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Design and synthesis of subtype-selective cyclooxygenase (COX) inhibitors derived from thalidomide

Hiroko Sano, Tomomi Noguchi, Aya Tanatani, Yuichi Hashimoto and Hiroyuki Miyachi*

Institute of Molecular and Cellular Biosciences, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

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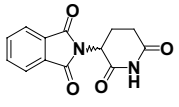
Abstract—A series of substituted indoline and indole derivatives with cyclooxygenase (COX)-inhibitory activity was prepared during our structural development studies based on thalidomide as a multi-template lead compound. Structure–activity relationship studies indicated that the nature of the substituent introduced at the benzene ring of the indoline (indole) backbone, and the length and type of the linking group between the nitrogen atom of indoline (indole) and the *N*-substituent are important for the activity. This study has led to the identification of COX-1-selective inhibitors, and these should be useful not only as pharmacological tools to investigate the physiology and pathophysiology of COX, but also as sophisticated leads for the development of novel drugs to treat COX-associated diseases, such as inflammatory diseases, and cancer.

1. Introduction

Thalidomide (**I**) (Fig. 1) is a sedative and/or hypnotic drug, which was used from the late 1950's to the early 1960's, but was withdrawn from the market because it was found to cause severe birth defects.[1–3] In spite of this tragedy, research on thalidomide was not halted, because of the drug's effectiveness against various diseases, including leprosy and AIDS.[2–4] Finally, the United States Food and Drug Administration (FDA) gave marketing approval to thalidomide for the treatment of Hansen's disease in 1998, with special precautions for usage. Several clinical studies of thalidomide for the treatment of multiple myeloma, colon cancer, prostate cancer, and other conditions are on-going in the US.



(I)

Figure 1. Structure of thalidomide.

In order to explain the pleiotropic effects elicited by thalidomide, we have postulated that thalidomide is a multi-target drug, and we have been engaged in structural development studies using thalidomide as a scaffold.[2,3,5–17] This systematic search has yielded many kinds of drug leads, such as tumor necrosis factor (TNF)-α production regulators (inhibitors and/or enhancers),[2,3,5–7] androgen receptor antagonists,[2,3,8,9] peptidase inhibitors,[3,10–13] glucosidase inhibitors,[15,16] and thymidine phosphorylase inhibitors.[16] As described above, thalidomide is effective for the treatment of certain kinds of cancers, such as colon and prostate cancers, probably because of its TNF-α production-inhibiting activity and antiangiogenic activity.[17,18] We suspected that cyclooxygenase (COX) might be another anticancer-related molecular target of thalidomide.

Prostaglandin and thromboxane biosynthesis involves the conversion of arachidonic acid to prostaglandin H_2 (PGH_2), a reaction catalyzed by the sequential actions of COX and prostaglandin endoperoxidase synthase (PGHS).[19] Three isozymes of COX (COX-1, COX-2, and COX-3) are known to date, of which COX-1, and COX-2 have been well defined. COX-1 is reported to be constitutively expressed in many organs or tissues, while COX-2 is inducible with various stimuli. However, recent molecular biological studies have indicated that this simple paradigm has many exceptions. For example, COX-1 can be regulated during development,[20] while

Keywords: COX-1; COX-1 selectivity; Indoline derivatives; Indole derivatives.
* Corresponding author. Tel.: +81 035 841 7848; fax: +81 035 841 8495; e-mail: miyachi@iam.u-tokyo.ac.jp

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COX-2 is constitutively expressed in the brain,[21] and in reproductive tissues.[22] Often, both isozymes are involved in physiological and pathophysiological conditions, while in some cases, each isozyme plays a distinct role.

Overexpression of COX-2 has been detected in various tumors and its role in carcinogenesis and angiogenesis has been well documented.[23–25] Therefore, COX-2 is thought to be a promising therapeutic target for cancer.[23–25] Attempts have been made to apply COX-2 inhibitors, such as celecoxib, rofecoxib, and sulindac, for chemoprevention of various cancers, including colon and prostate cancers.[26,27] But, very recently, clinical studies of a COX-2-selective inhibitor, rofecoxib (Bioxx), for preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas were discontinued and rofecoxib (Bioxx) was withdrawn from the market owing to an increased incidence of cardiovascular events, such as heart attack and stroke, in the treatment group compared to the placebo group.[28] Therefore, attention is now focused on the clinical effectiveness of selective COX inhibitors that are structurally different from diaryl heterocyclic type derivatives (such as rofecoxib) for the treatment of various cancers (Fig. 2).

Recently, experimental results have indicated a possible involvement of COX-1 in pain and cancer development, thus providing the rationale for the development of selective COX-1 inhibitors.[29–31] In fact, animal studies have demonstrated that COX-1 plays a role in intestinal polyposis and skin carcinogenesis, consistent with epidemiological data demonstrating that regular use of low-dose aspirin, which inhibits only platelet COX-1 activity, can reduce colon cancer incidence and mortality.[32–34] In addition, it has been suggested that COX-1 may play an important role in pain processing and sensitization in spinal cord and gracile nucleus after surgery.[35] Therefore, COX-1 is also thought to be a therapeutic target.

Thalidomide suppresses lipopolysaccharide-induced expression of COX-2.[36] In addition, we have recently demonstrated that thalidomide directly inhibits COX-1/

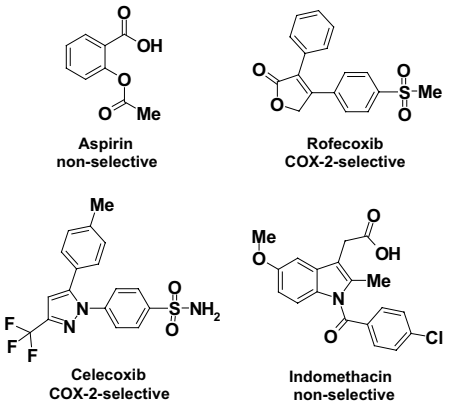


Figure 2. Structure of representative COX inhibitors.

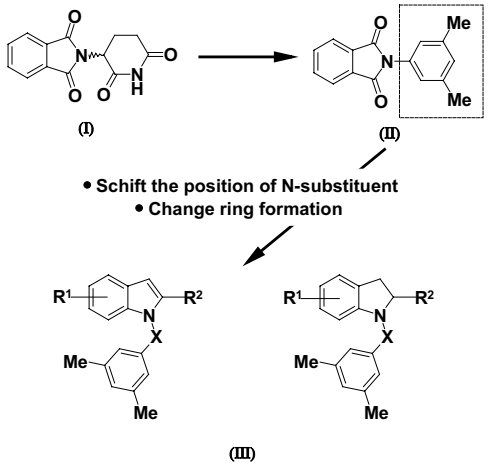


Figure 3. Structure development strategy.

COX-2 with efficacy comparable to that of the representative drug, aspirin.[37] Our earlier work on the COX-inhibiting activity of thalidomide afforded a new scaffold for small-molecular COX inhibitors, such as compound (**II**), which should offer opportunities for various kinds of structural development (Fig. 3).[38]

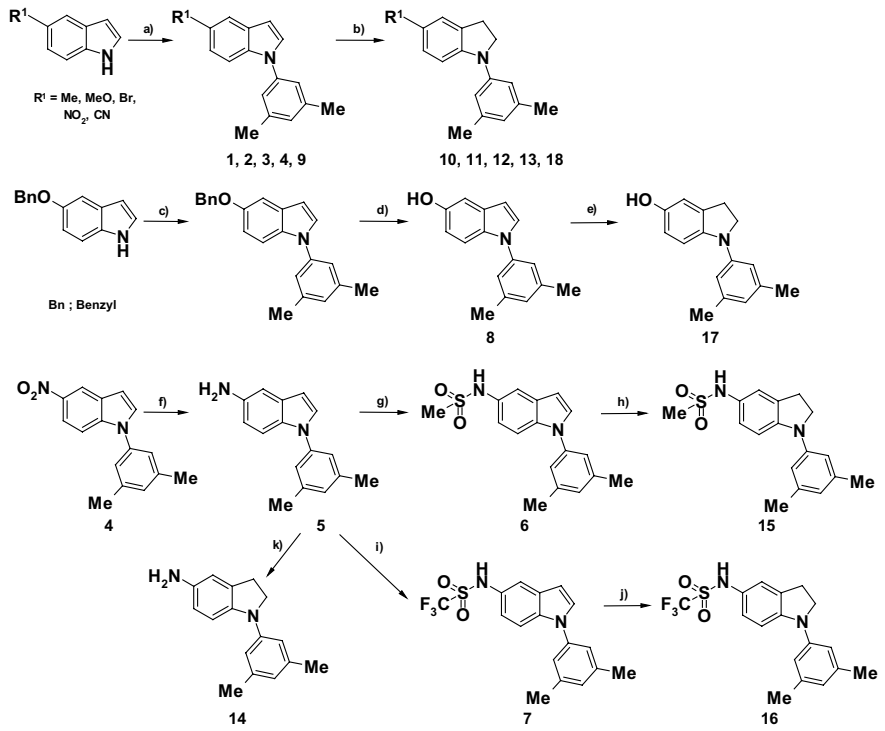
As a part of our continuing research directed toward the structural development of thalidomide as a multitemplate for lead discovery, we report here novel COX inhibitors derived from thalidomide, focusing on COX-1- and COX-2-inhibitory activities.

2. Chemistry

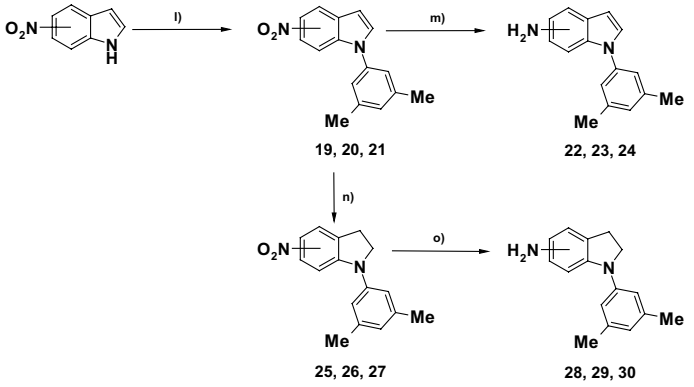
Synthetic routes to the present series of compounds, *N*-substituted indolines and *N*-substituted indoles, are outlined in Schemes 1–5.

The *N*-aryl-substituted indoles (**1**–**4**, **9**) were prepared by the copper-mediated coupling of substituted indoles with 3,5-dimethylphenylboronic acid.[39] The *N*-aryl-substituted indolines (**10**–**13**, **18**) were prepared by $NaBH_3CN$ reduction of the corresponding indole derivatives. 5-Benzyloxyindole was coupled with 3,5-dimethylphenylboronic acid, and subsequent debenzylation afforded compound (**8**). Compound **8** was treated with $NaBH_3CN$ to afford indoline derivative (**17**). 1-(3,5-Dimethylphenyl)-5-nitroindole (**4**) was reduced to give 5-amino derivative (**5**). Compound **5** was treated with either methanesulfonyl chloride or trifluoromethanesulfonic anhydride in the presence of triethylamine as a base to afford sulfonamide derivatives **6** or **7**, respectively. Compound **5** was treated with $NaBH_3CN$ to afford indoline derivative (**14**). Compounds **6** and **7** were treated with $NaBH_3CN$ also to afford indoline derivatives (**15**, **16**), respectively (Scheme 1).

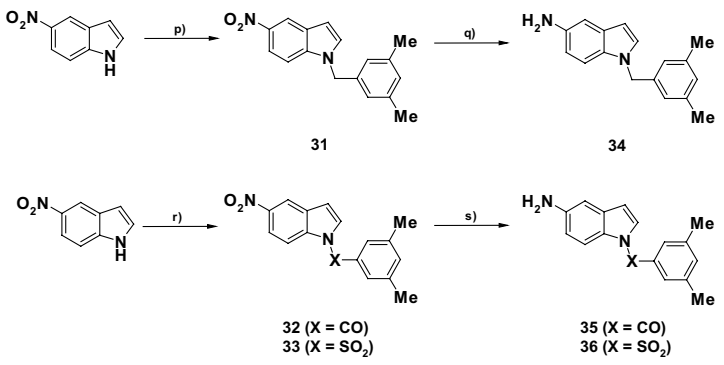
Nitro-substituted-indoles were coupled with 3,5-dimethylphenylboronic acid to afford compounds **19**, **20**, **21**, and subsequent reduction gave amino-substituted-indoles **22**, **23**, and **24**, respectively. On the other hand, **19**, **20**, **21** were treated with $NaBH_3CN$ to give **25**, **26**,



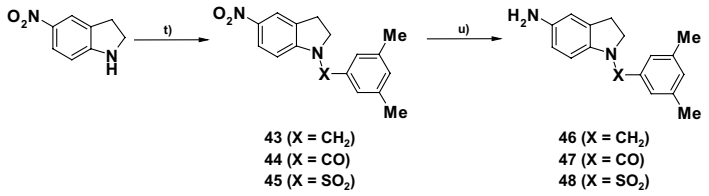
Scheme 1. Reagents and conditions: (a) 3,5-dimethylphenylboronic acid, $Cu(OAc)_2$, triethylamine, CH_2Cl_2; (b) $NaBH_3CN$, trifluoroacetic acid; (c) same as in (a); (d) H_2, 10% Pd–C, AcOEt; (e) same as in (b); (f) same as in (d); (g) methanesulfonyl chloride, triethylamine, CH_2Cl_2; (h) same as in (b); (i) trifluoromethane sulfonic anhydride, triethylamine, CH_2Cl_2; (j) same as in (b); (k) same as in (b).



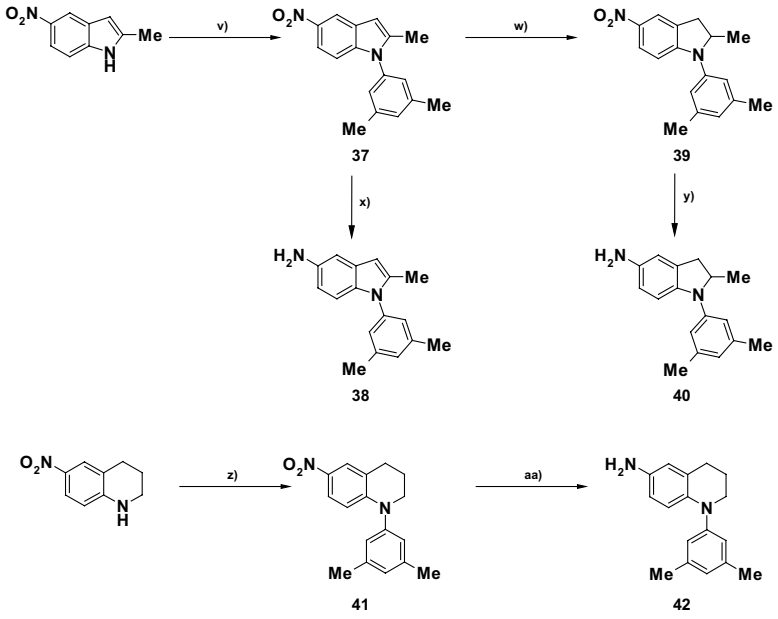
Scheme 2. Reagents and conditions: (l) 3,5-dimethylphenylboronic acid, $Cu(OAc)_2$, triethylamine, CH_2Cl_2; (m) H_2, 10% Pd–C, AcOEt; (n) $NaBH_3CN$, trifluoroacetic acid; (o) same as in (m).



Scheme 3. Reagents and conditions: (p) 3,5-dimethylbenzyl bromide, potassium carbonate, *N*,*N*-dimethyformamide; (q) H_2, 10% Pd–C, AcOEt; (r) (1) NaH, *N*,*N*-dimethylformamide; (2) 3,5-dimethylbenzoyl chloride (or 3,5-dimethy-benzenesulfonyl chloride), *N*,*N*-dimethylformamide; (s) same as in (q).



Scheme 4. Reagents and conditions: (t) (1) NaH, *N*,*N*-dimethylformamide; (2) 3,5-dimethylbenzyl bromide (or 3,5-dimethylbenzoyl chloride or 3,5-dimethylbenzenesulfonyl chloride), *N*,*N*-dimethylformamide; (u) 10% Pd–C, AcOEt.



Scheme 5. Reagents and conditions: (v) 3,5-dimethylphenylboronic acid, $Cu(OAc)_2$, triethylamine, CH_2Cl_2; (w) $NaBH_3CN$, trifluoroacetic acid; (x) H_2, 10% Pd–C, AcOEt; (y) same as in (x); (z) same as in (v); (aa) same as in (x).

27, and subsequent reduction gave amino-substituted-indolines **28**, **29**, and **30**, respectively (Scheme 2).

Compound **34** was prepared by the benzylation of 5-nitroindole to give **31**, and subsequent reduction. Compounds **35**, and **36** were prepared by the benzoylation (or sulfonylation) of 5-nitroindole to give **32**, **33**, and subsequent reduction respectively (Scheme 3).

5-Nitroindoline was treated with NaH, followed by the reaction with 3,5-dimethylbenzyl bromide (or 3,5-dimethylbenzoyl chloride or 3,5-dimethylbenzenesulfonyl chloride) to afford compounds **43**, **44**, and **45** respectively. These compounds were reduced to give amino derivatives **46**, **47**, and **48**, respectively (Scheme 4).

2-Methylindole derivatives and 2-methylindoline derivatives (**37**, **38**, **39**, **40**) were prepared using the same procedures as described for the preparation of the corresponding 2-unsubstituted indole derivatives and 2-unsubstituted indoline derivatives, respectively. 1,2,3,4-Tetrahydroquinoline derivatives (**41**, **42**) were prepared by the coupling of 6-nitro-1,2,3,4-tetrahydroquinoline with 3,5-dimethylphenylboronic acid (**41**), and subsequent reduction of the nitro group (**42**) (Scheme 5).

3. Biology

In vitro COX-inhibitory activity of the present series of compounds was measured with a colorimetric COX (ovine) inhibitor screening assay kit purchased from Cayman Chemical (Ann Arbor, MI, Catalog No. 760111) according to the supplier's protocol. The assay was performed in triplicate, and repeated at least two times.

4. Results and discussion

We have previously demonstrated that thalidomide directly inhibits COX-1/COX-2 with efficacy comparable to that of aspirin, a representative antiinflammatory drug that is used worldwide.[37] We also have found that the 3,5-dimethylphenyl group is a favorable substituent for potent COX-inhibiting activity from our earlier work on the COX-inhibiting activity of thalidomide analogues, *N*-substituted phenylphthalimides, as a new scaffold for small-molecular COX inhibitors.[38]

As a part of our continuing structural development studies of thalidomide, we are interested in the use of an indoline and/or an indole structure, instead of

phthalimide, with the 3,5-dimethylphenyl group as a nitrogen substituent, because our previous work indicated that the reduction of the phthalimide ring to a 2,3-dihydro-1*H*-isoindole ring enhanced COX-inhibiting activity.[38] We imagined that the alignment of the two phenyl rings of the *N*-substituted phenylindoline and/or *N*-substituted phenylindole skeleton might lead to a structure with some similarities to those of clinically used diaryl heterocyclic COX inhibitors, such as celecoxib.[40] Therefore, we initially prepared *N*-(3,5-dimethylphenyl)indoline, *N*-(3,5-dimethylphenyl)indole, *N*-(3,5-dimethylphenyl)isatine, and 3,3-difluoro-*N*-(3,5-dimethylphenyl)oxyindole, and found that among them, only *N*-(3,5-dimethylphenyl)indoline, showed weak but significant COX-inhibiting activity at the concentration of 30 μM. Although the activity was weak, we were encouraged by this result to synthesize further derivatives of *N*-(3,5-dimethylphenyl)indoline and its precursor *N*-(3,5-dimethylphenyl)indole, and to evaluate their COX-inhibiting activity (Tables 1–5).

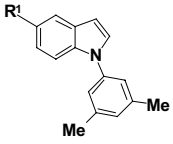
Substituent effects at the 5 position of the indoline and/or the indole benzene ring are summarized in Table 1. Roughly speaking, in the case of the indole series, strongly electron-donating groups, such as an amino group (**5**) and a hydroxyl group (**8**), provided potent (**5**) or moderate (**8**) COX-1-inhibiting activity at the concentration of 30 μM. Both compounds showed moderate COX-2-inhibiting activity at the concentration of 30 μM. In the indoline series, the same tendency was seen, with some exceptions (compounds **13** and **17**).

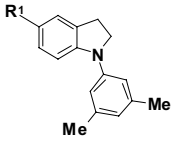
Therefore, we focused our attention on the amino group and its precursor nitro group as substituents.

Table 2 summarizes the effect of the position of the amino group (and the nitro group) at the benzene ring of indoline and/or indole derivatives. In a series of nitroindoles and nitroindolines, only 4-nitro derivatives showed moderate COX-1-inhibiting activity and other nitro derivatives showed weak and/or no activity at the concentration of 30 μM on both isozymes. On the other hand, in a series of aminoindolines and aminoindoles, most of the compounds showed moderate and/or potent COX-1-inhibiting activity, with some exceptions (**28**, **30**), and the 5-amino group (**5**, **14**) gave the most potent compounds in both series. However, amino compounds also showed little or no COX-2-inhibiting activity at the concentration of 30 μM, except **5** and **14**. 5-Amino group might be an important substituent in the present series of COX inhibitors to exhibit the activity, but the exact reason is unknown.

The nonselective COX inhibitor indomethacin has an *N*-benzoylindole structure, so we then focused our attention on the linking group between indoline (and indole) and the 3,5-dimethylphenyl group, and synthesized *N*-benzyl (**31, 34, 43, 46**), *N*-benzoyl (**32, 35, 44, 47**), and *N*-benzenesulfonyl (**33, 36, 45, 48**) derivatives. Their COX-inhibiting activities are summarized in Tables 3 and 4. All 5-nitroindole derivatives showed very weak or no activity at the concentration of 30 μM. In a series of 5-aminoindole derivatives, however, all the compounds exhibited potent COX-1-inhibiting activity and weak COX-2-inhibiting activity at the concentration of 30 μM. These results indicated that the length and kind of the linking group do not contribute to the activity in the case of the indole skeleton. Among 5-nitroindoline derivatives, only the benzoyl derivative (**44**) showed moderate nonselective COX-1/COX-2-inhibiting activity at the concentration of 30 μM, and other derivatives did not show any inhibitory activity at this concentration. On the other hand, in the case of 5-aminoindoline derivatives, the benzyl derivative (**46**) showed a unique profile: it exhibited potent nonselective COX-1/COX-2-inhibiting activity at the concentration of 30 μM,

Table 1. COX-inhibitory activity of compounds (**1**–**18**)

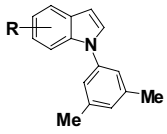


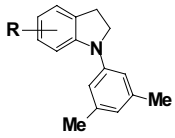


Compound	R^1	Inhibition[a] (%)		Compound	R^1	Inhibition[a] (%)	
		COX-1	COX-2			COX-1	COX-2
1	Me	IA[b]	IA[b]	**10**	Me	IA[b]	IA[b]
2	OMe	IA[b]	IA[b]	**11**	OMe	IA[b]	IA[b]
3	Br	IA[b]	IA[b]	**12**	Br	IA[b]	IA[b]
4	NO_2	IA[b]	IA[b]	**13**	NO_2	31.4	IA[b]
5	NH_2	99.3	40.5	**14**	NH_2	89.2	44.9
6	$NHSO_2Me$	IA[b]	IA[b]	**15**	$NHSO_2Me$	23.7	10.6
7	$NHSO_2CF_3$	IA[b]	IA[b]	**16**	$NHS0_2CF_3$	IA[b]	IA[b]
8	OH	48.9	30.6	**17**	OH	25.2	29.6
9	CN	IA[b]	IA[b]	**18**	CN	IA[b]	IA[b]
Aspirin		10.2	9.90				

[a] Compounds were screened for inhibitory activity on COX at the concentration of 30 μM.
[b] IA: inactive at the concentration of 30 μM.

Table 2. COX-inhibitory activity of compounds (**19**–**30**)

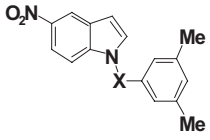


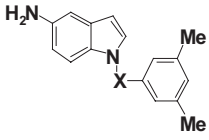


Compound	R^1	Inhibition[a] (%)		Compound	R^1	Inhibition[a] (%)	
		COX-1	COX-2			COX-1	COX-2
19	4-NO_2	33.8	15	**25**	4-NO_2	40.4	19.1
4	5-NO_2	IA[b]	IA[b]	**13**	5-N0$_2$	31.0	IA
20	6-NO_2	14.8	3.1	**26**	6-NO_2	16.0	IA[b]
21	7-NO_2	IA[b]	IA[b]	**27**	7-NO_2	IA[b]	IA[b]
22	4-NH_2	53.2	7.7	**28**	4-NH_2	IA[b]	IA[b]
5	5-NH_2	99.3	40.5	**14**	5-NH_2	89.2	44.9
23	6-NH_2	52.3	19.1	**29**	6-NH_2	36.2	6.60
24	7-NH_2	45.6	6.5	**30**	7-NH_2	IA[b]	IA[b]

[a] Compounds were screened for inhibitory activity on COX at the concentration of 30 μM.
[b] IA: inactive at the concentration of 30 μM.

Table 3. COX-inhibitory activity of compounds (**31**–**36**)

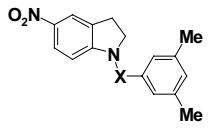


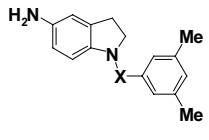


Compound	X	Inhibition[a] (%)		Compound	X	Inhibition[a]	
		COX-1	COX-2			COX-1	COX-2
4	—	IA[b]	IA[b]	**5**	—	99.3	40.5
31	CH_2	IA[b]	IA[b]	**34**	CH_2	83.0	22.5
32	CO	14.2	6.33	**35**	CO	88.1	13.8
33	SO_2	IA[b]	IA[b]	**36**	SO_2	77.8	34.1

[a] Compounds were screened for inhibitory activity on COX at the concentration of 30 μM.
[b] IA: inactive at the concentration of 30 μM.

Table 4. COX-inhibitory activity of compounds (**43**–**48**)



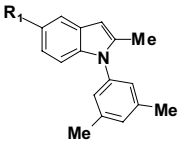


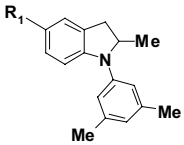
Compound	X	Inhibition[a] (%)		Compound	X	Inhibition[a] (%)	
		COX-1	COX-2			COX-1	COX-2
13	—	31.4	IA[b]	**14**	—	89.2	44.9
43	CH_2	IA[b]	8.88	**46**	CH_2	81.8	96.4
44	CO	68.6	53.5	**47**	CO	47.3	4.48
45	SO_2	IA[b]	8.40	**48**	SO_2	72.0	12.3

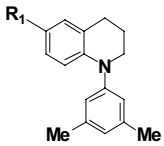
[a] Compounds were screened for inhibitory activity on COX at the concentration of 30 μM.
[b] IA: inactive at the concentration of 30 μM.

whereas other derivatives showed COX-1-selective inhibition at the concentration of 30 μM, like the 5-aminoindole derivatives. These results indicated that the length and/or the electronic character of the linking group greatly influence the activity and the selectivity in the case of the indoline skeleton. The dose–response

Table 5. COX-inhibitory activity of compounds (**37**–**42**)







Compound	R_1	Inhibition[a] (%)		Compound	R_1	Inhibition[a] (%)		Compound	R_1	Inhibition[a] (%)	
		COX-1	COX-2			COX-1	COX-2			COX-1	COX-2
37	NO_2	IA[b]	6.83	**39**[c]	NO_2	IA[b]	7.64	**41**[c]	NO_2	IA[b]	2.66
38	NH_2	87.3	14.7	**40**[c]	NH_2	96.5	78.9	**42**[c]	NH_2	3.35	20.1

[a] Compounds were screened for inhibitory activity on COX at the concentration of 30 μM.
[b] IA: inactive at the concentration of 30 μM.
[c] Assayed as a racemate.

relationships of representative compounds, with that of Aspirin are shown in Figure 4.

The binding pocket of COX-2 is reported to be larger than that of COX-1,[41] so we prepared ring-expanded (1,2,3,4-tetrahydroquinoline) and side-chain-introduced (2-methylindoline) derivatives, anticipating a change of isozyme selectivity. In the case of indole derivatives as mentioned in Table 5, the introduction of a methyl group at the 2-position of the indole ring did not affect the activity or the isozyme selectivity, that is, compound **38** exhibited comparably potent COX-1-inhibiting activity and weak COX-2-inhibiting activity at the concentration of 30 μM.

On the other hand, introduction of a methyl group at the 2-position of the indoline ring enhanced both COX-1- and COX-2-inhibiting activity, especially the latter, that is, compound **40** showed equipotent COX-1- and COX-2-inhibiting activity (non-isozyme-selective COX inhibition). Ring expansion of indoline to 1,2,3,4-tetrahydroquinoline (**42**) decreased the COX-inhibiting activity, but this compound showed weak COX-2 selectivity at the concentration of 30 μM.

Previously, we have reported that the electronic nature of a substituent introduced at the phthalimide moiety of methylthalidomide, the isoindolone moiety of *N*-substituted phenylisoindolone, and the isoindoline moiety of *N*-substituted phenylisoindoline dramatically influences the COX-1/2-inhibiting activity.[38] In the present series of indoline and/or indole derivatives, similar behavior was seen with substituents introduced at the benzene ring of the indoline and/or indole skeleton.

These results might indicate that these compounds are aligned in similar positions and recognize the same amino acid(s) of the binding pocket of both COX-1 and COX-2. The introduction of a methyl group at the 2-position of the indoline and the indole skeletons, and the ring expansion of the indoline skeleton to 1,2,3,4-tetrahydroquinoline, both affect the inhibitory potency and the isozyme-selectivity preferentially in favor of COX-2, but the degree was low. These results might

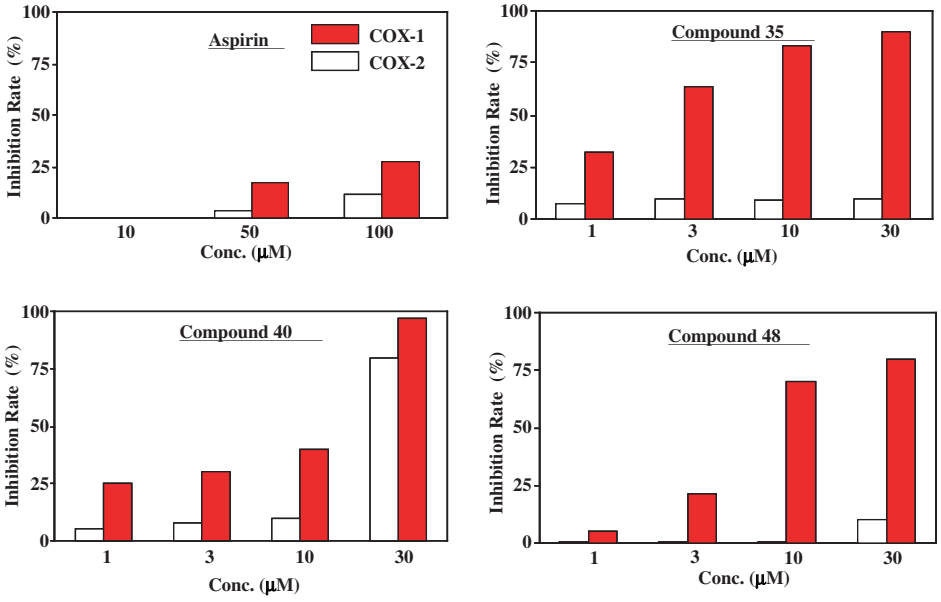


Figure 4. Dose–response relationship of the representative compounds.

indicate that these structural features were at least partly recognized by the additional side pocket of COX-2.[41] Further studies will be needed to ascertain whether this is the case.

In conclusion, we have succeeded in the creation of structurally simple and novel indoline and/or indole COX inhibitors. Some of the compounds show potent COX inhibiting activity preferentially to COX-1 subtype. The previous reports and the results presented in this paper should be useful for the development of superior COX inhibitors with COX subtype selectivity.

5. Experimental

5.1. General

Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Tokyo, and were within plus or minus 0.3% of the theoretical values. NMR spectra were recorded on a JEOL JNM-GX500 (500 MHz) spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. Mass spectra were recorded on a JEOL JMS-DX303 spectrometer.

5.2. General method for the preparation of 1-(3,5-dimethylphenyl)-1*H*-indole derivatives (1–4, 9)

A mixture of substituted-1*H*-indole, 1–2 equiv of 3,5-dimethylphenylboronic acid, 2 equiv of $Cu(OAc)_2$, 2 equiv of triethylamine, and powdered molecular sieves 3 Å was suspended in CH_2Cl_2 and the whole was stirred for 1–3 days. The reaction mixture was concentrated and the product was purified by silica gel column chromatography (*n*-hexane–ethyl acetate = 10:1–2:1 as the eluant).

5.2.1. 1-(3,5-Dimethylphenyl)-5-methyl-1*H*-indole (1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (m, 2H), 7.29 (d, J = 3.0 Hz, 1H), 7.12 (s, 2H), 7.04 (d, J = 8.6 Hz, 1H), 6.99 (s, 1H), 6.57 (d, J = 3.0 Hz, 1H), 2.47 (s, 3H), 2.40 (s, 6H). HRMS Calcd for $C_{17}H_{18}N$: 236.1439. Found: 236.1401.

5.2.2. 1-(3,5-Dimethylphenyl)-5-methoxy-1*H*-indole (2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 3.0 Hz, 1H), 7.13 (d, J = 2.6 Hz, 1H), 7.11 (s, 2H), 6.98 (s, 1H), 6.87 (dd, J = 9.0, 2.6 Hz, 1H), 6.57 (d, J = 3.0 Hz, 1H), 3.88 (s, 3H), 2.40 (s, 6H). HRMS Calcd for $C_{17}H_{18}NO$: 252.1388. Found: 252.1364.

5.2.3. 5-Bromo-1-(3,5-dimethylphenyl)-1*H*-indole (3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 3.0 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 3.0 Hz, 1H), 7.28 (dd, J = 8.6, 3.0 Hz, 1H), 7.08 (s, 2H), 7.02 (s, 1H), 6.59 (d, J = 3.0 Hz, 1H), 2.40 (s, 6H). HRMS Calcd for $C_{16}H_{14}BrN$: 300.0388. Found: 300.0418.

5.2.4. 1-(3,5-Dimethylphenyl)-5-nitro-1*H*-indole (4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (d, J = 3.0 Hz, 1H), 8.10 (dd, J = 9.4, 3.0 Hz, 1H), 7.52 (d, J = 9.4 Hz, 1H), 7.45 (d, J = 3.0 Hz, 1H), 7.09 (s, 2H), 7.08 (s, 1H), 6.82 (d, J=3.0 Hz, 1H), 2.42 (s, 6H); MS(FAB) m/z 267 $(M+H)^+$; mp 120–123 °C. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.89; H, 5.43; N, 10.49.

5.2.5. 5-Cyano-1-(3,5-dimethylphenyl)-1*H*-indole (9). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.43 (m, 2H), 7.07 (s, 2H), 7.06 (s, 1H), 6.72 (d, J = 3.4 Hz, 1H), 2.41 (s, 6H). HRMS Calcd for $C_{17}H_{15}N_2$: 247.1235. Found: 247.1235.

5.3. General method for the preparation of 1-(3,5-dimethylphenyl)-2,3-dihydro-1*H*-indole derivatives (10–13, 18)

To a mixture of indole derivative and trifluoroacetic acid was added 10–20 equiv of sodium cyanoborohydride portionwise at 0 °C under Ar. After the addition was complete, the reaction mixture was stirred at room temperature for 40–60 h. The whole was poured into dil. alkali solution, and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography (*n*-hexane–ethyl acetate = 10:1–2:1 as the eluant) to give the desired compound.

5.3.1. 2,3-Dihydro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-indole (10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (s, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.86 (s, 2H), 6.72 (m, 1H), 6.63 (s, 1H), 3.92 (t, J = 8.6 Hz, 2H), 3.08 (t, J = 8.6 Hz, 2H), 2.40 (s, 3H), 2.32 (s, 6H). HRMS Calcd for $C_{17}H_{18}N$: 237.1517. Found: 237.1530.

5.3.2. 2,3-Dihydro-1-(3,5-dimethylphenyl)-5-methoxy-1*H*-indole (11). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 3.0 Hz, 1H), 7.15 (d, J = 3.0 Hz, 1H), 7.11 (s, 2H), 6.98 (s, 1H), 3.91 (t, J = 8.6 Hz, 2H), 3.78 (s, 3H), 3.08 (t, J = 8.6 Hz, 2H), 2.32 (s, 6H). HRMS Calcd for $C_{17}H_{19}NO$: 253.1467. Found: 253.1512.

5.3.3. 5-Bromo-2,3-dihydro-1-(3,5-dimethylphenyl)-1*H*-indole (12). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (s, 1H), 7.12 (d, J = 9.0 Hz, 1H), 6.94 (d, J = 9.0Hz, 1H), 6.88 (s, 2H), 6.83 (s, 1H), 4.11 (t, J = 8.6 Hz, 2H), 3.19 (t, J = 8.6 Hz, 2H), 2.33 (s, 6H). HRMS Calcd for $C_{16}H_{16}BrN$: 302.0544. Found: 302.0556.

5.3.4. 2,3-Dihydro-1-(3,5-dimethylphenyl)-5-nitro-1*H*-indole (13). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (d, J = 2.1 Hz, 1H), 8.11 (dd, J = 9.0, 2.1 Hz, 1H), 7.51 (d, J = 9.0 Hz, 2H), 6.90 (s, 2H), 4.11 (t, J = 8.6 Hz, 2H), 3.19 (t, J = 8.6 Hz, 2H), 2.42 (s, 6H). HRMS Calcd for $C_{16}H_{16}N_2O_2$: 268.1212. Found: 268.1232.

5.3.5. 5-Cyano-2,3-dihydro-1-(3,5-dimethylphenyl)-1*H*-indole (18). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m,

2H), 6.95 (d, J = 8.1 Hz, 1H), 6.86 (s, 2H), 6.75 (s, 1H), 4.02 (t, J = 8.6 Hz, 2H), 3.14 (t, J = 8.6 Hz, 2H), 2.41 (s, 6H). HRMS Calcd for $C_{17}H_{16}N_2$: 248.1313. Found: 248.1316.

5.3.6. 5-Benzyloxy-1-(3,5-dimethylphenyl)-1*H*-indole. This compound was prepared from 5-benzyloxy-1*H*-indole, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (m, 4H), 7.40 (t, J = 9.0 Hz, 1H), 7.30 (d, J = 3.0 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 7.11 (s, 2H), 6.99 (s, 1H), 6.96 (dd, J = 9.0, 2.6 Hz, 1H), 6.71 (s, 1H), 6.57 (d, J = 3.0 Hz, 1H), 5.14 (s, 2H), 2.40 (s, 6H); MS(FAB) m/z 327 $(M+H)^+$.

5.3.7. 5-Hydroxy-1-(3,5-Dimethylphenyl)-1*H*-indole (8). This compound was prepared by the catalytic hydrogenation of 5-benzyloxy-1-(3,5-dimethylphenyl)-1*H*-indole with 10% Pd–C: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 3.0 Hz, 1H), 7.10 (s, 2H), 7.07 (t, J = 3.0 Hz, 1H), 6.98 (s, 1H), 6.78 (dd, J = 9.0, 3.0 Hz, 1H), 6.52 (d, J = 3.0 Hz, 1H), 4.60 (s, 1H), 2.40 (s, 6H). HRMS Calcd for $C_{16}H_{15}NO$: 237.1154. Found: 237.1127.

5.3.8. 2,3-Dihydro-5-hydroxy-1-(3,5-dimethylphenyl)-1*H*-indole (17). This compound was prepared from **8**, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-2,3-dihydro-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43–6.52 (m, 6H), 3.97 (t, J = 8.6 Hz, 2H), 3.11 (t, J = 8.6 Hz, 2H), 2.40 (s, 6H). HRMS Calcd for $C_{16}H_{17}NO$: 239.1310. Found: 239.1336.

5.3.9. 5-Amino-1-(3,5-dimethylphenyl)-1*H*-indole (5). A mixture of **4** (308 mg), 10% palladium on charcoal (30 mg) and ethyl acetate (20 mL) was hydrogenated at ambient temperature under hydrogen at atmospheric pressure for 3 h. After the reaction completed, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by silica gel column chromatography (*n*-hexane–ethyl acetate = 5:1 as the eluant) to give 224.1 mg (81.9%) of the desired compound: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 3.0 Hz, 1H), 7.10 (s, 2H), 6.97 (m, 2H), 6.68 (dd, J = 8.6, 3.0 Hz, 1H), 6.47 (d, J = 3.0 Hz, 1H), 2.39 (s, 6H). HRMS Calcd for $C_{16}H_{16}N_2$: 236.1313. Found: 236.1316.

5.3.10. 1-(3,5-Dimethylphenyl)-5-methanesulfonylamino-1*H*-indole (6). To a mixture of **5** (200 mg), 1 equiv of triethylamine and CH_2Cl_2 (2 mL) was added dropwise 1 equiv of methanesulfonyl chloride at 0 °C. After the addition was complete, the reaction mixture was stirred overnight at room temperature. The whole was poured into water, and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography (*n*-hexane–ethyl acetate = 2:1 as the eluant), and subsequent recrystalization to give 62.8 mg (23.5%) of the desired compound: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 2.1 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 3.0 Hz, 1H), 7.15 (dd, J = 8.6, 2.1 Hz, 1H), 7.08 (s, 2H), 7.04 (s, 1H), 6.70 (d, J = 3.0 Hz, 1H), 3.45 (s, 3H), 2.40 (s, 6H). HRMS Calcd for $C_{17}H_{17}N_2O_2S$: 313.1011. Found: 313.1012.

5.3.11. 1-(3,5-Dimethylphenyl)-5-trifluoromethanesulfonylamino-1*H*-indole (7). To a mixture of **5** (180 mg), 1 equiv of triethylamine and CH_2Cl_2 (1 mL) was added dropwise 1.1 equiv of trifluoromethanesulfonic anhydride at 0 °C. After the addition was complete, the reaction mixture was stirred overnight at room temperature. The whole was poured into water, and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography (*n*-hexane–ethyl acetate = 12:1 as the eluant) to give 86.7 mg (31.6%) of the desired compound: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 3.0 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.34 (d, J = 3.0 Hz, 1H), 7.16 (dd, J = 9.0, 3.0 Hz, 1H), 7.08 (s, 2H), 7.06 (s, 1H), 6.70 (d, J = 3.0 Hz, 1H), 2.41 (s, 6H). HRMS Calcd for $C_{17}H_{14}F_3N_2O_2S$: 367.0728. Found: 367.0724.

5.3.12. 2,3-Dihydro-1-(3,5-dimethylphenyl)-5-methanesulfonylamino-1*H*-indole (15). This compound was prepared from **6**, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-2,3-dihydro-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.14 (m, 1H), 7.08 (s, 2H), 7.01 (s, 1H), 4.00 (t, J = 8.6 Hz, 2H), 3.45 (s, 3H), 3.14 (t, J = 8.6 Hz, 2H), 2.40 (s, 6H). HRMS Calcd for $C_{17}H_{20}N_2O_2S$: 315.1167. Found: 315.1209.

5.3.13. 2,3-Dihydro-1-(3,5-dimethylphenyl)-5-trifluoromethanesulfonylamino-1*H*-indole (16). This compound was prepared from **7**, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-2,3-dihydro-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 9.0 Hz, 1H), 7.03 (m, 2H), 6.85 (s, 2H), 6.69 (s, 1H), 3.98 (t, J = 8.6 Hz, 2H), 3.12 (t, J = 8.6 Hz, 2H), 2.40 (s, 6H). HRMS Calcd for $C_{17}H_{17}F_3N_2O_2S$: 370.0963. Found: 370.1008.

5.3.14. 5-Amino-2,3-dihydro-1-(3,5-dimethylphenyl)-1*H*-indole (14). This compound was prepared from **5**, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-2,3-dihydro-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 9.0 Hz, 1H), 7.24 (d, J = 3.0 Hz, 1H), 7.09 (s, 1H), 6.96 (s, 1H), 6.67 (dd, J = 9.0, 3.0 Hz, 1H), 6.46 (d, J = 3.0 Hz, 1H), 3.88 (br, 2H), 3.03 (br, 2H), 2.39 (s, 6H). HRMS Calcd for $C_{16}H_{18}N_2$: 238.1470. Found: 238.1414.

5.3.15. 1-(3,5-Dimethylphenyl)-4-nitro-1*H*-indole (19). This compound was prepared from 4-nitro-1*H*-indole, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ

8.18 (d, J = 9.0 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.54 (d, J = 3.0 Hz, 1H), 7.41 (d, J = 3.0 Hz, 1H), 7.28 (m, 1H), 7.08 (s, 3H), 2.42 (s, 6H); MS(FAB) m/z 267 $(M+H)^+$; mp 128–130 °C. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.28; H, 5.47; N, 10.52.

5.3.16. 1-(3,5-Dimethylphenyl)-6-nitro-1*H*-indole (20). This compound was prepared from 6-nitro-1*H*-indole, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (d, J = 2.1 Hz, 1H), 8.06 (dd, J = 9.0, 2.1 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.09 (s, 3H), 6.74 (d, J = 2.1 Hz, 1H), 2.43 (s, 6H); MS(FAB) m/z 267 $(M+H)^+$; mp 138–142 °C. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.30; H, 5.48; N, 10.47.

5.3.17. 1-(3,5-Dimethylphenyl)-7-nitro-1*H*-indole (21). This compound was prepared from 7-nitro-1*H*-indole, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.35 (d, J = 3.0 Hz, 1H), 7.22 (t, J = 9.0 Hz, 1H), 7.01 (s, 1H), 6.88 (s, 2H), 6.79 (d, J = 3.0 Hz, 1H), 2.36 (s, 6H); MS(FAB) m/z 267 $(M+H)^+$; mp 95–98 °C. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.37; H, 5.53; N, 10.50.

5.3.18. 4-Amino-1-(3,5-dimethylphenyl)-1*H*-indole (22). This compound was prepared by the hydrogenation of **19** with 10% palladium on charcoal: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, J = 3.0 Hz, 1H), 7.12 (s, 2H), 7.03 (m, 2H), 6.99 (s, 1H), 6.57 (d, J = 3.0 Hz, 1H), 6.46 (dd, J = 9.0, 2.1 Hz, 1H), 2.39 (s, 6H). HRMS Calcd for $C_{16}H_{16}N_2$: 236.1313. Found: 236.1329.

5.3.19. 6-Amino-1-(3,5-dimethylphenyl)-1*H*-indole (23). This compound was prepared by the hydrogenation of **20** with 10% palladium on charcoal: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 9.0 Hz, 1H), 7.12 (d, J = 3.0 Hz, 1H), 7.09 (s, 2H), 6.97 (s, 1H), 6.87 (s, 1H), 7.61 (dd, J = 9.0, 3.0 Hz, 1H), 6.52 (d, J = 3.0 Hz, 1H), 2.40 (s, 6H); MS(FAB) m/z 236$(M+H)^+$; mp 90–92 °C. Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.09; H, 7.05; N, 11.58.

5.3.20. 7-Amino-1-(3,5-dimethylphenyl)-1*H*-indole (24). This compound was prepared by the hydrogenation of **21** with 10% palladium on charcoal: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, J = 9.0 Hz, 1H), 7.10 (d, J = 3.0 Hz, 1H), 7.06 (s, 2H), 7.05 (s, 1H), 6.98 (t, J = 9.0 Hz, 1H), 6.57 (d, J = 3.0 Hz, 1H), 6.49 (d, J = 8.1 Hz, 1H), 2.39 (s, 6H). HRMS Calcd for $C_{16}H_{16}N_2$: 236.1313. Found: 236.1352.

5.3.21. 2,3-Dihydro-1-(3,5-dimethylphenyl)-4-nitro-1*H*-indole (25). This compound was prepared from **19**, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-2,3-dihydro-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 2.1 Hz, 1H), 7.59 (dd, J = 9.0, 2.1 Hz, 1H), 7.19 (d, J = 9.0 Hz, 1H), 6.88 (s, 2H), 6.74 (s, 1H), 4.03 (t, J = 8.6 Hz, 2H), 3.18 (t, J = 8.6 Hz, 2H), 2.40 (s, 6H); MS(FAB) m/z 268 $(M+H)^+$; mp 108–112 °C. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.78; H, 6.16; N, 10.40.

5.3.22. 2,3-Dihydro-1-(3,5-dimethylphenyl)-6-nitro-1*H*-indole (26). This compound was prepared from **20**, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-2,3-dihydro-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, J = 9.0, 3.0 Hz, 2H), 7.80 (dd, J = 9.0, 3.0 Hz, 2H), 7.24 (m, 1H), 7.05 (d, J = 9.0 Hz, 1H), 4.16 (t, J = 8.6 Hz, 2H), 3.12 (t, J = 8.6 Hz, 2H), 2.36 (s, 3H), 2.08 (s, 3H); MS(FAB) m/z 268 $(M+H)^+$; mp 108–112 °C. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.78; H, 6.16; N, 10.40.

5.3.23. 2,3-Dihydro-1-(3,5-dimethylphenyl)-7-nitro-1*H*-indole (27). This compound was prepared from **21**, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-2,3-dihydro-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 9.0 Hz, 1H), 6.78 (t, J = 9.0 Hz, 1H), 6.74 (s, 1H), 6.59 (s, 2H), 4.16 (t, J = 8.6 Hz, 2H), 3.12 (t, J = 8.6 Hz, 2H), 2.26 (s, 6H); MS(FAB) m/z 268 $(M+H^+)$; mp 148–150 °C. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.67; H, 6.23; N, 10.37.

5.3.24. 4-Amino-2,3-dihydro-1-(3,5-dimethylphenyl)-1*H*-indole (28). This compound was prepared by the hydrogenation of **25** with 10% palladium on charcoal: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (t, J = 9.0 Hz, 1H), 7.86 (s, 2H), 6.61 (m, 2H), 6.16 (d, J = 9.0 Hz, 1H), 4.11 (t, J = 8.6 Hz, 2H), 3.19 (t, J = 8.6 Hz, 2H), 2.92 (t, J = 8.1 Hz, 2H), 2.31 (s, 6H). HRMS Calcd for $C_{16}H_{18}N_2$: 238.1470. Found: 238.1472.

5.3.25. 6-Amino-2,3-dihydro-1-(3,5-dimethylphenyl)-1*H*-indole (29). This compound was prepared by the hydrogenation of **26** with 10% palladium on charcoal: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (d, J = 9.0 Hz, 1H), 6.85 (s, 2H), 6.63 (s, 1H), 6.50 (d, J = 2.1 Hz, 1H), 6.09 (dd, J = 9.0, 2.1 Hz, 1H), 3.90 (t, J = 8.6 Hz, 2H), 2.99 (t, J = 8.6 Hz, 1H), 2.32 (s, 6H); MS(FAB) m/z 238 $(M+H)^+$; mp 82–84 °C. Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.73; N, 11.75. Found: C, 80.75; H, 7.73; N, 11.75.

5.3.26. 7-Amino-2,3-dihydro-1-(3,5-dimethylphenyl)-1*H*-indole (30). This compound was prepared by the hydrogenation of **27** with 10% palladium on charcoal: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (br, 1H), 6.86–6.77 (m, 3H), 6.69 (s, 1H), 6.64 (m, 1H), 4.09 (t, J = 8.6 Hz, 2H), 3.18 (t, J = 8.6 Hz, 2H), 2.30 (s, 6H). HRMS Calcd for $C_{16}H_{18}N_2$: 238.1470. Found: 238.1483.

5.3.27. 5-Amino-1-(3,5-dimethylbenzyl)-1*H*-indole (34). A mixture of 5-nitro-1*H*-indole (320 mg) and 1.2 equiv of potassium carbonate, 1.0 equiv of 3,5-dimethylbenzyl bromide and *N*,*N*-dimethylformamide (20 mL) was stirred at 50 °C overnight. The whole was poured into water, and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography (*n*-hexane–ethyl acetate = 3:1 as the eluant) to give 490 mg (87.5%) of the precursor nitro derivative **31**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, J = 2.1 Hz, 1H), 8.08 (dd, J = 9.0, 2.1 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.27 (s, 1H), 7.26 (s, 4H), 5.28 (s, 2H), 2.26 (s, 6H); MS(FAB) *m*/*z* 281 $(M+H)^+$. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.57; H, 5.75; N, 9.97.

The nitro derivative (**31**) (280 mg) was hydrogenated using 10% palladium on charcoal, to afford 240 mg (96.0%) of the desired compound (**34**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, J = 9.0 Hz, 1H), 7.03 (d, J = 3.0 Hz, 1H), 6.95 (d, J = 3.0 Hz, 1H), 6.88 (s, 1H), 6.74 (s, 2H), 6.64 (dd, J = 9.0, 3.0 Hz, 1H), 6.34 (d, J = 3.0 Hz, 1H), 5.16 (s, 2H), 2.24 (s, 6H), 1.56 (br, 2H); MS(FAB) *m*/*z* 250 $(M+H)^+$. Anal. Calcd for $C_{17}H_{16}N_2O_2 \cdot 1/6H_2O$: C, 80.59; H, 7.29; N, 11.06. Found: C, 80.71; H, 7.30; N, 10.83.

5.3.28. 1-(3,5-Dimethylbenzoyl)-5-nitro-1*H*-indole (35). A mixture of 5-nitro-1*H*-indole (320 mg) and 1.2 equiv of 60% NaH, and *N*,*N*-dimethylformamide (10 mL) was stirred for 30 min at 0 °C under an argon atmosphere. Then, a solution of 1.0 equiv of 3,5-dimethylbenzoyl chloride in *N*,*N*-dimethylformamide (5 mL) was added dropwise at 0 °C. After the addition was complete, the reaction mixture was stirred overnight at 60 °C. The whole was poured into water, and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography (*n*-hexane–ethyl acetate = 3:1 as the eluant) to give 500 mg (85.0%) of the precursor nitro compound **32**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (d, J = 2.1 Hz, 1H), 8.47 (d, J = 9.0 Hz, 1H), 8.27 (dd, J = 9.0, 2.1 Hz, 1H), 7.51 (d, J = 3.9 Hz, 1H), 7.35 (s, 2H), 7.28 (s, 1H), 6.75 (d, J = 3.9 Hz, 1H), 2.42 (s, 6H); MS(FAB) *m*/*z*, 295. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.17; H, 5.06; N, 9.42. The nitro derivative **32** (294 mg) was hydrogenated using 10% palladium on charcoal, to afford 233 mg (88.3%) of the desired compound (**35**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, J = 9.0 Hz, 1H), 7.30 (s, 2H), 7.21 (d, J = 3.9 Hz, 1H), 7.20 (s, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.76 (dd, J = 9.0, 2.1 Hz, 1H), 6.43 (d, J = 3.9 Hz, 1H), 2.38 (s, 6H), 1.56 (br, 2H); MS(FAB) *m*/*z* 265 $(M+H)^+$. Anal. Calcd for $C_{17}H_{16}N_2O \cdot 1HCl$: C, 66.88; H, 5.78; N, 9.18. Found: C, 67.04; H, 6.06; N, 8.73.

5.3.29. 1-(3,5-Dimethylbenzenesulfonyl)-5-nitro-1*H*-indole (33). This compound was prepared using the same procedures as described for the preparation of **32**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (d, J = 3.0 Hz, 1H), 8.47 (d, J = 3.0 Hz, 1H), 8.22 (dd, J = 9.0, 3.0 Hz, 1H), 8.08 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.50 (s, 1H), 7.20 (s, 1H), 6.82 (d, J = 3.0 Hz, 1H), 2.33 (s, 6H); MS(FAB) *m*/*z* 331 $(M+H)^+$. Anal. Calcd for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.06; H, 4.47; N, 8.33.

5.3.30. 5-Amino-1-(3,5-dimethylbenzenesulfonyl)-1*H*-indole (36). The nitro derivative **33** was hydrogenated using 10% palladium on charcoal, to afford the desired compound (**36**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 3.9 Hz, 1H), 7.43 (s, 2H), 7.11 (s, 1H), 6.78 (d, J = 2.1 Hz, 1H), 6.71 (dd, J = 9.0, 2.1 Hz, 1H), 6.48 (d, J = 3.9 Hz, 1H), 3.87 (br, 2H), 2.29 (s, 6H); MS(FAB) *m*/*z* 300 $(M+H)^+$. Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.68; H, 5.09; N, 9.21.

5.3.31. 2,3-Dihydro-1-(3,5-dimethylbenzyl)-5-nitro-1*H*-indole (43). This compound was prepared from 2,3-dihydro-5-nitro-1*H*-indole, using the same procedures as described for the preparation of **32**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.05 (d, J = 9.0 Hz, 1H), 7.91 (s, 1H), 6.94 (s, 1H), 6.86 (s, 2H), 6.35 (d, J = 9.0 Hz, 1H), 4.35 (s, 2H), 3.63 (t, J = 8.6 Hz, 2H), 3.09 (t, J = 8.6 Hz, 2H), 2.30 (s, 6H); MS(FAB) *m*/*z* 283 $(M+H)^+$. Anal. Calcd for $C_{17}H_{184}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.30; H, 6.49; N, 9.87.

5.3.32. 2,3-Dihydro-1-(3,5-dimethylbenzoyl)-5-nitro-1*H*-indole (44). This compound was prepared from 2,3-dihydro-5-nitro-1*H*-indole, using the same procedures as described for the preparation of **33**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (s, 2H), 7.15 (s, 4H), 4.18 (t, J = 8.6 Hz, 2H), 3.20 (t, J = 8.6 Hz, 2H), 2.36 (s, 6H); MS(FAB) *m*/*z* 297 $(M+H)^+$. Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.85; H, 5.44; N, 9.45. Found: C, 68.85; H, 5.51; N, 9.42.

5.3.33. 2,3-Dihydro-1-(3,5-dimethylbenzesulfonyl)-5-nitro-1*H*-indole (45). This compound was prepared from 2,3-dihydro-5-nitro-1*H*-indole, using the same procedures as described for the preparation of **32**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 9.0 Hz, 1H), 7.45 (s, 2H), 7.23 (s, 1H), 4.05 (t, J = 8.6 Hz, 2H), 3.10 (t, J = 8.6 Hz, 2H), 2.35 (s, 6H); MS(FAB) *m*/*z* 333 $(M+H)^+$. Anal. Calcd for $C_{17}H_{16}N_2O_3S$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.96; H, 4.89; N, 8.47.

5.3.34. 5-Amino-2,3-dihydro-1-(3,5-dimethylbenzyl)-1*H*-indole (46). This compound was prepared by the hydrogenation of **43** with 10% palladium on charcoal: ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.01 (s, 1H), 6.97 (d, J = 8.6 Hz, 1H), 6.92 (s, 2H), 6.89 (s, 1H), 6.58 (d, J = 8.6 Hz, 1H), 4.18 (s, 2H), 4.05 (t, J = 8.6 Hz, 2H), 3.10 (t, J = 8.6 Hz, 2H), 2.23 (s, 6H); MS(FAB) *m*/*z* 252 $(M+H)^+$. Anal. Calcd for $C_{17}H_{20}N_2 \cdot 2HCl$: C, 62.77; H, 6.82; N, 8.61. Found: C, 62.61; H, 6.65; N, 8.56.

5.3.35. 5-Amino-2,3-dihydro-1-(3,5-dimethylbenzoyl)-1*H*-indole (47). This compound was prepared by the

hydrogenation of **44** with 10% palladium on charcoal: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (s, 3H), 7.07 (s, 1H), 6.57 (s, 2H), 3.55 (br, 2H), 3.02 (t, J = 8.6 Hz, 2H), 2.34 (s, 6H). HRMS Calcd for $C_{17}H_{18}N_2O$: 266.1419. Found: 266.1448.

5.3.36. 5-Amino-2,3-dihydro-1-(3,5-dimethylbenzenesulfonyl)-1*H*-indole (48). This compound was prepared by the hydrogenation of **45** with 10% palladium on charcoal: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 9.0 Hz, 1H), 7.32 (s, 1H), 7.14 (s, 1H), 6.59 (d, J = 9.0 Hz, 2H), 6.48 (s, 1H), 3.87 (t, J = 8.6 Hz, 2H), 2.70 (t, J = 8.6 Hz, 2H), 2.29 (s, 6H); MS(FAB) m/z 302 $(M+H)^+$. Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.60; H, 6.07; N, 9.24.

5.3.37. 1-(3,5-Dimethylphenyl)-2-methyl-5-nitro-1*H*-indole (37). This compound was prepared from 2-methyl-5-nitro-1*H*-indole, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (d, J = 3.0 Hz, 1H), 7.97 (dd, J = 9.0, 3.0 Hz, 1H), 7.14 (s, 1H), 7.05 (d, J = 9.0 Hz, 1H), 6.93 (s, 2H), 6.53 (s, 1H), 2.41 (s, 6H), 2.30 (s, 3H); MS(FAB) m/z 281 $(M+H)^+$; mp 142–145 °C. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.92; H, 5.94; N, 9.79.

5.3.38. 5-Amino-1-(3,5-dimethylphenyl)-2-methyl-1*H*-indole (38). This compound was prepared by the reduction of the nitro-derivative (**37**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (s, 1H), 6.91 (m, 4H), 6.56 (dd, J = 8.6, 2.1 Hz, 1H), 6.20 (s, 1H), 2.38 (s, 6H), 2.26 (s, 3H). HRMS Calcd for $C_{17}H_{18}N_2$: 250.1470. Found: 250.1442.

5.3.39. 2,3-Dihydro-1-(3,5-dimethylphenyl)-2-methyl-5-nitro-1*H*-indole (39). This compound was prepared from **37**, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-2,3-dihydro-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 9.0 Hz, 1H), 7.96 (s, 1H), 6.88 (s, 1H), 6.86 (s, 2H), 6.51 (d, J = 9.0 Hz, 1H), 4.55 (m, 1H), 3.39 (m, 1H), 2.83 (m, 1H), 2.41 (s, 3H), 2.34 (s, 6H). HRMS Calcd for $C_{17}H_{18}N_2O_2$: 282.1368. Found: 282.1359.

5.3.40. 5-Amino-2,3-dihydro-1-(3,5-dimethylphenyl)-2-methyl-1*H*-indole (40). This compound was prepared by the hydrogenation of **39** with 10% palladium on charcoal: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (s, 1H), 6.96 (d, J = 3.0 Hz, 1H), 6.93 (s, 1H), 6.60 (d, J = 3.0 Hz, 2H), 6.21 (s, 1H), 4.23 (br s, 1H), 3.24 (br s, 1H), 2.63 (br s, 1H), 2.38 (s, 6H), 2.26 (s, 3H). HRMS Calcd for $C_{17}H_{20}N_2$: 252.1626. Found: 252.1583.

5.3.41. 1-(3,5-Dimethylphenyl)-5-nitro-1,2,3,4-tetrahydroquinoline (41). This compound was prepared, from 5-nitro-1,2,3,4-tetrahydroquinoline, using the same procedures as described for the General method for the preparation of 1-(3,5-dimethylphenyl)-1*H*-indole derivatives: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 3.0 Hz, 1H), 7.77 (dd, J = 9.0, 3.0 Hz, 2H), 6.94 (s, 1H), 6.70 (s, 1H), 6.37 (d, J = 9.0 Hz, 1H), 3.67 (t, J = 3.0 Hz, 2H), 2.91 (t, J = 3.0 Hz, 2H), 2.28 (s, 6H), 2.10 (quint., J = 6.0 Hz, 2H). HRMS Calcd for $C_{17}H_{18}N_2O_2$: 282.1368. Found: 282.1397.

5.3.42. 5-Amino-1-(3,5-dimethylphenyl)-1,2,3,4-tetrahydroquinoline (42). This compound was prepared by the hydrogenation of **41** with 10% palladium on charcoal ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 (s, 1H), 6.42–6.62 (br, 5H), 3.57 (t, J = 8.6 Hz, 2H), 2.73 (br, 2H), 2.28 (s, 6H), 2.00 (m, 2H). HRMS Calcd for $C_{17}H_{20}N_2$: 252.1626. Found: 252.1633.

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