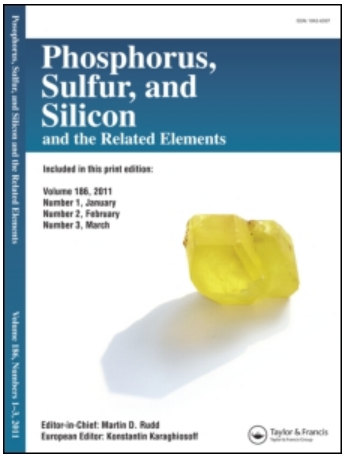

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Theoretical Calculations and Experimental Verification of the Antibacterial Potential of Some Monocyclic β-Lactams Containing Two Synergetic Buried Antibacterial Pharmacophore Sites

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THEORETICAL CALCULATIONS AND EXPERIMENTAL VERIFICATION OF THE ANTIBACTERIAL POTENTIAL OF SOME MONOCYCLIC β-LACTAMS CONTAINING TWO SYNERGETIC BURIED ANTIBACTERIAL PHARMACOPHORE SITES

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A new series of N-thiazole, 3-phenyl, 4-substituted phenyl azetidine-2-ones 4(a–h) have been synthesized in good yields starting from 2-aminothiazole 1. In the first step, then Schiff's bases 3(a–h) are prepared by the condensation of 2-aminothiazole 1 with different aryl aldehydes 2(a–h). Finally, monocyclic β-lactams, i.e. substituted azetidinones 4(a–h), were the products formed using three different methods by the dehydrative cyclocondensation of 3(a–h) with phenyl acetyl chloride in dioxane, phenyl acetic acid–thionyl chloride in dichloromethane and phenyl acetic acid–phosphorus oxychloride in dichloromethane in the presence of triethylamine. We found that latter method is the best as compared with the former two methods. The synthesized molecules 4(a–h) were screened for their antibacterial activity against four microorganisms:* Staphylococcus aureus *(Gram positive),* Pseudomonas vulgaris *(Gram positive),* Pseudomonas aeruginosa *(Gram negative), and Escherichia coli (Gram negative). Their antibacterial activities are reported, and on the basis of the screening data available, attempt is also made to elucidate the structure–activity relationship.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Antibacterial; β-lactams; Petra/Osiris/Molinspiration (POM) model; SAR; Schiff's bases; virtual screening

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INTRODUCTION

β-Lactam antibiotics are the most widely used antibiotics in chemotherapy.[1] Even more than 70 years after the discovery of penicillin, β-lactam antibiotics remain as one of the most targeted contributions of science to humans.[1] The first member of this class of compounds was synthesized by Staudinger in 1907.[2] But the importance of β-lactams as antibiotics was not recognized until the discovery of penicillin by Fleming in 1929.[3] An alarming increase in bacterial resistance to β-lactam antibiotics has pushed pharmaceutical companies to seek new β-lactam antibiotics.[4] Consequently, because of the growing resistance of bacteria towards β-lactam antibiotics and the need for medicines with a more specific antibacterial activity, several synthetic and semi-synthetic β-lactam antibiotics have been developed by the pharmaceutical industry all over the globe.[5]

Heterocyclic compounds having four-membered heterocyclic ring nucleus with nitrogen as the heteroatom are generally designated as 2-azetidinone, monobactam, or, more commonly, β-lactam.[6] β-Lactam antibiotics include penicillin, cephalosporin, cephamycins, carbapenems, nocardicins, monobactams, and beta lactamase inhibitors of which activity is related to the presence of 2-azetidinone nucleus in the system. Monobactams are monocyclic β-lactam antibiotics, which have been isolated from Gram-negative bacteria. These compounds show significant antibacterial activity and bind to essential penicillin-binding proteins (Figures 1 and 2) of susceptible organisms.[7] In addition to the monobactams and nocardicins, some other monocyclic β-lactams, such as functionalized beta-lactams compounds, have also shown good antibacterial activity.[8–10] Thus, contrary to nocardicins,[11] monobactams have biological properties similar to those of bicyclic β-lactam antibiotics.

Pharmacologically, thiazoles are among the most important classes of organic compounds. These compounds possess versatile types of biological activities; some of these are well known for their anti-inflammatory activities such as fentiazac and meloxicam, while compounds like nizatidine possess anti-ulcer activity.[12] Some of 2-aminothiazoline derivatives are known for their inhibition of kinurenine-3-hydroxylase,[13] and cyclin-dependent kinase enzymes.[14] Thus thiazole derivatives play a vital role in medicinal chemistry.

All these findings led us to develop azetidinones with an N-substituted thiazole moiety. The system of conversion of Schiff's bases to azetidinones using phenyl acetylchloride was previously reported.[15,16]

In continuation of our work on bioactive β-lactams, we describe here a general synthesis of new β-lactams bearing thiazole moiety (Scheme 1).

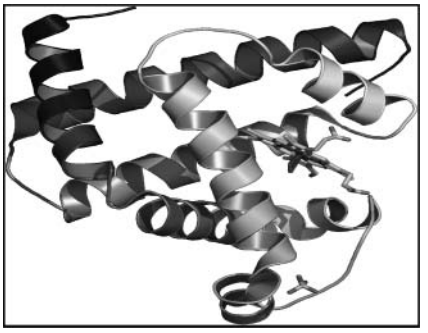


Figure 1 3-D structure of protein.

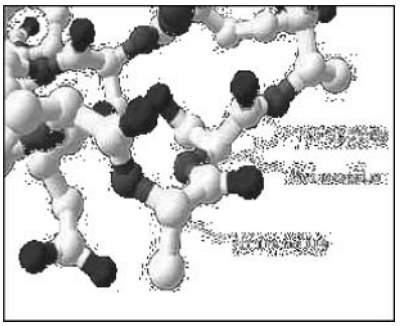
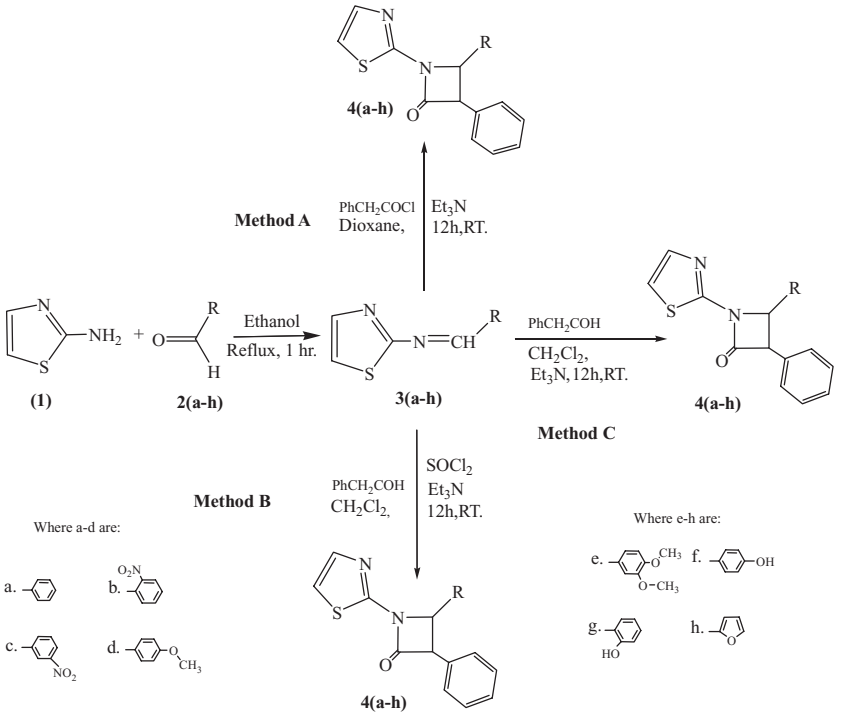


Figure 2 Section of a protein structure linked together by peptide bonds.

RESULTS AND DISCUSSION

Synthesis

The Schiff's bases **3**(**a–h**) were prepared by general method by refluxing 2-amino thiazole with different aromatic aldehydes. Dehydrative cyclocondensation of Schiff's bases with phenylacetyl chloride and in situ prepared phenyl acetyl chloride in the presence of triethylamine, respectively, afforded azetidinones by different methods as shown in Scheme 1.



Scheme 1 Synthesis of mono cyclic β-lactams **4**(**a–h**).

The 2-azetidinones **4(a–h)** have been synthesized in three different ways, first by the cyclocondensation of phenylacetyl chloride and Schiff's bases **3(a–h)** in the presence of triethylamine in dioxane stirred for overnight at room temperature (Method A). The same products were also synthesized by stirring a mixture of phenylacetic acid, Schiff's bases **3(a–h)**, triethylamine, and thionyl chloride in benzene overnight at room temperature (Method B). Finally, the same were prepared by dehydrative cyclocondensation of phenylacetic acid, Schiff's bases **3(a–h)**, triethylamine, and phosphorus oxychloride overnight at room temperature (Method C). The yield of the products with Methods A, B, and C was found to be around 60–65%, 40–50%, and 70–80%, respectively. The authenticity of the products prepared by all the methods was established by TLC, mp, elemental analysis, ^{1}H NMR, mass spectrometry, and IR spectroscopy.

The selected ^{1}H NMR data and assignments of the compounds are presented in Table I. The ^{1}H NMR spectra of the Schiff's base **3(a–h)** in DMSO-d_6 at room temperature using TMS as an internal standard showed the following signals: −CH=N− at 9.6 ppm (s, 1H), phenyl at 7.0–7.2 ppm as multiplet, −OH at 5.0 ppm (s, 1H) and $-OCH_3$ at 3.7 ppm, (s, 3H). The ^{1}H NMR spectra of the compounds **4(a–h)** showed the following signals: phenyl as multiplet 7.0–7.2 ppm, −OH at 5.0 ppm (s, 1H) and $-OCH_3$ at 3.7 (s, 3H). The absence of a signal for −CH=N− in all the compounds showed that cyclocondensation was achieved. The ^{1}H NMR showed a *cis* orientation of the C-3 and C-4 protons of the 2-azetidinone ring in 4, viz. each proton at C-3 and C-4 appeared as doublet with the coupling

Table I Selected IR and ^{1}H NMR data of compounds **4(a–h)**

Compound	IR (KBr) υ cm^{-1} β-Lactam–CO	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm & J Hz				
		(d,1H,CH, thiazole)	Aromatic H	(d,1H,CH, thiazole)	(d,1H,CH)	(d,1H,CH)
4a	1740	7.54 (d,1H,CH) J = 3.54 Hz	7.01–7.26 (10H,m,Arom)	6.52 (d,1H,CH) J = 3.54 Hz	5.18 (d,1H,CH) J = 4.58 Hz	4.27 (d,1H,CH) J = 5.04 Hz
4b	1680	7.54 (d,1H,CH) J = 3.54 Hz	7.01–7.26 (9H,m,Arom)	6.52 (d,1H,CH) J = 3.54 Hz	5.18 (d,1H,CH) J = 4.58 Hz	4.27 (d,1H,CH) J = 5.26 Hz
4c	1685	7.54 (d,1H,CH) J = 3.54 Hz	7.01–7.26 (m,10H,Arom)	6.52 (d,1H,CH) J = 3.54 Hz	5.18 (d,1H,CH) J = 4.58 Hz	4.27 (d,1H,CH) J = 5.26 Hz
4d	1720	7.54 (d,1H,CH) J = 3.54 Hz	7.01–7.26 (m,10H,Arom)	6.52 (d,1H,CH) J = 3.54 Hz	5.18 (d,1H,CH) J = 4.58 Hz	4.27 (d,1H,CH) J = 5.26 Hz
4e	1710	7.54 (d,1H,CH) J = 3.54 Hz	7.01–7.26 (m,10H,Arom)	6.52 (d,1H,CH) J = 3.54 Hz	5.18 (d,1H,CH) J = 4.58 Hz	4.27 (d,1H,CH) J = 5.26 Hz
4f	1690	7.54 (d,1H,CH) J = 3.54 Hz	7.01–7.26 (m,10H,Arom)	6.52 (d,1H,CH) J = 3.54 Hz	5.18 (d,1H,CH) J = 4.58 Hz	4.27 (d,1H,CH) J = 5.26 Hz
4g	1695	7.54 (1H, d, CH) J = 3.54 Hz	7.01–7.26 (m,10H,Arom)	6.52 (d,1H,CH) J = 3.54 Hz	5.18 (d,1H,CH) J = 4.58 Hz	4.27 (d,1H,CH) J = 5.26 Hz
4h	1715	7.54; 7.23; 7.15 3x(d,1H,CH) J = 3.54 Hz	7.01–7.26 (m,10H,Arom)	6.52 & 6.14 2x(d,1H,CH) J = 3.54 Hz	5.18 (d,1H,CH) J = 4.58 Hz	4.27 (d,1H,CH) J = 5.26 Hz

constant of 4.5 to 5.2 Hz needed for *cis* stereochemistry. There was no appreciable change in all the other signals of the compounds.

The IR spectrum of compounds **3**(**a–h**) indicates the presence of (-C = N) azomethine linkage peaks around 1620–1630 cm^{-1}. The absence of azomethine linkage peaks and the presence of β- lactam, C = O peaks around 1680–1740 cm^{-1} showed the achievement of cyclocondensation in compounds **4**(**a–h**).

Antibacterial Activity

The antibacterial activity of the series **4**(**a–h**) been carried out against some strains of bacteria. To determine the antibacterial activity of these agents, the Agar cup plate method was used, with ampicillin and streptomycin as the reference antibiotics.[17] The prepared compounds were examined against two strains each of Gram positive and Gram negative bacteria. The test results, presented in Table S1 (available online in the Supplemental Materials), suggests that compounds **4g** and **4h** are highly active against two strains each of Gram positive and Gram negative bacteria, showing the broadest spectrum of antibacterial activity. The rest of the compounds were found to be moderately active, slightly active, or inactive against the tested microorganisms. The results show that the prepared compounds are toxic against the bacteria.

STRUCTURE–ACTIVITY RELATIONSHIP

A perusal of antibacterial screening data indicates that all the compounds under investigation were moderately active to the test bacteria.

The structure of synthesized azetidinones **4**(**a–h**) for ease of analysis can be divided into four parts: azetidinone skeleton, thiazole side chain at N-1 of azetidinone skeleton, phenyl ring at C-3, and substituted phenyl ring at C-4 of azetidinone skeleton. We have fixed the former three parts and varied the latter one by attaching the phenyl ring with several functional groups, such as 2-NO_2, 3-NO_2, 4-OMe, 3, 4-di-OMe, 2-OH, and 4-OH, and replacing the phenyl ring by furan one in compound **4h**. These modifications in the azetidinone skeleton followed by the analysis of resulting molecules structure have resulted in the following findings:

The unsubstituted phenyl ring at C-3 is non-effective against Gram-negative strains and moderately effective against Gram-positive ones in compound **4a**. The introduction of an electron-withdrawing substituent such as nitro at position 2 and 3 on the C-3 phenyl ring masked the potency in case of compounds **4b** and **4c** as compared with **4a**.

On the other hand, compounds **4f** and **4g** had an activity quite comparable to the commercial antibiotics (ampicillin and streptomycin) tested under similar conditions. This activity was probably due to the presence of a strong polar substituent -OH at position 2 of the phenyl ring on the azetidinone moiety as compared to the similar substitution at position 4 in compound **4f**, which has shown moderate activity. In both the cases, the oxygen can act as a hydrogen bond acceptor, and the hydrogen can act as a hydrogen bond donor. One or all of these interactions may be important in binding the molecules to the binding site. Thus in both the cases, the hydroxyl group may be involved in some H-bonding, which increases the affinity of the molecule for the active site of the enzyme. So 2-OH is necessary for high activity of the compound **4g**. Conversion of OH to methyl ether or substitution of 4-OMe on the ring has reduced the activity as compared to compound **4g**. However, substituted 3,4-di-OMe has shown some moderate activity.

Further investigation of compound **4g** on a wider range of bacteria as well as with higher dilution is desirable. In compound **4h**, there is furan instead of phenyl as a pharmacophore, i.e. a heterocyclic moiety which can interact through Van der Waals and hydrophobic interactions, while the oxygen as a heteroatom can interact by hydrogen bonding or ionic bonding leading to better potency against the test bacteria. Further investigation in this case is also desirable. As far as molecular masses of these two compounds **4g** and **4h** are concerned, both the compounds have masses around 300 Dalton (322 for **4g** and 296 for **4h**). Optimizing compounds for high activity on a biological target almost often goes along with increased molecular weights. However, compounds with higher weights are less likely to be absorbed and therefore to ever reach the place of action and less active. Although an attempt was made to combine various groups in these molecules with the hope of achieving compounds of better potency, the results are not very encouraging in all the cases, except compounds **4g** and **4h**.

VIRTUAL SCREENINGS AND MOLECULAR PROPERTIES CALCULATIONS

PETRA Calculations

PETRA is a software package comprising various empirical methods for the calculation of physicochemical properties in organic molecules.[18] All methods are empirical in nature and have been developed over the last 20 years in the research group of Prof. J. Gasteiger. The following chemical effects can be quantified: heats of formation, bond dissociation energies, sigma charge distribution, π-charge distribution, inductive effect, resonance effect and delocalization energies, and polarizability effect.[18]

The series **4(a–h)** of monocyclic β-lactams have been subjected to delocalized-charge calculations using the PETRA method of the nonhydrogen common atoms (Figure 3), obtained from the partial π-charge of the heteroatoms, have been used to model the bioactivity against bacteria. We give here, as example, the compounds **4(g–h)**.

It is found that the negative charges of the oxygen and nitrogen atoms of 1,3-thiazolyl group and the partial π positive charges of sulfur and supplementary arm 2-OH contribute positively in favor of an antibacterial activity, and this is in good agreement with the mode of antibacterial action of the compounds bearing ($X^{\delta-}$—$Y^{\delta+}$) pharmacophore(s) site(s).

It was hypothesized that difference in charges between two heteroatoms of the same pharmacophore site ($X^{\delta-}$—$Y^{\delta+}$) may facilitate the inhibition of bacteria, more than viruses. It is further found that the activity increases with increase in negative charge of one heteroatom of the common pharmacophore fragment of the compounds **(4g and 4h)**. This synergistic and streamlined working procedure led to highly active isomeric/tautomeric Gram(+/-) receptor ligands.

OSIRIS Calculations[19]

Structure-based design is now fairly routine, but many potential drugs fail to reach the clinic because of ADME-Tox liabilities. One very important class of enzymes, responsible for many ADMET problems, is the cytochromes P450, which is summarized in Table S2 (Supplemental Materials).

Inhibition of these or production of unwanted metabolites can result in many adverse drug reactions. One of the most important programs, OSIRIS, is available online.[19]

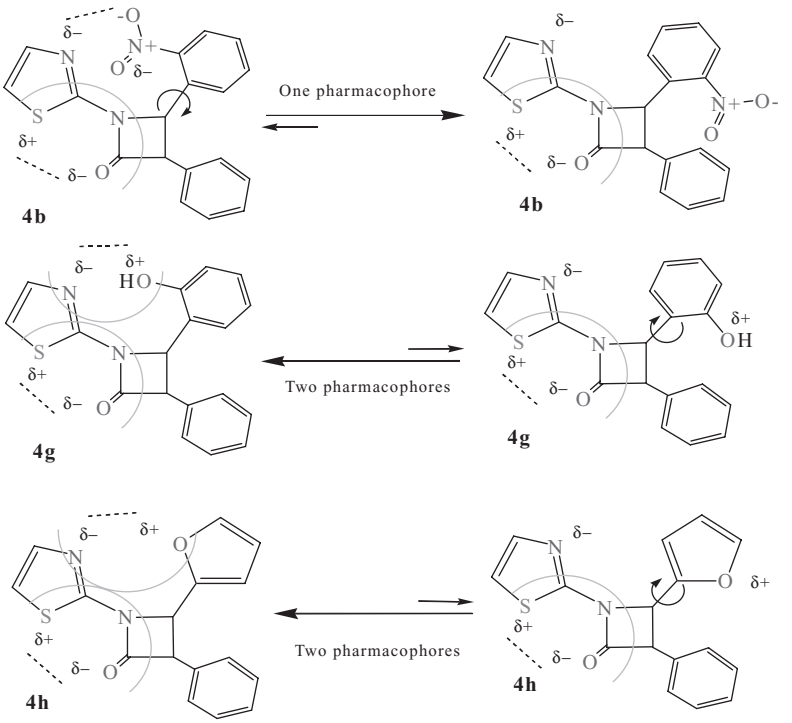


Figure 3 Possible potential antibacterial pharmacophore sites ($X^{\delta-}$—$Y^{\delta+}$) of compound **4(a–h)**.

With our recent publication of the drug design combination of various pharmacophore sites by using spiro-heterocyclic structure, it is now possible to predict activity and/or inhibition with increasing success in two targets (bacteria and HIV). This was done using a combined electronic/structure docking procedure, and an example will be given here. The remarkably well behaved mutagenicity of diverse synthetic molecules classified in the database of the Celeron Company (Switzerland) can be used to quantify the role played by various organic groups in promoting or interfering with the way a drug can associate with DNA.

Molinspiration Calculations[20]

CLogP (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (Table S3, Supplemental Materials).

The method is very robust and is able to process practically all organic and most organometallic molecules. Molecular polar surface area TPSA is calculated based on the methodology published by Ertl et al.[20] as a sum of fragment contributions. O- and N-centered polar fragments are considered. PSA has been shown to be a very good descriptor to characterize drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability, and blood–brain barrier penetration. Prediction results of compounds **4(a–h)** molecular properties (TPSA, GPCR ligand, and ICM) are valued (Table S3).

A number of important points emerge concerning the electronic and steric factors that have direct impact on bioactivity properties. The positive results we have recorded, while encouraging for purposes of new organometallic drug design, confirm that very likely most of these compounds could be used as potential antibacterial activity after minor modifications. Based on their structural properties, these compounds may be useful as chelating agents with higher potential activity.

CONCLUSIONS

The results of the present investigation support the suggested antibacterial pharmacophore sites of mono cyclic β-lactams. It has been suggested that some functional groups such as azomethine or hetero-aromatics present in these compounds displayed roles of biological activity that may be responsible for the increase of hydrophobic character and liposolubility of the molecules. This, in turn, enhances activity of the compounds and biological absorbance, and so all the synthesized cyclic β-lactams containing more than one antibacterial pharmacophore site have good antibacterial properties (**4g** and **4h**).

These results prompt several pertinent observations: (i) This type of cyclic β-lactam can furnish an interesting model for studying the interaction of antibiotics with viral target because of the possible charge modification of substituents and O/N/S of pharmacophore groups; and (ii) the future flexible pharmacophore site(s) geometric conformation enables us to prepare molecules for multitherapeutic materials with high selectivity (Figure 4).[21]

EXPERIMENTAL

The solvents and reagents used in the synthetic work were of laboratory grade and were purified by distillation or crystallization where necessary. Their boiling or melting points were compared with the available literature values. Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-400 (400 MHz) instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d6 as a solvent. Chemical shifts are given in parts per million (ppm). Infrared spectra were recorded on a Schimadzu-IR Prestige 21. Mass spectra were recorded on a Varian MAT CH-5 spectrometer. The reactions were monitored and the purity of products

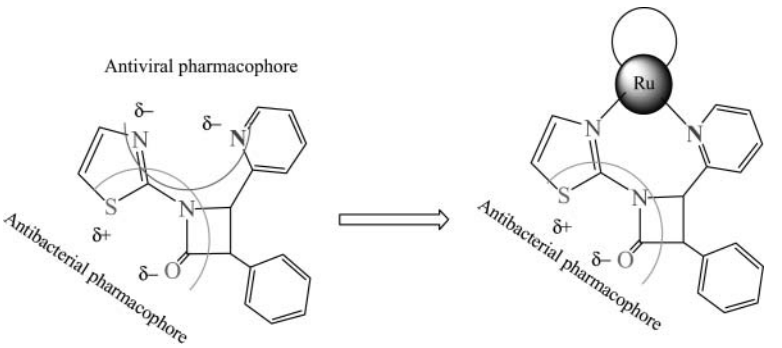


Figure 4 The combinaison of antitubercular and antiviral activities is possible on the basis of β-lactams **4(a–h)** squeleton. The University of Pennsylvania receives US$9.5 million grant as part of an American screening network to discover of bioactive organometallic ruthenium (II).[21]

was checked on precoated TLC plates (Silica gel 60 F254, Merck), visualizing the spots under ultraviolet light and iodine chamber. The antimicrobial screening was carried out at Department of Biochemistry, Saint Francis De Sales College, Nagpur.

Synthesis of N-Substituted Arylidinethiazol-2-amines: 3(a–h)

2-Hydroxy-benzaldehyde (0.01 M) in absolute ethanol (10 mL) was added to a stirred ethanolic solution (20 mL) of 2-aminothiazole (0.01 M), and the mixture was refluxed for 1 h. Chilled water was added until a slight cloudiness was persisted in the reaction solution. The reaction mixture was then set aside to cool. The oil which was separated out was induced to crystallize by rubbing with a glass rod. The resultant solid deposited was collected by filtration and washed well with cold ethanol. The same method was applied for the preparation of Schiff bases **3**(**a–h**) by using their respective aldehydes: benzaldehyde, 4-hydoxy benzaldehyde, 2-nitro-benzaldehyde, 3-nitro-benzaldehyde, 4-methoxy-benzaldehyde, 3,4-dimethoxy benzaldehyde, and furfuraldehyde. The products were obtained in 70–75% yield.

Preparation of 4-(Substituted phenyl)-3-phenyl-1-(thiazol-2-yl)-azetidin-2-ones: 4(a–h)

Method A: To a stirred solution of Schiff base (0.01 M) and Et_3N (0.02 M) in dioxane (50 mL), phenyl acetyl chloride (0.015 M) was added dropwise at 5–10°C. The mixture was stirred overnight at room temperature. The reaction progress was checked by TLC. After completion of the reaction, the contents were poured in stirred ice cold water and stirring was continued for 1 h. The solid that separated out was filtered, dried, and recrystallized from ethanol. The purity of the compounds was determined by their melting points and by thin layer chromatography. It was obtained in 60–65% yield.

Method B: To a stirred solution of Schiff base (0.01 M), Et_3N (0.02 M), and phenyl acetic acid (0.015 M) in anhydrous dichloromethane (50 mL), thionyl chloride (0.015 M) was added dropwise at 5–10°C. The mixture was allowed to stir at room temperature overnight. Reaction progress was monitored by TLC. After completion, the reaction was quenched in water. The organic layer was separated out, washed with water followed by washing with $NaHCO_3$ solution, and dried over magnesium sulfate. The products that were obtained after removing the solvent were recrystallized from ethanol. By this method, 40–50% yield was obtained.

Method C: To a stirred solution of Schiff base (0.01 M), phenyl acetic acid (0.01 M), and Et_3N (0.02 M) in anhydrous dichloromethane (50 mL), the solution of phosphorus oxychloride was added dropwise at 5–10°C. The mixture was allowed to stir at room temperature overnight. The reaction monitoring was done by TLC. After completion of the reaction, it was quenched in water. The organic layer was separated out, washed with water followed by washing with $NaHCO_3$ solution, and dried over magnesium sulfate. The products that were obtained after removing the solvent were recrystallized from ethanol. By this process, we obtained 70–80% yield.

2,3-Diphenyl-4-(1,3-thiazol-2-yl)cyclobutanone (4a). Yield 72%. Mp = 140°C. MS (FAB < 0, DMSO/MNBA): Calcd for $[M]^+$ $C_{18}H_{14}N_2OS$: 306 (100%), $[M+H]^+$ (m/z) = 307 (21.5%). Elemental analysis for $C_{18}H_{14}N_2OS$ Calcd (Found): C 70.56 (70.6), H 4.61 (4.55), N 9.14 (9.2), S 10.47 (10.45).

3-(2-Nitrophenyl)-2-phenyl-4-(1,3-thiazol-2-yl)cyclobutanone (4b). Yield 70%. Mp = 135°C. MS (FAB < 0, DMSO/MNBA): Calcd for $[M]^+$ $C_{18}H_{13}N_3O_3S$: 351 (100%),$[M+H]^+$ (m/z) = 352 (22.0%). Elemental analysis for $C_{18}H_{13}N_3O_3S$ Calcd (Found): C 61.53 (61.49), H 3.73 (3.76), N 11.96 (11.94), S 9.13 (9.10).

3-(3-Nitrophenyl)-2-phenyl-4-(1,3-thiazol-2-yl)cyclobutanone (4c). Yield 75%. Mp = 120°C. MS (FAB < 0, DMSO/MNBA): Calcd for $[M]^+$ $C_{18}H_{13}N_3O_3S$: 351 (100%), $[M + H]^+$ (m/z) = 352 (21.5%). Elemental analysis for $C_{18}H_{13}N_3O_3S$ Calcd (Found): C 61.53 (61.470), H 3.73 (3.75), N 11.96 (11.88), S 9.13 (9.16).

3-(4-Methoxyphenyl)-2-phenyl-4-(1,3-thiazol-2-yl)cyclobutanone (4d). Yield 78%. Mp = 170°C. MS (FAB < 0, DMSO/MNBA): Calcd for $[M]^+$ $C_{19}H_{16}N_2O_2S$: 336 (100%), $[M+H]^+$ (m/z) = 337 (22.5%). Elemental analysis for $C_{19}H_{16}N_2O_2S$ Calcd (Found): C 67.84 (67.85), H 4.79 (4.80), N 8.33 (8.35), S 9.53 (9.55).

3-(3,4-Dimethoxyphenyl)-2-phenyl-4-(1,3-thiazol-2-yl)cyclobutanone (4e). Yield 76%. Mp = 150°C. MS (FAB < 0, DMSO/MNBA): Calcd for $[M]^+$: 366 (100%), $[M+H]^+$ (m/z) = 337 (23.5%). Elemental analysis for $C_{20}H_{18}N_2O_3S$ Calcd (Found): C 65.55 (65.50), H 4.95 (4.93), N 7.64 (7.65), 8.75 (8.73).

3-(4-Hydroxyphenyl)-2-phenyl-4-(1,3-thiazol-2-yl)cyclobutanone (4f). Yield 78%. Mp = 115°C. MS (FAB < 0, DMSO/MNBA): Calcd for $[M]^+$ $C_{18}H_{14}N_2O_2S$: 322 (100%), $[M+H]^+$ (m/z) = 323 (25.1%). Elemental analysis for $C_{18}H_{14}N_2O_2S$ Calcd (Found): C 67.06 (67.10), H 4.38 (4.35), N8.69 (8.70), S 9.95 (9.90).

3-(2-Hydroxyphenyl)-2-phenyl-4-(1,3-thiazol-2-yl)cyclobutanone (4g). Yield 80%. Mp = 125°C. MS (FAB < 0, DMSO/MNBA): Calcd for $[M]^+$ $C_{18}H_{14}N_2O_2S$: 322 (100%), $[M+H]^+$ (m/z) = 323 (23.5%). Elemental analysis for $C_{18}H_{14}N_2O_2S$ Calcd (Found): C 67.06 (67.10), H 4.38 (4.40), N8.69 (8.700), S 9.95 (9.85).

3-(2-Furyl)-2-phenyl-4-(1,3-thiazol-2-yl)cyclobutanone (4h). Yield 77%. Mp = 110°C. MS (FAB < 0, DMSO/MNBA): Calcd for $[M]^+$ $C_{16}H_{12}N_2O_2S$: 296 (100%), $[M+H]^+$ (m/z) = 297 (23.5%). Elemental analysis for $C_{16}H_{12}N_2O_2S$ Calcd (Found): C 64.85 (64.90), H4.08 (4.10), N9.45 (9.40), S 10.82 (10.80).

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18. Note: The PETRA molecular properties calculations program is freely available online at the following site: http://www2.chemie-unierlangen.de/services/.
19. Note: The OSIRIS Property Explorer shown in this page is an integral part of Actelion's in-house substance registration system. It lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and color-coded. Properties with high risks of undesired effects such as mutagenicity or poor intestinal absorption are shown in red, whereas a green color indicates drug-conform behavior. http://www.organic-chemistry.org/prog/peo/
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