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α,α-Dibromoketone as Synthetic Equivalent to α-Bromoketones: Synthesis of Some New Thiazole as Antimicrobial Agents

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ABSTRACT

In the present paper, the syntheses of some new thiazoles incorporated with pyran moiety using α-bromo ketones and α,α-dibromo ketone are reported and found that both α-bromo ketones and α,α-dibromo ketone are synthetically equivalent. All the new compounds were characterized by spectral and analytical data. *In vitro* antibacterial activity shows that some of compounds are more potent than standard drugs against specific bacterial strains. All the compounds show fair antifungal activity, however, none of the compounds is more potent than the standard drug.

KEYWORDS

α-Bromo ketones, α,α-Dibromo ketones, Dehydroacetic acid, Hydrazones, Thiazoles, Antibacterial agents, Antifungal agents.

INTRODUCTION

Thiazoles are one of the most intensively investigated classes of aromatic five-membered heterocycles. Thiazoles continue to occupy a prime place in heterocyclic chemistry due to their presence in various bioactive heterocyclic molecules of pharmaceutical and agrochemical importance. Thiazole nucleus is known to exhibit various pharmacological profiles such as anti-inflammatory [1,2], antimicrobial [3-5], antiviral [6], antitumor [7], *etc*.

Thiazoles occupy a prominent position in the drug discovery process [8] and are found in several marketed drugs such as meloxicam [9], sulfathiazole [10], tiazofurin [11] *etc*. It can also be used in a scaffold hopping strategy [12] or as an amide isostere [13] during the course of probing structure activity relationships for lead optimization. As a result, thiazoles are frequently used as a core structure for the synthesis of chemical libraries [14].

The synthesis of thiazoles can be carried out by using large number of methods but Hantzsch thiazole synthesis is one of the important reactions between α-halo ketone and thioamides. α-Halo ketones are among the most versatile intermediates in organic synthesis and their high reactivity makes them prone to react with large number of nucleophiles to provide large number of biological active heterocycles. But

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α-halo ketones are associated with lachrymatory nature which makes handling difficult. In an important development, it has been observed that α,α-dihalo ketones behave as synthetic equivalent to α-halo ketones [15-17]. Being non-lachrymatory, generally solid at room temperature and soluble in commonly used reaction solvents, these compounds are easy to work with and can be handled easily. The present study is concerned with the use of α,α-dibromo derivatives of dehydroacetic acid (DHA) as precursor for synthesis of thiazoles. Dehydroacetic acid and its derivatives find wider application in the synthesis of heterocyclic compounds [18-21] and the area has been reviewed by our research laboratory and others [22].

EXPERIMENTAL

Melting points were taken on slides in an electrical apparatus Labindia visual melting range apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Perkin-Elmer 1800 FT-IR spectrophotometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Nuclear Magnetic Resonance (NMR) spectrophotometer at 300 MHz using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in ppm units (δ) downfield from TMS. The purity of compounds was checked by elemental analyses performed on Perkin-Elmer 2400 instrument. Mass spectra were recorded on 2500 ev (ESI source) using a water's Q-TOF micro instrument. All reagents were purchased from commercial sources and were used without purification.

4-Hydroxy-6-methyl-3-{2-[2-{1-(4-arylethylidene)-hydrazinyl]-1,3-thiazol-4-yl}-2*H* pyran-2-one (8 and 9): To a solution of α-bromo dehydroacetic acid (**2/3** 0.05 mol) in 20 mL ethanol was added *N*-1-(4-arylethylidene)thiosemicarbazone (**7**, 0.05 mol) and stirred at room temperature for about 20-30 min. The reaction was monitored by TLC. A solid product separated out of solution, filtered and washed with cold ethanol to give pure product Similar procedure was adopted using α,α-dibromo dehydroacetic acid (**4/5**).

4-Hydroxy-6-methyl-3-{2-[2-{1-(4-phenylethylidene)-hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (8a): m.p.: 196-198 °C; Yield: 79 %; IR (KBr, ν_{max}, cm^{-1}): 1597 (C=N), 1725 (C=O str.) 3265 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.26 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.23 (s, 1H), 7.30 (s, 1H, thiazole, C_5'-H), 7.59-7.85 (m, 5H, Ar), 11.8 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31. Found: C, 59.76; H, 4.40, N, 12.27; MS (ESI) *m/z* = 340.23 ($M + H^+$).

4-Hydroxy-6-methyl-3-{2-[2-{1-(4-methylphenyl)-ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (8b): m.p.: 235-237 °C; Yield: 78 %; IR (KBr, ν_{max}, cm^{-1}): 1599 (C=N), 1729 (C=O str.) 3242 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.31 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.21 (s, 1H), 7.21-7.37 (m, 4H, Ar), 7.33 (s, 1H, thiazole, C_5'-H), 11.9 (bs, 1H, NH); Analysis, calculated for $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.82. Found: C, 60.71; H, 4.80; N, 11.77. MS (ESI) *m/z* = 356.77 ($M + H^+$).

4-Hydroxy-6-methyl-3-{2-[2-{1-(4-chlorophenyl)-ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (8c): m.p.: 248-249 °C; Yield: 76 %; IR (KBr, ν_{max}, cm^{-1}): 1599 (C=N), 1715 (C=O str.) 3255 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.33 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.17 (s, 1H), 7.37 (s, 1H, thiazole, C_5'-H), 7.25-7.39 (m, 4H, Ar), 12.0 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{14}N_3O_3SCl$: C, 54.33; H, 3.75; N, 11.18. Found: C, 54.31; H, 3.72; N, 11.13.

4-Hydroxy-6-methyl-3-{2-[2-{1-(4-bromophenyl)-ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (8d): m.p.: 215-216 °C; Yield: 71 %; IR (KBr, ν_{max}, cm^{-1}): 1605 (C=N), 1710 (C=O str.) 3261 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.28 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.16 (s, 1H), 7.33 (s, 1H, thiazole, C_5'-H), 7.34-7.50 (m, 4H, Ar), 11.9 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{14}N_3O_3SBr$: C, 48.58; H, 3.56; N, 10.00. Found: C, 48.57; H, 3.50; N, 9.89.

4-Hydroxy-6-methyl-3-{2-[2-{1-(4-fluorophenyl)-ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (8e): m.p.: 199-202 °C; Yield: 75 %; IR (KBr, ν_{max}, cm^{-1}): 1603 (C=N), 1715 (C=O str.) 3248 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.36 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 6.12 (s, 1H), 7.39 (s, 1H, thiazole, C_5'-H), 7.49-7.81 (m, 4H, Ar), 12.0 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{14}N_3O_3SF$: C, 56.82; H, 3.93; N, 11.69. Found: C, 56.81; H, 3.87; N, 11.64.

4-Hydroxy-6-methyl-3-{2-[2-{1-(4-nitrophenyl)-ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (8f): m.p.: 270-272 °C; Yield: 71 %; IR (KBr, ν_{max}, cm^{-1}): 1609 (C=N), 1726 (C=O str.) 3248 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.38 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.21 (s, 1H), 7.39 (s, 1H, thiazole, C_5'-H), 8.01-8.28 (m, 4H, Ar), 12.00 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{14}N_4O_5S$: C, 52.84; H, 3.65; N, 14.50. Found: C, 52.78; H, 3.62; N, 14.47.

4-Hydroxy-6-methyl-3-{2-[2-{1-(4-hydroxyphenyl)-ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (8g): m.p.: 190-193 °C; Yield: 74 %; IR (KBr, ν_{max}, cm^{-1}): 1597 (C=N), 1713 (C=O str.) 3257 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.38 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 6.20 (s, 1H), 7.32 (s, 1H, thiazole, C_5'-H), 7.68-7.82 (m, 4H, Ar), 12.0 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{15}N_3O_4SBr$: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.09; H, 4.19; N, 11.69.

5-Bromo-4-hydroxy-6-methyl-3-{2-[2-(1-phenylethylidene)hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (9a): m.p.: 206-209 °C; Yield: 74 %; IR (KBr, ν_{max}, cm^{-1}): 1597 (C=N), 1725 (C=O str.) 3265 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.30 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.32 (s, 1H, thiazole, C_5'-H), 7.61-7.92 (m, 5H, Ar), 11.9 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{14}N_3O_3SBr$: C, 48.58; H, 3.36; N, 10.00. Found: C, 48.51; H, 3.32, N, 9.93;

5-Bromo-4-hydroxy-6-methyl-3-{2-[2-{1-(4-methyl-phenyl)ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (9b): m.p.: 181-184 °C; Yield: 77 %; IR (KBr, ν_{max}, cm^{-1}): 1597 (C=N), 1723 (C=O str.) 3248 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.33 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.25-7.33 (m, 4H, Ar), 7.37 (s, 1H, thiazole, C_5'-H), 11.9 (bs, 1H, NH); Analysis, calculated for $C_{18}H_{16}N_3O_3SBr$: C, 49.78; H, 3.71; N, 9.68. Found: C, 49.71; H, 3.66; N, 9.61.

5-Bromo-4-hydroxy-6-methyl-3-{2-[2-{1-(4-chloro-phenyl)ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (9c): m.p.: >300 °C; Yield: 72 %; IR (KBr, ν_{max}, cm^{-1}): 1601 (C=N), 1720 (C=O str.) 3265 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.39 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.39 (s,

1H, thiazole, C_5'-H), 7.58-7.83 (m, 4H, Ar), 12.0 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{13}N_3O_3SBrCl$: C, 44.90; H, 2.88; N, 9.24. Found: C, 44.81; H, 2.82; N, 9.13.

5-Bromo-4-hydroxy-6-methyl-3-{2-[2-{1-(4-bromophenyl)ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (9d): m.p.: 239-243 °C; Yield: 71 %; IR (KBr, ν_{max}, cm^{-1}): 1605 (C=N), 1716 (C=O str.) 3267 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.32 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.36 (s, 1H, thiazole, C_5'-H), 7.63-7.91 (m, 4H, Ar), 11.9 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{13}N_3O_3SBr_2$: C, 40.90; H, 2.62; N, 8.42. Found: C, 40.87; H, 2.60; N, 8.39.

5-Bromo-4-hydroxy-6-methyl-3-{2-[2-{1-(4-fluorophenyl)ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (9e): m.p.: > 300 °C; Yield: 69 %; IR (KBr, ν_{max}, cm^{-1}): 1599 (C=N), 1715 (C=O str.) 3264 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.33 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.36 (s, 1H, thiazole, C_5'-H), 7.63-7.76 (m, 4H, Ar), 12.0 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{13}N_3O_3SBrF$: C, 46.59; H, 2.99; N, 9.59. Found: C, 46.51; H, 2.93; N, 9.47.

5-Bromo-4-hydroxy-6-methyl-3-{2-[2-{1-(4-nitrophenyl)ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (9f): m.p.: > 300 °C; Yield: 74 %; IR (KBr, ν_{max}, cm^{-1}): 1612 (C=N), 1726 (C=O str.) 3232 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.39 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.45 (s, 1H, thiazole, C_5'-H), 8.16-8.47 (m, 4H, Ar), 12.02 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{13}N_4O_5SBr$: C, 43.88; H, 2.82; N, 12.04. Found: C, 43.79; H, 2.80; N, 12.00.

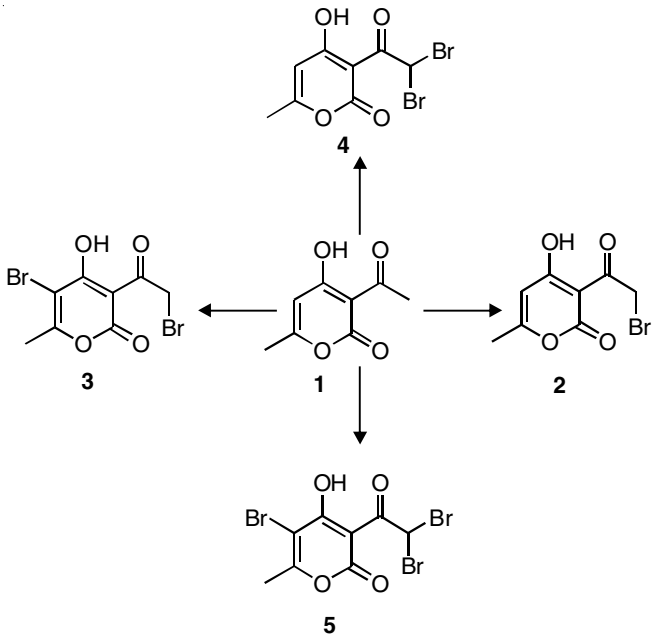
5-Bromo-4-hydroxy-6-methyl-3-{2-[2-{1-(4-hydroxyphenyl)ethylidene}hydrazinyl]-1,3-thiazol-4-yl}-2*H*-pyran-2-one (9g): m.p.: 243-245 °C; Yield: 72 %; IR (KBr, ν_{max}, cm^{-1}): 1605 (C=N), 1710 (C=O str.) 3233 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.36 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.30 (s, 1H, thiazole, C_5'-H), 7.81-7.92 (m, 4H, Ar), 11.9 (bs, 1H, NH); Analysis, calculated for $C_{17}H_{14}N_3O_4SBr$: C, 46.80; H, 3.23; N, 9.63. Found: C, 46.79; H, 3.19; N, 9.59.

Biological assay: The detailed procedure of biological assay *i.e.* collection of test microorganisms, preparation of medium, *in vitro* antibacterial assay, MIC and *in vitro* antifungal assay is given in our previous publication [23].

RESULTS AND DISCUSSION

Dehydroacetic acid derivatives such as 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**), 5-bromo-3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**), 3-(2,2-dibromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**4**) and 5-bromo-3-(2,2-dibromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**5**) are used in the present study to explore potential of synthetic equivalency. These derivatives were prepared from our recently reported method and method reported in the literature using bromine and *N*-bromosuccinimide from from 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (DHA, **1**) (**Scheme-I**) [24,25].

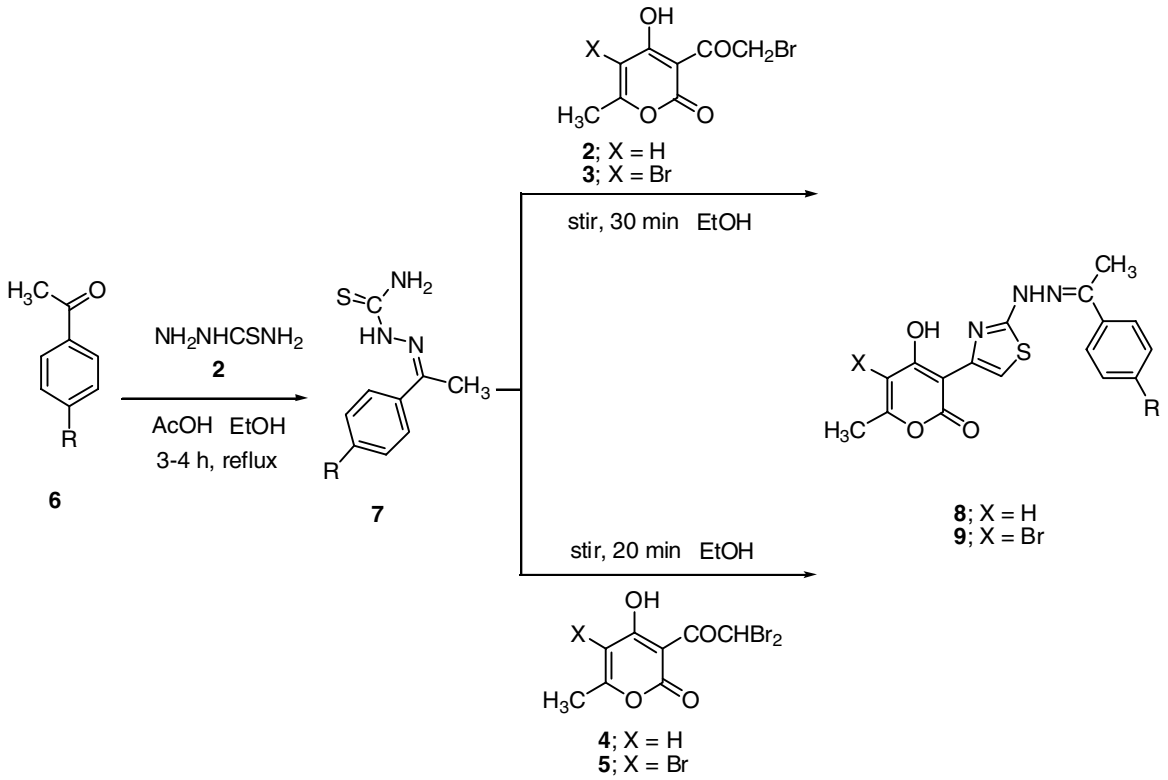
The starting material, 1-(1-(aryl)ethylidene)thiosemicarbazide (**7**) were prepared by the reaction of substituted acetophenones **6** with thiosemicarbazide according to literature procedure [26] (**Scheme-II**). Then, α-bromo dehydroacetic acid (**2**) was made to react with 1-(1-(phenyl)ethylidene)-



Scheme-I: Dehydroacetic acid derivatives used in the present study

thiosemicarbazide (**7a**) while stirring the reaction mixture at room temperature (**Scheme-II**). The progress of the reaction was monitored by TLC and it was found that after stirring for 30 min, reaction is complete and a reddish brown coloured solid was formed. ^{1}H NMR spectrum of **8a** showed three proton singlets at δ 2.26 and δ 2.39 respectively, due to CH_3 protons and a proton singlet at δ 7.30 due to thiazolyl proton. In the IR spectrum of **8a**, absorption bands were observed at 3265 cm^{-1} due to N-H stretching and at 1597 cm^{-1} due to C=N stretching. The generality of the reaction was studied by carrying out the reactions of α-bromo derivatives of dehydroacetic acid (**2, 3**) and different 1-(1-(aryl)ethylidene)thiosemicarbazide (**7a-g**). The adopted procedure in all the cases, afforded the expected thiazolyl hydrazones **8b-g** and **9b-g** in good yields ranges from 70-75 % (**Scheme-II**). All new compounds **8** and **9** were characterized by the combined application of IR, ^{1}H, ^{13}C NMR spectroscopy, mass spectroscopy and elemental analysis. Thus, we were successful in synthesis of thiazoles using α-bromo dehydroacetic acid (**2** and **3**).

Then, we carried out the reaction of α,α-dibromo dehydroacetic acid (**4** and **5**) with 1-(1-(aryl)ethylidene)thiosemicarbazide (**7a-g**). The progress of the reaction was observed with TLC and the reactions were completed in about 15-20 min. From data analysis, TLC comparison and elemental analysis it was found that the products obtained were same as obtained from α-bromo dehydroacetic acid derivatives. Thus, the present study offers a superior approach for the synthesis of thiazoles **8** and **9** as it is easier to prepare and handle α,α-dibromo derivatives as compared to α-bromo derivatives due to their non-lachrymatory nature and solid at room temperature. Further, it is also worthwhile to mention that the method adopted during this effort is significant since the reaction involves very simple experimentation under mild conditions. The study also revealed the behavioural analogy *i.e.* synthetic equivalency of α,α-dibromo derivatives with α-bromo derivatives in the present work.



where R = **a**: H; **b**: CH_3; **c**: Cl; **d**: Br; **e**: F; **f**: NO_2; **g**: OH

Scheme-II: Synthesis of compounds **8a-g** and **9a-g**

Biological screening

***In vitro* antibacterial activity:** All the newly synthesized compounds were screened for their *in vitro* antibacterial activity against two Gram-positive bacteria namely, *Staphylococcus aureus* and *Bacillus subtilis* and two Gram-negative bacteria namely, *Escherichia coli* and *Pseudomonas aeruginosa*. Standard antibiotics namely, ciprofloxacin, was used for comparison of antibacterial activity shown by compounds **8a-g** and **9a-g**. The results were recorded for each tested compounds as average diameter of zone of inhibition of bacterial growth adjoining the well in millimetres (Table-1). Minimum inhibitory concentration (MIC) measurements were performed using a modified agar well diffusion method (Table-2). MIC of those compounds was determined which were showing activity in primary screening.

From the results, it has been observed that in general, all the tested compounds possess good antibacterial activity against Gram-positive bacteria and Gram-negative bacteria. On the basis of zone of inhibition against test bacterium, eight compounds **8a, 8b, 8d, 8e, 9a, 9b, 9c** and **9e** showed excellent activity having maximum zone of inhibition > 20.0 mm as compared with standard drug ciprofloxacin which showed the zone of inhibition of 26.0 mm against *S. aureus*.

Similarly, on the basis of zone of inhibition five compounds **8a**, **8e**, **9a**, **9b** and **9c** were found to be most effective against *B. subtilis* showing maximum zone of inhibition > 20 mm as compared to standard drug ciprofloxacin which showed the zone of inhibition of 24 mm against *B. subtilis* (Table-1). Out of these active compounds, five compounds **8a**, **8e**, **9a, 9b, 9c** are in common which showed activity against both the Gram-positive bacteria. However, in case of the Gram-negative bacteria all the compounds showed good antibacterial activity against the test bacteria *E. coli* and *P. aeruginosa* as shown in Table-1. In case of *E. coli*, six compounds **8c**, **8e**, **8f**, **9a**, **9c** and **9d** showed maximum zone of inhibition > 18 mm in comparison to ciprofloxacin which showed 25 mm. Furthermore, in case of *P. aeruginosa*, four compounds **8c**, **8d, 9a** and **9b** showed the maximum zone of inhibition >18 mm in comparison to standard drug, ciprofloxacin, which showed 22 mm (Table-1 and Fig. 1).

TABLE-1
in vitro ANTIBACTERIAL ACTIVITY
OF COMPOUNDS **8a-g** AND **9a-g**

Compounds	Diameter of growth of inhibition zone (mm)[a]			
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
8a	23.3	20.6	–	–
8b	20.6	–	17.3	–
8c	19.3	19.6	18.3	20.0
8d	20.6	–	–	18.3
8e	23.3	20.6	19.3	16.0
8f	–	18.6	20.3	–
8g	18.6	19.3	–	15.0
9a	20.3	21.6	19.3	18.6
9b	21.6	20.6	–	18.3
9c	23.6	21.3	19.6	17.3
9d	–	17.3	18.3	–
9e	21.6	19.3	18.0	–
9f	18.6	–	–	–
9g	17.3	–	–	–
Ciprofloxacin	26.0	24.0	25.0	22.0

–No activity, [a]Values, including diameter of the well (8 mm), are means of three replicates.

TABLE-2
MIC OF COMPOUNDS **8a-g** AND **9a-g**

Compounds	MIC (µg/mL)			
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
8a	128	128	–	–
8b	64	128	–	–
8c	2	32	512	128
8d	128	–	256	64
8e	64	–	64	2
8f	–	128	128	256
8g	512	2	512	32
9a	128	2	64	64
9b	–	4	128	32
9c	–	32	64	64
9d	512	–	–	–
9e	2	32	128	–
9f	64	–	256	–
9g	32	512	–	64
Ciprofloxacin	5	5	5	5

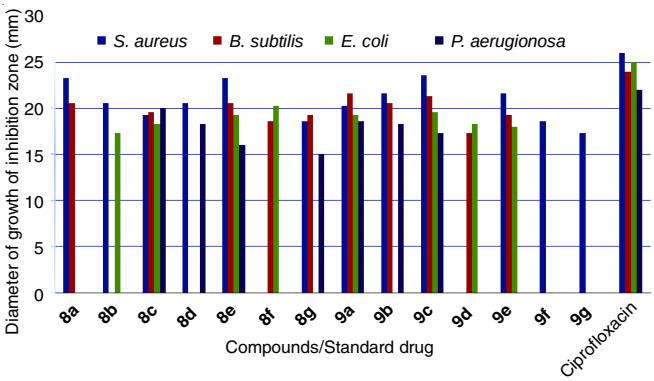


Fig. 1. Graphical view of antibacterial activity of compounds **8a-g** and **9a-g**

In the whole series, MIC of the synthesized compounds ranged between 2 and 512 µg/mL against the Gram-positive bacteria. In case of *S. aureus*, compounds **8c** and **9e** are most potent member having MIC ranged between 2 µg/mL in comparison to standard drug having MIC of 5 µg/mL. Other compounds showing good activity are **8b**, **8e, 9f** and **9g** having MIC of 64 µg/mL for first three members and 32 µg/mL for last member. In case of *B. subtilis*, most potent members having MIC ranged between 2 and 4 µg/mL are **8g**, **9a** and **9b.** Other compounds showing good activity having MIC 32 µg/mL are **8c, 9c** and **9e**. All other compounds showed reasonable activity against Gram-positive bacteria. In case of Gram-negative bacteria, MIC ranged between 2 and 512 µg/mL and the most potent members among all the tested compounds are **8e** having MIC of 2 µg/mL (Table-2 and Fig. 2).

Fig. 3 showed that the compounds **8c** and **9e** are more potent than standard drug ciprofloxacin against the bacterium species *S. aureus*. Similarly, compound **8g**, **9a** and **9b** are more active than the standard drug ciprofloxacin against *B. subtilis*. Compound **8e** is more potent that standard drug in case of *P. aeruginosa*. However, in case of *E. coli*, none of the compound is more potent than standard drug.

***In vitro* antifungal activity:** All the compounds tested for their *in vitro* antibacterial activity are also examined for their *in vitro* antifungal activity against two fungal strains, namely, *Aspergillus flavus* and *Aspergillus niger* through

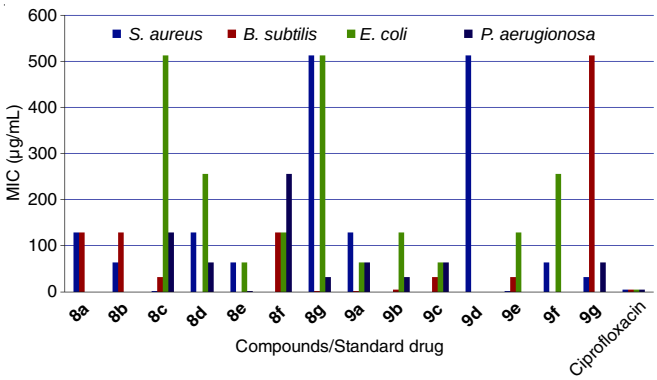


Fig. 2. Graphical view of MIC of compounds **8a-g** and **9a-g**

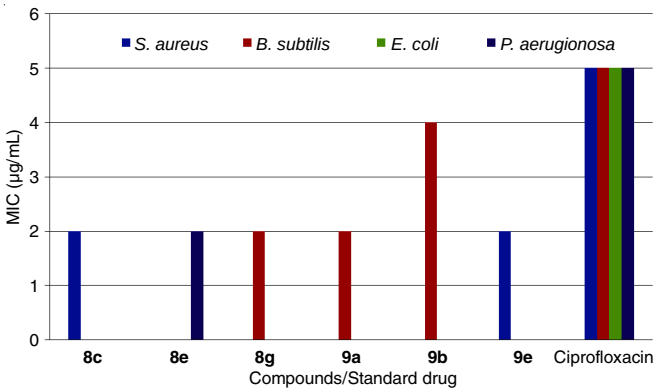


Fig. 3. Compounds which are more potent than standard drug against different species

poisoned food method. Standard drug fluconazole was used for comparison with antifungal activity shown by the compounds **8a-g** and **9a-g** and the results were recorded as percentage (%) of mycelial growth inhibition.

It has been revealed from the Table-3 that all the compounds showed variable antifungal activity against two pathogens. From the careful comparison of the results, it has been revealed that mainly the five compounds **9b, 9c, 9e** and **9f** showed good antifungal activity with > 62 % inhibition of mycelial growth against both fungi in comparison with standard drug (*A. niger* 81.1 % and *A. flavus* 77.7 %). All other compounds showed fair activity against fungal pathogens (Table-3 and Fig. 4).

TABLE-3
in vitro ANTIFUNGAL ACTIVITY OF
COMPOUNDS **8a-g** AND **9a-g**

Compounds	Mycelial growth inhibition (%)	
	A. flavus	*A. niger*
8a	55.5	61.1
8b	57.7	60.0
8c	62.5	55.5
8d	66.6	44.4
8e	61.1	55.5
8f	50.0	45.5
8g	62.5	44.4
9a	54.4	50.0
9b	60.0	62.5
9c	65.5	68.5
9d	62.5	61.1
9e	68.8	67.7
9f	65.5	62.5
9g	60.0	55.5
Fluconazole	77.7	81.1

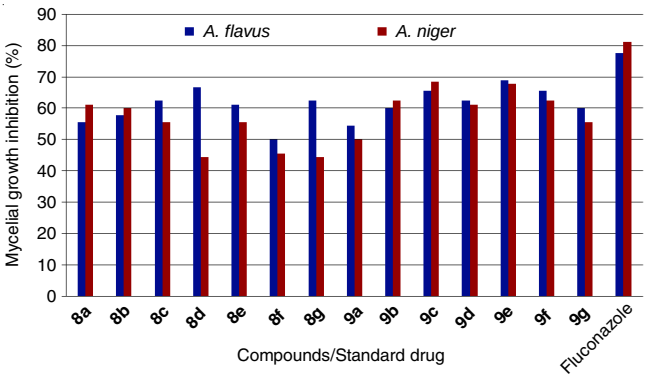


Fig. 4. Graphical view of antifungal activity of **8a-g** and **9a-g**

Thus, we can see from the data that none of the compounds is more potent than standard drug.

Conclusion

In conclusion, the present study offers an application of α-bromo- and α,α-dibromo derivative of dehydroacetic acid in an efficient and convenient synthesis of thiazoles and proves the synthetically equivalency of both the intermediates. Biological evaluation of these compounds proves them potent antibacterial agents. In case of antibacterial activity some of the compounds tested are even superior to the reference drug. However, antifungal activity data shows that the compounds have fair activity and none of the compounds is superior to reference drug.

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