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FULL PAPER

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Synthesis and anticancer activities of some new coumarin derivatives including the triazole ring and their in silico molecular docking studies

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Abstract

The synthesis, docking study, and investigation of the anticancer activities of some coumarin derivatives containing the triazole ring are reported in this study. The newly synthesized compounds were screened for their in vitro anticancer activity against the cell lines CRL5807 (human bronchioalveolar carcinoma), CRL5826 (human squamous cell carcinoma), MDA-MB231 (human breast cancer cells), HTB177 (human lung cancer), PC-3 (human prostate adenocarcinoma), PANC-1 (human pancreatic cancer cells), used as cancer cells, and CCD34Lu (normal human lung fibroblasts), used as a healthy cell line. Cytotoxicity effects of the samples were determined by the MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide) assay. In silico studies were also performed to explore the binding interactions of the molecules.

KEYWORDS
anticancer, coumarin, cytotoxicity, molecular docking, triazole

1 | INTRODUCTION

Cancer is a general definition of a broad group of diseases characterized by the uncontrolled proliferation of abnormal cells and metastasis to other organs of these cells. Moreover, cancer can affect nearly any part of the body and has various cellular and molecular subtypes, which can affect different molecular pathways.[1,2] It is the second major reason for death worldwide, and it was predicted to cause approximately 9.6 million deaths in 2018.[3] Recent reports have shown that the most common types of cancer among men are prostate, colorectal, lung, liver, and stomach cancer, whereas cervix, lung, breast, colorectal, and thyroid cancer are the most widespread cancer among women.[3]

Coumarins are very important compounds that widely occur in natural products.[4] They are also named as chromones.[5] Natural and synthetic derivatives of coumarins exhibit many biological properties such as anticancer,[6] antimicrobial, antioxidant,[7] antifungal,[8–11] anti-inflammatory,[12] anti-HIV, and antihypertension.[13] Besides, they also act as α-glucosidase and pancreatic lipase inhibitors.[14–16] In addition to these, coumarins can be used as dyes in the laser industry,[17] in the perfumery,[18] and as fluorescent laser dyes.[19] The structure-activity relationship in the previous studies shows that the use of the coumarin ring in heterocyclic compounds modulates inhibitory activities.[20,21] There are many new cancer types resulting in a large number of deaths.[22] Biological investigations of coumarin derivatives showed the engrossment of innumerable pathways by which coumarins act as anticancer agents.[23] Hybridization of coumarin and triazole is one of the most attractive strategies for achieving new potent anticancer agents that have better pharmacokinetic and pharmacodynamic properties.[24] Some research works have demonstrated that coumarin–triazole hybrid molecules have been investigated as potent anticancer agents (Figure 1).[23–26] Recently, our research group has synthesized some coumarin–triazole hybrid compounds as potent anticancer agents.[27]

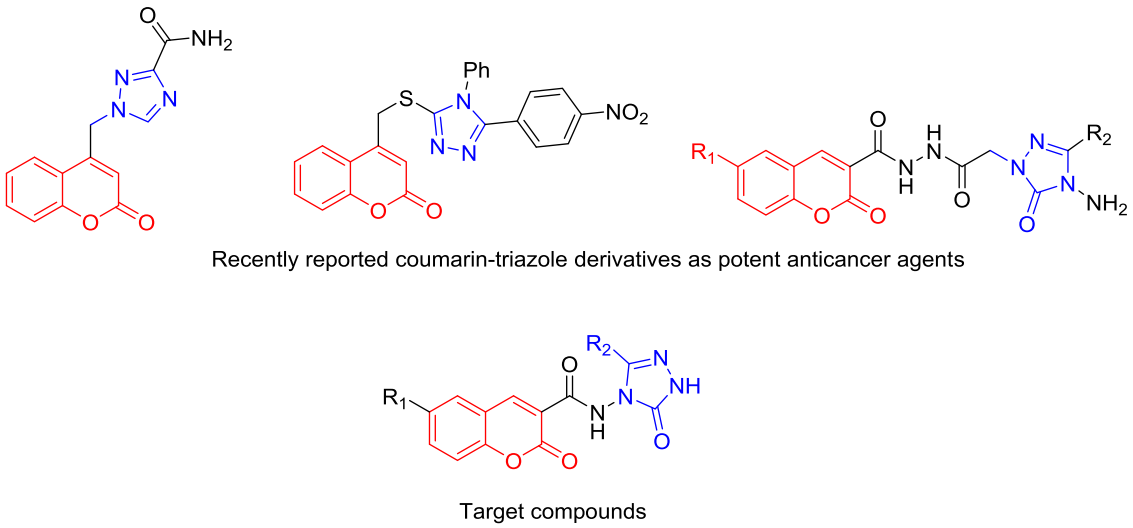
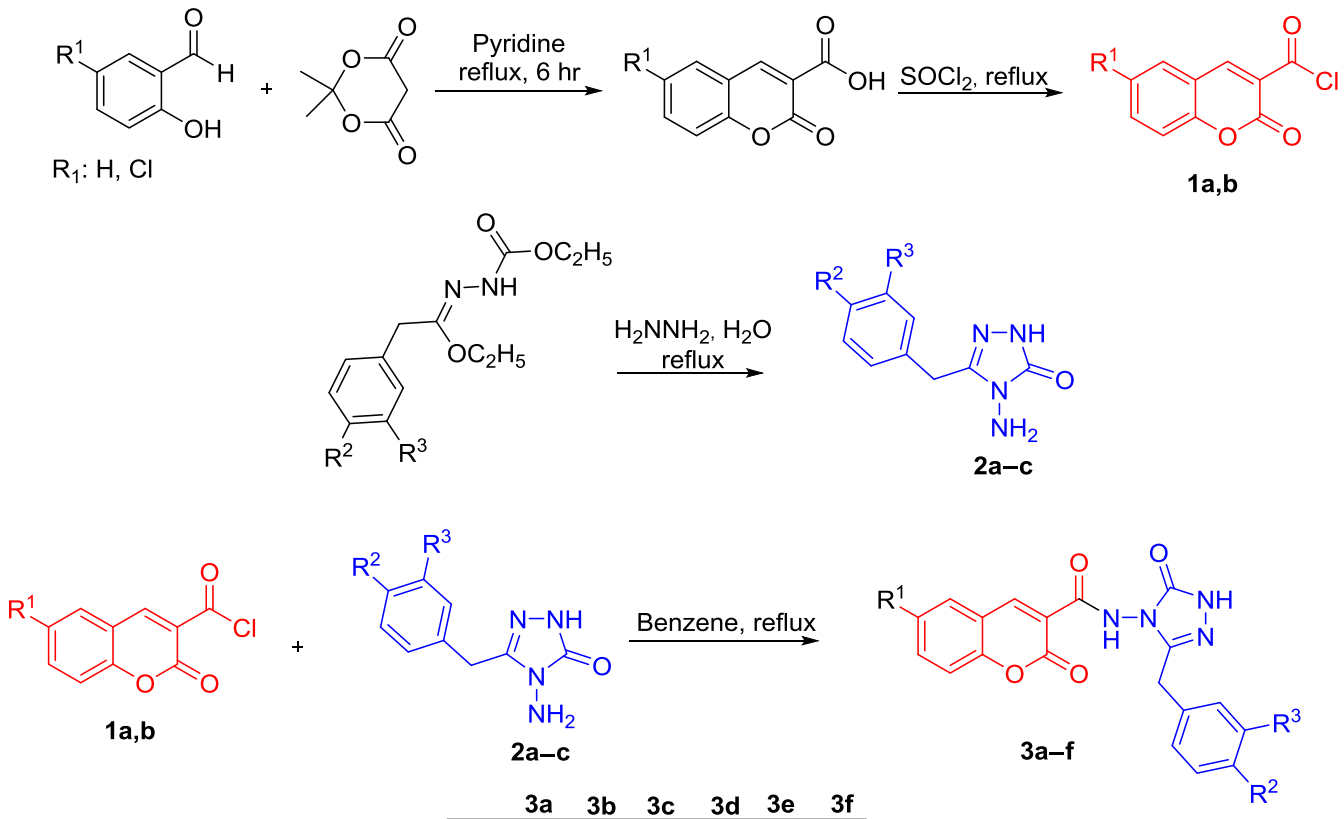


FIGURE 1 Structures of recently reported coumarin–triazole derivatives with anticancer activity and the target compounds



	3a	3b	3c	3d	3e	3f
R^1	H	Cl	H	Cl	H	Cl
R^2	F	F	Cl	Cl	H	H
R^3	H	H	Cl	Cl	Cl	Cl

SCHEME 1 The synthetic path of compounds **3a–f**

Considering the abovementioned facts, the exploration of potential and effective anticancer compounds is important for new drug development in cancer research. In this context, a series of novel coumarin derivatives containing triazole structures, which exhibit very important biological properties such as antioxidant, antimicrobial, antiviral, antitubercular, anti-inflammatory, anticonvulsant, and anticancer activities,[28–31] was synthesized and their anticancer activities were investigated.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The synthesis of coumarin derivatives containing the triazole ring (**3a**–**f**) was performed according to the pathways outlined in Scheme 1. The starting compounds **1a**,**b** and **2a**–**c** were synthesized according to a previously reported study.[27] Coumarin-3-carboxylic acid and 6-chloro-coumarin-3-carboxylic acid were prepared by the reaction of the respective salicylaldehydes and 2,2-dimethyl-1, 3-dioxane-4,6-dione in ethanol containing pyridine, which was treated with $SOCl_2$ to give starting materials **1a**,**b**. Treatment of compounds hydrazones with hydrazine monohydrate in water resulted in the synthesis of 4-amino-1,2,4-triazol-3-one derivatives **2a**–**c**, which is the second intermediate. Finally, coumarin–triazole derivatives were obtained from the reaction of compounds **1a**,**b** with molecules **2a**–**c** under reflux in benzene. Spectral investigations of synthesized compounds were carried out in accordance with the proposed structures of target molecules.

The ^{1}H nuclear magnetic resonance (NMR) spectra of synthesized compounds showed characteristic peaks for NH (triazole N-2) and CONH at 11.67–11.78 and 10.90–10.97 ppm, respectively. Coumarin H-4 signals were observed between 8.38 and 8.83 ppm. In the ^{13}C NMR spectra of compounds **3a**–**f**, triazole C-3 and coumarin C-5 signals were observed between 153.13 and 154.68 and 146.52 and 147.23 ppm, respectively. Coumarin C-2 and C-4 signals were shown at about 159.13–159.59 and 148.37–149.56 ppm, respectively. In the mass spectral data, suitable molecular ion peaks were observed according to the molecular formulae of compounds **3a**–**f**.

2.2 | Cytotoxicity

According to test results (Table 1 and Figure S1), **3e** and **3a** showed the lowest effect on all cell lines. **3a** has no effect on PC-3 cells. The effect of **3e** on CCD34Lu, HTB177, and PC-3 cells was observed, but IC_{50} could not be reached. Nevertheless, the most effective samples were determined as **3b** and **3d** for all cells and their most affected cells, respectively, MDA-MB231 and CRL5807 cells. Compound **3a** is one of the less effective samples, with its IC_{50} value being more than 39 μg/ml. Compound **3b** has the highest inhibitory effect on MB-MB231 cells, with its IC_{50} value being 0.86 ± 0.04 μg/ml. Molecule **3c** also has the highest effect on MDA-MB231 cells, with its IC_{50} value being 4.10 ± 0.4 μg/ml. Compound **3d** has the highest effect on CRL5807 cells, and its IC_{50} value is found to be 0.26 ± 0.2 μg/ml. Compounds **3e** and **3f** have also affected MDA-MB231 cells more than other cells, and their IC_{50} values were found to be 12.81 ± 1.4 and 2.00 ± 0.4 μg/ml, respectively.

It can be remarked that these compounds show higher inhibition effects on PANC-1 cells as compared with doxorubicin. Moreover, their overall high inhibition ability against MDA-MB231 cells leads to more detailed research on breast cancer.

2.3 | Molecular docking study

The docking study revealed that the docking scores of coumarin derivatives **3a**–**f** are in the range of −8.285 to −9.673 kcal/mol as compared with the docking score of doxorubicin, −15.354 kcal/mol, at the same catalytic site of human topoisomerase IIα. These results indicate that most of the studied compounds have a similar binding pattern with binding site residues of doxorubicin. The significant binding affinity toward human topoisomerase IIα implies that these compounds are very active against cancer cells.

The detailed analysis of the docking study reveals that hydrogen bonds and hydrophobic interactions predominate in protein–ligand interactions, which are shown in Table 2 and Figure 2 with a two-dimensional diagram. The docking simulation suggests that compound **3b** was buried in the active site of the enzyme, forming hydrogen bond interactions with Asn91, Asp94, Ser149, and Asn150

TABLE 1 IC_{50} values of cell lines for different formulations (μg/ml)

	CCD34Lu	CRL5807	CRL5826	MDA-MB231	HTB177	PC-3	PANC-1
3a	48.48 ± 2.6	39.69 ± 4.2	44.11 ± 5.63	<50	<50	–	43.80 ± 11.8
3b	5.47 ± 0.5	1.37 ± 0.01	1.59 ± 0.5	0.86 ± 0.04	4.48 ± 1.5	6.04 ± 2.7	4.56 ± 1.2
3c	28.96 ± 7.6	15.17 ± 6.1	9.4435 ± 1.9	4.10 ± 0.4	<50	<50	15.86 ± 0.02
3d	2.43 ± 0.9	0.26 ± 0.2	0.97 ± 0.1	0.60 ± 0.3	8.32 ± 3.1	10.04 ± 5.4	10.25 ± 3.8
3e	<50	21.13 ± 3.1	27.4 ± 11.7	12.81 ± 1.4	<50	<50	44.93 ± 1.8
3f	36.61 ± 21.4	2.23 ± 0.6	2.41 ± 0.8	2.00 ± 0.4	9.20 ± 3.0	11.40 ± 5.5	7.57 ± 0.7
Doxorubicin	18.87 ± 0.9	10.76 ± 0.5	6.85 ± 0.3	16.01 ± 0.8	2.90 ± 0.2	17.6 ± 0.9	<20

TABLE 2 The docking scores and interacting residues of studied compounds

Title	Docking score (kcal/mol)	H-bond residue (distance, Å)	Hydrophobic interactions residue (distance, Å)
3a	−8.285	Asn91 (2.01), Asp94 (2.40), Ser149 (3.45), Asn150 (1.91)	Asn95 (3.86), Ile141 (3.67), Ile141 (3.41), Phe142 (3.81), Thr215 (3.79)
3b	−8.882	Asn91 (1.98), Asp94 (2.14), Ser149 (2.35), Asn150 (2.08), Ser149 (3.54)	Asn91 (3.83), Asn95 (3.89), Ile141 (3.98), Ile141 (3.66), Ile141 (3.50), Phe142 (3.98), Thr215 (3.79)
3c	−9.673	Asn91 (1.78), Asp94 (2.32), Ser149 (2.12), Asn150 (2.14), Ser149 (3.55), Ser149 (3.57)	Asn91 (3.64), Ile141 (3.40), Thr215 (3.71)
3d	−8.622	Asn91 (2.89), Asp94 (2.17), Ser149 (3.60), Asn150 (2.04)	Ile141 (3.61), Ile141 (3.65), Ile141 (3.27), Thr215 (3.93)
3e	−8.837	Asn91 (2.08), Asp94 (2.19), Asn150 (1.81)	Ile141 (3.28), Phe142 (3.94), Thr215 (3.74), Ile217 (3.85)
3f	−9.212	Asn91 (1.79), Asp94 (2.22), Ser149 (2.40), Asn150 (2.00)	Asn91 (3.94), Ile141 (3.29), Ile141 (3.68), Thr215 (3.56)
Doxorubicin	−10.666	Asn91 (2.06), Asn95 (1.94), Arg98 (1.94), Asn120 (2.65), Asn150 (1.80)	Thr159 (3.24), Asn91 (3.73), Ala92 (3.89), Arg98 (3.91), Ile125 (3.59), Phe142 (3.94), Ile217 (3.61)

residues. The same interactions were also observed with the other compounds and doxorubicin.

3 | CONCLUSION

In this study, a new series of novel coumarin derivatives containing a triazole ring was designed and synthesized. The newly synthesized molecules were screened for their in vitro anticancer activity against CRL5807, CRL5826, MDA-MB231, HTB177, PC-3, PANC-1 cell lines, used as cancer cells, and CCD34Lu, as a healthy cell line. Among the tested molecules, compounds **3b** and **3d** showed significant cytotoxicity against all the cancer cell lines and their most affected cells, respectively, MDA-MB231 and CRL5807 cells. Compounds **3b** and **3d** showed higher antitumor inhibitory activities against the CCD34Lu cell line than the standard doxorubicin drug. Molecules **3b**–**f** exhibited a significant antitumor inhibitory activity against the MDA-MB231 cell lines as compared with the reference drug doxorubicin. The docking study suggests that the compounds can be considered as potential leads against cancer, with significant interactions with human topoisomerase IIα. This study could be utilized for the design of an effective drug for the treatment of cancer.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

The reaction progress was monitored by thin-layer chromatography (TLC) on silica gel plates (Merck 60, F_{254}, 0.2 mm). The melting points were determined on capillary tubes using the Stuart SMP30 melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were obtained using a Varian Mercury spectrometer. The mass spectra were recorded on Agilent 1260 Infinity series Accurate-Mass Time-of-Flight (TOF) LC/MS spectrometer.

The InChI codes of the investigated compounds, together with some biological activity data, are provided as Supporting Information.

4.1.2 | Synthesis of compounds 3a–f

A solution of compounds **2a**–**c** (0.01 mol) in dry benzene (10 ml) and compounds **1a**,**b** (0.01 mol) was taken in a round-bottom flask. The mixture was refluxed for 2 hr. After the completion of the reaction (TLC, eluent ethylacetate/hexane, 3:1), the mixture was cooled to room temperature; the product appeared as a white solid. It was filtrated and washed with ethanol to obtain the pure product.

*N-[3-(4-Fluorobenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-2-oxo-2H-chromene-3-carboxamide (**3a**)*

Yield: 85%, m.p.: 311–312°C, ^{1}H NMR (dimethyl sulfoxide [DMSO]-d_6), δ, ppm: 3.79 (2H, s, CH_2); 7.08 (2H, t, J = 8.0 Hz, Ar-H); 7.27–7.30 (2H, m, Ar-H); 7.47 (1H, t, J = 4.0 Hz, Ar-H); 7.54 (1H, d, J = 8.0 Hz, Ar-H); 7.81 (1H, t, J = 8 Hz, Ar-H); 8.00 (1H, d, J = 8 Hz, Ar-H); 8.83 (1H, s, CH, coumarin-H4); 10.90 (1H, s, CONH); 11.67 (1H, s, NH). ^{13}C attached proton test (APT; DMSO-d_6), δ, ppm: 30.39 (CH2); 115.49 (d, J_{CF} = 22 Hz); 116.76; 118.04; 118.56; 125.77; 131.02; 131.11; 131.37; 131.45; 135.31 (Ar-C); 147.23 (C═N); 149.56 (CH, coumarin-C4); 152.85 (coumarin-C3); 154.68 (C═O, triazole); 159.94 (C═O, coumarin C2); 161.72 (C═O); 164.64 (C-F, d, J = 241 Hz). LC–MS, m/z: 381.1018 $[M+H]^+$.

*6-Chloro-N-[3-(4-fluorobenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-2-oxo-2H-chromene-3-carboxamide (**3b**)*

Yield: 83%, m.p.: 347°C (decomp.), ^{1}H NMR (DMSO-d_6), δ, ppm: 3.78 (2H, s, CH_2); 7.09 (2H, t, J = 4.0 Hz, Ar-H); 7.27 (2H, t, J = 8 Hz, Ar-H);

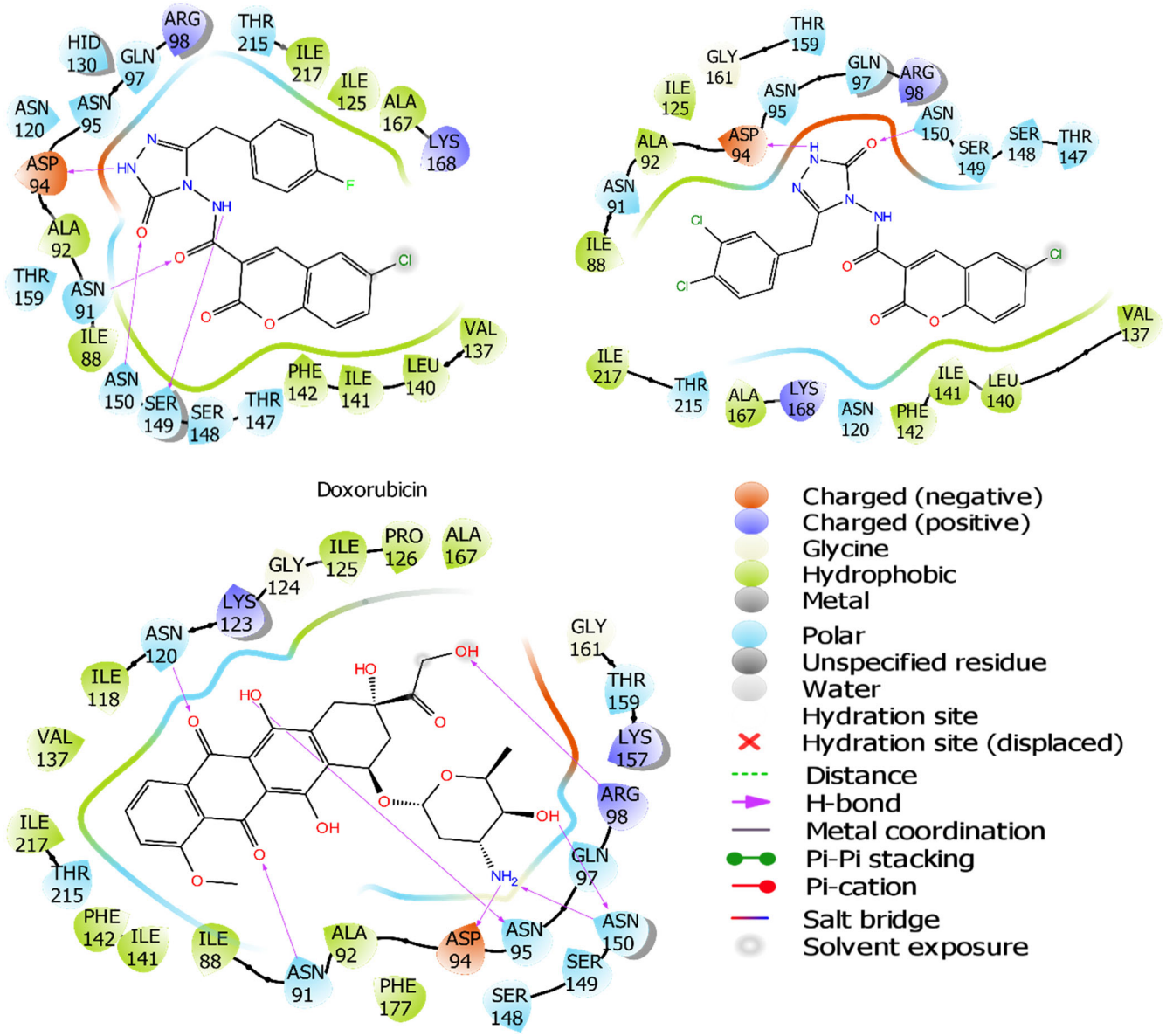


FIGURE 2 Two-dimensional interaction diagrams of compounds **3b**, **3c**, and doxorubicin at the catalytic site of human topoisomerase IIα

7.59 (1H, t, *J* = 8.0 Hz, Ar-H); 7.84 (1H, d, *J* = 8.0 Hz, Ar-H); 8.16 (1H, s, Ar-H); 8.81 (1H, s, CH, coumarin-H4); 10.97 (1H, s, CONH); 11.74 (1H, s, NH). ^{13}C APT (DMSO-d_6), *δ*, ppm: 30.31 (CH2); 115.53 (d, J_{CF} = 21 Hz); 118.83; 119.21; 119.95; 129.41; 129.83; 131.35; 131.41; 131.49; 134.68 (Ar-C); 147.21 (C=N); 148.37 (CH, coumarin-C4); 152.77 (coumarin-C3); 153.31 (C=O, triazole); 159.13 (C=O, coumarin C2); 161.42 (C=O); 161.62 (C-F, d, *J* = 241 Hz). LC–MS, *m/z*: 415.0627 [M (Cl^{35})+H]$^+$, 417.0598 [M (Cl^{37})+H]$^+$.

N-*[3-(3,4-Dichlorobenzyl)-5-oxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-2-oxo-2*H*-chromene-3-carboxamide* (***3c***)

Yield: 86%, m.p.: 311–312°C, ^{1}H NMR (DMSO-d_6), *δ*, ppm: 3.83 (2H, s, CH_2); 7.46–7.56 (4H, m, Ar-H); 7.81 (2H, t, *J* = 8 Hz, Ar-H); 8.01 (1H, d, *J* = 8.0 Hz, Ar-H); 8.82 (1H, s, CH, coumarin-H4); 10.94 (1H, s, CONH); 11.78 (1H, s, NH). ^{13}C APT (DMSO-d_6), *δ*, ppm: 30.23 (CH2); 116.76; 117.73; 118.57; 125.80; 128.79; 129.97; 130.06; 130.90; 131.10; 131.25; 131.61; 135.42; 136.41 (Ar-C); 146.57 (C=N); 149.80 (CH, coumarin-C4); 152.79 (coumarin-C3); 154.68 (C=O, triazole); 159.59 (C=O, coumarin C2); 161.58 (C=O). LC–MS, *m/z*: 415.0627 [M (Cl^{35})+H]$^+$, 417.0598 [M (Cl^{37})+H]$^+$.

*6-Chloro-*N*-[3-(3,4-dichlorobenzyl)-5-oxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-2-oxo-2*H*-chromene-3-carboxamide* (***3d***)

Yield: 85%, m.p.: >320°C, ^{1}H NMR (DMSO-d_6), *δ*, ppm: 3.83 (2H, s, CH_2); 7.24 (1H, d, *J* = 8 Hz, Ar-H); 7.50 (1H, d, *J* = 8 Hz, Ar-H); 7.53 (1H, s, Ar-H); 7.58 (1H, d, *J* = 8 (Hz, Ar-H); 7.82 (1H, d, *J* = 8 Hz, Ar-H); 8.14 (1H, s, Ar-H); 8.79 (1H, s, CH, coumarin-H4); 10.94 (1H, s, CONH); 11.74 (1H, s, NH). ^{13}C APT (DMSO-d_6), *δ*, ppm: 30.20 (CH2); 118.81; 119.01; 119.93; 129.45; 129.85; 130.00; 130.03; 130.90; 131.28; 131.58; 134.73; 136.40 (Ar-C); 146.52 (C=N); 148.49 (CH,

coumarin-C4); 152.75 (coumarin-C3); 153.31 (C=O, triazole); 159.13 (C=O, coumarin C2); 161.35 (C=O). LC–MS, *m/z*: 464.9804 [M ($Cl^{35}Cl^{35}Cl^{35}$)+H]$^+$, 466.9942 [M ($Cl^{35}Cl^{35}Cl^{37}$)+H]$^+$, 468.9910 [M ($Cl^{35}Cl^{37}Cl^{37}$)+H]$^+$, 486.9796 [M ($Cl^{35}Cl^{35}Cl^{35}$)+Na].

*N-[3-(3-Chlorobenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-2-oxo-2H-chromene-3-carboxamide (**3e**)*

Yield: 87%, m.p.: 278–279°C, ^{1}H NMR (DMSO-d_6), δ, ppm: 3.82 (2H, s, CH_2); 7.20–7.32 (4H, m, Ar-H); 7,48 (1H, t, J = 8 Hz, Ar-H); 7.55 (1H, d, J = 8.0 Hz, Ar-H); 7.81 (1H, d, J = 8 Hz, Ar-H); 8.02 (1H, d, J = 8.0 Hz, Ar-H); 8.38 (1H, s, CH, coumarin-H4); 10.96 (1H, s, CONH); 11.75 (1H, s, NH). ^{13}C APT (DMSO-d_6), δ, ppm: 30.74 (CH2); 116.77; 117.85; 118.58; 125.79; 127.23; 128.34; 129.42; 130.65; 131.08; 133.33; 135.37; 137.73 (Ar-C); 146.81 (C=N); 149.76 (CH, coumarin-C4); 152.79 (coumarin-C3); 154.68 (C=O, triazole); 159.59 (C=O, coumarin C2); 161.59 (C=O). LC–MS, *m/z*: 397.0754 [M (Cl^{35})+H]$^+$, 399.0728 [M (Cl^{37})+H]$^+$.

*6-Chloro-N-[3-(3-chlorobenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-2-oxo-2H-chromene-3-carboxamide (**3f**)*

Yield: 86%, m.p.: 315–316°C, ^{1}H NMR (DMSO-d_6), δ, ppm: 3.82 (2H, s, CH_2); 7.20–7.30 (4H, m, Ar-H); 7.59 (1H, d, J = 8 Hz, Ar-H); 7.81 (1H, d, J = 8.0 Hz, Ar-H); 8.15 (1H, s, Ar-H); 8.78 (1H, s, CH, coumarin-H4); 10.96 (1H, s, CONH); 11.73 (1H, s, NH). ^{13}C APT (DMSO-d_6), δ, ppm: 30.71 (CH2); 118.82; 119.08; 119.94; 127.25; 128.33; 129.40; 129.43; 129.84; 130.66; 133.33; 134.71; 137.71 (Ar-C); 146.76 (C=N); 148.47 (CH, coumarin-C4); 152.75 (coumarin-C3); 153.31 (C=O, triazole); 159.14 (C=O, coumarin C2); 161.33 (C=O). LC–MS, *m/z*: 431.0354 [M ($Cl^{35}Cl^{35}$)+H]$^+$, 433.0328 [M ($Cl^{35}Cl^{37}$)+H]$^+$.

4.2 | Cytotoxic activity assay

4.2.1 | Cell culture conditions

CRL5807 (human bronchioalveolar carcinoma), CRL5826 (human squamous cell carcinoma), MDA-MB231 (human breast cancer cells), HTB177 (human lung cancer), PC-3 (human prostate adenocarcinoma), PANC-1 (human pancreatic cancer cells) cell lines, used as cancer cells, and CCD34Lu (normal human lung fibroblasts; American Type Culture Collection), used as a healthy cell line. All cell lines were cultured in Dulbecco's modified Eagle's medium: nutrient mixture F-12 with 10% fetal bovine serum and 0.1% penicillin/streptomycin (Serox GmbH). Cells were incubated at 37°C in a 95% humidified atmosphere of 5% CO_2. Cytotoxicity effects of samples were determined by the MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide) assay, which colorimetrically determines the activity of mitochondrial reductase of viable cells.[1,32]

4.2.2 | Cytotoxicity assay

All cell lines were inoculated in a 96-well plate at 1×10^5 cells/ml initial cell concentration. Cells were treated with increasing concentrations of samples (0.5, 5, and 50 µg/ml) for 48 hr, and doxorubicin was used as the positive control (20, 2, and 0.2 µg/ml; see Figure S2). Cell viabilities of increasing concentrations of doxorubicin for different cells (0.2, 2, 20 µg/ml) were determined. At the end of the 48 hr, 20 µl MTT (from 2.5-mg/ml stock) was added to each well and cells were incubated for a further 4 hr at 37°C in a 95% humidified atmosphere of 5% CO_2. The medium was replaced with 150 µl DMSO for dissolving formazan crystals. Optical densities of the dissolved material were determined at 570 nm (reference filter, 620 nm) with UV–visible spectrophotometer. The percentage of the viable cells was determined with the following formula:

$$\% \text{ viable cells} = (A_{\text{sample}}/A_{\text{control}}) \times 100,$$

where A_{sample} is the absorbance of the sample and A_{control} is the absorbance of the control.

The half-maximal inhibitory concentration (IC_{50}) value is a concentration that inhibits cell viability by 50% under laboratory conditions. The calculation of the IC_{50} was performed by using GraphPad Prism 5 software.

4.3 | Protocol of the docking simulation

Protein coordinates of the crystal structure of human topoisomerase IIα (PDB ID: 1ZXM) were obtained from the Protein Data Bank (www.rcsb.org) with a resolution of 1.87 Å.[33] The docking simulations were performed with the Maestro Molecular Modeling platform (version 10.5) using Induced Fit Docking (IFD) protocol combined with the Glide/XP method.[34] The protein preparation protocol was performed to fill missing side chains, remove water molecules, except within 5 Å in the active site, update missing loop regions, and protonate residues at physiological pH. The LigPrep tool was used to obtain the lowest energy three-dimensional structures of ligand molecules at neutral pH and under the OPLS 2005 force field. All the conformations of studied molecules were docked into the receptor grid of radii of 20 Å. The binding site of the receptor structure was centered on the bonded ligand molecule.

CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interests.

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