



Research Article

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Synthesis and biological activity of 1,2,3-triazoyl chalcones

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ABSTRACT

Chalcones, with a chemical formula of *trans*-1,3-diaryl-2-propen-1-one, belong to flavonoids group. These are naturally synthesised by many plant species. As the extraction procedure from the natural sources is quite expensive and complicated, many researchers have proposed many synthetic procedures for this purpose. These compounds are of scientific interest because of the many useful properties it shows like anticancer, antimicrobial, antioxidant activities, etc. These chalcones in nature are present as intermediates in plant metabolic processes. These can also be used as precursor for the synthesis of heterocyclic compounds. These heterocyclic compounds obtained from chalcones further show many beneficial characteristics in medical field. 1, 2, 3-triazoyl chalcones, Compounds A3a-d are synthesized and their structure has been evaluated using ¹H-Nmr and IR, Their biological activity studies anti cancer and antibacterial studies have been carried out, In Gram Positive bacteria compound A3b and compound A3c were showing more Anti Bacterial activity at 150ug concentration, In Gram Negative bacteria compound A3b and compound A3c were showing more Anti Bacterial activity at 150ug concentration. The gel electrophoresis experiment does not show any apparent cleavage in the presence of H₂O₂ when compared with Control DNA. The compounds were treated with Breast cancer cell lines and MTT assay was done but the compounds did not show any anti cancer activity it was confirmed with standard Cisplatin.

Key words: Chalcones, flavonoids, Anti-bacterial activity, Anti-Cancer activity, DNA Cleavage Studies.

INTRODUCTION

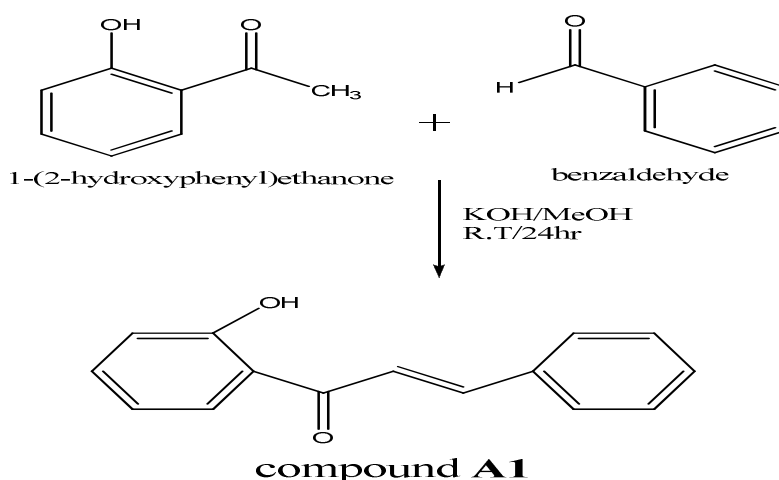
Chalcones are polyketide natural products that display various biological activities, including anticancer properties. Compelling data from laboratory studies indicate that chalcones have important effects on cancer cell growth and proliferation[1] Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α , β -unsaturated carbonyl system as, These are abundant in edible plants and considered to be precursors of flavonoids and isoflavonoids [2]As chalcones also contain this group, there are various applications of these compounds as such as antimicrobial, antitumor, anticancer [3, 4], radical scavenger, and topoisomerase I inhibitor. Chalcones exhibit anticancer activity by inhibition of kinases such as Epidermal growth factor receptor (EGFR), Vascular Endothelial Growth factor receptor-2 (VEGFR-2), etc, these kinases are important for consistent survival rates and continuous proliferation of cancer cells [5-6] Some of the chalcones are Licochalcone A This is a naturally occurring chalcone. This is an oxygenated form of chalcone which is mainly present in the roots of the plant named as Glycyrrhiza uralensis [7], Xanthohumol: This prenylated chalcone commonly is produced by Humulus lupulus L. (hop cones). Reports have shown that this compound has an extended spectrum of anticancer activity against a variety of human cancer cell types [8]. Xanthoangelol is naturally occurring chalcone can be extracted from stem of plant known as Angelica keiskei for leukemia treatment. Butein (3, 4, 2',4'-tetrahydroxychalcone) is natural chalcone which can be extracted from stems of plant Rhus verniciflua. This chalcone has exhibited anticancer activity against human colon adenocarcinoma by inhibition of proliferation [9], 2'-Hydroxy 2,3,4',6'-tetramethoxychalcone (HTMC) is another naturally occurring chalcone which is extracted from a therapeutically valuable plant named as Caesalpinia pulcherrima. This chalcone is characterized by its potential specific cytotoxic

activity when used against human lung cancer cell lines [10], Garcino this is naturally occurring tri-isoprenylated hydroxychalcone which is isolated from *Garcinia indica*. exhibits its activity by two main processes: phosphorylation of cytosolic phospholipase A2 (cPLA2) is blocked which in turn leads to modifications in metabolism of arachidonic acid, inhibits activation of STAT1[11], Flavokawain A, B, and C These chalcones are extracted from kava. These exhibit anticancer activity through inhibition of proliferation and induction of apoptosis when studied against human bladder cancer cell lines [12] etc. Diphenyl-2-propen-1-ones are original chalcones which are extensively studied for anticarcinogenic activity in this thesis.

EXPERIMENTAL SECTION

Preparation of 2'-hydroxychalcone A1: (Literature)

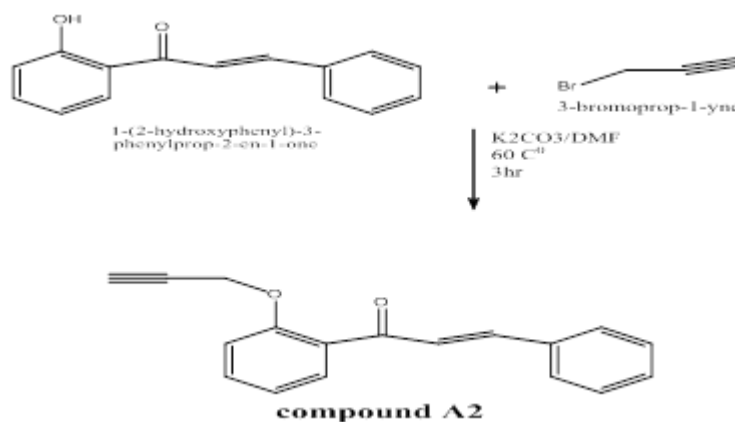
2'-hydroxyacetophenone (5 mmol) and benzaldehyde derivatives (5 mmol) were dissolved in methanol (10 ml) in round flask with stirring, Potassium hydroxide (15 mmol) was added in portions to give a blood-red solution. Resulting solution was stirred for 24 hours, during which 2'-hydroxychalcone precipitated as the potassium salt. The solution suspension was poured into cold 1 N HCl (10 ml), and further concentrated HCl was added until the solution was acidic, The resulting yellow solid was filtered, washed with water (2 x 20 ml), and recrystallized from corresponding solvent (MeOH or MeOH/CH₂Cl₂) to give the product (**A1**) (scheme-1).



Scheme 1

Preparation of 3-phenyl-1-(2-(prop-2-ynyloxy) phenyl) prop-2-en-1-one (A2): (Literature)

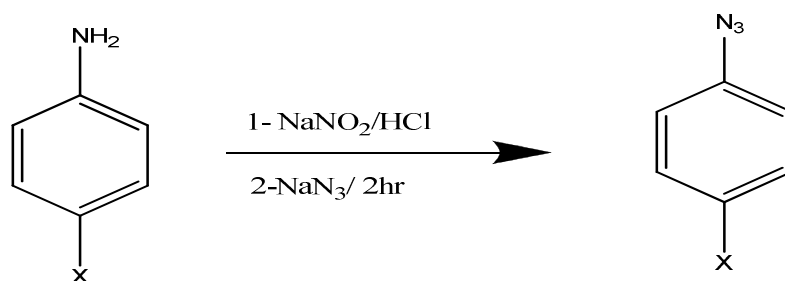
2'-hydroxychalcones(1 gm) was added in to R.P flask and dissolved with DMF solvent and after complete the dissolving, (1.3 gm) of Potassium carbonate (K₂CO₃) was added and after that(0.6 ml) of propargyl bromide was added and the solution was stirred at 60 C^o for 3 hours to obtain 3-phenyl-1-(2-(prop-2-ynyloxy)phenyl)prop-2-en-1-one compound **A2** (scheme-2).



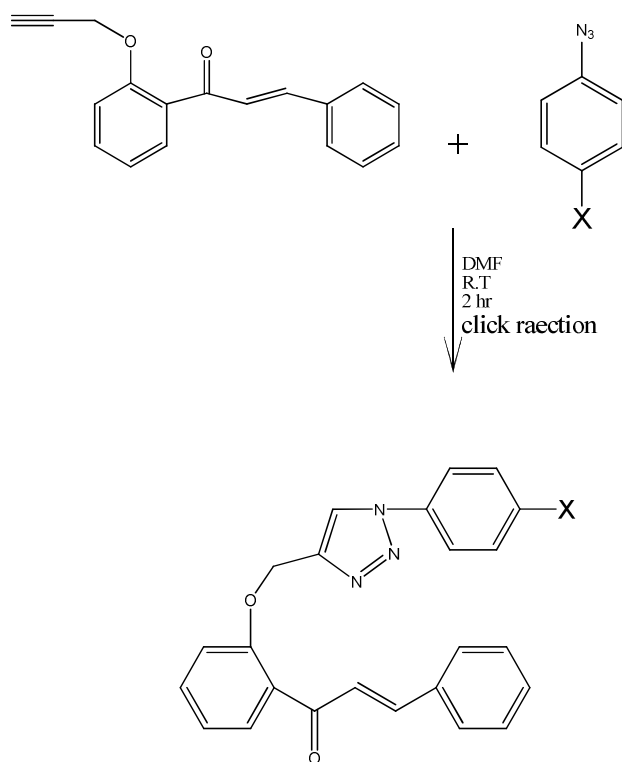
Scheme 2

Preparation of 1-azido-4-derivative:

P-substituted aniline (0.1 mol) was dissolved in 1:1 ratio of HCl: water and taken in a round bottom flask equipped with stirrer. The reaction was cooled to 0-5⁰C sodium nitrite (0.12 mol) was dissolved in water and added drop wise, sodium azide (0.1 mol) was dissolved in water and added drop wise, then the reaction is stirred for 30 min. The resultant precipitate was extracted with chloroform and washed successively with water. The organic layer was dried over anhydrous sodium sulphate, and the solvent stripped out in rotary evaporator to get 4-substituted azido benzene (Figure 3).

**Figure 3****Synthesis 1, 2, 3-Triazolyl Chalcones (A3):**

(0.2 mg) of compound **A2** Was dissolved by DMF solvent and (0.5 mg) of 4-substituted azidobenzene was added ,with stirring at room temperature for 3 hours , after that sodium ascorbate and copper sulphate was added together in the same time into the mixture and after complete the stirring for 2 hours ,the resultant was put in ice water and extracted into ethyl acetate and distillation the solvent , the resultant was compound **A3** (scheme 3).

**scheme 3 compound A3**

X= H, NO₂, Cl, F

X= H

IR (KBr): 3057, 1659, 1603, 756, 686 cm⁻¹.

¹HNMR, DMSO-d₆, 400MHz (δ ppm): 5.42 (s-2H,C6), 7.11-7.12 (bs-1H,C12), 7.25-7.27 (m-3H,C9,C10,C11), 7.45-7.63 (m-10H,C19-23,C15,C26-89), 7.71-7.73 (m-2H,C15,C16), 8.83 (s-1H,C4).

X=NO₂

IR (KBr): 3146, 1655, 1605, 1530, 1484, 764 cm⁻¹.

¹HNMR, DMSO-d₆, 400MHz (δ ppm): 5.44 (s-2H,C6), 7.11-7.14 (bs-3H), 7.47-7.60 (m-8H,C14,C29-23,C9-11), 8.21-8.33 (m-2H,C15,C16), 8.59 (s-1H,C12), 9.05 (s-1H,C4).

X=Cl

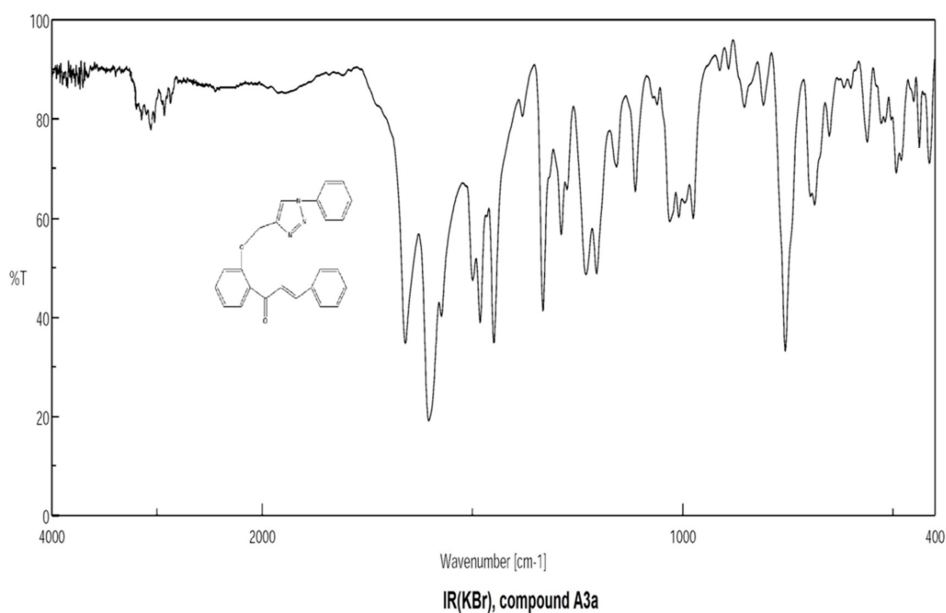
IR (KBr): 3148, 1659, 1603, 755, 697 cm⁻¹.

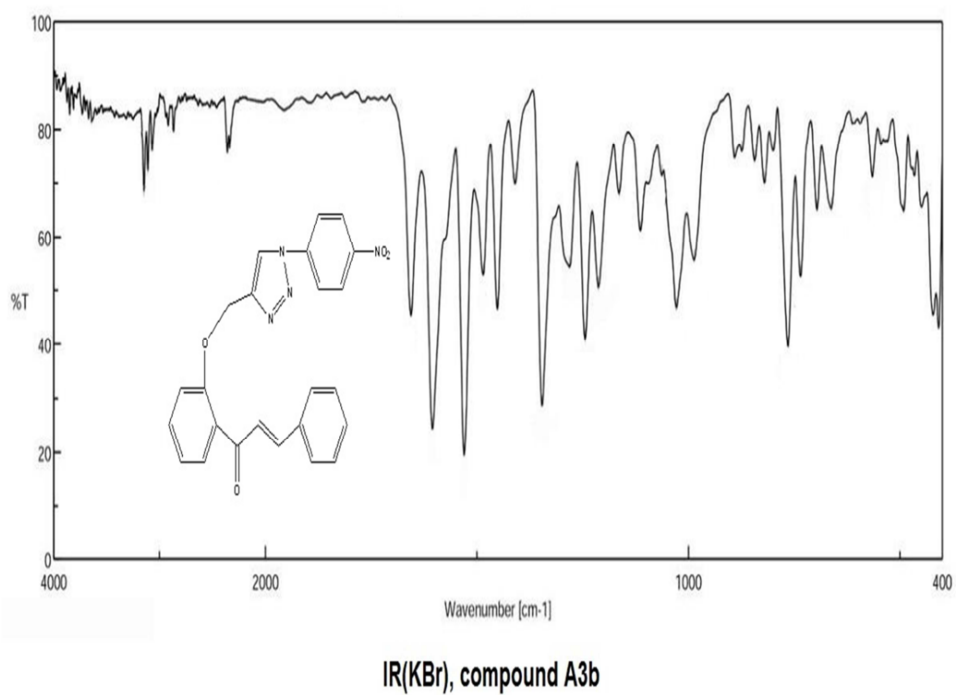
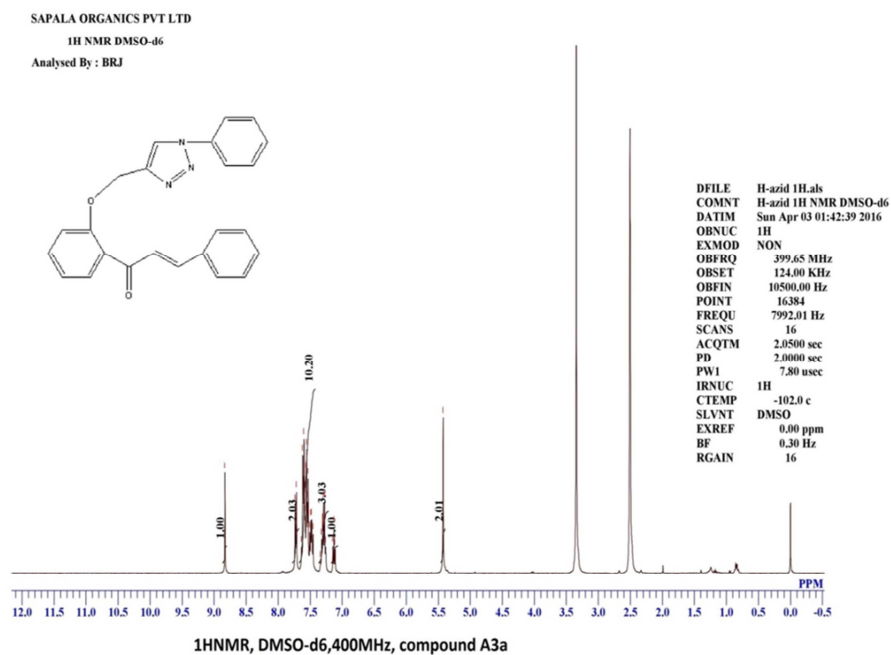
¹HNMR, DMSO-d₆, 400 MHz (δ ppm): 5.42 (bs-2H,C6), 7.14-7.22 (bs-1H,C29), 7.20-7.30 (m-3H,C15,C16,C25), 7.44-7.51 (m-4H,C9-12), 7.58-7.64 (m-5H,C19-23), 7.76 7.78 (m-2H,C26,C28), 8.84 (S-1H,C4).

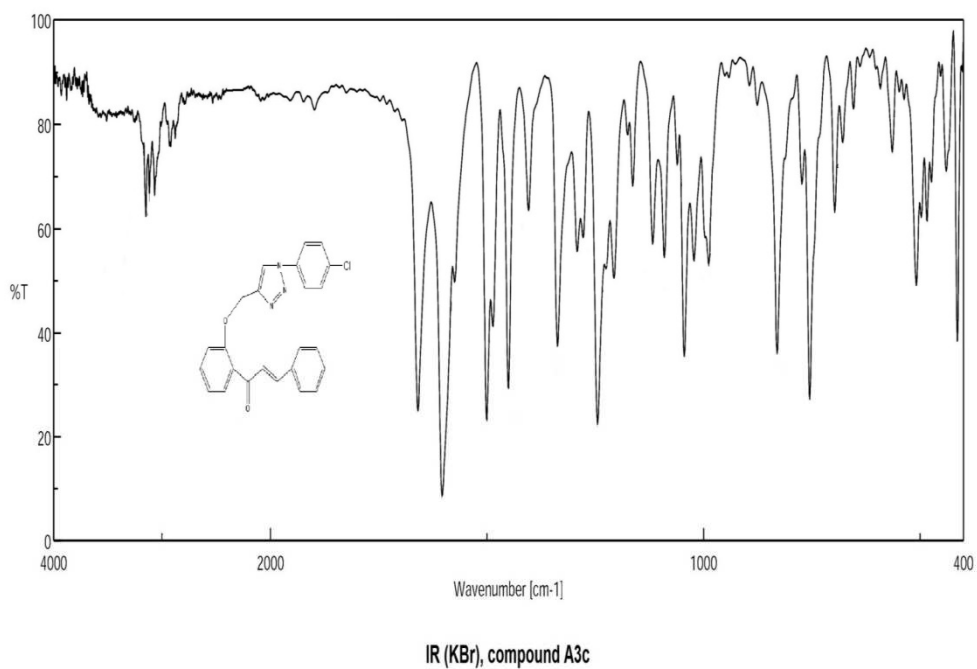
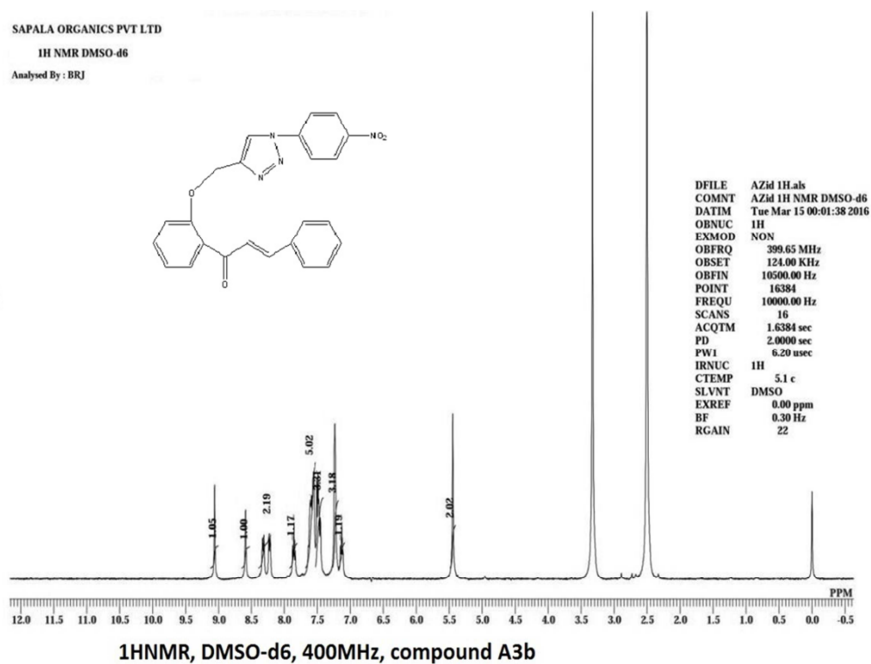
X= F

IR (KBr): 2925, 1657, 749, 1603, 615 cm⁻¹

¹HNMR, DMSO-d₆, 400MHz (δ ppm): 5.45 (bs-2H,C6), 7.14 (bs-1H,C12), 7.19-7.29 (m-4H,C25-29), 7.45- 7.54 (m-8H,C1,C9-11,C19-23), 7.72-7.80 (m-2H,C15,C16), 8.70 (s-1HC4).



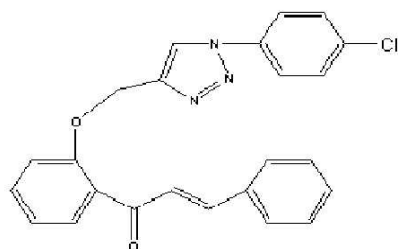




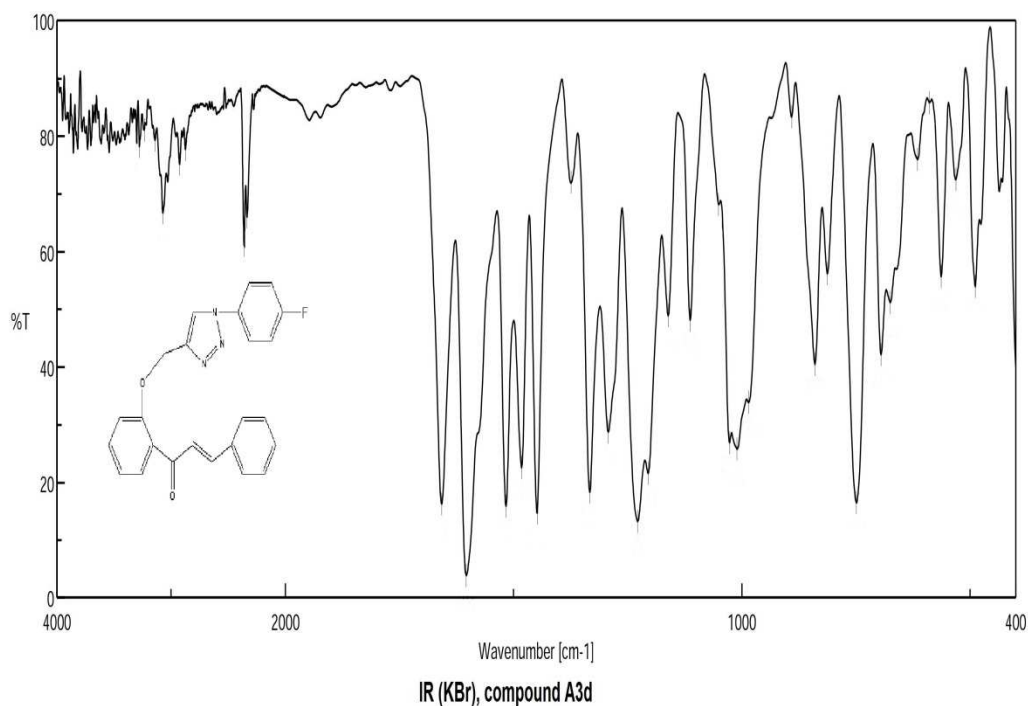
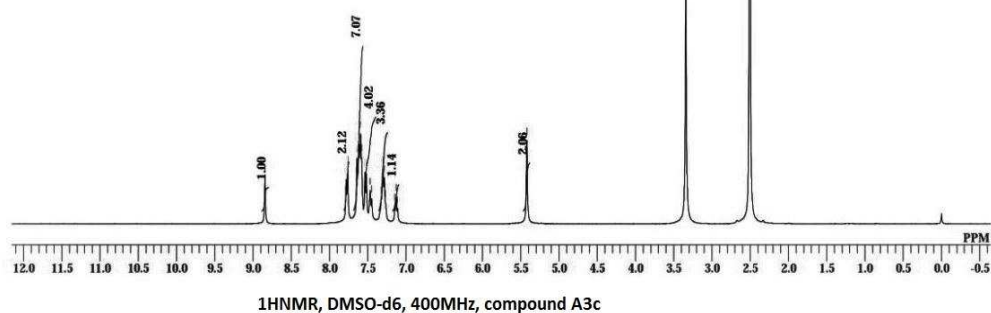
SAPALA ORGANICS PVT LTD

1H NMR DMSO-d6

Analysed By : GRJ



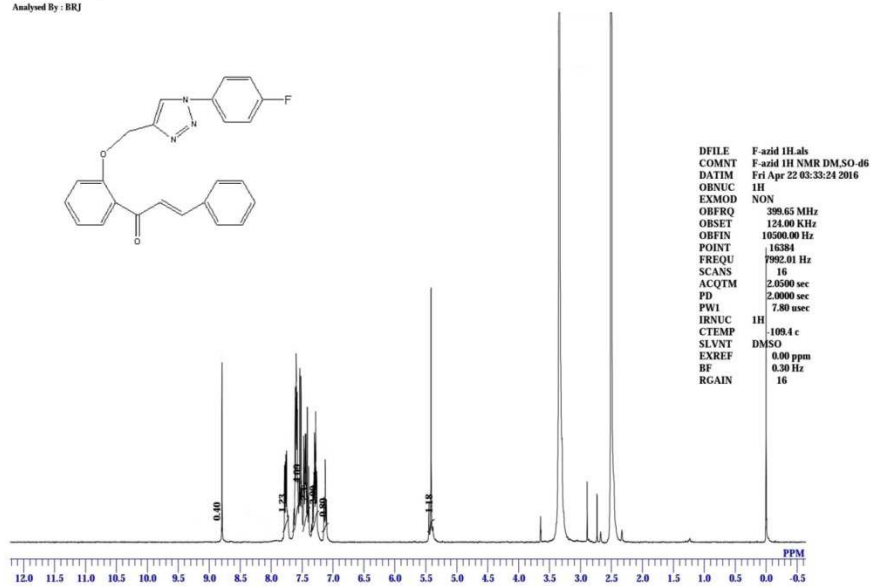
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EXMOD NON
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OBSET 124.00 KHz
OBFIN 10500.90 Hz
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SCANS 16
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PW1 6.20 usec
IRNUC 1H
CTEMP -5.8 c
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BF 0.30 Hz
RGAIN 17



SAPALA ORGANICS PVT LTD

1H NMR DMSO-d6

Analysed By: RKJ

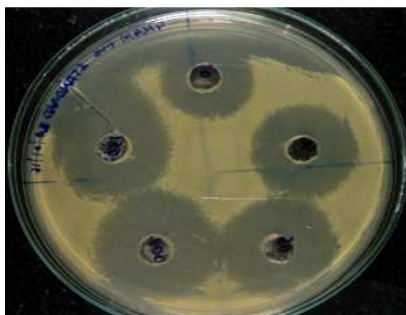


1HNMR, DMSO-d6, 400MHz, compound A3d

Anti bacterial activity studies:**1. Agar Well Diffusion Assay**

Gram Positive Strain : *Staphylococcus aureus*
 Gram Negative Strain : *E. Coli*
 Standard Drug for Gram Positive : Norfloxacin
 Standard Drug for Gram Negative : Ciprofloxacin
 Strain: Gram Positive

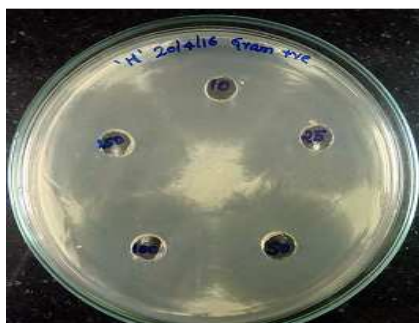
Strain/ Concentration (µg)	10 Zone of Inhibition (mm)	25 Zone of Inhibition (mm)	50 Zone of Inhibition (mm)	100 Zone of Inhibition (mm)	150 Zone of Inhibition (mm)
Gram Positive	9	10	12	13	13
Compound A3a	11	11	13	13	16
Compound A3b	11	12	13	13	15
Compound A3c	12	13	13	13	16

1. Standard: Norfloxacin

2. Compound: A3b



3. Compound: A3a

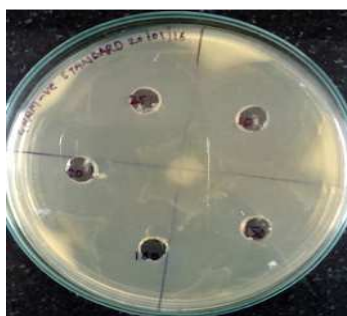


4. Compound: A3c

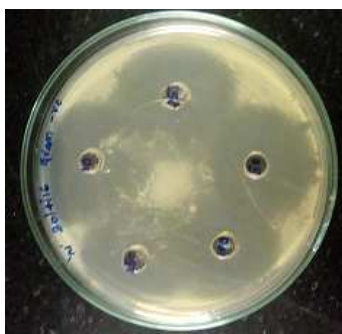
**Strain: Gram Negative**

Strain/ Concentration (µg)	10 Zone of Inhibition (mm)	25 Zone of Inhibition (mm)	50 Zone of Inhibition (mm)	100 Zone of Inhibition (mm)	150 Zone of Inhibition (mm)
Gram Negative	10	10	11	11	12
Compound 1	11	13	13	13	15
Compound 2	12	12	13	13	16
Compound 3	11	13	13	14	15

1. Standard:



2. Compound : A3b



3. Compound : A3a



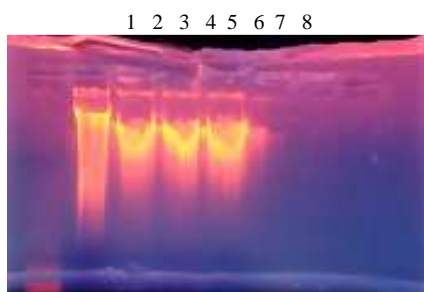
4. Compound : A3c



RESULTS AND DISCUSSION

The compounds were showing anti-bacterial activity in both Gram Positive bacteria and Gram Negative bacteria. In Gram Positive bacteria compound A3b and compound A3c were showing more Anti-Bacterial activity at 150ug concentration, In Gram Negative bacteria compound A3b and compound A3c were showing more Anti-Bacterial activity at 150ug concentration.

DNA Cleavage Studies:



Sl.No	Well	Sample Order
1	2	Control(onlyCT-DNA)
2	3	A3b
3	4	A3a
4	5	A3c

DNA Cleavage is measured by relaxation of supercoiled DNA to nicked circular conformation and linear conformation. During electrophoresis process supercoiled DNA will migrate faster when compared with DNA in nicked and linear confirmations. The above figure illustrates the gel electrophoresis experiment do not show any apparent cleavage in the presence of H₂O₂ when compared with Control DNA.

Anti-Cancer Activity Results

There is no anti-cancer activity in the compounds

The compounds were treated with Breast cancer cell lines and MTT assay was done but the compounds did not show any anti-cancer activity it was confirmed with standard Cisplatin.

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