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DESIGN, SYNTHESIS AND STRUCTURAL ELUCIDATION OF NOVEL 1, 5-BENZOOXAZEPINES CONTAINING THIENO [2, 3-*d*] PYRIMIDINE NUCLEUS AND ITS BIOLOGICAL ACTIVITY SCREENING

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ABSTRACT:
Oxazepines, which were synthesized by different methods shown in literature are of great importance in heterocyclic chemistry and more important in biology and pharmacology. Oxazepines are biologically very active molecules. In this work we synthesize new series of benzo [b] [1, 5]-oxazepine derivatives 6 a-j by applying the cyclocondensation of (E)-3-(thieno[2,3-*d*]pyrimidin-6-yl)-1-p-substituted prop-2-en-1-one derivatives 4a-j with 2-aminophenol (5) in methanol. 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-benzooxazepines 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, 6f and 6i possess good activity.
Key Words: chalcones, 2-aminophenol, cyclisation, 1, 5-benzooxazepines, Anti-microbial activity, Thieno [2, 3-*d*] Pyrimidine 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 [**I**]. Recent studies on biological evaluation of chalcones revealed some to be antibacterial, antifungal, Anti-inflammatory, anti hyperglycaemic [**II**], and anti-malarial agents [**III**].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

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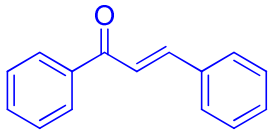
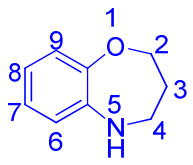


Fig.1 General structure of Chalcones

Several organic compounds containing a fused seven membered heterocyclic ring, i.e., benzoxazepines make up a broad class that attracted attention in the past few years owing to its wide range of biological activities, **Benzoxazepine** derivatives have documented consistent advances in the design of novel anticonvulsant agents benzoxazepine derivatives have been found to posses potent wide spectrum biological activities like anticonvulsant [**IV–VII**], antidepressant [**VIII**], CNS depressant [**IX**], antipsychotic [**X,XI**] and narcoleptic [**XII**].

The 1,5-benzoxazepines (1, 2,3) are important nitrogen- and oxygen-containing seven membered heterocyclic compounds in drug research since they possess diverse bioactivities .1,5-Benzoxazepines are the most well-known representatives of benzologs of 1,4-oxazepine (4) and one of the three possible benzo condensed derivatives, viz. 1,4-(5), 4,1- (6) and 1,5-benzoxazepines .

General structures of 1, 5-benzoxazepine



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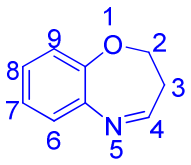

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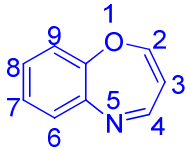

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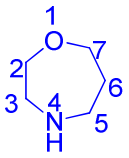

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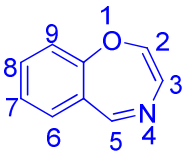

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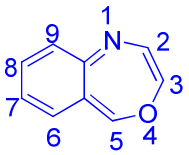


(6)

Benzoxazepines and their derivatives have biological activity **[XIII]** and pharmacological activities **[XIV].** Also acts on central nervous system as enzyme inhibitor **[XV],** analgesic **[XVI],** and antipsychotics **[XVII].** Benzo [1, 4] Oxazepines are crucial moieties in psychoactive drugs [**XVIII-XIX**]. It was found that dibenzo [b, f] [1,4]oxazepin-11(10H)ones to be selective inhibitors of human immune defiency virus (HIV) type 1 reverse transcriptase **[XX].** Known synthesis of benzoxazepines includes condensations of 2-aryloxyethylamines with 2-formylbenzoic acid **[XXI],** rearrangement of methyl 2-(8-methoxy2,3-dihydro-1,4-benzoxazepin-5-yl)benzoate using Bischler-Napieralski conditions **[XXII]** and scandium or copper-triflate catalyzed acyl amino alkylation of α-methoxy isoindolones with the formation of 1,4-benzoxazepines in moderate yields **[XXIII].** Some Oxazepines and benzoxazepines were synthesized from amides **[XXIV-XXVI],** amino acids **[XXVII-XXIX],** esters **[XXX],** acid chlorides **[XXXI]** ,flavones [**XXXII-XXXIII**], amines **[XXXIV]** and Mannich base **[XXXV-XXXVII].**

Thieno Pyrimidine is a bi cyclic heterocyclic compound consists of a five membered thiophene ring is fused to a six membered heterocyclic 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).

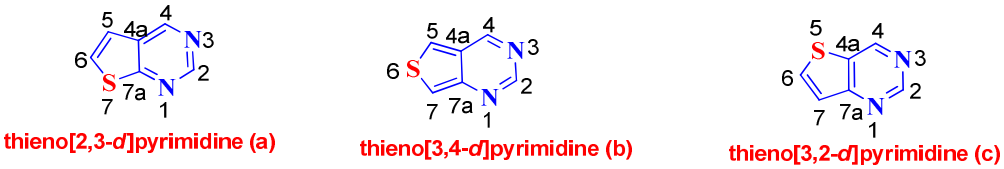


Fig: 3Structures of different isomers of Thieno Pyrimidine

As a logical consequence of thiophene – phenyl isosterism,similarly thieno pyrimidines can be considered as bio isosteres of quinazolines, which are extensively described in scientific and patent literature as displaying a plethora of biological activities. The synthesis of thieno pyrimidine derivatives as potential surrogates for the quinazoline core structure has therefore, become a routine strategy in modern drug design and development. Thieno Pyrimidines as isosteres of quinazolines are shown here.

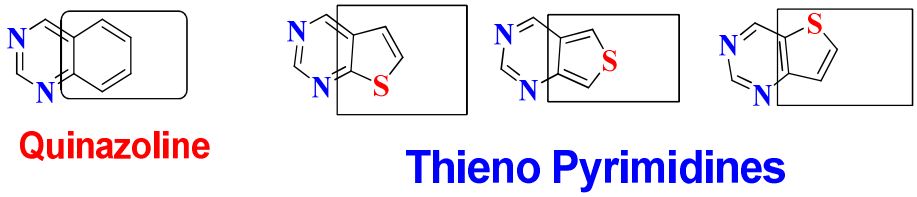


Fig: 4 Structures of thiophene – phenyl isosterism in Quinazolines and Thieno Pyrimidine

Heterocycles containing the Thieno Pyrimidine moiety (**Figure 3**) are of interest because of their interesting pharmacological and biological activities [**XXXVIII – XLIII**]. Thus, over the last two decades many thieno Pyrimidines have been found to exhibit a variety of pronounced activities, for example, as anti-inflammatory [**XLIV**], anti-microbial [**XLV**], antiviral [**XLVI**] and analgesic [**XLVII**] agents. Some Thieno Pyrimidine derivatives showed good antitumor activity [**XLVIII**].

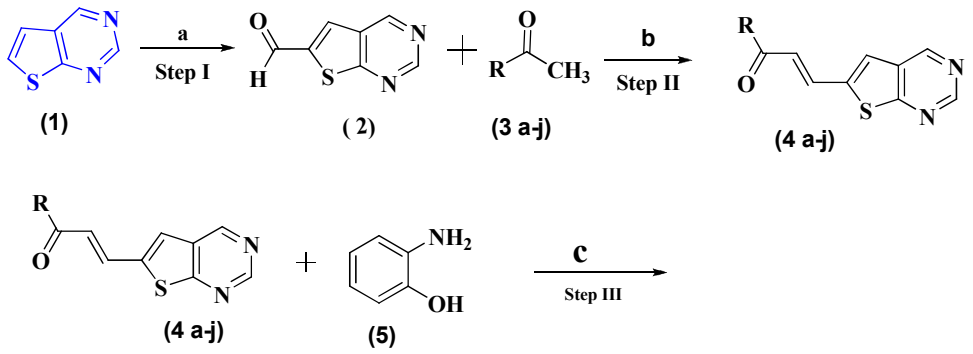
Encouraged by the significance of benzoxazepines cited in literature and the movement of our work in the bio-organic field, we have studied its anti-microbial activity. In this current

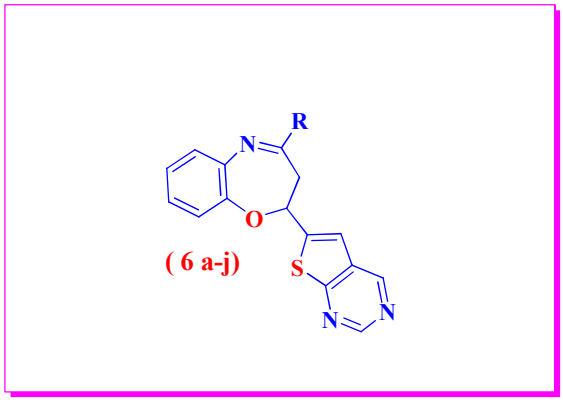
investigation, we report the synthesis, biological evaluation and preliminary structure activity relationship (SAR) of
Benzoxazepine derivatives.
The synthesis of the compounds as per the following Scheme **I** given below.
The synthetic route was depicted in scheme **I.**
The structures of all synthesized 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 five 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





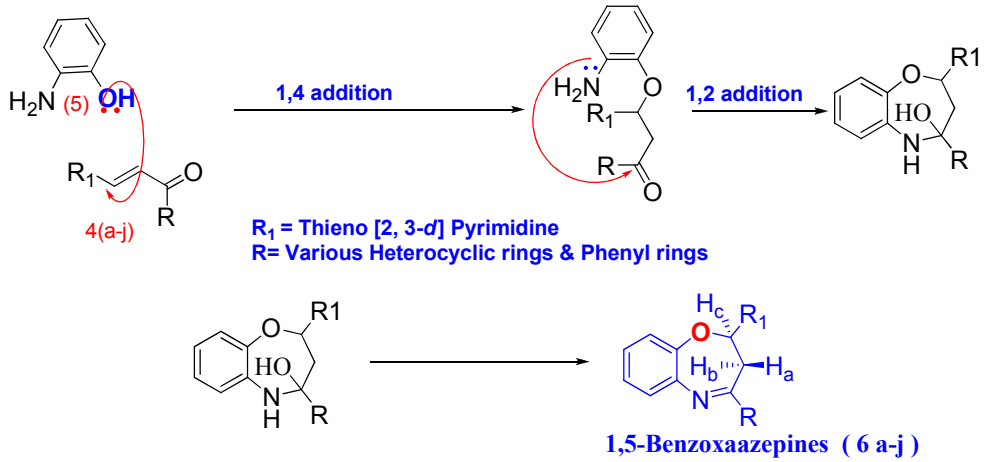
R = -Phenyl, -4 Methyl phenyl, -4 Methoxy phenyl, -4 tri fluoro methoxy phenyl, -4 Tri fluoro phenyl, -4 Nitro phenyl, - furan 2-yl, Thiophene 2-yl, pyrazin-2-yl , pyridin-2-yl acetyl groups.

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

Reagents and Reaction conditions: (a) *DMF,$POCl_3$,80^{O}C,4hrs* (b) *NaOH,Ethanol, RT, 24 hrs* (c) Methanol, AcOH, Reflux.

Benzoxazepines Containing Thieno [2, 3-*d*] Pyrimidine Nucleus (6 a-j).
Reagents and Reaction conditions: (a) *DMF,$POCl_3$,80^{O}C,4hrs* (b) *NaOH,Ethanol, RT, 24 hrs* (c) Methanol, AcOH, Reflux.

Fig. 5: A plausible mechanism pathway for the formation of 1,5-Benzoxaazepines (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 benzoxazepine ring appeared as a doublet of doublet. The doublet of **Ha** appeared at δ 1.9 ppm; doublet of **Hb** appeared at δ 2.2 ppm; and that of **Hc** appeared at δ 5.2 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 benzoxazepine 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 ^{1}H 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 (^{1}H 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 (^{1}H 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^{o}C.

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.

^{1}H 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 colour 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 colour 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 colour 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 colour 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 colour 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 colour 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 colour 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 colour 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 colour 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 colour 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]oxazepine (6a),
2-(thieno [2, 3-d] pyrimidin-6-yl)-4-p-tolyl-2,3-dihydrobenzo[b][1,4] oxazepine (6b),
4-(4-methoxyphenyl)-2-(thieno [2, 3-d] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4] oxazepine (6c),
2-(thieno [2, 3-d] pyrimidin-6-yl)-4-(4-(trifluoromethoxy) phenyl)-2, 3-dihydrobenzo[b][1,4] oxazepine (6d),2-(thieno [2, 3-d] pyrimidin-6-yl)-4-(4-(trifluoromethyl) phenyl)-2, 3-dihydrobenzo[b][1,4] oxazepine (6e), 4-(4-nitrophenyl)-2-(thieno [2, 3-d] pyrimidin-6-yl)-2,3-dihydrobenzo[b][1,4] oxazepine (6f), 4-(furan-2-yl)-2-(thieno [2, 3-d] pyrimidin-6-yl)-2,3-dihydrobenzo[b][1,4] oxazepine (6g),
2-(thieno [2, 3-d] pyrimidin-6-yl)-4-(thiophen-2-yl)-2,3-dihydrobenzo[b][1,4] oxazepine (6h),
4-(pyrazin-2-yl)-2-(thieno [2, 3-d] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4] oxazepine (6i),
4-(pyridin-2-yl)-2-(thieno[2,3-d]pyrimidin-6-yl)-2,3-dihydrobenzo[b][1,4] oxazepine (6j):
The methonolic solution (10 ml) of substituted chalconyl Thieno[2,3-*d*]Pyrimidines (0.1 mol) was added to 2-aminophenol(0.1 mol) with few drops of glacial acetic acid and refluxed for 4-5 hrs. after refluxing solvents were distilled off under reduced pressure and the solid thus

obtained were recrystallised from ethanol. The structure of compounds 6 a-j was 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]oxazepine (6a)*:*

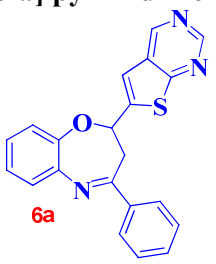


Fig. 6 Structure of 4-phenyl-2-(thieno[2,3-*d*]pyrimidin-6-yl)-2,3-dihydrobenzo[*b*][1,4]oxazepine

Yield: 65% ,

mp 126-127℃.

IR (KBr, cm^{-1}): 3110(Ar CH), 1645 (C=C Stretching), 1463(C=N Stretching), 685(C-S-C).

^{1}H NMR (400 MHz; CDCl$_3$): δH 5.1(1H,dd,O-CH),2.3(1H,dd), 1.9(1H,dd),9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.7(S, 1H), 6.9(1H,d), 7.1(1H,t), 7.3(1H,d), 7.5(1H,t), 7.6(3H,t), 7.9(2H,t).

^{13}C NMR (100 MHz; CDCl$_3$): δC 40, 80,125, 128.92, 124,135,140, 149,151.67, 155, 160.

MS (70 eV): m/z = 358(M+H)$^+$.

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

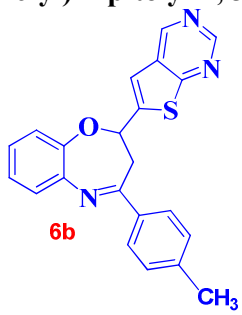


Fig.7 Structure of 2-(thieno[2,3-d]pyrimidin-6-yl)-4-*p*-tolyl-2,3-dihydrobenzo[*b*][1,4]oxazepine

Yield: 66%

IR (KBr, cm^{-1}): 3140(-Ar CH), 1625 (C=C Stretching), 1460(C=N Stretching), 665(C-S-C).

^{1}H NMR (400 MHz; CDCl$_3$): δH 2.3(3H,S), 5.2(1H,dd,O-CH),2.2(1H,dd), 1.8(1H,dd),9.34 (S, 1H, Ar-H), 8.78 (S, 1H, - Ar-H), 6.7(S,1H), 6.8(1H.d),7(1H,t), 7.3(1H,d),7.4(1H,t), 7.8(2H,d), 7.3(2H,d).

^{13}C NMR (100 MHz; CDCl$_3$): δC 23,40, 80, 125, 128.92, 124.03,135, 153, 156, 160.

MS (70 eV): m/z = 372(M+H)$^+$.

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

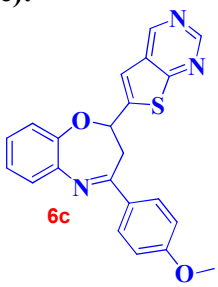


Fig.8 Structure of 4-(4-methoxyphenyl)-2-(thieno [2, 3-d] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]oxazepine

Yield: 60% ,
mp 139-140°C.
IR (KBr, cm^{-1}): 3120(-Ar CH), 2970(SP^3 CH), 1645(C=N Stretching), 1150(C-O-C Stretching), 688(C-O-C), 675(C-S-C).
^{1}H NMR (400 MHz; $CDCl_3$): δH 5.1(1H,dd,O-CH),2.3(1H,dd), 1.9(1H,dd),9.4 (S, 1H, Ar-H), 8.9 (S, 1H, - Ar-H), 6.73(S,1H), 6.7-7.2(4H,m),8.05(2H,d), 7.1(2H,d), 3.9(3H,S).
^{13}C NMR (100 MHz; $CDCl_3$): δC 56, 40, 80,120,125, 129, 125,135, 149,152, 155, 160.
MS (70 eV): m/z = 388(M+H)$^+$.

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

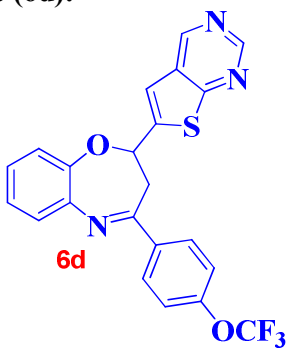


Fig.9 Structure of 2-(thieno[2,3-*d*]pyrimidin-6-yl)-4-(4-(trifluoromethoxy)phenyl)-2,3-dihydrobenzo[*b*][1,4]oxazepine

Yield: 70%,
mp 155-156°C
IR (KBr, cm^{-1}): 3110(-Ar CH), 1474 (C=N Stretching), 1624(C=C Stretching), 1340(C-F), 1160(C-O-C), 685(C-O-C), 675(C-S-C).
^{1}H NMR (400 MHz; $CDCl_3$): δH 5.1(1H,dd,O-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),6.8(1H,d), 7-7.4(3H,m).
^{13}C NMR (100 MHz; $CDCl_3$): δC 40, 78, 120,125, 129, 124.03,135, 149,151.67, 154.75, 162.
MS : m/z = 442(M+H)$^+$.

2-(thieno [2,3-*d*] pyrimidin-6-yl)-4-(4-(tri fluoro methyl) phenyl)-2, 3-dihydrobenzo[b][1,4]oxazepine (6e):

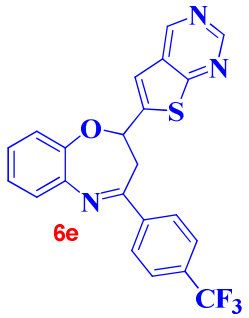


Fig.10 Structure of 2-(thieno[2,3-*d*]pyrimidin-6-yl)-4-(4-(trifluoromethyl)phenyl)-2,3-dihydrobenzo[*b*][1,4]oxazepine

Yield: 76%
mp 183-185°C
IR (KBr, cm^{-1}): 3130(Ar CH), 1470(C=N Stretching), 1380(C-F), 1190(C-O-C), 685(C-S-C).

^{1}H NMR (400 MHz; $CDCl_3$): δH 5.2(1H,dd,O-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), 6.8(1H,d), 7(1H,t),7.25(1H,t),7.4(1H,t).
^{13}C NMR (100 MHz; $CDCl_3$): δC 40, 80, 120,125, 129, 124.03,135, 149,153, 154.75, 158, 165.
MS (70 eV): m/z = 426$(M+H)^+$.

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

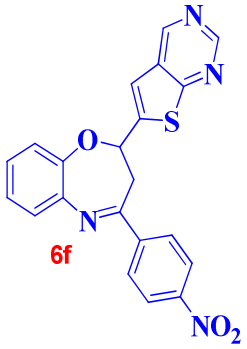


Fig.11Structure of 4-(4-nitrophenyl)-2-(thieno[2,3-*d*]pyrimidin-6-yl)-2,3-dihydrobenzo[*b*][1,4]oxazepine

Yield: 60%
M.p. 150-151°C
IR (KBr, cm^{-1}): 3120(Ar CH), 1643 (C=N Stretching), 1355 & 1567 (N-O Symmetric & Asymmetric stretching in Nitro Group), 685(C-S-C).
^{1}H NMR (400 MHz; $CDCl_3$): δH 5.3(1H,dd,O-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), 8.1(2H,d), 8.4(2H,d), 6.8(1H,d),7(1H,t),7.2 (1H,t), 7.4(1H,t).
^{13}C NMR (100 MHz; $CDCl_3$): δC 39, 80, 125, 128.92, 124.03,135, 149,151.67, 154.75, 159.62, 163.
MS (70 eV): m/z = 401$(M-H)^+$.

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

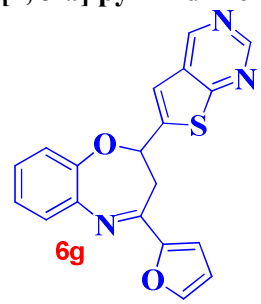
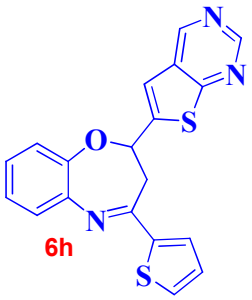


Fig.12. 4-(furan-2-yl)-2-(thieno [2, 3-*d*] pyrimidin-6-yl)-2, 3-dihydrobenzo[b][1,4]oxazepine

Yield: 65%
mp 142-143°C
IR (KBr, cm^{-1}): 3120(Ar CH), 1665 (C=N Stretching), 1072 (C-O-C stretching), 685(C-S-C).
^{1}H NMR (400 MHz; $CDCl_3$): δH 5.4(1H,dd,O-CH),2.5(1H,dd), 1.7(1H,dd), 9.3 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.6(S, 1H), 7.8(1H, d), 6.5(1H, t), 6.7(1H,d),6.9(1H,d), 7.1(1H, t), 7.2(1H,d), 7.34(1H,m).
^{13}C NMR (100 MHz; $CDCl_3$): δC 75, 40,115,125, 128.92, 124.03,135, 145,151,155, 154.75, 165.
MS: m/z = 348$(M+H)^+$.

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



6h

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

Yield: 65%

Mp 142-143°C

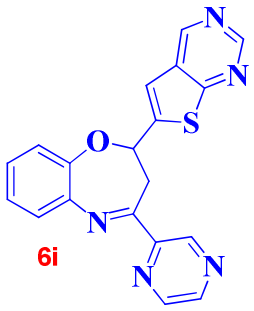
IR (KBr, cm^{-1}): 3120(Ar CH), 1460 (C=N Stretching), 1140 (C-O-C stretching), 680(C-S-C).

^{1}H NMR (400 MHz; $CDCl_3$): δH 5.3(1H,dd,O-CH),2.5(1H,dd), 1.7(1H,dd), 9.3 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.6(S, 1H), 7.7(1H, d), 7.2(1H, t), 6.7(1H,d),7.5(1H,d), 7.1(1H, t), 7.2(1H,d), 7.34(1H,m).

^{13}C NMR (100 MHz; $CDCl_3$): δC 75, 40,115,125, 128.92, 124.03,135, 145,149, 155, 163.

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

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



6i

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

Yield: 60%

mp 146-147°C

IR (KBr, cm^{-1}): 3130(Ar CH), 1465(C=N Stretching), 665(C-S-C).

^{1}H NMR (400 MHz; $CDCl_3$): δH 5.1(1H,dd,O-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), 6.7(1H,d), 7.4(1H,t),7.1(1H,t),7.3(1H,d).

^{13}C NMR (100 MHz; $CDCl_3$): δC 40, 78,120,125, 128.92, 124.03,135, 149,151, 155, 160, 163.

MS (70 eV): m/z = 360$(M+H)^+$.

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

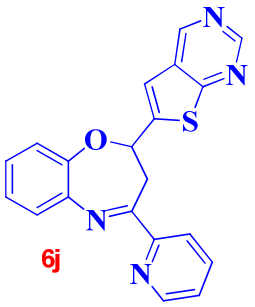


Fig.15. 4-(pyridin-2-yl)-2-(thieno[2,3-d]pyrimidin-6-yl)-2,3-dihydrobenzo[b][1,4]oxazepine

Yield: 62%,

Mp 198-199℃

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

^{1}H NMR (400 MHz; CDCl$_3$): δH 5.1(1H,dd,O-CH),2.4(1H,dd), 1.8(1H,dd), 9.4 (S, 1H, Ar-H), 8.8 (S, 1H, - Ar-H), 6.5(S, 1H), 6.7(1H,d), 7(1H,t), 7.4(1H,t), 7.3(1H,d), 8(1H,d), 7.8(1H,t), 7.7(1H,d),8.7(1H,d).

^{13}C NMR (100 MHz; CDCl$_3$): δC 40, 78,120,125, 128, 124.03,135, 149,151, 157, 160.

MS (70 eV): m/z = 359(M+H)$^+$.

Biological Activity

Antibacterial studies :

The newly prepared compounds were screened for their antibacterial activity against Bacillus subtilis, Staphylococcus aureus, Klebsiella pneumonia and Escherichia coli (clinical isolate) bacterial strains by disc diffusion method [**LII,LIII**]. A standard inoculums (1-2×107 c.f.u./ml 0.5 McFarland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The disks measuring 6 mm in diameters were prepared from Whatman no. 1 filter paper and sterilized by dry heat at 140°C for 1 h. The sterile disks previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. Solvent and growth controls were kept. Amoxicillin (30 µg) was used as positive control and the disk poured in DMSO was used as negative control and the test compounds were dissolved in DMSO at concentration of 100 and 50 µg/mL. The plates were inverted and incubated for 24 h at 37°C. The susceptibility was assessed on the basis of diameter of zone of inhibition against Gram-positive and Gram-negative strains of bacteria. Inhibition of zone of measured and compared with controls. The bacterial zone of inhibition values are given in (Table 1). The order of activity was 6h>6e>6f>6i>6d >6j >6g>>6a>6b>6c.

Table 1: Anti-bacterial activity of compounds 6(a-j):

Zone of inhibition measure in mm								
Synthesised Compounds	**Gram positive**				**Gram negative**			
	Bacillus subtilis		**Staphylococcus aureus**		**Klebsiella pneumonia**		**Escherichia coli**	
	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL
6a	7.5	3.5	8	7	9.5	7	10.5	7.5
6b	7	4.5	7	4.5	8.5	6.5	9	7
6c	6	3	7.5	5	8	6	9.5	6
6d	10	8	11.1	9.5	12	11	13.5	11
6e	12.5	10	14.5	10.5	15	13.5	16.5	12.5
6f	11.5	9	12.5	11	14.5	11.5	15.5	12

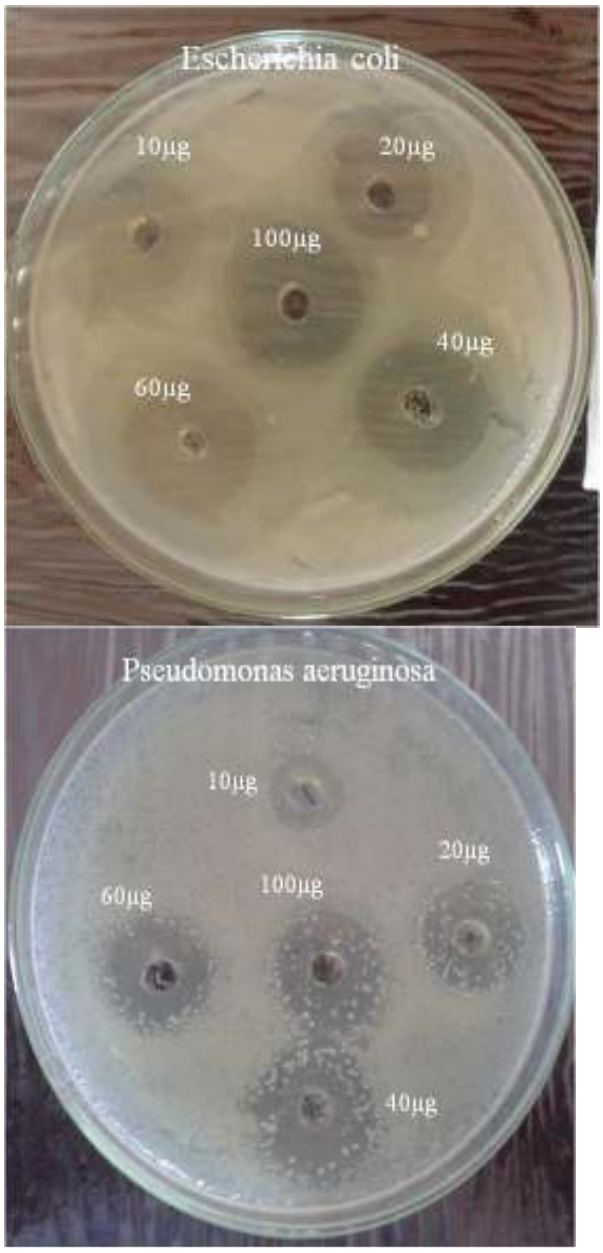
6g	8.5	6.5	9.0	6.5	10.15	8	11	8
6h	13	10.5	15	11.5	16.5	14	17	13
6i	11	9.5	11.5	8.5	12.5	12	13	11.5
6j	9.5	7	9.5	7.5	12	10	12.5	10.5
Amoxicillin	15.7	12.6	17.4	13	18	14.6	19.6	15.5
Control (**DMSO**)	---	---	----	-----	----	-----	-----	-----

Antifungal studies

The newly prepared compounds were screened for their antifungal activity against Candida albicans and Pseudomonas aeruginosa in DMSO by agar diffusion method [**LIV**]. Sabourauds agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting p^H 5.7. Normal saline was used to make suspension of corresponding species. Twenty millilitres of agar media was poured into each Petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37°C for 1 h using an agar punch, wells were made and each well was labelled. A control was also prepared in triplicate and maintained at 37°C for 3-4 days. The fungal activity of each compound was compared with Flucanazole as a standard drug. Inhibition zone were measured and compared with the controls. The fungal zone of inhibition values are given in (**Table 2**).

Table 2: Anti-fungal activity of compounds 6a-j:

Zone of inhibition measure in mm				
Synthesised Compounds	**Candida albicans**		**Pseudomonas aeruginosa**	
	100 µg/mL	40 µg/mL	100 µg/mL	40 µg/mL
6a	8.5	5	7.5	5.5
6b	8	5.5	7	3.5
6c	6.5	4.5	7	4
6d	11.5	6.5	9	6
6e	14.5	12	12.5	9.5
6f	13	11.5	10.5	8
6g	9.5	7.5	8	6.5
6h	17.5	12.5	16	12
6i	12.5	8	10.5	10
6j	11	9	10	9
Flucanazole	21	16	18.5	14
Control (**DMSO**)	---	---	---	---



Results and Discussions:

Chemistry:

The title compounds novel 1, 5-benzoxazepines 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 [**XLIX**]. Various chalcone derivatives 4(a-j) having Thieno[2,3-*d*] Pyrimidine core According to the reported procedure [**L**], These are further reacted with 2-amino phenol (5) to get target Novel 1, 5-Benzoxazepines Containing Thieno [2, 3-*d*] Pyrimidine based derivatives 6(a-j) According to the reported procedure[**LI**].

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.685& 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 Benzoxazepine 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, 6f and 6i possess good activity.

CONCLUSION:

We have synthesized a series of new chalcones 4 a-j and 1, 5-benzoxazepines 6a-j containing bioactive heteroaryl 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-benzoxazepines 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]oxazepine (6h) and 2-(thieno [2, 3-*d*] pyrimidin-6-yl)-4-(4-(tri fluoro methyl) phenyl)-2, 3-dihydrobenzo[b][1,4]oxazepine (6e)acts as potential antifungal and antibacterial agents.

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