Synthesis and Characterization of a Novel Heterocycle: 1-Substituted-4-arylazamethylene-6-arylpyrazolo[5,4-*d*]-1,3-oxazine

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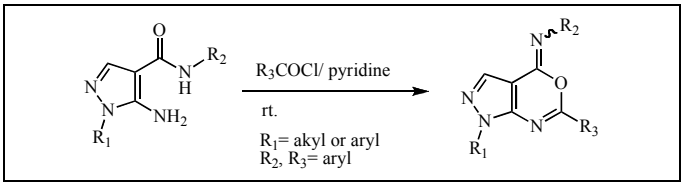

A series of novel heterocycles 1-aryl- or alkyl-substituted-4-arylazamethylene-6-arylpyrazolo[5,4-*d*]-1,3-oxazines were synthesized from the acylation of (5-amino-1-substituted-pyrazol-4-yl)-*N*-carboxamide in 63-89% isolated yields at room temperature within 12 hours. The structure was confirmed by X-ray crystal analysis.

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INTRODUCTION

As shown in Figure 1, quinazolinones **1** have been investigated synthetically [1-4], pharmacologically [2,4], and corresponding rearrangement isomers **2** were also studied for applications in medicinal chemistry [3,5-14] as well as in plant pest control [15]. The 1-aryl- or alkyl-substituted-5-hydropyrazolo[5,4-*d*]pyrimidin-4-one **3** were also well known synthetically [16-18]. These compounds have also been used to treat or prevent diseases or disorders associated with the activity of cannabinoid receptor 1 (CB1) [18]. Here we report the synthesis and characterization of the novel heterocycles 1-aryl- or alkyl-substituted-4-arylazamethylene-6-arylpyrazolo[5,4-*d*]-1,3-oxazines **4**.

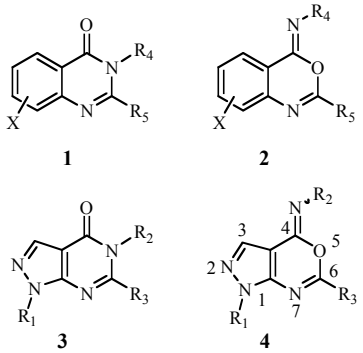
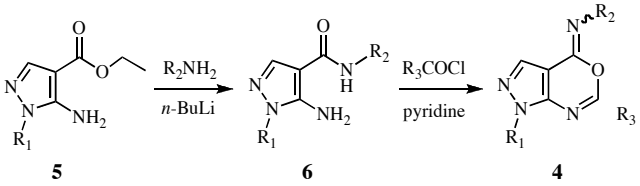


Figure 1 R_1, R_2, R_3, R_4, R_5 = aryl or alkyl; X = H, halogen or other groups.

RESULTS AND DISCUSSION

The synthesis of **4** is shown in Scheme 1. The precursors **6** were readily obtained through replacement of the ester group in **5** by preformed aniline anions. These were then reacted with more than two equivalents of aroyl chlorides at room temperature in pyridine to give the target products **4** [19] in good yields. The results are shown in Table 1.

Scheme 1



5 **6** **4**

In all cases, dry solvent and freshly redistilled aroyl chlorides were necessary in order to obtain **4** in good yields. If less strict conditions were used, a large amount of bis-amides **7** [20] formed as intermediates, which after further treatment with more than 1 equivalent of aroyl chloride, were converted to **4** smoothly with high yields as shown in Scheme 2. Interestingly, when bis-amides **7** were treated with $TiCl_4$ in 1,2-dichloroethane, the isomeric structures **3** were obtained. Compounds **3** have also known to be synthesized from **7** by the action of TMSCl/TEA [18].

The structure of compound **4c** was confirmed by the X-ray crystallography (Figure 2) [21].

The stability of **4** was also investigated. It was stable towards dilute hydrochloric acid at room temperature.

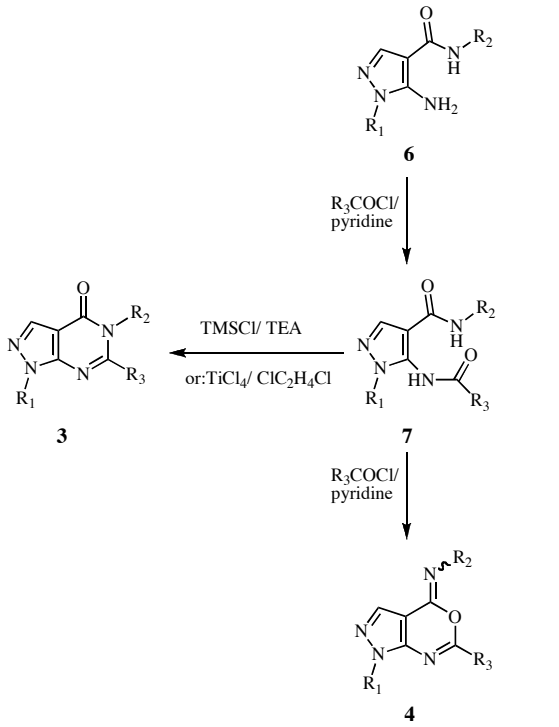
Table 1

Synthesis of Compounds **4**

Entry	R_1	R_2	R_3	Reaction time (h)[a]	Yield (%)[b]
4a	phenyl	4-chlorophenyl	4-chlorophenyl	8	89
4b	phenyl	4-methoxylphenyl	4-chlorophenyl	5	80
4c	phenyl	4-chlorophenyl	6-chloro-(3-pyridyl)	5	74
4d	phenyl	6-chloro-(3-pyridyl)	4-chlorophenyl	5	65
4e	phenyl	4-methylphenyl	4-chlorophenyl	5	68
4f	phenyl	4-methylphenyl	6-chloro-(3-pyridyl)	5	77
4g	phenyl	4-methoxylphenyl	6-chloro-(3-pyridyl)	5	80
4h	2-pyridyl	4-chlorophenyl	6-chloro-(3-pyridyl)	12	63
4i	cyclohexyl	4-methoxylphenyl	6-chloro-(3-pyridyl)	3	85

[a] Reaction conditions have not been optimized. [b] Isolated by chromatography on silica gel.

Scheme 2



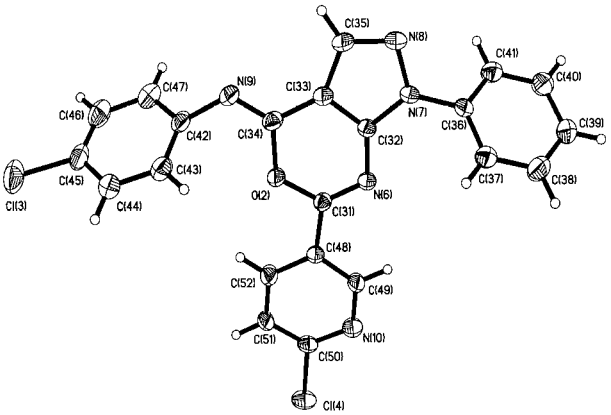
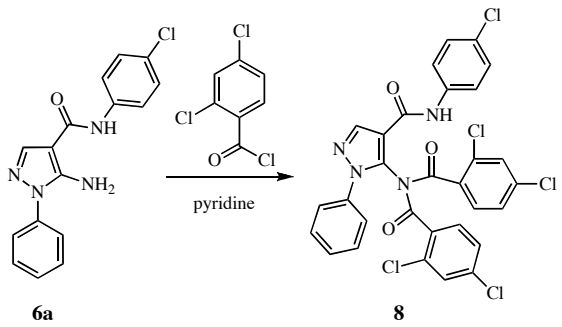


Figure 2 X-ray crystal structure of **4c**.

However, these decomposed at higher temperature in acidic condition to give acyclic compounds **7**. On the other hand, compounds **4** were stable under neutral or basic conditions even at higher temperature.

It is worth noting that the methodology works well for **4a-i**; however, it failed in case of R_3 = 2,4-dichlorophenyl. The acylation of substrate **6a** with 2,4-dichlorobenzoyl chloride only afforded **8** as shown in Scheme 3. The structure of compound **8** was confirmed by X-ray crystallography (Figure 3) [21].

Scheme 3



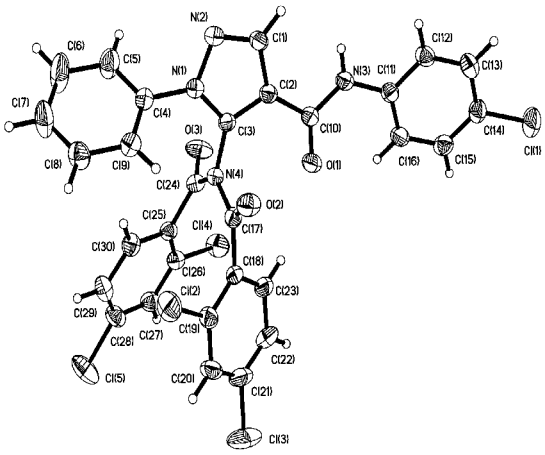


Figure 3 X-ray crystal structure of **8**.

EXPERIMENTAL

General Methods. Tetrahydrofuran (THF) was distilled freshly from calcium hydride immediately prior to use. Aroy chlorides were distilled prior to use. Pyridine was dried with calcium hydride. Unless otherwise indicated, all other reagents and solvent were purchased from commercial sources and were used without further purification. All the pyroreactions were performed by microwave synthesizer, Initiator, Biotage. The data of melting points (mp) are uncorrected. The nuclear magnetic resonance (nmr) spectra were recorded at 300 MHz and the coupling constant are reported in Hz.

General Procedure of synthesis of 6 from 5. A solution of aniline (11 mmol) in dry THF (15 mL) was cooled to -78 °C. A 2.5 *M* solution of *n*-butyllithium in hexane (4 mL, 10 mmol) was added dropwise *via* syringe over 5 minutes. The resulting brownish mixture was stirred for 10 minutes, then compound **5** (6 mmol) was added as a solid under a positive purge of nitrogen. The reaction mixture was warmed to room temperature within 30 minutes and quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate. The combined organic phase was washed with saturated brine and dried. Removal of the solvent gave the crude product as a dark-brown solid and recrystallization from methanol afforded **6**. The starting materials **5** were synthesized according to the literature [18].

(5-Amino-1-phenylpyrazol-4-yl)-*N*-(4-chlorophenyl) carboxamide (6a). This compound was obtained as a grey solid from 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylic acid **(5a)** and 4-chloroaniline with 93% yield. mp 237.0 °C (decomposed); ir (KBr): 3475, 3325 (NH_2), 1647 (CO-NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.72 (s, 1H), 8.20 (s, 1H), 7.79-7.74 (m, 2H), 7.62-7.52 (m, 4H), 7.48-7.36 (m, 3H), 6.55 (s, 2H) ppm; ^{13}C nmr: δ 162.8, 149.8, 138.6, 138.8, 138.0, 129.4 (2C), 128.5 (2C), 127.3, 126.4, 123.3 (2C), 121.4 (2C), 97.4 ppm; ms (esi): *m/z* 313 $(M+H)^+$. *Anal*. Calcd. for $C_{16}H_{13}ClN_4O$, C, 61.44; H, 4.19; N, 17.91. Found: C, 61.2; H, 4.23; N, 18.20.

(5-Amino-1-phenylpyrazol-4-yl)-*N*-(4-methoxylphenyl) carboxamide (6b): This compound was obtained as a grey solid from **5a** and 4-methoxylaniline with 88% yield. mp 209.0-210.0 °C, ir (KBr): 3419, 3290 (NH_2), 1649 (CO-NH), 1245 (OCH_3) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.67 (br, 1H), 7.58-7.49 (m, 4H), 7.46-7.41 (m, 3H), 7.21 (br, 1H), 6.91-6.88 (m, 2H), 5.60 (br, 1H), 3.81 (s, 3H) ppm; ^{13}C nmr: δ 162.8, 156.5, 149.2, 137.6, 137.0, 130.7, 129.8 (2C), 128.2 (2C), 123.8 (2C), 122.6, 114.2 (2C), 98.0, 55.5l ppm; ms (esi): *m/z* 309 $(M+H)^+$. *Anal*. Calcd. for $C_{17}H_{16}N_4O_2$, C, 66.22; H, 5.23; N, 18.17. Found: C, 66.40; H, 5.34; N, 18.02.

(5-Amino-1-phenylpyrazol-4-yl)-*N*-(6-chloro(3-pyridyl)) carboxamide (6c). This compound was obtained as a brown solid from **5a** and 5-chloro-3-pyridylamine with 66% yield. ir (KBr): 3412, 3303 (NH_2), 1660 (CO-NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.92 (s, 1H), 8.17 (d, J = 3.3, 1H), 8.18 (m, 2H), 7.60-7.41 (m, 6H), 6.57 (br, 2H) ppm; ^{13}C nmr: δ 162.2, 150.0, 143.2, 140.9, 138.6, 137.9, 135.7, 130.3, 129.5 (2C), 127.4, 124.0, 123.4 (2C), 97.0 ppm; ms (esi): *m/z* 314 $(M+H)^+$. *Anal*. Calcd. for $C_{15}H_{12}ClN_5O$, C, 57.42; H, 3.86; N, 22.32. Found: C, 57.34; H, 3.87; N, 22.69.

(5-Amino-1-phenylpyrazol-4-yl)-*N*-(4-methylphenyl) carboxamide (6d). This compound was obtained as a white solid from **5a** and 4-methyl-aniline with 90% yield. mp 255.5-256.5 °C; ir (KBr): 3467, 3313 (NH_2), 1647 (CO-NH), 1404 (CH_3) cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.50 (s, 1H), 8.17 (s, 1H), 7.60-7.56 (m, 6H), 7.56 (m, 1H), 7.12 (d, J = 8.4, 2H), 6.49 (br, 2H), 2.26 (s, 3H) ppm; ^{13}C nmr: δ 162.6, 149.7, 138.6, 138.1, 136.7, 131.8, 129.4 (2C), 128.9 (2C), 127.2, 123.2 (2C), 120.0 (2C), 97.6, 20.4 ppm; ms (esi): *m/z* 293 $(M+H)^+$. *Anal*. Calcd. for $C_{17}H_{16}N_4O$, C, 69.85; H, 5.52; N, 5.47. Found: C, 69.47; H, 5.60; N, 5.58.

(5-Amino-1-(2-pyridyl)pyrazol-4-yl)-*N*-(4-chlorophenyl) carboxamide (6e). This compound was obtained as a brown solid from 5-amino-1-(2-pyridyl)-1*H*-pyrazole-4-carboxylic acid **5b** and 4-chloroaniline with 65% yield. ir (KBr): 3410, 3302 (NH_2), 1653 (CO-NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.72 (s, 1H), 8.48 (dd, J = 4.8, 1.2, 1H), 8.24 (s, 1H), 8.02 (td, J = 7.5, 1.8, 1H), 7.90 (d, J = 8.1), 7.38-7.73 (m, 4H), 7.40-7.32 (m, 3H) ppm; ^{13}C nmr: δ 162.3, 153.5, 151.4, 147.1, 139.7, 139.6, 138.3, 128.5 (2C), 126.4, 121.3 (2C), 120.8, 113.1, 96.8 ppm; ms (esi): *m/z* 314 $(M+H)^+$. *Anal*. Calcd. for $C_{15}H_{12}ClN_5O$, C, 57.42; H, 3.86; N, 22.32. Found: C, 57.56; H, 3.74; N, 22.60.

(5-Amino-1-cyclohexylpyrazol-4-yl)-*N*-(4-methoxylphenyl) carboxamide (6f). This compound was prepared analogously from 5-amino-1-cyclohexyl-1*H*-pyrazole-4-carboxylic acid **(5c)** and 4-methoxylaniline with 82% yield: ir (KBr): 3415, 3296 (NH_2), 2931, 2854 (C_6H_{11}), 1610 (CO-NH), 1236 (OCH_3) cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.28 (s, 1H), 7.88 (s, 1H), 7.55 (m, 2H), 6.87(m, 2H), 6.30 (s, 2H), 4.02 (m, 1H), 3.72 (s, 3H), 2.50 (m, 2H), 1.81-1.64 (m, 7H), 1.43-1.30 (m, 2H), 1.23-1.15 (m, 1H) ppm; ^{13}C nmr: δ 162.7, 154.9, 148.7, 136.3, 132.5, 121.5 (2C), 113.6 (2C), 96.6, 55.1, 54.0, 31.6 (2C), 25.0 (2C), 24.9 ppm; ms (esi): *m/z* 315.1 $(M+H)^+$. *Anal*. Calcd. for $C_{17}H_{22}N_4O$, C, 64.95; H, 7.05; N, 17.82. Found: C, 64.78; H, 7.24; N, 17.99.

General procedure of synthesis of compounds 4. To a solution of **6** (1 mmol) in dry pyridine (10 mL), was added dropwise aroyl chloride (3 mmol) at room temperature. The mixture was stirred for 3-12 hours. Next 2/3 of solvent was evaporated off, 10 mL of water was added and stirred for 10 minutes at room temperature. The suspension was filtered and the resulting crude solid was purified by flash chromatography on silica gel to give the target product.

6-(4-Chlorophenyl)-4-[(4-chlorophenyl)azamethylene]-1-phenylpyrazolo[5,4-*d*]1,3-oxazine (4a) was prepared from **6a** and 4-chlorobenzoylchloride with 8 hours as a yellow amorphous solid (89% yield): mp 208.5-209.0 °C; ir (KBr): 1720 (C=N) cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.26 (d, J = 8.7, 1H), 8.19 (s, 0.6H), 8.03 (dd, J = 8.1, 1.2, 1H), 7.97-7.90 (m, 2H), 7.58-7.48 (m, 3H), 7.43-7.35 (m, 4H), 7.17-7.14 (m, 1H), 7.00-7.98 (d, J = 8.4, 1H), 6.85 (s, 0.4H) ppm; ms (esi): *m/z* 433 $(M+H)^+$. *Anal*. Calcd. for $C_{23}H_{14}Cl_2N_4O$, C, 63.76; H, 3.26; N, 12.93. Found: C, 63.69; H, 3.27; N, 12.90.

6-(4-Chlorophenyl)-4-[(4-methoxylphenyl)azamethylene]-1-phenylpyrazolo[5,4-*d*]1,3-oxazine (4b) was prepared from **6b** and 4-chlorobenzoylchloride with 5 hours as a yellow solid (80% yield). mp 198.0-200.0 °C; ir (KBr): 1713 (C=N), 1245 (OCh_3) cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.30 (d, J = 2.1, 0.5H), 8.27 (d, J = 2.1, 0.5H), 8.19 (d, J = 2.7, 0.5H), 8.06-7.95 (m, 2H), 8.00 (d, J = 2.4, 0.5H), 7.98 (s, 0.5H), 7.58-7.48 (m, 3H), 7.44-7.40 (m, 2H), 7.23 (dd, J = 6.9, 2.4,1H), 6.99-6.95 (m, 3H), 6.82 (s, 0.5H), 3.87 (s, 1.5H), 3.86 (s, 1.5H) ppm; ms (esi): *m/z* 429 $(M+H)^+$. *Anal*. Calcd. for $C_{24}H_{17}ClN_4O_2$, C, 67.21; H, 4.00; N, 13.06. Found: C, 67.20; H, 4.11; N, 12.87.

6-(6-Chloro(3-pyridyl))-4-[(4-chlorophenyl)azamethylene]-1-phenylpyrazolo[5,4-*d*]1,3-oxazine (4c) was prepared from **6a** and 6-chloropyridine-3-carbonyl chloride with 5 hours as a yellow solid (74% yield). mp 184.0-185.0 °C; ir (KBr): 1713 (C=N) cm^{-1}; ^1H nmr ($CDCl_3$): δ 9.31 (d, J = 2.1, 0.4H), 8.95 (d, J

= 2.1, 0.6H), 8.51 (dd, J = 8.4, 2.4, 0.4H), 8.22 (s, 0.6H), 8.19 (dd, J = 8.4, 2.4, 0.6H), 8.00 (d, 1.2H), 7.92 (d, J = 7.8, 0.8H), 7.58-7.49 (m, 2.4H), 7.46-7.35 (m, 3.6H), 7.13 (d, J = 8.7, 1.2H), 7.99 (d, J = 8.7, 0.8H), 6.88 (s, 0.4H) ppm ; ms (esi): *m/z* 434 $(M+H)^+$. *Anal.* Calcd. for $C_{22}H_{13}Cl_2N_5O$, C, 60.84; H, 3.02; N, 16.13. Found: C, 60.81; H, 3.03; N, 16.10.

4-[(6-Chloro(3-pyridyl))azamethylene]-6-(4-chlorophenyl)-1-phenylpyrazolo[5,4-*d*]1,3-oxazine (4d) was prepared from **6c** and 4-chlorobenzoylchloride with 5 hours as a yellow solid (65% yield). mp 178.5-179.5 °C, ir (KBr): 1713 (C=N) cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.39 (d, J = 2.4, 1H), 8.22 (s, 0.53H), 8.03 (dd, J = 6.9, 1.2, 2H), 7.02 (d, J = 8.7, 2H), 7.56-7.52 (m, 5H), 7.46-7.39 (m, 2H), 7.18 (s, 0.47H) ppm; ms (esi): *m/z* 434 $(M+H)^+$. *Anal.* Calcd. for $C_{22}H_{13}Cl_2N_5O$, C, 60.84; H, 3.02; N, 16.13. Found: C, 60.61; H, 3.05; N, 15.87.

6-(4-Chlorophenyl)-4-[(4-methylphenyl)azamethylene]-1-phenylpyrazolo[5,4-*d*]1,3-oxazine (4e) was prepared from **6d** and 4-chlorobenzoylchloride with 5 hours as a yellow solid (68% yield). mp 186.0-187.4 °C; ir (KBr): 1713 (C=N) cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.28 (d, J = 8.7, 1H), 8.21 (s, 0.5H), 8.04 (dd, J = 8.7, 1.2, 1H), 7.96 (dd, J = 8.7, 2.1, 2H), 7.55-7.48 (m, 3H), 7.43-7.40 (m, 2H), 7.25-7.13 (m, 3H), 6.94 (d, J = 8.4, 1H), 6.75 (d, J = 8.4, 1H), 2.40 (s, 3H) ppm; ms (esi): *m/z* 413 $(M+H)^+$. *Anal.* Calcd. for $C_{24}H_{17}ClN_4O$, C, 69.82; H, 4.15; N, 13.57. Found: C, 69.46; H, 4.04; N, 13.45.

6-(6-Chlro(3-pyridyl))-4-[(4-methylphenyl)azamethylene]-1-phenylpyrazole[5,4-*d*]-1,3-oxazine (4f) was prepared from **6d** and 6-chloropyridine-3-carbonyl chloride with 5 hours as a yellow solid (77% yield). mp 194.4-195.0 °C; ir (KBr): 1697 (C=N), 1462 (CH_3) cm^{-1}; ^1H nmr to see [19]; ms (esi): *m/z* 414 $(M+H)^+$. *Anal.* Calcd. for $C_{23}H_{16}ClN_5O$, C, 66.75; H, 3.90; N, 16.92. Found: C, 66.36; H, 3.93; N, 16.57.

6-(6-Chloro(3-pyridyl))-4-[(4-methoxylphenyl)azamethylene]-1-phenylpyrazolo[5,4-*d*]1,3-oxazine (4g) was prepared from **6b** and 6-chloropyridine-3-carbonyl chloride with 5 hours as a yellow solid (80% yield). mp 181.0-183.7 °C; ir (KBr): 1709 (C=N), 1250 (OCH_3) cm^{-1}; ^1H nmr ($CDCl_3$): δ 9.31 (d, J = 2.4, 0.4H), 9.00 (d, J = 2.1, 0.6H), 8.51 (dd, J = 8.4, 2.4, 0.4H), 8.24 (dd, J = 8.4, 2.4, 0.6H), 8.20 (s, 0.6H), 8.00 (d, J = 8.1, 1.2H), 7.92 (d, J = 8.1, 0.8H), 7.57-7.39 (m, 4H), 7.21-7.38 (m, 1H), 6.98-6.93 (m, 3H), 6.85 (s, 0.4H), 3.85 (s, 3H) ppm; ms (esi): *m/z* 430 $(M+H)^+$. *Anal.* Calcd. for $C_{23}H_{16}ClN_5O_2$, C, 64.26; H, 3.75; N, 16.29. Found: C, 63.95; H, 3.79; N, 15.98.

6-(6-Chloro(3-pyridyl))-4-[(4-chlorophenyl)azamethylene]-1-(2-pyridyl)pyrazolo[5,4-*d*]-1,3-oxazine (4h) was prepared from **6e** and 6-chloropyridine-3-carbonyl chloride in undried pyridine with 12 hours as a yellow solid (63% yield)**.** mp 211.0-211.5 °C; ir (KBr): 1713 (C=N) cm^{-1}; ^1H nmr ($CDCl_3$): δ 9.30 (d, J = 2.1, 0.33H), 8.98 (d, J = 2.1, 0.67H), 8.7-8.66 (m, 1H), 8.54 (dd, J = 8.7, 2.7, 0.33H), 8.28 (s, 0.67H), 8.23 (dd, J = 8.4, 2.4, 0.67H), 8.04-7.92 (m, 2H), 7.46-7.37 (m, 4H), 7.51 (d, J = 8.4, 0.33H), 7.17 (d, J = 0.9, 0.67H), 7.13 (d, J = 0.9, 0.33H), 6.94 (s, 0.33H) ppm; ms (esi): *m/z* 435 $(M+H)^+$. *Anal.* Calcd. for $C_{21}H_{12}Cl_2N_6O$, C, 57.95; H,2.78; N, 19.31. Found: C, 57.76; H, 2.85; N, 18.95.

6-(6-Chloro(3-pyridyl))-4-[(4-methoxylphenyl)azamethylene]-1-cyclohexylpyrazolo[5,4-*d*]1,3-oxazine (4i) was prepared from **6f** and 6-chloropyridine-3-carbonyl chloride with 3 hours as a yellow solid (85% yield). mp 94.0-95.0 °C, ir (KBr): 2933, 2858 (C_6H_{11}), 1707 (C=N), 1244 (OCH_3) cm^{-1}; ^1H nmr ($CDCl_3$): δ 9.31 (d, J = 2.4, 0.45H), 8.99 (d, J = 2.4, 0.55H), 8.54 (dd, J = 8.4, 2.4, 0.45H), 8.27 (dd, J = 8.4, 0.55H), 8.03 (s, 0.55H), 7.50 (d, J = 8.4, 0.45H), 7.42 (d, J = 8.4, 0.55H), 7.15 (dd, J = 6.9, 2.4, 1H), 6.94-6.91 (m, 3H), 6.67 (s, 0.45H), 4.58-4.55 (m, 1H), 3.85 (s, 1.65H), 3.83 (s, 1.35H), 2.07-1.90 (m, 6H), 1.78-1.31 (m, 4H) ppm; ms (esi): *m/z* 436 $(M+H)^+$. *Anal.* Calcd. for $C_{23}H_{22}ClN_5O_2$, C, 63.37; H, 5.09; N, 16.07. Found: C, 63.18; H, 5.14; N, 16.33.

Synthesis procedure for **4b** from 5-(4-chlorobenzamido)-*N*-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxamide **(7b)** is typical: To a solution of **7b** (223.2 mg, 0.5 mmol) in dry pyridine (5 mL), was added dropwise 4-chlorobenzoylchloride (175.0 mg, 1 mmol) at room temperature. The mixture was stirred for 4 hours. Next 2/3 of solvent was evaporated off, 5 mL of water was added and stirred for 10 minutes at room temperature. The suspension was filtered and washed with water for several times. Purification by flash chromatography on silica gel gave 201.0 mg (94%) of **4b** as a yellow solid.

In addition, synthesis of **4a, 4h** was tried by this method. The yields were 88%, 90% respectively.

The intermediate 5-(4-chlorobenzamido)-*N*-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carboxamide **(7a)** was obtained from decyclization of **4a**; **7b** was synthesized according to the reported [18,20a]; **7h** was isolated as shown in Scheme 2.

Procedure of decyclization of **4a** to **7a** is typical: A mixture of **4a** (108.2 mg, 0.25 mmol) in 5 mL of saturated HCl-ClC_2H_4Cl and 50 mg of water was placed in a sealed microwave tube, then heated to 120 °C for 3 hours. Lcms showed 83% conversion. mp 227.0-228.2 °C; ^1H nmr ($CDCl_3$): δ 9.82 (br, 1H), 8.16 (br, 1H), 7.92 (s, 1H), 7.80 (d, J = 8.7, 2H), 7.518-7.477 (m, 5H), 7.446-7.34 (m, 4H), 7.304-7.258 (m, 2H) ppm; ^{13}C nmr: δ 164.8, 161.8, 139.6, 139.5, 138.2, 137.7 (2C), 135.9, 130.6, 129.9, 129.3 (2C), 129.2 (2C), 129.1 (2C), 128.3, 123.0 (2C), 121.7 (2C), 117.7, 109.1 ppm; ms (esi): *m/z* 451 $(M+H)^+$. *Anal.* Calcd. for $C_{23}H_{16}Cl_2N_4O_2$, C, 61.21; H, 3.57; N, 12.41. Found: C, 61.33; H, 3.61; N, 12.57.

95% conversion of decyclization of **4b** to **7b:** ^1H nmr ($CDCl_3$): δ 10.07 (s, 1H), 8.55 (s, 1H), 7.85 (s, 1H), 7.75 (m, 2H), 7.43 (m, 2H), 7.35-7.28 (m, 7H), 6.76 (d, J = 9.0, 2H), 3.75 (s, 3H) ppm; ^{13}C nmr: δ 165.5, 161.7, 156.7, 139.2 (2C), 139.1, 138.4, 136.8, 130.4, 130.2, 129.3 (2C), 129.1 (2C), 129.0 (2C), 128.2, 123.2 (2C), 122.5, 114.1 (2C), 110.87, 55.4 ppm; ms (esi): *m/z* 467 $(M+H)^+$. *Anal.* Calcd. for $C_{24}H_{19}ClN_4O_3$, C, 64.50; H, 4.29; N, 12.54. Found: C, 64.32; H, 4.30; N, 12.64.

99% conversion of decyclization of **4h** to *N*-(4-(4-chlorophenylcarbamoyl)-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloropyridine-3-carboxamide **(7h)**: mp 229.5-230.0 °C; ^1H nmr (DMSO-d_6): δ 11.14 (s, 1H), 10.14 (s, 1H), 8.90 (d, J = 2.7, 1H), 8.44-8.42 (m, 1H), 8.37 (s, 1H), 8.29 (dd, J = 8.1, 2.4, 1H), 8.04 (td, J = 7.8, 1.8, 1H), 7.82 (d, J = 8.4, 1H), 7.75-7.71 (m, 3H), 7.44-7.37 (m, 3H) ppm; ^{13}C nmr: δ 163.0, 160.0, 153.4, 151.7, 149.4, 148.1, 140.0, 139.5, 139.1, 137.9, 137.1, 128.6 (2C), 128.5, 127.1, 124.5, 123.2 (2C), 121.5, 116.8, 113.0 ppm; ms (esi): *m/z* 453 $(M+H)^+$. *Anal.* Calcd. for $C_{21}H_{14}Cl_2N_6O_2$, C, 55.64; H, 3.11; N, 18.54. Found: C, 55.34; H, 3.14; N, 18.69.

General procedure of synthesis of Compounds 3 from 7. To a solution of **7** (0.25 mmol) in dry 1,2-dichloroethane (4 mL) was added $TiCl_4$ (0.11 mL, 1 mmol). The mixture was heated at 120 °C for 25 minutes in a microwave, cooled down and diluted with dichloroethane and quenched with water. The organic layer was separated and washed with water for several times, dried and concentrated. Recrystallization from acetonitrile afforded **3** as a solid.

5,6-Bis(4-chlorophenyl)-1-phenyl-5-hydropyrazolo[5,4-*d*]-pyrimidin-4-one 3a. (60% yield), white solid: mp 222.2-223.5 °C; ^1H nmr ($CDCl_3$): δ 8.32 (s, 1H), 8.15-8.11 (m, 2H), 7.54-

7.49 (m, 2H), 7.39-7.32 (m, 3H), 7.30-7.23 (m, 4H), 7.11-7.07 (m, 2H) ppm; ^{13}C nmr: δ 156.2, 150.3, 139.1, 138.5, 136.7, 136.3, 135.6, 134.9, 133.3, 130.7 (2C), 130.6 (2C), 130.5 (2C), 129.5 (2C), 129.1 (2C), 128.5 (2C), 127.2, 121.9 (2C), 105.7 ppm; ms (esi): *m/z* 433 $(M+H)^+$. *Anal*. Calcd. for $C_{23}H_{14}Cl_2N_4O$, C, 63.76; H, 3.26; N, 12.93. Found: C, 63.57; H, 3.30; N, 12.70.

5-(4-Methoxyphenyl)-6-(4-chlorophenyl)-1-phenyl-5-hydropyrazolo[5,4-*d*]pyrimidin-4-one 3b. (77% yield), grey solid: ^{1}H nmr ($CDCl_3$): δ 8.31 (s, 1H), 8.15-8.12 (m, 2H), 7.50 (m, 2H), 7.37-7.26 (m, 3H), 7.23-7.20 (m, 2H), 7.05-7.01 (m, 2H)□6.85 (m, 2H), 3.79 (s, 3H) ppm; ^{13}C nmr: δ 159.5, 158.3, 157.6, 150.5, 138.6, 136.6, 135.9, 133.8, 130.7 (2C), 130.2 (2C), 129.6, 129.1 (2C), 128.3 (2C), 127.1, 121.8 (2C), 114.5 (2C), 105.9, 55.4 ppm; ms (esi): *m/z* 429 $(M+H)^+$. *Anal*. Calcd. for $C_{24}H_{17}ClN_4O_2$, C, 67.21; H, 4.00; N,13.06. Found: C, 67.40; H, 4.11; N, 13.27.

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[19] We noticed that compounds **4** exist as a mixture of cis- and trans-isomers in solution, and the ratio of isomers depended on the solvents. For example, the ratio of the two isomers changed from about 1:1 in $CDCl_3$ to about 3:1 in DMSO-d_6. The ^{1}H nmr spectrum data are attached here: **4f** ($CDCl_3$): δ 9.31 (d, J = 2.1, 0.44H), 8.95 (d, J = 2.1, 0.56H), 8.51 (dd, J = 8.4, 2.4, 0.44H), 8.23 (dd, J = 8.4, 2.4, 0.56H), 8.21 (s, 0.56H), 8.00 (d, J = 8.1, 1.12H), 7.82 (d, J = 8.1, 0.88H), 7.57-7.40 (m, 4H), 7.23-7.09 (m, 3H), 6.93 (d, J = 8.1, 1H), 6.78 (s, 0.44H), 2.40 (s, 1.32H), 2.38 (s, 1.68H) ppm; **4f** (DMSO-d_6): δ 9.15 (d, J = 2.1, 0.25H), 8.81 (d, J = 2.1, 0.75H), 8.53 (dd, J = 8.4, 2.4, 0.25H), 8.31 (dd, J = 8.4, 2.4, 0.75H), 8.39 (s, 0.75H), 8.05 (d, J = 8.1, 1.5H), 7.82 (d, J = 8.1, 0.5H), 7.81-7.74 (m, 1H), 7.65-7.58 (m, 2H), 7.50-7.43 (m, 1H), 7.30-7.18 (m, 3.5H), 6.91 (d, J = 8.1, 0.5H), 6.58 (s, 0.25H), 2.37 (s, 0.75H), 2.38 (s, 2.25H) ppm.

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[21] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 639095 (**4c**) & 635094 (**8**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).