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Original Article

Synthesis, Characterization and Biological Evaluation of Novel 2,4-Dioxothiazolidine Derivatives as Potential Antimicrobial Agents

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2,4-Dioxothiazolidine,
Cinnamic acid,
Antibacterial,
Antifungal

Abstract

Objective: To develop a series of 2,4-dioxothiazolidine derivatives of aryl substituted cinnamic acid, characterization by elemental and spectral (IR, ^{1}H-NMR) studies and antimicrobial study.
Method: All compounds were synthesized from pure & standard substrates. Reactions were monitored by TLC & Melting points were determined by decibel melting point apparatus. The IR spectra were recorded on Perkin Elmer IR spectrophotometer using KBr pellets. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Brucker Avance II 400 NMR spectrophotometer. Antimicrobial activity was performed by measuring zone of inhibition.
Results: All the synthesized compounds were purified and give very good spectra of IR & NMR. Compunds were studied for their antimicrobial activity in comparison to the standard drugs. Thz 9 was found the most active compound in this series, where Ciprofloxacin was used as a standard drug for antibacterial activity and Clotrimazole for antifungal activity.
Conclusion: Compound Thz9 exhibited highest antimicrobial activity due to substitution of aryl ring by electron releasing methoxy groups at -ortho and -para position. Compound Thz9 was found more active than all other dimethoxy substituted compounds, the reason behind it may be that dimethoxy substitutions at *-ortho* and *-para* position on aryl ring enhanced the binding of molecule with the target. Almost in all compounds propyl ester has higher activity than methyl, ethyl esters, which means that heavy carbon chain ester increase the antimicrobial activity.

1. Introduction

Development of novel chemotherapeutic agents is an important and challenging task for the medicinal chemists and many research programs are directed towards the design and synthesis of new drugs for their chemotherapeutic usage. There is an urgent need for identification of novel lead structure for the designing of new, potent, and less toxic agents which ideally shorten the duration of therapy and are effective against resistant strain [1]. Thiazolidinedione compounds constitute an important class for new drug development in order to discover an effective compound against multidrug resistant microbial infection. Thiazolidinediones have been demonstrated to possess antidiabetic [2-4], neuroprotective[5], antibacterial [6-7], antitumour [8], antihyperlipidemic[9], anti-inflammatory, antioxidant[10], antithyroid [11], antiviral[12], anticancer [13-15] activities. These reports prompted us to synthesize the novel derivatives of 2,4-Dioxothiazolidine which would be effective against various strains of microorganisms[16-17]. Thiazolidinedione derivatives are also employed to treat CHF [18] & some other heart related problems [19-20]. The structures of all compounds have been evaluated by spectral analysis (IR and ^{1}H NMR). All the compounds have been screened for antimicrobial activity against two Gram positive bacteria *S. aureus, B. subtilis* and two Gram negative bacteria *E. coli, P. aeruginosa* and also against two fungal strains *C. albicans* and *A. niger*. Some of the synthesized compounds showed good antimicrobial activity against these strains even better than Ciprofloxacin and Clotrimazole (Table 2).

2. Materials and Methods

All reactions were monitored by thin layer chromatography (TLC) using silica gel G (Spectrochem Pvt. Ltd., Mumbai). The plates were developed by exposing to iodine chamber. Melting points (m.p.) were determined by decibel melting point apparatus and were uncorrected. Physicochemical data of all synthesized compounds is given in Table 1. Structures of the newly synthesized 2,4-thiazolidinedione derivatives have been ascertained on the basis of their consistent IR and ^{1}H NMR spectral assignments. The IR spectra were recorded on Perkin Elmer IR spectro- photometer using KBr pellets. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Brucker Avance II 400 NMR spectrophotometer using DMSO as solvent and TMS as internal standard and reported as chemical shift in δ values (ppm).

2.1. Chemistry

A general strategy for the synthesis of thiazolidine-2,4-diones is shown in Scheme 1. Perkin condensation of aryl aldehyde 1 with 4-hydroxyphenyl acetic acid 2 in the presence of acetic anhydride and triethylamine yielded the 3-Aryl-2-(4-hydroxyphenyl)-acrylic acid 3. Esterification of this substituted acid followed by condensation with 4-fluorobenzaldehyde in the presence of sodium hydride in dimethyl formamide yielded 3-Aryl-2-[4-(4-formylphenoxy)-phenyl]-acrylic acid alkyl ester 5. Knovenagel condensation of this ester with 2,4-thiazolidinedione in the presence of piperidinium benzoate followed by hydrogenation gave a good yield of final compound 3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)-phenoxy]-phenyl} -acrylic acid alkyl ester 7. A major challenge was selective hydrogenation of one of the double bond. Hydrogenation with 10% palladium on carbon as catalyst yielded mixture of products. By using ammonium formate as hydrogen donor in the presence of palladium catalyst produced minimal amounts of other products, and isolation of desired compounds in high purity was possible by repeated crystallization from methanol.

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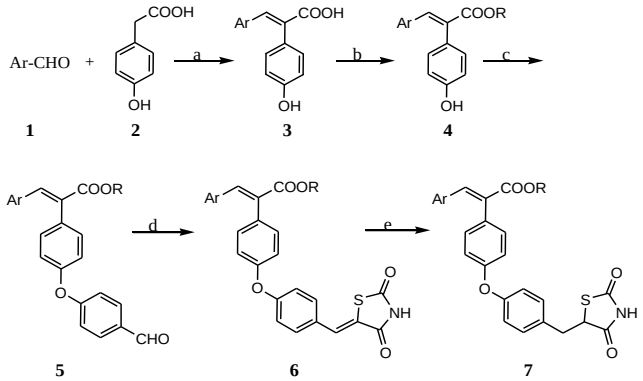


Scheme 1: Synthetic scheme for the synthesis of 3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl}-acrylic acid alkyl ester (Reagents and conditions: (a) acetic anhydride, Et_3N, 6 hrs, 130°C; (b) ROH, H_2SO4, 15 hrs, reflux; (c) 4-fluorobenzaldehyde, NaH, DMF, 18 hrs, 80°C; (d) 2,4-thiazolidinedione, piperidine, benzoic acid, toluene, 5 hrs, reflux; (e) Pd/C (10%), AcOH–$HCOONH_4$, 15 hrs, 125°C)

2.2. General procedure for the synthesis of 3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl) phenoxy]-phenyl}-acrylic acid alkyl ester (Thz1-15):

2.2.1. 3-Aryl-2-(4-hydroxyphenyl)–acrylic acid (3):

To a mixture of aryl aldehyde, (10 g, 0.06 mol) and 4-hydroxyphenylacetic acid (9.14 g, 0.06 mol) in a conical flask, acetic anhydride (20 mL, 0.212 mol) and triethylamine (8.4 mL, 0.06 mol) were added. The resulting mixture was heated at 130°C –140°C for 6 hrs with continuous stirring. Then it was cooled to room temperature. Concentrated HCl (20 mL) was added to the reaction mixture slowly over 30 min, while keeping the temperature of the mixture between 20-30°C. The resulting precipitate was, filtered and washed with water to give crude product (3) that was recrystallized from methanol-water (4:1) and dried at 40°C.

2.2.2. 3-Aryl-2-(4-hydroxyphenyl)–acrylic acid alkyl ester (4):

Alkylalcohol (60 mL) was added to the completely dried compound 3 (8.55 g, 0.028 mol) in RBF. Conc. sulfuric acid (2 mL) was added to the above suspension and the reaction mixture was refluxed for 15 hrs under nitrogen. Then filtered the resulting mixture and residue was taken in ethyl acetate (60 mL) in separating funnel and washed sequentially with water (2×20 mL), saturated aqueous $NaHCO_3$ (2×20 mL) and brine (2×20 mL). The organic layer was passed through anhydrous magnesium sulfate to remove any traces of water and filtered. Then the solvent was evaporated to dryness at water bath and compound 4 was obtained.

2.2.3. 3-Aryl-2-[4-(4-formylphenoxy)-phenyl]-acrylic acid alkyl ester (5):

Compound 4 (8.66 g, 0.027 mol) was taken in a conical flask and dissolved in dry DMF (32 mL) and sodium hydride (1.2 g, 0.03 mol) was added. To the resulting orange solution, 4-fluorobenzaldehyde (3.7 mL, 0.034 mol) was added. The resulting solution was heated at 80°C for 18 hrs with continuous stirring. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (60 mL) and washed first with water (3×20 mL) and then brine (1×20 mL). The organic layer was passed through anhydrous sodium sulfate, filtered and solvent was evaporated. The residue was suspended in methanol (60 mL) and then filtered to get compound 5 which were dried at 40°C.

2.2.4. 3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylidenmethyl)-phenoxy]-phenyl}-acrylic acid alkyl ester (6):

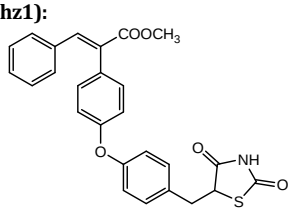
To a suspension of 5 (7.04 g, 0.016 mol) in anhydrous toluene (50 mL), 2,4-thiazolidinedione (1.97 g, 0.017 mol), benzoic acid (2.68 g, 0.022 mol) and piperidine (2.14 g, 0.025 mol) were added sequentially with continuous stirring. The resulting mixture was taken in a RBF and refluxed for 5 hrs. After refluxing the reaction mixture was cooled to room temperature and the resulting compound was filtered and washed with water. The residue so obtained was recrystallized in a mixture of methanol-diethyl ether (1 : 1, 60 mL). The compound 6 was obtained and dried in oven at 40°C.

2.2.5. 3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl}- acrylic acid alkyl ester (7):

To a solution of 6 (7.04 g, 0.013 mol) in glacial acetic acid (120 mL) in a conical flask, ammonium formate (47.06 gm, 0.74 mol) was added and stirred for 30 min. Slurry of Pd on carbon (10%, dry, 3.52 g) in glacial acetic acid (5.8 mL) was added to the flask and heated at 125°C for 15 hrs with continuous stirring. The resulting mixture was filtered and the filtrate was poured slowly into water (140 mL) with vigourous stirring and the solid that separated, was filtered and dried. The resulting solid was recrystallized in a mixture of methanol and ethanol (2:1) to yield compound 7.

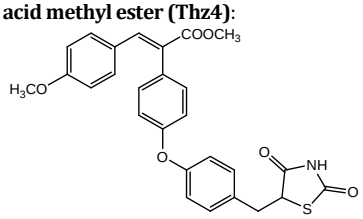
2.3. Spectral data of some compounds from each category:

3-Phenyl-2-{4-[4-(2,4-thiazolidin-5-methyl) phenoxy]-phenyl}-acrylic acid methyl ester (Thz1):



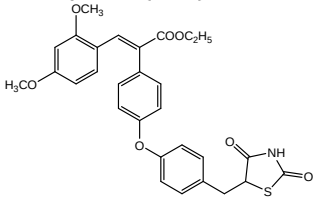
^{1}H-NMR, δ ppm (400 MHz, DMSO): 1.06-1.13 (s, 3H, $COOCH_3$), 7.06-7.31 (m, 8H, ArH-O-ArH), 7.35-7.58 (m, 5H, ArH), 7.04-7.12 (s, 1H, CH of Ar-CH=C<), 8.26 (s, 1H, NH), 3.64-3.72 (d, 2H, CH_2 of Ar-CH_2-Thz).
IR, cm^{-1} (KBr Pelletes): 1706.6 (C=O str., ketonic), 1734.1 (C=O str., $COOCH_3$), 3029.1 (C-H str., aromatic), 2835.3 (C-H str., aliphatic), 3214.0 (NH str.), 1268.4 (Ar-O-SAr str.), 1494.2 (C=C str., aromatic).

3-(4-Methoxyphenyl)-2-{4-[4-(2,4-thiazolidin-5-ylmethyl) phenoxy]-phenyl} - acrylic acid methyl ester (Thz4):



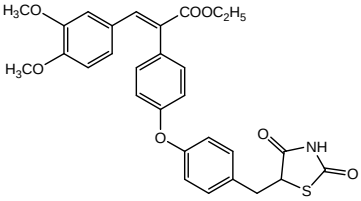
^{1}H-NMR, δ ppm (400 MHz, DMSO): 1.34-1.57 (s, 3H, $COOCH_3$), 3.75-4.0 (s, 3H, OCH_3), 7.2-7.9 (m, 12H, Ar-H), 7.00 (s, 1H, CH of Ar-CH=C <), 8.5 (s, 1H, NH), 3.59 (d, 2H, CH_2 of Ar-CH_2-Thz).
IR, cm^{-1} (KBr Pelletes): 1694.7 (C=O str., ketonic), 1734.1 (C=O str., $COOCH_3$), 3030.1 (C-H str., aromatic), 2835.3 (C-H str., aliphatic), 3214.0 (NH str.), 1286.7 (Ar-O-Ar str.), 1507.6 (C=C str., aromatic).

3-(2,4-Dimethoxyphenyl)-2-{4-[4-(2,4-thiazolidin-5-ylmethyl) phenoxy] - phenyl}- acrylic acid ethyl ester (Thz8):



^{1}H-NMR, δ ppm (400 MHz, DMSO): 1.14-1.18 (d, 5H, $COOC_2H_5$), 3.75-3.95 (s, 6H, OCH_3), 7.14-7.51 (m, 8H, ArH-O-ArH), 6.7-6.76 (m, 3H, ArH) 6.9-6.96 (s, 1H, CH of Ar-CH=C <), 8.21 (s, 1H, NH), 3.58 (d, 2H, CH_2 of Ar-CH_2-Thz).
IR, cm^{-1} (KBr Pelletes): 1673.0 (C=O str., ketonic), 1731.8 (C=O str., $COOC_2H_5$), 2941.0 (C-H str., aromatic), 2832.3 (C-H str., aliphatic), 3143.1 (NH str.), 1284.4 (Ar-O-Ar str.), 1461.8 (C=C str., aromatic).

3-(3,4-Dimethoxyphenyl)-2-{4-[4-(2,4-thiazolidin-5ylmethyl) phenoxy] -phenyl}-acrylic acid ethyl ester (Thz11):



^{1}H-NMR, δ ppm (400 MHz, DMSO): 1.14-1.18 (d, 5H, $COOC_2H_5$), 3.92-3.94 (s, 6H, OCH_3), 7.22-7.38 (m, 11H, ArH), 7.14 (s, 1H, CH of Ar-CH=C <), 8.22 (s,1H, NH), 3.72 (d, 2H, CH_2 of Ar-CH_2-Thz).
IR, cm^{-1} (KBr Pelletes): 1706.6 (C=O str., ketonic), 1734.1 (C=O str., $COOC_2H_5$), 3053.8 (C-H str., aromatic), 2835.3 (C-H str., aliphatic), 3214.0 (NH str.), 1265.3 (Ar-O-Ar str.), 1449.6 (C=C str., aromatic).

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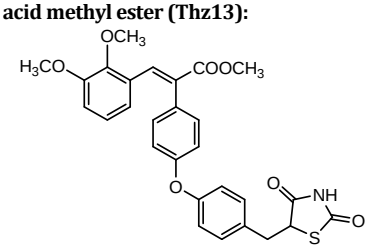
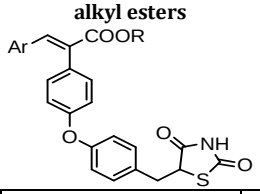
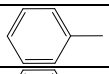
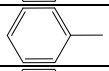
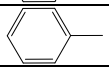
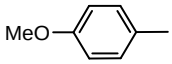
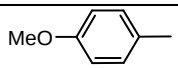
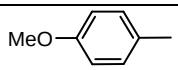
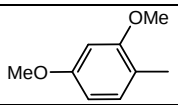
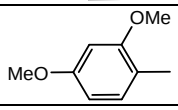
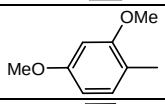
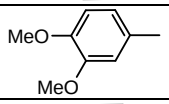
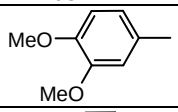
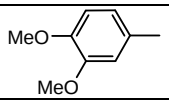
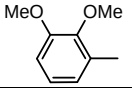
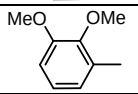
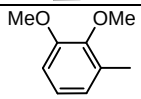
3-(2,3-Dimethoxyphenyl)-2-{4-[4-(2,4-thiazolidin-5ylmethyl)phenoxy]-phenyl}-acrylic acid methyl ester (Thz13):



^{1}H-NMR, δ ppm (400 MHz, DMSO): 1.14-1.18 (s, 3H, $COOCH_3$), 3.72-3.98 (s, 6H, OCH_3), 7.13-7.34 (m, 11H, ArH), 7.0-7.06 (s, 1H, CH of Ar-CH=C <), 8.22 (s, 1H, NH), 3.64 (d, 2H, CH_2 of Ar-CH_2-Thz).
IR, cm^{-1} (KBr Pelletes): 1701.6 (C=O str., ketonic), 1737.7 (C=O str., $COOCH_3$), 3028.8 (C-H str., aromatic), 2835.8 (C-H str., aliphatic), 3143.1 (NH str.), 1273.0 (Ar-O-Ar str.), 1454.0 (C=C str., aromatic).

Table 1: Physicochemical characteristics of synthesized 3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl}-acrylic acid alkyl esters



Comp.	-Ar	-R	Mol. Formula	Mol. Wt.	M.P. (°C)	R_f	% yield
Thz1		-CH_3	$C_{26}H_{21}NO_5S$	459.51	134-136	0.55	48.51
Thz2		-C_2H_5	$C_{27}H_{23}NO_5S$	473.54	141-143	0.62	34.10
Thz3		-C_3H_7	$C_{28}H_{25}NO_5S$	487.57	149-151	0.51*	52.09
Thz4		-CH_3	$C_{27}H_{23}NO_6S$	489.54	117-119	0.57	38.34
Thz5		-C_2H_5	$C_{28}H_{25}NO_6S$	503.57	127-129	0.49	42.80
Thz6		-C_3H_7	$C_{29}H_{27}NO_6S$	517.59	121-123	0.58	29.21
Thz7		-CH_3	$C_{28}H_{25}NO_7S$	519.57	112-114	0.64	47.40
Thz8		-C_2H_5	$C_{29}H_{27}NO_7S$	533.59	128-130	0.71	41.70
Thz9		-C_3H_7	$C_{30}H_{29}NO_7S$	547.62	123-125	0.59	33.28
Thz10		-CH_3	$C_{28}H_{25}NO_7S$	519.57	92-94	0.65	54.08
Thz11		-C_2H_5	$C_{29}H_{27}NO_7S$	533.59	97-99	0.56	46.90
Thz12		-C_3H_7	$C_{30}H_{29}NO_7S$	547.62	103-105	0.47*	53.45
Thz13		-CH_3	$C_{28}H_{25}NO_7S$	519.57	99-101	0.54	32.58
Thz14		-C_2H_5	$C_{29}H_{27}NO_7S$	533.59	111-113	0.42	27.17
Thz15		-C_3H_7	$C_{30}H_{29}NO_7S$	547.62	106-108	0.45	41.52

TLC mobile phase - Toluene: Chloroform (1:2), * Ethyl acetate: Benzene (1:2)

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2.4. Antimicrobial Activity

Nutrient agar media was used for bacterial growth [beef extract, 3g; bacteriological peptones, 5g; agar, 20g, the pH was adjusted to 6.2 ± 0.2 at 25 (±2) ˚C], while malt extract agar (MEA) for fungal isolates [malt extract, 20 g; bacteriological peptone, 5g; agar, 20g, the pH was adjusted to 5.4 ± 0.2 at 25 (±2) ˚C]. Each medium was prepared by dissolving the solid ingredient in 1 L of cold distilled water and then heated to 60-70 ˚C with stirring. Media were sterilized by autoclaving at 121 ˚C (1.5 atm) for 15-20 min.

By diffusion agar technique, the antibacterial and antifungal effects against several species are expressed as the measurement of diameter of their zone of inhibition. Four equidistant (1 cm diameter) holes were made using sterile cork borer in malt extract agar and nutrient agar sterile plates. Holes are filled with 100 µg/ml concentration of each of the synthesized compounds after completely dissolving in DMSO. Controlled holes were filled with DMSO solvent. Plates were left in a cooled incubator at 37 (±2) ˚C for bacterial isolates and incubation at 28 (±2) ˚C for fungal isolates used. Zone of inhibition developed due to active ingredients were measured after 24-48 h of incubation time. Ciprofloxacin is used as standard antibacterial agent while Clotrimazole was used as a standard antifungal agent.

3. Results

The antimicrobial sensitivity testing of the synthesized compounds were assayed using cup plate technique in the nutrient agar at 100 µg/ml concentration is shown in table 2. Ciprofloxacin standard were active at 50 µg/ml on all the Gram (+ve) bacteria with a zone of inhibition for *Bacillus subtilis* MTCC 96 (24 mm), *Staphylococcus aureus* MTCC 121 (29 mm) and Gram (-ve) bacteria *Pseudomonas aeruginosa* MTCC 2453 (21 mm) and *Escherichia coli* MTCC 40 (28 mm). From the antibacterial screening, it was concluded that compounds Thz9, Thz12, Thz15 showed larger zone of inhibition as compare to standard drug Ciprofloxacin against *Bacillus subtilis* (28, 26, 27 mm), *Staphylococcus aureus* (34, 32, 32 mm) and Gram (-ve) bacteria *Pseudomonas aeruginosa* (25, 22, 23 mm) and *Escherichia coli* (33, 32, 31 mm). While compound Thz4, Thz5, Thz6 showed nearly moderate zone of inhibition as compare to Ciprofloxacin *Bacillus subtilis* (22, 24, 24 mm), *Staphylococcus aureus* (22, 23, 25 mm) and Gram (-ve) bacteria *Pseudomonas aeruginosa* (19, 20, 19 mm) and *Escherichia coli* (25, 27, 27 mm). Clotrimazole standard were active at 50 µg/ml on most of the fungal strain with a zone of inhibition for *Candida albicans* MTCC 8184 (19 mm) and *A. niger* MTCC 8189 (18 mm). From the antifungal screening, it was concluded that compounds Thz9, Thz12, Thz15 shows larger zone of inhibition as compare to standard drug Clotrimazole against *Candida albicans* (24, 21, 24 mm) and *A. niger* (24, 21, 23 mm). While compound Thz4, Thz5, Thz6 showed nearly moderate zone of inhibition as compare to Clotrimazole *Candida albicans* (15, 15, 16 mm), *A. niger* (15, 16, 17 mm).

Table 2: Antimicrobial results of the synthesized and tested compounds

Compound	Concentration (µg/ml)	Zone of inhibition (in mm)					
		Gram positive		Gram negative		Fungal strain	
		B. subtilis (MTCC 96)	*S. aureus* (MTCC 121)	*P. aeruginosa* (MTCC 2453)	*E.coli* (MTCC 40)	*C. albicans* (MTCC 8184)	*A. niger* (MTCC 8189)
Thz1	100	17	21	15	22	12	11
Thz2	100	19	23	18	22	12	10
Thz3	100	21	24	18	24	14	14
Thz4	100	22	22	19	25	15	15
Thz5	100	24	23	20	27	15	16
Thz6	100	24	25	19	27	16	17
Thz7	100	23	26	20	28	20	18
Thz8	100	25	28	23	30	20	21
Thz9	100	28	34	25	33	24	24
Thz10	100	24	28	18	30	18	17
Thz11	100	25	29	20	30	19	19
Thz12	100	26	32	22	32	21	21
Thz13	100	22	24	19	29	21	16
Thz14	100	23	26	21	31	23	19
Thz15	100	27	32	23	31	24	23
Ciprofloxacin	50	24	29	21	28	-	-
Clotrimazole	50	-	-	-	-	19	18

4. Discussion

The synthesized compounds were successfully screened for their antimicrobial activity. The highest antibacterial activity against Gram positive species *Bacillus subtilis, Staphylococcus aeuras* and Gram negative species *Pseudomonas aeruginosa, Escherichia coli* was shown by compounds Thz9, Thz12, Thz15. The compounds Thz9, Thz12, Thz15 also exhibit highest antifungal activity against *Candida albicans* and *A. niger* species.

Compounds Thz1-3 has no substitution on aryl ring and has minimal antimicrobial activity among all synthesized compounds. Compounds Thz4-6 having mono methoxy substitution on aryl ring, were found more active than unsubstituted compounds, but were found less active than compounds having dimethoxy substitution Thz9, Thz12, Thz15 on aryl ring.

Compound Thz9 exhibited highest antimicrobial activity within all synthesized compounds, it may be due to substitution of aryl ring by electron releasing methoxy groups at -ortho and -para position. Chemically compound Thz9 is 3-(2,4-Dimethoxyphenyl)-2-{4-[4-(2,4-thiazolidin -5-ylmethyl) phenoxy]-phenyl}-acrylic acid propyl ester. Compound Thz9 was found more active than all other dimethoxy substituted compounds, the reason behind it may be that dimethoxy substitutions at *-ortho* and *-para* position on aryl ring enhanced the binding of molecule with the target. Almost in all compounds propyl ester has higher activity than methyl, ethyl esters, which means that heavy carbon chain ester increase the antimicrobial activity. This may be due to higher lipophilicity developed by heavy ester groups increase the binding/interaction of compounds with target site.

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