Synthesis, characterization and biological activities of substituted 4-(2, 3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepin-4-yl)phenol derivatives

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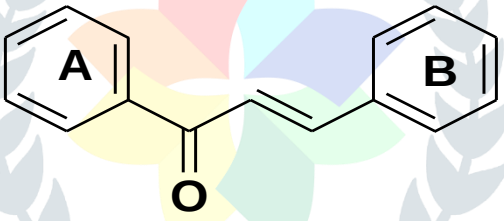
Abstract

Due to the importance of Diazepine and benzodiazepine in Pharmaceutical chemistry and chemical cell biology, their synthesis from various starting materials has been commonly reported. More than different types of target compounds are available. The individual approaches are grouped according to the type of the target compounds are scaffold. Synthesis of 4-(2,3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepin-4-yl)phenol and its derivatives bear functional groups was performed. Structure Determination of synthesized compounds has been made on the basis of the elemental analysis, ^{1}H NMR spectral studies. The antimicrobial activity of the synthesized compound has been studied against the species, Staphylococcus aureus, and Escherichia coli.

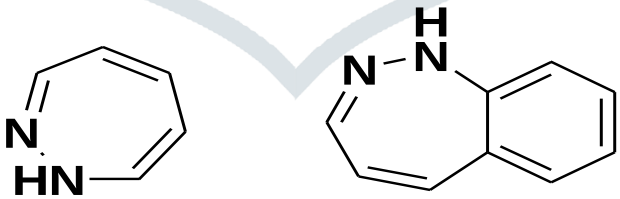
Keywords: Heterocyclic substituted Chalcone derivatives, Diazepine, Antimicrobial activity

1. Introduction

Chalcone, an important intermediate of flavonoid synthetic pathway, It has been shown to exhibit diverse biological and pharmacological activities such as, anti- cancer[1], antioxidant[2], anti-inflammatory[3], antimicrobial[4], anti- allergic[5], anti-HIV[6], and antimalarial properties[7] etc.



Diazepine derivatives are seven membered heterocyclic ring systems with two nitrogen atoms possessing a wide range of medicinal properties. Introduction of substituted group in the diazepine segment is expected to improve and its pharmacological activities



Reducing the use of volatile organic solvents can minimize the generation of waste, which is a requirement of one of the principles of green chemistry [8]. Recently, polyethylene glycol (PEG) has been found to be an interesting solvent system. PEG is an environmentally favourable reaction solvent, it is an inexpensive, potentially recyclable and water soluble, which facilitates its removal from there action. Pyrrole-azepinones [9] represent an interesting structural motif found in a variety of bio-active natural products such as hymenialdisine [10], stevensine, latonduine, and the paullones. In the last decade synthetic hymenialdisine derivatives have emerged as promising therapeutic molecules for the treatment of a range of diseases, including cancer [11]. Due to their biological properties, the synthesis of benzoazepinones has attracted significant interest in recent decades. For some time our laboratory has also been involved in the development of novel catalytic methods for the synthesis of potential bio-active diazepine derivatives. Most of the known activating compounds contain reactive, electrophilic chemical groups that react with cysteine and some nitrogen atom containing residues in the active site of the biological channel [12]. A considerable amount of investigation has been carried out to develop reversible ligands that target organic receptor and several agonists have been under biological and medical evaluation [13]. Recently, a series of compounds containing azepines, and oxazepines that function as extremely strong activators of the human biological and medicinal activities were accepted by literature. The present capacity extends our previous focus of seven-membered nitrogen-containing rings to the parent monocyclic azepines derivatives. It is an authoritative, exhaustive and most welcome contribution to the literature of heterocyclic compounds; Cancer is one of the main

causes of death in the world despite considerable progress in the understanding of its biology and medicinally. The traditional therapeutic strategies for the treatment of this disease are surgery, radiotherapy, immunotherapy [14] and chemotherapy techniques. For the time being, 70% of the patients diagnosed with cancer are cured either through one of these methods or by a combination of them. For some types of disseminated cancers, chemotherapy is the only effective therapy because it distributes anticancer drugs through the circulatory system [15]. They are currently unavailable in a program aimed at synthesizing originality of heterocyclic compounds that inhibit the growth of cancer cells.

2. Experimental details

2.1. Materials and characterization

All reactions were carried out under an argon atmosphere. Chemicals were purchased from Aldrich, Fluka and Acros and unless otherwise noted were used without further purification. All compounds were characterized by ^{1}H NMR, UV, and FTIR spectra techniques.

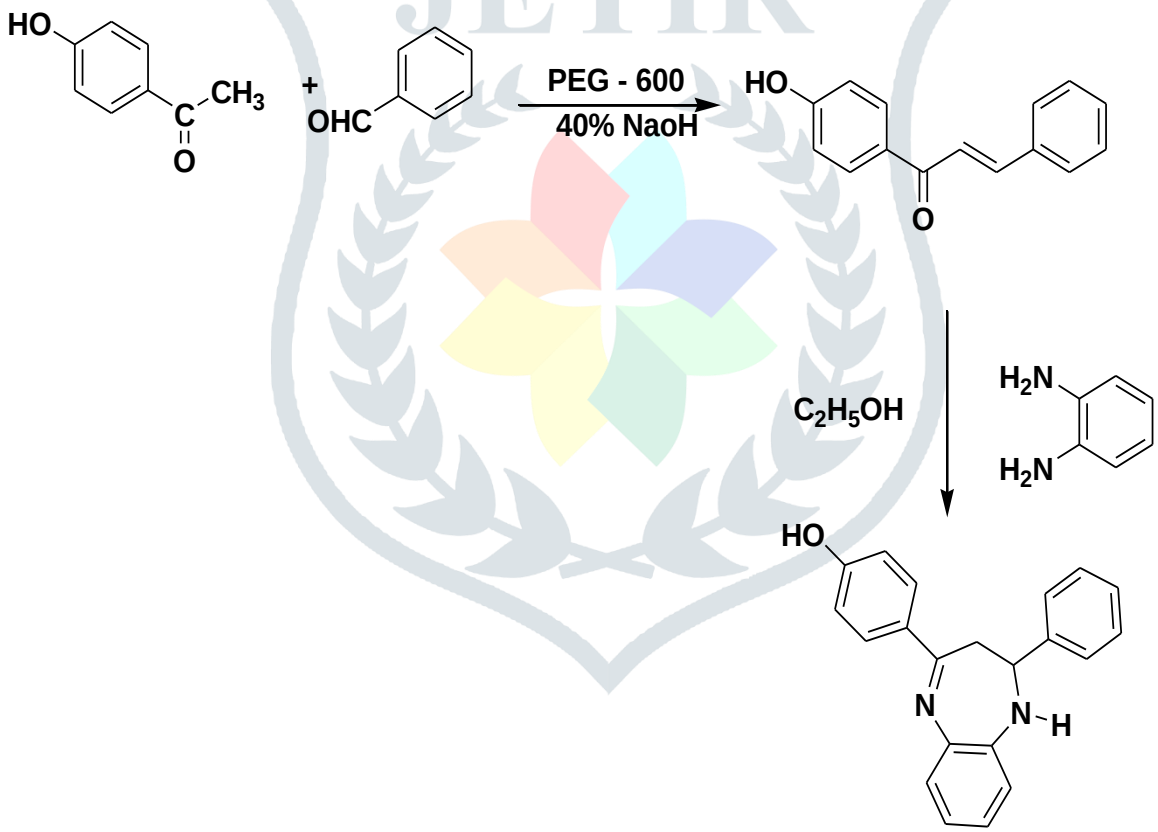
2.2. Synthesis

2.2.1. Step-1: Preparation of 1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one

Equmolar mixture of 4-hydroxyacetophenone and benzaldehyde and NaOH was stirred in PEG-600 at 65^{o}C (15mL) for 1 hour. After completion of the reaction (monitored by TLC), the crude mixture was worked up in ice-cold water (100mL). The product which separated out was filtered. The filtrate was evaporated to remove water leaving PEG behind. The same PEG was utilized to synthesize further chalcones. Synthesised compounds were recrystallized from ethanol to afford pure compound. (Yield – 85% & melting point: 151-153^o C

2.2.2. Step-2: Preparation of 4-(2,3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepin-4-yl)phenol

A mixture of chalcone in 25ml of absolute alcohol, and orthophenylenediamine was refluxed in oil bath at temperature 80-90^{o}C in the presence of piperidine as catalyst for an hour. Then the reaction mixture poured in to ice. The product was separated out and filtered. The separated product purified by column chromatography using 60-120 silica gel mesh size using dichloromethane and methanol as an eluent. Synthesised compounds were recrystallized from ethanol. (Yield – 80% & melting point: 125-127^{o}C. The synthesis scheme is given below,



3. Results and discussion

In the present work, 4-(2, 3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepin-4-yl)phenol and its analogues were synthesized. The Systematic Schemes illustrate the preparation of the target molecules. As a starting material benzaldehyde and substituted acetophenone was used to produce 1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one) and 4-(2,3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepin-4-yl)phenol. Furthermore these two molecules were used for the preparation of the Diazepine derivatives. The structures of the compounds were elucidated by UV, FTIR, ^{1}H NMR and elemental analysis. The UV-Vis spectra of Figs.(1) and (4) shown that C=O stretching 226 and 312 were observed respectively and also CH=CH stretching frequency 314 are observed. The IR spectra were given in Figs. (2) and (5), which showed the absent of the N–H absorption band at 3300 cm^{-1} and presence of the C=O stretching band at 1641 cm–1, whereas in compound (5), the presence of N–H stretching and also C=O stretching band were observed. In the ^{1}H NMR spectra of the compounds Figs.(3) and (6) showed the N-H proton as a doublet at about 4.83 ppm, but it was observed all the compounds. All other aromatic protons were observed at the expected regions in all the synthesized compounds. The screening results revealed that the compounds exhibited moderate to considerable activity when compared with reference standard *Staphylococcus aureus* and *Escherichia coli*. The results of antimicrobial activity indicated that compounds 5 and 6 showed maximum anti-inflammatory activity. Spectral details of (A1) and (A1A) were assigned in Table 1 and 2.

Table 1. Spectral details of 1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (A1)

UV (λ max: nm)	226, 314
FTIR (cm^{-1})	3107 (O-H), 2802 (Aromatic C-H str), 2899 (C-H), 1641 (C=O), 1590 (C=C str), 827 (C-H out plane bending)
^{1}H NMR (ppm)	6.89 - 6.91 (2d, 2H, -CH=CH), 7.4-8.0 (m, 9H, Ar-H),10.417 (s, 1H, Ar-OH)

Table 2. Spectral details of 4-(2,3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepin4-yl)phenol(A1A)

UV(λ max: nm)	312
FTIR (cm^{-1})	3337(O-H), 3100(Aromatic C-H str), 1649(C=N), 2107(-CH_2 bridge),1333(C=C str.), 1280 (C-O str. Strong band, often doublet), 824(N-H bending vib)
^{1}H NMR (ppm)	2.99 to 3.35 (t, 2H, -CH_2), 3.6 to 3.67(m, 1H, CH), 4.83 to 4.84 (d, 1H N-H), 6.87 to 7.89 (m, 13H, Ar-H), 11.11(s, 1H, Ar-OH)

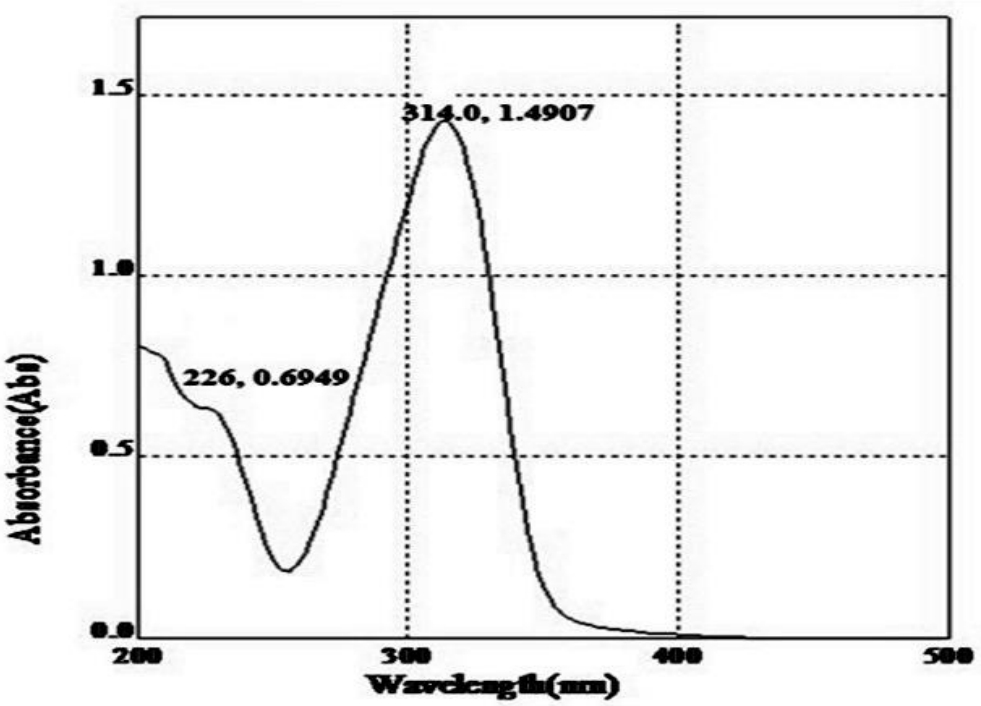


Fig. 1. UV-Vis Spectra of 1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (A1)

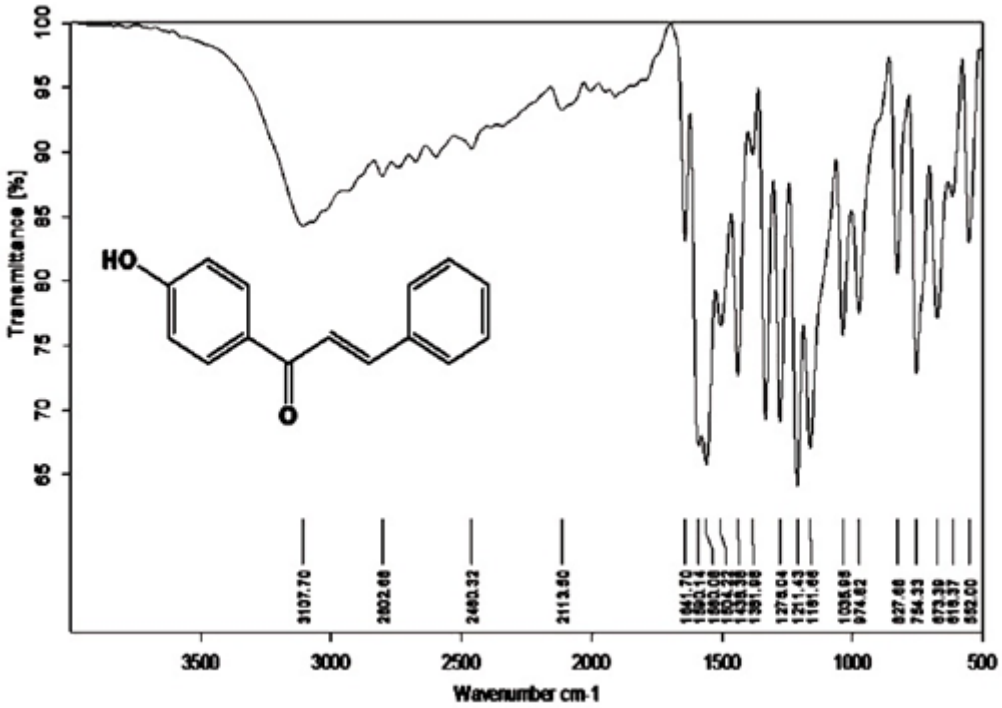


Fig. 2. FT-IR Spectra of 1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (A1)

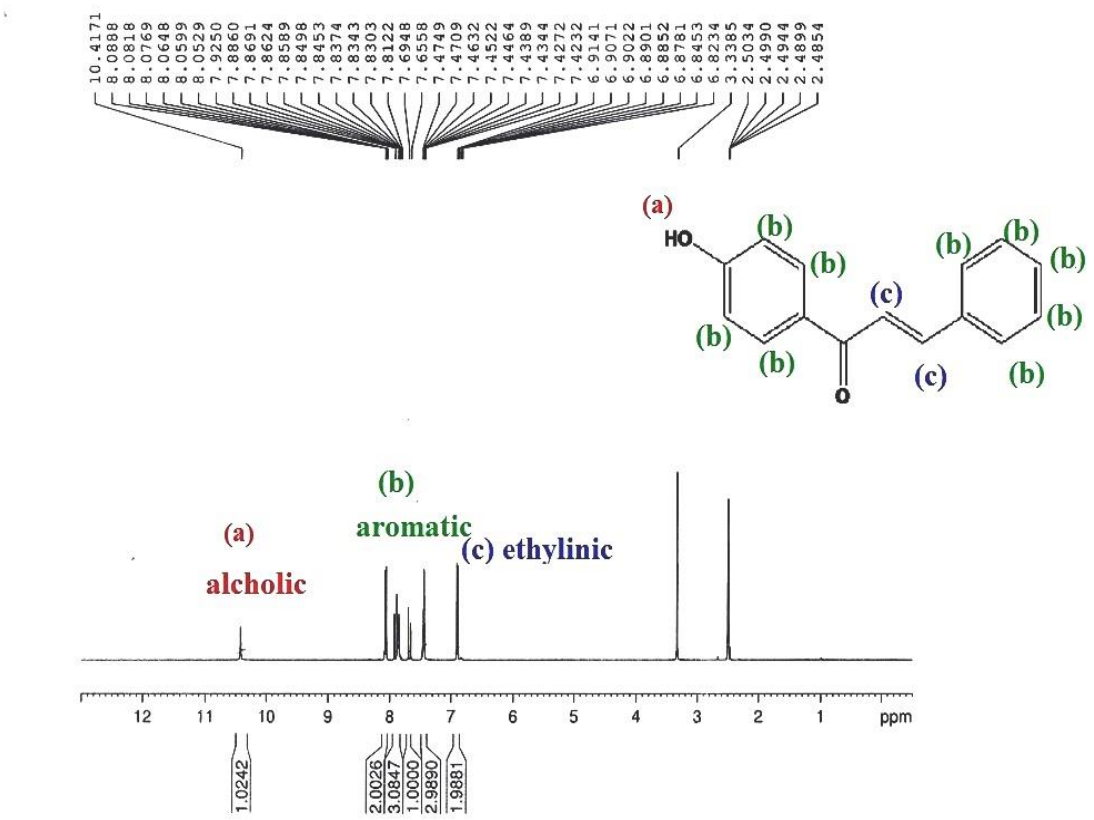


Fig. 3. [1]H NMR Spectra of 1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (A1)

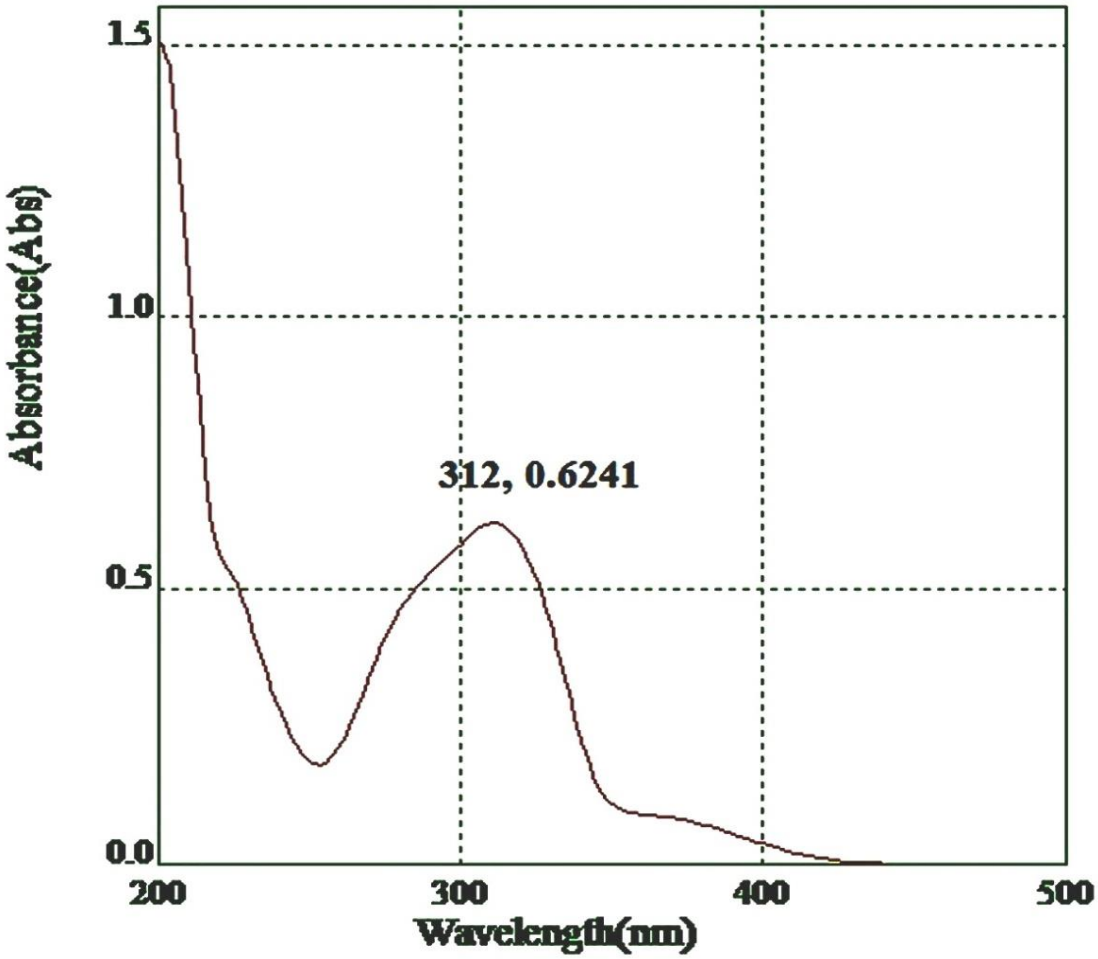


Fig. 4. UV-Vis Spectra of 4-(2,3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepin 4-yl)phenol(A1A)

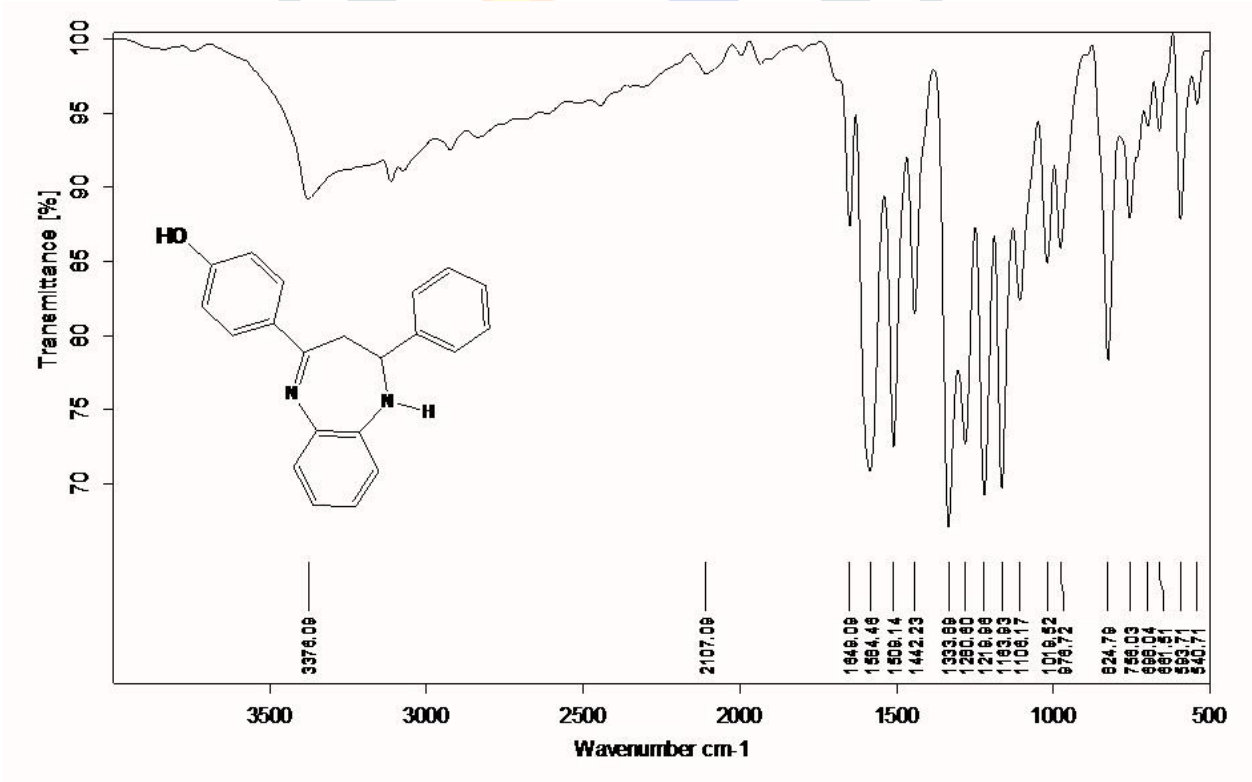


Fig. 5. FT-IR Spectra of 4-(2,3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepin 4-yl)phenol(A1A)

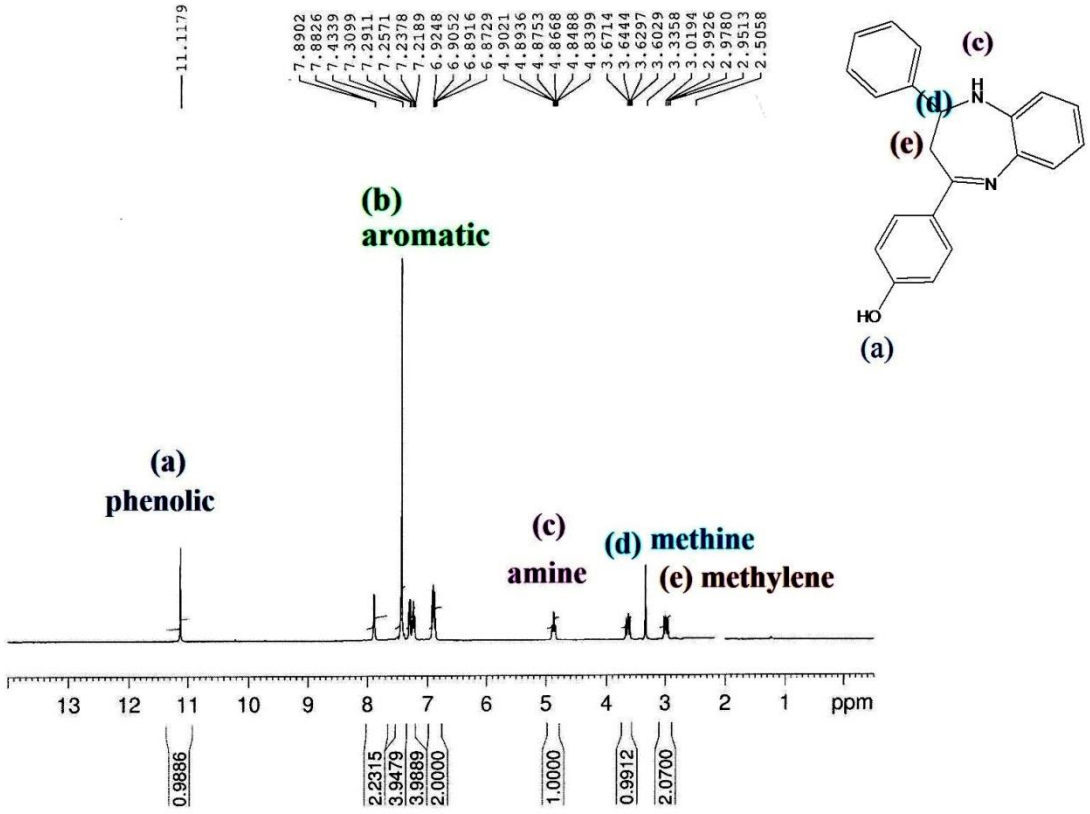


Fig. 6. [1]H NMR Spectra of 4-(2,3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepin4-yl)phenol(A1A)

4. Antimicrobial activity

The minimum inhibitory concentration (MIC), which is considered as the least concentration of the sample which inhibits the visible growth of a microbe was determined by the broth dilution method. From Table 3 and Fig. 7, illustrate the compounds 4 and 5 were adopted for broth dilution method to evaluate the MIC values. Simultaneously, in our work, the microbial activities three substituted chalcones and substituted diazepine derivatives were checked against the two microbes *Staphylococcus aureus and Escherichia coli.* The report of antimicrobial activity clearly shows that, the synthesized compounds of B1 and B1A shows excellent activity towards two tested bacterial strains towards both *Staphylococcus aureus* and *Escherichia coli* with lowest value of 7.81 (µg/mL) respectively, which are shown in Table 3 .

Table 3. The MIC values of synthesized compounds

Compounds	**Staphylococcus aureus (S.a)**	**Escherichia coli (E.c)**
A1	31.25	31.25
A1A	62.50	31.25
B1	31.50	62.50
B1A	7.81	7.81
C1	125	250
C1A	62.50	125

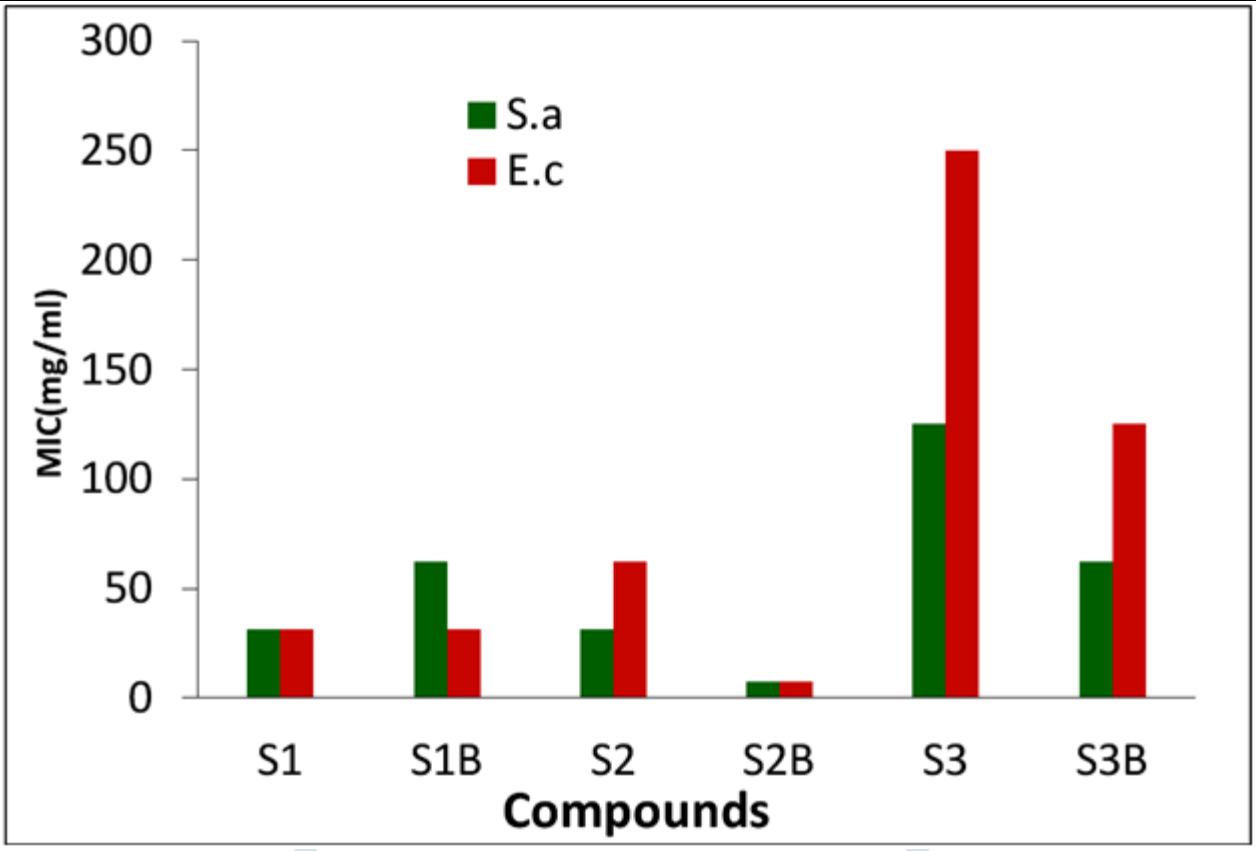


Fig. 7. Bar diagram of MIC values

5. Conclusions

A series of substituted diazepine derivatives were prepared successfully by Claisen-Schmidt condensation using green synthetic approach. Totally six compounds were synthesized successfully. Generally most of the researchers have synthesized chalcones using alcohol as solvent and catalyst like NaOH or KOH. Synthesis of Chalcones by using ethanol or methanol has generated vast organic solvents such as waste and which cannot reuse again. But, in our work the Chalcones have been synthesized using PEG-600 as solvent, which is eco-friendly, non-toxic, inexpensive, potentially recyclable and water soluble. So, Chalcones were synthesized by green chemistry approach in the first step. In the second step, the chalcones were condensed with orthophenylene diamine as per mentioned in the schemes. The chemical structures of the compounds (Compound (A1, A1A, B1, B1A, C1 and C1A) were confirmed by FT-IR, UV-Visible and ^{1}H-NMR spectra and were found to be in agreement with the chemical structures expected. Simultaneously, in our work, the microbial activities three substituted chalcones and substituted diazepine derivatives were checked against the two microbes *Staphylococcus aureus and Escherichia coli.* The report of antimicrobial activity clearly shows that, the synthesized compounds of B1 and B1A shows excellent activity towards two tested bacterial strains towards both *Staphylococcus aureus* and *Escherichia coli* with lowest value of 7.81 (µg/mL) respectively. All other synthesized compounds possess significant activity against tested bacterial strains. Very good activity of the A1 and A1A against *staphylococcus aureus* and *Escherichia coli* is due the presence of heterocyclic compounds in between the two phenyl rings and the presence of hydroxyl group. Hence as the title shows the compounds were synthesized and the microbial activities of those compounds were checked in two suitable microbes successfully.

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