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Satbir Mor & Savita Nagoria

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An efficient and convenient synthesis, characterization, and antimicrobial evaluation of some new tetracyclic 1,4-benzothiazines

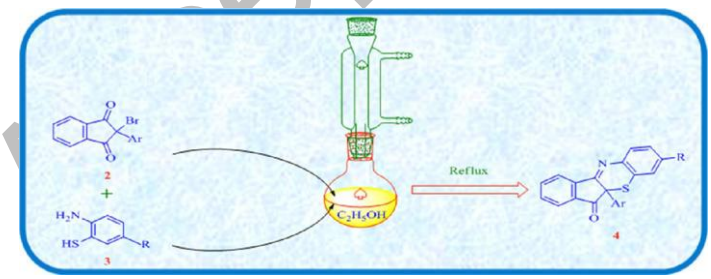
Satbir Mor[1], Savita Nagoria[1]

[1]Department of Chemistry, Guru Jambheshwar University of Science and Technology, Hisar, Haryana, India

Address Correspondence to Satbir Mor E-mail: satbir_mor@yahoo.co.in

Abstract

*In present study, a series of twenty new tetracyclic 1,4-benzothiazines (**4a**–**4t**) was conveniently synthesized in high yields and characterized by employing different spectral and physical techniques. The in vitro antimicrobial evaluation of the synthesized benzothiazine derivatives was performed by serial dilution technique against four bacterial strains, i.e., two Gram-positive bacteria viz.* Bacillus subtilis *(MTCC 441) and* Staphylococcus epidermidis *(MTCC 6880) and two Gram-negative bacteria viz.* Escherichia coli *(MTCC 1652) and* Pseudomonas aeruginosa *(MTCC 424), and two fungal strains viz.* Candida albicans *(MTCC 227) and* Aspergillus niger *(MTCC 8189). The derivatives **4l** and **4t** were found to be more potent than standard drug, i.e., Fluconazole against* A. niger *and* C. albicans*, respectively.*



KEYWORDS: 2-Aminobenzenethiols; Antimicrobial; 1,4-Benzothiazines; Bromination

INTRODUCTION

Emerging infectious diseases and the increase in incidence of drug resistance among pathogenic microorganisms have made the search for new antimicrobials inevitable for the improvements in human well being, including quality of life, and to wealth creation for individuals and nations. Consequently, the design as well as identification of potent and novel structural leads remains a major challenge for molecular architectures and medicinal chemistry researchers. 1,4-Benzothiazines undoubtedly constitute a privileged class of bioactive molecules, as compounds bearing this structural motif acquire remarkable biological activities and utilization as key structural template for the synthesis of various natural products of pharmaceutical interest.[1] These scaffolds have immense chemotherapeutic importance as antimicrobial,[2,3] antitumoral,[2,4] antidepressant,[5] anti-inflammatory,[6] antiarrhythmic,[7] antidiabetic,[8] antihypertensive,[9] antirheumatic,[10] antimalarial,[11] anti-HIV,[12] antitubercular,[13] agents, etc. Further, benzothiazines are known to possess unique properties such as potassium channel openers,[14,15] steel corrosion inhibitors,[16] photosensitizers[17] and dyes.[18] Also, such pharmacophores have been found to elicit their role, as calcium ion antagonist,[19] lipoxygenase inhibitors,[20] phosphodiesterase inhibitors,[21] neuroleptics,[22,23] antihistaminics,[24] antipsycotics,[25] antioxidants,[26] cytostatic agents,[27] and Na^+/H^+ exchange inhibitors,[28] etc. In addition, literature survey revealed that 1,4-benzothiazine is an ubiquitous motif which received attention due to their occurrence in the nature as red hair pigments[29] and their applications as precursors to thioesters for natural chemical ligation.[30] The multifarious applications of 1,4-benzothiazine derivatives have led to the development of various synthetic routes for their preparation,[31–34] however, the most convenient method for their

synthesis involves the treatment of dinucleophiles, *i.e.*, 2-aminothiophenol or its precursors with suitable α-halo ketones under appropriate reaction conditions. Prompted from these findings and in continuation of our research program aimed at the synthesis and biological evaluation of nitrogen and sulfur containing heterocyclic compounds,[35–38] herein, we report an efficient and convenient synthesis, characterization and *in vitro* antimicrobial evaluation of twenty new tetracyclic 1,4-benzothiazines (**4a**–**4t**).

RESULTS AND DISCUSSION

Chemistry

The synthetic route for the preparation of tetracyclic 1,4-benzothiazines (**4a**–**4t**) is outlined in Scheme 1. The convenient, efficient and versatile synthesis of tetracyclic 1,4-benzothiazines (**4**) began with phthalide as starting material. The key intermediates α-haloketones, *i.e.*, 2-aryl-2-bromo-1*H*-indene-1,3(2*H*)-diones (**2**) were synthesized by a two step procedure that involves reacting phthalide with appropriate 4-substituted benzaldehydes in the presence of sodium methoxide and ethylacetate to yield 2-aryl-1*H*-indene-1,3(2*H*)-diones[39,40] (**1**) which upon subsequent bromination in Br_2/chloroform afforded the corresponding 2-aryl-2-bromo-1*H*-indene-1,3(2*H*)-diones (**2**) in high yields.[41] The synthesis of 5-substituted 2-aminobenzenethiols (**3**) was accomplished in good yields by base catalyzed hydrolytic fission of 6-substituted 2-aminobenzothiazoles as described in the literature.[42–44] Finally, the target compounds (**4a**–**4t**) were achieved in high yields (82–95%) by the condensation of equimolar quantities of 2-aryl-2-bromo-1*H*-indene-1,3(2*H*)-diones (**2**) and appropriate 2-aminobenzenethiol/5-substituted 2-aminobenzenethiols (**3**) in refluxing dry ethanol for 8–13 h.

The structures of all the newly synthesized 1,4-benzothiazines (**4a**–**4t**) were elucidated on the basis of spectral (IR, ^{1}H NMR, ^{13}C NMR, COSY, DEPT, HSQC, HMBC and mass) as well as analytical results. The IR spectra of all these compounds (**4a**–**4t)** displayed the characteristic absorptions due to C=O stretching and C=N stretching in the regions at 1676–1697 cm^{-1} and 1645–1651 cm^{-1}, respectively. The ^{1}H NMR spectra of compounds (**4a**–**4t)**, in each case, exhibited a one-proton doublet in the region at δ 6.46–6.58 (J = 7.92–8.08 Hz) which was undoubtedly assigned to C_4-H. The compounds with substitution at C_8, displayed a one-proton doublet in the region at δ 6.60–7.21 safely assignable to C_9-H with coupling constant (J) ranging from 1.36–2.88 Hz which is due to meta coupling. The one-proton doublet (J = 7.44–7.68 Hz) exhibited in the region at δ 7.91–7.97 was easily assigned to C_1-H. The most characteristic feature of ^{1}H NMR spectra of 1,4-benzothiazines (**4a**–**4t)** was a one-proton doublet (J = 8.44–9.32 Hz) in the region at δ 9.04–9.18 due to C_6-H. The signals due to the remaining aliphatic and aromatic protons were observed in their expected regions (*vide experimental*). The salient feature of ^{13}C NMR spectra of 1,4-benzothiazines (**4a**–**4t**) was the signal observed in the most downfield region at δ 164.80–165.22 which was indubitably assigned to C_{11}. Further, it is worthy to mention here that with the variation of R, the change in chemical shift value of C_8 signal was observed. The signals due to the remaining aliphatic and aromatic carbons were observed in the expected regions (*vide experimental*). Further, the mass spectral data and elemental analysis results of 1,4-benzothiazines (**4a**–**4t**) were also found in good agreement with their molecular formulae (*vide experimental*).

In Vitro Antimicrobial Evaluation

All the synthesized 1,4-benzothiazine derivatives (**4a**–**4t**) were assessed for their *in vitro* antimicrobial activity against two Gram-positive bacterial strains *viz*. *Bacillus subtilis* (MTCC 441) and *Staphylococcus epidermidis* (MTCC 6880), two Gram-negative bacterial strains *viz*. *Escherichia coli* (MTCC 1652) and *Pseudomonas aeruginosa* (MTCC 424), and two fungal strains *viz*. *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 8189) by employing serial dilution technique.[45] Minimum inhibitory concentrations (MIC) were expressed in terms of µmol/mL. Ciprofloxacin and Fluconazole (Fig. 1) were used as reference drugs for antibacterial and antifungal evaluation, respectively. The results of antibacterial evaluation summarized in Table 1 and Fig. 2 revealed that the derivatives **4a**, **4f**, **4i** and **4n** against *B. subtilis*; **4a**, **4d**, **4f**, **4g**, **4i**, **4k**, **4l**, **4o** and **4p** against *S. epidermidis*; **4a**, **4d**, **4f**, **4g**, **4i**, **4k**, **4n**, **4o**, **4s** and **4t** against *E.coli*, and **4g** and **4h** against *P. aeruginosa* were moderately active as compared to the standard reference. However, all the tested derivatives were found to exhibit less inhibitory activity as compared to reference drug, *i.e.*, Ciprofloxacin. Further, the results of antifungal evaluation presented in Table 2 and Fig. 3 revealed that derivatives **4a**, **4f**, **4j** and **4p** exhibited moderate activity against *C. albicans* as compared to reference drug, *i.e.*, Fluconazole. Similarly, compound **4h** and **4r** also possessed appreciable antifungal activity against *A. niger* as compared to reference drug. Interestingly, the compounds **4t** against *C. albicans* and **4l** against *A. niger* were found to be more potent than the standard drug. Hence, **4t** and **4l** can be used as potential antifungal agents for further drug development. Moreover, comparison of antibacterial and antifungal evaluation results reveals that the antifungal activities are more prolific than antibacterial activities.

From the above antimicrobial results, following structure activity relationships (SAR) may be inferred

1. The unsubstitution at C_8 of 1,4-benzothiazine ring improved the antimicrobial efficacy against *S. epidermidis*, *E. coli* and *C. albicans*.

2. The presence of electron withdrawing groups such as F at $C_{4'}$ of C_{10a}-phenyl ring and Br at C_8 and/or $C_{4'}$ positions enhanced the antimicrobial activity against all the tested microbial strains except *P. aeruginosa*.

3. In most of the cases, presence of electron donating ethyl group at $C_{4'}$ of C_{10a}-phenyl ring increased the antimicrobial potency against all the tested microbial strains.

4. In some cases, presence of electron withdrawing NO_2 at $C_{4'}$ of C_{10a}-phenyl ring improved the antimicrobial activity against *S. epidermidis*, *B. subtilis*, *E. coli* and *C. albicans*.

5. In contrast to the above results, presence of electron withdrawing groups like NO_2, F and Br at $C_{4'}$ of C_{10a}-phenyl ring lessen the antibacterial activity against *P. aeruginosa*.

These results lead to the conclusion that there are different structural requirements for a compound to be effective against different microbial strains. However, no general trend toward structure activity relationship (SAR) has been established for antimicrobial activity of the tested 1,4-benzotiazine derivatives (**4**).

CONCLUSION

Conclusively, we have accomplished the synthesis of a series of twenty new tetracyclic 1,4-benzothiazines (**4a**–**4t**) through an efficient chemical transformation. All the synthesized 1,4-benzothiazines (**4a**–**4t**) have been investigated for their *in vitro* antimicrobial activity. Most of the tested compounds exhibited moderate to good activity towards Gram-positive and Gram-negative bacterial strains as well as the fungal strains. Among the target compounds, **4l** and **4t** were found to be more potent than standard drug against *A. niger* and *C. albicans*, respectively, which could be promising lead candidates for further drug discovery against fungal infections. Further work in this direction is continuing in our laboratory.

EXPERIMENTAL

Commercial reagents were utilized as received from suppliers without additional purification. 2-Aminothiophenol was purchased from Sigma-Aldrich. All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, ESI-MS and microanalysis. All the melting points (°C) were recorded on electrothermal apparatus in open capillary tubes and are uncorrected. Thin layer chromatography was used for monitoring the progress of the reaction and ascertaining the purity of the synthesized compounds on pre-coated TLC plates (Merck Keiselgel F_{254}) using hexane-ethyl acetate solvent system of different polarity and visualization was achieved by exposure to UV light. Columns were packed as slurry of silica gel (60–120 mesh) in hexane. Initially, compounds were adsorbed on silica gel in appropriate solvent and then loaded on column as slurry in hexane. The FTIR spectra were scanned on IR Affinity-1 FTIR (Shimadzu) spectrophotometer in KBr and wave numbers (ν) are reported in cm^{-1}. Nuclear Magnetic

Resonance spectra (^{1}H at 400 MHz and ^{13}C at 100 MHz) were recorded on 400 MHz Bruker AVANCE-III spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. DEPT (Distortionless Enhancement by Polarization Transfer) and 2D-NMR *viz.* COSY (correlation spectroscopy), HSQC (heteronuclear single-quantum coherence) and HMBC (heteronuclear multiple bond correlation) spectra of compound **4b** were also recorded on 400 MHz Bruker AVANCE-III spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are expressed in Hertz (Hz). Multiplicities in NMR signals are designated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet) and m (multiplet, for unresolved signals). Mass spectra were scanned on Waters Quadrupole Detector (TDQ), Waters gtof micro Mass spectrometer and Agilent 6410B Triple Quard LCMS spectrometer. Microanalyses were performed on Thermo Scientific FLASH-2000 CHN analyser. All the synthesized compounds were found in good agreement with the elemental analysis. Analytical results for C, H and N were found to be within ± 0.4 % of the theoretical values. Nomenclature of the compounds was assigned with the help of Chem Draw Ultra 12.0.

General Procedure For The Synthesis Of 2-Aryl-1H-Indene-1,3(2H)-Diones (1)

Condensation of equimolar quantities of phthalide and appropriate benzaldehyde under the influence of sodium methoxide and ethylacetate led to the formation of 2-aryl-1*H*-indene-1,3(2*H*)-dione (**1**).[39,40]

General Procedure For The Synthesis Of 2-Aryl-2-Bromo-1H-Indene-1,3(2H)-Diones (2)

The 2-aryl-1*H*-indene-1,3(2*H*)-diones (**1**) upon bromination in Br_2/chloroform furnished the corresponding 2-aryl-2-bromo-1*H*-indene-1,3(2*H*)-diones (**2**).[41]

General Procedure For The Synthesis Of 5-Substituted-2-Aminobenzenethiols (3)

The reaction of potassium thiocyanate and bromine (generating thiocyanogen, $[(SCN)_2]$, *in situ*) on appropriate anilines yielded the corresponding 6-substituted-2-aminobenzothiazoles, which upon subsequent base catalyzed hydrolytic fission afforded the corresponding 5-substituted 2-aminobenzenethiols (**3**) in good yields.[42–44]

Typical Procedure For The Synthesis Of 10a-(4-Nitrophenyl)Benzo[B]Indeno[1,2-E][1,4]Thiazin-11(10ah)-One (4a)

2-(4-Nitrophenyl)-1*H*-indene-1,3(2*H*)-dione (**1a**) was synthesized by condensation of equimolar quantities of phthalide and appropriate benzaldehyde under the influence of sodium methoxide and ethylacetate.[39,40] The 2-(4-Nitrophenyl)-1*H*-indene-1,3(2*H*)-diones (**1a**) upon bromination in Br_2/chloroform furnished the corresponding 2-bromo-2-(4-nitrophenyl)-1*H*-indene-1,3(2*H*)-dione (**2a**).[41] 2-Aminobenzenethiol (**3a**) required for the synthesis of 1,4-benzothiazines was purchased from Sigma-Aldrich. A solution of equimolar quantities of 2-bromo-2-(4-nitrophenyl)-1*H*-indene-1,3(2*H*)-dione (**2a**) and 2-aminobenzenethiol (**3a**) in dry ethanol (30 mL) was heated at reflux on a water bath for 10 h. Thereafter, the reaction mixture was cooled to room temperature and solid thus obtained was filtered, dried and purified on silica gel (60–120 mesh) column prepacked in hexane. Elution of the column with hexane:ethylacetate (19:1, v/v) gave a

homogeneous residue, which upon crystallization from chloroform furnished 10a-(4-Nitrophenyl)benzo[*b*]indeno[1,2-*e*][1,4]thiazin-11(10a*H*)-one (**4a**) in high yield (85%).

Spectral Data

Orange solid, yield 85%; mp 250–252 °C; IR (KBr, cm^{-1}): ν_{max} 3113, 3065 (aromatic C–H), 1684 (C=O), 1647 (C=N), 1512 (asymmetric N–O stretch.), 1346 (symmetric N–O stretch.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (d, 1H, J = 8.44 Hz, H-6), 8.41 (d, 2H, J = 8.20 Hz, H-3', H-5'), 7.97 (d, 1H, J = 7.52 Hz, H-1), 7.73 (d, 2H, J = 8.20 Hz, H-2', H-6'), 7.55–7.09 (m, 5H, H-2, H-3, H-7, H-8, H-9), 6.48 (d, 1H, J = 7.92 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.13 (C-11), 148.69 (C-4'), 141.47 (C-1'), 133.73 (C-5a), 131.87 (C-3), 131.09 (C-2', C-6'), 130.36 (C-4b), 129.03 (C-2), 128.56 (C-4a), 128.14 (C-7), 127.67 (C-11a), 125.77 (C-8), 125.61 (C-9), 124.93 (C-3', C-5'), 123.51 (C-1), 121.46 (C-4), 119.51 (C-6), 119.15 (C-9a), 115.32 (C-10a); ESI-MS *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{12}N_2O_3S$, 373.06; found, 373.14. *Anal*. calcd. for $C_{21}H_{12}N_2O_3S$: C, 67.73; H, 3.25; N, 7.52; found: C, 67.92; H, 3.48; N, 7.24.

General Procedure For *In Vitro* Antimicrobial Evaluation

All the newly synthesized twenty tetracyclic 1,4-benzothiazines (**4a**–**4t**) were screened for their *in vitro* antimicrobial activity against two Gram-positive bacteria *viz. B. subtilis* (MTCC 441) and *S. epidermidis* (MTCC 6880), two Gram-negative bacteria *viz. E. coli* (MTCC 1652) and *P. aeruginosa* (MTCC 424), and two fungi *viz. A. niger* (MTCC 8189) and *C. albicans* (MTCC 227) by employing serial dilution technique.[45] Initially, stock solutions were prepared by dissolving weighed amounts of synthesized compounds

in DMSO (1.0 mg of the test compound in 10 mL DMSO) to get a final concentration of 100 µg/mL. Fresh cultures were obtained by inoculation of respective microorganisms in suitable media *viz*. nutrient broth for bacterial strains and potato dextrose broth for fungal strains, followed by incubation at 37 ± 1 ºC for 24 h (all bacteria), 25 ± 1 ºC for 7 days (*A. niger*) and 37 ± 1 ºC for 48 h (*C. albicans*). The stock solutions of the test compounds were then serially diluted in test tubes containing 1 mL of sterile medium to get the concentrations of 50–0.39 µg/mL. Then 100 µL of the respective microorganism in sterile saline was inoculated to different dilutions of test compounds (each dilution in triplicates). The inoculated test tubes were incubated at 37 ± 1 ºC for 24 h (bacteria), 25 ± 1 ºC for 7 days (*A. niger*) and 37 ± 1 ºC for 48 h (*C. albicans*). Ciprofloxacin and Fluconazole were used as standard antibacterial and antifungal drugs, respectively, which were also assessed under similar conditions for comparison with the tested compounds. After incubation, microbial growth was monitored visually and spectrophotometrically and the results were recorded in terms of Minimum Inhibitory Concentration (MIC, µmol/mL). The data for the antibacterial activity are presented in Table 1 and Fig. 2, and results of antifungal activity are depicted in Table 2 and Fig. 3.

SUPPLEMENTARY MATERIAL

Full experimental detail, characterization/spectral data, and ^{1}H NMR, ^{13}C NMR spectra of all newly synthesized 1,4-benzothiazines (**4a**–**4t**) and 2D NMR spectra of **4b** can be accessed on the publisher's website.

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REFERENCES

1. Gupta, R. R. *Phenothiazines and 1,4-benzothiazines*: *Chemical and biomedical aspects*, Vol. 4 of Bioactive molecules, Elsevier: Amsterdam, 1988, pp 163–260.

2. Shamsuzzaman; Dar, A. M.; Khanam, H.; Gatoo, M. A. *Arab. J. Chem.* **2014**, *7*, 461–468.

3. Gautam, N.; Dixit, Y.; Dixit, R.; Gupta, S. K.; Gautam, D. C. *Phosphorus, Sulfur Silicon Relat. Elem.* **2013**, *188*, 1127–1136.

4. Zieba, A.; Sochanik, A.; Szurko, A.; Rams, M.; Mrozek. A; Cmoch, P. *Eur. J. Med. Chem.* **2010**, *45*, 4733–4739.

5. Krapcho, J.; Somerset, N. J. *US Patent* 3,715,353, **1973**.

6. Gowda, J.; Khader, A. M. A.; Kalluraya, B.; Shree, P.; Shabaraya, A. R. *Eur. J. Med. Chem.* **2011**, *46*, 4100–4106.

7. Hirasawa, A.; Haruno, A.; Matsuzaki, T.; Hashimoto, K. *Jpn. Heart J.* **1992**, *33*, 851–861.

8. Park, J. S.; Rhee, S. D.; Kang, N. S.; Jung, W. H.; Kim, H. Y.; Kim, J. H.; Kang, S. K.; Cheon, H. G.; Ahn, J. H.; Kim, K. Y. *Biochem. Pharmacol.* **2011**, *81*, 1028–1035.

9. Kajino, M.; Mizuno, K.; Tawada, H.; Shibouta, Y.; Nishikawa, K.; Meguro, K. *Chem. Pharm. Bull.* **1991**, *39*, 2888–2895.

10. Matsuoka, H.; Ohi, N.; Mihara, M.; Suzuki, H.; Miyamato, K.; Maruyama, N.; Tsuji, K.; Kato, N.; Akimoto, T.; Takeda, Y.; Yano, K.; Kuroki, T. *J. Med. Chem.* **1997**, *40*, 105–111.

11. Barazarte, A.; Lobo, G.; Gamboa, N.; Rodrigues, J. R.; Capparelli, M. V.; Alvarez-Larena, A.; Lopez, S. E.; Charris, J. E. *Eur. J. Med. Chem.* **2009**, *44*, 1303–1310.

12. Grandolini, G.; Perioli, L.; Ambrogi, V. *Eur. J. Med. Chem.* **1999**, *34*, 701–709.

13. Guleria, A.; Jangid, D. K.; Gautam, N.; Lakhotia, R.; Chowdhary, A.; Gautam, D. C. *Comb. Chem. High Throughput Screening* **2015**, *18*, 48–52.

14. Martelli, A.; Manfroni, G.; Sabbatini, P.; Barreca, M. L.; Testai, L.; Novelli, M.; Sabatini, S.; Massari, S.; Tabarrini, O.; Masiello, P.; Calderone, V.; Cecchetti, V. *J. Med. Chem.* **2013**, *56*, 4718–4728.

15. Calderone, V.; Spogli, R.; Martelli, A.; Manfroni, G.; Testai, L.; Sabatini, S.; Tabarrini, O.; Cecchetti, V. *J. Med. Chem.* **2008**, *51*, 5085–5092.

16. Aloui, S.; Forsal, I.; Sfaira, M.; Touhami, M. E.; Taleb, M.; Baba, M. F.; Daoudi, M. *Port. Electrochim. Acta* **2009**, *27*, 599–613.

17. Podsiadly, R. *J. Photochem. Photobiol. A: Chem.* **2009**, *208*, 147–153.

18. Ma, Y. T.; Huang, M. C.; Hsu, F. L.; Chang, H. F. *Phytochemistry* **1998**, *48*, 1083–1085.

19. Fujimura, K.; Fujita, M.; Suhara, H.; Kawashima, Y. *Bioorg. Med. Chem.* **1994**, *2*, 235–242.

20. Bakavoli, M.; Nikpour, M.; Rahimizadeh, M.; Saberi, M. R.; Sadeghian, H. *Bioorg. Med. Chem.* **2007**, *15*, 2120–2126.

21. Nosova, E. V.; Lipunova, G. N.; Charushin, V. N.; Chupakhin, O. N. *J. Fluor. Chem.* **2010**, *131*, 1267–1288.

22. Walfred, S. S.; Cochran, D. W.; Lee, Y. C.; Cresson, E. L.; Springer. J. P.; Williams, M.; Totaro, J. A.; Yarbrough, G. G. *J. Med. Chem.* **1983**, *26*, 564–569.

23. Grol, C. J.; Rollema, H. *J. Med. Chem.* **1975**, *18*, 857–861.

24. Sugimoto, Y.; Tarumi, T.; Zhao, Q. E.; Fujii, Y.; Kamei, C. *Methods Find Exp. Clin. Pharmacol.* **1998**, *20*, 457–462.

25. King, D. J.; Wager, E. *J. Psychopharmacol.* **1998**, *12*, 283–288.

26. Kumar, M.; Sharma, K.; Samarth, R. M.; Kumar, A. *Eur. J. Med. Chem.* **2010**, *45*, 4467–4472.

27. Grandolini, G.; Ambrogi, V.; Baiocchi, L.; Giannangeli, M.; Furlani, A.; Papaioannou, A.; Perioli, L.; Scarcia, V. *Heterocycl. Commun.* **1995**, *1*, 265–280.

28. Yamamoto, T.; Hori, M.; Watanabe, I.; Harada, K.; Ikeda, S.; Ohtaka, H. *Chem. Pharm. Bull.* **2000**, *48*, 843–849.

29. Napolitano, A.; Panzella, L.; Leone, L.; d'Ischia, M. *Acc. Chem. Res.* **2013**, *46*, 519–528.

30. Yeo, D. S. Y.; Srinivasan, R.; Chen, G. Y. J.; Yao, S. Q. *Chem. Eur. J.* **2004**, *10*, 4664–4672.

31. Liso, G.; Trapani, G.; Berardi, V.; Latrofa, A.; Marchini, P. *J. Heterocycl. Chem.* **1980**, *17*, 793–796.

32. Patmore, E. L.; Chafetz. H. *J. Org. Chem.* **1967**, *32*, 1254–1255.

33. Sharma, P. R.; Gupta, V.; Gautam, D. C.; Gupta, R. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 1483–1488.

34. Rathore, B. S.; Kumar, M. *Bioorg. Med. Chem.* **2006**, *14*, 5678–5682.

35. Mor, S.; Mohil, R.; Kumar, D.; Ahuja, M. *Med. Chem. Res.* **2012**, *21*, 3541–3548.

36. Mor, S.; Pahal, P.; Narasimhan, B. *Eur. J. Med. Chem.* **2012**, *53*, 176–189.

37. Mor, S.; Pahal, P.; Narasimhan, B. Eur. J. Med. Chem. **2012**, *57*, 196–210.

38. Mohil, R.; Kumar, D.; Mor, S. *J. Heterocycl. Chem.* **2014**, *51*, 203–211.

39. Shapiro, S. L.; Geiger, K.; Youlus, J.; Freedman, L. *J. Org. Chem.* **1961**, *26*, 3580–3582.

40. Cundasawmy, N. E.; Maclean, D. B. *Can. J. Chem.* **1972**, *50*, 3028–3036.

41. Hrnicar, P. *Chem. Zvesti*. **1962**, *16*, 673–677.

42. Brewster, R. Q.; Dains, F. B. *J. Am. Chem. Soc.* **1936**, *58*, 1364–1366.

43. Mital, R. L.; Jain, S. K. *J. Chem. Soc. C* **1969**, *16*, 2148–2150.

44. Matsui, M.; Marui, Y.; Kushida, M.; Funabiki, K.; Muramastu, H.; Shibata, K.; Hirota, K.; Hosoda, M.; Tai, K. *Dyes Pigm.* **1998**, *38*, 57–64.

45. Mosaddik, M. A.; Haque, M. E. *Phytother. Res.* **2003**, *17*, 1155–1157.

Supplemental data for this article can be accessed on the publisher's website.

Table 1. *In vitro* antibacterial activity of 1,4-benzothiazines (**4a**–**4t**).

Compounds	Minimum Inhibitory Concentration (MIC)[a]			
	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis[b]	*S. epidermidis*[c]	*E. coli*[d]	*P. aeruginosa*[e]
4a	0.03357	0.01678	0.01678	0.03357
4b	0.01617	0.03235	0.03235	0.03235
4c	0.03106	0.03106	0.03106	0.03106
4d	0.02770	0.01385	0.01385	0.02770
4e	0.03072	0.03072	0.03072	0.03072
4f	0.01758	0.01758	0.01758	0.03517
4g	0.03383	0.01692	0.01692	0.01692
4h	0.03243	0.03243	0.03243	0.01621
4i	0.01439	0.01439	0.01439	0.05756
4j	0.03206	0.03206	0.03206	0.06412
4k	0.03619	0.01810	0.01810	0.03619
4l	0.03478	0.01739	0.03478	0.03478
4m	0.03330	0.03330	0.03330	0.06659
4n	0.01473	0.02946	0.01473	0.02946
4o	0.03291	0.01645	0.01645	0.03291
4p	0.03077	0.01538	0.03077	0.03077
4q	0.02974	0.02974	0.02974	0.02974
4r	0.02865	0.02865	0.02865	0.02865
4s	0.02576	0.02576	0.01288	0.05153

4t	0.02836	0.02836	0.01418	0.02836
Ciprofloxacin	0.00471	0.00471	0.00471	0.00471

[a] Unit: µmol/mL

[b] *Bacillus subtilis* (MTCC 441)

[c] *Staphylococcus epidermidis* (MTCC 6880)

[d] *Escherichia coli* (MTCC 1652)

[e] *Pseudomonas aeruginosa* (MTCC 424)

Table 2. *In vitro* antifungal activity of 1,4-benzothiazines (**4a**−**4t**).

Compounds	Minimum Inhibitory Concentration (MIC)[a]	
	C. albicans[b]	*A. niger*[c]
4a	0.0168	0.0336
4b	0.0323	0.0647
4c	0.0311	0.0621
4d	0.0554	0.0554
4e	0.0614	0.0614
4f	0.0176	0.0703
4g	0.0677	0.0677
4h	0.0324	0.0162
4i	0.0576	0.0288
4j	0.0160	0.0321
4k	0.0362	0.1448
4l	0.0348	0.0087
4m	0.0333	0.0333
4n	0.0295	0.0295
4o	0.0329	0.0658
4p	0.0154	0.0308
4q	0.0297	0.0595
4r	0.0573	0.0143
4s	0.0515	0.0515
4t	0.0018	0.0284

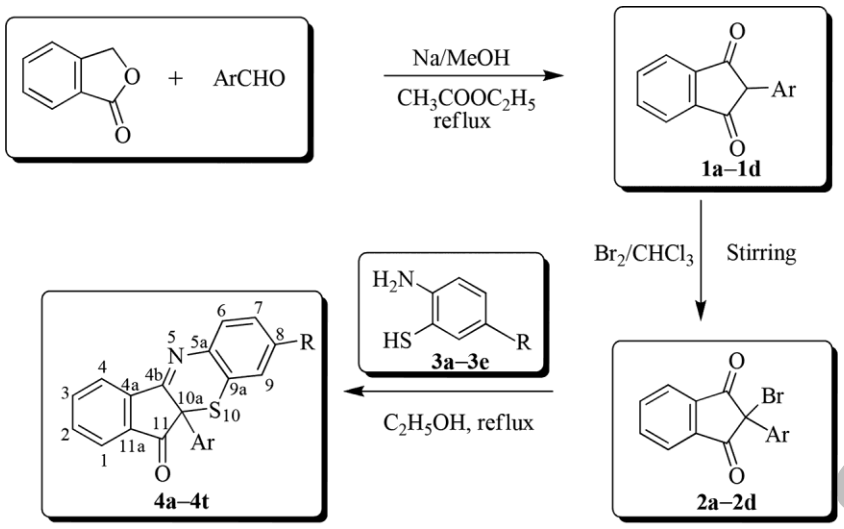
Fluconazole	0.0102	0.0102

[a] Unit: µmol/mL

[b] *Candida albicans* (MTCC 227)

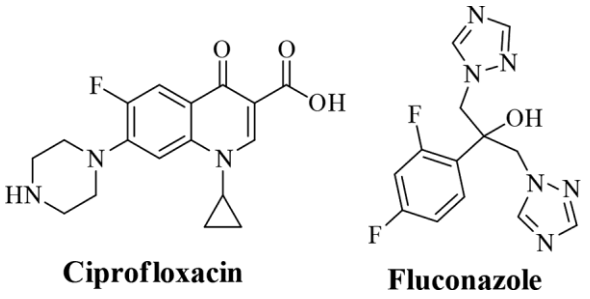
[c] *Aspergillus niger* (MTCC 8189)

Scheme 1. The reaction sequence for the synthesis of 1,4-benzothiazines (**4a**–**4t**).



Compounds	Ar	R	Compounds	Ar	R
4a	4-NO_2-C_6H_4	H	**4k**	4-F-C_6H_4	H
4b	4-NO_2-C_6H_4	CH_3	**4l**	4-F-C_6H_4	CH_3
4c	4-NO_2-C_6H_4	OCH_3	**4m**	4-F-C_6H_4	OCH_3
4d	4-NO_2-C_6H_4	Br	**4n**	4-F-C_6H_4	Br
4e	4-NO_2-C_6H_4	Cl	**4o**	4-F-C_6H_4	Cl
4f	4-C_2H_5-C_6H_4	H	**4p**	4-Br-C_6H_4	H
4g	4-C_2H_5-C_6H_4	CH_3	**4q**	4-Br-C_6H_4	CH_3
4h	4-C_2H_5-C_6H_4	OCH_3	**4r**	4-Br-C_6H_4	OCH_3
4i	4-C_2H_5-C_6H_4	Br	**4s**	4-Br-C_6H_4	Br
4j	4-C_2H_5-C_6H_4	Cl	**4t**	4-Br-C_6H_4	Cl

Fig. 1. Structures of Ciprofloxacin and Fluconazole.



Ciprofloxacin **Fluconazole**

Fig. 2. Graphical representation of *in vitro* antibacterial activity of 1,4-benzothiazines (**4a**−**4t**).

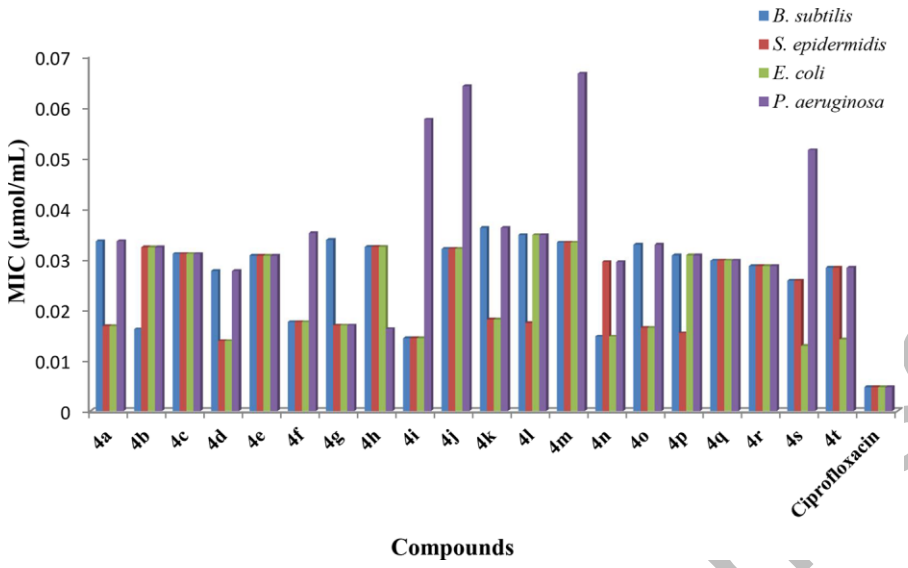


Fig. 3. Graphical representation of *in vitro* antifungal activity of 1,4-benzothiazines (**4a**−**4t**).