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Synthesis of pyrazolopyrimidinones as sildenafil derivatives and sclerotigenin

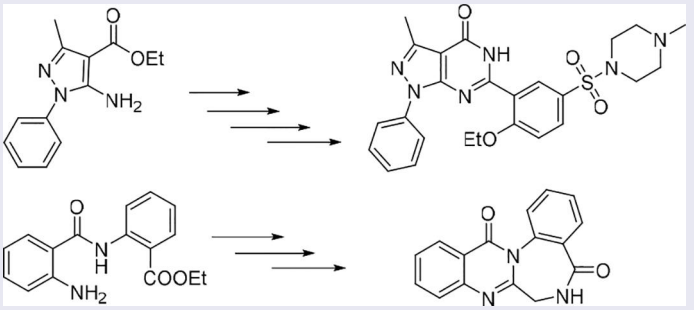
Hoon Gu Heo, Jin Yu, Raveendra Jillella, and Chang Ho Oh

Department of Chemistry, Hanyang University, Sungdong-gu, Seoul, Korea

ABSTRACT

A series of novel pyrazolo pyrimidinone derivatives (**3(a–d), 4(a–d)**, and **6(a–d))** was synthesized from various pyrazolo amides (**2a–d**) which are synthesized by the reaction between ethyl 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (**1**) and various lithium amides. In addition, we also described the synthesis of sclerotigenin drug molecule which has quinazoline moiety from simple 2-nitro benzoic acid with high yields.

GRAPHICAL ABSTRACT



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KEYWORDS
n-Heteropolycycle; pyrazolopyrimidinone; quinazolinone; sildenafil

Introduction

In recent years, pyrazolo pyrimidine derivatives and their related fused heterocylces have received significant attention due to pharmaceutical utility as purine analogues.[1] Among these, pyrazolo[3,4-*d*]pyrimidinone derivatives such as Sildenafil and Allopurinol (Fig. 1) are of great importance because they have possessed antiviral,[2] antimicrobial,[3] anti-inflammatory,[4] anticancer,[5] xanthine oxidase inhibitor,[6] herbicide,[7] adenosine receptors (A3) antagonists,[8] phosphodiesterase (PDE) inhibitor[9] properties. By considering these properties, synthesis of pyrazolo[3,4-*d*]-pyrimidinones have enormous roles in biological applications. Recently, our research group has developed first time on total synthesis of dictyopyrazole A–C (Fig. 1),[10] which is a natural alkaloid having quinazolinone moiety similar with pyrazolopyrimidinone drug molecules but not have pyrazole ring (Fig. 1).

As per the literature, Khaled. et al.[11] reported the synthesis of *N*-substituted Pyrazolo [3,4-*d*]pyrimidin-4-one derivatives through 3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]

CONTACT Chang Ho Oh changho@hanyang.ac.kr Department of Chemistry, Hanyang University, Wangsimniro 222, Sungdong-gu, Seoul 04763, Korea.
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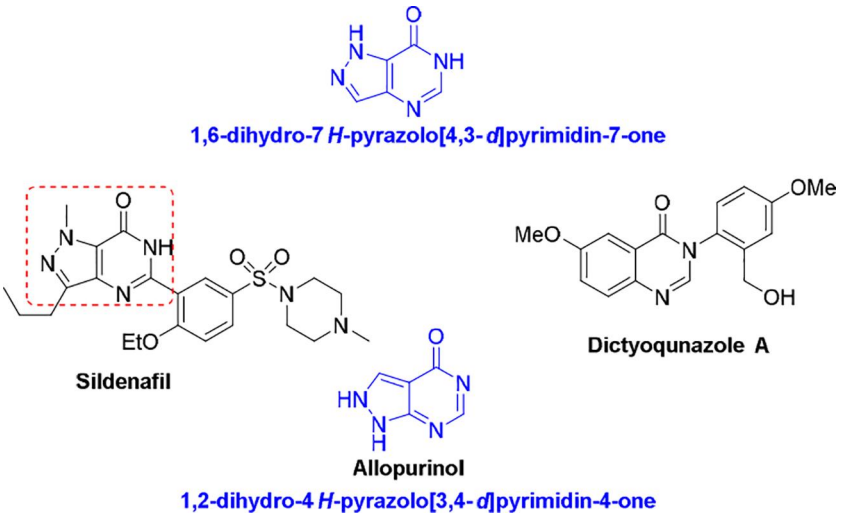


Figure 1. Pyrazolopyrimidinones and dictyoqunazole A.

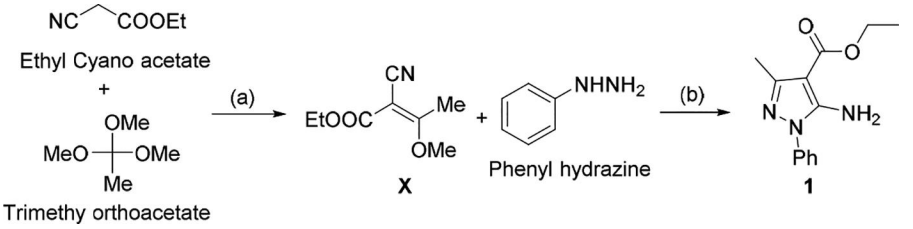
[1,3]oxazin-4-one as an intermediate. Sagar et al.[12] and Wang et al.[13] reported the biological study of the pyrazolopyrimidinone derivatives. However, due to the enormous importance of pyrazolopyrimidinone derivatives, to the best of our knowledge, herein we have described new pyrazolo[3,4-*d*]pyrimidinone derivatives with moderate to good yields from ethyl 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate as a starting substrate, which can be prepared by simple and easy method (Scheme 1).

In addition based on our previous method,[14] we also synthesized one more biologically important drug sclerotigenin that contains quinzolinone skeleton (Scheme 5). This alkaloid is a family of benzodiazepine-quinazolinones, and naturally isolated from the plant sclerotia of *Penicillium sclerotigeni*.[15] Several researchers reported the synthesis of sclerotigenin and its derivatives.[16] However, harsh reaction conditions, unsatisfactory yields, unavailability of the starting materials, and utilization of expensive reagents and catalysts are the disadvantages in many of these methods. Hence, it is time to develop inexpensive and environment-friendly synthetic routes to commercialize this highly biological active molecule. So, in this communication we reported simple and efficient synthetic routes for sclerotigenin from easily available starting material 2-nitro benzoic acid.

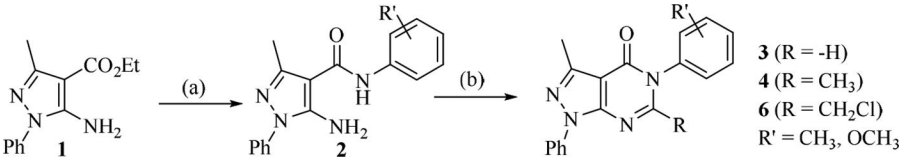
Results and discussion

Our synthesis is commenced with the preparation of the required substrate ethyl 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (**1**), which is a useful substrate for the preparation of all fused pyrazolopyrimidinones. The starting pyrazole carboxylate (1) was synthesized from ethyl cyanoacetate and trimethyl orthoacetate in methanol, produced intermediate (x), then after reaction with phenyl hydrazine in ethanol under reflux conditions as shown in Scheme 1.[17]

The synthesis of target compounds is outlined in Schemes 2 and 3. As shown in Scheme 2, primarily pyrazole amides (**2a–d**) were prepared by the reaction between (**1**)



Scheme 1. Synthetic route for starting precursor (**1**) for synthesis of target molecules. (a) Methanol, rt, 2 h, (b) ethanol, 4 h, reflux.



Scheme 2. Synthesis for pyrazolo[3,4-d]pyrimidinones. (a) Aryl amine, *n*-BuLi (b) formic acid, acetic acid, and chloroacetyl chloride.

and lithium amides. The lithium amides derived by reacting *n*-butyl lithium with substituted anilines. The yields of corresponding amides, which are shown in Fig. 2, (**2a–2d**) are 41–62%**,** respectively. For the synthesis of the corresponding pyrazolo[3,4-*d*] pyrimidin-4-ones (**3, 4**, and **6**), the obtained amides (**2a–d)** were subjected to various acids such as formic acid, acetic acid, and chloroacetyl chloride.

According to Scheme 3, pyrazolopyrimidinone compounds (**3a–d)** were prepared using precursors **2a–d** by the reaction with formic acid under reflux and obtained moderate to good yields about 48–88%, whereas the compounds **4a–d** were synthesized by the reaction of **2a–d** with acetic acid (yields 41–62%) as shown in Scheme 3. In contrast, pyrazolopyrimidinone compounds **6a–d** were synthesized in two steps. First step, the reaction of **2a–d** with chloroacetyl chloride in the presence of triethylamine produced (**5a–d**) with yields of 42–64%. Second step is as follows: The formed **5a–d** undergoes cyclocondensation in the presence of dehydrating reagent, i.e., trimethyl aluminum $Al(CH_3)_3$ in dichloroethane (DCE) under reflux for 6 h and finally afford to **6a–d** with 37–69% yields as shown in Scheme 3.

In continuing our study, we also synthesized a Sildenafil derivative **11**, which has pyrazolopyrimidinone skeleton. 5-Amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxamide **7** was synthesized from **1** by reaction with ammonia. Substrate **7** is transformed into **8** by the reaction with acetic anhydride under reflux condition. On the other hand,

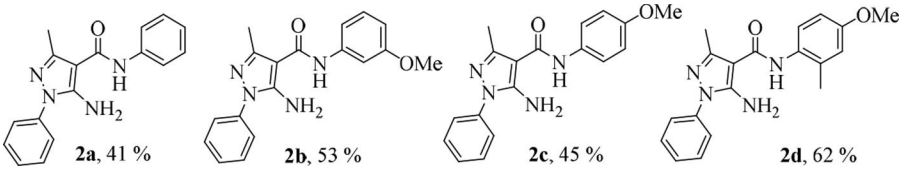
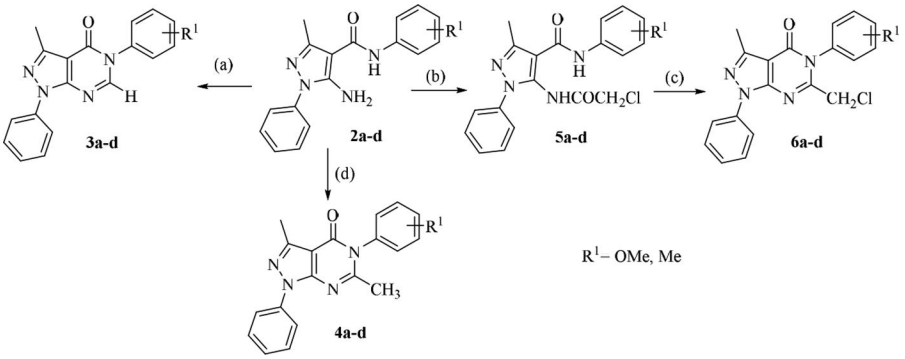
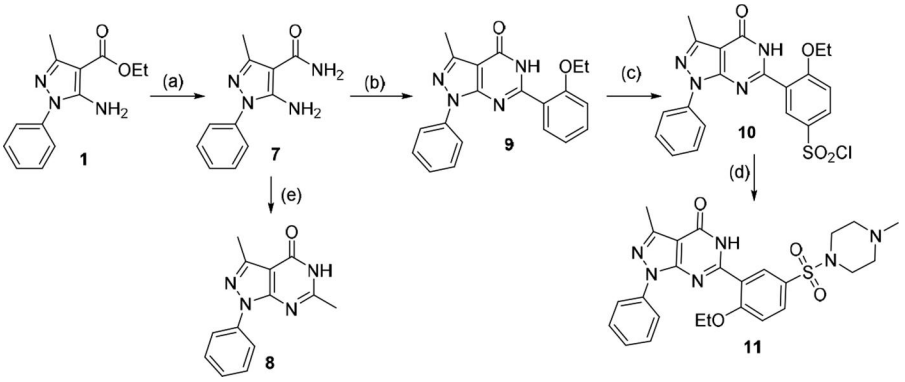


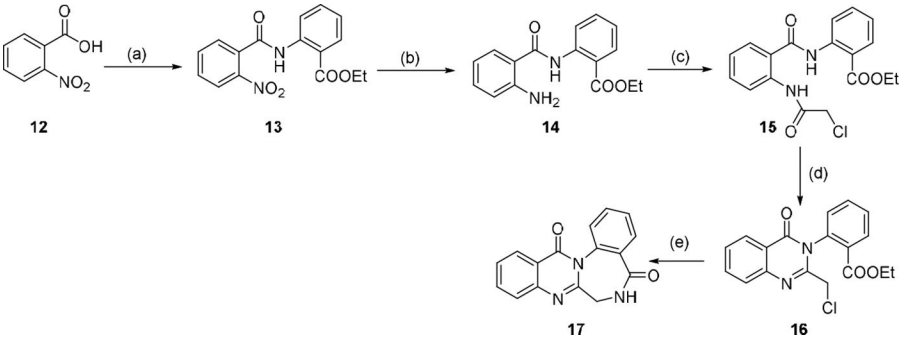
Figure 2. Diverse precursors of pyrazolo[3,4-*d*]pyrimidinones.



Scheme 3. Synthetic pathway for target compounds **3a–d**, **4a–d**, and **6a–d** from **2a–d**. (a) HCOOH, 130 °C (b) $ClCOCH_2Cl$, Et_3N (c) $Al(CH_3)_3$, DCE, reflux (d) CH_3COOH, 150–180 °C, or Ac_2O. *Note*: DCE, dichloroethane.



Scheme 4. Synthesis of sildenafil derivative. (a) aq Ammonia, 12 h, (b) 2-ethoxybenzoyl chloride, 47% (c) $HOSO_2Cl$, 53% (d) *N*-methyl piperazine, 84% (e) Ac_2O, 61%.



Scheme 5. Synthesis of sclerotigenin. (a) ethyl 2-aminobenzoate, oxalyl chloride, DMF (10 mol%), pyridine (2.7 eq.), DCE, rt, 4 h, 91% (b) 10% Pd/C (10 wt%), H2 (1 atm), MeOH, EtOAc, rt, 12 h, 97% (c) MeOH, EtOAc rt, 12 h, Et_3N (2.0 eq.), DCM, rt, 1 h 95% (d) *p*-TsOH (2.0 eq.), benzene, reflux, overnight, 60% (e) 7N NH_3 solution in methanol 70 °C, 2 h, 98%. *Note*: DCE, dichloroethane; DCM, dichloromethane; DMF, dimethylformamide.

compound **7** treated with 2-ethoxybenzoyl chloride obtained **9**. We performed further transformation of **9** into **10** by chlosulfonation in 53% yield. Finally, Sildenafil derivative **11** was obtained from compound **10** by substitution with *N*-methylpiperazine under mild conditions with 844% yield (Scheme 4).

Based on these above enthusiastic results, we elaborated our method for the synthesis of useful naturally occurring alkaloid, sclerotigenin (**17**). Our synthesis began with amide coupling of commercially available **12** (2-nitro benzoic acid) and ethyl 2-amino benzoate which afford **13** in quantitative yield. With gram quantities of **13** on hand further proceeded to reduction of nitro group to amine in the presence of palladium on carbon followed by amide coupling with chloroacetyl chloride afforded compound **15**,[18] which undergoes cyclization in the presence of *p*-TsOH and gives substituted benzoquinazolinone **16**.[19] Finally, the targeted sclerotigenin[20] (**17**) was synthesized from compound **16** by reacting with ammonia solution in MeOH (Scheme 5).

Conclusion

In conclusion, we have developed a novel and efficient method for the synthesis of biologically active Sildenafil derivative and other pyrazolopyrimidinone derivatives. We also elaborated our method for the synthesis of sclerotigenin alkaloid. Inexpensive starting materials and reagents are the advantages in this method. Biological studies of our heteropolycyclic compounds are now in progress for their anticancer study.

Experimental section

General procedure for synthesis of compounds (2a–d) and (3a–d)

In a round-bottomed flask, the solution of aniline (1.5 mmol) in dried tetrahydrofuran (THF) (0.3 M) was stirred under argon atmosphere at −78 °C. After 10 min, *n*-BuLi (2.5 mmol) was added to the stirring solution at −78 °C dropwise using cannula. Then after 10 min, to this stirring solution was added compound **1** (1.0 mmol) dropwise using 2-mL syringe in THF under argon atmosphere. The reaction mixture was stirred for 2–4 h by monitoring TLC of the reaction periodically. After completion of the reaction, mixture was quenched by water, saturated ammonium chloride, extracted with dichloromethane (DCM), and washed with brine. The crude mixture was dried over MgSO4 and filtered and concentrated under vacuum. The crude mixture was purified by flash column chromatography (SiO_2, EA/Hex = 1:2) to afford the pure product **2a** as a solid.

In a round-bottomed flask, a substrate **2a** (1.0 mmol) and acids stirred for 6–24 h under reflux condition by monitoring TLC of the reaction periodically. The reaction mixture was quenched by water, neutralized with 1 M NaOH, and then extracted with EA, washed with brine. The crude mixture was dried over $MgSO_4$ and filtered and concentrated under vacuum. The crude mixture was purified by flash column chromatography (SiO_2, EA/Hex = 1:2) to afford the pure product **3a**.

5-amino-3-methyl-N,1-diphenyl-1H-pyrazole-4-carboxamide (3a)

White solid, yield 41%, mp 135–137 °C; IR (KBr, cm^{-1}) 1694, 1570, 1542, 1506, 1224, 786, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.03 (d, J = 7.6 Hz, 2H), 7.57–7.50 (m, 5H), 7.40–7.34 (m, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 151.5, 149.2,

147.8, 138.4, 137.0, 129.7, 129.4, 129.3, 127.40, 127.2, 122.2, 105.8, 13.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{15}N_4O$: 303.116, found 303.113.

General procedure for synthesis of compounds (4a–d)

In a round-bottomed flask, a substrate **2a–d** (1.0 mmol) and acetic acid were stirred for 6–24 h under reflux by monitoring TLC of the reaction periodically. After the completion of the reaction, the mixture was quenched by water, neutralized with 1 M NaOH, extracted with EA, washed with brine. The crude mixture was dried over $MgSO_4$ and filtered and concentrated under vacuum. The crude mixture was purified by flash column chromatography (SiO_2, EA/Hex = 1:2) to afford the pure product (**4a–d)** yield 88–48%.

Synthesis of 3,6-dimethyl-1,5-diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5h) -one (4a)

White solid, yield 88%, mp 155–157 °C; IR (KBr, cm^{-1}) 2931, 1714, 1566, 1495, 1319, 754, 707; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, $J = 8.0$ Hz, 2H), 7.58–7.54 (m, 3H), 7.52–7.48 (m, 3H), 7.33 (t, $J = 7.4$ Hz, 1H), 7.24 (s, 1H), 2.64 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 158.3, 151.4, 147.5, 138.7, 137.6, 130.1, 129.5, 129.2, 128.3, 126.8, 122.0, 104.2, 25.0, 13.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{17}N_4O$: 317.132, found 317.135.

General procedure for synthesis of compounds (6a–d)

In a round-bottomed flask, the solution of compound **2a** (1.0 mmol) and triethylamine (2.0 mmol) in dried DCM (0.2 M) cooled to 0 °C, and to this stirring was added chloroacetyl chloride (2.5 mmol) after 5 min at 0 °C. The reaction mixture was kept under argon atmosphere and stirred for 24 h under reflux condition; the reaction mixture was cooled to room temperature. The reaction mixture was quenched by water, extracted with DCM, washed with saturated ammonium chloride and brine. The crude mixture was dried over $MgSO_4$ and filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, EA/Hex = 1:2) to afford the pure product **5a** as a solid.

In a round-bottomed flask, the solution of compound **5a** (1.0 mmol) in dried DCE (0.1 M) was taken and to this trimethylaluminum (3.0 mmol) was added dropwise at 0 °C, followed by stirring for 3 h at room and after the completion of the reaction cooled to room temp. The reaction mixture was quenched by water, neutralized with 1 M HCl, extracted with EA, and washed with saturated ammonium chloride and brine. The crude mixture was dried over $MgSO_4$ and filtered and concentrated under vacuum. The crude mixture was recrystallized from methanol to afford the pure product **6a** as a yellow solid.

Synthesis of 6-(chloromethyl)-3-me thyl-1,5-diphenyl-1H-pyrazolo[3,4-d] pyrimidin-4(5h)-one (6a)

Yellow solid, yield 37%, mp 186–188 °C; IR (KBr, cm^{-1}) 1695, 1551, 1514, 759, 707; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 6.4$ Hz, 3H), 7.51 (t, $J = 7.6$, 2H), 7.35 (t, $J = 6.8$ Hz, 3H), 4.25 (s, 2H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.89, 155.01, 150.59, 147.7, 148.5, 135.7, 130.0, 130.0, 129.2, 128.9, 127.1, 122.0, 104.8, 43.7, 13.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{16}ClN_4O$: 351.093, found 351.090.

Synthesis of 3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (8)

In a round-bottomed flask, the solution of compound **7** (1.0 mmol), dimethylaminopyridine (DMAP) (3 mol%), and triethylamine (2.2 mmol) in dried dimethylformamide (DMF) was taken and followed by the addition of acetic anhydride at 0 °C through 1-ml syringe. The reaction mixture was stirred for 24 h under reflux condition. The reaction mixture was cooled to room temp and then quenched with water, extracted with DCM, washed with saturated ammonium chloride and brine. The crude mixture was dried over $MgSO_4$ and filtered and concentrated under vacuum. The crude mixture was recrystallized from EA/Hex or ether to afford the pure products **8** (61%) as a pale brown solid. mp >300 °C; IR (KBr, cm^{-1}) 2852, 1677, 1592, 1504, 732, 652; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.02 (d, $J = 7.6$ Hz, 2H), 7.52 (t, $J = 7.5$ Hz, 2H), 7.34 (t, $J = 7.0$ Hz, 1H), 2.50 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.7, 158.6, 152.9, 145.7, 138.4, 129.1, 126.4, 121.3, 103.7, 21.5, 13.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_{13}N_4O$: 241.101, found 241.098.

Synthesis of 6-(2-ethoxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (9)

In a round-bottomed flask, the solution of compound **7** (1.0 mmol), DMAP (3 mol%), and triethylamine (2.2 mmol) in dried DMF of 5 mL was stirred at 0 °C. To this solution was added 2-ethoxybenzoyl chloride (2.0 mmol) dropwise using 1-mL syringe at 0 °C, and then followed by reflux for 24 h. The reaction mixture was cooled to room temp followed by quenching with water, extracted with DCM, washed with brine. The crude mixture was dried over $MgSO_4$ and filtered and concentrated under vacuum. The crude mixture was recrystallized from EA/Hex or ether to afford the pure products **9** (47%) as a white solid. mp 144–146 °C IR (KBr, cm^{-1}) 3080, 2978, 2929, 2217, 1686, 1543, 1484, 1302, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.19 (d, $J = 6.4$ Hz, 1H), 7.51 (t, $J = 8.0$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 2H), 7.40 (t, $J = 7.6$ Hz, 2H), 7.35 (d, $J = 6.8$ Hz, 1H), 7.09 (t, $J = 7.6$ Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 4.09-4.04 (q, $J = 6.8$ Hz, 2H), 2.55 (s, 3H), 1.14 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 165.5, 157.4, 149.8, 138.5, 135.1, 134.7, 133.0, 129.3, 128.3, 124.5, 121.5, 119.4, 112.6, 111.6, 65.2, 14.2, 14.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{20}H_{19}N_4O_2$: 347.143, found 347.147.

Synthesis of 4-ethoxy-3-(3-methyl-4-oxo-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d] pyrimidin-6-yl)benzene-1-sulfonyl chloride (10)

In a round-bottomed flask, to the solution of a chlorosulfonic acid (0.2 M) was added compound **9** (1.0 mmol) in DCM (0.3 M) dropwise using 5-ml syringe under argon atmosphere at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, 1 h at room. The reaction mixture was poured into ice water carefully and extracted with DCM, washed with brine. The crude mixture was dried over MgSO4 and filtered and concentrated under vacuum. The crude mixture was recrystallized from EA/Hex to afford the pure product **10** (53%) as a white solid. mp 146–148 °C; IR (KBr, cm^{-1}) 3073, 2985, 2940, 2222, 1689, 1548, 1291, 1176, 769, 581; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.97 (d, $J = 2.4$ Hz, 1H), 8.15 (dd, $J = 9.2$ Hz, 2.4 Hz, 1H), 7.55–7.45 (m, 5H), 7.15 (d, $J = 8.8$ Hz, 1H), 4.20 (d, $J = 6.8$ Hz, 2H), 2.47 (s, 3H), 1.10 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 160.0,

152.8, 138.9, 137.8, 137.2, 133.3, 133.2, 130.0, 129.6, 125.1, 120.7, 113.7, 113.3, 88.6, 66.9, 13.8, 13.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{20}H_{18}ClN_4O_4S$: 445.065, found 445.068.

Synthesis of 6-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (11)

To the solution of compound **10** (1.0 mmol) in dry THF (0.1 M) was added 1-methylpiperazine (2.0 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature And then quenched with water and extracted with DCM, washed with brine. The crude mixture was dried over MgSO4 concentrated under vacuum. The crude mixture was recrystallized from ether to afford the pure product **11**(84%) as a white solid. mp 190–192 °C; IR (KBr, cm^{-1}) 3070, 2938, 2853, 2799, 2223, 1686, 1549, 1282, 1154, 920; ^1H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.61 (s, 1H), 7.85 (d, $J = 8.8$ Hz, 1H), 7.55–7.47 (m, 5H), 7.06 (d, $J = 8.8$ Hz, 1H), 4.11 (q, $J = 6.8$ Hz, 2H), 3.01 (s, 4H), 2.47 (s, 7H), 2.26 (s, 3H), 1.02 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 159.7, 152.7, 139.2, 137.1, 134.0, 133.2, 129.9, 129.5, 128.6, 125.2, 119.8, 113.2, 88.2, 66.3, 54.0, 46.1, 45.7, 13.7, 13.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{29}N_6O_4S$: 509.189, found 509.191.

Synthesis of ethyl 2-(2-(2-chloroacetamido)benzamido)benzoate (15)

To the compound **14**(1.0 mmol) in DCM was added trimethylamine (2.0 mmol) and chloroacetyl chloride (2.0 mmol) at 0 °C under argon atmosphere. The reaction mixture was refluxed for 1 h. The crude was diluted with NH_4Cl, extracted with DCM, washed with $NaHCO_3$ and brine, dried over anhydrous MgSO4. The organic phase was concentrated under reduced pressure, and the residue was recrystallized from methanol to afford the pure product **15** (95%) as a pale brown solid. mp 118–121 °C; IR (KBr, cm^{-1}) 1666, 1585, 1525, 1438, 1262; ^1H NMR (400 MHz, $CDCl_3$) δ 12.13 (brs, NH), 11.99 (brs, NH), 8.84 (dd, $J = 9.2$, 0.8 Hz, 1H), 8.66 (dd, $J = 9.2$, 0.8 HZ, 1H), 8.12 (dd, $J = 9.6$, 1.6 Hz, 1H), 7.91 (dd, $J = 9.2$, 1.2 Hz, 1H), 7.63 (td, $J = 7.2$, 1.6 Hz, 1H), 7.58 (td, $J = 7.2$ Hz, 1.6 Hz, 1H), 4.42 (q, $J = 7.2$ Hz, 2H), 4.20 (s, 2H), 1.43 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 167.6, 165.3, 141.3, 139.3, 134.9, 133.1, 131.2, 127.4, 124.3, 123.4, 121.8, 120.9, 116.1, 61.9, 43.5, 14.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{18}ClN_2O_4$: 361.087, found 361.090.

Synthesis of ethyl 2-(2-(chloromethyl)-4-oxoquinazolin-3(4H)-yl)benzoate (16)

To the compound **15** (1.0 mmol) in benzene, *p*-TsOH (2.0 mmol) under nitrogen presence. The mixture was refluxed for 12 h and concentrated under reduced pressure followed by diluted with water, extracted with ether, washed with $NaHCO_3$, and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate and hexane to afford the pure product **16** (60%) as a pale yellow solid. mp 158–162 °C; IR (KBr, cm^{-1}) 1686, 1602, 1359, 1272; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29–8.23 (m, 2H), 7.81–7.74 (m, 3H), 7.67–7.65 (m, 1H), 7.55–7.46 (m, 2H), 4.34 (d, $J = 12$ Hz, 1H), 4.15-4.09 (m, 3H), 1.00 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 162.4, 151.7, 147.2, 136.1, 134.9, 133.9, 132.5, 131.3, 130.3, 128.8, 127.9, 127.8, 127.3, 121.4, 61.8, 43.8, 13.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2O_3$: 343.077, found 343.074.

Synthesis of 6,7-dihydrobenzo[6,7][1,4]diazepino[2,1-b]quinazoline-5, 13-dione (17)

To the compound **16** in a sealed tube was added 7N ammonia solutions in methanol. The mixture was heated at 70 °C for 2 h. Then, the mixture was evaporated under reduced pressure and recrystallized from ethyl acetate to afford the pure product **17** (98%) as a pale yellow solid. mp 268–272 °C; IR (KBr, cm^{-1}) 1685, 1612, 1461, 1356, 1251; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, $J = 9.2$, 1.2 Hz, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 7.82 (td, $J = 8.4$, 1.6 Hz, 1H), 7.69 (d, $J = 7.6$ Hz, 1H), 7.65–7.61 (m, 2H), 7.58–7.53 (m, 2H), 6.58 (brs, NH), 4.36–4.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 161.4, 153.6, 146.3, 135.1, 133.8, 131.5, 130.4, 129.8, 129.1, 128.1, 127.9, 127.6, 127.3, 121.5 47.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{16}H_{12}N_3O_2$: 278.0851, found 278.0848.

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References

[1] Chauhan, M.; Kumar, R. *Bioorg. Med. Chem.* **2013**, *21*, 5657.
[2] (a) Rashad, A. E.; Hegab, M. I.; Abdel-Megeid, R. E.; Fatahala, N. A.; Abdel-Megeid, F. M. E. *Eur. J. Med. Chem.* **2009**, *44*, 1535; (b) Gudmundsson, K. S.; Johns, B. A.; Weatherhead, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5689.
[3] (a) Shamroukh, A. H.; Rashad, A. E.; Ali, H. S.; Abdel-Megeid, F. M. E. *J. Heterocycl. Chem.* **2013**, *50*, 758; (b) Eweas, A. F.; Swelam, S. A.; Fathalla, O. A.; Fawzy, N. M.; Abdel-Moez, Sh. I. *Med. Chem. Res.* **2012**, *21*, 3848.
[4] (a)Yewale, S. B.; Ganorkar, S. B.; Baheti, K. G.; Shelke, R. U. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6616; (b) El-Tombany, A. A. *Sci. Pharm.* **2013**, *81*, 393.
[5] Ghorab, M. M.; Ragab, F. A.; Alqasoumi, S. I.; Alafeefy, A. M.; Aboulmagd, S. A. *Eur. J. Med. Chem.* **2010**, *45*, 171–178.
[6] Gupta, S.; Rodrigues, L. M.; Esteves, A. P.; Oliveira-Campos, A. M. F.; Jose Nascimento, M. S.; Nazareth, N.; Cidade, H.; Neves, M. P.; Fernandes, E.; Pinto, M. *Eur. J. Med. Chem.* **2008**, *43*, 771.
[7] (a) Liu, H.; Wang, H. Q.; Liu, Z. J. *Chin. J. Appl. Chem.* **2005**, *22*, 286; (b) Wang, T.; Luo, J.; Zheng, C. H. *Chin. J. Org. Chem.* **2010**, *30*, 1749.
[8] Cheong, S. L.; Venkatesan, G.; Paira, P.; Jothibasu, R.; Mandel, A. L.; Federico, S.; Spalluto, G.; Pastorin, G. *Int. J. Med. Chem.* **2011**, *48*, 0652.
[9] (a) Pacher, P.; Nivorozhkin, A.; Szabo, C. *Pharmacol. Rev.* **2006**, *58*, 87; (b) Rotella, D. P. *Comprehensive Med. Chem. II* **2006**, *2*, 919.
[10] Song, C. H.; Oh, C. H. *Synth. Commun.* **2015**, *45*, 768.
[11] Khaled, R. A. A.; Eman, K. A. A.; Mohamed A. A.; Rasha, R. A.; Bakar, R. B. *Molecules* **2014**, *19*, 3297.
[12] Sagar, S. R.; Agarwal, J. K.; Pandya, D. H.; Dash, R. P.; Nivsarkar, M.; Vasu, K. K. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4428.
[13] Wang, X.; Kolasa, T. E.; Kouhen, O. F.; Chovan, L. E.; Black, S. C. L.; Wagenaar, F. L.; Garton, J. A.; Moreland, R. B.; Honore, P.; Lau, Y. Y.; *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4303.
[14] Oh, B. K.; Ko, E. B.; Han, J. W.; Oh, C. H. *Syn. Com.* **2015**, *45*, 768.
[15] (a) Penhoat, M.; Bohn, P.; Dupas, G.; Papamicael, C.; Marsais, F.; Levacher, V. *Tetrahedron Asymmetry* **2006**, *17*, 281; (b) Liu, J. F.; Kaselj, M.; Isome, Y.; Chapnick, J.; Zhang, B.; Bi, G.;

Yohannes, D.; Yu, L.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 10488; (c) Grieder, A.; Thomas, A. W. *Synthesis* **2003**, 1707; (d) Snider, B. B.; Busuyek, M. V. *Tetrahedron* **2001**, *57*, 3301; (e) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417.

[16] (a) Ghosh, S. K.; Nagarajan, R. *RSC Adv.* **2016**, *6*, 27378; (b) Tseng, M. C.; Yang, H. Y.; Chu, Y. H. *Org. Biomol. Chem.* **2010**, *8*, 419; (c) Tseng, M. C.; Lai, C. Y.; Chu, Y. W.; Chu, Y. H. *Chem. Commun.* **2009**, 445; (d) Kshirsagar, U. A.; Santosh, B. M.; Argade, N. P. *Tetrahedron. Lett.* **2007**, *48*, 3243; (e) Lu, Y.; Nagashima, T.; Miriyala, B.; Conde, J.; Zhang, W. *J. Comb. Chem.* **2010**, *12*, 125; (f) Liu, J. F.; Kaselj, M.; Isome, Y.; Chapnick, J.; Zhang, B.; Bi, G.; Yohannes, D.; Yu, L.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 10488.

[17] Ferlin, M. G.; Marco, V. B. D.; Deanb, A. *Tetrahedron* **2006**, *62*, 6222.

[18] Oberg, C. T.; Strand, M.; Andersson, E. K.; Edlund, K.; Phuong, N.; Mei, Y. F.; Wadell, G.; Elofsson M. *J. Med Chem.* **2012**, *55*, 3170

[19] Witt, A.; Bergman, J. *J. Heterocycl. Chem.* **2002**, *39*, 351.

[20] Fang, J.; Zhou, J. *Org. Biomol. Chem.* **2012**, *10*, 2389.