Supplementary data

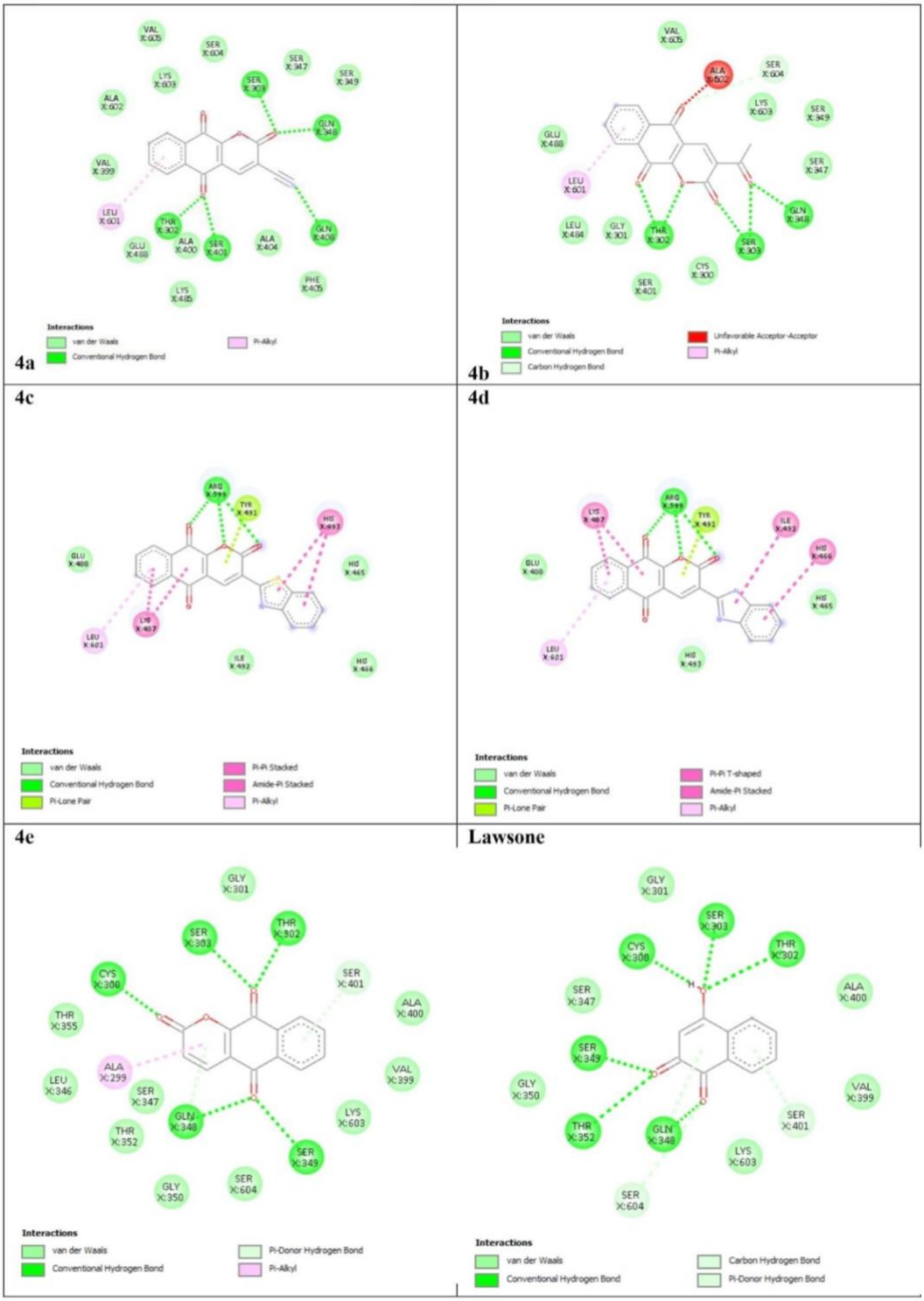
.

Correspondence to:

*Sandip Patil, Department of Chemistry (DST-FIST), MGSM's A.C.S. College, Chopda, 425107, Maharashtra, India

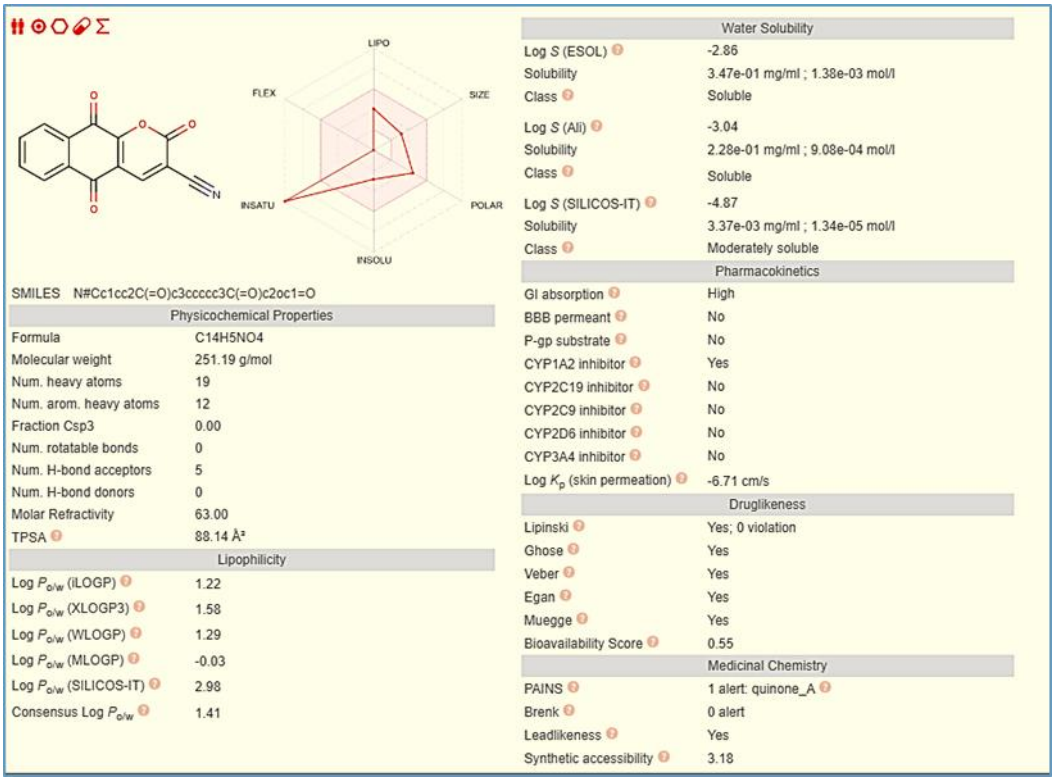
E-mail:srpatil_001@rediffmail.com

I-Molecular modelling



2D diagram of compounds **4a**, **4b**, **4c, 4d, 4e,** and **lawsone** showing their interaction with the Glucosamine-6-Phosphate Synthase enzyme (2VF5) active site.

II-Molecular properties of the coumarin derivatives (4a-4e) using SwissADME website.

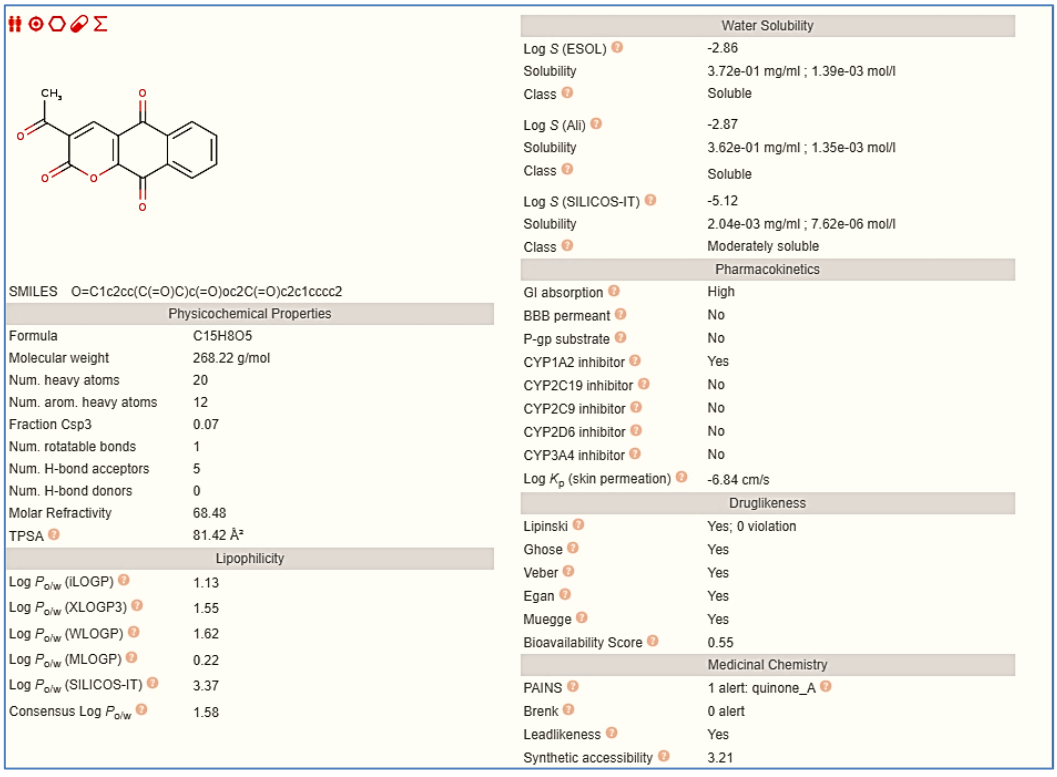


SMILES N#Cc1cc2C(=O)c3ccccc3C(=O)c2oc1=O

Physicochemical Properties	
Formula	C14H5NO4
Molecular weight	251.19 g/mol
Num. heavy atoms	19
Num. arom. heavy atoms	12
Fraction Csp3	0.00
Num. rotatable bonds	0
Num. H-bond acceptors	5
Num. H-bond donors	0
Molar Refractivity	63.00
TPSA	88.14 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.22
Log $P_{o/w}$ (XLOGP3)	1.58
Log $P_{o/w}$ (WLOGP)	1.29
Log $P_{o/w}$ (MLOGP)	-0.03
Log $P_{o/w}$ (SILICOS-IT)	2.98
Consensus Log $P_{o/w}$	1.41

Water Solubility	
Log *S* (ESOL)	-2.86
Solubility	3.47e-01 mg/ml ; 1.38e-03 mol/l
Class	Soluble
Log *S* (Ali)	-3.04
Solubility	2.28e-01 mg/ml ; 9.08e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-4.87
Solubility	3.37e-03 mg/ml ; 1.34e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.71 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: quinone_A
Brenk	0 alert
Leadlikeness	Yes
Synthetic accessibility	3.18

4a

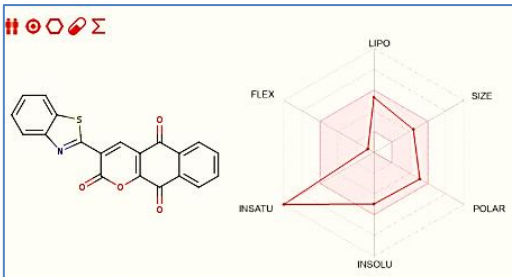


SMILES O=C1c2cc(C(=O)C)c(=O)oc2C(=O)c2c1cccc2

Physicochemical Properties	
Formula	C15H8O5
Molecular weight	268.22 g/mol
Num. heavy atoms	20
Num. arom. heavy atoms	12
Fraction Csp3	0.07
Num. rotatable bonds	1
Num. H-bond acceptors	5
Num. H-bond donors	0
Molar Refractivity	68.48
TPSA	81.42 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.13
Log $P_{o/w}$ (XLOGP3)	1.55
Log $P_{o/w}$ (WLOGP)	1.62
Log $P_{o/w}$ (MLOGP)	0.22
Log $P_{o/w}$ (SILICOS-IT)	3.37
Consensus Log $P_{o/w}$	1.58

Water Solubility	
Log *S* (ESOL)	-2.86
Solubility	3.72e-01 mg/ml ; 1.39e-03 mol/l
Class	Soluble
Log *S* (Ali)	-2.87
Solubility	3.62e-01 mg/ml ; 1.35e-03 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-5.12
Solubility	2.04e-03 mg/ml ; 7.62e-06 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.84 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: quinone_A
Brenk	0 alert
Leadlikeness	Yes
Synthetic accessibility	3.21

4b

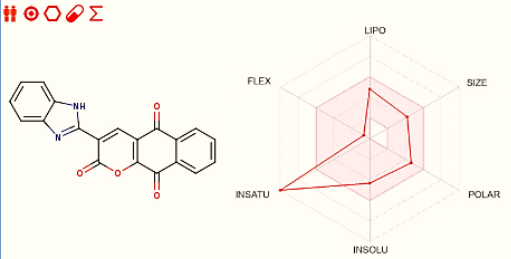


SMILES O=c1oc2C(=O)c3ccccc3C(=O)c2cc1c1nc2c(s1)cccc2

Physicochemical Properties	
Formula	C20H9NO4S
Molecular weight	359.35 g/mol
Num. heavy atoms	26
Num. arom. heavy atoms	21
Fraction Csp3	0.00
Num. rotatable bonds	1
Num. H-bond acceptors	5
Num. H-bond donors	0
Molar Refractivity	96.90
TPSA	105.48 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.46
Log $P_{o/w}$ (XLOGP3)	3.78
Log $P_{o/w}$ (WLOGP)	3.69
Log $P_{o/w}$ (MLOGP)	1.93
Log $P_{o/w}$ (SILICOS-IT)	5.61
Consensus Log $P_{o/w}$	3.50

Water Solubility	
Log *S* (ESOL)	-4.98
Solubility	3.75e-03 mg/ml ; 1.04e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.69
Solubility	7.36e-04 mg/ml ; 2.05e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.83
Solubility	5.38e-06 mg/ml ; 1.50e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.81 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: quinone_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.47

4c

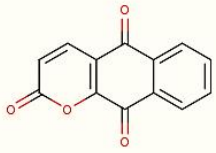


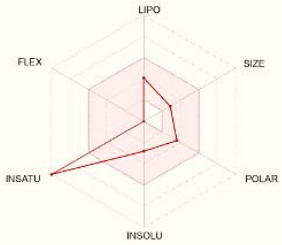
SMILES O=C1c2cc(c(=O)oc2C(=O)c2c1cccc2)c1nc2c([nH]1)cccc2

Physicochemical Properties	
Formula	C20H10N2O4
Molecular weight	342.30 g/mol
Num. heavy atoms	26
Num. arom. heavy atoms	21
Fraction Csp3	0.00
Num. rotatable bonds	1
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	93.37
TPSA	93.03 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.25
Log $P_{o/w}$ (XLOGP3)	2.89
Log $P_{o/w}$ (WLOGP)	2.96
Log $P_{o/w}$ (MLOGP)	1.53
Log $P_{o/w}$ (SILICOS-IT)	4.50
Consensus Log $P_{o/w}$	2.63

Water Solubility	
Log *S* (ESOL)	-4.31
Solubility	1.66e-02 mg/ml ; 4.85e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.50
Solubility	1.07e-02 mg/ml ; 3.13e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.78
Solubility	5.72e-06 mg/ml ; 1.67e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.34 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: quinone_A
Brenk	0 alert
Leadlikeness	Yes
Synthetic accessibility	3.33

4d





SMILES O=c1ccc2c(o1)C(=O)c1c(C2=O)cccc1

Physicochemical Properties	
Formula	C13H6O4
Molecular weight	226.18 g/mol
Num. heavy atoms	17
Num. arom. heavy atoms	12
Fraction Csp3	0.00
Num. rotatable bonds	0
Num. H-bond acceptors	4
Num. H-bond donors	0
Molar Refractivity	58.29
TPSA	64.35 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.41
Log $P_{o/w}$ (XLOGP3)	1.66
Log $P_{o/w}$ (WLOGP)	1.42
Log $P_{o/w}$ (MLOGP)	0.61
Log $P_{o/w}$ (SILICOS-IT)	2.99
Consensus Log $P_{o/w}$	1.62

Water Solubility	
Log *S* (ESOL)	-2.81
Solubility	3.50e-01 mg/ml ; 1.55e-03 mol/l
Class	Soluble
Log *S* (Ali)	-2.63
Solubility	5.36e-01 mg/ml ; 2.37e-03 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-4.79
Solubility	3.68e-03 mg/ml ; 1.63e-05 mol/l
Class	Moderately soluble

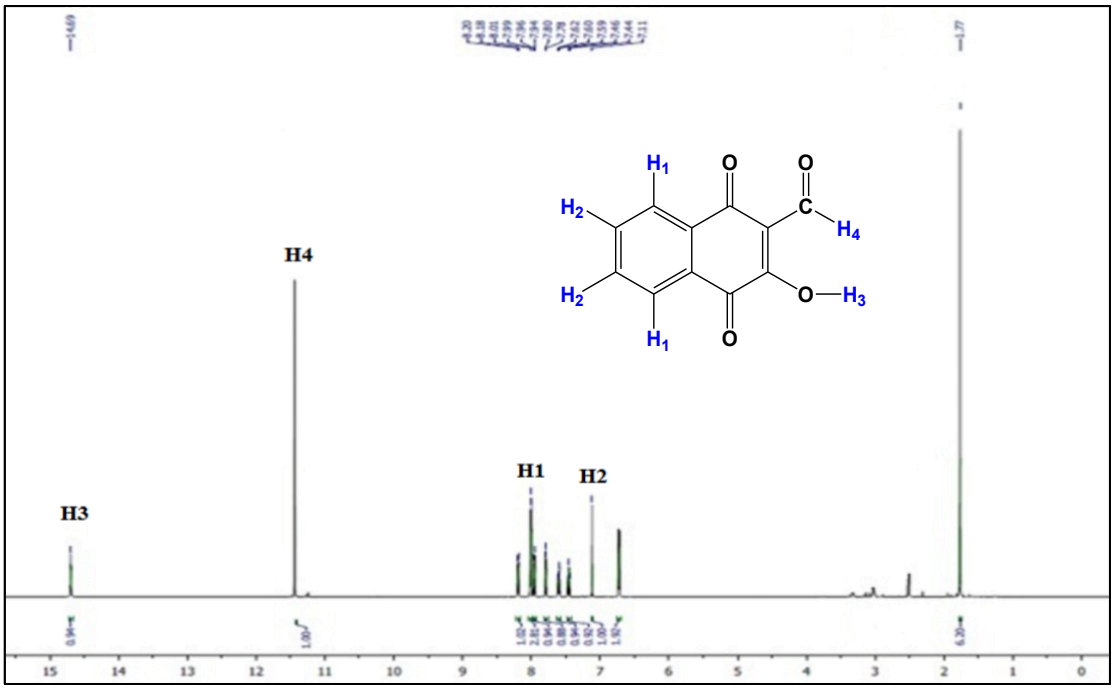
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.50 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

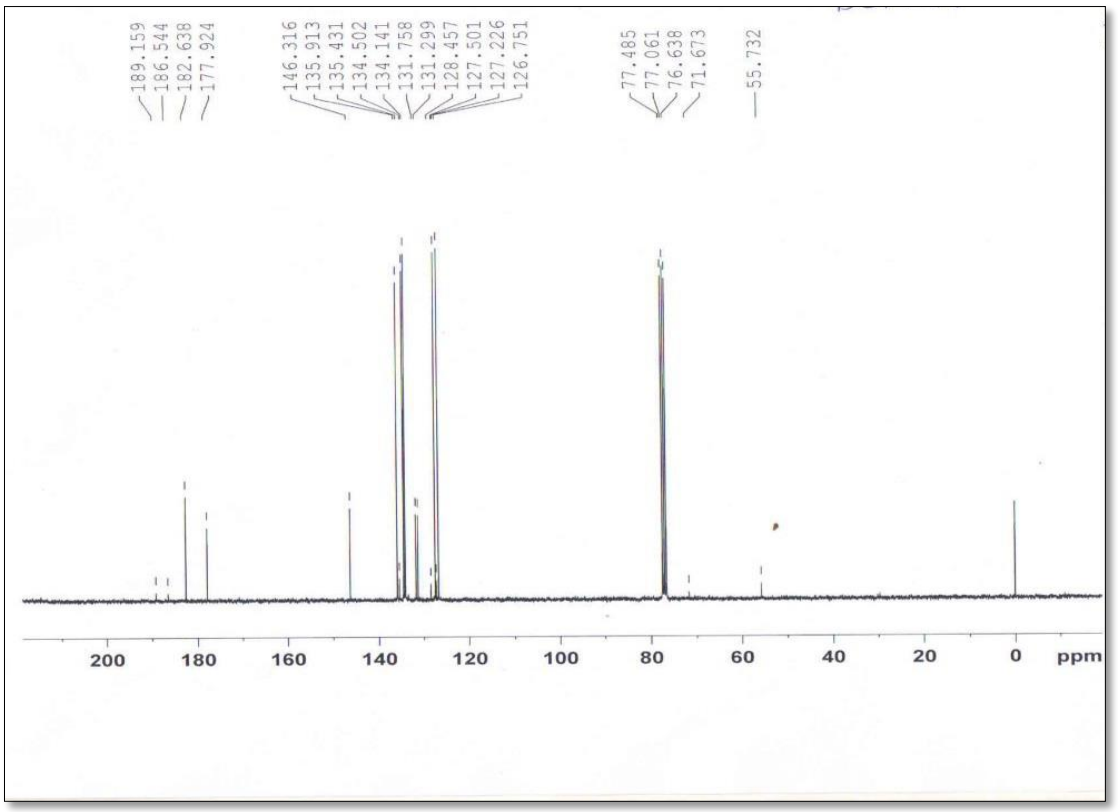
Medicinal Chemistry	
PAINS	1 alert: quinone_A
Brenk	0 alert
Leadlikeness	No; 1 violation: MW<250
Synthetic accessibility	3.02

4e

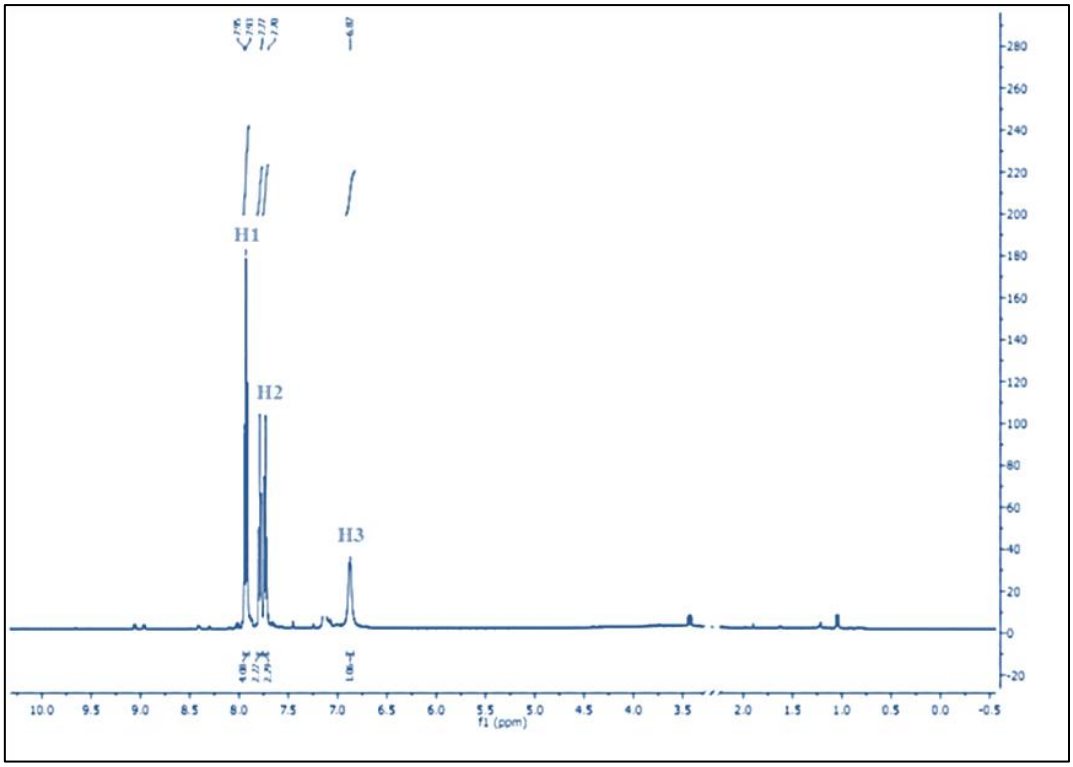
III- ^{1}H NMR and ^{13}C NMR spectra of the compounds.



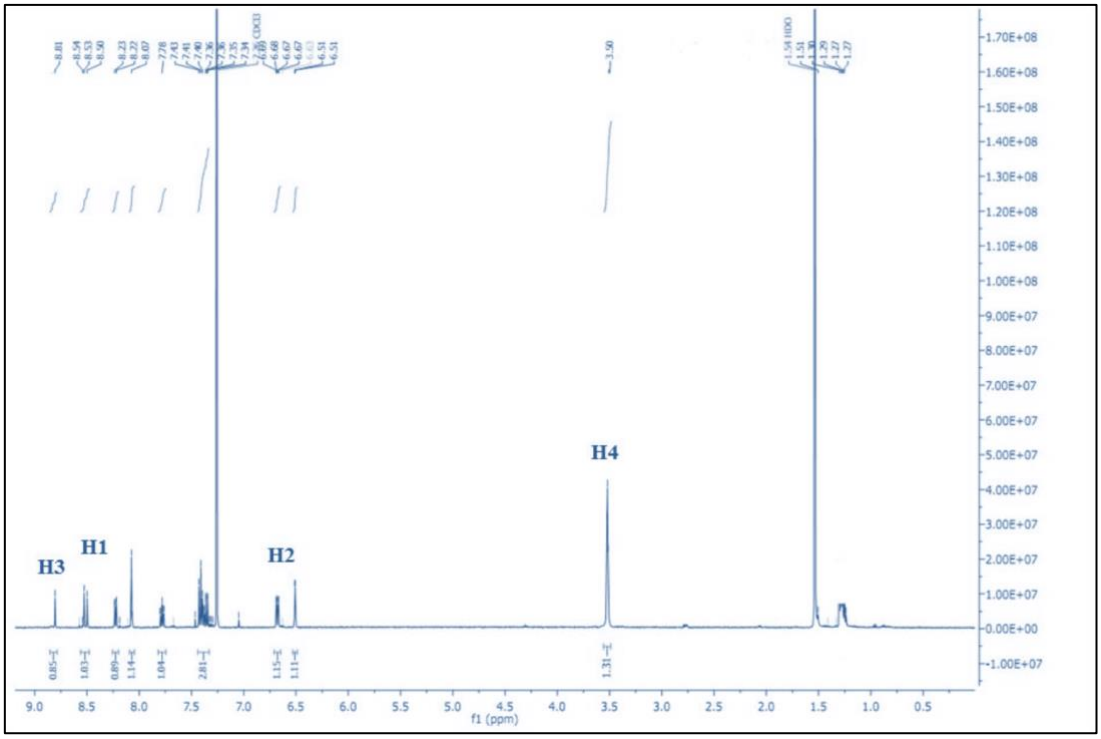
^{1}H NMR (500MHz, $CDCl_3$) of 3-Hydroxy-1, 4-dioxo-1, 4-dihydronaphthalene-2-carbaldehyde



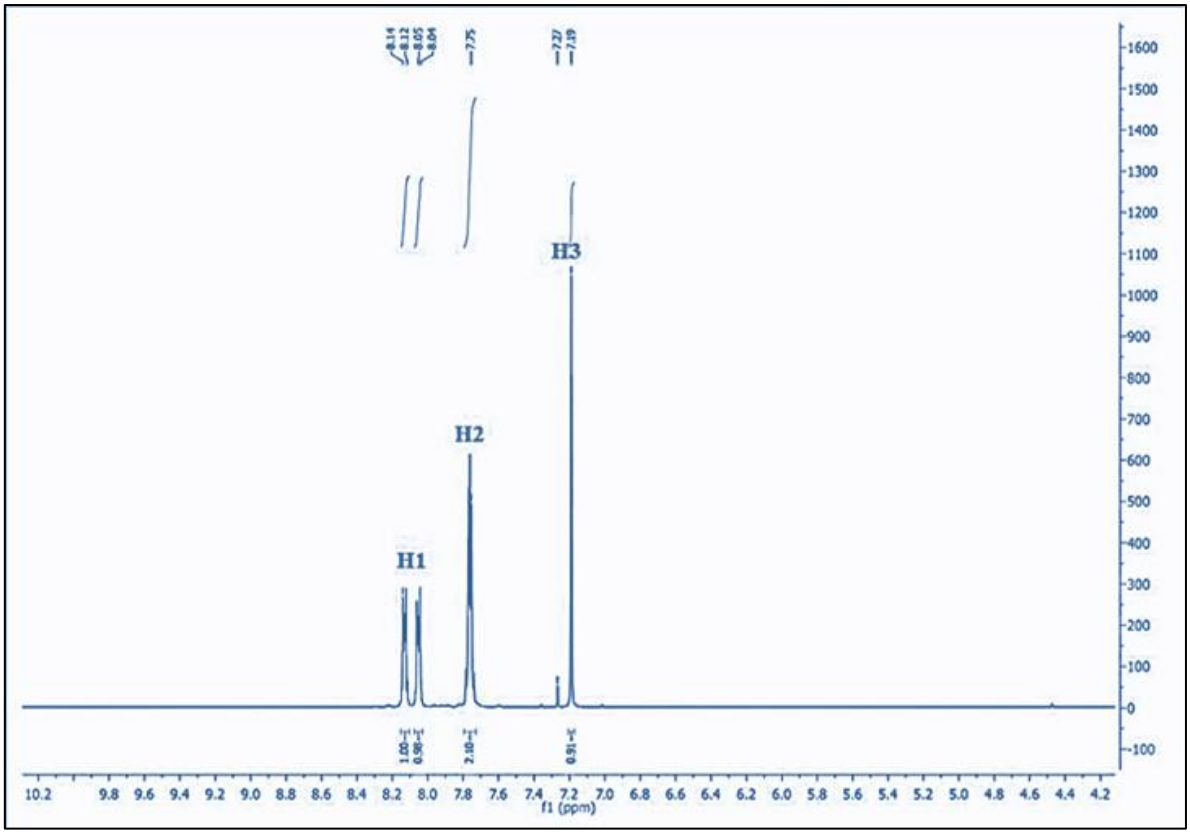
^{13}C NMR (500MHz, $CDCl_3$) of 3-Hydroxy-1, 4-dioxo-1, 4-dihydronaphthalene-2-carbaldehyde



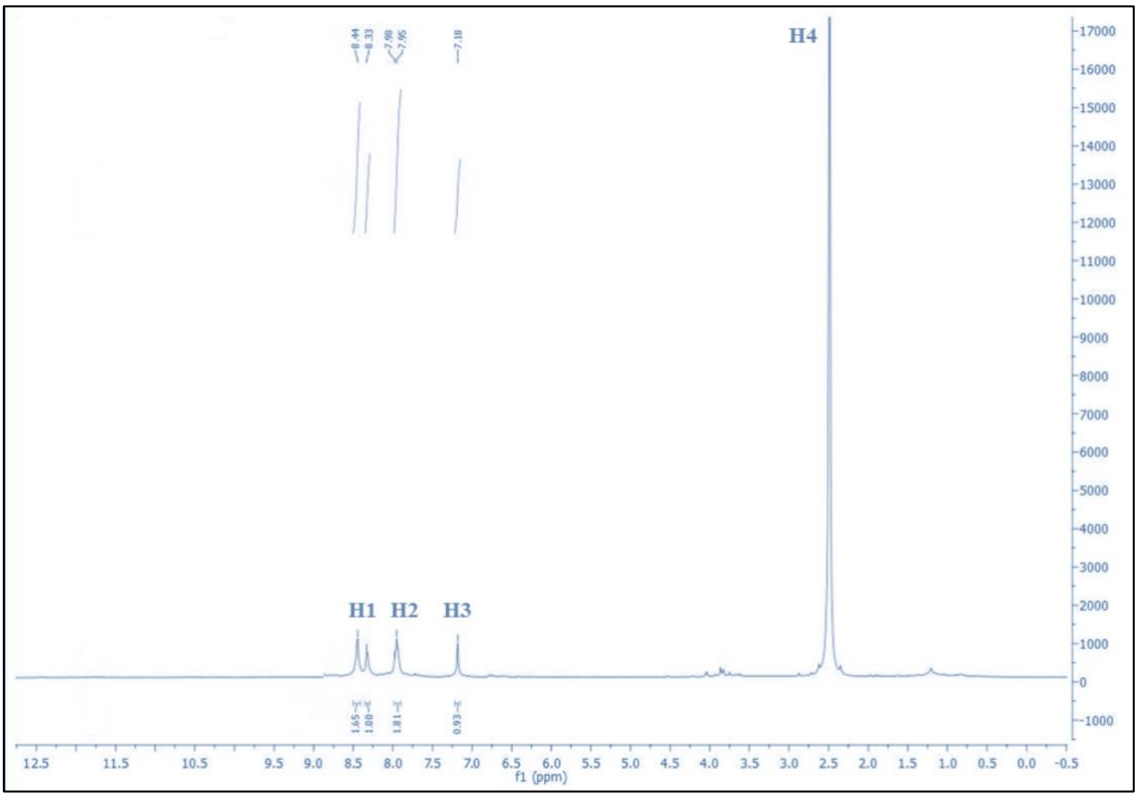
[1]H NMR spectra of 3-(Benzo[d]thiazol-2-yl)-2H-benzo[g]chromene-2, 5, 10-trione



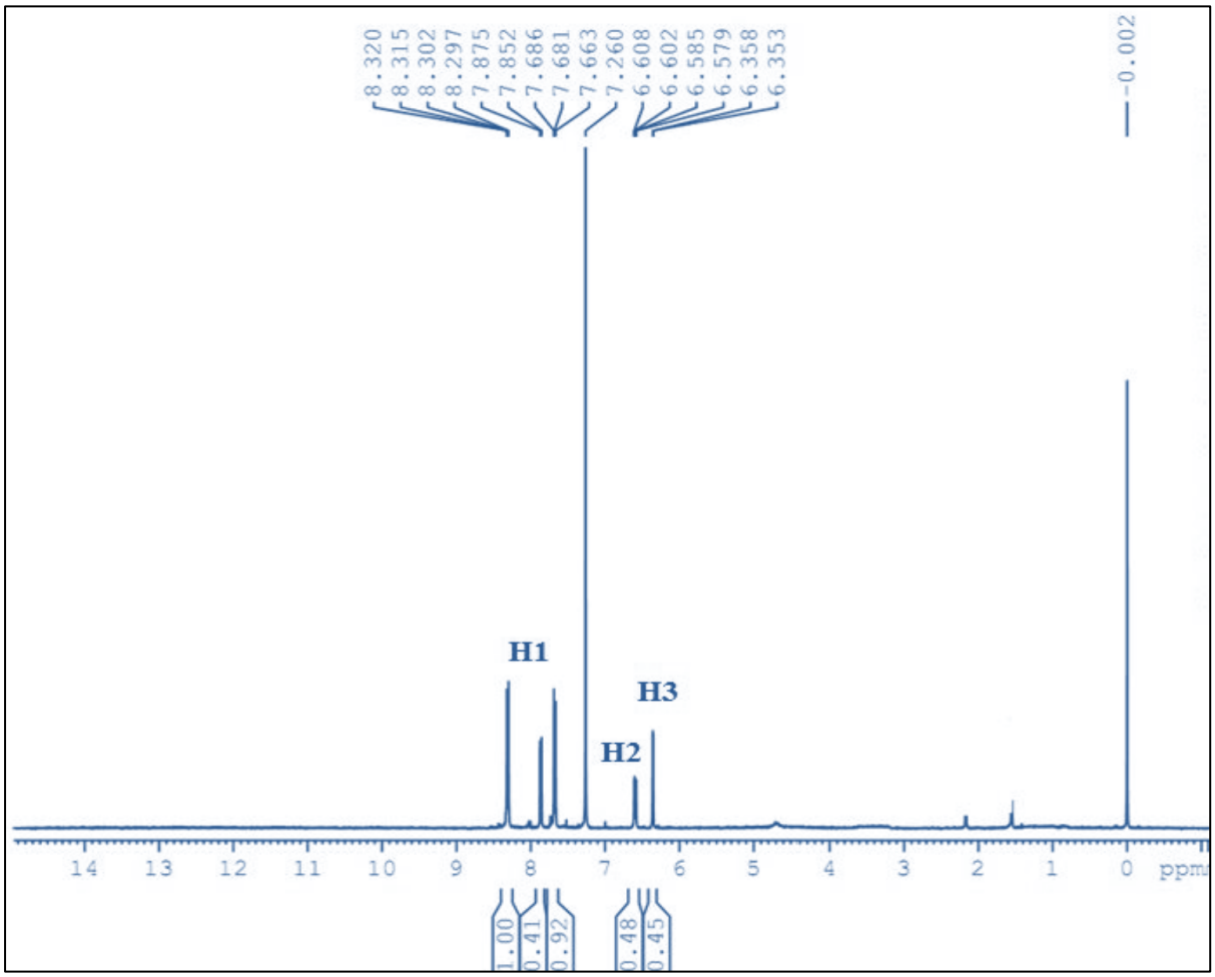
[1]H NMR spectra of 3-(1H-Benzo[d]imidazol-2-yl)-2H-benzo[g]chromene-2, 5, 10-trione



[1]H NMR spectra of 2, 5, 10-Trioxo-5, 10-dihydro-2H-benzo[g]chromene-3-carbonitrile



[1]H NMR Spectra of 3-Acetyl-2H-benzo[g]chromene-2, 5, 10-trione



[1]H NMR Spectra of 2H-Benzo[g]chromene-2,5,10-trione

Characterization data

3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalene-2-carbaldehyde (II)

Yellow solid; Yield 78%; m.p. 174–176 °C. FT-IR (KBr, *ν*max, cm^{-1}): 3148 (O–H), 3047 (C–H arom.), 2731 (C–H aldehydic), 1681 (C=O, aldehyde), 1655 (C=O, quinone), 1593 (C=C, quinone), 1569–1492 (C=C arom.). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.20–7.10 (m, 4H, arom.), 11.40 (s, 1H, –CHO), 14.80 (s, 1H, –OH). ^{1}3C NMR (126 MHz, $CDCl_3$) δ: 126.75, 131.76, 135.91, 146.31, 177.92, 186.54, 189.16. HRMS (*m/z*): $[M + H]^+$ calcd for $[C_{11}H_7O_4]^+$ 203.0183; found 203.0162.

2,5,10-Trioxo-5,10-dihydro-2H-benzo[*g*]chromene-3-carbonitrile (4a)

Light red solid; Yield 78%; m.p. 254–256 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.14 (dd, *J* = 7.8, 1.2 Hz, 2H, arom.), 7.75 (dd, *J* = 7.8, 1.2 Hz, 2H, arom.), 7.19 (s, 1H, 4-H). Anal. Calcd for $C_{14}H_5NO_4$: C, 66.94; H, 2.01; N, 5.58; O, 25.48. Found: C, 67.17; H, 4.07; N, 4.28; O, 24.48. MS (*m/z*): $[M]^+$ calcd for $C_{14}H_5NO_4$ 251.02; found 251.10.

3-Acetyl-2H-benzo[*g*]chromene-2,5,10-trione (4b)

Light red solid; Yield 76%; m.p. 196–198 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.44–8.33 (m, 2H, arom.), 7.98–7.95 (m, 2H, arom.), 7.18 (s, 1H, 4-H), 2.50 (s, 3H, $–COCH_3$). Anal. Calcd for $C_{15}H_8O_5$: C, 67.17; H, 3.01; O, 29.83. Found: C, 68.97; H, 4.11; O, 26.92. MS (*m/z*): $[M]^+$ calcd for $C_{15}H_8O_5$ 268.04; found 268.12.

3-(Benzo[*d*]thiazol-2-yl)-2H-benzo[*g*]chromene-2,5,10-trione (4c)

Yellow solid; Yield 82%; m.p. 246–248 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95–7.93 (m, 4H, arom.), 7.77–7.70 (m, 4H, arom.), 6.87 (s, 1H, 4-H). Anal. Calcd for $C_{20}H_9NO_4S$: C, 66.85; H, 2.52; N, 3.90; O, 17.81; S, 8.92. Found: C, 66.78; H, 2.45; N, 3.92; O, 17.86; S, 8.99. MS (*m/z*): $[M]^+$ calcd for $C_{20}H_9NO_4S$ 359.03; found 359.15.

3-(1H-Benzo[*d*]imidazol-2-yl)-2H-benzo[*g*]chromene-2,5,10-trione (4d)

Red solid; Yield 80%; m.p. 268–270 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.54–7.78 (m, 4H, arom.), 7.43–6.51 (m, 4H, arom.), 8.81 (s, 1H, 4-H), 3.50 (s, 1H, –NH). Anal. Calcd for $C_{20}H_{10}N_2O_4$: C, 70.18; H, 2.94; N, 8.18; O, 18.70. Found: C, 70.27; H, 2.85; N, 8.49; O, 18.39. MS (*m/z*): $[M]^+$ calcd for $C_{20}H_{10}N_2O_4$ 342.06; found 342.18.

2H-Benzo[*g*]chromene-2,5,10-trione (4e)

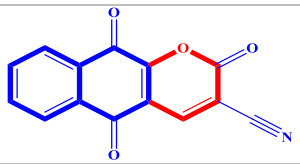
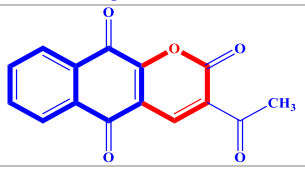
Light yellow solid; Yield 82%; m.p. 226–228 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.32–7.66 (m, 4H, arom.), 6.60 (d, *J* = 9.5 Hz, 1H, 4-H), 6.35 (d, *J* = 9.5 Hz, 1H, 3-H). Anal. Calcd for $C_{13}H_6O_4$: C, 69.03; H, 2.67; O, 28.29. Found: C, 70.59; H, 3.47; O, 25.94. MS (*m/z*): $[M]^+$ calcd for $C_{13}H_6O_4$ 226.03; found 226.11.

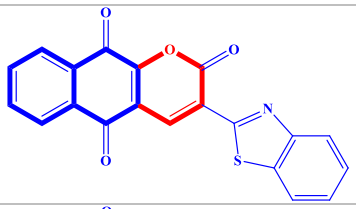
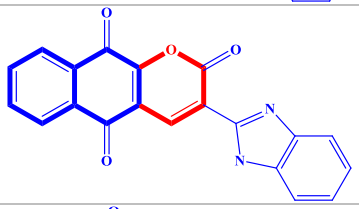
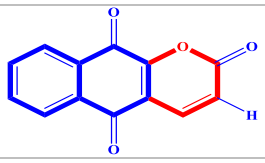
Table S1. Reaction optimization conditions and isolated yields for coumarin–naphthoquinone hybrids.

Entry	Catalyst	Catalyst loading (mol %)	Solvent system	Reaction conditions	Time	Yield (%)
1	–	–	Ethanol	Reflux	12 h (overnight)	–
2	–	–	Ethanol–water (1:1, v/v)	Reflux	12 h (overnight)	–
3	Na_2CO_3	10	Ethanol–water (1:1, v/v)	RT	360 min	35
4	TEA	10	Ethanol–water (1:1, v/v)	RT	360 min	42
5	DMAP	10	Ethanol–water (1:1, v/v)	RT	360 min	38
6	L-Proline	10	Ethanol–water (1:1, v/v)	Reflux	120 min	40
7	Piperidine	10	Ethanol–water (1:1, v/v)	Reflux	90 min	45
8	Meglumine	10	Ethanol–water (1:1, v/v)	RT	90 min	50
9	Meglumine	10	Water (H_2O)	RT	90 min	52
10	Meglumine	10	Ethanol–water (1:1, v/v)	RT	120 min	68
11	Meglumine	15	Ethanol–water (1:1, v/v)	RT	90 min	75
12	**Meglumine**	**20**	**Ethanol–water (1:1, v/v)**	**RT**	**90 min**	**82**
13	Meglumine	25	Ethanol–water (1:1, v/v)	RT	90 min	82

*Reaction conditions: 2-formyl lawsone (1.0 mmol), active methylene compound (1.0 mmol); RT = room temperature. Bold text indicates the optimized operational parameters selected for the general synthetic protocol.

Table S2. Chemical structures, physical appearance, and isolated yields of synthesized hybrids 4a–e.

Compound code	Structure of the product	C-3 Substituent (R)	Physical appearance	Yield (%)
4a		–CN (Cyano)	Light red crystals	78
4b		–$COCH_3$ (Acetyl)	Light red crystals	76

4c		Benzo[*d*]thiazol-2-yl	Yellow crystals	82
4d		1*H*-Benzo[*d*]imidazol-2-yl	Red crystals	80
4e		–H (Unsubstituted)	Light yellow crystals	82

*Reaction conditions: 2-formyl lawsone (1.0 mmol), active methylene compound (1.0 mmol), meglumine (20 mol %), EtOH–H_2O (1:1, v/v), room temperature, 90 min.

Table S3. Zones of inhibition (mm) of test compounds against selected microorganisms.

Compound	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*S. cerevisiae*
	Zone of inhibition (mm) at 100 µg/well concentration					
4a	22	17	20	16	17	14
4b	20	10	21	14	20	16
4c	30	23	28	25	25	22
4d	27	21	26	24	21	19
4e	20	19	21	20	23	17
Lawsone	17	14	11	12	15	—
Ciprofloxacin	25	21	24	22	—	—
Fluconazole	—	—	—	—	24	20

*Assays were performed in triplicate; values represent the mean zone of inhibition diameter (mm) including the well diameter (6 mm). A em-dash (—) indicates no inhibition or that the compound was not evaluated against the respective strain.

Table S4. Molecular docking analysis of synthesized hybrids 4a–e and reference drugs against glucosamine-6-phosphate synthase.

Compound code	Estimated free energy of binding, Δ_G_ (kcal/mol)	Binding amino acid residues	Bond length (Å)	Estimated inhibition constant, K_i (µM)
4a	−6.64	Gln348, Ser303, Ser401	3.00, 2.88, 3.15, 2.91	13.51
4b	−6.68	Gln348, Ser303, Thr302	3.10, 2.95, 2.91, 2.97, 3.22, 3.07	12.70
4c	**−7.93**	**Arg599**	**2.68, 2.86, 3.11**	**1.54**
4d	**−7.66**	**Arg599**	**2.65, 2.87,**	**2.45**

			3.16	
4e	−6.77	Cys300, Ser303, Gln348, Thr302	2.95, 2.97, 3.35, 2.95	10.95
CPF	−5.85	Asp460, Arg453, Glu563	2.95, 2.89, 2.78	51.70
FCA	−4.33	Arg599	3.36, 3.95, 2.77	672.98

*Note: Target receptor PDB ID: 2VF5 (chain X). CPF = ciprofloxacin, FCA = fluconazole. Bold text highlights the lead compounds with the highest predicted binding affinities.

Table S5. Molecular and pharmacokinetic properties of the coumarin derivatives 4a–e predicted via the SwissADME platform.

Predicted parameters	**4a**	**4b**	**4c**	**4d**	**4e**
log *P* (lipophilicity)	1.41	1.58	3.50	2.63	1.62
Water solubility	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble
GI absorption	High	High	High	High	High
BBB permeability	No	No	No	No	Yes
P-gp substrate	No	No	No	No	Yes
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	No	No	Yes	No	No
CYP2C9 inhibitor	No	No	Yes	No	No
CYP2D6 inhibitor	No	No	No	No	No
CYP3A4 inhibitor	No	No	Yes	No	No
Lipinski rule	Yes	Yes	Yes	Yes	Yes
Ghose filter	Yes	Yes	Yes	Yes	Yes
Veber rule	Yes	Yes	Yes	Yes	Yes
Egan filter	Yes	Yes	Yes	Yes	Yes
Muegge filter	Yes	Yes	Yes	Yes	Yes
Bioavailability score	0.55	0.55	0.55	0.55	0.55

*GI = gastrointestinal; BBB = blood–brain barrier; CYP = cytochrome P450.

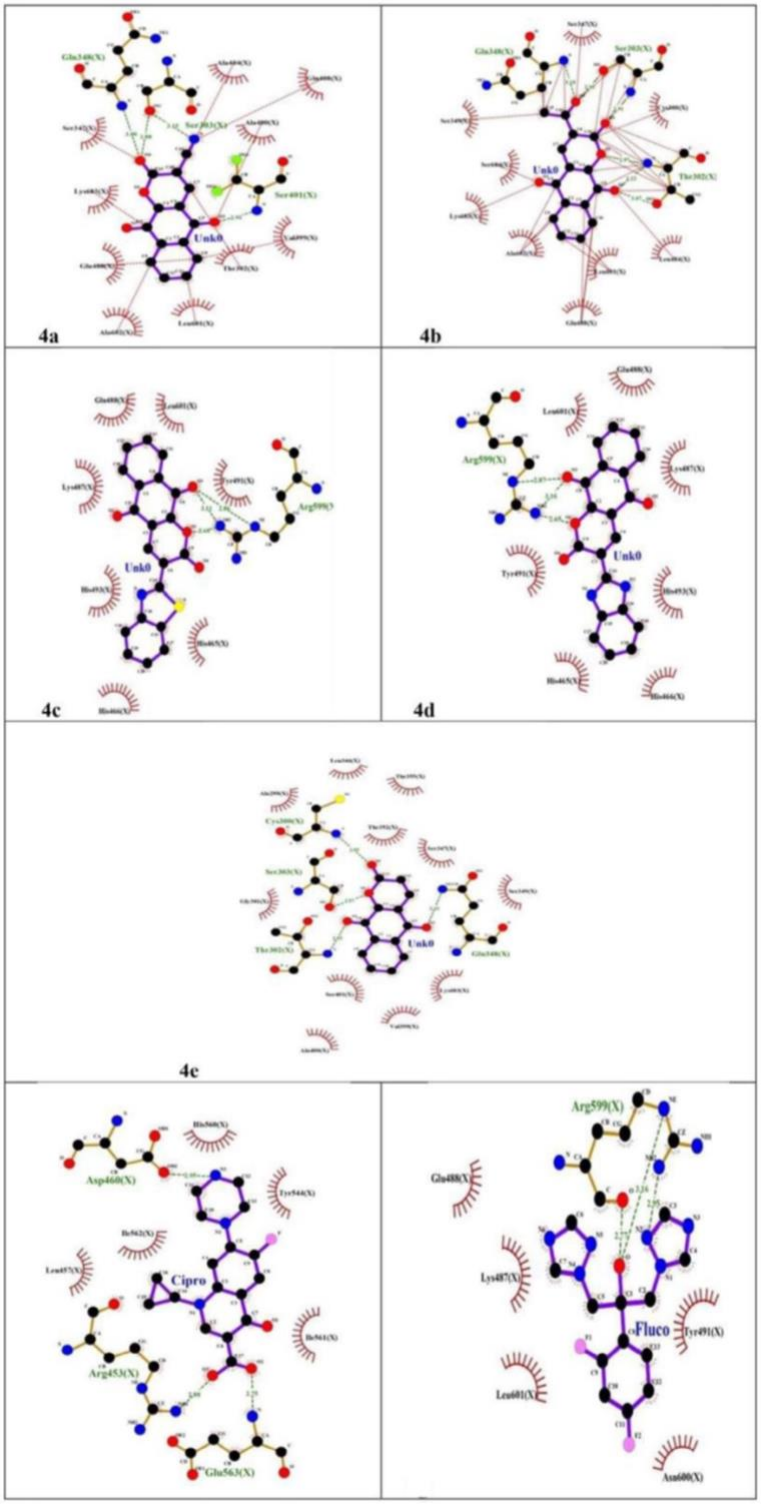


Fig. S1. LigPlot results-2D representation of protein-ligand interactions for active site of 2VF5 protein.