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Synthesis, characterization, biological evaluation and QSAR studies of 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5] benzothiazepines as potential antimicrobial agents

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ABSTRACT

A novel series of 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3**) has been synthesized and screened for their antimicrobial activity against Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria and fungi (*Aspergillus fumigates* and *Candida albicans*). The antimicrobial evaluation data indicated that the compounds, **3d**, **3g**, **3h**, **3k**–**3p** exhibited very promising antibacterial activity and the derivatives **3k**, **3l**, **3o** and **3p** exhibited high antifungal activity. The QSAR studies carried out to find out the correlation between the antimicrobial activity and physicochemical properties of synthesized benzothiazepines (**3**) indicated the predominance of electronic parameters in describing their antimicrobial activity.

1. Introduction

Heterocycles containing nitrogen and sulfur as heteroatoms undoubtedly constitute an important class of highly applicable bioactive molecules because of their interesting biological activities and uses as key structural motif for the synthesis of various products of pharmaceutical interest. Benzothiazepines are fused seven membered heterocycles containing nitrogen and sulfur as heteroatoms which are extremely versatile and important class of privileged scaffolds that features in a large number of life saving drugs [1–3]. Perusal of literature on biological and pharmacological studies reported for 1,5-benzothiazepines reveals that these compounds have immense chemotherapeutic importance as antihypertensives [4], calcium channel modulators [5,6], anticonvulsants [7], CNS depressants [8,9], antagonists [10], vasodilators [11], antiasthemics [12], blood platelet aggregation inhibitors [13], antiarrhythmic agents [14], anticancer agents [15], antibacterials [16], antifungals [17], anti-HIV agents [18], free radical scavengers [19], gastrin receptor antagonists [20], anti-inflammatory, antiallergic agents [21–25], etc.

A review by Bariwal et al. [26] provides an excellent account of the diverse pharmacological properties associated with this moiety. In addition, 1,5-benzothiazepines are used as starting materials for the preparation of other fused heterocyclic rings [27]. Owing to their importance from a pharmacological and synthetic point of view, several approaches have been reported for the synthesis of 1,5-benzothiazepines such as 2-aminobenzenethiols with α,β-unsaturated ketones [28] or ω-bromoacetophenones and aromatic aldehydes [29] or chalcone in the presence of SiO_2 [30] or chalcone analogs of dehydroacetic acid [31], α,β-unsaturated ketones with bis(2-nitrophenyl)disulfide in the presence of $TiClO_4$/Sm [32], 2-aminophenyldisulfide with itaconic anhydride and dimethylitacone [33], photochemical reaction of 2-phenylbenzothiazole with ethoxyacetylene/ethoxy propyne [34], microwave activated reaction between 3-(4′-fluoro-2′-methylbenzoyl)-2-propenoic acid with 2-aminothiolphenol [35], reaction of substituted 2-aminobenzenethiol and methyl-(±)-trans-3-(4-methoxy/benzyloxyphenyl)glycidate in an ionic liquid *viz.*, [BMIM]Br and [BMIM]PF_6 [36], etc. The most convenient method for the synthesis of these compounds involves the treatment of dinucleophiles, 2-aminobenzenethiols with α,β-unsaturated ketones.

QSAR studies are undoubtedly important in drug design. Once a correlation between structure and activity is established, newly designed compounds, including those not yet synthesized, can be readily screened on the computer to select the structures with

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desired properties. Then, it is possible to select the most promising compounds to synthesize and test in the laboratory. Consequently, the QSAR strategies can save resources and accelerate the process of developing new molecules for use as drugs, materials, and additives or for any other purposes [37i–xii]. Unfortunately, almost all QSAR models are able to predict the biological activity against only one single target (protein, cell line, microbial specie, etc.). However, in many cases we need to predict the biological activity of the new compounds for many different targets. Gonzalez-Diaz et al. have called this situation the multi-target QSAR case and have given a classification of the different multi-target schemes for QSAR of models: (a) multiple output-coded ot-QSAR, (b) output-coded mt-QSAR, or (c) input-coded mt-QSAR. The three schemes, in turn, may be linear or non-linear or all of them. In case (a), with linear equations, we use many one-target QSAR (ot-QSAR) equations to predict the biological activity of different targets. Consequently, the multi-target information is coded in the output variables. In case (b) mt information is coded in many output variables (one for each target) but we use only one equation or model, for instance, a Canonical Regression Analysis in the linear case or an Artificial Neural Network (ANN) in the non-linear case. In case (c) we use different types of input variables to code the mt information. At least three sub-cases have been described by Gonzalez-Diaz et al. for input-coded mt-QSAR. In sub-case (c.1) mt information is introduced inside the molecular descriptor, see works co-authored by Prado-Prado et al. [37xiii–xxii]. In sub-case (c.2) mt information is introduced outside the molecular descriptor in a target structure-less variable (we do not need to know the target structure). This is the case of the deviation between the molecular descriptor of the compound and the average value of the same descriptors for all compounds active for a given target. This scheme is very useful when the target is not a protein but a cell line or microbial specie and we do not known the specific molecular target. For this last situation see works co-authored by Conchu et al. [37xxiii], or Speck-Planche et al. [37xxiv–x]. In sub-case (c.3) of output-coded mt-QSAR we use molecular descriptors for both drugs and targets to code the mt information [37xxxi–iv]. In the present work, we need to study the biological activity of new 1,5-benzothiazepines vs. different bacterial and fungi species. To solve this problem, we shall use as a first approximation scheme.

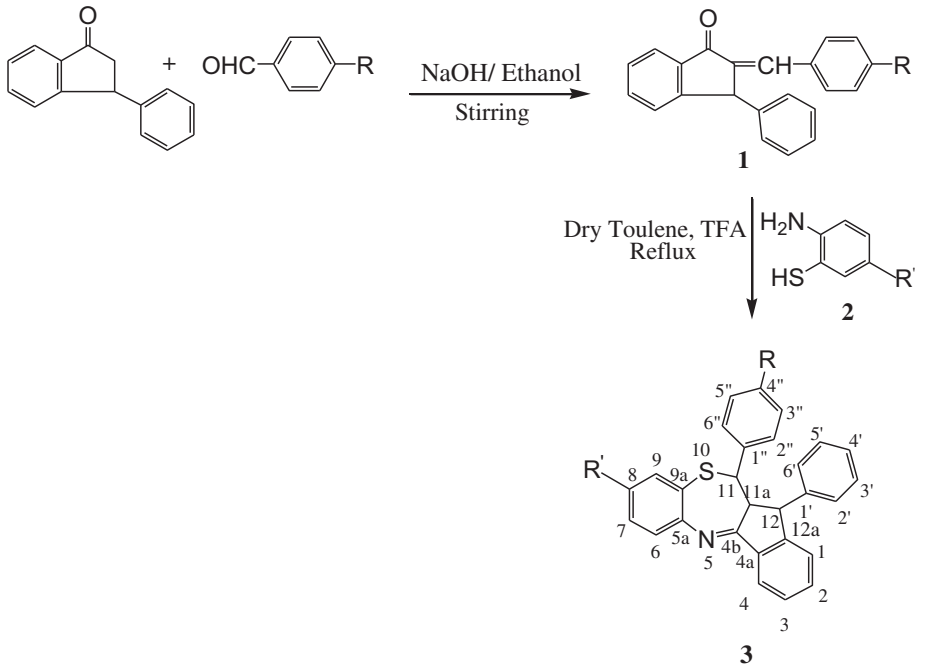
Inspired by the manifold applications of 1,5-benzothiazepine nuclei and in continuation of our interest in the synthesis and biological evaluation studies of heterocyclic compounds containing nitrogen and sulfur as heteroatoms, we report herein the synthesis, characterization, antimicrobial activities (antibacterial and antifungal) and QSAR studies of a novel series of sixteen 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**).

2. Results and discussion

2.1. Chemistry

The condensation reaction between α,β-unsaturated ketones and 2-aminobenzenethiols was studied. The α,β-unsaturated ketones taken were 2-(*E*)-benzylidene/*p*-substituted benzylidene-3-phenyl indan-1-ones (**1**) which, in turn, were prepared by condensation of 3-phenyl indan-1-one with appropriately substituted aldehydes in base-catalyzed conditions ($NaOH/C_2H_5OH$) [38]. The 5-substituted-2-aminobenzenethiols (**2**) needed for the purpose were synthesized in good yields by base-catalyzed hydrolytic fission of 6-substituted-2-aminobenzothiazoles as per literature procedures [39,40]. The condensation of equimolar quantities of 2-(*E*)-benzylidene/*p*-substituted benzylidene-3-phenyl indan-1-ones (**1**) with 2-aminobenzenethiol/5-substituted-2-aminobenzenethiols (**2**) in toluene using trifluoroacetic acid (TFA) as a catalyst [41,42] furnished 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**) in good yields (70–83.20%) (Scheme 1).

The structures of all the newly synthesized 1,5-benzothiazepines (**3a**–**3p**) were corroborated on the basis of spectral and analytical results. The IR spectra of compounds (**3a**–**3p**) exhibited strong absorptions in the region 1614–1594 cm^{-1} due to C=N stretching [43] and absence of the characteristic >C=O and NH_2 absorptions in the regions at 1695–1650 cm^{-1} and 3400–3100 cm^{-1} respectively indicates that the amino group of the 2-aminobenzenethiols (**2**) and carbonyl group of 2-(*E*)-benzylidene/*p*-substituted benzylidene-3-phenyl indan-1-ones (**1**) have undergone reaction to furnish 1,5-benzothiazepines (**3**). The ^1H NMR spectra of **3a**–**3p** exhibited two doublets and one double doublet, each integrating for one proton which can be safely assigned to the three protons attached to the sp^3 hybridized carbons, i.e. C_{11}–H, C_{12}–H and C_{11a}–H respectively. The double doublet in the upfield region at δ 2.99–3.95 (J = 11.7–12.0 Hz and 4.2–5.0 Hz) can be safely assigned to C_{11a}–H due to shielding by two phenyl groups present at C_{11} and C_{12} [44,45]. Further, signals appeared as doublets in the regions at δ 3.62–4.56 (J = 4.2–5.0 Hz) and δ 3.90–5.02 (J = 11.7–12.0 Hz) are assigned to C_{12}–H and C_{11}–H respectively, based on the relative positions of chemical shifts of protons present in similar environments in the ^1H NMR spectra of analogous compounds [46]. The C_{11}–H, C_{11a}–H and C_{12}–H present in 1,5-benzothiazepines (**3**) are chiral centers. The coupling constant (J) values indicate that C_{11}–H and C_{11a}–H protons are *trans* oriented and C_{11a}–H and C_{12}–H are *cis* oriented as in the case of related tetracyclic 1,5-benzothiazepines. This similarity also indicates a diastereoselective formation of one diastereomer of tetracyclic 1,5-benzothiazepines (**3a**–**3p**) as sole isolable products. This unequivocally finds support from the results on the synthesis of the analogous compounds under acidic conditions as reported in the literature [4,47–49]. The compounds **3a**, **3e**, **3i** and **3m** in which there is no substitution at C_8, the multiplet in ^1H NMR spectra in the region at δ 6.27–7.01 is due to C_7–H and C_9–H [50]. However, in the compounds **3b**–**3d**, **3f**–**3h**, **3j**–**3l**, **3n**–**3p**, with substitution at C_8, these protons i.e. C_7–H and C_9–H could not be distinguished and appeared in the aromatic region at δ 6.52–7.92 along with the remaining protons (vide experimental). At lowest field was exhibited one proton doublet of doublet in the region at δ 7.86–8.34 due to C_4–H with coupling constant (J) ranging from 7.5 to 8.1 and 2.0 to 2.1 Hz [51]. The aliphatic protons were found to display signals in their characteristic regions. Further, the ratio of the aromatic to aliphatic protons was found satisfactory. In ^{13}C NMR spectra, three characteristic absorption signals in the regions at δ 53.18–54.10, δ 57.02–58.90 and δ 65.49–67.59 were assigned to three sp^3 carbons, i.e. C_{11a}, C_{12}, and C_{11} respectively [42,52]. The signals in the aromatic regions at δ 124.60–126.15, δ 134.37–135.65, δ 131.07–132.98, δ 123.28–124.82, δ 133.16–134.79 and δ 141.33–143.97 are in accord with the observed trends for carbon atoms C_1–C_4, C_{4a} and C_{12a} respectively of the indane moiety [53]. Further, signals in the regions at δ 137.27–138.91, δ 118.64–123.52, δ 112.48–126.42, δ 126.30–154.60, δ 118.10–125.27 and δ 118.10–120.80 were assigned to the carbon atoms C_{5a}, C_6–C_9 and C_{9a} respectively which is in accord with the values reported in the literature for the analogous compounds [54–56]. With the variation of R', the change in chemical shift values due to C_8 signal was observed as found in benzothiazines [57]. The signal in the region at δ 162.23–165.81 was assigned to C_{4b} which is in obeisance with the chemical shift values observed for the carbon of C=N moiety present in the ring of benzothiazepines [58]. The signals due to the remaining aromatic and aliphatic carbons were observed in the expected regions. Further, the mass spectral data and analytical



3a: R = R' = H
3b: R = H, R' = CH_3
3c: R = H, R' = OCH_3
3d: R = H, R' = Cl
3e: R = CH_3, R' = H
3f: R = CH_3, R' = CH_3
3g: R = CH_3, R' = OCH_3
3h: R = CH_3, R' = Cl
3i: R = OCH_3, R' = H
3j: R = OCH_3, R' = CH_3
3k: R = OCH_3, R' = OCH_3
3l: R = OCH_3, R' = Cl
3m: R = Cl, R' = H
3n: R = Cl, R' = CH_3
3o: R = Cl, R' = OCH_3
3p: R = Cl, R' = Cl

Scheme 1. Synthesis of 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**).

data of **3a**–**3p** are in good agreement with their molecular formula.

2.2. Biological section

The analogs of 1,5-benzothiazepine are reported to have antimicrobial activities against a variety of bacterial and fungal strains i.e. – *Bacillus subtilis*, *Bacillus sphaericus*, *Klebsiella aerogenes*, *Chromobacterium violaceum*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Candida krusei*, *Candida parapsilosis*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, etc. [59–62]. Keeping in view of this, we carried out antimicrobial screening of synthesized 1,5-benzothiazepine derivatives (**3**) against some selected species as discussed below.

2.2.1. Antibacterial activity

The *in vitro* antibacterial activity of the synthesized 1,5-benzothiazepines (**3a**–**3p**) was tested against two Gram-positive bacteria *viz. B. subtilis* (MTCC 441) and *S. aureus* (MTCC 7443), two Gram-negative bacteria *viz. E. coli* (MTCC 42) and *P. aeruginosa* (MTCC 7952) using serial dilution technique and Minimum inhibitory concentrations (MIC) were determined as described in literature [63]. While carrying out antibacterial activity penicillin and streptomycin were used as reference compounds and MIC were determined in terms of μmol/mL (Fig. 1, Table 1).

A perusal of the results from Fig. 1 and Table 1 reveals that some of the derivatives exhibited notable antibacterial activity, almost comparable to penicillin (MIC, 0.0046 μmol/mL) and streptomycin (MIC, 0.0107 μmol/mL) *viz.* **3m** (MIC, 0.0071 μmol/mL) against *B. subtilis* and **3h** (MIC, 0.0069 μmol/mL) and **3k** (MIC, 0.0067 μmol/mL) against *S. aureus*. The compounds **3c** (MIC, 0.0288 μmol/mL), **3d** (MIC, 0.0142 μmol/mL), **3g** (MIC, 0.0279 μmol/mL), **3h** (MIC, 0.0138 μmol/mL), **3k** (MIC, 0.0269 μmol/mL), **3l** (MIC, 0.0267 μmol/mL), **3n** (MIC, 0.0276 μmol/mL) and **3o** (MIC, 0.0267 μmol/mL) exhibited notable activity against *E. coli*, almost comparable to penicillin (MIC, 0.0374 μmol/mL). The compounds **3g** (MIC, 0.0069 μmol/mL), **3l** (MIC, 0.0066 μmol/mL) and **3n** (MIC, 0.0069 μmol/mL) exhibited notable activity against *P. aeruginosa*, almost comparable to penicillin (MIC, 0.0187 μmol/mL). However, **3d** and **3p** exhibited negligible activity against *B. subtilis*, **3i** and **3n** against *S. aureus*, **3p** against *E. coli* and **3e** and **3i** against *P. aeruginosa*.

Percent change in antibacterial activity of different derivatives **3b**–**3p** over parent compound 11,12-diphenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepine (**3a**) was calculated using the following formula:

$$\text{Percent change in antibacterial activity} = (P - D)/P \times 100$$

where *P* and *D* are minimum inhibitory concentrations (MIC) in μmol/mL for the parent compound and derivative respectively (Fig. 2, Table 2).

It is depicted from the data presented in Fig. 2 and Table 2 that derivatives **3m** exhibited high activity against *B. subtilis*, **3c**, **3g**, **3h**, **3k and 3l** against *S. aureus*, **3c**, **3d**, **3g**, **3h**, **3k**, **3l**, **3n**–**3p** against *E. coli* and **3g**, **3l** and **3o** against *P. aeruginosa* compared to the

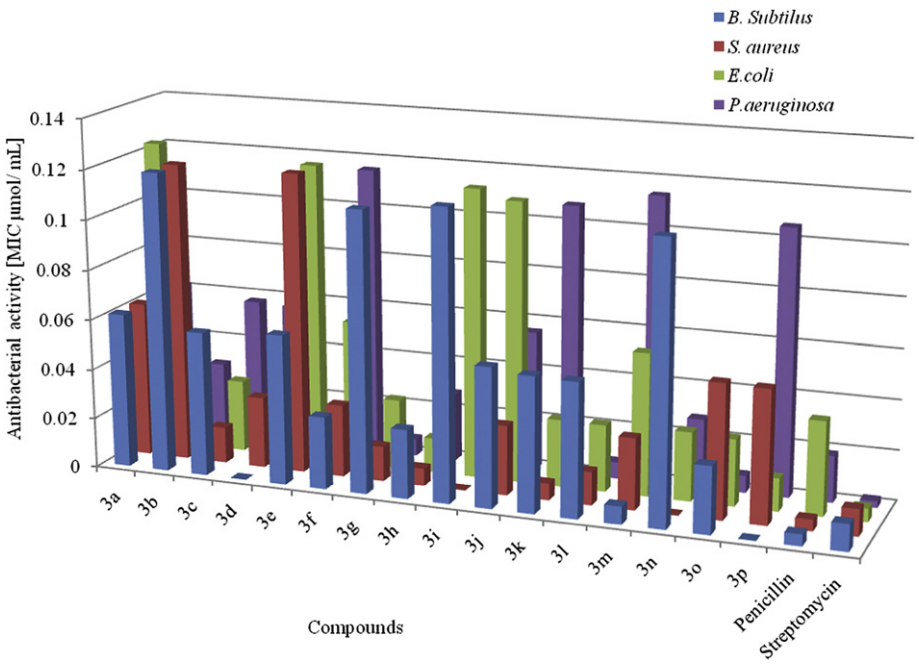


Fig. 1. Graphical representation of *in vitro* antibacterial activity of 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**).

parent compound **3a**. The derivatives **3f**, **3h** and **3o** were moderately active against *B. subtilis*, **3d**, **3f**, **3j** and **3m** against *S. aureus*, **3f** and **3m** against *E. coli*, and **3b**, **3h** and **3n** against *P. aeruginosa* as compared to the parent compound **3a**. Also the derivatives **3c**, **3e**, **3j**–**3l** exhibited slight increase in antibacterial activity against *B. subtilis*, **3o** and **3p** against *S. aureus*, **3e**, **3i** and **3j** against *E. coli* and **3c**, **3d** and **3j** against *P. aeruginosa*. Further, the derivatives **3b**, **3g**, **3i** and **3n** exhibited lower percent change in antibacterial activity against *B. subtilis*, **3b** and **3e** against *S. aureus* and **3f**, **3k**, **3m** and **3p** against *P. aeruginosa* as compared to the parent compound **3a.** None of the derivatives exhibited lower percent change in antibacterial activity against *E. coli* as compared to the parent compound **3a**, i.e. with the variation of *R* and *R*′ in the compounds **3b**–**3p** only enhanced activity was observed. However, some of the derivatives did not show any percent change in antibacterial activity over parent compound **3a**, amongst them were **3d** and **3p** against *B. subtilis*, **3i** and **3n** against *S. aureus*, **3b** against *E. coli* and **3e** and **3i** against *P. aeruginosa*. However, no general rule toward structure–activity relationship has been established for their antibacterial activity.

Table 1
In vitro antibacterial activity of 1,5-benzothiazepines (**3a**–**3p**).

Compounds	Minimum inhibitory concentration (MIC)[a]			
	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis[b]	*S. aureus*[c]	*E. coli*[d]	*P. aeruginosa*[e]
3a	0.0619	0.0619	0.1239	0.0619
3b	0.1197	0.1197	–	0.0299
3c	0.0576	0.0144	0.0288	0.0576
3d	–	0.0285	0.0142	0.057
3e	0.0598	0.1197	0.1197	–
3f	0.0289	0.0289	0.0579	0.1158
3g	0.1117	0.0139	0.0279	0.0069
3h	0.0276	0.0069	0.0138	0.0276
3i	0.1153	–	0.1153	–
3j	0.0558	0.0279	0.1117	0.0558
3k	0.0539	0.0067	0.0269	0.1078
3l	0.0534	0.0133	0.0267	0.0066
3m	0.0071	0.0285	0.057	0.1141
3n	0.1106	–	0.0276	0.0276
3o	0.0267	0.0534	0.0267	0.0069
3p	–	0.0529	0.0132	0.1058
Penicillin	0.0046	0.0046	0.0374	0.0187
Streptomycin	0.0107	0.0107	0.0053	0.0026

[a] Unit: µmol/mL.
[b] *Bacillus subtilis* (MTCC 441).
[c] *Staphylococcus aureus* (MTCC 7443).
[d] *Escherichia coli* (MTCC 42).
[e] *Pseudomonas aeruginosa* (MTCC 7952).

2.2.2. Antifungal activity

All the synthesized 1,5-benzothiazepines (**3a**–**3p**) were screened for their *in vitro* antifungal activity against two fungi *viz. A. fumigates* (MTCC 2550) and *C. albicans* (MTCC 183). Minimum inhibitory concentration (MIC) was determined using serial dilution technique [63]. While carrying out antifungal activity fluconazole was used as reference compound and MIC were determined in terms of µmol/mL (Fig. 3, Table 3).

It is inferred from the data presented in Fig. 3 and Table 3 that compounds **3k** and **3p** are most effective against *A. fumigates* and **3k**, **3l**, **3o** and **3p** exhibit high activity against *C. albicans*. The compounds **3o** (MIC, 0.0069 µmol/mL) and **3p** (MIC, 0.0066 µmol/mL) exhibited notable activity comparable to fluconazole (MIC, 0.0101 µmol/mL) for *C. albicans* and *A. fumigates* respectively. Further, compound **3e** was found inactive against *A. fumigates* and *C. albicans*.

The percent change in antifungal activity of different derivatives **3b**–**3p** over parent compound 11,12-diphenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepine (**3a**) was calculated using the same formula as employed for antibacterial activity (Fig. 4, Table 4).

A perusal of data from Fig. 4 and Table 4 depicted that the derivatives **3d**, **3h**, **3k**, **3l**, **3o** and **3p** exhibited high activity against *A. fumigates* and the derivatives **3f**, **3k**, **3l**, **3o** and **3p** against *C. albicans* compared to parent compound **3a**. The derivatives **3b**, **3c**, **3g**, **3i**, **3m** and **3n** were moderately active against *A. fumigates*, derivatives **3d**, **3g** and **3h** against *C. albicans* compared to the parent compound **3a**. The derivatives **3f** and **3j** exhibited nearly same activity against *A. fumigates* and **3b** and **3n** against *C. albicans* as

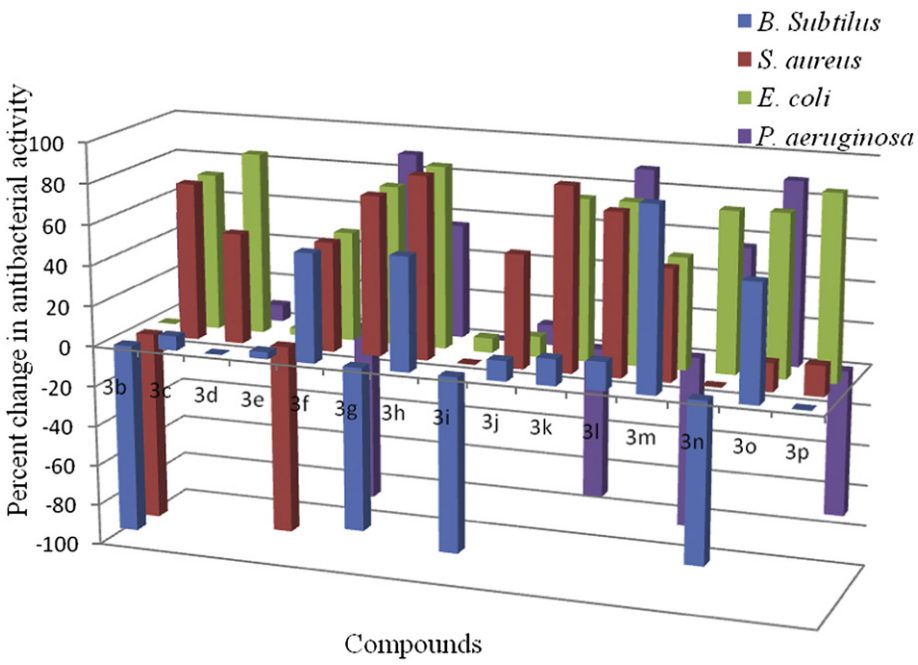


Fig. 2. Percent change in antibacterial activity of 1,5-benzothiazepines (**3b**–**3p**) over parent compound **3a**.

shown by parent compound **3a**. The derivatives **3c**, **3i**, **3j** and **3m** showed lower percent change in activity against *C. albicans* while no derivative showed lower percent change in antifungal activity against *A. fumigates* as compared to parent compound **3a**, i.e. with substitution at C_8 and $C_{4''}$ carbons antifungal activity against *A. fumigates* was found to be enhanced except **3e** which did not show any significant change in their antifungal activity against *A. fumigates* as well as *C. albicans* over parent compound **3a.** Hence, the distinctive differences in the antibacterial and antifungal activities of the compounds **3a**–**3p** further justify the purpose of this study.

Table 2
Percent change[a] in antibacterial activity of 1,5-benzothiazepines (**3b**–**3p**) over parent compound **3a**.

Compounds	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis[b]	*S. aureus*[c]	*E. coli*[d]	*P. aeruginosa*[e]
3a	–	–	–	–
3b	−93.37	−93.37	–	51.69
3c	06.94	76.73	76.75	06.94
3d	–	53.95	88.53	07.91
3e	03.39	−93.37	03.38	–
3f	53.31	53.31	53.26	−87.07
3g	−80.45	77.54	77.48	88.85
3h	55.41	88.85	88.86	55.41
3i	−86.26	–	06.94	–
3j	09.85	54.92	09.84	09.85
3k	12.92	89.17	78.28	−74.15
3l	13.73	78.51	78.45	89.33
3m	88.52	53.95	53.99	−84.32
3n	−78.67	–	77.72	55.41
3o	56.86	13.73	78.45	88.85
3p	–	14.53	89.34	−70.92

[a] Percent change in antibacterial activity $= (P - D)/P \times 100$ where P and D are Minimum inhibitory concentration (MIC) in μmol/mL for the parent compound and derivative respectively.
[b] *Bacillus subtilis* (MTCC 441).
[c] *Staphylococcus aureus* (MTCC 7443).
[d] *Escherichia coli* (MTCC 42).
[e] *Pseudomonas aeruginosa* (MTCC 7952).

From the antimicrobial results the following structure–activity relationship may be concluded:

1. Results of antimicrobial activity indicated that electron withdrawing chloro group at *p*-position of the phenyl nucleus attached to 11th position of the benzothiazepine ring increased the antimicrobial activity of synthesized compounds against *B. subtilis*, *E. coli*, *A. fumigates* and *C. albicans*, whereas, presence of electron donating methoxy group at *p*-position of the phenyl nucleus attached to 11th position of the benzothiazepine ring increased the antimicrobial activity against *S. aureus* and *P. aeruginosa*.
2. In contrast to 11th position of benzothiazepine nucleus, presence of that electron withdrawing chloro group at 8th position of benzothiazepine ring improved the antimicrobial activity against *E. coli*, *A. fumigates* and *P. aeruginosa*, whereas, presence of electron donating methoxy group at 8th position of benzothiazepine ring increased the antimicrobial activity against *S. aureus* and *C. albicans*.
3. Presence of unsubstituted phenyl ring of the benzothiazepine nucleus (unsubstitution at 8th position of benzothiazepine) improved the antimicrobial activity against *B. subtilis*.
4. From these results we may conclude that there are different structural requirements for a compound to be effective against different targets. The above mentioned findings are summarized in Fig. 5.

2.3. QSAR studies

In order to understand the experimental antimicrobial data on a theoretical basis, we established a quantitative structure–activity relationship (QSAR) between the *in vitro* antimicrobial activity of synthesized 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**) and descriptors coding for lipophilic, electronic, steric and topological properties of the molecules under consideration using the linear free energy relationship model (LFER) described by Hansch and Fujita [64]. Biological activity data determined as MIC values were first

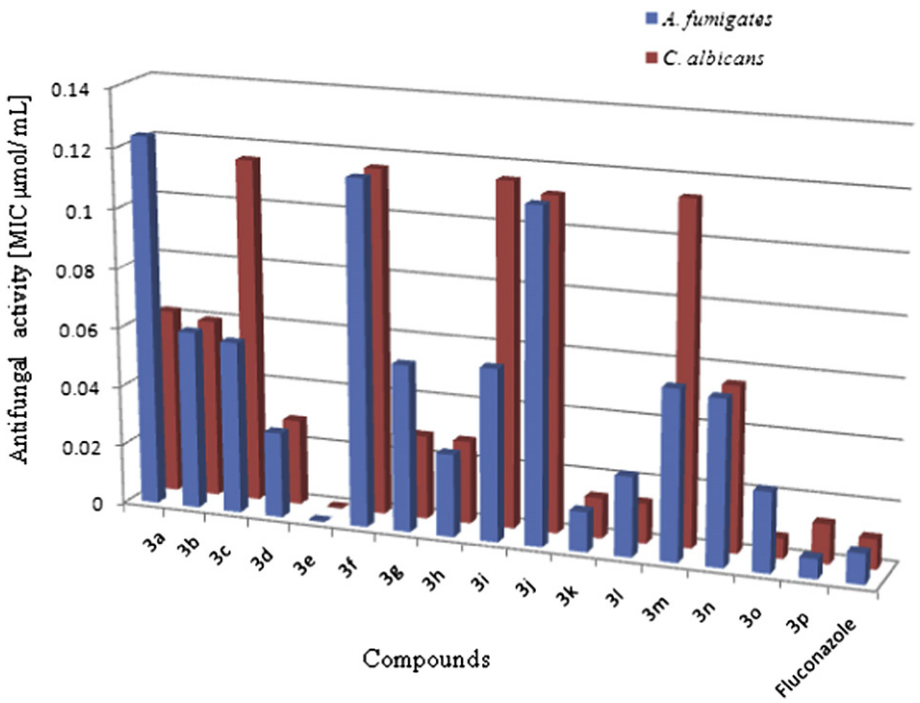


Fig. 3. Graphical representation of *in vitro* antifungal activity of 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**).

converted into pMIC values and used as dependent variables in a QSAR study and are presented in Table 5. The different molecular descriptors (independent variables) like log of octanol–water partition coefficient (log *P*), molar refractivity (MR), Kier's molecular connectivity ($^{n}\chi$, $^{n}\chi^{v}$) and shape (κ_{n}, $\kappa\alpha_{n}$) topological indices, Randic topological index (*R*), Balaban topological index (*J*), Wiener topological index (*W*), Total energy (Te), energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), dipole moment (μ), electronic energy (Ele.E), nuclear energy (Nu.E) and molecular surface area (SA) calculated for 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno [2,1-*c*][1,5]benzothiazepines (**3a**–**3p**) are used as independent variables and the values of selected descriptors taken in the regression analysis are presented in Table 6 [65–70].

Table 3
In vitro antifungal activity of 1,5-benzothiazepines (**3a**–**3p**).

Compounds	Minimum inhibitory concentration (MIC)[a]	
	A. fumigates[b]	*C. albicans*[c]
3a	0.1239	0.0619
3b	0.0598	0.0598
3c	0.0576	0.1153
3d	0.0285	0.0285
3e	–	–
3f	0.1158	0.1158
3g	0.0558	0.0279
3h	0.0276	0.0276
3i	0.0576	0.1153
3j	0.1117	0.1117
3k	0.0134	0.0134
3l	0.0267	0.0133
3m	0.0570	0.1141
3n	0.0553	0.0553
3o	0.0267	0.0069
3p	0.0066	0.0132
Fluconazole	0.0101	0.0101

[a] Unit: µmol/mL.
[b] *Aspergillus fumigates* (MTCC 2550).
[c] *Candida albicans* (MTCC 183).

In the present study, a data set of all the synthesized 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**) was subjected to linear free energy regression analysis for model generation. Preliminary analysis was carried out in terms of correlation analysis. A correlation matrix constructed for antifungal activity against *A. fumigates* is presented in Table 7. The correlations of different molecular descriptors with antimicrobial activity are presented in Table 8. In general, high co-linearity ($r > 0.8$) was observed between most of the parameters. The high interrelationship was observed between $^{2}\chi$ and MR ($r = 0.999$) and low interrelationship was observed between $^{0}\chi$ and LUMO ($r = -0.005$).

In the present investigation, different outliers are identified against different microorganisms, and the models have been developed after removal of the outliers (compound numbers in brackets) *B. subtilis* (**3f**, **3i**, **3m**, **3n**), *S. aureus* (**3h**, **3o**), *E. coli* (**3d**, **3h**–**3j**), *A. fumigates* (**3d**, **3j**, **3p**) and *C. albicans* (**3c**, **3g**, **3i**, **3j**, **3o**). In multivariate statistics, it is common to define three types of outliers [71].

(i) *X*/*Y* relation outliers are substances for which the relationship between the descriptors (*X* variables) and the dependent variables (*Y* variables) is not same as in the (rest of the) training data.
(ii) *X* outliers are substances whose molecular descriptors do not lie in the same range as in the (rest of the) training data.
(iii) *Y* outliers are only defined for training or test samples. They are the substances for which reference value of response is invalid.

As there was no difference in the activity (Table 5) as well as the molecular descriptor range of these outliers when compared to other 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**) indicated the fact that these outliers belong to the category of *Y* outliers (substances for which the reference value of response is invalid).

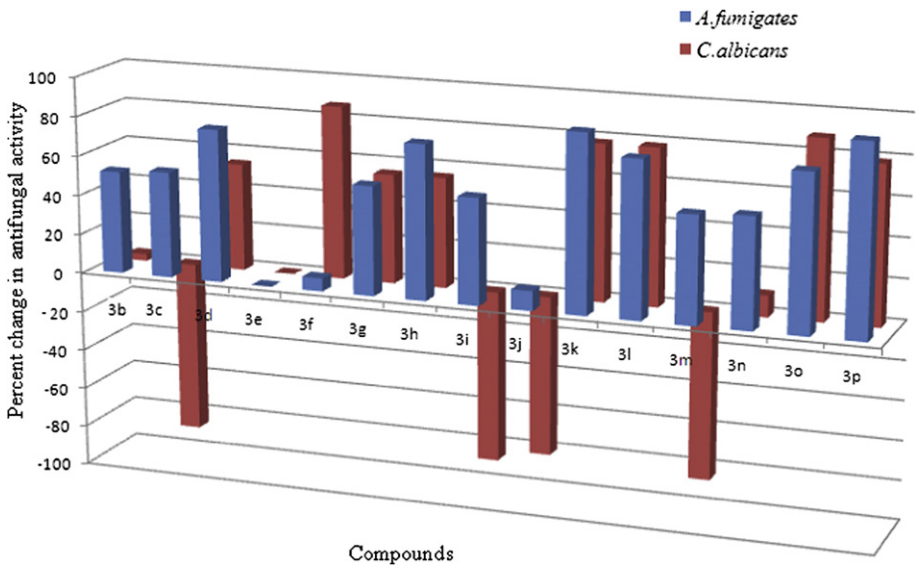


Fig. 4. Percent change in antifungal activity of 1,5-benzothiazepines (**3b**–**3p**) over parent compound **3a**.

Correlation matrix (Table 7) indicated the importance of the electronic parameter, Total energy (Te) in describing antifungal activity of synthesized 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**) against *A. fumigates* (Eq (1)).

QSAR model of antifungal activity against *A. fumigates*

$$\mathrm{pMIC_{af}} = -0.00084\,\mathrm{Te} - 2.699 \quad (1)$$

$$n = 12 \quad r = 0.859 \quad q^2 = 0.623 \quad s = 0.148 \quad F = 28.14$$

Here and thereafter, n – number of data points, r – correlation coefficient, q^2 – cross-validated r^2 obtained by leave one out method, s – standard error of the estimate and F – Fischer statistics.

The total energy (Te) calculated by semiempirical methods can be used as a measure of non-specific interactions of drug with its target site i.e. the total energies of protonated and neutral molecules can be considered as a good measure of hydrogen bonds (the higher the energy, the stronger the bond) and can be used to determine the correct localization of the most favorable hydrogen bond acceptor site [72].

As the coefficient of Te in Eq (1) is negative, therefore, the antifungal activity against *A. fumigates* will decrease with increase in value of Te. This is clearly evident from Table 6 that compound **3a** having highest Te value of −4272.82 has lowest $\mathrm{pMIC_{af}}$ value ($\mathrm{pMIC_{af}} = 0.91$ μM/mL, Table 5). Similarly, compound **3p** having low Te value of −4993.03 (Table 6), has high antifungal activity against *A. fumigates* ($\mathrm{pMIC_{af}} = 2.18$ μM/mL, Table 5). The QSAR model expressed by Eq (1) was cross-validated by its appreciable q^2 values ($q^2 = 0.623$) obtained by leave one out (LOO) method. The value of q^2 greater than 0.5 is the basic requirement for qualifying a QSAR model to be valid one [73]. The comparison of observed and predicted antimicrobial activities is presented in Table 9. It can be seen from the results that the observed and predicted antimicrobial activities lie close to each other as evidenced by their low residual values. The plot of predicted $\mathrm{pMIC_{af}}$ against observed $\mathrm{pMIC_{af}}$ (Fig. 6) also favors the model expressed by Eq (1). Further, the plot of observed $\mathrm{pMIC_{af}}$ vs. residual $\mathrm{pMIC_{af}}$ (Fig. 7) indicated that there was no systemic error in model development as the propagation of residuals was observed on both positive and negative sides [74].

In case of *C. albicans* also, the developed QSAR model (Eq (2)) indicated the predominance of Total energy (Te) in describing the antifungal activity of synthesized 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**). In order to improve value of correlation coefficient, we coupled Te with molar refractivity (MR) which resulted in a QSAR model (Eq (3)) with improvement in value of correlation coefficient from 0.780 to 0.840.

QSAR model of antifungal activity against *C. albicans*

$$\mathrm{pMIC_{ca}} = -0.00097\,\mathrm{Te} - 3.157 \quad (2)$$

$$n = 10 \quad r = 0.780 \quad q^2 = 0.421 \quad s = 0.246 \quad F = 12.43$$

$$\mathrm{pMIC_{ca}} = -0.0579\,\mathrm{MR} - 0.0016\,\mathrm{Te} - 1.455 \quad (3)$$

$$n = 10 \quad r = 0.840 \quad q^2 = 0.437 \quad s = 0.227 \quad F = 8.39$$

Table 4
Percent change[a] in antifungal activity of 1,5-benzothiazepines (**3b**–**3p**) over parent compound **3a**.

Compounds	*A. fumigates*[b]	*C. albicans*[c]
3a	–	–
3b	51.73	03.39
3c	53.51	−86.26
3d	76.99	53.95
3e	–	–
3f	06.53	87.07
3g	54.96	54.92
3h	77.72	55.41
3i	53.51	−86.26
3j	09.84	−80.45
3k	89.18	78.35
3l	78.45	78.51
3m	53.99	−84.32
3n	55.36	10.66
3o	78.45	88.85
3p	94.67	78.67

[a] Percent change in antifungal activity = $(P - D)/P \times 100$ where P and D are Minimum inhibitory concentration (MIC) in μmol/mL for the parent compound and derivative respectively.
[b] *Aspergillus fumigates* (MTCC 2550).
[c] *Candida albicans* (MTCC 183).

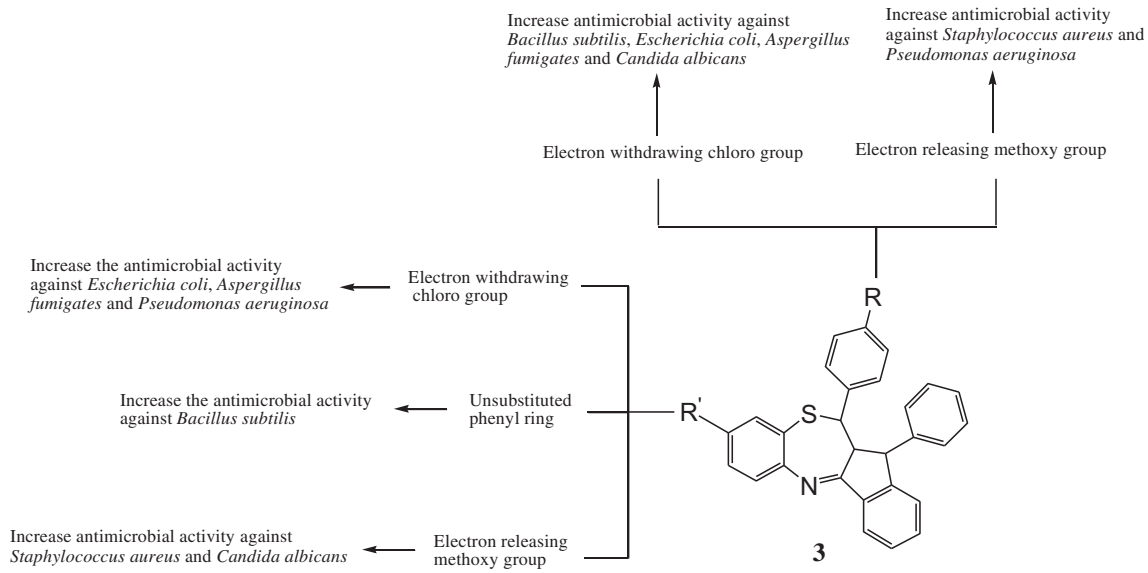


Fig. 5. Structure–activity relationship for antimicrobial activity of synthesized 1,5-benzothiazepines (**3a**–**3p**).

The coefficient of Te is negative in Eq (2), which indicates that the antibacterial activity will increase with the decrease in Te value of the synthesized benzothiazepines (**3**), which can be clearly seen from the results of antifungal activity against *C. albicans* (Table 5) and values of Te are presented in Table 6.

Antibacterial activity of the synthesized benzothiazepines (**3**) against *S. aureus* was best described by topological parameter, $\kappa\alpha_2$ (Eq (4)).

QSAR model of antibacterial activity against *S. aureus*

$$\mathrm{pMIC_{sa}} = 0.677\,\kappa\alpha_2 - 0.043 \quad (4)$$

$$n = 12 \quad r = 0.816 \quad q^2 = 0.552 \quad s = 0.234 \quad F = 20.00$$

The positive correlation of molecular descriptor with antibacterial activity reveals that decrease in value of $\kappa\alpha_2$ (Table 6) will lead to increase in antibacterial activity against *S. aureus*.

According to Kier, the shape of a molecule may be partitioned into attributes, each describable by the count of bonds of various path lengths. The basis for devising a relative index of shape is given by the relationship of the number of path of length *l* in the molecule *i*, ${}^{l}P_i$, to some reference values based on molecules with a given number of atoms, *n*, in which the values of ${}^{l}P$ are maximum and minimum, ${}^{l}P_{\max}$ and ${}^{l}P_{\min}$ [75].

The modified kappa shape indices are given by

$$\kappa\alpha_1 = (n+\alpha)(n+\alpha-1)^2/({}^{1}P_i+\alpha)^2$$

$$\kappa\alpha_2 = (n+\alpha-1)(n+\alpha-2)^2/({}^{2}P_i+\alpha)^2$$

$$\kappa\alpha_3 = (n+\alpha-3)(n+\alpha-2)^2/({}^{3}P_i+\alpha)^2, n \text{ is odd}$$

$$\kappa\alpha_3 = (n+\alpha-3)(n+\alpha-2)^2/({}^{3}P_i+\alpha)^2, n \text{ is even}.$$

The model described by Eq (5) depicted the importance of energies of highest occupied molecular orbital (HOMO) in describing the antibacterial activity against *B. subtilis*.

QSAR model of antibacterial activity against *B. subtilis*

$$\mathrm{pMIC_{bs}} = -2.313\,\mathrm{HOMO} - 17.70 \quad (5)$$

$$n = 10 \quad r = 0.716 \quad q^2 = 0.166 \quad s = 0.156 \quad F = 8.43$$

The coefficient of HOMO is negative in Eq (5), which indicates that the antibacterial activity will increase with the decrease in HOMO value of the synthesized compounds (**3**), which can be clearly seen from the results of antifungal activity against *B. subtilis* (Table 5) and values of HOMO presented in Table 6.

The electronic parameter HOMO, which denotes the energy of highest occupied molecular orbital directly relates to the electronic affinity and characterizes the sensibility of the benzothiazepine toward an attack by electrophile [76]. This was evidenced by high antibacterial activity of compound **3m** (against *B. subtilis*, pMICbs = 2.15, HOMO = −8.29) which contain the electronegative chloro group on *p*-position of the phenyl nucleus attached to 11th position of the benzothiazepine ring. This chloro group may be attacked by the electrophilic amino acid residue of bacteria which may be responsible for the high antibacterial activity of compound **3m**. It is important to note a fact here that the compounds **3n**–**3p** are also having electronegative chloro substituent on *p*-position of the phenyl nucleus attached to 11th position of the

Table 5
In vitro antimicrobial activity (pMIC) of 1,5-benzothiazepines (**3a**–**3p**) for QSAR studies.

Compounds	pMICbs	pMICsa	pMICec	pMICpa	pMICaf	pMICca
3a	1.21	1.21	0.91	1.21	0.91	1.21
3b	0.92	0.92	–	1.52	1.22	1.22
3c	1.24	1.84	1.54	1.24	1.24	0.94
3d	–	1.55	1.85	1.24	1.55	1.55
3e	1.22	0.92	0.92	–	–	–
3f	1.54	1.54	1.24	0.94	0.94	0.94
3g	0.95	1.86	1.55	2.16	1.25	1.55
3h	1.56	2.16	1.86	1.56	1.56	1.56
3i	0.94	–	0.94	–	1.24	0.94
3j	1.25	1.55	0.95	1.25	0.95	0.95
3k	1.27	2.17	1.57	0.97	1.87	1.87
3l	1.27	1.88	1.57	2.18	1.57	1.88
3m	2.15	1.55	1.24	0.94	1.24	0.94
3n	0.96	–	1.56	1.56	1.26	1.26
3o	1.57	1.27	1.57	2.16	1.57	2.16
3p	–	1.28	1.88	0.98	2.18	1.88

Table 6
Values of selected descriptors used for QSAR studies.

Comp.	log *P*	MR	$^0\chi$	$^0\chi^v$	$^1\chi$	$^1\chi^v$	$\kappa\alpha_1$	$\kappa\alpha_2$	$\kappa\alpha_3$	*R*	*J*	*W*	Te	LUMO	HOMO	μ
3a	6.96	126.38	19.92	17.36	14.90	11.39	18.10	7.52	3.06	1.43	1.20	2055.00	−4272.82	−0.60	−8.18	2.40
3b	7.43	131.42	20.79	18.29	15.29	11.80	19.02	7.77	3.25	1.72	1.20	2256.00	−4428.69	−0.59	−8.16	2.19
3c	6.71	132.84	21.49	18.69	15.83	11.91	19.91	8.31	3.45	1.64	1.19	2488.00	−4748.66	−0.57	−8.16	2.37
3d	7.48	131.18	20.79	18.48	15.29	11.89	19.29	7.93	3.34	1.72	1.20	2256.00	−4632.92	−0.78	−8.31	3.43
3e	7.43	131.42	20.79	18.29	15.29	11.80	19.02	7.77	3.25	1.72	1.20	2271.00	−4428.69	−0.59	−8.17	2.41
3f	7.90	136.46	21.66	19.21	15.69	12.21	19.95	8.01	3.46	2.01	1.20	2482.00	−4584.56	−0.58	−8.12	2.03
3g	7.18	137.88	22.36	19.62	16.22	12.32	20.84	8.56	3.64	1.93	1.19	2725.00	−4904.54	−0.55	−8.12	2.10
3h	7.95	136.22	21.66	19.40	15.69	12.30	20.21	8.18	3.54	2.01	1.20	2482.00	−4788.79	−0.77	−8.29	3.60
3i	7.95	136.22	21.66	19.40	15.69	12.30	20.21	8.18	3.54	2.01	1.20	2482.00	−4788.79	−0.77	−8.29	3.60
3j	7.18	137.88	22.36	19.62	16.22	12.32	20.84	8.56	3.64	1.93	1.19	2740.00	−4904.57	−0.59	−8.15	1.44
3k	6.46	139.30	23.07	20.02	16.76	12.43	21.73	9.11	3.84	1.84	1.19	2995.00	−5224.54	−0.56	−8.14	2.28
3l	7.23	137.65	22.36	19.81	16.22	12.42	21.11	8.72	3.73	1.93	1.19	2740.00	−5108.79	−0.77	−8.29	3.02
3m	7.48	131.18	20.79	18.48	15.29	11.89	19.29	7.93	3.34	1.72	1.20	2271.00	−4632.93	−0.68	−8.29	2.90
3n	7.95	136.22	21.66	19.40	15.69	12.30	20.21	8.18	3.54	2.01	1.20	2482.00	−4788.80	−0.67	−8.25	2.87
3o	7.23	137.65	22.36	19.81	16.22	12.42	21.11	8.72	3.73	1.93	1.19	2725.00	−5108.77	−0.65	−8.26	3.25
3p	8.00	135.99	21.66	19.60	15.69	12.40	20.48	8.34	3.63	2.01	1.20	2482.00	−4993.03	−0.86	−8.41	3.39

benzothiazepine ring as well HOMO value closer to **3m** but they are less effective against *B. subtilis*. This may be due to the fact that **3n**–**3p** are also containing substituent at 8th position of benzothiazepine nucleus which was absent in **3m.** This is in accordance with point no. 3 of SAR of benzothiazepine and electronic affinity of molecule which characterizes the sensibility of the molecule toward an attack by electrophile.

The Eq (6), derived for the synthesized 1,5-benzothiazepines (**3**) indicated the importance of the electronic parameter, Total energy (Te) in describing the antibacterial activity against *E. coli*.

QSAR model of antibacterial activity against *E. coli*

$$\mathrm{pMIC_{ec}} = -0.00085\,\mathrm{Te} - 2.66 \qquad (6)$$

$$n = 11 \quad r = 0.852 \quad q^2 = 0.589 \quad s = 0.166 \quad F = 23.59$$

The negative coefficient of Te in Eq (6) indicates the inverse relation between Te values and antibacterial activity values of the synthesized compounds (**3**) (Tables 5 and 6).

It is important to mention here that no statistically significant correlation was observed between molecular descriptors and antibacterial activity of the synthesized compounds (**3**) against *P. aeruginosa* and we have also predicted the antimicrobial activity of the compounds for which experimental values were not available using developed QSAR models.

As in case of Eq (1), the predictive ability of Eqs (2)–(6) against respective microorganisms is supported by the low residual activity values (Table 9). Further, the high q^2 values observed also supports the suitability of the QSAR models ($q^2 > 0.5$) described by Eqs (4) and (6). In case of the QSAR models derived for *C. albicans* and *B. subtilis* (Eqs (3) and (5)), the q^2 value is less than 0.5, which shows that the developed models are invalid one. But one should not forget the recommendations of Golbraikh and Tropsha [73] who have reported that the only way to estimate the true predictive power of a QSAR model is to test their ability to predict accurately the biological activities of compounds. As the observed and predicted values are close to each other (Table 9), the QSAR models for *C. albicans* and *B. subtilis* are valid ones.

It is important to note a fact here that the different compounds which are removed as outliers against corresponding microorganisms at the beginning of the study showed high residual values (Table 9) which justified their removal as outliers.

Summarizing, the antimicrobial activity of synthesized 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3a**–**3p**) is governed by electronic parameters.

Generally for QSAR studies, the biological activities of compounds should span 2–3 orders of magnitude, but in the present study, the range of antimicrobial activities of 1,5-benzothiazepines (**3**) is within one order of magnitude. But it is important to note that the predictability of the QSAR models developed in the present study is highly evidenced by the low residual values. This is in accordance with results suggested by Bajaj et al. [77], who stated that the reliability of the QSAR model lies in its predictive ability even though the activity data are in the narrow range. Further, recent literature reveals that the QSAR have been

Table 7
Correlation matrix for the antifungal activity of 1,5-benzothiazepines (**3a**–**3p**) against *A. fumigates*.

	log AF	log *P*	MR	$^0\chi$	$^0\chi^v$	$^1\chi$	$^1\chi^v$	$^2\chi$	$^2\chi^v$	$\kappa\alpha_1$	$\kappa\alpha_2$	Te	LUMO	HOMO	μ
log AF	1.000	−0.325	0.655	0.757	0.718	0.780	0.670	0.656	0.382	0.796	0.836	−0.859	−0.241	−0.266	0.348
log P		1.000	0.094	−0.202	0.069	−0.381	0.196	0.119	0.629	−0.181	−0.417	0.269	−0.562	−0.462	0.475
MR			1.000	0.955	0.990	0.883	0.983	0.999	0.821	0.950	0.842	−0.866	−0.146	−0.042	0.196
$^0\chi$				1.000	0.959	0.982	0.914	0.948	0.627	0.993	0.959	−0.944	−0.005	0.060	0.083
$^0\chi^v$					1.000	0.893	0.992	0.992	0.818	0.969	0.875	−0.915	−0.225	−0.150	0.287
$^1\chi$						1.000	0.827	0.872	0.473	0.973	0.986	−0.945	0.097	0.137	−0.006
$^1\chi^v$							1.000	0.988	0.885	0.929	0.807	−0.869	−0.305	−0.222	0.356
$^2\chi$								1.000	0.838	0.946	0.834	−0.865	−0.176	−0.074	0.226
$^2\chi^v$									1.000	0.650	0.443	−0.564	−0.518	−0.407	0.517
$\kappa\alpha_1$										1.000	0.967	−0.973	−0.095	−0.049	0.179
$\kappa\alpha_2$											1.000	−0.978	0.012	0.016	0.091
TE												1.000	0.176	0.183	−0.276
LUMO													1.000	0.931	−0.897
HOMO														1.000	−0.928
μ															1.000

Table 8
Correlation of molecular descriptors with the antimicrobial activity of 1,5-benzothiazepines (**3a**–**3p**).

Mol. Des.	pMICbs	pMICsa	pMICec	pMICpa	pMICaf	pMICca
log *P*	0.211	−0.534	0.097	−0.051	−0.325	−0.257
MR	0.273	0.639	0.750	0.331	0.655	0.518
$^{0}\chi$	0.240	0.746	0.731	0.340	0.757	0.610
$^{0}\chi^{v}$	0.338	0.664	0.823	0.339	0.718	0.606
$^{1}\chi$	0.204	0.789	0.679	0.330	0.780	0.634
$^{1}\chi^{v}$	0.367	0.605	0.830	0.327	0.670	0.572
$^{2}\chi$	0.289	0.633	0.769	0.332	0.656	0.528
$^{2}\chi^{v}$	0.423	0.286	0.722	0.239	0.382	0.352
$^{3}\chi$	0.344	0.306	0.667	0.248	0.348	0.288
$^{3}\chi^{v}$	0.414	0.022	0.566	0.156	0.155	0.167
κ_1	0.226	0.765	0.712	0.337	0.770	0.623
κ_2	0.162	0.815	0.602	0.307	0.775	0.637
κ_3	0.229	0.767	0.713	0.332	0.769	0.622
$\kappa\alpha_1$	0.302	0.755	0.800	0.346	0.796	0.676
$\kappa\alpha_2$	0.278	0.816	0.754	0.333	0.836	0.732
$\kappa\alpha_3$	0.338	0.743	0.832	0.342	0.802	0.694
R	0.204	0.789	0.679	0.330	0.780	0.634
J	−0.117	−0.799	−0.457	−0.262	−0.731	−0.590
W	0.221	0.770	0.687	0.325	0.782	0.626
Te	−0.379	−0.768	−0.853	−0.336	−0.859	−0.780
Ele. E	−0.230	−0.771	−0.708	−0.331	−0.783	−0.635
Nu. E	0.210	0.763	0.683	0.327	0.769	0.611
LUMO	−0.570	0.080	−0.481	−0.018	−0.241	−0.518
HOMO	−0.716	0.117	−0.462	−0.003	−0.266	−0.429
μ	0.690	−0.031	0.477	0.163	0.348	0.452

applied to describe the relationship between narrow range of biological activity and physicochemical properties of the molecules [78–80].

3. Conclusion

In summary, the present study reports the synthesis of a series of sixteen new 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3**) using easily obtainable starting compounds under environmentally benign conditions in high yields. The structures of the synthesized compounds were established on the basis of spectral as well as analytical results. The *in vitro* antimicrobial activities of the title compounds were evaluated against various Gram-positive and Gram-negative bacteria and fungi. Most of the compounds exhibited convincing biological activities, however, with a degree of variation. Moreover, both antibacterial and antifungal activities were found to be prolific. The QSAR studies carried out to find out the correlation between the antimicrobial activity and physicochemical properties of the synthesized 1,5-benzothiazepines (**3**) indicated the predominance of electronic parameters in describing their antimicrobial activity. The importance of this investigation lies in the possibility that the new compounds might be more efficacious drugs against bacteria and fungi and working on these foundations, their biological effects could be utilized for designing more potent antibacterial and antifungal agents of therapeutic use.

4. Experimental

4.1. Chemistry

Melting points were determined in open capillaries and are uncorrected. The purity of the synthesized compounds was tested using precoated TLC plates (SIL G/UV_{254}, ALUGRAM) and visualization was achieved via UV light/iodine absorption. The IR absorption spectra were recorded on Perkin Elmer Spectrum, BX II FTIR spectrometer, using (KBr) pellets and absorption frequencies (ν) are stated in cm^{-1}. The ^{1}H, ^{13}C NMR spectra ($CDCl_3$) were measured on Bruker Advance 300/500 MHz spectrometer. The chemical shifts are expressed in parts per million (δ ppm). Tetramethylsilane (TMS) was used as an internal standard. Coupling constants (*J*) were measured in Hz. Mass spectra were recorded on Agilent 6310 LCMS ION TRAP. Elemental analysis was carried out using Vario Micro Cube Elementar CHNS analyzer. Analytical results found for C, H, N and S are within ±0.4% of the theoretical values. Solvents were dried as per literature procedures. Penicillin, streptomycin (Hi-Media) and fluconazole (Aurobindo Pharmaceuticals Pvt. Ltd, Mandal, A. P., India) were respectively used as standard antibacterial and antifungal agents against microorganisms studied.

4.2. General procedure for the synthesis of 2-(E)-benzylidene/p-substituted benzylidene-3-phenyl indan-1-ones (*1*)

The 2-(*E*)-Benzylidene/*p*-substituted benzylidene-3-phenyl indan-1-ones (**1**) were obtained by the condensation of 3-phenyl indan-1-one and the appropriate *p*-substituted benzaldehydes

Table 9
Comparison of observed, predicted and residual antimicrobial activities of 1,5-benzothiazepines (**3a**–**3p**).

Comp.	pMICbs			pMICsa			pMICec			pMICaf			pMICca		
	Obs	Pre	Res	Obs	Pre	Res	Obs	Pre	Res	Obs	Pre	Res	Obs	Pre	Res
3a	1.21	1.22	−0.01	1.21	1.05	0.16	0.91	0.97	−0.06	0.91	0.89	0.02	1.21	1.11	0.10
3b	0.92	1.17	−0.25	0.92	1.22	−0.30	–	**1.10**	–	1.22	1.02	0.20	1.22	1.07	0.15
3c	1.24	1.18	0.06	1.84	1.59	0.25	1.54	1.38	0.16	1.24	1.29	−0.05	0.94[a]	1.36	−0.42
3d	–	**1.51**	–	1.55	1.33	0.22	1.85[a]	1.28	0.57	1.55[a]	1.19	0.36	1.55	1.42	0.13
3e	1.22	1.19	0.03	0.92	1.22	−0.30	0.92	1.10	−0.18	–	**1.02**	–	–	**0.93**	–
3f	1.54[a]	1.08	0.46	1.54	1.38	0.16	1.24	1.24	0.00	0.94	1.15	−0.21	0.94	1.04	−0.10
3g	0.95	1.08	−0.13	1.86	1.75	0.11	1.55	1.51	0.04	1.25	1.42	−0.17	1.55[a]	1.32	0.23
3h	1.56	1.48	0.08	2.16[a]	1.49	0.67	1.86[a]	1.41	0.45	1.56	1.32	0.24	1.56	1.38	0.18
3i	0.94[a]	1.48	−0.54	–	**1.49**	–	0.97[a]	−0.06	0.97	1.24	1.32	−0.08	0.94[a]	1.23	−0.29
3j	1.25	1.14	0.11	1.55	1.75	−0.20	0.95[a]	1.51	−0.56	0.95[a]	1.42	−0.47	0.95[a]	1.32	−0.37
3k	1.27	1.12	0.15	2.17	2.12	0.05	1.57	1.78	−0.21	1.87	1.69	0.18	1.87	1.92	−0.05
3l	1.27	1.48	−0.21	1.88	1.86	0.02	1.57	1.68	−0.11	1.57	1.59	−0.02	1.88	1.82	0.06
3m	2.15[a]	1.48	0.67	1.55	1.33	0.22	1.24	1.28	−0.04	1.24	1.19	0.05	0.94	1.42	−0.48
3n	0.96[a]	1.39	−0.43	–	**1.49**	–	1.56	1.41	0.15	1.26	1.32	−0.06	1.26	1.38	−0.12
3o	1.57	1.41	0.16	1.27[a]	1.86	−0.59	1.57	1.68	−0.11	1.57	1.59	−0.02	2.16[a]	1.66	0.50
3p	–	**1.75**	–	1.28	1.60	−0.32	1.88	1.58	0.30	2.18[a]	1.50	0.68	1.88	1.73	0.15

Bold values indicate the predicted activities calculated using the developed QSAR models for the compounds whose antibacterial/antifungal activities have not been determined experimentally.

[a] Outliers.

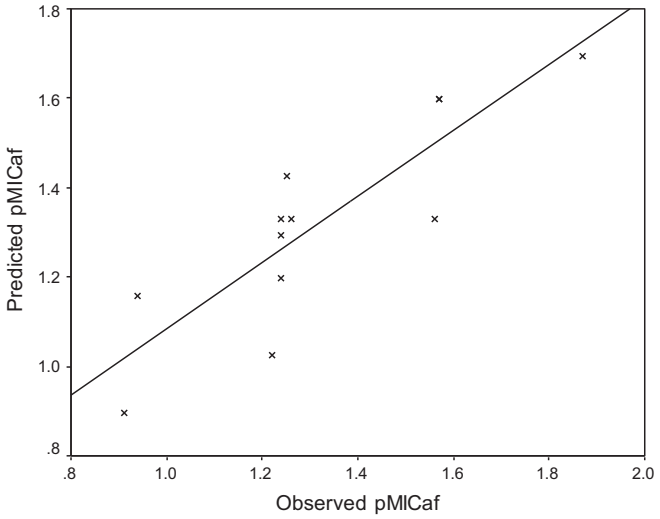


Fig. 6. Plot of predicted $pMIC_{af}$ against the observed $pMIC_{af}$ for the QSAR model developed by Eq (1).

in $NaOH/C_2H_5OH$ according to the procedure as described in literature [38].

4.3. General procedure for the synthesis of 5-substituted-2-aminobenzenethiols (**2**)

The 5-substituted-2-aminobenzenethiols (**2**) were prepared by base-catalyzed hydrolytic fission of 6-substituted-2-aminobenzothiazoles which, in turn, were obtained from the reaction of potassium thiocyanate and bromine (generating thiocyanogen, $[(SCN)_2]$, *in situ*) on *p*-substituted anilines as described in the literature [39,40].

4.4. General procedure for the synthesis of 11-p-substituted phenyl-12-phenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzothiazepines (**3**)

2-(*E*)-Benzylidene/*p*-substituted benzylidene-3-phenyl indan-1-one (**1**) (0.003 mol) and appropriate 5-substituted-2-aminobenzenethiol (0.003 mol) were dissolved in dry toluene (20 mL) and catalytic amount of trifluoroacetic acid (TFA) was added. The reaction mixture was then refluxed for 12–15 h. Thereafter, the solvent was removed under reduced pressure. The crude solid so obtained was crystallized from dry methanol which furnished 11-*p*-substituted phenyl-12-phenyl-11a,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines (**3**) in good yields. The spectral and analytical data of **3a**–**3p** are given as follows.

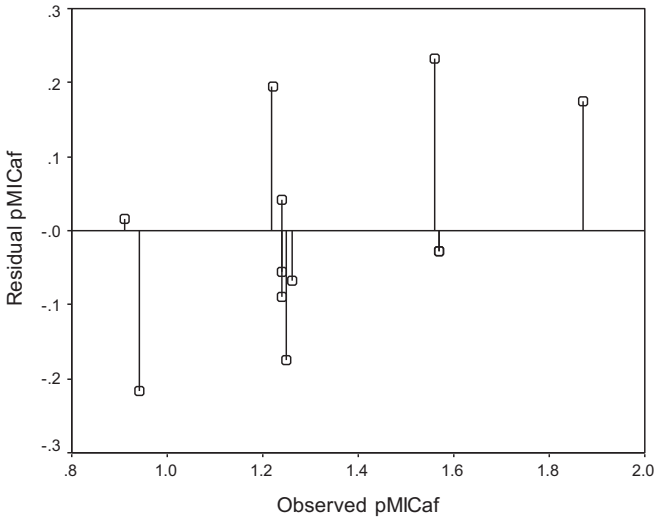


Fig. 7. Plot of residual $pMIC_{af}$ against the observed $pMIC_{af}$ for the QSAR model developed by Eq (1).

4.4.1. 11,12-Diphenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzo thiazepine (**3a**)

Yield 70%; mp 180–182 °C; IR (KBr): 1596 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.22 (dd, 1H, J = 11.7 Hz, 4.2 Hz, H-11a), 3.69 (d, 1H, J = 4.2 Hz, H-12), 4.63 (d, 1H, J = 11.7 Hz, H-11), 6.27–6.30 (m, 2H, H-7, 9), 6.99–7.58 (m, 15H, H-1, 2, 3, 6, 8, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 4″, 5″, 6″), 8.15 (dd, 1H, J = 7.5 Hz, 2.1 Hz, 4-H); ^{13}C NMR ($CDCl_3$): δ 53.58 (C-11a), 57.83 (C-12), 65.49 (C-11), 118.5 (C-9a), 121.01 (C-6), 123.28 (C-7), 123.78 (C-4), 125.27 (C-9), 125.97 (C-1), 126.54 (C-8), 126.84 (C-3′, 5′), 126.93 (C-2′, 6′), 127.65 (C-1′), 127.93 (C-4′), 128.33 (C-3″, 5″), 128.55 (C-2″, 6″), 128.94 (C-1"), 129.72 (C-4"), 132.98 (C-3), 133.26 (C-4a), 135.09 (C-2), 138.42 (C-5a), 143.45 (C-12a), 156.40 (C-4b); ESI-MS m/z: $(M + H)^+$ 404.7; *Anal.* Calcd. for $C_{28}H_{21}NS$ (403.54): C, 83.34; H, 5.25; N, 3.47; S, 7.95. Found: C, 83.01; H, 4.95; N, 3.82; S, 7.63.

4.4.2. 8-Methyl-11,12-diphenyl-11a,12-dihydro-11H-indeno[2,1-c] benzothiazepine (**3b**)

Yield 72.58%; mp 188 °C; IR (KBr): 1601 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 3.15 (dd, 1H, J = 11.7 Hz, 4.2 Hz, H-11a), 3.68 (d, 1H, J = 4.2 Hz, H-12), 3.96 (d, 1H, J = 11.7 Hz, H-11), 6.52–7.65 (m, 16H, H-1, 2, 3, 6, 7, 9, 2′, 3,' 4′, 5′, 6′, 2″, 3″, 4″, 5″, 6″), 7.86 (dd, 1H, J = 7.5 Hz, 2.1 Hz, 4-H); ^{13}C NMR ($CDCl_3$): δ 20.58 (CH_3), 54.02 (C-11a), 57.02 (C-12), 66.42 (C-11), 118.75 (C-9a), 121.60 (C-9), 123.20 (C-6), 124.15 (C-4), 125.97 (C-1), 126.30 (C-7), 126.54 (C-8), 126.80, (C-3′, 5′), 126.98 (C-2′, 6′), 127.58 (C-1′), 127.99 (C-4′), 128.13 (C-3″, 5″), 128.55 (C-2″, 6″), 128.60 (C-1"), 129.88 (C-4″), 132.50 (C-3), 133.80 (C-4a), 135.09 (C-2), 138.40 (C-5a), 143.78 (C-12a), 157.12 (C-4b); ESI-MS m/z: $(M + H)^+$ 418.2; *Anal.* Calcd. for $C_{29}H_{23}NS$ (417.56): C, 83.41; H, 5.55; N, 3.35; S, 7.68. Found: C, 83.08; H, 5.62; N, 3.62; S, 7.38.

4.4.3. 8-Methoxy-11,12-diphenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzothiazepine (**3c**)

Yield 74.41%; mp 180–181 °C; IR (KBr): 1594 (C=N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.99 (dd, 1H, J = 11.7 Hz, 4.2 Hz, H-11a,), 3.68 (d, 1H, J = 4.2 Hz, H-12), 3.80 (s, 3H, OCH_3), 3.90 (d, 1H, J = 11.7 Hz, H-11), 6.67–7.55 (m, 16H, 1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 4″, 5″, 6″), 7.93 (dd, 1H, J = 7.5 Hz, 2.0 Hz, 4-H); ^{13}C NMR ($CDCl_3$): δ 55.69 (OCH_3), 53.42 (C-11a), 58.03 (C-12), 67.12 (C-11), 112.60 (C-7), 118.12 (C-9), 119.32 (C-9a), 122.40 (C-6), 124.24 (C-4), 125.92 (C-1), 126.80 (C-3′, 5′), 126.93 (C-2′, 6′), 127.59 (C-1′), 127.89 (C-4′), 128.34 (C-3″, 5″), 128.55 (C-2″, 6″), 128.92 (C-1″), 129.59 (C-4″), 131.34 (C-3), 134.00 (C-4a), 135.65 (C-2), 138.41 (C-5a), 141.33 (C-12a), 154.40 (C-8), 156.80 (C-4b); ESI-MS m/z: $(M + H)^+$ 434; *Anal.* Calcd. for $C_{29}H_{23}NOS$ (433.56) : C, 80.34; H, 5.35; N, 3.23; S, 7.40. Found: C, 80.12; H, 5.02; N, 3.52; S, 7.13.

4.4.4. 8-Chloro-11,12-diphenyl-11a,12-dihydro-11H-indeno[2,1-c] [1,5]benzothiazepine (**3d**)

Yield 78.37%; mp 196 °C; IR (KBr): 1595 (C]N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.22 (dd, 1H, J = 11.7 Hz, 4.2 Hz, H-11a), 3.62 (d, 1H, J = 4.2 Hz, H-12), 4.1 (d, 1H, J = 11.7 Hz, H-11), 6.62–7.61 (m, 16H, 1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 4″, 5″, 6″), 8.01 (dd, 1H, J = 7.8 Hz, 2.1 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 54.10 (C-11a), 57.96 (C-12), 67.09 (C-11), 118.60 (C-9a), 120.60 (C-6), 121.90 (C-9), 123.34 (C-

7), 124.10 (C-4), 125.20 (C-1), 126.85 (C-3′, 5′), 126.96 (C-2′, 6′), 127.60 (C-1′), 127.92 (C-4′), 128.20 (C-8), 128.42 (C-3″, 5″), 128.60 (C-2″, 6″), 128.98 (C-1″), 130.10 (C-4″), 132.60 (C-3), 133.29 (C-4a), 135.10 (C-2), 138.41 (C-5a), 143.20 (C-12a), 158.32 (C-4b); ESI-MS *m/z*: $(M)^+$ 438, $(M + 1)^+$ 439.1, $(M + 2)^+$ 440; *Anal*. Calcd. for $C_{28}H_{20}ClNS$ (437.98): C, 76.78; H, 4.60; N, 3.20; S, 7.32. Found: C, 77.03; H, 4.22; N, 3.49; S, 7.58.

4.4.5. 12-Phenyl-11-p-tolyl-11a,12-dihydro-11H-indeno[2,1-c][1,5] benzothiazepine (**3e**)

Yield 74.22%; mp 117–119 °C; IR (KBr): 1604 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H, CH_3), 3.95 (dd, 1H, *J* = 11.7 Hz, 4.2 Hz, H-11a), 4.42 (d, 1H, *J* = 4.2 Hz, H-12), 5.02 (d, 1H, *J* = 11.7 Hz, H-11), 6.57–6.71 (m, 2H, H-7, 9), 6.82–7.79 (m, 14H, H-1, 2, 3, 6, 8, 2′, 3′, 4′, 5′, 6′, 2″, 3′, 5″, 6″), 7.98 (dd, 1H, *J* = 8.1 Hz, 2.1 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 21.05 (CH_3), 53.60 (C-11a), 58.25 (C-12), 67.15 (C-11), 119.40 (C-9a), 119.96 (C-6), 122.02 (C-7), 123.16 (C-9), 124.12 (C-4), 125.24 (C-1), 126.60 (C-8), 126.62 (C-3′, 5′), 126.80 (C-2′, 6′), 127.56 (C-1′), 127.96 (C-4′), 128.35 (C-3″, 5″), 128.77 (C-2″, 6″), 130.72 (C-1″), 132.40 (C-3), 133.16 (C-4a), 135.34 (C-2), 137.90 (C-5a), 141.06 (C-4″), 143.29 (C-12a), 157.12 (C-4b); ESI-MS *m/z*: $(M + Na)^+$ 440.4; *Anal*. Calcd. For $C_{29}H_{23}NS$ (417.56): C, 83.41; H, 5.55; N, 3.35; S, 7.68. Found: C, 83.06; H, 5.32; N, 3.63; S, 7.98.

4.4.6. 8-Methyl-12-phenyl-11-p-tolyl-11a,12-dihydro-11H-indeno [2,1-c][1,5]benzothiazepine (**3f**)

Yield 76.14%; mp 125–127 °C; IR (KBr): 1612 (C=N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.66 (dd, 1H, *J* = 12.0 Hz, 5.0 Hz, H-11a), 3.91 (d, 1H, *J* = 5.0 Hz, H-12), 4.69 (d, 1H, *J* = 12.0 Hz, H-11), 6.56–7.74 (m, 15H, H- 1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 5″, 6″), 7.93 (dd, 1H, *J* = 7.5 Hz, 2.0 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 20.75 (CH_3), 21.05 (CH_3), 53.80 (C-11a), 58.10 (C-12), 67.59 (C-11), 118.60 (C-9a), 120.23 (C-9), 122.96 (C-6), 123.92 (C-4), 125.24 (C-1), 126.42 (C-7), 126.82 (C-3′, 5′), 127.02 (C-2′, 6′), 127.65 (C-1′), 128.10 (C-4′), 128.60 (C-3″, 5″), 128.92 (C-2″, 6″), 131.24 (C-1″), 131.88 (C-3), 133.70 (C-4a), 135.40 (C-2), 136.12 (C-8), 138.10 (C-5a), 140.23 (C-4"), 142.73 (C-12a), 156.45 (C-4b); ESI-MS *m/z*: $(M + H)^+$ 432.4; *Anal*. Calcd. for $C_{30}H_{25}NS$ (431.59): C, 83.49; H, 5.84; N, 3.25; S, 7.43. Found: C, 83.15; H, 5.56; N, 3.58; S, 7.11.

4.4.7. 8-Methoxy-12-phenyl-11-p-tolyl-11a,12-dihydro-11H-indeno [2,1-c][1,5]benzothiazepine (**3g**)

Yield 78.24%; mp 130–132 °C; IR (KBr): 1596 (C=N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 3.42 (dd, 1H, *J* = 12.0 Hz, 5.0 Hz, H-11a), 3.81 (s, 3H, OCH_3), 4.32 (d, 1H, *J* = 5.0 Hz, H-12), 4.69 (d, 1H, *J* = 12.0 Hz, H-11), 6.62–7.78 (m, 15H, H-1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 5″, 6″), 7.96 (dd, 1H, *J* = 7.5 Hz, 2.0 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 21.06 (CH_3), 53.90 (C-11a), 55.29 (OCH_3), 58.10 (C-12), 67.43 (C-11), 112.48 (C-7), 118.10 (C-9), 119.30 (C-9a), 122.60 (C-6), 124.10 (C-4), 125.80 (C-1), 126.53 (C-3′, 5′), 126.72 (C-2′, 6′), 127.56 (C-1′), 127.92 (C-4′), 128.12 (C-3″, 5″), 128.40 (C-2″, 6″), 130.68 (C-1″), 132.12 (C-3), 133.68 (C-4a), 134.98 (C-2), 137.96 (C-5a), 140.42 (C-4″), 143.75 (C-12a), 154.58 (C-8), 156.52 (C-4b); ESI-MS *m/z*: $(M + H)^+$ 448.3; *Anal*. Calcd. for $C_{30}H_{25}NOS$ (447.59): C, 80.50; H, 5.63; N, 3.13; S, 7.16. Found: C, 80.25; H, 5.92; N, 3.45; S, 6.91.

4.4.8. 8-Chloro-12-phenyl-11-p-tolyl-11a,12-dihydro-11H-indeno [2,1-c][1,5]benzothiazepine (**3h**)

Yield 82.29%; mp 135–136 °C; IR (KBr): 1610 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 3.66 (dd, 1H, *J* = 11.7 Hz, 4.2 Hz, H-11a), 3.94 (d, 1H, *J* = 4.2 Hz, H-12), 4.56 (d, 1H, *J* = 11.7 Hz, H-11), 6.60–7.73 (m, 15H, H-1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 5″, 6″), 7.91 (dd, 1H, *J* = 8.1 Hz, 2.1 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 21.58 (CH_3), 53.58 (C-11a), 57.96 (C-12), 66.12 (C-11), 118.82 (C-9a), 120.25 (C-6), 121.40 (C-9), 122.96 (C-7), 123.75 (C-4), 125.89 (C-1), 126.40 (C-3′, 5′), 126.92 (C-2′, 6′), 127.88 (C-1′), 128.06 (C-4′), 128.31 (C-3″, 5″), 128.50 (C-8), 128.83 (C-2″, 6″), 131.42 (C-1″), 132.20 (C-3), 133.88 (C-4a), 135.60 (C-2), 138.50 (C-5a), 141.10 (C-4″), 142.92 (C-12a), 157.25 (C-4b); ESI-MS *m/z*: $(M)^+$ 452.2, $(M + 1)^+$ 453, $(M + 2)^+$ 454.2; *Anal*. Calcd. for $C_{29}H_{22}ClNS$ (452.01): C, 77.06; H, 4.91; N, 3.10; S, 7.09. Found: C, 77.37; H, 5.22; N, 3.41; S, 7.38.

4.4.9. 11-(4-Methoxyphenyl)-12-phenyl-11a,12-dihydro-11H-indeno [2,1-c][1,5]benzothiazepine (**3i**)

Yield 75.22%; mp 194–196 °C; IR (KBr): 1601 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (dd, 1H, *J* = 11.7 Hz, 4.2 Hz, H-11a), 3.80 (s, 3H, OCH_3), 3.99 (d, 1H, *J* = 4.2 Hz, H-12), 4.32 (d, 1H, *J* = 11.7 Hz, H-11), 6.76 (d, 2H, *J* = 8.4 Hz, H-3″, 5″), 6.88–7.01 (m, 2H, H-7, 9), 7.15–7.70 (m, 12H, H-1, 2, 3, 6, 8, 2′, 3′, 4′, 5′, 6′, 2″, 6″), 7.92 (dd, 1H, *J* = 8.1 Hz, 2.1 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 53.18 (C-11a), 55.13 (OCH_3), 57.80 (C-12), 65.80 (C-11), 113.89 (C-3″, 5″), 120.80 (C-9a), 121.46 (C-6), 123.28 (C-4), 123.35 (C-7), 124.20 (C-9), 125.66 (C-1), 126.30 (C-8), 126.60 (C-3′, 5′), 126.93 (C-2′, 6′), 127.47 (C-1′), 128.58 (C-4′), 128.89 (C-2″, 6″), 130.06 (C-1″), 131.73 (C-3), 133.31 (C-4a), 134.37 (C-2), 137.27 (C-5a), 143.36 (C-12a), 156.50 (C-4b), 158.07 (C-4"), ESI-MS *m/z*: $(M + H)^+$ 434.4; *Anal*. Calcd. for $C_{29}H_{23}NOS$ (433.56): C, 80.34; H, 5.35; N, 3.23; S, 7.40. Found: C, 80.66; H, 5.02; N, 3.52; S, 7.12.

4.4.10. 11-(4-Methoxyphenyl)-8-methyl-12-phenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzothiazepine (**3j**)

Yield 79.19%; mp 202 °C; IR (KBr): 1605 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H, CH_3), 3.56 (dd, 1H, *J* = 11.7 Hz, 4.7 Hz, H-11a), 3.83 (s, 3H, OCH_3), 4.32 (d, 1H, *J* = 4.7 Hz, H-12), 4.96 (d, 1H, *J* = 11.7 Hz, H-11), 6.87–7.71 (m, 15H, H-1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 5″, 6″), 7.96 (dd, 1H, *J* = 7.8 Hz, 2.1 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 21.42 (CH_3), 53.72 (C-11a), 55.25 (OCH_3), 57.80 (C-12), 65.60 (C-11), 113.98 (C-3″, 5″), 119.60 (C-9a), 120.51 (C-9), 123.02 (C-6), 123.60 (C-4), 124.60 (C-1), 126.19 (C-7), 126.80 (C-3′, 5′), 127.01 (C-2′, 6′), 127.25 (C-2″, 6″), 127.62 (C-1′), 128.65 (C-4′), 130.21 (C-1″), 131.07 (C-3), 133.25 (C-4a), 134.65 (C-2), 135.50 (C-8), 137.92 (C-5a), 143.64 (C-12a), 156.63 (C-4b), 159.12 (C-4″), ESI-MS *m/z*: $(M + H)^+$ 448.7; *Anal*. Calcd. for $C_{30}H_{25}NOS$ (447.59): C, 80.50; H, 5.63; N, 3.13; S, 7.16. Found: C, 80.79, H, 5.91; N, 3.41; S, 7.33.

4.4.11. 8-Methoxy-11-(4-methoxyphenyl)-12-phenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzothiazepine (**3k**)

Yield 77.26%; mp 190–191 °C; IR (KBr): 1599 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.66 (dd, 1H, *J* = 11.7 Hz, 4.5 Hz, H-11a), 3.83 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.38 (d, 1H, *J* = 4.5 Hz, H-12), 5.0 (d, 1H, *J* = 11.7 Hz, H-11), 6.78–7.65 (m, 15H, H-1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 5″, 6″), 7.98 (dd, 1H, *J* = 7.8 Hz, 2.1 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 53.40 (C-11a), 55.02 (OCH_3), 55.43 (OCH_3), 58.03 (C-12), 65.92 (C-11), 112.60 (C-7), 113.98 (C-3″, 5″), 118.25 (C-9), 119.96 (C-9a), 121.42 (C-6), 124.17 (C-4), 125.85 (C-1), 126.76 (C-3′, 5′), 126.99 (C-2′, 6′), 127.56 (C-1′), 127.83 (C-4′), 129.04 (C-2″, 6″), 130.22 (C-1″), 131.07 (C-3), 134.79 (C-4a), 135.54 (C-2), 138.25 (C-5a), 142.85 (C-12a), 154.25 (C-8), 157.23 (C-4b), 159.40 (C-4″), ESI-MS *m/z*: $(M + H)^+$ 464.3; *Anal*. Calcd. for $C_{30}H_{25}NO_2S$ (463.59): C, 77.72; H, 5.44; N, 3.02; S, 6.92. Found: C, 77.98; H, 5.13; N, 3.36; S, 6.63.

4.4.12. 8-Chloro-11-(4-methoxyphenyl)-12-phenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzothiazepine (**3l**)

Yield 79.98%; mp 196–198 °C; IR (KBr): 1614 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.66 (dd, 1H, *J* = 11.7 Hz, 4.2 Hz, H-11a), 3.87 (s, 3H, OCH_3), 4.40 (d, 1H, *J* = 4.2 Hz, H-12), 4.78 (d, 1H, *J* = 11.7 Hz, H-11), 6.75–7.69 (m, 15H, H-1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 5″, 6″), 7.98 (dd, 1H, *J* = 7.8 Hz, 2.1 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 53.90 (C-11a), 55.13 (OCH_3), 58.10 (C-12), 65.70 (C-11), 113.98 (C-

3", 5"), 118.90 (C-9a), 121.40 (C-6), 121.96 (C-9), 122.96 (C-7), 124.16 (C-4), 126.15 (C-1), 126.65 (C-3′, 5′), 126.95 (C-2′, 6′), 127.80 (C-1′), 128.14 (C-4′), 128.50 (C-8), 129.11 (C-2″, 6″), 130.25 (C-1″), 131.07 (C-3), 133.96 (C-4a), 135.60 (C-2), 137.92 (C-5a), 143.49 (C-12a), 158.23 (C-4b), 159.60 (C-4″); ESI-MS *m*/*z*: $(M)^+$ 468.2, $(M + 1)^+$ 469, $(M + 2)^+$ 470.3; *Anal*. Calcd. for $C_{29}H_{22}ClNOS$ (468.01): C, 74.42; H, 4.74; N, 2.99; S, 6.85. Found: C, 74.17; H, 4.49; N, 2.65; S, 6.60.

4.4.13. 11-(4-Chlorophenyl)-12-phenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzothiazepine (**3m**)

Yield 80.42%; mp 146–147 °C; IR (KBr): 1599 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.49 (dd, 1H, *J* = 12.0 Hz, 5.0 Hz, H-11a), 4.31 (d, 1H, *J* = 5.0 Hz, H-12), 4.75 (d, 1H, *J* = 12.0 Hz, H-11), 6.90–6.94 (m, 2H, H-7, 9), 7.04–7.78 (m, 14H, H-1, 2, 3, 6, 8, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 5″, 6″), 7.92 (dd, 1H, *J* = 7.5 Hz, 2.0 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 54.10 (C-11a), 57.92 (C-12), 65.80 (C-11), 118.17 (C-9a), 118.64 (C-6), 120.99 (C-7), 122.70 (C-9), 124.26 (C-4), 125.90 (C-1), 127.52 (C-8), 128.50 (C-3′, 5′), 128.61 (C-2′, 6′), 128.65 (C-1′), 129.02 (C-4′), 129.77 (C-2″, 6″), 131.57 (C-3), 132.41 (C-3″, 5″), 134.10 (C-4a), 135.59 (C-2), 137.80 (C-1″), 138.35 (C-5a), 140.98 (C-4″) 143.55 (C-12a), 156.26 (C-4b); ESI-MS *m*/*z*: $(M)^+$ 438.3, $(M + 1)^+$ 439, $(M + 2)^+$ 440.4; *Anal*. Calcd. for $C_{28}H_{20}ClNS$ (437.98): C, 76.78; H, 4.60; N, 3.20; S, 7.32. Found: 76.46; H, 4.28; N, 3.37; S, 7.02.

4.4.14. 11-(4-chlorophenyl)-8-methyl-12-phenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzothiazepine (**3n**)

Yield 81.41%; mp 153 °C; IR (KBr): 1612 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, CH_3), 3.56 (dd, 1H, *J* = 11.7 Hz, 4.2 Hz, H-11a), 4.56 (d, 1H, *J* = 4.2 Hz, H-12), 4.90 (d, 1H, *J* = 11.7 Hz, H-11), 6.82–7.75 (m, 15H, H-1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 5″, 6″), 7.89 (dd, 1H, *J* = 7.8 Hz, 2.1 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 21.15 (CH_3), 53.58 (C-11a), 58.07 (C-12), 65.80 (C-11), 119.93 (C-9a), 121.14 (C-9), 123.52 (C-6), 123.78 (C-4), 125.94 (C-1), 126.35 (C-7), 128.48 (C-3′, 5′), 128.60 (C-2′, 6′), 128.90 (C-1′), 129.04 (C-4′), 129.60 (C-2″, 6″), 130.98 (C-3″, 5″), 131.42 (C-3), 133.61 (C-4a), 135.25 (C-2), 135.60 (C-8), 137.14 (C-1″), 138.62 (C-5a), 140.25 (C-4″), 143.72 (C-12a), 157.12 (C-4b); ESI-MS *m*/*z*: $(M)^+$ 452, $(M + 1)^+$ 453, $(M + 2)^+$ 454.1; *Anal*. Calcd. for $C_{29}H_{22}ClNS$ (452.01): C, 77.06; H, 4.91; N, 3.10; S, 7.09. Found: C, 77.37; H, 4.63; N, 3.46; S, 7.40.

4.4.15. 11-(4-Chlorophenyl)-8-methoxy-12-phenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzothiazepine (**3o**)

Yield 82.69%; mp 140–140 °C; IR (KBr): 1606 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41 (dd, 1H, *J* = 11.7 Hz, 4.5 Hz, H-11a), 3.68 (d, 1H, *J* = 4.5 Hz, H-12), 3.78 (s, 3H, OCH_3), 3.90 (d, 1H, *J* = 11.7 Hz, H-11), 6.59–7.63 (m, 15H, H-1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 5″, 6″), 7.88 (dd, 1H, *J* = 8.1 Hz, 2.1 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 54.01 (C-11a), 55.50 (OCH_3), 58.12 (C-12), 66.10 (C-11), 112.54, (C-7), 118.10 (C-9a), 118.32 (C-9), 121.60 (C-6), 124.82 (C-4), 125.60 (C-1), 128.36 (C-3′, 5′), 128.53 (C-2′, 6′), 128.82 (C-1′), 128.96 (C-4′), 129.34 (C-2″, 6″), 130.72 (C-3″, 5″), 131.44 (C-3), 134.60 (C-4a), 135.40 (C-2), 137.48 (C-1″), 137.90 (C-5a), 141.10 (C-4″), 142.84 (C-12a), 154.60 (C-8), 158.03 (C-4b); ESI-MS *m*/*z*: $(M)^+$ 468.3, $(M + 1)^+$ 469, $(M + 2)^+$ 470.1; *Anal*. Calcd. for $C_{29}H_{22}ClNOS$ (468.01): C, 74.42; H, 4.74; N, 2.99; S, 6.85. Found: C, 74.70; H, 4.45; N, 2.69; S, 6.53.

4.4.16. 11-(4-Chlorophenyl)-8-chloro-12-phenyl-11a,12-dihydro-11H-indeno[2,1-c][1,5]benzothiazepine (**3p**)

Yield 83.20%; mp 161 °C; IR (KBr): 1611 (C=N) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.48 (dd, 1H, *J* = 12.0 Hz, 5.0 Hz, H-11a), 3.65 (d, 1H, *J* = 5.0 Hz, H-12), 4.31 (d, 1H, *J* = 12.0 Hz, H-11), 6.64–7.92 (m, 15H, H-1, 2, 3, 6, 7, 9, 2′, 3′, 4′, 5′, 6′, 2″, 3″, 5″, 6″), 8.04 (dd, 1H, *J* = 7.5 Hz, 2.0 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 53.60 (C-11a), 58.90 (C-12), 66.25 (C-11), 119.34 (C-9a), 121.06 (C-9), 122.18 (C-6), 122.37 (C-7), 124.33 (C-4), 125.97 (C-1), 128.57 (C-3′, 5′), 128.69 (C-2′, 6′), 128.92 (C-1′), 129.10 (C-4′), 129.57 (C-2″, 6″), 129.84 (C-8), 130.72 (C-3″, 5″), 131.71 (C-3), 134.17 (C-4a), 135.25 (C-2), 137.88 (C-1″), 138.91 (C-5a), 141.06 (C-4″), 143.97 (C-12a), 156.77 (C-4b); ESI-MS *m*/*z*: $(M)^+$ 472.1, $(M + 1)^+$ 473, $(M + 2)^+$ 474; *Anal*. Calcd. for $C_{28}H_{19}Cl_2NS$ (472.43): C, 71.19; H, 4.05; N, 2.96; S, 6.79. Found: C, 70.83; H, 4.32; N, 2.61; S, 6.45.

4.5. Antibacterial activity

The sixteen newly synthesized 1,5-benzothiazepines (**3a**–**3p**) were screened for their *in vitro* antibacterial activity against two Gram-positive bacteria *viz. B. subtilis* (MTCC 441) and *S. aureus* (MTCC 7443) and two Gram-negative bacteria *viz. E. coli* (MTCC 42) and *P. aeruginosa* (MTCC 7952) using serial dilution technique [63]. Initially, stock solutions were prepared by dissolving weighed amounts of synthesized compounds in DMSO followed by dilution to a final concentration of 100 μg/mL in Luria broth media. From this serial two-fold dilutions were prepared ranging from 100 to 1.56 μg/mL. Penicillin and streptomycin were taken as reference compounds and DMSO as a negative control. The respective Gram-positive bacteria *B. subtilis* and *S. aureus* and Gram-negative bacteria *E. coli* and *P. aeruginosa* were grown in Luria broth media at 37 °C and harvested by centrifugation. Bacteria were given three times wash with Phosphate buffer saline. Then 100 μL of the broth containing test bacteria were inoculated to different dilutions of test compounds in each well of a 96-well plate (each dilution in triplicates). The inoculated plates were incubated for 24 h at 37 °C. After 24 h bacterial growth was monitored visually and spectrophotometrically. Penicillin and streptomycin were also tested under similar conditions for comparison with the compounds synthesized. The data for antibacterial activity in Minimum inhibitory concentration (MIC, μmol/mL) are presented in Fig. 1 and Table 1.

4.6. Antifungal activity

The *in vitro* antifungal activity of the sixteen newly synthesized 1,5-benzothiazepines (**3a**–**3p**) was tested against two fungi *A. fumigates* (MTCC 2550) and *C. albicans* (MTCC 183). The pattern which was used for screening bacteria was translated exactly for antifungal activity. Initially, stock solutions were prepared by dissolving weighed amounts of synthesized compounds in DMSO followed by dilution to a final concentration of 100 μg/mL in Potato dextrose broth media. From this serial two-fold dilutions were prepared ranging from 100 to 1.56 μg/mL Fluconazole was used as reference against fungi and DMSO as a negative control. Fungal samples, *A. fumigates* and *C. albicans* were grown on Sabouraud dextrose broth media at 28 °C for 2–3 weeks and for 48 h respectively. Fungal spores were harvested with centrifugation, and washed with sterile distilled water. Then 100 μL of the broth containing test fungi were inoculated to different dilutions of test compounds in each well of a 96-well plate (each dilution in triplicates) and incubated for 72 h at 28 °C. Finally, the Minimum inhibitory concentration (MIC) was assigned by CFU assay. Antifungal activity of the reference drug, Fluconazole was also assessed under similar conditions. The data for antifungal activity in Minimum inhibitory concentration MIC (μmol/mL) are presented in Fig. 3 and Table 3.

4.7. QSAR studies

The structures of synthesized 1,5-benzothiazepines (**3a**–**3p**) are first pre-optimized with the Molecular Mechanics Force Field (MM^+) procedure included in Hyperchem 6.03 [81] and the resulting geometries are further refined by means of the semi-empirical method PM3 (parametric Method-3). We chose

a gradient norm limit of 0.01 kcal/Å for the geometry optimization. The lowest energy structure was used for each molecule to calculate physicochemical properties using TSAR 3.3 software for Windows [82]. Furthermore, the regression analysis was performed using the SPSS software package [83]. The predictive powers of the equation were validated by determination of cross-validated r^2 (q^2) using leave one out (LOO) cross-validation method [84].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2012.09.003. These data include MOL files and InChiKeys of the most important compounds described in this article.

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