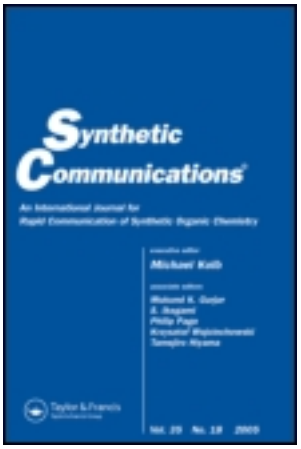

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A Facile Synthesis of Pyrimidone Derivatives and Single-Crystal Characterization of Pymetrozine

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A FACILE SYNTHESIS OF PYRIMIDONE DERIVATIVES AND SINGLE-CRYSTAL CHARACTERIZATION OF PYMETROZINE

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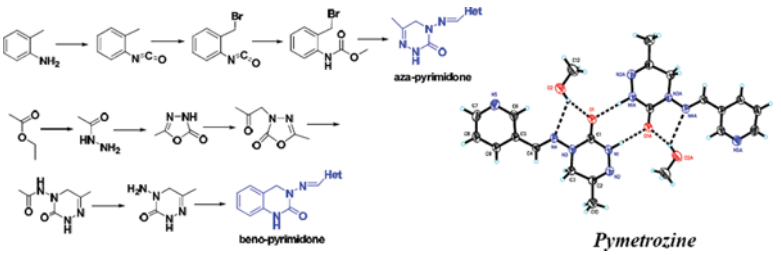
GRAPHICAL ABSTRACT



Abstract *A facile and efficient synthetic methodology for the preparation of aza-pyrimidone and beno-pyrimidone derivatives is described, in which the triazinone ring and dihydroquinazolin-2(1H)-one was convenient constructed. The structures of all the newly synthesized compounds were characterized by mass, ^1H NMR, and infrared spectroscopy. In additional, the crystal of pymetrozine was obtained to find useful information such as configuration and molecular action mechanisms.*

Keywords Crystal; pymetrozine; pyrimidone; synthesis

INTRODUCTION

The regulation of insect feeding is only fragmentarily understood because of the complexity of mechanisms that are under the control of internal and external signals. This insufficient understanding may in part be due to the lack of compounds specifically that could interfere with insect feeding at critical steps.[1,2] To the best to our knowledge, only 6-methyl-4-[(pyridin-3-ylmethylene)amino]-4,5-dihydro-1, 2,4-triazin-3(2*H*)-one (pymetrozine) and 1-propionyl-3- (pyridine-3-ylmethylamino)-3,4-dihydroquinazolin-2(*1H*)-one (R-768) are novel types of antifeedant with an

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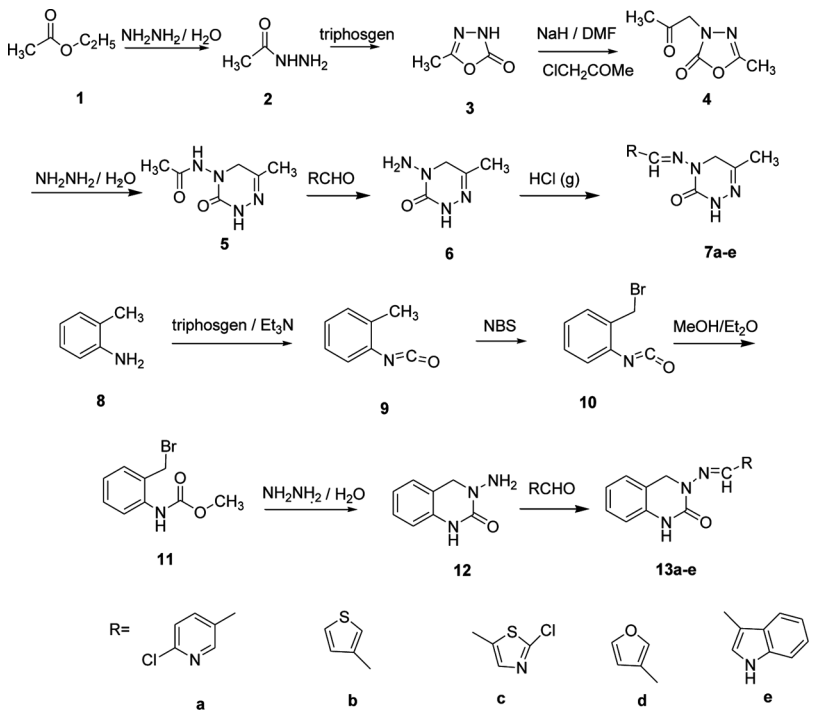
unknown biochemical mode of action.[3–6] The analogous structures of the two kinds of compounds have attracted great interest.[7–9] It is well known that the high activity of pymetrozine is attributed to the structure of pyrimidone moiety, but it is not clear how it works. Kaufman and Kayser pointed that pymetrozine might act on some target protein receptor,[10] so a functionalized pyrimidone moiety consequently has attracted considerable synthetic interest. In this article, we describe a synthetic study on aza-pyrimidone and beno-pyrimidone derivatives, in which the triazinone ring and dihydroquinazolin-2(1*H*)-one were convenient constructed. In additional, *cis-trans* isomerism in pesticide molecules is associated with structure–bioactivity relationship, so we prepared the crystal of pymetrozine to realize the real configuration of these aza-pyrimidone and beno-pyrimidone derivatives.

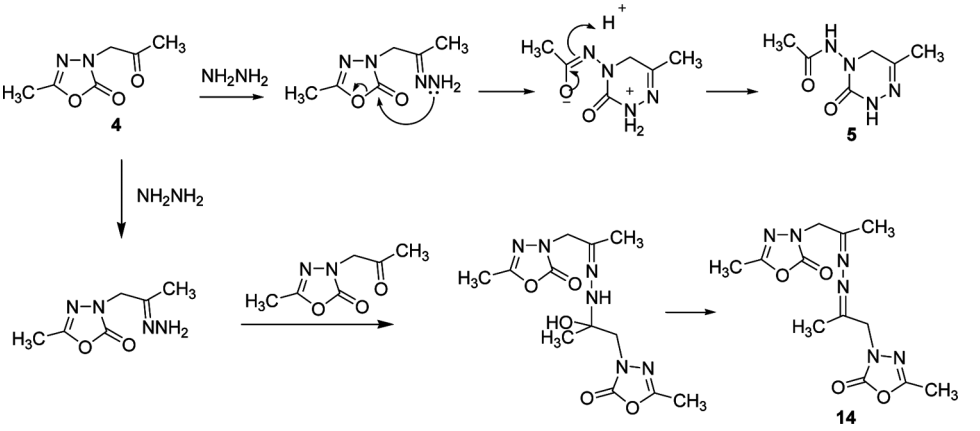
RESULTS AND DISCUSSION

The synthesis of aza-pyrimidone and beno-pyrimidone derivatives was conducted as shown in Scheme 1.[11]

Treatment of ethyl acetate **1** with hydrazine hydrate afforded acetohydrazide **2** (98.0% yield), which was cyclized with triphosgen to give the 5-methyl-1,3,4-oxadiazol-2(3*H*)-one **3** (95.0% yield). After reaction with chloroacetone in the presence of NaH (82.0% yield), ring-opening reaction and cyclization of the resulting oxadiazole-3-acetone **4** with hydrazine hydrate gave trizone **5** in 87.0% yield. In the synthesis of compound **5**, the molar ratio of hydrazine hydrate and compound **4**



Scheme 1. Preparation of pyrimidone derivatives.

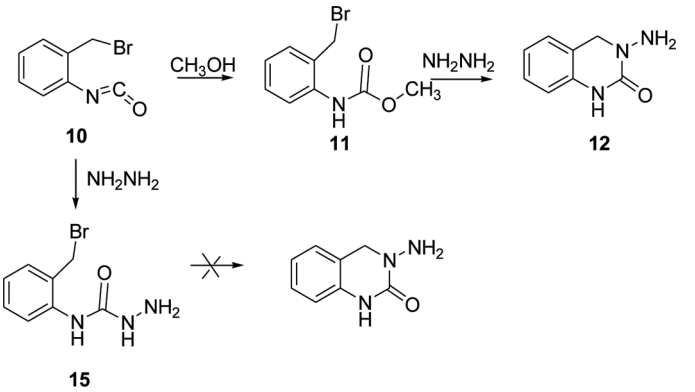


Scheme 2. Synthesis of compound **5**.

strongly influenced the pathway of this reaction to give different products. When the molar ratio of hydrazine hydrate and compound **4** is more than 2.0, the intramolecular nucleophilic addition reaction could produce compound **5** through the reaction of ring expansion.[12] Otherwise, when it is less than 2.0, the imine compound **14** will be obtained through the formation of intermediate as shown in the mechanism with compound **4** (Scheme 2). Hydrogen chloride gas and 1 M hydrochloric acid were added to **5** to produce 4-amino-6-methyl-3-O-2-,3,4,5-tetrahydro-1,2,4-triazine **6**. The final Schiff base was produced easily when **6** was dissolved in ethanol and two to three drops of concentrated hydrochloric acid were added. The yield reached 75.0–88.0%.

Treatment of o-toluidine **8** with triphosgen afforded 1-isocyanato-2-methylbenzene **9** (85.0% yield), which was halogenated with N-bromosuccinimide (NBS) to give 5-methyl-1,3,4-oxadiazol-2(3*H*)-one **10** (75.0% yield). After reaction with methanol (90.2% yield), cyclization of the resulting methyl *N*-[2-(bromomethyl)phenyl]carbamate **11** with hydrazine hydrate gave 3-amino-benzo[*b*] pyrimidin-2-one **12** in 86.0% yield. For the synthesis of **12, 11** was selected as starting material obtained from **10** instead of 4-(2-(bromomethyl)phenyl)semicarbazide **15**, because **15** cannot be cyclized to produce **12** (Scheme 3).

Because of the existence of a Schiff base in the aza-pyrimidone and beno-pyrimidone derivatives, these compounds have two kinds of configuration. As we all know, there are many *cis-trans* isomerous pesticides and the bioactivity of these pesticides varies enormously. For example, the bio-activity of *E*-methomyl (Lannate) is far less than that of the *Z*-methomyl as the C=N isomerous pesticide.[13] We prepared the single crystal of pymetrozine in methanol. According to the x-ray data of pymetrozine, it is clear that pymetrozine has the *trans* structure. The trizinone ring and pyridine form the *E* structure through the C=N of the Schiff bases. In additional, the atoms of trizinone ring and Schiff bases are coplanar to obtain the lowest energy for the formation of an intramolecular hydrogen bond among O(1), N(4), and H of methanol [O(2)-H(2) •••N(4) = 3.187(3) Å, O(2)-H(2) •••O(1) = 2.821(3) Å] (Fig. 1). This may imply that pymetrozine also could form



Scheme 3. Synthesis of compound **12**.

the five-member ring with the action goals through the nonbond interaction. The x-ray structure also showed that there are two molecular actions for the dimer aggregation state formation of an intramolecular hydrogen bond between O(1) and N(1) [N(1)-H(1) •••O(1 W) = 2.915(2) Å]. Full crystallographic details were deposited at the Cambridge Crystallographic Data Centre (CCDC 689819).

EXPERIMENTAL

All melting points were determined using a micro-melting-point apparatus made in Beijing and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker WP-500SY (500-MHz) spectrometer with tetramethylsilane (TMS) as the internal standard. The chemical shifts are reported in parts per million (ppm) relative to TMS. Infrared (IR) spectra were measured on KBr disks using a Nicolet FT-IR-20SX instrument. High-resolution mass spectra were obtained on a Micro Mass GCT CA 055 spectrometer. Combustion analyses for elemental composition were made with an Italian MOD 1106 analyzer. Analytical thin-layer chromatography (TLC) was carried out on precoated plated (silica gel 60F254), and spots were visualized with ultraviolet light. All chemicals or reagents were purchased from standard commercial suppliers.

X-Ray Data

$C_{11}H_{15}N_5O_2$, Mr = 249.28, monoclinic, $P_2(1)/c$, a = 8.8612(12), b = 11.4273(15), c = 12.6305(16) Å, V = 1275.8(3) Å^3, Dx = 1.205 g cm^{-3}, Z = 4, m = 0.094 cm^{-1}, T = 293(2) K. A colorless pymetrozine crystal, which was prepared by slow evaporation from methanol, was used for data collection with a Rigaku AFC7 R diffractometer. Cell constants and a full matrix were used for data collection, obtained from a least-squares refinement. A total of 7386 reflections were collected. No decay correction was applied. The data were corrected for Lorentz and polarization effects. The final cycle of full-matrix least-squares refinement was based on 2787 observed reflections [I>s(I)] and 174 variable parameters and converged with

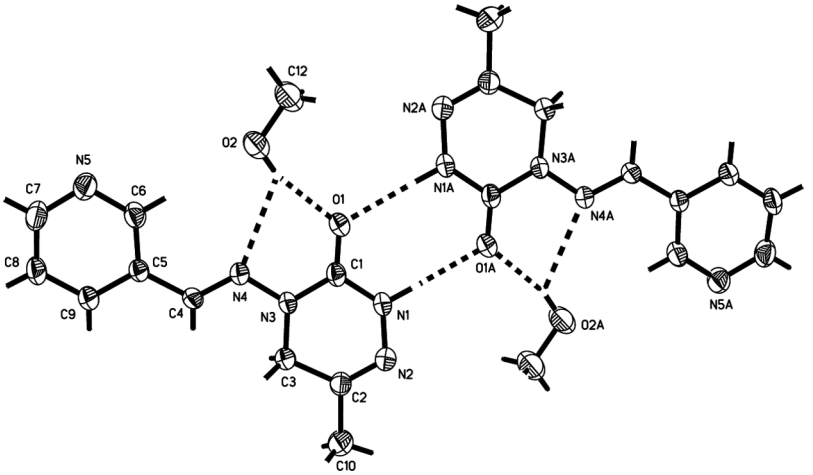


Figure 1. X-ray crystal structure of pymetrozine in methanol.

R = 0.0489 and Rw = 0.0967. The program package SHELX-97 was used for structure solution and full-matrix least-squares refinement on F2.

Oxadiazolones 3 and 4

These compounds were prepared by the corresponding literature methods. Compound **3**: Yield: 95%; mp: 112.0–114.3 °C (literature value[13]: yield: 98%; mp: 110.0–111.5 °C). Compound **4**: Yield: 82%; mp: 86.7–88.0 °C (literature value[14]: yield: 90%; mp: 85 °C).

4-Acylamino-6-methyl-2,3,4,5-tetrahydro-3-o-1,2,4-triazin 5

Hydrazine hydrate (10 mmol) was added to a solution of compound **4** (10 mmol) in 40 mL 1-propanol. The reaction mixture was refluxed for 3 h. Then the solvent was removed, and the resulting solid was washed by 1-propanol and filtered. Then pure compound **5** was obtained. Yield: 87%; mp: 206.0–208.0 °C. IR (KBr, cm^{-1}): 3480, 3260, 3200, 1700, 1660, 1580, 1500, 1380, 1350, 1320, 1240, 1010, 700, 600; EI-MS (m/z, %): 171 ($M^+ + H$, 0.38), 128 ($M^+ + H\text{-}CH_3CO$, 61.65), 113 ($M^+ + H\text{-}CH_3CONH$, 71.47), 112 ($C_4H_6N_3O$, 100.00), 60 (42.62), 43 (17.06).

4-Amino-6-methyl-2,3,4,5-tetrahydro-3-o-1,2,4-triazin 6

HCl gas (0.03 mol) was bubbled in a stirred solution of compound **5** (0.02 mol) in methanol at 45–50 °C. Then the reaction mixture was stirred for 2 h at this temperature. When the reaction completed, the reaction mixture was cooled to 10–15 °C, and its pH value was modulated to 5 by 30% sodium hydrate. After the solvent and water were removed, the resulting solid was dissolved in ethanol and

filtered. The solvent of the filtrate was removed to give compound **6** as a colorless solid. Yield: 72%; p: 128.0–130.0 °C. ^{1}H NMR (CD_3COCD_3, 500 MHz): δ 4.02 (s, 2H, CH_2), 1.87 (s, 3H, CH_3) ppm; IR (KBr, cm^{-1}): 3240, 3170, 3100, 2960, 1680, 1660, 1480, 1330, 1170, 1010, 890, 730; GC-MS (*m/z*, %): 128 (M^+, 100.00), 113 (M^+-CH_3, 47.22), 112 (M^+-NH_2, 0.93), 98 (M^+-NNH_2, 3.70), 70 (M^+-$CONNH_2$, 6.48), 44 (CH_2NNH_2, 42.59).

6-Methyl-2,3,4,5-tetrahydro-1,2,4-triazin-3-one Derivative 7

Two or three drops of hydrochloric acid were added to a solution of compound **6** (1 mmol) in 15 mL ethanol at 50 °C. After this, aldehyde (1 mmol) was added. When the solid was found, the reaction mixture was heated to reflux. TLC (ethyl acetate / petroleum ether = 2:1, v/v). After the completion of reaction, the reaction mixture was cooled by ice water, and the compound **7** was precipitated and recrystallized by methanol.

6-Methyl-4-[(2-chloro-pyridin-3-yl-methylene)amino]-1,2,4-triazin-3-one (7a). Yield: 88%; mp: 228.3–229.2 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.18 (s, 1H, NH), 8.66 (s, 1H, CH), 8.15 (dd, 1H, J = 1.18 Hz, 1.38 Hz, CH), 7.89 (s, 1H, CH), 7.59 (d, 1H, J = 8.32 Hz, CH), 4.36 (s, 2H, CH_2), 1.94 (s, 3H, CH_3) ppm; IR (KBr, cm^{-1}): 3230, 3130, 2920, 1690, 1670, 1470, 1320, 1240, 1150, 1050, 730; GC/mass (*m/z*, %): 251 (M^+, 10), 113 ($C_4H_7N_3O^+$, 61), 112 ($C_4H_7N_3O^+$, 61), 98 ($C_3H_4N_3O^+$, 100). Anal. calcd. for $C_{10}H_{10}ClN_5O$: 251.0573; found: 251.0577.

6-Methyl-4-[(thiophene-3-yl-methylene)amino]-1,2,4-triazin-3-one (7b). Yield: 80%; mp 224.3–226.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.03 (s, 1H, NH), 7.92 (s, 1H, CH), 7.82 (d, 1H, J = 2.70 Hz, CH), 7.60 (dd, 1H, J = 2.87 Hz, 5.02 Hz, CH), 7.43 (d, 1H, J = 4.68 Hz, CH), 4.30 (s, 2H, CH_2), 1.92 (s, 3H, CH_3) ppm; IR (KBr, cm^{-1}): 3240, 3120, 3070, 2950, 1700, 1670, 1480, 1320, 1220, 1170; EI-MS (*m/z*, %): 222 (M^+, 9.23), 113 (M^+-C_5H_4NS, 49.49), 98 ($C_3H_4N_3O^+$, 100.00). Anal. calcd. for $C_9H_{10}N_4OS$: 222.0575. Found: 222.0576.

6-Methyl-4-[(2-chlor-thiazole-3-yl-methylene)amino]-1,2,4-triazin-3-one (7c). Yield: 83%; mp: 232.2–235.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.18 (s, 1H, NH), 8.08 (s, 1H, CH), 7.93 (s, 1H, CH), 4.32 (s, 2H, CH_2), 1.92 (s, 3H, CH_3) ppm; IR (KBr, cm^{-1}): 3264, 3140, 2920, 1700, 1680 1480, 1400, 1320, 1140, 1050; EI-MS (*m/z*, %): 257 (M^+, 6.32), 118 (C_3H_4ClNS, 6.39), 113 (M^+-$C_4H_2ClN_2S$, 29.91). 98 ($C_3H_4N_3O$, 100.00). Anal. calcd. for $C_8H_8ClN_5OS$: 257.0115. Found: 257.0889.

6-Methyl-4-[(furan-3-yl-methylene)amino]-1,2,4-triazin-3-one (7d). Yield: 75%; mp: 239.0–239.8 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.98 (s, 1H, NH), 8.03 (s, 1H, CH), 7.83 (s, 1H, CH), 7.72 (d, 1H, J = 1.55 Hz, CH), 6.73 (d, 1H, J = 1.62 Hz, CH), 4.26 (s, 2H, CH_2), 1.90 (s, 3H, CH_3) ppm; IR (KBr, cm^{-1}): 3240, 3120, 3070, 2950, 1700, 1670, 1480, 1330, 1230, 1140; EI-MS (*m/z*, %): 206 (M^+, 7.59), 113 (M^+-C_5H_4NO, 30.57), 98 ($C_3H_4N_3O^+$, 100.00). Anal. calcd. for $C_9H_{10}N_4O_2$: 206.0804. Found: 206.0802.

6-Methyl-4-[(indole-3-yl-methylene)amino]-1,2,4-triazin-3-one (7e). Yield: 85%; mp: 243.3–247.4 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.46 (s, 1H, NH), 9.90 (s, 1H, NH), 8.13 (s, 1H, CH), 7.73 (d, 1H, $J = 2.70$ Hz, CH), 7.42 (d, 1H, $J = 8.06$ Hz, CH), 7.32 (d, 1H, $J = 7.76$ Hz, CH), 7.17(t, 1H, $J = 7.51$ Hz, 7.57 Hz, CH), 7.11 (t, 1H, $J = 7.45$ Hz, CH), 4.33 (s, 2H, CH_2), 1.94 (s, 3H, CH_3) ppm; IR (KBr, cm^{-1}): 3230, 3120, 2980 2280, 1690, 1670, 1490, 1330, 1250, 1140, 840, 740, 510; EI-MS (*m*/*z*, %): 255 (M^+, 14.31), 142 ($C_9H_6N_2$ 100.00), 113 (M^+-$C_9H_9N_2$ 19.02), 98 ($C_3H_4N_3O$, 57.42). Anal. calcd. for $C_{13}H_{13}N_5O$: 255.1120. Found: 255.1091.

Compounds 9 and 10

These compounds were prepared by the corresponding literature methods. Compound **9**: yield: 85%; bp: 62.0–64.0 °C (3.33 kPa) [literature value[15]: Yield: 88%; bp: 80.0 °C (3.99 kPa)]. Compound **10:** Yield: 75%; mp: 10.2–12.3 °C (literature value[16]: yield: 72%; mp: 8.0–12.0 °C).

Methyl N-[2-(Bromomethyl)phenyl]carbamate 11

Absolute ether (10 mL) was added to the stirred compound **10** in 20 mL methanol. When some white solid was formed, the reaction mixture was placed in the refrigerator for 12 h. After that, the solution was filtered, and the white solid was dried to give compound **11**. Yield: 90.2%; mp: 134.0–136.5 °C; GC/mass (*m*/*z*, %): 163 (M^+-HBr, 100), 133 (M^+-CH_4BrO, 55), 104 (M^+-$C_2H_4BrO_2$, 27).

3-Amino-benzo[*b*]pyrimidin-2-one 12

Hydrazine hydrate (5 mmol) was added to the solution of compound **11** (5 mmol) in 10 mL methanol in 10 min at 35–45 °C. Then the reaction mixture was stirred for 8 h at this temperature and refluxed for 5 h. After the reaction mixture cooled, the solvent was removed, and a white solid was precipitated. The solid was purified using column chromatography to give compound **12** as a white powder. Yield: 86.0%; mp: 182.0–187.1 °C[17]; GC/Mass (*m*/*z*, %): 163 (M^+, 100), 132 (M^+-$NHNH_2$, 87), 104 (M^+- $NHNH_2$-CO), 77 ($C_6H_5^+$, 14).

Benzo[*b*]pyrimidin-2-one Derivative 13

Two to three drops of hydrochloric acid were added to a solution of compound **12** (1 mmol) in 10 mL ethanol at 30 °C. Then aldehyde (1 mmol) was added. When the solid was found, the reaction mixture was stirred for 5 h at 60 °C. After completion of the reaction finished [TLC (ethyl acetate/petroleum ether = 3:1, v/v)], the mixture was cooled by ice water, and compound **13** was precipitated and recrystallized by methanol.

3-[(2-Chlor-pyridin-3-yl-methylene)amino]-benzo[*b*]pyrimidin-2-one (13a). Yield: 85%; mp: 218.3–220.6 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.92 (s, 1H, NH), 8.69 (d, 1H, $J = 1.68$ Hz, CH), 8.13 (m, 1H, $J = 1.99$ Hz, 8.32 Hz, H), 8.06

(s, 1H, CH), 7.60 (d, 1H, $J = 8.32$ Hz, CH), 7.20 (t, 2H, $J = 7.72$ Hz, CH), 6.97 (t, 1H, $J = 7.49$ Hz, CH), 6.87 (d, 1H, $J = 7.89$ Hz, CH), 4.93 (s, 1H, CH_2) ppm; IR (KBr, cm^{-1}): 3220, 3140, 3080, 2930, 1680, 1610, 1480, 1420, 1320, 1220, 1140, 1100, 750, 730; EI-MS (m/z, %) 286 (M^+, 3.83), 147 ($C_8H_7N_2O^+$, 100.00), 148 ($C_8H_8N_2O^+$, 21.21), 132 ($C_8H_6NO^+$, 3.31), 104 ($C_2H_6N^+$, 3.95), 77 ($C_6H_5^+$, 3.58). Anal. calcd. for $C_{14}H_{11}ClN_4O$: 286.0626. Found: 286.0628.

3-[(Thiophene-3-yl-methylene)amino]-benzo[*b*]pyrimidin-2-one (13b). Yield: 75%; mp: 238.2–240.0 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 9.75 (s, 1H, NH), 8.13 (s, 1H, CH), 7.84 (d, 1H, $J = 2.23$ Hz, CH), 7.61 (dd, 1H, $J = 3.07$ Hz, 2.85 Hz, CH), 7.49 (d, 1H, $J = 5.03$ Hz, CH), 7.23–7.18 (m, 2H, CH), 6.96 (t, 1H, $J = 7.46$ Hz, CH), 6.87 (d, 1H, $J = 7.94$ Hz, CH), 4.88 (s, 2H, CH_2) ppm; IR (KBr, cm^{-1}): 3400, 3200, 3080, 2920, 2890, 1680, 1610, 1480, 1430, 1320, 1220, 750; EI-MS (m/z, %) 257 (M^+, 3.83), 147 ($C_8H_7N_2O^+$, 100.00), 148 ($C_8H_8N_2O^+$, 21.21), 132 ($C_8H_6NO^+$, 3.31), 104 ($C_2H_6N^+$, 3.95), 77 ($C_6H_5^+$, 3.58). Anal. calcd. for $C_{13}H_{11}N_3OS$: 257.0620. Found: 257.0623.

3-[(2-Chloro-thiazole-3-yl-methylene)amino]-benzo[*b*]pyrimidin-2-one (13c). Yield: 78%; Mp: 231.6–233.0 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 9.93 (s, 1H, NH), 8.24 (s, 1H, CH), 7.94 (s, 1H, CH), 7.19 (t, 2H, $J = 7.44$ Hz, 7.54 Hz, CH), 6.97 (t, 1H, $J = 7.40$ Hz, CH), 6.85 (d, 1H, $J = 7.91$ Hz, CH), 4.89 (s, 2H, CH_2) ppm; IR (KBr, cm^{-1}): 3230, 3100, 2980, 1700, 1610, 1480, 1410, 1320, 1220, 1050, 750, 730, 600; EI-Ms(m/z, %) 292 (M^+, 3.23), 147 ($C_8H_7N_2O^+$, 100.00), 148 ($C_8H_8N_2O^+$, 18.20), 132 ($C_8H_6NO^+$, 8.06), 104 ($C_2H_6N^+$, 5.83), 77 ($C_6H_5^+$, 4.73). Anal. calcd. for $C_{12}H_9ClN_4OS$: 292.0194. Found: 292.0192.

3-[(Furan-3-yl-methylene)amino]-benzo[*b*]pyrimidin-2-one (13d). Yield: 70%; mp: 234.9–236.0 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 9.80 (s, 1H, NH), 8.16 (s, 1H, CH), 8.01 (d, 1H, $J = 1.57$ Hz, CH), 7.17 (t, 2H, $J = 7.53$ Hz, 7.56 Hz, CH), 7.13 (d, 1H, $J = 2.11$ Hz, CH), 7.03 (d, 1H, $J = 1.63$ Hz, CH), 6.90 (t, 1H, $J = 7.43$ Hz, Hz, CH), 6.83 (d, 1H, $J = 7.93$ Hz, CH), 4.74 (s, 2H, CH_2) ppm; IR (KBr, cm^{-1}): 3400, 3200, 3080, 2920, 2890, 1680, 1610, 1480, 1400, 1320, 1210, 750; EI-MS (m/z, %) 241 (M^+, 5.52), 147 ($C_8H_7N_2O^+$, 100.00), 148 ($C_8H_8N_2O^+$, 18.84), 132 ($C_8H_6NO^+$, 5.01), 104 ($C_2H_6N^+$, 4.80), 77 ($C_6H_5^+$, 4.55). Anal. calcd. for $C_{13}H_{11}N_3O_2$: 241.0852. Found: 241.0855.

3-[(Indole-3-yl-methylene)amino]-benzo[*b*]pyrimidin-2-one (13e). Yield: 90%; mp: 218.0–220.3 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 9.65 (s, 1H, NH), 8.39 (s, 1H, NH), 8.38 (s, 1H, CH), 7.84 (s, 1H, CH), 7.46 (d, 1H, $J = 8.03$ Hz, CH), 7.27–7.14 (m, 5H, Ar-H), 6.95 (t, 1H, $J = 7.40$ Hz, CH), 6.89 (d, 1H, $J = 7.91$ Hz, CH), 4.91 (s, 2H, $J = 1.63$ Hz, CH_2) ppm; IR (KBr, cm^{-1}): 3240, 3080, 2980, 2920, 1700, 1500, 1320, 1480, 1220, 1750; EI-MS (m/z, %) 290 (M^+, 7.81), 147 ($C_8H_7N_2O^+$, , 100.00), 148 ($C_8H_8N_2O^+$, 15.59), 132 ($C_8H_6NO^+$, 3.44), 104 ($C_2H_6N^+$, 3.30), 77 ($C_6H_5^+$, 3.51). Anal. calcd. for $C_{17}H_{14}N_4O$: 290.1176. Found: 290.1172.

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