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# AN EFFICIENT SYNTHESIS OF FUNCTIONALIZED CHROMENO[4,3-*d*]PYRAZOLO[3,4-*b*]PYRIDINE DERIVATIVES

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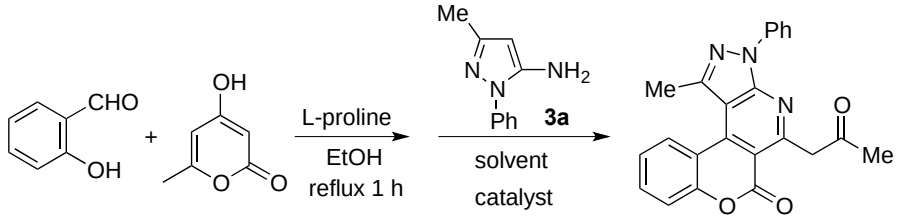
**Abstract** — A series of functionalized chromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine derivatives were synthesized via one-pot three-component reaction of salicylaldehydes, 4-hydroxy-6-methyl-2*H*-pyran-2-one and pyrazol-5-amines catalyzed by L-proline and $CuSO_4$ in ethanol. The structures of all synthesized were identified by their IR, $^1$H NMR, $^{13}$C NMR and HRMS analyses, and the structure of compound **4h** was confirmed by X-ray diffraction analysis.

Nitrogen-containing heterocyclic compounds are ubiquitous system in natural products and are considered as privileged structures in drug discovery.[1] Among the various heteroaromatic compounds, coumarin is one of important heterocyclic compound found in many plants. Compounds bearing the coumarin moiety exhibit antitumor,[2] anti-inflammatory,[3] anti-coagulant,[4] and anti-oxidant[5] activities. Some coumarin derivatives have a high fluorescent quantum yield[6] and have been widely used as laser dyes, fluorescent probes, solar energy collector, and nonlinear optical dyes.[7] Meanwhile, some heteroaryl-condensed coumarin derivatives have been to attract interest because of their broad spectrum of useful biological activities and fluorescent properties.[8] Diverse synthetic methodologies available for the construction of coumarin derivatives have been developed, including Pechmann reaction,[9] Knoevenagel condensation,[10] Wittig reaction,[11] C-H activating methods,[12] and multi-component reactions.[13] However, to the best of our knowledge, only a few literatures[14] reported the preparation of chromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine derivatives. As a part of our research on the synthesis of novel functionalized coumarin derivatives,[15] herein, we reported the efficient synthesis of novel functionalized chromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine derivatives.

At first the reaction conditions were examined. According to our previously reported synthetic procedure of 3-(1-hydroxy-3-oxobut-1-en-1-yl)-2*H*-chromen-2-one from the reaction of salicylaldehydes with

4-hydroxy-6-methyl-2*H*-pyran-2-one,[16] salicylaldehydes (**1a**) was treated with 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**) in ethanol catalyzed by L-proline (10 mol%) for 1 h to give the desired 3-(1-hydroxy-3-oxobut-1-en-1-yl)-2*H*-chromen-2-one. Then 3-methyl-1-phenyl-pyrazol-5-amine (**3a**) was added and the mixture was stirred at different conditions to optimize the reaction conditions. The results are summarized in Table 1. In the absence of catalyst, the desired product **4a** was only obtained in 12% yield (Table 1, entry 1). To improve the yield, several catalysts were evaluated, i.e. *p*-TSA, piperidine, $CuSO_4 \cdot 5H_2O$, $CuSO_4$, $CuSO_4 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$ and CuI (Table 1, entries 2-8). The results showed that the best catalyst was $CuSO_4$. Subsequently, we further evaluated the effect of solvents. Of all the solvents tested, i.e. ethanol, acetonitrile, DMF, toluene, acetic acid, and THF, ethanol gave the best result (Table 1, entries 5 and 9-13). To optimize the catalyst loading, 5, 10, 15, 20, and 25 mol% of

**Table 1.** Optimization of the reaction conditions for the synthesis of compound **4**[a]




**1a** **2** **4a**

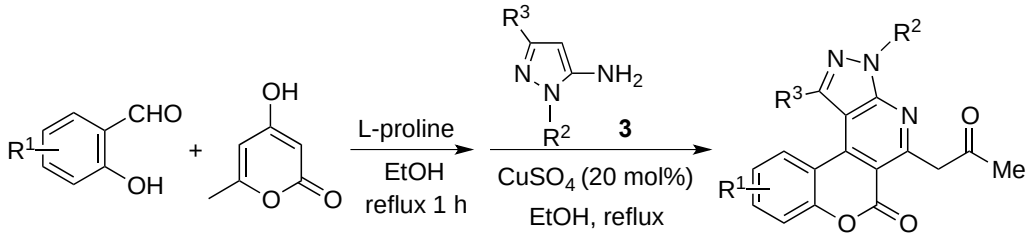
| Entry | Catalyst (mol%) | Solvent | Temperature (°C) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | no | EtOH | reflux | 24 | 12 |
| 2 | *p*-TSA (10) | EtOH | reflux | 24 | 15 |
| 3 | piperidine (10) | EtOH | reflux | 6 | trace |
| 4 | $CuSO_4 \cdot 5H_2O$ (10) | EtOH | reflux | 6 | 66 |
| 5 | $CuSO_4$ (10) | EtOH | reflux | 6 | 70 |
| 6 | $CuSO_4 \cdot 2H_2O$ (10) | EtOH | reflux | 6 | 55 |
| 7 | $Cu(OAc)_2 \cdot H_2O$ (10) | EtOH | reflux | 24 | 10 |
| 8 | CuI (10) | EtOH | reflux | 24 | 13 |
| 9 | $CuSO_4$ (10) | MeCN | reflux | 10 | 53 |
| 10 | $CuSO_4$ (10) | DMF | 120 | 4 | 51 |
| 11 | $CuSO_4$ (10) | toluene | 110 | 14 | 47 |
| 12 | $CuSO_4$ (10) | AcOH | 110 | 6 | 62 |
| 13 | $CuSO_4$ (10) | THF | reflux | 16 | 36 |
| 14 | $CuSO_4$ (5) | EtOH | reflux | 9 | 65 |
| 15 | $CuSO_4$ (15) | EtOH | reflux | 6 | 71 |
| 16 | $CuSO_4$ (20) | EtOH | reflux | 5 | 76 |
| 17 | $CuSO_4$ (25) | EtOH | reflux | 5 | 74 |
| 18 | $CuSO_4$ (20) | EtOH | 20 | 12 | 43 |
| 19 | $CuSO_4$ (20) | EtOH | 40 | 12 | 56 |
| 20 | $CuSO_4$ (20) | EtOH | 60 | 8 | 62 |

[a]Yield was determined by HPLC-MS

$CuSO_4$ was tested (Table 1, entries 5 and 14-17). A 20 mol% loading of $CuSO_4$ was sufficient to promote the reaction. The reaction was then conducted at different temperature, such as: 20, 40, 60 °C, and refluxing temperature, to determine the optimum temperature for this transformation. All these experiments were conducted in ethanol catalyzed by $CuSO_4$ (20 mol%) (Table 1, entries 5 and 18-20). So the best temperature for this transformation was at refluxing temperature. Based on all these experiments, the optimum reaction conditions were identified as using ethanol as solvent and 20 mol% $CuSO_4$ as the catalyst at refluxing temperature for several hours.

The optimized reaction conditions were then tested for library construction with substituted salicylaldehydes and pyrazol-5-amines. The results are summarized in Table 2. It was found that there were no remarkable effect of the electronic effect of the substituted groups of salicylaldehydes and pyrazol-5-amines to the yields.

**Table 2.** The Synthesis of functionalized chromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine derivatives **4**




**1** **2** **4**

| Entry | Compound | $R^1$ | $R^2$ | $R^3$ | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **4a** | H | Ph | Me | 5 | 78 |
| 2 | **4b** | 5-Cl | Ph | Me | 6 | 62 |
| 3 | **4c** | 3-MeO | Ph | Me | 20 | 55 |
| 4 | **4d** | 4-MeO | Ph | Me | 18 | 56 |
| 5 | **4e** | 5-Cl | Ph | Ph | 20 | 46 |
| 6 | **4f** | 3-MeO | Ph | Ph | 24 | 45 |
| 7 | **4g** | 4-MeO | Ph | Ph | 24 | 45 |
| 8 | **4h** | 5-Cl | Me | Me | 6 | 57 |
| 9 | **4i** | H | Me | Ph | 14 | 71 |
| 10 | **4j** | 5-Br | Me | Ph | 17 | 68 |
| 11 | **4k** | 5-MeO | Me | Ph | 15 | 61 |
| 12 | **4l** | 3,5-$Cl_2$ | Me | Ph | 10 | 59 |

The structures of all the products were identified by their IR, $^1$H NMR, $^{13}$C NMR and HRMS spectra. The structure of compound **4h** was further confirmed by X-ray diffraction analysis. The molecular structure of the product **4h** is shown in Figure 1.

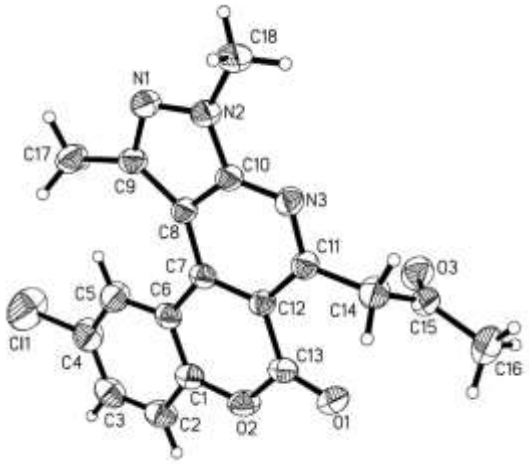
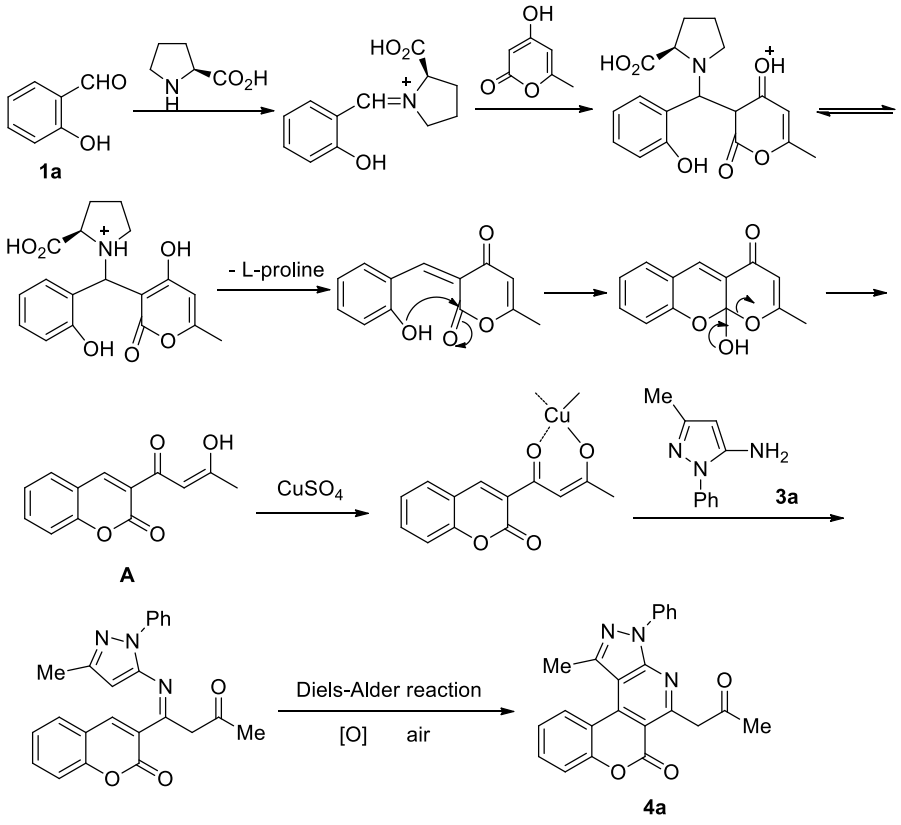



**Figure 1.** The crystal structure of compound **4h**

Based on the references,[14b,16] the proposed mechanism for the synthesis of compound **4a** is shown in Scheme 1. The intermediate **A** was formed by the condensation reactions of salicylaldehyde (**1a**) with 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**) catalyzed by L-proline. The intermediate **A** then reacted with 3-methyl-1-phenylpyrazol-5-amine (**3a**) to form imine catalyzed by $CuSO_4$. The desired product **4a** was obtained by the Diels-Alder and oxidation in air from the imine.




**Scheme 1.** The proposed mechanism for one-pot domino reaction

In conclusion, we have developed a facile and efficient protocol for the construction of functionalized chromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine derivatives via a novel one-pot three-component reaction of salicylaldehydes, 4-hydroxy-6-methyl-2*H*-pyran-2-one and pyrazol-5-amines catalyzed by $CuSO_4$ in ethanol. This protocol has the advantages of mild reaction conditions, easily accessible starting materials, and wide range of substrates, which makes it a useful and attractive method for the synthesis of the complex chromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridines in synthetic and medicinal chemistry. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

## EXPERIMENTAL

IR spectra were recorded on a Varian F-1000 spectrometer in KBr with absorptions in $cm^{-1}$. $^1H$ NMR (400 MHz or 300 MHz) and $^{13}C$ NMR (100 MHz or 75 MHz) spectra were recorded on a Varian Inova-300 MHz and Varian Inova-400 MHz in $CDCl_3$ solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. High-resolution mass spectra (HRMS) for all the compounds were determined on Bruker MicrOTOF-QII mass spectrometer with ESI resource. X-Ray diffraction analysis was recorded on a Rigaku Mercury CCD/AFC diffractometer.

**Starting Materials.** All chemicals used in this study were commercially available.

**Typical experimental procedure for the synthesis of chromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine derivatives 4.** A mixture of salicylaldehydes **1** (1 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one **2** (1 mmol) and L-proline (0.10 mmol) in EtOH (10 mL) was stirred at 80 °C for 1 h. Then pyrazol-5-amines **3** (1 mmol) and $CuSO_4$ (0.20 mmol) was added to the reactor and stirred at 80 °C for 4-48 h. After completion of the reaction confirmed by TLC (eluent acetone/petroleum ether (PE), V/V = 1:3), the reaction mixture was concentrated in vacuo to remove the solvent. The product purified by column chromatography (PE-acetone = 5:1) to afford the pure product **4**.

**1-Methyl-5-(2-oxopropyl)-3-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4a**: white solid; mp 203-205 °C. IR (KBr) 2960, 1726, 1594, 1547, 1507, 1443, 1248, 772 $cm^{-1}$; $^1H$ NMR (400 MHz, $DCl_3$) δ 8.31 (d, *J* = 7.6 Hz, 1H, ArH), 8.19 (d, *J* = 6.8 Hz, 2H, ArH), 7.63 (t, *J* = 6.8 Hz, 1H, ArH), 7.53 (t, *J* = 6.8 Hz, 2H, ArH), 7.42-7.35 (m, 3H, ArH), 4.62 (s, 2H, $CH_2$), 2.93 (s, 3H, $CH_3$), 2.43 (s, 3H, $CH_3$); $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 205.1, 160.3, 159.3, 152.6, 151.6, 143.0, 142.6, 138.5, 133.0, 129.4, 129.2, 127.0, 124.0, 122.3, 117.6, 116.7, 110.8, 109.7, 54.9, 30.6, 19.3; HRMS Calculated for $C_{23}H_{17}N_3O_3Na$: $[M+Na]^+$ 406.1168, found: 406.1169.

**10-Chloro-1-methyl-5-(2-oxopropyl)-3-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4b**: white solid; mp 235-238 °C; IR (KBr) 2959, 1734, 1608, 1278, 1180, 1021, 829, 753, 689 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H, ArH), 8.18 (d, *J* = 8.0 Hz, 2H, ArH), 7.61-7.52 (m, 3H, ArH), 7.38 (d, *J*

= 8.0 Hz, 2H, ArH), 4.63 (s, 2H, $CH_2$), 2.98 (s, 3H, $CH_3$), 2.43 (s, 3H, $CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 205.0, 159.9, 159.4, 151.7, 151.0, 142.8, 141.4, 138.5, 132.8, 129.6, 129.3, 128.9, 127.2, 122.6, 119.0, 118.0, 110.9, 109.5, 54.9, 30.6, 19.5; HRMS Calculated for $C_{23}H_{16}ClN_3O_3$: $[M]^+$ 417.0880, found: 417.0877.

**8-Methoxy-1-methyl-5-(2-oxopropyl)-3-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4c** : white solid; mp 247-249 °C; IR (KBr) 2936, 1739, 1545, 1506, 1181, 1024, 968, 833, 789, 681 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 2H, ArH), 7.87 (d, *J* = 8.0 Hz, 1H, ArH), 7.53 (t, *J* = 8.0 Hz, 2H, ArH), 7.36 (t, *J* = 7.6 Hz, 2H, ArH), 7.20 (d, *J* = 6.8 Hz, 1H, ArH), 4.63 (s, 2H, $CH_2$), 4.01 (s, 3H, $CH_3O$), 2.93 (s, 3H, $CH_3$), 2.43 (s, 3H, $CH_3$); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 205.2, 159.4, 157.2, 148.0, 145.8, 143.4, 138.6, 129.2, 127.0, 125.0, 123.7, 122.5, 120.8, 117.5, 114.7, 110.0, 108.1, 101.9, 56.6, 54.8, 30.6, 19.4; HRMS Calculated for $C_{24}H_{19}N_3O_4$: $[M]^+$ 413.1376, found: 413.1380.

**9-Methoxy-1-methyl-5-(2-oxopropyl)-3-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4d** : white solid; mp 213-216 °C; IR (KBr) 3097, 1721, 1559, 1487, 1389, 1248, 1143, 969, 783, 738, 693 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.24-8.17 (m, 3H, ArH), 7.52 (t, *J* = 8.0 Hz, 2H, ArH), 7.35 (t, *J* = 7.6 Hz, 1H, ArH), 6.97 (d, *J* = 8.8 Hz, 1H, ArH). 6.88 (s, 1H, ArH), 4.59 (s, 2H, $CH_2$), 3.93 (s, 3H, $CH_3O$), 2.91 (s, 3H, $CH_3$), 2.42 (s, 3H, $CH_3$); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 205.2, 160.6, 159.5, 154.6, 151.7, 143.0, 138.6, 130.6, 129.2, 128.9, 122.5, 112.2, 109.9, 109.4, 109.3, 101.3, 56.1, 54.9, 30.6, 19.4; HRMS Calculated for $C_{24}H_{18}N_3O_4$: $[M-H]^-$ 412.1297, found: 412.1348.

**10-Chloro-5-(2-oxopropyl)-1,3-diphenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4e** : white solid; mp 202-204 °C; IR (KBr) 3048, 1720, 1608, 1540, 1502, 1355, 1312, 1247, 1198, 1162, 1023, 762, 702, 672 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.6 Hz, 2H, ArH), 7.56-7.50 (m, 7H, ArH), 7.41 (d, *J* = 6.4 Hz, 2H, ArH), 7.33 (s, 1H, ArH), 7.28 (s, 1H, ArH), 4.69 (s, 2H, $CH_2$), 2.46 (s, 3H, $CH_3$); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 205.0, 160.3, 159.7, 151.6, 150.9, 147.3, 141.1, 138.5, 134.0, 132.7, 131.4, 129.8, 129.6, 129.3, 129.1, 128.9, 127.5, 122.9, 118.1, 116.7, 111.3, 107.8, 54.9, 30.6; HRMS Calculated for $C_{28}H_{18}ClN_3O_3$: $[M]^+$ 479.1037, found: 479.1065.

**8-Methoxy-5-(2-oxopropyl)-1,3-diphenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4f**: gray solid; mp 253-256 °C; IR (KBr) 2852, 1734, 1548, 1497, 1250, 1161, 1128, 863, 830, 757, 701 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.6 Hz, 2H, ArH), 7.57-7.38 (m, 8H, ArH), 6.99 (d, *J* = 6.8 Hz, 1H, ArH), 6.93 (d, *J* = 8.0 Hz, 1H, ArH), 6.66 (t, *J* = 8.0 Hz, 1H, ArH), 4.69 (s, 2H, $CH_2$), 3.96 (s, 3H, $CH_3O$), 2.46 (s, 3H, $CH_3$); $^{13}$C NMR: (75 MHz, $CDCl_3$) δ 205.2, 160.0, 159.8, 147.6, 147.3, 142.7, 138.7, 134.4, 129.7, 129.3, 129.2, 128.7, 127.3, 123.1, 122.9, 122.7, 116.5, 114.6, 111.4, 108.1, 56.5, 54.9, 29.9; HRMS Calculated for $C_{29}H_{20}N_3O_4$: $[M-H]^-$ 474.1454, found: 474.1510.

**9-Methoxy-5-(2-oxopropyl)-1,3-diphenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4g**: gray solid; mp 150-152 °C; IR (KBr) 2919, 1730, 1539, 1488, 1381, 1275, 1156, 1006, 902, 851, 768, 701

$cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.6 Hz, 2H, ArH), 7.56-7.39 (m, 8H, ArH), 7.44 (t, *J* = 8.0 Hz, 1H, ArH), 6.81 (d, *J* = 8.4 Hz, 1H, ArH), 6.27 (d, *J* = 8.8 Hz, 1H, ArH), 4.65 (s, 2H, $CH_2$), 3.83 (s, 3H, $CH_3O$), 2.46 (s, 3H, $CH_3$); $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 205.2, 163.4, 160.6, 159.8, 154.6, 151.8, 147.5, 145.9, 142.7, 138.7, 134.4, 132.8, 129.7, 129.2, 128.9, 127.3, 122.8, 111.3, 109.9, 109.0, 107.5, 100.7, 56.0, 55.0, 30.6; HRMS Calculated for $C_{29}H_{21}N_3O_3$: $[M]^+$ 475.1532, found: 475.1521.

**10-Chloro-1,3-dimethyl-5-(2-oxopropyl)chromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4h**: gray solid; mp 166-168 °C; IR (KBr) 2943, 1718, 1561, 1474, 1385, 1357, 1278, 1248, 1205, 1169, 1096, 970, 778, 675 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, ArH), 7.54 (d, *J* = 8.4 Hz, 1H, ArH), 7.32 (d, *J* = 8.4 Hz, 1H, ArH), 4.57 (s, 2H, $CH_2$), 4.12 (s, 3H, $CH_3$), 2.87 (s, 3H, $CH_3$), 2.42 (s, 3H, $CH_3$); $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 205.0, 160.0, 158.9, 152.0, 150.9, 141.3, 141.2, 132.6, 129.4, 128.6, 118.9, 118.0, 109.8, 107.6, 54.7, 34.1, 30.5, 19.4; HRMS Calculated for $C_{18}H_{14}ClN_3O_3$: $[M]^+$ 355.0724, found: 355.0722.

**3-Methyl-5-(2-oxopropyl)-1-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4i**: cyan solid; mp 237-240 °C; IR (KBr) 2917, 1721, 1589, 1555, 1470, 1383, 1253, 1201, 1166, 851, 827, 687 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.49-7.41 (m, 6H, ArH), 7.33 (t, *J* = 8.4 Hz, 2H, ArH), 6.71 (t, *J* = 7.6 Hz, 1H, ArH), 4.66 (s, 2H, $CH_2$), 4.28 (s, 3H, $CH_3$), 2.47 (s, 3H, $CH_3$); $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 205.3, 160.6, 159.2, 152.6, 152.1, 146.3, 142.5, 134.6, 132.8, 131.5, 129.6, 129.0, 128.8, 123.2, 116.8, 115.8, 110.5, 106.2, 54.8, 34.5, 30.6; HRMS Calculated for $C_{23}H_{17}N_3O_3Na$: $[M+Na]^+$ 406.1168, found: 406.1160.

**10-Bromo-3-methyl-5-(2-oxopropyl)-1-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4j**: yellow solid; mp 218-220 °C; IR (KBr) 2991, 1724, 1546, 1512, 1444, 1306, 1257, 1167, 918, 826, 694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.53-7.47 (m, 7H, ArH), 7.20 (d, *J* = 7.6 Hz, 1H, ArH), 4.66 (s, 2H, $CH_2$), 4.28 (s, 3H, $CH_3$), 2.47 (s, 3H, $CH_3$); $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 205.2, 160.1, 159.3, 152.0, 151.4, 146.3, 141.0, 135.5, 134.3, 129.7, 129.5, 129.1, 118.4, 117.4, 116.2, 110.5, 106.1, 54.8, 34.6, 30.6; HRMS Calculated for $C_{23}H_{16}BrN_3O_3$: $[M]^+$ 461.0375, found: 461.0376.

**10-Methoxy-3-methyl-5-(2-oxopropyl)-1-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one 4k**: yellow solid; mp 176-178 °C; IR (KBr) 2988, 1722, 1603, 1591, 1556, 1502, 1473, 1444, 1390, 1351, 1201, 1156, 1025, 903, 826, 781, 749, 695 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 6.8 Hz, 2H, ArH), 7.49-7.44 (m, 3H, ArH), 7.28 (s, 1H, ArH), 7.03 (d, *J* = 8.4 Hz, 1H, ArH), 6.90 (s, 1H, ArH), 4.67 (s, 2H, $CH_2$), 4.29 (s, 3H, $CH_3$), 2.90 (s, 3H, $CH_3O$), 2.48 (s, 3H, $CH_3$); $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 205.3, 160.8, 159.3, 155.0, 152.2, 146.9, 146.0, 142.5, 134.8, 129.7, 129.1, 128.9, 122.3, 118.1, 116.1, 112.7, 110.6, 105.7, 54.8, 54.7, 34.6, 30.6; HRMS Calculated for $C_{24}H_{19}N_3O_4$: $[M]^+$ 413.1376, found: 413.1371.

**8,10-Dichloro-3-methyl-5-(2-oxopropyl)-1-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one**

**4l:** yellow solid; mp 176-178 °C; IR (KBr) 3065, 1732, 1559, 1537, 1524, 1450, 1399, 1262, 1012, 788, 701 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.53-7.42 (m, 7H, ArH), 4.67 (s, 2H, $CH_2$), 4.29 (s, 3H, $CH_3$), 2.48 (s, 3H, $CH_3$); $^{13}C$ NMR: (75 MHz, $CDCl_3$) δ 205.1, 159.4, 152.1, 147.0, 146.2, 143.7, 140.7, 134.1, 133.7, 132.5, 129.9, 129.7, 129.5, 129.1, 128.6, 127.2, 122.5, 117.9, 110.5, 106.2, 102.4, 54.8, 34.7, 30.6; HRMS Calculated for $C_{23}H_{15}Cl_2N_3O_3$: $[M]^+$ 451.0490, found: 451.0486.

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## REFERENCES

1. (a) J. Clardy and C. Walsh, *Nature*, 2004, **432**, 829; (b) D. L. Boger, C. W. Boyce, M. A. Labroli, C. A. Sehon, and Q. Jim, *J. Am. Chem. Soc.*, 1999, **121**, 54.
2. (a) M. E. Riveiro, C. Shayo, F. Monczor, N. Fernandez, A. Baldi, N. D. Kimpe, J. Rossi, S. Debenedetti, and C. Davio, *Cancer Lett.*, 2004, **210**, 179; (b) M. E. Riveiro, D. Maes, R. Vazquez, M. Vermeulen, S. Mangelinckx, J. Jacobs, S. Debenedetti, C. Shayo, N. De Kimpe, and C. Davio, *Bioorg. Med. Chem.*, 2009, **17**, 6547.
3. J. Y. Cho, T. L. Hwang, T. H. Chang, Y. P. Lim, P. J. Sung, T. H. Lee, and J. Chen, *J. Food Chem.*, 2012, **135**, 17.
4. J. Oldenburg, M. Watzka, S. Rost, and C. R. Muller, *J. Thromb. Haemost.*, 2007, **5**, 1.
5. V. D. Kancheva, L. Saso, P. V. Boranova, A. Khan, M. K. Saroj, M. K. Pandey, S. Malhotra, J. Z. Nechev, S. K. Sharma, A. K. Prasad, M. B. Georgieva, C. Joseph, A. L. DePass, R. C. Rastogi, and V. S. Parmar, *Biochimie*, 2010, **92**, 1089.
6. (a) T. Hirano, H. Kubo, T. Shiraishi, K. Hiromoto, T. Fujiwara, and H. Kagechika, *Tetrahedron Lett.*, 2012, **53**, 5916; (b) K. K. Sanap and S. D. Samant, *Tetrahedron Lett.*, 2012, **53**, 5407.
7. (a) Y. R. Zhao, Q. Zheng, K. Dakin, K. Xu, M. L. Martinez, and W. H. Li, *J. Am. Chem. Soc.*, 2004, **126**, 4653; (b) M. Obi, S. Morino, and K. Ichimura, *Chem. Mater.*, 1999, **11**, 656; (c) C. C. Woodroofe, A. C. Won, and S. J. Lippard, *Inorg. Chem.*, 2005, **44**, 3112; (d) J. M. Serin, D. W. Brousmiche, and J. M. J. Frechet, *J. Am. Chem. Soc.*, 2002, **124**, 11848; (e) T. S. Reddy and A. R. Reddy, *Dyes Pigm.*, 2013, **96**, 525.
8. (a) V. Colotta, L. Cecchi, G. Filacchioni, F. Melani, G. Palazzino, C. Martini, G. Giannaccinif, and A. Lucacchimif, *J. Med. Chem.*, 1988, **31**, 1; (b) K. T. Li, Y. B. Lin, and D. Y. Yang, *Org. Lett.*, 2012, **14**, 1190; (c) C. H. Lin and D. Y. Yang, *Org. Lett.*, 2013, **15**, 2802.

9. (a) Z. Wu, X. L. Fu, N. Yang, and Q. A. Wang, *Chem. Res. Chin. Univ.*, 2013, **29**, 460; (b) Y. Sakamoto, S. Boinapally, C. Katan, and M. Abe, *Tetrahedron Lett.*, 2013, **54**, 7171; (c) M. N. Sun, J. F. Hu, X. Y. Song, D. H. Wu, L. L. Kong, Y. P. Sun, D. M. Wang, Y. Wang, N. H. Chen, and G. Liu, *Eur. J. Med. Chem.*, 2013, **67**, 39.
10. (a) G. B. Olimpo, M. Natalia, Y. Osvaldo, C. Julio, V. Victor, T. U. Marco, and K. C. Bruce, *Eur. J. Med. Chem.*, 2013, **67**, 60; (b) K. Paul, S. Bindal, and V. Luxami, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3667.
11. N. Gagey, P. Neven, and L. Jullien, *Angew. Chem. Int. Ed.*, 2007, **46**, 2467.
12. Y. Li, Y. J. Ding, J. Y. Wang, Y. M. Su, and X. S. Wang, *Org. Lett.*, 2013, **15**, 2574.
13. (a) W. C. Lin and D. Y. Yang, *J. Org. Chem.*, 2013, **78**, 11798; (b) K. Pradhan, S. Paul, and A. R. Das, *Tetrahedron Lett.*, 2013, **54**, 3105.
14. (a) L. V. Frolova, I. Malik, P. Y. Uglinskii, S. Rogelj, A. Kornienko, and I. V. Magedov, *Tetrahedron Lett.*, 2011, **52**, 6643; (b) J. H. Chen, W. M. Liu, J. J. Ma, H. T. Xu, J. S. Wu, X. L. Tang, Z. Y. Fan, and P. F. Wang, *J. Org. Chem.*, 2012, **77**, 3475.
15. (a) H. Y. Wang, X. C. Liu, X. Feng, Z. B. Huang, and D. Q. Shi, *Green Chem.*, 2013, **15**, 3307; (b) H. Y. Wang, X. C. Liu, Z. B. Huang, and D. Q. Shi, *J. Heterocycl. Chem.*, 2015, **52**, 380; (c) X. C. Liu, W. Lin, H. Y. Wang, Z. B. Huang, and D. Q. Shi, *J. Heterocycl. Chem.*, 2014, **51**, 1036; (d) P. P. Jin, X. C. Liu, D. Q. Liu, Z. B. Huang, and D. Q. Shi, *J. Heterocycl. Chem.*, 2015, **52**, 1625; (e) J. X. Wang, W. Lin, H. T. Liu, M. H. Hu, X. Feng, J. F. Ren, Z. B. Huang, and D. Q. Shi, *Chin. J. Org. Chem.*, 2015, **35**, 927.
16. C. L. Shi and D. Q. Shi, *J. Chem. Res.*, 2011, 585.