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# DESIGN, SYNTHESIS, STRUCTURAL ELUCIDATION AND ANTIMICROBIAL SCREENING OF NOVEL 1, 5-BENZOTHIAZEPINES CONTAINING THIENO [2, 3-*D*] PYRIMIDINE NUCLEUS

**Virupakshi Prabhakar[*1], Kondra Sudhakar Babu[2], L.K. Ravindranath[2], J.Latha[3], B.Venkateswarlu[4]**

[*1]*Faculty of Engineering Chemistry, SVR ENGINEERING COLLEGE, Jawaharlal Nehru Technological University- Ananthapuramu (JNTU-A), NANDYAL, PIN 518502, KURNOOL (Dist), A.P., INDIA.*
[2] *Department of Chemistry, Sri Krishnadevaraya University, Ananthapuramu, (A P), INDIA.*
[3]*Department of Environmental Science, Sri Krishnadevaraya University College of Engineering & Technology, S.K.University, Ananthapuramu – 515003 (A.P), India.*
[4] Faculty of Engineering Chemistry, PBR VITS, Jawaharlal Nehru Technological University (JNTU-A), KAVALI, NELLORE (Dist), (A.P.) INDIA.
.***Corres. Author E-mail:- Virupakshi.prabhakar@gmail.com***

**ABSTRACT:**
New series of benzo [b] [1,5]-thiazepine derivatives 6 a-j were synthesized by applying the cyclo condensation of (E)-3-(thieno[2,3-*d*]pyrimidin-6-yl)-1-p-substituted prop-2-en-1-one derivatives 4a-j with o-aminothiophenol(5) in DMF. The new intermediate chalcone derivatives 4a-j were obtained from interaction of various p-substituted acetophenone & heterocyclic acetyl derivatives 3(a-j) and thieno [2, 3-*d*] pyrimidine-6-carbaldehyde. The synthesized 1, 5-benzothiazepines 6a-j have been screened for their antimicrobial activity. From anti-bacterial and anti-fungal activity screening results, it has been observed that compounds 6h, 6e, 6i and 6d possess good activity.

**KEY WORDS:** chalcones, o-aminothiophenol, cyclisation, 1, 5-benzothiazepines, anti-microbial activity, thieno [2, 3-*d*] pyrimidine core ring.

## INTRODUCTION:

Chalcones constitute an important class of natural products and some of them possess a wide range of pharmacological activities such as anticancer, anti-tubercular, antiviral [**1**]. Recent studies on biological evaluation of Chalcones revealed some to be antibacterial, antifungal, Anti-inflammatory, anti hyperglycaemic [**2**], and anti-malarial agents [**3**].The chalcones are **α, β** unsaturated ketones containing the reactive keto ethylene group. These compounds are

also known as benzylidene acetophenones or benzalacetophenones, which are documented as Chalcones by Kostanecki and Tambor

The chalcones are unsaturated ketones containing the reactive keto ethylene group

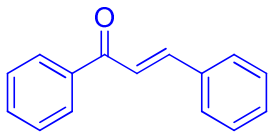

**Fig.1 General structure of Chalcones**

Organic synthetic chemistry is now a fast growing research field in chemistry. Among the various organic compounds, heterocyclic compounds have been associated with various biologically activities. Due to bioactivity connected with hetero cycle and ease of preparation, a number of researchers are takings more interested into the study of this. N- And S-containing heterocycles, such as thiazepine and its derivatives, exhibit a broad spectrum of biological activity [**4,5**]. Thiazepine fused with a benzene ring is known as benzo thiazepine, and it is associated with antibacterial, antifungal [**6**], antimicrobial [**7**], anticonvulsant [**8**], and anti-breast cancer activity [**9**], acting as a central nervous system depressant [**10**].
The 1,5-benzothiazepines [**11**] (1, 2,3) are Important nitrogen- and sulfur-containing seven membered heterocyclic compounds in drug research since they possess diverse bioactivities [**12-19**]. 1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine (4) and one of the three possible benzo condensed derivatives, viz. 1,4-(5), 4,1- (6) and 1,5- benzo thiazepines [**20-23**].

**General structures of 1, 5-benzothiazepine**

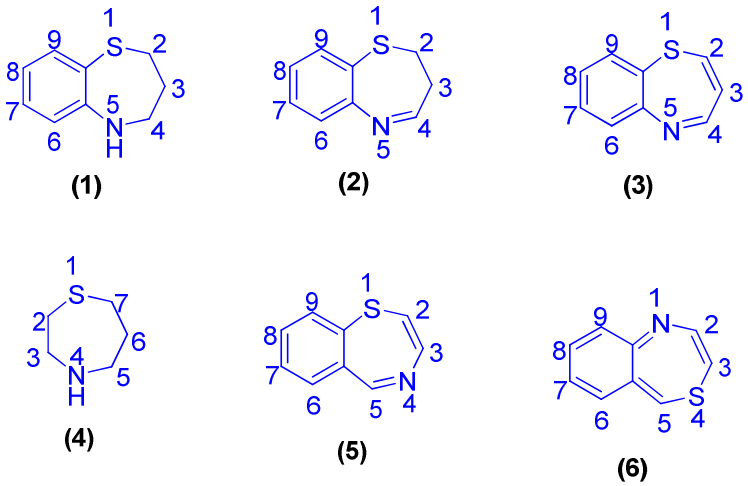


**Fig.2 Various isomers of BenzoThiazepines.**

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The importance of the l, 5-benzothiazepine nucleus has been well established as illustrated by a large number of compounds which have been patented as chemotherapeutic agents [**24**]. A number of biological activities have been associated with it, such as anti-feedant [**25**], coronary vasodilatory [**26**], tranquilizer [**27**], antidepressant [**28**], CNS stimulant [**29**], antihypertensive [**30**], calcium channel blocker **[31]**, antiulcer [**32**], calcium antagonist [**33**],

antimicrobial [**34**] and anticonvulsant agents [**35**]. l,5-Benzothiazepine molecules have been found to be useful in mucosal blood flow, as antiulcer and gastric secretion inhibitor. Recently, anticancer activities [**36**], hemodynamic effects [**37**], and spasmolytic activities [**38**] have also been reported [**39**]. Diltiazem has been used in the treatment of hypertension, angina pectoris, arrhythmias and other cardiac disorders. It also increases the supply of blood and oxygen to heart [**40-41**]. Thiazesim act as psycho topic agent, clentiazem have antiatherogenic effect [**42**], and clothiapine shows anti-muscarinic potential [**43**].

Thieno Pyrimidine is a bicyclic heterocyclic compound consists of a five membered thiophene ring is fused to a six membered hetero cyclic ring with two nitrogen atoms. The fusion may occur in three different orientations that results in three important types of thieno pyrimidines namely; **Thieno[2,3-*d*]Pyrimidine (a)**, thieno[3,2-*d*]Pyrimidine (b) and thieno[3,4-*d*] pyrimidine (c).

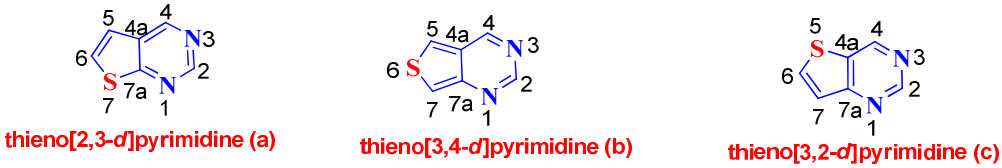



**Fig: 3Structures of different isomers of Thieno Pyrimidine**

Heterocycles containing the thieno pyrimidine moiety (**Figure 3**) are of interest because of their interesting pharmacological and biological activities [**44–49**]. Thus, over the last two decades many thieno pyrimidines have been found to exhibit a variety of pronounced activities, for example, as anti-inflammatory [**50**], anti-microbial [**51**], antiviral [**52**] and analgesic [**53**] agents. Some thieno pyrimidine derivatives showed good antitumor activity [**54**].

Encouraged by the significance of benzo thiazepine cited in literature and the movement of our work in the bio-organic field, we have studied its anti-microbial activity. In this current investigation, we report the synthesis, biological evaluation and preliminary structure activity relationship (SAR) of benzo thiazepine derivatives.

The synthesis of the compounds as per the following Scheme **I** given below.

The synthetic route was depicted in scheme **I.**

The structures of all synthesized compounds were assigned on the basis of IR, Mass, $^{1}$H & $^{13}$C NMR spectral data analysis. Further these compounds were subjected for antifungal and antibacterial activity.

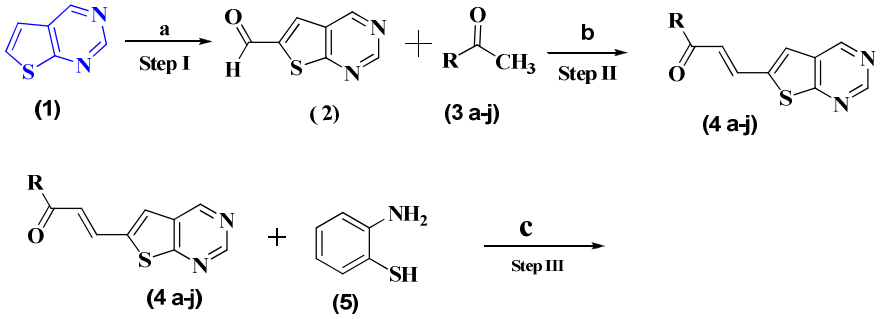
## MATERIALS AND METHODS

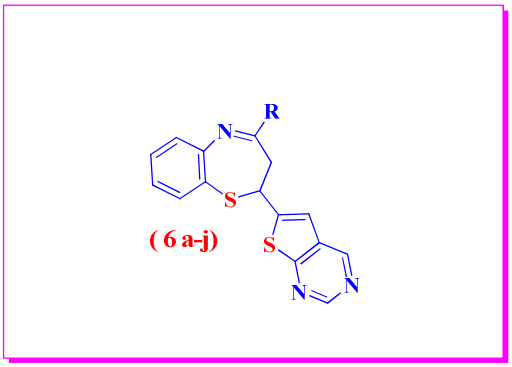
In this Investigation chemicals were purchased from local dealer with S.D fine make was used. Chemicals were 99 % pure; purity has been checked by thin layer chromatography and melting point. Conventional method has been used for synthesis of thieno [2, 3-*d*] pyrimidine derivatives. Stirring and reflux method were used for synthesis of Thieno [2, 3-*d*] Pyrimidine derivatives 6 (a-j) respectively.

The synthetic route was depicted in scheme **I.**

The title compounds 6(a-j) were synthesized in three sequential steps using different reagents and reaction conditions, the 6(a-j) were obtained in moderate yields. The structure were established by spectral (IR, $^{1}$H-NMR, $^{13}$C-NMR and mass) data.

## Synthetic Scheme



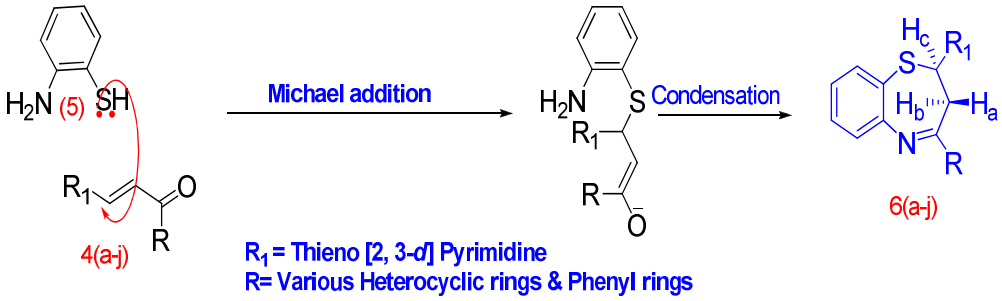




R = -Phenyl, -4 Methyl phenyl, -4 Methoxy phenyl, -4 tri fluoro methoxy phenyl, -4 Tri fluoro phenyl, -4 Nitro phenyl, - furan 2-yl, Thiophene 2-yl, pyrazin-2-yl , pyridin-2-yl acetyl groups.

**Fig 4: Synthetic path way of preparation of Novel 1, 5-Benzothiazepines Containing Thieno [2, 3-*d*] Pyrimidine Nucleus (6 a-j).**

**Reagents and Reaction conditions: (a)** *DMF,POCl$_3$,80$^O$C,4hrs* (b) *KOH,Ethanol, RT, 24 hrs* (c) DMF, Piperidine, AcOH, Reflux.

**Fig. 5: A plausible mechanism pathway for the formation of 1,5-Benzothiazepines ( 6 a-j ):**




Designed series of molecules 6 (a-j) were characterized by spectral analysis before being evaluated for their Anti- microbial activity. In its $^1$H NMR spectra, **Ha, Hb** and **Hc** protons of the benzothiazepine ring appeared as a doublet of doublet. The doublet of **Ha** appeared at δ 1.822 ppm; doublet of **Hb** appeared at δ 2.112 ppm; and that of **Hc** appeared at δ 3.665 ppm. Doublets of **Ha** and **Hb** are due to diastereotopic nature of methylene protons. Among $\mathbf{H_a}$, $\mathbf{H_b}$

and $\mathbf{H_c}$ protons, $\mathbf{H_c}$ is the most deshielded due to its close proximity to benzene ring. $\mathbf{H_C}$ couples not only with $\mathbf{H_a}$ but also with $\mathbf{H_b}$ and appears as doublet of doublet instead of a triplet i.e., the methylene protons of benzo thizepine ring (**Ha and Hb**) exhibited a typical **ABX** spin system with **Hc** as a doublet of doublets as shown in diagram-7(a-g). Further it showed signals due to substituent and aromatic protons at the expected region. All compounds displayed the signals in the similar pattern.

**EXPERIMENTAL SECTION:**

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. DMF was distilled from $CaH_2$ and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous $Na_2SO_4$, filtered through a fitted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for $^1H$ for $^{13}C$, respectively, in $CDCl_3$ solution with tetra methyl silane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra ($^1H$ NMR and $^{13}C$ NMR) were recorded using tetra methyl silane (TMS) in the solvent of $CDCl_3$-$d_1$ or DMSO-$d_6$ as the internal standard ($^1H$ NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm ,DMSO at 2.50 ppm; $^{13}C$ NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm).

The antimicrobial tests were carried out at the Pharmaceutical Chemistry Department, Faculty of Pharmacy, Sri Krishnadevaraya University. ChemDrawUltra-12.0 has been used for the nomenclature of the prepared compounds.

## Synthesis:

***General procedure for synthesis of thieno [2, 3-d] pyrimidine-6-carbaldehyde [Compound 2]:***

Thieno[2,3-*d*] pyrimidine (1) (10 g, 0.0735 mol) was dissolved in dry DMF(100 mL),under anhydrous condition, it was cooled to $0^OC$, $POCl_3$ (15 mL) was added drop wise for 30 min. and stirring continued for 4 h at $80^oC$ After completion of reaction (TLC), The reaction mass was poured over crushed ice, basified with NaOH , Extracted with chloroform and dried over anhydrous $Na_2SO_4$ . Organic layer was concentrated under reduced pressure and purified through silica gel column (Neutral Alumina) using Chloroform as eluting solvent to yield product (2) [yield 60%, 7.2g ]. off yellow solid. m.p. 76-78$^oC$.

**IR (KBr, $cm^{-1}$):** 3110 $cm^{-1}$ (Ar C-H stret), 2720 (C-H Stretch), 1725 $cm^{-1}$ (C=O Stretch),1550 $cm^{-1}$ (C=C Stret), Wave numbers respectively.

**$^1H$ NMR (400 MHz; $CDCl_3$):** δH 8.2 (S, 1H, Ar-H), 8.8 (S, 1H, Ar-H), 9.4 (S, 1H, Ar-H), 10.04 (S,
-**H**-C=O).

**$^{13}C$ NMR (100 MHz; $CDCl_3$):** δC 130, 135, 145, 149, 158, 190.

**MS (70 eV):** m/z = 165$(M+H)^+$.

***General procedure for synthesis of (E)-1-phenyl-3-(thieno [2, 3-d]pyrimidin-6-yl)prop-2-en-1-one (4a), (E)-3-(thieno[2,3-d]pyrimidin-6-yl)-1-p-tolylprop-2-en-1-one(4b), (E)-1-(4-methoxyphenyl)-3-(thieno[2,3-d]pyrimidin-6-yl)prop-2-en-1-one (4c), (E)-3-(thieno[2,3-d]pyrimidin-6-yl)-1-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one (4d), (E)-3-(thieno[2,3-d]pyrimidin-6-yl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (4e), (E)-1-(4-nitrophenyl)-3-(thieno[2,3-d]pyrimidin-6-yl)prop-2-en-1-one (4f), (E)-1-(furan-2-yl)-3-(thieno[2,3-d]pyrimidin-6-yl)prop-2-en-1-one (4g), (E)-3-(thieno[2,3-d]pyrimidin-6-yl)-1-***

***(thiophen-2-yl)prop-2-en-1-one(4h), (E)-1-(pyrazin-2-yl)-3-(thieno[2,3-d]pyrimidin-6-yl)prop-2-en-1-one (4i), (E)-1-(pyridin-2-yl)-3-(thieno[2,3-d]pyrimidin-6-yl)prop-2-en-1-one (4j):***

Various acetyl derivatives (3 a-j) (10 m.mol) were dissolved in ethanol, 2 mL 20% NaOH solution was added to it. and stirred for 10 min at RT. Then thieno[2,3-*d*]pyrimidine-6-carbaldehyde (2) was added and stirring continued for 24h at Room temperature, after completion of reaction (TLC), reaction mixture was poured over crushed ice and stirred. The precipitate obtained was filtered and recrystallised by using Ethanol to obtain the chalcone derivatives (4a-j).

**(E)-1-phenyl-3-(thieno [2, 3-*d*] pyrimidin-6-yl) prop-2-en-1-one (4a):**

**Yield:** 85% (yellow color solid);

**IR (KBr, $cm^{-1}$):** 3140(-Ar CH), 1652 (C=O Stretching), 1620(C=C Stretching), 675(C-S-C).

**$^1$H NMR (400 MHz; $CDCl_3$):** δH 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 8.3(S,1H), 7.56 (d, 1H, CO-CH=), 7.95 (d, 1H, β C-H), 7.6-7.9(5H,m).

**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 128.92, 124.03, 128.11, 151.67, 154.75, 159.62, 195.

**MS (70 eV):** m/z = $266(M+H)^+$.

**(E)-3-(thieno [2, 3-*d*] pyrimidin-6-yl)-1-p-tolylprop-2-en-1-one (4b):**

**Yield:** 86% (light yellow color solid);

**IR (KBr, $cm^{-1}$):** 3120(-Ar CH), 2970($SP^3$ CH), 1675 (C=O Stretching), 1630(C=C Stretching), 668(C-S-C).

**$^1$H NMR (400 MHz; $CDCl_3$):** δH 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 8.23(S,1H), 7.56 (d, 1H, CO-CH=), 7.95 (d, 1H, β C-H), 7.98(2H,d), 7.4(2H,d), 2.3(3H,S).

**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 23, 125, 128.92, 124.03,135, 151.67, 154.75, 159.62, 190.

**MS (70 eV):** m/z = $281(M+H)^+$.

**(E)-1-(4-methoxyphenyl)-3-(thieno [2, 3-*d*] pyrimidin-6-yl) prop-2-en-1-one (4c):**

**Yield:** 90% (yellow color solid);

**IR (KBr, $cm^{-1}$):** 3120(-Ar CH), 2970($SP^3$ CH), 1655 (C=O Stretching), 1630(C=C Stretching), 1160(C-O-C Stretching), 668(C-S-C).

**$^1$H NMR (400 MHz; $CDCl_3$):** δH 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 8.23(S,1H), 7.56 (d, 1H, CO-CH=), 7.95 (d, 1H, β C-H), 8.2(2H,d), 7.2(2H,d), 3.9(3H,S).

**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 56, 120,125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 185.

**MS (70 eV):** m/z = $297(M+H)^+$.

**(E)-3-(thieno [2, 3-*d*]pyrimidin-6-yl)-1-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one (4d):**

**Yield:** 90% (yellow color solid);

**IR (KBr, $cm^{-1}$):** 3110(-Ar CH), 1640 (C=O Stretching), 1625(C=C Stretching), 1340(C-F), 1160(C-O-C), 675(C-S-C).

**$^1$H NMR (400 MHz; $CDCl_3$):** δH 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 8.23(S,1H), 7.56 (d, 1H, CO-CH=), 7.95 (d, 1H, β C-H), 8.2(2H,d), 7.2(2H,d), 3.9(3H,S).

**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 56, 120,125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 185.

**MS (70 eV):** m/z = $351(M+H)^+$.

**(E)-3-(thieno [2, 3-*d*] pyrimidin-6-yl)-1-(4-(trifluoromethyl) phenyl) prop-2-en-1-one (4e):**

**Yield:** 90% (yellow color solid);

**IR (KBr, $cm^{-1}$):** 3130(Ar CH), 1665 (C=O Stretching), 1640(C=C Stretching), 1360(C-F), 1160(C-O-C), 685(C-S-C).

**$^1$H NMR (400 MHz; $CDCl_3$):** δH 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 8.23(S,1H), 7.55 (d, 1H, CO-CH=), 7.90 (d, 1H, β C-H), 8.1(2H,d), 7.8(2H,d).
**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 120,125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 189.
**MS (70 eV):** m/z = 335$(M+H)^+$.

**(E)-1-(4-nitrophenyl)-3-(thieno [2, 3-*d*] pyrimidin-6-yl) prop-2-en-1-one (4f):**
**Yield:** 80% (yellow color solid);
**IR (KBr, $cm^{-1}$):** 3110(Ar CH), 1655 (C=O Stretching), 1646(C=C Stretching), 1336 & 1550 (N-O Symmetric & Asymmetric stretching in Nitro Group), 680(C-S-C).
**$^1$H NMR (400 MHz; $CDCl_3$):** δH 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 8.23(S,1H), 7.55 (d, 1H, CO-CH=), 7.95 (d, 1H, β C-H), 8.2(2H,d), 8.5(2H,d).
**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 189.
**MS (70 eV):** m/z = 310$(M-H)^+$.

**(E)-1-(furan-2-yl)-3-(thieno [2, 3-*d*] pyrimidin-6-yl) prop-2-en-1-one (4g):**
**Yield:** 85% (yellow color solid);
**IR (KBr, $cm^{-1}$):** 3110(Ar CH), 1655 (C=O Stretching), 1646(C=C Stretching), 1140 (C-O-C stretching in Furan ring), 685(C-S-C).
**$^1$H NMR (400 MHz; $CDCl_3$):** δH 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 8. 3(S,1H), 6.75 (d, 1H, CO-CH=), 7.6 (d, 1H, β C-H), 8(1H,d), 7.9(1H,t), 8.7(1H,d).
**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 115,125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 195.
**MS (70 eV):** m/z = 257$(M-H)^+$.

**(E)-3-(thieno [2, 3-*d*] pyrimidin-6-yl)-1-(thiophen-2-yl) prop-2-en-1-one (4h):**
**Yield:** 85% (pale yellow color solid);
**IR (KBr, $cm^{-1}$):** 3120(Ar CH), 1665 (C=O Stretching), 1650(C=C Stretching), 680(C-S-C).
**$^1$H NMR (400 MHz; $CDCl_3$):** δH 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 8. 3(S, 1H), 6.75 (d, 1H, CO-CH=), 7.6 (d, 1H, β C-H), 8(1H, d), 7.4(1H,t), 8.2(1H,d).
**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 195.
**MS (70 eV):** m/z = 273$(M-H)^+$.

**(E)-1-(pyrazin-2-yl)-3-(thieno [2, 3-*d*] pyrimidin-6-yl) prop-2-en-1-one (4i):**
**Yield:** 80% (yellow color solid);
**IR (KBr, $cm^{-1}$):** 3100(Ar CH), 1670 (C=O Stretching), 1655(C=C Stretching), 1470(C=N), 685(C-S-C).
**$^1$H NMR (400 MHz; $CDCl_3$):** δH 9.3 (S, 1H, Ar-H), 8.9 (S, 1H, - Ar-H), 8. 3(S, 1H), 6.75 (d, 1H, CO-CH=), 7.65 (d, 1H, β C-H), 8.8(1H, d), 8.6(1H,d), 9.4(1H,S).
**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 120,125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 195.
**MS (70 eV):** m/z = 269$(M+H)^+$.

**(E)-1-(pyridin-2-yl)-3-(thieno [2, 3-*d*] pyrimidin-6-yl) prop-2-en-1-one (4j):**
**Yield:** 82% (yellow color solid);
**IR (KBr, $cm^{-1}$):** 3100(Ar CH), 1670 (C=O Stretching), 1655(C=C Stretching), 1460(C=N), 685(C-S-C).
**$^1$H NMR (400 MHz; $CDCl_3$):** δH 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 8. 25(S, 1H), 6.75 (d, 1H, CO-CH=), 7.55 (d, 1H, β C-H), 8.3(1H, d), 8.1(1H,d), 8(1H,d), 8.9(1H,d).
**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 120,125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 195.
**MS (70 eV):** m/z = 266$(M-H)^+$.

***General procedure for synthesis of***
***4-phenyl-2-(thieno [2, 3-d] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6a),***
***2-(thieno [2, 3-d] pyrimidin-6-yl)-4-p-tolyl-2,3-dihydrobenzo[b][1,4]thiazepine (6b),***
***4-(4-methoxyphenyl)-2-(thieno [2, 3-d] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6c),***
***2-(thieno [2, 3-d] pyrimidin-6-yl)-4-(4-(trifluoromethoxy) phenyl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6d),***
***2-(thieno [2, 3-d] pyrimidin-6-yl)-4-(4-(trifluoromethyl) phenyl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6e),***
***4-(4-nitrophenyl)-2-(thieno [2, 3-d] pyrimidin-6-yl)-2,3-dihydrobenzo[b][1,4]thiazepine (6f),***
***4-(furan-2-yl)-2-(thieno [2, 3-d] pyrimidin-6-yl)-2,3-dihydrobenzo[b][1,4]thiazepine(6g),***
***2-(thieno [2, 3-d] pyrimidin-6-yl)-4-(thiophen-2-yl)-2,3-dihydrobenzo[b][1,4]thiazepine (6h),***
***4-(pyrazin-2-yl)-2-(thieno [2, 3-d] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6i),***
***4-(pyridin-2-yl)-2-(thieno[2,3-d]pyrimidin-6-yl)-2,3-dihydrobenzo[b][1,4]thiazepine (6j):***
A mixture of (4 a-j) (0.1 mol) and 2-aminothiophenol (0.1 mol) was dissolved in DMF (10mL). A few drops of piperidine were added to the solution and it was then refluxed for 4 h. It was then acidified with glacial acetic acid (2 mL) and reaction mixture was further refluxed for 2 hrs. The progress of the reaction was monitored by TLC. After completion the reaction mixture was left overnight at room temperature. Then the reaction mass was poured in ice cold water and the obtained solid was filtered. The crude was crystallized form EtOH: DMF. The structure of compounds 6 a-j were confirmed on the basis of analytical and spectral data.

**4-phenyl-2-(thieno [2, 3-*d*] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6a)*:***

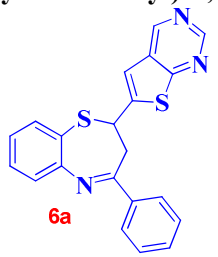



Fig. 6 Structure of 4-phenyl-2-(thieno[2,3-*d*]pyrimidin-6-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine

**Yield:** 65% (yellow color solid);
mp 126-127℃.
**IR (KBr, $cm^{-1}$):** 3110(Ar CH), 1655 (C=O Stretching), 1460(C=N Stretching), 685(C-S-C).
**$^{1}$H NMR (400 MHz; $CDCl_3$):** δH 3.8(1H,dd,S-CH),2.3(1H,dd), 1.8(1H,dd),9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.7(S, 1H), 7.3-7.5(5H,m), 7.6-8.1(5H,m).
**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 40, 46,125, 128.92, 124.03,135,140, 149,151.67, 154.75, 159.62.
**MS (70 eV):** m/z = 374$(M-H)^+$.

**2-(thieno [2, 3-*d*] pyrimidin-6-yl)-4-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepine (6b):**

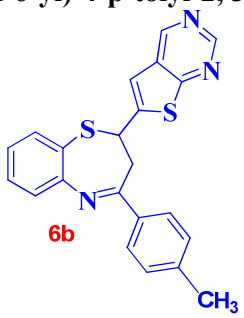



Fig.7 Structure of 2-(thieno[2,3-*d*]pyrimidin-6-yl)-4-*p*-tolyl-2,3-dihydrobenzo[*b*][1,4]thiazepine

**Yield:** 66%

**IR (KBr, cm$^{-1}$):** 3140(-Ar CH), 2960(SP$^3$ CH), 1640(C=N Stretching), 665(C-S-C).

**$^1$H NMR (400 MHz; CDCl$_3$):** δH 2.3(3H,S), 3.8(1H,dd,S-CH),2.3(1H,dd), 1.8(1H,dd),9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.7(S,1H), 7.2-7.4(4H,m), 7.8(2H,d), 7.3(2H,d).

**$^{13}$C NMR (100 MHz; CDCl$_3$):** δC 23,41, 46, 125, 128.92, 124.03,135, 153, 156, 160.

**MS (70 eV):** m/z = 386(M-H)$^+$.

**4-(4-methoxyphenyl)-2-(thieno [2, 3-*d*] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6c):**

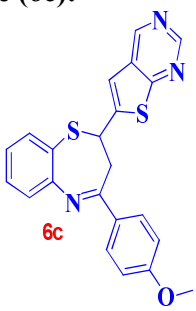



Fig.8 Structure of 4-(4-methoxyphenyl)-2-(thieno [2, 3-d] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine

**Yield:** 60% ,

mp 139-140°C.

**IR (KBr, cm$^{-1}$):** 3130(-Ar CH), 2990(SP$^3$ CH), 1645(C=N Stretching), 1150(C-O-C Stretching), 675(C-S-C).

**$^1$H NMR (400 MHz; CDCl$_3$):** δH 3.7(1H,dd,S-CH),2.4(1H,dd), 1.9(1H,dd),9.4 (S, 1H, Ar-H), 8.9 (S, 1H, - Ar-H), 6.73(S,1H), 8.1(2H,d), 7.1(2H,d), 3.9(3H,S).

**$^{13}$C NMR (100 MHz; CDCl$_3$):** δC 40,45,56, 120,125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62.

**MS (70 eV):** m/z = 404(M+H)$^+$.

**2-(thieno [2, 3-*d*] pyrimidin-6-yl)-4-(4-(trifluoromethoxy) phenyl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6d):**

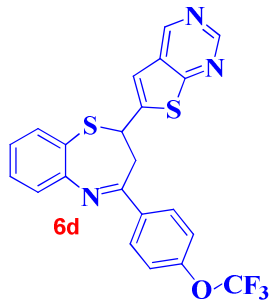



Fig.9 Structure of 2-(thieno[2,3-*d*]pyrimidin-6-yl)-4-(4-(trifluoromethoxy)phenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine

**Yield:** 70%,
mp 155-156°C
**IR (KBr, cm$^{-1}$):** 3110(-Ar CH), 1640 (C=N Stretching), 1625(C=C Stretching), 1360(C-F), 1140(C-O-C), 675(C-S-C).
**$^{1}$H NMR (400 MHz; $CDCl_3$):** δH 3.7(1H,dd,S-CH),2.4(1H,dd), 1.9(1H,dd),9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.63(S,1H), 8.1(2H,d), 7.1(2H,d),7.2 (2H,t), 7.4(2H,t).
**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 56, 120,125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62.
**MS (70 eV):** m/z = 456(M-H)$^{+}$.

**2-(thieno [2, 3-*d*] pyrimidin-6-yl)-4-(4-(trifluoromethyl) phenyl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6e):**

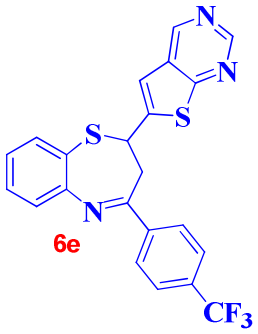



Fig.10 Structure of 2-(thieno[2,3-*d*]pyrimidin-6-yl)-4-(4-(trifluoromethyl)phenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine

**Yield:** 76%
mp 183-185°C
**IR (KBr, cm$^{-1}$):** 3130(Ar CH), 1670(C=N Stretching), 1380(C-F), 1190(C-O-C), 685(C-S-C).
**$^{1}$H NMR (400 MHz; $CDCl_3$):** δH 3.5(1H,dd,S-CH),2.5(1H,dd), 1.7(1H,dd),9.4 (S, 1H, Ar-H), 8.7 (S, 1H, - Ar-H), 6.7(S,1H), 7.8(2H,d), 7.7(2H,d),7.2 (2H,t), 7.4(2H,t).
**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 40,45,120,125, 128.92, 124.03,135, 149,153, 154.75, 160, 189.
**MS (70 eV):** m/z = 442(M+H)$^{+}$.

**4-(4-nitrophenyl)-2-(thieno [2, 3-*d*] pyrimidin-6-yl)-2,3-dihydrobenzo[b][1,4]thiazepine (6f):**

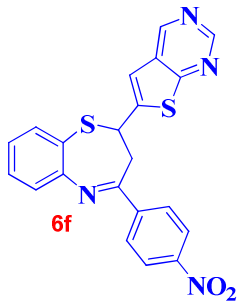



Fig.11Structure of 4-(4-nitrophenyl)-2-(thieno[2,3-*d*]pyrimidin-6-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine

**Yield:** 60%

mp 150-151°C

**IR (KBr, $cm^{-1}$):** 3120(Ar CH), 1645 (C=N Stretching), 1366 & 1557 (N-O Symmetric & Asymmetric stretching in Nitro Group), 685(C-S-C).

**$^1$H NMR (400 MHz; $CDCl_3$):** δH 3.5(1H,dd,S-CH),2.5(1H,dd), 1.7(1H,dd), 9.4 (S, 1H, Ar-H), 8.7 (S, 1H, - Ar-H), 6.5(S, 1H), 8.2(2H,d), 8.5(2H,d), 7.2 (2H,t), 7.4(2H,t).

**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 40,45,125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 189.

**MS (70 eV):** m/z = 417$(M-H)^+$.

**4-(furan-2-yl)-2-(thieno [2, 3-*d*] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine(6g):**

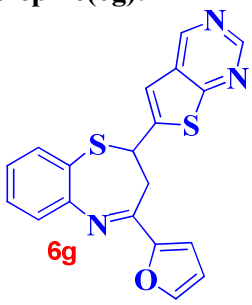



Fig.12. 4-(furan-2-yl)-2-(thieno [2, 3-*d*] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine

**Yield:** 65%

mp 142-143°C

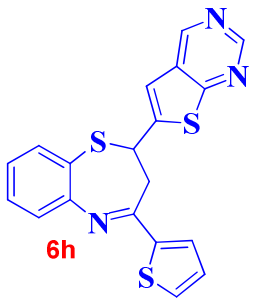
**IR (KBr, $cm^{-1}$):** 3120(Ar CH), 1665 (C=N Stretching), 1150 (C-O-C stretching in Furan ring), 685(C-S-C).

**$^1$H NMR (400 MHz; $CDCl_3$):** δH 3.5(1H,dd,S-CH),2.5(1H,dd), 1.7(1H,dd), 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.6(S, 1H), 8(1H, d), 6.5(1H, t), 7.1(1H, d), 7.3(2H,d), 7.4(2H,d).

**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 40,47,115,125, 128.92, 124.03,135, 149,151.67, 154.75, 160.

**MS (70 eV):** m/z = 364$(M+H)^+$.

**2-(thieno [2, 3-*d*] pyrimidin-6-yl)-4-(thiophen-2-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6h):**



6h

**Fig.13. 2-(thieno [2, 3-*d*] pyrimidin-6-yl)-4-(thiophen-2-yl)-2,3-dihydrobenzo[b][1,4]thiazepine**

**Yield:** 65%

mp 142-143°C

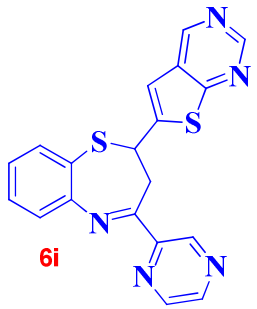
**IR (KBr, cm$^{-1}$):** 3120(Ar CH), 1660 (C=N Stretching), 1140 (C-O-C stretching in Furan ring), 680(C-S-C).

**$^{1}$H NMR (400 MHz; $CDCl_3$):** δH 3.8(1H,dd,S-CH),2.4(1H,dd), 1.8(1H,dd), 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.6(S, 1H), 7.7(1H, d), 7.2(1H, t), 7.5(1H, d), 7.5(2H,d), 7.4(2H,d).

**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 40,47,115,125, 128.92, 124.03,135, 149,151, 155, 160.

**MS (70 eV):** m/z = 380(M+H)$^{+}$.

**4-(pyrazin-2-yl)-2-(thieno [2, 3-*d*] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine (6i):**



6i

**Fig.14. 4-(pyrazin-2-yl)-2-(thieno[2,3-*d*]pyrimidin-6-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepine**

**Yield:** 60%

mp 146-147°C

**IR (KBr, cm$^{-1}$):** 3130(Ar CH), 1655(C=N Stretching), 665(C-S-C).

**$^{1}$H NMR (400 MHz; $CDCl_3$):** δH 3.8(1H,dd,S-CH),2.4(1H,dd), 1.8(1H,dd), 9.3 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.6(S, 1H), 8.5(1H, d), 8.8(1H,d), 9.4(1H,S) 7.6(4H,m).

**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 41,46,120,125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 195.

**MS (70 eV):** m/z = 376(M+H)$^{+}$.

**4-(pyridin-2-yl)-2-(thieno[2,3-*d*]pyrimidin-6-yl)-2,3-dihydrobenzo[b][1,4]thiazepine (6j):**

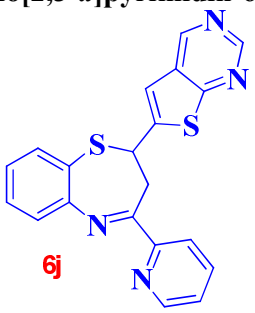



Fig.15. 4-(pyridin-2-yl)-2-(thieno[2,3-d]pyrimidin-6-yl)-2,3-dihydrobenzo[b][1,4]thiazepine

**Yield:** 62%,

Mp 198-199°C

**IR (KBr, cm$^{-1}$):** 3100(Ar CH), 1655(C=N Stretching), 680(C-S-C).

**$^{1}$H NMR (400 MHz; $CDCl_3$):** δH 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.7(S, 1H), 8(1H, d), 7.8(1H, d), 7.7(1H, d), 8.7(1H, d).

**$^{13}$C NMR (100 MHz; $CDCl_3$):** δC 41, 46,120,125, 128, 124.03,135, 149,151, 157, 160.

**MS (70 eV):** m/z = 373(M-H)$^{+}$.

**Antimicrobial activity:**

The cup plate agar diffusion method [**58**] was employed for determining the antimicrobial activity of the newly synthesized compounds 6 (a-j)) against two gram positive bacteria viz., Bacillus subtilis, Staphylococci aureus and two gram negative bacteria viz., Escherichia coli, Pseudomonas aeruginosa in addition to fungi (Candida albicans). The solutions of different compounds under test at a concentration of 500 and 600 µg/ml in 5% DMSO were poured in the cup/well of bacteria seeded agar plates. These plates were incubated at 37°C for 24 hours for E. coli, whereas plates of other three bacteria were incubated at 27°C for 24 hr. The standard antibiotics used were ampicillin (all at 500 µg/ml).and standard antifungal used were nystatin at 500 µg/ml, the control solution (only 5% DMSO) did not reveals any inhibition. The zone of inhibition produced by each compound was measured in mm. The results of antimicrobial studies are given in Table 1. The discussion and comparison of antibacterial activity were given with respect to ampicillin antibiotic and antifungal screening was compared with Nystatin.

**Table 1. Antimicrobial activity of synthesized Chalcones 4 a-j and 1, 5-Benzo thiazepines 6a-j:**

| Comp. NO. | Concent-ration (µg/ml) | Microorganism (inhibition zone (mm) ) | | | | |
|---|---|---|---|---|---|---|
| | | Basillus Subtilis | Staphylococcus aureus | Escherichia coli | Pseudomonas aeruginosa | Candida albicans |
| 4a | 500 | --- | ---- | ---- | ---- | ---- |
| | 600 | ---- | ----- | ----- | ----- | ---- |
| 4b | 500 | 3.5 | 2.9 | 4.5 | 3.1 | 1.4 |
| | 600 | 3.7 | 2.9 | 4.6 | 3.2 | 1.5 |
| 4c | 500 | 2.1 | 3 | 3.2 | 1.5 | 0.9 |
| | 600 | 2.2 | 3.1 | 3.3 | 1.6 | 1.1 |
| 4d | 500 | 4.6 | 3.1 | 2.6 | 0.8 | 0.7 |
| | 600 | 4.7 | 3.3 | 2.7 | 0.9 | 0.8 |
| 4e | 500 | 5.6 | 4.9 | 4.8 | 2.7 | 1.2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 600 | 5.7 | 5.3 | 4.9 | 2.8 | 1.3 |
| 4f | 500 | 4 | 3.8 | 4.5 | 3.9 | 1.1 |
| | 600 | 4.1 | 3.9 | 4.6 | 4 | 1.1 |
| 4g | 500 | 3.5 | 2.9 | 4.5 | 3.1 | 1.4 |
| | 600 | 3.7 | 2.9 | 4.6 | 3.2 | 1.5 |
| 4h | 500 | 6.3 | 6.1 | 5.4 | 4.6 | 2.7 |
| | 600 | 6.4 | 6.2 | 5.5 | 4.7 | 2.9 |
| 4i | 500 | 5.4 | 4.7 | 4.6 | 2.5 | 1.1 |
| | 600 | 5.2 | 4.9 | 4.8 | 2.7 | 1.3 |
| 4j | 500 | 4.3 | 3.4 | 2.8 | 1.8 | 0.7 |
| | 600 | 4.5 | 3.5 | 2.9 | 1.9 | 0.8 |
| 6a | 500 | 9 | 9.2 | 9.1 | 9.5 | 7.0 |
| | 600 | 9.3 | 9.3 | 9.4 | 9.7 | 7.2 |
| 6b | 500 | 10.9 | 11.1 | 10.5 | 10.7 | 8.1 |
| | 600 | 12 | 12.3 | 11.6 | 10.9 | 8.3 |
| 6c | 500 | 10 | 10.2 | 10.1 | 10.5 | 7.2 |
| | 600 | 10.3 | 10.3 | 10.4 | 10.9 | 7.4 |
| 6d | 500 | 15.3 | 15.1 | 12.3 | 13.2 | 10.6 |
| | 600 | 16.5 | 15.3 | 12.7 | 13.5 | 10.8 |
| 6e | 500 | 18.8 | 17 | 16.2 | 16.1 | 16 |
| | 600 | 18.9 | 17.2 | 17.4 | 17.3 | 16.3 |
| 6f | 500 | 12.9 | 13.1 | 12.5 | 11.7 | 9.1 |
| | 600 | 13 | 13.3 | 12.6 | 11.9 | 9.2 |
| 6g | 500 | 13 | 12.4 | 11.6 | 11.2 | 9.5 |
| | 600 | 13.2 | 12.7 | 11.8 | 11.4 | 9.7 |
| 6h | 500 | 19.4 | 19.2 | 19.4 | 19.4 | 19.6 |
| | 600 | 19.6 | 19.3 | 19.7 | 19.6 | 19.8 |
| 6i | 500 | 16.2 | 15.7 | 13.6 | 13.4 | 10.8 |
| | 600 | 16.4 | 15.8 | 13.8 | 13.6 | 11.1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 6j | 500 | 14.4 | 13.8 | 12.7 | 12.1 | 9.8 |
| | 600 | 14.5 | 13.9 | 12.8 | 12.3 | 9.6 |
| Ampicillin | 500 | 24 | 22 | 25 | 21 | --- |
| Nystatine | 500 | --- | --- | ---- | ---- | 20.8 |

**Results and Discussions:**

**Chemistry:**

The title compounds novel 1, 5-benzothiazepines containing thieno [2, 3-*d*] pyrimidine based derivatives 6(a-j) were synthesized in good yields (scheme-I). All these compounds were tested for Anti-microbial activity showed considerable activity when compared to the standard drug.

In the present communication thieno [2, 3-*d*] pyrimidine-6-carbaldehyde (2) was synthesised from thieno [2, 3-*d*] pyrimidine (1) According to the reported procedure [**55**]. Various chalcone derivatives 4(a-j) having thieno[2,3-*d*] pyrimidine core according to the reported procedure [**56**], These are further reacted with 2-amino benzene thiol(5) to get target novel 1, 5-benzothiazepines containing thieno [2, 3-*d*] pyrimidine based derivatives 6(a-j) according to the reported procedure[**57**].

**Characterization:**

The IR spectrum of the title Compounds 6(a-j) has given stretching vibration at 3110cm$^{-1}$, due to the stretching vibration corresponding to Ar-H Stretching vibrations. The absorption peak at 2935 cm$^{-1}$ is due to The stretching vibration corresponding to the $SP^3$ C-H ( methyl group).The strong Intensity absorption at 1350 & 1530 cm$^{-1}$ is due to The stretching vibration of -N-O Stretching in Nitro group, The weak Intensity absorption at 1620 cm$^{-1}$ corresponds to a C=N Stretching vibration.1150cm$^{-1}$ corresponding to C-O-C Stretching.

It has been observed from chemical structure of compound 6(a-j) that different pair of protons. The protons of Methyl group which is attached to benzene ring appeared as a singlet at δ =2.3 ppm, the protons of Methoxy group appeared as a Singlet at δ =3.8 ppm. The protons attached benzene & Pyrimidine rings appeared between δ =6.8-8.8 ppm respectively. The chemical shifts of the final compounds carbon chemical shifts are vary from δ = 195 to 23 ppm. The carbon nucleus under the influence of a strong electronegative environment appeared down field, the carbon chemical shift of the methyl group at δ= 23 ppm. The carbon chemical shift of the Methoxy group at δ= 55 ppm. The carbon chemical shift of the aldehyde carbon at δ= 195 ppm.

Readily available starting materials and simple synthesizing procedures make this method very attractive and convenient for the synthesis of 1, 5 Benzo Thiazepine derivatives. Formation of products was confirmed by recording their $^1$H NMR, $^{13}$C NMR, FT-IR, mass spectra.

**Anti microbial activity screening:**

The results of Anti microbial studies of newly synthesized compounds reveal that the compounds possess significant Anti-microbial activities. The results of these studies are given in **Table 1**. From anti-bacterial and anti-fungal activity screening results, it has been observed that compounds 6h, 6e, 6i and 6d possess good activity.

**Conclusion:**

We have synthesized a series of new chalcones 4 a-j and 1, 5-benzothiazepines 6a-j containing bioactive hetero aryl pharmacophore such as Thieno[2,3,-*d*]pyrimidine using convenient method. The antimicrobial activity of representative chalcones 4a-j showed very weak degree of, but the testing 1, 5-benzothiazepines 6 a-j showed excellent antimicrobial activity. An accessible approach for the synthesis of 1, 4-benzothiazepines was presented. The potential antimicrobial activity of the synthesized compounds validates the significance of this study. Among the synthesized compounds, 2-(thieno[2,3-*d*]pyrimidin-6-yl)-4-(thiophen-2-yl)-2,3-dihydrobenzo[b][1,4]thiazepine (6h) and 2-(thieno[2,3-*d*]pyrimidin-6-yl)-4-(4-(trifluoromethyl)phenyl)-2,3-dihydrobenzo[b][1,4]thiazepine (6e) acts as potential antifungal and antibacterial agents.

**References**

[**1**] Nowakowska Z, Kedzia B, Schroedere *Eur. J. Med. Chem*. **2008**, *43, 707-713*.

[**2**] Narender T, Papi Redy KA, *Tetrahedron Lett.* **2007**, *48, 3177-3180*.

[**3**] Mishra N, Arora P, Kumar B, Mishra L C, Bhattacharya A, Awasthi S K, Bhasin V K. *Eur. J. Med. Chem.* **2008**, *43, 1530- 1535*.

[**4**] Struga M., Kossakowski J., Koziol A. E., Kedzierska E., Fidecka S., Colla P. L., Ibba C., Collu G., Sanna G., Secc B. andLoddod R.,"**Synthesis, pharmacological and antiviral activity of 1,3-thiazepine derivatives**", *Eur. J. Med. Chem.,Vol. 44, pp.4960–4969*, **2009**.

[**5**] Campiani G., Butini S., Fattorusso C., Trotta F., Gemma S., Catalanotti B., Nacci V., Fiorini I., Cagnotto A., Mereghetti I., Mennini T., Minetti P., Di Cesare M. A., Stasi M. A., Di Serio S., Ghirardi O., Tinti O. andCarminati P.,"Novel Atypical Antipsychotic Agents: Rational Design, an Efficient Palladium-Catalyzed Route, and Pharmacological Studies", *J. Med. Chem. Vol.,48, pp. 1705–1708*, **2005**.

[**6**] Khan A. J., Baseer M. A., Dhole J. M. and Shah S. N., "**Synthesis, Experimental Studies of the Antimicrobial Potential of Some Novel 1, 5- Benzo Thiazepine Derivatives**", *Int. J. Pharma. Sci. Res.,Vol. 2, No. 10, pp. 2619–2622*, **2011**.

[**7**] Wang L., Zhang P., Zhang X., Zhang Y., Li Y. and WangY.,"**Synthesis and biological evaluation of a novel series of 1, 5-benzothiazepine derivatives as potential antimicrobial agents***", Eur. J. Med. Chem.,Vol. 44, pp. 2815–2821*, **2009**.

[**8**] Garg N., Chandra T., Jain A. B. and Kumar A., "**Synthesis and evaluation of some new substituted benzothiazepine and benzoxazepine derivatives as anticonvulsant agents**", *Eur. J. Med. Chem.,Vol. 45, pp. 1529–1535*, **2010.**

[**9**] Ameta K. L.,Rathore, N. S. and Kumar B., "**Synthesis and in vitro anti-breast cancer activity of some novel 1, 5-benzothiazepine derivatives**", *J. Serb. Chem. Soc.,Vol. 77, No. 6, pp. 725–731***, 2012**. [**10**] Nikalje A. P. andVyawahare, D., "**Facile green synthesis of 2, 4-substituted -2, 3- dihydro-1, 5 Benzothiazepine derivatives as novel anticonvulsant and central nervous system (CNS) depressant agents**", *African J. Pure Appl. Chem.,Vol. 5, No. 12, pp. 422–428*, **2011**.

[**11**] Shinichi Y, Yoshikazu M A, Katsuji M, Yoshinori I, Yasuhiko O, Ryuzo Y, Tadashi N, Hiroyasu S. *J. Org. Chem***., 1996***, 61, 8586-8590*;

(b) Kruokawa J, Adachi-Akahane. S, Nagao. T, *Eur. J. Pharmacol*. **1997**, *325, 229-236*.

[**12**] Miyata O, Tetsuro S, Ichiya N, Takeaki N, *Tetrahedron*, **1997**, *53, 2421-2438*.

[**13**] Garandolini G,Perioli L, Ambrogi V, *Eur. J. Med. Chem*., **1999**, *34, 701-709*.

[**14**] Yang X,Buzon L, Hamanaka E,Liu. K K-C, *Tetrahedron*, **2000**, *11, 4447-4450*.
[**15**] Urbanski M J, Chen R H, Demarest K T, Gannet J, Look R, Ericson E, Murray W V, Rybezynski P J, Zhang X, *Bioorg. Med. Chem. Lett***., 2003**, *13, 4031-4034*.
[**16**] Santo R Di, Costi R, Farmaco, **2005**, *60, 385-392*.
[**11**]. Anshu, D., Ruby, S., Dharmendra, S., Ashok, L., Asha, S. *Phosphorus, Sulfur, Silicon Relat. Elem*., *185, 2472* (**2010**).
[**12**]. Ghotekar, D.S., Joshi, R.S., Mandhane, P.G., Bhagat, S.S., Gill, C.H. *Indian J. Chem., Sect. B, 49B, 1267* (**2010**).
[**13**]. Pant, S., Sharma, P., Pant, U.C. *Phosphorus, Sulfur, Silicon Relat. Elem*., *183, 2974* (**2008**).
[**14**]. Desai, K.G., Desai, K.R. *Indian J. Chem., Sect. B, 46B, 1179* (**2007**).
[**15**]. Garg, N., Chandra, T., Archana; Jain, A.B., Kumar,A. *Eur. J. Med. Chem., 45, 1529* (**2010**).
[**16**]. Sarro, G.D., Chimirri, A., Sarro, A.D., Gitto, R., Grasso, S., Zappala, M. *Eur. J. Med. Chem*., *30, 925* (**1995**).
[**17**]. Saini, R.K., Joshi,Y.C., Joshi, P. *Phosphorus, Sulfur, Silicon Relat. Elem., 183, 2181* (**2008**).
[**18**]. Grandolini, G., Perioli, L., Ambrogi, V. Eur. J. Med. Chem., 34, 701 (1999).
[**19**]. Yamada, S., Mori, Y., Morimatsu, K., Ishizu, Y., Ozaki, Y., Yoshioka, R., Nakatani, T., Seko, H. *J. Org. Chem., 61, 8586* (**1996**).
[**20**]. Maayan, S., Ohad, N. and Soliman, K., *Bioorg. Med. Chem*., *13, 433* (**2005**).
[**21**]. Nowakowska, *Eur. J. Med. Chem., 42, 125* (**2007**).
[**22**]. Go, M.L., Wu, X. and Liu, X.L., *Current Medicinal Chemistry*, *12, 483* (**2005**).
[**23**]. Mark, C. and Nagarathnam, D., *J. Nat. Prod., 54, 1656* ( **1991**)
[**24**]. Grandolini G., Perioli L., and Ambrogi V., *Eur. J. Med. Chem., 34(9), 70* (**1999**).
[**25**]. Reddy, J. R.; Ashok, D.; Sharma, P. N., *Indian J. Chem. B, 32, 404* (**1993**).
[**26**]. Kugita, H.; Takeo, S.; Matsushima, M., *Chem. Abstr., 77, 5554* (**1972**).
[**27**]. Kugita, H.; Inoue, H.; Ikezaki, M., *Chem. Abstr., 75, 63848* (**1971**).
[**28**]. Geyer, H. M.; Watzman, N.; Buckley, J. P*., J. Pharmacol. Sci*., *59, 964* (**1970**).
[**29**]. Kawashima Co. Lt., *Chem. Abstr., 103, 105014* (**1985**).
[**30**]. Inoue, H.; Konda, M.; Hashiyama, T.; Otsuka, H.; Takahashi, K.; Gaino, M.; Date, T.; Aoe, K.; Takeda, M.; Murata, S.; Narita, H.; Nagao, T., *J. Med. Chem., 34, 675* (**1991**).
[**31**]. Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S., *Chem. Pharm. Bull., 19, 595* (**1971)**.
[**32**]. Ohno, S.; Izumi, K.; Mizukoshi, K.; Kato, K.; Hori, M., *Chem. Pharm. Bull., 31, 1780* (**1983)**.
[**33**]. Elks, J.; Ganellin, C. R., *Dictionary of Drugs, Chapmann and Hall., 867* (**1990**).
**[34]**. Dandia, A.; Upreti, M.; Rani, B.; Pant, U. C.; Gupta, I. J., *J. Fluorine Chem., 91, 171* (**1998**).
[**35**]. Jayashree, A.; Darbarwar, M., *Indian J. Chem. B, 32, 1063* (**1993**).
[**36**]. Ahmed N. K., Can. Pat. Appl. 1991, Waters J., Furnace-Door. U.S.Appl., 44l083, 1980.
[**37**]. Dumont L., Derouin M., Chartand C., Archambeault P., Gaeceau D., and Calle G., *Can. J. Physiol. Pharmacol., 69(4), 512* (**1991**).
[**38**]. Bariwal J. B., Upadhayay K. D., and Manvar A. T., *Eur. J. Med. Chem.,43(11), 2279* (**2008**).
[**39**]. Narta H., Muruta S., and Suzuki T., *Chem. Pharm. Bull*., *38, 407* (**1990**).
[**40**]. Ganjali M. R., Razavi T., and Dinarvand R., *Int. J. Electrochemical Sci., 3, 1543* (**2008**).
[**41**]. Opera T. I., Davis A. M., and Teague S. J*., J. Chem. Inf. Comput. Sci., 41, 1308* (**2001**).

[**42**]. Hagiwara M., Adachi S., and Nagao T., *Pharmacology and Experimental Therapeutics, 28l(1), l73* (**1997**).
[**43**]. Liegeois J. F., Bruliwyler J., and Rogister F., *Curr. Med. Chem., 6, 471* (**1995**).
[**44**]. Quintela, J.; Peinador, C.; Moreira, M.; Alfonso, A.; Botana, L.; Riguera, R. "**Pyrazolopyrimidines: synthesis, effect on histamine release from rat peritoneal mast cells and cytotoxic activity"**. *Eur. J. Med. Chem.* **2001**, *36, 321–332*.
[**45**]. Heyman, F.R.; Bousquer, P.; Cunha, G.; Moskey, M.; Ahmed, A.; Soni, N.; Marcotte, P.; Pease, P.; Glaser, K.; Yates, M.; Bouska, J.; Albert, D.; Blak-Schaefer, D.P.; Stewart, K.; Rafferty, P.; Davidsen, S.; Curtin, M. "**Thienopyrimidine urea inhibitors of KDR kinase"**. *Bioorg. Med. Chem. Lett.* **2007**, *17, 1246–1249.*
[**46**]. Ashalatha, B.V.; Narayana, B.; Vijaya raj, K.K.; Kumari, S. "**Synthesis of some new bioactive 3amino-2-mercabto -5, 6, 7, 8- tetra hydro [1] benzothieno [2,3-*d*] pyrimidin-4-one derivatives"**. *Eur. J. Med. Chem.* **2007**, *42, 719–728.*
[**47**]. Katada, J.; Lijima, K.; Muramatsu, M.; Takami, M.; Yasuda, E.; hayashi, M.; Hattori, M.; Hayashi, Y. "**Cytotoxic effects of NSL-1406, anew thieno pyrimidine derivative, on leukocytes and osteoclasts"**. *Bioorg. Med. Chem. Lett.* **1999**, *9, 797–802.*
[**48**]. K.Jain, K.; Bariwal, J.; Kathiravan, M.; Phoujdar, M.; Sahne, R.; Chauhan, B.; Shah, A.; Yadav, M. "**Recent advances in selective α1-adrenoreceptor antagonists as antihypertensive agents".** *Bio org. Med. Chem. Lett.* **2008**, *16, 4759–4800.*
[**49**]. Gewald, K. **" 2 amino thiophene from a-oxo mercaptans and methylene-active nitriles.** *Chem. Ber.* **1965**, *98, 3571–3577.*
[**50**]. Alagarsamy, V.; Vijayakumar, S.; Solomon, V.R. "**Synthesis of 2-mercapto-3-substituted-5, 6 dimethyl thieno[2,3-*d*]pyrimidin-4(3H)-ones as new analgesic, anti-inflammatory agents."** *Bio med. Phamacol.* **2007**, *61, 285–291*.
[**51**]. Bhutyan, M.; Rahman, M.; Abdurrahim, K.; Hossain, M.; Abunaser, M. **Synthesis and anti microbial evaluation of some new thienopyrimidine derivatives.** *Acta Pharm*. **2006**, *56, 411–450.*
[**52**]. E$_l$-Sherbeny, M.A.; El-Ashmawy, M.B.; El-Subbagh, H.I.; El-Emam, A.A.; "**Synthesis, antimicrobial and antiviral evaluation of certain thieno pyrimidine derivatives."** *Eur. J. Med. Chem.* **1995**, *30, 445–449*.
[**53**]. Alagarsamy, V.; Meena, S.; Ramseshu, K.V.; Solomon, V.R.; Thirumuruganb, K.; Dhanabala, K.; Murugan, M. "**Synthesis, analgesic, anti-inflammatory, ucerogenic index and antibacterial activities of novel 2-methylthio-3-substituted-5,6,7,8-tetrahydrobenzo (b) thieno[2,3-*d*]pyrimidin4-(3H)-ones."** *Eur. J. Med. Chem.* **2006**, *41, 1293–1300.*
[**54**]. El-Shafei, A.; Fadda, A.A.; Khalil, A.M.; Ameen. T.A.E.; Badria, F.A. "**Synthesis, antitumor Evaluation, molecular modeling and quantitative structure–activity relationship (QSAR) of some novel arylazo pyrazolo diazine and triazine analogs."** *Bioorg. Med. Chem.* **2009**, *17, 5096–5105.*
**[55].** Hirota, K.; Shirahashi, M.; Senda, S. and Yogo, M. "**Synthesis of 6-substitutedthieno[2,3-d]pyrimidine-2,4(1H, 3H)-diones"**. *J. Heterocycl. Chem.27, 717* (**1990**).
**[56].**Zhang, Yan-Lei; Wang, Yong-Qiang *Tetrahedron Letters* ( 2014) , vol. 55, # 21 p. 3255 - 3258.
**[57].** Kamal M.El-Gaml**, Synthesis and Antimicrobial Screening of New Chalcones and 1,5-Benzothiazepines Containing Quinoline Nucleus,** *American Journal of Chemistry* (2014), 4(2): 82-87.
**[58].** Barry A L. Procedure for testing antimicrobial agents in agar media. In: V.L. Corian (Ed.). Antibiotics in Laboratory Medicine. Williams and Wilkins, Baltimore, MD, 1, (1991).
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