CHAPTER 5

CONVENIENT METHOD FOR SYNTHESIS OF THIAZOLO [3,2-a] PYRIMIDINE DERIVATIVES

Where R₁ and R₂ = Aryl
5.1 Introduction

Thiazolo[4,5-d]pyrimidine 1 (a guanosine analogue) exhibited \textit{in vivo} activity against a variety of RNA and DNA viruses\textsuperscript{1} and also had antitumor and antimetastatic properties.\textsuperscript{2} The guanine derivative 2 showed potent \textit{in vitro} activity against human cytomegalovirus (HCMV).\textsuperscript{3} Thiazolo[4,5-d]pyrimidine-5,7-dione analogues (such as for example compound 3) have been reported as having anti-inflammatory activities, due to TNF inhibition.\textsuperscript{4} 2-Oxo-3-arylthiazolo[4,5-d]pyrimidine analogues (compound 4) have been synthesized as antagonists of the corticotrophin releasing hormone (CRH) R1 receptor.\textsuperscript{5} 2-Thio-3-aryl-thiazolo[4,5-d] pyrimidine derivatives have been described as having anticancer\textsuperscript{6} (compound 6), anti-inflammatory and Anti -microbial activity\textsuperscript{7} (compound 7). 2-Aminothiazolo[4,5-d]pyrimidines (compound 8) which act as CXCR2 receptor antagonists are also known.\textsuperscript{8} Recently, 2,7-substituted-thiazolo[4,5-d] pyrimidines (compound 5) have been described as ATP-competitive inhibitors of protein kinase \textsuperscript{9}(figure-1).

\begin{figure}
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\includegraphics[width=\textwidth]{figure1.png}
\caption{Thiazolo[4,5-d]pyrimidines}
\end{figure}

Besides their structural resemblance to purines, thiazolo [5,4-d] pyrimidines can also be considered as bioisosteres of a pyrido [3,2-d] pyrimidine skeleton. The term bioisosterism has been introduced by Friedman in the early 50s to describe the phenomenon that structurally related substances show similar or antagonistic biological activities. According to Friedman’s definition, bioisosteres are compounds
which fit the definitions of isosteres and which have a similar type of biological activity, whether through agonist or antagonist actions.\textsuperscript{10} Later on, Thornber proposed a broadening of the term bioisosteres, defining them as subunits or groups or molecules with physicochemical properties of similar biological effects.\textsuperscript{11} In drug design, the purpose of exchanging one bioisostere for another is to enhance the desired biological or physicochemical properties of a compound without making significant changes in chemical structure. Ring equivalent bioisosteres have been used frequently in drug discovery programs.\textsuperscript{12} Very often this strategy led to the synthesis of different heterocyclic core structures, such as phenyl, thiophene, furan and pyridine analogues. Examples of ring isosterism in different therapeutic areas are given in (\textbf{figure-2}).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure-2.png}
\caption{Examples of ring bio-isomerism}
\end{figure}

Biginelli reported the synthesis of functionalized 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) via three-component condensation reaction of an aromatic aldehydes, urea and ethyl acetoacetate (\textbf{Figure-3}). In the past decade, this multicomponent reaction has experienced a remarkable revival, mainly due to the interesting pharmacological properties associated with this dihydropyrimidine scaffold.\textsuperscript{13}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure-3.png}
\caption{Biginelli reaction}
\end{figure}

Biginelli reaction\textsuperscript{14} is not only important to synthesize analogs of DHPM ring using different building block as potent bioactive heterocycles, but diverse fused and non-fused heterocycles can be synthesized by careful applications and various scaffolds derived from DHPMs (\textbf{figure-4}).
As displayed in above figure, it can be understood that a number of new moieties can be generated from DHPM ring\textsuperscript{15}.

### 5.2 Alternative synthetic routes of DHPM

**Intramolecular Heck cyclization of DHPM**

The intramolecular Heck reaction can be observed in DHPM skeleton. The starting material for the intramolecular Heck reaction, DHPM was prepared by selective \( N3 \)-acylation of 4-(\( o \)-bromophenyl)-dihydropyrimidone with acryloyl chloride\textsuperscript{16} (figure-5).

![Figure-5](image)

Applying intramolecular Heck reaction, tricyclic ring system can be obtained as shown below\textsuperscript{17} (figure-6).
Chapter 5  Synthesis of thiazolo[3,2-a]pyrimidine derivatives

The computational experiments reveal that the formation of a tricyclic ring system did not flatten out the overall geometry. On the contrary, the aryl ring was still locked in a pseudoaxial position, resembling other non fused 4-aryl-dihydropyrimidines. In fact, here, the intramolecular Heck strategy allows locking of the aryl ring in the proposed bioactive, that is, the pseudoaxial, orientation.

Jiirgen Wichmann et al. A series of 5H-thiazolo[3, 2-a]pyrimidine derivatives 1 was studied with respect to the inhibition of I S,3R-ACPD (10−tM)-stimulated GTP y35S binding on rat mGlu2 receptor transfected cell membranes. The influence of substituents at position 6 and 7 as well as the substitution pattern of the two phenyl-rings in position 2 and 5 on the activity is discussed.

N3-Arylation of DHPMs

N3-arylated DHPM analogues cannot be obtained by classical Biginelli condensation strategies involving N-arylureas. Here, the corresponding N1-substituted derivative will be formed exclusively.

Department of Chemistry, Saurashtra University, Rajkot-360005 188
Krzysztof Danel\textsuperscript{24} reported protocol appropriately substituted 2,3-dihydro-7\(H\)-thiazolo[3,2-\(a\)]pyrimidin-7-ones 9-12 and 18 were considered as annulated analogues of HEPT (1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)- thymine), and some of these compounds were also found active against HIV-1, the most active one being 2,3-dihydro-5-[(3,5-dimethylphenyl)methyl]-3-ethoxy-6-ethyl-7\(H\)-thiazolo[3,2-\(a\)]pyrimidin-7-one (10b). S-Alkylation of 5-alkyl-6-(arylmethyl)-2-thiouracils 1-4 was performed with 2-bromoacetaldehyde acetals to furnish the S-[bis(alkoxy)ethyl] derivatives 5-8 and with allyl bromide to furnish S-allyl derivatives 17. The target compounds 9-12 were obtained by an \(N_1\) regioselective intramolecular cyclization reaction of silylated 5-8 using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as the catalyst. Treatment of the S-allyl derivatives 17 with bromine in dry methylene chloride afforded the 3-(bromomethyl) derivatives 18 (\textbf{figure-9}).

![Figure-9](image)

\section*{Bicyclic systems derived from DHPMs}

Many bicyclic systems can be synthesized from DHPM scaffold. Pyrazolo[4,3-\(d\)]pyrimidine derivatives synthesized by reacting sodium azide with \(N\)-Me, 6-Br-Me DHPM. The possible mechanism of this transformation is shown in below and involves decomposition of the diazide to vinyl diazo derivative, which undergoes spontaneous 1,5-electrocyclization to 3\(H\)-pyrazole. Subsequent migration of the ester substituent from the tetrahedral carbon to N2 (thermal van Alphen-Hüttel rearrangement) yields pyrazolo[4,3-\(d\)]pyrimidine. The structure confirming the position of the ester group at N2 was established by an X-ray analysis.

Use of the 4-chloroacetoacetate building block in a Biginelli-type condensation is very useful to get variety of bicyclic systems. The resulting functionalized DHPM appeared to be an ideal common chemical template for the generation of a variety of interesting bicyclic scaffolds such as (\textbf{Figure-10,11}) furo[3,4-\(d\)]pyrimidines, pyrrolo[3,4-\(d\)]pyrimidines, and pyrimido[4,5-\(d\)]pyridazines.
Solid-phase and solution-phase protocols for the synthesis of furo[3,4-$d$]pyrimidines, pyrrolo[3,4-$d$]-pyrimidines, and pyrimido[4,5-$d$]pyridazines are reported. The multistep solid-phase sequence involves the initial high-speed, microwave-promoted acetoacetylation of hydroxymethyl polystyrene resin with methyl 4-chloroacetoacetate. The immobilized 4-chloroacetoacetate precursor was subsequently subjected to three component Biginelli-type condensations employing urea and a variety of aromatic aldehydes. The resulting 6-chloromethyl-functionalized resin-bound dihydropyrimidones served as common chemical platforms for the generation of the desired heterobicyclic scaffolds using three different traceless cyclative cleavage strategies. The corresponding furo[3,4-$d$]pyrimidines were
obtained by microwave flash heating in a rapid, thermally triggered, cyclative release. Treatment of the chloromethyl dihydropyrimidone intermediates with a variety of primary amines followed by high-temperature microwave heating furnished the anticipated pyrrolo[3,4-\textit{d}]pyrimidine scaffolds via nucleophilic cyclative cleavage. In a similar way, reaction with monosubstituted hydrazines resulted in the formation of pyrimido[4,5-\textit{d}]pyridazines. All compounds (Figure-12) were obtained in moderate to good overall yields and purities.

![Chemical Structures](image)

**Figure-12**

Preparation of thiazolo[3,2-\textit{a}]pyrimidine derivatives was very well reported in literature. Two approaches are generally employed for synthesis.

- **Azole approach:**

  Various methods for (figure-13) synthesis of thiazolo [3,2-\textit{a}]pyrimidine derivatives using thiazole as starting material.
Literature survey on synthetic methodology for thiazolo[3,2-α]pyrimidine derivatives can be summarized in chart 1 & 2 where various methods are illustrated for synthesis of this class of compounds. Thiazolo[3,2-α]pyrimidine 2 was prepared in 30% yield by the reaction of 2-aminothiazole 1 with ethyl cyanoacetate in a sodium ethoxide/ethanol mixture or using polyphosphoric acid or acetic acid. However, oxothiazolopyrimidine 3 was obtained upon treatment with phosphorous pentoxide and methanesulfonic acid.
The reaction of 1 with ethyl acetoacetate at 140-150°C resulted in the formation of compound that was then converted to the Z-isomer upon heating at 250°C, and cyclized to give 4. 2-Aminothiazole 5 cyclized with acetyl acetone at 100°C, in the presence of methane sulfonic acid-phosphorus pentoxide or formic acid-phosphorus pentoxide, followed by treatment with 70% perchloric acid, to give the thiazolopyrimidin-4-ium salt 5. The ester 6 was obtained from 2-aminothiazole 1 with an excess of methyl methane tricarboxylate in 61% yield. Cyclocondensation of 1 with diethyl ethoxymethylene malonate in acetic acid followed by hydrolysis of the ester gave 7. Similarly, 2-aminothiazole 1 reacted with benzylidene in ethanol to give 8. Stanovink et al.25-37 131-171 reported the synthesis of a series of thiazolopyrimidine derivatives upon reacting 2-aminothiazole with a variety of different reagents. Thus, dimethylaminobut-2-enoate (or pentenoate), reacted with 1 to give thiazolo pyrimidines 23.25-37

The reaction of 2-aminothiazole 1 with 2-hydropolyfluoroalk-2-enoate in basic medium gave two isomers, 7-oxo 2 and its isomeric 5-oxo 3 (figure-14). The structure of both 2 and 3 was established through 1H NMR, 13C NMR and mass spectra.38 2-Aminothiazole derivatives, (R’ = -H, -CO2Et; R2 = Ph, aryl, -Me), reacted with the acetylenic derivative and ester derivative in ethanol and polyphosphoric acid, respectively, to give the isomeric oxothiazolopyrimidine derivatives 4 and 5, in 5-32% and 8-97% yield, respectively.39 Condensation of 2-aminothiazole 1 in absolute ethanol with the sodium salt of ethyl oximinocyanooacetate gave after acidification (pH 6) with diluted hydrochloric acid, the nitroso derivative 6 in 92% yield.40 Treatment of the 2-aminothiazaole derivatives 5 with the hydrazone derivatives gave the oxothiazolo [3,2-α] pyrimidine derivatives 7.41
Reported synthetic approaches

2-Amino-2-thiazoline reacted with 2-acylamino-3-dimethylamino-propenoates in acetic acid to yield 6-acylamino-5-oxo-2,3-dihydro-5-thiazolo[3,2-α]pyrimidines in 73 and 12% yields, respectively\(^\text{42}\) (figure-15).

Moreover, 2-amino-2-thiazoline reacted with an aromatic aldehyde and diethyl malonate, to give (figure-16) a mixture of thiazolidino [3,2-α] pyrimidines. Furthermore, malononitrile reacted to give following product.\(^\text{43-44}\)
2-Amino-2-thiazoline reacted with potassium 2-ethoxycarbonyl-2-fluorovinyl alcolholate in a sodium methoxide/methanol mixture to give 6-fluoro-2,3-dihydro-5-oxothiazolo[3,2-a]pyrimidine.\(^{45}\) (Figure-17)

2-(Methylthio)-2-thiazoline reacted with 3-alanine to give a 5-oxothiazolo[3, 2-a]-pyrimidine (Figure-18) derivative in 23% yield.\(^{46}\)

Pyrimidinethione derivatives were alkylated with monochloroacetic acid or chloroacetyl chloride and then cyclized to give thiazopyrimidine derivatives.\(^{47-61}\) Thus, pyrimidinethione reacted in DMF\(^{47}\) or in an acetic anhydride/pyridine mixture\(^{51}\) to give thiazolo-pyrimidines (figure-19). Alkylation in the presence of an aromatic aldehyde gave the yield. Similarly, pyrimidinethione derivatives reacted with monochloroacetic acid\(^{52-54}\) in acetic acid/acetic anhydride/sodium acetate mixture or with chloroacetyl chloride in dry dioxane to give the corresponding thiazolopyrimidines.
Azine approach

Dihydropyrimidines are well-known calcium channel blockers. According to the literature analogous derivatives are anti-inflammatory agents. Thus Bo’szing and co-workers\textsuperscript{63} decided to synthesize the pyrimidothiazines and assay these compounds for the same profile. Acute anti-inflammatory activity was tested by inhibition of the carrageenan-induced paw edema in rats\textsuperscript{62} (Figure 20).

Adam et al.\textsuperscript{63} filed US patent for phenyl substituted thiazolo pyrimidine derivatives synthesized from DHPM (figure- 21). These compounds and their salts are novel and are distinguished by valuable therapeutic properties. Specifically it has been found that the compound of Markus structure given below was metabotropic glutamate receptor antagonists. These compounds are capable of high affinity binding to group II mGluR receptors.
Compounds displayed by general formulae given below exhibit excellent adenosine A$_3$ receptor antagonism (figure-22) where A is an optionally substituted benzene ring. B may be substituted and R$_1$ is optionally substituted cyclic group.$^{64}$

![Figure-22](image)

Amr, A. E. et al.$^{65}$ described the analgesic and antiparkinsonian activity of some thiazolo pyrimidine derivatives as shown below (figure-23). Out of them compound of type III are potent antiparkinsonian agents.

![Figure-23](image)

Matthieu Montes et al.$^{66}$ reported thiazolopyrimidine structure based compound (Figure-24) as CDC25 phosphatases inhibitor. CDC25 phosphatases play critical roles in cell cycle regulation and are attractive targets for anticancer therapies. Several small non-peptide molecules are known to inhibit CDC25, but many of them appear to form a covalent bond with the enzyme or act through oxidation of the thiolate group of the catalytic cysteine.

![Figure-24](image)
K. Gewald et al.\textsuperscript{67} Thiazolo[5,4-d]pyrimidine-1-N-oxides, prepared from 6-chloro-1,3-dimethyl-5-nitropyrimidinone by reaction with mercapto compounds (HSCH\textsubscript{2}R), followed by base catalyzed dehydrative cyclization, can be easily deoxygenated to yield thiazolopyrimidines (figure-25). Reductive deoxygenation by treatment of the thiazolopyrimidine oxides with sodium dithionite or oxidative deoxygenation with dimethylformamide at reflux temperature can generate the desired thiazolo-pyrimidines.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure25.png}
\caption{Figure-25}
\end{figure}

L. D. S. Yadav et al.\textsuperscript{68} demonstrated one-pot reactions of glycine, acetic anhydride and thiazole Schiff bases (2a–f) diastereoselectively and expeditiously annulated a pyrimidine ring on the thiazole nucleus to yield 6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin-5-ones (4a–f) under microwave irradiation and solvent-free conditions (figure-26).

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure26.png}
\caption{Figure-26}
\end{figure}

Fatmah A. M Al-Omary et al.\textsuperscript{69} developed a novel series of thiazolo[2,3-b]quinazoline (14-23, 26 and 27), and pyrido[4,3-d]thiazolo[3,2-a] pyrimidine (34-43, 45 and 46) analogues. The obtained compounds were evaluated for their in-vitro antitumor activity at the National Cancer Institute (NCI) 60 cell lines panel assay. Among them, four compounds showed remarkable broad-spectrum antitumor activity. Two Compounds 22 and 38 were almost nine fold more active than 5-FU, with GI50,
TGI, and LC<sub>50</sub> values of 2.5, >100, >100; and 2.4, 9.1, 36.2 mM, respectively (figure-27).

**Figure-27**
5.3 Biological activity associated with various substituted thiazolo[3,2-α]pyrimidine derivatives.

Kappe et al.\textsuperscript{70} reported that $N_3$-acylated DHPMs can be rapidly synthesized in a high throughput fashion by combining microwave-assisted acylations with microwave-assisted scavenging techniques. Scavenging experiments can be carried out employing either supported nucleophilic amine sequestration reagents or water.\textsuperscript{70} $N$-acylated DHPMs are pharmacologically very important scaffolds as most of bioactive DHPMs are $N$-acylated. $N$-acylation of DHPM can be performed (figure-28) as shown below.

$N_3$-Substituted DHPMs (Figure-29) have been identified to possess potent pharmacological profiles. Following compound exhibited high binding affinity and subtype selectivity for the cloned human R1a receptor.\textsuperscript{71} Systematic modifications of above compounds led to identification of highly potent and subtype-selective compounds with high binding affinity ($K_i$ 0.2 nM) for R1a receptor and greater than 1500-fold selectivity over R1b and R1d adrenoceptors. The compounds were found to be functional antagonists in human, rat, and dog prostate tissues (figure-30, 31).
Modifications to the C5 position also play important role in potency of DHPM ring. 4-aryldihydropyrimidinones attached to an aminopropyl-4-arylpiperidine via a C-5 amide as selective R1A receptor subtype antagonists. In receptor binding assays, these types of compounds generally display $K_i$ values for the R1a receptor subtype $<1$ nM while being greater than 100-fold selective versus the R1b and R1d receptor subtypes (Figure 32). Many of these compounds were also evaluated in vivo and found to be more potent than terazosin in both a rat model of prostate tone and a dog model of intra-urethral pressure without significantly affecting blood pressure.\(^7^2\)

Mithun Ashok et al.\(^7^3\) have reported a new series of new 2-(arylidine)-5-(4-methylthiophenyl)-6-carboethoxy-7-methyl-5$H$-thiazolo[3,2-$a$]pyrimidine-3(1$H$)-ones. The newly synthesized compounds (Figure-33) were screened for their antibacterial and antifungal activities and have exhibited moderate to excellent growth inhibition of bacteria and fungi.
Hui Zhi et al. have developed a novel AchE inhibitors. A docking screening model of AchE inhibitor was used to evaluate a series of 5H-thiazolo[3,2-a]pyrimidine derivatives (Figure-34). The virtual screening hits were analyzed in drug likeness and physic chemical features. Therefore were focused to those compounds. To investigate the relationship between the bioactivities and the structure, 10 target compounds with the 5H-thiazolo[3,2-a]pyrimidine scaffold were synthesized as potential AchE inhibitors.

![Figure-34](image-url)
5.4 Current research work

The $-2H$-thiazolo[3,2-$a$]pyrimidine derivatives have considerable chemical and pharmacological importance because of a broad range of biological activities displayed by these classes of molecules. As we demonstrated, the tremendous biological potential of substituted pyrimidine derivatives encouraged us to synthesize some new highly functionalized substituted $-2H$-thiazolo[3,2-$a$]pyrimidine derivatives. A series of $5H$-thiazolo[3,2-$a$]pyrimidine derivatives 1 was studied with respect to the inhibition of I S,3R--ACPD (10⁻¹M)-stimulated GTP γ35S binding on rat mGlu2 receptor transfected cell membranes. Various methodologies have been described for the synthesis of substituted pyrimidine derivatives. However, the existing methods are suffer with some drawbacks, such as; yield, time, product isolation, purification,
5.5 Results and discussion

<table>
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<td><strong>Scheme-03</strong></td>
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Where R = Ar-Cl, Ar-Br, Ar-F, Ar-Cl, Ar-OMe, Ar-Me,

In order to optimize the reaction conditions, \( \text{N,4-bis(4-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-2-thioxopyrimidine-5-carboxamide} \) \( 6a \) was used as the precursor for the synthesis of \( \text{N,5-bis(4-fluorophenyl)-3,5-dihydro-7-isopropyl-2H-thiazolo[3,2-α]pyrimidine -6-carboxamide} \) \( 8a \). Initially we examined the reaction of \( \text{K}_2\text{CO}_3/\text{TEA} (0.12 \text{ mmol}), \text{TBAB}/\text{TEAB} (0.12 \text{ mmol}) \) with \( 6a \) (0.1 mmol). This potassium salt of THPM precursor by reacting with dibromoethane afforded desired compounds. In order to find suitable reaction conditions, various solvents (10-15 mL) were investigated (Table 1). Complete consumption of the bromine was indicated by the disappearance of the yellow-brown color from the reaction mixture, which takes about 5-10 minutes depending upon the solvent used. Only in the case of DMF (Table 2) warming up of the reaction to 40°C for at least 45 minutes was necessary to assure the complete consumption of bromine.

The reaction performance under different solvent conditions at room temperature has been monitored by TLC analysis. It was found that in all other
solvents the reactions were not completed within this time. Additionally it was observed that prolonged reaction time at room temperature did not yield the desired cyclized thiazolo pyrimidine 8a. The reaction temperature was therefore elevated. It was observed that open chain intermediate 6a gets converted into the desired thiazolo pyrimidine 8a at 80°C. The progress of the reaction was monitored by TLC After heating the reactions for 2 hours the best yields were obtained in case of DCE (83%), THF (81%), DMF (82%) and iPr-OH (76%), t-BuOH, Toluene. In the case of chloroform, where the first step yield was quantitative, the conversion to 8a was incomplete. From all experiments 1,2-Dichlormethane (DCM) was chosen as the optimal reaction solvent. Compounds were purified by acid-base treatment.

**Brief Spectral Analysis Discussion Compound VBA 8a.**

The structure of compound VBA 8a was established on the basis of their elemental analysis and spectral data (MS, IR, and ¹H NMR). The analytical data for VBA 8a revealed a molecular formula C₂₂H₂₁F₂N₃OS (m/z 413). The ¹H NMR spectrum revealed a singlet at δ_H = 1.24 ppm assigned to 6 protons of (i-prCH₃), a singlet at δ_H = 2.28 ppm assigned to 6 protons of (i-prCH₃), a singlet at δ_H = 3.24-3.26 ppm assigned to 2 protons of (-CH₂), a singlet at δ_H = 3.78-3.85 ppm assigned to 2 protons of (-CH₂), a singlet at δ_H = 5.16 ppm assigned to 1 proton of (-ArH-) group of asymmetric proton, one singlet at δ_H = 7.02-7.06 ppm assigned to 4 proton of (-Ar-H) group, one triplet at δ_H = 7.22-7.25 ppm assigned to protons of Ar-H (2H), one triplet at δ_H = 7.60-7.63 ppm assigned to protons of Ar-H (2H), one singlet at δ_H = 10.17 ppm assigned to -ArCONH groups.
Table 1: Synthesis of Novel highly substituted pyrimidine using various a ketene dithioacetal.

<table>
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<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Yield %</th>
<th>Time h.</th>
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<td>4-FC₆H₄</td>
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<td>VBA-8b</td>
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<td>6-8</td>
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<tr>
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<td>4-6</td>
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</table>
Chapter 5                                                                  Synthesis of thiazolo[3,2-a]pyrimidine derivatives

Figure: 35 Proposed mechanism for the formation of substituted 2H-thiazolo[3,2-a] pyrimidine.
5.6 Conclusion

In summary, we have developed a convenient and selective method for the synthesis of $2H$-thiazolo[3,2-$a$]pyrimidine derivatives by exploiting the reaction of formed dibromoethane with 1,2,3,4-tetrahydro-6-isopropyl-2-thioxopyrimidine of type 1. The possibility of introducing a variety of substituents at different positions of the $2H$-thiazolo[3,2-$a$]pyrimidine ring system was achieved by this method. The present method delivers new screening candidates in an easy way and is well suited for robotic synthesis. The achievable $2H$-thiazolo[3,2-$a$]pyrimidine derivatives may help in the understanding of the privileged nature of the DHPM core. The present methodology gives various functionalized thiazolopyrimidine for biological interest.
5.7 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 SHIMADZU FTIR-8400 spectrophotometer using DRS prob. $^{1}H$ (400 MHz) and $^{13}C$(100 MHz) NMR spectra were recorded on a BRUKER AVANCE II spectrometer in CDCl$_3$ and DMSO respectively. $^{13}C$ NMR were recorded on 100 MHz spectrometer, referred to the internal solvent signals (77.0 for CDCl$_3$ or 40.0 for DMSO-d$_6$). Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a SHIMADZU GCMS-QP 2010 mass spectrometer. Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected. The chemicals used in this work were purchased from Merck and Spectrochem Chemical Companies. All chemicals were reagent grade and used without further purification, and all solvents were freshly distilled before use.

- **General process for the synthesis of 4-methyl-3-oxo-$N$-arylpentanamide 2a-t.**
  A mixture containing the primary amine (10 mmol), methyl isobutyrylacetate (10 mmol), and catalytic amount of sodium or potassium hydroxide (10 %) was reflux at 110°C for the approximately 15-20 h. The progress of reaction was monitored by TLC. After completion of reaction, the solvent was removed under vacuum when the reaction was completed. The solid or oil was crystallized from methanol to give pure.

- **General process for the synthesis of substituted $N$-(Aryl)-4-(4-Aryl)-1,2,3,4-tetrahydro-6-isopropyl-2-thioxopyrimidine-5-carboxamide VBA-6a-g.**
  To a solution of substituted benzaldehyde (1 mmol), 4-methyl-3-oxo-$N$-arylpentanamide (1 mmol), thiourea (1.4 mmol) were added to MeOH (10 mL) sequentially at room temperature. After the addition of HCl/etidronic acid (1.0 mmol), the mixture was stirred for 1 h at ambient temperature. Then reflux reaction mixture at 70-80°C temp. The progress of reaction was monitored by TLC. The crude product was collected by filtration and washed with hexane to give 0.55 g (91%) of THPM (8a-o) as brown solid.
General procedure for the synthesis of substituted \( \text{N-(Aryl)-4-(4-Aryl)-1,2,3,4-tetrahydro-6-isopropyl-2-thioxopyrimidine-5-carboxamide VBA-8a-o.} \)

To a solution of the thioxopyrimidine (6a-g) (1 mmol, 1 equiv.) in 2 ml of 1,2-dibromoethane (7) (1.5 mmol, 1.5 equiv.) and \((\text{K}_2\text{CO}_3)\) (1 mmol, 1 equiv.), TBAB/TEAB (1 mmol, 1 equiv.), were dissolved in DMF added slowly at ambient temperature. The resulted wine red solution was subjected to shaking until the disappearance of the color. The reaction mixture was heated to \(80^\circ\text{C}\) for 2 hours. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was treated with aqueous solution of saturated \(\text{NaHCO}_3\) followed by extraction with 10 ml ethyl acetate/water (1:1) mixture. The organic extracts were dried over anhydrous \(\text{Na}_2\text{SO}_4\). After filtration the solvent was evaporated under reduced pressure and the crude product washed with (10/90, E.A/H mixtures) to obtain pure product \(\text{VBA 8a-o.}\)
Spectral data of the synthesized thiazolo[3,2-\(\alpha\)]pyrimidine compounds VBA-8a-o.

N,5-bis(4-fluorophenyl)-3,5-dihydro-7-isopropyl-2\(H\)-thiazolo[3,2-\(\alpha\)]pyrimidine-6-carboxamide (VBA-8a): Light brown solid; \(R_f\) 0.65 (7:3 H-E.A); mp 241-243°C; IR (KBr): 3439, 3200, 3144, 3047, 2982, 2929, 2874, 1678, 1645, 1614, 1552, 1535, 1506, 1450, 1410, 1334, 1301, 1220, 1159, 1101, 1047, 1012, 962, 835, 788, 704, cm\(^{-1}\); \(^1\)H NMR: (400 MHz, DMSO): \(\delta_H\) 1.24 (s, 6H, 2 \(\times\) iprCH\(_3\)), 2.28 (m, 1H, -iprCH), 3.24-3.26 (m, 2H, -CH\(_2\)), 3.78-3.85 (m, 2H, -CH\(_2\)), 5.16 (s, 1H, -ArCH), 7.02-7.06 (s, 4H, ArH), 7.22-7.25 (t, 2H, ArH), 7.60-7.63 (t, 2H, ArH), 10.17 (s, 1H, -ArCONH); \(^13\)C NMR: (100 MHz, DMSO) \(\delta_C\) 13.83, 18.85, 20.09, 22.10, 26.28, 28.73, 29.06, 31.31, 45.45, 53.01, 61.45, 114.13, 114.34, 114.76, 114.98, 121.12, 121.19, 127.96, 128.04, 134.97, 165.49; MS \(m/z\): 413.48(M\(^+\)); Anal. Calcd. For C\(_{22}\)H\(_{21}\)F\(_2\)N\(_3\)O\(_3\): C, 63.90; H, 5.12; N, 10.16%. Found: C, 63.78; H, 5.02; N, 10.27%.

N-(4-chlorophenyl)-3,5-dihydro-7-isopropyl-5-(3,4-dimethoxyphenyl)-2\(H\)-thiazolo[3,2-\(\alpha\)]pyrimidine-6-carboxamide (VBA-8b): Light brown solid; \(R_f\) 0.62 (7:3 H-E.A); mp 255-257°C; IR (KBr): 3460, 3107, 3034, 2924, 2852, 1672, 1606, 1548, 1516, 1498, 1462, 1392, 1257, 1211, 1145, 1026, 877, 815, 767, 740, cm\(^{-1}\); \(^1\)H NMR: (400 MHz, DMSO): \(\delta_H\) 1.45 (s, 6H, 2 \(\times\) -iprCH\(_3\)), 2.52 (m, 1H, -iprCH), 3.26 (s, 2H, -CH\(_2\)), 3.80 (s, 2H, -CH\(_2\)), 5.29(s, 1H, -ArCH), 6.70-6.89 (m, 4H, ArH), 7.02 (s, 1H, ArH), 7.38-7.42 (s, 1H, ArH), 7.95 (s, 1H, ArH), 10.63 (s, 1H, -ArCONH); \(^13\)C NMR: (100MHz, DMSO) \(\delta_C\) 19.24, 20.39, 29.02, 55.39, 55.57, 110.12, 110.69, 116.57, 118.38, 119.62, 121.18, 124.27, 127.48, 148.35, 159.58; MS \(m/z\): 472(M\(^+\)); Anal. Calcd. for C\(_{24}\)H\(_{26}\)ClN\(_3\)O\(_3\): C, 63.07; H, 5.55; N, 8.90%. Found: C, 61.28; H, 5.35; N, 8.82%.

N-(4-bromophenyl)-3,5-dihydro-7-isopropyl-5-(3,4-dimethoxyphenyl)-2\(H\)-thiazolo[3,2-\(\alpha\)]pyrimidine-6-carboxamide (VBA-8c): Light brown solid; \(R_f\) 0.62 (7:3 H-E.A); mp 246-248°C; IR (KBr): 3446, 3054, 2978, 2839, 1606, 1546, 1516, 1494, 1472, 1392, 815, 725, 538, cm\(^{-1}\); MS \(m/z\): 516.45(M\(^+\)); Anal. Calcd. for C\(_{24}\)H\(_{26}\)BrN\(_3\)O\(_3\): C, 55.81; H, 5.07; N, 8.14%. Found: C, 55.27; H, 4.99; N, 8.07%.

N-(4-bromophenyl)-3,5-dihydro-7-isopropyl-5-(2,5-dimethoxyphenyl)-2\(H\)-thiazolo[3,2-\(\alpha\)]pyrimidine-6-carboxamide (VBA-8d): Light brown solid; \(R_f\) 0.62
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(7:3 H-E.A); mp 250-252°C; IR (KBr): 3462, 3067, 2963, 2812, 1606, 1546, 1516, 1499, 1472, 1389, 817, 716, 528, cm\(^{-1}\); MS m/z: 516.45(M\(^{+}\)); Anal. Calcd. for C\(_{24}\)H\(_{26}\)BrN\(_3\)O\(_3\)S: C, 55.81; H, 5.07; N, 8.14%. Found: C, 55.26; H, 5.14; N, 8.77%.

\(N\)-(4-bromophenyl)-3,5-dihydro-5-(4-hydroxyphenyl)-7-isopropyl-2\(H\)-thiazolo[3,2-\(a\)]pyrimidine-6-carboxamide (VBA-8e): Light brown solid; \(R_f\) 0.58 (7:3 H-E.A); mp 255-257°C; IR (KBr): 3457, 3062, 2957, 2838, 1606, 1546, 1518, 1502, 1472, 1393, 817,709, 535, cm\(^{-1}\); MS m/z: 472.4(M\(^{+}\)); Anal. Calcd. for C\(_{22}\)H\(_{22}\)BrN\(_3\)O\(_2\)S: C, 55.93; H, 4.69; N, 8.90%. Found: C, 55.78; H, 4.58; N, 8.37%.

\(N\)-(4-bromophenyl)-3,5-dihydro-7-isopropyl-5-(3-nitrophenyl)-2\(H\)-thiazolo[3,2-\(a\)]pyrimidine-6-carboxamide (VBA-8f): Yellow solid; \(R_f\) 0.62 (7:3 H-E.A); mp 262-264°C; IR (KBr): 3446, 3075, 2946, 2852, 1618, 1595, 1546, 1518, 1506, 1472, 1399, 835, 804, 729, 514, cm\(^{-1}\); MS m/z: 501.4(M\(^{+}\)); Anal. Calcd. for C\(_{22}\)H\(_{21}\)BrN\(_4\)O\(_3\)S: C, 52.70; H, 4.22; N, 11.17%. Found: C, 52.49; H, 4.87; N, 11.47%.

\(N\)-(3-chloro-4-fluorophenyl)-3,5-dihydro-7-isopropyl-5-(3,4-dimethoxyphenyl)-2\(H\)-thiazolo[3,2-\(a\)]pyrimidine-6-carboxamide (VBA-8h): Light brown solid; \(R_f\) 0.60 (7:3 H-E.A); mp 248-250°C; IR (KBr): 3455, 3069, 2953, 2841, 1609, 1548, 1515,1503, 1467, 1384, 847, 719, 503, cm\(^{-1}\); MS m/z: 490.84(M\(^{+}\)); Anal. Calcd. for C\(_{22}\)H\(_{21}\)BrClN\(_3\)OS C, 53.83; H, 4.31; N, 8.56%. Found: C, 53.16; H, 4.75; N, 8.17%.

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152.09, 154.52, 162.48, 168.80: MS $m/z$: 489.99(M$^+$); Anal. Calcd. for C$_{24}$H$_{25}$ClFN$_3$O$_3$S: C, 58.83; H, 5.14; N, 8.58%. Found: C, 58.97; H, 5.75; N, 8.47%.

5-(4-fluorophenyl)-3,5-dihydro-7-isopropyl-N-p-tolyl-2H-thiazolo[3,2-a]pyrimidine-6-carboxamide (VBA-8i): Light brown solid; $R_f$ 0.58 (7:3 H-E.A); mp 268-270°C; IR (KBr): 3428, 3048, 2927, 2849, 1654, 1541, 1509, 1435, 1254, 862, 705, cm$^{-1}$; MS $m/z$: 409.52(M$^+$); Anal. Calcd. for C$_{23}$H$_{24}$FN$_3$OS: C, 67.46; H, 5.91; N, 10.26%. Found: C, 67.87; H, 5.58; N, 10.07%.

5-(3-bromophenyl)-3,5-dihydro-7-isopropyl-N-p-tolyl-2H-thiazolo[3,2-a]pyrimidine-6-carboxamide (VBA-8j): Yellow solid; $R_f$ 0.58 (7:3 H-E.A); mp 247-249°C; IR (KBr): 3435, 3039, 2947, 2838, 1663, 1547, 1443, 1259, 857, 735, 540, cm$^{-1}$; MS $m/z$: 470.43(M$^+$); Anal. Calcd. for C$_{23}$H$_{24}$BrN$_3$OS: C, 58.72; H, 5.14; N, 8.93%. Found: C, 58.58; H, 5.25; N, 8.72%.

5-(4-chlorophenyl)-3,5-dihydro-7-isopropyl-N-p-tolyl-2H-thiazolo[3,2-a]pyrimidine-6-carboxamide (VBA-8k): Light brown solid; $R_f$ 0.58 (7:3 H-E.A); mp 237-239°C; IR (KBr): 3414, 3029, 2956, 2823, 1659, 1552, 1519, 1452, 1262, 838, 718, cm$^{-1}$; MS $m/z$: 425.97(M$^+$); Anal. Calcd. for C$_{23}$H$_{24}$ClN$_3$OS: C, 64.85; H, 5.68; N, 9.86%. Found: C, 64.97; H, 5.39; N, 9.02%.

5-(4-chlorophenyl)-3,5-dihydro-7-isopropyl-N-(4-methoxyphenyl)-2H-thiazolo[3,2-a]pyrimidine-6-carboxamide (VBA-8l): Light brown solid; $R_f$ 0.60 (7:3 H-E.A); mp 255-257°C; IR (KBr): 3510, 3045, 2927, 2848, 1645, 1557, 1508, 1447, 1264, 1104, 878, 756, cm$^{-1}$; MS $m/z$: 441.97(M$^+$); Anal. Calcd. for C$_{25}$H$_{29}$N$_3$O$_4$S: C, 64.22; H, 6.25; N, 8.99%. Found: C, 64.28; H, 5.76; N, 9.23%.

3,5-dihydro-7-isopropyl-5-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-2H-thiazolo[3,2-a]pyrimidine-6-carboxamide (VBA-8m): Light brown solid; $R_f$ 0.64 (7:3 H-E.A); mp 255-257°C; IR (KBr): 3485, 3032, 2957, 2848, 1645, 1557, 1508, 1447, 1264, 1104, 878, 756, cm$^{-1}$; MS $m/z$: 467.58(M$^+$); Anal. Calcd. for C$_{25}$H$_{29}$N$_3$O$_4$S: C, 64.22; H, 6.25; N, 8.99%. Found: C, 64.65; H, 6.07; N, 8.45%.

3,5-dihydro-7-isopropyl-5-(3,4-dimethoxyphenyl)-N-p-tolyl-2H-thiazolo[3,2-a]pyrimidine-6-carboxamide (VBA-8n): Light brown solid; $R_f$ 0.66 (7:3 H-E.A); mp 255-257°C; IR (KBr): 3485, 3354, 3073, 2968, 2875, 1645, 1542, 1516, 1457, 1218,
1115, 863, 738, cm$^{-1}$; MS $m/z$: 451.58(M$^+$); Anal. Calcd. for C$_{25}$H$_{29}$N$_3$O$_3$S: C, 66.49; H, 6.47; N, 9.31%. Found: C, 66.58; H, 6.23; N, 9.62%.

$N$-(3-chloro-4-fluorophenyl)-5-(4-chlorophenyl)-3,5-dihydro-7-isopropyl-2$H$-thiazolo[3,2-$a$]pyrimidine-6-carboxamide (VBA-8o): Light brown solid; $R_f$ 0.58 (7:3 H-E.A); mp 262-264°C; IR (KBr): 3494, 3342, 3078, 2974, 2867, 1645, 1542, 1522, 1459, 1205, 1138, 854, 715, cm$^{-1}$; MS $m/z$: 456.32(M$^+$); Anal. Calcd. for C$_{22}$H$_{12}$Cl$_2$FNO$_3$S: C, 57.91; H, 2.65; N, 9.21%. Found: C, 57.09; H, 2.73; N, 9.37%.
5.8 Spectral data of the synthesized compounds VBA 8 a-o

$^1$H NMR spectrum of VBA-8a

![1H NMR spectrum of VBA-8a](image)

$^{13}$C NMR spectrum of VBA- 8a

![$^{13}$C NMR spectrum of VBA- 8a](image)
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DEPT$^{13}$C NMR spectrum of VBA 8a

\[ \text{\text{\emph{Formula Image}}}_1 \]

$^1$H NMR spectrum of VBA- 8b

\[ \text{\text{\emph{Formula Image}}}_2 \]

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$^{13}$C NMR spectrum of VBA- 8b

DEPT$^{13}$C NMR spectrum of VBA- 8b
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$^1\text{H NMR spectrum of VBA- 8h}$

$^{13}\text{C NMR spectrum of VBA- 8h}$
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DEPT$^{13}$C NMR spectrum of VBA- 8h

![DEPT$^{13}$C NMR spectrum of VBA- 8h](image)

Mass spectrum of VBA- 8a

![Mass spectrum of VBA- 8a](image)
Mass spectrum of VBA- 8b

Mass spectrum of VBA- 8h
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Mass spectrum of VBA- 8l

IR spectrum of VBA 8a
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IR spectrum of VBA 8b

IR spectrum of VBA 8h
Chemical Purity of VBA 8a

UPLC:
Column: Water Acquility C18 (100 X 2.1 mm)
Injection volume: 1 µL,
Mobile phase: 0.05% TFA in H2O: ACN (30:70) premix;
Diluent: Methanol
Column Temp-30°C;
Flow-0.2mL/min.
Wave length: 254
HPLC Mode: Gradient
5.9 References:


2. R. K. Robins; H. B. Cottam, WO89005649


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