Microwave Assisted Synthesis and Biological Evaluation of 1, 2, 4-Triazolo [1, 5-A] Pyrimidines

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Abstract: A microwave assisted synthesis of three new series of 1, 2, 4-triazolo [1, 5-a] pyrimidines (PK-101 to PK-110) has been synthesized by the mixture of 5-(methylthio)-2H-1,2,4-triazol-3-amine (0.01 mol), 4,4,4-trifluoro-1-(4-methoxyphenyl)butane-1,3-dione (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) in ethanol (5 mL) was irradiated under microwave conditions at 120 °C for 10-15 min. The structures of all the newly synthesized compounds are elucidated by FT-IR, mass spectra, ¹H NMR and elemental analysis. The newly synthesized compounds are subjected to various biological activities viz., antimicrobial, anticyclobacterial, anticancer and antiviral.

Keywords: Pyrazolo [3, 4-d] pyrimidines, antimicrobial activity, anticancer and antiviral and antituberculosis activity anticyclobacterial activity.

I. INTRODUCTION

The condensation of a ring of 1, 2, 4-triazole and another one of pyrimidine gives rise to the formation of bicyclic heterocycles known as 1, 2, 4-triazolopyrimidines. Four different possibilities exist for the relative orientation of both rings, so four different isomeric families of compounds are defined: 1,2,4-triazolo[1,5-a]pyrimidine (1), 1,2,4-triazolo[1,5-c]pyrimidine (2), 1,2,4-triazolo[4,3-a]pyrimidine (3) and 1,2,4-triazolo[4,3-c]pyrimidine (4).

Among these isomeric families of compounds, 1, 2, 4-triazolo [1, 5-a] pyrimidine derivatives are thermodynamically more stable and, thus, the most studied ones [1], a few of them being commercially available. Revisions surveying the synthesis, reactivity, spectroscopic characterization and crystallographic studies of 1,2,4-triazolo[1,5-c]pyrimidines [2], 1,2,4-triazolo[4,3-a]pyrimidines [3] and 1,2,4-triazolo[4,3-c]pyrimidines [4] have also been published.

The 1,2,4-triazolo[1,5-a]pyrimidines have aroused increasing attention from the chemical and biological view points, due to their diverse pharmacological activities, such as antitumor potency [5, 6], inhibition of KDR kinase [7], antifungal effect [8] and macrophage activation [9]. They have proved to be promising anticancer agents with dual mechanisms of tubulin polymerization promotion as well as cyclin dependent kinases 2 inhibition [10].

By far the most triazolo[1,5-a]pyrimidine synthesis are condensations of dinucleophilic 5-amino-1,2,4-triazoles with 1,3-bifunctional synths as shown in the formation of triazolo[1,5-a]pyrimidine (15) (Scheme 3.27) [11-14]. New synthetic conditions recently described involve melting under microwave irradiation, a reaction that is environmental friendly and gives higher yields than conventional heating in solvent [15]. Furthermore, certain lithium 1,3-diketones have proven to be better synths than the corresponding diketones [16].

Previous mechanistic conclusions have been confirmed by isolating stable intermediate 5-amino-1, 2, 4-triazole derivatives such as enamine (16) (Scheme 3.28) on reacting 5-amino-1, 2, 4-triazoles with 3-ketovinyl ethers [17], 3-ketoamines [18], 3-ketoaldehydes [19], enamine-2-carboxylic esters [20] or ethoxymethylene malonates [21].
II. CURRENT WORK

Microwave assisted organic synthesis has become an important tool to medicinal chemists for rapid organic synthesis. A huge number of research papers have appeared over the last decades on the application of microwave technology in organic synthesis. Some of the major advantages of microwave assisted organic synthesis include spectacular decrease in reaction time, improved conversions, clean product formation and wide scope for the development of new reaction conditions.

The biological importance of 1, 2, 4-triazolo [1, 5-α] pyrimidines is well reported. Over the years, various substituted derivatives of these heterocycles have shown utility against a range of biological targets. For example, they have demonstrated activity against malaria and bronchospasm and shown activity as coronary vasodilators, antihypertensive agents, leishmanicides, antibiotics, adenosine A₂a antagonists, immunosuppressants, antitumor agents, fungicides, xanthine oxidase inhibitors, and phosphodiesterase inhibitors.

The microwave assisted synthesis of three new series of of 1, 2, 4-triazolo [1, 5-α] pyrimidines (PK-101 to PK-110) has been undertaken. The structures of all the newly synthesized compounds are elucidated by FT-IR, mass spectra, ¹H NMR and elemental analysis. The newly synthesized compounds are subjected to various biological activities viz., antimicrobial, antimycobacterial, anticancer and antiviral.

III. REACTION SCHEME

\[
\begin{align*}
\text{Reagents and conditions: (a) EtOH, MW, 120 ºC, 10-15 min} \\

\text{PK-101 T0 110}
\end{align*}
\]

Table I Physical and analytical data:

<table>
<thead>
<tr>
<th>Code</th>
<th>R₁</th>
<th>M.F.</th>
<th>M.W.</th>
<th>M.P. ºC</th>
<th>Yield %</th>
<th>R₁</th>
<th>R₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK-101</td>
<td>4-OCH₃</td>
<td>C₂H₅F₃N₂O₂S</td>
<td>476</td>
<td>221-227</td>
<td>78</td>
<td>0.55</td>
<td>0.73</td>
</tr>
<tr>
<td>PK-102</td>
<td>4-F</td>
<td>C₂H₅F₃N₂O₂S</td>
<td>464</td>
<td>228-230</td>
<td>72</td>
<td>0.52</td>
<td>0.70</td>
</tr>
<tr>
<td>PK-103</td>
<td>4-CH₃</td>
<td>C₂H₅F₃N₂O₂S</td>
<td>460</td>
<td>198-200</td>
<td>53</td>
<td>0.45</td>
<td>0.66</td>
</tr>
<tr>
<td>PK-104</td>
<td>4-NO₂</td>
<td>C₂H₅F₃N₂O₂S</td>
<td>491</td>
<td>235-237</td>
<td>63</td>
<td>0.56</td>
<td>0.65</td>
</tr>
<tr>
<td>PK-105</td>
<td>4-Cl</td>
<td>C₂H₅F₃N₂O₂S</td>
<td>480</td>
<td>240-242</td>
<td>75</td>
<td>0.55</td>
<td>0.75</td>
</tr>
<tr>
<td>PK-106</td>
<td>3-Cl</td>
<td>C₂H₅F₃N₂O₂S</td>
<td>480</td>
<td>188-190</td>
<td>68</td>
<td>0.44</td>
<td>0.71</td>
</tr>
<tr>
<td>PK-107</td>
<td>3-NO₂</td>
<td>C₂H₅F₃N₂O₂S</td>
<td>491</td>
<td>256-258</td>
<td>65</td>
<td>0.52</td>
<td>0.72</td>
</tr>
<tr>
<td>PK-108</td>
<td>2-Cl</td>
<td>C₂H₅F₃N₂O₂S</td>
<td>480</td>
<td>260-262</td>
<td>72</td>
<td>0.48</td>
<td>0.65</td>
</tr>
<tr>
<td>PK-109</td>
<td>2-NO₂</td>
<td>C₂H₅F₃N₂O₂S</td>
<td>491</td>
<td>255-257</td>
<td>70</td>
<td>0.44</td>
<td>0.60</td>
</tr>
<tr>
<td>PK-110</td>
<td>2-OCH₃</td>
<td>C₂H₅F₃N₂O₂S</td>
<td>476</td>
<td>221-223</td>
<td>60</td>
<td>0.45</td>
<td>0.76</td>
</tr>
</tbody>
</table>


IV. EXPERIMENTAL

Materials and Methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. Microwave assisted reaction were carried out in QPro-M microwave synthesizer. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct
Injection Probe technique. $^1$H NMR was determined in DMSO-$d_6$ solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

**Synthesis of 4, 4, 4-trifluoro-1-(aryl) butane-1, 3-dione**

Synthesis of 4, 4, 4-trifluoro-1-(aryl) butane-1, 3-dione was achieved using previously published methods [23].

**General procedure for the synthesis of (5-trifluoromethyl)-4, 7-dihydro-7-(aryl)-2-(methylthio)[1, 2, 4] triazolo[1, 5-a] pyrimidin-6-yl (4-methoxyphenyl) methanone (PK-101 to 110)**

A mixture of the 5-(methylthio)-2H-1,2,4-triazol-3-amine (0.01 mol), 4,4,4-trifluoro-1-(4-methoxyphenyl)butane-1,3-dione (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) in ethanol (5 mL) was irradiated under microwave conditions at 120 °C for 10-15 min. The microwave irradiation was operated in 30-second cycles. The reaction mixture was allowed to stand overnight at room temperature and then was filtered to give the solid triazolopyrazolopyrimidine products PK 101-110, which were washed with ethanol and dried in air. Triazolopyrimidines were obtained in high purity and did not require further purification by recrystallization.

(5-(trifluoromethyl)-4,7-dihydro-7-(4-methoxyphenyl)-2-(methylthio)[1,2,4] triazolo[1,5-a] pyrimidin-6-yl)(4-methoxyphenyl)methanone (PK-101)

Yield: 72%;

mp 226-228 °C;

IR (cm$^{-1}$): 3232 (N-H stretching of secondary amine), 3116 (C-H symmetrical stretching of CH$_3$ group), 2935 (C-H asymmetrical stretching of CH$_3$ group), 1715 (C=O stretching of carbonyl group), 1645 (C=N stretching of triazole ring), 1522 and 1481 (C=C stretching of aromatic ring), 1437 (C-H asymmetrical deformation of CH$_3$ group), 1408 (C-N-C stretching of pyrimidine ring), 1340 (C-H symmetrical deformation of CH$_3$ group), 1276 (C-N stretching of pyrimidine ring), 1240 (C-O-C asymmetrical stretching of ether linkage), 1172 (C-H in plane deformation of aromatic ring), 1060 (C-O-C symmetrical stretching of ether linkage), 868 (C-H out of plane deformation of 1,4-disubstitution);

$^1$H NMR (DMSO-$d_6$) δ ppm: 2.48 (3H, SCH$_3$), 3.79 (s, 3H, H$_a$), 6.39 (s, 3H, H$_b$), 6.94-6.97 (d, 2H, H$_{a'd'}$, J = 8.4 Hz), 7.03-7.09 (m, 4H, H$_{d'd''e''}$), 7.71-7.73 (m, 3H, H$_{f'g'}$), 11.27 (s, 1H, H$_h$);

MS: m/z 464;


(5-(trifluoromethyl)-4,7-dihydro-2-(methylthio)-7-p-tolyl-[1,2,4] triazolo[1,5-a] pyrimidin-6-yl)(4-methoxyphenyl)methanone (PK-103)

Yield: 78%;

mp 228-230 °C;

IR (cm$^{-1}$): 3232 (N-H stretching of secondary amine), 3116 (C-H symmetrical stretching of CH$_3$ group), 2935 (C-H asymmetrical stretching of CH$_3$ group), 1715 (C=O stretching of carbonyl group), 1645 (C=N stretching of triazole ring), 1522 and 1481 (C=C stretching of aromatic ring), 1437 (C-H asymmetrical deformation of CH$_3$ group), 1408 (C-N-C stretching of pyrimidine ring), 1340 (C-H symmetrical deformation of CH$_3$ group), 1276 (C-N stretching of pyrimidine ring), 1240 (C-O-C asymmetrical stretching of ether linkage), 1172 (C-H in plane deformation of aromatic ring), 1060 (C-O-C symmetrical stretching of ether linkage), 868 (C-H out of plane deformation of 1,4-disubstitution);

$^1$H NMR (DMSO-$d_6$) δ ppm: 2.48 (3H, SCH$_3$), 3.79 (s, 3H, H$_a$), 6.39 (s, 3H, H$_b$), 6.94-6.97 (d, 2H, H$_{a'd'}$, J = 8.4 Hz), 7.03-7.09 (m, 4H, H$_{d'd''e''}$), 7.71-7.73 (m, 3H, H$_{f'g'}$), 11.27 (s, 1H, H$_h$);

MS: m/z 464;


(5-(trifluoromethyl)-4,7-dihydro-2-(methylthio)-7-p-tolyl-[1,2,4] triazolo[1,5-a] pyrimidin-6-yl)(4-methoxyphenyl)methanone (PK-103)
Yield: 53%;

mp 198-200 °C;

IR (cm⁻¹): 3261 (N-H stretching of secondary amine), 3035 (C-H stretching of aromatic ring), 2922 (C-H asymmetrical stretching of CH₃ group), 2876 (C-H asymmetrical stretching of CH₃ group), 1670 (C=O stretching of carbonyl group), 1606 (C=N stretching of triazole ring), 1550 (N-H deformation of pyrimidine ring), 1516 and 1482 (C=C stretching of aromatic ring), 1440 (C-H asymmetrical deformation of CH₃ group), 1412 (C-H symmetrical deformation of CH₃ group), 1330 (C-N stretching), 1249 (C-O-C stretching), 1029 (C-H in plane deformation of aromatic ring), 822 (C-H out of plane bending of 1,4-disubstituion);

¹H NMR (DMSO-d₆) δ ppm: 2.15 (s, 3H, H₳), 2.45 (3H, SCH₃), 3.81 (s, 3H, H₳), 6.28 (s, 1H, H₳), 6.85-6.87 (d, 2H, H₳), J = 8.80 Hz), 6.97 (d, 2H, H₳), 7.03-7.05 (d, 2H, H₳), J = 8.40 Hz), 7.27-7.30 (d, 2H, H₳), J = 8.00 Hz), 7.71-7.74 (d, 3H, H₳), 11.26 (s, 1H, H₳);

MS: m/z 460;

Anal. Calcd. for C₂₂H₁₆ClF₃N₄O₃S: C, 55.25; H, 3.25; N, 12.89. Found: C, 55.10; H, 4.02; N, 13.40%.

(7-(4-chlorophenyl)-5-(trifluoromethyl)-4,7-dihydro-2-(methylthio)-1,2,4-triazolo[1,5-a]pyrimidine-6-yl)(4-methoxyphenyl)methanone

(PK-105)

Yield: 75%;

mp 240-242 °C;

IR (cm⁻¹): 3219 (N-H stretching of secondary amine), 3048 (C-H stretching of aromatic ring), 2965 (C-H asymmetrical stretching of CH₃ group), 2874 (C-H asymmetrical stretching of CH₃ group), 1666 (C=O stretching of carbonyl group), 1595 (C=N stretching of triazole ring), 1516 (N-H deformation of pyrimidine ring), 1440, 1400 (C=C stretching of aromatic ring), 1411 (C-H asymmetrical deformation of CH₃ group), 1344 (C-H symmetrical deformation of CH₃ group), 1280 (C-N stretching), 1248 (C-O-C stretching), 1033 (C-H in plane deformation of aromatic ring), 815 (C-H out of plane bending of 1,4-disubstituion);

¹H NMR (DMSO-d₆) δ ppm: 2.48(3H, SCHR₳), 3.81 (s, 3H, H₳), 6.39 (s, 3H, H₳), 6.95-6.97 (d, 2H, H₳), J = 8.40 Hz), 7.07-7.09 (d, 2H, H₳), J = 8.00 Hz), 7.30-7.32 (d, 2H, H₳), J = 8.00 Hz), 7.74-7.80 (m, 3H, H₳), 11.36 (s, 1H, H₳);

MS: m/z 480;

Anal. Calcd. for C₂₃H₂₆ClF₃N₅O₃S: C, 55.25; H, 3.25; N, 12.89. Found: C, 55.10; H, 4.02; N, 13.40%.

V. IR SPECTRAL STUDY

IR spectra were recorded on Shimadzu FT-IR-8400 model using KBr pellet method. Various functional groups present in molecule were identified by characteristic frequency obtained for them. For triazolopyrimidines PK-101 to 110, confirmatory bands for secondary amine and carbonyl groups were observed at 3159-3427 cm⁻¹ and 1658-1712 cm⁻¹ respectively. Another characteristic C=N stretching band of triazole ring was observed at 1521-1641 cm⁻¹, which suggested formation of desired products VP-101 to 110.

VI. ¹H NMR SPECTRAL STUDY

¹H NMR spectra were recorded in DMSO-d₆ solution on a Bruker Ac 400 MHz spectrometer using TMS as an internal standard. Number of protons and their chemical shifts were found to support the structure of the synthesized compounds.

¹H NMR spectra confirmed the structures of triazolopyrimidines PK-101 to 110 on the basis of following signals: a singlet for the methine proton of pyrimidine ring at 6.28-6.72 δ ppm, a singlet for the methine proton of triazole ring at 7.27-7.37 δ ppm and singlet for secondary amine group of pyrimidine proton at 11.05-11.46 δ ppm, respectively.

VII. BIOLOGICAL EVALUATION

Antimicrobial evaluation

All of the synthesized compounds (PK-101 to 110) were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria Staphylococcus aureus MTCC-96, Streptococcus pyogenes MTCC 443, two Gram-negative bacteria Escherichia coli MTCC 442, Pseudomonas aeruginosa MTCC 441 and three fungal strains Candida albicans MTCC 227, Aspergillus Niger MTCC 282, Aspergillus clavatus MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture International Journal of Research and Innovation in Applied Science (IJRIAS)|Volume I, Issue VIII, November 2016|ISSN 2454-6194

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REFERENCES AND NOTES