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Double Alkynylation of Quinoline-5,8-diones and their *In-silico* and Antimicrobial Studies

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ABSTRACT: A double alkynylation of quinoline-5,8-dione to furnished bis-alkynylquinoline-5,8-dione in good yields and their in silico and antimicrobial studies is described. This was achieved by cross-coupling of 6,7-dibromoquinoline-5,8-dione with various terminal alkynes in the presence of bis(triphenylphosphine) palladium(II) chloride as a pre-catalyst and tetrabutyl ammonium fluoride trihydrate. The structures of the synthesised compounds were confirmed by UV/Visible, Fourier Transform-Infrared and ^{1}H and ^{13}C-NMR spectral data. The synthesised compounds exhibited good activity against *Escherichia Coli 1, Escherichia Coli 12, Klebsiella Pneumonia, Pseudomonas aeroginosa and Staphylococcus aureus* compare to the gentamycin and ampicillin. Molecular docking simulation study of the binding interactions of compounds with receptors disclosed significant binding affinity for *P. aeruginosa* LpxC than the *E. coli* glutaredoxin.

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Quinoline-5,8-dione and its derivatives have numerous biological activities such as antifungal, antibacterial, antiparasitic and antitumor activities (Behforouz, 1998) While some polynuclear quinones containing dihaloquinolinequinones skeleton function as tuberculostatic and cytostatic substances (Harinath and Subba Rao, 1996) various synthetic alkylene-iminoquinones have shown promising ability to inhibit tumour nuclei growth (Schellhammer and Petterson, 1960). Pratt and co-workres described remarkable amoebicidal activity of 7-undecyl-6-hydroxy-5,8-quinolinequinone (Pratt and Drake, 1960). Moreover, naturally occurring lavendamycin and streptonigrin containing quinoline-5,8-dione group were reported to exhibit antibiotic and antitumor activities (Yasuda and Boger, 1987). Quinoline-5,8-dione anti-cancer drugs have been known to interact with DNA , and through alkylation and chain-cutting of DNA they perform double action (Chinigos *et al.*, 1987). Anilinoquinoline-5,8-dione prevents the release of intracellular Ca^{+} and antigen-induced leukotrienes. It also stops acetylcholine-induced vasorelaxation (Johnson and Wick, 2006). The worry intrinsic ability of micro-organism to acquire resistance or insensitivity to otherwise potent antimicrobial agents has necessitated the continued discovery of new chemotherapeutic drugs (Egu *et al.*, 2017). Therefore, quinoline-5,8-dione an established antimicrobial lead, had undergone various transformations with a view to obtaining an improved drugs (Monika *et al.*, 2017).

We have previously studied and reported the regioselective 6-alkynylation of 6,7-dibromoquinoline-5,8-dione with their significant antibacterial activities against *Staphylococcus aureus, Klebsiella pneumonia, Pseudomonas aeruginosa, Escherichia coli 1 and Escherichia coli 12* (Ezugwu *et al.*, 2017). In continuation of our earlier studies, we are now describing intermolecular double alkynylation of 6,7-dibromoquinoline-5,8-dione and their in silico evaluations.

MATERIALS AND METHODS

Reagents and Apparatus: All chemicals were purchased from Sigma-Aldrich and were used without further purifications. All the reactions were conducted in inert atmospheres. The melting point for soilds were taken using Fisher-Johns melting point apparatus and

were uncorrected. The Uv/Visible data were obtained on UV-2500PC series spectrophotometer via 1cm quartz cells. IR spectra in KBr pellet were obtained with Shimadzu FTIR-8400S Fourier Transform Infrared Spectrophotometer.^{1}H-NMR and ^{13}C-NMR spectra were recorded on Joel 400MHz at Strathclyde University, Scotland.Chemical shifts are recorded in ppm relative to TMS as internal standard.

General procedure for synthesis of bis-alkynylated quinoline-5,8-diones: The procedure reported by Ezugwu *et al.* (Ezugwu *et al.*, 2017) was adopted with little modification; the mole ratio of 6,7-dibromoquinoline-5,8-dione to alkyne was 1:2 instead of 1:1. To a mixture of 6,7-dibromoquinoline-5,8-dione (0.5 mmol) and alkyne (1.2 mmol) were added $PdCl_2(PPh_3)_2$ (3 mol %) and TBAF.$3H_2O$ (3-6 equiv) with stirring under N_2 at 80 °C for 12 to 73 min (as monitored by TLC). The resulting mixture was washed with water and then extracted with diethyl ether.The combined organic extract was dried and concentrated in vacuum.The crude product was recrystallized from ethanol to give the desired products (2a-e) in good yields.

Synthesis of 6,7-Bis-(3-hydroxyprop-1-yn-1-yl)quinoline-5,8-dione, 2a: The reaction of 6,7-dibromoquinoline-5,8-dione, (0.5 mmol) with prop-2-yn-1-ol (1.2 mmol) in the presence of $PdCl_2(PPh_3)_2$ (3mol %), and TBAF.$3H_2O$ (6 equiv) provided compound 2a as black solid after recrystalisation. Yield 59% (0.1g). mp 197-199 °C. Uv-Visible λmax (log ε): 739 (1.02), 351 (2.06), 334 (1.99) nm. IR (KBr) Vmax: 3434 cm^{-1} (O-H Stretch), 2263cm^{-1} (C≡C); 1607cm^{-1}(C=O); 1467cm^{-1}(C=C aromatic rings); 1384cm^{-1} (C-N stretch).^{1}H-NMR[DMSO-d_6]δ:7.80-7.55(3H,m,Ar-H),4.23(1H,s,OH),1.57(2H,s). ^{13}C-NMR [DMSO]:139.83-128.45,122.61,120.94 (Ar-C),61.33, 58.12 (C≡C), 23.65, 19.80, 14.07 (C-aliphatic).

Synthesis of 6,7-Bis-(3-hydroxy-3-methylbut-1-yn-1-yl)quinoline-5,8-dione, 2b: The reaction of 6,7-dibromoquinoline-5,8-dione, (0.5 mmol) with 2-methyl-3-butyn-2-ol (1.2 mmol) in the presence of $PdCl_2(PPh_3)_2$ (3mol %), and TBAF.$3H_2O$ (6 equiv) under inert atmosphere afforded compound 2b as a pinkish oily liquid. Yield 60% (0.12 g). Uv-Visible λmax (log ε) : 735 (1.2), 492.2 (1.43), 351 (1.78) nm. IR (NaCl) Vmax: 3396cm^{-1} (O-H Stretch); 2880cm^{-1}, 2954cm^{-1} (C-H aliphatic); 2168cm^{-1} (C≡C); 1702cm^{-1} (C=O);1465cm^{-1}(C=C aromatic rings);1379cm^{-1} (C-N stretch). ^{1}H-NMR [DMSO-d_6]δ:3.45(m,3H,-CH_3),2.75(s,-CH_3),1.79(m,3H,-CH_3). ^{13}C-NMR [DMSO] δ: 89.86, 69.59, 63.70 (C≡C), 23.79, 19.58, 13.13 (C-aliphatic).

Synthesis of 6,7-Bis (phenylethynyl)quinoline-5,8-dione, 2c: The 6,7-dibromoquinoline-5,8-dione, (0.5 mmol) coupled with phenylacetylene (1.2 mmol) in the presence of $PdCl_2(PPh_3)_2$ (3mol %), and TBAF.$3H_2O$ (6 equiv) at 92-93 °C furnished black solid after recrystallisation. Yield 80% (0.184g). mp 92-93 °C. Uv-Visible λmax (log ε) : 739 (1.78), 351 (2.3) nm. IR (KBr) Vmax: 2381cm^{-1} (C≡C); 1691cm^{-1}(C=O), 1459cm^{-1}(C=C,aromatic rings); 1389cm^{-1}(C-N,stretch). ^{1}H-NMR[DMSO-d_6]δ:6.96-6.76(m,5H,Phenyl-H),7.86-7.00(m,3H,heteroaryl-H).^{13}C-NMR[DMSO-d_6]δ:176.44,175.16 (C=O), 146.63-123.48 (Ar-C), 89.38 (C≡C).

Synthesis of 6,7-Bis(oct-1-yn-1-yl)quinoline-5,8-dione, 2d: Compound 6,7-dibromoquinoline-5,8-dione (0.5 mmol) reacted with 1-octyne (1.2 mmol) in the presence of $PdCl_2(PPh_3)_2$ (3mol %), and TBAF.$3H_2O$ (6 equiv) under N_2 at 80 °C to provide brownish oily liquid. Yield 46% (0.11g). Uv-Visible λmax (log ε): 736 (1.20), 351 (2.11) nm. FT-IR (NaCl) υmax: 2881cm^{-1}, 2948cm^{-1} (C-H aliphatic); 2250cm-1 (C≡C); 1715cm^{-1} (C=O), 1466cm^{-1}(C=C aromatic rings); 1388cm^{-1} (C-N stretch).^{1}H-NMR[DMSO-d_6]δ:7.63-7.55(m,3H,heteroaryl-H),3.36-3.16(t,2H,-CH_2),1.61-1.53(m,6H,(-CH_2)$_3$),1.35-1.26(m,2H,-CH_2),0.94-0.91(t,3H,-CH_3). ^{13}C-NMR [DMSO-d_6] δ: 132.08-129.48 (Ar-C), 14.07, 19.78, 23.64 (C-aliphatic).

Synthesis of 6,7-Bis(hex-1-yn-1-yl)quinoline-5,8-dione, 2e: 6,7-Dibromoquinoline-5,8-dione, (0.5 mmol) coupled with 1-hexyne (1.2 mmol) in the presence of $PdCl_2(PPh_3)_2$ (3mol %), and TBAF.$3H_2O$ (6 equiv) at 80 °C to afford a black oily liquid. Yield 65% (0.13 g). UV-Visible λmax (log ε): 739 (1.2), 477 (1.5), 351 (1.82) nm. IR (NaCl) υmax: 2876cm^{-1}, 2958cm^{-1} (C-H aliphatic), 2089cm^{-1} (C≡C), 1717cm^{-1} (C=O), 1473cm^{-1} (C=C aromatic rings), 1380cm^{-1} (C-N Stretch). ^{1}H-NMR[DMSO-d_6]δ:3.19-3.14(t,2H,-CH_2),1.61-1.53(m,2H,-CH_2),1.35-1.26(m,2H,-CH_2),0.97-0.92(t,3H,-CH_3).^{13}C-NMR[DMSO-d_6]δ: 23.64,19.74,14.07 (C-aliphatic).

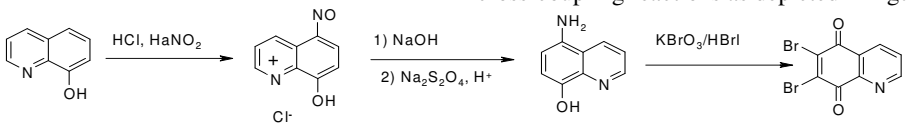
Anti-microbial properties: The anti-microbial evaluation of the synthesized bis-alkynylated quinoline-5,8-diones was done via agar well diffusion method as reported by Perecz *et al* (Perecz *et al.*, 1990) without modification. The bacterial strains employed in the screening were *Staphylococcus aureus, Klebsiella pneumonia, Pseudomonas aeruginosa, Escherichia coli 1 and Escherichia coli 12*. The activity of the compounds was based on the diameter of zone of inhibition (IZD) of the growth of the

microorganisms and the minimum concentration required to effect inhibition (MIC) of the growth.

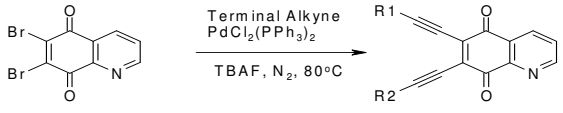
In-silico Studies: The synthesized compounds were drawn using Marvin Sketch chemical drawing software. Structure Checker tool in the software was applied to ensure that the structural features of the compounds including bond length, overlapping atoms and valence were correct. They were further optimized through energy minimization. The crystal structures of the proteins used for the docking (*Pseudomonas aeruginosa*LpxC, PDB code: 3P3E, and *E. coli*glutaredoxin, PDB code: 1GRX) were downloaded from the protein data bank (https://www.rcsb.org/structure). The proteins were prepared and used for molecular docking simulation.

RESULTS AND DISCUSSION

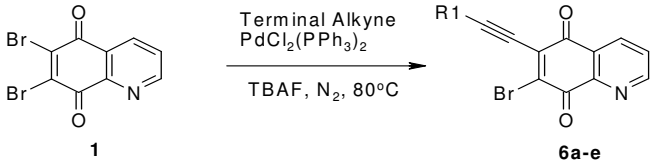
The precursor, 6,7-dibromoquinoline-5,8-dione(1) was first prepared by multistep synthesis as described by Harinath and Subba (Harinath and Subba, 1996) and Pratt and Drake (Pratt and Drake, 1960). The synthesis of bis-alkynylated quinoline-5,8-diones **(2a - e)** was achieved by palladium –catalyzed cross-coupling of the intermediate 6,7-dibromoquinoline-5,8-dione with five different alkynes using $PdCl_2(PPh_3)_2$ in the presence of TBAF,$3H_2O$ and under an inert atmosphere. The reaction of 6,7-dibromoquinoline-5,8-dione and alkynes was conducted in the absence of copper, amine and solvent condition, which is a modification of the conventional Sonogashira coupling reaction (Bohm and Herrmann 2000, Mery *et al*., 2003, Ezeokonkwo *et al.,* 2015, Onoabedje *et al*., 2016). Reacting 6,7-dibromoquinoline-5,8-dione and the relevant alkyne in a stoichiometric ratio of 1:2 under the reaction condition furnished the bis-alkynylated products in good yields (not presented here). However, there was a decrease in yields as compared to the mono-alkynylated products reported in our previous work (Ezugwu et al. 2017) (Scheme 3). The reaction of phenyl acetylene with 6,7-dibromoquinoline-5,8-dione gave the highest yield (80%) within 72min. The molecular structures of the synthesised compounds are consistent with ^{1}H NMR, ^{13}NMR, and IR spectral data. Compounds **2a-e** showed characteristic absorption band in the range of 2089-2381 cm^{-1} assigned to C≡C stretching, The C=O stretching vibration frequencies quinolinedione is observed at 1607-1717 cm^{-1}. The absorption bands at 1459-1473 cm^{-1} and 1379-1389 cm^{-1} were assigned to C=C and C=N stretches respectively. The absence of 687—741 cm^{-1} bands due to C-Br in mono-alkynlatedquinoline-5,8-diones (Ezugwu *et al.* 2017) confirmed the formation of the bis-alkynylated products **2a-e**. The peaks attributed to heteroaryl protons are observed as multiplets in the range of 7.00-7.86 ppm. In the ^{13}C NMR spectra, the C≡C carbon of alkynyl group was observed for most of the compounds at 58.12-89.86 ppm. The dialkynylation involves a nucleophilic attack by the alkyne on the positions 6 and 7 of the dibromoquinoline-5,8-dione. The first attack is on more favoured position 6 of the compound [10]. To form the bis-alkynylated derivatives, the electron rich alkynyl group mounts a second nucleophilic attack at the less favoured 7-position of the 6-alkynylated quinoline-5,8-dione leading to elimination of bromide ion, Br-, and formation of compounds **2a-e**. The proposed mechanism of this reaction is in line with the common copper, amine and solvent free Sonogashira cross-coupling reactions as depicted in figure **4.**



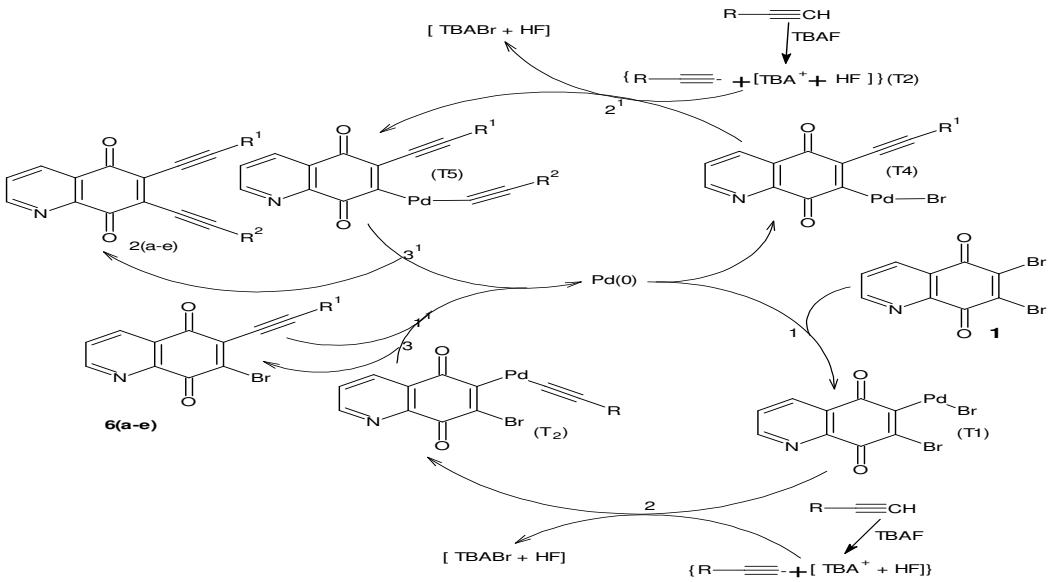
Scheme 1: *Multistep synthesis of 6,7-dibromoquinoline-5,8-dione*



Scheme 2: *Synthesis of Bis-alkynlated quinolone-5,8-diones, $R^1 = R^2$ = —CH_2OH (2a), —C $(CH_3)_2OH$(2b), —C_6H_5(2c), —C_6H_{13}(2d), —C_4H_9(2e)*



Scheme 3: Synthesis of Mono-alkynlated quinolone-5,8-diones (Ezugwu *et al.*, 2017); R^1 is —CH_2OH (6a), —C $(CH_3)_2OH$(6b), —C_6H_5(6c), —C_6H_{13}(6d), —C_4H_9(6a)



Scheme 3: Mechanism of bis-cross coupling Reaction
Where R is ,—CH_2OH, —C $(CH_3)_2OH$, —C_6H_5, —C_6H_{13}, —C_4H_9. The ligand, L=Triphenylphosphine (pph_3), was eliminated for the simplicity of the mechanism pathway Scheme 4 and 5.

Antimicrobial Activity Evaluation: The antimicrobial activity of all the synthesized compounds were studied using micro-organisms, which include:*E.coli 1, E.coli 12, Klebsiella pneumonia, Staphylococcus aureus, and Pseudomonas aeruginosa. Agar diffusion method as described by* Perecz *et al.* (Perecz *et al.* 1990) *was adopted.* Ampicillin and gentamycin were used as standard drugs because they exhibit strong spectrum of antibacterial activities.All the compounds have some degree of activity against the tested organisms. However, *E.coli* 1 and *Pseudomonas aeruginosa* were resistance to compounds **2a** and **2c,**while *E.coli 12* and *Staphylococcus aureus* were resistance to compound **2a.** The activity of the synthesized compounds (2b, 2d & 2e) against *E.coli 1* was found to be excellent (MIC range 0.16 -0.45 mg/mL) compared to gentamycin and ampicilin (MIC = 100 mg/mL). For *E.coli 12,* the highest activity was recorded for compound **2c** (MIC=0.22 mg/mL) while compound **2e** exhibited the least potency (MIC=2.82 mg/mL). From comparative study, all of the synthesized compounds (MIC 0.22 to 2.82 mg/mL) were more active compared to gentamycin and ampicilin (MIC=100 mg/mL). Compounds **2d** exhibited the least activity (MIC = 2.80 mg/mL). The synthesized compounds (MIC 0.16 to 0.80 mg/mL), showed maximum potency against *staphylococcus aureus* as compared to gentamycin and ampicilin (2.5 mg/mL). Compounds 2b, 2d and 2e exhibited higher potency as compared to the standard drugs.The highest activity was observed on compounds **2b** and **2e** (MIC 0.13 mg/mL). The double alkynylation of quinoline-5,8-dione increased the potency against some of the microbes compared to the monoalkynylated products. For example, di-substitution with 1-octyne (**2d)** has a better activity against *staphylococcus aureus* than the monosubstituted product **(6d).**

Molecular docking: The molecular docking result to evaluate the binding energy of the synthesized compounds against 3P3E and 1GRX receptors is given in Table 3

Table 2: Results of Inhibition Zone Diameter (IZD) and minimum inhibition concentration (MIC) test of bis-alkynylated derivatives of quinoline-5,8-diones on targeted organisms (mg/ml).

Bacteria strain	*E.coli 1*		*E.coli 12*		*Klebsiella pneumonia*		*Staphylococcus aureus*		*Pseudomonas aeruginosa*	
Compounds↓	IZD (mm)	MIC (mg/ml)	IZD (mm)	MIC (mg/ml)	IZD (mm)	MIC (mg/ml)	IZD (mm)	MIC (mg/ml)	IZD (mm)	MIC (mg/ml)
2a	—	_	10	1.41	14	0.30	_	_	_	_
2b	11	0.32	20	0.30	14	0.32	11	0.80	14	0.13
2c	—	_	9	0.22	9	0.35	17	0.22	--	_
2d	12	0.45	12	0.45	13	2.80	14	0.16	13	0.16
2e	13	0.16	15	2.82	14	0.56	13	0.56	14	0.13
Ampicilin		100		100		5.00		2.5		20
Gentamycin		100		100		5.00		2.5		10

Table 3: Free binding energy, ΔG (kcal/mol) of the synthesized compounds

Comp	3P3E from *P. aeruginosa* ΔG, (kcal/mol)	1GRX from *E. coli* ΔG, (kcal/mol)	comp	3P3E from *P. aeruginosa* ΔG, (kcal/mol)	1GRX from *E. coli* ΔG, (kcal/mol)
6a	-12.08	-10.21	2a	-11.30	-9.00
6b	-11.92	-8.34	2b	-12.73	-8.88
6c	-12.15	-8.54	2c	-11.44	-8.19
6d	-11.19	-9.31	2d	-11.07	-8.83
6e	-11.87	-8.67	2e	-11.33	-9.19
native ligand	-10.70	-11.53	Gentamycin	-15.59	-13.24

3P3E: Crystal Structure of the Pseudomonas aeruginosaLpxC; 1GRX: Structure of E. coliglutaredoxin

Interaction with LpxC: LpxC is the enzyme responsible for the first committed step in the biosynthesis of lipid A. It is a promising drug target in the development of antibiotics, which can selectively act against Gram-negative pathogens such as *Pseudomonas aeruginosa* and members of the *Enterobacteriaceae*. In order to gain more insight in the binding interactions with LpxC, the 2D ligand interaction of the co-crystallized ligand (inhibitor), N-[(1S,2R)-2-hydroxy-1-(hydroxycarbamoyl)propyl]-4-(4-phenylbuta-1,3-diyn-1-yl)benzamide shown in figure 1, was studied. Various atoms of the inhibitor interacted with different amino acid residues namely: PHE 191, LEU 18, MET 62, SER 210, THR 190 and HIS 237.

These chemical interactions resulted in the strong binding affinity observed (Table 3). Figure 2 showed that the ligand atoms of compound **2a** interacted with THR 190, PHE 191, PHE 160 and ASP 196 of LpxC. The binding energy of the native inhibitor was similar to that of 2a: 11.33 and 11.33 kcal/mol respectively. Both the mono and di-substituted quinoline-5,8-dione showed significant binding affinity to LpxC. However, the mono- and the di-substituted compounds did not show any significant difference in their inhibitory activity as the enzyme. The 2D interaction of compound 6a with LpxC is shown in figure 5.

The binding energy of 6a was found to be higher (-12.08 kcal/mol) than the co-crystallized inhibitor (-10.70 kcal/mol) used as reference. However, the standard drug (gentamycin) had a higher binding energy (-15.59 kcal/mol) when compared to the binding energy of mono-, di-substituted and native (co-crystallized) ligand. The binding poses of compounds 2a and 6a are shown in figures **3** and **4** respectively. The green dotted lines indicate hydrogen bonding while the blue dotted lines indicate van dar Waal interaction. From the foregoing, there is a strong indication that the mono and di-substituted quinoline-5,8-diones are potential inhibitors of LpxC.

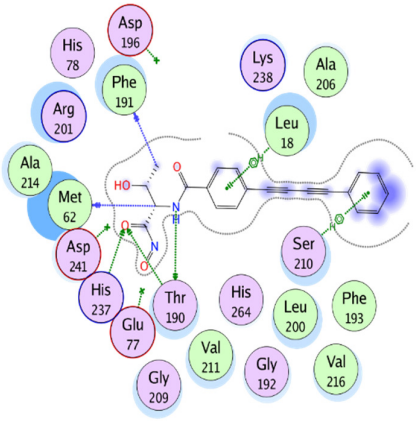


Fig 1: The 2D ligand interaction of the co-crystallized inhibitor, N-[(1S,2R)-2-hydroxy-1-(hydroxycarbamoyl)propyl]-4-(4-phenylbuta-1,3-diyn-1-yl)benzamide with LpxC

Interaction with glutaredoxin (PDB Code: 1GRX) **from *E. coli:*** Glutaredoxin from Escherichia coli is a small protein (85 residues, M, = 10,000) involved in electron transfer reactions via the reversible oxidation of two SH groups to a disulfide bond (Holmgren 1989). E. *coli*glutaredoxin catalyzes glutathione-dependent redox reactions such as reduction of ribonucleotides with ribonucleotide (Holmgren 1985).

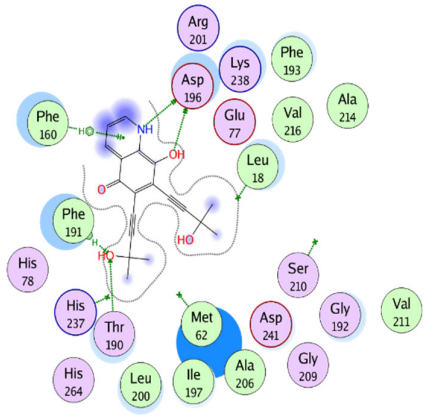


Fig 2: The 2D ligand interaction of compound 2a with LpxC

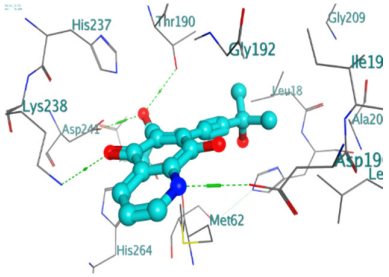


Fig 3: The binding pose of compound 2a in the binding cavity of LpxC

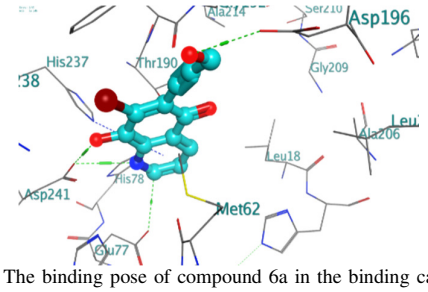


Fig 4: The binding pose of compound 6a in the binding cavity of LpxC

The synthesized compounds demonstrated significant binding affinity with the receptor though they have more binding affinity for *P. aeruginosa* LpxC than the *E. coli* glutaredoxin. Again, there is no significant difference in the binding energy of both mono- and di-substituted quinolone-5,8-diones. Among the mono- and di-substituted quinolone-5,8-diones, compound 6a showed the highest binding energy (-10.21 kcal/mol).

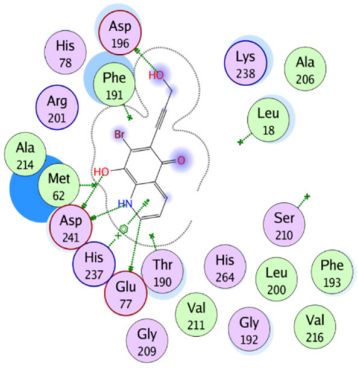


Fig 5: The 2D interaction of compound 6a with LpxC

It's binding pose in the binding cavity of *E. coli* glutaredoxin and the corresponding 2D ligand interactions are shown in figures **6** and **7** respectively. The un-substituted bromine atom interacted with TYR 72. The hydroxy group in the substituted terminal alkyne interacted with VAL 59. There was a keto-enol tautomeric shift in the quinolone nucleus that resulted in the hydrogen bond interaction between the -OH group and THR 73. There were also H-bond interaction between the N atom and TYR 13 as well as π-bond interaction between one of the 6-membered rings and the TYR 13 amino acid.

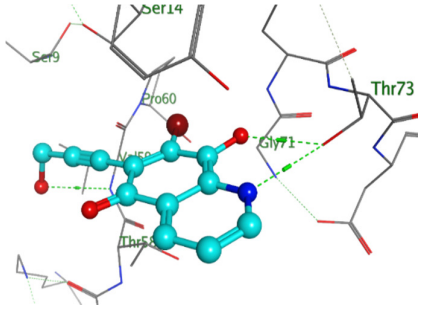


Fig 6: Binding pose of compound1a with **glutaredoxin**

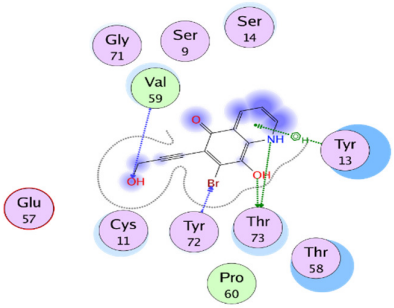


Fig 7: 2D interaction of 1a with glutaredoxin from *E. coli*

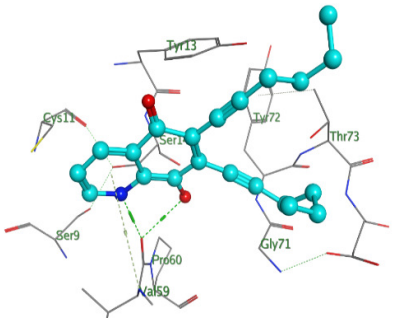


Fig 8: Compound 2e in the binding cavity of glutaredoxin from *E. coli*

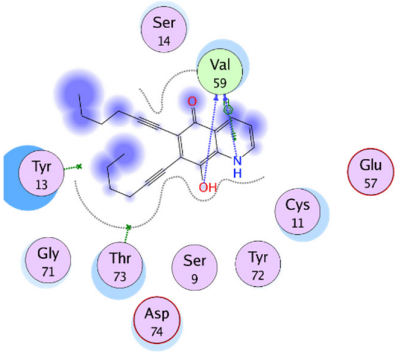


Fig 9: 2D interaction of 2e with glutaredoxin from *E. Coli*

Conclusion: New bis-alkynylated quinoline-5,8-diones were synthesized via palladium catalysed cross-coupling. The alkynylated quinoline-5,8-diones

have good antibacterial activity against *E.coli 1, E.coli 12, Klebsiella pneumonia, Staphylococcus aureus, and Pseudomonas aeruginosa*. They also possess significant binding affinity for *P. aeruginosa* LpxC than the *E. coli* glutaredoxin. However, there is need for further research in order to determine the toxicity of the synthesized products.

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