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A Dynamic Multicomponent Approach for One-Pot Synthesis of 3-Thioisoindolinones

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Abstract: A dynamic multicomponent reaction concept has been successfully applied to the syntheses of 3-thioisoindolinones and tricyclic γ-lactams. The reactions were efficiently designed and operated in the absence of any catalyst under mild reaction conditions, resulting in the convenient variation of substituents on the *N*- and *S*-positions of the target products.

Keywords: cyclization · dynamic chemistry · heterocycles · isoindolinone · multicomponent reactions

1 Introduction

Isoindolinone (**1**, Figure 1) constitutes a common core structure in heterocyclic synthesis, found in many natural products and biologically active compounds.[1–8] Substituents on the isoindolinone structure, especially at the 2-(*N*-atom) and 3-positions, have been reported in many studies as essential for the isoindolinone binding activities, such as in non-steroidal anti-inflammatory drugs,[4,8] anxiolytic drugs,[6] non-nucleoside HIV reverse transcriptase inhibitors,[5,7] HIV-1 integrase inhibitors,[3] and DNA gyrase inhibitors.[2] Therefore, in order to meet the synthetic requirements, isoindolinone synthetic routes have been developed from traditional multistep reactions to modern multicomponent reactions in single processes, using a variety of substrate components and catalysts.[2,3,9–14]

For over two centuries, multicomponent reactions have been established as efficient synthetic methodologies for the synthesis of complex molecules.[15–25] Three or more components undergo multistep tandem/cascade reactions in one-pot processes to form the desired products without isolation of any intermediates. Multicomponent reactions are thus commonly used in heterocyclic syntheses for the preparation of many natural products and bioactive substances.[18,20,23,25] From economic and practical points of view, the development of synthetically viable routes to these compounds is highly attractive, especially in high throughput and medicinal areas for circumventing tedious work in the generation of large collections of compounds by changing substituents on the target core structures. This synthetic concept is of broad interest – from the pharmaceutical industry to academic laboratories – for the development of more facile, concise and efficient preparations of known target compounds, as well as for exploiting new and more sophisticated reactions for new compounds and catalysts.

Recently, we reported a tandem reaction concept for the stereoselective synthesis of 3-substituted isoindolinone derivatives.[26–28] The reversible nitroaldol reactions between 2-cyanobenzaldehyde and different nitroalkanes generated nitroaldol adducts, which subsequently underwent cyclization and irreversible rearrangement, resulting in diastereomerically enriched 3-subsituted isoindolinone products. In the present study, the synthesis of isoindolinone derivatives has been further addressed, with the objective of developing a versatile synthetic pathway, with a higher degree of substitution on the core motif.

In this context, 3-thioisoindolinones **2** have been identified as particularly versatile intermediates for the synthesis of bioactive isoindolinones, such as isoindolines,[29]

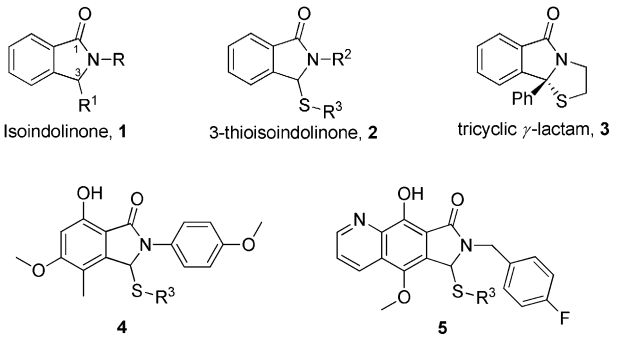

Figure 1. Examples of isoindolinone and 3-thioisoindolinone structures.

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phthalimides,[30] and polycyclic dihydroisoindolizidinones.[12,31] Recently, their potential inhibitory activities toward non-nucleoside HIV reverse transcriptase (**3**),[5,7] DNA gyrase (**4**),[2] and HIV-1 integrase (**5**)[3] have been reported, showing the importance of thiol substituents. Even though the syntheses of 3-thioisoindolinones have been reported in stepwise reactions using acid catalysts and high reaction temperatures, only low conversions to the desired products were obtained.[2,3,9,13] Therefore, the objective of the present study has been to develop an efficient synthetic strategy to *N*- and *S*-substituted 3-thioisoindolinones **2** in a one-pot process.

2 Results and Discussion

Our strategy, which incorporates four substituents (R^2, R^3, R^4, and R^5) on the isoindolinone core structure, was designed as a one-pot catalyst-free reaction as shown in Scheme 1. The substituents on the *N*- and the *S*-centers (R^2 and R^3, respectively) of isoindolinone **2** could be easily modified using a series of primary amines **7** and thiols **8**, while the substituents on the aromatic ring could be varied using different methyl 2-formylbenzoates **6**.

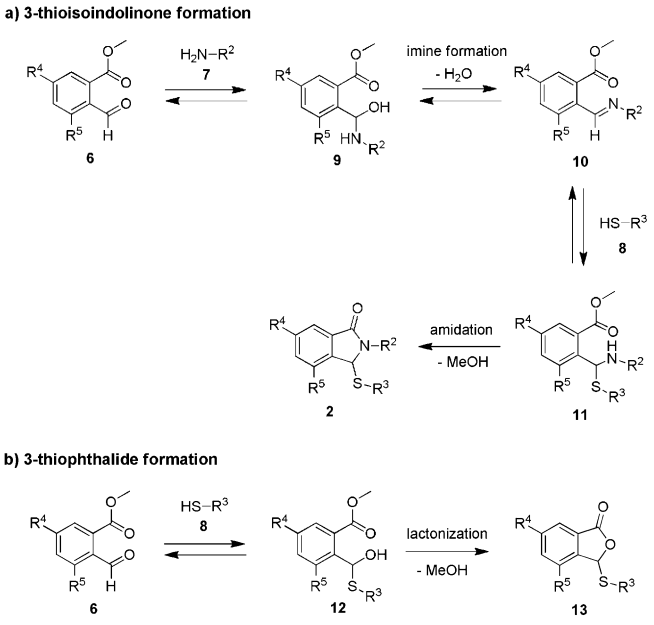
Scheme 1. Multicomponent approach to 3-thioisoindolinone derivatives 2.

This method is based on two consecutive dynamic processes, followed by kinetic cyclization of the resulting intermediate (Scheme 2 a). Thus, the reaction of a parent benzaldehyde with a primary amine and a thiol led to the formation of thioaminal intermediate **11**, and spontaneous cyclization subsequently yielded the product isoindolinone **2**. This strategy proved highly efficient, and the reactions between methyl 2-formylbenzoate **6**, primary amine **7** and thiol **8** in organic solvents in the presence of drying agent conveniently provided the desired product **2** in high yields. Following the formation of imine **10**, addition of thiol **8** led to the thioaminal intermediate **11**, which underwent intramolecular amidation to generate product **2**.

Considering the reaction mechanism, the reversible imine formation is a key step in the 3-thioisoindolinone synthesis, a process where water is released. However, the addition of $MgSO_4$ as drying agent proved to be an efficient way to displace the equilibrium toward imine formation. Subsequently, reversible nucleophilic addition of thiol **8** to the imine provided intermediate **11**, identified by NMR, which was irreversibly transformed to stable amide product **2**. In principle, the reaction between aldehyde **6** and thiol **8** can also easily lead to an alternative 3-thiophthalide product **13** (Scheme 2 b),[32] but this route was not observed under these conditions. These pathways, based on the two reversible reactions that form either thioaminal **11** or hemithioacetal **12**, and the subsequent cyclization, correspond to a Curtin-Hammett-type situation, where intramolecular amidation of intermediate **11** occurs faster than lactonization of intermediate **12**, providing the more favored amide product **2**.

The resulting multicomponent isoindolinone reaction proved straightforward and efficient. Mixtures of aromatic compound **6**, amine **7**, and thiol **8** in organic solvent were stirred overnight in the presence of drying agent and under ambient atmosphere and temperature. The resulting reaction mixture was filtered and washed with saturated ammonium chloride solution, and the desired products were obtained in very high conversion and high purity. The reaction times could also be shortened using higher temperatures, without concomitant byproduct formation.

A series of 3-substituted isoindolinones were subsequently produced, in order to demonstrate the versatility of the strategy. Thus, two methyl 2-formylbenzoates **6a** and **6b** were selected and allowed to react with combinations of different amines and thiols as shown in Table 1. A variety of aliphatic (**7a**), aromatic (**7b**, **7c**) and chiral aromatic (**7d**) amines were chosen to modify the substituent on the *N*-center. Various thiols were also selected to introduce different *S*-substituents, namely alkyl (**8d**), phenyl (**8c**), benzyl (**8e**), and two esters of different lengths (**8a**, **8b**). For products from compound **6a**, isoindolinone **15** was obtained from *n*-butylamine **7a** and thiol



Scheme 2. Proposed reaction mechanisms for the formation of a) 3-thioisoindolinone 2 and b) 3-thiophthalide 13.[31]

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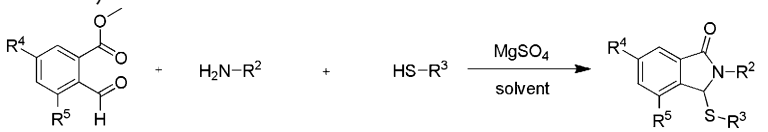
Table 1. Multicomponent reactions for synthesis of 3-thioisoindolinones **15–26**.



6a; R^4, R^5 = H
6b; R^4, R^5 = OMe

7a; R^2 = *n*-butyl
7b; R^2 = phenyl
7c; R^2 = benzyl
7d; R^2 = (*S*)-CH(CH_3)Ph

8a; R^3 = CH_2CO_2Me
8b; R^3 = $CH_2CH_2CO_2Me$
8c; R^3 = phenyl
8d; R^3 = *n*-butyl
8e; R^3 = benzyl

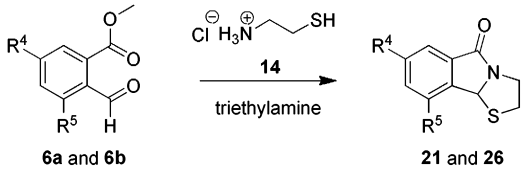
3-thiolisoindolinone

Entry	Starting material			Product	% Yield[a]
	Aromatic	Amine	Thiol		
1	**6a**	**7a**	**8a**	**15**[b]	91
2	**6a**	**7b**	**8b**	**16**[b]	92
3	**6a**	**7b**	**8c**	**17**[b]	91
4	**6a**	**7c**	**8d**	**18**[b]	94
5	**6a**	**7d**	**8a**	**19**[c]	75
6	**6a**	**7d**	**8c**	**20**[c]	71
7	**6a**	**14**; $ClH_3N(CH_2)_2SH$		**21**[d]	93
8	**6b**	**7a**	**8e**	**22**[b]	92
9	**6b**	**7b**	**8a**	**23**[b]	93
10	**6b**	**7c**	**8e**	**24**[b]	92
11	**6b**	**7d**	**8a**	**25**[c]	68
12	**6b**	**14**; $ClH_3N(CH_2)_2SH$		**26**[d]	91

[a] % yield of isolated product. Reaction conditions: [b] R. T., CH_2Cl_2, 12 h. [c] Reflux, toluene, 24 h, 1:1 diastereomeric ratio. [d] R. T., CH_2Cl_2, triethylamine (2 eq.), 12 h.

8a in dichloromethane at room temperature (Table 1, entry 1). With the more sterically hindered amines **7b** and **7c**, products **16–18** were still obtained at room temperature from thiol **8b**, thiophenol **8c** and *n*-butanethiol **8d**, respectively (Table 1, entries 2–4). Chiral amine **7d**, (*S*)-1-phenylethylamine, was used in order to probe the influence of the stereochemistry at the 3-position of the isoindolinone. When the reactions with this amine were carried out at room temperature, the corresponding products were produced at low conversion. However, when the reactions were performed in refluxing toluene, high product yields were obtained. This indicates that the steric congestion of the chiral moiety on amine **7d** affects product formation. No chiral induction at the 3-position was recorded in this case, and the reactions with methyl thioglycolate **8a** and thiophenol **8c** (Table 1, entries 5 and 6) gave the corresponding products **19** and **20** in a 1:1 diastereomeric ratio.

3-Thioisoindolinones **22–25** were obtained from methyl 2-formyl-3,5-dimethoxybenzoate **6b** (Table 1, entries 8–11). The reaction with *n*-butylamine **7a** and benzylthiol **8e** at room temperature produced the corresponding product **22**. The reactions of compound **6b** with the more sterically congested amines **7b** and **7c** still provided products **23** and **24** from thiols **8a** and **8e**, respectively, at room temperature. This indicated that the 3-methoxy group of compound **6b** does not affect the product formation. The reaction between compound **6b**, chiral amine **7d**, and thioester **8a**, in refluxing toluene, yielded the product **25** in a 1:1 diastereomeric ratio (Table 1, entry 11).



6a and **6b** **21** and **26**

Scheme 3. Tricyclic γ-lactam formation.

Tricyclic γ-lactams, potential non-nucleosidic HIV reverse transcriptase inhibitors, have been reported.[4,5] In our current work, the preparation of tricyclic γ-lactams was demonstrated using cysteamine hydrochloride salt **14** (Table 1, entries 7 and 12). Two equivalents of triethylamine base were added to these reactions to deprotonate the ammonium salt. The reactions between compounds **6a** and **6b** with cysteamine in dichloromethane at room temperature efficiently provided the tricyclic isoindolinones **21** and **26**, respectively (Scheme 3).

3 Conclusions

In this study, a multicomponent reaction concept has been successfully developed for the syntheses of 3-thioisoindolinones and tricyclic γ-lactams. The substituents at the *N*- and the *S*-positions of the isoindolinone structure, important moieties for binding activities in inhibition studies, were easily modified using different amines and thiols as starting materials. The multicomponent reactions were simply carried out in the presence of drying agent in

organic solvent, where the reaction temperature and reaction time primarily depended on the steric constriction of the amine substituents. This synthetic strategy is applicable to the efficient preparation of different 3-thioisoindolinones and tricyclic isoindolinones under mild reaction conditions, resulting in high yields of the target products.

4 Experimental Section

General

Reagents were purchased from commercial sources and used as received. ^{1}H and ^{13}C NMR data were recorded at 500 (125) MHz. Chemical shifts are reported as δ values (ppm) with $CDCl_3$ (^{1}H NMR δ 7.26, ^{13}C-NMR δ 77.2) as internal standard. J values are given in Hertz (Hz). Mass spectrometry measurements were performed on an LCQ Advance Max (Finnigan) instrument. High resolution mass spectrometry measurements were performed on a ThermoElectron LTQ-Orbitrap high-resolution mass spectrometer. Thin-layer chromatography (TLC) was performed on precoated silica plates (0.20 mm), visualized with UV detection. Flash column chromatography was performed on silica gel 60, 0.040–0.063 mm.

General Procedure for Synthesis of 3-Thioisoindolinones 15–18 and 22–24

A solution of methyl 2-formylbenzoate (**6a** or **6b**, 0.45 mmol), amine (0.54 mmol) and thiol (0.54 mmol) in dichloromethane (5 mL) was stirred in the presence of magnesium sulfate (250 mg) for 12 h. The reaction mixture was filtered and washed with ammonium chloride solution (three times), followed by saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, and the resulting solution was evaporated under vacuum. The crude reaction was purified, if necessary, by short column chromatography using a mixture of ethyl acetate and hexane as eluent (1:4, v/v).

Methyl 2-(2-butyl-3-oxoisoindolin-1-ylthio)acetate (15): Colorless oil, 120 mg, 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 0.94 (t, J=7.4 Hz, 3H, CH_3), 1.31–1.41 (m, 2H, CH_2), 1.52–1.65 (m, 2H, CH_2), 2.63 (dd, J=15.2, 4.3 Hz, 2H, CH_2), 3.29–3.37 (m, 1H, CH_2), 3.50 (s, 3H, CH_3), 3.91–3.99 (m, 1H, CH_2), 5.56 (s, 1H, CH), 7.46–7.52 (m, 1H, CH), 7.56–7.62 (m, 2H, 2×CH), 7.83 (d, J=7.5 Hz, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 14.1, 20.4, 28.8, 30.5, 39.2, 52.9, 63.5, 123.8, 124.0, 129.6, 132.3, 132.8, 142.3, 167.6, 170.1. MS (ESI): (m/z) calcd.: 316.09 $[M+Na]^+$, found: 316.03. HRMS (ESI): (m/z) calcd. for $C_{15}H_{19}NO_3SNa$: 316.0977 $[M+Na]^+$, found: 316.0980.

Methyl 3-(3-oxo-2-phenylisoindolin-1-ylthio)propanoate (16): White solid, mp 125.3–126.0°, 135 mg, 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 2.11–2.22 (m, 3H, CH_2), 2.22–2.31 (m, 1H, CH_2), 3.59 (s, 3H, CH_3), 6.15 (s, 1H, CH), 7.29 (t, J=7.2 Hz, 1H, CH), 7.47 (t, J=8.1 Hz, 2H, 2×CH), 7.54–7.61 (m, 3H, 3×CH), 7.66–7.72 (m, 2H, 2×CH), 7.93 (d, J=7.8 Hz, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 21.9, 34.1, 51.9, 64.9, 123.8, 124.2, 124.2, 126.2, 129.2, 129.6, 132.0, 133.0, 136.4, 142.7, 166.6, 171.8. MS (ESI): (m/z) calcd.: 350.08 $[M+Na]^+$, found: 350.08. HRMS (ESI): (m/z) calcd. for $C_{18}H_{17}NO_3SNa$: 350.0821 $[M+Na]^+$, found: 350.0819.

2-Phenyl-3-(phenylthio)isoindolin-1-one (17): White solid, mp 149.6–150.5°, 130 mg, 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 6.34 (s, 1H, CH), 6.89 (d, J=7.4 Hz, 2H, 2×CH), 7.0 (t, J=7.5 Hz, 2H, 2×CH), 7.2 (t, J=7.4 Hz, 1H, CH), 7.28 (t, J=7.3 Hz, 1H, CH), 7.40 (t, J=7.3 Hz, 1H, CH), 7.48 (t, J=7.9 Hz, 2H, 2×CH), 7.60–7.68 (m, 4H, 4×CH), 7.7 (d, J=7.9 Hz, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 67.0, 123.5, 123.8, 123.9, 125.7, 127.7, 128.6, 129.1, 129.4, 131.9, 132.4, 136.1, 136.8, 142.5, 166.5. MS (ESI): (m/z) calcd.: 340.07 $[M+Na]^+$, found: 340.07. HRMS (ESI): (m/z) calcd. for $C_{20}H_{15}NOSNa$: 340.0766 $[M+Na]^+$, found: 340.0762.

2-Benzyl-3-(butylthio)isoindolin-1-one (18): White solid, mp 68–69.5°, 141 mg, 94% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 0.45 (t, J=7.1 Hz, 3H, CH_3), 0.84–1.01 (m, 4H, 2×CH_2), 1.43–1.52 (m, 1H, CH_2), 1.58–1.68 (m, 1H, CH_2), 4.08 (d, J=14.6 Hz, 1H, CH_2), 4.98 (s, 1H, CH), 5.07 (d, J=14.8 Hz, 1H, CH_2), 6.92–6.98 (m, 1H, CH), 6.98–7.08 (m, 4H, 4×CH), 7.15–7.22 (m, 1H, CH), 7.23–7.30 (m, 2H, CH_2), 7.5 (d, J=7.87 Hz, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 13.8, 22.3, 25.9, 31.2, 43.1, 63.0, 123.8, 123.9, 128.0, 128.9, 129.0, 129.1, 132.3, 132.4, 137.2, 144.0, 167.7. MS (ESI): (m/z) calcd.: 334.12 $[M+Na]^+$, found: 334.12. HRMS (ESI): (m/z) calcd. for $C_{19}H_{21}NOSNa$: 334.1236 $[M+Na]^+$, found: 334.1237.

3-(Benzylthio)-2-butyl-4,6-dimethoxyisoindolin-1-one (22): Yellow solid, mp 74.6–76.0°, 155 mg, 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 0.89 (t, J=7.4 Hz, 3H, CH_3), 1.23–1.34 (m, 2H, CH_2), 1.38–1.53 (m, 2H, CH_2), 3.17 (d, J=13.9 Hz, 1H, CH_2), 3.25 (d, J=13.6 Hz, 1H, CH_2), 3.22–3.29 (m, 1H, CH), 3.80 (s, 3H, CH_3), 3.79–3.87 (m, 1H, CH), 3.85 (s, 3H, CH_3), 5.40 (s, 1H, CH), 6.45 (d, J=2.0 Hz, 1H, CH), 6.93 (d, J=2.0 Hz, 1H, CH), 6.96–7.01 (m, 2H, 2×CH), 7.10–7.18 (m, 3H, 3×CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 14.1, 20.4, 30.5, 32.0, 39.0, 55.9, 56.2, 61.7, 98.2, 103.0, 123.5, 127.0, 127.2, 128.5, 129.0, 134.9, 138.0, 155.5, 162.8, 167.5. MS (ESI): (m/z) calcd.: 394.14 $[M+Na]^+$, found 394.00. HRMS (ESI): (m/z) calcd. for $C_{21}H_{25}NO_3SNa$: 394.1447 $[M+Na]^+$, found: 394.1443.

Methyl 2-(5,7-dimethoxy-3-oxo-2-phenylisoindolin-1-ylthio)acetate (23): Colorless liquid, 155 mg, 93% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 2.81 (d, J=15.1 Hz, 1H, CH_2), 2.89 (d, J=15.0 Hz, 1H, CH_2), 3.46 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 6.16 (s, 1H, CH), 6.66 (d, J=2.2 Hz, 1H, CH), 7.01 (d, J=2.1 Hz, 1H, CH), 7.27 (t, J=7.0 Hz, 1H, CH), 7.46 (t, J=8.1 Hz, 2H,

2×CH), 7.60 (d, J=8.0 Hz, 2H, 2×CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 29.7, 52.5, 56.0, 56.1, 62.6, 98.3, 103.7, 121.8, 123.9, 126.2, 129.2, 134.6, 136.4, 155.5, 163.1, 166.3, 169.9. MS (ESI): (m/z) calcd.: 396.08 $[M+Na]^+$, found 396.07. HRMS (ESI): (m/z) calcd. for $C_{19}H_{19}NO_5SNa$: 396.0876 $[M+Na]^+$, found: 396.0869.

2-Benzyl-3-(benzylthio)-4,6-dimethoxyisoindolin-1-one (24): Colorless liquid, 168 mg, 92% yield. 1H NMR (500 MHz, $CDCl_3$, 25°) δ 3.29 (d, J=13.6 Hz, 1H, CH_2), 3.36 (d, J=13.6 Hz, 1H, CH_2), 3.85 (s, 3H, CH_3), 3.97 (s, 3H, CH_3), 4.38 (d, J=14.7 Hz, 1H, CH_2), 5.31 (d, J=14.9 Hz, 1H, CH_2), 5.33 (s, 1H, CH), 6.54 (d, J=2.0 Hz, 1H, CH), 7.05–7.12 (m, 3H, 3×CH), 7.22–7.30 (m, 3H, 3×CH), 7.31–7.41 (m, 5H, 5×CH); 13C NMR (125 MHz, CDCl3, 25°) δ 31.5, 43.0, 55.8, 56.2, 61.4, 98.4, 103.2, 123.4, 127.0, 127.9, 128.3, 128.5, 128.9, 129.0, 134.6, 137.2, 138.0, 155.6, 162.9, 167.4. MS (ESI): (m/z) calcd.: 428.12 $[M+Na]^+$, found 428.13. HRMS (ESI): (m/z) calcd. for $C_{24}H_{23}NO_3SNa$: 428.1290 $[M+Na]^+$, found: 428.1283.

General Procedure for Synthesis of 3-Thioisoindolinones 19, 20 and 25

A solution of methyl 2-formylbenzoate (**6a** or **6b**, 0.45 mmol), (*S*)-1-phenylethylamine **7d** (0.54 mmol) and thiol (0.54 mmol) was stirred in refluxing toluene (10 mL) in the presence of magnesium sulfate (250 mg) for 24 h. The reaction mixture was filtered and washed with ammonium chloride solution (three times), followed by saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, and the resulting solution was evaporated under vacuum. The crude reaction was purified by column chromatography using a mixture of ethyl acetate and hexane as eluent (1:4, v/v).

Methyl 2-(3-oxo-2-((*S*)-1-phenylethyl)isoindolin-1-ylthio)acetate (19): 115 mg, 75% yield.

Diastereomer 1: Yellow solid, mp 71.2–72.8°, 56 mg, 36% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 1.93 (d, J=7.2 Hz, 3H, CH_3), 2.39–2.50 (m, 2H, CH_2), 3.42 (s, 3H, CH_3), 5.37 (q, J=7.8, 6.2 Hz, 1H, CH), 5.55 (s, 1H, CH), 7.23 (t, J=6.6 Hz, 1H, CH), 7.30 (t, J=7.2 Hz, 2H, 2×CH), 7.47 (t, J=7.2 Hz, 1H, CH), 7.50–7.60 (m, 4H, 4×CH), 7.82 (d, J=7.0 Hz, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 18.5, 28.4, 52.5, 52.5, 63.9, 123.6, 123.8, 127.6, 128.6, 129.4, 132.3, 132.7, 141.9, 142.4, 169.4, 169.8. MS (ESI): (m/z) calcd.: 364.09 $[M+Na]^+$, found 364.07. HRMS (ESI): (m/z) calcd. for $C_{19}H_{19}NO_3SNa$: 364.0977 $[M+Na]^+$, found: 364.0974.

Diastereomer 2: Colorless liquid, 59 mg, 39% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 1.92 (d, J=7.4 Hz, 3H, CH_3), 2.63 (d, J=15.2 Hz, 1H, CH_2), 2.76 (d, J=15.6 Hz, 1H, CH_2), 3.46 (s, 3H, CH_3), 5.21 (s, 1H, CH), 5.68 (q, J=7.0, 7.8 Hz, 1H, CH), 7.29 (t, J=7.8 Hz, 1H, CH), 7.36 (t, J=7.2 Hz, 2H, 2×CH), 7.42–7.50 (m, 4H, 4×CH), 7.54 (t, J=7.4 Hz, 1H, CH), 7.83 (d, J=7.4 Hz, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 17.6, 28.9, 51.9, 52.6, 62.8, 123.6, 123.7, 128.1, 128.4, 128.9, 129.2, 132.0, 132.3, 139.6, 142.9, 168.0, 169.8. MS (ESI): (m/z) calcd.: 364.09 $[M+Na]^+$, found 364.13. HRMS (ESI): (m/z) calcd. for $C_{19}H_{19}NO_3SNa$: 364.0977 $[M+Na]^+$, found: 364.0972.

2-((*S*)-1-phenylethyl)-3-(phenylthio)isoindolin-1-one (20)[30]: 110 mg, 71% yield.

Diastereomer 1: Yellow solid, mp 149.3–150.3°, 54 mg, 35% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 2.03 (d, J=7.2 Hz, 3H, CH_3), 5.29 (q, J=7.0, 7.6 Hz, 1H, CH), 5.62 (s, 1H, CH), 7.00 (d, J=7.6 Hz, 2H, 2×CH), 7.06 (t, J=7.6 Hz, 2H, 2×CH), 7.16 (t, J=7.3 Hz, 1H, CH), 7.22–7.27 (m, 1H, CH), 7.31 (t, J=7.4 Hz, 2H, 2×CH), 7.35 (t, J=7.3 Hz, 1H, CH), 7.45–7.55 (m, 4H, 4×CH), 7.61 (d, J=7.8 Hz, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 19.6, 54.0, 67.8, 123.3, 123.6, 127.6, 127.7, 128.8, 128.9, 129.0, 131.7, 132.8, 135.0, 142.4, 143.0, 168.5. MS (ESI): (m/z) calcd.: 368.11 $[M+Na]^+$, found: 368.00.

Diastereomer 2: Colorless liquid, 56 mg, 36% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 2.03 (d, J=7.2 Hz, 3H, CH_3), 5.44 (s, 1H, CH), 5.72 (q, J=7.6, 7.1 Hz, 1H, CH), 7.00–7.07 (m, 4H, 4×CH), 7.13 (t, J=7.2 Hz, 1H, CH), 7.28–7.38 (m, 5H, 5×CH), 7.41 (t, J=7.2 Hz, 1H, CH), 7.46 (d, J=7.1 Hz, 2H, 2×CH), 7.64 (d, J=7.5 Hz, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 18.4, 52.2, 66.0, 123.5, 123.5, 128.0, 128.4, 128.5, 128.7, 128.8, 128.8, 130.3, 131.7, 131.8, 134.1, 140.1, 143.8, 168.2. MS (ESI): (m/z): calcd.: 368.11 $[M+Na]^+$, found: 368.07.

Methyl 2-(5,7-dimethoxy-3-oxo-2-((*S*)-1-phenylethyl)isoindolin-1-ylthio)acetate (25): 124 mg, 68% yield.

Diastereomer 1: Colorless liquid, 61 mg, 33.5% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 1.98 (d, J=7.3 Hz, 3H, CH_3), 2.62 (d, J=15.6 Hz, 1H, CH_2), 2.73 (d, J=15.3 Hz, 1H, CH_2), 3.48 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 5.24 (q, J=7.4, 7.4 Hz, 1H, CH), 5.46 (s, 1H, CH), 6.56 (d, J=1.9 Hz, 1H, CH), 6.91 (d, J=2.1 Hz, 1H, CH), 7.22 (t, J=7.5 Hz, 1H, CH), 7.29 (t, J=7.8 Hz, 2H, 2×CH), 7.52 (d, J=7.3 Hz, 2H, 2×CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 18.8, 29.1, 52.5, 53.2, 55.9, 56.0, 62.7, 97.9, 103.1, 122.4, 127.55, 127.59, 128.6, 135.4, 142.1, 155.4, 162.8, 168.0, 170.2. MS (ESI): (m/z) calcd.: 424.11 $[M+Na]^+$, found: 424.00. HRMS (ESI): (m/z) calcd. for $C_{21}H_{23}NO_5SNa$: 424.1189 $[M+Na]^+$, found: 424.1183.

Diastereomer 2: Colorless liquid, 63 mg, 34.5% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 1.92 (d, J=7.2 Hz, 3H, CH_3), 2.74 (d, J=15.0 Hz, 1H, CH_2), 2.81 (d, J=15.0 Hz, 1H, CH_2), 3.48 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 5.15 (s, 1H, CH), 5.59 (q, J=7.2, 7.1 Hz, 1H, CH), 6.54 (d, J=2.0 Hz, 1H, CH), 6.93 (d, J=2.0 Hz, 1H, CH), 7.28 (t, J=7.1 Hz, 1H, CH), 7.35 (t, J=7.4 Hz, 2H, 2×CH), 7.46 (d, J=7.6 Hz, 2H, 2×CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 17.7, 29.3, 52.3, 52.5, 55.9, 56.0, 61.2, 98.1, 103.1, 122.6, 128.0, 128.5, 128.8, 134.6, 139.6, 155.2, 162.8, 167.7, 170.0. MS (ESI): (m/z) calcd.: 424.11 $[M+Na]^+$, found: 423.93. HRMS (ESI): (m/z)

calcd. for $C_{21}H_{23}NO_5SNa$: 424.1189 $[M+Na]^+$, found: 424.1180.

General Procedure for Synthesis of 3-Thioisoindolinones 21 and 26

A solution of methyl 2-formylbenzoate (**6a** or **6b**, 0.45 mmol), cysteamine hydrochloride **14** (61 mg, 0.54 mmol) and triethylamine (126 μL, 0.9 mmol) in dichloromethane (10 mL) was stirred in the presence of magnesium sulfate (250 mg) for 12 h. The reaction mixture was filtered and washed with ammonium chloride solution (three times), followed by saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, and the resulting solution was evaporated under vacuum. The crude reaction was purified by column chromatography using a mixture of ethyl acetate and hexane as eluent (1:4, v/v).

2,3-Dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (21)[33,34]: White solid, mp 103.4–104.5°, 80 mg, 93% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 3.34–3.45 (m, 3H, CH_2), 4.42–4.50 (m, 1H, CH_2), 5.87 (s, 1H, CH), 7.50 (t, $J=8.3$ Hz, 2H, 2×CH), 7.58 (t, $J=7.4$ Hz, 1H, CH), 7.80 (d, $J=7.4$ Hz, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 36.9, 44.9, 66.4, 123.6, 124.8, 129.6, 131.6, 133.0, 145.5, 171.3. MS (ESI): (*m/z*) calcd.: 192.05 $[M+H]^+$, found: 192.13.

7,9-Dimethoxy-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (26): White solid, mp 143.0–144.5°, 103 mg, 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 25°) δ 3.30–3.40 (m, 3H, CH_2), 3.85 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 4.36–4.42 (m, 1H, CH_2), 5.78 (s, 1H, CH), 6.60 (d, $J=1.7$ Hz, 1H, CH), 6.87 (d, $J=1.7$ Hz, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25°) δ 36.5, 44.5, 56.1, 56.3, 64.2, 98.8, 103.7, 126.6, 134.0, 155.8, 163.2. MS (ESI): (*m/z*) calcd.: 252.06 $[M+H]^+$, found: 252.07. HRMS (ESI): (*m/z*) calcd. for $C_{12}H_{13}NO_3SNa$: 274.0508 $[M+Na]^+$, found: 274.0508.

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