Vibrational Spectroscopy, Quantum Computational and Molecular Docking Studies on 2-[(1H-benzimidazol-1-yl)-methyl]benzoic acid

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To obtain a thorough understanding of optimized parameters, quantum chemical density functional calculations were carried out at the Becke3-Lee-Yang-parr (B3LYP) [20] level using 6-311++G(d,p) basis set using Gaussian 09W [21] computer package, same method was applied in one of our article DFT study on thiophene derivative [22]. The Gaussian 09W programme was used to calculate vibrational frequencies and IR intensities using the optimized molecular structure. The VEDA program was used to assign hypothetical vibrational assignments to the 21HBMBA molecule using potential energy distribution (PED) [23]. The ^{1}H NMR chemical shifts were calculated using the Gauge-Independent Atomic Orbital (GIAO) technique using the B3LYP/6-311++G(d,p) basis set since the geometry of the molecule containing Tetra Methyl Silane (TMS) was fully optimized. The title compound optimized geometry was then employed to conduct a natural bond orbital (NBO) study. Atoms in molecule (AIM) theory were used to calculate topological parameter, electron localization function using Multiwfn software [24]. The Gauss View 6 program [9] was used to create an optimum geometry MEP diagram for the 21HBMBA molecule. The theoretical UV-Vis spectra for DCM, DMSO, EtOH, MeOH and gas phase were explored using the TD-DFT and CPCM solvent model technique with the 6-311++G(d,p) basis set in order to better understand the electronic characteristics. Mulliken population analyses as well as condensed Fukui functions were presented. The same approach was used to determine the dipole moment (μ), linear polarizability (α) and first order hyperpolarizability (β) in the NLO investigation. The SwissADME Tool [25] was used to determine the drug-likeness and ADME features of the compound. Molecular docking investigation was carried out using the Autodock 4.2.6 software programme [26].

Table S1. Optimized bond parameters of 21HBMBA in different solvents.

Bond length (Å)					Bond angle (°)				
B3LYP/6-311++G(d,p)					B3LYP/6-311++G(d,p)				
Parameter	Gas	EtOH	DCM	DMSO	Parameter	Gas	EtOH	DCM	DMSO
N22 – C23	1.39	1.39	1.39	1.39	N22 – C19 – H21	125.54	125.54	125.38	125.39
N22 – C19	1.30	1.30	1.31	1.31	N22 – C19 – N17	119.72	114.10	114.11	114.11
C19 – N17	1.39	1.39	1.37	1.37	C19 – N17 – C20	105.86	105.86	106.10	106.09
N17 – C20	1.39	1.39	1.38	1.38	C20 – C23 – N22	110.22	110.22	109.98	109.99
C20 – C23	1.41	1.41	1.41	1.41	C23 – C25 – H28	120.14	120.14	120.53	120.51
C20 – C24	1.39	1.39	1.39	1.39	C23 – C25 – C29	118.12	118.12	118.05	118.05
C26 – C29	1.40	1.40	1.40	1.40	C25 – C29 – H31	119.64	119.64	119.61	119.61
N17 – C11	1.46	1.46	1.46	1.46	C29 – C26 – C24	121.56	121.56	121.60	121.60
C11 – C6	1.52	1.52	1.52	1.52	C24 – C20 – N17	133.05	133.05	132.96	132.96
C6 – C2	1.41	1.41	1.41	1.41	C20 – N17 – C11	127.64	127.64	127.84	127.84
C2 – C1	1.49	1.49	1.49	1.49	N17 – C11 – C6	114.46	114.46	114.39	114.40
C1 – O3	1.35	1.35	1.34	1.34	C19 – N17 – C11	126.21	126.21	125.84	125.85
O3 – H7	0.96	0.96	0.97	0.97	C11 – C6 – C2	124.04	124.02	124.13	124.12
C1 – O4	1.21	1.21	1.21	1.21	C2 – C1 – O4	125.76	125.76	125.42	125.43
C2 – C5	1.40	1.40	1.40	1.40	C2 – C1 – O3	112.81	112.81	112.83	112.83
C13 – C9	1.39	1.39	1.39	1.39	C1 – O3 – H7	106.72	106.72	107.82	107.79
C13 – C10	1.39	1.39	1.39	1.39	O3 – C1 – O4	121.40	121.40	121.72	121.71
C10 – H14	1.08	1.08	1.08	1.08	C1 – C2 – C5	118.41	118.41	118.26	118.27

Table S2. Calculated vibrational frequencies (cm⁻¹) assignments of 21HBMBA based on B3LYP/6311++G(d.p)basis set.

Mode no	Experimental wave number (cm⁻¹)	Theoretical wave number (cm⁻¹)		I_{IR}[c]	I_{RAMAN}[d]	Assignments (PED)[a,b]
	FTIR	Unscaled	Scaled			
87	3435	3766	3619	33	65	γ OH(100)
86	-	3250	3123	0	33	γ CH(25)
85	-	3215	3089	1	63	γ CH(43)
84	-	3201	3077	3	86	γ CH(49)
83	-	3193	3068	6	74	γCH(36)

82	-	3192	3067	3	100	γCH(47)
81	-	3178	3055	4	60	γCH(60)
80	-	3178	3054	2	41	γCH(24)
79	-	3166	3042	1	32	γCH(44)
78	-	3162	3039	2	25	γCH(57)
77	2919	3131	3009	0	26	γCH(75)
76	2858	3045	2927	10	56	γCH(75)
75	2413	1777	1708	100	26	γOC(83)
74	1649	1652	1588	7	3	γCC(34)
73	-	1640	1576	3	23	γCC(42)+ βHCC(21)
72	-	1618	1555	1	10	γCC(14)+ βCCC(13)+ βCCN(12)+ βCNC(13)
71	1504	1616	1553	4	9	γCC(22)+ βCCC(10)
70	-	1530	1470	26	19	γNC(48)+ βHCN(18)
69	-	1521	1462	2	3	βHCC(40)+ βCCC(19)
68	-	1512	1453	0	3	γCC(18)+ βHCC(12)
67	-	1486	1428	9	6	βHCH(31)+ βHCC(12)+ τHCCC(16)
66	-	1479	1421	7	1	γCC(13)+ βHCC(28)
65	1401	1475	1417	10	3	βHCC(16)+ βHCH(20)
64	-	1413	1358	4	4	βHCH(19)+ βHCC(13)+ τHCCC(15)
63	-	1389	1335	2	13	γNC(11)+ βHCC(28)

62	-	1381	1327	16	10	γNC(17)+ τHCCC(27)
61	-	1363	1310	28	4	γOC(17)+ γCC(15)+ βHOC(33)+ βOCO(12)
60	1308	1359	1306	3	2	γNC(11)+ γCC(15)
59	-	1330	1279	2	2	γCC(36)
58	-	1316	1264	2	1	βHCC(26)
57	-	1306	1255	18	29	γNC(19)+ βHCN(11)+ βHCC(15)
56	1235	1288	1238	7	5	βHCN(15)+ βHCC(17)
55	1174	1224	1176	10	3	γNC(17)+ βHCN(36)
54	-	1211	1164	3	11	γCC(27)+ βHCC(10)
53	-	1202	1155	64	5	γCC(16)+ βHOC(38)
52	-	1194	1148	11	7	γCC(17)+ βHCC(16)
51	-	1190	1144	6	3	βHCC(58)
50	-	1175	1130	1	1	βHCC(44)
49	1112	1155	1110	17	17	γCC(13)+ γOC(11)+ βHCC(23)
48	-	1135	1090	5	2	γCC(14)+ βHCC(33)
47	-	1099	1056	1	1	γNC(16)+ βCCC(11)+ βNCN(22)
46	-	1081	1039	34	1	γOC(34)+ βCCC(13)
45	-	1072	1030	3	20	γCC(34)+ βHCC(16)
44	-	1030	990	3	13	βHCC(11)+ βCCC(12)+ βCCN(18)+ βCNC(10)

43	-	1010	970	0	0	τHCCC(69)+ τCCCC(10)
42	-	985	947	0	0	τHCCC(75)
41	-	973	935	0	0	τHCCC(46)+ τCCCC(16)
40	-	957	920	3	1	βHCC(17)+ τHCCC(36)
39	-	938	901	1	0	τHCNC(29)+ τHCCC(32)
38	-	906	871	1	0	τHCCC(69)
37	-	895	860	1	1	γNC(13)+ βCCC(24)+ βNCN(14)
36	-	878	844	4	0	τHCNC(46)
35	-	853	819	1	0	γCC(13)+ βCCC(21)+ τHCCC(12)
34	-	852	819	0	0	τHCNC(15)+ τHCCC(31)
33	-	819	787	0	0	τHCCC(10)
32	-	800	768	0	3	βCNC(12)+ τHCCC(15)
31	-	786	756	6	13	βCNC(11)+ τHCCC(16)
30	740	774	744	1	0	τHCNC(14)+ τCCCC(18)+ τCNCN(30)
29	-	754	725	19	3	τHCCC(19)
28	-	748	719	24	0	τHCNC(34)+ τHCCC(32)
27	-	734	706	21	8	τHCCC(21)
26	-	718	690	0	3	τCCCC(10)
25	-	649	624	13	1	βOCO(43)+ βCCC(10)
24	-	642	617	1	1	τCNCN(15)

23	-	625	601	1	2	τCNCN(22)
22	-	599	576	23	1	τHOCC(67)
21	-	593	570	2	2	βCCC(11)+ τHOCC(17)
20	-	582	560	1	1	τCCCC(13)+ τCNCN(13)
19	523	554	532	0	2	βCCC(14)
18	-	531	511	2	1	βOCC(26)+ τCCCC(10)
17	461	489	470	2	0	βCCN(20)+ βCNC(19)
16	420	458	440	2	2	βCCC(11)+ βOCC(11)+ τCCCC(10)
15	-	430	413	2	0	τCCCC(23)
14	-	427	410	2	0	τCCCC(13)
13	-	401	385	1	2	γCC(21)+ βOCO(12)+ βCCC(12)
12	-	346	333	2	0	βCCC(24)+ βCCC(12)
11	-	308	296	0	0	βCCN(11)
10	-	258	248	1	0	βOCC(21)+ βCCC(30)
9	-	244	235	1	1	βCCC(20)+ τCNCN(12)
8	-	232	223	1	0	τCCCC(28)+ τCNCN(14)
7	-	176	169	1	1	βCNC(26)+ τCCCC(11)
6	-	139	133	0	2	βCNC(10)
5	-	123	118	0	1	τCCCC(24)+ τOCCC(10)
4	-	85	82	1	1	τCCCC(15)+ τOCCC(32)+ τCCNC(22)

3	-	50				τCCCC(14)+ τOCCC(27)+
			48	0	2	τCCNC(10)
2	-	41	39	0	3	τOCCC(22)+ τCCNC(12)
1	-	19	18	0	3	τCCCC(32)+ τCCNC(36)

[a] γ-stretching, γa-Symmetrical stretching, γas-asymmetrical stretching, β-bending, τ -torsion, vs-very strong, s-strong, m-medium, w-weak. [b] scaling factor: 0.961 for B3LYP/6-311++ G(d,p). [c]Relative absorption intensities normalized with highest peak absorption equal to 100. [d] Relative Raman intensities normalized to 100.

Table S3. Second order perturbation theory of the Fock matrix NBO analysis of 21HBMBA.

DONOR	TYPE	ED/e	ACCEPTOR	TYPE	ED/e	E(2) kcal/mol	E(j)-E(i) a.u.	F(i,j) a.u.
C2 – C5	π	1.64369	C1 – O4	π*	0.02061	20.80	0.27	0.068
			C6 – C10	π*	0.02031	21.10	0.29	0.070
			C9 – C13	π*	0.01631	17.91	0.28	0.064
C6 – C10	π	1.97405	C2 – C5	π*	0.02111	18.52	0.28	0.065
			C9 – C13	π*	0.31266	21.22	0.28	0.070
C9 – C13	π	1.97959	C2 – C5	π*	0.35671	23.14	0.28	0.072
			C6 – C10	π*	0.31620	18.88	0.29	0.066
C19 – N22	π	1.98297	C20 – C23	π*	0.03706	18.57	0.34	0.078
C20 – C23	π	1.96442	C19 – N22	π*	0.31525	14.09	0.26	0.055
			C24 – C26	π*	0.01406	19.37	0.28	0.067
			C25 – C29	π*	0.01316	18.69	0.29	0.067
C24 – C26	π	1.97503	C20 –C23	π*	0.47362	19.26	0.28	0.069
			C25 – C29	π*	0.31141	17.22	0.29	0.064
C25 – C29	π	1.97688	C20 – C23	π*	0.47362	18.35	0.28	0.067
			C24 – C26	π*	0.34111	20.25	0.28	0.068
O3	LP(1)	1.97733	C1 – O4	π*	0.24500	6.41	1.23	0.079
	LP(2)	1.82430	C1 – O4	π*	0.02061	42.69	0.35	0.111

O4	**LP(1)**	1.97775	C1 – C2	π*	0.06392	2.53	1.12	0.048
			C1 – O3	π*	0.09384	1.13	1.04	0.031
O4	**LP(2)**	1.85275	C1 – C2	π*	0.06392	16.74	0.69	0.098
			C1 – O3	π*	0.09384	32.54	0.61	0.128
N17	**LP(1)**	1.59999	C6 – C10	π*	0.02031	1.10	0.27	0.016
			C6 – C11	π*	0.02881	5.00	0.64	0.056
			C11 – H15	π*	0.01914	4.54	0.64	0.053
			C19 – N22	π*	0.00647	44.62	0.28	0.102
			C20- C23	π*	0.03706	32.25	0.30	0.089
N22	**LP(1)**	1.92210	C11 – N17	π*	0.03424	0.61	0.68	0.018
			N17 – C19	π*	0.04143	8.03	0.79	0.072
			C19 – H21	π*	0.02102	1.99	0.78	0.036
			C20 – C23	π*	0.03706	5.92	0.90	0.066
			C23 – C25	π*	0.02285	0.51	0.94	0.020

Table S4. Hybrid, Polarization coefficient and Atomic Orbital contribution in selected Natural Bond Orbitals of 21HBMBA.

Bond Orbital	Hybrid A (h_A)	Atomic Orbital (%)	Polarization Coefficient (C_A)	Hybrid B (h_B)	Atomic Orbital (%)	Polarization Coefficient (C_B)
C1 - C2	$Sp^{1.55}$	s(39.91%)p(60.75%)d(0.04%)	0.6959	$Sp^{2.45}$	s(28.94%)p(71.01%)d(0.05%)	0.7182
C1 - O3	$Sp^{2.71}$	s(26.89%)p(72.89%)d(0.22%)	0.5657	$Sp^{1.99}$	s(33.37%)p(66.54%)d(0.09%)	0.8246
C1 - O4	$Sp^{1.98}$	s(33.51%)p(66.33%)d (0.16%)	0.5925	$Sp^{1.48}$	s(40.27%)p(59.60%)d (0.13%)	0.8056
C1–O4	$Sp^{99.99}$	s(0.27%)p (99.24%) d(0.49%)	0.5421	$Sp^{99.99}$	s(0.37%)p(99.51%)d (0.12%)	0.8403
O3 – H7	$Sp^{3.67}$	s(21.39%)p(78.52%)d (0.09%)	0.8652	S	s(99.88%)p(0.12%)	0.5014
C10 – H14	$Sp^{2.55}$	s(28.14%)p (71.81%)d (0.05%)	0.7776	S	s(99.95%)p(0.05%)	0.6287
C11 – N17	$Sp^{3.39}$	s(22.74%)p (77.12%)d (0.14%)	0.6056	$Sp^{1.98}$	s(33.61%)p(66.37%)d(0.02%)	0.7958
N17– C19	$Sp^{2.07}$	s(32.60%)p (67.35%)d (0.04%)	0.8023	$Sp^{2.33}$	s(30.01%)p(69.87%)d(0.12%)	0.5969
N17– C20	$Sp^{1.98}$	s(33.59%)p(66.37%)d (	0.7914	$Sp^{2.72}$	s(26.86%)p(73.04%)d (	0.6113

		0.04%)			0.10%)	
C19 – N22	Sp$^{1.82}$	s(35.48%)p (64.43%)d (0.09%)	0.6445	Sp$^{1.86}$	s(34.94%)p (64.95%) d (0.10%)	0.7646
C19 – N22	Sp$^{1.00}$	s(0.00%)p (99.78%)d (0.22%)	0.6331	Sp$^{1.00}$	s(0.00%)p (99.82%) d (0.18%)	0.7741
N22–C23	Sp$^{2.15}$	s(31.67%)p (68.24%)d (0.09%)	0.7602	Sp$^{2.42}$	s(29.20%)p (70.71%)d(0.09%)	0.6496
LP (1) O3	Sp$^{1.21}$	s(45.23%)p (54.73%)d (0.03%)	---	---	---	---
LP (2) O3	Sp^1	s(0.00%)p (99.94%)d (0.06%)	---	---	---	---
LP (1) O4	Sp$^{0.68}$	s(59.39%)p (40.59%)d (0.02%)	---	---	---	---
LP (2) O4	Sp$^{99.99}$	s(0.03%)p (99.89%)d (0.08%)	---	---	---	---
LP (1) N17	Sp$^{99.99}$	s(0.15%)p(99.84%)d(0.01%)	---	---	---	---
LP (1) N22	Sp$^{1.98}$	s(33.55%)p (66.37%)d (0.08%)	---	---	---	---

Table S5. Natural Hybrid Orbital directionality and bond bending (deviations from line of nuclear centers) of 21HBMBA.

Bond Orbital	Deviation angle (°)		Line of centers	
	Hybrid A	Hybrid B	Polar (θ)	Azimuthal (ϕ)
σ C1 - C2	1.9	1.7	83.1	92.1
σ C1 – O3	3.9	1.4	151.5	218.6
σ C1 – O4	7.7	7.3	47.8	297.2
σ C1 – O4	85.4	85.9	47.8	297.2
σ C2 – C5	1.6	1.6	123.2	141.4
σ C2 – C5	88.3	88.7	123.2	141.4
σ C2 – C6	1.9	2.4	46.7	39.9
σ O3 – H7	3.3	-	90.7	273.1
σ C5 – C9	1.5	1.3	81.8	97.2
σ C6 – C10	-	1.2	82.5	98.1
σ C6 – C10	89.1	89.4	82.5	98.1

σ C6 –C11	2.4	3.7	56.2	327.0
σ C9 – C13	89.9	90.0	45.6	40.8
σ C10 – C13	1.1	1.4	122.6	142.3
σ C10 – H14	1.1	-	46.4	41.2
σ C11 – H15	2.0		44.8	64.8
σ C11 – N17	2.3		120.7	339.3
σ N17 – C19	5.3		95.6	288.5
σ N17 – C20	6.8	6.2	115.6	39.1
σ C19 – N22	-	5.3	119.1	353.9
σ C19 – N22	90.0	89.8	119.1	353.9
σ C20 – C23	3.2	1.0	109.1	316.6
σ C20 – C23	90.3	90.3	109.1	316.6
σ C20 – C24	4.7	2.4	96.6	84.1
σ N22 – C23	5.9	1.6	103.0	74.0
σ C23 – C25	2.4	-	118.5	22.4
σ C24 – C26	-	1.9	118.4	21.3
σ C24 – C26	90.5	90.1	118.4	21.3
σ C24 – H27	1.4	-	70.5	136.4
σ C25 – C29	-	1.8	96.8	84.0
σ C25 – C29	89.8	89.9	96.8	84.0
σ C26 – C29	1.9	1.7	110.3	317.0

Table S6. Comparison of electronic properties of 21HBMBA optimized in different solvents calculated by TD-DFT/B3LYP method.

	TD/DFT				
Solvent	λ_{max} (nm)	Band Energy (eV)	Energy	Oscillator Strength	Assignments
Ethanol	315.20	3.9335	31725.8	0.0009	H→L (95.3%)
	307.02	4.0383	32571.07	0.0006	H-1→L(95.4%)
	260.73	4.7553	38354.06	0.0438	H-2→L(71.5%)
DCM	318.97	3.8870	31350.75	0.0008	H→L (95.4%)
	310.71	3.9903	32183.92	0.0005	H-1→L(95.5%)
	260.71	4.7556	38356.48	0.0393	H-2→L(66.7%)
DMSO	313.76	3.9516	31871.79	0.0008	H→L (94.9%)
	305.73	4.0554	32708.99	0.0006	H-1→L(95%)
	260.83	4.7535	38339.54	0.0450	H-2→L(73%)

Table S7. Energy of 21HBMBA in different solvents.

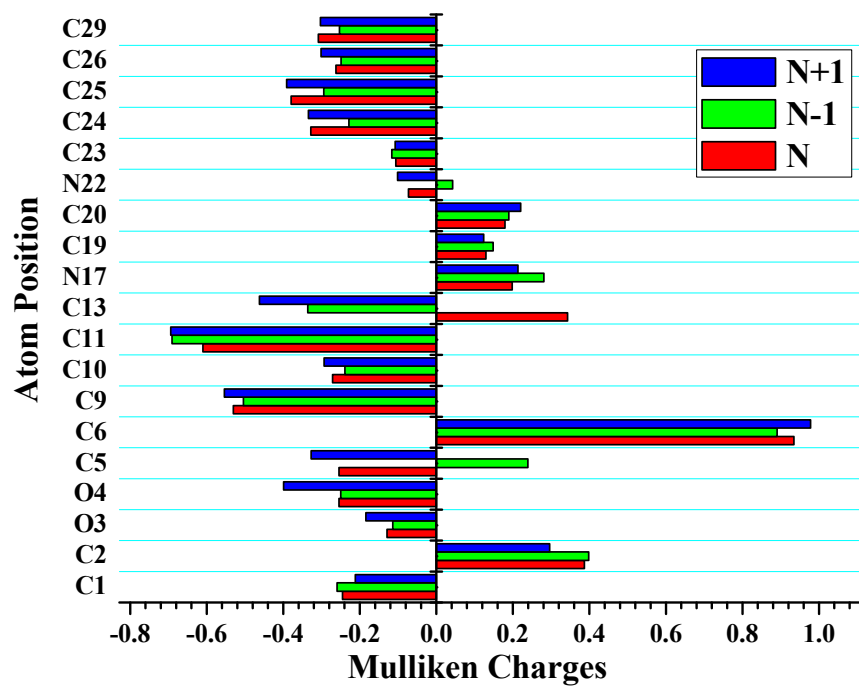| solvent	Energy (a.u)
DCM	-839.03772044
DMSO	-839.04001079
EtOH	-839.03950497

Figure S1. The histogram of calculated Mulliken charge of 21HBMBA.

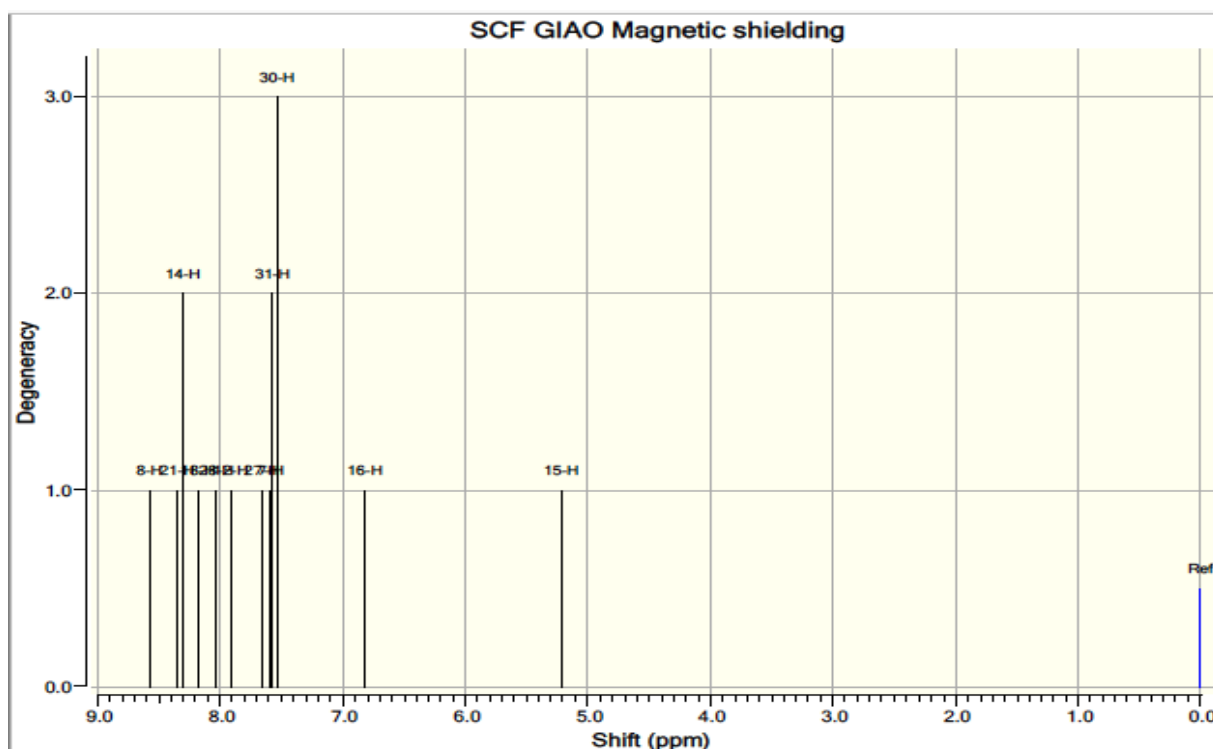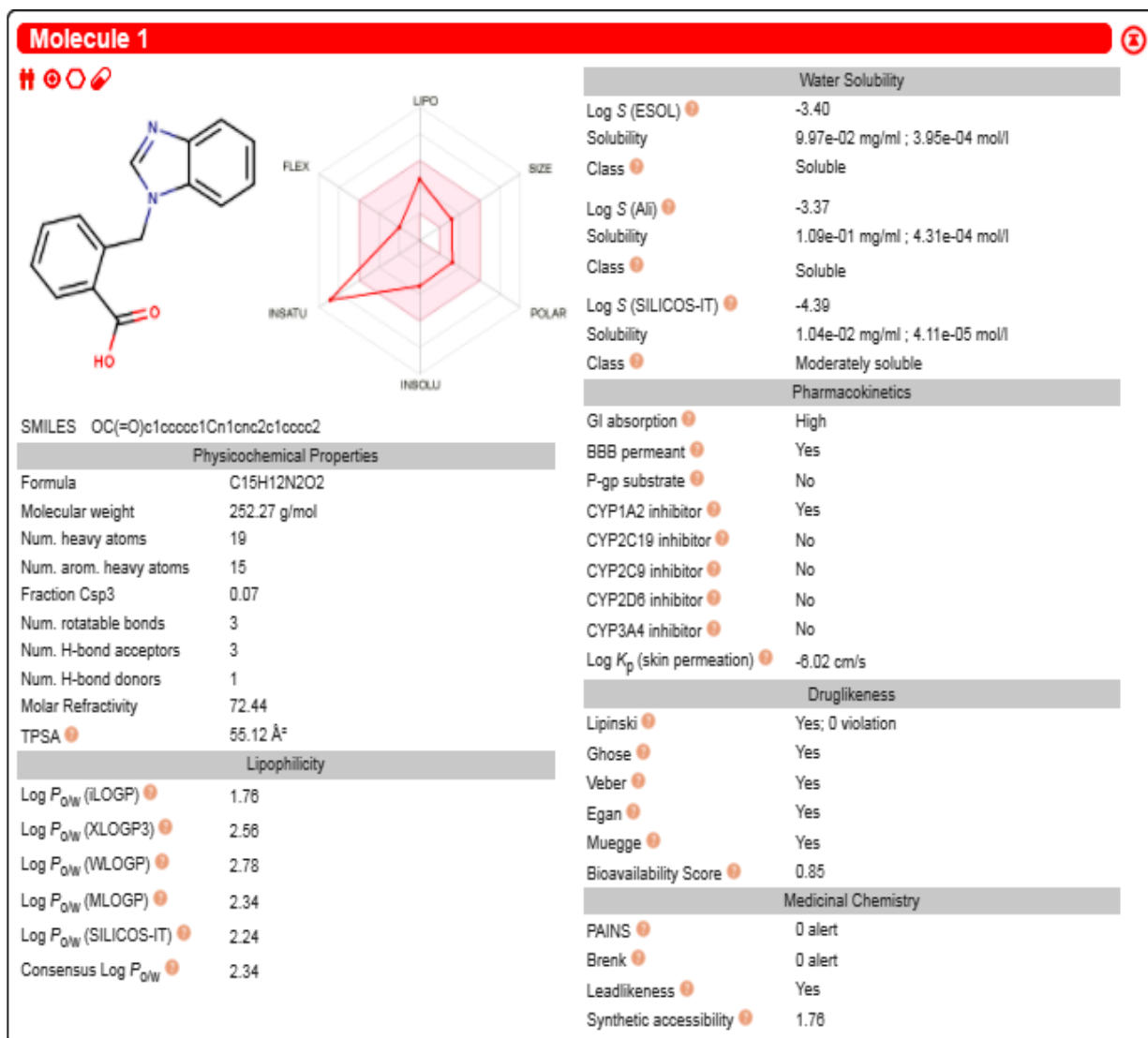**Figure S2. (a)** Experimental ¹H NMR **(b)** Theoretical ¹H of 21HBMBA.

Figure S3. Drug similarity qualities of 21HBMBA.

SMILES CCCc1nc2c(n1Cc1ccc(cc1)c1ccccc1C(=O)O)cc1c(c2)cccc1

Physicochemical Properties

Formula	C28H24N2O2
Molecular weight	420.50 g/mol
Num. heavy atoms	32
Num. arom. heavy atoms	25
Fraction Csp3	0.14
Num. rotatable bonds	6
Num. H-bond acceptors	3
Num. H-bond donors	1
Molar Refractivity	129.96
TPSA	55.12 Å²

Lipophilicity

Log $P_{o/w}$ (iLOGP)	3.13
Log $P_{o/w}$ (XLOGP3)	6.26
Log $P_{o/w}$ (WLOGP)	6.56
Log $P_{o/w}$ (MLOGP)	4.81
Log $P_{o/w}$ (SILICOS-IT)	6.13
Consensus Log $P_{o/w}$	5.38

Water Solubility

Log S (ESOL)	-6.57
Solubility	1.12e-04 mg/ml ; 2.67e-07 mol/l
Class	Poorly soluble
Log S (Ali)	-7.20
Solubility	2.62e-05 mg/ml ; 6.24e-08 mol/l
Class	Poorly soluble
Log S (SILICOS-IT)	-9.67
Solubility	8.91e-08 mg/ml ; 2.12e-10 mol/l
Class	Poorly soluble

Pharmacokinetics

GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-4.42 cm/s

Druglikeness

Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	No; 1 violation: WLOGP>5.6
Veber	Yes
Egan	No; 1 violation: WLOGP>5.88
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.85

Medicinal Chemistry

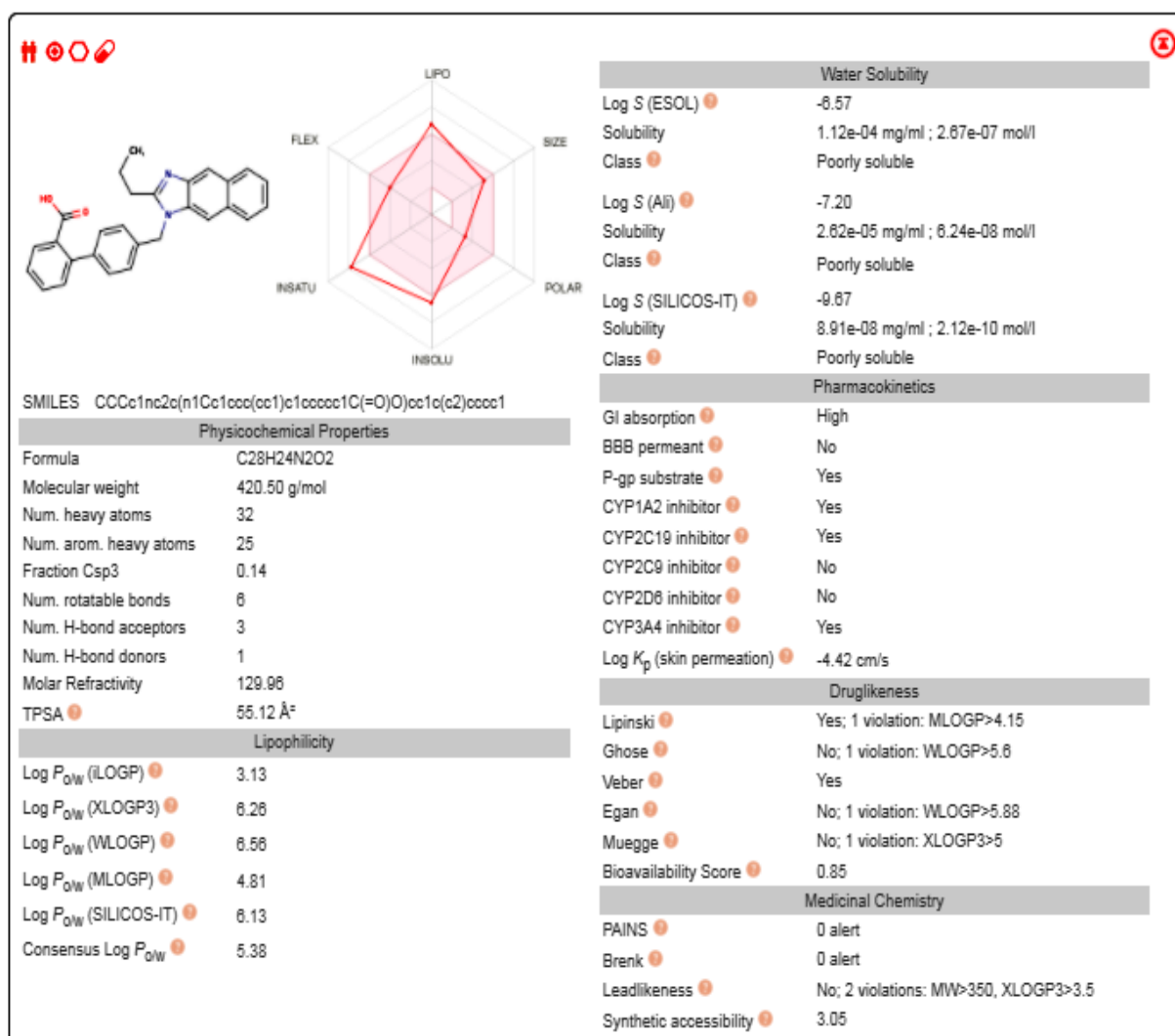|	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.05

Figure S4. Drug similarity qualities of 21HBMBA derivative.