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Research article

Synthesis of anthraquinone-connected coumarin derivatives via grindstone method and their evaluation of antibacterial, antioxidant, tyrosinase inhibitory activities with molecular docking, and DFT calculation studies

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ABSTRACT

Anthraquinones and coumarins have excellent pharmacological activities and are an important class of natural plant metabolites with various biological activities. In this study, anthraquinone-9,10-dione and coumarin derivatives were combined to develop a novel anthraquinone-connected coumarin-derivative sequence. The synthesised novel anthraquinone-connected coumarin derivatives (**1a-t**) were screened for *in vitro* antibacterial, antioxidant, and tyrosinase inhibitory activities. The antibacterial activities of the synthesised compounds (**1a–t**) were tested against both gram-positive and gram-negative bacteria. Specifically, compound **1t** was more active against *E. aerogenes* than ciprofloxacin. With regard to antioxidant activity, compound **1o** (50.68 % at 100 μg/mL) was highly active compared to the other compounds, whereas it was less active than the standard BHT (76.74 % at 100 μg/mL). In terms of compound **1r** (9.31 ± 0.45 μg/mL) was highly active against tyrosinase inhibitory activity compared with kojic acid (10.42 ± 0.98 μg/mL). In the molecular docking study, compound **1r** had a higher docking score (−8.8 kcal mol^{-1}) than kojic acid (−1.7 kcal mol^{-1}). DFT calculations were performed to determine the energy gap of highly active compound **1r** (ΔE = 0.11) and weakly active compound **1a** (ΔE = 0.12). In this study, we found that every molecule displayed significant antibacterial, antioxidant, and tyrosinase inhibitory properties. Based on these reports, compounds **1r** and **1t** may act as multi-target agents.

1. Introduction

Anthracene-9,10-dione is the most important natural product present in plants, bacteria, fungi, and lichens [1]. Anthraquinones are a significant family of natural and synthetic chemicals with several uses, and there is growing interest in the development of novel anthraquinone derivatives with biological activity [2]. In particular, 9,10-dione derivatives have piqued the interest of medicinal chemists because of their remarkable pharmacological properties, including anti-tumour [3,4], anti-inflammatory [5], antimalarial

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[6], antioxidants, antibacterial [7,8], antiifungal [9], anti-leukemic [10], anti-HIV [11], and anti-tumour activities [12]. A range of human cancer cell lines, including A2780, HeLa, H7420, Ketr3, and SW 1990, were shown to be cytotoxic by previously described anthraquinone derivatives, such as racemic trimeric quinone and polycyclic quinones, with an IC_{50} of 6.2–9.3 μM [13]. Semisynthetic anthraquinones, including E−1, AE-1, FLE, and FLAE, demonstrate strong antiproliferative effects against HT-29, PC-3, and HeLa cells, although they showed only moderate antioxidant activities [14].

Coumarins are a chemical subclass of lactones that have several other names, including 1,2-benzopyrone and *O*-hydroxycinnamic acid-8-lactone [15,16]. Following are the six basic categories of natural coumarins: simple coumarins, furocoumarins, pyranocoumarins (linear and angular types), dihydro furanocoumarins, phenyl coumarins, and bi-coumarins [17]. Tonka bean (*Dipteryx odorata*) was used to produce the first parent coumarin in 1820 [18,19]. These heterocyclic molecules exhibit various therapeutic effects, including antimicrobial, anti-inflammatory, and antioxidant activities [20–23]. The anticancer properties of coumarin and its compounds include activity against leukaemia, prostate, kidney, breast, larynx, lung, colon, central nervous system (CNS), and malignant melanoma [24]. Viral attachment to host cells and cell membrane fusion are two steps in the HIV replication cycle that can be blocked by coumarin-based derivatives [25]. A previously reported green coumarin derivative displayed moderate inhibition of tyrosinase activity but showed no notable antibacterial, antifungal, or antioxidant properties in assays [26]. Some naturally bioactive anthraquinone and coumarin derivatives are shown in Fig. 1 [27–29].

Coumarin and anthraquinone derivatives are multitarget compounds with antibacterial activity, particularly against *E. coli* and *S. aureus,* etc [30–33]. Based on the above selection, coumarin and anthraquinone derivatives were screened for antibacterial activity in current work, these multi-target compounds of coumarin and anthraquinone derivatives also act as antioxidants and have tyrosinase activity, according to previously reported literature [34–38]. In cosmetic products, tyrosinase inhibitors are being utilized more often to preserve skin whiteness. The idea that antioxidants have an oxidative effect is the foundation for their application in skin-lightning procedures [39]. The tyrosinase-inhibiting and free radical-scavenging activities were strongly linked to total phenolic and content compounds. The stronger the inhibiting and scavenging properties against free radicals and tyrosinase, the higher the concentration of antioxidants, such as kojic acid, which is well known for its anti-tyrosinase and antioxidant properties [40]. The mechanism of the interaction between tyrosinase and antioxidants has been reported in previous studies [41]. Hence, the present study aimed to explore anthraquinone-connected coumarin-based multitarget agents. A novel anthraquinone-connected coumarin derivative was synthesised using the grindstone method. The anthraquinone-connected coumarin-derivative (**1a-t**) compounds were screened for antibacterial, antioxidant, and tyrosinase inhibitory activities. In addition, high- and low-activity compounds were used in computational studies (molecular docking and DFT calculations).

2. Experimental section

2.1. Chemistry

All analytical grade chemicals were purchased from Sigma-Aldrich. Nicolet iS5 (Thermo Scientific FTIR) was used to record the FTIR spectra (4000-400 cm^{-1}) of the synthesised compounds. The ^{1}H and ^{13}C NMR spectra were analysed using a Bruker DRX-300 MHz and 75 MHz instrument. The percentages of N, S, H, and C were ascertained using a Vario EL III element analyser. PerkinElmer GCMS (Clarus sq8) was used to record the mass spectra.

2.1.1. Synthesis of compound 1a

A mixture of ethyl-3-oxobutanoate (0.01 mol) and an anthraquinone-9,10-dione derivative (0.01 mol) was combined with $AlCl_3$ using the grindstone method for 1 h at room temperature. After 1 h, solid material was obtained. TLC (Thin Layer Chromatography)

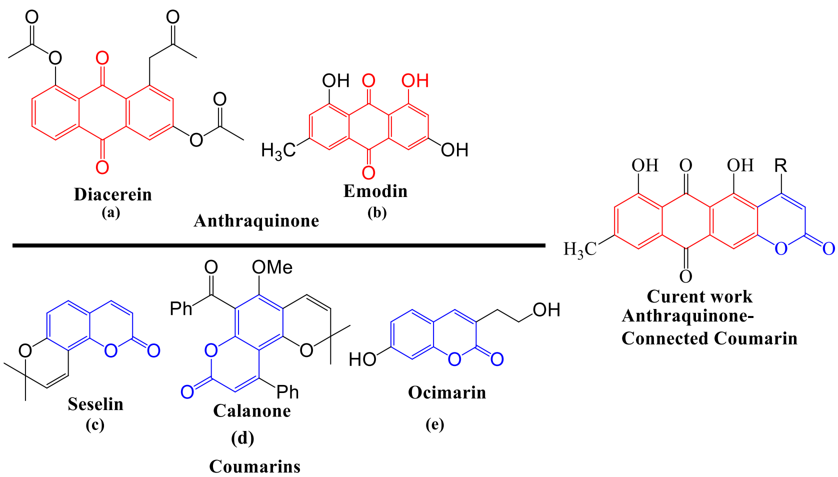
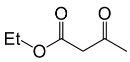
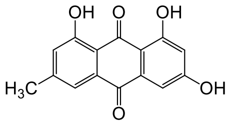
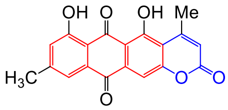
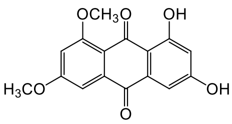
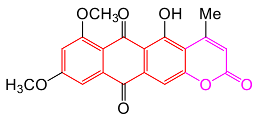
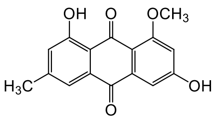
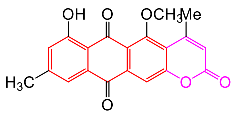
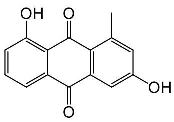
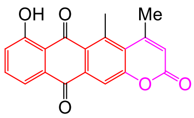
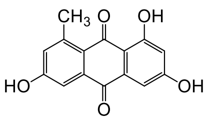
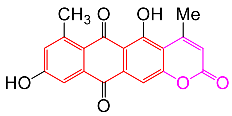
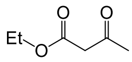
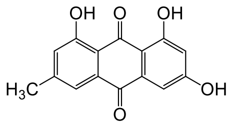
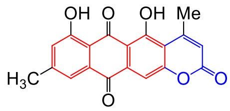
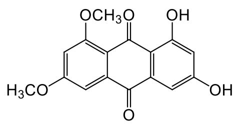
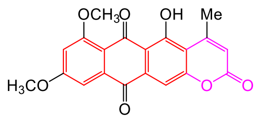
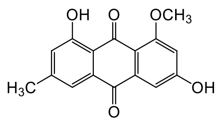
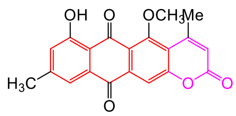
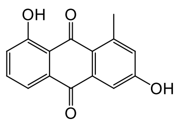
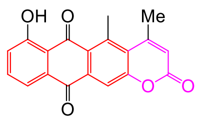
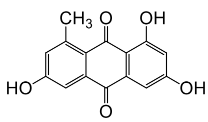
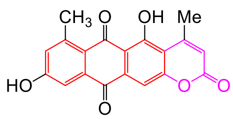
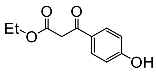
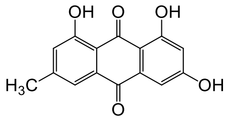
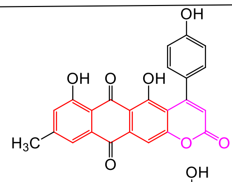
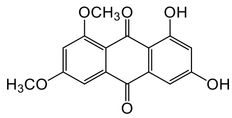
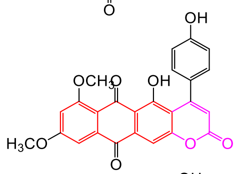
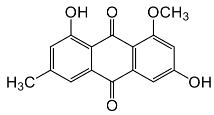
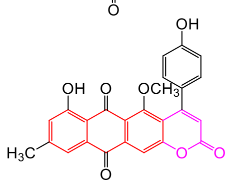
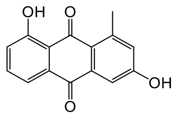
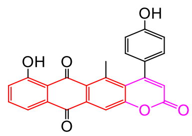
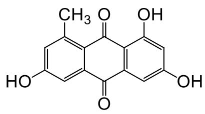
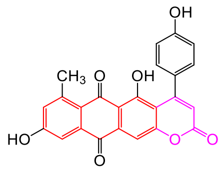


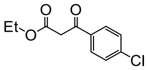
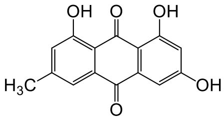
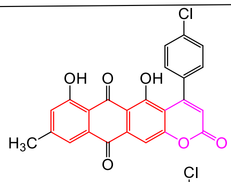
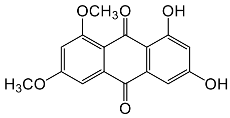
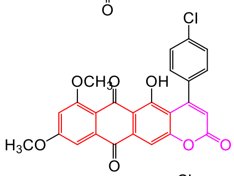
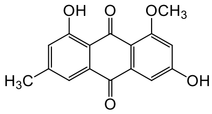
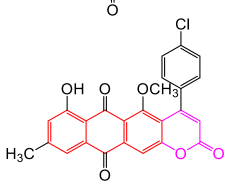
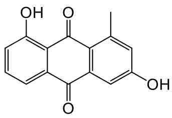
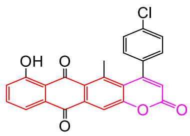
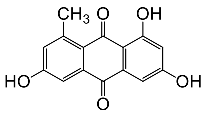
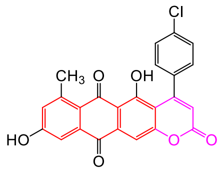
Fig. 1. Some basic natural product of Anthraquinone and Coumarins.

Table 1
Synthesis of anthraquinone-connected coumarin derivatives **1(a–t)**.

entry	ethyl 3-oxo butanoate	anthraquinone-9,10-dione	product	yield (%)
1a				65
1b				69
1c				77
1d				72
1e				69

entry	ethyl 3-oxo butanoate	anthraquinone-9,10-dione	product	yield (%)
1a				65
1b				69
1c				77
1d				72
1e				69

entry	ethyl 3-(4-hydroxyphenyl)-3-oxopropanoate	anthraquinone-9,10-dione	product	yield (%)
1k				81
1l				89
1m				86
1n				82
1o				67

entry	ethyl 3-(4-chlorophenyl)-3-oxopropanoate	anthraquinone-9,10-dione	product	yield (%)
1p				89
1q				89
1r				74
1s				66
1t				74

was used to identify and confirm the product, and column chromatography was used to separate the final product using a 4:6 ratio of hexane, and ethyl acetate, and a suitable amount of alcohol was used to recrystallise the separated solid material. All the other compounds (**1b-t**) were synthesised using the above method. Table 1 shows the optimisation of the reaction with the yield of compounds (**1a-t**). Detailed physical values, spectral, mass, and Analytical values of compounds (**1a-t**) were reported in supporting information (SI) file (Page 2–7).

2.2. Biological activity

2.2.1. In vitro antibacterial activity

The anthraquinone-connected coumarin derivatives (**1a-t**) was evaluated against *in vitro* antibacterial activity both gram-positive and gram-negative bacteria, such as MTCC-739 (*Escherichia coli*), MTCC-2453 (*Pseudomonas aeruginosa*), recultured (*Enterobacter aerogenes*), MTCC-1306 (*Bacillus cereus*), and MTCC-96 (*Staphylococcus aureus*) was determined using the agar-disc diffusion technique, followed by previously reported method [42].

2.2.2. Anti-tyrosinase activity

The anthraquinone-connected coumarin derivatives (**1a-t**) were screened for antityrosinase activity using a previously reported method [43].

The formula below was used to calculate the percentage of tyrosinase activity inhibition:

$$Tyrosinase\ inhibitory\ activity\ (\%) = \frac{(A-B)-(C-D)}{(A-B)} \times 100 \quad (1)$$

2.2.3. Antioxidant activity

The synthesised anthraquinone-connected coumarin derivatives (**1a-t**) were screened for antioxidant activity of DPPH radical scavenging activity using a previously reported method [44].

The fraction of free radical scavenging (%) was computed as follows:

$$Scavenging\ \% = \frac{A_{control-}\ A_{sample}}{A_{control}} \times 100 \quad (2)$$

2.3. Molecular docking

Using AutoDock Vina 1.1.2, the synthesised compounds were subjected to *in silico* molecular docking tests with the 2Y9X protein. The experiment followed a previously reported method [45].

3. Results and discussion

3.1. Chemistry

Anthraquinone-connected coumarin (**1a-t**) derivatives were synthesised using the grindstone method (one-pot multicomponent synthesis). Anthracene-9,10-dione and ethyl 3-oxobutanoate were combined with $AlCl_3$ by the grindstone method for 1 h at room temperature. Thin-layer chromatography (TLC) was used to both identify and confirm the product and to separate it through column chromatography. The yield of the product was 89–65 %. The synthesis route is outlined in Scheme 1.

The synthesised compounds were confirmed by IR, ^{1}H and ^{13}C NMR, and mass spectrometry. The –OH, C═O, and -C-O were matched by each compound in the IR range of 3690-3225, 1865-1550, and 1227-1055 cm^{-1}, respectively. The ^{1}H NMR spectra show that the important proton peaks at 6.81, 5.35, and 3.83 ppm, resulting from the protons CO–CH = , –OH, and –OCH_3, were matched by each molecule. ^{13}C NMR spectra showed signals of 190.6–160.8, 62.2–55.8, and 24.1–21.6 ppm corresponding to C═O, –OCH_3, and Ph-CH_3, respectively. The signals from the molecular ions corresponded to the predicted molecular weights of all the produced compounds, according to mass spectroscopic research. All compounds were characterised by molecular weight using mass spectrometry, and the compound **1a** molecular ion EI-MS peak was confirmed by (*m/z*): 337.017 (M+, 20.9 %) [46]. The SI contains the complete ^{1}H and ^{13}C NMR spectra in detailed form (Figs. S1–S40).

3.2. Biological screening

3.2.1. Antioxidant activity

The anthraquinone-connected coumarin derivatives (**1a-t**) were screened for DPPH scavenging activity, and compound **1o** (50.68 % at 100 μg/mL) was highly active compared with the other compounds, whereas it was less active compared with standard BHT (76.74 % at 100 μg/mL).

Compounds **1o**, **1n**, and **1q** (50.68, 49.32, and 48.62 % at 100 μg/mL) were more active than the other compounds, whereas compound **1f** (28.65 % at 100 μg/mL) was less active than the other compounds. Fig. 2 shows the antioxidant activities of compounds (**1a-t**).

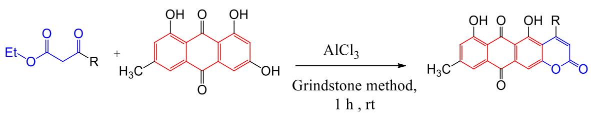
3.2.2. Tyrosinase inhibitory activity

The study of the tyrosinase-inhibiting effects of the compounds employed L-dopa as a substrate, as shown in Fig. 3. The test findings for various substances conflicted with those for the inhibition of melanin production. Compound **1r** (IC_{50}: 9.31 ± 0.45 μg/mL) exhibited the most inhibitory effect, with a significantly greater activity than kojic acid (IC_{50}: 10.42 ± 0.45 μg/mL). Table 2 summarises the outcomes of the study.

All synthetic anthraquinone-connected coumarin derivatives were prepared using a slightly modified version of Bradford's method for testing tyrosinase inhibition using L-dopa as the substrate. Kojic acid was chosen as the reference compound because it effectively inhibits tyrosinase, and as such, is a popular ingredient for skin whitening. The IC_{50} values of the anthraquinone-connected coumarin derivatives against monophenolase and diphenolase are summarised in Table 2. The logarithmic concentration-inhibition curves used to compute the IC_{50} values for each drug were obtained. A detailed calculation of the IC_{50} value is included in the SI file (Tables S1–S21).

Compound **1r** was among the most effective inhibitors and had an IC_{50} value of 9.31 ± 0.45 μg/mL. Since kojic acid exhibits competitive suppression of the substances that chelate copper in the active region of the enzyme, we can assume that the compounds bind to the dicopper centre via their a-hydroketone group (Fig. 3).

Tyrosine activity is mediated by the enzyme (En) and dopamine (Dopa), and Series 1 is found only in enzymes. In the process of forming the copper complex, the enzyme dopamine with the sample is involved in the reaction to form the copper complex, which is known as anti-tyrosine activity, and the enzyme dopamine with kojic acid is involved in the reaction to reduce the copper complex.



Scheme 1. Synthetic route of compound.

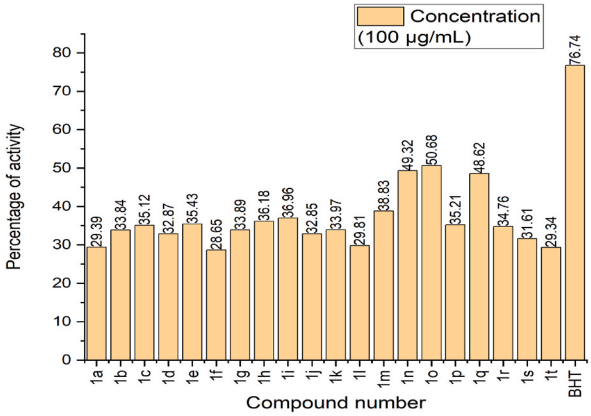


Fig. 2. Antioxidant activities of compounds (**1a-1t**) and standard BHT against DPPH method concentration at 100 μg/mL.

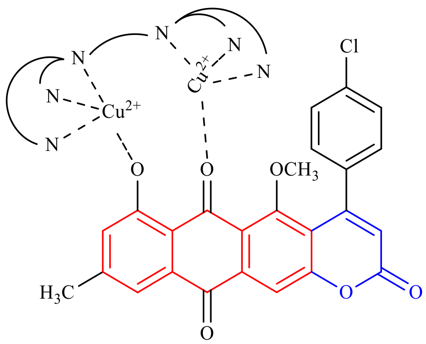


Fig. 3. The binding of compound **1r** to the dinuclear complexes.

Table 2
Tyrosinase from mushrooms Inhibitory functions of substances (**1a-t**) and standard kojic acid.

Compound No.	Concentration (μg/mL)[a]			IC_{50} (μg/mL)[a]
	25 μg/mL	50 μg/mL	100 μg/mL	
1a	12.05 ± 0.74	30.12 ± 0.45	38.55 ± 0.17	>100
1b	34.94 ± 0.41	49.40 ± 0.31	63.86 ± 0.36	59.95 ± 0.46
1c	40.96 ± 0.62	31.33 ± 0.17	44.58 ± 0.36	>100
1d	21.69 ± 0.65	27.71 ± 0.25	39.76 ± 0.12	>100
1e	32.53 ± 0.01	48.19 ± 0.28	50.60 ± 0.25	52.88 ± 0.65
1f	13.25 ± 0.14	22.30 ± 0.17	44.58 ± 0.15	>100
1g	22.89 ± 0.21	32.53 ± 0.32	62.65 ± 0.65	78.02 ± 0.49
1h	44.58 ± 0.23	19.28 ± 0.26	46.99 ± 0.21	>100
1i	52.84 ± 0.32	61.45 ± 0.14	63.86 ± 0.45	46.45 ± 0.69
1j	28.92 ± 0.11	30.24 ± 0.88	48.19 ± 0.36	>100
1k	25.30 ± 0.21	26.51 ± 0.32	31.33 ± 0.17	>100
1l	18.07 ± 0.23	32.53 ± 0.66	33.73 ± 0.35	>100
1m	33.73 ± 0.33	44.58 ± 0.25	66.87 ± 0.74	61.96 ± 0.48
1n	9.64 ± 0.64	34.94 ± 0.41	44.58 ± 0.63	>100
1o	40.96 ± 0.45	13.25 ± 0.66	45.78 ± 0.52	>100
1p	13.25 ± 0.46	21.69 ± 0.21	43.37 ± 0.48	>100
1q	27.71 ± 0.23	36.14 ± 0.32	51.81 ± 0.55	94.08 ± 0.32
1r	69.63 ± 0.74	73.60 ± 0.45	86.34 ± 0.21	9.31 ± 0.45
1s	28.07 ± 0.95	51.81 ± 0.19	67.47 ± 0.14	60.12 ± 0.85
1t	26.32 ± 0.31	47.56 ± 0.22	59.70 ± 0.11	71.48 ± 0.17
Kojic acid	55.67 ± 0.12	68.62 ± 0.32	85.54 ± 0.23	10.42 ± 0.98

[a] The IC_{50} values represent means ± SD of three different experiments.

Finally, the (enzyme, dopamine, with the sample) produced the highest activity, 0.427 at 270 nm and 0.5 intensity. In addition (the enzyme with dopamine) produced a 0.357 activity range at 270 nm and a 0.4 intensity of, therefore, (enzyme, dopamine, with kojic acid), anti-tyrosine activity produced a low activity range. The enzyme with the test compound and the enzyme with kojic acid did not involve the tyrosine reaction, which produces a low activity range. The enzyme with the test compound and the enzyme with kojic acid are not involved in the tyrosine reaction (Fig. 4. Tyrosinase kinetic activity study).

3.2.3. Antibacterial studies

The anthraquinone-connected coumarin derivatives (**1a-t**) was evaluated against *in vitro* antibacterial activity, compound **1t** showed high active against *E. aerogenes* (MIC = 0.25 μg/mL, 32 mm) than ciprofloxacin (MIC = 0.5, 30 mm), while the other compounds showed moderate activity against *E. aerogenes*. Compounds **1h** (14 mm) and **1t** (16 mm) were highly active compared to the other compounds whereas they were moderately active against *E. coli* compared to ciprofloxacin (27 mm). Compound **1t** showed moderate activity against *S. aureus* (16 mm) compared to ciprofloxacin (25 mm), whereas the other compounds were less active than **1t**. All compounds were less active against *P. aeruginosa* and *B. cereus* than the standard ciprofloxacin. Table 3 displays the results of the first antimicrobial testing compounds and standards (100 μg/disc), and the MIC values are shown in Table 4.

3.3. Docking results

The Auto Dock Vina program was utilized to evaluate the docking behaviour of compounds **1a**, **1r**, and standard kojic acid with the mushroom tyrosinase-binding protein 2Y9X.Compound **1r** showed the highest docking score (-8.8 kcal mol^{-1}) and bond length (1.98) compared to kojic acid (-1.7 kcal mol^{-1}) and bond length (1.97, 1.65, and 2.72). In compound **1r**, residues 190, Ile 191, Asp192, Pro201, Pro204, Lys208, Ser407, Arg406, Lys435, Pro436, Leu437, Asp438, Pro439, and Thr440 engaged in hydrophobic connections. The lowest active compound **1a** has a higher docking score (-3.4 kcal mol^{-1}) than kojic acid and compound **1a** compared with compound **1r**, and has a lower docking score. In the control kojic acid, residues Thr321, Asn323, Asn332, Thr333, Pro334, Val404, Glu405, Arg406, Ser407, Ser412, Ala413, Tyr415, Pro436, and Asp438 engaged in hydrophobic connections. Fig. 5 shows the 2D and 3D structures of compounds **1a**, **1r,** and kojic acid with the 2Y9X protein. Compared to the controls, the results showed that compounds **1a** and **1r** and kojic acid had similar inhibitory capabilities [47]. Table 5 displays the findings of molecular docking.

3.4. HOMO-LUMO analysis

The B3LYP/6-31G (d, p) basis set was used to theoretically investigate the HOMO-LUMO energy levels [48]. Compound **1a** ($\Delta E = 0.12$) had a higher energy gap than compound **1r** ($\Delta E = 0.11$). Fig. 6 shows the HOMO-LUMO energy diagrams of **1a** and **1r**. The HOMO and LUMO analyses and data are presented in the SI file. The DFT values are listed in Table 6. Fig. 7 shows the electron densities of compounds **1a** and **1r**, Fig. 8 shows the electrostatic potential map of compounds **1a** and **1r**, and Fig. 9 shows the interaction strengths of compounds **1a** and **1r**.

3.5. Structure–activity relationship

The SAR is the correlation between the biological consequences of crucial substances and their chemical characteristics within a testing framework. We identified several crucial elements when examining the connections between structure and activity.

The para position of the phenyl group served as the lipophilic moiety. The compound 1**a,** which has a $-CH_3$ group with anthraquinone connected coumarin, was less active in antioxidant, antibacterial, and tyrosinase inhibitory activities. Compound **1r,** which has 9-methyl and 7-hydroxy groups with anthraquinone-connected to coumarins, was less active in antioxidant and antibacterial activities, and highly active in tyrosinase inhibition. In a previous study, compound **1r** displayed lower tyrosinase inhibition activity than that of other coumarin derivatives [49]. Compound **1t,** with 9-hydroxy and 7-methyl groups with anthraquinone-connected

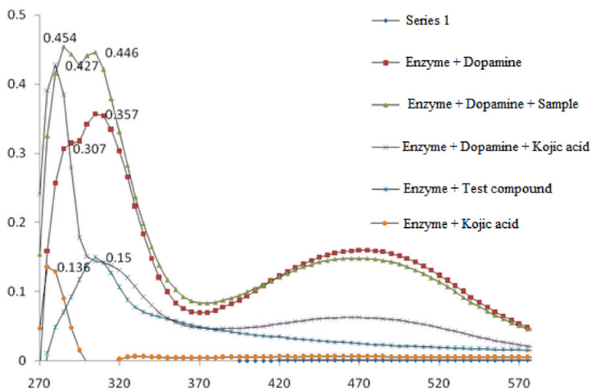


Fig. 4. Tyrosinase kinetic activity study.

Table 3
Antimicrobial activity of the compounds (**1a-t**).

Compound	Diameter of Growth Inhibition Zone (mm)[a]				
	Gram-negative bacteria			Gram-positive bacteria	
	E. coli	*P. aeruginosa*	*E. aerogenes*	*S. aureus*	*B. cereus*
1a	08	–	12	–	–
1b	10	–	–	–	–
1c	–	–	12	–	08
1d	08	–	10	–	08
1e	10	–	14	08	–
1f	12	08	–	08	–
1g	12	–	–	10	–
1h	14	–	–	12	08
1i	12	–	–	08	08
1j	12	–	–	08	08
1k	10	–	08	08	08
1l	10	–	–	10	–
1m	12	–	–	08	12
1n	10	–	15	08	08
1o	10	–	08	08	08
1p	10	08	10	08	08
1q	16	08	15	10	10
1r	15	08	–	13	13
1s	08	08	08	08	08
1t	16	08	32	16	08
Ciprofloxacin	27	26	30	25	22

[a] (−): Inactive (growth inhibition zone <8 mm).

Table 4
The minimal inhibitory concentrations (MIC, μg/ml) of compounds (1a-t).

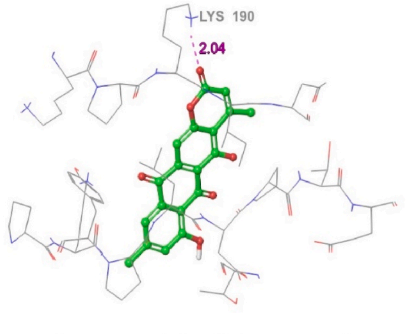
Comp. No.	Minimal Inhibitory Concentration (MIC, μg/mL)[a]				
	Gram-negative bacteria			Gram-positive bacteria	
	E. coli	*P. aeruginosa*	*E. aerogenes*	*S. aureus*	*B. cereus*
1q	32	64	32	64	64
1r	32	64	>100	64	64
1t	8	64	0.25	16	08
Ciprofloxacin	0.5	1	0.5	1	2

[a] ND: Not Determined.

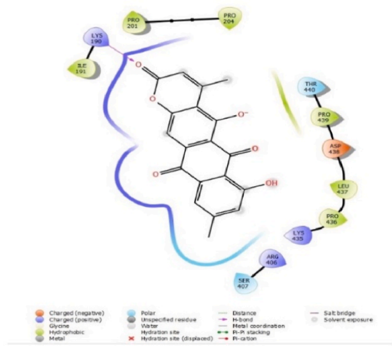
coumarins, had lower antioxidant and tyrosinase inhibitory activities, and highly active in antibacterial activity. In a previous study, compound **1t** showed equipotential antibacterial activities (against gram-negative bacteria) compared with other coumarin derivatives [50]. Fig. 10 shows the SAR of the highly active compounds. The lipophilicity of the compound enhanced its antimicrobial properties; however, as the molecular weight of the compound increased, the antimicrobial properties decreased. The molecular weight of log (Ko/w) suggests that the steric properties of the compound may impede its ability to integrate into the cell wall and membrane, as suggested by its lipophilicity [51].

4. Conclusion

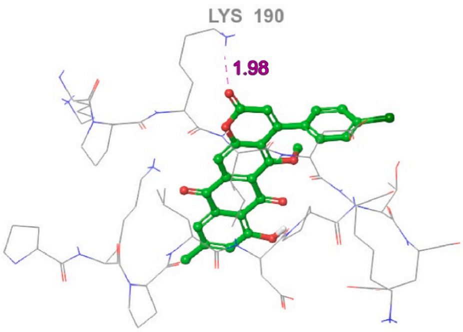
Anthraquinone-connected coumarin (**1a–t**) derivatives were synthesised using the grindstone method. The synthesised compounds were screened for DPPH free radical scavenging, tyrosinase inhibition, and antibacterial activities. Addition to *in silico* Molecular docking and DFT calculations were also performed. In terms of antioxidant activity, compound **1o** (50.68 % at 100 μg/mL) was more active than were the other compounds and compound **1r** (IC_{50}: 9.31 ± 0.45 μg/mL) was highly active to tyrosinase inhibition compared with kojic acid (IC_{50}: 10.42 ± 0.45 μg/mL). The synthesised derivatives (**1a–t**) were screened for preliminary *in vitro* antibacterial screening, compound **1t** showed higher activity against *E. aerogenes* (MIC = 0.25 μg/mL, 32 mm) than ciprofloxacin (MIC = 0.5 μg/mL, 30 mm). In the molecular docking study, compound **1r** had a higher docking score (−8.8 kcal mol^{-1}) compared with kojic acid (−1.7 kcal mol^{-1}). In DFT calculations, Compound **1a** ($\Delta E = 0.12$) had a higher energy gap than compound **1r** ($\Delta E = 0.11$). From these reports, compounds **1r** and **1t** are a starting point for designing improved derivatives based on the insights gained from structure-activity relationship research, with the aim of developing a new drug that can target multiple disease pathways simultaneously, often referred to as a "one drug-multiple targets" strategy.



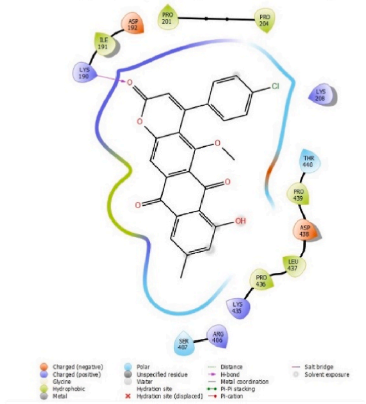
Compound **1a** (3d structure)



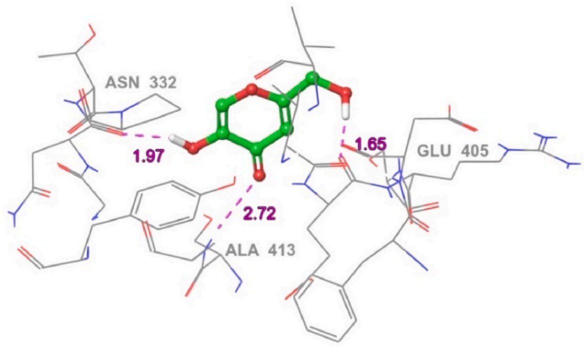
Compound **1a** (2d structure)



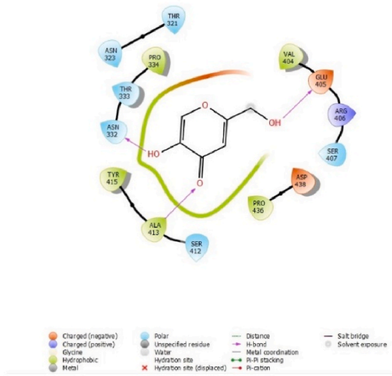
Compound **1r** (3d structure)



Compound **1r** (2d structure)



Kojic acid (3d structure)



Kojic acid (2d structure)

Fig. 5. Molecular docking comparison of kojic acid with compounds **1a** and **1r**. 3D binding conformation (left) and 2D binding conformation (right) showing the closest interactions between the active site residues of protein **2Y9X** and the most active (**1r**), and least active (**1a**) synthesised derivatives and kojic acid.

Table 5
Molecular Docking Interactions of **1a, 1r** and kojic acid with protein 2Y9X.

S. No	Compound/Drug	Dock Score	Interacting residues	Bond Length
1.	Compound **1a**	−3.4	Lys 190	2.04
2.	Compound **1r**	−8.8	Lys190	1.98
3.	Kojic acid	−1.7	Asn332, Glu405, Ala413	1.97, 1.65, 2.72

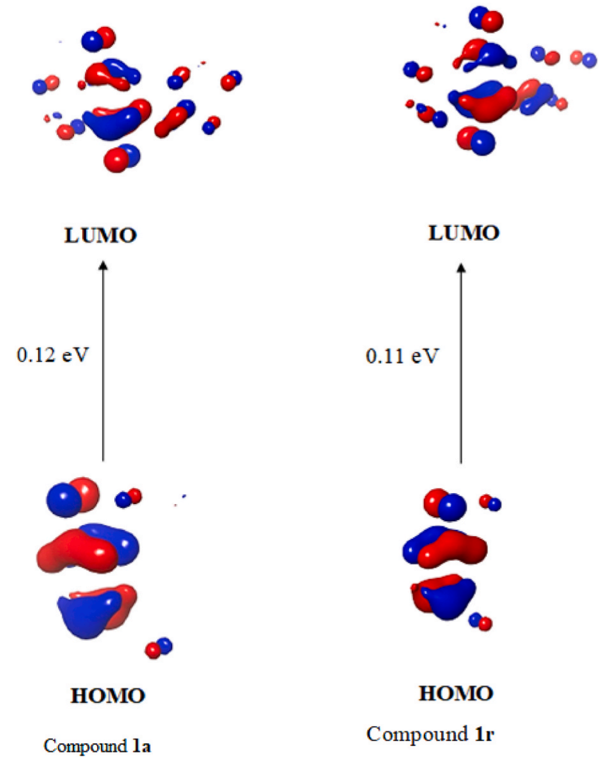


Fig. 6. HOMO-LUMO energy diagram of **1a** and **1r**.

Table 6
Frontier Molecular Orbital Energy and Reactivity Properties for compound **1a** and **1r**.

PROPERTY	1a	1r
HOMO	−0.25	−0.25
LUMO	−0.13	−0.14
Energy gap ΔE (LUMO-HOMO)	0.12	0.11
Ionization Energy (I = εHOMO = -HOMO)	0.25	0.25
Electron Affinity(A = εLUMO = -LUMO)	0.13	0.14
Global Hardness (η = (I–A)/2	0.06	0.05
Global Softness (s = 1/η)	16.66	20
Chemical Potential (μ = -(I + A)/2	−0.19	−0.19
Electronegative (χ = -μ)	0.19	0.19
Electrophilicity Index (ω = μ2/2η)	0.3	0.36
Nucleophilicity Index (N = 1/ω)	3.33	2.77

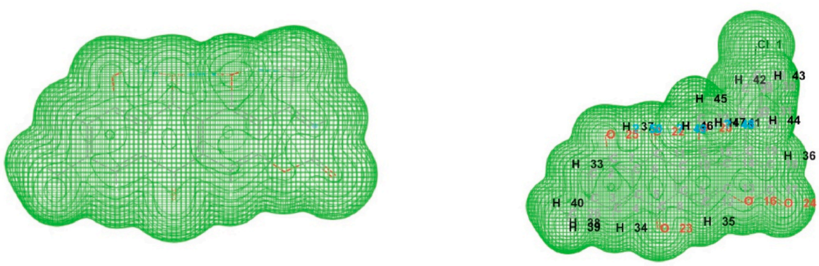


Fig. 7. Electron density of compound **1a,** and **1r**.

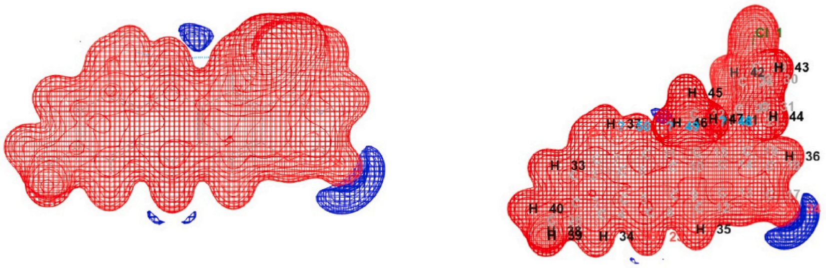


Fig. 8. Electrostatic potential Map of compound **1a,** and **1r**.

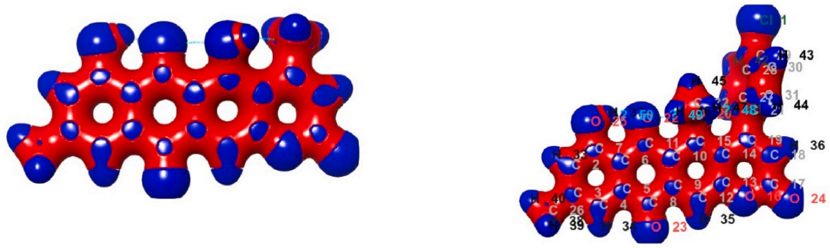


Fig. 9. Interaction strength of compound **1a,** and **1r**.

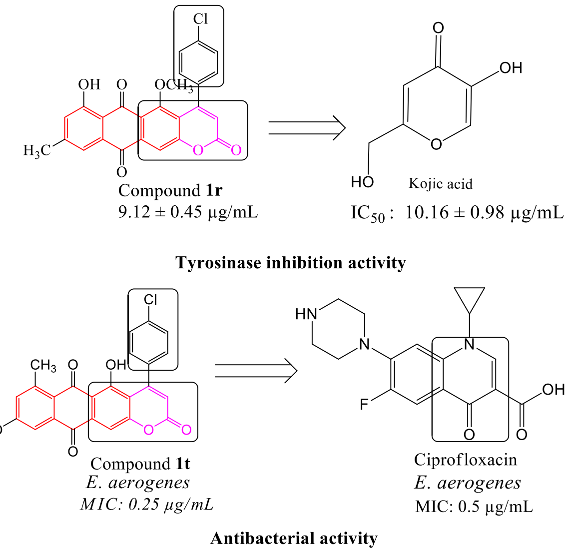


Fig. 10. Comparison of highly active compounds and their structure-activity relationship.

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Additional information

No additional information was available for this study.

Data availability

The data will be made available upon request.

CRediT authorship contribution statement

Velmurugan Loganathan: Methodology. **Anis Ahamed:** Investigation. **Surendrakumar Radhakrishnan:** Data curation. **Abdel-Rhman Z. Gaafar:** Software. **Raman Gurusamy:** Formal analysis. **Idhayadhulla Akber:** Writing – original draft, Supervision, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25168.

References

[1] R. Singh, S.M.S. Chauhan, 9, 10-Anthraquinones and other biologically active compounds from the genus Rubia, Chem. Biodivers. 1 (9) (2004) 1241–1264, https://doi.org/10.1002/cbdv.200490088.
[2] I.H. Gecibesler, F. Disli, S. Bayindir, M. Toprak, A.R. Tufekci, A.S. Yaglıoglu, S. Adem, The isolation of secondary metabolites from Rheum ribes L. and the synthesis of new semi-synthetic anthraquinones: isolation, synthesis and biological activity, Food Chem. 342 (2021) 128378, https://doi.org/10.1016/j.foodchem.2020.128378.
[3] A. Ashnagar, J.M. Bruce, P.L. Dutton, R.C. Prince, One-and two-electron reduction of hydroxy-1, 4-naphthoquinones and hydroxy-9, 10-anthraquinones: the role of internal hydrogen bonding and its bearing on the redox chemistry of the anthracycline antitumour quinones, Biochimica et Biophysica Acta (BBA)-General Subjects 801 (3) (1984) 351–359, https://doi.org/10.1016/0304-4165(84)90138-7.
[4] P. Ge, R.A. Russell, The synthesis of anthraquinone derivatives as potential anticancer agents, Tetrahedron 53 (51) (1997) 17469–17476, https://doi.org/10.1016/S0040-4020(97)10195-8.
[5] J.P. Yadav, V. Arya, S. Yadav, M. Panghal, S. Kumar, S. Dhankhar, L. Cassia occidentalis, A review on its ethnobotany, phytochemical and pharmacological profile, Fitoterapia 81 (4) (2010) 223–230, https://doi.org/10.1016/j.fitote.2009.09.008.
[6] C.P. Osman, N.H. Ismail, R. Ahmad, N. Ahmat, K. Awang, F.M. Jaafar, Anthraquinones with antiplasmodial activity from the roots of Rennellia elliptica Korth. (Rubiaceae), Molecules 15 (10) (2010) 7218–7226, https://doi.org/10.3390/molecules15107218.
[7] W. Xiang, Q.S. Song, H.J. Zhang, S.P. Guo, Antimicrobial anthraquinones from Morinda angustifolia, Fitoterapia 79 (7–8) (2008) 501–504, https://doi.org/10.1016/j.fitote.2008.04.008.
[8] G. Rath, M. Ndonzao, K. Hostettmann, Antifungal anthraquinones from Morinda lucida, International journal of pharmacognosy 33 (2) (1995) 107–114, https://doi.org/10.3109/13880209509055208.
[9] P. Chang, K.H. Lee, Cytotoxic antileukemic anthraquinones from Morinda parvifolia, Phytochemistry 23 (8) (1984) 1733–1736, https://doi.org/10.1016/S0031-9422(00)83480-9.
[10] D.S. Alves, L. Pérez-Fons, A. Estepa, V. Micol, Membrane-related effects underlying the biological activity of the anthraquinones emodin and barbaloin, Biochem. Pharmacol. 68 (3) (2004) 549–561, https://doi.org/10.1016/j.bcp.2004.04.012.
[11] R.F. Schinazi, C.K. Chu, J.R. Babu, B.J. Oswald, V. Saalmann, D.L. Cannon, M. Nasr, Anthraquinones as a new class of antiviral agents against human immunodeficiency virus, Antivir. Res. 13 (5) (1990) 265–272, https://doi.org/10.1016/0166-3542(90)90071-E.
[12] S.M.M. Nor, M.A.H.M. Sukari, S.S.S.A. Azziz, W.C. Fah, H. Alimon, S.F. Juhan, Synthesis of new cytotoxic aminoanthraquinone derivatives via nucleophilic substitution reactions, Molecules 18 (7) (2013) 8046–8062, https://doi.org/10.3390/molecules18078046.
[13] C. Li, C. Dong, J. Fu, J. Xie, S. Lai, H. Wang, J. Kang, The racemic trimeric quinone and polycyclic quinones isolated from the aerial parts of Morinda umbellata L, Phytochemistry 183 (2021) 112622, https://doi.org/10.1016/j.phytochem.2020.112622.
[14] I.H. Gecibesler, F. Disli, S. Bayindir, M. Toprak, A.R. Tufekci, A.S. Yaglıoglu, S. Adem, The isolation of secondary metabolites from Rheum ribes L. and the synthesis of new semi-synthetic anthraquinones: isolation, synthesis and biological activity, Food Chem. 342 (2021) 128378, https://doi.org/10.1016/j.foodchem.2020.128378.
[15] B. Nikhil, B. Shikha, P. Anil, N.B. Prakash, Diverse pharmacological activities of 3-substituted coumarins: a review, Int. Res. J. Pharm. 3 (2012) 24–29.
[16] C. Kontogiorgis, A. Detsi, D. Hadjipavlou-Litina, Coumarin-based drugs: a patent review (2008–present), Expert Opin. Ther. Pat. 22 (4) (2021) 437–454, https://doi.org/10.1517/13543776.2012.678835.
[17] K.N. Venugopala, V. Rashmi, B. Odhav, Review on natural coumarin lead compounds for their pharmacological activity, BioMed Res. Int. (2013), https://doi.org/10.1155/2013/963248, 2013.
[18] N. Prahadeesh, M. Sithambaresan, U. Mathiventhan, A study on hydrogen peroxide scavenging activity and ferric reducing ability of simple coumarins, Emerg. Sci. J. 2 (6) (2018) 417–427, https://doi.org/10.28991/esj-2018-01161.
[19] M.V. Kulkarni, G.M. Kulkarni, C.H. Lin, C.M. Sun, Recent advances in coumarins and 1-azacoumarins as versatile biodynamic agents, Curr. Med. Chem. 13 (23) (2006) 2795–2818, https://doi.org/10.2174/092986706778521968.
[20] L. Tao, Y.T. Zhuo, Z.H. Qiao, J. Li, H.X. Tang, Q.M. Yu, Y.P. Liu, Prenylated coumarins from the fruits of Artocarpus heterophyllus with their potential anti-inflammatory and anti-HIV activities, Nat. Prod. Res. 36 (10) (2022) 2526–2533, https://doi.org/10.1080/14786419.2021.1913590.
[21] Y.H. He, X.F. Shang, H.X. Li, A.P. Li, C. Tang, B.Q. Zhang, Y.Q. Liu, Antifungal activity and action mechanism study of coumarins from Cnidium monnieri fruit and structurally related compounds, Chem. Biodivers. 18 (12) (2021) e2100633, https://doi.org/10.1002/cbdv.202100633.
[22] X.C. Yang, P.L. Zhang, K.V. Kumar, S. Li, R.X. Geng, C.H. Zhou, Discovery of unique thiazolidinone-conjugated coumarins as novel broad spectrum antibacterial agents, Eur. J. Med. Chem. 232 (2022) 114192, https://doi.org/10.1016/j.ejmech.2022.114192.

[23] V.P. Koyiparambath, K. Prayaga Rajappan, T.M. Rangarajan, A.G. Al-Sehemi, M. Pannipara, V. Bhaskar, B. Mathew, Deciphering the detailed structure–activity relationship of coumarins as Monoamine oxidase enzyme inhibitors—an updated review, Chem. Biol. Drug Des. 98 (4) (2021) 655–673, https://doi.org/10.1111/cbdd.13919.

[24] N. Bhattarai, A.A. Kumbhar, Y.R. Pokharel, P.N. Yadav, Anticancer potential of coumarin and its derivatives, Mini Rev. Med. Chem. 21 (19) (2021) 2996–3029, https://doi.org/10.2174/1389557521666210405160323.

[25] Z. Xu, Q. Chen, Y. Zhang, C. Liang, Coumarin-based derivatives with potential anti-HIV activity, Fitoterapia 150 (2021) 104863, https://doi.org/10.1016/j.fitote.2021.104863.

[26] L. Dinparast, S. Hemmati, G. Zengin, A.A. Alizadeh, M.B. Bahadori, H. S Kafil, S. Dastmalchi, Rapid, efficient, and green synthesis of coumarin derivatives via Knoevenagel condensation and investigating their biological effects, ChemistrySelect 4 (31) (2019) 9211–9215, https://doi.org/10.1002/slct.201901921.

[27] M. Martorell, N. Castro, M. Victoriano, X. Capó, S. Tejada, S. Vitalini, A. Sureda, An Update of Anthraquinone Derivatives Emodin, Diacerein, and Catenarin in Diabetes. Evidence-Based Complementary and Alternative Medicine, eCAM, 2021, https://doi.org/10.1155/2021/3313419.

[28] B.J. Deans, J. Just, J. Chhetri, L.K. Burt, J.N. Smith, N.L. Kilah, J.A. Smith, Pressurized hot water extraction as a viable bioprospecting tool: isolation of coumarin natural products from previously unexamined Correa (Rutaceae) species, ChemistrySelect 2 (8) (2017) 2439–2443, https://doi.org/10.1002/slct.201602006.

[29] M. Costa, T.A. Dias, A. Brito, F. Proença, Biological importance of structurally diversified Chromenes, Eur. J. Med. Chem. 123 (2016) 487–507, https://doi.org/10.1016/j.ejmech.2016.07.057.

[30] X.C. Yang, C.M. Zeng, S.R. Avula, X.M. Peng, R.X. Geng, C.H. Zhou, Novel coumarin aminophosphonates as potential multitargeting antibacterial agents against Staphylococcus aureus, Eur. J. Med. Chem. 245 (2023) 114891, https://doi.org/10.1016/j.ejmech.2022.114891.

[31] H.L. Qin, Z.W. Zhang, L. Ravindar, K.P. Rakesh, Antibacterial activities with the structure-activity relationship of coumarin derivatives, Eur. J. Med. Chem. 207 (2020) 112832, https://doi.org/10.1016/j.ejmech.2020.112832.

[32] L. Jiang, Y. Ma, Y. Chen, M. Cai, Z. Wu, Y. Xiong, J. Wang, Multi-target antibacterial mechanism of ruthenium polypyridine complexes with anthraquinone groups against Staphylococcus aureus, RSC Med. Chem. 14 (4) (2023) 700–709, https://doi.org/10.1039/D2MD00430E.

[33] H.A. Alhadrami, W.H. Abdulaal, H.M. Hassan, N.A. Alhakamy, A.M. Sayed, In silico-based discovery of natural anthraquinones with potential against multidrug-resistant E. coli, Pharmaceuticals 15 (1) (2022) 86, https://doi.org/10.3390/ph15010086.

[34] N. George, B. Al Sabahi, M. AbuKhader, K. Al Balushi, M.J. Akhtar, S.A. Khan, Design, synthesis and in vitro biological activities of coumarin linked 1,3,4-oxadiazole hybrids as potential multi-target directed anti-Alzheimer agents, J. King Saud Univ. Sci. 34 (4) (2022) 101977, https://doi.org/10.1016/j.jksus.2022.101977.

[35] L. Lu, X. Zhang, Y. Kang, Z. Xiong, K. Zhang, X. Xu, H. Li, Novel coumarin derivatives as potential tyrosinase inhibitors: synthesis, binding analysis and biological evaluation, Arab. J. Chem. 16 (6) (2023) 104724, https://doi.org/10.1016/j.arabjc.2023.104724.

[36] S. Masuri, B. Era, F. Pintus, E. Cadoni, M.G. Cabiddu, A. Fais, T. Pivetta, Hydroxylated coumarin-based thiosemicarbazones as dual antityrosinase and antioxidant agents, Int. J. Mol. Sci. 24 (2) (2023) 1678, https://doi.org/10.3390/ijms24021678.

[37] V. Loganathan, I. Akber, M.Z. Ahmed, ShadabKazmi, G. Raman, Spectroscopic Studies on the Antioxidant and Anti-tyrosinase Activities of Anthraquinone Derivatives, Journal of King Saud University - Science, 2023 102971, https://doi.org/10.1016/j.jksus.2023.102971.

[38] H.J. Zeng, D.Q. Sun, S.H. Chu, J.J. Zhang, G.Z. Hu, R. Yang, Inhibitory effects of four anthraquinones on tyrosinase activity: insight from spectroscopic analysis and molecular docking, Int. J. Biol. Macromol. 160 (2020) 153–163, https://doi.org/10.1016/j.ijbiomac.2020.05.193.

[39] A.M. Muddathir, K. Yamauchi, I. Batubara, E.A.M. Mohieldin, T. Mitsunaga, Anti-tyrosinase, total phenolic content and antioxidant activity of selected Sudanese medicinal plants, South Afr. J. Bot. 109 (2017) 9–15, https://doi.org/10.1016/j.sajb.2016.12.013.

[40] H.X. Cui, F.F. Duan, S.S. Jia, F.R. Cheng, K. Yuan, Antioxidant and Tyrosinase Inhibitory Activities of Seed Oils from Torreya grandis Fort, ex Lindl, BioMed Research International, 2018, https://doi.org/10.1155/2018/5314320.

[41] L. Xia, A. Idhayadhulla, Y.R. Lee, Y.J. Wee, S.H. Kim, Anti-tyrosinase, antioxidant, and antibacterial activities of novel 5-hydroxy-4-acetyl-2,3-dihydronaphtho[1,2-b] furans, Eur. J. Med. Chem. 86 (2014) 605–612, https://doi.org/10.1016/j.ejmech.2014.09.025.

[42] I. Ouerghemmi, I.B. Rebey, F.Z. Rahali, S. Bourgou, L. Pistelli, R. Ksouri, M.S. Tounsi, Antioxidant and antimicrobial phenolic compounds from extracts of cultivated and wild-grown Tunisian Ruta chalepensis, J. Food Drug Anal. 25 (2) (2017) 350–359, https://doi.org/10.1016/j.jfda.2016.04.001.

[43] F.S. Al-Khattaf, A. Mani, A.A. Hatamleh, I. Akbar, Antimicrobial and cytotoxic activities of isoniazid connected menthone derivatives and their investigation of clinical pathogens causing infectious disease, Journal of Infection and Public Health 14 (4) (2021) 533–542, https://doi.org/10.1016/j.jiph.2020.12.033.

[44] K. Selvaraj, A. Daoud, S. Alarifi, A. Idhayadhulla, Tel-Cu-NPs catalyst: synthesis of naphtho [2, 3-g] phthalazine derivatives as potential inhibiters of tyrosinase enzymes and their investigation in kinetic, molecular docking, and cytotoxicity studies, Catalysts 10 (12) (2020) 1442, https://doi.org/10.3390/catal10121442.

[45] R.S. Kumar, M. Moydeen, S.S. Al-Deyab, A. Manilal, A. Idhayadhulla, Synthesis of new morpholine-connected pyrazolidine derivatives and their antimicrobial, antioxidant, and cytotoxic activities, Bioorg. Med. Chem. Lett 27 (1) (2017) 66–71, https://doi.org/10.1016/j.bmcl.2016.11.032.

[46] S. Chidambaram, M.A. El-Sheikh, A.H. Alfarhan, S. Radhakrishnan, I. Akbar, Synthesis of novel coumarin analogues: investigation of molecular docking interaction of SARS-CoV-2 proteins with natural and synthetic coumarin analogues and their pharmacokinetics studies, Saudi J. Biol. Sci. 28 (1) (2021) 1100–1108, https://doi.org/10.1016/j.sjbs.2020.11.038.

[47] L. Velmurugan, A. Ahamed, A. Idhayadhulla, S. Alarifi, R. Gurusamy, Antioxidant, Antibacterial, and Cytotoxic Activities of Cimemoxin Derivatives and Their Molecular Docking Studies, Journal of King Saud University-Science, 2023 103011, https://doi.org/10.1016/j.jksus.2023.103011.

[48] J. Mullaivendhan, A. Ahamed, G. Raman, S. Radhakrishnan, I. Akber, Synthesis and antibacterial activity of pyrano[3,2-g]chromene-4,6-dione derivatives and their molecular docking and DFT calculation studies, Results in Chemistry (2023) 101175, https://doi.org/10.1016/j.rechem.2023.101175.

[49] Li Lu, Xin Zhang, Yu Kang, Zhuang Xiong, Kun Zhang, Xuetao Xu, Liping Bai, Hongguang Li, Novel coumarin derivatives as potential tyrosinase inhibitors: synthesis, binding analysis and biological evaluation, Arab. J. Chem. 16 (6) (2023) 104724, https://doi.org/10.1016/j.arabjc.2023.104724.

[50] Hua-Li Qin, Zai-Wei Zhang, Lekkala Ravindar, K.P. Rakesh, Antibacterial activities with the structure-activity relationship of coumarin derivatives, Eur. J. Med. Chem. 207 (2020) 112832, https://doi.org/10.1016/j.ejmech.2020.112832.

[51] G.A. Kemegne, P. Mkounga, J.J. Essia Ngang, S.L. Sado Kamdem, A.E. Nkengfack, Antimicrobial structure activity relationship of five anthraquinones of emodine type isolated from Vismia laurentii, BMC Microbiol. 17 (1) (2017) 1–8, https://doi.org/10.1186/s12866-017-0954-1.