One-pot three-component synthesis of 1,4-bis[thiazolo[4,5-d]pyrimidin-7(6*H*)-one]piperazine derivatives

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A simple one-pot efficient method is described for the synthesis of 1,4-bis[thiazolo[4,5-d]pyrimidin-7(6*H*)-one] piperazine derivatives by a domino three-component process involving an aza-Wittig reaction/heterocyclisation in the presence of sodium ethoxide as catalyst. Ethyl 4-[(triphenylphosphanylidene)amino]-2,3-dihydro-3-phenyl-2-thioxothiazole-5-carboxylate reacted with aromatic isocyanates to give carbodiimide intermediates. This was followed by the addition of piperazines to give the corresponding guanidine intermediates. The guanidine intermediates were then cyclised in the presence of catalytic amount of sodium ethoxide to give 1,4-bis[thiazolo[4,5-d]pyrimidin-7(6*H*)-one]piperazine derivatives in good yields.

Keywords: thiazolo[4,5-d]pyrimidinone, multicomponent reactions, piperazine

In recent years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because these reactions increase efficiency by combining several operational steps without the need for isolation of intermediates or changes in the conditions.[1–3] This principle, therefore, is highly efficient in terms of time as well as resources. Among the known MCRs some useful reactions are those based on isocyanides. In the development of strategies for the preparation of heterocycles, the aza-Wittig reaction has proved to be a powerful tool for the synthesis of 5–8 membered nitrogen heterocycles.[4–6] The iminophosphoranes of heterocyclic and heteroaromatic β-enamino esters have proved to be versatile intermediates for the construction of many hetero-condensed systems. Many important nitrogen heterocycles have been synthesized via the aza-Wittig reaction of β-ethoxycarbonyl iminophosphorane with an aromatic isocyanate and a subsequent heterocyclisation reaction with various nucleophiles under mild conditions.[7–10]

Thiazolo[4,5-d]pyrimidines are widely recognised as pharmaceutically and biologically useful heterocycles because of their structural similarities to the purine bases. As such, thiazolo[4,5-d]pyrimidines have been found to possess anti-HIV, anticancer, anti-inflammatory and antimicrobial activities.[11–13] An important synthetic route for thiazolo[4,5-b]pyrimidines in previous reports is the condensation reaction of 4-aminothiazole-5-carboxylate and isothiourea. However, this method is characterized by a long reaction time and low yield[14].Recently, we have been investigated the synthesis of fused pyrimidinones via the aza-Wittig reaction. As a continuation of our search for new biologically-active heterocycles,[15–16] we now report an efficient synthesis (Scheme 1) of 1,4-bis[thiazolo[4,5-d] pyrimidin-7(6*H*)-one]piperazine derivatives, a series of compounds which have not been reported before.

Results and discussion

The key iminophosphorane **1** was synthesised according to the literature.[17]

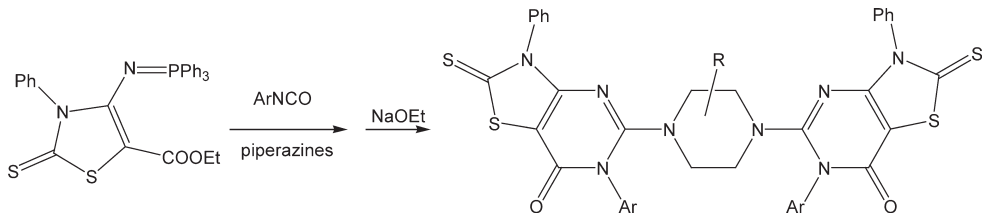
The iminophosphorane **1** reacted with an aromatic isocyanate to give the carbodiimides **2**. The reaction proceeded smoothly in THF at room temperature. The reaction of carbodiimides **2** with piperazine derivatives at room temperature gave intermediate guanidines **3** via the initial double nucleophilic addition of piperazine to the carbodiimide. Even in refluxing toluene, **3** did not cyclise. However, in dry ethylene chloride and in the presence of a catalytic amount of EtONa, compounds **3** were converted smoothly to the 1,4-bis[thiazolo[4,5-d]pyrimidin-7(6*H*)-one] piperazine derivatives **4** in satisfactory yields at room temperature. The results are given in Table 1.

We found that the heterocyclisation occurred via nucleophilic displacement of the neighbouring ester ethoxide group to give the corresponding target compounds **4** by intramolecular heteroconjugate addition and annulation. Irrespective of the fact whether substituted piperazines or unsubstantiated piperazine, the cyclisation proceeded very smoothly with the same

Table 1 Preparation of 1,4-bis[thiazolo[4,5-d]pyrimidin-7(6*H*)-one]piperazine derivatives

Compd	Ar	R	Yield/%[a]
4a	Ph	H	89
4b	Ph	2-Me	87
4c	Ph	2,5-diMe	76
4d	Ph	2,6-diMe	75
4e	Ph	2-Et	81
4f	4-Me–C_6H_4	H	80
4g	4-Me–C_6H_4	2-Me	74
4h	4-Me–C_6H_4	2,5-diMe	72
4i	4-Me–C_6H_4	2,6-diMe	73
4j	4-Me–C_6H_4	2-Et	75
4k	4-Cl–C_6H_4	H	86
4l	4-Cl–C_6H_4	2-Me	80
4m	4-Cl–C_6H_4	2,5-diMe	77
4n	4-Cl–C_6H_4	2,6-diMe	78
4o	4-Cl–C_6H_4	2-Et	82

[a]Isolated yields based on iminophosphorane **1**.



Scheme 1

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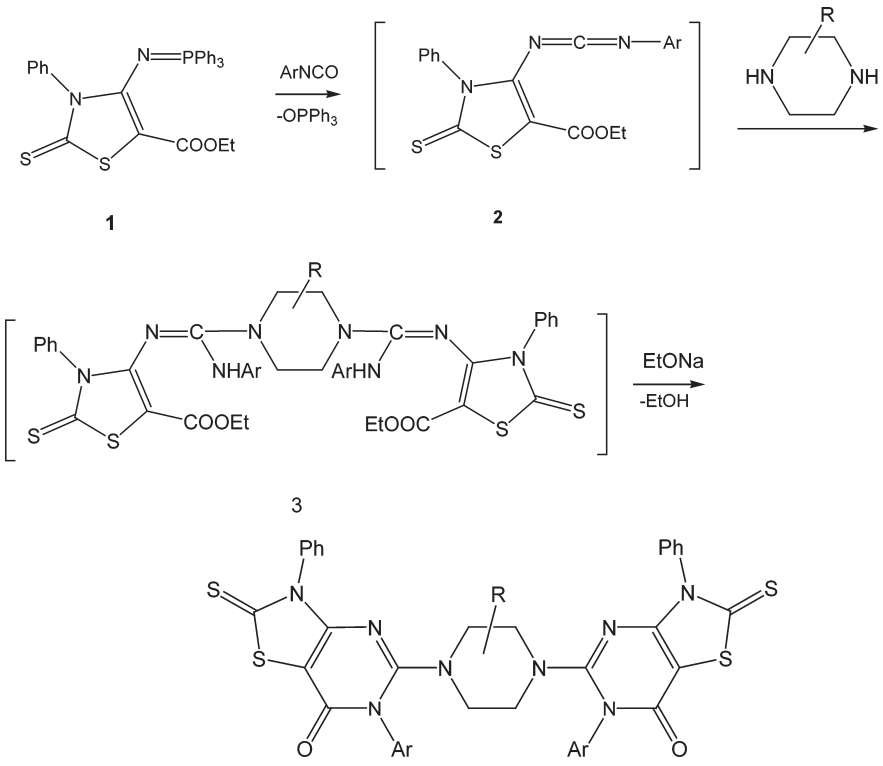

Scheme 2

regioselectivity.No matter whether the substituents on the benzene ring were electron-withdrawing or electron-donating groups, the cyclisation was completed easily under mild conditions. The reaction pathway was showed as Scheme 2.

The structures of compounds **4** were fully confirmed by IR, ^{1}H NMR, MS spectroscopic data. For example, the electrospray ionisation mass spectrum (ESI-MS) for **4a** showed the expected molecular ion peaks *m/z* at 757.1 (M^++H) and the two-dimensional ionization pattern was in accord with the proposed structure. The IR spectrum (KBr) showed a strong absorption at 1698 cm^{-1} assigned to the C=O group. In the ^{1}H NMR spectrum, the –CH_2 proton appears at 2.65 ppm, in addition to the aromatic proton multiplets.

Experimental

Melting points were determined using an X-4 model apparatus and were uncorrected. IR spectra were recorded on a Nicolet 7500 NXR IR spectrometer as KBr pellets with absorption given in cm^{-1}. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Plus 300 (300Hz) spectrometer and chemical shifts (δ) were given in ppm using $(CH_3)_4Si$ as an internal reference (δ = 0). Mass spectral (MS) data were obtained on a Finnigan LCQ Advantage MAX mass spectrometer. Elemental analyses were obtained with a Perkin-Elmer CHN 2400 elemental analysis instrument.

Synthesis of 1,4-Bis[thiazolo [4,5-d]pyrimidin-7(6H)-one]piperazine derivatives **4***; general synthesis*

The aromatic isocyanate was added (0.006 mol) to the solution of iminophosphorane **1** (0.006 mol) in THF (10 mL) at 0–5 °C. When the resulting iminophosphorane **1** reacted with aromatic isocyanate, triphenylphosphine oxide was formed. After the reaction mixture was left to stand for 5–6 h at 0–5 °C, the solvent was removed under reduced pressure and Et_2O/petroleum ether (1:2, 12 mL) was added to precipitate triphenylphosphine oxide. Removal of the solvent gave carbodiimides **2**, which were used directly without further purification. The piperazine derivatives (0.003 mol) were added to the solution of **2** prepared above in CH_2Cl_2 (10 mL) to give intermediate guanidines **3**. After the reaction mixture was left to stand for 2–3 h, the solvent was removed and EtONa in anhydrous EtOH (8 mL,10%) was added. The mixture was stirred for 3–5 h at room temperature. The solution was concentrated and the residue was recrystallised from EtOH to give the target compound **4**. TLC was used to follow the progress of all the above reactions.

1,4-Bis[4-oxo-3,6-diphenyl-2-thioxothiazolo[4,5-d]pyrimidin-2(4H)-yl]piperazine (**4a**): White crystals; m.p. 218–219 °C; IR (KBr): 3341, 2946, 1698 (C=O), 1551, 1437, 1349 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.65 (t, *J* = 7.2 Hz, 8H, $4CH_2$), 6.62–7.15 (m, 12H, ArH), 7.23 (m, 4H, ArH), 7.54 (m, 4H, ArH); ESI-MS *m/z*: 757.1 (M^++H). Anal. Calcd for $C_{38}H_{28}N_8O_2S_4$: C, 60.30; H, 3.73; N, 14.80. Found: C, 60.28; H, 3.77; N 14.77%.

1,4-Bis[4-oxo-3,6-diphenyl-2-thioxothiazolo[4,5-d]pyrimidin-2(4H)-yl]-2-methyl piperazine (**4b**): White crystals; m.p. 253–254 °C; IR (KBr): 3342, 2946, 1689 (C=O), 1551, 1443, 1358 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, *J* = 6.4 Hz, 3H, CH_3), 2.42 (d, *J* = 7.2 Hz, 2H, CH_2), 2.51 (t, *J* = 7.2 Hz, 4H, $2CH_2$), 2.98 (m, 1H, CH), 6.46–7.20 (m, 12H, ArH), 7.24 (m, 4H, ArH), 7.55 (m, 4H, ArH); ESI-MS *m/z*: 771.1 (M^++H). Anal. Calcd for $C_{39}H_{30}N_8O_2S_4$: C, 60.76; H, 3.92; N, 14.58. Found: C, 60.73; H, 3.89; N, 14.54%.

1,4-Bis[4-oxo-3,6-diphenyl-2-thioxothiazolo[4,5-d]pyrimidin-2(4H)-yl]-2,5-dimethyl piperazine (**4c**): White crystals; m.p. 238–239 °C; IR (KBr): 3345, 2946, 1687 (C=O), 1540, 1451, 1342 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, *J* = 7.0 Hz, 6H, $2CH_3$), 2.55 (d, *J* = 7.2 Hz, 4H, $2CH_2$), 3.04 (t, *J* = 6.2 Hz, 2H, 2CH), 6.46–7.25 (m, 12H, ArH), 7.24 (m, 4H, ArH), 7.56 (m, 4H, ArH); ESI-MS *m/z*: 785.1 (M^++H). Anal. Calcd for $C_{40}H_{32}N_8O_2S_4$: C, 61.20; H, 4.11; N, 14.27. Found: C, 61.21; H, 4.15; N, 14.25%.

1,4-Bis[4-oxo-3,6-diphenyl-2-thioxothiazolo[4,5-d]pyrimidin-2(4H)-yl]-2,6-dimethyl piperazine (**4d**): White crystals; m.p. 262–263 °C; IR (KBr): 3342, 2943, 1688 (C=O), 1543, 1455, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, *J* = 7.0 Hz, 6H, $2CH_3$), 2.51 (d, *J* = 7.2 Hz, 4H, $2CH_2$), 3.04 (t, *J* = 6.8 Hz, 2H, 2CH), 6.46–7.20 (m, 12H, ArH), 7.24 (m, 4H, ArH), 7.53 (m, 4H, ArH); ESI-MS *m/z*: 785.1 (M^++H). Anal. Calcd for $C_{40}H_{32}N_8O_2S_4$: C, 61.20; H, 4.11; N, 14.27. Found: C, 61.18; H, 4.09; N, 14.24%.

1,4-Bis[4-oxo-3,6-diphenyl-2-thioxothiazolo[4,5-d]pyrimidin-2(4H)-yl]-2-ethyl piperazine (**4e**): White crystals; m.p. >300 °C; IR (KBr):

3338, 2940, 1685 (C=O), 1552, 1458, 1359 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, *J* = 7.0 Hz, 3H, CH_3), 1.37 (m, 2H, $2CH_2$), 2.53 (d, *J* = 7.2 Hz, 2H, CH_2), 2.56 (t, *J* = 7.2 Hz, 4H, $2CH_2$), 6.54–7.13 (m, 12H, ArH), 7.24 (m, 4H, ArH), 7.53 (m, 4H, ArH); ESI-MS *m/z*: 785.1 (M^++H). Anal. Calcd for $C_{40}H_{32}N_8O_2S_4$: C, 61.20; H, 4.11; N, 14.27. Found: C, 61.24; H, 4.10; N, 14.26%.

1,4-Bis[4-oxo-3-phenyl-6-(4-methylphenyl)-2-thioxothiazolo[4,5-d] pyrimidin-2(4H)-yl]piperazine (**4f**): White crystals; m.p. >300 °C; IR (KBr): 3328, 2941, 1688 (C=O), 1553, 1466, 1349 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.35 (s, 6H, $2CH_3$), 2.65 (t, *J* = 7.2 Hz, 8H, $4CH_2$), 6.62–7.20 (m, 10H, ArH), 7.28 (m, 4H, ArH), 7.58 (m, 4H, ArH); ESI-MS *m/z*: 785.1 (M^++H). Anal. Calcd for $C_{40}H_{32}N_8O_2S_4$: C, 61.20; H, 4.11; N, 14.27. Found: C, 61.19; H, 4.10; N, 14.29%.

1,4-Bis[4-oxo-3-phenyl-6-(4-methylphenyl)-2-thioxothiazolo[4,5-d] pyrimidin-2(4H)-yl]-2-methyl piperazine (**4g**): White crystals; m.p. 253–254 °C; IR (KBr): 3332, 2943, 1686 (C=O), 1550, 1466, 1368 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, *J* = 6.4 Hz, 3H, CH_3), 2.35 (s, 6H, $2CH_3$), 2.42 (d, *J* = 7.0 Hz, 2H, CH_2), 2.51 (t, *J* = 7.2 Hz, 4H, $2CH_2$), 2.98 (m, 1H, CH), 6.46–7.20 (m, 10H, ArH), 7.24 (m, 4H, ArH), 7.53 (m, 4H, ArH); ESI-MS *m/z*: 799.2 (M^++H). Anal. Calcd for $C_{41}H_{34}N_8O_2S_4$: C, 61.63; H, 4.29; N, 14.02. Found: C, 61.61; H, 4.25; N, 14.03%.

1,4-Bis[4-oxo-3-phenyl-6-(4-methylphenyl)-2-thioxothiazolo[4,5-d] pyrimidin-2(4H)-yl]-2,5-dimethyl piperazine (**4h**): White crystals; m. p. 238–239 °C; IR (KBr): 3342, 2965, 1689 (C=O), 1553, 1457, 1348 cm^{-1}; ^1H NMR ($CDCl_3$,300 MHz): δ 1.15 (d, *J* = 7.0 Hz, 6H, $2CH_3$), 2.35 (s, 6H, $2CH_3$), 2.55 (d, *J* = 7.2 Hz, 4H, $2CH_2$), 3.04 (t, *J* = 6.2 Hz, 2H, 2CH), 6.46–7.20 (m, 10H, ArH), 7.24 (m, 4H, ArH), 7.53 (m, 4H, ArH); ESI-MS *m/z*: 813.1 (M^++H). Anal. Calcd for $C_{42}H_{36}N_8O_2S_4$: C, 62.04; H, 4.46; N, 13.78. Found: C, 62.05; H, 4.44; N, 13.80%.

1,4-Bis[4-oxo-3-phenyl-6-(4-methylphenyl)-2-thioxothiazolo[4,5-d] pyrimidin-2(4H)-yl]-2,6-dimethyl piperazine (**4i**): White crystals; m. p. 262–263 °C; IR (KBr): 3338, 2932, 1687 (C=O), 1548, 1462, 1348 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, *J* = 7.0 Hz, 6H, $2CH_3$), 2.35 (s, 6H, $2CH_3$), 2.51 (d, *J* = 7.2 Hz, 4H, $2CH_2$), 3.04 (t, *J* = 6.8 Hz, 2H, 2CH), 6.46–7.20 (m, 10H, ArH), 7.24 (m, 4H, ArH), 7.53 (m, 4H, ArH); ESI-MS *m/z*: 813.2 (M^++H). Anal. Calcd for $C_{42}H_{36}N_8O_2S_4$: C, 62.04; H, 4.46; N, 13.78. Found: C, 62.02; H, 4.43; N, 13.76%.

1,4-Bis[4-oxo-3-phenyl-6-(4-methylphenyl)-2-thioxothiazolo[4,5-d] pyrimidin-2(4H)-yl]-2-ethyl piperazine (**4j**): White crystals; m.p. >300 °C; IR (KBr): 3338, 2937, 1695 (C=O), 1564, 1447, 1349 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, *J* = 7.0 Hz, 3H, CH_3), 1.37 (m, 2H, $2CH_2$), 2.35 (s, 6H, $2CH_3$), 2.53 (d, *J* = 7.2 Hz, 2H, CH_2), 2.56 (t, *J* = 6.8 Hz, 4H, $2CH_2$), 6.54–7.13 (m, 10H, ArH), 7.24 (m, 4H, ArH), 7.53 (m, 4H, ArH); ESI-MS *m/z*: 813.2 (M^++H). Anal. Calcd for $C_{42}H_{36}N_8O_2S_4$: C, 62.04; H, 4.46; N, 13.78. Found: C, 62.07; H, 4.47; N, 13.81%.

1,4-Bis[4-oxo-3-phenyl-6-(4-chlorophenyl)-2-thioxothiazolo[4,5-d] pyrimidin-2(4H)-yl]piperazine (**4k**): White crystals; m.p. 218–219 °C; IR (KBr): 3328, 2942, 1688 (C=O), 1552, 1453, 1341 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.65 (t, *J* = 7.2 Hz, 8H, $4CH_2$), 6.62–7.20 (m, 10H, Ar-H), 7.24 (m, 4H, ArH), 7.53 (m, 4H, ArH); ESI-MS *m/z*: 625.1 (M^++H). Anal. Calcd for $C_{38}H_{26}N_8O_2S_4Cl_2$: C, 55.27; H, 3.17; N, 13.57. Found: C, 55.24; H, 3.13; N, 13.59%.

1,4-Bis[4-oxo-3-phenyl-6-(4-chlorophenyl)-2-thioxothiazolo[4,5-d] pyrimidin-2(4H)-yl]-2-methyl piperazine (**4l**): White crystals; m.p. 253–254 °C; IR (KBr): 3330, 2945, 1686 (C=O), 1553, 1470, 1368 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, *J* = 6.4 Hz, 3H, CH_3), 2.42 (d, *J* = 7.0 Hz, 2H, CH_2), 2.51 (t, *J* = 7.2 Hz, 4H, $2CH_2$), 2.98 (m, 1H, CH), 6.46–7.20 (m, 10H, ArH), 7.24 (m, 4H, ArH), 7.53 (m, 4H, ArH); ESI-MS *m/z*: 839.2 (M^++H). Anal. Calcd for $C_{39}H_{28}N_8O_2S_4Cl_2$: C, 55.77; H, 3.36; N, 13.34. Found: C, 55.78; H, 3.33; N, 13.35%.

1,4-Bis[4-oxo-3-phenyl-6-(4-chlorophenyl)-2-thioxothiazolo[4,5-d] pyrimidin-2(4H)-yl]-2,5-dimethyl piperazine (**4m**): White crystals; m.p. 238–239 °C; IR (KBr): 3342,2963, 1689 (C=O), 1547, 1453, 1352 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, *J* = 7.0 Hz, 6H, $2CH_3$), 2.55 (d, *J* = 7.2 Hz, 4H, $2CH_2$), 3.04 (t, *J* = 6.2 Hz, 2H, 2CH), 6.46–7.25 (m, 10H, ArH), 7.27 (m, 4H, ArH), 7.55 (m, 4H, ArH); ESI-MS *m/z*: 853.1 (M^++H). Anal. calcd for $C_{40}H_{30}N_8O_2S_4Cl_2$: C, 56.26; H, 3.54; N, 13.12. found: C, 56.22; H, 3.51; N, 13.10%.

1,4-Bis[4-oxo-3-phenyl-6-(4-chlorophenyl)-2-thioxothiazolo[4,5-d] pyrimidin-2(4H)-yl]-2,6-dimethyl piperazine (**4n**): White crystals; m. p. 262–263 °C; IR (KBr): 3331, 2940, 1687 (C=O), 1548, 1546, 1348 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, *J* = 7.0 Hz, 6H, $2CH_3$), 2.51 (d, *J* = 7.2 Hz, 4H, $2CH_2$), 3.04 (t, *J* = 6.8 Hz, 2H, 2CH), 6.46–7.20 (m, 10H, ArH), 7.25 (m, 4H, ArH), 7.55 (m, 4H, ArH); ESI-MS *m/z*: 853.2 (M^++H). Anal. Calcd for $C_{40}H_{30}N_8O_2S_4Cl_2$: C, 56.26; H, 3.54; N, 13.12. Found: C, 56.27; H, 3.56; N, 13.14%.

1,4-Bis[4-oxo-3-phenyl-6-(4-chlorophenyl)-2-thioxothiazolo[4,5-d] pyrimidin-2(4H)-yl]-2-ethyl piperazine (**4o**): White crystals; m.p. >300 °C; IR (KBr): 3338, 2944, 1685 (C=O), 1539, 1441, 1343 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, *J* = 7.0 Hz, 3H, CH_3), 1.37 (m, 2H, $2CH_2$), 2.53 (d, *J* = 7.2 Hz, 2H, CH_2), 2.56 (t, *J* = 6.8 Hz, 4H, $2CH_2$), 6.54–7.13 (m, 10H, ArH), 7.24 (m, 4H, ArH), 7.53 (m, 4H, ArH); ESI-MS *m/z*: 853.1 (M^++H). Anal. Calcd for $C_{40}H_{30}N_8O_2S_4$ Cl_2: C, 56.26; H, 3.54; N, 13.12. Found: C, 56.27; H, 3.55; N 13.15%.

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