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SYNTHESIS OF *N*,*N*-DISUBSTITUTED 1-ARYL-1,3-DIHYDRO-2*H*-ISOINDOLE-2-CARBOTHIOAMIDES

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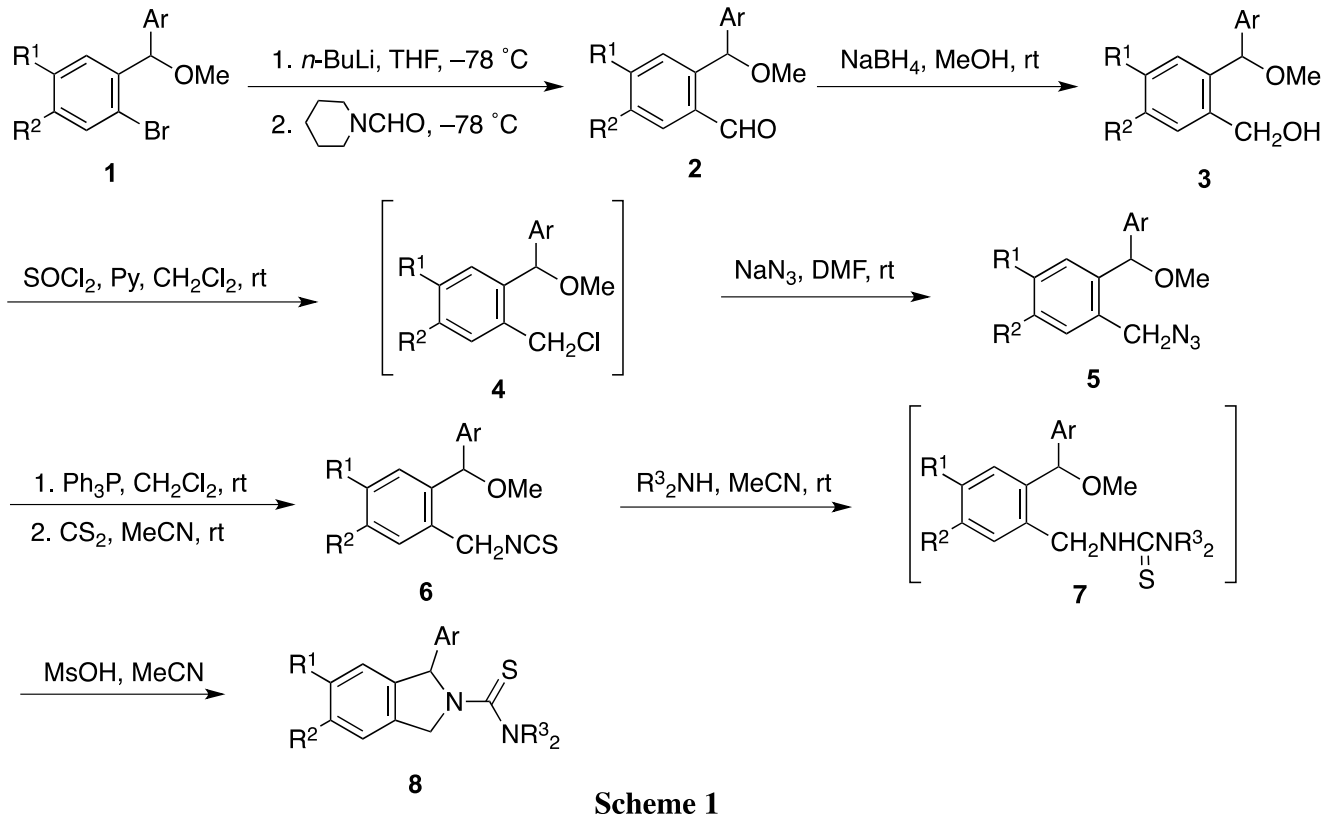
Abstract – A convenient method for the synthesis of *N*,*N*-disubstituted 1-aryl-1,3-dihydro-2*H*-isoindole-2-carbothioamides starting from 2-[aryl(methoxy)methyl]phenyl bromides is described. Thus, the reaction of 1-[aryl(methoxy)methyl]-2-(isothiocyanatomethyl)benzenes, derived from the starting materials by an easily operated five-step sequence under mild conditions, with secondary amines provides the corresponding thiourea derivatives, which cyclize on treatment with methanesulfonic acid to afford the desired products.

INTRODUCTION

1,3-Dihydro-2*H*-isoindole-2-carbothioamides have recently attracted much attention in the medicinal application.[1] Although the methods for the preparation of these compounds are commonly based on the reaction of 1,3-dihydro-2*H*-isoindoles with isothiocyanates, the synthesis of 1-oxo-1,3-dihydro-2*H*-isoindole-2-carbothioamides reported by Wan *et al*.[2] consists of the reaction of phthalaldehyde with thioureas. More recently, Váña *et al*. reported the unexpected formation of 1,3-dihydro-2*H*-isoindole-2-carbothioamide derivatives from the reaction of 3-bromoisobenzofuran-1(3*H*)-one with thioureas through the corresponding isothiuronium salts.[3] However, there have been no reports on the synthesis of *N*,*N*-disubstituted 1,3-dihydro-2*H*-isoindole-2-carbothioamides. On the other hand, we previously reported a convenient method for the preparation of *N*-substituted 3-arylbenzo[*c*]thiophen-1(3*H*)-imines, which was based on the reaction of 2-[aryl(methoxy)methyl]phenyllithiums with isothiocyanates, followed by acid-mediated cyclization of the resulting thioamide derivatives.[4] In this paper, we wish to report an application of this previous methodology for the synthesis of heterocyclic compounds utilizing these lithium compounds to the general preparation of *N*,*N*-disubstituted 1,3-dihydro-2*H*-isoindole-2-carbothioamide derivatives.[5]

RESULTS AND DISCUSSION

Our synthetic route to *N*,*N*-disubstituted 1-aryl-1,3-dihydro-2*H*-isoindole-2-carbothioamides (**8**) relies on the methanesulfonic acid-mediated cyclization of the thiourea derivatives (**7**), generated *in situ* from the reaction of 1-[aryl(methoxy)methyl]-2-(isothiocyanatomethyl)benzenes (**6**) with secondary amines, as illustrated in Scheme 1. A five-step sequence was used to convert 2-[aryl(methoxy)methyl]phenyl bromides (**1**) into the isothiocyanates (**6**). Thus, the readily available (see Experimental) starting materials (**1**) were treated with butyllithium in THF –78 ˚C to generate the corresponding 2-[aryl(methoxy)methyl]phenyllithiums by the bromine/lithium exchange, which were allowed to react with 1-formylpiperidine at the same temperature to give 2-[aryl(methoxy)methyl]benzaldehydes (**2**) in good to excellent yields, as shown in Table 1. The reduction of these aldehydes with sodium borohydride in methanol at room temperature afforded the corresponding benzyl alcohol derivatives (**3**). The yields were good to excellent as compiled in Table 1 as well. Treatment of these alcohols (**3**) with thionyl chloride in the presence of pyridine in dichloromethane at room temperature gave the corresponding benzyl chloride derivatives (**4**), which were used in the next step without any purification after aqueous workup. The chloro substituent in each of **4** was replaced with an azide group using sodium azide (DMF, room temperature) to afford the corresponding benzyl azide derivatives (**5**) in good overall yields from **3**. Finally, treatment of these azides with triphenylphosphine in dichloromethane at room temperature, followed by the reaction of the resulting aza-phosphoranes with carbon disulfide in acetonitrile at the same temperature, provided the desired isothiocyanates (**6**) in moderate-to-fair yields.



Scheme 1

Table 1. Preparation of isothiocyanates (**6**)

Entry	**1**[a]	**2**[a]	Yield/%[b]	**3**[a]	Yield/%[b]	**5**[a]	Yield/%[b,c]	**6**[a]	Yield/%[b]
1	**1a**	**2a**	90	**3a**	92	**5a**	84	**6a**	60
2	**1b**	**2b**	99	**3b**	86	**5b**	71	**6b**	58
3	**1c**	**2c**	92	**3c**	96	**5c**	79	**6c**	64
4	**1d**	**2d**	95	**3d**	93	**5d**	72	**6d**	54
5	**1e**	**2e**	95	**3e**	97	**5e**	70	**6e**	54
6	**1f**	**2f**	84	**3f**	92	**5f**	75	**6f**	62

[a] **a** (R^1 = R^2 = H, Ar = Ph); **b** (R^1 = R^2 = H, Ar = 4-ClC_6H_4); **c** (R^1 = R^2 = H, Ar = 4-$MeOC_6H_4$); **d** (R^1 = Cl, R^2 = H, Ar = 4-$MeOC_6H_4$); **e** (R^1 = OMe, R^2 = H, Ar = Ph); **f** (R^1 = R^2 = OMe, Ar = Ph). [b] Yields of isolated products. [c] Based on **3**.

The reaction of **6** with secondary amines proceeded quickly and cleanly in dichloromethane at room temperature to generate the corresponding thiourea derivatives (**7**), as judged from TLC analyses on silica gel. Initial reactions of these thioureas with various acids (one equivalent), such as concentrated hydrobromic acid, trifluoromethanesufonic acid and *p*-toluenesulfonic acid monohydrate, resulted in the isolation of the products only in low yields (about 10%) from considerably intractable mixtures of products. Gratifyingly, however, the use of rather less acidic methanesulfonic acid as an acid led to the production of the desired products (**8**) in generally moderate yields. The reaction conditions (temperature and reaction time) as well as the yields of the products are summarized in Table 1. The precursors without electron-donating methoxy substituents on the benzene rings (*e.g.* **7a**-**7f**) underwent the cyclization at room temperature at an appropriate rate (Entries 1-6). Among them the precursors with a 4-chlorophenyl substituent (*e.g.* **7e** and **7f**) required much more reaction time, though the yields were comparable. On the other side, using those with a methoxy substituent on the one of the two benzene rings (*e.g.* **7g**-**7j**), the cyclization proceed quickly even at 0 ˚C. However, in the case of using other than **7h** and **7i**, which are carrying a chloro substituent, the yields of the products (**8g**) and (**8j**) decreased somewhat (Entries 7 and 10). The reaction of the precursor carrying two methoxy substituents on the benzene ring proceeded at much lower temperature (–20 ˚C), but the yield of the product (**8k**) was low. This lowering of the yields of the products (**8g**), (**8j**), and (**8k**) may come from the lability of these compounds under the reaction conditions.

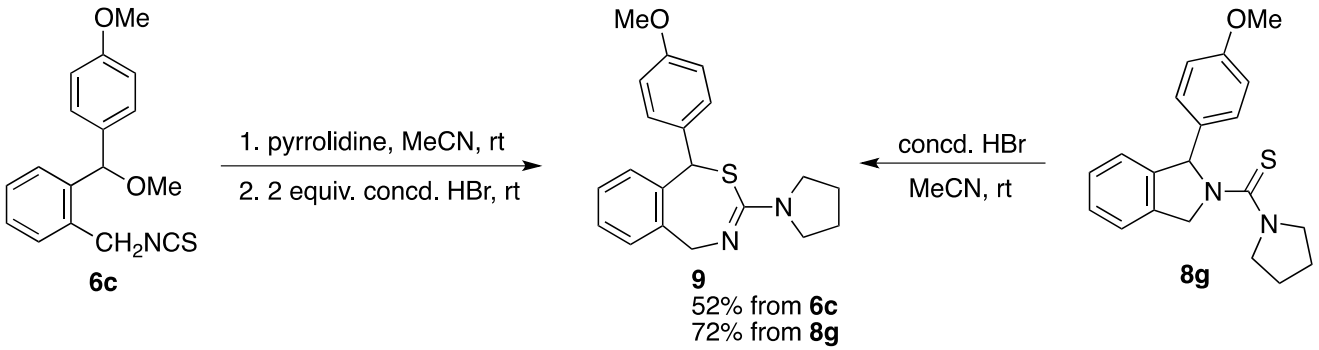
The thiourea structure of compounds **8** was confirmed on the basis of their ^{13}C NMR spectra. They uniformly exhibit signals around δ 190 due to the thiocarbonyl carbon. However, in 1972, Bream and Schmutz have reported the formation of 3-(dimethylamino)-1-phenyl-1,5-dihydro-2,4-benzothiazepine by the hydrogen chloride mediated cyclization of *N*′-({2-[hydroxy(phenyl)methyl]phenyl}methyl)-*N,N*-dimethylthiourea.[6] So, we again attempted the reaction of one of the thiourea derivatives with concentrated hydrobromic acid. Thus, the thiourea derivative (**7g**), derived from **6c** and pyrrolidine, was treated with two equivalents of concentrated hydrobromic acid at room temperature, as shown in Scheme 2. Just after addition of the acid, the spot due to **8g** was observed by TLC analysis on silica gel, but this

disappeared shortly and a product of high polarity appeared. After complete consumption of **7g**, the mixture was worked up and this highly polar product was isolated as described in Experimental. Elemental analysis and HR-MS spectrum of this product revealed that its molecular formula is same to that of **8g**. Its ^{13}C NMR spectra exhibited no signal around δ 190 and a signal at δ 150.10 newly appeared. We determined this product to be 1-(4-methoxyphenyl)-3-(pyrrolidin-1-yl)-1,5-dihydro-2,4-benzothiazepine (**9**). This new signal is assignable to C(3), and the other signals and ^{1}H NMR data are well consistent with this structure. Treatment of **8g** with concentrated hydrobromic acid under the same conditions gave also the same product. These results indicate that compound **8g** is first formed and this rearranges to **9**.

Table 2. Preparation of *N,N*-disubstituted 1,3-dihydro-1*H*-isoindole-3-carbothioamides (**8**)

Entry	**6**	R^2_2NH	Temp	Time	**8**	Yield/%[a]
1	**6a**	Et_2NH	rt	2 h	**8a**	62
2	**6a**	pyrrolidine	rt	2 h	**8b**	58
3	**6a**	piperidine	rt	2 h	**8c**	62
4	**6a**	morpholine	rt	2 h	**8d**	54
5	**6b**	piperidine	rt	overnight	**8e**	60
6	**6b**	morpholine	rt	overnight	**8f**	55
7	**6c**	pyrrolidine	0 ˚C	20 min	**8g**	37
8	**6d**	Et_2NH	0 ˚C	30 min	**8h**	50
9	**6d**	pyrrolidine	0 ˚C	30 min	**8i**	53
10	**6e**	piperidine	0 ˚C	1 h	**8j**	41
11	**6f**	pyrrolidine	–20 ˚C	10 min	**8k**	32

[a] Yields of isolated products based on **6**.



Scheme 2

In summary, we have developed the first method for the synthesis of *N,N*-disubstituted 1,3-dihydro-2*H*-isoindole-2-carbothioamide derivatives, which are hard to prepare by previous synthetic methods. This synthetic route utilized an operationally simple seven-step and six-flask sequence starting from readily available 2-[aryl(methoxy)methyl]phenyl bromides under mild reaction conditions. Efforts toward the synthesis of other heterocycles utilizing these starting materials are in progress in our laboratory and will be reported in due course.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless state otherwise) using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a Thermo Scientific Exactive spectrometer (ESI, positive) or a JEOL JMS-T100GCV (EI, TOF; 70eV) spectrometer. Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. (2-Bromo-5-methoxyphenyl)phenylmethanol,[7] 1-bromo-2-[methoxy(phenyl)methyl]benzene (**1a**),[4] 1-bromo-2-[(4-chlorophenyl)(methoxy)methyl]benzene (**1b**),[4] 1-bromo-2-[methoxy(4-methoxyphenyl)methyl]benzene (**1c**),[4] and 1-bromo-4,5-dimethoxy-2-[methoxy(phenyl)methyl]benzene (**1f**)[8] were prepared according to the appropriate reported procedure. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

1-Bromo-4-chloro-2-[methoxy(4-methoxyphenyl)methyl]benzene (1d). This compound was prepared by the reaction of 4-$MeOC_6H_4MgBr$ and 2-bromo-4-chlorobenzaldehydes, followed by *O*-methylation of the resulting alcohol, according to the procedure used for the preparation of **1a** and **1b**.[4]

(2-Bromo-5-chlorophenyl)(4-methoxyphenyl)methanol: yield: 94%; a colorless oil; R_f 0.32 (AcOEt/hexane 1:5); IR (neat) 3390, 1611 cm^{-1}; ^{1}H NMR δ 2.28 (d, J = 3.4 Hz, 1H), 3.79 (s, 3H), 6.04 (s, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.13 (dd, J = 8.6, 2.9 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 2.9 Hz, 1H). HR-MS (EI). Calcd for $C_{14}H_{12}BrClO_2$ (M): 325.9709. Found: *m/z* 325.9710.

1d: yield: 83%; a white solid; mp 86–88 ˚C (hexane/CH_2Cl_2); IR (KBr) 1611, 1246, 1076 cm^{-1}; ^{1}H NMR δ 3.37 (s, 3H), 3.79 (s, 3H), 5.50 (s, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.11 (dd, J = 8.6, 2.3 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 2.3 Hz, 1H). Anal. Calcd for $C_{15}H_{14}BrClO_2$: C, 52.74; H, 4.13. Found: C, 52.63; H, 4.06.

1-Bromo-4-methoxy-2-[methoxy(phenyl)methyl]benzene (1e). This compound was prepared in 67% yield by *O*-methylation of (2-bromo-5-methoxyphenyl)phenylmethanol[7] according to the procedure used for the preparation of **1a** and **1b**.[4] A white solid; mp 81–83 ˚C (hexane/CH_2Cl_2); IR (KBr) 1233, 1080 cm^{-1}; ^{1}H NMR δ 3.40 (s, 3H), 3.78 (s, 3H), 5.61 (s, 1H), 6.71 (dd, J = 8.6, 2.9 Hz, 1H), 7.11 (d, J = 2.9 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.33 (dd, J = 8.0, 7.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.6 Hz, 1H). Anal. Calcd for $C_{15}H_{15}BrO_2$: C, 58.65; H, 4.92. Found: C, 58.65; H, 4.63.

Typical Procedure for the Preparation of Aldehydes (2). 2-[Methoxy(phenyl)methyl]benzaldehyde (2a). To a stirred solution of **1** (0.86 g, 3.1 mmol) in THF (6 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 3.10 mmol) dropwise. After 15 min, *N*-formylpiperidine (0.35 g, 3.1 mmol) was added and stirring was continued for an additional 40 min before addition of saturated aqueous NH_4Cl (15 mL). The mixture was warmed to rt and extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **2a** (0.57 g, 81%); a colorless oil; R_f 0.36 (AcOEt/hexane 1:15); IR (neat) 2823, 2743, 1695 cm^{-1}; ^1H NMR δ 3.40 (s, 3H), 6.16 (s, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.31 (t, J = 7.4 Hz, 2H), 7.37 (d, J = 7.4 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.68 (d, J = 7.4 Hz, 1H), 7.85 (d, J = 7.4 Hz, 1H), 10.23 (s, 1H). HR-MS (EI). Calcd for $C_{15}H_{14}O_2$ (M): 226.0994. Found: *m/z* 226.1003.

2-[(4-Chlorophenyl)(methoxy)methyl]benzaldehyde (2b): a colorless oil; R_f 0.43 (AcOEt/hexane 1:7); IR (neat) 2823, 2743, 1697 cm^{-1}; ^1H NMR δ 3.38 (s, 3H), 6.18 (s, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.63 (t, J = 7.4 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.83 (d, J = 7.4 Hz, 1H), 10.16 (s, 1H). HR-MS (EI). Calcd for $C_{15}H_{13}ClO_2$ (M): 260.0604. Found: *m/z* 260.0610.

2-[Methoxy(4-methoxyphenyl)methyl]benzaldehyde (2c): a colorless oil; R_f 0.44 (AcOEt/hexane 1:7); IR (neat) 2822, 2745, 1697 cm^{-1}; ^1H NMR δ 3.38 (s, 3H), 3.77 (s, 3H), 6.10 (s, 1H), 6.84 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.46 (td, J = 7.4, 1.1 Hz, 1H), 7.61 (ddd, J = 8.0, 7.4, 1.1 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.83 (dd, J = 7.4, 1.1 Hz, 1H), 10.21 (s, 1H). HR-MS (EI). Calcd for $C_{16}H_{16}O_3$ (M): 256.1099. Found: *m/z* 256.1111.

4-Chloro-2-[methoxy(4-methoxyphenyl)methyl]benzaldehyde (2d): a colorless oil; R_f 0.41 (AcOEt/hexane 1:5); IR (neat) 2833, 2740, 1699 cm^{-1}; ^1H NMR δ 3.37 (s, 3H), 3.78 (s, 3H), 6.06 (s, 1H), 6.85 (d, J = 9.2 Hz, 2H), 7.26 (d, J = 9.2 Hz, 2H), 7.42 (dd, J = 8.6, 2.3 Hz, 1H), 7.73 (d, J = 2.3 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 10.14 (s, 1H). HR-MS (EI). Calcd for $C_{16}H_{15}ClO_3$ (M): 290.0710. Found: *m/z* 290.0697.

4-Methoxy-2-[methoxy(phenyl)methyl]benzaldehyde (2e): a white solid; mp 65–67 ˚C (hexane); IR (KBr) 2825, 2729, 1695 cm^{-1}; ^1H NMR δ 3.41 (s, 3H), 3.90 (s, 3H), 6.24 (s, 1H), 6.93 (dd, J = 8.6, 2.9 Hz, 1H), 7.23–7.32 (m, 4H), 7.38 (dd, J = 8.6, 1.7 Hz, 2H), 7.79 (d, J = 8.6 Hz, 1H), 10.04 (s, 1H). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.85; H, 6.36.

4,5-Dimethoxy-2-[methoxy(phenyl)methyl]benzaldehyde (2f):[8] a colorless oil; R_f 0.28 (AcOEt/hexane 1:3); IR (neat) 2823, 2723, 1678 cm^{-1}; ^1H NMR δ 3.42 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 6.11 (s, 1H), 7.14 (s, 1H), 7.25 (t, J = 7.4 Hz, 1H), 7.31–7.35 (m, 4H), 7.38 (s, 1H), 10.21 (s, 1H).

Typical Procedure for the Preparation Alcohols 3. {2-[Methoxy(phenyl)methyl]phenyl}methanol (3a). To a stirred solution of **2a** (0.56 g, 2.5 mmol) in MeOH (9 mL) at rt was added $NaBH_4$ (94 mg, 2.5

mmol). After 15 min, saturated aqueous NH_4Cl (15 mL) was added and the organic solvent was removed by evaporation. The resulting mixture was extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **3a** (0.51 g, 90%); a colorless oil; R_f 0.36 (AcOEt/hexane 1:5); IR (neat) 3339, 1602 cm^{-1}; ^1H NMR δ 2.60 (t, J = 6.3 Hz, 1H), 3.43 (s, 3H), 4.54 (dd, J = 12.0, 6.3 Hz, 1H), 4.60 (dd, J = 12.0, 6.3 Hz, 1H), 5.55 (s, 1H), 7.25–7.41 (m, 9H). HR-MS (EI). Calcd for $C_{15}H_{16}O_2$ (M): 228.1150. Found: *m/z* 228.1156.

{2-[(4-Chlorophenyl)(methoxy)methyl]phenyl}methanol (3b): a colorless oil; R_f 0.31 (AcOEt/hexane 1:7); IR (neat) 3399 cm^{-1}; ^1H NMR δ 2.51 (t, J = 6.3 Hz, 1H), 3.41 (s, 3H), 4.55 (dd, J = 12.6, 6.3 Hz, 1H), 4.57 (dd, J = 12.6, 6.3 Hz, 1H), 5.52 (s, 1H), 7.23–7.35 (m, 7H), 7.40 (dd, J = 6.9, 1.7 Hz, 1H). HR-MS (EI). Calcd for $C_{15}H_{15}ClO_2$ (M): 262.0761. Found: *m/z* 262.0748.

{2-[Methoxy(4-methoxyphenyl)methyl]phenyl}methanol (3c): a colorless oil; R_f 0.40 (AcOEt/hexane 1:2); IR (neat) 3423, 1611 cm^{-1}; ^1H NMR δ 2.56 (t, J = 6.3 Hz, 1H), 3.40 (s, 3H), 3.80 (s, 3H), 4.53 (dd, J = 12.6, 6.3 Hz, 1H), 4.60 (dd, J = 12.6, 6.3 Hz, 1H), 5.50 (s, 1H), 6.88 (d, J = 9.2 Hz, 2H), 7.24 (d, J = 9.2 Hz, 2H), 7.27–7.33 (m, 3H), 7.39 (dd, J = 8.6, 2.3 Hz, 1H). HR-MS (EI). Calcd for $C_{16}H_{18}O_3$ (M): 258.1256. Found: *m/z* 258.1262.

{4-Chloro-2-[methoxy(4-methoxyphenyl)methyl]phenyl}methanol (3d): a colorless oil; R_f 0.32 (AcOEt/hexane 1:2); IR (neat) 3412, 1611 cm^{-1}; ^1H NMR δ 2.34 (t, J = 6.3 Hz, 1H), 3.39 (s, 3H), 3.81 (s, 3H), 4.47–4.50 (m, 1H), 4.55–4.59 (m, 1H), 5.43 (s, 1H), 6.89 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.27 (dd, J = 8.6, 2.3 Hz, 1H), 7.32–7.34 (m, 2H). HR-MS (EI). Calcd for $C_{16}H_{17}ClO_3$ (M): 292.0866. Found: *m/z* 292.0865.

{4-Methoxy-2-[methoxy(phenyl)methyl]phenyl}methanol (3e): a colorless oil; R_f 0.35 (AcOEt/hexane 1:2); IR (KBr) 3406, 1611 cm^{-1}; ^1H NMR δ 2.50 (t, J = 6.3 Hz, 1H), 3.43 (s, 3H), 3.78 (s, 3H), 4.45–4.49 (m, 1H), 4.51–4.55 (m, 1H), 5.53 (s, 1H), 6.82 (dd, J = 8.0, 2.9 Hz, 1H), 6.85 (d, J = 2.9 Hz, 1H), 7.28–7.31 (m, 2H), 7.34–7.35 (m, 4H). HR-MS (EI). Calcd for $C_{16}H_{18}O_3$ (M): 258.1256. Found: *m/z* 258.1257.

{4,5-Dimethoxy-2-[methoxy(phenyl)methyl]phenyl}methanol (3f): a white solid; mp 87–89 ˚C (hexane/CH_2Cl_2); IR (neat) 3468, 1608 cm^{-1}; ^1H NMR δ 2.40 (t, J = 6.3 Hz, 1H), 3.42 (s, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 4.48–4.52 (m, 1H), 4.56–4.60 (m, 1H), 5.51 (s, 1H), 6.78 (s, 1H), 6.93 (s, 1H), 7.29 (t, J = 7.4 Hz, 1H), 7.33–7.38 (m, 4H). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.64; H, 7.01.

Typical Procedure for the Preparation of Azides (5). 1-(Azidomethyl)-2-[methoxy(phenyl)methyl]benzene (5a). To a stirred solution of **3a** (0.50 g, 2.2 mmol) in CH_2Cl_2 (9 mL) containing pyridine (0.17 g, 2.2 mmol) at rt was added $SOCl_2$ (0.26 g, 2.2 mmol) dropwise. After 40 min,

the mixture was diluted by adding CH_2Cl_2 (15 mL) and saturated aqueous $NaHCO_3$ (20 mL) was added. The layers were separated, and the aqueous was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (15 mL), dried (Na_2SO_4), and concentrated by evaporation to crude chloride, which was dissolved in DMF (10 mL). To this solution was added NaN_3 (0.14 g, 2.2 mmol) at rt and the mixture was stirred overnight. Water (20 mL) was added and the resulting mixture was extracted with AcOEt (3 × 15 mL). The combined extracts were washed with water (3 × 20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **5a** (0.36 g, 70%); a pale-yellow oil; R_f 0.36 (CH_2Cl_2/hexane 1:3); IR (neat) 2099, 1601 cm^{-1}; ^1H NMR δ 3.40 (s, 3H), 4.30 (d, J = 13.7 Hz, 1H), 4.38 (d, J = 13.7 Hz, 1H), 5.49 (s, 1H), 7.27–7.38 (m, 8H), 7.45 (d, J = 7.4 Hz, 1H). HR-MS (ESI). Calcd for $C_{15}H_{16}NO$ [(M–N_2)+H]: 226.1232. Found: *m/z* 226.1225.

1-(Azidomethyl)-2-[(4-chlorophenyl)(methoxy)methyl]benzene (5b): a colorless oil; R_f 0.50 (AcOEt/hexane 1:7); IR (neat) 2099 cm^{-1}; ^1H NMR δ 3.39 (s, 3H), 4.27 (d, J = 13.7 Hz, 1H), 4.38 (d, J = 13.7 Hz, 1H), 5.46 (s, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.34–7.41 (m, 4H). HR-MS (ESI). Calcd for $C_{15}H_{15}ClNO$ [(M–N_2)+H]: 260.0842. Found: *m/z* 260.0836.

1-(Azidomethyl)-2-[methoxy(4-methoxyphenyl)methyl]benzene (5c): a colorless oil; R_f 0.28 (AcOEt/hexane 1:10); IR (neat) 2098, 1610 cm^{-1}; ^1H NMR δ 3.38 (s, 3H), 3.79 (s, 3H), 4.28 (d, J = 13.7 Hz, 1H), 4.35 (d, J = 13.7 Hz, 1H), 5.44 (s, 1H), 6.86 (d, J = 9.2 Hz, 2H), 7.20 (d, J = 9.2 Hz, 2H), 7.32–7.39 (m, 3H), 7.48 (d, J = 7.4 Hz, 1H). HR-MS (ESI). Calcd for $C_{16}H_{18}NO_2$ [(M–N_2)+H]: 256.1338. Found: *m/z* 256.1326.

1-(Azidomethyl)-4-chloro-2-[methoxy(4-methoxyphenyl)methyl]benzene (5d): a pale-yellow oil; R_f 0.33 (AcOEt/hexane 1:10); IR (neat) 2101, 1611 cm^{-1}; ^1H NMR δ 3.37 (s, 3H), 3.80 (s, 3H), 4.23 (d, J = 14.3 Hz, 1H), 4.28 (d, J = 14.3 Hz, 1H), 5.37 (s, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 1H), 7.33 (dd, J = 8.6, 2.3 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H). HR-MS (EI). Calcd for $C_{16}H_{16}ClN_3O_2$ (M): 317.0931. Found: *m/z* 317.0940.

1-(Azidomethyl)-4-methoxy-2-[methoxy(phenyl)methyl]benzene (5e): a colorless oil; R_f 0.38 (AcOEt/hexane 1:10); IR (neat) 2097, 1610 cm^{-1}; ^1H NMR δ 3.41 (s, 3H), 3.82 (s, 3H), 4.21 (d, J = 13.7 Hz, 1H), 4.29 (d, J = 13.7 Hz, 1H), 5.47 (s, 1H), 6.84 (dd, J = 8.6, 2.9 Hz, 1H), 7.07 (d, J = 2.9 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 7.27–7.35 (m, 5H). HR-MS (EI). Calcd for $C_{16}H_{17}N_3O_2$ (M): 283.1321. Found: *m/z* 283.1330.

1-(Azidomethyl)-4,5-dimethoxy-2-[methoxy(phenyl)methyl]benzene (5f): a colorless oil; R_f 0.33 (AcOEt/hexane 1:5); IR (neat) 2101, 1607 cm^{-1}; ^1H NMR δ 3.40 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 4.27 (d, J = 13.7 Hz, 1H), 4.32 (d, J = 13.7 Hz, 1H), 5.45 (s, 1H), 6.82 (s, 1H), 6.98 (s, 1H), 7.26–7.35 (m, 5H). HR-MS (EI). Calcd for $C_{17}H_{19}N_3O_3$ (M): 313.1426. Found: *m/z* 313.1430.

Typical Procedure for the Preparation of Isothiocyanates (6). 1-(Isothiocyanatomethyl)-2-[methoxy(phenyl)methyl]benzene (6a). A mixture of **5a** (0.27 g, 1.1 mmol) and PPh_3 (0.28 g, 1.1 mmol) in CH_2Cl_2 (9 mL) was stirred at rt for a day. The organic solvent was removed by evaporation and the residue was dissolved in MeCN (6 mL). To this solution was added CS_2 (0.81 g, 11 mmol) under stirring and it was continued for 30 min. The solvent and excess CS_2 were removed by evaporation. The residue was purified by column chromatography on SiO_2 to give **6a** (0.17 g, 60%); a colorless oil; R_f 0.70 (AcOEt/hexane 1:4); IR (neat) 2164, 2097, 1601 cm^{-1}; ^1H NMR δ 3.39 (s, 3H), 4.61 (d, J = 16.0 Hz, 1H), 4.73 (d, J = 16.0 Hz, 1H), 5.37 (s, 1H), 7.25–7.43 (m, 9H). HR-MS (EI). Calcd for $C_{16}H_{15}NOS$ (M): 269.0874. Found: *m/z* 269.0878.

1-[(4-Chlorophenyl)(methoxy)methyl]-2-(isothiocyantomethyl)benzene (6b): a colorless oil; R_f 0.52 (AcOEt/hexane 1:4); IR (neat) 2164, 2095 cm^{-1}; ^1H NMR δ 3.38 (s, 3H), 4.58 (d, J = 16.6 Hz, 1H), 4.73 (d, J = 16.6 Hz, 1H), 5.34 (s, 1H), 7.20 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.33–7.44 (m, 4H). HR-MS (EI). Calcd for $C_{16}H_{14}ClNOS$ (M): 303.0485. Found: *m/z* 303.0495.

1-(Isothiocyantomethyl)-2-[methoxy(4-methoxyphenyl)methyl]benzene (6c): a colorless oil; R_f 0.49 (AcOEt/hexane 1:3); IR (neat) 2163, 2095, 1611 cm^{-1}; ^1H NMR δ 3.37 (s, 3H), 3.80 (s, 3H), 4.62 (d, J = 16.6 Hz, 1H), 4.70 (d, J = 16.6 Hz, 1H), 5.32 (s, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.36–7.39 (m, 2H), 7.40–7.42 (m, 2H). HR-MS (EI). Calcd for $C_{17}H_{17}NO_2S$ (M): 299.0980. Found: *m/z* 299.092.

1-Chloro-4-(isothiocyantomethyl)-3-[methoxy(4-methoxyphenyl)methyl]benzene (6d): a colorless oil; R_f 0.41 (AcOEt/hexane 1:7); IR (neat) 2171, 2094, 1611 cm^{-1}; ^1H NMR δ 3.37 (s, 3H), 3.80 (s, 3H), 4.57 (d, J = 16.6 Hz, 1H), 4.61 (d, J = 16.6 Hz, 1H), 5.26 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 7.33 (s, 2H), 7.46 (s, 1H). HR-MS (EI). Calcd for $C_{17}H_{16}ClNO_2S$ (M): 333.0590. Found: *m/z* 333.0592.

1-(Isothiocyanatomethyl)-4-methoxy-2-[methoxy(phenyl)methyl]benzene (6e): a white solid; mp 38–40 ˚C (hexane/CH_2Cl_2); IR (KBr) 2163, 2086, 1610 cm^{-1}; ^1H NMR δ 3.41 (s, 3H), 3.82 (s, 3H), 4.52 (d, J = 16.0 Hz, 1H), 4.61 (d, J = 16.0 Hz, 1H), 5.35 (s, 1H), 6.87 (dd, J = 8.6, 2.9 Hz, 1H), 7.00 (d, J = 2.9 Hz, 1H), 7.26–7.35 (m, 6H). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.12; H, 5.87; N, 4.50.

1-(Isothiocyanatomethyl)-4,5-dimethoxy-2-[methoxy(phenyl)methyl]benzene (6f): a colorless oil; R_f 0.30 (AcOEt/hexane 1:5); IR (neat) 2160, 2087, 1608 cm^{-1}; ^1H NMR δ 3.40 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 4.57 (d, J = 16.0 Hz, 1H), 4.63 (d, J = 16.0 Hz, 1H), 5.34 (s, 1H), 6.88 (s, 1H), 6.93 (s, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.35 (dd, J = 8.0, 7.4 Hz, 2H). HR-MS (EI). Calcd for $C_{18}H_{19}NO_3S$ (M): 329.1086. Found: *m/z* 329.1094.

General Procedure for the Preparation of Dihydroisoindoles (8). To a stirred solution of **6** (1.0 mmol) in CH_2Cl_2 (10 mL) at rt was added one of the amines (1.0 mmol). After 5 min, MsOH (96 mg, 1.0 mmol) was added dropwise at the temperature indicated in Table 1 and stirring was continued for the period indicated in Table 2 before saturated aqueous $NaHCO_3$ (15 mL) was added. The organic solvent was removed by evaporation and the mixture was extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **8**.

***N,N*-Diethyl-1-phenyl-1,3-dihydro-2*H*-isoindole-2-carbothioamides (8a):** a pale-yellow oil; R_f 0.50 (AcOEt/hexane 1:3); IR (neat) 1336, 1149 cm^{-1}; ^1H NMR δ 1.09 (t, J = 7.4 Hz, 6H), 3.35–3.42 (m, 2H), 3.72–3.79 (m, 2H), 4.77 (d, J = 14.9 Hz, 1H), 5.40 (dd, J = 14,9, 2.3 Hz, 1H), 6.90 (d, J = 2.3 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 7.19–7.28 (m, 8H); ^{13}C NMR δ 12.82, 46.73, 59.15, 71.47, 122.00, 123.26, 127.03, 127.51, 127.70, 127.76, 128.50, 134.85, 140.90, 142.44, 190.60. HR-MS (ESI). Calcd for $C_{19}H_{23}N_2S$ (M+H): 311.1582. Found: *m/z* 311.1575. Anal. Calcd for $C_{19}H_{22}N_2S$: C, 73.51; H, 7.14; N, 9.02. Found: C, 73.46; H, 7.23; N, 8.97.

(1-Phenyl-1,3-dihydro-2*H*-isoindol-2-yl)(pyrrolidin-1-yl)methanethione (8b): a white solid; mp 160–162 ˚C (hexane/CH_2Cl_2); IR (KBr) 1348, 1147 cm^{-1}; ^1H NMR δ 1.70–1.81 (m, 2H), 1.95–2.04 (m, 2H), 3.48–3.52 (m, 2H), 3.72–3.78 (m, 2H), 4.74 (d, J = 14.3 Hz, 1H), 5.44 (dd, J = 14.3, 2.3 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.19–7.23 (m, 2H), 7.26–7.32 (m, 6H); ^{13}C NMR δ 25.61, 53.14, 58.85, 71.36, 121.95, 123.18, 126.88, 127.42, 127.62, 127.75, 128.54, 134.77, 141.05, 142.77, 185.53. HR-MS (ESI). Calcd for $C_{19}H_{21}N_2S$ (M+H): 309.1425. Found: *m/z* 309.1440. Anal. Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08; S, 10.39. Found: C, 73.84; H, 6.32; N, 9.11; S, 10.61.

(1-Phenyl-1,3-dihydro-2*H*-isoindol-2-yl)(piperidin-1-yl)methanethione (8c): a pale-yellow solid; mp 153–155 ˚C (hexane/CH_2Cl_2); IR (KBr) 1338, 1118 cm^{-1}; ^1H NMR δ 1.49–1.51 (m, 2H), 1.59–1.64 (m, 2H), 1.64–1.72 (m, 2H), 3.34–3.40 (m, 2H), 3.52–3.57 (m, 2H), 4.82 (d, J = 14.9 Hz, 1H), 5.34 (dd, J = 14.9, 1.1 Hz, 1H), 6.93 (s, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.19–7.29 (m, 8H); ^{13}C NMR δ 24.43, 25.65, 52.30, 58.67, 71.34, 122.00, 123.28, 126.84, 127.44, 127.70, 127.73, 128.49, 134.90, 140.84, 142.32, 192.09. HR-MS (EI). Calcd for $C_{20}H_{22}N_2S$ (M): 322.1504. Found: *m/z* 322.1505. Anal. Calcd for $C_{20}H_{22}N_2S$: C, 74.49; H, 6.88; N, 8.69; S, 9.94. Found: C, 74.39; H, 6.75; N, 8.69; S, 9.88.

(Morpholin-4-yl)(1-phenyl-1,3-dihydro-2*H*-isoindol-2-yl)methanethione (8d): a pale-yellow solid; mp 121–123 ˚C (hexane/CH_2Cl_2); IR (KBr) 1341, 1115 cm^{-1}; ^1H NMR δ 3.25–3.30 (m, 2H), 3.59–3.63 (m, 2H), 3.68–3.73 (m, 2H), 3.76–3.80 (m, 2H), 4.90 (d, J = 14.9 Hz, 1H), 5.38 (d, J = 14.9 Hz, 1H), 6.83 (s, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.21–7.32 (m, 8H); ^{13}C NMR δ 51.36, 58.69, 66.37, 71.52, 122.11, 123.33, 126.76, 127.71, 127.91, 127.93, 128.63, 134.56, 140.60, 141.89, 192.13. HR-MS (ESI, positive). Calcd

for $C_{19}H_{21}N_2OS$ (M+H): 325.1374. Found: *m/z* 325.1369. Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.46; H, 6.47; N, 8.57.

[1-(4-Chlorophenyl)-1,3-dihydro-2*H*-isoindol-2-yl](piperidin-1-yl)methanethione (8e): a pale-yellow solid; mp 161–163 ˚C (hexane/CH_2Cl_2); IR (KBr) 1335, 1089 cm^{-1}; ^1H NMR δ 1.43–1.57 (m, 2H), 1.62–1.68 (m, 2H), 1.69–1.74 (m, 2H), 3.39–3.42 (m, 2H), 3.53–3.58 (m, 2H), 4.78 (d, *J* = 14.9 Hz, 1H), 5.25 (d, *J* = 14.9 Hz, 1H), 6.98 (s, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 7.21–7.43 (m, 7H); ^{13}C NMR δ 24.44, 25.71, 52.36, 58.51, 70.68, 122.08, 123.23, 127.88, 127.93, 128.55, 128.66, 133.21, 134.93, 140.39, 140.96, 192.14. HR-MS (EI). Calcd for $C_{20}H_{21}ClN_2S$ (M): 356.1114. Found: *m/z* 356.1129. Anal. Calcd for $C_{20}H_{21}ClN_2S$: C, 67.31; H, 5.93; N, 7.85. Found: C, 67.24; H, 6.09; N, 7.88.

[1-(4-Chlorophenyl)-1,3-dihydro-2*H*-isoindol-2-yl](morphorin-4-yl)methanethione (8f): a white solid; mp 145–147 ˚C (hexane/CH_2Cl_2); IR (KBr) 1335, 1108 cm^{-1}; ^1H NMR δ 3.30–3.34 (m, 2H), 3.62–3.66 (m, 2H), 3.71–3.75 (m, 2H), 3.78–3.82 (m, 2H), 4.85 (d, *J* = 14.9 Hz, 1H), 5.28 (dd, *J* = 14.9, 1.2 Hz, 1H), 6.91 (d, *J* = 1.2 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.20–7.32 (m, 7H); ^{13}C NMR δ 51.43, 58.43, 66.39, 70.82, 122.14, 123.27, 128.07, 128.10, 128.48, 128.78, 133.46, 134.56, 140.12, 140.49, 192.18. HR-MS (EI). Calcd for $C_{19}H_{19}ClN_2OS$ (M): 358.0907. Found: *m/z* 358.0924. Anal. Calcd for $C_{19}H_{19}ClN_2OS$: C, 63.59; H, 5.34; N, 7.81. Found: C, 63.51; H, 5.38; N, 7.79.

[1-(4-Methoxyphenyl)-1,3-dihydro-2*H*-isoindol-2-yl](pyrrolidin-1-yl)methanethione (8g): a colorless viscous oil; R_f 0.33 (AcOEt/hexane 1:3); IR (neat) 1611, 1344, 1172 cm^{-1}; ^1H NMR δ 1.73–1.78 (m, 2H), 1.97–2.00 (m, 2H), 3.46–3.50 (m, 2H), 3.72–3.78 (m, including s at 3.75, combined 5H), 4.71 (d, *J* = 14.3 Hz, 1H), 5.42 (dd, *J* =14.3, 1.7 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 1.7 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 7.18–7.26 (m, 5H); δ 25.56, 53.07, 55.12, 58.60, 70.75, 113.84, 121.87, 123.14, 127.51, 127.69, 128.16, 134.72, 135.02, 141.28, 158.79, 185.42. HR-MS (EI). Calcd for $C_{20}H_{22}N_2OS$ (M): 338.1453. Found: *m/z* 338.1469. Anal. Calcd for $C_{20}H_{22}N_2OS$: C, 70.97; H, 6.55; N, 8.28. Found: C, 70.76; H, 6.64; N, 8.20.

6-Chloro-*N*,*N*-diethyl-1-(4-methoxyphenyl)-1,3-dihydro-2*H*-isoindole-2-carbothioamides (8h): a colorless viscous oil; R_f 0.46 (AcOEt/hexane 1:5); IR (neat) 1609, 1336, 1114 cm^{-1}; ^1H NMR δ 1.11 (t, *J* = 6.9 Hz, 6H), 3.36–3.43 (m, 2H), 3.70–3.75 (m, 2H), 3.76 (s, 3H), 4.67 (d, *J* = 14.3 Hz, 1H), 5.29 (dd, *J* =14.3, 1.1 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.87 (br s, 1H), 6.98 (s, 1H), 7.18–7.20 (m, 3H), 7.24 (dd, *J* = 8.0, 1.1 Hz, 1H); ^{13}C NMR δ 12.81, 46.64, 55.18, 58.37, 70.62, 113.92, 123.23, 123.49, 127.96, 128.40, 133.34, 133.54, 134.04, 143.15, 159.09, 190.72. HR-MS (ESI). Calcd for $C_{20}H_{24}ClN_2OS$ (M+H): 375.1298. Found: *m/z* 375.1293. Anal. Calcd for $C_{20}H_{23}ClN_2OS$: C, 64.07; H, 6.18; N, 7.47. Found: C, 64.07; H, 6.29; N, 7.42.

[6-Chloro-1-(4-methoxyphenyl)-1,3-dihydro-2*H*-isoindol-2-yl](pyrrolidin-1-yl)methanethione (8i): a white solid; mp 163–165 ˚C (hexane/CH_2Cl_2); IR (KBr) 1609, 1343, 1172 cm^{-1}; ^1H NMR δ 1.73–1.81 (m,

2H), 1.98–2.03 (m, 2H), 3.47–3.50 (m, 2H), 3.70–3.75 (m, 2H), 3.76 (s, 3H), 4.65 (d, *J* = 14.3 Hz, 1H), 5.36 (dd, *J* = 14.3, 2.3 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.99 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.20–7.24 (m, 3H); ^{13}C NMR δ 25.57, 33.12, 55.16, 58.05, 70.52, 113.99, 123.20, 123.43, 127.93, 128.22, 133.21, 133.53, 134.32, 143.24, 159.01, 185.44. HR-MS (EI). Calcd for $C_{20}H_{21}ClN_2OS$ (M): 372.1063. Found: *m/z* 372.1064. Anal. Calcd for $C_{20}H_{21}ClN_2OS$: C, 64.42; H, 5.68; N, 7.51. Found: C, 64.21; H, 5.85; N, 7.35.

(6-Methoxy-1-phenyl-1,3-dihydro-2*H*-isoindol-2-yl)(piperidin-1-yl)methanethione (8j): a pale-yellow solid; mp 121–123 ˚C (hexane/CH_2Cl_2); IR (KBr) 1616, 1337, 1116 cm^{-1}; ^{1}H NMR δ 1.50–1.53 (m, 2H), 1.61–1.64 (m, 2H), 1.69–1.73 (m, 2H), 3.34–3.39 (m, 2H), 3.50–3.55 (m, 2H), 3.71 (s, 3H), 4.75 (d, *J* = 14.3 Hz, 1H), 5.25 (dd, *J* = 14.3, 1.7 Hz, 1H), 6.55 (d, *J* = 1.7 Hz, 1H), 6.82 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 7.22–7.24 (m, 1H), 7.26–7.31 (m, 4H); ^{13}C NMR δ 24.44, 25.66, 52.31, 55.36, 58.20, 71.44, 107.97, 114.40, 122.82, 126.88, 126.93, 127.46, 128.50, 142.22 (2 overlapped Cs), 159.55, 191.98. HR-MS (EI). Calcd for $C_{21}H_{24}N_2OS$ (M): 352.1609. Found: *m/z* 352.1613. Anal. Calcd for $C_{21}H_{24}N_2OS$: C, 71.56; H, 6.86; N, 7.95; S, 9.10. Found: C, 71.27; H, 6.67; N, 7.80; S, 8.98.

(6,7-Dimethoxy-1-phenyl-1,3-dihydro-2*H*-isoindol-2-yl)(pyrrolidin-1-yl)methanethione (8k): a yellow oil; R_f 0.28 (AcOEt/hexane 3:2); IR (neat) 1613, 1331, 1106 cm^{-1}; ^{1}H NMR δ 1.75–1.79 (m, 2H), 1.98–2.00 (m, 2H), 3.47–3.51 (m, 2H), 3.71–3.75 (m, 2H), 3.77 (s, 3H), 3.88 (s, 3H), 4.66 (d, *J* = 13.7 Hz, 1H), 5.37 (dd, *J* = 13.7, 2.9 Hz, 1H), 6.49 (s, 1H), 6.76 (s, 1H), 6.92 (d, *J* = 2.9 Hz, 1H), 7.23–7.32 (m, 5H); ^{13}C NMR δ 14.17, 25.63, 53.15, 55.98, 56.05, 58.87, 71.47, 104.47, 105.61, 126.33, 127.00, 127.43, 128.55, 132.85, 142.84, 149.24, 185.35. HR-MS (ESI). Calcd for $C_{21}H_{24}N_2NaO_2S$ (M+Na): 391.1456. Found: *m/z* 391.1444. Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.57; N, 7.60. Found: C, 68.30; H, 6.70; N, 7.71.

1-(4-Methoxyphenyl)-3-(pyrrolidin-1-yl)-1,5-dihydro-2,4-benzothiazepine (9). To a stirred solution of **6c** (0.14 g, 0.45 mmol) in MeCN (4 mL) at rt was added pyrrolidine (32 mg, 0.45 mmol). After 5 min, concentrated HBr (0.15 g, 0.90 mmol) was added dropwise at 0 ˚C. The temperature was raised to rt and stirring was continued for an additional 2 h before saturated aqueous $NaHCO_3$ (15 mL) was added. The organic solvent was removed by evaporation and the mixture was extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was purified by recrystallization from hexane/CH_2Cl_2 to afford **9** (79 mg, 52%); a beige solid; mp 134–136 ˚C; IR (KBr) 1608, 1586 cm^{-1}; ^{1}H NMR δ 1.73–1.75 (m, 4H), 3.26–3.28 (m, 4H), 3.82 (s, 3H), 4.53 (d, *J* = 13.7 Hz, 1H), 5.05 (d, *J* = 13.7 Ha, 1H), 5.95 (s, 1H), 6.88 (d, *J* = 6.9 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.23 (dd, *J* = 7.4, 6.9 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 24.67, 47.38, 47.99, 50.96, 55.19, 113.98, 127.30, 127.37,

127.51, 128.91, 129.99, 131.4, 139.01, 139.44, 150.10, 158.78. HR-MS (EI). Calcd for $C_{20}H_{22}N_2OS$ (M): 338.1453. Found: *m/z* 338.1465. Anal. Calcd for $C_{20}H_{22}N_2OS$: C, 70.97; H, 6.55; N, 8.28. Found: C, 70.70; H, 6.54; N, 8.21.

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