CHAPTER-2

STUDIES ON DIHYDRO[1,5-\(\alpha\)]PYRIMIDINE DERIVATIVES
CHAPTER-2

SECTION-I

STUDIES ON
DIHYDRO TRIAZOLO[1,5-α]
PYRIMIDINE DERIVATIVES
INTRODUCTION:

Pyrimidine is a heterocyclic aromatic organic compound similar to benzene and pyridine, containing two nitrogen atoms at positions 1 and 3 of the six-member ring. It is isomeric with two other forms of diazine.

A pyrimidine has many properties in common with pyridine, as the number of nitrogen atoms in the ring increases the ring pi electrons become less energetic and electrophilic aromatic substitution gets more difficult while nucleophilic aromatic substitution gets easier. Pyrimidine is the most important member of all the diazines as this ring system occurs widely in living organisms. (In addition to being essential components of naturally occurring nucleic acids, pyrimidines are integral parts of such biologically important compounds as antiviral agents\(^1\), antitumor agent\(^2\) and cardiovascular agent.\(^3\) Because of their biological importance, these compounds have been the subject of considerable synthetic activity during the past several years.\(^4\) A sizeable portion of this work is directed toward the selective functionalization of the pyrimidine nitrogens.\(^5\))

In the last several decades, fused pyrimidine derivatives is a class of heterocyclic compound that have attracted significant interest in medicinal chemistry as they have a wide range of pharmaceutical and pharmacological applications such as antineoplastic, antiviral, antibacterial, expectorant, urinary tract infection, parkinsonism, anthelmintic, vasodilator, liver disorder, infections of the respiratory tract and ear, treatment of gastrointestinal roundworms, peripheral neuropathies and disorders associated with hyperuricaemia. The fact that a majority of clinically active heterocyclic drugs possess a nitrogen hetero atomic system with one or two phenyl rings, at least one carbonyl group in their structure and presence of hydrogen donor/acceptor unit. In the entire pioneering experiments important core fragments\(^6\) is defined by presence of hydrogen donor/acceptor unit (HAD), hydrophobic domain (A) (aryl ring substituted/unsubstituted) and electron donor atom (D).\(^7\) This common feature was found in the structures of well-established marketed drugs such as Uramustine,
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PiritreximIsotionate, Tegafur, Floxuridine, Fluorouracil, Cytarabine and Methotrexate etc. The pyrimidine and fused pyrimidine marketed drugs are tabulated in Table No. 8.

**LIST OF PYRIMIDINE AND FUSED PYRIMIDINE MARKETED DRUGS:**

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Structure</th>
<th>Pharmaceutical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="structure1.png" alt="Fluorouracil" /> <img src="structure2.png" alt="Tegafur" /></td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>2</td>
<td><img src="structure3.png" alt="Metioprim" /> <img src="structure4.png" alt="Piromidic Acid" /></td>
<td>Antibacterial</td>
</tr>
<tr>
<td>3</td>
<td><img src="structure5.png" alt="Flucytosine" /></td>
<td>Antifungal</td>
</tr>
<tr>
<td>4</td>
<td><img src="structure6.png" alt="Broxuridine" /> <img src="structure7.png" alt="Idoxuridine" /></td>
<td>Antiviral</td>
</tr>
<tr>
<td>5</td>
<td><img src="structure8.png" alt="Pyrantel Embonate" /></td>
<td>Anthelmintic</td>
</tr>
<tr>
<td>Chapter</td>
<td>Compound</td>
<td>Classification</td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td>----------------</td>
</tr>
<tr>
<td>6</td>
<td>Trapidil</td>
<td>Vasodilators</td>
</tr>
<tr>
<td>7</td>
<td>Orotic Acid</td>
<td>Liver Disorder</td>
</tr>
<tr>
<td>8</td>
<td>Brodimoprim</td>
<td>Respiratory tract and ear infections</td>
</tr>
<tr>
<td>9</td>
<td>Tisopurine</td>
<td>Disorders associated with hyperuricaemia</td>
</tr>
<tr>
<td>10</td>
<td>Tasuldine</td>
<td>Expectorant and mucolytic</td>
</tr>
<tr>
<td>12</td>
<td>Piribedil</td>
<td>Parkinsonism</td>
</tr>
</tbody>
</table>
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SYNTHETIC ASPECT:

Multi-Component Reactions:

The “ideal synthesis” should lead to the desired product in as few steps as possible, in good overall yield and by using environmentally compatible reagents. The synthetic variables that have to be optimized are time, costs, overall yield and simplicity of performance, safety and environmental acceptability. In multistep syntheses the temporal and preparative complexity increases in proportion to the number of steps. It is reflected in many isolation and purification operations, such as crystallization, extraction, distillation, or chromatography.8

Most organic reactions in the textbooks of organic chemistry are reactions of either single or two starting materials. Reactions that use more than two different starting materials are called multi component reactions (MCRs). In the light of chemical productivity and generation of molecular diversity an “ideal” MCR should not only comprise more than two starting materials but also these starting materials would be different and all or most of the atoms of those starting materials would be incorporated into the final product.9

One of the most promising synthetic strategies for generating collections of small molecules by DOS (Diversity-Oriented Synthesis) involves the sequencing of multicomponent reactions (MCRs) with subsequent transformations, including cyclizations and refuctionalizations, that form new compounds possessing increased
molecular complexity and diversity. This process of sequencing MCRs with subsequent cyclizations is commonly referred to as the build/couple/pair strategy of DOS. Ideally, the MCRs will be sufficiently versatile that each input for the MCR can incorporate a wide range of functionalities and substituents. Using the tactic of functional group pairing, the MCR adduct is then selectively transformed in ring forming processes and refunctionalizations comprising the synthome into the target heterocyclic structures.

Multi-component reactions (MCR), an important class of organic tandem reactions, are one-pot processes with at least three components to form a single product, which incorporates most or even all of the starting materials. The huge interest for such multi-component reactions during the last years has been oriented toward developing combinatorial chemistry procedures, because of their high efficiency and convenience of these reactions in comparison with multistage procedures. Hence, most of the scientific efforts have been focused on the development of multi-component procedures to prepare diverse heterocyclic compound libraries. Also, the utility of MCR under microwave irradiation in the synthesis of heterocyclic compounds enhanced the reaction rates and improved the regioselectivity. MCRs have also found wide application in the synthesis of natural products and other targets of interest.

MCRs have been known for over 100 years. Although it would be difficult to identify the first example of an MCR, the Hantzsch dihydropyridine (DHP) synthesis was reported in 1882, followed by the Biginelli 3CR in 1893. The first isocyanide-based MCRs were disclosed by Passerini (3CR) and Ugi (4CR) in 1921 and 1959, respectively. Here mentioned in detail is the venerable 3CR-Biginelli dihydropyrimidine synthesis.

**Biginelli Reaction**

In 1893, Italian chemist Pietro Biginelli reported on the acid catalyzed cyclocondensation reaction of ethyl acetoacetate (1), benzaldehyde (2), and urea (3). The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1H)-one (Scheme1).
Apart from a series of publications by the late Karl Folkers in the mid-1930s, the “Biginelli reaction” or “Biginelli condensation” as it was henceforth called was largely ignored in the early part of the 20th century. The synthetic potential of this new heterocycle synthesis therefore remained unexplored for quite some time. In the 1970s and 1980s, interest slowly increased, and the scope of the original cyclocondensation reaction shown in Scheme 1 was gradually extended by variation of all three building blocks (Figure 1), allowing access to a large number of multifunctionalized dihydropyrimidines of type 4.
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Alternative synthetic routes for better yield, shorter reaction time to synthesize new analogs:

Various modifications have been applied to Biginelli reaction to get better yield and to synthesize biologically active analogs. Different catalysts have been reported to increase the yield of the reaction. Microwave synthesis strategies have also applied to shorten the reaction time. Solid phase synthesis and combinatorial chemistry has made possible to generate library of DHPM analogs.

Catalysts

Min Yang and coworkers\(^\text{22}\) have synthesized the different DHPMs by using different inorganic salts as a catalyst. They found that the yields of the one-pot Biginelli reaction can be increased from 20-50% to 81-99%, while the reaction time shorted from 18-24 hrs. to 20-30 min. This report discloses a new and simple modification of the Biginelli type reaction by using Yb(OTf)\(_3\) and YbCl\(_3\) as a catalyst under solvent free conditions. One additional important feature of this protocol is the catalyst can be easily recovered and reused.

Indium(III)chloride was emerged as a powerful Lewis catalyst imparting high region and chemo selectivity in various chemical transformations. B. C. Ranu and coworkers\(^\text{23}\) reported indium(III)chloride (InCl\(_3\)) as an efficient catalyst for synthesis of 3,4-dihydropyrimidin-2(1H)-ones. A variety of substituted aromatic, aliphatic and heterocyclic aldehydes have been subjected to this condensation very efficiently. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1H)-thiones.
M. M. Heravi et al. have reported a simple, efficient and cost-effective method for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones by one pot three component cyclocondensation reaction of a 1,3-dicarbonyl compound, an aldehyde and urea or thiourea using 12-tungstophosphoric acid\(^{24}\) and 12-molybdophosphoric acid\(^ {25}\) as a recyclable catalyst.

Many researchers\(^ {26}\) have investigated an efficient Biginelli reaction under solvent free conditions for one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)ones/thiones using various catalyst as described under.

**Solid phase synthesis**

The generation of combinatorial libraries of heterocyclic compounds by solid phase synthesis is of great interest for accelerating lead discovery and lead optimization in pharmaceutical research.\(^ {27,28}\) The first solid-phase modification of the Biginelli condensation was reported by Wipf and Cunningham\(^ {29}\) in 1995. In this sequence, \(\gamma\)-aminobutyric acid derived urea was attached to Wang resin using standard procedures. The resulting polymer-bound urea was condensed with excess \(\alpha\)-ketoester and aromatic...
aldehydes in THF at 55 °C in the presence of a catalytic amount of HCl to afford the corresponding immobilized DHPMs. Subsequent cleavage of product from the resin by 50 % trifluoroacetic acid (TFA) provided DHPMs in high yields and excellent purity.

Gross\textsuperscript{30} et al. developed a protocol for based on immobilized $\alpha$-ketoamides to increase the diversity of DHPM. The resulting synthetic protocol proved to be suitable for the preparation of a small library using different building blocks. They found that the expected DHPM derivatives were formed in high purity and yield, if aromatic aldehyde and $\alpha$-ketoamide building blocks were used. The usage of an aliphatic aldehyde leads to an isomeric DHPM mixture. Purities and yields were not affected if thiourea was used instead of urea.

**Liquid phase synthesis**

In the solid phase synthesis there are some disadvantages of this methodology compared to standard solution-phase synthesis, such as difficulties to monitor reaction progress, the large excess of reagents typically used in solid-phase supported synthesis, low loading capacity and limited solubility during the reaction progress and the heterogeneous reaction condition with solid phase.\textsuperscript{31} Recently, organic synthesis of small molecular compounds on soluble polymers, i.e. liquid phase chemistry has increasingly become attractive field.\textsuperscript{32} It couples the advantages of homogeneous solution chemistry with those of solid phase chemistry.

Moreover owing to the homogeneity of liquid-phase reactions, the reaction conditions can be readily shifted from solution-phase systems without large changes and the amount of excessive reagents is less than that in solid-phase reactions. In the recent years, Task Specific room temperature Ionic Liquids (TSILs) has emerged as a powerful alternative to conventional molecular organic solvents or catalysts. Liu Zuliang\textsuperscript{33} et al.
reported cheap and reusable TSILs for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones via one-pot three component Biginelli reaction.

Ionic liquid-phase bound acetoacetate react with thiourea and various aldehydes with a cheap catalyst to afford ionic liquid-phase supported 3,4-dihydropyrimidin-2(1H)-thiones by Jean Pierre Bazureau and co-workers.\textsuperscript{34} 3,4-Dihydropyrimidinones was synthesized in one-pot of aldehydes, \(\alpha\)-dicarbonyl compounds and urea, catalyzed by non-toxic room temperature ionic liquid 1-n-butyl-3-methylimidazolium saccharinate (BMImSac).\textsuperscript{35}

\begin{center}
\includegraphics[width=\textwidth]{diagram}
\end{center}

**Microwave assisted synthesis**

In general, the standard procedure for the Biginelli condensation involves one pot condensation of the three building blocks in a solvent such as ethanol using a strongly acidic catalyst that is hydrochloric acid.\textsuperscript{36} One major drawback of this procedure, apart from the long reaction times involving reflux temperatures, are the moderate yields frequently observed when using more complex building blocks. Microwave irradiation (MWI) has become recognized tool in organic synthesis, because the rate enhancement, higher yields and often, improved selectivity with respect to conventional reaction conditions.\textsuperscript{37} The publication by Anshu Dandia\textsuperscript{38} et al. described microwave-enhanced solution-phase Biginelli reactions employing ethyl acetoacetate, thiourea and a wide variety of aromatic aldehydes as building blocks. Upon irradiation of the individual reaction mixtures (ethanol, catalytic HCl) in an open glass beaker inside the cavity of a domestic microwave oven the reaction times were reduced from 2 – 24 hrs. of conventional heating 80 °C, reflux to 3 – 11 min. under microwave activation (ca. 200 – 300 W). At the same time the yields of DHPMs obtained were markedly improved compared to those reported earlier using conventional conditions.
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In recent years, solvent free reactions using either organic or inorganic solid supports have received increasing attention. There are several advantages to performing synthesis in dry media: (i) short reaction times, (ii) increased safety, (iii) economic advantages due to the absence of solvent. In addition, solvent free MWI processes are also clean and efficient. M. Gopalakrishnan and co-workers have reported Biginelli reaction under microwave irradiation in solvent-free conditions using activated fly ash as a catalyst, activated fly ash, an industrial waste (pollutant) is an efficient and novel catalyst for some selected organic reactions in solvent free conditions under microwave irradiation.

THERAPEUTIC IMPORTANCE:

4-Aryl-1,4-dihydropyridines (DHPs) of the nifedipine type e.g. nifedipine are the most studied class of organic calcium channel modulators. More than 30 years after the introduction of nifedipine (1), many DHP analogs have now been synthesized and numerous second-generation commercial products have appeared in the market e.g. nitrendipine, nicardipine and amlodipine. The aza-analogs such as dihydropyrimidines (2) which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators. Over the past several lead-compounds were developed e.g. (2) SQ 32926 and (3) SQ 32574 that are superior in potency and duration of antihypertensive activity to classical dihydropyridine drugs and compare favorably with second-generation analogs such as amlodipine and nicardipine.
K. Atwal et al. synthesized the 3-substituted 1,4-dihydropyrimidine (4) and documented that vasorelaxant activity was critically dependent on the size of the C5 ester group, isopropyl ester being the best, a variety of substituents (carbamate, acyl, sulfonyl, alkyl) were tolerated at N3. The dihydropyrimidines (4) are significantly more potent than corresponding 2-heteroalkyl-1,4-dihydropyrimidines. Dihydropyridine enantiomer usually show 10-15 fold difference in activity, while the enantiomers of dihydropyrimidine (5) show more than a 1000 fold difference in activity. These results strengthen the requirement of an enamino ester for binding to the dihydropyridine receptor and indicate a nonspecific role for the N3-substituent.

George C. Rovnyak et al. examined a series of novel dihydropyrimidine calcium channel blockers that contain a basic group attached to either C5 or N3 of the heterocyclic ring. One of these compounds was identified as a lead, and the individual enantiomers (6a) (R) and (6b) (S) were synthesized. Dihydropyrimidine (6a) is equipotent to nifedipine and amlodipine in vitro. In the spontaneously hypertensive rat, dihydropyrimidine (6a) is more potent and longer acting than nifedipine and compares most favorably with the long-acting dihydropyridine derivative amlodipine. Dihydropyrimidine (6a) has the potential advantage of being a single enantiomer.
Selma Sarac and co-workers\textsuperscript{45,46} have synthesized 4-aryl-3,4-dihydropyrimidin-2(1H)-one/thione derivatives. The calcium channel blocker activities of all compounds performed on isolated rat ileum. Product (7), 2-nitrophenyl derivative and (8), 2-bromophenyl derivative have potent antispasmodic activity on BaCl\textsubscript{2} stimulated rat ileum.

N. Dhanapalan and co-workers\textsuperscript{47} have synthesized dihydropyrimidinones and describe compound (9) have a high binding affinity ($K_i = 0.2$nM) for $\alpha$1a receptor and greater than 1500 fold selectivity over $\alpha$1b and $\alpha$1d adreno receptors. Modification of the linker in (9) gave compounds (10) and (11)\textsuperscript{48} viz $\mu$-opioid receptor. They have also identified that compound (12)\textsuperscript{49} was a lead compound with a binding and functional profile comparable to that of (9). 12 have negligible affinity for the $\mu$-opioid receptor.
The synthesis and differential antiproliferative activity of Monastrol (13a), O xo-
monastrol (13b) and eight oxygenated derivatives (14a,b–18a,b) on seven human cancer
cell lines are described by Dennis Russowsky\(^5\). For all evaluated cell lines, Monastrol
(13a) was shown to be more active than its Oxo-analogue, except for HT-29 cell line,
suggesting the importance of the sulfur atom for the antiproliferative activity. Monastrol
(13a) and the thio derivatives (15a, 16a) and (18a) displayed relevant antiproliferative
properties with 3,4-methylenedioxy derivative (18a) being approximately more than 30
times more potent than Monastrol (13a) against colon cancer (HT-29) cell line.
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Work done from our laboratory

J. D. Akbari and coworkers\(^{51}\) has reported following new series and activities of some new DHPM’s synthesis of some new 1,2,3,4-tetrahydropyrimidine-2-ones and their thiazolo[3,2-a]pyrimidine derivatives (19) as a potential biological agents. Synthesis of some new pyrazolo[3,4-d]pyrimidines and thiazolo[4,5-d]pyrimidines\(^{52}\) (20) and evaluation of their antimicrobial activities. Green chemistry approach\(^{53}\) to synthesis of some new trifluoromethyl containing tetrahydropyrimidines under solvent free conditions. Synthesis and antimicrobial activities of some new pyrazolo[3,4-d]pyrimidines and thiazolo[4,5-d]pyrimidines.\(^{54}\)

M. J. Ladani\(^{55}\) reported synthesis and biological study of oxopyrimidines and thiopyrimidines (21) of 2-(2,4-dichlorophenyl)imidazo[1,2-a]pyridin-3-carbaldehyde, multi-component synthesis of dihydropyrimidines (22) by iodine catalyst at ambient temperature and in vitro antimycobacterial activity was reported by P. D. Zalavadiya.
In the past years, considerable evidence has been accumulated to demonstrate the pharmacodynamics and various biological importances of dihydropyrimidine derivatives. To further evaluate the potential of such type of compounds, the synthesis have been carried out which have been described as under.

**SECTION-I:** Synthesis and biological screening of 5-Isopropyl-7-substituted-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-\(\alpha\)]pyrimidine-6-carboxamides.

**SECTION-II:** TGA, DSC, UV-VIS/NIR and Single Crystal X-ray analysis of 5-Isopropyl-7-(4-methoxyphenyl)-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro [1,2,4]triazolo [1,5-\(\alpha\)]pyrimidine-6-carboxamide.

**SECTION-III:** Synthesis and biological screening of 3-Cyano-5-isopropyl-2-(methylthio)-7-substituted-N-(4-(trifluoromethyl)phenyl)-4,7-dihydropyrazolo[1,5-\(\alpha\)]pyrimidine-6-carboxamides.
SYNTHESIS AND BIOLOGICAL SCREENING OF 5-ISOPROPYL-7-SUBSTITUTED-N-(4-(TRIFLUOROMETHYL)PHENYL-4,7-DIHYDRO-[1,2,4]TRIAZOLE [1,5-a] PYRIMIDINE-6-CARBOXYLAMIDES

INTRODUCTION:

Fusion of pyrimidine ring with different heterocyclic scaffolds gives rise to a new class of hybrid heterocycles possessing improved activity. Various fused pyrimidines like purines, pteridines, quinazolines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines, pyridopyrimidines and pyrrolopyrimidines were studied in the past decade and were found to possess remarkable pharmacological properties. The condensation of pyrimidine ring with another ring of 1,2,4-triazole 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)

All these isomeric families of compounds are thermodynamically more stable and, thus, the most studied ones, a few of them being commercially available.
SYNTHETIC ASPECT:

By far the most triazolo[1,5-\(\alpha\)]pyrimidine synthesis are condensations of dinucleophilic 5-amino-1,2,4-triazoles with 1,3-bifunctional synthons as shown in the formation of triazolo[1,5-\(\alpha\)]pyrimidine.\(^{56,57}\) 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.\(^{58}\) Furthermore, certain lithium 1,3-diketonates have proven to be better synthons than the corresponding diketones.\(^{59}\)

Previous mechanistic conclusions have been confirmed by isolating stable intermediate 5-amino-1,2,4-triazole derivatives such as enamine (I) (Figure 4.17) on reacting 5-amino-1,2,4-triazoles with 3-ketovinyl ethers,\(^{60}\) 3-ketoamines,\(^{61}\) 3-ketoaldehydes,\(^{62}\) enamine-2-carboxylic esters\(^{63}\) or ethoxymethylene malonates.\(^{62}\)

That means, the overall reaction starts with the interaction of the amino-1,2,4-triazole amino group and the enolic (or analogous) functionality of the three-carbon synthon. In the two-step examples, just mentioned, the first step proceeds under milder conditions (sometimes just in ethanol at room temperature), but the final cyclization (or the one-step reaction, if the intermediate is not trapped) requires stronger means (e.g., PPA or boiling acetic acid). Under extreme conditions, triazolylamide (I) was subject to flash vacuum pyrolysis between 300 and 450 °C to give about 50% triazolo[1,5-\(\alpha\)]pyrimidine (II).\(^{64}\)
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 Libraries of fused 3-aminopyrimidin-4-ones (I) and other compounds were just recently prepared by the solid-phase and by the solution-phase parallel synthesis. The latter method turned out to be advantageous with respect to yield and purity.

 Figure below shows two parallel paths of pyrimidine ring annulation: the conventional method, route A and route B using a reactive amino-1,2,4-triazole derivative. Amidine (III) is formed from 5-amino-1,2,4-triazole and DMF. Dimethylacetal can be regarded as the result of incorporating one carbon of the three-carbon synthon (I) into the 5-amino-1,2,4-triazole molecule; condensation with a reactive two-carbon component leads to target triazolo[1,5-α]pyrimidine (II).

 Path B also serves in confirming the structure of product (II). Similar syntheses of 7-aryl and 7-heterocyclyl triazolo[1,5-α]pyrimidines have also been described, for example, that of an antipyrene derivative.
Y. Tominaga\textsuperscript{71} et al. have reported direct synthesis of 1,2,4-triazolo[1,5-
\textit{a}]pyrimidine derivatives via condensation of 3-amino-1,2,4-triazole with ketene
dithioacetals by heating at 150°C for 3hrs. in 55% yield (Figure-4.21).

K. Kumari\textsuperscript{72} et al. have reported a facile and efficient ionic liquid-catalyzed multi-
component synthesis of tetrahydro-1,2,4-triazolo[5,1-\textit{b}]quinazolin-8(4H)-ones and
dihydro-1,2,4-triazolo[1,5-\textit{a}]pyrimidines in excellent yields from 3-amino-1,2,4-triazole,
aldehydes and dimedone or ethyl acetoacetate respectively, by simple grinding using a
mortar and pestle at room temperature.
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THERAPEUTIC IMPORTANCE:

Triazolo[1,5-\(a\)]pyrimidine, an attractive skeleton, has been identified to possess promising biological and pharmaceutical importance. T. Novinson\(^{73}\) et al. synthesized 2-(alkylthio)-1,2,4-triazolo[1,5-\(a\)]pyrimidines as adenosine cyclic 3',5'-monophosphate phosphodiesterase inhibitors with potential as new cardiovascular agents.

![Chemical Structure](image1)

Synthesis of fused 1,2,4-triazolo[1,5-c]pyrimidine derivatives as human adenosine A3 receptor ligands was carried out by T. Okamura\(^{74}\) et al.

![Chemical Structure](image2)

X. Zhai\(^{75}\) et al. designed 2,7-disubstituted triazolo[1,5-\(a\)]pyrimidines and synthesized compounds were screened for antiproliferative activity.

X-L. Zhao\(^{76}\) et al. synthesized certain novel [1,2,4]triazolo[1,5-\(a\)]pyrimidine derivatives and studied anti-tumor activity of these compounds.

![Chemical Structure](image3)

Synthesis of pyrimidine moiety bearing 1,2,4-triazolo[1,5-\(a\)]pyrimidine was carried out by Y. Luo\(^{77}\) et al. The synthesized compounds were then screened against antimicrobial activity.

![Chemical Structure](image4)
H.M. Ashour\textsuperscript{78} et al. synthesized thieno[2’,3’:4,5]pyrimido[1,2-\textit{b}] [1,2,4]triazines and thieno[2,3-\textit{d}] [1,2,4]triazolo[1,5-\textit{a}]pyrimidines and further anti-inflammatory and analgesic studies were done of the synthesized compounds.

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\includegraphics[width=0.3\textwidth]{image1.png}
\end{center}

Antifungal activity of novel [1,2,4]triazolo[1,5-\textit{a}]pyrimidine derivatives was studies by Q. Chen\textsuperscript{79} et al.

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\includegraphics[width=0.3\textwidth]{image2.png}
\end{center}

One of the synthetic pathways to 1,2,4-triazolo[1,5-\textit{a}]pyrimidines is based on the Biginelli like cyclocondensation of aromatic aldehydes and acetoacetic acid derivatives with aminoazoles containing a guanidine fragment. There are literary data about the synthesis of triazolo pyrimidines by treatment of 5-amino-1,2,4-triazole or 5-aminotetrazole with aldehydes and ethyl acetoacetate or cyclic $\beta$-diketones.\textsuperscript{80} The cyclocondensation were realized by heating of the starting materials in ethanol with catalytic amounts of hydrochloric acid under reflux conditions\textsuperscript{80(a-c)} or using DMF as solvent.\textsuperscript{80(d-e)} The use of acetoacetamides in these or similar reactions has not been described.

Looking to the diversified pharmacological properties of 1,2,4-triazolo[1,5-\textit{a}]pyrimidines, synthesis of these moiety was undertaken by the condensation of acetoacetonilide derivative in presence of amino triazole and various substituted aldehydes in DMF.
The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, $^1$H NMR, $^{13}$C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and two fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.
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PLAUSIBLE REACTION MECHANISM:
EXPERIMENTAL SECTION:

Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (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. 1H (400 MHz), 13C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in CDCl3 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.

[A] General synthetic procedure for the 4-methyl-3-oxo-N-(4-(trifluoromethyl)phenyl)pentanamide: (Intermediate-I)

Equimolar mixture of 4-(trifluoromethyl)aniline (10 mmol), 1,3-diketone (10 mmol) and catalytic amount of potassium hydroxide (KOH) in 1,4-dioxane was refluxed for 4-5 hours. The progress of the reaction was monitored by thin layer chromatography. After completion of reaction, reaction mixture was allowed to cool at room temperature and poured onto crushed ice. The obtained solid was filtered and purified by trituration with hexane to give pure buff color product. Yield = 75%. (Intermediate-I)

[B] General procedure for the preparation 5-isopropyl-7-substituted-n-(4-(trifluoromethyl)phenyl)-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamides:

A mixture of 4-methyl-3-oxo-N-(4-(trifluoromethyl)phenyl)pentanamide (10 mmol), 1,2,4-triazol-3-amine (12 mmol) and different substituted aldehyde (10 mmol) was heated at 140-150 °C for 25-30 min. in presence 3-4 drops of DMF. The completion of reaction was confirmed by analytical thin layer chromatography (TLC). After completion of reaction, reaction mixture was allowed to cool at room temperature and poured onto crushed ice. The resulting solid was filtered, washed with water and dried under vacuo to give crude product. The obtained crude product was purified by trituration with methanol and purity of all these synthesized compounds (5a-5j) was checked by TLC. The physical constants of the products are recorded in Table No.9.

[C] Biological evaluation of 5-isopropyl-7-substituted-n-(4-(trifluoromethyl)phenyl)-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamides:

Antimicrobial testing was carried out as described in Chapter-1, Section-II, antimicrobial activity. The MIC values of the test compounds are recorded in Table No.10.
Table No. 9: Physical constants of 5-isopropyl-7-substituted-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamides:

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<th>Molecular weight gm/mole</th>
<th>m.p. °C</th>
<th>Yield %</th>
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<td>70</td>
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<td>H</td>
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<td>183-185</td>
<td>75</td>
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<tr>
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ANALYTICAL DATA:

5-Isopropyl-7-(4-methoxyphenyl)-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (5a): m.p.- 210-212°C; IR (KBr) (cm\(^{-1}\)): 3360, 3089 (-NH amide sym. str.), 3089 (Ar, C-H str.), 1672 (C=O str.), 1637 (C=N str.), 1568 (N-H str.), 1323 (triazole ring sys. str.), 1253 (C-N str.), 1060 (C-F str.), 848 (para substitution); \(^1\)H NMR (400 MHz, CDCl\(_3\)):\(\delta\) ppm 1.16-1.18 (d, 3H, \(J=8.0\) Hz), 1.28-1.30 (d, 3H, \(J=8.0\) Hz), 3.26-3.35 (m, 1H, isopropyl -CH), 3.75 (s, 1H, OCH\(_3\)), 6.5 (s, 1H, chiral carbon), 6.85-6.87 (d, 2H, \(J=8.0\) Hz, ArH), 7.12-7.14 (d, 2H, \(J=8.0\) Hz, ArH), 7.614-7.635 (d, 2H, \(J=8.0\) Hz, ArH), 7.72-7.74 (d, 2H, \(J=8.0\) Hz, ArH), 10.01 (s, 1H, -NH), 10.31 (s, 1H, amide -NH); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)):\(\delta\) ppm 19.65, 19.68 (C11, C11'), 28.76 (C10), 55.21 (C1), 59.63 (C6), 102.25 (C12), 114.58 (C3,3'), 119.50 (C15,15'), 122.97-123.38 (C16,16'), 125.66-125.94 (C18), 128.30 (C4,4'), 132.46 (C17), 142.71 (C14), 149.88 (C7), 150.81 (C8), 159.05 (C2), 162.40 (C9), 165.57 (C13); MS: \(m/z = 457\) [M].

5-Isopropyl-7-phenyl-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (5b): m.p.- 183-185°C; IR (KBr) (cm\(^{-1}\)): 3244, 3101 (-NH amide sym. str.), 3043 (Ar, C-H str.), 1658 (C=O str.), 1585 (N-H str.), 1319 (triazole ring sys. str.), 1253 (C-N str.), 1064 (C-F str.), 693 (mono substitution); \(^1\)H NMR (400 MHz, CDCl\(_3\)):\(\delta\) ppm 1.17-1.19 (d, 3H, \(J=8.0\) Hz), 7.12-7.14 (d, 2H, \(J=8.0\) Hz, ArH), 7.62-7.64 (d, 2H, \(J=8.0\) Hz, ArH), 7.68 (s, 1H, triazole ring), 7.71-7.73 (d, 2H, \(J=8.0\) Hz, ArH), 10.07 (s, 1H, -NH), 10.35 (s, 1H, amide -NH); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)):\(\delta\) ppm 19.59, 19.70 (C11, C11'), 28.76 (C10), 55.21 (C1), 59.63 (C6), 102.25 (C12), 114.58 (C3,3'), 119.50 (C15,15'), 122.97-123.38 (C16,16'), 125.66-125.94 (C18), 128.30 (C4,4'), 132.46 (C17), 142.71 (C14), 149.88 (C7), 150.81 (C8), 159.05 (C2), 162.40 (C9), 165.57 (C13); MS: \(m/z = 427\) [M].

7-(4-Cyanophenyl)-5-isopropyl-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (5c): m.p.- 178-180°C; IR (KBr) (cm\(^{-1}\)): 3412, 3182 (-NH amide sym. str.), 3095 (Ar, C-H str.), 1674 (C=O str.), 1647 (C=N str.), 1578 (N-H str.), 1321 (triazole ring sys. str.), 1249 (C-N str.), 1060 (C-F str.), 839 (para substitution); \(^1\)H NMR (400 MHz, CDCl\(_3\)):\(\delta\) ppm 1.17-1.19 (d, 3H, \(J=8.0\) Hz), 3.25-3.35 (m, 1H, isopropyl -CH), 6.55 (s, 1H, chiral carbon), 7.12-7.33 (m, 5H, ArH), 7.62-7.64 (d, 2H, \(J=8.0\) Hz, ArH), 7.68 (s, 1H, triazole ring), 7.71-7.73 (d, 2H, \(J=8.0\) Hz, ArH), 10.07 (s, 1H, -NH), 10.35 (s, 1H, amide -NH); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)):\(\delta\) ppm 19.59, 19.70 (C11, C11'), 28.79 (C9), 60.53 (C5), 102.18 (C11), 119.42 (C14, C14'), 122.96-123.43 (C17), 125.94-125.66 (C15, C15'), 126.92 (C1), 128.19 (C2, C2'), 128.35 (C3, C3'), 128.59 (C16), 140.41 (C4), 142.66 (C13), 144.86 (C6), 148.20 (C7), 150.01 (C8), 165.48 (C12); MS: \(m/z = 427\) [M].

7-(4-Cyanophenyl)-5-isopropyl-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (5c): m.p.- 178-180°C; IR (KBr) (cm\(^{-1}\)): 3412, 3182 (-NH amide sym. str.), 3095 (Ar, C-H str.), 1674 (C=O str.), 1647 (C=N str.), 1578 (N-H str.), 1321 (triazole ring sys. str.), 1249 (C-N str.), 1060 (C-F str.), 839 (para substitution); \(^1\)H NMR (400 MHz, CDCl\(_3\)):\(\delta\) ppm 1.17-1.19 (d, 3H, \(J=8.0\) Hz),
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1.23-1.25 (d, 3H, J=8.0 Hz), 3.18-3.25 (m, 1H, isopropyl -CH), 6.62 (s, 1H, chiral carbon), 7.34-7.37 (d, 2H, J=12.0 Hz, ArH), 7.63-7.65 (d, 2H, J=8.0 Hz, ArH), 7.69-7.72 (d, 2H, J=8.0 Hz, ArH), 7.71 (s, 1H, triazole ring), 7.80-7.82 (d, 2H, J=8.0 Hz, ArH), 10.20 (s, 1H, -NH), 10.39 (s, 1H, amide -NH);

13C NMR (100 MHz,CDCl3):δ ppm 19.57, 19.61 (C11,C11’), 29.04 (C10), 60.11 (C6), 101 (C12), 111.07 (C2), 118.43 (C1), 119.35 (C15,C15’), 122.94-123-64 (C18), 125.63-125.98 (C16 ,C16’), 127.91 (C4,C4’), 132.73 (C3,C3’), 142.46 (C14), 145.10 (C5), 145.41 (C7), 148.31 (C8), 150.39 (C9), 165.22 (C13);

MS: m/z = 452 [M]+.

5-Isopropyl-7-(p-tolyl)-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (5d): m.p. 195-197°C; IR (KBr) (cm⁻¹): 3368, 3078 (-NH amide sym. str.), 3030 (Ar, C-H str.), 1671 (C=O str.), 1639 (C=N str.), 1562 (N-H str.), 1323 (triazole ring sys. str.), 1251 (C-N str.), 1060 (C-F str.), 827 (para substitution); 1H NMR (400 MHz, CDCl3):δ ppm 1.16-1.18 (d, 3H, J=8.0 Hz), 1.27-1.29 (d, 3H, J=8.0 Hz), 2.19 (s, 3H, CH3), 3.26-3.35 (m, 1H, isopropyl -CH), 6.53 (s, 1H, chiral carbon), 6.89-7.11 (m, 4H, ArH), 7.61-7.63 (d, 2H, J=8.0 Hz, ArH), 7.67 (s, 1H, triazole ring), 7.73-7.75 (d, 2H, J=8.0 Hz, ArH), 10.05(s, 1H, -NH), 10.32 (s, 1H, amide -NH). MS: m/z = 441 [M]+.

7-(4-Chlorophenyl)-5-isopropyl-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (5e): m.p. 201-203°C; IR (KBr) (cm⁻¹): 3444, 3061 (-NH amide sym. str.), 3070 (Ar, C-H str.), 1687 (C=O str.), 1645 (C=N str.), 1565 (N-H str.), 1321 (triazole ring sys. str.), 1250 (C-N str.), 1058 (C-F str.), 833 (para substitution), 661 (C-Cl str.); 1H NMR (400 MHz, CDCl3):δ ppm 1.19-1.21 (d, 3H, J=8.0 Hz), 1.24-1.26 (d, 3H, J=8.0 Hz), 3.19-3.26 (m, 1H, isopropyl -CH), 6.63 (s, 1H, chiral carbon), 7.15-7.17 (d, 2H, J=8.0 Hz, ArH), 7.31-7.33 (d, 2H, J=8.0 Hz, ArH) 7.62-7.64 (d, 2H, J=8.0 Hz, ArH), 7.69 (s, 1H, triazole ring), 7.77-7.79 (d, 2H, J=8.0 Hz, ArH), 10.10 (s, 1H, -NH), 10.31 (s, 1H, amide -NH); MS: m/z = 461 [M]+.

7-(2,4-Dichlorophenyl)-5-isopropyl-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (5f): m.p. 187-189°C; IR (KBr) (cm⁻¹): 3389, 3115 (-NH amide sym. str.), 3089 (Ar, C-H str.), 1674 (C=O str.), 1643 (C=N str.), 1569 (N-H str.), 1321 (triazole ring sys. str.), 1250 (C-N str.), 1063 (C-F str.); 1H NMR (400 MHz, CDCl3):δ ppm 1.18-1.20 (d, 3H, J=8.0 Hz), 1.25-1.27 (d, 3H, J=8.0 Hz), 2.19 (s, 3H, CH3), 3.26-3.35 (m, 1H, isopropyl -CH), 6.53 (s, 1H, chiral carbon), 6.89-7.11 (m, 4H, ArH), 7.61-7.63 (d, 2H, J=8.0 Hz, ArH), 7.67 (s, 1H, triazole ring), 7.73-7.75 (d, 2H, J=8.0 Hz, ArH), 10.05(s, 1H, -NH), 10.32 (s, 1H, amide -NH). MS: m/z = 461 [M]+.
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7-(3,4-Dimethoxyphenyl)-5-isopropyl-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (5g): m.p. 168-170°C; IR (KBr) (cm⁻¹): 3381, 3174 (-NH amide sym. str.), 3084 (Ar, C-H str.), 1672 (C=O str.), 1634 (C=N str.), 1568 (N-H str.), 1323 (triazole ring sys. str.), 1251 (C-N str.), 1060 (C-F str.); ¹H NMR (400 MHz, CDCl₃): δ ppm 1.14-1.16 (d, 3H, J=8.0 Hz), 1.26-1.28 (d, 3H, J=8.0 Hz), 3.23-3.31 (m, 1H, isopropyl -CH), 3.75 (s, 6H, 2OCH₃), 6.63 (s, 1H, chiral carbon), 6.61-6.68 (m, 2H, ArH), 6.90 (s, 1H, ArH), 7.61-7.63 (d, 2H, J=8.0 Hz, ArH), 7.64 (s, 1H, triazole ring), 7.72-7.74 (d, 2H, J=8.0 Hz, ArH), 10.12 (s, 1H, -NH), 10.35 (s, 1H, amide -NH); MS: m/z = 496 [M⁺].

5-Isopropyl-7-(3-methoxyphenyl)-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (5h): m.p. 184-186°C; IR (KBr) (cm⁻¹) 3370, 3091 (-NH amide sym. str.), 3088 (Ar, C-H str.), 1672 (C=O str.), 1637 (C=N str.), 1568 (N-H str.), 1324 (triazole ring sys. str.), 1253 (C-N str.), 1060 (C-F str.), 789 (meta substitution); ¹H NMR (400 MHz, CDCl₃): δ ppm 1.16-1.18 (d, 3H, J=8.0 Hz), 1.28-1.30 (d, 3H, J=8.0 Hz), 3.27-3.34 (m, 1H, isopropyl -CH), 3.76 (s, 1H, OCH₃), 6.53 (s, 1H, chiral carbon), 6.75-6.80 (m, 2H, ArH), 6.96 (m, 1H, ArH), 7.18 (t, 1H, ArH), 7.62-7.64 (d, 2H, J=8.0 Hz, ArH), 7.65 (s, 1H, triazole ring), 7.73-7.75 (d, 2H, J=8.0 Hz, ArH), 10.06 (s, 1H, -NH), 10.33 (s, 1H, amide -NH); MS: m/z = 457 [M⁺].

7-(4-Fluorophenyl)-5-isopropyl-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (5i): m.p. 174-176°C; IR (KBr) (cm⁻¹) 3358, 3064 (-NH amide sym. str.), 3072 (Ar, C-H str.), 1670 (C=O str.), 1639 (C=N str.), 1565 (N-H str.), 1323 (triazole ring sys. str.), 1252 (C-N str.), 1061 (C-F str.), 835 (para substitution); ¹H NMR (400 MHz, CDCl₃): δ ppm 1.18-1.20 (d, 3H, J=8.0 Hz), 1.25-1.27 (d, 3H, J=8.0 Hz), 3.20-3.26 (m, 1H, isopropyl -CH), 6.61 (s, 1H, chiral carbon), 7.10-7.12 (d, 2H, J=8.0 Hz, ArH), 7.19-7.21 (d, 2H, J=8.0 Hz, ArH) 7.63-7.65 (d, 2H, J=8.0 Hz, ArH), 7.71 (s, 1H, triazole ring), 7.75-7.77 (d, 2H, J=8.0 Hz, ArH), 10.13 (s, 1H, -NH), 10.29 (s, 1H, amide -NH); MS: m/z = 445 [M⁺].
5-Isopropyl-7-(4-nitrophenyl)-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-\[1,2,4\]triazolo[1,5-\(\alpha\)]pyrimidine-6-carboxamide (5j): m.p. 169-171°C; IR (KBr) (cm\(^{-1}\)): 3397, 3081 (-NH amide sym. str.), 3076 (Ar, C-H str.), 1674 (C=O str.), 1641 (C=N str.), 1569 (N-H str.), 1323 (triazole ring sys. str.), 1251 (C-N str.), 1060 (C-F str.), 838 (para substitution); \(^1\)H NMR (400 MHz, CDCl\(_3\)); δ ppm 1.17-1.19 (d, 3H, \(J=8.0\) Hz), 1.23-1.25 (d, 3H, \(J=8.0\) Hz), 3.18-3.25 (m, 1H, isopropyl -CH), 6.59 (s, 1H, chiral carbon), 7.36-7.38 (d, 2H, \(J=8.0\) Hz, ArH), 7.61-7.63 (d, 2H, \(J=8.0\) Hz, ArH), 7.71 (s, 1H, triazole ring), 7.80-7.82 (d, 2H, \(J=8.0\) Hz, ArH), 7.91-7.93 (d, 2H, \(J=8.0\) Hz, ArH), 10.18 (s, 1H, -NH), 10.34 (s, 1H, amide -NH); MS: \(m/z = 472\) [M]+.

STRUCTURE NUMBERING FOR \(^{13}\)C NMR:
5a, 5b and 5c
SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS:

Mass spectrum of compound 5a

Mass spectrum of compound 5b
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IR spectrum of compound 5a

IR spectrum of compound 5b
CHAPTER-2: Section-I

$^1$H NMR spectrum of compound 5a

Expanded spectrum of compound 5a
CHAPTER-2: Section-I

$^1$H NMR spectrum of compound 5b

Expanded spectrum of compound 5b
CHAPTER-2: Section-I

$^{13}$C NMR spectrum of compound 5a

$^{13}$C NMR spectrum of compound 5b
Table No.10: Antimicrobial activity of 5-isopropyl-7-substituted-n-(4-(trifluoro methyl)phenyl)-4,7-dihydro[1,2,4]triazolo[1,5-a] pyrimidine-6-carboxamides: (5a-5j)

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<td>Minimal fungicidal concentration µg/ml</td>
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RESULT AND DISCUSSION:

The structures of all synthesized compounds were confirmed by IR, $^1$H and $^{13}$C-NMR, Mass spectra. IR spectra of the compounds showed characteristic frequencies of triazole ring system, C=O and C=N stretching bands at 1320 cm$^{-1}$, 1630 cm$^{-1}$ and 1580 cm$^{-1}$, respectively. In the $^1$H-NMR spectra, proton of pyrimidine ring bearing chiral carbon was seen as singlet at 6.60-6.65 ppm. The proton of triazole ring was observed as a singlet between 7.60 and 7.75 ppm. The presence of two –NH, one of pyrimidine ring and another of amide linkage were observed at 10.00-10.15 and 10.30-10.40 ppm respectively. In the $^{13}$C-NMR spectra, carbon of (C=O) of amide linkage was observed at 165-166 ppm whereas carbon of (C=N) of triazole ring was observed at 145-150 ppm respectively. The chiral carbon of pyrimidine ring was observed between 58-61 ppm. The protons and carbons belonging to the aromatic ring and phenyl substituents were observed at expected chemical shift and integral values.

Antibacterial activity

The MIC values of 5a-5j and standard drugs against selected microbes are presented in Table 10. Compounds 5d, 5e and 5f (50 µg/ml) showed comparative activity whereas compound 5g (100 µg/ml) showed moderate activity against S. Subtilis with respect to standard drugs Ampicillin, Ciprofloxacin and Norfloxacin. Comparative activity against S. Aureus with respect to standard drugs Ampicillin, Ciprofloxacin and Norfloxacin was showed by compounds 5c and 5f (50 µg/ml) respectively and compounds 5b and 5d (125 µg/ml) showed moderate activity. Comparative resistance against E. Coli with respect to standard drug Ciprofloxacin was shown by compounds 5d, 5e and 5f. Compounds 5h and 5g (100 µg/ml and 125 µg/ml) showed moderate activity against Shigella with respect to standard drug Ampicillin.

Antifungal activity

Compounds 5c and 5h (50 µg/ml) showed prominent and compounds 5e and 5j (125 µg/ml) showed moderate activity against C. Albicans with respect to standard drugs Clotrimazole and Terbenafeine. Compound 5g (50 µg/ml) showed prominent activity against A. Niger with respect to standard drugs Clotrimazole and Terbenafeine, however compounds 5d, 5f and 5i (100 µg/ml) showed comparative activity against A. Niger with respect to standard drugs.

From the results obtained of MIC studies on antimicrobial stains, it can be assumed that newly synthesized compounds showed better activity towards both bacterial as well as fungal strains. The compounds with electron withdrawing groups however showed better results in comparison to those bearing electron donating group substitutions.
CHAPTER-2: Section-I

REFERENCES:


CHAPTER-2: Section-I


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