Summary of Ph. D. Thesis

Introduction

Infectious diseases are responsible for a significant proportion of deaths worldwide and according to the World Health Organization, antimicrobial agents are considered to be “miracle drugs” that are the leading weapons in the treatment of infectious diseases. Unfortunately, a number of the current clinically efficacious antimicrobial agents are becoming less effective because of the development of microbial resistance. So, there is an urgent need for the discovery or optimization of novel antimicrobial agents that are active against resistant microbial strains (Jin et al., 2012).

Cancer is the worldwide health problem and the most alarming disease of human. Lack of a wide assortment of anticancer drugs to capitalize on novel discoveries regarding tumor genesis, coupled with the unique growth patterns of assorted repertoires of cancer, have ambitious the attention of researchers toward the discovery of new, more active, more selective and less toxic compounds (Abdel-Jalil et al., 2010).

Quantitative structure–activity relationships (QSARs) are among the most widely used techniques in rational drug design, which finds the mathematical relationship between physicochemical properties of compounds and their experimentally determined biological activities. Thus, the derived QSAR model can be subsequently used to predict the biological activities of new derivatives. A good QSAR model both enhances our understanding of the specifics of drug action and provides a theoretical foundation for lead optimization. Moreover, QSAR techniques increase the probability of success with reduced time and cost in drug discovery (Pasha et al., 2007).

4-Thiazolidinones and 2-azetidinones constitute an important class of heterocyclic compounds which have been recognized as useful building blocks for the synthesis of a large number of medicinal compounds.

Keeping in view of aforementioned facts in mind the present study was designed with the objective of synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone and work was planned as follows

Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.
Summary of Ph. D. Thesis

Plan of work

a) Synthesis of different derivatives of 4-thiazolidinone/2-azetidinone
b) Characterization of synthesized compounds by physicochemical and spectral means.
c) Determination of in vitro antimicrobial activity of synthesized compounds against representative bacterial and fungal strains by tube dilution method.
d) Determination of minimum bactericidal concentration (MBC) and fungicidal concentration (MFC) of the synthesized compounds.
e) Development of QSAR models to describe the antimicrobial activity of synthesized compounds, which can be used further to predict the activities of new compounds proposed to be synthesized in future.

1. A comprehensive review on biological activities of 4-thiazolidinone derivatives.

4-Thiazolidinone scaffold has been consistently rewarded as a promising versatile lead molecule with a pivotal position in modern medicinal chemistry. 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group in the 4-position and formed by the attack of sulphur nucleophile on imine carbon followed by intramolecular cyclisation with elimination of water. Various classes of structurally different 4-thiazolidinones have been designed, synthesized and evaluated for anticancer, antimicrobial, antimycobacterial, antiviral, anti-HIV, analgesic, anti-inflammatory, antioxidant, anticonvulsant, antidiabetic, antimalarial, anti-alzheimer, anti-arthritis, anti-hypertensive, antiarrhythmic, antiprotocoal and hypolipidemic activities.

Book chapter published from aforementioned work:


2. A comprehensive review on biological activities of 2-azetidinone derivatives.

The 2-carbonyl derivative of azetidine is designated as 2-azetidinone or, more commonly, β-lactam is present in the most commonly used antibiotics, penicillin and cephalosporin. 2-Azetidinone derivatives occupy a pivotal position in modern

Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.
medicinal chemistry has attracted the attention of many researchers to explore this skeleton for its multiple biological potentials i.e. antimicrobial, anticancer, antitubercular, anti-inflammatory, anticonvulsant, antidiabetic and antiviral activities.

**Book chapter published from aforementioned work:**


3. **Synthesis, antimicrobial, anticancer evaluation of 2-(aryl)-4-thiazolidinone derivatives and their QSAR studies (Series I)**

   A series of 2-(aryl)-4-thiazolidinones clubbed with quinazolinone nucleus (1-17, Scheme I) has been synthesized and characterized by physicochemical and spectral means. The title compounds were screened for their *in vitro* antimicrobial and anticancer potentials. Results of antimicrobial and anticancer study revealed that compound 7 (pMIC<sub>am</sub> = 1.69 µM/ml) and 2 (IC<sub>50</sub> = 12.83 µM) were found to be the most potent antimicrobial and anticancer activity respectively. Further, QSAR studies carried out in order to find out a relationship between the antimicrobial activity of synthesized compounds and their structural parameters indicated the importance of topological parameter, valence third order molecular connectivity index ($\chi^{3}$), lipophilic parameter, log P and electronic parameters, dipole moment and energy of highest occupied molecular orbital ($\mu$ and HOMO, Eq. 1) in describing the antimicrobial activity. The structural requirements for the antimicrobial and anticancer activities of synthesized compounds are summarized in Fig. 1.

**MLR mt-QSAR model for antimicrobial activity**

$$pMIC_{am} = 0.145 \text{ HOMO} - 0.072 \mu + 2.463$$  \hspace{1cm} \text{Eq. 1}$$

$$n = 13 \hspace{0.5cm} r = 0.888 \hspace{0.5cm} q^{2} = 0.696 \hspace{0.5cm} s = 0.041 \hspace{0.5cm} F = 18.74$$

**Research article accepted from aforementioned work:**


Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.
Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.
**Summary of Ph. D. Thesis**

4. **Synthesis, antimicrobial, anticancer evaluation and QSAR studies of thiazolidin-4-ones clubbed with quinazolinone (Series II)**

A series of 3-(5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl)-2-phenyl quinazolin-4(3H)-one derivatives (1-18, Scheme II) was synthesized and evaluated as antimicrobial and anticancer agents. Compounds 7 and 16 were found to be most potent anticancer (7, IC50 = 5.27 μM) and antimicrobial (16, pMICam = 1.71 μM/ml) agents respectively. The QSAR studies indicated the importance of topological parameters, valence first and second order molecular connectivity indices ($1\chi_v$ and $2\chi_v$) and the electronic parameters, total energy ($Te$) and cosmic energy ($Cos E$) in determining the antimicrobial activity of synthesized 4-thiazolidinone derivatives ($1\chi_v$ and LUMO Eq. 2). The structural requirements for the antimicrobial and anticancer activities of synthesized compounds are summarized in Fig. 2.

**MLR-QSAR model for antibacterial activity against S. aureus**

$$pMIC_{sa} = 0.0414 \ 1\chi_v - 0.0791 \ LUMO + 0.$$  
Eq. 2

n= 15  \quad r = 0.977 \quad q^2 = 0.924 \quad s = 0.0061 \quad F = 125.06$

**Publication from the aforementioned work:**


**Synthesis, antimicrobial, anticancer evaluation and QSAR studies of thiazolidin-4-ones clubbed with quinazolinone” Current Topics In Medicinal Chemistry, 2013, 13, 2034-2046 Journal impact factor = 3.45**

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Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.
Scheme II. Synthetic route followed for the synthesis of 3-(5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one derivatives (Series II)

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Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.
In the present study, a series of 2-azetidinone derivatives (1-17, Scheme III) was synthesized and evaluated for its in vitro antimicrobial and anticancer potentials. The synthesized compounds exhibited more potent antimicrobial activity than anticancer activity. Compound 12 (pMIC\textsubscript{am} = 1.87 µM/ml) and compound 5 (IC\textsubscript{50} = 49.52 µM) were found to be most potent antimicrobial and anticancer agents respectively. The structural requirements for the antimicrobial and anticancer activities of synthesized compounds are summarized in Fig. 3. QSAR studies indicated the
importance of total energy (Te), cosmic total energy (Cos E) and Kier’s third order shape index ($\kappa_3$, Eq. 3) in describing the antimicrobial activities of synthesized derivatives.

**LR mt-QSAR model for antimicrobial activity**

\[
p_{\text{MIC}_{\text{am}}} = 0.244 \, \kappa_3 + 0.470 \quad \text{Eq. 3}
\]

\[n = 12 \quad r = 0.870 \quad q^2 = 0.610 \quad s = 0.067 \quad F = 31.28\]

![Scheme III](image_url)

**Scheme III. Scheme for the synthesis of 2-azetidinone derivatives (Series III)**

<table>
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<tr>
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<th>Compound</th>
<th>Ar</th>
<th>Compound</th>
<th>Ar</th>
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<td>1</td>
<td>H$_2$CO</td>
<td>7</td>
<td>vinyl</td>
<td>13</td>
<td>phenylCHO</td>
</tr>
<tr>
<td>2</td>
<td>OCH$_3$</td>
<td>8</td>
<td>phenylCH$_3$</td>
<td>14</td>
<td>phenylN-CH$_3$</td>
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<td>3</td>
<td>Cl</td>
<td>9</td>
<td>OCH$_3$</td>
<td>15</td>
<td>OCH$_3$</td>
</tr>
<tr>
<td>4</td>
<td>OCH$_2$CH$_3$</td>
<td>10</td>
<td>Br</td>
<td>16</td>
<td>phenylCl</td>
</tr>
<tr>
<td>5</td>
<td>OCH$_3$</td>
<td>11</td>
<td>OCH$_3$</td>
<td>17</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>12</td>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
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</tr>
</tbody>
</table>

Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.
Studies of novel derivatives of 4-(2-iminothiazolidin-3-one)/2-azetidinones (Series III) and tested in vitro for its antimicrobial and anticancer potentials. In general, the synthesized compounds were found to be potent antimicrobial agents than anticancer agents. Anticancer screening results indicated that compound 13 (IC$_{50}$ = 15.18 μM) was the most effective one and was more potent than standard drug, carboplatin (IC$_{50}$ > 100 μM). Antimicrobial activity results indicated that compound 14 (pMIC$_{ec}$ = 2.14 μM) was the most active one. The structural requirements for the antimicrobial and anticancer activities of synthesized compounds are summarized in Fig. 4. The QSAR studies indicated that the antimicrobial activity of the synthesized compounds was governed by lipophilic parameter, log P (Eq. 4), topological parameter, κα$_3$ and electronic parameters cos E and Nu. E.

**QSAR model for antibacterial activity against B. subtilis**

\[
pMIC_{bs} = 0.348 \log P + 0.719 \quad \text{Eq. 4}
\]

\[
n = 12 \quad r = 0.849 \quad q^2 = 0.632 \quad s = 0.087 \quad F = 25.85
\]

**Research article accepted from aforementioned work**


6. **4-Thiazolidinone derivatives: Synthesis, antimicrobial, anticancer evaluation and QSAR studies (Series IV)**

A series of 4-thiazolidinone derivatives (1–18) was synthesized (Scheme IV) and tested in vitro for its antimicrobial and anticancer potentials. In general, the synthesized compounds were found to be potent antimicrobial agents than anticancer agents. Anticancer screening results indicated that compound 13 (IC$_{50}$ = 15.18 μM) was the most effective one and was more potent than standard drug, carboplatin (IC$_{50}$ > 100 μM). Antimicrobial activity results indicated that compound 14 (pMIC$_{ec}$ = 2.14 μM) was the most active one. The structural requirements for the antimicrobial and anticancer activities of synthesized compounds are summarized in Fig. 4. The QSAR studies indicated that the antimicrobial activity of the synthesized compounds was governed by lipophilic parameter, log P (Eq. 4), topological parameter, κα$_3$ and electronic parameters cos E and Nu. E.

**QSAR model for antibacterial activity against B. subtilis**

\[
pMIC_{bs} = 0.348 \log P + 0.719 \quad \text{Eq. 4}
\]

\[
n = 12 \quad r = 0.849 \quad q^2 = 0.632 \quad s = 0.087 \quad F = 25.85
\]

**Research article communicated from aforementioned work**

Summary of Ph. D. Thesis

Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.

Arabian Journal of Chemistry. Journal Impact factor = 2.62
Figure 4. Structural requirements for the antimicrobial and anticancer activities synthesized 4-thiazolidinone derivatives (Series IV)

7. Synthesis, antimicrobial, anticancer evaluation and QSAR studies of thiazolidin-4-one derivatives (Series V)

A novel series of 4-thiazolidinone derivatives (1-17) was synthesized (Scheme V) 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 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, IC₅₀ = 18.59 µM) was the most effective one. The structural requirements for the antimicrobial and anticancer activities of synthesized compounds are summarized in Fig. 5. QSAR studies indicated the importance of topological parameter, Kier’s alpha third order shape index (α₃) as well as electronic parameters, cosmic total energy (cos E) and energy of highest occupied molecular orbital (HOMO, Eq. 5) in describing the antimicrobial activity of synthesized compounds.

**QSAR model for antimicrobial activity**

\[
pMIC_{am} = -0.449 \text{HOMO} - 2.300 \quad \text{Eq. 5}
\]

\[
n = 12 \quad r = 0.846 \quad q^2 = 0.565 \quad s = 0.086 \quad F = 25.19
\]

Research article communicated from aforementioned work

Deep A, Kumar P, Narasimhan B, Mishra RK, Mani V, Ramasamy K, Lim SM, Synthesis, antimicrobial, anticancer evaluation and QSAR studies of thiazolidin-4-one derivatives”

*Acta Poloniae Pharmaceutica Drug Research.* Impact factor = 0.7

Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.
Summary of Ph. D. Thesis

Scheme V. Scheme for the synthesis of 2,5-disubstituted 4-thiazolidinone derivatives (Series V)

<table>
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<td>(\text{C}_6\text{H}_5) (\text{OCH}_3) (\text{OCH}_3)</td>
</tr>
<tr>
<td>3</td>
<td>(\text{C}_6\text{H}_5) (\text{NCH}_3) (\text{NCH}_3)</td>
<td>(\text{C}_6\text{H}_5) (\text{H}_3\text{CO}) (\text{OCH}_3)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{C}_6\text{H}_5) (\text{Cl})</td>
<td>(\text{C}_6\text{H}_5) (\text{F})</td>
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<tr>
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<tr>
<td>6</td>
<td>(\text{C}_6\text{H}_5) (\text{N}) (\text{C}_2\text{H}_5) (\text{C}_2\text{H}_5)</td>
<td>(\text{C}_6\text{H}_5) (\text{NO}_2)</td>
</tr>
<tr>
<td>7</td>
<td>(\text{C}_6\text{H}_5) (\text{Cl})</td>
<td>(\text{C}_6\text{H}_5) (\text{NO}_2)</td>
</tr>
<tr>
<td>8</td>
<td>(\text{C}_6\text{H}_5) (\text{N}) (\text{C}_2\text{H}_5) (\text{C}_2\text{H}_5)</td>
<td>(\text{C}_6\text{H}_5) (\text{Cl})</td>
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Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.
Summary of Ph. D. Thesis

Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.

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<td><img src="image17" alt="Image" /></td>
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**Figure 5.** Structural requirements for the antimicrobial and anticancer activities of synthesized 2,5-disubstituted 4-thiazolidinone derivatives (Series V)

Electron withdrawing groups → Increase antifungal activity against *C. albicans*.

Electron releasing groups → Increase antimicrobial activity against *B. subtilis, S. aureus, A. niger* and anticancer activity against MCF-7 (ATCC HTB-22) cancer cell line.

Increase antibacterial activity against *E. coli* and anticancer activity against MCF-7 (ATCC HTB-22) cancer cell line.
8. 2-Azetidinone derivatives: Synthesis, antimicrobial, anticancer evaluation and QSAR studies (Series VI)

A series of 2-azetidinone derivatives was synthesized (1-18, Scheme VI) and evaluated for its in vitro antimicrobial and anticancer activities. Antimicrobial activity results revealed the synthesized compounds displayed average antimicrobial and anticancer potentials and compounds 4 and 17 were found to be most potent antimicrobial and anticancer agents respectively. The structural requirements for the antimicrobial and anticancer activities of synthesized compounds are summarized in Fig. 6. Developed QSAR models indicated the importance of topological parameters, Balaban index (J) as well as valence zero and first order molecular connectivity indices ($\chi^v$, Eq. 6) in determining the antimicrobial activity of the synthesized compounds.

**QSAR model for antimicrobial activity**

\[
pMIC_{am} = -0.096 \chi^v + 2.325 \quad \text{Eq. 6}
\]

\[
n = 11 \quad r = 0.789 \quad q^2 = 0.500 \quad s = 0.058 \quad F = 14.87
\]

\[\begin{align*}
\text{Electron withdrawing groups} & \quad \text{Increase antimicrobial activity against C. albicans and S.aureus.} \\
\text{Electron releasing groups} & \quad \text{Increase antimicrobial and anticancer activity against E. coli, B. subtilis, A. niger and MCF-7 (ATCC HTB-22) cancer cell line.} \\
\text{Increase anticancer activity against MCF-7 (ATCC HTB-22) cancer cell line.}
\end{align*}\]

**Figure 6.** Structural requirements for the antimicrobial and anticancer activities of 2-azetidinone derivatives (Series VI)

**Research article accepted from aforementioned work**


**Acta Poloniae Pharmaceutica Drug Research.** Impact factor = 0.7

Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.
Synthesis, antimicrobial evaluation and QSAR studies of novel derivatives of 4-thiazolidinone/2-azetidinone.