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SYNTHESIS AND EVALUATION OF NEW SUBSTITUTED N- (NAPHTHALEN-1-YLMETHYL)-2-OXO-2H-CHROMENE-3- CARBOXAMIDE DERIVATIVES AS ANTIMICROBIAL AGENTS

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ABSTRACT

Naphthalene structure consists of a fused pair of benzene rings. 6-Substituted Naphthalene 2-carboxamide derivatives (R=Br, CF_3) are found to be most potent antimicrobial, antitubercular agents. Numerous biological activities have been attributed to simple coumarins as well as pyranocoumarins, furocoumarins and analogues, e.g. antimicrobial, antiviral, anticancer, enzymes inhibition, anti-inflammatory, antioxidant, and central nervous system activities. Coumarin derivatives have also been used as anticoagulants and also exhibit anti-HIV and anti-tuberculosis (anti-TB) activities. The synthesized compounds are purified by column chromatography and characterized by analytical and spectral data (IR, 1H NMR and Mass). The synthesized compounds were evaluated for antibacterial and antifungal activities.

KEYWORDS: Diethyl Malonate, Triethyl amine, Coumarins, Antibacterial agents, Anti-fungal agents.

INTRODUCTION

Antimicrobial susceptibility testing can be used for drug discovery, epidemiology and prediction of therapeutic outcome. In this review, we focused on the use of antimicrobial testing methods for the *in vitro* investigation of extracts and pure drugs as potential antimicrobial agents.

After the revolution in the “golden era”, when almost all groups of important antibiotics (tetracyclines, cephalosporins, aminoglycosides and macrolides) were discovered and the main problems of chemotherapy were solved in the 1960s, the history repeats itself nowadays and these exciting compounds are in danger of losing their efficacy because of the increase in microbial resistance.[1] Currently, its impact is considerable with treatment failures associated with multidrug-resistant bacteria and it has become a global concern to public health.[2],[3]

For this reason, discovery of new antibiotics is an exclusively important objective. Natural products are still one of the major sources of new drug molecules today. They are derived from prokaryotic bacteria, eukaryotic microorganisms, plants and various animal organisms. Microbial and plant products occupy the major part of the antimicrobial compounds discovered until now.[4]

Plants and other natural sources can provide a huge range of complex and structurally diverse compounds. Recently, many researchers have focused on the investigation of plant and microbial extracts, essential oils, pure secondary metabolites and new synthetized molecules as potential antimicrobial agents.[5], [6], [7] However, when we reviewed the published articles on the antimicrobial effect of these natural products, the comparison between results is often difficult, because of the use of different non-standardized approaches inoculum preparation techniques, inoculum size, growth medium, incubation conditions and endpoints determination.

The fact that a plant extract exhibits antimicrobial activity is of interest, but this preliminary part of data should be trustworthy and allow researchers to compare results, avoiding work in which researchers use the antimicrobial activity investigation only as a complement to a phytochemical study.

A variety of laboratory methods can be used to evaluate or screen the *in vitro* antimicrobial activity of an extract or a pure compound. The most known and basic methods are the disk-diffusion and broth or agar dilution methods. Other methods are used especially for antifungal testing, such as poisoned food technique. To further study the antimicrobial effect of an agent in depth, time-kill test

and flow cytofluorometric methods are recommended, which provide information on the nature of the inhibitory effect (bactericidal or bacteriostatic) (time-dependent or concentration-dependent) and the cell damage inflicted to the test microorganism.

Owing to the new attraction to the properties of new antimicrobial products like combating multidrug-resistant bacteria, it is important to develop a better understanding of the current methods available for screening and/or quantifying the antimicrobial effect of an extract or a pure compound for its applications in human health, agriculture and environment. Therefore, in this review, the techniques for evaluating the *in vitro* antimicrobial activity were discussed in detail.

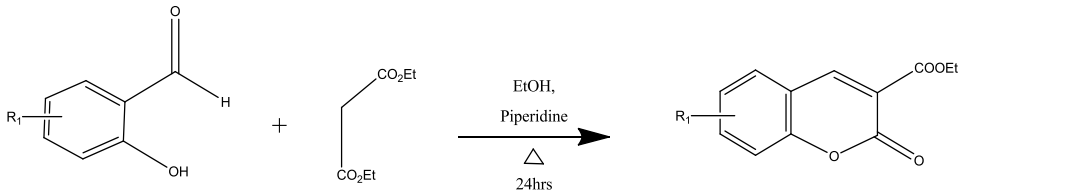
MARERIALS AND METHODS

Reagents and various solvents are used for synthetic work. All the reactions were performed in dried Borosil glass beakers, round bottom flasks, conical flasks. Precoated silica gel plates (MERK) were used for TLC. Compounds melting points were determined by the open capillary method. JASCO UV Chamber was used for the detection of spots in TLC. IR spectra were recorded on the BRUKER FTIR spectrometer.

1H NMR spectra were recorded on a BRUKER-400MHZ spectrometer using DMSO as solvent. The chemical shift data were expressed as values relative to TMS in δ ppm.

SCHEME-I

STEP -1: Preparation of ethyl 2-oxo-2H-chromene-3-carboxylate

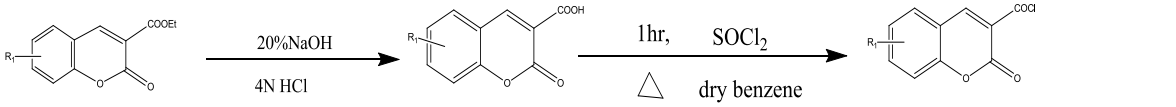


Substituted-hydroxybenzaldehyde (1) + diethyl malonate (2) → ethyl 2-oxo-2*H*-chromene-3-carboxylate (3)

1a: R_1=5-OCH_3, **1b:** R_1= 4-diethylamine, **1c:** R_1=5-NO_2, **1d:** R_1=5-Cl, **1e:** R_1= H

3a: R_1=6-OCH_3, **3b:** R_1= 7-diethylamine, **3c:** R_1=6-NO_2, **3d:** R_1=6-Cl, **3e:** R_1= H

STEP -2: Preparation of 2-oxo-2H-chromene-3-carbonyl chloride



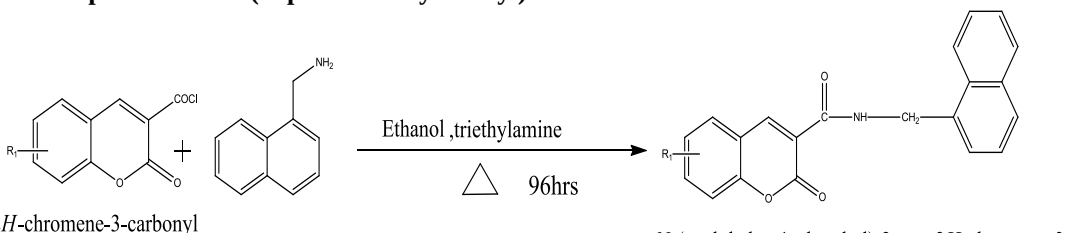
ethyl 2-oxo-2*H*-chromene-3-carboxylate (3) → 2-oxo-2*H*-chromene-3-carboxylic acid (4) → 2-oxo-2*H*-chromene-3-carbonyl chloride (5)

3a: R_1=6-OCH_3, **3b:** R_1= 7-diethylamine, **3c:** R_1=6-NO_2, **3d:** R_1=6-Cl, **3e:** R_1= H

4a: R1=6-OCH_3, **4b:** R1= 7-diethylamine, **4c:** R1=6-NO_2, **4d:** R1=6-Cl, **4e:** R1= H

5a: R1=6-OCH_3, **5b:** R1= 7-diethylamine, **5c:** R1=6-NO_2, **5d:** R1=6-Cl, **5e:** R1= H

STEP -3: Preparation of N-(naphthalen-1-ylmethyl)-2-oxo-2H-chromene-3-carboxamide



2-oxo-2*H*-chromene-3-carbonyl chloride (5) + naphthalen-1-ylmethanamine (6) → *N*-(naphthalen-1-ylmethyl)-2-oxo-2*H*-chromene-3-carboxamide (7)

5a: R_1=6-OCH_3, **5b:** R_1= 7-diethylamine, **5c:** R_1=6-NO_2, **5d:** R_1=6-Cl, **5e:** R_1= H

7a: R_1=6-OCH_3, **7b:** R_1= 7-diethylamine, **7c:** R_1=6-NO_2, **7d:** R_1=6-Cl, **7e:** R_1= H

General procedure

STEP-1: Preparation of ethyl 2-oxo-2H-chromene-3-carboxylate (3)

Mixture of the appropriate salicylaldehyde (**1,** 0.50 mole) in EtOH (90 mL) is refluxed under magnetic stirring with diethyl malonate (**2,** 0.55mole) and catalytic amounts of piperidine for 24 h. After cooling to room temperature, the solution is filtered to give the desired 2-oxo-2H-chromene-3carboxylic acid ethyl ester **(3).**

STEP-2: Preparation 2-oxo-2H-chromene-3-carbonyl chloride (5)

Compound **(3)** on hydrolysis with NaOH 20% (100 mL), followed by acidification with hydrochloric acid (4 N) resulted in to the desired 2-oxo-2Hchromene-3-carboxylic acid **(4)** The 2-oxo-2H-chromene-3-carboxylic acid (**4,** 0.05 mol) is added with thionyl chloride (5ml) and **(4)** refluxed for 3 h at 100 C under magnetic stirring. After cooling to room temperature, the solution was filtered to give the desired chromene carbonyl chloride **(5). 5a).** 6-methoxy-2oxo-2H-chromene-3-carbonyl chloride; light brown crystals; m.p:92-94^{o}C, % yield: 62; R_f: 0.12. **5b).** 7-(diethyl amino)-2 oxo-2H-chromene-3-carbonyl chloride; yellow solid; m.p:80-82^{o}C, % yield: 73.5; Rf: 0.8. **5c).** 6-Chloro-2oxo-2H-chromene-3-carbonyl chloride; white solid; m.p:123-125^{o}C, % yield: 73; Rf: 0.4. **5d).** 6-Nitro-2oxo-2H-chromene-3-carbonyl chloride; reddish brown solid; m.p:90-92^{o}C, % yield: 53.5; R_f: 0.26. **5e).** 2oxo-2H-chromene-3-carbonyl chloride; white crystal; m.p:106-108^{o}C, % yield: 70; R_f: 0.32.

STEP-3: Preparation of N-(naphthalen-1-ylmethyl)-2-oxo-2H-chromene-3-carboxamide (7)

A solution of the naphthalene-1-yl methanamine **(6,** 0.0072 mol) in the ethanol (30 mL) is added dropwise to a solution of the appropriate 2-oxo-2H-chromene-3-acyl chloride **(5,** 0.0072 mol) and triethylamine (1 mL). The reaction mixture is stirred for 96h at reflux, then cooled to room temperature and filtered off to remove triethylammonium salt. The organic layer is concentrated under vacuum, cooled to 4^{o}C to give the final compounds **(7). 7a).** 6-methoxy-N-(naphthalen-1-ylmethyl)-2-oxo-2H-chromene-3-carboxamide; light brown crystals; m.p: 183^{0}C; %yield:57; R_f:0.34. (Mobile phase: hexane: ethyl acetate; 7:3). 7b).7-(diethylamino)-N-(naphthalen-1-ylmethyl)-2-oxo-2H-chromene-3-carboxamide; reddish brown solid; m.p: 1900C; %yield:63; Rf:0.25. **7c).**6-Chloro-N-(naphthalen-1-ylmethyl)-2-oxo-2H-chromene-3-carboxamide; white solid; m.p: 153^{0}C; %yield:69; R_f:0.36. **7d (**6-Nitro-2-oxo-2H-chromene-3-carboxamide) yellow solid; m.p: 201^{0}C, percentage yield: 47; R_f: 0.25. **7e).** N-(naphthalen-1-ylmethyl)-2-oxo-2H-chromene-3-carboxamide; light brown crystal; m.p: 161^{0}C; %yield: 70; R_f: 0.32.

EVALUATION OF ANTIMICROBIAL ACTIVITY

The antibacterial activity of substituted chalcones **(7a-7e**) had been assayed against four different strains of bacteria by cup-plate agar diffusion method by measuring the zone of inhibition. The test organisms were sub cultured using nutrient broth medium. The tubes containing sterilized medium were inoculated with respective bacterial strains. After incubation at 37±1^{o}c for 24 hours they were stored in refrigerator. The stock cultures were maintained. Bacterial inoculum was prepared by transferring a loopful of culture to nutrient broth in conical flask. The flasks were incubated at 37±l^{o}c for 48 hours before the experimentation. Solution of test compound was prepared by dissolving the sample in DMSO. A reference standard for both Gram positive and Gram-negative bacteria was made by dissolving accurately weighed quantity of Moxifloxacin in sterile distilled water. The nutrient agar medium was sterilized by autoclaving at 121^{o}C for 15min. The petriplates, tubes and flasks plugged with cotton were sterilized in hot air oven at 160^{o}c for two hours. Into each sterilized petri plate, about 25mL of molten nutrient agar medium inoculated with the respective strains of bacteria was transferred aseptically. The plates were left at room temperature to allow solidification. In each plate, cups of 5 mm diameter were made with sterile borer. Then 100µl of the test solution was added to the respective cups aseptically and labelled accordingly. The plates were kept undisturbed for at least 2 hours in refrigerator to allow diffusion of the solution properly into the nutrient agar medium. After the incubation of the plates at 37±1^{o}c for 24 hours, the diameter of the zone of inhibition surrounding each of the cups was measured with the help of the scale and tabulated.

Anti-fungal Activity

The anti-fungal activity of all compounds was determined on potato dextrose agar medium against *Rhizopusoryzae*, *Aspergillus Niger, Aspergillus flavus, Candida albicans* and *Saccharomyces cerevisiae* organisms using Amphotericin-B as a standard and DMF was used as control. The sterile molten potato dextrose medium was cooled to 45^{o}c and inoculated with test organisms and mixed the contents thoroughly and poured into the sterile petri dishes under aseptic conditions. All the inoculated petri dishes were incubated at 28^{0}c for 4 days and the extent diameter of inhibition was measured as the zone of inhibition in millimeters.

Preparation of test solution

10mg of each compound was dissolved in 10ml of DMF, from this stock solution further required concentration of 100µg/ml were prepared by dilution using DMF.

Preparation of standard anti-fungal solution

Ketoconazole was used as standard anti-fungal for comparison and solution were prepared by using sterile water, so that the concentrations of the solution were 100µg/ml.

Methods of testing

The method of testing fungicidal activity is the same as that of antibacterial testing. DMF was used as a solvent

control.

RESULTS AND DISCUSSION

Spectral characterization

Synthesized title compounds are characterized by their spectral analysis. For instance, the compound **7b**, in its I.R spectrum showed characteristic N-H (str) absorption band at 3400 cm-1. Carbonyl (C=O) Stretching was seen at 1635 cm^{-1}. Aliphatic and aromatic C-H, (str) bands were present at 2926 and 3046 cm-1 respectively. 1H-NMR spectrum of the compound **7b** showed signals due to ethyl, methylene and aromatic protons present. Six protons of two methyl groups appeared as a triplet at 1.29-1.27 ppm (J= 4Hz) and two methylene groups for four protons appeared as a quartet at 3.68-3.64 ppm. The two protons of methylene group attached to amide nitrogen observed as a doublet at 4.68-7.66 ppm. All eleven protons aromatic protons resonated between 7.37-8.019 ppm. Mass spectrum of the compound **7b** (Molecular weight - 400.4) showed M+1 peak at m/z 401. Based on the spectral analysis, the compound is characterized as 7- (diethylamino)-N-(naphthalene-1-ylmethyl)-2-oxo-2H-chromene-3-carboxamide.

Antibacterial activity

Result of antibacterial activity of substituted N-(naphthalen-1-ylmethyl)-2-oxo-2H-chromene-3-carboxamides **(7a-7e)** against Gram-negative bacteria at various concentrations on different strains of bacteria was given in Table:1

Table 1: Antibacterial activity against E. coli (Zones of inhibition in mm).

Compounds	50µg/ml (in mm)	100µg/ml (in mm)	300µg/ml (in mm)
7a	12	16	16
7b	15	18	15
7c	14	17	18
7d	17	19	19
7e	14	17	15
MXN	19	22	22

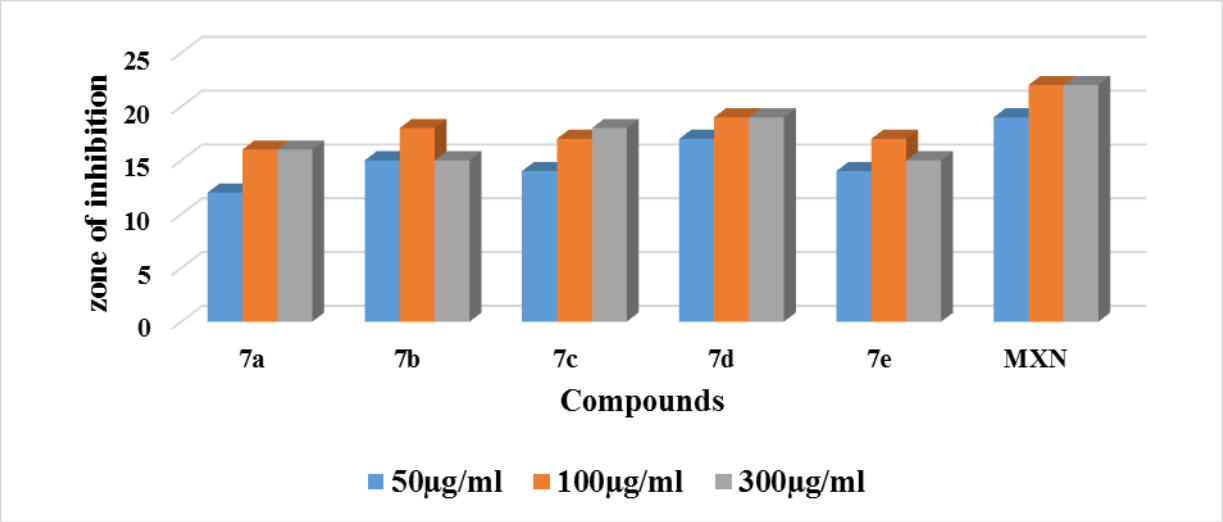


Figure 1: Antibacterial activity against E. coli (Zones of inhibition in mm)

Table 2: Antibacterial activity against *Klebsiella pneumonia* (Zones of inhibition in mm)

Compounds	50µg/ml (in mm)	100µg/ml (in mm)	300µg/ml (in mm)
7a	11	13	16
7b	9	11	13
7c	10	12	15
7d	12	15	17
7e	09	12	14
MXN	16	20	24

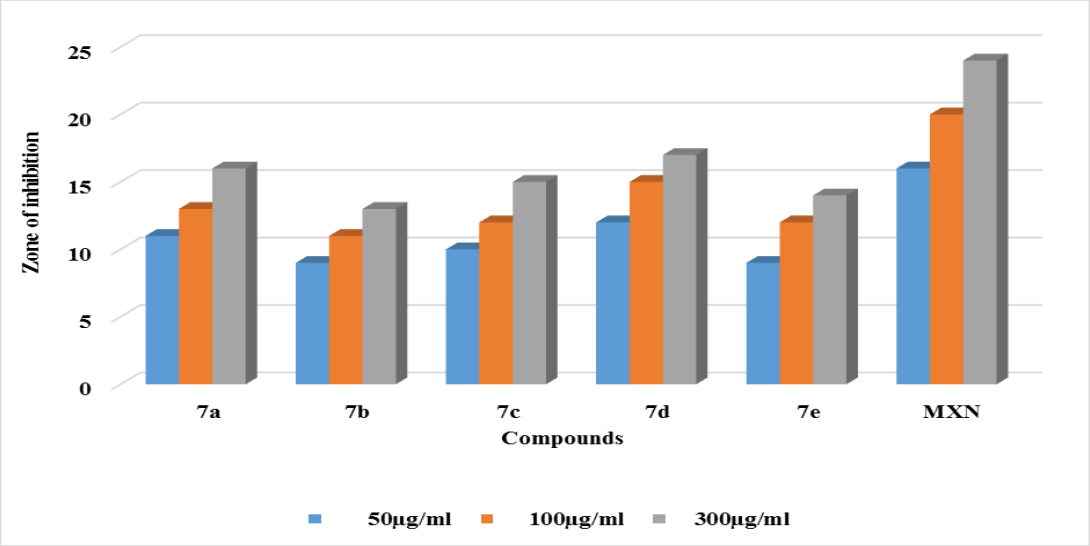


Figure 2: Antibacterial activity against *Klebsiella pneumonia* (Zones of inhibition in mm).

Table 3: Antibacterial activity against *Bacillus substilis* - (Zones of inhibition in mm)

Compounds	50µg/ml (in mm)	100µg/ml (in mm)	300µg/ml (in mm)
7a	12	13	18
7b	16	19	21
7c	14	16	18
7d	12	17	18
7e	15	17	18
MXN	18	20	23

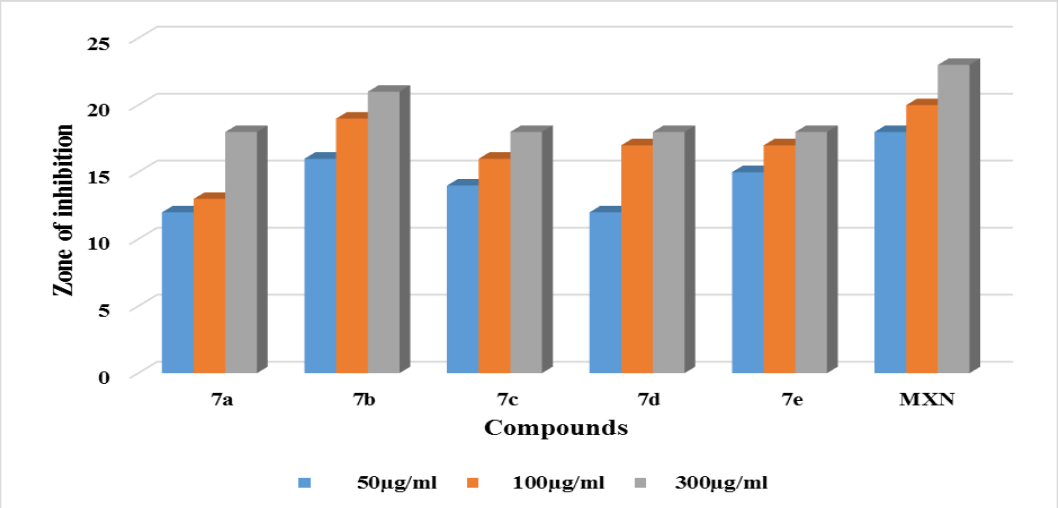


Figure 3: Antibacterial activity against *Bacillus substilis* (Zones of inhibition in mm)

Table 4: Antibacterial activity against Staphylococcus aureus (Zones of inhibition in mm)

Compounds	50µg/ml (in mm)	100µg/ml (in mm)	300µg/ml (in mm)
7a	12	16	18
7b	16	19	20
7c	09	15	16
7d	10	18	19
7e	10	12	16
MXN	19	22	24

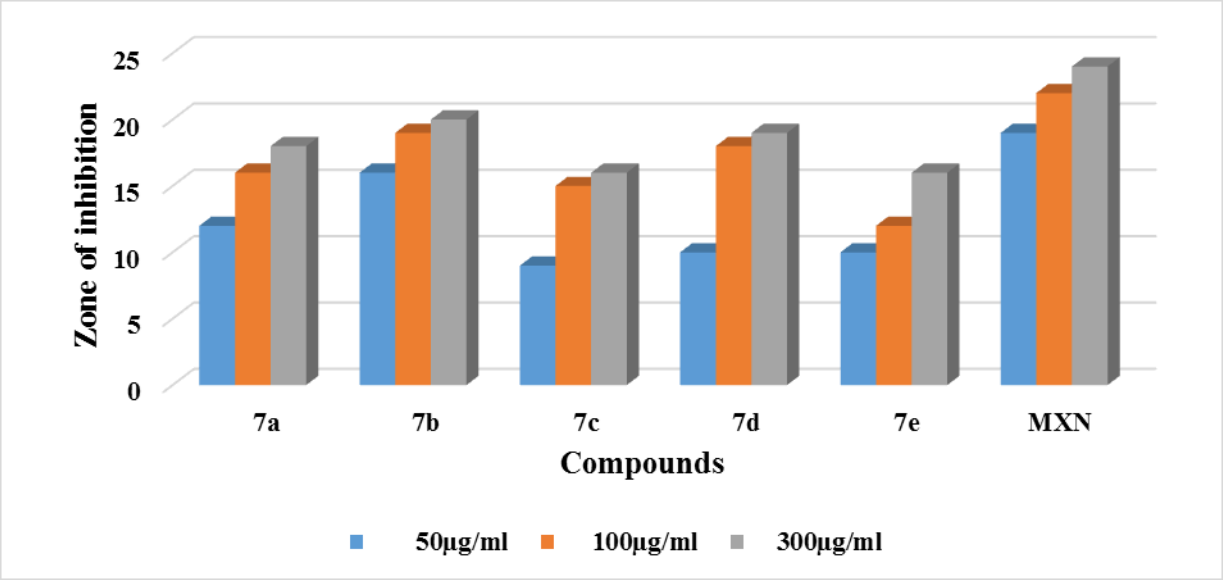


Figure 4: Antibacterial activity against Staphylococcus aureus (Zones of inhibition in mm).

Antibacterial activity (zone of inhibition in mm) of synthesize N-(naphthalen-1-ylmethyl)-2-oxo-2H-chromene-3-carboxamides (7a-7e).

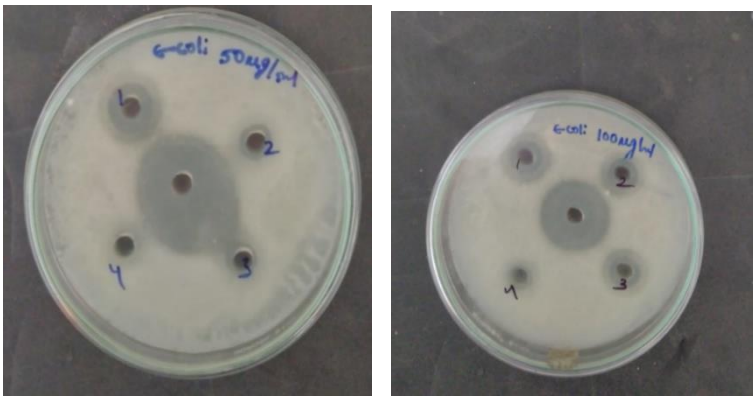


Figure 5: *E.Coli*-(Zone of inhibition in mm)

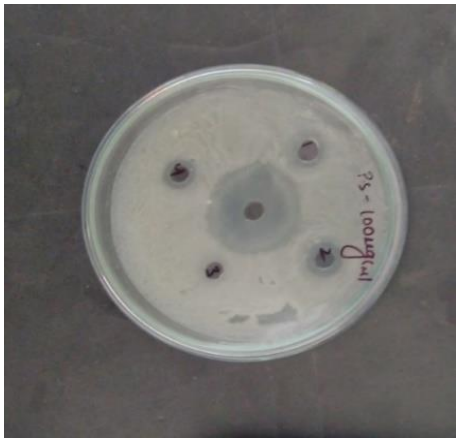


Figure 6: *Klebsiella Pnuemonia*- (Zone of inhibition in mm).

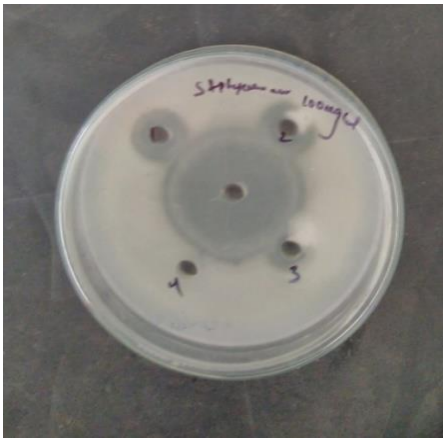


Figure 7: Staphylococcusaureus-(Zone of inhibition in mm).

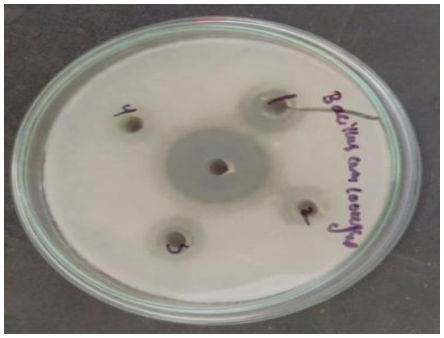


Figure 8: *Bacillus subtilis* - (Zone of inhibition in mm)

The synthesized derivatives **7a-7e** has been evaluated for their antimicrobial activity against Gram-positive (*Staphylococcus aureus, Bacillus subtilis*) and Gram-negative (*Escherichia coli, Klebsiella pneumonia*) bacteria by measuring the zone of inhibition. The results have been compared with a broad-spectrum antibacterial agent Moxifloxacin as standard drug. The compound **7d** substituted with 6-Cl group showed significant zone of inhibition 19mm at 300µg/ml against E. coli. when compared 22mm zone of inhibition shown by standard Moxifloxacin at 300µg/ml. However, the compounds **7a** and **7d** substituted with methoxy, 6-Cl groups showed significant zone of inhibition 16mm, 17mm at 300µg/ml against Klebsiella pneumonia. when compared 24mm zone of inhibition shown by standard Moxifloxacin at 300µg/ml. The compounds **7b, 7e** substituted with 7-diethylamine, 6-Cl groups showed significant zone of inhibition of 21mm, 18mm at 300µg/ml Bacillus substilis. when compared 23mm zone of inhibition shown by standard Moxifloxacin at 300µg/ml. The compounds **7b, 7d** substituted with 7-diethylamine, 6-Cl groups showed significant zone of inhibition of 20mm, 19mm at 300µg/ml against Staphylococcus aureus. When compared 24mm zone of inhibition shown by standard Moxifloxacin at 300µg/ml.

Antifungal activity

Antifungal activity of compounds 7a-7e (Zone of inhibition in mm) Among the series the compound **7d** showed the potent activity with zone of inhibition 21mm against S. cervisiae at 100µg/ml. when compared 24mm zone of inhibition shown by standard ketoconazole at 100µg/ml.

Table 5: Antifungal activity of compounds 7a-7e (Zone of inhibition in mm) (Conc: 100µg/ml).

Compounds	C. albicans (in mm)	A. niger (in mm)	S. cervisiae (in mm)
7a	10	12	8
7b	13	8	12
7c	15	12	19
7d	18	12	21
7e	6	10	14
Ketoconazole	25	22	24

Note: 8-12 mm poor activity, 13-16 mm moderate activity, 18-25 mm significant activity.

CONCLUSION

The synthesized compounds are purified by column chromatography. Compounds are characterized by the analytical and spectral (IR, ^{1}H NMR and Mass) data. The synthesized compounds were evaluated for anti-microbial activity. When the two moieties are fused or combined and screened for antibacterial studies, they showed moderate to strong antibacterial activity against Gram positive and Gram-negative bacteria. It is clearly concluded that the synthesized compounds with substitution at 4, 5th position of Benzopyrone naphthalene conjugates showed potent antibacterial activity against Gram positive and Gram-negative bacteria. The compound **7d** substituted with 6-Cl group showed zone of inhibition of 19mm at 300µg/ml against E. coli. when compared to 22mm shown by standard Moxifloxacin at 300µg/ml. However, the compounds **7a** and **7d** substituted with 6-methoxy, 6-Chloro groups showed significant zones of inhibition of 16mm & 17mm at 300µg/ml against Klebsiella pneumonia, respectively when compared 24mm zone of inhibition shown by standard Moxifloxacin at 300µg/ml. The compounds **7b, 7e** substituted with 7-diethylamine, 6-Chloro groups showed significant zone of inhibition of 21mm, 18mm at 300µg/ml Bacillus substilis. when compared to 23mm zone of inhibition shown by standard Moxifloxacin at 300µg/ml. The compounds **7b, 7d** substituted with 7-diethylamino, 6-Chloro groups showed significant zone of inhibition of 20mm, 19mm at 300µg/ml against Staphylococcus aureus. when compared 24mm shown by standard Moxifloxacin at 300µg/ml. Among the series the compound **7d** showed the potent antifungal activity with zone of inhibition 21mm against S. cervisiae at 100µg/ml. when compared 24mm zone of inhibition shown by standard ketoconazole at 100µg/ml.

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