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Ethylenediamine diacetate-catalyzed three-component reaction for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones and their spirooxindole derivatives

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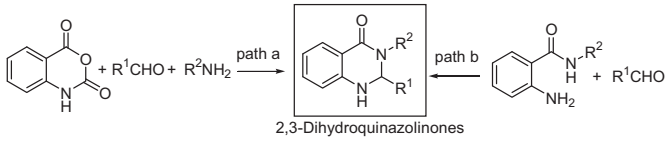
ABSTRACT

Ethylenediamine diacetate (EDDA)-catalyzed one-pot syntheses of biologically interesting 2,3-dihydroquinazolin-4(1*H*)-ones and their spirooxindole derivatives from isatoic anhydride, amines, and benzaldehydes or isatins via a three-component condensation in aqueous media have been described. This method is of great value because of high yields and ease of handling.

1. Introduction

2,3-Dihydroquinazolinone derivatives are an important class of fused heterocycles that display a wide range of biological, pharmacological, and medicinal properties involving antitumor, antibiotic, antipyretic, analgesic, antihypertonic, diuretic, antihistamine, antidepressant, and vasodilating activities.[1] In addition 2,3-dihydroquinazolinones have been shown to act as potent tubulin inhibitors with impressive antiproliferative activity against several human cancer cell lines.[2] Furthermore, these compounds can act analogously to the antimitotic agent colchicine.[3] Given the importance of such activities, a number of synthetic methods for their synthesis from isatoic anhydride (path a) and anthranilamide (path b) have been reported (Scheme 1). Three-component condensation of an isatoic anhydride, a primary amine, and an aromatic aldehyde has been widely described under a variety of catalysts such (path a) as [bmim]BF_4,[4] *p*-TsOH,[5] silica sulfuric acid,[6] $Al(H_2PO_4)_3$,[7] $KAl(SO_4)_2{\cdot}12H_2O$ (alum),[8] montmorillonite K-10,[9] zinc perfluorooctanoate,[10] gallium triflate,[11] and Amberlyst-15/microwave.[12] The method through path b includes condensation of 2-aminobenzamides with aldehydes in the presence of *p*-TsOH/DDQ,[13] I_2,[14] $FeCl_3$,[15] $CuCl_2$,[16] $TiCl_4$/Zn,[17] chiral phosphoric acid,[18] and ionic liquid/water.[19]



Scheme 1.

Spirooxindole derivatives also represent an important class of naturally occurring substances with highly pronounced biological activities and properties.[20,21] The unique structural array and highly prominent pharmacological activities have subsequently stimulated interest in the synthesis of spirooxindole derivatives. Thus, development of new and simple synthetic methods for the preparation of such derivatives bearing the biologically active dihydroquinazolinone ring has become an interesting challenge. Very recently, two methods for the synthesis of spirooxindoles bearing the dihydroquinazolinone ring through multicomponent reactions have been developed (Scheme 2). The typical procedure involves the condensation of isatoic anhydride with isatins and amines using $KAl(SO_4)_2{\cdot}12H_2O$ as a catalyst (path c).[22] Another method has shown formation of a spirooxindole derivative from 2-aminobenzamide with isatin in the presence of chiral phosphoric acid (path d).[18a]

Although several methods for the synthesis of 2,3-dihydroquinazolinones and spirooxindole derivatives have been reported, there is still a demand for simple and cost effective methods. Recently, the Brønsted acids and bases have demonstrated their potential to serve as active catalysts for a variety of

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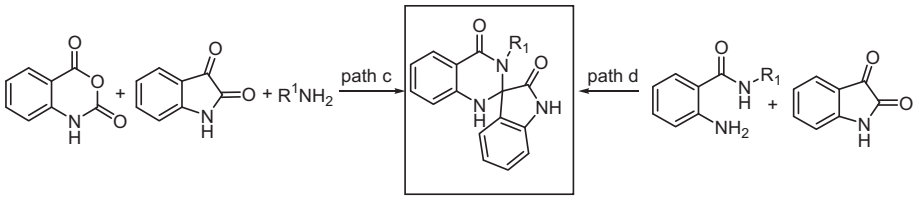


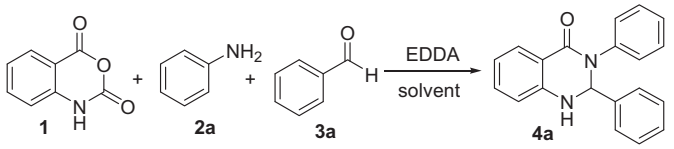
Scheme 2.

synthetically useful reactions in organic synthesis.[23] In particular, we developed a new and useful methodology for a variety of benzopyrans using ethylenediamine diacetate (EDDA) as effective Brønsted acid and base catalyst.[24] We also developed an environmentally benign method for the synthesis of a variety of pyrans starting from cyclic 1,3-dicarbonyls and α,β-unsaturated aldehydes in water.[25] As a part of an ongoing study into the synthetic efficacy of EDDA as a catalyst for organic reactions, this study examines EDDA-catalyzed three-component reactions of isatoic anhydride, amines, and benzaldehydes to afford 2,3-dihydroquinazolin-4(1*H*)-one derivatives. We also examine EDDA-catalyzed three-component reactions of isatoic anhydride, amines, and isatins to afford spirooxindole derivatives bearing dihydroquinazolinone rings. We report herein an efficient and convenient one-pot synthesis of a variety of biologically interesting 2,3-dihydroquinazolin-4(1*H*)-ones and spirooxindole derivatives with dihydroquinazolinone rings in aqueous medium.

2. Results and discussion

Presently, the development of environmental friendly techniques is one of the priority goals of chemical research, with water emerging as a versatile solvent for organic chemistry in recent years.[26] Water as a solvent is not only inexpensive and environmentally benign, but also gives completely new reactivities.[27] Therefore, we investigated a EDDA-catalyzed, three-component reaction of isatoic anhydride (**1**), aniline (**2a**), and benzaldehyde (**3a**) to afford **4a**, under several solvents, including ethanol, acetonitrile, methylene chloride, toluene, and water (Table 1). When the reaction was carried out in the presence of 20 mol % EDDA in water, the expected product (**4a**) was obtained in high yield (94%) and with better reaction times compared with other organic solvents. With nonpolar methylene chloride and toluene, the desired adduct was not produced, likely due to insolubility of the isatoic anhydride.

Table 1
Reaction of **1** with **2a** and **3a** in the presence of EDDA under several solvents



Entry	EDDA (mol %)	Solvent	Condition	Yield (%)
1	—	Ethanol	Reflux, 12 h	25
2	10	Ethanol	Reflux, 12 h	50
3	20	Ethanol	Reflux, 12 h	55
4	40	Ethanol	Reflux, 12 h	60
5	—	Acetonitrile	Reflux, 12 h	<5
6	20	Acetonitrile	Reflux, 12 h	20
7	40	Acetonitrile	Reflux, 12 h	30
8	20	Methylene chloride	Reflux, 12 h	No reaction
9	20	Toluene	Reflux, 12 h	No reaction
10	—	Water	Reflux, 12 h	36
11	10	Water	Reflux, 12 h	80
12	20	Water	Reflux, 5 h	94

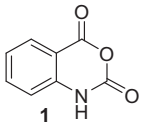
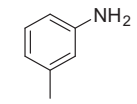
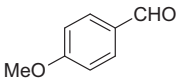
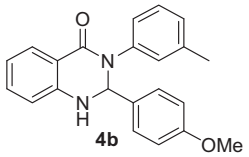
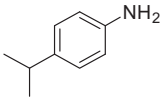
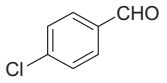
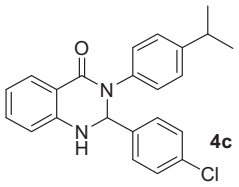
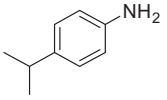
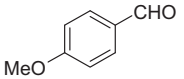
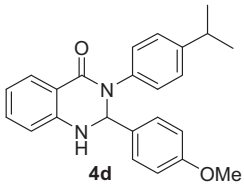
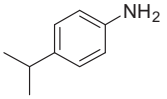
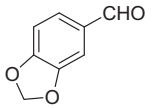
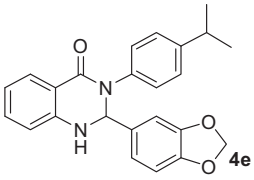
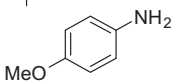
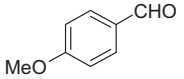
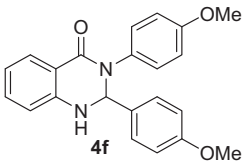
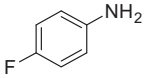
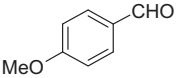
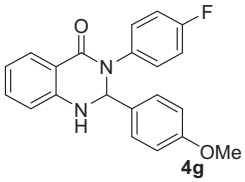
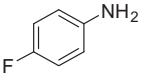
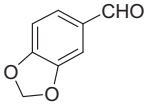
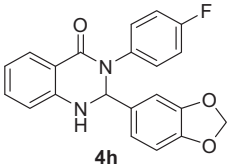
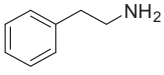
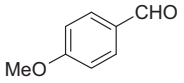
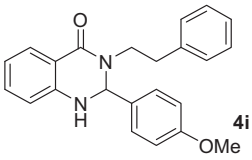
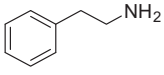
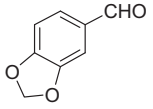
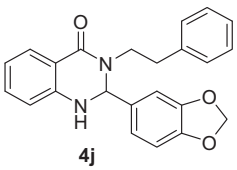
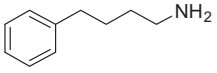
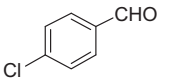
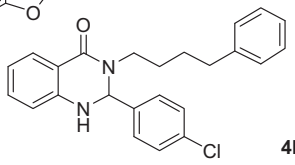
Importantly, the use of water as a solvent offers environmental benefits as well as significant rate enhancements, due likely to select factors, including the hydrophobic effect, a large dielectric constant, extensive hydrogen bonding, high heat capacity, and optimum oxygen solubility.[28] By comparing with reported results, EDDA in water revealed itself a much better catalyst for the formation of **4a** than [bmim]BF_4 (80%),[4] *p*-TsOH/ethanol (65%),[5] silica sulfuric acid/H_2O (85%),[6] alum/H_2O (65%),[8] montmorillonite K-10/ethanol (80%),[9] zinc perfluorooctanoate/H_2O (60%),[10] gallium triflate/ethanol (79%),[11] and Amberlyst-15/microwave (81%).[12] In particular, this protocol is convincingly superior to the recently reported catalytic methods, such as other Brønsted acid (TsOH/ethanol, 65%),[5] or solvent free conditions (Amberlyst-15/microwave, 81%).[12]

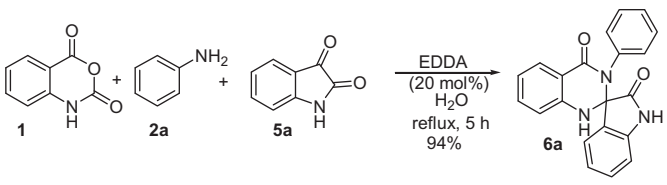
After optimizing the conditions, the generality toward various amines and benzaldehydes was next explored. The results obtained are listed in Table 2. The direct three-component reactions worked well with a variety of arylamines bearing either electron-donating (entries 1–5) or -withdrawing groups (entries 6 and 7), phenethylamine (entries 8 and 9) and 4-phenylbutylamine (entry 10). Also the reactions with arylamines and a range of benzaldehydes carrying either electron-donating or -withdrawing groups on the benzene ring afforded desired products **4b**–**h** in high yields. With other primary amines having an aromatic ring, desired products **4i**–**k** were produced in 88–92% yield (entries 8–10). These reactions provided rapid access to various 2,3-dihydroquinazolin-4(1*H*)-one derivatives **4a**–**k**.

As an application of this methodology to synthesize spirooxindole derivatives bearing dihydroquinazolinone ring, EDDA-catalyzed three-component reactions of isatoic anhydride (**1**), aniline (**2a**), and isatin (**5a**) were next carried out. Treatment of **1** with **2a** and **5a** in the presence 20 mol % EDDA in water at reflux for 5 h provided compound **6a** in 94% yield (Scheme 3). The assignment of **6a** was easily defined by observing the chemical shifts of the characteristic protons and comparison with reported data in the literature.[22] The ^{1}H NMR spectrum of **6a** showed an amide proton at δ=10.39 ppm as a singlet and one amine proton at δ=7.30 ppm as a singlet. In the IR spectrum, the absorption bands at 1721 and 1644 cm^{-1}, corresponding to two carbonyls of the amide, confirmed the presence of this structure.

To explore generality and scope, additional reactions of isatoic anhydride (**1**) with various amines and several isatins were next attempted. The results obtained are listed in Table 3. Reactions with anilines bearing both electron-donating (entries 1 and 2) and -withdrawing groups (entry 3) on the benzene ring provided products **6b**–**d** in 89–96% yield. With other primary amines having an aromatic ring, desired products **6e**–**i** were produced in 82–92% yield (entries 4–8). Interestingly, when employing aliphatic amines with a chain and cyclic ring, the expected cycloadducts **6j** and **6k** were obtained in 91 and 89% yields, respectively. With ammonium acetate, **6l** was also produced (93%). In addition, reactions of 5-bromoisatin (**5b**) and 1-methylisatin (**5c**) with several anilines successfully afforded products **6m**–**q** in 82–93% yield (entries 12–16). These reactions provided rapid access to various spirooxindole derivatives **6b**–**q** with the dihydroquinazolinone moiety.

Table 2
EDDA catalyzed one-pot synthesis of 2,3-dihydroquinazolinones in water

Entry	Isatoic anhydride	Amine	Aldehyde	Time (h)	Product	Yield (%)
1				10	 **4b**	86
2				7	 **4c**	93
3				8	 **4d**	91
4				7	 **4e**	90
5				6	 **4f**	92
6				6	 **4g**	90
7				7	 **4h**	89
8				8	 **4i**	88
9				7	 **4j**	87
10				6	 **4k**	92



Scheme 3.

The formation of **4a** and **6a** can be explained by the mechanism as shown in Scheme 4. According to observation of evolution in the reaction mixture and other reported mechanisms catalyzed by Brønsted acid and Lewis acid, EDDA could act as a Brønsted acid. The carbonyl group of isatoic anhydride (**1**) could be protonated by EDDA to give intermediate **7**, which could facilitate nucleophilic attack of aniline (**2a**) on the carbonyl unit. Nucleophilic addition of aniline (**2a**) to **7**, followed by decarboxylation, produced 2-aminobenzamide **8**. Condensation of **8** with protonated benzaldehyde gave imine **9**, which underwent intramolecular cyclization to afford final product **4a**. Similarly, condensation of **8** with protonated isatin, prepared using EDDA, gave imine **10**, which underwent intramolecular cyclization to afford product **6a**.

In summary, the one-pot three-component condensation of isatoic anhydride with various amines and benzaldehydes provided 2,3-dihydroquinazolin-4(1*H*)-one derivatives in an aqueous

Table 3
EDDA catalyzed one-pot synthesis of spirooxindole derivatives with dihydroquinazolinones in water

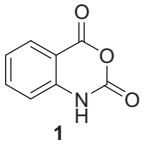
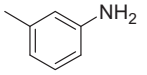
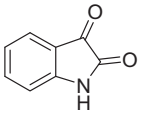
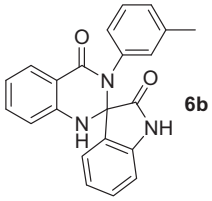
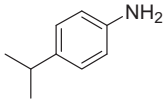
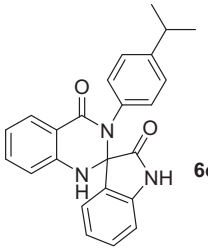
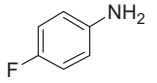
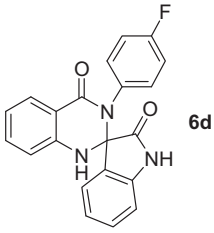
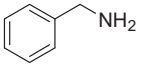
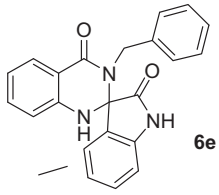
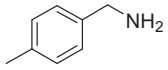
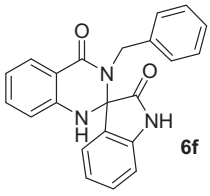
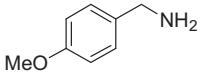
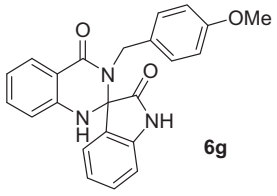
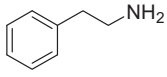
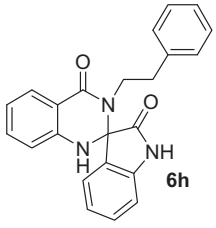
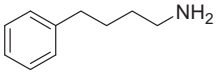
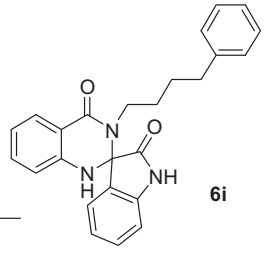
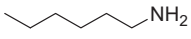
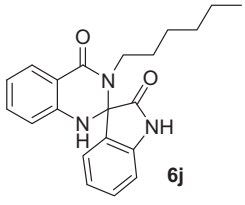
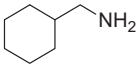
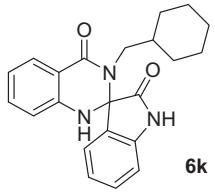
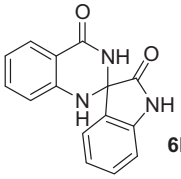
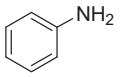
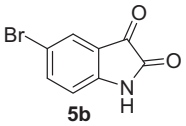
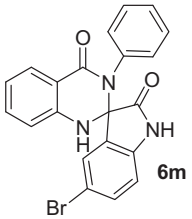
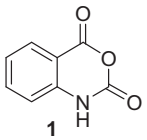
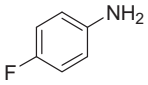
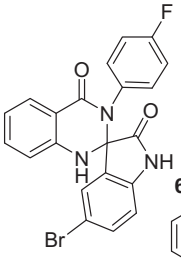
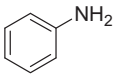
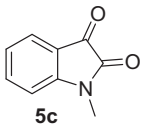
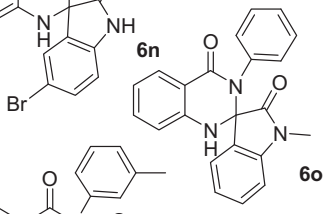
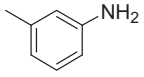
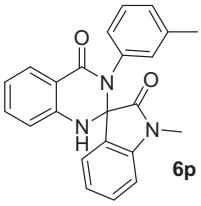
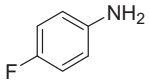
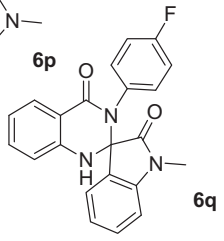
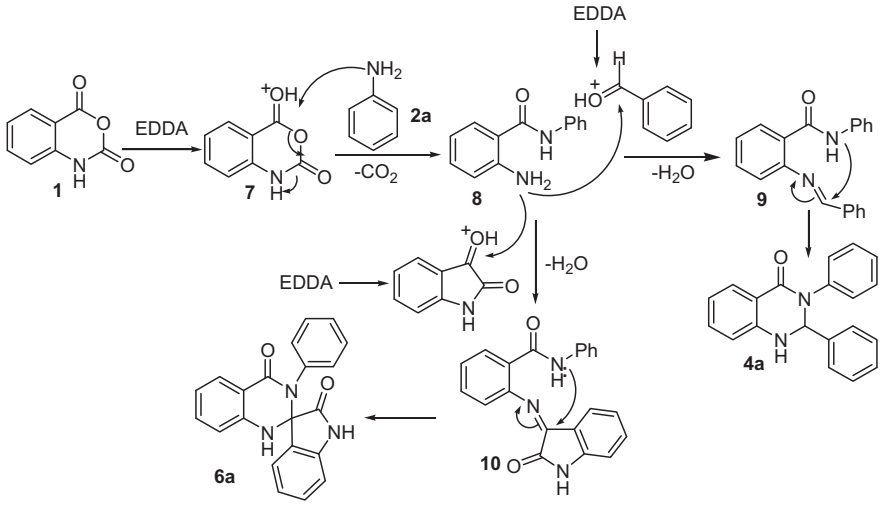
Entry	Isatoic anhydride	Amine	Isatin	Time (h)	Product	Yield (%)
1	 **1**		 **5a**	7	 **6b**	92
2				6	 **6c**	96
3				9	 **6d**	89
4				7	 **6e**	90
5				10	 **6f**	82
6				10	 **6g**	88
7				6	 **6h**	92
8				7	 **6i**	92
9				7	 **6j**	91
10				7	 **6k**	89
11	NH_4OAc			6	 **6l**	93

Table 3 *(continued)*

Entry	Isatoic anhydride	Amine	Isatin	Time (h)	Product	Yield (%)
12				8		93
13				10		82
14				10		90
15				8		92
16				8		88



Scheme 4. A possible mechanism for the formation of **4a** and **6a**.

medium. Also, three-component reaction of isatoic anhydride with a variety of amines and several isatins was successfully applied to the synthesis of biologically interesting spirooxindole derivatives bearing the dihydroquinazolinone moiety in aqueous media. This methodology offers several advantages, including high product yield, ease of experimental procedure, and amenability to large-scale operations.

3. Experimental

3.1. General

All the experiments were carried out in aqueous medium. Isatoic anhydride, aldehydes, Isatins, and amines were obtained from Aldrich chemicals. Merck, pre-coated silica gel plates (Art. 5554)

with a fluorescent indicator were used for analytical TLC. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in DMSO-d_6 as the solvent chemical shift. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS were carried out at the Korea Basic Science Institute.

3.2. Typical procedure for 4a–k

To a solution of isatoic anhydride (**1**) (1.0 mmol), amines (1.0 mmol), and benzaldehydes (1.0 mmol) in water (10 mL) was added EDDA (36 mg, 0.2 mmol) and the reaction mixture was refluxed for 5–10 h under nitrogen atmosphere. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered, and recrystallized in ethanol to afford the pure product.

3.2.1. Compound ***4a***. Mp 205–206 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.77 (1H, d, J=7.8 Hz), 7.64 (1H, s), 7.42–7.18 (11H, m), 6.79 (1H, d, J=8.1 Hz), 6.74 (1H, t, J=7.2 Hz), 6.30 (1H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.2, 146.5, 140.7, 140.6, 133.7, 128.5, 128.3, 128.2, 127.9, 126.5, 126.2, 125.9, 117.4, 115.3, 114.7, 72.6; IR (KBr) 3427, 3294, 3061, 2832, 1633, 1511, 1392, 1332, 1257, 1158, 1025, 754 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{16}N_2O$: 300.1263. Found: 300.1265.

3.2.2. Compound ***4b***. Mp 209–210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75 (1H, d, J=7.5 Hz), 7.54 (1H, s), 7.33–7.19 (5H, m), 7.14 (1H, s), 7.03 (2H, t, J=8.7 Hz), 6.88–6.85 (2H, m), 6.77 (1H, t, J=8.1 Hz), 6.22 (1H, s), 3.71 (3H, s), 2.27 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.2, 159.0, 146.5, 140.8, 137.8, 133.6, 132.7, 128.3, 127.9, 127.8, 126.8, 126.6, 123.2, 117.4, 115.4, 114.7, 113.6, 72.3, 55.0, 20.8; IR (KBr) 3424, 3301, 2961, 2833, 1634, 1507, 1393, 1301, 1248, 1170, 1026, 830, 766 cm^{-1}; HRMS m/z (M^+) calcd for $C_{22}H_{20}N_2O_2$: 344.1525. Found: 344.1525.

3.2.3. Compound ***4c***. Mp 190–192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (1H, d, J=8.4 Hz), 7.74 (1H, d, J=6.9 Hz), 7.68 (1H, d, J=2.4 Hz), 7.59 (1H, d, J=8.4 Hz), 7.37–7.17 (7H, m), 6.78–6.71 (2H, m), 6.29 (1H, d, J=2.4 Hz), 2.93–2.84 (1H, m), 1.18 (6H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.05, 146.2, 139.9, 138.4, 133.7, 132.8, 130.1, 128.9, 128.3, 127.02, 126.5, 121.04, 117.6, 115.4, 114.8, 71.8, 32.9, 23.7; IR (KBr) 3425, 3282, 2960, 1645, 1511, 1390, 1327, 1240, 990, 8826, 754 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{21}ClN_2O$: 376.1342. Found: 376.1339.

3.2.4. Compound ***4d***. Mp 171–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75 (1H, d, J=7.5 Hz), 7.55 (1H, s), 7.32–7.21 (7H, m), 6.86 (2H, d, J=8.4 Hz), 6.74 (2H, t, J=8.4 Hz), 6.19 (1H, s), 3.70 (3H, s), 2.91–2.82 (1H, m), 1.19 (6H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.1, 159.05, 146.4, 145.9, 138.6, 133.5, 132.8, 127.8, 127.6, 126.3, 125.9, 117.3, 115.4, 114.7, 113.6, 72.2, 54.9, 32.9, 23.7; IR (KBr) 3420, 3298, 2956, 1630, 1508, 1392, 1332, 1249, 1177, 1027, 833, 700 cm^{-1}; HRMS m/z (M^+) calcd for $C_{24}H_{24}N_2O_2$: 372.1838. Found: 372.1840.

3.2.5. Compound ***4e***. Mp 210–212 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74 (1H, d, J=7.5 Hz), 7.58 (1H, s), 7.28–7.18 (5H, m), 6.94 (1H, s), 6.83–6.63 (4H, m), 6.18 (1H, s), 5.98 (2H, s), 2.92–2.85 (1H, m), 1.19 (6H, d, J=6.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.1, 147.3, 147.1, 146.3, 146.0, 138.5, 134.9, 133.6, 127.9, 126.4, 125.8, 119.9, 117.4, 115.4, 114.8, 107.8, 106.6, 101.1, 72.2, 32.9, 23.7; IR (KBr) 3437, 2960, 1644, 1509, 1401, 1237, 1028, 755 cm^{-1}; HRMS m/z (M^+) calcd for $C_{24}H_{22}N_2O_3$: 386.1630. Found: 386.1629.

3.2.6. Compound ***4f***. Mp 227–228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74 (1H, d, J=7.8 Hz), 7.44 (1H, s), 7.31–7.23 (3H, m), 7.15 (2H, d, J=8.7 Hz), 6.89–6.84 (4H, m) 6.75 (2H, t, J=7.8 Hz), 6.16 (1H, s), 3.73 (3H, s), 3.70 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3, 159.1, 157.2, 146.6, 133.5, 132.7, 127.9, 127.8, 127.4, 117.3, 115.2, 114.6, 113.7, 113.6, 72.8, 55.1, 55.0; IR (KBr) 3426, 2936, 2837, 1636, 1510, 1394, 1441, 1243, 1174, 1025, 996, 830, 762 cm^{-1}; HRMS m/z (M^+) calcd for $C_{22}H_{20}N_2O_3$: 360.1474. Found: 360.1477.

3.2.7. Compound ***4g***. Mp 259–260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74 (1H, d, J=7.8 Hz), 7.49 (1H, s), 7.29–7.12 (7H, m), 6.86 (2H, d, J=8.7 Hz), 6.76 (2H, t, J=7.8 Hz), 6.23 (1H, s), 3.70 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.5, 159.2, 146.8, 133.7, 132.2, 128.8, 128.7, 128.09, 127.9, 117.4, 115.4, 115.1, 115.0, 114.6, 113.6, 72.6, 55.0; IR (KBr) 3427, 3302, 1643, 1504, 1390, 1305, 1245, 1026, 994, 832, 760 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{17}FN_2O_2$: 348.1274. Found: 348.1272.

3.2.8. Compound ***4h***. Mp 252–253 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74 (1H, d, J=7.5 Hz), 7.55 (1H, s), 7.31–7.26 (2H, m), 7.22–7.14 (2H, m), 6.95 (1H, s), 6.86–6.72 (5H, m), 6.21 (1H, s), 5.98 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ162.4, 147.3, 147.2, 136.7, 134.1, 133.7, 128.8, 128.7, 127.8, 120.5, 117.5, 115.4, 115.1, 114.9, 114.6, 107.7, 106.9, 101.1, 72.7; IR (KBr) 3426, 1641, 1501, 1447, 1393, 1248, 1027, 996, 758 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{15}FN_2O_3$: 362.1067. Found: 362.1064.

3.2.9. Compound ***4i***. Mp 183–185 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.72 (1H, d, J=7.8 Hz), 7.35–7.17 (9H, m), 6.93 (2H, d, J=8.7 Hz), 6.75–6.67 (2H, m), 5.82 (1H, s), 4.06–3.97 (1H, m), 3.73 (3H, s), 3.05–2.87 (2H, m), 2.76–2.52 (1H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3, 159.4, 146.5, 139.0, 133.1132.9, 128.6, 128.5, 128.3, 127.7, 127.4, 126.2, 117.0, 114.7, 114.2, 113.8, 70.3, 55.1, 46.0; IR (KBr) 3426, 3299, 1629, 1509, 1408, 1299, 1249, 1173, 1025, 997, 763 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{22}N_2O_2$: 358.1681. Found: 358.1679.

3.2.10. Compound ***4j***. Mp 147–148 °C; 1H NMR (300 MHz, DMSO-d_6) δ 7.65 (1H, d, J=7.8 Hz) 7.29–7.16 (6H, m), 6.88–6.78 (3H, m), 6.69–6.62 (3H, m), 5.98 (2H, s), 5.76 (1H, s), 4.04–3.88 (1H, m), 3.01–2.84 (2H, m), 2.77–2.67, (1H, m); 13C NMR (75 MHz, DMSO-d_6) δ 162.1, 147.4, 147.3, 146.3, 139.0, 134.9, 133.1, 128.5, 128.3, 127.3, 126.1, 119.7, 117.0, 114.6, 114.1, 107.9, 106.4, 101.1, 70.2, 46.0, 33.5; IR (KBr) 3427, 1634, 1484, 1411, 1248, 1026, 994, 756 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{20}N_2O_3$: 372.1474. Found: 372.1471.

3.2.11. Compound ***4k***. Mp 129–130 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (1H, d, J=7.8 Hz), 7.39–7.11 (11H, m), 6.81–6.61 (2H, m), 5.83 (1H, d, J=2.1 Hz), 3.41–3.35 (2H, m), 2.53 (2H, t, J=6.9 Hz), 1.58–1.45 (4H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.2, 145.9, 142.03, 140.2, 133.2, 132.9, 128.4, 128.26, 128.21, 127.9, 127.4, 125.6, 117.3, 115.0, 114.3, 69.4, 44.3, 34.8, 28.3, 27.1; IR (KBr) 3426, 3297, 2938, 2859, 1630, 1489, 1437, 1413, 1320, 1089, 996, 826, 749 cm^{-1}; HRMS m/z (M^+) calcd for $C_{24}H_{23}ClN_2O$: 390.1499. Found: 390.1499.

3.3. Typical procedure for 6a–q

To a solution of isatoic anhydride (**1**) (1.0 mmol), amines (1.0 mmol), and isatins (1.0 mmol) in water (10 mL) was added EDDA (36 mg, 0.2 mmol) and the reaction mixture was refluxed for 5–10 under nitrogen atmosphere. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered, and recrystallized in ethanol to afford the pure product.

3.3.1. Compound ***6a***. Mp 264–266 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.39 (1H, s), 7.68 (1H, d, J=7.5 Hz), 7.60 (1H, s), 7.53 (1H, d, J=7.5 Hz), 7.30 (1H, t, J=7.8 Hz) 7.24–7.12 (4H, m), 7.01–6.98 (2H, m), 6.92 (1H, t, J=7.5 Hz), 6.78–6.70 (2H, m), 6.64 (1H, d, J=7.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.6, 163.8, 146.3, 141.4, 138.3, 134.2, 134.0, 129.9, 129.7, 129.2, 128.3, 127.9, 118.4, 115.0, 114.6, 114.1, 112.6, 76.8; IR (KBr) 3447, 3303, 1721, 1644, 1615, 1486, 1358, 1194,

1105, 1012, 964, 865, 752 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{15}N_3O_2$: 341.1164. Found: 341.1161.

3.3.2. Compound ***6b***. Mp 274–276 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.40 (1H, s), 7.66 (1H, d, J=7.8 Hz), 7.59 (1H, s), 7.53 (1H, d, J=7.2 Hz), 7.30 (1H, t, J=7.8 Hz), 7.15 (1H, t, J=7.5 Hz), 7.07 (1H, t, J=7.2 Hz), 6.98–6.90 (3H, m), 6.82 (1H, s), 6.75 (1H, t, J=8.4 Hz), 6.70 (1H, d, J=8.1 Hz), 6.64 (1H, d, J=7.5 Hz), 2.15 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.3, 163.9, 146.5, 143.6, 138.3, 134.1, 131.4, 128.8, 128.7, 127.9, 127.1, 126.6, 123.1, 118.2, 115.1, 114.6, 109.3, 76.6, 21.2 IR (KBr) 3298, 3206, 3093, 1724, 1643, 1616, 1485, 1361, 1236, 1193, 1100, 1048, 963, 751 cm^{-1}; HRMS m/z (M^+) calcd for $C_{22}H_{17}N_3O_2$: 355.1321. Found: 355.1318.

3.3.3. Compound ***6c***. Mp 276–278 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.36 (1H, s), 7.66 (1H, d, J=7.5 Hz), 7.56 (1H, s), 7.52 (1H, d, J=7.5 Hz), 7.29 (1H, t, J=8.1 Hz), 7.15 (1H, t, J=7.5 Hz), 7.08–6.87 (5H, m), 6.77–6.63 (3H, m), 2.79–2.73 (1H, m), 1.09 (6H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.3, 163.6, 147.4, 146.0, 141.5, 135.6, 133.5, 130.6, 129.0, 127.5, 127.4, 126.3, 126.2, 122.1, 117.6, 114.5, 114.0, 110.0, 76.3, 32.7, 23.6, 23.5; IR (KBr) 3311, 3066, 2961, 1725, 1632, 1511, 1484, 1359, 1214, 1190, 1105, 1051, 955, 817, 752 cm^{-1}; HRMS m/z (M^+) calcd for $C_{24}H_{21}N_3O_2$: 383.1634. Found: 383.1630.

3.3.4. Compound ***6d***. Mp 295–296 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.47 (1H, s), 7.67 (2H, t, J=3.3 Hz), 7.59 (1H, d, J=10.5 Hz), 7.31 (1H, t, J=7.2 Hz), 7.18 (1H, t, J=7.5 Hz), 7.09–6.92 (5H, m), 6.78–6.65 (3H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.4, 163.9, 146.3, 141.4, 134.4, 134.3, 134.1, 129.8, 129.7, 127.9, 118.4, 116.2, 115.9, 114.8, 114.6, 114.2, 112.6, 76.9 IR (KBr) 3272, 3066, 1726, 1642, 1616, 1509, 1483, 1360, 1328, 1221, 1197, 1154, 1099, 961, 827, 750 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{14}FN_3O_2$: 359.1070. Found: 359.1068.

3.3.5. Compound ***6e***. Mp 210–211 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.34 (1H, s), 7.72 (1H, d, J=7.8 Hz), 7.45 (1H, s), 7.36–7.24 (3H, m), 7.17–7.15 (3H, m), 6.93–6.88 (3H, m), 6.83 (1H, d, J=7.8 Hz), 6.76 (1H, t, J=7.5 Hz), 6.67 (1H, d, J=7.5 Hz), 4.48 (1H, d, J=15.3 Hz), 4.15 (1H, d, J=15.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.4, 164.5, 146.4, 142.9, 137.8, 133.8, 131.7, 128.2, 127.8, 127.2, 126.8, 126.7, 122.4, 118.1, 115.1, 114.4, 110.9, 75.5, 46.3. IR (KBr) 3297, 3090, 2944, 1727, 1625, 1483, 1383, 1323, 1242, 1191, 968. 750 cm^{-1}; HRMS m/z (M^+) calcd for $C_{22}H_{17}N_3O_2$: 355.1321. Found: 355.1318.

3.3.6. Compound ***6f***. Mp 257–258 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.26 (1H, s), 7.70 (1H, d, J=7.8 Hz), 7.39 (1H, s), 7.35–7.22 (3H, m), 6.95–6.89 (3H, m), 6.81–6.71 (4H, m), 6.64 (1H, d, J=8.1 Hz), 4.35 (1H, d, J=15.0 Hz), 4.18 (1H, d, J=15.3 Hz), 2.22 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.9, 163.9, 145.9, 142.4, 135.7, 134.1, 133.2, 131.1, 128.2, 127.4, 127.3, 126.2, 121.8, 117.5, 114.6, 113.8, 110.3, 74.9, 45.4, 20.6; IR (KBr) 3322, 3092, 2946, 1726, 1625, 1482, 1435, 1379, 1324, 1242, 1198, 1113, 1027, 963, 747 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{19}N_3O_2$: 369.1477. Found: 369.1475.

3.3.7. Compound ***6g***. Mp 227–228 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.20 (1H, s), 7.71 (1H, d, J=7.8 Hz), 7.37–7.22 (4H, m), 6.95 (1H, t, J=7.8 Hz), 6.81–6.62 (7H, m), 4.28 (2H, s), 3.68 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.9, 163.9, 158.1, 145.9, 142.5, 133.2, 131.1, 128.9, 127.3, 126.3, 121.9, 117.5, 114.7, 113.8, 113.1, 110.4, 74.8, 54.9, 45.1; IR (KBr) 3280, 3062, 2957, 1723, 1640, 1477, 1326, 1118, 1024, 944, 752 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{19}N_3O_3$: 385.1426. Found: 385.1423.

3.3.8. Compound ***6h***. Mp 287–288 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.56 (1H, s), 7.68 (1H, d, J=7.5 Hz), 7.53 (1H, d, J=7.2 Hz), 7.46–7.41 (2H, m), 7.28–7.10 (5H, m), 6.96 (1H, d, J=7.8 Hz), 6.80 (2H, d, J=8.1 Hz), 6.73 (1H, t, J=7.2 Hz), 6.63 (1H, d, J=7.8 Hz), 3.36 (1H, t, J=11.4 Hz), 2.86–2.68 (2H, m), 2.57 (1H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.2, 163.3, 145.7, 142.2, 138.6, 133.2, 131.3, 128.4, 128.0, 127.2, 127.1, 126.2, 125.9, 122.4, 117.5, 114.3, 113.7, 110.6, 75.3, 44.9, 34.2; IR (KBr) 3279, 3062, 2956, 2873, 1723, 1639, 1513, 1477, 1394, 1325, 1272, 1234, 1189, 1023, 944, 751 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{19}N_3O_2$: 369.1477. Found: 369.1479.

3.3.9. Compound ***6i***. Mp 173–175 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.50 (1H, s), 7.62 (1H, d, J=7.5 Hz), 7.43 (1H, d, J=7.5 Hz), 7.37 (1H, d, J=8.1 Hz), 7.35 (1H, s), 7.25–7.20 (3H, m), 7.14 (1H, d, J=6.9 Hz), 7.09–7.02 (3H, m), 6.92 (1H, d, J=7.8 Hz), 6.70 (1H, t, J=7.2 Hz), 6.60 (1H, d, J=8.1 Hz), 3.20 (1H, t, J=9.3 Hz), 2.81 (1H, t, J=9.0 Hz), 2.33 (2H, t, J=6.6 Hz), 1.37–1.25 (4H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.7, 163.8, 146.1, 142.6, 142.3, 133.6, 131.7, 128.6, 127.8, 127.5, 126.2, 126.0, 122.8, 117.9, 115.0, 114.2, 111.1, 75.6, 43.1, 35.0, 28.8, 28.1; IR (KBr) 3260, 2935, 1726, 1689, 1624, 1400, 1365, 1325, 1191, 1030, 749 cm^{-1}; HRMS m/z (M^+) calcd for $C_{25}H_{23}N_3O_2$: 397.1790. Found: 397.1794.

3.3.10. Compound ***6j***. Mp 170–171 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.53, (1H, s),7.66 (1H, d, J=7.8 Hz), 7.52 (1H, d, J=7.5 Hz), 7.42 (1H, d, J=7.8 Hz), 7.37 (1H, s), 7.26 (1H, t, J=7.5 Hz) 7.12 (1H, t, J=7.5 Hz), 6.95 (1H, d, J=7.8 Hz), 6.72 (1H, t, J=7.2 Hz), 6.62 (1H, d, J=8.1 Hz), 3.17–3.07 (1H, m), 2.83–2.74 (1H, m), 1.40–1.22 (2H, m), 1.13–1.00 (6H, m), 0.74 (3H, t, J=6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.8, 163.8, 146.1, 142.6, 133.5, 131.7, 127.8, 127.5, 126.3, 122.8, 117.9, 115.0, 114.2, 111.0, 75.6, 43.3, 30.9, 28.0, 26.3, 22.1, 14.2; IR (KBr) 3261, 2952, 2930, 2860, 1727, 1690, 1624, 1479, 1325, 1109, 1024, 943, 749 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{23}N_3O_2$: 349.1790. Found: 349.1793.

3.3.11. Compound ***6k***. Mp 190–192 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.54 (1H, s), 7.66 (1H, d, J=7.5 Hz) 7.52 (1H, d, J=7.5 Hz), 7.39 (1H, t, J=7.5 Hz), 7.33 (1H, s), 7.24 (1H, t, J=7.2 Hz), 7.11 (1H, t, J=7.5 Hz), 6.94 (1H, d, J=7.8 Hz), 6.73 (1H, t, J=7.2 Hz), 6.64 (1H, d, J=7.8 Hz), 3.18–3.11 (1H, dd, J=6.9 and 13.8 Hz), 2.79–2.71 (1H, dd, J=7.5 and 13.5 Hz), 1.58–1.27 (6H, m), 1.06–0.68 (5H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.7, 164.6, 146.2, 142.6, 133.5, 131.7, 127.7, 127.6, 126.6, 122.6, 117.9, 115.3, 114.2, 110.9, 75.7, 48.9, 37.4, 31.1, 31.0, 26.3, 26.0, 25.9; IR (KBr) 3265, 2925, 2851, 1732, 1622, 1483, 1440, 1391, 1322, 1189, 1111, 951, 750 cm^{-1}; HRMS m/z (M^+) calcd for $C_{22}H_{23}N_3O_2$: 361.1790. Found: 361.1791.

3.3.12. Compound ***6l***. Mp 261–263 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.25 (1H, s), 8.30 (1H, s), 7.60 (1H, d, J=7.5 Hz), 7.46 (1H, d, J=6.9 Hz), 7.33 (1H, t, J=7.5 Hz), 7.24 (1H, s), 7.20 (1H, d, J=8.4 Hz), 7.05 (1H, t, J=6.9 Hz), 6.84 (1H, d, J=8.1 Hz), 6.68 (1H, t, J=7.5 Hz), 6.61 (1H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.4, 164.3, 147.2, 142.5, 133.7, 131.2, 129.9, 127.3, 125.7, 122.7, 117.6, 114.8, 114.3, 110.5, 71.4; IR (KBr) 3474, 3288, 3066, 1708, 1621, 1519, 1478, 1326, 1266, 1192, 1151, 1105, 1048, 960, 750 cm^{-1}; HRMS m/z (M^+) calcd for $C_{15}H_{11}N_3O_2$: 265.0851. Found: 265.0847.

3.3.13. Compound ***6m***. Mp 277–279 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.54 (1H, s), 7.74 (1H, s), 7.68 (1H, d, J=8.4 Hz), 7.66 (1H, s), 7.35–7.18 (5H, m), 7.03 (2H, d, J=7.8 Hz), 6.77 (1H, t, J=6.9 Hz), 6.70 (1H, d, J=8.1 Hz), 6.60 (1H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.08, 163.2, 145.7, 140.9, 137.8, 133.7, 133.5, 129.4, 129.2, 128.7, 127.7, 127.4, 117.8, 117.6, 114.5, 114.09, 113.6, 112.09, 76.3; IR (KBr) 3372, 3324, 3247, 1742, 1619, 1484, 1361, 1276, 1190, 1067, 873, 814, 750 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{14}BrN_3O_2$: 419.0269. Found: 419.0272.

3.3.14. Compound ***6n***. Mp 275–277 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.60 (1H, s), 7.80 (1H, s), 7.70–7.66 (2H, m), 7.38–7.30 (2H, m), 7.14–7.08 (4H, m), 6.78 (1H, t, J=7.2 Hz), 6.70 (1H, d, J=8.4 Hz),

6.64 (1H, d, J=8.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.6, 163.6, 146.0, 143.0, 134.0, 133.7, 131.0, 127.4, 126.4, 126.1, 122.8, 117.8, 115.5, 115.3, 114.3, 114.1, 108.9, 76.2. IR (KBr) 3269, 1732, 1641, 1618, 1510, 1482, 1359, 1225, 1195, 954, 823, 750 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{13}BrFN_3O_2$: 437.0175. Found: 437.0174.

3.3.15. Compound ***6o***. Mp 238–240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70 (1H, d, J=7.5 Hz), 7.61 (2H, d, J=7.8 Hz), 7.34–7.13 (5H, m), 7.01 (1H, t, J=6.9 Hz), 6.93 (2H, d, J=7.5 Hz), 6.85 (1H, d, J=8.1 Hz), 6.78 (1H, t, J=7.5 Hz), 6.72 (1H, d, J=8.1 Hz), 3.02 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.8, 163.5, 146.0, 143.1, 137.9, 133.6, 130.9, 128.6, 127.6, 127.4, 126.6, 126.1, 122.7, 117.8, 116.2, 114.5, 114.1, 108.9, 76.1, 25.9; IR (KBr) 3265, 1728, 1636, 1616, 1491, 1362, 1274, 1172, 1128, 1093, 942, 884, 751 cm^{-1}; HRMS m/z (M^+) calcd for $C_{22}H_{17}N_3O_2$: 355.1321. Found: 355.1318.

3.3.16. Compound ***6p***. Mp 232–234 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.71 (1H, d, J=8.1 Hz), 7.60 (1H, d, J=7.5 Hz), 7.58 (1H, s), 7.36–7.25 (2H, m), 7.09–6.94 (3H, m), 6.87 (1H, d, J=7.5 Hz), 6.81–6.71 (4H, m), 3.03 (3H, s), 2.15 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.7, 163.4, 146.0, 143.1, 137.8, 133.5, 130.8, 129.5, 128.2, 128.1, 127.3, 126.6, 126.0, 122.6, 117.7, 114.5, 114.0, 108.8, 76.07, 25.8, 20.5; IR (KBr) 3283, 3059, 2935, 1727, 1643, 1612, 1487, 1356, 1244, 1167, 1125, 1090, 1038, 965, 872, 751 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{19}N_3O_2$: 369.1477. Found: 369.1475.

3.3.17. Compound ***6q***. Mp 220–222 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.68 (1H, d, J=7.8 Hz), 7.64–7.60 (2H, m), 7.34–7.25 (2H, m), 7.05–6.95 (5H, m), 6.86 (1H, d, J=7.8 Hz), 6.77 (1H, t, J=7.8 Hz), 6.69 (1H, d, J=7.5 Hz), 3.01 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.1, 164.1, 146.5, 143.5, 134.6, 134.5, 134.2, 131.5, 127.9, 126.9, 126.6, 123.3, 118.3, 116.1, 115.8, 114.8, 114.6, 109.5, 76.7, 26.4; IR (KBr) 3274, 3061, 2943, 1727, 1640, 1613, 1510, 1354, 1219, 1155, 1130, 1093, 1033, 961, 799, 752 cm^{-1}; HRMS m/z (M^+) calcd for $C_{22}H_{16}FN_3O_2$: 373.1227. Found: 373.1227.

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References and notes

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