SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF CHALCONES AND PYRIMIDINES FROM 4-IMIDAZOLE-1-YL-ACETOPHENONE

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ABSTRACT

Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α,β-unsaturated carbonyl system. Pyrimidines are one of the important heterocyclic compounds with various biological activities. In this view, it was proposed to synthesize some novel pyrimidines from chalcones. Chalcones are prepared by treating 4-imidazole-1-yl-acetophenone with different aromatic aldehydes. These chalcones on condensation with guanidine HCl and KOH gave 4-(4-(1H –imidazole-1-yl)-pyrimidin-2-amine derivatives. They have been screened for their antibacterial activity against Gram positive bacteria B.subtilis & B.pumilus and gram negative bacteria E.coli & P.vulgaris and antifungal activity against A.niger & P.crysogenum.

KEYWORDS: Chalcones, pyrimidines, 4- imidazole-1-yl-acetophenone, 4-(4-(1H –imidazole-1-yl)-pyrimidin-2-amine.

INTRODUCTION

Most of the present diseases are due to the invasion by the pathogenic organisms like bacteria, fungal, virus, rikettesia. To treat these diseases many potent and broad spectrum antibiotics were discovered e.g. ampicillin, amoxicillin, carbenicillin, oflaxacin, tetracyclines etc, even through antibiotics are life saving drugs in therapeutics but they are potentially
harmful. Those effects include allergic and anaphylactic reaction, super infections, development of resistance, destruction of normal non pathogenic bacteria flora and selective toxicity like a plastic anemia, kidney damage etc.

A dramatic increase in antibiotic resistance especially among gram-positive and gram-negative triggered a clear need for the discovery of new antimicrobials rather than analogs of the existing once traditionally. Small molecules have been a reliable source for discovering novel biologically active compounds.

The compounds with backbone of Chalcones have been reported to possess various biological activities such as analgesic,[1] anti-microbial,[2] anti-inflammatory,[3] anti-cancer,[4-7] anti-viral,[8-10] anti-diabetic.[11-13] They are also well known as valuable intermediates in organic synthesis of many heterocycles that exhibit a multitude of biological activities.[14]

Chalcones and pyrimidines have been associated with various biological and pharmacological activities like antibacterial, anti-inflammatory, analgesic, anti-hypertensive and CNS activities.

**MATERIALS AND METHODS**

The chemicals and reagents (Table I) used in the present project were of AR and LR grade, procured from Aldrich, Hi-media, Lancaster, Loba, Merck, NR chem. Qualigens, Rolex, Reachchem, S.D– Fine Chem. Ltd, and Sigma.

**Chemistry**

The synthesis of chalcone and pyrimidines derivatives was performed the following stpes shown in scheme a mixture of 4-imidazole-1-yl-acetophenone and 2,4-dichloro benzaldehyde was stirred in ethanol and then aqueous solution of 40% potassium hydroxide was added to it. After completion of the reaction, it was poured into crushed ice and acidified with dil.HCl. The chalcone precipitated out as solid. The precipitate was filtered, dried and purified by column chromatography using hexane and ethyl acetate mixture as mobile phase.
General procedure for the synthesis of chalcones

A mixture of 4-imidazole-1-yl-acetophenone (0.0026 mol) and benzaldehyde derivative (0.0026 mol) was stirred in ethanol (20 ml) and then aqueous solution of 40% potassium hydroxide (6ml) was added to it. The mixture was stirred for 6-8 hrs and kept overnight in freeze. After completion of the reaction, it was poured into crushed ice and acidified with dil.HCl. The chalcone precipitated out as solid. The precipitate was filtered, dried and
purified by column chromatography using hexane and ethyl acetate mixture (10:90) as mobile phase

RESULTS AND DISCUSSION

4.4-1 Synthesis of 3-(4-chlorophenyl)-1-[4-(1H-imidazol-1-yl)phenyl]prop-2-en-1-one

Yield 60%, mp. 97-98°C, IR (C=Cl),731.74(C=C,)1603(C-H),3119.78(C=O),1673.76(N-C),1303.77(C=C),1421.45 NMR8.06(1H,d,=CH-Ar),7.59(1H,d,Ar-CH=),7.15(1H,s,C-2 of imidazole),7.16(1H,d,C-4 of imidazole),7.46(1H,d,C-5 of imidazole),7.44-7.89(8H,m,Ar-H),Mass 308.57.

4.4-2 Synthesis of 1-(4-(1H-imidazol-1-yl)phenyl)-3-<p>-tolylprop-2-en-1-one

Yield 70.1%, mp. 170-171°C, IR (C-Cl),654.79(C=C) ,1653.47(C-H),2891.46(C=O),1677.47 (C-C),1481.82(N-C ),1300.71 8.33(1H,d,=CH-Ar),NMR 7.42(1H,d,Ar-CH=),7.15(1H,s,C-2 of imidazole),7.16(1H,d,C-4 of imidazole),7.46(1H,d,C-5 of imidazole),7.32-7.89(7H,m,Ar-H),Mass343.01.

4.4-3 Synthesis of 1-(4-(1H-imidazol-1-yl)phenyl)-3-(2,4-dichlorophenyl)prop-2-en-1-one

Yield 60.10%, mp. 158-159°C, (C-Cl),842.89(C-H),2919.13(C=O),1666.75(N-C),1304.61(C-C),1483.06(6H,s,-N(CH3)2), NMR7.59(1H,d,=CH-Ar),8.06(1H,d,Ar-CH=),7.15(1H,s,C-2 of imidazole),7.16(1H,d,C-4 of imidazole),7.46-(1H,s,C-5 of imidazole),6.71-7.89(8H,m,Ar-H),1.00 Mass 317.19.

4.4-4 Synthesis of 1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one

Yield 50.63%, mp 97-98°C , (C-Cl), 811.12(C=C),1657.10(C-H), 2917.78(C=O) , 1600.72(N-C),1323.67 (C-C),1423.74 NMR, 8.06(1H,d,=CH-Ar),7.59(1H,d,Ar-CH=),7.15(1H,s,C-2 of imidazole),7.16(1H,d,C-4 of imidazole),7.46(1H,d,C-5 of imidazole),7.19-7.89(8H,m,Ar-H),Mass305.

4.4-5 Synthesis of 1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one

Yield 65%, mp.109-110°C, (C-Cl),654.79(C=C),1653.47(C-H),2891.46(C=O),1677.47( C-C ), 1481.82(N-C ) ,1300.71(C-O),1125.36 NMR, 3.83(3H,s,=OCH3),8.06(1H,d,=CH-Ar),7.59(1H,d,Ar-CH=),7.15(1H,s,C-2 of imidazole),7.16(1H,d,C-4 of imidazole),7.46(1H,d,C-5 of imidazole),6.94-7.89(8H,m,Ar-H),Mass304.15.
4.4-6 synthesis of 1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

Yield 65%, mp. 97-98°C, (C-Cl), 731.749(C=C), 1603(C-H), 3119.78(C=O), 1673.76(N-C), 1303.77(C-C), 1421.4, NMR. 2.34(3H, s, CH3), 7.15(1H, s, C-2 of imidazole), 7.16(1H, d, C-4 of imidazole), 7.46(1H, d, C-5 of imidazole), 7.18-7.89(8H, m, Ar-H), Mass 306.15.

**GENERAL PROCEDURE FOR THE SYNTHESIS OF PYRIMIDINES**

A mixture of chalcone (0.001mol, 0.3g) and guanidine HCL (0.001 mol, 0.3g) was stirred in ethanol (20 ml) and then potassium hydroxide (0.002mol, 0.1g) was added to it. The mixture was reflux for 3-4 hrs on boiling water bath after the reaction the solvent was evaporated on rotary evaporator. The mixture was poured into crushed ice. The Pyrimidine precipitated out as solid. The precipitate was filtered, dried and purified by column chromatography using hexane and ethyl acetate mixture (10:90) as mobile phase.

4.4-7 synthesis of 4-(4-(1H-imidazol-1-yl)phenyl)-6-p-tolylpyrimidin-2-amine

Yield 60%, mp. 89-90°C, (C-Cl), 811.12(C=C), 1657.10(C-H), 2917.78(C=O), 1600.72(N-C), 1323.67(C-C), 2917.78(N-C), 5.5(2H, s, NH2 of Pyrimidine), 7.15(1H, s, C-2 of imidazole), 7.16(1H, d, C-4 of imidazole), 7.46(1H, d, C-5 of imidazole), 7.43-8.03(7H, m, Ar-H), Mass 382.25.

4.4-8 synthesis of 4-(4-(1H-imidazol-1-yl)phenyl)-6-(4-(dimethylamino)phenyl)pyrimidin-2-amine

Yield 55.59%, mp. 119-120°C, IR(C-Cl), 674.12(C=C), 1671.16(C-H), 2923.01(N-H), 3334.73(C-C), 1489.97(N-C), 1330.13, NMR. 5.23(2H, s, NH2 of Pyrimidine), 7.15(1H, s, C-2 of imidazole), 7.16(1H, d, C-4 of imidazole), 7.46(1H, d, C-5 of imidazole), 7.30-8.15(8H, m, Ar-H), Mass331.35.

4.4-9 synthesis of 4-(4-(1H-imidazol-1-yl)phenyl)-6-(2-chlorophenyl)pyrimidin-2-amine

Yield 48.10%, mp. 147-148°C, (C-Cl), 654.79(C=C), 1653.47(C-H), 2891.46(C=O), 1677.47(C-C), 1481.82(N-C), 1300.71NMR, 5.88(2H, s, NH2 of Pyrimidine), 7.15(1H, s, C-2 of imidazole), 7.16(1H, d, C-4 of imidazole), 7.46(1H, d, C-5 of imidazole), 7.35-7.79(8H, m, Ar-H), Mass 347.8.

4.4-10 synthesis of 4-(4-(1H-imidazol-1-yl)phenyl)-6-(4-fluorophenyl)pyrimidin-2-amine

Yield 30.63%, mp. 93-94°C, IR(C-Cl ), 842.89(C-H), 2919.13(C=O), 1666.75(N-C), 1300.71NMR.
1304.61(C-C), 1481.00 NMR, 3.06(6H,s,N(CH3)2), 5.56(2H,s,NH2 of Pyrimidine), 7.85(1H,s,CH of Pyrimidine), 7.15(1H,s,C-2 of imidazole), 7.16(1H,d,C-4 of imidazole), 7.46(1H,d,C-5 of imidazole), 6.82-7.79(8H,m,Ar-H), Mass 356.42.

**4.4-11 synthesis of 4-(6-(4-(1H-imidazol-1-yl)phenyl)-2-aminopyrimidin-4-yl)phenol**

Yield 42%, mp. 104-105°C, IR(C-Cl), 731.74(C=C), 1603(C-H), 3.06(6H,s,N(CH3)2), 5.56(2H,s,NH2 of Pyrimidine), 7.15(1H,s,C-2 of imidazole), 7.16(1H,d,C-4 of imidazole), 7.46(1H,d,C-5 of imidazole), 6.86-7.79(8H,m,Ar-H), Mass 347.80.

**4.4-12 synthesis of 4-(4-(1H-imidazol-1-yl)phenyl)-6-(2,4-dichlorophenyl)pyrimidin-2-amine**

Yield 64%, mp. 124-125°C, IR(C-Cl), 674.12(C=O), 1671.16(C-H), 2923.01(N-H), 3334.73(C-C), 1489.97(N-O), 1330.13(C-C), 1489.97(N-C), 1518.71(NMR, 5.23(2H,s,NH2 of Pyrimidine), 7.85(1H,s,CH of Pyrimidine), 7.15(1H,s,C-2 of imidazole), 7.16(1H,d,C-4 of imidazole), 7.46(1H,d,C-5 of imidazole), 6.68-8.32(8H,m,Ar-H), Mass 358.35.

**BIOLOGICAL ACTIVITY**

**CHALCONES**

**Antibacterial activity**

From the above results it is evident that compounds 1 to 6 showed significant antibacterial activity at both 0.05 ml (50µg) and 0.1 ml (100µg) concentration levels when compared with standard drug Benzyl Penicillin. In particular compounds 4 5 & 6 showed maximum activity where as compounds 2 & 3 showed moderate activity.

**Antibacterial activity of Chalcones and pyrimidines (Compounds 1-12):**

<table>
<thead>
<tr>
<th>Compound code</th>
<th>B.subtilis</th>
<th>B.pumilis</th>
<th>E.coli</th>
<th>P.vulgaris</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Zone of inhibition (in mm)</td>
<td>50 µl</td>
<td>100 µl</td>
<td>50 µl</td>
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<tr>
<td>Standard</td>
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<td>33</td>
<td>31</td>
<td>32</td>
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<tr>
<td>Pyrimidine</td>
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</table>
Standard drug: Benzyl Penicillin  Note: “–“ No zone of inhibition

Antifungal activity
Compounds 1 to 6 showed moderate to significant antifungal activity at both 0.05 ml (50 µg) and 0.1 ml (100 µg) concentration level when compared with standard drug Fluconazole. Compounds 4 carrying fluorine at 4-position & Compound 5 carrying, hydroxyl at 4-position on the aromatic ring of chalcone showed remarkable activity.

Antifungal activity of Chalcones and pyrimidines (compounds 1 -12).

<table>
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<th>A.niger</th>
<th>P.crysogenum</th>
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<tbody>
<tr>
<td>50 µl</td>
<td>100 µl</td>
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<tr>
<td>Standard</td>
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</table>

Standard drug: Fluconazole  Note: “–“ No zone of inhibition

CONCLUSION
In conclusion, a new class of chalcone and pyrimidines derivatives were synthesized and evaluated for anti bacterial activity were effective against B.pumilis, B.subtilis, E.coli, p.vulgaris and it is interesting to note the result of anti-bacterial and anti fungal evaluation of chalcone and pyrimidines are effective against A.niger, P.crysogenum these results makes novel chalcone and Pyrimidine derivatives interesting lead molecules for further synthetic and biological evaluation. Finally it can be concluded that this class of compounds certainly holds great promise towards the purist to discover novel classes of antimicrobial agents.
ACKNOWLEDGMENTS
I am also grateful to express my heartful thanks to my parents, friends and also thanks for their experience advices and constant encouragement.

REFERENCES