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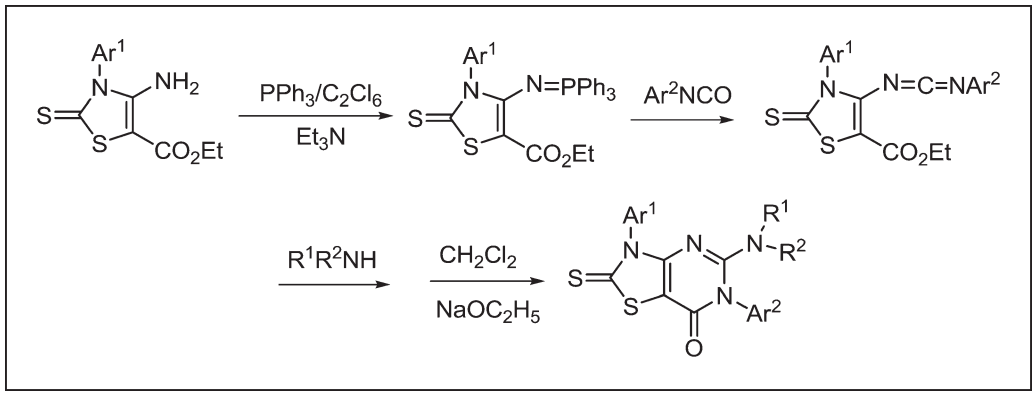

Sixteen 5-alkylamino-3,6-diaryl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-ones **4a–4p** were designed and easily synthesized via a tandem aza-Wittig reaction. The iminophosphorane **2**, obtained from reaction of **1** with triphenylphosphine, hexachloroethane and Et_3N, reacted with aromatic isocyanate to give carbodiimide **3**. carbodiimide **3** reacted with alkylamines to provide the title compounds in 45–61% isolated yields in presence of catalytic amount of ethoxide. The structures of compounds **4** were confirmed by ^1H NMR, IR, MS, and elemental analysis.

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INTRODUCTION

Thiazolo[4,5-d]pyrimidines are widely recognized as pharmaceutically and biologically useful heterocycles because of their structural similarities to purine bases. As such, thiazolo[4,5-d]pyrimidines have been found to possess anti-HIV [1], anticancer [2], anti-inflammatory [3], and antimicrobial activities [4,5]. An important synthetic route for thiazolo[4,5-d]pyrimidines in previous reports is the condensation reaction of 4-aminothiazole-5-carboxylate and isothiocyanate. However, this method is characterized as a long reaction time and low yield [6].

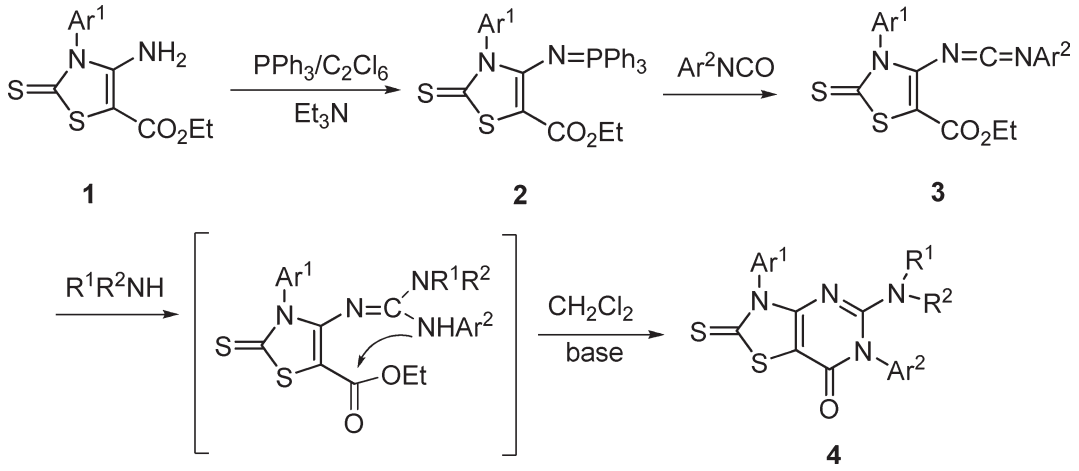
Recently, we have been interested in the synthesis of fused pyrimidinones via aza-Wittig reaction of β-ethoxycarbonyl iminophosphorane with aromatic isocyanate and subsequent reaction with various nucleophile under mild condition [7]. As a continuation of our research for new biologically active heterocycles [8], here we wish to report an efficient synthesis of 5-alkylamino-3,6-diaryl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-ones, a series of compounds which have not been reported before.

RESULTS AND DISCUSSION

The iminophosphorane **2**, which was prepared in a satisfactory yield by the reaction of **1** with triphenylphosphine, hexachloroethane and Et_3N [9,10], reacted with aryl isocyanate to give carbodiimide **3**. In refluxing toluene, **3** did not react with alkylamines to provide the target compounds. However, in CH_2Cl_2 and in the presence of a catalytic amount of EtONa, compounds **3** were converted smoothly to the 5-alkylamino-3,6-diaryl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-ones **4** in satisfactory yields at room temperature (Scheme 1). Irrespective of the fact whether primary or secondary amines were used, and whether the substitutes on the amines were bulky or small groups, the cyclization proceeded very smoothly in the same regioselectivity. Thin layer chromatography was used to follow the progress of every above reaction. Most of the compounds **4** were readily soluble in polar organic solvents. The results are listed in Table 1.

All products **4** were obtained as yellow crystals after recrystallization from CH_2Cl_2/petroleum ether and were confirmed by their elemental analysis and spectral data.

Scheme 1



For example, the ^{1}H NMR spectra data of **4m** showed the signals of NH at δ 4.72 as triplet, which were not the same as the proton of PhNH, the chemical shift of which is greater than δ 7.0. Its methylene protons displayed a doublet also, which strongly suggested the existence of an $NHCH_2$-group. In IR spectral of **4m–4p**, the relatively strong absorption of N—H appeared at 3336–3431 cm^{-1}, which was only one peak. The stretching resonance of C=O showed strong absorption at about 1675–1697 cm^{-1}. The MS spectrum of **4m** displayed strong molecule ion peaks. The structure of **4** was also established on the basis of elemental analysis data. The difference between found value and calculated value of elemental analysis of all compounds was under 0.5%.

EXPERIMENTAL

Melting points were determined with a WRS-1B Digital melting point apparatus and are uncorrected. EI-MS were measured on a Finnigan Trace MS spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^{1}H NMR were recorded in $CDCl_3$ on a Varian Mercury 400 spectrometer and resonances are given in ppm (δ) relative to TMS. Elementary analyses were taken on a Perkin-Elmer CHN 2400 elementary analysis instrument. All the solvent and materials are reagent grades and purified before use.

Thiazolecarboxylate derivatives **1** was prepared according to the literature procedures in 68.8% yield [11]. Yellow crystal, mp 221.8–222.4°C, ^{1}H NMR (400 MHz $CDCl_3$): δ (ppm): 7.63–7.32 (m, 5H, Ph-H), 5.63 (s, 2H, —NH_2), 4.28(q, 2H, J = 7.2 Hz, —CH_2), 0.97(t, 3H, J = 6.8 Hz, —CH_3).

Table 1

Reaction conditions of the target compounds.

Compds	Ar^1	Ar^2	R^1R^2N	r.t. (h)	Yield (%)[a]
4a	Ph	Ph	Et_2N	3	54
4b	Ph	Ph	$(i\text{-}Pr)_2N$	3	58
4c	Ph	Ph	$(n\text{-}Amyl)_2N$	2	56
4d	Ph	4-ClPh	Et_2N	3	58
4e	Ph	4-ClPh	$(i\text{-}Pr)_2N$	2	60
4f	Ph	4-ClPh	$(n\text{-}Amyl)_2N$	2	59
4g	Ph	4-FPh	Et_2N	3	58
4h	Ph	4-FPh	$(i\text{-}Pr)_2N$	3	61
4i	Ph	4-FPh	$(n\text{-}Amyl)_2N$	2	56
4j	4-FPh	Ph	Et_2N	3	54
4k	4-FPh	Ph	$(i\text{-}Bu)_2N$	3	55
4l	4-FPh	Ph	$(n\text{-}Amyl)_2N$	2	45
4m	Ph	Ph	$2\text{-}MePhCH_2NH$	3	57
4n	Ph	Ph	$3\text{-}MePhCH_2NH$	3	55
4o	Ph	4-ClPh	$2\text{-}MePhCH_2NH$	3	54
4p	Ph	4-ClPh	$3\text{-}MePhCH_2NH$	3	52

[a] Yields of isolated products based on iminophosphosphorane 2.

Preparation of iminophosphorane 2. A solution of **1** (14.0 g, 0.05 mol) in CH_3CN (150 mL) was added triphenylphosphine (26.5 g, 0.1 mol) and C_2Cl_6 (24.0 g, 0.1 mol). The mixture was treated with triethylamine (28.0 mL, 0.2 mol), then stirred for 4–5 h at 20°C, the solution was condensed and the residue was recrystallized from CH_3CH_2OH to give iminophosphorane **2** in yield 98.5%. Yellow crystal, m.p. 224.1–225.0°C ^{1}H NMR (400 MHz $CDCl_3$): δ (ppm): 7.50–7.27 (m, 20H, Ph-H), 3.75 (q, 2H, J = 6.8 Hz, —CH_2), 0.97 (t, 3H, J = 7.2 Hz, —CH_3); EI-MS (70 eV, m/z) (relative intensity %): (m/z) 540 (M^+, 100), 512(28), 262(99), 183(90), 107(54).

Preparation of carbodiimides 3. To a solution of iminophosphorane **2** (0.54 g, 1 mmol) in anhyd CH_2Cl_2 (10 mL) was added aromatic isocyanate (1.1 mmol) under N_2 at r.t. After the reaction mixture was left unstirred for 5–12 h, the solvent was removed off under reduced pressure and Et_2O/petroleum ether was added to precipitate triphenylphosphine oxide. Removal of the solvent gave carbodiimides **3**, which were used directly without further purification partly because they easily decomposed.

General procedure for the preparation of compounds 4a–4p. To the solution of carbodiimides **3** prepared above in ethanol (15 mL) was added alkylamine (1.1 mmol) and a catalytic amount of sodium ethoxide in ethanol. After the mixture had been stirred for 2–3 h at 303 K, the solution was concentrated and the residue was recrystallized from CH_3CN to give pure 5-alkylamino-3,6-diaryl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-ones **4a–4p**.

5-Diethylamino-3,6-diphenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4a). Yellow crystals, m.p. 206.2–207.1°C. ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 0.68 (t, J = 7.2 Hz, 6H, $2CH_3$), 3.09 (q, J = 7.2 Hz, 4H, $2CH_2$), 7.28–7.59 (m, 10H, Ph-H); IR (KBr) υ (cm^{-1}): 2974 (C—H), 1687 (C=O), 1573, 1528(Ph); Elemental Anal. Calcd. for $C_{21}H_{20}N_4OS_2$ (408.5): C, 61.74; H, 4.93; N, 13.71; S, 15.70; Found: C, 61.31; H, 5.01; N, 13.50; S, 15.23.

5-Di(i-propyl)amino-3,6-diphenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4b). Yellow crystals, m.p. 254.1–255.6°C. ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 0.82 (d, J = 6.4 Hz, 12H, $4CH_3$), 3.49 (m, 2H, 2CH), 7.25–7.58 (m, 10H, Ph-H); IR (KBr) υ (cm^{-1}): 2962 (C—H), 1689 (C=O), 1571, 1525 (Ph); Elemental Anal. Calcd. for $C_{23}H_{24}N_4OS_2$ (436.6): C, 63.27; H, 5.54; N, 12.83; S, 14.69; Found: C, 63.37; H, 5.33; N, 12.69; S, 14.15.

5-Di(n-amyl)amino-3,6-diphenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4c). Yellow crystals, m.p. 151.1–151.7°C. ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 0.77–0.85 (m, 10H, $2CH_2CH_3$), 1.06–1.10 (m, 8H, $2CH_2CH_2$), 2.82 (t, J = 8.0 Hz, 4H, $2CH_2$), 7.29–7.57 (m, 10H, Ph-H); IR (KBr) υ (cm^{-1}): 2953 (C—H), 1684 (C=O), 1573, 1530(Ph); Elemental Anal. Calcd. for $C_{27}H_{32}N_4OS_2$ (492.7): C, 65.22; H, 6.55; N, 11.37; S, 13.02; Found: C, 65.73; H, 6.50; N, 11.26; S, 12.53.

6-(4-Chlorophenyl)-5-diethylamino-3-phenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4d). Yellow crystals, m.p. 246.1–247.3°C. ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 0.73 (t, J = 7.2 Hz, 6H, $2CH_3$), 2.95 (q, J = 7.2 Hz, 4H, $2CH_2$), 7.24–7.57 (m, 9H, Ph-H); IR (KBr) υ (cm^{-1}): 2965 (C—H), 1683 (C=O), 1572, 1525(Ph); Elemental Anal. Calcd. for $C_{21}H_{19}ClN_4OS_2$ (443.0): C, 56.94; H, 4.32; N, 12.65; S, 14.48; Found: C, 56.28; H, 4.31; N, 12.38; S, 14.15.

6-(4-Chlorophenyl)-5-di(i-propyl)amino-3-phenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4e). Yellow crystals, m.p. > 270°C. ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 0.85 (d, J = 6.4 Hz, 12H, $4CH_3$), 3.47 (m, 2H, 2CH), 7.22–7.60 (m, 9H, Ph-H); IR (KBr) υ (cm^{-1}): 2981 (C—H), 1675 (C=O), 1570, 1529 (Ph); Elemental Anal. Calcd. for $C_{23}H_{23}ClN_4OS_2$ (471.0): C, 58.65; H, 4.92; N, 11.89; S, 13.61; Found: C, 57.13; H, 4.87; N, 11.44; S, 13.24.

6-(4-Chlorophenyl)-5-di(n-amyl)amino-3-phenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4f). Yellow crystals, m.p. 177.2–178.7°C. ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 0.79–0.86 (m, 10H, $2CH_2CH_3$), 1.08–1.14 (m, 8H, $2CH_2CH_2$), 2.83 (t, J = 8.0 Hz, 4H, $2CH_2$), 7.22–7.57 (m, 9H, Ph-H); IR (KBr) υ (cm^{-1}): 2957(C—H), 1682 (C=O), 1571, 1532(Ph); Elemental Anal. Calcd. for $C_{27}H_{31}ClN_4OS_2$ (527.1): C, 61.52; H, 5.93; N, 10.63; S, 12.17; Found: C, 60.77; H, 5.85; N, 10.84; S, 11.84.

5-Diethylamino-6-(4-fluorophenyl)-3-phenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4g). Yellow crystals, m.p. 219.5–220.4°C. ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 0.72 (t, J = 7.2 Hz, 6H, $2CH_3$), 2.95 (q, J = 7.2 Hz, 4H, $2CH_2$), 7.20–7.57 (m, 9H, Ph-H); IR (KBr) υ (cm^{-1}): 2976 (C—H), 1684 (C=O), 1571, 1526(Ph); Elemental Anal. Calcd. for $C_{21}H_{19}FN_4OS_2$ (426.5): C, 59.13; H, 4.49; N, 13.14; S, 15.04; Found: C, 59.28; H, 4.91; N, 12.79; S, 15.51 .

5-Di(i-propyl)amino-6-(4-fluorophenyl)-3-phenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4h). Yellow crystals, m.p. 265.1–265.4°C. ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 0.85 (d, J = 6.8 Hz, 12H, $4CH_3$), 3.47 (m, 2H, 2CH), 7.15–7.60 (m, 9H, Ph-H); IR (KBr) υ (cm^{-1}): 2977 (C—H), 1679 (C=O), 1573, 1529(Ph); Elemental Anal. Calcd. for $C_{23}H_{23}FN_4OS_2$ (454.6): C, 60.77; H, 5.10; N, 13232; S, 14.11; Found: C, 60.43; H, 4.81; N, 12.85; S, 14.54.

5-Di(n-amyl)amino-6-(4-fluorophenyl)-3-phenyl-2-thioxo-2,3,6,7-tetra hydrothiazolo[4,5-d]pyrimidin-7-one (4i). Yellow crystals, m.p. 153.5–154.1°C. ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 0.79–0.87 (m, 10H, $2CH_2CH_3$), 1.08–1.13 (m, 8H, $2CH_2CH_2$), 2.83 (t, J = 8.0 Hz, 4H, $2CH_2$), 7.19–7.56 (m, 9H, Ph-H); IR (KBr) υ (cm^{-1}): 2958 (C—H), 1681 (C=O), 1572, 1532(Ph); Elemental Anal. Calcd. for $C_{27}H_{31}FN_4OS_2$ (510.7): C, 63.50; H, 6.12; N, 10.97; S, 12.56; Found: C, 63.45; H, 6.65; N, 10.46; S, 12.91.

5-Diethylamino-3-(4-fluorophenyl)-6-phenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4j). Yellow crystals, m.p. 172.6–173.2°C. ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 0.71 (t, J = 7.2 Hz, 6H, $2CH_3$), 2.96 (q, J = 7.2 Hz, 4H, $2CH_2$), 7.25–7.50 (m, 9H, Ph-H); IR (KBr) υ (cm^{-1}): 2976 (C—H), 1689 (C=O), 1573, 1528(Ph); Elemental Anal. Calcd. for $C_{21}H_{19}FN_4OS_2$ (426.5): C, 59.13; H, 4.49; N, 13.14; S, 15.04; Found: C, 59.36; H, 4.58; N, 12.89; S, 15.59.

5-Di(i-butyl)amino-3-(4-fluorophenyl)-6-phenyl-2-thioxo-2,3,6,7-tetra hydrothiazolo[4,5-d]pyrimidin-7-one (4k). Yellow crystals, m.p. 193.6–195.1°C. ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 0.67 (d, J = 6.4 Hz, 12H, $4CH_3$), 1.62–1.73 (m, 2H, 2CH), 7.25–7.51 (m, 9H, Ph-H); IR (KBr) υ (cm^{-1}): 2964 (C—H), 1681 (C=O), 1574, 1529(Ph); Elemental Anal. Calcd. for $C_{25}H_{27}FN_4OS_2$ (482.6): C, 62.21; H, 5.64; N, 11.61; S, 13.29; Found: C, 62.58; H, 5.87; N, 12.03; S, 13.57.

5-Di(n-amyl)amino-3-(4-fluorophenyl)-6-phenyl-2-thioxo-2,3,6,7-tetra hydrothiazolo[4,5-d]pyrimidin-7-one (4l). Yellow crystals, m.p. 173.6–174.2°C. ^{1}H NMR (400 MHz $CDCl_3$) δ

(ppm): 0.78–0.88 (m, 10H, $2CH_2CH_3$), 1.08–1.14 (m, 8H, $2CH_2CH_2$), 2.84 (t, J = 8.0 Hz, 4H, $2CH_2$), 7.22–7.49 (m, 9H, Ph-H); IR (KBr) υ (cm^{-1}): 2957 (C—H), 1682 (C=O),1571,1532(Ph); Elemental Anal. Calcd. for $C_{27}H_{31}FN_4OS_2$ (510.7): C, 63.50; H, 6.12; N, 10.97; S, 12.56; Found: C, 63.37; H, 5.95; N, 10.88; S, 12.14.

3,6-diphenyl-5-(2-methylbenzylamino)-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4m). Yellow crystals, m.p. 271.2–273.2°C. ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 1.98 (s, 3H,CH_3), 4.19 (d, J = 6.0 Hz, 2H, CH_2), 4.72 (s, 1H, NH), 6.69–7.63 (m, 14H, Ph-H); EI-MS (70eV, m/z)(relative intensity %) 456 (M^+, 100), 351(47), 336(7), 181(48), 105(93), 91(43), 77(99); IR (KBr) υ (cm^{-1}): 3426 (N—H), 2923 (C—H), 1697 (C=O), 1545(Ph); Elemental Anal. Calcd. for $C_{25}H_{20}N_4OS_2$ (456.6): C, 65.76; H, 4.42; N, 12.27; S, 14.05; Found: C, 64.71; H, 3.80; N, 11.74; S, 14.51.

3,6-diphenyl-5-(3-methylbenzylamino)-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4n). Yellow crystals, m.p. 221.8–222.3°C. ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 2.29 (s, 3H, CH_3), 4.17 (d, J = 5.6 Hz, 2H, CH_2), 4.87 (s, 1H, NH), 6.86–7.52 (m, 14H, Ph-H); IR (KBr) υ (cm^{-1}): 3370 (N—H), 2976 (C—H), 1689 (C=O), 1544 (Ph); Elemental Anal. Calcd. for $C_{25}H_{20}N_4OS_2$ (456.6): C, 65.76; H, 4.42; N, 12.27; S, 14.05; Found: C, 65.38; H, 4.40; N, 12.38; S, 13.89.

6-(4-chlorophenyl)-5-(2-methylbenzylamino)-3-phenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4o). Yellow crystals, m.p. 263.4–265.1°C. ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 2.00 (s, 3H,CH_3), 4.20 (d, J = 5.6 Hz, 2H, CH_2), 4.69 (s, 1H, NH), 6.70–7.59 (m, 13H, Ph-H); IR (KBr) υ (cm^{-1}): 3360 (N—H), 2935 (C—H), 1675 (C=O), 1542(Ph); Elemental Anal. Calcd. For $C_{25}H_{19}ClN_4OS_2$ (491.0): C, 61.15; H, 3.90; N, 11.41; S, 13.06; Found: C, 61.68; H, 4.22; N, 11.25; S, 13.47.

6-(4-Chlorophenyl)-5-(3-methylbenzylamino)-3-phenyl-2-thioxo-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-7-one (4p). Yellow crystals, m.p. 251.5–253.1°C. ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 2.27 (s, 3H,CH_3), 4.15 (d, J = 6.0 Hz, 2H, CH_2), 4.81 (s, 1H, NH), 6.65–7.61 (m, 13H, Ph-H); IR (KBr) υ (cm^{-1}): 3303 (N—H), 2931 (C—H), 1678 (C=O), 1544 (Ph); Elemental Anal. Calcd. For $C_{25}H_{19}ClN_4OS_2$ (491.0): C, 61.15; H, 3.90; N, 11.41; S, 13.06; Found: C, 61.52; H, 3.76; N, 11.01; S, 13.02.

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