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Acid Catalyzed One Pot Synthesis of Nitro Substituted Pyrazolo [1,5-a] Pyrimidine Derivatives

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ABSTRACT

In this paper we have described the Acid catalyzed synthesis of nitro substituted Pyrazolo[1,5-a]pyrimidine derivatives in moderate to good yield. The reaction of various substituted aldehydes with 1-(2-chlorophenyl)-2-nitroethanone as active methylene compound and 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile afforded the Pyrazolo[1,5-a]pyrimidine derivatives in the presence acid and Methanol as a solvent. We have also optimized the reaction condition using the various solvent. We have confirmed the structure on the basis of IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

Keywords: Pyrazolo[1,5-a]pyrimidine, Triazolo pyrimidine

I. INTRODUCTION

The pyrazolopyrimidine derivatives have considerable chemical and pharmacological importance because a broad range of biological activities have been displayed by these classes of molecules. Biaryls and heterobiaryls have attracted significant attention from the scientific community because of their relevance in medicinal chemistry. Heterobiaryls frequently can be observed in numerous bioactive small molecules, and in particular, heterobiaryls fused with various heterocycles, such as pyrazole, pyridine, and pyrimidine, have been used as key pharmacophores.[1] Pyrazolo[1,5-*a*]pyrimidines have attracted considerable interest because of their biological activity. For instance, this heterocyclic system is found as purine analogues and has useful properties as antimetabolites in purine biochemical reactions.[2] Several compounds of this class display interesting antitrypanosomal[3] and antischistosomal activities.[4] They are used as HMG-CoA reductaseinhibitors,[5] COX-2 selective inhibitors,[6] 30,50-cyclic-AMP phosphodiesteraseinhibitors,[7] CRF_1 antagonists,[8a-d] selective peripheral benzodiazepine receptor ligands,[9a-c] potassium channel[10] and histamine-3 receptor ligands[11] and antianxiety agents.[12.]. As we demonstrated, the tremendous biological potential of pyrazolopyrimidine derivatives encouraged us to synthesize some new highly functionalized pyrazolopyrimidine derivatives. Various methodologies have been described for the synthesis of pyrazolopyrimidine derivatives such as very well-known method for this is one pot synthesis of ethylacetoacetate, 3-aminopyrazole and aldehyde through Biginelli reaction. However, the existing methods are suffer with some drawbacks, such as; yield, time, product isolation, isomer formation. In our work we introduced novel 2-nitro-1-phenylethanone as active methylene compound and 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile for the formation of pyrazolo[1,5-*a*]pyrimidine ring system. The newly synthesized compounds were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

II. EXPERIMENTAL

All chemicals and solvents were purchased from Spectrochem Pvt Ltd., Mumbai of AR grade and were used without further purification. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F^{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H (400

MHz), ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in $CDCl_3$ and DMSO. Chemical shifts are expressed in δ *ppm* downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected. Physical constants of the synthesized compounds **Pl-01a to 01t** are shown in Table 1.

Synthesis of 1-(2-chlorophenyl)-2-nitroethanol (Int-2).

A mixture of 2-chlorobenzaldehyde (0.1mol), nitromethane (0.1 mol) and sodium acetate(0.2 mol) was stirred at RT for 24 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under reduced pressure. The residue was poured in water and extracted with ethylacetate. The organic layer was dried and evaporated to afford Int-a in form of viscous oil. This oil was forwarded to next step without further purification.

Synthesis of 1-(2-chlorophenyl)-2-nitroethanone (Int-3).

To the suspension of $K_2Cr_2O_7$(24.8 mmol) in 15ml water, **Int-2** was added drop wise at 0^0C. This mixture was allowed to stir for 30 min and then solution of sulphuric acid (10 ml con H_2SO_4 and 6 ml water) was drop wise added at same temperature. Here the exothermicity was controlled by keeping addition rate very slow. After completion of addition reaction mixture was stirred for 15 min at the same temp. Color of the reaction mixture turns dark green then it was poured over crushed ice. Separated solid was immediately filtered before temperature rise and was dissolved in saturated $NaHCO_3$ solution. Filtration was again carried out to separate non-dissolved matter. Filtrate was acidified with con HCl. Precipitated solid was filtered and wash with distilled water. Crystallization was carried out from methanol to afford pure **Int-3**.

Synthesis of 2-(bis(methylthio)methylene)malononitrile (Int-5).

A 100mL conical flask equipped with magnetic stirrer and septum was charged with a solution of malononitril(**4**), (10 mmol) in DMF (10 mL). Dry K_2CO_3 (10 mmol) was added and the mixture was stirred at RT for 2 h. CS_2 (30 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. Then, methyl iodide (20 mmol) was added at 0-5 ^{o}C and the mixture was stirred for 4 h at room temperature. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, it was poured into 50ml cold water. The precipitated crude product was purified by filtration followed by crystallization from EtOH.

Synthesis of 5-amino-3-(methylthio)-1*H*-pyrazole-4-carbonitril (Int-6).

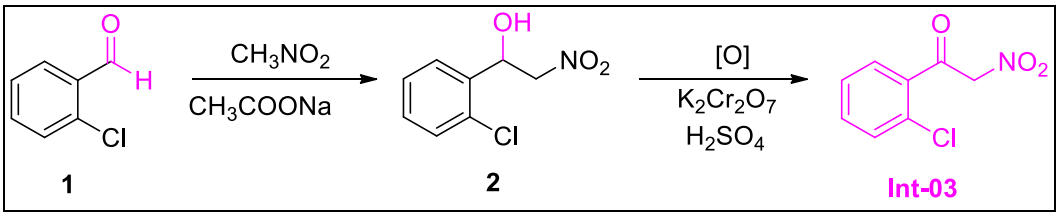
To the solution of 2-(bis(methylthio) methylene) malononitrile (**Int-05**) (0.1mol) in isopropyl alcohol (100mL), hydrazine hydrate (0.1mol) was added. The reaction mixture was stirr to 0^oC for 2 h. After completion of the reaction, it was poured into 50mL cold water. The precipitated crude product was purified by filtration followed by crystallization from EtOH.

General synthesis of pyrazolopyrimidine (PL-01a to 01t).

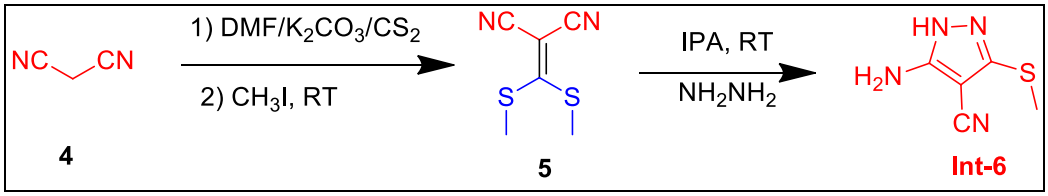
In 50ml RBF **Int-3**(2.5mmol), **Int-6**(2.5mmol) and substituted aldehyde were suspended in 20 ml methanol under stirring on magnetic stirrer. 2-3 drops of acid was added in to the reaction mixture and reaction mixture was refluxed for 10 to 12 h. The reaction was monitored by TLC. After the completion of reaction, water was decanted and solid residue was triturated with methanol to afford pure compound.

III. REACTION SCHEME

Scheme-1Synthesis of 1-(2-chlorophenyl)-2-nitroethanone



Scheme-2 Synthesis of 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile



Scheme-3 Synthesis of Pyarzolopyrimidine

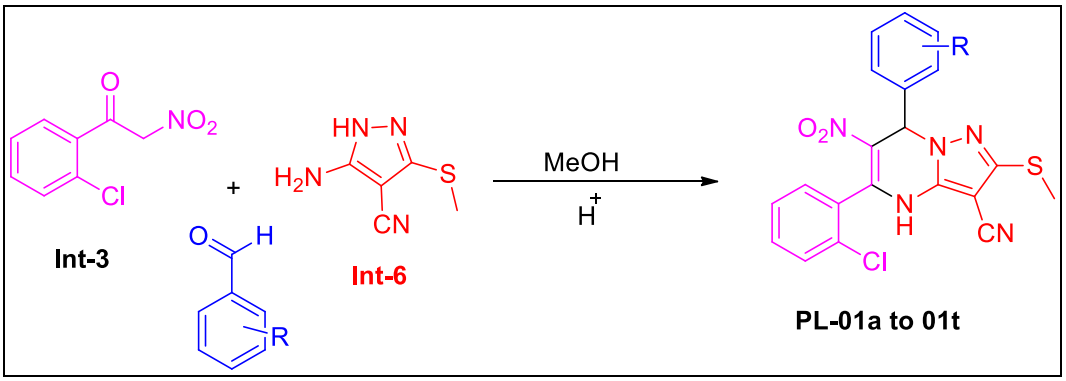
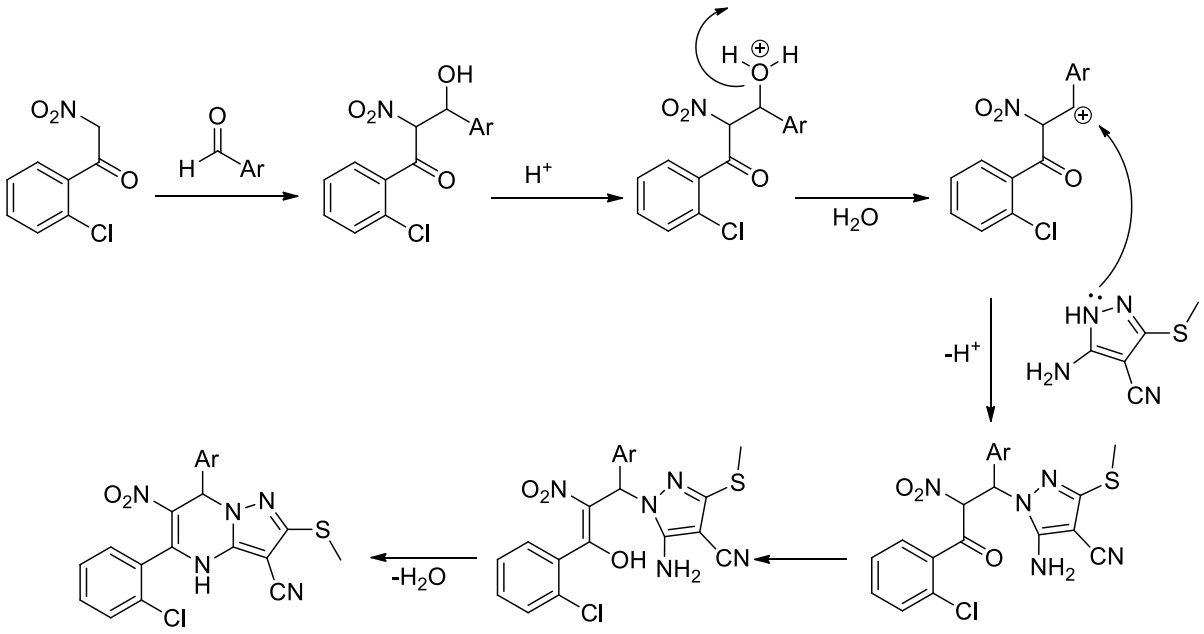


Table-1: Physical Data of The synthesized Pyrazolopyrimidines derivatives

Entry	R	Time h	Yield %	Melting Range ^{0}C
PL-01a	-H	12	90	204-206
PL-01b	-4-Cl	12	88	216-218
PL-01c	-4-Br	12	81	232-234
PL-01d	-4(N,N-dimethylamino)	15	75	248-250
PL-01e	-4-Me	13	92	218-220
PL-01f	-4-F	12	87	228-230
PL-01g	-2-Cl	12	84	214-216
PL-01h	-2,4-di Cl	12	78	242-244
PL-01i	-3,4-di OMe	14	93	206-208
PL-01j	-3-OMe	14	91	218-220
PL-01k	-2-OH	16	77	224-226

PL-01l	-3-OH	16	83	218-219
PL-01m	-2,5-di OMe	15	90	172-174
PL-01n	-3-Cl	13	78	232-234
PL-01o	-3-Br	12	79	238-240
PL-01p	-4-OH	16	75	238-240
PL-01q	-2-NO_2	18	85	206-208
PL-01r	-3-NO_2	16	81	214-216
PL-01s	Cinnamaldehyde	10	73	144-146
PL-01t	Naphthaldehyde	11	78	184-186



Figuer-1. Plausible mechanism for the formation of Pyrazolo[1,5-a]pyrimidine

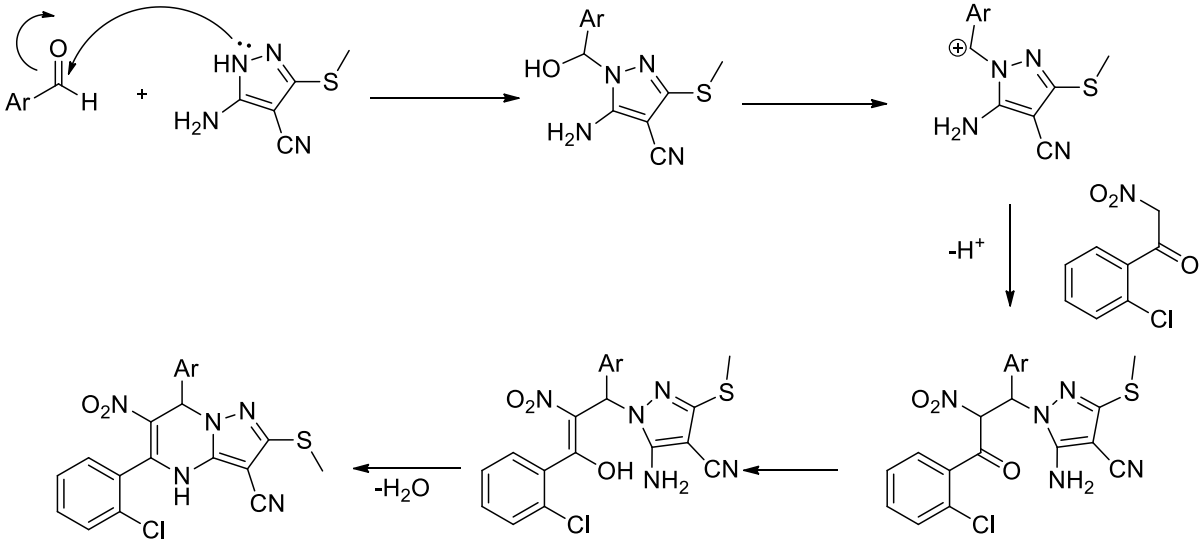


Figure 2. Proposed mechanism for the formation of Pyrazolo[1,5-a]pyrimidine

IV. CONCLUSION

In summary, we have described the Novel synthesis of nitro substituted Pyrazolo[1,5-a]pyrimidine derivatives in moderate to good yield. The reaction of various substituted aldehydes with 1-(2-chlorophenyl)-2-nitroethanone and 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile afforded the Pyrazolopyrimidine derivatives in the presence acid and methanol as a solvent. We have confirmed the structure on the basis of spectroscopic technique.

5. Spectral data of the synthesized compounds

1-(2-chlorophenyl)-2-nitroethanone (Int-3): IR (KBr): pale yellow solid; Melting range:48-50°C; R_f 0.24 (2:8 hexane-EtOAc); ^{1}H NMR: *δppm* 5.9(s, 2H, -CH_2-), 7.42-7.57(m, 3H, Ar-H), 7.77-7.79(m, 1H, Ar-H); MS (*m/z*): 199 (M^+).

5-(2-chlorophenyl)-2-(methylthio)-6-nitro-7-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carbonitrile(PL-1a): IR (KBr): yellow solid; Melting range:200-202°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3335, 2931, 2851, 1626, 1591, 1577, 1537, 1488, 1433, 1312, 1285, 1250, 1172, 1123, 1059, 974, 831, 753 cm^{-1}; ^{1}H NMR(400 MHz, DMSO): *δppm* 2.39(s, 3H, -SCH3), 6.71(s, 1H, -CH), 6.95(m, 1H, -NH), 7.18-7.48(m, 9H, Ar-H), 8.91(s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO) *δppm*: 17.37, 24.49, 25.51, 33.88, 47.95, 60.69, 99.57, 123.72, 127.36, 127.84, 128.57, 128.90, 128.98, 130.16, 131.42, 132.30, 138.65, 139.44, 144.43, 162.32, 124.10, 132.72, 141.47; MS (*m/z*): 423 (M^+); Anal. Calcd for $C_{20}H_{14}ClN_5O_2S$: C, 59.59; H, 5.00; N, 13.36; S, 6.12; Found: C, 59.52; H, 5.10; N, 13.29; S, 6.07.

5-(2-chlorophenyl)-7-(4-chlorophenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (Pl-1b): yellow solid; Melting range: 214-216°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3341, 2930, 2850, 1632, 1576, 1535, 1492, 1477, 1434, 1312, 1280, 1249, 1176, 1122, 1087, 1060, 975, 836, 774, 752 cm^{-1}; ^{1}H NMR(400 MHz, DMSO): *δppm* 2.41(s, 3H, -SCH_3), 6.68(s, 1H, -CH), 6.92-6.94(m, 1H, -NH), 7.24-7.44(m, 8H, Ar-H), 8.93(s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO) *δppm*: 17.26, 25.49, 32.86, 48.00, 60.03, 99.70, 123.67, 127.70, 128.65, 128.90, 129.22, 130.21, 131.53, 132.09, 132.62, 134.91, 136.86, 137.17, 139.65, 141.83, 144.83, 162.23 ;MS (*m/z*): 457 (M^+); Anal. Calcd for $C_{20}H_{13}Cl_2N_5O_2S$: C, 55.92; H, 4.51; N, 12.54; S, 5.74; Found: C, 55.87; H, 4.47; N, 12.48; S, 5.67.

7-(4-bromophenyl)-5-(2-chlorophenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (Pl-1c): yellow solid; Melting range:238-240°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3338, 2930, 2850, 1632, 1575, 1535, 1477, 1434, 1312, 1280, 1250, 1176, 1124, 1065, 1009, 974, 835, 772, 752 cm^{-1}; MS (*m/z*): 501 (M^+); Anal. Calcd for $C_{20}H_{13}BrClN_5O_2S$: C, 51.79; H, 4.18; N, 11.62; S, 5.32 Found C, 51.73; H, 4.11; N, 11.72; S, 5.24.

5-(2-chlorophenyl)-7-(4-(dimethylamino)phenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (Pl-1d): yellow solid; Melting range:242-244°C; R_f 0.36 (4:6 hexane-EtOAc); IR (KBr): 3343, 2929, 2848, 1630, 1626, 1574, 1529, 1480, 1433, 1311, 1279, 1250, 1219, 1169, 1129, 1059, 975, 945, 837, 775 cm^{-1}; ^{1}H NMR(400 MHz, DMSO): *δppm* 2.40(s, 3H, -SCH_3), 2.85(s, 6H, -$N(CH_3)_2$), 6.57-6.59(d, 2H, Ar-H, J=8.8Hz), 6.64(s, 1H, -CH), 7.18-7.43(m, 6H, Ar-H), 6.98(m, 1H, -NH), 8.82(s, 1H. -NH); ^{13}C NMR (100 MHz, DMSO) *δppm*: 17.52, 24.55, 25.52, 32.91, 40.37, 47.89, 60.38, 99.38, 112.02, 124.22, 126.00, 127.28, 128.20, 128.74, 129.95, 131.28, 132.09, 132.65, 139.40, 140.85, 144.00, 150.67, 162.46 ;MS (*m/z*): 466 (M^+); Anal. Calcd for $C_{22}H_{19}ClN_6O_2S$: C, 59.30; H, 5.51; N, 14.82; S, 5.65 Found: C, 59.23; H, 5.44; N, 14.77; S, 5.59.

5-(2-chlorophenyl)-2-(methylthio)-6-nitro-7-(p-tolyl)-4,7-dihydropyrazolo[1,5-*a*] pyrimidine-3-carbonitrile (Pl-1e): yellow solid; Melting range: 220-222°C; R_f 0.42 (4:6 hexane-EtOAc); IR (KBr): 758, 1058, 1124, 1174, 1223, 1250, 1282, 1312, 1434, 1476, 1536, 1576, 1630, 2931, 3343 cm^{-1}; ^{1}H NMR(400 MHz, DMSO): *δppm* 2.23(s, 3H, -CH_3), 2.39(s, 3H, -SCH_3), 6.68(s, 1H, -CH), 6.94(m, 1H, -NH), 7.06-7.08(d, 2H, Ar-H, J=7.6Hz), 7.22-7.42(m, 6H, Ar-H), 8.88(s, 1H. -NH); ^{13}C NMR (100 MHz, DMSO) *δppm*:17.29, 21.25, 24.49, 25.52, 32.88, 47.94, 60.47, 99.51, 123.89, 127.24, 127.61, 128.59, 129.39, 129.97, 132.35, 132.05, 132.47, 135.44, 138.80, 139.44, 141.29, 144.33, 162.36 ;MS (*m/z*): 341 (M^+); Anal. Calcd for $C_{21}H_{16}ClN_5O_2S$: C, 60.27; H, 5.25; N, 13.02; S, 5.96; Found: C, 60.21; H, 5.19; N, 13.12; S, 5.91.

5-(2-chlorophenyl)-7-(4-fluorophenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (Pl-1f): yellow solid; Melting range: 228-230°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3337, 2929, 2851, 1623, 1576, 1534, 1491, 1430, 1313, 1282, 1229, 1174, 1124, 1063, 975, 894, 841, 768 cm^{-1}; MS (*m/z*): 441 (M^+); Anal. Calcd for $C_{20}H_{15}ClFN_5O_2S$: C, 57.61; H, 4.65; N, 12.92; S, 5.92; Found: C, 57.52; H, 4.61; N, 12.86; S, 5.84.

5,7-bis(2-chlorophenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3- carbonitrile (Pl-1g): yellow solid; Melting range: 212-214°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3337, 2929, 2852, 1627, 1578, 1534, 1488, 1433, 1289, 1274, 1225, 1173, 1124, 1054, 972, 890, 833,754 cm^{-1}; MS (*m/z*): 457 (M^+); Anal. Calcd for $C_{20}H_{13}Cl_2N_5O_2S$: C, 55.92; H, 4.51; N, 12.54; S, 5.74; Found: C, 55.83; H, 4.43; N, 12.44; S, 5.68.

5-(2-chlorophenyl)-7-(2,4-dichlorophenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo [1,5-*a*]pyrimidine-3-carbonitrile (Pl-1h): yellow solid; Melting range:218-220°C; R_f 0.38 (4:6 hexane-EtOAc); IR (KBr): 3333, 2929, 2850, 1626, 1578, 1535, 1489, 1438, 1397, 1315, 1288, 1253, 1226, 1175, 1104, 1057, 968, 860, 821 cm^{-1}; ^{1}H NMR(400 MHz, DMSO): *δppm* 2.40(s, 3H, -SCH_3), 6.68(s, 1H, -CH), 7.13-7.45(m, 9H, Ar-H, -NH, -CH), 9.01(s, 1H. -NH); ^{13}C NMR (100 MHz, DMSO) *δppm*:17.13, 25.50, 32.85, 48.02, 58.91, 99.29, 122.56, 127.42, 127.65, 128.56, 129.95, 130.04, 130.44, 131.55, 132.14, 132.60, 133.61, 134.51, 135.30, 139.53, 142.28, 144.86, 162.24; MS (*m/z*): 491 (M^+); Anal. Calcd for $C_{20}H_{12}Cl_3N_5O_2S$: C, 52.67; H, 4.08; N, 11.81; S, 5.41; Found: C, 52.62; H, 4.18; N, 11.73; S, 5.35.

5-(2-chlorophenyl)-7-(3,4-dimethoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo [1,5-*a*]pyrimidine-3-carbonitrile (Pl-1i): yellow solid; Melting range:204-206°C; R_f 0.38 (4:6 hexane-EtOAc); IR (KBr): 3374, 2959, 2846, 1654, 1579, 1581, 1538, 1421, 1341, 1252, 1262, 1275, 1188, 1007, 915, 836 cm^{-1}; ^{1}H NMR(400 MHz, DMSO): *δppm* 2.41(s, 3H, -SCH_3), 3.76(s, 3H, -OCH_3), 3.78(s, 3H, -OCH3), 6.66(s, 1H, -CH), 6.74(m, 1H, -NH), 6.95-6.98(d, 2H, Ar-H, J=8Hz), 7.04-7.43(m, 5H, Ar-H), 8.89(s, 1H. -NH); ^{13}C NMR (100 MHz, DMSO) *δppm*:17.34, 24.48, 25.49, 32.87, 47.93, 56.01, 60.48, 99.49, 110.39, 110.95, 111.23, 120.63, 123.67, 126.93, 127.33, 128.60, 129.92, 130.78, 131.40, 132.04, 132.43, 139.22, 141.25, 144.33, 149.05, 132.31; MS (*m/z*): 483 (M^+); Anal. Calcd for $C_{22}H_{18}ClN_5O_4S$: C, 57.58; H, 5.18; N, 11.99; S, 5.49; Found: C, 57.52; H, 5.11; N, 11.88; S, 5.42.

5-(2-chlorophenyl)-7-(3-methoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo [1,5-*a*]pyrimidine-3-carbonitrile (Pl-1j): yellow solid; Melting range:218-220°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3383, 3336, 2929, 2850, 1627, 1586, 1580, 1533, 1587, 1435, 1311, 1278, 1249, 1224, 1171, 1143, 1045, 975, 886, 773 cm^{-1}; MS (*m/z*): 453 (M^+); Anal. Calcd for $C_{21}H_{16}ClN_5O_3S$: C, 58.53; H, 5.09; N, 12.64; S, 5.79; Found: C, 58.47; H, 5.19; N, 12.58; S, 5.71.

5-(2-chlorophenyl)-7-(2-hydroxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo [1,5-*a*]pyrimidine-3-carbonitrile (Pl-1k): yellow solid; Melting range:218-220°C; R_f 0.30 (4:6 hexane-EtOAc); IR (KBr): 3369, 3289, 3185, 2941, 2851, 1629, 1580, 1553, 1489, 1432, 1369, 1319, 1284, 1250, 1223, 1173, 1123, 1059, 1033, 975, 874, 819, 754 cm^{-1}; ^{1}H NMR(400 MHz, DMSO): *δppm* 2.50(s, 3H, -SCH_3), 6.80-7.46(m, 10H, Ar-H, -CH, -NH), 8.75(s, 1H, -OH), 8.96(s, 1H. -NH); ^{13}C NMR (100 MHz, DMSO) *δppm*: 13.59, 24.50, 25.47, 32.80, 48.09, 55.33, 99.35, 118.79, 120.92, 121.86, 124.58, 127.10, 127.43, 128.69, 130.16, 130.72, 131.43, 132.00, 132.38, 139.40, 142.73, 144.65, 154.89, 161.96 ; MS (*m/z*): 439 (M^+); Anal. Calcd for $C_{20}H_{14}ClN_5O_3S$: C, 57.83; H, 4.85; N, 12.97; S, 5.94; Found: C, 57.77; H, 4.72; N, 12.77; S, 5.87.

5-(2-chlorophenyl)-7-(3-hydroxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo [1,5-*a*]pyrimidine-3-carbonitrile (Pl-1l): yellow solid; Melting range: 216-218°C; R_f 0.36 (4:6 hexane-EtOAc); IR (KBr): 3323, 2931, 2851, 1620, 1579, 1538, 1469, 1453, 1312, 1279, 1249, 1226, 1174, 1062, 977, 795, 758 cm^{-1}; MS (*m/z*): 439 (M^+); Anal. Calcd for $C_{20}H_{14}ClN_5O_3S$: C, 57.83; H, 4.85; N, 12.97; S, 5.94; Found: C, 57.75; H, 4.77; N, 12.87; S, 5.82.

5-(2-chlorophenyl)-7-(2,4-dimethoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo [1,5-*a*]pyrimidine-3-carbonitrile (Pl-1m): yellow solid; Melting range:176-178°C; R_f 0.38 (4:6 hexane-EtOAc); IR (KBr): 3295, 2932, 2851, 1632, 1576, 1535, 1502, 1477, 1311, 1277, 1223, 1177, 1042, 797, 747 cm^{-1}; MS (*m/z*): 483 (M^+); Anal. Calcd for $C_{22}H_{18}ClN_5O_4S$: C,

57.58; H, 5.18; N, 11.99; S, 5.49; Found: C, 57.49; H, 5.11; N, 11.81; S, 5.37.

5-(2-chlorophenyl)-7-(3-chlorophenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5*a*] pyrimidine-3-carbonitrile (Pl-1n): yellow solid; Melting range: 230-232°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3337, 2929, 2852, 1624, 1589, 1535, 1486, 1434, 1364, 1314, 1285, 1250, 1172, 1124, 1062, 975, 796, 771, 748 cm^{-1}; MS (*m/z*): 457 (M^+); Anal. Calcd for $C_{20}H_{13}Cl_2N_5O_2S$: C, 55.92; H, 4.51; N, 12.54; S, 5.74; Found: C, 55.84; H, 4.46; N, 12.44; S, 5.68.

7-(3-bromophenyl)-5-(2-chlorophenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (Pl-1o): yellow solid; Melting range:230-232°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3334, 2930, 2852, 1624, 1582, 1578, 1535, 1478, 1434, 1312, 1282, 1250, 1172, 1124, 1063, 973, 813, 769 cm^{-1}; MS (*m/z*): 501 (M^+); Anal. Calcd for $C_{20}H_{13}BrClN_5O_2S$: C, 51.79; H, 4.18; N, 11.62; S, 5.32; Found: C, 51.71; H, 4.13; N, 11.54; S, 5.23.

5-(2-chlorophenyl)-7-(4-hydroxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo [1,5-*a*]pyrimidine-3-carbonitrile (Pl-1p): yellow solid; Melting range:238-240°C; R_f 0.32 (4:6 hexane-EtOAc); IR (KBr): 3324, 3160, 2930, 2852, 1621, 1573, 1543, 1480, 1434, 1367, 1314, 1280, 1248, 1225, 1174, 1064, 977, 828, 771, 749 cm^{-1}; MS (*m/z*): 439 (M^+); Anal. Calcd for $C_{20}H_{14}ClN_5O_3S$: C, 57.83; H, 4.85; N, 12.97; S, 5.94; Found: C, 57.76; H, 4.77; N, 12.89; S, 5.88.

5-(2-chlorophenyl)-2-(methylthio)-6-nitro-7-(2-nitrophenyl)-4,7-dihydropyrazolo[1,5-*a*] pyrimidine-3-carbonitrile (Pl-1q): yellow solid; Melting range:200-202°C; R_f 0.34 (4:6 hexane-EtOAc); IR (KBr): 3332, 2927, 2852, 1628, 1575, 1534, 1484, 1433, 1355, 1313, 1286, 1253, 1174, 1059, 978, 858, 823, 783, 750 cm^{-1}; MS (*m/z*): 468 (M^+); Anal. Calcd for $C_{20}H_{13}ClN_6O_4S$: C, 54.88; H, 4.43; N, 14.77; S, 5.64; Found: C, 54.81; H, 4.37; N, 14.71; S, 5.58.

5-(2-chlorophenyl)-2-(methylthio)-6-nitro-7-(3-nitrophenyl)-4,7-dihydropyrazolo[1,5-*a*] pyrimidine-3-carbonitrile (Pl-1r): yellow solid; Melting range: 208-210°C; R_f 0.34 (4:6 hexane-EtOAc); IR (KBr): 3374, 3339, 2928, 2851, 1627, 1571, 1532, 1484, 1439, 1344, 1311, 1285, 1228, 1174, 1062, 978, 897, 812, 746, 723 cm^{-1}; ^{1}H NMR(400 MHz, DMSO): *δppm* 2.41(s, 3H, $-SCH_3$), 6.80(s, 1H, -CH), 6.86(m, 1H, -NH), 7.30-8.13(m, 7H, Ar-H), 8.40(s, 1H, Ar-H), 9.06(s, 1H. -NH); ^{13}C NMR (100 MHz, DMSO) *δppm*: 17.04, 24.50, 25.48, 32.82, 48.05, 59.93, 99.89, 122.35, 122.37, 124.00, 127.53, 128.47, 129.77, 130.07, 131.68, 131.93, 132.52, 133.79, 139.17, 140.38, 142.47, 145.23, 148.51, 162.05 ;MS (*m/z*): 468 (M^+); Anal. Calcd for $C_{20}H_{13}ClN_6O_4S$: C, 54.88; H, 4.43; N, 14.77; S, 5.64; Found: C, 54.79; H, 4.34; N, 14.70; S, 5.59.

(E)-5-(2-chlorophenyl)-2-(methylthio)-6-nitro-7-styryl-4,7-dihydropyrazolo[1,5-*a*] pyrimidine-3-carbonitrile (Pl-1s): yellow solid; Melting range:144-146°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3345, 3032, 2956, 2824, 1610, 1565, 1588, 1546, 1472, 1428, 1311, 1290, 1120, 1066, 967, 852, 778 cm^{-1}; MS (*m/z*): 449 (M^+); Anal. Calcd for $C_{20}H_{16}ClN_5O_2S$: C, 61.14; H, 5.13; N, 12.73; S, 5.83; Found: C, 61.09; H, 5.07; N, 12.67; S, 5.71.

5-(2-chlorophenyl)-2-(methylthio)-7-(naphthalen-1-yl)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (Pl-1t): yellow solid; Melting range:178-180°C; R_f 0.48 (4:6 hexane-EtOAc); IR (KBr): 3350, 2931, 2852, 1624, 1575, 1543, 1482, 1439, 1309, 1284, 1227, 1169, 1061, 969, 784, 752 cm^{-1}; MS (*m/z*): 473 (M^+); Anal. Calcd for $C_{24}H_{16}ClN_5O_2S$: C, 62.76; H, 4.92; N, 12.20; S, 5.59; Found: C, 62.63; H, 4.85; N, 12.13; S, 5.52.

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