

SYNTHESIS OF SOME THIAZOLIDINE DERIVATIVES OF 1,4-BENZOQUINONE AS POTENTIAL ANTIMICROBIAL AGENTS

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تم في هذا البحث تشييد بعض من مركبات 1,4-بنزوكينون المحمل عليها في موضع 2 مشتقات الثيازوليدين ومحمل عليها في موضع 5 مجموعة الأنيلينو والأنيلينو المستبدلة. وقد تم اثبات التركيب البنائي لهذه المركبات بواسطة التحليل الدقي للعناصر المكونة ودراسة أطيافها في الأشعة تحت الحمراء والرنين النووي المغناطيسي. كما تمت دراسة تأثير هذه المركبات على بعض البكتيريا الموجبة الجرام والسالبة الجرام وكذلك على أحد أنواع الفطر.

*A series of 2,5-disubstituted-1,4-benzoquinone derivatives were synthesized and evaluated for their antimicrobial activity. Coupling of 2,5-dihydroxybenzoic acid (gentisic acid) with the selected thiazolidine derivative using EDC and HOBt afforded the corresponding (4R)-3-(2,5-dihydroxybenzoyl)-5,5-dimethyl-N-substituted benzylthiazolidine-4-carboxamide **2a-d**. These compounds were subsequently oxidized with ferric chloride to afford the corresponding 1,4-benzoquinones **3a-d**. The reaction between 1,4-benzoquinone derivatives and the appropriate amine resulted in the targeted 2,5-disubstituted-1,4-benzoquinone derivatives **4a-l**. The structure of the newly synthesized compound were confirmed by elemental microanalyses, IR and ¹H NMR spectra. The antimicrobial activity of target compounds **4a-l** was performed against *Escherichia coli* (*E. coli*) ATCC 25922 as Gram-negative bacteria, *Staphylococcus aureus* (*S. aureus*) ATCC 19433 as Gram-positive bacteria and *Candida albicans* (*C. albicans*) as yeast like fungi were determined.*

INTRODUCTION

The evergrowing clinical importance of developing drug-resistant bacterial pathogens has lent additional urgency to microbiological and antibacterial research.¹ In addition, in recent years, fungal infection became an important complication and a major cause of morbidity and mortality in immuno-compromised individuals such as those suffering from tuberculosis, cancer or AIDS and in organ transplant cases.^{2,3} Within a program aimed at developing new medicinal agents related to 1,4-benzoquinone derivatives, some pyrazolyl, oxadiazolyl or thiadiazolyl derivatives of 1,4-benzoquinone were synthesized in our laboratory and evaluated for their antimicrobial effects.⁴⁻⁷ Moreover, thiazolidine derivatives have been reported to exhibit antimicrobial activity.⁸ In addition and as a continuation of our continuous related program, 1,4-benzoquinone derivatives were synthesized having within their structure the

thiazolidine function attached to position 2 through a carbonyl linker and 4-substituted anilino moiety attached to position 5, in order to investigate the effect of the thiazolidine moiety on the antimicrobial activity of the 1,4-benzoquinone derivatives.

EXPERIMENTAL

Melting points were uncorrected and determined in open glass capillaries using a Thomas capillary melting point apparatus. IR spectra were recorded on 470-Shimadzu infrared spectrophotometer. ¹H-NMR spectra were obtained from a Varian XL-200 MHz Spectrometer, and the chemical shifts are given in δ (ppm) down field from tetramethylsilane (TMS) as an internal standard. Elemental analyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University, Cairo, Egypt.

Synthesis of the compounds

(4R)-3-(2,5-Dihydroxybenzoyl)-5,5-dimethyl-N-substituted benzylthiazolidine-4-carboxamide **2a-d**

To a solution of the appropriate N-Boc thiazolidine derivatives⁹ **1a-d** (5 mmol), in (20 ml) 4 N HCl/Dioxane, at 0° anisole (1.9 ml, 10 mmol) was added and stirred for 2 h at room temperature. The solvent was evaporated *in vacuo* and ether (10 ml) was added. The mixture was centrifuged, and the residue was dissolved in dimethylformamide (DMF) (15 ml). To the above solution, were added at 0° gentisic acid (693 mg, 4.5 mmol), hydrated hydroxybenzotriazole (HOBt.H₂O) (766 mg, 5 mmol), 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydrochloride (EDC.HCl) (1.05 g, 5.5 mmol) and triethylamine (Et₃N) (1.39 ml, 10 mmol). The mixture was stirred for an overnight at room temperature. The solvent was then removed under vacuum and the residue was extracted with ethyl acetate (AcOEt). The combined organic extracts were successively washed with 10% citric acid, 5% NaHCO₃ and finally with brine. The extracts were then dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The residues were crystallized from AcOEt / n-hexane, Table 1.

IR (KBr, cm⁻¹) (**2a-d**): 3332-3325 (OH), 3140-3134 (NH), 1678-1673 (C=O), 1668-1665 (C=O).

¹HNMR (**2a**): (DMSO-d₆, δ, ppm): 1.42 (s, 3H, thiazol-C₅-CH₃), 1.46 (s, 3H, thiazol-C₅-CH₃), 4.03 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.24 (m, 2H, thiazol-CH₂), 4.53 (s, 2H, CH₂NH), 6.74-7.22 (m, 8H, Ar-H), 8.48 (br s, 1H, NH, D₂O exchangeable), 10.32 (s, 1H, OH, D₂O exchangeable), 12.94 (s, 1H, OH, D₂O exchangeable).

¹HNMR (**2b**): (DMSO-d₆, δ, ppm): 1.44 (s, 3H, thiazol-C₅-CH₃), 1.51 (s, 3H, thiazol-C₅-CH₃), 4.09 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.28 (m, 2H, thiazol-CH₂), 4.54 (s, 2H, CH₂NH), 6.71-7.27 (m, 7H, Ar-H), 8.45 (br s, 1H, NH, D₂O exchangeable), 10.29 (s, 1H, OH, D₂O exchangeable), 12.85 (s, 1H, OH, D₂O exchangeable).

¹HNMR (**2c**): (DMSO-d₆, δ, ppm): 1.42 (s, 3H, thiazol-C₅-CH₃), 1.56 (s, 3H, thiazol-C₅-CH₃), 4.11 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.31 (m, 2H, thiazol-CH₂), 4.47 (s, 2H, CH₂NH), 6.71-7.28 (m, 7H, Ar-H), 8.42 (br s, 1H, NH, D₂O exchangeable), 10.31 (s, 1H, OH,

D₂O exchangeable), 12.87 (s, 1H, OH, D₂O exchangeable).

¹HNMR (**2d**): (DMSO-d₆, δ, ppm): 1.47 (s, 3H, thiazol-C₅-CH₃), 1.54 (s, 3H, thiazol-C₅-CH₃), 4.12 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.33 (m, 2H, thiazol-CH₂), 4.44 (s, 2H, CH₂NH), 6.73-7.32 (m, 7H, Ar-H), 8.46 (br s, 1H, NH, D₂O exchangeable), 10.34 (s, 1H, OH, D₂O exchangeable), 12.91 (s, 1H, OH, D₂O exchangeable).

(4R)-3-[(3,6-Dioxo-1,4-cyclohexadienyl) carbonyl]-5,5-dimethyl-N-substituted benzylthiazolidine-4-carboxamide **3a-d**

To a solution of the appropriate hydroquinone **2a-d** (5 mmol) in dimethylformamide (DMF) (10 ml), a solution of ferric chloride (10%, 20 ml) was portionwise added with stirring for 15 min.⁴ The reaction mixture was diluted with water (50 ml), whereupon orange precipitates were formed. The solid products were filtered, washed with water till free from ferric ion, dried and recrystallized from aqueous dimethylformamide. Table 1.

IR (KBr, cm⁻¹) (**3a-d**): 3154-3148 (NH), 1680-1675 (C=O), 1671-1665 (C=O).

¹HNMR (**3a**): (DMSO-d₆, δ, ppm): 1.46 (s, 3H, thiazol-C₅-CH₃), 1.51 (s, 3H, thiazol-C₅-CH₃), 4.07 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.28 (m, 2H, thiazol-CH₂), 4.51 (s, 2H, CH₂NH), 6.78-7.64 (m, 8H, Ar-H), 8.52 (br s, 1H, NH, D₂O exchangeable).

¹HNMR (**3b**): (DMSO-d₆, δ, ppm): 1.40 (s, 3H, thiazol-C₅-CH₃), 1.46 (s, 3H, thiazol-C₅-CH₃), 4.10 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.32 (m, 2H, thiazol-CH₂), 4.52 (s, 2H, CH₂NH), 6.74-7.63 (m, 7H, Ar-H), 8.47 (br s, 1H, NH, D₂O exchangeable).

¹HNMR (**3c**): (DMSO-d₆, δ, ppm): 1.41 (s, 3H, thiazol-C₅-CH₃), 1.52 (s, 3H, thiazol-C₅-CH₃), 4.08 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.33 (m, 2H, thiazol-CH₂), 4.46 (s, 2H, CH₂NH), 6.72-7.68 (m, 7H, Ar-H), 8.53 (br s, 1H, NH, D₂O exchangeable).

¹HNMR (**3d**): (DMSO-d₆, δ, ppm): 1.44 (s, 3H, thiazol-C₅-CH₃), 1.52 (s, 3H, thiazol-C₅-CH₃), 4.11 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.34 (m, 2H, thiazol-CH₂), 4.47 (s, 2H, CH₂NH), 6.71-7.67 (m, 7H, Ar-H), 8.54 (br s, 1H, NH, D₂O exchangeable).

Table 1: Physical and analytical data of compounds **2a-d** and **3a-d**.

Comp. No.	R ¹	Yield (%)	Mp °	Mol. Formula (Mol. wt.)	Analyses (%)				
					Calcd/Found				
					C	H	F	N	S
2a	H	82	256-7	C ₂₀ H ₂₂ N ₂ O ₄ S (386.46)	62.16 62.1	5.74 5.5	-----	7.25 7.5	8.30 8.4
2b	2-F	78	264-5	C ₂₀ H ₂₁ FN ₂ O ₄ S (404.45)	59.39 59.7	5.23 5.5	4.70 4.3	6.93 6.6	7.93 7.6
2c	3-F	74	267-8	C ₂₀ H ₂₁ FN ₂ O ₄ S (404.45)	59.39 59.5	5.23 5.3	4.70 4.9	6.93 7.1	7.93 7.4
2d	4-F	80	263-4	C ₂₀ H ₂₁ FN ₂ O ₄ S (404.45)	59.39 59.2	5.23 5.6	4.70 4.4	6.93 7.0	7.93 8.2
3a	H	72	decomp.	C ₂₀ H ₂₀ N ₂ O ₄ S (384.45)	62.48 62.5	5.24 5.4	-----	7.29 7.6	8.34 8.5
3b	2-F	79	decomp.	C ₂₀ H ₁₉ FN ₂ O ₄ S (402.44)	59.69 59.7	4.76 4.5	4.72 4.9	6.96 7.9	7.97 8.0
3c	3-F	83	decomp.	C ₂₀ H ₁₉ FN ₂ O ₄ S (402.44)	59.69 59.3	4.76 4.4	4.72 4.3	6.96 7.5	7.97 8.2
3d	4-F	86	decomp.	C ₂₀ H ₁₉ FN ₂ O ₄ S (402.44)	59.69 59.4	4.76 4.8	4.72 4.5	6.96 7.7	7.97 7.7

(4R)-3-(5-Substituted anilino-[(3,6-dioxo-1,4-cyclohexadienyl)carbonyl]-5,5-dimethyl-N-substituted benzylthiazolidine-4-carboxamide 4a-l

To a solution of the appropriate benzoquinone **3a-d** (1 mmol) and aniline or substituted aniline (0.5 mmol) in ethanol (15 ml) was added 5 drops of glacial acetic acid.¹⁰⁻¹² The mixture was heated under reflux for 0.5 h and filtered while hot. The precipitates were washed with 5 ml boiling ethanol, dried and crystallized from aqueous dimethylformamide, Table 2. All compounds decompose before melting.

IR (KBr, cm⁻¹) (**4a-l**): 3252-3238, 3152-3147 (NH), 1680-1677 (C=O), 1672-1669 (C=O), 1667-1665 (C=O).

¹HNMR (**4a**): (DMSO-d₆, δ, ppm): 1.44 (s, 3H, thiazol-C₅-CH₃), 1.52 (s, 3H, thiazol-C₅-CH₃), 4.09 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.29 (m, 2H, thiazol-CH₂), 4.49 (s, 2H, CH₂NH), 6.52-7.67 (m, 12H, Ar-H), 8.50 (br s,

1H, NH, D₂O exchangeable), 12.22 (s, 1H, NH, D₂O exchangeable).

¹HNMR (**4b**): (DMSO-d₆, δ, ppm): 1.41 (s, 3H, thiazol-C₅-CH₃), 1.44 (s, 3H, thiazol-C₅-CH₃), 4.12 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.31 (m, 2H, thiazol-CH₂), 4.53 (s, 2H, CH₂NH), 6.52-7.71 (m, 11H, Ar-H), 8.50 (br s, 1H, NH, D₂O exchangeable), 12.24 (s, 1H, NH, D₂O exchangeable).

¹HNMR (**4c**): (DMSO-d₆, δ, ppm): 1.39 (s, 3H, thiazol-C₅-CH₃), 1.48 (s, 3H, thiazol-C₅-CH₃), 4.10 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.32 (m, 2H, thiazol-CH₂), 4.45 (s, 2H, CH₂NH), 6.57-7.69 (m, 11H, Ar-H), 8.52 (br s, 1H, NH, D₂O exchangeable), 12.25 (s, 1H, NH, D₂O exchangeable).

¹HNMR (**4d**): (DMSO-d₆, δ, ppm): 1.43 (s, 3H, thiazol-C₅-CH₃), 1.48 (s, 3H, thiazol-C₅-CH₃), 4.09 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.37 (m, 2H, thiazol-CH₂), 4.45 (s, 2H, CH₂NH), 6.57-7.72 (m, 11H, Ar-H), 8.55 (br s, 1H, NH, D₂O exchangeable), 12.24 (s, 1H, NH, D₂O exchangeable).

Table 2: Physical* and analytical data of compounds **4a-l**.

Comp. No.	R ¹	R ²	Yield (%)	Mol. Formula (Mol. wt.)	Analyses (%)				
					Calcd/Found				
					C	H	F	N	S
4a	H	H	80	C ₂₆ H ₂₅ N ₃ O ₄ S (475.56)	65.67 65.5	5.30 5.2	----	8.84 8.7	6.74 6.4
4b	2-F	H	75	C ₂₆ H ₂₄ FN ₃ O ₄ S (493.55)	63.27 63.5	4.90 5.1	3.85 4.1	8.51 8.3	6.50 6.3
4c	3-F	H	81	C ₂₆ H ₂₄ FN ₃ O ₄ S (493.55)	63.27 62.9	4.90 4.7	3.85 3.6	8.51 8.4	6.50 6.2
4d	4-F	H	78	C ₂₆ H ₂₄ FN ₃ O ₄ S (493.55)	63.27 63.1	4.90 4.8	3.85 3.7	8.51 8.3	6.50 6.3
4e	H	4-CH ₃	82	C ₂₇ H ₂₇ N ₃ O ₄ S (489.58)	66.24 66.5	5.56 5.4	-----	5.58 5.6	6.55 6.8
4f	2-F	4-CH ₃	86	C ₂₇ H ₂₆ FN ₃ O ₄ S (507.57)	63.89 63.7	5.16 5.2	3.74 3.9	8.28 8.5	6.32 6.0
4g	3-F	4-CH ₃	82	C ₂₇ H ₂₆ FN ₃ O ₄ S (507.57)	63.89 63.5	5.16 5.4	3.74 3.5	8.28 8.5	6.32 6.1
4h	4-F	4-CH ₃	77	C ₂₇ H ₂₆ FN ₃ O ₄ S (507.57)	63.89 64.1	5.16 5.3	3.74 3.9	8.28 7.9	6.32 6.5
4i	H	4-Cl	74	C ₂₆ H ₂₄ ClN ₃ O ₄ S (510.00)	61.23 61.5	4.74 4.5	-----	8.24 8.1	6.29 5.9
4j	2-F	4-Cl	83	C ₂₆ H ₂₃ ClFN ₃ O ₄ S (527.99)	59.14 58.9	4.39 4.5	3.60 3.3	7.96 7.6	6.07 6.2
4k	3-F	4-Cl	76	C ₂₆ H ₂₃ ClFN ₃ O ₄ S (527.99)	59.14 59.2	4.39 4.2	3.60 3.7	7.96 7.8	6.07 5.8
4l	4-F	4-Cl	80	C ₂₆ H ₂₃ ClFN ₃ O ₄ S (527.99)	59.14 59.4	4.39 4.1	3.60 3.4	7.96 8.2	6.07 6.4

*All compounds decompose before melting.

¹HNMR (**4e**): (DMSO-d₆, δ, ppm): 1.42 (s, 3H, thiazol-C₅-CH₃), 1.53 (s, 3H, thiazol-C₅-CH₃), 2.34 (s, 3H, Ar-CH₃), 4.08 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.31 (m, 2H, thiazol-CH₂), 4.47 (s, 2H, CH₂NH), 6.53-7.68 (m, 11H, Ar-H), 8.47 (br s, 1H, NH, D₂O exchangeable), 12.62 (s, 1H, NH, D₂O exchangeable).

¹HNMR (**4f**): (DMSO-d₆, δ, ppm): 1.39 (s, 3H, thiazol-C₅-CH₃), 1.45 (s, 3H, thiazol-C₅-CH₃), 2.36 (s, 3H, Ar-CH₃), 4.10 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.33 (m, 2H, thiazol-

CH₂), 4.51 (s, 2H, CH₂NH), 6.55-7.73 (m, 10H, Ar-H), 8.51 (br s, 1H, NH, D₂O exchangeable), 12.58 (s, 1H, NH, D₂O exchangeable).

¹HNMR (**4g**): (DMSO-d₆, δ, ppm): 1.40 (s, 3H, thiazol-C₅-CH₃), 1.47 (s, 3H, thiazol-C₅-CH₃), 2.37 (s, 3H, Ar-CH₃), 4.08 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.33 (m, 2H, thiazol-CH₂), 4.42 (s, 2H, CH₂NH), 6.55-7.71 (m, 10H, Ar-H), 8.49 (br s, 1H, NH, D₂O exchangeable), 12.65 (s, 1H, NH, D₂O exchangeable).

¹HNMR (**4h**): (DMSO-d₆, δ, ppm): 1.41 (s, 3H, thiazol-C₅-CH₃), 1.44 (s, 3H, thiazol-C₅-CH₃), 2.35 (s, 3H, Ar-CH₃), 4.08 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.34 (m, 2H, thiazol-CH₂), 4.46 (s, 2H, CH₂NH), 6.56-7.71 (m, 10H, Ar-H), 8.52 (br s, 1H, NH, D₂O exchangeable), 12.64 (s, 1H, NH, D₂O exchangeable).

¹HNMR (**4i**): (DMSO-d₆, δ, ppm): 1.42 (s, 3H, thiazol-C₅-CH₃), 1.50 (s, 3H, thiazol-C₅-CH₃), 4.011 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.30 (m, 2H, thiazol-CH₂), 4.47 (s, 2H, CH₂NH), 6.53-7.69 (m, 11H, Ar-H), 8.51 (br s, 1H, NH, D₂O exchangeable), 12.82 (s, 1H, NH, D₂O exchangeable).

¹HNMR (**4j**): (DMSO-d₆, δ, ppm): 1.42 (s, 3H, thiazol-C₅-CH₃), 1.46 (s, 3H, thiazol-C₅-CH₃), 4.10 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.32 (m, 2H, thiazol-CH₂), 4.51 (s, 2H, CH₂NH), 6.55-7.73 (m, 10H, Ar-H), 8.47 (br s, 1H, NH, D₂O exchangeable), 12.82 (s, 1H, NH, D₂O exchangeable).

¹HNMR (**4k**): (DMSO-d₆, δ, ppm): 1.40 (s, 3H, thiazol-C₅-CH₃), 1.44 (s, 3H, thiazol-C₅-CH₃), 4.08 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.34 (m, 2H, thiazol-CH₂), 4.46 (s, 2H, CH₂NH), 6.56-7.74 (m, 10H, Ar-H), 8.51 (br s, 1H, NH, D₂O exchangeable), 12.78 (s, 1H, NH, D₂O exchangeable).

¹HNMR (**4l**): (DMSO-d₆, δ, ppm): 1.41 (s, 3H, thiazol-C₅-CH₃), 1.45 (s, 3H, thiazol-C₅-CH₃), 4.08 (d, J = 17.7 Hz, 1H, thiazol-C₄-H), 4.35 (m, 2H, thiazol-CH₂), 4.42 (s, 2H, CH₂NH), 6.54-7.70 (m, 10H, Ar-H), 8.53 (br s, 1H, NH, D₂O exchangeable), 12.84 (s, 1H, NH, D₂O exchangeable).

Antimicrobial activity

The microdilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) were used for the determination of antibacterial and antifungal activity.¹³ Test organisms are *Escherichia coli* (*E. coli*) ATCC 25922 as Gram-negative bacteria, *Staphylococcus aureus* (*S. aureus*) ATCC 19433 as Gram-positive bacteria and *Candida albicans* (*C. albicans*) as yeast like fungi. Ampicillin trihydrate and clotrimazole were used as standard antibacterial and antifungal agents respectively. Solutions of the test compounds, ampicillin trihydrate and clotrimazole were prepared in DMSO at concentration of 1600 µg/ml. The test compounds were two-fold serially diluted (800,

400,.....6.25 µg / ml). To each well, equal volume of double strength broth previously inoculated with standardized inoculum of the three test organisms (1 x 10⁶ CFU / ml) (Colony Forming Unit / ml) was added. The inoculated plates were incubated at 36°. The MIC values were determined after 24 h.

Table 3.

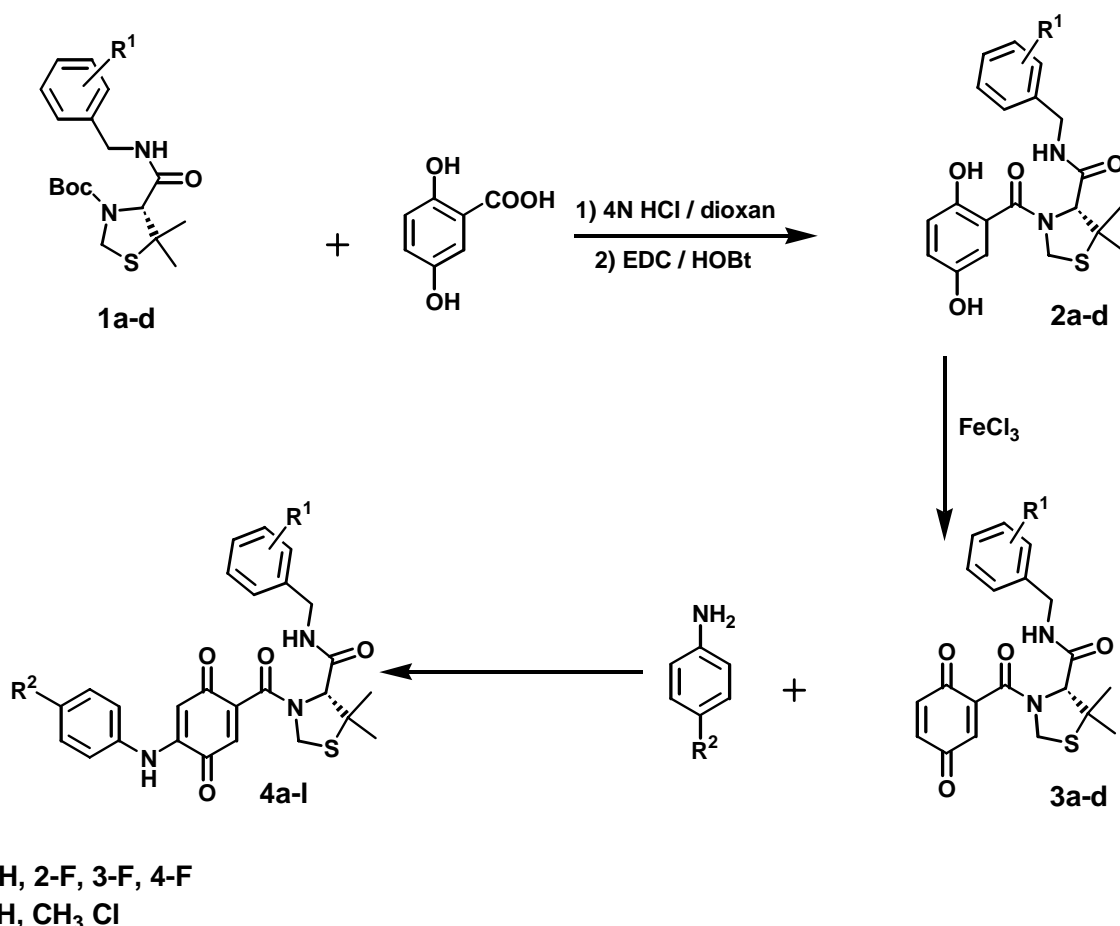
Table 3: Minimal inhibitory concentrations (MIC, µg/ml) of test compounds.

Test compound	<i>E. coli</i>	<i>S. aureus</i>	<i>C. albicans</i>
4a	12.5	25	>200
4b	25	50	>200
4c	25	25	>200
4d	12.5	12.5	>200
4e	50	50	>200
4f	50	25	>200
4g	50	25	>200
4h	12.5	12.5	>200
4i	100	100	>200
4j	50	100	>200
4k	50	50	>200
4l	12.5	12.5	>200
Ampicillin	25	12.5	---
Clotrimazole	---	---	12.5

RESULTS AND DISCUSSION

Chemistry

The target compounds were synthesized through the reaction sequence shown in Scheme 1. The selected thiazolidine derivatives were obtained by deprotection of N-Boc substituted thiazolidines **1a-c** using 4 N HCl/Dioxane. Condensation of 2,5-dihydroxybenzoic acid (gentisic acid) with the appropriate thiazolidine derivative was performed using 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydrochloride (EDC.HCl) and hydroxybenzotriazole (HOBt). EDC.HCl was used as a water soluble carbodiimide to form an active ester between gentisic acid and hydroxybenzotriazole. The so formed active ester can easily coupled with the N-deprotected thiazolidine derivative to afford the (4R)-3-(2,5-dihydroxybenzoyl)-5,5-dimethyl-N-substituted benzylthiazolidine-4-carboxamide **2a-d** in good yields. The latter



Scheme 1

compounds were oxidized with ferric chloride to the corresponding 1,4-benzoquinones **3a-d**. The reaction between 1,4-benzoquinone derivatives **3a-d** and aniline or 4-substituted aniline resulted in the sought for 2,5-disubstituted-1,4-benzoquinone derivatives **4a-l**, Tables 1 & 2.

Antimicrobial activity

The designed compounds **4a-l** were evaluated for their antimicrobial activity. The microdilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) was used for the determination of antibacterial and antifungal activity respectively. The minimal inhibitory concentrations (MICs) listed in Table 3 showed that all test compounds were inactive against *C. albicans* and showed higher activity against *E. coli* than *S. aureus*. The activity of compounds **4a**, **4d**, **4h** and **4l** was double that of ampicillin against *E. coli*. While compounds **4b** and **4c**

were equipotent to ampicillin against the same organism. Other compound showed 50% activity or less than that of ampicillin, while compounds **4d**, **4h** and **4l** were equipotent to ampicillin against *S. aureus*. In addition, the activity of **4a**, **4c**, **4f** and **4g** was 50% of that of ampicillin against *S. aureus*, whereas other compounds possessed activity against *S. aureus* less than 50% of that of ampicillin. It is worth-mentioning that, the fluoro derivatives showed a pronounced antibacterial activity in this study.

It could be safely concluded that introduction of fluorine atom in the para-position of the phenyl group attached to the thiazolidine ring system of the novel compounds, resulted in the most active compounds against *E. coli* and *S. aureus* (**4d**, **4h** and **4l**).

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