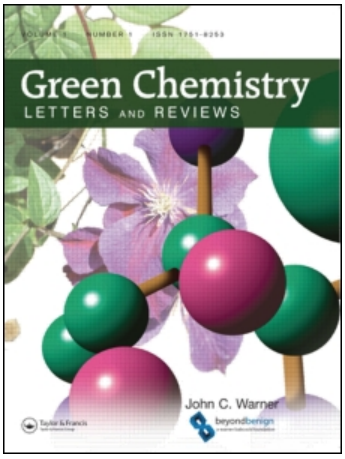

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Zeolite as an efficient and recyclable activation surface for the synthesis of bis-thiazolidinones: theoretical screening owing to experimental biology

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RESEARCH LETTER

Zeolite as an efficient and recyclable activation surface for the synthesis of bis-thiazolidinones: theoretical screening owing to experimental biology

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Zeolite 5Å has been used as an efficient and cost effective activating catalyst for the synthesis of bis-thiazolidinones **4 (a–h)** starting from bis-imines **3 (a–h)** and thioacetic acid. The reactions were performed under microwave irradiation in solventless condition. The catalyst was recycled and used for several times. This reaction is scalable to multigram scale and the methodology has resulted in an efficient synthesis. A benign, environmentally friendly, efficient, and extremely fast procedure for synthesis of bis-thiazolidinones has been demonstrated. The produced bis-thiazolidinone molecules were characterized on the basis of elemental analysis, IR, mass, and ^{1}H-NMR spectral data. The synthesized moieties were screened virtually using some of bioinformatical softwares and discussed.

Keywords: zeolite; bis-thiazolidinones; solventless; virtual screening

Introduction

Thiazolidinone derivatives are a traditionally known class of biologically active compounds. Thiazolidinones and their derivatives are an important class of heterocyclic compounds because of their broad biological activities, such as COX-1 inhibition (*1*), anti-inflammatory (*2*), antiproliferative (*3,4*), antihistaminic (*5*), and anti-HIV activities (*6,7*). Numerous reports have appeared in the literature, which highlight their chemistry and use. In recent years, several new methods for the preparation of thiazolidinone derivatives and reactions have been reported in the literature. Recently, Wang et al. (*8*) and Desai and Desai (*9*) reported the facile microwave-enhanced synthesis of thiazolidinones using $ZnCl_2$ in dimethylformamide (DMF). However, these reactions suffered from drawbacks such as longer reaction times, the use of high boiling solvents, low yields, and use of reactants with high toxicity, which limit their use for the synthesis of complex molecules. Thus, a simple, solvent-less, cost effective, and efficient approach for the synthesis of functionalized 4-thiazolidinone is our interest. A combination of the mineral supported and microwave irradiation has been used to carry out a wide range of reactions under solvent-free conditions (*10–12*). Synthesis of organic compounds under solvent-free conditions, especially adapted to microwave irradiation, leads to increased safety and environmental aspects (*13*). For this purpose, heterogeneous catalysis plays a fundamental role, mainly due to its economic and environmental advantages (i.e. minimum execution time, low corrosion, waste minimization, recycling of the catalyst, easy transport and disposal of catalysts) (*14*). Of course the combination of heterogeneous catalysis with the use of solvent-less conditions under microwaves represents a suitable way toward the so-called ideal synthesis (*15*). In conventional methodology the yield is sometimes lower than in microwave protocols. Microwave irradiation facilitates the polarization of the molecule under irradiation causing rapid reaction to occur, increases the yield and so-called atom economy. Thus, to eliminate all the discussed drawbacks, an efficient and extremely fast procedure for the synthesis of 4-thiazolidinones **4 (a–h)** by the reaction of bis-imine **3 (a–h)** with thioglycolic acid in the presence of zeolite 5Å as an activator under microwave irradiation has been demonstrated. The high synthetic utility and pharmacological importance of thiazolidinones family have prompted us to conduct a pharmacological study of the antibacterial activity of the compounds **3 (a–h)** (Scheme 1). Herein, we performed an investigation of compounds **3 (a–h)** because they represent an attractive model for a theoretical and experimental study of the pharmacophore and their medical applications because of the large variability and combination in their substituents. The main interesting tasks of this work were (1) to develop robust synthetic protocol for the heterocycles;

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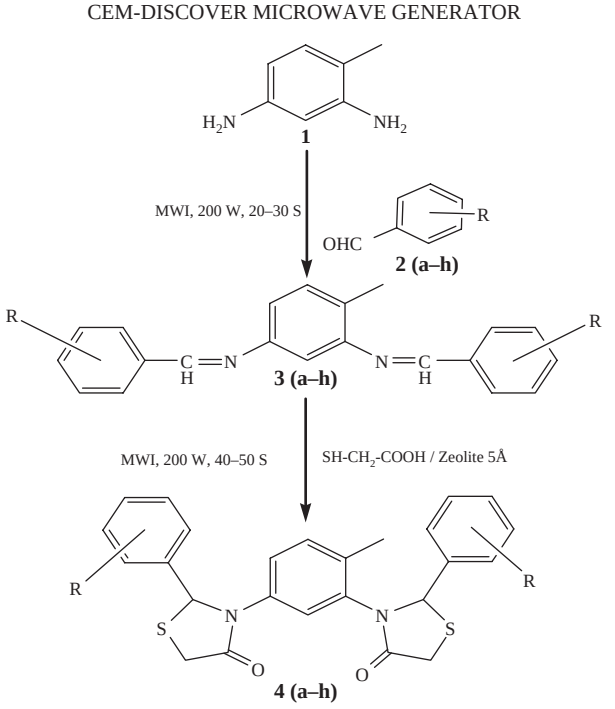

Scheme 1. Schematic representation of zeolite-catalysed microwave production of bis-thiazolidinones.

(2) to interpret the calculated/predicted results for designing of new compounds; (3) to perform docking or pharmacophore modeling based on structures to support the lead optimization process; and (4) to find the right molecule for the right target.

Results and discussion

Recently, there has been a growing interest in the use of inorganic solid acids in organic synthesis (*16,17*). Solid acids, compared to liquid acids, have many advantages, such as simplicity in handling and environmental protection (*18*). Among the reported solid acids, zeolites have attracted an increasing attention because of their availability, suitable acidity, and thermal stability. The use of zeolites also reveals some features, such as reduction in the thermal degradation, better selectivity, and easy work-up after reaction. There is no previous report on the synthesis of bis-thiazolidinones that occurs without force conditions. Zeolite 5Å is an aluminosilicate mineral having a three-dimensional interconnecting network of silica and alumina tetrahedra. Its chemical formula is 0.80 CaO: 0.20 Na_2O: 1 Al_2O_3: 2.0 ± 0.1 SiO_2: XH_2O and it has the calcium form of the type A crystal structure. The pore size of 5Å zeolite is about 5Å. It can absorb all kinds of molecules smaller than this size (*19*). The high silica content yields high chemical resistance. It is stable until 500–600°C. It can absorb small molecules, such as water, hydrochloric acid, ammonia, methanol, or hydrogen sulfide. It has several advantages, including being environmentally friendly, non-toxic, inexpensive, recoverable, and reusable. Therefore, we decided to explore its suitability in heterocyclization reaction. Our synthetic approach is very clear. First, Schiff's bases *N*,*N*′-bis(substituted benzilidine)-toluene-2,4-diamine were prepared from the reaction of toluene-2,4-diamine and different aromatic aldehydes using a reported method by MORE technique (*20,21*). Finally, bis-imines on heterocyclization with mercaptoacetic acid using zeolite 5Å under microwaves produced bis-thiazolidinones as shown in Scheme 1.

In all experiments, two starting materials, i.e. bis-imine, mercaptoacetic acid, (molar ratio 1:1), and zeolite 5Å (0.100 g), were irradiated under microwave irradiation. After each reaction, the catalyst was recycled and used for the next reactions without any activity loss. The method is very easy and can be used for synthesis of different thiazolidinones **4 (a–h)** depending on different substituted groups. The most important and salient feature of the present reaction is scalability and the recyclability of the catalyst. It was observed that the catalyst could be reused at least seven times. The use of the recycled catalyst in the reaction had no effect either on the yield of the product or the quality of the product. Moreover, no side products were observed in these reactions. Furthermore, the reaction can be scaled up to a multigram scale. Structural features of the synthesized azomethine and thiazolidinones were obtained from FTIR, elemental analysis, ^{1}H-NMR, and mass spectral studies.

In the IR spectra of the *N*,*N*′-bis(substituted benzilidine)-toluene-2,4-diamine, the characteristic absorption around 1620–1750 cm^{-1} is assigned to ($-C=N$) azomethine linkages and to ($-C=O$) carbonyl functionality, respectively. But, the fact that stretching frequencies for $-C=N$ groups were absent in the spectra of the bis-thiazolidinones confirmed the heterocyclization. The ^{1}H-NMR spectrum of the *N*,*N*′-bis(substituted benzilidine)-toluene-2,4-diamine in duetarated dimethylsulphoxide (DMSO-d_6) at room temperature using tetramethylsilane (TMS) as an internal standard showed the following signals: the Ar–CH_3 proton around 2.3 ppm (s, 3H), $-CH=N-$ around 9.6 ppm (s, 1H), and phenyl as multiplet around 6.7–7.2 ppm (m, 11H). One singlet around 5.50 ppm which account for one methylene protons on each S–C–H in the spectra of bis-thiazolidinones, confirmed the cyclization. Mass spectrum of **3b** and **4b** showed a molecular ion at 330 and 478 (M^+), confirms the molecular formula $C_{21}H_{18}N_2O_2$ and $C_{25}H_{22}N_2O_4S_2$, respectively. The other signals and peaks of ^{1}H-NMR and IR are in complete agreement with the assigned structures, and are listed in the "Experimental" section.

Virtual screenings and molecular properties calculations using Molinspiration

*C*Log*P*, octanol/water partition coefficient, was calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (Tables 1 and 2). The method is used to process practically all organic and most organometallic molecules. The total 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. The polar surface area (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, as it is the surface sum over all polar atoms (usually oxygen and nitrogen), including attached hydrogen. Prediction results of compounds **4 (a–h)** molecular properties are shown in Table 2.

It is clear from the tabular data that the compounds **4c** and **4d** are having good PSA values comparable with ampicillin. The method for calculation of molecule volume developed at Molinspiration is based on group contributions and the values obtained in our case for streptomycin are in good agreement. Druglikeness is a complex balance of various molecular properties and structural features, which determine whether a particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size, and flexibility and presence of various pharmacophoric features, influence the behavior of molecules in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability, and many others. It is predicted that the negative charges of the oxygen and nitrogen atoms of the thiazolidinone group and the partial pi positive charges of sulfur and the supplementary arm 2-OH contribute positively in favor of an antibacterial activity. It was hypothesized that the difference in charges between two heteroatoms of the same pharmacophore site 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. Expert system for calculation of druglikeness score toward GPCRLs, ICMs, kinase inhibitors, nuclear receptor ligands, and protease inhibitors based on Molinspiration technology has been tested. The results of which are tabulated in Table 2 and are in good agreement with the reference drugs used.

Table 2. Druglikeness of compounds **4 (a–h)** (*22*).

Compound	GPCRL	ICM	KI	NRL
4a	−0.30	−0.27	−0.72	−0.57
4b	−0.49	−0.62	−0.84	−0.65
4c	−0.41	−0.59	−0.81	−0.74
4d	−0.49	−0.62	−0.84	−0.65
4e	−0.33	−0.29	−0.74	−0.75
4f	−0.35	−0.34	−0.76	−0.78
4g	−0.31	−0.43	−0.71	−0.64
4h	−0.29	−0.51	−0.70	−0.64
AMP	−0.56	−0.55	−0.90	−0.87
STREP	−0.67	−1.15	−0.76	−1.11

Notes: AMP, ampicillin; STREP, streptomycin; GPCRL, G protein coupled receptors ligand; ICM, ion channel modulator; KI, kinase inhibitor; and NRL, nuclear receptor ligand.

Experimental

General

All reagents, solvents, and catalyst are analytical grade from a commercial source and used directly. All the melting points were determined in Sonar scientific melting point apparatus and are uncorrected. Potential antibacterial pharmacophore site of compound **4b**

Table 1. Molinspiration calculations of compounds **4 (a–h)** (*22*).

Compound	*C*log*P*	Molecular weight (g/mole)	TPSA (Å)	OH–NH interaction	*N* Violation.	Volume (ml/kg)
4a	4.11	478.59	81.07	2	0	404.82
4b	4.95	478.59	81.07	2	0	404.82
4c	4.89	536.59	132.26	0	1	435.35
4d	4.94	536.59	132.26	0	1	435.35
4e	6.42	515.48	40.610	0	2	415.86
4f	6.49	515.48	40.610	0	2	415.86
4g	5.18	506.64	59.08	0	2	439.88
4h	5.07	446.59	40.61	0	2	480.60
AMP	−0.87	349.00	112.73	4	0	299.00
STREP	−5.35	582.00	336	16	3	497.00

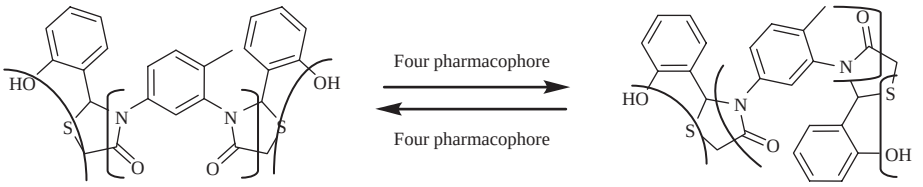

Figure 1. Possible potential antibacterial pharmacophore sites of compound **4b**.

is shown in Figure 1. The purity of compounds was checked routinely by thin layer chromatography (TLC) (0.5 mm thickness) using silica gel-G coated Al-plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. IR spectra (υ_{max} in cm^{-1}) were recorded on a Shimadzu FTIR 8300 spectrophotometer using KBr technique; ^{1}H-NMR spectra on a Bruker WM 400 MHz NMR instrument using $CDCl_3$ and DMSO-d_6 as solvent and TMS as internal reference (chemical shifts in Δ ppm); and mass spectra on a Jeol JMS D-300 spectrometer operating at 75 eV. The elemental analysis (C, H, N, and S) of compounds was performed on Carlo Erba-1108 elemental analyzer. The results were found to be in good agreement with the calculated values. The microwave assisted reactions are carried out in a 'CEM Discover' manufactured by CEM Technologies Corporation. In this unit, microwaves are generated by magnetron at a frequency of 2450 MHz having an output energy range of 100–500 W. Before each reaction, same zeolite 5Å was dried at 120°C and reutilized.

Synthesis

Microwave mediated general synthesis of N,N′-bis(substituted benzilidine)-toluene-2,4-diamines ***3 (a–h)***

N,N′-bis(salicylidine)-toluene-2,4-diamine was obtained by condensation of toluene-2,4-diamine and salicylaldehyde. In a typical solvent-less preparation, a mixture of diamine (**1**) (2.46 mmol, 1.5 g) and salicylaldehyde (4.92 mmol, 3.0 g) without solvent was taken in a flask capped with a funnel placed in a microwave oven and irradiated at 200 W for 20 seconds. The reaction was monitored by TLC. After completion of the reaction, the resultant mixture was allowed to attain the room temperature. After cooling, the resultant solid was crushed, washed with cold ethanol, filtered, and dried under vacuum to give the crude product. The crude product was recrystallized from methanol. Same method was followed for the production of other bis-imines.

Yield. 95%. M.P. 120°C. ^{1}H-NMR (ppm, $CDCl_3$-d_6): 2.3 (s, 3H, $-CH_3$), 9.6 (s, 2H, $-CH=N$), 6.7–7.2 (m, 11H, C_6H_5), and 13.3 (s, 2H, $-OH$). MS (*m*/*z*) 330 (100%) and 331 (10%). Analysis calculated for $C_{21}H_{18}N_2O_2$: C, 76.30; H, 5.40; N, 8.45; and O, 10%. Found: C, 76.33; H, 5.45; N, 8.48; and O, 9.69%. IR (cm^{-1}, KBr): 1618 ($-C=N$), 1750 ($-C=O$), and 3200 ($-OH$).

Microwave mediated zeolite catalyzed general synthesis of 2-substituted phenyl-3-(3-(2-substituted-phenyl-4-oxothiazolidin-3-yl)phenyl)thiazolidin-4-ones ***4 (a–h)***

A mixture of *N,N′*-bis(salicylidine)toluene-2,4-diamine **(3b)** (3.23 mmol, 1.0 g), $SHCH_2COOH$ (thioaceticacid) (3.23 mmol, 0.30 g), and zeolite 5Å (0.10 g) was taken in a conical flask capped with a funnel placed in a microwave oven and irradiated (400 W) for 40–50 seconds. The reaction was monitored by TLC. After completion of reaction, the pasty solid obtained was allowed to cool. To that, 15 ml acetone was added and stirred for 5 minutes up to the dissolution of the pasty solid. The zeolite was filtered out of the mother liquor for the other reaction. The mother liquor was poured into the crushed ice and the pH of the solution was set to 10 by 10% $NaHCO_3$ solution. The reaction mass was then stirred, filtered, and washed with cold water. The crude product was recrystallized from methanol. Same process was used for the production of other thiazolidinones.

Yield. 92%. M.P. 140°C. ^{1}H-NMR (ppm, DMSO-d_6): 2.4 (s, 3H, $-CH_3$), 3.59 (s, 4H, -CH_2-thiazolidinone), 5.50 (S, 2H, –S–C–H), 6.5–7.6 (m, 11H, C_6H_5), and 13.10 (s, 2H, –OH). MS (*m*/*z*) 478.1 (100%) and 479.1 (49.0%). Analysis calculated for $C_{25}H_{22}N_2O_4S_2$: C, 62.74; H, 4.63; N, 5.85; O, 13.37; and S, 13.40%. Found: C, 62.80; H, 4.78; N, 5.80; O, 13.74; and S, 13.49%. IR (cm^{-1}, KBr): 1295 (–C=O), 740, (C–S–C), and 3250 (–OH).

2-(4-hydroxyphenyl)-3-(3-(2-4-hydroxy phenyl)-4-oxothiazolin-3-yl)-4-methylphenyl-thiazolidine-4-one ***(4a)***

Yield. 94%. M.P. 135°C. ^{1}H-NMR (ppm, DMSO-d_6): 2.45 (s, 3H, $-CH_3$), 3.60 (s, 4H, -CH_2-thiazolidinone), 5.49 (S, 2H, –S–C–H), 6.50–7.65 (m, 11H, C_6H_5), and 13.51 (s, 2H, $-OH$). MS (*m*/*z*) 478.1 (100%) and 479.1 (52%). Analysis calculated for $C_{25}H_{22}N_2O_4S_2$: C, 62.74; H, 4.63; N, 5.85; O, 13.37; and S, 13.40%. Found: C, 62.81; H, 4.78; N, 5.75;

O, 13.34; and S, 13.45%. IR (cm^{-1}, KBr): 1755 (−C = O), 745 (C–S–C), and 3300 (Ar–OH).

*2-(2-nitrophenyl)-3-(3-(2-2-nitrophenyl)-4-oxothiazolin-3-yl)-4-methylphenyl-thiazollidine-4-one (**4c**)*
Yield. 95%. M.P. 150°C. ^{1}H-NMR (ppm, DMSO-d_6): 2.50 (s, 3H, $-CH_3$), 3.65 (s, 4H, -CH_2-thiazolidinone), 5.45 (S, 2H, −S–C–H), and 6.55–7.80 (m, 11H, C_6H_5). MS (*m*/*z*) 536.1 (100%) and 537.1 (54%). Analysis calculated for $C_{25}H_{20}N_4O_6S_2$: C, 55.96; H, 3.76; N, 10.44; O, 17.89; and S, 11.95%. Found: C, 55.89; H, 3.78; N, 10.45; O, 17.84; and S, 11.85%. IR (cm^{-1}, KBr): 1760 (−C = O), 748, (C–S–C), and 1340 (Ar–NO_2).

*2-(3-nitrophenyl)-3-(3-(2-3-nitrophenyl)-4-oxothiazolin-3-yl)-4-methylphenyl-thiazolidine-4-one (**4d**)*
Yield. 89%. M.P. 155°C. ^{1}H-NMR (ppm, DMSO-d_6): 2.55 (s, 3H, $-CH_3$), 3.65 (s, 4H, -CH_2-thiazolidinone), 5.48 (S, 2H, −S–C–H), and 6.5–7.8 (m, 11H, C_6H_5). MS (*m*/*z*) 478.1 (100%) and 479.1 (51%). Analysis calculated for $C_{25}H_{20}N_4O_6S_2$: C, 55.96; H, 3.76; N, 10.44; O, 17.89; and S, 11.95%. Found: C, 55.95; H, 3.75; N, 10.45; O, 17.88; and S, 11.95%. IR (cm^{-1}, KBr): 1765 (−C = O), 750, (C–S–C), and 1345 (Ar–NO_2).

*2-(4-chlorophenyl)-3-(3-(2-4-chlorophenyl)-4-oxothiazolin-3-yl)-4-methylphenyl-thiazolidine-4-one (**4e**)*
Yield. 91%. M.P. 130°C. ^{1}H-NMR (ppm, DMSO-d_6): 2.50 (s, 3H, $-CH_3$), 3.60 (s, 4H, -CH_2-thiazolidinone), 5.48 (S, 2H, −S–C–H), and 6.50–7.85 (m, 11H, C_6H_5). MS (*m*/*z*) 514.1 (100%) and 515.1 (56.0%). Analysis calculated for $C_{25}H_{20}Cl_2N_2O_2S_2$: C, 58.25; H, 3.91; N, 5.43; O, 6.21; and S, 12.44%. Found: C, 58.20; H, 3.95; N, 5.45; O, 6.25; and S, 12.45%. IR (cm^{-1}, KBr): 1756 (−C = O), 755, (C–S–C), and 835 (Ar–Cl).

*2-(2-chlorophenyl)-3-(3-(2-2-chlorophenyl)-4-oxothiazolin-3-yl)-4-methylphenyl-thiazolidine-4-one (**4f**)*
Yield. 89%. M.P. 140°C. ^{1}H-NMR (ppm, DMSO-d_6): 2.55 (s, 3H, $-CH_3$), 3.63 (s, 4H, -CH_2-thiazolidinone), 5.44 (S, 2H, −S–C–H), and 6.54–7.81 (m, 11H, C_6H_5). MS (*m*/*z*) 514.1 (100%) and 515.1 (57.0%). Analysis calculated for $C_{25}H_{20}Cl_2N_2O_2S_2$: C, 58.25; H, 3.91; N, 5.43; O, 6.21; and S, 12.44%. Found: C, 58.21; H, 3.93; N, 5.48; O, 6.29; and S, 12.50%. IR (cm^{-1}, KBr): 1760 (–C = O), 755 (C–S–C), and 830 (Ar–Cl).

*2-(4-methoxyphenyl)-3-(3-(2-4-methoxyphenyl)-4-oxothiazolin-3-yl)-4-methylphenyl-thiazolidine-4-one (**4g**)*
Yield. 90%. M.P. 160°C. ^{1}H-NMR (ppm, DMSO-d_6): 2.60 (s, 3H, $-CH_3$), 3.55 (s, 4H, -CH_2-thiazolidinone), 5.50 (S, 2H, −S–C–H), 6.50–7.85 (m, 11H, C_6H_5), and 3.95 (S, 3H, $-OCH_3$). MS (*m*/*z*) 506.1 (100%) and 507.1 (53%). Analysis calculated for $C_{27}H_{26}N_2O_4S_2$: C, 64.01; H, 5.17; N, 5.53; O, 12.63; and S, 12.66%. Found: C, 64.10; H, 5.15; N, 5.55; O, 12.68; and S, 12.65%. IR (cm^{-1}, KBr): 1750 (−C = O), 740, (C–S–C), and 2850 (Ar–OCH_3).

*3-(4-methyl-3-(4-oxo-2-phenylthiazolidin-3-yl)phenyl)-2-phenylthiazolidin-one (**4h**)*
Yield. 96%. M.P. 148°C. ^{1}H-NMR (ppm, DMSO-d_6): 2.45 (s, 3H, $-CH_3$), 3.65 (s, 4H, -CH_2-thiazolidinone), 5.49 (S, 2H, −S–CH), and 6.45–7.55 (m, 13H, C_6H_5). MS (*m*/*z*) 446.1 (100%) and 447.1 (40%). Analysis calculated for $C_{25}H_{22}N_2O_2S_2$: C, 67.24; H, 4.97; N, 6.27; O, 7.17; and S, 14.36%. Found: C, 67.20; H, 4.95; N, 5.45; O, 7.15; and S, 14.45%. IR (cm^{-1}, KBr): 1755 (−C = O) and 740 (C–S–C).

Conclusion

We have developed a zeolite-catalyzed, simple, solvent-free, cost effective, and environmentally benign technique for the synthesis of bis-thiazolidinones. This reaction is scalable to multigram scale. These compounds have been synthesized in high yield by using zeolite 5Å and avoiding the use of any solvent under microwaves. In addition, the catalyst can be recovered by filtration, drying, and utilized at least seven times without lowering its activity. The results of the present theoretical biological investigation support the suggested antibacterial pharmacophore sites of bis-thiazolidinones. It has been suggested that some functional groups present in these compounds displayed the biological activity that may be responsible for the increase of the hydrophobic character and liposolubility of the molecules. This, in turn, enhances the activity of the compounds and biological absorbance, so that the entire synthesized cyclic bis-thiazolidinones containing more than one antibacterial pharmacophore site have good antibacterial properties (**4b, 4f**).

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