The Free Internet Journal for Organic Chemistry

Paper

Archive for Organic Chemistry

Arkivoc **2018**, part iii, 76-89

Synthesis of new 3-[(alkylthio)methyl]-1-hydroxy-2-(4'-substituted phenyl)indoles and their mechanistic studies on substituent effects

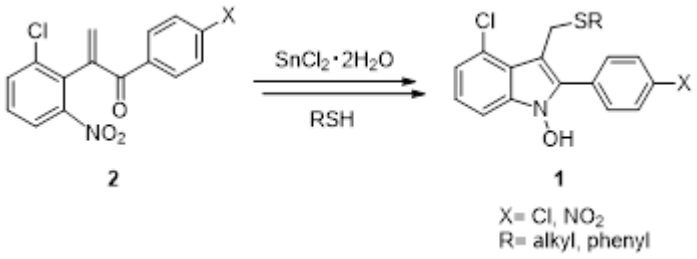
Hyunsung Cho, Hyejin Kim, Yoo Jin Lim, and Sang Hyup Lee*

College of Pharmacy and Innovative Drug Center, Duksung Women's University, Seoul 01369, Republic of Korea
E-mail: sanghyup@duksung.ac.kr

Received 07-27-2017 **Accepted** 12-15-2017 **Published on line** 12-20-2017

Abstract

The synthesis and mechanistic studies of new 3-[(alkylthio)methyl]-1-hydroxy-2-(4'-substituted phenyl)indoles **1** were presented. New substrates **2** were prepared by the application of efficient three-step synthesis with minor modifications, and used to produce target 1-hydroxyindoles **1**. Substrates **2** were reacted with thiol nucleophiles in the presence of $SnCl_2 \cdot 2H_2O$ and 4Å molecular sieves to afford sixteen novel 1-hydroxyindoles **1**, by a consecutive process involving nitro reduction, intramolecular cyclization, and nucleophilic 1,5-addition. Studies on the mechanistic aspects of these reactions with focus on the effects of *p*-substituent (X) in phenyl ring at C(1) in **2** were performed.

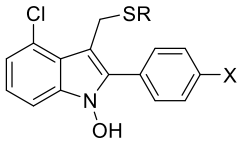


Keywords: 2-Phenylindoles, 1-hydroxyindoles, stannous chloride, nitro reduction, intramolecular cyclization, 1,5-addition

Introduction

1-Hydroxyindole derivatives containing N(1)-OH constitute an important class of compounds because of their unique structural features and biological activities. Due to the presence of a hydroxy group, their physicochemical properties differ from those of indoles. Although initial studies on these compounds were reported[1-5] in 1960s and 1970s, the majority focused on limited numbers of derivatives and provided only brief descriptions on the chemical entities. Furthermore, these studies were hampered by structural ambiguities and chemical instabilities caused by tautomerization and aerial oxidation. After several decades, Henmi *et.al.* reported on 1-hydroxyindoles with appropriate levels of spectral data,[6] and subsequently, Somei and Wong *et.al.* described synthesis and general chemical features of 1-hydroxyindoles.[7,8,9] However, the studies on these compounds and their structural characteristics had not been broadly conducted for decades, presumably due to difficulties associated with preparation, characterization, and storage.[8.10] Nevertheless, it is believed the unique physicochemical properties of these compounds such as polarity and acidity reflect meaningful biological and medicinal profiles.[7] Although rare, the 1-hydroxyindole structure is found in living organisms.[11-13] Particularly, the occurrence of 1-hydroxytryptophan and 1-hydroxytryptamine in living organisms imply the significance of 1-hydroxyindoles.[8] Furthermore, biological studies have shown that 1-hydroxyindoles have substantial biological activities including antiproliferative[14] and platelet aggregation inhibitory activities.[15] Despite the emerging significance of these compounds, further studies have been restricted by a lack of efficient synthetic methodologies and a limited range of derivatives. Thus, there is strong demand for tolerable synthetic methods and production of diverse derivatives of 1-hydroxyindoles.

We initiated a program to construct different multi-substituted 1-hydroxyindoles and to investigate their structural features and formation mechanisms. Recently, we reported the synthesis of 1-hydroxyindole-2-carboxylates,[16-20] and 1-hydroxy-2-phenylindoles[21,22] with a limited number of derivatives. These initial successes prompted us to expand our studies for the construction of diverse derivatives. Here, we report the synthesis of novel 3-[(alkylthio)methyl]-1-hydroxy-2-(4'-substituted phenyl)indoles **1** and their mechanistic investigation with focus on the effects of substituents.



X= Cl, NO_2
R= alkyl, phenyl

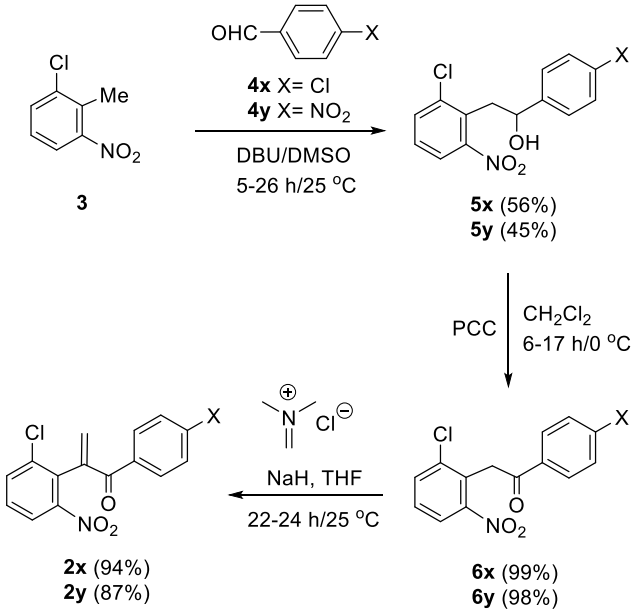
1

Figure 1

Results and Discussion

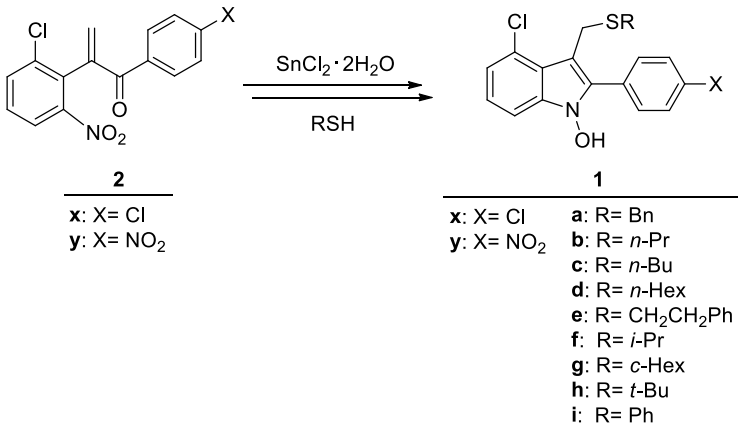
This study was undertaken to produce new multi-substituted 1-hydroxyindoles **1** using peculiar indole formation reactions consisting of three successive processes, and to investigate their mechanistic aspects with emphasis on the effects of substituents (X) in phenyl ring at C(1) in **2**. In our previous studies, we found that the substituent at C(1) in **2** significantly affect the results of reactions.[22] Thus, we sought to introduce a *p*-chloro (a moderate electron-withdrawing group) or a *p*-nitro group (a strong electron-withdrawing group)

onto the phenyl ring, and determine their effects on the formation of **1**. Accordingly, we prepared corresponding new substrates **2** by applying analogous procedures[21,23] with minor modifications. As shown in Scheme 1, nitrotoluene compounds **3** were reacted with 4-substituted benzaldehyde **4** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford nitro alcohols **5** in reasonable yields (56%–45%), though surprisingly, these yields were slightly lower than that obtained with unsubstituted benzaldehyde (70%).[21] In view of the electron-withdrawing effects of the chloro and nitro groups, these results were unexpected. The nitro alcohols **5** were oxidized with pyridinium chlorochromate (PCC) to yield nitro ketones **6** in excellent yields (98–99%). The methylene group was introduced by the reacting nitro ketones **6** and dimethylmethyleneammonium chloride in the presence of NaH, to produce conjugate nitro ketones **2** in excellent yields (87–94%). Consequently, we achieved the synthesis of substrates **2** from **3** in good yields through three-step sequences.



Scheme 1. Synthesis of conjugate nitroketones **2**.

We then aimed to expand the scope of multi-substituted 1-hydroxyindole derivatives by reacting substrates **2** with thiol nucleophiles and reducing agent. $SnCl_2{\cdot}2H_2O$ was used as an appropriate reducing agent, according to previous procedures.[21,24] After pretreatment of $SnCl_2{\cdot}2H_2O$ (3.3 equiv) and thiol nucleophiles (5.0 eq) with 4Å molecular sieves in dimethoxyethane (DME), substrates **2** were added to produce 3-[(alkylthio)methyl]-1-hydroxy-2-(4'-substituted phenyl)indoles **1**, as depicted in Scheme 2. We employed substrates **2** containing an electron-withdrawing *p*-substituent (X) in phenyl ring at C(1) and thiol nucleophiles to give **1** (Table 1). Notably, we were interested in the effects of *p*-substituent (X) on the reactions and employed a *p*-chloro or a *p*-nitro group in phenyl ring with focus on their electron-withdrawing ability, along with the comparison with the results using a *p*-hydrogen. Consequently, we achieved efficient syntheses of multi-substituted 1-hydroxyindoles **1** that might be difficult to prepare otherwise.



2

x: X= Cl
y: X= NO_2

1

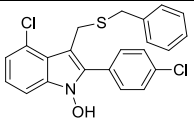
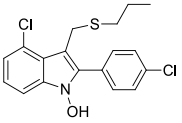
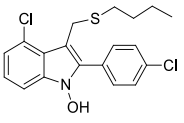
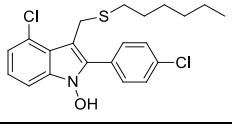
x: X= Cl
y: X= NO_2

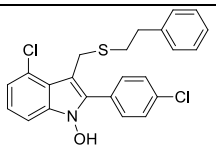
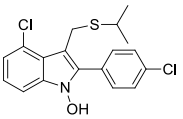
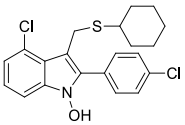
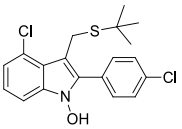
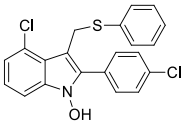
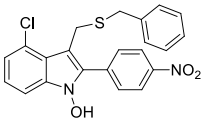
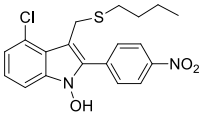
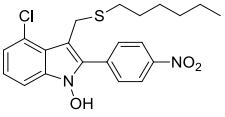
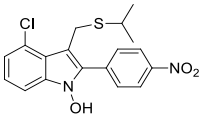
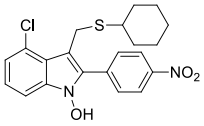
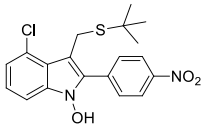
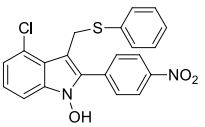
a: R= Bn
b: R= *n*-Pr
c: R= *n*-Bu
d: R= *n*-Hex
e: R= CH_2CH_2Ph
f: R= *i*-Pr
g: R= *c*-Hex
h: R= *t*-Bu
i: R= Ph

Scheme 2. Synthesis of 1-hydroxyindoles **1**.

Reactions of substrate **2x** (X= Cl) with thiol nucleophiles (entries 1–9) provided **1xa**–**1xi** in good to moderate yields (46–66%). In general, aliphatic thiols as nucleophiles provided moderate results, though secondary and tertiary thiols provided slightly better results than primary thiols. Notably, aromatic thiol provided best result. These observations suggest steric hindrance of or low electron density at the sulfur atom positively influenced reactions. Reactions of substrate **2y** (X= NO_2) with thiol nucleophiles (entries 10-16) provided **1ya**–**1yi** in moderate to poor yields (23–51%). In general, the use of aliphatic or aromatic thiols as nucleophiles provided moderate to poor results, but of these, benzyl mercaptane provided the best yield (51%). Furthermore, the results of substrate **2y** that contains a strong electron-withdrawing substituent (X= NO_2) were poorer than the results of substrate **2x** that contains a moderate electron-withdrawing substituent (X= Cl). Notably, in the case of **2y** containing another *p*-nitro group in phenyl ring at C(1), we considered a possibility that the *p*-nitro group could be also reduced. However, we expected that the *o*-nitro group in phenyl ring at C(2) in **2y** could be more easily reduced than the *p*-nitro group in phenyl ring at C(1), probably due to the presence of electron-withdrawing *o*-chloro group in the phenyl ring. Thus, we believed that the interference of another *p*-nitro group in different phenyl ring would not much affect the reaction results.

Table 1. Synthesis of 1-hydroxyindoles **1**[a]

Entry	Substrate 2	NuH	Time (h)	Product	Yield (%)
1	**2x**	BnSH	2	 **1xa**	56
2	**2x**	PrSH	2	 **1xb**	49
3	**2x**	BuSH	2	 **1xc**	53
4	**2x**	HexSH	2	 **1xd**	60

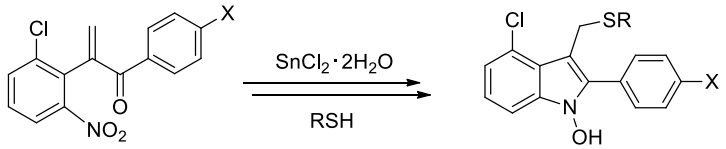
Entry	Substrate 2	NuH	Time (h)	Product	Yield (%)
5	**2x**	$PhCH_2CH_2SH$	2	 **1xe**	46
6	**2x**	*i*-PrSH	2	 **1xf**	65
7	**2x**	*c*-HexSH	2	 **1xg**	55
8	**2x**	*t*-BuSH	2	 **1xh**	63
9	**2x**	PhSH	4	 **1xi**	66
10	**2y**	BnSH	4	 **1ya**	51
11	**2y**	BuSH	6	 **1yc**	38
12	**2y**	HexSH	4	 **1yd**	41
13	**2y**	*i*-PrSH	4	 **1yf**	32
14	**2y**	*c*-HexSH	4	 **1yg**	37
15	**2y**	*t*-BuSH	5	 **1yh**	23
16	**2y**	PhSH	4	 **1yi**	47

[a]All reactions were run in 0.1 mmol scale of **2**.

Significantly, in order to further examine the effects of substituent X on reaction mechanism we compared the results of formation of **1z** (X= H),[21,22] **1x** (X= Cl), and **1y** (X= NO_2) from substrates **2z**, **2x**, and **2y**,

respectively, and seven thiol nucleophiles (Table 2). Analysis showed substrate **2x** provided best results and substrate **2y** worst results, and this was consistently observed for all seven nucleophiles. When we compared the average yields for all products, they were found to be 50% (for **1z**), 60% (for **1x**), and 38% (for **1y**), which led us to conclude that the presence of *p*-chloro group in phenyl ring induced the reaction most efficiently.

Table 2. Comparison of reaction results with substrates **2z**, **2x** and **2y**



2
z: X= H
x: X= Cl
y: X= NO_2

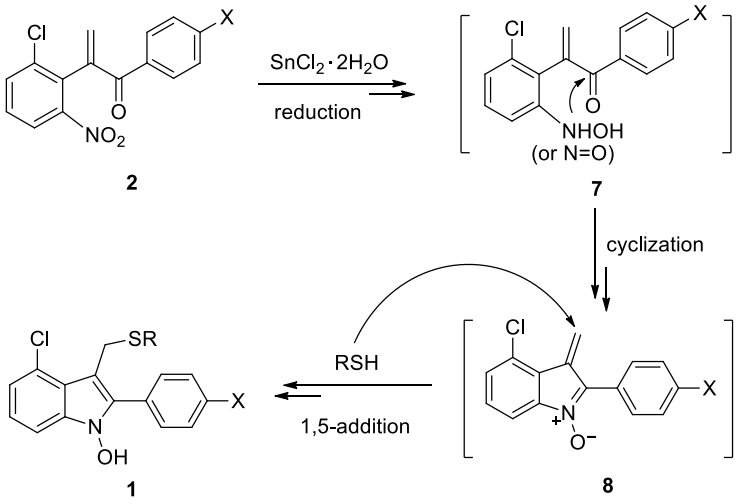
1
z: X= H
x: X= Cl
y: X= NO_2

Entry	NuH	Yield (%)		
		1z[a] (X= H)	**1x** (X= Cl)	**1y** (X= NO_2)
1	BnSH	54	56	51
2	BuSH	52	53	38
3	HexSH	52	60	41
4	*i*-PrSH	60	65	32
5	*c*-HexSH	40	55	37
6	*t*-BuSH	46	63	23
7	PhSH	47	66	47
Average yield		50	60	38

[a]Ref 21 and 22.

According to the generally-accepted pathway where the reaction proceeds in the order nitro reduction → intramolecular cyclization → nucleophilic 1,5-addition, we propose an analogous pathway for **1**, as shown in Scheme 3. In particular, we attempted to elucidate the effect of substituent X on this reaction. Based on our previous studies,[21,22] we recognized that the conjugate nitrone **8** could serve as a critical intermediate and hence influence results. Therefore, we considered that the steric effect of X in **8** was probably negligible, but that its electronic effect would be significant. The electron withdrawing effect of X in **8** would reduce electron density at the exocyclic methylene group at C(3), and thus, increase the reactivity of **8**, but it would also stabilize the nitrone group, which would decrease the reactivity of nitrone **8**. These two effects seemed to compensate each other. Consequently, we found that the results were not linearly dependent on the electron withdrawing ability of X, and that best results were obtained for a *p*-chloro substituent (yields followed the order Cl > H> NO_2) (Table 2). In addition, we also attempted these reactions with alcohol or selenol rather than thiol nucleophiles. Based on our previous observations[22] that unsubstituted phenyl group at C(1) in **2z** did not seem sufficiently electron-withdrawing for inducing the reactions with alcohol nucleophile, we attempted to induce these reactions with alcohol nucleophiles using **2x** and **2y**, which contained electron-withdrawing *p*-substituent in the phenyl ring at C(1). However, even substrate **2y**, which contained high electron-withdrawing *p*-nitro group did not provide satisfactory results. When a selenol (*e.g.*, benzeneselenol) was used as a nucleophile, some reactions seemed to occur due to immediate changes in color and suspending conditions of

reaction media, but results were inconclusive, probably due to its high nucleophilicity and susceptibility to oxidation condition. Taken together, we found that these reactions appeared to be governed by several factors such as the reactivity of intermediates and nucleophiles, and the electronic effects of substituents at C(1) in **2**, and that the *p*-chloro group as a moderate electron-withdrawing substituent in phenyl ring at C(1) afforded best results. Further efforts are required to elucidate reaction mechanisms and expand the scope of the reactions with various nucleophiles.



Scheme 3. Reaction mechanism for formation of **1**.

Conclusions

We describe the syntheses of new 3-[(alkylthio)methyl]-1-hydroxy-2-(4'-substituted phenyl)indoles **1** and a discussion of reaction mechanisms. By using new substrates **2** prepared by using three-step procedures, we performed one-pot reactions of nitro reduction ($SnCl_2 \cdot 2H_2O$), intramolecular cyclization, and nucleophilic 1,5-addition processes, leading to the syntheses of sixteen derivatives of **1**. Notably, aromatic or hindered thiol nucleophiles provided good results. We suggest that the electron-withdrawing tendency of X in phenyl ring at C(1) in **2** has two conflicting effects, that is, it increases the reactivity of the exocyclic methylene group at C(3) in **8**, but stabilizes and thus, decreases the reactivity of the nitrone group in **8**. Taken together, highest yields were observed for substrate **2x**, which possessed a moderate electron-withdrawing *p*-chloro group in phenyl ring at C(1).

Experimental Section

General. Reagents and solvents were obtained commercially and used without further purification. Reactions were followed by thin-layer chromatography (TLC), which was conducted on 0.25 mm Merck silica gel plates (60F-254). Preparative TLC (PTLC) separations were performed on the same silica gel plates, and column chromatography was conducted using Merck silica gels (230-400 mesh). All melting points were measured in open capillary tubes using a Buchi B-545 melting point apparatus and are uncorrected. FT-IR spectra were recorded on a Perkin-Elmer Spectrum GX spectrometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were

measured on a Bruker DRX 300 spectrometer in CD_3CN and tetramethylsilane (TMS) was used as the internal reference. Mass spectra (EI or ESI) were obtained by Dr. Sung Hong Kim using a Jeol JMS700 mass spectrometer at the Korea Basic Science Center (KBSI; Daegu, Korea). HPLC analyses were performed using the following Waters Associate Units: 515 A pump, 515 B pump, dual λ absorbance 2487 detector, 717 plus autosampler, and a C_{18} μBondapak (stainless steel) column (3.9 x 300 mm). Product analyses were performed using a linear gradient condition: from 100% A (aqueous 0.025 M triethylammonium acetate, pH 6.5) and 0% B (acetonitrile) to 80% A and 20% B over 1 min, and then to 10% A and 90% B over 30 min. The flow rate was 1 mL/min, and the eluent was monitored at 254 nm.

Synthesis of substrates 2. Substrates **2** were prepared according to analogous procedures[21] with minor modification, through three step synthetic sequences (**3** → **5** → **6** → **2**).

Nitro alcohols (5). To a stirred solution of nitrotoluene **3** (1.0 mmol, 1.0 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.37 mL, 2.5 mmol, 2.5 equiv) in DMSO (3 mL) was added 4-substituted benzaldehyde (**4**, 3.0 mmol, 3.0 equiv). After stirring for 5–26 h at 25 °C, the reaction mixture was quenched with water (30 mL), extracted with EtOAc (2 × 30 mL) and sequentially washed with saturated aqueous NH_4Cl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and H_2O (30 mL). Organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Residue was purified by column chromatography (1:6 → 2:1 EtOAc/hexanes) to give **5** as a white solid.

2-(2'-Chloro-6'-nitrophenyl)-1-(4"-chlorophenyl)-ethan-1-ol (5x). 175 mg, Yield 56%; mp 143–144 °C; R_f 0.23 (1:5 EtOAc/hexanes); HPLC t_R 24.2 min; IR (KBr) 3437, 3025, 1367, 703 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 7.72 (d, *J* 4.2 Hz, 1H, Ar), 7.68 (m, 2H, Ar), 7.41 (t, *J* 8.1 Hz, 1H, Ar), 7.36–7.25 (m, 4H, Ar), 4.81 (dt, *J* 9.1, 4.3 Hz, 1H, C*H*-OH), 3.61 (d, *J* 4.3 Hz, 1H, CH-O*H*), 3.50 (dd, *J* 13.9, 9.1 Hz, 1H, C*H*H), 3.32 (dd, *J* 13.9, 4.2 Hz, 1H, CH*H*), ^{13}C NMR (75 MHz, CD_3CN) δ 154.0 (Ar), 144.6 (Ar), 137.6 (Ar), 134.9 (Ar), 134.0 (Ar), 131.9 (Ar), 129.8 (Ar), 129.7 (Ar), 128.7 (Ar), 124.5 (Ar), 73.0 (CH-OH), 39.3 (CH_2); MS *m/z* 312 $[M+H]^+$; HRMS (+EI) calcd for $C_{14}H_{11}Cl_2NO_3$ $[M]^+$ 311.0116, found 311.0117.

2-(2'-Chloro-6'-nitrophenyl)-1-(4"-nitrophenyl)-ethan-1-ol (5y). 144 mg, Yield 45%; mp 122–123 °C; R_f 0.18 (1:5 EtOAc/hexanes); HPLC t_R 22.5 min; IR (KBr) 3435, 3025, 1371, 703 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.15 (d, *J* 8.8 Hz, 2H, Ar), 7.72 (t, *J* 9.2 Hz, 2H, Ar), 7.53 (d, *J* 8.8 Hz, 2H, Ar), 7.43 (t, *J* 8.1 Hz, 1H, Ar), 4.97 (dt, *J* 9.1, 8.9 Hz, 1H, C*H*-OH), 3.77 (d, *J* 4.4 Hz, 1H, CH-O*H*), 3.51 (dd, *J* 13.9, 9.1 Hz, 1H, C*H*H), 3.37 (dd, *J* 13.9, 4.4 Hz, 1H, CH*H*), ^{13}C NMR (75 MHz, CD_3CN) δ 154.0 (Ar), 153.1 (Ar), 148.8 (Ar), 137.7 (Ar), 135.0 (Ar), 131.5 (Ar), 130.0 (Ar), 128.0 (Ar), 124.9 (Ar), 124.7 (Ar), 72.9 (CH-OH), 39.1 (CH_2); MS *m/z* 323 $[M+H]^+$.

Nitro ketones (6). To a stirred solution of nitro alcohol **5** (1.0 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added pyridinium cholorochromate (PCC, 741 mg, 3.0 mmol, 3.0 equiv) at 0 °C. After stirring for 6–17 h at 0 °C, the reaction mixture was treated with saturated aqueous $Na_2S_2O_3$ (20 mL) and additional H_2O (20 mL). The reaction mixture was extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Residue was purified by column chromatography (1:5 → 1:1 EtOAc/hexanes) to give **6** as a white solid.

2-(2'-Chloro-6'-nitrophenyl)-1-(4"-chlorophenyl)-ethan-1-one (6x). 307 mg, Yield 99%; mp 89–90 °C; R_f 0.46 (1:3 EtOAc/hexanes); HPLC t_R 23.7 min; IR (KBr) 3025, 1634, 1371, 704 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.03 (d, *J* 8.7 Hz, 2H, Ar), 7.95 (d, *J* 8.2 Hz, 1H, Ar), 7.80 (d, *J* 8.2 Hz, 1H, Ar), 7.56 (d, *J* 8.7 Hz, 2H, Ar), 7.51 (t, *J* 8.2 Hz, 1H, Ar), 4.82 (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN) δ 195.0 (C=O), 152.5 (Ar), 140.9 (Ar), 138.4 (Ar), 136.3 (Ar), 135.6 (Ar), 131.3 (Ar), 130.6 (Ar), 130.5 (Ar), 130.3 (Ar), 125.1 (Ar), 41.6 (CH_2); MS *m/z* 309 $[M]^+$; HRMS (+EI) calcd for $C_{14}H_{10}Cl_2NO_3$ $[M+H]^+$ 310.0038, found 310.0035.

2-(2'-Chloro-6'-nitrophenyl)-1-(4"-nitrophenyl)-ethan-1-one (6y). 314 mg, Yield 98%; mp 104–106 °C; R_f 0.42 (1:5 EtOAc/hexanes); HPLC t_R 22.8 min; IR (KBr) 3025, 1634, 1372, 703 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.35 (d, *J* 8.9 Hz, 2H, Ar), 8.24 (d, *J* 8.9 Hz, 2H, Ar), 7.98 (d, *J* 8.2 Hz, 1H, Ar), 7.82 (d, *J* 8.2 Hz, 1H, Ar), 7.54 (t, *J* 8.2 Hz, 1H, Ar), 4.89 (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN) δ 195.3 (C=O), 152.3 (Ar), 152.2 (Ar), 142.1 (Ar), 138.4 (Ar), 135.7 (Ar), 130.8 (Ar), 130.7 (Ar), 129.9 (Ar), 125.4 (Ar), 125.1 (Ar), 42.1 (CH_2); MS *m/z* 320 $[M]^+$; HRMS (+EI) calcd for $C_{14}H_9ClN_2O_5$ $[M]^+$ 320.0200, found 320.0196.

Conjugate nitroketones (2). To a mixture of NaH (60% in mineral oil, 44 mg, 1.1 mmol, 1.1 equiv) in anhydrous THF (23 mL) at 0 °C was added a solution of nitro ketone **6** (1.0 mmol, 1.0 equiv) in THF (12 mL) at 0 °C. After stirring for 1 hour, dimethylmethyleneammonium chloride (313 mg, 3.0 mmol, 3.0 equiv) was added and stirring was continued for 22–24 h at 25 °C. After cooling to 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with EtOAc (2 × 30 mL) and washed with H_2O (2 ×30 mL). Organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Residue was purified by column chromatography (1:15 → 1:5 EtOAc/hexanes) to give **2** as a white solid.

2-(2′-Chloro-6′-nitrophenyl)-1-(4"-chlorophenyl)-prop-2-en-1-one (2x). 299 mg, Yield 94%; mp 128–129 °C; R_f 0.47 (1:4 methylene chloride/hexanes×4); HPLC t_R 24.7 min; IR (KBr) 3025, 1654, 1583, 1493, 703 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.00 (d, *J* 8.3 Hz, 1H, Ar), 7.84 (d, *J* 8.3 Hz, 3H, Ar), 7.63–7.50 (m, 3H, Ar), 6.24 (d, *J* 11.9 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN) δ 194.2 (C=O), 151.2 (C(2)*C*CH_2), 143.2 (Ar), 139.7 (Ar), 137.0 (Ar), 136.8 (Ar), 135.8 (Ar), 133.7 (Ar), 133.3 (Ar), 132.6 (Ar), 131.7 (Ar), 130.2 (CH_2), 124.6 (Ar); MS *m/z* 322 $[M+H]^+$; HRMS (+EI) calcd for $C_{15}H_9Cl_2NO_3$ $[M]^+$ 320.9959, found 320.9958.

2-(2′-Chloro-6′-nitrophenyl)-1-(4"-nitrophenyl)-prop-2-en-1-one (2y). 405 mg, Yield 87%; mp 140–141 °C; R_f 0.68 (1:4 ethyl ether/hexanes × 5); HPLC t_R 23.3 min; IR (KBr) 3025, 1637, 1583, 1493, 700 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.33 (dd, *J* 8.9, 2.1 Hz, 2H, Ar), 8.06–7.97 (m, 3H, Ar), 7.87 (d, *J* 8.1 Hz, 1H, Ar), 7.62 (t, *J* 8.1 Hz, 1H, Ar), 6.30 (d, *J* 9.1 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN) δ 194.2 (C=O), 151.5 (C(2)*C*CH_2), 151.1 (Ar), 143.7 (Ar), 143.3 (Ar), 137.1 (Ar), 136.0 (Ar), 134.9 (Ar), 132.9 (Ar), 131.9 (Ar), 131.8 (Ar), 125.1 (CH_2), 124.7 (Ar); MS *m/z* 333 $[M+H]^+$; HRMS (+EI) calcd for $C_{15}H_9ClN_2O_5$ $[M]^+$ 332.0200, found 332.0198.

General procedure for the synthesis of 2-phenyl-1-hydroxyindoles (1). To a mixture of 4 Å molecular sieves (10 wt %) and $SnCl_2{\cdot}2H_2O$ (3.3 equiv) in DME (0.35 mL) was added nucleophile (5.0 equiv), and the mixture was stirred at room temperature for 30 min. Then, conjugate nitro ketone **2** (0.10 mmol, 1.0 equiv) was added at room temperature and the reaction mixture was warmed to 40 °C. After stirring for 2–6 h in the dark, the reaction mixture was cooled to room temperature and purified by PTLC or column chromatography to give **1**.

3-[(Benzylthio)methyl]-4-chloro-1-hydroxy-2-(4'-chlorophenyl)-1*H*-indole (1xa). Use of benzylmercaptan (59 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (2 h) afforded the title compound **1xa** (23 mg, 56%) as a white solid. mp 80–82 °C; R_f 0.35 (1:4 EtOAc/hexanes); HPLC t_R 26.9 min; IR (KBr) 3435, 3025, 1601, 1493, 1452, 703 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.96 (br s, 1H, N(1)OH), 7.60 (d, *J* 8.5 Hz, 2H, Ar), 7.46 (d, *J* 8.5 Hz, 2H, Ar), 7.35 (t, *J* 8.5 Hz, 3H, Ar), 7.29–7.05 (m, 3H, Ar), 7.08 (d, *J* 7.6 Hz, 2H, Ar), 3.97 (s, 2H, S*C*H_2Ph), 3.64 (s, 2H, C(3)CH_2S); ^{13}C NMR (75 MHz, CD_3CN) δ 140.3 (Ar), 137.8 (Ar), 137.7 (Ar), 135.5 (Ar), 133.3 (Ar), 130.8 (Ar), 130.2 (Ar), 130.1 (Ar), 130.0 (Ar), 129.7 (Ar), 129.2 (Ar), 128.8 (Ar), 128.1 (Ar), 127.2 (Ar), 124.6 (Ar), 122.5 (Ar), 37.8 (S*C*H_2Ph), 28.4 (C(3)*C*H_2S); MS *m/z* 414 $[M+H]^+$; HRMS (+EI) calcd for $C_{22}H_{17}Cl_2NOS$ $[M]^+$ 413.0408, found 413.0403.

4-Chloro-2-(4'-chlorophenyl)-1-hydroxy-3-[(n-propylthio)methyl]-1*H*-indole (1xb). Use of *n*-propanethiol (45 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (2 h) afforded the title compound **1xb** (18 mg, 49%) as a white solid. mp 72–73 °C; R_f 0.27 (1:12 EtOAc/hexanes); HPLC t_R 28.1 min; IR (KBr) 3433, 3025, 1601, 1493, 1452, 703 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.89 (br s, 1H, N(1)OH), 7.67 (d, *J* 8.6 Hz, 2H, Ar), 7.54 (d, *J* 8.6 Hz, 2H, Ar), 7.38 (d, *J* 8.0 Hz, 1H, Ar), 7.15–7.07 (m, 2H, Ar), 4.07 (s, 2H, C(3)CH_2S), 2.34 (t, *J* 7.3 Hz, 2H,

SCH_2CH$_2$), 1.40 (sextet, *J* 7.3 Hz, 2H, CH_2CH$_3$), 0.82 (t, *J* 7.3 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (75 MHz, CD$_3$CN) δ 137.9 (Ar), 137.8 (Ar), 135.6 (Ar), 133.4 (Ar), 129.9 (Ar), 129.2 (Ar), 129.1 (Ar), 127.3 (Ar), 124.6 (Ar), 122.5 (Ar), 109.2 (Ar), 108.4 (Ar), 35.1 (S*C*H$_2$CH$_2$), 27.8 (C(3)*C*H$_2$S), 23.6 (*C*H$_2$CH$_3$), 14.1 (CH$_2$*C*H$_3$); MS *m/z* 366 [M+H]$^+$; HRMS (+EI) calcd for $C_{18}H_{17}Cl_2NOS$ [M]$^+$ 365.0408, found 365.0405.

3-[(n-Butylthio)methyl]-4-chloro-2-(4'-chlorophenyl)-1-hydroxy-1*H*-indole (1xc). Use of *n*-butanethiol (54 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (2 h) afforded the title compound **1xc** (20 mg, 53%) as a white solid. mp 70–72 °C; R_f 0.33 (1:5 EtOAc/hexanes); HPLC t_R 28.9 min; IR (KBr) 3433, 3025, 1601, 1493, 1452, 696 cm^{-1}; ^{1}H NMR (300 MHz, CD$_3$CN) δ 8.87 (br s, 1H, N(1)OH), 7.67 (d, *J* 8.5 Hz, 2H, Ar), 7.54 (d, *J* 8.5 Hz, 2H, Ar), 7.38 (d, *J* 8.0 Hz, 1H, Ar), 7.18 (t, *J* 8.0 Hz, 1H, Ar), 7.10 (d, *J* 8.0 Hz, 1H, Ar), 4.08 (s, 2H, C(3)CH$_2$S), 2.33 (t, *J* 7.3 Hz, 2H, SCH_2CH$_2$), 1.48–1.07 (m, 4H, (CH_2)$_2$CH$_3$), 0.79 (t, *J* 7.1 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (75 MHz, CD$_3$CN) δ 137.9 (Ar), 137.7 (Ar), 135.6 (Ar), 133.5 (Ar), 130.0 (Ar), 129.4 (Ar), 129.1 (Ar), 127.2 (Ar), 124.6 (Ar), 122.5 (Ar), 109.2 (Ar), 107.9 (Ar), 32.9 (S*C*H$_2$CH$_2$), 32.6 (SCH$_2$*C*H$_2$), 27.7 (C(3)*C*H$_2$S), 23.1 (*C*H$_2$CH$_3$), 14.3 (CH$_2$*C*H$_3$); MS *m/z* 380 [M+H]$^+$; HRMS (+EI) calcd for $C_{19}H_{19}Cl_2NOS$ [M]$^+$ 379.0564, found 379.0560.

4-Chloro-2-(4'-chlorophenyl)-3-[(n-hexylthio)methyl]-1-hydroxy-1*H*-indole (1xd). Use of *n*-hexanethiol (71 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (2 h) afforded the title compound **1xd** (24 mg, 60%) as a white solid. mp 58–60 °C; R_f 0.21 (1:1 methylene chloride/hexanes); HPLC t_R 31.2 min; IR (KBr) 3435, 3025, 1601, 1493, 1452, 703 cm^{-1}; ^{1}H NMR (300 MHz, CD$_3$CN) δ 8.62 (s, 1H, N(1)OH), 7.65 (d, *J* 8.6 Hz, 2H, Ar), 7.53 (d, *J* 8.6 Hz, 2H, Ar), 7.37 (d, *J* 8.0 Hz, 1H, Ar), 7.17 (t, *J* 8.0 Hz, 1H, Ar), 7.09 (d, *J* 8.0 Hz, 1H, Ar), 4.07 (s, 2H, C(3)CH$_2$S), 2.30 (t, *J* 7.3 Hz, 2H, SCH_2CH$_2$), 1.36–1.09 (m, 8H, (CH_2)$_4$CH$_3$), 0.86 (t, *J* 14.0 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (75 MHz, CD$_3$CN) δ 138.0 (Ar), 137.8 (Ar), 135.6 (Ar), 133.5 (Ar), 130.0 (Ar), 129.5 (Ar), 129.2 (Ar), 127.3 (Ar), 124.7 (Ar), 122.6 (Ar), 109.3 (Ar), 108.0 (Ar), 32.9 (S*C*H$_2$CH$_2$), 32.6 (*C*H$_2$CH$_2$CH$_3$), 30.9 (C(3)*C*H$_2$S), 29.8 (SCH$_2$*C*H$_2$), 27.7 (S(CH$_2$)$_2$*C*H$_2$), 23.8 (*C*H$_2$CH$_3$), 14.8 (CH$_2$*C*H$_3$); MS *m/z* 408 [M+H]$^+$; HRMS (+EI) calcd for $C_{21}H_{23}Cl_2NOS$ [M]$^+$ 407.0877, found 407.0874.

4-Chloro-2-(4'-chlorophenyl)-1-hydroxy-3-[(phenylethylthio)methyl]-1*H*-indole (1xe). Use of phenylethanethiol (67 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (2 h) afforded the title compound **1xe** (20 mg, 46%) as a white solid. mp 61–62 °C; R_f 0.18 (1:1 methylene chloride/hexanes); HPLC t_R 28.9 min; IR (KBr) 3434, 3025, 1601, 1493, 1452, 703 cm^{-1}; ^{1}H NMR (300 MHz, CD$_3$CN) δ 8.81 (s, 1H, N(1)OH), 7.65 (d, *J* 8.7 Hz, 2H, Ar), 7.53 (d, *J* 8.7 Hz, 2H, Ar), 7.38 (d, *J* 8.1 Hz, 1H, Ar), 7.29–7.16 (m, 5H, Ar), 7.13–7.08 (m, 1H, Ar), 7.03 (d, *J* 8.1 Hz, 1H, Ar), 4.13 (s, 2H, C(3)CH$_2$S), 2.73–2.62 (m, 4H, S(CH_2)$_2$Ph); ^{13}C NMR (75 MHz, CD$_3$CN) δ 142.2 (Ar), 137.8 (Ar), 137.6 (Ar), 135.6 (Ar), 133.4 (Ar), 130.1 (Ar), 130.0 (Ar), 129.8 (Ar), 129.7 (Ar), 129.6 (Ar), 127.4 (Ar), 124.7 (Ar), 122.5 (Ar), 120.9 (Ar), 109.2 (Ar), 107.8 (Ar), 37.1 (S*C*H$_2$CH$_2$Ph), 34.7 (SCH$_2$*C*H$_2$Ph), 28.1 (C(3)*C*H$_2$S); MS *m/z* 428 [M+H]$^+$; HRMS (+EI) calcd for $C_{23}H_{19}Cl_2NOS$ [M]$^+$ 427.0564, found 427.0560.

4-Chloro-2-(4'-chlorophenyl)-1-hydroxy-3-[(isopropylthio)methyl]-1*H*-indole (1xf). Use of isopropanethiol (71 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (2 h) afforded the title compound **1xf** (31 mg, 65%) as a white solid. mp 113–114 °C; R_f 0.23 (2:3 methylene chloride/hexanes); HPLC t_R 27.5 min; IR (KBr) 3434, 3025, 1601, 1493, 1452, 695 cm^{-1}; ^{1}H NMR (300 MHz, CD$_3$CN) δ 9.19 (br s, 1H, N(1)OH), 7.70 (d, *J* 8.7 Hz, 2H, Ar), 7.55 (d, *J* 8.7 Hz, 2H, Ar), 7.37 (d, *J* 7.8 Hz, 1H, Ar), 7.17 (t, *J* 7.8 Hz, 1H, Ar), 7.09 (d, *J* 7.8 Hz, 1H, Ar), 4.10 (s, 2H, C(3)CH$_2$S), 2.83 (septet, *J* 6.7 Hz 1H, SC*H*(CH$_3$)$_2$), 1.11 (d, *J* 6.7 Hz, 6H, SCH(CH_3)$_2$); ^{13}C NMR (75 MHz, CD$_3$CN) δ 137.8 (Ar), 137.6 (Ar), 135.5 (Ar), 133.4 (Ar), 129.9 (Ar), 129.4 (Ar), 127.1 (Ar), 124.5 (Ar), 122.4 (Ar), 120.9 (Ar), 109.2 (Ar), 107.5 (Ar), 36.5 (S*C*H(CH$_3$)$_2$), 26.8 (C(3)*C*H$_2$S), 24.0 (SCH(*C*H$_3$)$_2$); MS *m/z* 366 [M+H]$^+$; HRMS (+EI) calcd for $C_{18}H_{17}Cl_2NOS$ [M]$^+$ 365.0408, found 365.0410.

4-Chloro-2-(4'-chlorophenyl)-3-[(cyclohexylthio)methyl]-1-hydroxy-1*H*-indole (1xg). Use of cyclohexanethiol (61 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (2 h) afforded the title compound **1xg** (22

mg, 55%) as a white solid. mp 132–133 °C; R_f 0.28 (1:5 EtOAc/hexanes); HPLC t_R 30.1 min; IR (KBr) 3434, 3025, 1601, 1493, 1452, 697 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.68 (br s, 1H, N(1)OH), 7.69 (d, *J* 8.7 Hz, 2H, Ar), 7.55 (d, *J* 8.7 Hz, 2H, Ar), 7.38 (d, *J* 8.0 Hz, 1H, Ar), 7.18 (t, *J* 8.0 Hz, 1H, Ar), 7.38 (d, *J* 8.0 Hz, 1H, Ar), 4.10 (s, 2H, C(3)CH_2S), 2.55–2.43 (m, 1H, CH_2SCH), 1.79–1.47 (m, 4H, cyclic SCH(CH_2)$_2$$CH_2$), 1.35–1.06 (m, 6H, cyclic SCH(CH_2)$_2$(CH_2)$_2$$CH_2$); ^{13}C NMR (75 MHz, CD_3CN) δ 137.9 (Ar), 137.6 (Ar), 135.6 (Ar), 133.5 (Ar), 130.0 (Ar), 129.5 (Ar), 129.2 (Ar), 127.3 (Ar), 124.7 (Ar), 122.5 (Ar), 109.2 (Ar), 108.1 (Ar), 44.6 (SCH(CH_2)$_2$), 34.8 (SCHCH_2), 27.3 (C(3)CH_2S), 27.0 (SCH(CH_2)$_2$$CH_2$), 26.1 (SCHCH$_2$$CH_2$); MS *m/z* 406 $[M+H]^+$; HRMS (+EI) calcd for $C_{21}H_{21}Cl_2NOS$ $[M]^+$ 405.0721, found 405.0719.

3-[(t-Butylthio)methyl]-4-chloro-2-(4'-chlorophenyl)-1-hydroxy-1*H*-indole (1xh). Use of *t*-butanethiol (51 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (2 h) afforded the title compound **1xh** (24 mg, 63%) as a white solid. mp 152–153 °C; R_f 0.15 (1:1 methylene chloride/hexanes); HPLC t_R 28.9 min; IR (KBr) 3434, 3025, 1601, 1493, 1452, 697 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.93 (br s, 1H, N(1)OH), 7.82 (d, *J* 8.5 Hz, 2H, Ar), 7.55 (d, *J* 8.5 Hz, 2H, Ar), 7.38 (d, *J* 7.8 Hz, 1H, Ar), 7.17 (t, *J* 7.8 Hz, 1H, Ar), 7.09 (d, *J* 7.8 Hz, 1H, Ar), 4.10 (s, 2H, C(3)CH_2S), 1.33 (s, 9H, SC(CH_3)$_3$); ^{13}C NMR (75 MHz, CD_3CN) δ 137.8 (Ar), 137.5 (Ar), 135.5 (Ar), 133.2 (Ar), 129.8(Ar), 129.4 (Ar), 127.0 (Ar), 124.5 (Ar), 122.5 (Ar), 121.1 (Ar), 109.2 (Ar), 106.2 (Ar), 43.9 (SC(CH_3)$_3$), 31.3 (SC(CH_3)$_3$), 25.0 (C(3)CH_2S); MS *m/z* 380 $[M+H]^+$; HRMS (+EI) calcd for $C_{19}H_{19}Cl_2NOS$ $[M]^+$ 379.0564, found 379.0562.

4-Chloro-2-(4'-chlorophenyl)-1-hydroxy-3-[(phenylthio)methyl]-1*H*-indole (1xi). Use of thiophenol (51 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (4 h) afforded the title compound **1xi** (27 mg, 66%) as a white solid. mp 58–60 °C; R_f 0.10 (1:1 methylene chloride/hexanes); HPLC t_R 29.3 min; IR (KBr) 3434, 3025, 1601, 1493, 1452, 701 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.74 (br s, 1H, N(1)OH), 7.55–7.37 (m, *5*H, Ar), 7.25–7.10 (m, 7H, Ar), 4.49 (s, 2H, C(3)CH_2S); ^{13}C NMR (75 MHz, CD_3CN) δ 138.1 (Ar), 137.9 (Ar), 137.8 (Ar), 135.6 (Ar), 133.2 (Ar), 131.5 (Ar), 130.3 (Ar), 129.9 (Ar), 129.0 (Ar), 127.8 (Ar), 127.1 (Ar), 124.8 (Ar), 122.7 (Ar), 120.8 (Ar), 109.3 (Ar), 106.0 (Ar), 31.5 (C(3)CH_2S); MS *m/z* 400 $[M+H]^+$; HRMS (+EI) calcd for $C_{21}H_{15}Cl_2NOS$ $[M]^+$ 399.0251, found 399.0249.

3-[(Benzylthio)methyl]-4-chloro-1-hydroxy-2-(4'-nitrophenyl)-1*H*-indole (1ya). Use of benzylmercaptan (59 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (4 h) afforded the title compound **1ya** (22 mg, 51%) as a white solid. mp 50–52 °C; R_f 0.14 (7:3 methylene chloride/hexanes); HPLC t_R 27.4 min; IR (KBr) 3433, 3025, 1601, 1493, 1452, 697 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.89 (br s, 1H, N(1)OH), 8.24 (d, *J* 7.7 Hz, 2H, Ar), 7.84 (d, *J* 7.7 Hz, 2H, Ar), 7.40 (d, *J* 7.7 Hz, 1H, Ar), 7.31–7.16 (m, 6H, Ar), 7.11 (d, *J* 7.7 Hz, 1H, Ar), 4.03 (s, 2H, SC*H*2Ph), 3.69 (s, 2H, C(3)CH_2S); ^{13}C NMR (75 MHz, CD_3CN) δ 148.9 (Ar), 140.1(Ar), 138.2 (Ar), 137.0 (Ar), 136.6 (Ar), 132.5 (Ar), 130.2 (Ar), 129.7 (Ar), 128.1 (Ar), 127.5 (Ar), 125.3 (Ar), 124.8 (Ar), 122.9 (Ar), 121.0 (Ar), 109.5 (Ar), 108.5 (Ar), 37.8 (S*C*H2Ph), 28.4 (C(3)CH_2S). MS *m/z* 425 $[M+H]^+$.

3-[(n-Butylthio)methyl]-4-chloro-1-hydroxy-2-(4'-nitrophenyl)-1*H*-indole (1yc). Use of *n*-butanethiol (54 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (6 h) afforded the title compound **1yc** (15 mg, 38%) as a white solid. mp 104–106 °C; R_f 0.23 (3:2 methylene chloride/hexanes); HPLC t_R 27.7 min; IR (KBr) 3435, 3025, 1601, 1493, 1452, 701 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.83 (br s, 1H, N(1)OH), 8.35 (d, *J* 7.0 Hz, 2H, Ar), 7.93 (d, *J* 7.0 Hz, 2H, Ar), 7.41 (d, *J* 7.8 Hz, 1H, Ar), 7.21 (t, *J* 7.8 Hz, 1H, Ar), 7.13 (d, *J* 7.8 Hz, 1H, Ar), 4.11 (s, 2H, C(3)CH_2S), 2.37 (t, *J* 7.1 Hz, 2H, SC$H_2$$CH_2$), 1.41–1.18 (m, 4H, ($CH_2$)$_2$$CH_3$), 0.78 (t, *J* 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, CD_3CN) δ 149.0 (Ar), 138.4 (Ar), 137.3 (Ar), 136.7 (Ar), 132.7 (Ar), 127.5 (Ar), 125.4 (Ar), 124.9 (Ar), 124.0 (Ar), 122.9 (Ar), 120.9 (Ar), 109.5 (Ar), 32.9 (SCH_2CH_2), 32.8 (SCH$_2$$CH_2$), 27.8 (C(3)$CH_2$S), 23.1 ($CH_2CH_3$), 14.3 ($CH_2CH_3$); MS *m/z* 391 $[M+H]^+$; HRMS (+EI) calcd for $C_{19}H_{19}ClN_2O_3S$ $[M]^+$ 390.0805, found 390.0801.

4-Chloro-3-[(n-hexylthio)methyl]-1-hydroxy-2-(4'-nitrophenyl)-1*H*-indole (1yd). Use of *n*-hexanethiol (71 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (4 h) afforded the title compound **1yd** (17 mg, 41%) as a white solid. mp 37–39 °C; R_f 0.23 (3:2 methylene chloride/hexanes); HPLC t_R 30.0 min; IR (KBr) 3433, 3025, 1601, 1493, 1452, 703 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.73 (br s, 1H, N(1)OH), 8.35 (d, *J* 9.0 Hz, 2H, Ar), 7.93 (d, *J* 9.0 Hz, 2H, Ar), 7.41 (d, *J* 7.9 Hz, 1H, Ar), 7.22 (t, *J* 7.9 Hz, 1H, Ar), 7.13 (d, *J* 7.9 Hz, 1H, Ar), 4.11 (s, 2H, C(3)CH_2S), 2.34 (t, *J* 7.3 Hz, 2H, SCH_2CH_2), 1.41–1.02 (m, 8H, $(CH_2)_4CH_3$), 0.84 (t, *J* 7.0 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, CD_3CN) δ 149.0 (Ar), 138.4 (Ar), 137.3 (Ar), 136.7 (Ar), 132.8 (Ar), 127.6 (Ar), 125.4 (Ar), 124.9 (Ar), 124.0 (Ar), 122.9 (Ar), 121.0 (Ar), 109.5 (Ar), 33.1 (SCH_2CH_2), 32.6 ($CH_2CH_2CH_3$), 30.8 (C(3)CH_2S), 29.7 (SCH_2CH_2), 27.7 ($S(CH_2)_2CH_2$), 23.7 (CH_2CH_3), 14.7 (CH_2CH_3); MS *m/z* 419 $[M+H]^+$; HRMS (+EI) calcd for $C_{21}H_{23}ClN_2O_3S$ $[M]^+$ 418.1118, found 418.1113.

4-Chloro-1-hydroxy-3-[(isopropylthio)methyl]-2-(4'-nitrophenyl)-1*H*-indole (1yf). Use of isopropanethiol (46 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (4 h) afforded the title compound **1yf** (12 mg, 32%) as a white solid. mp 124–125 °C; R_f 0.24 (3:2 methylene chloride/hexanes); HPLC t_R 26.7 min; IR (KBr) 3435, 3025, 1601, 1493, 1452, 703 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 9.39 (br s, 1H, N(1)OH), 8.36 (d, *J* 8.8 Hz, 2H, Ar), 7.97 (d, *J* 8.8 Hz, 2H, Ar), 7.41 (d, *J* 7.8 Hz, 1H, Ar), 7.21 (t, *J* 7.8 Hz, 1H, Ar), 7.12 (d, *J* 7.8 Hz, 1H, Ar), 4.14 (s, 2H, C(3)CH_2S), 2.87 (septet, *J* 6.7 Hz 1H, S$CH(CH_3)_2$), 1.14 (d, *J* 6.7 Hz, 6H, SCH(CH_3)$_2$); ^{13}C NMR (75 MHz, CD_3CN) δ 149.0 (Ar), 138.3 (Ar), 137.3 (Ar), 136.5 (Ar), 132.7 (Ar), 127.5 (Ar), 125.2 (Ar), 124.8 (Ar), 122.8 (Ar), 120.9 (Ar), 109.5 (Ar), 109.0 (Ar), 36.7 (S$CH(CH_3)_2$), 26.8 (C(3)CH_2S), 24.0 (SCH(CH_3)$_2$); MS *m/z* 377 $[M+H]^+$; HRMS (+EI) calcd for $C_{18}H_{17}ClN_2O_3S$ $[M]^+$ 376.0648, found 376.0642.

4-Chloro-3-[(cyclohexylthio)methyl]-1-hydroxy-2-(4'-nitrophenyl)-1*H*-indole (1yg). Use of cyclohexanethiol (61 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (4 h) afforded the title compound **1yg** (15 mg, 37%) as a white solid. mp 102–103 °C; R_f 0.49 (1:5 EtOAc/hexanes×2); HPLC t_R 29.7 min; IR (KBr) 3434, 3025, 1601, 1493, 1452, 702 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.95 (br s, 1H, N(1)OH), 8.34 (d, *J* 8.8 Hz, 2H, Ar), 7.95 (d, *J* 8.8 Hz, 2H, Ar), 7.40 (d, *J* 7.8 Hz, 1H, Ar), 7.20 (t, *J* 7.8 Hz, 1H, Ar), 7.12 (d, *J* 7.8 Hz, 1H, Ar), 4.13 (s, 2H, C(3)CH_2S), 2.58–2.46 (m, 1H, CH_2SCH), 1.80–1.46 (m, 4H, cyclic SCH(CH_2)$_2CH_2$), 1.32–1.06 (m, 6H, cyclic SCH$(CH_2)_2(CH_2)_2CH_2$); ^{13}C NMR (75 MHz, CD_3CN) δ 149.0 (Ar), 138.4 (Ar), 137.3 (Ar), 136.5 (Ar), 132.7 (Ar), 127.6 (Ar), 125.3 (Ar), 124.9 (Ar), 122.9 (Ar), 120.9 (Ar), 109.5 (Ar), 109.4 (Ar), 44.9 (S$CH(CH_2)_2$), 34.8 ($SCHCH_2$), 27.2 (C(3)CH_2S), 27.0 ($SCH(CH_2)_2CH_2$), 26.2 ($SCHCH_2CH_2$); MS *m/z* 417 $[M+H]^+$; HRMS (+EI) calcd for $C_{21}H_{21}ClN_2O_3S$ $[M]^+$ 416.0961, found 416.0956.

3-[(t-Butylthio)methyl]-4-chloro-1-hydroxy-2-(4'-nitrophenyl)-1*H*-indole (1yh). Use of *t*-butanethiol (51 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (5 h) afforded the title compound **1yh** (9.2 mg, 23%) as a white solid. mp 144–145 °C; R_f 0.26 (3:2 methylene chloride/hexanes); HPLC t_R 27.8 min; IR (KBr) 3437, 3025, 1601, 1493, 1452, 699 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.89 (br s, 1H, N(1)OH), 8.35 (d, *J* 9.0 Hz, 2H, Ar), 8.07 (d, *J* 9.0 Hz, 2H, Ar), 7.41 (d, *J* 8.0 Hz, 1H, Ar), 7.21 (t, *J* 8.0 Hz, 1H, Ar), 7.12 (d, *J* 8.0 Hz, 1H, Ar), 4.13 (s, 2H, C(3)CH_2S), 1.35 (s, 9H, SC$(CH_3)_3$); ^{13}C NMR (75 MHz, CD_3CN) δ 149.0 (Ar), 138.2 (Ar), 137.3 (Ar), 136.5 (Ar), 132.4 (Ar), 127.4 (Ar), 125.3 (Ar), 124.8 (Ar), 122.9 (Ar), 121.1 (Ar), 109.5 (Ar), 107.9 (Ar), 44.1 (S$C(CH_3)_3$), 31.3 (SC(CH_3)$_3$), 24.9 (C(3)CH_2S); MS *m/z* 391 $[M+H]^+$; HRMS (+EI) calcd for $C_{19}H_{19}ClN_2O_3S$ $[M]^+$ 390.0805, found 390.0802.

4-Chloro-1-hydroxy-2-(4'-nitrophenyl)-3-[(phenylthio)methyl]-1*H*-indole (1yi). Use of thiophenol (51 μL, 0.50 mmol, 5.0 equiv) as a nucleophile in general procedure (4 h) afforded the title compound **1yi** (19 mg, 47%) as a white solid. mp 130–131 °C; R_f 0.18 (3:2 methylene chloride/hexanes); HPLC t_R 27.0 min; IR (KBr) 3433, 3025, 1601, 1493, 1452, 696 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.94 (br s, 1H, N(1)OH), 8.24 (d, *J* 8.9 Hz, 2H, Ar), 7.70 (d, *J* 8.9 Hz, 2H, Ar), 7.42 (d, *J* 7.9 Hz, 1H, Ar), 7.24 (d, *J* 7.9 Hz, 1H, Ar), 7.20–7.13 (m, 6H, Ar), 4.51 (s, 2H, C(3)CH_2S); ^{13}C NMR (75 MHz, CD_3CN) δ 148.9 (Ar), 138.2 (Ar), 137.3 (Ar), 137.0 (Ar), 136.8 (Ar), 132.5 (Ar),

132.1 (Ar), 130.3 (Ar), 128.1 (Ar), 127.5 (Ar), 125.4 (Ar), 124.8 (Ar), 123.0 (Ar), 120.8 (Ar), 109.5 (Ar), 107.7 (Ar), 31.7 (C(3)*C*H_2S); MS *m/z* 411 $[M+H]^+$; HRMS (+EI) calcd for $C_{21}H_{15}ClN_2O_3S$ $[M]^+$ 410.0492, found 410.0489.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) Grant (2012R1A1A2001033 and 2016R1D1A1B03930981), and by Priority Research Centers Program through NRF (2016R1A6A1A03007648) funded by the Ministry of Education, Science and Technology (MEST).

References

1. Mousseron-Canet, M.; Boca, J.-P. *Bull. Soc. Chim. France* **1967**, 1296.
2. Mousseron-Canet, M.; Boca, J.-P.; Tabacik, V. *Spectrochim. Acta* **1967**, *23A*, 717-725. https://doi.org/10.1016/0584-8539(67)80325-8
3. Acheson, R. M.; Bolton, R. G.; Hunter, I. *J. Chem. Soc.*(*C*) **1970**, 1067-1070. https://doi.org/10.1039/j39700001067
4. Acheson, R. M.; Littlewood, D. M.; Rosenburg, H. E. *J. Chem. Soc., Chem. Commun*. **1974**, 671a. https://doi.org/10.1039/c3974000671a
5. Acheson, R. M.; Hunt, P. G.; Littlewood, D. M.; Murrer, B. A.; Rosenburg, H. E. *J. Chem. Soc., Perkin I* **1978**, 1117-1125. https://doi.org/10.1039/p19780001117
6. Henmi, T.; Sakamoto, T.; Kikugawa, Y. *Heterocycles* **1997**, *44*, 157–163. https://doi.org/10.3987/COM-95-S2
7. Somei, M. *Adv. Heterocycl. Chem*. **2002**, *82*, 101–155. https://doi.org/10.1016/S0065-2725(02)82027-X
8. Somei, M. *Heterocycles* **1999**, *50*, 1157–1211. https://doi.org/10.3987/REV-98-SR(H)8
9. Wong, A.; Kuethe, J. T.; Davies, I. W. *J. Org. Chem.,* **2003***, 68,* 9865–9866. https://doi.org/10.1021/jo035351l
10. Yamada, F.; Kawanishi, A.; Tomita, A.; Somei, M. *Arkivoc* **2003**, 8, 102–111. http://dx.doi.org/10.3998/ark.5550190.0004.811
11. Takasugi, M.; Monde, K.; Katsui, N.; Shirata, A. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 285-289. https://doi.org/10.1246/bcsj.61.285
12. Sasaki, T.; Otani, T.; Matsumoto, H.; Unemi, N.; Hamada, M.; Takeuchi, T.; Hori, M. *J. Antibiot*. **1998**, *8*, 715–721. https://doi.org/10.7164/antibiotics.51.715
13. Constantine, K. L.; Mueller, L.; Huang, S.; Abid, S.; Lam, K. S.; Li, W.; Leet, J. E. *J. Am. Chem. Soc*. **2002**, *124*, 7284–7285. https://doi.org/10.1021/ja026249t
14. Granchi, C.; Calvaresi, E. C.; Tuccinardi, T.; Paterni, I.; Macchia, M.; Martinelli, A.; Hergenrother, P. J.; Minutolo, F. *Org. Biomol. Chem.* **2013**, *11*, 6588–6596. https://doi.org/10.1039/c3ob40870a

15. Somei M.; Yamada, K.; Hasegawa, M.; Tabata, M.; Nagahama, Y.; Morikawa, H.; Yamada, F. *Heterocycles* **1996**, *43*, 1855–1858. https://doi.org/10.3987/COM-96-7537
16. Nicolaou, K. C.; Lee, S. H.; Estrada, A. A.; Zak, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3736–3740. https://doi.org/10.1002/anie.200500724
17. Nicolaou, K. C.; Estrada, A. A.; Lee, S. H.; Freestone, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 5364–5368. https://doi.org/10.1002/anie.200601808
18. Nicolaou, K. C.; Estrada, A. A.; Freestone, G. C.; Lee, S. H.; Alvarez-Mico, X. *Tetrahedron* **2007**, *63*, 6088–6114. https://doi.org/10.1016/j.tet.2007.03.072
19. Park, Y. K.; Kim, H.; Kim, D. S.; Cho, H.; Moon, A.; Jeong, C.; Yoon, H.-R.; Lee, S. H. *Bull. Kor. Chem. Soc*. **2015**, *36*, 2095–2100. https://doi.org/10.1002/bkcs.10410
20. Park, Y. K.; Kim, H.; Lee, S. H. *Bull. Kor. Chem. Soc*. **2016**, *37*, 82–90. https://doi.org/10.1002/bkcs.10630
21. Lee, S. H.; Kim, H.; Park, Y. K.; Cho, H. *Synlett* **2015**, *26*, 1069–1072. https://doi.org/10.1055/s-0034-1380275
22. Kim, H.; Lee, S. H. *Heterocycles* **2016**, *92*, 2004–2017. https://doi.org/10.3987/COM-16-13544
23. Coffman, K. C.; Palazzo, T. A.; Hartley, T. P.; Fettinger, J. C.; Tantillo, D. J.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 2062-2065. https://doi.org/10.1021/ol400787y
24. Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839–842. https://doi.org/10.1016/S0040-4039(01)80041-1

