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Synthesis, Characterization, Molecular Docking, and *In Silico* ADME Study for Some New Different Derivatives for Succiniohydrazide

Asmaa A. Maryoosh[1,2*] and Oday H. R. Al-Jeilawi[1]
[1] Department of Chemistry, College of Sciences, University of Baghdad, Baghdad, Iraq.
[2] Department of Chemistry, College of Science, Mustansiriyah University, Baghdad, Iraq.
*Corresponding Author.

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Abstract

Many studies have found effective oral influenza virus inhibitors based on an aryl benzoyl hydrazide scaffold and antiviral. This study aims to prepare a new series of derivatives containing succinohydrazide as a precursor. In the first step, after synthesis of their precursor, it has been prepared di benzoyl succinohydrazide using a two-step process that involved reacting (o,m,p)-chloro benzoic acid with thionyl chloride to obtain freshly prepared substituted benzoyl chloride derivatives that were then reacted with succinohydrazide, or by a second method, directly reacting substituted benzoyl chloride with succinohydrazide to give benzoylsuccinohydrazide derivatives. After that, different derivatives were prepared involving the reaction of succinohydrazide with substituted benzene sulphonyl chloride, benzyl chloride, and phenacyl chloride. FTIR, ^{1}HNMR, and ^{13}CNMR spectra have been used to verify the structures of newly synthesized compounds. The Swiss ADME method with boiled egg prediction was used to analyze its pharmacokinetic properties. Then, genetic optimization of linkage docking (GOLD) was used in theoretical studies to investigate the binding mechanism of the protein-ligand produced with the protein (1SA0). Among all synthesis compounds, compound 2b has excellent results compared with colchicine and can be considered a good anti-bacterial against Escherichia coli and an anti-breast cancer drug.

Keywords: ADME, benzohydrazide, benzylhydrazide, Lipinsky rule, molecular docking, sulfonohydrazide,

1. Introduction

Microtubules (α,β-tubulin heterodimers) are essential components of eukaryotic cell structure and play important roles in a variety of cellular processes, including cell shape determination and repair, motility regulation, intracellular building organization, secretion, cellular transport, and cell division (1,2). Microtubules have been identified as a viable target

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for chemotherapeutic drugs targeting breast cancer cells during the last three decades due to their critical roles in the cell's life cycle (3, 4). Tubulin, a (α, β-heterodimer) first discovered as the cellular colchicine-binding protein, targets many small-molecule ligands that interact with microtubule dynamics and are therapeutically beneficial, notably in cancer therapy (5). Colchicine binding sites have been modified in terms of chemical structure and pharmacokinetic properties and examined to develop a highly effective, low-toxicity medicine for cancer treatment (6). Sulfonamide is one of the essential building blocks in organic chemistry, with numerous pharmaceutical and pharmacological agents exhibiting antibacterial, antibacterial, antitiviral, anti-obesity, anhydrase, HIV protease inhibitors, diuretics, antithyroid, antitumor, and anti-neuropathic pain activity (7,8). New oxadiazole-ringed sulfonamides may inhibit b-glucuronidase (9). Previously proven to have great potential, sulphonamides containing aliphatic moieties were synthesized and tested for their α-glucosidase, anti-urease, antibacterial, and antibacterial properties (10). In organic solvent-free water-based sulfonyl hydrazide synthesis, an equimolar amount of sulfonyl chlorides and hydrochlorides react at 60˚C for 1 hour in water with Et3N to form a series of substituted hydrazides (11).

Many researchers have found effective oral influenza virus inhibitors based on an aryl benzoyl hydrazide scaffold and antiviral (12). Drug development, materials, and agrochemicals use benzylic derivatives. In environmentally friendly solvents, many methods produce benzylic derivatives on beneficial pharmaceutical molecules (13). Some benzyl derivatives are used as inhibitors of the corrosion of carbon steel in HCl and H_2SO_4 media (14,15). Some compounds from aryl sulfonylhydrazides and benzylic ammonium salts have good efficiency and simple handling (16). Aryl benzoyl hydrazide derivatives have been studied in silico as influenza virus antivirals, and these showed significant antiviral factors and antimicrobial agents (17,18). Lipinski's rule of five (Ro5) is used in drug development to predict if a bioactive molecule is orally bioavailable based on drug physicochemical features like absorption, distribution, metabolism, and excretion (ADME) (19). Early prediction of ADME parameters has been shown to significantly reduce the rate of pharmacokinetic failure in clinical phases during the design phase and determine if a compound has a chance to be a promising drug (20).

GOLD refers to the "genetic method for docking flexible ligands into a protein binding site." It shows the optimum orientation for a ligand that links to a protein's active site (21,22). The "BOILED-Egg" predicts small molecule intestinal absorption and brain penetration (23). It estimates small molecules' lipophilicity, polarity, human intestinal absorption (HIA), and brain access (BBB) (20) and tests therapeutic candidate assessment (20). Drug-likeness, medicinal chemistry, ADME pharmacokinetics, and physicochemical features are connected to this model (22). This study aims to prepare a new series of derivatives containing succinohydrazide as a precursor.

2. Materials and Methods

2.1. Instruments

All chemical compounds were used without further purification and obtained from BDH, Fluka, Aldrich, and Merck companies. Thin-layer chromatography (TLC) was used on pre-

coated Merck (Macherey-Nagel, Germany) silica gel 60-F plates with a layer thickness of 0.25 mm (Merck). A mixture of hexane 3:2 ethanol was used to develop the solvent system TLC eluent, and an ultraviolet lamp detected the spots. A molecular docking study was done at the College of Pharmacy /Al-Nahrain University. The melting points of the synthesized compounds were recorded using an electro-thermal melting point apparatus. The IR analysis was conducted using an FT-IR ALPHA II spectrometer (Bruker) at Mustansiriyah University/College of Science. NMR analyses were performed via ^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz (VARIAN-INOVA). The solvent used was (DMSO-d6), and the internal reference was TMS.

2.2. Synthesis of succinohydrazide (1)

Succinohydrazide was produced using previously reported methods and described [24] physical properties show in **Table 1**. FT-IR (υ, cm^{-1}): 3306,3286 (NH_2), 3180 (N-H), 2981,2875 (C-$H_{aliph.}$), 1622 (C=O_{amide}); ^{1}H NMR ($\delta\sigma_H$, ppm): 8.98 (2H, s, N<u>H</u>-C=O), 4.14 (4H, s, N<u>H</u>$_2$), 2.61-2.57 (4H, t, C<u>H</u>$_2$); ^{13}C NMR (δ_C, ppm): 171.22 (C=O), 29.40 (<u>C</u>H_2-CH_2).

2.3. Synthesis of N'^{1},N'^{4}-dibenzoylsuccinohydrazide (2a) and N'1,N'4-bis(4-methoxy benzoyl) succinohydrazide (2b)

Succinohydrazide was put in a round bottom flask fixed in an ice bath (0.6 g, 4 mmol) with 15 mL of THF as a reaction solvent, and the mixture was homogenized using a magnetic stirrer. An (8 mmol) of (benzoyl chloride or p- methoxybenzoylchloride) was introduced dropwise with steady stirring at 0˚C for 1 hour. TLC checked the reaction, and when the reaction was done, it was neutralized by adding 5% sodium bicarbonate solution until it neutralized and was allowed to settle down. Finally, after filtering out the separated solid, the solid was washed with distilled water to obtain compounds (2a-b). **Table 1** shows the physical properties (25).

2.3.1. N'1, N'4-dibenzoylsuccinohydrazide (2a)

The FT-IR (υ, cm^{-1}): 3192 (N-H), 3030 (C-H_{arom}), 2933,2878 (C-$H_{aliph.}$), 1692 (NHC=O_{amide} CH_2),1667 (NHC=O_{amide}Ph), 1594,1573 (C=$C_{arom.}$); ^{1}H NMR (δ_H, ppm): 10.32 (2H, s, NH-C=OPh),9.96 (2H, s, N<u>H</u>-C=OCH_2), 7.95–7.47 (10H, m, Ar-H), 2.56-2.51 (4H, t, C<u>H</u>$_2$); ^{13}C NMR (δ_C, ppm): 171.05 (NH<u>C</u>=$O_{amide}CH_2$),165.92 (NHC=O_{amide}Ph), 132.22-127.87 (Ar-C), 28.96 (<u>C</u>H_2-CH_2).

2.3.2. N'1, N'4-bis (4-methoxybenzoyl) succinohydrazide (2b)

The FT-IR (υ, cm^{-1}): 3208 (N-H), 3021 (C-$H_{arom.}$), 2977,2844 (C-$H_{aliph.}$), 1686 (NHC=O_{amide} CH_2),1637 (NHC=O_{amide}Ph), 1606,1577 (C=$C_{arom.}$) 1025,843 (*p*-sub.); ^{1}H NMR (δ_H, ppm): 10.17 (2H, s, N<u>H</u>-C=OPh),9.89 (2H, s, N<u>H</u>-C=OCH_2), 7.87–7.00 (8H, q, Ar-H), 3.81 (6H, s, O<u>CH</u>$_3$), 2.61-2.54 (4H, t, C<u>H</u>$_2$); ^{13}C NMR (δ_C, ppm): 171.12 (NH<u>C</u>=$O_{amide}CH_2$),165.46 (NHC=O_{amide}Ph), 162.42-114.12 (Ar-C), 55.83 OCH_3, 29.01(<u>C</u>H_2-CH_2).

2.4. Synthesis of N'^{1},N'^{4}-bis(2-chlorobenzoyl)succinohydrazide (2c), N'^{1},N'^{4}-bis(3-chloro benzoyl)succinohydrazide (2d), N'^{1},N'^{4}-bis(4-chlorobenzoyl)succinohydrazide (2e)

A 100 mL one-neck round bottom flask was attached to a reflux condenser (0.3 g, 2 mmol) of each different substituted chloro benzoic acid, then added (2.5 mL, 3 mmol) of thionyl chloride. The reaction was performed under reflux conditions for 3 hours to obtain the corresponding acid chloride. The excess of thionyl chloride was evaporated, and without separation, succinohydrazide (1) was added, followed by continuous reflux for (3-6) hours. Check the end of

the reaction by TLC. The product (2c-2e) was obtained as crystals. Physical properties are shown in **Table 1** (26).

2.4.1. N'1, N'4-bis (2-chlorobenzoyl) succinohydrazide (2c)

The FT-IR (υ, cm^{-1}): 3202 (N-H), 3081 (C-$H_{arom.}$), 2929, 2855 (C-$H_{aliph.}$), 1698 (NHC=O_{amide} CH_2), 1622 (NHC=O_{amide}Ph), 1605, 1576 (C=$C_{arom.}$) 1098,831 (*o*-sub.).

2.4.2. N'1, N'4-bis (3-chlorobenzoyl) succinohydrazide (2d)

The FT-IR (υ,cm^{-1}): 3207 (N-H), 3031 (C-$H_{arom.}$), 2950,2870 (C-$H_{aliph.}$), 1686 (NHC=$O_{amide}CH_2$), 1638 (NHC=O_{amide}Ph),1597,1570 (C=$C_{arom.}$) 1138, 897 (*m*-sub.); ^{1}H NMR (δ_H, ppm): 10.47(2H, s , N<u>H</u>-C=OPh),10.04 (2H, s , N<u>H</u>-C=OCH_2), 7.87 – 7.49 (8H, m, Ar-H), 2.57-2.53 (4H, t,C<u>H</u>$_2$); ^{13}C NMR (δ_C, ppm): 170.98 (NH<u>C</u>=$O_{amide}CH_2$), 164.53 (NHC=O_{amide}Ph), 134.89-127.70 (Ar-C), 28.88(<u>C</u>H_2-CH_2).

2.4.3. N'1, N'4-bis (4-chlorobenzoyl) succinohydrazide (2e)

The FT-IR (υ, cm^{-1}): 3174 (N-H), 3048 (C-$H_{arom.}$), 2922, 2850 (C-$H_{aliph.}$), 1679 (NHC=O_{amide} CH_2), 1639 (NHC=O_{amide}Ph), 1591,1573 (C=$C_{arom.}$) 1091,850 (*p*-sub); ^{1}H NMR (δ_H, ppm): 10.39 (2H, s, PhNH-C=O), 9.96 (2H, s, CH_2N<u>H</u>-C=O), 7.91 – 7.52 (8H, q, Ar-H), 2.82-2.47 (4H, t, C<u>H</u>$_2$); ^{13}C NMR (δ_C, ppm):174.01(CH_2NHC=O_{amide}),166.88 (PhNHC=O_{amide}), 138.23-129.21 (Ar-C), 29.23 (<u>C</u>H_2-CH_2).

2.5. Succinyl dibenzenesulfonohydrazide derivatives (3a-c) [10]

A mixture of compound (1) (0.6 g, 4 mmol) and various substitutes (benzene sulphonyl chloride, p-bromo benzene sulphonyl chloride (1.047 mL, 8 mmol) in ethanol (25 mL), and a few drops of GAA were added and stirred for (10-15 min). In comparison, p-methylbenzene sulphonyl chloride (1.525 g, 8 mmol) in 25 mL ethanol and the addition of a few drops of GAA under reflux conditions for (30 min) led to the formation of a white precipitate with a good yield. The release of a gas that changes the color of the blue litmus paper to red was noticed, a checked completion reaction by TLC. The fine white powder was obtained after being filtered, dried, and recrystallized with n-hexane. **Table 1** lists the physical properties.

2.5.1. N', N'''-succinyldibenzenesulfonohydrazide (3a)

The FT-IR (υ, cm^{-1}): 3206 (N-H), 3065 (C-$H_{arom.}$), 2971, 2 927(C-$H_{aliph.}$), 1688 (NHC=O_{amide}), 1583, 15 12(C=$C_{arom.}$)1376, 11 62(SO_2).

2.5.2. N', N'''-succinylbis (4-bromobenzenesulfonohydrazide) (3b)

The FT-IR (υ, cm^{-1}): 3289 (N-H), 3102 (C-$H_{arom.}$), 2996, 2931 (C-$H_{aliph.}$), 1665 (NHC=O_{amide}) 1601, 1577 (C=$C_{arom.}$)1386,1174 (SO_2) 1000,824 (*p*-sub); ^{1}H NMR (δ_H, ppm): 10.91 (2H, s, N<u>H</u>-SO_2),9.78 (2H, s, N<u>H</u>-C=O),7.57–7.52(8H, q, Ar-H), 2.61-2.60 (4H, t, C<u>H</u>2); ^{13}C NMR (δ_C,ppm):170.92 (NHC=O_{amide}), 147.35-122.52 (Ar-C), 27.62 (<u>C</u>H_2-CH_2).

2.5.3. N', N'''-succinylbis (4-methylbenzenesulfonohydrazide) (3c)

The FT-IR (υ, cm^{-1}): 3271 (N-H), 3060 (C-$H_{arom.}$), 2979, 2860 (C-$H_{aliph.}$), 1669 (NHC=O_{amide}), 1574, 1534 (C=$C_{arom.}$)1362,1159 (SO_2) 1007,811(*p*-sub); ^{1}H NMR (δ_H, ppm): 10.97 (2H, s, N<u>H</u>-SO_2), 10.46 (2H, s, N<u>H</u>-C=O),7.50–7.11(8H, q, Ar-H), 2.63-2.59(4H, t, C<u>H</u>$_2$);^{13}C NMR (δ_C, ppm): 173.77 (NHC=O_{amide}), 138.79-125.94 (Ar-C), 28.13 (<u>C</u>H_2-CH_2) 21.22 (CH_3).

2.6. Synthesis of dibenzyl succinohydrazide derivatives(4a-c) [27] **with modification**

In a round-bottom flask, a mixture of compound (1) (0.6 g, 4 mmol) was added to 10 mL DMF with heating, and (1.11 mL, 8 mmol) from Et_3N was added as a catalyst; (8 mmol) of benzyl chloride with a different substituent in DMF (10 mL) was added. After 15-25 hours of reflux, the mixture was poured over grinding ice and extracted with diethyl ether. The physical characteristics are detailed in **Table 1**.

2.6.1. N'1, N'4-dibenzylsuccinohydrazide (4a)

The FT-IR (υ, cm^{-1}): 3400 (N-H), 3033 (C-$H_{arom.}$), 2978, 2882 (C-$H_{aliph.}$), 1664 (NHC=O_{amide}), 1639, 1540 (C=$C_{arom.}$).

2.6.2. N'1, N'4-bis (2-nitrobenzyl) succinohydrazide (4b)

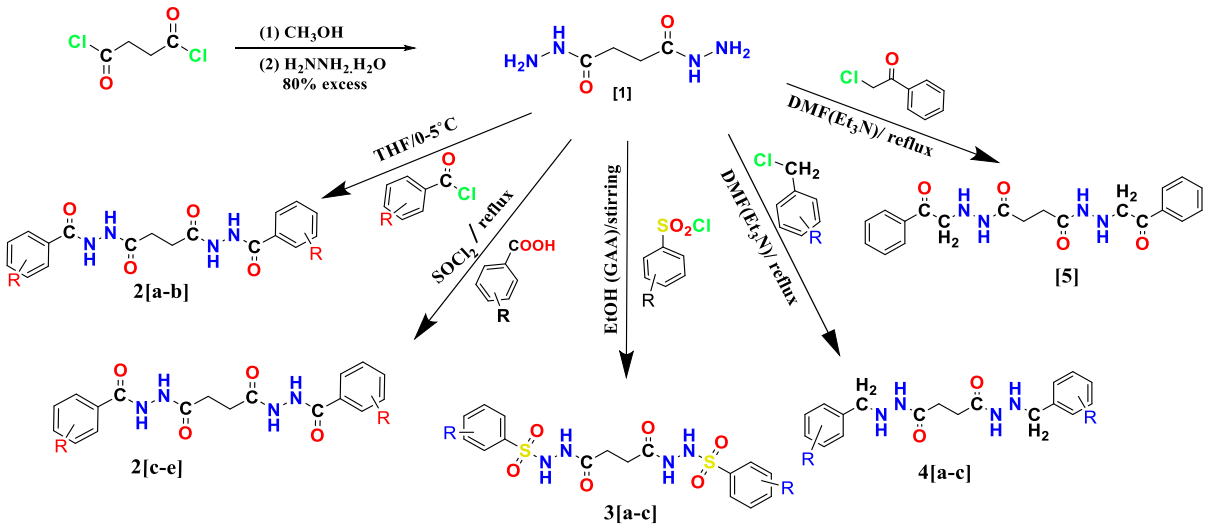
The FT-IR (υ, cm^{-1}): 3391 (N-H), 3088 (C-$H_{arom.}$), 2946, 2880 (C-$H_{aliph.}$), 1668 (NHC=O_{amide}), 1623,160 (C=$C_{arom.}$)1521, 1319 (NO_2)1130, 743 (*o*-sub).

2.6.3. N'1, N'4-bis (4-nitrobenzyl) succinohydrazide (4c)

The FT-IR (υ, cm^{-1}): 3214 (N-H), 3073 (C-$H_{arom.}$), 2968, 2887 (C-$H_{aliph.}$), 1668 (NHC=O_{amide}), 1655, 1598 (C=$C_{arom.}$)1510,1339 (NO_2) 1106,850 (*p*-sub); ^{1}H NMR (δ_H, ppm): 9.01 (2H, s, NH-C=O), 5.35 (2H, s, $NHCH_2$), 8.15–7.63 (8H, q, Ar-H), 4.13 (PhCH_2), 2.74-2.71 (4H, t, CH_2); ^{13}C NMR (δ_C, ppm): 170.99 (C=O_{amide}), 146.39-123.63 (Ar-C), 54.18 (PhCH_2), 29.20(CH_2-CH_2).

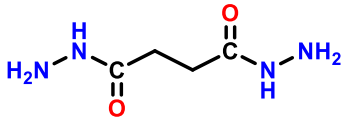
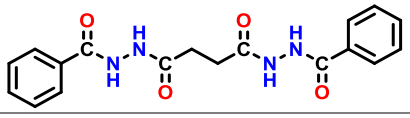
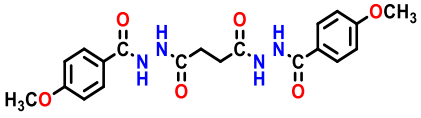
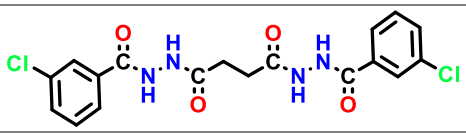
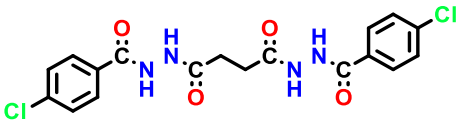
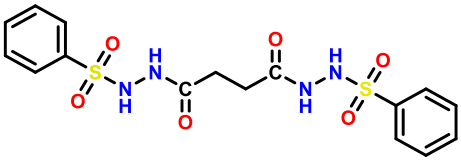
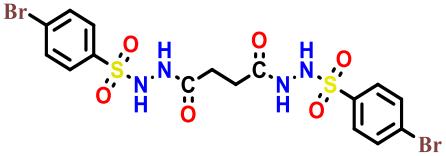
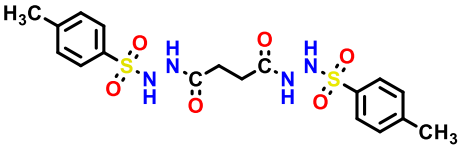
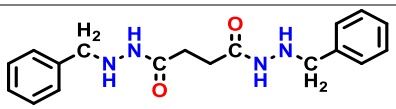
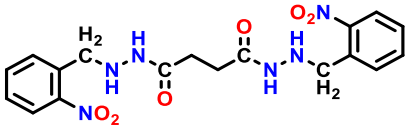
2.7. Synthesis of N'1,N'4-bis(2-oxo-2-phenylethyl) succinohydrazide (5) (28).

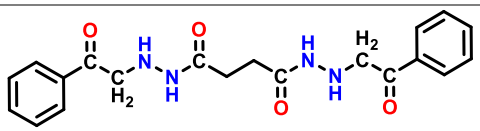
A mixture of compound (1) (0.3 g, 2 mmol) and phenacyl chloride (0.6 g, 4 mmol) in 15 mL of DMF in the presence of Et_3N (0.55 mL, 4 mmol) was refluxed for 5 hours (According to TLC results). The mixture was put on grinding ice after the end of the reaction. The product is then extracted using diethyl ether in a separation funnel and dried. The physical properties of the compound are detailed in **Table 1**. FT-IR (υ, cm^{-1}): 3124 (N-H), 3059 (C-Harom.), 2980, 2878 (C-Haliph.), 1717 (C=OKetone) 1686 (C=Oamide), 1640, 1595 (C=Carom.).



Scheme1. Synthesis of derivatives (1-5).

Table 1. Chemical formula, physical properties, and molecular weight of the synthesized compounds (1-5).

No.	Chemical structure	Color	Melting point (°C)	Stirring/ reflux time reaction	Yield (%)	M.wt (g/mol)
1		bright white*	172-170	3 hr. Stirring	95	146.15
2a		white	187-190	1 hr. stirring	85	354.37
2b		white	210-213	0.5 hr. Stirring	88	414.42
2c		Dark off white	183-186	9 hr. reflux	80	423.25
2d		Dark off white	175-178	5.25 h. reflux	68	423.25
2e		Dark off white	180-182	4 hr. reflux	75	423.25
3a		white	166-168	0.5 hr. stirring	75	426.46
3b		white	318 dec.	0.25 hr. stirring	70	584.25
3c		white	>300	0.5 hr. reflux	80	454.52
4a		Off white	Gummy	15 reflux	60	354.37
4b		orange	Gummy	19 hr. reflux	69	416.39

4c		orange	108-110	18 reflux	75	416.39
5		Pale yellow	101-104	5 reflux	56	382.42

***Literature (169-170) °C)**(24)

2.8. Computational study; molecular docking ADME analysis

Molecular docking determines the optimal orientation of a ligand that binds to a protein's active site, and the ligand's affinity impacts its binding and interaction (18). The Protein Data Bank (PDB:1SA0) https://www.rcsb.org offered enzyme crystal structures for docking. Swiss ADME with BOILED-Egg predicted the synthesized compound's physicochemical characteristics and pharmacokinetics, which was designed to forecast the tendency of small compounds to be absorbed by the gastrointestinal system or to access the brain (29). Good ADME features make synthetic compounds drug-like (30). Following Lipinski's requirements, the rule created by Christopher Lipinski of Pfizer in 1997 specifies that an orally active medicine should have no more than one violation of the following conditions: (1) ≤ 5 hydrogen bonding donors, (2) hydrogen bonding acceptors ≤ 10 (3) Molecular weight shouldn't go above 500 m/z. (4) The lipophilicity (CLogP) ≤ 5 (25). Oral drugs have a lower M.wt. and fewer H-bond donors, acceptors, and rotatable bonds than injectable. Pulmonary medicines have greater PSA because pulmonary permeability is less susceptible to polar hydrogen-bonding functionality (22). Drug properties like intestinal absorption and brain access help estimate drug development phases. The brain or bowel penetration method and estimating tool are used. BOILED-Egg accurately predicts its small compound's adipogenesis and polarization (29). Predictions of each brain region are obtained depending on physical and chemical properties and immediately converted into the molecular design (20). The data obtained is shown in **Table 2**.

3. Result and Discussion

3.1. Chemistry

As mentioned in the literature, succinohydrazide was prepared in this work. It was a precursor for synthesizing diverse derivatives by reacting with different organic compounds (benzoyl chloride, sulphonyl chloride, and phenacyl chloride). These reactions undergo the nucleophile-substitution mechanism. However, benzyl chloride reactions undergo an unimolecular nucleophilic substitution (SN1) mechanism. Steps The TLC technique monitored the synthesis of all these compounds, which was analyzed by FT-IR, ^{1}H, and ^{13}C NMR spectroscopy, as shown in **Scheme 1**.

3.2. Spectral analysis

All spectra were interpreted by Silverstein Spectrometric Identification of Organic Compounds 7th Ed. (31). The existence of a secondary amine group was indicated by the absence of NH_2 absorption in succinohydrazide 3305–3286 cm^{-1} and the appearance of N-H absorption in the range of 3400–3124 cm^{-1}. In addition, in derivatives from 2a–2e, the absorption band between 1698–1664 cm^{-1} contains $NHC=O_{amide}CH_2$ and 1669–1622 cm^{-1} contains $NHC=O_{amide}Ph$, whereas in 3a–3c derivatives, the absorption band between 1688–1665 contains $NHC=O_{amide}$ with the presence of two bands of SO_2 between 1386–1362 and 1174–1159. 4a–4c illustrate the existence of $NHC=O_{amide}CH_2$ between 1668 and 1664 and are distinguished by the appearance of two strong bands, 1521–1510 and 1339–1319, corresponding to NO_2. The bands observed in 1717 $C=O_{Ketone}$ and 1686 $C=O_{amide}$ are present in phenacyl derivative 5. The signal in the ^1H NMR spectra for derivative 1 is 8.98 for NH-C=O and 4.14 for free NH_2. Signals are seen at 10.47–10.17 ppm for NH adjacent to $PhC=O_{amide}$ and 10.04–9.89 ppm for NH adjacent to $CH_2C=O_{amid}$ in 2a–2e. Furthermore, 3b and 3c show signals in 10.97, 10.91 for $NH-SO_2$ and 10.46, 9.78 for $NHC=O_{amid}$, while 4c shows signals in 9.01 for NH-C=O, 5.35 for $NH-CH_2$, and 4.13 for CH_2-Ph. ^{13}C NMR indicates signals in 171.12 to 170.98 ppm for $CH_2C=O_{amid}$ and 165.92 to 164.53 ppm for $PhC=O_{amide}$. Signals 173.77 and 170.92 for NH-C=O appear in sulphonyl derivatives 3b and 3c. Finally, 4c shows $C=O_{amid}$ at 170.99 and $Ph-CH_2$ at 54.18. As a consequence, the synthesis of derivatives is approved.

3.3. *In silico* pharmacokinetics ADME properties

When synthesized compounds exhibit strong ADME qualities, they may be considered excellent candidates for drug-like properties. Oral bioavailability is more likely in molecules with five hydrogen bond donors HBD, ten hydrogen bond accepter HBA, a molecular weight< 500 g/mol, and a calculated Log P< 5 (20). Orally inactive compounds violate at least two of the Five Rules (32). The results in **Table 2**. indicate that all synthesis compounds 2a to 5 have no violations of Lipinski's rule except for 3b, which was excluded from the molecular docking study according to the ADME result. It has one violation in M.wt. that exceeded 500 g/mol, and all Compounds 2a to 5 have the highest docking scores by hydrogen bonds with the target protein (1SA0). The log shows no exceeding the normal range for any of the compounds. In the Lipinski rule of five, a score of 0.55 indicates strong bioavailability and permeability. It was estimated that the topological polar surface area (TPSA) indicates drug bioavailability. Oral bioavailability is likely low for substances with a TPSA greater than 140 that are passively absorbed; therefore, all prepared compounds fulfill this condition except for 3a, 3b, 3c, 4b, and 4c. The BOILED-Egg study 2b has high absorption in the gastrointestinal absorption score (GI absorption score), which estimates how well a molecule is absorbed in the small intestine after being taken orally and has excellent pharmacokinetic qualities based on the obtained results. If the result were high, the absorption would be high. The Swiss ADME software has also studied the blood-brain barrier (BBB) permeant. All synthesized compounds have no (BBB), indicating they aren't BBB- permeant. 2a, 2c, 2d, 2e, 4a, and 5; these derivatives expect to achieve high absorption in the digestive system but aren't penetrated in the central nervous system (CNS) by p-glycoprotein. This data is illustrated in **Tables 2, 3.** and **Figure 1**.

Table 2. Predicted ADME properties of the synthesized compounds.

	Physiochemical properties						Medicinal chemistry	Drug linkness	Pharmacokinetics		
Comp. NO.	**M.wt[a] (≤ 500)**	**NO HBD[b] (≤ 5)**	**NO HBA[c] (≤ 10)**	**NO RB[d]**	**TPSA[e] (Å²)**	**Log *Po*/w (iLOGP)[F] (≤ 5)**	**Synthetic accessibility**	**B.S[g]**	**P-gp[h]**	**BBB permeant[i]**	**GI Abs[j]**
2a	354.37	4	4	11	116.40	1.80	2.41	0.55	NO	NO	High
2b	414.42	4	6	13	134.88	2.53	2.67	0.55	YES	NO	High
2c	423.25	4	4	11	116.40	2.06	2.61	0.55	NO	NO	High
2d	423.25	4	4	11	116.40	2.64	2.50	0.55	NO	NO	High
2e	423.25	4	4	11	116.40	2.12	2.49	0.55	NO	NO	High
3a	426.46	4	8	11	167.30	0.65	3.19	0.55	YES	NO	Low
3b	584.25	4	8	11	167.30	0.99	3.26	0.55	YES	NO	Low
3c	454.52	4	8	11	167.30	1.59	3.33	0.55	YES	NO	Low
4a	326.40	4	4	11	82.26	1.88	2.48	0.55	NO	NO	High
4b	416.39	4	8	13	173.90	1.64	3.00	0.55	YES	NO	Low
4c	416.39	4	8	13	173.90	1.03	2.79	0.55	YES	NO	Low
5	382.42	4	6	13	116.40	2.05	2.79	0.55	NO	NO	High

[a] Molecular weight, [b] Number of hydrogen bond donor, [c] Number of hydrogen bond acceptors, [d]Number of rotatable bonds [e]Topological polar surface area, [f] logarithm of n-octanol-water partition coefficient, [g] Bioavailability score, [h]glyco protein substrate, [i]Blood–brain barrier, [j]GI gastrointestinal system.

Table 3. Docking scores estimated binding energy (kcal/mol) the binding energies for derivatives and colchicine docked with 1SA0.

Comp. number	Binding Energy (PLP Fitness) (Kcal/mol)	No. of Amino acids included in H-bonding	Amino acids included in H-bonding	No. of bonding	Power of bonding
2a	67.18	2	LYS 254	1	2.857
			ASN 101	1	2.923
2b	66.87	1	GLN 247	1	3.029
2c	69.99	1	LYS 254	1	2.616
2d	67.52	2	SER 178	1	2.841
			THR 179	1	2.736
2e	66.25	1	LYS 254	1	2.539
3a	68.62	2	LYS 254	1	2.812
			ASN 101	1	2.760
3c	67.07	2	ASN 101	2	2.914
					2.911
			TYR 224	1	2.986
4a	67.40	2	ASN 101	1	2.815
			GLN 11	1	2.944
4b	69.57	2	GLY 144	1	2.984
			LYS 254	1	2.796
4c	65.05	3	TYR 224	1	2.910
			LYS 254	1	3.065
			THR 179	1	3.023
5	71.77	1	LYS 254	1	2.825
Colchicine	52.44	3	ASN 101	1	2.733
			LYS 254	1	2.989
			SER 178	1	2.928

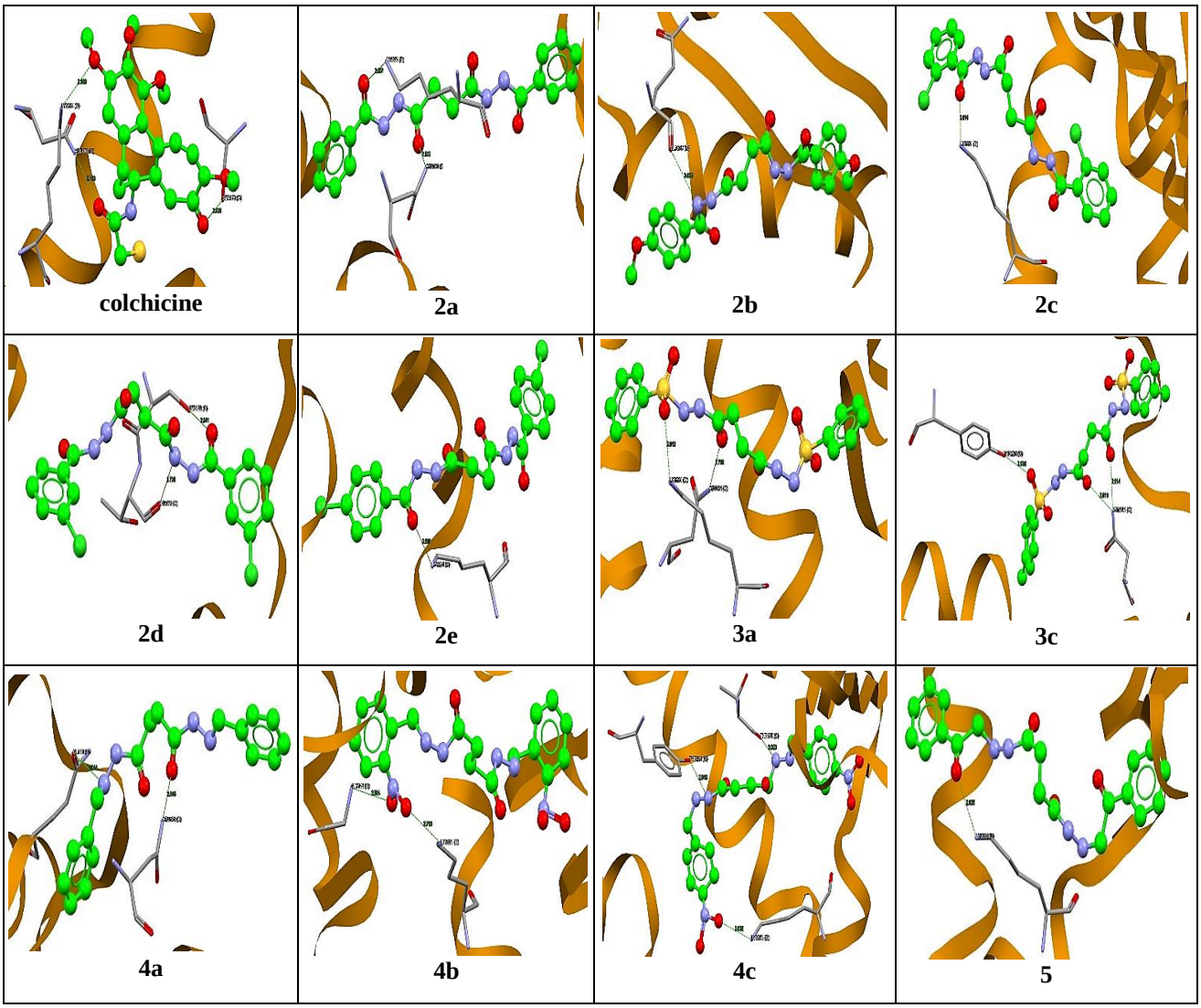


Figure 1. Interactions between target protein residues and various ligands: Ligands are shown as ball and stick shapes, with green, blue, red, and yellow representing carbon, nitrogen, oxygen, and sulfur atoms, respectively. Side chain residues are shown as sticks, with gray, blue, and red representing carbon, nitrogen, and oxygen atoms, sequentially.

4. Conclusion

The purpose of the current study was to prepare a series of different derivatives (1–5) derived from benzoyl chloride, benzyl chloride, sulphonyl chloride, and phenacyl chloride. After that study, molecular docking and ADME were supported by a Boiled Egg study with product yields ranging from 58 to 88%, and all of the prepared derivatives were proved by FT-IR, ^{1}H NMR, and ^{13} CNMR spectra. Among the prepared compounds, according to molecular docking studies, all synthesized compounds gave excellent results by showing the best bonding into the active site of 1SA0 protein, which candidate it to be good anti-bacterial against Escherichia coli and anti-breast cancer so that all synthesis compounds give excellent results by showing the best bonding (theoretically) in the active site of the 1SA0 protein, compared to colchicine drug. One of the more significant findings to emerge from this study is that the 2b derivative exhibits the most excellent absorption in GI and has a good bonding with the active

site of the protein more than the colchicine drug, and derivative 5 has the highest bonding into the active site of 1SA0 protein more than colchicine drug. Still, it can't penetrate the (CNS).

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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Ethical Clearance

This work has been approved by the Scientific Committee at the University of Baghdad/ College of Sciences, Department of Chemistry.

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