Full Paper

3,4-Disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones: Synthesis, Antimicrobial Evaluation and QSAR Investigations Using Hansch Analysis

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The 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione derivatives were synthesized and characterized by physicochemical and spectral means, and the results of antimicrobial study of these compounds against *Staphylococcus aureus, Escherichia coli,* and *Candida albicans* by tube dilution method indicated that 4-(4-chlorophenyl)-3-(4-nitrophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **6** and 4-(4-fluorophenyl)-3-(4-nitrophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **12** were the most potential ones. Further, the QSAR studies by Hansch analysis applied to find out the correlation between physicochemical characteristics of synthesized compounds with antimicrobial activity demonstrated the contribution of electronic parameter, total energy (Te) and the topological parameter (valence second order molecular connectivity index ($^2\chi^v$)). Excellent statistically significant models were developed by Hansch approach (r^2 = 0.828 – 0.898) for the three microorganisms under study. The cross-validated r^2 (q^2), which is an indication of the predictive capability of the model for all cases was also very good (q^2 = 0.776 – 0.875).

Keywords: Antibacterial / Antifungal / Quinazoline-2-thione / QSAR / q^2

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Introduction

Literature reports reveal that the heterocyclic quinazoline derivatives possess various biological activities, *e.g.*, anticonvulsant [1], antiphlogistic [2], muscle relaxant [3], antimalarial, antihistamine [4], and anti-inflammatory activities [5]. Further, they have also been reported to have antimicrobial activity against different pathogenic microorganisms [6 – 12].

The quantitative structure-activity relationship (QSAR) study is a useful tool for rational search of bioactive compounds. The QSAR study describes a definite role of a structural feature in a molecule, in a quantitative term, with a definite contribution to the activity of a particular physiochemical property of that structural feature [13].

Keeping in view the diverse therapeutic activities of quinazolines, we planned to synthesize bioactive heterocycles [14, 15] and performed the correlation of biological activities with their physicochemical properties [21 – 25]. Here, we report a study on the synthesis and QSAR investigations of 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones for their *in-vitro* antimicrobial activity against *Staphylococcus aureus, Escherichia coli,* and *Candida albicans*.

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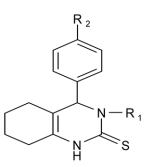
Abbreviations: quantitative structure-activity relationship (QSAR); minimum inhibitory concentration (MIC); molar refractivity (MR); total energy (Te); highest occupied molecular orbital (HOMO); lowest unoccupied molecular orbital (LUMO); leave-one-out (LOO)

Table 1. Physicochemical characteristics of 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione derivatives.



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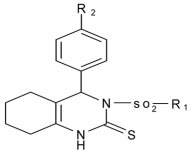

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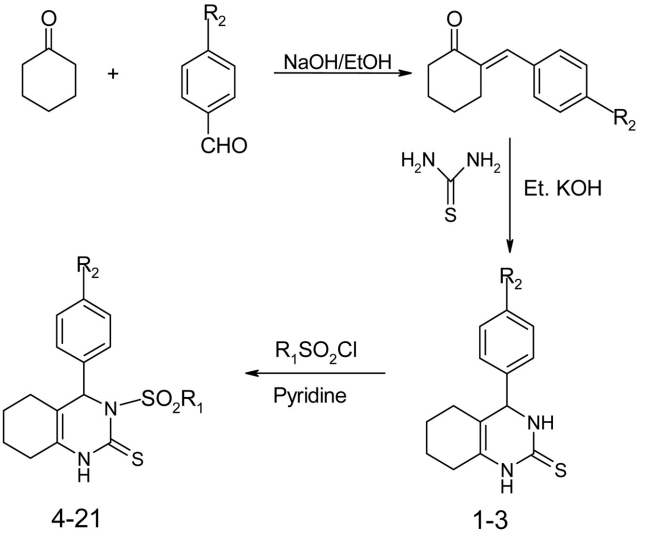
Comp.	R_1	R_2	Mol. formula	**Mw.**	Mp. (°C)	R_f Value	Yield (%)
1	H	Cl	$C_{14}H_{15}ClN_2S$	278.80	208–210	0.48	61
2	H	F	$C_{14}H_{15}FN_2S$	262.23	202–204	0.42	76
3	H	OCH_3	$C_{14}H_{18}N_2OS$	274.38	220–222	0.38	84
4	C_6H_5-	Cl	$C_{20}H_{19}ClN_2O_2S_2$	418.95	102–104	0.77	51
5	CH_3-	Cl	$C_{15}H_{17}ClN_2O_2S_2$	356.88	98–100	0.85	62
6	4-NO_2-C_6H_4-	Cl	$C_{20}H_{18}ClN_3O_4S_2$	463.95	94–96	0.81	46
7	$C_{10}H_7$-	Cl	$C_{24}H_{21}ClN_2O_2S_2$	469.01	116–118	0.60	51
8	4-Cl-C_6H_4-	Cl	$C_{20}H_{18}Cl_2N_2O_2S_2$	453.40	106–108	0.75	67
9	4-CH_3-C_6H_4-	Cl	$C_{21}H_{21}ClN_2O_2S_2$	432.98	88–90	0.87	72
10	C_6H_5-	F	$C_{20}H_{19}FN_2O_2S_2$	402.50	174–176	0.80	60
11	CH_3-	F	$C_{15}H_{17}FN_2O_2S_2$	340.43	164–166	0.69	66
12	4-NO_2-C_6H_4-	F	$C_{20}H_{18}FN_3O_4S_2$	447.50	134–136	0.76	62
13	$C_{10}H_7$-	F	$C_{24}H_{21}FN_2O_2S_2$	452.56	128–130	0.71	58
14	4-Cl-C_6H_4-	F	$C_{20}H_{18}ClFN_2O_2S_2$	436.95	146–148	0.77	59
15	4-CH_3-C_6H_4-	F	$C_{21}H_{21}FN_2O_2S_2$	416.53	96–98	0.86	61
16	C_6H_5-	OCH_3	$C_{21}H_{22}N_2O_3S_2$	414.54	138–140	0.81	55
17	CH_3-	OCH_3	$C_{16}H_{20}N_2O_3S_2$	352.46	156–158	0.72	60
18	4-NO_2-C_6H_4-	OCH_3	$C_{21}H_{21}N_3O_5S_2$	459.53	146–148	0.67	56
19	$C_{10}H_7$-	OCH_3	$C_{25}H_{24}N_2O_3S_2$	464.60	140–142	0.56	62
20	4-Cl-C_6H_4-	OCH_3	$C_{21}H_{21}ClN_2O_3S_2$	448.98	118–120	0.77	53
21	4-CH_3-C_6H_4-	OCH_3	$C_{22}H_{24}N_2O_3S_2$	428.56	126–128	0.74	58

Chemistry

The intermediates 4-(4-substituted phenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones **1–3** were prepared by the reaction of 4-substituted benzylidene cyclohexanones with thiourea in the presence of ethanolic potassium hydroxide. Compounds **1–3** were reacted with various substituted sulfonyl chlorides in presence of pyridine to afford the title compounds (Scheme 1).

The formation of the title products is indicated by the disappearance of a peak due to NH at the third position of the starting material [4-(4-substituted phenyl)-1,2,3,4,5,6,7,8-octahydroquninazoline-2-thiones] in IR and ^{1}H-NMR spectra of all the compounds **4–21**. The physicochemical characteristics of the synthesized compounds are presented in Table 1.

The IR and NMR spectra of these compounds have shown the presence of peaks due to C=S, NH, and aryl groups. The mass spectra of the title compounds are in conformity with the assigned molecular structure and showed molecular ion peaks corresponding to their molecular formula. Elemental analysis (C, H, N) indicated that the calculated and observed values were within the acceptable limits (± 0.4%). The synthesized compounds



Scheme 1. Synthesis of 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones.

were screened for their *in-vitro* antimicrobial activity against Gram-positive *Staphylococcus aureus,* Gram-negative *Escherichia coli* and fungi *Candida albicans* using tube dilution method [16]. The minimum inhibitory concen-

Table 2. Antimicrobial activity data of 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione derivatives.

Compound	pMIC (μm/mL)		
	S. aureus	*E. coli*	*C. albicans*
1	2.14	2.35	2.35
2	2.24	2.32	2.24
3	2.14	2.26	2.14
4	2.72	2.67	2.67
5	2.55	2.46	2.65
6	2.82	2.76	2.87
7	2.72	2.72	2.83
8	2.75	2.70	2.70
9	2.64	2.79	2.68
10	2.65	2.70	2.76
11	2.53	2.58	2.63
12	2.81	2.81	2.81
13	2.75	2.66	2.75
14	2.69	2.80	2.74
15	2.62	2.72	2.62
16	2.62	2.77	2.77
17	2.45	2.55	2.59
18	2.76	2.76	2.66
19	2.67	2.67	2.76
20	2.65	2.75	2.70
21	2.54	2.63	2.68
Standard	3.33[a)]	3.33[a)]	3.16[b)]

[a)] Ciprofloxacin.
[b)] Fluconazole

tration (MIC) values in terms of pMIC in μM/mL are presented in Table 2. The QSAR studies have been carried out to find out the correlation between the antimicrobial activity of quinazolines and their physicochemical characteristics using TSAR 3D version 3.3 for Windows [17].

Results and discussion

The compounds 4-(4-chlorophenyl)-3-(4-nitrophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **6** against *S. aureus* and *C. albicans* and 4-(4-fluorophenyl)-3-(4-nitrophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **12** against *E. coli* emerged as the most active antimicrobial agents amongst the synthesized substituted quinazolines.

In the present study, an attempt has been made to find structural requirements for the inhibition of different microbial strains using the Hansch approach on synthesized quinazolines with different molecular descriptors like log of the octanol-water partition coefficient (log P) [18], molar refractivity (MR) [19], Kiers molecular connectivity ($^2\chi^v$) and shape (κ, κα) topological indices [20], randic topological index (R) [26], Balaban topological index (J) [27], Wiener topological index (W) [28], total energy (Te), energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) [29, 30]. The values of selected descriptors are presented in Table 3.

In the first step of the regression analysis, the correlation between each individual parameter and antimicrobial activity was calculated (Table 4). It indicated that high interrelationships were observed between all the

Table 3. Selected molecular descriptors calculated for 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione derivatives.

Comp.	log P	MR	$^0\chi$	$^0\chi^v$	$^1\chi$	$^1\chi^v$	$^2\chi$	$^2\chi^v$	Te	LUMO
1	3.24	80.32	12.54	11.70	8.74	7.14	7.97	5.71	−2981.01	−0.35
2	2.86	75.73	12.54	10.88	8.74	6.73	7.97	5.24	−3092.32	−0.35
3	2.47	81.98	13.24	11.91	9.28	7.15	8.14	5.46	−3096.78	−0.13
4	4.50	113.63	19.02	17.14	12.98	11.27	12.20	9.56	−4637.93	−1.03
5	2.82	93.86	15.91	14.76	10.38	10.00	10.41	8.55	−3970.82	−1.11
6	4.46	120.96	21.47	18.33	14.29	11.77	13.72	10.00	−5468.65	−1.78
7	5.50	130.08	21.59	19.30	14.95	12.67	14.18	10.76	−5177.33	−1.08
8	5.02	118.44	19.89	18.26	13.38	11.78	12.82	10.17	−4998.02	−1.18
9	4.97	118.67	19.89	18.07	13.38	11.68	12.82	10.06	−4793.82	−0.99
10	4.12	109.05	19.02	16.33	12.98	10.86	12.20	9.09	−4749.24	−1.04
11	2.44	89.27	15.91	13.94	10.38	9.59	10.41	8.08	−4082.13	−1.12
12	4.08	116.37	21.47	17.51	14.29	11.36	13.72	9.53	−5579.96	−1.79
13	5.13	125.50	21.59	18.48	14.95	12.26	14.18	10.29	−5288.64	−1.09
14	4.64	113.85	19.89	17.44	13.38	11.37	12.82	9.70	−5109.33	−1.19
15	4.59	114.09	19.89	17.25	13.38	11.27	12.82	9.59	−4905.10	−0.99
16	3.73	115.29	19.73	17.36	13.52	11.28	12.37	9.31	−4753.70	−0.94
17	2.05	95.51	16.61	14.97	10.91	10.02	10.58	8.30	−4086.66	−1.00
18	3.69	122.62	22.17	18.54	14.82	11.78	13.89	9.75	−5584.40	−1.75
19	4.73	131.74	22.29	19.51	15.49	12.69	14.35	10.51	−5293.11	−1.00
20	4.25	120.10	20.60	18.47	13.91	11.79	12.99	9.92	−5113.79	−1.08
21	4.20	120.33	20.60	18.28	13.91	11.69	12.99	9.81	−4909.58	−0.90

Table 4. Correlation matrix for antibacterial activity of 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione derivatives against *S. aureus*.

	pMICsa	Log P	MR	$^{0}\chi$	$^{0}\chi^{v}$	$^{1}\chi$	$^{1}\chi^{v}$	$^{2}\chi$	$^{2}\chi^{v}$	TE	pMICec	pMICca
pMICsa	1.000	0.690	0.863	0.913	0.891	0.880	0.916	0.926	0.924	−0.948		
Log P		1.000	0.837	0.763	0.798	0.801	0.762	0.785	0.767	−0.721	0.689	0.694
MR			1.000	0.980	0.991	0.989	0.969	0.979	0.951	−0.940	0.854	0.902
$^{0}\chi$				1.000	0.981	0.993	0.967	0.996	0.950	−0.986	0.900	0.917
$^{0}\chi^{v}$					1.000	0.976	0.988	0.980	0.978	−0.951	0.883	0.937
$^{1}\chi$						1.000	0.955	0.989	0.931	−0.966	0.869	0.885
$^{1}\chi^{v}$							1.000	0.977	0.996	−0.944	0.889	0.952
$^{2}\chi$								1.000	0.964	−0.983	0.897	0.926
$^{2}\chi^{v}$									1.000	−0.934	0.895	0.960
TE										1.000	−0.924	−0.916

Table 5. Table showing statistically significant equations obtained for antimicrobial activity of 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione used in the present study.

S. No.	QSAR Model	n	r	q^2	F	S
pMICsa						
1	0.058 $^{0}\chi$ + 1.496	21	0.912	0.790	94.87	0.083
2	0.069 $^{0}\chi^{v}$ + 1.444	21	0.890	0.738	72.85	0.093
3	0.082 $^{1}\chi$ + 1.536	21	0.880	0.790	65.25	0.097
4	0.103 $^{1}\chi^{v}$ + 1.473	21	0.915	0.799	98.94	0.082
5	0.113 $^{2}\chi^{v}$ + 1.572	21	0.924	0.819	111.49	0.078
6	0.052 κ_1 + 1.541	21	0.912	0.789	94.06	0.083
7	0.060 $\kappa\alpha_1$ + 1.477	21	0.919	0.806	104.51	0.080
8	−0.420 LUMO + 2.156	21	0.877	0.705	63.34	0.098
9	0.082 R + 1.536	21	0.880	0.709	65.25	0.097
pMICec						
1	0.047 $^{0}\chi$ + 1.756	21	0.899	0.765	80.71	0.073
2	0.056 $^{0}\chi^{v}$ + 1.709	21	0.882	0.730	67.22	0.078
3	0.082 $^{1}\chi^{v}$ + 1.752	21	0.888	0.748	71.43	0.076
4	0.071 $^{2}\chi$ + 1.776	21	0.896	0.758	77.88	0.074
5	0.089 $^{2}\chi^{v}$ + 1.832	21	0.894	0.766	76.16	0.074
6	0.042 κ_1 + 1.787	21	0.905	0.777	86.00	0.071
7	0.124 $\kappa\alpha_2$ + 1.733	21	0.884	0.730	68.63	0.077
pMICca						
1	0.081 $^{2}\chi$ + 1.673	21	0.886	0.716	69.96	0.088
2	−0.0002 Te + 1.694	21	0.885	0.708	69.02	0.088

parameters ($r > 0.8$) except in case of IP (Ionization Potential), LUMO, and HOMO. Hence, these descriptors cannot be combined in multiple linear regression analysis. If combined, it may result in a change in signs of the coefficients, a change in the values of the previous coefficient, a change of a significant variable into an insignificant one or an increase in standard error of the estimate on addition of an additional parameter to the model [18]. The linear regression analysis carried out has resulted in the following best QSAR models, Eq. (1–6). The other statistically significant models obtained are presented in Table 5.

QSAR Model for antibacterial activity against *S. aureus*

$$pMICsa = -0.0002\ Te + 1.499 \quad (1)$$

$n = 21\ r^2 = 0.898\ q^2 = 0.875\ s = 0.065\ F = 169.19\ p < 0.001$

$$pMICsa = 0.090\ ^{2}\chi + 1.502 \quad (2)$$

$n = 21\ r^2 = 0.857\ q^2 = 0.821\ s = 0.077\ F = 114.35\ p < 0.001$

QSAR Model for antibacterial activity against *E. coli*

$$pMICec = -0.0002\ Te + 1.768 \quad (3)$$

$n = 21\ r^2 = 0.853\ q^2 = 0.823\ s = 0.063\ F = 111.18\ p < 0.001$

Table 6. Table showing observed and predicted antimicrobial activity of 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione derivatives.

Compound	pMICsa			pMICec			pMICca		
	Obs.	Pre.	Resi	Obs.	Pre.	Resi	Obs.	Pre.	Resi
1	2.14	2.20	−0.06	2.35	2.33	0.02	2.35	2.30	0.05
2	2.24	2.23	0.01	2.32	2.35	−0.03	2.24	2.25	−0.01
3	2.14	2.23	−0.09	2.26	2.35	−0.09	2.14	2.27	−0.13
4	2.72	2.59	0.13	2.67	2.64	0.03	2.67	2.70	−0.03
5	2.55	2.43	0.12	2.46	2.51	−0.05	2.65	2.60	0.05
6	2.82	2.79	0.03	2.76	2.79	−0.03	2.87	2.75	0.12
7	2.72	2.72	0.00	2.72	2.74	−0.02	2.83	2.83	0.00
8	2.75	2.67	0.08	2.70	2.70	0.00	2.70	2.77	−0.07
9	2.64	2.63	0.01	2.79	2.67	0.12	2.68	2.76	−0.08
10	2.65	2.62	0.03	2.70	2.66	0.04	2.76	2.66	0.10
11	2.53	2.46	0.07	2.58	2.53	0.05	2.63	2.55	0.08
12	2.81	2.81	0.00	2.81	2.81	0.00	2.81	2.70	0.11
13	2.75	2.74	0.01	2.66	2.76	−0.10	2.75	2.78	−0.03
14	2.69	2.70	−0.01	2.80	2.73	0.07	2.74	2.72	0.02
15	2.62	2.65	−0.03	2.72	2.69	0.03	2.62	2.71	−0.09
16	2.62	2.62	0.00	2.77	2.66	0.11	2.77	2.68	0.09
17	2.45	2.46	−0.01	2.55	2.53	0.02	2.59	2.57	0.02
18	2.76	2.81	−0.05	2.76	2.81	−0.05	2.66	2.72	−0.06
19	2.67	2.74	−0.07	2.67	2.76	−0.09	2.76	2.80	−0.04
20	2.65	2.70	−0.05	2.75	2.73	0.02	2.70	2.74	−0.04
21	2.54	2.65	−0.11	2.63	2.69	−0.06	2.68	2.73	−0.05

$$pMICec = 0.048 + 1.734\ \kappa\alpha_1 \quad (4)$$

$n = 21\ r^2 = 0.833\ q^2 = 0.798\ s = 0.068\ F = 95.98\ p < 0.001$

QSAR Model for antifungal activity against *C. albicans*

$$pMICca = 0.104\ {}^2\chi^v + 1.701 \quad (5)$$

$n = 21\ r^2 = 0.844\ q^2 = 0.802\ s = 0.074\ F = 104.31\ p < 0.001$

$$pMICca = 0.096\ {}^1\chi^v + 1.610 \quad (6)$$

$n = 21\ r^2 = 0.828\ q^2 = 0.776\ s = 0.079\ F = 91.76\ p < 0.001$

In the above QSAR models, Eq. (1-6), n is the number of data points, r is the multiple-correlation coefficient, q^2 is cross-validated r^2 obtained by the 'leave-one-out' (LOO) method, s is the standard error of estimate, F represents the Fischer ratio between the variances of calculated and observed activities, and the p-value is the significance level of the regression. All the QSARs manifest good statistics and account for more than 80% of the total variance in the antimicrobial activity of quinazolines. The Fischer-ratio values obtained for the QSARs exceed the tabulated value by a large margin as desired for a meaningful correlation.

Equations 1 and 2 describe the antibacterial activity of quinazolines against *S. aureus*. The negative coefficient of Te in Eq. (1) indicated that antibacterial activities of quinazolines against *S. aureus* are indirectly proportional to its magnitude, i. e. that antibacterial activity increases with the decrease in magnitude of Te. This is evidenced by the values of Te in Table 3, where the values of Te for compounds **6** and **12** (Te = −5468.65 and −5579.96, respectively) are lower than those for other compounds which makes them the most active compounds (pMICsa = 2.82, 2.81, respectively). Similarly, compound **1** with the high Te value of −2981.01 has a minimum activity (pMICsa = 2.14). Similar results were observed for antibac-

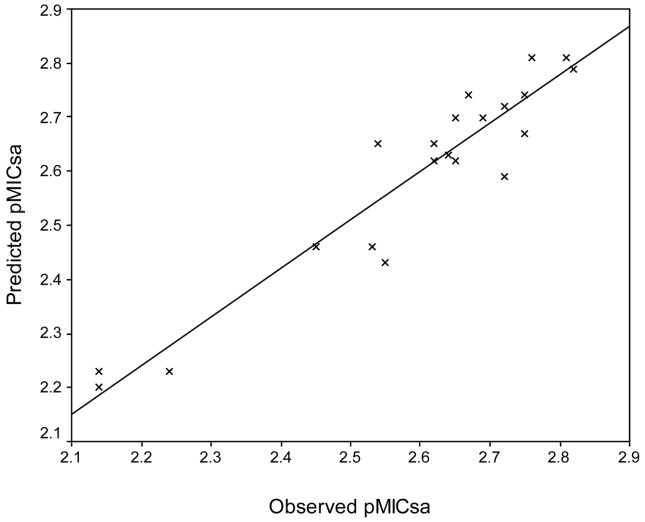


Figure 1. Graph between observed and predicted antibacterial activity of quinazolines against *S. aureus*.

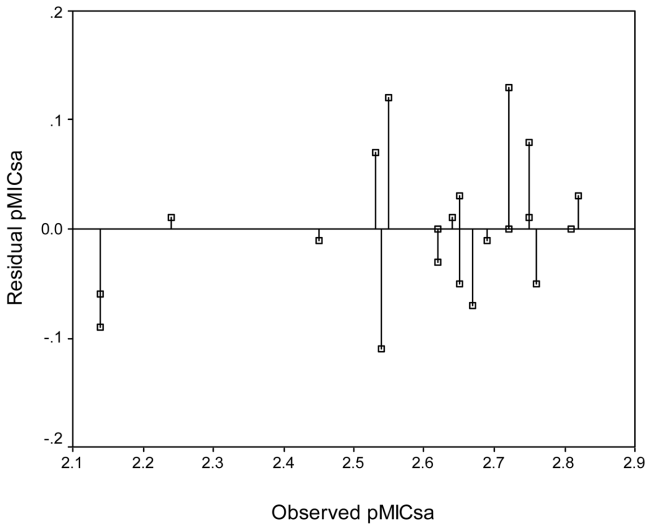


Figure 2. Graph between observed and residual antibacterial activity of quinazolines against *S. aureus*.

terial activity of quinazolines against *E. coli* with the molecular descriptor, Te. Being the positive coefficient, $^{2}\chi^{v}$ showed an opposite trend in case of antifungal activity of the quinazolines against *C. albicans*.

It is worth mentioning that all the generated regressions exhibit good predictive ability as established by high q^2 values ($q^2 < 0.75$) and the best being recorded for Eq. (1) ($q^2 = 0.875$). Besides the validation made by the LOO procedure, the generated correlations were also tested for the ability to reproduce pMIC values of the compounds in the series, and a comparison was made with observed values (Table 6). Further, the good agreement between experimental data and model computation is achieved using the above mentioned model 1 Eq. (1), was evidenced by Fig. 1.

The plot of residuals of linear regression predicted values of pMICsa against the experimental pMICsa values (Fig. 2) indicated that no systemic error exists in the development of QSAR model as the residuals propagated on both sides of zero [31].

Conclusions

The 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione derivatives were synthesized in appreciable yield, and the spectral data were found in agreement with the assigned molecular structures. 4-(4-Chlorophenyl)-3-(4-nitrophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **6** and 4-(4-fluorophenyl)-3-(4-nitrophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **12** were found to be the most potential antimicrobial agents. On the basis of QSAR studies by Hansch analysis, it can be concluded that the importance of electron-withdrawing constituents in enhancing the biological activity is evident from the contribution of the parameter Te. Reduction of total energy (Te) being favorable for the antibacterial activity indicates that the charge-transfer phenomenon is taking place in drug-receptor interaction upon binding; moreover, the inverse relationship between Te and the biological activity is shown by their negative influence on the antibacterial activity. The antifungal QSAR results indicated the positive contribution of the valence second order molecular connectivity index ($^{2}\chi^{v}$). The positive coefficient of the descriptor suggests that non-branched molecules will have enhanced antifungal activity.

The authors have declared no conflict of interest.

Experimental

Melting points were determined using Bells India melting point apparatus (Bells India Ltd., New Dehli, India) and are uncorrected. The infrared (IR) spectra were recorded with Shimadzu 8400S-FTIR spectrophotometer (Shimadzu, Tokyo, Japan) in KBr discs. The ^{1}H-NMR spectra in $CDCl_3$ were recorded on Bruker-DPX 300 NMR spectrophotometer (Bruker Bioscience, Billerica, MA, USA) using TMS as an internal standard. Mass spectra were obtained on a Shimadzu-2010A instrument. Elemental analysis was performed on a Perkin-Elmer 2400 C, H, N analyzer (Perkin Elmer, Beaconsfield, UK) and values were within the acceptable limits of the calculated values. Purity of all the synthesized compounds were ascertained by single spot during TLC plates made of silica gel-G (chromatographic grade) and iodine was used as a developing agent.

Chemistry

*4-(4-Chlorophenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **1***

A mixture of 2-*p*-chlorobenzylidene cyclohexanone (2.2 g, 0.01 mol), thiourea (0.76 g, 0.01 mol) and potassium hydroxide (1 g) in ethanol (100 mL) was heated under reflux for 4 h. The reaction mixture was concentrated to half of its volume, diluted with water, then acidified with acetic acid, and left overnight. The solid thus obtained was filtered, washed with water, and recrystallized from ethanol. Yield: 61.15%, mp.: 208 – 210°C; IR (KBr) cm^{-1}: 3178 (N-H), 1548 (C=C), 1220 (C=S), 828 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 7.71 (1H, s, NH), 7.18 – 7.36 (4H, m, ArH), 6.52 (1H, s, NH), 4.90 (1H, s, N-CH), 1.55-1.99 (8H, m, $4 \times CH_2$).

*4-(4-Fluorophenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **2***

Compound **2** was prepared by adopting the same procedure as for compound **1**. IR (KBr) cm^{-1}: 3197 (N-H), 1506 (C=C), 1224 (C=S), 838 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 7.67 (1H, s, NH), 6.9 – 7.48 (4H, m, ArH), 6.5 (1H, s, NH), 4.92 (1H, s, N-CH), 1.46 – 2.64 (8H, m, $4 \times CH_2$).

*4-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydro-quinazoline-2-thione **3***

Compound **3** was prepared by adopting the same procedure as for compound **1**. IR (KBr) cm^{-1}: 3193 (N-H), 1542 (C=C), 1249 (C=S), 833 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 7.57 (1H, s, NH), 6.88 – 7.26 (4H, m, ArH), 6.47 (1H, s, NH), 4.88 (1H, s, N-CH), 3.85 (3H, s, OCH_3), 1.55 – 1.99 (8H, m, 4 × CH_2).

*4-(4-Chlorophenyl)-3-phenylsulfonyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **4***

A mixture of 4-(4-chlorophenyl)-1,2,3,4,5,6,7,8-octahydro-quinazoline-2-thione **1** (1.112 g, 0.004 mol) and benzene sulfonylchloride (0.48 mL, 0.004 mol) in pyridine (10 mL) was heated in a water-bath for 3.5 h. The reaction mixture was cooled and poured into diluted HCl. The solid thus obtained was filtered, washed with water, and crystallized from alcohol. IR (KBr) cm^{-1}: 3182 (N-H), 1531 (C=C), 1220 (C=S), 1326, 1176 (SO_2), 833 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.64 – 7.6 (9H, m, ArH), 6.64 (1H, s, NH), 4.91 (1H, s, N-CH), 1.25 – 2.67 (8H, m, 4 × CH_2); MS *m/z*: 419 [M^+]; Anal. Calcd. for $C_{20}H_{19}ClN_2O_2S_2$: C, 57.34; H, 4.57; N, 6.69. Found: C, 57.40; H, 4.58; N, 6.65.

*4-(4-Chlorophenyl)-3-methylsulfonyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **5***

Compound **5** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3076 (N-H), 1531 (C=C), 1280 (C=S), 1380, 1176 (SO_2), 835 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.96 – 7.55 (4H, m, ArH), 6.5 (1H, s, NH), 5.0 (1H, s, N-CH), 1.26-3.20 (11H, m, 4 × CH_2, CH_3); MS *m/z*: 35 [M^+]; Anal. Calcd. for $C_{15}H_{17}ClN_2O_2S_2$: C, 50.48; H, 4.80; N, 7.84. Found: C, 50.50; H, 4.85; N, 7.88.

*4-(4-Chlorophenyl)-3-(4-nitrophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **6***

Compound **6** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3190 (N-H), 1537 (C=C), 1288 (C=S), 1336, 1188 (SO_2), 833 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 8.04 – 8.07 (4H, m, Ar-NO_2), 6.90 – 7.51 (4H, m, ArH), 6.06 (1H, s, NH), 4.84 (1H, s, N-CH), 1.37 – 3.27 (8H, m, 4 × CH_2); MS *m/z*: 464 [M^+]; Anal. Calcd. for $C_{20}H_{18}ClN_3O_4S_2$: C, 51.77; H, 3.91; N, 9.06. Found: C, 51.74; H, 3.95; N, 9.12.

*4-(4-Chlorophenyl)-3-(1-naphthylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **7***

Compound **7** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3201 (N-H), 1537 (C=C), 1282 (C=S), 1326, 1190 (SO_2), 833 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.76 – 7.68 (11H, m, ArH), 6.42 (1H, s, N-H), 4.83 (1H, s, N-CH), 1.18 – 3.18 (8H, m, 4 × CH_2); MS *m/z*: 469 [M^+]; Anal. Calcd. for $C_{24}H_{21}ClN_2O_2S_2$: C, 61.46; H, 4.51; N, 5.97. Found: C, 61.50; H, 4.53; N, 5.95.

*4-(4-Chlorophenyl)-3-(4-chlorophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **8***

Compound **8** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3132 (N-H), 1591 (C=C), 1282 (C=S), 1328, 1188 (SO_2), 831 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.9 – 7.69 (8H, m, ArH), 5.63 (1H, s, N-H), 4.83 (1H, s, N-CH), 1.25 – 3.49 (8H, m, 4 × CH_2); MS *m/z*: 453 [M^+]; Anal. Calcd. for $C_{20}H_{18}Cl_2N_2O_2S_2$: C, 52.98; H, 4.00; N, 6.18. Found: C, 52.94; H, 4.06; N, 6.20.

*4-(4-Chlorophenyl)-3-(4-methylphenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **9***

Compound **9** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3082 (N-H), 1595 (C=C), 1285 (C=S), 1328, 1176 (SO_2), 835 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.97 – 7.56 (8H, m, ArH), 6.5 (1H, s, N-H), 5.4 (1H, s, N-CH), 2.37 (3H, s, CH_3), 2.17 – 2.97 (8H, m, 4 × CH_2); MS *m/z*: 432 [M^+]; Anal. Calcd. for $C_{21}H_{21}ClN_2O_2S_2$: C, 58.25; H, 4.88; N, 6.46. Found: C, 58.28; H, 4.85; N, 6.49.

*4-(4-Fluorophenyl)-3-phenylsulfonyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **10***

Compound **10** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3062 (N-H), 1531 (C=C), 1226 (C=S), 1328, 1157 (SO_2), 840 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 7.2 – 7.7 (9H, m, ArH), 6.68 (1H, s, NH), 5.65 (1H, s, N-CH), 1.3-2.9 (8H, m, 4 × CH_2); MS *m/z*: 402 [M^+]; Anal. Calcd. for $C_{20}H_{19}FN_2O_2S_2$: C, 59.68; H, 4.76; N, 6.96. Found: C, 59.65; H, 4.80; N, 6.95.

*4-(4-Fluorophenyl)-3-methylsulfonyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **11***

Compound **11** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3114 (N-H), 1531 (C=C), 1226 (C=S), 1319, 1157 (SO_2), 838 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 7.07 – 7.6 (4H, m, ArH), 6.5 (1H, s, NH), 4.68 (1H, s, N-CH), 1.26 – 3.10 (11H, m, 4 × CH_2, CH_3); MS *m/z*: 340 [M^+]; Anal. Calcd. for $C_{15}H_{17}FN_2O_2S_2$: C, 52.92; H, 5.03; N, 8.22. Found: C, 52.90; H, 5.07; N, 8.25.

*4-(4-Fluorophenyl)-3-(4-nitrophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **12***

Compound **12** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3093 (N-H), 1575 (C=C), 1223 (C=S), 1338, 1157 (SO_2), 840 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 8.01 – 8.3 (4H, m, Ar-NO_2), 7.01 – 7.75 (4H, m, ArH), 6.65 (1H, s, NH), 5.54 (1H, s, N-CH), 1.25 – 2.82 (8H, m, 4 6 CH_2); MS *m/z*: 447 [M^+]; Anal. Calcd. for $C_{20}H_{18}$ $FN_3O_4S_2$: C, 53.68; H, 4.05; N, 9.38. Found: C, 53.65; H, 4.09; N, 9.45.

*4-(4-Fluorophenyl)-3-(1-naphthylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **13***

Compound **13** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3190 (N-H), 1506 (C=C), 1226 (C=S), 1330, 1157 (SO_2), 840 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 7.07 – 8.06 (11H, m, ArH), 6.56 (1H, s, N-H), 5.53 (1H, s, N-CH), 1.04 – 2.8 (8H, m, 4 6 CH_2); MS *m/z*: 452 [M^+]; Anal. Calcd. for $C_{24}H_{21}FN_2O_2S_2$: C, 63.69; H, 4.67; N, 6.18. Found: C, 63.65; H, 4.71; N, 6.20.

*4-(4-Fluorophenyl)-3-(4-chlorophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **14***

Compound **14** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3205 (N-H), 1533 (C=C), 1226 (C=S), 1330, 1157 (SO_2), 838 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 7.0 – 7.69 (8H, m, ArH), 5.60 (1H, s, N-H), 4.92 (1H, s, N-CH), 1.20-3.42 (8H, m, 4 × CH_2); MS *m/z*: 437 [M^+]; Anal. Calcd. for $C_{20}H_{18}ClFN_2O_2S_2$: C, 54.97; H, 4.15; N, 6.41. Found: C, 54.95; H, 4.21; N, 6.45.

4-(4-Fluorophenyl)-3-(4-methylphenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione ***15***

Compound **15** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3055 (N-H), 1533 (C=C), 1226 (C=S), 1332, 1157 (SO_2), 838 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.8 – 7.5 (9H, m, ArH & N-H), 4.64 (1H, s, N-CH), 2.38 (3H, s, CH_3), 2.6 – 2.8 (2H, m, CH_2), 1.25 – 1.75 (6H, m, 3 x CH_2); MS m/z: 416 [M^+]; Anal. Calcd. for $C_{21}H_{21}FN_2O_2S_2$: C, 60.55; H, 5.08; N, 6.73. Found: C, 60.59; H, 5.12; N, 6.76.

4-(4-Methoxyphenyl)-3-phenylsulfonyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione ***16***

Compound **16** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3040 (N-H), 1508, (C=C), 1251 (C=S), 1371, 1174 (SO_2), 835 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.9 – 7.51 (9H, m, ArH), 6.47 (1H, s, NH), 4.88 (1H, s, N-CH), 3.85 (3H, s, OCH_3), 1.25 – 2.70 (8H, m, 4 × CH_2); MS *m/z*: 414 [M^+]; Anal. Calcd. for $C_{21}H_{22}N_2O_3S_2$: C, 60.84; H, 5.34; N, 6.75. Found: C, 60.81; H, 5.40; N, 6.72.

4-(4-Methoxyphenyl)-3-methylsulfonyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione ***17***

Compound **17** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3024 (N-H), 1539 (C=C), 1249 (C=S), 1353, 1174 (SO_2), 833 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.88 – 7.26 (4H, m, ArH), 6.52 (1H, s, NH), 4.88 (1H, s, N-CH), 3.82 (3H, s, OCH_3), 1.25 – 2.80 (11H, m, 4 × CH_2); MS m/z: 352 [M^+]; Anal. Calcd. for $C_{16}H_{20}N_2O_3S_2$: C, 54.51; H, 5.72; N, 7.94. Found: C, 54.54; H, 5.75; N, 7.99.

4-(4-Methoxyphenyl)-3-(4-nitrophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione ***18***

Compound **18** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3101 (N-H), 1531 (C=C), 1249 (C=S), 1338, 1174 (SO_2), 833 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 8.1 – 8.06 (4H, m, Ar-NO_2), 6.85 – 7.72 (4H, m, ArH), 6.5 (1H, s, NH), 5.6 (1H, s, N-CH), 3.82 (3H, s, OCH_3), 1.25 – 2.85 (8H, m, 4 × CH_2); MS m/z: 459 [M^+]; Anal. Calcd. for $C_{21}H_{21}N_3O_5S_2$: C, 54.88; H, 4.60; N, 9.14. Found: C, 54.85; H, 4.62; N, 9.17.

4-(4-Methoxyphenyl)-3-(1-naphthylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione ***19***

Compound **19** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3096 (N-H), 1533 (C=C), 1249 (C=S), 1336, 1174 (SO_2), 833 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.83 – 7.8 (11H, m, ArH), 6.52 (1H, s, N-H), 4.88 (1H, s, N-CH), 3.82 (3H, s, OCH_3), 1.25 – 2.82 (8H, m, 4 × CH_2); MS *m/z*: 465 [M^+]; Anal. Calcd. for $C_{25}H_{24}N_2O_3S_2$: C, 64.63; H, 5.20; N, 6.02. Found: C, 64.60; H, 5.22; N, 6.08.

4-(4-Methoxyphenyl)-3-(4-chlorophenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione ***20***

Compound **20** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3082 (N-H), 1541 (C=C), 1249 (C=S), 1355, 1174 (SO_2), 833 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.88 – 7.7 (8H, m, ArH), 6.47 (1H, s, N-H), 4.88 (1H, s, N-CH), 3.82 (3H, s, OCH_3), 1.25 – 2.82 (8H, m, 4 × CH_2); MS m/z: 449 [M^+]; Anal. Calcd. for $C_{21}H_{21}ClN_2O_3S_2$: C, 56.17; H, 4.71; N, 6.23. Found: C, 56.14; H, 4.75; N, 6.27.

4-(4-Methoxyphenyl)-3-(4-methylphenylsulfonyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione ***21***

Compound **21** was prepared by adopting the same procedure as for compound **4**. IR (KBr) cm^{-1}: 3090 (N-H), 1539 (C=C), 1249 (C=S), 1361, 1174 (SO_2), 833 (C-H); ^{1}H-NMR ($CDCl_3$) δ: 6.8 – 7.5 (8H, m, ArH), 6.4 (1H, s, NH), 4.88 (1H, s, N-CH), 3.84 (3H, s, OCH_3), 1.59 (3H, s, CH_3), 2.7 – 2.8 (2H, m, CH_2), 0.88 – 1.25 (6H, m, 3 × CH_2); MS *m/z*: 428 [M^+]; Anal. Calcd. for $C_{22}H_{24}N_2O_3S_2$: C, 61.65; H, 5.64; N, 6.53. Found: C, 61.71; H, 5.60; N, 6.50.

Biology

Evaluation of antimicrobial activity

The synthesized compounds were evaluated for antimicrobial activity using tube-dilution method. This method depends upon the inhibition of growth of a microbial culture in a uniform solution of antibiotic in a liquid medium that is favourable to its rapid growth in the absence of the antibiotic [16]. In this method, 1 mL of 10 μg/mL of test solution in DMSO was transferred to a sterile test tube containing 1 mL of sterile nutrient media then it was serially diluted to give concentrations of 5, 2.5, 1.25, 0.625, 0.312 μg/mL. To all the tubes, 0.1 mL of microbial suspension in saline was added and the tubes were incubated at 37°C for 24 h (bacteria) and 48 h (fungi). After the incubation period, the tubes were observed visually for turbidity and inhibition was determined by the absence of growth. MIC was determined by the lowest concentration of sample that prevented the development of turbidity. From the MIC values observed, the intermediate concentrations between MIC values were prepared and the accurate MIC values were determined. The double strength nutrient broth (I. P.; Indian Pharmacopoeia) and sabouraud dextrose broth (I. P.) [32] were used as a medium in case antibacterial and antifungal activity, respectively.

QSAR-Studies

The calculation of molecular descriptors of 3,4-disubstituted-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione derivatives as well as the regression analysis were carried out by using the molecular package TSAR 3D version 3.3 [17]. The descriptors were calculated as per standard procedure [26 – 30].

The LOO cross-validation procedure was applied to estimate the predictive capability of the QSAR models [33]. The cross-validated coefficient, q^2 was calculated with the following equation:

$$q^2 = 1 - [\Sigma\gamma\,(\gamma_{pred} - \gamma_{actual})^2 / \gamma\,(\Sigma\gamma_{actual} - \gamma_{mean})^2]$$

where γ_{pred}, γ_{actual} and γ_{mean} are predicted, actual, and mean values of the target property, respectively. And PRESS = $\Sigma\gamma\,(\gamma_{pred} - \gamma_{actual})^2$ is the sum of predictive sum of squares.

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