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Efficient synthesis of pentasubstituted pyrroles via one-pot reactions of arylamines, acetylenedicarboxylates, and 3-phenacylideneoxindoles

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ABSTRACT

An efficient synthetic method for the pentasubstituted pyrroles was successfully developed via the one-pot domino reactions of arylamines, acetylenedicarboxylates, and 3-phenacylideneoxindoles. The reaction mechanism involved the sequential Michael addition and ring closure of the in situ generated β-active enamino ester.

1. Introduction

The pyrrole ring is widely present in numerous natural products, synthetic pharmaceuticals, and molecular metarials.[1,2] Therefore, considerable attention has been paid to develop efficient methods for the synthesis of these privileged molecules. Classical methods for the synthesis of polysubstituted pyrroles included Knorr reaction, Hantzsch reaction, and Paal–Knorr condensation reaction.[3,4] Recently, new approaches based on the multicomponent reactions and cycloisomerizations have drawn extensive and enduring attentions.[5–8] The multicomponent reactions containing active Huisgen's 1,4-dipoles, which were formed in situ from the addition of nucleophiles to electron-deficient alkynes, have become one of the most efficient methods for preparation of diverse substituted pyrroles. As for some examples, these reactions are included the Huisgen's 1,4-dipoles derived from additions of alkyl(aryl) isocyanides to dimethyl acetylenedicarboxylate are trapped by succinimide,[9] cyclobutene-1,2-diones,[10] and benzoyl chloride.[11] Triarylphosphine induced domino reactions of acetylenedicarboxylates with some unsaturated compounds[12–15] and tertiary amines as well as other catalyst assisted domino reactions[16–18] are also efficient synthetic methods for the functionalized pyrroles. The new approaches toward the syntheses of polysubstituted pyrroles are $FeCl_3$ catalyzed three-component reactions of amines, DMAD, and phenacyl bromide[19] or nitrostyrene.[20] Very recently, Jiang reported three-component reactions of aromatic aldehydes, arylamines, and acetylenedicarboxylates to give 3-arylamino-2-pyrrolidinones.[21] We found that this three-component reaction under acid catalyst afforded novel 3-hydroxy-2-pyrrolidinones.[22] Despite numerous diverse approaches toward the synthesis of pyrroles have been developed so far, the development of new and efficient methods for their synthesis remains an area of current interest. As part of our current studies on investigation of the versatile reactivity of electron-deficient alkynes and the design of new routes for the preparation of biologically active heterocyclic compounds,[23] Here we wish to report an efficient synthetic method for the functionalized pyrroles containing 3-isatinyl group from the one-pot domino reactions of arylamines, acetylenedicarboxylates, and 3-phenacylideneoxindoles.

2. Results and discussions

According to our previously established procedure for the preparation of 3-hydroxy-2-pyrrolidinones by three-component reactions, firstly *p*-methylaniline reacted with dimethyl acetylenedicarboxylate in ethanol to give the active β-enamino ester. Then 3-*p*-chlorophenacylideneoxindole was added to the solution of β-enamino ester, but no reaction was observed both at room or at reflux temperature. Then we tried various Lewis acids as catalyst for his reaction and found that iodine and ferric trichloride showed some catalytic activity. The best result was obtained by using acetic acid both as catalyst and solvent. Thus *p*-methylaniline firstly

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reacted with dimethyl acetylenedicarboxylate in acetic acid at room temperature for the formation of an active β-enamino ester. Then an equal molar of 3-*p*-chlorophenacylideneoxindole was added, and the reaction proceeded smoothly in refluxing acetic acid for 24 h to give the desired pentasubstituted pyrrole **4a** in good yield (74%, Table 1, entry 1). Then various amines and 3-phenacylideneoxindoles with different substituents were utilized under the same reaction conditions. From the results shown in Table 1, we could see that all of the reactions proceeded smoothly to afford the corresponding pentasubstituted pyrroles **4b**–**4k** in satisfactory yields (Table 1, entries 2–11). Arylamines with electron-donating methyl, methoxyl groups and weak electron-withdrawing chloro groups reacted efficiently to yield the desired products. The reaction of benzylamine, α-phenylethylamine, and β-phenylamines also resulted in high yields of the pentasubstituted pyrroles **4l**–**4m** (Table 1, entries 12–14). Diethyl acetylenedicarboxylate could also be successfully used in the reaction (Table 1, entries 16 and 17). The structures of the polysubstituted pyrroles were fully characterized by ^{1}H and ^{13}C NMR, HRMS, IR spectra, and the structure of compound **4e** was further confirmed by single-crystal X-ray diffraction studies (Fig. 1).

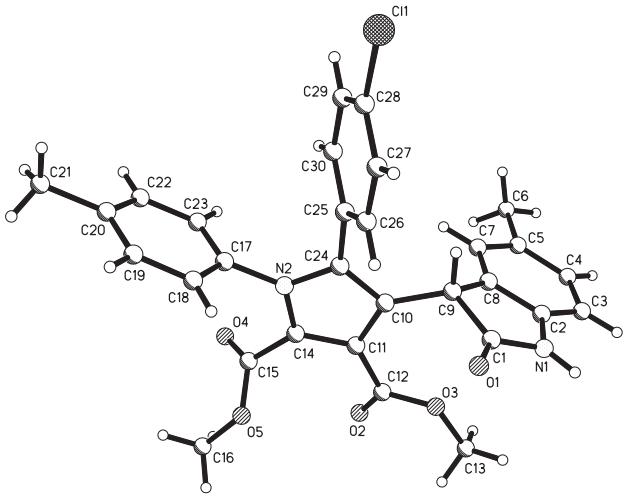
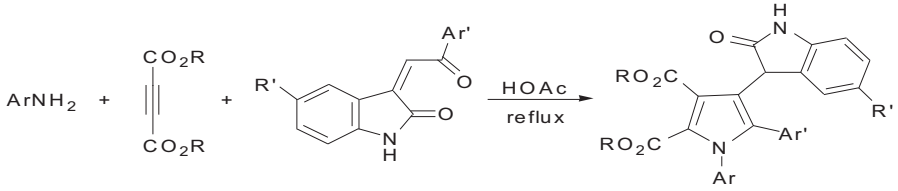


Fig. 1. Molecular structure of polysubstituted pyrrole **4e**.

Table 1
Synthesis of pentasubstituted pyrroles via domino reactions[a]

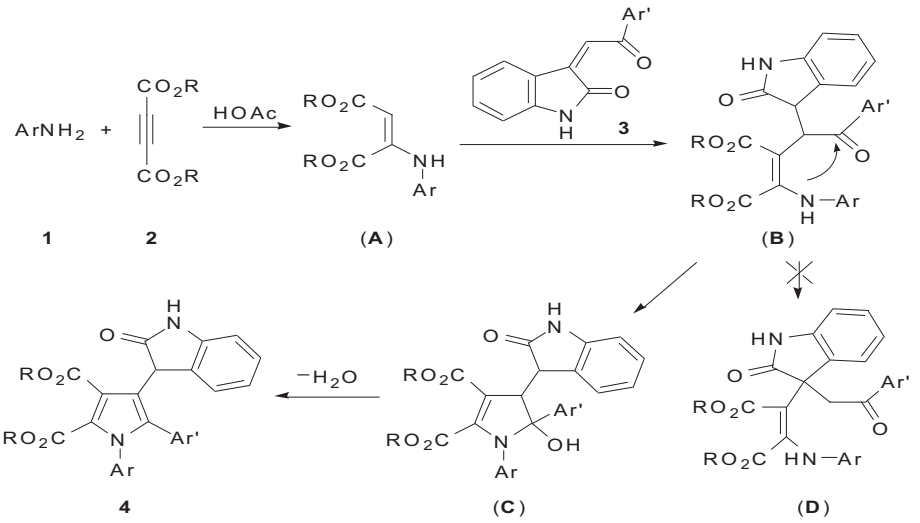


Entry	Compd	Ar	Ar′	R	R′	Yield[b] (%)
1	**4a**	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	CH_3	H	74
2	**4b**	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	CH_3	CH_3	85
3	**4c**	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	CH_3	F	83
4	**4d**	*p*-$CH_3C_6H_4$	C_6H_5	CH_3	CH_3	78
5	**4e**	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	CH_3	CH_3	80
6	**4f**	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	CH_3	Cl	87
7	**4g**	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	CH_3	Cl	88
8	**4h**	*p*-$CH_3C_6H_4$	C_6H_5	CH_3	Cl	76
9	**4i**	*p*-$(CH_3)_3CC_6H_4$	*p*-ClC_6H_4	CH_3	CH_3	81
10	**4j**	C_6H_5	*p*-$CH_3OC_6H_4$	CH_3	Cl	75
11	**4k**	*p*-ClC_6H_4	*p*-ClC_6H_4	CH_3	CH_3	72
12	**4l**	$C_6H_5CH_2$	*p*-ClC_6H_4	CH_3	CH_3	82
13	**4m**	$C_6H_5(CH_3)CH$	*p*-$CH_3C_6H_4$	CH_3	Cl	85
14	**4n**	$C_6H_5CH_2CH_2$	*p*-$CH_3C_6H_4$	CH_3	F	81
15	**4o**	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	CH_3	Cl	89[c]
16	**4p**	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	CH_3CH_2	Cl	77
17	**4q**	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	CH_3CH_2	Cl	79

[a] Reactions were performed with arylamine (2.2 mmol), acetylenedicarboxylate (2.2 mmol) in acetic acid (10.0 mL), rt, 12 h; then 3-phenacylideneoxindoles (2.0 mmol), reflux, 24 h.
[b] Isolated yields based on 3-phenacylideneoxindole.
[c] 1-Benzyl-5-chloro-3-*p*-methylphenacylideneoxindole was used.

The efficient preparation of the functionalized pyrroles containing 3-isatinyl group by this three-component reaction is very interesting. First, despite numerous diverse approaches toward the syntheses of polysubstituted pyrroles with various substituents have been furnished, only a few reports on the synthesis of isatinyl pyrroles were documented in literature.[24–26] Secondly it is unusual to obtain the isatinyl substituted products from the reactions of 3-phenacylideneoxindoles since the reactions of isatin and 3-isatinylidene compounds usually gave the spirocyclic oxindoles[27,28] To explain the mechanism of this one-pot three-component reaction, a plausible reaction course was proposed based on the previously reported reactions, which is illustrated in Scheme 1. The first reaction is the formation of active β-enamino ester (**A**) by the addition of arylamine to acetylenedicarboxylate. Secondly Michael addition of β-enamino ester (**A**) to the exocyclic carbon atom of 3-phenacylideneoxindole gives the intermediate (**B**). Thirdly the intramolecular nucleophilic addition of amino group to carbonyl group in adduct (**B**) produces a cyclic intermediate (**C**). At last the dehydration of (**C**) yields the final isatinyl substituted pyrroles **4**. If β-enamino ester (**A**) attacks the carbon atom at 3-position of 3-phenacylideneoxindole, another kind of adduct (**D**) would be formed and through its further reactions spiro[oxindole-3,4′-pyridine] derivatives might be finally produced. It might be due to more steric hindrance at 3-position of oxindole, the selective reaction of β-enamino ester at exocyclic carbon atom gives the desired oxindole substituted pyrrole derivatives.

In conclusion, we have described a one-pot domino reaction of arylamines, acetylenedicarboxylate, phenacylideneoxindoles and



Scheme 1. The proposed formation mechanism of the polysubstituted pyrroles.

found an efficient procedure for the synthesis of polysubstituted pyrroles, especially with an isatinyl group as substituent. The reaction mechanism was briefly discussed. Prominent among the advantages of this new method are operational simplicity, good yields of products in short reaction times, and easy work-up procedures. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

3. Experimental section

3.1. General

All reagents and solvents were commercial available with analytical grade and used as received. Evaporation removal of organic solvents was carried out with a rotary evaporator in conjunction with a water aspirator. Melting points were taken on a hot-plate microscope apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-600 instrument. IR spectra were obtained on a Bruker Tensor27 spectrometer (KBr disc). HRMS were measured at AB 5800 MALDI-TOF/TOF instrument. X-ray data were collected on a Bruker Smart APEX-2 diffractometer.

3.2. General procedure for the one-pot reactions of arylamines, acetylenedicarboxylate, and 3-phenacylideneoxindoles

A mixture of an arylamine (2.2 mmol) and acetylenedicarboxylate (2.2 mmol) in 10.0 mL acetic acid was stirred at room temperature overnight. Then 3-phenacylideneoxindoles (2.0 mmol) were added. The reaction mixture was refluxed for about 1 day. After adding some water (30 mL), the resulting precipitate was collected by filtration and washed with a small portion of cold ethanol to give the crude product, which was recrystallized in ethanol to give pure product for analysis.

3.2.1. Compound ***4a***. White solid, 74%, mp 258–260 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.45 (s, 1H, NH), 7.37 (br s, 3H, ArH), 7.14–7.00 (m, 7H, ArH), 6.88–6.81 (m, 2H, ArH), 4.36 (br s, 1H, CH), 3.57 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 177.2, 163.3, 160.9, 142.7, 138.1, 134.2, 133.4, 132.6, 129.7, 129.2, 128.2, 128.1, 128.0, 127.7, 127.6, 123.4, 121.0, 116.6, 108.9, 52.2, 50.9, 43.9, 20.5; IR (KBr) ν: 3190, 3083, 2947, 2885, 1710, 1618, 1561, 1514, 1473, 1446, 1359, 1332, 1293, 1250, 1231, 1201, 1170, 1131, 1087, 1038, 1017, 978, 952, 891, 833, 782 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{29}H_{22}ClN_2O_5$ ([M−H]$^-$): 513.1223. Found: 513.1216.

3.2.2. Compound ***4b***. White solid, 85%, mp 280–282 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.31 (s, 1H, NH), 7.35 (br s, 3H, ArH), 7.19 (br s, 2H, ArH), 6.95–6.82 (m, 5H, ArH), 6.68 (br s, 1H, ArH), 4.30 (br s, 1H, CH), 3.73 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 161.0, 158.9, 140.3, 133.4, 132.6, 129.9, 129.8, 129.4, 129.3, 129.2, 128.1, 128.0, 127.8, 124.2, 116.6, 113.7, 109.0, 108.6, 55.2, 52.2, 51.0, 50.8, 20.6; IR (KBr) ν: 3178, 3078, 3039, 2999, 2945, 2918, 2839, 1702, 1626, 1608, 1556, 1512, 1484, 1448, 1400, 1364, 1325, 1298, 1247, 1204, 1173, 1139, 1287, 1033, 977, 953, 883, 838, 805, 780 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{30}H_{24}N_2O_6$ ([M−H]$^-$): 543.1328. Found: 543.132.

3.2.3. Compound ***4c***. White solid, 83%, mp 271–274 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.42 (s, 1H, NH), 7.18–7.09 (m, 5H, ArH), 6.98–6.77 (m, 6H, ArH), 4.35 (br s, 1H, CH), 3.73 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 177.3, 161.1, 158.8, 157.0, 139.0, 137.9, 131.8, 131.7, 130.9, 130.8, 130.7, 129.6, 129.2, 128.8, 127.8, 126.2, 115.5, 113.7, 113.5, 111.3, 109.4, 109.3, 55.2, 52.2, 44.6, 20.7; IR (KBr) ν: 3175, 3132, 3082, 3052, 2995, 2950, 2883, 1734, 1709, 1630, 1562, 1484, 1450, 1364, 1296, 1245, 1191, 1139, 973, 952, 889, 848, 828, 809, 778 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{30}H_{24}FN_2O_6$ ([M−H]$^-$): 527.1624. Found: 527.1616.

3.2.4. Compound ***4d***. White solid, 78%, mp 267–268 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.31 (s, 1H, NH), 7.27–7.12 (m, 9H, ArH), 6.94 (d, J=7.2 Hz, 1H, ArH), 6.82 (s, 1H, ArH), 6.68 (s, 1H, ArH), 4.29 (br s, 1H, CH), 3.57 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 177.4, 163.4, 161.1, 140.3, 138.0, 134.4, 130.9, 130.8, 129.9, 129.1, 128.5, 128.1, 127.7, 124.0, 116.4, 116.3, 108.6, 52.2, 50.7, 44.2, 44.0, 20.6, 20.5; IR (KBr) ν: 3169, 3042, 2946, 2921, 2865, 1700, 1628, 1558, 1514, 1489, 1449, 1402, 1360, 1320, 1290, 1251, 1202, 1177, 1138, 1111, 1089, 1040, 1021, 977, 931, 885, 843, 809, 789, 764 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{30}H_{25}N_2O_5$ ([M−H]$^-$): 493.1769. Found: 493.1763.

3.2.5. Compound ***4e***. White solid, 80%, mp 286–287 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.32 (s, 1H, NH), 7.35 (br s, 3H, ArH), 7.14 (br s, 5H, ArH), 6.94 (d, J=7.2 Hz, 1H, ArH), 6.82 (s, 1H, ArH), 6.68 (br s, 1H,

ArH), 4.35 (br s, 1H, CH), 3.58 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 177.3, 177.2, 163.4, 161.0, 140.3, 138.2, 134.2, 133.4, 132.6, 132.4, 129.9, 129.8, 129.2, 128.8, 128.2, 128.1, 128.0, 127.8, 127.7, 124.1, 116.8, 116.7, 116.6, 108.7, 52.2, 50.9, 43.9, 20.6; IR (KBr) ν: 3189, 3081, 3033, 2945, 1920, 2865, 1701, 1625, 1558, 1154, 1483, 1447, 1363, 1325, 1294, 1253, 1204, 1177, 1139, 1088, 1039, 1018, 979, 953, 880, 832, 807, 778 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{30}H_{24}ClN_2O_5$ ($[M-H]^-$): 527.1371. Found: 527.1374.

3.2.6. Compound ***4f***. White solid, 87%, mp 259–260 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.53 (s, 1H, NH), 7.20–7.06 (m, 8H, ArH), 6.81 (br s, 3H, ArH), 4.35 (br s, 1H, CH), 3.68 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 177.2, 161.2, 159.2, 141.7, 138.0, 134.5, 132.3, 132.2, 129.1, 127.7, 127.3, 125.1, 123.4, 123.3, 121.0, 115.6, 113.6, 110.2, 54.9, 52.2, 50.9, 50.8, 50.7, 44.3, 20.5; IR (KBr) ν: 3191, 3118, 3048, 2946, 2863, 1712, 1616, 1565, 1498, 1477, 1446, 1408, 1362, 1293, 1250, 1204, 1173, 1131, 1112, 1089, 1039, 974, 951, 927, 885, 837, 811, 790 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{30}H_{24}ClN_2O_6$ ($[M-H]^-$): 543.1315. Found: 543.1322.

3.2.7. Compound ***4g***. White solid, 88%, mp 274–276 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.53 (s, 1H, NH), 7.20–7.04 (m, 10H, ArH), 6.80 (br s, 1H, ArH), 4.37 (br s, 1H, CH), 3.57 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 177.1, 163.4, 161.2, 141.8, 138.0, 134.5, 132.1, 130.8, 129.1, 128.8, 127.7, 127.4, 126.1, 125.1, 123.3, 115.5, 110.2, 52.2, 50.9, 44.2, 20.7, 20.6; IR (KBr) ν: 3170, 3040, 2948, 2861, 1711, 1619, 1562, 1514, 1477, 1451, 1403, 1369, 1291, 1252, 1204, 1170, 1131, 1087, 1038, 973, 952, 929, 883, 845, 817, 790 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{30}H_{24}N_2O_5$ ($[M-H]^-$): 527.1379. Found: 527.1371.

3.2.8. Compound ***4h***. White solid, 76%, mp 276–278 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.54 (s, 1H, NH), 7.28–7.13 (m, 10H, ArH), 7.06 (s, 1H, ArH), 6.80 (br s, 1H, ArH), 4.37 (br s, 1H, CH), 3.58 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 178.5, 173.4, 162.5, 143.1, 139.4, 135.7, 133.5, 132.3, 130.5, 130.4, 129.9, 129.5, 129.1, 128.8, 126.5, 124.7, 116.9, 111.6, 53.7, 52.3, 45.6, 22.4, 21.9; IR (KBr) ν: 3160, 3058, 2945, 2751, 1709, 1621, 1556, 1513, 1480, 1451, 1362, 1289, 1251, 1234, 1200, 1169, 1132, 1089, 1039, 1020, 975, 933, 883, 842, 812, 785 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{29}H_{22}ClN_2O_5$ ($[M-H]^-$): 513.1223. Found: 513.1218.

3.2.9. Compound ***4i***. White solid, 81%, mp 266–268 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.33 (s, 1H, NH), 7.37–7.18 (m, 8H, ArH), 6.94 (d, J=7.2 Hz, 1H, ArH), 6.81 (s, 1H, ArH), 6.68 (br s, 1H, ArH), 4.28 (br s, 1H, CH), 3.56 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3), 1.29 (s, 9H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 160.9, 151.1, 140.3, 135.2, 134.2, 133.4, 132.6, 132.1, 129.9, 129.7, 129.5, 128.2, 128.1, 127.8, 127.5, 126.8, 125.4, 124.1, 116.8, 108.7, 52.3, 52.2, 44.0, 34.4, 30.9, 20.6; IR (KBr) ν: 3166, 3034, 2966, 2948, 1708, 1627, 1565, 1514, 1484, 1447, 1403, 1356, 1322, 1295, 1246, 1205, 1177, 1139, 1087, 1039, 1017, 983, 954, 884, 833, 805 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{33}H_{30}N_2O_5$ ($[M-H]^-$): 569.1849. Found: 569.184.

3.2.10. Compound ***4j***. White solid, 75%, mp 236–238 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.63 (s, 1H, NH), 7.33–7.18 (m, 8H, ArH), 7.06 (s, 1H, ArH), 6.82 (br s, 3H, ArH), 4.40 (br s, 1H, CH), 3.67 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 161.0, 159.2, 141.8, 137.1, 133.4,,132.3, 132.2, 132.1, 128.6, 128.5, 128.0, 127.4, 125.1, 123.3, 120.9, 115.6, 113.6, 110.3, 55.0, 52.0, 50.9; IR (KBr) ν: 2949, 2837, 1736, 1691, 1613, 1563, 1525, 1496, 1450, 1390, 1356, 1290, 1249, 1219, 1174, 1133, 1111, 1088, 1027, 963, 920, 886, 841, 814, 787 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{29}H_{22}ClN_2O_6$ ($[M-H]^-$): 529.1172. Found: 529.1163.

3.2.11. Compound ***4k***. White solid, 72%, mp 297–299 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.32 (s, 1H, NH), 7.42 (d, J=7.2 Hz, 3H, ArH), 7.33–7.32 (m, 5H, ArH), 6.95 (d, J=7.8 Hz, 1H, ArH), 6.83 (s, 1H, ArH), 6.68 (br s, 1H, ArH), 4.40 (br s, 1H, CH), 3.59 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 177.7, 161.0, 160.1, 140.8, 140.6, 139.1, 137.6, 136.4, 134.1, 133.8, 133.7, 133.2, 133.0, 132.9, 131.0, 130.8, 130.5, 130.4, 130.0, 129.2, 128.8, 128.6, 128.5, 128.4, 128.3, 126.9, 125.6, 124.8, 123.7, 119.7, 117.4, 109.6, 109.2, 52.7, 51.6, 44.7, 44.3, 21.1; IR (KBr) ν: 3084, 3035, 2945, 1703, 1626, 1557, 1523, 1491, 1446, 1397, 1361, 1324, 1295, 1253, 1239, 1203, 1139, 1085, 1037, 1014, 978, 952, 850, 833, 805 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{29}H_{21}Cl_2N_2O_5$ ($[M-H]^-$): 547.0833. Found: 547.0825.

3.2.12. Compound ***4l***. White solid, 82%, mp 206–208 °C; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.82 (s, 1H, NH), 7.24–7.16 (m, 7H, ArH), 6.94 (d, J=7.8 Hz, 1H, ArH), 6.85 (br s, 3H, ArH), 6.70 (br s, 1H, ArH), 5.32 (s, 2H, CH_2), 4.42 (br s, 1H, CH), 3.70 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 178.8, 164.7, 161.4, 139.0, 137.4, 135.5, 131.7, 128.6, 128.2, 127.7, 127.4, 126.1, 124.9, 124.2, 120.3, 109.2, 52.1, 51.5, 49.7, 44.4, 21.1; IR (KBr) ν: 3197, 3035, 2952, 1706, 1626, 1555, 1515,,1481, 1459, 1439, 1409, 1347, 1317, 1286, 1232, 1161, 1121, 1095, 1057, 1016, 982, 947, 894, 836, 808, 768 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{30}H_{24}ClN_2O_5$ ($[M-H]^-$): 527.1379. Found: 527.1372.

3.2.13. Compound ***4m***. White solid, 85%, mp 256–257 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.53 (s, 1H, NH), 7.31–7.27 (m, 6H, ArH), 7.15–7.02 (m, 4H, ArH), 6.91–6.78 (m, 2H, ArH), 5.39 (s, 1H, CH), 4.37–4.11 (m, 1H, CH), 3.36–3.29 (m, 6H, OCH_3), 2.32 (s, 3H, CH_3), 1.80 (d, J=48.6 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 177.0, 162.4, 162.3, 141.7, 139.5, 139.4, 138.9, 132.4, 132.1, 131.2, 131.1, 130.9, 129.3, 128.1, 127.4, 127.3, 127.2, 127.1, 126.6, 126.5, 126.4, 126.3, 125.0, 124.9, 123.0, 115.1, 110.1, 110.0, 56.0, 55.5, 52.1, 52.0, 50.5, 50.4, 44.3, 20.8, 19.0, 18.9; IR (KBr) ν: 3325, 3027, 2980, 2947, 1729, 1707, 1619, 1565, 1520, 1480, 1451, 1376, 1352, 1330, 1282, 1231, 1168, 1106, 1063, 968, 927, 885, 817, 788 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{31}H_{26}ClN_2O_5$ ($[M-H]^-$): 541.1536. Found: 541.1527.

3.2.14. Compound ***4n***. White solid, 81%, mp 187–188 °C; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.50 (s, 1H, NH), 7.22–7.19 (m, 5H, ArH), 7.04 (br s, 1H, ArH), 6.89–6.88 (m, 2H, ArH), 6.86–6.83 (m, 2H, ArH), 6.72 (br s, 2H, ArH), 4.44 (br s, 1H, CH), 4.30–4.28 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 2.87–2.82 (m, 2H, CH_2), 2.36 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 179.3, 161.7, 159.7, 158.1, 139.3, 137.6, 131.2, 130.4, 129.3, 128.8, 128.6, 126.6, 126.2, 125.5, 114.1, 113.9, 110.0, 109.9, 52.1, 51.4, 47.8, 44.9, 37.7, 21.3; IR (KBr) ν: 3331, 2949, 2837, 1736, 1691, 1613, 1562, 1496, 1449, 1389, 1356, 1290, 1249, 1219, 1174, 1133, 1111, 1088, 1026, 962, 919, 885, 841, 786 cm^{-1}; MS (m/z): HRMS (ESI) calcd for $C_{31}H_{26}FN_2O_5$ ($[M-H]^-$): 525.1831. Found: 525.1825.

3.2.15. Compound ***4o***. White solid, 89%, mp 177–179 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 7.40 (s, 2H, ArH), 7.32–7.22 (m, 6H, ArH), 7.15 (br s, 7H, ArH), 6.85 (br s, 1H, ArH), 5.00–4.61 (m, 3H, CH_2, CH), 3.58 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 176.6, 164.8, 162.5, 143.6, 139.4, 137.6, 135.8, 132.7, 132.2, 130.5, 130.1, 129.8, 129.1, 128.8, 128.7, 127.5, 124.7, 116.7, 111.1, 53.6, 52.4, 45.0, 44.7, 22.1, 21.9; IR (KBr) ν: 3027, 2947, 2918, 2888, 1711, 1608, 1563, 1515, 1492, 456, 1430, 1356, 1302, 1251, 1218, 1189, 1166, 1129, 1089, 1020, 969, 927, 895, 847,

816, 775 cm^{-1}; MS (*m*/*z*): HRMS (ESI) calcd for $C_{37}H_{30}ClN_2O_5$ ($[M-H]^-$): 617.1849. Found: 617.1833.

3.2.16. Compound ***4p***. White solid, 77%, mp 246–248 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.54 (s, 1H, NH), 7.26–7.07 (m, 6H, ArH), 6.88–6.79 (m, 5H, ArH), 4.33 (br s, 1H, CH), 4.03–4.00 (m, 2H, CH_2), 3.78 (br s, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 1.03–0.97 (m, 6H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 160.5, 159.2, 158.8, 141.8, 141.7, 132.3, 132.1, 129.8, 129.4, 127.6, 127.3, 125.1, 123.4, 121.2, 113.6, 110.2, 60.8, 59.7, 55.2, 55.0, 13.6, 13.5; IR (KBr) ν: 3166, 2968, 2936, 2838, 1709, 1615, 1569, 1513, 1474, 1449, 1410, 1377, 1297, 1247, 1201, 1173, 1129, 1084, 1032, 941, 909, 886, 835, 810, 790 cm^{-1}; MS (*m*/*z*): HRMS (ESI) calcd for $C_{32}H_{28}ClN_2O_7$ ($[M-H]^-$): 587.1591. Found: 587.158.

3.2.17. Compound ***4q***. White solid, 79%, mp 258–260 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.54 (s, 1H, NH), 7.20–7.18 (m, 2H, ArH), 7.14–7.06 (m, 8H, ArH), 6.79 (br s, 1H, ArH), 4.35 (br s, 1H, CH), 4.05–4.00 (m, 2H, CH_2), 3.79 (br s, 2H, CH_2), 2.26 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 1.02–0.98 (m, 6H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 177.6, 163.6, 161.0, 142.3, 138.4, 135.1, 132.5, 131.3, 131.0, 129.5, 129.3, 129.1, 128.3, 127.8, 126.7, 125.5, 123.9, 116.6, 115.7, 110.7, 61.4, 60.2, 44.7, 44.6, 21.2, 21.0, 14.1, 13.9; IR (KBr) ν: 3166, 3047, 2977, 2859, 1708, 1616, 1573, 1517, 1499, 1471, 1448, 1411, 1294, 1247, 1200, 1168, 1123, 1081, 1038, 1018, 994, 937, 908, 883, 859, 814, 786 cm^{-1}; MS (*m*/*z*): HRMS (ESI) calcd for $C_{32}H_{28}ClN_2O_5$ ($[M-H]^-$): 555.1665. Found: 555.1683.

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Supplementary data

Crystallographic data of **4e** (CCDC 869520) have been deposited at the Cambridge Crystallographic Database Centre. These data can be obtained free of charge via www.ccdc.ac.ck./data_request/cif. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.056.

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