Journal of Chemical Health Risks

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JCHR (2025) 15(3), 144-153 | ISSN:2251-6727

Synthesis, Characterization and its Biological Activity of Novel Bis (Biphenylsulfonylacetamido) Oxacalix[4] Arene Derived from Oxacalixarene

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(Received: 16 March 2025 Revised: 20 April 2025 Accepted: 01 May2025)

KEYWORDS

Oxacalix[4]arene, Anti-cancer activity, Anti-tuberculosis ,Anti-oxidant activity.

ABSTRACT:

Introduction: Supramolecular chemistry involves the study of non-covalent interactions between molecules, enabling the design of complex molecular systems with tailored properties. These interactions, such as hydrogen bonding, electrostatic forces, π-π stacking, and van der Waals forces, allow the formation of supramolecular compounds with unique structural and functional characteristics. These compounds are increasingly being explored for their potential applications in biological systems, as they can mimic natural biomolecular interactions. The dynamic nature of supramolecular assemblies provides opportunities for the development of compounds with enhanced selectivity and efficiency in targeting biological macromolecules, such as enzymes, receptors, and nucleic acids. This research investigates novel supramolecular compounds designed to interact with specific biological targets, offering promising strategies for drug discovery and therapeutic interventions in various diseases.

Objective: This study focused on designing of Oxacalix[4]arene based novel compound and evaluating its anti-tuberculosis ,anti-oxidant and anti-cancer activity.

Methods: Conventional reaction method was used for the synthesis of Bis (biphenylsulfonylacetamido) Oxacalix[4] arene

Compound and H^1 NMR , ESI-MS and IR Spectroscopy was used for the characterization of compound. Anti-tuberculosis activity was performed using Zone Inhibition Method. Anti- oxidant study was assessed using DPPH technique. In-vitro cytotoxicity was assessed on the Hella cell line using the MTT assay.

Result: H^1 NMR , ESI-MS and IR Spectroscopy confers the synthesis of Bis (biphenylsulfonylacetamido) Oxacalixarene

Compound. In vitro assessments on Hella cells demonstrated a concentration-dependent reduction in cell survival, yielding an IC_{50} of 358.3 µg/ml. When the compound was tested for anti-oxidant activity it found to be active compared to the standard ascorbic acid. The largest zone of inhibition (ZI) produced by the test compound was compared to that of the positive control to determine its antibacterial efficacy against *M. tuberculae*.

Conclusion: The result highlights the successful synthesis of novel compound and its efficacy towards anti-cancer , anti-oxidant and anti-tuberculosis activity , making it an intriguing topic for upcoming research on drug development.

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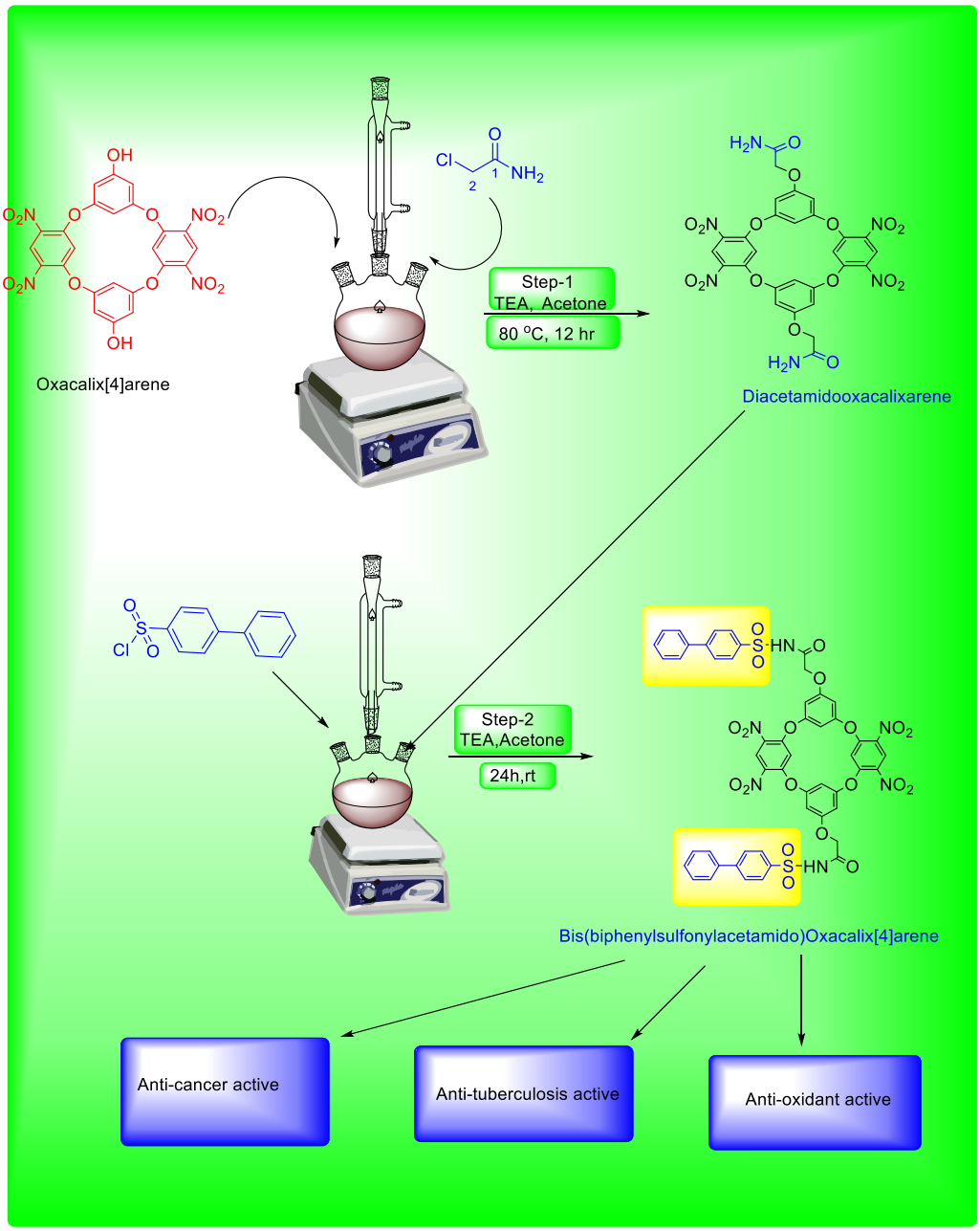
JCHR (2025) 15(3), 144-153 | ISSN:2251-6727

Graphical Abstract



1.Introduction

Tuberculosis is an contagion triggered by Mycobacteria tuberculosis[1,2,3]. It can almost mark any tissue of the body. The most common ones are lungs, pleura, lymph, nodes, intestines, spine and brain. According to Global TB report 2023, mortality of TB is 3.31 lakhs in India[4]. The mortality rate from tuberculosis is rather high—roughly 50%—if treatment is not received. Treatment-related issues with tuberculosis occur when bacteria become resilient to first-line medications such as isoniazid, rifampicin, ethambutol, streptomycin, and pyrazinamide[5,6,].

There is an imperative necessity to develop an anti-tuberculosis agent highlighted by the ongoing rise in TB(Tuberculosis) cases in worldwide[7,8]. The treatment of tuberculosis has benefited greatly from host-directed

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therapies, which have been made possible by host immunological effector systems[8]. In recent years, synthetic macrocycles have fascinated significant interest from the medicinal chemistry field because of their organized conformational characteristics and diverse biological functions[9,10].

Human papillomavirus (HPV) is the most prevalent epidemiologic contagion affecting the reproductive system and ranks among the leading causes of sexually transmitted infections globally.[11]. Cervical cancer is the most frequently occurring disease associated with HPV[12]. Cervical cancer ranks as the fourth most prevalent cancer among women worldwide approximately 604,000 new diagnoses and 342,000 fatalities each year[13].Therefore, to synthesis anti-cancer agent is immense important in pharmaceutical industry. Due to their distinct chemical and physical properties, along with excellent biocompatibility and ease of functionalization, calixarenes have emerged as an effective option for encapsulating anticancer medications[14].

Food-based antioxidant molecules are crucial for maintaining human health[15], The primary sources of antioxidant chemicals include phenolic acids, carotenes, vitamin C, vitamin E, phytate, and phytoestrogens. Such antioxidants have been identified as potentially lowering the risk of heart disease, cancer, and other chronic illnesses. By scavenging radicals before they assault the substrates, antioxidants serve a crucial role in preventing oxidative damage to proteins, lipids, and DNA. The stable free radical diphenylpicrylhydrazyl (DPPH) is the basis of one such approach that is currently widely used. Using the DPPH (2,2-diphenyl-1-picrylhydrazylhydrate) radical photometric test, antioxidant activity was determined by following its discolouration [15].

Supramolecules are defined as macrocycles that engage in specific non-covalent interactions with other molecules, such as hydrogen bonding, ion-dipole, and dipole-dipole interactions. Third-generation supramolecules could be referred to as calixarenes, while cyclodextrin and crown ethers are first and second generation supramolecules, respectively. A cyclo oligomerization of a formaldehyde and p-substituted phenol derivative, such as 4-tertbutylcalix[4]arene yields calix[n]arenes, which are readily functionalized at both rims of the central annulus. This makes calixarenes potentially valuable building blocks for the creation of novel, inventive receptors. Furthermore, a way to create new-aeon macrocyclic host molecules with undiscovered chemical and physical properties is to incorporate bridging atoms other than carbon into the "classical" carbon-bridged Calixarenes framework[30].

One of the most adaptable platforms, calix[n]arene or [1n] metacyclophanes are a crucial and essential component of supramolecular structures[27.] There is a great deal of potential to use conformational preferences for a variety of applications because of their desired functionalization and relative ease of fabrication[16,14]. Calix[4]arenes exhibit a wide range of host-guest chemistry with different small molecules and have the ability to interact with biologically significant entities. Calix[4]arene would offer a supramolecular platform that is easily derivatized at both its upper and lower rims based on the requirement to perform specific tasks, such as water purification, anti-cancer activities, and analyte detection[29].

Furthermore, recent developments in the related sector produce heterocalixarenes, which have garnered a lot of attention lately because of their unique structure and unique physical and chemical characteristics. In contrast to traditional calixarenes, heterocalixaromatics have the structural property of self-fine tunability of bridging heteroatoms and their diverse conjugations with the nearby aromatics[26]. Consequently, heteracalixaromatics has superior biological activity and offers a strong foundation for building functional structures.As a representative example of heteracalixaromatics ,Oxacalix[4]arene derivatives gained lot of attention in pharmaceutical industry as it demonstrates diverse range of biological activities such as antitumor, anti-cancer, anti-bacterial activities[14,17,18,19]. Because of its distinct chemico-physical qualities, excellent biocompatibility, and easily functionalizable traits, Oxacalixarene is a great option to encapsulate anticancer medications. In the heteracalixarene family, oxacalixarenes are new synthesized host molecules with exceptional complexing capabilities[20,19]. In addition to altering the symmetry of oxacalixarenes, the substitution of oxygen atoms for the methylene bridges found in calixarene structures improves their recognition properties. These macrocycles are easily accessible since they may be produced at room temperature in a single step using high yield nucleophilic aromatic substitution (SNAr)

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processes[16,21]. According to ab-initio calculations and solid-state x-ray structures , the 1,3 alternative Oxacalixarene conformation appears to be the most promising for producing pre-organized supramolecular receptors. These are regarded as rigid aromatic crown ethers with a three-dimensional structure and special conformational characteristics.

From the literature survey it was found that antituberculosis, anti-cancer, anti-bacterial agents have calixarene nucleus[22,23,24,25]. Here, we report the synthesis and anti-tuberculosis, anti-oxidant and anti-cancer efficacy of oxacalix[4]arene based derivative.

2. Objectives

To synthesis Bis (biphenylsulfonylacetamido) Oxacalix[4] arene compound diacetamidooxacalixarene and biphenyl Sulphonyl chloride were used in 1:2 mole ratio. Completion of the reaction was monitored by TLC. To characterize the synthesized compound spectral studies like H^1 NMR,ESI-MS, IR spectroscopy were performed. To find out the antituberculosis efficacy using M.Tuberculae gram positive pathogen. To evaluvate the antioxidant and cytotoxic activities using DPPH radical scavening method and MTT assay respectively.

3. Material and methods

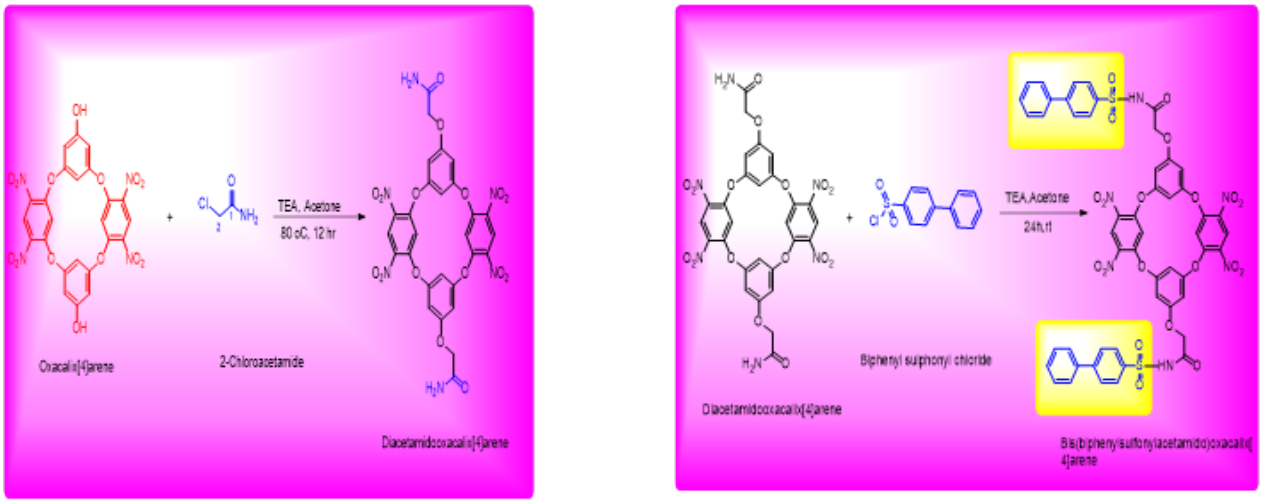
All chemicals, including biphenyl-4-sulfonyl chloride (CAS No. 1623-93-4, purity ≥99.0%), were purchased from Sigma-Aldrich. Solvents and reagents for the synthesis were obtained from Finar Chemicals and used directly without further purification. The reaction progress was monitored using thin-layer chromatography on E-Merck silica gel 60 F254 plates, and visualized under UV light (254 nm) or iodine vapor. The ^1H and ^{13}C NMR spectra were recorded in DMSO using a Bruker spectrometer at 400 MHz and 100 MHz, respectively, with TMS as the internal standard. Mass spectra of the individual derivatives were obtained using a Schmindzu mass spectrophotometer.

Synthesis

Basic Oxacalixarene was synthesized using phloroglucinol and 1,5-difluro,2,4-dinitrobenzene. The mixture of Oxacalixarene and 2-chloroacetamide (1:2 mole ratio) was stirred for 30 minutes in the presence of TEA (Triethyl amine) and acetone. Then reaction mixture was refluxed at 80°C for 12 h. The reaction mixture was quenched in ethyl acetate and water. The mixture of diacetamidooxacalixarene and biphenyl Sulphonyl chloride was refluxed in the presence of TEA and acetone for 24 h. Then mixture was dumped in to ice water and product was separated by using separation followed by washing and distillation using Rota vapor.

Step-1

Step-2



Scheme 1: Synthesis of Bis (biphenylsulfonylacetamido) Oxacalix[4] arene

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Table 1. Physical Parameters of Diacetamidooxacalixa[4]arene and Bis (biphenylsulfonylacetamido) Oxacalix[4] arene

Sr.No	Name of compound	Solubility	Colour	M.P	Yield	TLC System
1.	Diacetamidooxacalix[4]arene	Ethyl acetate	brown	140°C-145°C	70%	Ethyl acetate: hexane (6:4)
2.	Bis(biphenylsulfonylacetamido) Oxacalix[4]arene	Ethyl acetate	Yellowish brown	170°C-180°C	60%	Ethyl acetate: hexane (7:3)

4. Result and Discussion

In present study Oxacalix[4]arene based novel compound was synthesized and examined for anti-tuberculosis, anti-oxidant and anti-cancer activity. The synthesized compound was characterized by H^1 NMR,IR and Mass spectroscopy. Compound showed moderate antimicrobial activity when compare with the reference drug. When the compound was tested for anti-oxidant activity it found to be active compared to the standard ascorbic acid. When the compound was examined for cyto toxic assay it shows an excellent activity against the cancer cell.

Analytical discussion

Diacetamidooxacalixarene

^{1}H NMR :(400 MHz, DMSO-d6 □ ppm): □ = 4.51(s, 4H), 6 to 7.5 (m, 8H), 7.52 (s,4H), 8.86 (s,2H)

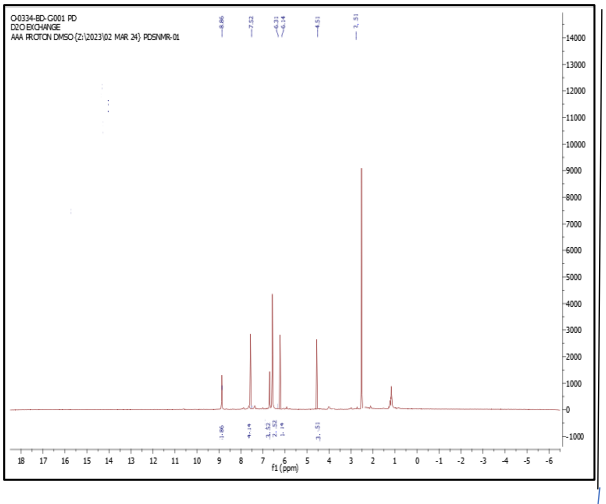

Figure-1 H^1 NMR Spectra of Diacetamidooxacalixarene

ESI-MS (m/z): 696.49, (100.0%), 340.55(24 %)

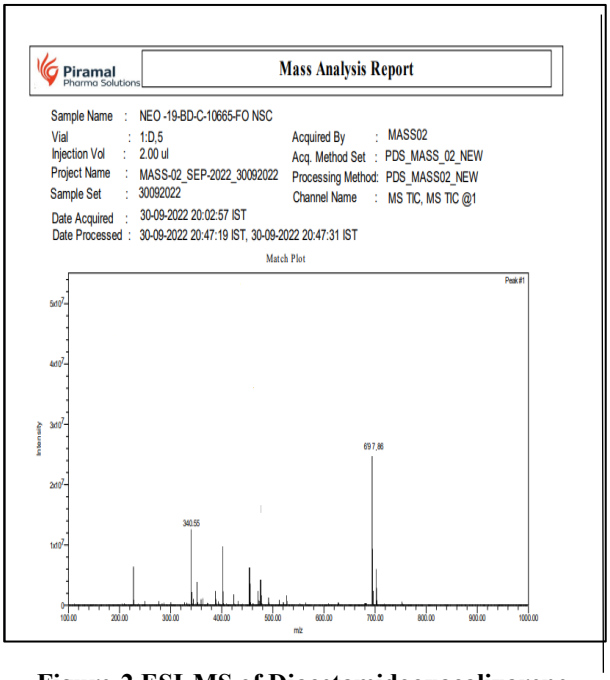

Figure-2 ESI-MS of Diacetamidooxacalixarene

FT-IR Spectra

N–H stretch (amide): 3458 cm^{-1}, C=O stretch (amide): 1680 cm^{-1}, C–N stretch (amide): 1278 cm^{-1}, Aromatic C–C stretch (oxacalixarene): 1579 cm^{-1}, C–H bending (methyl groups) :1456 cm^{-1}, CH3 stretch (acetamide groups): 2923 cm^{-1}

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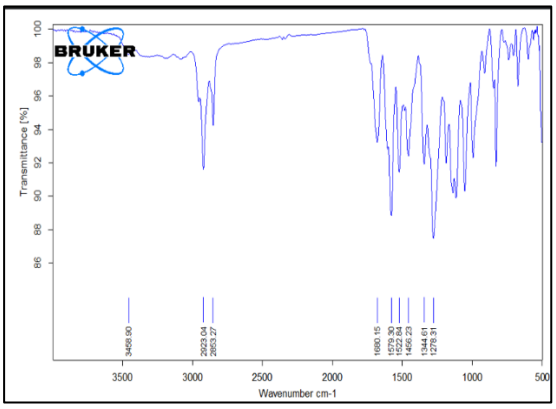

Figure-3 IR Spectra of Diacetamidooxacalixarene

Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

^{1}HNMR (400 MHz,DMSO-d6 □ ppm): □ =4.57 (s, 4H), 6 to 8.9 (m, 28H), 11.55(s ,2H)

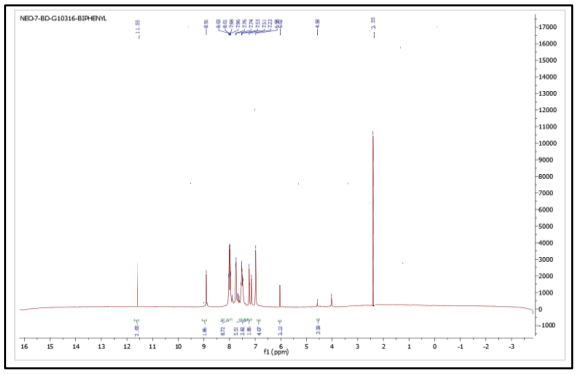

Figure-4 H^1 NMR Spectra of Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

ESI-MS(m/z): 1127.76 (100 %) , 1069.17(32%) ,928.08 (26 %).

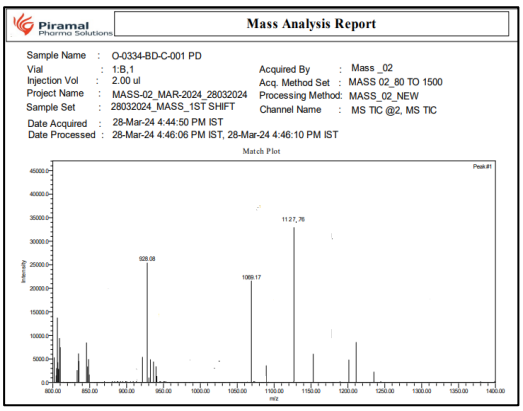

Figure-5 ESI-MS of Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

FT-IR Spectra :

C=O stretch (amide group) :1588 cm^{-1},C–N stretch (amide group): 1282 cm^{-1},N-H bending (Amide II band) : 1530 cm^{-1},S=O stretch (sulfonyl group) : 1178 cm^{-1},C–O stretch (ether and oxacalixarene) : 1090 cm^{-1},Aromatic C–C stretch (biphenyl and oxacalixarene) : 1454 cm^{-1},Aromatic C–H stretch (biphenyl rings) :2920 cm^{-1},CH3 stretch (if present in acetamido groups) : 2850 cm^{-1}C–H bending (methyl groups) : 1454 cm^{-1}

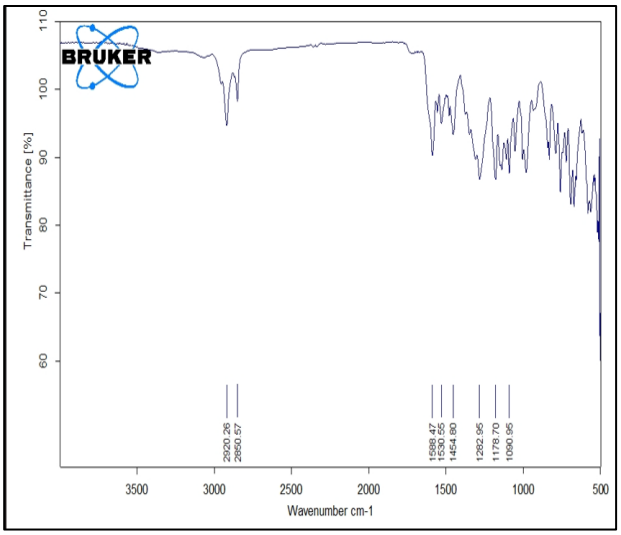

Figure-6 IR Spectra of Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

Anti-microbial activity assay

The antibacterial activity was assessed using the Zone of Inhibition method. A 100 µl aliquot of *M. tuberculae* bacterial culture was evenly distributed on Mueller-Hinton agar (MHA) plates. Discs, each containing 10 µl of different concentrations of the test compound (ranging from 0 to 100 mg/ml), were placed on the inoculated agar. A disc impregnated with only the solvent was used as a negative control, and a Ciprofloxacin disc (10 µg) was used as a positive control. The plates were incubated at 37°C for 24 hours in an incubator (Basil Scientific Corp., India). After incubation, the diameter of the zones of inhibition surrounding the discs was measured. The largest zone of inhibition (ZI) produced by the test compound was compared to that of the positive control to determine its antibacterial efficacy against *M. tuberculae*.

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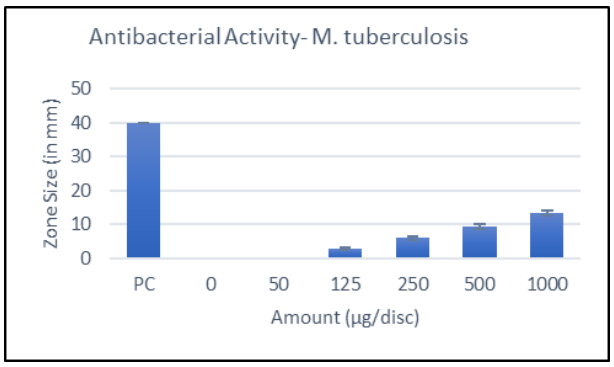

Figure-7 Anti-tuberculosis activity of Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

Figure 8 Image for Anti tuberculosis activity of Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

Anti -Oxidant activity:

The DPPH technique is a reliable and thoroughly studied synthetic solid radical for assessing a compound's antioxidant capacity. Ascorbic Acid (AA), a common antioxidant reference material, was used to compare antioxidant activity. Spectrophotometry demonstrated that the DPPH is reduced by absorbing the hydrogen or electron, and that the colour of the DPPH (2.7 mL, 2.5 mM) changes from purple to yellow when varying doses of TCTH-AuNps (10, 50, 100, 150, 200, 250, and 300 lL) are present.

The radical-scavenging activity (RSA) was expressed in percent- age of inhibition using the following equation.

$$\%RSA = \frac{(A_{DPPH} - A_S)}{A_{DPPH}} \times 100$$

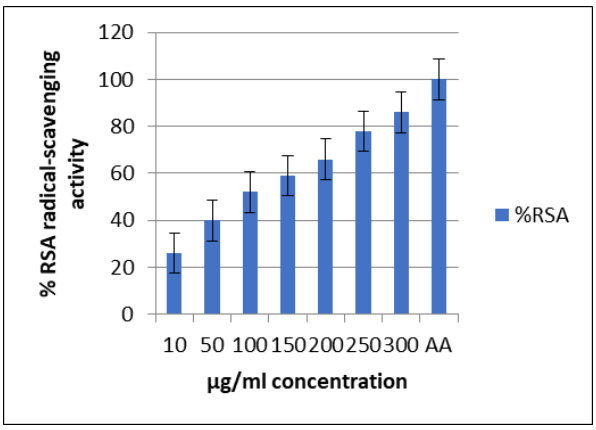

Figure 9 Anti-oxidant activity of Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

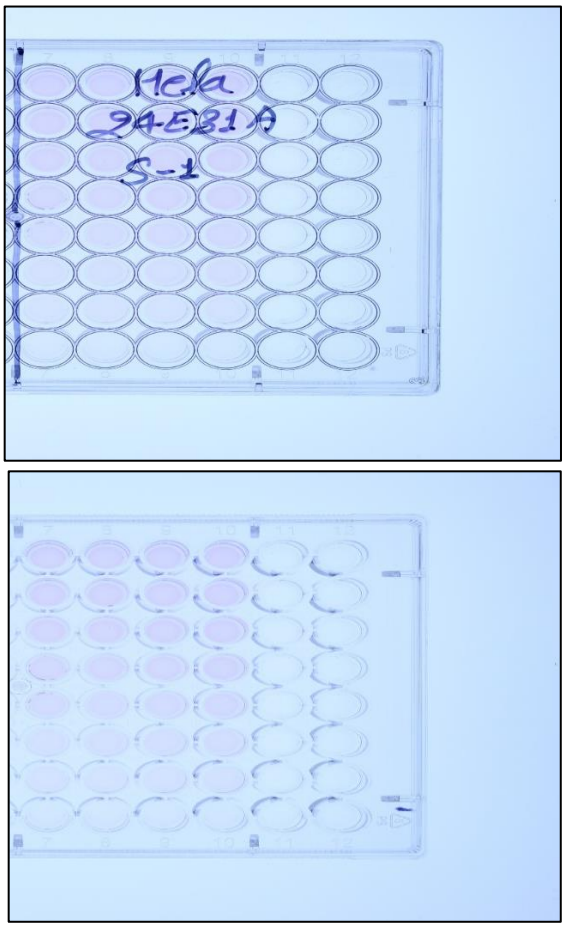

Figure-10 Images for anti-oxidant activity of Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

Anti- cancer activity

The cytotoxicity of the test samples was evaluated on the HeLa cell line (human cervical cancer cells, obtained

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from NCCS Pune) using the MTT assay. HeLa cells (10,000 cells per well) were seeded into a 96-well plate and incubated for 24 hours at 37°C in a 5% CO2 environment, in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. Following this incubation, the cells were treated with various concentrations of the test samples, ranging from 1 to 1000 µg/ml. The test samples were dissolved in DMSO and further diluted in incomplete culture medium (without FBS). After a 24-hour exposure period, MTT solution was added at a final concentration of 250 µg/ml, and the cells were incubated for an additional 2 hours. The supernatant was removed, and the formazan product was solubilized in 100 µl of DMSO. Absorbance at 540 nm and 660 nm was measured using an iMark microplate reader (Bio-Rad, USA). IC50 values were determined using GraphPad Prism 6 software. Cell images were captured using an inverted microscope (Olympus EK2) with a 10 MP AmScope digital camera (Aptima CMOS). The IC50 values are presented as Mean ± SEM.

% Viable cells = (Atest / AControl) *100 (Atest = Absorbance of t

Table 2 : *IC50* value of Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

Sample code	*IC50* value (µg/ml) *IC50* value ± SEM
Bis (biphenylsulphonyla-cetamido) oxacalix[4]arene	358.3 ± 0.043

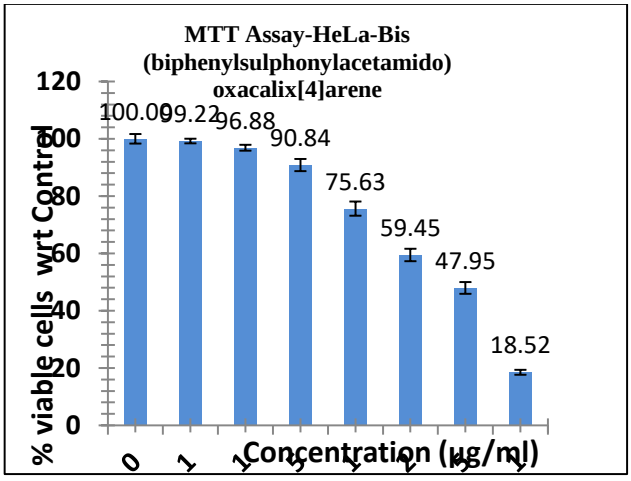

Figure- 11 Anti-cancer activity of Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

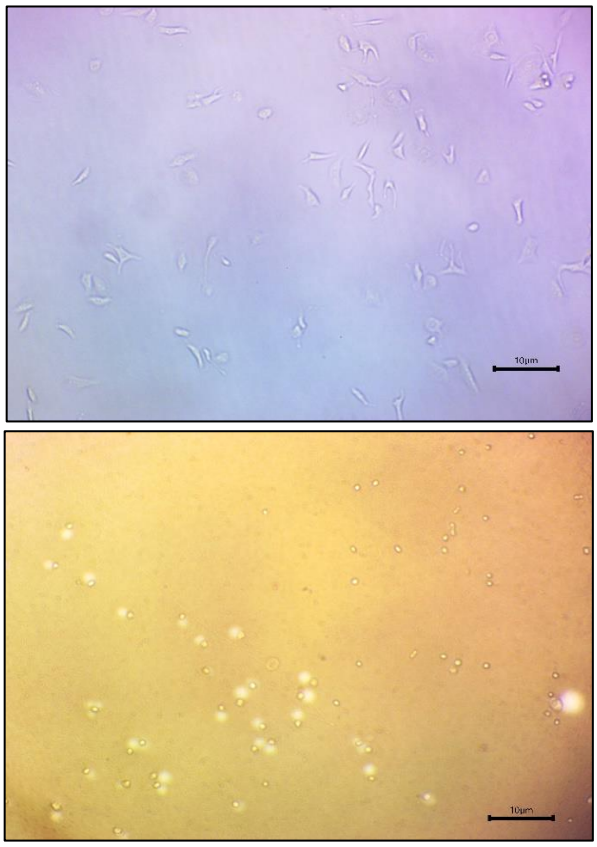

Figure- 12 Images for anti-cancer activity of Bis(biphenylsulfonylacetamido)Oxacalix[4]arene

5. Conclusion

In present study oxacalixa[4]rene based novel compound was synthesized and examined for antituberculosis, anti- oxidant and anticancer activity. The synthesized compound was characterized by H^1 NMR and Mass spectroscopy. Compound showed moderate antimicrobial activity when compare with the reference drug. When the compound was tested for anti-oxidant activity it found to be low active compared to the standard ascorbic acid. The compound shows excellent anti-cancer effectiveness due to previous confirmation and an understanding of the structural aspects of HDAC inhibition.

6. Acknowledgement

I deeply appreciate Ganpat University for offering the essential resources and assistance that contributed to the success of this research.

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7. Conflict of interest

The authors confirm that there are no financial conflicts of interest or personal connections that may have affected the results of this study.

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