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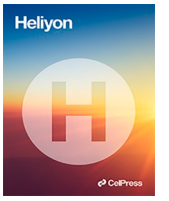

Research article

Synthesis of designed new 1,3,4-oxadiazole functionalized pyrano [2,3-f] chromene derivatives and their antimicrobial activities

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ABSTRACT

Diethyl 2-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methylene)malonate **(2)** was synthesized from coumarin 1 and diethyl ethoxymethylene malonate in ethanol, followed by cyclization in diphenyl ether to give chromene-9-carboxylate **(3)**. Sugar hydrazones **5a-c** were formed by reacting hydrazide **4** with D-galactose, D-mannose, and D-xylose, then acetylated to per-*O*-acetyl derivatives **6a-c**. Heating **5a-c** with acetic anhydride at 100 °C gave oxadiazolines **7a-c**. Compound **8**, obtained by refluxing **4** with carbon disulfide, was alkylated to **9** or reacted to give **10**. Further reactions yielded acetoxy derivative **13** and hydroxy derivative **14**. Compounds **17a-e** and **18a-e** were synthesized using thiomorpholinophenyl ureido/thioureido-s-triazine. These compounds were characterized and evaluated for antibacterial activity against Gram (+ve) bacteria (*B. subtilis*, *S. aureus*) and Gram (-ve) bacteria (*E. coli*, *P. aeruginosa*) in addition to yeast-like fungi (*C. albicans*). Compounds **11**, **13**, **15**, **16**, **17c-e**, and **18a-e** showed the highest antibacterial activity. Molecular docking was performed to study their binding with transpeptidases.

1. Introduction

Health issues are increasingly serious clinical concerns. To address these challenges, medicinal chemists are actively developing innovative treatments [1]. Heterocyclic compounds, especially those with five- or six-membered rings containing nitrogen, oxygen, or sulfur, are widely used in therapy [2]. Compounds like oxadiazoles, which contain nitrogen atoms, are of particular interest in medical and pharmaceutical research [3]. Over the past 20 years, significant advancements have been made in discovering natural products based on chromene, with 2H-chromenes and 2-oxo-2H-chromenes (coumarins) being the most studied.

Chromene and its derivatives are important organic compounds widely found in nature [4], known for their biological and pharmacological properties, including anti-HIV [5], anti-cancer [6,7], antibacterial [8–10], and anti-neurodegenerative activities

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[11–13]. They are also used as organic pesticides [14] and intermediates [15] in synthesizing natural and synthetic compounds. For organic and medicinal chemists, the challenge lies in developing new, environmentally friendly synthetic techniques. Current trends focus on one-pot, one-step, solvent-free, and catalyst-free methods [16–18], which offer benefits like reduced reaction times and simplified purification processes [19].

The ring of 1,3,4-oxadiazole is a crucial heterocyclic compound due to its broad biological activity [20]. This ring structure, characterized by the substitution of two nitrogen atoms for methylene groups, reduces aromaticity and introduces conjugated diene characteristics, enhancing its therapeutic potential [21]. Among its isomers, the 1,3,4-oxadiazole isomer is particularly noted for its diverse therapeutic applications [22–29].

The potent pharmacological actions of 1,3,4-oxadiazole may stem from its toxophoric –N=C–O– bond [30]. Among them, substituted 1,3,4-oxadiazoles are quite interesting from a medicinal standpoint [31]. Specifically, 2,5-diaryl-1,3,4-oxadiazoles have greater stability in comparison to their corresponding 2,5-dialkyl derivatives.

The 1,3,4-oxadiazole ring is present in a variety of drugs (Fig. 1), including Furamizole, a nitrofuran derivative with potent antibacterial activity [32]. Anti-arrhythmic therapy uses the medications Nesapidil and Raltegravir, which are antiviral drugs. The FDA-approved anticancer medication Zibotentan has the most distinctive derivatives available on the market in its 1,3,4-oxadiazole nucleus [33]. Tiodazosin is a medication used to treat hypertension [34].

Additionally, sugar-based 1,3,4-oxadiazoles are a vital class of heterocyclic compounds [35] known for their broad spectrum of biological activities, particularly as antimicrobial agents against bacteria and fungi. These compounds also exhibit properties such as anti-epileptic activity [36], apoptosis induction [37], antimycobacterial effects [38], and antifungal [39], and serve as inhibitors for various biological targets.

In previous work [40,41], The main goal of our present work is to synthesize some heterocyclic compounds that are characterized by multi-directional biological activity, such as antibiotics, antimicrobials, and anticancer agents. Hence the importance of this work, in which we constructed some different Oxadiazole compounds and evaluated them biologically as antibacterial agents.

2. Results and discussion

2.1. Chemistry

The Von Pechmann reaction provides coumarins when phenols condense with ethyl acetoacetate in an acidic media. When sulfuric acid is present, resorcinol and ethyl acetoacetate produce 7-hydroxy-4-methylcoumarin **(1)** [42].

Compound **2** was produced in high yield by refluxing the starting coumarin **1** with diethyl ethoxymethylene malonate in ethanol (Scheme 1). Compound **2** showed the molecular ion (M^+) peak at *m/z* 346 (M^+, 48 %) in its mass spectrum, while the infrared spectrum revealed the carbonyl ester group absorption band at 1695 cm^{-1}. After boiling in diphenyl ether, **2** underwent cyclization to get compound **3** (Scheme 1). Compound **3's** ^{1}H NMR spectrum showed ethyl group signals as a quartet at δ 4.31 ppm (J = 5.5 Hz) and a triplet at δ 1.28 ppm (J = 5.5 Hz), addition to four aromatic protons at δ 6.27 (singlet signal due to C_3-H coumarin), 7.02, 7.84 (two

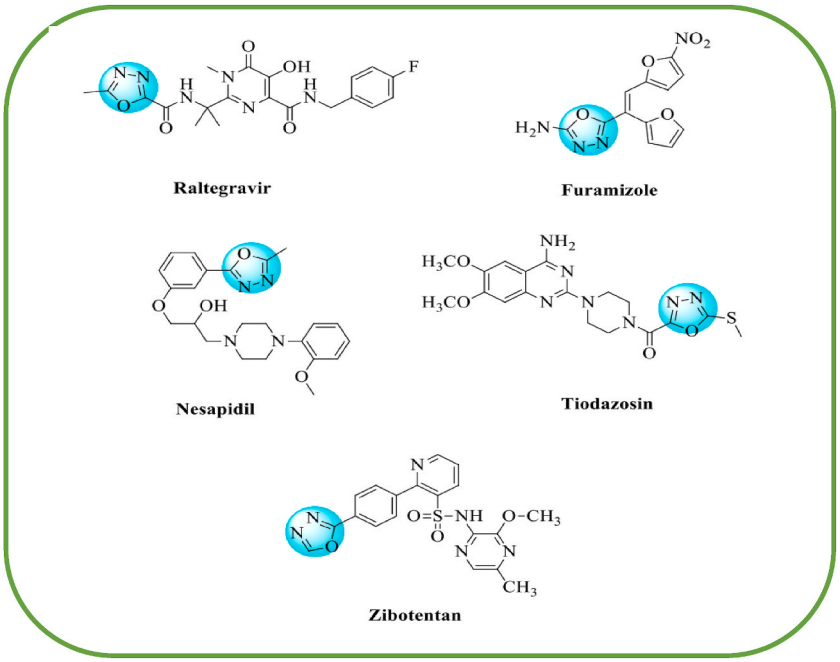
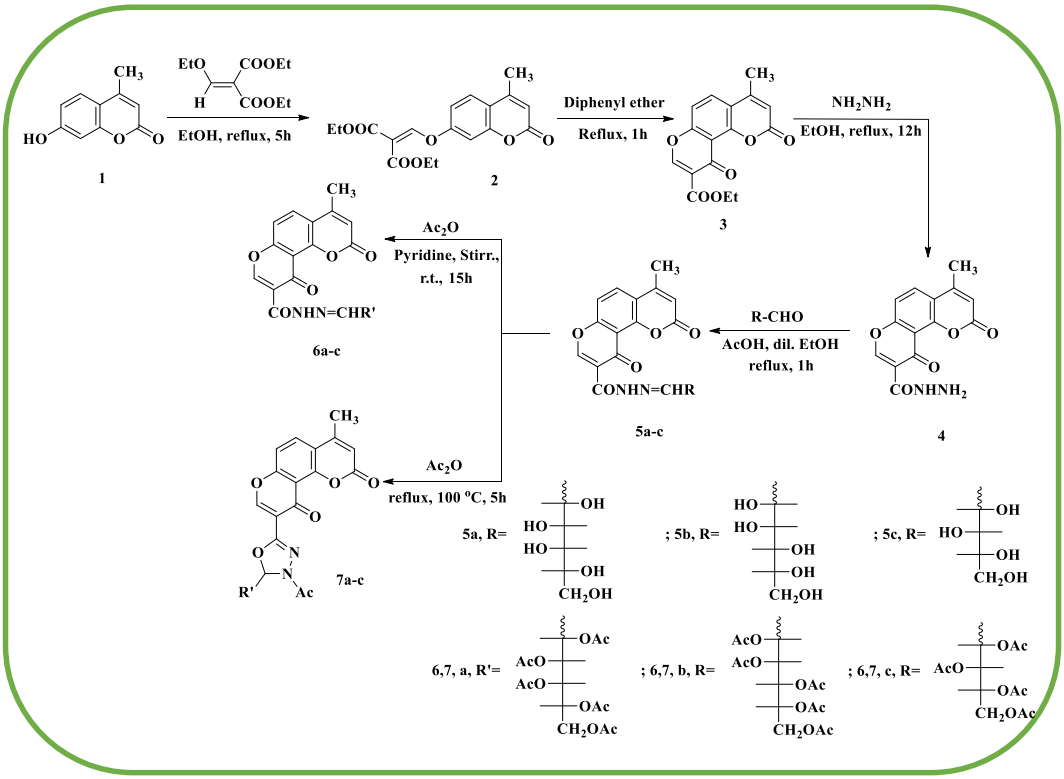
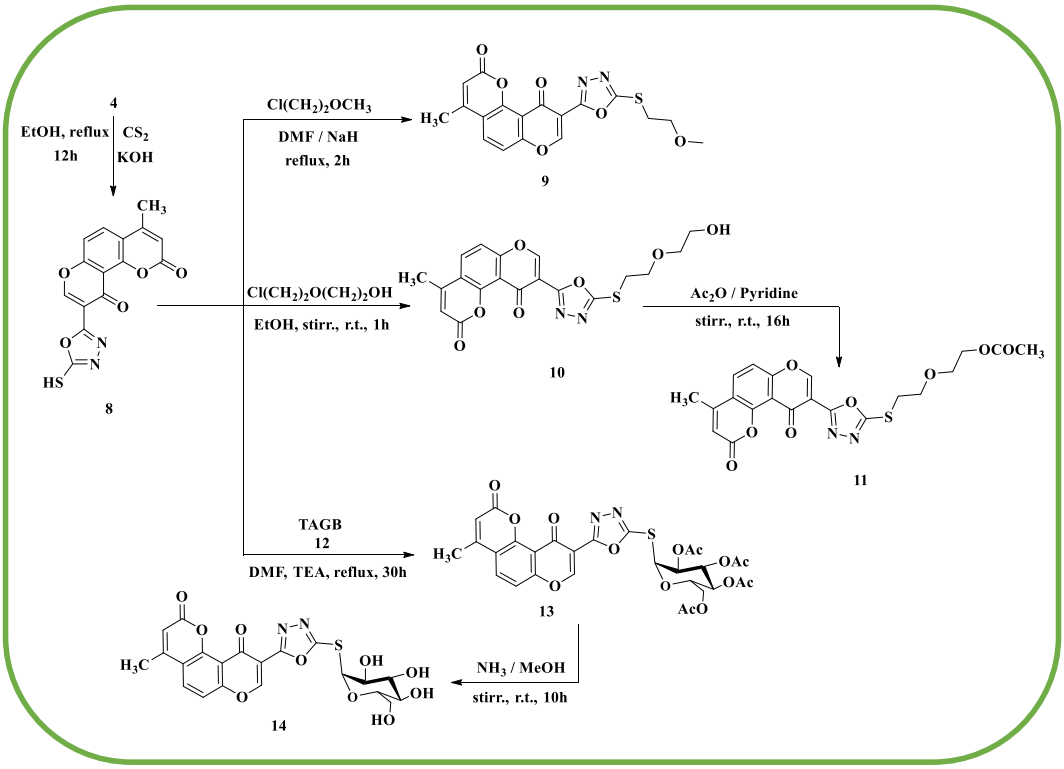


Fig. 1. Some drugs containing 1,3,4-oxadiazole moiety.



Scheme 1. Synthesis of compounds 5a-c, 6a-c and 7a-c.



Scheme 2. Synthesis of compounds 8-14.

doublets AB system, J = 18 Hz due to C_5-H and C_6-H coumarin), and 8.57 ppm (singlet signal due to C_8-H pyran ring) beside CH_3 protons at δ 2.42 ppm as singlet signal. Compound **3** displayed characteristic bands at 1710 (COOEt), and 1641 cm^{-1} (C=O) groups in its IR spectrum. The equivalent acid, hydrazide **4**, was given by treating **3** with hydrazine hydrate (Scheme 1). In hydrazide derivative **4**, the ethyl group has vanished, and the protons of the $CONHNH_2$ group are visible at δ 4.65 (NH_2) and 8.65 ppm (NH).

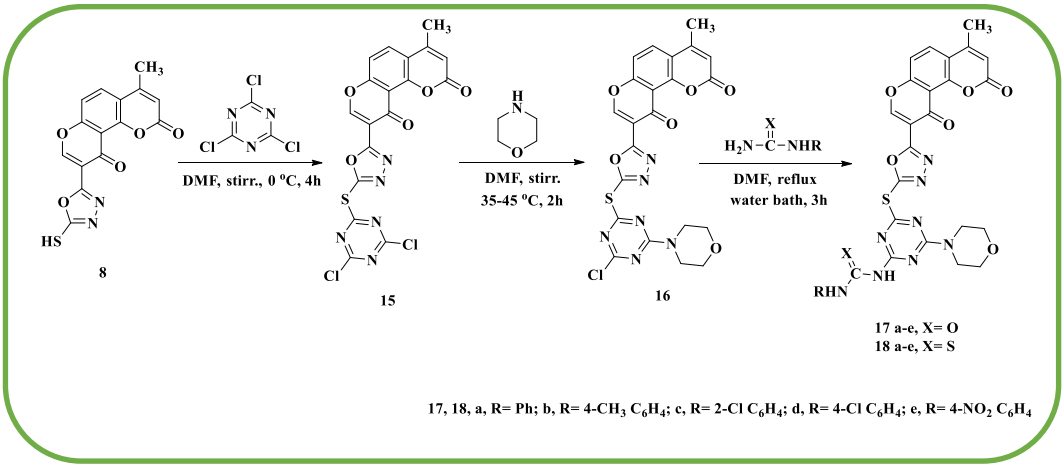
The corresponding sugar hydrazones **5a–c** were produced in 90–95 % yields when **4** interacted with D-galactose, D-mannose, and/or D-xylose in an aqueous ethanolic solution with a catalytic quantity of acetic acid (Scheme 1). Characteristic bands were visible in the IR spectra of samples **5a–c**. These bands corresponded to the hydroxyl groups around 3451–3420 and 3310 cm^{-1} for NH. The sugar chain protons at δ 3.45–5.61 ppm, the aromatic protons at δ 6.40 (singlet), 7.00, 7.75 (two doublets AB system, J = 18 Hz), and 8.35 ppm (singlet), the N=CH proton at δ 8.85 ppm, and the proton for NH at δ 11.15 ppm were all detected in **5a′s** ^{1}H NMR spectrum. The per-*O*-acetyl derivatives, **6a-c**, were obtained in 71–86 % yield by agitating in pyridine acetic anhydride with the sugar hydrazones **5a-c** at 25 °C (Scheme 1). The infrared spectra of samples **6a–c** displayed distinct absorption bands at ν 3310 cm^{-1} for NH and ν 1737 cm^{-1} corresponding to the acetyl carbonyl groups. Compound **6b′s** ^{1}H NMR spectrum revealed signals at δ 1.82–2.43 ppm due to *O*-acetyl group protons, while the remaining sugar chain protons were detected in the δ 4.26–5.68 ppm range. Conversely, oxadiazoline derivatives **7a-c** were obtained by heating sugar hydrazone **5a-c** with acetic anhydride to 100 °C (Scheme 1). The carbonyl groups and the disappearance of the NH peak, respectively, were represented by distinctive bands in the infrared spectra of samples **7a–c**, which were located at ν 1740-1640 cm^{-1}. The oxadiazoline proton appeared within the aromatic proton range at δ 6.24 ppm, while the proton signals of acetyl groups were observed in the region of δ 1.18–2.10 ppm in the ^{1}H NMR spectrum of sample **7a**.

With anhydrous KOH methanol, **4** was refluxed with carbon disulfide to obtain compound **8** with an 83 % yield (Scheme 2). In its ^{1}H NMR spectrum, the aromatic protons were represented by four signals at δ 6.30 (singlet), 7.00, 7.90 (two doublets AB system, J = 18 Hz), and 8.70 ppm (singlet), and the SH protons appeared at δ 13.52 ppm as a singlet signal. The M^+ peak was visible in the MS at *m/z* 328 (M^+, 38 %). Compound **8** yielded **9** when it reacted with 2-chloroethyl methyl ether in DMF and sodium hydride at 25 °C (Scheme 2). The ^{1}H NMR spectra revealed triplet signals for CH_2O at δ 3.65 ppm (J = 5.5 Hz), the two S-CH_2 groups at δ 3.78 ppm (J = 5.5 Hz), and a singlet signal of *O*-methyl protons at δ 3.49 ppm.

In an ethanolic NaOH solution, compound **8** reacted with 2-chloroethoxy ethanol to give compound **10** in a 94 % yield (Scheme 2). The Mass, IR, and ^{1}H NMR spectroscopy were used to assert its structure. The M^+ peak appeared in MS of **10** at m/z 416 (M^+, 30 %). With acetic anhydride in pyridine, compound **10** was acetylated to yield compound **11**. The IR spectrum revealed a band at 1735 cm^{-1} that corresponds to $COCH_3$ moiety, confirming its structure.

Furthermore, compound **13** was obtained when 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (TAGB) **(12)** reacted with **8** in DMF at 25 °C, which was catalyzed by TEA (Scheme 2). The acetyl group appeared as a band at 1751 cm^{-1} in the infrared spectra of **13**. The acetyl protons' signal at δ 1.99 ppm, at δ 6.11 (singlet) due to aromatic protons, 7.30, 7.70 (two doublets AB system, J = 18 Hz), and 8.32 ppm (singlet), and the CH_3 singlet signal at δ 2.38 ppm were all appeared in the ^{1}H NMR spectrum. At 25 °C, **13** reacted with a methanolic ammonia solution to produce compound **14** (Scheme 2). The typical band at 3373 cm^{-1}, which corresponds to the hydroxyl groups, appeared in the IR spectrum of compound **14**.

Furthermore, compound **15** was obtained by treating compound **8** with s-triazine trichloride (Scheme 3). This was followed by condensation with morpholine, which produced **16**, which was transformed into compounds **17a-e** and **18a-e** by reacting with aryl urea and/or aryl thiourea (Scheme 3). IR and ^{1}HNMR were used to describe the compounds **17a-e** and **18a-e**. Compound **17a′s** IR spectrum exhibits a peak at ν 1685 cm^{-1}, indicating the existence of an amidic carbonyl group. Compound **17a′s** ^{1}HNMR spectrum reveals a signal at δ 9.35 and 10.20 ppm of two NH groups.



Scheme 3. Synthesis of compounds 15-18.

2.2. Antimicrobial evaluation

The antibacterial activity of thirty newly synthesized compounds was tested *in vitro* against yeast-like fungi (*C. albicans*), Gram-positive bacteria (S. *aureus* and *B. subtilis*), and Gram-negative bacteria (*P. aeruginosa* and *E. coli*).

The Agar-diffusion method was used in this experiment. Cephalothin, chloramphenicol, and cycloheximide were the reference drugs. Minimum Inhibitory Concentration (MIC) was determined by the two-fold serial dilution method [43]. The MIC is shown in Table 1 (μg/mL).

According to the information in Table 1, a large number of the compounds under investigation exhibited a variety of inhibitory effects on the spread of the tested Gram + ve and Gram-ve bacterial strains as well as against fungal strains. In general, a large number of the compounds studied proved to be more efficient against Gram + ve bacteria than against Gram-ve bacteria. It is noticed that compounds belonging to 1,3,4-oxadiazolyl pyrano chrome **11** and **13**, and oxadiazolyl thio s-triazine **16–18** exhibited better antibacterial potentials than the rest of the other compounds.

Based on the data, compounds **11**, **13**, **15**, **16**, **17c-e**, and **18a-e** showed broad-spectrum antibacterial activity against the studied species. In this perspective, these compounds were demonstrated to be equipotent to chloramphenicol, as appeared by their capacity to inhibit *B. subtilis* growth (MIC 3.125 μg/mL) and their 50 % reduced efficacy against *S. aureus* in comparison to chloramphenicol, with the exception of compounds **15** and **16**, where it is likewise 3.125 μg/mL. Compounds **7a–c**, **8**–**10**, **14**, and **17a–b** showed 50 % of chloramphenicol's growth inhbtion of *B. subtilis* and *S. aureus* (MIC 6.25 μg/mL). Compounds **2-6a-c**, on the other hand, showed modest growth inhibitory activity against Gram + ve bacteria based on their MIC values (12.5–50 μg/mL). Compounds **11**, **13**, and **18a-e** showed significant growth suppression in their antibacterial activities against the tested Gram-ve bacteria (MIC 12.5 μg/mL), whereas the rest compounds displayed moderate growth inhibition against the same organism (MIC 25–100 μg/mL). In relation to the pyranochromene compound's oxadiazole ring's antifungal strain activity, the findings showed that compounds **18c–e** inhibited the growth of *C. albicans* 50 % lower than cycloheximide (MIC 6.25 μg/mL).

In combination with oxadiazole and oxadiazolothio s-triazine rings, pyranochromene compound **4** exhibits a robust and high antibacterial activity value. This implies that the antibacterial activities were enhanced to be equipotent to a pharmaceutical reference by the inclusion of sulfur and nitrogen atoms.

Compounds with CS and CO groups showed stronger antibacterial activity than those with electron-donating groups. The presence

Table 1
Antimicrobial activity of the newly synthesized compounds.

MIC (μg/mL)					
	Gram Positive bacteria		Gram Negative bacteria		Fungi
Compound No.	*S. aureus*	*B. subtilis*	*P. aeruginosa*	*E. coli*	*C. albicans*
2	50	50	100	100	100
3	50	50	100	100	100
4	25	25	100	50	50
5a	25	12.5	25	50	50
5b	25	12.5	25	50	100
5c	25	12.5	50	50	100
6a	12.5	12.5	50	100	100
6b	12.5	12.5	50	100	100
6c	12.5	12.5	50	100	100
7a	6.25	6.25	25	50	50
7b	6.25	6.25	25	50	100
7c	6.25	6.25	25	50	100
8	6.25	12.5	25	50	50
9	6.25	6.25	25	50	50
10	6.25	6.25	25	50	50
11	3.125	6.25	12.5	25	12.5
13	3.125	6.25	12.5	25	12.5
14	6.25	6.25	50	25	50
15	3.125	3.125	25	25	50
16	3.125	3.125	25	50	25
17a	6.25	6.25	25	50	50
17b	6.25	6.25	50	50	100
17c	3.125	6.25	25	25	50
17d	3.125	6.25	25	25	25
17e	3.125	6.25	25	25	25
18a	3.125	6.25	12.5	25	12.5
18b	3.125	6.25	12.5	25	12.5
18c	3.125	6.25	12.5	25	6.25
18d	3.125	6.25	12.5	25	6.25
18e	3.125	6.25	12.5	25	6.25
Chloramphenicol	3.125	3.125	6.25	6.25	–
Cephalothin	6.25	6.25	6.25	6.25	–
Cycloheximide	–	–	–	–	3.125

and position of the -NHCSNH- group and polar nitro and chloro substitutions at the C_2 and C_4 positions of the phenyl ring are key factors for optimizing compounds 17a-e and 18a-e.

The compounds showed greater effectiveness against Gram-positive bacteria compared to Gram-negative. This suggests their antibacterial activity is linked to the bacteria's cell wall. Gram-positive bacteria have a thick peptidoglycan-rich wall, making them more susceptible to certain antibiotics that target cell wall synthesis, while Gram-negative bacteria, with their thinner, lipopolysaccharide-rich wall, are less affected [44].

2.3. Molecular docking study

In comparison to the reference drug (cephalothin), the newly synthesized compounds demonstrated significant action against Gram-positive bacteria *S. aureus* and *B. subtilis*, as confirmed by the results of the antimicrobial activity. As a result, the potential for these substances to prevent the growth of Gram-positive bacteria was investigated under the name cephalothin.

Cefalotin or cephalothin is a first-generation semi-synthetic cephalosporin with a broad antimicrobial activity [45]. The bactericidal activity of cephalothin results from inhibition of cell wall synthesis by affinity for penicillin-binding proteins (PBPs) [46]. The PBPs are transpeptidases which are vital in peptidoglycan biosynthesis [47,48].

Transpeptidase is an enzyme that catalyzes the transpeptidation reaction between pentapeptide chains and adjacent peptide chains in the bacterial cell wall. It forms a domain in class A and B of penicillin-binding proteins peptidoglycan [49]. Therefore, the inhibition of one of these enzymes that has a significant impact on the microbial life cycle could influence protein synthesis, nucleic acid cleavage, assembly, and replication, or by altering the components and function of the cell wall [49]. Thus, to pre-assess the anti-bacterial behavior of the active compounds **11, 13, 15, 16, 17c-e, and 18a-e** towards *S. aureus* and *B. subtilis*, the docking study was carried out to predict the scoring function, the binding affinity, and the orientation of the active compounds **11, 13, 15, 16, 17c-e, and 18a-e** at the active sites of transpeptidases enzyme, PDB: 5TW8 (Auth A, with ceftaroline **(**AI8) as inhibitor) of *S. aureus*.

Accordingly, the X-ray crystallographic structure of transpeptidases enzyme, PDB: 5TW8 with the native inhibitor, ceftaroline (AI8) of *S. aureus*, was recovered from the protein data bank https://www.rcsb.org/structure/5TW8 (accessed on 09-02-2024). To validate the molecular docking process, the native ligand (AI8) was first re-docked into the active pocket of the enzyme. The ligand that was re-docked exhibited a docking score (S) of −8.4 kcal/mol. It was able to recreate all of the important connections, including alkyl and Pi-alkyl interactions, with the active amino acids of the active pocket, which include SER75, SER139, SER262, TYR291, and GLU114, through hydrogen bond interaction (Fig. 2a and b).

Every molecule under study exhibited super-impossibility to AI8. Similar to AI8, they demonstrated a strong binding mode with the active pocket and restored the contacts with the essential amino acids of the transpeptidases enzyme (Figs. 2b and 3a-l, and 4a-l). Additionally, they showed greater binding energy values (−8.7 to −11.2 kcal/mol) than the original ligand AI8 against the transpeptidases enzyme's binding site (PDB: 5TW8) (Table 2) (see Fig. 4).

Remarkably, all studied compounds revealed the same hydrogen interaction with the key amino acids to AI8. Especially with the key amino acid SER75, SER262, TYR291, except compounds **18a**, **18b**, **18c**, and **18d**. They showed hydrogen interaction only with TYR291.

Compound **18e** was the only one that showed superior interaction with the active pocket of the transpeptidase, PDB: 5TW8. It restored the same interactions with all the main amino acids identical to the original compound AI8, including SER75, SER139, SER262, TYR291, and GLU114 via hydrogen interactions, besides PHE241 (Pi-Pi-stacked), ALA74 (Pi-alkyl) interactions. In addition, compound **18e** showed additional hydrogen interactions with GLU297, GLY261, LYS259, SER116, LYS78, and ASN141 (Fig. 5a–d).

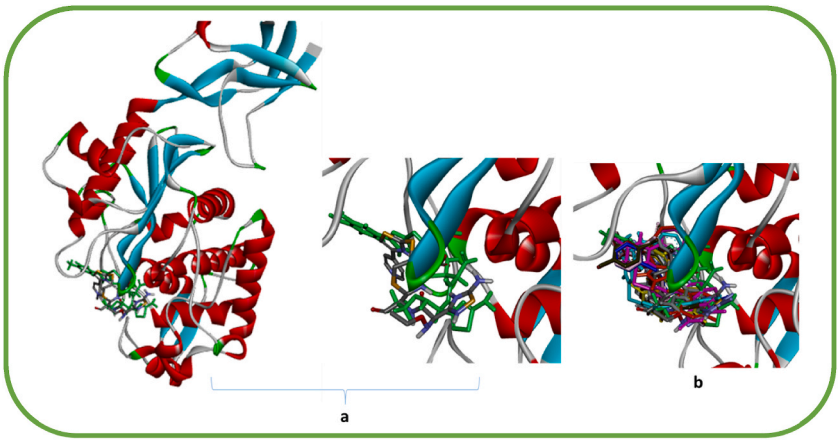


Fig. 2. a): The 3D orientation of original ligand AI8 of transpeptidases enzyme (elemental colored), the re-docked ligand (green), **b):** The 3D orientation of the re-docked ligand (green), **11** (dark blue); **13**; (orang); **15** (faint purple); **16** (pink); **17c** (yellow); **17d** (maroon); **17e** (silver metallic); 18a (pink metallic); 18b (greenish brown); 18c (blue); 18d (dark red); 18e (blue sky) inside the binding pocket of transpeptidases enzyme (PDB: 5TW8).

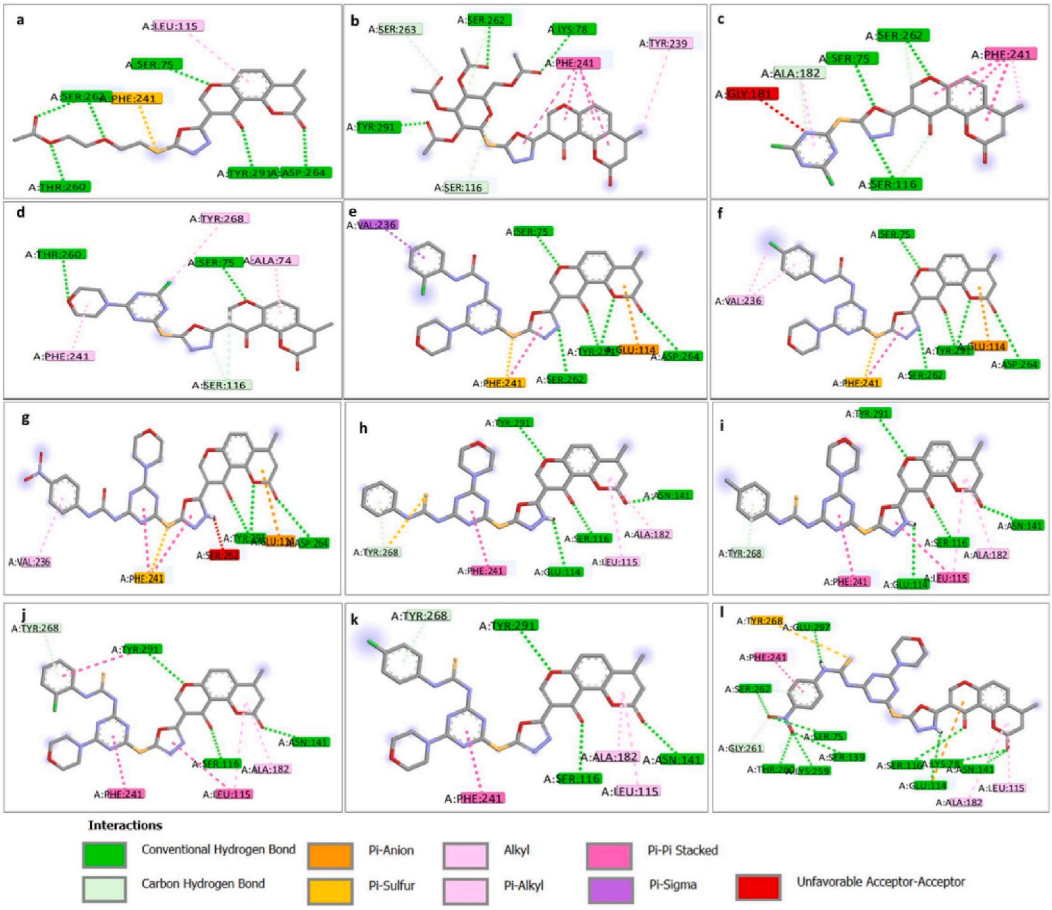


Fig. 3. a-l. The 2D interaction of compounds **11, 13, 15, 16, 17c-e,** and **18a-e** inside the binding pocket of transpeptidase enzyme, PDB: 5TW8, illustrating the formed hydrogen bonds, attractive charge, pi-pi bond, and pi-alkyl.

It might be concluded that the activity of compound **18e** proved to be able to inhibit transpeptidase, a bacterial enzyme that cross-links the peptidoglycan chains to form rigid cell walls, confirming the importance of the presence of the fused pyrano [2,3-f] chromene next to oxadiazole moiety and besides 3-(4-nitrophenyl-urea) 1,3,5-triazine in agreement with the mentioned clarification described by Refs. [50–52].

3. Experiment

3.1. Instruments

The melting point is measured and left uncorrected when using the Gallenkamp electric melting point device. At the Mansoura University, Faculty of Science, we recorded the IR spectra at ν/cm-^{1} (KBr) using a PerkinElmer Infrared Spectrophotometer Model 157, Grating. The ^{1}H NMR spectra were obtained using a Varian spectrophotometer at 300 MHz and a Bruker spectrophotometer at 400 MHz (Cairo University, Faculty of Science and Mansoura University, Faculty of Pharmacy, respectively). Tetramethylsilane (TMS) was used as the internal reference, and DMSO-d_6 was the solvent. Joel ECA-500 ll (Mansoura University, Faculty of Science) is where ^{13}C NMR was conducted. The mass spectra (EI) at 70 eV were recorded at the Micro Analytical Unit, Faculty of Science, Cairo University, and Al-Azhar University, Cairo, Egypt, using the Kratos MS instrument and/or a Varian MAT 311 A Spectrometer. In Giza, Egypt, at the microanalytical center of Cairo University, elemental studies (C, H, and N) were conducted.

3.2. Chemistry

3.2.1. Synthesis of 7-hydroxy-4-methyl-2H-chromen-2-one (1)

It was prepared according to previously reported work [42].

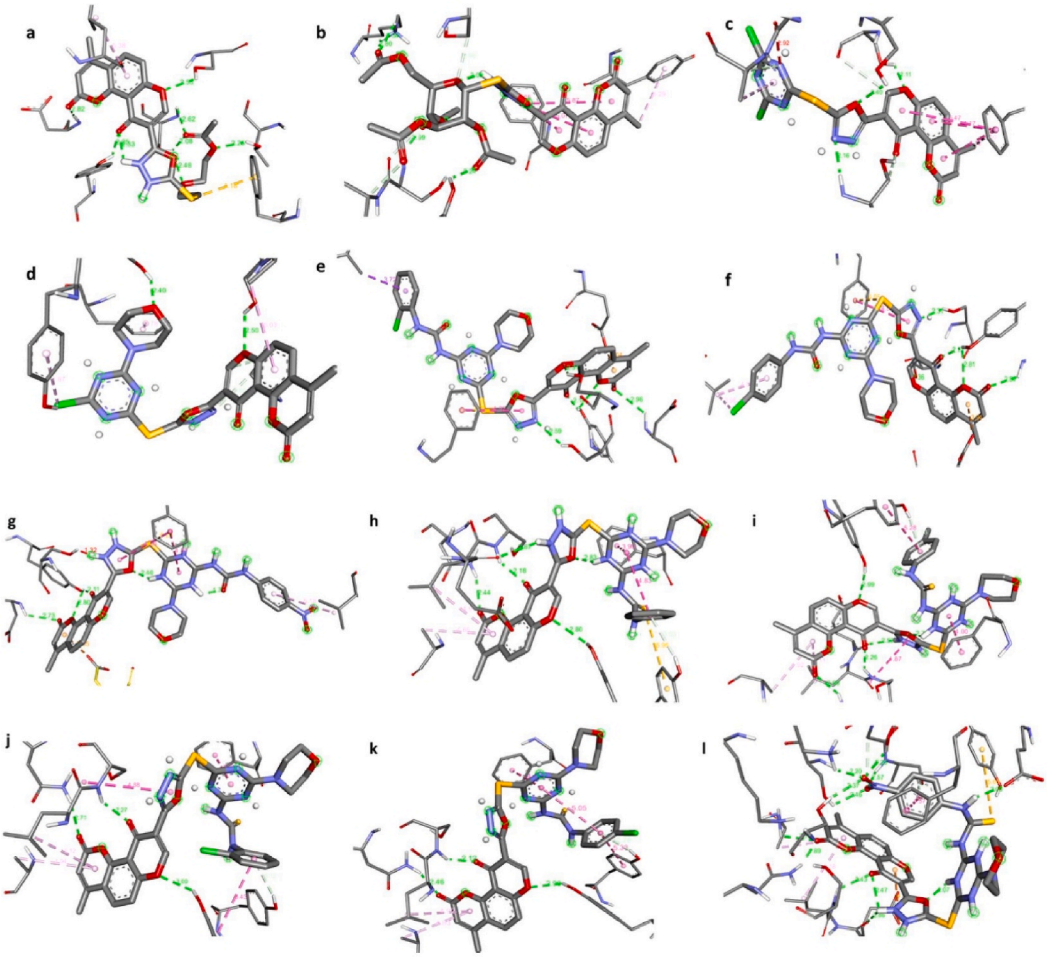


Fig. 4. a-l. The 3D configurations of compounds **11, 13, 15, 16, 17c-e,** and **18a-e** inside the binding pocket of transpeptidase enzyme (PDB: 5TW8).

Table 2
The binding energy values of compounds **11, 13, 15, 16, 17c-e, and 18a-e** against transpeptidase enzyme, PDB: 5TW8 (with AI8 as inhibitor) of *S. aureus*.

Compound no.	Binding energy Kcal/mol	Compound no.	Binding energy Kcal/mol
AI8 (ceftaroline)	−8.4	**AI8 (ceftaroline)**	−8.4
11	−8.7	**17e**	−10.7
13	−9.2	**18a**	−10.2
15	−10.1	**18b**	−10.4
16	−10.5	**18c**	−10.4
17c	−11.2	**18d**	−10.4
17d	−11.1	**18e**	−10.7

3.2.2. Synthesis of diethyl 2-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methylene)malonate (2)

Diethyl ethoxymethylene malonate (2.16 g, 0.01 mol) was dropped to a solution of coumarin **1** (1.76 g, 0.01 mol) in abs. ethanol (25 mL). After 5 h of reflux to the mixture of reaction, remove the solvent under reduced pressure. The semisolid derivative **2** was recrystallized from ethanol after being dried.

Yield, 91 %; m.p. = 110–112 °C; IR (KBr): ν_{max}, cm^{-1}: 1695 (C=O), 1640 (C=C); ^{1}H NMR (DMSO-d6): δ = 1.23 (t, 6H, $2CH_3$), 2.40 (s, 3H, CH_3), 4.20 (q, 4H, $2CH_2$), 6.27 (s, 1H, Ar-H), 6.95 (d, 1H, J = 18 Hz, Ar-H), 7.05 (s, 1H, Ar-H), 7.57 (d, 1H, J = 18 Hz, Ar-H), 8.13 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d6): δ = 14.6 (2C), 20.8, 61.2 (2C), 105.9, 110.8, 112.8, 114.0 (2C), 125.8, 152.5, 154.5 (2C), 160.9, 163.0, 165.5 (2C). MS (*m/z*, %): 346 (M^+, 48). Anal. Calcd for $C_{18}H_{18}O_7$ (346.34): C, 62.42; H, 5.24 %. Found: C, 62.21; H, 5.19 %.

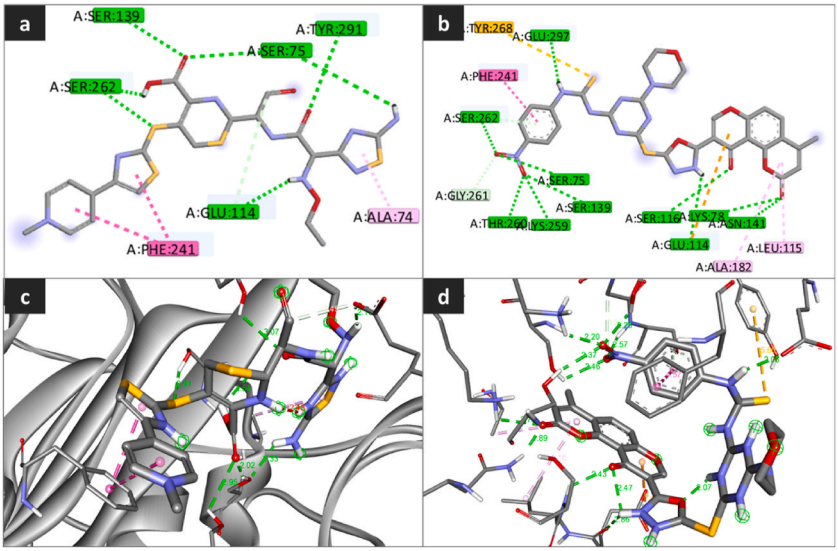


Fig. 5. a), b) The 2D interactions of **AI8** and **18e** inside the binding pocket of transpeptidase enzyme (PDB: 5TW8), c) and d) clarifying the 3D configurations of **AI8** and **18e** inside the binding pocket of transpeptidase enzyme (PDB: 5TW8).

3.2.3. Synthesis of ethyl 4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromene-9-carboxylate (3)

Refluxing compound **2** (3.46 g, 0.01 mol) for an hour in boiling diphenyl ether, the reaction mixture was cooled and filtered. The isolated precipitate was washed and dried with diethyl ether. Following the addition of 70 % ethanol, the resulting product recrystallized, yielding **3**.

Yield, 79 %; m.p. = 221–223 °C; IR (KBr): ν_{max}, cm^{-1}: 1710 (COOEt), 1641 (C=O); ^{1}H NMR (DMSO-d6): δ = 1.28 (t, 3H, J = 5.5 Hz, CH_3), 2.42 (s, 3H, CH_3), 4.31 (q, 2H, J = 5.5 Hz, CH_2), 6.27 (s, 1H, Ar-H), 7.02 (d, 1H, J = 18 Hz, Ar-H), 7.84 (d, 1H, J = 18 Hz, Ar-H), 8.57 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d6): δ = 14.5 19.9, 61.6, 110.6, 111.8, 113.0, 114.9, 118.9, 131.8, 149.2, 152.8, 156.9, 160.5, 163.8, 165.1, 177.7. Anal. Calcd for $C_{16}H_{12}O_6$ (300.27): C, 64.00; H, 4.03 %. Found: C, 63.88; H, 3.96 %.

3.2.4. Synthesis of 4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromene-9-carbohydrazide (4)

Compound **3** (3.00 g, 0.01 mol) in 50 mL of ethanol was mixed with 1.50 g of hydrazine hydrate (0.03 mol), and the mixture was refluxed for 12 h. The mixture was left to cool to room temperature, filtering, drying, and recrystallizing it from ethanol, the pyranochromene derivative **4** was produced.

Yield, 83 %; m.p. = 270–272 °C; IR (KBr): ν_{max}, cm^{-1}: 3340 (NH_2), 3279 (NH), 3178 (NH), 1677 (CONH), 1654 (C=O), 1633 (C=C); ^{1}H NMR (DMSO-d6): δ = 2.43 (s, 3H, CH_3), 4.65 (s, 2H, NH_2), 6.29 (s, 1H, Ar-H), 7.00 (d, 1H, J = 18 Hz, Ar-H), 7.71 (d, J = 18 Hz, 1H, Ar-H), 8.31 (s, 1H, Ar-H), 8.65 (s, 1H, NH); ^{13}C NMR (DMSO-d6): δ = 19.6, 110.5, 112.3, 113.9 (2C), 118.9, 131.9, 149.8, 152.9, 156.5, 160.3, 162.9, 166.0, 177.8. MS (*m/z*, %): 286 (M^+, 37). Anal. Calcd for $C_{14}H_{10}N_2O_5$ (286.24): C, 58.75; H, 3.92; N, 9.79 %. Found: C, 58.63; H, 3.44; N, 9.66 %.

3.3. Synthesis of compound 5a-c

3.3.1. General procedure

A well-stirred solution of compound **4** (2.86 g, 0.01 mol) in ethanol (10 mL) and the equivalent monosaccharide (0.01 mol) in water (2 mL) was added to 0.5 mL of glacial acetic acid. The reaction mixture was refluxed for an hour. The resulting solution was concentrated, cooled, and then filtered off. After drying and washing with ethanol, the precipitate recrystallized from ethanol.

3.3.2. 4-Methyl-2,10-dioxo-N'-((3R,4S,5R,E)-2,3,4,5,6-pentahydroxyhexylidene)-2H,10H-pyrano [2,3-f]chromene-9-carbohydrazide (5a)

Yield, 90 %, m.p. = 210–212 °C, IR (KBr): ν_{max}, cm^{-1}: 3451-3420 (OH), 3310 (NH), 1659 (CONH), 1645 (C=O), 1580 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 3.45–5.61 (m, 11H, 5OH, CH_2, 4CH), 6.40 (s, 1H, Ar-H), 7.00 (d, 1H, J = 18 Hz, Ar-H), 7.75 (d, 1H, J = 18 Hz, Ar-H), 8.35 (s, 1H, Ar-H), 8.85 (s, 1H, =CH), 11.15 (s, 1H, NH); ^{13}C NMR (DMSO-d6): δ = 20.5, 64.5, 66.6, 71.0 (2C), 72.5, 110.8, 112.9, 115.0 (2C), 118.3, 131.6, 149.5, 152.9 (2C), 156.6, 160.4, 162.2, 168.1, 177.0. Anal. Calcd for $C_{20}H_{20}N_2O_{10}$ (448.38): C, 53.57; H, 4.50; N, 6.25 %. Found: C, 53.44; H, 4.38; N, 6.18 %.

3.3.3. 4-Methyl-2,10-dioxo-N'-((3R,4R,5R,E)-2,3,4,5,6-pentahydroxyhexylidene)-2H,10H-pyrano [2,3-f]chromene-9-carbohydrazide (5b)

Yield, 93 %, m.p. = 220–222 °C, IR (KBr): ν_{max}, cm^{-1}: 3402 (OH, NH), 1663 (CONH), 1639 (C=O), 1610 (C=N). Anal. Calcd for

$C_{20}H_{20}N_2O_{10}$ (448.38): C, 53.57; H, 4.50; N, 6.25 %. Found: C, 53.50; H, 4.35; N, 6.17 %.

3.3.4. 4-Methyl-2,10-dioxo-N'-((3R,4R,E)-2,3,4,5-tetrahydroxypentylidene)-2H,10H-pyrano [2,3-f]chromene-9-carbohydrazide (5c)

Yield, 95 %, m.p. = 195–197 °C, IR (KBr): ν_{max}, cm^{-1}: 3416 (OH), 3303 (NH), 1642 (CONH), 1615 (C=O). Anal. Calcd for $C_{19}H_{18}N_2O_9$ (418.36): C, 54.55; H, 4.34; N, 6.70 %. Found: C, 54.48; H, 4.29; N, 6.66 %.

3.4. Synthesis of 6a-c

3.4.1. General procedure

After adding 1.2 mL (0.01 mol) of acetic anhydride to a 7 mL solution of **5a–c** (0.01 mol) in pyridine, the mixture was stirred for 15 h at 25 °C. Chloroform was used to collect the product after the resulting solution was added to crushed ice.

3.4.2. (2R,3S,4R,E)-6-(2-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromene-9-carbonyl) hydrazineylidene)hexane-1,2,3,4,5-pentayl pentaacetate (6a)

Yield, 77 %, m.p.: semi-solid, IR (KBr): ν_{max}, cm^{-1}: 3310 (NH), 1737 ($COCH_3$), 1666 (CONH), 1639 (C=O); ^{1}H NMR (DMSO-d6): δ 2.06 (s, 12H, 4$COCH_3$), 2.20 (s, 3H, $COCH_3$), 2.39 (s, 3H, CH_3), 4.31 (d, 2H, CH_2), 5.24–5.70 (m, 4H, 4CH), 6.29 (s, 1H, C_3-H pyran), 7.11 (d, 1H, J = 18 Hz, Ar-H), 7.43 (s, 1H, C_2-H pyran), 7.77 (d, 1H, J = 18 Hz, Ar-H), 8.09 (d, 1H, CH=N), 12.10 (s, 1H, NH); ^{13}C NMR (DMSO-d6): δ = 19.8, 21.7 (5C), 62.1, 65.5, 68.0, 71.0, 72.3, 110.0, 112.8, 114.9 (2C), 118.0, 131.4, 149.4, 152.4 (2C), 156.3, 160.0, 162.0, 168.0, 171.5 (5C), 177.0. Anal. Calcd for $C_{30}H_{30}N_2O_{15}$ (658.57): C, 54.71; H, 4.59; N, 4.25 %. Found: C, 54.68; H, 4.47; N, 4.19 %.

3.4.3. (2R,3R,4R,E)-6-(2-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromene-9-carbonyl) hydrazineylidene)hexane-1,2,3,4,5-pentayl pentaacetate (6b)

Yield, 86 %, m.p. = 78–80 °C, IR (KBr): ν_{max}, cm^{-1}: 3270 (NH), 1739 ($COCH_3$), 1671 (CONH), 1635C=O), 1612 (C=N); ^{1}H NMR (DMSO-d6): δ 1.82–2.43 (m, 18H, 5$COCH_3$ + CH_3), 4.26 (d, 2H, CH_2), 5.13–5.68 (m, 4H, 4CH), 6.40 (s, 1H, Ar-H), 7.02 (d, 1H, J = 18 Hz, Ar-H), 7.51 (s, 1H, Ar-H), 7.79 (d, 1H, J = 18 Hz, Ar-H), 7.90 (d, 1H, CH=N), 12.20 (s, 1H, NH); ^{13}C NMR (DMSO-d6): δ = 19.0, 20.9 (5C), 61.9, 64.9, 67.7, 70.7, 71.9, 110.0, 112.1, 114.0 (2C), 117.6, 130.7, 148.5, 152.0 (2C), 155.9, 159.7, 161.6, 167.5, 170.7 (5C), 176.6. Anal. Calcd for $C_{30}H_{30}N_2O_{15}$ (658.57): C, 54.71; H, 4.59; N, 4.25 %. Found: C, 54.66; H, 4.45; N, 4.11 %.

3.4.4. (2R,3R,E)-5-(2-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromene-9-carbonyl)hydrazineylidene)pentane-1,2,3,4-tetrayl tetraacetate (6c)

Yield, 71 %, m.p. = 115–117 °C, IR (KBr): ν_{max}, cm^{-1}: 3270 (NH), 1740 ($COCH_3$), 1685 (CONH), 1631 (C=O), 1610 (C=N); ^{1}H NMR (DMSO-d6): δ 2.10 (s, 9H, 3$COCH_3$), 2.25 (s, 3H, $COCH_3$), 2.40 (s, 3H, CH_3), 4.44 (d, 2H, CH_2), 5.30–5.56 (m, 3H, 3CH), 6.40 (s, 1H, C_3-H pyran), 7.24 (d, 1H, J = 18 Hz, Ar-H), 7.43 (s, 1H, C_2-H pyran), 7.89 (d, 1H, J = 18 Hz, Ar-H), 8.20 (d, 1H, CH=N), 12.20 (s, 1H, NH); ^{13}C NMR (DMSO-d6): δ = 20.1, 22.0 (4C), 60.5, 62.8, 66.0, 68.4, 110.8, 113.4, 115.5 (2C), 118.5, 131.9, 149.8, 153.2 (2C), 157.0, 160.6, 162.3, 168.2, 171.9 (4C), 177.7. Anal. Calcd for $C_{27}H_{26}N_2O_{13}$ (586.51): C, 55.29; H, 4.47; N, 4.78 %. Found: C, 55.18; H, 4.38; N, 4.61 %.

3.5. Synthesis of 7a-c

3.5.1. General procedure

The sugar hydrazone derivatives **5a** (4.48 g, 0.01 mol), **5b** (4.48 g, 0.01 mol), and **5c** (4.10 g, 0.01 mol) were subjected to reflux for 3 h in a solution of acetic anhydride (15 mL). After adding the resultant solution to crushed ice, the product was removed by using chloroform.

3.5.2. (2S,3S,4R)-1-(3-acetyl-5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)pentane-1,2,3,4,5-pentayl pentaacetate (7a)

Yield, 63 %, m.p. = 90–92 °C, IR (KBr): ν_{max}, cm^{-1}: 1740 ($COCH_3$), 1642 (C=O), 1615 (C=N); ^{1}H NMR (DMSO-d6): δ 1.90 (s, 3H, $COCH_3$), 2.04 (s, 15H, 5$COCH_3$), 2.45 (s, 3H, CH_3), 4.24 (d, 2H, CH_2), 5.09–6.00 (m, 4H, 4CH), 6.25 (d, 1H, oxadiazol-CH), 6.49 (s, 1H, C_3-H pyran), 6.66 (s, 1H, C_2-H pyran), 7.15 (d, 1H, J = 18 Hz, Ar-H), 7.80 (d, 1H, J = 18 Hz, Ar-H); ^{13}C NMR (DMSO-d6): δ = 18.9, 20.0, 20.1 (4C), 23.1, 60.3, 61.5, 67.1, 68.0, 74.0, 75.0, 110.1, 112.7 (2C), 114.6, 118.0, 131.2, 149.1 (2C), 152.5, 156.2 (2C), 159.9, 167.0, 169.0 (5C), 177.0. Anal. Calcd for $C_{32}H_{32}N_2O_{16}$ (700.61): C, 54.86; H, 4.60; N, 4.00 %. Found: C, 54.77; H, 4.56; N, 3.88 %.

3.5.3. (2S,3R,4R)-1-(3-acetyl-5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)pentane-1,2,3,4,5-pentayl pentaacetate (7b)

Yield, 86 %, m.p. = 74–76 °C, IR (KBr): ν_{max}, cm^{-1}: 3425 (NH), 1743 (COCH3), 1630 (C=O); ^{1}H NMR (DMSO-d6): δ 1.98 (s, 3H, $COCH_3$), 2.11 (s, 15H, 5$COCH_3$), 2.32 (s, 3H, CH_3), 4.30 (d, 2H, CH_2), 5.12–6.06 (m, 4H, 4CH), 6.30 (d, 1H, oxadiazol-CH), 6.55 (s, 1H, C_3-H pyran), 6.70 (s, 1H, C_2-H pyran), 7.20 (d, 1H, J = 18 Hz, Ar-H), 7.83 (d, 1H, J = 18 Hz, Ar-H); ^{13}C NMR (DMSO-d6): δ = 18.1, 19.6, 19.9 (4C), 22.5, 60.7, 61.8, 67.4, 68.3, 74.2, 75.7, 110.5, 113.0 (2C), 115.1, 118.1, 131.7, 149.5 (2C), 153.0, 156.7 (2C), 160.2, 167.4, 169.5 (5C), 177.5. Anal. Calcd for $C_{32}H_{32}N_2O_{16}$ (700.61): C, 54.86; H, 4.60; N, 4.00 %. Found: C, 54.79; H, 4.58; N, 3.98.

3.5.4. (2S,3R)-1-(3-acetyl-5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)butane-1,2,3,4-tetrayl tetraacetate (7c)

Yield, 25 %, m.p. = oily (viscous), IR (KBr): ν_{max}, cm^{-1}: 3250 (NH), 1746 (COCH3), 1636 (C=O), 1538 (C=N); ^{1}H NMR (DMSO-d6): δ 2.00 (s, 3H, $COCH_3$), 2.15 (s, 12H, $4COCH_3$), 2.36 (s, 3H, CH_3), 4.20 (d, 2H, CH_2), 5.30–5.80 (m, 3H, 3CH), 6.34 (d, 1H, oxadiazol-CH), 6.60 (s, 1H, C_3-H pyran), 6.75 (s, 1H, C_2-H pyran), 7.24 (d, 1H, J = 18 Hz, Ar-H), 7.88 (d, 1H, J = 18 Hz, Ar-H); ^{13}C NMR (DMSO-d6): δ = 19.9, 20.9, 21.2 (3C), 24.0, 61.4, 64.2, 66.7, 75.0, 76.0, 111.4, 113.8 (2C), 115.9, 118.0, 132.3, 150.1 (2C), 153.8, 157.8 (2C), 161.1, 168.0, 170.0 (4C), 178.4. Anal. Calcd for $C_{29}H_{28}N_2O_{14}$ (628.54): C, 55.42; H, 4.49; N, 4.46 %. Found: C, 55.37; H, 4.41; N, 4.40 %.

3.5.5. Synthesis of 9-(5-mercapto-1,3,4-oxadiazol-2-yl)-4-methyl-2H,10H-pyrano [2,3-f]chromene-2,10-dione (8)

Compound **4** (2.80 g, 0.01 mol) was mixed with 5 mL of carbon disulphide, along with potassium hydroxide (0.56 g, 0.01 mol) in 2 mL of water. The reaction mixture was refluxed for 20 h. After the solvent evaporated, the residue was filtered off, diluted in water, and acidified with diluted hydrochloric acid. The precipitate was extracted from the ethanol and recrystallized after being filtered off and cleaned with water.

Yield, 83 %; m.p. = 290–292 °C; IR (KBr): ν_{max}, cm^{-1}: 1640 (C=O), 1376 (C=S); ^{1}H NMR (DMSO-d6): δ = 2.30 (s, 3H, CH_3), 6.30 (s, 1H, Ar-H), 7.00 (d, 1H, Ar-H), 7.90 (d, 1H, Ar-H), 8.70 (s, 1H, Ar-H), 13.52 (s, 1H, SH); ^{13}C NMR (DMSO-d6): δ = 18.5, 110.9, 112.1, 114.4, 118.0 (2C), 131.4, 145.0, 150.1, 152.2, 156.5, 159.6, 160.5 (2C), 175.1. MS (*m/z*, %): 328 (M^+, 22). Anal. Calcd for $C_{15}H_8N_2O_5S$ (328.30): C, 54.88; H, 2.46; N, 8.53 %. Found: C, 54.80; H, 2.33; N, 8.41 %.

3.5.6. Synthesis of 9-(5-((2-methoxyethyl)thio)-1,3,4-oxadiazol-2-yl)-4-methyl-2H,10H-pyrano [2,3-f]chromene-2,10-dione (9)

A solution of **8** (3.28 g, 0.01 mol) in DMF (15 mL) was mixed with anh. NaH (0.24 g, 0.01 mol). The mixture was stirred at 25 °C for 2 h. Chloroethyl methyl ether (0.95 g, 0.01 mol) was then added. The reaction mixture was added to ice-cold water after being agitated for 30 h at 25 °C. The reaction mixture was extracted using ethyl acetate. After that, at reduced pressure, the solvent evaporated to produce **9**.

Yield, 48 %; m.p. = 180–182 °C; IR (KBr): ν_{max}, cm^{-1}: 1643 (C=O); ^{1}H NMR (DMSO-d6): δ = 2.43 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 3.65 (t, 2H, J = 5.5 Hz, O-CH_2), 3.78 (t, 2H, J = 5.5 Hz, S-CH_2), 6.20 (s, 1H, Ar-H), 7.05 (d, 1H, J = 18 Hz, Ar-H), 7.40 (d, 1H, J = 18 Hz, Ar-H), 8.31 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d6): δ = 19.4, 37.9, 58.8, 74.4, 116.5, 112.6, 114.9, 118.5 (2C), 131.8, 145.5, 150.4, 152.3, 156.9, 159.8, 160.9 (2C), 175.5. Anal. Calcd for $C_{18}H_{14}N_2O_6S$ (386.38): C, 55.96; H, 3.65; N, 7.25 %. Found: C, 55.88; H, 3.56; N, 7.11 %.

3.5.7. Synthesis of 9-(5-((2-(2-hydroxyethoxy)ethyl)thio)-1,3,4-oxadiazol-2-yl)-4-methyl-2H,10H-pyrano [2,3-f]chromene-2,10-dione (10)

A solution of **8** (3.28 g, 0.01 mol) in abs. ethanol (15 mL) was mixed with NaOH (0.4 g, 0.01 mol), and the mixture was agitated for an hour at 25 °C. The mixture was refluxed for 30 h after 1.24 g (0.01 mol) of 2-(2-Chloroethoxy)ethanol was added. The solvent was removed under reduced pressure. Ethanol was used to recrystallize the resultant solid.

Yield, 94 %; m.p. = 102–104 °C, IR (KBr): ν_{max}, cm^{-1}: 3400 (OH, NH), 1639 (C=O), 1588 (C=N), 1484 (C-O-C); ^{1}H NMR (DMSO-d6): δ = 2.35 (s, 3H, CH_3), 3.60 (t, 2H, S-CH_2), 3.71 (t, 2H, O-CH_2), 3.88 (t, 2H, $\underline{CH_2}$-OH), 3.99 (t, 2H, O-CH_2), 5.10 (s, 1H, OH), 6.40 (s, 1H, Ar-H), 7.24 (d, 1H, J = 19 Hz, Ar-H), 7.59 (d, 1H, J = 19 Hz, Ar-H), 8.51 (s, 1H, Ar-H). MS (*m/z*, %): 416 (M^+, 30). Anal. Calcd for $C_{19}H_{16}N_2O_7S$ (416.40): C, 54.80; H, 3.87; N, 6.73 %. Found: C, 54.71; H, 3.74; N, 6.66 %.

3.5.8. Synthesis of 2-(2-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)ethoxy)ethyl acetate (11)

After adding 1.02 g (0.01 mol) of acetic anhydride to the 10.4 g (0.01 mol) solution in 7 ml of pyridine, the reaction mixture was stirred for 16 h at 25 °C. After adding the resultant solution to the crushed ice, the mixture was filtered, washed with water, and allowed to dry.

Yield, 54 %; m.p. = 198–200 °C; IR (KBr): ν_{max}, cm^{-1}: 1735 ($COCH_3$), 1633 (C=O), 1583 (C=N). ^{1}H NMR (DMSO-d6): δ = 2.23 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.55 (t, 2H, S-CH_2), 3.68 (t, 2H, O-CH_2), 3.82 (t, 2H, $\underline{CH_2}$-OH), 3.92 (t, 2H, O-CH_2), 6.11 (s, 1H, Ar-H), 7.30 (d, 1H, J = 19 Hz, Ar-H), 7.62 (d, 1H, J = 19 Hz, Ar-H), 8.26 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d6): δ = 19.1, 20.9, 37.4, 66.9, 68.9, 72.7, 110.5, 112.0, 114.0, 117.9 (2C), 131.0, 145.0, 150.0, 152.1, 156.3, 159.5, 160.4 (2C), 170.6, 174.9. Anal. Calcd for $C_{21}H_{18}N_2O_8S$ (458.44): C, 55.02; H, 3.96; N, 6.11 %. Found: C, 55.00; H, 3.87; N, 6.02 %.

3.5.9. Synthesis of (2R,3R,5R,6R)-2-(acetoxymethyl)-6-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (13)

TEA (0.5 mL) was used to catalyze a solution of **8** (3.28 g, 0.01 mol) in DMF (15 mL), (TAGB) (12) (4.11 g, 0.01 mol) was added. The reaction mixture was agitated at 25 °C for 30 h. The mixture was filtered off, cleaned with water, and let to dry after being added to the crushed ice.

Yield, 63 %; m.p. = 222–224 °C; IR (KBr): ν_{max}, cm^{-1}: 1751 ($COCH_3$), 1635 (C=O), 1554 (C=N); ^{1}H NMR (DMSO-d6): δ = 1.99 (s, 12H, $4CO\underline{CH_3}$), 2.38 (s, 3H, CH_3), 4.25–4.41 (m, 2H, CH_2), 4.80–5.60 (m, 5H, CH-sugar), 6.11 (s, 1H, Ar-H), 7.30 (d, 1H, Ar-H), 7.70 (d, 1H, Ar-H), 8.32 (s, 1H, Ar-H). Anal. Calcd for $C_{29}H_{26}N_2O_{14}S$ (658.59): C, 52.89; H, 3.98; N, 4.25 %. Found: C, 52.76; H, 3.83; N, 4.21 %.

3.5.10. Synthesis of 4-methyl-9-(5-(((2R,3R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)thio)-1,3,4-oxadiazol-2-yl)-2H,10H-pyrano [2,3-f]chromene-2,10-dione (14)

A solution containing **13** (6.58 g, 0.01 mol) was obtained in a methanolic ammonia solution (30 mL methanol, 34 % ammonia, 50 mL) during a 10-h incubation period at 25 °C. The solvent evaporated under reduced pressure, resulting in a solid powder as the end product.

Yield, 92 %; m.p. = 228–230 °C; IR (KBr): ν_{max}, cm^{-1}: 3373 (OH), 1642 (C=O), 1589 (C=N); ^{1}H NMR (DMSO-d6): $\delta = 2.40$ (s, 3H, CH_3), 3.59–3.85 (m, 6H, 4CH + CH_2), 4.10–4.30 (m, 4H, 4OH), 5.00 (d, 1H, S-CH-O), 6.35 (s, 1H, C_3-H coumarin), 7.22 (d, 1H, AB system, Ar-H), 7.92 (d, 1H, AB system, Ar-H), 8.57 (s, 1H, C_2-H pyran); ^{13}C NMR (DMSO-d6): $\delta = 19.3$, 61.9, 70.6, 74.6, 80.1, 86.6, 92.9, 110.0, 111.6, 113.5, 117.4 (2C), 130.2, 144.2, 149.5, 151.5, 155.9, 158.5, 159.9 (2C), 174.1. Anal. Calcd for $C_{21}H_{18}N_2O_{10}S$ (490.44): C, 51.43; H, 3.70; N, 5.71 %. Found: C, 51.36; H, 3.61; N, 5.59 %.

3.5.11. Synthesis of 9-(5-((4,6-dichloro-1,3,5-triazin-2-yl)thio)-1,3,4-oxadiazol-2-yl)-4-methyl-2H,10H-pyrano [2,3-f]chromene-2,10-dione (15)

At 0–5 °C, a stirred solution of cyanuric chloride (1.84 g, 0.01 mol) in D.M.F. (92 mL) was mixed with oxadiazole 8 (3.28 g, 0.01 mol) in D.M.F. (17 mL). The solution was neutralized by adding 10 % Na_2CO_3 solution. For 4 h, the stirring was maintained at 0–5 °C. Toluene: ethyl acetate (80:20) was used as the eluent in TLC, which was used to monitor the reaction's progression. The process was stopped, and the mixture produced was put into crushed ice. Following filtration, the product was washed with water and left to crystallize the ethanol, yielding **15**.

Yield, 72 %; m.p. = 180–182 °C; IR (KBr): ν_{max}, cm^{-1}: 1640 (C=O), 1610 (C=N), 750 (C-Cl). ^{1}H NMR (DMSO-d6): $\delta = 2.39$ (s, 3H, CH_3), 6.40 (s, 1H, Ar-H), 7.11 (d, 1H, J = 18 Hz, Ar-H), 7.70 (d, 1H, J = 18 Hz, Ar-H), 8.85 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d6): $\delta =$ 19.0, 111.7, 112.6, 115.0, 118.7 (2C), 131.9, 145.8, 150.5, 152.5, 157.0, 159.8, 161.2 (2C), 169.8 (2C), 175.7, 198.0. MS (*m/z*, %): 476 (M^+, 60), 474 ($M^+ - 2$, 28). Anal. Calcd for $C_{18}H_7Cl_2N_5O_5S$ (476.24): C, 45.40; H, 1.48; N, 14.71 %. Found: C, 45.33; H, 1.41; N, 14.66 %.

*3.5.12. Synthesis **of 9-(5-((4-chloro-6-morpholino-1,3,5-triazin-2-yl)thio)-1,3,4-oxadiazol-2-yl)-4-methyl-2H,10H-pyrano [2,3-f]chromene-2,10-dione (16)***

Morpholine (0.87 mL, 0.01 mol) dissolved in D.M.F. (5 mL) was gradually added to a well-stirred solution of **15** (4.76 g, 0.01 mol) in D.M.F. (10 mL) while keeping the temperature at 35 °C. The pH was balanced by adding 10 % sodium carbonate solution. The temperature was gradually increased to 45 °C in 2 h. The reaction was monitored using TLC with benzene:acetone (95:5) as the eluent. The mixture was poured into crushed ice, to produce solid needles, the substance was filtered, washed with water, and allowed to crystallize from the ethanol.

Yield, 68 %; m.p. = 184–186 °C; IR (KBr): ν_{max}, cm^{-1}: 1645 (C=O), 1615 (C=N), 760 (C-Cl). ^{1}H NMR (DMSO-d6): $\delta = 2.45$ (s, 3H, CH_3), 3.48 (t, 4H, $2CH_2$), 3.61 (t, 4H, $2CH_2$), 6.39 (s, 1H, Ar-H), 7.25 (d, 1H, J = 18 Hz, Ar-H), 7.61 (d, 1H, J = 18 Hz, Ar-H), 8.51 (s, 1H, Ar-H). MS (*m/z*, %): 526 (M^+, 58), 524 ($M^+ - 2$, 31). Anal. Calcd for $C_{22}H_{15}ClN_6O_6S$ (526.91): C, 50.15; H, 2.87; N, 15.95 %. Found: C, 50.01; H, 2.73; N, 15.88 %.

3.5.13. Synthesis of compounds (17a-e and 18a-e)

A solution of **16** (5.26 g, 0.01 mol) and appropriate phenyl urea and/or phenyl thiourea derivatives (0.01 mol) in DMF (18 mL) was refluxed for 3 h using a water bath set at 80–90 °C. The reaction was monitored by TLC using toluene: ethylacetate (80:20) as eluent. The mixture was then poured into crushed ice once the procedure was stopped. The result was separated from the ethanol by filtering, washing with water, and recrystallizing.

3.5.14. Synthesis of 1-(4-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)-6-morpholino-1,3,5-triazin-2-yl)-3-phenylurea (17a)

Yield, 71 %; m.p. 185–187 °C; IR (KBr): ν_{max}, cm^{-1}: 3150 (NH), 1685 (CO, amidic), 1645 (CO), 1610 (C=N), 1590 (C=C), 1040 (C-O-C); ^{1}H NMR (DMSO-d6): $\delta = 2.25$ (s, 3H, CH_3), 3.74 (t, 4H, $2CH_2$), 3.86 (t, 4H, $2CH_2$), 6.15 (s, 1H, Ar-H), 7.10–7.50 (m, 7H, Ar-H), 8.41 (s, 1H, Ar-H), 9.35 (s, 1H, NH), 10.20 (s, 1H, NH); ^{13}C NMR (DMSO-d6): $\delta = 20.1$, 49.0 (2C), 66.5 (2C), 109.8, 110.5, 114.9, 118.1 (2C), 121.2 (2C), 128.5 (3C), 130.4, 139.0, 145.1, 148.0, 151.0 (2C), 156.0, 159.8, 168.0 (2C), 171.0, 175.5 (2C), 197.0. Anal. Calcd for $C_{29}H_{22}N_8O_7S$ (626.60): C, 55.59; H, 3.54; N, 17.88 %. Found: C, 55.50; H, 3.48; N, 17.80 %.

3.5.15. Synthesis of 1-(4-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)-6-morpholino-1,3,5-triazin-2-yl)-3-(p-tolyl)urea (17b)

Yield, 76 %; m.p. 210–212 °C; IR (KBr): ν_{max}, cm^{-1}: 3155 (NH), 1680 (CO, amidic), 1650 (CO), 1615 (C=N), 1585 (C=C), 1045 (C-O-C); ^{1}H NMR (DMSO-d6): $\delta = 2.15$ (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.68 (t, 4H, $2CH_2$), 3.80 (t, 4H, $2CH_2$), 6.25 (s, 1H, Ar-H), 7.05 (d, 1H, J = 18 Hz, Ar-H), 7.25 (d, 2H, J = 19 Hz, Ar-H), 7.45 (d, 2H, J = 18 Hz, Ar-H), 7.77 (d, 1H, J = 19 Hz, Ar-H), 8.55 (s, 1H, Ar-H), 9.45 (s, 1H, NH), 10.31 (s, 1H, NH). Anal. Calcd for $C_{30}H_{24}N_8O_7S$ (640.63): C, 56.25; H, 3.78; N, 17.49 %. Found: C, 56.16; H, 3.69; N, 17.40 %.

3.5.16. Synthesis of 1-(2-chlorophenyl)-3-(4-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)-6-morpholino-1,3,5-triazin-2-yl)urea (17c)

Yield, 69 %; m.p. 215–217 °C; IR (KBr): ν_{max}, cm^{-1}: 3160 (NH), 1675 (CO, amidic), 1660 (CO), 1620 (C=N), 1575 (C=C), 1035 (C-

O-C), 785 (C-Cl); ^{1}H NMR (DMSO-d6): $\delta = 2.41$ (s, 3H, CH_3), 3.74 (t, 4H, $2CH_2$), 3.86 (t, 4H, $2CH_2$), 6.27 (s, 1H, Ar-H), 7.05–7.48 (m, 6H, Ar-H), 8.51 (s, 1H, Ar-H), 9.32 (s, 1H, NH), 10.20 (s, 1H, NH). Anal. Calcd for $C_{29}H_{21}ClN_8O_7S$ (661.05): C, 52.69; H, 3.20; N, 16.95 %. Found: C, 52.61; H, 3.15; N, 16.88 %.

3.5.17. Synthesis of 1-(4-chlorophenyl)-3-(4-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f] chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)-6-morpholino-1,3,5-triazin-2-yl)urea (17d)

Yield, 70 %; m.p. 185–187 °C; IR (KBr): ν_{max}, cm^{-1}: 3160 (NH), 1675 (CO, amidic), 1660 (CO), 1620 (C=N), 1575 (C=C), 1035 (C-O-C), 785 (C-Cl); ^{1}H NMR (DMSO-d6): $\delta = 2.40$ (s, 3H, CH_3), 3.55 (t, 4H, $2CH_2$), 3.70 (t, 4H, $2CH_2$), 6.45 (s, 1H, Ar-H), 7.30 (d, 1H, J = 18 Hz, Ar-H), 7.50 (d, 2H, J = 19 Hz, Ar-H), 7.70 (d, 2H, J = 18 Hz, Ar-H), 7.85 (d, 1H, J = 19 Hz, Ar-H), 8.50 (s, 1H, Ar-H), 9.25 (s, 1H, NH), 10.11 (s, 1H, NH). Anal. Calcd for $C_{29}H_{21}ClN_8O_7S$ (661.05): C, 52.69; H, 3.20; N, 16.95 %. Found: C, 52.59; H, 3.13; N, 16.90 %.

3.5.18. Synthesis of 1-(4-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)-6-morpholino-1,3,5-triazin-2-yl)-3-(4-nitrophenyl)urea (17e)

Yield, 65 %; m.p. 190–192 °C; IR (KBr): ν_{max}, cm^{-1}: 3145 (NH), 1675 (CO, amidic), 1645 (CO), 1600 (C=N), 1595 (C=C), 1530 (sym. NO_2), 1350 (asym. NO_2), 1045 (C-O-C); ^{1}H NMR (DMSO-d6): $\delta = 2.41$ (s, 3H, CH_3), 3.74 (t, 4H, $2CH_2$), 3.86 (t, 4H, $2CH_2$), 6.27 (s, 1H, Ar-H), 7.05 (d, 1H, J = 18 Hz, Ar-H), 7.17 (d, 2H, J = 19 Hz, Ar-H), 7.84 (d, 3H, Ar-H), 8.56 (s, 1H, Ar-H), 9.32 (s, 1H, NH), 10.20 (s, 1H, NH). Anal. Calcd for $C_{29}H_{21}N_9O_9S$ (671.60): C, 51.86; H, 3.15; N, 18.77 %. Found: C, 51.77; H, 3.07; N, 18.70 %.

3.5.19. Synthesis of 1-(4-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)-6-morpholino-1,3,5-triazin-2-yl)-3-phenylthiourea (18a)

Yield, 65 %; m.p. 160–162 °C; IR (KBr): ν_{max}, cm^{-1}: 3160 (NH), 1650 (CO), 1615 (C=N), 1595 (C=C), 1350 (C=S), 1051 (C-O-C); ^{1}H NMR (DMSO-d6): $\delta = 2.45$ (s, 3H, CH_3), 3.70 (t, 4H, $2CH_2$), 3.80 (t, 4H, $2CH_2$), 6.30 (s, 1H, Ar-H), 7.00–7.41 (m, 7H, Ar-H), 8.59 (s, 1H, Ar-H), 11.00 (s, 1H, NH), 13.50 (s, 1H, NH). Anal. Calcd for $C_{29}H_{22}N_8O_6S_2$ (642.67): C, 54.20; H, 3.45; N, 17.44 %. Found: C, 54.11; H, 3.40; N, 17.33 %.

3.5.20. Synthesis of 1-(4-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)-6-morpholino-1,3,5-triazin-2-yl)-3-(p-tolyl)thiourea (18b)

Yield, 68 %; m.p. 155–157 °C; IR (KBr): ν_{max}, cm^{-1}: 3145 (NH), 1645 (CO), 1610 (C=N), 1580 (C=C), 1355 (C=S), 1040 (C-O-C); ^{1}H NMR (DMSO-d6): $\delta = 2.35$ (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.70 (t, 4H, $2CH_2$), 3.80 (t, 4H, $2CH_2$), 6.20 (s, 1H, Ar-H), 7.10 (d, 1H, J = 19 Hz Ar-H), 7.42 (s, 4H, Ar-H), 7.80 (d, 1H, J = 19 Hz, Ar-H), 8.60 (s, 1H, Ar-H), 11.36 (s, 1H, NH), 13.35 (s, 1H, NH); ^{13}C NMR (DMSO-d6): $\delta = 18.0$, 21.9, 49.5 (2C), 67.0 (2C), 110.1, 111.3, 114.4, 118.6 (2C), 126.0 (2C), 129.0 (2C), 130.8, 135.0, 137.0, 145.6, 148.2, 151.5, 156.2, 160.0, 162.2 (2C), 171.8, 175.9 (2C), 180.0, 196.9. Anal. Calcd for $C_{30}H_{24}N_8O_6S_2$ (656.69): C, 54.87; H, 3.68; N, 17.06 %. Found: C, 54.79; H, 3.59; N, 16.98 %.

3.5.21. Synthesis of 1-(2-chlorophenyl)-3-(4-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)-6-morpholino-1,3,5-triazin-2-yl)thiourea (18c)

Yield, 70 %; m.p. 205–207 °C; IR (KBr): ν_{max}, cm^{-1}: 3160 (NH), 1660 (CO), 1620 (C=N), 1575 (C=C), 1350 (C=S), 1035 (C-O-C), 780 (C-Cl); ^{1}H NMR (DMSO-d6): $\delta = 2.37$ (s, 3H, CH_3), 3.57 (t, 4H, $2CH_2$), 3.70 (t, 4H, $2CH_2$), 6.37 (s, 1H, Ar-H), 7.25–7.69 (m, 6H, Ar-H), 8.66 (s, 1H, Ar-H), 13.46 (s, 1H, NH), 14.30 (s, 1H, NH). Anal. Calcd for $C_{29}H_{21}ClN_8O_6S_2$ (677.11): C, 51.44; H, 3.13; N, 16.55 %. Found: C, 51.39; H, 3.05; N, 16.49 %.

3.5.22. Synthesis of 1-(4-chlorophenyl)-3-(4-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)-6-morpholino-1,3,5-triazin-2-yl)thiourea (18d)

Yield, 68 %; m.p. 161–163 °C; IR (KBr): ν_{max}, cm^{-1}: 3155 (NH), 1641 (CO), 1615 (C=N), 1570 (C=C), 1335 (C=S), 1035 (C-O-C), 780 (C-Cl); ^{1}H NMR (DMSO-d6): $\delta = 2.39$ (s, 3H, CH_3), 3.75 (t, 4H, $2CH_2$), 3.88 (t, 4H, $2CH_2$), 6.31 (s, 1H, Ar-H), 7.20 (d, 1H, J = 18 Hz, Ar-H), 7.40 (d, 2H, J = 19 Hz, Ar-H), 7.59 (d, 2H, J = 19 Hz, Ar-H), 7.73 (d, 1H, J = 18 Hz, Ar-H), 8.40 (s, 1H, Ar-H), 11.55 (s, 1H, NH), 13.21 (s, 1H, NH). Anal. Calcd for $C_{29}H_{21}ClN_8O_6S_2$ (677.11): C, 51.44; H, 3.13; N, 16.55 %. Found: C, 51.37; H, 3.09; N, 16.50 %.

3.5.23. Synthesis of 1-(4-((5-(4-methyl-2,10-dioxo-2H,10H-pyrano [2,3-f]chromen-9-yl)-1,3,4-oxadiazol-2-yl)thio)-6-morpholino-1,3,5-triazin-2-yl)-3-(4-nitrophenyl)thiourea (18e)

Yield, 76 %; m.p. 131–193 °C; IR (KBr): ν_{max}, cm^{-1}: 3145 (NH), 1645 (CO), 1600 (C=N), 1595 (C=C), 1530 (sym. NO_2), 1350 (asym. NO_2), 1333 (C=S), 1045 (C-O-C); ^{1}H NMR (DMSO-d6): $\delta = 2.45$ (s, 3H, CH_3), 3.50 (t, 4H, $2CH_2$), 3.60 (t, 4H, $2CH_2$), 6.35 (s, 1H, Ar-H), 7.15 (d, 1H, J = 18 Hz, Ar-H), 7.75 (d, 2H, J = 19 Hz, Ar-H), 7.90 (d, 1H, J = 18 Hz, Ar-H), 8.07 (d, 2H, J = 19 Hz, Ar-H), 8.65 (s, 1H, Ar-H), 11.95 (s, 1H, NH), 13.43 (s, 1H, NH). Anal. Calcd for $C_{29}H_{21}N_9O_8S_2$ (687.66): C, 50.65; H, 3.08; N, 18.33 %. Found: C, 50.58; H, 3.00; N, 18.27 %.

3.6. Biological activity

It was carried out in accordance with the protocols documented in earlier research [53].

3.7. Molecular docking

Using PyRx tools Autodock Vina (version 1.1.2), a molecular docking study of the compounds under inquiry was carried out in conjunction with: a: the crystal structure of the transpeptidase enzyme, PDB: 5WT8 of *S. aureus* [54]. The transpeptidase enzyme's crystal structure, PDB: 5WT8, was obtained from the protein data bank at https://www.rcsb.org. Using the VEGA ZZ 2.3.2 tool, the native ligand and water molecules were extracted from the proteins. Polar hydrogen and Kollman charges were then added, and Autodock Vina tools were used to convert the proteins into PDBQT format. Every designed chemical is recorded as a mol file, which Open Babel software uses to protonate, minimize, and convert to a pdb file. In order to specify the number of torsions and to construct a pdbqt file, the generated pdb file was uploaded to Autodock Vina tools. The grid map was made using AutoGrid and a grid box. Each chemical produced a certain number of docked positions, and these were graded based on the binding energy. The most complicated and fitting pose for the receptor under study was determined to have the lowest binding energy and a 0 root-mean-square deviation (RMSD). With BIOVIA Discovery Studio 2021, the molecular interactions and binding mechanisms of the top postures were graphically analyzed.

4. Conclusion

We present here a series of (1,3,4-oxadiazol-2-yl)pyrano [2,3-f]chromene, containing galactose, mannose, and xylose hydrazones that were synthesized via hydrazides reaction with monosaccharides, trying to find new candidates with better antibacterial properties. Acetic anhydride-induced cyclization of sugar hydrazones provided derivatives of substituted oxadiazolines. Additionally, **17a–e** and **18a–e** were synthesized using 1,3,4-oxadiazoly thiomorpholinophenyl ureido and/or (phenyl thioureido)-s-triazine. Selected Gram (+ve) (*B. subtilis*, *S. aureus*) and Gram (-ve) bacteria (*E. coli*, *P. aeruginosa*) were used in addition to a yeast-like fungi (*C. albicans*) to test the newly synthesized compounds' antimicrobial activities. Compounds **11**, **13**, **15**, **16**, **17c-e**, and **18a-e** showed the highest antibacterioal activity. Furthermore, a molecular docking study has been studied to assess the binding behavior of the active compounds with the target crystal structure of transpeptidases (a bacterial enzyme that cross-links the peptidoglycan chains to form rigid cell walls)

Ethical approval

Not applicable.

Consent to participate

All authors participated directly in the current research work.

Consent to publish

The authors agree to publish the article under the Creative Commons Attribution License.

Availability of data and materials

All relevant data are within the manuscript and available from the corresponding author upon request.

CRediT authorship contribution statement

Kahdr Alatawi: Writing – original draft, Visualization, Resources, Methodology. **Ahmad Fawzi Qarah:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Haifa Alharbi:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis. **Ali Alisaac:** Writing – review & editing, Writing – original draft, Software, Resources, Formal analysis. **Matokah M. Abualnaja:** Writing – original draft, Resources, Methodology, Formal analysis. **Roba M.S. Attar:** Writing – review & editing, Validation, Methodology, Formal analysis, Data curation. **Amerah Alsoliemy:** Writing – original draft, Visualization, Software, Methodology, Formal analysis. **Nashwa M. El-Metwaly:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38294.

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