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Soluble Poly(ethylene glycol) Supported Efficient Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles

Zheng Li, Jingya Yang, Junke Wang, and Xicun Wang

Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu, 730070, People's Republic of China

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ABSTRACT: *An efficient soluble poly(ethylene glycol) (PEG) supported liquid-phase parallel synthetic method for 2,5-disubstituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles is described. 2-Aryl-5-(4′-methoxycarbonylphenoxymethyl)-1,3,4-oxadiazoles and 2-aryloxymethyl-5-(4′-methoxycarbonylphenoxyacetamido)-1,3,4-thiadiazoles are synthesized in high yield and high purity using this polymer supported strategy.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:664–669, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20253

INTRODUCTION

Substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles have been of interest to the medicinal chemist for many years. They have been shown to possess antimicrobial [1], antimitotic [2], anti-inflammatory [3], insecticidal [4], antitubercular [5], and anticonvulsant [1]activities. They have been synthesized by traditional method with several approaches. Three of the more popular for 1,3,4-oxadiazoles are the cyclization of diacylhydrazides [6], the cyclization of acylthiosemicarbazides [7], and the oxidation of acylhydrozones [8]. One of the popular for 1,3,4-thiadiazoles is the cyclization of acylthiosemicarbazides [9]. Unfortunately, one major drawback of the conventional method lies in the fact that it often provides low to moderate yields of the desired target products, recrystallization and chromatography steps are inevitable, and the resultant loss of products cannot be neglected in some cases.

Recently, organic synthesis of small molecular compounds on soluble polymers, i.e. liquid-phase chemistry, has increasingly become the attractive field [10]. It couples the advantages of homogeneous solution chemistry (high reactivity and ease of analysis without the cleavage procedure) and those of solid-phase chemistry (use of excessive reagents and easy isolation and purification of products). Moreover, because of the homogeneity of liquid-phase reactions, the reaction conditions can be easily shifted from solution-phase systems without large changes, and the amount of the excessive reagents is less than that in solid-phase reactions. Among the various soluble polymers, poly(ethylene glycol) (PEG) is the most useful and promising.

Based on the above facts, herein we report an easy handling liquid-phase synthetic strategy for a library of 2,5-disubstituted 1,3,4-oxadiazoles and 2,5-disubstituted 1,3,4-thiadiazoles by using PEG as soluble polymer support. To the best our knowledge, this is the first example of liquid-phase polymer supported synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles.

Correspondence to: Zheng Li; e-mail:lizheng@nwnu.edu.cn.
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RESULTS AND DISCUSSION

PEG-bound phenoxyacetyl chloride (**1**) (PEG-6000 as support) was prepared according to our previously reported procedure [11]. Compound **1** was reacted with a variety of substituted aroyl hydrazines in CH_2Cl_2 using pyridine as a catalyst at room temperature to afford PEG-bound diacyl hydrazines (**2a–j**) in high yield. Compounds **2a–j** were further refluxed with $POCl_3$to efficiently give PEG-bound disubstituted 1,3,4-oxadiazoles (**3a–j**). Compounds **3a–j** were purified by precipitation and washed with ether, and further cleaved from the polymer via transesterification with sodium methoxide in methanol to afford targeted compounds, 2-aryl-5-(4′-methoxycarbonylphenoxymethyl)-1,3,4-oxadiazoles (**4a–j**), in 74–90% overall yield (based on compound **1**) (Scheme 1).

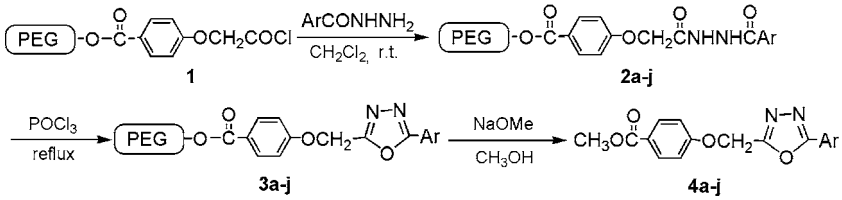
PEG-bound phenoxyacetyl chloride (**1**) (PEG-6000 as support) on treatment with ammonium thiocyanate at ambient temperature gave PEG-bound isocyanate **5** as an intermediate. It is noteworthy to mention that the conventional solution reactions to prepare isocyanates without polymer support have to perform the reactions in the presence of phase transfer catalyst (PTC) [12] such as PEG-400, quaternary ammonium salts. However, the current reaction for compound **5** can readily take place without any additional PTC. Consequently, we concluded that PEG support in this reaction also acted as a PTC. It can easily form complex $[PEG\text{-}NH_4]^+SCN^-$ with ammonium thiocyanate to make the nucleophilic substitution to carry out smoothly. The similar situation was also reported by Lamaty and coworkers [13]. Compound **5** in situ reacted with aryloxyacetyl hydrazines at room temperature to afford PEG-bound di(aryloxyacetyl)thiosemicarbazides **6a–k** in high yield. The whole course of the reactions was easily followed by TLC analysis (observation of disappearing aryloxyacetyl hydrazines). Compounds **6a–k** were refluxed in glacial acetic acid to give PEG-bound disubstituted 1,3,4-thiadiazoles **7a–k**. Compounds **7a–k** were purified by precipitation and washed with ether, and further cleaved from the support with sodium methoxide in methanol to afford the desired compounds, 2-aryloxymethyl-5-(4′-methoxycarbonylphenoxyacetamido)-1,3,4-thiadiazoles (**8a–k**), in 76–89% overall yield (based on compound **1**). Other basic reagents such as sodium hydroxide, ammonia, and potassium carbonate were also tested for the cleavage reaction, but low yield and some separating problems were usually encountered (Scheme 2).

The title compounds **4a–j, 8a–k** were characterized by ^{1}H NMR, MS, IR, and elemental analyses. Each crude product was then analyzed by HPLC and gave around 91–99% purity (Table 1).

In summary, we have devised a soluble polymer supported methodology for the controlled stepwise synthesis of 2,5-disubstituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. Reactions involved here are highly efficient in giving the desired compounds in high yield and high purity just by simple precipitation and washings. This method is versatile and adaptable for the parallel synthesis of the targeted structures on the soluble polymer support.

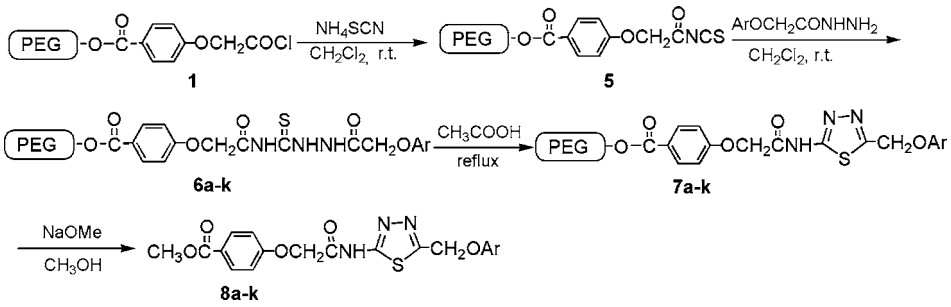
EXPERIMENTAL

IR spectra were recorded using KBr pellets on a Nicolet AVATAR 360 FT-IR spectrophotometer and ^{1}H NMR spectra on a Avanci-D2X-200 instrument using $CDCl_3$ and DMSO-d_6 as solvents and Me_4Si as internal standard. Mass spectra were recorded on a QP-1000A GC-MS using the impact mode (70 eV). Elemental analyses were performed on a Vario El elemental analysis instrument. The product purity was determined using 1671-CHA HPLC (Shimadzu, Japan) with UV–VIS detector. Melting points were determined with an electrothermal melting point apparatus and uncorrected. PEG-bound phenoxyacetyl chloride (**1**) [11], aroyl hydrazines



Ar=C_6H_5 (**a**), 3-$CH_3C_6H_4$ (**b**), 4-$CH_3C_6H_4$ (**c**), 3-$O_2NC_6H_4$ (**d**), 4-$O_2NC_6H_4$ (**e**), 2-ClC_6H_4 (**f**), 4-ClC_6H_4(**g**), 4-$CH_3OC_6H_4$ (**h**), 2-IC_6H_4 (**i**), 4-IC_6H_4 (**j**)

SCHEME 1



Ar=C_6H_5 (**a**), 2-$CH_3C_6H_4$ (**b**), 3-$CH_3C_6H_4$ (**c**), 4-$CH_3C_6H_4$ (**d**), 4-$O_2NC_6H_4$ (**e**), 4-ClC_6H_4 (**f**), 2, 4-$Cl_2C_6H_3$ (**g**), 4-$CH_3OC_6H_4$ (**h**), 2-$CH_3OC_6H_4$ (**i**), 1-Naphthyl (**j**), 2-Naphthyl (**K**)

SCHEME 2

[14], and aryloxyacetyl hydrazines [15] were prepared according to the literature procedures.

General Procedure for Preparation of **2a–j**

To the solution of PEG-bound phenoxyacetyl chloride (**1**) (3.19 g, 0.5 mmol) in 15 mL of CH_2Cl_2, aroyl hydrazines (2 mmol) and 1 to 2 drops of pyridine were added. The mixture was stirred at room temperature for 4 h, then the solution was concentrated into a third of its volume under reduced pressure, and the appropriate volume of diethyl ether was added until the precipitation was completed. The precipitate was collected by filtration and washed with diethyl ether to obtain **2a–j** (90–99% yield based on compound **1**).

General Procedure for Preparation of **3a–j**

The compounds **2a–j** (0.5 mmol) in 15 mL of $POCl_3$ were refluxed for 8 h, then excess of $POCl_3$ was removed under vacuum. Ether (10–15 mL) was added into the residue and stirred for several minutes. Then the white solid was collected by filtration and washed with diethyl ether to give compounds **3a–j** (88–96% yield based on compounds **2a–j**).

TABLE 1 The PEG-Supported Liquid-Phase Synthesis of **4a–j** and **8a–k**

Product	*Ar*	*mp (°C)*	*Overall Yield (%)*[a]	*Crude Purity (%)*[b]
4a	C_6H_5	184–185	78	96
4b	3-$CH_3C_6H_4$	167–169	82	94
4c	4-$CH_3C_6H_4$	182–183	87	97
4d	3-$O_2NC_6H_4$	190–191	89	93
4e	4-$O_2NC_6H_4$	207–208	74	96
4f	2-ClC_6H_4	173–174	87	98
4g	4-ClC_6H_4	127–128	90	93
4h	4-$CH_3OC_6H_4$	205–206	78	92
4i	2-IC_6H_4	177–178	83	98
4j	4-IC_6H_4	217–218	88	95
8a	C_6H_5	204–205	82	93
8b	2-$CH_3C_6H_4$	143–144	89	95
8c	3-$CH_3C_6H_4$	137–138	86	99
8d	4-$CH_3C_6H_4$	162–163	81	92
8e	4-$O_2NC_6H_4$	195–197	80	99
8f	4-ClC_6H_4	210–211	87	98
8g	2,4-$Cl_2C_6H_3$	255–256	79	93
8h	4-$CH_3OC_6H_4$	198–199	78	92
8i	2-$CH_3OC_6H_4$	209–210	76	98
8j	1-Naphthyl	219–220	80	95
8k	2-Naphthyl	235–237	79	91

[a]Yield based on compound **1**.
[b]Purity determined by HPLC analysis (UV detection at $\lambda = 254$ nm, gradient elution acetonitrile/water (v/v) = 80:20) of crude products.

General Procedure for Preparation of **4a–j**

To the solution of sodium methoxide (0.06 g, 1.1 mmol) in 15 mL of methanol, the compounds **4a–j** (0.5 mmol) were added. The solution was stirred for 8 h at room temperature. Then the solvent was removed under reduced pressure, the residue was acidified with diluted HCl (0.2 M) until the pH 5–6, and the precipitate was formed. After the filtration, the solid was washed with warm water to give compounds **4a–j** as products (94–98% yield based on compounds **3a–j**). The analytic data for compounds **4a–j** are given below:

4a: White powder. IR (KBr): $\nu = 1714$ (C=O), 1603 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.96–7.92 (m, 9H, Ar-H), 5.48 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3). MS *m/z*: 310 (M^+). Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.93; H, 4.46; N, 8.85.

4b: White powder. IR (KBr): $\nu = 1708$ (C=O), 1594 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.94–7.94 (m, 8H, Ar-H), 5.47 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3). MS *m/z*: 324 (M^+). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.73; H, 5.01; N, 8.55.

4c: White powder. IR (KBr): $\nu = 1721$ (C=O), 1601 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.93–7.91 (m, 8H, Ar-H), 5.52 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3). MS *m/z*: 324 (M^+). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.58; H, 4.89; N, 8.61.

4d: White powder. IR (KBr): $\nu = 1708$ (C=O), 1603 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.21–8.67 (m, 8H, Ar-H), 5.64 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3). MS *m/z*: 355 (M^+). Anal. Calcd for $C_{17}H_{13}N_3O_6$: C, 57.47; H, 3.69; N,11.83. Found: C, 57.58; H, 3.74; N, 11.76.

4e: White powder. IR (KBr): $\nu = 1723$ (C=O), 1600 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.15–8.23 (m, 8H, Ar-H), 5.62 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3). MS *m/z*: 355 (M^+). Anal. Calcd for $C_{17}H_{13}N_3O_6$: C, 57.47; H, 3.69; N,11.83. Found: C, 57.40; H, 3.62; N, 11.89.

4f: White powder. IR (KBr): $\nu = 1700$ (C=O), 1601 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.98–7.98 (m, 8H, Ar-H), 5.54 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3). MS *m/z*: 344 (M^+). Anal. Calcd for $C_{17}H_{13}ClN_2O_4$: C, 59.23; H, 3.80; N,8.13. Found: C, 59.31; H, 3.87; N, 8.21.

4g: White powder. IR (KBr): $\nu = 1703$ (C=O), 1599 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.96–7.94 (m, 8H, Ar-H), 5.52 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3). MS *m/z*: 344 (M^+). Anal. Calcd for $C_{17}H_{13}ClN_2O_4$: C, 59.23; H, 3.80; N, 8.13. Found: C, 59.15; H, 3.89; N, 8.18.

4h: White powder. IR (KBr): $\nu = 1711$ (C=O), 1589 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.94–7.90 (m, 8H, Ar-H), 5.46 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3). MS *m/z*: 340 (M^+). Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.58; H, 4.81; N, 8.16.

4i: White powder. IR (KBr): $\nu = 1719$ (C=O), 1603 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.98–7.94 (m, 8H, Ar-H), 5.50 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3). MS *m/z*: 436 (M^+). Anal. Calcd for $C_{17}H_{13}IN_2O_4$: C, 46.81; H, 3.00; N, 6.42. Found: C, 46.75; H, 3.08; N, 6.37.

4j: White powder. IR (KBr): $\nu = 1719$ (C=O), 1603 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.90–7.92 (m, 8H, Ar-H), 5.53 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3). MS *m/z*: 436 (M^+). Anal. Calcd for $C_{17}H_{13}IN_2O_4$: C, 46.81; H, 3.00; N,6.42. Found: C, 46.88; H, 3.11; N, 6.34.

General Procedure for Preparation of **5** *and* **6a–k**

The suspension of compound **1** (3.20 g, 0.5 mmol) and ammonium thiocyanate (0.15 g, 2 mmol) in 15 mL of CH_2Cl_2 was stirred for 5 h at room temperature to afford **5** as an intermediate. Then aryloxyacetyl hydrazines (2 mmol) were added, and the mixture was stirred for another 2 h at room temperature. The resulting mixture was filtered to remove the insoluble salts, and the solution was concentrated into a third of its volume under reduced pressure. Then the appropriate volume of diethyl ether was added until the precipitation was completed. The precipitate was collected by filtration and washed with diethyl ether to obtain compounds **6a–k** (90–99% yield based on compound **1**). The purity of **6a–k** was monitored by TLC (observing the disappearance of aryloxyacetyl hydrazines) by using acetone and petroleum ether (1:3) as eluent.

General Procedure for Preparation of **7a–k**

The solution of compounds **6a–k** (0.5 mmol) in 10 mL of glacial acetic acid was refluxed for 7 h, then the excess of glacial acetic acid was removed under reduced pressure, and the residue was washed with diethyl ether (2×10 mL) to give **7a–k** as solids (>96% yield based on compounds **6a–k**).

General Procedure for Preparation of **8a–k**

To the solution of sodium methoxide (0.06 g, 1.1 mmol) in 15 mL of methanol, compounds **7a–k** (0.5 mmol) were added. The solution was stirred

for 8 h at room temperature. Then the solvent was removed under reduced pressure, and the residue was acidified with diluted HCl (0.2 M) until the pH 5 and the precipitate was formed. After the filtration, the solid was washed with 5% $NaHCO_3$ and hot water, respectively, to give compounds **8a–k** as products (>99% yield based on compounds **7a–k**). The analytic data for compounds **8a–k** are given below:

8a: White powder. IR (KBr): $\nu = 3103$ (N—H), 1721, 1684 (C=O), 1605, 1512 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.93$ (s, 1H, NH), 7.02–8.13 (m, 9H, Ar-H), 5.51 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3). MS *m/z*: 399 (M^+). Anal. Calcd for $C_{19}H_{17}N_3O_5S$: C, 57.13; H, 4.29; N, 10.52. Found: C, 57.03; H, 4.33; N, 10.45.

8b: White crystalline solid. IR (KBr): $\nu = 3105$ (N—H), 1724, 1684 (C=O), 1605, 1501 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.90$ (s, 1H, NH), 6.94–8.00 (m, 8H, Ar-H), 5.49 (s, 2H, CH_2), 5.02 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3). MS *m/z*: 413 (M^+). Anal. Calcd for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16. Found: C, 58.21; H, 4.57; N, 10.21.

8c: White crystalline solid. IR (KBr): $\nu = 3168$ (N—H), 1711, 1691 (C=O), 1611, 1499 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.91$ (s, 1H, NH), 6.79–8.10 (m, 8H, Ar-H), 5.50 (s, 2H, CH_2), 5.01 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3). MS *m/z*: 413 (M^+). Anal. Calcd for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16. Found: C, 57.93; H 4.72; N, 10.25.

8d: White crystalline solid. IR (KBr): $\nu = 3216$ (N—H), 1719, 1690 (C=O), 1605, 1500 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.92$ (s, 1H, NH), 7.02–8.10 (m, 8H, Ar-H), 5.50 (s, 2H, CH_2), 5.02 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3). MS *m/z*: 413 (M^+). Anal. Calcd for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16. Found: C, 58.21; H, 4.68; N, 10.20.

8e: Yellow crystalline solid. IR (KBr): $\nu = 3115$ (N—H), 1725, 1688 (C=O), 1605, 1511 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.94$ (s, 1H, NH), 7.02–8.13 (m, 8H, Ar-H), 5.60 (s, 2H, CH_2), 5.04 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3). MS *m/z*: 444 (M^+). Anal. Calcd for $C_{19}H_{16}N_4O_7S$: C, 51.35; H, 3.63; N, 12.61. Found: C, 51.21; H, 3.55; N, 12.49.

8f: Pale yellow, crystalline solid. IR (KBr): $\nu = 3186$ (N—H), 1718, 1692 (C=O), 1608, 1501 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.93$ (s, 1H, NH), 6.97–7.94 (m, 8H, Ar-H), 5.51 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3). MS *m/z*: 433 (M^+). Anal. Calcd for $C_{19}H_{16}ClN_3O_5S$: C, 52.60; H, 3.72; N, 9.69. Found: C, 52.71; H, 3.76; N, 9.78.

8g: Yellow powder. IR (KBr): $\nu = 3188$ (N—H), 1726, 1693 (C=O), 1621, 1489 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.94$ (s, 1H, NH), 6.84–8.05 (m, 7H, Ar-H), 5.52 (s, 2H, CH_2), 5.04 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3). MS *m/z*: 467 (M^+). Anal. Calcd for $C_{19}H_{15}Cl_2N_3O_5S$: C, 48.73; H, 3.23; N, 8.97. Found: C, 48.88; H, 3.17; N, 8.86.

8h: White crystalline solid. IR (KBr): $\nu = 3305$ (N—H), 1719, 1690 (C=O), 1605, 1500 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.89$ (s, 1H, NH), 6.84–7.92 (m, 8H, Ar-H), 5.42 (s, 2H, CH_2), 5.00 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3). MS *m/z*: 429 (M^+) Anal. Calcd for $C_{20}H_{19}N_3O_6S$: C, 55.94; H, 4.46; N, 9.78. Found: C. 56.16; H, 4.52; N, 9.85.

8i: White crystalline solid. IR (KBr): $\nu = 3185$ (N—H), 1723, 1684 (C=O), 1622, 1533 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.88$ (s, 1H, NH), 7.02–8.13 (m, 8H, Ar-H), 5.44 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3). MS *m/z*: 429 (M^+). Anal. Calcd for $C_{20}H_{19}N_3O_6S$: C, 55.94; H, 4.46; N, 9.78. Found: C. 55.81; H, 4.50; N, 9.87.

8j: Pale yellow crystalline solid. IR (KBr): $\nu = 3125$ (N–H), 1720, 1687 (C=O), 1599, 1489 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.91$ (s, 1H, NH), 6.90–7.99 (m, 11H, Ar-H), 5.51 (s, 2H, CH_2), 5.02 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3). MS *m/z*: 449 (M^+). Anal. Calcd for $C_{23}H_{19}N_3O_5S$: C, 61.46; H, 4.26; N, 9.35. Found: C. 61.53; H, 4.16; N, 9.27.

8k: White crystalline solid. IR (KBr): $\nu = 3195$ (N–H), 1728, 1680 (C=O), 1598, 1497 (C=N, C=C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 12.93$ (s, 1H, NH), 6.79–7.99 (m, 11H, Ar-H), 5.49 (s, 2H, CH_2), 5.01 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3). MS *m/z*: 449(M^+). Anal. Calcd. for $C_{23}H_{19}N_3O_5S$: C, 61.64; H, 4.26; N, 9.35. Found: C, 61.78; H, 4.33; N, 9.45.

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