Clinical and Experimental Health Sciences

Synthesis and Anti-Biofilm Activity Studies on Novel Quinazolinone-Thiadiazole Hybrids

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ABSTRACT

Objective: In this study it was aimed to synthesize novel 1,3,4-thiadizole bearing 4(3H)-quinazolinone compounds, elucidate their structure and evaluate their anti-biofilm activity.

Methods: Four novel 4(3H)-quinazolinone compounds (1-4) were synthesized with a two step reaction starting from 5-bromoanthranilic acid. Their anti-biofilm activity was investigated.

Results: The final compounds' structures were clarified by elemental analysis and spectroscopic methods (IR, 1H-NMR, 13C-NMR and MS). In the result of anti-biofilm activity studies, they possessed 26.0-30.0% biofilm formation inhibition.

Conclusion: Among the tested compounds, 6-bromo-3-{4-[5-(4-nitrophenylamino)-1,3,4-thiadiazol-2-yl]phenyl}-2-methylquinazolin-4(3H)-one formulated compound 3 was found as the most active one with 30.0% biofilm formation inhibition.

Keywords: 4(3H)-Quinazolinones, 1,3,4-thiadiazoles, anti-biofilm activity, P. aeruginosa

1. INTRODUCTION

P. aeruginosa is a gram negative opportunistic pathogen which is known as the reason of many chronic infections ending with morbidity and mortality. It perfoms pathogenity by forming biofilms and biofilm-associated *P. aeruginosa* infections could hardly be treated because of their strong resistance to antibiotics. Biofilm is the structural aggregation of the bacteria by adhesion over the living or non-living hosts. The Quorum sensing (QS) system is known as a cell-to-cell communication system controlling the biofilm formation in Gram (-) and Gram (+) bacteria. By blocking QS system, pathogenic host effects produced by infections could be reduced (1-3).

Quinazolinones are important pharmacophoric groups which are known for several years. Owing to their significant bioactivity, quinazolinone ring is also located in many commercially available drugs. As examples to them; raltitrexed is used against colorectal cancer (4,5), ketanserin as anti-hypertensive (6), albaconazole as antifungal (7-9), fenquizone as diuretic (10), febrifugine as antimalarial (11) and afloqualone as muscle relaxant (12), etc (Figure 1). Especially, 4(3*H*)-quinazolinones get attention for their diverse range of biological activities as antihypertensive (13), anticancer (14,15), anticonvulsant (16), antioxidant (17), anti-inflammatory (18), antimalarial (19), anthelmintic (20) and antiviral (21,22) activities. And also, there are many studies informing their effect on a variety of enzymes like monoamine oxidase, a-glucosidase and acetylcholinesterase (23-26). Besides, according to the recent studies, 4(3*H*)-quinazolinones have attracted great attention for their remarkable antibacterial, antifungal and anti-biofilm activities (27-31).

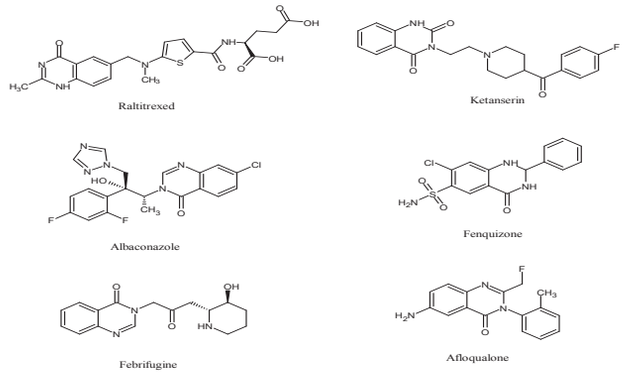

Figure 1. *4(3H)-quinazolinone compounds used as active drug substances.*

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1,3,4-Thiadiazoles are well known five membered heterocyclic structures for their various biological activities. They are commonly known for their carbonic anhydrase (CA) inhibitory effects by being located in important CA inhibitors like acetazolamide, methazolamide etc. Moreover, they arouse interest with their notable antituberculosis and antimicrobial activities (32,33).

In our previous study we have synthesized 4(3*H*)-Quinazolinones with the reaction of anthranilic acids and sulfonamides. The obtained thiadiazole bearing compounds showed remarkable potential at biofilm formation inhibition (34). Inspired by the therapeutic potential of 4(3*H*)-quinazolinones, 1,3,4-thiadiazoles and depending on the results we have previously obtained; in this study we targeted to assemble these two active groups and discover novel potent anti-biofilm agents.

2. METHODS

All of the chemicals, reagents and solvents were purchased from Sigma Aldrich (St. Louis, MO, USA) and Merck (Darmstadt, Germany). Melting points were determined by Schmelzpunktbestimmer SMP II apparatus. The IR spectra were recorded on a Schimadzu FTIR 8400 S Spectrometer. The NMR spectra were recorded (in DMSO-d_6) with a Varian Mercury Agilent spectrometer (Palo Alto, CA, USA) and Bruker AV spectrometer (400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR, decoupled). The chemical shift values are expressed in ppm (δ scale) using tetramethylsilane as an internal standard. The mass spectral measurements were carried out by Electron Spray Ionization (ES) method on LC-MS-Agilent 1100. Elemental analysis was performed on Leco 215 CHNS-932 analyzer.

2.1. Chemistry

General Synthesis Procedure of 4(3*H*)-Quinazolinone Derivatives (1-4): At first, 5-(4-aminophenyl)-*N*-substituted-1,3,4-thiadiazol-2-amines were synthesized according to the literature method (35,36). And then, 4(3*H*)-quinazolinone compounds (1-4) were achieved by a double-step reaction. At the first step, 5-bromoanthranilic acid (0.003 mol) was refluxed with 0.9 mL acetic anhydride to obtain the intermediate product, which was common for all derivatives. The completion of the reaction was checked with TLC and the excess of the acetic acid was evaporated under reduced pressure. At the final step, the intermediate product was reacted with equimolar moles of various 5-(4-aminophenyl)-*N*-substituted-1,3,4-thiadiazol-2-amine compounds at acetic acid media (34). At the end of the reaction, (1-4) compounds were precipitated by adding cold water and crushed ice in reaction media. The obtained solid was filtered, dried and purified with methanol.

6-Bromo-3-{4-[5-(ethylamino)-1,3,4-thiadiazol-2-yl] phenyl}-2-methylquinazolin-4(3*H*)-one (1): Yellow solid. Yield 95%; m.p. 261-262 °C; MW: 442.33 g/mol; FT-IR $u_{max.}$ (cm^{-1}): 3173 (N-H), 1690 (C=O), 1090 (Ar-Br). ^{1}H-NMR (DMSO-d_6/TMS) d (ppm): 1.22 (3H, t, – $CH_2C\mathbf{H}_3$), 2.16 (3H, s, Ar-CH_3), 3.36-3.39 (2H, m, – $C\mathbf{H}_2CH_3$), 7.57 (2H, d, *J:* 8.40 Hz, Ar-H), 7.64 (1H, d, *J:* 9.20 Hz, Ar-H), 7.94 (2H, d, *J:* 8.80 Hz, Ar-H), 7.99-8.01 (1H, dd, *J:* 8.60 Hz, *J:* 2.20 Hz, Ar-H), 8.03 (1H, t, – NH-), 8.18 (1H, d, *J:* 2.40 Hz, Ar-H). ^{13}C-NMR (DMSO-d_6/TMS) d (ppm): 5.62, 14.72, 24.59, 119.21, 122.59, 127.85, 128.80, 129.62, 129.76, 132.02, 137.95, 138.84, 146.81, 155.11, 155.51, 160.74, 169.23 **(**C=O**)**. MS (ES m/z): 442.00 (M^+). Elemental analysis for $C_{19}H_{16}BrN_5OS$ Calculated/Found (%): C: 51.59/51.44, H: 3.65/3.47, N: 15.83/15.69, S: 7.25/7.39.

6-Bromo-3-{4-[5-(phenethylamino)-1,3,4-thiadiazol-2-yl] phenyl}-2-methylquinazolin-4(3*H*)-one (2): Brown solid. Yield 93%; m.p. 218 °C; MW: 518.43 g/mol; FT-IR $u_{max.}$ (cm^{-1}): 3337 (N-H), 1670 (C=O), 1090 (Ar-Br). ^{1}H-NMR (DMSO-d_6/TMS) d (ppm): 2.17 (3H, s, Ar-CH_3), 2.94 (2H, t, – NH-CH_2-C$\mathbf{H}_2$-), 3.57-3.62 (2H, q, – NH-C$\mathbf{H}_2$-CH_2-), 7.23-7.34 (5H, m, Ar-H), 7.57 (2H, d, *J:* 8.40 Hz, Ar-H), 7.64 (1H, d, *J:* 8.80 Hz, Ar-H), 7.94 (2H, d, *J:* 8.40 Hz, Ar-H), 7.99-8.02 (1H, dd, *J:* 9.00 Hz, *J:* 2.60 Hz, Ar-H), 8.15 (1H, t, – NH-), 8.19 (1H, d, *J:* 2.40 Hz, Ar-H). ^{13}C-NMR (DMSO-d_6/TMS) d (ppm): 24.59, 34.95, 46.65, 119.22, 122.58, 126.71, 127.88, 128.81, 128.87, 129.23, 129.62, 129.76, 131.99, 137.94, 138.87, 139.64, 146.80, 155.31, 155.50, 160.74, 169.17 **(**C=O**)**. MS (ES m/z): 518.07 (M^+). Elemental analysis for $C_{25}H_{20}BrN_5OS$ Calculated/Found (%): C: 57.92/57.72, H: 3.89/3.92, N: 13.51/13.31, S: 6.19/6.41.

6-Bromo-3-{4-[5-(4-nitrophenylamino)-1,3,4-thiadiazol-2-yl]phenyl}-2-methylquinazolin-4(3*H*)-one (3): Yellow solid. Yield 90%; m.p. 218-220 °C; MW: 535.37 g/mol; FT-IR $u_{max.}$ (cm^{-1}): 3320 (N-H), 1711 (C=O), 1096 (Ar-Br). ^{1}H-NMR (DMSO-d_6/TMS) d (ppm): 2.16 (3H, s, Ar-CH_3), 7.61-7.91 (5H, m, Ar-H), 7.97-8.00 (1H, dd, *J:* 9.00 Hz, *J:* 2.20 Hz, Ar-H), 8.09 (2H, d, *J:* 8.40 Hz, Ar-H), 8.17 (1H, d, *J:* 2.40 Hz, Ar-H), 8.28 (2H, d, *J:* 8.80 Hz, Ar-H), 11.35 (1H, s, – NH-). ^{13}C-NMR (DMSO-d_6/TMS) d (ppm): 25.42, 114.38, 117.41, 119.16, 119.59, 122.56, 126.00, 128.18, 128.69, 129.99, 133.51, 136.90, 140.39, 168.57, 169.07 **(**C=O**)**. MS (ES m/z): 537.00 (M^++3). Elemental analysis for $C_{23}H_{15}BrN_6O_3S$ Calculated/Found (%): C: 51.60/51.53, H: 2.82/2.79, N: 15.70/15.71, S: 5.99/6.03.

6-Bromo-3-{4-[5-(cyclohexylamino)-1,3,4-thiadiazol-2-yl] phenyl}-2-methylquinazolin-4(3*H*)-one (4): Brown solid. Yield 87%; m.p. 252-254 °C; MW: 496.42 g/mol; FT-IR $u_{max.}$ (cm^{-1}): 3358 (N-H), 1672 (C=O), 1089 (Ar-Br). ^{1}H-NMR (DMSO-d_6/TMS) d (ppm): 1.22-2.11 (11H, m, cyclohegzyl – CH_2 – and – CH-), 2.16 (3H, s, Ar-CH_3), 7.56 (2H, d, *J:* 8.00 Hz, Ar-H), 7.64 (1H, d, *J:* 9.20 Hz, Ar-H), 7.66 (0.37H, s, – NH-), 7.93 (2H, d, *J:* 8.40 Hz, Ar-H), 7.99-8.01 (1H, dd, *J:* 8.60 Hz, *J:* 2.20 Hz, Ar-H), 8.18 (1H, d, *J:* 2.40 Hz, Ar-H). ^{13}C-NMR (DMSO-d_6/TMS) d (ppm): 24.59, 24.77, 25.70, 32.55, 54.25, 119.21, 122.60, 127.84, 128.81, 129.63, 129.74, 132.05, 137.96, 138.79, 146.82, 154.89, 155.53, 160.76, 168.45 **(**C=O**)**. MS (ES m/z): 497.89 (M^++2). Elemental analysis for $C_{23}H_{22}BrN_5OS$ Calculated/Found (%): C: 55.65/55.29, H: 4.47/4.47, N: 14.11/13.77, S: 6.46/6.51.

2.2. Biofilm Assay

Anti-biofilm capacity of new substituted-4(3*H*)-quinazolinone derivatives was investigated using Crystal Violet (CV) staining, as described by Ulusoy et al (37). An overnight culture of *Pseudomonas aeruginosa* PAO1 was prepared and diluted to an optical density (OD600) of 0.05. One milliliter of the diluted culture was transferred to polystyrene tubes and incubated at 37 °C in the presence of new substituted-4(3*H*)-quinazolinone derivatives. After 24 hours, the nonadherent cells were removed by washing the tubes with distilled water. The remaining biofilms were stained with a 0.4% CV solution. The CV bound to the biofilms was then solubilized using 95% ethanol, and the absorbance was measured at 595 nm using a microplate reader. Biofilm inhibition was calculated using the formula:

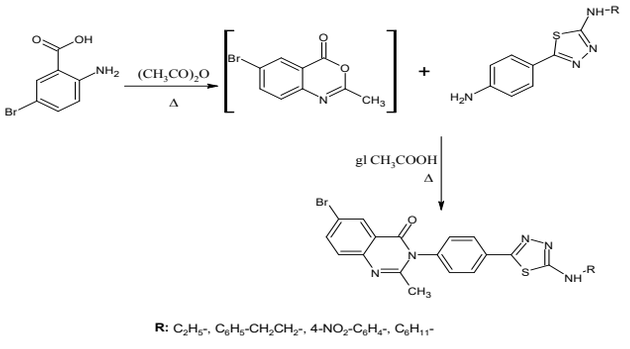
%BI=(ODC−ODFODC)×100\%\text{BI}=\left(\frac{\text{ODC} – \text{ODF}}{\text{ODC}} \right) \times 100%BI=(ODCODC−ODF)×100

Where **%BI** is the percentage of biofilm inhibition. **ODC** is the absorbance value at 595 nm of the control sample (without nanofibers). **ODF** is the absorbance value at 595 nm of the sample with the substituted-4(3*H*)-quinazolinone derivatives.

3. RESULTS

3.1. Chemistry

Within the context of this study, four novel 4(3*H*)-quinazolinone compounds **(1-4)** were synthesized via a two step reaction starting from 5-bromoanthranilic acid. Firstly, anthranilic acid was reacted with acetic anhydride to obtain the intermediate product. Secondly, amine compounds were added to the reaction in acetic acid media and refluxed. The synthesis route of the final compounds is given in **Scheme 1**. The amine derivatives used in this reaction were achived by a four step reaction starting from benzocaine. The intimate description of the reaction methods were given in our previous literature (35,36).



Scheme 1. *Synthetic route of compounds* ***1-4****.*

The final compounds' purity was checked by TLC and their melting points were calculated. Their yield was between 52-95%. The physicochemical properties belonging to compounds **(1-4)** were given in Table 1.

Table 1. *The physicochemical properties of compounds* ***(1-4)****.*

Compound	R:	Molecular formula	M.A (g/mol)	M.p. (°C)	Yield (%)	Colour
1	C_2H_5-	$C_{19}H_{16}BrN_5OS$	442.33	261-262	95	Light yellow
2	C_6H_5-CH_2CH_2-	$C_{25}H_{20}BrN_5OS$	518.43	218	94	Light brown
3	4-NO_2-C_6H_4-	$C_{23}H_{15}BrN_6O_3S$	535.37	218-220	52	Yellow
4	C_6H_{11}-	$C_{23}H_{22}BrN_5OS$	496.42	252-254	82	Brown

3.2. Biofilm Assay

Antibiotics are able to target free floating planktonic cells but they could not penetrate the biofim matrix. The ability to form biofilm makes bacteria resistant to several antibiotics. To enhance the anti-biofilm capacity could give way to get over bacterial resistance. *P. aeruginosa* is a well known biofilm former (2). From this point of view, the newly synthesized compounds' activity was tested on biofilm formation of *P.* aeruginosa PAO1.The results were presented in Table 2.

Table 2. *The biofilm formation inhibition (%) values of compounds* ***(1-4)****.*

Compound	Biofilm Formation Inhibition (%)
6-Bromo-3-{4-[5-(ethylamino)-1,3,4-thiadiazol-2-yl] phenyl}-2-methylquinazolin-4(3*H*)-one (1)	26.0
6-Bromo-3-{4-[5-(phenethylamino)-1,3,4-thiadiazol-2-yl]phenyl}-2-methylquinazolin-4(3*H*)-one (2)	27.2
6-Bromo-3-{4-[5-(4-nitrophenylamino)-1,3,4-thiadiazol-2-yl]phenyl}-2-methylquinazolin-4(3*H*)-one (3)	30.0
6-Bromo-3-{4-[5-(cyclohexylamino)-1,3,4-thiadiazol-2-yl]phenyl}-2-methylquinazolin-4(3*H*)-one (4)	27.5

4. DISCUSSION

The newly synthesized (1-4) compounds' structures were identified by a variety of spectroscopic methods (FT-IR, ^{1}H-NMR, ^{13}C-NMR and MS). According to the IR absorption spectra, amide C=O stretching bands, which were distinctive for 4(3*H*)-quinazolinone structure, were confirmed at 1711-1670 cm^{-1}. Also, N-H stretching and C-Br stretching bands were detected at 3377-3173 cm^{-1} and 1096-1089 cm^{-1}, respectively. In regard to the ^{1}H-NMR spectra, 4(3*H*)-quinazolinone C_5-H, C_7-H and C_8-H protons became prominent with their *J* value calculations. C_5-H protons were recorded at 8.17-8.19 ppm as dublets with meta interaction. C_7-H protons were detected between 7.97-8.02 ppm as double doublets. C_8-H protons were determined at 7.64 ppm as doublets, except compound 3. Also, at ^{13}C-NMR spectra, the amide C=O were retained at 168.45-169.23 ppm. In addition, with other spectroscopic data, the elemental analysis and MS spectral analysis results confirmed the (1-4) compounds' structure and they were in accordance with the literature (34,38).

In reference to biofilm assay results, all of the compounds showed remarkale antibiofilm activity with 26-30% biofilm inhibition values. Among them

6-bromo-3-{4-[5-(4-nitrophenylamino)-1,3,4-thiadiazol-2-yl]phenyl}-2-methylquinazolin-4(3*H*)-one **(3)** was the most effective one and 6-bromo-3-{4-[5-(ethylamino)-1,3,4-thiadiazol-2-yl]phenyl}-2-methylquinazolin-4(3*H*)-one **(1)** was the least effective one with biofilm formation inhibition values 30.0 and 26.0, respectively.

5. CONCLUSION

Four novel 4(3*H*)-quinazolinone compounds were synthesized and their structures were elucidated by elemental analysis and various spectroscopic methods (IR, ^{1}H-NMR, ^{13}C-NMR and MS). According to the anti-biofilm assay results, 4-nitrophenyl substituted compound 3 was the most effective one with 30.0% inhibition value and it could be evaluated as a lead compound for further studies.

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Ethics Committee Approval: *This study didn't need an Ethics Committee Approval.*

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Author Contributions:

Research idea: ST, SK
Design of the study: ST, SU, SK, GBT
Acquisition of data for the study: ST, SU, SK, GBT
Analysis of data for the study: ST, SU, SK, GBT
Interpretation of data for the study: ST, SU, SK, GBT
Drafting the manuscript: ST, SU, SK, GBT
Revising it critically for important intellectual content: ST, SU, SK, GBT
Final approval of the version to be published: ST, SU, SK, GBT.

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