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Synthesis of N'-Benzylidene-2-((Substituted-Phenyl) (3-(5-(4-Nitrophenyl) Thiophene-2- Yl) Oxiran-2-Yl) Methoxy) Acetohydrazide and Its Pharmacological Activities

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Propenones, Acetate and Hydrazide.

ABSTRACT:
A series of novel N'-benzylidene-2-((substituted-phenyl)(3-(5-(4- nitrophenyl)thiophen-2-yl)oxiran- 2-yl) methoxy) acetohydrazide have been prepared through a multistep synthesis . The key features of this reaction are the incorporation of four heterocyclic rings in the structure of target products, using commonly available and inexpensive catalysts, high yields, and simple reaction conditions. Final salt products were obtained by self-capturing of a proton by the nitrogen of the thiophene moiety. The easy work-up and mild reaction conditions are notable features of this protocol. The antibacterial, and ant inflammatory activities of the synthetic products were examined. Most of the compounds showed good activities in comparison to references.

Introduction

The rise in immuno compromised patients in recent years is closely linked to the rise in fungal infections [1,2]. The majority of mycoses that are found are categorized as superficial or systemic. While Aspergillus spp., Cryptococcus neoformans, and Candida species are the principal culprits behind systemic mycoses, dermatophytes, a group of fungi that includes species from the Microsporum and Trichophyton genera, are also responsible for superficial infections [3, 4]. Even though various antifungal medications are available to treat fungal infections, issues with toxicity, resistance, and efficacy profiles severely restrict their use [2, 6]. Therefore, it is imperative to find new structures with antifungal qualities as this could result in the creation of novel medications for the treatment of fungal infections.

The pyrazoline and chalcone moieties are significant groups of compounds that are frequently utilized as essential building blocks for compounds that are physiologically active and are thought to be potential prospects for antifungal medications. Chalcones' wide range of actions as anti-inflammatory [7], antifungal [8,9], antibacterial [10], antioxidant [11], antimalarial [12,13], and anticancer [14,15] drugs have been thoroughly investigated. One of our earlier investigations showed that the inhibition of the manufacture of fungal cell-wall polymers like (1,3)β-D-glucan synthase is linked to the mode of action of several chalcones against fungal infections. From a medicinal perspective, chalcones can inhibit glutathione-S-transferases (GSTs), which are enzymes linked to drug resistance [16, 17]. This may lead to the development of new drugs for the treatment of infections brought on by fungi. Furthermore, earlier research has shown that the yeast genotype, strain cell density, and chalcone substitution pattern all affect the antifungal efficacy of the compound. About substitution patterns, some scientists have discovered that while the EDG groups obstruct this reaction and reduce the antifungal activity, the EWG groups at the para-position increase the electron shortage at C-β, making it an appealing electrophilic center for thiol assault. Because of steric effects, a similar result was observed when EWG groups were in the ortho-position [18, 19] potentially result in the creation of novel medications for the treatment of fungal infections [16, 17].

In this paper, we describe the synthesis of chalcones as intermediate and hydrazide derivatives, containing the thiophene moiety in their structures, and the evaluation of their antifungal activity .

Materials and Methods

Solvents and reagents from Merck Millipore (Billerica, MA, USA) or Sigma-Aldrich (St. Louis, MO, USA) were used without purification. Thin layer chromatography (TLC) was performed on pre-coated silica gel 60GF254 (Merck) plates measuring 0.2 mm in diameter. Melting points were measured using an SMP3 melting point equipment (Stuart, Staffordshire, UK). An ATR-equipped Nicolet

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6700 from Thermo Scientific (Waltham, MA, USA) was used to obtain FT-IR spectra. The 1H- and 13C-NMR spectra were recorded on a DPX 400 spectrometer (Bruker, Billerica, MA, USA) operating at 400 and 100 MHz, respectively, using CDCl3 as the solvent and TMS as the internal standard. A spectrometer, GCMS-QP2010

Experimental Section

General procedure for the Synthesis of 1,3-diaryl-2-propene-1-ones (1)

To solution of 3 g of sodium hydroxide in 30 mL of water and 18 mL of ethyl alcohol in 500 mL round bottom flask. Flask provided with a mechanical stirrer, 7 mL of acetophenone was added. The reaction mixture cooled to 0-5 oC, into that 6 mL of pure aryl aldehyde was added.Stirred the reaction mixture for 3 h at 20-25 oC temperature, reaction was monitored by TLC technique up to completion. After the reaction completed, pH 6-7 was adjusted by using diluted hydrochloric acid. The reaction mixture washed with ether, ether layer was separated. The organic layer was dried by anhydrous Na2SO4 and stiff of the solvent using vacuum. The isolated crude chalcone was purified by silica column chromatography technique with methanol and dichloromethane with good yield (96%).

General Procedure for the Synthesis of para Substituted phenyl) (3-(5-(4- nitrophenyl) thiophen - 2-yl) oxiran-2-yl) methanone.(2)

To the reaction mixture, a solution of 30% H2O2 was added dropwise at 0^0 C and added little amount of Sodium hydroxide(6ml) in the presence of alcohol medium , stirred for 1.5 h to complete the epoxidation step. Progress of the reaction mixture was monitored by TLC by using mobile phase (Ethyl acetate: Hexane). Reaction was Completed for 3hrs. Now vacuum filtration was progressed the solid product was recovered and analysed using spectroscopic methods. The highest yield of 43% was obtained in ethanol when 2.5 molar equivalent of H2O2was used.

General procedure for the Synthesis of (para substituted phenyl)(3-(5-(4- nitrophenyl)thiophen-2-yl)oxiran-2-yl)methanol.(3)

Into a 25 mL round-bottom flask, para Substitutedphenyl)(3-(5-(4-nitrophenyl) thiophene-2-yl)oxiran-2-yl)methanone (1 mmol) and methanol (20 mL) were added, followed by NaBH4 (38 mg, 1 mmol) and the solution stirred for three min. The reaction was quenched with1 M HCl until a pH of 6 was reached (~1.5 mL) and evaporated in vacum to dryness. The crudeproduct was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated in vacum to dryness.

General Procedure for the Synthesis of methyl-2-((substitutedphenyl)(3-(5-(4- nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetate.(4)

To the reaction mixture, a solution of (para substituted phenyl)(3-(5-(4-nitrophenyl)thiophen- 2-yl)oxiran-2-yl)methanol which was dissolved in DMF was refluxed in the presence of methyl2-bromobutanoate (0.01mole) for 5hrs, Progress of the reaction mixture was monitored by TLCby using mobile phase (Ethyl acetate: Hexane). Reaction was Completed for 5hrs. Reaction mixture was allowed to cool and poured to Ice mixture.Precipitate obtained was filtered by Using Vacuum Filtration and dried , Recrystallization was done by Using Ethanol.

General Procedure for the Synthesis of 2-((Substitutedphenyl)(3-(5-(4- nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetic acid.(5)

To the reaction mixture, methyl-2-((substitutedphenyl) (3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl) methoxy)acetate was dissolved in water and it was refluxed for 2hrs by using
Sodium Hydroxide solution (2ml), After completion of reaction . Reaction mixture was allowed to cool and poured to Ice mixture. Precipitate obtained was filtered by Using Vacuum Filtration and dried.

General Procedure for the Synthesis of ethyl 2-((Susbtituted-phenyl)(3-(5- (4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetate.(6)

2-((Substituted phenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetic acid. (0.01 mole) in 20 ml of absolute alcohol and 0.5 ml conc. sulphuric acid was refluxed for 12 hrs. The excess alcohol was removed by distillation. The contents were cooled to room temperature, poured into ice. The product obtained was filtered through sintered glass crucibleand dried.

General Procedure for the Synthesis of 2-((Substituted-phenyl)(3-(5-(4- nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetohydrazide.(7)

ethyl2-((Susbtituted-phenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetate (0.01 mole) in 20 ml of absolute alcohol and 0.5 ml Hydrazine hydrate was refluxed for 8 hrs.The contents were cooled to room temperature, poured into ice. The product obtained was filtered through sintered glass crucible and dried.

General Procedure for the Synthesis of N'-benzylidene-2-((substituted-phenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetohydrazide.(8)

(E)-N'-benzylidene-2-((4-chlorophenyl)(3-(5-(4-

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nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetohydrazide (0.01 mole) in 20 ml of absolute alcohol and glacial acetic acid (5ml) in the presence of substituted Aldehyde (0.01mole) was refluxed for 3hrs. The contents were cooled to room temperature, poured into ice. The product obtained was filtered throughsintered glass crucible and dried.

Table-1: Characterization data of N'-benzylidene-2- ((substituted-phenyl) (3-(5-(4-nitrophenyl) thiophen-2-yl)oxiran-2-yl)methoxy) acetohydrazide

CompNo.	R	R^1	MeltingPoint(^oC)	Mol.Formula(Mol.Wt)	%Yield
8a	p-Cl	p-NO_2	198	593	87
8b	p-Br	p-NO_2	196	637	73
8c	p-NO_2	p-Br	203	637	80
8d	3-Cl	p-Br	198	626	78
8e	p-CH_3	p-Br	199	606	60
8f	3-Br	p-Br	196	670	65
8g	3-OH	p-Cl	195	564	55
8h	3-NO_2	p-Cl	194	593	87
8i	p-Br	p-Cl	193	626	65
8j	3-Cl	p-Cl	192	582	60

Solvent of crystallization: Ethanol

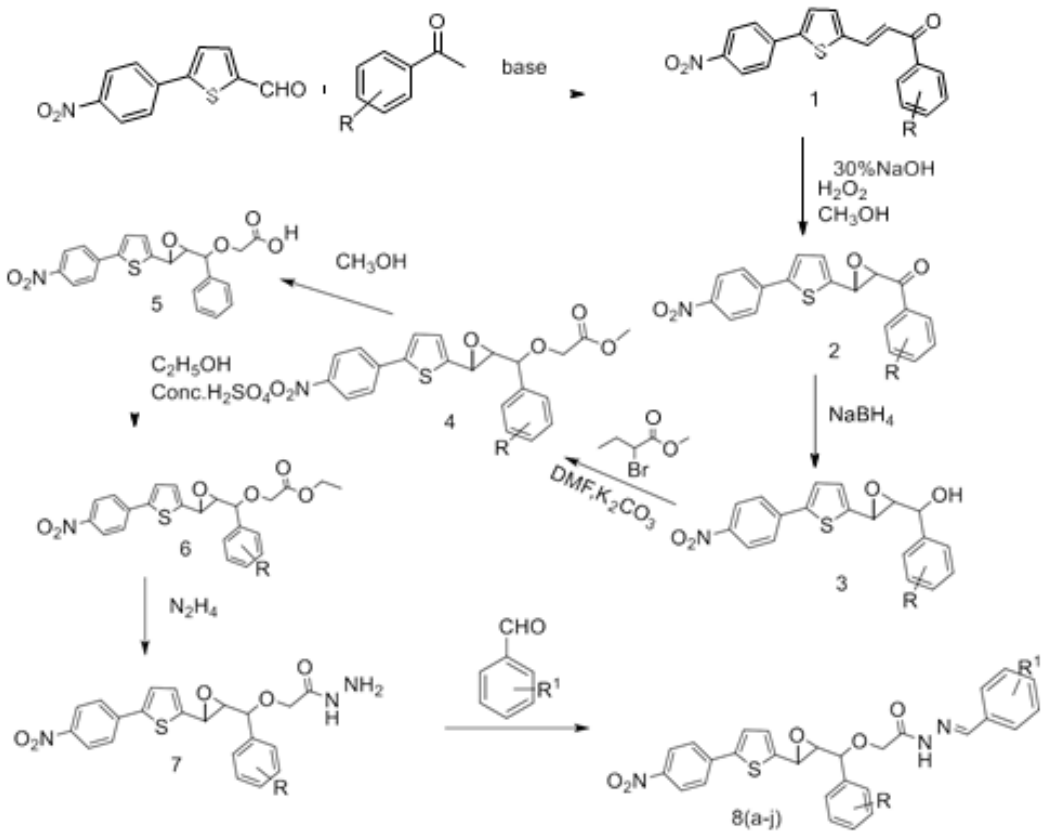

Figure 1: Spectral data of Synthesized Compounds

Compound 1a

^{1}H NMR: δ 6.55 (1H, d, *J* = 9.5 Hz), 6.79 (2H, d, *J* = 8.9Hz), 7.03 (1H, d, *J* = 8.6 Hz), 7.42-7.56 (4H, 7.49 (d, *J* = 8.9, Hz), 7.50 (d, *J* = 8.7Hz)), 7.63-7.80 (3H), 7.69 (d, *J* = 8.6 Hz), 7.74 (d, *J* = 8.7Hz)), 8.03 (1H,d, *J* = 9.5 Hz).

IR (KBr,Cm^{-1}):1500(-C=O- Stretching),1520(C=C stretching).Mass (m/z):380

Compound 2a

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^{1}H NMR: δ 4.20-4.32 (2H), 4.26 (d, *J* = 8.1 Hz), 4.26 (d, *J* = 8.1 Hz)), 6.83-7.16 (4H, 6.89 (d, *J* = 8.9Hz), 6.99 (d, *J* = 8.5 Hz), 7.10 (d, *J* = 8.5 Hz)), 7.40 (2H, d, *J* = 8.9Hz), 7.54 (2H, d, *J* = 8.7Hz), 7.94 (2H, d, *J* = 8.7, 1.9, 0.4 Hz).

IR (KBr,Cm^{-1}):1510(-C=O- Stretching),1550(C=C stretching),2980(-C=N- stretching). Mas (m/z):396

Compound 3a

^{1}H NMR: δ 3.65 (1H, d, *J* = 8.1Hz), 3.91 (1H, d, *J* = 8.1 Hz), 5.00 (1H, d, *J* = 5.0 Hz), 6.89 (2H, d, *J* = 0.5 Hz), 6.99-7.16 (2H, 7.05 (d, *J* = 8.5 Hz), 7.10 (d, *J* = 8.5 Hz)), 7.22-7.47 (4H, 7.28 (d, *J* = 8.3, Hz), 7.40(d, *J* = 8.9Hz)), 7.56 (2H, d, *J* = 8.3, Hz).

Compound 4a

^{1}H NMR: δ 3.63-3.77 (4H, 3.70 (d, *J* = 8.1, Hz), 3.72 (s)), 3.88 (1H, d, *J* = 8.1 Hz), 4.11-4.21 (2H, 4.16 (s), 4.16 (s)), 5.04 (1H, d, *J* = 5.3 Hz), 6.89 (2H, d, *J* = 8.9, Hz), 6.99-7.16 (2H), 7.05 (d, *J* = 8.5 Hz), 7.10 (d, *J* = 8.5 Hz)), 7.34-7.63 (6H, 7.40 (d, *J* = 8.9Hz), 7.49 (d, *J* = 8.3Hz), 7.56 (d, *J* = 8.3Hz))

^{13}C NMR: δ 52.2 (1C, s), 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 124.0 (1C, s), 127.0 (1C, s), 127.2 (2C, s), 128.5-128.8 (4C, 128.6 (s), 128.7 (s)), 131.6 (1C, s), 133.7 (1C, s), 134.3 (1C, s), 134.6 (1C, s), 148.4 (1C, s), 151.1 (1C, s), 168.5 (1C, s).

Compound 5a

^{1}H NMR: δ 3.66 (1H, d, *J* = 8.1 Hz), 3.93 (1H, d, *J* = 8.1 Hz), 4.17-4.26 (2H), 4.21 (s), 4.21 (s)), 5.04 (1H, d, *J* = 5.3 Hz), 6.89 (2H, d, *J* = 8.9 Hz), 6.99-7.16 (2H), 7.05 (d, *J* = 8.5 Hz), 7.10 (d, *J* = 8.5 Hz)), 7.34-7.63 (6H), 7.40 (d, *J* = 8.9Hz), 7.49 (d, *J* = 8.3Hz), 7.56 (d, *J* = 8.3, Hz)).

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 67.6 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 124.0 (1C, s), 127.0 (1C, s), 127.2 (2C, s), 128.5-128.8 (4C, 128.6 (s), 128.7 (s)), 131.6 (1C, s), 133.7 (1C, s), 134.3 (1C, s), 134.6 (1C,s), 148.4 (1C, s), 151.1 (1C, s), 173.4 (1C, s).

Compound 6a

^{1}H NMR: δ 1.19 (3H, t, *J* = 7.1 Hz), 3.70 (1H, d, *J* = 8.1, 5.3 Hz), 3.88 (1H, d, *J* = 8.1 Hz), 4.08-4.21 (4H, 4.14 (q, *J* = 7.1 Hz), 4.14 (q, *J* = 7.1 Hz), 4.16 (s), 4.16 (s)), 5.04 (1H, d, *J* = 5.3 Hz), 6.89 (2H, d, *J* = 8.9, 1.1, 0.5 Hz), 6.99-7.16 (2H, 7.05 (d, *J* = 8.5 Hz), 7.10 (d, *J* = 8.5 Hz)), 7.34-7.63 (6H), 7.40 (d, *J* = 8.9Hz), 7.49 (d, *J* = 8.3Hz), 7.56 (d, *J* = 8.3Hz)).

^{13}C NMR: δ 14.2 (1C, s), 57.1 (1C, s), 58.8 (1C, s), 61.2 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 124.0 (1C, s), 127.0 (1C, s), 127.2 (2C, s), 128.5-128.8 (4C, 128.6 (s), 128.7 (s)), 131.6 (1C, s), 133.7 (1C, s), 134.3 (1C, s), 134.6 (1C, s), 148.4 (1C, s), 151.1 (1C, s), 167.6 (1C, s).

Compound 7a

^{1}H NMR: δ 3.70 (1H, d, *J* = 8.1Hz), 3.88 (1H, d, *J* = 8.1 Hz), 4.20-4.30 (2H), 4.25 (s), 4.25 (s)), 5.04 (1H, d, *J* = 5.3 Hz), 6.89 (2H, d, *J* = 8.9Hz), 6.99-7.16 (2H, 7.05 (d, *J* = 8.5 Hz), 7.10 (d, *J* = 8.5 Hz)), 7.34-7.63(6H, 7.40 (d, *J* = 8.9Hz), 7.49 (d, *J* = 8.3 Hz), 7.56 (d, *J* = 8.3, Hz)).

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 124.0 (1C, s), 127.0 (1C, s), 127.2 (2C, s), 128.5-128.8 (4C, 128.6 (s), 128.7 (s)), 131.6 (1C, s), 133.7 (1C, s), 134.3 (1C, s), 134.6 (1C,s), 148.4 (1C, s), 151.1 (1C, s), 169.8 (1C, s).

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Compound 8a

^{1}H NMR: δ 3.74 (1H, d, *J* = 8.1, 5.3 Hz), 3.88 (1H, d, *J* = 8.1 Hz), 4.15-4.25 (2H, 4.20 (s), 4.20 (s)), 5.04 (1H, d, *J* = 5.3 Hz), 6.89 (2H, d, *J* = 8.9, Hz), 6.99-7.16 (2H, 7.05 (d, *J* = 8.5 Hz), 7.10 (d, *J* = 8.5 Hz)), 7.33- 7.63 (10H), 7.40 (d, *J* = 8.0, Hz), 7.40 (d, *J* = 8.9, Hz), 7.48 (d, *J* = 8.0, Hz), 7.49 (d, *J* = 8.3, Hz), 7.56(d, *J* = 8.3, Hz)), 7.84 (1H, s).

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 117.7 (2C, s), 124.0 (1C, s), 127.0 (1C, s), 127.2 (2C, s), 128.5-128.8 (4C, 128.6 (s), 128.7 (s)), 129.4 (2C, s), 131.6 (1C, s), 133.6- 133.9 (2C, 133.7 (s), 133.8 (s)), 134.3 (1C, s), 134.6 (1C, s), 139.5 (1C, s), 146.5 (1C, s), 148.4 (1C, s), 151.1 (1C, s), 169.8 (1C, s).

Compound 8b

^{1}H NMR: δ 3.67 (1H, d, *J* = 8.1, Hz), 3.88 (1H, d, *J* = 8.1 Hz), 4.15-4.25 (2H), 4.20 (s), 4.20 (s)), 5.03 (1H, d, *J* = 5.3 Hz), 6.89 (2H, d, *J* = 8.9, Hz), 6.99-7.16 (2H), 7.05 (d, *J* = 8.5 Hz), 7.10 (d, *J* = 8.5 Hz)), 7.26-7.54 (10H), 7.33 (d, *J* = 8.3, Hz), 7.38 (d, *J* = 8.3, Hz), 7.40 (d, *J* = 8.0, Hz), 7.40 (d, *J* = 8.9, Hz), 7.48 (d, *J* = 8.0,Hz)), 7.85 (1H, s)

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 117.7 (2C, s), 122.3 (1C, s), 124.0 (1C, s), 127.0 (1C, s), 127.3 (2C, s), 128.6 (2C, s), 129.4 (2C, s), 131.5-131.8 (3C, 131.6 (s), 131.7 (s)), 133.8 (1C, s), 134.3 (1C, s), 134.6 (1C, s), 139.5 (1C, s), 146.5 (1C, s), 148.4 (1C, s), 151.1 (1C, s), 169.8 (1C, s)

Compound 8c

^{1}H NMR: δ 3.77-3.99 (2H, 3.83 (d, *J* = 8.1, Hz), 3.92 (d, *J* = 8.1 Hz), 4.15-4.25 (2H), 4.20 (s), 4.20 (s)), 5.01 (1H, d, *J* = 4.8 Hz), 6.89 (2H, d, *J* = 8.9, 1.1, 0.5 Hz), 6.99-7.16 (4H, 7.05 (d, *J* = 8.5 Hz), 7.09 (d, *J* = 8.6, Hz), 7.10 (d, *J* = 8.5 Hz)), 7.29-7.67 (8H), 7.36 (d, *J* = 8.3 Hz), 7.40 (d, *J* = 8.9Hz), 7.51 (d, *J* = 8.6, Hz),7.60 (d, *J* = 8.3Hz)), 7.85 (1H, s).

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 117.7 (2C, s), 122.3 (1C, s), 124.0 (1C, s), 127.0 (1C, s), 127.5-127.6 (4C, 127.5 (s), 127.6 (s)), 128.6 (2C, s), 131.5-131.8 (3C, 131.6 (s), 131.7 (s)), 133.8 (1C, s), 134.3 (1C, s), 134.6 (1C, s), 139.5 (1C, s), 146.5 (1C, s), 148.4 (1C, s), 151.1 (1C, s), 169.8 (1C, s).

Compound 8d

^{1}H NMR: δ 3.74 (1H, d, *J* = 8.1Hz), 3.88 (1H, d, *J* = 8.1 Hz), 4.15-4.25 (2H), 4.20 (s), 4.20 (s)), 5.04 (1H, d, *J* = 5.3 Hz), 6.89 (2H, d, *J* = 8.9, Hz), 6.99-7.16 (4H), 7.05 (d, *J* = 8.5 Hz), 7.09 (d, *J* = 8.6, Hz), 7.10 (d, *J* = 8.5 Hz)), 7.34-7.63 (8H, 7.40 (d, *J* = 8.9Hz), 7.49 (d, *J* = 8.3 Hz), 7.51 (d, *J* = 8.6Hz), 7.56 (d, *J* = 8.3,0.5 Hz)), 7.85 (1H, s).

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 122.3 (1C, s), 124.0 (1C, s), 127.0 (1C, s), 127.2 (2C, s), 127.5 (2C, s), 128.5-128.8 (4C, 128.6 (s), 128.7 (s)), 131.5-131.8 (3C, 131.6 (s), 131.7 (s)), 133.6-133.9 (2C, 133.7 (s), 133.8 (s)), 134.3 (1C, s), 134.6 (1C, s), 146.5 (1C, s), 148.4 (1C, s), 151.1 (1C, s), 169.8 (1C, s)

Compound 8e

^{1}H NMR: δ 2.27 (3H, s), 3.65 (1H, d, *J* = 8.1Hz), 3.93 (1H, d, *J* = 8.1 Hz), 4.15-4.25 (2H, 4.20 (s), 4.20 (s)),5.04 (1H, d, *J* = 5.3 Hz), 6.89 (2H, d, *J* = 8.9, Hz), 6.99-7.23 (6H), 7.05 (d, *J* = 8.5 Hz), 7.09 (d, *J* = 8.6Hz), 7.10 (d, *J* = 8.5 Hz), 7.17 (d, *J* = 8.0Hz)), 7.24-7.57 (6H, 7.30 (d, *J* = 8.0Hz), 7.40 (d, *J* = 8.9, Hz), 7.51(d, *J* = 8.6, Hz)), 7.85 (1H, s).

^{13}C NMR: δ 21.3 (1C, s), 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 122.3 (1C, s), 124.0 (1C, s), 126.4 (2C, s), 127.0 (1C, s), 127.5 (2C, s), 128.6 (2C, s), 129.1 (2C, s), 131.5-131.8 (3C, 131.6 (s), 131.7 (s)), 133.8 (1C, s), 134.3 (1C, s), 134.6 (1C, s), 141.5 (1C, s), 146.5 (1C, s), 148.4 (1C, s), 151.1 (1C, s), 169.8 (1C, s).

Compound 8f

^{1}H NMR: δ 3.65 (1H, d, *J* = 8.1 Hz), 3.88 (1H, d, *J* = 8.1 Hz), 4.15-4.25 (2H, 4.20 (s), 4.20 (s)), 5.02 (1H, d, *J* = 5.3 Hz), 6.83-7.16 (7H, 6.89 (d, *J* = 8.9 Hz), 7.00 (d, *J* = 8.0,Hz), 7.05 (d, *J* = 8.5 Hz), 7.09 (d, *J* = 8.6, Hz), 7.10 (d, *J* = 8.5 Hz)), 7.24-7.65 (7H, 7.30 (t, *J* = 8.0Hz), 7.37 (d, *J* = 8.0Hz), 7.40 (d, *J* = 8.9,Hz), 7.51(d, *J* = 8.6, Hz), 7.60 (d, *J* = 1.5Hz)), 7.85 (1H, s).

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 118.4 (1C, s), 122.3 (1C, s), 124.0 (1C, s), 126.5 (1C, s), 127.0 (1C, s), 127.5 (2C, s), 128.6 (2C, s), 130.0-130.2 (2C, 130.1 (s), 130.1 (s)), 131.0 (1C, s), 131.5-131.8 (3C, 131.6 (s), 131.7 (s)), 133.8 (1C, s), 134.3 (1C, s), 134.6 (1C, s), 146.5(1C, s), 148.4 (1C, s), 151.1 (1C, s), 169.8 (1C, s)

Compound 8g

^{1}H NMR: δ 3.58 (1H, d, *J* = 8.1Hz), 3.88 (1H, d, *J* = 8.1 Hz), 4.15-4.25 (2H, 4.20 (s), 4.20 (s)), 4.88 (1H, d, *J* = 5.5 Hz), 6.83-7.23 (10H, 6.89 (d, *J* = 8.9,Hz), 6.90 (d, *J* = 8.2,Hz), 7.03 (d, *J* = 8.2,Hz), 7.05 (d, *J* = 8.5

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Hz), 7.10 (d, *J* = 8.5 Hz), 7.13 (d, *J* = 1.8,Hz), 7.17 (d, *J* = 8.3,Hz), 7.17 (d, *J* = 8.2,Hz)), 7.34-7.48 (4H, 7.40 (d, *J* = 8.9,Hz), 7.42 (d, *J* = 8.3, Hz)), 7.83 (1H, s)

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 113.6 (1C, s), 114.2-114.3 (3C, 114.2 (s), 114.3 (s)), 115.7 (2C, s), 124.0 (1C, s), 126.5 (1C, s), 127.0 (1C, s), 128.6 (2C, s), 129.0 (1C, s), 130.1 (2C, s), 131.6 (1C, s), 133.8 (1C, s), 134.3 (1C, s), 134.6 (1C, s), 146.4-146.7 (2C, 146.5 (s), 146.6 (s)), 148.4 (1C, s), 151.1 (1C, s), 157.4 (1C, s), 169.8 (1C, s)

Compound 8h

^{1}H NMR: δ 3.58 (1H, d, *J* = 8.1, Hz), 3.88 (1H, d, *J* = 8.1 Hz), 4.15-4.25 (2H), 4.20 (s), 4.20 (s)), 4.88 (1H,d, *J* = 5.5 Hz), 6.83-7.23 (10H, 6.89 (d, *J* = 8.9, Hz), 6.90 (d, *J* = 8.2, Hz), 7.03 (d, *J* = 8.2,Hz), 7.05 (d, *J* = 8.5 Hz), 7.10 (d, *J* = 8.5,Hz), 7.10 (d, *J* = 8.5 Hz), 7.13 (d, *J* = 1.8,Hz), 7.17 (d, *J* = 8.2,Hz)), 7.40 (2H, d, *J* = 8.9, Hz), 7.55 (2H, d, *J* = 8.5,Hz), 7.86 (1H, s)

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 113.6 (1C, s), 114.2-114.3 (3C, 114.2 (s), 114.3 (s)), 124.0 (1C, s), 126.5 (1C, s), 127.0 (1C, s), 128.5-128.8 (4C, 128.6 (s), 128.7 (s)), 129.0 (1C, s),129.2 (2C, s), 131.6 (1C, s), 133.6-133.9 (2C, 133.7 (s), 133.8 (s)), 134.3 (1C, s), 134.6 (1C, s), 146.4-146.7 (2C, 146.5 (s), 146.6 (s)), 148.4 (1C, s), 151.1 (1C, s), 169.8 (1C, s).

IR (KBr,Cm^{-1}):1400(-C=N- Sretching),1580(-C=C- stretching),3100(-NH- stretching).Mass (m/z):593

Compound 8i

^{1}H NMR: δ 3.67 (1H, d, *J* = 8.1, Hz), 3.88 (1H, d, *J* = 8.1 Hz), 4.15-4.25 (2H, 4.20 (s), 4.20 (s)), 5.03 (1H, d, *J* = 5.3 Hz), 6.89 (2H, d, *J* = 8.9,Hz), 6.99-7.17 (4H), 7.05 (d, *J* = 8.5 Hz), 7.10 (d, *J* = 8.5,Hz), 7.10 (d, *J* = 8.5 Hz)), 7.26-7.47 (6H, 7.33 (d, *J* = 8.3,Hz), 7.38 (d, *J* = 8.3Hz), 7.40 (d, *J* = 8.9Hz)), 7.55 (2H, d, *J* = 8.5, Hz), 7.86 (1H, s).

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 122.3 (1C, s), 124.0 (1C, s), 127.0 (1C, s), 127.3 (2C, s), 128.5-128.8 (4C, 128.6 (s), 128.7 (s)), 129.2 (2C, s), 131.5-131.8 (3C, 131.6 (s), 131.7 (s)), 133.6-133.9 (2C, 133.7 (s), 133.8 (s)), 134.3 (1C, s), 134.6 (1C, s), 146.5 (1C, s), 148.4 (1C, s), 151.1 (1C, s), 169.8 (1C, s).

Compound 8j

^{1}H NMR: δ 3.68 (1H, d, *J* = 8.1, Hz), 3.88 (1H, d, *J* = 8.1 Hz), 4.15-4.25 (2H, 4.20 (s), 4.20 (s)), 4.99 (1H, d, *J* = 5.3 Hz), 6.89 (2H, d, *J* = 8.9,Hz), 6.99-7.17 (5H, 7.05 (d, *J* = 8.5 Hz), 7.07 (t, *J* = 7.9,Hz), 7.10 (d, *J* = 8.5,Hz), 7.10 (d, *J* = 8.5 Hz)), 7.25 (1H, d, *J* = 8.1,Hz), 7.34-7.62 (6H, 7.41 (d, *J* = 8.1,Hz), 7.40 (d, *J* = 8.9, Hz), 7.49 (d, *J* = 1.7Hz), 7.55 (d, *J* = 8.5,Hz)), 7.86 (1H, s).

^{13}C NMR: δ 57.1 (1C, s), 58.8 (1C, s), 65.5 (1C, s), 73.9 (1C, s), 114.3 (2C, s), 124.0 (1C, s), 126.5 (1C, s), 127.0-127.0 (2C, 127.0 (s), 127.0 (s)), 127.5 (1C, s), 128.5-128.8 (5C, 128.6 (s), 128.7 (s), 128.7 (s)), 129.2 (2C, s), 130.4 (1C, s), 131.6 (1C, s), 133.6-133.9 (2C, 133.7 (s), 133.8 (s)), 134.3 (1C, s), 134.6 (1C, s), 146.5 (1C, s), 148.4 (1C, s), 151.1 (1C, s), 169.8 (1C, s).

Spectral data of Synthesised compounds

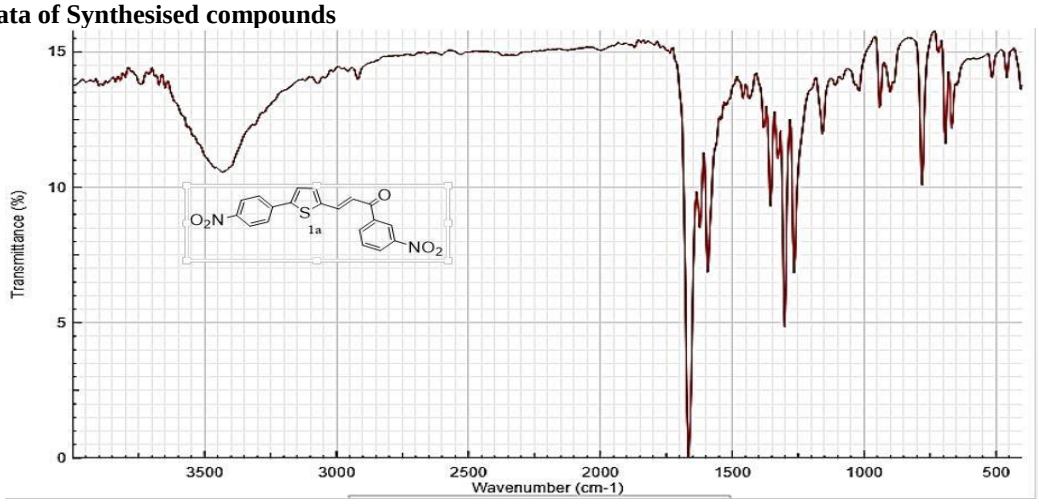

Figure 2: IR spectra of Compound 1,3-diaryl-2- propene-1-ones (1a)

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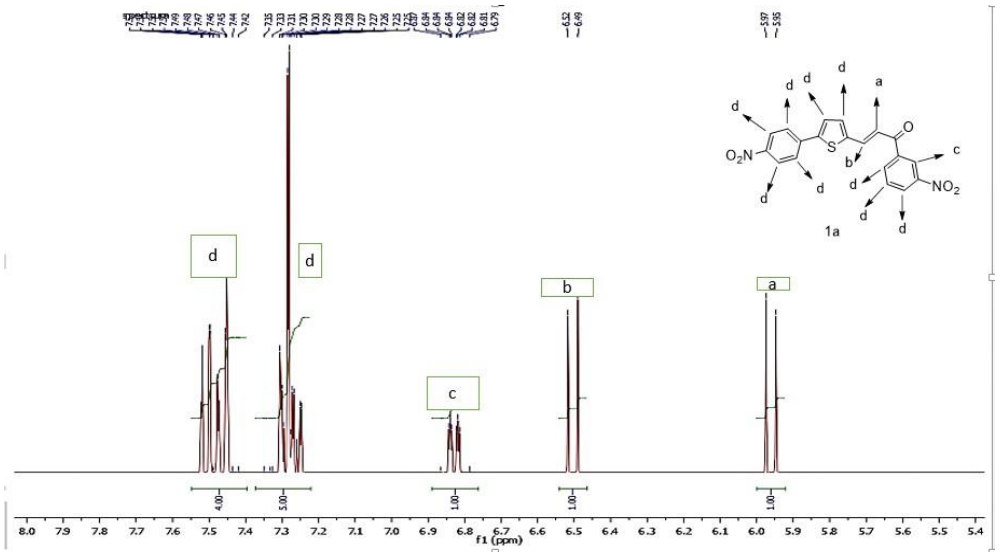

Figure 3: ^{1}HNMR spectra of Compound 1,3-diaryl-2- propene-1-ones (1a)

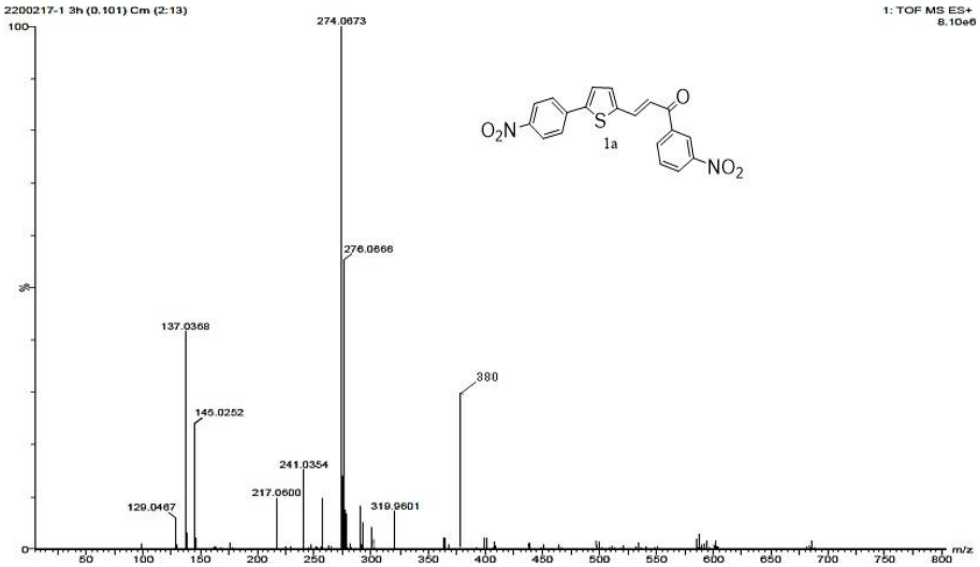

Figure 4: Mass spectra of Compound 1,3-diaryl-2- propene-1-ones (1a)

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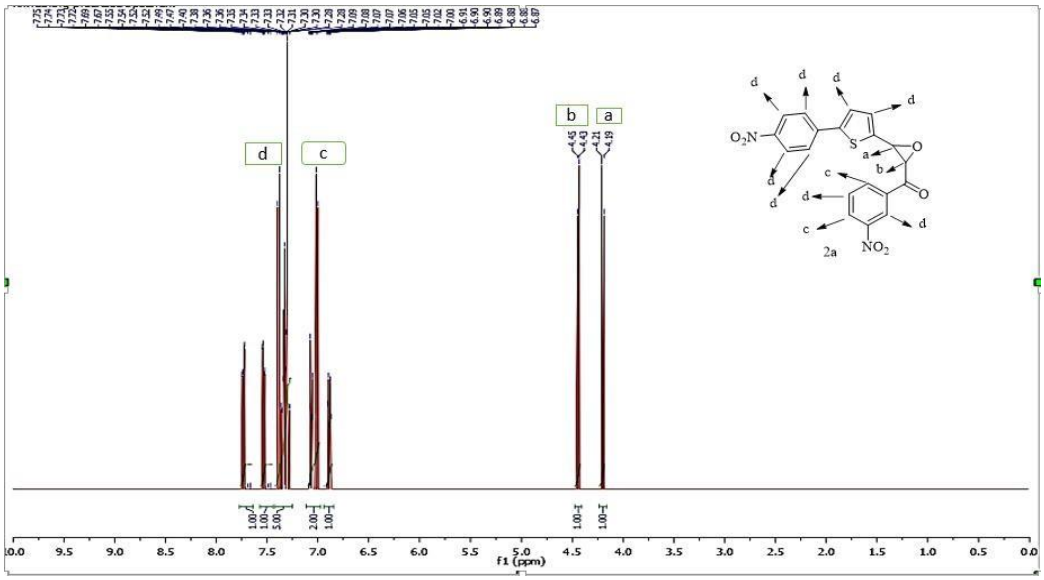

Figure 5: **^{1}HNMR spectra of Compound (3-nitrophenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methanone (2a)**

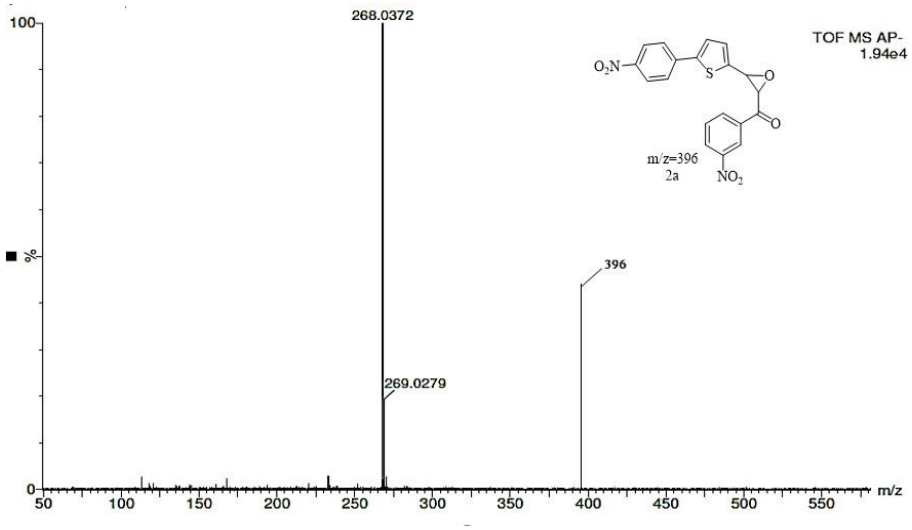

Figure 6: Mass spectra of Compound (3-nitrophenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl) oxiran-2-yl)methanone (2a)

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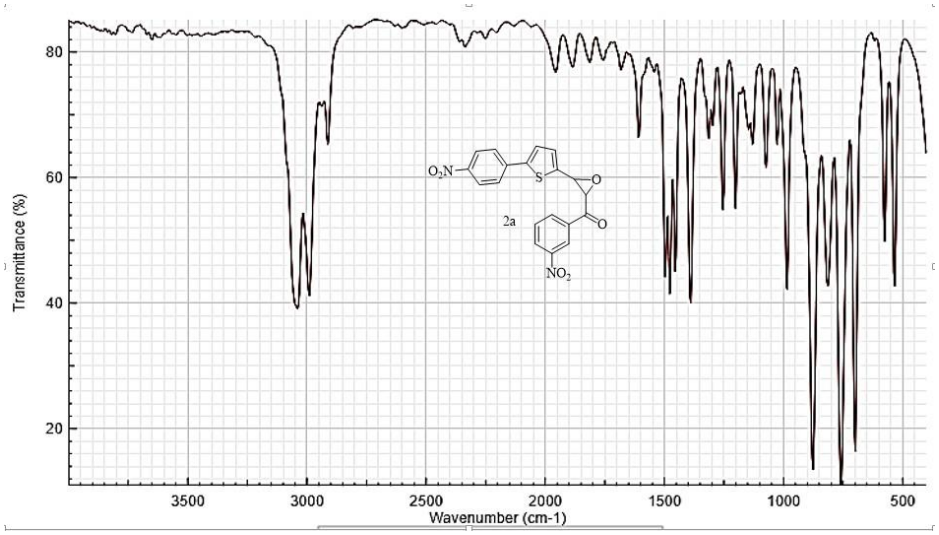


Figure 7: IR spectra of Compound (3-nitrophenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methanone

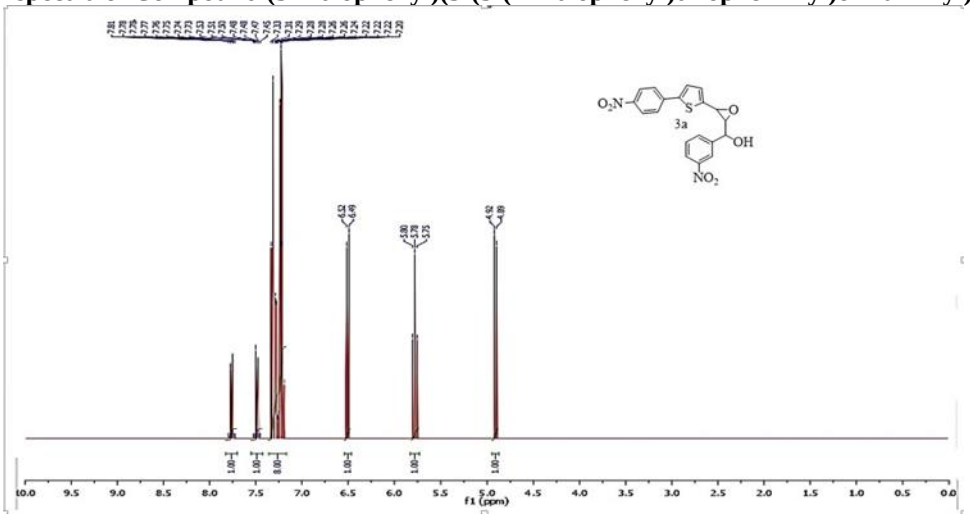
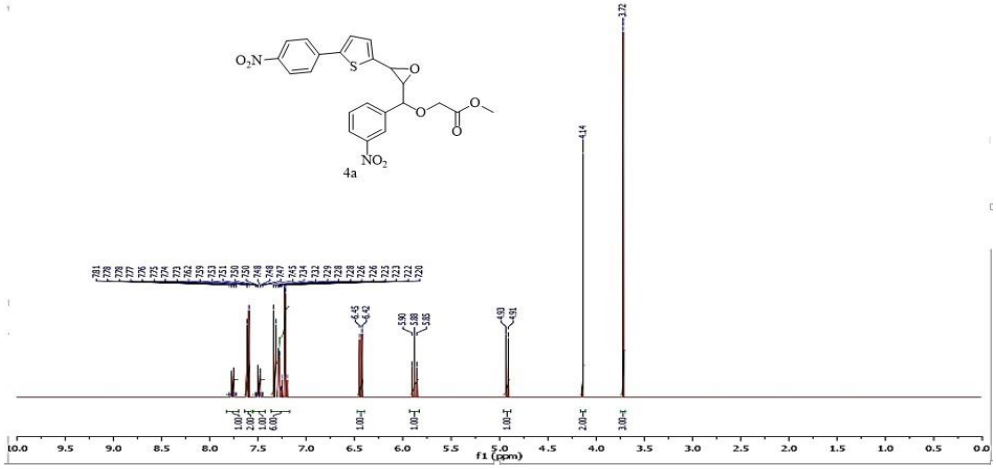


Figure 8: ^{1}HNMR spectra of (3-nitrophenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methanol



(3a)

Figure 9: ^{1}HNMR spectra of methyl 2-((3-nitrophenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetate. (4a)

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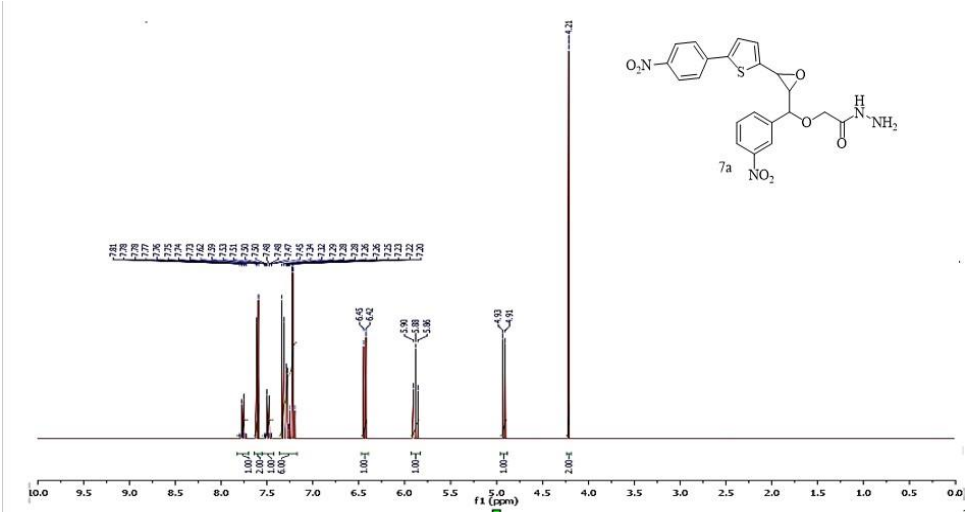

Figure 10: ^{1}HNMR spectra of. 2-((Nitro phenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetohydrazide (7a)

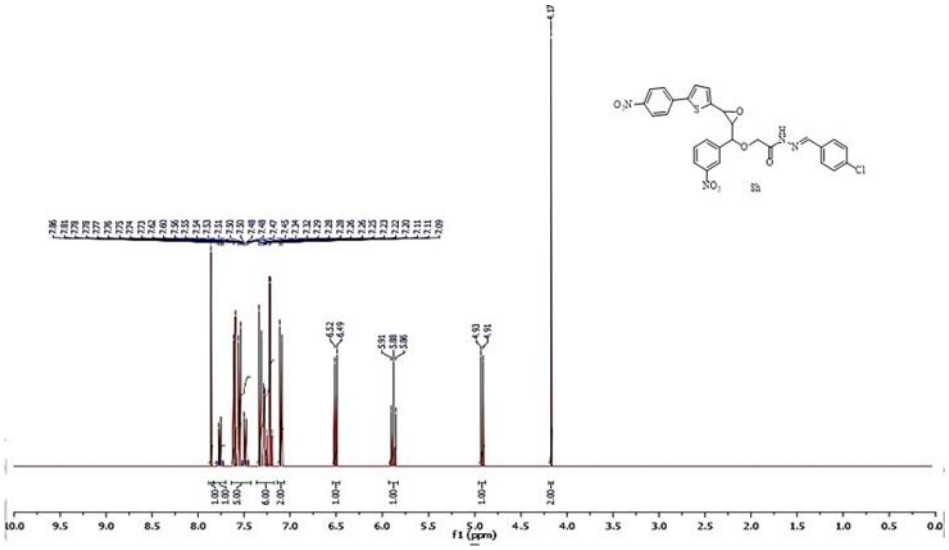

Figure 11: ^{1}HNMR spectra of. (E)-N'-(4-chlorobenzylidene)-2-((3-nitrophenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetohydrazide (8h)

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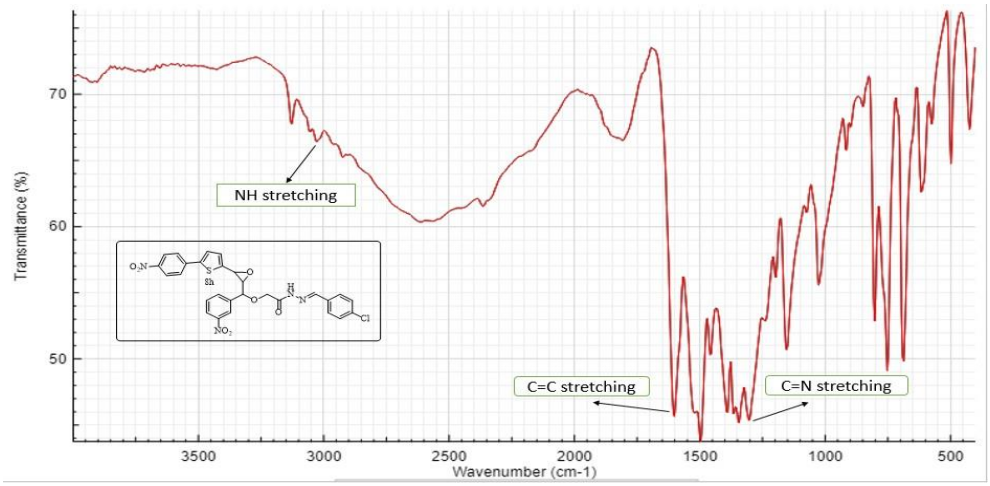

Figure 12: IR spectra of. (E)-N'-(4-chlorobenzylidene)-2-((3-nitrophenyl)(3-(5(4nitrophenyl)thiophen- 2-yl)oxiran-2-yl)methoxy)acetohydrazide (8h)

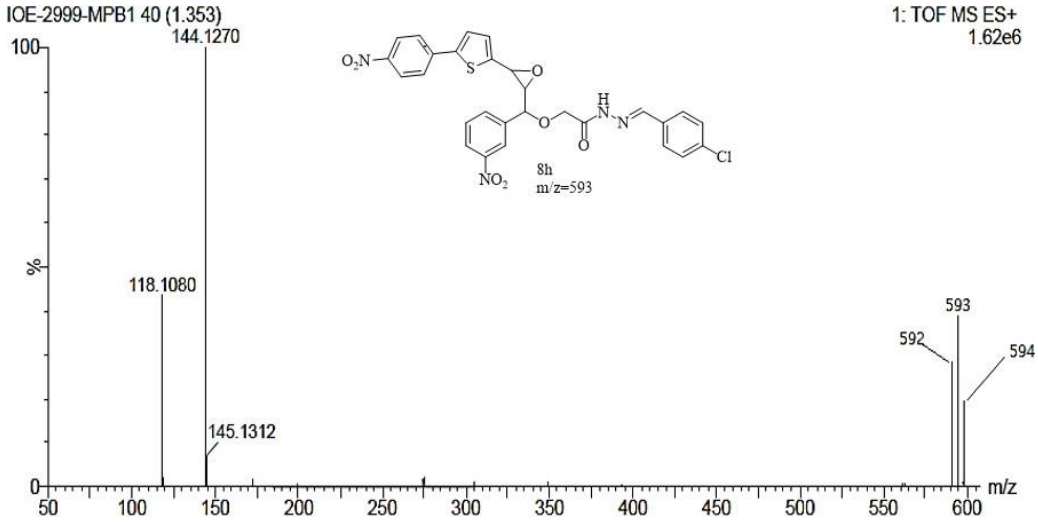

Figure 13: Mass spectra of. (E)-N'-(4-chloro benzylidene)-2-((3-nitrophenyl) (3-(5-(4-nitro phenyl) thiophen - 2-yl)oxiran-2-yl)methoxy)acetohydrazide (8h)

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Pharmacological activity Antiinflammatory Activity

As a reaction of the immune system, inflammation influences several enzymatic and cellular functions that aid in protecting the body against various types of invasive infections. The synthesised hydrazine hybrids' anti-inflammatory properties were assessed by measuring how much less nitric oxide was produced by LPS-stimulated mice macrophages. Short-lived and secreted by a range of cells in response to various pathogenic stimuli is hydrazide. In addition to acting as a vasodilator, platelet inhibitor, and inhibitor of neutrophil adhesion, hydrazides has modulatoryaction in a range of inflammatory diseases. As a result, N'-benzylidene-2-((substituted-phenyl)(3-(5- (4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetohydrazide helps to shield the immune system from infections and other stressors.

The anti-inflammatory assay involves inducing inflammation reactions in macrophage cultures by a simulated microbial infection. Macrophages in the culture medium produce a significant amount of N'-benzylidene-2-((substituted-phenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2- yl) methoxy) acetohydrazide in response to the microbial infection. Compounds with anti- inflammatory activity can decrease inflammatory processes, which in turn causes the release of hydrazide hybrids in the culture medium. The ratio of each compound's anti-inflammatory activityto cell viability is used to assess its anti-inflammatory potential. Table 02 reports the anti-inflammatory assay results. In order to calculate anti-inflammatory ratios, the IC50 values for cell viability were also evaluated.

Using dexamethasone as a reference, all substances were investigated in three categories to assess their anti-inflammatory effect. Compared to the reference chemical dexamethasone, which has an anti-inflammatory ratio of 32, compounds 8b and 8c demonstrated stronger action, with anti- inflammatory ratio values of 38 and 62, respectively. These substances are hence powerful hydrazide inhibitors. Other studied compounds with modest action similar to dexamethasone are 8d and 8e, which had anti-inflammatory ratios of 26 and 25, respectively.

Table 2 summarises the IC50 values and anti-inflammatory ratios of all drugs tested against hydrazides

Entry	IC50 hydrazonerelease (µM)	IC50-cell viability (µM)	Anti inflammatoryratio	IC50 (mM) ± Std. HepG2
8a	35.41 ± 2.04	256.83 ± 12.14	7	0.26 ± 0.02
8b	13.04 ± 2.47	> 500	> 38	0.48 ± 0.04
8c	7.92 ± 1.07	> 500	> 62	0.51 ± 0.01
8d	10.67 ± 1.22	267.48 ± 11.65	26	0.24 ± 0.02
8e	20.88 ± 3.21	> 500	> 25	0.56 ± 0.03
8f	9.90 ± 2.18	147.25 ± 1.65	14	0.13 ± 0.02
8g	57.45 ± 2.34	114.15 ± 1.66	2	0.14 ± 0.00
8h	60.41 ± 8.34	323.39 ± 12.14	5	0.43 ± 0.00
8i	91.88 ± 2.64	264.17 ± 8.74	3	0.41 ± 0.05
8j	9.88 ± 2.21	146.20 ± 1.60	13	0.10 ± 0.01
Dexamethasone	5.01 ± 1.32	159.1 ± 26.34	32	-

Antimicrobial Activity

All of our compounds, *i.e.,* hydrazones 8(a-j) were tested for antimicrobial activity against four test organisms: *Staphylococcus aureus* ATCC6538P, *Escherichia coli* ATCC873, *Pseudomonas aeruginosa* ATCC9027 and *Candida albicans* ATCC2091 using rifampicin (5 µg/disc) and ampicillin (10 µg/disc) as standard drugs.

Determination of Antimicrobial Activity

All compounds were tested against four different microorganisms: *Staphylococcus aurous*, Escherichia *coli*, *Pseudomonas aeruginosa* and *Candida albicans.* The agar well-diffusion method was applied for the determination of inhibition zone and minimum inhibitory concentration (MIC). Briefly, broth culture (0.75 mL) containing *ca*. 106 colon-forming units (CFU) per mL of the teststrain was added to nutrient agar medium (75 mL) at 45 °C, mixed well, and then poured into a 15 cm sterile metallic Petri plate. The medium was allowed to solidify and 8 mm wells were dug with asterile metallic borer, then a DMSO solution of the test sample (1 mL) at 1 mg/mL was added to therespective wells. DMSO served as negative control, and the standard antimicrobial drugs rifampicin (5 µg/disc) and ampicillin (10 µg/disc) were used as positive controls. Triplicate plates for each microorganism strain were prepared and were incubated aerobically at 37 °C for 24 h. The activity was determined by measuring the diameter of zone showing complete inhibition (mm), thereby, the zones were precisely measured with the aid of a Venier caliper (precision 0.1 mm). The growth inhibition was calculated with reference to the positive control. For the individual compounds that showed inhibition zones >10 mm, MIC values were determined by means of the *agar well-diffusion* method for

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concentrations of 1.0, 0.50, 0.25, 0.125, 0.063 and 0.031 mg/mL in DMSO. The testswere performed in triplicate, and the results were averaged. Minimum bactericidal concentrations
(MBC) were determined for all chloro derivatives which exhibit good activities for concentrations of1.0, 0.50, 0.25, 0.125, 0.063 and 0.031 mg/mL in DMSO. The results are listed in below Tables

Table 3 Antimicrobial activities of all the synthesized compounds

Compound	**Zone of inhibition (mm)**		**Minimum inhibition concentration(MIC) g/mL**	
	S. aureus	***C. albicans***	***S. aureus***	***C. albicans***
8a	-	20	-	250
8b	-	15	-	-
8c	**17**	**20**	**100**	**50**
8d	14	20	120	500
8e	12	15	-	-
8f	**19**	**22**	**63**	**31**
8g	18	25	125	31
8h	22	26	50	50
8i	**18**	**20**	**63**	**125**
8j	17	17	-	-
Rifampicin	32	-	-	-
Ampicillin	30	-	-	-
DMSO	-	14	-	-

(-) Indicates No Activity

The agar well-diffusion method was used for studying the potential activities of these compounds. All compounds only showed potent activity against *Staphylococcus aureus* and
Candida albicans in the following ranking:8(a-e). Minimum inhibitory concentration (MIC) values for the individual compounds that showed inhibition zones > 10 were determined by means of the *agar well-diffusion* method in DMSO. The results of antimicrobial activities of our synthesized compounds against *S. aureus* and *C. albicans* are shown in Table 3 as zone of inhibition (in mm) and minimum inhibitory concentration, MIC (mg/mL). Minimum bactericidal concentrations (MBC)were determined for all Chloro derivatives exhibited good activities. These results are listed in below table 4.

Table 4. Determination of minimum bactericidal concentration (MBC) µg/mL of chloro-derivatives.

Conc µg/mL	1000	500	250	125	63	31	1000	500	250	125	63	31
	S. aureus						*C. albicans*					
8c	-	-	-	+	+	+	-	-	-	-	+	+
8f	-	-	-	+	+	+	-	-	+	+	+	+
8i	-	-	+	+	+	+	-	-	-	-	+	+

Result and discussion

All the synthesized compounds have been characterized on the basis of their physical data and spectral analysis. Structures of all of the newly synthesized compounds were established by IR, NMR (^{1}H, ^{13}C) analyses. The IR spectra of the compound 8h reveals the presence of a broad band at 3400 cm^{-1} for the N–H stretching vibration,. Peaks at 1612 cm^{-1} are for the C=C group, and peaks in the regions 1375 cm^{-1} indicate the presence of C=N stretching. From 1HNMR spectra Compound 8h we observed aromatic peaks in the range of ∂: 6.891-7.859 ppm ,and peak at ∂:3.656ppm confirms CH_2 peak of epoxide. In summary, we have presented a multistep cyclo-condensation protocol synthesis that offers several benefits, including simple setup, a quick and selective method for simultaneously preparingthe target library, the use of low-cost materials, an environmentally

friendly process, and the provision of antimicrobial and anti-inflammatory properties. The synthesised compounds N'-benzylidene-2-((substituted- phenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetohydrazide, which include compounds 8a, 8b, 8c, 8d, 8e, 8f, 8g, 8h, and 8i, demonstrated

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significant anti-inflammatory activity that was on par with Dexamethasone and in antimicrobial activity against Rifampicin and Ampicillin. Nevertheless, the addition of N'-benzylidene-2-((substituted-phenyl)(3-(5-(4-nitrophenyl)thiophen-2-yl)oxiran-2-yl)methoxy)acetohydrazide moieties enhanced the antibacterial and anti-inflammatory properties even further. Furthermore, a few of the compounds showed strong antibacterial and anti-inflammatory characteristics, which could be attributed to the addition of a thiophene ring and electron-withdrawing groupslike Cl.

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