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Synthesis, Biological Evaluation, and SAR Studies of Varyingly Substituted 4-Thioflavonols

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Abstract

A series of 4-thioflavonols compounds were synthesized by treating flavonols with lawsons reagent with variable substituent groups at A, B, and AB rings. All the synthesized compounds were checked for antibacterial and antifungal activity. We report that many compounds were found active against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Methicillin-resistant Staphylococcus aureus*, bacterial strains and, *C. albicans*, *C. parapsilosisstrains* and *C. krusei* fungal strains. Most of the synthesized 4-thioflavonols compounds were found to show enhanced antimicrobial activity than respective flavonol compounds.

Keywords

Flavonols, 4-Thioflavonols, Flavonoids, Lawsons Reagent, Antibacterial Activity, Antifungal Activity, One Pot Synthesis, Sulfur Compounds, SAR Studies

1. Introduction

Flavonoids are an important group of naturally occurring compounds with many physiological properties [1]. They are chromone-derived heterocyclic benzopyran compounds containing a chromone core [2]. Flavonols are the largest group of flavonoids found in both vegetables and plants like quercetin is present in many plant foods [3]. Quercitin, kaempferol, and myricetin are the most common flavonols in edible food. Onion, apple, green tea, and caper are dietary sources of flavonols [4]. They are biologically active and show many bioactive properties

such as anticancer [5], antimicrobial [6], anti-inflammatory [7], and many other activities. Thioflavonols are Thio analogs of flavonols (3-hydroxy-2-(phenyl)-4*H*-chrome-4-thione) in which an S atom is substituted for an O atom at the 4th position in the C ring. it can be prepared by treating flavonols with lawsons reagent [8]. Although S-containing isoflavones have shown considerable Pharmacol activities [9], no such work is reported for 4-thioflavonols. In a paper, thioaurones were rearranged into Thioflavonols in which the O atom at position 1 replaces the S atom, but no Pharmacol applications were given [10]. This research work is superior in the sense that it gives one pot synthesis method for conversion of substituted flavonols into 4-thioflavonols. It also gives further move in checking for biological activities and structure activity relationship of synthesized products. Therefore, we checked the effect of the S atom at position 4 by substituting with O as S containing heterocyclic benzopyran compounds show promising biological activities and a suitable scaffold in medicinal chemistry [11]. This paper describes the synthesis of various 4-thioflavonols and their treatment against certain bacterial and fungal strains treating bacterial and fungal infections.

2. Material and Methods

Chemicals used in the present study were purchased from Merck and Sigma-Aldrich (Germany). All the solvents were used after distillation. Melting points were determined in open capillaries using the Gallenkamp melting point apparatus and are uncorrected. FTIR spectra were recorded on Bio-Rad Merlin Spectrophotometer using KBr discs. 1H NMR spectra were recorded on Bruker (500 MHz) AM-250 in DMSO-d6 solution using TMS as the internal standard. CNMR spectra were recorded on Bruker (125 MHz) AM-75 in DMSO-d6 resolution.

The procedure for synthesizing a representative compound from every series (4 - 5) is given below. In contrast, the synthesis of the remainder of the members of every series is supported by a similar process with variation in substitution patterns in reactants for various targets.

2.1. Synthesis of 4 Series (E20 - E29)

All of the compounds in the **four** series were synthesized according to quality procedure [12] as in scheme 1. 1 mmol of O-hydroxy acetophenone, 10 mL of 95% alcohol, and 10 mL of 30% base (KOH) were added 0.1 mmol of respective aldehyde. The reaction mixture was allowed to stir for 3 hours or more, giving reddish liquid chalcone formation 0.2 mL of H_2O_2 was added and kept stirring until reaction completion. Then neutralized the solution with 18% HCl solution and extracted flavonol by filtration. The product was dried and recrystallized with ethanol.

Physical and spectral data of all compounds (E20 - E29) is available in the cited literature.

2.2. General Procedure for Synthesis of 5 Series (1 - 10)

1:2 mixture of substituted flavonol (1.5 mmol) and Lawesson's reagent (3 mmol) was added to 30 mL anhydrous toluene refluxed and stirred under strictly dry conditions 24 hours. A red-colored solution was obtained. The solvent was evaporated on a rotatory evaporator under reduced pressure, and the residue was collected and recrystallized with the help of ethanol in a wonderfully smart yield.

2.3. Biological Activity

The disc diffusion method investigated the antibacterial activity of the synthesized substituted thioflavonols. Five strains of bacteria were used. Bacterial strains were used, including *Staphylococcus aureus* (ATCC#6538), *Escherichia coli* (ATCC25922), and *Pseudomonas aeruginosa* (ATCC 9721), and two methicillin-resistant *Staphylococcus aureus*, MRSA9, and MRSA11, which were isolated clinically.

Dimethyl sulphoxide and Cefixime (4 mg/mL in DMSO) were used as controls for gram-negative and gram-positive bacteria. 4 mg/mL in DMSO dissolved samples were prepared. Test bacterial strains were used at 0.5% McFarland's solution equivalent turbidity to create a lawn on the nutrient agar plates. Wells of 8 mm diameter were prepared at a certain distance. Samples were poured on respective wells as 80 µL/well. The respective wells were also accompanied by antibacterial drugs (reference) and DMSO. They were acting respectively as positive and negative controls. Plates were incubated for 24 h at 37˚C. Results for antibacterial were measured as diameter of the zone of inhibition in mm.

The antifungal activity of synthetic compounds was tested by the well diffusion method. Three fungal strains *viz*. *Candida albicans* (ATCC#9002) and *Candida parapsilosis* (ATCC#22019) and *Candida Krusei.* The standard drug was Clotrimazole (1 mg/mL in DMSO). 4 mg of the sample was dissolved in 1 mL of DMSO in sample preparation. Each fungal strain was an aliquot of spore suspension at 1×10^8 spores/mL. It was spread evenly on prepared plates of Sabouraod dextrose agar (SDA) with a sterile glass rod. Wells of 8 mm were prepared with the help of the sterile cork bore at a specific distance. The Samples (8 µL/well) and the reference standard were then poured into respective wells. Plates were then incubated at 28˚C for 24 - 48 hours. Antifungal activity was expressed as of zone of inhibition, and results for antibacterial were measured as diameter of zone of inhibition in mm.

3. Result and Discussion

3.1. Chemistry

As described earlier, flavonols were thought to change into 4-thioflavonols by replacing O at the 4th position. Its purpose was to check the effect of modification on the biological activities of flavonols.

Flavonols (4 series) were synthesized by Claisen Schmidt aldol condensation, as shown in **Figure 1**. Flavonols were prepared by substituting o-hydroxy

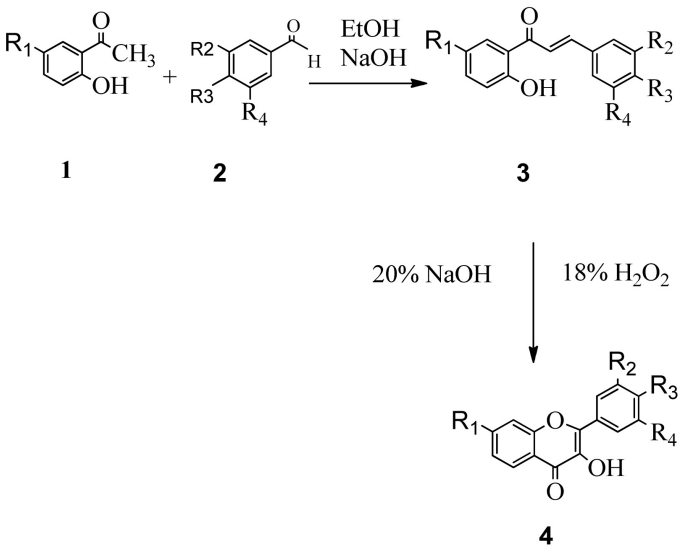


Figure 1. Scheme of synthesis of A, B-ring substituted flavonol.

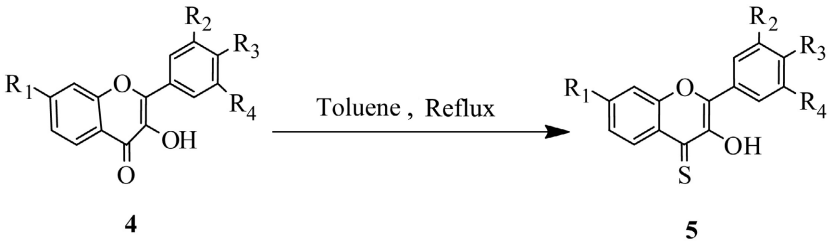
acetophenone (**1**) and benzaldehyde (**2**). A one-pot synthesis method of flavonols was adopted in which synthesized chalcone (**3**) was converted into flavonols (**4**) by cyclization. O-hydroxy acetophenone (**1**) was taken in a conical flask with 20 mL of ethanol. 10 mL of 30% solution of KOH was added. Substituted benzaldehyde (**2**) was added dropwise. Flask was covered with aluminum foil, and the solution was set on stirring for 24 hours. Reaction speed was monitored with the help of TLC. When the reaction was completed for chalcone synthesis, about 3 mL of 18% H_2O_2 was added drop wise into this reaction mixture for cyclization of chalcone (**3**) into respective flavonols (**4**). This mixture was set on stirring overnight, and TLC assessed reaction speed. After reaction completion, the reaction mixture was neutralized with 10% HCl, and precipitates formed were filtered. Then washed and dried off afterward. Synthesized product was purified by performing.Recrystallization was done with the help of ethanol. Flavonol (4 series) from E20 - E29 was obtained in a good yield of ~80%. The substitution pattern in all the synthesized compounds (4 series) is given in **Table 1**.

Thioflavonols, series 5 (1 - 10), were synthesized from previously synthesized flavonols 4 series (E20 - E29) by refluxing them with strictly anhydrous toluene with lawesson's reagent [13] **Figure 2**. The substitution pattern for all the synthesized 4-thioflavonols is given in **Table 2**.

Physical and spectral data of all compounds in series 5 (1 - 10) are given as follows.

3.1.1. 3-Hydroxy-2-(Thiophene)-4*H*-Chromen-4-Thione (1)

Red Crystalline; Yield: 91%; mp 191˚C; UV λ_{max} = 372 nm FT-IR (cm^{-1}): 1552.59 (c=c str), 1591.16 (c=s str), 1700 - 1800 (aromatic ring overtones), 3064.68 (sp^2 C-H bond str), 3400 (OH str) ^{1}HNMR (500 MHz, DMSO-d_6): δppm 9.02 (s, 1H), 8.43 (m, J = 4, 1H, Ar-H), 7.90 (m, J = 4.5, 1H, Ar-H), 7.59 (dd, J = 9, 1H, Ar-H), 7.35 (d, J = 3, 1H) 7.08 (d, J = 4, 2H) ^{13}CNMR (125 MHz, DMSO-d_6): δppm



4 5

Figure 2. Scheme f synthesis of A, B-ring substituted 4-thioflavones.

Table 1. Substituent values for flavonols 4 series (E20 - E29).

Compound	R_1	R_2	R_3	R_4
E20	H	H	H	H
E21	H	OCH_3	OCH_3	OCH_3
E22	H	H	$N(CH_3)_2$	H
E23	H	H	Cl	H
E24	H	H	OCH_3	OCH_3
E25	H	H	OCH_3	H
E26	H	H	F	H
E27	Br	H	$CH_2CH(CH_3)_2$	H
E28	Br	H	OCH_3	H
E29	H	H	$CH_2CH(CH_3)_2$	H

Table 2. Substituent values for 4-thioflavonols 5 series (1 - 10).

Compound	R_1	R_2	R_3	R_4
1	H	H	H	H
2	H	OCH_3	OCH_3	OCH_3
3	H	H	$N(CH_3)_2$	H
4	H	H	Cl	H
5	H	OCH_3	OCH_3	H
6	H	H	OCH_3	H
7	H	H	F	H
8	Br	H	$CH_2CH(CH_3)_2$	H
9	Br	H	OCH_3	H
10	H	H	$CH_2CH(CH_3)_2$	H

186.36 (C-4, C=S), 173.09 (C-3, C-OH), 162.80, (C-2), 146.40 (C-9, Ar-C), 143.03 (C-5, Ar-CH), 138.62 (C-2', C-S), 133.95 (C-1', Ar-C), 125.23 (C-3', C-S = Ar-CH), 124.49 (C-4'), 123.81 (C-5'), 115 (C-6, C-7 Ar-CH).

3.1.2. 2-(2,3,4-Trimethoxyphenyl)-3-Hydroxy-4*H*-Chromen-4-Thione (2)

Orange crystalline; Yield: 77%; mp 183˚C; UV λ_{max} = 448 nm FT-IR (cm^{-1}): 1506.30 (C=C str), 1577.66 (C=S str), 1733.89 (aromatic ring overtone), 3400.27 (OH str) ^{1}HNMR (500 MHz, DMSO-d_6): δ ppm 8.95 (s, 1H), 8.45 (m, J = 4.5, 3H, Ar-H), 7.85 (m, J = 4.5, 2H, Ar-H), 7.60 (ddd, J = 9, 1H, Ar-H), 3.95 (s, 9H, -OCH_3) ^{13}CNMR (125 MHz, DMSO-d_6): δppm 188.01 (C-4, C=S), 172.10 (C-3, C-OH), 149.12, 169.67 (C-2), 157.22 (C-3', 4', 5' = Ar-C-OCH_3), 147.71 (C-9, Ar-C), 138.39 (C-10, Ar-C), 130.34 (C-2', C-6' = Ar-CH), 128.30 (C-8 = Ar-CH), 126.68 (C-1', Ar-C), 118.59 (C-5, C-7 = Ar-CH), 112.40 (C-6, Ar-CH), 57.04 (C-OCH_3).

3.1.3. 2-(4-Dimethylaminophenyl)-3-Hydroxy-4*H*-Chromen-4-Thione (3)

Purple shining crystals; Yield: 68%; mp 187˚C; UV λ_{max} = 322 nmFT-IR (cm^{-1}): 1514.02 (C=C str), 1581 (C=S str), 1700 (aromatic ring overtone), 2896 (sp3 C-H bond str), 3421 (O-H str) ^{1}HNMR (500 MHz, DMSO-d_6): δ ppm 9.05 (s, 1H) 8.97 (d, J = 3.0 Hz, 1H, Ar-H), 8.25 (d, J = 6 Hz, 2H, Ar-H), 8.07 (dd, J = 6, 2H, Ar-H), 7.96 (d, J = 6.0 Hz, 1H, Ar-H), 2.85 (d, J = 3, 6H, N $(CH_3)_2$) ^{13}CNMR (125 MHz, DMSO-d_6): δppm 189.01 (C-4, C=S), 172.67 (C-3, C-OH), 164.34, 152.41 (C-2), 163.21 (C-4', Ar-C-N $(CH_3)_2$), 158.84 (C-9, Ar-C), 156.67 (C-10, Ar-C), 149.84 (C-3', C-5' = Ar-CH), 143.30 (C-2', 6' = Ar-CH), 136.68 (C-1', Ar-C), 129.02 (C-8, Ar-CH), 121.33 (C-5, C-7' = Ar-CH), 11.03 (C-6, Ar-CH), 30.04 (C=N$(CH_3)_2$).

3.1.4. 3-Hydroxy-2-(4-Chlorophenyl)-4*H*-Chromen-4-Thione (4)

Light orange crystals; Yield: 82%; mp 181˚C; UV λ_{max} = 360 nm IR (cm^{-1}): 1550 (C=C str), 1590 (C=S str), 1652 - 1733 (aromatic ring overtones), 3380 (O-H str) ^{1}HNMR (500 MHz, DMSO-d_6): δ 9.02 (s, 1H), 8.43 (m, J = 3.6, 1H, Ar-H), 7.90 (m, J = 6, 1H, Ar-H) 7.59 (ddd, J = 3, 2H, Ar-H), 7.48 (m, J = 3, Ar-H) ^{13}CNMR (125 MHz, DMSO-d_6: δppm 188.24 (C-4, C=S), 164.83 (C-3, C-OH), 162.84 (C-4', C-Cl), 150.29 (C-2), 146.40 (C-9, Ar-C), 141.19 (C-3', C-5', Ar-CH), 134.33 (C-10, Ar-C), 131.88 (C-1' = Ar-CH), 128.10 (C-2', C-6' = Ar-CH), 127.49 (C-8, Ar-CH), 119.49 (C-5, Ar-CH), 116.63 (C-6, C-7 = Ar-CH).

3.1.5. 2-(3,4-Dimethoxyphenyl)-3-Hydroxy-4*H*-Chromen-4-Thione

Orange crystals; Yield: 82%; mp 181˚C; UV λ_{max} = 452 nm FT-IR (cm^{-1}): 1517.87 (C=C), 1593.09 (C=S), 1600 - 1800 (aromatic ring overtone), 2900 (sp_3 H bond str), 2833 (OCH_3 str) 3483 - 3421 (O-H str) ^{1}HNMR (500 MHz, DMSO-d_6): δppm 9.5 (s, 1H) 8.95 (d, J = 3.6 Hz, 3H, Ar-H), 7.92 (m, J = 6 Hz, 2H, Ar-H), 7.85 (ddd, J = 8.5, 1H, Ar-H), 7.43 (m, J = 6.0 Hz, 1H, Ar-H), 3.95 (s, 6H, -OCH_3) C^{13}CNMR (125 MHz, DMSO-d_6): δ ppm 187.07 (C-4, C=S), 169.10 (C-3, C-OH), 168.67 (C-2), 154.22 (C-3', 4', =Ar-C-OCH_3), 150.61 (C-9, Ar-C), 146.29 (C-10, Ar-C), 132.56 (C-8, Ar-CH), 129.30 (C-2', C-5', Ar-CH), 126.76 (C-1', Ar-C), 121.37 (C-6', Ar-CH), 118.30 (C-5, Ar-CH), 110.12 (C-6, C-7, Ar-CH), 58.02 (C-OCH_3).

3.1.6. 2-(4-Methoxyphenyl)-3-Hydroxy-4*H*-Chromen-4-Thione (6)

Orange crystalline; Yield: 83%; mp 210˚C; UV λ_{max} = 352 nm IR (cm^{-1}): 1527 (C=C), 1563.09 (C=S), 1650 - 1850 (aromatic ring overtone), 2920 (sp_3 C-H bond str), 2833 (OCH_3 str) 3553 - 3431 (O-H str) ^{1}HNMR (500 MHz, DMSO-d_6): δppm 9.02 (s, 1H), 8.43 (m, J = 4, 3H, Ar-H), 7.90 (m, J = 4.5, 2H, Ar-H), 7.59 (ddd, J = 9, 1H, Ar-H), 7.48 (m, J = 3, 2H, Ar-H) 3.88 (s, 3H, -OCH_3)^{13}CNMR (125 MHz, DMSO-d_6): δppm 186.36 (C-4, C=S), 173.09 (C-3, C-OH), 162.80 (C-2), 154.76 (C-4', C-OCH_3), 146.40 (C-9, Ar-C), 143.03 (C-10, Ar-C), 133.95 (C-1', Ar-C), 131.23 (C-3', C-5' = Ar-CH), 129.49 (C-2', C-6', Ar-CH), 121.81 (C-8 Ar-CH), 118.78 (C-5 = Ar-CH), 115 (C-6, C-7, Ar-CH), 56.04 (C-OCH_3).

3.1.7. 2-(4-Florophenyl)-3-Hydroxy-4*H*-Chromen-4-One (7)

Red crystalline; Yield: 75%; mp 121˚C; UV λ_{max} = 428 nm IR (cm^{-1}): 1580 (C=C str), 1590 (C=S str), 1652 - 1822 (aromatic ring overtones), 3340 (O-H str) ^{1}HNMR (500 MHz, DMSO-d_6): δ ppm 9.02 (s, 1H), 8.43 (m, J = 3.6, 1H, Ar-H), 7.90 (m, J = 6, 1H, Ar-H) 7.59 (ddd, J = 3, 2H, Ar-H), 7.48 (m, J = 3, Ar-H) ^{13}CNMR (125 MHz, DMSO-d_6): δ ppm 188.14 (C-4, C=S), 164.83 (C-3, C-OH), 162.84 (C-4', C-F), 150.29 (C-2), 146.40 (C-9, Ar-C), 141.19 (C-3', C-5', Ar-CH), 134.33 (C-10, Ar-C), 131.81 (C-1', Ar-CH), 128.10 (C-2', C-6' = Ar-CH), 127.49 (C-8, Ar-CH), 119.49 (C-5 Ar-CH), 116.63 (C-6, C-7 = Ar-CH).

3.1.8. 2-(4-Isobutylphenyl)-3-Hydroxy-7-Bromo-4*H*-Chromen-4-Thione (8)

Shining red crystals; Yield: 76 %; mp 194˚C; UV λ_{max} = 374 nm IR (cm^{-1}): (KBr pellets): 1567.09 (C=C), 1685.21 (C=S), 3452.80 (OH) ^{1}HNMR (500 MHz, DMSO-d_6): δppm 9.03 (s, 1H) 8.50 (d, J = 3.0 Hz, 1H, Ar-H), 8.27 (d, J = 6 Hz, 2H, Ar-H), 8.01 (dd, J = 6, 1H, Ar-H), 7.90 (d, J = 6.0 Hz, 1H, Ar-H), 7.41 (d, J = 6 Hz, 2H, Ar-H), 2.55 (d, J = 3 Hz, 2H, $\underline{CH_2}CH(CH_3)_2$), 1.92 (m, J = 8 Hz, 1H, $CH_2\underline{CH}(CH_3)_2$), 0.90 (d, J = 9.0 Hz, 6H, $CH_2CH\underline{(CH_3)_2}$) ppm ^{13}CNMR (125 MHz, DMSO-d_6): δppm 185.95 (C-4, C=S), 149.22 (C-3, C-OH), 147.06 (C-2), 145.78 (C-7, -C-Br), 142.84 (C-8, Ar-CH), 136.39 (C-6 Ar-CH), 129.96 (C-9, Ar-C), 129.84 (C-10, Ar-C), 128.15 (C-1', Ar-CH), 122.11 (C-2', C-6' = Ar-CH), 119.44 (C-3', C-5', Ar-CH), 44.96 (C=$\underline{CH_2}CH(CH_3)_2$), 30.01 (C=$CH_2\underline{CH}(CH_3)_2$), 22.61 (C=$CH_2CH\underline{(CH_3)_2}$).

3.1.9. 2-(4-Methoxyphenyl)-3-Hydroxy-7-Bromo-4*H*-Chromen-4-Thione (9)

Red shining crystals; Yield: 81%; mp 88˚C; UV λ_{max} = 438 nm; IR (cm^{-1}): (KBr pellets): 1577.07 (C=C), 1685.21 (C=S), 3443.86 (OH) ^{1}HNMR (500 MHz, DMSO-d_6): δppm 9.0 (m, 1H), 8.39 9 (m, J = 6, 6H, Ar-H), 7.93 (dd, J = 6, 2H, Ar-H), 7.18 (s, J = 3, 2H, Ar-H), 3.88 (s, 3H, -OCH_3) ^{13}CNMR (125 MHz, DMSO-d_6): δppm 184.77 (C-4, C=S), 162.30 (C-3, C-OH), 149.12, 149.67 (C-7, C-Br), 143.12 (C-4', Ar-C-OCH_3), 136.17 (C-1', Ar-C), 131.39 (C-7, Ar-CH), 129.84 (C-5, Ar-CH), 129.30 (C-9 = Ar-C), 122.68 (C-10, Ar-C), 122.02 (3'-C, 5'-C = Ar-CH), 119.33 (2'-C, 6'-C = Ar-CH), 115.03 (C-5, Ar-CH), 56.04 (C-OCH_3).

3.1.10. 3-Hydroxy-2-(4-Isobutylphenyl)-4*H*-Chromen-4-Thione (10)

Light orange crystals; Yield: 70%; mp 147˚C; UV λ_{max} = 380 nm IR (cm^{-1}): (KBr pellets): 1677.74 (C=S), 1527.52 (C=C), 3456.56 (OH); ^{1}HNMR (500 MHz, DMSO-d_6): δppm 8.95 (s, 1H) 8.44 (m, J = 6 Hz, 1H, Ar-H), 8.28 (m, J = 3 Hz, 2H, Ar-H), 7.89 (m, J = 9, 2H, Ar-H), 7.59 (ddd, J = 3.0 Hz, 1H, Ar-H), 7.41 (m, J = 3 Hz, 2H, Ar-H), 2.55 (d, J = 6 Hz, 2H, $\underline{CH_2}CH(CH_3)_2$), 1.91 (m, J = 8 Hz, 1H, $CH_2\underline{CH}(CH_3)_2$), 0.89 (d, J = 9.0 Hz, 6H, $CH_2CH(\underline{CH_3)_2}$) ppm ^{13}CNMR (125 MHz, DMSO-d_6): δppm 187.47 (C-4, C=S), 150.29 (C-3, C-OH), 146.42 (C-2), 145.54 (C-9, Ar-C), 142.35 (C-10, Ar-C), 142.35 (C-10, Ar-C), 134.17 (C-1', Ar-C), 129.95 (C-8, Ar-CH), 129.05 (C-5, Ar-CH), 128.18 (C-2', C-6' = Ar-CH), 126.75 (C-6, C-7, Ar-CH), 119.42 (C-3', C-5' = ArCH), 40.15 (C=$\underline{CH_2}CH(CH_3)_2$), 30.03 (C=$CH_2\underline{CH}(CH_3)_2$), 22.61 (C= $CH_2CH(\underline{CH_3)_2}$).

3.2. Antibacterial Essay of Compounds

The synthesized compound has shown encouraging results for in vitro bioactivities against various classes of bacteria and fungus as mentioned above. Results show that synthesized compounds showed significant antibacterial activity (**Table 3**). Compound 9 shows 20 mm ZOI against E-COLI gram-positive bacteria than standard drug cefixime. Compound 8 also shows significant activity against MRSA11 gram-positive bacteria of 18 mm ZOI than standard drug cefixime. Compound 10 shows much improved antibacterial activity at 20 mm ZOI than standard as 15 mm against MRSA 11. Compound 9 also shows against MRSA 10 of 15 mm of ZOI. All the compounds (1 - 10) showed ZOI for MRSA II strain especially.

3.3. Antifunga Essay of Compounds

Compounds (**1 - 10**) also show significant antifungal activity against yeast (*C. albicans* and *C. parapsoriasis*, and *C. krusei*) (**Table 4**). Antifungal studies found compounds 3, 4, and 5 inactive against all fungal strains. Compound 1 was found inactive against *C. parapsilosis* and *C. krusei.* Compounds 8 and 10 were found inactive against *C. parapsilosis*. Compound 9 was found inactive against *C. parapsilosis* and *C. krusei.* All other compounds were moderate to potent inhibitors against all three strains. These compounds showed 9 - 10 mm.

3.4. Structure Activity Relationship

From **Table 3** it is noted that structural modification in flavonols and synthesis of respective synthesized 4-thioflavonols led to enhanced antibacterial activities than its parent flavonol compounds. Compound 1 shows the improved antibacterial activity of ZOI 12 ± 1.5 mm than its parent flavonol E20 of 11 ± 2 mm. Compounds 3 and 4 show ZOI 13 ± 1 mm and 14 ± 1.5 mm respectively for staphylococcus aureus bacterium than respective flavonols inactive against SA bacterium. Thus a modification in structure led to enhanced biological activity. Similarly, compound 3 shows ZOI of 13 ± 1 mm more than Parent flavonol E22, which shows ZOI at 11 ± 1.5 mm against MRSA II bacterium. Thus, it is proved

Table 3. Antibacterial activities of series of compounds, relative to the standard drug Cefixime.

CODES		STRAINS				
		SA	PS	E-COLI	MRSA 11	MRSA 10
1	1	13 ± 1 mm	12 ± 1.5 mm	8 ± 0.5 mm	11 ± 2 mm	-
2	2	12 ± 1.5 mm	-	9 ± 1 mm	-	-
3	3	13 ± 1 mm	-	-	-	13 ± 1 mm
4	4	14 ± 1.5 mm	9 ± 1 mm	-	11 ± 2 mm	-
5	5	-	-	-	-	-
6	6	-	-	-	-	-
7	7	-	11 ± 1.5 mm	-	14 ± 4 mm	-
8	8	-	8 ± 1 mm	14 ± 1.5 mm	18 ± 2 mm	-
9	9	-	-	20.6 ± 0.8 mm	-	15.1 ± 0.6 mm
10	10	-	11 ± 2 mm	-	20 ± 3 mm	-
11	E20	15 ± 1.5 mm	11 ± 2 mm	14 ± 2 mm	11 ± 2 mm	12 ± 1 mm
12	E21	20 ± 1 mm	9 ± 1 mm	10 ± 1 mm	14 ± 3 mm	13 ± 2 mm
13	E22	12 ± 1.5 mm	-	-	12 ± 4 mm	11 ± 1.5 mm
14	E24	-	12 ± 1 mm	-	11 ± 2 mm	12 ± 1 mm
15	Negative	-	-	-	-	-
16	Positive	15 ± 1 mm	14 ± 2 mm	15 ± 2 mm	15 ± 2 mm	16 ± 1 mm

Table 4. Antifungal activities of series of compounds, relative to the standard drug Imipenem.

S/No	CODES	STRAINS		
		CA	CP	CK
1	1	9 ± 1 mm	-	-
2	2	-	10.2 ± 2 mm	-
3	3	-	-	-
4	4	-	-	-
5	5	-	-	9.4 ± 1 mm
6	6	9.2 ± 2.1 mm	9.4 ± 2.1 mm	9.7 ± 1 mm
7	7	9.1 ± 1 mm	9.8 ± 1 mm	9 ± 2.1 mm
8	8	10.2 ± 2 mm	-	9 ± 2.1 mm
9	9	9.5 ± 1 mm	-	-
10	10	9.8 ± 1 mm	-	10.6 ± 2 mm
11	E20	-	-	-

Continued

12	E21	-	10.5 ± 2 mm	-
13	E22	-	-	-
14	E24	-	-	-
	Negative (DMSO)	-	-	-
	Positive clotrimazole	14 mm	13 mm	15 mm

that a bit of transformation in flavonol structure by modifying C=O at C-4 with C=S led to enhanced antibacterial activity.

It is clear from Table 4 that synthesized modified 4-thioflavonols show enhanced antifungal activities than their respective flavonols. Compound E20 flavonol is inactive against *Candida albicans*, but when converted to compound 1, it shows 9 ± 1 mm ZOI against CA. Compound 5 shows the antifungal activity of 9.4 ± 1 mm ZOI than parent flavonol E24, which is inactive against Candida krusei. So, it is evident that a modification in structure from flavonols to 4-thioflavonols led to enhanced antifungal activity.

4. Conclusions

Flavonols and Thioflavonols were synthesized by substituting them with halogen, methoxy, n, n-dimethyl, trimethoxy, and tert-butyl substitution at the respective compounds' A, B, and AB rings. Synthesized Thioflavonols were checked for their antibacterial and antifungal activity. It is deduced from obtained results that various substitutions of the rings are responsible for the decrease or enhancement of specific bioactivity. Electronegativity at ring A and methoxy substitution at the B ring in the compound showed a marked enhancement in percentage inhibition for antibacterial activity. Electronegativity at ring A and methoxy substitution at ring B in a compound showed enhanced activity against bacterial strains. A tert-butyl substitution at the B ring in a compound also showed enhanced antibacterial activity.

Thiophene and dimethoxy substitutions at ring B showed antifungal activity in remarkable inhibition zones while its parent compounds were inactive against specific fungal strains.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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