Water mediated one pot synthesis of nitro functionalized pyrazolo [1,5-a]pyrimidine derivatives

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Abstract: *The new method to synthesis of nitro functionalized pyrazolo[1,5-a]pyrimidine derivatives by the condensation of 1-(2-chlorophenyl)-2-nitroethanone, 5-amino pyrazole derivative and substituted aldehydes by using water as solvent in presence of H_3BO_3 at refluxed temperature. The investigation of antimicrobial and antifungal screening data revealed that all the tested compounds showed moderate to significant activity.*

Key Words: *nitro functionalized pyrazolo[1,5-a]pyrimidine, 1-(2-chlorophenyl)-2-nitroethanone, 5-amino pyrazole, boric acid.*

1. INTRODUCTION:

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[18-20] 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[3,21] and antischistosomal activities.[4, 22,23] They are used as HMG-CoA reductaseinhibitors,[5, 24-26] COX-2 selective inhibitors,[6] 30,50-cyclic-AMP phosphodiesteraseinhibitors,[7, 27-29] CRF_1 antagonists,[8a-d] selective peripheral benzodiazepine receptor ligands,[9a-c] potassium channel[10] and histamine-3 receptor ligands[11] and antianxiety agents.[12,30]

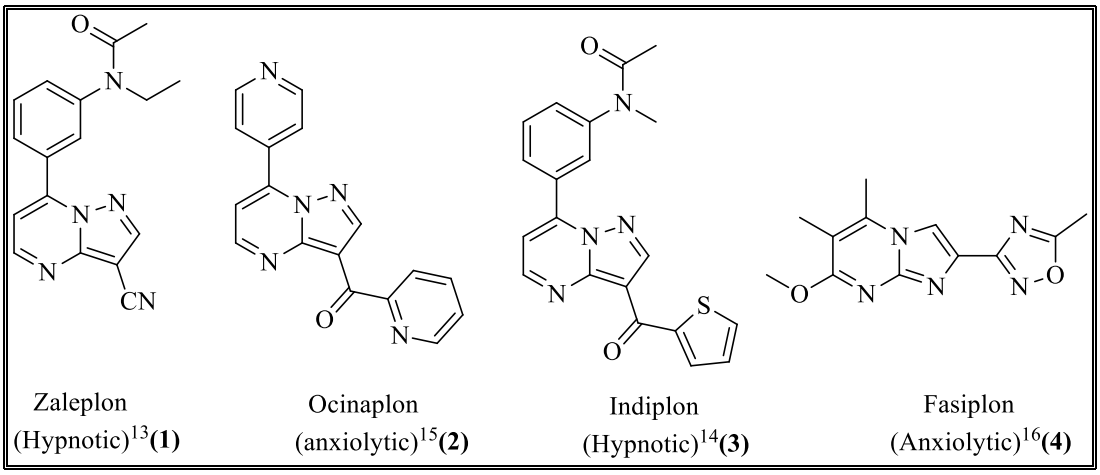
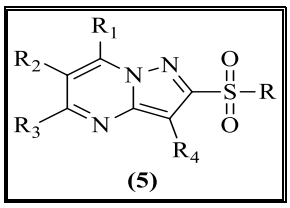


Figure-1

Some pyrazolopyrimidines serve as efficient sedative-hypnotic and anxiolytic drugs like zaleplon (Sonata, hypnotic),[13] indiplon (hypnotic),[14] and ocinaplon (anxiolytic),[15] fasiplon (anxiolytic),[16] (**Figure-1**) these drugs are related to the class of nonbenzodiazepines, and their therapeutic effect is due to allosteric enhancement of the action of the inhibitory neurotransmitter GABA at the $GABA_A$ receptor.[13-14] These examples emphasize the importance of pyrazol-fused heterobiaryls, as well as pyrazolopyridines, as key pharmacophores in bioactive small molecules.

Pyrazolopyrimidines have multiple pharmacological activities including hypnotic, anti-inflammatory, anti-tumor, antimycobacterial, antidiabetic, antiphlogistic agents, antidepressants, analgesics and anti-viral. Several diverse biological activities have been reported for pyrazolopyrimidine ring systems which are described as below.

Ivashchenko et al.[17] reported that substituted 3-(arylsulfonyl)pyrazolo[1,5-a] pyrimidines**(5)** (**Figure-2**) are claimed as antagonists of serotonin 5-HT6 receptors for treating and preventing pathol. states and diseases of the central nervous system in humans and warm-blooded animals, the pathogenesis of which is caused by disorder in the serotonin 5-HT6 receptor activation.



(5)

Figure-2

2. EXPERIMENTAL SECTION:

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

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-b)

To the suspension of $K_2Cr_2O_7$(24.8 mmol) in 15ml water, **Int-a** 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-b**.

Synthesis of 2-cyano-N-cyclohexylacetamide (Int-1)

In a 250mL round bottom flask equipped with magnetic stirrer and thermometer was placed ethyl 2-cyanoacetate (0.25mol), cyclohexaylamine (0.25mol) and toluene (100mL). The reaction mixture was heated up to 110-115 ºC for 8 h. The progress of reaction was monitored by thin layer chromatography. The reaction mixture was cooled to room temperature and the solid product was filtered, washed with toluene to afford 90% yield.

Synthesis of 2-cyano-N-cyclohexyl-3,3-bis(methylthio)acrylamide (Int-2)

A 100 mL conical flask equipped with magnetic stirrer and septum was charged with a solution of 2-cyano-*N*-cyclohexylacetamide (**1**), (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 RT. Then, methyl iodide (20 mmol) was added at 0-5 ºC 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-N-cyclohexyl-3-(methylthio)-1H-pyrazole-4-carboxamide (Int-3)

To the solution of 2-cyano-*N*-cyclohexyl-3,3-bis(methylthio)acrylamide (**2**) (0.1mol) in isopropyl alcohol (100mL), hydrazine hydrate (0.1mol) was added. The reaction mixture was heated to reflux 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 (HRKPY-4a-z)

In 50ml RBF **Int-b**(2.5mmol), **Int-3**(2.5mmol) and substituted aldehyde were suspended in 20 ml water under stirring on magnetic stirrer. H_3BO_3(2.5 mmol) 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.

Spectroscopic data for the synthesized compounds:

1-(2-chlorophenyl)-2-nitroethanone (Int-b): 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)-*N*-cyclohexyl-2-(methylthio)-6-nitro-7-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4a): 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* 1.19-1.86(m, 2H, -CH_2-, cyclohexane), 2.39(s, 3H, -SCH3), 3.8(m, 1H, -CH, cyclohexane), 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*): 523 (M^+); Anal. Calcd for $C_{26}H_{26}ClN_5O_3S$: 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)-*N*-cyclohexyl-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4b): 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}; ^1H NMR(400 MHz, DMSO): *δppm* 1.18-1.85(m, 10H, cyclohexane) 2.41(s, 3H, -SCH_3), 3.7(m, 1H, cyclohexane), 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*): 557 (M^+); Anal. Calcd for $C_{26}H_{25}Cl_2N_5O_3S$: 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)-*N*-cyclohexyl-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4c): 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*): 601 (M^+); Anal. Calcd for $C_{26}H_{25}BrClN_5O_3S$: 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)-*N*-cyclohexyl-7-(4-(dimethylamino)phenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4d): 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}; ^1H NMR(400 MHz, DMSO): *δppm* 1.18-1.86(m, 10H, cyclohexane), 2.40(s, 3H, -SCH_3), 2.85(s, 6H, -$N(CH_3)_2$), 3.75(m, 1H, -CH), 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*): 566 (M^+); Anal. Calcd for $C_{28}H_{31}ClN_6O_3S$: 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)-*N*-cyclohexyl-2-(methylthio)-6-nitro-7-(p-tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4e): 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}; ^1H NMR(400 MHz, DMSO): *δppm* 1.19-1.85(m, 10H, cyclohexane), 2.23(s, 3H, -CH_3), 2.39(s, 3H, -SCH_3), 3.77(m, 1H, -CH, cyclohexane), 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 $C_{27}H_{28}ClN_5O_3S$: 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)-*N*-cyclohexyl-7-(4-fluorophenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4f): 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*): 541 (M^+); Anal. Calcd for $C_{26}H_{25}ClFN_5O_3S$: 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)-*N*-cyclohexyl-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4g): 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*): 557 (M^+); Anal. Calcd for $C_{26}H_{25}Cl_2N_5O_3S$: 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)-*N*-cyclohexyl-7-(2,4-dichlorophenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4h): 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}; ^1H NMR(400 MHz, DMSO): *δppm* 1.19-1.85(m, 10H, cyclohexane), 2.40(s, 3H, -SCH_3), 3.88(m, 1H, -CH, cyclohexane), 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*): 591 (M^+); Anal. Calcd for $C_{26}H_{24}Cl_3N_5O_3S$: 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)-*N*-cyclohexyl-7-(3,4-dimethoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4i): 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}; ^1H NMR(400 MHz, DMSO): *δppm* 1.18-1.85(m, 10H, cyclohexane), 2.41(s, 3H, -SCH_3), 3.76(s, 3H, -OCH_3), 3.78(s, 3H, -OCH3), 3.82(m, 1H, -CH, cyclohexane), 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*): 583 (M^+); Anal. Calcd for $C_{28}H_{30}ClN_5O_5S$: 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)-*N*-cyclohexyl-7-(3-methoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4j): 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*): 553 (M^+); Anal. Calcd for $C_{27}H_{28}ClN_5O_4S$: 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)-*N*-cyclohexyl-7-(2-hydroxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4k): 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* 1.16-1.81(m, 10H, cyclohexane), 2.50(s, 3H, -SCH_3), 3.75(m, 1H, -CH, cyclohexane), 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*): 539 (M^+); Anal. Calcd for $C_{26}H_{26}ClN_5O_4S$: 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)-*N*-cyclohexyl-7-(3-hydroxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4l): 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*): 539 (M^+); Anal. Calcd for $C_{26}H_{26}ClN_5O_4S$: 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)-*N*-cyclohexyl-7-(2,4-dimethoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4m): 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*): 583 (M^+); Anal. Calcd for $C_{28}H_{30}ClN_5O_5S$: 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)-*N*-cyclohexyl-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4n): 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*): 557 (M^+); Anal. Calcd for $C_{26}H_{25}Cl_2N_5O_3S$: 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)-*N*-cyclohexyl-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4o): 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*): 601 (M^+); Anal. Calcd for $C_{26}H_{25}BrClN_5O_3S$: 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)-*N*-cyclohexyl-7-(4-hydroxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4p): 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*): 539 (M^+); Anal. Calcd for $C_{26}H_{26}ClN_5O_4S$: 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)-*N*-cyclohexyl-2-(methylthio)-6-nitro-7-(2-nitrophenyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4q): 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*): 568 (M^+); Anal. Calcd for $C_{26}H_{25}ClN_6O_5S$: 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)-*N*-cyclohexyl-2-(methylthio)-6-nitro-7-(3-nitrophenyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4r): 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* 1.20-1.86(m, 10H, cyclohexane), 2.41(s, 3H, -SCH_3), 3.76(m, 1H, -CH, cyclohexane), 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*): 568 (M^+); Anal. Calcd for $C_{26}H_{25}ClN_6O_5S$: 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)-*N*-cyclohexyl-2-(methylthio)-6-nitro-7-styryl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4s): 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*): 549 (M^+); Anal. Calcd for $C_{28}H_{28}ClN_5O_3S$: 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)-*N*-cyclohexyl-2-(methylthio)-7-(naphthalen-1-yl)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4t): 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*): 573 (M^+); Anal. Calcd for $C_{30}H_{28}ClN_5O_3S$: 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.

5-(2-chlorophenyl)-*N*-cyclohexyl-7-(4-hydroxy-3-methoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4u): yellow solid; Melting range:138-140°C; R_f 0.36 (4:6 hexane-EtOAc); IR (KBr): 3363, 2932, 2849, 1624, 1573, 1519, 1486, 1433, 1313, 1282, 1247, 1177, 1126, 1033, 977, 777, 757 cm^{-1}; ^1H NMR(400 MHz, DMSO): *δppm* 1.18-1.34(m, 10H, cyclohexane), 2.43(s, 3H, -SCH_3), 3.77(s, 3H, -OCH_3), 3.81(m, 1H, -CH, cyclohexane), 5.79(s, 1H, -OH), 6.65(s, 1H, -CH), 6.76-7.44(m, 8H, Ar-H, -NH), 8.89(s, 1H. -NH); ^{13}C NMR (100 MHz, DMSO) *δppm*: 17.46, 24.52, 25.49, 32.88, 47.95, 56.03, 60.55, 99.67, 110.32, 114.55, 119.56, 123.78, 127.37, 128.60, 129.94, 130.23, 131.40, 132.02, 132.40, 139.22, 141.20, 144.34, 146.18, 146.55, 162.36 ;MS (*m/z*): 569 (M^+); Anal. Calcd for $C_{27}H_{28}ClN_5O_5S$: C, 56.89; H, 4.95; N, 12.29; S, 5.62; Found: C, 56.83; H, 4.90; N, 12.20; S, 5.57.

5-(2-chlorophenyl)-7-(4-cyanophenyl)-*N*-cyclohexyl-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4v): yellow solid; Melting range:222-224°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3331, 2929, 2849, 1635, 1578, 1537, 1473, 1439, 1313, 1285, 1249, 1176, 1123, 1061, 977, 840, 775, 754 cm^{-1}; ^{13}C NMR (100 MHz, DMSO) *δppm*: 17.01, 24.50, 25.47, 32.84, 48.07, 60.14, 99.83, 112.86, 118.36, 122.57, 127.45, 128.26, 128.57, 130.05, 131.66, 131.81, 131.99, 132.62, 139.35, 142.18, 143.14, 145.20 162.08; MS (*m/z*): 548 (M^+); Anal. Calcd for $C_{27}H_{25}ClN_6O_3S$: C, 59.06; H, 4.59; N, 15.31; S, 5.84; Found: C, 59.16; H, 4.50; N, 15.24; S, 5.80.

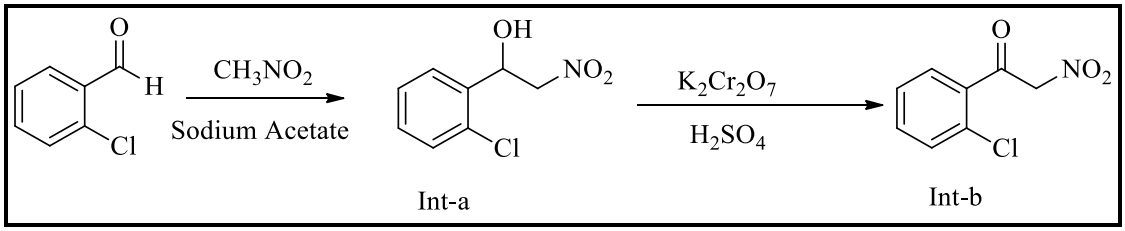
5-(2-chlorophenyl)-*N*-cyclohexyl-7-(3-cyclopropoxy-4-(difluoromethoxy)phenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4w): yellow solid; Melting range:158-160°C; R_f 0.38 (4:6 hexane-EtOAc); IR (KBr): 3335, 2929, 2853, 1623, 1578, 1574, 1494, 1433, 1313, 1280, 1219, 1173, 1125, 1052, 1007, 822, 769 cm^{-1}; ^1H NMR(400 MHz, DMSO): *δppm* 0.27(m, 2H, cyclopropane), 0.56(m, 2H, cyclopropane), 1.18-1.86(m, 10H, cyclohexane), 2.42(s, 3H, -SCH_3), 3.77-3.79(d, 1H, -CHF_2), 3.81(m, 1H, -CH, cyclohexane), 3.86(s, 1H, -CH), 6.334-7.43(m, 10H, Ar-H, -NH), 8.92(s, 1H. -NH); ^{13}C NMR (100 MHz, DMSO) *δppm*: 3.29, 10.07, 17.30, 25.48, 32.87, 47.99, 60.27, 73.95, 99.63, 113.50, 113.77, 116.08, 118.74, 122.65, 123.20, 127.40, 128.57, 129.98, 131.52, 132.00, 132.23, 136.65, 139.64, 141.65, 144.62, 150.57, 162.25 ;MS (*m/z*): 645 (M^+); Anal. Calcd for $C_{30}H_{30}ClF_2N_5O_5S$: C, 55.77; H, 4.68; N, 10.84; S, 4.96; Found: C, 55.70; H, 4.61; N, 10.79; S, 4.90.

5-(2-chlorophenyl)-*N*-cyclohexyl-7-(4-methoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4x): yellow solid; Melting range:224-226°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3342, 2930, 2850, 1628, 1576, 1541, 1481, 1477, 1430, 1312, 1276, 1246, 1174, 1121, 1030, 973, 840, 759 cm^{-1}; ^1H NMR(400 MHz, DMSO): *δppm* 1.17-1.78(m, 10H, cyclohexane), 2.38(s, 3H, -SCH_3), 3.68(m, 1H, -CH, cyclohexane), 3.73(s, 3H, -OCH_3), 6.63(s, 1H, -CH), 6.92-6.94(d, 2H, Ar-H, J=8.4Hz), 7.37-7.39(d, 2H, Ar-H, J=8.4Hz), 7.46-7.62(m, 4H, Ar-H), 10.85(s, 1H. -NH); MS (*m/z*): 548 (M^+); Anal. Calcd for $C_{27}H_{28}ClN_5O_4S$: C, 58.53; H, 5.09; N, 12.64; S, 5.79; Found: C, 58.49; H, 5.01; N, 12.58; S, 5.73.

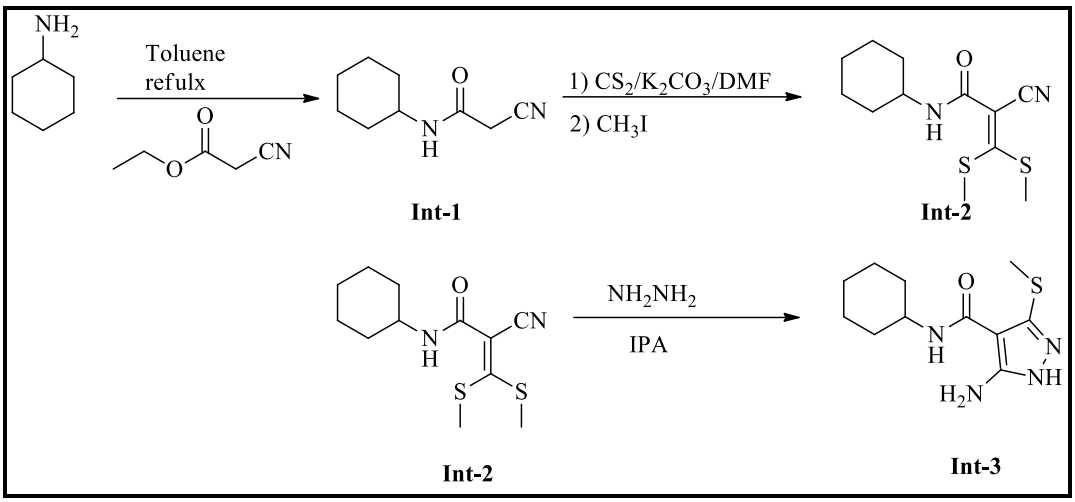
5-(2-chlorophenyl)-*N*-cyclohexyl-2-(methylthio)-6-nitro-7-(m-tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4y): yellow solid; Melting range: 196-198°C; R_f 0.40 (4:6 hexane-EtOAc); IR (KBr): 3331, 2928, 1578, 1545, 1487, 1441, 1295, 1248, 1187, 1066, 742 cm^{-1}; MS (*m/z*): 537 (M^+); Anal. Calcd for $C_{27}H_{28}ClN_5O_3S$: C, 60.27; H, 5.25; N, 13.02; S, 5.96; Found: C, 60.20; H, 5.20; N, 13.12; S, 5.90.

5-(2-chlorophenyl)-*N*-cyclohexyl-7-(3-hydroxy-4-methoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (HRKPY-4z): yellow solid; Melting range:142-144°C; R_f 0.36 (4:6 hexane-EtOAc); IR (KBr): 3362, 3042, 2936, 2852, 1632, 1585, 1556, 1466, 1308, 1292, 1217, 1138, 1121, 1062, 981, 762 cm^{-1}; MS (*m/z*): 569 (M^+); Anal. Calcd for $C_{27}H_{28}ClN_5O_5S$: C, 56.89; H, 4.95; N, 12.29; S, 5.62; Found: C, 56.81; H, 4.90; N, 12.20; S, 5.56.

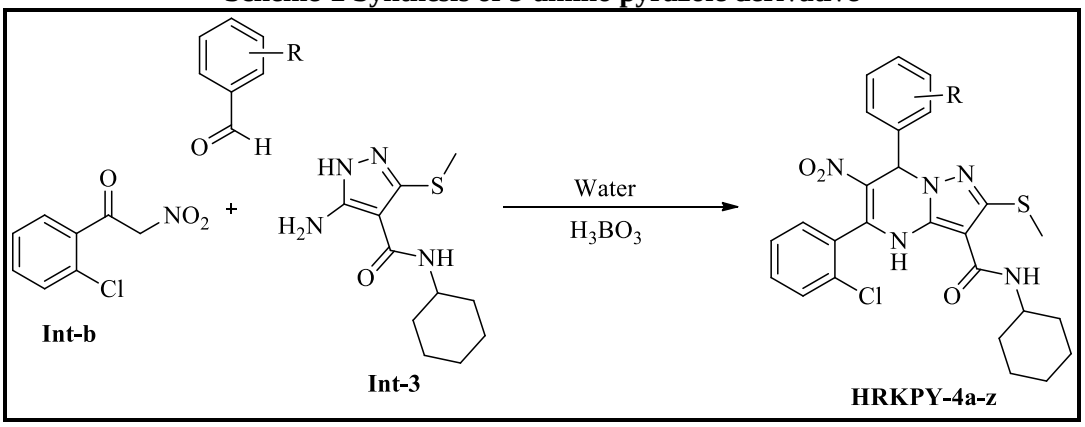
3. RESULTS AND DISCUSSION:



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



Scheme-2 Synthesis of 5-amino pyrazole derivative



Scheme-3 Synthesis of Pyarzolopyrimidine

Int-b, 1-(2-chlorophenyl)-2-nitroethanone described in **scheme-1** was synthesized by Henry reaction. The aldol type coupling of aldehyde and nitromethane in presence of sodium acetate by using ethanol as solvent to gives **Int-a**. Although Int-a contains 2^0 alcohol, which on oxidation with $K_2Cr_2O_7+H_2SO_4$ afford **Int-b** which contains highly acidic protons of methylene because it makes salt with $NaHCO_3$. The ^1H NMR of Int-b also supports the structure. Here the (s, 2H) at 5.9 *δppm* confirms the presence of deshielded methylene proton and (m, 4H) at 7.42-7.79 *δppm* shows ortho disubstituted aromatic ring. Cyclohexylamine and ethylcyanoacetate were condensed in toluene to afford **Int-1**, which when reacted with K_2CO_3, CS_2 and Methyliodide to form ketenedithioacetals **(Int-2)** which was cyclised on reaction with hydrazinehydrate in IPA to yield 5-aminopyrazole (**Int-3)**.

The series of nitro functionalized pyrazolo[1,5-a]pyrimidine (**HRKPY-4a-z)** was synthesized by condensation of **Int-b**, **Int-3** and substituted aldehydes by using water as solvent in presence of H_3BO_3 at refluxed temperature. The structures of **HRKPY-4a-z** were established on the basis of their spectral data (mass, IR, ^1H NMR and ^{13}C NMR). Various substituted aldehydes used are listed in **Table-1** with isolated yield, time required for the reaction and MP. Two plausible mechanisms[39,40] is explained in **Figure-3**.

Here compound **HRKPY-1** was synthesized by different reaction conditions. It is found from TLC and mass analysis. Three reagents con. HCl, acetic acid and Boric acid were used to obtain final products. In acetic acid product formation is very less but using con. HCl or Boric acid gives good yield. Here comparison is given with solvents, catalyst and yield in **Table-2**.

The structures of (**HRKPY-4a-z**) were established on the basis of their elemental analysis and spectral data (MS, IR, and ^1H NMR). The analytical data for **HRKPY-4u** revealed a molecular formula $C_{27}H_{28}ClN_5O_5S$ (m/z 569). The ^1H NMR spectrum revealed a multiplate at δ = 1.180-1.341 ppm (10H) assigned to cyclohexane(5xCH_2), a singlet at δ = 2.438 ppm (3H) assigned to (S-CH_3), a singlet at δ = 3.776 ppm (3H) assigned to (-OCH_3), a multiplate at δ = 3.819 (1H) ppm assigned cyclohexane (-CH), a singlet at δ = 5.790 (1H) ppm assigned (-OH), a singlet at δ = 6.652 (1H) ppm assigned (-CH), a multiplate at δ = 6.76-7.44 (8H) assigned to the aromatic protons and one cyclohexyl(-CONH), a singlet at δ = 8.893 ppm (1H) assigned to the -NH protons of triazolo pyrimidine ring.

Table-1: Opimisation of reaction condition in the Synthesis of substituted Pyrazolopyrimidines

Entry	R	Time h	Yield %	Melting Range ^0C
HRKPY-4a	-H	12	90	200-202

HRKPY-4b	-4-Cl	12	88	214-216
HRKPY-4c	-4-Br	12	81	238-240
HRKPY-4d	-4(N,N-dimethylamino)	15	75	242-244
HRKPY-4e	-4-Me	13	92	220-222
HRKPY-4f	-4-F	12	87	228-230
HRKPY-4g	-2-Cl	12	84	212-214
HRKPY-4h	-2,4-di Cl	12	78	218-220
HRKPY-4i	-3,4-di OMe	14	93	204-206
HRKPY-4j	-3-OMe	14	91	218-220
HRKPY-4k	-2-OH	16	77	218-220
HRKPY-4l	-3-OH	16	83	216-218
HRKPY-4m	-2,5-di OMe	15	90	176-178
HRKPY-4n	-3-Cl	13	78	230-232
HRKPY-4o	-3-Br	12	79	230-232
HRKPY-4p	-4-OH	16	75	238-240
HRKPY-4q	-2-NO_2	18	85	200-202
HRKPY-4r	-3-NO_2	16	81	208-210
HRKPY-4s	Cinnamaldehyde	10	73	144-146
HRKPY-4t	Naphthaldehyde	11	78	178-180
HRKPY-4u	-3-OMe-4-OH	14	85	138-140
HRKPY-4v	-4-CN	12	92	222-224
HRKPY-4w	-3-CHF_2	15	76	158-160
HRKPY-4x	-4-OMe	15	92	224-226
HRKPY-4y	-3-Me	13	90	196-198
HRKPY-4z	-3-OH-4-OMe	16	83	142-144

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

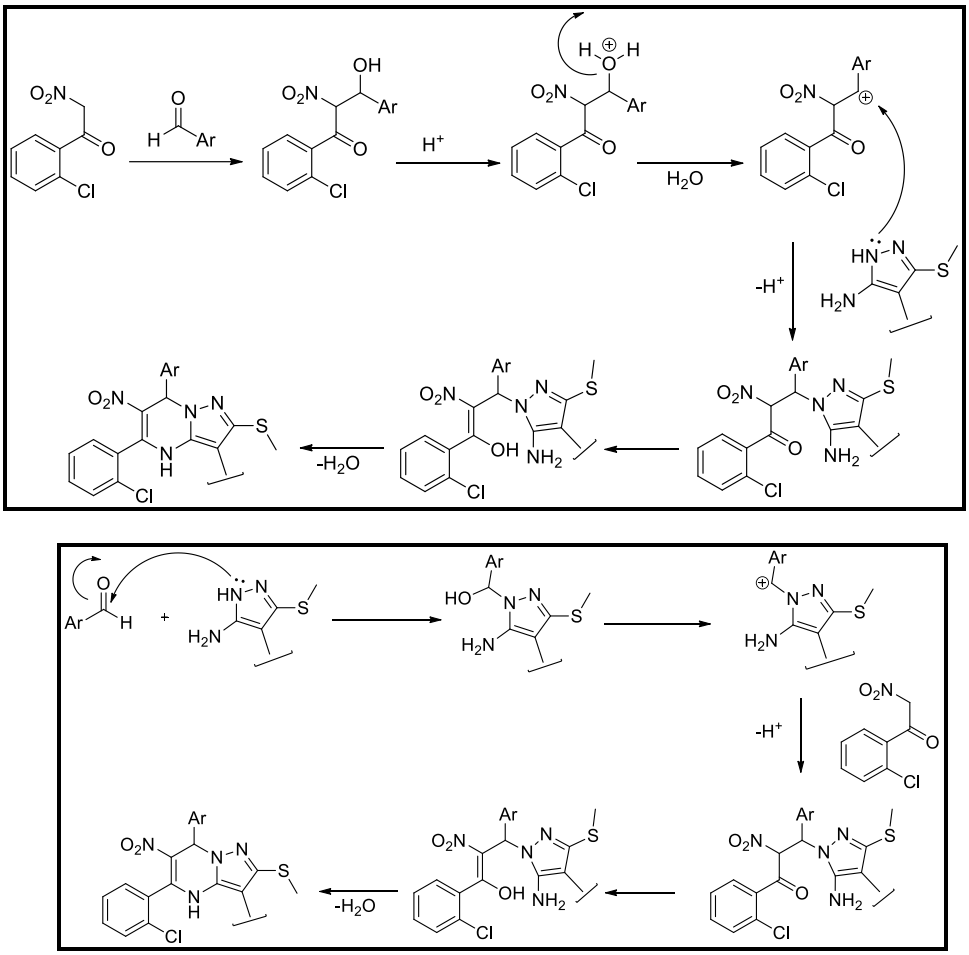


Figure-3 : Proposed mechanism[39,40] for the formation of triazolopyrimidine

Table-2: Comparison of yield with different solvent and catalyst for HRKPY-4a

Solvent	catalyst	Yield %	Solvent	catalyst	Yield %
Water	H_3BO_3	90	DMF	H_3BO_3	84
	Con HCl	76		Con HCl	71
	Acetic acid	56		Acetic acid	52
Methanol	H_3BO_3	88	THF	H_3BO_3	77
	Con HCl	70		Con HCl	65
	Acetic acid	65		Acetic acid	43

Antimicrobial evaluation

Table-3: Antimicrobial evaluation data

Compounds and standard drugs	Antibacterial activity				Antifungal acitivity	
	Minimum inhibitory concentration µg/ml				Minimum inhibitory concentration µg/ml	
	Gram +Ve Bacteria		Gram -Ve Bacteria			
	S. aureus	***S.pyogenes***	***E.coli***	***P.aeruginosa***	***C.albicans***	***A.niger***
Ciprofloxacin	7.8	7.8	15.625	15.625	-	-
Chloramphenicol	7.8	7.8	7.8	7.8	-	-
Nystatin	-	-	-	-	31.25	31.25
Greseofulvin					15.625	15.625
HRKPY-1	31.25	31.25	**15.625**	**15.625**	**15.625**	**31.25**
HRKPY-2	15.625	15.625	**15.625**	**7.81**	**31.25**	**31.25**
HRKPY-3	31.25	62.5	31.25	31.25	**15.625**	62.5
HRKPY-4	62.5	62.5	31.25	62.5	**15.625**	62.5
HRKPY-5	15.625	31.25	15.625	62.5	**31.25**	62.5
HRKPY-6	7.81	31.25	**7.81**	62.5	**31.25**	62.5
HRKPY-7	15.625	15.625	**15.625**	62.5	**31.25**	62.5
HRKPY-8	15.625	62.5	31.25	31.25	**31.25**	62.5
HRKPY-9	**7.81**	31.25	**15.625**	**15.625**	**15.625**	**15.625**
HRKPY-10	31.25	31.25	31.25	**15.625**	**15.625**	**15.625**
HRKPY-11	31.25	15.625	31.25	31.25	**15.625**	62.5
HRKPY-12	31.25	**7.8**	31.25	31.25	**15.625**	**31.25**
HRKPY-13	31.25	31.25	31.25	**7.81**	**15.625**	**31.25**
HRKPY-14	31.25	62.5	**15.625**	**7.81**	**31.25**	**31.25**
HRKPY-15	15.625	15.625	**15.625**	**15.625**	**31.25**	**31.25**
HRKPY-16	15.625	**7.81**	**15.625**	62.5	**31.25**	62.5
HRKPY-17	**7.81**	15.625	**15.625**	62.5	62.5	**15.625**
HRKPY-18	15.625	62.5	**15.625**	62.5	**31.25**	62.5
HRKPY-19	31.25	62.5	62.5	31.25	**31.25**	62.5
HRKPY-20	**7.81**	31.25	**7.8**	**15.625**	**15.625**	62.5
HRKPY-21	15.625	31.25	**15.625**	**15.625**	62.5	**31.25**
HRKPY-22	15.62	**7.8**	**15.625**	**7.8**	**31.25**	**31.25**
HRKPY-23	15.62	15.625	**7.81**	**15.625**	62.5	**31.25**
HRKPY-24	31.25	62.5	**15.625**	31.25	62.5	62.5

4. CONCLUSIONS:

We have described the water mediated synthesis of nitro functionalized 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-*N*-cyclohexyl-3-(methylthio)-1*H*-pyrazole-4-carboxamide afforded the nitro functionalized pyrazolo[1,5-a]pyrimidine derivatives in the presence boric acid and water as a solvent. We have confirmed the structure on the basis of spectroscopic technique. All the synthesized compounds were evaluated for their antimicrobial activity. The investigation of antimicrobial and antifungal screening data revealed that all the tested compounds showed moderate to significant activity.

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