Supplementary Data for the manuscript

"Transformation of 3-(4-methoxybenzylidene)-5-(p-tolyl)-2(3H)-Furanone into New Nitrogen-containing Heterocyclic Candidates as Insecticidal Agents" by Nourhan M. Gad *et al*.

This file provides extended computational and physicochemical datasets supporting the main manuscript. It includes:

- **Table S1**: Space-model analysis of *Z/E* stereoisomers for selected compounds (**4**, **7**, **8**, and **9**). The table reports total MM2 energies (kcal/mol) and 1,4-van der Waals (VDW) interactions used to infer the preferred configuration for each compound.
- **Tables S2–S5:** Detailed residue-level docking interaction data for all synthesized compounds with AChE and Met receptors.
- **Figure S1:** Molecular dynamics (MD) results for Met–ligand systems over 100 ns, including RMSD and RMSF profiles for compound 4, pyriproxyfen, and the redocked co-crystallized ligand (HNJ) transferred to the modeled Met PAS-B domain.
- **Figure S2:** Ligand–protein contact histograms and interaction frequency maps for Met–ligand complexes (compound 4, pyriproxyfen, and HNJ), illustrating interaction persistence within the hormone-binding cavity across the simulation trajectory.
- **Figures S3–S9:** SwissADME analyses of the synthesized compounds, covering lipophilicity, solubility, bioavailability, and drug-likeness parameters.

These supplementary materials provide extended structural, dynamic, and pharmacokinetic characterization supporting the analyses presented in the main manuscript.

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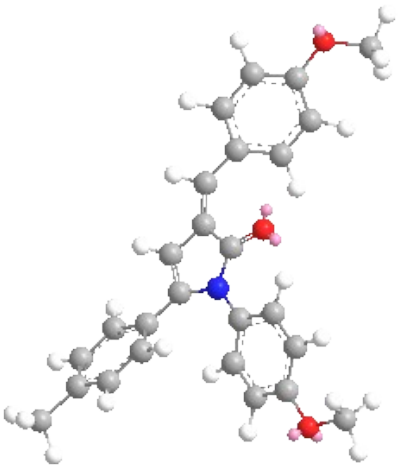
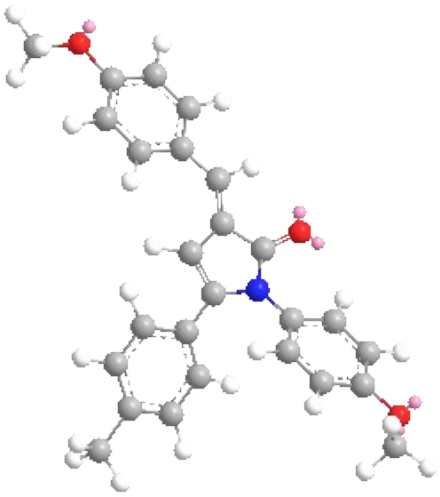
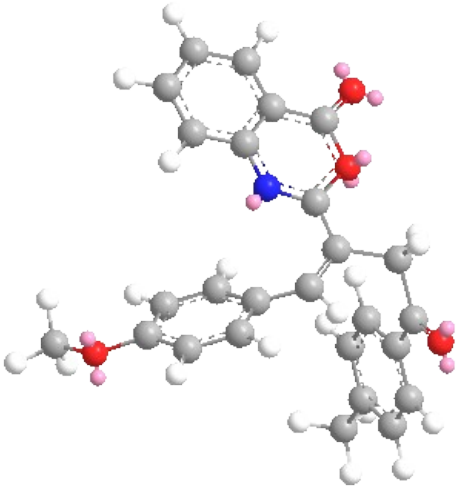
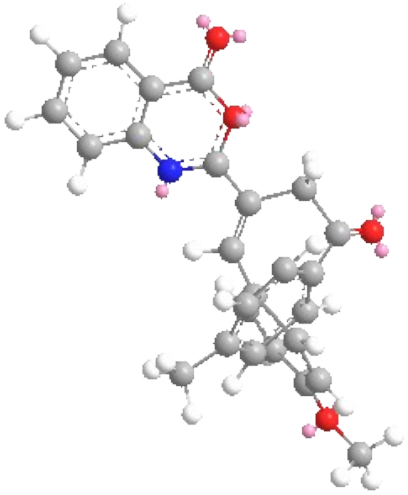
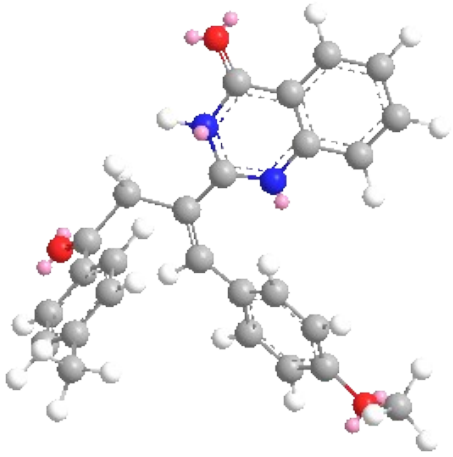
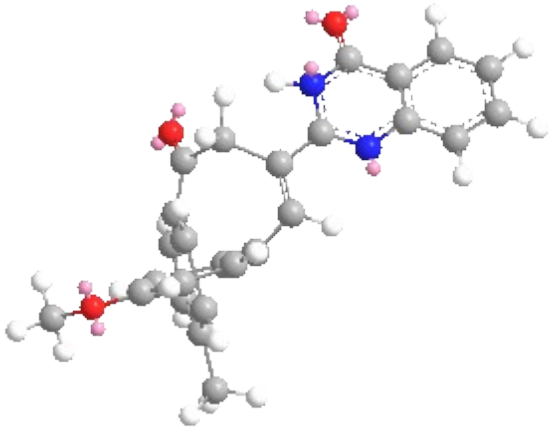
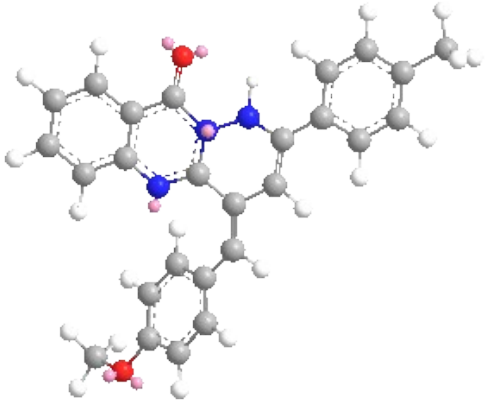
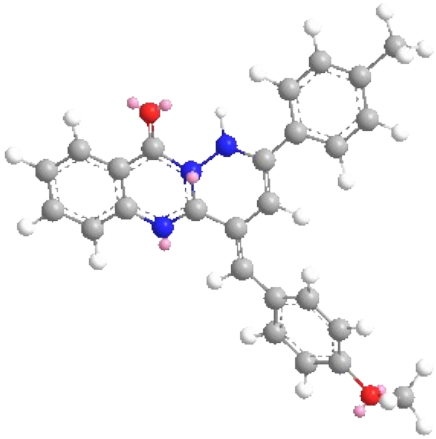
Table S1. Space-model analysis of *Z/E* stereoisomers for selected compounds (**4**, **7**, **8**, and **9**). The table reports total MM2 energies (kcal/mol) and 1,4-van der Waals (VDW) interactions used to infer the preferred configuration for each compound.

Compds.	***Z*-isomer**	***E*-isomer**
4	 [a] E = 66.03 [b] 1,4-VDW = 31.26	 E = 60.75 1,4-VDW = 31.37
7	 E = 47.31 1,4-VDW = 33.93	 E = 1092.68 1,4-VDW = 36.90

8	 E = 45.54 1,4-VDW = 30.23	 E = 1001.50 1,4-VDW = 22.22
9	 E = 41.79 1,4-VDW = 37.77	 E = 39.58 1,4-VDW = 37.50

[b] VDW: van-der Waal interactions.

[a] E: Total Energy in kcal/mol.

Table S2: Summary of molecular docking interaction data for all synthesized compounds with the acetylcholinesterase (AChE) model, including interaction types, distances, and estimated binding energies.

Compound	Ligand atom	Receptor atom	Residue	Interaction Type	Distance	E (kcal/mol)
1	O 7	CB	HIS 567 (A)	H-acceptor	3.19	-0.6
	6-ring	5-ring	TRP 212 (A)	pi-pi	4.07	
	6-ring	6-ring	TRP 212 (A)	pi-pi	4.13	
2	O 8	CB	HIS 567 (A)	H-acceptor	3.16	-0.7
	5-ring	CD2	HIS 567 (A)	pi-H	4.08	-1.5
	6-ring	5-ring	TRP 212 (A)	pi-pi	4.05	
	6-ring	6-ring	TRP 212 (A)	pi-pi	4.06	
3	C 25	OE1	GLU 326 (A)	H-donor	3.34	-0.5
	O 7	CD2	HIS 567 (A)	H-acceptor	3.44	-0.5
	O 24	OH	TYR 258 (A)	H-acceptor	3.23	-0.8
	6-ring	5-ring	TRP 212 (A)	pi-pi	4.19	
	6-ring	6-ring	TRP 212 (A)	pi-pi	4.17	
4	O 7	CB	HIS 567 (A)	H-acceptor	3.24	-0.5
	5-ring	CD2	HIS 567 (A)	pi-H	4.09	-1.6
	6-ring	5-ring	TRP 212 (A)	pi-pi	3.98	
	6-ring	6-ring	TRP 212 (A)	pi-pi	3.83	
5	O 34	CB	HIS 567 (A)	H-acceptor	3.28	-0.5
	C 52	6-ring	TRP 360 (A)	H-pi	3.78	-0.5
	5-ring	CD2	HIS 567 (A)	pi-H	4.12	-1.6
	6-ring	5-ring	TRP 212 (A)	pi-pi	3.99	
	6-ring	6-ring	TRP 212 (A)	pi-pi	3.66	
7	O 37	CA	GLY 568 (A)	H-acceptor	3.2	-0.7
	6-ring	5-ring	TRP 212 (A)	pi-pi	3.54	
	6-ring	6-ring	TRP 212 (A)	pi-pi	3.6	
8	O 38	CA	GLY 568 (A)	H-acceptor	3.18	-0.7
	6-ring	5-ring	TRP 212 (A)	pi-pi	3.62	
	6-ring	6-ring	TRP 212 (A)	pi-pi	3.62	
9	O 21	OH	TYR 249 (A)	H-acceptor	2.63	-1.3
	6-ring	CA	GLY 246 (A)	pi-H	3.76	-1.7
	6-ring	5-ring	TRP 212 (A)	pi-pi	4.09	
10	O 9	CD2	HIS 567 (A)	H-acceptor	3.34	-0.5
	6-ring	CB	HIS 567 (A)	pi-H	4.48	-0.7
11	S 8	OH	TYR 258 (A)	H-acceptor	3.03	-2.7
	6-ring	NE2	HIS 567 (A)	pi-cation	4.01	-0.5
	6-ring	5-ring	TRP 212 (A)	pi-pi	4.34	
12	6-ring	NE2	HIS 567 (A)	pi-cation	3.99	-0.5
	6-ring	5-ring	TRP 212 (A)	pi-pi	4.33	

13	O 7	CB	HIS 567 (A)	H-acceptor	3.17	-0.7
	5-ring	CD2	HIS 567 (A)	pi-H	4.03	-0.9
	6-ring	5-ring	TRP 212 (A)	pi-pi	4	
	6-ring	6-ring	TRP 212 (A)	pi-pi	3.93	
14	6-ring	CD2	HIS 567 (A)	pi-H	4.27	-0.6
Chlorpyrifos	S 4	N	GLY 247 (A)	H-acceptor	4.43	-0.5
	S 4	CB	SER 327 (A)	H-acceptor	3.61	-0.9
	S 4	NE2	HIS 567 (A)	H-acceptor	4.45	-3.2
	C 11	5-ring	TRP 212 (A)	H-pi	3.74	-0.6
Native CCL	C07 8	OE1	GLU 326 (A)	H-donor	3.5	-0.5
	O12 15	N	GLY 247 (A)	H-acceptor	2.77	-1.8
Redocked CCL	O12 15	N	GLY 247 (A)	H-acceptor	2.88	-0.9
	O12 15	N	ALA 328 (A)	H-acceptor	3.31	-0.7
	5-ring	CD2	HIS 567 (A)	pi-H	4.02	-0.8

Table S3: Two-dimensional interaction diagrams illustrating the binding orientations and contact patterns of the synthesized compounds within the AChE active site obtained from docking analysis	
1	**2**
3	**4**
5	**7**

8	**9**
10	**11**
12	**13**
14 7S	**Chlorpyrifos**

Native Cocrystallized ligand	Redocked Cocrystallized Ligand

Table S4: Summary of molecular docking interaction data for the synthesized compounds with the Methoprene-tolerant (Met) receptor model, including interaction types, distances, and binding-energy estimates.

Compound	Ligand atom	Receptor atom	Residue	Interaction Type	Distance	E (kcal/mol)
1	C 25	5-ring	HIS 23 (B)	H-pi	4.1	-0.6
	6-ring	SG	CYS 115 (B)	pi-H	4.9	-0.5
2	C 33	5-ring	HIS 23 (B)	H-pi	4.09	-0.5
	5-ring	CG2	THR 21 (B)	pi-H	4.08	-1.1
	6-ring	SG	CYS 115 (B)	pi-H	4.92	-0.5
3	C 35	5-ring	HIS 23 (B)	H-pi	3.69	-0.6
4	C 40	NE2	HIS 23 (B)	H-donor	3.29	-0.6
5	C 38	NE2	HIS 23 (B)	H-donor	3.28	-0.6
7	O 15	SD	MET 56 (B)	H-donor	3.61	-0.9
	C 16	5-ring	HIS 23 (B)	H-pi	3.67	-1.6
8	C 28	NE2	HIS 23 (B)	H-donor	3.21	-0.6
8	N 4	SG	CYS 115 (B)	H-acceptor	3.59	-0.5
9	C 17	5-ring	HIS 23 (B)	H-pi	3.67	-0.7
10	N 7	OD1	ASN 117 (B)	H-donor	2.84	-2.3
	C 28	5-ring	HIS 23 (B)	H-pi	4.17	-0.5
	6-ring	CG2	THR 21 (B)	pi-H	4.04	-0.6
11	S 8	CA	GLY 27 (B)	H-acceptor	3.15	-1.1
	S 8	CG	PRO 52 (B)	H-acceptor	3.89	-0.7
	C 23	5-ring	HIS 23 (B)	H-pi	3.89	-0.5
12	C 22	5-ring	HIS 23 (B)	H-pi	4.01	-1
	6-ring	5-ring	HIS 23 (B)	pi-pi	4.4	
13	C 33	NE2	HIS 23 (B)	H-donor	3.26	-0.6
	5-ring	SG	CYS 115 (B)	pi-H	4.48	-0.8
14	N 7	O	PRO 52 (B)	H-donor	3.2	-1.7
	C 39	NE2	HIS 23 (B)	H-donor	3.23	-0.5
Pyriproxyfen	6-ring	CD1	LEU 68 (B)	pi-H	3.94	-0.6
	6-ring	5-ring	HIS 23 (B)	pi-pi	4.37	
Native CCL	No Detected Interactions					
Redocked CCL	N 25	SD	MET 56 (B)	H-donor	3.2	-1.4
	O 8	CE1	HIS 23 (B)	H-acceptor	3.35	-0.6

Table S5: Two-dimensional interaction diagrams showing the binding orientations and interaction patterns of the synthesized compounds within the Met receptor binding cavity as predicted by docking	
1	**2**
3	**4**
5	**7**

8	**9**
10	**11**
12	**13**

14	**pyriproxyfen**
Native Cocrystallized ligand	**Redocked Cocrystallized Ligand**

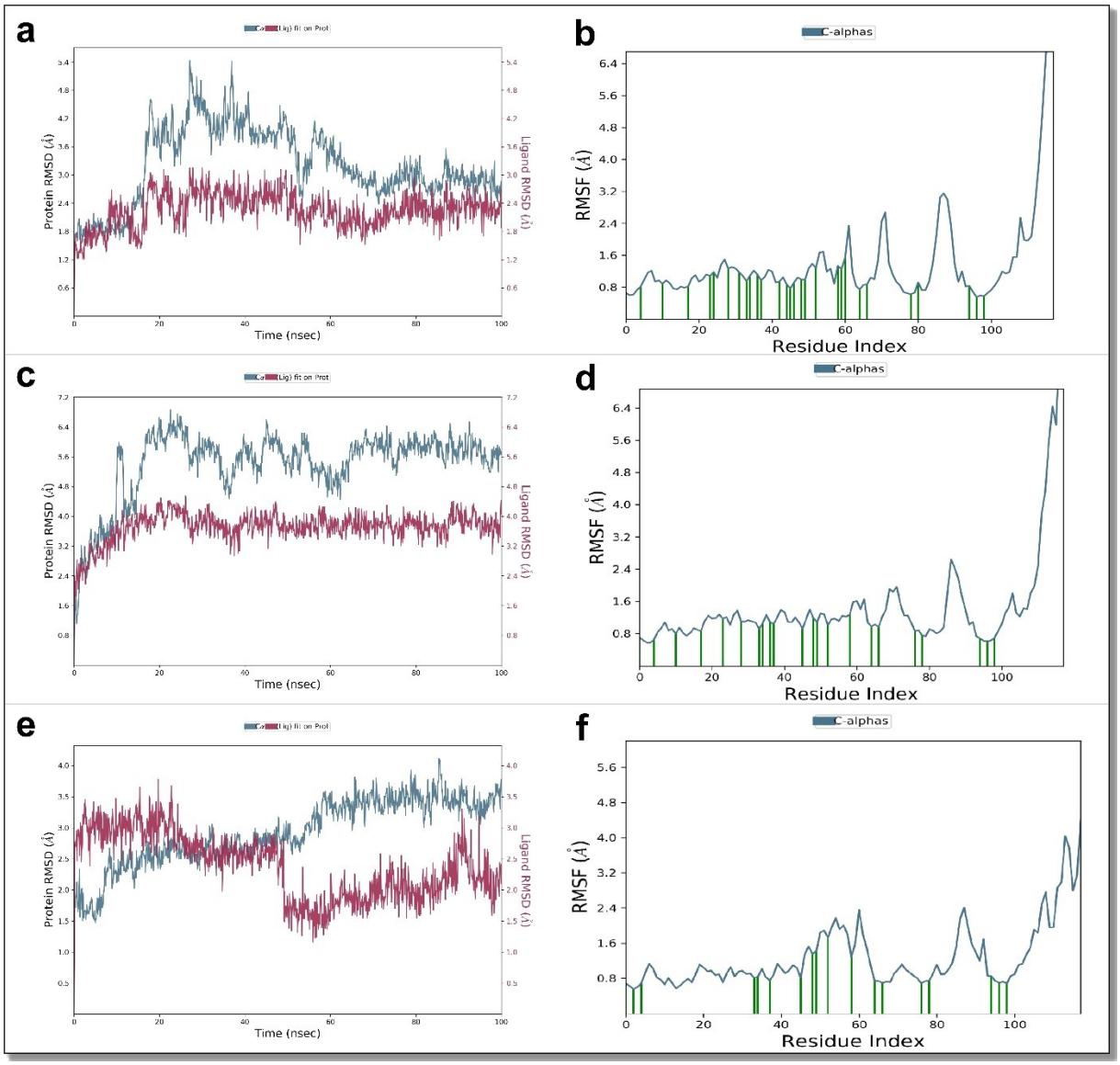


Fig. S1: MD results for Met–ligand systems over 100 ns: (a) RMSD of compound **4**; (b) RMSF of compound **4**; (c) RMSD of pyriproxyfen; (d) RMSF of pyriproxyfen; (e) RMSD of the redocked co-crystallized ligand (HNJ) transferred to the modeled Met PAS-B domain; (f) RMSF of the same ligand.

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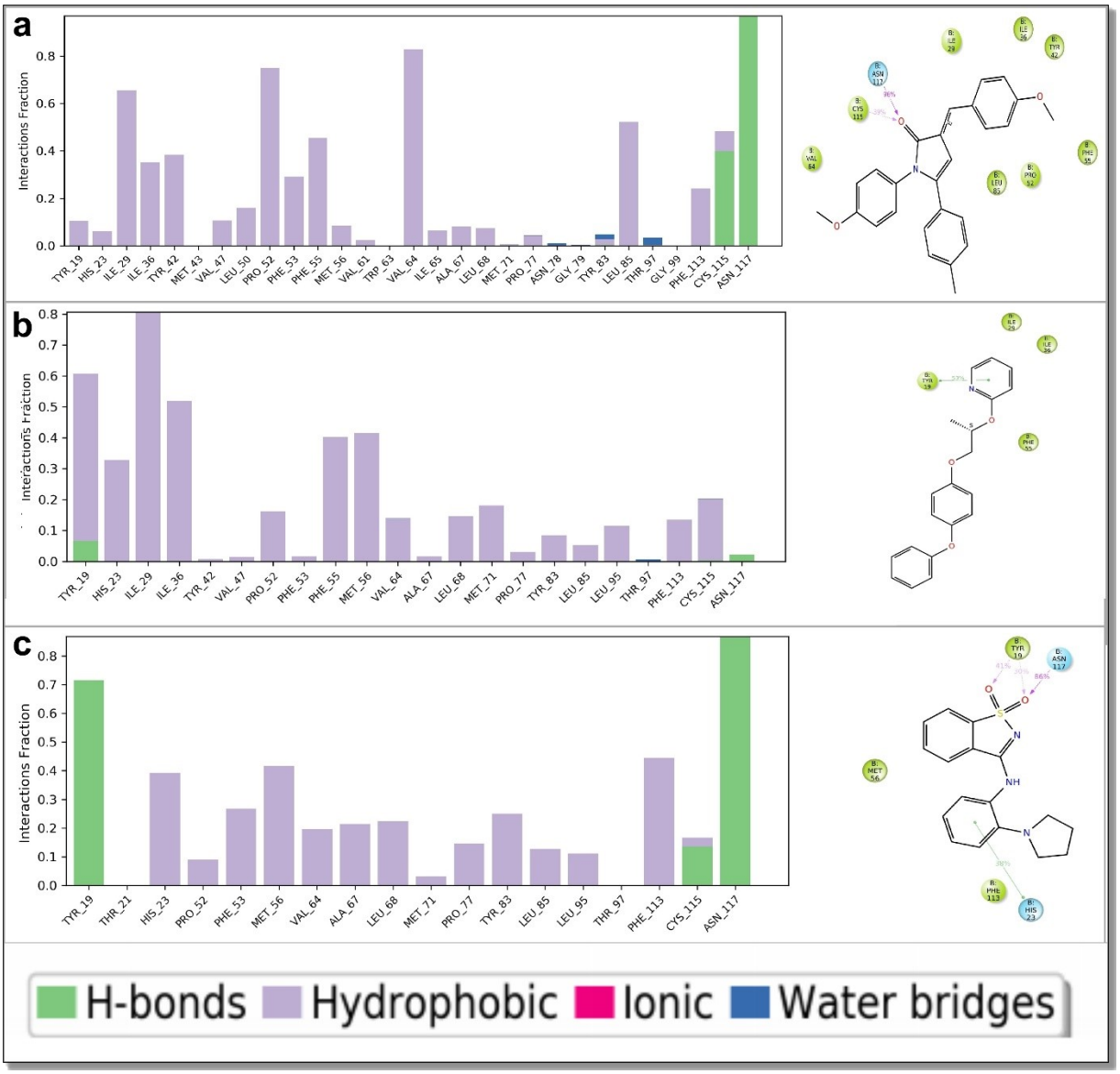


Fig. S2: Ligand–protein contact histograms and interaction frequency maps for Met–ligand complexes: (a) compound **4**; (b) pyriproxyfen; and (c) the redocked co-crystallized ligand (HNJ), showing consistent contacts with residues within the hormone-binding pocket across the simulation trajectory.

Fig. S3

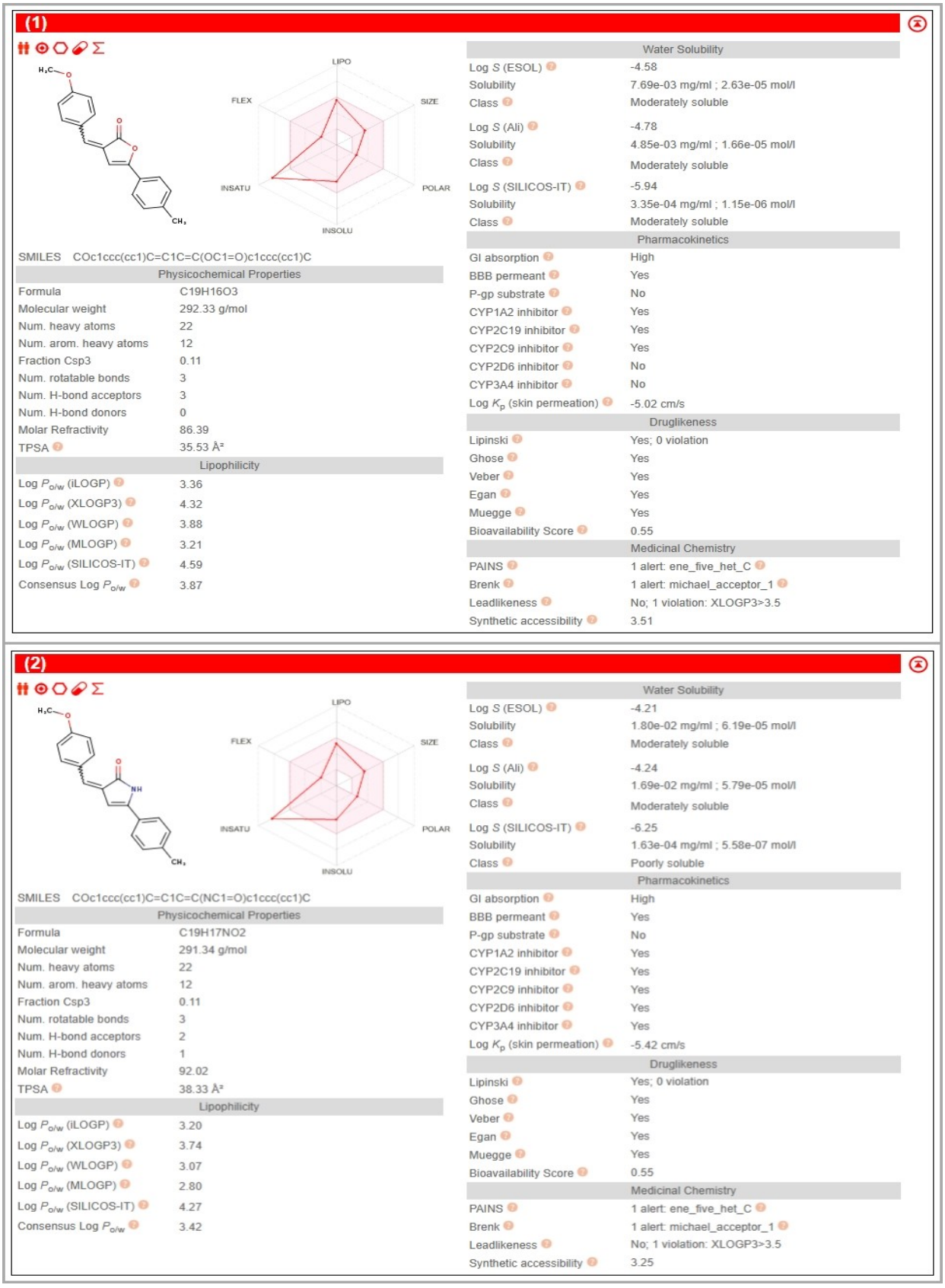
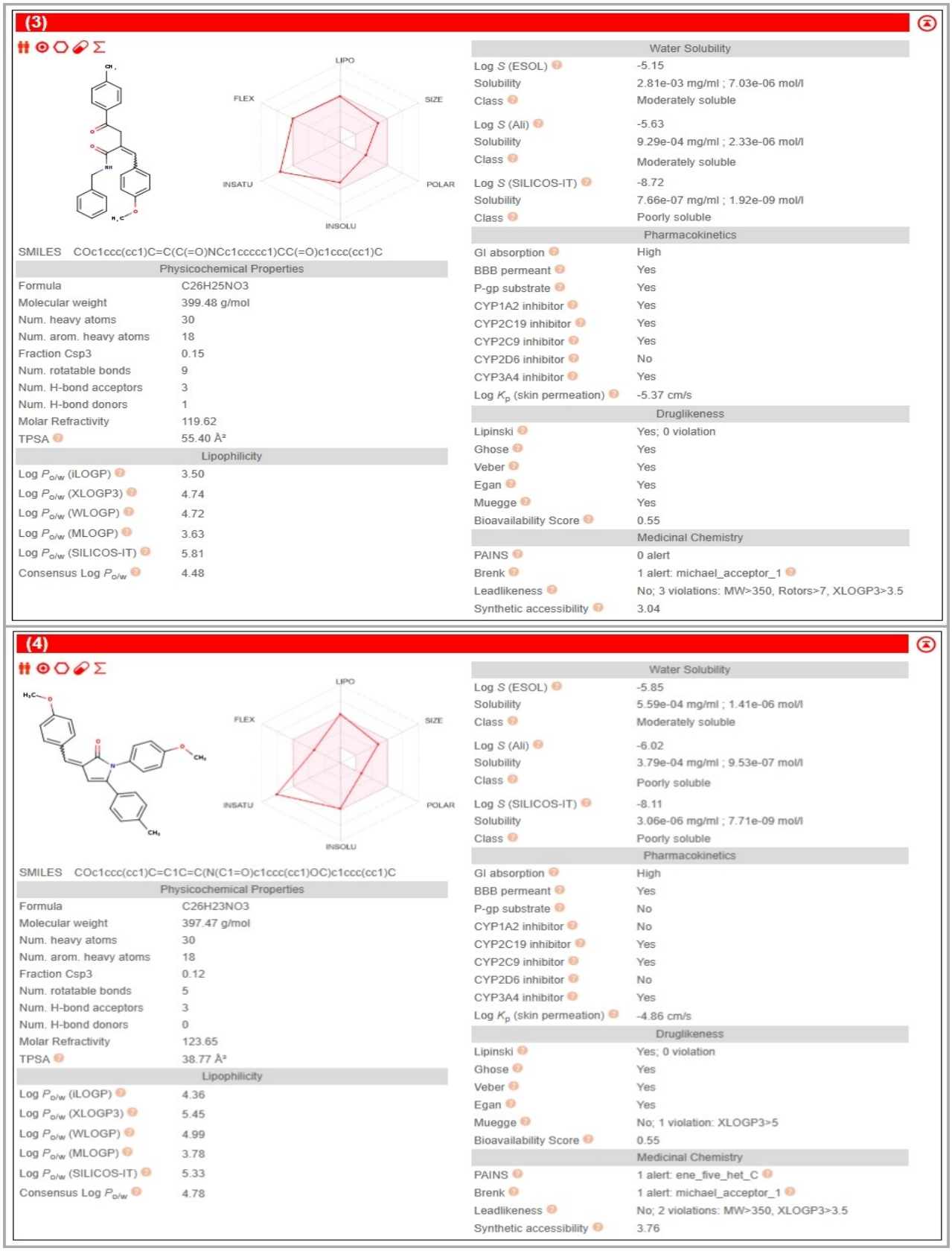

(1)
LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX
SMILES COc1ccc(cc1)C=C1C=C(OC1=O)c1ccc(cc1)C
Physicochemical Properties
Formula C19H16O3
Molecular weight 292.33 g/mol
Num. heavy atoms 22
Num. arom. heavy atoms 12
Fraction Csp3 0.11
Num. rotatable bonds 3
Num. H-bond acceptors 3
Num. H-bond donors 0
Molar Refractivity 86.39
TPSA 35.53 Å²
Lipophilicity
Log Po/w (iLOGP) 3.36
Log Po/w (XLOGP3) 4.32
Log Po/w (WLOGP) 3.88
Log Po/w (MLOGP) 3.21
Log Po/w (SILICOS-IT) 4.59
Consensus Log Po/w 3.87
Water Solubility
Log S (ESOL) -4.58
Solubility 7.69e-03 mg/ml ; 2.63e-05 mol/l
Class Moderately soluble
Log S (Ali) -4.78
Solubility 4.85e-03 mg/ml ; 1.66e-05 mol/l
Class Moderately soluble
Log S (SILICOS-IT) -5.94
Solubility 3.35e-04 mg/ml ; 1.15e-06 mol/l
Class Moderately soluble
Pharmacokinetics
GI absorption High
BBB permeant Yes
P-gp substrate No
CYP1A2 inhibitor Yes
CYP2C19 inhibitor Yes
CYP2C9 inhibitor Yes
CYP2D6 inhibitor No
CYP3A4 inhibitor No
Log Kp (skin permeation) -5.02 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge Yes
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 1 alert: ene_five_het_C
Brenk 1 alert: michael_acceptor_1
Leadlikeness No; 1 violation: XLOGP3>3.5
Synthetic accessibility 3.51
(2)
LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX
SMILES COc1ccc(cc1)C=C1C=C(NC1=O)c1ccc(cc1)C
Physicochemical Properties
Formula C19H17NO2
Molecular weight 291.34 g/mol
Num. heavy atoms 22
Num. arom. heavy atoms 12
Fraction Csp3 0.11
Num. rotatable bonds 3
Num. H-bond acceptors 2
Num. H-bond donors 1
Molar Refractivity 92.02
TPSA 38.33 Å²
Lipophilicity
Log Po/w (iLOGP) 3.20
Log Po/w (XLOGP3) 3.74
Log Po/w (WLOGP) 3.07
Log Po/w (MLOGP) 2.80
Log Po/w (SILICOS-IT) 4.27
Consensus Log Po/w 3.42
Water Solubility
Log S (ESOL) -4.21
Solubility 1.80e-02 mg/ml ; 6.19e-05 mol/l
Class Moderately soluble
Log S (Ali) -4.24
Solubility 1.69e-02 mg/ml ; 5.79e-05 mol/l
Class Moderately soluble
Log S (SILICOS-IT) -6.25
Solubility 1.63e-04 mg/ml ; 5.58e-07 mol/l
Class Poorly soluble
Pharmacokinetics
GI absorption High
BBB permeant Yes
P-gp substrate No
CYP1A2 inhibitor Yes
CYP2C19 inhibitor Yes
CYP2C9 inhibitor Yes
CYP2D6 inhibitor Yes
CYP3A4 inhibitor Yes
Log Kp (skin permeation) -5.42 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge Yes
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 1 alert: ene_five_het_C
Brenk 1 alert: michael_acceptor_1
Leadlikeness No; 1 violation: XLOGP3>3.5
Synthetic accessibility 3.25

Fig.S4


(3)
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SIZE
POLAR
INSOLU
INSATU
FLEX
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Physicochemical Properties
Formula C26H25NO3
Molecular weight 399.48 g/mol
Num. heavy atoms 30
Num. arom. heavy atoms 18
Fraction Csp3 0.15
Num. rotatable bonds 9
Num. H-bond acceptors 3
Num. H-bond donors 1
Molar Refractivity 119.62
TPSA 55.40 Å²
Lipophilicity
Log Po/w (iLOGP) 3.50
Log Po/w (XLOGP3) 4.74
Log Po/w (WLOGP) 4.72
Log Po/w (MLOGP) 3.63
Log Po/w (SILICOS-IT) 5.81
Consensus Log Po/w 4.48
Water Solubility
Log S (ESOL) -5.15
Solubility 2.81e-03 mg/ml ; 7.03e-06 mol/l
Class Moderately soluble
Log S (Ali) -5.63
Solubility 9.29e-04 mg/ml ; 2.33e-06 mol/l
Class Moderately soluble
Log S (SILICOS-IT) -8.72
Solubility 7.66e-07 mg/ml ; 1.92e-09 mol/l
Class Poorly soluble
Pharmacokinetics
GI absorption High
BBB permeant Yes
P-gp substrate Yes
CYP1A2 inhibitor Yes
CYP2C19 inhibitor Yes
CYP2C9 inhibitor Yes
CYP2D6 inhibitor No
CYP3A4 inhibitor Yes
Log Kp (skin permeation) -5.37 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge Yes
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 0 alert
Brenk 1 alert: michael_acceptor_1
Leadlikeness No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility 3.04
(4)
LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX
SMILES COc1ccc(cc1)C=C1C=C(N(C1=O)c1ccc(cc1)OC)c1ccc(cc1)C
Physicochemical Properties
Formula C26H23NO3
Molecular weight 397.47 g/mol
Num. heavy atoms 30
Num. arom. heavy atoms 18
Fraction Csp3 0.12
Num. rotatable bonds 5
Num. H-bond acceptors 3
Num. H-bond donors 0
Molar Refractivity 123.65
TPSA 38.77 Å²
Lipophilicity
Log Po/w (iLOGP) 4.36
Log Po/w (XLOGP3) 5.45
Log Po/w (WLOGP) 4.99
Log Po/w (MLOGP) 3.78
Log Po/w (SILICOS-IT) 5.33
Consensus Log Po/w 4.78
Water Solubility
Log S (ESOL) -5.85
Solubility 5.59e-04 mg/ml ; 1.41e-06 mol/l
Class Moderately soluble
Log S (Ali) -6.02
Solubility 3.79e-04 mg/ml ; 9.53e-07 mol/l
Class Poorly soluble
Log S (SILICOS-IT) -8.11
Solubility 3.06e-06 mg/ml ; 7.71e-09 mol/l
Class Poorly soluble
Pharmacokinetics
GI absorption High
BBB permeant Yes
P-gp substrate No
CYP1A2 inhibitor No
CYP2C19 inhibitor Yes
CYP2C9 inhibitor Yes
CYP2D6 inhibitor No
CYP3A4 inhibitor Yes
Log Kp (skin permeation) -4.86 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge No; 1 violation: XLOGP3>5
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 1 alert: ene_five_het_C
Brenk 1 alert: michael_acceptor_1
Leadlikeness No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility 3.76

Fig. S5

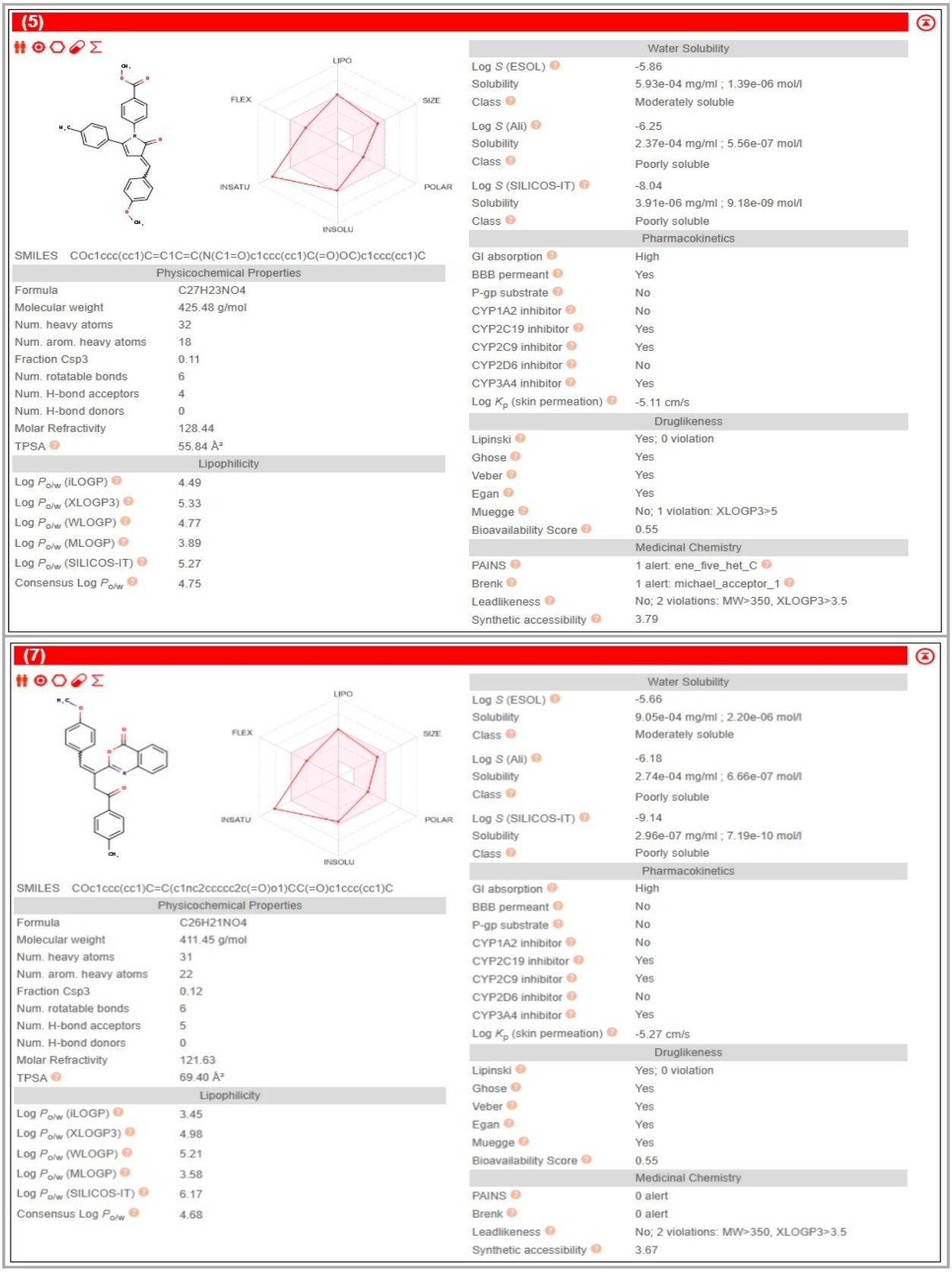
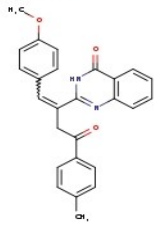
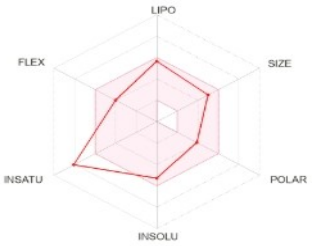

(5)
LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX
SMILES COc1ccc(cc1)C=C1C=C(N(C1=O)c1ccc(cc1)C(=O)OC)c1ccc(cc1)C
Physicochemical Properties
Formula C27H23NO4
Molecular weight 425.48 g/mol
Num. heavy atoms 32
Num. arom. heavy atoms 18
Fraction Csp3 0.11
Num. rotatable bonds 6
Num. H-bond acceptors 4
Num. H-bond donors 0
Molar Refractivity 128.44
TPSA 55.84 Å²
Lipophilicity
Log Po/w (iLOGP) 4.49
Log Po/w (XLOGP3) 5.33
Log Po/w (WLOGP) 4.77
Log Po/w (MLOGP) 3.89
Log Po/w (SILICOS-IT) 5.27
Consensus Log Po/w 4.75
Water Solubility
Log S (ESOL) -5.86
Solubility 5.93e-04 mg/ml ; 1.39e-06 mol/l
Class Moderately soluble
Log S (Ali) -6.25
Solubility 2.37e-04 mg/ml ; 5.56e-07 mol/l
Class Poorly soluble
Log S (SILICOS-IT) -8.04
Solubility 3.91e-06 mg/ml ; 9.18e-09 mol/l
Class Poorly soluble
Pharmacokinetics
GI absorption High
BBB permeant Yes
P-gp substrate No
CYP1A2 inhibitor No
CYP2C19 inhibitor Yes
CYP2C9 inhibitor Yes
CYP2D6 inhibitor No
CYP3A4 inhibitor Yes
Log Kp (skin permeation) -5.11 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge No; 1 violation: XLOGP3>5
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 1 alert: ene_five_het_C
Brenk 1 alert: michael_acceptor_1
Leadlikeness No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility 3.79
(7)
LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX
SMILES COc1ccc(cc1)C=C(c1nc2ccccc2c(=O)o1)CC(=O)c1ccc(cc1)C
Physicochemical Properties
Formula C26H21NO4
Molecular weight 411.45 g/mol
Num. heavy atoms 31
Num. arom. heavy atoms 22
Fraction Csp3 0.12
Num. rotatable bonds 6
Num. H-bond acceptors 5
Num. H-bond donors 0
Molar Refractivity 121.63
TPSA 69.40 Å²
Lipophilicity
Log Po/w (iLOGP) 3.45
Log Po/w (XLOGP3) 4.98
Log Po/w (WLOGP) 5.21
Log Po/w (MLOGP) 3.58
Log Po/w (SILICOS-IT) 6.17
Consensus Log Po/w 4.68
Water Solubility
Log S (ESOL) -5.66
Solubility 9.05e-04 mg/ml ; 2.20e-06 mol/l
Class Moderately soluble
Log S (Ali) -6.18
Solubility 2.74e-04 mg/ml ; 6.66e-07 mol/l
Class Poorly soluble
Log S (SILICOS-IT) -9.14
Solubility 2.96e-07 mg/ml ; 7.19e-10 mol/l
Class Poorly soluble
Pharmacokinetics
GI absorption High
BBB permeant No
P-gp substrate No
CYP1A2 inhibitor No
CYP2C19 inhibitor Yes
CYP2C9 inhibitor Yes
CYP2D6 inhibitor No
CYP3A4 inhibitor Yes
Log Kp (skin permeation) -5.27 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge Yes
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 0 alert
Brenk 0 alert
Leadlikeness No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility 3.67

Fig. S6

(8)



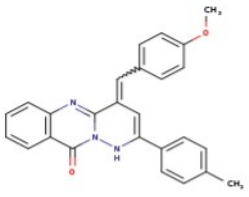


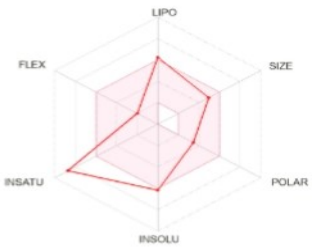
SMILES COc1ccc(cc1)C=C(c1nc2ccccc2c(=O)[nH]1)CC(=O)c1ccc(cc1)C

Physicochemical Properties	
Formula	C26H22N2O3
Molecular weight	410.46 g/mol
Num. heavy atoms	31
Num. arom. heavy atoms	22
Fraction Csp3	0.12
Num. rotatable bonds	6
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	123.71
TPSA	72.05 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.33
Log $P_{o/w}$ (XLOGP3)	4.40
Log $P_{o/w}$ (WLOGP)	4.94
Log $P_{o/w}$ (MLOGP)	3.58
Log $P_{o/w}$ (SILICOS-IT)	6.30
Consensus Log $P_{o/w}$	4.51

Water Solubility	
Log *S* (ESOL)	-5.29
Solubility	2.12e-03 mg/ml ; 5.18e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.63
Solubility	9.62e-04 mg/ml ; 2.34e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-9.14
Solubility	2.97e-07 mg/ml ; 7.24e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.68 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.27

(9)





SMILES COc1ccc(cc1)C=c1cc([nH]n2c1nc1ccccc1c2=O)c1ccc(cc1)C

Physicochemical Properties	
Formula	C26H21N3O2
Molecular weight	407.46 g/mol
Num. heavy atoms	31
Num. arom. heavy atoms	26
Fraction Csp3	0.08
Num. rotatable bonds	3
Num. H-bond acceptors	3
Num. H-bond donors	1
Molar Refractivity	124.25
TPSA	59.39 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.16
Log $P_{o/w}$ (XLOGP3)	5.39
Log $P_{o/w}$ (WLOGP)	4.27
Log $P_{o/w}$ (MLOGP)	4.56
Log $P_{o/w}$ (SILICOS-IT)	5.54
Consensus Log $P_{o/w}$	4.79

Water Solubility	
Log *S* (ESOL)	-6.18
Solubility	2.66e-04 mg/ml ; 6.54e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-6.39
Solubility	1.65e-04 mg/ml ; 4.06e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-9.23
Solubility	2.42e-07 mg/ml ; 5.94e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-4.96 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: polycyclic_aromatic_hydrocarbon_2
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.45

Fig. S7

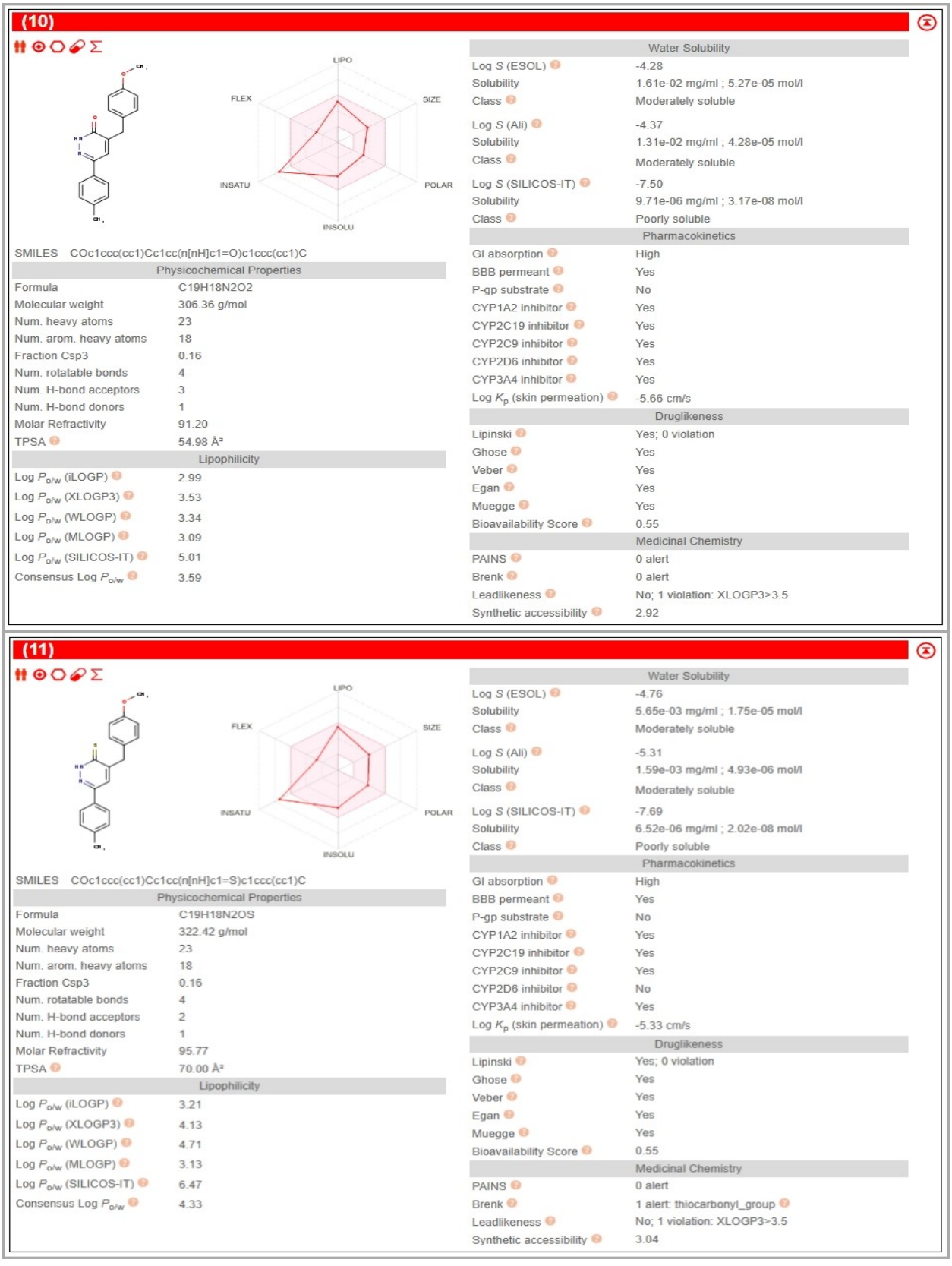

(10)
LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX
SMILES COc1ccc(cc1)Cc1cc(n[nH]c1=O)c1ccc(cc1)C
Physicochemical Properties
Formula C19H18N2O2
Molecular weight 306.36 g/mol
Num. heavy atoms 23
Num. arom. heavy atoms 18
Fraction Csp3 0.16
Num. rotatable bonds 4
Num. H-bond acceptors 3
Num. H-bond donors 1
Molar Refractivity 91.20
TPSA 54.98 Å²
Lipophilicity
Log Po/w (iLOGP) 2.99
Log Po/w (XLOGP3) 3.53
Log Po/w (WLOGP) 3.34
Log Po/w (MLOGP) 3.09
Log Po/w (SILICOS-IT) 5.01
Consensus Log Po/w 3.59
Water Solubility
Log S (ESOL) -4.28
Solubility 1.61e-02 mg/ml ; 5.27e-05 mol/l
Class Moderately soluble
Log S (Ali) -4.37
Solubility 1.31e-02 mg/ml ; 4.28e-05 mol/l
Class Moderately soluble
Log S (SILICOS-IT) -7.50
Solubility 9.71e-06 mg/ml ; 3.17e-08 mol/l
Class Poorly soluble
Pharmacokinetics
GI absorption High
BBB permeant Yes
P-gp substrate No
CYP1A2 inhibitor Yes
CYP2C19 inhibitor Yes
CYP2C9 inhibitor Yes
CYP2D6 inhibitor Yes
CYP3A4 inhibitor Yes
Log Kp (skin permeation) -5.66 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge Yes
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 0 alert
Brenk 0 alert
Leadlikeness No; 1 violation: XLOGP3>3.5
Synthetic accessibility 2.92
(11)
LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX
SMILES COc1ccc(cc1)Cc1cc(n[nH]c1=S)c1ccc(cc1)C
Physicochemical Properties
Formula C19H18N2OS
Molecular weight 322.42 g/mol
Num. heavy atoms 23
Num. arom. heavy atoms 18
Fraction Csp3 0.16
Num. rotatable bonds 4
Num. H-bond acceptors 2
Num. H-bond donors 1
Molar Refractivity 95.77
TPSA 70.00 Å²
Lipophilicity
Log Po/w (iLOGP) 3.21
Log Po/w (XLOGP3) 4.13
Log Po/w (WLOGP) 4.71
Log Po/w (MLOGP) 3.13
Log Po/w (SILICOS-IT) 6.47
Consensus Log Po/w 4.33
Water Solubility
Log S (ESOL) -4.76
Solubility 5.65e-03 mg/ml ; 1.75e-05 mol/l
Class Moderately soluble
Log S (Ali) -5.31
Solubility 1.59e-03 mg/ml ; 4.93e-06 mol/l
Class Moderately soluble
Log S (SILICOS-IT) -7.69
Solubility 6.52e-06 mg/ml ; 2.02e-08 mol/l
Class Poorly soluble
Pharmacokinetics
GI absorption High
BBB permeant Yes
P-gp substrate No
CYP1A2 inhibitor Yes
CYP2C19 inhibitor Yes
CYP2C9 inhibitor Yes
CYP2D6 inhibitor No
CYP3A4 inhibitor Yes
Log Kp (skin permeation) -5.33 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge Yes
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 0 alert
Brenk 1 alert: thiocarbonyl_group
Leadlikeness No; 1 violation: XLOGP3>3.5
Synthetic accessibility 3.04

Fig. S8

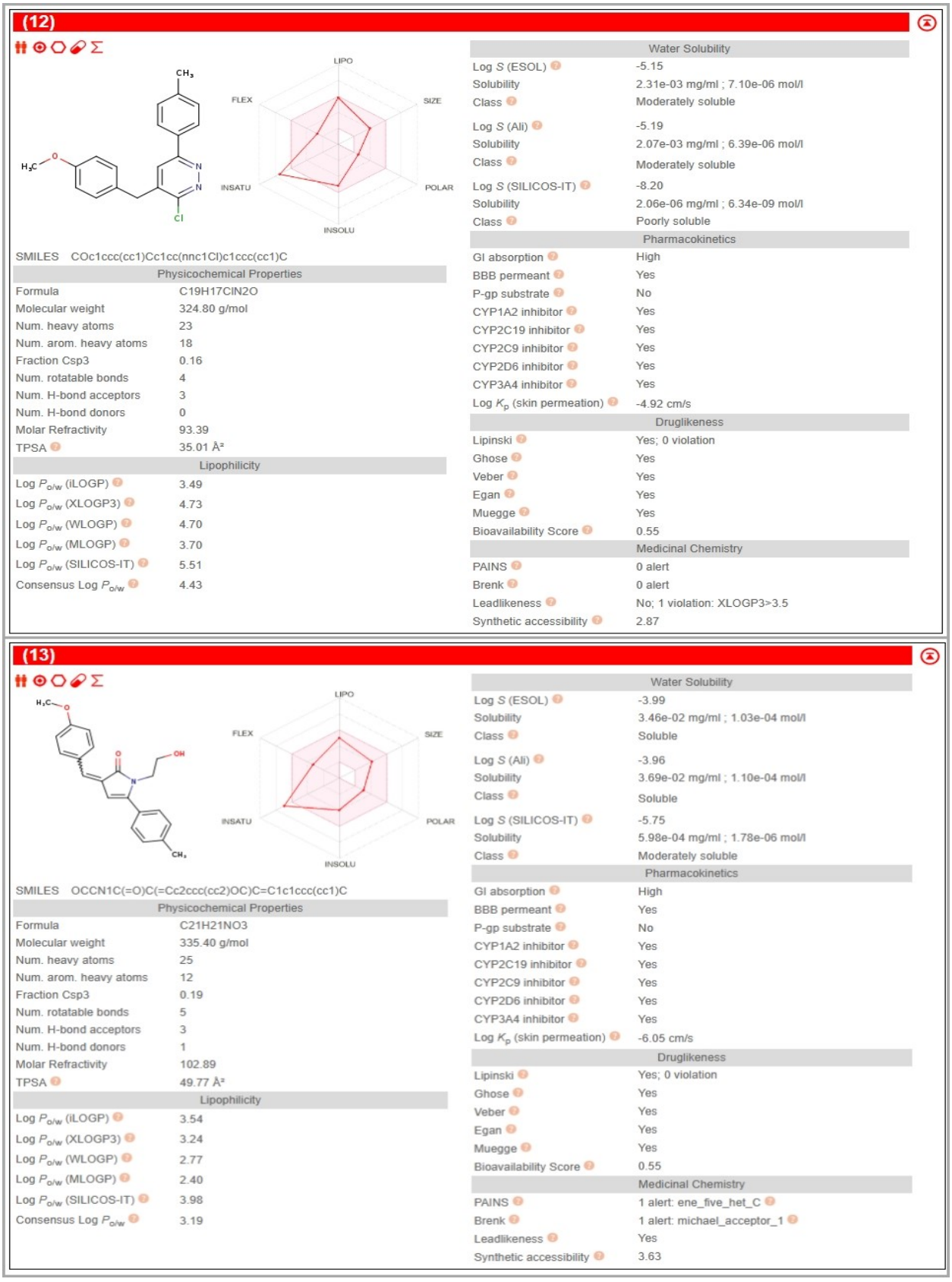
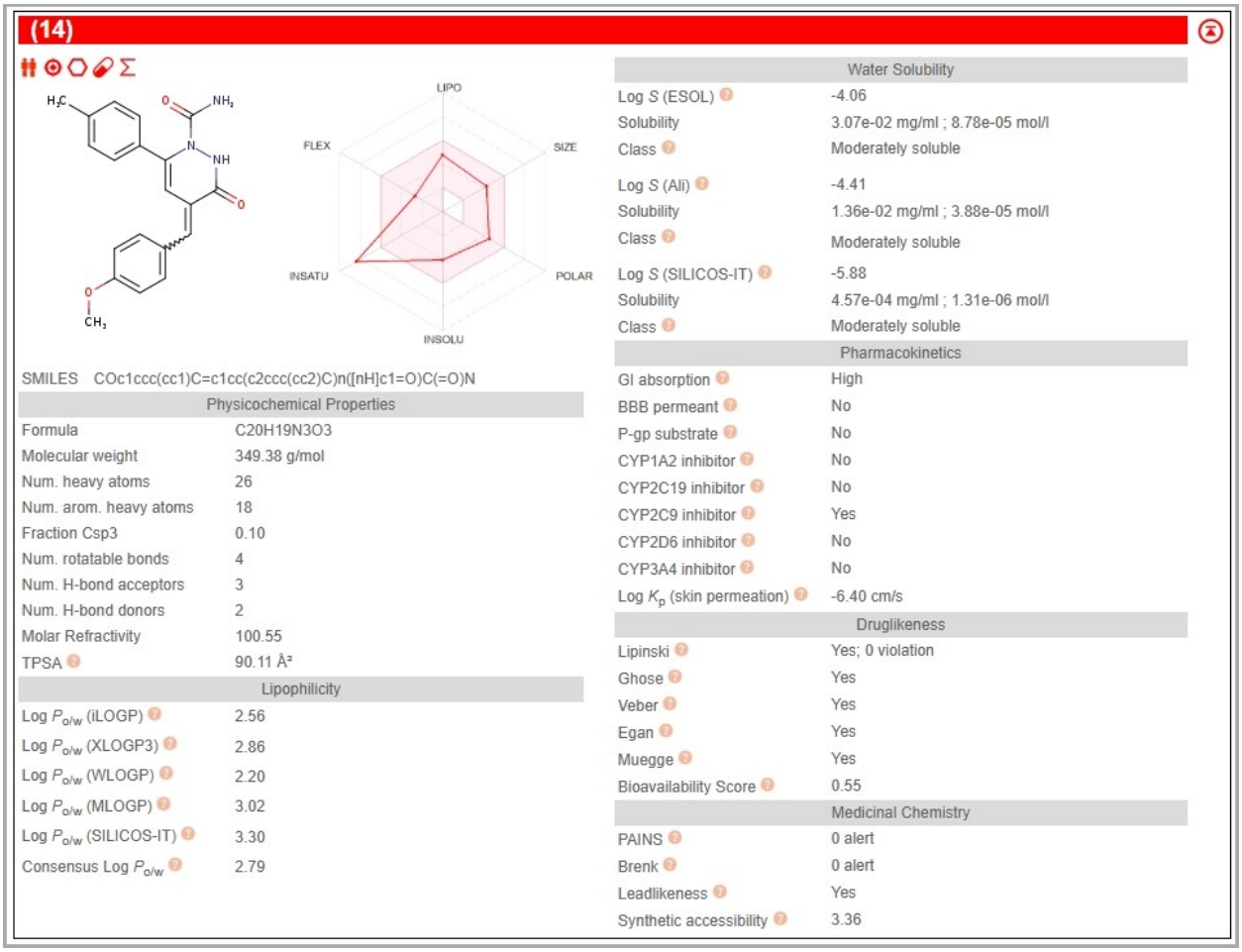

(12)
LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX
SMILES COc1ccc(cc1)Cc1cc(nnc1Cl)c1ccc(cc1)C
Physicochemical Properties
Formula C19H17ClN2O
Molecular weight 324.80 g/mol
Num. heavy atoms 23
Num. arom. heavy atoms 18
Fraction Csp3 0.16
Num. rotatable bonds 4
Num. H-bond acceptors 3
Num. H-bond donors 0
Molar Refractivity 93.39
TPSA 35.01 Å²
Lipophilicity
Log Po/w (iLOGP) 3.49
Log Po/w (XLOGP3) 4.73
Log Po/w (WLOGP) 4.70
Log Po/w (MLOGP) 3.70
Log Po/w (SILICOS-IT) 5.51
Consensus Log Po/w 4.43
Water Solubility
Log S (ESOL) -5.15
Solubility 2.31e-03 mg/ml ; 7.10e-06 mol/l
Class Moderately soluble
Log S (Ali) -5.19
Solubility 2.07e-03 mg/ml ; 6.39e-06 mol/l
Class Moderately soluble
Log S (SILICOS-IT) -8.20
Solubility 2.06e-06 mg/ml ; 6.34e-09 mol/l
Class Poorly soluble
Pharmacokinetics
GI absorption High
BBB permeant Yes
P-gp substrate No
CYP1A2 inhibitor Yes
CYP2C19 inhibitor Yes
CYP2C9 inhibitor Yes
CYP2D6 inhibitor Yes
CYP3A4 inhibitor Yes
Log Kp (skin permeation) -4.92 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge Yes
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 0 alert
Brenk 0 alert
Leadlikeness No; 1 violation: XLOGP3>3.5
Synthetic accessibility 2.87
(13)
LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX
SMILES OCCN1C(=O)C(=Cc2ccc(cc2)OC)C=C1c1ccc(cc1)C
Physicochemical Properties
Formula C21H21NO3
Molecular weight 335.40 g/mol
Num. heavy atoms 25
Num. arom. heavy atoms 12
Fraction Csp3 0.19
Num. rotatable bonds 5
Num. H-bond acceptors 3
Num. H-bond donors 1
Molar Refractivity 102.89
TPSA 49.77 Å²
Lipophilicity
Log Po/w (iLOGP) 3.54
Log Po/w (XLOGP3) 3.24
Log Po/w (WLOGP) 2.77
Log Po/w (MLOGP) 2.40
Log Po/w (SILICOS-IT) 3.98
Consensus Log Po/w 3.19
Water Solubility
Log S (ESOL) -3.99
Solubility 3.46e-02 mg/ml ; 1.03e-04 mol/l
Class Soluble
Log S (Ali) -3.96
Solubility 3.69e-02 mg/ml ; 1.10e-04 mol/l
Class Soluble
Log S (SILICOS-IT) -5.75
Solubility 5.98e-04 mg/ml ; 1.78e-06 mol/l
Class Moderately soluble
Pharmacokinetics
GI absorption High
BBB permeant Yes
P-gp substrate No
CYP1A2 inhibitor Yes
CYP2C19 inhibitor Yes
CYP2C9 inhibitor Yes
CYP2D6 inhibitor Yes
CYP3A4 inhibitor Yes
Log Kp (skin permeation) -6.05 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge Yes
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 1 alert: ene_five_het_C
Brenk 1 alert: michael_acceptor_1
Leadlikeness Yes
Synthetic accessibility 3.63

Fig.S9


(14)
LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX
SMILES COc1ccc(cc1)C=c1cc(c2ccc(cc2)C)n([nH]c1=O)C(=O)N
Physicochemical Properties
Formula C20H19N3O3
Molecular weight 349.38 g/mol
Num. heavy atoms 26
Num. arom. heavy atoms 18
Fraction Csp3 0.10
Num. rotatable bonds 4
Num. H-bond acceptors 3
Num. H-bond donors 2
Molar Refractivity 100.55
TPSA 90.11 Å²
Lipophilicity
Log Po/w (iLOGP) 2.56
Log Po/w (XLOGP3) 2.86
Log Po/w (WLOGP) 2.20
Log Po/w (MLOGP) 3.02
Log Po/w (SILICOS-IT) 3.30
Consensus Log Po/w 2.79
Water Solubility
Log S (ESOL) -4.06
Solubility 3.07e-02 mg/ml ; 8.78e-05 mol/l
Class Moderately soluble
Log S (Ali) -4.41
Solubility 1.36e-02 mg/ml ; 3.88e-05 mol/l
Class Moderately soluble
Log S (SILICOS-IT) -5.88
Solubility 4.57e-04 mg/ml ; 1.31e-06 mol/l
Class Moderately soluble
Pharmacokinetics
GI absorption High
BBB permeant No
P-gp substrate No
CYP1A2 inhibitor No
CYP2C19 inhibitor No
CYP2C9 inhibitor Yes
CYP2D6 inhibitor No
CYP3A4 inhibitor No
Log Kp (skin permeation) -6.40 cm/s
Druglikeness
Lipinski Yes; 0 violation
Ghose Yes
Veber Yes
Egan Yes
Muegge Yes
Bioavailability Score 0.55
Medicinal Chemistry
PAINS 0 alert
Brenk 0 alert
Leadlikeness Yes
Synthetic accessibility 3.36