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# SYNTHESIS, ANTIMICROBIAL, ANTICANCER EVALUATION AND QSAR STUDIES OF THIAZOLIDIN-4-ONE DERIVATIVES

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**Abstract:** In this study, a novel series of 4-thiazolidinone derivatives (**1**-**17**) was synthesized and evaluated for its *in vitro* antimicrobial and anticancer potentials. *N*-(2-(5-(4-nitrobenzylidene)-2-(4-chlorophenyl)-4-oxothiazolidin-3-ylamino)-2-oxoethyl) benzamide (**7**, $pMIC_{am}$ = 1.86 μM/mL) was found to be the most active antimicrobial agent. The anticancer study results demonstrated that *N*-(2-(5-(4-hydroxybenzylidene)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-ylamino)-2-oxoethyl) benzamide (**10**, $IC_{50}$ = 18.59 μM) was the most active anticancer agent. QSAR studies indicated the importance of topological parameter, Kier's α third order shape index ($\kappa\alpha_3$) as well as electronic parameters, cosmic total energy (cos E) and energy of highest occupied molecular orbital (HOMO) in describing the antimicrobial activity of synthesized compounds.

**Keywords:** thiazolidin-4-one, antimicrobial, anticancer, QSAR

Cancer is considered to be one of the most intractable diseases because of the innate characteristics of cancer cells to proliferate uncontrollably, avoid apoptosis, invade and metastasize. The burden of cancer is increasing across the world and thus it is the leading cause of deaths in economically developed countries and second leading cause of deaths in developing countries. Hence, in the field of chemotherapeutic drugs, the search for new, more active and less toxic compounds is still very intense, and new promising anticancer approaches are being tested (1).

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens. Thus, search of novel antimicrobial agents is a field of current and growing interest. A potential approach to overcome the resistance problem is to design innovative agents with a different mode of action so that no cross-resistance with the present therapeuticals can occur (2).

Thiazolidin-4-one derivatives are known to exhibit diverse biological activities such as: anticancer (3-5), antimicrobial (6, 7), antiviral (8), antimycobacterial (9, 10), analgesic and anti-inflammatory (11), anti-HIV (12) and anticonvulsant (13).

Inspired by the above facts and in continuation of our ongoing research program in the field of synthesis and antimicrobial and anticancer activities of medicinally important compounds we hereby report the synthesis, antimicrobial, anticancer activities and QSAR studies of some novel thiazolidin-4-ones derivatives.

## RESULTS AND DISCUSSION

### Chemistry

The general procedure for the synthesis of 4-thiazolidinone derivatives (**1**-**17**) was described in Scheme 1. The structures of all compounds have

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Table 1. Physicochemical properties and anticancer activity of the synthesized compounds (**1**-**17**).

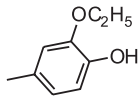
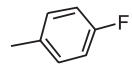
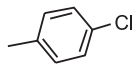
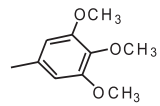
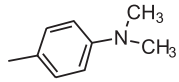
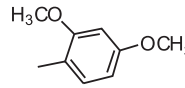
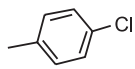
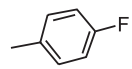
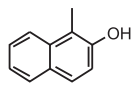
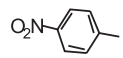
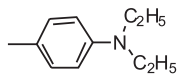
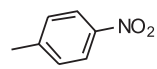
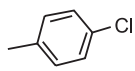
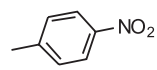
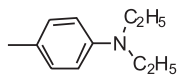
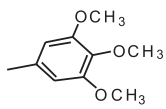
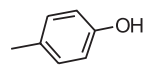
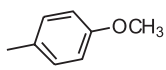
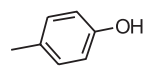
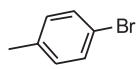
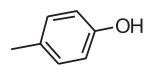
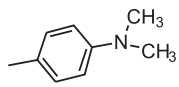
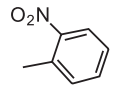
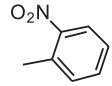
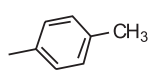
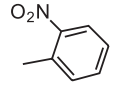
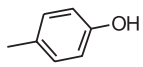
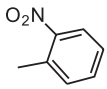
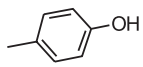
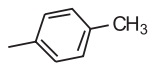
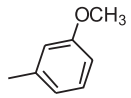
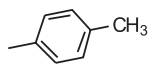
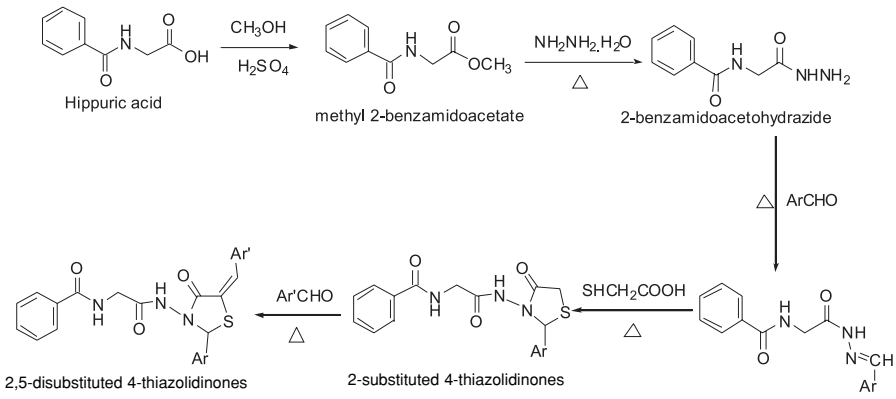
| Comp. | Ar | Ar' | Molecular formula | M. W. | $R_f$ value* | Anticancer activity [$IC_{50}$ (μM)] |
|---|---|---|---|---|---|---|
| **1** |  |  | $C_{27}H_{24}FN_3O_5S$ | 521.56 | 0.58 | > 191.73 |
| **2** |  |  | $C_{28}H_{26}ClN_3O_6S$ | 568.04 | 0.72 | 72.18 |
| **3** |  |  | $C_{29}H_{30}N_4O_5S$ | 546.64 | 0.66 | 120.74 |
| **4** |  |  | $C_{25}H_{19}ClFN_3O_3S$ | 495.95 | | 64.52 |
| **5** |  |  | $C_{29}H_{22}N_4O_6S$ | 554.57 | 0.59 | 34.26 |
| **6** |  |  | $C_{29}H_{29}N_5O_5S$ | 559.64 | 0.55 | 85.77 |
| **7** |  |  | $C_{25}H_{19}ClN_4O_5S$ | 522.96 | 0.69 | > 191.22 |
| **8** |  |  | $C_{29}H_{29}ClN_4O_3S$ | 549.08 | 0.60 | 81.96 |
| **9** |  |  | $C_{28}H_{27}N_3O_7S$ | 549.59 | 0.53 | > 181.95 |
| **10** |  |  | $C_{26}H_{23}N_3O_5S$ | 489.54 | 0.66 | 18.59 |
| **11** |  |  | $C_{25}H_{20}BrN_3O_4S$ | 538.41 | 0.58 | 78.01 |
| **12** |  |  | $C_{27}H_{25}N_5O_5S$ | 531.58 | 0.61 | 88.42 |
| **13** |  |  | $C_{25}H_{19}ClN_4O_5S$ | 522.96 | 0.72 | 74.58 |
| **14** |  |  | $C_{26}H_{22}N_4O_5S$ | 502.54 | 0.53 | 111.43 |

Table 1. Cont.

| Comp. | Ar | Ar' | Molecula formula | M. W. | $R_f$ value* | Anticancer activity [$IC_{50}$ (μM)] |
|---|---|---|---|---|---|---|
| **15** |  |  | $C_{25}H_{20}N_4O_6S$ | 504.51 | 0.55 | > 198.21 |
| **16** |  |  | $C_{26}H_{23}N_3O_4S$ | 473.54 | 0.64 | 158.38 |
| **17** |  |  | $C_{27}H_{25}N_3O_4S$ | 487.57 | 0.76 | 143.57 |
| 5-FU** | | | | | | 6.00 |
| Carboplatin | | | | | | > 100 |

*Benzene, **5-Fluorouracil




Scheme 1. Scheme for the synthesis of 2,5-disubtituted 4-thiazolidinone derivatives (1-17)

been confirmed by IR and NMR spectra which were in full agreement with assigned molecular structures. The physicochemical properties of synthesized compounds are presented in Table 1.

**Antimicrobial activity**

The antimicrobial activity of the synthesized compounds was carried out using the tube dilution method and results are described in Table 2. The antimicrobial activity results of the synthesized compounds indicated that compound **2** was found to be the most potent antimicrobial agent against *B. subtilis* and *A. niger* (pMIC = 1.96 μM/mL). In case of *S. aureus,* compound **12** (pMIC = 1.93 μM/mL) was found to be most potent antimicrobial agent. Against Gram negative bacterium *E. coli,* compound **5** (pMIC = 1.95 μM/mL) was found to be most potent antibacterial agent. The synthesized compounds were found to be most potent against the fungal strain *C. albicans* and compound **7** (pMIC = 2.22 μM/mL) was found to be most potent antifungal agent against *C. albicans.*

**Anticancer activity**

The *in vitro* anticancer activity of the synthesized derivatives was determined against an estro-

gen receptor positive human breast adenocarcinoma, MCF-7 (ATCC HTB-22) cancer cell line using the sulforhodamine B (SRB) assay (15) and the results are presented in Table 1. In general, the synthesized compounds showed average anticancer activity as none of the synthesized compounds displayed better anticancer potential than standard drug 5-FU (5-fluorouracil, $IC_{50}$ = 6.00 µM) and more than 50% compounds showed better anticancer potential than standard drug carboplatin ($IC_{50}$ = >100 µM). Compound **10** ($IC_{50}$ = 18.59 µM) was found to be the most potent anticancer agent as compared to the standard drugs (15).

**Structure activity relationship**

From the anticancer and antimicrobial screening results of synthesized, 4-thiazolidinone derivatives the following structure activity relationship (SAR) can be derived:

1. The presence of electron withdrawing groups (-$NO_2$, -Cl, compound **7**) on benzylidene portion improved the antifungal activity of the synthesized compounds against *C. albicans*.
2. The presence of electron releasing groups (compounds **2** and **12**) on benzylidene portion improved the antimicrobial activity of the synthesized compound against *A. niger, S. aureus* and *B. subtilis*.
3. The presence of fused aromatic ring substitution (2-OH naphthaldehyde, compound **5**) in benzylidene portion improved antibacterial and anticancer activity against *E. coli* and MCF-7 (ATCC HTB-22) cancer cell line.
4. The presence of electron releasing groups (-$OCH_3$, -OH, compound **10**) on benzylidene portion improved the anticancer activity of the synthesized compound against an estrogen receptor positive human breast adenocarcinoma, MCF-7 (ATCC HTB-22) cancer cell line.

From these result we may conclude that different structural requirements are required for a compound to be effective against different targets. This is similar to the results of Sortino et al. (16).

These findings are summarized in Figure 1.

**QSAR studies**

For quantitative structure activity relationship (QSAR) studies, the biological activity data determined as MIC values were first transformed into pMIC values (i.e., –log MIC) and used as dependent variables in QSAR study (Table 2). The different molecular descriptors selected and the values of selected descriptors are listed in Table 3 and Table 4, respectively.

Here, we have attempted for development of multi-target QSAR (mt-QSAR) models by calculating the average antimicrobial, antifungal and antibacterial activity values of synthesized 4-thiazolidinone derivatives (Table 2). Our earlier studies (17-21) indicated that the mt-QSAR models are better than one-target QSAR (ot-QSAR) models in describing the antimicrobial activity. During regression analysis, outliers i.e., compounds **1**, **2**, **4**, **8** and **16** were not included as their response values were outside the range of other synthesized thiazolidinone derivatives.

Preliminary analysis carried out in terms of correlation analysis (Table 5) indicated that high colinearity (r > 0.5) was observed between different parameters and antibacterial activity of 4-thiazolidinone derivatives. The data presented in Table 6 are the result of correlation of molecular descriptors with antibacterial, antifungal and antimicrobial activities of synthesized compounds.

The high correlation of topological parameter, Kier's a third order shape index ($\kappa\alpha_3$) with antibacterial activity (Table 5) indicated its importance in describing antibacterial activity of the 4-thiazolidinone derivatives (Eq. 1).

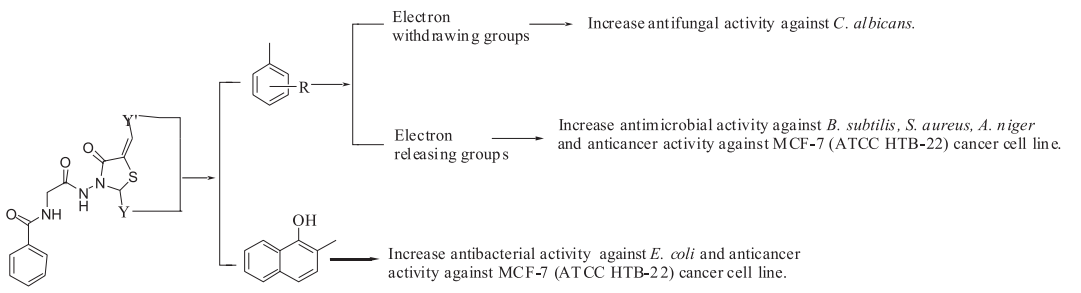



Figure 1. Structural requirements for the antimicrobial and anticancer activities of 2,5-disubtituted 4-thiazolidinone derivatives (**1-17**)

***QSAR model for antibacterial activity***

$$pMIC_{ab} = -0.309\ \kappa\alpha_3 + 3.536 \quad \text{Eq. 1}$$

n = 12 r = 0.830 $q^2$ = 0.571 s = 0.088 F = 22.16

Here and thereafter, n = number of data points, r = correlation coefficient, $q^2$ = cross validated $r^2$ obtained by leave one out method, s = standard error of the estimate and F = Fischer statistics.

The negative correlation between Kier's a third order shape index ($\kappa\alpha_3$) and antibacterial activity of the synthesized compounds indicates a fact that antibacterial activity of synthesized compounds will increase with a decrease in their $\kappa\alpha_3$ values and vice versa, which was verified by the high antibacterial activity value of compound **13** ($pMIC_{ab}$ = 1.82 µM/mL) which has low $\kappa\alpha_3$ value (6.02).

When we coupled $\kappa\alpha_3$ with energy of highest occupied molecular orbital (HOMO) (electronic parameter) the improvement r value from 0.830 to 0.911 was observed (Eq. 2).

***MLR-QSAR model for antibacterial activity***

$$pMIC_{ab} = -0.219\ \kappa\alpha_3 - 0.232\ HOMO + 0.983 \quad \text{Eq. 2}$$

n = 12 r = 0.911 $q^2$ = 0.731 s = 0.069 F = 22.00

The developed QSAR model (Eq. 2) was cross validated by the $q^2$ value ($q^2$ = 0.731; $q^2 > 0.5$) obtained by leave one out (LOO) method, the low residual values (Table 7) (22) as well as by the plot of predicted $pMIC_{ab}$ against observed $pMIC_{ab}$ (Fig. 2). The absence of systemic error in the model development was indicated by the plot of observed $pMIC_{ab}$ *vs.* residual $pMIC_{ab}$ (Fig. 3) as the propagation of error was observed on both sides of zero (23).

In case of antifungal activity, electronic parameter, cosmic total energy (cos E, Table 6) was found most dominant in expressing antifungal activity of the synthesized compounds (Eq. 3).

***QSAR model for antifungal activity***

$$pMIC_{af} = 0.255\ \cos E + 1.138 \quad \text{Eq. 3}$$

n = 12 r = 0.801 $q^2$ = 0.455 s = 0.155 F = 17.87

In order to improve the value of correlation coefficient, we coupled cos E with topological parameter, Randic index (R) which improved r value from 0.801 to 0.854.

***MLR-QSAR model for antifungal activity***

$$pMIC_{af} = 0.0314\ \cos E - 0.0865\ R + 2.600 \quad \text{Eq. 4}$$

n = 12 r = 0.854 $q^2$ = 0.468 s = 0.142 F = 12.16

Equation 4 was cross validated by its $q^2$ value ($q^2$ = 0.468) which less than 0.5 indicated that Eq. 4

Table 2. Antimicrobial activity (pMIC in µM/mL) of synthesized compounds.

| Compound | $pMIC_{bs}$ | $pMIC_{ec}$ | $pMIC_{sa}$ | $pMIC_{an}$ | $pMIC_{ca}$ | $pMIC_{ab}$ | $pMIC_{af}$ | $pMIC_{am}$ |
|---|---|---|---|---|---|---|---|---|
| **1** | 1.32 | 1.32 | 1.02 | 1.62 | 1.62 | 1.22 | 1.62 | 1.38 |
| **2** | 1.96 | 1.66 | 1.36 | 1.96 | 1.96 | 1.66 | 1.96 | 1.78 |
| **3** | 1.34 | 1.04 | 1.64 | 1.04 | 1.64 | 1.34 | 1.34 | 1.34 |
| **4** | 1.90 | 1.30 | 1.30 | 1.90 | 2.20 | 1.50 | 2.05 | 1.72 |
| **5** | 1.35 | 1.95 | 1.65 | 1.35 | 1.65 | 1.65 | 1.50 | 1.59 |
| **6** | 1.05 | 1.35 | 1.65 | 1.35 | 1.95 | 1.35 | 1.65 | 1.47 |
| **7** | 1.62 | 1.92 | 1.62 | 1.92 | 2.22 | 1.72 | 2.07 | 1.86 |
| **8** | 1.64 | 1.34 | 1.64 | 1.64 | 1.94 | 1.54 | 1.79 | 1.64 |
| **9** | 1.34 | 1.64 | 1.34 | 1.64 | 1.04 | 1.44 | 1.34 | 1.40 |
| **10** | 1.89 | 1.29 | 1.59 | 1.29 | 1.29 | 1.59 | 1.29 | 1.47 |
| **11** | 1.63 | 1.63 | 1.33 | 1.03 | 1.33 | 1.53 | 1.18 | 1.39 |
| **12** | 1.33 | 1.03 | 1.93 | 1.33 | 1.93 | 1.43 | 1.63 | 1.51 |
| **13** | 1.92 | 1.92 | 1.62 | 1.62 | 1.62 | 1.82 | 1.62 | 1.74 |
| **14** | 1.60 | 1.60 | 1.60 | 1.30 | 1.30 | 1.60 | 1.30 | 1.48 |
| **15** | 1.91 | 1.61 | 1.61 | 1.30 | 1.91 | 1.71 | 1.61 | 1.67 |
| **16** | 1.28 | 0.98 | 1.88 | 1.28 | 0.98 | 1.38 | 1.13 | 1.28 |
| **17** | 1.59 | 1.89 | 1.29 | 1.29 | 1.29 | 1.59 | 1.29 | 1.47 |
| SD | 0.28 | 0.32 | 0.23 | 0.29 | 0.38 | 0.16 | 0.29 | 0.17 |
| Std. | 2.61* | 2.61* | 2.61* | 2.61* | 2.64** | | | |

*Norfloxacin; **Fluconazole

Table 3. QSAR descriptors used in the study.

| No. | QSAR descriptor | Type |
|---|---|---|
| 1 | log P | Lipophilic |
| 2 | Zero order molecular connectivity index ($^0\chi$) | Topological |
| 3 | First order molecular connectivity index ($^1\chi$) | Topological |
| 4 | Second order molecular connectivity index ($^2\chi$) | Topological |
| 5 | Valence zero order molecular connectivity index ($^0\chi^v$) | Topological |
| 6 | Valence first order molecular connectivity index ($^1\chi^v$) | Topological |
| 7 | Valence second order molecular connectivity index ($^2\chi^v$) | Topological |
| 8 | Kier's alpha first order shape index ($\kappa\alpha_1$) | Topological |
| 9 | Kier's alpha second order shape index ($\kappa\alpha_2$) | Topological |
| 10 | Kier's first order shape index ($\kappa_1$) | Topological |
| 11 | Randic topological index (R) | Topological |
| 12 | Balaban topological index (J) | Topological |
| 13 | Wiener's topological index (W) | Topological |
| 14 | Kier's second order shape index ($\kappa_2$) | Topological |
| 15 | Ionization potential | Electronic |
| 16 | Dipole moment ($\mu$) | Electronic |
| 17 | Energy of highest occupied molecular orbital (HOMO) | Electronic |
| 18 | Energy of lowest unoccupied molecular orbital (LUMO) | Electronic |
| 19 | Total energy (Te) | Electronic |
| 20 | Nuclear energy (Nu. E) | Electronic |
| 21 | Molar refractivity (MR) | Steric |

Table 4. Values of selected descriptors calculated for QSAR studies.

| No. | Cos E | $^0\chi$ | $^0\chi^v$ | $\kappa_3$ | $\kappa\alpha_3$ | R | Te | LUMO | HOMO | $\mu$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 8.30 | 26.36 | 20.69 | 8.26 | 6.63 | 17.85 | -6686.75 | -0.86 | -8.49 | 4.96 |
| 2 | 19.61 | 27.94 | 23.10 | 8.31 | 6.88 | 18.84 | -7050.71 | -1.03 | -8.49 | 3.55 |
| 3 | 9.48 | 27.94 | 23.02 | 8.53 | 6.94 | 18.80 | -6746.50 | -0.51 | -8.01 | 2.02 |
| 4 | 5.91 | 24.08 | 19.40 | 7.51 | 6.06 | 16.40 | -6094.62 | -0.93 | -8.57 | 3.22 |
| 5 | 19.32 | 28.23 | 21.70 | 7.76 | 5.97 | 19.31 | -6953.94 | -1.77 | -8.90 | 7.05 |
| 6 | 20.95 | 28.65 | 22.96 | 9.01 | 7.23 | 19.30 | -6937.19 | -1.35 | -8.39 | 10.49 |
| 7 | 25.64 | 25.66 | 20.29 | 8.01 | 6.39 | 17.31 | -6453.93 | -1.55 | -9.03 | 7.03 |
| 8 | 21.56 | 27.07 | 22.89 | 8.28 | 6.86 | 18.41 | -6466.21 | -0.61 | -8.35 | 8.60 |
| 9 | 14.83 | 27.94 | 22.35 | 8.31 | 6.74 | 18.84 | -7011.03 | -0.83 | -8.40 | 3.57 |
| 10 | 2.26 | 24.79 | 19.69 | 7.76 | 6.17 | 16.94 | -6059.60 | -0.74 | -8.32 | 0.87 |
| 11 | 1.70 | 24.08 | 20.28 | 7.51 | 6.16 | 16.40 | -5923.32 | -0.84 | -8.43 | 2.02 |
| 12 | 19.78 | 27.23 | 21.54 | 8.28 | 6.55 | 18.24 | -6625.53 | -1.16 | -8.40 | 5.65 |
| 13 | 17.37 | 25.66 | 20.29 | 7.57 | 6.02 | 17.35 | -6453.86 | -1.29 | -8.75 | 5.32 |
| 14 | 16.23 | 25.66 | 20.09 | 7.79 | 6.08 | 17.33 | -6249.71 | -1.25 | -8.70 | 5.67 |
| 15 | 10.85 | 25.66 | 19.54 | 7.79 | 6.06 | 17.33 | -6414.46 | -1.29 | -8.71 | 5.90 |
| 16 | 0.39 | 24.08 | 19.28 | 7.51 | 5.95 | 16.40 | -5739.59 | -0.73 | -8.38 | 2.65 |
| 17 | 4.93 | 24.79 | 20.24 | 7.76 | 6.19 | 16.94 | -5895.01 | -0.84 | -8.30 | 2.46 |

Table 5. Correlation matrix for the antibacterial activity of the synthesized compounds.

| | $pMIC_{ab}$ | Cos E | $^{0}\chi$ | $^{0}\chi^{v}$ | $\kappa_3$ | $\kappa\alpha_3$ | R | LUMO | HOMO | μ |
|---|---|---|---|---|---|---|---|---|---|---|
| $pMIC_{ab}$ | 1.000 | | | | | | | | | |
| Cos E | 0.099 | 1.000 | | | | | | | | |
| $^{0}\chi$ | -0.548 | 0.572 | 1.000 | | | | | | | |
| $^{0}\chi^{v}$ | -0.776 | 0.332 | 0.893 | 1.000 | | | | | | |
| $\kappa_3$ | -0.779 | 0.402 | 0.776 | 0.833 | 1.000 | | | | | |
| $\kappa\alpha_3$ | -0.830 | 0.248 | 0.662 | 0.832 | 0.962 | 1.000 | | | | |
| R | -0.525 | 0.535 | 0.993 | 0.882 | 0.735 | 0.617 | 1.000 | | | |
| LUMO | -0.500 | -0.750 | -0.223 | 0.112 | 0.089 | 0.283 | -0.239 | 1.000 | | |
| HOMO | -0.765 | -0.590 | 0.121 | 0.429 | 0.414 | 0.541 | 0.109 | 0.881 | 1.000 | |
| μ | 0.052 | 0.834 | 0.521 | 0.277 | 0.437 | 0.258 | 0.502 | -0.819 | -0.543 | 1.000 |

Table 6. Correlation of antibacterial, antifungal and antimicrobial activities of synthesized compounds with their molecular descriptors.

| Descriptors | $pMIC_{ab}$ | $pMIC_{af}$ | $pMIC_{am}$ |
|---|---|---|---|
| Cos E | 0.099 | 0.801 | 0.570 |
| log P | 0.445 | 0.275 | 0.437 |
| MR | -0.675 | 0.115 | -0.323 |
| $^{0}\chi$ | -0.548 | 0.218 | -0.183 |
| $^{0}\chi^{v}$ | -0.776 | 0.007 | -0.452 |
| $^{1}\chi$ | -0.525 | 0.177 | -0.195 |
| $^{1}\chi^{v}$ | -0.680 | 0.087 | -0.344 |
| $^{2}\chi$ | -0.400 | 0.282 | -0.055 |
| $^{2}\chi^{v}$ | -0.630 | 0.077 | -0.321 |
| $^{3}\chi$ | -0.295 | 0.448 | 0.113 |
| $^{3}\chi^{v}$ | -0.488 | 0.023 | -0.272 |
| $\kappa_1$ | -0.604 | 0.213 | -0.219 |
| $\kappa_2$ | -0.690 | 0.157 | -0.305 |
| $\kappa_3$ | -0.779 | 0.240 | -0.304 |
| $\kappa\alpha_1$ | -0.675 | 0.167 | -0.290 |
| $\kappa\alpha_2$ | -0.761 | 0.084 | -0.394 |
| $\kappa\alpha_3$ | -0.830 | 0.131 | -0.404 |
| R | -0.525 | 0.177 | -0.195 |
| J | -0.282 | -0.030 | -0.185 |
| W | -0.581 | 0.229 | -0.195 |
| Te | 0.364 | -0.347 | -0.008 |
| Ee | 0.531 | -0.214 | 0.175 |
| Ne | -0.543 | 0.203 | -0.190 |
| SA | -0.813 | -0.001 | -0.478 |
| IP | 0.765 | 0.621 | 0.846 |
| LUMO | -0.500 | -0.668 | -0.721 |
| HOMO | -0.765 | -0.621 | -0.846 |
| μ | 0.052 | 0.683 | 0.467 |

may not be a valid one but as per the recommendations of Golbraikh and Tropsha, the only way to estimate the predictive power of a QSAR model is to test its ability to accurately predict the biological activity (23). As the observed and predicted values are close to each other (Table 7), the mt-QSAR model for antifungal activity Eq. (4) is a valid one.

Electronic parameter, energy of highest occupied molecular orbital (HOMO) was found to be most effective in describing antimicrobial activity of the synthesized compounds (Eq. 5, Table 6).

***QSAR model for antimicrobial activity***

$$pMIC_{am} = -0.449\ HOMO - 2.300 \qquad \text{Eq. 5}$$

$n = 12\ r = 0.846\ q^2 = 0.565\ s = 0.086\ F = 25.19$

Antimicrobial activity of the synthesized compounds is negatively correlated with HOMO (Eq. 5) which means that antimicrobial activity of the synthesized compounds will decrease with an increase in their HOMO values (Tables 2 and 4). The validity of Eq. 5 is evidenced by its high $q^2$ value (0.565) as well the low residual values (Table 7). Further, the plot of predicted $pMIC_{am}$ against observed $pMIC_{am}$ (Fig. 4) also favors the developed model expressed by Eq. 5. The plot of observed $pMIC_{am}$ *vs.* residual $pMIC_{am}$ (Fig. 5) indicated that there was no systemic error in model development as the propagation of error was observed on both sides of zero.

The high residual values observed in case of outliers (**1**, **2**, **4**, **8** and **16**) justified their removal while developing QSAR models. It was observed from mt-QSAR models [Eq. 1-5] that the most effective parameters are topological parameter, Kier's a third order shape index ($\kappa\alpha_3$) as well as electronic parameters, cosmic total energy (cos E) and energy of highest occupied molecular orbital (HOMO).

## EXPERIMENTAL

Melting points were recorded in open capillary tubes and were uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FTIR spectrometer. $^1$H nuclear magnetic resonance ($^1$H NMR) spectra were determined by Bruker Avance II 400 NMR spectrometer in appropriate deuterated solvents and are expressed in parts per million (δ, ppm) downfield from tetramethylsilane (internal standard). NMR data are given as multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) and number of protons. Reaction progress was observed by thin layer chromatography making use of commercial silica gel plates (Merck).

Table 7. Observed (Obs.), predicted (Pred.) and residual (Res.) antimicrobial activities of the synthesized compounds obtained by mt-QSAR models.

| Comp. | $pMIC_{ab}$ | | | $pMIC_{af}$ | | | $pMIC_{am}$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | Obs. | Pred. | Res. | Obs. | Pred. | Res. | Obs. | Pred. | Res. |
| **1** | 1.22 | 1.50 | -0.28 | 1.62 | 1.32 | 0.30 | 1.38 | 1.51 | -0.13 |
| **2** | 1.66 | 1.45 | 0.21 | 1.96 | 1.59 | 0.37 | 1.78 | 1.51 | 0.27 |
| **3** | 1.34 | 1.32 | 0.02 | 1.34 | 1.27 | 0.07 | 1.34 | 1.30 | 0.04 |
| **4** | 1.50 | 1.64 | -0.14 | 2.05 | 1.37 | 0.68 | 1.72 | 1.55 | 0.17 |
| **5** | 1.65 | 1.74 | -0.09 | 1.50 | 1.54 | -0.04 | 1.59 | 1.70 | -0.11 |
| **6** | 1.35 | 1.35 | 0.00 | 1.65 | 1.59 | 0.06 | 1.47 | 1.47 | 0.00 |
| **7** | 1.72 | 1.68 | 0.04 | 2.07 | 1.91 | 0.16 | 1.86 | 1.76 | 0.10 |
| **8** | 1.54 | 1.42 | 0.12 | 1.79 | 1.68 | 0.11 | 1.64 | 1.45 | 0.19 |
| **9** | 1.44 | 1.46 | -0.02 | 1.34 | 1.44 | -0.10 | 1.40 | 1.47 | -0.07 |
| **10** | 1.59 | 1.56 | 0.03 | 1.29 | 1.21 | 0.08 | 1.47 | 1.44 | 0.03 |
| **11** | 1.53 | 1.59 | -0.06 | 1.18 | 1.23 | -0.05 | 1.39 | 1.49 | -0.10 |
| **12** | 1.43 | 1.50 | -0.07 | 1.63 | 1.64 | -0.01 | 1.51 | 1.47 | 0.04 |
| **13** | 1.82 | 1.69 | 0.13 | 1.62 | 1.64 | -0.02 | 1.74 | 1.63 | 0.11 |
| **14** | 1.60 | 1.67 | -0.07 | 1.30 | 1.61 | -0.31 | 1.48 | 1.61 | -0.13 |
| **15** | 1.71 | 1.68 | 0.03 | 1.61 | 1.44 | 0.17 | 1.67 | 1.61 | 0.06 |
| **16** | 1.38 | 1.62 | -0.24 | 1.13 | 1.19 | -0.06 | 1.28 | 1.46 | -0.18 |
| **17** | 1.59 | 1.55 | 0.04 | 1.29 | 1.29 | 0.00 | 1.47 | 1.43 | 0.04 |

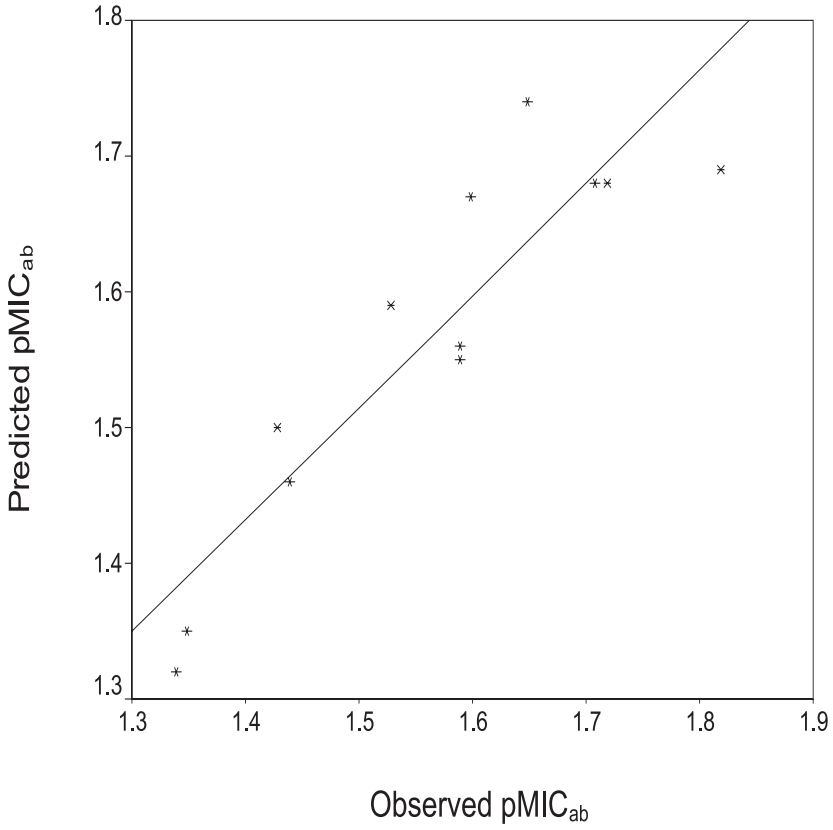



Figure 2. Plot of observed pMIC$_{ab}$ against predicted pMIC$_{ab}$ by Eq. 2

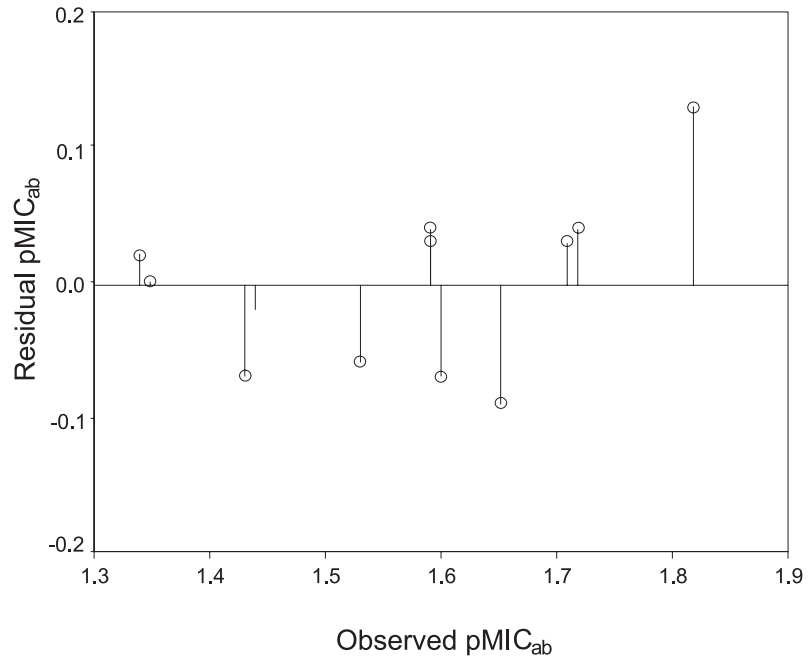
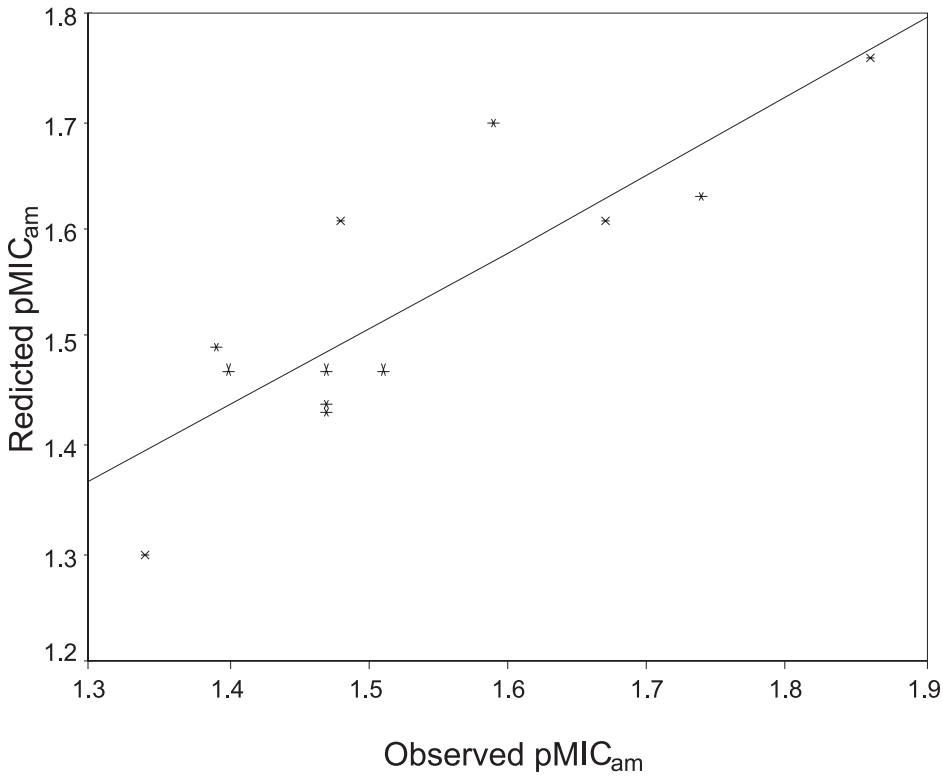



Figure 3. Plot of observed pMIC$_{ab}$ against residual pMIC$_{ab}$ by Eq. 2




igure 4. Plot of observed pMIC$_{am}$ against predicted pMIC$_{am}$ by Eq. 5

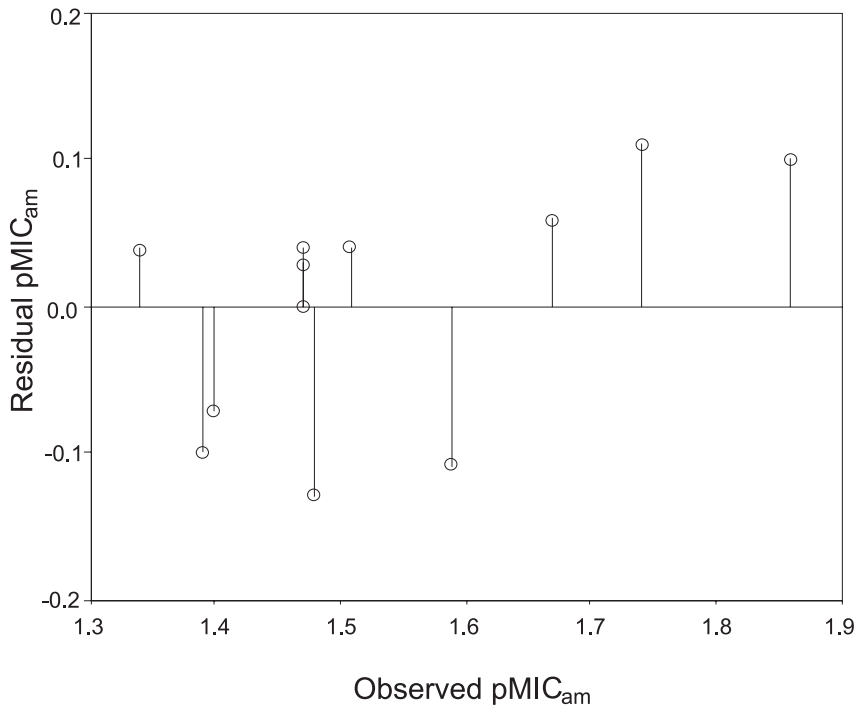



Figure 5. Plot of observed pMIC$_{am}$ against residual pMIC$_{am}$ by Eq. 5

**General procedure for synthesis of 2,5-disubstituted-4-thiazolidinone derivatives**

A mixture of (0.25 M) hippuric acid and excess of methanol (250 mL) with 1 mL of sulfuric acid was refluxed for 3–4 h in round bottom flask. The mixture was cooled; the precipitated solid was separated by filtration and recrystallized from methanol to yield methyl 2-benzamidoacetate. A mixture of methyl 2-benzamidoacetate (0.2 M) and excess of hydrazine hydrate (0.3 M) and ethanol (250 mL) was refluxed for about 3 h and allowed to cool. The resultant solid was separated by filtration and recrystallized from ethanol to afford 2-benzamidoacetohydrazide. A mixture of 2-benzamidoacetohydrazide (0.025 M) and required aromatic aldehydes (0.025 M) was refluxed in methanol (50 mL) in the presence of catalytic amount of glacial acetic acid for about 2 h. The reaction mixture was then cooled and the precipitated solid was separated by filtration and recrystallized from methanol to give the corresponding hydrazones of hippuric acid. A mixture of corresponding hydrazone of hippuric acid (0.015 M) and required amount of thioglycolic acid (0.015 M) in DMF (50 mL) containing a pinch of anhydrous zinc chloride was refluxed for about 6 h to yield 4-thiazolidinones (**1**–**17**). The reaction mixture was then cooled and poured onto the crushed ice. The solid thus obtained was filtered, washed with water and the product was recrystallized from rectified spirit. A mixture of 2-substituted-4-thiazolidinone (0.01 M), corresponding aromatic aldehyde (0.01 M) and anhydrous sodium acetate in glacial acetic acid (20 mL) was refluxed for 5–7 h and then poured on crushed ice to precipitate the 2,5-disubstituted 4-thiazolidinones (**1**-**17**).

**N-{2-[5-(4-fluorobenzylidene)-2-(3-ethoxy-4-hydroxyphenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (1)**

M.p.: 222-224$^{o}$C; yield: 72%; IR (KBr, cm$^{-1}$): 3545 (OH), 3307 (NH), 3083 (C-H arom.), 1689 (C=O), 1229 (C-N), 1631 (C=C arom.), 1156 (C-O-C str., -$OC_2H_5$), 1077 (C-F), 716 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.02 (s, 1H, NH), 7.90-7.29 (m, 12H, ArH), 7.27 (s, 1H, CH), 4.43 (d, 2H, $CH_2$), 4.42 (s, 1H, OH), 3.98 (m, 2H, $CH_2$ of -$OC_2H_5$), 3.36 (s, 2H, $CH_2$ of thiazolidinone), 1.24 (t, 3H, $CH_3$ of -$OC_2H_5$).

**N-{2-[5-(3,4,5-trimethoxybenzylidene)-2-(4-chlorophenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (2)**

M.p.: 254-256$^{o}$C; yield: 80%; IR (KBr, cm$^{-1}$): 3321 (NH), 3073 (C-H arom.), 1692 (C=O), 1634 (C=C arom.), 1257 (C-N), 1136 (C-O-C str.,-$OCH_3$), 820 (C-Cl), 709 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.01 (s, 1H, NH), 7.91-7.52 (m, 11H, ArH), 7.48 (s, 1H, CH), 4.43 (d, 2H, $CH_2$), 3.74 (s, 9H, $(OCH_3)_3$), 3.36 (s, 2H, $CH_2$ of thiazolidinone).

**N-{2-[5-(2,4-dimethoxybenzylidene)-2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (3)**

M.p.: 211-213$^{o}$C; yield: 81%; IR (KBr, cm$^{-1}$): 3316 (NH), 2992 (C-H arom.), 2977 (C-H str., $CH_3$), 1687 (C=O), 1600 (C=C arom.), 1374 (C-N str., aryl tertiary amine), 1286 (C-N), 1157 (C-O-C str., -$OCH_3$), 711 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.26 (s, 1H, NH), 7.92-7.51 (m, 12H, ArH), 7.46 (s, 1H, CH), 4.38 (d, 2H, $CH_2$), 3.82 (s, 6H, $(OCH_3)_2$), 3.34 (s, 2H, $CH_2$ of thiazolidinone), 2.97 (s, 6H, $(NCH_3)_2$).

**N-{2-[5-(4-fluorobenzylidene)-2-(4-chlorophenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (4)**

M.p.: 199-201$^{o}$C; yield: 78%; IR (KBr, cm$^{-1}$): 3300 (NH), 1686 (C=O),1628 (C=C arom.), 1280 (C-N), 1048 (C-F), 749 (C-Cl), 715 (C-S). $^1$H NMR (DMSO-$d_6$, 400 MHz, δ, ppm): 8.16-7.48 (m, 13H, ArH), 8.01 (s, 1H, NH), 7.26 (s, 1H, CH), 4.43 (d, 2H, $CH_2$), 3.34 (s, 2H, $CH_2$ of thiazolidinone).

**N-{2-[5-(4-nitrobenzylidene)-2-(2-hydroxynaphthalen-1-yl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (5)**

M.p.: 213-215$^{o}$C; yield: 69%; IR (KBr, cm$^{-1}$): 3647 (OH), 3418 (NH), 3057 (C-H arom.), 1699 (C=O), 1637 (C=C arom.), 1343 (C-$NO_2$), 1282 (C-N), 710 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.40-7.57 (m, 15H, ArH), 8.00 (s, 1H, NH), 7.26 (s, 1H, CH), 4.47 (s, 1H, OH), 4.03 (d, 2H, $CH_2$), 3.34 (s, 2H, $CH_2$ of thiazolidinone).

**N-{2-[5-(4-nitrobenzylidene)-2-(4-(diethylamino)phenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (6)**

M.p.: 187-189$^{o}$C; yield: 71%; IR (KBr, cm$^{-1}$): 3355 (NH), 3086 (C-H arom.), 2888 (C-H str., $CH_3$), 1698 (C=O), 1637 (C=C arom.), 1426 (C-N str., aryl tertiary amine), 1345 (C-$NO_2$), 1251 (C-N), 745 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.18-7.50 (m, 13H, ArH), 8.00 (s, 1H, NH), 7.48 (s, 1H, CH), 4.47 (d, 2H, $CH_2$), 3.35 (s, 2H, $CH_2$ of thiazolidinone), 2.65 (m, 4H, $(CH_2)_2$), 1.12 (t, 6H, $(CH_3)_2$).

**N-{2-[5-(4-nitrobenzylidene)-2-(4-chlorophenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (7)**

M.p.: 191-193°C; yield: 75%; IR (KBr, $cm^{-1}$): 3355 (NH), 3083 (C-H arom.), 1698 (C=O), 1640 (C=C arom.), 1345 (C-$NO_2$), 1251 (C-N), 747 (C-Cl), 708 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.00 (s, 1H, NH), 7.92-7.51 (m, 13H, ArH), 7.47 (s, 1H, CH), 4.46 (d, 2H, $CH_2$), 3.99 (s, 2H, $CH_2$ of thiazolidinone).

**N-{2-[5-(2-chlorobenzylidene)-2-(4-(diethylamino)phenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (8)**

M.p.: 230-232°C; yield: 68%; IR (KBr, $cm^{-1}$): 3351 (NH), 2972 (C-H arom.), 1685 (C=O), 1595 (C=C arom.), 1352 (C-N str., aryl tertiary amine), 2811 (C-H str., $CH_3$), 1271 (C-N), 752 (C-Cl), 703 (C-S); $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.01 (s, 1H, NH), 7.64-7.45 (m, 13H, ArH), 6.77 (s, 1H, CH), 4.44 (d, 2H, $CH_2$), 3.46 (s, 2H, $CH_2$ of thiazolidinone), 2.51 (m, 4H, $(CH_2)_2$), 1.13 (t, 6H, $(CH_3)_2$).

**N-{2-[5-(4-hydroxybenzylidene)-4-oxo-2-(3,4,5-trimethoxyphenyl)thiazolidin-3-ylamino]-2-oxoethyl}benzamide (9)**

M.p.: 271-273°C; yield: 77%; IR (KBr, $cm^{-1}$): 3540 (OH), 3385 (NH), 2973 (C-H arom.), 1698 (C=O), 1644 (C=C arom.), 1294 (C-N), 1127 (C-O-C str., -$OCH_3$), 713 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 7.93 (s, 1H, NH), 7.89-7.00 (m, 11H, ArH), 6.88 (s, 1H, CH), 4.44 (s, 1H, OH), 4.43 (d, 2H, $CH_2$), 3.85 (s, 9H, $(OCH_3)_3$), 3.51 (s, 2H, $CH_2$ of thiazolidinone).

**N-{2-[5-(4-hydroxybenzylidene)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (10)**

M.p.: 201-203°C; yield: 64%; IR (KBr, $cm^{-1}$): 3543 (OH), 3373 (NH), 3095 (C-H arom.), 1682 (C=O), 1631 (C=C aromatic), 1281 (C-N), 732 (C-S), 679 (C-Br). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.24-7.72 (m, 13H, ArH), 7.92 (s, 1H, NH), 6.83 (s, 1H, CH), 4.46 (s, 1H, OH). 4.13 (d, 2H, $CH_2$), 4.01 (s, 3H, $(OCH_3)$), 3.39 (s, 2H, $CH_2$ of thiazolidinone).

**N-{2-[5-(4-hydroxybenzylidene)-2-(4-bromophenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (11)**

M.p.: 195-197°C; yield: 83%; IR (KBr, $cm^{-1}$): 3504 (OH), 3317 (NH), 3062 (C-H arom.), 1692 (C=O), 1630 (C=C arom.), 1284 (C-N), 721 (C-S), 675 (C-Br). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 7.99 (s, 1H, NH), 7.91-7.51 (m, 13H, ArH), 7.48 (s, 1H, CH), 4.42 (s, 1H, OH), 4.14 (d, 2H, $CH_2$), 3.42 (s, 2H, $CH_2$ of thiazolidinone).

**N-{2-[5-(2-nitrobenzylidene)-2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (12)**

M.p.: 211-213°C; yield: 76%; IR (KBr, $cm^{-1}$): 3389 (NH), 3061 (C-H arom.), 2972 (C-H str., $CH_3$), 1687 (C=O), 1599 (C=C arom.), 1346 (C-N str., aryl tertiary amine), 1262 (C-N), 1234 (C-$NO_2$), 741 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.05 (s, 1H, NH), 8.03-7.56 (m, 13H, ArH), 7.48 (s, 1H, CH), 4.42 (d, 2H, $CH_2$), 3.94 (s, 2H, $CH_2$ of thiazolidinone), 2.97 (s, 6H, $(NCH_3)_2$).

**N-{2-[5-(2-nitrobenzylidene)-2-(2-chlorophenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (13)**

M.p.: 229-231°C; yield: 65%; IR (KBr, $cm^{-1}$): 3299 (NH), 3011 (C-H arom.), 1689 (C=O), 1624 (C=C arom.), 1342 ($NO_2$), 1267 (C-N), 756 (C-Cl), 703 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.09-7.79 (m, 13H, ArH), 8.02 (s, 1H, NH), 7.42 (s, 1H, CH), 4.45 (d, 2H, $CH_2$), 3.36 (s, 2H, $CH_2$ of thiazolidinone).

**N-{2-[5-(2-nitrobenzylidene)-4-oxo-2-p-tolylthiazolidin-3-ylamino]-2-oxoethyl}benzamide (14)**

M.p.: 247-249°C; yield: 83%; IR (KBr, $cm^{-1}$): 3630 (OH), 3372 (NH), 3104 (C-H arom.), 2855 (C-$CH_3$), 1688 (C=O), 1604 (C=C arom.), 1344 ($NO_2$), 1264 (C-N), 742 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.11-7.81 (m, 13H, ArH), 8.03 (s, 1H, NH), 7.48 (s, 1H, CH), 4.41 (d, 2H, $CH_2$), 3.50 (s, 2H, $CH_2$ of thiazolidinone), 2.39 (s, 3H, $CH_3$).

**N-{2-[5-(2-nitrobenzylidene)-2-(4-hydroxyphenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (15)**

M.p.: 226-228°C; yield: 69%; IR (KBr, $cm^{-1}$): 3581 (OH), 3380 (NH), 3125 (C-H arom.), 1689 (C=O), 1599 (C=C arom.), 1345 ($NO_2$), 1263 (C-N), 740 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.05-7.68 (m, 13H, ArH), 8.04 (s, 1H, NH), 7.46 (s, 1H, CH), 4.49 (s, 1H, OH), 4.41 (d, 2H, $CH_2$), 3.94 (s, 2H, $CH_2$ of thiazolidinone).

**N-{2-[5-(4-methylbenzylidene)-2-(4-hydroxyphenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (16)**

M.p.: 180-182°C; yield: 70%; IR (KBr, $cm^{-1}$): 3634 (OH), 3372(NH), 3070 (C-H arom.), 2966 (C-$CH_3$), 1687 (C=O), 1633 (C=C arom.), 1264 (C-N), 1130 (C-O-C, $OCH_3$), 742 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.15-7.78 (m, 13H, ArH), 8.04 (s, 1H, NH), 7.46 (s, 1H, CH), 4.46 (s,

1H, OH), 4.41 (d, 2H, $CH_2$), 3.94 (s, 2H, $CH_2$ of thiazolidinone), 2.51 (s, 3H, $CH_3$).

**N-{2-[5-(4-methylbenzylidene)-2-(3-methoxyphenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (17)**

M.p.: 172-174°C; yield: 86%; IR (KBr, $cm^{-1}$): 3472 (NH), 3093 (C-H arom.), 2976 (C-$CH_3$), 1651 (C=O), 1629 (C=C arom.), 1245 (C-N), 1124 (C-O-C, $OCH_3$), 771 (C-S). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.04 (s, 1H, NH), 7.98-7.68 (m, 13H, ArH), 7.46 (s, 1H, CH), 4.41 (d, 2H, $CH_2$), 3.94 (s, 2H, $CH_2$ of thiazolidinone), 3.80 (s, 3H, -$OCH_3$), 2.51 (s, 3H, $CH_3$).

**Antimicrobial assay**

The antimicrobial activity of the synthesized compounds was performed against Gram-positive bacteria: *Staphylococcus aureus*, *Bacillus subtilis*, the Gram-negative bacterium *Escherichia coli* and fungal strains: *Candida albicans* and *Aspergillus niger* using the tube dilution method (14). The compounds were all dissolved in DMSO. Dilutions of test and standard compounds were prepared in double strength nutrient broth - Indian Pharmacopoeia (bacteria) or Sabouraud dextrose broth - Indian Pharmacopoeia (fungi) (24). The samples were incubated at 37°C for 24 h (bacteria), at 25°C for 7 days (*A. niger*) and at 37°C for 48 h (*C. albicans*) and the results were recorded in terms of minimum inhibitory concentration (MIC).

**Evaluation of anticancer activity**

The anticancer activity of synthesized compounds (**1**-**17**) was determined against an estrogen receptor positive human breast adenocarcinoma, MCF-7 (ATCC HTB-22) cancer cell line. The compounds were all dissolved in DMSO as stock of 100 mg/mL. The cytotoxicity of DMSO against MCF7 has been tested. DMSO of ≤ 0.1% did not result in cell killing. The highest concentration of each compound tested (100 µg/mL) contained only 0.1% DMSO. The cell line was cultured in RPMI 1640 (Sigma) supplemented with 10% fetal bovine serum (FBS) (PAA Laboratories) and 1% penicillin/streptomycin (PAA Laboratories). Culture was maintained in a humidified incubator at 37°C in an atmosphere of 5% $CO_2$. Anticancer activity of synthesized compounds at various concentrations was assessed using the sulforhodamine B (SRB) assay as previously described by Skehan et al. (15), but with minor modifications, following 72 h of incubation. Assay plates were read using a spectrophotometer at 570 nm. Data generated were used to plot a dose-response curve of which the concentration of test compounds required to kill 50% of cell population ($IC_{50}$) was determined (15).

***QSAR studies***

The structures of synthesized 4-thiazolidinone derivatives were first pre-optimized with the Molecular Mechanics Force Field ($MM^+$) procedure included in Hyperchem 6.03 (25) and the resulting geometries were further refined by means of the semiempirical method PM3 (Parametric Method-3). We had chosen a gradient norm limit of 0.01kcal/Å for the geometry optimization. The lowest energy structure was used for each molecule to calculate physicochemical properties using TSAR 3.3 software for Windows (26). Further, the regression analysis was performed using the SPSS software package (27).

## CONCLUSION

A novel series of 4-thiazolidinone derivatives (**1**-**17**) was synthesized and evaluated for its *in vitro* antimicrobial (against *S. aureus, B. subtilis, E. coli, C. albicans* and *A. niger*) and anticancer (against breast cancer MCF-7 cell line) activities. Results of antimicrobial activity indicated that the synthesized compounds were found to be most potent against the fungal strain *C. albicans* and compound **7** (N-{2-[5-(4-nitrobenzylidene)-2-(4-chlorophenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide, pMIC = 2.22 µM/mL) was found to be most potent antifungal agent against *C. albicans*. The anticancer study results demonstrated that N-{2-[5-(4-hydroxybenzylidene)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-ylamino]-2-oxoethyl}benzamide (**10**, $IC_{50}$ = 18.59 µM) was the most effective anticancer agent. QSAR studies indicated the importance of topological parameter, Kier's a third order shape index ($\kappa\alpha_3$) as well as electronic parameters, cosmic total energy (cos E) and energy of highest occupied molecular orbital (HOMO) in describing the antimicrobial activity of synthesized compounds.

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