Efficient One-Pot Synthesis of Spiro[indoline-3,1′-pyrazolo[1,2-*b*] phthalazine] Derivatives *via* Three-Component Reaction

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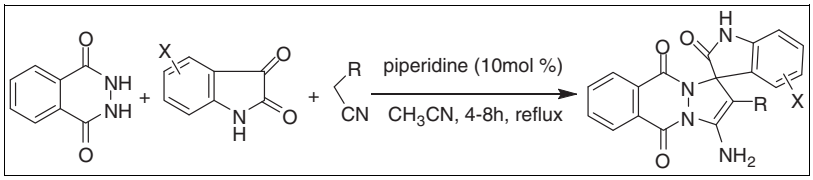

An efficient one-pot synthesis of spiro[indoline-3,1′-pyrazolo[1,2-*b*]phthalazine] derivatives via three-component reaction of phthalhydrazide, isatin, and malononitrile (cyanoacetic ester) is described. This new protocol has the advantages of high efficiency, mild reaction conditions, one-pot procedure, and convenient operation.

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INTRODUCTION

Multicomponent reactions [1] are special types of synthetically useful organic reactions in which three or more different starting materials react to give a final product in a one-pot procedure. Such reactions are one of the best tools in modern organic synthesis to generate compound libraries for screening purposes because of their productivity, simple procedures, convergence, and facile execution [2]. This methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation quite closely approaching the concept of an ideal synthesis and is particularly well adapted for combinatorial synthesis [3].

The indole nucleus is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents [4]. Compounds carrying the indole moiety exhibit antibacterial and antifungal activities [5]. Furthermore, it has been reported that sharing of the indole three-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity [6–8]. The spirocyclic oxindole core is featured in a number of natural alkaloids as well as medicinally relevant compounds [9–14].

Heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically active compounds [15]; among them, such prominent drug molecules are Viagra, Celebrex, and Analginum. On the other hand, phthalazine derivatives have received more and more attention in the recent years because they show some pharmacological and biological activities [16]. Phthalazine derivatives were reported to possess anticonvulsant [17], cardiotonic [18], and vasorelaxant [19] activities. Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives. Therefore, numerous methods have been reported for the synthesis of phthalazine derivatives [20–27].

However, most of the reported procedures describe synthesis of only a narrow range of phthalazines. Thus, there is a need to develop general protocols for efficient preparation of heterocycles containing both spiroindole and phthalazine moiety. In view of these observations, and in continuation of our earlier interest on the developments of new routes to spirooxindole derivatives [28], herein, we investigate a three-component reaction of phthalhydrazide, isatin, and malononitrile (cyanoacetic ester) to afford a series of spiro[indoline-3,1′-pyrazolo[1,2-*b*]phthalazine] derivatives catalyzed by piperidine.

RESULTS AND DISCUSSION

Initially, in order to obtain spiro[indoline-3,1′-pyrazolo [1,2-*b*]phthalazine] derivatives **4**, we tested the three-component reaction of phthalhydrazide **1**, isatin **2a**, and malononitrile **3a** as a simple model reaction in various reaction conditions (Scheme 1). The effects of solvents and catalysts were evaluated for this model reaction, and the results are summarized in Table 1. It was found that when the reaction was carried out in the presence of *p*-TSA, only trace product was detected (Table 1, entry 1). Next, we examined this reaction by using different bases as catalyst (Table 1, entries 2–8). Inorganic bases such as KOH and K_2CO_3 can catalyze this reaction with low yields (Table 1, entries 2 and 3). The use of organic bases led to moderate-to-good product formation (Table 1, entries 4–8), and piperidine was identified as the optimal catalyst with **4a** being isolated in 89% yield (Table 1, entry 7). Subsequently, we further turned to testing the effect of solvents. AcOH, THF, $CHCl_3$, or EtOH showed

Scheme 1

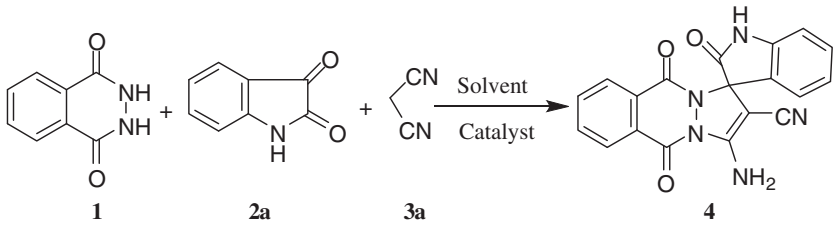


Table 1

Optimization of reaction conditions.

Entry	Conditions	Catalyst	Time (h)	Isolated yield (%)
1	CH_3CN (reflux)	*p*-TSA	4	trace
2	CH_3CN (reflux)	KOH	4	38
3	CH_3CN (reflux)	K_2CO_3	4	36
4	CH_3CN (reflux)	EtONa	4	82
5	CH_3CN (reflux)	TEA	4	81
6	CH_3CN (reflux)	pyridine	4	58
7	CH_3CN (reflux)	piperidine	4	89
8	CH_3CN (reflux)	DABCO	4	58
9	AcOH (90°C)	piperidine	4	72
10	THF (reflux)	piperidine	4	75
11	$CHCl_3$ (reflux)	piperidine	4	80
12	EtOH (reflux)	piperidine	4	78

no superiority to CH_3CN (Table 1, entries 9–12). Therefore, CH_3CN is the solvent of choice for this reaction.

Under the optimized reaction conditions, a series of desired spiro[indoline-3,1′-pyrazolo[1,2-*b*]phthalazine] derivatives **4** were synthesized (Scheme 2, Table 2).

As shown in Table 2, it was found that this method works with a wide variety of substrates. The protocol was effective with different position-substituted isatins. Additionally, the reaction with cyanoacetic ester also proceeded smoothly; however, the reaction time of cyanoacetic ester with isatins and phthalhydrazide was longer than those of malononitrile, and the yields were also slightly lower, which is probably because of the lower reactivities of the cyanoacetic ester.

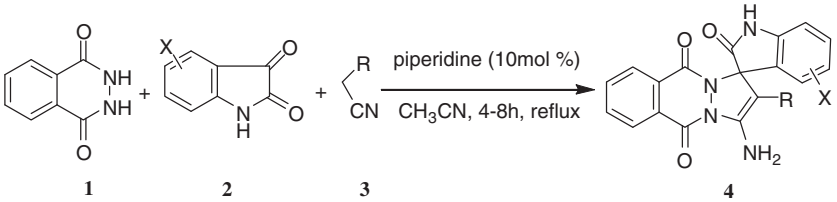
The proposed mechanism for the synthesis of spirooxindole derivative **4** is described in Scheme 3. The process represents a typical cascade reaction in which the isatin **2** first condenses with malononitrile **3** to afford isatylidene malononitrile derivative **A** in the presence of piperidine. This step was regarded as a fast Knoevenagel condensation. Then, **A** is attacked via 1,4-conjugate addition of

Table 2

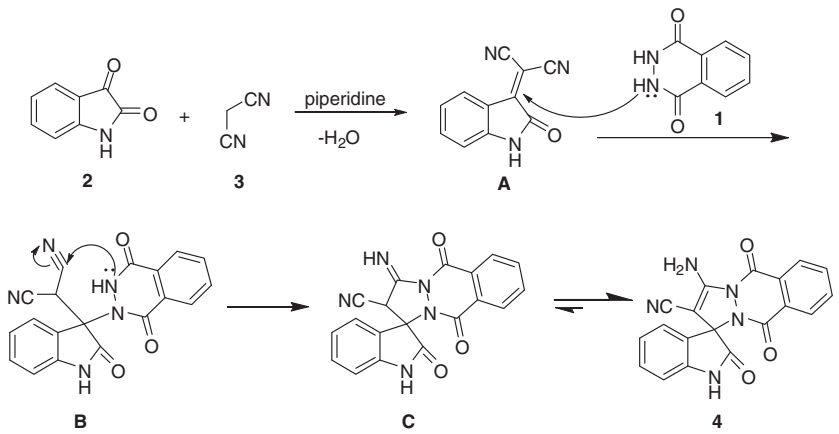
Synthesis of spirooxindole derivatives **4**.

Entry	R	X	Products	Time (h)	Isolated yield (%)
1	CN	H	**4a**	4	89
2	CN	4-Br	**4b**	4	87
3	CN	5-Br	**4c**	4	85
4	CN	6-Br	**4d**	4	85
5	CN	4-Cl	**4e**	4	82
6	CN	5-Cl	**4f**	4	83
7	CN	5-F	**4g**	4	87
8	CO_2Me	H	**4h**	8	79
9	CO_2Et	H	**4i**	8	78
10	CO_2Et	5-F	**4j**	8	80
11	CO_2Pr-*i*	H	**4k**	8	74

Scheme 2



Scheme 3 Proposed mechanism for the synthesis of spirooxindole derivatives **4**.



phthalhydrazide **1** to give the intermediate **B** followed by cyclization affords the corresponding product **4**.

All the products were characterized by ^{1}H NMR, IR, and HRMS spectra. The structure of **4f** was further confirmed by X-ray diffraction analysis. The molecular structure of the product **4f** is shown in Figure 1, and its crystallographic data are shown in Table 3.

In summary, we have described a simple one-pot three-component reaction involving phthalhydrazide, isatin, and malononitrile (cyanoacetic ester) for the synthesis of spiro[indoline-pyrazolo[1,2-*b*]phthalazine] derivatives. Particularly, valuable features of this method include the good yields of the products, broader substrate scope, mild reaction conditions, convenient operation, and the straightforwardness of the procedure, which make it a useful and attractive process for the synthesis of these important compounds.

EXPERIMENTAL

Melting points were determined in open capillaries and uncorrected. IR spectra were recorded on a Varian F-1000 spectrometer

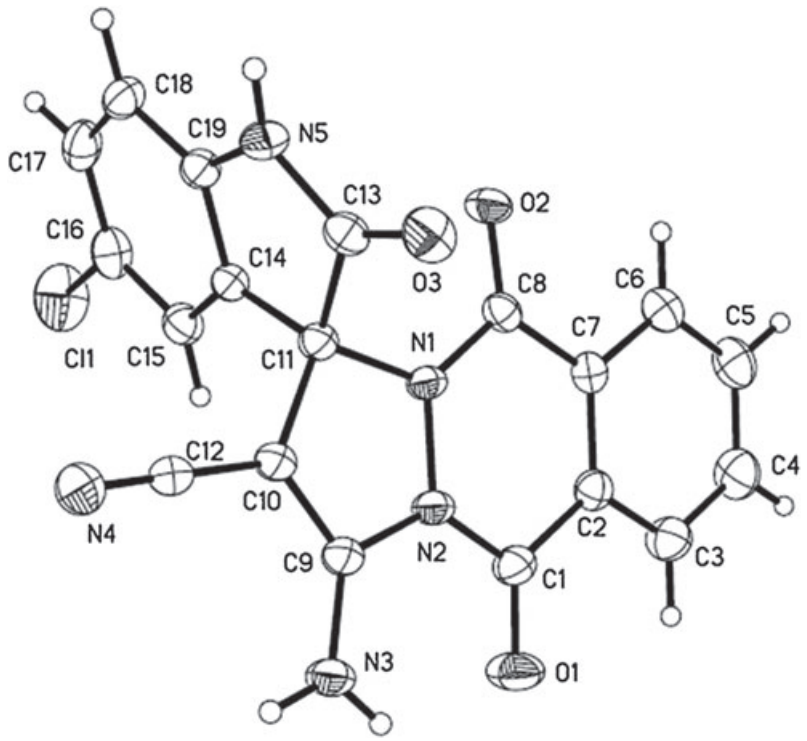


Figure 1. Molecular structure of **4f**.

Table 3

Crystallographic data of compound **4f**.

Empirical formula	$C_{19}H_{10}ClN_5O_3$
Formula weight	391.77
Temperature	223(2) K
Wavelength	0.71075 Å
Crystal system	Monoclinic
Space group	*C*2/*c*
Unit cell dimensions	$a = 25.004(4)$ Å, $\alpha = 90°$ $b = 11.3912(13)$ Å, $\beta = 120.921(3)°$ $c = 14.022(2)$ Å, $\gamma = 90°$
Volume	3426.1(8) $Å^3$
Z	8
Density (calculated)	1.519 Mg/m^3
Absorption coefficient	0.256 mm^{-1}
F(000)	1600
Crystal size	0.60 × 0.40 × 0.30 mm
Theta range for data collection	3.04–27.48°
Limiting indices	$-32 \le h \le 26$, $-12 \le k \le 14$, $-18 \le l \le 18$
Reflections collected	9478
Independent reflections	3898 [R(int) = 0.0302]
Data/restraints/parameters	3898/0/254
Goodness of fit on F^2	1.094
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0502$, $wR_2 = 0.1102$
R indices (all data)	$R_1 = 0.0755$, $wR_2 = 0.1211$
Largest difference peak and hole	0.229 and −0.244 e $Å^{-3}$

in KBr pellet. ^{1}H NMR and ^{13}C NMR spectra were obtained from a solution in DMSO-d_6 with Me_4Si as internal standard using Varian Inova-400 MHz or Inova-300 MHz spectrometer. HRMS analyses were carried out using TOF-MS or GCT-TOF instrument.

General procedure for the synthesis of 4. A mixture of phthalhydrazide (1 mmol), isatin (1 mmol), malononitrile or cyanoacetic ester (1 mmol), and piperidine (0.1 mmol) in CH_3CN (5 mL) was stirred at 80°C for 4–8 h. After completion of the reaction confirmed by TLC (eluent acetone/petroleum ether, 1:2), the reaction mixture was cooled to room temperature. Then, the solvent was removed under vacuum. The solid was recrystallized from ethanol and DMF to afford the pure **4** as a yellow powder.

3′-Amino-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (4a). Mp 263–265°C; IR (potassium bromide): 3350, 3302, 3194, 2208, 1755, 1655, 1570, 1472, 1366, 1259, 1164, 920, 797, 740, 700 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 6.91 (d, J = 7.8 Hz, 1H, ArH), 7.00 (t, J = 7.5 Hz, 1H, ArH), 7.30 (t, J = 7.5 Hz, 1H, ArH), 7.47 (d, J = 7.2 Hz, 1H, ArH), 7.99–8.06 (m, 3H, ArH), 8.29–8.31 (m, 1H, ArH), 8.35 (s, 2H, NH_2), 10.94 (s, 1H, NH); HRMS [Found: *m/z* 357.0862 (M^+), Calcd for $C_{19}H_{11}N_5O_3$: M, 357.0859].

3′-Amino-4-bromo-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′- carbonitrile (4b). Mp >300°C; IR (potassium bromide): 3389, 3330, 3245, 2202, 1757, 1690, 1665, 1615, 1446, 1410, 1374, 1267, 1165, 906, 775, 699 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.98 (d, J = 7.6 Hz, 1H, ArH), 7.20 (d, J = 8.0 Hz, 1H, ArH), 7.30 (t, J = 8.0 Hz, 1H, ArH), 8.04–8.11 (m, 3H, ArH), 8.32–8.35 (m, 1H, ArH), 8.50 (s, 2H, NH_2), 11.26 (s, 1H, NH); HRMS [Found: *m/z* 434.9967 (M^+), Calcd for $C_{19}H_{10}^{79}BrN_5O_3$: M, 434.9967].

3′-Amino-5-bromo-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (4c). Mp >300°C; IR (potassium bromide): 3358, 3228, 3165, 2194, 1749, 1702, 1661, 1612, 1568, 1449, 1414, 1375, 1257, 1171, 1141, 1090, 1058, 923, 826, 694 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.08 (s, 1H, ArH), 7.23 (d, J = 8.0 Hz, 1H, ArH), 7.49 (d, J = 8.0 Hz, 1H, ArH), 7.95–8.14 (m, 3H, ArH), 8.29–8.31 (m, 1H, ArH), 8.41 (s, 2H, NH_2), 11.13 (s, 1H, NH); HRMS [Found: *m/z* 434.9963 (M^+), Calcd for $C_{19}H_{10}^{79}BrN_5O_3$: M, 434.9967].

3′-Amino-6-bromo-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (4d). Mp: 155-157°C; IR (potassium bromide): 3166, 3031, 2979, 2849, 1652, 1619, 1514, 1488, 1430, 1371, 1287, 1186, 900, 801 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) 1.38 (s, 3H, CH_3), 2.04–2.15 (m, 4H, 2 × CH_2), 2.28 (s, 3H, CH_3), 3.37–3.57 (m, 2H, CH_2), 6.16 (s, 1H, NH), 6.55 (d, J = 8.1 Hz, 1H, ArH), 7.18–7.21 (m, 1H, ArH), 7.74 (s, 1H, ArH). HRMS [Found: *m/z* 434.9968 (M^+), Calcd for $C_{19}H_{10}^{79}BrN_5O_3$: M 434.9967].

3′-Amino-4-chloro-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (4e). Mp >300°C; IR (potassium bromide): 3388, 3331, 3247, 3191, 2201, 1759, 1703, 1666, 1619, 1454, 1372, 1267, 1167, 1095, 913, 777, 699 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.95 (d, J = 7.6 Hz, 1H, ArH), 7.06 (d, J = 8.4 Hz, 1H, ArH), 7.38 (t, J = 8.0 Hz, 1H, ArH), 7.95–8.11 (m, 3H, ArH), 8.33–8.35 (m, 1H, ArH), 8.50 (s, 2H, NH_2), 11.28 (s, 1H, NH); HRMS [Found: *m/z* 391.0468 (M^+), Calcd for $C_{19}H_{10}^{35}ClN_5O_3$: M, 391.0472].

3′-Amino-5-chloro-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (4f). Mp 254–255°C; IR (potassium bromide): 3354, 3250, 3193, 2206, 1762, 1657, 1565, 1476, 1366, 1261, 1164, 869, 824, 702 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.88 (d, J = 8.4 Hz, 1H, ArH), 7.31 (d, J = 8.4 Hz, 1H, ArH), 7.86 (s, 1H, ArH), 7.96–8.35 (m, 6H, ArH and NH_2), 11.03 (s, 1H, NH); HRMS Calcd for $C_{19}H_{11}^{35}ClN_5O_3$ [M + H]: 392.0544, found: 392.0542.

3′-Amino-5-fluoro-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (4g). Mp 258–259°C; IR (potassium bromide): 3352, 3246, 3192, 2208, 1759, 1656, 1568, 1485, 1365, 1260, 1171, 792, 700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.93 (q, J = 4.0 Hz, 1H, ArH), 7.15 (t, J = 8.8 Hz, 1H, ArH), 7.50 (d, J = 7.6 Hz, 1H, ArH), 8.01–8.37 (m, 6H, ArH, and NH_2), 10.94 (s, 1H, NH); HRMS Calcd for $C_{19}H_{10}FN_5O_3Na$ [M + Na]: 398.0660, found: 398.0660.

Methyl 3′-amino-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (4h). Mp 267–269°C; IR (potassium bromide): 3436, 3325, 3161, 3071, 3027, 2925, 1733, 1705, 1674, 1620, 1523, 1472, 1384, 1263, 1300, 1141, 1100, 780, 752, 703 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.44 (s, 3H, CH_3O), 6.83 (d, J = 7.6 Hz, 1H, ArH), 6.88 (t, J = 7.6 Hz, 1H, ArH), 7.21 (t, J = 7.6 Hz, 1H, ArH), 7.31 (d, J = 7.6 Hz, 1H, ArH), 7.87–7.89 (m, 1H, ArH), 7.98–8.06 (m, 4H, ArH, and NH_2), 8.29–8.31 (m, 1H, ArH), 10.77 (s, 1H, NH); HRMS [Found: *m/z* 390.0970 (M^+), Calcd for $C_{20}H_{14}N_4O_5$: M, 390.0964].

Ethyl 3′-amino-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (4i). Mp 280–281°C; IR (potassium bromide): 3440, 3332, 2984, 1745, 1704, 1659, 1391, 1296, 1140, 1028, 927, 780, 699 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.88 (t, $J = 6.8$ Hz, 3H, CH_3), 3.84–3.88 (m, 2H, CH_2O), 6.83 (d, $J = 7.6$ Hz, 1H, ArH), 6.89 (t, $J = 7.6$ Hz, 1H, ArH), 7.22 (t, $J = 7.6$ Hz, 1H, ArH), 7.30 (d, $J = 7.2$ Hz, 1H, ArH), 7.87-7.89 (m, 1H, ArH), 7.99-8.07 (m, 4H, ArH, and NH_2), 8.30-8.32 (m, 1H, ArH), 10.71 (s, 1H, NH); HRMS Calcd for $C_{21}H_{16}N_4O_5Na$ [M + Na]: 427.1013, found: 427.1012.

Ethyl 3′-amino-5-fluoro-2,5′,10′-trioxo-5′,10′-dihydro spiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (4j). Mp 294–295°C; IR (potassium bromide): 3442, 3338, 3071, 2983, 1749, 1706, 1656, 1530, 1488, 1397, 1297, 1161, 1032, 886, 794, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.91 (t, $J = 6.0$ Hz, 3H, CH_3), 3.86–3.90 (q, $J = 9.6$ Hz, 2H, CH_2O), 6.82 (q, $J = 4.0$ Hz, 1H, ArH), 7.02–7.07 (m, 1H, ArH), 7.33 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.0$ Hz, 1H, ArH), 7.99–8.32 (m, 9H, ArH, and NH_2), 10.79 (s, 1H, NH); HRMS Calcd for $C_{21}H_{15}FN_4O_5Na$ [M + Na]: 445.0919, found: 445.0916.

Isopropyl 3′-amino-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (4k). Mp 267–269°C; IR (potassium bromide): 3421, 3339, 2976, 1751, 1699, 1662, 1536, 1472, 1394, 1292, 1264, 1143, 1098, 1032, 796, 752, 701 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.66 (s, 3H, CH_3), 1.02 (d, $J = 6.0$ Hz, 3H, CH_3), 4.66-4.70 (m, 1H, CH), 6.83 (d, $J = 7.6$ Hz, 1H, ArH), 6.89 (t, $J = 7.6$ Hz, 1H, ArH), 7.23 (t, $J = 7.6$ Hz, 1H, ArH), 7.30 (d, $J = 7.2$ Hz, 1H, ArH), 7.87-8.30 (m, 6H, ArH and NH_2), 10.77 (s, 1H, NH); HRMS [Found: m/z 418.1274 (M^+), Calcd for $C_{22}H_{18}N_4O_5$: M, 418.1277].

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