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DESIGN, SYNTHESIS, CHARACTERIZATION, AND ANTI-MICROBIAL AND INFLAMMATORY ACTIVITY OF NOVEL 3-CHLORO-2-OXO-4-SUBSTITUTED PHENYLAZETIDINONE AND 2-SUBSTITUTED PHENYLTHIAZOLIDINONE-1, 8-NAPHTHALIMIDE DERIVATIVE SPACERS

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Abstract: A series of novel 1, 8-naphthalimide-3-Chloro-2-azetidinones and 4-thiozolidinones *via* corresponding Schiff bases,Theseare synthesized from2-(4-aminophenyl)-1*H*-benzo[*de*] isoquinoline-1, 3(2*H*)dione andvarious aryl aldehydes were novel analogues synthesized and pursuing our recent interest regarding antimicrobial and anti-inflammatory activities. All the synthesized compounds show excellent anti-inflammatory activity against both MMP-2 and MMP-9 gelatinase zymography, whereas considerable good activity against Gram-positive and Gram-negative bacterial strains and antifungal activity. Moreover all the synthesized compounds were docked against1JXA -Glucosamine-6-phosphatsynthese: Co-crystal, 3LPS-Topoisomerase IV,3TTZ–Gyrase enzymes.

Key words: 1, 8-Naphthalimides, Schiff bases, 3-Chloro-2-azetidinones, 4-Thiozolidinones, antimicrobial, anti-inflammatory, molecular docking.

Introduction:1, 8-Naphthalimide derivatives are important class of heterocyclic compounds because of use in medicinal and agro chemistry as active agents. 1, 8-naphthalimide derivatives (NIs) are groups of aromatic compounds that have generated intense interest for a number of years due to their diverse applications in the medicinal and environmental sciences [i, ii].Naphthalimides one type of cyclic imides with strong hydrophobicity and desirable largeπ-conjugated backbone could easily interact with various active targets in biological systems via non-covalent forces such as π– π stacking and exhibit diverse biological activities which includes anticancer [iii],Antibacterial[iv], antitrypanosoma[v], analgesic[vi], anti-conceptive potency[vii] etc. Moreover, it has been shown that naphthalimides act both as effective DNA intercalating agents, and potent topoisomerase II inhibitors. This has resulted in the wide-ranging applications of NI-based molecules for the development and design of new antitumor drugs[viii], they have exhibited a variety of beneficial biological activities include that antiviral[ix], anti-inflammatory[x],antimalarial[xi], antitubercular[xii], fungicidal[xiii], anticonvulsant[xiv], antimitotic[xv], tyrosine inhibitory[xvi], cytotoxic[xvii],and anti-HIV[xviii], Promoted by these findings and as a part of our current

research interest in the synthesis of 1,8-Naphthalimides derivatives as potential antimicrobial agents, We determined to prepare the small molecules having two biological moieties in one structural framework i.e., 3-chloro-2-azidititidinones/4-thiazolidinones and 1,8-Naphthalaimides with aryl spacers. The synthesis of 3-chloro-2-azidititidinones/4-thiazolidinones proceeds via corresponding Schiff bases (**Scheme-1**). These newly synthesized compounds were screened for their antimicrobial activities shown in **Fig.1**

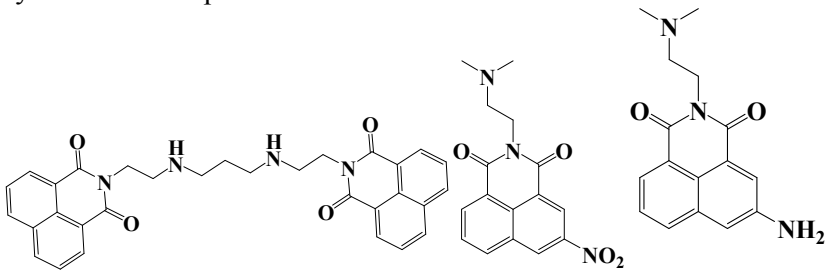
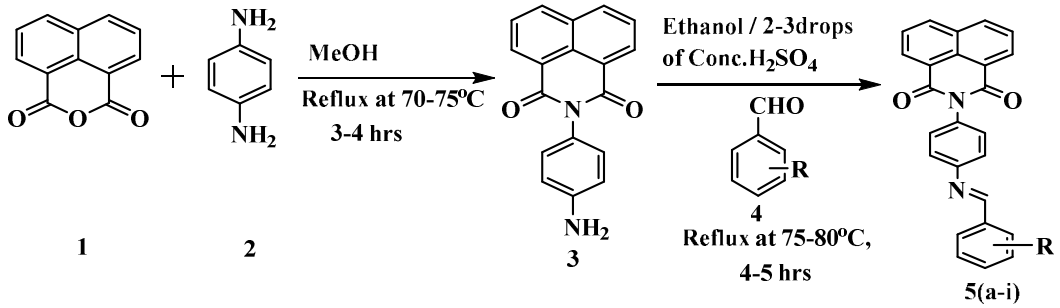


Fig.1: Structures of medicinally important substituted 1, 8- naphthalimide derivatives.

Results and Discussion:

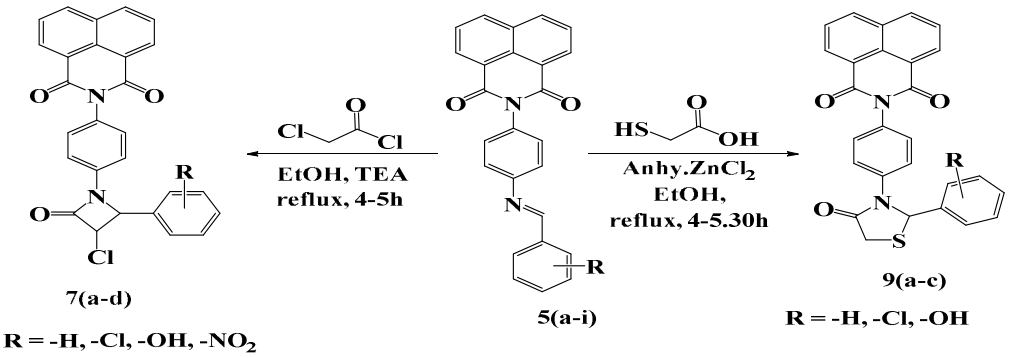
Chemistry:

The aim of present work was to synthesize new 3-Chloro-2-aziditdiones / 4-thiazolidinones from 1,8-naphthalimides with aryl spacers. In the first step the 1,8-naphthalic anhydride were treated with 1,4- phenylenediamineto produce corresponding compound **3**, which is in turn reacted with various aryl aldehydes under acid catalyzed condition to afford the corresponding Schiff bases (5**a-i**)(**Scheme-I**).



(5a–i): R=a)-H, b)2-OH, c)2-Cl, d)4-Cl, e)4-NO_2, f)3-NO_2, g)4-OMe,h) 3,4-$(OMe)_2$, i)4-Me
Scheme-I. Synthesis of novel(*E*)-2-(4-((substituted benzylidene)amino)phenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-diones(5**a-i**).

The (*E*)-2-(4-((substituted benzylidene)amino)phenyl)-1*H*-benzo[*de*] isoquinoline-1,3(2*H*)-diones (5**a-i**)on treatment with chloroacetyl chloride in the presence of triethylamine (TEA) gives corresponding 3-chloro-2-azetdiones (**7a-b**), whereas upon reaction with thioglycolic acid in the presence of $ZnCl_2$ produced corresponding 4-thiazolidinones (**9a-b**) (**Scheme-II**).1, 8-Naphthalimide derivatives, we have synthesized a series of 1, 8-Naphthalimide - linked Schiff's bases, azitidinones and thiazolidinones with high purity. The newly synthesized compounds were characterized by FT-IR, ^{1}H-NMR, ^{13}C NMR, and Mass spectroscopy.



Scheme-II. Synthesis of 2-(4-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) phenyl)-1*H*-benzo [*de*]isoquinoline-1,3(2*H*)-diones (**7a-b**) and synthesis of 2-(4-(2-(substituted phenyl)-4-oxothiazolidin-3-yl)phenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-diones (**9a-b**).

Biological screening

In vitro *anti-inflammatory activity*

All newly synthesized compounds **5(a–j), 7(a-b)** and **9(a-b)**were screened for their *in vitro* anti-inflammatoryactivity against matrix metalloproteinases (MMPs) family such as MMP-2 andMMP-9 using gelatin gemography. The *in vitro* anti-inflammatory activity results ofMMP-2 and MMP-9 gelatinase detection as clear white band over deep blue backgroundafter staining. The percentage of band was calculated from the percentage inhibition valuesof each screened samples from the gel electrophoresis method. Results of synthesized**5(a–j), 7(a-b)** and **9(a-b)** compounds are summarized in **Table 1**against both MMP-2 and MMP-9.The anti-inflammatory activity of synthesized compounds is compared with marketedstandard drug molecule tetracycline. Compounds**5c-d**, **7b** and **9b** (-Cl substitution contains 1, 8- naphthalimide derivatives)and**5e-f**, **7a** and **9a**(-NO_2substituted 1, 8-naphthalimide derivatives)are found to be highly active against MMP-2; they showed 90% inhibitionand tetracycline exhibited 95% inhibition, -NO_2 substitution of 1, 8-naphthalimide derivatives) show inhibition 82 and 75%,respectively, against MMP-2.

Table 1. The *in vitro* anti-inflammatory result of compounds **5(a-i), 7(a-b), 9(a-b).**

Entry	Product code	% Band of MMP		% Inhibition of MMP	
		MMP-2	MMP-9	MMP-2	MMP-9
1	**5a**	40	30	54	40
2	**5b**	35	55	39	28
3	**5c**	30	28	41	30
4	**5d**	29	35	**82**	**85**
5	**5e**	44	100	**88**	**88**
6	**5f**	21	60	**85**	**87**
7	**5g**	18	50	52	20
8	**5h**	14	100	45	25
9	**5i**	17	10	44	45
10	**7a**	18	15	**87**	**85**
11	**7b**	13	25	**89**	**87**
12	**9a**	11	12	**88**	**88**
13	**9b**	25	13	**90**	**89**

Tetracycline	–	00	00	95	90
DMSO	–	–	–	–	–

*Bold numbers are approximately equal active.

However,Compounds**5(a–e)**, **7(a-b)** and **9(a-b)**are moderately active or evensome compounds are not found active against MMP-9, whereas standard drug tetracyclineshowed 90% inhibition against MMP-9. Interestingly, substitution on1, 8-naphthalimide nucleus of all the synthesized scaffolds **5(f–i)** is exhibited promisinginhibition against MMP-9, which is very close to standard drug molecule tetracycline.Form the anti-inflammatory results, we confirmed that substitution on naphthalimide nucleus show promising activity against both matrix metalloproteinases(MMP-2 and MMP-9), similar to drug molecule tetracycline. In anti-inflammatory activity against MMP-2 and MMP-9.

In vitro *antibacterial activity*

All the 1, 8-naphthalimide derivatives**5(a-i), 7(a-b), 9(a-b)**, were screened for their *in vitro* antibacterialactivity by agar well diffusion method, against Gram-positive bacteria such as *Bacillus subtilis* and *Bacillus megaterium,* and Gram-negative bacteria such as *E.coli* and *Pseudomonas aeruginosa*. All the compounds showed significant antibacterialactivity against all the tested microorganisms compared with standard Streptomycin,and compounds showed MIC values range from 50–100 μg/mL, whereas MIC valueof standard drug streptomycin showed at 12.5 μg/ml. For some of the compounds, the zoneof inhibition (ZOI) ranges from 8 to 15 mm, whereas the standard streptomycin exhibitedthe zone of inhibition of 20 mm.Compounds **7a, 7b,9a** and **9b**showed maximum zone of inhibition (ZOI) against Grampositive*B. subtilis*bacterial strains and compounds **7a, 7b,9a** and **9b**against *B.megaterium*bacterial strain. Most of the compounds exhibited maximum zone of inhibition (ZOI).

Table 2. The *in vitro* anti-bacterial result of compounds **5(a-j), 7(a-b), 9(a-b)**(MIC/ZOI).

Product code	Bacterial strain				Bacterial strain			
	Gram(+)				Gram(-)			
	B.subtilis		*B. megaterium*		E.coli		P.aeruginosa	
	ZOI	MIC	ZOI	MIC	ZOI	MIC	ZOI	MIC
5a	2	-	2	300	8	50	1	-
5b	5	-	-	250	13	100	2	-
5c	1	250	3	-	2	300	1	200
5d	1	-	4	200	7	250	4	-
5e	5	300	5	300	5	300	7	**300**
5f	15	100	4	200	2	-	1	**200**
5g	9	50	8	300	15	50	4	-
5h	3	200	1	-	3	150	1	200
5i	4	100	1	-	3	-	2	300
7a	9	300	8	200	8	300	3	-
7b	2	200	10	100	6	300	2	**200**
9a	1	200	2	300	1	100	2	**300**
9b	1	-	2	-	3	300	2	**300**
Streptomycine	20	12.5	20	12.5	21	12.5	20	12.5

*Bold numbers are approximately equal active; ZOI=zoneof inhibition; MIC= minimum inhibition concentration.

In vitro *antifungal activity*

Anti-fungal activities were screened for all the synthesized 1, 8-naphthalimide derivatives Byusing agar well diffusion method, against fungal organisms *Aspergillus niger*and *Pencillium notatum*. All these compounds showed significant antifungal activity against tested microorganisms compared with standard Ketoconazole minimum inhibitory concentration (MIC) (µg/mL) of allcompounds against*A. Niger* and *P. Notatum*zone of inhibition (ZOI) (mm) of all compounds against *B. subtilis, B. megaterium, E.coli*, and*P. aeruginosa*.

Table 3. Antifungal activity of compound 5(a-i), 7(a-b), 9(a-b).

Minimum inhibitory concentrations (MIC µg/mL)		
Product code	A. niger	P. notatum
5a	-	50
5b	>100	100
5c	50	**100**
5d	25	**>100**
5e	50	**100**
5f	>100	**>100**
5g	50	50
5h	-	100
5i	100	100
7a	-	**>100**
7b	100	**>100**
9a	50	**50**
9b	50	**>100**
Ketoconazole	3.125	3.125

*Bold numbers are approximately equal active; MIC= minimum inhibition concentration.

Docking studies

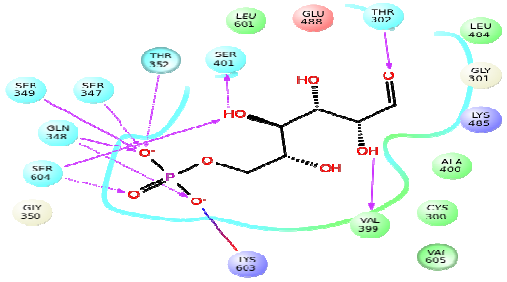
The molecular docking studies shows that most of the compounds designed are showing score compare to corresponding ligands (**Table-4**). In the case of 1JXA – Glucosamine-6-phospatsynthese the compound **3** and **7a** is showing the good docking score. The compounds **7a** and **9b** are exhibiting the higher docking score with compare to the corresponding ligand 3LPS-Topoisomerase IV. In the case of 3TTZ–Gyrase the compounds **9a** are showing higher docking scores.(**Fig. 2**)

Table 4: The docking scores of the selected compounds

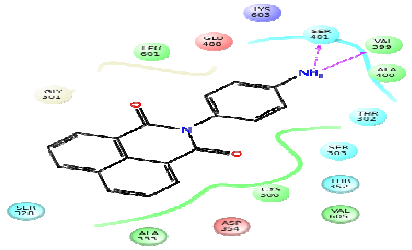
S.No.	**Ligand Entry ID**	**Docking score**
	1JXA -Glucosamine-6-phosphatsynthese	
1	Cocrystal	-6.505
2	**3**	-5.116
3	**7a**	-4.783
	3LPS-Topoisomerase IV	
1	Cocrystal	-3.404
2	**9b**	-5.174
3	**7a**	-4.937
	3TTZ- Gyrase	
1	Cocrystal	-7.978

2	**9b**	-7.003
3	**9a**	-6.989

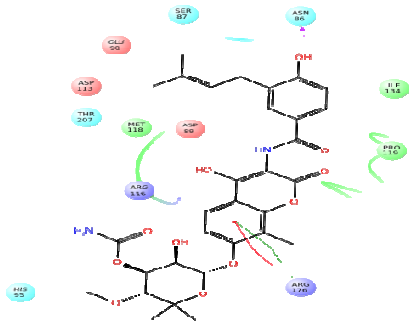
Fig. 2.Diagrams of docking studies of top score compounds with their representative Co-crystals.



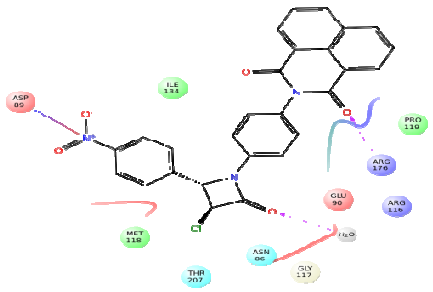
1JXA -Glucosamine-6-phosphatsynthese: Co-crystal



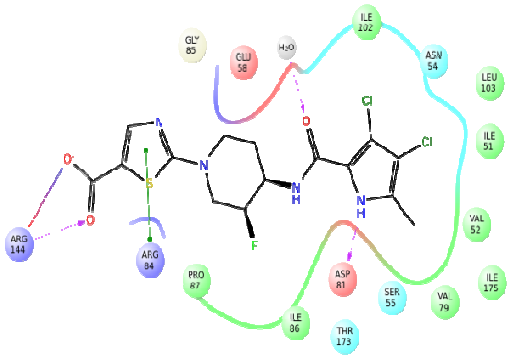
Compound 3



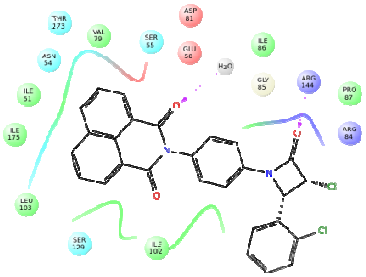
3LPS-Topoisomerase IV: Co-Crystal



Compound 7a



3TTZ- Gyrase: Co-crystal



Compound 9b

Experimental

Materials and method

All the reagents were obtained commercially of analytical grade and used without further Purification unless otherwise stated. The melting points were determined by open capillary method. The IR spectra (KBr) were recorded on a Shimadzu FT-IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on bruker 400 MHzspectrometer using DMSO-d6 as solvent and tetramethylsilane (TMS) as an internal standard,and the chemical shifts are expressed in ppm (δ-scale). The mass spectra wererecorded using Agilent- single Quartz

2-(4-aminophenyl)-1H-benzo[de] isoquinoline-1,3(2H)-dione (3)

A mixture of 1, 8-naphthalic anhydride (0.01mmol) and 1, 4-diaminobenzene (0.02mmol) in methanol (20mL) reflux at 70-75^{O}C for 3-4h after the completion of reaction mixture was filtered. The filtrate to get solid. The resultant solid product was recrystallized with ethanol to give compound.

Colour: yellowish powder;yield:70%; mp: 294-296^{o}C.; IR (KBr, cm^{-1}): 3417, 3347 (NH); 3049 (Ar-H); 1654 and 1678 (C=O); 1586 (C-N); 779 (Ar-H); ^{1}H-NMR(500MHz, $CDCl_3$): δ= 8.65(d, *J*=8.0 Hz, 2H), 8.26(d, *J*=8.2 Hz, 2H), 7.82-7.75(m,2H), 7.08(d ,*J*=8.6 Hz,2H), 6.83 (d ,*J*= 9.5 Hz, 2H) 3.74(s,2H); ^{13}C-NMR(126 MHz, $CDCl_3$): δ= 158.8, 158.6, 142.2, 137.6, 137.8, 130, 129.7, 128.4, 125.8, 125.9, 123.7, 122.4, 122.6, 116.6, 116.7; Mass (ESI) m/z: 289.134 [M+, 100%]; Anal. Calcd For :$C_{18}H_{12}N_2O_2$, C, 62.69; H, 3.51; N, 13.92, found C, 62.89; H, 3.71; N, 13.92%.

General Procedure for the Synthesis of (E)-2-(4-(benzylideneamino) substituted phenyl)-1H-benzo [de] isoquinoline-1,3(2H)-dione 5(a-i).

Synthesis of 2-(4-aminophenyl)-1*H*-benzo [*de*] isoquinoline-1,3 (2*H*)-dione (**3**) from Naphthalic anhydride (**1**) react with 1,4-diamino benzene (**2**) in the presence of methanol reflux for 4h which in turn prepared(*E*)-2-(4-(benzylideneamino) substituted phenyl)-1*H*-benzo [*de*] isoquinoline-1,3(2*H*)-diones (**5a-i**) from 2-(4-aminophenyl)-1*H*-benzo [*de*] isoquinoline-1,3 (2*H*)-dione (**3**) with the substituted aromatic aldehydes (**4**) in the presence of ethanol under acidic medium reflux for 5h. The residue was purified by recrystallization using ethanol to obtain the pure product.

(E)-2-(4-(benzylideneamino)phenyl)-1H-benzo[de] isoquinoline-1,3(2H)-dione(5a)

Colour: Brown powder;Yield: 65%; m.p: 348-350^{o}C.; IR (KBr, cm^{-1}): 3427 (NH); 2922, 2852 (Ar-H); 1682 (C=O); 1584 (C=N); 772 (Ar-H); ^{1}H-NMR (500MHz, $CDCl_3$) : δ=8.74 (s, 1H); 8.21 (d, *J* = 7.4 Hz, 2H), 8.05 (d, *J* = 7.1 Hz, 2H), 7.93 (t, 2H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 2H), 6.94 (t, 3H).;Mass (ESI) m/z: 377[M+, 100%]; Anal. Calcd For : $C_{25}H_{16}N_2O_2$; C, 79.77; H, 4.28; N, 7.44; O, 8.50, found C, 79.79; H, 4.29; N, 7.48; O, 8.55% .

(E)-2-(4-((2-hydroxybenzylidene)amino)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (5b)

Colour: White powder;Yield 60%; m.p: 275-277 ^{o}C.;IR (K Br, cm^{-1}): 3422 (NH); 2922 (Ar-H); 1647 (C=O); 1584 (C=N).; ^{1}H-NMR (500MHz, $CDCl_3$) : δ= 8.82 (s, 1H); 8.51 (d, *J* = 7.6 Hz, 2H), 8.30 (d, *J* = 6.8 Hz, 2H), 7.85 (t, 2H), 7.79 (d, *J* = 6.6 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 7.1 Hz, 2H), 7.39 (t, 1H), 7.25 (t,1H), 7.15 (d, *J* = 6.8 Hz, 1H), 5.48 (s,1H).; Mass (ESI) m/z: 377 [M+, 100%]; Anal. Calcd For : $C_{25}H_{16}N_2O_3$; C, 76.52; H, 4.11; N, 7.14; O, 12.23 found C, 76.56; H, 4.19; N, 7.18; O, 12.27% .

(E)-2-(4-((2-chlorobenzylidene) amino) phenyl)-1H-benzo[de] isoquinoline-1,3(2H)-dione (5c)

Colour: Grey powder;Yield 63%; m.p: 284-286 ^{o}C.; IR (K Br, cm^{-1}): 3424 (NH); 2923 (Ar-H); 1663 (C=O); 1570 (C=N);772 (Ar-H).; ^{1}H-NMR (500MHz, $CDCl_3$) : δ= 8.79 (s, 1H); 8.54 (d, *J* = 7.8 Hz, 2H), 8.33 (d, *J* = 6.2 Hz, 2H), 7.88 (t, 2H), 7.72 (d, *J* = 6.2 Hz, 2H), 7.68 (d, *J* = 7.0 Hz, 1H), 7.46 (d, *J* = 6.5 Hz, 2H), 7.35 (d, *J* = 7.1 Hz, 1H), 7.28 (t,1H), 7.20 (t, 1H).; Mass (ESI) m/z: 411.11[M+, 100%]; Anal. Calcd For : $C_{25}H_{16}ClN_2O_2$; C, 73.08; H, 3.68; Cl, 8.63; N, 6.82; O, 7.79 found C, 73.28; H, 3.78; Cl, 8.73; N, 6.84; O, 7.82% .

(E)-2-(4-((4-chlorobenzylidene) amino)phenyl)-1H-benzo[de] isoquinoline-1,3(2H)-dione (5d)

Colour: Grey powder;Yield 63%; m.p: 286-288 ^{o}C.; IR (K Br, cm^{-1}): 3429 (NH); 2928 (Ar-H); 1674 (C=O); 1576 (C=N); 775 (Ar-H).; ^{1}H-NMR (500MHz, $CDCl_3$) : δ= 8.81 (s, 1H); 8.62 (d, *J* = 7.4 Hz, 2H), 8.41 (d, *J* = 6.4 Hz, 2H), 7.92 (t, 2H), 7.82 (d, *J* = 6.6 Hz, 2H), 7.58

(d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 6.8 Hz, 2H), 7.48 (d, *J* = 6.8 Hz, 2H).; Mass (ESI) m/z: 411.11[M+, 100%]; Anal. Calcd For : $C_{25}H_{16}ClN_2O_2$; C, 73.08; H, 3.68; Cl, 8.63; N, 6.82; O, 7.79 found C, 73.28; H, 3.78; Cl, 8.73; N, 6.84; O, 7.82% .

(E)-2-(4-((4-nitrobenzylidene)amino)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (5e)

Colour: Light brown powder;Yield 58%; m.p: 343-345^oC.;IR (K Br, cm^{-1}): 3432 (NH); 2921 (Ar-H); 1626 (C=O); 1590 (C=N); 776 (Ar-H).; ^{1}H-NMR (500MHz, $CDCl_3$) : δ= 8.65 (s, 1H); 8.58 (d, *J* = 7.2 Hz, 2H), 8.34 (d, *J* = 6.6 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 2H), 7.73 (t, 3H), 7.25 (d, *J* = 8.6 Hz, 1H), 7.20 (d, *J* = 10.9 Hz, 3H), 7.01 (t,1H), 6.96 (d, *J* = 8.1 Hz, 1H).; Mass (ESI) m/z: 421.96 [M+, 100%]; Anal. Calcd For: $C_{25}H_{15}N_3O_2$; C, 71.25; H, 3.59; N, 9.97; O, 15.19 found C, 71.28; H, 3.69; N, 9.99; O, 15.29 %.

(E)-2-(4-((3-nitrobenzylidene) amino)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (5f)

Colour: Brown powder;Yield 62%; m.p: 298-300^oC.;IR (K Br, cm^{-1}): 3436 (NH); 2922 (Ar-H); 1632 (C=O); 1567 (C=N); 771 (Ar-H).; ^{1}H-NMR (500MHz, $CDCl_3$) : δ= 8.62 (s, 1H); 8.58 (s, 1H); 8.45 (d, *J* = 6.8 Hz, 2H), 8.30 (d, *J* = 6.2 Hz, 2H), 8.22 (d, *J* = 7.1 Hz, 1H), 8.18 (d, *J* = 6.7 Hz, 1H), 7.76 (t, 2H), 7.71 (t, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 8.9 Hz, 2H).; Mass (ESI) m/z: 421.96 [M+, 100%]; Anal. Calcd For: $C_{25}H_{15}N_3O_2$; C, 71.25; H, 3.59; N, 9.97; O, 15.19 found C, 71.28; H, 3.69; N, 9.99; O, 15.29 %.

(E)-2-(4-((4-methoxybenzylidene)amino)phenyl)-1H-benzo[de] Isoquinoline-1, 3(2H)-dione (5g)

Colour: Dark Yellow powder;Yield 65%; m.p: 241-243^oC.; IR (K Br, cm^{-1}): 3432 (NH); 2925 (Ar-H); 1656 (C=O); 1587 (C=N); 773 (Ar-H).; ^{1}H-NMR (500MHz, $CDCl_3$) : δ= 8.68 (s, 1H), 8.45 (d, *J* = 6.5 Hz, 2H), 8.32 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 6.4 Hz, 2H), 7.74 (t, 2H), 7.66 (d, *J* = 7.0 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 6.1 Hz, 2H), 3.88 (s, 3H).; Mass (ESI) m/z: 406.22 [M+, 100%]; Anal. Calcd For: $C_{26}H_{18}N_2O_3$; C, 76.83; H, 4.46; N, 6.89; O, 11.81 found C, 76.85; H, 4.49; N, 6.89; O, 11.86 %.

(E)-2-(4-((3, 4-dimethoxybenzylidene)amino)phenyl)-1H-benzo[de] isoquinoline-1,3(2H) dione (5h)

Colour: Pale yellow powder;Yield 55%; m.p: 246-248^oC.;IR (K Br, cm^{-1}): 3432 (NH); 2925 (Ar-H); 1656 (C=O); 1587 (C=N); 773 (Ar-H).; ^{1}H-NMR (500MHz, $CDCl_3$) : δ= 8.55 (s, 1H), 8.51 (d, *J* = 7.1 Hz, 2H), 8.28 (d, *J* = 7.5 Hz, 2H), 7.75 (t, 2H), 7.58 – 7.46 (m, 3H), 7.44 – 7.28 (m, 3H), 7.22 (d, *J* = 7.9 Hz, 2H), 3.95 (d, *J* = 6.8 Hz, 3H), 3.87 (d, *J* = 17.8 Hz, 2H).; Mass (ESI) m/z: 436.19 [M+, 100%]; Anal. Calcd For: $C_{27}H_{20}N_2O_4$; C, 74.30; H, 4.62; N, 6.42; O, 14.66 found C, 74.35; H, 4.68; N, 6.47; O, 14.69%.

(E)-2-(4-((4-methylbenzylidene)amino)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (5i)

Colourless Solid; Yield 62%; m.p: 258-260^oC.;IR (KBr, cm^{-1}): 3432 (NH); 2925 (Ar-H); 1656 (C=O); 1587 (C=N); 773 (Ar-H).; ^{1}H-NMR (500MHz, CDCl3) : δ= 8.62 (s, 1H), 8.58 (d, *J* = 7.2 Hz, 2H), 8.38 (d, *J* = 7.6 Hz, 2H), 8.12 (t, 2H), 7.96 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 6.8 Hz, 2H), 7.62 (d, *J* = 6.8 Hz, 2H), 7.44 (d, *J* = 6.4 Hz, 2H), 2.10 (s, 3H).; Mass (ESI) m/z: 390.18 [M+, 100%]; Anal. Calcd For: $C_{26}H_{18}N_2O_2$; C, 79.98; H, 4.65; N, 7.17; O, 8.20 found C, 79.98; H, 4.68; N, 7.19; O, 8.26%.

General procedure for the Synthesis of 2-(4-(2-(substituted phenyl)-4-oxothiazolidin-3-yl)phenyl)-1H-benzo[de] isoquinoline-1,3(2H)-dione 7(a-b).

The stirred compounds (**5a-i**) (0.01mol) and few drops of Triethylamine (TEA) in ethanol (50ml) was added mono chloroacetyl chloride (**6**) (0.014 mol) at 50 ^oC. The reaction mixture was stirred for 30 min at room temperature on refluxed for 6-7hours. The reaction mixture was filtered to remove triethylamine hydrochloride and the resultant solution was poured on to crushed ice with constant stirring. The solid thus obtained was recrystallized from ethanol to get compound with good yields.

2-(4-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (7a)

Colour: Yellow powder; yield 40%; m.p: 230 - 232°C.;IR (K Br, cm^{-1}): 2927 (Ar-H); 1684, 1660 (C=O).; ^{1}H-NMR 500MHz, $CDCl_3$) : δ= 8.61 (d, *J*=7.0 Hz, 2H), 8.52 (d, *J*=6.4 Hz,2H), 8.21 (d, *J*=7.8 Hz, 2H), 7.82 (t, 2H), 7.10 (d, *J*=7.4 Hz, 1H), 7.55(d, *J*=7.0 Hz, 2H), 7.34 (d, *J*=6.4 Hz, 2H), 5.52 (d, *J*= 8.2 Hz, 1H), 5.18 (d, *J*= 9.8 Hz, 2H).; Mass (ESI) m/z: 497.18 [M+, 100%]; Anal. Calcd For: $C_{27}H_{16}ClN_3O_5$; C, 65.13; H, 3.24; Cl, 7.12; N, 8.44; O, 16.07 found C, 65.33; H, 3.21; Cl, 7.22; N, 8.49; O, 16.24% .

2-(4-(3-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (7b)

Colour: Grey powder; Yield 45%; m.p: 206 – 208° C.;IR (K Br, cm^{-1}) : 3320 (Ar –H); 1690,1660 (C=O); 820 (Ar –H).;^{1}H-NMR (500MHz, $CDCl_3$): δ= 8.55 (d, *J*= 6.8 Hz, 2H), 8.38 (d, *J*=6.2 Hz, 2H), 7.82 (t, 2H), 7.54 (d, *J*=7.8 Hz,1H), 7.38 (d, *J*=6.4 Hz, 2H), 7.12 (t, 2H), 7.40 (d, *J*=7.0 HZ, 1H), 6.85 (t, 2H), 6.45 (d, *J* =7.8 Hz, 2H), 5.48 (d, *J*=9.4 Hz, 1H), 5.24 (d, *J*= 10.6 Hz, 2H).; Mass (ESI) m/z: 486.18 [M+, 100%]; Anal. Calcd For: $C_{27}H_{16}Cl_2N_2O_3$; C, 66.54; H, 3.31; Cl, 14.55; N, 5.75; O, 9.85 found C, 66.59; H, 3.36; Cl, 14.59; N, 5.78; O, 9.88 % .

General procedure for the Synthesis of 2-(4-(2-(4-substituted phenyl)-4-oxothiazolidin-3-yl) phenyl) -1H-benzo[de]isoquinoline-1,3(2H)-dione 9(a-b).

A mixture of compounds (**5a-i**) (0.01 mol) and anhydrous $ZnCl_2$ (1 pinch) in ethanol (50 mL) stirring at ambient temperature and thioglycolic acid (0.014 mol) was added with drop wise and refluxed for 8-9 h. After the completion of reaction mixture was filtered. The filtrate was concentrated and poured on crushed ice to get solid. The resultant solid product was recrystallized with methanol to give compound.

2-(4-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (9a)

Colour: Grey collared powder; Yield 40% ; m.p: 218- 220° C.; IR (K Br, cm^{-1}) ; 3224 (Ar – H), 1696, 1674 (C=O).; ^{1}H-NMR (500MHz, $CDCl_3$) : δ= 8.55 (d, *J* = 7.2 Hz, 2H), 8.42 (d, *J* = 6.8 Hz, 2H), 8.24 (d, *J* = 8.20Hz, 1H), 7.74 (t,2H), 7.68 (d, *J*=6.8 Hz, 1H), 7.35 (d, *J*= 6.8Hz, 2H), 7.16 (d, *J*= 8.0 Hz, 2H), 7.74 (t,2H), 7.68 (d, *J*= 6.8 Hz, 1H),7.35(d, *J*= 6.8 Hz, 2H), 7.16 (d, *J*=8.0 Hz , 2H), 5.18 (t, 1H), 3.62 (d, *J*= 9.6 Hz, 1H), 3.44 (d, *J*=6.6 Hz, 1H).; Mass (ESI) m/z: 496.18 [M+, 100%]; Anal. Calcd For: $C_{27}H_{17}N_3O_5S$; C, 65.45; H, 3.46; N, 8.48; O, 16.14; S, 6.47 found C, 65.55; H, 3.49; N, 8.58; O, 16.24; S, 6.49 % .

2-(4-(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (9b)

Colour: Grey collared powder; Yield: 40% ; m.p: 219- 221°C.;IR (K Br, cm^{-1}): 3224 (Ar- H); 1696, 1674 (C=O); ^{1}H-NMR 500MHz, $CDCl_3$) : δ= 8.47 (d, *J*=6.6 Hz, 2H), 8.34 (d, *J*= 6.2 Hz, 2H), 7.86 (t, 2H), 7.74(d, *J*= 7.2 Hz, 1H), 7.30 (d, *J*=6.0 Hz, 2H), 7.24 (t, 1H), 7.16 (t, 1H), 7.04 (d, *J*=7.8 Hz, 2H), 6.98 (t, 1H), 5.22 (t, 1H), 3.75 (d, *J*= 9.4 Hz, 1H), 3.48 (d, *J*= 6.2 Hz, 1H).; Mass (ESI) m/z: 484.18 [M+, 100%]; Anal. Calcd For: $C_{27}H_{17}ClN_2O_3S$; C, 66.87; H, 3.53; Cl, 7.31; N, 5.78; O, 9.90; S, 6.61 found C, 66.87; H, 3.55; Cl, 7.36; N, 5.83; O, 9.94; S, 6.68%.

Conclusions:

In conclusion, we have developed a simple synthesis of 1, 8- naphthalimide derivatives are environmentallydemonstrated the application ofsynthetic organic chemistry. The major advantage of the 3-chloro azitidinones/4-thiazolidinones synthesisof desired compounds by means of 1, 8-naphthalimide derivativesmore versatile synthetic utility is enhanced as it does notrequire any purification, and it involves a shorter workup. Furthermore, we testedthe

series of synthesized compounds to evaluate their anti-inflammatory and antimicrobialactivity. Our results have shown that among the compounds **5(a–i), 7(a-b), 9(a-b)**, -Cl, -NO_2, substituted naphthalimide derivatives showed excellent anti-inflammatory activity againstboth MMP-2 and MMP-9 gelatinase zymography, whereas antimicrobial screeningresults are not found promising against tested microorganism. The active compoundsof the series development of noveland more efficient anti-inflammatory agent. Furthermore, in molecular studies results proved that **3,7a** and **9a** compounds showed strong binding with the enzymes 1JXA -Glucosamine-6-phosphatsynthese, 3LPS-Topoisomerase IV, and 3TTZ- Gyrase Co-crystal.

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