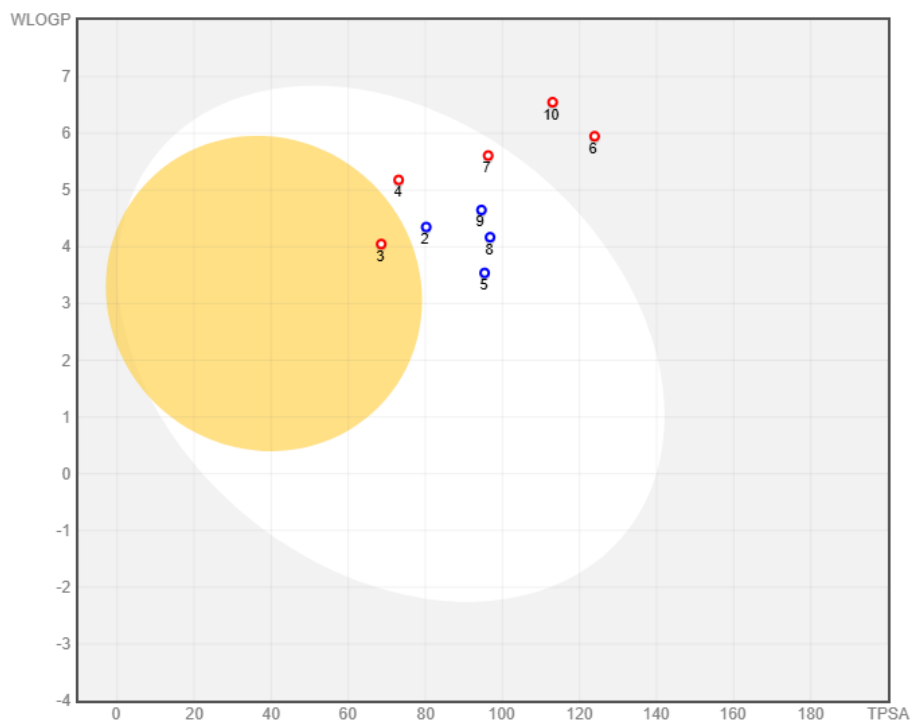


Supplementary Data File

1. SWISSADME profiling of the synthesized candidates

Cpds	Smiles
2	<chem>N=C1C(C2C3=CC(OC)=C(OC)C=C3)=C(N=CN1)OC4=C2C5=C(C=C4)C=CC=C5</chem>
3	<chem>OC1=C(C#N)C(C2=CC(OC)=C(OC)C=C2)C3=C(O1)C=CC4=C3C=CC=C4</chem>
4	<chem>CCO/C=N/C1=C(C#N)C(C2=CC(OC)=C(OC)C=C2)C3=C(O1)C=CC4=C3C=CC=C4</chem>
5	<chem>N=C1C(C2C3=CC(OC)=C(OC)C=C3)=C(N=CN1N)OC4=C2C5=C(C=C4)C=CC=C5</chem>
6	<chem>N=C1C(C2C3=CC(OC)=C(OC)C=C3)=C(N=CN1NS(C4=CC=C(C)C=C4)(=O)=O)OC5=C2C6=C(C=C5)C=CC=C6</chem>
7	<chem>N=C1C(C2C3=CC(OC)=C(OC)C=C3)=C(N=CN1C4=C(C)N(C)N(C5=CC=CC=C5)C4=O)OC6=C2C7=C(C=C6)C=CC=C7</chem>
8	<chem>COC1=C(OC)C=CC(C2C(C3=NC4=O)=C(N=CN3N4)OC5=C2C6=C(C=C5)C=CC=C6)=C1</chem>
9	<chem>COC(C=C1)=C(OC)C=C1C2C(C3=NC(CC#N)=NN3C=N4)=C4OC5=C2C6=C(C=C5)C=CC=C6</chem>
10	<chem>COC(C=C1)=C(OC)C=C1C2C(C3=NC(/C(C#N)=C/C4=CC(OC)=C(OC)C=C4)=NN3C=N5)=C5OC6=C2C7=C(C=C6)C=CC=C7</chem>



Actions

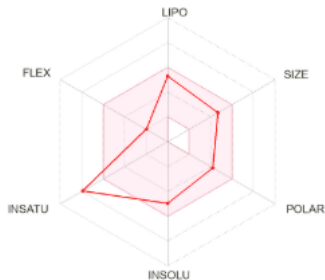
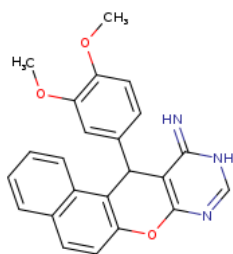
- Show Molecules Name

Legends

- BBB
- HIA
- PGP+
- PGP-

Remarks

None



SMILES COc1ccc(cc1OC)C1c2c(nc[nH]c2=N)Oc2c1c1cccc1cc2

Physicochemical Properties

Formula	C ₂₃ H ₁₉ N ₃ O ₃
Molecular weight	385.42 g/mol
Num. heavy atoms	29
Num. arom. heavy atoms	22
Fraction Csp ³	0.13
Num. rotatable bonds	3
Num. H-bond acceptors	5
Num. H-bond donors	2
Molar Refractivity	109.62
TPSA ²	80.22 Å ²

Lipophilicity

Log <i>P</i> _{o/w} (iLOGP) ²	2.83
Log <i>P</i> _{o/w} (XLOGP3) ²	3.77
Log <i>P</i> _{o/w} (WLOGP) ²	4.35
Log <i>P</i> _{o/w} (MLOGP) ²	2.55
Log <i>P</i> _{o/w} (SILICOS-IT) ²	4.90
Consensus Log <i>P</i> _{o/w} ²	3.68

Water Solubility

Log S (ESOL) ²	-4.97
Solubility	4.15e-03 mg/ml ; 1.08e-05 mol/l
Class ²	Moderately soluble
Log S (Alii) ²	-5.15
Solubility	2.74e-03 mg/ml ; 7.11e-06 mol/l
Class ²	Moderately soluble
Log S (SILICOS-IT) ²	-8.38
Solubility	1.59e-06 mg/ml ; 4.12e-09 mol/l
Class ²	Poorly soluble

Pharmacokinetics

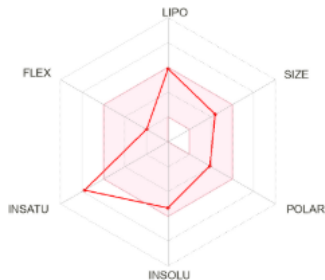
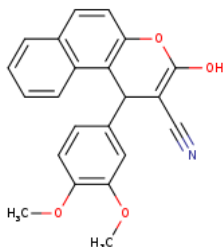
GI absorption ²	High
BBB permeant ²	No
P-gp substrate ²	Yes
CYP1A2 inhibitor ²	Yes
CYP2C19 inhibitor ²	Yes
CYP2C9 inhibitor ²	Yes
CYP2D6 inhibitor ²	Yes
CYP3A4 inhibitor ²	Yes
Log <i>K</i> _p (skin permeation) ²	-5.97 cm/s

Druglikeness

Lipinski ²	Yes; 0 violation
Ghose ²	Yes
Veber ²	Yes
Egan ²	Yes
Muegge ²	Yes
Bioavailability Score ²	0.55

Medicinal Chemistry

PAINS ²	0 alert
Brenk ²	0 alert
Leadlikeness ²	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility ²	4.02



SMILES N#CC1=C(O)Oc2c(C1c1ccc(cc1)OC)OC)c1ccccc1cc2

Physicochemical Properties

Formula	C22H17NO4
Molecular weight	359.37 g/mol
Num. heavy atoms	27
Num. arom. heavy atoms	16
Fraction Csp3	0.14
Num. rotatable bonds	3
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	101.22
TPSA	71.71 Å²

Lipophilicity

Log $P_{o/w}$ (iLOGP)	2.90
Log $P_{o/w}$ (XLOGP3)	4.81
Log $P_{o/w}$ (WLOGP)	4.67
Log $P_{o/w}$ (MLOGP)	2.22
Log $P_{o/w}$ (SILICOS-IT)	4.02
Consensus Log $P_{o/w}$	3.72

Water Solubility

Log S (ESOL)	-5.34
Solubility	1.65e-03 mg/ml ; 4.58e-06 mol/l
Class	Moderately soluble
Log S (Ali)	-6.05
Solubility	3.21e-04 mg/ml ; 8.94e-07 mol/l
Class	Poorly soluble
Log S (SILICOS-IT)	-6.62
Solubility	8.60e-05 mg/ml ; 2.39e-07 mol/l
Class	Poorly soluble

Pharmacokinetics

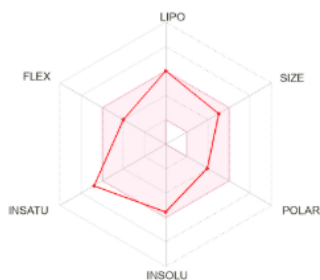
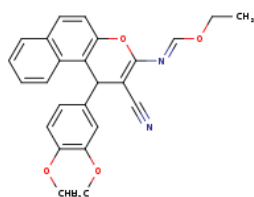
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.08 cm/s

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	3.97



SMILES CCO/C=N/C1=C(C#N)C(c2c(O1)ccc1c2cccc1)c1ccc(c(c1)OC)OC

Physicochemical Properties

Formula	C ₂₅ H ₂₂ N ₂ O ₄
Molecular weight	414.45 g/mol
Num. heavy atoms	31
Num. arom. heavy atoms	16
Fraction Csp ³	0.20
Num. rotatable bonds	6
Num. H-bond acceptors	6
Num. H-bond donors	0
Molar Refractivity	118.84
TPSA	73.07 Å ²

Lipophilicity

Log $P_{o/w}$ (iLOGP)	4.07
Log $P_{o/w}$ (XLOGP3)	5.03
Log $P_{o/w}$ (WLOGP)	5.18
Log $P_{o/w}$ (MLOGP)	2.78
Log $P_{o/w}$ (SILICOS-IT)	5.36
Consensus Log $P_{o/w}$	4.48

Water Solubility

Log S (ESOL)	-5.56
Solubility	1.13e-03 mg/ml ; 2.73e-06 mol/l
Class	Moderately soluble
Log S (Alii)	-6.31
Solubility	2.05e-04 mg/ml ; 4.95e-07 mol/l
Class	Poorly soluble
Log S (SILICOS-IT)	-7.78
Solubility	6.93e-06 mg/ml ; 1.67e-08 mol/l
Class	Poorly soluble

Pharmacokinetics

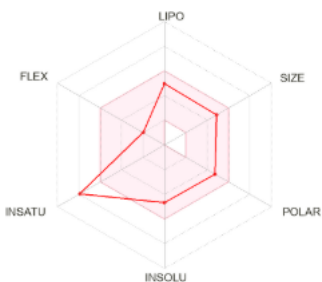
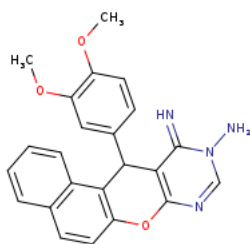
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.26 cm/s

Druglikeness

Lipinski	Yes; 0 violation
Ghose	Yes
Weber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55

Medicinal Chemistry

PAINS	0 alert
Brenk	2 alerts: imine_1, imine_2
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.54



SMILES COC1ccc(cc1OC)C1c2c(ncn(c2=N)N)Oc2c1c1cccc1cc2

Physicochemical Properties

Formula	C ₂₃ H ₂₀ N ₄ O ₃
Molecular weight	400.43 g/mol
Num. heavy atoms	30
Num. arom. heavy atoms	22
Fraction Csp ³	0.13
Num. rotatable bonds	3
Num. H-bond acceptors	5
Num. H-bond donors	2
Molar Refractivity	113.40
TPSA	95.38 Å ²

Lipophilicity

Log <i>P</i> _{o/w} (iLOGP)	2.75
Log <i>P</i> _{o/w} (XLOGP3)	3.21
Log <i>P</i> _{o/w} (WLOGP)	3.54
Log <i>P</i> _{o/w} (MLOGP)	2.84
Log <i>P</i> _{o/w} (SILICOS-IT)	3.13
Consensus Log <i>P</i> _{o/w}	3.09

Water Solubility

Log S (ESOL)	-4.69
Solubility	8.18e-03 mg/ml ; 2.04e-05 mol/l
Class	Moderately soluble
Log S (Ali)	-4.89
Solubility	5.22e-03 mg/ml ; 1.30e-05 mol/l
Class	Moderately soluble
Log S (SILICOS-IT)	-7.19
Solubility	2.59e-05 mg/ml ; 6.47e-08 mol/l
Class	Poorly soluble

Pharmacokinetics

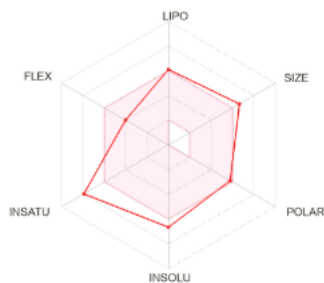
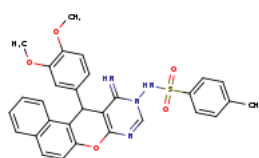
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log <i>K</i> _p (skin permeation)	-6.46 cm/s

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: MW>350
Synthetic accessibility	4.23



SMILES COc1ccc(cc1OC)C1c2c(ncn(c2=N)NS(=O)(=O)c2ccc(cc2)C)Oc2c1c1cccc1cc2

Physicochemical Properties

Formula	C30H26N4O5S
Molecular weight	554.62 g/mol
Num. heavy atoms	40
Num. arom. heavy atoms	28
Fraction Csp3	0.13
Num. rotatable bonds	6
Num. H-bond acceptors	7
Num. H-bond donors	2
Molar Refractivity	151.07
TPSA ²	123.91 Å ²

Lipophilicity

Log $P_{o/w}$ (iLOGP) ²	3.49
Log $P_{o/w}$ (XLOGP3) ²	5.17
Log $P_{o/w}$ (WLOGP) ²	5.95
Log $P_{o/w}$ (MLOGP) ²	3.42
Log $P_{o/w}$ (SILICOS-IT) ²	3.99
Consensus Log $P_{o/w}$ ²	4.40

Water Solubility

Log S (ESOL) ²	-6.66
Solubility	1.22e-04 mg/ml ; 2.20e-07 mol/l
Class ²	Poorly soluble
Log S (Ali) ²	-7.52
Solubility	1.68e-05 mg/ml ; 3.03e-08 mol/l
Class ²	Poorly soluble
Log S (SILICOS-IT) ²	-10.26
Solubility	3.02e-08 mg/ml ; 5.45e-11 mol/l
Class ²	Insoluble

Pharmacokinetics

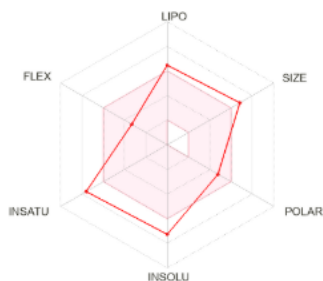
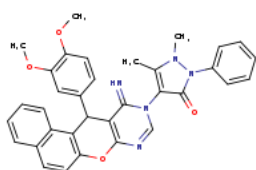
GI absorption ²	Low
BBB permeant ²	No
P-gp substrate ²	No
CYP1A2 inhibitor ²	No
CYP2C19 inhibitor ²	No
CYP2C9 inhibitor ²	Yes
CYP2D6 inhibitor ²	No
CYP3A4 inhibitor ²	No
Log K_p (skin permeation) ²	-6.01 cm/s

Druglikeness

Lipinski ²	Yes; 1 violation: MW>500
Ghose ²	No; 3 violations: MW>480, WLOGP>5.6, MR>130
Veber ²	Yes
Egan ²	No; 1 violation: WLOGP>5.88
Muegge ²	No; 1 violation: XLOGP3>5
Bioavailability Score ²	0.55

Medicinal Chemistry

PAINS ²	0 alert
Brenk ²	0 alert
Leadlikeness ²	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility ²	4.91



SMILES COc1cc(ccc1OC)C1c2c(ccc3c2cccc3)Oc2c1c(=N)n(cn2)c1c(C)n(c1=O)c1cccc1C

Physicochemical Properties

Formula	C34H29N5O4
Molecular weight	571.63 g/mol
Num. heavy atoms	43
Num. arom. heavy atoms	33
Fraction Csp3	0.15
Num. rotatable bonds	5
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar Refractivity	164.41
TPSA	96.29 Å²

Lipophilicity

Log $P_{o/w}$ (iLOGP)	4.46
Log $P_{o/w}$ (XLOGP3)	5.78
Log $P_{o/w}$ (WLOGP)	5.61
Log $P_{o/w}$ (MLOGP)	4.07
Log $P_{o/w}$ (SILICOS-IT)	4.99
Consensus Log $P_{o/w}$	4.98

Water Solubility

Log S (ESOL)	-7.26
Solubility	3.12e-05 mg/ml ; 5.45e-08 mol/l
Class	Poorly soluble
Log S (Ali)	-7.57
Solubility	1.53e-05 mg/ml ; 2.68e-08 mol/l
Class	Poorly soluble
Log S (SILICOS-IT)	-10.26
Solubility	3.11e-08 mg/ml ; 5.45e-11 mol/l
Class	Insoluble

Pharmacokinetics

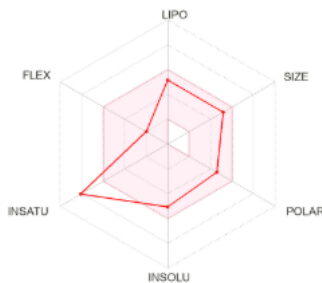
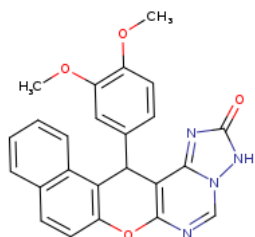
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.68 cm/s

Druglikeness

Lipinski	Yes; 1 violation: MW>500
Ghose	No; 4 violations: MW>480, WLOGP>5.6, MR>130, #atoms>70
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55

Medicinal Chemistry

PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	5.08



SMILES Cc1ccc(cc1OC)C1c2c(ccc3c2ccc3)Oc2c1c1nc(=O)[nH]n1cn2

Physicochemical Properties

Formula	C24H18N4O4
Molecular weight	426.42 g/mol
Num. heavy atoms	32
Num. arom. heavy atoms	25
Fraction Csp3	0.12
Num. rotatable bonds	3
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar Refractivity	118.11
TPSA	90.74 Å ²

Lipophilicity

Log $P_{o/w}$ (ILOGP)	2.76
Log $P_{o/w}$ (XLOGP3)	3.52
Log $P_{o/w}$ (WLOGP)	3.87
Log $P_{o/w}$ (MLOGP)	2.79
Log $P_{o/w}$ (SILICOS-IT)	3.64
Consensus Log $P_{o/w}$	3.32

Water Solubility

Log S (ESOL)	-5.08
Solubility	3.53e-03 mg/ml ; 8.29e-06 mol/l
Class	Moderately soluble
Log S (Ali)	-5.11
Solubility	3.31e-03 mg/ml ; 7.77e-06 mol/l
Class	Moderately soluble
Log S (SILICOS-IT)	-7.89
Solubility	5.46e-06 mg/ml ; 1.28e-08 mol/l
Class	Poorly soluble

Pharmacokinetics

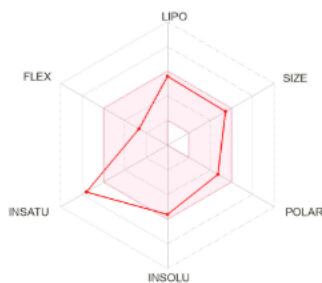
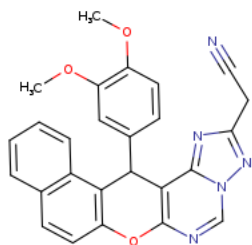
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.40 cm/s

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	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.97



SMILES N#CCc1nn2c(n1)c1c(nc2)Oc2c(C1c1ccc(c(c1)OC)OC)c1ccccc1cc2

Physicochemical Properties

Formula	C ₂₆ H ₁₉ N ₅ O ₃
Molecular weight	449.46 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	25
Fraction Csp ³	0.15
Num. rotatable bonds	4
Num. H-bond acceptors	7
Num. H-bond donors	0
Molar Refractivity	124.81
TPSA	94.56 Å ²

Lipophilicity

Log <i>P</i> _{o/w} (iLOGP)	3.28
Log <i>P</i> _{o/w} (XLOGP3)	4.30
Log <i>P</i> _{o/w} (WLOGP)	4.65
Log <i>P</i> _{o/w} (MLOGP)	2.80
Log <i>P</i> _{o/w} (SILICOS-IT)	3.93
Consensus Log <i>P</i> _{o/w}	3.79

Water Solubility

Log S (ESOL)	-5.62
Solubility	1.09e-03 mg/ml ; 2.42e-06 mol/l
Class	Moderately soluble
Log S (Ali)	-6.00
Solubility	4.50e-04 mg/ml ; 1.00e-06 mol/l
Class	Moderately soluble
Log S (SILICOS-IT)	-8.46
Solubility	1.58e-06 mg/ml ; 3.51e-09 mol/l
Class	Poorly soluble

Pharmacokinetics

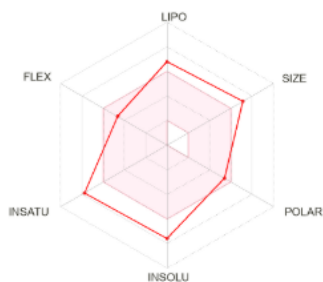
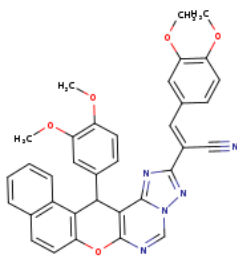
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log <i>K</i> _p (skin permeation)	-5.99 cm/s

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	4.15



SMILES N#C/C(=C/c1ccc(c(c1)OC)OC)/c1nc2n(n1)cnc1c2C(c2ccc(c(c2)OC)OC)c2c(O1)ccc1c2cccc1

Physicochemical Properties

Formula	C35H27N5O5
Molecular weight	597.62 g/mol
Num. heavy atoms	45
Num. arom. heavy atoms	31
Fraction Csp3	0.14
Num. rotatable bonds	7
Num. H-bond acceptors	9
Num. H-bond donors	0
Molar Refractivity	168.20
TPSA ²	113.02 Å ²

Lipophilicity

Log $P_{o/w}$ (iLOGP) ²	4.65
Log $P_{o/w}$ (XLOGP3) ²	6.36
Log $P_{o/w}$ (WLOGP) ²	6.55
Log $P_{o/w}$ (MLOGP) ²	3.24
Log $P_{o/w}$ (SILICOS-IT) ²	5.57
Consensus Log $P_{o/w}$ ²	5.27

Water Solubility

Log S (ESOL) ²	-7.60
Solubility	1.50e-05 mg/ml ; 2.51e-08 mol/l
Class ²	Poorly soluble
Log S (Ali) ²	-8.52
Solubility	1.79e-06 mg/ml ; 2.99e-09 mol/l
Class ²	Poorly soluble
Log S (SILICOS-IT) ²	-10.74
Solubility	1.10e-08 mg/ml ; 1.83e-11 mol/l
Class ²	Insoluble

Pharmacokinetics

GI absorption ²	Low
BBB permeant ²	No
P-gp substrate ²	No
CYP1A2 inhibitor ²	No
CYP2C19 inhibitor ²	No
CYP2C9 inhibitor ²	Yes
CYP2D6 inhibitor ²	No
CYP3A4 inhibitor ²	Yes
Log K_p (skin permeation) ²	-5.43 cm/s

Druglikeness

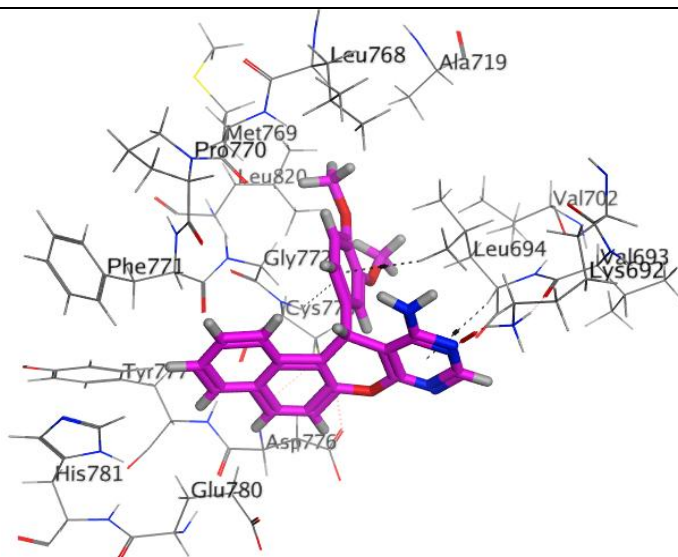
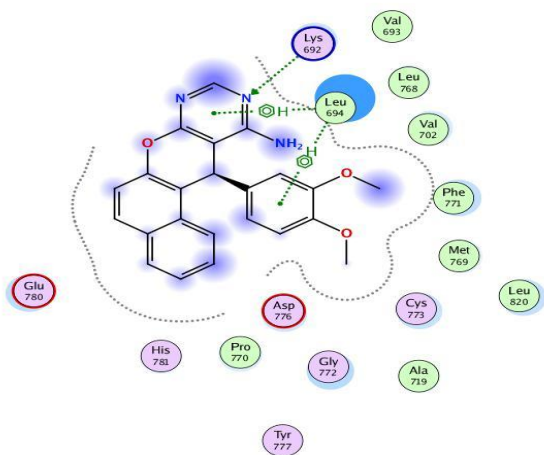
Lipinski ²	Yes; 1 violation: MW>500
Ghose ²	No; 4 violations: MW>480, WLOGP>5.6, MR>130, #atoms>70
Veber ²	Yes
Egan ²	No; 1 violation: WLOGP>5.88
Muegge ²	No; 1 violation: XLOGP3>5
Bioavailability Score ²	0.55

Medicinal Chemistry

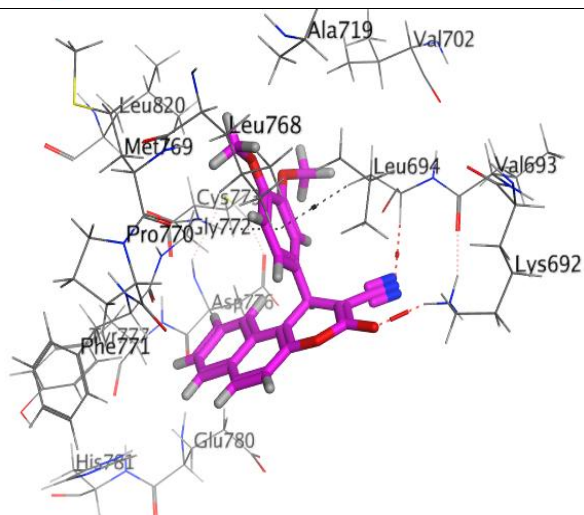
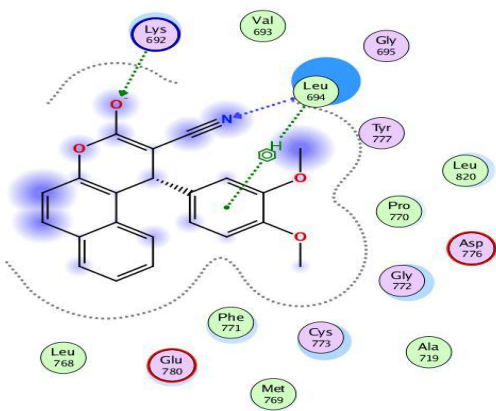
PAINS ²	0 alert
Brenk ²	1 alert: conjugated_nitrile_group ²
Leadlikeness ²	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility ²	5.13

Detailed 2D and 3D interaction diagrams of the synthesized compounds derivatives docked to EGFR tyrosine kinase (PDB ID: 4HJO). Comparisons include binding interactions of each derivative alongside the reference inhibitor doxorubicin and the co-crystallized ligand (AQ4). Notably, many of the derivatives exhibit interaction profiles that closely resemble those of the co-crystallized ligand, supporting the reliability and accuracy of the docking protocol. The diagrams highlight hydrogen bonding, π -interactions, ionic contacts, and other key molecular interactions within the active site environments.

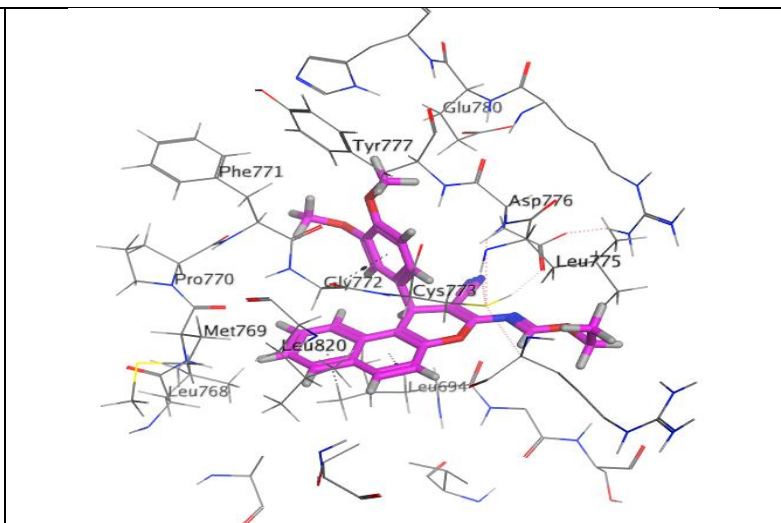
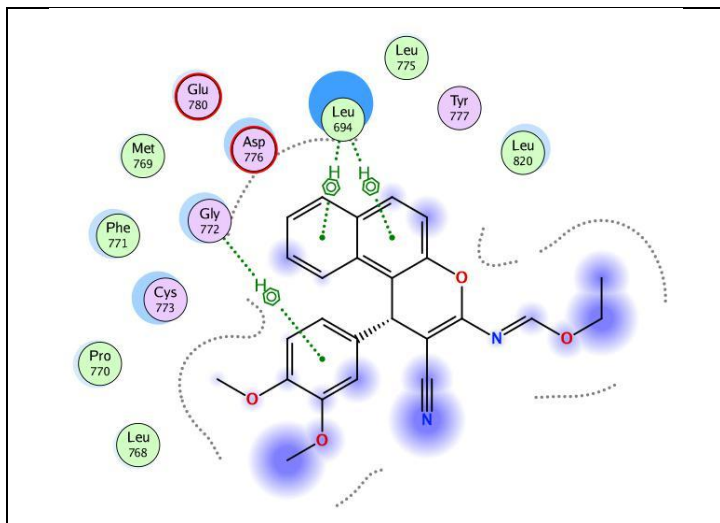
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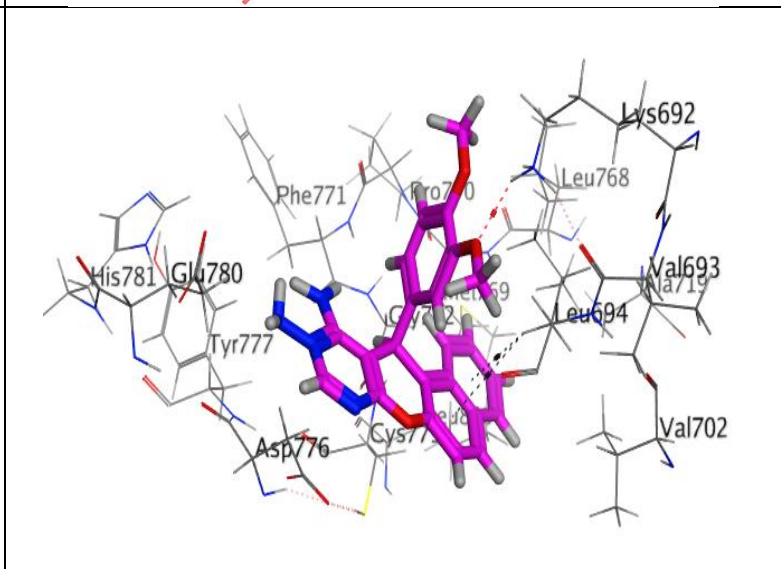
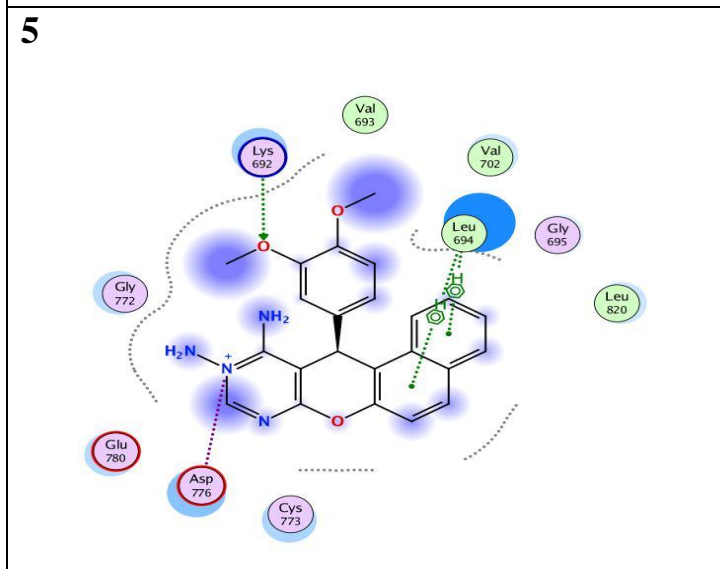
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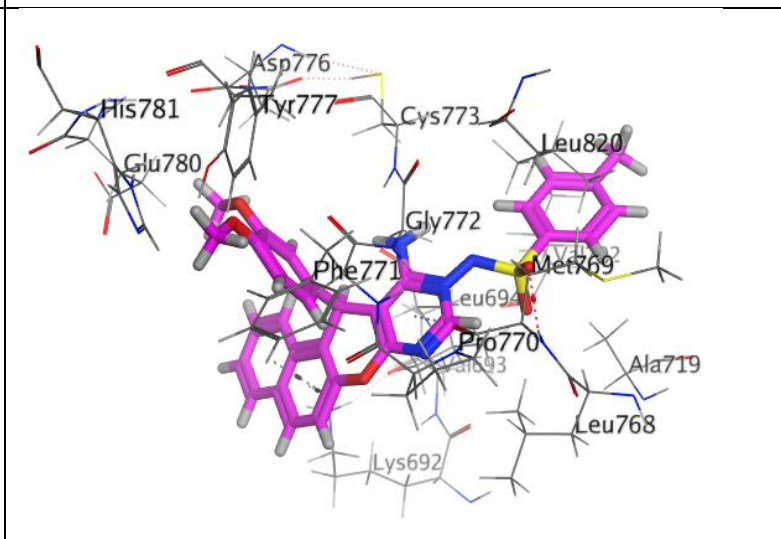
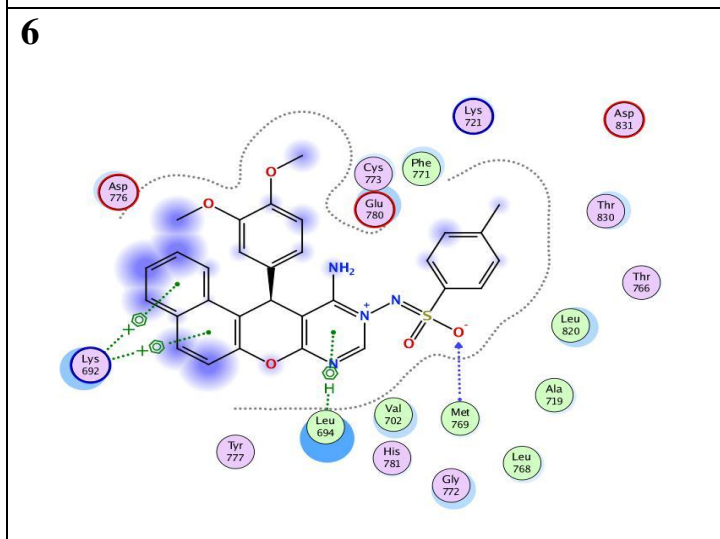
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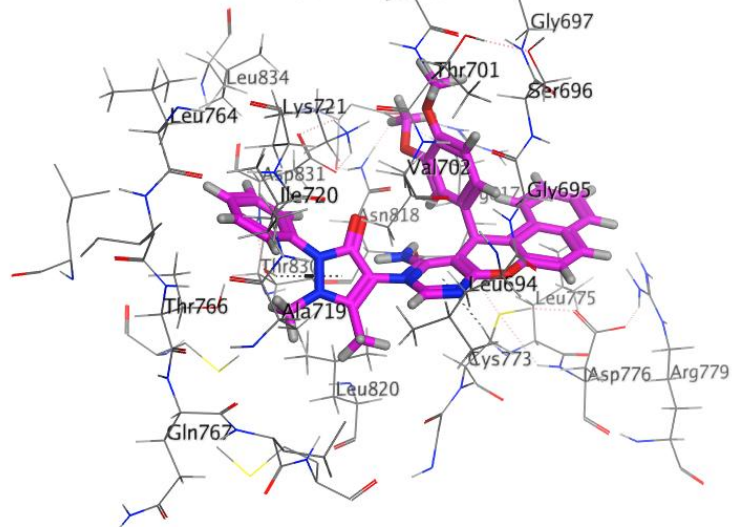
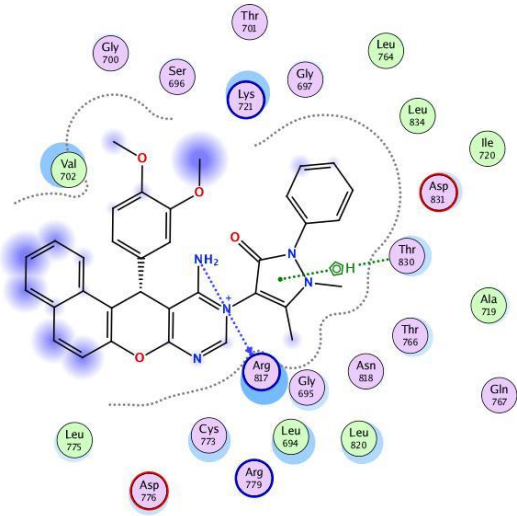
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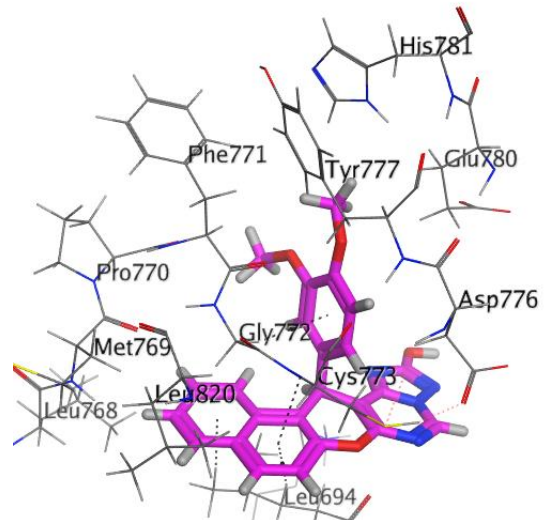
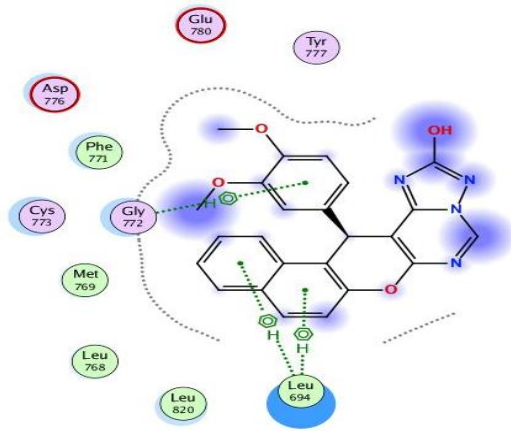
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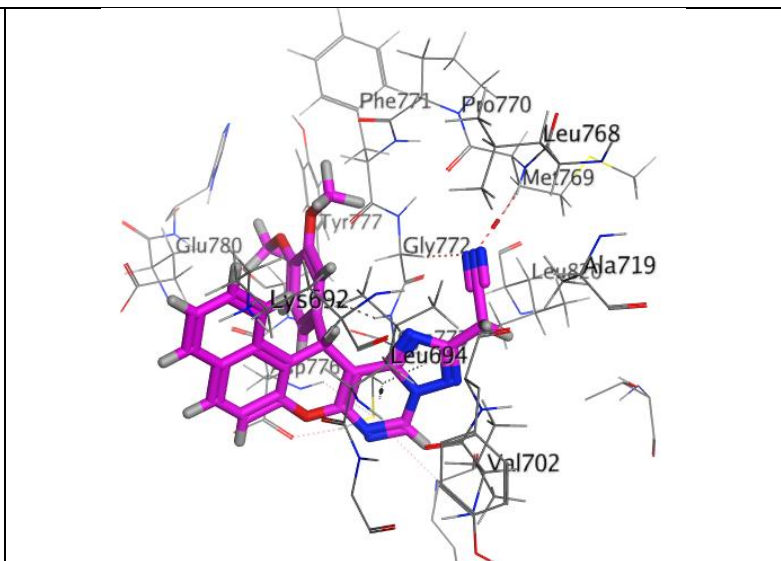
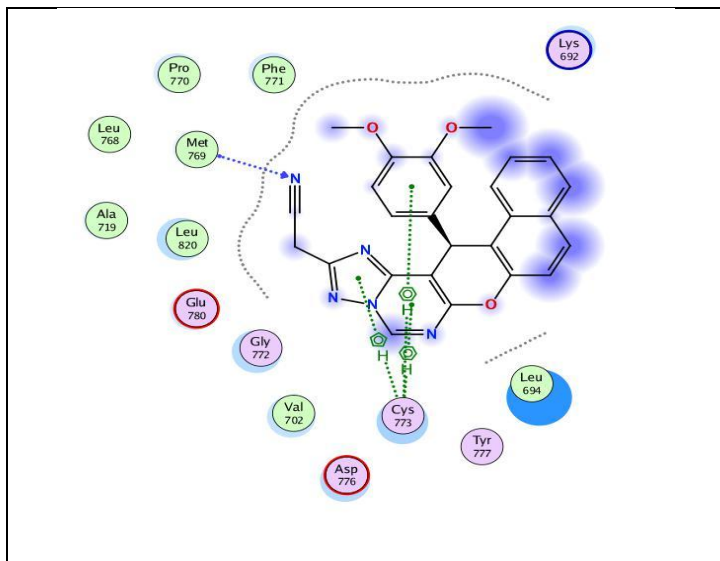
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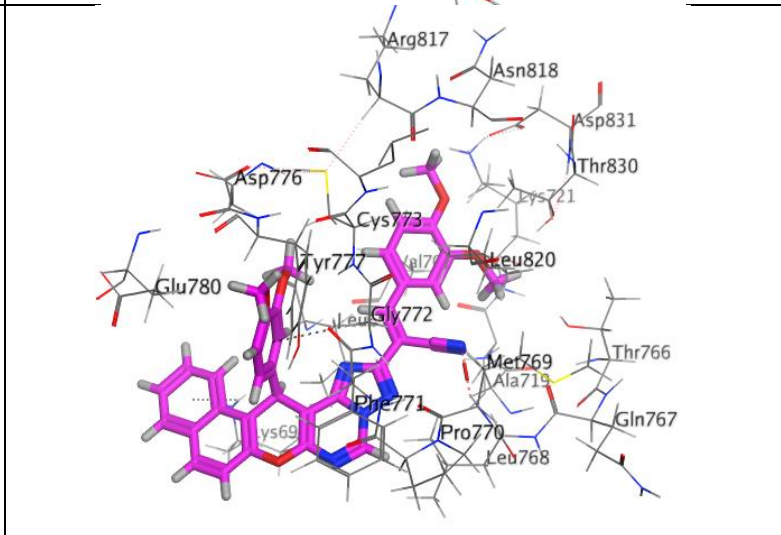
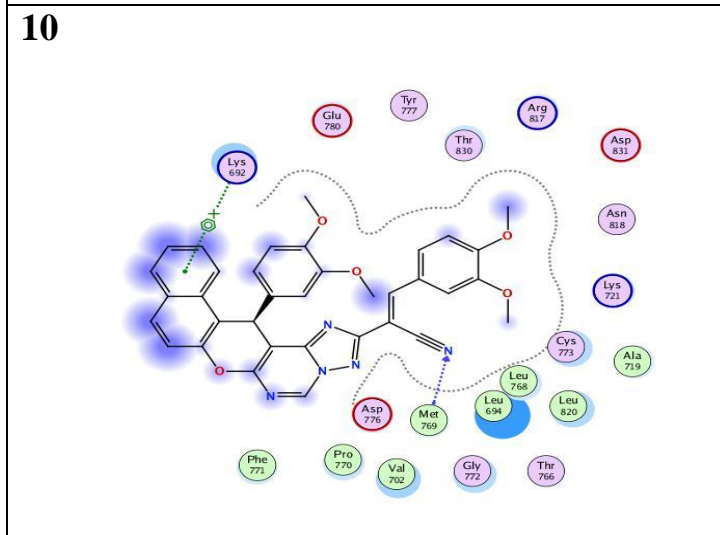
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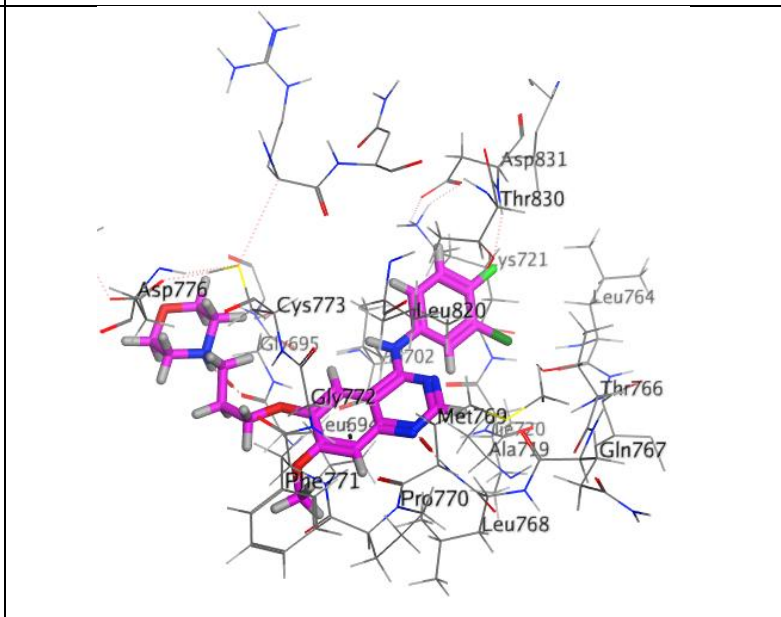
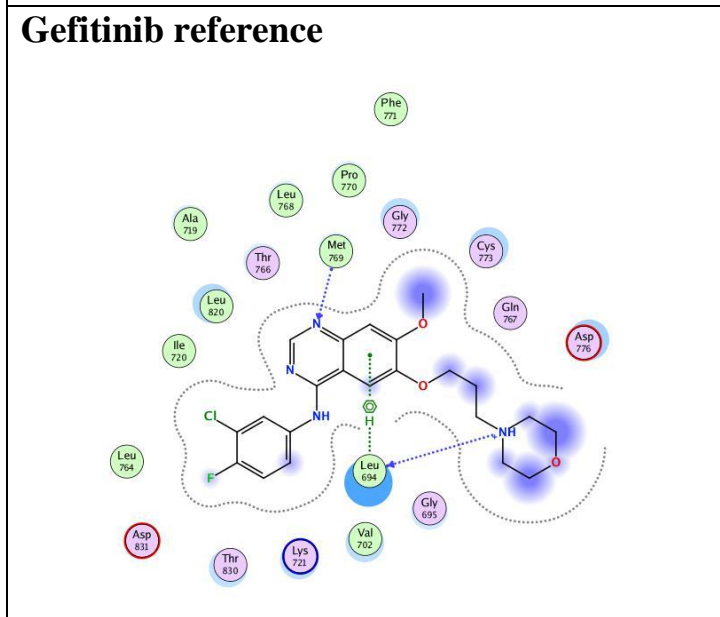
9



10



Gefitinib reference



Co-Crystallized ligand

