Synthesis, Crystal Structure Analysis, Computational Modelling and Evaluation of Anti-Cervical Cancer Activity of Novel 1,5-Dicyclooctyl Thiocarbohydrazone

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Supplementary Table S1 Percentage of all the contact interactions involved in the supramolecular arrangement	
Contacts	Compound 3
H···H/H…H (%)	68.5
C···H (%)	7.5
N···H (%)	8.4
S···H (%)	12.7
C···C (%)	1.9

Supplementary Table S2 Enrichment Ratio of Chemical Species of **3**					
Contact%					
Inside / Outside Atom	N	H	S	C	
C	0.4	3.2	-	1.9	5.4
H	2.5	68.5	4.5	4.4	81.3
N	0.2	4.4	-	0.4	5.0
S	-	8.3	-	-	8.3
Surface%	4.7	84.3	4.5	6.6	
Random Contact %					
	N	H	S	C	
C	-	3.2	-	1.9	5.1
H	4.4	68.5	8.3	3.2	84.4
N	0.2	4.0	-	0.4	4.6
S	-	4.5	-	-	4.5
	4.6	80.2	8.3	5.5	
Enrichment Ratio					
	N	H	S	C	
C	-	1	-	1	
H	0.56	1	0.54	1.37	

N	1	1.1	-	1	
S	-	1.84	-	-	

Supplementary Table S3 Interaction energies (kJ/mol) and Symop of the molecular pairs calculated from energy framework calculation of compound **3**

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	1	-x, -y, -z	6.12	B3LYP/6-31G(d,p)	-29.2	-9.8	-98.6	51.2	-92.2
	1	x, y, z	10.81	B3LYP/6-31G(d,p)	1.4	-0.3	-1.9	0.0	-0.5
	1	-x, -y, -z	5.10	B3LYP/6-31G(d,p)	-36.0	-15.8	-84.5	72.7	-78.5
	1	x, y, z	7.09	B3LYP/6-31G(d,p)	-28.9	-12.1	-52.6	64.9	-45.3
	1	-x, -y, -z	8.01	B3LYP/6-31G(d,p)	-0.7	-3.1	-42.5	26.2	-23.9
	1	x, y, z	12.55	B3LYP/6-31G(d,p)	9.5	-1.0	-23.5	0.0	-11.1
	1	-x, -y, -z	11.43	B3LYP/6-31G(d,p)	-1.5	-0.1	-2.5	0.0	-3.8

Supplementary Table S4 EPINET representation for Topology of Crystal **3**

Atom	**CN**	**Sp**	**vdW**	**Hb**	**Composition**
S1	1	0	9	0	C1
N1	3	0	0	0	H1C1N1
H1	1	0	6	0	N1
N2	3	0	3	0	H1C1N1
H2	1	0	7	0	N1

N3	3	0	2	0	H1C1N1
H3	1	0	4	0	N1
N4	3	0	1	0	H1C1N1
H4	1	0	5	0	N1
C1	3	0	1	0	C2N1
C2	3	0	3	0	N2S1
C3	3	0	2	0	C2N1
C4	4	0	0	0	H2C2
H5	1	0	8	0	C1
H6	1	0	7	0	C1
C5	4	0	0	0	H2C2
H7	1	0	8	0	C1
H8	1	0	6	0	C1
C6	4	0	0	0	H2C2
H9	1	0	6	0	C1
H10	1	0	5	0	C1
C7	4	0	0	0	H2C2
H11	1	0	7	0	C1
H12	1	0	7	0	C1
C8	4	0	0	0	H2C2
H13	1	0	6	0	C1
H14	1	0	4	0	C1
C9	4	0	0	0	H2C2
H15	1	0	6	0	C1
H16	1	0	8	0	C1
C10	4	0	0	0	H2C2
H17	1	0	6	0	C1
H18	1	0	8	0	C1
C11	4	0	0	0	H2C2
H19	1	0	7	0	C1

H20	1	0	6	0	C1
C12	4	0	0	0	H2C2
H21	1	0	6	0	C1
H22	1	0	6	0	C1
C13	4	0	0	0	H2C2
H23	1	0	7	0	C1
H24	1	0	6	0	C1
C14	4	0	0	0	H2C2
H25	1	0	9	0	C1
H26	1	0	7	0	C1
C15	4	0	0	0	H2C2
H27	1	0	5	0	C1
H28	1	0	7	0	C1
C16	4	0	0	0	H2C2
H29	1	0	7	0	C1
H30	1	0	7	0	C1
C17	4	0	0	0	H2C2
H31	1	0	7	0	C1
H32	1	0	7	0	C1

Supplementary Table S5 The Total Energy of optimized structure at 6-311++G(d,p) basis set	
Zero-point correction (Hartree/Particle)	0.461436
Thermal correction to Energy	0.484133
Thermal correction to Enthalpy	0.485077
Thermal correction to Gibbs Free Energy	0.407646
Sum of electronic and zero-point Energies	-1282.841819
Sum of electronic and thermal Energies	-1282.819122
Sum of electronic and thermal Enthalpies	-1282.818178
Sum of electronic and thermal Free Energies	-1282.895608
Total entropy Cal/Mol-Kelvin	162.967

Supplementary Table S6 Experimental and Calculated Bond length and Bond Angle for compound **3**					
Atom No.	Experimental	Calculated	Atom No.	Experimental	Calculated

	Bond length (Å)	Bond length (Å)		Bond Angle (˚)	Bond Angle (˚)
N1 H1	0.84	1.0124	H1 N1 N2	123	122.826
N1 N2	1.385	1.374	H1 N1 C17	117	116.3242
N1 C17	1.345	1.366	N2 N1 C17	120.2	120.8322
S1 C17	1.669	1.6936	N1 N2 C1	116.9	118.9155
N2 C1	1.28	1.2884	H3 N3 N4	124	122.1938
N3 H3	0.83	1.0171	H3 N3 C17	117	115.4391
N3 N4	1.383	1.3706	N4 N3 C17	118.5	122.278
N3 C17	1.353	1.3506	N3 N4 C9	119.3	118.9836
N4 C9	1.278	1.2878	N2 C1 C8	112.8	115.4715
C1 C8	1.513	1.5162	N2 C1 C2	126	122.6909
C1 C2	1.509	1.5078	C8 C1 C2	121.1	121.8358
C8 H8A	0.97	1.099	C1 C8 H8A	108.7	109.4941
C8 H8B	0.97	1.0987	C1 C8 H8B	108.7	108.3703
C8 C7	1.52	1.5404	C1 C8 C7	114.3	113.4488
C9 C10	1.5	1.5164	H8A C8 H8B	107.6	107.0553
C9 C16	1.503	1.5156	H8A C8 C7	108.7	109.7681
C10 H10A	0.97	1.0954	H8B C8 C7	108.7	108.4918
C10 H10B	0.97	1.0916	N4 C9 C10	125.4	126.167
C10 C11	1.524	1.5563	N4 C9 C16	115.4	114.2921
C11 H11C	0.97	1.0956	C10 C9 C16	119.2	119.4761
C11 H11D	0.97	1.0941	C9 C10 H10A	108.6	111.1511
C11 C19	1.605	1.5414	C9 C10 H10B	108.6	107.6463
C16 H16C	0.97	1.0926	C9 C10 C11	114.4	114.1954
C16 H16D	0.97	1.0978	H10A C10 H10B	107.6	106.2757
C16 C18	1.497	1.5397	H10A C10 C11	108.7	107.5832
C2 H2A	0.97	1.0917	H10B C10 C11	108.7	109.7058
C2 H2B	0.97	1.0921	C10 C11 H11C	108.9	109.5985
C2 C3	1.518	1.5439	C10 C11 H11D	108.8	107.6226
C3 H3A	0.97	1.0951	C10 C11 C19	113.6	112.5814
C3 H3B	0.97	1.0959	H11C C11 H11D	107.7	105.6189
C3 C4	1.516	1.5355	H11C C11 C19	108.9	110.5219
C4 H4A	0.97	1.0968	H11D C11 C19	108.9	110.6245
C4 H4B	0.97	1.0945	C9 C16 H16C	108	109.2952
C4 C5	1.526	1.5447	C9 C16 H16D	108	106.2011
C5 H5A	0.97	1.0973	C9 C16 C18	117.1	117.5291
C5 H5B	0.97	1.0948	H16C C16 H16D	107.3	106.8768
C5 C6	1.529	1.5386	H16C C16 C18	108	108.9819
C6 H6A	0.97	1.0979	H16D C16 C18	108	107.4286
C6 H6B	0.97	1.0958	N1 C17 S1	125.1	126.6622
C6 C7	1.52	1.5392	N1 C17 N3	114	113.8967
C7 H7A	0.97	1.0944	S1 C17 N3	120.9	119.4405
C7 H7B	0.97	1.0947	C1 C2 H2A	108.1	108.7937
C18 H18	0.93	1.0923	C1 C2 H2B	108.1	106.5046

C18 C21	1.4	1.547	C1 C2 C3	116.7	119.1771
C19 H19A	0.93	1.0953	H2A C2 H2B	107.3	105.3956
C19 C20	0.92	1.5408	H2A C2 C3	108.1	108.4825
C20 H19B	0.93	1.0963	H2B C2 C3	108.1	107.647
C20 C21	1.52	1.5372	C2 C3 H3A	108.5	105.8898
C21 H21	0.93	1.0959	C2 C3 H3B	108.5	110.4482
			C2 C3 C4	114.9	117.2087
			H3A C3 H3B	107.5	105.3302
			H3A C3 C4	108.5	106.8208
			H3B C3 C4	108.5	110.3106
			C3 C4 H4A	108.3	108.529
			C3 C4 H4B	108.3	106.9005
			C3 C4 C5	116.3	118.8068
			H4A C4 H4B	107.4	105.7923
			H4A C4 C5	108.2	108.64
			H4B C4 C5	108.2	107.4316
			C4 C5 H5A	108.4	109.6039
			C4 C5 H5B	108.4	106.6437
			C4 C5 C6	115.4	116.2219
			H5A C5 H5B	107.5	105.5244
			H5A C5 C6	108.4	109.8232
			H5B C5 C6	108.4	108.4396
			C5 C6 H6A	108.6	109.4468
			C5 C6 H6B	108.5	109.118
			C5 C6 C7	114.9	115.4221
			H6A C6 H6B	107.6	105.419
			H6A C6 C7	108.6	109.8507
			H6B C6 C7	108.5	107.0892
			C8 C7 C6	116.1	116.1024
			C8 C7 H7A	108.3	108.3221
			C8 C7 H7B	108.3	107.5323
			C6 C7 H7A	108.3	108.8316
			C6 C7 H7B	108.3	109.0759
			H7A C7 H7B	107.4	106.5698
			C16 C18 H18	114.5	109.4081
			C16 C18 C21	130.9	117.1189
			H18 C18 C21	114.6	110.7488
			C11 C19 H19A	110.6	109.1677
			C11 C19 C20	138.8	114.7776
			H19A C19 C20	110.6	108.542
			C19 C20 H19B	109	108.5177
			C19 C20 C21	143	116.1679
			H19B C20 C21	108.6	108.948
			C18 C21 C20	122.2	117.3509
			C18 C21 H21	119	108.157

			C20 C21 H21	119	107.0797

Supplementary Table S7 Experimental and calculated ^{1}H NMR and ^{13}C NMR chemical shifts of the compound **3** using B3LYP/6-311++G (d, p) level of theory

^{13}C NMR			^{1}H NMR		
Atom no.	Theoretical	Exp.	Atom no.	Theoretical	Exp.
1 C	36.6775	25.44	7 H	1.676	1.705
2 C	35.4962	24.13	8 H	2.8195	2.357
3 C	38.2264	27.37	9 H	1.29	1.041
4 C	169.895	162.09	10 H	1.9447	1.705
5 C	30.0475	25.44	11 H	1.6842	1.705
6 C	35.5826	39.07	12 H	2.2161	2.357
17 C	31.0713	27.37	13 H	1.967	1.062
20 C	32.4473	28.30	14 H	1.8669	1.705
26 C	183.5211	174.76	15 H	2.2358	2.357
31 C	175.3121	162.09	16 H	2.5824	2.357
32 C	44.7006	39.07	18 H	1.0343	1.041
33 C	34.7827	24.13	19 H	1.8294	1.062
34 C	33.0444	25.44	21 H	1.3201	1.364
39 C	22.0254	25.44	22 H	1.9153	1.467
40 C	32.0641	27.37	25 H	8.3732	10.457
43 C	27.7191	27.37	28 H	10.4774	10.457
46 C	31.6434	28.30	35 H	2.1942	2.357
			36 H	2.6294	2.357
			37 H	2.6341	2.357
			38 H	2.0659	2.357
			41 H	1.3753	1.705
			42 H	2.0327	1.705
			44 H	1.7841	1.705
			45 H	1.7275	1.705
			47 H	1.8931	1.364
			48 H	1.7678	1.467
			49 H	0.8135	1.041
			50 H	1.7935	1.062
			51 H	1.4513	1.364
			52 H	1.6116	1.467

Supplementary Table S8 Experimental and theoretical absorption wavelengths λ (nm), excitation energies E (eV) and oscillation Constants (f) of **3** using long range functional and 6-311++G (d, p) basis set

S. No	*Excitation*	*Energy (eV)*	*Wave Length (nm)*	*Oscillation Constant (f)*	*Contribution of probable transition (%)*	*Assign ment*	*Observ ed*
B3LYP/6-311++G (d, p)							
1.	H-2 → L	4.5340	273.45	0.6544	49.14	π -π^*	274 nm
B3WP91/6-311++G (d, p)							
1.	H-2 → L	4.4883	276.24	0.6075	48.57	π -π^*	274 nm
PBE-PBE/6-311++G (d, p)							
1.	H-2 → L	3.8307	323.66	0.3790	45.52	π -π^*	274 nm

Supplementary Table S9 Calculated Polarizability (|α0|), Anisotropy of Polarizability (Δα) and First Hyperpolarizability (β0) for **3**

Dipole moment		**Polarizability**		**Hyperpolarizability**	
μx	-3.7089	αxx	426.678	βxxx	362.426
μy	-8.4708	αyy	8.2670	βyyy	795.543
μz	-0.239	αzz	385.791	βzzz	-426.87
μ	9.5511	αxy	7.14686	βxyy	721.905
		αxz	33.0226	βxxy	52.2736
		αyz	285.655	βxxz	-114.52
		α0	40.54436136	βxzz	-474.65
		Δα	59.2117873	βyzz	-3.6363
				βyyz	-21.14
				βxyz	87.6668
				β0	10.2251

Supplementary Table S10 NBO of **3** at 6-311++G(d,p) level of theory

Donor (i)			*Acceptor (j)*			*$E^{(2)}$ (kJ/mol)*
orbital / lp (occupancy)	*$ED_{A,}$ % $ED_{B,}$%*	*NBO hybrid Orbitals*	*Orbital (occupancy)*	*$ED_{A,}$ % $ED_{B,}$ %*	*NBO hybrid Orbitals*	
σ (C2-C4) 1.96980	49.47 50.53	0.7034 ($sp^{2.59}$)C2 0.7108 ($sp^{2.03}$)C4	σ*(N23-N24) 0.02685	54.32 45.68	0.7370($sp^{3.51}d^{0.01}$)N23 -0.6759($sp^{2.18}$)N24	6.37
σ (C6-H16) 1.97391	61.19 38.81	0.7822($sp^{3.46}$)C6 0.6230($sp^{0.00}$)H16	σ*(C4-N23) 0.01935	60.52 39.48	0.7780($sp^{2.18}$)C4 -0.6283($sp^{1.27}$)N23	5.31
σ (N24-H25) 1.98178	72.39 27.61	0.8508($sp^{2.29}$)N24 0.5254($sp^{0.00}$)H25	π*(C26-S52) 0.01600	41.09 58.91	0.6410($sp^{1.65}$)C26 -0.7675($sp^{4.48}d^{0.04}$)S52	5.74
σ (C26-S52) 1.98582	23.98 76.02	0.4896($sp^{1.00}$)C26 0.8719($sp^{1.00}$)S52	σ*(C26-S52) 0.56574	76.02 23.98	0.8719($sp^{1.00}$)C26 -0.4896($sp^{1.00}$)S52	5.61
σ (C30-C32) 1.97029	50.67 49.33	0.7118($sp^{2.00}$)C30 0.7024($sp^{2.60}$)C32	σ*(N27-N29) 0.03697	46.31 53.69	0.6805($sp^{2.21}$)N27 -0.7327($sp^{3.52}d^{0.01}$)N29	6.48
σ (C31-H34) 1.97495	61.30 38.70	0.7829($sp^{3.44}$)C31 0.6221($sp^{0.00}$)H34	σ*(N29-C30) 0.01994	39.07 60.93	0.6250($sp^{1.20}$)N29 -0.7806($sp^{2.19}$)C30	5.37
σ (C32-H37) 1.96179	60.81 39.19	0.7798($sp^{3.61}$)C32 0.6260($sp^{0.00}$)H37	π*(N29-C30) 0.16897	39.00 61.00	0.6245($sp^{1.00}$)N29 - 0.7810($sp^{99.99}d^{19.12}$)C30	5.47
lp 1 (N23) 1.92546		($sp^{1.95}$)N23	σ*(C4-C6) 0.04182	50.22 49.78	0.7087($sp^{1.81}$)C4 -0.7056($sp^{2.62}$)C6	11.31
lp 1 (N23) 1.92546		($sp^{1.95}$)N23	σ*(N24-H25) 0.04955	27.61 72.39	0.5254($sp^{2.29}$)N24 -0.8508($sp^{0.00}$)H25	8.69

lp 1 (N24) 1.63180		$(sp^{1.00})$N24	π*(C4-N23) 0.15287	60.01 39.99	$0.7747(sp^{99.99}d^{19.26})$C4 $-0.6323(sp^{1.00})$N23	22.28
lp 1 (N24) 1.63180		$(sp^{1.00})$N24	σ*(C26-S52) 0.56574	76.02 23.98	$0.8719(sp^{1.00})$C26 $-0.4896(sp^{1.00})$S52	84.81
lp 1 (N25) 1.65297		$(sp^{1.00})$N25	σ*(C26-S52) 0.56574	76.02 23.98	$0.8719(sp^{1.00})$C26 $-0.4896(sp^{1.00})$S52	75.11
lp 1 (N25) 1.65297		$(sp^{1.00})$N25	π*(N29-C30) 0.16897	39.00 61.00	$0.6245(sp^{1.00})$N29 $-0.7810(sp^{99.99}d^{19.12})$C30	23.47
lp 1 (N29) 1.91573		$(sp^{2.07})$N29	σ*(N27-H28) 0.03567	28.57 71.43	$0.5345(sp^{2.31})$N27 $-0.8452(sp^{0.00})$H28	8.79
lp 1 (N29) 1.91573		$(sp^{2.07})$N29	σ*(C30-C31) 0.04009	50.19 49.81	$0.7085(sp^{1.84})$C30 $-0.7058(sp^{2.59})$C31	10.75
lp 2 (S52) 1.89751		$(sp^{99.99}d^{0.20})$S52	σ*(N24-C26) 0.05491	38.19 61.81	$0.6180(sp^{1.61})$N24 $-0.7862(sp^{2.15})$C26	12.31
lp 2 (S52) 1.89751		$(sp^{99.99}d^{0.20})$S52	σ*(C26-N27) 0.04746	61.84 38.16	$0.7864(sp^{2.25})$C26 $-0.6178(sp^{1.59})$N27	9.77

Supplementary Table S11 The Physicochemical Properties and Drug likeness properties of synthesized compound 3 (calculated using Admetlab2.0 software)

Physicochemical Property		**Metabolism Property**	
Molecular Weight	322.22	**CYP1A2 inhibitor**	0.858
nHA	4	**CYP1A2 substrate**	0.782
nHD	2	**CYP2C19 inhibitor**	0.724
TPSA	48.78	**CYP2C19 substrate**	0.068
logS	-5.042	**CYP2C9 inhibitor**	0.21
logP	5.819	**CYP2C9 substrate**	0.949
Medicinal Chemistry		**CYP2D6 inhibitor**	0.008
SAscore	2.632	**CYP2D6 substrate**	0.132
Lipinski Rule	Accepted	**CYP3A4 inhibitor**	0.889
Pfizer Rule	Rejected	**CYP3A4 substrate**	0.085
GSK Rule	Rejected	**Distribution Property**	
Golden Triangle	Accepted	**PPB**	99.2%
PAINS	0 alerts	**VD**	3.528
Absorption Property		**BBB Penetration**	0.41
Caco-2 Permeability	-5.579	**Fu**	6.009%
MDCK Permeability	1.1e-05	**Excretion Property**	
Pgp-inhibitor	0.025	**CL**	2.117
Pgp-substrate	0.001	**$T_{½}$**	0.946
HIA	0.007	**Toxicity Property**	
$F_{20\%}$	0.9	**hERG Blockers**	0.011
$F_{30\%}$	0.722	**AMES Toxicity**	0.689

Supplementary Table S12 The summary of binding affinities (kcal/mol), Inhibition constant, Van der Waals interactions, Hydrophobic and the H-bond as hydrophilic interactions

S.No.	**Residues involved in hydrogen bonding interaction**	**Residues involved in hydrophobic interaction**	**Residues involved in Van der Waals interaction**	**No. of bonds**			**Inhibition Constant K_i**	**Binding energy (ΔG) (kcal/mol)**
				H-bonds	**Hydrophobi**	**Van der Waals**		

	s	**s**	**s**		**c bonds**	**bonds**	**(µM)**	
4xr8	Gln 336 (A) N2.....NE2 2.98 (Å) Glu 382 (A) N1…..O 2.75 (Å)	Ile 179 (A), Arg 383 (A), Pro 335 (A)	Tyr 177 (A), Ile 334 (A), Gln 73 (A),	2	3	3	0.57	-8.52
7vze	Gly 535 (A) N1…..O 2.65 (Å) Met 540 (A) N1…..O 2.82 (Å) Met 540 (A) N3…..O 2.88 (Å)	Lys 539 (A), Glu 576 (A), Pro 541 (A), Gln 538 (A), Gln 565 (A), Val 567 (A), Val 566 (A), Ile 574 (A), Val 542 (A), His 577 (A), Tyr 536 (A)	Ala 575 (A)	3	11	1	1.08	-8.14