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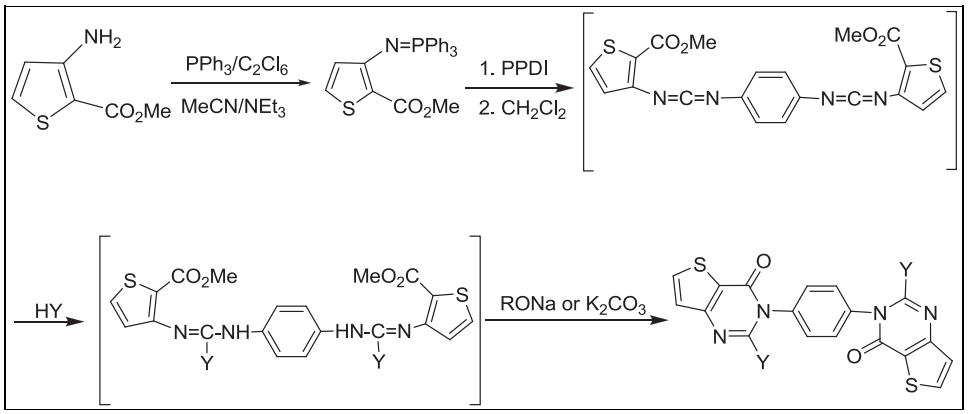

Tandem aza-Wittig reaction of iminophosphorane with 1,4-phenylene diisocyanate followed by intramolecular heteroconjugate addition annulation after addition of a nucleophilic reagent (amine, phenol, and alcohol), in the presence of catalytic K_2CO_3 or NaOR, gives selectively the functionalized substituted 2,2′-di(alkylamino, aryloxy)-3,3′-(1, 4-phenylene)bis(thieno[3,2-*d*]pyrimidin-4(3*H*)-ones) and 2,2′-di(alkylamino or alkoxy)-3,3′-(1, 4-phenylene)bis(3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-ones).

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INTRODUCTION

The development of efficient and mild synthetic methods for heterocyclic compounds represents a broad area of organic chemistry. In recent years, the aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of heterocyclic compounds, especially nitrogen-containing heterocyclic compounds [1]. The intermolecular aza-Wittig reaction followed by cyclizing has been utilized for the synthesis of many important nitrogen heterocycles [2]. Especially thienopyrimidine derivatives, they are an important class of S-heterocyclic and N-heterocyclic compounds in pharmaceutical discovery research because of their significant activities such as anticancer, antifungal, and antibacterial activities [3–6].

Iminophosphoranes-containing thiophene ring, derived from aminothiophene, have proved to be very versatile building blocks for the construction of fused thienopyrimidine system by the aza-Wittig reaction. We have previously published the synthesis of fused thienopyrimidines on the basis of the tandem aza-Wittig reaction. As a continuation of our work on the aza-Wittig-type methodology, we report here a simple, general, and effective strategy for the preparation of substituted derivatives of 2, 2′-di (alkylamino, aryloxy)-3, 3′-(1, 4-phenylene)bis(thieno[3, 2-*d*]pyrimidin-4(3*H*)-ones) and 2, 2′-di(alkylamino, alkoxy)-3, 3′-(1, 4-phenylene)bis(3, 5, 6, 7-tetrahydro-4*H*-cyclopenta [4, 5]thieno[2, 3-*d*]pyrimidin-4-ones).

RESULTS AND DISCUSSION

In recent years, our work has been concerned with the discovery and development of synthesis of new heterocyclic compounds containing thienopyrimidine moiety. We have previously reported on the synthesis of novel tricyclic ring systems, containing the thienopyrimidine skeleton, with antibacterial and antifungal activities [7]. Among them, 3, 3′-diphenyl-2, 2′-(1, 3-phenylenedioxy)bis(3, 5, 6, 7-tetrahydro-4*H*-cyclopenta[4, 5]thieno[2, 3-*d*]pyrimidin-4-ones), because of two connected thienopyrimidine, showed significant activity of anticitrinin [8]. We now describe here, as a further extension of the aza-Wittig-type methodology, the synthesis of connected thienopyrimidines.

Heterocyclic compounds **5a–g** and **6a-g** were obtained in a reaction of the corresponding iminophosphoranes with aromatic isocyanates, followed by heterocyclization on addition of amines, phenol, or alcohol.

The key iminophosphoranes **2a–b** were obtained by a modified Kirsanov reaction of the aminothiophene **1a–b** with *in situ* prepared dichlorotriphenylphosphorane using

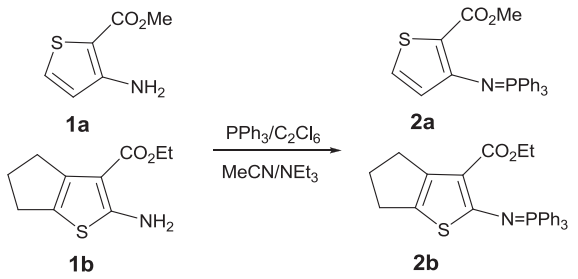
a hexachloroethane-triphenylphosphine-triethylamine reagent system (Scheme 1). The molecular structure of iminophposphoranes was supported by the spectral data and elemental analysis.

Iminophosphorane **2** reacted with half equiv of 1,4-Phenylene Diisocyanate (PPDI) to give carbodiimide **3**, which was allowed to react with amine to provide guanidine intermediates **4**. In the presence of a catalytic amount of sodium ethoxide, **4** were converted easily to substituted **5a–e** at room temperature. While the formation of products **5f–g** were carried out by heterocyclization on addition of phenols in the presence of K_2CO_3 (Scheme 2)

Owing to the unstability of carbodiimide **3**, the preparation of carbodiimides **3** must be carried out at low temperature (0–5°C) and long reaction time (8–l2 h) under dry conditions. Otherwise, hydrolysis or polymerization side reaction of carbodiimide should take place, which will result in low yields [9].

The participation of carbodiimide **3** and the corresponding guanidine-type compound **4** as intermediates in this process has been confirmed experimentally [10].

Scheme 1. Preparation of iminophosphorane.



Moreover, we considered the possibility of extending this design strategy to the preparation of 2, 2′-di(alkylamino or alkoxy)-3, 3′-(1, 4-phenylene)bis(3, 5, 6, 7-tetrahydro-4*H*-cyclopenta[4, 5]thieno[2, 3-*d*]pyrimidin-4-ones) **6**. We reacted 1, 4-phenylene diisocyanate with iminophosphorane **2b**, under similar reaction conditions, which furnished new compounds **6** (Scheme 3).

EXPERIMENTAL

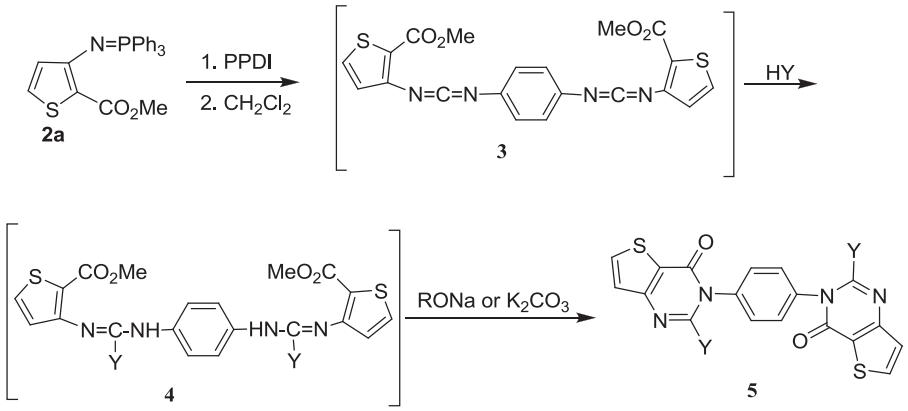
Measurements. Melting points were uncorrected. Mass spectra were measured on a Finnigan Trace MS spectrometer (California, USA). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian (California, USA) Mercury 600 and 400 spectrometers, and resonances were given in δ relative to TMS. Elementary analyses were carried out on a Vario EL III elementary analysis instrument.

Preparation of iminophosphorane 2. To a mixture of aminothiophene **1** (8 mmol), PPh_3 (3.14 g, 12 mmol), and C_2Cl_6 (2.84 g, 12 mmol) in dry MeCN (40 mL) was added dropwise NEt_3 (2.42 g, 24 mmol) at room temperature. After stirring for 4 h, the solvent was removed under reduced pressure, and the residue was recrystallized from EtOH to give methyl 3-[(triphenylphosphoranylidene)amino]thiophene-2-carboxylate **2a** or ethyl 2-[(triphenylphosphoranylidene)amino]-5, 6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylate **2b**.

2a: White crystals (yield 71%). mp: 115–117°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.82–7.45 (m, 15H, Ar-H), 7.03 (d, J = 5.2 Hz, 1H, Ar-H), 6.20 (d, J = 5.2 Hz, 1H, Ar-H), 3.84 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 163.8, 156.0, 132.5, 131.8, 130.9, 129.9, 129.3, 129.1, 128.7, 128.5, 128.3, 124.7, 50.8; MS *m/z* (%): 417 (M^+, 86), 384 (43), 358 (100), 183 (66), 77 (87), 59 (59); *Anal*. Calcd for $C_{24}H_{20}NO_2PS$: C, 69.05; H, 4.83; N, 3.36. Found C, 69.29; H, 4.61; N, 3.59.

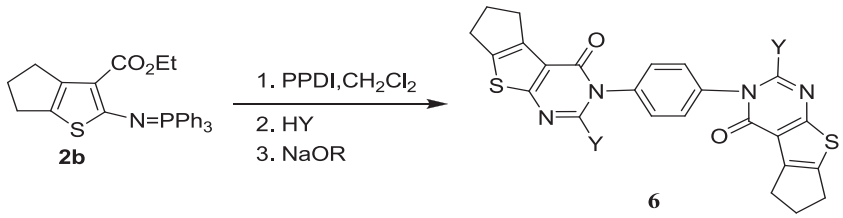
2b: Yellow solid (yield 86%). mp: 183–184°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.47–7.88 (m, 15H, Ar-H), 4.27 (q, J = 6.8 Hz, 2H, OCH_2), 2.88 (t, J = 6.4 Hz, 2H, CH_2), 2.59

Scheme 2. Preparation of compounds **5a–g**.



5a: Y=dipropylamino
5b: Y=diisopropylamino
5c: Y=dibutylamino
5d: Y=diisobutylamino
5e: Y=dihexylamino
5f: Y=4-(methylthio)phenoxy
5g: Y=3-(trifluoromethyl)phenoxy

Scheme 3. Preparation of compounds **6a–g**.



6a: Y=dipropylamino
6b: Y=diisopropylamino
6c: Y=dibutylamino
6d: Y=diisobutylamino
6e: Y=diamylamino
6f: Y=*n*-butylamino
6g: Y=*n*-propoxy

(t, $J = 6.4$ Hz, 2H, CH_2), 2.19 (m, 2H, CH_2), 1.34 (t, $J = 6.8$ Hz, 3H, CH_3); MS *m/z*: 471 (M^+, 79); *Anal*. Calcd for $C_{28}H_{26}NO_2PS$: C, 71.32; H, 5.56; N, 2.97. Found: C, 71.55; H, 5.32; N, 3.21.

General procedure of 2, 2′-dialkylamino-3, 3′-(1, 4-phenylene) bis(thieno[3, 2-*d*]pyrimidin −4(3*H*)-ones) 5a–e. To a solution of iminophosphorane **2a** (0.84 g, 2 mmol) in dry CH_2Cl_2 (5 mL) was added 1, 4-phenylene diisocyanate (1 mmol) at room temperature. Then, the reaction mixture was left to stand for 8–12 h at 0–5°C until the iminophosphorane had disappeared (TLC monitored). To the solution prepared earlier was added amine (2 mmol). After the reaction mixture was allowed to stand for 0.5–6 h (TLC monitored), the solvent was removed, and anhydrous ethanol (10 mL) with several drops of EtONa in EtOH was added. The solution was then concentrated under reduced pressure, and residual was recrystallized from CH_2Cl_2 and EtOH (1:2) to give compounds **5a–f**.

5a: 2, 2′-Di(dipropylamino)-3, 3′-(1, 4-phenylene)bis(thieno [3, 2-d]pyrimidin-4 (3H)-one). White crystals (yield 51%). mp: 248°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.74–7.18 (m, 8H, Ar-H), 3.01 (t, $J = 7.8$ Hz, 8H, NCH_2), 1.35 (m, 8H, CH_2), 0.78 (t, $J = 7.4$ Hz, 12H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 159.2, 156.9, 156.8, 137.4, 134.5, 129.5, 124.6, 116.9, 53.0, 20.7, 11.6; *Anal*. Calcd for $C_{30}H_{36}N_6O_2S_2$: C, 62.47; H, 6.29; N, 14.57. Found: C, 62.69; H, 6.01; N, 14.79.

5b: 2, 2′-Di(diisopropylamino)-3, 3′-(1, 4-phenylene)bis(thieno [3, 2-d]pyrimidin-4 (3H)-one). White crystals (yield 52%). mp: >300°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 7.72–7.16 (m, 8H, Ar-H), 3.55 (m, 4H, 4NCH), 1.13 (d, 24H, $8CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 159.8, 156.7, 155.4, 138.0, 134.2, 129.8, 124.8, 117.2, 50.2, 21.6; MS *m/z* (%): 576 (M^+, 2), 367 (17), 277(17), 210 (43), 151 (100), 100 (48); *Anal*. Calcd for $C_{30}H_{36}N_6O_2S_2$: C, 62.47; H, 6.29; N, 14.57. Found: C, 62.71; H, 6.02; N, 14.79.

5c: 2, 2′-Di(dibutylamino)-3, 3′-(1, 4-phenylene)bis(thieno[3, 2-d]pyrimidin-4(3H) -one). White crystals (yield 49%). mp: 174–176°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.74–7.18 (m, 8H, Ar-H), 3.04 (t, $J = 7.4$ Hz, 8H, $4NCH_2$), 1.33–1.16 (m, 16H, $8CH_2$), 0.86(t, $J = 7.2$ Hz, 12H, $4CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 159.0, 156.7, 156.6, 137.1, 134.4, 129.2, 124.5, 116.7, 50.8, 29.3, 20.2, 13.7; MS *m/z* (%): 632 (M^+, 4), 380 (20), 151 (42), 125 (29), 57 (65), 41 (100); *Anal*. Calcd for $C_{34}H_{44}N_6O_2S_2$: C, 64.52; H, 7.01; N, 13.28. Found: C, 64.79; H, 6.78; N, 13.54.

5d: 2, 2′-Di(diisobutylamino)-3, 3′-(1, 4-phenylene)bis(thieno [3, 2-d]pyrimidin-4 (3H)-one). White crystals (yield 47%). mp >300°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.73–7.15 (m, 8H, Ar-H), 2.91 (d, $J = 7.2$ Hz, 8H, $4NCH_2$), 1.86 (m, 4H, 4CH), 0.81 (m, 24H, $8CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 159.0, 157.0, 156.4, 137.3, 134.5, 129.1, 124.4, 116.0, 58.5, 27.1, 20.5; MS *m/z* (%): 632 (M^+, 14), 589 (100), 533 (71), 477 (56), 366 (35), 207 (34), 151 (90); *Anal*. Calcd for $C_{34}H_{44}N_6O_2S_2$: C, 64.52; H, 7.01; N, 13.28. Found: C, 64.79; H, 6.77; N, 13.59.

5e: 2, 2′-Di(dihexylamino)-3, 3′-(1, 4- phenylene)bis(thieno [3, 2-d]pyrimidin-4 (3H)-one). White crystals (yield 39%). mp: 100–101°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 7.73–7.18 (m, 8H, Ar-H), 3.03 (t, $J = 7.8$ Hz, 8H, $4NCH_2$), 1.35–1.15 (m, 32H, $16CH_2$), 0.85 (t, $J = 6.6$ Hz, 12H, $4CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 159.0, 156.8, 156.6, 137.2, 134.5, 129.1, 124.5, 116.7, 51.0, 31.4, 27.2, 26.7, 22.5, 14.0; MS *m/z* (%): 744 (M^+, 26), 674 (41), 493 (100), 436 (88), 250 (36), 151 (34); *Anal*. Calcd for $C_{42}H_{60}N_6O_2S_2$: C, 67.70; H, 8.12; N, 11.28. Found: C, 67.95; H, 7.92; N, 11.53.

General procedure of 2, 2′-diaryloxy-3, 3′-(1, 4-phenylene)bis (thieno[3, 2-*d*]pyrimidin −4(3*H*)-ones) 5f–g. To a solution of iminophosphorane **2a** (0.84 g, 2 mmol) in dry CH_2Cl_2 (5 mL) was added 1, 4-phenylene diisocyanate (1 mmol) at room temperature. Then, the reaction mixture was left to stand for 8–12 h at 0–5°C until the iminophosphorane had disappeared (TLC monitored). The solvent was evaporated, and the residue was dissolved in MeCN (3 mL), a catalytic amount of K_2CO_3 was added, and the mixture was refluxed for 5 h (TLC monitored) then filtered off. The filtrate was then concentrated under reduced pressure, and residue was recrystallized from CH_2Cl_2 and EtOH (1:2) to give compounds **5f–g**.

5f: 2, 2′-Di[4-(methylthio)phenoxy]-3, 3′-(1, 4-phenylene)bis (thieno[3, 2-d] pyrimidin-4(3H) -one). White crystals (yield 45%). mp: 190–192°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 7.77–7.09 (m, 16H, Ar-H), 2.49 (s, 6H, $2SCH_3$); MS *m/z* (%): 654 (M^+, 14), 268 (17), 247 (31), 200 (27), 139 (100), 111 (29), 96 (74); *Anal*. Calcd for $C_{32}H_{22}N_4O_4S_4$: C, 58.70; H, 3.39; N, 8.56. Found: C, 58.95; H, 3.11; N, 8.79.

5g: 2, 2′-Di[3-(trifluoromethyl)phenoxy]-3, 3′-(1, 4-phenylene) bis(thieno[3, 2-d] pyrimidin-4(3H)-one). White crystals (yield 55%). mp >300°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 7.80–7.13 (m, 16H, Ar-H); MS *m/z* (%): 698 (M^+, 54), 537 (64), 269

(100), 188 (32), 96 (74); *Anal*. Calcd for $C_{32}H_{16}F_6N_4O_4S_2$: C, 55.01; H, 2.31; N, 8.02. Found: C, 55.27; H, 2.01; N, 8.27.

General procedure of 2, 2′-di(alkylamino)-3, 3′-(1, 4-phenylene)bis(3, 5, 6, 7-tetrahydro -4*H*-cyclopenta[4, 5]thieno[2, 3-*d*]pyrimidin-4-ones) 6a–f. The experimental process is similar to the formation of 2, 2′-dialkylamino-3, 3′-(1, 4-phenylene) bis(thieno[3, 2-*d*]pyrimidin-4(3*H*)-ones) **5a–e**.

6a: 2, 2′-Di(dipropylamino)-3, 3′-(1, 4-phenylene)bis(3, 5, 6, 7-tetrahydro-4H-cyclopenta[4, 5]thieno[2, 3-d2]pyrimidin-4-ones). White crystals (yield 41%). mp: 253–255.6°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 7.40–7.27 (d, 4H, Ar-H), 2.99–1.35 (m, 28H, $14CH_2$), 0.76 (t, $J = 6.6$ Hz, $4CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 168.7, 159.3, 154.3, 140.1, 137.2, 134.3, 129.2, 114.3, 53.4, 52.3, 29.4, 28.9, 27.7, 20.6, 11.5; MS *m/z* (%): 656 (M^+, 100). *Anal*. Calcd for $C_{31}H_{34}N_6O_2S_2$: C, 63.45; H, 5.84; N, 14.32; Found: C, 63.69; H, 5.61; N, 14.58.

6b: 2, 2′-Di(diisopropylamino)-3, 3′-(1, 4-phenylene)bis(3, 5, 6, 7-tetrahydro-4H-cyclopenta[4, 5] thieno[2, 3-d]pyrimidin-4-ones). White crystals (yield 69%). mp: 173°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 7.36–7.26 (d, 4H, ArH), 3.53–2.89 (m, 12H, $6CH_2$), 2.44–2.39 (m, 4H, 4CH), 0.12–0.11 (d, 24H, $8CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 168.3, 159.9, 153.2, 140.0, 137.8, 134.5, 129.6, 114.7, 50.2, 29.4, 28.9, 27.7, 21.6. MS *m/z* (%): 656 (M^+, 100). *Anal*. Calcd for $C_{31}H_{34}N_6O_2S_2$: C, 63.45; H, 5.84; N, 14.32; Found: C, 63.68; H, 5.59; N, 14.57.

6c: 2, 2′-Di(dibutylamino)-3, 3′-(1, 4-phenylene)bis(3, 5, 6, 7-tetrahydro-4H-cyclopenta[4, 5] thieno[2, 3-d]pyrimidin-4-ones). White crystals (yield 48%). mp: 253.8–254.5°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 7.40–7.28 (d, 4H, ArH), 3.03–1.16 (m, 36H, $18CH_2$), 0.85 (t, $J = 7.2$ Hz, 12H, $4CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 168.7, 159.2, 154.3, 140.1, 137.1, 134.3, 129.1, 114.3, 50.9, 29.5, 29.4, 28.9, 27.7, 20.2, 13.7. MS *m/z* (%): 712 (M^+, 100). *Anal*. Calcd for $C_{33}H_{38}N_6O_2S_2$: C, 64.47; H, 6.23; N, 13.67; Found: C, 64.71; H, 6.01; N, 13.95.

6d: 2, 2′-Di(diisobutylamino)-3, 3′-(1, 4-phenylene)bis(3, 5, 6, 7-tetrahydro-4H-cyclopenta[4, 5] thieno[2, 3-d]pyrimidin-4-ones). White crystals (yield 63%). mp: 269–271°C. ^{1}HNMR ($CDCl_3$, 600 MHz) δ (ppm): 7.43–7.26 (d, 4H, Ar-H), 2.99–2.39 (m, 24H, $12CH_2$), 1.84 (s, 4H, 4CH), 0.81–0.79 (d, 24H, $8CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 168.9, 159.1, 154.2, 140.1, 137.3, 133.9, 129.1, 113.8, 58.6, 29.4, 28.9, 27.7, 27.2, 20.5. MS *m/z* (%): 712 (M^+, 100). *Anal*. Calcd for $C_{33}H_{38}N_6O_2S_2$: C, 64.47; H, 6.23; N, 13.67; Found: C, 64.73; H, 6.02; N, 13.91.

6e: 2, 2′-Di(diamylamino)-3, 3′-(1, 4-phenylene)bis(3, 5, 6, 7-tetrahydro-4H-cyclopenta[4, 5]thieno[2, 3-d]pyrimidin-4-ones). White crystals (yield 41%). mp: 220.3–220.4°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 7.40 (s, 4H, Ar-H), 3.01–1.12 (m, 44H, $22CH_2$), 0.87–0.84 (t, $J = 7.2$ Hz, 12H, $4CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 168.7, 159.2, 154.2, 140.1, 137.1, 134.2, 129.1, 114.3, 51.1, 29.4, 29.2, 28.9, 27.7, 27.1, 22.2, 13.9. MS *m/z* (%):768 (M^+, 70). *Anal*. Calcd for $C_{33}H_{38}N_6O_2S_2$: C, 64.47; H, 6.23; N, 13.67; Found: C, 64.76; H, 5.99; N, 13.93.

6f: 2, 2′-Di(n-butylamino)-3, 3′-(1, 4-phenylene)bis(3, 5, 6, 7-tetrahydro-4H-cyclopenta[4, 5]thieno[2, 3-d]pyrimidin-4-one). White crystals (yield 64%). mp: 270–272°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 7.49(s, 4H, Ar-H), 5.18 (s, 2H, 2NH), 3.37–1.27 (m, 24H, $12CH_2$), 0.91–0.89 (t, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 171.9, 159.2, 150.1, 139.5, 136.2, 131.9, 131.6, 111.4, 41.9, 31.3, 29.4, 29.0, 27.7, 20.0, 13.8; MS *m/z*: 600 (M^+, 100); *Anal*. Calcd for $C_{40}H_{52}N_6O_2S_2$: C, 67.38; H,7.35;N,11.79. Found: C, 67.59; H, 7.07; N, 12.01.

Synthesis of 2, 2′-dipropoxy-3, 3′-(1, 4-phenylene)bis(3, 5, 6, 7-tetrahydro-4H-cyclopenta[4, 5] thieno[2, 3-d]pyrimidin-4-one) 6g. To the solution of carbodiimides prepared earlier in C_3H_7OH (15 mL) was added 1 equiv of C_3H_7ONa in C_3H_7OH. The mixture was stirred for 6 h at room temperature (TLC monitored). The solution was condensed, and the residue was recrystallized from CH_2Cl_2 and EtOH to give **6g**. White crystals (yield 61%). mp: 276.6–277.6°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 7.30 (s, 4H, Ar-H), 4.31 (s, 4H, OCH_2), 3.02 (s, 4H, CH_2), 2.93 (s, 4H, CH_2), 2.44 (m, 4H, CH_2), 1.65 (s, 4H, CH_2), 0.84 (s, 6H, CH_3); MS *m/z*: 574 (M^+, 20); *Anal*. Calcd for $C_{30}H_{30}N_4O_4S_2$: C, 62.70; H, 5.26; N, 9.75. Found: C, 62.91; H, 5.05; N, 10.02.

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