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Facile multi-components one-pot synthesis of dipyrazolo[1,5-*a*:3',4'-*d*]pyrimidine as potent bioactive scaffolds

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An efficient, three-component, catalyst free synthesis of dipyrazolo[1,5-*a*:3',4'-*d*]pyramid scaffolds has been carried out using 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**), 5-amino pyarazole (**2a-b**) and substituted aromatic aldehydes. The reaction underwent cyclocondensation reaction in reflux condition with moderate to good (62%–90 %) yields. The twenty newly prepared molecules were analyzed by means of ^{1}H & ^{13}C NMR, Mass, and IR spectroscopies and their activities against the bacterial and fungal strains were screened. Some of tested compounds have shown excellent antibacterial activities while another four were found to have good antifungal activity.

1. Introduction

Pyrimidine scaffold is found in several naturally occurring compounds and they make the core structures of many biologically active scaffolds and much more pharmaceutical industrial materials.[1, 2] For the most part, significant fused dipyrazoloes is diprazolopyrimidine derivative which acquires a range of biological potent molecules.[3] The MCRs (Multi-components reaction) approach is more convenient in comparison to conventional synthesis because of flexibility and atom-efficient character.[4] We used the MCRs for an optimization of a synthesis of dipyrazolo[1,5-a:3',4'-d]pyrimidines. Pyrazolopyrimidines have shown different types of pharmacological activities such as antitumor,[5, 6] anticancer,[7] DPP-4 inhibitory activity,[8, 9] PDE-4 inhibitory,[10, 11] antiproliferative,[12] COX-2-inhibitory,[13] 11β-HSD1 inhibitory,[14] antibacterial[15, 16] and many others.[17] Thus, the synthesis of these moieties has been widely accounted in the most recent couple of years.[2, 13, 18-20] Despite the potential utility of previously mentioned synthetic methods, many of them suffer from usage of organic solvent and catalysts as well as strong acidic/basic conditions, long reaction times, and low yields of the target products.[2]

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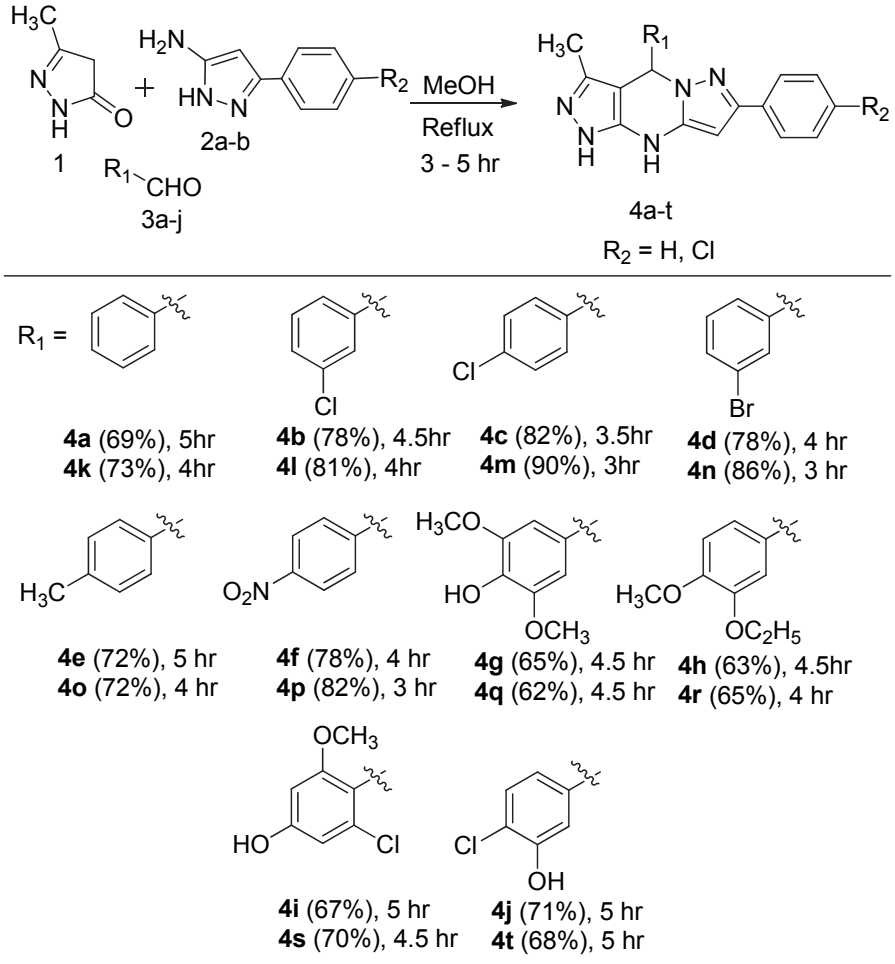
Herein, we report an efficient catalyst free synthesis of these important biologicaly active pyrazolopyrimidines based on cyclocondensation reaction of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**), 3-phenyl-1*H*-pyrazol-5-amine (**2a**), 3-(4-chlorophenyl)-1*H*-pyrazol-5-amine (**2b**) and substituted aromatic aldehydes (**3a-j**) run in a reflux condition.

2. Results and Discussion

2.1 Chemistry

Our preliminary study involving the synthesis of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**), 3-phenyl-1*H*-pyrazol-5-amine (**2a**) and 3-(4-chlorophenyl)-1*H*-pyrazol-5-amine (**2b**) were based on earlier reported procedures.[11, 21, 22] The catalyst free, one-pot, high yielding condensation reaction of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**), 3-(4-substitutedphenyl)-1*H*-pyrazol-5-amines (**2a-b**) and aromatic aldehydes (**3a-j**) was carried out using methanol as a solvent at reflux temperature to furnish desired dipyrazolo[1,5-*a*:3',4'-*d*]pyrimidine **(4a-t)** (Scheme 1).



Scheme 1. Synthesis of dipyrazolo[1,5-*a*:3',4'-*d*]pyrimidin

The reaction run at room temperature with constant stirring, gives a poor yield, what could be easily understanding taking in consideration a low solubility of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**) in methanol at that temperature. Thus, we found that this MCRs reaction was more efficient under a reflux condition with utilization of an equimolar mixture of the starting materials in methanol, and good yields of the products were obtained after 3-5 hr. Unfortunately trace amount of Hantzsch-type dihydropyridines were also formed in the reaction.[23, 24]

The chemical structures of newly synthesized compounds (**4a-t**) were proved by the spectral and microanalytical techniques. The compounds **4a-t** showed IR absorption bands at 3410-3430 cm^{-1} of cyclic secondary amine (−NH) stretching. The ^{1}H NMR spectra of newly prepared scaffolds **4a-t** posses characteristic peaks at: 4.82 ppm (hydro pyrimidine CH); two signals for two NH groups at 2.06 ppm (pyrimidine) and 10.45 ppm (pyrazole). The ^{13}C NMR spectrum possess characteristic peaks at: 159.41 and 149.14 ppm (pyrazole rings); 64.28 ppm (hydro pyrimidine CH). The mass spectra molecular ion peak of compound **4c** was detected at m/z 362.21 and 364.22 (M+).

2.2 Biological Activities

The newly synthesized compounds (**4a-t**) were evaluated by Lipinski filter.[25] Only four compounds have a logP value >5 (**4l-4o**), remaining all compounds follow the Lipinski rules of five. The *in-vitro* antibacterial activity of the 20 new synthesized compounds was evaluated using the agar well diffusion method.[26-28] The compounds were dissolving and tested at 1mg/ml concentration in dimethylsulfoxide (DMSO). The tested bacteria were: *Staphylococcus aureus* (*S.a)* and *Enterococcus facialis*ts *(E.f)* a gram (+Ve) and *Escherichia coli* (*E.c)* and *Salmonella typhi* (*S.t)* as a gram (-Ve) bacteria. The *in-vitro* antifungal analysis was screened against two fungi: *Candida albicans* (*C.a*) and *Aspergillus niger* (*A.n*). The agar well diffusion analysis was performed using nutrient agar medium, as described previously.[29, 30]

After making agar mediated petri dishes to make well 5mm sterilize cork borer was used, and the solutions of tested compounds in DMSO at concentrations of 0, 25, 50, 75 and 100 µg/ml were poured into each well The two reference drugs clarithromycin and cefixime were used as antibacterial references and ketoconazole as an antifungal agent. The inhibition % was calculated using the Equation 1. Antibacterial and antifungal activity was determined by calculate the zone of inhibition in mm.

$$\%\text{Inhibition} = \frac{\text{I}}{\text{M}}(100), \quad (1)$$

where, I= Diameter zone of inhibition (mm) and M= Diameter of petri dish (90 mm).

Lipophilicity of the molecules delivers the good antimicrobial effect. The lipophilicity of the molecules, expressed as logP, clarifies the principal indicator for the action. The o/w partition coefficient ClogP was computed utilizing the product ACD/logP.

Table 1. Antibacterial activity of dipyrazolopyrimidine derivatives

Sample code	Gram (+) Bacteria				Gram (-) Bacteria			
	S. a		***E. f***		***E. c***		***S. t***	
	Z.I (mm)	% Inhibition	Z.I (mm)	% Inhibition	Z.I (mm)	% Inhibition	Z.I (mm)	% Inhibition
4g	**19**	21.11	14	15.55	18	20.00	**20**	22.22
4h	18	20.00	**22**	22.22	16	17.77	14	15.55
4j	**19**	21.11	15	16.66	**20**	22.22	16	17.77
4q	**23**	23.33	**20**	20.00	16	17.77	13	14.44
4t	**19**	21.11	**20**	22.22	**22**	23.33	**21**	20.00
Clarithromycin	25	27.77	23	25.55	25	27.77	23	25.55
Cefixime	23	25.55	24	26.66	23	25.55	25	27.77

Z.I = Zone of inhibition, zone diameter of growth inhibition (mm) after 24 h.

The results of antibacterial evaluation of synthesized dipyrazolopyrimidine and comparison their activities with the activities of known reference drugs are shown in the Table 1. The only compounds **4h**, **4q**, and **4t** have shown higher antibacterial activity against gram +Ve bacteria *Staphylococcus aureus* and *Enterococcus faecalis*, while **4g** and **4j** were moderately active. The only compounds **4g**, **4j,** and **4t** have shown good antibacterial activity against gram -Ve bacteria *Escherichia coli* and *Salmonella typhi*. All other obtained compounds appears to be inactive. The active compounds have a lipophilic nature with logP value below 5.

The *in-vitro* antifungal zone of inhibition results are shown in Table 2.

Table 2. Antifungal activity of dipyrazolopyrimidine derivatives.

Sample code	Fungal strains			
	A. n.		***C. a.***	
	Z.I (mm)	% Inhibition	Z.I (mm)	% Inhibition
4c	**25**	23.33	17	18.89
4i	**27**	26.67	**30**	24.44
4n	**23**	25.56	**28**	23.33
4s	**26**	28.89	**28**	31.11
Ketoconazole	28	31.11	34	37.78

Z.I = Zone of inhibition, zone diameter of growth inhibition (mm) after 7 days.

Among the tested compounds a significant antifungal activity (in comparison with reference ketoconazole) against fungal strains *A. niger* and *C. Albican*s exhibit the compounds **4n** and **4s.** The compounds **4c** and **4i** showed moderate only.

3. Conclusions

In conclusion, we have developed a facile, simple reaction procedure for the synthesis of biologically significant dipyrazolo[1,5-*a*:3',4'-*d*]pyramid scaffold. The procedure has such features as: one pot synthesis, catalyst free, short reaction times, simple work up, and moderate to excellent yields. Preliminary *in-vitro* antibacterial study indicates that compounds **4g**, **4h**, **4j**, **4q** and **4t** have antibacterial activities and compounds **4c**, **4i**, **4n**, and **4s** have antifungal activity, which are almost comparable with reference drugs.

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4. Experimental

4.1. Materials and Methods

Ethyl acetoacetate, aromatic aldehyde and analytical grade solvents were purchase from commercial sources and used as received. All the reaction continuously monitored by TLC Plate (Merck silica gel PF_{254} plates) with Ethyl acetate/ hexane mixtures as mobile phase and spot visualized in iodine and UV chamber. Melting point measured in open capillary tube. Microanalysis was carried out on Perkin Elmer 2400 CHNS analyzer, the FT-IR spectra were recorded from 400 to 4000 cm^{-1} with SHIMADZU FT-IR system using KBr pellet method. NMR ^{1}H and ^{13}C spectra were recorded on Bruker F113V (600 MHz) and referenced internally with TMS and DMSO-d_6 solvent. Mass spectrum was recorded on MS Micromass.

4.2. General procedure

Synthesis of 3-methyl-7-(substituted phenyl)-4-(substituted phenyl)-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4a-t).

A mixture of the 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**, 0.01 mol), 3- substituted phenyl-1*H*-pyrazol-5-amine (**2a-b**, 0.01 mol) and substituted aromatic aldehydes (**3a-j**, 0.01 mol) in methanol (15 mL) was

refluxed for 4 to 5 hr. Reaction time was measured by TLC. After completion, the reaction mixture was kept at room temperature for 12 hours and filtered to get the solid dipyrazolopyrimidine products (**4a-t**), which were washed with methanol and dried in air.

4.3 Physical and Spectral Data

3-methyl-4, 7-diphenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4a)

Yield: 69%; light yellow solid; IR(KBr): υ 3411, 3385, 3012, 2911, 2834, 1605, 1520, 1444, 703, 692 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 1.72 (s, 3H), 2.32 (s, b, 1H), 5.21 (s, 1H), 6.9 (s, 1H), 7.43-7.68 (m, 8H), 7.83 (d, 2H, *J* = 8.2 Hz), 12.71 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 159.8, 152.8, 150.5, 141.6, 138.3, 135.6, 128.5, 126.1, 123.3, 101.5, 97.4, 58.8, 15.8; mp: 181-183 ºC; Anal. Calcd for $C_{20}H_{17}N_5$: C, 73.37; H, 5.23; N, 21.39; Found: C, 73.47; H, 5.20; N, 21.29; m/z 327.9 (M+1).

4-(3-chlorophenyl)-3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4b)

Yield: 78%; light pink solid; IR(KBr): υ 3423, 2980, 2874, 1601, 1545,1447, 810, 773, 690 cm^{-1}; ^1H NMR (600 MHz, $_{DMSO-d6}$): δ 1.71 (s, 3H), 2.31 (s, b, 1H), 5.21 (s, 1H), 6.95 (s, 1H), 7.10-7.11 (d, 1H, *J* = 3.2 Hz), 7.23-7.56 (m, 6H), 7.71 (d, 2H, *J* = 7.2 Hz), 12.52 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 163.1, 155.2, 152.7, 139.2, 134.8, 130.7, 129.4 128.1, 126.4, 118.4, 104.8, 99.7, 62.3, 15.1; mp: 216-218ºC; Anal. Calcd for $C_{20}H_{16}ClN_5$: C, 66.39; H, 4.46; Cl, 9.80; N, 19.36; Found: C, 66.36; H, 4.53; Cl, 9.40; N, 19.71; m/z 361.4, 363.6 (M+).

4-(4-chlorophenyl)-3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4c)

Yield: 82%; light pink solid; IR(KBr): υ 3403, 2924, 2812, 2729, 1595, 1500,1447, 814, 761, 692 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 1.67 (s, 3H), 2.08 (s, b, 1H), 5.07 (s, 1H), 7.1 (s, 1H), 7.15-7.16 (d, 2H, *J* = 8.2 Hz), 7.34-7.49 (m, 5H), 7.58-59 (d, 2H, *J* = 8.0 Hz), 12.61 (s, 1H); ^{13}C NMR (150 MHz, $_{DMSO-d6}$): δ 161.3, 158.7, 150.2, 143.5, 131.2, 130.3, 128.1, 126.4, 118.4, 100.7, 59.7, 16.4; mp: 208-210 ºC; Anal. Calcd for $C_{20}H_{16}ClN_5$: C, 66.39; H, 4.46; Cl, 9.80; N, 19.36; Found: C, 66.53; H, 4.50; Cl, 9.29; N, 19.68; m/z 362.2(M+1), 364.2 (M+2).

4-(3-bromophenyl)-3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4d)

Yield: 78%; yellow solid; IR(KBr): υ 3360, 3117, 2878, 1592, 1507,1470, 1432, 883, 765, 668 cm^{-1}; ^1H NMR (600 MHz, $_{DMSO-d6}$): δ 1.89 (s, 3H), 2.9 (s, b, 1H), 5.12 (s, 1H), 6.79 (s, 1H), 7.04-7.11 (m, 2H), 7.21-7.42 (m, 5H), 7.76 (d, 2H, *J* = 8.2 Hz), 12.65 (s, 1H); ^{13}C NMR (150 MHz, $_{DMSO-d6}$): δ 160.2, 156.7, 151.9, 140.4, 133.7, 130.1, 129.8 128.1, 122.6, 104.6, 89.9, 65.1, 15.9; mp: 190-192ºC; Anal. Calcd for $C_{20}H_{16}BrN_5$: C, 59.13; H, 3.97; Br, 19.67; N, 17.24; Found: C, 59.51; H, 4.03; Br, 19.47; N, 17.01; m/z 405.5, 407.8 (M+).

3-methyl-7-phenyl-4-(p-tolyl)-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4e)

Yield: 72%; yellow solid; IR(KBr): υ 3403, 3380, 3005, 2970, 2812, 1621, 1580, 1425, 1458, 853, 771, 680 cm^{-1}; ^1H NMR (600 MHz, $_{DMSO-d6}$): δ 1.81 (s, 3H), 2.18 (s, 3H), 2.7(s, b, 1H), 5.12 (s, 1H), 6.89 (s, 1H), 7.35-7.49 (m, 4H), 7.54-7.68 (m, 5H), 12.73 (s, 1H); ^{13}C NMR (150 MHz, $_{DMSO-d6}$): δ 158.8, 156.5, 149.9, 140.1, 138.8, 132.6, 129.4, 128.9, 126.4, 105.4, 98.6, 55.9, 23.3, 15.6; mp: 175-177ºC; Anal. Calcd for $C_{21}H_{19}N_5$: C, 73.88; H, 5.61; N, 20.51; Found: C, 73.79; H, 5.66; N, 20.58; m/z 341.3 (M+).

3-methyl-4-(4-nitrophenyl)-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4f)

Yield: 78%; Dark yellow solid; IR(KBr): υ 3389, 3330, 3093, 2875, 2812, 1597, 1509, 1454, 1344, 1176, 878, 770, 697 cm^{-1}; ^1H NMR (600 MHz, DMSO-d6): δ 1.68 (s, 3H), 2.1 (s, b, 1H), 5.09 (s, 1H), 6.91 (s, 1H), 7.38-7.51 (m, 5H), 7.63-7.72 (m, 4H), 12.72 (s, 1H);^{13}C NMR (150 MHz, DMSO-d6): δ 162.4, 155.3, 150.6, 147.4, 140.4, 139.3 135.7, 131.1, 130.5, 129.8 127.8, 126.3, 106.2, 92.9, 59.7, 15.2; mp: 238-240 ºC; Anal. Calcd for $C_{20}H_{16}N_6O_2$: C, 64.51; H, 4.33; N, 22.57; Found: C, 64.60; H, 4.35; N, 22.52; m/z 371.9 (M+).

2,6-dimethoxy-4-(3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidin-4-yl)phenol (4g)

Yield: 65%; light orange solid; IR(KBr): υ 3497, 3404, 3045, 2898, 1601, 1539, 1512, 1457, 1423, 1214, 916, 770, 697 cm^{-1}; ^1H NMR (600 MHz, DMSO-d6): δ 1.83 (s, 3H), 2.42 (s, b, 1H), 3.78 (s, 6H), 5.41 (s, 1H), 5.65 (s, 1H), 6.48 (s, 2H), 6.98 (s, 1H), 7.14-7.37 (m, 5H), 12.64 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 160.9, 156.5, 151.2, 150.3,138.9, 134.7, 132.9, 130.1, 128.8, 125.8, 110.5, 101.5, 97.6, 66.3, 58.4, 15.9; mp: 204-207ºC; Anal. Calcd for $C_{22}H_{21}N_5O_3$: C, 65.50; H, 5.25; N, 17.36; Found: C, 65.41; H, 5.20; N, 17.39; m/z 403.8 (M+).

4-(3-ethoxy-4-methoxyphenyl)-3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4h)

Yield: 63%; yellow solid; IR(KBr): υ 3412, 3388, 2995, 2937, 1515, 1458, 1425, 1260, 1028, 812, 765, cm^{-1}; ^1H NMR (600 MHz, DMSO-d6): δ 1.31 (t, 3H), 2.03 (s, 3H), 2.06 (s, b, 1H), 3.72 (s, 3H), 3.83-3.85 (q, 2H), 4.82 (s, 1H), 6.70-6.89 (m, 5H), 6.94-7.23 (m, 3H), 7.41 (d, 2H, *J* = 8.2 Hz), 11.45 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 159.4, 149.1, 148.0, 147.8, 147.3, 130.8, 128.9, 128.1, 113.8, 113.0, 112.1, 111.5, 103.6, 94.5, 64.2, 55.6, 18.7, 15.2; mp: 151-153ºC; Anal. Calcd for $C_{22}H_{21}N_5O_3$: C, 68.81; H, 5.77; N, 17.44; Found: C, 68.83; H, 5.75; N, 17.39; m/z 401.3 (M+).

5-chloro-2-methoxy-4-(3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidin-4-yl) phenol(4i)

Yield: 67%; orange solid; IR(KBr): υ 3545,3455, 3049, 2921, 1587, 1518, 1462, 1427, 1245, 998, 881, 779 cm^{-1}; ^1H NMR (600 MHz, DMSO-d6): δ 1.71 (s, 3H), 2.14 (s, b, 1H), 3.92 (s, 3H), 5.08 (s, 1H), 5.48 (s, 1H), 6.80 (d, *J* = 7.6 Hz 2H), 6.91 (s, 1H), 7.53-7.68 (m, 5H), 12.67 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 158.4, 155.7, 149.9, 148.5, 146.3, 138.1, 135.5, 130.1, 128.4, 127.3, 120.5, 102.9, 93.9, 61.9, 57.3, 14.2; mp: 180-182ºC; Anal. Calcd for $C_{21}H_{18}ClN_5O_2$: C, 61.84; H, 4.45; Cl, 8.69; N, 17.17; Found: C, 61.79; H, 4.48; N, 17.19; m/z 406.9 (M+).

2-chloro-5-(3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidin-4-yl)phenol (4j)

Yield: 71%; pale yellow solid; IR(KBr): υ 3505, 3398, 3013, 2879, 1541, 1514, 1458, 1423, 1093, 882, 830, 639 cm^{-1}; ^1H NMR (600 MHz, DMSO-d6): δ 1.68 (s, 3H), 2.52 (s, b, 1H), 5.42 (s, 1H), 6.61-6.69 (m, 2H), 6.92-7.2 (m, 4H), 7.93-7.95 (d, 2H, *J* = 8.8 Hz), 8.82 (s, b, 1H), 12.72 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 159.2, 157.2, 154.6, 149.2, 138.7, 134.5, 132.7,130.5, 129.9, 127.1, 122.5,118.6,103.8, 94.3, 62.8,14.7; mp: 186-188ºC; Anal. Calcd for $C_{20}H_{16}ClN_5O$: C, 63.58; H, 4.27; Cl, 9.38; N, 18.54; Found: C, 63.59; H, 4.38; N, 17.10; m/z 377.2, 379.8 (M+).

7-(4-chlorophenyl)-3-methyl-4-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4k)

Yield: 73%; yellow solid; IR(KBr): υ 3403, 3010, 2920, 2832, 1595, 1520, 1457, 825, 790, 767 cm^{-1};

^{1}H NMR (600 MHz, DMSO-d6): δ 1.80 (s, 3H), 2.81 (s, b, 1H), 5.11 (s, 1H), 6.72 (s, 1H), 7.13-7.23 (m, 5H), 7.45-7.46 (d, 2H, *J* = 8.2 Hz) 8.02-8.03(d, 2H, *J* = 8.0 Hz), 12.31(s, b, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 160.1, 155.7, 152.6, 140.2, 137.2, 130.9, 129.1,126.2, 105.5, 94.9, 59.2, 15.7; mp: 175-178ºC; Anal. Calcd for $C_{20}H_{16}ClN_5$: C, 66.39; H, 4.46; Cl, 9.80; N, 19.36; Found: C, 66.42; H, 4.49; N, 19.33; Cl, 9.76: m/z 361.25, 363.12 (M+).

4-(3-chlorophenyl)-7-(4-chlorophenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4l)

Yield: 81%; light yellow solid; IR(KBr): υ 3391, 3012, 2980, 2832, 1592, 1537, 1463, 832, 803, 753 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d6): δ 1.83 (s, 3H), 3.01 (s, b, 1H), 5.34 (s, 1H), 6.86 (s, 1H), 7.10-7.11 (d, 1H, *J* = 4.6 Hz), 7.26-7.29 (m, 3H) 7.48-7.49 (d, 2H, *J* = 8.0 Hz) 8.01-8.02(d, 2H, *J* = 7.8 Hz) 11.9(s, b, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 159.3, 154.6, 150.1, 141.5, 135.9, 134.3, 132.3, 131.3, 129.7,128.2, 125.9, 124.5, 104.8, 93.6, 61.7, 15.2; mp: 207-209ºC; Anal. Calcd for $C_{20}H_{15}Cl_2N_5$: C, 60.62; H, 3.82; Cl, 17.89; N, 17.67; Found: C, 60.58; H, 3.83; N, 17.71; Cl, 17.67; m/z 395.21, 397.45 (M+).

4,7-bis(4-chlorophenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4m)

Yield: 90%; light yellow solid; IR(KBr): υ 3394, 3010, 2986, 2825, 1590, 1535, 1461, 828, 803, 764 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d6): δ 1.88 (s, 3H), 2.98 (s, b, 1H), 5.51 (s, 1H), 6.67 (s, 1H), 7.17-7.18 (d, 2H, *J* = 7.6 Hz), 7.28 (d, 2H, *J* = 7.8 Hz) 7.58 (d, 2H, *J* = 7.8 Hz) 8.12 (d, 2H, *J* = 8.0 Hz), 12.1(s, b, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 159.7, 153.4, 150.5, 140.6, 135.1, 132.6, 129.3, 128.8, 104.6, 93.2, 61.3, 15.6; mp: 171-174ºC; Anal. Calcd for $C_{20}H_{15}Cl_2N_5$: C, 60.62; H, 3.82; Cl, 17.89; N, 17.67; Found: C, 60.65; H, 3.79; N, 17.72; Cl, 17.84; m/z 395.26, 397.40 (M+).

4-(3-bromophenyl)-7-(4-chlorophenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4n)

Yield: 86%; dark yellow solid; IR(KBr): υ 3413, 3060, 2926, 2875, 1595, 1545, 1464, 810, 684 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d6): δ 1.81 (s, 3H), 2.67 (s, b, 1H), 5.71 (s, 1H), 6.61 (s, 1H), 7.12-7.13(m, 2H), 7.29-7.31 (m, 2H) 7.51-7.52 (d, 2H, *J* = 7.6 Hz) 8.09-810 (d, 2H, *J* = 7.8 Hz), 12.3(s, b, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 159.1, 153.4, 150.1, 139.6, 135.3, 134.6, 132.3, 129.6, 128.2, 124.5, 104.8, 93.9, 60.3, 15.2; mp: 210-212ºC; Anal. Calcd for $C_{20}H_{15}ClBrN_5$: C, 54.50; H, 3.43; Br, 18.13; Cl, 8.04; N, 15.89; Found: C, 54.52; H, 3.41; N, 15.89; Cl, 8.08; Br, 18.10; m/z 439.12, 341.42 (M+).

7-(4-chlorophenyl)-3-methyl-4-(p-tolyl)-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine (4o)

Yield: 72%; off white solid; IR(KBr): υ 3408, 3020, 2933, 2812, 1594, 1515, 1469, 844, 760 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d6): δ 1.91 (s, 3H), 2.34 (1H, s), 3.23 (s, b, 1H), 5.72 (s, 1H), 6.75 (s, 1H), 7.11 (s, 4H), 7.45 (d, 2H, *J* = 7.8 Hz) 7.81 (d, 2H, *J* = 7.8 Hz), 12.72 (s, b, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 160.2, 154.3, 151.5, 139.9, 136.9, 135.4, 132.3, 129.8, 128.4, 127.8, 104.9, 93.8, 60.7, 24.7, 15.6; mp: 164-166ºC; Anal. Calcd for $C_{21}H_{18}ClN_5$: C, 67.11; H, 4.83; Cl, 9.43; N, 18.63; Found: C, 67.12; H, 4.82; N, 18.63; Cl, 9.43; m/z 375.76, 377.40 (M+).

7-(4-chlorophenyl)-3-methyl-4-(4-nitrophenyl)-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d] pyrimidine(4p)

Yield: 82%; dark yellow solid; IR(KBr): υ 3408, 3025, 2981, 2856, 1590, 1510, 1535, 1461, 1339, 844, 795 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d6): δ 1.79 (s, 3H), 3.27 (s, b, 1H), 5.82 (s, 1H), 6.93 (s, 1H), 7.52-7.54 (m, 4H), 7.88-789 (d, 2H, *J* = 7.8 Hz) 8.13 (d, 2H, *J* = 8.0 Hz), 12.61 (s, b, 1H); ^{13}C NMR (150

MHz, DMSO-d6): δ 158.7, 153.1, 149.7, 145.8, 139.6, 135.3, 132.5,130.3, 129.7, 126.5, 103.9,94.6, 61.8, 13.3; mp: 231-233°C; Anal. Calcd for $C_{20}H_{15}ClN_6O_2$: C, 59.05; H, 3.72; Cl, 8.71; N, 20.66;; Found: C, 59.09; H, 3.71; N, 20.63; Cl, 8.69; m/z 406.23, 408.48 (M+).

4-(7-(4-chlorophenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidin-4-yl)-2,6-dimethoxyphenol(4q)

Yield: 62%; orange solid; IR(KBr): υ 3484, 3392, 3025, 2913, 1595, 1542, 1521, 1452, 1423, 1224, 912, 774, 696 cm^{-1} ; ^1H NMR (600 MHz, DMSO-d6): δ 1.85 (s, 3H), 3.82 (s, b, 1H), 3.68 (s, 6H), 5.47 (s, 1H), 5.72 (s, 1H), 6.43 (s, 2H), 6.92 (s, 1H), 7.58-7.59 (d, 2H, *J* = 7.8 Hz), 7.89 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, DMSO-d6): δ 159.2, 153.4, 149.6, 148.8, 138.2, 134.9, 132.1, 130.4, 129.1, 127.2, 108.3, 103.7, 95.3, 65.1, 57.2, 15.1; mp: 168-170°C; Anal. Calcd for $C_{22}H_{20}ClN_5O_3$: C, 60.34; H, 4.60; Cl, 8.10; N, 15.99; Found: C, 60.30; H, 4.61; N, 16.01; Cl, 8.11; m/z 437.18, 439.24(M+).

7-(4-chlorophenyl)-4-(3-ethoxy-4-methoxyphenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4r)

Yield: 65%; orange solid; IR(KBr): υ 3404, 3392, 3015, 2957, 1593, 1515, 1458, 1425, 1260, 1028, 842, 812, 765, cm^{-1}; ^1H NMR (600 MHz, DMSO-d6): δ 1.21 (t, 3H), 1.71 (s, 3H), 3.25 (s, b, 1H), 3.84 (s, 3H), 3.97-4.03 (q, 2H), 5.73 (s, 1H), 6.70-6.78 (m, 4H), 7.58-7.59 (d, 2H, *J* = 7.4 Hz), 7.87 (d, 2H, *J* = 7.8 Hz), 12.82 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 158.2, 152.3, 149.1, 148.8, 148.6, 147.4, 138.5, 135.4, 132.4, 129.6, 128.8, 126.7, 122.1, 115.2, 112.3 103.5, 94.2, 65.2, 57.3, 14.2,15.7; mp: 198-201°C; Anal. Calcd for $C_{23}H_{22}ClN_5O_2$: C, 63.37; H, 5.09; Cl, 8.13; N, 16.07; Found: C, 63.30; H, 5.11; N, 16.15; Cl, 8.13; m/z 435.34, 437.23(M+).

5-chloro-4-(7-(4-chlorophenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidin-4-yl)-2-methoxyphenol(4s)

Yield: 70%; light orange solid; IR(KBr): υ 3523, 3420, 3082, 2916, 1589, 1519, 1465, 1429, 1260, 998, 881, 842, 779 cm^{-1}; ^1H NMR (600 MHz, DMSO-d6): δ 1.83 (s, 3H), 3.06 (s, b, 1H), 3.94 (s, 3H), 5.08 (s, b, 1H), 5.61 (s, 1H), 6.72 (s, 1H), 6.83 (s, 1H), 7.12 (s, 1H), 7.61-7.62 (d, 2H, *J* = 7.8 Hz), 7.83-7.85 (d, 2H, *J* = 8.4 Hz), 12.70 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 158.3, 154.6, 149.2, 148.2, 145.3, 138.3, 135.7, 132.7, 130.2, 129.1, 128.8, 127.1, 120.5, 118.3, 103.8, 93.2, 61.5, 57.1, 15.1; mp: 177-179°C; Anal. Calcd for $C_{21}H_{17}Cl_2N_5O_2$: C, 57.03; H, 3.87; Cl, 16.03; N, 15.83; Found: C, 57.14; H, 3.84; N, 15.81; Cl, 16.02; m/z 441.15, 443.56 (M+).

2-chloro-5-(7-(4-chlorophenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidin-4-yl)phenol(4t)

Yield: 68%; light yellow solid; IR(KBr): υ 3518, 3408, 3023, 2928, 1594, 1527, 1451, 1423, 1093, 881, 844, 832, 676 cm^{-1}; ^1H NMR (600 MHz, DMSO-d6): δ 1.82 (s, 3H), 3.12 (s, b, 1H), 5.61 (s, 1H), 6.81 (d, 2H, *J* = 4.8 Hz), 6.84 (s, 1H), 7.24-7.25 (d, 2H, *J* = 7.2 Hz), 7.64-7.65 (d, 2H, *J* = 8.0 Hz), 7.81-7.82 (d, 2H, *J* = 7.8 Hz), 8.82 (s, b, 1H), 12.62 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ 159.2, 157.2, 154.6, 149.2, 138.7, 134.5, 132.7, 130.5, 129.9, 127.1, 122.5,118.6, 103.8, 94.3, 62.8, 15.7; ; mp: 169-171 °C; $C_{20}H_{15}Cl_2N_5O$: C, 58.27; H, 3.67; Cl, 17.20; N, 16.99; Fond: C 58.25, H 3.69, N 17.01, Cl 17.22; m/z 411.23, 413.42 (M+).

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