

## Synthesis, biological activity and molecular docking of 2-(2H-chromen-3-yl)-[1,3,4]oxadiazole derivatives

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### ABSTRACT

Some new 2-(2H-chromen-3-yl)-[1,3,4]oxadiazole derivatives **8a-e** using Huisgen synthesis of 1,3,4-oxadiazoles reaction. Their structures were verified by <sup>1</sup>H NMR and elemental analyses. Compounds **8a-e** were tested against 60 human cancer cell lines for *in vitro* cytotoxic activities according to the international scientific programme of the US National Institute of Health – DTP (Developmental Therapeutics Program), National Cancer Institute (Bethesda, Maryland, USA). Compounds with moderate activity against certain cancer cell lines were identified. In addition, in collaboration with CO-ADD (The Community for Open Antimicrobial Drug Discovery), we have studied the antibacterial activity against the ESCAPE group of strains and the antifungal activity against *C. Albicans* ATCC 90028 and *C. Neoformans* ATCC 208821. The studies allowed us to identify 3-[5-(6-bromo-2H-chromen-3-yl)-[1,3,4]oxadiazol-2-yl]-pyridine as a compound with high antibacterial activity against *E. Coli* ATCC 25922 with MIC 8 µg/ml. Docking studies have shown high affinity of this compound for the bacterial DNA gyrase of *Escherichia coli*.

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## 1. Introduction

Cancer<sup>1-3</sup> and infection<sup>4,5</sup> diseases are the leading causes of mortality worldwide. Chemotherapy remains the major method of treating malignant tumours, either alone or in combination with surgery and radiation therapy. Organic substances are also the main source for development of new drugs for treatment of diseases caused by pathogenic microorganisms. Nowadays, significant progress has been made in the design of anti-cancer and antimicrobial drugs, which has significantly improved the effectiveness of therapy for various types of cancer and infections. However, many types of cancer are still untreatable. Tumour cells develop resistance to existing chemotherapy drugs. They are characterised by a large number of side effects.<sup>1-3</sup> The emergence of antibiotic resistance in bacterial pathogens has also significantly limited the number of effective antibiotics available for clinical use, increased costs, longer treatment times and higher mortality rates.<sup>4,5</sup>

In this regard, the development of effective and low-toxic antitumour and antimicrobial agents is an important task of modern medicinal chemistry. They are searched for among various classes of compounds, including 1,3,4-oxadiazoles. 1,3,4-oxadiazole and its derivatives are important pharmacological scaffolds, including in the development of drugs for the treatment of cancer and infection diseases.<sup>6-11</sup> Potent anticancer and antimicrobial activity has been reported for a lot of substituted 1,3,4-oxadiazole derivatives. According to the FDA, the oxadiazole derivative Zytotenten (see **Fig. 1**) is in the final stages of clinical trials for the treatment of prostate cancer. It inhibits cell proliferation, invasion and metastasis. Another 1,3,4-oxadiazole derivative – Furamizole (see **Fig. 1**) exhibits strong antibacterial activity.

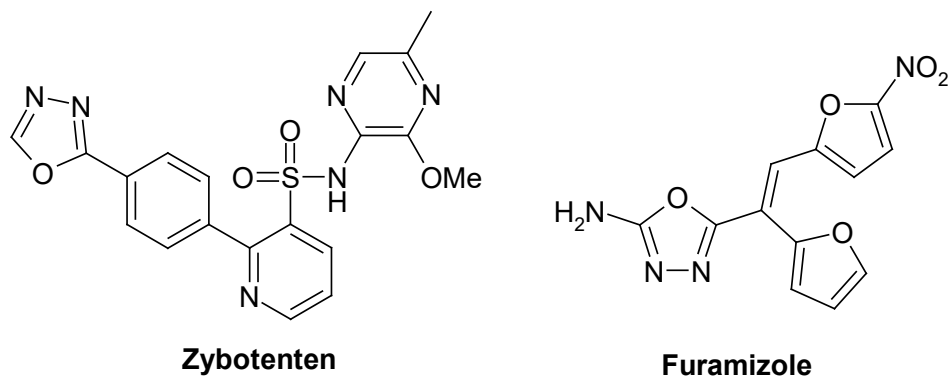
The aim of this work is the synthesis of 2-(2H-chromen-3-yl)-[1,3,4]oxadiazole derivatives and the study of their antitumour and antimicrobial activity.

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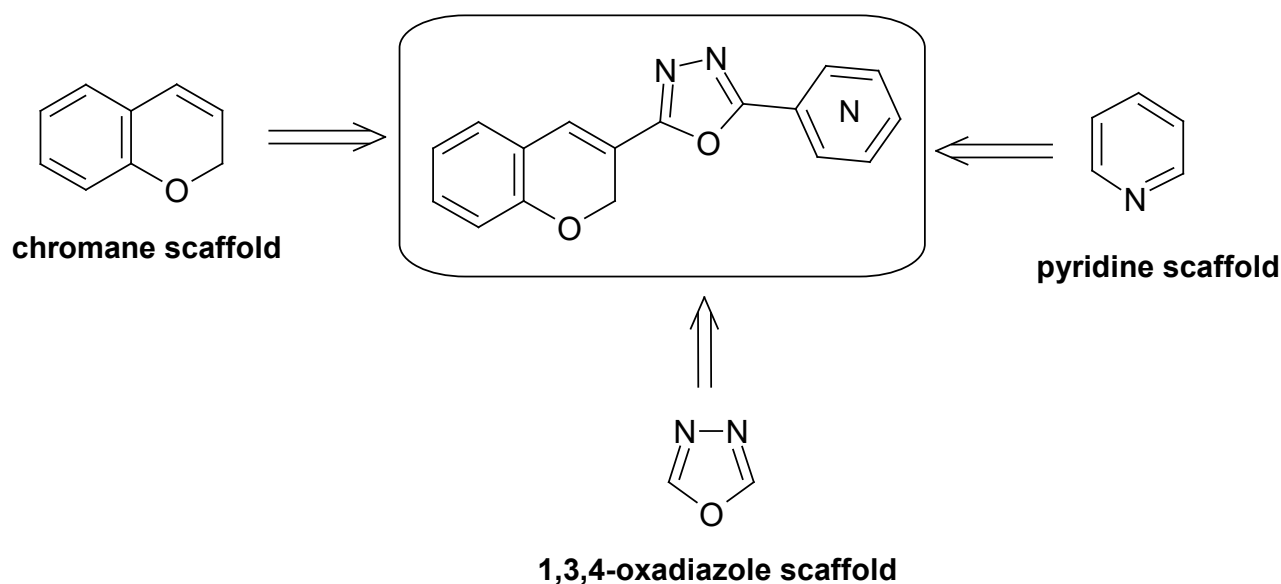
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**Fig. 1.** Pharmaceuticals with anticancer and antimicrobial activity.

These compounds incorporate the chromene scaffold (see Fig. 2). Compounds with chromene ring are present in natural and synthetic products with a wide spectrum of biological activities. Currently, both heterocycles (*2H*-chromene and [1,3,4]oxadiazole) are regarded as privileged structures in medicinal chemistry.<sup>12-15</sup> In designing the targets, we used the concept of molecular hybridisation based on the combination of different pharmacophoric moieties.<sup>16</sup>



**Fig. 2.** Design of target 2-(*2H*-chromen-3-yl)-[1,3,4]oxadiazoles.

## 2. Results and Discussion

### Synthesis of the target 2-(*2H*-chromen-3-yl)-[1,3,4]oxadiazoles

For the synthesis of the target 1,3,4-oxadiazoles, we chose the Huisgen reaction of 5-substituted-1*H*-tetrazoles **2a-c** with chloroanhydride of acids.<sup>17-22</sup> This method was chosen due to the readily available starting materials and the simplicity of the experimental procedures at all stages of the synthesis. It was also noted that the target products formed as a result of the reaction of 5-substituted-1*H*-tetrazoles with acid chloroanhydride are characterised by high purity.

The starting tetrazoles **2a-c** were obtained by the (3+2) cycloaddition reaction of pyridinecarbonitriles with sodium azide according to the procedure described in the work<sup>23</sup> (see Fig. 3).

The Baylis-Hilman reaction<sup>17-22</sup> of salicylic aldehydes **3a, b** with ethyl acrylate **7** in the presence of potassium carbonate as a base was used for constructing of the chromene ring. The resulting ester **4a, b** was converted to the corresponding acylchlorides by hydrolysis with aqueous sodium hydroxide and further chlorination of the acid **5a, b** using thionyl chloride (see Fig. 4). The physicochemical and spectral characteristics of intermediates **3-6** are consistent with the literature data.<sup>17-22</sup>

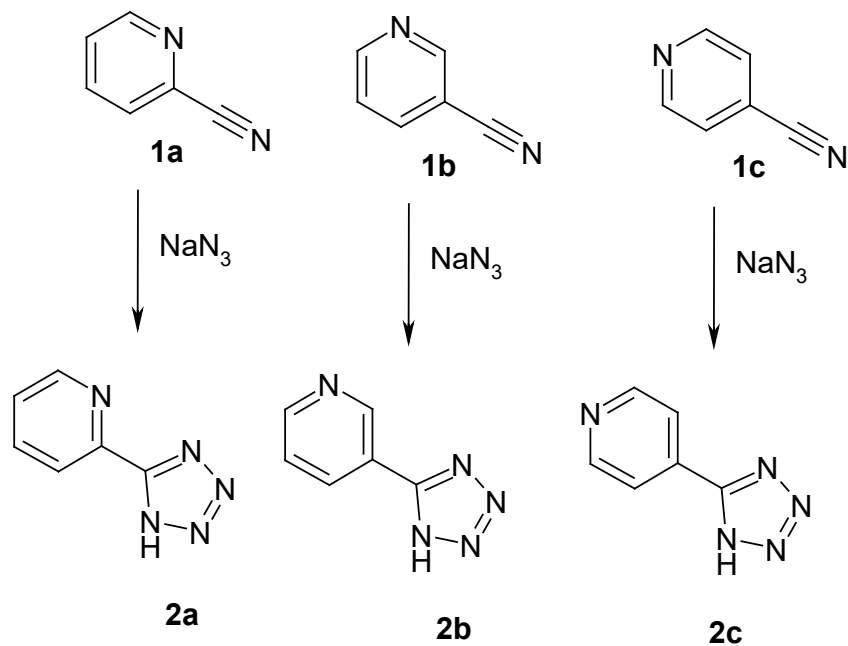


Fig. 3. Scheme of synthesis of tetrazoles **2a-c**.

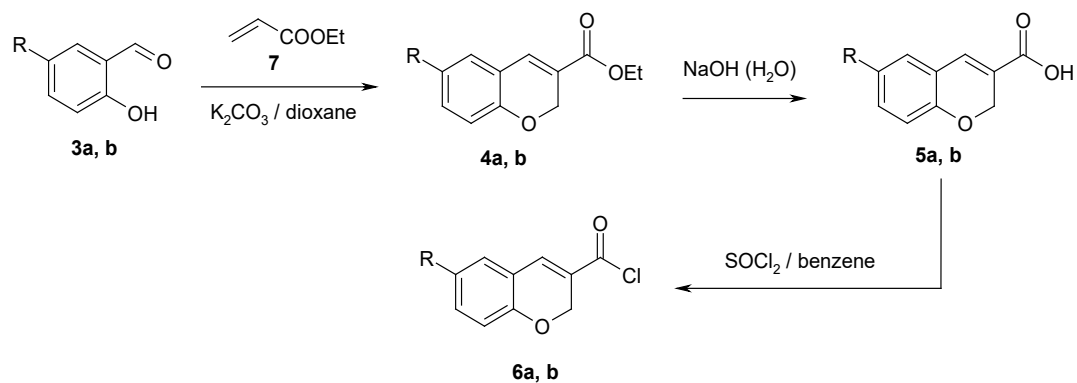
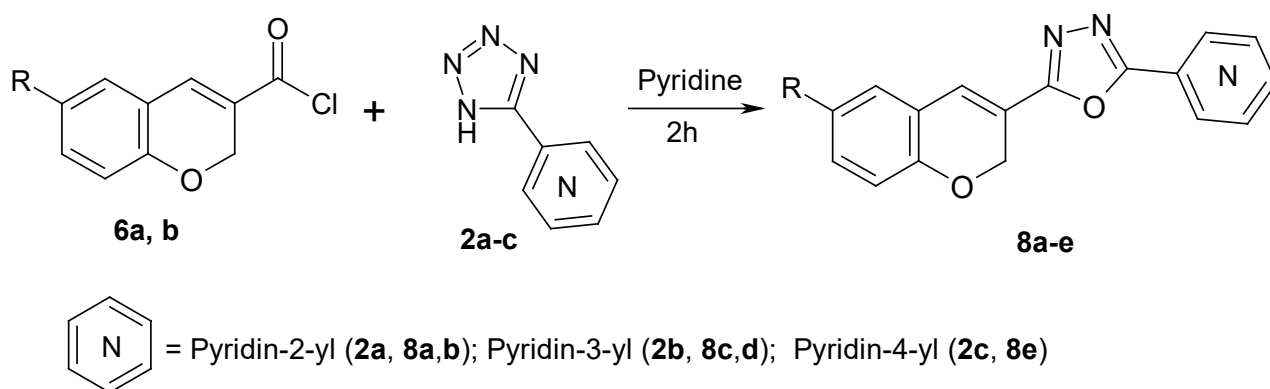


Fig. 4. Scheme of synthesis of 2*H*-chromene-3-carbonyl chlorides **6a, b**.

The reaction of the obtained chloroanhydrides **6a, b** with 5-substituted tetrazoles **2a-c** has been studied. The acylation takes place at position 1 of the tetrazole cycle, followed by a thermal rearrangement with elimination of the nitrogen. In result 1,3,4-oxadiazole derivatives **8a-e** are formed (see Fig. 5).



**8a:** R = H, Pyridin-2-yl; **8b:** R = Br, Pyridin-2-yl; **8c:** R = H, Pyridin-3-yl;  
**8d:** R = Br, Pyridin-3-yl; **8e:** R = H, Pyridin-4-yl

Fig. 5. Scheme of synthesis of 2-(2*H*-chromen-3-yl)-[1,3,4]oxadiazoles **8a-e**.

The synthesised compounds **8a-e** are white substances with a high melting point, well soluble in polar organic solvents: DMFA, DMSO, acetic acid and insoluble in water and classical non-polar organic solvents.

### The antitumour activity of 2-(2*H*-chromen-3-yl)-[1,3,4]oxadiazoles

The antitumour activity of the synthesised compounds was evaluated using high-throughput biological screening in accordance with the international scientific program of the US National Institute of Health – Developmental Therapeutics Program, National Cancer Institute, USA.<sup>24-28</sup> The compounds were tested against 60 human tumour cell lines, which were derived from nine different types of human cancer: leukemia, nonsmall cell lung cancer, central nervous system cancer, melanoma, colon cancer, renal cancer, ovarian cancer, prostate cancer and breast cancer. The percentage of growth (GP) of cancer cell lines was calculated as a quantitative criterion for the activity of the compounds compared to the control. The range of mitotic activity shows the lowest and highest growth found in different cancer lines.

The results of the antitumour activity studies for compounds **8a-d** are presented in **Table 1**. The experiment showed that the obtained compounds exhibited rather high antitumour activity, except for amide **8c**. The average mitotic activity was 41.43 – 99.98%. The most sensitive was the melanoma cell line MDA-MB-435. Most of the studied compounds had a cytotoxic effect on this cell line. The antitumor properties of compounds of a similar nature were reported recently.<sup>29, 30</sup>

**Table 1.** Cytotoxic activity of the tested compounds **8a-d** in the concentration  $10^{-5}$  M against 60 cancer cell lines.

Compound	Mitotic activity against 60 lines, GP, %		Most sensitive lines (cancer line/type), GP, %
	Average growth, %	Range of growth, %	
<b>8a</b>	41.43	-36.22 – 105.21	MDA-MB-468 (Breast cancer) 25.31 SF-295 (CNS cancer) 24.44 HCT-15 (Non-Small cell lung cancer) 22.47 NCI-H460 (Non-small cell lung cancer) 21.21 M14 (Melonoma) 18.43 SK-MEL-5 (Melanoma) 17.17 KM12 (Non-Small cell lung cancer) 15.59 LOX IMVI (Melanoma) 15.35 CAKI-1 (Renal cancer) 16.21 UACC-62 (Melanoma) 9.41 MDA-MB-435 (Melanoma) -36.22 ACHN (Renal cancer) 52.15 MDA-MB-468 (Breast cancer) 40.32 SR (Leukemia) 35.68 CAKI-1 (Renal cancer) 34.21 UACC-62 (Melanoma) 18.07 MDA-MB-435 (Melanoma) -14.33
<b>8b</b>	67.53	-14.33 – 100.51	UO-31 (Renal Cancer) 78.46 MDA-MB-468 (Breast cancer) 25.11 HCT-15 (Colon cancer) 21.44 UACC-62 (Melanoma) 21.38 CAKI-1 (Renal cancer) 21.21 NCI-H460 (Non-small cell lung cancer) 22.15 HT29 (Colon cancer) 20.33 KM12 (Colon cancer) 21.12 M14 (Melanoma) 18.11 MDA-MB-435 (Melanoma) -31.66
<b>8c</b>	99.98	78.46 – 118.66	
<b>8d</b>	45.04	-31.66 – 80.34	

### The antimicrobial activity of 2-(2*H*-chromen-3-yl)-[1,3,4]oxadiazoles

The antimicrobial activity of compounds **8a-e** was studied by CO-ADD<sup>31</sup>, with the support of the Wellcome Trust (UK) and the University of Queensland (Australia). The test bacteria studied were strains that belong to the group of hospital-acquired pathogens, highly virulent and antibiotic-resistant microorganisms – ESCAPE (*Escherichia coli* (*E. coli*) ATCC 25922, *Klebsiella pneumoniae* (*K. pneumoniae*) ATCC 700603, *Acinetobacter baumannii* (*A. baumannii*) ATCC 19606, *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC 27853 and *Staphylococcus aureus* (*S. aureus*) ATCC 43300). The antifungal activity against *Candida albicans* (*C. albicans*) ATCC 90028 and *Cryptococcus neoformans* (*C. Neoformans*) ATCC 208821 strains was also investigated. The results of the primary screening of antibacterial and antifungal activity of compounds **8a-e** are shown in **Table 2**.

**Table 2.** Antibacterial and antifungal activity of synthesised compounds **8a-e** (GI, %).

Compound	<i>S. aureus</i> ATCC 43300	<i>E. coli</i> ATCC 25922	<i>K. pneumoniae</i> ATCC 700603	<i>P. aeruginosa</i> ATCC 27853	<i>A. baumannii</i> ATCC 19606	<i>C. albicans</i> ATCC 90028	<i>C. neoformans</i> ATCC 208821
<b>8a</b>	21.3; 17.9	0.9; 10.5	12.8; 4.1	8.7; -3.4	3.5; -1.4	14.2; 15.1	-21.1; -7.4
<b>8b</b>	23.1; 11.2	45.5; 48.8	33.2; 25.4	20.0; 7.2	24.3; 18.4	5.2; -7.8	10.1; 4.1
<b>8c</b>	10.1; 15.1	22.1; 24.1	-2.8; 9.8	10.1; 20.0	14.7; 11.3	4.5; 11.2	11.7; 13.2
<b>8d</b>	-7.6; -6.3	96.2; 99.0	25.3; 31.2	12.8; 4.2	11.1; -10.4	8.4; 12.3	24.2; 11.1
<b>8e</b>	13.5; -4.2	15.1; 0.4	9.1; 16.2	3.1; 14.4	12.1; 10.1	11.1; 12.7	11.6; -5.1

All tested compounds did not show antifungal activity. A pronounced antibacterial effect was observed for compound **8d** and a moderate one for **8b** against the strain of Gram-negative rod-shaped bacterium *E. coli* ATCC 25922. For the active compound **8d**, the minimum inhibitory concentration against *E. coli* strain ATCC 25922 was determined, as well as cytotoxicity against human embryonic kidney cells (Hk CC<sub>50</sub>) and human erythrocytes (Hm HC<sub>10</sub>) (Table 3).

**Table 3.** Results of the determination of the minimum inhibitory concentration (MIC) and cytotoxicity against human embryonic kidney cells and human erythrocytes of compound **8d** and classic antibiotics (µg/ml).

Compound	MIC <i>E. coli</i> ATCC 25922	Hk CC <sub>50</sub> *	Hm HC <sub>10</sub> **	SI = HC <sub>10</sub> / MIC
<b>8d</b>	8; 8	>32; >32	>32; >32	>4; >4
<b>β-Lactam</b>	0.12 – >128	ND***	ND	ND
<b>Mecillinam</b>	0.12	ND	ND	ND
<b>Oxacillin and Nafcillin</b>	>128	ND	ND	ND
<b>Aminoglycosides</b>	0.25 – 4	ND	ND	ND
<b>Gentamicin</b>	0.5	ND	ND	ND
<b>Streptomycin</b>	4	ND	ND	ND
<b>Tetracyclins</b>	1 – 2	ND	ND	ND
<b>Macrolides</b>	>64	ND	ND	ND

\*Hk CC<sub>50</sub> is the concentration at 50% cytotoxicity;

\*\*Hm HC<sub>10</sub> is the concentration at 10% hemolysis;

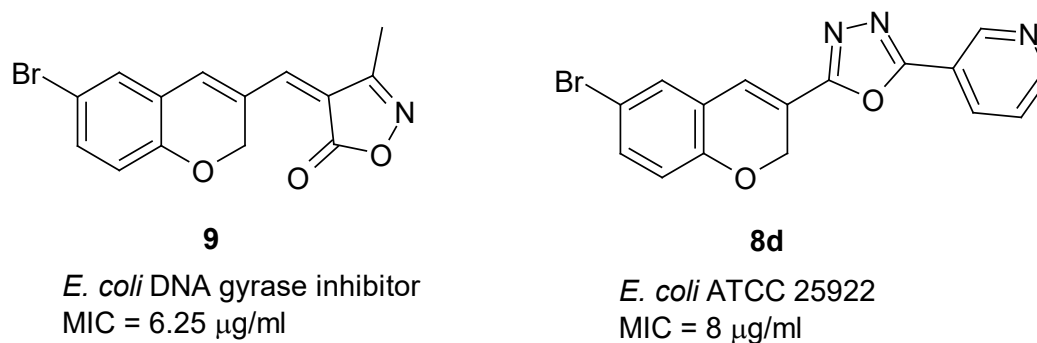
\*\*\*ND – not determined.

*E. coli* is a gram-negative, rod-shaped bacterium that lives in the lower intestine of humans and other warm-blooded organisms. Most strains of *E. coli* are harmless and make up the majority of the normal intestinal flora in humans and animals. However, in some cases, strains of *E. coli* cause severe chronic purulent inflammatory diseases and even tissue necrosis. Such diseases include: sinusitis, stomatitis, periodontitis, bronchitis and bronchial asthma, various urogenital diseases (colpitis, adnexitis, cystitis, pyelonephritis, prostatitis), etc.

We compared the activity of the compound under study with the data from a study that provides MIC values for a number of known antibacterial agents. According to the work<sup>32</sup> the sensitivity of the *E. coli* ATCC 25922 strain to β-lactam antibiotics was in a different concentration range MIC = 0.12 – >128 µg/ml. In particular, *E. coli* ATCC 25922 strain is the most sensitive to Mecillinam (MIC = 0.12 µg/ml). At the same time, Oxacillin and Nafcillin showed antimicrobial effects in significantly higher concentrations. The range of effective concentrations of aminoglycoside antibiotics was in the narrower range of 0.25 – 4 µg/ml. Tetracycline antibiotics were also present in rather low concentrations of 1 – 2 µg/ml. At the same time, for macrolide antibiotics, the MIC was >64 µg/ml.

## Docking studies

It should be noted<sup>33</sup> that compound **8d** with a similar structure **9** also had a significant effect on *E. coli* (see Fig. 6). According to the web-tool<sup>34</sup>, the AP Tanimoto similarity score between these compounds is 0.341549 and MCS Tanimoto similarity score is 0.3793.



**Fig. 6.** Compound **8d** and known *E. coli* DNA gyrase inhibitor **9**.

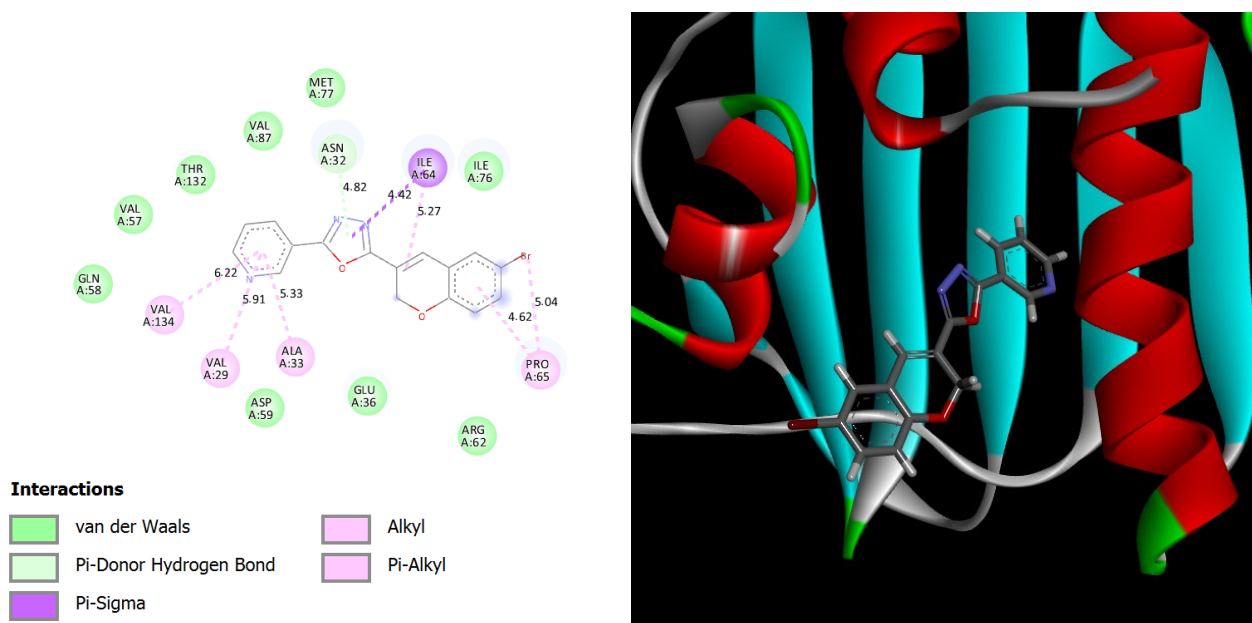
In order to elucidate the possible mechanism of antibacterial action of compound **8d**, we also performed docking studies<sup>35, 36</sup> on DNA gyrase.

Binding scores and information about of amino acids involved in interactions of the docked compound **8d** on the active sites of DNA gyrase of *E. coli* is shown in Table 4 and visualised in Fig. 7.

Compound **8d** is characterised by Pi-Donor Hydrogen Bond of Asparagine acid and Pi-Sigma of Isoleucine with 1,3,4-oxadiazole ring. Pi-Alkyl interactions involving amino acids with an alkyl fragment (Valine, Alanine, and Proline) and aromatic π-system benzene and pyridine systems also play an important role in binding. Isoleucine is also involved in the interaction with the alkene fragment of the chromene cycle (Table 4).

**Table 4.** Binding scores and amino acids involved in interactions of the docked compound **8d** on the active sites of DNA gyrase of *E. coli* (PDBID:1KZN).

Compound	Binding energy, kcal/mol	Interacting residues					
		Pi-Donor Hydrogen Bond		Pi-Sigma		Pi-Alkyl	
		Amino acid	Distance, Å	Amino acid	Distance, Å	Amino acid	Distance, Å
<b>8d</b>	DNA gyrase of <i>E. coli</i>	Asn A:32	4.82	Ile A:64	4.42	Val A:134	6.22
						Val A:29	5.91
						Ala A:33	5.33
						Pro A:65 (Ar)	4.62
						Pro A:65 (Br)	5.04
						Ile A:64	5.27

**Fig. 7.** Compound **8d** into the active sites of DNA gyrase of *E. coli*.

### 3. Conclusions

In conclusion, a new series of 2-(2*H*-chromen-3-yl)-[1,3,4]oxadiazole derivatives were synthesised. Their structures were characterised by <sup>1</sup>H NMR spectroscopy and elemental analyses. The antitumor and antimicrobial activities of the prepared compounds were investigated. 3-[5-(6-bromo-2*H*-chromen-3-yl)-[1,3,4]oxadiazol-2-yl]-pyridine was identified as a hit compound with antibacterial activity against *E. coli* strain ATCC 25922. Docking studies have shown high affinity of this compound for the bacterial DNA gyrase of *Escherichia coli*.

### Funding.

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### 4. Experimental

#### 4.1. Materials and Methods

All reagents and solvents were purchased from Sigma Aldrich Chemicals and were used without further purification. The <sup>1</sup>H NMR spectra were obtained on a Varian instrument at an operating frequency of 400 MHz, solvent – DMSO<sub>d6</sub>. Chemical shifts were reported as δ in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard. The coupling constant *J* was expressed in Hz.

The docking studies were performed using the Autodock Vina<sup>35</sup> and Discovery Studio<sup>36</sup> software packages.

## 4.2. General procedure

*Method of synthesis of 2-(2H-chromen-3-yl)-[1,3,4]oxadiazole derivatives 8a-e.* An equimolar mixture of 0.01 mol of appropriate acylchloride (**6a, b**) and 0.01 mol of tetrazole (**2a-c**) is dissolved in pyridine and heated for 2 h. After cooling, dilute with water. The resulting precipitate (**8a-e**) is filtered off and recrystallised from the DMFA-ethanol mixture.

*2-[5-(2H-Chromen-3-yl)-[1,3,4]oxadiazol-2-yl]-pyridine (8a).* Yield 68 %. M.p. = 199°C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ, ppm: 8.76 (d, *J* = 4.8 Hz, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 8.02 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.41 – 7.30 (m, 2H), 7.30 – 7.13 (m, 3H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.89 (dd, *J* = 13.8, 7.5 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.23 (s, 2H). Anal. calc. for C<sub>16</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>, % C 69.31, H 4.00, N 15.15; found C 69.42, H 4.11, N 15.07.

*3-[5-(6-Bromo-2H-chromen-3-yl)-[1,3,4]oxadiazol-2-yl]-pyridine (8b).* Yield 81 %. M.p. = 209°C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ, ppm: 8.76 (d, *J* = 4.6 Hz, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 8.07 – 7.95 (m, 1H), 7.60 (d, *J* = 9.1 Hz, 2H), 7.53 (d, *J* = 2.2 Hz, 1H), 7.34 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 5.24 (s, 2H). Anal. calc. for C<sub>16</sub>H<sub>10</sub>BrN<sub>3</sub>O<sub>2</sub>, % C 53.96, H 2.83, N 11.80; found C 54.05, H 2.74, N 11.85.

*3-[5-(2H-Chromen-3-yl)-[1,3,4]oxadiazol-2-yl]-pyridine (8c).* Yield 73 %. M.p. = 188°C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ, ppm: 9.27 (s, 1H), 8.78 (d, *J* = 3.3 Hz, 1H), 8.47 (s, 1H), 8.45 (dt, *J* = 8.0, 1.8 Hz, 1H), 7.62 (t, *J* = 6.4 Hz, 2H), 7.35 – 7.20 (m, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 5.22 (s, 2H). Anal. calc. for C<sub>16</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>, % C 69.31, H 4.00, N 15.15; found C 69.24, H 4.08, N 15.13.

*3-[5-(6-Bromo-2H-chromen-3-yl)-[1,3,4]oxadiazol-2-yl]-pyridine (8d).* Yield 79 %. M.p. = 217°C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ, ppm: 9.25 (d, *J* = 1.7 Hz, 1H), 8.78 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.54 (m, 2H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.36 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H). Anal. calc. for C<sub>16</sub>H<sub>10</sub>BrN<sub>3</sub>O<sub>2</sub>, % C 53.96, H 2.83, N 11.80; found C 53.83, H 2.89, N 11.71.

*4-[5-(2H-Chromen-3-yl)-[1,3,4]oxadiazol-2-yl]-pyridine (8e).* Yield 72 %. M.p. = 163°C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ, ppm: 8.00 (s, 2H), 7.63 (s, 1H), 7.36 – 7.21 (m, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 5.22 (s, 2H). Anal. calc. for C<sub>16</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>, % C 69.31, H 4.00, N 15.15; found C 69.44, H 4.12, N 15.03.

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