Available online at www.ilcpa.pl

International Letters of Chemistry, Physics and Astronomy

17(3) (2014) 281-294 ISSN 2299-3843

Synthesis, characterization of biologically potent novel chalcones bearing urea, thiourea and acetamide linkages

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ABSTRACT

Three series of some novel chalcone based urea, thiourea and acetamide derivatives were designed, synthesized and screened for their antimicrobial and antifungal activities. All the synthesized compounds are first reported. The structures of the compounds were elucidated with the aid of elemental analysis and spectral methods including IR, ^{1}H-NMR spectral data. The prepared compounds were evaluated for antibacterial activity against two Gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus pyogenus*), two Gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*). The title compounds were also investigated for their antifungal activity using the broth micro dilution method. The bioassay results showed that compounds a few compounds showed good to superior *in vitro* antibacterial and antifungal activity.

***Keywords*:** Chalcone; urea; thiourea; acetamide; antimicrobial activity and antifungal activity

1. INTRODUCTION

A higher occurrence of opportunistic microbial infections caused by various bacteria due to the fruition and broaden of multidrug-resistant microorganisms has become a widespread medical problem. Such infections most frequently cause severe morbidity and transience in incapacitated and resistant compromised patients. Such infections nearly all frequently affect resistant compromised individuals, patients with malignancies, and transplant recipients. Moreover, with an signal of around two million deaths each year. These facts further emphasize the imperative necessity to find new effectual and secure compounds to maintain and improve the management and prevention of opportunistic microbial and tubercular infections in an innovative era of exhaustive infectious disease control, elimination, and eradication. Chalcones comprise an important class of natural products belonging to the flavonoid family, which exhibit motivating biological activities together with anti-inflammatory [1], anti bacterial [2], anti oxidant [3], anti malarial [4] and anti

cancer [5]. Due to their abundance in plants and ease of synthesis, this class of compounds has generated great interest for possible therapeutic uses. They are also effective in vivo as cell proliferating inhibitors, antitumor promoting and chemo preventing agents [6]. The above literature survey led us to consider the chalcone nucleus as a possible scaffold

Chalcone based urea, thiourea and acetamide derivatives which are of substantial industrial importance, and are linked to a series of biological actions including herbicidal activity [7], inhibition of nitric oxide [8], antimicrobial [9], anti-HIV [10], anti-viral [11], HDL-elevating [12], and analgesic properties [13,14]. Some chalcone-urea derivatives exhibited anti-inflammatory [15] and anti-malarial activity [16].

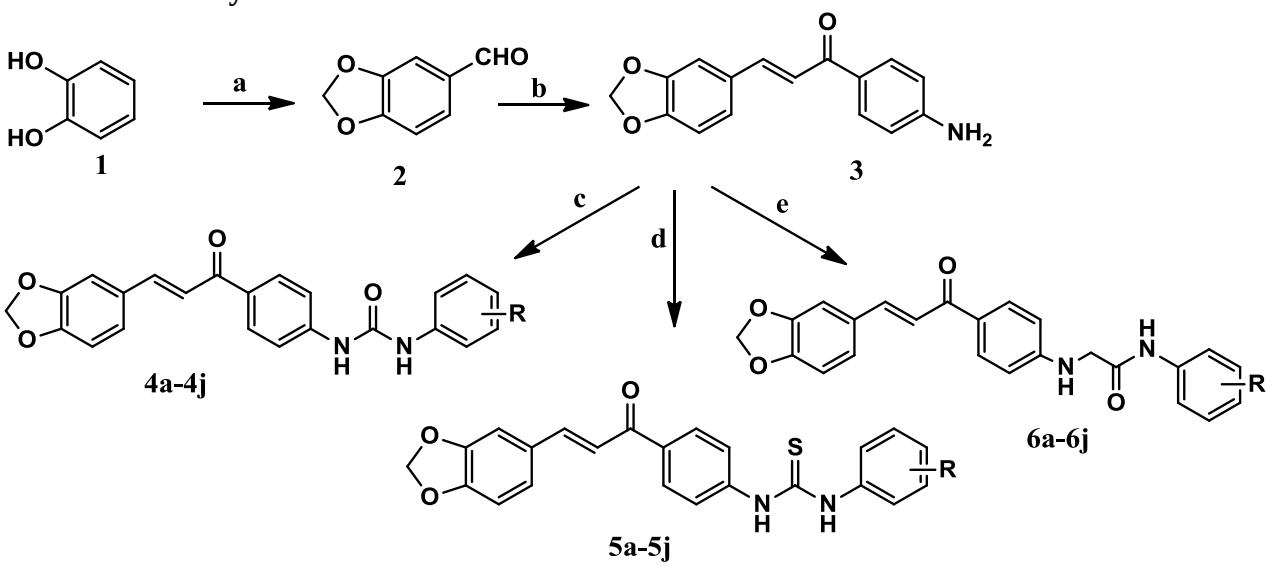
In view of the need to discover potent novel antimicrobial agents, and our previous positive results on chalcones, we have synthesized novel chalcone thiourea, urea and acetamide derivatives and evaluated their antimicrobial and antifungal activity against different strains of bacteria and fungal using the broth micro dilution method and compared with some reference drugs.

2. RESULTS AND DISCUSSION

2. 1. Materials and Methods

All reagents were of analytical grade and use directly. All the melting points were determined in open glass capillary and are uncorrected. Progress of reaction was monitored by thin layer chromatography (TLC) using silica gel-G coated aluminium plates (0.5 mm thickness, Merck) and spots were visualized under UV radiation, purified by recrystalization and column chromatography. The IR spectra were recorded on BRUKER TENSOR Series using KBr pellets. ^{1}H NMR spectra were recorded on 300MHz BRUKER ULTRASHIELD using DMSO-d6 as a solvent and TMS as an internal reference and chemical shift values were expressed in δ ppm.

2. 2. Chemistry



Scheme 1. Synthesis of the title compounds. (**a**) anhydrous DMF, KF, CH_2Cl_2, 110-120 °C (**b**) 4-aminoactophenone, MSA, r.t (**c**) Ar-NCO, THF, reflux (**d**) Ar-NCS, THF, reflux (**e**) Ar-NHCOCH$_2$Cl, THF, reflux.

In this work, the synthesis of the series proceeded as depicted in **Schemes 1**. 1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3aryl urea **(4a-4j)**, 1-[4-(3-Benzo[1,3] dioxol-5-yl-2-propenone-1-yl)-phenyl]-3aryl thiourea **(5a-5j)** and 2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-aryl- acetamide **(6a-6j)** were prepared in three steps. The intermediate Benzo[1,3]dioxole-5-carbaldehyde **2** was prepared by known method from catechol **1** [17], which was condensed with 4-amino acetophenone in the presence MSA (Methyl Sulfonic Acid) at r.t to get the yield 1-(4-Amino-phenyl)-3-benzo[1,3]dioxol-5-yl-propenone **3** [18]. Compound **3** was condensed with various isocyanate isothiocyanate and 2-chloro-N-aryl acetamide to afforded **(4a-4j)**, **(5a-5j)** and **(6a-6j)** respectively. All the synthesized compounds were fully characterized by IR, ^{1}H-NMR spectroscopy and elemental analysis [19-25].

3. EXPERIMENTAL SECTION

3. 1. Preparation of Benzo[1,3]dioxole-5-carbaldehyde (2)

A solution of catechol **1** (1.0 g, 0.0090 mol) in 300 ml anhydrous DMF (30 mL) was shaken with of KF (0.72 g, 0.0045 mol) of and the mixture warmed up somewhat. CH_2Cl_2 (0.85 g, 0.0099 mol) was then added to the cooled solution, and the mixture heated at 110-120 °C with an efficient reflux condenser for 2-3 hours. The cooled reaction mixture was extracted with ether, and the etheral extracts washed with water to remove DMF and with cold 5 % NaOH. The solution was dried over $MgSO_4$, and the solvent removed by evaporation. The residue was extracted with hot hexane followed by cooling, and evaporation of the extracts to give a 90 % yield of 1,3-benzodioxole. M.P.: 37 °C.

3. 2. Preparation of 1-(4-Amino-phenyl)-3-benzo[1,3]dioxol-5-yl-propenone (3)

4-amino acetophenone (5 g, 0.0369 mol) as allowed to stir with Benzo[1,3]dioxole-5-carbaldehyde (4.21, 0.0281 mol) in MSA (7 ml, 0.1476) for 5 min at room temperature. The reaction mixture was diluted with water. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The progress of reaction was monitored by TLC using toluene:ethyl acetate (6:4) as eluent. Solvent was removed under vacuum and crude product was purified by column chromatography to yield 60 %. M.P.: 145 °C.

3. 3. General Preparation of 1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3aryl urea (4a-4j)

A mixture of **3** (2.1 g, 0.00783 mol) and aryl isocyanate (00783 mol) in THF (10 mL) was refluxed for 5-6 hours. The progress of reaction was monitored by TLC using toluene: acetone (7:3) as eluent. After the completion of reaction, the solvent was removed by distillation and the resulting solid was recrystallized from methanol.

3. 4. Spectral data

[1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-phenyl-urea (4a)
^{1}H NMR: 4.78(s, 2H), 5.74(d, 1H), 5.66(d, 1H), 6.10(d, 1H), 6.06(d, 1H), 6.42(m, 1H), 6.49(d, 2H), 6.74 (d, 2H), 7.00(dd, 2H), 7.08(ddd, 2H), 7.77(ddd, 1H), 7.89(s, 1H), 7.96(s, 1H). **IR (KBr cm^{-1}):** 1680(-C=O), 1490(-C=C), 1214(-C-O), 2969(-C-H), 3060(-C-H), 1605(-NH), 3462(-CO-NH). **Anal. Calcd. For** $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25, **Found**: C, 71.44; H, 4.65; N, 7.20, **mp** 173 °C, **Yield:** 83 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-(2-fluoro-phenyl)-urea (4b)
^{1}H NMR: (400 MHz, DMSO-d_6) δ ppm: 3.64(s, 2H), 4.69(d, 1H), 4.81(d, 1H), 7.3(d, 1H), 7.34(d, 1H), 7.44(s, 1H), 7.46(d, 2H), 7.51(d, 2H),7.79(dd, 1H), 8.0(dd, 1H), 8.18(dd, 1H), 8.21(dd, 1H), 9.16(s, 1H) & 9.49(s, 1H). **IR (KBr cm^{-1}):** 1680(-C=O), 1493(-C=C), 1210(-C-O), 2968(-C-H), 3060(-C-H), 1602(-NH), 3465(-CO-NH), 3060 (C-H), 782(-C-F) **Anal. Calcd. For** $C_{23}H_{17}FN_2O_4$: C, 68.25; H, 4.20; N, 6.92 **Found**: C, 68.25; H, 4.15; N, 6.87. **mp** 171 °C, **Yield:** 85 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-(3-fluoro-phenyl)-urea (4c)
^{1}H NMR: (400 MHz, DMSO-d_6) δ ppm: 3.68(s, 2H), 4.74(d, 1H), 4.81(d, 1H), 7.41(d, 1H), 7.45(s, 1H), 7.6(d, 1H), 7.52(d, 2H), 7.68(s, 2H), 7.72(s, 1H), 7.78(dd, 1H), 8.03(dd, 1H), 8.14(ddd, 1H), 9.21(s, 1H) & 9.54(s, 1H). **IR (KBr cm^{-1}):** 1682(-C=O), 1495(-C=C), 1212 (C-O), 2960(-C-H), 3064(C-H), 1606(-NH), 3468(-CO-NH), 3062(C-H), 820(C-F). **Anal. Calcd. For** $C_{23}H_{17}FN_2O_4$: C, 68.25; H, 4.20; N, 6.92 **Found**: C, 68.25; H, 4.15; N, 6.87. **mp** 173 °C, **Yield:** 74 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-(4-fluoro-phenyl)-urea(4d)
^{1}H NMR: 4.83(s, 2H), 6.76(d, 1H), 6.77(d, 1H), 7.23(d, 1H), 7.23(d, 1H), 7.43(d, 1H), 7.44(d, 2H), 7.62(d, 2H), 7.83(d, 2H), 8.25(d, 2H), 9.0(s, 1H), 9.4(s, 1H). **IR (KBr cm^{-1}):** 1682(-C=O), 1495(-C=C), 1212(-C-O), 2960(-C-H), 3064(C-H), 1606(-NH), 3468(-CO-NH), 3062(C-H), 912(C-F). **Anal. Calcd. For** $C_{23}H_{17}FN_2O_4$: C, 68.25; H, 4.20; N, 6.92 **Found**: C, 68.25; H, 4.15; N, 6.87. **mp** 180 °C, **Yield:** 68 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-o-tolyl-urea (4e)
^{1}H NMR : 2.32(s, 1H), 3.59(s, 2H), 4.76(d, 1H), 4.81(d, 1H), 7.43(d, 1H), 7.48(s, 1H), 7.58(s, 1H), 7.49(d, 2H), 7.59(s, 2H), 7.69 (dd, 1H), 7.72 (ddd, 1H), 7.74(dd, 1H), 7.79(ddd, 1H), 8.68(s, 1H), 9.06(s, 1H). **IR (KBr cm^{-1}):** 1685(-C=O), 1485(-C=C), 1209(-C-O), 2959(-C-H), 3044(C-H), 1601(-NH), 3470(-CO-NH), 3067(C-H), 580(Ar- CH_3). **Anal. Calcd. For** $C_{24}H_{20}N_2O_4$: C, 71.97; H, 4.99; N, 6.99 **Found**: C, 71.92; H, 4.94; N, 6.94. **mp** 161 °C, **Yield:** 62 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-m-tolyl-urea (4f)
^{1}H NMR: 2.36(s, 3H), 3.62(s, 2H), 4.76(d, 1H), 4.79(d, 1H), 7.4(d, 1H), 7.41(s, 1H), 7.54(s, 1H), 7.47(d, 2H), 7.6(s, 2H), 7.6(s, 1H), 7.68(dd, 1H), 7.71(dd, 1H), 7.81(dd, 1H), 8.78(s, 1H), 9.13(s, 1H). **IR (KBr cm^{-1}):** 1662(-C=O), 1492(-C=C), 1210(-C-O), 2969(-C-H), 3061(C-H), 1606(-NH), 3460 (-CO-NH), 3065(C-H), 512 (Ar- CH_3) **Anal. Calcd. For** $C_{24}H_{20}N_2O_4$: C, 71.97; H, 4.99; N, 6.99 **Found**: C, 71.92; H, 4.94; N, 6.94. **mp** 159 °C, **Yield:** 71 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-p-tolyl-urea (4g)
^{1}H NMR: 2.36(s, 3H), 3.58(s, 2H), 4.23(d, 1H), 4.81(d, 1H), 7.24(d, 1H), 7.38(s, 1H), 7.51(s, 1H), 7.44(d, 2H), 7.59(s, 2H), 7.54(d, 2H), 7.69(d, 2H), 8.9(s, 1H), 9.24(s, 1H). **IR (KBr cm^{-1}):** 1692(-C=O), 1490(-C=C), 1214(-C-O), 2966(-C-H), 3069(C-H), 1606(-NH), 3462(-CO-NH), 3067(C-H), 612 (Ar- CH_3). **Anal.Calcd. For** $C_{24}H_{20}N_2O_4$: C, 71.97; H, 4.99; N, 6.99 **Found**: C, 71.92; H, 4.94; N, 6.94. **mp** 166 °C, **Yield:** 65 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-'phenyl]-3-(2-chloro-phenyl)-urea (4h)
^{1}H NMR: 3.61(s, 2H), 4.71(d, 1H), 4.79(d, 1H), 7.28(d, 1H), 7.34(d, 1H), 7.41(s, 1H), 7.46(d, 2H), 7.52(d, 2H), 7.8(dd, 1H), 7.92(dd, 1H), 8.09(dd, 1H), 8.18(dd, 1H), 9.2(s, 1H), 9.51(s, 1H). **IR (KBr cm^{-1}):** 1695 (-C=O), 1497 (-C=C), 1211 (-C-O), 2962 (-C-H), 3069 (C-H), 1608(-NH), 3476(-CO-NH), 3064(C-H), 726(C- Cl). **Anal. Calcd. For** $C_{23}H_{17}ClN_2O_4$: C, 65.58; H, 4.03; N, 6.65 **Found**: C, 65.53; H, 3.98; N, 6.60. **mp** 173 °C, **Yield:** 81 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-'phenyl]-3-(3-chloro-phenyl)-urea (4i)
^{1}H NMR: 3.66(s, 2H), 4.72(d, 1H), 4.81(d, 1H), 7.19(d, 1H), 7.29(d, 1H), 7.44(s, 1H), 7.49(d, 2H), 7.54(d, 2H), 7.68(s, 1H), 7.79(dd, 1H), 8.09(dd, 1H), 8.14(ddd, 1H), 9.21(s, 1H), 9.64(s, 1H). **IR (KBr cm^{-1}):** 1680(-C=O), 1490(-C=C), 1214(-C-O), 3106(-C-H), 2955(C-H), 1605(-NH), 3446(-CO-NH), 3062(C-H), 780(C- Cl). **Anal. Calcd. For** $C_{23}H_{17}ClN_2O_4$: C, 65.58; H, 4.03; N, 6.65 **Found**: C, 65.53; H, 3.98; N, 6.60. **mp** 175 °C, **Yield:** 79 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-'phenyl]-3-(4-chloro-phenyl)-urea (4j)
^{1}H NMR: 3.7(s, 2H), 4.74(d, 1H), 4.84(d, 1H), 7.21(d, 1H), 7.26(d, 1H), 7.49(s, 1H), 7.51(d, 2H), 7.59(d, 2H), 7.89(d, 2H), 8.32(d, 2H), 9.13(s, 1H), 9.62(s, 1H). **IR (KBr cm^{-1}):** 1665(-C=O), 1487(-C=C), 1215(-C-O), 2960(-C-H), 3069(C-H), 1608(-NH), 3462(-CO-NH), 3060(C-H), 825(C- Cl). **Anal. Calcd. For** $C_{23}H_{17}ClN_2O_4$: C, 65.58; H, 4.03; N, 6.65 **Found**: C, 65.53; H, 3.98; N, 6.60. **mp** 178 °C, **Yield:** 85 %

3. 5. General Preparation of 1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3aryl thiourea (5a-5j)

A mixture of **3** (2.1 g, 0.00783 mol) and aryl isothiocyanate (00783 mol) in THF (10 mL) was refluxed for 5-6 hours. The progress of reaction was monitored by TLC using toluene: acetone (6:4) as eluent. After the completion of reaction, the solvent was removed by distillation and the resulting solid was recrystallized from methanol.

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-phenyl-thiourea (5a)
^{1}H NMR: 4.81(s, 2H), 5.71(d, 1H), 5.73(d, 1H), 6.13(d, 1H), 6.16(d, 1H), 6.38(m, 1H), 6.43(d, 2H), 6.69(d, 2H), 6.97(dd, 2H), 7.04(ddd, 2H), 7.72(ddd, 1H), 7.87(s, 1H), 7.91(s, 1H). **IR (KBr cm^{-1}):** 1650(-C=O), 1490(-C=C), 1214(-C-O), 1530(C=S), 3410(-NH), 3276 (-CS-NH), 2969 (-C-H), 3060 (-C-H). **Anal.Calcd. For** $C_{23}H_{18}N_2O_3S$: C, 68.57; H, 4.47; N, 6.95 **Found**: C, 68.61; H, 4.51; N, 6.90. **mp** 190 °C, **Yield:** 78 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-(2-fluoro-phenyl)-thiourea (5b)
^{1}H NMR: 4.86(s, 2H), 5.64(d, 1H), 5.72(d, 1H), 6.14(d, 1H), 6.18(d, 1H), 6.24(s, 1H), 6.43(d, 2H), 6.59(d, 2H), 6.98(dd, 1H), 7.05(dd, 1H), 7.13(d, 1H), 7.17(dd, 1H), 7.83(s, 1H), 7.89(s, 1H). **IR (KBr cm^{-1}):** 1685 (-C=O), 1504 (-C=C), 1223 (-C-O), 1538(C=S), 3412(-NH), 3272(-CS-NH), 2971(-C-H), 3063(-C-H), 814(C-F). **Anal. Calcd. For** $C_{23}H_{17}FN_2O_3S$: C, 65.64; H, 4.04; N, 6.65 **Found**: C, 65.69; H, 4.09; N, 6.60. **mp** 182 °C, **Yield:** 78 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-(3-fluoro-phenyl)- thiourea (5c)
^{1}H NMR: 4.89(s, 2H), 5.65(d, 1H), 5.71(d, 1H), 6.12(d, 1H), 6.17(d, 1H), 6.25(s, 1H), 6.45(d, 2H), 6.62(d, 2H), 6.95(s, 1H), 6.98(dd, 1H), 7.04(dd, 1H), 7.14(dd, 1H), 7.89(s, 1H), 8.24(s, 1H). **IR (KBr cm^{-1}):** 1687(-C=O), 1506(-C=C), 1225(-C-O), 1544(C=S), 3414(-

NH), 3275(-CS-NH), 2974(-C-H), 3065(-C-H), 729(C-F). **Anal. Calcd. For** $C_{23}H_{17}FN_2O_3S$: C, 65.64; H, 4.04; N, 6.65 **Found**: C, 65.59; H, 4.00; N, 6.70. **mp** 176 °C, **Yield:** 80 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-(4-fluoro-phenyl)- thiourea (5d)

^{1}H NMR: 4.91(s, 2H), 5.63(d, 1H), 5.69(d, 1H), 6.11(d, 1H), 6.18(d, 1H), 6.24(s, 1H), 6.47(d, 2H), 6.64(d, 2H), 6.96(d, 2H), 7.08(d, 2H), 7.84(s, 1H), 8.03(s, 1H). **IR (KBr cm^{-1}):** 1672(-C=O), 1509(-C=C), 1228(-C-O), 1548(C=S), 3416(-NH), 3277(-CS-NH), 2978(-C-H), 3067(-C-H), 830(C-F). **Anal. Calcd. For** $C_{23}H_{17}FN_2O_3S$: C, 65.64; H, 4.04; N, 6.65 **Found**: C, 65.71; H, 4.08; N, 6.58. **mp** 177 °C, **Yield:** 75 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-o-tolyl-thiourea (5e)

^{1}H NMR: 2.34(s, 3H), 4.88(s, 2H), 5.61(d, 1H), 5.7(d, 1H), 6.09(d, 1H), 6.14(d, 1H), 6.29(m, 1H), 6.46(d, 2H), 6.67(d, 2H), 6.94(d, 1H), 6.96(dd, 1H), 6.99(dd, 1H), 7.03(dd, 1H), 7.84(s, 1H), 8.01(s, 1H). **IR (KBr cm^{-1}):** 1675(-C=O), 1512(-C=C), 1231(-C-O), 1551(C=S), 3418(-NH), 3279(-CS-NH), 2983(-C-H), 3071(-C-H), 519(Ar-CH_3). **Anal. Calcd. For** $C_{24}H_{20}N_2O_3S$: C, 69.14; H, 4.80; N, 6.72 **Found**: C, 69.20; H, 4.85; N, 6.78. **mp** 183 °C, **Yield:** 77 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-m-tolyl-thiourea (5f)

^{1}H NMR: 2.38(s, 3H), 4.89(s, 2H), 5.63(d, 1H), 5.71(d, 1H), 5.96(d, 1H), 6.04(d, 1H), 6.13(m, 1H), 6.43(d, 2H), 6.68(d, 2H), 6.93(m, 1H), 6.97(d, 1H), 7.02(d, 1H), 7.1(dd, 1H), 7.84(s, 1H), 8.21(s, 1H). **IR (KBr cm^{-1}):** 1678(-C=O), 1515(-C=C), 1233(-C-O), 1554(C=S), 3421(-NH), 3232(-CS-NH), 2985(-C-H), 3075(-C-H), 585(Ar-CH_3). **Anal. Calcd. For** $C_{24}H_{20}N_2O_3S$: C, 69.14; H, 4.80; N, 6.72 **Found**: C, 69.10; H, 4.75; N, 6.65. **mp** 188 °C, **Yield:** 69 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-phenyl]-3-p-tolyl-thiourea (5g)

^{1}H NMR: 2.34(s, 3H), 4.79(s, 2H), 4.98(d, 1H), 5.78(d, 1H), 5.89(d, 1H), 6.31(m, 1H), 6.47(d, 2H), 6.58(d, 2H), 6.84(d, 2H), 6.91(d, 2H), 7.8(s, 1H), 8.21(s, 1H). **IR (KBr cm^{-1}):** 1681(-C=O), 1517(-C=C), 1235(-C-O), 1555(C=S), 3423(-NH), 3235(-CS-NH), 2987(-C-H), 3078(-C-H), 676(Ar-CH_3). **Anal. Calcd. For** $C_{24}H_{20}N_2O_3S$: C, 69.14; H, 4.80; N, 6.72 **Found**: C, 69.22; H, 4.86; N, 6.78. **mp** 191 °C, **Yield:** 72 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-'phenyl]-3-(2-chloro-phenyl)- thiourea (5h)

^{1}H NMR: 4.94(s, 2H), 5.66(d, 1H), 5.71(d, 1H), 6.13(d, 1H), 6.18(d, 1H), 6.29(m, 1H), 6.42(d, 2H), 6.62(d, 2H), 6.96(dd, 1H), 6.99(dd, 1H), 7.06 (dd, 1H), 7.14(dd, 1H), 7.85(s, 1H), 7.89(s, 1H). **IR (KBr cm^{-1}):** 1678(-C=O), 1493(-C=C), 1210(-C-O), 1532(C=S), 3429(-NH), 3275(-CS-NH), 2960(-C-H), 3062(-C-H), 726(C-Cl). **Anal. Calcd. For** $C_{23}H_{17}ClN_2O_3S$: C, 63.17; H, 3.89; N, 6.40 **Found**: C, 63.12; H, 3.92; N, 6.45. **mp** 187 °C, **Yield:** 65 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-'phenyl]-3-(3-chloro-phenyl)- thiourea (5i)

^{1}H NMR: 4.98(s, 2H), 5.65(d, 1H), 5.69(d, 1H), 6.19(d, 1H), 6.21(d, 1H), 6.31(s, 1H), 6.44(d, 2H), 6.71(d, 2H), 6.91(m, 1H), 6.94(dd, 1H), 6.96(dd, 1H), 7.04(ddd, 1H), 7.86(s, 1H), 8.15(s, 1H). **IR (KBr cm^{-1}):** 1685(-C=O), 1507(-C=C), 1212(-C-O), 1530(C=S), 3400(-

NH), 3278(-CS-NH), 2979(-C-H), 3065(-C-H), 785(C-Cl). **Anal. Calcd. For** $C_{23}H_{17}ClN_2O_3S$: C, 63.17; H, 3.89; N, 6.40 **Found**: C, 63.22; H, 3.98; N, 6.35. **mp** 186°C, **Yield:** 60 %

1-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone-1-yl)-'phenyl]-3-(4-chloro-phenyl)- thiourea (5j)

^{1}H NMR: 4.9(s, 2H), 5.67(d, 1H), 5.72(d, 1H), 6.14(d, 1H), 6.19(d, 1H), 6.28(s, 1H), 6.41(d, 2H), 6.63(d, 2H), 6.72(d, 2H), 6.83(d, 2H), 7.84(s, 1H), 8.23(s, 1H). **IR (KBr cm^{-1}):** 1680(-C=O), 1502(-C=C), 1219 (-C-O), 1535(C=S), 3406(-NH), 3269(-CS-NH), 2970(-C-H), 3060(-C-H), 829(C-Cl). **Anal. Calcd. For** $C_{23}H_{17}ClN_2O_3S$: C, 63.17; H, 3.89; N, 6.40 **Found**: C, 63.10; H, 3.82; N, 6.35. **mp** 185 °C, **Yield:** 71 %

3. 6. General Preparation of 2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-aryl- acetamide (6a-6j)

A mixture of 3 (2.1 g, 0.00783 mol) and 2-chloro-N-arylacetamide (0.00783 mol) in THF (10 mL) were refluxed for 4 hrs. Progress of reaction was monitored by TLC using ethanol: toluene (1:4) as eluent. After the completion of reaction, the content was added to cold water. The solid product was obtained and filtered, dried and purified by crystallization from Ethanol.

2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-phenyl-acetamide (6a)

^{1}H NMR: 3.73(s, 2H), 5.61(s, 2H), 5.89(d, 1H), 5.91(d, 1H), 6.68(d, 1H), 6.78(d, 1H), 6.79(s, 1H), 6.81(d, 2H), 6.92(d, 2H), 7.14(d, 2H), 7.26(dd, 2H), 7.48(ddd, 1H), 7.73(s, 1H), 7.75(s, 1H). **IR (KBr cm^{-1}):** 1683(-C=O), 1519(-C=C), 1236(-C-O), 3261(-NH), 3458(-CO-NH), 2987(-C-H), 3078(-C-H). **Anal. Calcd. For** $C_{24}H_{20}N_2O_4$: C, 71.92; H, 4.99; N, 6.99 **Found**: C, 71.87; H, 4.93; N, 6.95. **mp** 162 °C, **Yield:** 73 %

2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-(2-fluoro-phenyl)-acetamide (6b)

^{1}H NMR: 3.69(s, 2H), 4.78(s, 2H), 5.79(d, 1H), 5.82(d, 1H), 6.66(d, 1H), 6.69(d, 1H), 6.81(s, 1H), 6.8(d, 2H), 6.88(d, 2H), 7.24(dd, 1H), 7.31(dd, 1H), 7.33(dd, 1H), 7.46(dd, 1H), 7.74(s, 1H), 7.86(s, 1H). **IR (KBr cm^{-1}):** 1691(-C=O), 1523(-C=C), 1241(-C-O), 3271(-NH), 3467(-CO-NH), 2997(-C-H), 3083(-C-H), 715(C-F). **Anal. Calcd. For** $C_{24}H_{19}FN_2O_4$: C, 68.83; H, 4.54; N, 6.69 **Found**: C, 68.88; H, 4.49; N, 6.64. **mp** 150 °C, **Yield:** 58 %

2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-(3-fluoro-phenyl)-acetamide (6c)

^{1}H NMR: 3.74(s, 2H), 4.81(s, 2H), 5.77(d, 1H), 5.82(d, 1H), 6.68(d, 1H), 6.73(d, 1H), 6.82(s, 1H), 6.78(d, 2H), 6.85(d, 2H), 7.18(m, 1H), 7.31(dd, 1H), 7.41(dd, 1H), 7.44(d, 1H), 7.75(s, 1H), 7.8(s, 1H). **IR (KBr cm^{-1}):** 1692(-C=O), 1527(-C=C), 1243(-C-O), 3275(-NH), 3471(-CO-NH), 3004(-C-H), 3085(-C-H), 744 (C-F). **Anal. Calcd. For** $C_{24}H_{19}FN_2O_4$: C, 68.83; H, 4.54; N, 6.69 **Found**: C, 68.79; H, 4.50; N, 6.62. **mp** 147 °C, **Yield:** 63 %

2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-(4-fluoro-phenyl)-acetamide (6d)

^{1}H NMR: 3.76(s, 2H), 4.73(s, 2H), 5.71(d, 1H), 5.83(d, 1H), 6.66(d, 1H), 6.7(d, 1H), 6.83(s, 1H), 6.75(d, 2H), 6.83(d, 2H), 7.25(d, 2H), 7.36(d, 2H), 7.54(s, 1H), 7.8(s, 1H). **IR (KBr cm^{-1}):** 1695(-C=O), 1531(-C=C), 1245(-C-O), 3277(-NH), 3474(-CO-NH), 3007(-C-H), 3089(-

C-H), 833(C-F). **Anal. Calcd. For** $C_{24}H_{19}FN_2O_4$: C, 68.83; H, 4.54; N, 6.69 **Found**: C, 68.90; H, 4.48; N, 6.74. **mp** 143 °C, **Yield:** 65 %

2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-o-tolyl-acetamide (6e)
^{1}H NMR: 2.32(s, 3H), 3.68(s, 2H), 4.76(s, 2H), 5.69(d, 1H), 5.8(d, 1H), 6.67(d, 1H), 6.71(d, 1H), 6.77(s, 1H), 6.81(d, 2H), 6.86(d, 2H), 7.18(dd, 1H), 7.26(dd, 1H), 7.42(dd, 1H), 7.48(dd, 1H), 7.8(s, 1H), 8.3(s, 1H). **IR (KBr cm^{-1}):** 1697 (-C=O), 1533(-C=C), 1247(-C-O), 3281(-NH), 3477(-CO-NH), 3101(-C-H), 3091(-C-H), 510(Ar-CH_3). **Anal. Calcd. For** $C_{25}H_{22}N_2O_4$: C, 72.38; H, 5.30; N, 6.75, **Found**: C, 72.33; H, 5.35; N, 6.70. **mp** 148 °C, **Yield :** 78 %

2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-m-tolyl-acetamide (6f)
^{1}H NMR: 2.38(s, 3H), 3.69(s, 2H), 4.77(s, 2H), 5.68(d, 1H), 5.85(d, 1H), 6.65(d, 1H), 6.73(d, 1H), 6.78(s, 1H), 6.84(d, 2H), 6.91(d, 2H), 7.17(s, 1H), 7.31(dd, 1H), 7.39(dd, 1H), 7.46(ddd, 1H), 7.84(s, 1H), 8.26(s, 1H). **IR (KBr cm^{-1}):** 1701(-C=O), 1534(-C=C), 1249(-C-O), 3286(-NH), 3479(-CO-NH), 3105(-C-H), 3096(-C-H), 573(Ar-CH_3). **Anal. Calcd. For** $C_{25}H_{22}N_2O_4$: C, 72.38; H, 5.30; N, 6.75, **Found**: C, 72.43; H, 5.25; N, 6.80. **mp** 144°C, **Yield:** 72 %

2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-p-tolyl-acetamide (6g)
^{1}H NMR: 2.34(s, 3H), 3.71(s, 2H), 4.76(s, 2H), 5.69(d, 1H), 5.79(d, 1H), 6.67(d, 1H), 6.76(d, 1H), 6.8(s, 1H), 6.87(d, 2H), 6.94(d, 2H), 7.24(d, 2H), 7.36(d, 2H), 7.9(s, 1H), 8.31(s, 1H). **IR (KBr cm^{-1}):** 1707(-C=O), 1537(-C=C), 1252 (-C-O), 3289(-NH), 3482(-CO-NH), 3107(-C-H), 3105(-C-H), 823(Ar-CH_3) **Anal. Calcd. For** $C_{25}H_{22}N_2O_4$: C, 72.38; H, 5.30; N, 6.75, **Found**: C, 72.49; H, 5.38; N, 6.69. **mp** 145 °C, **Yield:** 70 %

2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-(2-chloro-phenyl)-acetamide (6h)
^{1}H NMR: 3.72(s, 2H), 4.81(s, 2H), 5.82(d, 1H), 5.89(d, 1H), 6.64(d, 1H), 6.71(d, 1H), 6.79(s, 1H), 6.79(d, 2H), 6.89(d, 2H), 7.23(dd, 1H), 7.29(dd, 1H), 7.34(ddd, 1H), 7.44(dd, 1H), 7.76(s, 1H), 7.9(s, 1H). **IR (KBr cm^{-1}):** 1685(-C=O), 1512(-C=C), 1239(-C-O), 3265(-NH), 3461(-CO-NH), 2991(-C-H), 3072(-C-H), 729(C-Cl). **Anal. Calcd. For** $C_{24}H_{19}ClN_2O_4$: C, 66.22; H, 4.36; N, 6.43 **Found**: C, 66.29; H, 4.40; N, 6.39. **mp** 160 °C, **Yield:** 69 %

2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-(3-chloro-phenyl)-acetamide (6i)
^{1}H NMR: 3.79(s, 2H), 4.78(s, 2H), 5.78(d, 1H), 5.84(d, 1H), 6.66(d, 1H), 6.71(d, 1H), 6.81(s, 1H), 6.76(d, 2H), 6.84(d, 2H), 7.18(m, 1H), 7.28(dd, 1H), 7.38(ddd, 1H), 7.43(d, 1H), 7.74(s, 1H), 8.1(s, 1H). **IR (KBr cm^{-1}):** 1687 (-C=O), 1515(-C=C), 1241(-C-O), 3267(-NH), 3463(-CO-NH), 2993(-C-H), 3075(-C-H), 782(C-Cl). **Anal. Calcd. For** $C_{24}H_{19}ClN_2O_4$: C, 66.22; H, 4.36; N, 6.43 **Found**: C, 66.18; H, 4.30; N, 6.48. **mp** 166 °C, **Yield:** 65 %

2-[4-(3-Benzo[1,3]dioxol-5-yl-2-propenone)-phenylamino]-N-(4-chloro-phenyl)-acetamide (6j)
^{1}H NMR: 3.81(s, 2H), 4.74(s, 2H), 5.74(d, 1H), 5.81(d, 1H), 6.64(d, 1H), 6.69(d, 1H), 6.82(s, 1H), 6.74(d, 2H), 6.81(d, 2H), 7.24(d, 2H), 7.31(d, 2H), 7.52(s, 1H), 7.79(s, 1H). **IR (KBr cm^{-1}):** 1689(-C=O), 1521(-C=C), 1238(-C-O), 3269(-NH), 3465(-CO-NH), 2995(-C-

H), 3081(-C-H), 820(C-Cl). **Anal. Calcd. For** $C_{24}H_{19}ClN_2O_4$: C, 66.22; H, 4.36; N, 6.43 **Found**: C, 66.29; H, 4.40; N, 6.50. **mp** 154 °C, **Yield:** 68 %

4. ANTIBACTERIAL ACTIVITY

The minimum inhibitory concentration (MIC) of the synthesized compound were tested against two representative Gram-positive (*Staphylococcus aureus* MTCC 443 and *Staphylococcus pyogenus* MTCC 443) and two Gram-negative (*Escherichia coli* MTCC 442 and *Pseudomonas aeruginosa* MTCC 443) and assayed *in vitro* using broth micro dilution method by standards gradual dilution starting from (250, 200, 125,100, 50, 25, 12.5, 6.25, 3.125) μg/mL.

Ciprofloxacin and Chloramphenicol were used as reference antibacterial agents. Solution of the test compounds and reference drugs were dissolved in DMSO. The *in vitro* results of the antibacterial activity of the newly synthesized 30 compounds are presented in **Table 1**.

Some of the compounds displayed moderate the good antibacterial activity in the range of 62.5-125 μg/ml. Here the Gram-negative bacteria *E. coli* appered with relative high sensitivity towards 4-fluro, 2-chloro and 4-chloro group substituted analogues 4d, 4h, 4j, 5d, 5h, 5j, 6d, 6h and 6j at 100 μg/ml MIC level. With regard to the activity against *P. aeruginosa*, the best inhibition was displayed by compound bearing 2-fluoro group 4b, 5b and 6b (62.5 μg/ml).

On the other hand investigation of antibacterial activity of the synthesized compounds against few Gram-positive strains related that *S. pyogenus* is more sensitive against most of the synthesized analogous as compared to *S. aureus*. It was found that present of 2-fluro (62.5 μg/ml) and 2-methyl group (100 μg/ml) on para position of 4b, 4e, 5b, 5e, 6b and 6e accelerate the antibacterial activity against *S. pyosens*. More over the Gram-negative bacteria S.aureus showed relative high sensitivity towards the analogs 4a, 4f, 5a, 5f, 6a and 6f at 100 μg/ml MIC level.

Table 1. Antibacterial activity of title compounds.

Compd. No	**ANTIBACTERIAL ACTIVITY TABLE**				
	MINIMUM INHIBITORY CONCENTRATION				
	-R	*E. coli* MTCC 442 μg/ml	*P. aeruginosa* MTCC 443 μg/ml	*S. aureus* MTCC 443 μg/ml	*S. pyogenus* MTCC 443 μg/ml
4a	-H	250	250	100	100
4b	2-F	100	62.5	250	62.5
4c	3-F	200	200	200	200
4d	4-F	100	100	250	125
4e	2-CH_3	250	200	125	100

4f	3-CH_3	200	125	100	250
4g	4-CH_3	125	100	62.5	125
4h	2-Cl	100	200	200	200
4i	3-Cl	200	250	125	200
4j	4-Cl	100	250	200	125
5a	-H	100	250	100	125
5b	2-F	250	62.5	250	62.5
5c	3-F	100	100	200	250
5d	4-F	100	250	250	62.5
5e	2-CH_3	250	200	125	100
5f	3-CH_3	200	125	100	250
5g	4-CH_3	62.5	100	250	250
5h	2-Cl	100	200	200	200
5i	3-Cl	200	250	125	200
5j	4-Cl	100	250	100	125
6a	-H	125	250	100	125
6b	2-F	250	62.5	250	62.5
6c	3-F	100	500	200	200
6d	4-F	100	250	250	125
6e	2-CH_3	250	200	125	100
6f	3-CH_3	100	125	100	250
6g	4-CH_3	125	100	100	250
6h	2-Cl	100	125	200	200
6i	3-Cl	200	250	125	200
6j	4-Cl	100	125	200	125
Standard Drug	Ciprofloxacin	25	25	50	50
	Chloramphenicol	50	50	50	50

5. ANTIFUNGAL ACTIVITY

The minimum inhibitory concentration (MIC) of the synthesized compound was tested against fungi (*Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323) and assayed *in vitro* using broth micro dilution method standards with gradual dilution starting from (250, 200, 125,100, 50, 25, 12.5, 6.25, 3.125) µg/mL. Nystatin and Greseofulvin were used as reference antibacterial agents. Solution of the test compounds and reference drugs were dissolved in DMSO. The *in vitro* results of the antifungal activity of the newly synthesized 30 compounds are presented in **Table 2**.

Some of the compounds displayed moderate the good antibacterial activity. The *in vitro* antifungle activity of the synthesized analogues indicated that halogen and methyl group substituted analogs 4d, 4e, 4i, 5d, 5e, 5i, 6d, 6e and 6i have shown high efficacy against *C. albicans* & *A. clavatus* at 100 ug/ml MIC level.

Table 2. Antifungal activity of title compounds.

Compd. No.	**ANTIFUNGAL ACTIVITY TABLE**			
	MINIMUM INHIBITORY CONCENTRATION			
	-R	*C. albicans* MTCC 227 µg/ml	*A. niger* MTCC 282 µg/ml	*A. clavatus* MTCC 1323 µg/ml
4a	-H	500	>1000	1000
4b	2-F	500	500	>1000
4c	3-F	1000	500	>1000
4d	4-F	100	250	100
4e	2-CH_3	100	1000	100
4f	3-CH_3	500	>1000	500
4g	4-CH_3	250	500	500
4h	2-Cl	500	>1000	1000
4i	3-Cl	100	500	100
4j	4-Cl	250	1000	>1000
5a	-H	250	500	250
5b	2-F	200	250	500
5c	3-F	250	500	>1000
5d	4-F	100	250	100
5e	2-CH_3	100	1000	100
5f	3-CH_3	1000	200	500
5g	4-CH_3	250	500	100
5h	2-Cl	500	250	1000

5i	3-Cl	100	500	100
5j	4-Cl	250	500	>1000
6a	-H	125	1000	250
6b	2-F	100	200	>1000
6c	3-F	250	500	100
6d	4-F	100	250	100
6e	2-CH_3	100	1000	100
6f	3-CH_3	250	200	500
6g	4-CH_3	100	500	250
6h	2-Cl	62.5	250	1000
6i	3-Cl	100	500	100
6j	4-Cl	125	250	>1000
Standard Drug	Nystatin	100	100	100
	Greseofulvin	500	100	100

6. CONCLUSIONS

In conclusion, a new class of chalcone based urea, thiourea, acetamidd derivatives were synthesized and evaluated as antibacterial agents. The newly synthesized compounds exhibited promising antibacterial activities against two representative Gram-positive (*Staphylococcus aureus* and *Staphylococcus pyogenus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*). These results makes novel chalcone and their urea, thiourea and acetamided derivatives interesting lead molecules for further synthetic and biological evaluation. It can be concluded that this class of compounds certainly holds great promise towards the pursuit to discover novel classes of antifungal agents. Further studies to acquire more information concerning structure - activity relationships are in progress.

Acknowledgements

The authors are thankful to Dr (Ms.) N. K. Shah, Head of the Chemistry Department and Director of School of Sciences, Gujarat University for all the support and facilities. The authors also express their sincere thanks to the Oxygen health care for spectral analysis. Dhruvin Shah and Nirali Mewada are also thankful to UGC for providing financial assistance.

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(Received 30 June 2014; accepted 10 July 2014)