Synthesis, Characterisation and biological activity of some Heterocyclic Derivatives

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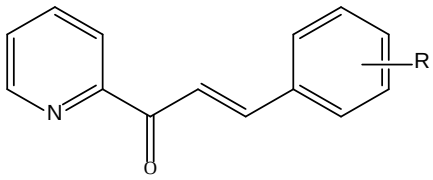
Abstract: In this study the chemistry of Heterocyclic Chalcones has generated intensive scientific interest due to their biological and industrial applications. Chalcones are natural biocides and are well known intermediates in the synthesis of heterocyclic compounds exhibiting various biological activities. A new series of Heterocyclic chalcones showed diversified biological activities. According to Claisen-Schmidt condensation a series of novel substituted thiophenyl chalcones were synthesized and evaluated for their antibacterial and antifungal activity against three different bacterial strains such as *Moraxella*, *Enterobacter* and *Pseudomonas aeruginosa* and three fungal strains against *Candida albicans*, *A.niger* and *Trichophyton*. The synthesized compounds have been characterized by TLC, elemental analysis, IR and ^{1}H & ^{13}C NMR spectroscopy.

Key words: Claisen-Schmidt condensation, Chalcone, antibacterial & antifungal activity

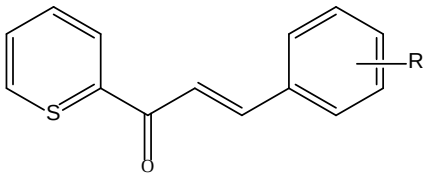
Introduction

The chemistry and biological activities of Heterocyclic chalcone **(1)** have been of interest for a long time. Chalcones are intermediary compounds of the biosynthetic pathway of the naturally flavonoids.

Structure of heterocyclic chalcones obtained from the Claisen Schmidt condensation between heteroaryl methyl ketones and substituted benzaldehydes.



pyridine-2-yl-chalcone



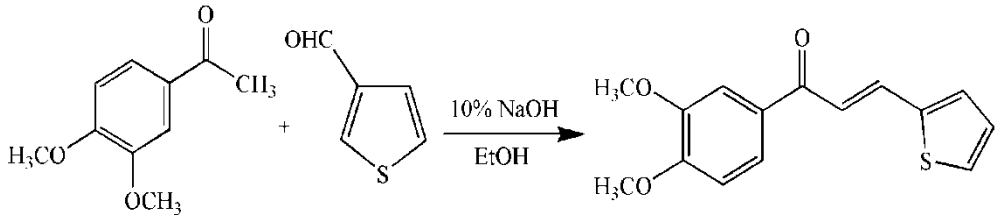
thiophene-2-yl-chalcone

The benefit of synthesis and comparative investigation of biological activity of synthetic chalcone analogues with similar structure is the possibility to study the structure-activity relationship. The compounds with chalcone derivative as backbone have been reported to possess varied biological and pharmacological activities, including antimicrobial[(2-4)], anti-

inflammatory[5], analgesic[6], cytotoxic[7], antimalarial[8], antitubercular[9], anti-HIV[10], antifeedant[11], anticonvulsant[12] and antioxidant[13] activities. Thus chalcone continue to attract considerable scientific attention because of their association with a variety of biological activity properties are well documented in the literature.

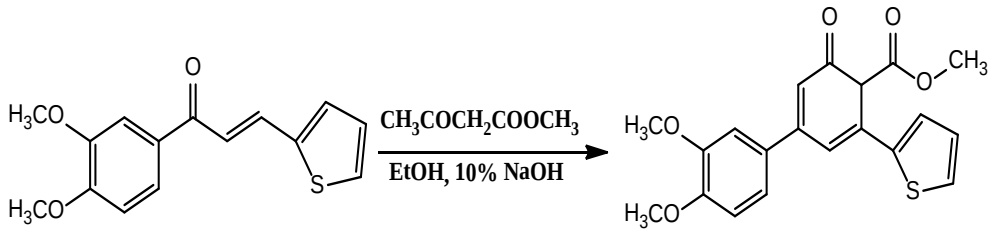
Synthesis of 1-(3,4-dimethoxyphenyl)-3-thiophen-2-yl-propenone:

Equimolar mixture of 2,3-dimethoxyacetophenone (0.01 mol) and thiophene–2–cabaldehyde (0.01 mol) were dissolved in 20 ml of ethanol in a 250 mL round bottomed flask. The reaction mixture was magnetically stirred for 3h in ice-cold condition, during stirring 10 ml of 10% sodium hydroxide solution was added drop wise. A flocculants precipitate was formed. The precipitate was filtered and washed with cold water. The solid obtained was purified by column chromatography using silica gel 60-120 mesh and n-hexane: acetone (7:3 v/v) as elevate.



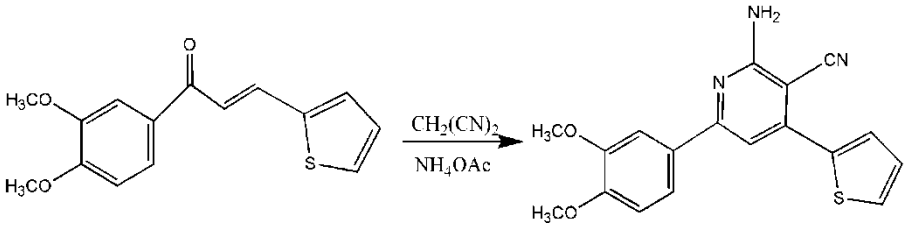
Synthesis of 4-(3,4-dimethoxyphenyl)-2-oxo-6-thiophen-2-yl-cyclohex-3-ene carboxylic acid methyl ester (III)

A mixture of 1-(3,4-dimethoxyphenyl)-3-thiophen-2-yl-propenone (0.001mol) and methylacetoacetate (0.001 mol) in ethanol was refluxed for 4 h in the presence of 0.8 mL of 10% NaOH. The reaction mixture was cooled and poured into 50 mL of ice-cold water. The precipitate was collected by filtration, washed with water and dried in air giving brown solid. The yield of the product was 78%, melting point 140^0C.



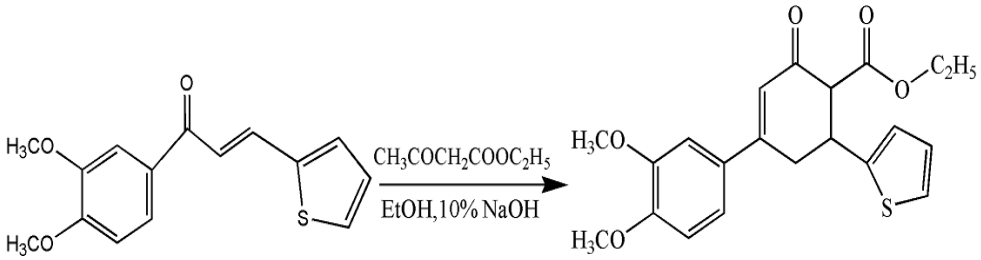
Synthesis of 2-Amino-6-(3,4-dimethoxyphenyl)-4-thiophen-2-yl-nicotinonitrile (V)

A mixture of 1-(3,4-dimethoxyphenyl)-3-thiophen-2-yl-propenone (0.001 mol) and malononitrile (0.001 mol) and ammonium acetate (0.077g) in ethanol (20 mL) was refluxed 8 h. The reaction mixture was cooled and poured into ice-cold water. The precipitate was collected, filtration and dried in air. The solid obtained was recrystallized in ethanol gave an orange yellow crystal. The yield of the product was 73%, melting point 202^0C.



Synthesis of 4-(3,4-dimethoxyphenyl)-2-oxo-6-thiophen-2-yl-cyclohex-3-ene- carboxylic acid ethyl ester (VII)

A mixture of 1-(3,4-dimethoxyphenyl)-3-thiophen-2-yl-propenone (0.001 mol) and ethylacetoacetate (0.001 mol) in ethanol was refluxed for 6 h in 10-15 mL of ethanol in the presence of 10% 10 mL NaOH. The progress of the reaction was monitored by TLC using methanol: chloroform (3:10 v/v) as eluent. The solid obtained was recrystallized in ethanol gave an brown crystal. The yield of the product was 80%, melting point 124^0C.



Result and Discussion

4-(3,4-dimethoxyphenyl)-2-oxo-6-thiophen-2-yl-cyclohex-3-ene carboxylic acid methyl ester: IR spectra: C_6H_5: 3080.20, -CH_3: 2832.76, C=N: 1597.04, C-C: 1120.97, C-O-C: 1268.46, Ring C-C: 1514.05 and C_4H_4S: 859.78. **^{1}HNMR:** C_4H_4S: 6.99-7.01(m), -C_6H_5: 6.86 (m), CH=CH: 6.83 (m), 3-CH_3: 3.89 (m), -CH: 3.88 (m) and -C=C: 2.26 (d). **^{13}CNMR:** C_6H_5S: 122.82-128.22, 140.45, -C_6H_5: 110.59-120.32, 149.14, C=O: 171.94, -COO: 197.32, 3-CH_3: 55.98 and CH=CH: 153.16.

2-Amino-6-(3,4-dimethoxyphenyl)-4-thiophene-2-yl-nicotinonitrile:

IR spectra: -NH_2: 3109.06, C_6H_5: 3079.76, -CH_3: 2906.18, C≡N: 2285.62, C=N: 1596.45, C-N: 1024.91, C-C: 1121.22, C-O-C: 1205.31 and C_4H_4S: 810.22. **^{1}HNMR:** C_4H_4S: 7.07-7.22 (m), -

C_6H_5: 6.88-7.40 (m), C_5H_5N: 7.41 (d), -NH_2: 3.96 (d) and –CH_3: 3.93 (m). **^{13}CNMR:** C_4H_4S: 122.76-127.27, 140.38, -C_6H_5: 111.47-120.25, 133.61, 149.07, -C-N: 164.74, C_5H_5N: 110.54, 153.18, 154.07, - C≡N: 118.75 and –CH_3: 55.86.

4-(3,4-dimethoxyphenyl)-2-oxo-6-thiophen-2-yl-cyclohex-3-ene carboxylic acid methyl ester: IR spectra: C_6H_5: 3080.23, -CH_3: 2928.00, -C=O: 1647.75, -COO-: 1269.69, C-O-C: 1205.21and C_4H_4S: 809.86. **^{1}HNMR:** C_4H_4S: 6.91-7.09 (m), -C_6H_5: 6.94 (m), CH=CH: 6.91 (m), 3-CH_3: 3.97 (m), -CH: 3.96 (m) and -C=C: 2.27, 4.10 (m). **^{13}CNMR:** C_6H_5S: 122.82-128.37, 140.45, -C_6H_5: 110.60-120.32, 149.14, -C=O: 197.32, -COO: 175.21, 3-CH_3: 55.93, 13.60 and CH=CH: 153.16.

BIOLOGICAL EVALUATION

Antimicrobial activity

The antimicrobial activity of synthesized compounds was carried out using agar well diffusion method. The bacterial strains were collected from different infectious status of patients who had not administered any antibacterial and antifungal drugs for at least 2 weeks with the suggestions of an authorized physician, in Eumic analytical Lab and Research Institute, Tiruchirappalli, Tamilnadu state, India. The *in vitro* antimicrobial activity was carried out against 24 h culture of three bacterial strains *Moraxella, Enterobacter* and *Pseudomonas aeruginosa.* Three fungal strains were *Candida albicans, A.niger* and *Trichophyton*. The compounds were tested at 25, 50, 75 and 100µg/mL differend concentration against both bacterial and fungal strains. DMSO was used as a vehicle. *Erythromycin* and *Ciprofloxacin* were used as standard drugs for comparison of antibacterial and antifungal activities respectively. The zone of inhibition was compared with standard drug after 24 h of incubation at 37oC for antibacterial activity and 8 h at 37oC for antifungal activity.

Antimicrobial activity of 4-(3,4-dimethoxyphenyl)-2-oxo-6-thiophen-2-yl-cyclohex-3-ene carboxylic acid methyl ester (C-III)

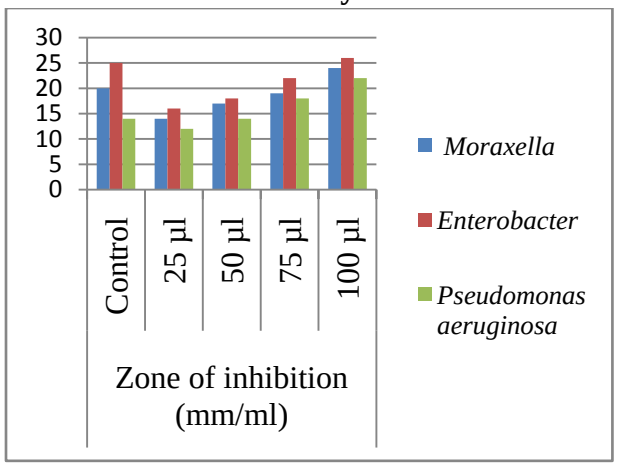
Antibacterial activity

Bacterial Strain	Zone of inhibition (mm/ml)				
	Control	25 µl	50 µl	75 µl	100 µl
Moraxella	20	14	17	19	24
Enterobacter	25	16	18	22	26
Pseudomonas aeruginosa	14	12	14	18	22

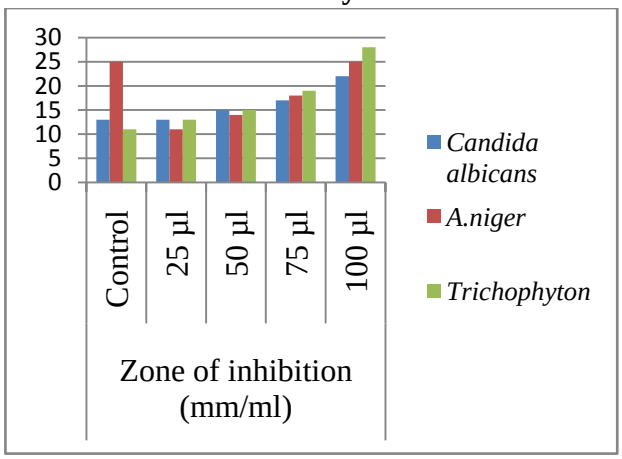
Antifungal activity

Fungi strain	Zone of inhibition (mm/ml)				
	Control	25 µl	50 µl	75 µl	100 µl
Candida albicans	13	13	15	17	22
A.niger	25	11	14	18	25
Trichophyton	11	13	15	19	28

Graphical representation of antibacterial activity



Graphical representation of antibacterial activity



Antimicrobial activity of2-Amino-6-(3,4-dimethoxyphenyl)-4-thiophen-2-yl-nicotinonitrile (V)

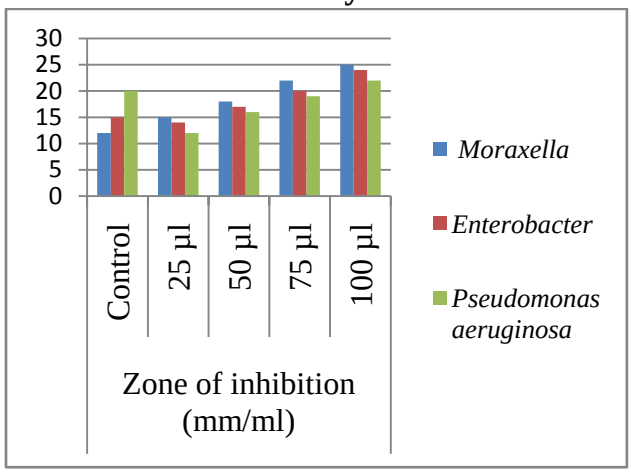
Antibacterial activity

Bacterial Strain	Zone of inhibition (mm/ml)				
	Control	25 µl	50 µl	75 µl	100 µl
Moraxella	12	15	18	22	25
Enterobacter	15	14	17	20	24
Pseudomonas aeruginosa	20	12	16	19	22

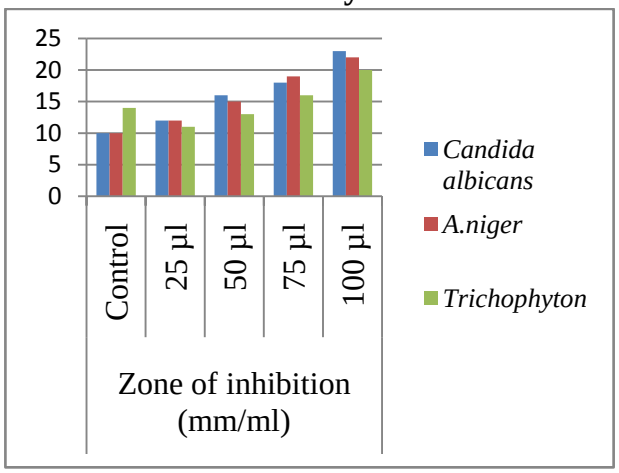
Antifungal activity

Fungi strain	Zone of inhibition (mm/ml)				
	Control	25 µl	50 µl	75 µl	100 µl
Candida albicans	10	12	16	18	23
A.niger	10	12	15	19	22
Trichophyton	14	11	13	16	20

Graphical representation of antibacterial activity



Graphical representation of antifungal activity



Antimicrobial activity of 4-(3,4-dimethoxyphenyl)-2-oxo-6-thiophen-2-yl-cyclohex-3-ene- carboxylic acid ethyl ester (VII)

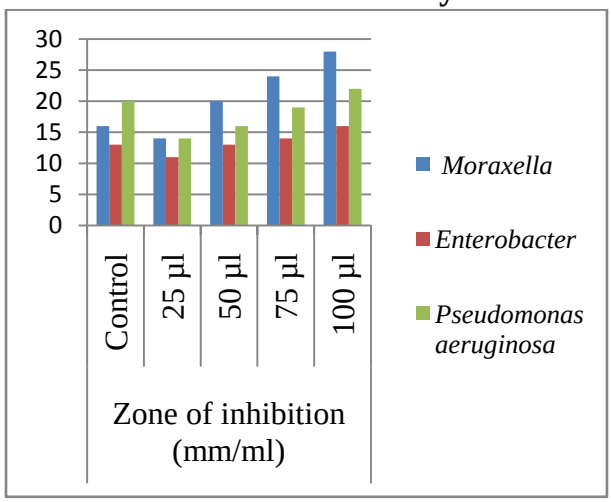
Antibacterial activity

Bacterial Strain	Zone of inhibition (mm/ml)				
	Control	25 µl	50 µl	75 µl	100 µl
Moraxella	16	14	20	24	28
Enterobacter	13	11	13	14	16
Pseudomonas aeruginosa	20	14	16	19	22

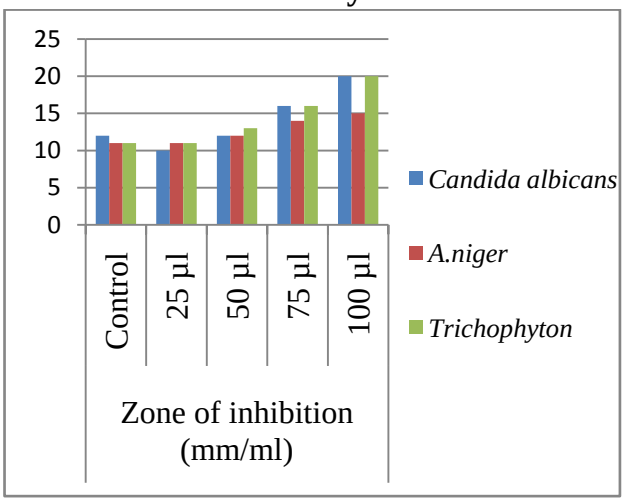
Antifungal activity

Fungi strain	Zone of inhibition (mm/ml)				
	Control	25 µl	50 µl	75 µl	100 µl
Candida albicans	12	10	12	16	20
A.niger	11	11	12	14	15
Trichophyton	11	11	13	16	20

Graphical representation of antibacterial activity



Graphical representation of antifungal activity



CONCLUSION

A series of Chalcone derivatives were successfully synthesized and characterized spectroscopically by IR, ^{1}H and ^{13}C-NMR. All the synthesized products were screened for their *in - vitro* antibacterial and antifungal properties. The experimental results revealed that all compounds displayed moderate to good antibacterial and antifungal activity with reference to the standard against the tested organisms.

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