PART-II: STUDIES ON CYCLOHEXENONES

INTRODUCTION

Cyclohexenone is a series of compounds that is important in agricultural and medicinal chemistry. Cyclohexenones are derivatives of cyclohexane with carbonyl group at 1-position and double bond at 2-position (I). There are several types of cyclohexanone derivatives but the groups attached to carbon atom exerted the greatest difference in structure and properties. Cyclohexenones can be synthesized by the treatment of \( \alpha, \beta \)-unsaturated carbonyl compounds with ethylacetoacetate in alkaline media.

![Cyclohexenone structure](image)

In current years, cyclohexenone derivatives have gained lots of interest because of its prominent pharmacological properties. Cyclohexenones ring systems have a major feature in medicinal chemistry and possess good biological activities such as anticancer, anticonvulsant, antagonist, antibacterial, antifungal etc. In view of these facts, it was planned to synthesize cyclohexenone derivatives to obtain better therapeutically active derivatives, which have been described as below.

SYNTHETIC ASPECT:

Different methods for the preparation of cyclohexenone derivatives have described in literature.\(^1\)-\(^{14}\)

(I) A review of the earlier literature by Girald et al.\(^{15}\) describes representative synthetic procedure of cyclohexenone derivatives (II).
Page Phillip C. et al.\textsuperscript{16} have prepared ethyl substituted cyclohexenone derivatives (III).

**MECHANISM:**

The addition reaction between ethylacetoacetate and chalcone gives cyclohexenone via Michael addition which has been carried out in basic media by using sodium ethoxide in ethanol. During the reaction nucleophilic addition of carbanion takes place to the C=C of the acceptor. The chalcone compound is known as acceptor and ethylacetocetate is known as donor.
THERAPEUTIC IMPORTANCE:

Cyclohexenone and its derivatives having vast contribution in medicinal chemistry. So they are widely used in pharmaceutical industry. Considerable interest has been shown in the chemistry of cyclohexenones due to their wide spectrum of therapeutic activities which are listed as under.

1. Anticancer.¹⁷
2. Anticonvulsant.¹⁸-¹⁹
3. Antiplatelet.²⁰
4. Antitubercular.²¹
5. Cardiovascular.²²
6. Antithrombitics.²³
7. Antibiotic.²⁴-²⁵
8. Antifungal.²⁶-²⁷
9. Antagonist.²⁸

Hermann S. et al.²⁹ have reported cyclohexenones as herbicides. Harimaya et al.³⁰ have synthesized new cyclohexenone derivatives possessing progesterone receptor binding inhibitory activity. Engle Stefan et al.³¹ have synthesized herbicidal activity of cyclohexenone derivatives (IV) which has been investigated. Rheinheimer J. et al.³² have synthesized 5-(dioxabicyclohept-6-yl)cyclohexenone oxime ethers as herbicides and plant growth regulators.

Cyclohexenone (V) as anticancer and anti-inflammatory agents have been investigated.³³
Bastiaan et al.\textsuperscript{34} have synthesized novel cyclohexenone derivatives (VI) which are useful in the diagnosis of Parkinson’s disease. Anticonvulsant activity of some cyclohexenone derivatives (VII) has been reported by Natalie D. et al.\textsuperscript{35}

\begin{center}
\begin{tabular}{ccc}
(V) & (VI) & (VII) \\
\end{tabular}
\end{center}

Emam H. A. et al.\textsuperscript{36} have prepared cyclohexenone derivatives (VIII) from chalcone.
Toshiyuki et al.\textsuperscript{37} have prepared some novel cyclohexenones and screened for allergy inhibitor, antithrombotic platelet aggregation inhibitors and fibrinogen antagonist activity. Parekh et al.\textsuperscript{38} synthesized new cyclohexenones as antimicrobial agent.

In view of therapeutic activities shown by cyclohexenones systems prompted to synthesize some new cyclohexenone derivatives in search of agents possessing higher biological activity with least side effect have been described as under.

SECTION–I: SYNTHESIS AND BIOLOGICAL EVALUATION OF ETHYL-4'-(CYCLOPROPANE CARBOXAMIDO-N-YL)-5-ARYL-3-OXO-3,4,5,6-TETRAHYDRO-BIPHENYL-4-CARBOXYLATE.
SECTION–I

SYNTHESIS AND BIOLOGICAL EVALUATION OF ETHYL-4’-(CYCLOPROPANE CARBOXAMIDO-N-YL)-5-ARYL-3-OXO-3,4,5,6-TETRAHYDRO-BIPHENYL-4-CARBOXYLATE.

Cyclohexenone and their derivatives are associated with variety of pharmacodynamic activities such as anticonvulsant, antifungal, antibiotic, antidiabetic etc. Observing these interesting properties of cyclohexenones formed developed considerable interest to synthesize Ethyl-4’-(cyclopropane carboxamido-N-yl)-5-(4-methoxyphenyl)-3-oxo-3,4,5,6-tetrahydro-biphenyl-4-carboxylate of the type (V) by the condensation of N-[4-(3-Aryl-acryloyl)phenyl]cyclopropane carboxamide with ethylacetoacetate in presence of sodium ethoxide in order to study their biodynamic activities.

The structure elucidation of synthesized compounds has been done on the basis of Elemental analysis, Infrared and $^1$H Nuclear Magnetic Resonance spectroscopy and further supported by Mass spectrometry. Purity of all compounds has been checked by thin layer chromatography. All the compounds have been evaluated for their in vitro biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards A. niger at a concentration of 40 μg. The biological activities of synthesized compounds were compared with standard drugs.
REACTION SCHEME

MeOH
R-CHO
8 Hrs
Stirring at RT

Type-I
R = Aryl

EtOH
Reflux
Sodium ethoxide
10 Hrs

Type-V
R = Aryl
IR SPECTRAL STUDIES OF ETHYL-4'-(CYCLOPROPANE CARBOXAMIDO-N-YL)-5-(4-METHOXYPHENYL)-3-OXO-3,4,5,6-TETRAHYDRO-BIPHENYL-4-CARBOXYLATE.

Instrument: Bruker Benchtop Infrared; Frequency range: 4000-400cm\(^{-1}\) (KBr disc)

<table>
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<tr>
<th>Type</th>
<th>Vibration Mode</th>
<th>Frequency in cm(^{-1})</th>
<th>Ref.</th>
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<td></td>
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<td>Observed</td>
<td>Reported</td>
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<td>Alkane</td>
<td>C-H str.(asym)</td>
<td>2937</td>
<td>2990-2830</td>
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<tr>
<td>Aromatic</td>
<td>C-H i.p.(def)</td>
<td>1179</td>
<td>1300-1100</td>
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<tr>
<td></td>
<td>C=C str.</td>
<td>1511,1586</td>
<td>1450-1600</td>
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<tr>
<td>Cyclohexenone</td>
<td>C=O str.</td>
<td>1246</td>
<td>1320-1020</td>
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<tr>
<td></td>
<td>C=C str.</td>
<td>1649</td>
<td>1650-1550</td>
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<tr>
<td>Ester</td>
<td>C=O str.</td>
<td>1738</td>
<td>1750-1725</td>
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<tr>
<td>Amide</td>
<td>C=O</td>
<td>1649</td>
<td>1680-1630</td>
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NMR SPECTRAL STUDIES OF ETHYL-4'-(CYCLOPROPANE CARBOXAMIDO-N-YL)-5-(4-METHOXYPHENYL)-3-OXO-3,4,5,6-TETRAHYDRO-BIPHENYL-4-CARBOXYLATE.

Internal standard: TMS; Solvent: DMSO; Instrument: BRUKER Spectrometer (400MHz)

<table>
<thead>
<tr>
<th>No.</th>
<th>Chemical shift (δ ppm)</th>
<th>Multiplicity</th>
<th>No. of Protons</th>
<th>Assignment of proton(s)</th>
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<td>1</td>
<td>0.81-1.80</td>
<td>m</td>
<td>5 H</td>
<td>10,11,12</td>
<td>A</td>
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<td>2</td>
<td>3.73</td>
<td>s</td>
<td>3 H</td>
<td>29</td>
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<td>3</td>
<td>6.53-7.69</td>
<td>m</td>
<td>9 H</td>
<td>1,2,4,5,14,15,17,18,23</td>
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<td>4</td>
<td>2.99-3.11</td>
<td>d</td>
<td>2 H</td>
<td>19</td>
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<td>1.50,4.07</td>
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<td>m</td>
<td>2H</td>
<td>20,21</td>
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<td>7</td>
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<td>S</td>
<td>1 H</td>
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<td></td>
<td>Total No. of protons</td>
<td></td>
<td>27 H</td>
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MASS SPECTRAL STUDIES OF ETHYL-4'-(CYCLOPROPANE CARBOXAMIDO-N-YL)-5-(4-METHOXYPHENYL)-3-OXO-3,4,5,6-TETRAHYDRO-BIPHENYL-4-CARBOXYLATE.
MASS FRAGMENTATION

m/z = 433
(Base Peak)

m/z = 387

m/z = 374

m/z = 274

m/z = 334

m/z = 161

m/z = 199

m/z = 319

m/z = 120

m/z = 69

m/z = 159

m/z = 92.05

m/z = 41
EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF ETHYL-4'-(CYCLOPROPANE CARBOXAMIDO-N-YL)-5-ARYL-3-OXO-3,4,5,6-TETRAHYDRO-BIPHENYL-4-CARBOXYLATE.

(A) Synthesis of N-[4-[3-(4-Methoxyphenyl)acryloyl]phenyl]cyclopropane carboxamide.

See, Part-I, Section-I (B).

(B) Synthesis of Ethyl-4'-(cyclopropane carboxamido-N-yl)-5-(4-methoxyphenyl)-3-oxo-3,4,5,6-tetrahydro-biphenyl-4-carboxylate.

A mixture of N-[4-[3-(4-Methoxyphenyl)acryloyl]phenyl]cyclopropane carboxamide 0.5 gm (0.01mol), ethylacetoacetate 0.4 gm (0.02 mol) and sodium ethoxide 0.22 gm (0.02 mol) were dissolved in ethanol. The whole reaction mass was refluxed for 10 hrs. The reaction mixture was poured into crushed ice and acidified with dilute HCl. Solid separated was filtered and recrystallized from ethanol. Yield 78.65%, M.P. 223°C. Elemental Analysis Calculated for C_{26}H_{27}NO_{5} ; Requires : C-72.04%; H-6.28%; N-3.23 %; O-18.45 %; Found : C-72.01%; H-6.27; N-3.20%; O-18.41%. Similarly, other Ethyl-4'-(cyclopropane carboxamido-N-yl)-5-aryl-3-oxo-3,4,5,6-tetrahydro-biphenyl-4-carboxylate were prepared. The physical data are recorded in Table No.5.

(C) Biological Evaluation of Ethyl-4'-(cyclopropane carboxamido-N-yl)-5-aryl-3-oxo-3,4,5,6-tetrahydro-biphenyl-4-carboxylate.

Antimicrobial testing was carried out as described in Part-I, Section-I (C). The zone of inhibition of tested compounds is recorded in Graphical Chart No.5.
CONCLUSION

Antibacterial activity

The antimicrobial screening data indicated that among cyclohexenone derivatives tested compounds 5b, 5c, 5h, 5j and 5k showed excellent growth inhibition against *B. subtilis*. However, the compounds 5h, 5i and 5j were shown significant activity against *E. coli*. The compounds 5a, 5h, 5i, 5j and 5k showed greater degree of antibacterial activity against *S. aureus*. However, the compounds 5d, 5g and 5j exhibited good to excellent activity against *P. aeruginosa*. The remaining cyclohexenone derivatives possess moderate to mild activity against all four bacterial species.

Antifungal activity

The screening data indicated that among cyclohexenone derivatives tested compounds 5b, 5e, 5f, 5g and 5k showed good to moderate activity against *A. niger*. All other compounds exhibit mild to moderate antifungal activity against *A. niger*. 
TABLE NO. 5: PHYSICAL CONSTANTS OF ETHYL-4'-(CYCLOPROPANE CARBOXAMIDO-N-YL)-5-ARYL-3-OXO-3,4,5,6- TETRAHYDRO-BIPHENYL-4-CARBOXYLATE.

<table>
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<tr>
<th>Compound No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P. (°C)</th>
<th>% Yield</th>
<th>Nitrogen % Found</th>
<th>Nitrogen % Calcd</th>
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<tr>
<td>5a</td>
<td>-C₆H₅</td>
<td>C₂₅H₂₃NO₄</td>
<td>403.47</td>
<td>254</td>
<td>74.21</td>
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<td>5b</td>
<td>-4-OCH₃-C₆H₅</td>
<td>C₂₆H₂₆NO₅</td>
<td>433.50</td>
<td>223</td>
<td>78.65</td>
<td>3.20</td>
<td>3.23</td>
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<tr>
<td>5c</td>
<td>-4-N(CH₃)₂C₆H₄</td>
<td>C₂₅H₂₆N₂O₄</td>
<td>446.54</td>
<td>187</td>
<td>80.13</td>
<td>6.24</td>
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<tr>
<td>5d</td>
<td>-C₆H₃O</td>
<td>C₂₅H₂₃NO₅</td>
<td>393.43</td>
<td>184</td>
<td>78.54</td>
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<td>5e</td>
<td>-2-Cl-C₆H₅</td>
<td>C₂₅H₂₃ClNO₄</td>
<td>437.92</td>
<td>155</td>
<td>77.12</td>
<td>3.18</td>
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<td>5f</td>
<td>-4-F-C₆H₅</td>
<td>C₂₅H₂₃FNO₄</td>
<td>421.46</td>
<td>180</td>
<td>70.45</td>
<td>3.31</td>
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<tr>
<td>5g</td>
<td>-4-OH-C₆H₅</td>
<td>C₂₅H₂₃NO₅</td>
<td>419.47</td>
<td>191</td>
<td>72.45</td>
<td>3.30</td>
<td>3.34</td>
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<tr>
<td>5h</td>
<td>-4-OH-3-OCH₃-C₆H₅</td>
<td>C₂₅H₂₆NO₆</td>
<td>449.19</td>
<td>184</td>
<td>75.65</td>
<td>3.09</td>
<td>3.12</td>
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<tr>
<td>5i</td>
<td>-2-OH-C₆H₅</td>
<td>C₂₅H₂₃NO₅</td>
<td>419.47</td>
<td>188</td>
<td>71.45</td>
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<tr>
<td>5j</td>
<td>-2-NO₂-C₆H₅</td>
<td>C₂₅H₂₃N₂O₆</td>
<td>448.47</td>
<td>180</td>
<td>69.52</td>
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<td>5k</td>
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<td>76.81</td>
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GRAPHICAL CHART NO.5: ANTIMICROBIAL ACTIVITY OF ETHYL-4'-(CYCLOPROPANE CARBOXAMIDO-N-YL)-5-ARYL-3-OXO-3,4,5,6-TETRAHYDRO-BIPHENYL-4-CARBOXYLATE.
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A. R. Kartizky and R. Alans Jones;