Identification of Indoline-2-thione Analogs as Novel Potent Inhibitors of α-Melanocyte Stimulating Hormone Induced Melanogenesis

Pillaiyar Thanigaimalai,[a] Ki-Cheul Lee,[a] Vinay Kumar Sharma,[a] Niti Sharma,[a] Eunmiri Roh,[b] Youngsoo Kim,[b] and Sang-Hun Jung*,[a]

[a] *College of Pharmacy and Institute of Drug Research and Development, Chungnam National University; Daejeon 305–764, Korea: and* [b] *College of Pharmacy, Chungbuk National University; Cheongju 361–763, Korea.*

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Based on the hits, 3,4-dihydroquinazoline-2-thione (1) and benzimidazole-2-thione (2), a series of indole-2-thione (3) and indole-2-thiol inhibitors (4) of melanogenesis were designed, synthesized and evaluated in melanoma B16 cells under the stimulant of α-melanocyte stimulating hormone (α-MSH). The indole-2-thione compounds (3a—g) exhibited an effective inhibitory activity on melanin synthesis. The Structure–Activity Relationship (SAR) studies of 2 have revealed that in potent inhibitor 3a (>100% inhibition at 30 μM, IC_{50}=1.40 μM) the role of nitrogen (3-*N*) at 3-position is insignificance. In addition, the hydrophobic substituents of 3 were better than the hydrophilic one. However, conversion of thione (–C=S, 3) to thiol (–C–SH, 4) led to decrease in the potency.

Key words melanogenesis inhibitor; benzimidazole-2-thione; inoline-2-thione; indole-2-thiol

In human, melanin is the primary pigment responsible for hair and skin color, which is produced from melanocytes through the process called melanogenesis.[1,2] Melanin protects the skin from sun related injuries. However, the extra accumulation of melanin in different parts of the skin can cause diverse hyperpigmentary disorders such as melasma, freckles and age spot.[3,4] The biosynthesis of melanin is controlled at many different levels by a variety of proteins and enzymes such as tyrosinase, tyrosinase related protein-1 (TRP-1) and TRP-2, which are known to be involved in the melanogenesis pathway. Several factors affect the activities of these enzymes and related proteins including, α-melanocyte stimulating hormone (α-MSH), fibroblast growth factor (FGF), endothelin-1 and UV light.[5,6]

The production of melanin is controlled by a key regulatory tyrosinase, copper containing multifunctional enzyme.[7] Thus, the inhibition of tyrosinase is expected to provide effective therapeutic means for the treatment of dermatological disorders.[8—10] Majority of currently known hypopigmenting agents act directly or indirectly on this enzyme *via* several mechanisms.[8,11,12] The chemical agents, including *N*-phenylthiourea (PTU), hydroquinone, kojic acid, and arbutin (Fig. 1), have been used as hypopigmenting agents, but none are completely satisfying because of their lower activity or severe side effects.[11] Therefore, it is necessary to develop ideal melanogenesis inhibitors with higher activity and lower side effects.

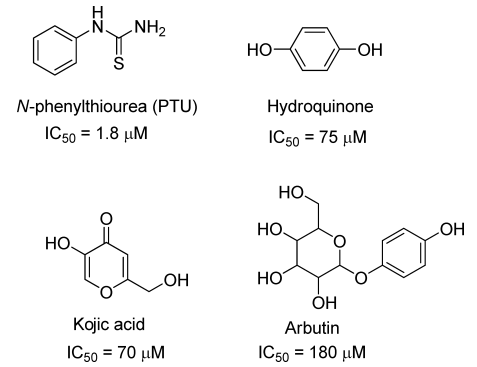


Fig. 1. Chemical Structures and Activity of Known Hypopigmenting Agents

As part of our effort to discover new hypopigmenting agents, the random screening yielded 3,4-dihydroquinazoline-2-thione (**1**, Fig. 2, >100% inhibition at 10 μM, IC_{50}= 0.8 μM) as a potent inhibitor of melanogenesis in melanoma B16 cells under the stimulus of α-melanocyte stimulating hormone (α-MSH) through cAMP pathway.[13] Unlike other hypopigmenting agents, this compound **1** had no effect on tyrosinase enzyme.[13] As a continued effort to develop a more potent analog, we subsequently explored the Structure–Activity Relationship (SAR) of **1** in previous reports.[14—16] This resulted in the identification of benzimdazole-2(3*H*)-thione analog **2** (Fig. 2, >100% inhibition at 10 μM, IC_{50}= 1.5 μM)[16] as equipotent to compound **1**. Here, in the current report, we further scrutinized the SAR of **2** in terms of defining the role of nitrogen at 3-position (3-N) and thione (–C=S) in **2**. Hence, a series of indoline-2-thiones **3**, and indole-2-thiols **4** were designed, synthesized (Fig. 2) and evaluated for their hypopigmenting activity in melanoma B16 cell line under the stimulus of α-MSH.

Chemistry The compounds **3** and **4** were prepared according to Chart 1. Briefly; intermediate **6** was synthesized by the Wolff–Kishner reduction of isatin **5**.[17] The compound **8** was obtained in one pot by sequential treatment of **6** with

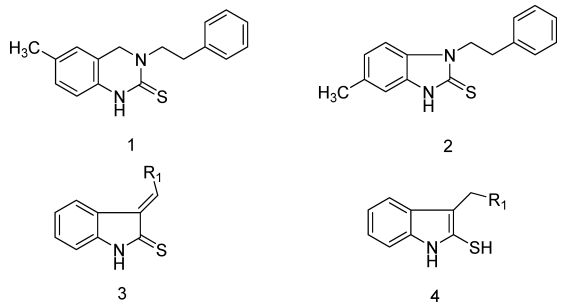
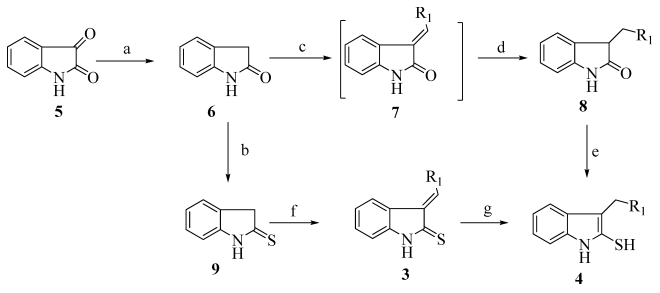


Fig. 2. The Target Structures of Melanogenesis Inhibitors **1**—**4**
The substituents of **3** and **4** are indicated in Table 1.

* To whom correspondence should be addressed. e-mail: jungshh@cnu.ac.kr

appropriate aldehydes in the presence of piperidine at reflux condition for 3—5 h to yield **7**[18—23] and then with sodium borohydride at room temperature.[21] Meanwhile carbonyl compound **6** was treated with phosphorous pentasulfide (P_2S_5) in the presence of sodium carbonate at room temperature to obtain the indoline-2-thione **9**.[24,25] The compound **3**[26] was obtained by the treatment of indoline-2-thione (**9**) with various aldehydes using the same condition as for the preparation of **7**. Interestingly, the benzylideneindole-2-thiones may exist as either *Z* or *E* isomer depending on the substituents at the C-3 position of the 3-benzylideneindoline-2-thione. The previous study[26] determined *E* and *Z* isomers based on chemical shift of vinyl-H in ^{1}H-NMR as chemical shift of *E*-isomer (δ=6.95—7.26) of benzylideneindole-2-thiones is less de-shielded compared to *Z*-isomer (δ=7.30—7.50). Thus, in the current study, we observed that the compound **3a**—**g** are *E*-isomers with their chemical shift values of vinyl-H in the range of 6.95—7.26.

The reduction of **3** with sodium borohydride gave the target compound **4**. The compound **4** could also be obtained by treating the intermediate **8** with Lawesson's reagent under refluxing condition in toluene. The similar result was also observed in previous findings.[24,25] All the thiol compounds (**4a**—**g**) were confirmed by IR with a characteristic S–H stretching vibration at near 2560—2565 cm^{-1} as a broad and diffuse band, and the ^{1}H-NMR spectra with a clear singlet for benzylic proton have strongly supported the presence of indolethiol form.



Reagents and condition: (a) $NH_2NH_2 \cdot H_2O$, 6 N HCl; (b) P_2S_5, Na_2CO_3, THF; (c) R_1-CHO, piperidine, ethanol; (d) $NaBH_4$, ethanol, reflux; (e) Lawesson's reagent, toluene, reflux; (f) R_1-CHO, piperidine, reflux; (g) $NaBH_4$, ethanol, reflux. *Note: Substituents are indicated in Table 1.

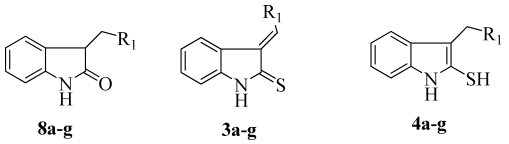
Chart 1. Synthetic Outline for the Preparation of **3** and **4**

Results and Discussion

As described previously, the inhibitory ability of a new series of compounds **8a**—**g**, **3a**—**g** and **4a**—**g** were assayed on melanoma B16 cells under the stimulus of α-MSH (100 nM) for 3 d incubation period.[14,15] Melanoma B16 cells (CRL6323) were obtained from ATCC (Manassas, U.S.A.). The amount of melanin released into the culture media was determined by measuring the absorbance at 405 nm with synthetic melanin as the standard.[27] The data for % inhibition and IC_{50} values are given in Table 1.

As shown in the Table 1, all carbonyl compounds, **8a**—**g**, did not show any notable inhibition however, the thiones (**3a**—**g**) were found to be more potent against melanogenesis as we reported in our earlier studies.[14—16] Accordingly, 3-benzylideneindoline-2-thione (**3a**, >100% inhibition at 30 μM, IC_{50}=1.40 μM) displayed 50-fold more potent inhibitory activity than kojic acid, a well known hypopigmenting agent, and similar potency to the lead **2** (IC_{50}=1.40 μM) in melanoma B 16 cell line. This implies that the nitrogen at 3-position of **2** does not have any specific role against melanogenesis. In an attempt to further improve the potency, we then examined a series of analogs with various hydrophobic substituent at 4-position on benzylidene side chain of **3a**. Accordingly, the compound with methyl (**3b**, >100% inhibition at 30 μM, IC_{50}=3.2 μM), ethyl (**3c**, >100% inhibition at 30 μM, IC_{50}=2.5 μM) or chloro (**3d**, >100% inhibition at 30 μM, IC_{50}=1.4 μM) showed comparable activity to that of **3a**. This study confirms that the presence of hydrophobic substituent on the benzylidene side chain of **3** does not have any influence on their activity enhancement. Conversely, the hydrophilic substituents led to decreased activity as indicated in the methoxy derivative (**3e**, 87% inhibition at 30 μM,

Table 1. The Melanogenesis Inhibitory Activity of **8a**—**g**, **3a**—**g**, and **4a**—**g**



8a-g **3a-g** **4a-g**

Entry No:	R_1	% of inhibition at 30 μM[a]	IC_{50} (μM)[a]	Entry No:	R_1	% of inhibition at 30 μM[a]	IC_{50} (μM)[a]
8a[20]	Ph	<10	>30	**3e**[26]	4-OCH_3Ph	87	6.70
8b[20]	4-CH_3Ph	<10	>30	**3f**	1-Naphthyl	>100	3.40
8c[22]	4-CH_3CH_2Ph	<10	>30	**3g**	Cyclohexyl	>100	3.60
8d[20]	4-ClPh	<10	>30	**4a**[24]	Ph	53	24.20
8e[20]	4-OCH_3Ph	<10	>30	**4b**	4-CH_3Ph	85	14.03
8f[22]	1-Naphthyl	<10	>30	**4c**	4-CH_3CH_2Ph	89	12.15
8g[23]	Cyclohexyl	<10	>30	**4d**	4-ClPh	79	14.34
3a[24]	Ph	>100	1.40	**4e**	4-OCH_3Ph	55	18.23
3b	4-CH_3Ph	>100	5.20	**4f**	1-Naphthyl	59	15.62
3c	4-CH_3CH_2Ph	>100	2.50	**4g**	Cyclohexyl	<10	>30
3d[26]	4-ClPh	>100	1.40	**1**		>100	0.80
2		>100	1.40	Kojic acid			70

a) The values of percentage of inhibitions have taken as a mean value from 3—5 independent experiments.

IC_{50}=6.7 μM), showing less activity than **3a**—**d**.

Furthermore, the importance of phenyl group is demonstrated with the derivative of naphthyl (**3f**, >100% inhibition at 30 μM, IC_{50}=3.4 μM) or cyclohexyl (**3g**, >100% inhibition at 30 μM, IC_{50}=3.6 μM). These results illustrated that the overall lipophilicity of compounds **3** favors melanogenesis inhibition in the melanoma B16 cells.

We next attempted further modification of the thione group of **3**, and the results are summarized in Table 1. In compound **4a** (53% inhibition at 30 μM, IC_{50}=24.2 μM), the activity decreased nearly 20 fold to the corresponding thione **3a**. The same trend has also been observed in the analogs, **4b** (85% inhibition at 30 μM, IC_{50}=14.0 μM), **4c** (89% inhibition at 30 μM, IC_{50}=12.1 μM), **4d** (79% inhibition at 30 μM, IC_{50}=14.3 μM), **4e** (55% inhibition at 30 μM, IC_{50}=18.2 μM), **4f** (59% inhibition at 30 μM, IC_{50}=15.6 μM) and **4g** (<10% inhibition at 30 μM, IC_{50}=>30 μM). From the above study, it can be concluded that the thiones (**3**) are more favorable than thiols (**4**) for their melanogenesis inhibitory activity and the benzylidene side chain of **3** is an essential motif for retaining intact indoline-2-thione function.

Conclusion

Based on the hits, **1** and **2**, a series of novel inhibitors (**3**, **4**) of melanogenesis were designed, synthesized and evaluated in melanoma B16 cells under the stimulus of α-MSH. The selected compounds (**3a**—**g**) exhibited an effective inhibitory activity on melanin synthesis without any cytotoxicity in melanoma B 16 cells (data not shown). The SAR studies of **2** have revealed that in potent inhibitor **3a** (>100% inhibition at 30 μM, IC_{50}=1.40 μM) the role of nitrogen (3-*N*) at 3-position is insignificant. However, conversion of thione (–C=S, **3**) to thiol (–C–SH, **4**) led to decrease in the inhibitory potency. Detailed mechanistic studies directed towards identification of the molecular target of these indoline-2-thiones as hypopigmenting agents are ongoing and will be reported in due course.

Experimental

Chemistry Melting points (mp) were determined on Electro thermal 1A 9100 MK2 apparatus and were uncorrected. All commercial chemicals were used as obtained and all solvents were purified by the standard procedures prior to use. Thin layer chromatography was performed on E Merck silica gel GF-254 pre-coated plates and the identification was done with UV light and colorization with 10% phosphomolybdic acid spray followed by heating. Flash column chromatography was performed with E Merck silica gel (230—400 mesh). Infra red spectrum was recorded by using (neat sample without solvent or KBr) FT-IR spectrum with Nicolet-380 models. NMR spectra were measured against the peak of tetramethylsilane by Varian Unity Inova 400 NMR (400 MHz) spectrometer. High resolution-mass spectrum (HR-MS) was recorded on API2000 mass spectrometer (PE Sciex, Toronto, Canada).

Synthesis of Oxoindole (6)[17] The solution of isatin **5** (14 g, 0.10 mol) in hydrazine monohydrate (60 ml, 1.2 mol) was refluxed at 140 °C for 4 h. The reaction mixture was poured into ice cold water and acidified by 6 N HCl. After standing at room temperature for 2 d, 7.5 g of pure oxo-indole crystals was obtained. Yield 60%; light yellow solid; mp 126—128 °C.

General Synthetic Procedure for the Preparation Compounds 8[18—23] A reaction mixture of oxoindole, **6** (1 eq), an appropriate benzaldehyde (1.2 eq), and piperidine (0.1 eq) in ethanol (1—2 ml/1 mmol) was stirred at 90 °C for 3—5 h. As soon as the reaction was completed, the mixture was cooled to ambient temperature and treated with $NaBH_4$ (2 eq). The mixture was then stirred for additional 1 h at 90 °C. The reaction mixture was cooled and the solvent removed under reduced pressure. Precipitate or oily compounds were purified by silica gel column chromatography to produce appropriate derivative.

Synthesis of Thioindole (9)[24,25] 0.06 mol of P_2S_5 and 0.06 mol of Na_2CO_3 were suspended in 20 ml of anhydrous THF at 0 °C and the mixture was stirred for 20 min. Oxoindole (0.05 mol) **1** was dissolved in 25 ml anhydrous THF and added drop wise to this mixture. This was stirred at 0 °C for 30 min, allowed to adapt to room temperature, and stirred overnight. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate (3×50 ml). The organic layer was washed with brine (3×20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude compound, which was purified by silica gel column chromatography. Yield 83%; yellow solid; mp 146—148 °C.

Synthesis of 3-Benzylideneindoline-2-thione (3a)[24] A reaction mixture of indole-2-thione (**9**, 1 eq), benzaldehyde (1.2 eq), and piperidine (0.1 eq) in ethanol (1—2 ml/1 mmol) was stirred at 90 °C for 3—5 h. After the reaction was completed, the mixture was cooled to ambient temperature then poured into water and extracted with methylene chloride. The resulting organic phase was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was then purified by column chromatography to give **3a**. Yield 71%, a yellow waxy solid.

(*E*)-3-(4-Methylbenzylidene)indoline-2-thione (3b) Using the same reaction condition for the preparation of **3a**, compound **3b** was obtained from the reaction of **9** with *p*-tolualdehyde (1.2 eq). Yield 67%; yellow waxy solid; IR (neat) 3258, 3174, 1686, 1583, 1503, 1487, 1444, 1437 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 2.43 (s, 3H, Ar-CH_3), 6.92 (d, J=8.4 Hz, 1H, Ar-H), 7.02 (t, J=8.0 Hz, 1H, Ar-H), 7.22—7.44 (m, 6H, –C=CH–, Ar-H), 7.89 (d, J=8.4 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H, Ar-H). HR-MS Calcd for $C_{16}H_{13}NS$ *m*/*z* 251.0769, Found 251.0771.

(*E*)-3-(4-Ethylbenzylidene)indoline-2-thione (3c) Using the same reaction condition for the preparation of **3a**, compound **3c** was obtained from the reaction of **9** with *p*-ethylbenzaldehyde (1.2 eq). Yield 68%; yellow waxy solid; IR (neat) 3376, 1684, 1584, 1505, 1488, 1465,1436, 1410 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.08 (t, J=5.2 Hz, 3H, CH_3), 2.46 (q, J=5.6 Hz, 2H, CH_2), 6.30 (d, J=8.4 Hz, 1H, Ar-H), 6.58 (t, J=7.6 Hz, 1H, Ar-H), 6.86 (m, 2H, Ar-H), 7.11—7.22 (m, 3H, –C=CH–, Ar-H), 7.84 (d, J=8.4 Hz, 1H, Ar-H), 8.30 (d, J=8.0 Hz, 1H, Ar-H), 8.59 (bs, 1H, NH). HR-MS Calcd for $C_{17}H_{15}NS$ *m*/*z* 265.0925, Found 265.0922.

(*E*)-3-(4-Chlorobenzylidene)indoline-2-thione (3d)[26] Using the same reaction condition for the preparation of **3a**, compound **3d** was obtained from the reaction of **9** with *p*-chlorobenzaldehyde (1.2 eq). Yield 63%; yellow solid; mp 133—135 °C.

(*E*)-3-(4-Methoxybenzylidene)indoline-2-thione (3e)[26] Using the same reaction condition for the preparation of **3a**, compound **3e** was obtained from the reaction of **9** with *p*-anisaldehyde (1.2 eq). Yield 69%; yellow solid; mp 169—171 °C.

(*E*)-3-(Naphthalen-1-ylmethylene)indoline-2-thione (3f) Using the same reaction condition for the preparation of **3a**, compound **3f** was obtained from the reaction of **9** with 1-naphthaldehyde (1.2 eq). Yield 62%; yellow waxy solid; IR (neat) 3256, 1682, 1593, 1538, 1497, 1434 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 6.69 (d, J=7.6 Hz, 1H, Ar-H), 7.11—7.23 (m, 4H, –C=CH–, Ar-H), 7.36—7.51 (m, 4H, Ar-H), 7.58 (d, J=8.0 Hz, 1H, Ar-H), 7.74 (d, J=7.6 Hz, 1H, Ar-H), 7.86—7.89 (m, 1H, Ar-H), 8.29 (d, J=8.4 Hz, 1H, Ar-H). HR-MS Calcd for $C_{19}H_{13}NS$ *m*/*z* 287.0769, Found 287.0773.

(*E*)-3-(Cyclohexylmethylene)indoline-2-thione (3g) Using the same reaction condition for the preparation of **3a**, compound **3f** was obtained from the reaction of **9** with cyclohexylcarboxaldehyde (1.2 eq). Yield 68%; light yellow solid; mp 123—125 °C; IR (neat) 3397, 1680, 1590, 1557, 1503, 1454 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.82—1.92 (m, 10H, C_6H_{10}), 2.21 (m, 1H, C_6H_{11}), 6.99 (d, J=8.4 Hz, 1H, –CH=CH–), 7.08 (t, J=7.8 Hz, 1H, Ar-H), 7.34 (t, J=8.4 Hz, 1H, Ar-H), 7.67 (d, J=8.0 Hz, 1H, Ar-H), 8.22 (d, J=8.4 Hz, 1H, Ar-H), 8.28 (br s, 1H, NH). HR-MS Calcd for $C_{15}H_{17}NS$ *m*/*z* 243.1082, Found 243.1079.

Synthesis of 3-Benzyl-1*H*-indole-2-thiol (4a)[24] Method A (Known Procedure): To the ethanolic solution of **3** (0.5 g, 1 mmol) added $NaBH_4$ (2 eq) portion wise over 10 min at room temperature. Then the reaction mixture was allowed to reflux for 2 h with stirring. Solvent was evaporated from the mixture and poured into water than extracted with methyelene chloride (50 ml). This resulting organic phase was evaporated under reduced pressure and purified by column chromatography to yield **4a**.

Method B: Compound **4a** was also obtained from the intermediate **8a** (1 eq) by the reflux with Lawesson's reagent (1.2 eq) in toluene (30 ml) for overnight. After evaporation under reduced pressure, the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with brine and dried over Na_2SO_4. The resulting organic phase was evaporated under reduced pressure and the crude product was purified by column chromatography to yield **4a**. The product from Method B has the

same characteristics as one obtained from Method A.

Yield 68%; light yellow solid; mp 145—147 °C; IR (neat) 3356, 2560, 1622, 1555, 1494, 1465, 1434 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.91 (s, 2H, CH_2), 6.88—6.99 (m, 2H, Ar-H), 7.22—7.42 (m, 5H, Ar-H), 7.64 (d, J=8.0 Hz, 1H, Ar-H), 8.08 (d, J=8.4 Hz, 1H, Ar-H), 8.08 (br s, 1H, NH). HR-MS Calcd for $C_{15}H_{13}NS$ m/z 239.0769, Found 239.0766.

The above two methods are applied for the preparation of compounds **4b**—**g** from the appropriate compounds **3** or **8**.

3-(4-Methylbenzyl)-1*H*-indole-2-thiol (4b) Yield 59%; yellow semisolid; IR (neat) 3354, 2562, 1624, 1556, 1504, 1488, 1466 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 2.37 (s, 3H, Ar-CH_3), 3.98 (s, 2H, CH_2), 6.99—7.12 (m, 2H, Ar-H), 7.23—7.57 (m, 4H, Ar-H), 7.69 (d, J=8.0 Hz, 1H, Ar-H), 8.10 (d, J=8.4 Hz, 1H, Ar-H), 8. Twelve (br s, 1H, NH). HR-MS Calcd for $C_{16}H_{15}NS$ m/z 253.0925, Found 253.0927.

3-(4-Ethylbenzyl)-1*H*-indole-2-thiol (4c) Yield 64%; yellow semisolid; IR (neat) 3354, 2564, 1622, 1538, 1498, 1440 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.01 (t, J=5.6 Hz, 3H, CH_3), 2.42 (q, J=5.6 Hz, 2H, Ar-CH_2), 3.97 (s, 2H, CH_2), 6.98—7.13 (m, 2H, Ar-H), 7.26—7.53 (m, 4H, Ar-H), 7.71 (d, J=8.4 Hz, 1H, Ar-H), 8.11 (d, J=8.4 Hz, 1H, Ar-H), 8.11 (br s, 1H, NH). HR-MS Calcd for $C_{17}H_{17}NS$ m/z 267.1082, Found 267.1085.

3-(4-Chlorobenzyl)-1*H*-indole-2-thiol (4d) Yield 59%; yellow solid; mp 119—121 °C; IR (neat) 3353, 2562, 1620, 1505, 1488, 1465 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.99 (s, 2H, CH_2), 7.01—7.12 (m, 2H, Ar-H), 7.22 (d, J=8.0 Hz, 2H, Ar-H), 7.49 (d, J=8.0 Hz, 2H, Ar-H), 7.73 (d, J=8.4 Hz, 1H, Ar-H), 8.07 (d, J=8.4 Hz, 1H, Ar-H), 8.10 (br s, 1H, NH). HR-MS Calcd for $C_{15}H_{12}ClNS$ m/z 273.0379, Found 273.0375.

3-(4-Methoxybenzyl)-1*H*-indole-2-thiol (4e) Yield 49%; Yellow solid; mp 144—146 °C; IR (neat) 3350, 2563, 1622, 1547, 1537, 1456 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.72 (s, 3H, OCH_3), 3.92 (s, 2H, CH_2), 6.55 (d, J=8.0 Hz, 2H, Ar-H), 6.94 (d, J=8.4 Hz, 2H, Ar-H), 7.09 (t, J=8.0 Hz, 1H, Ar-H), 7.23 (t, J=8.0 Hz, 1H, Ar-H), 7.53 (d, J=8.4 Hz, 1H, Ar-H), 7.68 (d, J=8.4 Hz, 1H, Ar-H), 8.07 (br s, 1H, NH). HR-MS Calcd for $C_{16}H_{15}NOS$ m/z 269.0874, Found 269.0871.

3-(Naphthalen-1-ylmethyl)-1*H*-indole-2-thiol (4f) Yield 69%; yellow solid; mp 96—98 °C; IR (neat) 3354, 2563, 1623, 1538, 1497, 1348 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 4.55 (s, 2H, CH_2), 6.71 (d, J=8.0 Hz, 1H, Ar-H), 7.11—7.20 (t, J=8.0 Hz, 1H, Ar-H), 7.22—26 (t, J=8. 0 Hz, 1H, Ar-H), 7.36—7.48 (m, 4H, Ar-H), 7.64 (d, J=8.4 Hz, 1H, Ar-H), 7.66 (d, J=8.0 Hz, 1H, Ar-H), 7.78 (d, J=8.4 Hz, 1H, Ar-H), 8.02 (br s, 1H, NH), 8.11 (d, J=8.4 Hz, Ar-H). HR-MS Calcd for $C_{19}H_{15}NS$ m/z 289.0925, Found 289.0922.

3-(Cyclohexylmethyl)-1*H*-indole-2-thiol (4g) Yield 55%; yellow viscous solid; IR (neat) 3354, 2560, 1622, 1537, 1496, 1505, 1442 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.93—1.82 (m, 11H, C_6H_{11}), 2.58 (d, J=4.6 Hz, 2H, CH_2), 6.98 (t, J=7.6 Hz, 1H, Ar-H), 7.19 (d, J=8.0 Hz, 1H, Ar-H), 7.55 (d, J=8.4 Hz, 1H, Ar-H), 8.01 (d, J=8.4 Hz, 1H, Ar-H), 8.18 (br s, 1H, NH). HR-MS Calcd for $C_{15}H_{19}NS$ m/z 245.1238, Found 245.1236.

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