# Conventional and Non-Conventional Synthesis of Novel (4*E*)-4-((3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-aryl-1*h*-pyrazol-4-yl) methylene)-3-alkyl-1-aryl-1*h*-pyrazol-5(4*h*)-ones

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*Abstract :* A conventional and non-conventional Knoevenagel condensation of 3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-aryl-1*H*-pyrazole-4-carbaldehyde and 3-alkyl-1-aryl-1*H*-pyrazol-5(4*H*)-one gave (4*E*)-4-((3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-aryl-1*H*-pyrazol-4-yl)methylene)-3-alkyl-1-aryl-1*H*-pyrazol-5(4*H*)-one. The structures of the synthesized compounds were confirmed with the help of spectral techniques.

***IndexTerms – conventional, non-conventional, Knoevenagel condensation.***

## I. INTRODUCTION

Knoevenagel condensation is a reaction in which C-C bond formation takes place and extensively used in synthesis of olefins and pharmacologically active compounds. This condensation is catalysed by different catalysts such as L-tyrosine[1], [BmIm]OH[2], lipoprotein lipase[3], tetrabutylphosphonium prolinate[4], thermally decomposed mesoporous Ni-Fe hydrotalcite[5] etc. Fluorinated compounds are of great interest to synthetic and medicinal chemist due to unique physical biological properties imparted by fluorine[6]. Fluorinated compound possess variety of biological activities like antimicrobial[7], antibacterial[8] and anticancer[9].

Thiazole and its derivative have attracted many researchers due to their pharmacological potentials. Thiazole containing compounds exhibits $EP_1$ receptor antagonist[10], VEGF-A inhibitors[11], cytotoxic[12], C-aryl glucoside SGLT2 Inhibitor[13], vascular adhesion protein-1 (VAP-1) inhibitors[14] activities. Pyrazolone derivatives possess numerous biological activities like neuraminidase inhibitors[15], nonallergenic antipyretic analgesics[16], HIV-1 integrase inhibitors[17], anti-orthopoxvirus[18] and anti-bacterial agents[19].

Now a days microwave & ultrasound irradiations have been extensively used to activate organic reactions. It is a green approach which has many advantages over conventional methods[20, 21]. Many organic reactions have been carried out in higher yield, shorter reaction time and milder conditions under microwave and ultrasound irradiation[22-25].

In view of activities associated with fluorinated compounds, thiazole, pyrazolone and use of eco-friendly techniques we describes here the synthesis of (4*E*)-4-((3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-aryl-1*H*-pyrazol-4-yl)methylene)-3-alkyl-1-aryl-1*H*-pyrazol-5(4*H*)-one derivatives by conventional and non-conventional methods.

## II. Experimental Section

The melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity-1S Fourier transform infrared spectrophotometer. $^1$H NMR spectra were recorded on Bruker Avance II 400 MHz NMR spectrometer using TMS as an internal standard and $CDCl_3$ as a solvent. The mass spectra were recorded on Acquity TQD Waters mass spectrometer. Microwave irradiation was carried out in Raga synthetic microwave system and for ultrasound method Bio techno labs ultrasonicator was used.

### (4*E*)-4-((3-(2-(4-Fluorophenyl)-4-methylthiazol-5-yl)-1-aryl-1*H*-pyrazol-4-yl)methylene)-3-alkyl-1-aryl-1*H*-pyrazol-5(4*H*)-one, 3a-j

**Conventional method:** Equimolar amounts of 3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-aryl-1*H*-pyrazole-4-carbaldehyde **1** (0.002 mol) and pyrazolone **2** (0.002 mol) were taken in glacial acetic acid (15 mL). The reaction mixture was refluxed till completion of reaction (checked by TLC). After completion of reaction, contents were then poured into crushed ice. Solid obtained was filtered, dried and purified by recrystallization from acetic acid to get pure compounds **3a-j**. The physical data of compounds synthesized by above method is given in **Table 1**.

**Microwave method**: Equimolar amounts of 3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-aryl-1*H*-pyrazole-4-carbaldehyde **1** (0.002 mol) and pyrazolone **2** (0.002 mol) were taken in glacial acetic acid (15 mL). Contents of flask were subjected for microwave irradiation at 350W for time as shown in table, till completion of reaction (checked by

TLC). After completion of reaction, contents were poured into crushed ice. Solid obtained was filtered, dried and purified by recrystallization from acetic acid to get pure compounds **3a-j**. Formations of products were also confirmed by M. P., mixed M. P. and TLC. The physical data of compounds synthesized by above method is given in **Table 1**.

**Ultrasound Method**: Equimolar amounts of 3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-aryl-1*H*-pyrazole-4-carbaldehyde **1** (0.002 mol) and pyrazolone **2** (0.002 mol) were taken in glacial acetic acid (15 mL). Contents of flask were subjected for ultrasound irradiation for time as shown in table, till completion of reaction (checked by TLC). After completion of reaction, contents were poured into crushed ice. Solid obtained was filtered, dried and purified by recrystallization from acetic acid to get pure compounds **3a-j**. Formations of products were also confirmed by M. P., mixed M. P. and TLC. The physical data of compounds synthesized by above method is given in **Table 1**.

**3a**: IR: 3138, 1693, 1597, 1512, 1217 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ 2.30 (s, 3H), 2.59 (s, 3H), 7.16-8.01 (m, 14H), 10.28 (s, 1H); Mass: *m/z* 537 (M+); Elem. anal. calcd. for $C_{30}H_{21}F_2N_5OS$: C, 67.03; H, 3.94; N, 13.03 %. Found: C, 67.07; H, 3.98; N, 13.08 %.

**3b**: IR: 3135, 1690, 1594, 1516, 1214 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ 2.31 (s, 3H), 2.62 (s, 3H), 7.16-8.00 (m, 13H), 10.28 (s, 1H); Mass: *m/z* 555 (M+); Elem. anal. calcd. for $C_{30}H_{20}F_3N_5OS$: C, 64.86; H, 3.63; N, 12.61 %. Found: C, 64.91; H, 3.67; N, 12.65 %.

**3c**: IR: 3136, 1692, 1593, 1514, 1213 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ 2.30 (s, 3H), 2.58 (s, 3H), 7.15-8.09 (m, 13H), 10.21 (s, 1H); Mass: *m/z* 571 (M+); Elem. anal. calcd. for $C_{30}H_{20}ClF_2N_5OS$: C, 62.99; H, 3.52; N, 12.24 %. Found: C, 63.03; H, 3.57; N, 12.28 %.

**3d**: IR: 3138, 1694, 1592, 1516, 1211 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ 2.58 (s, 3H), 7.16-8.01 (m, 14H), 10.21 (s, 1H); Mass: *m/z* 591 (M+); Elem. anal. calcd. for $C_{30}H_{18}F_5N_5OS$: C, 60.91; H, 3.07; N, 11.84 %. Found: C, 60.95; H, 3.12; N, 11.89 %.

**3e**: IR: 3140, 1690, 1591, 1514, 1213 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ 1.04 (t, 3H), 1.80 (sextet, 2H), 2.58-2.62 (m, 5H), 7.15-8.01 (m, 14H), 10.23 (s, 1H); Mass: *m/z* 565 (M+); Elem. anal. calcd. for $C_{32}H_{25}F_2N_5OS$: C, 67.95; H, 4.45; N, 12.38 %. Found: C, 67.99; H, 4.49; N, 12.42 %.

**3f**: IR: 3139, 1694, 1598, 1515, 1211 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ 2.31 (s, 3H), 2.58 (s, 3H), 7.15-8.01 (m, 15H), 10.29 (s, 1H); Mass: *m/z* 519 (M+); Elem. anal. calcd. for $C_{30}H_{22}FN_5OS$: C, 69.35; H, 4.27; N, 13.48 %. Found: C, 69.39; H, 4.31; N, 13.52 %.

**3g**: : IR: 3135, 1690, 1594, 1516, 1214 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ 2.30 (s, 3H), 2.61 (s, 3H), 7.15-8.00 (m, 14H), 10.27 (s, 1H); Mass: *m/z* 537 (M+); Elem. anal. calcd. for $C_{30}H_{21}F_2N_5OS$: C, 67.03; H, 3.94; N, 13.03 %. Found: C, 67.07; H, 3.98; N, 13.08 %.

**3h**: IR: 3138, 1690, 1593, 1513, 1212 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ 2.31 (s, 3H), 2.58 (s, 3H), 7.15-8.08 (m, 14H), 10.22 (s, 1H); Mass: *m/z* 553 (M+); Elem. anal. calcd. for $C_{30}H_{21}ClFN_5OS$: C, 65.04; H, 3.82; N, 12.64 %. Found: C, 65.08; H, 3.86; N, 12.68 %.

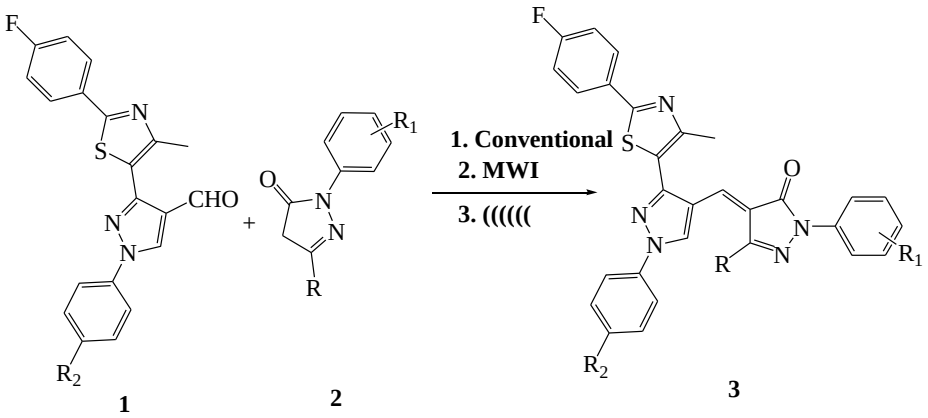
**3i**: IR: 3139, 1694, 1591, 1517, 1212 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ 2.59 (s, 3H), 7.15-8.01 (m, 15H), 10.20 (s, 1H); Mass: *m/z* 573 (M+); Elem. anal. calcd. for $C_{30}H_{19}F_4N_5OS$: C, 62.82; H, 3.34; N, 12.21 %. Found: C, 62.86; H, 3.38; N, 12.25 %

**3j**: IR: 3142, 1691, 1592, 1515, 1213 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ 1.05(t, 3H), 1.81 (sextet, 2H), 2.57-2.61 (m, 5H), 7.16-8.07 (m, 15H), 10.24 (s, 1H); Mass: *m/z* 547 (M+); Elem. anal. calcd. for $C_{32}H_{26}FN_5OS$: C, 70.18; H, 4.79; N, 12.79 %. Found: C, 70.22; H, 4.83; N, 12.83 %.

**Table 1: Characterization data of the synthesized compounds**

| Compd | R | $R_1$ | $R_2$ | M.P. ($^0$C) | Conventional Method | | Microwave Method | | Ultrasound Method | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Time (Min) | Yield (%) | Time (Min) | Yield (%) | Time (Min) | Yield (%) |
| 3a | $CH_3$ | H | F | 220 | 58 | 74 | 5 | 80 | 21 | 88 |
| 3b | $CH_3$ | 4-F | F | 276 | 60 | 76 | 7 | 79 | 23 | 87 |
| 3c | $CH_3$ | 3-Cl | F | 280 | 60 | 71 | 7.5 | 81 | 20 | 90 |
| 3d | $CF_3$ | H | F | 256 | 51 | 70 | 8 | 78 | 21 | 92 |
| 3e | $C_3H_7$ | H | F | 160 | 67 | 68 | 7 | 80 | 22 | 91 |
| 3f | $CH_3$ | H | H | 230 | 63 | 73 | 6.5 | 78 | 24 | 88 |
| 3g | $CH_3$ | 4-F | H | 278 | 60 | 74 | 7.5 | 80 | 21 | 87 |
| 3h | $CH_3$ | 3-Cl | H | 240 | 68 | 76 | 8 | 82 | 23 | 90 |
| 3i | $CF_3$ | H | H | 228 | 54 | 69 | 6 | 77 | 20 | 89 |
| 3j | $C_3H_7$ | H | H | 180 | 55 | 72 | 5.5 | 80 | 26 | 90 |

**Scheme-1**

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