and methoxy usually afforded better yields when compared to those bearing electron-withdrawing groups like chloro and nitro. The nature of the side chain played a significant role in terms of conversion to the desired heterocycle, since the results varied according to the parent amino acid.

In most cases, except for entries 6, 7 and 13, selenium-bearing examples were obtained in lower yields than their sulfur-bearing analogues. Characteristically, diphenyl diselenide was detected as an impurity in all the crude selenium-bearing oxadiazoles **7da-fe**, indicating that decomposition is a major challenge when reacting these organoselenium compounds. These chalcogen-related yield differences were thus attributed to the greater sensitivity of organoselenium as compared to organosulfur derivatives.

3. Conclusions

We have developed an efficient, eco-friendly and broadly applicable general method for the preparation of new 3,5-disubstituted 1,2,4-oxadiazoles derivatives containing chalcogen atoms. These compounds were prepared in moderate to good yields in a one-pot protocol using environmentally benign solvents and an easily removable coupling reagent. Moreover, the cyclization was carried out under microwave irradiation, with water as solvent, allowing the synthesis of the target compounds in a short reaction time, followed by an easy workup. Even though a limited number of substituents have been presented, the method can be extended to other substrates, since amino acids are inexpensive and easily available starting materials. The compounds prepared here showed interesting structures for future biological screenings, which will be conducted at our institution.

Table 2
Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles **7aa-fe** by microwave irradiation.[a]



R^1 = a: Me, **b:** *i*-Bu, **c:** Bn.
R^2 = a: H, **b:** Me, **c:** OMe, **d:** NO_2, **e:** Cl.
Y = S, Se.

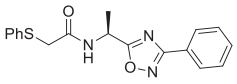
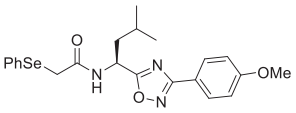
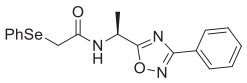
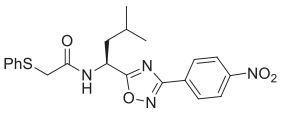
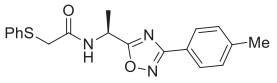
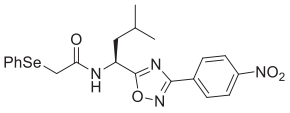
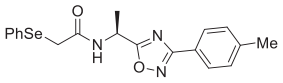
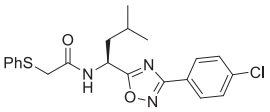
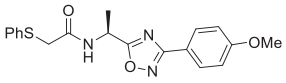
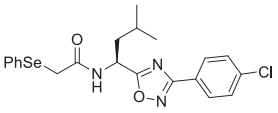
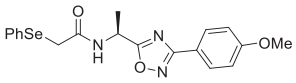
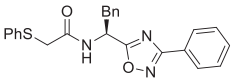
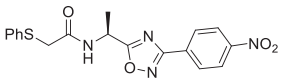
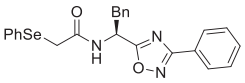
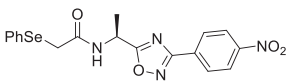
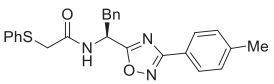
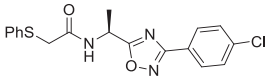
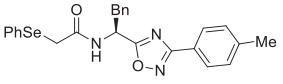
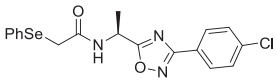
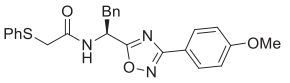
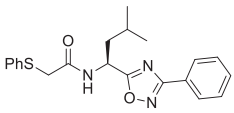
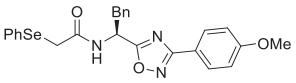
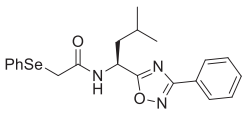
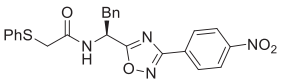
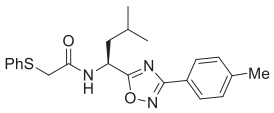
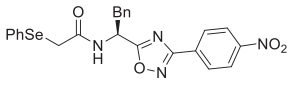
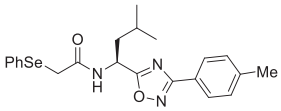
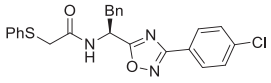
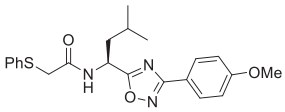
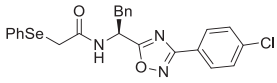
Entry		Product		Yield (%)[b]	Entry		Product		Yield (%)[b]
1	**5a** + **6a**		**7aa**	90	16	**5d** + **6a**		**7da**	79
2	**5a** + **6b**		**7 ab**	86	17	**5d** + **6b**		**7 db**	81
3	**5a** + **6c**		**7ac**	72	18	**5d** + **6c**		**7dc**	59
4	**5a** + **6d**		**7ad**	64	19	**5d** + **6d**		**7dd**	56
5	**5a** + **6e**		**7ae**	67	20	**5d** + **6e**		**7de**	45
6	**5b** + **6a**		**7ba**	52	21	**5e** + **6a**		**7ea**	70
7	**5b** + **6b**		**7bb**	57	22	**5e** + **6b**		**7eb**	73
8	**5b** + **6c**		**7bc**	77	23	**5e** + **6c**		**7ec**	47
9	**5b** + **6d**		**7bd**	79	24	**5e** + **6d**		**7ed**	45
10	**5b** + **6e**		**7be**	57	25	**5e** + **6e**		**7ee**	41
11	**5c** + **6a**		**7ca**	76	26	**5f** + **6a**		**7fa**	50
12	**5c** + **6b**		**7 cb**	67	27	**5f** + **6b**		**7 fb**	32

Table 2 (*continued*)

Entry		Product		Yield (%)[b]	Entry		Product		Yield (%)[b]
13	**5c** + **6c**		**7cc**	35	28	**5f** + **6c**		**7fc**	47
14	**5c** + **6d**		**7cd**	51	29	**5f** + **6d**		**7fd**	38
15	**5c** + **6e**		**7ce**	45	30	**5f** + **6e**		**7fe**	22

[a] Conditions: ***i***) Chalcogen amino acid derivatives **5a-f** (1.0 mmol), EDC (1.2 equiv.), acetone (1.0 mL), r.t., 20 min. Then, arylamidoxime **6a-e**. ***ii***) Solvent was removed under vacuum; then, water (1.0 mL) was added, followed by microwave heating (100 W, 100 °C, 10 min).
[b] Isolated yields.

4. Experimental section

4.1. General information

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz in a Brucker Avance III HD NMR spectrometer. Chemical shifts are reported in ppm, referenced to the solvent peak of tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ) expressed in ppm, multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained either at 100 MHz in an AVANCE III HD NMR spectrometer. Spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ or DMSO-d_6. Samples were diluted in 1:1 (*v/v*) acetonitrile:water mixture, containing 0.1% formic acid. Analyses were performed by infusion mode in an ACQUITYTM UPLC system from Waters Corp. (Milford, MA, USA) equipped with sampler manager and quadrupole time of flight (Q-TOF) MS detector. The Xevo G2 Q-TOF mass spectrometer was equipped with an electrospray ionization source (ESI). Detections were performed in positive ion mode and high resolution. Optimized MS conditions were: capillary voltage 2.50 kV, cone voltage 15 V, extractor cone 3.30 V, desolvation gas 300 L/h, cone gas 10 L/h, desolvation temperature 300 °C, and source temperature 150 °C. Acquisition mass range was monitored from 50 to 1000 Da. System control and data acquisition were performed using MassLynx V 4.1 software. Column chromatography was performed using Merck Silica Gel (230–400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254 (0.25 mm thickness). For visualization, TLC plates were placed under ultraviolet light (254 nm) and then soaked in acidic vanillin, followed by heating. The product yields included in all Tables refer to isolated yields.

4.1.1. General procedure for the synthesis of ***2a–c*** *[33a]*

To a suspension of L-amino acid (**1a-c**) (100 mmol) in MeOH (100.0 mL), cooled in an ice-water bath, thionyl chloride (11.89g; 7.25 mL; 100 mmol) was added dropwise while stirring. After this period, the solvent was evaporated under vacuum and the residue was dissolved in methanol and precipitated with diethyl ether. The salt was collected by filtration and washed with diethyl ether to give the α-amino esters hydrochlorides **2a-c** solids. The white solid obtained was used in the next reaction without purification.

4.1.2. General procedure for the synthesis of ***3a–c*** *[33a]*

Crude L-amino ester hydrogen chloride salt (**2a-c**) (100.0 mmol) was dissolved in water (50.0 mL). K_2CO_3 (41.46 g; 300 mmol) was added, followed by ethyl acetate (30.0 mL) and the mixture was cooled in an ice-water bath. The 2-chloroacetyl chloride (150.0 mmol) in ethyl acetate (50.0 mL) was added dropwise. The mixture was stirred at room temperature overnight. The solvent was then removed on a rotary evaporator to near dryness. Then, saturated NH_4Cl and ethyl acetate (3 × 20.0 mL) were added. The layers were separated and the organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel, using hexane/ethyl acetate (8:2) as the eluent, furnishing the pure compounds **3a-c**.

*4.1.2.1. (S)-Methyl-2-(2-chloroacetamido)propanoate (**3a**).* Yield: 15.27 g, 85%; gum; R_f = 0.45 (Hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (s, 1H), 4.52 (q, J = 8.0 Hz, 1H), 3.99 (s, 2H), 3.69 (s, 3H), 1.38 (d, J = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 165.7, 52.4, 48.4, 42.3, 17.9.

*4.1.2.2. (S)-Methyl-2-(2-chloroacetamido)-4-methyl-pentanoate (**3b**).* Yield: 15.52 g, 70%; gum; R_f = 0.40 (Hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, J = 7.5 Hz, 1H), 4.66–4.61 (m, 1H), 4.08 (s, 2H), 3.75 (s, 3H), 1.72–1.60 (m, 3H), 0.96 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 165.9, 52.3, 51.0, 42.3, 41.1, 24.7, 22.6, 21.8.

*4.1.2.3. (S)-Methyl-2-(2-chloroacetamido)-3-phenyl-propanoate (**3c**).* Yield: 17.39 g, 68%; White solid, mp: 73.3–74.5 °C; R_f = 0.40 (Hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 3H), 7.13 (d, J = 8.0 Hz, 2H), 7.00 (s, 1H), 4.90–4.85 (m, 1H), 4.00 (s, 2H), 3.73 (s, 3H), 3.21–3.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 165.6, 135.5, 129.3, 128.7, 127.3, 53.5, 52.4, 42.4, 37.9.

4.1.3. General procedure for the synthesis of ***4a–c*** *[11c]*

In a twin-necked round-bottom flask under argon atmosphere, at room temperature, Et_3N (25.0 mmol) was added to a solution of thiophenol (22.0 mmol in 30.0 mL of MeCN). After a solution of compound **3a-c** (20.0 mmol) dissolved in MeCN (20.0 mL) was added slowly to this solution. The reaction mixture was stirred

under reflux for 12 h. Following this period, the reaction content was extracted with dichloromethane (3 × 30.0 mL) and washed with saturated aqueous NH_4Cl (50.0 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. Then, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel, being eluted with a mixture of hexane/ethyl acetate.

*4.1.3.1. (S)-Methyl-2-[2-phenylthio)acetamido]propanoate (**4a**).* Yield: 4.66 g, 92%; White solid, mp: 61.6–63.9 °C; R_f = 0.35 (Hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5H), 7.23–7.21 (m, 1H), 4.58–4.54 (m, 1H), 3.70 (s, 3H), 3.63 (s, 2H), 1.33 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 167.6, 134.6, 129.3, 129.0, 127.0, 52.5, 48.4, 37.8, 18.2.

*4.1.3.2. (S)-Methyl-4-methyl-2-[2-(phenylthio)acetamido]pentanoate (**4b**).* Yield: 4.90 g, 83%; gum; R_f = 0.35 (Hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 4H), 7.21–7.17 (m, 1H), 7.09–7.07 (m, 1H), 4.58–4.57 (m, 1H), 3.69 (d, J = 17.2 Hz, 1H); 3.66 (s, 3H), 3.61 (d, J = 17.2 Hz, 1H), 1.62–1.55 (m, 1H), 1.48–1.29 (m, 2H), 0.82 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 167.7, 134.6, 129.3, 128.6, 126.8, 52.3, 51.1, 41.4, 37.5, 24.7, 22.8, 21.8.

*4.1.3.3. (S)-Methyl-3-phenyl-2-[2-(phenylthio)acetamido]propanoate (**4c**).* Yield: 5.07 g, 77%; White solid. R_f = 0.32 (Hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.19 (m, 9H), 6.98–6.96 (m, 2H), 4.87–4.82 (m, 1H), 3.67 (s, 3H), 3.61 (s, 2H), 3.07–3.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.6, 167.8, 135.7, 134.7, 129.4, 129.3, 128.7, 128.6, 127.2, 126.9, 53.5, 52.4, 38.0, 37.7.

*4.1.4. General procedure for the synthesis of **4d–f** [33b]*

Under an argon atmosphere, $NaBH_4$ (0.945 g, 25.0 mmol) was added to a solution of diphenyl diselenide (11.0 mmol) in THF (15.0 mL) at room temperature. Ethanol was added dropwise (3.3 mL) and the mixture was stirred for 10 min. After this time, a solution of compound (**3a-c**) (20.0 mmol) in THF (15.0 mL) was added and the resulting mixture was stirred at room temperature overnight. Then, saturated NH_4Cl and ethyl acetate (3 × 5.0 mL) were added. The layers were separated and the organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel, using hexane/ethyl acetate as the eluent, furnishing the pure compounds **4d-f**.

*4.1.4.1. (S)-Methyl-2-[2-(phenylselenyl)acetamido]propanoate (**4d**).* Yield: 4.38 g, 73%; White solid, R_f = 0.35 (Hexane/EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.52 (m, 2H), 7.25–7.24 (m, 3H), 7.09 (d, J = 6.8 Hz, 1H), 4.47–4.41 (m, 1H), 3.68 (s, 3H), 3.55 (s, 2H), 1.30 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 168.3, 132.4, 128.9, 128.8, 127.3, 52.0, 48.0, 29.7, 17.6.

*4.1.4.2. (S)-Methyl-4-methyl-2-[2-(phenylselenyl)acetamido]pentanoate (**4e**).* Yield: 4.31 g, 63%; White solid, R_f = 0.32 (Hexane/EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.50 (m, 2H), 7.28–7.24 (m, 3H), 6.77 (d, J = 7.9 Hz, 1H), 4.59–4.54 (m, 1H), 3.68 (s, 3H), 3.59 (d, J = 14.6 Hz, 1H), 3.55 (d, J = 14.6 Hz, 1H), 1.62–1.54 (m, 1H), 1.51–1.42 (m, 2H), 0.85 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 168.5, 132.4, 129.4, 129.3, 127.7, 52.2, 51.2, 41.5, 30.1, 24.7, 22.8, 21.9.

*4.1.4.3. (S)-Methyl-3-phenyl-2-[2(phenylselenyl)acetamido]propanoate (**4f**).* Yield: 5.27 g, 70%; White solid, R_f = 0.32 (Hexane/EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.41 (m, 2H), 7.26–7.22 (m, 6H), 7.03–7.01 (m, 2H), 6.82 (d, J = 7.2 Hz, 1H), 4.84–4.80 (m, 1H), 3.68 (s, 3H), 3.52 (s, 2H), 3.07–3.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 168.5, 135.8, 132.5, 129.5, 129.3, 129.2, 128.7, 127.8, 127.3, 53.8, 52.4, 38.0, 30.3.

*4.1.5. General procedures for the synthesis of chalcogen α-acetamido acid derivatives (**5a-f**) [33c]*

30.0 mL (30.0 mmol) of a 1.0 M solution of $LiOH_{(aq)}$ was added to a solution of chalcogen α-acetamido ester derivatives (**4a-f**) (10.0 mmol) in THF (30.0 mL). This mixture was stirred at room temperature for 1 h (monitored by TLC). After removal of THF under reduced pressure, the basic aqueous residue was acidified by addition of aqueous 1.0 M HCl and then extracted with ethyl acetate (3 × 20.0 mL). The layers were separated and the organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel, using hexane/ethyl acetate/methanol as the eluent, affording the pure compounds **5a-f**.

*4.1.5.1. (S)-2-[2-(phenylthio)acetamido]propanoic acid (**5a**).* Yield: 1.67 g, 70%; White solid, mp: 99.0–100.8 °C; *Rf* = 0.33 (Hexane/EtOH, 7:3); $[\alpha]_D^{22}$ = 4.40 (c = 0.001; EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.34 (d, J = 7.0 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.31–7.27 (m, 2H), 7.20–7.16 (m, 1H), 4.25 (q, J = 8.0 Hz, 1H), 3.69 (s, 2H), 1.27 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.8, 167.6, 136.1, 128.9, 128.1, 125.9, 47.9, 36.3, 17.3. HRMS (TOF MS ES+) *m/z* calculated for $C_{11}H_{13}NO_3S$ $[M + H]^+$: 240.0694; found: 240.0673.

*4.1.5.2. (S)-4-Methyl-2-[2-(phenylthio)acetamido]pentanoic acid (**5b**).* Yield: 2.33 g, 83%; White solid, mp: 125.0–127.6 °C; *Rf* = 0.32 (Hexane/EtOH, 7:3); $[\alpha]_D^{22}$ = +3.20 (c = 0.001; EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.30 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.8 Hz, 2H), 7.29–7,26 (m, 2H), 7.19–7.16 (m, 1H), 4.25–4.20 (m, 1H), 3.73 (d, J = 14.6 Hz, 1H), 3.65 (d, J = 14.6 Hz, 1H, 1.54–1.49 (m, 3H), 0.85 (d, J = 6.1 Hz, 3H), 0.78 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.9, 167.9, 136.1, 128.9, 128.0, 125.9, 50.7, 36.2, 24.2, 22.9, 21.3., 21.2. HRMS (TOF MS ES+) *m/z* calculated for $C_{14}H_{19}NO_3S$ $[M + H]^+$: 282.1164; found: 282.1164.

*4.1.5.3. (S)-3-Phenyl-2-[2-(phenylthio)acetamido]propanoic acid (**5c**).* Yield: 2.42 g, 77%; White solid, mp: 159.0–161.7 °C; *Rf* = 0.32 (Hexane/EtOH, 7:3); $[\alpha]_D^{22}$ = +44.80 (c = 0.001; EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.40 (d, J = 7.9 Hz, 1H), 7.33–7.18 (m, 10H), 4.49–4.44 (m, 1H), 3.66 (s, 2H), 3.06 (dd, J [1] = 13.8 Hz, J [2] = 4.6 Hz, 1H), 2.90 (dd, J [1] = 13.7 Hz, J [2] = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.6, 167.9, 137.3, 136.1, 129.1, 128.9, 128.2, 127.8, 126.5, 125.7, 53.7, 36.8, 36.1. HRMS (TOF MS ES+) *m/z* calculated for $C_{17}H_{17}NO_3S$ $[M + H]^+$: 316.1007; found: 316.0985.

*4.1.5.4. (S)-2-[2-(phenylselenyl)acetamido]propanoic acid (**5d**).* Yield: 1.71 g, 60%; White solid, mp: 96.0–99.0 °C; *Rf* = 0.20 (Hexane/EtOH, 6:4); $[\alpha]_D^{22}$ = −0.60 (c = 0.001; EtOAc. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.35 (d, J = 7.2 Hz, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.31–7.23 (m, 3H), 4.23–4.16 (m, 1H), 3.63 (d, J = 12.6 Hz, 1H), 3.58 (d, J = 12.6 Hz, 1H), 1.23 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.8, 168.6, 131.4, 130.3, 129.1, 126.8, 47.8, 28.8, 17.2. HRMS (TOF MS ES+) *m/z* calculated for $C_{11}H_{13}NO_3Se$ $[M + H]^+$: 288.0139; found: 288.0126.

*4.1.5.5. (S)-4-Methyl-2-[2-(phenylselenyl)acetamido] pentanoic acid (**5e**).* Yield: 1.74 g, 53%; White solid, mp: 139.0–144.0 °C; *Rf* = 0.20 (Hexane/EtOH, 7:3); $[\alpha]_D^{22}$ = −2.20 (c = 0.001; EtOAc. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.15 (d, J = 7.2 Hz, 1H), 7.5547.51 (m, 2H), 7.30–7.22 (m, 3H), 4.25–4.19 (m, 1H), 3.65 (d, J = 12.6 Hz, 1H), 3.57 (d, J = 12.6 Hz, 1H), 1.63–1.53 (m, 1H), 1.51–1.47 (m, 2H), 0.87 (d,

J = 6.4 Hz, 3H), 0.82 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.5, 168.7, 131.3, 130.1, 128.9, 126.6, 50.4, 28.8, 24.1, 22.6, 21.3, 21.2. HRMS (TOF MS ES+) *m/z* calculated for $C_{14}H_{19}NO_3Se$ $[M + H]^+$: 330.0608; found: 330.0601.

*4.1.5.6. (S)-3-Phenyl-2-[2-(phenylselenyl)acetamido] propanoic acid (**5f**).* Yield: 2.64 g, 73%; White solid, mp: 155.0–159.0 °C; *Rf* = 0.24 (Hexane/EtOH, 7:3); $[\alpha]_D^{22}$ = +55.00 (c = 0.001; EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.36 (d, J = 8.0 Hz, 1H), 7.49–7.47 (m, 2H), 7.26–7.19 (m, 8H), 4.50–4.45 (m, 1H), 3.60 (s, 2H), 3.06 (dd, J^1 = 14.0 Hz, J^2 = 5.2 Hz, 1H), 2.91 (dd, J^1 = 14.0 Hz, J^2 = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.5, 168.8, 137.3, 131.2, 130.4, 129.0, 129.0, 128.1, 126.6, 126.3, 53.6, 36.8, 28.8. HRMS (TOF MS ES+) *m/z* calculated for $C_{17}H_{17}NO_3Se$ $[M + H]^+$: 364.0452; found: 364.0443.

*4.1.6. General procedures for the synthesis of arylamidoximes (**6a-e**) [33]*

$NH_2OH{\cdot}HCl$ (66.0 mmol) was slowly added to a stirred solution of the corresponding nitrile (30.0 mmol) and Et_3N (69.0 mmol) in ethanol (50.0 mL) at room temperature. The mixture was heated at 75 °C until complete disappearance of the starting material (as monitored by TLC). Then, the solvent was removed on a rotary evaporator to near dryness. Saturated NH_4Cl and ethyl acetate (3 × 30.0 mL) were then added. The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (7:3) as the eluent.

*4.1.7. General procedures for the synthesis of 1,2,4-oxadiazoles (**7aa-fe**) [29d]*

In a sealed tube in a microwave reactor, 1.0 mmol of chalcogen α-acetamido acid derivatives (**5a-f**) was added to EDC.HCl (1.1 mmol, 0.199 g) and the two were dissolved in acetone (1.0 mL). The mixture was magnetically stirred for approximately 20 min to form the reactive intermediate. After this time, 1.1 mmol of arylamidoxime (**6a-e**) was added and the mixture was homogenized. The acetone was removed in a rotary evaporator without heating and H_2O (1.0 mL) was added to the mixture. The tube was sealed and placed into a microwave irradiation CEM Discover® at 100 W power, temperature of 100 °C for 10 min. Then, saturated NH_4Cl and ethyl acetate (3 × 5.0 mL) were added. The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator. The crude products were purified by column chromatography on silica gel, using hexane/ethyl acetate as the eluent, furnishing the pure products **7aa-fe**.

*4.1.7.1. (S)-N-[1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl]-2-(phenylthio)-acetamide (**7aa**).* Yield: 305.2 mg, 90%; White solid, mp: 81.0–82.0 °C; R_f = 0.32 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −97.94 (c = 0.01; MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 7.9 Hz, 1H), 7.49–7.40 (m, 3H), 7.35 (d, J = 8.1 Hz, 2H), 7.26–7.22 (m, 2H), 7.18–7.14 (m, 1H), 5.44–5.36 (m, 1H), 3.66 (s, 2H), 1.54 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.1, 168.2, 167.8, 134.3, 131.3, 129.2, 129.0, 128.8, 127.4, 127.0, 126.4, 43.0, 37.7, 19.3. HRMS (TOF MS ES+) *m/z* calculated for $C_{18}H_{17}N_3O_2S$ $[M + H]^+$: 340.1120; found: 340.1124.

*4.1.7.2. (S)-2-(phenylthio)-N-{1-[3-(p-tolyl)-1,2,4-oxadiazol-5-yl] ethyl}-acetamide (**7 ab**).* Yield: 303.7 mg, 86%; White solid, mp: 84.0–87.5 °C; R_f = 0.35 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −90.52 (c = 0.01; MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 7.6 Hz, 1H, 7.36 (d, J = 7.8 Hz, 2H), 7.28–7.16 (m, 5H), 5.44–5.37 (m, 1H), 3.67 (s, 2H), 2.39 (s, 3H), 1.55 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8, 168.1, 167.6, 141.5, 134.2, 129.4, 129.2, 128.9, 127.3, 126.9, 123.5, 43.0, 37.7, 21.4, 19.4. HRMS (TOF MS ES+) *m/z* calculated for $C_{19}H_{19}N_3O_2S$ $[M + H]^+$: 354.1276; found: 354.1271.

*4.1.7.3. (S)-N-{1-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]ethyl}-2-(phenylthio)acetamide (**7ac**).* Yield: 265.8 mg, 72%; White solid, mp: 77.0–78.5 °C; R_f = 0.29 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −72.70 (c = 0.01; MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.9 Hz, 2H), 7.54 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.27–7.23 (m, 2H), 7.19–7.15 (m, 1H), 6.95 (d, J = 8.9 Hz, 2H), 5.43–5.35 (m, 1H), 3.83 (s, 3H), 3.67 (s, 2H), 1.54 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6, 167.8, 167.7, 161.9, 134.2, 129.1, 128.9, 128.9 (2C), 126.8, 118.7, 114.1, 55.2, 42.9, 37.6, 19.2. HRMS (TOF MS ES+) *m/z* calculated for $C_{19}H_{19}N_3O_3S$ $[M + H]^+$: 370.1225; found: 370.1202.

*4.1.7.4. (S)-N-{1-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]ethyl}-2-(phenylthio)acetamide (**7ad**).* Yield: 245.8 mg, 64%; White solid, mp: 92.0–93.5 °C; R_f = 0.28 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −42.50 (c = 0.01; MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, J = 8.8 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.31–7.28 (m, 2H), 7.24–7.20 (m, 3H), 5.49–5.41 (m, 1H), 3.71 (s, 2H), 1.61 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.1, 167.7, 166.8, 149.6, 134.2, 132.3, 129.3, 128.7, 128.5, 127.0, 124.0, 43.1, 37.5, 19.3. HRMS (TOF MS ES+) *m/z* calculated for $C_{18}H_{16}N_4O_4S$ $[(M + H)^+]$: 385.0971; found: 385.0969.

*4.1.7.5. (S)-N-{1-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl}-2-(phenylthio)acetamide (**7ae**).* Yield: 250.0 mg, 67%; White solid, mp: 86.0–87.0 °C; R_f = 0.38 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −46.32 (c = 0.01; MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.5 Hz, 2H), 7.47–7.42 (m, 3H), 7.35 (d, J = 7.7 Hz, 2H), 7.29–7.26 (m, 2H), 7.22–7.18 (m, 1H), 5.45–5.38 (m, 1H), 3.69 (s, 2H), 1.57 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.3, 167.6, 167.4, 137.5, 134.2, 129.3, 129.1, 128.8, 128.7, 127.0, 124.9, 43.0, 37.6, 19.4. HRMS (TOF MS ES+) *m/z* calculated for $C_{18}H_{16}ClN_3O_2S$ $[M + Na]^+$: 396.0549; found: 396.0559.

*4.1.7.6. (S)-N-[3-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-2-(phenylthio)acetamide (**7ba**).* Yield: 225.2 mg, 52%; White solid, mp: 75.6–77.5 °C; R_f = 0.51 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −29.76 (c = 0.01; MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.2 Hz, 2H), 7.51–7.43 (m, 3H), 7.36–7.32 (m, 3H), 7.28–7.24 (m, 2H), 7.19–7.15 (m, 1H), 5.46–5.40 (m, 1H), 3.75 (d, J = 16.9 Hz, 1H), 3.66 (d, J = 16.9 Hz, 1H), 1.82–1.69 (m, 2H), 1.49–1.39 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9, 168.1, 167.7, 134.0, 131.2, 129.2, 128.7, 128.3, 127.4, 126.8, 126.3, 45.2, 42.5, 37.2, 24.4, 22.6, 21.5. HRMS (TOF MS ES+) *m/z* calculated for $C_{21}H_{23}N_3O_2S$ $[M + H]^+$: 382.1589; found: 382.1603.

*4.1.7.7. (S)-N-{3-methyl-1-[3-(p-tolyl)-1,2,4-oxadiazol-5-yl]butyl}-2-(phenylthio)acetamide (**7bb**).* Yield: 198.2 mg, 57%; White solid, mp: 63.8–67.3 °C; R_f = 0.53 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −55.85 (c = 0.01; MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 7.2 Hz, 2H), 7.30 (d, J = 8.8 Hz, 1H), 7.28–7.24 (m, 4H), 7.19–7.16 (m, 1H), 5.45–5.39 (m, 1H), 3.74 (d, J = 16.9 Hz, 1H), 3.65 (d, J = 16.9 Hz, 1H), 2.40 (s, 3H), 1.81–1.68 (m, 2H), 1.50–1.40 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8, 168.2, 167.6, 141.6, 134.2, 129.5, 129.3, 128.6, 127.4, 126.9, 123.7, 45.4, 42.7, 37.4, 24.5, 22.6, 21.7, 21.5. HRMS (TOF MS ES+) *m/z* calculated for $C_{22}H_{25}N_3O_2S$ $[M + Na]^+$: 418.1565; found: 418.1559.

*4.1.7.8. (S)-N-{1-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-3-methylbutyl}-2-(phenylthio)acetamide(**7bc**).* Yield: 316.6 mg, 77%; White solid, mp: 63.8–68.3 °C; R_f = 0.44 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −29.88 (c = 0.01; MeOH). ^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.95 (d, J = 8.9 Hz, 2H), 7.35–7.32 (m, 3H), 7.27–7.24 (m, 2H), 7.19–7.15 (m, 1H), 6.96 (d, J = 8.9 Hz, 2H), 5.44–5.38 (m, 1H), 3.85 (s, 3H), 3.74 (d, J = 16.8 Hz, 1H), 3.66 (d, J = 16.8 Hz, 1H), 1.81–1.68 (m, 2H), 1.51–1.40 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6, 167.9, 167.6, 162.0, 134.1, 129.2, 129.0, 128.5, 126.8, 118.9, 114.2, 55.3, 45.3, 42.6, 37.3, 24.5, 22.5, 21.6. HRMS (TOF MS ES+) *m/z* calculated for $C_{22}H_{25}N_3O_3S$ $[M + Na]^+$: 434.1514; found: 434.1521.

*4.1.7.9. (S)-N-{3-methyl-1-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl] butyl}-2-(phenylthio)acetamide(**7bd**).* Yield: 336.6 mg, 79%; White solid, mp: 85.8–86.3 °C; R_f = 0.48 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −27.10 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 8.9 Hz, 2H), 8.18 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.29–7.22 (m, 3H), 7.20–7.17 (m, 1H), 5.46–5.40 (m, 1H), 3.74 (d, J = 16.8 Hz, 1H), 3.67 (d, J = 16.8 Hz, 1H), 1.85–1.72 (m, 2H), 1.56–1.45 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.1, 167.8, 166.8, 149.7, 134.3, 132.5, 129.3, 128.5 (2C), 126.9, 124.0, 45.6, 42.6, 37.4, 24.7, 22.5, 21.7. HRMS (TOF MS ES+) *m/z* calculated for $C_{21}H_{22}N_4O_4S$ $[M + Na]^+$: 449.1259; found: 449.1266.

*4.1.7.10. (S)-N-{1-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-3-methylbutyl}-2-(phenylthio)acetamide (**7be**).* Yield: 236.6 mg, 57%; White solid, mp: 81.0–82.0 °C; R_f = 0.47 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −28.46 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.34–7.31 (m, 3H), 7.28–7.24 (m, 2H), 7.20–7.16 (m, 1H), 5.44–5.38 (m, 1H), 3.75 (d, J = 16.9 Hz, 1H), 3.67 (d, J = 16.9 Hz, 1H), 1.81–1.69 (m, 2H), 1.50–1.40 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 167.8, 167.4, 137.4, 134.1, 129.3, 129.1, 128.8, 128.4, 126.9, 125.0, 45.4, 42.5, 37.2, 24.5, 22.5, 21.6. HRMS (TOF MS ES+) *m/z* calculated for $C_{21}H_{22}ClN_3O_2S$ $[M + H]^+$: 416.1200; found: 416.1220.

*4.1.7.11. (S)-N-[2-phenyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl]-2-(phenylthio)acetamide (**7ca**).* Yield: 315.5 mg, 76%; White solid, mp: 67.0–70.5 °C;R_f = 0.43 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −16.84 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 6.8 Hz, 2H), 7.51–7.42 (m, 4H), 7.25–7.18 (m, 8H), 6.99–6.97 (m, 2H), 5.68–5.62 (m, 1H), 3.63 (s, 2H), 3.26–3.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 168.2, 167.7, 134.6, 134.2, 131.3, 129.3, 129.1, 128.8, 128.7, 128.6, 127.5, 127.4, 126.9, 126.4, 48.1, 39.4, 37.5. HRMS (TOF MS ES+) *m/z* calculated for $C_{24}H_{21}N_3O_2S$ $[M + Na]^+$: 438.1252; found: 438.1246.

*4.1.7.12. (S)-N-{2-phenyl-1-[3-(p-tolyl)-1,2,4-oxadiazol-5-yl]ethyl}-2-(phenylthio)acetamide (**7 cb**).* Yield: 287.5 mg, 67%; White solid, mp: 80.5–82.5 °C; R_f = 0.46 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −5.28 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.4 Hz, 1H), 7.24–7.16 (m, 10H), 6.99–9.97 (m, 2H), 5.67–5.61 (m, 1H), 3.63 (s, 2H), 3.26–3.23 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 168.1, 167.7, 141.6, 134.6, 134.2, 129.4, 129.2, 129.1, 128.6 (2C), 127.4, 127.3, 126.8, 123.5, 48.0, 39.3, 37.5, 21.5. HRMS (TOF MS ES+) *m/z* calculated for $C_{25}H_{23}N_3O_2S$ $[M + Na]^+$: 452.1409; found: 452.1409.

*4.1.7.13. (S)-N-{1-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-2-phenylethyl}-2-(phenylthio)acetamide(**7 cc**).* Yield: 155.8 mg, 35%; White solid, mp: 70.0–75.0 °C; R_f = 0.37 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −0.42 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 9.0 Hz, 2H), 7.42 (d, J = 8.3 Hz, 1H), 7.26–7.21 (m, 4H), 7.19–7.17 (m, 4H), 7.00–6.97 (m, 2H), 6.95 (d, J = 9.0 Hz, 2H), 5.65–5.60 (m, 1H), 3.84 (s, 3H), 3.62 (s, 2H), 3.25–3.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 167.9, 167.7, 162.0, 134.7, 134.3, 129.2, 129.1 (2C), 128.7, 128.6, 128.5, 127.3, 126.9, 118.9, 114.2, 55.3, 48.1, 39.3, 37.5. HRMS (TOF MS ES+) *m/z* calculated for $C_{25}H_{23}N_3O_3S$ $[M + H]^+$: 446.1538; found: 446.1526.

*4.1.7.14. (S)-N-{1-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]-2-phenylethyl}-2-(phenylthio)acetamide (**7cd**).* Yield: 142.6 mg, 51%; White solid, mp: 133.5–137.0 °C; R_f = 0.39 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −18.98 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 8.9 Hz, 2H), 8.17 (d, J = 8.9 Hz, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.27–7.18 (m, 8H), 7.01–6.99 (m, 2H), 5.69–5.64 (m, 1H), 3.65 (s, 2H), 3.29–3.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9, 167.9, 166.7, 149.5, 134.4, 134.2, 132.2, 129.3, 129.0, 128.8, 128.5, 128.4, 127.5, 126.9, 124.0, 48.1, 39.2, 37.3. HRMS (TOF MS ES+) *m/z* calculated for $C_{24}H_{20}N_4O_4S$ $[M + Na]^+$: 483.1103; found: 483.1086.

*4.1.7.15. (S)-N-{1-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-2-phenylethyl}-2-(phenylthio)acetamide (**7ce**).* Yield: 202.1 mg, 45%; White solid, mp: 116.5–120.0 °C; R_f = 0.51 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −7.46 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.3 Hz, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.27–7.17 (m, 8H), 6.98–6.96 (m, 2H), 5.67–5.62 (m, 1H), 3.64 (s, 2H), 3.26–3.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1, 167.8, 167.3, 137.4, 134.4, 134.1 (2C), 129.2, 129.1, 129.0, 128.7, 128.3, 127.4, 126.8, 124.7, 48.0, 39.2, 37.3. HRMS (TOF MS ES+) *m/z* calculated for $C_{24}H_{20}ClN_3O_2S$ $[M + H]^+$: 450.1043; found: 450.1028.

*4.1.7.16. (S)-N-[1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl]-2-(phenylselenyl)acetamide(**7da**).* Yield: 305.8 mg, 79%; White solid, mp: 76.5–80.0 °C; R_f = 0.22 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −22.52 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.2 Hz, 2H), 7.56–7.54 (m, 2H), 7.50–7.44 (m, 3H), 7.26–7.24 (m, 3H), 7.10 (d, J = 8.0 Hz, 1H), 5.43–5.36 (m, 1H), 3.59 (s, 2H), 1.54 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.1, 168.4, 168.2, 132.8, 131.3, 129.4, 128.8, 128.6, 127.9, 127.4, 126.4, 43.1, 30.0, 19.5. HRMS (TOF MS ES+) *m/z* calculated for $C_{18}H_{17}N_3O_2Se$ $[M + H]^+$: 410.0384; found: 410.0370.

*4.1.7.17. (S)-2-(phenylselenyl)-N-{1-[3-(p-tolyl)-1,2,4-oxadiazol-5-yl]ethyl}acetamide (**7 db**).* Yield: 324.9 mg, 81%; White solid, mp: 94.5–98.0 °C; R_f = 0.25 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −19.72 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.1 Hz, 2H), 7.57–7.54 (m, 2H), 7.28–7.23 (m, 5H), 7.04 (d, J = 8.1 Hz, 1H)], 5.42–5.35 (m, 1H), 3.60 (s, 2H), 2.41 (s, 3H), 1.54 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.1, 168.4 (2C), 141.8, 133.1, 129.7, 129.6, 128.8, 128.1, 127.6, 123.7, 43.3, 30.3, 19.8. HRMS (TOF MS ES+) *m/z* calculated for $C_{19}H_{19}N_3O_2Se$ $[M + H]^+$: 402.0721; found: 402.0715.

*4.1.7.18. (S)-N-{1-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]ethyl}-2-(phenylselenyl)acetamide (**7dc**).* Yield: 246.1 mg, 59%; White solid, mp: 83.6–84.8 °C; R_f = 0.21 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −22.84 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 9.0 Hz, 2H), 7.57–7.55 (m, 2H), 7.27–7.25 (m, 3H), 7.0l (s, 1H), 6.98 (d, J = 9.0 Hz, 2H), 5.42–5.34 (m, 1H), 3.87 (s, 3H), 3.60 (s, 2H), 1.54 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8, 168.3, 167.9, 162.0, 132.9, 129.4, 129.1, 128.6, 118.9, 114.2, 55.3, 43.2, 30.1, 19.6. HRMS (TOF MS ES+) *m/z* calculated for $C_{19}H_{19}N_3O_3Se$ $[M + H]^+$: 418.0670; found: 418.0662.

*4.1.7.19. (S)-N-{1-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]ethyl}-2-(phenylselenyl)acetamide (**7dd**).* Yield: 25.9 mg, 56%; Yellow solid, mp: 94.0–98.8 °C; R_f = 0.19 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −10.78 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, J = 8.9 Hz, 2H), 8.22 (d, J = 8.9 Hz, 2H), 7.56–7.54 (m, 2H), 7.28–7.26 (m, 3H), 6.96 (d, J = 6.9 Hz, 1H), 5.46–5.39 (m, 1H), 3.62 (s, 2H), 1.58 (d,

J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.1, 168.4, 166.8, 149.6, 132.6, 132.3, 129.5, 128.5, 128.0, 126.6, 124.1, 43.3, 30.0, 19.5. HRMS (TOF MS ES+) *m/z* calculated for $C_{18}H_{16}N_4O_4Se$ $[M + H]^+$: 433.0415; found: 433.0429.

*4.1.7.20. (S)-N-{1-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl}-2-(phenylselenyl)acetamide (**7de**).* Yield: 189.4 mg, 45%; Yellow solid, mp: 110.0–114.0 °C; R_f = 0.21 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −1.02 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.5 Hz, 2H), 7.56–7.53 (m, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.27–7.24 (m, 3H), 7.00 (d, J = 7.2 Hz, 1H), 5.46–5.39 (m, 1H), 3.60 (s, 2H), 1.55 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.4, 168.3, 167.5, 137.5, 132.8, 129.5, 129.2, 128.8, 128.6, 128.0, 124.9, 43.2, 30.1, 19.6. HRMS (TOF MS ES+) *m/z* calculated for $C_{18}H_{16}ClN_3O_2Se$ $[M + H]^+$: 422.0175; found: 422.0164.

*4.1.7.21. (S)-N-[3-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-2-(phenylselenyl)acetamide (**7ea**).* Yield: 300.3 mg, 70%; White solid, mp: 75.6–77.5 °C; R_f = 0.48 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −26.88 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.2 Hz, 2H), 7.52–7.42 (m, 5H), 7.24–7.20 (m, 3H), 7.07 (d, J = 8.6, 1H), 5.43–5.37 (m, 1H), 3.63 (d, J = 14.6 Hz, 1H), 3.58 (d, J = 14.6 Hz, 1H), 1.80–1.67 (m, 2H), 1.56–1.45 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 168.7, 168.3, 132.5, 131.3, 129.5, 128.9, 128.8, 127.9, 127.5, 126.6, 45.6, 42.8, 30.0, 24.6, 22.6, 21.9. HRMS (TOF MS ES+) *m/z* calculated for $C_{21}H_{23}N_3O_2Se$ $[M + Na]^+$: 452.0853; found: 452.0842.

*4.1.7.22. (S)-N-{3-methyl-1-[3-(p-tolyl)-1,2,4-oxadiazol-5-yl]butyl}-2-(phenylselenyl)acetamide (**7eb**).* Yield: 323.5 mg, 73%; White solid, mp: 59.6–60.2 °C; R_f = 0.51 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −22.86 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.2 Hz, 2H), 7.53–7.50 (m, 2H), 7.27–7.22 (m, 5H), 7.00 (d, J = 8.6 Hz, 1H), 5.43–5.37 (m, 1H), 3.63 (d, J = 14.6 Hz, 1H), 3.58 (d, J = 14.7 Hz, 1H), 2.40 (s, 3H), 1.80–1.66 (m, 2H), 1.55–1.45 (m, 1H), 0.90 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9, 168.4, 168.2, 141.5, 132.4, 129.5, 129.4, 128.7, 127.7, 127.4, 123.6, 45.5, 42.7, 29.9, 24.5, 22.5, 21.7, 21.5. HRMS (TOF MS ES+) *m/z* calculated for $C_{22}H_{25}N_3O_2Se$ $[M + H]^+$: 444.1190; found: 444.1187.

*4.1.7.23. (S)-N-{1-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-3-methylbutyl}-2-(phenylselenyl)acetamide (**7ec**).* Yield: 215.8 mg, 47%; White solid, mp: 51.4–52.3; R_f = 0.49 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −21.02 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 9.0 Hz, 2H), 7.53–7.51 (m, 2H), 7.25–7.23 (m, 3H), 6.97 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 8.6 Hz, 1H), 5.42–5.36 (m, 1H), 3.86 (s, 3H), 3.64 (d, J = 14.8 Hz, 1H), 3.58 (d, J = 14.7, 1H), 1.80–1.66 (m, 2H), 1.55–1.44 (m, 1H), 0.90 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8, 168.4, 168.0, 162.0, 132.5, 129.5, 129.1, 128.7, 127.9, 119.0, 114.3, 55.4, 45.6, 42.9, 30.0, 24.6, 22.6, 21.8. HRMS (TOF MS ES+) *m/z* calculated for $C_{22}H_{25}N_3O_3Se$ $[M + H]^+$: 460.1139; found: 460.1150.

*4.1.7.24. (S)-N-{3-methyl-1-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]butyl}-2-(phenylselenyl)acetamide (**7ed**).* Yield: 193.1 mg, 45%; White solid, mp: 88.2–92.1 °C; R_f = 0.48 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −16.60 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, J = 9.0 Hz, 2H), 8.21 (d, J = 9.1 Hz, 2H), 7.53–7.50 (m, 2H), 7.27–7.25 (m, 3H), 6.96 (d, J = 8.4 Hz, 1H), 5.44–5.38 (m, 1H), 3.66 (d, J = 14.8 Hz, 1H), 3.61 (d, J = 14.8 Hz, 1H), 1.83–1.70 (m, 2H), 1.57–1.46 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.1, 168.5, 166.7, 149.5, 132.4, 132.2, 129.5, 128.7, 128.4, 127.8, 124.0, 45.6, 42.5, 29.7, 24.6, 22.6, 21.7. HRMS (TOF MS ES+) *m/z* calculated for $C_{21}H_{22}N_4O_4Se$ $[M + H]^+$: 475.0885; found: 475.0867.

*4.1.7.25. (S)-N-{1-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-3-methylbutyl}-2-(phenylselenyl)acetamide(**7ee**).* Yield: 189.8 mg, 41%; White solid, mp: 78.3–82.4 °C; R_f = 0.56 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −15.90 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.6 Hz, 2H), 7.52–7.50 (m, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.25–7.23 (m, 3H), 6.96 (d, J = 8.6, 1H), 5.42–5.36 (m, 1H), 3.64 (d, J = 14.8 Hz, 1H), 3.59 (d, J = 14.8 Hz, 1H), 1.80–1.67 (m, 2H), 1.55–1.45 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.3, 168.4, 167.4, 137.4, 132.3, 129.4, 129.1, 128.8, 128.7, 127.8, 125.0, 45.5, 42.7, 29.8, 24.6, 22.5, 21.7. HRMS (TOF MS ES+) *m/z* calculated for $C_{21}H_{22}ClN_3O_2Se$ $[M + H]^+$: 464.0644; found: 464.0652.

*4.1.7.26. (S)-N-[2-phenyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl]-2-(phenylselenyl)acetamide (**7fa**).* Yield: 231.5 mg, 50%; Yellow solid, mp: 115.0–118.0 °C; R_f = 0.52 (Hexane–EtOAc, 8:2); $[\alpha]_D^{23}$ = −0.08 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.8 Hz, 2H), 7.47–7.43 (m, 4H), 7.26–7.23 (m, 6H), 7.09–7.04 (m, 4H), 5.66–5.63 (m, 1H), 3.58 (s, 2H), 3.29–3.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3, 168.5, 167.4, 137.5, 134.7, 132.5, 129.4, 129.2, 129.1, 128.8 (2C), 127.8, 127.4, 124.9, 48.3, 39.4, 30.0. HRMS (TOF MS ES+) *m/z* calculated for $C_{24}H_{21}N_3O_2Se$ $[M + H]^+$: 464.0877; found: 464.0854.

*4.1.7.27. (S)-N-{2-phenyl-1-[3-(p-tolyl)-1,2,4-oxadiazol-5-yl]ethyl}-2-(phenylselenyl)acetamide (**7 fb**).* Yield: 152.6 mg, 32%; Yellow solid, mp: 95.5–100.0 °C; R_f = 0.52 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −12.12 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.1 Hz, 2H), 7.45–7.42 (m, 2H), 7.25 (d, J = 7.9 Hz, 2H), 7.22–7.18 (m, 6H)], 7.10 (d, J = 8.1 Hz, 1H), 7.02–7.01 (m, 2H), 5.64–5.58 (m, 1H), 3.53 (s, 2H), 3.25–3.22 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.7, 168.5, 168.1, 141.6, 134.7, 132.5, 129.5, 129.4, 129.2, 128.7, 128.6, 127.8, 127.4, 127.3, 123.6, 48.3, 39.3, 30.0, 21.5. HRMS (TOF MS ES+) *m/z* calculated for $C_{25}H_{23}N_3O_2Se$ $[M + H]^+$: 478.1034; found: 478.1024.

*4.1.7.28. (S)-N-{1-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-2-phenylethyl]-2-(phenylselenyl)acetamide(**7fc**).* Yield: 109.7 mg, 47%; Yellow solid, mp: 76.5–80.0 °C; R_f = 0.39 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −10.34 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.7 Hz, 2H), 7.44–7.42 (m, 2H), 7.21–7.19 (m, 6H), 7.11 (d, J = 7.9 Hz, 1H), 7.03–7.01 (m, 2H), 6.95 (d, J = 8.4 Hz, 2H), 5.63–5.58 (m, 1H), 3.83 (s, 3H), 3.53 (s, 2H), 3.25–3.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 168.5, 167.8, 162.0, 141.6, 134.8, 132.5, 129.3, 129.1, 128.6, 127.7, 127.3, 123.5, 118.8, 114.2, 55.3, 48.3, 39.3, 30.0. HRMS (TOF MS ES+) *m/z* calculated for $C_{25}H_{23}N_3O_3Se$ $[M + H]^+$: 494.0983; found: 494.0996.

*4.1.7.29. (S)-N-{1-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]-2-phenylethyl}-2-(phenylselenyl)acetamide (**7fd**).* Yield: 193.1 mg, 38%; Yellow solid, mp: 122.5–125.0 °C; R_f = 0.43 (Hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = −0.26 (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, J = 9.0 Hz, 2H), 8.20 (d, J = 9.0 Hz, 2H), 7.43–7.41 (m, 2H), 7.25–7.23 (m, 6H), 7.07 (d, J = 8.1 Hz, 1H), 7.04–7.02 (m, 2H), 5.67–5.61 (m, 1H), 3.58 (s, 2H), 3.28–3.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0, 168.5, 166.7, 149.5, 134.4, 132.3, 129.5, 129.1, 128.9, 128.5, 127.8, 127.8, 127.6, 124.1, 123.8, 48.4, 39.3, 29.9. HRMS (TOF MS ES+) *m/z* calculated for $C_{24}H_{20}N_4O_4Se$ $[M + H]^+$: 509.0728; found: 509.0730.

*4.1.7.30. (S)-N-{1-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-2-phenylethyl}-2-(phenylselenyl)acetamide(**7fe**).* Yield: 129.2 mg, 22%; Yellow solid, mp: 79.5–83.0 °C; R_f = 0.43 (Hexane/EtOAc, 8:2);

$[\alpha]_D^{23} = -0.596$ (c = 0.01; EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.3 Hz, 2H), 7.48–7.42 (m, 4H), 7.22–7.18 (m, 7H), 7.03–7.00 (m, 2H), 5.65–5.60 (m, 1H), 3.54 (s, 2H), 3.26–3.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 168.6, 168.1, 134.6, 132.4, 131.3, 129.3, 129.1, 128.7 (2C), 128.6, 127.7, 127.4, 127.3, 126.2, 48.2, 39.2, 29.9. HRMS (TOF MS ES+) *m/z* calculated for $C_{24}H_{20}ClN_3O_2Se$ $[M + H]^+$: 498.0488; found: 498.0485.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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