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MULTI COMPONENT SYNTHESIS AND CHARACTERIZATION OF DERIVATIVES OF 2-AMINO-7, 7-DIMETHYL-5-OXO-4-PHENYL-5, 6, 7,8-TETRAHYDRO-4H-CHROMENE-3-CARBONITRILE AND ANTI- MICROBIAL ACTIVITY

Kudrapu Leelamanikant[1] and Dr. N. Krishnarao[1]*

[1]*Department of Organic Chemistry, PRISM PG & DG College (Affiliated to Andhra University), Visakhapatnam, India, 530016.

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***Corresponding Author**
Dr. N. Krishnarao
Department of Organic Chemistry, PRISM PG & DG College (Affiliated to Andhra University), Visakhapatnam, India, 530016.

ABSTRACT
In present investigate the synthesis of 2-amino-7, 7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile can be obtained the reaction of substituted aromatic aldehydes (1.2mmol), dimedone (1mol),malonitrile(1mol), in the presence of Methanesulphonic acid in ethanol as solvent at 75^0C condition. All the compounds were examined by advanced spectroscopic data (1HNMR, 13C NMR& LCMS) and the structural determination was calculated by elemental analysis. In addition to the all newly synthesized compounds were screened by their microbial activity.

KEYWORDS: Dimedone, malno nitrile, Aromatic aldehyde, MSA, 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile, Biological activity.

1. INTRODUCTION

2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile is an important class of Oxygen-containing heterocyclic in which benzene ring is fused to pyran ring and these called benzopyrans. These compounds are also called as chromenes. The chromenes are widely distributed in many natural products such as alkaloids, tocopherels, flavonoids and anthocyanin.[1] A large number of chromenes heterocycles have been isolated from natural sources exhibiting significant pharmaceutical potential.

The naturally occurring chromenes which has been isolated from the bark of the tree M.conrauri and potentially use for the treatment of intestinal Parastites.[2] 2-Aino-4-(3-bromo-4,5-dimethoxy phenyl)-7-(dimethyl amino) -4H-chromene-3-carbonitrile and 2-amino -7-(dimethylamino)-4-(7-methoxy-1,3-benzodionol-5-yl)-4H-chromene-3-carbonitrile belongs to a novel class of microtubule inhibitors and the substitution of 4- aryl group increase the anticancer activity of the compound.[3] Benzopyrans are widely employed as potential biodegradable agrochemicals[4] photoactive materials[5], cosmetics and pigments.[6] Benzo[b]pyrans have a broad spectrum of biological properties and it is well known structural scaffold of several natural products and artificial drugs.[7] These are used for antibacterial and anti-fungal activity[8,9], anticancer activity[10-13], insecticidal activity[14], antimicrobial and anti-inflammatory agent[15,16], anti-oxidant[17], anti-anaphylactic and diuretic agent.[18]

2. METHODS AND MATERIALS

2.1. EXPERIMENTAL

All the chemicals and synthetic grade reagents can be procured from Sigma Aldrich India and Merck chemicals .They were used without further purification. The reaction progress was monitored by thin layer chromatography. The melting point of the all the newly synthesized compounds were determined open at one end and were uncorrected using an Electrochemical Mk3 apparatus. 1HNMR & 13cNMR spectrum were recorded on 400MHz Brucker spectrometer in CDCl3 as a solvent and chemical shift values are recorded in units $(ppm) relative to tetramethylsilanes (Me4Si) as an internal standarad.Molecular mass of the synthesized compound were determined by LCMS spectrometers.

2.2. General procedure for synthesis

A mixture of aromatic aldehydes (1.2 mmol), malonitrile (1mmol), dimedone (1mmol) are introduced in 100 ml of RB flask, ethanol was added gradually until the mixture was dissolved. A catalytic amount of Methanesulphonic acid added to the above miture.The reaction mixture was carried out on the magnetic stirrer under reflux. The progress of the reaction was monitored by TLC in ethyl acetate: n-hexane (3:7). After completion of the reaction, the mixture was cooled to room temperature and poured on 10 ml ice cold water. The crude was filtered and

washed with ethyl acetate and a saturated solution of anhydrous sodium bicarbonate several times. The solid product can be separated by coulam chromatography (Ethylacetate:n-hexane, 3:7) Scheme - I.

2.2.1.2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a)

White solid; yield-87%; m.p – 228-230^{0}c ;^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:7.836-7.221(m,5H,Ar-H),6.461(s,2H,NH_2),4.135(s,1H,CH),2.232(s,2HCH2).2.212-1.582(m,2H),1.105 (s,3H, CH3).^{13} CNMR (100MHz,$CDCl_3$)δinppm:193.4,158.1,153.8,143.6,128.7, 126.2,124.3,118.7, 113.6,57.2,49.8,39.5,36.9,31.4,26.8. LCMS(m/z):293.85. Molecular formula: $C_{18}H_{18}N_2O_2$. Elemental analysis: Calculated: C-73.65, H-6.16, N-9.52; Obtained: C-73.69, H-6.15, N-9.51

2.2.2.2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4b)

white solid; yield-92%; m.p – 205-206^{0}c ;^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 9.532(s,1H,-OH),7.105-6.865(m,4H,Ar-H). 6.559 (s,2H,NH_2), 4.212(s,1H,CH), 2.225(s,1H,CH_2),2.219-1.792 (m,2H,CH_2), 1.087(s,3H,CH_2), 0.985 (s,3H, CH_3). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 195.51,157.75,155.28,153.88,135.74,130.88,118.97,116. 50,112.88,56.75,50.82,38.74,37.83, 30.79,27.81. LCMS (m/z): 310.09. Molecular formula: $C_{18}H_{18}N_2O_3$. Elemental analysis: calculated: C-69.66,H-5.84 , N-9.03; Obtained: C-69.69, H-5.83, N-9.02.

2.2.3.2-Amino-4-(3-ethoxy-4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4c)

White solid; yield-93%; m.p – 229-231^{0}c ; ^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 9.552(s,1H,-OH),6.987-6.664(m,3H,Ar-H),6.518(s,2H,NH_2), 4.521(s,1H,CH), 4.117-4.082(s,2H-,CH_2), 1.229 (t,J=7.3Hz,3H), 2.20(s,2H,CH3), 2.03(d,J=8.0Hz,2H), 1.229(t,J=7.3Hz,3H), 1.04(s,3H,CH_3), 1.051 (s,3H,CH_2).^{13} CNMR(100MHz, $CDCl_3$)δinppm:194.7, 157.8,153.9,146.6,143.8,134.6,121.5, 118.7,114.8,113.2, 112.6,63.7,57.6,49.7,38.4,37.0,31.4,26.2,14.2.LCMS (m/z):354.53. Molecular formula: $C_{20}H_{22}N_2O_4$. Elemental analysis: calculated: C-67.78, H-6.26, N-7.90, Obtained:C-67.82, H-6.25, N-7.89.

2.2.4.2-Amino-4-(4-hydroxy-3-methoxy phenyl)-7, 7-dimethyl-5-oxo-5,6,7,8-Tetrahydro-4H-chromene-3-carbonitrile (4d)

White solid; yield-92%; m.p – 230-232^{0}c ; ^{1}HNMR(400MHz,$CDCl_3$)δinppm: 9.459(s,1H,OH), 7.287-6.676(m,3H,Ar-H),6.654(s,2H, NH_2), 4.318(s,1H,CH), 3.567(s,3H, OCH_3), 2.226(s, 2H, CH_2), 2.122(d, J=8.8Hz, 2H), 1.885-1.851(m, 2H, CH_2), 1.068(s, 3H, CH_3), 0.987(s, 3H, CH_3). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 165.82, 163.25, 155.59, 131.68, 128.86, 122.52, 118.09, 114.87, 110.09, and 55.45. LCMS (m/z):339.79. Molecular formula: $C_{19}H_{20}N_2O_4$. Elemental analysis: calculated: C-71.70, H-5.21, N-16.72; Obtained: C-71.75, H-5.20, N-16.70.

2.2.5.2-Amino-4-(2,4,6-trimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4e)

Whitesolid;yield-95%;m.p–241-242^{0}c;^{1}HNMR(400MHz, $CDCl_3$)δinppm:6.674(s,2H,NH_2),6.207 (s,1H,Ar-H),4.218(s,1H, CH), 3.675(s,9H,OCH_3), 2.233(s, 2H, CH_2),1.278(s, 2H, CH_2), 1.056(s,3H,CH_3),0.88(s,3H,CH_3).^{13}CNMR(100MHz,CD Cl_3)δinppm:194.59,160.77,159.51, 157.77, 153.83, 118.72, 113.91, 100.59, 92.29, 57.83, 54.58, 50.76, 36.97, 31.54, 24.04, 26.07. LCMS (m/z) 384.28. Molecular formula: $C_{21}H_{24}N_2O_5$. Elemental analysis: Calculated: C-65.61, H-6.29, N-7.29; Obtained: 65.69, H-6.28, N-7.29.

2.2.6.2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahyro-4H-chromene-3-carbonitrile (4f)

Red solid; yield-90%; m.p – 208-210^{0}c ;^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 7.824(d,J=8.8Hz, 1H,Ar-H),7.554(d,J=7.0Hz,1H,Ar-H),7.214(d,J=8.8Hz,1H,Ar-H),7.105(s,1H,Ar-H),6.571(s, 2H,NH_2),4.127(s, 1H, CH), 2.231(s,2H, CH_2),1.722(s, 2H, CH_2), 1.018(s, 3H, CH_3), 0.942(s, 3H,CH_3).^{13} CNMR(100MHz,$CDCl_3$) δinppm:197.22,157.17,154.52,143.52,130.51,129.84,120 .64, 118.88, 112.17,58. 06, 50.08, 39.53, 37.79, 31.25, 27.81. LCMS (m/z):373.12. Molecular formula: $C_{18}H_{17}BrN_2O_2$. Elemental analysis: calculated: C-57.92, H-4.59, Br-21.41, N-7.51. Obtained: 57.96, H-4.58,Br-21.40, N-7.50.

2.2.2.7.4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-4-yl)benzoic acid (4g)

White solid; yield-89%; m.p – 235-237^{0}c ;^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 12.037(s,1H,-COOH), 8.120(d, J=8.0Hz, 1H, Ar-H), 8.057 (d,J=7.2Hz, 1H, Ar-H), 7.652(d,J=7.6Hz, 1H, Ar-H), 7.238(s,1H, Ar-H), 6.569(s,2H,NH_2), 4.226 (s, 1H, CH), 2.224(s,2H, CH_2), 2.123-1.823(m,2H, CH_2), 1.028(s,3H, CH_3), 1.014(s,3H, CH_3). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 197.23,164.55,157.22,153.54,148.66,127.71,126.17,125. 09,119.42,112.26,57.27,49.08, 39.52, 36.17,32.36,26.69. LCMS (m/z): 338.49. Molecular formula: $C_{19}H_{18}N_2O_4$. Elemental analysis: calculated: C-67.44, H-5.36, N-8.28; Obtained: C-67.49,H-5.35, N-8.27.

3. BIOLOGICAL ACTIVITY

Anti-Bacterial Assay

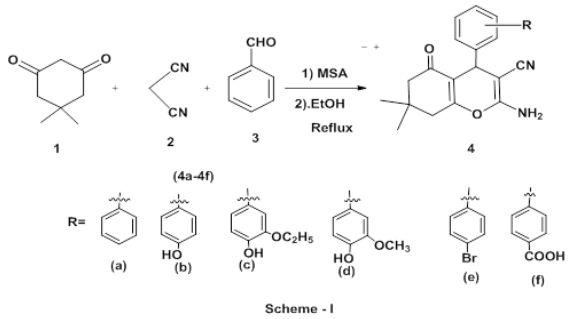
The anti-bacterial activities of desired compounds synthesized compounds are examined against 5 pathogenic bacteria strains. The result of antibiotic activity studies for the compounds. The gram negative bacteria screened were Escherichia Coli, Pseudomonas aeruginosa. The gram positive bacteria screened were S-aureas and Bacillus .The target compounds were used at the concentration of 250 µglml and 500 µglml using

DMSO as a solvent the amoxylin 10 µglml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested microorganism.

Anti-Fungal Assays

Anti-fungal activity of new synthesized compounds was examined by disc diffusion method against the organism of aspergillusniger and Candida albicans 1. Compared were treated at the concentrations of 500 µglml and 1000 µglml using DMSO as a solvent. The standard drug was used as ketoconazole 50 µglml against both organisms.

4. RESULT AND DISCUSSION



Scheme - I

All newly titled synthesized compounds can be synthesized under reflux condition. These target compounds can be obtained, we used to Methanesulphonic acid and in protic solvent. This catalyst can be used to develop the reaction conditions and reaction is completed maximum 2 hours. The rate of reaction was developed by using this catalyst. We used various substituted aryl aldehydes such as electron donating group of aldehydes and electron withdrawing group of aldehydes and halogen containing aldehydes.

All the synthesized compounds were examined anti-bacterial activity as well as antifungal. The electron withdrawing group of compounds didn't show any activities. Other hand electron withdrawing group of compounds exhibited poor activity compared with electron donating groups. All halogen compounds exhibit excellent activity. The compound which possess electron donating group shows moderate activity as shown in Table-I.

Table I: Antimicrobial activity screening activity synthesized scaffold.

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
4a	10	10	06	04	09	07
4b	19	18	11	20	07	08
4c	21	18	10	19	06	08
4d	18	20	09	20	17	21
4e	16	10	11	13	09	07
4f	21	22	20	20	17	18
4g	12	10	13	15	12	12
Streptomycin	25	25	22	22	NA	NA
Ketoconazole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

5.CONCLUSION

The reaction condition carried atreflux for all the newly synthesised compounds. The yield of the titled compounds obtained from 86-94%. The compound possesses electron donating group gives maximum yeild than that of the compound possesses electron withdrawing group. The rate of reaction developed by using the reagent as well as protic solvent. All the compounds tested by anti microbial activity against gram positive, gram negitive and fungal. The compound having halogens showed excelent active potential. Other wise the compounds having electron donating group which showed better active potential than that of the electron with drwing group.

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