Synthesis of Some Novel Chromene Derivatives and Its Biological Evaluation.

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Abstract: A novel series of 2-amino-4-[2-chloro-5-(4-substitutedphenyl)pyridin-3-yl]-4H-chromene-3carbonitrile derivatives were efficiently synthesized. Chromene (Benzopyran) was one of the privileged scaffold which appears as an important structural component in various natural products and also possess useful photochemical properties. The derivatives of benzopyran moiety can be capable of interacting with a variety of cellular targets which leads to their wide ranging biological activities such as antitumor, antihepatotoxic, antioxidant, anti-inflammatory, diuretic, anticoagulant, antispasmolytic, estrogenic, antiviral, antifungal, antimicrobial, anti-helminthic, hypothermal, vasodilatory, anti-HIV, antitubercular, herbicidal, anticonvulsant and analgesic activity. The structure of the synthesized compounds are established based on TLC, IR, NMR, MASS Spectrometric methods and elemental analyses.All the prepared compounds were screened for their antibacterial activities and antifungal activities.

Keywords: Pyrimidochromene, Amidines, antimicrobial and antifungal activity.

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I. INTRODUCTION

Benzopyran (chromene) is one of the privileged medicinal pharmacophore, which appears as an important structural component in natural compounds and generated great attention because of their interesting biological activity.Benzopyrans are an important group of organic compounds that are used as bactericides [1-3], fungicides [4], anti-inflammatory [5], and anticancer agents [6]. Benzopyrans derivatives are an important class of compounds, widely present in plants, including edible vegetables and fruits [7]. Chromene constitutes the backbone of various types of polyphenols and is widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins [8]. The biological activity of some natural chromene-based structures led to the development of synthetic analogs, some of them displaying remarkable effects as pharmaceuticals [4, 9-12].These pharmacological properties make us thought in the synthesis of some benzopyran derivatives in hoping that maybe have a prospective pharmaceutical importance.

REACTION SCHEME Synthesis of 2-amino-4-[2-chloro-5-(4-substitutedphenyl)pyridin-3-yl]-4H-chromene-3-carbonitrile derivatives



Where: R= H, Me, OMe, Cl

II. EXPERIMENTAL PROCEDURE

Material and Method: (a) Synthesis of 4-(substituted phenyl)-3-buten-2-oneoxime[1]

Synthesis of these compounds has been reported in the literature^[13]. Charged Ethanol (10 ml) and 5% Sodiumhydroxide solution (20 ml) in a three-necked round-bottomed flask equipped with a thermometer pocket, reflux condenser, guard tube and mechanical stirrer. Added p-substituted benzylideneacetone (1.0 gm) (Prepared by Org.Synth. Coll. Vol.-I, p.77) and Hydroxylamine hydrochloride (2.0 gm) in to the clear solution. Heated thereaction mass for 15 minutes then the reaction mass diluted with water (200 ml) and theoxime was separated. This crude product was recrystallisation from Xylene gave white crystal of α -oxime.

(b) Synthesis of 5-(4-substitutedphenyl)-2-chloro-3-formyl pyridine [II]

Synthesis of these compounds has been reported in the literature ^[14]. Charged Dimethyl formamide (9.66 ml, 60 moles) and 4-(substituted phenyl)-3-buten-2-oneoxime(5mmoles) in a three-necked round-bottom flask equipped with a thermometer pocket, reflux condenser, guard tube and mechanical stirrer. Reaction mixture

cooled to0^oC. To it phosphorous oxy-chloride (40mmoles) was added drop wise with stirring over a period of

30-40 minutes at $0-5^{\circ}$ C. Stirred the reaction mixture for 1 hour at room temperature and then stirred at 90° C for 4 hours. After the completion of their action the reaction mass cooled to room temperature and poured in crushed ice and neutralized with sodium acetate. The crude solid was filtered and washed with water, mother liquid extracted with chloroform and evaporated to dryness. The resulting crudes was crystallized from Diethyl ether to give a compound.

(c) Synthesis of {[2-chloro-5-(4-substitutedphenyl)pyridin-3-yl]methylidene} propane nitrile(III)

5-(4-substitutedphenyl)-2-chloro-3-formyl pyridine (0.01mole), malononitrile (0.01mole) and ethanol (10ml)

were charged in R. B. flask with mechanical stirrer, thermometer pocket and reflux condenser. There action mixture was slowly heated. When the entire compound was dissolved then 2-3drops of triethylamine was added to mixture and refluxed for 0.5 to1 hr. After the completion of reaction (checked by TLC), the product was filtered and washed with chilled ethanol. The product was recrystallised with methanol. All the other compounds (IIIa-d) were synthesized by above procedure.

(d) Synthesis of 2-amino-3-cyano-4-[2-chloro-5-(4-substitutedphenyl)3-pyridilyl]-4H-chromene derivatives 2-chloro-5-(4-substitutedphenyl) pyridin-3-yl] methylidene} propanedinitrile (0.01 mole), appropriate phenolornaphthol(0.01mole) and ethanol (10ml) were taken in R.B.flask with mechanical stirring, thermometers pocket and condenser. Triethylamine (2-3drops) was added as acatalyst. There action mixture was refluxed for 60 to 90 minutes. After the completion of reaction (checked by TLC), the separated product was filtered and washed with chilled ethanol. The product was crystallized with Ethanol.

III. **RESULTS AND DISCUSSION**

Spectroscopy Analysis and Analytical data of Synthesis of {[2-chloro-5-(4-substitutedphenyl)pyridin-3yl]methylidene}propanedinitrile derivatives (III)



Where R = H, Me, OMe, CI

R=H, M.P 122-126 C⁰, Yield 87%, **IRcm⁻¹** 3040(C-Hstr.of=CH-), 2240(C=Nstr.), 1570 & 1480(C=C str.ofaromaticring),740(C-Clstr).¹H NMR δ_{H} ppm 7.18-8.93(1H,s,-CH=C- and 7H,mAr-H).Mol. For. C15H8N3Cl, Mol.Wt. 265, Anal.data. (Found/Cal) C% 68.85/67.92, H% 2.67/3.01, N% 16.53/15.84.

R=Me, M.P 195-200 C⁰, Yield 85%, **IRcm**⁻¹3048(C-H str of =CH-), 2889(C-H str of -CH₃), 2245(C=N str.), 1575& 1485 (C=C str of aromatic ring), 735 (C-Cl str).¹H NMR δ_Hppm 2.40(3H, s, -CH₃), 7.18-8.93(1H,s,-CH=C- and 6H,mAr-H).Mol. For. C16H10N3Cl, Mol. Wt. 279, Anal. data. (Found/Cal) C% 67.28/68.81, H% 3.17/3.58, N% 16.56/15.05.

R=OMe, M.P 159-163 C⁰, Yield 80%, **IRcm⁻¹**3038(C-H str of =CH-), 2889(C-H str of -CH₃), 2235(C≡N str.), 1560 & 1465 (C=C str of aromatic ring), 1275,1040(C-O-C str. of Ar-O), 747(C-Cl str.). ¹H NMR δ_Hppm 3.99(3H, s, -OCH₃), 7.20-8.92(1H,s,-CH=C- and 6H,mAr-H).Mol. For. C16H10N3Cl, Mol. Wt. 295, Anal. data. (Found/Cal) C% 66.35/65.08, H% 3.22/3.38, N% 15.58/14.23.

R=Cl, M.P 215-217 C⁰, Yield 75%, **IRcm**⁻¹3046(C-H str of =CH-), 2250(C≡Nstr), 1570 & 1465 (C=C str of aromatic ring), 732(C-Cl str). ¹H NMR δ_{H} ppm 7.25-8.82(1H,s,-CH=C- and 6H,mAr-H).Mol. For. C15H7N3Cl₂, Mol. Wt. 300, Anal. data. (Found/Cal) C% 58.96/60.00, H% 1.83/2.33, N% 15.33/14.00.

Synthesisof2-amino-3-cyano-4-[2-chloro-5-(4-substitutedphenyl)3-pyridilyl]-4H-chromenederivatives



Where R = H, Me, OMe, Cl

R=H, M.P 270-273 C⁰, Yield 78%, **IRcm⁻¹** 3060, 3020(C-Hstr.of-CH-), 2240(C=Nstr.),1565 & 1460(C=C str. Of aromatic ring), 1312(C-N str. Of Ar-NH2), 1210(C-O-C str. of Ar-O),740(C-Cl str.). ¹H NMR δ_{H} ppm 5.86(1H,s,-CH) 7.37-8.20(13H,m Ar-H), 7.19(2H, s, -NH2).Mol. For. C25H16ClN3O, Mol. Wt. 409, Anal. data. (Cal/Found) C% 73.34/71.69, H% 3.91/3.55, N% 10.26/11.05.

R= -Me, M.P 185-189 C⁰, Yield 81%, IRcm⁻¹3062, 3025, 2900(C-H str of -CH₃), 2240(C≡N str.), 1570& 1475

(C=C str of aromatic ring), 1310(C-N str. Of Ar-NH₂), 1215(C-O-C str. of Ar-O), 735 (C-Cl str.). ¹H NMR $\delta_{\rm H}$ ppm 2.42(3H, s, -CH₃), 4.82(2H, s, -NH₂) 7.28-7.87(12H,m Ar-H).Mol. For. C26H18ClN3O, Mol. Wt. 423, Anal. data. (Cal/Found) C% 73.75/72.54, H% 4.25/4.11, N% 9.92/10.47.

R = **OMe**, M.P 198-201 C⁰, Yield 72%, **IRcm**⁻¹3060,3020(C-H str of -CH-), 2815(C-H str of O-CH₃), 2245(C=N str.), 1565& 1470(C=C str of aromatic ring), 1311(C-N str. of Ar-NH₂), 1230 &1030(C-O-C str of asym. And sym. str of -OCH₃), 1212(C-O-C str. of Ar-O), 740(C-Cl str). ¹H NMR δ_{H} ppm 3.81(3H, s, -OCH₃), 5.87(1H, s, -CH-), 6.60(2H,s,-NH₂), 7.20-8.13(12H, m, Ar-H). **Mol. For.** C26H18ClN3O, **Mol. Wt.** 439, **Anal. data**. (Cal/Found) C% 71.07/72.62, H% 4.10/4.02, N% 9.56/10.02.

R = **Cl**, M.P 223-226 C⁰, Yield 70%, **IRcm**⁻¹3065,3022(C-H str of -CH-), 2240(C≡N str.), 1575 & 1465(C=C str of aromatic ring), 1310(C-N str. of Ar-NH₂), 1215(C-O-C str. Of Ar-O), 740(C-Cl str.). ¹H NMR δ_Hppm 5.87(1H, s, -CH-), 6.78(2H,s,-NH₂), 7.18=7.93(12H, m, Ar-H).**Mol. For**. C25H15Cl₂N3O, **Mol. Wt**. 444, **Anal. data**. (Cal/Found) C% 67.56/66.12, H% 3.37/3.92, N% 9.45/10.02.



Where R = H, Me, OMe, Cl

R = **H**, M.P 278-282 C⁰, Yield 88%, **IRcm⁻¹** 3065, 3022(C-Hstr.of-CH-), 2236(C≡Nstr.),1560& 1465(C=C str. of aromatic ring), 1310(C-N str. of Ar-NH₂), 1215(C-O-C str. of Ar-O),738(C-Cl str.). ¹**H** NMR $\delta_{\rm H}$ ppm 5.87(1H,s,-CH) 7.28-8.12(13H, m Ar-H), 6.63(2H, s, -NH₂).**Mol. For**. C25H16Cl₂N3O, **Mol. Wt**. 409, **Anal. data**. (Cal/Found) C% 73.34/72.18, H% 3.91/3.34, N% 10.26/9.32.

R = -Me, M.P 245-248 C⁰, Yield 88%, **IRcm**⁻¹3060, 3020, 2905(C-H str of -CH₃), 2240(C≡N str.), 1570 & 1475 (C=C str of aromatic ring), 1315(C-N str. Of Ar-NH₂), 1212(C-O-C str. of Ar-O), 740 (C-Cl str.). ¹H NMR δ_{H} ppm 2.48(3H, s, -CH₃), 6.85(2H, s, -NH₂) 7.18-8.07(12H,m Ar-H), 5.90(1H, s, -CH-).Mol. For. C26H18ClN3O, Mol. Wt. 423, Anal. data. (Cal/Found) C% 73.75/74.54, H% 4.25/4.85, N% 9.92/8.80.

R = **OMe**, M.P 210-214 C⁰, Yield 83%, **IRcm**⁻¹3065,3015(C-H str of -CH-), 2820(C-H str of O-CH₃), 2240(C≡N str.), 1565 & 1470(C=C str of aromatic ring), 1310(C-N str. of Ar-NH₂), 1234& 1032(C-O-C str of asym. And sym. Str. of -OCH₃), 1215(C-O-C str. of Ar-O), 738(C-Cl str.). ¹H NMR δ_Hppm 3.80(3H, s, -OCH₃), 5.90(1H, s, -CH-), 6.48(2H,s,-NH₂), 7.25-8.11(12H, m, Ar-H).**Mol. For**. C26H18ClN3O₂, **Mol. Wt**. 439, **Anal. data**. (Cal/Found) C% 71.07/72.62, H% 4.10/3.65, N% 9.56/10.43.

R = **Cl**, M.P 234-236 C⁰, Yield 72%,**IRcm**⁻¹3065,3022(C-H str of -CH-), 2242(C=N str.), 1572& 1467(C=C str of aromatic ring), 1310(C-N str. of Ar-NH₂),1215(C-O-C str. of Ar-O), 732(C-Cl str.). ¹**H NMR** δ_H**ppm** 5.88(1H, s, -CH-), 6.57(2H,s,-NH₂), 7.11-7.90(12H, m, Ar-H).Mol. For. C25H15Cl₂N3O, **Mol. Wt**. 444, **Anal. data**. (Cal/Found) C% 67.56/68.12, H% 3.37/4.02, N% 9.45/8.15.



Where R = H, Me, OMe, Cl

R = **H**, M.P 196-200 C⁰, Yield 86%, **IRcm⁻¹** 3480(O-H str. of Ar-OH), 3070,3025(C-H.str..of-CH-), 2239(C≡N str.),1580 & 1475(C=C str. Of aromatic ring), 1312(C-N str. Of Ar-NH₂), 1210(C-O-C str. of Ar-O),740(C-Cl str.). ¹**H NMR** δ_{**H**}**ppm** 5.91(1H,s,-CH), 7.01-8.33(10H, m Ar-H), 6.81(2H, s, -NH₂), 9.73(1H, s, -OH).**Mol. For**. C21H14ClN3O₂, **Mol. Wt**. 375, **Anal. data**. (Cal/Found) C% 67.20/66.34, H% 3.73/3.55, N% 11.20/12.14.

R = -Me, M.P 182-185 C⁰, Yield 79%, **IRcm**⁻¹ 3475(O-H str. of Ar-OH), 3065, 3022, 2915(C-H str. of-CH-, - CH₃), 2238(C≡N str.),1585 & 1480(C=C str. of aromatic ring), 1312(C-N str. of Ar-NH₂), 1211(C-O-C str. of Ar-O),745(C-Cl str.). ¹H NMR $\delta_{\rm H}$ ppm 5.87(1H,s,-CH), 2.39(3H, s,-CH₃),6.97-8.11(9H, m Ar-H), 6.68(2H, s, - NH₂), 10.11(1H, s, -OH).Mol. For. C22H16ClN3O₂, Mol. Wt. 389, Anal. data. (Cal/Found) C% 67.86/68.26, H% 4.11/3.78, N% 10.79/11.64.

R = **OMe**, M.P 225-229 C⁰, Yield 76%, **IRcm**⁻¹3465(O-H str. of Ar-OH), 3070, 3010(C-H str. of-CH-), 2825(C-H str. of O-CH₃), 2242(C≡Nstr.),1580 & 1485(C=C str. of aromatic ring), 1312(C-N str. of Ar-NH₂), 1230 & 1030(C-O-C str. of asym. And sym. str of -OCH₃), 1210(C-O-C str. of Ar-O),745(C-Cl str.). ¹H NMR δ_Hppm 3.82(3H, s, -OCH₃), 5.95(1H,s,-CH), 6.90-8.15(9H, m Ar-H), 6.47(2H, s, -NH₂), 10.05(1H, s, -OH).Mol. For. C22H16ClN3O₃Mol. Wt. 405, Anal. data. (Cal/Found) C% 65.18/63.36, H% 3.95/3.79, N% 10.37/10.91.

R = **Cl**, M.P 187-191 C⁰, Yield 65%, **IRcm**⁻¹3470(O-H str of Ar-OH), 3080, 3030(C-H.str..of-CH-),2240(C≡N str.),1580 & 1480(C=C str. of aromatic ring), 1312(C-N str. Of Ar-NH2), 1211(C-O-C str. of Ar-O),735(C-Cl str.). ¹**H NMR** δ_{**H**}**ppm** 5.91(1H,s,-CH), 6.91-8.01(9H, m Ar-H), 6.48(2H, s, -NH₂), 10.16(1H, s, -OH).**Mol. For**. C21H₁3Cl₂N3O₂**Mol. Wt**. 410, **Anal. data**. (Cal/Found) C% 61.46/62.26, H% 3.17/2.78, N% 10.24/10.64.



Where R = H, Me, OMe, Cl

R = **H**, M.P 229-231 C⁰, Yield 61%, **IRcm⁻¹** 3480(O-H str. of Ar-OH), 2915(C-H str. of-CH-), 2230(C≡N str.),1585& 1480(C=C str. of aromatic ring), 1310(C-N str. of Ar-NH₂), 1215(C-O-C str. of Ar-O),820(C-Cl str.). ¹**H NMR** δ_{H} **ppm** 5.97(1H,s,-CH), 7.11-8.38(9H, m Ar-H), 6.87(2H, s, -NH₂), 9.80(1H, s, -OH), 10.11(1H, s, -OH).**Mol. For**. C21H14ClN3O₃**Mol. Wt**. 391, **Anal. data**. (Cal/Found) C% 64.45/62.96, H% 3.58/3.48, N% 10.74/11.54.

 $\mathbf{R} = -\mathbf{Me}$, M.P 208-211 C⁰, Yield 67%, **IRcm**⁻¹3475(O-H str. of Ar-OH), 2910(C-H str. of-CH-), 2225(C=N)

str.),1580 & 1485(C=C str. of aromatic ring), 1312(C-N str. of Ar-NH₂), 1216(C-O-C str. of Ar-O),810(C-Cl str). ¹H NMR δ_{H} ppm2.41(3H, s, -CH₃), 5.90(1H,s,-CH), 6.97-8.03(8H, m Ar-H), 6.81(2H, s, -NH₂), 10.23(1H, s, -OH), 10.01(1H, s, -OH).Mol. For. C22H16ClN3O₃Mol. Wt. 405, Anal. data. (Cal/Found) C% 65.18/66.36, H% 3.95/3.78, N% 10.37/11.24.

R = **OMe**, M.P 230-234 C⁰, Yield 59%,**IRcm**⁻¹3485(O-H str. of Ar-OH), 2910(C-H str. of-CH-), 2820(C-H str. of O-CH₃), 2240(C≡Nstr.),1585& 1485(C=C str. of aromatic ring), 1312(C-N str. of Ar-NH₂), 1232 & 1032(C-O-C str. of asym. And sym. str of -OCH₃), 1215(C-O-C str. of Ar-O), 795(C-Cl str.). ¹H NMR δ_Hppm 3.87(3H, s, -OCH₃), 5.85(1H,s,-CH), 7.13-8.23(8H, m Ar-H), 6.87(2H, s, -NH₂), 10.11(1H, s, -OH), 10.38(1H, s, -OH).**Mol. For**. C22H₁₆ClN₃O₄**Mol. Wt**. 421, **Anal. data**. (Cal/Found) C% 62.70/64.15, H% 3.80/3.64, N% 9.97/10.74.

R = **Cl**, M.P 236-239 C⁰, Yield 57%,**IRcm**⁻¹3480(O-H str. of Ar-OH), 2915(C-H str. of-CH-), 2245(C≡N str.),1575 & 1485(C=C str. Of aromatic ring), 1312(C-N str. Of Ar-NH₂), 1211(C-O-C str. of Ar-O), 800(C-Cl str.). ¹**H NMR** δ_{H} **ppm** 5.91(1H,s,-CH), 7.11-8.05(8H, m Ar-H), 6.47(2H, s, -NH₂), 10.15(1H, s, -OH), 10.35(1H, s, -OH).**Mol. For**. C21H13Cl₂N3O₃**Mol. Wt**. 426, **Anal. data**. (Cal/Found) C% 59.18/57.86, H% 3.05/2.88, N% 9.85/10.23

Synthesis of new Chromene derivatives (C-1to16). Substituted anilines, phenols, naphthols and malononitrileare commercial products and were used without further rpurification. All the solvents were distilled before use. All

the melting points ware uncorrected and expressed in ^oC. Elemental analyses (%C,H,N) were carried out byPerkinElmer2400CHN analyzer. IR spectra of all the compounds have been recorded on Nicolet Impact400DFT-IR spectrophotometer using KBr. The¹H-NMR spectra have been recorded on a Bruker Avance(400MHz) spectrophotometer using solvent as internal standard in CDCl₃ and MSO-d₆. Some selected FT-IR, ¹H-NMR and Mass spectra. Examination of the IR-spectra of these compounds reveals the expected frequencies. Some of the important frequencies are indicated as :3150-3020cm⁻¹ (Aromatic C-H stretching), 2240cm⁻¹ (C=N stretching), 1610.1498cm⁻¹ (Aromatic C=C with C=N stretching).

Compound Name	Inhibition Zone (in mm)against			Growth diameter in mm (%inhibitation)	
	E. coli	B.substilis	B.cereus	S.rolfsii	A.parasiticus
C-1	11	12	11	26(69)	27(68)
C-2	11	14	12	23(73)	24(71)
C-3	18	20	17	19(77)	19(77)
C-4	15	17	15	21(75)	20(76)
C-5	15	21	13	22(74)	21(75)
C-6	11	11	11	27(68)	28(66)
C-7	10	10	11	24(71)	25(70)
C-8	15	11	18	20(76)	20(76)
C-9	14	10	10	21(75)	22(74)
C-10	15	11	21	20(76)	21(75)
C-11	15	13	14	26(69)	24(71)
C-12	10	14	11	24(71)	25(70)
C-13	16	17	15	20(76)	19(77)
C-14	10	11	11	20(76)	20(76)
C-15	15	18	17	21(75)	22(74)
C-16	10	10	10	26(69)	26(69)
Ciprofloxacine	38	37	40	-	-
Ampicilline	30	25	30	-	-
Griseofulvin	-	-	-	00(100)	00(100)

 TABLE 1
 ANTIMICROBIAL ACTIVITY OF NEW CHROMENEDERIVATIVE

IV. RESULT OF ANTIMICROBIALACTIVITY

All the synthesized compounds C-1 to C-16 were tested against microorganism species at 1000 ppmconcentration. The observed results of antibacterial screening reported in above table indicate that compounds C-3, C-4, C-5 and C-13 shows good activity against the bacterial species used. The results indicate *B.Substilis*shows good results compared to other two speciesused. Compounds C-1, C-6 and C-16 shows poor activity against the bacterial speciesused. From the antifungal assay it has been also observed that compounds having methoxy substituents on quinoline ring show the highest activity against *A.Parasiticus S.Rolfsii*. Rest of the compounds show significant activity but it could not reach the effectiveness of the conventional fungicidal Griseofulvine.

V. CONCLUSION

In concluded a new series of derivatives C 1 to 16 were synthesized. ExaminationoftheIR-spectraofthesecompoundsrevealstheexpectedfrequencies. Someoftheimportantfrequenciesareindicatedas:3150-3020cm⁻¹ (AromaticC-H stretching),2240cm⁻¹ (C=Nstretching),1610,1498cm⁻¹ (AromaticC=CwithC=N stretching). 1630-1590 cm-1 (Aromatic C=C stretching), 850-700 (C-Cl stretching). The characteristic IR band of these compounds appears at 850-700 cm-1 (C-Cl stretching) and at 1730-1700 cm-1 (C=O stretching) confirmed the structure. 1H-NMR spectra also showed the peak at 2.11-2.40 (4H, m CH2), 5.51 (1H, s, CH), 0.91-1.07 (6H, s, CH3) δ value. The other protons of the compound were resonated at expected frequencies and biological study. The investigation of antimicrobial activities data revealed that some of the derivatives displayed excellent activity and the showed moderate activity against standard drugs.

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