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Original Article

Synthesis and Biological Potentials of Novel Benzodipyrone-Based Derivatives

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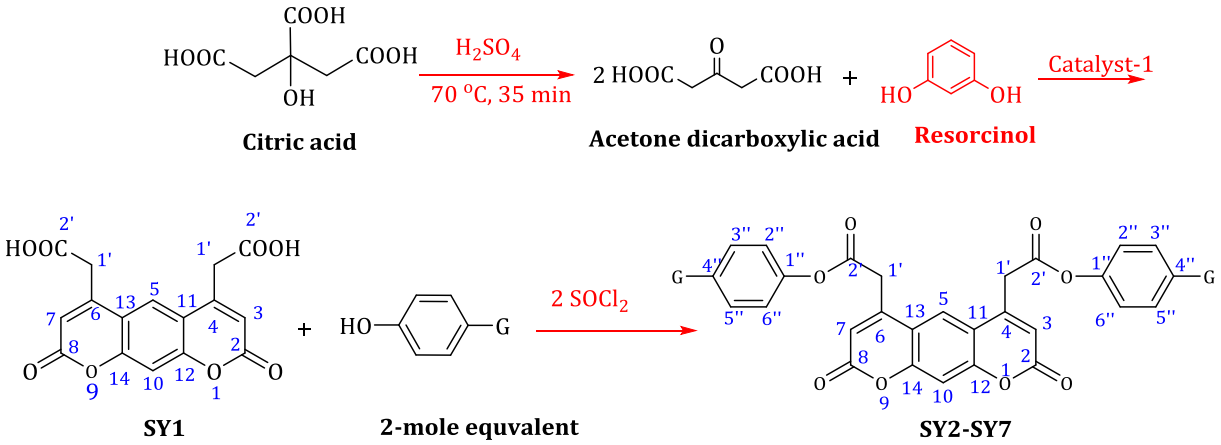
ABSTRACT

In this research, the acetone dicarboxylic acid was prepared from citric acid under the influence of conc. H_2SO_4. Then, the Pechmann reaction was used to produce a novel benzodipyrone molecule (**SY1**). The latter was reacted with a variety of substituted phenols to produce the **SY2-SY7** congeners. The chemical structures of the synthesized benzodipyrone-based derivatives were recognized by examining the analytically spectral charts. The anticancer, antibacterial, and hypoglycemic potentials of our compounds were assessed *in vitro*. The initial potential was tested using an IC_{50} measure versus six tumorigenic cell lines. A broth-dilution test was applied to assess the antimicrobial potential versus six aerobic gram-negative bacteria, four anaerobic bacteria, two fungi, and one non-pathogenic bacterial strain. Furthermore, the hypoglycemic potential was evaluated in comparison to two different types of blood glucose-controlling enzymes, yeast α-glucosidase and porcine α-amylase. The results obtained from investigating the first potential revealed that our compounds, specifically **SY4**, had a potent-to-moderate wide-range anti-tumor activity. This activity is combined with a low risk of toxicity to the normal cells. Besides, these compounds exhibited promising antimicrobial potential, particularly **SY5** for aerobic gram-negative bacteria, **SY2** for anaerobic bacteria, and **SY1** for pathogenic fungi. This potential is coupled with the relative safety of our compounds towards the tested normal flora bacteria. Furthermore, the compounds revealed moderate-to-weak inhibitory effects versus the tested blood glucose-controlling enzymes, with **SY2** and **SY3** exhibiting the best hypoglycemic potential. The authors concluded that our synthesized compounds offer privileged bioactive platforms which may liberate a new window for the discovery of the novel therapeutically active medications.

GRAPHICAL ABSTRACT



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Introduction

The most serious public health problems worldwide are cancer and microbial resistance. Since 1990, their frequency has increased; more particularly in almost each area in the world [1]. Despite the development of a variety of investigational drugs from native [2] and artificial resources [3], the effective prophylaxis, and therapy of several cancer types and infections remains a challenge. As a result, there is still a pressing need to construct the unique chemical structures and study their molecular activities to identify a workable alternative to these difficult medical conditions [4].

Coumarin itself is a natural heterocyclic organic aromatic compound that is presented in a wide variety of microorganisms and higher plants [5-8]. It was initially isolated from the seeds of a flowering plant known as tonka beans in 1820. Many therapeutic characteristics have been discovered in this natural substance and the majority of its synthetic counterparts. Some of these documented bioactivities include antimutagenic [9], virucidal [10,11], bactericidal and fungicidal [12,13], inflammatory suppressors [14,15], coagulant inhibitors [16,17], triglyceride dropping [18], and CNS stimulating agents [19]. However, hydroxycoumarins were revealed to have a strong antioxidant and the preventive effect against the oxidative overload by eliminating superoxide radicals [20]. Moreover, the discovery of coumarins with a low estrogenic activity has paved the path for their application in menopausal complaint therapy [21]. Due to the undesirable consequences such as moderate nausea, diarrhea, and hepatotoxicity, the FDA has limited the use of numerous coumarins as smoking aromas, which are used as stationary phases and flavorings [22,23]. Coumarins are used in cosmetics, agrochemicals, and as optical brightening agents in addition to their medicinal applications [24].

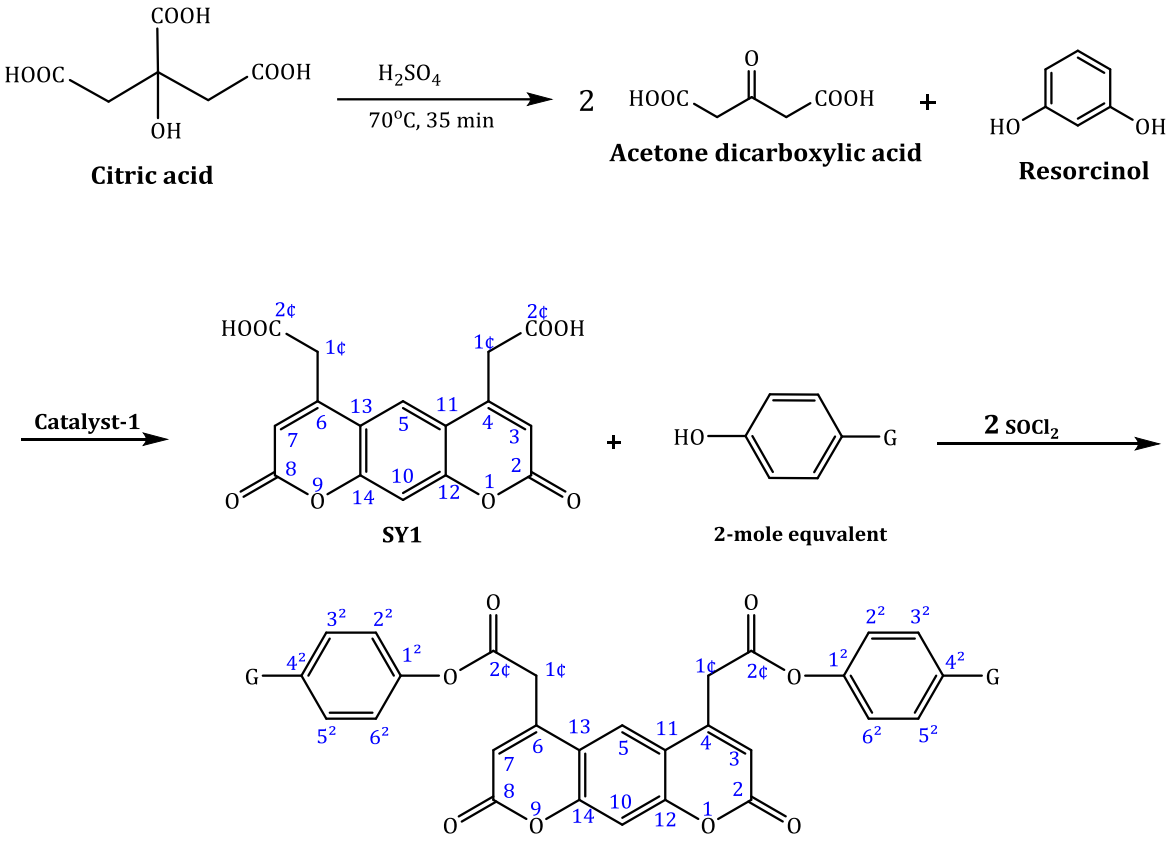
This work aims to synthesize several functionalized novel benzodipyrone derivatives with improved antitumor, antibacterial, and hypoglycemic potentials. This aim was realized by synthesizing **SY1** via the Pechmann reaction. The latter compound was used as a starting point for coupling with different substituted phenols, resulting in the synthesis of six congeners entitled here as **SY2-SY7**. The antitumor activity of our compounds was assessed versus six tumorous-cell lines, viz. MCF-7, HeLa, SKG, AMN3, SK-OV-3, and KYSE-30. The antimicrobial properties of these compounds were evaluated versus six aerobic gram-negative bacteria (*Pseudomonas aeruginosa, Klebsiella pneumonia, Haemophilus influenza, Escherichia coli, Salmonella typhi, and Shigella dysenteriae*), four anaerobic bacteria (*Bacteroides fragilis, Clostridium perfringens, Fusobacterium necrophorum, and Prevotella melaninogenica*), two fungi (*Candida albicans and Aspergillus niger*), and one non-pathogenic bacterial strain (*Escherichia coli*, BAA-1427). Furthermore, the hypoglycemic effect was evaluated in comparison to two different types of blood glucose-controlling enzymes, yeast α-glucosidase (YG) and porcine α-amylase (PA).

Materials and Methods

The chemicals expended for synthesizing **SY1** and its congeners **SY2-SY7** were assumed from documented international resources and utilized without any additional purification. The melting points (M.P) of the synthesized congeners were detected based on the USP-dependent capillary method via an electrothermal digital CIA-9300 instrument. The thin-layer chromatography (TLC) consists of standard silica gel aluminum-based plates and an eluting mixture of $CHCl_3$: acetone (4:1) was used to assure the fulfillment of reactions, as well as the purity of synthesized chemical intermediates and congeners. The employed instruments to scan the UV, FTIR, ^{1}H-, and ^{13}C-NMR spectra of the synthesized congeners included UV- 1600PC UV-Vis, Bruker-α- ATR-FTIR, and Bruker Avance DRX-300 MHz spectrophotometers, respectively. The tumorous-cell lines and pathogenic standard bacteria employed in this work were purchased from Sigma-Aldrich Company and were prepared for usage according to each leaflet's instructions.

Plan of the Synthesis

Scheme 1 depicts the graphic stages applied to synthesize **SY1** and its congeners **SY2-SY7**.



SY1: 2,2'-(2,8-Dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl)diacetic acid
SY2: G= OCH_3; Bis(4-methoxyphenyl) 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl)diacetate
SY3: G= CH_3 ; Di-*p*-tolyl 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl)diacetate
SY4: G=F ; Bis(4-fluorophenyl) 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl)diacetate
SY5: G= Cl ; Bis(4-chlorophenyl) 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl)diacetate
SY6: G= Br ; Bis(4-bromophenyl) 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl)diacetate
SY7: G= I ; Bis(4-iodophenyl) 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl)diacetate

Scheme 1: The synthetic steps of SY1 and its congeners SY2-SY7

Synthesis of Acetone Dicarboxylic Acid

Anhydrous citric acid (0.1 mole, 19.2 g) in 30 mL concentrated H_2SO_4 was stirred for 60 min at temperature adjusted at 25 °C, and then slowly heated to 70 °C (the rate of heating controlled by foaming). The generation of carbon monoxide ceased after 60 min of stirring at this temperature, and the clear solution was formed, which was then poured into 250 g of the crushed ice water. Ethyl acetate was used to extract the resulted solution, and the acquired ethyl acetate containing phase was concentrated and dried to produce light yellow acetone dicarboxylic acid with a yield of 40% [25].

Synthesis of 2,2'-(2,8-Dioxo-2,8-dihydropyrano[3,2-g]chromene-4,6-diyl)diacetic acid (SY1)

The mixture of resorcinol (5 mmol, 0.55 g), acetone dicarboxylic acid (10 mmol, 1.46 g), and the [Msim]HSO4 as a promoter (0.096 mmol, 25 mg) was agitated under solvent-free conditions at 40 °C for 30 min. The resulted semi-solid crude was diluted with ethyl acetate (10 mL) when TLC documented the finishing of the reaction, and the promoter can be isolated via a decantation. By washing the organic phase with water (25 mL), separating both phases, and evaporating the organic layer, the target **SY1** compound was acquired and purified by recrystallization from ethanol affording a white powder. Following drying, the recovered ionic liquid may be utilized without any additional purification in the following run [26].

SY1: 2,2'-(2,8-Dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl)diacetic acid. White powder, yield= 42%, M.P = 198-200 °C, λ_{max} (Ethanol, nm) = 386 nm, R_f value (chloroform: acetone 4:1) = 0.26. IR ν_{max} (cm^{-1}): 3062 (br, O-H, carboxylic acid), 3013 (C-H, aryl), 2890 (C-H, alkane), 1732 (CO, lactone), 1690 (CO, COOH), 1590 (C=C, aryl).

^{1}H-NMR (ppm): 11.09 (2H, s, COOH), 7.92 (1H, s, H-5), 7.12 (1H, s, H-10), 6.35 (2H, s, H-3, H-7), 2.49 (4H, s, C-1`, C-1`). ^{13}C-NMR (ppm): 173.1 (C, C-2`, C-2`), 162.2 (C, C-2, C-8), 154.5 (C, C-4, C-6), 153.0 (C, C-12, C-14), 125.1 (C, C-5), 115.8 (C, C-11, C-13), 113.4 (C, C-10), 108.5 (C, C-3, C-7), and 30.9 (C, C-1`, C-1`).

Synthetic technique of SY2-SY7 Congeners

In a salt-ice bath, a two-nick round-bottomed flask containing **SY1** (5 mmol, 1.65 g) in 25 mL of refreshed $SOCl_2$ was immersed. The side-nick was enclosed by a stopper provided with a blue litmus paper, while the central nick was enveloped by a condenser. The mixture was slowly stirred under anhydrous conditions for 30 min, and then for the same period at RT, and refluxed for 3 hours. The course of the reaction was detected depending on the color change of the litmus paper which was replaced regularly every 30 min. As the color of the blue litmus paper no longer changed, the excess of $SOCl_2$ was distilled off. The white solid material which remained in the concave of the flask represented the acyl-chloride derivative of **SY1** [27,28].

To the same flask containing the white residue, a solution of substituted phenols (9.6 mmol) and pyridine (1 mL) in 50 mL of anhydrous diethyl ether was added in one portion at RT and stirred under dehydrated conditions for 30 min. The reaction was refluxed for a period of time, evidenced by changing the color of the litmus paper as described above. As the reaction was finished, H_2O (50 mL) was added to the mixture, and the organic layer was separated, dehydrated, and vaporized. The **SY** congener was acquired [29,30] by the recrystallization of a mixture of propanone and CH_2Cl_2 (1:2).

SY2: G= OCH_3; Bis(4-methoxyphenyl) 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl)diacetate. Light yellow powder, 82%, M.P 156-158 °C, λ_{max} (Ethanol, nm) = 512 nm, R_f value (chloroform: acetone 4:1) = 0.69. IR ν_{max} (cm^{-1}): 3096 (C-H, alkene-lactone), 2917 (C-H, CH_3), 2820 (C-H, CH_2), 1733 (C=O, cyclic lactone ester), 1710 (C=O, side chain ester), 1668 (C=C, lactone), 1595 (C=C, aryl), 1266, 1028 (C-O-C, ether). ^{1}H-NMR (ppm): 7.92 (1H, s, H-5), 7.12 (1H, s, H-10), 7.01 (4H, d, *J*= 6 Hz, H-3", H-5"), 6.74 (4H, d, *J*= 6 Hz, H-2", H-6"), 6.35 (2H, s, H-3, H-7), 4.12 (6H, s, OCH_3), 3.12 (4H, s, H-1`, H-1`). ^{13}C-NMR (ppm): 169.5 (C, C-2`, C-2`), 162.2 (C, C-2, C-8), 156.4 (C, C-4", C-4"), 154.5 (C, C-4, C-6), 153.0 (C, C-12, C-14), 144.6 (C, C-1", C-1"), 125.1 (C, C-5), 120.1 (C, C-2", C-6"), 115.8 (C, C-11, C-13), 113.4 (C, C-3", C-5"), 112.3 (C, C-3, C-7), 51.1 (C, OCH3), and 28.3 (C, C-1`, C-1`).

SY3: G= CH_3; Di-p-tolyl 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl)diacetate. Light yellow powder, 80%, M.P 150-152 °C, λ_{max} (Ethanol, nm) = 510 nm, R_f value (chloroform: acetone 4:1) = 0.66. IR ν_{max} (cm^{-1}): 3090 (C-H, alkene-lactone), 2877 (C-H, CH_3), 2818 (C-H, CH_2), 1733 (C=O, cyclic lactone ester), 1712 (C=O, side chain ester), 1668 (C=C, lactone), 1597 (C=C, aryl). ^{1}H-NMR (ppm): 7.92 (1H, s, H-5), 7.26 (4H, d, *J*= 6 Hz, H-3", H-5"), 7.24 (4H, d, *J*= 6 Hz, H-2",H-6"), 7.12 (1H, s, H-10), 6.35 (2H, s, H-3, H-7), 3.12 (4H, s, H-1`, H-1`), 2.75 (6H, s, CH3). ^{13}C-NMR (ppm): 169.5 (C, C-2`, C-2`), 162.2 (C, C-2, C-8), 154.5 (C, C-4, C-6), 153.0 (C, C-12, C-14), 149.3 (C, C-1", C-1"), 134.2 (C, C-4", C-4"), 125.1 (C, C-3", C-5"), 122.0 (C, C-5), 119.0 (C, C-2", C-6"), 115.8 (C, C-11", C-13"), 113.4 (C, C-10), 108.5 (C, C-3, C-7), 27.5 (C, C-1`, C-1`), and 24.1 (C, CH_3).

SY4: G=F; Bis(4-fluorophenyl) 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl) diacetate. Light yellow powder, 58%, M.P 167-169 °C, λ_{max} (Ethanol, nm) = 490 nm, R_f value (chloroform: acetone 4:1) = 0.56. IR ν_{max} (cm^{-1}): 3070 (C-H, alkene-lactone), 2820 (C-H, CH_2), 1733 (C=O, cyclic lactone ester), 1711 (C=O, side chain ester), 1692 (C=C, lactone), 1590 (C=C, aryl), 1077 (C-F). ^{1}H-NMR (ppm): 7.92 (1H, s, H-5), 7.27 (4H, d, *J*= 6 Hz, H-3", H-5"), 7.25 (4H, d, *J*= 6 Hz, H-2", H-6"), 7.12 (1H, s, H-10), 6.35 (2H, s, H-3, H-7), 3.12 (4H, s, H-1`, H-1`). ^{13}C-NMR (ppm): 169.5 (C, C-2`, C-2`), 162.2 (C, C-2, C-8), 158.7 (C, C-4", C-4"), 154.4 (C, C-4, C-6), 153.0 (C, C-12, C-14), 147.9 (C, C-1", C-1"), 125.1 (C, C-5), 120.7 (C, C-2", C-6"), 115.8 (C, C-11, C-13), 113.4 (C, C-3", C-5"), 109.4 (C, C-10), 108.5 (C, C-3, C-7), and 27.5 (C, C-1`, C-1`).

SY5: G= Cl; Bis(4-chlorophenyl) 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*]chromene-4,6-diyl) diacetate. Light yellow powder, 60 %, M.P 143-145 °C, λ_{max} (Ethanol, nm) = 496 nm, R_f value

(chloroform: acetone 4:1) = 0.57. IR ν_{max} (cm^{-1}): 3068 (C-H, alkene-lactone), 2820 (C-H, CH_2), 1730 (C=O, cyclic lactone ester), 1710 (C=O, side chain ester), 1667 (C=C, lactone), 1594 (C=C, aryl), 985 (C-Cl). ^{1}H-NMR (ppm): 7.92 (1H, s, H-5), 7.36 (4H, d, *J*= 6 Hz, H-2", H-6"), 7.34 (4H, d, *J*= 6 Hz, H-3", H-5"), 7.12 (1H, s, H-10), 6.35 (2H, s, H-3, H-7), 3.12 (4H, s, H-1`, H-1`). ^{13}C-NMR (ppm): 169.5 (C, C-2`, C-2`), 162.2 (C, C-2, C-8), 154.4 (C, C-4, C-6), 153.0 (C, C-12, C-14), 150.4 (C, C-1", C-1"), 132.0 (C, C-4", C-4"), 125.1 (C, C-3", C-5"), 122.9 (C, C-5), 120.5 (C, C-2", C-6"), 115.8 (C, C-11, C-13), 113.4 (C, C-10), 108.5 (C, C-3, C-7), and 33.2 (C, C-1`, C-1`).

SY6: G= Br; Bis(4-bromophenyl) 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-g]chromene-4,6-diyl) diacetate. Light yellow powder, 62 %, M.P 136-139 °C, λ_{max} (Ethanol, nm) = 491 nm, R_f value (chloroform: acetone 4:1) = 0.59. IR ν_{max} (cm^{-1}): 3066 (C-H, alkene-lactone), 2819 (C-H, CH_2), 1732 (C=O, cyclic lactone ester), 1709 (C=O, side chain ester), 1664 (C=C, lactone), 1593 (C=C, aryl), 900 (C-Br). ^{1}H-NMR (ppm): 7.92 (1H, s, H-5), 7.78 (4H, d, *J*= 6 Hz, H-3", H-5"), 7.76 (4H, d, *J*= 6 Hz, H-2", H-6"), 7.11 (1H, s, H-10), 6.35 (2H, s, H-3, H-7), 3.13 (4H, s, H-1`, H-1`). ^{13}C-NMR (ppm): 169.5 (C, C-2`, C-2`), 162.2 (C, C-2, C-8), 154.4 (C, C-4, C-6), 153.0 (C, C-12, C-14), 151.3 (C, C-1", C-1"), 125.1 (C, C-3", C-5"), 123.6 (C, C-2", C-6"),121.3 (C, C-5), 118.5 (C, C-4", C-4"), 115.8 (C, C-11, C-13), 113.4 (C, C-10), 108.5 (C, C-3, C-7), and 33.2 (C, C-1`, C-1`).

SY7: G= I; Bis(4-iodophenyl) 2,2'-(2,8-dioxo-2,8-dihydropyrano[3,2-*g*] chromene-4,6-diyl) diacetate. Light yellow powder, 51 %, M.P 122-125 °C, λ_{max} (Ethanol, nm) = 491 nm, R_f value (chloroform: acetone 4:1) = 0.59. IR ν_{max} (cm^{-1}): 3064 (C-H, alkene-lactone), 2823 (C-H, CH_2), 1732 (C=O, cyclic lactone ester), 1711 (C=O, side chain ester), 1661 (C=C, lactone), 1592 (C=C, aryl), 866 (C-I). ^{1}H-NMR (ppm): 7.92 (1H, d, *J*= 6 Hz, H-3", H-5"), 7.84(1H, s, H-5), 7.11 (1H, s, H-10), 6.84 (4H, d, *J*= 6 Hz, H-2", H-6"), 6.35 (2H, s, H-3, H-7), 3.13 (4H, s, H-1`, H-1`). ^{13}C-NMR (ppm): 169.5 (C, C-2`, C-2`), 162.2 (C, C-2, C-8), 154.4 (C, C-4, C-6), 153.0 (C, C-12, C-14), 151.2 (C, C-1", C-1"), 129.6 (C, C-3", C-5"), 125.1 (C, C-5), 120.7 (C, C-2", C-6"), 115.8 (C, C-11, C-13), 113.4 (C, C-10), 108.5 (C, C-3, C-7), 93.0 (C, C-4", C-4"), and 33.2 (C, C-1`, C-1 `).

Assessments of In Vitro Biological Potentials

Assessment of the Preliminary Cytotoxic Potential

Our derivatives, along with their control substance 5-fluorouracil (5-FU), were dissolved in DMSO to produce six concentration levels (400, 200, 100, 50, 25, and 12.5 µg/mL). Then, after dividing the tumorous cell lines into a 96-well plate to achieve 10,000 cells per well, each well was treated separately with various concentrations of the synthesized benzodipyrone-based derivatives after 24 hours. After 72 hours of incubation, the vitality of the cells was measured by removing the medium and incubating the cells for 90 minutes at 37 °C with 28 µL MTT solutions (3.27mM). The absorption spectra of the treated well (As) and control well (Ac) were measured using a microplate reader set at 492 nm. Every synthesized chemical evaluated was subjected to this procedure in triplicate [31,32]. To calculate the percentage of growth inhibition, the following mathematical equation was applied:

Growth inhibition % = (Ac-As)/Ac X 100

Assessments of the Antimicrobial Potential

The activity of the synthesized benzodipyrone-based derivatives as antibacterial and antifungal candidates was evaluated in this study using the well-known broth-dilution technique.

Assessment of the Activity towards Aerobic Gram Negative Bacteria

Mueller-Hinton broth (MHB) was used as a growing medium for the bacteria. The reference was ciprofloxacin (CPF), while the negative qualifying drug was methyl sulfoxide (DMSO). A 2 mL of the testing composite with a concentration of 100 mg/mL was allowed to dry first, and the remaining was evaluated.

The mother solution was made by combining 7.5 mg of the residue with 5 mL of methyl sulfoxide. A series of 13 two-fold dilutions with a range of labeled concentrations between 1024 and 0.25 g/mL were then established using autoclaved distilled water as a thinning liquid. As a pre-incubation solution, 3 mL of MHB, 0.2 mL of

inoculant diluted to 0.5 McFarland with autoclaved distilled water, and 1 mL of a preset concentration were put in a marked test tube. After a 24-hour incubation period at 37 °C, the growth of bacteria was examined with the naked eye. The previous scientific approaches were repeated with diluted quantities based on the values of 4, 1, 0.5, or 0.05, depending on which concentration revealed minor bacterial proliferation. The first microbiological variable was calculated in the final step as the minimum inhibitory concentration (MIC), which is measured in micrograms per milliliter [36].

Assessment of the Activity towards Anaerobic Bacteria

Despite minor differences, the method utilized to assess the activity of the synthesized composites against anaerobic pathogenic bacteria was identical to that used to assess activity against aerobic pathogenic bacteria. The only difference in the microbiological variables is the notation MABC, which stands for the minimum anaerobic bactericidal concentration. The differences were in the growth medium, which was Brucella-agar mixed with sheep blood (5%) and the reference drug, Metronidazole (MNZ). In addition, cultures were incubated for 48 hours at 37 °C in a container containing an anaerobic milieu (10 % CO_2, 10 % H_2, and 80 % N_2), an anaerobe marker, and a metal catalyst (palladium) [37].

Assessment of the Activity towards Pathogenic Fungi

The fungicidal activity of the synthesized composites was evaluated using a slightly different method than that was utilized to examine their activity against aerobic bacteria. Except for the term MFC, which stands for the minimum fungicidal concentration, all of the microbiological variables are the same. The Sabouraud-dextrose broth was used as the growth medium. The reference agent was Nystatin (NYS). The incubation period was 48 hours at 30 °C [38].

Assessment of the Hypoglycemic Potential

The suppressive capacity of the synthesized benzodipyrone-based derivatives against two phenotypes of the enzyme, porcine-amylase and yeast-glucosidase, was tested *in vitro* both of which is significant in controlling blood glucose levels. The IC_{50} measure, which is the dose of the synthesized drug necessary to inhibit enzyme activity by 50% under the experimental circumstances, is used to describe this capacity. Prior to execute these two tests, different dosages of the chemical under research (2 mg/mL) were created. The concentrations of 1000, 800, 400, 200, 100, 50, and 25 µM were obtained using MeOH as a solvent [39-43].

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

20 µL of the synthesized benzodipyrone-based derivative were mixed with the same volume of the reference solution, both containing 0.1 unit/mL of the YG enzyme. *Para*-nitrophenyl glucopyranoside was solubilized in a K_3PO_4 (pH 6.8) solution to reach the target concentration level of 375 M. After that, 40 µL of this solution was combined with the compound-enzyme mixture and maintained at 37 °C for 30 minutes. A K_3PO_4 solution containing 80 µL of carbonic acid disodium salt (0.2 M) was added to the mixture to complete the reaction. The ability of the chemical to decrease enzyme activity was assessed using a colorimetric technique at 405 nm, and the receding percent was calculated using the equation:

$$YG\ receding\ \% = Abscontrol - Abssample \div Abscontrol \times 100$$

The utilized standard was acarbose (AC). The reference solution was made in the same way as the examined solution, except using DMSO instead of the synthesized compound [44].

Assessment of Porcine α-Amylase (PA) Abating Influence

20 µl of the synthesized benzodipyrone-based derivative and the same volume of the reference solution, both of which contained 2 units/ml of the PA enzyme, were mixed together. To produce 2 mL of 0.5 mM concentration, the starch substrate was dispersed in K_3PO_4 buffer (pH 6.8). After that, the assessed combination was held at 25 °C for 10 minutes. Then, 2 ml of a solution of 0.4 M aqueous sodium hydrate, 12 % anhydrous L-potassium sodium tartrate, and 1 % *o*-dinitrocarboxylphenol were added to finish the

reaction. The obtained sample was warmed in a water bath for 15 minutes before being thinned with H_2O to achieve the necessary amount of 10 ml. Next, an ice bath was used to bring the temperature of the mixture to 25 °C. The effectiveness of the chemical combination to reduce enzymatic activity was measured using a colorimetric technique at 540 nm. The percentage of abating was calculated using the following formula:

$$PA\ abating\ \% = Abscontrol - Abssample \div Abscontrol \times 100$$

The standard used was AC. The reference solution was made in the same way as the examined solution, except using DMSO instead of the synthesized compound [45].

Results and Discussion

Chemical Synthesis

Initially the authors used two moles of acetone dicarboxylic acid with one mole of resorcinol in the presence of sulfuric acid as catalyst; however, coumarin molecule was produced because the second hydroxyl in resorcinol was very weak [46-50]. Then, we used 4 moles, and 6 moles of acetone dicarboxylic acid, respectively, with one mole of resorcinol in the presence of sulfuric acid, but the result was further coumarin molecule. Finally by using special catalyst ([Msim]HSO_4), benzodipyrone-based derivatives was produced [51-53]. The analytical methods such as IR, ^{1}H NMR, and ^{13}C NMR spectroscopies were used to analyze the synthesized benzodipyrone-based derivatives.

In Vitro Biological Potentials

Preliminary Cytotoxic Potential

The activities of the novel benzodipyrone-based derivatives were determined using the minimum inhibitory concentration (IC_{50}) measure. They were tested against six tumorigenic cell lines: MCF-7, HeLa, SKG, AMN3, SK-OV-3, and KYSE-30 [33,34], as indicated in Table 1.

Table 1: The results of the assessment of **SY1-SY7** cytotoxic activity

Compound symbol	IC50 (µM) ± SD (n=3)						
	MCF-7	HeLa	SKG	AMN3	SK-OV-3	KYSE-30	RWPE-1
5-FU	12.42±0.99	13.37 ±1.05	22.12 ±0.98	24.89 ±1.12	22.43 ±1.16	30.72 ±1.02	34.79±0.96
SY1	91.26±1.08	62.16 ±1.15	100.02 ±1.16	63.79 ±1.08	64.67 ±0.93	69.01 ±1.12	40.24±1.08
SY2	28.56±0.92	24.45 ±0.95	46.29 ±1.15	54.16 ±1.00	57.92 ±1.12	50.16 ±0.92	55.01±1.12
SY3	34.21±1.00	41.12 ±1.08	42.12 ±1.08	67.54 ±0.93	40.16 ±1.00	53.79 ±1.17	48.17±1.22
SY4	13.08±1.05	13.42 ±1.00	31.15 ±1.00	28.43 ±0.94	25.08 ±1.06	41.45 ±1.07	112.45±1.16
SY5	22.65±1.10	16.35 ±1.15	31.24 ±1.15	30.65 ±1.08	28.89 ±0.96	41.67 ±1.00	57.67±0.99
SY6	84.16±1.05	53.34 ±1.00	82.76 ±1.04	63.14 ±1.16	57.38 ±1.18	57.43 ±1.18	44.12±0.91
SY7	88.91±1.15	54.09 ±0.96	79.45 ±0.98	69.21 ±1.10	63.19 ±0.98	60.26 ±1.02	40.63±1.06

The order of IC_{50} values of the synthesized benzodipyrone-based derivatives concerning each tumorigenic cell line are recorded in Table 2.

Table 2: The order of the antitumor activity of **SY1-SY7** versus the investigated tumorigenic cell lines

Order of activity	MCF-7	HeLa	SKG	AMN3	SK-OV-3	KYSE-30
1	**SY4**	**SY4**	**SY4**	**SY4**	**SY4**	**SY4**
2	**SY5**	**SY5**	**SY5**	**SY5**	**SY5**	**SY5**
3	**SY2**	**SY2**	**SY3**	**SY2**	**SY3**	**SY2**
4	**SY3**	**SY3**	**SY2**	**SY6**	**SY6**	**SY3**
5	**SY6**	**SY6**	**SY7**	**SY1**	**SY2**	**SY6**
6	**SY7**	**SY7**	**SY6**	**SY3**	**SY7**	**SY7**
7	**SY1**	**SY1**	**SY1**	**SY7**	**SY1**	**SY1**
8	**SA1**	**SA1**	**SA7**	**SA1**	**SA7**	**SA1**

A number of conclusions on the anticancer activity of the synthesized benzodipyrone-based derivatives against tumorigenic cell lines were drawn from these two tables. To begin with, the fluorinated and chlorinated chemicals (**SY4** and **SY5**, respectively) reveal the greatest potency against all examined cell lines. This is due to the fluoride and chloride moieties that have a significant electron-withdrawing ability, which makes the resulting molecule more active. Secondly, the anticancer activity of benzodipyrone-based compounds was lower than that of 5-FU, as the reference [54-56].

The toxicity of these compounds was tested using RWPE-1 as a model organism (human normal prostate epithelial cells) [57-60]. The novel benzodipyrone-based derivatives were revealed to be safer than 5-FU against the test normal cell line.

Antimicrobial Potential

Aerobic Gram-Negative Bacteria

The pathogenic aerobic gram-negative bacterial strains used in this study were *Pseudomonas aeruginosa* (27853-ATCC, P-aeruginosa), *Klebsiella pneumonia* (700603-ATCC, K-pneumonia), *Haemophilus influenza* (49247-ATCC, H-influenza), *Escherichia coli* (25922-ATCC, E-coli), *Salmonella typhi* (6539-ATCC, S-typhi), and *Shigella dysenteriae* (13313-ATCC, S-dysenteriae). The safety profile of the synthesized benzodipyrone-based derivatives on normal flora bacteria was evaluated using the non-pathological *Escherichia coli* strain (BAA-1427, E-coli).

The initial finding, as presented in Table 3, is that the synthesized benzodipyrone-based derivatives exhibit a less bacterial growth inhibitory effect on the pathogenic bacterial strains than the reference, CPF. The second is that these derivatives have bacterial growth inhibitory effect in the following order: **SY5, SY2, SY3, SY4, SY6, SY7**, and **SY1**. Among our derivatives, **SY5** exhibits the most activity. This might be because the chloride moiety is one of the most potent electron-withdrawing replacements, resulting in the production of a highly active molecule [61].

Another two findings came from determining the safety profile of the synthesized benzodipyrone-based derivatives by examining their effects on natural flora. The first is that, as compared to CPF, they are all less toxic to the normal floral *E. coli* strain than CPF. The second is that the toxicity of these substances is in the following sequence, starting with the least toxic: **SY1**, **SY5**, **SY6**, **SY4**, **SY7**, **SY3**, and **SY2** [62-65].

Table 3: Bacterial growth inhibitory influence of **SY1-SY7** compounds versus gram-negative aerobic bacteria

Aerobic gram-negative bacteria	Micro-biological variable	Symbols of the standard and tested synthetic composites							
		CPF	SY1	SY2	SY3	SY4	SY5	SY6	SY7
P-aeruginosa ATCC 27853	MIC	0.75	12.00	3.50	4.50	5.50	1.90	7.50	7.00
K-pneumonia ATCC 700603	MIC	0.40	10.00	3.00	4.50	5.00	1.95	6.50	7.50
H-influenzae ATCC 49247	MIC	0.60	12.00	3.50	6.00	6.50	1.65	6.00	7.00
E-coli ATCC 25922	MIC	0.85	16.00	3.00	6.50	7.00	1.40	8.00	7.50
S-typhi ATCC 6539	MIC	0.80	14.00	4.00	6.00	7.50	1.95	8.50	9.50
S-dysenteriae ATCC 13313	MIC	0.55	14.00	4.50	5.50	5.00	1.85	7.50	9.00
E-coli BAA-1427	MIC	0.90	14.00	6.00	8.00	10.00	12.00	12.00	10.00

Anaerobic Bacteria

In this work, four anaerobic pathogenic bacterial strains were utilized, namely *Bacteroides fragilis* (*BF*), *Clostridium perfringens* (*CP*), *Fusobacterium necrophorum* (*FN*), and *Prevotella melaninogenica* (*PM*). The results recorded in Table 4 revealed that the synthesized benzodipyrone-based derivatives have much less activity compared with MNZ, as the standard drug. The order of their bacterial growth inhibitory effect against the test pathogen is: **SY2, SY3, SY5, SY4, SY7, SY6, and SY1**.

Table 4: Bacterial growth inhibitory effect of **SY1-SY7** compounds versus anaerobic bacteria

Anaerobic bacteria	Micro-biological variable	Symbols of the standard and tested synthetic composites							
		MNZ	SY1	SY2	SY3	SY4	SY5	SY6	SY7
BF ATCC 25285	MIC	3.00	52.00	10.00	16.00	32.00	28.00	44.00	36.00
CP ATCC 13124	MIC	0.75	48.00	8.00	12.00	30.00	24.00	40.00	30.00
FN ATCC 25286	MIC	1.75	32.00	8.00	14.00	36.00	26.00	40.00	48.00
PM ATCC 25845	MIC	0.75	44.00	10.00	12.00	40.00	30.00	36.00	48.00

Pathogenic Fungi

The fungal growth inhibitory influence of the synthesized benzodipyrone-based derivatives was tested against two pathological fungal strains, *Candida albicans* (10231-ATCC, C-albicans) and *Aspergillus niger* (16888-ATCC, A-niger).

Several critical remarks are made as indicated in Table 5. The most notable is that, as compared to NYS, the synthesized benzodipyrone compounds (**SY1, SY4**, and **SY5**) have a very strong fungal growth inhibitory effect [66-68]. On the other hand, **SY6** and **SY7** exhibit virtually no efficacy against the tested fungal strains. This might be due to the decreased electron withdrawing capability of the bromide and iodide moieties in these two compounds compared to the other substituents, making the molecule less active [69,70]. The following is the order in which these chemicals have fungal growth inhibitory effects: **SY1, SY4, SY5, SY3, SY2, SY7, and SY6**.

Table 5: Fungal growth inhibitory effect of **SY1-SY7** compounds versus two pathogenic fungi

Pathogenic fungi	Micro-biological variable	Symbols of the standard and tested synthetic composites							
		NYS	SY1	SY2	SY3	SY4	SY5	SY6	SY7
C-albicans ATCC 10231	MIC	4.00	1.25	5.00	4.00	1.55	1.60	20.00	12.00
A-niger ATCC 16888	MIC	8.00	1.50	12.00	14.00	1.90	1.85	32.00	24.00

Hypoglycemic Potential

Some key observations were made based on Table 6. First, the synthesized benzodipyrone compounds block both the YG and PA enzymes in the same way. Second, our compounds revealed a less hypoglycemic effect than AC, as the standard. Third, **SY2** and **SY3** have the strongest suppressive properties of these novel chemicals. That could be attributed to the OCH_3 and CH_3 moieties, respectively. The order of hypoglycemic effect of these new benzodipyrone compounds was **SY2, SY3, SY1, SY4, SY5, SY6**, and **SY7** [71].

Table 6: The results of investigating the hypoglycemic potential of the synthesized benzodipyrone-based derivatives **SY1-SY7** and the reference

Compound's symbol	Assay and results			
Acarbose	**YG receding influence RC_{50}±SD**	283.04±0.88	**PA abating influence RC_{50}±SD**	263.26±0.92
SY1		396.72±1.01		348.22±0.91
SY2		364.31±0.95		326.47±0.96
SY3		366.84±0.91		334.13±0.90
SY4		403.05±0.94		352.67±0.93
SY5		413.38±0.94		353.12±1.01
SY6		421.94±0.99		370.28±0.86
SY7		424.02±1.02		372.39±0.98

Conclusion

This work reports the creation of a novel chemical nucleus symbolized here as SY1, from which a series of six congeners (SY2-SY7) were synthesized by coupling with various phenol-derived products. The results of investigating the anticancer, antibacterial, and hypoglycemic properties of the synthesized compounds revealed that fluorinated congeners can be effective anti-tumor applicants with a broad spectrum of action. Besides, the chlorinated congeners indicated promise as antibacterial applicants. Concerning the hypoglycemic effect, the methoxy-congeners have the strongest suppressive properties among the synthesized compounds. Finally, these congener-phenotypes can be thought of as the privileged platforms and bio-medically verified scaffolds for the discovery of novel therapeutically active candidates.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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