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Synthesis and characterization of some novel isoxazoles via chalcone intermediates

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ABSTRACT

The synthesis and characterization of some novel isoxazoles derivatives have been presented. Acylation of resorcinol followed by nuclear prenylation with isoprene gives Chroman. Chroman on treatment with p-substituted benzaldehydes affords substituted chalcones. Isoxazoles have been prepared from chalcones by treating with hydroxylamine hydrochloride. The structure of isoxazoles has been characterized by spectral analysis.

Keywords: Heterocyclics, Chroman, Chalcones, Isoxazoles.

INTRODUCTION

Heterocyclic compounds are very widely distributed in nature, and are essential to life in various ways. Particularly these compounds are important because of the wide variety of physiological activities associated with this class of substances. Heterocyclic rings are present in several compounds, e. g, most of the members of vitamin B complex, antibiotics, chlorophyll, haemin, other plant pigments, amino acids and proteins, drugs, dye stuffs, enzymes, the genetic material DNA etc.

The paramount importance of heterocycles in nature product chemistry and pharmacology constantly drive the search for new methods for the construction of heterocyclic unit viz., isoxazoles and pyrazoles. These isoxazoles and pyrazoles were prepared from chalcones which are important intermediate products and they also possess biological and pharmacological activities [1].

Isoxazoles possess interesting medicinal [2] properties and have some industrial utility [3]. Many biologically active isoxazoles and reduced isoxazole derivatives have been reported, viz., the naturally occurring antituberculosis, antibiotic cycloserine, the mono amine oxidase inhibitor: isocarboxazid, useful in psychotherapy and Isoxazole steroids show anabolic activity, eg., Denazole [4]. The CNS active isoxazoles, ibotenic acid, muscimol and muscazone are isolated from amanita muscaria and other amanita species. Isoxazole derivatives were used as inhibitors for ulcers [5], lipoxygenase [6], acetyl choline esterase [7]. 3-Substituted 5-methylthio isoxazoles were found to exhibit anthelmintic activity [8]. Spiroisoxazolines [9] and benzofuroisoxazoles [10] were used as anti-convergents. 5-Amino-3-methyl-4-ureidoisoxazoles were found to exhibit anti leukemic activity [11]. Some new 2-isoxazole derivatives prepared from α,β-dibromo chalcones showed mild antibacterial activity [12]. A group of 4,5-diphenyl isoxazoles, 3,4-diphenyl-5-trifluoro methyl isoxazoles and 4,5-diphenyl-3-methyl sulfonoamido isoxazole possessing a variety of substitutions (H, F, MeS, MeSO, MeSO2) at the para position of one of the phenyl rings were used as analgesic and selective COX-2 inhibitory, and anti-inflammatory agents [13]. Isoxazolyl naphthoquinones act as potential trypanocidal and antibacterial agents [14].

MATERIALS AND METHODS

General procedure. FT-IR spectra are recorded as KBr pellet on Nicolet 380 FT-IR Instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H NMR spectra are recorded on Varian 300 MHz spectrometer using DMSO-d6 as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra are recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts are dried over sodium sulfate after work up. Unless otherwise mentioned all the solvents and reagents used are of commercial grade.

Step 1: Synthesis of 1-(2,4-dihydroxyphenyl)ethanone (8): Freshly fused 33g of Zinc chloride was dissolved in 32 mL of acetic acid while heating and when all the zinc chloride is almost dissolved, 22 g of resorcinol was added and heated to 140-150^{o}C for 15 minutes with stirring. This was left for 1 hour and then 100 mL 50% aqueous HCl was added to break the zinc chloride complex. Within 5 minutes, precipitation commenced when the mixture came to room temperature. It was cooled to 5^{o}C and then filtered. The precipitate is washed with 5% dilute HCl and water. A red precipitate obtained was crystalized from 20% HCl to give 1-(2,4-dihydroxyphenyl) ethanone. Yield 76.4%, M.F. $C_8H_8O_3$, M. Wt. 152.15. IR (ν_{max}, cm^{-1}): 2996.28 (C-H), 3395.99 (-OH), 1592.14 and 1471.71 (C-C in Ar), 1703.25 (C=O). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 2.5 (s, 3H, -CH_3), 5.5 (s, 2H, -OH), 6.3 (s, 1H, Ar-H), 6.5 (d, 1H, Ar-H), 7.4 (d, 1H, Ar-H). MS *m/z* (%) = 153.26 (M+1). Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30; O, 31.55%. Found: C, 63.19; H, 5.28, O, 31.53%.

Step 2: Synthesis of 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone (nuclear prenylation of 1-(2,4-dihydroxyphenyl)ethanone) (9): A solution of isoprene (1.5 mL, 0.015 mol) in Xylene (5 mL) was added drop wise over a period of 8 hours to a mixture of 1-(2,4-dihydroxyphenyl)ethanone (1.41 g, 0.0072 mol) and Polyphosphoric acid (2 mL) in xylene (3 mL) with constant stirring at 30-35^{o}C. Stirring was continued for further 14 hours. The reaction mixture was extracted in chloroform (100 mL) and the chloroform solution was washed with

aqueous $NaHCO_3$ (5%, 3 X 60 mL), dried over $MgSO_4$ and removed under reduced pressure to give gummy material. This on column chromatography over silica gel yielded the chroman on elution with hexane/EtOAc (96:4). Yield 80.2%, M.F. $C_{13}H_{16}O_3$, M. Wt. 220.26. IR (ν_{max}, cm^{-1}): 2986.25 (C-H), 3378.35 (O-H), 1753.16 (C=O), 1592.18 and 1466.94 (C-C in Ar), 1174.86 (C-O-C). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.50 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 2.4 (s, 3H, $-CH_3$), 5.0 (s, 1H, -OH), 6.5 (s, 1H, Ar-H), 7.3 (s, 1H, Ar-H). MS *m/z* (%) = 221.15 (M+1). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; O, 21.79%. Found: C, 70.88; H, 7.34; O, 21.78%.

Step 3: Condensation of 1-(7-hydroxy-2,2-dimethyl chroman-6-yl) ethanone with substituted benzaldehydes:

General procedure: A mixture of 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone (0.01 mol), substituted benzaldehyde (0.01 mol) in ethanol (30 mL) and aqueous potassium hydroxide (15 g in 15 mL of water) were stirred at room temperature for 24 hours. On acidification with hydrochloric acid an yellow (or) orange red chalcone derivatives.

Synthesis of (E)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-(4-hydroxy phenyl) prop-2-en-1-one (10a): Compound 10a was prepared by using 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone and 4-hydroxy benzaldehyde with the above general procedure. Yield: 74.2%, M.F. $C_{20}H_{20}O_4$, M. Wt. 324.37. IR (ν_{max}, cm^{-1}): 2954.19 (C-H), 3351.49 (O-H), 1728.32 (C=O), 3159.54 (C-H in Ar-H), 772.22 (C-H in Ar-H), 1601.38 and 1436.22 (C-C in Ar), 1146.67 (C-O-C); ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 4.9 (s, 2H, -OH), 6.2 (s, 1H, Ar-H), 6.5 (d, 1H, -CH=CH-), 6.6 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H), 7.6 (d, 1H, -CH=CH-), 7.9 (d, 1H, Ar-H). MS *m/z* (%) = 325.38 (M+1). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21; O, 19.73%. Found: C, 74.00; H, 6.23; O, 19.77%.

Synthesis of (E)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-(4-methoxy phenyl) prop-2-en-1-one (10b): Compound 10b was prepared by using 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone and 4-methoxy benzaldehyde with the above general procedure. Yield:70.9%, M.F.$C_{21}H_{22}O_4$, M. Wt. 338.4. IR (ν_{max}, cm^{-1}): 2953.98 (C-H), 3352.18 (O-H), 1728.57 (C=O), 3159.65 (C-H in Ar-H), 772.31 (C-H in Ar-H), 1601.71 and 1436.22 (C-C in Ar), 1146.82 (C-O-C), 2889.80 (C-H in $-OCH_3$). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 3.7 (s, 3H, $-OCH_3$), 6.2 (s, 1H, Ar-H), 6.5 (d, 1H, -CH=CH-), 6.7 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H), 7.6 (d, 1H, -CH=CH-), 7.9 (d, 1H, Ar-H). MS *m/z* (%) = 339.38 (M+1). Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55; O, 18.91%. Found: C, 74.52; H, 6.56; O, 18.92%.

Synthesis of (E)-3-(4-(dimethylamino)phenyl)-1-(7-hydroxy-2,2-dimethyl chroman -6-yl) prop-2-en-1-one (10c): Compound 10c was prepared by using 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone and 4-dimethyl amino benzaldehyde with the above general procedure. Yield: 77.5%, M. F. $C_{22}H_{25}NO_3$, M. Wt. 351.44. IR (ν_{max}, cm^{-1}): 2953.98 (C-H), 3159.65 (C-H in Ar-H), 3385.49 (O-H), 1601.71, 1574.61 and 1458.83 (C-C in Ar), 1707.64 (C=O), 1213.39 (Ar-O-C), 1349.45 (C-N). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 2.9 (s, 6H, $-N(CH_3)_2$), 4.9 (s, 1H, -OH), 6.3 (s, 1H, Ar-H), 6.5 (d, 1H, Ar-H), 6.7 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H), 7.6 (d, 1H, -CH=CH-), 7.9 (d, 1H, -CH=CH). MS *m/z* (%) = 352.40 (M+1). Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99; O, 13.66%. Found: C, 75.22; H, 7.14; N, 4.00; O, 13.64%.

Synthesis of (E)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-(4-nitrophenyl) prop-2-en-1-one (10d): Compound 10d was prepared by using 1-(7-hydroxy-2,2-dimethylchroman-6-yl) ethanone and 4-nitro benzaldehyde with the above general procedure. Yield: 78.2%, M. F. $C_{20}H_{19}NO_5$, M. Wt. 353.37. IR (ν_{max}, cm^{-1}): 2967.56 (C-H), 3164.18 (C-H in Ar-H), 3296.49 (O-H), 1594.44, 1563.19 and 1445.77 (C-C in Ar), 1709.37 (C=O), 1212.80 (Ar-O-C), 1462.46 (N-O). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 6.8 (s, 1H, Ar-H), 7.4 (d, 1H, Ar-H), 7.6 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H), 8.5 (d, 1H, -CH=CH-), 8.7 (d, 1H, -CH=CH). MS *m/z* (%) = 354.21 (M+1). Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96; O, 22.64%. Found: C, 67.96; H, 5.43; N, 3.99; O, 22.62%.

Synthesis of (E)-3-(4-bromophenyl)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)prop-2-en-1-one (10e): Compound 10e was prepared by using 1-(7-hydroxy-2,2-dimethylchroman-6-yl) ethanone and 4-bromo benzaldehyde with the above general procedure. Yield: 68.2%, M. F. $C_{20}H_{19}BrO_3$, M. Wt. 387.27. IR (ν_{max}, cm^{-1}): 2954.09 (C-H), 3158.81 (C-H in Ar-H), 3385.87 (O-H), 1602.18, 1575.86 and 1459.26 (C-C in Ar), 1708.51 (C=O), 1213.26 (Ar-O-C), 772.45 (C-Br). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H), 8.5 (d, 1H, -CH=CH-), 8.7 (d, 1H, -CH=CH). MS *m/z* (%) = 388.33 (M+1). Anal. Calcd for $C_{20}H_{19}BrO_3$: C, 62.03; H, 4.95; O, 12.39%. Found: C, 62.05; H, 4.94; O, 12.40%.

Synthesis of (E)-3-(4-chlorophenyl)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)prop-2-en-1-one (10f): Compound 10f was prepared by using 1-(7-hydroxy-2,2-dimethylchroman-6-yl) ethanone and 4-chloro benzaldehyde with the above general procedure. Yield: 73.5%, M. F. $C_{20}H_{19}ClO_3$, M. Wt. 342.82. IR (ν_{max}, cm^{-1}): 2954.35 (C-H), 3353.45 (O-H), 1602.22, 1574.32 and 1458.91 (C-C in Ar), 1707.40 (C=O), 1213.15 (Ar-O-C), 694.76 (C-Cl). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H), 8.5 (d, 1H, -CH=CH-), 8.7 (d, 1H, -CH=CH). MS *m/z* (%) = 343.88 (M+1). Anal. Calcd for $C_{20}H_{19}ClO_3$: C, 70.07; H, 5.59; O, 14.00%. Found: C, 70.10; H, 5.58; O, 14.02%.

Synthesis of 4-((E)-3-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-oxoprop-1-enyl)benzoic acid (10g): Compound 10g was prepared by using 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone and 4-formylbenzoic acid with the above general procedure. Yield: 80.1%, M. F. $C_{21}H_{20}O_5$, M. Wt. 352.38. IR (ν_{max}, cm^{-1}): 2954.18 (C-H), 3159.00 (C-H in Ar-H), 3385.27 (O-H), 1602.51, 1575.96 and 1446.18 (C-C in Ar), 1708.83 (C=O), 1213.29 (Ar-O-C). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H), 8.5 (d, 1H, -CH=CH-), 8.7 (d, 1H, -CH=CH), 10.1 (bs, 1H, -COOH). MS *m/z* (%) = 353.61 (M+1). Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72; O, 22.70%. Found: C, 71.60; H, 5.73; O, 22.67%.

Synthesis of (E)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-(4-vinylphenyl) prop-2-en-1-one (10h): Compound 10h was prepared by using 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone and 4-vinylbenzaldehyde with the above general procedure. Yield: 84.1%, M. F. $C_{22}H_{22}O_3$, M. Wt. 334.41. IR (ν_{max}, cm^{-1}): 2955.68 (C-H), 3163.10 (C-H in Ar-H), 3383.72 (O-H), 1598.70, 1564.30 and 1522.94 (C-C in Ar), 1708.98 (C=O), 1212.83 (Ar-O-C). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.2 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 5.1 – 5.3 (dd,

-CH=CH_2), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H), 8.5 (d, 1H, -CH=CH-), 8.7 (d, 1H, -CH=CH). MS *m/z* (%) = 335.61 (M+1). Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63; O, 14.35%. Found: C, 79.04; H, 6.65; O, 14.31%.

Synthesis of 4-((E)-3-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-oxoprop-1-enyl)benzonitrile (10i): Compound 10i was prepared by using 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone and 4-formylbenzonitrile with the above general procedure. Yield: 78.1%. M. F. $C_{21}H_{19}NO_3$, M. Wt.: 333.38. IR (ν_{max}, cm^{-1}): 2954.62 (C-H), 3167.29 (C-H in Ar-H), 3349.75 (O-H), 1599.65, 1575.18 and 1445.85 (C-C in Ar), 1707.88 (C=O), 1212.54 (Ar-O-C), 2349.06 (CN). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, -CH_3), 2.2 (m, 4H, -CH_2-), 4.9 (s, 1H, -OH), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H), 8.5 (d, 1H, -CH=CH-), 8.7 (d, 1H, -CH=CH). MS *m/z* (%) = 334.34 (M+1). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20; O, 14.40%. Found: C, 75.68; H, 5.75; N, 4.21; O, 14.36%.

Synthesis of (E)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-p-tolylprop-2-en-1-one (10j): Compound 10j was prepared by using 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone and 4-methyl benzaldehyde with the above general procedure. Yield: 86.1%, M. F. $C_{21}H_{22}O_3$, M. Wt. 322.4. IR (ν_{max}, cm^{-1}): 2922.76 (C-H), 3155.57 (C-H in Ar-H), 3385.05 (O-H), 1601.71, 1575.22 and 1459.12 (C-C in Ar), 1707.91 (C=O), 1213.27 (Ar-O-C). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, -CH_3), 2.0 (m, 4H, -CH_2-), 2.5 (s, 3H, -CH_3), 4.9 (s, 1H, -OH), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H), 8.5 (d, 1H, -CH=CH-), 8.7 (d, 1H, -CH=CH). MS *m/z* (%) = 323.88 (M+1). Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88; O, 14.89%. Found: C, 78.25; H, 6.89; O, 14.86%.

Step 4: Synthesis of 3-(4-substituted phenyl)-5-(2", 2"-dimethyl-7"-hydroxy chroman) isoxazole:

General Procedure:7-Hydroxy-6-(4'-substituted) cinnamoyl -3,4- dihydro -2,2- dimethyl -2H-benzo (1,2b) pyran and hydroxylamine hydrochloride in presence of KOH/absolute ethanol was refluxed on a water bath for 4 hours. Then the reaction mixture was neutralized with acetic acid and the whole contents were poured in ice cold water, which result the formation of a brown precipitate. This was chromatographed over silica gel, and crystallized from methanol as brown needles.

Synthesis of 3,4-dihydro-6-(3-(4-hydroxyphenyl)isoxazol-5-yl)-2,2-dimethyl-2H-chromen-7-ol (11a): Compound 11a was synthesized by using (E)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-(4-hydroxyphenyl) prop-2-en-1-one (10a) with the above process. Yield: 72.2%, M. F. $C_{20}H_{19}NO_4$, M. Wt. 337.37, Purity by HPLC: 99.86%. IR (ν_{max}, cm^{-1}): 2938.83 (C-H), 3075.22 (C-H in Ar-H), 3345.25 (O-H), 1607.92, 1503.19 and 1453.99 (C-C in Ar), 1214.96 (Ar-O-C), 1630.41 (C=N-O). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, -CH_3), 2.0 (m, 4H, -CH_2-), 4.9 (s, 1H, -OH), 5.6 (s, 1H, =CH-), 6.2 (s, 1H, Ar-H), 6.5 (d, 1H, Ar-H), 7.6 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H). MS *m/z* (%) = 338.25 (M+1). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15; O, 18.97%. Found: C, 71.22; H, 5.64; N, 4.18; O, 18.96%.

Synthesis of 3,4-dihydro-6-(3-(4-methoxyphenyl)isoxazol-5-yl)-2,2-dimethyl-2H-chromen-7-ol (11b): Compound 11b was synthesized by using (E)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (10b) with the above process. Yield: 75.1%, M. F.

$C_{20}H_{19}NO_4$, M. Wt. 351.4, Purity by HPLC: 98.74%. IR (ν_{max}, cm^{-1}): 2923.13 (C-H), 3075.19 (C-H in Ar-H), 3345.43 (O-H), 1607.94, 1503.13 and 1454.03 (C-C in Ar), 1214.99 (Ar-O-C), 1630.47 (C=N-O), 2835.82 (C-H in $-OCH_3$). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 3.7 (s, 3H, $-CH_3$), 4.9 (s, 1H, -OH), 5.5 (s, 1H, =CH-), 6.1 (s, 1H, Ar-H), 6.5 (d, 1H, Ar-H), 6.7 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H). MS *m/z* (%): 252.38 (M+1). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.78; H, 6.02; N, 3.99; O, 18.21%. Found: C, 71.80; H, 6.03; N, 4.00; O, 18.17%.

Synthesis of 6-(3-(4-(dimethylamino)phenyl)isoxazol-5-yl)-3,4-dihydro-2,2-dimethyl-2H-chromen-7-ol (11c): Compound 11c was synthesized by using (E)-3-(4-(dimethylamino)phenyl)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)prop-2-en-1-one (10c) with the above process. Yield: 82.2%, M. F. $C_{22}H_{24}N_2O_3$, M. Wt. 364.44, Purity by HPLC: 99.82%. IR (ν_{max}, cm^{-1}): 2923.24 (C-H), 3075.24 (C-H in Ar-H), 3345.26 (O-H), 1607.97, 1503.21 and 1453.98 (C-C in Ar), 1214.76 (Ar-O-C), 1630.61 (C=N-O), 1348.18 (C-N in $-N(CH_3)_3$). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 2.9 (s, 6H, $-N(CH_3)_2$), 4.9 (s, 1H, -OH), 5.6 (s, 1H, =CH-), 6.3 (s, 1H, Ar-H), 6.5 (d, 1H, Ar-H), 6.7 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H). MS *m/z* (%): 365.40 (M+1). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69; O, 13.17%. Found: C, 72.52; H, 6.62; N, 7.70; O, 13.16%.

Synthesis of 3,4-dihydro-2,2-dimethyl-6-(3-(4-nitrophenyl)isoxazol-5-yl)-2H-chromen-7-ol (11d): Compound 11d was synthesized by using (E)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-(4-nitrophenyl)prop-2-en-1-one (10d) with the above process. Yield: 81.2%, M. F. $C_{20}H_{18}N_2O_5$, M. Wt. 366.37, Purity by HPLC: 99.80%. IR (ν_{max}, cm^{-1}): 2938.85 (C-H), 3075.20 (C-H in Ar-H), 3344.97 (O-H), 1607.88, 1503.093 and 1453.92 (C-C in Ar), 1214.61 (Ar-O-C), 1630.52 (C=N-O), 1453.92($-NO_2$). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 5.6 (s, 1H, =CH-), 6.9 (s, 1H, Ar-H), 7.4 (d, 1H, Ar-H), 7.6 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H). MS *m/z* (%): 367.21 (M+1). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65; O, 21.84%. Found: C, 65.58; H, 4.94; N, 7.68; O, 21.80%.

Synthesis of 6-(3-(4-bromophenyl)isoxazol-5-yl)-3,4-dihydro-2,2-dimethyl-2H-chromen-7-ol (11e): Compound 11e was synthesized by using (E)-3-(4-bromophenyl)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)prop-2-en-1-one (10e) with the above process. Yield: 81.23%, M. F. $C_{20}H_{18}BrNO_3$, M. Wt. 400.27, Purity by HPLC: 96.2%. IR (ν_{max}, cm^{-1}): 2923.05 (C-H), 3075.20 (C-H in Ar-H), 3345.38 (O-H), 1608.01, 1502.99 and 1453.95 (C-C in Ar), 1214.78 (Ar-O-C), 1630.59 (C=N-O), 747.61(C-Br). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 5.6 (s, 1H, =CH-), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.7 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H). MS *m/z* (%): 401.42 (M+1). Anal. Calcd for $C_{20}H_{18}BrNO_3$: C, 60.01; H, 4.53; N, 3.50; O, 11.99%. Found: C, 60.05; H, 4.55; N, 3.52; O, 12.01%.

Synthesis of 6-(3-(4-chlorophenyl)isoxazol-5-yl)-3,4-dihydro-2,2-dimethyl-2H-chromen-7-ol (11f): Compound 11f was synthesized by using (E)-3-(4-chlorophenyl)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)prop-2-en-1-one (10f) with the above process. Yield: 86.3%, M. F. $C_{20}H_{18}ClNO_3$, M. Wt. 355.81, Purity by HPLC: 99.87%. IR (ν_{max}, cm^{-1}): 2923.07 (C-H), 3075.15 (C-H in Ar-H), 3345.32 (O-H), 1608.03, 1502.87 and 1453.95 (C-C in Ar), 1214.74 (Ar-O-C), 1630.63 (C=N-O), 747.58 (C-Cl). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 5.6 (s, 1H, =CH-), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H,

Ar-H), 8.1 (d, 2H, Ar-H). MS *m/z* (%): 356.88 (M+1). Anal. Calcd for $C_{20}H_{18}ClNO_3$: C, 67.51; H, 5.10; N, 3.94; O, 13.49%. Found: C, 67.50; H, 5.11; N, 3.96; O, 13.50%.

Synthesis of 4-(5-(7-hydroxy-2,2-dimethylchroman-6-yl)isoxazol-3-yl) benzoic acid (11g): Compound 11g was synthesized by using 4-((E)-3-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-oxoprop-1-enyl)benzoic acid (10g) with the above process. Yield: 94.2%, M. F. $C_{21}H_{19}NO_5$, M. Wt. 365.38, Purity by HPLC: 79.2%. IR (ν_{max}, cm^{-1}): 2923.17 (C-H), 3075.17 (C-H in Ar-H), 3345.09 (O-H), 1607.90, 1503.19 and 1454.04 (C-C in Ar), 1214.82 (Ar-O-C), 1630.52 (C=N-O). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 5.6 (s, 1H, =CH-), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H), 10.1 (bs, 1H, -COOH). MS *m/z* (%): 366.61 (M+1). Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83; O, 21.89%. Found: C, 69.05; H, 5.25; N, 3.80; O, 21.90%.

Synthesis of 3,4-dihydro-2,2-dimethyl-6-(3-(4-vinylphenyl)isoxazol-5-yl)-2H-chromen-7-ol (11h): Compound 11h was synthesized by using (E)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-(4-vinylphenyl)prop-2-en-1-one (10h) with the above process. Yield: 78.4%, M. F. $C_{22}H_{21}NO_3$, M. Wt. 347.41, Purity by HPLC: 99.92%. IR (ν_{max}, cm^{-1}): 2923.18 (C-H), 3075.19 (C-H in Ar-H), 3345.24 (O-H), 1607.96, 1503.12 and 1453.98 (C-C in Ar), 1214.97 (Ar-O-C), 1630.53 (C=N-O). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.2 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 5.1 – 5.3 (d, 3H, -CH=C), 5.6 (s, 1H, =CH-), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H). MS *m/z* (%): 348.61 (M+1). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03; O, 13.82%. Found: C, 76.05; H, 6.10; N 4.05; O, 13.80%.

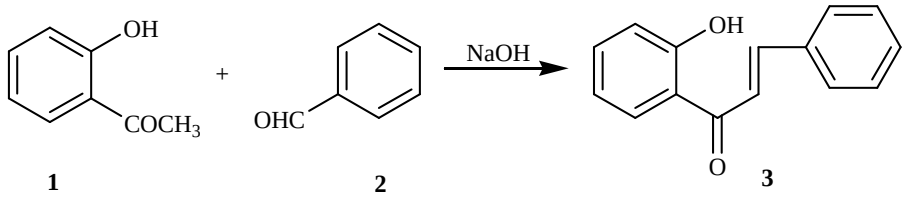
Synthesis of 4-(5-(7-hydroxy-2,2-dimethylchroman-6-yl)isoxazol-3-yl) benzonitrile (11i): Compound 11i was synthesized by using of 4-((E)-3-(7-hydroxy-2,2-dimethyl chroman-6-yl)-3-oxoprop-1-enyl)benzonitrile (10i) with the above process. Yield: 72.2%, M. F. $C_{21}H_{18}N_2O_3$, M. Wt. 346.38, Purity by HPLC: 99.94%. IR (ν_{max}, cm^{-1}): 2923.18 (C-H), 3075.19 (C-H in Ar-H), 3345.24 (O-H), 1607.96, 1503.12 and 1453.98 (C-C in Ar), 1214.97 (Ar-O-C), 1630.53 (C=N-O),1992.60 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.2 (m, 4H, $-CH_2-$), 4.9 (s, 1H, -OH), 5.6 (s, 1H, =CH-), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H). MS *m/z* (%): 347.34 (M+1). Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09; O, 13.86%. Found: C, 72.84; H, 5.25; N, 8.11; O, 13.80%.

Synthesis of 3,4-dihydro-2,2-dimethyl-6-(3-p-tolylisoxazol-5-yl)-2H-chromen -7-ol (11j): Compound 11j was synthesized by using Synthesis of (E)-1-(7-hydroxy-2,2-dimethylchroman-6-yl)-3-p-tolylprop-2-en-1-one (10j) with the above process. Yield: 75.4%, M. F. $C_{21}H_{21}NO_3$, M. Wt. 335.4, Purity by HPLC: 99.83%. IR (ν_{max}, cm^{-1}): 2923.07 (C-H), 3075.15 (C-H in Ar-H), 3345.32 (O-H), 1608.03, 1502.87 and 1453.95 (C-C in Ar), 1214.74 (Ar-O-C), 1630.63 (C=N-O). ^{1}H-NMR (400 MHz, DMSO-d6): δ_H 1.5 (d, 6H, $-CH_3$), 2.0 (m, 4H, $-CH_2-$), 2.5 (s, 3H, $-CH_3$), 4.9 (s, 1H, -OH), 5.6 (s, 1H, =CH-), 6.4 (s, 1H, Ar-H), 7.1 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, Ar-H). MS *m/z* (%): 336.88 (M+1). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18; O, 14.31%. Found: C, 75.22; H, 6.33; N, 4.20; O, 14.25%.

RESULTS AND DISCUSSION

In this paper, the synthesis and characterization of some novel isoxazoles have been presented. These isoxazoles were prepared from chalcones which are important intermediate products as they possess varied biological and pharmacological activities. They can be obtained by the acid or base catalyzed aldol condensation of O-hydroxy acetophenones with benzaldehydes [15-17]. Synthesis of various chalcones is reported in the literatures [18].

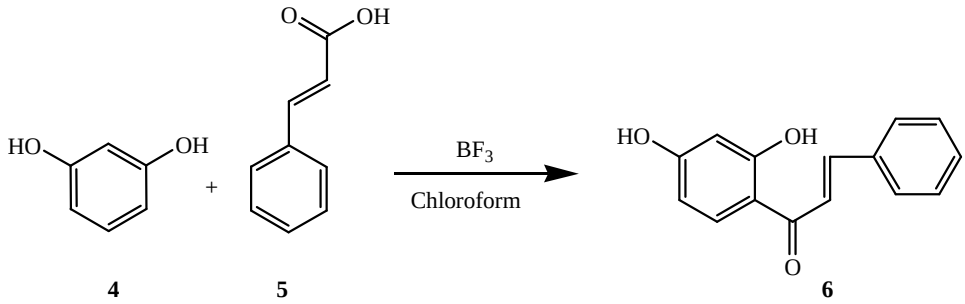
For example, 2-hydroxy acetophenone (1) and benzaldehyde (2) reacts in the presence of 0.1M NaOH to give the chalcone (3) (scheme 1).



1 **2** **3**

Scheme 1

Resorcinol (4) condenses with Cinnamic acid (5) in chloroform in the presence of boron trifluoride to yield the chlalcone (6) [19] (scheme 2).



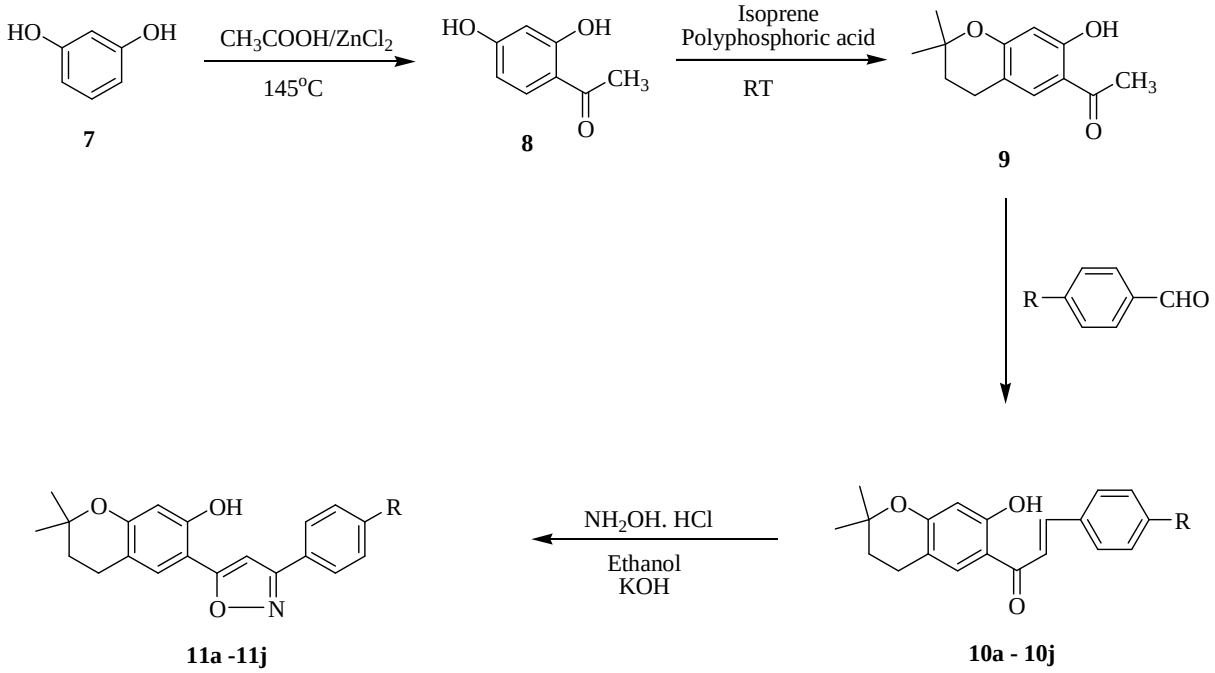
4 **5** **6**

Scheme 2

Resorcinol reacts with acetic acid in the presence of zinc chloride at 145^{o}C gives 2-acetyl derivate (8). `The chroman (9) on condensation with substituted benzaldehydes in the presence of 30% alcoholic alkali at room temperature resulted the formation of the corresponding chalcone derivatives (10a-10j) as needles and characterized by comparing its spectral data (IR, NMR) with structure. The condensation of above chalcone with hydroxylamine hydrochloride in potassium hydroxide/absolute ethanol at reflux temperature results the formation of corresponding Isoxazole derivatives (11a-11j) (Scheme 3).

Ahluwalia et at [20] reported the synthesis of 2,2-dimethyl chromans in very good yield by condensing polyphenol derivatives with isoprene in presence of orthophosphoric acid as catalyst. Polyphosphoric acid was found to be a better condensing agent compared to orthophosphoric acid to result in a more or less homogeneous reaction mixture leading to the cyclic chroman derivatives in very good yields. A solution of isoprene in xylene was added drop wise during 8 hours to a mixture of resacetophenone and Polyphosphoric acid in xylene with constant stirring

at 30-35^{o}C. Stirring was continued for further 1 hour. The reaction mixture was taken into reduced pressure to give a yellow gummy material. This on column chromatography over silica gel yielded the chroman in hexane / EA elutes (96:4) and the unreacted resactophenone from hexane / EA elutes.



Scheme 3

The resacetophenone (8) on nuclear prenylation [21] with isoprene in the presence of polyphosphoric acid at room temperature resulted the formation of 2,2-dimethyl-6-acetyl-7-hydroxy chroman (9) in good yields and it is crystallized as colorless needles.

The chroman (9) on condensation with different substituted benzaldehydes in the presence of 30% alcoholic alkali [22] at room temperature results the formation of chalcone derivatives in good yields. The thin layer chromatography (TLC) of these chalcones showed characteristic colors with methanol – H_2SO_4 (9:1) as a spraying reagent. They also exhibited the characteristic color test with antimony trioxide. With the above procedure, compounds (10a-10j) were synthesized.

The chalcones (10a-10j) which were synthesized have been taken for the preparation of corresponding new isoxazole derivatives (11a-11j).

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