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Synthesis and Biological Evaluation of Furyl-Carboxamide Derivatives as Potential Anticancer Agents

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Abstract: Topoisomerase II (Top-II) is an essential therapeutic target in cancer treatment owing to its overexpression in a wide variety of cancerous cells, including colorectal and breast cancer. Significant efforts have been made to discover and develop competitive inhibitors of the Top-II enzyme as potential anticancer agents. Herein, molecular modeling was employed to identify a new series of furyl-2-carboxamide derivatives as potential anticancer agents. Compounds **3**, **5**, and **7** were synthesized and characterized with the aid of several spectroscopic techniques, such as FT-IR, NMR, and mass spectroscopy, as well as elemental analysis. The anticancer activity properties of compounds **3**, **5**, and **7** were evaluated *in vitro* using an MTT assay in a human colorectal HCT-116 cell line with different concentration dilutions. The results indicate that the anthraquinone compound **3** is 1.3-1.6 times more potent against human colon cancer HCT-116 cells than the pyridine and benzophenone compounds **7** and **5**, respectively, which reveals the importance of the anthraquinone moiety in exerting the inhibitory activity of the compound. Our findings recommend that further optimization of this series would benefit colon cancer treatment.

Keywords: Anticancer, furyl-2-carboxamide, docking, MTT assay, Top-II.

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INTRODUCTION

In developing countries, cancer is a multifaceted illness leading cause of death. Cancer kills one in every eight people worldwide, making it the second most common cause of death in the United States and Europe, behind only heart disease (1). According to estimates, 15 million new cancer patients will be diagnosed each year by 2020 (2). Surgeons created new cancer treatment methods in the last decades of the twentieth century by combining both surgeries, chemotherapy and/or radiation. In the last years, the use of multiple chemotherapy medications has resulted in the successful and effective treatment of various cancers. Anticancer drug resistance is a complicated process that occurs as drug targets shift and new chemotherapy agents have progressed rapidly and effectively (3). The essential pharmacophore of heterocyclic plays a role in the production of pharmacologically active chemical structures. Sulfur, nitrogen, and oxygen-containing in heterocyclic nuclei as therapeutic agents are an essential part of the processing of drug discovery, investigation, and development (6). Some of the synthesized compounds with the heterocyclic group showed a significant cytotoxic activity as compared to a reference control (7). For that reason, there is a growing need to identify suitable druggable

macromolecules that can be targeted selectively by antitumor agents in cancer cells. In an effort to find unique targets for anticancer agents, the Top II inhibitors have been demonstrated as plausible ones, which have been proved to play a crucial role in the pathology of cancer.

In this work, we tailored the backbone of 2-furoyl chloride to probe the effect of introducing benzophenone, anthraquinone, and pyridine on the accommodating Top-II binding pocket. The prospective derivatives were synthesized to investigate their structure-activity relationship (SAR) and improve their inhibitory activity as anticancer compounds.

MATERIALS AND METHODS

General synthetic procedure

Three novel derivatives of *2-furan-carboxamide N-(9,10-dioxo-9,10-dihydroanthracen-2-yl), N-(2-Benzoylphenyl), and N-(pyridine-2-yl)* were synthesized by fusion at high temperature, in which 2-furoyl chloride **1** was thoroughly mixed with 2-aminoanthraquinone **2**, 2-aminobenzophenone **4** and 2-aminopyridine **6** derivatives, respectively, and refluxed at 120 °C for 18 h. Then 1,4-dioxane was added, and the mixture was stirred for an additional 24 h at room temperature (8). The resulting products were filtered and recrystallized from chloroform/methanol to give the desired compounds **3**, **5**, and **7** (Scheme 1). ^{1}H NMR, ^{13}C NMR, IR, and MS analysis were used to confirm the structures of the target compounds.

Analytical procedures

Apparatus SMP10 (Stone, Staffordshire, UK). ^{1}H NMR and ^{13}C NMR spectra were collected on a Varian Oxford NMR300 spectrometer (Santa Clara, CA, USA). The samples were dissolved in $CDCl_3$ at a content of 0:3 – 0:7 wt-% and placed in 5-mm NMR tubes. High-resolution (HR) mass spectra were measured in the negative ion mode using the electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker Apex-4 (Tesla) instrument (Bremen, Germany). The samples were dissolved in acetonitrile, diluted in spray solution (methanol/water, 5:4.9, v/v+0.1-part formic acid), and infused using a syringe pump with a flow rate of 2 µL/min. External calibration was done using an arginine cluster in the mass range *m/z* 175 – 871.

Infrared (IR) spectra were recorded on a Shimadzu 8400F FT-IR spectrophotometer (Kyoto, Japan). The samples were dissolved in $CHCl_3$ and analyzed as thin solid films using NaCl plates or KBr discs (Merck, Darmstadt, Germany). Thin-layer chromatography (TLC) was performed on aluminum plates pre-coated with fluorescent silica gel, and the spots were visualized by UV light at 254 and/or 360 nm.

2-Furan-carboxamide N-(9,10-dioxo-9,10-dihydroanthracen-2-yl) **3**

2-Furoyl chloride **1** (0.43 g, 3.45 mmol) was treated with 2-aminoanthraquinone **2** (0.40 g, 1.8 mmol) and processed as described in general procedure section. Recrystallization afforded the *title compound* (0.554 g, 97.54%) as a brown-green solid; Rf: 0.58 (chloroform : methanol, 9.8 : 0.2); m.p.: 285 °C (decomposed); ^{1}H-NMR (300 MHz, DMSO-d_6): rotamers δ = 10.66 (s, 1H, NHCO), 8.52 (br s, 1H, Ar-H, H_3-furan), 8.21 (d, 1H, Ar-H), 8.19-8.07, d, 8.06-7.83, m; 7.40, d, 7.35, s, 7.29-7.27, d, (8H, Ar-H); ^{13}C-NMR (DMSO-d_6) rotomers: δ = 182.80 (CO-ketone), 181.67 (CO-ketone), 156.97 (CONH), 147.2776, 146.9122 (CH-Ar), 144.7427, 134.9315 (CH-Ar), 134.6143, 134.3856, 133.5075, 128.6764, 128.5715, 127.1481, 127.0549 (CH-Ar), 125.0627 (CH-Ar), 117.3430, 116.3521, 112.8203 ppm; IR: 3497 (CONH), 2921 (C-H aromatic), 1689, 1734 (ketone), 1282 (C-O). HRMS (ESI, positive mode): *m/z* ($M^+ + H^+$): Found 318.07608 ($C_{19}H_{12}N_1O_4$) requires 317.30.

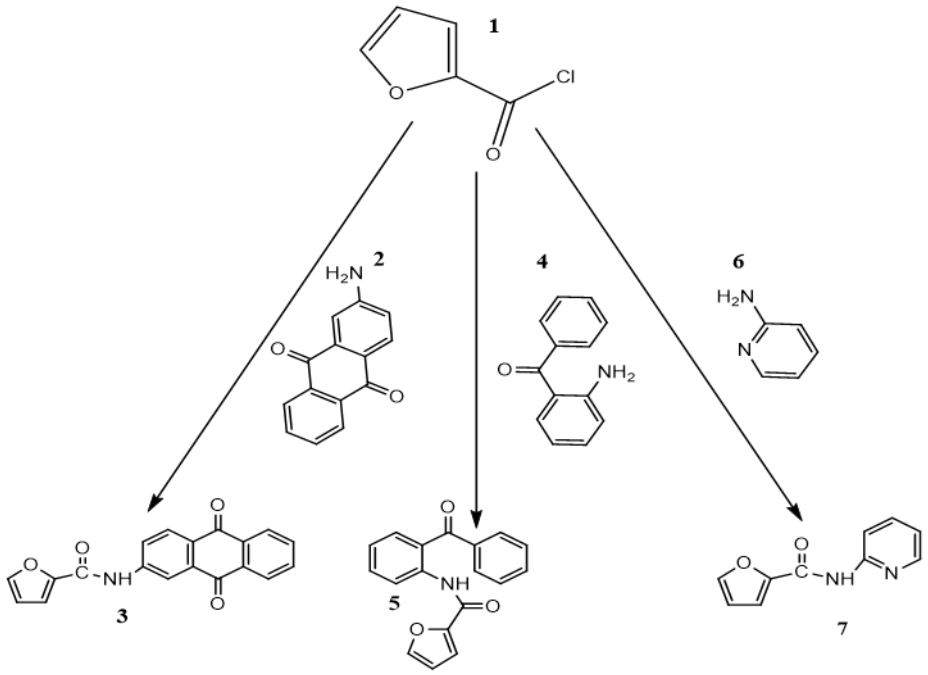
N-(2-Benzoylphenyl)-2-furan-2-carboxamide

2-Aminobenzophenone **4** (0.35 g, 1.77 mmol) and 2-furoylchloride **1** (0.43 g, 4.19 mmol) were mixed and processed as described in general procedure section. Recrystallization afforded the *title compound* (0.238 g, 46.2%) as a pale yellow solid; Rf: 0.8 (chloroform:methanol, 9.8:0.2); m.p.: 117 °C; ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 10.99 (br s, 1H, NHCO), 8.0474 (br s, 1H, Ar-H-2'), 8.0312 (d,1H, Ar-H-6'), 7.6718 (s, 1H, Ar-H-5), 7.6570 (d, 2H, Ar-H-2''&6''), 7.6261 (dd,1H, Ar-H-4''), 7.6107 (d, 2H, Ar-H-3''&5''), 7.5930 (m, 1H, Ar-H-5'), 7.5753 (d, 1H, Ar-H-4'), 7.5609 (d, 1H, Ar-H-3), 7.4785 (d, 1H, Ar-H-4), 7.1539 (d, 1H, Ar-H-4), 6.6238 (d, 1H, Ar-H-4); ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 197.2320 (CO-ketone), 156.4341 (CONH), 147.6107 (C-2), 146.4400 (C-5), 137.9514 (C-1'), 137.7469 (C-1''), 133.3220 (C-3'), 133.0372 (C-2'), 131.9800 (C-2''&6''), 130.1420 (C-6'), 128.7292 (C-3''&5''), 128.5554 (C-4''), 124.2936 (C-5'), 123.4369 (C-4'), 115.7523 (C-3), 112.8763 (C-4) ppm. IR: 3340 (CONH), 3086 (C-H aromatic), 1612 (ketone), 1435 (C=C aromatic); HRMS (ESI, positive mode): *m/z* ($M^+ + H^+$): Found 292.09682 ($C_{18}H_{14}N_1O_3$) requires 291.31.

N-(Pyridine-2-yl) furan-2-carboxamide **7**

2-Furylchloride **1** (0.43 g, 4.19 mmol) was added to 2-aminopyridine **6** (0.42 g, 4.46 mmol) and processed as described in general procedure section. Recrystallization afforded a white brown crystal solid (0.155 g, 18.5%); Rf: 0.13 (chloroform:methanol, 9.8:0.2); m.p.: 223 °C (decomposed); ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.0217 (br s, 1 H, NHCO), 8.4473 (d, 1H, Ar-H), 8.2207 (s, 1H, Ar-H), 8.0172 (s, 1H, Ar-H), 7.8940 (d, 1H, Ar-H), 7.4229 (m, 3H, Ar-H), 7.0094 (dd, 1H, Ar-H), 6.7292 (dd, 1H, Ar-H); ^{13}C-NMR (DMSO-d_6): rotamers δ = 157.5104

(CONH), 149.5901 (CH-Ar), 148.2859 (CH-Ar), 146.0175 (CH-Ar), 144.3656 (CH-Ar), 142.2762 (CH-Ar), 120.7421 (CH-Ar), 118.4750 (CH-Ar), 116.6861 (CH-Ar), 113.0626 (CH-Ar) ppm; IR (thin film): v = 3344 (NHCO), 2950 (C-H aromatic), 1327 (C=C aromatic), 1073 (CO) cm^{-1}; HRMS (ESI, positive mode): *m/z* ($M^+ + H^+$): Found 189.06585 ($C_{10}H_9N_2O_2$) requires 188.93.



Scheme 1: Preparation of 2-furan-carboxamide *N*-(9,10-dioxo-9,10-dihydroanthracen-2-yl) **3**, *N*-(3-benzoylphenyl)-2-furamide **5** and *N*-(pyridine-2-yl) furan-2-carboxamide **7**.

Experimental Section

MTT assay was purchased from (Bioworld/USA, CN: 42000092-3), Human carcinoma HCT-116 (colorectal) cell line was sourced from the American Type Culture Collection (ATCC, USA, CN: 302007, CCL-247™) and stored in liquid nitrogen. All other chemicals (fine super grade) were purchased from Across Organics (Amman, Jordan).

MTT assay: measuring cell viability

The method has been described previously by (9) and was adapted from Mosmann (10). MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] reagent was used to evaluate the antiproliferative activity of compounds **3**, **5**, and **7** on human cancer colorectal HCT-116 cell line. The carcinoma cells were maintained in RPMI-1640 medium supplemented with 10% (v/v) heat-inactivated fetal bovine serum (FBS), 1% L-glutamine (100X) and 1% penicillin-streptomycin (100X). The cells were seeded into 96-well plates at a density of 3×10^3 per well (180 µL per well) and allowed to adhere for 24 hrs at 37 °C/5% CO_2. Agent top stock solutions (10 mM in DMSO) were then freshly made. Serial dilutions were prepared in the same media as mentioned above for addition to colon cancer cells. Control wells received vehicle alone (20 µL per well). Final test agent concentrations in the wells were; 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 50 and 100 µM. The final concentration of DMSO in the wells never exceeded 1%. Vehicle control assays were performed (0.0001-1% DMSO). Experimental plates were incubated for a further 72 hrs period at 37 °C/5% CO_2. Cell viability was recorded at the time of agent addition (T_0), and after 72 hrs exposure: following the addition of MTT solution (2 mg/mL in PBS: 50 µL per well), experimental plates were incubated for 3 hrs to allow reduction of MTT by viable cells to insoluble dark purple formazan crystals. The supernatant in each well was then aspirated, and cellular formazan was solubilized by the addition of DMSO (150 µL per well). Absorbance was read at a wavelength of 550 nm using a Shimadzu UV-1601 spectrophotometer plate reader. The measured intensity is proportional to metabolic activity, which correlates with viable cell numbers. Estimated GI_{50} values (test agent concentrations that inhibit cell growth by 50%) were calculated using Microsoft Excel 2010 software. Results are expressed as the mean of three independent experiments (n = 8 per trial) (10).

RESULTS AND DISCUSSION

Growth inhibitory and cytotoxic effect of the synthesized furyl carboxamide derivatives

The antiproliferative activities of the furyl carboxamide derivatives **3**, **5**, and **7** plus the known anticancer drug Doxorubicin (9) were evaluated *in vitro* using MTT assay (9-10) against human carcinoma

colorectal HCT-116 cell line. Colorectal carcinoma is the third most common cancer and caused more than 935,173 deaths globally in 2020 (11). Thus, developing new therapies for such malignant diseases represents a severely unmet need.

The concentrations at which cell growth is inhibited by 50% (GI_{50}) after 72 hrs exposure of cells to furyl carboxamide derivatives **3**, **5**, **7**, and Doxorubicin were obtained from dose-response curves after considering the initial optical density acquired at the time of treatment. GI_{50} values are presented in Table 1, while Figure 1 shows the structure of Doxorubicin as a reference drug used as an antiproliferation-active compound (12).

Table 1: Growth inhibitory activity of compounds **3**, **5**, **7**, and Doxorubicin against human colorectal carcinoma HCT-116 cell line. GI_{50} values are represented as mean±standard deviation of at least three independent experiments (n = 8 per trial).

Compound	GI_{50} (μM) ± S.D.
	HCT-116 Cell Line
3	23.3 ± 1.3
5	36.6 ± 2.8
7	30.5 ± 8.4
Doxorubicin	0.190 ± 0.065

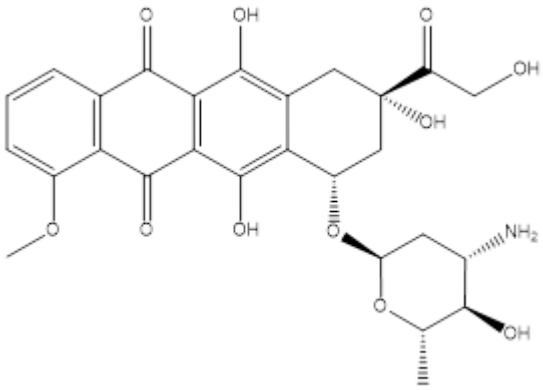


Figure 1: Structure of doxorubicin (11).

As can be deduced from the table, the three compounds **3**, **5**, and **7** show significant and almost identical cellular growth inhibitory activity against human carcinoma colon HCT-116 cell line in the examined concentration range (0.01-100 μM). The highest growth inhibitory activity against colon cancer cells is shown by compound **3**, which contains the anthraquinone core structure like Doxorubicin, with a GI_{50} value of 23.3 μM, followed by compound **7**, containing pyridine moiety, and compound **5**, containing benzophenone structure, with GI_{50} values of 30.5 μM and 36.6 μM, respectively. The results indicate that the anthraquinone compound **3** is 1.3-1.6 times more potent against human colon cancer HCT-116 cells than the pyridine and benzophenone compounds **7** and **5**, respectively.

On a direct comparison of compound **3** with Doxorubicin, it can be deduced that Doxorubicin has potent growth inhibitory (GI50 = 0.190 μM) and antitumor activity of 122-fold greater than anthraquinone compound **3** against human colon cancer HCT-116 cell line, as shown in Figures 2 and 3.

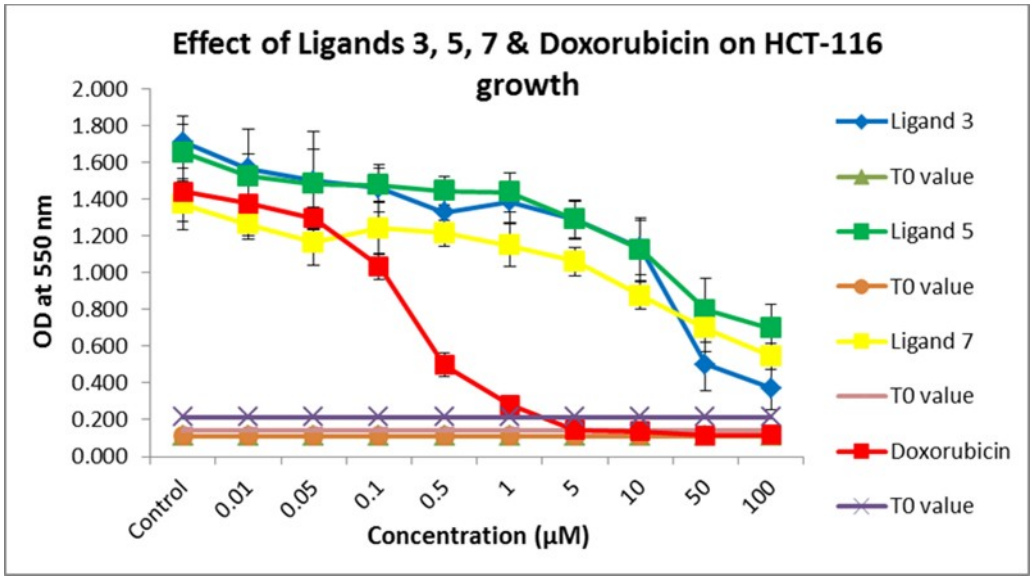


Figure 2: Dose-response curves that show the growth inhibitory effects of compounds 3, 5, 7, and Doxorubicin against human colorectal carcinoma HCT-116 cell line cell. Values are mean±SD, n = 8, graphs are representative of experiments performed on at least three separate occasions.

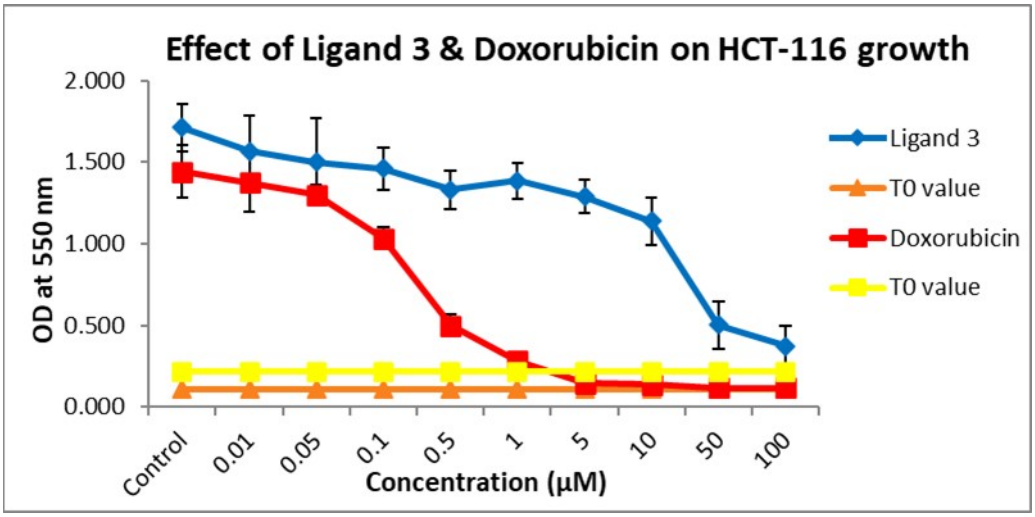


Figure 3: Dose-response curves that show the growth inhibitory effects of compound **3** & Doxorubicin against human colorectal carcinoma HCT-116 cell line cell. Values are mean ± SD, n = 8, graphs representative of experiments performed on at least three separate occasions.

Induced-Fit Docking (IFD)

In order to investigate the anticancer activity of compounds **3**, **5**, and **7** in the HCT-116 cell line, molecular docking simulations were performed using Biovia Discovery Studio (DS) and Schrodinger (Schro) software with CDOCKER Algorithm. Both compound **3** and Doxorubicin were docked to the binding site of the topoisomerase II crystal structure (PDB ID: 6CA8) to investigate the nature of their binding interactions with topoisomerase II targeted enzyme. The x-ray diffraction structure of topoisomerase II (PDB ID: 6CA8) with a resolution of 2.33 Å was obtained from RCSB website. Figures **4**, **5**, and **6** show the nature of interactions between the synthesized compound **3** and Doxorubicin with the binding site of the topoisomerase II enzyme.

It is clearly seen that our synthesized compound **3** is well docked inside the binding pocket of Top-II but interacts with amino acid residues different than those that Doxorubicin interacts with, except LYS A:747 residue. Compound **3** showed hydrogen bonds with ARG:737 and THR A:791 as well as π-π stacking with GLN: 790, π-alkyl bond with PRO A:748 and LYS A:747, Van der Waals interactions with HIS A783, GLY A749 and SER A:787, and π-lone pair TYR A:733. However, Doxorubicin showed hydrogen bonds with LYS A:747, GLU A:878, GLN

A:750, GLY A:801, LYS A:953, and GLY A:820, carbon-hydrogen bond with ASN A:890, and π-alkyl bond PHE A:799.

From Figures 4 and 5, we realize that the compound inhibition mechanisms follow in both hydrophobic and hydrogen bonding interactions with the enzyme understudy. Also, the strength of the inhibitor's interaction with Top-II is a reflection to the frequency of hydrogen bonds exist between the inhibitor and binding pocket. In addition, from Figure 6, it is obviously seen that the binding pocket of Doxorubicin is different from that of compound **3**, which implicates the strength of binding interaction of both compounds. The docking score is a negative value that describes the tightness (binding affinity) of the drug-target interactions and is reported as the free energy of binding in kcal/mol.

The results showed a correlation between the docking score (-33.416 kcal/mol) of compound **3** with the number of hydrogen bond, hydrophobic, and π-π stacking interactions present in the compounds under study. However, the docking score of Doxorubicin was (-150.329 kcal/mol), which corresponds to the number of hydrogen bond, hydrophobic and π-π stacking interactions.

The comparison between the growth inhibitory activities (GI_{50} values) of compounds **3** and **5** revealed that the fixation of the 2-phenyl ring is more favorable. Many furan-like compounds with various structures have been studied previously for their cytotoxic activities. However, our present understanding of the relationships between their chemical structures and anticancer properties is still very limited. The structural modifications of the furyl-2-carboxamide derivatives primarily focused on the alteration of the lipophilic part along with their substituents and conformational restriction of the biphenyl ring to give rigid cyclic analogs.

DISCUSSION

Furan carboxamides were chosen in this work since they are novel and provide reasonable antioxidant activity as their counterpart analog as indole carboxamide (14). In addition, furan and other privileged structure such as pyridazine, pyridazine as a privileged structure (15), quinoline (16), pyran (17), and other heterocyclic structures have been investigated as the scaffold and a core for potential anticancer agents. Therefore, it is important to keep searching for a potent anticancer agent with remarkable selectivity and lower toxicity. Therefore, we chose to evaluate the furan scaffold as an anticancer. Many procedures have been performed to synthesize the proposed compounds, but the fusion method showed superior yield, which was adopted for the three compounds, as shown in Scheme 1.

From the results in Table 1, it was found that compound **3** showed moderate antitumor activity comparable to that of Doxorubicin. Anthraquinone derivative exhibited better anticancer activity than benzophenone and pyridine derivatives which supports a previous study (14) where this compound showed encouraging antioxidant activity using DPPH *in vitro* test, which could explain its effect as a potential anticancer agent. On the other hand, its structure may be considered as conformationally constrained congeners of Doxorubicin that would bind to the receptor similarly, which implicates its activity to inhibit cancer cell growth via multiple mechanisms, including DNA cross-linking by disrupting topoisomerase II and free radical generation damaging the cell membrane, proteins, and DNA.

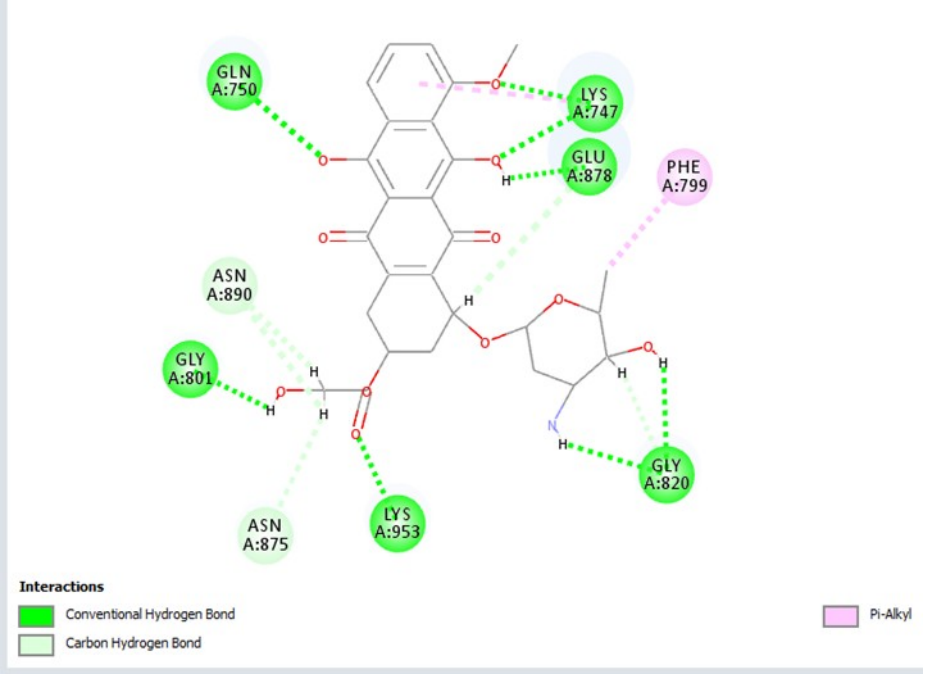


Figure 4: 2D interaction of compound **3** with the binding site of topoisomerase II.

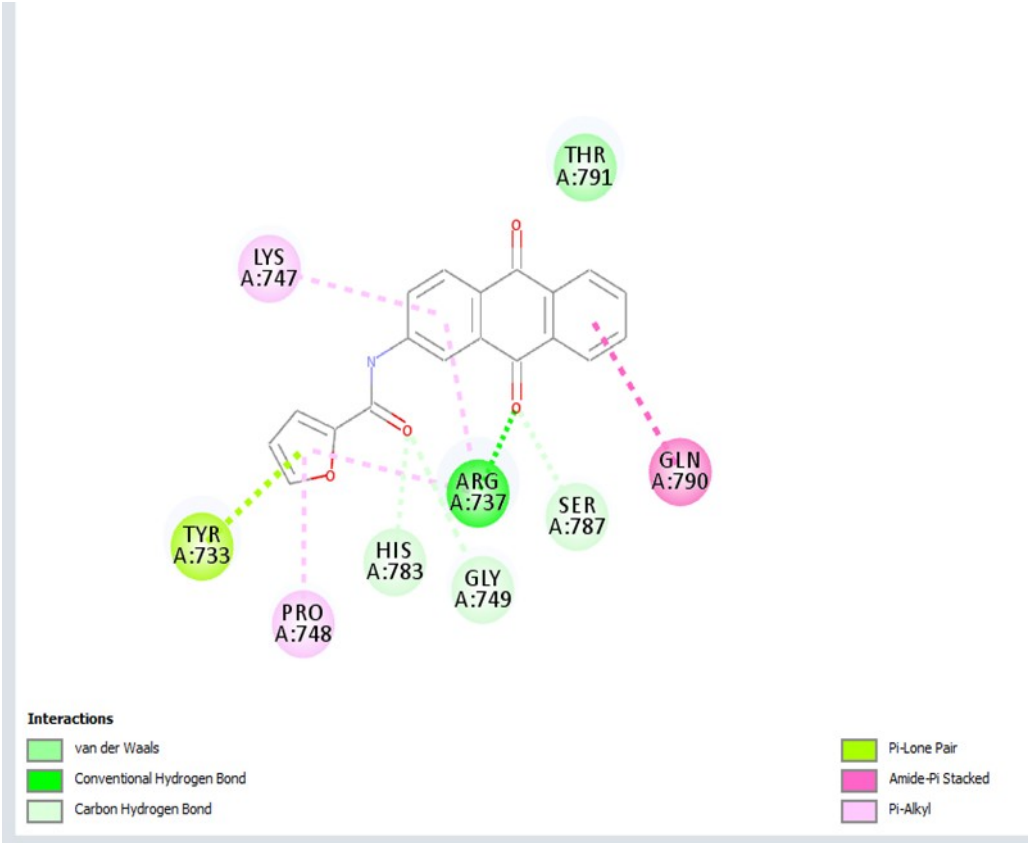


Figure 5: 2D interaction of Doxorubicin with the binding site of topoisomerase II.

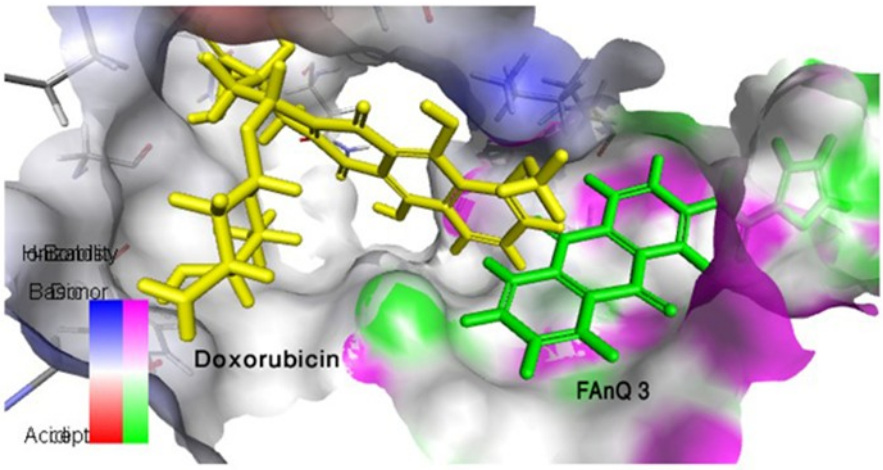


Figure 6: 3D interactions of Doxorubicin and compound **3** with the topoisomerase II enzyme binding site.

CONCLUSION

In this work, we provided a series of new 2-furyl carboxamide derivatives **3**, **5**, and **7** as cytotoxic agents against human colorectal cancer cells and found that compound **3** showed the best antiproliferative activities towards the HCT116 cell line. Compound **3** had a rigid shape structure like Doxorubicin which would affect the binding affinity to the receptor. Furthermore, the prediction results of the physicochemical properties of compound **3** demonstrated that it might be an essential scaffold for future structural design in developing highly efficient antiproliferative agents.

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