Supporting information

Spectrochemical, Medicinal, and Toxicological Studies of Moxifloxacin and its Novel Analogs: A Quantum Chemistry and Drug Discovery Approach

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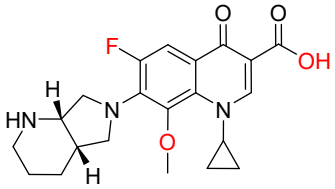
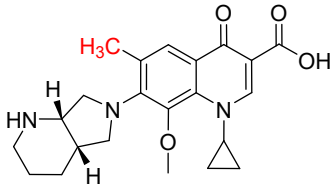
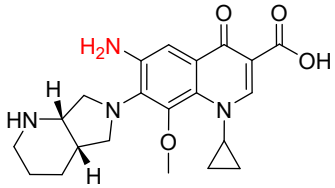
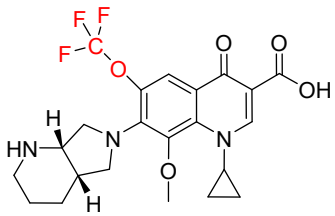
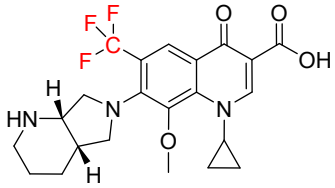
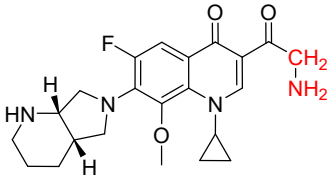
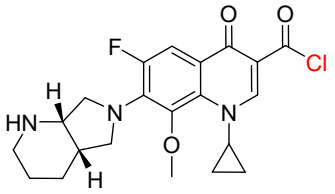
Table S1 Chemical structures and IUPAC name of MOX and its analogs.

Name	Structure	IUPAC Name
MOX		1-cyclopropyl-6-fluoro-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
MOX1		1-cyclopropyl-8-methoxy-6-methyl-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
MOX2		6-amino-1-cyclopropyl-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
MOX3		1-cyclopropyl-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-6-(trifluoromethoxy)-1,4-dihydroquinoline-3-carboxylic acid
MOX4		1-cyclopropyl-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-6-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxylic acid
MOX5		1-cyclopropyl-6-fluoro-3-glycyl-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)quinolin-4(1H)-one
MOX6		1-cyclopropyl-6-fluoro-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carbonyl chloride

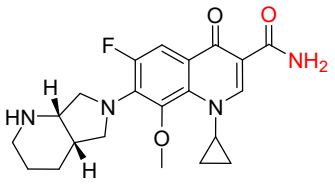
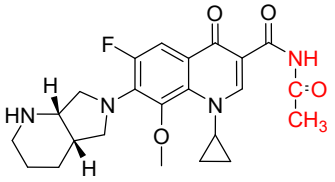
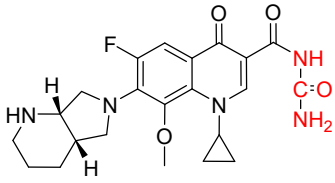
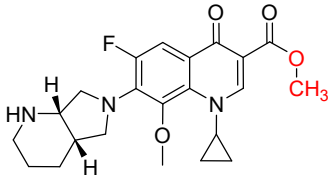
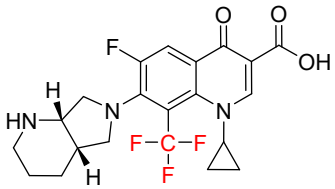
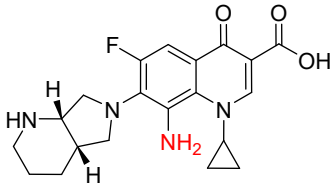
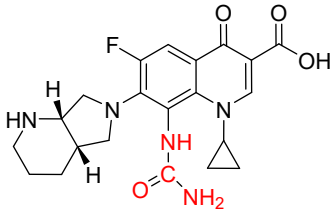
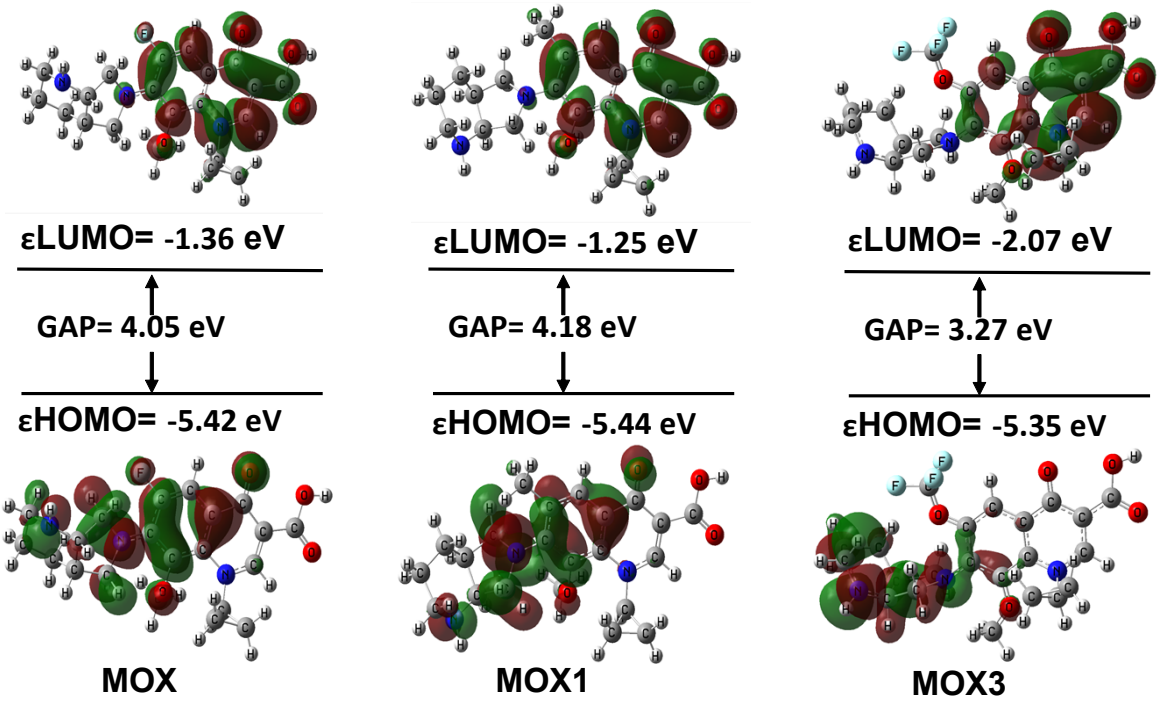
MOX7		1-cyclopropyl-6-fluoro-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
MOX8		N-acetyl-1-cyclopropyl-6-fluoro-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
MOX9		N-carbamoyl-1-cyclopropyl-6-fluoro-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
MOX10		Methyl 1-cyclopropyl-6-fluoro-8-methoxy-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate
MOX11		1-cyclopropyl-6-fluoro-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-8-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxylic acid
MOX12		8-amino-1-cyclopropyl-6-fluoro-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
MOX13		1-cyclopropyl-6-fluoro-7-((4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-8-ureido-1,4-dihydroquinoline-3-carboxylic acid

Table S2 Energy (eV) of HOMO-LUMO, gap, hardness (η), softness (S), and chemical potential (μ) of MOX and its analogs.

Name	εHOMO (eV)	εLUMO (eV)	Gap (eV)	η	S	μ
MOX	-5.42	-1.36	4.05	2.02	0.24	-3.39
MOX1	-5.44	-1.25	4.18	2.09	0.23	-3.35
MOX2	-5.12	-1.12	4.00	2.00	0.24	-3.12
MOX3	-5.35	-2.07	3.27	1.63	0.30	-3.71
MOX4	-5.86	-2.26	3.59	1.79	0.27	-4.06
MOX5	-5.51	-1.52	3.99	1.99	0.25	-3.52
MOX6	-5.82	-1.93	3.89	1.94	0.25	-3.80
MOX7	-5.67	-1.48	4.18	2.09	0.23	-3.58
MOX8	-5.68	-1.63	4.04	2.02	0.24	-3.66
MOX9	-5.36	-1.21	4.14	2.07	0.24	-3.29
MOX10	-5.36	-1.27	4.09	2.04	0.24	-3.32
MOX11	-5.96	-2.42	3.54	1.77	0.28	-4.19
MOX12	-5.44	-1.30	4.14	2.07	0.24	-3.37
MOX13	-5.31	-1.70	3.61	1.80	0.27	-3.51



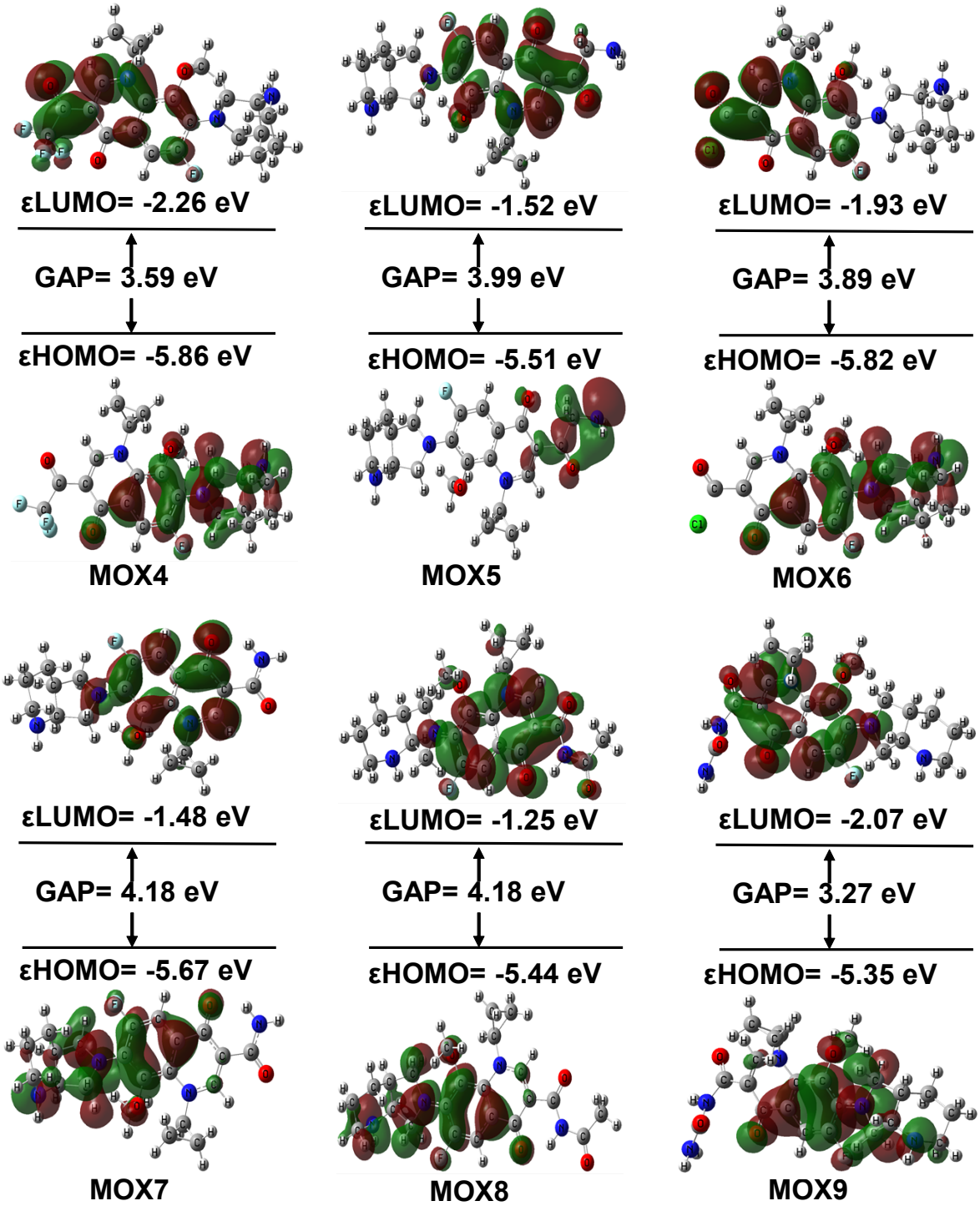


Fig. S1 Frontier molecular orbital (HOMO-LUMO energy gap) of MOX and its analogs.

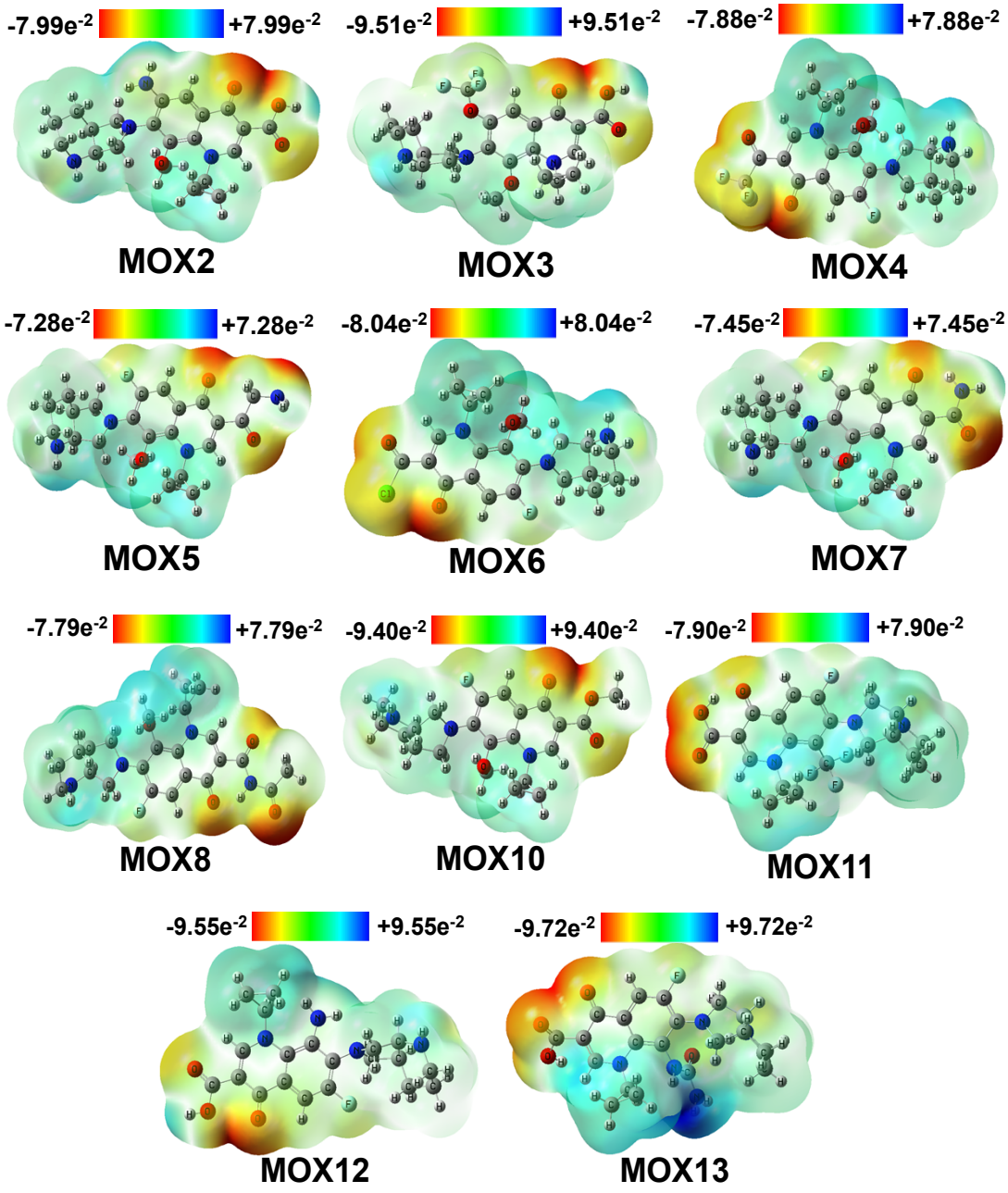
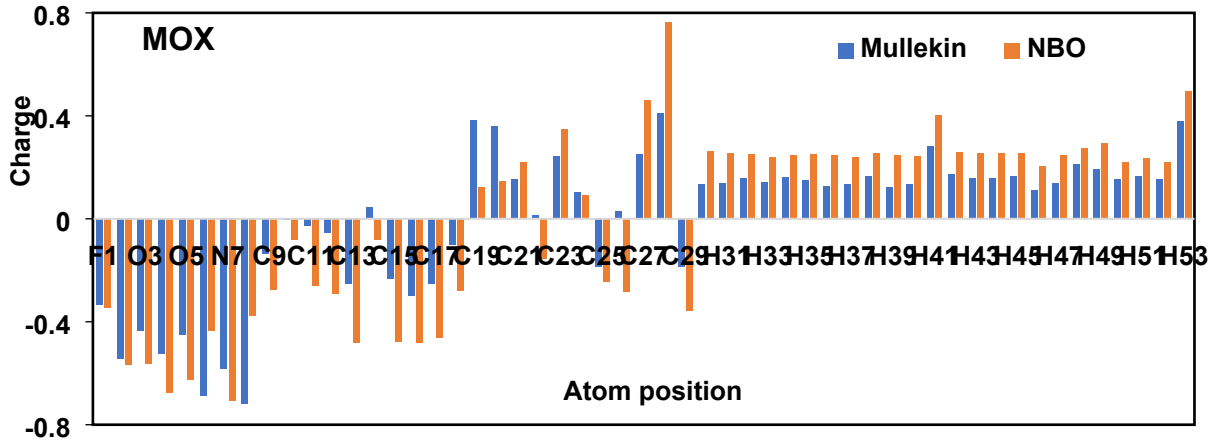
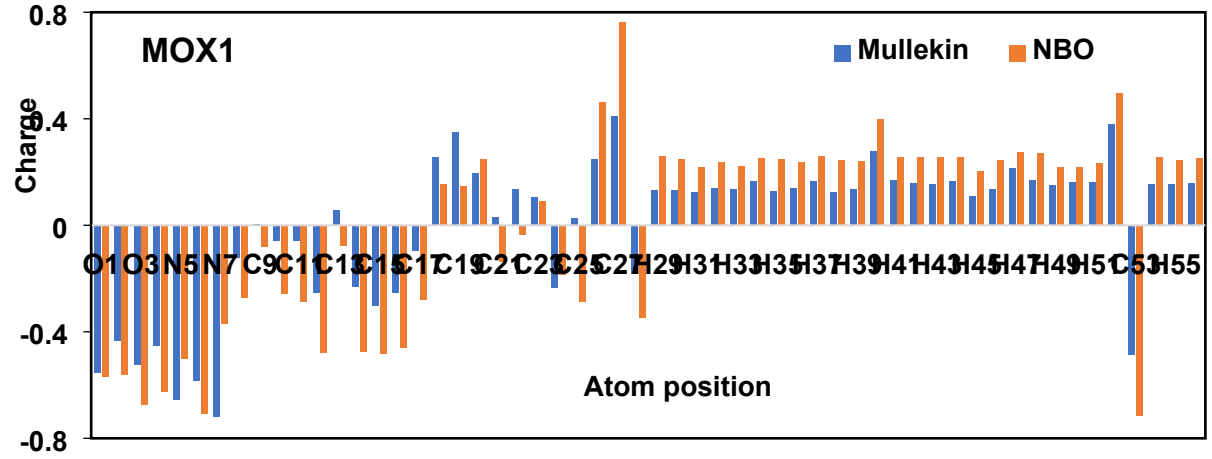
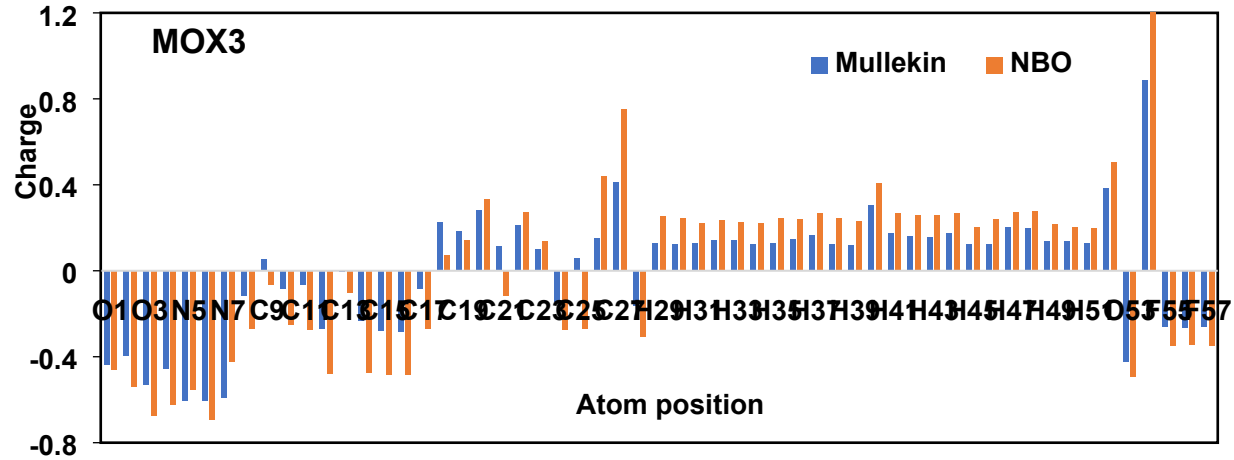
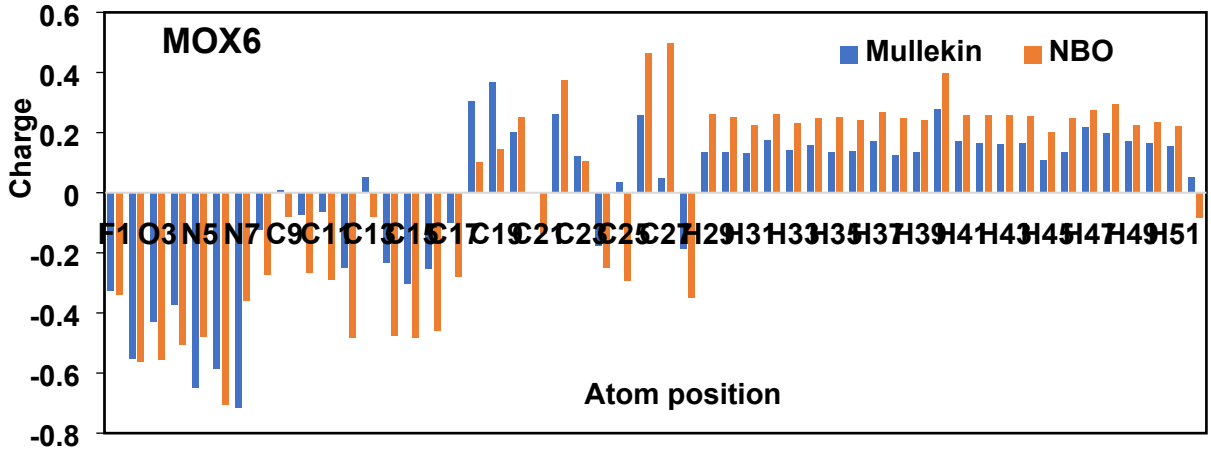


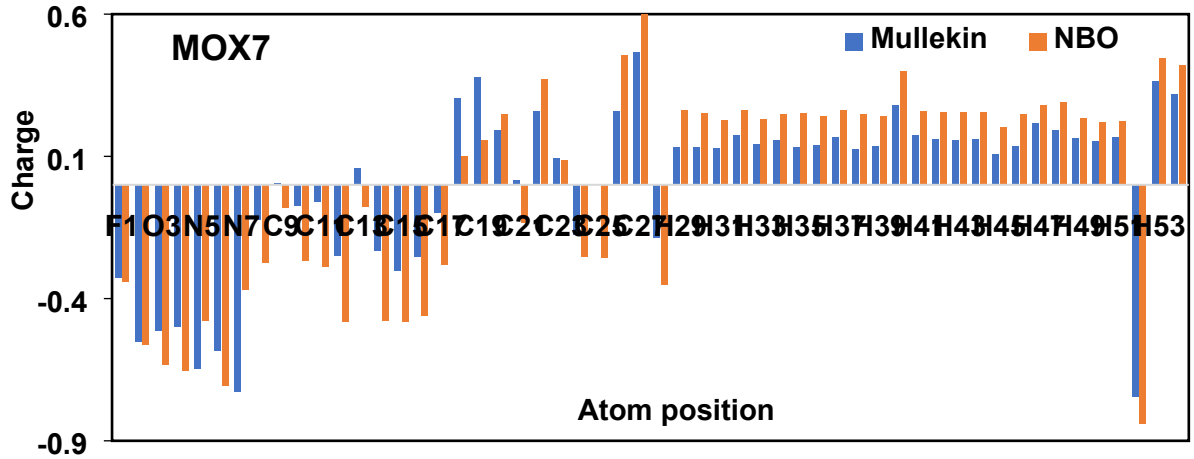
Fig. S2 ESP map of MOX derivatives.

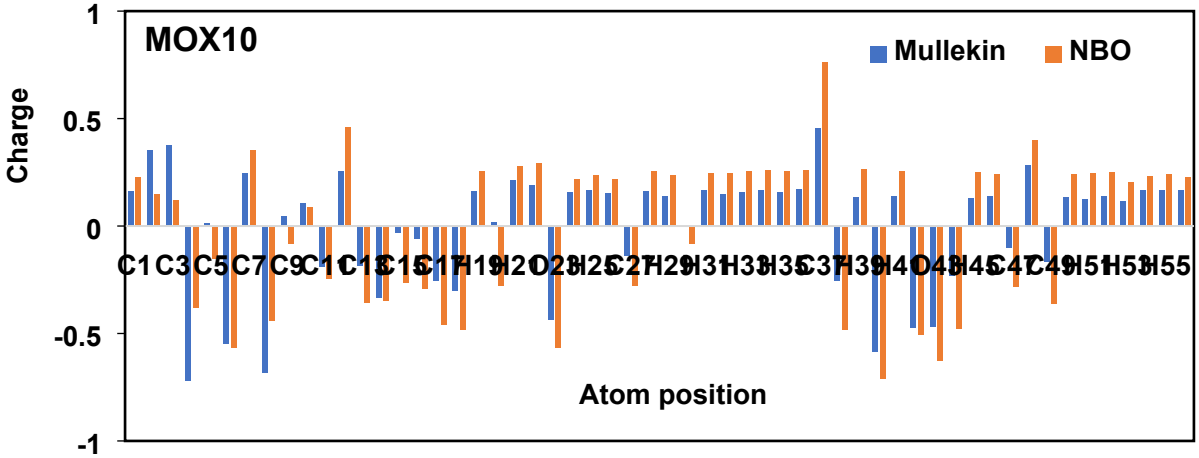

MOX
Mullekin
NBO
Charge
0.8
0.4
0
-0.4
-0.8
F1 O3 O5 N7 C9 C11 C13 C15 C17 C19 C21 C23 C25 C27 C29 H31 H33 H35 H37 H39 H41 H43 H45 H47 H49 H51 H53
Atom position


MOX1
Mullekin
NBO
Charge
0.8
0.4
0
-0.4
-0.8
O1 O3 N5 N7 C9 C11 C13 C15 C17 C19 C21 C23 C25 C27 H29 H31 H33 H35 H37 H39 H41 H43 H45 H47 H49 H51 C53 H55
Atom position


MOX3
Mullekin
NBO
Charge
1.2
0.8
0.4
0
-0.4
-0.8
O1 O3 N5 N7 C9 C11 C13 C15 C17 C19 C21 C23 C25 C27 H29 H31 H33 H35 H37 H39 H41 H43 H45 H47 H49 H51 O53 F55 F57
Atom position


MOX6
Mullekin
NBO
Charge
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
F1 O3 N5 N7 C9 C11 C13 C15 C17 C19 C21 C23 C25 C27 H29 H31 H33 H35 H37 H39 H41 H43 H45 H47 H49 H51
Atom position


MOX7
Mullekin
NBO
Charge
0.6
0.1
-0.4
-0.9
F1 O3 N5 N7 C9 C11 C13 C15 C17 C19 C21 C23 C25 C27 H29 H31 H33 H35 H37 H39 H41 H43 H45 H47 H49 H51 H53
Atom position


MOX10
Mullekin
NBO
Charge
1
0.5
0
-0.5
-1
C1 C3 C5 C7 C9 C11 C13 C15 C17 H19 H21 O23 H25 C27 H29 H31 H33 H35 C37 H39 H41 O43 H45 C47 C49 H51 H53 H55
Atom position

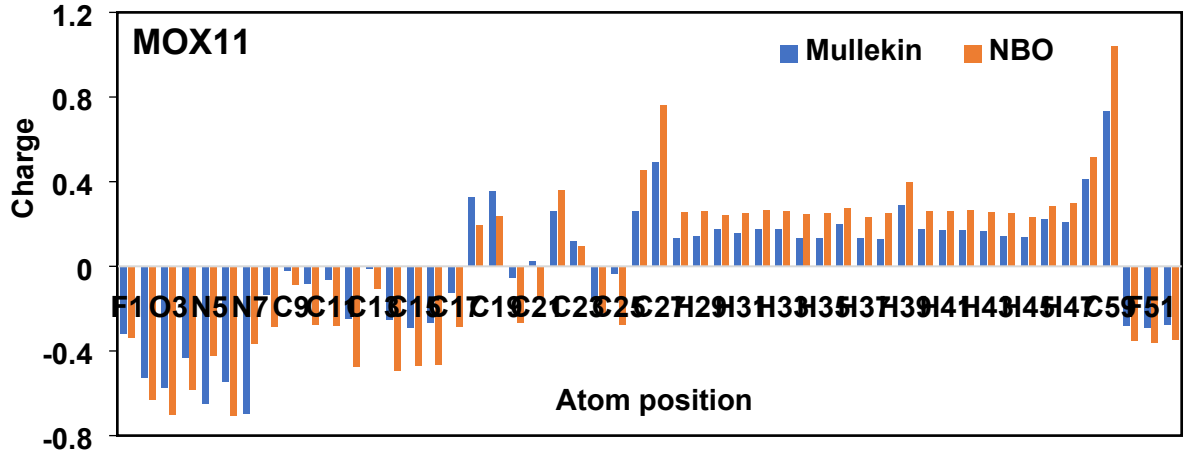


Fig S3 Atomic partial charge of MOX and its analogs.

Table S3 Electronic absorption of MOX and its analogs, calculated at TD-DFT/6-31g level of theory.

Name	Excited state	Wavelength (nm)	Excitation energy(eV)	Configurations composition	Oscillator strength
MOX	$S_0 \rightarrow S_1$	550.51	2.2522	(0.70022) H→L	0.0300
MOX1	$S_0 \rightarrow S_1$	520.72	2.3810	(0.69947) H→L	0.0256
MOX2	$S_0 \rightarrow S_1$	499.38	2.4828	(-0.10149) H-2→L, (-0.13749) H-1→L, (0.68020) H→L	0.0477
MOX3	$S_0 \rightarrow S_1$	429.01	2.8900	(-0.11053) H-3→L, (0.17674) H-2→L, (0.66155) H→L	0.0055
MOX4	$S_0 \rightarrow S_1$	619.59	2.0011	(0.69975) H→L	0.0002
MOX5	$S_0 \rightarrow S_1$	442.51	2.8018	(0.62801) H-1→L, (-0.12600) H-1→L+1, (-0.27400) H→L	0.0035
MOX6	$S_0 \rightarrow S_1$	597.22	2.0760	(0.70104) H→L	0.0222
MOX7	$S_0 \rightarrow S_1$	423.00	2.9310	(0.61348) H-2→L, (0.10793) H-2→L+1, (-0.16872) H-1→L	0.0043
MOX8	$S_0 \rightarrow S_1$	534.24	2.3208	(0.70015) H→L	0.0441
MOX9	$S_0 \rightarrow S_1$	552.99	2.2421	(0.69991) H→L	0.0166
MOX10	$S_0 \rightarrow S_1$	561.28	2.2089	(0.69993) H→L	0.0308
MOX11	$S_0 \rightarrow S_1$	629.82	1.9686	(0.70569) H→L	0.0153
MOX12	$S_0 \rightarrow S_1$	440.68	2.8135	(0.48324) H-1→L, (0.50153) H→L	0.0136

MOX13	$S_0 \rightarrow S_1$	438.05	2.8304	(0.68072) H-2→L, (0.11928) H-1→L	0.0003

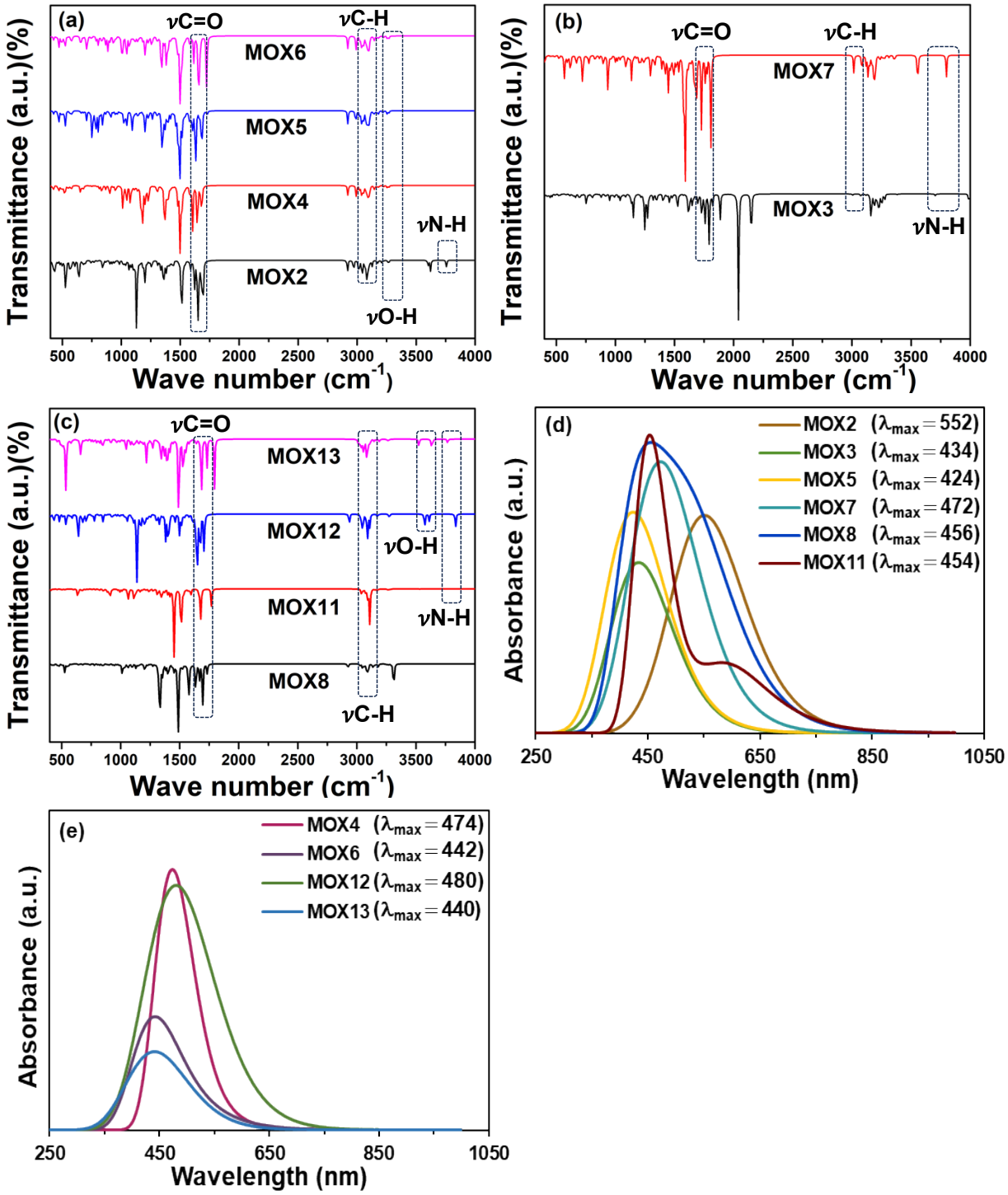


Fig. S4 (a), (b), (c) FT-IR spectra, and (d), (e) UV-visible spectra of MOX derivatives

Table S4 Vibrational frequencies of MOX and derivatives

Name	Assignment	Vibrational frequency (cm^{-1})
MOX	νC-H	3210
	νC=O	1697
	νC-C	1436
	νO-H	3602
	νC=C[a]	1623
MOX1	νC-H	3085
	νC=O	1696
	νC=C[a]	1624
	νN-H	3573
	νO-H	3602
MOX2	νC-H	3070
	νN-H	1622
	νC=C[a]	1506
	νO-H	3648
	νC=O	1692
MOX3	νC-H	3063
	νC=C[a]	1608
	νC-F	1174
	νC=O	1695
MOX4	νC-H	3176
	νC=C[a]	1511
	νC=O	1645
	νN-H	3578
	νC-F	1182
MOX5	νC-H[a]	3096
	νN-H	3575
	νC=C[a]	1664
	νC=O	1630
	νC-F	1220
MOX6	νC-H[a]	3254
	νC=C[a]	1654
	νC=O	1655
	νC-F	1299
MOX7	νN-H	3460
	νC-H[a]	3096
	νC=C[a]	1664
	νC=O	1710
	νC-F	1297
MOX8	νN-H	3580
	νC-H[a]	3255
	νC=C[a]	1636
	νC=O	1694
	νC-F	1291
MOX9	νN-H	3610

	νC-H[a]	3087
	νC=C	1660
	νC=O	1692
MOX10	νC-H[a]	3087
	νN-H	3575
	νC=C[a]	1644
	νC=O	1686
MOX11	νN-H	3522
	νC=C[a]	1670
	νC=O	1585
	νC-F	1058
MOX12	νN-H	3565
	νC-H	3087
	νC=O	1663
	νC-F	1101
MOX13	νN-H	3620
	νC-H	3073
	νC=O	1722
	νC=C[a]	1483
	νC=F	1149

a = aromatic

Table S5 The binding affinity and nonbonding interactions of MOX and its analogues with the receptor protein.

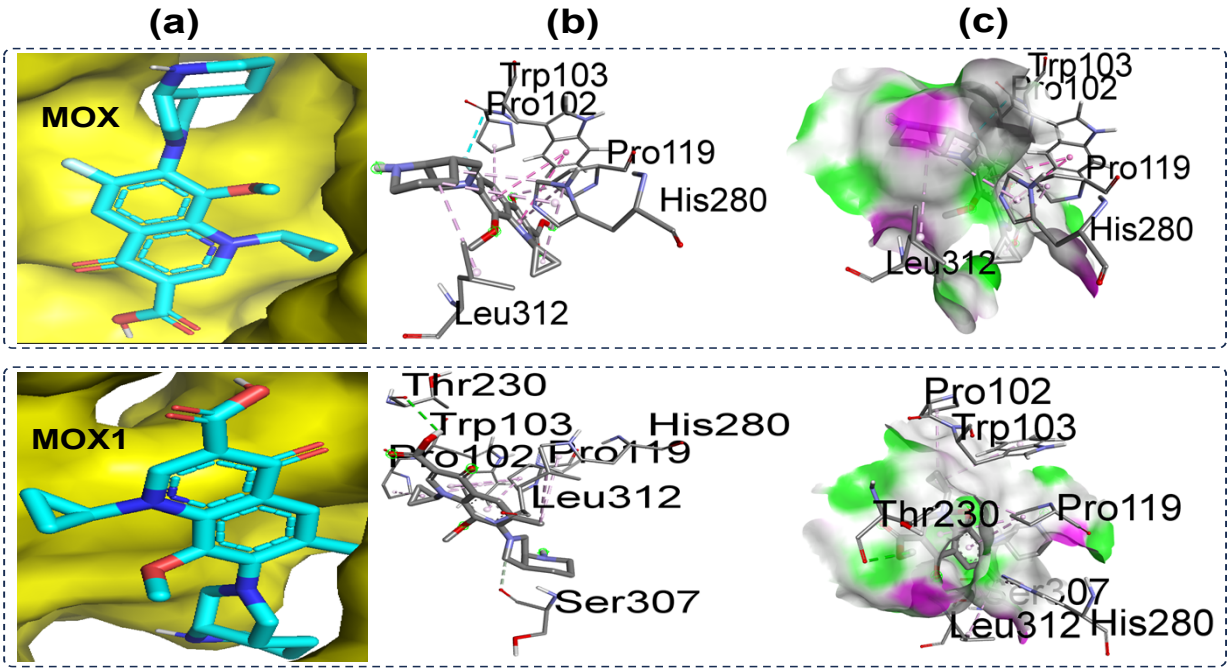
Name	Binding affinity (kcal/mol)	Residues in contact	Interaction's type	Bond distance (Å)
MOX	-7.2	PRO102	HF	3.62
		TRP103	PPT	5.14
		TRP103	PPT	5.10
		PRO119	A	5.29
		LEU312	A	4.71
		PRO119	A	4.95
		PRO119	PA	5.33
		PRO102	PA	5.24
		PRO119	PA	4.74
		HIS280	PA	4.94
MOX1	-8.4	TRP103	H	2.11
		ASP94	H	2.61
		TRP103	H	1.91
		SER104	H	3.09
		GLY120	H	3.75
		GLN101	PDH	2.96
		PRO119	A	5.18
		PRO124	A	4.53
		ARG98	PA	5.11
		ARG98	PA	5.08
		TRP103	PA	5.07
		TRP103	PA	5.02
		TRP103	PA	4.90
		TRP103	H	2.11
MOX2	-7.0	TRP103	PPT	5.18

		TRP103	PPT	5.14
		PRO119	A	5.34
		LEU312	A	4.73
		PRO119	A	4.88
		PRO119	PA	5.26
		PRO102	PA	5.34
		PRO119	PA	4.68
		HIS280	PA	4.99
MOX3	-7.7	ARG98	H	2.60
		ARG98	H	2.29
		GLN101	H	2.20
		SER104	H	2.72
		GLN277	H	2.22
		GLN277	H	2.10
		ASP94	HF	3.51
		GLN101	HF	3.23
		PRO123	A	5.41
		PRO124	A	4.73
		PRO123	A	4.78
		VAL97	A	4.76
		PRO124	A	4.73
		TRP103	PA	5.47
MOX4	-7.8	PRO102	HF	3.21
		GLY117	HF	3.44
		GLY117	HF	3.19
		TRP103	PPT	5.18
		TRP103	PPT	5.17
		LEU312	A	4.43
		PRO119	A	4.57
		PRO119	PA	5.09
		PRO102	PA	5.16
		PRO119	PA	4.78
		HIS280	PA	4.91
MOX5	-7.4	GLY117	H	2.41
		PRO102	HF	3.21
		TRP103	PPT	5.21
		TRP103	PPT	5.16
		TRP103	PPT	5.65
		LEU312	A	4.44
		PRO119	A	4.59
		PRO119	PA	5.03
		PRO102	PA	5.22
		PRO119	PA	4.73
		HIS280	PA	4.92
MOX6	-7.5	PRO102	HF	3.28
		TRP103	PPT	5.36
		TRP103	PPT	5.18
		LEU312	A	4.47
		PRO119	A	4.64
		PRO119	PA	5.00
		PRO102	PA	5.36
		PRO119	PA	4.65
		HIS280	PA	4.90

MOX7	-7.6	ASP308	H	2.91
		PRO102	HF	3.46
		PRO119	A	5.40
		LEU312	A	4.53
		PRO119	A	4.89
		PRO119	PA	4.88
		PRO119	PA	4.43
		HIS280	PA	4.93
MOX8	-8.3	GLY117	H	2.98
		PHE116	H	2.00
		TRP103	PPT	5.07
		TRP103	PPT	5.09
		TRP103	PPT	5.73
		PRO119	A	5.29
		LEU312	A	4.78
		PRO119	A	4.85
		PRO119	PA	5.10
		PRO102	PA	5.40
		PRO119	PA	4.60
		HIS280	PA	5.02
MOX9	-8.3	ASP122	H	2.04
		PRO229	H	2.44
		PRO102	H	2.68
		HIS280	HF	3.26
		PRO119	PA	4.99
		PRO119	PA	4.22
		TRP103	PA	5.34
MOX10	-7.9	TRP103	H	2.03
		ARG98	H	2.66
		TRP103	H	2.08
		GLN277	H	2.66
		SER104	C	2.94
		GLY120	C	3.75
		GLN101	PDH	3.04
		PRO124	A	4.53
		ARG98	PA	5.03
		ARG98	PA	5.28
		PRO124	PA	5.43
		TRP103	PA	5.17
		TRP103	PA	5.18
		TRP103	PA	4.94
MOX11	-7.8	GLY311	C; HF	3.27
		GLY311	C; HF	3.16
		GLY311	HF	3.68
		PRO119	A	5.23
		PRO119	A	5.12
		LEU312	A	5.06
		PRO119	PA	4.68
		PRO119	PA	4.16
		HIS280	PA	4.73
MOX12	-7.2	THR230	H	2.43
		HIS280	C	3.66
		PRO102	A	4.61

		PRO119	PA	5.48
		PRO119	PA	4.50
MOX13	-8.5	GLY120	H	2.45
		ARG98	H; HF	2.27
		TRP103	H	1.96
		SER104	C	3.06
		PRO119	C	3.61
		ARG98	HF	3.50
		PRO124	A	4.64
		PRO124	PA	5.26
		ARG98	PA	4.98
		TRP103	PA	5.31
		TRP103	PA	4.64

H=Conventional hydrogen bond, A=Alkyl, =Pi-Alkyl, HF=Halogen (fluorine), PPT=Pi-Pi T-shaped, PDH=Pi-donor hydrogen bond, C=Conventional carbon bond



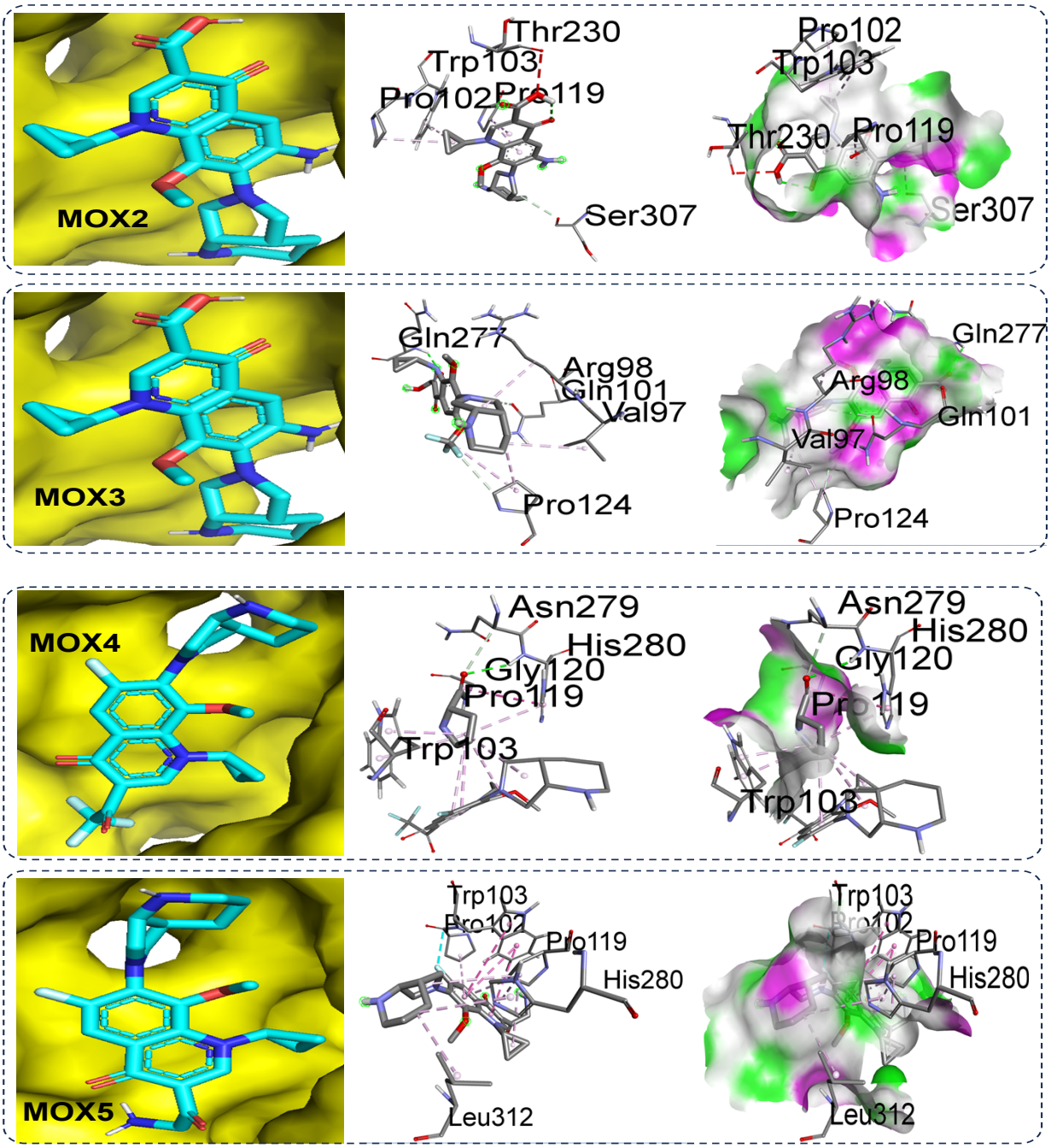


Fig. S5 (a) Docked conformation of MOX and its derivatives at the inhibition binding site of receptor protein 5BS8 (b) Non-bonding interactions and, (c) Hydrogen bond surface area of MOX and its derivatives with the receptor protein.

Table S6 Prediction of biological activities of MOX and some of its derivatives using PASS

Name	AB	AM	AA	TI	DSI	ST	TDP	BC	TC	AS	HT	QTP	HG	KP	TR
MOX	0.66	0.70	0.63	0.82	0.81	0.88	0.84	0.78	0.66	0.73	0.62	0.75	0.80	0.73	0.72
MOX1	0.57	0.63	0.47	0.61	0.67	0.93	0.91	0.89	0.84	0.93	0.86	0.52	0.66	0.92	0.78
MOX2	0.61	0.64	0.33	0.63	0.69	0.92	0.91	0.88	0.84	0.92	0.83	0.54	0.64	0.91	0.83
MOX3	0.58	0.70	0.70	0.55	0.52	0.92	0.80	0.88	0.80	0.94	0.80	0.31	0.43	0.80	0.74
MOX4	0.46	0.48	0.37	0.73	0.54	0.85	0.94	0.85	0.70	0.83	0.67	0.62	0.51	0.90	0.65
MOX5	0.51	0.54	0.40	0.72	0.57	0.90	0.94	0.87	0.76	0.86	0.68	0.62	0.66	0.90	0.76
MOX6	0.48	0.57	0.37	0.68	0.56	0.83	0.93	0.79	0.63	0.76	0.60	0.53	0.53	0.83	0.61
MOX7	0.58	0.66	0.52	0.67	0.59	0.92	0.93	0.89	0.76	0.88	0.76	0.52	0.58	0.81	0.79
MOX8	0.56	0.62	0.62	0.61	0.55	0.90	0.91	0.85	0.72	0.85	0.67	0.50	0.47	0.74	0.75
MOX9	0.53	0.57	0.31	0.60	0.60	0.83	0.83	0.76	0.56	0.71	0.50	0.39	0.54	0.70	0.55
MOX10	0.61	0.67	0.50	0.83	0.70	0.93	0.95	0.95	0.88	0.93	0.88	0.76	0.75	0.95	0.91
MOX11	0.63	0.56	0.63	0.68	0.67	0.90	0.93	0.84	0.85	0.86	0.70	0.49	0.56	0.91	0.59
MOX12	0.55	0.50	0.54	0.56	0.66	0.92	0.92	0.86	0.77	0.88	0.76	0.51	0.58	0.92	0.72
MOX13	0.54	0.40	0.49	0.51	0.62	0.87	0.79	0.73	0.57	0.73	0.57	0.29	0.59	0.78	0.47

AB = Antibacterial, AM = Antimycobacteria, AA = Antiamyloidogenic, TI = Topoisomerase II inhibitor, DSI = DNA synthesis inhibitor, ST = Stomatitis, TDP = Torsades de pointes, BC = Bradycardic, TC = Tachycardic, AS = Asthma, HT = Hepatitis, QTIP = QT interval prolongation, HG = Hyperglycemic, KP = Keratopathy, TR = Tremor, Hyp = Hypertensive.

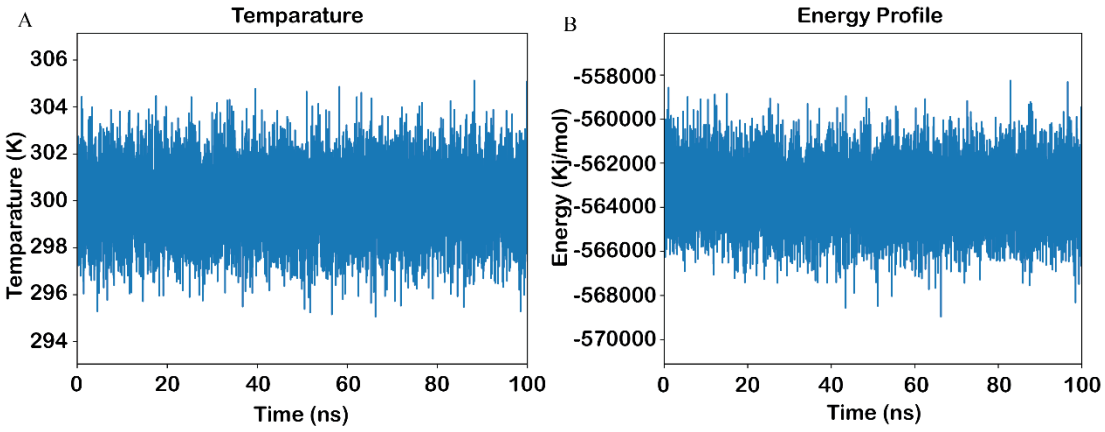


Fig. S6 Potential energy and temperature plots from 100 ns molecular dynamics simulation. Number them as (A) Temperature Plot, and (B) Energy File.