Synthesis and Herbicidal Activity of 2-(3-(Trifluoromethyl)-5-(alkoxy)-1H-pyrazol-1-yl)-4-aryloxypyrimidine Derivatives
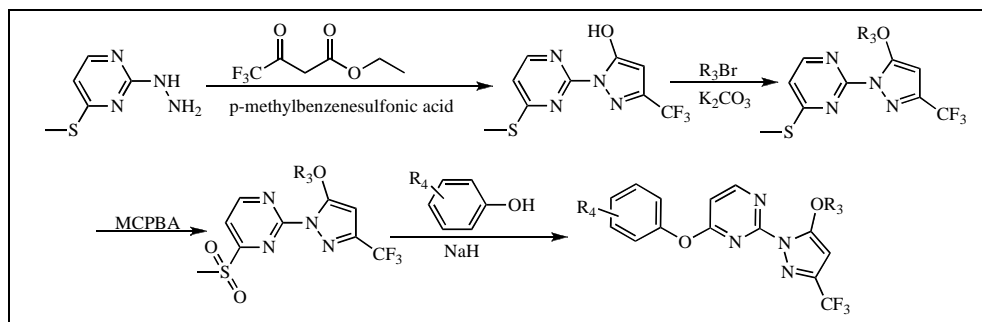
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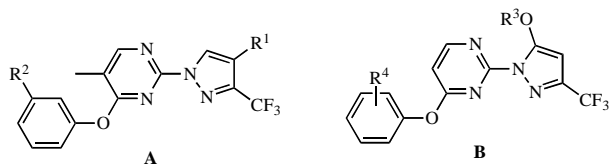University, Tianjin 300071, P. R. China
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A series of 2-(3-(trifluoromethyl)-5-(alkoxy)-1H-pyrazol-1-yl)-4-aryloxypyrimidine derivatives were designed and synthesized. The structures of all the title compounds were confirmed by ^{1}H NMR and elementary analysis. These compounds were screened for herbicidal activity against rape and barnyard grass. Compound **B13** exhibited moderate herbicidal activity.

INTRODUCTION

Pyrimidine derivatives are very important molecules in biology and are widely used in the areas of pesticide, such as imazosulfuron, ethirmol and mepanipyrim [1-4]. Particularly in the late 1990s, pyrimidyl(thio)-oxy-benzoate, classified as acetolactate synthase inhibitors, were found to exhibit high selectivity and herbicidal activity at very low rates of application and Pyrithiobac-sodium is one of the representatives [5-7]. Since the discovery of pyrithiobac-sodium with practical herbicidal activity, a lot of analogs were synthesized in order to find more potent herbicides [8-10]. For example, a new series of herbicides **A** which belonged to carotenoid bio-synthesis inhibitors exhibited high hebicidal activity and bleaching effect [11]. The substituent R^1 at **A** was mainly hydrogen, halogen, alkyl, alkoxy and cyano *etc*.

Therefore, it is significant to introduce different groups at the pyrazole and pyrimidine ring of **A** in order to develop new herbicides and observe the attributions of substituent for their herbicidal activities. Because 2,4-dichlo-pyrimidine is easily obtained, we designed and synthesized a series of new 2-(3-(trifluoromethyl)-5-(alkoxy)-1H-pyrazol-1-yl)-4-aryloxypyrimidine derivatives **B** using 2,4-dichloropyrimidine as starting material and according to the following route (Scheme 1).

The structures of **B** were established by defined ^{1}H NMR and elemental analysis. The herbicidal activity was assayed. Preliminary herbicidal experiments exhibited that some of them displayed moderate or weak activity for two weeds. All the compounds have no bleaching activity under the test condition.

RESULTS AND DISCUSSION

In our initial synthesis of **B**, the synthesis route is shown in Scheme **2**. It is well known that the chloride at 4-position of the pyrimidine ring is more active than at 2-position, so 2-chloro-4-phenoxypyrimidine **I** was obtained easily. However, when **I** was reacted with hydrazine hydrate, three products were obtained and unfortunately, the desired product **K** was obtained in only very low yield. The results of experiment showed that the 4-phenoxy group was an equal or even better leaving group than the 2-chloro group. In order to obtain **B** with higher yield, Scheme **1** was designed.

On the basis of literature [12,13], compound **D** was obtained selectively by reaction of 2,4-dichloropyrimidine with sodium thiomethoxide in tetrahydrofuran at –10 °C, and then, displacement of the 2-chloro group by hydrazine hydrate proceeded smoothly without competitive displacement of the 4-methylthio substituent in the presence of NEt$_3$ in ethanol at 0-5 °C, finally, **E** was obtained in good yield.

According to the previous method [14-17] for the synthesis of aryl pyrazole, the cyclocondensation reaction of trifluoroacetoacetate with **E** did not proceed in glacial acetic acid or ethanol. However, when the solvent was replaced by toluene and catalytic amount *p*-methyl-

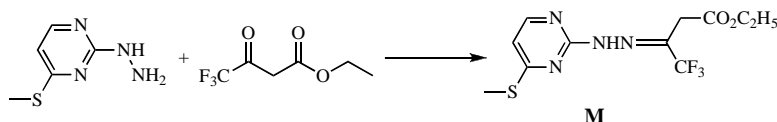temperatures, the by-product **M** would be obtained in large amounts (Scheme **3**).

The alkylation of **F** went successfully in the presence of potassium carbonate to give **G**. Sulfone **H** was easily obtained by oxidation of the methylthio group with *m*-
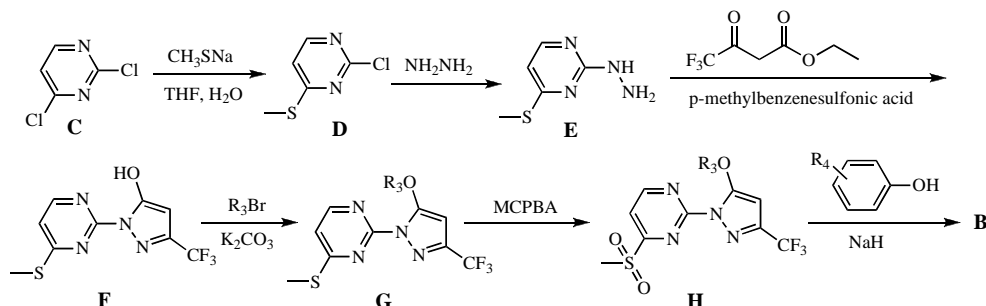
Scheme 1. General synthetic routes preparing compounds **B**
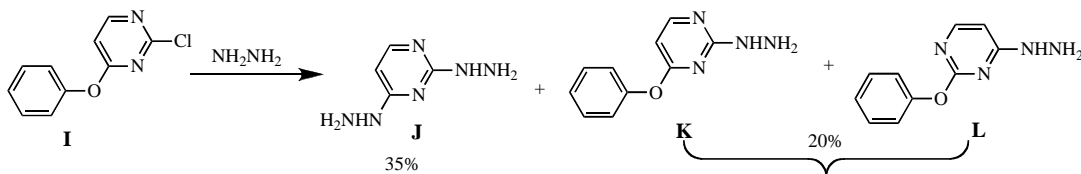
Scheme 2

Scheme 3

Table 1

Physical properties and Elemental Analysis Data of Compounds **B1**-**B18**

Compd.	R^3	R^4	Formula	Yield/ %	mp/°C	Elemental analysis (Calcd.)/ %		
						C	H	N
B1	CH$_2$CCH	2-CH$_3$	C$_{18}$H$_{13}$F$_3$N$_4$O$_2$	75.1	90-91	57.63 (57.76)	3.39 (3.50)	15.10 (14.97)
B2	CH$_2$CCH	3-CH$_3$	C$_{18}$H$_{13}$F$_3$N$_4$O$_2$	80.4	52-53	57.60 (57.76)	3.45 (3.50)	15.12 (14.97)
B3	CH$_2$CCH	4-CH$_3$	C$_{18}$H$_{13}$F$_3$N$_4$O$_2$	85.3	93-94	57.63 (57.76)	3.52 (3.50)	15.06 (14.97)
B4	CH$_2$CCH	2-Cl	C$_{17}$H$_{10}$ClF$_3$N$_4$O$_2$	70.8	59-60	51.97 (51.73)	2.39 (2.55)	14.32 (14.19)
B5	CH$_2$CCH	3-Cl	C$_{17}$H$_{10}$ClF$_3$N$_4$O$_2$	83.4	79-80	51.70 (51.73)	2.48 (2.55)	14.16 (14.19)
B6	CH$_2$CCH	4-Cl	C$_{17}$H$_{10}$ClF$_3$N$_4$O$_2$	86.8	104-105	51.70 (51.73)	2.40 (2.55)	14.01 (14.19)
B7	CH$_2$CCH	2-Br	C$_{17}$H$_{10}$BrF$_3$N$_4$O$_2$	81.3	109-110	46.49 (46.49)	2.35 (2.30)	12.73 (12.76)
B8	CH$_2$CCH	3-Br	C$_{17}$H$_{10}$BrF$_3$N$_4$O$_2$	85.4	79-80	46.20 (46.49)	2.30 (2.30)	12.90 (12.76)
B9	CH$_2$CCH	4-F	C$_{17}$H$_{10}$F$_4$N$_4$O$_2$	90.4	95-96	53.76 (53.98)	2.48 (2.66)	14.62 (14.81)
B10	CH$_2$CCH	2-OCH$_3$	C$_{18}$H$_{13}$F$_3$N$_4$O$_3$	88.6	109-110	55.30 (55.39)	3.07 (3.36)	14.58 (14.35)
B11	CH$_2$CCH	3-CF$_3$	C$_{18}$H$_{10}$F$_6$N$_4$O$_2$	89.6	84~85	50.62 (50.48)	2.38 (2.35)	12.89 (13.08)
B12	CH$_2$CCH	H	C$_{17}$H$_{11}$F$_3$N$_4$O$_2$	87.5	87-88	56.81 (56.67)	3.01 (3.08)	15.50 (15.55)
B13	CH(CH$_3$)CO$_2$Et	3-CF$_3$	C$_{20}$H$_{16}$F$_6$N$_4$O$_4$	95.6	104-105	49.11 (48.99)	3.31 (3.29)	11.21 (11.43)
B14	CH$_2$CO$_2$Et	3-CF$_3$	C$_{19}$H$_{14}$F$_6$N$_4$O$_4$	96.8	98-99	47.75 (47.91)	2.97 (2.96)	11.68 (11.76)
B15	CH$_2$CH=CH$_2$	3-CF$_3$	C$_{18}$H$_{12}$F$_6$N$_4$O$_2$	95.4	79-80	50.40 (50.24)	2.80 (2.81)	13.20 (13.02)
B16	CH$_2$CH$_3$	3-CF$_3$	C$_{17}$H$_{12}$F$_6$N$_4$O$_2$	45.6	103-104	48.81 (48.81)	3.03 (2.89)	13.20 (13.39)
B17	(CH$_2$)$_2$CH$_3$	3-CF$_3$	C$_{18}$H$_{14}$F$_6$N$_4$O$_2$	65.3	62-63	49.92 (50.01)	3.13 (3.26)	13.05 (12.96)
B18	(CH$_2$)$_3$CH$_3$	3-CF$_3$	C$_{19}$H$_{16}$F$_6$N$_4$O$_2$	86.5	75-76	51.13 (51.13)	3.58 (3.61)	12.61 (12.55)

benzenesulfonic acid was used, compound **F** was obtained in good yield. Further investigation showed that reaction temperature was very important and the optimal range was 100-105 °C. If the cyclization proceeds at other

CPBA in 95.4% yield in chloroform at room temperature. Coupling sulfone **H** with substituted phenols in the presence of sodium hydride afford excellent yields of the desired 2-pyrazolyl-4-aroxypyrimidines **B**.

Table 2

^{1}H NMR (δ, CDCl$_3$) of Compounds **B1-B18**

Compd	^{1}H NMR (CDCl$_3$, δ, ppm)
B1	2.17 (s, 1H, CH$_3$), 2.57 (t, 1H, J = 2.4 Hz, CH), 4.42 (d, 2H, J = 2.4 Hz, CH$_2$), 6.09 (s, 1H, pyrazole-H), 6.80 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.22~7.31 (m, 4H, C$_6$H$_4$), 8.66 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B2	2.40 (s, 1H, CH$_3$), 2.59 (t, 1H, J = 2.0 Hz, CH), 4.53 (d, 2H, J = 2.0 Hz, CH$_2$), 6.10 (s, 1H, pyrazole-H), 6.79 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.01~7.35 (m, 4H, C$_6$H$_4$), 8.65 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B3	2.38 (s, 1H, CH$_3$), 2.59 (t, 1H, J = 2.4 Hz, CH), 4.55 (d, 2H, J = 2.4 Hz, CH$_2$), 6.09 (s, 1H, pyrazole-H), 6.79 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.09~7.25 (m, 4H, C$_6$H$_4$), 8.64 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B4	2.57 (t, 1H, J = 1.8 Hz, CH), 4.43 (d, 2H, J = 1.8 Hz, CH$_2$), 6.07 (s, 1H, pyrazole-H), 6.93 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.29~7.53 (m, 4H, C$_6$H$_4$), 8.70 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B5	2.58 (t, 1H, J = 2.4 Hz, CH), 4.64 (d, 2H, J = 2.4 Hz, CH$_2$), 6.09 (s, 1H, pyrazole-H), 6.88 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.14~7.40 (m, 4H, C$_6$H$_4$), 8.70 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B6	2.63 (t, 1H, J = 1.8 Hz, CH), 4.62 (d, 2H, J = 1.8 Hz, CH$_2$), 6.07 (s, 1H, pyrazole-H), 6.88 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.23~7.43 (m, 4H, C$_6$H$_4$), 8.70 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B7	2.58 (t, 1H, J = 1.5 Hz, CH), 4.43 (d, 2H, J = 1.5 Hz, CH$_2$), 6.07 (s, 1H, pyrazole-H), 6.93 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.24~7.69 (m, 4H, C$_6$H$_4$), 8.72 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B8	2.60 (t, 1H, J = 1.2 Hz, CH), 4.66 (d, 2H, J = 1.2 Hz, CH$_2$), 6.10 (s, 1H, pyrazole-H), 6.89 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.22~7.48 (m, 4H, C$_6$H$_4$), 8.71 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B9	2.62 (t, 1H, J = 1.8 Hz, CH), 4.61 (d, 2H, J = 1.8 Hz, CH$_2$), 6.07 (s, 1H, pyrazole-H), 6.86 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.06~7.24 (m, 4H, C$_6$H$_4$), 8.69 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B10	2.58 (t, 1H, J = 1.5 Hz, CH), 3.76 (s, 3H, CH$_3$), 4.40 (d, 2H, J = 1.5 Hz, CH$_2$), 6.09 (s, 1H, pyrazole-H), 6.84 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.02~7.26 (m, 4H, C$_6$H$_4$), 8.66 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B11	2.57 (t, 1H, J = 1.8 Hz, CH), 4.54 (d, 2H, J = 1.8 Hz, CH$_2$), 6.07 (s, 1H, pyrazole-H), 6.93 (d, 1H, J = 5.8 Hz, pyrimidine 5-H), 7.49~7.60 (m, 4H, C$_6$H$_4$), 8.73 (d, 1H, J = 5.8 Hz, pyrimidine 6-H)
B12	2.60 (t, 1H, J = 1.8 Hz, CH), 4.53 (d, 2H, J = 1.8 Hz, CH$_2$), 6.10 (s, 1H, pyrazole-H), 6.83 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.22~7.46 (m, 5H, C$_6$H$_5$), 8.67 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B13	1.22 (t, 3H, J = 6.8 Hz, CH$_2$*CH$_3$*), 1.27 (d, 3H, J = 6.8 Hz, CH*CH$_3$*), 4.19 (qd, 2H, J = 7.5, 1.5 Hz, *CH$_2$*CH$_3$), 4.57 (q, 1H, J = 6.8 Hz, *CH*CH$_3$), 5.81 (s, 1H, pyrazole-H), 6.94 (d, 1H, J = 5.6 Hz, pyrimidine 5-H), 7.51~7.54 (m, 4H, C$_6$H$_4$), 8.74 (d, 1H, J = 5.6 Hz, pyrimidine 6-H)
B14	1.27 (t, 3H, J = 7.1 Hz, CH$_2$*CH$_3$*), 4.23 (q, 2H, J = 7.1 Hz, *CH$_2$*CH$_3$), 4.42 (s, 2H, O*CH$_2$*), 5.88 (s, 1H, pyrazole-H), 6.93 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 7.45~7.56 (m, 4H, C$_6$H$_4$), 8.73 (d, 1H, J = 5.7 Hz, pyrimidine 6-H)
B15	4.48 (d, 2H, J = 5.4 Hz, O*CH$_2$*), 5.23~5.28 (m, 2H, CH=*CH$_2$*), 5.66~5.72 (m, 1H, *CH*=CH$_2$), 5.86 (s, 1H, pyrazole-H), 6.92 (d, 1H, J = 5.4 Hz, pyrimidine 5-H), 7.46~7.55 (m, 4H, C$_6$H$_4$), 8.73 (d, 1H, J = 5.4 Hz, pyrimidine 6-H)
B16	1.15 (t, 3H, J = 6.9 Hz, CH$_2$*CH$_3$*), 4.03 (q, 2H, J = 6.9 Hz, *CH$_2$*CH$_3$), 5.84 (s, 1H, pyrazole-H), 6.92 (d, 1H, J = 5.6 Hz, pyrimidine 5-H), 7.50~7.58 (m, 4H, C$_6$H$_4$), 8.73 (d, 1H, J = 5.6 Hz, pyrimidine 6-H)
B17	0.80 (t, 3H, J = 7.4 Hz, CH$_2$*CH$_3$*), 1.48~1.55 (m, 2H, CH$_2$*CH$_2$*CH$_3$), 3.92 (t, 2H, J = 6.8 Hz, *CH$_2$*CH$_2$CH$_3$), 5.84 (s, 1H, pyrazole-H), 6.92 (d, 1H, J = 5.6 Hz, pyrimidine 5-H), 7.42~7.57 (m, 4H, C$_6$H$_4$), 8.73 (d, 1H, J = 5.6 Hz, pyrimidine 6-H)
B18	0.87 (t, 3H, J = 7.3 Hz, CH$_2$*CH$_3$*), 1.25~1.52 (m, 4H, CH$_2$*CH$_2$CH$_2$*CH$_3$), 3.98 (t, 2H, J = 6.8 Hz, *CH$_2$*CH$_2$CH$_2$CH$_3$), 5.84 (s, 1H, pyrazole-H), 6.91 (d, 1H, J = 5.6 Hz, pyrimidine 5-H), 7.39~7.55 (m, 4H, C$_6$H$_4$), 8.73 (d, 1H, J = 5.6 Hz, pyrimidine 6-H)

Table 3

Bioassay Test of Compounds **B1-B18** Against Rape and Barnyard Grass (100 mg L^{-1}, inhibitory rate %)

Compound	B1	B2	B3	B4	B5	B6	B7	B8	B9
rape	13.7	42.7	12.9	3.4	4.2	14.3	11.2	14.3	9.8
barnyard grass	8.0	75.1	31.6	11.8	49.8	12.9	10.6	7.9	17.7
Compound	**B10**	**B11**	**B12**	**B13**	**B14**	**B15**	**B16**	**B17**	**B18**
rape	21.9	10.9	21.6	5.2	62.0	8.7	3.3	14.8	6.3
barnyard grass	5.6	2.8	26.9	12.8	78.2	9.7	5.0	28.3	22.5

The structures of the title compounds were characterized by ^{1}H NMR spectroscopy and elemental analyses. Physical properties and elemental analysis data are presented in Table 1. The ^{1}H NMR data for the compounds **B** are given in Table 2. The ^{1}H NMR of spectra of **B** showed a singlet at δ 6.05-6.10 ppm, which attributed to CH of pyrazole ring. The propargyl group shows a weak triplet at 2.55-2.65 ppm and a doublet at 4.40-4.70 ppm. These phenomena were observed in compounds **B1**-**B12**.

The preliminary herbicidal activity of target compounds was evaluated against barnyard grass and rape using a previously reported procedure [18]. Their herbicidal data were presented in Table 3. All the compounds have no bleaching activity under the test condition. It was suggested that the methyl group in the pyrimidine ring may be important for bleaching activity. The compound with electron-donating group at the *meta* position in benzene ring such as **B2**, has relatively higher herbicidal activity than others. The inhibitory rate of **B2** was 75.1% to barnyard grass and 42.7% to rape at 100 mg L^{-1}. Under the test condition, compound **B14** had better activity (R^3 = OCH$_2$CO$_2$Et). The inhibitory rate of **B14** was 78.2% to barnyard grass and 62.0% to rape at 100 mg L^{-1}.

CONCLUSION

In conclusion, a series of 2-(3-(trifluoromethyl)-5-(alkloxy)-1H-pyrazol-1-yl)-4-aryloxypyrimidine derivatives were synthesized by a facile and mild method in good yield. These compounds were screened for herbicidal activity against rape and barnyard grass (Table 3). Preliminary bioassay results indicated that some compounds display moderate or weak herbicidal activity against rape and barnyard grass.

EXPERIMENTAL

General Methods. Proton NMR spectra were obtained at 300 MHz using Bruker AV300 spectrometer in $CDCl_3$ solution with TMS as internal standard. Chemical shift values were given in parts per million. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. Melting points were taken on an XT4A melting-point apparatus and were uncorrected. Mass spectra were recorded with a Thermofinnigan Polaris-Q GC-MS instrument. All reagents and chemicals were purchased from commercial sources.

Synthesis of 2-chloro-4-(methylthio)pyrimidine (D). To a solution of 2,4-dichro-pyrimidine (8.94 g, 0.06 mol) stirring in 150 mL of tetrahydrofuran was added dropwise sodium thiomethoxide (22.0%, 21.0 g, 0.066 mol) at –10 °C. After that, the mixture was allowed to warm slowly and stir at room temperature until the reaction was completed as monitored by TLC. The solvent was evaporated under reduced pressure and the residue was extracted with ether (3x50 mL). The organic layer was washed twice with saturated brine (2x20 mL), dried over sodium sulfate, and evaporated in vacuum to give a red solid. The solid was recrystallized from petroleum ether (bp 60-90 °C) to give pure white solid in 80.0% yield; mp 65-66 °C; ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H, SCH_3), 7.07 (d, J = 5.7 Hz, 1H, pyrimidine 5-H), 8.17 (d, J = 5.7 Hz, 1H, pyrimidine 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.23, 161.07, 156.18, 117.27, 12.89.

Synthesis of 1-(4-(methylthio)pyrimidin-2-yl)hydrazine (E). Hydrazine hydrate (85%, 16.94 g, 0.288 mol) was added dropwise to a solution of 2-chloro-4-(methylthio)pyrimidine (7.68 g, 0.048 mol) in 120 mL of ethanol at 0-5 °C. The mixture was allowed to warm and stir at room temperature overnight. The suspended solid was filtered and washed with water. The filtrate was evaporated under reduced pressure to give a residue which was dissolved in 80 mL of $CHCl_3$. After washing with saturated brine, the organic layer was dried over sodium sulfate and evaporated in vacuum. The combined solid were recrystallized from $CHCl_3$ to give white crystal in 90.2% yield; mp 96-98 °C; ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 3H, SCH_3), 3.96 (br, 2H, NH*NH₂*), 6.52 (d, J = 5.7 Hz, 1H, pyrimidine 5-H), 6.54 (br, 1H, *NH*NH₂), 8.01 (d, J = 5.7 Hz, 1H, pyrimidine 6-H).

Synthesis of 3-(trifluoromethyl)-1-(4-(methylthio)-pyrimidin-2-yl)-1H-pyrazol-5-ol (F). 1-(4-(methylthio)pyrimidin-2-yl)hydrazine (**E**, 3.12 g, 0.02 mol), trifluoroacetoacetate (3.68 g, 0.02 mol) and 0.05 g p-methylbenzenesulfonic acid were dissolved in 100 mL of toluene. The solution was heated and refluxed in a 250 mL flask equipped with a water-separator condenser until no water appeared (ca. 1 h). Then this solution was stirred at 100-105 °C for 5 h. After the above mixture was cooled, saturated brine (30 mL) was added to the reaction mixture and the water layer was separated. The organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude product **F**, which was recrystallized from ethanol. **F** was obtained in 85.3% yield as a yellow solid; mp 98-99 °C; ^{1}H NMR ($CDCl_3$): δ 2.69 (s, 6H, SCH_3), 5.88 (s, 1H, pyrazole-H), 7.13 (d, J = 6.0 Hz, 1H, pyrimidine 5-H), 8.31 (d, J = 6.0 Hz, 1H, pyrimidine 6-H), 12.22 (bs, 1H, OH). GC-MS m/e (%): 276 (M^+, 100), 223 (34), 207 (46), 139 (48), 125 (20), 69 (17).

Synthesis of 2-(3-(trifluoromethyl)-5-(alkoxy)-1H-pyrazol-1-yl)-4-(methylthio)pyrimidine (G). A mixture of 3-(trifluoromethyl)-1-(4-(methylthio)pyrimidin-2-yl)-1H-pyrazol-5-ol (**F**, 5.52 g, 0.02 mol), RBr (0.022 mol) and potassium carbonate (2.76 g, 0.02 mol) in 40 mL of N,N-dimethylformamide was heated at 70 °C with stirring for 8 hours, and then water (100 mL) was added. The precipitate was washed with water and petroleum ether, filtered, dried to obtain in 75.3-85.4% yield.

Synthesis of 2-(3-(trifluoromethyl)-5-(alkoxy)-1H-pyrazol-1-yl)-4-(methylsulfonyl)pyrimidine (H). G (0.01 mol) was dissolved in 100 mL of chloroform at room temperature. m-CPBA (6.9 g, 50%) was added in a small portion, so as not to allow the temperature to rise above 35 °C. The reaction mixture was stirred overnight at room temperature. After washing twice with aqueous sodium bisulfite, three times with aqueous sodium bicarbonate and then with saturated brine, the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure to give a white solid in 93.2-96.3% yield.

General synthetic procedures for target compounds (B). To a stirred suspension of 0.05 g (1.25 mmol) of 60% dispersion of sodium hydride in mineral oil in 20 mL of dry tetrahydrofuran at room temperature was added 0.78 mmol of (un)substituted phenol and the mixture stirred for 30 min. A sample of **H** (0.75mmol) was added, the mixture was stirred at room temperature. After the reaction was completed as monitored by TLC (petroleum ether (bp 60-90 °C): ethyl acetate (3:1, v/v), the mixture was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, the combined extracts were dried over anhydrous sodium sulfate and the solvent removed. The crude product was purified by flash chromatography on silica gel (200-300 mesh) using a mixture of petroleum ether (bp 60-90 °C):ethyl acetate (3:1, v/v).

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