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The *in vitro* Effects of New Albocarbon-based Coumarins on Blood Glucose-controlling Enzymes

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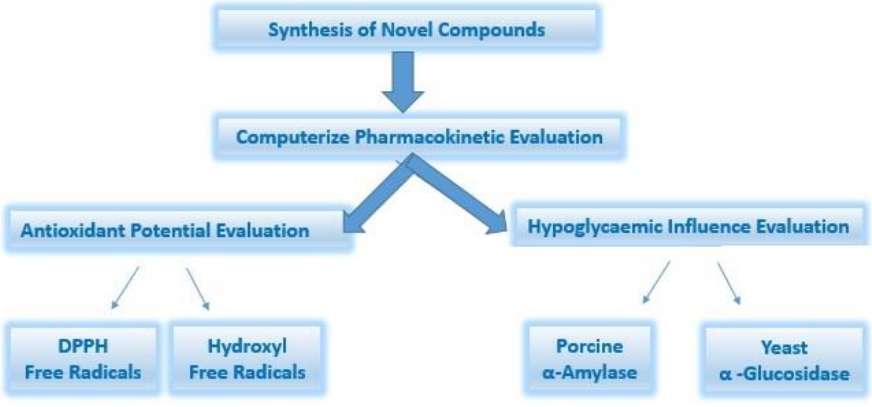
ABSTRACT

The majority of the world's most hazardous pathologies are linked to the oxidative damaging effect of free moieties. One of the diseases associated with these damaging radicals is diabetes. This disease is widely distributed among people of all ages, with the elderly being the most affected. Therefore, it is essential to conduct comprehensive investigations in order to promote the creation of the novel free radical-housing and hypoglycemic compounds. This study involves the synthesis of eight novel albocarbon-based coumarins, which were confirmed by various spectrophotometers. Their hypoglycemic and free radical-housing effects were analyzed. The pharmacokinetic profile was checked in silico using pre-ADMET, known as a free online program. The hypoglycemic influence was tested against two types of the blood glucose-controlling enzymes. In addition, the new compounds' potency index was measured. The free radical-housing potential was analyzed by testing these coumarins' ability to scavenge DDPT and hydroxyl harmful radicals. Pharmacokinetic studies demonstrated that the synthesized albocarbon-based coumarins penetrate the gastrointestinal mucosa very well, and the majority of these compounds penetrate the blood-brain barrier only slightly. These findings suggest the good oral bioavailability along with low neurological toxicity profiles. The investigation of the hypoglycemic influence of these new compounds revealed that they had a less potent enzyme inhibition capacity compared to the standard, with LY5 being the most powerful one. Besides, the assessment of the free radical-housing potential of these synthesized albocarbon-based coumarins also indicated that all of them were less active than the reference. Among them, LY0 was the strongest free radical-housing compound from these recognitions, along with the safety and good pharmacokinetic parameters in accordance with the computer-based study. The researchers believed that these new albocarbon-based coumarins can be applied for the creation of new successful drugs with hypoglycemic and free radical-housing effects which can help in the modulation of much serious pathology.

GRAPHICAL ABSTRACT



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Introduction

The idea of the oxidative damaging effect has been adopted since the eighties of the last century as the main cause of many illnesses which are considered as a nightmare for humanity. This kind of stress is caused by either the increased activity of harmful free radical species or the ineffectiveness of the body's defensive mechanisms as a result of a decrease or even lack of powerful antioxidant capability. Many life-threatening disorders, such as malignancy, atherosclerosis, vascular diseases, diabetes, coronary artery diseases, and many other diseases, are linked to these damaging free radicals. Among these diseases, diabetes (DM) is considered the most disabling disorder that affects the patient's quality of life and sometimes leads to death if it is not well controlled. DM is a lifelong illness which affects 3.6–5.3% of the populace in industrialised nations, with type 2 DM accounting for 86–89% of cases. Both DM types could lead to major life-threatening consequences such as atherosclerosis, neuropathy, retinopathy, and nephropathy, which may lead to the coronary artery disease, blindness, and renal failure. Around 200 million individuals around the world are diabetic, especially the elderly, who represent more than 30% of patients in affluent nations. Dietary control and physical activity are front-line measures of management. If they are not enough to control the condition, hypoglycaemic medications are prescribed to improve glycaemic control and prevent diabetes complications [1–4].

Coumarins constitute an interesting group of compounds. Researchers have been focused for decades on studying their crucial biological features and preparing analogues for therapeutic applications. Coumarins are a class of heterocyclic compounds with a benzopyrone structure. These molecules offer a number of appealing properties which make them an important part of drug research and innovation. In addition to their multifarious bioactivities, they have a simple structure, low molecular weight, good bioavailability, excellent safety profile, and high solubility in many solvent systems. Their skeletons have been employed as a precursor in the preparation of biologically active heterocyclic compounds with anti-inflammatory, anti-microbial, anti-tumour, painkilling, antioxidant, hypoglycaemic, anticoagulant, and many other activities [5–12].

Albocarbon-based coumarins are considered promising compounds in the future for the production of modern drugs with favourable biological activities. Albocarbon-based coumarins are those with bonding phenyl groups to either 3,4-, 5,6-, 6,7-, or 7,8-positions that result in a plethora of appealing bioactivities. They are a prospective family of new compounds due to the make-up of their structure with an expanded π-electron arrangement. F, G, and H, subfamilies of albocarbon-based coumarins and their related agents contain both an electron-acceptor and an electron donor which are conjugated electronically through the compound's backbone. They are of particular significance owing to their charge-transfer nature intramolecularly. This resulted in great attention to their use as scaffolds for new drug developmental approaches [13–22].

In this work, a number of the novel albocarbon-based coumarins have been synthesised, and then tested for their hypoglycaemic as well as free radical-housing effects. Begin by synthesising **LY0** from 6-amino-7-chloronaphthalen-2-ol. **LY0** is then used to create **LY1,** which further produces a series of derivatives by reaction with different phenolic derivatives. These compounds were assessed for possible hypoglycaemic influence against two different enzymes. The free radical-housing potential was examined for these compounds against DPPH and hydroxyl harmful radicals. The pharmacokinetic data for our albocarbon-based coumarins was studied via computer using the pre-ADMET, a free online programme.

Materials and Methods

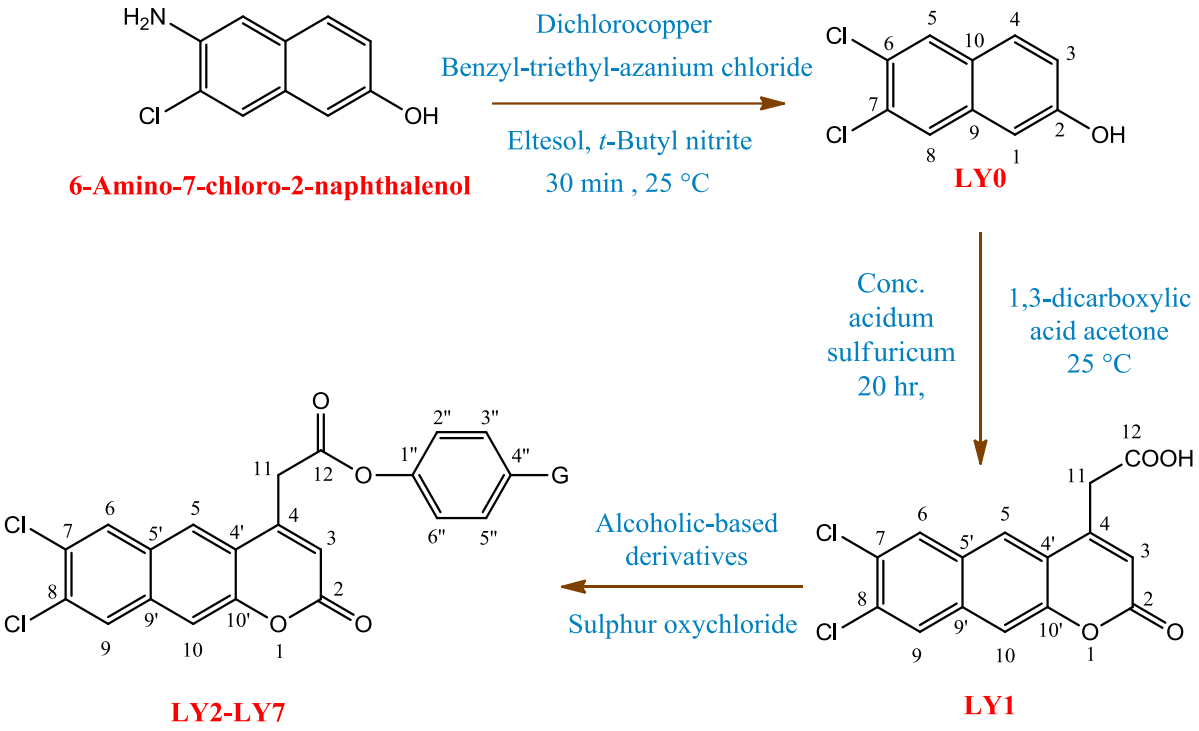
Instruments and Chemicals

Chemicals, reagents, and solvents utilised in this study were sourced from the reputable international suppliers and used without further purification. The melting points (mp) of the synthesised composites were determined using the USP-dependent capillary technique on an

electrothermal CIA 9300 apparatus. To ensure the purity of the produced agents and the fulfilment of reactions, the thin-layer chromatography (TLC) is being utilised, employing typical silica gel aluminium-based plates, and a combination of chloroform ($CHCl_3$) as well as propanone (4:1) as an eluting solution. The synthetic composite UV scanning was done by UV-1600PC UV-Vis. Bruker α-ATR-FTIR was used for FTIR scanning. Testing of ^{1}H-and ^{13}C-NMR spectra was done by the Bruker Avance DRX-300 MHz spectrophotometer.

Synthetic Scenario

Scheme 1 displays the steps for the synthesis of **LY0** and its based coumarins compounds starting from 6-amino-7-chloro-2-naphthol.



LY2: G= OCH_3; **LY3**: G= CH_3; **LY4**: G= F;
LY5: G= Cl; **LY6**: G= Br; **LY7**: G= I

Scheme 1: Chemical synthesis of LY0 and its based compounds

Synthesis of LY0

A combination of 6.00 mmol of eltesol (1.03 g), 5.00 mmol of 6-amino-7-chloro-2-naphthol (0.96 g), 6.00 mmol of benzyl-triethyl-azanium chloride (1.37 g), 0.22 mmol of dichlorocopper (0.03 g), and 6.00 mmol of *t*-butyl nitrite (0.71 mL), were mixed and milled for 30 minutes at 25 °C using a mortar and pestle. Water and ether were utilized to rinse the mortar separately, using 20 mL of each three times. The prepared crude was recrystallized from aqueous ethyl alcohol after vaporizing the organic phase [23,24].

6,7-Dichloro-2-naphthol (LY0): White crystals; Yield= 52% (0.55 g); mp=132-134 °C; R_f = 0.16; λ_{max} (ethanol)= 267 nm; IR ν_{max} (cm^{-1}): 915 (s, C-Cl), 1561 (s, aryl C=C), 2957 (w, alkyl C-H), 3076 (m, aryl C-H), and 3300 (broader band, naphtholic O-H); ^{1}H-NMR (300 MHz, ppm, DMSO-d_6): δ= 5.56 (1H, s, OH), 7.22 (1H, d, H-3, *J*=9Hz), 7.55 (1H, s, H-1), 7.62 (1H, s, H-8), 7.72 (1H, s, H-5), and 8.15 (1H, d, H-4, *J*=9Hz); ^{13}C-NMR (75 MHz, ppm, DMSO-d_6): δ= 111.4 (CH, C-1), 120.1 (CH, C-3), 127.3 (CH, C-8), 128.3 (CH, C-5), 128.7 (C, C-6), 129.8 (C, C-10), 131.4 (CH, C-4), 132.5 (C, C-7), 135.5 (C, C-9), and 158.1 (C, C-2).

Synthesis of LY1

In a conical flask, 25 mL of concentrated dihydrogen sulfate were cooled using an ice bath. When the temperature dropped below 10 °C, 13.22 mmol of **LY0** (2.75 g) and 15.00 mmol of

1,3-dicarboxylic acid acetone (3.5 mL) were mixed, placed in a separatory funnel, and added drop by drop to the chilled dihydrogen sulfate with stirring. During the addition, attention should be paid to keep the mixture temperature below 10 °C. After completing the addition, the obtained mixture remained at 25 °C with continuous stirring for 20 hours. Then, it was poured into a beaker containing water and crushed ice and mixed. The formed precipitate was filtered using a filter paper, washed with cold water, and allowed to dry at 25 °C, affording **LY1** compound [25,26].

11-(7,8-Dichloro-2-oxo-2*H*-benzo[*g*]chromen-4-yl)acetic acid (**LY1)**: Pale yellowish powder; Yield= 48% (0.78 g); mp=154-156 ^{o}C; R_f = 0.11; λ_{max} (ethanol)= 411nm; IR ν_{max} (cm^{-1}): 941 (s, aryl C-Cl), 1548 (m, aryl C=C), 1590 (s, *cis* C=C), 1692 (s, dimeric carboxylic acid C=O), 1734 (s, cyclic C=O ester), 2891 (w, alkyl C-H), 3015 (broader band, carboxylic acid O-H), 3062 (m, *cis* C-H); ^{1}H-NMR (300 MHz, ppm, DMSO-d_6): δ= 3.12 (2H, s, H-11), 6.35 (1H, s, H-3), 7.12 (1H, s, H-10), 7.60 (1H, s, H-9), 7.72 (1H, s, H-6), 7.92 (1H, s, H-5), and 11.09 (1H, s, H-12); ^{13}C-NMR (75 MHz, ppm, DMSO-d_6): δ= 30.9 (CH_2, C-11), 113.4 (CH, C-10), 115.8 (CH, C-3), 125.1 (CH, C-5), 125.5 (CH, C-9), 126.0 (C, C-7), 127.5 (C, C-4'), 128.1 (C, C-5'), 129.0 (CH, C-6), 130.1 (C, C-8), 132.6 (C, C-9'), 151.8 (C, C-10'), 153.0 (C, C-4), 162.2 (C, C-2), and 173.1 (C, C-12).

Synthesis of the Albocarbon-Based Coumarins LY2-LY7

A two-nick round-bottomed flask containing a mixture of 25 mL of the refreshed sulphur oxychloride and 5.00 mmol of **LY1** (1.60 g) was placed in a salt-ice bath. A stopper containing blue litmus test paper was used to confine the side-nick, while a condenser was attached to the centre. Then, the mixture was stirred gently under anhydrous conditions for 30 minutes, followed by stirring for an additional 30 minutes at 25 °C. After that, the obtained mixture was refluxed for 3 hours. A litmus test paper, which was replaced every 30 minutes, was used to detect the reaction's progress. The excess of sulphur oxychloride was distilled out when the colour of the litmus paper remained blue. The **LY1** acyl compound remained in the concave of the flask as a white solid substance [27,28].

Under water-free conditions, a solution of 4.80 mmol of phenolic derivative with 1 mL of azine in 50 mL of anhydrous 1,1'-oxydiethane was poured into the same flask and stirred for 30 minutes at 25 °C. The refluxing of the mixture is continued for some time until the colour of the litmus paper remains blue. After that, 50 mL of water was added to the mixture. The organic layer was then isolated, dried, and vaporised. A 1:2 mixture of propyldihydride and salesthin was used for the recrystallization to obtain the **LY1** compound [29,30]. In the Results and Discussion section, the spectrophotometrically collected data from ^{1}H- and ^{13}C-NMR are listed and discussed.

4''-Methoxyphenyl-11-(7,8-dichloro-2-oxo-2*H*-benzo[*g*]chromen-4-yl)acetate(**LY2**)**:** Off-white powder; Yield= 78% (1.08 g); mp= 146-148 °C; R_f = 0.32; λ_{max} (ethanol)= 345 nm; IR ν_{max} (cm^{-1}): 985 (s, aryl C-Cl), 1216 and 1144 (s, aryl-alkyl ether C-O-C), 1595 (s, aryl C=C), 1665 (s, *cis* C=C), 1710 (s, acyclic C=O ester), 1731 (s, cyclic C=O ester), 2821 (w, alkyl C-H), 2917 (w, methoxy C-H), and 3096 (m, *cis* C-H).

4''-Tolyl-11-(7,8-dichloro-2-oxo-2*H*-benzo[*g*]chromen-4-yl)acetate (**LY3**)**:** Pale yellowish powder; Yield=72% (1.11 g); mp= 138-140 °C; R_f = 0.30; λ_{max} (ethanol)= 398 nm; IR ν_{max} (cm^{-1}): 985 (s, aryl C-Cl), 1597 (s, aryl C=C), 1668 (s, *cis* C=C), 1713 (s, acyclic C=O ester), 1733 (s, cyclic C=O ester), 2877 and 2818 (w, alkyl C-H), and 3090 (m, *cis* C-H).

***4*''-Fluorophenyl-11-(7,8-dichloro-2-oxo-2*H*-benzo[*g*]chromen-4-yl)acetate** (**LY4**)**:** White powder; Yield= 42% (1.13 g); mp= 144-148 °C; R_f = 0.21; λ_{max} (ethanol)= 316 nm; IR ν_{max} (cm^{-1}): 986 (s, aryl C-Cl), 1077 (s, aryl C-F), 1597 (s, aryl C=C), 1666 (s, *cis* C=C), 1711 (s, acyclic C=O ester), 1733 (s, cyclic C=O ester), 2820 (w, alkyl C-H), and 3070 (m, *cis* C-H).

4''-Chlorophenyl-11-(7,8-dichloro-2-oxo-2*H*-benzo[*g*]chromen-4-yl)acetate (**LY5**)**:** Off-white powder; Yield= 43% (1.03 g); mp= 133-135 °C; R_f = 0.24; λ_{max} (ethanol)= 374 nm; IR ν_{max} (cm^{-1}): 985 (s, aryl C-Cl), 1595 (s, aryl C=C), 1667 (s, *cis* C=C), 1710 (s, acyclic C=O ester), 1730 (s,

cyclic C=O ester), 2820 (w, alkyl C-H), and 3068 (m, *cis* C-H).

4''-Bromophenyl-11-(7,8-dichloro-2-oxo-2*H*-benzo[*g*]chromen-4-yl)acetate (LY6): Pale yellowish powder; Yield= 42% (1.1 g); mp= 123-125 °C; R_f = 0.28; λ_{max} (ethanol)= 409 nm; IR ν_{max} (cm^{-1}): 900 (s, C-Br), 986 (s, aryl C-Cl), 1593 (s, aryl C=C), 1664 (s, *cis* C=C), 1709 (s, acyclic C=O ester), 1732 (s, cyclic C=O ester), 2819 (w, alkyl C-H), and 3066 (m, *cis* C-H).

4''-Iodophenyl-11-(7,8-dichloro-2-oxo-2*H*-benzo[*g*]chromen-4-yl)acetate (LY7): Gray-like powder; Yield= 43% (1.3 g); mp= 112-114 °C; R_f = 0.29; λ_{max} (ethanol)= 326 nm; IR ν_{max} (cm^{-1}): 800 (s, aryl C-I), 986 (s, aryl C-Cl), 1592 (s, aryl C=C), 1661 (s, *cis* C=C), 1711 (s, acyclic C=O ester), 1733 (s, cyclic C=O ester), 2823 (w, alkyl C-H), and 3064 (m, *cis* C-H).

Computerized Pharmacokinetic Studies

By using the web application pre-ADMET (https://preadmet.qsarhub.com/adme/), the pharmacokinetic characteristics of the synthesised albocarbon-based coumarins **LY0-LY7** were analysed *in silico*. This analysis involved their absorption, distribution, metabolism, and excretion [31,32].

Bioactivity Analysis In vitro

Hypoglycemic Influence Assessment

The suppressive potential of the synthesised compounds against two phenotypes of the enzyme, porcine α-amylase and yeast α-glucosidase, which are important in managing glucose levels in the blood, was analysed *in vitro*. To describe this impact, the RC_{50} measurement is used, which is the dosage of the synthesised compound required to suppress enzymatic activity by 50% under the experimental conditions. Different doses of the compound under investigation (2 mg/mL) were generated prior to performing these two experiments. With MeOH as a solvent, concentration levels of 1000, 800.00, 400.00, 200.00, 100.00, 50.00, and 25.00 µM were generated [33–37].

Assessment of the Yeast α -Glucosidase (YG) Receding Influence

20 µL of the specified concentration of the synthesised compound, along with the same volume of the reference solution, both containing 0.1 unit/mL of the YG enzyme, were combined together. In a K_3PO_4 (pH 6.8) solution, *para*-nitrophenyl glucopyranoside was solubilized to obtain the desired concentration level of 375 µM. After that, 40 µL of this solution was mixed with the compound-enzyme combination, and the resultant mixture was kept for 30 minutes at 37 °C. The reaction was ended by adding a K_3PO_4 solution containing 80 µL of carbonic acid disodium salt (0.2 M) to the combination. The compound's ability to recede the activity of the enzyme was measured using a colorimetric method at 405 nm, and the receding percent was determined using the following equation:

$$YG\ receding\ \% = Abs_{control} - Abs_{sample} \div Abs_{control} \times 100$$

The standard used was acarbose (AC). The reference solution was made in the same way as the examined solution, except using DMSO instead of the synthesised compound [38].

Assessment of Porcine α-Amylase (PA) Abating Influence

20 µL of the specified concentration of the synthesised compound, along with the same volume of the reference solution, both containing 2 units/mL of the PA enzyme, were combined together. The starch substrate was dispersed in K_3PO_4 buffer (pH 6.8) to obtain 2 mL of a 0.5 mM concentration level. Then, the evaluated combination was kept for 10 minutes at 25 °C. The reaction was ended by adding 2 mL of a solution of 0.4 M aqueous sodium hydrate, 12% anhydrous L-potassium sodium tartrate, and 1% of *o*-dinitrocarboxylphenol. The resulting sample was heated for 15 min. in a water bath, then H_2O was used as a thinner liquid to obtain 10 mL as the desired volume. After that, the temperature of the combination was allowed to reach 25 °C using an ice bath. The compound combination's ability to abate enzymatic activity was determined using a colorimetric method at 540 nm. The abating percent was estimated using the following equation:

$$PA\ abating\ \% = Abs_{control} - Abs_{sample} \div Abs_{control} \times 100$$

The standard used was AC. The reference solution was made in the same way as the examined solution, except using DMSO instead of the synthesised compound [39].

Free Radical-Housing Potential Assessment

The ability of the synthesised compounds to eliminate DPPH (1,1-diphenyl-2-picryl-hydrazyl) free radicals and hydroxyl moieties, as well as donate an electron in redox reactions, was measured using vitamin C (L-ascorbic acid, L-AA) as a reference. Using MeOH as a solvent system, a series of seven concentration solutions were produced from the compound under investigation (1 mg/mL), which were: 400.00, 200.00, 100.00, 50.00, 25.00, 12.50, and 6.25 micrograms per millilitre. Several diluted concentrations of L-AA with MeOH were prepared, including 200, 100, 50, 25, 12.5, and 6.25 micrograms per millilitre. The L% (liquidating percentage) estimates of the given concentrations were calculated for each compound using this equation:

$$L(\%) = Abs_{control} - Abs_{sample} \div Abs_{control} \times 100$$

The absorptions of the examined and reference samples at a specific wavelength were denoted by the symbols "Abs_{sample}" and "$Abs_{control}$", respectively.

The concentration of the tested compound which can neutralise half of the free radicals or reduce half of the oxidised iron particles is known as the liquidating activity of the compound (LC_{50}). This measurement was created by using a non-linear regression to depict the relationship between L percent value and its associated logarithmic concentration [40,41].

Assessment of Liquidating Assay of DPPH-Free Radical

A mixture of 1.5 mL of the tested compound with 0.5 mL of a methanolic DPPH solution at a particular concentration (0.1 mM) was prepared. The mixed solution was overlaid with aluminium platelets to hide it from sunlight. Then, the coated mixture was kept for 30 minutes at 25 °C. At 517 nm, the mixture's ability to eliminate the violet colour of the DPPH was measured colorimetrically. To make the reference solution, 1.5 mL of MeOH were combined with 0.5 mL of methanolic DPPH [42,43].

Assessment of Liquidating Assay of Hydroxyl-Free Radical

A 1.5 mL solution of the tested compound at the assigned concentration was mixed with 2.4 mL of 0.2 M K_3PO_4 (pH 7.8). The combination was then treated with 0.17 M peroxan (150 µL), 0.001 M $FeCl_3$ (60 µL), and 0.001 M 1,10-Phenanthrolin-10-ium iodide (90 µL). The obtained solution was kept at 25 °C for 5 minutes until being spectrophotometrically trialled at 560 nm. All of the aforesaid components were included in the reference solution, except that employed buffer type was used instead of the tested compound [44,45].

Results and Discussion

Scenario of the Chemical Synthesis

The schematic chemical synthesis for **LY0-LY7** compounds was depicted in Scheme 1. Firstly, **LY0** was synthesised by reacting 6-amino-7-phenolchloro-2-naphthol, benzyltriethyl-ammonium chloride, dichlorocopper, tertbutyl nitrite, and eltesol together by an aromatic nucleophilic substitution reaction. Liquical was used for drying the organic face, followed by the sample's recrystallization from aqueous ethyl alcohol [46,47].

Concerning **LY1**, which is the precursor of **LY2**–**LY7** compounds, the synthesis method involves the condensation of **LY0** compound and 1,3-dicarboxylic acid acetone with the aid of concentrated H_2SO_4 via a Pechmann type condensation reaction. This reaction is considered the most widely used one for the synthesis of coumarin-related compounds. With the aid of a condensing agent, the starting materials utilised in this reaction are simple and include β-carbonyl group-containing ester and phenol. The nature of the resulted product and its yield depend on the reactant's reactivity and type. The last step, the synthesis of **LY2**–**LY7** compounds, included converting the carboxylic acid moiety of the **LY1** compound into an acid chloride-derived product by reacting with sulphur oxychloride. The reaction of the produced intermediate with phenolic derivatives leads to the formation of the final compounds. Each one had a different group substituted at the *para*-position of the benzene ring. These groups are methoxy for **LY2**, methyl for **LY3**, fluoride for **LY4**, chloride for **LY5**, bromide for **LY6**, and

iodide for **LY7** [48,49]. Only a few studies exist in the literature aiding the use of halophenol as a starting material in this type of reaction because the nucleophilicity of this form of phenol is poor due to the deactivation effect of the halogen attached to it. In this work, the yields of the synthesized **LY2**–**LY7** compounds were improved by the precise monitoring of the reaction conditions [50–52].

Computer Aided Investigations of Pharmacokinetic Properties

As drug discovery and development are very complex and diverse processes, a number of *in silico* evaluations have been created to offer data on the pharmacokinetic characteristics of the compounds under investigation [51,53]. The examination of the parameters listed in Table-1 revealed a number of interesting points, including that these novel albocarbon-based coumarins have high HIA percentages ranging from 97.69% to 100.00%, indicating a high theoretical oral bioavailability. They have moderate Caco2 cell permeability with P-glycoprotein (Pggp-1) inhibiting capability. These parameters can indicate good intestinal absorption for these compounds [54]. On the other hand, the inhibitory capacity of these albocarbon-based coumarins against the CYP2C9 enzyme could suggest good anti-inflammatory activity as this enzyme produces eicosatrienoic acid epoxide, which is an inflammatory signalling molecule, from arachidonic acid metabolism [55,56]. While the inhibition of CYP3A4 by these compounds (except **LY1**) can result in a decrease in the metabolism of some toxins, including the parent drug, that leads to its accumulation and an increased risk of toxicity. Likewise, this action can affect the metabolism of other drugs taken simultaneously with these compounds, leading to drug-drug interaction [57]. Additionally, the produced albocarbon-based coumarins have a very high plasma protein binding capacity, which can result in a decrease in the volume of distribution and a reduction in the half-life of these compounds [58]. Finally, the poor penetration across the blood-brain barrier (except for **LY0**) might mean that these compounds will have low toxicity as a result of a lack of neurological side effects. This limited number of adverse effects is critical in determining CNS toxicity [59].

Table 1: Computer based pharmacokinetic parameters for the synthesized **LY0-LY7** compounds

Compound symbol	Lipinski rule	BBB-P	HIA	CYP3A4	CYP2D6	CYP2C9	PPB	Pggp-1	Caco2-P
LY0	Yes; 0 violation	6.61	100.00	Inhibitor	Non	Inhibitor	99.0	Inhibitor	38.41
LY1	Yes; 0 violation	0.06	97.75	Non	Non	Inhibitor	95.7	Inhibitor	15.19
LY2	Yes; 1 violation: MLOGP>4.15	0.11	97.69	Inhibitor	Non	Inhibitor	96.2	Inhibitor	36.42
LY3	Yes; 1 violation: MLOGP>4.15	0.33	97.87	Inhibitor	Non	Inhibitor	97.5	Inhibitor	36.40
LY4	Yes; 1 violation: MLOGP>4.15	0.14	97.82	Inhibitor	Non	Inhibitor	100	Inhibitor	36.26
LY5	Yes; 1 violation: MLOGP>4.15	0.21	98.04	Inhibitor	Non	Inhibitor	100	Inhibitor	38.99
LY6	Yes; 1 violation: MLOGP>4.15	0.23	98.15	Inhibitor	Non	Inhibitor	100	Inhibitor	36.91
LY7	No; 2 violations: MW>500, MLOGP>4.15	0.23	98.31	Inhibitor	Non	Inhibitor	100	Inhibitor	35.56

*Chemical Backbones of the Synthetic Albocarbon-Based Coumarins **LY2-LY7***

In addition to the physical properties and IR data analysis listed in the experimental section, the chemical backbones of the albocarbon-based coumarins **LY2-LY7** were established by investigating their NMR outcomes. The findings revealed that these albocarbon-based coumarins share a core structure, as displayed in Figure 1.

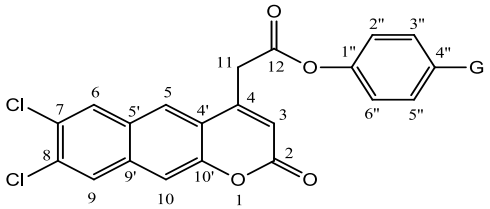


Figure 1: The shared core structure of the albocarbon-based coumarins LY2-LY7

The collected NMR scores and their interpretation regarding this central structure are illustrated below. The ^{1}H-NMR (300 MHz, ppm, DMSO-d_6) chemical shifts included 7.92 (1H, s, H-5), 7.72 (1H, s, H-6), 7.60 (1H, s, H-9), 7.12 (1H, s, H-10), 6.35 (1H, s, H-3), and 3.12 (2H, s, H-11). While the ^{13}C-NMR (75 MHz, ppm, DMSO-d_6) chemical shifts involved 169.5 (C, C-12), 162.2 (C, C-2), 153.0 (C, C-4), 151.8 (C, C-10'), 132.6 (C, C-9'), 130.1 (C, C-8), 129.0 (CH, C-6), 128.1 (C, C-5'), 127.5 (C, C-4'), 126.4 (CH, C-9), 125.1 (CH, C-5), 124.0 (C, C-7), 115.8 (CH, C-3), 113.4 (CH, C-10), and 28.3 (CH_2, C-11).

The differences in the NMR spectra of the albocarbon-based coumarins **LY2-LY7** involving those related to their ^{1}H- and ^{13}C-NMR are reported in Tables 2 and 3, respectively.

Table 2: The variation in the ^{1}H-NMR spectra of the albocarbon-based coumarins **LY2**-**LY7** compared to their core structure

Compound symbol	H-2'',6'' (2H, d, *J*= 6Hz, ppm)	H-3'',5'' (2H, d, *J*= 6Hz, ppm)	Variable functional group at position 4''
LY2	6.74	7.01	4.12 ppm (3H, s, OCH_3)
LY3	7.02	7.25	2.75 ppm (3H, s, CH_3)
LY4	7.26	7.04	----------
LY5	7.35	7.53	----------
LY6	6.95	7.77	----------
LY7	6.83	7.85	----------

Table 3: The variation in the ^{13}C-NMR spectra of the albocarbon-based coumarins **LY2**-**LY7** compared to their core structure

Compound symbol	C-1'' (C, ppm)	C-2'' and 6'' (CH, ppm)	C-3'' and 5'' (CH, ppm)	C-4'' (C, ppm)	Variable functional group at position 4''
LY2	144.6	112.3	120.1	156.4	51.1 ppm (CH_3, OCH_3)
LY3	149.3	119.0	122.0	134.2	24.1 ppm (CH_3, CH_3)
LY4	147.9	120.7	108.5	158.7	----------
LY5	150.4	120.5	122.9	132.0	----------
LY6	151.3	121.3	123.6	118.5	----------
LY7	151.2	120.7	129.6	93.0	----------

Assessment of Hypoglycemic Influence

DM is becoming one of the most serious and disabling disorders in the world. The strategy to manage this aberrant metabolic situation is to interfere with its underlying pathophysiological causes. As a result, the potential of the synthesised albocarbon-based coumarins to perform as hypoglycaemic agents was explored. The suppressive ability of these synthesised compounds was tested against two enzymes

involved in glycaemic control, namely YG and PA. The results which are obtained from these tests are listed in Table 4. Diagrams representing the potential of these novel albocarbon-based coumarins against these two enzymes as well as the potency index for these compounds as compared to AC are depicted in Figures 2, 3, and 4.

Table 4: The hypoglycemic influence of LY0-LY7

Compound's symbol	Assay and results				Potency index			
	YG receding influence RC_{50}±SD		PA abating influence RC_{50}±SD		YG		PA	
AC		283.01±0.90		263.28±0.96		100.00%		100.00%
LY0		385.08±0.99		389.34±0.98		63.93%		52.12%
LY1		392.82±0.97		423.62±0.95		61.20%		39.10%
LY2		373.22±1.03		346.12±0.94		68.12%		68.54%
LY3		374.98±1.04		352.09±0.96		67.50%		66.27%
LY4		366.01±1.06		328.98±1.02		70.67%		75.05%
LY5		361.14±0.92		324.46±1.06		72.39%		76.76%
LY6		389.76±0.98		411.65±0.93		62.28%		43.65%
LY7		397.23±1.08		439.01±1.09		59.64%		33.25%

RC_{50} was measured in µg/mL, and every run was made in a triplet (n=3).

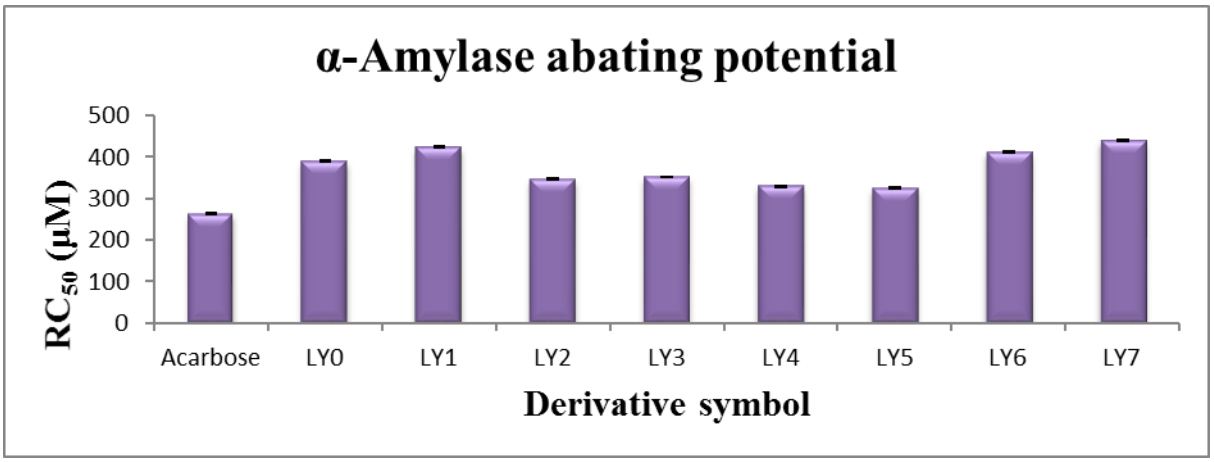


Figure 2: The hypoglycaemic influence of **LY0-LY7** against PA enzyme

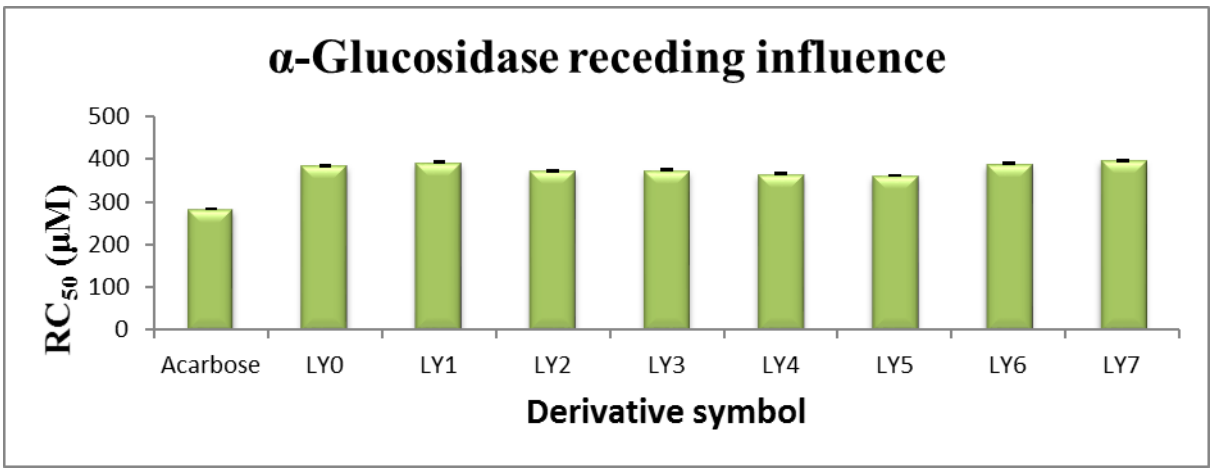


Figure 3: The hypoglycemic influence of **LY0-LY7** against YG enzyme

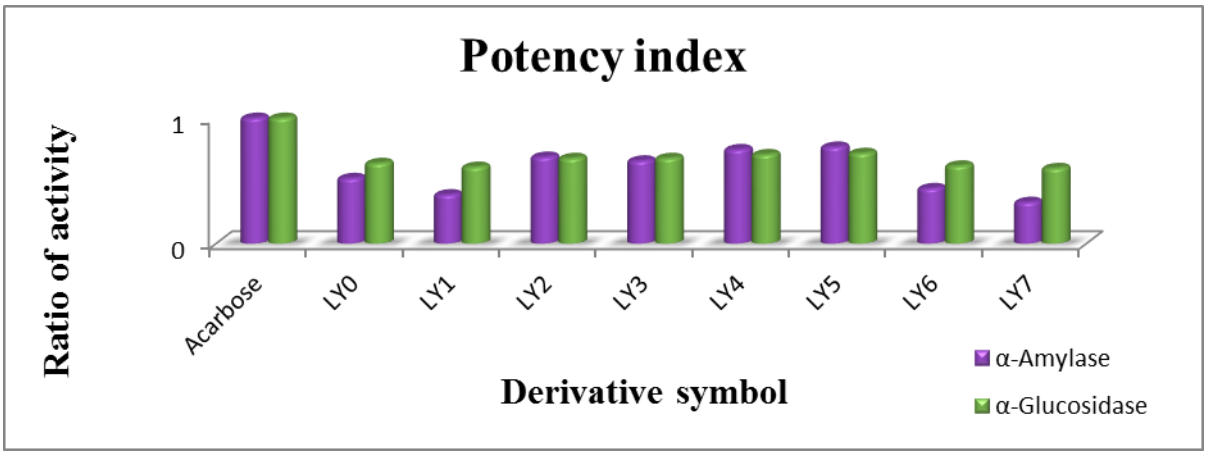


Figure 4: The potency index of **LY0**-**LY7** against PA and YG enzymes

From the previous Table and Figures, some important observations were notified. First, the synthesised albocarbon-based coumarins had the same pattern in the suppression of both enzymes, YG and PA. Second, our compounds had a hypoglycaemic influence lower than AC, the reference. Third, the suppressive potential of **LY5** and **LY4** was the most powerful of these new compounds that could be attributed to the chloride and fluoride moieties, respectively. These halogens had a strong electron-withdrawing capacity, making the resulting compound more active. Fourth, the hypoglycaemic influence of **LY7** was the weakest among this group of compounds. This might be attributed to the iodide moiety that had the least electron-withdrawing capacity compared to the other halogens that lead to less active compounds. The final observation was the order of hypoglycaemic influence of these novel albocarbons, which was as follows: **LY5**, **LY4**, **LY2**, **LY3**, **LY0**, **LY6**, **LY1**, and **LY7** [60].

Assessment of Free Radical-Housing Potential

Research on free radical-housing potential has gotten a lot of attention recently because of its possible involvement in the prophylaxis and control of numerous illnesses which influence human health, including malignancy, Alzheimer's, diabetes mellitus, hypertension, coronary artery disease, and many other diseases. The discovery of novel free radical-housing agents has attracted the public's attention. Table 6 illustrates the free radical-housing potential of the synthesised albocarbon-based coumarins. The ability of these new compounds to eliminate DDPH and hydroxyl harmful radicals is represented in Figures 5 and 6, respectively.

Table 5: The free radical-housing potential of **LY0**-**LY7**

Compound's symbol	Assay and results			
L-AA	**Liquidating assay of DPPH-free radical LC_{50}±SD**	45.84±1.04	**Liquidating assay of hydroxyl-free radical LC_{50}±SD**	50.79±1.01
LY0		56.12±1.25		59.41±1.12
LY1		90.06±1.12		77.52±1.00
LY2		62.45±1.20		64.26±0.98
LY3		63.67±1.03		68.03±1.11
LY4		87.23±0.95		85.29±1.18
LY5		84.35±1.08		73.81±1.02
LY6		94.46±1.02		92.47±1.09
LY7		97.14±1.17		92.89±0.99

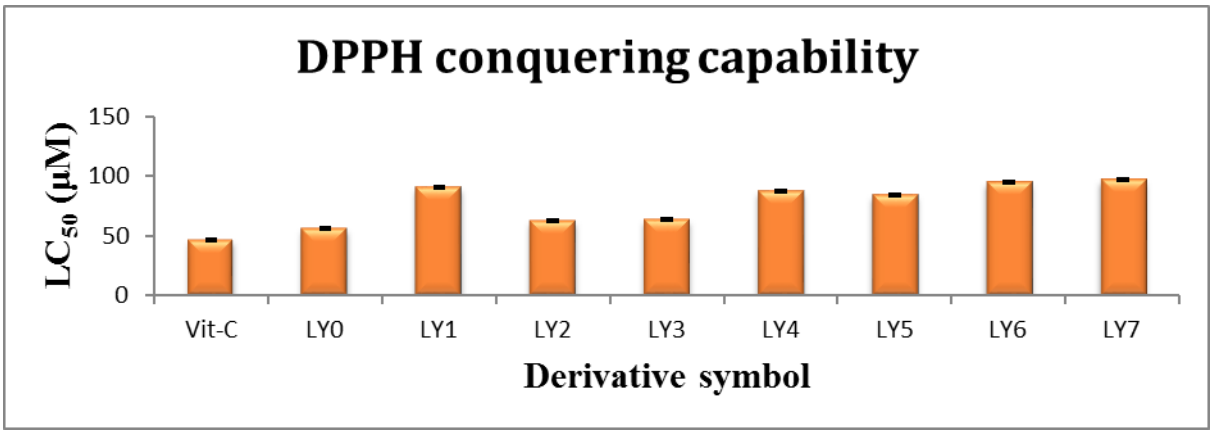


Figure 5: The free radical-housing potential of **LY0**-**LY7** against DPPH free moieties

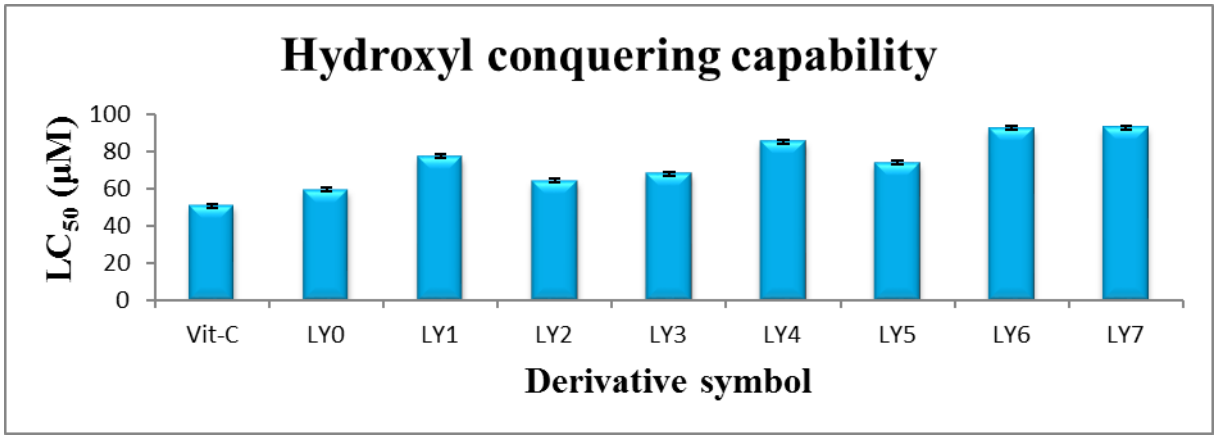


Figure 6: The free radical-housing potential of **LY0**-**LY7** against hydroxyl free moieties

From these Figures and Tables, a number of issues were observed. First, **LY0** had the strongest free radical-housing potential as compared to L-AA, as a standard. This might be attributed to the presence of a hydroxyl group which attached directly to the coumarin nucleus, which had an electron-donating ability that made the compound more active in housing the free radicals. Second, **SA7** had the weakest activity among this group. This might be due to the size of the iodide moiety in this compound, which is considered large compared to the other halogens, resulting in the weaker activity of the resultant compound. Finally, the order of free radical-housing potential of these albocarbon-based coumarins is as follow: **LY0**, **LY2**, **LY3**, **LY5**, **LY1**, **LY6**, and **LY7** [61,62].

Conclusion

This research demonstrated the synthesis of eight novel albocarbon-based coumarins from 6-amino-7-phenolchloro-2-naphthol as a starting material. From the pharmacokinetic parameters gathered from the web application pre-ADMET, these compounds were shown to have good oral bioavailability, which makes them the promising orally administered drugs in the future. The hypoglycaemic and free radical-housing effects of the synthesised albocarbon-based coumarins revealed a number of significant findings. First, the synthesised compounds had a weaker hypoglycaemic influence than AC, the standard. In addition, the activity of these novel coumarins against both of the enzymes, PA and YG, followed the same pattern. Second, the free radical-housing potential of the albocarbon-based coumarins was weaker than that of L-AA, with **LY0** having the most powerful activity as compared to the others. From these findings, along with their good oral absorption profiles and low penetration across the blood-brain barrier, these coumarins could provide a valuable platform for the scanning of new drugs with hypoglycaemic and free radical-housing effects in the future.

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All the authors met the criteria of authorship based on the recommendations of the international Committee of Medical Journal Editors.

Conflict of Interest
There are no conflicts of interest in this study.

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References
[1]. Lorenzati B., Zucco C., Miglietta S., Lamberti F., Bruno G., *Pharmaceuticals,* 2010, **3**:3005 [Crossref], [Google Scholar], [Publisher]
[2]. Sesti G., *Diabetes Care,* 2011, **34**:S272 [Crossref], [Google Scholar], [Publisher]
[3]. Ismael R.N., Mustafa Y.F., Al-qazaz H.K., *J. Med. Chem. Sci.,* 2022, **5**:607 [Crossref], [Google Scholar], [Publisher]
[4]. Jebir R.M., Mustafa Y.F., *J. Med. Chem. Sci.,* 2022, **5**:652 [Crossref], [Google Scholar], [Publisher]
[5]. Lv H., Tu P., Jiang Y., *Mini Rev. Med. Chem.,* 2014, **14**:603 [Crossref], [Google Scholar], [Publisher]
[6]. Mustafa Y.F., Abdulaziza N.T., Jasim M.H., *Egypt. J. Chem.,* 2021, **64**:1807 [Crossref], [Google Scholar], [Publisher]
[7]. Mustafa Y.F., Oglah M.K., Bashir M.K., *Syst. Rev. Pharm.,* 2020, **11**:482 [Google Scholar], [Publisher]
[8]. Oglah M.K., Bashir M.K., Mustafa Y.F., Mohammed E.T., Riyadh R., *Syst. Rev. Pharm.,* 2020, **11**:717 [Google Scholar], [Publisher]
[9]. Mustafa Y.F., Abdulaziz N.T., *NeuroQuantology,* 2021, **19**:175 [Crossref], [Google Scholar], [Publisher]
[10]. Mustafa Y.F., *J. Med. Chem. Sci.,* 2021, **4**:612 [Crossref], [Google Scholar], [Publisher]
[11]. Mustafa Y.F., Najem M.A., Tawffiq Z.S., *J. Appl. Pharm. Sci.,* 2018, **8**:49 [Crossref], [Google Scholar], [Publisher]
[12]. Budi H.S., Jameel M.F., Widjaja G., Alasady M.S., Mahmudiono T., Mustafa Y.F., et al., *Braz. J. Biol.* 2022, **84** [Crossref], [Google Scholar], [Publisher]
[13]. Mustafa Y.F., Mohammed N.A., *Biochem. Cell. Arch.,* 2021, **21**:1991 [Google Scholar], [Publisher]
[14]. Mahmood A.A.J., Mustafa Y.F., Abdulstaar M., *Int. Med. J. Malaysia,* 2014, **13**:3 [Crossref], [Google Scholar], [Publisher]
[15]. Mustafa Y.F., Bashir M.K., Oglah M.K., *Syst. Rev. Pharm.,* 2020, **11**:598 [Google Scholar], [Publisher]
[16]. Mustafa Y.F., Mohammed E.T., Khalil R.R., *Egypt. J. Chem.,* 2021, **64**:4461 [Crossref], [Google Scholar], [Publisher]
[17]. Aldewachi H., Mustafa Y.F., Najm R., Ammar F., *Syst. Rev. Pharm.,* 2020, **11**:289 [Google Scholar], [Publisher]
[18]. Mustafa Y.F., Bashir M.K., Oglah M.K., Khalil R.R., Mohammed E.T., *NeuroQuantology,* 2021, **19**:129 [Crossref], [Google Scholar], [Publisher]
[19]. Mustafa Y.F., Khalil R.R., Mohammed E.T., Bashir M.K., Oglah M.K., *Arch. Razi Inst.,* 2021, **76**:1297 [Crossref], [Google Scholar], [Publisher]
[20]. Mustafa Y.F., Abdulaziz N.T., *Syst. Rev. Pharm.,* 2020, **11**:438 [Google Scholar], [Publisher]
[21]. Mustafa Y.F., Kasim S.M., Al-Dabbagh B.M., Al-Shakarchi W., *Appl. Nanosci.,* 2021 [Crossref], [Google Scholar], [Publisher]
[22]. Waheed S.A., Mustafa Y.F., *J. Med. Chem. Sci.,* 2022, **5**:703 [Crossref], [Google Scholar], [Publisher]
[23].Oglah M.K., Mustafa Y.F., *J. Glob. Pharma*

Technol., 2020, **12**:854 [Google Scholar], [Publisher]
[24].Mustafa Y.F., *NeuroQuantology,* 2021, **19**:99 [Crossref], [Google Scholar], [Publisher]
[25].Jasim S.F., Mustafa Y.F., *J. Med. Chem. Sci.,* 2022, **5**:676 [Crossref], [Publisher]
[26].Bashir M.K., Mustafa Y.F., Oglah M.K., *Syst. Rev. Pharm.,* 2020, **11**:598 [Google Scholar], [Publisher]
[27].Oglah M.K., Mustafa Y.F., Bashir M.K., Jasim M.H., *Syst. Rev. Pharm.,* 2020, **11**:472 [Google Scholar], [Publisher]
[28].Mustafa Y.F., *Appl. Nanosci.,* 2021 [Crossref], [Google Scholar], [Publisher]
[29].Bashir M.K., Mustafa Y.F., Oglah M.K., *Period. Tche Quim.,* 2020, **17**:871 [Google Scholar], [Publisher]
[30].Raya I., Chen T., Pranoto S.H., Surendar A., Utyuzh A.S., Al-Jnabi S., et al., *Mater. Res.,* 2021, **24**:e20210245 [Crossref], [Google Scholar], [Publisher]
[31].Hmood K.S., Razzak Mahmood Kubba A.A., *Syst. Rev. Pharm.,* 2020, **12**:184 [Google Scholar], [Publisher]
[32].Nejres A.M., Mustafa Y.F., Aldewachi H.S., *Int. J. Pavement Eng.,* 2022, **23**:39 [Crossref], [Google Scholar], [Publisher]
[33].Kasim S.M., Abdulaziz N.T., Mustafa Y.F., *J. Med. Chem. Sci.,* 2022, **5**:546 [Crossref], [Publisher]
[34].Mustafa Y.F., *J. Glob. Pharma Technol.,* 2019, **11**:1 [Google Scholar], [Publisher]
[35].Jasim S.F., Mustafa Y.F., *Iraqi J. Pharm.,* 2021**,** **18**:104 [Crossref] [Google Scholar], [Publisher]
[36].Mohammed E.T., Mustafa Y.F., *Syst. Rev. Pharm.,* 2020, **11**:64 [Google Scholar], [Publisher]
[37].Ismael R.N., Mustafa Y.F., Al-Qazaz H.K., *Iraqi J. Pharm.,* 2021**,** **18**:162 [Crossref], [Google Scholar], [Publisher]
[38].Doan H. Van, Riyajan S., Iyara R., Chudapongse N., *BMC Complement. Altern. Med.,* 2018, **18**:267 [Crossref], [Google Scholar], [Publisher]
[39].Caccetta R., Al-salami H., *Metabolomics Tools Nat. Prod. Discov.,* 2013, **1055**:207 [Crossref], [Google Scholar], [Publisher]
[40].Oglah M.K., Mustafa Y.F., *Med. Chem. Res.,* 2020, **29**:479 [Crossref], [Google Scholar], [Publisher]
[41].Mustafa Y.F., Khalil R.R., Mohammed E.T., *Syst. Rev. Pharm.,* 2020, **11**:382 [Google Scholar], [Publisher]
[42].Khalil R.R., Mustafa Y.F., *Syst. Rev. Pharm.,* 2020, **11**:57 [Google Scholar], [Publisher]
[43].Atia Y.A., Bokov D.O., Zinnatullovich K.R., Kadhim M.M., Suksatan W., Abdelbasset W.K., et al., *Mater. Chem. Phys.,* 2022, **278**:125664 [Crossref], [Google Scholar], [Publisher]
[44].Mustafa Y.F., Mohammed E.T., Khalil R.R., *Syst. Rev. Pharm.,* 2020, **11**:570 [Google Scholar], [Publisher]
[45].Ansari M.J., Jasim S.A., Taban T.Z., Bokov D.O., Shalaby M.N., Al-Gazally M.E., et al.,, *J. Clust. Sci.,* 2022 [Crossref], [Google Scholar], [Publisher]
[46].Waheed S.A., Mustafa Y.F., *Iraqi J. Pharm.,* 2021**,** **18**:126 [Crossref], [Google Scholar], [Publisher]
[47].Mustafa Y.F., Oglah M.K., Bashir M.K., Mohammed E.T., Khalil R.R., *Clin. Schizophr. Relat. Psychoses,* 2021, **15**:1 [Google Scholar], [Publisher]
[48].Jebir R.M., Mustafa Y.F., *Iraqi J. Pharm.,* 2021**,** **18**:139 [Crossref], [Google Scholar], [Publisher]
[49].Khalil R.R., Mohammed E.T., Mustafa Y.F., *Clin. Schizophr. Relat. Psychoses*, 2021, **15**, 1. [Google Scholar], [Publisher]
[50].Mustafa Y.F., Khalil R.R., Mohammed E.T., *Egypt. J. Chem.,* 2021, **64**:3711 [Crossref], [Google Scholar], [Publisher]
[51].Alheety K.A., Jamel N.M., Ahmed B.J., *J. Pharm. Sci. Res.,* 2019, **11**:3344 [Google Scholar], [Publisher]
[52].Mustafa Y.F., *Saudi Pharm. J.,* 2018, **26**:870 [Crossref] [Google Scholar] [Publisher]
[53].Waheed N.A., Waheed S.A., *Int. J. Pharm. Res.,* 2020 [Crossref], [Google Scholar], [Publisher]
[54].O'Hagan S., Kell D.B., *PeerJ,* 2015, **3**:e1405 [Crossref], [Google Scholar], [Publisher]
[55].Kim S.H., Kim D.H., Byeon J.Y., Kim Y.H., Kim D.H., Lim H.J., et al., *Arch. Pharm. Res.,* 2017, **40**:382 [Crossref], [Google Scholar], [Publisher]
[56].Roomi A.B., Widjaja G., Savitri D., Jalil A.T., Mustafa Y.F., Thangavelu L., et al., *J. Nanostruct.,* 2021, **11**:514 [Crossref], [Google Scholar], [Publisher]
[57].Dresser G.K., Spence J.D., Bailey D.G., *Clin.*

Pharmacokinet., 2000, **38**:41 [Crossref], [Google Scholar], [Publisher]
[58].Tian H., Xu Y., Wang J., Tian W., Sun J., Zhang T., et al., *Biomed. Res. Int.,* 2018, **2018**:6374374 [Crossref], [Google Scholar], [Publisher]
[59].Wei Z., *J. Toxicol. Clin. Toxicol.,* 2001, **39**:711 [Crossref], [Google Scholar] [Publisher]
[60].El Omari N., Sayah K., Fettach S., El Blidi O., Bouyahya A., Faouzi M.E.A., et al., *Evid. Based Complement. Altern. Med.,* 2019, **2019** [Crossref], [Google Scholar], [Publisher]
[61].Raya I., Widjaja G., Hachem K., Rodin M.N., Ali A.A., Mustafa M.K., et al., *J. Nanostructures* 2021, **11**, 728 [Crossref], [Google Scholar], [Publisher]
[62].Sies H., *Redox Biol.,* 2015, **4**:180 [Crossref], [Google Scholar], [Publisher]

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