SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF INDAZOLINE TETRALONE

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ABSTRACT
A series of 2-substituted benzylidene -tetralones were synthesized by using synthetic scheme aldol condensation and further condense with phenyl hydrazine and synthesize substituted indazoline derivatives. All these compounds have been analyzed by IR, NMR and Mass spectroscopy for structure assignment and were further evaluated for their antimicrobial activity. The Antibacterial activities of these compounds were studied using agar diffusion method. Among these compound Dichloro & fluoro indazoline indazoline derivatives are highly potent and against antimicrobial activity.

KEYWORDS: Tetralone, Benzylidene, Indazoline, Antimicrobial activity.

INTRODUCTION
1, 2, 3, 4-Tetrahydronaphthyl-heterocycles bearing compounds constitute a class of continued interest to the pharmaceutical, chemical and agrochemical communities. Many of these compounds have useful applications such as anticancer1-5, antibacterial6,7, Antiviral8, and analgesic activities11,12. Literature survey indicated that this type of compounds could be enzymatically oxidized within the living cells to give products related to Naphthaquinones which are known to possess various potent biological activities. The present work deals with synthesis of some benzylidene derivative of tetralone using 1-tetralone as a key starting material and form indazoline derivatives which were further investigate for antimicrobial activity.

2. MATERIALS AND METHODS
Melting point range of the synthesized compounds was determined by open capillary method using the melting point apparatus. Thin layer chromatographic analysis of the synthesized compounds was done on silica gel G coated glass plate. An IR spectrum of the intermediates and final compounds synthesized, the can be recorded by a modified reflectance technique which depends on the total internal reflectance of light in Bruker ATR spectrophotometer.

3. Experimental Section
Scheme: 1 Synthesis of 2-benzylidene tetralone-1
A mixture of α-tetralone (10 m.mole. 1.32 ml) & p-chlorobenzenaldehyde (10 m.mole. 1.4 g) in ethanol (50ml) was stirred, cooled to 10 °C and then treated with a solution of 5% alc. KOH (0.56g) in ethanol (11.2ml). The cooling bath was removed & the solution allowed to warm at room temperature, a crystalline product started separating at 22°C. After standing overnight at room temperature, the mixture was poured onto 200 ml of ice-water (200 ml). This product was filtered, washed with cold water allowed to dry over night. The product was crystallized with methanol.
Scheme 1:

\[
\text{Proposed Mechanism}
\]

**MECHANISM OF BENZYLIDINE FROM TETRALONE AND 6 METHOXY TETRALONE**

\[
\begin{align*}
\text{R} = \text{H} & \quad \text{Tetralone} \\
\text{R} = \text{CH}_3 & \quad \text{6-Methoxy Tetralone}
\end{align*}
\]

**Physical data of benzylidene derivatives (1-5)**

<table>
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<th>S NO</th>
<th>STRUCTURE</th>
<th>M.W</th>
<th>M. F.</th>
<th>M.P.</th>
<th>%Yield</th>
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<td>3</td>
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<td>C(_{17})H(_23)FO</td>
<td>105-108(^\circ)C</td>
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</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure" /></td>
<td>303</td>
<td>C(_{17})H(_22)Cl(_2)</td>
<td>156-158(^\circ)C</td>
<td>91.88</td>
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Scheme: 2: Synthesis of Indazoline derivative of 2-benzylidene tetralone
A mixture of 2-benzylidene tetralone-1 (2.34 gm, 10 mmol) and phenyl hydrazine (6 ml, 0.04 mol) and sodium metal (0.5 g) were taken in ethanol (20 ml) stirred it for 5 minutes then reflux for 10 hours. Monitoring of reaction was done by TLC every one hour. Then removed solvent under reduced pressure and remaining residue was purified by crystallization and column chromatography.

\[
\text{O} \quad \text{NaOBu, BuOH} \quad \text{RNHNH}_2 \rightarrow \text{O}
\]

Physical data of indazoline derivatives (6-10)

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<th>M.F</th>
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<td>C_{23}H_{29}N_{2}Cl_{2}</td>
<td>139-141°C</td>
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3. RESULTS AND DISCUSSION
3.1 Spectral investigation
1. Synthesis of 2-benzylidene tetralone - (1)
Yield: 3.79 gm (80.98 %) M.P: 98-100 °C.
Mass (FAB) [M+H]+ : 235.2, 1H NMR(200 MHz, CDCl3): δ 7.16-7.25 (m, 8H, Ar-H); 7.62 (s, 1H, olefinic proton); 2.85-3.12 (t, 2H, CH2); 3.07-3.31 (t, 1H, CH2). I.R: CO, 1611.4 cm⁻¹; C=CH, 1594.3 cm⁻¹

2. Synthesis of 2-(4-Chloro benzylidene) tetralone (2)
Yield: 1.92g (76.2%), M.P:105-108 °C.
Mass (FAB)[M+H]+: 251, 1H NMR(200 MHz, CDCl3): δ 7.36-7.50 (m, 8H, Ar-H); 7.82 (s, 1H, olefinic proton); 2.95-2.98 (t, 2H, CH2); 3.07-3.11 (t, 1H, CH2). I.R: C=O, 1619.4 cm⁻¹; C=CH, 1591.7 cm⁻¹

3. Synthesis of 2-(4-fluoro benzylidene) tetralone (3)
Yield:1.92g (76.2%), M.P:105-108 °C.
Mass (FAB)[M+H]+: 251, 1H NMR(200 MHz, CDCl3): δ 7.34-8.14 (m, 8H, Ar-H); 8.141(δ,1H olefinic proton); 2.95-2.98 (t, 2H, CH2); 3.07-3.11 (t, 1H, CH2). I.R: CO, 1616.0 cm⁻¹; CH, 1591.7 cm⁻¹

4. Synthesis of 2-(2, 4-dichloro-benzylidene) tetralone (4)
Yield: 2.78 g (91.88%), M.P 156-158 °C.
Mass (FAB)[M+H]+: 303 1H NMR(200 MHz, CDCl3): δ 7.34-8.14 (m, 8H, Ar-H); 8.141(δ,1H olefinic proton); 2.95-2.98 (t, 2H, CH2); 3.07-3.11 (t, 1H, CH2). I.R: C=O, 1609.6 cm⁻¹; C=O, 1669.6 cm⁻¹

5. Synthesis of 2-(2, 6-dichloro-benzylidene) tetralone (5)
Yield: 2.65 (87.45%), M.P: 157 162 °C.
Mass (FAB) [M+H]+: 303 1H NMR(200 MHz, CDCl3): δ 7.34-8.14 (m, 8H, Ar-H); 8.143 (δ,1H, olefinic proton); 2.95-2.98 (t, 2H, CH2); 3.07-3.11 (t, 1H, CH2). I.R: C=O, 1669.9 cm⁻¹; C=O, 1611.4 cm⁻¹

6. Synthesis of Indazole derivative of 2-benzylidene tetralone
Yield: 1.46g (45.23%), M.P: 122-126 °C.
Mass (FAB) [M+H]+: 324 1H NMR(200 MHz, CDCl3): δ 2.56-2.70 (q, 1H, CH3). 2.88-2.91 (t, 1H, CH2). 2.17 -2.34 (q, 2H, CH2). 3.25 (d, 1H, CH), 7.09-8.07 (m, 14H, Ar-H). I.R: C=N 1492 cm⁻¹. NH= 3440 cm⁻¹

7. Synthesis of Indazole derivative of 2-(4-Chloro benzylidene) tetralone
Yield: 1.0g (35.6%), M.P: 128-132 °C.
Mass (FAB) [M+H]+: 359 1H NMR(200 MHz, CDCl3): δ 2.65-2.67 (t, 2H, CH2). 2.04 -2.08 (q, 1H, CH2). 2.1 -2.5 (q, 1H, CH), 3.9 (d, 1H, CH), 6.42-7.99 (m, 13H, Ar-H). I.R: C=N 1494 cm⁻¹. NH= 3443 cm⁻¹

8. Synthesis of Indazole derivative of 2-(4-fluoro benzylidene) tetralone
Yield: 1.23g (36.29%), M.P: 145-150 °C.
Mass (FAB)[M+H]+: 342 1H NMR(200 MHz, CDCl3): δ 2.56-2.70 (q, 1H, CH2). 2.88 -2.91 (t, 1H, CH2). 2.17 -2.34 (q, 2H, CH2). 3.25 (d, 1H, CH). 7.09-8.07 (m, 14H, Ar-H). I.R: C=N 1494 cm⁻¹. NH= 3443 cm⁻¹

9. Synthesis of Indazole derivative of 2-(2, 4-dichloro-benzylidene) tetralone
Yield: 1.65g (42.2 %), M.P: 135-138 °C.
Mass (FAB)[M+H]+: 392 1H NMR(200 MHz, CDCl3): δ 2.37 (t, 1H, CH2). 2.86 -2.91 (t, 1H, CH2). 2.26 (q, 1H, CH). 3.63 (d, 1H, CH). 7.096 -7.26 (m, 13H, Ar-H). I.R: C=N 1494 cm⁻¹. NH= 3443 cm⁻¹

10. Synthesis of Indazole derivative of 2-(2, 6-dichloro-benzylidene) tetralone
Yield: 1.92 gm (71.6%), M.P: 145-146 °C.
Mass (FAB) [M+H]+: 269. 1H NMR(200 MHz, CDCl3): δ 2.65 -2.67 (t, 2H, CH2). 2.04 -2.08 (q, 1H, CH2). 2.1 -2.5 (q, 1H, CH), 3.9 (d, 1H, CH). 6.42-7.99 (m, 13H, Ar-H). I.R: C=N 1494 cm⁻¹. NH= 3443 cm⁻¹

3.2 Antimicrobial Assay (Agar Diffusion Technique)
All the synthesized compounds were tested for in vitro antibacterial and antifungal activities against E.coli, P.aeruginosa, and C.albicans strains with respect to Ciprofloxacin and Fluconazole as the positive control drugs. Zone of inhibition (in mm) values for analogs and positive control drugs were determined by disc plate method.13 All the compounds were dissolved in DMSO; the plates were incubated at 26 °C for 24 hrs and the resulting zone of inhibition (in mm) was measured. Antimicrobial screening for analogs and positive control drugs were performed at a concentration of 100 and 200 μg/mL and the results are illustrated in Table-3. From the antimicrobial screening results it was observed that the compound. The antimicrobial screening results reveal that condensation of heterocyclic ring on benzylidene derivatives show marked antibacterial activity against Escherichia coli and pseudomonaas bacterial strain and introduction of chloro and fluro group possess potent anti microbial activity like IZT 7, 8 due to electron withdrawing nature and IZT10 show maximum antibacterial and antifungal activity.
Table 6.1: Antibacterial and antifungal study of different synthesized compounds

<table>
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<tr>
<th>S. No.</th>
<th>Compound</th>
<th>Zone of Inhibition (mm)</th>
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<td>P.aeruginosa (MTCC424)</td>
<td>C.albicans (MTCC227)</td>
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<tr>
<td>1.</td>
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<td>37</td>
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<tr>
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<tr>
<td>14.</td>
<td>Fluconazole</td>
<td>-</td>
<td>-</td>
<td>36</td>
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</tbody>
</table>

4. CONCLUSION
In this paper we have discuss synthesis of Indazolines from 2-arylidene-1-tetralone All the synthesized compounds were evaluated for their antimicrobial activity. The antimicrobial screening results reveals that by condensation of heterocyclic ring on benzylidene derivatives show marked antibacterial activity against Escherichia coli bacterial strain and introduction of chloro and fluoro group possess potent anti microbial activity like IZT 7, 8 due to electron withdrawing nature and IZT10 show maximum antibacterial and antifungal activity.

5. REFERENCES
12. Ebeid MY, Fathalla OA, EL-zahar MI, Kamel MM, Abdou WAM and Anwar
MM. Newtetraly thiazoles – The Anti-HIV And Anticancer Screening of 3-[4-6-(1,2,3,4-Tetrahydroanaphthyl)-Thiazol-2-yl-2-(p-Chlorophenyl)-Thiazolidin-4- One. Bull Fac Pharm Cairo Univ. 1996;34(2):125–35.


