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Design, synthesis and biological evaluation of dihydroisoxazole of indole derivatives as anti-microbial agents

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ABSRTACT

*In the present study, a new series of Oxazoline derivatives **[5a-5l]** were prepared from the N-cyclopentyl indolyl chalcones **[4a-4l]** with hydroxylamine hydrochloride in presence of base gives 65-78% yield after column purification. The purity of the compounds was checked by TLC in ethylacetate: hexane (3:7). The structures of all the compounds were established by ^{1}H - NMR, IR, LCMS. The synthesized compounds **[5a-5l]** were evaluated for their anti-microbial activity. Out of **12** compounds reported here, many of them displayed decent anti-bacterial and anti-fungal profiles. We report herewith most prominent molecules **5c, 5d, 5l** have been identified as the lead with the most prominent results.*

Key words: Chalcones, Anti-microbial activity, Indole, hydroxylamine hydrochloride.

INTRODUCTION

Bacterial and fungal infections represent one of the most prevalent health problems that cause functional disability, leading to lifestyle sacrifice and further complications. Upcoming needs for the clinical drugs candidates for the improvement signifies an exciting and challenging approach to improve the clinical efficacy of current drugs in the development of new therapeutic approaches.

Indoles are one of the most important nitrogen containing heteroaryl compound, found extensively in biological system which play very important role in biochemical process. Indole alkaloids have been proved to be medicinally important natural compounds. Indole ring constitute an important heterocycle for drug design such as the classical NSAIDs indomethacin and indoxole. Further Indole derivatives have been reported to possess promising biological activities including analgesic [1], antipyretic [2], antifungal [3], anti-inflammatory [4-6] activities. Indole derivatives also shows anthelmintic [7], cardiovascular [8], anticonvulsant [9-10], antimicrobial [11-12] and selective COX-2 inhibitory activities [13-16]. Thus the efficient synthesis of novel substituted indole derivative compounds still represent highly pursued target. In fact, Valdecoxib is an isoxazoline derivatives now widely used in the market as an anti-inflammatory drug [17].

Nitrogen and oxygen containing heterocyclic compounds having considerable attention due to their wide range of pharmacological activity. Isoxazolines represent one of the active classes of compounds possessing a wide spectrum of biological activities. Isoxazolines have been reported to possess antidiabetic [18] diuretic [19], analgesic [20], anthelimentic [21] and hypolipaemic [22] activity. A literature survey reveals that very few references are available

for the synthesis of isoxazole associated with indole compounds. I report here a new 3- substituted indoles incorporating an extra heterocyclic ring such as isoxazole and which is screened in vitro for their anti-bacterial and anti-fungal activity.

EXPERIMENTAL SECTION

Melting points were taken on a precision melting point apparatus (DBK) instrument and are uncorrected. IR spectra were obtained in potassium bromide (KBr) disks on a Bruker IR-spectrometer, and ^{1}H NMR spectra were obtained on deuterated choroform ($CDCl_3$) or DMSO-d_6 solution on a Varian 400 MHz spectrometer. Mass spectra were recorded on a Micro Mass Spectrometer by waters. All the raw materials, reagents and solvents used were of commercial grade only. All reactions were routinely followed by TLC.

2.1.General procedure for the synthesis of 1H-indole-3-carbaldehyde (2) : A solution of indole (0.21 mole) in 100 ml dimethylformamide was prepared and kept aside. A formylation complex was also prepared by cooling 80 ml dimethylformamide in an external ice bath (internal temperature about 12^0C), followed by the addition of 20 ml phosphorus oxychloride dropwise over the course of 30 min. This formylation mixture was then warmed to 25 ^{0}C and added the solution of indole in dimethylformamide dropwise (with continued stirring) over a period of 30 min. Stirring was continued for yet another 45 min, during which time the temperature was raised to 40 ^{0}C. The reaction mixture was then poured onto chipped ice which produced a clear red solution. This was made basic with the addition of 200 ml of 5 N sodium hydroxide which allowed the separation of a yellow solid. This was diluted by the addition of 200 ml hot water and, after cooling the product was removed by filtration and washed with cold water. The product was recrystallized from aqueous dimethylformamide to yield 1H-indole-3-carbaldehyde **2** (98%) as faint orange needles**.**

mp.:196-198^{0}C; 'H NMR (DMSO-d6): δ 10.1(s, 1H, NH), 7.53-8.09 (m, 4H, indole Ar-H), 9.99 (s, 1H, CHO), 8.20 (s, 1H, indole H); IR (KBr) cm^{-1}: 3163 (NH), 3039 (Ar-H), 1647 (C=O), 1581 (C=O) ; ESI- MS(m/z) : 146 $(M+H)^+$.

***2.2.General Procedure for the synthesis of 1-Cyclopentyl-3-formyl Indole (3)* : A** mixture of 20 g (0.140mol) of 3-formylindole, 15.6ml (0.150 mole) of Bromocyclopentane, 100mL of DMF, and 20.7 g **(**0.150 mole) of K_2C0_3 was refluxed for 4 h. Upon cooling, the solid was filtered off and washed with DMF and the DMF phase concentrated. The residue was taken up with chloroform, washed twice with water, dried, and concentrated to give a brown oil which was purified by column chromatography ($Si0_2$, 10% methanol / chloroform) to yield 17.8 g (60%) of the expected 1-cyclopentyl-3-formylindole **3** as an oil (Brown)**.**

'H NMR ($CDC1_3$): δ 1.56 (m, 6H, CH_2 cyclopentyl), 2.08 (m, 2H, CH_2 cyclopentyl), 3.71 (m, lH, CH, cyclopentyl), 7.4 (m, 2H, indole H), 7.81 (s, lH, indole H), 8.5 (m, lH, indole H H),7.1 (m, 1H, indole H), 9.99 **(s,** lH,-CHO); IR (KBr) cm^{-1}: 3053 & 2962 (Ar-H), 2873 (-CHO), 1656 (C=O), 1527 (C=C); ESI-MS (m/z): 214 $(M+H)^+$.

***2.3.General Procedure for Synthesis of 1-cyclopentyl-1H-indole-3-yl)-3-phenylprop-2-en-1-one (chalcone) 4(a-l)*:** Equimolar quantities of 1-cyclopentyl-3-formyl Indole (0.0046mol) and acetophenones (0.0046mole) were taken in conical flask and dissolved in minimum of ethanol (15 ml). To this suspension KOH (0.0138 mole) in minimum quantity of water was added and the resulting mixture was stirred for overnight. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature and the crude product was collected by filtration and washed with cold ethanol. The final compound was recrystallised from ethanol.

The other compounds of this series were prepared according to the general procedure. Their percentage yield and melting points are recorded in Table 1. Their structures have been confirmed by Mass, IR and 1H NMR spectra.

***2.4.General procedure for Synthesis of 5-(1-cyclopentyl-1H-indol-3-yl)-3-phenyl-4,5-dihydroisoxazole 5(a-l)*:** To a suspension Chalcones **4(a-l)** (0.0030 mole) in 20 ml of ethanol were added hydroxylamine hydrochloride (0.0030 mole) and potasium hydroxide (0.0090mole).The reaction mass was heated to reflux for 8-12 h. After completion of reaction (checked by TLC), reaction mixture was cooled to room temperature and added 50 ml chilled water slowly. The reaction mass was neutralized with dilute hydrochloric acid, the separated product **(5a-5l**) was filtered, washed with cold water (10 ml) and crystallized from ethanol.

Similarly the other derivatives of the series were prepared. Their structures have been confirmed by IR, ^{1}HNMR and Mass spectra.

SPECTRAL ANALYSIS

2.3.1. **3-(*1-cyclopentyl-1H-indol-3-yl)-1-phenylprop-2-en-1-one (4a)*:** Yellow solid. IR(KBr,cm^{-1}); 3070 & 2949 (Ar-H), 1647 (C=O) ,1581 & 1562 (C=C); 'H NMR ($CDC1_3$): δ 1.82-1.95 (m, 7H, CH_2, cyclopentyl H), 2.26 (m, 2H, CH_2, cyclopentyl,H), 7.25-7.60 (m, 4H, indole Ar-H), 8.11 (s, lH, indole H), 8.06 (d, 1H, vinylic H), 8.02 (d, 1H, vinylic H), 7.62-7.88 (m, 5H, Ar-H); ESI-MS (m/z) : 316 $(M+H)^+$.

2.3.2. **3-(*1-cyclopentyl-1H-indol-3-yl)-1-(p-tolyl)prop-2-en-1-one (4b) :*** Faint yellow solid. IR(KBr ,cm^{-1}) : 3028 & 2951 (Ar-H),1647 (C=O),1556 (C=C);'H NMR ($CDC1_3$): δ 1.71 -1.92 (m, 7H, CH_2 cyclopentyl), 2.24 (m, 2H, CH_2 cyclopentyl), 2.43 (s , 3H, methyl), 7.30 (m, 4H, indole, Ar-H), 8,07 (s, lH, indole H), 7.97 (d, 2H, Ar-H), 7.42 (d, 1H, Ar-H), 7.43 (d, 2H, vinylic H) 7.56(d, 2H ,vinylic H);ESI-MS(m/z) : 330 $(M+H)^+$.

2.3.3 **3-(*1-cyclopentyl-1H-indol-3-yl)-1-(4-bromophenyl)prop-2-en-1-one(4c):*** pale yellow solid. IR (KBr,cm^{-1}): 3058 & 2951 (Ar-H) ,1682 (C=O), 1616 & 1592 (C=C); 'H NMR ($CDC1_3$): δ 1.59-1.99 (m, 7H, CH_2 cyclopentyl), 2.29 (m, 2H, CH_2 cyclopentyl), 6.93-7.47 (m, 4H, indole Ar-H), 8.02 (s, lH, indole H), 7.48 (d, 1H,vinylic H),7.61 (d, 1H, vinylic H), 7.65 (d, 2H Ar-H), 7.80 (d, 2H, Ar-H) ; ESI-MS(m/z): 394 $(M+H)^+$.

2.3.4. **3-(*1-cyclopentyl-1H-indol-3-yl)-1-(4-Flurophenyl)prop-2-en-1-one(4d):*** pale yellow solid. IR (KBr,cm^{-1}): 3054 (Ar-H),1665 (C=O) ,1545 (C=C) ; 'H NMR ($CDC1_3$): δ 1.65-2.21 (m, 7H, CH_2 cyclopentyl), 2.35 (m, 2H, CH_2 cyclopentyl), 7.32 (m, 4H, indole Aro.H), 8.21 (m, lH, indole) 7.32 (d,1H, vinylic H),7.51 (d, 1H, vinylic H),7.45 (d, 2H, Ar-H), 7.65 (d, 2H, Ar-H) ; ESI-MS(m/z): 334 $(M+H)^+$.

2.3.5. **3-(*1-cyclopentyl-1H-indol-3-yl)-1-(4-Chlorophenyl)prop-2-en-1-one(4e):*** pale yellow solid. IR (KBr,cm^{-1}): 3065 (Ar-H),1658 (C=O) ,1534 (C=C) ; 'H NMR ($CDC1_3$): δ 1.43-2.21 (m, 7H, CH_2 cyclopentyl), 2.56 (m, 2H, CH_2 cyclopentyl), 7.21 (m, 4H, indole), 8.06 (m, lH,indole Aro.H), 7.42 (d, 1H,vinylic H), 7.51 (d, 1H, vinylic H), 7.32 (d, 2H, Ar-H), 7.39 (d, 2H, Ar-H) ; ESI-MS(m/z) : 350 $(M+H)^+$.

2.3.6. **3-(*1-cyclopentyl-1H-indol-3-yl)-1-(4-Iodoophenyl)prop-2-en-1-one(4f):*** pale yellow solid. IR (KBr,cm^{-1}): 3065 (Ar-H),1658 (C=O) ,1534 (C=C) ; 'H NMR ($CDC1_3$): δ 1.58-2.25 (m, 7H, CH_2 cyclopentyl), 2.43 (m, 2H, CH_2 cyclopentyl), 7.21 (m, 4H, indole), 8.12 (m, lH, indole H) 7.22 (d, 1H,vinylic H), 7.30 (d, 1H, vinylic H), 7.36 (d, 2H, Ar-H), 7.49 (d, 2H, Ar-H) ; ESI-MS(m/z) : 441 $(M+H)^+$.

2.3.7. **3-(*1-cyclopentyl-1H+98-indol-3-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one(4g):*** yellow liquid. IR(KBr ,cm^{-1}): 3029 (Ar-H),1657 (C=O) ,1598 (C=C),3399 (OH) ; 'H NMR ($CDC1_3$): δ 1.83-2.01(m, 7H, CH_2 cyclopentyl), 2.28 (m, 2H, CH_2 cyclopentyl), 4.80 (s,1H, OH), 6.96-7.49 (m, 4H, indole H), 8.40 (s, lH, indole H), 7.40-7.91 (m, 4H Ar-H), 7.45 (d, 1H, vinylic H), 7.49 (d, 1H, vinylic H) ; ESI-MS(m/z): 332 $(M+H)^+$.

2.3.8. **3-(*1-cyclopentyl-1H-indol-3-yl)-1-(4-hydroxyphenyl)prop-2-en-1-one(4h):*** pale yellow solid. ; IR (KBr,cm^{-1}): 3065 (Ar-H),1676 (C=O) ,1544 (C=C) ,3323 (OH) ;'H NMR ($CDC1_3$): δ 1.70-2.05 (m, 7H, CH_2 cyclopentyl), 2.32 (m, 2H, CH_2 cyclopentyl), 4.85 (s, 1H, OH), 7.10-7.49 (m, 4H, indole H), 8.23 (s, lH, indole H), 7.54 (d, 2H, Ar-H), 7.67 (d, 2H, Ar-H),7.56 (d, 1H, vinylic H),7.63 (d, 1H, vinylic H) ESI-MS(m/z): 332 $(M+H)^+$.

2.3.9. **3-(*1-cyclopentyl-1H-indol-3-yl)-1-(2-hydroxy-4-methyl phenyl)prop-2-en-1-one(4i):*** pale yellow solid. ; IR (KBr,cm^{-1}) : 3032 (Ar-H),1655 (C=O) ,1565 (C=C) ,3321 (OH) ; 'H NMR ($CDC1_3$): δ 1.85-2.03 (m, 7H, CH_2 cyclopentyl), 2.28 (m, 2H, CH_2 cyclopentyl) , 5.04 (s,1H, OH), 2.24 (s, 3H methyl H), 6.92-7.12 (m, 4H, indole H), 8.11 (s, lH, indole H) 7.20 (s, 1H, Ar-H),7.12 (d, 1H, Ar-H), 7.40 (d, 1H, Ar-H), 7.54 (d, 1H, vinylic H), 7.56 (d, 1H, vinylic H) ESI-MS (m/z): 346 $(M+H)^+$.

2.3.10. **3-(*1-cyclopentyl-1H-indol-3-yl)-1-(2-hydroxy-4-chlorophenyl)prop-2-en-1-one(4j):*** Pale Yellow solid. ; IR (KBr, cm^{-1}) : 2954 (Ar-H),1648 (C=O) ,1512 (C=C) ,3363 (OH) ; 'H NMR ($CDC1_3$): δ 1.59-1.99 (m, 7H, CH_2 cyclopentyl), 2.26 (m, 2H, CH_2, cyclopentyl) , 5.21 (s, 1H, OH), 7.41-7.55 (m, 4H, indole H), 8.05 (s, lH, indole H), 7.23 (s, 1H Ar-H), 7.12 (d, 1H, Ar-H),7.32 (d, 1H Ar-H), 7.39 (d, 1H, vinylic H), 7.56 (d, 1H, vinylic H) ESI-MS(m/z): 366 $(M+H)^+$.

2.3.11. **3-(*1-cyclopentyl-1H-indol-3-yl)-1-(2-hydroxy-4-bromophenyl)prop-2-en-1-one (4k):*** pale yellow solid. ; IR (KBr,cm^{-1}) : 2992 (Ar-H),1667(C=O) ,1565 (C=C) ,3400(OH) ; 'H NMR ($CDC1_3$): δ 1.59-2.01 (m, 7H, CH_2 cyclopentyl), 2.31 (m, 2H, CH_2 cyclopentyl) , 5.23 (s, 1H, OH), 7.12-7.38 (m, 4H, indole H), 8.15 (s, lH, indole H),

7.65 (s, 1H, Ar-H), 7.23 (d, 1H, Ar-H), 7.22 (d, 1H, Ar-H), 7.43 (d, 1H, vinylic H), 7.50 (d, 1H, vinylic H) ESI-MS(m/z): 410 $(M+H)^+$.

2.3.12. **3-(*1-cyclopentyl-1H-indol-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (4l):*** pale yellow solid. IR (KBr,cm^{-1}) : 3053 (Ar-H),1656 (C=O),1612 (C=C); 'H NMR ($CDC1_3$): δ 1.81 -1.98 (m, 6H, CH_2 cyclopentyl), 2.24 (m, 2H, CH_2 cyclopentyl), 2.43(m, 1H, CH cyclopentyl), 3.90 (s , 3H ,methoxy H), 6.95-7.51 (m, 4H, indole Ar-H), 8.11 (s, lH, indole H), 7.81 (d, 2H Ar-H), 8.02 (d, 2H, Ar-H), 7.46 (d, 1H, vinylic H) ,7.47 (d, 1H ,vinylic H); ESI-MS(m/z): 346 $(M+H)^+$.

2.4.1. 5-(1-cyclopentyl-1H-indol-3-yl)-3-phenyl-4,5-dihydroisoxazole (5a): Faint yellow solid, yield : 68% ; M.p. 112-114^{0}C ***;*** IR (KBr,cm^{-1}): 1636 (C=N), 3088 & 2920 (Ar-H), 1521 & 1571 (C=C),1435 (C-O)***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) : δ 1.83-1.99 (m, 7H,Cyclopentyl H), 2.01-2.28 (m, 2H, Cyclopentyl H), 3.45 (dd, 1H oxazoline H), 3.69 (dd, 1H ,oxazoline H), 5.91 (t, 1H, oxazoline H) , 8.01 (s, 1H, indole H), 7.02-7.88 (m, 9H, Aro. H); MS: m/z 331 $(M+H)^+$.

2.4.2. 5-(1-cyclopentyl-1H-indol-3-yl)-3-(p-tolyl)-4,5-dihydroisoxazole (5b): Buff white solid , yield :76% ; M.p. 133-135^{0}C ***;*** IR (KBr,cm^{-1}):1636 (C=N), 3088 (Ar-H), 1521 (C=C),1436 (C-O)***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) : δ 1.72-1.99 (m, 7H Cyclopentyl H), 2.12-2.30 (m, 2H, Cyclopentyl H), 2.50 (s, 3H,methyl H), 3.61 (dd, 1H,oxazoline H), 3.72 (dd, 1H, oxazoline H), 5.94 (t, 1H oxazoline H) ,7.87 (s, 1H, indole H), 7.01-7.74 (m, 8H,Aro. H); MS: m/z 345 $(M+H)^+$.

2.4.3. 3-(4-bromophenyl)-5-(1-cyclopentyl-1H-indol-3-yl)-4,5-dihydroisoxazole (5c): Faint brown solid , yield: 65% ; M.p. 110-112^{0}C ***;*** IR (KBr,cm^{-1}): 1616 (C=N), 3095 (Ar-H), 1514 (C=C) ,1460(C-O)***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) : δ 1.46-2.08 (m, 8H, Cyclopentyl H), 3.21 (m, 1H, Cyclopentyl H), 3.84 (dd, 1H, oxazoline H), 3.99 (dd, 1H, oxazoline H), 5.90 (t, 1H ,oxazoline H) ,8.10 (s, 1H, indole H),7.02-7.72 (m, 8H Aro. H); MS: m/z 345 $(M+H)^+$.

2.4.4. 3-(4-flurophenyl)-5-(1-cyclopentyl-1H-indol-3-yl)-4,5-dihydroisoxazole (5d): Gray solid , yield: 70% ; M.p. 107-109^{0}C ***;*** IR (KBr,cm^{-1}): 1605 (C=N), 3048 (Ar-H), 1578 (C=C) ,1456 (C-O)***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) : δ 1.34-2.12 (m, 8H ,Cyclopentyl H), 3.43 (m, 1H ,Cyclopentyl H), 3.88 (dd, 1H oxazoline H), 3.77 (dd, 1H, oxazoline H), 5.76 (t, 1H, oxazoline H) , 8.21 (s, 1H, indole H), 7.21-7.87 (m, 8H,Aro. H); MS: m/z 349 $(M+H)^+$.

2.4.5. 3-(4-chlorophenyl)-5-(1-cyclopentyl-1H-indol-3-yl)-4,5-dihydroisoxazole (5e): Gray solid , yield: 78% ; M.p. 171-173^{0}C ***;*** IR (KBr,cm^{-1}): 1634 (C=N), 3065 (Ar-H), 1575 (C=C) ,1423 (C-O)***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) : δ 1.54-2.45 (m, 8H,Cyclopentyl H), 3.65 (m, 1H, Cyclopentyl H), 3.78 (dd, 1H, oxazoline H), 3.80 (dd, 1H, oxazoline H), 5.54 (t, 1H, oxazoline H) ,8.10 (s, 1H , indole H), 7.12-7.54 (m, 8H, Aro. H); MS: m/z 365 $(M+H)^+$.

2.4.6. 3-(4-iodophenyl)-5-(1-cyclopentyl-1H-indol-3-yl)-4,5-dihydroisoxazole (5f): faint yellow solid , yield: 67% ; M.p. 191-193^{0}C ***;*** IR (KBr,cm^{-1}): 1644 (C=N), 3027 (Ar-H), 1552 (C=C) ,1462 (C-O)***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) : δ 1.21-2.45 (m, 8H,Cyclopentyl H), 3.61 (m, 1H, Cyclopentyl H), 3.34 (dd, 1H, oxazoline H), 3.57 (dd, 1H, oxazoline H), 5.61 (t, 1H, oxazoline H) ,7.95 (s, 1H, indole H), 7.12-7.75 (m, 8H, Aro. H); MS: m/z 457 $(M+H)^+$.

2.4.7. 2-(5-(1-cyclopentyl-1H-indol-3-yl)-4,5-dihydroisoxazol-3-yl)phenol (5g): Brown solid, yield : 62% ; M.p. 156-158^{0}C ***;*** IR (KBr,cm^{-1}):1635 (C=N), 3060 (Ar-H), 1555 (C=C), 1445(C-O)***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) : δ 1.67-1.95 (m, 7H, Cyclopentyl H), 2.21-2.43 (m, 2H, Cyclopentyl H), 5.32 (s, 1H, Hydroxyl H), 3.56 (dd, 1H, oxazoline H), 3.87 (dd, 1H, oxazoline H), 5.65 (t, 1H, oxazoline H) , 8.23 (s, 1H, indole H), 7.32-7.85 (m, 8H, Aro. H); MS: m/z 347 $(M+H)^+$.

2.4.8. 4-(5-(1-cyclopentyl-1H-indol-3-yl)-4,5-dihydroisoxazol-3-yl)phenol (5h): Brown solid, yield : 74% ; m.p. 190-192^{0}C ***;*** IR (KBr,cm^{-1}): 1622 (C=N), 3054 (Ar-H), 1532 (C=C),1452 (C-O)***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) :δ 1.44-1.85 (m, 7H,Cyclopentyl H), 2.10-2.54 (m, 2H, Cyclopentyl H), 5.40 (s, 1H, Hydroxyl H), 3.59 (dd, 1H, oxazoline H), 3.77 (dd, 1H, oxazoline H), 5.85 (t, 1H, oxazo line H) , 8.06 (s, 1H, indole H), 7.10-7.72 (m, 8H, Aro. H); MS: m/z 347 $(M+H)^+$.

2.4.9. 2-(5-(1-cyclopentyl-1H-indol-3-yl)-4,5-dihydroisoxazol-3-yl)-5-methylphenol (5i): colourless solid, yield : 74% ; M.p. 145-147^{0}C ***;*** IR (KBr,cm^{-1}): 1619 (C=N), 3028 (Ar-H), 1556 (C=C) ,1443 (C-O)***;*** ^{1}H NMR: (400 MH_z ,

DMSO-d_6) :δ 1.76-2.12 (m, 8H, Cyclopentyl H), 2.34 (m, 1H, Cyclopentyl H),2.54 (s, 3H, methyl H),5.29 (s, 1H, Hydroxyl H),3.45 (dd, 1H, oxazoline H),3.69 (dd, 1H, oxazoline H), 5.43 (t, 1H, oxazoline H) , 8.10 (s, 1H, indole H),7.02-7.65 (m, 7H, Aro. H); MS: m/z 361$(M+H)^+$.

2.4.10. 5- chloro-2-(5-(1-cyclopentyl-1H-indol-3-yl)-4,5-dihydroisoxazol-3-yl)phenol (5j): Buff white solid. yield : 65% ; M.p. 197-199^{0}C ***;*** IR (KBr,cm^{-1}):1643 (C=N), 3067 (Ar-H), 1564 (C=C) ,1424(C-O)***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) :δ 1.43-2.00 (m, 8H,Cyclopentyl H), 2.21 (m, 1H, Cyclopentyl H), 5.54 (s, 1H, Hydroxyl H),3.65 (dd, 1H, oxazoline H), 3.91 (dd, 1H, oxazoline H), 5.90 (t, 1H, oxazoline H) , 8.21 (s, 1H, indole H), 7.21-7.75 (m, 7H,Aro.H); MS: m/z 381$(M+H)^+$.

2.4.11. 5-bromo-2-(5-(1-cyclopentyl-1H-indol-3-yl)-4,5-dihydroisoxazol-3-yl)phenol (5k) : Gray solid. yield : 78% ; M.p. 114-116^{0}C ***;*** IR (KBr,cm^{-1}): 1632 (C=N), 3040 (Ar-H), 1534 (C=C) ,1476 (C-O)***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) :δ 1.54-2.10 (m, 8H, Cyclopentyl H), 2.36 (m, 1H, Cyclopentyl H), 5.44 (s, 1H, Hydroxyl H), 3.76 (dd, 1H, oxazoline H), 3.98 (dd, 1H, oxazoline H), 5.84 (t, 1H, oxazoline H) , 8.01 (s, 1H, indole H), 7.11-7.67 (m, 7H, Aro. H); MS: m/z 426 $(M+H)^+$.

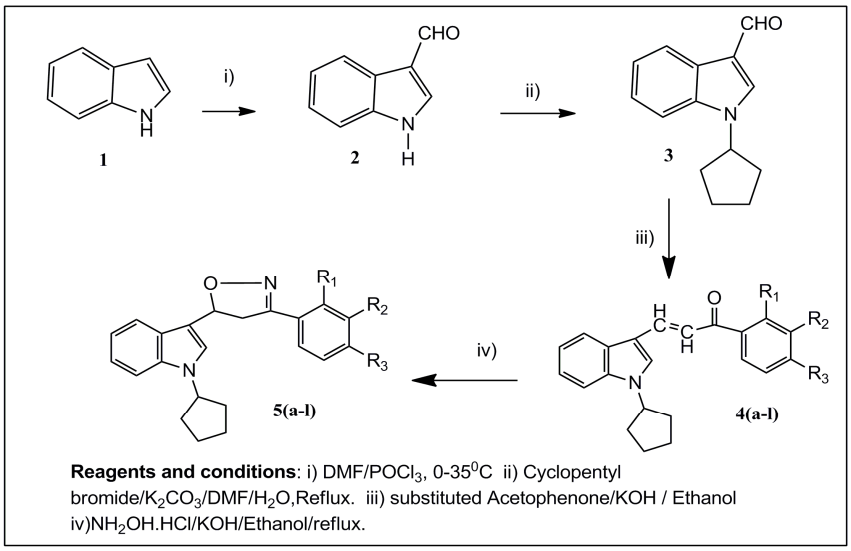
2.4.12. 2-(5-(1-cyclopentyl-1H-indol-3-yl)-4,5-dihydroisoxazol-3-yl)-5-methoxyphenol (5l) : colourless solid , yield : 70% ; M.p.212-214^{0}C ***;*** IR (KBr,cm^{-1}): 1642 (C=N), 3087 (Ar-H), 1566 (C=C) ,1478 (C-O) ***;*** ^{1}H NMR: (400 MH_z , DMSO-d_6) :δ 1.43-2.01 (m, 8H, Cyclopentyl H), 2.22 (m, 1H, Cyclo pentyl H) , 3.93 (s, 3H, methoxy H) , 5.65 (s, 1H, Hydroxyl H), 3.45 (dd, 1H, oxazoline H), 3.67 (dd, 1H, oxazoline H), 5.56 (t, 1H, oxazoline H) , 7.89 (s, 1H, indole H), 7.23-7.79 (m, 7H, Aro. H); MS: m/z 377 $(M+H)^+$.

RESULTS AND DISCUSSION

CHEMISTRY

Commercially available Indole initially was treated with $POCl_3$ in DMF to afford Indole-3-Carbaldehyde (**2**). Compound **2** upon treatment with Cyclopentyl bromide in DMF gave N-cyclopentyl Indole-3-Carbaldehyde (**3**). It was then further treated with different substituted acetophenone to give substituted Chalcones **4(a-l)** (as shown in scheme, Table 1).

Finally, Commercially available hydroxylamine hydrochloride and Chalcones prepared in KOH was heated at reflux condition and precipitation was collected after cooling and filtration to yield the corresponding Oxazoline **5** (**a-l**) in the expected yield (Scheme 1).



Scheme-I Synthesis of Oxazolines from N- cyclopentyl Indolyl chalcones

Table 1. Physical data of new series of 3-(1-cyclopentyl-1H-indol-3-yl)-1-phenylprop-2-en-1-one

Compound	R_1	R_2	R_3	Molecular formula	Yield (%)	M.P/ B.P. ^{0}C
4a	H	H	H	$C_{22}H_{21}NO$	82	190-192
4b	H	H	CH_3	$C_{23}H_{23}NO$	80	143-145
4c	H	H	Br	$C_{22}H_{20}NOBr$	64	120-122
4d	H	H	F	$C_{22}H_{20}NOF$	72	88-90
4e	H	H	Cl	$C_{22}H_{20}NOCl$	66	165-167
4f	H	H	I	$C_{22}H_{20}NOI$	81	187-190
4g	OH	H	H	$C_{22}H_{21}NO_2$	70	110-112
4h	H	H	OH	$C_{22}H_{21}NO_2$	78	161-163
4i	OH	H	CH_3	$C_{23}H_{22}NO_2$	65	143-145
4j	H	H	Cl	$C_{22}H_{20}NO_2Cl$	76	198-200
4k	OH	H	Br	$C_{22}H_{20}NO_2Br$	69	98-100
4l	H	H	OCH_3	$C_{23}H_{22}NO_2$	74	113-115

The progress of all reactions was monitored by thin layer chromatography. The synthesized derivatives **5 (a-l)** were isolated in moderate to good yield.

ANTIMICROBIAL ACTIVITY

Applying the agar plate diffusion technique, all the synthesized compounds **(5a-l)** were screened in their vitro antibacterial activity against Gram Positive Bacteria and Gram Negative Bacteria. The antibacterial activity was evaluated against different bacterial strains such as *Staphylococcus aureus* (ATCC 9027), *Bacillus subtilus* (ATCC 6633) and *Escherichia coli* (ATCC 8789), *Pseudomonas aeruginosa* (ATCC 9027) and *Salmonella abony* (NCTC-6017). Ciprofloxacin is used as a standard drug for the comparison of antibacterial activity.

The antifungal activity was evaluated against different fungal strains such as *Candida albicans* (ATCC 10231) and *Aspergillus niger* (ATCC 16404). MIC values of antifungal activity were determined using standard agar dilution method. Fluconazole is used as standard drugs for the comparison of antifungal activity. Dimethyl sulfoxide is used as solvent control. From the antimicrobial testing compounds **5(a-l),** it is observed that all the newly synthesized compounds shows Excellent to moderate level of antibacterial and antifungal activity shown by Table-2.

The antimicrobial activity data (Table 2), reveals that compounds **5c, 5d, 5e, 5f, 5i, 5l** have found to be most active and potent as antimicrobial agents, among them **5c, 5d, 5l** have been identified as the most prominent results and others are inferior activity when compared with standard. The structure activity relationship of the series can be explained that, halogen present derivatives are more potent antimicrobial activity than the other derivatives. Among the series indicating the future scope for optimization

Table -2. Antimicrobial Activity of Synthesized compounds (5a-l)

Sr. No.	Comp. No.	Inhibition Zone Diameter(mm)						
		I	II	III	IV	V	VI	VII
1	5a	07	08	06	09	09	10	10
2	5b	10	10	09	10	10	11	09
3	5c	12	13	11	11	12	12	11
4	5d	12	14	11	11	13	12	13
5	5e	10	11	10	10	13	12	12
6	5f	10	10	11	10	12	11	10
7	5g	09	10	08	09	10	10	09
8	5h	08	08	09	10	10	09	09
9	5i	11	10	11	12	10	10	11
10	5j	10	12	09	10	11	10	10
11	5k	10	11	09	10	10	11	08
12	5l	11	13	10	12	12	11	12
13	Ciprofloxacin	-	18	-	14	16	15	14
14	fluconazole	13	-	12	-	-	-	-

Fungus Culture: I-Aspergillus niger III-Candida albicans
Gram Positive Bacteria: II-Bacillus subtilis VII- Staphylococcus aureus
Gram Negative Bacteria: IV- E. coli V- Pseudomonas aeruginos VI- Sallemonella abony.

CONCLUSION

In this manuscript, for the first time, a synthesis of new molecules of isoxazole was attempted from chalcones, and these novel synthesized derivatives were characterized by means of their Mass, IR, H^1 NMR spectral data and their subsequent evaluation as antibacterial and antifungal agent have been explained. . In this series from all synthesized derivatives, halogen substitution on phenyl ring displayed decent antibacterial and antifungal profile when compared with standard reference. Among the series, most prominent molecules **5c, 5d, 5l** have been reported and identified as a prominent Antimicrobial activity.

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