Efficient One-Pot Synthesis of Spirooxindole Derivatives by Ethylenediamine Diacetate Catalyzed Reactions in Water

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Abstract: A simple and efficient one-pot synthetic approach was used for the preparation of biologically interesting spirooxindole derivatives by means of three-component reactions of isatins, malononitrile, and 1,3-dicarbonyl compounds catalyzed by ethylenediamine diacetate (EDDA) in an aqueous medium. This method is of great value because of its environmentally benign character, high yield, and easy handling.

Key words: spiro compounds, indoles, catalysis, Brønsted acids, Brønsted bases, water

Spirocyclic compounds represent an important class of naturally occurring substances with highly pronounced biological properties.[1] Molecules bearing the spirooxindole moiety are widely found in nature (Figure 1)[2] and have been shown to possess a variety of important biological activities.[2d,3] The unique structural array and highly prominent pharmacological activities have stimulated interest in the synthesis of spirooxindole derivatives. Thus, the development of new and simple synthetic methods for the preparation of spirooxindole derivatives has become an interesting challenge. Consequently, many synthetic methodologies have been developed for constructing these spirooxindole derivatives, most of which are based on cycloaddition or condensation reactions.[4] In particular, domino multicomponent reactions have emerged as an efficient and powerful tool in the synthesis of complex molecules as a one-pot procedure.[5] Several reactions for the synthesis of spirooxindoles through multicomponent reactions have been developed, by using tetrabutylammonium fluoride[6] and triethylbenzylammonium chloride (TEBA)[7] as phase-transfer catalysts, indium(III) chloride[8] as a Lewis acid catalyst, and electrocatalysis.[9] Although several methods for the synthesis of spirooxindole derivatives have been reported, there is still a demand for simple and facile methods.

Recently, the potential of Brønsted acids and bases as active catalysts for a variety of synthetically useful reactions in organic chemistry has been demonstrated.[10] Herein, we have developed a new and useful methodology for preparing a variety of benzopyrans by using ethylenediamine diacetate (EDDA) as an effective Brønsted acid and base catalyst.[11] These reactions involve a formal [3+3] cycloaddition through a domino aldol-type/6π-electrocyclization or Knoevenagel/6π-electrocyclization.[11] Very recently, a new and efficient synthetic approach for biologically interesting tetrahydroquinoline and benzopyranobenzopyran analogues from 1,3-dicarbonyls or resorcinols through domino Knoevenagel/hetero-Diels–Alder reactions or aldol-type/hetero-Diels–Alder reactions was also developed in this laboratory.[12] As a part of an ongoing study into the synthetic efficacy of EDDA as a catalyst for organic reactions, this study examines domino, three-component reactions of isatins, malononitrile, and 1,3-dicarbonyls to afford a variety of spirooxindole derivatives. We report a simple and efficient one-pot synthesis of a variety of spirooxindole derivatives in accordance with this approach.

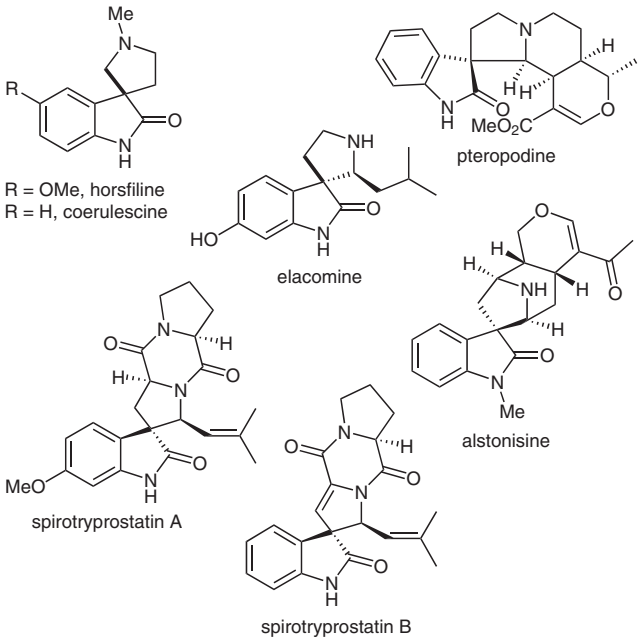

Figure 1 Selected spirooxindole natural products

The development of environmentally friendly techniques is one of the priorities of chemical research at present, with water emerging as a versatile solvent for organic chemistry in recent years.[13] Water as a solvent is not only inexpensive and environmentally benign, but also gives completely new reactivity.[14] Therefore, we first investigated an EDDA-catalyzed, three-component reaction of isatin (**1**), malononitrile (**2**), and 5,5-dimethylcyclohexane-1,3-dione (**3**) to afford a spirooxindole derivative in an aqueous medium. The reaction of isatin (**1**), malononitrile (**2**), and 5,5-dimethylcyclohexane-1,3-dione (**3**) in

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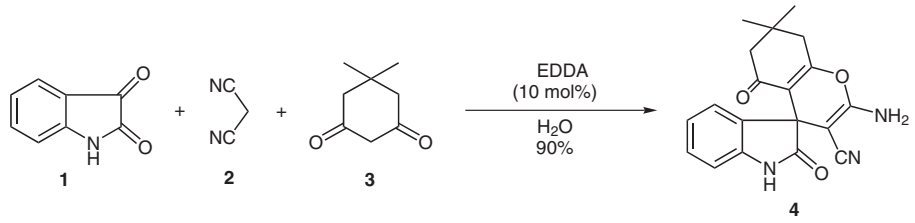


Scheme 1

the presence of 10 mol% EDDA at 60 °C for one hour in water provided compound **4** in 90% yield (Scheme 1). The identity of **4** was easily confirmed by comparison of its characteristic ^{1}H NMR chemical shifts with reported data in the literature.[8] The ^{1}H NMR spectrum of **4** showed an amide proton as a singlet at δ = 10.35 and two amine protons as a broad singlet at δ = 7.43. In the IR spectrum, the absorption bands at 1723 and 1656 cm^{-1} corresponding to two carbonyls of the amide and enone confirmed the presence of this structure.

In related work, it was reported that this reaction in the absence of any catalyst in water afforded compound **4** in very low yield (23%).[7] We found that EDDA in water was a far superior catalyst for this cyclization than *p*-toluenesulfonic acid (56%), sodium dodecylsulfate (78%), tetrabutylammonium bromide (85%), and cetyltrimethylammonium chloride (87%) in aqueous medium.[7] We observed that while malononitrile (**2**) was added to isatin (**1**) in the presence of EDDA at 60 °C in water, the reaction mixture changed to a reddish-brown color due to the formation of the Knoevenagel product. Upon addition of dimedone (**3**) to this mixture and stirring for 30 minutes, the reaction mixture became colorless. After optimizing the conditions, the generality of this reaction with regard to various isatins and 1,3-dicarbonyls was next explored. The results are summarized in Table 1.

Table 1 EDDA-Catalyzed Reactions of Isatins, Malononitrile, and 1,3-Dicarbonyls

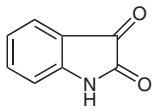
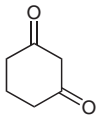
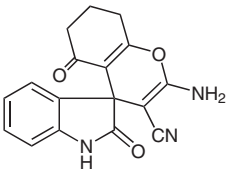
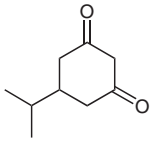
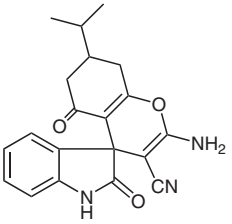
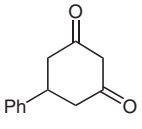
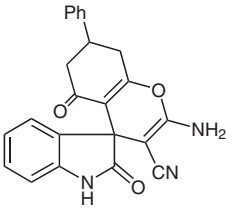
Entry	Isatin	1,3-Dicarbonyl	Product[a]	Time (h)	Yield (%)[b]
1	 **1**	 **8**	 **15**	1	95
2		 **9**	 **16**	1	90
3		 **10**	 **17**	1	83

Table 1 EDDA-Catalyzed Reactions of Isatins, Malononitrile, and 1,3-Dicarbonyls (continued)

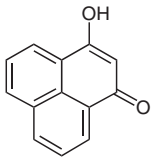
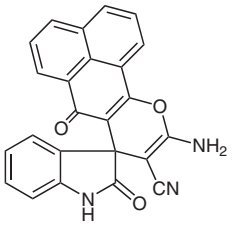
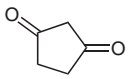
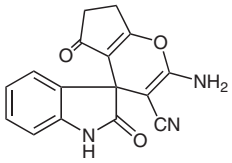
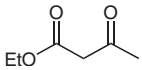
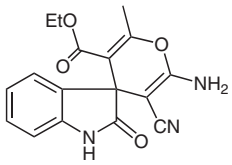
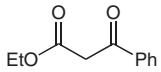
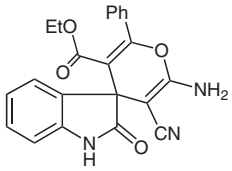
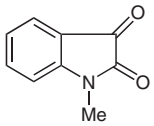
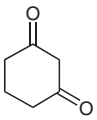
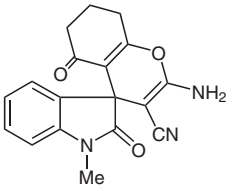
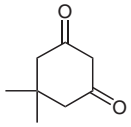
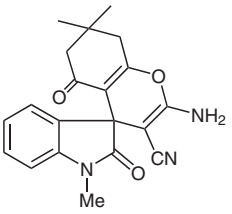
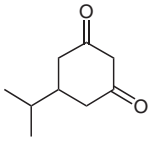
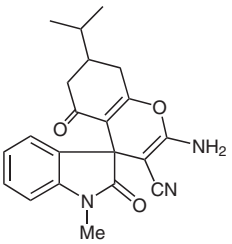
Entry	Isatin	1,3-Dicarbonyl	Product[a]	Time (h)	Yield (%)[b]
4		 **11**	 **18**	2	90
5		 **12**	 **19**	1	92
6		 **13**	 **20**	1	85
7		 **14**	 **21**	2	78
8	 **5**	 **8**	 **22**	1	85
9		 **3**	 **23**	1	84
10		 **9**	 **24**	2	81

Table 1 EDDA-Catalyzed Reactions of Isatins, Malononitrile, and 1,3-Dicarbonyls (continued)

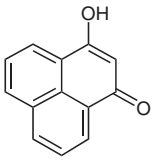
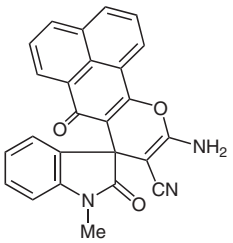
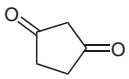
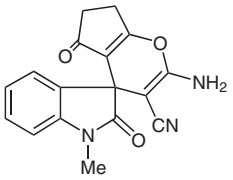
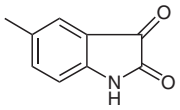
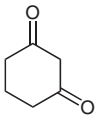
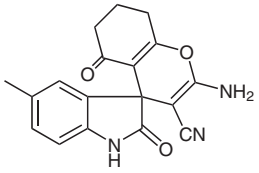
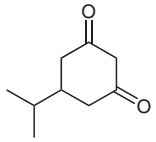
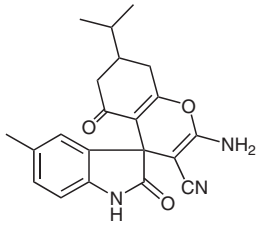
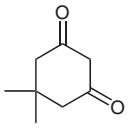
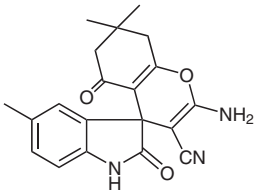
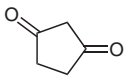
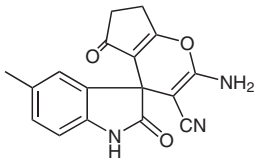
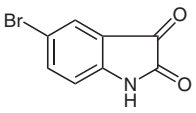
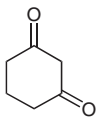
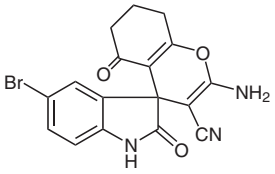
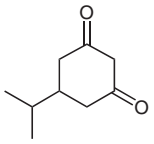
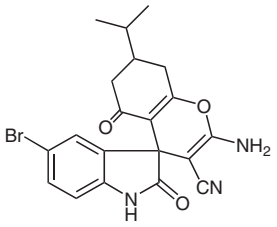
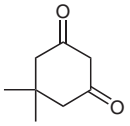
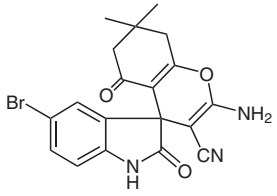
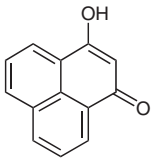
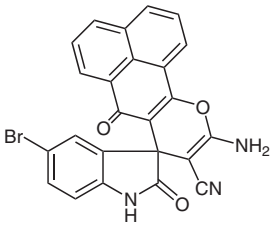
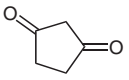
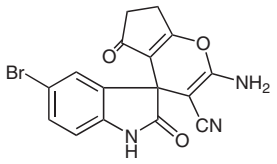
Entry	Isatin	1,3-Dicarbonyl	Product[a]	Time (h)	Yield (%)[b]
11		 **11**	 **25**	2	75
12		 **12**	 **26**	1	88
13	 **6**	 **8**	 **27**	1	87
14		 **9**	 **28**	2	72
15		 **3**	 **29**	1	90
16		 **12**	 **30**	1	88
17	 **7**	 **8**	 **31**	1	87

Table 1 EDDA-Catalyzed Reactions of Isatins, Malononitrile, and 1,3-Dicarbonyls (continued)

Entry	Isatin	1,3-Dicarbonyl	Product[a]	Time (h)	Yield (%)[b]
18		 **9**	 **32**	2	73
19		 **3**	 **33**	1	89
20		 **11**	 **34**	1	85
21		 **12**	 **35**	1	89

[a] All products were characterized by IR, ^{1}H and ^{13}C NMR, and mass spectroscopy.
[b] Yields of isolated products obtained by filtration of the reaction mixture.

The reactions of isatins and malononitrile with a number of cyclic and acyclic 1,3-carbonyls were investigated. Treatment of **1** and **2** with cyclohexane-1,3-dione (**8**), 5-isopropylcyclohexane-1,3-dione (**9**), and 5-phenylcyclohexane-1,3-dione (**10**) in the presence of 10 mol% EDDA at 60 °C for one hour in water afforded products **15**–**17** in 95, 90, and 83% yield, respectively (Table 1, entries 1–3). Interestingly, with 3-hydroxy-1*H*-phenalen-1-one (**11**) and cyclopentane-1,3-dione (**12**), the cycloaddition reactions were also successful. The reaction of **1** and **2** with 3-hydroxy-1*H*-phenalen-1-one (**11**) afforded product **18** in 90% yield, whereas with cyclopentane-1,3-dione (**12**), adduct **19** formed in 92% yield (entries 4 and 5). In particular, with acyclic β-keto esters **13** and **14**, cycloadducts **20** and **21** were produced in 85 and 78% yields, respectively (entries 6 and 7). Similarly, reactions of 1-methylisatin (**5**) and malononitrile (**2**) with several 1,3-dicarbonyls provided products **22**–**26** in 75–88% yield (entries 8–12). Importantly, reactions of isatins carrying electron-donating and electron-withdrawing substituents on the benzene ring were also successful. Reactions of 5-methylisatin (**6**) substituted with an electron-donating group with malononitrile (**2**) and several 1,3-dicarbonyls afforded cycloadducts **27**–**30** in 72–90% yield (entries 13–16), while the reactions of 5-bromoisatin (**7**) containing an electron-withdrawing group afforded products **31**–**35** in 73–89% yield (entries 17–21). These reactions provide a rapid synthetic route to biologically interesting spirooxindole derivatives. All products were characterized by IR and ^{1}H and ^{13}C NMR spectra, as well as FAB-HRMS analysis. In cases of compounds **16**, **17**, **24**, **28**, and **32**, the cycloadducts were produced as 1:1 mixtures of diastereomers. In addition, the structure of **23** was confirmed by X-ray crystallographic analysis, and is shown in Figure 2.

The formation of spirooxindole **4** can be explained by a domino Knoevenagel condensation and Michael addition followed by cyclization, as shown in Scheme 2. Isatin (**1**) was first protonated by EDDA to give protonated isatin **36**, which was then attacked by the anion produced by the malononitrile in the presence of EDDA to yield intermediate **37**. The dehydration of **37** in the presence of EDDA gave isatylidene malononitrile **38** as a Knoevenagel con-

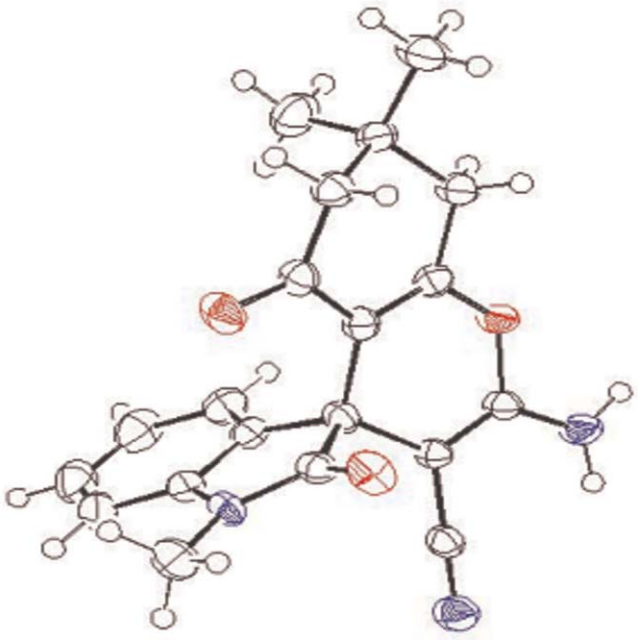
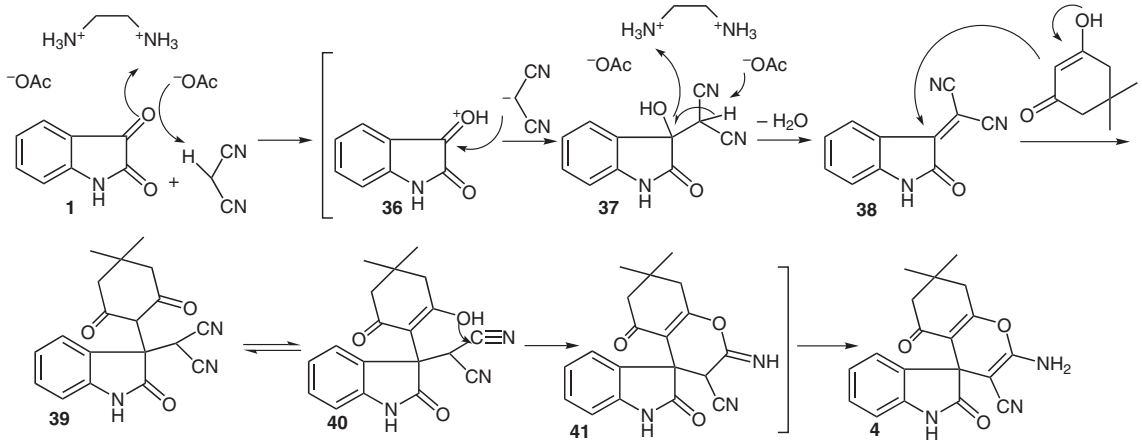


Figure 2 X-ray crystal structure of compound **23**

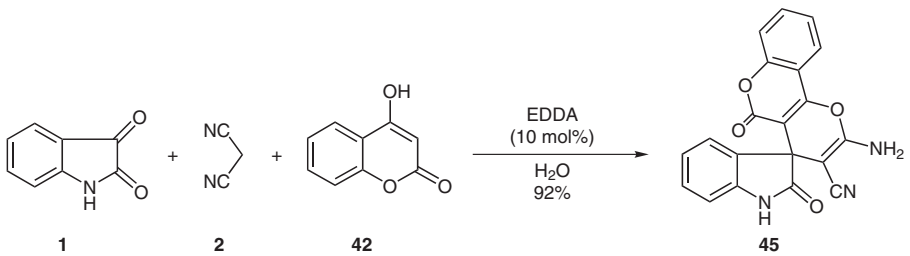
densation product. Such a process for producing intermediate **38** generated by an EDDA-catalyzed reaction of 1,3-diketones to carbonyls was suggested by Tietze.[15] Then, intermediate **38** was attacked by the enol of dimedone **3** of the Michael reaction in the presence of EDDA to give intermediate **39**, which then underwent a keto–enol tautomerization to furnish the enol intermediate **40**. Nucleophilic addition of the hydroxyl group of intermediate **40** to the cyano moiety afforded imine intermediate **41**, which finally underwent further reaction to give desired product **4**.

To further extend the usefulness of this methodology, the one-pot reaction of isatins and malononitrile with several 4-hydroxycoumarin derivatives was investigated. As shown in Scheme 3, reaction of isatin (**1**) and malononitrile (**2**) with 4-hydroxycoumarin (**42**), in the presence of 10 mol% EDDA as a catalyst at 60 °C for one hour in water, provided adduct **45** (92%) without any formation of the possible regioisomers. The structural assignment of **45** is derived from the IR carbonyl absorptions at 1718 and 1674 cm^{-1} for the amide and ester groups. Further, clear confirmation of the structure was obtained from the ^{13}C NMR spectrum that showed the expected carbonyl peaks due to the ester and amide groups at δ = 177.4 and 158.7.

Additional reactions of several isatins, malononitrile, and 4-hydroxycoumarins bearing substituents on the benzene ring were carried out under standard conditions. The results are collected in Table 2. Reaction of isatin (**1**) and malononitrile (**2**) with 6-methyl-4-hydroxycoumarin (**43**) and 6,7-dimethyl-4-hydroxycoumarin (**44**) gave products **46** (91%) and **47** (92%), whereas treatment of 1-methylisatin (**5**) and malononitrile (**2**) with 6-methyl-4-hydroxycoumarin (**43**) afforded adduct **48** in 85% yield (entries 1–3). In the cases of isatins bearing substituents on the benzene ring, the reactions were also successful. Treatment of isatin **6** with **43** for one hour in water provided adduct **49**



Scheme 2 Plausible mechanism for the synthesis of spirooxindole **4**

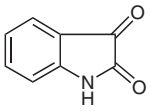
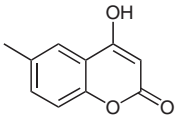
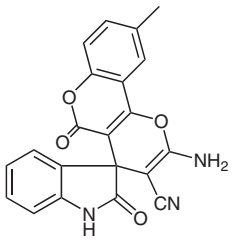
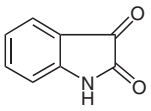
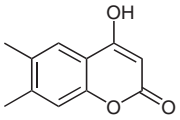
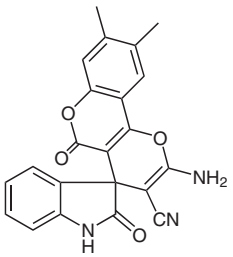
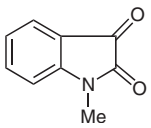
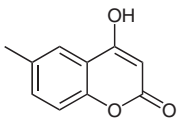
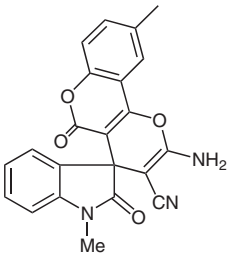
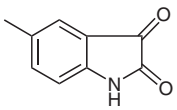
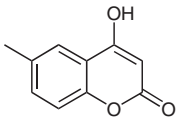
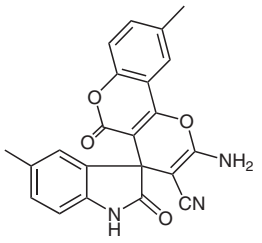
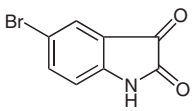
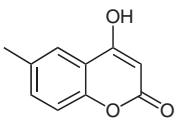
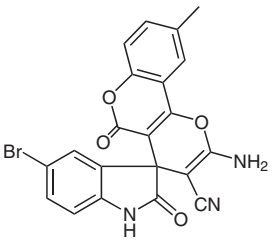


Scheme 3

(88%), whereas that of **7** with **43** gave **50** in 88% yield (entries 4 and 5).

In summary, an efficient and facile one-pot synthesis of spirooxindole derivatives was achieved through a multicomponent reaction involving various isatins, malononitrile, and a number of cyclic and acyclic 1,3-dicarbonyls in the presence of a catalytic amount of EDDA in an aqueous medium. The key strategy for the formation of a variety of spirooxindoles was a domino Knoevenagel condensation/Michael addition, followed by cyclization. This methodology offers several advantages, including high product yield, an easy experimental procedure, being environmentally benign, and being amenable to large-scale operation.

Table 2 EDDA-Catalyzed Reactions of Isatins, Malononitrile, and 4-Hydroxycoumarins

Entry	Isatin	4-Hydroxycoumarin	Product[a]	Time (h)	Yield (%)[b]
1	 **1**	 **43**	 **46**	1	91
2	 **1**	 **44**	 **47**	1	92
3	 **5**	 **43**	 **48**	1	85
4	 **6**	 **43**	 **49**	1	88
5	 **7**	 **43**	 **50**	1	88

[a] All products were characterized by IR, ^{1}H and ^{13}C NMR, and mass spectroscopy.
[b] Yields of isolated products obtained by filtration of the reaction mixture.

All experiments were carried out in an aqueous medium. Isatin, malononitrile, 1,3-dicarbonyl compounds, coumarins, and ethyl acetoacetate were obtained from Aldrich Chemicals. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX (300 and 75 MHz, respectively) spectrometer; DMSO-d_6 was used as the solvent. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS spectra (FAB) were obtained at the Korea Basic Science Institute on a Jeol JMS 700 spectrometer.

Spiro Compounds 4, 15–35, and 45–50; General Procedure

To a soln of the appropriate isatin (1.0 mmol), malononitrile (**2**; 1.0 mmol), and the appropriate 1,3-dicarbonyl (1.0 mmol) in H_2O (5.0 mL) was added EDDA (18.0 mg, 0.1 mmol) at r.t. The reaction mixture was stirred at 60 °C for 1–2 h and then cooled to r.t. The solid was collected by filtration, washed with H_2O (2 × 10.0 mL) and cold EtOH (5.0 mL), and dried in a vacuum oven; this gave the corresponding product as a white powder.

Compound 4[8]

The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **3** (140 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **4**.

Yield: 302 mg (90%); solid; mp >300 °C.

IR (KBr): 3361, 2198, 1720, 1658, 1468, 1217 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.35 (s, 1 H, NH), 7.18 (s, 2 H, NH_2), 7.12–6.70 (m, 4 H), 2.55–2.43 (m, 2 H), 2.14–1.99 (m, 2 H), 0.96 (s, 3 H), 0.93 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 194.7, 177.8, 164.0, 158.6, 141.9, 134.2, 128.0, 122.8, 121.5, 117.1, 110.6, 109.1, 57.4, 49.9, 46.7, 31.8, 27.4, 26.9.

Compound 15[8]

The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **8** (112 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **15**.

Yield: 291 mg (95%); solid; mp >300 °C.

IR (KBr): 3341, 3295, 3176, 2198, 1711, 1679, 1656, 1617, 1468, 1350, 1216, 1012, 755 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.37 (s, 1 H, NH), 7.19 (s, 2 H, NH_2), 7.16–6.75 (m, 4 H), 2.70–2.62 (m, 2 H), 2.27–2.18 (m, 2 H), 1.97–1.88 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 195.4, 1787.5, 166.4, 159.0, 142.4, 134.9, 128.5, 123.6, 122.0, 117.7, 112.3, 109.5, 58.1, 47.3, 36.8, 27.2, 20.2.

Compound 16

The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **9** (154 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **16**.

Yield: 314 mg (90%); 1:1 diastereomeric mixture; mp 283–285 °C.

IR (KBr): 3305, 2195, 1703, 1667, 1340, 1213, 1049 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.35 (s, 1 H, NH), 7.16 (s, 2 H, NH_2), 7.12–6.73 (m, 4 H), 2.64–2.42 (m, 2 H), 2.23–1.99 (m, 2 H), 1.88–1.790 (m, 1 H), 1.58–1.51 (m, 1 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.82 (d, J = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ (one isomer) = 195.1, 178.0, 165.9, 158.7, 142.0, 134.5, 128.2, 123.3, 121.5, 117.3, 111.6, 109.1, 57.4, 46.8, 38.2, 30.9, 30.5, 30.3, 19.3.

^{13}C NMR (75 MHz, DMSO-d_6): δ (other isomer) = 195.0, 178.0, 165.4, 158.7, 141.9, 134.3, 128.1, 123.2, 121.5, 111.4, 117.3, 109.1, 57.4, 46.8, 38.2, 30.8, 30.5, 30.3, 19.2.

HRMS–FAB: m/z [M]$^+$ calcd for $C_{20}H_{19}N_3O_3$: 349.1426; found: 349.1425.

Compound 17

The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **10** (188 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **17**.

Yield: 317 mg (83%); 1:1 diastereomeric mixture; mp 295–297 °C.

IR (KBr): 3310, 2194, 1722, 1671, 1619, 1341, 1215 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.85 (s, 1 H, NH), 6.83–6.20 (m, 11 H), 2.31–1.76 (m, 5 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ (one isomer) = 194.6, 178.4, 165.8, 165.2, 159.2, 142.8, 142.6, 134.9, 134.7, 128.9, 127.4, 123.8, 122.0, 117.8, 112.3, 109.6, 58.2, 47.3, 43.8, 38.0, 34.5.

^{13}C NMR (75 MHz, DMSO-d_6): δ (other isomer) = 194.6, 178.4, 165.8, 165.1, 159.1, 142.8, 142.5, 134.6, 134.6, 128.6, 127.3, 123.6, 122.0, 117.7, 112.2, 109.6, 58.0, 47.3, 43.7, 37.9, 34.3.

HRMS–FAB: m/z [M + H]$^+$ calcd for $C_{23}H_{18}N_3O_3$: 384.1348; found: 384.1345.

Compound 18

The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **11** (196 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 2 h afforded **18**.

Yield: 351 mg (90%); solid; mp >300 °C.

IR (KBr): 3404, 2199, 1725, 1666, 1624, 1333, 1218 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.60 (s, 1 H, NH), 8.43–6.87 (m, 12 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 183.3, 177.8, 161.8, 158.5, 157.8, 142.1, 135.3, 133.3, 132.6, 131.1, 129.6, 128.9, 128.0, 127.1, 126.9, 126.2, 123.1, 121.4, 120.7, 120.3, 117.0, 109.0, 57.0, 47.6.

HRMS–FAB: m/z [M]$^+$ calcd for $C_{24}H_{13}N_3O_3$: 391.0957; found: 391.0960.

Compound 19

The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **12** (98 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **19**.

Yield: 269 mg (92%); solid; mp >300 °C.

IR (KBr): 3347, 2195, 1718, 1665, 1346, 1232 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.55 (s, 1 H, NH), 7.48 (s, 2 H, NH_2), 7.22–6.80 (m, 4 H), 2.82–2.80 (m, 2 H), 2.37–2.35 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 199.7, 177.5, 176.6, 160.5, 142.0, 132.0, 128.8, 124.1, 121.9, 117.5, 114.8, 109.4, 56.4, 46.5, 33.1, 24.8.

HRMS–FAB: m/z [M + H]$^+$ calcd for $C_{16}H_{12}N_3O_3$: 294.0879; found: 294.0882.

Compound 20

The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **13** (130 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **20**.

Yield: 276 mg (85%); solid; mp 255–256 °C.

IR (KBr): 3473, 2193, 1719, 1676, 1620, 1471, 1377, 1288 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.35 (s, 1 H, NH), 7.19–7.13 (m, 1 H), 7.09 (s, 2 H, NH_2), 7.04–7.02 (m, 1 H), 6.92 (d, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.5 Hz, 1 H), 3.76 (q, J = 6.3 Hz, 2 H), 2.29 (s, 3 H), 0.77 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 178.9, 164.9, 159.4, 158.8, 142.6, 134.9, 128.9, 123.8, 122.2, 117.8, 109.7, 105.1, 60.6, 57.1, 49.4, 18.9, 13.4.

HRMS–FAB: m/z [M + H]$^+$ calcd for $C_{17}H_{16}N_3O_4$: 326.1141; found: 326.1141.

Compound 21
The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **14** (192 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 2 h afforded **21**.

Yield: 301 mg (78%); solid; mp 261–263 °C.

IR (KBr): 3470, 2195, 1720, 1670, 1380, 1220 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 9.62 (s, 1 H, NH), 7.39–7.28 (m, 8 H), 7.13–7.08 (m, 1 H), 6.94–6.87 (m, 1 H), 6.79 (d, *J* = 7.5 Hz, 1 H), 3.62–3.55 (q, *J* = 6.9 Hz, 2 H), 0.57 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 178.4, 164.9, 160.4, 155.7, 142.7, 133.5, 132.9, 130.7, 129.3, 128.7, 124.4, 122.4, 117.8, 109.9, 107.1, 60.7, 56.7, 50.2, 13.2.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{18}N_3O_4$: 388.1297; found: 388.1299.

Compound 22[6]
The reaction of **5** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **8** (112 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **22**.

Yield: 272 mg (85%); solid; mp 271–273 °C.

IR (KBr): 3465, 2194, 1703, 1671, 1606, 1467, 1352, 1217 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.27–7.22 (m, *J* = 7.2 Hz, 1 H), 7.18 (s, 2 H, NH_2) 7.03–7.04 (m, 1 H), 6.99–6.94 (m, 2 H), 3.36 (s, 3 H), 2.68–2.64 (m, 2 H), 2.23–2.18 (m, 2 H), 1.94–1.90 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 194.7, 176.4, 165.9, 161.7, 158.6, 143.4, 133.4, 128.2, 122.7, 122.2, 117.0 107.9, 57.2, 46.4, 36.2, 26.6, 26.2, 19.6.

Compound 23[7]
The reaction of **5** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **3** (140 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **23**.

Yield: 293 mg (84%); solid; mp 264–266 °C.

IR (KBr) 3441, 2194, 1686, 1608, 1468, 1352, 1219 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.27–7.22 (m, 1 H), 7.20 (s, 2 H, NH_2), 7.05–6.95 (m, 3 H), 3.27 (s, 3 H), 2.50 (s, 2 H), 2.18–2.05 (m, 2 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 194.6, 176.4, 164.0, 158.7, 144.3, 143.5, 133.4, 128.2, 122.6, 122.2, 110.6, 108.0, 57.1, 49.9, 46.4, 31.8, 27.4, 27.0, 26.2, 22.8.

Compound 24
The reaction of **5** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **9** (154 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 2 h afforded **24**.

Yield: 294 mg (81%); 1:1 diastereomeric mixture; mp 256–258 °C.

IR (KBr): 3394, 2196, 1675, 1609, 1488, 1342, 1212 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.27–7.22 (m, 1 H), 7.17 (s, 2 H), 7.08–6.96 (m, 3 H), 3.14 (s, 3 H), 2.68–2.55 (m, 2 H), 2.23–2.02 (m, 2 H), 1.90–1.88 (m, 1 H), 1.62–1.55 (m, 1 H), 0.89 (d, 3 H), (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 194.9, 176.3, 165.9, 165.4, 158.7, 143.5, 133.5, 128.2, 122.7, 122.1, 111.3, 107.9, 57.1, 46.4, 38.1, 30.7, 30.4, 30.2, 26.2, 19.1.

^{13}C NMR (75 MHz, DMSO-d_6): δ (one isomer) = 194.9, 176.3, 165.9, 165.4, 158.7, 143.5, 133.5, 128.2, 122.8, 122.1, 111.5, 107.9, 57.1, 46.4, 38.1, 30.7, 30.4, 30.2, 26.2, 19.2.

^{13}C NMR (75 MHz, DMSO-d_6): δ (other isomer) = 194.9, 176.3, 165.9, 165.4, 158.7, 143.4, 133.3, 128.2, 122.7, 122.1, 111.3, 107.9, 57.1, 46.4, 38.1, 30.6, 30.4, 30.2, 26.2, 19.1.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}N_3O_3$: 364.1661; found: 364.1664.

Compound 25
The reaction of **5** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **11** (196 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 2 h afforded **25**.

Yield: 303 mg (75%); solid; mp >300 °C.

IR (KBr): 3358, 1722, 1574, 1515, 1473, 1227 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.30–8.27 (m, 6 H), 7.91–7.73 (m, 4 H), 7.20–7.12 (m, 2 H), 3.14 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 181.0, 177.1, 159.4, 155.4, 144.3, 136.0, 133.6, 132.0, 131.8, 130.4, 129.0, 127.7, 127.1, 126.9, 125.3, 123.6, 122.9, 120.9, 117.7, 113.3, 108.7, 105.9, 57.5, 47.9, 27.0.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{16}N_3O_3$: 406.1192; found: 406.1195.

Compound 26
The reaction of **5** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **12** (98 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **26**.

Yield: 270 mg (88%); solid; mp 278–280 °C.

IR (KBr): 3558, 2194, 1702, 1611, 1490, 1348, 1236 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.51 (s, 2 H, NH_2), 7.33–7.28 (m, 1 H), 7.12 (d, *J* = 7.2 Hz, 1 H), 7.05–7.02 (m, 2 H), 3.15 (s, 3 H), 2.84–2.81 (m, 2 H), 2.37–2.34 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 200.5, 178.5, 176.0, 161.6, 144.3, 132.1, 129.9, 124.7, 123.6, 118.2, 115.6, 109.3, 57.0, 47.1, 34.0, 27.3, 25.7.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}N_3O_3$: 308.1035; found: 308.1038.

Compound 27
The reaction of **6** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **8** (112 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **27**.

Yield: 279 mg (87%); solid; mp 292–293 °C.

IR (KBr): 3360, 2196, 1705, 1661, 1349, 1212 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 10.22 (s, 1 H, NH), 7.10 (s, 2 H, NH_2), 6.93 (d, *J* = 7.8 Hz, 1 H), 6.81 (s, 1 H), 6.67 (d, *J* = 7.8 Hz, 1 H), 2.65 (t, *J* = 5.5 Hz, 2 H), 2.27–2.22 (m, 2 H), 2.21 (s, 3 H), 1.93 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 194.7, 177.9, 165.7, 161.7, 158.4, 139.5, 134.5, 130.2, 128.2, 123.6, 111.9, 108.7, 57.8, 46.8, 36.3, 26.6, 20.5, 19.6.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_3O_3$: 322.1192; found: 322.1194.

Compound 28
The reaction of **6** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **9** (154 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 2 h afforded **28**.

Yield: 261 mg (72%); 1:1 diastereomeric mixture; mp 275–276 °C.

IR (KBr): 3442, 2197, 1710, 1672, 1342, 1213 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 10.24 (s, 1 H, NH), 7.14 (s, 2 H, NH), 6.93 (d, *J* = 7.0 Hz, 1 H), 6.82 (s, 0.5 H), 6.79 (s, 0.5 H), 6.66 (d, *J* = 7.0 Hz, 1 H), 2.68–2.50 (m, 2 H), 2.20 (s, 3 H), 2.17–2.08 (m, 2 H), 1.92–1.84 (m, 1 H), 1.62–1.52 (m, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ (one isomer) = 195.6, 178.5, 166.3, 159.1, 140.0, 135.0, 130.8, 128.9, 124.3, 117.8, 112.1, 109.3, 58.2, 47.4, 38.6, 31.4, 31.3, 30.8, 21.1, 19.6.

^{13}C NMR (75 MHz, DMSO-d_6): δ (other isomer) = 195.4, 178.4, 165.9, 159.1, 139.9, 134.8, 130.8, 128.8, 124.1, 117.8, 111.9, 109.3, 58.2, 47.4, 38.6, 31.4, 31.3, 30.8, 21.1, 19.6.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{21}H_{22}N_3O_3$: 364.1661; found: 364.1664.

Compound 29

The reaction of **6** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **3** (140 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **29**.

Yield: 314 mg (90%); solid; mp 298–299 °C.

IR (KBr): 3367, 2190, 1710, 1660, 1352, 1221 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.22 (s, 1 H, NH), 7.11 (s, 2 H, NH_2), 6.90 (d, *J* = 7.6 Hz, 1 H), 6.78 (s, 1 H), 6.68 (d, *J* = 7.6 Hz, 1 H), 2,28 (s, 3 H), 2.20 (s, 2 H), 2.08 (s, 2 H), 1.04 (s, 3 H), 1.02 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 194.6, 177.8, 163.8, 161.7, 158.6, 139.5, 134.4, 130.3, 128.3, 123.4, 110.8, 108.8, 57.8, 50.0, 46.8, 31.8, 27.3, 27.1, 24.3, 20.5.

Compound 30

The reaction of **6** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **12** (98 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **30**.

Yield: 270 mg (88%); solid; mp >300 °C.

IR (KBr): 3357, 2195, 1725, 1660, 1492, 1347, 1235 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.47 (s, 1 H, NH), 7.48 (s, 2 H, NH_2), 7.04 (d, *J* = 7.8 Hz, 1 H), 6.91 (s, 1 H), 6.76 (d, *J* = 8.1 Hz, 1 H), 2.86–2.84 (m, 2 H), 2.42–2.40 (m, 2 H), 2.26 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 200.2, 177.9, 177.1, 160.9, 140.0, 132.6, 131.3, 129.5, 125.1, 118.0, 115.4, 109.7, 57.2, 47.1, 33.6, 25.3, 21.0.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{17}H_{14}N_3O_3$: 308.1035; found: 308.1036.

Compound 31[9]

The reaction of **7** (226 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **8** (112 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **31**.

Yield: 334 mg (87%); solid; mp 298–300 °C.

IR (KBr): 3360, 2190, 1715, 1673, 1474, 1349, 1216 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.51 (s, 1 H, NH), 7.32–7.16 (m, 4 H), 6.74 (d, *J* = 8.2 Hz, 1 H), 2.75–2.61 (m, 2 H), 2.35–2.18 (m, 2 H), 2.05–1.90 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 195.6, 178.2, 167.0, 159.2, 141.8, 137.4, 131.3, 126.5, 117.6, 113.8, 111.7, 111.5, 57.4, 47.6, 36.7, 27.2, 20.1.

Compound 32

The reaction of **7** (226 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **9** (154 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 2 h afforded **32**.

Yield: 312 mg (73%); 1:1 diastereomeric mixture; mp 283–285 °C.

IR (KBr): 3310, 2197, 1733, 1668, 1613, 1472, 1216 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.50 (s, 1 H, NH), 7.30–7.18 (m, 4 H), 6.73 (d, *J* = 8.4 Hz, 1 H), 2.66–2.41 (m, 2 H), 2.24–2.06 (m, 2 H), 1.92–1.85 (m, 1 H), 1.58–1.50 (m, 1 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ (one isomer) = 195.0, 177.3, 166.1, 166.0, 158.4, 141.0, 136.5, 130.5, 125.8, 116.7, 112.9, 110.7, 56.5, 46.7, 37.7, 30.6, 30.4, 29.9, 18.9, 18.7.

^{13}C NMR (75 MHz, DMSO-d_6): δ (other isomer) = 194.8, 177.2, 166.1, 166.0, 158.4, 141.0, 136.3, 130.5, 125.7, 116.7, 112.9, 110.7, 56.5, 46.7, 37.7, 30.6, 30.4, 29.9, 18.9, 18.7.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{20}H_{19}BrN_3O_3$: 428.0610; found: 428.0613.

Compound 33[9]

The reaction of **7** (226 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **3** (140 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **33**.

Yield: 368 mg (89%); solid; mp >300 °C.

IR (KBr): 3293, 2194, 1726, 1658, 1473, 1351, 1220 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.54 (s, 1 H, NH), 7.36–7.32 (m, 1 H), 7.31 (s, 2 H), 7.22 (s, 1 H), 6.78 (d, *J* = 8.2 Hz, 1 H), 2.65–2.55 (m, 2 H), 2.21–2.16 (m, 2 H), 1.05 (s, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 195.5, 178.1, 165.0, 159.3, 141.9, 137.2, 131.4, 126.4, 117.6, 113.8, 111.6, 110.6, 57.3, 50.4, 47.5, 32.4, 28.0, 27.6.

Compound 34

The reaction of **7** (226 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **11** (196 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **34**.

Yield: 398 mg (85%); solid; mp >300 °C.

IR (KBr): 3409, 2200, 1726, 1664, 1473, 1338, 1224 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.72 (s, 1 H, NH), 8.50–8.40 (m, 3 H), 8.30–8.28 (d, *J* = 7.2 Hz, 1 H), 7.94–7.83 (m, 2 H), 7.57 (s, 2 H), 7.38–7.34 (m, 2 H), 6.86–6.83 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 181.5, 178.6, 159.7, 156.1, 142.5, 137.8, 136.4, 134.4, 132.2, 131.9, 130.8, 130.7, 128.1, 127.6, 127.2, 125.8, 121.4, 118.0, 114.3, 113.1, 112.1, 57.5, 48.9.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{24}H_{13}BrN_3O_3$: 470.0140; found: 470.0142.

Compound 35

The reaction of **7** (226 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **12** (98 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **35**.

Yield: 331 mg (89%); solid; mp >300 °C.

IR (KBr): 3363, 2193, 1710, 1676, 1474, 1345, 1234 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.68 (s, 1 H, NH), 7.54 (s, 2 H, NH_2), 7.39–7.30 (m, 2 H), 6.80 (d, *J* = 8.1 Hz, 1 H), 2.81–2.80 (m, 2 H), 2.39–2.37 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 200.3, 178.4, 176.8, 161.1, 141.8, 134.8, 132.1, 127.6, 117.8, 114.8, 114.2, 111.9, 56.3, 47.2, 33.6, 25.4.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{16}H_{11}BrN_3O_3$: 371.9984; found: 371.9980.

Compound 45[8]

The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **42** in H_2O (10 mL) at 60 °C for 1 h afforded **45**.

Yield: 328 mg (92%); solid; mp >300 °C.

IR (KBr): 3306, 2203, 1717, 1673, 1609, 1472, 1358, 1108 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.64 (s, 1 H, NH), 7.94 (d, *J* = 8.1 Hz, 1 H), 7.78–7.73 (m, 1 H), 7.62 (s, 2 H, NH_2), 7.55–7.46 (m, 2 H), 7.19 (d, *J* = 7.5 Hz, 2 H), 6.95–6.90 (m, 1 H), 6.85 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 177.4, 158.7, 158.5, 155.3, 152.2, 142.4, 133.8, 133.3, 129.1, 125.2, 124.3, 122.9, 122.3, 117.2, 116.8, 112.7, 109.7, 101.7, 57.4, 47.9.

Compound 46

The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **43** (176 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **46**.

Yield: 337 mg (91%); solid; mp >300 °C.

IR (KBr): 3280, 2195, 1705, 1665, 1625, 1360, 1220 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.64 (s, 1 H, NH), 7.75 (s, 1 H), 7.60–7.57 (m, 3 H), 7.39 (d, *J* = 8.4 Hz, 1 H), 7.23–7.16 (m, 2 H), 6.95–6.90 (m, 1 H), 6.85 (d, *J* = 7.5 Hz, 1 H), 2.44 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 177.6, 166.0, 162.5, 158.9, 155.4, 152.1, 150.6, 142.6, 134.8, 133.8, 129.3, 124.4, 123.1, 122.6, 116.4, 112.5, 109.9, 101.8, 57.6, 48.1, 20.7.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{21}H_{14}N_3O4$: 372.0984; found: 372.0986.

Compound 47

The reaction of **1** (147 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **44** (190 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **47**.

Yield: 354 mg (92%); solid; mp >300 °C.

IR (KBr): 3202, 2199, 1706, 1668, 1624, 1468, 1361, 1064 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.62 (s, 1 H, NH), 7.68 (s, 1 H), 7.57 (s, 1 H), 7.30 (s, 1 H), 7.23–7.14 (m, 3 H), 6.95–6.83 (m, 2 H), 2.35 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 177.7, 166.2, 162.6, 158.9, 155.5, 150.9, 144.1, 142.6, 134.0, 133.6, 129.3, 124.3, 123.3, 122.6, 117.4, 110.3, 109.9, 100.8, 57.6, 48.0, 20.2, 19.4.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{22}H_{16}N_3O_4$: 386.1141; found: 386.1145.

Compound 48

The reaction of **5** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **43** (176 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **48**.

Yield: 327 mg (85%); solid; mp 299–300 °C.

IR (KBr): 3328, 2203, 1715, 1674, 1606, 1492, 1358 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.76 (s, 1 H), 7.65–7.57 (m, 3 H), 7.40–7.23 (m, 3 H), 7.08–7.01 (m, 2 H), 3.17 (s, 3 H), 2.44 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 176.1, 166.0, 162.4, 158.8, 155.5, 150.7, 144.1, 134.8, 133.9, 132.7, 129.5, 124.2, 123.2, 122.6, 116.8, 112.5, 108.9, 101.6, 57.2, 47.7, 26.9, 20.9.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{22}H_{16}N_3O_4$: 386.1141; found: 386.1143.

Compound 49

The reaction of **6** (161 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **43** (176 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **49**.

Yield: 338 mg (88%); solid; mp >300 °C.

IR (KBr): 3359, 2199, 1708, 1672, 1498, 1358, 1212 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.52 (s, 1 H, NH), 7.75 (s, 1 H), 7.62–7.58 (m, 4 H), 7.04–6.96 (m, 2 H), 6.74–6.72 (m, 1 H), 2.44 (s, 3 H), 2.19 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 177.6, 166.0, 158.8, 155.4, 152.0, 150.6, 140.1, 134.8, 133.9, 131.4, 129.6, 125.0, 123.1, 122.6, 116.8, 112.6, 109.7, 101.9, 57.7, 48.1, 21.0, 20.9.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{22}H_{16}N_3O_4$: 386.1141; found: 386.1143.

Compound 50

The reaction of **7** (226 mg, 1.0 mmol), **2** (66 mg, 1.0 mmol), and **43** (176 mg, 1.0 mmol) in H_2O (10 mL) at 60 °C for 1 h afforded **50**.

Yield: 395 mg (88%); solid; mp >300 °C.

IR (KBr): 3359, 2199, 1708, 1672, 1498, 1358, 1212 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.77 (s, 1 H, NH), 7.75 (s, 1 H), 7.67 (s, 2 H), 7.60–7.58 (m, 1 H), 7.51 (s, 1 H), 7.40–7.38 (m, 2 H), 6.83–6.80 (d, *J* = 8.4 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 177.9, 159.6, 156.4, 151.3, 142.5, 136.4, 135.4, 132.6, 128.1, 123.2, 117.9, 117.4, 114.8, 113.3, 112.3, 101.7, 57.6, 49.8, 21.5.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{21}H_{13}BrN_3O_4$: 450.0089; found: 450.0086.

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