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Synthesis and Biological Evaluation of Novel Benzothiazepines As Potential Antifungal, Anti-Tubercular and Cytotoxic Agents

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ABSTRACT

The present study describes the synthesis and biological activity of chalcone based 1,5-benzothiazepine derivatives from3,4-dichloroacetophenone by condensation with 2-aminothiophenol. The chemical characterization data of 1,5-benzothiazepine derivatives was done by elemental analysis, IR, 1H NMR, 13C NMR, and mass spectral methods. The results of the biological evaluation of synthesized compounds for their preliminary antifungal, antitubercular, and cytotoxic activities are included. The antifungal activity of 1,5-benzothiazepines was greater for benzothiazepine scaffolds, which are much more required for the activity. Most of the compounds were nearly equipotent against both the fungal species *Aspergillus niger* and *Candida tropicalis*. However, compound **o,** containing a 2"-thienyl ring present at the 5th position of the pyrazoline scaffold, was the most potent, with a MIC of 1 µg/mL. The compounds **h** and **m** containing 4”-trifluorophenyl and 2”-furyl scaffolds were next in activity against both *Aspergillus niger* and *Candida tropicalis* with MICs of 2 µg/mL. Most of the othercompounds were also active against both the fungal strains at MIC 4–16 µg/mL, respectively. The cytotoxicity of the 1,5-benzothiazepines was found to be greater for the compound **o (**MIC = 2 µg/mL**)** containing a 2”-thienyl ring at the 2nd position of the benzothiazepine scaffold, which was found to be more potent than the standard cytotoxic.

Key Words: *Benzothiazepines, chalcones, Cytotoxic, MIC, Scaffold and Cytotoxic*

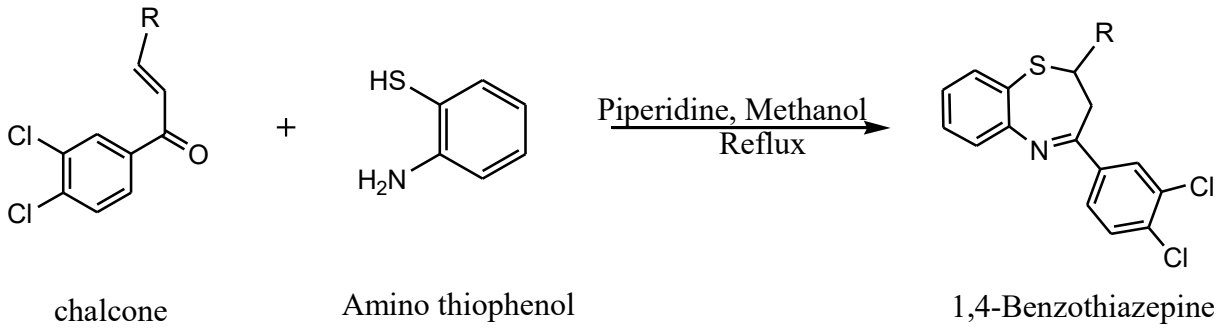
1. INTRODUCTION

1,5-benzothiazepines are one of the important classes of heterocyclic compounds with broad array of biological activities. The importance of l,5-benzothiazepine [Junjappa H et.al., 1990] nucleus has been well established as illustrated by a large number of compounds which have been patented as chemotherapeutic agents [Deepu Ch et.al., 2015]. The activities have been associated with it include, such as anti-feedant [Ambrogi V et.al., 1990], vasodilators [Eleftheriou P et.al., 2012], tranquilizer [Reddy KV et.al., 2000], antidepressant [Cherkupally SR et.al., 2008], coronary CNS stimulant [Watzman N et.al., 1970], antihypertensive [Frimayanti N et.al., 2020], calcium channel blocker [Inoue H et.al., 1991], antiulcer [Kugita H et.al., 1971], calcium antagonist [Ohno S et.al., 1983], antimicrobial [Cherkupally SR et.al., 2008] and anticonvulsant agents [Dandia A et.al., 1998]. Recently, anticancer activities [Insuasty D et.al., 2017], spasmolytic activities [Dumont L et.al., 1991; Bariwal JB et.al., 2008] hemodynamic effects have also been reported. Their analogues are used in treatment of various cardiac disorders, increases the supply of blood and oxygen to heart [Narita H et.al., 1990; Ganjali MR et.al., 2008], psychotropic agent, antiatherogenic effect [Oprea TI et.al., 2001], antimuscarinic potential [Bariwal JB et.al., 2008]. All of the synthesized 1, 5-benzothiazepines were assessed using conventional techniques for their antifungal, antitubercular, and cytotoxic properties based on the aforementioned bioactivities. The results of the biological evaluation are presented in **table 3 and figures 1, 2 & 3** respectively.

2. MATERIAL AND METHODS

Chemistry:

The reagents utilized in the synthesis were all bought from commercial sources. A nearby supply of Phenyl hydrazine hydrochloride was used. S.D. Fine Chem. Ltd., a Mumbai, India-based Company, was in which some of the solvents were acquired. Utilizing silica gel-G for TLC monitoring, the reactions were examined with a UV lamp. All melting points were calculated in open capillary tubes and conveyed in °C and were uncorrected. The results for the ^{1}H NMR and ^{13}C NMR spectra of the compounds, which were recorded using TMS as an internal standard on an Avance 400 MHz NMR spectrophotometer, are expressed in ppm. A Carlo Erba 1108 elemental analyzer was used to conduct the elemental analyses. The results of the C, H, and N elemental analyses were within ±0.4% of the calculated values.



Scheme 1: Protocol for the synthesis of benzothiazepine derivatives from chalcones

2.1 Synthesis and characterization of 1, 5-benzothiazepines

The synthesis of 3,4-dichloroacetophenone based 1, 5-benzothiazepines is shown in **Scheme-1**. The reaction involves the condensation of bi-electrophilic keto vinyl chain of the chalconederivatives with the binucleophilic 2-aminothiophenol to form the corresponding 1, 5-benzothiazepine derivatives. The procedure is a slight modification of the existing method that has been employed by Junjappa and co-workers[1].

2.1.1 General procedure for the synthesis of 1, 5-benzothiazepines

After dissolving the chalcone derivative and 2-aminothiophenol in dry methanol, piperidine was added catalytically. The mixture was then allowed to reflux until a solid crystal formed. Following cooling, the solid product was collected and cleaned using cold methanol and diethyl ether. From ethanol, the crude solid was recrystallized.

2.1.2 Synthesis of 2, 3-dihydro-2-(4-methylphenyl)-4-(3,4-dichlorophenyl)-1,5-benzothiazepine (a-o)

A catalytic quantity of piperidine was added to 0.001 mole of first step product (a-o) and 0.0015 mole of 2-aminothiophenol that had been dissolved in dry methanol. After 8 hours of reflux, the mixture separated into crystalline solid. Following cooling, the solid product was gathered and cleaned using cold methanol and diethyl ether. From ethanol, the crude solid was recrystallized.

2.2 Biological evaluation:

2.2.1 Antifungal evaluation

The antifungal activity of the 1,5-benzothiazepines was performed by serial tube dilution method employing fluconazole as standard drug. The results of the activity are displayed in table 3.

2.2.2 Antitubercular evaluation

The antitubercular activity of the 1,5-benzothiazepines was performed by MABA assay employing pyrazinamide as standard drug. The results of the activity are displayed in table 3.

2.2.3 Anticancer evaluation

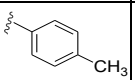
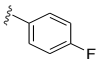
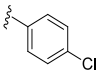
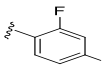
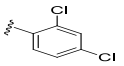
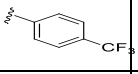
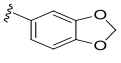
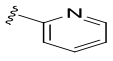
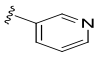
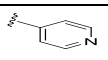
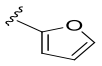
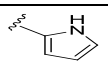
The cytotoxic activity of the 1,5-benzothiazepines was performed by MTT [Kotireddy V et.al., 2017] assay employing methotrexate as standard drug. The results of the activity are displayed in table 3.

3. RESULTS AND DISCUSSION

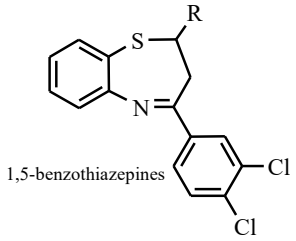
3.1 Chemistry

All the synthesized 1,5-benzothiazepine derivatives exhibited characteristic absorption bands in the IR spectra (cm^{-1}) in between 1590-1620 (C=N of benzothiazepine), 1350-1380 (C-N), 670-710 (C-S) and at different parts of the spectrum based on the particular substituents that are included in each substance. The ^1H NMR spectra of the 1,5-benzothiazepines shown characteristic doublet of doublets (dd) resonance signal at δ 5.10-5.50 (C2-H), 3.00-3.90 (C3-H-3a) with the coupling constants *J2,3a* = 5.1 Hz, *J2,3b* = 12 Hz and *J3a,3b* = 14.4 Hz, *J3a,2* = 9.9 Hz respectively. The spectra also shown other important signal around δ 3.00-3.70 (C3-H-3b) as triplet with the coupling constant value *J3b,3a* = *J3b,2* = 12.9 Hz. The spectra additionally displayed the peaks between the corresponding sections of the spectrum that corresponded to the various substituent protons and aromatic protons. The pyrimidine ring's carbons were shown distinct peaks at δ 51.16 (C-2), 42.48 (C-3), and 163.48 (C-4) in the chalcone by ^{13}C NMR spectra, distinct from those of the other carbons. The molecular ion was disclosed in the mass spectra acquired by the EI method, whereas the $[M+H]^+$ ions were revealed in the mass spectra obtained by the positive mode ionization method. Elemental analysis was used to check the composition of the synthesized compounds, and the results showed good agreement with the intended values.

Table 1: Physical characterization and elemental analysis of benzothiazepine compounds (a-o)

S.No	R	Mol. formula	Mol. Mass	M.P. (^0C)	Yield (%)	Elemental analysis					
						% Calculated			% Found		
						C	H	N	C	H	N
a		$C_{22}H_{17}Cl_2NS$	398.35	165-167	77	66.33	4.30	3.52	66.05	4.12	3.25
b		$C_{21}H_{14}FCl_2NS$	402.31	143-145	82	62.69	3.51	3.48	62.12	3.22	3.06
c		$C_{21}H_{14}FCl_2NS$	402.31	129-131	89	62.69	3.51	3.48	62.12	3.22	3.06
d		$C_{21}H_{14}Cl_3NS$	418.77	227-229	84	60.23	3.37	3.34	62.02	3.08	3.12
e		$C_{21}H_{14}Cl_3NS$	418.77	177-179	94	60.23	3.37	3.34	62.02	3.08	3.12
f		$C_{21}H_{13}F_2Cl_2NS$	420.30	149-151	85	60.01	3.12	3.33	59.45	2.95	3.16
g		$C_{21}H_{13}Cl_4NS$	453.21	155-157	74	55.65	2.89	3.09	55.19	2.64	3.01
h		$C_{22}H_{14}Cl_2F_3NS$	452.32	133-135	79	58.42	3.12	3.10	58.11	2.86	2.98
i		$C_{22}H_{15}Cl_2NO_2S$	428.33	141-143	89	61.69	3.53	3.27	61.22	3.12	3.05
j		$C_{20}H_{14}Cl_2SN_2$	385.31	152-154	90	62.34	3.66	7.27	62.09	3.29	7.11
k		$C_{20}H_{14}Cl_2SN_2$	385.31	144-145	93	62.34	3.66	7.27	62.09	3.29	7.11
l		$C_{20}H_{14}Cl_2SN_2$	385.31	121-123	71	62.34	3.66	7.27	62.09	3.29	7.11
m		$C_{19}H_{13}C_{l2}NOS$	374.28	139-141	75	60.97	3.50	3.74	60.45	3.14	3.33
n		$C_{19}H_{14}Cl_2ON_2S$	373.30	118-120	86	61.13	3.78	7.50	60.96	3.48	7.32

o		$C_{19}H_{13}Cl_2ONS_2$	390.35	119-121	82	58.46	3.36	3.59	58.10	3.07	3.24



1,5-benzothiazepines

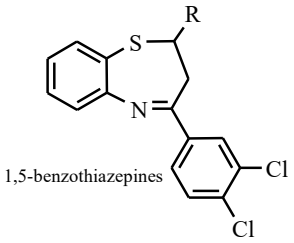
Table 2: Spectral Data of titled Compounds (3a-o)

S. No.	FT-IR values (cm $^{-1}$)	^{1}H NMR, Chemical shift (δ) in ppm
a	1597 (C=N), 1508 (C=C), 1371(C-N), 694 (C-S), 901(C-Cl)	5.13 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.55 (dd, J3a,3b = 14.4 Hz, J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.18 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 7.15-8.19 (11H, Ar-H), 2.26 (s, 3H, -CH3)
b	1625 (C=N), 1509 (C=C), 1399(C-N), 689 (C-S), 933(C-F), 835 (C-Cl)	5.22 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.52 (dd,J3a,3b = 14.4 Hz, J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.26 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 7.18-8.05 (11H, Ar-H)
c	1615 (C=N), 1512 (C=C), 1389 (C-N), 691 (C-S), 935 (C-F), 831 (C-Cl)	5.33 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.76 (dd, J3a,3b = 14.4Hz, J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.22 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 7.63-8.19 (11H, Ar-H)
d	1595 (C=N), 1502 (C=C), 1384 (C-N), 778 (C-Cl), 667(C-S), 835 (C-Cl)	5.31 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 4.06 (dd, J3a,3b = 14.4Hz, J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.78 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 7.72-8.49 (11H, Ar-H)
e	1596(C=N), 1510 (C=C), 1365(C-N), 688 (C-S), 805(C-Cl), 828 (C-Cl)	5.44 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.79 (dd, J3a,3b = 14.4Hz, J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.52 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 7.61-8.56 (11H, Ar-H)

f	1612 (C=N), 1501 (C=C), 1382 (C-N), 689 (C-S), 829 (C-Cl), 926 (C-F)	5.43 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.85 (dd, J3a,3b = 14.4Hz, J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.58 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 7.65-8.25 (10H, Ar-H)
g	1598(C=N), 1506 (C=C), 1384(C-N), 681 (C-S), 821(C-Cl)	5.26 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.45 (dd, J3a,3b = 14.4Hz, J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.34 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 7.22-8.22 (10H, Ar-H)
h	1593(C=N), 1502 (C=C), 1382(C-N), 687(C-S), 925(C-F), 805 (C-Cl)	5.33 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.52 (dd, J3a,3b = 14.4Hz, J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.15 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 7.15-8.21 (11H, Ar-H)
i	1592(C=N), 1502 (C=C), 1370(C-N), 1232 (-O-CH2-O-), 689 (C-S), 841 (C-Cl)	5.19 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.45 (dd, J3a,3b = 14.4Hz, J3a,2 = 9.1 Hz, 1H, C3-H-3a), 3.11 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 7.21 (1H, s, Ar-H), 7.44 (3H, m, Ar-H), 6.18 (2H, s, O-CH2-O), 7.24-7.99 (10H, Ar-H)
j	1599(C=N), 1506 (C=C), 1382(C-N), 815(C-Cl), 698(C-S)	5.13 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.36 (dd, J3a,3b = 14.4Hz, J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.23 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 6.69-8.10 (11H, Ar-H)

k	**1606(C=N), 1508 (C=C), 1388(C-N), 823(C-Cl), 654(C-S)**	**5.22 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.33 (dd, J3a,3b = 14.4 Hz,J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.28 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b),6.72-8.11 (11H, Ar-H)**
l	**1605(C=N), 1503(C=C), 1386(C-N), 828(C-Cl), 644(C-S)**	**5.28 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.10 (dd, J3a,3b = 14.4 Hz, J3a, 2 = 9.9 Hz, 1H, C3-H-3a), 3.29 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 6.68-7.85 (11H, Ar-H)**
m	**1608(C=N), 1509(C=C), 1390(C-N), 1211 (C-O-C), 679 (C-S), 836 (C-Cl)**	**5.15 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.28 (dd, J3a,3b = 14.4 Hz,J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.15 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b),6.79-8.05 (10H, Ar-H)**
n	**1648(C=N), 1505(C=C), 1365(C-N), 3211 (-NH), 678 (C-S), 821 (C-Cl)**	**5.05 (1H, s, -NH), 5.23 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.26(dd, J3a,3b = 14.4 Hz, J3a,2 = 9.9 Hz, 1H, C3-H 3a), 3.05(t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b), 6.69-8.22 (10H, Ar-H)**
o	**1633(C=N), 1611(C=C),1519(CH=CH), 628 (C-S), 823 (C-Cl)**	**5.55 (dd, J2,3a = 5.1 Hz, J2,3b = 12 Hz, 1H, C2-H), 3.75 (dd, J3a,3b = 14.4 Hz,J3a,2 = 9.9 Hz, 1H, C3-H-3a), 3.60 (t, J3b,3a = J3b,2 = 12.9 Hz, 1H, C3-H-3b),7.10-8.19 (10H, Ar-H)**

Table 3: Results of the Pharmacological activities of benzothiazepine derivatives (a-o)



1,5-benzothiazepines

S.No	Compound	R	Antitubercular activity	Cytotoxic activity	Anti-fungal activity	
			MIC (µg/mL) of *M. Tuberculosis* $H_{37}Rv$	DU-145	*An*	*Ct*
1	**a**	4"-methyl phenyl	150	98 ± 2	8	8
2	**b**	4"-fluoro phenyl	50	38 ± 2	8	4
3	**c**	2"-fluoro phenyl	100	96 ± 2	8	8
4	**d**	4"-chloro phenyl	100	42 ± 2	4	16
5	**e**	2"-chloro phenyl	100	36 ± 2	8	8
6	**f**	2",4"-fluoro phenyl	12.5	86 ± 2	8	4

7	**g**	2",4"-dichloro phenyl	50	72 ± 2	8	8
8	**h**	4"-trifluoro phenyl	12.5	88 ± 1	**2**	**2**
9	**i**	3",4"-methylene dioxy phenyl	150	46 ± 2	8	8
10	**j**	2"-pyridinyl	100	95 ± 2	16	16
11	**k**	3"-pyridinyl	100	70 ± 2	8	16
12	**l**	4"-pyridinyl	100	52 ± 2	16	8
13	**m**	2"-furfuryl	25	36 ± 2	**2**	**2**
14	**n**	2"-pyrrolyl	25	**12 ± 2**	8	8
15	**o**	2"-thienyl	**3.12**	**2 ± 1**	**1**	**1**
16	Standard	Pyrazinamide	**3.12**	---	---	---
		Methotrexate	---	5 ± 1	---	---
		Fluconazole	---	---	≤1	≤1

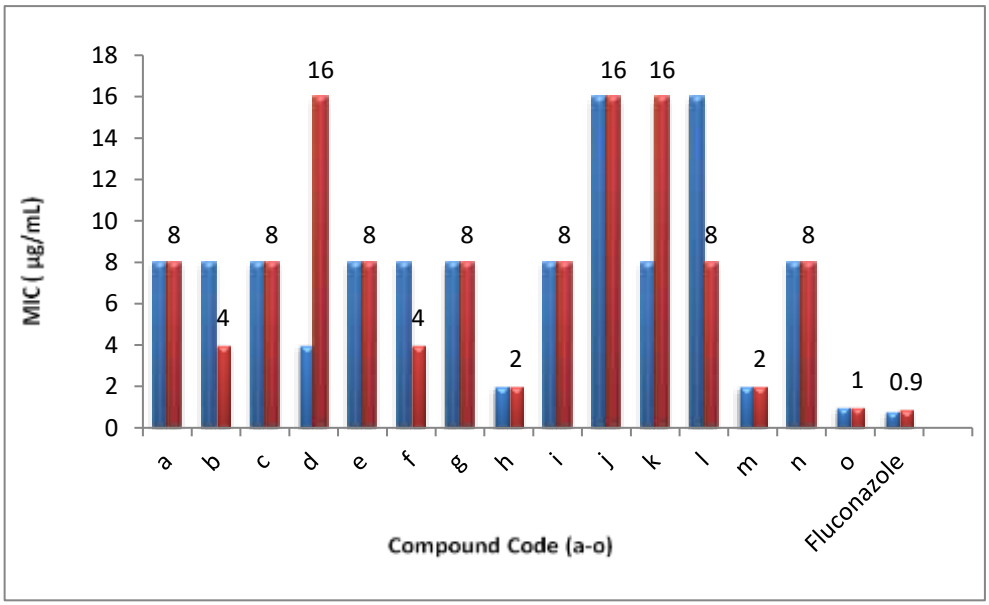


Figure 1: Graphical representation of MIC (µg/mL) values of synthetic (a-o) compounds in anti-fungal activity by Serial dilution assay.

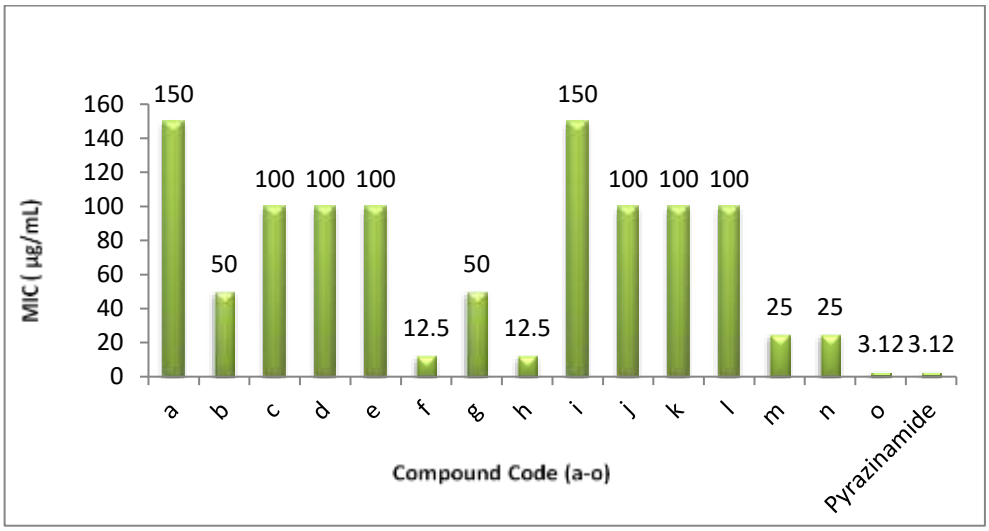


Figure 2: Graphical representation of MIC (µg/mL) values of synthetic (a-o) compounds in anti-Tubercular activity by Serial dilution assay.

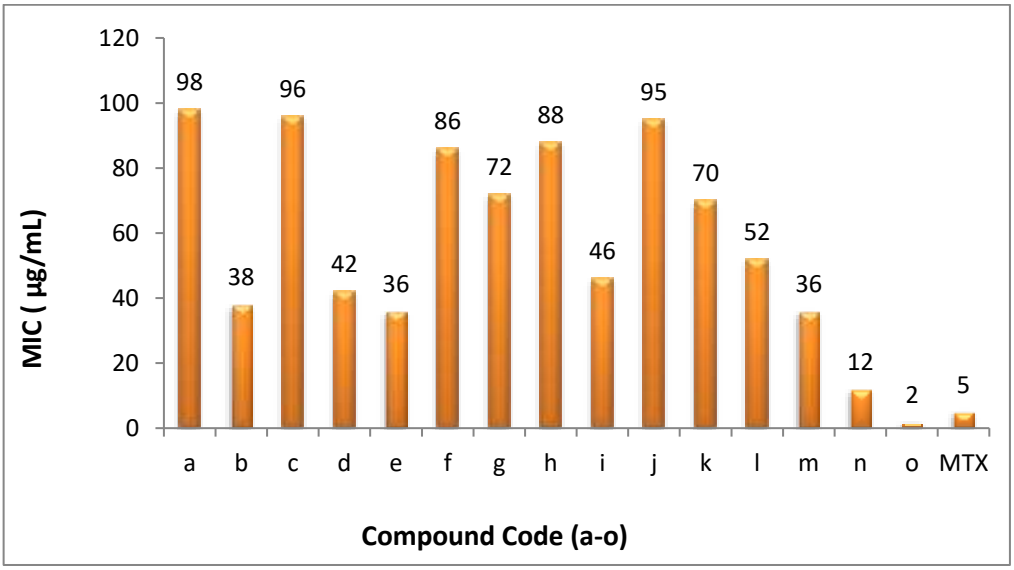


Figure 3: Graphical representation of MIC (µg/mL) values of synthetic (a-o) compounds in cytotoxic activity by MTT assay.

3.2 Biological evaluation

3.2.1 Anti-fungal activity

Results of the antifungal activity clearly notify that the chalcones exhibited significant antifungal activity with altered MIC values against the tested organisms, but not as much of the standard fluconazole. The antifungal activity of 1,5-benzothiazepines was more than chalcones and Pyrazolines representing that benzothiazepine scaffold is much required for the activity than the open chain chalcones and 5-membered Pyrazolines. Most of the compounds were nearly equipotent against both the fungal species *Aspergillus niger* and *Candidatropicalis*. However, compound**o**containing 2"-thienyl ring present at the 5thposition of thepyrazoline scaffold was the most potent with MIC 1 µg/mL. The compounds **h** and **m** containing 4"-trifluorophenyl and 2"-furyl scaffolds were next in activity against both *Aspergillus niger* and *Candida tropicalis* with MIC 2 µg/mL. Most of the other compoundswere also active against both the fungal strains at MIC 4-16 µg/mL respectively.

A Structure-Activity-Relationship study based on the above results indicated that 1,5-benzothiazepine scaffold can be a potential moiety for the antifungal activity compared to chalcones and pyrazolines.

3.2.2 Anti-tubercular activity

The results of the antitubercular activity of novel 1,5-benzothiazepines **(a-o)** revealed that all the compounds exhibited poor activity against *M. tuberculosis* H37Rv strain. The benzothiazepines were found to be less potent than their corresponding chalcones and pyrazolines. However, the compound **o** was unique in its activity because of its equal potency with pyrazinamide. The compound **f** and **h** containing 2",4"-difluorophenyl and 4"-trifluorophenyl moieties shown considerable activity at MIC 12.5 µg/mL. All the other compounds were somewhat potent with MIC values ranging between 25-150 µg/mL.

A Structure-Activity-Relationship study based on the above results indicated 1,5-benzothiazepine nucleus had contributed poorly with regard to antitubercular activity. However compound **o** can be modified by incorporating addition electron withdrawing or releasing substituents for enhancing the antitubercular activity.

3.2.3 Cytotoxic activity

The synthesized 1,5-benzothiazepines **(a-o)** were evaluated for their in vitro cytotoxic activity against prostate cancer cell line DU-145 by employing MTT assay and most of the compounds exhibited considerable activity compared to the standard drug methotrexate. The cytotoxicity of the 1,5-benzothiazepines was found to be more than the corresponding chalcones and pyrazolines. The compound **o (**MIC- 2 µg/mL**)** containing 2"-thienyl ring at 2nd position of the benzothiazepine scaffold was found to be most potent than the standard, methotrexate. The compound **n**, containing 2"-pyrrolyl was next in potency with an MIC of 12 µg/mL. All other compounds also exhibited significant cytotoxic activity at MIC less than 100 µg/mL.

The structure activity relationships based on the above results indicated that five membered heterocyclic rings are most essential for the cytotoxic activity. Further modification of the 2"-thienyl and 2"-pyrrolyl rings by incorporating different electron withdrawing or releasing groups may enhance the cytotoxic activity of chalcones.

4. CONCLUSION

A new series of 1,5-benzothiazepines were synthesized with a good biological activity. All the synthesized compounds characterized using standard procedures for their antifungal, antitubercular, and cytotoxic properties by In-vitro methods. A research of the relationship between structure and activity found that the antifungal, antitubercular, and cytotoxic activities required the presence of the 2"-thienyl, 4"-trifluorophenyl, 2"-furyl, and 2"-pyrrolyl moieties. The activity of 1,5-benzothiazepines may be enhanced by additional modification of structure by adding various electron-withdrawing or releasing groups. The above results reflect in drug discovery and development of lead molecule by conducting various in-silico and in-vivo studies in further days.

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CONFLICT OF INTEREST

The authors are declared that there is no conflict of interest.

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