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Design and synthesis of 4'-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methyl)biphenyl-2-carbonitrile analogs as bacterial *Peptide deformylase* inhibitors

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Herein, we report the synthesis and screening of 4'-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methyl)biphenyl-2-carbonitrile analogs 11(a-j) as bacterial *Peptide deformylase* (PDF) enzyme inhibitors. The compounds 11b (IC_{50} value= 139.28 µM), 11g (IC_{50} value= 136.18 µM) and 11h (IC_{50} value= 131.65 µM) had shown good PDF inhibition activity. The compounds 11b (MIC range= 103.36-167.26 µg/mL), 11g (MIC range= 93.75-145.67 µg/mL) and 11h (MIC range= 63.61-126.63 µg/mL) had also shown potent antibacterial activity when compared with standard ampicillin (MIC range= 100.00-250.00 µg/mL). Thus, the active derivatives were not only PDF inhibitors but also efficient antibacterial

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agents. In order to gain more insight on the binding mode of the compounds with PDF enzyme, the synthesized compounds 11(a-j) were docked against PDF enzyme of *E. coli* and compounds exhibited good binding properties. The results suggest that this class of compounds has potential for development and use in future as antibacterial drugs.

Keywords: biphenyl, thiazolidinedione, bacterial PDF inhibition, antibacterial activity, molecular docking study

Running title: Bacterial PDF inhibition of biphenyl-thiazolidinedione

The discovery of antibiotics and their impact on bacterial infections represents one of the great success stories of 20th –century medicine but there is growing concern about increasing antibiotic resistance (1).The latest antibiotic Linezolid (Zyvox ^{TM}) was approved by US-FDA in 2000, unfortunately, already a few cases of Linezolid resistance pathogens in hospital isolates have been reported (2).While vancomycin is an efficient therapeutic agent for most antibiotic-resistant Gram-positive bacteria, vancomycin-resistant *S. aureus* was reported in U.S. in 2002 (3, 4). This crisis has resulted in an intensive research effort to develop a new class of compounds that exhibit novel mechanisms of antibacterial activity. Although microbial genomes have revealed an abundance of potentially useful targets, little has so far resulted from these much-heralded efforts (5-7). Recent reports from several laboratories have suggested that peptide deformylase (PDF), an enzyme responsible for removing the N-terminal of formyl group from newly synthesized polypeptides and may be suitable target for antibacterial drug discovery (8-10). PDF is present in all bacteria and essential for bacterial survival (11). Indeed, PDF inhibitors have been reported to act as broad-spectrum antibacterial agents (12). The fact that the PDF is essential for producing the mature protein in bacterial cells provides a rational basis to choose it as a potential and novel target for antibacterial agents.

In the past few years, different classes of PDF inhibitor like, peptidic inhibitors, pseudopeptidic inhibitors and non-peptidic inhibitors as antibacterial agents have been reported (13). The non

peptidic PDF inhibitors, which are assumed to be less prone to degradation, are not much explored (14-19). The non-peptidic inhibitors like, biaryl acid analogues were developed by Merck Research Laboratories and evaluated as PDF inhibitor against *E. coli* PDF enzyme.A representative structure for these biaryl acid analogs is shown in Figure 1. The biaryl acid analogs are composed of a "head group" of aromatic/heterocyclic rings, a biaryl group, and an acidic group on the biaryl B-ring. Structure-activity relationship (SAR) studies of biaryl acid analogues revealed that substitution at the head group, biaryl group, and the nature of acidic group all contributed to the inhibitory activity of these compounds against PDF enzyme. The acidic group of these compounds may bind to the metal ion and instead interact with an amino acid residue within PDF active site much like the binding of the angiotensin II receptor.The structure of two biaryl acid compounds **1** (IC_{50}= 3.9 μM) and **2** (IC_{50}= 22.8 μM) are presented in Figure 2 (20).The thiazolidinedione (TZD) scaffold has attracted significant interest of researchers and has become an important class of heterocyclic compounds because of their utility for miscellaneous biological activities including antimicrobial activity (21, 22). The structure of two antibacterial compounds **3** (MIC range= 6.25-12.5 μg/mL) (23) and **4** (MIC range= 4.00-128.00 μg/mL) (24) having TZD scaffold are presented in Figure 2. With aim to improve the antibacterial activity of biaryl acid analogs as PDF inhibitors, we coupled the biphenyl moiety and TZD nucleus. Based on these reports, we, therefore, decided to explore some new biphenyl containing cyano (-*CN*) group as acid pharmacophore coupled with TZD scaffold for bacterial PDF enzyme inhibition activity.

In continuous of our work on synthesis of bioactive molecules (25-29), we report the synthesis of a novel series of 4'-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methyl)biphenyl-2-carbonitrile analogs **11(a-j)**, and the study of their effects on inhibition of *E. coli* PDF enzyme. The various aromatic rings with different substituent have been introduced at "head group" position of TZD with aim to improve the overall properties of the synthesized series. The compounds were also evaluated for antibacterial activity against Gram-negative bacteria namely, *E. coli* and Gram-positive bacteria namely, *B. subtilis*. To explore the underlying mechanisms of PDF inhibition, we docked synthesized compounds against *E. coli* PDF enzyme.

The synthetic approaches employed for synthesis of titled compounds **11(a-j)** are outlined in Scheme 1. 2,4-thiazolidinedione **7** was synthesized by refluxing commercially available starting

materials thiourea **5** and chloracetic acid **6**(30). The compounds **8(a-j)** was synthesized via Knoevenagel condensation reaction by reacting 2,4-thiazolidinedione **7** and various aromatic aldehydes in presence of sodium acetate and acetic acid (31). The 4'-(bromomethyl)biphenyl-2-carbonitrile **10** was synthesized from commercially available 4'-methylbiphenyl-2-carbonitrile **9** in good yield (85 %) according to published procedure (32). Further, to expand the series, the compounds **11(a-j)** were prepared by reacting the compound **10** with various synthesized compounds **8(a-j)**in *N,N*-dimethylformamide (DMF) using K_2CO_3 as catalyst (Supporting information). The compounds **11(a-j)** were obtained in good yields (74-86 %). The compounds **11(a-j)** were characterized by means of IR, ^{1}H NMR, ^{13}C NMR and Mass Spectrometry and data confirmed the proposed structures (Supporting information).

The PDF enzyme was extracted from *E. coli* (NCIM-2931) bacteria and stabilized using 5 mM $NiCl_2$. The synthesized compounds **11(a-j)** were tested against *E. coli* PDF-Ni enzyme using spectrophotometric method (33). The IC_{50} values (concentration that decreased PDF by 50 %) of synthesized compounds is presented in Table 1. The synthesized compounds **11(a-j)** had shown moderate (IC_{50} range= 131.65- 227.54 μM) PDF inhibition activity. Compounds **11b** (IC_{50}= 139.28μM), **11g** (IC_{50}= 136.18μM) and **11h** (IC_{50}= 131.65μM) were considered to be shown as significant*E. coli* PDF-Ni enzyme inhibition activity when compared with other synthesized compounds. Compounds **11a** (IC_{50}= 179.33 μM), **11c** (IC_{50}= 227.54 μM), **11d** (IC_{50}= 152.41 μM), **11e** (IC_{50}= 214.58 μM), **11f** (IC_{50}= 204.87μM), **11i** (IC_{50}= 172.39 μM) and**11j** (IC_{50}= 176.21μM) were found to be less active against *E. coli* PDF-Ni enzyme when compared with other active compounds**11b**, **11g** and **11h**.

Structure-activity studies of 4'-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methyl)biphenyl-2-carbonitrile analogs**11(a-j)** revealed that head group, biaryl group and acidic group (-*CN*) all contributed to inhibitory activity against bacterial PDF enzyme. The compounds **11(a-j)** showed varied PDF inhibition activity depending upon the various substituents present on phenyl ring (head group). From the assay data summarized in Table 1, compound **11a** (IC_{50}= 179.33 μM) with *Ar= phenyl* showed less PDF inhibition activity. Introduction of *4-Cl* substituent on phenyl ring **11b** (IC_{50}= 139.28 μM) led to increase in PDF inhibition activity by 1.5 fold when compared with compound **11a**. The replacement *4-Cl* with *2-Cl***11c** (IC_{50}= 227.54 μM) on phenyl ring led

to decrease in PDF inhibition activity by 2 folds and gave least active compounds of the synthesized series **11(a-j)**. The replacement of *4-Cl* substituent with *4-F* **11d** (IC_{50}= 152.41 μM) on phenyl ring led to decrease in PDF enzyme inhibition activity. The introduction of *2,6-di-Cl***11h** (IC_{50}= 131.65 μM) led to most potent PDF inhibitors of the synthesized series **11(a-j)**. Further, replacement of *4-Cl* with *4-OCH_3* **11e** (IC_{50}= 214.58 μM) showed decrease in PDF enzyme inhibition activity by 1.5 fold. The substitution of *2,4-di-OCH_3* group on phenyl ring **11f** (IC_{50}= 204.87 μM) led to decrease in PDF inhibition activity. The replacement of *2,4-di-OCH_3* group with *2,5-di-OCH_3***11g** (IC_{50}= 136.18 μM) and *3,4-di-OCH_3***11i** (IC_{50}= 172.39 μM) showed improved PDF inhibition activity by 1.5 fold when compared with compound *2,4-di-OCH_3***11f**. The introduction of 3,4,5-trimethoxygroup on phenyl ring **11j** (IC_{50}= 176.21 μM) showed similar PDF inhibition activity when compared with compound **11a**(IC_{50}= 179.33 μM). Thus, compounds **11b**, **11d**and **11h** with electron withdrawing groups (except **11c**) like, halogens were more active than compounds **11e**, **11f**, **11i** and **11j** (except **11g**) with electron donating groups like, -*OCH_3*, on phenyl ring .

The antibacterial activity was evaluated against one Gram-negative bacteria namely, *E. coli* (NCIM-2256) and one Gram-positive bacteria namely, *B. subtilis* (NCIM-2063) using ampicillin as standard drug. Minimum inhibitory concentration (MIC) values were determined using standard agar method (34). Dimethyl sulfoxide was used as solvent control. MIC values of the tested compounds are presented in Table 1. Interestingly, our results demonstrated that most potent PDF inhibitors that is **11b** (MIC range= 167.26-103.36 μg/mL), **11g**(MIC range= 145.67-93.75 μg/mL) and **11h** (MIC range= 63.61-126.63 μg/mL) showed also a significantly potent antibacterial activity against *E. coli* and *B. subtilis* when compared with standard ampicillin (MIC range= 100.00-250.00 μg/mL). All the synthesized compounds **11(a-j)** (MIC range= 63.61-251.97 μg/mL) had shown significant antibacterial activity when compared with ampicillin (MIC range= 100.00-250.00 μg/mL). All the synthesized compounds, except **11j** (MIC= 251.97 μg/mL) had shown better antibacterial activity against *B. subtilis*when compared with standard ampicillin(MIC= 250.00 μg/mL). The compounds **11a** (MIC= 84.23 μg/mL), **11f** (MIC= 88.65 μg/mL), **11g** (MIC= 93.75 μg/mL), **11h** (MIC= 63.61 μg/mL), **11i** (MIC= 91.29 μg/mL) and **11j** (MIC= 78.55 μg/mL) had shown better antibacterial activity against *E. coli* when compared with standard ampicillin(MIC= 100.00 μg/mL). Compounds **11a**, **11f**, **11g**, **11h**

and **11i** had shown broad spectrum of antibacterial activity against both Gram-positive (*B. subtilis*) and Gram-negative (*E. coli*) bacteria when compare with standard ampicillin.

The activity data (Table 1) revealed that synthesized compounds **11(a-j)** had significant antibacterial activity. The replacement of H atom of phenyl ring of head group **11a** (MIC range= 84.23-228.15 µg/mL) by *4-Cl***11b** resulted improved in antibacterial activity against *B. subtilis* (MIC= 167.26 µg/mL) but decrease in activity against*E. coli*(MIC= 103.36 µg/mL). The replacement of *4-Cl* by *2-Cl***11c** on phenyl ring improved the antibacterial activity against *B. subtilis* (MIC= 118.38 µg/mL) by 1.5 fold and decrease in activity against *E. coli* (MIC= 155.45 µg/mL) by 1.5 fold. When *4-Cl***11b** was replaced with *4-F* **11d** on phenyl ring, there was increase in antibacterial activity against *B. subtilis* (MIC= 96.59 µg/mL) by 1.7fold bur there was no significant change in antibacterial activity against *E. coli* (MIC= 102.29 µg/mL). Introduction of *2,6-di-Cl***11h** (MIC range= 63.61-126.63 µg/mL) on phenyl ring led to most potent antibacterial when compared with remaining synthesized compounds. Further, introduction of *4-OCH_3* **11e** on phenyl ring resulted in decrease in antibacterial activity against *E. coli* (MIC= 123.33 µg/mL) and increase in activity against *B. subtilis* (MIC= 179.69 µg/mL) when compared with compound **11a**. The introduction of *2,4-di-OCH_3***11f** (MIC range= 88.65-165.59 µg/mL), *2,5-di-OCH_3***11g** (MIC range= 93.75-145.67 µg/mL) and *3,4-di-OCH_3***11i** (MIC range= 91.29-206.56 µg/mL) had shown significant antibacterial activity when compared with standard ampicillin (MIC range= 100.00-250.00 µg/mL). The introduction of *3,4,5-tri-OCH_3***11j**had shown improved antibacterial activity against *E. coli*(MIC= 78.55 µg/mL) but led to least activeagainst *B. subtilis*(MIC= 251.97 µg/mL) when compared with ampicillin. The activity data suggested that compounds **11e**, **11f**, **11g**, **11i** and **11j** with electron-donating substituent like, *-OCH_3*on phenyl ring of head group showed better antibacterial activity against *E. coli*than compounds **11b, 11c and 11d** with electron-withdrawing substituent (except **11h**) like,**-***Cl and -F* group. On the other hand, compounds **11b**, **11c**, **11d**and **11h** with electron-withdrawing substituent like, halogens onphenyl ring of head group showed better antibacterial activity against *B. subtilis* than compounds **11e**, **11f**, **11g**, **11i and 11j**with electron-donating substituent like, *-OCH_3*.

In order to gain more insight on the binding mode of the compounds with *Peptide deformylase* (PDF), we docked the synthesized compounds **11(a-j)** against crystal structure of *E. coli* PDF-Ni (PDB ID: 1G2A) (35) which is obtained Protein Data Bank. The standard operating procedure

implemented in VLife MDS 4.3 package was followed for GRIP batch docking of final synthesized compounds against three-dimensional structures of *E. coli* PDF-Ni enzyme (36). Docking calculation and hydrogen bond interactions are shown in Table 2. The interaction energy of the compounds **11(a-j)** and their PDF inhibition activity showed the corresponding results. The active compounds **11b**, **11g** and **11h** showed lowest interaction energy that is -61.57 kcal/mol, -63.10 kcal/mol and -70.13 kcal/mol, respectively. The docking results indicated that thesynthesized compounds **11(a-j)** held in the active pocket by combination of hydrophobic and van der Waals interactions with the PDF enzyme. The various hydrophobic and van der Waal's interactions occurred between these compounds and active site of PDF enzyme include GLU41, GLU42, GLY43, ILE44, GLY45, ILE86, GLU87, GLU88, GLY89, CYS90, LEU91, PRO94, GLU95, ARG97, LEU125, ILE128, CYS129 and HIS132.

The docking study of most active compound **11h** revealed (Figure 3) that compound is buried deep into the active site by forming various hydrophobic and van der Waal's interactions with amino acid residues like, GLU41, GLY43, ILE44, GLY45, ILE86, GLU87, GLU88, GLY89, CYS90, GLU95, LEU91, ARG97, LEU125, ILE128 and HIS132. The amino acids ILE44 (2.26 Å) and ARG97 (1.46 Å) had formed strong hydrogen bonds with oxygen of 2-C=O (thiazolidinone nucleus) and nitrogen of CN group, respectively with compound **11h**. The chloro groups were held in active pocket by forming interactions with amino acid residues like, GLU87, GLU88, GLY89, ILE128, CYS129 and HIS132. Thus, chloro group may be responsible for increased in PDF inhibition activity.The docking study of least active compound **11c** (Figure 3) had shown least binding energy that is -33.07 kcal/mol. The docking study revealed that compound **11c** was held in active pocket by forming various hydrophobic and van der Waal's interactions with amino acid residues like, GLY43, ILE44, GLY45, LEU46, ILE86, GLU87, GLU88, GLY89, CYS90, LEU91, ARG97, LEU125, ILE128, CYS129, HIS132, GLU133 and HIS136. The amino acids GLY89 (2.29 Å) and ARG97 (2.24 Å) had formed strong hydrogen bonds with oxygen of 4-C=O (thiazolidinone nucleus) and nitrogen of CN group, respectively with compound **11c**. The chloro group had formed weak van der Waal's interactions with amino acids GLY45 and HIS136. Due to poor binding interactions with PDF enzyme, compound **11c** may have shownthe least PDF enzyme inhibition activity among the synthesizedcompounds.

In summary, a series of 4'-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methyl)biphenyl-2-carbonitrile analogs **11(a-j)** was synthesized efficiently in good yields. The synthesized compounds were evaluated for *in vitro*bacterial PDF enzyme inhibition and antibacterial activities. The compounds **11b** (IC_{50}= 139.28 µM), **11g** (IC_{50}= 136.18 µM) and **11h** (IC_{50}= 131.65 µM) showed good PDF enzyme inhibition activity. Also, these active compounds **11b** (MIC range= 103.36-167.26 µg/mL), **11g** (MIC range= 93.75-145.67 µg/mL) and **11h** (MIC range= 63.61-126.63 µg/mL) had shown potent antibacterial activity when compared with standard ampicillin (MIC range= 100.00-250.00 µg/mL). Further, to understand the mechanism of PDF inhibition, we docked the synthesized compounds **11(a-j)** against *E. coli* PDF-Ni enzyme. Molecular docking study showed good binding of these compounds to the active site of *E. coli* PDF-Ni enzyme and thus had potential to inhibit PDF enzyme.These preliminary encouraging results of biological screening of the tested compounds could offer an excellent framework in this field that may lead to discovery of potent and novel antibacterial agent.

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Conflicts of interest

Authors have no conflicts of interest.

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Figure Legends

Figure 1. General structure of biaryl acid analogs for bacterial PDF enzyme inhibition.

Figure 2. The structures of reported of biaryl acid analogs, thiazolidinedione derivatives and synthesized compounds **11(a-j)**.

Figure 3. Docking study of compounds **11c** and**11h** with *E. coli* PDF-Ni (PDB ID: 1G2A).

Scheme

Scheme 1. Synthesis of titled compounds **11(a-j)**; Reagents: (a) H_2O, Conc. HCl, Reflux for 12 h; (b) Ar-CHO, NaOAc, AcOH, Reflux; (c) NBS, H_2O_2, DCM, Reflux; (d) Compounds **8(a-j)**, K_2CO_3, DMF, RT, Stir.

Table

Table 1: Bacterial PDF enzyme inhibition and antibacterial activities of synthesized compounds **11(a-j)**.

Table 2: Docking statistics of synthesized compounds **11(a-j)** against *E. coli* PDF-Ni enzyme.

Table 1: Bacterial PDF enzyme inhibition and antibacterial activities of synthesized compounds **11(a-j)**.

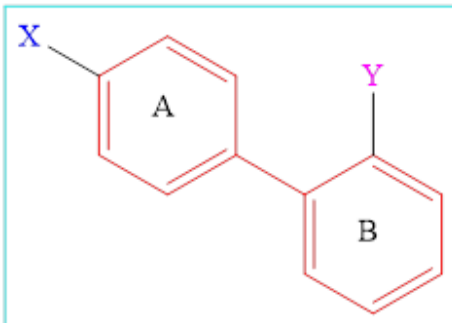
Entry	IC_{50} ± SEM (μM)	MIC ± SEM (μg/mL)	
	E. coli PDF-Ni	*E. coli*	*B. subtilis*
11a	179.33 ± 3.65	84.23 ± 2.58	228.15 ± 4.89
11b	139.28 ± 3.26	103.36 ± 2.14	167.26 ± 3.76
11c	227.54 ± 4.59	155.45 ± 1.98	118.38 ± 3.85
11d	152.41 ± 2.68	102.29 ± 1.59	96.59 ± 2.96
11e	214.58 ± 2.84	123.33 ± 2.15	179.69 ± 4.45
11f	204.87 ± 3.25	88.65 ± 1.51	165.59 ± 3.88
11g	136.18 ± 2.89	93.75 ± 2.51	145.67 ± 2.45
11h	131.65 ± 1.65	63.61 ± 1.95	126.63 ± 3.35
11i	172.39 ± 2.78	91.29 ± 2.49	206.56 ± 2.16
11j	176.21 ± 3.59	78.55 ± 3.05	251.97 ± 4.56
Ampicillin	ND	100.00 ± 1.55	250.00 ± 2.25

Experiments were performed in triplicates and compared to DMSO-treated controls; Standard errors were all within 10% of the mean; ND: not done.

Table 2: Docking statistics of synthesized compounds **11(a-j)** against *E. coli* PDF-Ni enzyme.

Entry	Affinity (kcal/mol)	H-bonds	H-bonding ligand		H-binding receptor			H-bonds length (Å)
			Element	Atom No.	Residue	Element		
11a	-45.16	02	4-O of TZD	19	ILE44	H	707	2.44
			N of CN	29	ARG97	H	1543	1.64
11b	-61.57	02	4-O of TZD	19	ILE44	H	707	2.38
			2-O of TZD	20	LEU91	H	1436	2.09
11c	-33.07	02	4-O of TZD	19	GLY89	H	1414	2.29
			N of CN	29	ARG97	H	1542	2.24
11d	-49.86	03	2-O of TZD	20	ILE44	H	707	2.01
			N of CN	30	GLY89	H	1414	2.46
			F	28	GLU95	H	1500	2.19
11e	-40.14	02	4-O of TZD	19	ILE44	H	707	2.29
			N of CN	31	ARG97	H	1543	2.00
11f	-46.03	02	S of TZD	17	GLY89	H	1414	2.00
			2-O of TZD	20	GLY89	H	1414	2.45
11g	-63.10	02	2-O of TZD	20	ILE44	H	707	1.86
			O of 2-OCH_3	28	ARG97	H	1543	1.64
11h	-70.13	02	2-O of TZD	20	ILE44	H	707	2.26
			N of CN	31	ARG97	H	1546	1.46
11i	-46.35	02	4-O of TZD	19	GLY89	H	1414	2.02
			N of CN	31	ARG97	H	1542	1.85
11j	-48.82	03	2-O of TZD	20	LEU91	H	1436	1.86
			N of CN	29	ARG97	H	1543	2.07
			O of 3-OCH_3	34	CYC129	H	2053	2.32

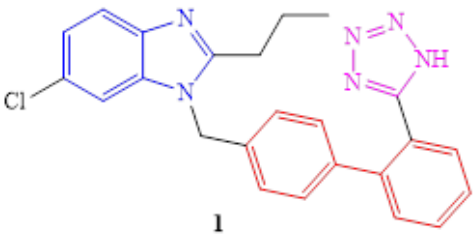
TZD: 2,4-thiazolidinedione nucleus.



X= Head Group (e.g.; aromatic/heterocyclic rings)

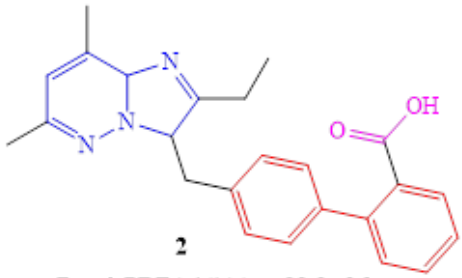
A, B= Biaryl Group (e.g.; biphenyl)

Y= Acid Group (e.g.; tetrazole, carboxylate, cyano etc.)



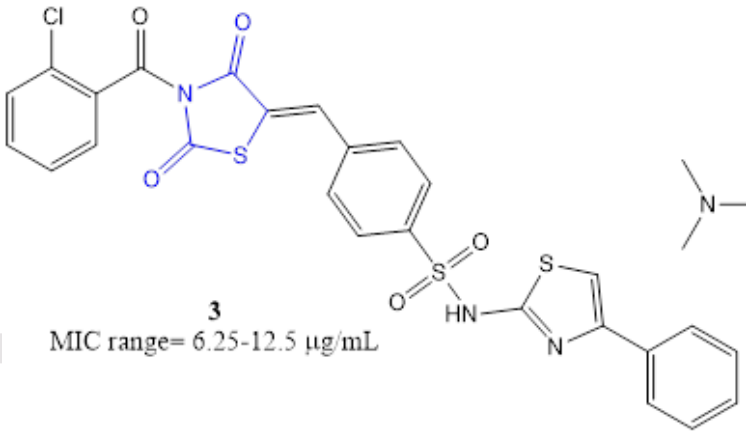
1

E. coli PDF inhibition: 3.9 μM



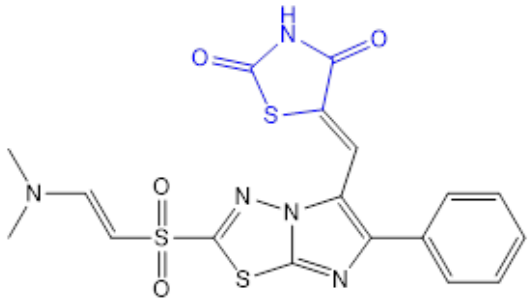
2

E. coli PDF inhibition: 22.8 μM



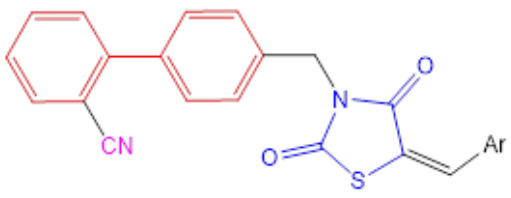
3

MIC range= 6.25-12.5 μg/mL

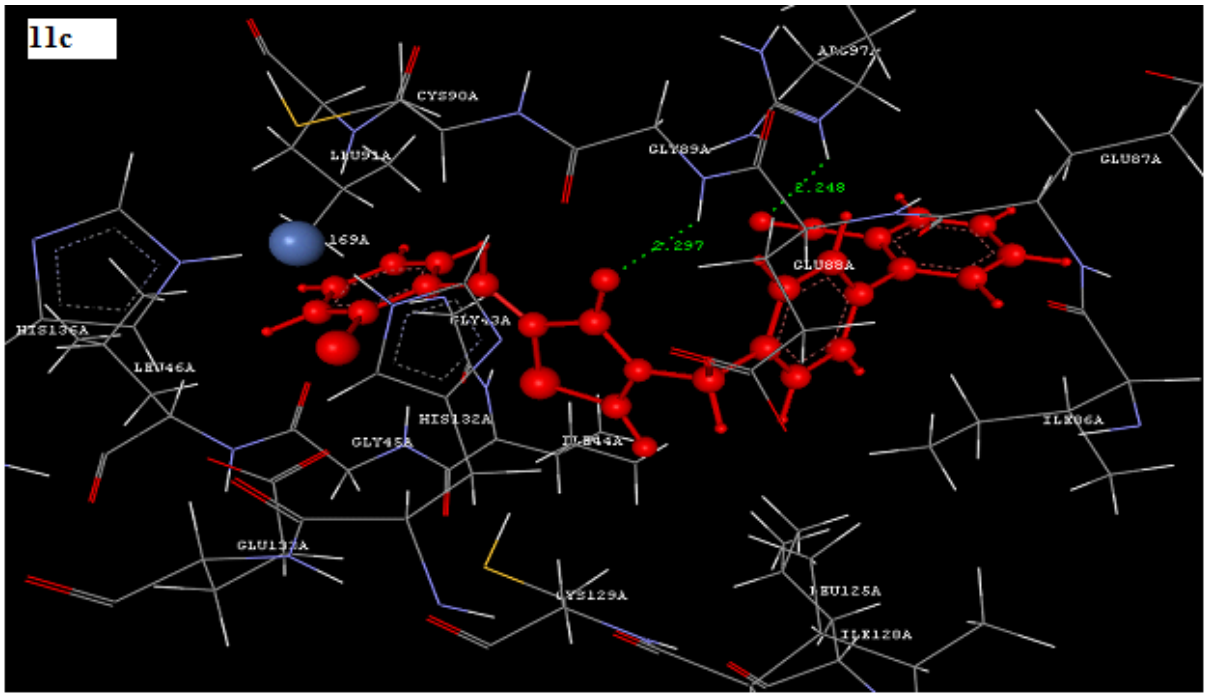


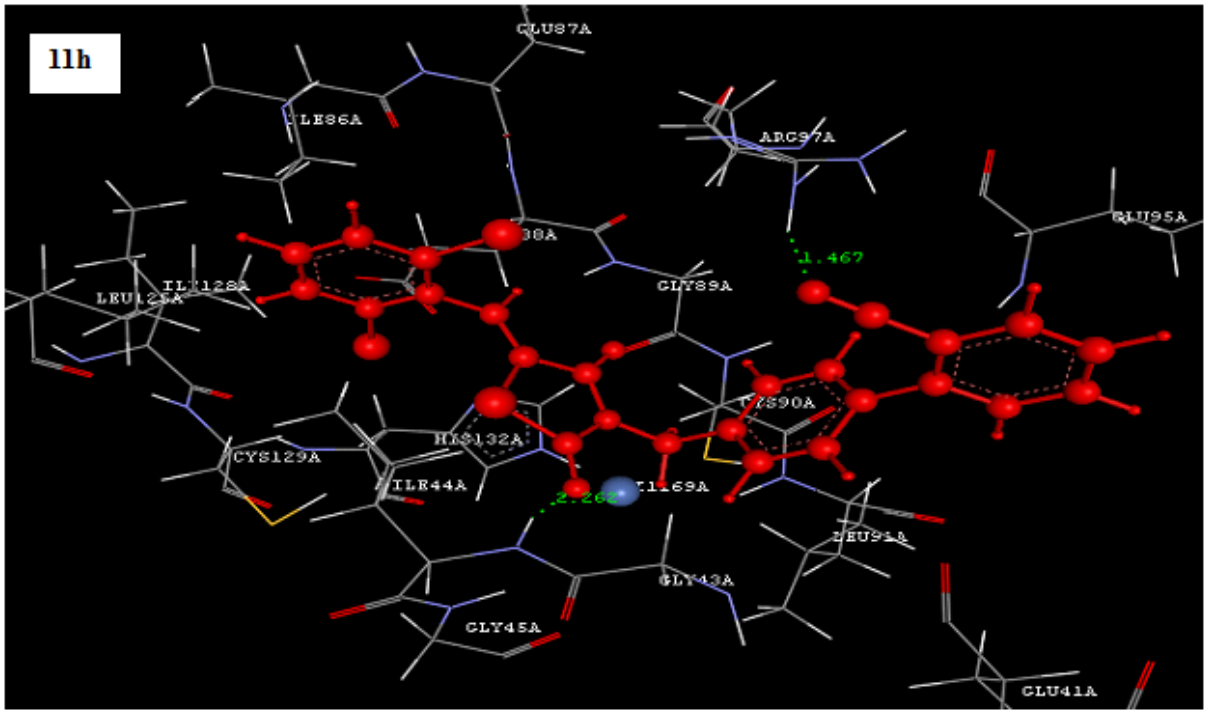
4

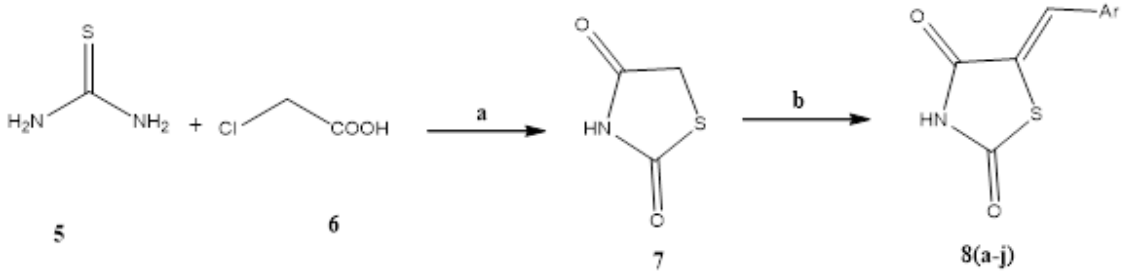
MIC range= 6.25-12.5 μg/mL



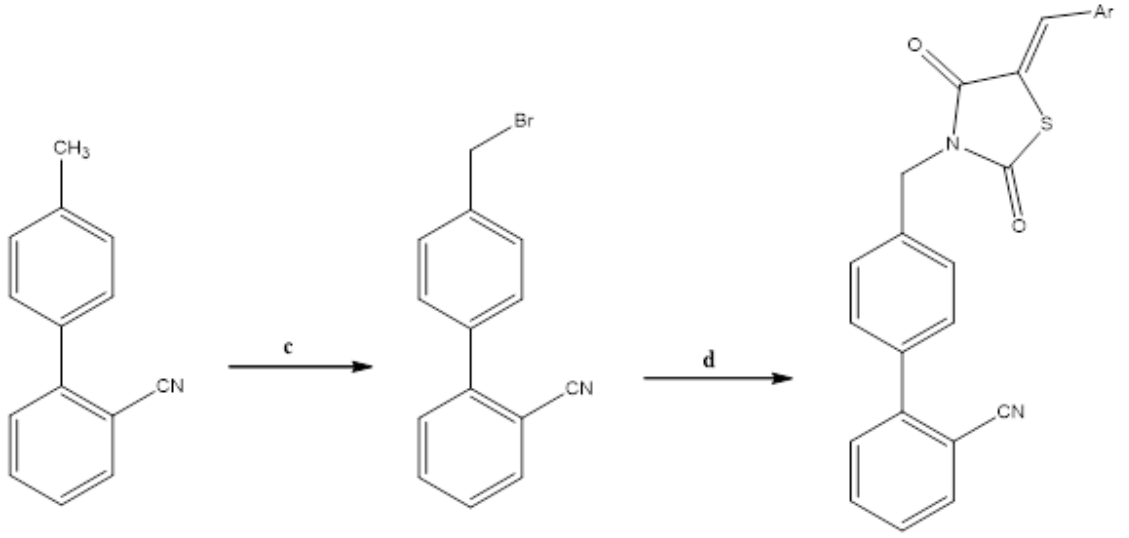
Synthesized biphenyl-thiazolidinediones **11(a-j)**





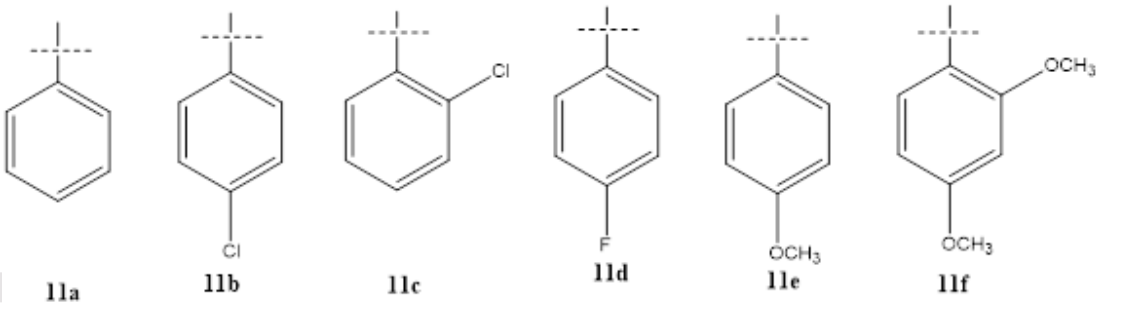


5 6 7 8(a-j)

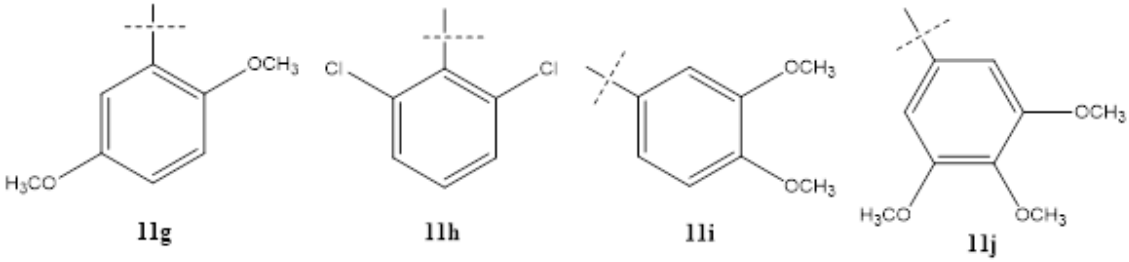


9 10 11(a-j)

Where Ar=



11a 11b 11c 11d 11e 11f



11g 11h 11i 11j