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New efficient synthesis of pyrimido[1,6-*c*]quinazolin-4-ones by a Biginelli 3CC/Staudinger/aza-Wittig sequence

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ABSTRACT

Dihydropyrimidinone azides **1**, obtained from trimethylsilyl chloride-catalyzed Biginelli reaction of 2-azidobenzaldehyde, ethyl acetoacetate, and urea (or thiourea) at room temperature, reacted with triphenylphosphine to give iminophosphorane **2**. A tandem aza-Wittig reaction of iminophosphorane **2** with isocyanate, acyl chloride or CS_2 in the presence of K_2CO_3 or NEt_3 generated pyrimido[1,6-*c*]quinazolin-4-ones **4**, **6** or **8** in moderate to good yield.

1. Introduction

The multicomponent reaction (MCR) was considered as a powerful synthetic tool for preparing target molecules of biological relevance in an efficient manner. In addition these MCRs involve the stepwise one-pot transformation of three or more reactants into a single product that contains portions of all the starting components and are especially suitable in combinatorial and medicinal chemistry.[1] Other benefits of MCRs are the intrinsic labor and time-saving nature and the high purity of products they generate owing to their high selectivity.[2] The Biginelli reaction, one of the most useful multicomponent reactions, offers an efficient way to access multifunctionalized 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs). Such heterocycles have proved to be efficient calcium channel modulators, mitotic kinesine inhibitors, adrenergic receptor antagonists, antibacterial and antiviral agents.[3] Such a wide spectrum of biological activity allows consideration of the DHPMs structural unit as one of the most important drug-like scaffolds.[4] Furthermore, most notable among these are the batzelladine alkaloids A and B, which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy.[5]

In the study of the Biginelli multicomponent process much emphasis was placed on catalysts screening: various Bronsted and Lewis acids were reported to mediate the Biginelli reaction.[6] However, far less attention has been paid to the further functionalization of the Biginelli adducts,[7] in spite of the fact that the structures thus obtained may present significant biological activity.

The nitrogen-containing heterocyclic molecules, particularly with fused heterocyclic structures, have demonstrated a high degree of binding affinity when they serve as ligands for various biological receptors. Some of the fused Biginelli derived heterocycles have been attracted attention for medicinal chemistry in drug discovery area. For example, the thiazolo[3,2-*a*]pyrimidine **A** is a micromolar inhibitor of the group 2 GPCR metabotropic glutamate receptor, whereas pyrido[3,4-*c*]quinoline **B** has been used in the treatment of asthma (Fig. 1).[8] However, despite of the important drug-like scaffolds of DHPMs, other fused DHPMs were less investigated previously and there is no report on synthesis of 3,11b-dihydro-4*H*-pyrimido[1,6-*c*]quinazolin-4-(thi)ones.

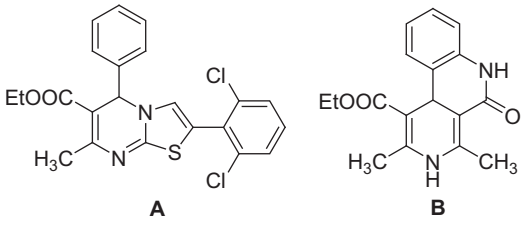

Figure 1. Examples of fused Biginelli derived heterocycles having biological activities.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen heterocyclic compounds.[9] Thus, it is envisioned that combining the efficiency of the Biginelli reaction with a post-condensation aza-Wittig reaction would facilitate access to a series of fused DHPMs, which are of considerable interest as potential biological active compounds or pharmaceuticals. Recently we have been interested in the synthesis of various heterocycles via aza-Wittig reaction, with the aim of evaluating their biological

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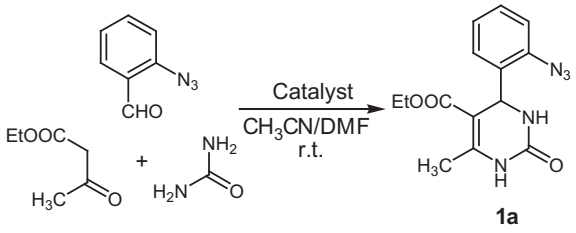
activities.[10] Here we wish to report a fundamentally new approach to the synthesis of previously unreported 3,11b-dihydro-4*H*-pyrimido[1,6-*c*]quinazolin-4-(thi)ones by the Biginelli reaction between easily accessible 2-azidobenzaldehyde, ethyl acetoacetate, and (thio)ureas, followed by a Staudinger/aza-Wittig cyclization of the Biginelli products.

2. Results and discussion

Although many aldehydes were utilized in the Biginelli reaction, 2-azidobenzaldehyde was not used previously in the reaction to prepare corresponding tetrahydropyrimidine azides **1**. It has been reported that the Biginelli reaction can be efficiently promoted by various acids such as HCl, $Bi(OTf)_3$, BF_3, H_3BO_3, LaX_3 (X=Cl, OTf), $Yb(OTf)_3$, $In(OTf)_3$, $ZrCl_4$, $Mn(OAc)_3$, $FeCl_3\cdot 6H_2O$, $NiCl_3\cdot 6H_2O$, $RuCl_3$, etc. as catalyst, however, many of the reactions were carried out at refluxing temperature, which is not suitable for preparing the thermal labile azides **1**. Some catalysts, such as Me_3SiCl, Me_3SiI, $SiCl_4$, were also successfully utilized in the Biginelli reaction under room temperature condition.[11] Initially, the Biginelli reaction of 2-azidobenzaldehyde, ethyl acetoacetate, and urea was chosen as a model to optimize the reaction condition (Scheme 1). We used a CH_3CN/DMF (4:1) solution of 2-azidobenzaldehyde (3 mmol), ethyl acetoacetate (3 mmol), and urea (3.6 mmol) in the presence of HCl, H_2SO_4, or Me_3SiCl that was stirred at room temperature for 4 h (Table 1). With HCl and H_2SO_4 as catalysts, the desired product was formed only in moderate yields. TMSCl proved to be a very effective catalyst and provided high yield of the azide **1a** as 0.5 equiv amount of it was used. Further increasing the amount of TMSCl (1.0 equiv) did not improve the product yield considerably.



Scheme 1. Preparation of compound **1a**.

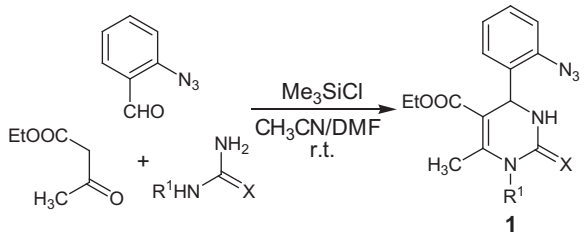
Table 1
Optimization of the reaction conditions

Entry	Catalyst	Proportion	Yield[a] [%]
1	NON	—	0
2	HCl	1:1	61
3	HCl	1:0.5	46
4	H_2SO_4	1:1	50
5	H_2SO_4	1:0.5	33
6	TMSCl	1:0.1	46
7	TMSCl	1:0.2	52
8	TMSCl	1:0.5	91
9	TMSCl	1:1	92

[a] Isolated yields of **1a** based on 2-azidobenzaldehyde.

With the optimized condition, various ureas and thioureas were employed for the Biginelli reaction in the presence of 0.5 equiv amount of Me_3SiCl (Scheme 2). All reactions proceeded smoothly to give the corresponding dihydropyrimidinone azides **1** (Table 2) in good yields at room temperature.

The obtained azides **1** were further reacted with triphenylphosphine, and the iminophosphoranes **2** was obtained in excellent isolated yields (88–94%) via Staudinger reaction (Scheme 3). When solutions of iminophosphoranes **2** in dry CH_2Cl_2 or CH_3CN



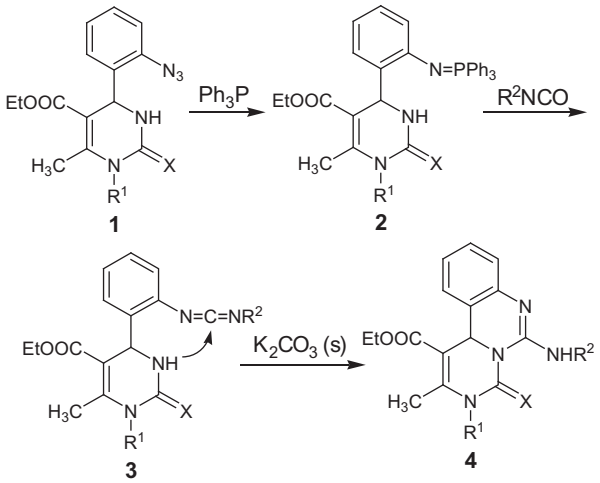
Scheme 2. Preparation of compounds **1**.

Table 2
Preparation of azides **1** via Biginelli reaction

Compd	X	R^1	Yield[a] [%]
1a	O	H	91
1b	S	H	90
1c	O	Et	77
1d	O	Me	87
1e	O	Ph	88
1f	S	Ph	82

[a] Isolated yields of **1** based on 2-azidobenzaldehyde.

were treated with aromatic or aliphatic isocyanates at room or refluxing temperature, carbodiimides **3** were isolated in moderate to good yields. The direct cyclization of **3** to **4** through the addition of pyrimidinone NH to the carbodiimide moiety didn't occur under the reaction condition. This is probably due to the low nucleophilicity of the NH on the pyrimidinone ring. Heating of carbodiimide **3** in toluene resulted in a complex mixture owning to the unstablity of the carbodiimide **3** at high temperature. However, in the presence of catalytic amount of potassium carbonate in CH_3CN at room temperature, carbodiimides **3** cyclized easily to give pyrimido[1,6-*c*]quinazolin-4-ones **4** in moderate to good overall yields (Scheme 3, Table 3). It's noteworthy that the reaction proceeds under mild conditions to give various substituted pyrimido[1,6-*c*]quinazolin-4-ones, and the overall transformation can be run in a one-pot procedure from azides **1**, or with isolation of the intermediate iminophosphoranes **2** or carbodiimides **3**.



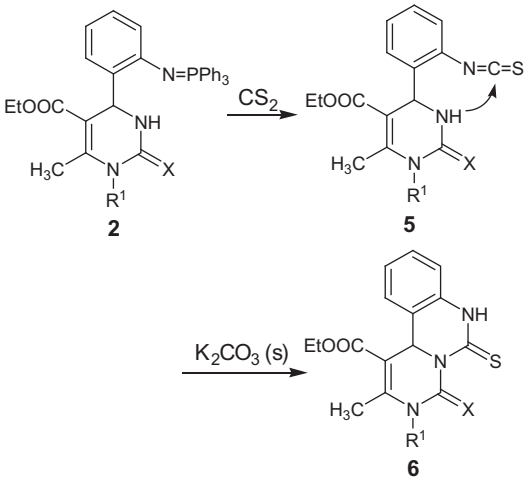
Scheme 3. Preparation of compounds **4**.

The reaction of iminophosphoranes **2** with CS_2 in refluxing CH_3CN also gave the isothiocyanate **5**. In the presence of catalytic amount of potassium carbonate in CH_3CN, **5** was easily transferred into **6** in good yield (Scheme 4).

Table 3
Preparation of compounds **4** and **6**

Compd	X	R^1	R^2	Yield[a] [%]
4a	S	H	Ph	57
4b	O	H	Ph	59
4c	S	H	*i*-Pr	85
4d	S	H	4-Cl–C_6H_4	57
4e	O	Et	Ph	60
4f	O	H	*i*-Pr	75
4g	O	Me	Ph	64
4h	O	Ph	Ph	75
4i	O	Ph	*i*-Pr	64
4j	O	Me	*i*-Pr	78
4k	S	H	3-Me–C_6H_4	72
4l	O	Me	4-Cl–C_6H_4	60
4m	O	Ph	4-Cl–C_6H_4	69
4n	O	Me	4-F–C_6H_4	62
4o	O	Ph	4-F–C_6H_4	69
4p	O	Et	*i*-Pr	73
4q	S	Ph	Ph	72
4r	S	Ph	*i*-Pr	77
6a	S	H		86
6b	O	H		82

[a] Isolated yields based on iminophosphorane **2**.



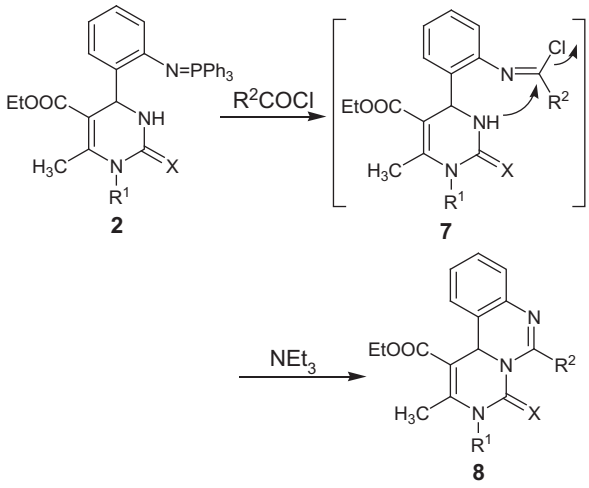
Scheme 4. Preparation of compounds **6**.

Iminophosphoranes **2** reacted with acyl chlorides in the presence of triethylamine in CH_3CN at refluxing temperature to give directly 2-substituted pyrimido[1,6-*c*]quinazolines **8** in good yields (61–92%, Table 4, Scheme 5). The formation of **8** can be viewed as an

Table 4
Preparation of compounds **8** from iminophosphoranes **2**

Compd	X	R^1	R^2	Yield[a] [%]
8a	S	H	Ph	65
8b	S	H	3-Cl–C_6H_4	61
8c	O	Me	Ph	81
8d	O	Ph	Ph	84
8e	O	Me	4-Me–C_6H_4	80
8f	O	Ph	4-Me–C_6H_4	81
8g	O	Me	2-Cl–C_6H_4	76
8h	O	Ph	2-Cl–C_6H_4	79
8i	O	Me	3-Cl–C_6H_4	81
8j	O	Ph	3-Cl–C_6H_4	81
8k	O	Me	2-F–C_6H_4	80
8l	O	Me	4-F–C_6H_4	63
8m	S	Ph	Ph	88
8n	S	Ph	4-NO_2–C_6H_4	90
8o	S	Ph	3-Cl–C_6H_4	77
8p	S	Ph	4-Me–C_6H_4	74
8q	S	Ph	2-Cl–C_6H_4	92

[a] Isolated yields based on iminophosphorane **2**.



Scheme 5. Preparation of compounds **8**.

initial aza-Wittig reaction between the iminophosphorane **2** and acyl chloride in presence of triethylamine affording the intermediate imidoyl chloride **7**, which undergoes cyclization to give **8**.

The structure of pyrimido[1,6-*c*]quinazolines **4**, **6**, and **8** was confirmed by their spectrum data. Furthermore a single crystal of **8a** was obtained from a CH_2Cl_2 solution of **8a**. X-ray structure analysis verified again the proposed structure (Fig. 2).

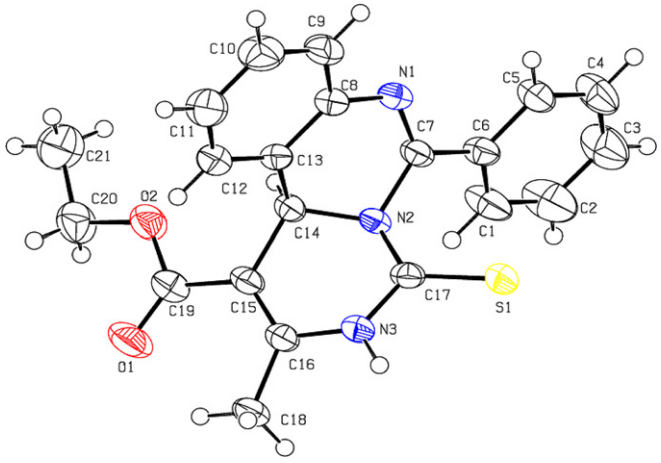


Figure 2. ORTEP diagram of the crystal structure of tricyclic compound **8a** (50% thermal ellipsoids).

3. Conclusion

We have developed a new MCR, yielding 3,11b-dihydro-4*H*-pyrimido[1,6-*c*]quinazolin-4-(thi)ones, by a sequence of a trimethylsilyl chloride-catalyzed Biginelli reaction, Staudinger reaction and a tandem aza-Wittig ring closure. This method utilizes easily accessible starting material and allows mild reaction conditions, straightforward product isolation, and good yields.

4. Experimental

4.1. General

Melting points were uncorrected. 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}. NMR

were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 400 or 600 spectrometer and resonances relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument. The X-ray diffraction data were collected on a *Bruker SMART AXS CCD* diffractometer, Mo Kα, 2θ=1.86–27.50°. 2-Azidobenzaldehyde was easily prepared from the reaction of sodium azide with 2-nitrobenzaldehyde according to the literature reports.[12]

4.2. Synthesis of azides 1 via Biginelli reaction

*4.2.1. 4-(2-Azidophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**1a**).* 2-Azidobenzaldehyde (0.29 g, 2.0 mmol), urea (0.14 g, 2.4 mmol), and ethyl acetoacetate (0.26 g, 2.0 mmol) were added to acetonitrile/DMF (4 mL/1 mL) sequentially at room temperature. After the addition of Me_3SiCl (0.11 g, 1.0 mmol), the mixture was stirred for 4 h at ambient temperature. The crude product was collected by filtration and washed with ethanol to give 0.55 g (91%) of azide **1a** as white solid. Mp: 206–208 °C. IR (KBr): 3242, 3112, 2957, 2128, 1716, 1702, 1637 cm^{-1}. ^1H NMR (DMSO-d_6, 600 MHz): δ 9.20 (s, 1H, NH), 7.55 (s, 1H, NH), 7.36–7.16 (m, 4H, Ar–H), 5.44 (s, 1H, CH), 3.90 (q, J=7.2 Hz, 2H, OCH_2), 2.29 (s, 3H, CH_3), 1.00 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 272 (M^+-N_2-1, 2), 200 (11), 155 (10), 103 (14), 42 (100). Anal. Calcd for $C_{14}H_{15}N_5O_3$: C, 55.81; H, 5.02; N, 23.24. Found: C, 55.63; H, 5.17; N, 23.46.

*4.2.2. 4-(2-Azidophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (**1b**).* Operation as above with thiourea (0.18 g, 2.4 mmol), compound **1b** (0.57 g, 90%) was also isolated as white solid. Mp: 176–177 °C. IR (KBr): 3402, 3198, 2984, 2124, 1710 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.03 (s, 1H, NH), 7.36–7.09 (m, 5H, Ar–H), 5.69 (d, J=3.0 Hz, 1H, CH), 4.06 (q, J=7.2 Hz, 2H, OCH_2), 2.44 (s, 3H, CH_3), 1.10 (t, J=7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{14}H_{15}N_5O_2S$: C, 52.98; H, 4.76; N, 22.07. Found: C, 52.84; H, 4.79; N, 22.26.

*4.2.3. 4-(2-Azidophenyl)-5-ethoxycarbonyl-1-ethyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**1c**).* Operation as above with 1-ethylurea (0.21 g, 2.4 mmol), compound **1c** (0.51 g, 77%) was also isolated as white solid. Mp: 143–145 °C. IR (KBr): 3406, 3218, 2988, 2957, 2127, 1682 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.32–7.04 (m, 4H, Ar–H), 5.73 (s, 1H, NH), 5.57 (s, 1H, CH), 4.06–4.03 (m, 2H, OCH_2), 3.92–3.66 (m, 2H, NCH_2), 2.63 (s, 3H, CH_3), 1.17 (t, J=7.2 Hz, 3H, CH_3), 1.09 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 329 (M^+, 2), 300 (20), 228 (100), 200 (48), 185 (34), 70 (52). Anal. Calcd for $C_{16}H_{19}N_5O_3$: C, 58.35; H, 5.81; N, 21.26. Found: C, 58.38; H, 5.71; N, 21.51.

*4.2.4. 4-(2-Azidophenyl)-1,6-dimethyl-5-ethoxycarbonyl-3,4-dihydropyrimidin-2(1H)-one (**1d**).* Operation as above with 1-methylurea (0.18 g, 2.4 mmol), compound **1d** (0.55 g, 87%) was also isolated as white solid. Mp: 158–160 °C. IR (KBr): 3422, 3239, 2926, 2129, 1680 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.32–7.05 (m, 4H, Ar–H), 5.76 (s, 1H, NH), 5.59 (s, 1H, CH), 4.05 (q, J=7.2 Hz, 2H, OCH_2), 3.19 (s, 3H, NCH_3), 2.62 (s, 3H, CH_3), 1.10 (t, J=7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{15}H_{17}N_5O_3$: C, 57.13; H, 5.43; N, 22.21. Found: C, 57.35; H, 5.21; N, 22.37.

*4.2.5. 4-(2-Azidophenyl)-5-ethoxycarbonyl-6-methyl-1-phenyl-3,4-dihydropyrimidin-2(1H)-one (**1e**).* Operation as above with 1-phenylurea (0.33 g, 2.4 mmol), compound **1e** (0.66 g, 88%) was also isolated as white solid. Mp: 211–213 °C. IR (KBr): 3351, 2979, 2130, 1685 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.44–7.14 (m, 9H, Ar–H), 5.85 (s, 1H, NH), 5.70 (s, 1H), 4.04–4.12 (m, 2H, OCH_2), 2.21 (s, 3H, CH_3), 1.12 (t, J=7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{20}H_{19}N_5O_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.74; H, 5.01; N, 18.75.

*4.2.6. 4-(2-Azidophenyl)-5-ethoxycarbonyl-6-methyl-1-phenyl-3,4-dihydropyrimidine-2(1H)-thione (**1f**).* Operation as above with 1-phenylthiourea (0.36 g, 2.4 mmol), compound **1f** (0.64 g, 82%) was also isolated as white solid. Mp: 179–181 °C. IR (KBr): 3410, 3157, 2130, 1702, 1685 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.70–7.16 (m, 9H, Ar–H), 7.00 (br s, 1H, NH), 5.70 (d, J=3.2 Hz, 1H, CH), 4.13–4.06 (m, 2H, OCH_2), 2.22 (s, 3H, CH_3), 1.12 (t, J=7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{20}H_{19}N_5O_2S$: C, 61.05; H, 4.87; N, 17.80. Found: C, 61.28; H, 4.63; N, 17.95.

4.3. Synthesis of the iminophosphoranes 2 via Staudinger reaction

*4.3.1. 5-Ethoxycarbonyl-6-methyl-4-(2-(triphenylphosphoranylideneamino)phenyl)-3,4-dihydropyrimidin-2(1H)-one (**2a**).* To a stirred solution of azide **1a** (0.60 g, 2 mmol) in CH_2Cl_2 (10 mL) was added dropwise triphenylphosphine (0.52 g, 2 mmol) in CH_2Cl_2 (5 mL) at room temperature. After the reaction mixture was stirred for 2 h at ambient temperature, the solvent was removed off under reduced pressure and the residual was recrystallized from methylene dichloride/petroleum ether to give 0.96 g (90%) of iminophosphorane **2a** as white solid. Mp: 253–255 °C. IR (KBr): 3242, 3112, 2957, 1716, 1702, 1637 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.77–7.45 (m, 15H, Ar–H), 7.17 (s, 1H, NH), 7.04 (s, 1H, NH), 6.94 (d, J=4.8 Hz, 1H, Ar–H), 6.78–6.75 (m, 1H, Ar–H), 6.57 (t, J=7.2 Hz, 1H, Ar–H), 6.40 (d, J=7.8 Hz, 1H, Ar–H), 6.17 (s, 1H, CH), 4.06 (q, J=7.2 Hz, 2H, OCH_2), 2.45 (s, 3H, CH_3), 1.06 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 535 (M^+, 56), 462 (8), 277 (30), 262 (100), 183 (54). Anal. Calcd for $C_{32}H_{30}N_3O_3P$: C, 71.76; H, 5.65; N, 7.85. Found: C, 71.95; H, 5.51; N, 7.95.

*4.3.2. 5-Ethoxycarbonyl-6-methyl-4-(2-(triphenylphosphoranylideneamino)phenyl)-3,4-dihydropyrimidine-2(1H)-thione (**2b**).* Operation as above with azide **1b** (0.63 g, 2 mmol), compound **2b** (0.97 g, 88%) was also isolated as white solid. Mp: 242–244 °C. IR (KBr): 3236, 3118, 2956, 1711, 1702, 1638 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.79 (s, 1H, NH), 7.79–7.38 (m, 16H, Ar–H and NH), 6.90–6.38 (m, 4H, Ar–H), 6.19 (s, 1H, CH), 4.08 (q, J=7.2 Hz, 2H, OCH_2), 2.43 (s, 3H, CH_3), 1.08 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 551 (M^+, 53), 478 (20), 277 (34), 262 (100), 183 (52), 108 (18). Anal. Calcd for $C_{32}H_{30}N_3O_2PS$: C, 69.67; H, 5.48; N, 7.62. Found: C, 69.41; H, 5.24; N, 7.76.

*4.3.3. 5-Ethoxycarbonyl-1-ethyl-6-methyl-4-(2-(triphenylphosphoranylideneamino)phenyl)-3,4-dihydropyrimidin-2(1H)-one (**2c**).* Operation as above with azide **1c** (0.66 g, 2 mmol), compound **2c** (1.06 g, 94%) was also isolated as white solid. Mp: 195–197 °C. IR (KBr): 3240, 3110, 2958, 1714, 1700, 1641 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.77–6.38 (m, 20H, Ar–H and NH), 6.09 (s, 1H, CH), 4.08–4.03 (m, 2H, OCH_2), 3.86–3.65 (m, 2H, NCH_2), 2.65 (s, 3H, CH_3), 1.15 (t, J=7.2 Hz, 3H, CH_3), 1.04 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 563 (M^+, 100), 534 (21), 490 (7), 300 (14), 262 (86), 183 (23). Anal. Calcd for $C_{34}H_{34}N_3O_3P$: C, 72.45; H, 6.08; N, 7.46. Found: C, 72.23; H, 6.22; N, 7.21.

*4.3.4. 1,6-Dimethyl-5-ethoxycarbonyl-4-(2-(triphenylphosphoranylideneamino)phenyl)-3,4-dihydropyrimidin-2(1H)-one (**2d**).* Operation as above with azide **1d** (0.63 g, 2 mmol), compound **2d** (1.00 g, 91%) was also isolated as light yellow solid. Mp: 212–214 °C. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.77–7.46 (m, 15H, Ar–H), 7.05–6.38 (m, 5H, Ar–H and NH), 6.09 (s, 1H, CH), 4.06 (q, J=7.2 Hz, 2H, OCH_2), 3.17 (s, 3H, NCH_3), 2.63 (s, 3H, CH_3), 1.05 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 549 (M^+, 20), 476 (8), 286 (13), 277 (14), 262 (100),

183 (52), 56 (44). Anal. Calcd for $C_{33}H_{32}N_3O_3P$: C, 72.12; H, 5.87; N, 7.65. Found: C, 72.04; H, 5.70; N, 7.91.

*4.3.5. 5-Ethoxycarbonyl-6-methyl-1-phenyl-4-(2-(triphenylphosphoranylideneamino)phenyl)-3,4-dihydropyrimidin-2(1H)-one (**2e**).* Operation as above with azide **1e** (0.75 g, 2 mmol), compound **2e** (1.12 g, 92%) was also isolated as light yellow solid. Mp: 230–232 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.78–6.41 (m, 25H, Ar–H and NH), 6.21 (s, 1H, CH), 4.13–4.05 (m, 2H, OCH_2), 2.22 (s, 3H, CH_3), 1.09 (t, J=7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{38}H_{34}N_3O_3P$: C, 74.62; H, 5.60; N, 6.87. Found: C, 74.87; H, 5.63; N, 6.72.

*4.3.6. 5-Ethoxycarbonyl-6-methyl-1-phenyl-4-(2-(triphenylphosphoranylideneamino)phenyl)-3,4-dihydropyrimi dine-2(1H)-thione (**2f**).* Operation as above with azide **1f** (0.63 g, 2 mmol), compound **2f** (1.00 g, 93%) was also isolated as white solid. Mp: 229–230 °C. IR (KBr): 3244, 3116, 2958, 1714, 1708, 1635 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.04 (s, 1H, NH), 7.82–6.40 (m, 24H, Ar–H), 6.21 (s, 1H, CH), 4.17–4.08 (m, 2H, OCH_2), 2.22 (s, 3H, CH_3), 1.12 (t, J=7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{38}H_{34}N_3O_2PS$: C, 72.71; H, 5.46; N, 6.69. Found: C, 72.64; H, 5.42; N, 6.88.

4.4. Synthesis of pyrimido[1,6-*c*]quinazolin-4-ones 4

*4.4.1. 1-Ethoxycarbonyl-6-phenylamino-2-methyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**4a**).* To a solution of iminophosphorane **2b** (0.55 g, 1 mmol) in CH_3CN (10 mL) was added phenylisocyanate (0.12 g, 1 mmol) under nitrogen at room temperature. After stirred for 2 h at room temperature, K_2CO_3 (0.014 g, 0.1 mmol) was added and the mixture was stirred for 1 h. The solvent was removed off under reduced pressure and the residue was recrystallized from methylene dichloride and ethanol to give 0.22 g (57%) of compound **4a** as light yellow solid. Mp: 160–161 °C. IR (KBr): 3297, 1634, 1591 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.93 (s, 1H, NH), 7.75–6.85 (m, 10H, Ar–H and NH), 5.64 (s, 1H, CH), 4.25 (q, J=7.2 Hz, 2H, OCH_2), 2.43 (s, 3H, CH_3), 1.23 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 392 (M^+, 100), 319 (20), 300 (21), 260 (55), 181 (14). Anal. Calcd for $C_{21}H_{20}N_4O_2S$: C, 64.27; H, 5.14; N, 14.28. Found: C, 64.16; H, 5.17; N, 14.53.

*4.4.2. 1-Ethoxycarbonyl-6-phenylamino-2-methyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4b**).* Operation as above with iminophosphorane **2a** (0.54 g, 1 mmol) at room temperature for 2 h, compound **4b** (0.22 g, 59%) was also isolated as white solid. Mp: 247–249 °C. IR (KBr): 3300, 1706, 1648 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.22 (s, 1H, NH), 7.67 (d, J=7.8 Hz, 2H, Ar–H), 7.58 (s, 1H, NH), 7.30–6.83 (m, 7H, Ar–H), 5.54 (s, 1H, CH), 4.23–4.17 (m, 2H, OCH_2), 2.31 (s, 3H, CH_3), 1.21 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.5, 150.8, 147.3, 144.2, 142.7, 138.8, 128.8, 128.6, 127.3, 123.5, 123.2, 122.8, 119.6, 97.5, 60.5, 53.9, 18.3, 14.1. MS m/z: 376 (M^+, 100), 347 (54), 302 (46), 260 (23), 220 (27), 77 (50). Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 67.17; H, 5.18; N, 14.85.

*4.4.3. 1-Ethoxycarbonyl-6-isopropylamino-2-methyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**4c**).* Operation as above with isopropylisocyanate (0.09 g, 1 mmol) at refluxing temperature for 4 h, compound **4c** (0.30 g, 85%) was also isolated as light yellow solid. Mp: 216–218 °C. IR (KBr): 3365, 3124, 2982, 1700, 1646 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.88 (s, 1H, NH), 7.26–6.79 (m, 4H, Ar–H), 5.51 (s, 1H, CH), 5.17 (s, 1H, NH), 4.28–4.19 (m, 3H, OCH_2 and NCH), 2.39 (s, 3H, CH_3), 1.38 (d, J=6.6 Hz, 3H, CH_3), 1.30 (d, J=6.6 Hz, 3H, CH_3), 1.22 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.3, 165.4, 148.0, 143.7, 143.4, 128.8, 127.2, 122.7, 122.6, 122.5, 99.5, 60.6, 54.3, 44.0, 22.8, 21.7, 17.6, 14.1. MS m/z: 358 (M^+, 100), 325 (21%), 301 (23%), 269 (26%), 226 (95%), 184 (53%), 169 (46%). Anal. Calcd for $C_{18}H_{22}N_4O_2S$: C, 60.31; H, 6.19; N, 15.63. Found: C, 60.12; H, 6.26; N, 15.68.

*4.4.4. 6-(4-Chlorophenylamino)-1-ethoxycarbonyl-2-methyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**4d**).* Operation as above with 4-chlorophenylisocyanate (0.15 g, 1 mmol) at room temperature for 1 h, compound **4d** (0.24 g, 57%) was also isolated as white solid. Mp: 214–216 °C. IR (KBr): 3434, 3336, 2992, 1692, 1640 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.96 (s, 1H, NH), 7.69–6.85 (m, 9H, Ar–H and NH), 5.63 (s, 1H, CH), 4.28–4.22 (m, 2H, OCH_2), 2.42 (s, 3H, CH_3), 1.23 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.4, 165.2, 144.8, 143.4, 142.1, 136.7, 129.0, 128.9, 128.6, 127.3, 124.0, 123.3, 122.8, 121.1, 99.8, 60.8, 54.5, 18.0, 14.2. MS m/z: 426 (M^+, 29), 293 (34), 280 (16), 256 (13), 127 (100), 110 (29). Anal. Calcd for $C_{21}H_{19}ClN_4O_2S$: C, 59.08; H, 4.49; N, 13.12. Found: C, 59.29; H, 4.25; N, 13.03.

*4.4.5. 1-Ethoxycarbonyl-3-ethyl-6-phenylamino-2-methyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4e**).* Operation as above with iminophosphorane **2c** (0.56 g, 1 mmol) at room temperature for 2 h, compound **4e** (0.24 g, 60%) was also isolated as white solid. Mp: 201–203 °C. IR (KBr): 3310, 1668, 1635 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.74–6.87 (m, 10H, Ar–H and NH), 5.50 (s, 1H, CH), 4.27–4.22 (m, 2H, OCH_2), 3.65–3.72 (m, 2H, NCH_2), 2.63 (s, 3H, CH_3), 1.19 (t, J=6.6 Hz, 3H, CH_3), 1.11 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9, 150.8, 149.4, 145.5, 143.1, 138.9, 128.6, 128.5, 127.3, 123.3, 122.9, 122.5, 119.6, 100.6, 60.5, 52.5, 38.8, 15.9, 14.5, 14.1. MS m/z: 404 (M^+, 100), 374 (45), 330 (28), 286 (29), 227 (32), 92 (95). Anal. Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.27; H, 5.84; N, 13.96.

*4.4.6. 1-Ethoxycarbonyl-6-isopropylamino-2-methyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4f**).* Operation as above with iminophosphorane **2a** (0.54 g, 1 mmol) and isopropylisocyanate (0.09 g, 1 mmol) at refluxing temperature for 4 h, compound **4f** (0.26 g, 75%) was also isolated as white solid. Mp: 280–282 °C. IR (KBr): 3113, 2967, 1696, 1648 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.79 (s, 1H, NH), 7.23–6.79 (m, 4H, Ar–H), 5.46 (s, 1H, CH), 5.16 (d, J=6.0 Hz, 1H, NH), 4.28–4.17 (m, 3H, NCH and OCH_2), 2.38 (s, 3H, CH_3), 1.28 (d, J=6.6 Hz, 6H, $2CH_3$), 1.18 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 150.6, 147.4, 146.7, 143.9, 128.4, 127.0, 122.6, 122.4, 97.6, 60.3, 53.8, 43.7, 22.8, 22.3, 18.1, 14.1. MS m/z: 342 (M^+, 100), 313 (30), 271 (26), 226 (19), 210 (19), 184 (13). Anal. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36. Found: C, 63.06; H, 6.53; N, 16.10.

*4.4.7. 2,3-Dimethyl-1-ethoxycarbonyl-6-phenylamino-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4g**).* Operation as above with iminophosphorane **2d** (0.55 g, 1 mmol) at room temperature for 4 h, compound **4g** (0.25 g, 64%) was also isolated as white solid. Mp: 235–237 °C. IR (KBr): 3331, 1679, 1634 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.76–6.87 (m, 10H, Ar–H and NH), 5.53 (s, 1H, CH), 4.25–4.20 (m, 2H, OCH_2), 3.16 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 1.20 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.8, 151.2, 149.9, 145.2, 143.2, 138.8, 128.7, 128.6, 127.3, 123.4, 123.2, 123.0, 122.6, 119.6, 100.2, 60.6, 52.5, 30.9, 16.7, 14.1. MS m/z: 390 (M^+, 25), 361 (26), 317 (13), 260 (11), 243 (18), 212 (20), 92 (100). Anal. Calcd for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.54; H, 5.75; N, 14.21.

*4.4.8. 1-Ethoxycarbonyl-2-methyl-3-phenyl-6-phenylamino-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4h**).* Operation as above with iminophosphorane **2e** (0.61 g, 1 mmol) at room temperature for 3 h, compound **4h** (0.34 g, 75%) was also isolated as white solid. Mp: 206–208 °C. ^{1}H NMR ($CDCl_3$, 400 MHz):

δ 7.69–6.97 (m, 15H, Ar–H and NH), 5.68 (s, 1H, CH), 4.24 (q, *J*=7.2 Hz, 2H, OCH_2), 2.20 (s, 3H, CH_3), 1.21 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 150.6, 149.5, 145.1, 143.3, 138.8, 136.6, 129.2, 129.1, 129.0, 128.6, 128.4, 127.2, 123.4, 123.0, 122.9, 122.4, 119.7, 101.1, 60.6, 53.1, 18.5, 14.1. MS *m*/*z*: 452 (M^+−1, 26), 423 (13), 378 (12), 258 (10), 145 (21), 118 (66), 77 (100). Anal. Calcd for $C_{27}H_{24}N_4O_3$: C, 71.67; H, 5.35; N, 12.38. Found: C, 71.72; H, 5.30; N, 12.24.

*4.4.9. 1-Ethoxycarbonyl-6-isopropylamino-2-methyl-3-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4i**).* Operation as above with iminophosphorane **2e** (0.61 g, 1 mmol) and isopropylisocyanate (0.09 g, 1 mmol) at refluxing temperature for 4 h, compound **4i** (0.27 g, 64%) was also isolated as white solid. Mp: 200–202 °C. IR (KBr): 3340, 2972, 1693, 1629 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38–6.92 (m, 9H, Ar–H), 5.55 (s, 1H, CH), 5.16 (d, *J*=8.0 Hz, 1H, NH), 4.30–4.19 (m, 3H, OCH_2 and NCH), 2.18 (s, 3H, CH_3), 1.27 (d, *J*=6.8 Hz, 6H, $2CH_3$), 1.20 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.7, 150.4, 149.2, 148.1, 144.2, 136.9, 129.2, 128.7, 128.5, 128.4, 127.0, 122.4, 122.3, 122.2, 100.7, 60.4, 53.0, 43.5, 22.5, 21.9, 18.4, 14.0. MS *m*/*z*: 418 (M^+, 100), 389 (56), 344 (36), 304 (30), 274 (29), 118 (87). Anal. Calcd for $C_{24}H_{26}N_4O_3$: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.63; H, 6.12; N, 13.57.

*4.4.10. 2,3-Dimethyl-1-ethoxycarbonyl-6-isopropylamino-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4j**).* Operation as above with iminophosphorane **2d** (0.55 g, 1 mmol) and isopropylisocyanate (0.09 g, 1 mmol) at refluxing temperature for 4 h, compound **4j** (0.28 g, 78%) was also isolated as white solid. Mp: 154–156 °C. IR (KBr): 3366, 2974, 1685, 1631 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25–6.81 (m, 4H, Ar–H), 5.41 (s, 1H, CH), 5.02 (d, *J*=8.0 Hz, 1H, NH), 4.31–4.17 (m, 3H, OCH_2 and NCH), 3.13 (s, 3H, NCH_3), 2.59 (s, 3H, CH_3), 1.33 (d, *J*=6.4 Hz, 3H, CH_3), 1.29 (d, *J*=6.4 Hz, 3H, CH_3), 1.18 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9, 151.2, 149.8, 148.4, 144.2, 128.4, 127.0, 122.5, 122.4, 122.2, 100.2, 60.4, 52.4, 43.6, 30.7, 22.7, 22.1, 16.6, 14.1. MS *m*/*z*: 355 (M^+−1, 100), 326 (27), 286 (9), 240 (11), 44 (9). Anal. Calcd for $C_{19}H_{24}N_4O_3$: C, 64.03; H, 6.79; N, 15.72. Found: C, 64.27; H, 6.78; N, 15.53.

*4.4.11. 1-Ethoxycarbonyl-2-methyl-6-(3-methylphenylamino)-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**4k**).* Operation as above with 3-methylphenylisocyanate (0.13 g, 1 mmol) at room temperature for 4 h, compound **4k** (0.29 g, 72%) was also isolated as white solid. Mp: 136–138 °C. IR (KBr): 3393, 2979, 1635, 1588 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 1H, NH), 7.59–6.84 (m, 9H, Ar–H and NH), 5.64 (s, 1H, CH), 4.26–4.23 (m, 2H, OCH_2), 2.42 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 1.23 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.5, 165.3, 145.1, 143.8, 142.6, 138.8, 137.9, 128.9, 128.8, 127.5, 124.6, 123.7, 123.4, 122.8, 120.4, 117.1, 99.7, 60.8, 54.4, 21.6, 17.8, 14.2. MS *m*/*z*: 406 (M^+, 1), 376 (7), 275 (86), 216 (34), 170 (40), 128 (86), 76 (100). Anal. Calcd for $C_{22}H_{22}N_4O_2S$: C, 65.00; H, 5.46; N, 13.78. Found: C, 65.24; H, 5.32; N, 13.85.

*4.4.12. 6-(4-Chlorophenylamino)-2,3-dimethyl-1-ethoxycarbonyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4l**).* Operation as above with iminophosphorane **2d** (0.55 g, 1 mmol) and 4-chlorophenylisocyanate (0.15 g, 1 mmol) at room temperature for 1 h, compound **4l** (0.25 g, 60%) was also isolated as white solid. Mp: 204–205 °C. IR (KBr): 3328, 1680, 1634 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J*=8.8 Hz, 2H, Ar–H), 7.38 (s, 1H, NH), 7.30–6.87 (m, 6H, Ar–H), 5.52 (s, 1H, CH), 4.24–4.21 (m, 2H, OCH_2), 3.16 (s, 3H, NCH_3), 2.62 (s, 3H, CH_3), 1.20 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.7, 151.3, 149.8, 144.9, 142.9, 137.6, 128.7, 128.6, 127.8, 127.2, 123.6, 123.1, 122.7, 120.6, 100.4, 60.7, 52.5, 30.9, 16.7, 14.2. MS *m*/*z*: 424 (M^+, 100), 395 (56), 350 (48), 242 (28), 75 (16), 56 (95). Anal. Calcd for $C_{22}H_{21}ClN_4O_3$:, C, 62.19; H, 4.98; N, 13.19. Found: C, 62.16; H, 4.73; N, 13.28.

*4.4.13. 6-(4-Chlorophenylamino)-2-methyl-3-phenyl-1-ethoxycarbonyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4m**).* Operation as above with iminophosphorane **2e** (0.61 g, 1 mmol) and 4-chlorophenylisocyanate (0.15 g, 1 mmol) at room temperature for 2 h, compound **4m** (0.34 g, 69%) was also isolated as white solid. Mp: 153–155 °C. IR (KBr): 3304, 1675, 1631 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.00 (m, 14H), 5.66 (s, 1H), 4.26 (q, *J*=7.2 Hz, 2H), 2.21 (s, 3H), 1.23 (t, *J*=7.2 Hz, 3H). MS *m*/*z*: 486 (M^+, 100), 457 (69), 412 (31), 275 (22), 118 (59), 77 (35). Anal. Calcd for $C_{27}H_{23}ClN_4O_3$: C, 66.60; H, 4.76; N, 11.51. Found: C, 66.75; H, 4.54; N, 11.78.

*4.4.14. 2,3-Dimethyl-1-ethoxycarbonyl-6-(4-fluorophenylamino)-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4n**).* Operation as above with iminophosphorane **2d** (0.55 g, 1 mmol) and 4-fluorophenylisocyanate (0.14 g, 1 mmol) at room temperature for 1 h, compound **4n** (0.25 g, 62%) was also isolated as white solid. Mp: 203–204 °C. IR (KBr): 3309, 1676, 1634 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72–6.87 (m, 9H), 5.52 (s, 1H), 4.25–4.21 (m, 2H), 3.16 (s, 3H), 2.62 (s, 3H), 1.20 (t, *J*=7.2 Hz, 3H). MS *m*/*z*: 408 (M^+, 100), 379 (67), 334 (48), 242 (30), 213 (22), 56 (41). Anal. Calcd for $C_{22}H_{21}FN_4O_3$: C, 64.70; H, 5.18; N, 13.72. Found: C, 64.78; H, 5.33; N, 13.57.

*4.4.15. 1-Ethoxycarbonyl-6-(4-fluorophenylamino)-2-methyl-3-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4o**).* Operation as above with iminophosphorane **2e** (0.61 g, 1 mmol) and 4-fluorophenylisocyanate (0.14 g, 1 mmol) at room temperature for 2 h, compound **4o** (0.32 g, 69%) was also isolated as white solid. Mp: 126–128 °C. IR (KBr): 3312, 2981, 1677, 1635 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.95–7.66 (m, 14H, Ar–H and NH), 5.67 (s, 1H, CH), 4.25 (q, *J*=7.2 Hz, 2H, OCH_2), 2.21 (s, 3H, CH_3), 1.22 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 159.8, 157.4, 150.9, 149.5, 145.1, 143.2, 136.7, 134.9, 129.5, 128.8, 128.7, 127.2, 123.6, 123.1, 122.5, 121.3, 121.2, 115.1, 114.9, 101.4, 60.8, 53.2, 18.5, 14.2. MS *m*/*z*: 470 (M^+, 100), 441 (64), 396 (39), 304 (18), 275 (20), 118 (43), 77 (34). Anal. Calcd for $C_{27}H_{23}FN_4O_3$: C, 68.93; H, 4.93; N, 11.91. Found: C, 68.68; H, 4.74; N, 11.95.

*4.4.16. 1-Ethoxycarbonyl-3-ethyl-6-isopropylamino-2-methyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**4p**).* Operation as above with iminophosphorane **2c** (0.56 g, 1 mmol) and isopropylisocyanate (0.09 g, 1 mmol) at refluxing temperature for 4 h, compound **4p** (0.27 g, 73%) was also isolated as white solid. Mp: 94–96 °C. IR (KBr): 3350, 2977, 1685, 1630 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24–6.81 (m, 4H, Ar–H), 5.37 (s, 1H, CH), 5.01 (d, *J*=7.6 Hz, 1H, NH), 4.31–4.16 (m, 3H, OCH_2 and NCH), 3.70–3.63 (m, 2H, NCH_2), 2.61 (s, 3H, CH_3), 1.37–1.09 (m, 12H, $4CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.0, 150.6, 149.2, 148.6, 144.1, 128.3, 127.1, 122.4, 122.3, 122.2, 100.4, 60.3, 52.4, 43.5, 38.6, 22.7, 22.1, 15.9, 14.6, 14.1. MS *m*/*z*: 370 (M^+, 20), 341 (6), 299 (8), 227 (16), 69 (100). Anal. Calcd for $C_{20}H_{26}N_4O_3$: C, 64.84; H, 7.07; N, 15.12. Found: C, 64.93; H, 7.21; N, 15.04.

*4.4.17. 1-Ethoxycarbonyl-2-methyl-3-phenyl-6-phenyl amino-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**4q**).* Operation as above with iminophosphorane **2f** (0.63 g, 1 mmol) at room temperature for 2 h, compound **4q** (0.34 g, 72%) was also isolated as white solid. Mp: 224–225 °C. IR (KBr): 3410, 2982, 1681, 1637 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.75–6.73 (m, 15H, Ar–H and NH), 5.64 (s, 1H, CH), 4.30–4.24 (m, 2H, OCH_2), 2.21 (s, 3H, CH_3), 1.24 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.8, 165.6, 147.4, 147.0, 143.1, 140.5, 138.5, 130.7, 129.6, 128.9, 128.7, 128.4, 127.4, 123.7,

123.4, 123.3, 122.4, 119.8, 104.0, 60.9, 53.6, 18.8, 14.1. MS *m*/*z*: 469 (M^++1, 23), 360 (11), 349 (10), 118 (23), 77 (100). Anal. Calcd for $C_{27}H_{24}N_4O_2S$: C, 69.21; H, 5.16; N, 11.96. Found: C, 69.15; H, 5.28; N, 11.73.

*4.4.18. 1-Ethoxycarbonyl-6-isopropylamino-2-methyl-3-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**4r**).* Operation as above with iminophosphorane **2f** (0.63 g, 1 mmol) isopropylisocyanate (0.09 g, 1 mmol) at refluxing temperature for 4 h, compound **4r** (0.33 g, 77%) was also isolated as white solid. Mp: 170–172 °C. IR (KBr): 3386, 2974, 1740, 1635 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.44–6.71 (m, 9H, Ar–H), 5.51 (s, 1H, CH), 4.85 (d, *J*=7.6 Hz, 1H, NH), 4.29–4.22 (m, 3H, OCH_2 and NCH), 2.18 (s, 3H, CH_3), 1.35–1.22 (m, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.0, 165.7, 150.0, 147.3, 144.1, 140.7, 130.7, 129.6, 128.8, 128.6, 127.2, 122.9, 122.6, 122.2, 104.0, 60.8, 53.6, 44.0, 22.9, 21.7, 18.8, 14.2. MS *m*/*z*: 434 (M^+, 1), 220 (2), 195 (3), 135 (5), 118 (20), 77 (100), 43 (69). Anal. Calcd for $C_{24}H_{26}N_4O_2S$: C, 66.33; H, 6.03; N, 12.89. Found: C, 66.26; H, 6.17; N, 12.81.

4.5. Synthesis of pyrimido[1,6-*c*]quinazolin-4-ones 6

*4.5.1. 1-Ethoxycarbonyl-2-methyl-7,11b-dihydro-4H-pyrimido[1,6-c]-quinazoline-4,6(1H)-dithione (**6a**).* To a solution of iminophosphorane **2b** (0.55 g, 1 mmol) in CH_3CN (5 mL) was added CS_2 (5.0 mL) at room temperature. After the reaction mixture was refluxed for 12 h, K_2CO_3 (0.014 g, 0.1 mmol) was added and the mixture was stirred for 2 h. The white precipitated solid was collected by filtration and washed with ethanol to give 0.29 g (86%) of **6a** as white solid. Mp: 195–197 °C. IR (KBr): 3445, 3289, 3143, 3000, 1668, 1520 cm^{-1}. ^1H NMR (DMSO-d_6, 600 MHz): δ 12.97 (s, 1H, NH), 11.06 (s, 1H, NH), 7.35–6.93 (m, 4H, Ar–H), 5.41 (s, 1H, CH), 4.17–4.13 (m, 2H, OCH_2), 2.38 (s, 3H, CH_3), 1.15 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 179.1, 175.2, 164.8, 145.9, 135.8, 129.0, 127.5, 124.9, 123.5, 115.8, 97.6, 60.0, 52.9, 16.9, 14.1. MS *m*/*z*: 334 (M^++1, 14), 300 (47), 259 (100), 225 (47), 140 (48). Anal. Calcd for $C_{15}H_{15}N_3O_2S_2$: C, 54.03; H, 4.53; N, 12.60. Found: C, 54.16; H, 4.51; N, 12.36.

*4.5.2. 1-Ethoxycarbonyl-2-methyl-6-thioxo-3,6,7,11b-tetrahydro-4H-pyrimido[1,6-c]quinazolin-4-one (**6b**).* Operation as above with iminophosphorane **2a** (0.54 g, 1 mmol), compound **6b** (0.26 g, 82%) was also isolated as white solid. Mp: 252–254 °C. IR (KBr): 3427, 3160, 2994, 1668, 1706, 1664 cm^{-1}. ^1H NMR (DMSO-d_6, 600 MHz): δ 12.63 (s, 1H), 9.94 (s, 1H), 7.36–6.90 (m, 4H), 5.33 (s, 1H), 4.15–4.10 (m, 2H), 2.34 (s, 3H), 1.12 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 178.2, 164.8, 149.1, 147.8, 136.0, 128.7, 127.1, 124.6, 123.2, 115.3, 94.9, 59.7, 53.4, 17.6, 14.1. MS *m*/*z*: 317 (M^+, 11), 284 (19), 243 (100), 154 (66), 136 (54). Anal. Calcd for $C_{15}H_{15}N_3O_3S$: C, 56.77; H, 4.76; N, 13.24. Found: C, 56.88; H, 4.72; N, 13.28.

4.6. Synthesis of pyrimido[1,6-*c*]quinazolin-4-ones 8

*4.6.1. 1-ethoxycarbonyl-2-methyl-6-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**8a**).* To a solution of iminophosphorane **2b** (0.55 g, 1 mmol) and benzoyl chloride (0.14 g, 1 mmol) in CH_3CN (10 mL) was added NEt_3 (0.28 g, 2 mmol). The mixture was stirred at reflux temperature for 6 h and then cooled to room temperature. The white precipitated solid was collected by filtration and recrystallized from methylene dichloride/petroleum ether to give 0.25 g (65%) of **8a** as yellow crystals. Mp: 259–261 °C. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.10–6.96 (m, 10H, Ar–H and NH), 5.50 (s, 1H, CH), 4.26 (q, *J*=7.2 Hz, 2H, OCH_2), 2.46 (s, 3H, CH_3), 1.24 (t, *J*=7.2 Hz, 3H, CH_3). MS *m*/*z*: 377 (M^+, 100), 348 (61), 304 (64), 271 (22), 245 (61), 77 (56), 42 (63). Anal. Calcd for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13. Found: C, 66.85; H, 5.21; N, 11.06.

*4.6.2. 6-(3-Chlorophenyl)-1-ethoxycarbonyl-2-methyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**8b**).* Operation as above with 3-chlorobenzoyl chloride (0.18 g, 1 mmol) for 4 h, **8b** (0.25 g, 61%) was also isolated as white solid. Mp: 267–268 °C. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.10–6.98 (m, 9H, Ar–H and NH), 5.49 (s, 1H, CH), 4.27 (q, *J*=6.6 Hz, 2H, OCH_2), 2.46 (s, 3H, CH_3), 1.26 (t, *J*=7.2 Hz, 3H, CH_3). MS *m*/*z*: 411 (M^+, 100), 382 (37), 365 (48), 337 (44), 279 (35), 215 (19), 83 (17). Anal. Calcd for $C_{21}H_{18}ClN_3O_2S$: C, 61.23; H, 4.40; N, 10.20. Found: C, 61.43; H, 4.56; N, 10.14.

*4.6.3. 2,3-Dimethyl-1-ethoxycarbonyl-6-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**8c**).* Operation as above with iminophosphorane **2d** (0.55 g, 1 mmol) for 6 h, **8c** (0.30 g, 81%) was also isolated as white solid. Mp: 156–157 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.09–6.97 (m, 9H, Ar–H), 5.44 (s, 1H, CH), 4.24 (q, *J*=7.2 Hz, 2H, OCH_2), 3.13 (s, 3H, NCH_3), 2.67 (s, 3H, CH_3), 1.21 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9, 154.6, 150.8, 150.4, 142.4, 134.7, 131.2, 129.0, 128.5, 128.4, 128.2, 126.9, 125.0, 122.7, 99.7, 60.5, 51.8, 30.6, 16.9, 14.1. MS *m*/*z*: 375 (M^+, 100), 346 (99), 301 (93), 271 (23), 178 (17), 103 (14), 77 (11). Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.14; H, 5.87; N, 11.15.

*4.6.4. 3,6-Diphenyl-1-ethoxycarbonyl-2-methyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**8d**).* Operation as above with iminophosphorane **2e** (0.61 g, 1 mmol) for 4 h, **8d** (0.37 g, 84%) was also isolated as white solid. Mp: 210–211 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.10–6.82 (m, 14H, Ar–H), 5.55 (s, 1H, CH), 4.31–4.23 (m, 2H, OCH_2), 2.28 (s, 3H, CH_3), 1.24 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9, 154.6, 150.4, 149.9, 142.6, 136.7, 134.7, 131.3, 130.1, 129.1, 128.9, 128.8, 128.6, 128.4, 128.2, 127.2, 125.2, 122.6, 100.8, 60.7, 52.3, 18.8, 14.2. MS *m*/*z*: 437 (M^+, 38), 408 (100), 362 (57), 271 (51), 243 (63), 180 (36), 118 (27). Anal. Calcd for $C_{27}H_{23}N_3O_3$: C, 74.12; H, 5.30; N, 9.60. Found: C, 74.15; H, 5.46; N, 9.41.

*4.6.5. 2,3-Dimethyl-1-ethoxycarbonyl-6-(4-methylphenyl)-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**8e**).* Operation as above with iminophosphorane **2d** (0.55 g, 1 mmol) and 4-methylbenzoyl chloride (0.15 g, 1 mmol) for 8 h, **8e** (0.31 g, 80%) was also isolated as white solid. Mp: 199–200 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, *J*=8.4 Hz, 2H, Ar–H), 7.47–6.96 (m, 6H, Ar–H), 5.42 (s, 1H, CH), 4.28–4.19 (m, 2H, OCH_2), 3.12 (s, 3H, NCH_3), 2.67 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 1.21 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.0, 154.6, 150.8, 150.4, 142.6, 141.7, 132.0, 129.2, 129.0, 128.4, 128.2, 126.7, 124.9, 122.7, 99.7, 60.5, 51.8, 30.6, 21.5, 16.9, 14.1. MS *m*/*z*: 389 (M^+, 91), 360 (97), 301 (100), 285 (18), 223 (22), 56 (65). Anal. Calcd for $C_{23}H_{23}N_3O_3$: C, 70.93; H, 5.95; N, 10.79. Found: C, 70.71; H, 5.74; N, 10.81.

*4.6.6. 1-Ethoxycarbonyl-2-methyl-6-(4-methylphenyl)-3-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**8f**).* Operation as above with iminophosphorane **2e** (0.61 g, 1 mmol) and 4-methylbenzoyl chloride (0.15 g, 1 mmol) for 8 h, **8f** (0.37 g, 81%) was also isolated as white solid. Mp: 205–206 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, *J*=8.4 Hz, 2H, Ar–H), 7.49–6.80 (m, 11H, Ar–H), 5.53 (s, 1H, CH), 4.30–4.24 (m, 2H, OCH_2), 2.39 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 1.24 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.0, 154.7, 150.5, 150.0, 142.9, 141.8, 136.9, 132.1, 129.4, 129.3, 129.1, 128.6, 128.5, 128.4, 128.3, 127.0, 125.2, 122.6, 100.9, 60.7, 52.4, 21.6, 18.9, 14.2. MS *m*/*z*: 452 (M^++1, 12), 422 (79), 375 (36), 259 (57), 220 (65), 213 (60), 193 (100), 118 (52). Anal. Calcd

for $C_{28}H_{25}N_3O_3$: C, 74.48; H, 5.58; N, 9.31. Found: C, 74.37; H, 5.75; N, 9.38.

*4.6.7. 6-(2-Chlorophenyl)-2,3-dimethyl-1-ethoxycarbonyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**8g**).* Operation as above with iminophosphorane **2d** (0.55 g, 1 mmol) and 2-chlorobenzoyl chloride (0.18 g, 1 mmol) for 8 h, **8g** (0.31 g, 76%) was also isolated as white solid. Mp: 156–157 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90–6.98 (m, 8H, Ar–H), 5.65 (s, 1H, CH), 4.32–4.19 (m, 2H, OCH_2), 3.11 (s, 3H, NCH_3), 2.63 (s, 3H, CH_3), 1.22 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.8, 152.7, 149.8, 148.4, 141.9, 135.0, 132.0, 131.3, 130.8, 129.7, 128.8, 128.2, 127.2, 126.7, 124.6, 122.9, 98.9, 60.4, 51.7, 30.3, 16.8, 13.9. MS m/z: 409 (M^+, 60), 378 (100), 336 (50), 301 (25), 55 (88). Anal. Calcd for $C_{22}H_{20}ClN_3O_3$: C, 64.47; H, 4.92; N, 10.25. Found: C, 64.68; H, 4.74; N, 10.07.

*4.6.8. 6-(2-Chlorophenyl)-1-ethoxycarbonyl-2-methyl-3-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**8h**).* Operation as above with iminophosphorane **2e** (0.61 g, 1 mmol) and 2-chlorobenzoyl chloride (0.18 g, 1 mmol) for 8 h, **8h** (0.37 g, 79%) was also isolated as white solid. Mp: 207–208 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88–6.94 (m, 13H, Ar–H), 5.76 (s, 1H, CH), 4.34–4.22 (m, 2H, OCH_2), 2.22 (s, 3H, CH_3), 1.24 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 471 (M^+, 47), 422 (100), 397 (43), 250 (53), 215 (76), 118 (44). Anal. Calcd for $C_{27}H_{22}ClN_3O_3$: C, 68.71; H, 4.70; N, 8.90. Found: C, 68.48; H, 4.84; N, 8.75.

*4.6.9. 6-(3-Chlorophenyl)-2,3-dimethyl-1-ethoxycarbonyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**8i**).* Operation as above with iminophosphorane **2d** (0.55 g, 1 mmol) and 3-chlorobenzoyl chloride (0.18 g, 1 mmol) for 4 h, **8i** (0.33 g, 81%) was also isolated as white solid. Mp: 190–192 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (s, 1H, Ar–H), 7.95 (d, J=7.6 Hz, 1H, Ar–H), 7.49–6.97 (m, 6H, Ar–H), 5.43 (s, 1H, CH), 4.26–4.23 (m, 2H, OCH_2), 3.13 (s, 3H, NCH_3), 2.68 (s, 3H, CH_3), 1.22 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 410 (M^++1, 73), 379 (100), 335 (69), 301 (25), 244 (13), 212 (12), 136 (12), 77 (13). Anal. Calcd for $C_{22}H_{20}ClN_3O_3$: C, 64.47; H, 4.92; N, 10.25. Found: C, 64.63; H, 4.76; N, 10.28.

*4.6.10. 6-(3-Chlorophenyl)-1-ethoxycarbonyl-2-methyl-3-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**8j**).* Operation as above with iminophosphorane **2e** (0.61 g, 1 mmol) and 3-chlorobenzoyl chloride (0.18 g, 1 mmol) for 4 h, **8j** (0.38 g, 81%) was also isolated as white solid. Mp: 154–155 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (s, 1H, Ar–H), 7.98 (d, J=7.6 Hz, 1H, Ar–H), 7.51–6.82 (m, 11H, Ar–H), 5.54 (s, 1H, CH), 4.31–4.26 (m, 2H, OCH_2), 2.28 (s, 3H, CH_3), 1.25 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 471 (M^+, 63), 441 (100), 397 (67), 280 (41), 210 (20), 118 (52). Anal. Calcd for $C_{27}H_{22}ClN_3O_3$: C, 68.71; H, 4.70; N, 8.90. Found: C, 68.54; H, 4.85; N, 8.78.

*4.6.11. 2,3-Dimethyl-1-ethoxycarbonyl-6-(2-fluorophenyl)-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**8k**).* Operation as above with iminophosphorane **2d** (0.55 g, 1 mmol) and 2-fluorobenzoyl chloride (0.14 g, 1 mmol) for 4 h, **8k** (0.31 g, 80%) was also isolated as white solid. Mp: 195–196 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33–6.99 (m, 8H, Ar–H), 5.48 (s, 1H, CH), 4.31–4.21 (m, 2H, OCH_2), 3.13 (s, 3H, NCH_3), 2.68 (s, 3H, CH_3), 1.23 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 393 (M^+, 2), 307 (11), 184 (21), 118 (100), 77 (71). Anal. Calcd for $C_{22}H_{20}FN_3O_3$: C, 67.17; H, 5.12; N, 10.68. Found: C, 67.39; H, 5.04; N, 10.41.

*4.6.12. 2,3-Dimethyl-1-ethoxycarbonyl-6-(4-fluorophenyl)-3,11b-dihydro-4H-pyrimido[1,6-c]quinazolin-4-one (**8l**).* Operation as above with iminophosphorane **2d** (0.55 g, 1 mmol) and 4-fluorobenzoyl chloride (0.14 g, 1 mmol) for 4 h, **8l** (0.25 g, 63%) was also isolated as white solid. Mp: 201–203 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10–6.97 (m, 8H, Ar–H), 5.42 (s, 1H, CH), 4.27–4.20 (m, 2H, OCH_2), 3.12 (s, 3H, NCH_3), 2.67 (s, 3H, CH_3), 1.21 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.0, 153.6, 150.8, 150.5, 142.4, 131.1, 130.5, 130.4, 129.0, 128.9, 128.6, 127.1, 125.1, 122.8, 115.7, 115.5, 100.0, 60.6, 51.9, 30.7, 17.0, 14.2. MS m/z: 393 (M^+, 21), 364 (42), 348 (6), 262 (13), 197 (12), 56 (100). Anal. Calcd for $C_{22}H_{20}FN_3O_3$: C, 67.17; H, 5.12; N, 10.68. Found: C, 67.36; H, 5.02; N, 10.89.

*4.6.13. 3,6-diphenyl-1-ethoxycarbonyl-2-methyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**8m**).* Operation as above with iminophosphorane **2f** (0.63 g, 1 mmol) for 6 h, **8m** (0.40 g, 88%) was also isolated as white solid. Mp: 230–232 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19–6.72 (m, 14H, Ar–H), 5.49 (s, 1H, CH), 4.30–4.22 (m, 2H, OCH_2), 2.27 (s, 3H, CH_3), 1.23 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.0, 165.8, 155.8, 148.1, 142.5, 140.1, 134.8, 131.2, 130.9, 129.5, 128.9, 128.7, 128.5, 128.2, 128.0, 127.2, 125.3, 122.5, 103.3, 60.9, 52.8, 19.0, 14.2. MS m/z: 453 (M^+, 38), 308 (53), 188 (47), 118 (100), 77 (86). Anal. Calcd for $C_{27}H_{23}N_3O_2S$: C, 71.50; H, 5.11; N, 9.26. Found: C, 71.67; H, 5.01; N, 9.03.

*4.6.14. 1-Ethoxycarbonyl-2-methyl-6-(4-nitrophenyl)-3-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**8n**).* Operation as above with iminophosphorane **2f** (0.63 g, 1 mmol) and 4-nitrobenzoyl chloride (0.16 g, 1 mmol) for 4 h, **8n** (0.45 g, 90%) was also isolated as yellow solid. Mp: 280–282 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33–6.72 (m, 13H, Ar–H), 5.51 (s, 1H, CH), 4.36–4.24 (m, 2H, OCH_2), 2.28 (s, 3H, CH_3), 1.25 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.8, 165.6, 153.7, 148.6, 148.0, 142.0, 141.0, 139.8, 131.1, 129.6, 129.2, 128.9, 128.8, 128.7, 128.4, 125.8, 123.8, 122.8, 103.5, 61.1, 52.8, 19.1, 14.2. MS m/z: 498 (M^+, 47), 425 (67), 390 (65), 290 (45), 244 (39), 118 (71), 77 (100). Anal. Calcd for $C_{27}H_{22}N_4O_4S$: C, 65.05; H, 4.45; N, 11.24. Found: C, 65.28; H, 4.57; N, 11.18.

*4.6.15. 1-Ethoxycarbonyl-2-methyl-6-(4-nitrophenyl)-3-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**8o**).* Operation as above with iminophosphorane **2f** (0.63 g, 1 mmol) and 3-chlorobenzoyl chloride (0.18 g, 1 mmol) for 4 h, **8o** (0.38 g, 77%) was also isolated as white solid. Mp: 173–175 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (s, 1H, Ar–H), 8.04 (d, J=7.2 Hz, 1H, Ar–H), 7.54–6.71 (m, 11H, Ar–H), 5.46 (s, 1H, CH), 4.29–4.23 (m, 2H, OCH_2), 2.27 (s, 3H, CH_3), 1.24 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.0, 165.6, 154.5, 148.0, 142.2, 139.9, 136.8, 134.4, 131.1, 130.6, 129.7, 129.5, 129.0, 128.7, 128.0, 127.8, 127.6, 126.2, 125.4, 122.6, 103.4, 60.9, 52.8, 19.0, 14.1. MS m/z: 487 (M^+, 12), 307 (61), 188 (22), 118 (82), 77 (100), 44 (39). Anal. Calcd for $C_{27}H_{22}ClN_3O_2S$: C, 66.45; H, 4.54; N, 8.61. Found: C, 66.31; H, 4.68; N, 8.87.

*4.6.16. 1-Ethoxycarbonyl-2-methyl-6-(4-methylphenyl)-3-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**8p**).* Operation as above with iminophosphorane **2f** (0.63 g, 1 mmol) and 4-methylbenzoyl chloride (0.15 g, 1 mmol) for 8 h, **8p** (0.35 g, 74%) was also isolated as white solid. Mp: 172–173 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, J=8.0 Hz, 2H, Ar–H), 7.52–6.70 (m, 11H, Ar–H), 5.47 (s, 1H, CH), 4.28–4.23 (m, 2H, OCH_2), 2.40 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.23 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 468 (M^++1, 6), 118 (58), 104 (24), 92 (10), 77 (100). Anal. Calcd for $C_{28}H_{25}N_3O_2S$: C, 71.92; H, 5.39; N, 8.99. Found: C, 71.84; H, 5.48; N, 8.82.

*4.6.17. 6-(2-chlorophenyl)-1-ethoxycarbonyl-2-methyl-3-phenyl-3,11b-dihydro-4H-pyrimido[1,6-c]quinazoline-4-thione (**8q**).* Operation as above with iminophosphorane **2f** (0.63 g, 1 mmol) and 2-chlorobenzoyl chloride (0.18 g, 1 mmol) for 6 h, **8q**

(0.38 g, 92%) was also isolated as white solid. Mp: 205–206 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, J=7.2 Hz, 1H), 7.56–6.82 (m, 12H), 5.73 (s, 1H), 4.35–4.23 (m, 2H), 2.22 (s, 3H), 1.24 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.0, 165.9, 153.9, 147.3, 142.0, 140.2, 134.9, 133.0, 131.1, 130.6, 130.0, 129.3, 129.2, 128.7, 128.6, 128.2, 127.6, 126.7, 125.3, 122.5, 102.1, 60.9, 52.9, 19.2, 14.1. MS m/z: 487 (M^+, 19), 425 (4), 384 (100), 175 (6), 137 (7), 118 (24), 89 (20), 77 (100). Anal. Calcd for $C_{27}H_{22}ClN_3O_2S$: C, 66.45; H, 4.54; N, 8.61. Found: C, 66.65; H, 4.69; N, 8.57.

4.7. Isolation of some of the intermediates 3 and 5

*4.7.1. 5-Ethoxycarbonyl-6-methyl-4-(2-((phenylimino)methyleneamino)phenyl)-3,4-dihydropyrimidin-2(1H)-one (**3b**).* To a stirred solution of azide **1a** (0.30 g, 1 mmol) in CH_2Cl_2 (10 mL) was added dropwise triphenylphosphine (0.26 g, 1 mmol) in CH_2Cl_2 (5 mL) at room temperature. After the reaction mixture was stirred for 2 h at ambient temperature, phenylisocyanate (0.12 g, 1 mmol) was added under nitrogen at room temperature. After stirred for 2 h at room temperature, the solvent was removed off under reduced pressure and the residue was eluted with ether/petroleum ether through a short silica gel to give 0.26 g (68%) of carbodiimide **3b** as white solid. Mp: 152–154 °C. IR (KBr): 3417, 3230, 3106, 2140, 1701, 1641 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.02 (s, 1H), 7.36–7.10 (m, 9H), 5.86 (s, 1H), 5.83 (s, 1H), 4.05 (q, J=7.2 Hz, 2H), 2.44 (s, 3H), 1.10 (t, J=7.2 Hz, 3H). MS m/z: 376 (M^+, 97), 347 (38), 303 (90), 284 (99), 260 (100). Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 67.24; H, 5.49; N, 14.81.

*4.7.2. 5-Ethoxycarbonyl-4-(2-((isopropylimino)methyleneamino)-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**3f**).* Operation as above with isopropylisocyanate (0.09 g, 1 mmol) at refluxing temperature for 4 h, compound **3f** (0.28 g, 82%) was also isolated as white solid. Mp: 265–267 °C. IR (KBr): 3227, 3103, 2124, 1692, 1637 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.41 (s, 1H, NH), 7.22–7.01 (m, 4H, Ar–H), 5.88 (s, 1H, NH), 5.78 (s, 1H, CH), 4.03 (q, J=7.2 Hz, 2H, OCH_2), 3.88–3.83 (m, 1H, NCH), 2.42 (s, 3H, CH_3), 1.37 (d, J=6.6 Hz, 6H, CH_3), 1.08 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 342 (M^+, 78), 313 (68), 277 (100), 227 (88), 226 (65), 199 (63), 183 (76). Anal. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36. Found: C, 63.06; H, 6.62; N, 16.14.

*4.7.3. 1,6-Dimethyl-5-ethoxycarbonyl-4-(2-((isopropylimino)methyleneamino)phenyl)-3,4-dihydropyrimidin-2(1H)-one (**3j**).* Operation as above with azide **1d** (0.32 g, 1 mmol) and isopropylisocyanate (0.09 g, 1 mmol) at refluxing temperature for 4 h, compound **3j** (0.31 g, 86%) was also isolated as white solid. Mp: 124–125 °C. IR (KBr): 3417, 3244, 2978, 2137, 1679, 1629 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19–7.02 (m, 4H, Ar–H), 5.90 (s, 1H, NH), 5.70 (d, J=3.2 Hz, 1H, CH), 4.10–4.01 (m, 2H, OCH_2), 3.90–3.83 (m, 1H, NCH), 3.18 (s, 3H, NCH_3), 2.62 (s, 3H, CH_3), 1.38 (d, J=3.2 Hz, 6H, $2CH_3$), 1.09 (t, J=7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{19}H_{24}N_4O_3$: C, 64.03; H, 6.79; N, 15.72. Found: C, 64.11; H, 6.67; N, 15.94.

*4.7.4. 5-Ethoxycarbonyl-4-(2-isothiocyanatophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**5b**).* To a solution of iminophosphorane **2b** (0.55 g, 1 mmol) in CH_3CN (5 mL) was added CS_2 (5 mL) at room temperature. After the reaction mixture was refluxed for 12 h, the solvent was removed off under reduced pressure and the residue was eluted with ether/petroleum ether through a short silica gel to give 0.28 g (87%) of isothiocyanate **5b** as white solid. Mp: 247–248 °C. IR (KBr): 3357, 3116, 2977, 2089, 1698, 1635 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.62 (s, 1H, NH), 7.31–7.23 (m, 4H, Ar–H), 5.85 (s, 1H, NH), 5.71 (s, 1H, CH), 4.03 (q, J=7.2 Hz, 2H, OCH_2), 2.41 (s, 3H, CH_3), 1.11 (t, J=7.2 Hz, 3H, CH_3). MS m/z: 317 (M^+, 8), 284 (82), 243 (100), 183 (86), 155 (56), 137 (62). Anal. Calcd for $C_{15}H_{15}N_3O_3S$: C, 56.77; H, 4.76; N, 13.24. Found: C, 56.94; H, 4.70; N, 13.12.

5. Crystallographic material

Compound **8a**: formula $C_{21}H_{19}N_3O_2S$, yellow crystal. The crystal is of monoclinic, space group $P2(1)/n$ with a=9.6802(6) Å, b=19.7155 (10) Å, c=10.3032(6) Å, β=104.431(1)°, V=1904.32(19) Å^3, Z=4, D_c=1.317 g/cm^3, $F(000)$=792, μ=0.191 mm^{-1}, R=0.0418 and wR=0.0449 for 4134 observed reflections with $I>2\sigma(I_0)$. Crystallographic data for **8a** have been deposited in the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 761594. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.08.046. These data include MOL files and InChiKeys of the most important compounds described in this article.

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