Synthesis, ADME Study, and Antimicrobial Evaluation of Novel Naphthalene-Based Derivatives

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**ABSTRACT**

In recent times, many researchers in pharmaceutical chemistry have been preoccupied with the quest for new potent anti-infective agents to combat antimicrobial resistance. A novel series of naphthalene-based derivatives were synthesized as part of these studies. Different spectral techniques, such as UV-Vis, FTIR, 13C-NMR, and 1H-NMR were used to affirm the synthesized compounds' chemical structures, while an ADME study was conducted to investigate their pharmacokinetics and drug-like properties. The potential of the synthesized naphthalene-based derivatives as anti-infective candidates versus pathogenic microbes was evaluated using a broth microdilution assay. These microbes involved six aerobic gram-negative bacteria, four anaerobic bacteria, and two fungi. In addition, their safety was assessed versus normal bacterial flora. From the obtained results, the authors reported the following principal outcomes: Compound SF5 revealed a significant aerobic gram-negative bactericidal impact while indicating high safety versus the non-pathological bacterial strain. Most of the synthesized naphthalene-based derivatives demonstrated outstanding potential as fungicidal candidates, but compound SF1 was the most potent one. According to ADME analysis, almost all of the synthesized derivatives have good theoretical pharmacokinetics and drug-likeness characteristics making them suitable as oral-derived agents.

**KEYWORDS**

Naphthalene-based derivatives
Antimicrobial
Bactericidal
Fungicidal
Normal flora

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Introduction
Since the dawn of time, humankind has been plagued by infectious diseases. Fleming’s discovery of penicillin in 1923 gave hope of eradicating these diseases. The modern battle versus pathological microbes began with this discovery, which led to the production of many antimicrobials [1]. Later, the ability to prevent and treat infections caused by bacteria, fungi, and viruses became limited due to the emergence of resistance versus antimicrobial agents. Antibiotic resistance has risen as a result of unregulated use and overprescribing of antibiotics, as well as poor sanitation and a lack of hygiene [2]. This resistance has an influential socio-economic consequence due to increased mortality and morbidity from transmissible diseases. Despite the rise in drug-resistant infections, only a small number of novel agents have been discovered and approved for medicinal use. Consequently, more effort should be stimulated into exploring new antimicrobials [3,4].

The coumarins are members of a large heteroaromatic family [5]. They are intriguing molecules for many fields of study due to the conjugated systems found in their fused rings [6]. Coumarin compounds are used in industry as additives in food and as ingredients in perfumes and cosmetics. However, its most important usage is to synthesize different products in the pharmaceutical industry [7]. Coumarins, from natural and/or synthetic sources have different biomedical potentials, such as anti-diabetic [8,9], anti-viral [10,11], anti-tubercular [12], anti-fungal [13-15], anti-coagulant [16,17], anti-cancer [18-22], anti-bacterial [23-27], and antioxidant [28-31] properties. Moreover, these molecules have many appealing characteristics, such as low toxicity, high bioavailability, simple planar structure, and low molecular weight, which confirm that they could play a significant role in drug development and research [32-34].

Benzocoumarins, also known as benzochromenones, are a prime bioactive fused-coumarin class. In the past few years, numerous researchers have concentrated their endeavors on isolating, synthesizing, and studying the bioactivities of these coumarin-based compounds due mainly to their expander system of π-conjugation compared to coumarins [35]. These studies revealed that the compounds with a benzocoumarin core have various biomedical properties, including anti-diabetic, anti-microbial, anti-oxidant, anti-dyslipidemic, and anti-cancer activities [36,37]. The anti-bacterial and anti-fungal properties have taken precedence among the investigated activities. As a result, benzocoumarins may be useful as scaffolds for promising antimicrobials [38,39].

This work aims to synthesize a novel trifunctionalized naphthalene-based derivative series. An ADME study was performed utilizing a pre-ADMET predictor, an online server to analyze the pharmacokinetic parameters and drug-like properties of the prepared naphthalene-based derivatives. The antimicrobial potentials of the synthesized compounds were evaluated versus pathogenic microbes, including six aerobic gram-negative bacteria, four anaerobic bacteria, and two fungi, employing a common broth microdilution assay. Furthermore, to determine their safety, the toxicity of our compounds was assessed versus normal bacterial flora, as well. The latter investigation was conducted by measuring the anti-bacterial activity of the compounds against an aerobic gram-negative bacterium named Escherichia coli (NFES-co, BAA-1427).

Materials and Methods
Chemical compounds, solvents, and reagents used to synthesize naphthalene-based derivatives, as well as the microbiological evaluation systems were procured from some international resources, such as Haihang, Bioworld, Chem-Lab, Labcorp, Sigma-Aldrich, Scharlau, and others. The procured chemical and microbiological agents were employed directly without further purification. An ultrasonic-water bath (40 kHz, 350 W, Power Sonic410, Korea) was operated as a sonication system. A digital electrothermal apparatus (CIA9300) was utilized to measure the melting temperatures (Mp) of the synthesized naphthalene-based derivatives without pre-correction via an open-capillary approach. The synthesis status progression was checked, and the synthesized compounds’ purity was determined.
using thin-layer chromatography (TLC). An aluminum-based silica gel sheet (F254) and a mixture of chloroform: MeOH (4:1) served as the fixed and moveable phases in this technique. Moreover, spectrometers involved Bruker Avance DRX-300 MHz, Bruker-α- ATR-FTIR, and UV-1600PC UV-Vis were operated to record the prepared naphthalene-based derivatives spectra of $^{13}$C- and $^1$H-NMR, FTIR, and UV, respectively.

**The Schedule of Chemical Synthesis**

The chemical pathway’s steps for preparing naphthalene-based derivatives from 6-amino-7-chloronaphthalen-2-ol are depicted in Scheme 1.

**Synthesis of Compound SF0**

At room temperature (RT), 6-amino-7-chloronaphthalen-2-ol (1.930 g, 10.00 mmol) and nitric acid sodium salt (3.450 g, 50.00 mmol) were mixed and stirred for 15 minutes in 90.00 mL of MeOH. At that temperature, 11.50 mL of ethanoic acid was slowly added to the resultant solution, and the stirring was continued strenuously for 6 hours. The gathered solid product was re-crystallized from an aqueous EtOH solution after vaporizing the solvent [40].

7-Chloro-6-methoxynaphthalen-2-ol (SF0): French pink; Yield= 43% (0.89 g); Mp= 160-162 °C; Rf = 0.23; $\lambda_{\text{max}}$(EtOH)=517 nm; $\lambda_{\text{max}}$(cm $^{-1}$): 3300 (br, phenolic O-H), 3076 (m, aromatic C-H), 2957 (w, alkyl C-H), 1561 (s, aromatic C=C), 1281, 1073 (s, ether C-O-C), 916 (s, C-Cl); $^1$H-NMR (ppm, 300 MHz, DMSO-$d_6$): $\delta$ = 8.08 (1H, d, $J$= 9 Hz, 4-H), 7.62 (1H, s, 8-H), 7.48 (1H, s, 1-H), 7.33 (1H, s, 5-H), 7.22 (1H, d, $J$= 9 Hz, 3-H), 5.56 (1H, s, 2-OH), 4.02 (3H, s, 6-OCH$_3$); $^{13}$C-NMR (ppm, 75 MHz, DMSO-$d_6$): $\delta$ = 157.1 (C, C-6), 155.7 (C, C-2), 133.1 (C, C-9), 131.4 (CH, C-4), 129.8 (C, C-10), 128.5 (CH, C-8), 126.9 (C, C-7), 120.2 (CH, C-3), 111.4 (CH, C-1), 108.6 (CH, C-5), and 50.1 (CH$_3$, OCH$_3$-6).

**Synthesis of Compound SF1**

**Method A**

With the assistance of heating, SF0 (2.750 g, 13.18 mmol) was dissolved in acetone dicarboxylic acid (3.50 mL, 15.00 mmol). After that, the resulting solution was dropped very slowly from a separatory funnel into 25.00 mL of precooled concentrated H$_2$SO$_4$ submerged in an ice bath. During the addition, the reaction mixture was stirred, and the temperature was kept under 10.0°C. The reaction mixture was then retained at
RT for 20 hours with continuous stirring before being shed over the ice/water combination. The precipitate was filtered off and rinsed well with cooled water [42,43].

Method B
With the assistance of heating, SF0 (2.750 g, 13.18 mmol) was dissolved in acetone dicarboxylic acid (3.50 mL, 15.00 mmol). After that, the resulting solution was dropped very slowly from a separatory funnel into 25.00 mL of precooled concentrated H₂SO₄ submerged in a salted ice bath. A condenser was fitted the middle neck, whereas a plug furnished with blue litmus paper plugged the other. In a less environment, the mixture was stirred, and the temperature was kept under 10.0°C. The reaction mixture was then settled for a half hour. This was followed by 3 hours of refluxing. The reaction progression was tracked by the litmus-paper color change which was renewed every half-hour. The distillation of SOCl₂ excess when the litmus paper blue color remained unchanged gave the alkanoyl chloride intermediate in the flask bottom as a solid white product [44].

At RT, a solution of phenolic-based derivative (4.80 mmol) and azabenzene (1.00 mL) in 50.00 mL of anhydrous ethoxylene was poured into the same flask housing the white crude. The mixture was agitated for a half-hour in moisture-less environment. According to the change in litmus-paper color, the reaction was refluxed for a time, as mentioned previously. Then, 50.00 mL of water was added to the mixture when the reaction was completed, followed by separating, dehydrating, and evaporating the organic layer. From a CH₂Cl₂: dimethylketone (2:1) mixture, the derivatives of SF1 were recrystallized [44].

11-[(8-Chloro-7-methoxy-2-oxo-2H-benzo[g]chromen-4-yl)acetate (SF1): Yellowish powder; Yield= 79.76% (3.35 g in method A) and 88.09% (3.70 g in method B); Mp= 186-188 °C; Rf = 0.19; λmax (EtOH)= 467 nm; IR νmax (cm⁻¹): 3062 (w, cis-alkene C=H), 3015 (br, carboxylic acid O=H), 2957 (w, methoxy C=H), 2891 (w, alkyl C=H), 1734 (s, lactonic ester C=O), 1692 (s, carboxylic acid C=O), 1590 (s, cis-alkene C=C), 1548 (m, aromatic C=C), 1448, 1274, 1192 (s, ether C-O-C), 941 (s, C-Cl); 1H-NMR (ppm, 300 MHz, DMSO-d6): δ= 11.09 (1H, s, 12-OH), 7.92 (1H, s, 5-H), 7.60 (1H, s, 9-H), 7.43 (1H, s, 6-H), 7.12 (1H, s, 10-H), 6.35 (1H, s, 3-H); 4.03 (3H, s, 7-OCH₃), 3.12 (2H, s, 11-H); 13C-NMR (ppm, 75 MHz, DMSO-d6): δ= 173.1 (C, C-12), 162.2 (C, C-2), 154.4 (C, C-7), 153.0 (C, C-4), 151.8 (C, C-10'), 130.2 (C, C-9'), 128.1 (C, C-5'), 127.5 (C, C-4'), 126.4 (CH, C-9), 125.1 (CH, C-5), 124.5 (C, C-8), 115.8 (CH, C-3), 113.4 (CH, C-10), 109.4 (CH, C-6), 50.1 (CH₃, OCH₃-7), 30.9 (CH₂, C-11).

Synthesis of Compounds SF2-SF7
Compound SF1 (1.593 g, 5.00 mmol) was added to refreshed SOCl₂ (25.00 mL) in a twin-neck flask and submerged in a salted ice bath. A condenser fitted the middle neck, whereas a plug furnished with blue litmus-paper plugged the other. In moisture-less environment, the mixture was stirred gently for a half-hour, then at RT for another half-hour. This was followed by 3 hours of refluxing. The reaction progression was tracked by the litmus-paper color change which was renewed every half-hour. The distillation of SOCl₂ excess when the litmus paper blue color remained unchanged gave the alkanoyl chloride intermediate in the flask bottom as a solid white product [44].

At RT, a solution of phenolic-based derivative (4.80 mmol) and azabenzene (1.00 mL) in 50.00 mL of anhydrous ethoxethylene was poured into the same flask housing the white crude. The mixture was agitated for a half-hour in moisture-less environment. According to the change in litmus-paper color, the reaction was refluxed for a time, as mentioned previously. Then, 50.00 mL of water was added to the mixture when the reaction was completed, followed by separating, dehydrating, and evaporating the organic layer. From a CH₂Cl₂: dimethylketone (2:1) mixture, the derivatives of SF1 were recrystallized [44].

4''-Methoxyphenyl 11-[(8-chloro-7-methoxy-2-oxo-2H-benzo[g]chromen-4-yl)acetate (SF2): White powder; Yield= 76.27% (1.62 g); Mp= 171-173 °C; Rf = 0.63; λmax (EtOH)= 331 nm; IR νmax (cm⁻¹): 3096 (m, cis-alkene C=H), 2917 (m, methoxy C=H), 2821 (w, alkyl C=H), 1731 (s, lactonic ester C=O), 1710 (s, ester C=O), 1665 (s, cis-alkene C=C), 1595 (s, aromatic C=C), 1266, 1028 (s, ether C-O-C), 985 (s, C-Cl); 1H-NMR (ppm, 300 MHz, DMSO-d6): δ= 7.92 (1H, s, 5-H), 7.60 (1H, s, 9-H), 7.43 (1H, s, 6-H), 7.12 (1H, s, 10-H), 7.01 (2H, d, J= 6 Hz, 3''-, 5''-H), 6.74 (2H, d, J= 6 Hz, 2'', 6''-H), 6.35 (1H, s, 3-H), 4.12 (3H, s, 4''-OCH₃), 4.03 (3H, s, 7-OCH₃), 3.12 (2H, s, 11-H); 13C-NMR (ppm, 75 MHz, DMSO-d6): δ= 169.5 (C, C-12), 162.2 (C, C-2), 154.4 (C, C-7), 153.0 (C, C-4), 151.8 (C, C-10'), 144.6 (C, C-1''), 130.2 (C, C-9'), 128.1 (C, C-5'), 127.5 (C, C-4'), 126.4 (CH, C-9), 125.1 (CH, C-5), 124.5 (C, C-8), 115.8 (CH, C-3), 113.4 (CH, C-10), 109.4 (CH, C-6), 51.1 (CH₃, OCH₃-4''), 50.1 (CH₃, OCH₃-7), and 28.3 (CH₂, C-11).

4''-Tolyl 11-[(8-chloro-7-methoxy-2-oxo-2H-benzo[g]chromen-4-yl)acetate (SF3): Off-white powder; Yield= 74.36% (1.52 g); Mp= 156-158 °C; Rf = 0.58; λmax (EtOH)= 378 nm; IR νmax (cm⁻¹): 3090 (m, cis-alkene C=H), 2912 (w, methoxy C=H), 2819 (w, alkyl C=H), 1733 (s, lactonic ester C=O), 1713
(s, ester C=O), 1668 (s, cis-alkene C=C), 1597 (s, aromatic C=C), 1267, 1030 (s, ether C-O-C), 985 (s, C-Cl); 1H-NMR (ppm, 300 MHz, DMSO-d6): δ = 7.92 (1H, s, 5-H), 7.60 (1H, s, 9-H), 7.43 (1H, s, 6-H), 7.25 (2H, d, J = 6 Hz, 3"-, -5"-H), 7.12 (1H, s, 10-H), 7.02 (2H, d, J = 6 Hz, 2"-, -6"-H), 6.35 (1H, s, 3-H), 4.02 (3H, s, 7-OCH3), 3.12 (2H, s, 11-H), 2.75 (3H, s, 4"-CH3); 13C-NMR (ppm, 75 MHz, DMSO-d6): δ = 169.5 (C, C-12), 162.2 (C, C-2), 154.4 (C, C-7), 153.0 (C, C-4), 151.8 (C, C-10), 150.4 (C, C-1''), 132.0 (C, C-4''), 130.2 (C, C-9), 128.1 (C, C-5'), 127.5 (C, C-4'), 126.4 (CH, C-9), 125.1 (CH, C-5), 124.5 (C, C-8), 122.0 (CH, C-3", -5"), 119.0 (CH, C-2", -6"), 115.8 (CH, C-3), 113.4 (CH, C-10), 109.4 (CH, C-6), 50.1 (CH3, OCH3-7), 27.5 (CH2, C-11), and 24.1 (CH3, CH3-4").

4"-Fluorophenyl 11-(8-chloro-7-methoxy-2-oxo-2H-benzo[g]chromen-4-yl)acetate (SF4): White powder; Yield = 69.28% (1.43 g); Mp = 166-168 °C; Rf = 0.42; λmax (EtOH) = 330 nm; IR νmax (cm⁻¹): 3070 (m, cis-alkene C=C), 2918 (w, methoxy C-H), 2820 (w, alkyl C-H), 1733 (s, lactonic ester C=O), 1711 (s, ester C-O), 1666 (s, cis-alkene C=C), 1597 (s, aromatic C=C), 1266, 1028 (s, ether C-O-C), 1077 (s, C-F), 986 (s, C-Cl); 1H-NMR (ppm, 300 MHz, DMSO-d6): δ = 7.92 (1H, s, 5-H), 7.60 (1H, s, 9-H), 7.43 (1H, s, 6-H), 7.26 (2H, d, J = 6 Hz, 2"-, -6"-H), 7.12 (1H, s, 10-H), 7.04 (2H, d, J = 6 Hz, 3", -5"-H), 6.35 (1H, s, 3-H), 4.02 (3H, s, 7-OCH3), 3.12 (2H, s, 11-H); 13C-NMR (ppm, 75 MHz, DMSO-d6): δ = 169.5 (C, C-12), 162.2 (C, C-2), 154.4 (C, C-7), 153.0 (C, C-4), 151.8 (C, C-10), 151.8 (C, C-1'''), 151.3 (C, C-1'-'), 130.2 (C, C-9), 128.1 (C, C-5'), 127.5 (C, C-4'), 126.4 (CH, C-9), 125.1 (CH, C-5), 124.5 (C, C-8), 122.0 (CH, C-3", -5"), 113.4 (CH, C-10), 109.4 (CH, C-6), 50.1 (CH3, OCH3-7), and 27.5 (CH2, C-11).

4"-iodophenyl 11-(8-chloro-7-methoxy-2-oxo-2H-benzo[g]chromen-4-yl)acetate (SF7): White powder; Yield = 64.54% (1.68 g); Mp = 136-138 °C; Rf = 0.51; λmax (EtOH) = 339 nm; IR νmax (cm⁻¹): 3064 (m, cis-alkene C-H), 2913 (w, methoxy C-H), 2823 (w, alkyl C-H), 1733 (s, lactonic ester C=O), 1711 (s, ester C-O), 1661 (s, cis-alkene C=C), 1592 (s, aromatic C-C), 1265, 1028 (s, ether C-O-C), 866 (s, C-Cl), 864 (s, C-H); 1H-NMR (ppm, 300 MHz, DMSO-d6): δ = 7.92 (1H, s, 5-H), 7.85 (2H, d, J = 6 Hz, 3", -5"-H), 7.60 (1H, s, 9-H), 7.43 (1H, s, 6-H), 7.11 (1H, s, 10-H), 6.83 (2H, d, J = 6 Hz, 2"-, -6"-H), 6.35 (1H, s, 3-H), 4.00 (3H, s, 7-OCH3), 3.13 (2H, s, 11-H); 13C-NMR (ppm, 75 MHz, DMSO-d6): δ = 169.5 (C, C-12), 162.2 (C, C-2), 154.4 (C, C-7), 153.0 (C, C-4), 151.8 (C, C-10), 151.8 (C, C-1'''), 130.2 (C, C-9'), 129.6 (CH, C-3", -5"), 128.1 (C, C-5'), 127.5 (C, C-4'), 126.4 (CH, C-9), 125.1 (CH, C-5), 124.5 (C, C-8), 122.9 (CH, C-3", -5"), 120.5 (CH, C-2", -6"), 115.8 (CH, C-3), 113.4 (CH, C-10), 109.4 (CH, C-6), 50.1 (CH3, OCH3-7), and 33.2 (CH2, C-11).
Valuation of the Anti-Aerobic Gram-Negative Bacterial Potential (anti-ANBac)

To estimate anti-ANBac potential, a broth microdilution assay was used with methylsulfoxide (DMSO) as a negative criterion, Ciprofloxacin (Cipr) as an anti-ANBac reference, and Mueller-Hinton broth (MHB) as an evolution-enhanced culture. In brief, 7.500 mg of a test compound in 5.00 mL of DMSO was used to make the principal solution. An aqueous diluent was then used to prepare a set of thirteen diluted concentrations in a doubly serial manner, with orders between 1024 and 0.25 μg/mL. In a coded test tube, 3.00 mL of MHB, 0.20 mL of a bioinoculant calibrated to 0.50 McFarland, and 1.00 mL of the appointed concentration were pipetted consecutively. At 37.0 °C, the samples were incubated for 24 hours. Then, the bacterial evolution was investigated by the eye. To specify the Minimum Inhibitory Concentration (MIC), the former proceedings were repeated for the identified concentration that indicated nearly zero bacterial revolution by utilizing diluted quantities on a 4.0, 1.0, 0.50, and 0.050 basis. In addition, from the second set, 0.50 mL of the diluted concentrations with 3.00 mL of MHB was brooded to measure the Minimum Bactericidal Concentration (MBC). Following that, the MBC values were divided over the MIC values to compute the Potency Factor (PF). The result optimization was achieved by triplicating the procedure steps [45,46].

Valuation of the Anti-Anaerobic Bacterial Potential (anti-AABac)

A procedure similar which is used for evaluating the anti-ANBac potential was employed to estimate the anti-AABac potential, with certain noticeable differences. Utilizing both Metronidazole (Metr) as an anti-AABac reference and Brucella blood agar (5% sheep blood) as an evolution-enhanced culture were among the changed measures. Besides this, a palladium metal as an activator, an anaerobe marker, and an anaerobic milieu (10.0% H₂, 10.0% CO₂, and 80.0% N₂) were used to support the system which incubates the anaerobic bacteria for 48 hours at 37.0 °C [40].

Valuation of the Antifungal Potential

The procedure steps followed to screen the antifungal potential of the eight prepared compounds differed slightly from those employed to evaluate their anti-ANBac potential. Variations comprised incubating the fungi at 30.0 °C for 48 hours as well as utilizing Nystatin (Nyst) as a reference and Sabouraud-dextrose broth as a culturing medium [47].

Computer-Based Pharmacokinetic Properties (ADME)

The ADME (absorption, distribution, metabolism, and excretion) and drug-like properties of the synthesized naphthale-based derivatives were analyzed utilizing the pre-ADMET predictor server which depends on the two-dimensional skeletal formula of the tested compounds [48].

Results and Discussion

Designing the Synthetic Pathway

As illustrated in Scheme 1, the design and synthesis of naphthale-based derivatives involved several steps. These steps begin with the aromatic nucleophilic substitution reaction by forming a diazonium salt intermediate at the C-6 position of 6-amino-7-chloronaphthalen-2-ol utilizing nitric acid sodium salt, MeOH, and ethanoic acid to produce SF0. It is noteworthy that this reaction is novel and was used for the first time here to substitute the amino group in the aromatic ring with the methoxy group [40]. Then, by applying two methods based on the Pechmann reaction, a naphthale-based derivative, SF1, was prepared. The classic Pechmann reaction was chosen for the synthesis of this derivative because of the starting material’s generality and availability, as well as the product’s high yield [35].

In method A, the 2-naphthol compound SF0 was condensed with acetone dicarboxylic acid, affording the tri-functionalized naphthale-based derivative SF1 in a good yield of 79.76% by using concentrated H₂SO₄ as a catalyst at RT for 24
hours [41]. While in method B, the condensation of SF0 with acetone dicarboxylic acid was achieved using concentrated H2SO4 as a catalyst to produce SF1 with an excellent yield of 88.09% by employing an ultrasound bath for 1.5 hours at 30.0°C. It’s important to mention that ultrasound-promoted reaction is a green method for chemical synthesis. Moreover, the sonication in method B reduced reaction time and increased the yield percentage [42,43].

Finally, the SF1 carboxylic acid group was transformed by the SOCl2 catalyst to prepare the acyl chloride-based intermediate. Then, different para-substituted phenolic compounds reacted with the generated intermediate to obtain the target derivatives (SF2-SF7) [44]. At the para position of the employed phenols, the group’s nature impacted the yield percentage of the prepared derivatives. The good electron-donating group gave the most elevated percentage, whereas the good electron-withdrawing group gave the most decreased percentage. Spectroscopical data was used to affirm the structures of the synthesized compounds.

**Computer-Based Pharmacokinetic Evaluation**

The analysis of the ADME profile of drug candidates is a significant constraint during drug discovery and lead compound selection. About 50% of the candidates failed in the development stages due to unacceptable ADME profiles. To avoid this failure, *in-silico* technologies were successfully applied to predict ADME-related properties and provide guidance in the initial stages of drug discovery processes. Besides, studying these properties may aid in choosing the proper lead compounds before conducting *in-vitro* and *in-vivo* studies, which results in saving time and funds [49-52].

The assessment of the obtained results, as reported in Table 1, revealed a number of intriguing points. First of all, the synthesized naphthalene-based derivatives had excellent human intestinal absorption (HIA) in the range of 97.46-98.93% and moderate Caco-2 cell line permeability. These findings indicated that the absorption through the intestine might depend on other mechanisms besides passive diffusion. This is due to Caco-2 cell models’ expression lacking certain transporters, mucus-secretory cells, and non-cellular parameters like bile acids and phospholipids which can also affect the absorption process. Further, tight junctions of the Caco-2 system make it less permeable to the compounds that can be absorbed paracellularly [53–55].

Moreover, SF2-SF7 derivatives inhibited the P-glycoprotein (P-gp) transporter. Hence, they can increase apical-to-basolateral intestinal permeability and bioavailability of drugs which are substrates for this efflux system. Also, the inhibition of the P-gp transporter can lead to several drug-drug interactions in the distribution and elimination processes [56]. In addition, the prepared naphthalene-based derivatives except SF1 inhibited the CYP3A4 enzyme, which is responsible for metabolizing and eliminating about 50% of marketed drugs, so inhibiting this enzyme will result in a drug-drug interaction [57]. Further, the synthesized derivatives inhibited the CYP2C9 enzyme, which may lead to drug-drug interactions with drugs which use this enzyme for their metabolism [58,59].

Likewise, the synthesized derivatives except SF0 had a high plasma protein binding capacity ranging between 89.46-100.00%, resulting in a low volume of distribution, a long plasma half-life, and a low clearance rate. High plasma protein binding capacity can also affect the efficacy because only the free fraction of the drug is responsible for pharmacological activity [60]. Also, the synthesized derivatives were non-permeable across the blood-brain barrier except SF0 which was permeable. Brain penetration is a critical factor considered when trying to avoid or target the brain during the designing step. Impermeability of compounds in the blood-brain barrier reduces or eliminates the risk of undesirable CNS side effects and toxicity [61-63].

Finally, Lipinski’s rule comprises four physicochemical parameter requirements that determine drug-likeliness for the oral delivery system, which involve H-bond acceptors ≤ 10, H-bond donors ≤ 5, a molecular mass ≤ 500.0, and log P ≤ 5.0. Generally, orally administered drugs should have no more than one break-up of these requirements to display good aqueous solubility.
and intestinal permeability profiles, or else absorption and bioavailability are likely to be poor. According to the in-silico study, the synthesized derivatives except SF0 complied with Lipinski’s rule. As a result, these compounds have lower attrition rates during drug development and clinical trials, and thus have a better chance of reaching the market [64,65].

Table 1: In-silico-based pharmacokinetic profile of the synthesized naphthalene-based derivatives

<table>
<thead>
<tr>
<th>Derivative code</th>
<th>Caco2-P nm/sec</th>
<th>Pgp inhibition</th>
<th>HIA</th>
<th>CYP3A4 inhibition</th>
<th>CYP2D6 inhibition</th>
<th>CYP2C9 inhibition</th>
<th>PPB %</th>
<th>BBB-P Cbrain/C.blood</th>
<th>Lipinski’s rule</th>
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<tr>
<td>SF0</td>
<td>32.85</td>
<td>Non</td>
<td>97.1%</td>
<td>Inhibitor</td>
<td>Non</td>
<td>Inhibitor</td>
<td>19.94</td>
<td>2.19</td>
<td>Suitable</td>
</tr>
<tr>
<td>SF1</td>
<td>2016</td>
<td>Non</td>
<td>98.93%</td>
<td>Non</td>
<td>Non</td>
<td>Inhibitor</td>
<td>89.46</td>
<td>0.010</td>
<td>Suitable</td>
</tr>
<tr>
<td>SF2</td>
<td>34.99</td>
<td>Inhibitor</td>
<td>96.79%</td>
<td>Inhibitor</td>
<td>Non</td>
<td>Inhibitor</td>
<td>91.89</td>
<td>0.07</td>
<td>Suitable</td>
</tr>
<tr>
<td>SF3</td>
<td>34.66</td>
<td>Inhibitor</td>
<td>95.60%</td>
<td>Inhibitor</td>
<td>Non</td>
<td>Inhibitor</td>
<td>92.88</td>
<td>0.16</td>
<td>Suitable</td>
</tr>
<tr>
<td>SF4</td>
<td>34.80</td>
<td>Inhibitor</td>
<td>94.26%</td>
<td>Inhibitor</td>
<td>Non</td>
<td>Inhibitor</td>
<td>92.51</td>
<td>0.06</td>
<td>Suitable</td>
</tr>
<tr>
<td>SF5</td>
<td>36.60</td>
<td>Inhibitor</td>
<td>93.69%</td>
<td>Inhibitor</td>
<td>Non</td>
<td>Inhibitor</td>
<td>93.94</td>
<td>0.08</td>
<td>Suitable</td>
</tr>
<tr>
<td>SF6</td>
<td>34.81</td>
<td>Inhibitor</td>
<td>92.46%</td>
<td>Inhibitor</td>
<td>Non</td>
<td>Inhibitor</td>
<td>96.65</td>
<td>0.08</td>
<td>Suitable</td>
</tr>
<tr>
<td>SF7</td>
<td>33.88</td>
<td>Inhibitor</td>
<td>91.76%</td>
<td>Inhibitor</td>
<td>Non</td>
<td>Inhibitor</td>
<td>100.00</td>
<td>0.09</td>
<td>Violated</td>
</tr>
</tbody>
</table>

Caco2-P: Caco2 cell permeability (human colorectal carcinoma), Pgp: P-glycoprotein, HIA: Human intestinal absorption, CYP3A4: Cytochrome-P450 3A4, CYP2D6: Cytochrome-P450 2D6, CYP2C9: Cytochrome-P450 2C9, PPB: Plasma protein binding, BBB-P: Blood-brain barrier penetration, Lipinski’s rule: Role of five.

Assessment of the Antimicrobial Potentials

Anti-ANBac Potential

In this study, the pure synthesized naphthalene-based derivatives were tested in-vitro versus six strains of pathological ANBac via a broth microdilution assay. These strains comprised Shigella dysenteriae (Sh-dy, 13313-ATCC), Salmonella typhi (Sa-ty, 6539-ATCC), Escherichia coli (Es-co, 25922-
ATCC), Haemophilus influenzae (Ha-in, 49247-ATCC), Klebsiella pneumonia (Kl-pn, 700603-ATCC), and Pseudomonas aeruginosa (Ps-ae, 27853-ATCC). The scores are displayed in Table 2 and illustrated as a diagram in Figure 1. According to the study’s findings, the synthesized derivatives had potential versus tested pathological ANBac strains in a varied pattern, but less than Cipr, with MIC and MNBC values ranging between 1.40-16.00 μg/mL and 2.05-28.15 μg/mL, respectively. The ranking of declining anti-ANBac potential matches with the order: SF5, SF2, SF3, SF0, SF4, SF6, SF7, and SF1, revealing that as the hydrophobicity of the synthesized derivatives increased, the anti-ANBac impact increased [66]. Compound SF5 exhibited superior bactericidal impact versus all the tested pathological ANBac strains. The authors attributed this remarkable impact to the moderate size of the Cl atom attached to position 4” in SF5, which, in addition, could behave as an acceptor of hydrogen bonds equinocially. From the author’s perspective, both the lipophilic and hydrophilic characteristics of the p-chlorophenyl unit in the chemical backbone of SF5 help interrupt the bacterial cell wall and fit with the targets [67,68]. Likewise, the presence of a carboxylic acid moiety, which is a hydrophilic functional group at position 12 of the compound SF1, may be the reason for its lower anti-ANBac potential than the other synthesized derivatives [69]. The PF values of naphthalene-based derivatives were in the range of 1.08–3.73, which suggests their bactericidal property versus all tested pathological ANBac strains [70].

Table 2: The data reported from the anti-ANBac potential assessment of the synthesized naphthalene-based derivatives

<table>
<thead>
<tr>
<th>ANBac strain</th>
<th>Parameters</th>
<th>Codes of the reference and tested synthesized derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cipr</td>
</tr>
<tr>
<td>NFEs-co</td>
<td>MIC</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>MNNBC</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.06</td>
</tr>
<tr>
<td>Sh-dy</td>
<td>MIC</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>MNNBC</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.45</td>
</tr>
<tr>
<td>Sa-ty</td>
<td>MIC</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>MNNBC</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.25</td>
</tr>
<tr>
<td>Es-co</td>
<td>MIC</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>MNNBC</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.12</td>
</tr>
<tr>
<td>Ha-in</td>
<td>MIC</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>MNNBC</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.08</td>
</tr>
<tr>
<td>Kl-pn</td>
<td>MIC</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>MNNBC</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.13</td>
</tr>
<tr>
<td>Ps-ae</td>
<td>MIC</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>MNNBC</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.13</td>
</tr>
</tbody>
</table>

The data were expressed in terms of μg/mL; MNPB: Minimum Non-Pathogenic Bactericidal Concentration; MNBC: Minimum Aerobic Gram-Negative Bactericidal Concentration

On the other hand, the pure synthesized naphthalene-based derivatives were investigated in-vitro versus the non-pathogenic ANBac strain (NFEs-co). The scores are displayed in Table 2 and illustrated as a diagram in Figure 2. Interestingly, the tested derivatives showed lower anti-NFEs-co impact compared to Cipr, with MIC and MNBC values ranging between 6.00-14.00 μg/mL and 3.50- 56.00 μg/mL, respectively. As a result, the authors concluded that the prepared naphthalene-based derivatives are less toxic to the tested normal flora than Cipr. The ranking of increasing the anti-NFEs-co potential matches the order: SF1, SF5, SF6, SF4, SF7, SF0, SF3, and SF2. Compound SF1 revealed the lowest anti-NFEs-co impact and the highest safety profile versus the...
tested normal flora, among other synthesized derivatives [71]. Also, the PF values of SF5 and SF4 compounds were 4.67 and 4.40, respectively, which demonstrates their bacteriostatic property versus the tested NFEs-co strain, while the other synthesized derivatives had PF values in the range of 0.44-3.50, which indicates their bactericidal property [70].

**Figure 1:** The diagram expresses the parameters of the anti-ANBac potential assessment of the synthesized naphthalene-based derivatives

**Figure 2:** The diagram expresses the parameters of the anti-NFEs-co potential assessment of the synthesized naphthalene-based derivatives

**Anti-AABac Potential**

An established Brucella-agar microdilution assay was used to assess the potential of pure synthesized naphthalene-based derivatives *in vitro* versus four pathological AABac strains under anaerobic conditions. These strains comprised *Prevotella melaninogenica* (**Pr-me**, 25845-ATCC), *Fusobacterium necrophorum* (**Fu-ne**, 25286-ATCC), *Clostridium perfringens* (**Cl-pe**, 13124-ATCC), and *Bacteroides fragilis* (**Ba-fr**, 25285-ATCC). The scores are demonstrated in Table 3 and depicted as a diagram in Figure 3. The synthesized derivatives revealed anti-AABac potential versus all tested strains but less than Metr, with MIC and MABC values ranging between 8.00-52.00 μg/mL and 10.00-84.00 μg/mL, respectively. In addition, they exhibited a varied pattern of anti-AABac activity which was in the following descending order: SF2, SF3, SF5, SF4, SF0, SF6, SF7, and SF1, indicating that as the hydrophilicity of the synthesized derivatives increased, the anti-AABac impact decreased [66]. Compound SF2 showed higher bactericidal impact versus tested AABac strains than other
synthesized derivatives, but it remained lower than Metr. The authors attributed this superior activity of SF2 to the existence of an electron-donating methoxy group at position 4'' of its chemical backbone, which may enhance bacterial cellular uptake [47]. Furthermore, the lower anti-AABac potential of SF1 compared to the other synthesized derivatives may be due to the existence of a hydrophilic carboxylic acid moiety at position 12 of its chemical backbone [69]. The PF values of the synthesized naphthalene-based derivatives were in the range of 1.22–2.63, which implies their bactericidal property versus all tested AABac strains [70].

**Table 3**: The data reported from the anti-AABac potential assessment of the synthesized naphthalene-based derivatives

<table>
<thead>
<tr>
<th>AABac strain</th>
<th>Parameters</th>
<th>Codes of the reference and tested synthesized derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Metr</td>
</tr>
<tr>
<td>Pr-me</td>
<td>MIC</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>MABC</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.20</td>
</tr>
<tr>
<td>Fu-ne</td>
<td>MIC</td>
<td>1.75</td>
</tr>
<tr>
<td></td>
<td>MABC</td>
<td>1.80</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.03</td>
</tr>
<tr>
<td>Cl-pe</td>
<td>MIC</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>MABC</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.27</td>
</tr>
<tr>
<td>Ba-fr</td>
<td>MIC</td>
<td>3.00</td>
</tr>
<tr>
<td></td>
<td>MABC</td>
<td>3.52</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.17</td>
</tr>
</tbody>
</table>

The data were expressed in terms of μg/mL; MABC: Minimum Anaerobic Bactericidal Concentration.

**Figure 3**: The diagram expresses the parameters of the anti-AABac potential assessment of the synthesized naphthalene-based derivatives

**Anti-fungal Potential**

The Sabouraud-dextrose broth dilution assay was employed to evaluate the anti-fungal potential of pure synthesized naphthalene-based derivatives in-vitro versus Aspergillus niger (As-ni, 16888-ATCC) and Candida albicans (Ca-al, 10231-ATCC) which are two fungal pathogens. The scores are indicated in Table 4 and represented as a diagram in Figure 4. The synthesized derivatives exhibited potential versus tested fungi strains, with MIC and MFC values in the range of 1.25-32.00 μg/mL and 1.70-44.00 μg/mL, respectively. Also, the synthesized derivatives demonstrated a similar pattern of fungicidal impact, which corresponded with the following descending order: SF1, SF5, SF4, SF0, SF2, SF3, SF7, and SF6. Compounds SF1, SF5, SF4, and SF0 had an excellent fungicidal impact, even better than Nyst.
versus As-ni and Ca-al. Compounds SF2, SF3, SF7, and SF6 had a good fungicidal impact versus tested fungi, however they were less effective than Nyst, except SF3, which had similar activity to Nyst versus Ca-al. The authors assumed the superior potential of SF1, SF5, and SF4 was due to functional groups present in their chemical backbones, including COOH at position 12 in SF1, Cl at position 4’ in SF5, and F at position 4’’ in SF4. The attachment of these groups to a highly conjugated system can enhance fitting and bind to the target pockets along with improving cellular uptake [47]. The PF values of naphthalene-based derivatives were in the range of 1.22–2.63, which alludes to their fungicidal property versus As-ni and Ca-al [70,72–74].

Table 4: The results of the anti-fungal potential evaluation of the synthesized naphthalene-based derivatives

<table>
<thead>
<tr>
<th>Fungal strain</th>
<th>Parameters</th>
<th>Codes of the reference and tested synthesized derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nyst</td>
</tr>
<tr>
<td>As-ni</td>
<td>MIC</td>
<td>8.00</td>
</tr>
<tr>
<td></td>
<td>MFC</td>
<td>12.00</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.50</td>
</tr>
<tr>
<td>Ca-al</td>
<td>MIC</td>
<td>4.00</td>
</tr>
<tr>
<td></td>
<td>MFC</td>
<td>6.00</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>1.50</td>
</tr>
</tbody>
</table>

The data were expressed in terms of μg/mL; MFC: Minimum Fungicidal Concentration.

Figure 4: The diagram expresses the parameters of the anti-fungal potential assessment of the synthesized naphthalene-based derivatives

Conclusion
In summary, a novel series of tri-functionalized naphthalene-based derivatives was successfully synthesized based on the Pechmann condensation reaction. According to the antimicrobial screening conducted on the synthesized derivatives, intriguing results have been revealed. The synthesized naphthalene-based derivatives showed anti-infective potential with different patterns. The chlorinated-derivative SF5 demonstrated a distinctive bactericidal impact on aerobic gram-negatives. It also exhibited a high safety versus the normal flora strain. In addition, the synthesized derivatives had a moderate bactericidal impact on anaerobic strains. Interestingly, most synthesized derivatives had excellent fungicidal impact versus the tested fungi strains, even better than the used reference antibiotic. The maximum fungicidal impact was achieved with the derivative SF1. Also, the results of in-silico analysis indicated that most of the synthesized derivatives had appropriate theoretical pharmacokinetic properties and suitable drug-likeness for the oral delivery system. As a result, they have lower attrition rates during drug development and clinical trials. The data provided here could aid in the development of effective anti-infective medicines with low toxicity.

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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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