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Microwave Mediated Cyclocondensation of 2-aminothiazole into β-lactam Derivatives: Virtual Screening and In Vitro Antimicrobial Activity with Various Microorganisms

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Abstract: The efficient and rapid synthesis of novel N-thiazole, 3-phenyl, 4-substituted phenyl azetidin-2-ones **4 (a–h)** has been established in good yields starting from 2-aminothiazole **1.** In the first step, schiff's bases **3 (a-h)** were prepared by the condensation of 2-aminothiazole **I** with different aryl aldehydes **2 (a-h)**. Finally, monocyclic β –Lactams i.e. substituted azetidinones **4 (a-h)** were the products obtained by the dehydrative cyclocondensation of **3 (a-h)** with phenyl acetyl chloride in dioxane in the presence of triethylamine. Both microwave and conventional condensation were carried out in dioxane as a solvent in the presence of triethylamine. The microwave synthesis route afforded better yield with shorter reaction time. The novel heterocycles were characterized by elemental analysis and spectral features. All the compounds were screened practically using POM model. 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).The antibacterial screening data shows that the compounds **4a**, **4g** and **4h** are highly active against the used strains.
Keywords: β-Lactams, Microwave, Phosphorus oxychloride, Schiff's bases, POM, Antibacterial.

Introduction

Pharmacologically, 2-aminothiazoles are among the most important classes of organic compounds. These compounds possess versatile type of biological activities; some of these are well known for their anti-inflammatory activities such as Fentiazac[1] and Meloxicam,[2] while compounds like Nizatidine possess anti-ulcer activity.[3]Some of 2-aminothiazoline der4at4es are known for their inhibition of kinurenine-3-hydroxylase[4] and cyclin-dependent kinase enzymes.[5]
2-Azetidinones, commonly known as β-lactams, are well-known heterocyclic compounds among organic and medicinal chemists. The activity of the famous antibiotics such as penicillins, cephalosporins and carbapenems are attributed to the presence of 2-azetidinone ring in them. Recently, some other types of biological activity besides the antibacterial activity have been reported in compounds containing 2-azetidinone ring.[6,7] Such biological activities include antifungal, antitubercular, antitumor, cholesterol absorption inhibition and enzyme inhibition activity. The β-lactams also serve as synthons for many biologically important classes of organic Compounds.[8] Due to this, the chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists for further research.
Microwave-induced organic reaction enhancement (MORE) has gained popularity as a non-conventional technique for rapid organic synthesis[9] in the last few years and many researchers have described accelerated reaction rates, with a large number of papers that have appeared proving the synthetic utility of MORE chemistry in day to day organic synthesis.[10,11] It can be termed as 'e-chemistry' because it is easy, effective, economical, and eco-friendly, and is believed to be a step toward achieving green chemistry objectives. Within the framework of 'Green Chemistry' we have now developed an environmentally benign and novel approach for the synthesis of azetidine-2-ones.

In view of the above versatility in synthetic method as a part of our research [12,13] and with a view to further assess the pharmacological profile of this class of compounds, it was thought worthwhile to synthesize some new congeners of β-lactam heterocycles by incorporating the 2-aminothiazole and azetidinone moieties in a single molecular framework. Thus, herein we are reporting a simple, novel and environmentally benign approach using facile, microwave synthesis of 2-azetidinones **4 (a–h)** from precursors **3 (a–h)** and phenyl acetyl chloride using triethylamine. The research work is scanned in **Scheme 1**.

Experimental

General

The solvents and reagents used in the synthetic work were of analytical grade obtained from Qualigens India and were purified by distillation or crystallization where necessary and 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 Perkin Elmer FT-NMR Cryo-magnet Spectrometer 400 MHz (Bruker) instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as a solvent. Chemical shifts are g4en in parts per million (ppm). Infrared spectra were recorded on Schimadzu-IR Prestige 21. Mass spectra were recorded on a Waters Micromass Q-T of Micro spectrometer. The reactions were monitored and the purity of products was checked out on pre-coated TLC plates (Silica gel 60 F254, Merck), visualizing the spots under ultraviolet light and iodine chamber. The microwave assisted reactions are carried out using KENSTAR-OM-20DSP, 2450 MHz), wherein this unit, microwaves are generated by magnetron at a frequency of 2450 MHz having an output energy range of 100–500 W. The antimicrobial screening was carried out at Department of Microbiology, Nagpur University, Nagpur.

General procedure for the conventional synthesis of N-substituted arylidinethiazol-2-amine 3 (a-h) (schiff's bases):

2-hydroxy benzaldehyde **3 a** (0.01 M) in absolute ethanol (10 ml) was added to a stirred ethanol solution (20 ml) of 2-aminothiazole **1** (0.01 M) and the mixture was refluxed for 1 hr. Chilled water was added until a slight cloudiness was persisted in the reaction solution. The reaction mixture was then set aside to cool. The oily layer which was separated out was induced to crystallize by rubbing with a glass rod. The resultant solid deposited was collected by filtration and well washed with cold ethanol. Recrystalization was afforded with methanol. The same method was applied for the preparation of Schiff bases **3 (b-h)** by using their respect4e aldehydes, Viz. 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.

General procedure for the Microwave synthesis of N-substituted arylidinethiazol-2-amine 3 (a-h) (schiff's bases):

In a typical preparation, mixture of 2-hydroxy benzaldehyde **3 a** (1.0 mm) and 2-aminothiazole **1** (1.0 mm) in ethanol were taken in a flask capped with funnel placed in a microwave oven and irradiated at 500 watt for 30 seconds. After completion of the reaction (monitored by TLC), the resultant mixture was allowed to attain room temperature. The solvent was removed and residue recrystallized from methanol to afford the schiff's base. The same method was used for the preparation of schiff's bases **3 (b-h)** by using their respective aldehydes, Viz. benzaldehyde, 4-hydoxy benzaldehyde, 2-nitro benzaldehyde, 3-nitro benzaldehyde, 4-methoxy benzaldehyde, 3, 4-dimethoxy benzaldehyde, and furfuraldehyde. The products were obtained in 85-90 % yield.

Convention synthesis of 4-(substituted phenyl)-3-phenyl-1-(thiazol-2-yl)-azetidin-2-one 4 (a-h):

To a stirred solution of schiff's bases **3 (a)** (0.01 M) and triethylamine (0.02 M) in dioxane (50 ml), phenyl acetyl chloride (0.015 M) was added drop wise at 5-10 °C. The mixture was stirred for 8-10 hrs 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 hr. The solid separated out was filtered, dried and recrystalized from ethanol. The purity of the compounds was determined by their melting points and by thin layer chromatography. Other compounds **4 (b–h)** were prepared in the similar way using **3 (b–h)**, respectively. The products were obtained in 60-65% yield.

Microwave synthesis of 4-(substituted phenyl)-3-phenyl-1-(thiazol-2-yl)-azetidin-2-one 4 (a-h):

A mixture of **3 a** (0.01 M) in 30 ml dioxane, phenylacetyl chloride (0.015 M) and triethylamine (0.02 M) was placed in a flask copped with funnel inside a microwave oven and irradiated at 400 W, for 2 min. After completion of the reaction (monitored by TLC), it was then diluted with ice cold water. The solid product formed was filtered, dried, and recrystallized from ethanol, yield 89%, as a yellow solid. Other compounds **4 (b–h)** were prepared in the similar way using **3 (b–h)**, respectively. The products were obtained in 85-95 % yield.

Antibacterial activity

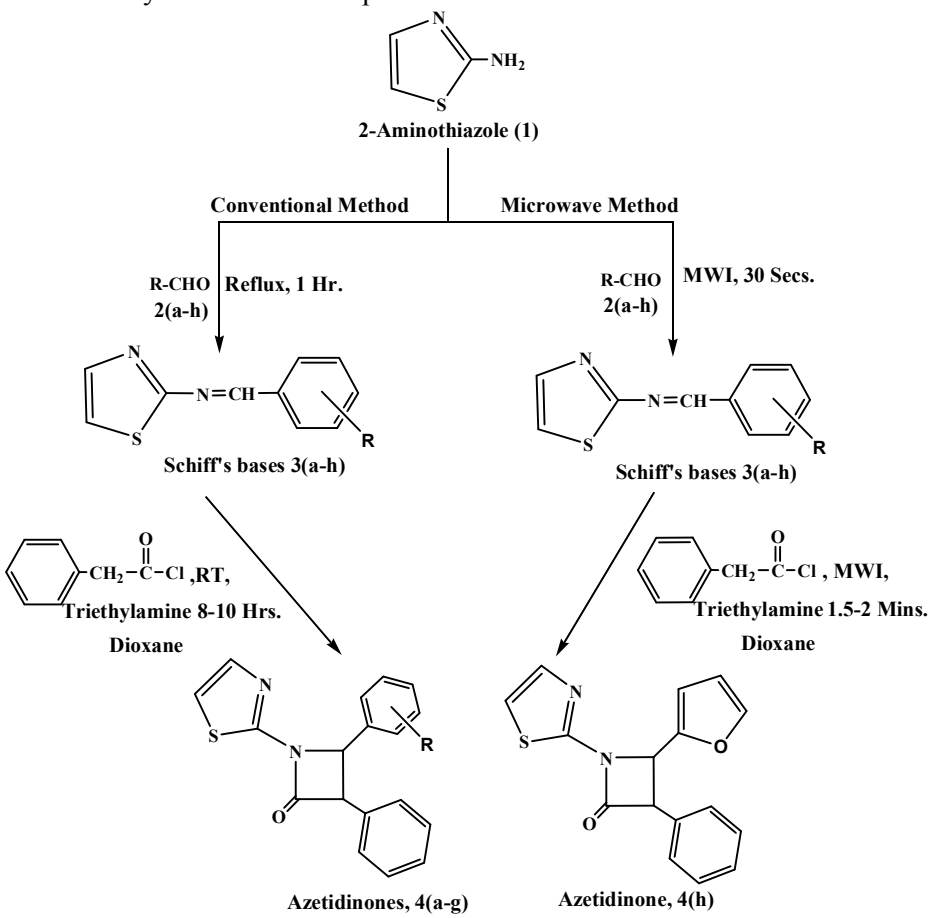
The agar cup plate method using Hi-Media agar medium was employed to study the antibacterial activity of **4(a-h)** against *S. aureus* , *P. vulgaris* , *P. aeruginosa* and *E. coli* . Preparation of nutrient broth,

subculture, base layer medium, agar medium and peptone water was done as per the standard procedure [16]. Each test compound (50 mg) was dissolved in dimethylformamide (50 ml, 1000 µg/ml), which was used as sample solution. Sample size for all the compounds was fixed at 0.1 ml. Using a sterilized cork borer, cups were scooped out of agar medium contained in a petri dish which was previously inoculated with the microorganisms. The test compound solution (0.1 ml) was added in the cups and the petri dishes were subsequently incubated at 37°C for 48 h. Ampicillin and Streptomycin were used as reference drugs and dimethylformamide as a negative control. Zones of inhibition produced by each compound were measured in mm, and the results are listed in **Table 5**.

Results and Discussion

Chemistry

Conventional methodology sometimes has lower yields than microwave protocols. Microwave irradiation facilitates the polarization of the molecule under irradiation causing rapid reaction to occur. A comparat4e study in terms of yield and reaction period is shown in **Table I**. The synthetic route of above mentioned compounds is shown in **Scheme 1**. All the compounds synthesised were adequately characterized by their elemental analysis and IR, ^{1}H-NMR, spectroscopies and by mass spectrometry. The schiff's bases **3 (a-h)** were prepared by general method by refluxing 2-amino thiazole with different aromatic aldehydes .On dehydrat4e cyclocondensation of schiff's bases with phenyl acetyl chloride in the presence of triethylamine respectively afforded azetidinones as shown in **Scheme 1**. The yield of the products found to be around 60-65 %. The authenticity of the products prepared by all the methods was established by TLC, MP, Elemental analysis, ^{1}HNMR, Mass and IR spectroscopy. The ^{1}HNMR showed a Cis orientation of the C-3and 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 constant of 4.5 to 5.2 Hz needed for Cis stereochemistry. The IR spectrum of **4 (a-h)** indicate the presence of β- lactam, > C=O peaks in the range of 1680-1740 cm^{-1}. In **Table 1,** the physical data of the synthesized compounds **4 (a–h)** is reported.



Where R is:

a) H, b) 2-NO2 c) 3-NO2 d) 4-OMe e) 3,4-Di-OMe f) 4-OH g) 2-OH

All the reactions that used microwave irradiation (MWI) were completed within 2 min, whereas similar reactions under conventional method gave poor yields with comparatively longer reaction time period **(Table 1)**, demonstrating that the effect of microwave irradiation is not purely thermal. Microwave irradiation facilitates the polarization of the molecules under irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state. The effect4eness of microwave irradiation and conventional heating for the synthesis of compounds **4 (a–h)** has been compared **(Table 1)**. Under microwave irradiation conditions, the yields of **4 (a–h)** are high (85-95%). Whereas using conventional heating the yields are only 60-65%.

Virtual screenings and molecular properties calculations [14,15]

Petra Calculations

PETRA is a program package comprising various empirical methods for the calculation of physicochemical properties in organic molecules. 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, induct4e effect, resonance effect and delocalization energies and polarizability effect.

The series **4(a-h)** of monocyclic β-lactams have been subjected to delocalised-charge calculations using Petra method of the non-hydrogen common atoms (Figure 1), obtained from the partial pi-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 negat4e charges of the oxygen and nitrogen atoms of 1,3-thiazolyl group and the partial pi positive charges of sulfur and supplementary arm 2-OH contribute posit4ely in favour of an antibacterial activity, more, and this is in good agreement with the mode of antbacterial 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.

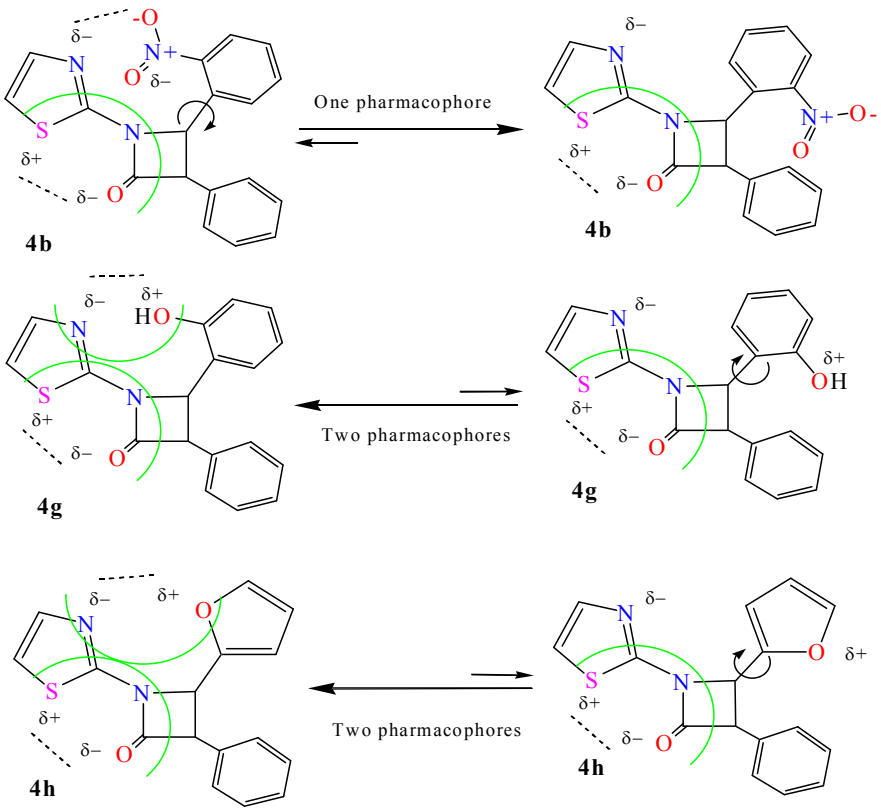


Figure 1. Possible potential antibacterial pharmacophore sites ($X^{\delta-}$---$Y^{\delta+}$) of compound 4(a-h).

Osiris Calculations

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. Inhibition of these or production of unwanted metabolites can result in many adverse drug reactions. Of the most important program, Osiris is already available online.

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 divers synthetic molecules classified in data base of CELERON Company of Swiss, 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

CLogP (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (Table 4). 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. as a sum of fragment contributions. O- and N- centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing 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 4). A number of important points emerge concerning the electronic and steric factors which have direct impact on bioactivity properties. The posit4e 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 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 role 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, so as, the entire 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-lactams can furnish an interesting model for studying the interaction of antibiotics with viral target because the possible charge modification of substituents and O/N/S of pharmacophore groups; (ii) The future flexible pharmacophore site (s) geometric conformation enables us to prepare molecules for multi-therapeutic materials with high selectivity (Figure 4).

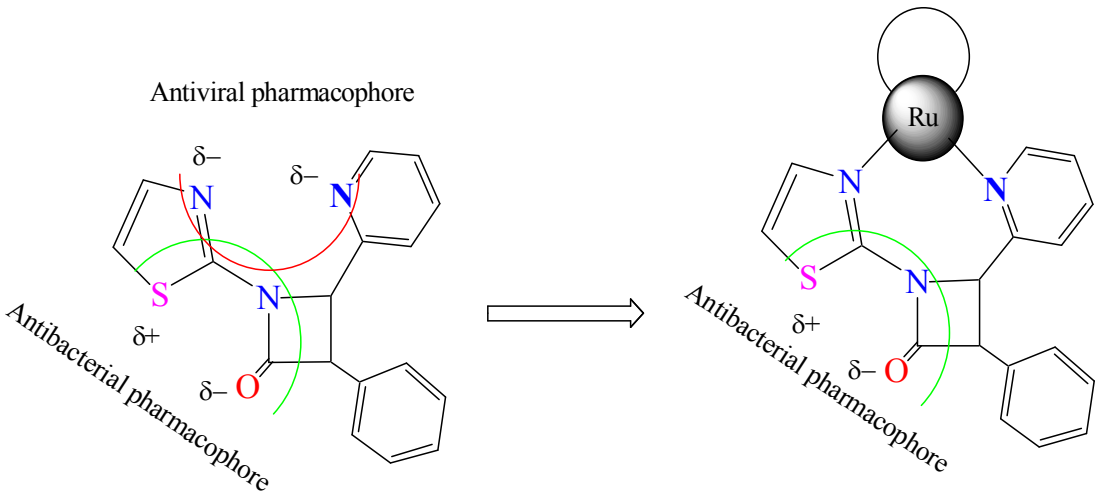


Figure 2. The combinaison of antitubercular and antiviral activities is possible on the basis of β-lactams 4(a-h) skeleton.

Antibacterial screening

The antibacterial activity of the series **4 (a–h)** been carried out against some strain 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 [14]. The prepared compounds were examined against two strains each of gram posit4e and gram negative bacteria. The test results, presented in **Table 5**, suggest that compounds **4a, 4g** and **4h** are highly active against two strains each of gram posit4e and gram negat4e bacteria showing the broadest spectrum of antibacterial activity. The rest of the compounds were found to be moderately act4e, slightly act4e or inact4e 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 act4e to the test bacteria. On the other hand, compounds **4a**, **4g** and **4h** had an activity quite comparable to the commercial antibiotics (Ampicillin and Streptomycin) tested under similar conditions. This activity in compound **4a** 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 **4b**. In compound **4g**, there is disubstituted methoxy group as compared with compound **4f** showing good potency against gram negat4e microorganisms. In compound **4h**, there is presence of furan instead of phenyl as a pharmacophore. As far as molecular masses of these two compounds **4a** and **4h** are concerned, both the compounds have masses around 300 Dalton (322 for **4a** 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.

The spectral data of the synthesized azetidinones **4 (a-h)** compounds are as follows.

2,3-diphenyl-4-(1,3-thiazol-2-yl)cyclobutanone **(4a)**

Yield 89%. Mp = 140 °C. IR (KBr, cm^{-1}): 1740 (β-lactam–CO). ^{1}H-NMR (400 MHz, DMSO-d6) ppm: 7.54 (d, 1H, CH, J = 3.54 Hz), 7.01-7.26 (m, 10H, Aromatic), 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). 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 90% M.p.= 135 °C. IR (KBr, cm^{-1}): 1680 (β-lactam–CO). ^{1}H-NMR (400 MHz, DMSO-d6) ppm : 7.54 (d, 1H, CH, J = 3.54 Hz), 7.01-7.26 (m, 9H, Aromatic), 6.52 (d, 1H, CH, J = 3.54 Hz), 5.18 (d, 1H, CH, J = 4.54 Hz), 4.27 (d, 1H, CH, J = 5.26 Hz). 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 95%. Mp = 120 °C. IR (KBr, cm^{-1}): 1685 (β-lactam–CO). ^{1}H-NMR (400 MHz, DMSO-d6) ppm: 7.54 (d, 1H, CH, J = 3.54 Hz), 7.01-7.26 (m, 9H, Aromatic), 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). 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 92%. Mp = 170 °C. IR (KBr, cm^{-1}): 1720 (β-lactam–CO). ^{1}H-NMR (400 MHz, DMSO-d6) ppm: 7.54 (d, 1H, CH, J = 3.54 Hz), 7.01-7.26 (m, 9H, Aromatic), 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) 3.75 (s, 3H, OCH3). 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 85%. Mp = 150 °C. IR (KBr, cm^{-1}): 1710 (β-lactam–CO). ^{1}H NMR (400 MHz, DMSO-d6) ppm: 7.54 (d, 1H, CH, J = 3.54 Hz), 7.01-7.26 (m, 8H, Aromatic), 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) 3.75 (s, 6H, OCH_3). 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 85%. Mp = 115 °C. IR (KBr, cm^{-1}): 1690 (β-lactam–CO). ^{1}H NMR (400 MHz, DMSO-d6) ppm: 7.54 (d, 1H, CH, J = 3.54 Hz), 7.01-7.26 (m, 9H, Aromatic), 6.52 (d, 1H, CH, J = 3.54 Hz), 5.18 (d, 1H,

CH, J = 4.58 Hz), 12.00 (s, 1H, OH), 4.27 (d, 1H, CH, J = 5.26 Hz). 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), N 8.69 (8.70), S 9.95 (9.90).

***3-(2-hydroxyphenyl)-2-phenyl-4-(1,3-thiazol-2-yl)cyclobutanone* (4g)**

Yield 90%. Mp = 125°C. IR (KBr, cm^{-1}): 1695 (β-lactam–CO). ^1H NMR (400 MHz, DMSO-d6). ppm: 7.54 (d, 1H, CH, J = 3.54 Hz), 7.01-7.26 (m, 9H, Aromatic), 6.52 (d, 1H, CH, J = 3.54 Hz), 5.18 (d, 1H, CH, J = 4.58 Hz), 12.00 (s, 1H, OH), 4.27 (d, 1H, CH, J = 5.26 Hz). 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), N 8.69 (8.700), S 9.95 (9.85).

***3-(2-furyl)-2-phenyl-4-(1,3-thiazol-2-yl)cyclobutanone* (4h)**

Yield 88%. Mp = 110 °C. IR (KBr, cm^{-1}): 1715 (β-lactam–CO). ^1H NMR (400 MHz, DMSO-d6) ppm: 7.54 (d, 1H, CH, J = 3.54 Hz), 7.23 (d, 1H, CH, J = 4.87 Hz), 7.15 (s, 1H, CH); 7.01-7.26 (m, 4H, Aromatic), 6.52 (d, 1H, CH, J = 4.58 Hz), 6.14 (d, 1H, CH, J = 4.87 Hz) , 5.18 (d, 1H, CH, J = 4.58 Hz), 4.27 (d, 1H, CH, J = 5.26 Hz). 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).

Acknowledgement

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Table 1. Comparative study in terms of yield and reaction period for microwave and conventional techniques for 4 (a–h).

Compounds	Microwave Technique		Conventional Technique	
	Time (Min.)	Yield (%)	Time (Hrs.)	Yield (%)
4a	2.0	89	8.0	60
4b	2.0	90	8.5	65
4c	1.5	95	8.0	62
4d	1.5	92	9.0	65
4e	2.0	85	9.0	64
4f	2.0	85	9.5	60
4g	1.5	90	9.5	65
4h	2.0	88	10.0	62

Table 2. Analytical and Spectral data of Compounds 4 (a-h).

Compounds	Molecular Formula	M.P	Color
4a	$C_{18}H_{14}N_2O_2S$	115	Yellow
4b	$C_{18}H_{14}N_2O_2S$	125	Yellow
4c	$C_{18}H_{14}N_2OS$	140	Pale Yellow
4d	$C_{18}H_{13}N_3O_3S$	135	Yellow
4e	$C_{18}H_{13}N_3O_3S$	120	Yellow
4f	$C_{19}H_{16}N_2O_2S$	170	Orange
4g	$C_{20}H_{18}N_2O_3S$	150	Red
4h	$C_{16}H_{12}N_2O_2S$	110	Brown

Table 3. Osiris calculations of compounds 4a-h.

Compd.	Toxicity Risks				Osiris calculations				
	MUT	TUMO	IRRI	REP	MW	CLP	S	DL	D-S
4a					306	3.67	-4.11	-1.67	0.67
4b					351	3.54	-4.57	-2.31	0.29
4c					351	3.54	-4.57	-0.31	0.38
4d					336	3.57	-4.13	5.19	0.72
4e					366	3.46	-4.15	6.66	0.71
4f					322	3.37	-3.81	5.43	0.77
4g					322	3.37	-3.81	4.81	0.76
4h					296	2.77	-3.79	4.89	0.81
AMP					349	-0.04	-1.57	10.72	0.91
STREP					581	-7.83	-0.96	0.83	0.43

AMP : Ampicillin; STREP: Streptomycin; MUT : Mutagenic; TUMO : Tumorogenic; IRRI : Irritant; REP : Reproductive Effective. MW: Molecular Weight in g/mol; CLP: ClogP; S: Solubility; DL: Drug-Likness; D-S: Drug-Score.

Table 4. Molinspiration calculations of compounds 4a-h.

Compd.	Molinspiration calculations						Drug-likeness			
	MW g/mol	cLogP	TPSA	OH--NH Interract.	N viol.	Vol.	GPCRL	ICM	KI	NRL
4a	306	3.93	33.20	0	0	268	-0.21	-0.21	-0.47	-1.02
4b	351	3.84	79.02	0	0	291	-0.42	-0.28	-0.64	-0.91
4c	351	3.86	79.02	0	0	291	-0.35	-0.32	-0.55	-1.00
4d	336	3.98	42.43	0	0	293	-0.19	-0.27	-0.44	-0.91
4e	366.	3.57	51.67	0	0	319	-0.18	-0.25	-0.39	-0.86
4f	322	3.45	53.43	1	0	322	-0.16	-0.17	-0.42	-0.79
4g	322	3.87	53.43	1	0	276	-0.20	-0.15	-0.55	-0.81
4h	296	3.18	46.34	0	0	250	-0.32	-0.51	-0.80	-1.81
AMP	349	-0.87	112.73	4	0	299	-0.56	-0.55	-0.90	-0.87
STREP	582	-5.35	336	16	3	497	-0.67	-1.15	-0.76	-1.11

AMP : Ampicillin; STREP: Streptomycin ; GPCRL: GPCR ligand; ICM: Ion channel modulator; KI: Kinase inhibitor; NRL: Nuclear receptor ligand.

Table 5. Antibacterial activity of compounds 4 (a-h).

Compounds	Gram Posit4e Bacteria		Gram Negat4e bacteria	
	S.aureus	P.vulgaris	E.coli	P.aeruginosa
Ampicillin	+ + +	+ +	+ +	+ + +
Streptomycin	+ + +	+ + +	+ + +	+ + +
4a	+ + +	+ + +	+ + +	+ + +
4b	+ +	-	++	+ +
4c	+ + +	+ +	-	-
4d	+ +	-	-	+
4e	+ +	-	-	+
4f	+ +	-	-	+
4g	+ + +	-	+ + +	+ + +
4h	+ + +	+ + +	+ + +	+ + +

Key to symbols: Inactive = - (inhibition zone < 5 mm); Slightly active = + (inhibition zone 5-10 mm); Moderately active = + + (inhibition zone 10-15 mm); Highly active = + + + (inhibition zone > 15 mm).

References

1. Lednicer D., Mitscher L. A., George G. I., "Organic Chemistry of Drug Synthesis," Vol. 4, Wiley, New York, 1990, pp. 95-97.
2. Rehman M. Z., Anwar C. J., Ahmad S., Bull. Korean Chem. Soc., 2005, 26, 1771- 1775.
3. Knadler M. P., Bergstrom R. F., Callaghan J. T., Rubin A., Drug Metab. Dispos., 1986, 14, 175-182.
4. Rover S., Cesura M. A., Huguenin P., Szente A., *J. Med. Chem.* 1997, 40, 4378-4385.
5. Kim K. S., Kimball S. D., Misra R. N., Rawlins D. B., Hunt J. T., Xiao H.-Y., Lu S., Qian L., Han W.-C., Shan W., Mitt T., Cai Z.-W., Poss M. A., Zhu H., Sack J. S., Tokarski J. S., Chang C. J., Pavletich N., Kamath A., Humphreys W. G., Marathe P., Bursuker J., Kellar K. A., Roongta U., Batorsky R., Mulheron J. G., Bol D., Fairchild C. R., Lee F. Y., Webster K. R., *J.* Med. Chem. 2002, 45, 3905-3927.
6. Singh, G. S. Mini-Rev. Med. Chem. 2004, 4, 69.
7. Singh, G. S. Mini-Rev. Med. Chem. 2004, 4, 93.
8. Reviews: (a) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswami, D., Govande, V. V.; Shinkre, B. A.; Jayanthi, A. Curr. Med. Chem **11**, (2004), 1889; b) Alcaide, B.; Almendros, P. Curr. Med. Chem. 2004, 11, 1921.
9. (a) Varma, S. Green Chem. 1991, 1, 43; (b) Desai, K. G.; Desai, K. R. J. Sulfur Chem. (Taylor and Francis Groups). 2006, 27, 315.
10. Borah, R.; Kalita, D. J.; Sharma, J. C. Indian J. Chem. 2002, 41B, 1032.
11. Kidwai, M.; Dave, B. Indian J. Chem. 2002, 41B, 2430.
12. Pagadala, R.; Parvez, A.; Jyotsna, M. J. coord. chem. 2009, 62(24), 4009.
13. Parvez, A.; Pagadala R.; Jyotsna, M. J. coord. chem. 2010**,** 62(24), 323.
14. Parvez, A.; Jyotsna, M.; Taibi Ben H. 2009, Manuscript accepted for publication in phosphorus, sulphur, silicon and related elements. (GPSS-2009-0124.R_1).
15. Parvez, A.; Jyotsna, M.; Tiwari V. 2010, Manuscript accepted for publication in Green Chemistry letters and reviews. (TGCL-2009-0123).
16. A. L. Barry, The Antimicrobial Susceptibility Test: Principle and Practices, 4th ed., Edited by Illuslea and Feger Philadelphia, 1976, 180–193.

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