Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Spectroscopic Characterization, Molecular Docking and Machine Learning Studies of Sulphur containing Hydrazide Derivatives

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Supplementary Table S1. The comparative study of overview of TSCZ and TCHZ at different basis sets.

Properties	**TSCZ**			**TCHZ**		
Basis set	**6-31G (d,p)**	**6-31+G (d',p')**	**6-311+G (d,p)**	**6-31G (d,,p)**	**6-31+G (d ', p')**	**6-311+G (d,p)**
Charge	0	0	0	0	0	0
Spin	S	S	S	S	S	S
Energy (Hartree)	-603.5490	-603.5638	-603.6404	-658.8712	-658.8889	-658.9792
RMS Gradient Norm (Hartree/Bohr)	0.00001	0.00006	0.00008	0.00000	0.00001	0.00100
Dipole moment (Debye)	4.0744	3.8856	3.8040	5.0402	4.8368	4.7930
Polarizability (α) (a.u.)	48.6431	61.0295	61.7657	57.0082	70.9082	71.6270
Point group	C_1	C_1	C_1	C_1	C_1	C_1

Supplementary Table S2. The comparative study of Total Energy of optimized structures at different basis sets.

Name	TSCZ			TCHZ		
	6-31G (d,p)	6-31+G(d',p')	6-311+G(d,p)	6-31G (d,,p)	6-31+G (d', p')	6-311+G (d,p)
Zero-point correction (Hartree /Particle)	0.0786	0.0783	0.0782	0.0958	0.0954	0.0954
Thermal correction to Energy	0.0846	0.0844	0.0843	0.1033	0.1030	0.1028
Thermal correction to Enthalpy	0.0855	0.0854	0.0853	0.1042	0.1039	0.1037
Thermal correction to Gibbs Free Energy	0.0491	0.0487	0.0486	0.0638	0.0629	0.0635
Sum of electronic and zero-point Energies	-603.4683	-603.4855	-603.5623	-658.7754	-658.7935	-658.8838
Sum of electronic and thermal Energies	-603.4623	-603.4793	-603.5561	-658.7680	-658.7859	-658.8764
Sum of electronic and thermal Enthalpies	-603.4614	-603.4784	-603.5552	-658.7670	-658.7850	-658.8754
Sum of electronic and thermal Free	-603.4978	-603.5151	-603.5918	-658.8074	-658.8260	-658.9157

Energies						
Total entropy Cal/Mol-Kelvin	76.613	77.185	77.120	85.009	86.442	84.674

Supplementay Table S3. Calculated and experimental FT-IR values for TSCZ at different basis sets.

Scaled theoretical frequency						
B3LYP 631-G(d,p)	**B3LYP 631-G(d', p')**	**B3LYP 6311+ G(d, p)**	**Cam-B3LYP 6311+ G(d, p)**	**B3WP91 6311+ G(d, p)**	**Experimental**	**Assignments**
493.161	485.730	486.534	488.153	485.156	496	$\omega(N_9H_{10}C_3N_5)(37)+ \tau(H_8C_3N_2S_4)(24)+ \omega(C_3H_8N_1N_2)(21)+ \tau(H_7N_1N_2H_8)(10)$
580.7685	577.223	577.436	581.910	582.592	539	$\rho(H_8C_3N_2+N_1C_3N_2)(24)+ \tau(H_8C_3N_2S_4)(14)+ \rho(N_5N_2C_3+S_4C_3N_2)(14)+ \delta'(H_8N_1N_2+ N_1C_3N_2)(7)+ \vartheta(N_1N_2)(6)+ \delta'(N_5S_4C_3+ N_5N_2C_3+S_4N_2C_3)(6)+ \omega(N_2N_5S_4C_3)(5)+ \vartheta(C_3S_4)(5)+ \vartheta(C_3N_5)(5)$
602.8814	596.549	598.807	612.509	602.105	622	$\omega(N_2N_5S_4C_3)(81)+ \omega(H_9H_{10}C_3N_5)(6)+ \omega(C_3H_8N_1N_2)(5)$
688.9626	688.648	688.836	706.313	701.882	728	$\vartheta(C_3S_4)(61)+ \vartheta(N_1N_2)(10)+ \vartheta(N_5H_{10})(9)+ \vartheta(N_5C_3)(8)$
927.1226	912.609	912.748	922.844	919.737	-	$\omega(H_7H_6N_2N_1)(49)+ \vartheta(N_1N_2)(29)+ \delta_{SC}(H_{10}C_3N_5+H_{10}H_9N_5+H_{10}H_9N_5)(8)+ \vartheta(S_4C_3)(5)$
1012.682	997.046	996.982	997.558	998.123	-	$\delta_{SC}(H_{10}C_3N_2+H_8H_9N_5+C_3H_9N_5)(29)+$

						$\omega(H_7H_6N_2N_1)(25)+$ $\vartheta(N_2C_3)(23)+$ $\rho(H_8C_3N_2+N_1C_3N_2)(8)$ $\rho(H_{10}H_9N_5+C_3H_9N_5)(7)$
1190.468	1176.845	1173.056	1201.263	1192.197	1092	$\vartheta(N_1N_2)(52)+$ $\vartheta(C_3N_5)(23)+$ $\omega(H_7H_6N_2N_1)(11)+$ $\delta_{SC}(H_{10}C_3N_5+H_{10}H_9N_5+C_3H_9N_5)(6)$
1261.7	1249.172	1246.153	1268.128	1261.974	-	$\vartheta(C_3N_5)(40)+$ $\delta'(H_8N_1N_2+$ $H_8C_3N_2+N_1C_3N_2)(20)+$ $\rho(N_5N_2C_3+S_4N_2C_3)(14)+$ $\vartheta(C_3S_4)(12)+$ $\rho(H_{10}H_9N_5+C_3H_9N_5)(5)$
1295.116	1282.457	1285.899	1292.868	1289.518	-	$\delta_{SC}(H_6N_1N_2+H_6H_7N_1+N_2H_7N_1)(68)+$ $\rho(H_6H_7N_1+N_2H_7N_1)(21)+\omega(H_7H_6N_2N_1)(8)$
1354.03	1341.062	1337.198	1362.663	1352.715	1470	$\vartheta(N_2C_3)(44)+$ $\delta_{SC}(H_{10}C_3N_5+H_{10}H_9N_5+C_3H_9N_5)(15)+$ $\vartheta(C_3S_4)(12)+$ $\delta'(N_5S_4C_3+N_5N_2C_3+S_4N_2C_3)(9)$
1442.311	1435.741	1437.405	1464.61	1445.087	-	$\delta'(H_8N_1N_2+$ $H_8C_3N_2+N_1C_3N_2)(49)+$ $\rho(H_8C_3N_2+N_1C_3N_2)(25)+$ $\vartheta(N_2C_3)(9)+$ $\vartheta(C_3N_5)(7)$
1556.356	1548.295	1550.883	1557.941	1546.684	1578	$\rho(H_{10}H_9N_5+C_3H_9N_5)(65)+$ $\delta_{SC}(H_{10}C_3N_5+H_{10}H_9N_5+C_3H_9N_5)(24)+$ $\vartheta(C_3N_5)(7)$
1628.858	1620.034	1624.578	1631.015	1624.596	1821	$\rho(H_6H_7N_1+N_2H_7N_1)(63)+$ $\delta_{SC}(H_6N_2N_1+H_6H_7N_1+N_2H_7N_1)(29)$
3258.759	3274.947	3271.163	3313.852	3282.379	2688	$\vartheta(N_1H_6)(75)+$ $\vartheta(N_1H_7)(24)$
3333.708	3352.006	3341.908	3380.29	3357.428	-	$\vartheta(N_1H_7)(75)+$ $\vartheta(N_1H_6)(25)$
3383.007	3381.878	3374.567	3414.453	3394.246	3390	$\vartheta(N_5H_9)(72)+$ $\vartheta(N_5H_{10})(27)$
3410.724	3410.924	3401.251	3442.331	3419.164	-	$\vartheta(N_2H_8)(99)$

3517.221	3513.758	3498.926	3535.387	3520.363	3794	$\vartheta(N_5H_{10})(72)+ \vartheta(N_5H_9)(27)$
ϑ= stretching mode, ρ= rocking mode, τ= torsion mode, ω= wagging mode and δ'= deformation mode						

Supplementary Table S4. Calculated and experimental FT-IR values for TCHZ at B3LYP- 6311+G (d,p) basis sets.

Scaled theoretical frequency					**Experimental**	**Assignments**
B3LYP 631-G(d,p)	**B3LYP 631-G(d', p')**	**B3LYP 6311+ G(d,p)**	**Cam-B3LYP 6311+ G(d,p)**	**B3WP91 6311+ G(d,p)**		
568.631	564.846	576.400	586.305	575.120	-	$\rho(H_9N_1N_2+C_3N_1N_2)(20)+ \rho(S_4N_2C_3+N_5N_2C_3)(19)+\vartheta(C_3S_4)(21)+ \tau(H_9N_2C_3S_4)(10)$
580.675	577.051	583.614	592.771	584.210	591	$\tau(H_9N_2C_3S_4)(61)+ \omega(N_1H_9C_3N_2)(14)+ \tau(H_8N_1N_2H_9)(13)$
613.216	608.367	612.048	629.554	612.687	673	$\omega(N_2S_4N_5C_3)(78)+ \tau(H_{10}N_5N_6H_{12})(11)+ \omega(N_1H_9C_3N_2)(9)$
732.086	726.982	726.177	741.999	735.900	749	$\vartheta(C_3S_4)(27)+\vartheta(N_1N_2)(15)+\vartheta(N_2C_3)(15)+\omega(H_{11}H_{12}N_5N_6)(10)+\rho(H_{10}N_6N_5+C_3N_6N_5)(10)+\omega(H_8H_7N_2N_1)(6)+\rho(S_4N_2C_3+N_5N_2C_3)(5)$

864.691	849.643	857.696	849.783	846.424	-	$\omega(H_{11}H_{12}N_5N_6)(63)+ \vartheta(N_5N_6)(17)+ \tau(H_{10}N_5N_6H_{12})(6)$
966.503	945.376	954.376	954.471	949.957	927	$\omega(H_8H_7N_2N_1)(63)+ \vartheta(N_1N_2)(21)$
1050.515	1040.872	1037.228	1071.711	1062.371	1012	$\vartheta(N_5N_6)(55)+ \vartheta(C_3N_5)(14)+ \vartheta(C_3S_4)(9)+ \rho(H_9N_1N_2+C_3N_1N_2)(7)+ \delta'(S_4N_5C_3+S_4N_2C_3+N_5N_2C_3)(6)$
1175.179	1163.676	1163.758	1183.843	1176.561	1127	$\vartheta(N_1N_2)(18)+ \omega(H_8H_7N_2N_1)(12)+ \rho(H_9N_1N_2+C_3N_1N_2)(12)+ \rho(S_4N_2C_3+N_5N_2C_3)(12)+ \rho(H_{10}N_6N_5+C_3N_6N_5)(12)+ \vartheta(C_3S_4)(9)+ \delta'(H_{10}C_3N_5+H_{10}N_6N_5+C_3N_6N_5)(5)$
1212.517	1205.032	1198.865	1229.123	1219.684	-	$\vartheta(C_3N_5)(27)+ \vartheta(N_1N_2)(24)+ \delta'(S_4N_5C_3+S_4N_2C_3+N_5N_2C_3)(11)+ \rho(H_{10}N_6N_5+C_3N_6N_5)(6)+ \vartheta(N_2C_3)(8)+ \vartheta(C_3S_4)(8)+ \vartheta(N_5N_6)(6)$
1240.024	1231.75	1239.521	1244.049	1237.702	-	$\delta_{SC}(H_{12}N_5N_6+H_{12}H_{11}N_6+N_5H_{11}N_6)(74)+ \rho(H_{12}N_{11}N_6+N_5H_{11}N_6)(20)+ \omega(H_{11}H_{12}N_5N_6)(5)$
1296.88	1284.741	1293.777	1296.744	1292.166	1272	$\delta_{SC}(H_7N_2N_1+H_7H_8N_1+N_2H_8N_1)(73)+ \rho(H_7H_8N_1+N_2H_8N_1)(19)+ \omega(H_8H_7N_2N_1)(7)$
1311.631	1303.729	1300.068	1322.627	1311.182	-	$\delta'(H_9C_3N_1+H_9N_1N_2+C_3N_1N_2)(23)+ \vartheta(N_2C_3)(17)+ \rho(H_9N_1N_2+C_3N_1N_2)(11)+ \vartheta(C_3N_5)(23)+ \rho(H_{10}N_6N_5+C_3N_6N_5)(5)$

1443.248	1436.686	1437.043	1460.831	1443.514	1485	δ'($H_{10}C_3N_5$+$H_{10}N_6N_5$+$C_3N_6N_5$)(51)+ ρ($H_{10}N_6N_5$+$C_3N_6N_5$)(17)+ ϑ(C_3S_4)(10)
1468.846	1457.497	1453.436	1486.22	1468.761	1533	δ'($H_9C_3N_1$+$H_9N_1N_2$+$C_3N_1N_2$)(36)+ ϑ(N_2C_3)(13)+ ϑ(C_3S_4)(15)+ ρ($H_9N_1N_2$+$C_3N_1N_2$)(13)+ ϑ(N_1N_2)(5)
1609.192	1601.102	1606.244	1612.537	1603.753	1609	ρ($H_{12}N_{11}N_6$+$N_5H_{11}N_6$)(64)+ δ_{SC}($H_{12}N_5N_6$+$H_{12}H_{11}N_6$+$N_5H_{11}N_6$)(26)
1628.701	1619.585	1626.458	1630.102	1623.187	1636	ρ($H_7H_8N_1$+$N_2H_8N_1$)(65)+ δ_{SC}($H_7N_2N_1$+$H_7H_8N_1$+$N_2H_8N_1$)(28)
3269.503	3285.731	3266.526	3322.242	3298.045	3171	ϑ(N_1H_7)(51)+ ϑ(N_1H_8)(49)
3296.203	3306.922	3285.694	3344.222	3322.864	3212	ϑ(N_6H_{12})(60)+ ϑ(N_6H_{11})(40)
3331.812	3350.253	3323.623	3381.84	3358.569	3267	ϑ(N_1H_8)(51)+ ϑ(N_1H_7)(49)
3385.363	3392.217	3363.338	3422.999	3403.325	-	ϑ(N_6H_{11})(60)+ ϑ(N_6H_{12})(40)
3408.937	3413.978	3385.662	3442.739	3423.833	3315	ϑ(N_5H_{10})(99)
3430.783	3430.41	3401.666	3450.316	3429.75	-	ϑ(N_2H_9)(98)
ϑ = stretching mode, ρ= rocking mode, τ= torsion mode, ω= wagging mode and δ'= deformation mode						

Supplementary Table S5. NMR for TSCZ at different basis sets.

Theoretical				**Observed (In ppm)**
	B3LYP	**CAM-B3LYP**	**B3WP91**	

	6-31G (d, p)	6-31+G(d', p')	6-311+G(d, p)	6-311+G(d, p)	6-311+G(d, p)	
1N	65.6143	79.1697	84.8662	79.1378	79.8725	-
2N	135.7789	141.6387	151.3925	145.4639	146.4119	-
3C	182.4626	188.7991	201.6306	204.5578	196.2313	184.16
4S	512.5350	500.4744	447.4701	478.3479	470.4228	-
5N	102.3049	105.7989	114.7261	112.2984	112.2595	-
6H	3.2286	3.7634	3.8946	3.7364	3.8081	3.425
7H	3.0718	3.374	3.4991	3.4905	3.3145	3.425
8H	6.1571	6.5546	6.6096	6.5764	6.493	7.211
9H	5.1972	5.0733	5.1585	5.156	5.1002	6.956
10H	5.0932	5.3311	5.4038	5.5054	5.3487	6.956

Supplementary Table S6. NMR for TCHZ at different basis sets.

	Theoretical					**Observed (In ppm)**
	B3LYP			**CAM-B3LYP**	**B3WP91**	
	6-31G (d, p)	**6-31+G(d', p')**	**6-311+G(d, p)**	**6-311+G(d, p)**	**6-311+G(d, p)**	
1N	66.1186	71.0119	79.0921	72.4595	71.4214	-
2N	134.9267	138.6477	145.5627	143.998	143.3943	-
3C	182.4447	184.0560	196.3457	201.2413	191.5341	181.87
4S	560.0569	558.0082	437.1710	527.7217	531.5622	-
5N	128.03822	133.2937	132.1572	137.4981	137.7152	-

6N	61.3822	65.9055	70.2534	66.8583	67.7024	-
7H	3.3234	3.3976	3.3862	3.4767	3.3481	4.487
8H	3.3120	3.4007	3.3809	3.4753	3.3469	4.487
9H	8.0240	7.9121	7.6091	7.9674	7.8841	8.709
10H	6.4902	6.4641	6.2829	6.5717	6.5071	8.709
11H	3.3634	3.4774	3.1815	3.4982	3.3481	4.487
12H	3.3237	3.4415	3.1425	3.4982	3.4165	4.487

Supplementary Table S7. NBO calculation of TSCZ using TD/DFT B3LYP 631G(d, p) basis set.

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 (C3 - S 4) 1.9935	26.78 73.22	0.5175 ($sp^{99.99}{}_d{}^{3.25}$)C3 0.8557 ($sp^{99.99}{}_d{}^{9.89}$)S4	**σ***(C3-S4) 0.0132	39.99 60.01	0.6324($sp^{1.62}$)C3 -0.7747($sp^{4.46}$)S4	6.82
Lp1(N1) 1.9579		($sp^{4.29}$)N1	**σ***(N2-C3) 0.06780	39.14 60.86	0.6256($sp^{1.52}$)N2 -0.7801($sp^{2.25}$)C3	8.97
Lp1(N2) 1.7196		($sp^{0.21}$)N2	**σ***(N1-H7) 0.0680	30.15 69.85	0.5491($sp^{2.62}$)N1 -0.8358($sp^{0.00}$)H7	5.01
Lp1(N2) 1.7196		($sp^{0.21}$)S4	**σ***(C3-S4) 0.0132	39.99 60.01	0.6324($sp^{1.62}$)C3 -0.7747($sp^{4.46}$)S4	68.54
lp2(S4) 1.8782		(sp^{1})S4	**σ***(N2-C3) 0.0680	39.14 60.86	0.6256($sp^{1.52}$)N2 -0.7801($sp^{2.25}$)C3	10.76
lp2 (S4) 1.8782		(sp^{1})S4	**σ***(C3-N5) 0.0509	60.55 39.45	0.7781($sp^{2.22}$)C3 -0.6281($sp^{1.63}$)N5	10.52

lp1 (N5) **1.7565**		$(sp^{20.76})$N5	**σ***(C3-S4) 0.0132	39.99 60.01	0.6324$(sp^{1.62})$C3 -0.7747$(sp^{4.46})$S4	60.68

Supplementary Table S8. NBO calculation of TSCZ using TD/DFT B3LYP 631G(d', p') basis set.

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 (C3-S4) **1.9828**	28.85 71.15	0.5371$(sp^{99.99}d^{0.37})$C3 0.8435$(sp^{99.53}d^{0.98})$S4	**σ*** (C3-S4) 0.4677	71.15 28.85	0.8435$(sp^{99.99}d^{0.37})$C3 -0.5371$(sp^{99.99}d^{0.98})$S4	5.76
lp1(N1) **1.9621**		$(sp^{3.43})$N1	**σ*** (N2-C3) 0.0739	39.02 60.98	0.6246$(sp^{1.58})$N2 -0.7809$(sp^{2.30})$C3	7.89
lp1(N2) **1.7289**		$(sp^{27.70}d^{0.01})$N2	**σ*** (C3-S4) 0.4677	71.15 28.85	0.8435$(sp^{99.99}d^{0.37})$C3 -0.5371$(sp^{99.99}d^{0.98})$S4	56.88
lp2(S4) **1.8799**		(sp^{1})S4	**σ*** (N2-C3) 0.0739	39.02 60.98	0.6246$(sp^{1.58})$N2 -0.7809$(sp^{2.30})$C3	11.96
lp2(S4) **1.8799**		(sp^{1})S4	**σ*** (C3-N5) 0.0502	59.90 40.10	0.7740$(sp^{2.18})$C3 -0.6332$(sp^{1.72})$N5	10.59
lp1(N5) **1.7771**		$(sp^{15.82})$N5	**σ*** (C3-S4) 0.4677	71.15 28.85	0.8435$(sp^{99.99}d^{0.37})$C3 -0.5371$(sp^{99.99}d^{0.98})$S4	54.36

Supplementary Table S9. NBO of TSCZ using TD/DFT B3LYP 6-311+G (d, p) basis set.

Donor (i)	Acceptor (j)	$E_{(2)}$

orbital / lp (occupancy)	ED_A, % ED_B,%	NBO hybrid Orbitals	Orbital (occupancy)	ED_A, % ED_B, %	NBO hybrid Orbitals	(kJ/mol)
σ (C3-S4) 1.9823	29.07 70.93	0.5392($sp^{99.99}d^{0.40}$)C3 0.8422($sp^{99.99}d^{1.11}$)S4	σ* (C3-S4) 0.4667	70.93 29.07	0.8422($sp^{99.99}$) -0.5392($sp^{99.99}d^{1.11}$)S4	5.52
σ (N5-H9) 1.9822	69.43 30.57	0.8333($sp^{2.62}$)N5 0.5529($sp^{0.00}$)H9	π* (C3-S4) 0.02771	41.40 58.60	0.6434($sp^{1.66}$)C3 -0.7655($sp^{4.47}d^{0.03}$)S4	5.47
lp1 (N1) 1.9624	-	($sp^{3.22}$)N1	σ* (N2-C3) 0.0744	38.78 61.22	0.6227($sp^{1.52}$)N2 -0.7824($sp^{2.27}$)C3	8.33
lp1 (N2) 1.7292	-	($sp^{28.12}$)N2	σ* (C3-S4) 0.4667	70.93 29.07	0.8422($sp^{99.99}$) -0.5392($sp^{99.99}d^{1.11}$)S4	58.27
lp2(S4) 1.8834	-	($sp^{0.22}$)S4	σ* (N2-C3) 0.0744	38.78 61.22	0.6227($sp^{1.52}$)N2 -0.7824($sp^{2.27}$)C3	12.73
lp2(S4) 1.8834	-	($sp^{0.22}$)S4	σ* (C3-N5) 0.0515	60.22 39.78	0.7760($sp^{2.19}$)C3 -0.6307($sp^{1.60}$)N5	11.56
lp1(N5) 1.7769	-	($sp^{16.14}$)N5	σ* (C3-S4) 0.4667	70.93 29.07	0.8422($sp^{99.99}$) -0.5392($sp^{99.99}d^{1.11}$)S4	54.81

Supplementary Table S10. NBO of TSCZ using TD/DFT CAM- B3LYP 6-311+G (d, p) basis set.

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 (N5-H9) 1.9843	69.60 30.40	0.8343($sp^{2.52}$)N5 0.5514($sp^{0.00}$)H9	π* (C3-S4) 0.0193	40.98 59.02	0.6402($sp^{1.63}$)C3 -0.7682($sp^{4.19}d^{0.03}$)S4	5.48

lp1 (N1) 1.9651	-	$(sp^{3.55})$N1	σ* (N2-C3) 0.06992	38.57 61.43	0.6210$(sp^{1.47})$N2 -0.7838$(sp^{2.27})$C3	9.33
lp1 (N2) 1.7321	-	$(sp^{60.48}d^{0.01})$N2	σ* (N1-H6) 0.0152	31.18 68.82	0.5584$(sp^{2.76})$N1 -0.8296$(sp^{0.00})$H6	5.37
lp1 (N2) 1.7321	-	$(sp^{60.48}d^{0.01})$N2	σ* (N1-H7) 0.0121	31.55 68.45	0.5617$(sp^{2.85})$N1 -0.8274 $(sp^{0.00})$H7	5.21
lp1 (N2) 1.7321	-	$(sp^{60.48}d^{0.01})$N2	σ* (C3-S4) 0.4609	72.73 27.27	0.8528$(sp^{99.99}d^{1.44})$ -0.5222$(sp^{99.99}d^{3.61})$S4	83.13
lp2(S4) 1.8907	-	(sp^{1})S4	σ* (N2-C3) 0.0699	38.57 61.43	0.6210$(sp^{1.47})$N2 -0.7838$(sp^{2.27})$C3	15.14
lp2(S4) 1.8907	-	(sp^{1})S4	σ* (C3-N5) 0.0479	60.42 39.58	0.7773$(sp^{2.18})$C3 -0.6292$(sp^{1.54})$N5	13.68
lp1(N5) 1.7777	-	$(sp^{27.96}d^{0.01})$N5	σ* (C3-S4) 0.4609	72.73 27.27	0.8528$(sp^{99.99}d^{1.44})$ -0.5222$(sp^{99.99}d^{3.61})$S4	74.17

Supplementary Table S11. NBO calculation of TCHZ using TD/DFT B3LYP 631G (d, p) basis set.

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	
lp1(N1) 1.9701		$(sp^{3.10})$N1	**σ*** (N2-C3) 0.0645	39.50 60.50	0.6285$(sp^{1.58})$N2 -0.7778$(sp^{2.14})$C3	8.72

lp2(S4) **1.9009**		$(sp^{99.99}d^{2.65})$S4	**σ*** (N2-C3) 0.0645	39.50 60.50	0.6285$(sp^{1.58})$N2 -0.7778$(sp^{2.14})$C3	10.46
lp2(S4) **1.9009**		$(sp^{99.99}d^{2.65})$S4	**σ*** (C3-N5) 0.0544	60.23 39.77	0.7761$(sp^{2.19})$C3 -0.6306$(sp^{1.63})$N5	9.29
lp3(S4) **1.7005**		(sp^{1})S4	π* (N2-C3) 0.5688	22.45 77.55	0.4738$(sp^{99.99}d^{0.26})$N2 -0.8806$(sp^{99.99}d^{4.61})$C3	60.59
lp1(N5) **1.7093**		$(sp^{49.05}d^{0.01})$N5	π* (N2-C3) 0.5688	22.45 77.55	0.4738$(sp^{99.99}d^{0.26})$N2 -0.8806$(sp^{99.99}d^{4.61})$C3	68.80

Supplementary Table S12. NBO calculation of TCHZ using TD/DFT B3LYP 631G(d', p') basis set

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 (N2-H9) **1.9815**	73.51 26.49	0.8574$(sp^{2.18})$N2 0.4738$(sp^{0.00})$H9	π* (C3-S4) 0.0186	40.22 59.78	0.6342$(sp^{1.64})$C3 -0.7732$(sp^{4.68}\ d^{0.04})$S4	5.35
σ (C3-S4) **1.9879**	26.32 73.68	0.5130$(sp^{99.99}d^{0.74})$C3 0.8584$(sp^{99.99}d^{1.44})$S4	**σ*** (C3-S4) 0.5138	73.68 26.32	0.8584$(sp^{99.99}d^{0.74})$C3 -0.5130$(sp^{99.99}d^{1.44})$S4	6.62
lp1(N1) **1.6981**		$(sp^{3.39})$N1	**σ*** (N2-C3) 0.0711	39.13 60.87	0.6256$(sp^{1.59})$N2 -0.7802$(sp^{2.20})$C3	8.49
lp1(N2) **1.6922**		$(sp^{99.99}d^{0.23})$N2	**σ*** (C3-S4) 0.5138	73.68 26.32	0.8584$(sp^{99.99}d^{0.74})$C3 -0.5130$(sp^{99.99}d^{1.44})$S4	78.89
lp2(S4) **1.8744**		$(sp^{99.99}d^{2.17})$S4	**σ*** (N2-C3) 0.0711	39.13 60.87	0.6256$(sp^{1.59})$N2 -0.7802$(sp^{2.20})$C3	11.79

lp2(S4) **1.8744**		$(sp^{99.99}d^{2.17})$S4	**σ*** (C3-N5) 0.0617	61.17 38.83	0.7821$(sp^{2.27})$C3 -0.6231$(sp^{1.57})$N5	10.44
lp1(N5) **1.7464**		(sp^{1})N5	**σ*** (C3-S4) 0.5138	73.68 26.32	0.8584$(sp^{99.99}d^{0.74})$C3 -0.5130$(sp^{99.99}d^{1.44})$S4	63.13
lp1(N6) **1.9552**		$(sp^{4.21})$N6	**σ*** (N5-H10) 0.0292	27.22 72.78	0.5218$(sp^{2.14})$N5 -0.8531$(sp^{0.00})$H10	7.60

Supplementary Table S13. NBO of TCHZ using TD/DFT B3LYP 6-311+G (d, p) basis set.

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 (N2-H9) 1.9815	71.45 28.55	0.8453$(sp^{2.34})$N2 0.5343$(sp^{0.00})$H1	π* (C3-S4) 0.0182	41.03 58.97	0.6405$(sp^{1.66})$C3 -0.7679$(sp^{4.40}d^{0.03})$S4	5.43
σ (C3-S4) 1.9880	26.65 73.35	0.5162$(sp^{99.99}d^{0.84})$C3 0.8565$(sp^{99.99}d^{1.61})$S4	σ* (C3-S4) 0.5091	73.35 26.65	0.8565$(sp^{99.99}d^{0.84})$C3 -0.5162$(sp^{99.99}d^{1.61})$S4	6.47
lp1(N1) 1.9667	-	$(sp^{3.18})$N1	σ* (N2-C3) 0.0694	38.67 61.33	0.6218$(sp^{1.50})$N2 -0.7832$(sp^{2.17})$C3	8.58
lp1(N2) 1.6913	-	$(sp^{0.22})$N2	σ* (C3-S4) 0.5091	73.35 26.65	0.8565$(sp^{99.99}d^{0.84})$C3 -0.5162$(sp^{99.99}d^{1.61})$S4	79.74
lp2(S4) 1.8780	-	$(sp^{99.99}d^{2.67})$S4	σ* (N2-C3) 0.0694	38.67 61.33	0.6218$(sp^{1.50})$N2 -0.7832$(sp^{2.17})$C3	12.34
lp2(S4) 1.8780	-	$(sp^{99.99}d^{2.67})$S4	σ* (C3-N5) 0.0596	61.58 38.42	0.7847$(sp^{2.26})$C3 -0.6199$(sp^{1.49})$N5	11.24

lp1(N5) 1.7475	-	$(sp^{99.99}d^{0.01})$N5	σ* (C3-S4) 0.5091	73.35 26.65	0.8565$(sp^{99.99}d^{0.84})$C3 -0.5162$(sp^{99.99}d^{1.61})$S4	62.63
lp1(N5) 1.7475	-	$(sp^{99.99}d^{0.01})$N5	σ* (N6-H12) 0.0141	31.60 68.40	0.5621$(sp^{2.71})$N6 -0.8270$(sp^{0.00})$H12	5.16
lp1(N6) 1.9586	-	$(sp^{3.99})$N6	σ* (N5-H10) 0.0289	29.41 70.59	0.5423$(sp^{2.33})$N5 -0.8402$(sp^{0.00})$H10	7.30

Supplementary Table S14. NBO of TCHZ using TD/DFT CAM- B3LYP 6-311+G (d, p) basis set.

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 (N2-H9) 1.9819	71.59 28.41	0.8461$(sp^{2.34})$N2 0.5330$(sp^{0.00})$H1	σ* (C3-S4) 0.0133	40.63 59.37	0.6374$(sp^{1.63})$C3 -0.7705$(sp^{4.21}d^{0.03})$S4	5.82
σ (C3-S4) 1.9774	59.37 40.63	0.7705$(sp^{1.63})$C3 0.6374$(sp^{4.21}d^{0.03})$S4	σ* (N5-N6) 0.0209	47.68 52.32	0.6905$(sp^{2.38})$N5 -0.7233$(sp^{2.72})$N6	5.31
lp2(S4) 1.8863	-	$(sp^{99.99}d^{1.79})$S4	σ* (N2-C3) 0.0666	38.75 61.25	0.6225$(sp^{1.50})$N2 -0.7826$(sp^{2.18})$C3	15.04
lp2(S4) 1.8863	-	$(sp^{99.99}d^{1.79})$S4	σ* (C3-N5) 0.0572	61.53 38.47	0.7844$(sp^{2.26})$C3 -0.6203$(sp^{1.49})$N5	13.54
lp3(S4) 1.6128	-	(sp^{1})S4	π* (N2-C3) 0.5942	20.13 79.87	0.4487(sp^{1})N2 -0.8937(sp^{1})C3	114.01
lp1(N5) 1.7536	-	(sp^{1})N5	π* (N2-C3) 0.5942	20.13 79.87	0.4487(sp^{1})N2 -0.8937(sp^{1})C3	81.11

lp1(N5) 1.7536	-	(sp^1)N5	σ* (N6-H11) 0.0128	31.36 68.64	0.5600($sp^{2.64}$)N6 -0.8285($sp^{0.00}$)H11	5.91
lp1(N5) 1.7536	-	(sp^1)N5	σ* (N6-H12) 0.0128	31.36 68.64	0.5600($sp^{2.64}$)N6 -0.8285($sp^{0.00}$)H12	5.91
.lp1(N6) 1.9600	-	($sp^{4.46}$)N6	σ* (N5-H10) 0.0273	29.24 70.76	0.5408($sp^{2.30}$)N5 -0.8412($sp^{0.00}$)H10	8.71

Supplementary Table S15. Local electronic descriptors (Fukui function, local softness and local electrophilicity) calculated at different functionals.

B3LYP 6-311+G(d, p)						
TSCZ						
Atom	f_k^+	f_k^-	S_k^+	S_k^-	ω_k+	ω_k-
1 N	0.0309	-0.2029	0.0168	-0.1102	0.1175	-0.7711
2 N	-0.1063	0.0068	-0.0577	0.0036	-0.4038	0.0258
3 C	-0.4039	-0.2436	-0.2195	-0.1323	-1.53505	-0.9255
4 S	-0.4048	-0.4896	-0.2200	-0.2661	-1.5384	-1.8605
5 N	-0.1159	-0.0707	-0.0629	-0.0384	-0.4404	-0.268
TCHZ						
1 N	0.1114	-0.1964	0.0626	-0.1104	0.4025	-0.7092
2 N	-0.0407	0.0144	-0.0228	0.0081	-0.1470	0.0519

3 C	-0.4704	-0.1985	-0.2645	-0.1116	-1.6991	-0.7169
4 S	-0.6823	-0.5012	-0.3836	-0.2817	-2.4643	-1.8102
5 N	0.0576	-0.0221	0.0324	-0.0124	0.20819	-0.0799
6 N	0.0244	-0.0962	0.0137	-0.0541	0.08811	-0.3473
CAM –B3LYP 6-311+G(d, p)						
TSCZ						
1 N	0.0309	-0.2029	0.0168	-0.1102	0.1175	-0.7711
2 N	-0.1063	0.0068	-0.0577	0.0036	-0.4038	0.0258
3 C	-0.4039	-0.2436	-0.2195	-0.1323	-1.53505	-0.9255
4 S	-0.4048	-0.4896	-0.2200	-0.2661	-1.5384	-1.8605
5 N	-0.1159	-0.0707	-0.0629	-0.0384	-0.4404	-0.268
TCHZ						
1 N	0.1114	-0.1964	0.0626	-0.1104	0.4025	-0.7092
2 N	-0.0407	0.0144	-0.0228	0.0081	-0.1470	0.0519
3 C	-0.4704	-0.1985	-0.2645	-0.1116	-1.6991	-0.7169
4 S	-0.6823	-0.5012	-0.3836	-0.2817	-2.4643	-1.8102
5 N	0.0576	-0.0221	0.0324	-0.0124	0.20819	-0.0799
6 N	0.0244	-0.0962	0.0137	-0.0541	0.08811	-0.3473
B3WP91 6-311+G(d, p)						
TSCZ						
1 N	0.1005	-0.2460	0.0278	-0.0682	0.1144	-0.2804

2 N	0.0721	-0.5730	0.0199	-0.1587	0.0820	-0.6521
3 C	0.1559	-0.3241	0.0432	-0.0898	0.1774	-0.3688
4 S	0.5626	3.1587	0.1558	0.8749	0.6402	3.5946
5 N	0.1089	-1.0152	0.0301	-0.2812	0.1239	-1.1553
TCHZ						
1 N	0.0622	-0.1023	0.0205	-0.0337	0.1196	-0.1967
2 N	0.0508	-0.4557	0.0167	-0.1504	0.0978	-0.8763
3 C	0.2100	-0.6988	0.0693	-0.2306	0.4039	-1.3439
4 S	0.5533	3.0937	0.1826	1.0209	1.0640	5.9495
5 N	0.0236	-0.8232	0.0078	-0.2717	0.0453	-1.5831
6 N	0.1001	-0.0137	0.0330	-0.0045	0.1925	-0.0264

Supplementary Table S16. Local reactivity at different basis sets.

	S_k^+			S_k^-			ω+			ω-		
	631G(d,p)	631+G(d',p')	6311+G(d,p)	631G(d,p)	631+G(d'',p')	6311+G(d,p)	631G(d,p)	631+G(d',p')	6311+G(d,p)	631G(d,p)	631+G(d',p')	6311+G(d,p)
TSCZ	-0.0958	0.0608	0.0168	-0.0848	-0.0942	-0.1102	-0.5798	0.4191	0.1175	-0.5134	-0.6488	-0.7711
	-0.0511	-0.1132	-0.05775	-0.0414	-0.0181	0.0036	-0.3097	-0.7798	-0.4038	-0.2508	-0.1248	0.0258
	-0.1337	-0.2143	-0.2195	-0.0399	-0.0815	-0.1323	-0.8094	-1.4761	-1.53505	-0.2418	-0.5615	-0.9255
	-0.1947	-0.2122	-0.22	-0.3252	-0.3024	-0.2661	-1.1787	-1.4620	-1.5384	-1.9678	-2.0828	-1.8605
	-0.0943	-0.0681	-0.0629	0.0785	-0.0509	-0.0384	-0.5711	-0.469	-0.4404	0.4750	-0.3503	-0.268

TCHZ	-0.0943	0.1728	0.0626	-0.0778	-0.1264	-0.1104	-0.6883	1.1012	0.4025	-0.5683	-0.8056	-0.7092
	-0.0375	-0.1636	-0.0228	-0.0385	0.0190	0.0081	-0.2740	-1.0424	-0.1470	-0.2807	0.1213	0.0519
	-0.1436	-0.2669	-0.2645	-0.0312	-0.0583	-0.1116	-1.0480	-1.7005	-1.6991	-0.2278	-0.3717	-0.7169
	-0.1509	-0.3588	-0.3836	-0.3201	-0.3135	-0.2817	-1.1016	-2.2864	-2.4643	-2.3357	-1.9974	-1.8102
	-0.0315	-0.0841	0.0324	-0.0285	-0.0203	-0.0124	-0.2302	-0.5363	0.20819	-0.2079	-0.1295	-0.0799
	-0.0880	0.1326	0.0137	-0.0499	-0.0684	-0.0541	-0.6427	0.8453	0.08811	-0.3645	-0.4361	-0.3473

Supplementary Table S17. Details of molecular docking results: the summary of binding affinities (kcal/mol) and the H-bond as hydrophobic interactions.

Compound Name	**Protein id**	**Residues involved in Hydrogen Bond interactions**	**Residues involved in Hydrophobic interaction**	**No. of Bonds**		**Inhibition Constant Ki (uM)**	**Binding Energy (ΔG) (kcal/mol)**
				H-Bond	**Hydrophobic Bonds**		
TSCZ	**6CLU**	Asp78 (A) N2……..…..O **2.94 (Å)** Asp78 (A) N1……..…..O **2.83 (Å)**	Asp78 (A), Asp42 (A)	**4**	**2**	**3.81**	**-3.30**

		Ala41(A) N3……...O **2.75 (Å)** Met37(A) N3……...O **2.78 (Å)**					
	2WJE	Glu108 (A) N3……. OE2 **2.58 (Å)** His7 (A) N2……. NE2 **2.70 (Å)** Glu80 (A) N2……. OE2 **2.78 (Å)** Asp199 (A) N1……. OD2 **3.06 (Å)** Arg206 (A) S……. NB2 **3.16 (Å)**	His42 (A), His5 (A), Asp199 (A), Glu80 (A), Glu108 (A).	**5**	**5**	**3.28**	**-3.39**
TCHZ	**6CLU**	Met37 (A) N1……...O **2.60 (Å)** Ala41 (A) N4……...O **2.56 (Å)** Asp78 (A)	Asp78 (A).	**4**	**1**	**7.57**	**-2.89**

		N3……...O **2.83 (Å)** Asp78 (A) N3……...O **3.22 (Å)**				
	2WJE	Glu108 (A) N1……. OC2 **3.14 (Å)** Asp199 (A) N1……. OD2 **3.25 (Å)** Asp199 (A) N4……. OD2 **2.45 (Å)** Arg139 (A) N4……. NB1 **2.85 (Å)**	His5 (A), Asp199 (A), Glu80 (A), Glu108 (A).	**4**	**4**	**2.39**	**-3.58**

Supplementary Table S18. Molecular properties of the molecules under study of physicochemical properties of TSCZ and TCHZ

Properties	TSCZ	TCHZ
Formula	CH5N3S	CH6N4S
Molecular weight	91.14 g/mol	106.15 g/mol
Log $P_{o/w}$ (iLOGP)	0.43	0.14
Num. heavy atoms	5	6
Num. arom. heavy atoms	0	0

Fraction Csp3	0.00	0.00
Num. rotatable bonds	1	2
Num. H-bond acceptors	1	2
Num. H-bond donors	3	4
Molar Refractivity	22.93	25.73
TPSA	96.16 Å²	108.19 Å²
Lipinski	Yes; 0 violation	Yes; 0 violation
Bioavailability Score	0.55	0.55
PAINS	0 alert	0 alert
Brenk	2 alerts: hydrazine, thiocarbonyl_group	2 alerts: hydrazine, thiocarbonyl_group
Leadlikeness	No; 1 violation: MW<250	No; 1 violation: MW<250
Synthetic accessibility	2.12	2.28