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Highly efficient and practical synthesis of 2-amino chromene derivatives using ionic base

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ABSTRACT

*The treatment of substituted benzaldehydes with malenonitrial and orcinol in presence of using ionic base anhydrous potassium carbonate and ethanol as solvent leads to give 2-Amino-3-Cyano Chromene Derivatives **3a 1-10** and 2-Amino-3-Carboxylate Chromene Derivatives **3b 1-10** obtain by using Ethyl cyanoacetate in place of malenonitrial. All the synthesized cromene derivatives have purity check by TLC. The structures of the compounds were established by elemental analyses and spectral data. All the products were also screened in vitro for their antimicrobial and antifungal activity.*

Key words: Chromene, Malenonitrial, Orcinol, Aldehyde, Antimicrobial.

INTRODUCTION

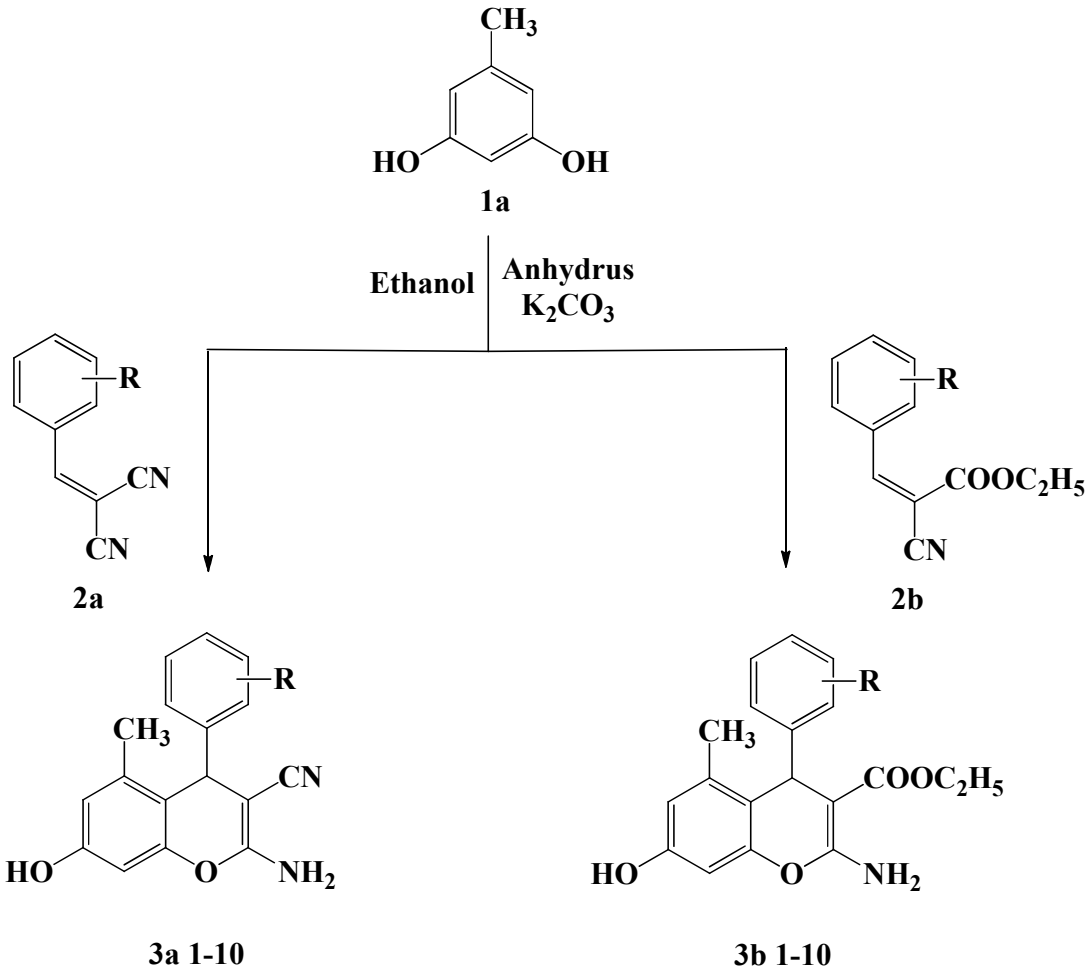
Chromene derivatives are an important class of compounds, widely present in plants, including edible vegetables and fruits [1]. Numerous bioactive natural products have been identified, and the presence of the chromene-based structure has been associated with the capacity to prevent disease [2]. Synthetic analogues have been developed over the years, some of them displaying remarkable effects as pharmaceuticals [3], including antifungal [4], anti-microbial [5], molluscidial [6], anticoagulant, spasmolytic, diuretic, anticancer and antianaphylactic characteristics [7]. 4H-Pyran derivatives are also potential calcium channel antagonists [8] which are structurally similar to biologically active 1, 4-dihydropyridines. Moreover, nitrogen-containing heterocycles [9, 10] are also of broad pharmaceutical interest and significance, which justifies our continuing efforts in designing novel heterocyclic molecules of biological importance. On the other hand, have become very popular in the discovery of biologically active novel compounds due to its simple experimentation, atom economy and high yields of the products [11]. 2-Amino-4H-pyran derivatives represent an important class of compounds.

A four component Knoevenagel-Michael addition-cyclization sequence has been studied for the synthesis of dihydropyranopyrazole derivatives from hydrazine hydrate, a malonitrile, a β-ketoester, and an aldehyde or a ketone. The reaction was described under catalyst- and solvent-free conditions [12] and using piperidine in ultrapure aqueous media [13], both at room temperature. Kidwai et al. [14] has prepared the same class of the compounds using water as a solvent and potassium carbonate as the required base catalyst

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. 1H NMR was determined in DMSO-d6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Reaction Scheme



R= H, CH_3, OCH_3, NO_2, Cl, Br

Synthesis of Substituted Cyanoarylidene (2a and 2b).

The product Substituted Cyanoarylidene (2a and 2b) has been synthesized by the reaction of different substituted aldehyde and malononitrial or ethyl cyanoacetate in presence of base (pipyridine) [15].

General method for the Synthesis of 2-amino-7-hydroxy-5-methyl-4-(substitutedphenyl)-4H-chromene-3-carbonitrile (3a 1-10).

0.01 mole of Substituted Cyanoarylidene 2a and 0.01 mole of 5-methyl resorcinol dissolve in absolute ethanol. Stirring the reaction mixture at room temperature, gradually added 0.03 mole of anhydrous potassium carbonate and

stirring the reaction mixture at room temperature for 5-6 hours. After completion of reaction, pour the reaction mixture in dilute hydrochloric acid and neutralized it, separated the solid product filter, dry and crystallized from ethanol.

2-amino-7-hydroxy-5-methyl-4-phenyl-4H-cromene-3-carbonitrile (3a1)
Yield: 60%; MP: 205-207^{0}C; IR (KBr, cm^{-1}): 3437 (O-H), 3339 (amine N-H str), 3038 (aromatic C–H str), 2185 (C≡N Str), 1290 (amine C-N Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.50 (s, 1H, OH), 6.80-6.82 (m, 5H, Aromatic), 6.70 (s, 2H, NH_2), 6.38 (s, 1H, ArH), 6.31 (s, 1H, ArH) 4.40 (s, 1H, 4-H), 1.85 (s, 3H, CH_3); MS: m/z 278(M^+), 262, 211, 202, 170, 159, 91, 77, 66.; Elemental Analysis for $C_{17}H_{14}N_2O_2$: Calculated: C, 73.37; H, 5.07; N, 10.07; %. Found: C, 73.27; H, 5.0; N, 10.01; %.

2-amino-7-hydroxy-4-(4-methoxyphenyl)-5-methyl-4H-cromene-3-carbonitrile (3a2)
Yield: 70%; MP: 210-212^{0}C; IR (KBr, cm^{-1}): 3441 (O-H), 3337 (amine N-H str), 3048 (aromatic C–H str), 2180 (C≡N Str), 1296 (amine C-N Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.59 (s, 1H, OH), 6.93-6.96 (d, 2H, ArH), 6.82-6.84 (d, 2H, ArH), 6.72 (s, 2H, NH_2), 6.37 (s, 1H, ArH), 6.32 (s, 1H, ArH), 4.46 (s, 1H, 4-H), 3.7 (s, 3H, OCH_3), 1.89 (s, 3H, CH_3); MS: m/z 308(M^+), 293, 277, 211, 202, 159, 133, 91, 77, 66.; Elemental Analysis for $C_{18}H_{16}N_2O_3$: Calculated: C, 70.12; H, 5.23; N, 9.09; %. Found: C, 70.10; H, 5.21; N, 9.0; %.

2-amino-7-hydroxy-4-(2-methoxyphenyl)-5-methyl-4H-cromene-3-carbonitrile (3a3)
Yield: 65%; MP: 198-200^{0}C; IR (KBr, cm^{-1}): 3440 (O-H), 3337 (amine N-H str), 3044 (aromatic C–H str), 2187 (C≡N Str), 1293 (amine C-N Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.54 (s, 1H, OH), 7.12 (d, 1H, ArH), 6.93-6.96 (m, 3H, ArH), 6.72 (s, 2H, NH_2), 6.37 (s, 1H, ArH), 6.32 (s, 1H, ArH) 4.46 (s, 1H, 4-H), 3.7 (s, 3H, OCH_3), 1.89 (s, 3H, CH_3); MS: m/z 308(M^+), 293, 277, 202, 159, 133, 77, 66.; Elemental Analysis for $C_{18}H_{16}N_2O_3$: Calculated: C, 70.12; H, 5.23; N, 9.09; %. Found: C, 70.02; H, 5.20; N, 9.05; %.

2-amino-7-hydroxy-5-methyl-4-(4-nitrophenyl)-4H-cromene-3-carbonitrile (3a4)
Yield: 66%; MP: 172-174^{0}C; IR (KBr, cm^{-1}): 3438 (O-H), 3340 (amine N-H str), 3045 (aromatic C–H str), 2182 (C≡N Str), 1419 (Nitro N=O str), 1290 (amine C-N Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.50 (s, 1H, OH), 8.14 (d, 2H, ArH), 7.49 (d, 2H, ArH), 6.76 (s, 2H, NH_2), 6.31 (s, 1H, ArH), 6.30 (s, 1H, ArH) 4.56 (s, 1H, 4-H), 1.92 (s, 3H, CH_3); MS: m/z 323(M^+), 292, 211, 202, 186, 159, 133, 91, 77, 66.; Elemental Analysis for $C_{17}H_{13}N_3O_4$: Calculated: C, 63.16; H, 4.05; N, 13.00; %. Found: C, 63.11; H, 4.0; N, 12.80; %.

2-amino-7-hydroxy-5-methyl-4-(2-nitrophenyl)-4H-cromene-3-carbonitrile (3a5)
Yield: 61%; MP: 158-160^{0}C; IR (KBr, cm^{-1}): 3430 (O-H), 3344 (amine N-H str), 3040 (aromatic C–H str), 2180 (C≡N Str), 1416 (Nitro N=O str), 1295 (amine C-N Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.48 (s, 1H, OH), 7.96-8.10 (d, 2H, ArH), 7.45-7.48 (t, 2H, ArH), 6.71 (s, 2H, NH_2), 6.24 (s, 1H, ArH), 6.34 (s, 1H, ArH), 4.50 (s, 1H, 4-H), 1.92 (s, 3H, CH_3); MS: m/z 323(M^+), 211, 202, 186, 159, 133, 91, 77, 66.; Elemental Analysis for $C_{17}H_{13}N_3O_4$: Calculated: C, 63.16; H, 4.05; N, 13.00; %. Found: C, 63.12; H, 3.95; N, 12.90; %.

2-amino-7-hydroxy-5-methyl-4-(p-tolyl)-4H-cromene-3-carbonitrile (3a6)
Yield: 72%; MP: 170-172^{0}C; IR (KBr, cm^{-1}): 3438 (O-H), 3337 (amine N-H str), 3048 (aromatic C–H str), 2963 (methyl C-H Str), 2180 (C≡N Str), 1296 (amine C-N Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.59 (s, 1H, OH), 6.93-6.96 (d, 2H, ArH), 6.82-6.84(d, 2H, ArH), 6.72 (s, 2H, NH_2), 6.37 (s, 1H, ArH), 6.32 (s, 1H, ArH), 4.46 (s, 1H, 4-H), 2.34 (s, 3H, CH_3), 1.89 (s, 3H, CH_3); MS: m/z 292(M^+), 277, 211, 202, 159, 133, 91, 77, 66.; Elemental Analysis for $C_{18}H_{16}N_2O_2$: Calculated: C, 73.95; H, 5.52; N, 9.58; %. Found: C, 73.75; H, 5.50; N, 9.50; %.

2-amino-4-(4-bromophenyl)-7-hydroxy-5-methyl-4H-cromene-3-carbonitrile (3a7)
Yield: 78%; MP: 148-150^{0}C; IR (KBr, cm^{-1}): 3445 (O-H), 3340 (amine N-H str), 3049 (aromatic C–H str), 2180 (C≡N Str), 1290 (amine C-N Str), 642 (C-Br Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.46 (s, 1H, OH), 7.85 (d, 2H, ArH), 7.12 (d, 2H, ArH), 6.72 (s, 2H, NH_2), 6.41 (s, 1H, ArH), 6.19 (s, 1H, ArH), 4.74 (s, 1H, 4-H), 2.10 (s, 3H, CH_3); MS: m/z 356(M^+), 325, 292, 211, 202, 186, 159, 133, 91, 77, 66.; Elemental Analysis for $C_{17}H_{13}BrN_2O_2$: Calculated: C, 57.16; H, 3.67; N, 7.84; %. Found: C, 57.08; H, 3.65; N, 7.81; %.

2-amino-4-(3-bromophenyl)-7-hydroxy-5-methyl-4H-cromene-3-carbonitrile (3a8)
Yield: 75%; MP: 160-162^{0}C; IR (KBr, cm^{-1}): 3430 (O-H), 3344 (amine N-H str), 3040 (aromatic C–H str), 2180 (C≡N Str), 1295 (amine C-N Str), 642 (C-Br Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.48 (s, 1H, OH), 7.22-7.30 (m,

4H, ArH), 6.70 (s, 2H, NH_2), 6.41 (s, 1H, ArH), 6.19 (s, 1H, ArH) 4.70 (s, 1H, 4-H), 1.95 (s, 3H, CH_3); MS: m/z 356(M^+), 325, 292, 211, 202, 186, 159, 133, 91, 77, 66.; Elemental Analysis for $C_{17}H_{13}BrN_2O_2$: Calculated: C, 57.16; H, 3.67; N, 7.84; %. Found: C, 57.14; H, 3.61; N, 7.83; %.

2-amino-4-(4-chlorophenyl)-7-hydroxy-5-methyl-4H-cromene-3-carbonitrile (3a9)
Yield: 77%; MP: 194-196^{0}C; IR (KBr, cm^{-1}): 3445 (O-H), 3340 (amine N-H str), 3049 (aromatic C–H str), 2180 (C≡N Str), 1290 (amine C-N Str), 785 (C-Cl Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.46 (s, 1H, OH), 7.37 (d, 2H, ArH), 7.17 (d, 2H, ArH), 6.72 (s, 2H, NH_2), 6.41 (s, 1H, ArH), 6.19 (s, 1H, ArH), 4.74 (s, 1H, 4-H), 2.10 (s, 3H, CH_3); MS: m/z 312(M^+), 297, 281, 211, 202, 186, 159, 133, 91, 77, 66.; Elemental Analysis for $C_{17}H_{13}ClN_2O_2$: Calculated: C, 65.29; H, 4.19; N, 8.96; %. Found: C, 65.27; H, 4.11; N, 8.95; %.

2-amino-4-(3-chlorophenyl)-7-hydroxy-5-methyl-4H-cromene-3-carbonitrile (3a10)
Yield: 80%; MP: 178-180^{0}C; IR (KBr, cm^{-1}): 3430 (O-H), 3344 (amine N-H str), 3040 (aromatic C–H str), 2180 (C≡N Str), 1295 (amine C-N Str), 785 (C-Cl Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.48 (s, 1H, OH), 7.34-7.38 (m, 4H, ArH), 6.70 (s, 2H, NH_2), 6.41 (s, 1H, ArH), 6.19 (s, 1H, ArH) 4.70 (s, 1H, 4-H), 1.95 (s, 3H, CH_3); MS: m/z 312(M^+), 297, 281, 211, 202, 186, 159, 133, 91, 77, 66.; Elemental Analysis for $C_{17}H_{13}ClN_2O_2$: Calculated: C, 65.29; H, 4.19; N, 8.96; %. Found: C, 65.09; H, 4.15; N, 8.88; %.

General method for the Synthesis of Ethyl-2-amino-7-hydroxy-5-methyl-4-(substituted phenyl)-4H-chromene-3- Carboxylate (3b 1-10).
0.01 mole of Substituted Cyanoarylidene 2b and 0.01 mole of 5-methyl resorcinol dissolve in absolute ethanol. Stirring the reaction mixture at room temperature, gradually added 0.03 mole of anhydrous potassium carbonate and stirring the reaction mixture at room temperature for 5-6 hours. After completion of reaction, pour the reaction mixture in dilute hydrochloric acid and neutralized it, separated the solid product filter, dry and crystallized from ethanol.

Ethyl-2-amino-7-hydroxy-5-methyl-4-phenyl-4H-chromene-3-carboxylate (3b1)
Yield: 56%; MP: 180-182^{0}C; IR (KBr, cm^{-1}): 3410 (O-H), 3298 (amine N-H str), 2971 (aromatic C–H str), 1665 (Ester C=O Str), 1511 (O-H in plane bending), 1240 (ethers C-O-C asym str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.45(s, 1H, OH), 7.34(s, 2H, NH_2), 6.70-6.75(m, 5H, Aromatic), 6.30(s, 2H, ArH), 4.75(s, 1H, ArH), 3.99(q, 3H, CH_2CH_3), 1.97(s, 3H, CH_3), 1.17-1.22(t, 2H, CH_2CH_3); MS: m/z 325(M^+), 310, 279, 248, 211, 144, 91, 77, 66.; Elemental Analysis for $C_{19}H_{19}NO_4$: Calculated: C, 70.14; H, 5.89; N, 4.31; %. Found: C, 70.16; H, 5.80; N, 4.25; %.

Ethyl-2-amino-7-hydroxy-4-(4-methoxyphenyl)-5-methyl-4H-chromene-3-carboxylate(3b2)
Yield: 60%; MP: 166-168^{0}C; IR (KBr, cm^{-1}): 3414 (O-H), 3298 (amine N-H str), 2972 (aromatic C–H str), 1660 (Ester C=O Str), 1512 (O-H in plane bending), 1245 (ethers C-O-C asym str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.49 (s, 1H, -OH), 7.44 (s, 2H, NH_2), 6.97-6.99 (d, 2H, Ar-H) 6.74-6.76 (d, 2H, Ar-H), 6.35 (s, 2H, Ar-H), 4.70(s, 1H, Ar-H), 3.99-4.04 (q, 3H, CH_2CH_3), 3.66 (s, 3H, OCH_3), 1.99(s, 3H, CH_3), 1.17-1.22 (t, 2H, CH_2CH_3); MS: m/z 355(M^+), 310, 294, 279, 248, 211, 188, 107, 91, 77, 66.; Elemental Analysis for $C_{20}H_{21}NO_5$: Calculated: C, 67.59; H, 5.96; N, 3.94; %. Found: C, 67.54; H, 5.96; N, 3.91; %.

Ethyl-2-amino-7-hydroxy-4-(2-methoxyphenyl)-5-methyl-4H-chromene-3-carboxylate(3b3)
Yield: 58%; MP: 174-176^{0}C; IR (KBr, cm^{-1}): 3412 (O-H), 3290 (amine N-H str), 2970 (aromatic C–H str), 1662 (Ester C=O Str), 1511 (O-H in plane bending), 1240 (ethers C-O-C asym str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.46 (s, 1H, -OH), 7.42 (s, 2H, NH_2), 7.12 (d, 1H, ArH), 6.77-6.79 (m, 3H, ArH), 6.35 (s, 2H, ArH), 4.70 (s, 1H, ArH), 3.99-4.04 (q, 3H, CH_2CH_3), 3.60 (s, 3H, OCH_3) 1.99 (s, 3H, CH_3), 1.17-1.22 (t, 2H, CH_2CH_3); MS: m/z 355(M^+), 310, 294, 279, 248, 211, 188, 107, 91, 77, 66.; Elemental Analysis for $C_{20}H_{21}NO_5$: Calculated: C, 67.59; H, 5.96; N, 3.94; %.Found: C, 67.58; H, 5.93; N, 3.90; %.

Ethyl-2-amino-7-hydroxy-5-methyl-4-(4-nitrophenyl)-4H-chromene-3-carboxylate (3b4)
Yield: 65%; MP: 148-150^{0}C; IR (KBr, cm^{-1}): 3438 (O-H), 3340 (amine N-H str), 3045 (aromatic C–H str), 1662 (Ester C=O Str), 1419 (Nitro N=O str), 1290 (amine C-N Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.50 (s, 1H, OH), 8.14 (d, 2H, ArH), 7.49 (d, 2H, ArH), 6.76 (s, 2H, NH_2), 6.31 (s, 1H, ArH), 6.30 (s, 1H, ArH), 4.56 (s, 1H, 4-H), 3.99-4.04 (q, 3H, CH_2CH_3), 1.92 (s, 3H, CH_3), 1.17-1.22 (t, 2H, CH_2CH_3); MS: m/z 370(M^+), 325, 279, 248, 211, 144, 91, 77, 66.; Elemental Analysis for $C_{19}H_{18}N_2O_6$: Calculated: C, 61.62; H, 4.90; N, 7.56; %. Found: C, 61.61; H, 4.95; N, 7.51; %.

Ethyl-2-amino-7-hydroxy-5-methyl-4-(2-nitrophenyl)-4H-chromene-3-carboxylate (3b5)
Yield: 65%; MP: 148-150^{0}C; IR (KBr, cm^{-1}): 3430 (O-H), 3345 (amine N-H str), 3045 (aromatic C–H str), 1660 (Ester C=O Str), 1419 (Nitro N=O str), 1290 (amine C-N Str); ^{1}H-NMR (DMSO-d$_6$): δ (ppm) 9.50 (s, 1H, OH), 7.96 (d, 1H, ArH), 7.72 (d, 1H, ArH), 7.50-7.52 (t, 2H, ArH), 6.76 (s, 2H, NH_2), 6.31 (s, 1H, ArH), 6.30 (s, 1H, ArH), 4.56 (s, 1H, 4-H), 3.99-4.04 (q, 3H, CH_2CH_3), 1.92 (s, 3H, CH_3), 1.17-1.22(t, 2H, CH_2CH_3); MS: m/z 370(M^+), 325, 279, 248, 211, 144, 91, 77, 66.; Elemental Analysis for $C_{19}H_{18}N_2O_6$: Calculated: C, 61.62; H, 4.90; N, 7.56; %. Found: C, 61.60; H, 4.85; N, 7.50; %.

Ethyl-2-amino-7-hydroxy-5-methyl-4-(p-tolyl)-4H-chromene-3-carboxylate (3b6)
Yield: 68%; MP: 192-194^{0}C; IR (KBr, cm^{-1}): 3441 (O-H), 3337 (amine N-H str), 3048 (aromatic C–H str), 2963 (methyl C-H Str), 1665 (Ester C=O Str), 1511 (O-H in plane bending), 1296 (amine C-N Str), 1240 (ethers C-O-C asym str)); ^{1}H-NMR (DMSO-d$_6$): δ (ppm) 9.59 (s, 1H, OH), 6.93-6.96 (d, 2H, ArH), 6.82-6.84(d, 2H, ArH), 6.72 (s, 2H, NH_2), 6.37 (s, 1H, ArH), 6.32 (s, 1H, ArH), 4.46 (s, 1H, 4-H), 3.99 (q, 3H, CH_2CH_3), 2.34 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 1.17-1.22 (t, 2H, CH_2CH_3); MS: m/z 339(M^+), 293, 278, 211, 202, 133, 91, 77, 66.; Elemental Analysis for $C_{20}H_{21}NO_4$: Calculated: C, 70.78; H, 6.24; N, 4.13; %. Found: C, 70.72; H, 6.21; N, 4.11; %.

Ethyl-2-amino-4-(4-bromophenyl)-7-hydroxy-5-methyl-4H-chromene-3-carboxylate (3b7)
Yield: 70%; MP: 200-2020C; IR (KBr, cm^{-1}): 3445 (O-H), 3340 (amine N-H str), 3049 (aromatic C–H str), 1666 (Ester C=O Str), 1290 (amine C-N Str), 642 (C-Br Str); ^{1}H-NMR (DMSO-d6): δ (ppm) 9.46 (s, 1H, OH), 7.85 (d, 2H, ArH), 7.12 (d, 2H, ArH), 6.72 (s, 2H, NH_2), 6.41 (s, 1H, ArH), 6.19 (s, 1H, ArH), 4.74 (s, 1H, 4-H), 4.01-4.04 (q, 3H, CH_2CH_3), 2.10 (s, 3H, CH_3), 1.17-1.22(t, 2H, CH_2CH_3); MS: m/z 403(M^+), 405(M+2), 357, 278, 248, 211, 144, 91, 77, 66.; Elemental Analysis for $C_{19}H_{18}BrNO_4$: Calculated: C, 56.45; H, 4.49; N, 3.46; %. Found: C, 56.36; H, 4.48; N, 3.40; %.

Ethyl-2-amino-4-(3-bromophenyl)-7-hydroxy-5-methyl-4H-chromene-3-carboxylate (3b8)
Yield: 75%; MP: 174-176^{0}C; IR (KBr, cm^{-1}): 3445 (O-H), 3340 (amine N-H str), 3049 (aromatic C–H str), 1660 (Ester C=O Str), 1292 (amine C-N Str), 642 (C-Br Str); ^{1}H-NMR (DMSO-d6): δ (ppm) 9.48 (s, 1H, OH), 7.22-7.30 (m, 4H, ArH), 6.70 (s, 2H, NH_2), 6.41 (s, 1H, ArH), 6.19 (s, 1H, ArH), 4.70 (s, 1H, 4-H), 4.04-4.06 (q, 3H, CH_2CH_3), 1.95 (s, 3H, CH_3), 1.17-1.22(t, 2H, CH_2CH_3); MS: m/z 403(M^+), 405(M+2), 357, 278, 248, 211, 144, 91, 77, 66.; Elemental Analysis for $C_{19}H_{18}BrNO_4$: Calculated: C, 56.45; H, 4.49; N, 3.46; %. Found: C, 56.41; H, 4.48; N, 3.40; %.

Table-1 Physical Data of all synthesised Compounds

Code	R	M.F.	M.W. (gm/mole)	M.P. (^{0}C)	% of yield
3a1	H	$C_{17}H_{14}N_2O_2$	278	205-207	60
3a2	4-OCH_3	$C_{18}H_{16}N_2O_3$	308	210-212	70
3a3	2-OCH_3	$C_{18}H_{16}N_2O_3$	308	198-200	65
3a4	4-NO_2	$C_{17}H_{13}N_3O_4$	323	172-174	66
3a5	2-NO_2	$C_{17}H_{13}N_3O_4$	323	158-160	61
3a6	4-CH_3	$C_{18}H_{16}N_2O_2$	292	170-172	72
3a7	4-Br	$C_{17}H_{13}BrN_2O_2$	356	148-150	78
3a8	3-Br	$C_{17}H_{13}BrN_2O_2$	356	160-162	75
3a9	4-Cl	$C_{17}H_{13}ClN_2O_2$	312	194-196	77
3a10	3-Cl	$C_{17}H_{13}ClN_2O_2$	312	178-180	80
3b1	H	$C_{19}H_{19}NO_4$	325	180-182	56
3b2	4-OCH_3	$C_{20}H_{21}NO_5$	355	166-168	60
3b3	2-OCH_3	$C_{20}H_{21}NO_5$	355	174-176	58
3b4	4-NO_2	$C_{19}H_{18}N_2O_6$	370	148-150	65
3b5	2-NO_2	$C_{19}H_{18}N_2O_6$	370	142-144	55
3b6	4-CH_3	$C_{20}H_{21}NO_4$	339	192-194	68
3b7	4-Br	$C_{19}H_{18}BrNO_4$	403	200-202	70
3b8	3-Br	$C_{19}H_{18}BrNO_4$	403	174-176	75
3b9	4-Cl	$C_{19}H_{18}ClNO_4$	359	176-178	72
3b10	3-Cl	$C_{19}H_{18}ClNO_4$	359	130-132	78

Ethyl-2-amino-4-(4-chlorophenyl)-7-hydroxy-5-methyl-4H-chromene-3-carboxylate (3b9)
Yield: 72%; MP: 176-178^{0}C; IR (KBr, cm^{-1}): 3445 (O-H), 3340 (amine N-H str), 3049 (aromatic C–H str), 1666 (Ester C=O Str), 1290 (amine C-N Str), 780 (C-Cl Str); ^{1}H-NMR (DMSO-d$_6$): δ (ppm) 9.46 (s, 1H, OH), 7.37 (d,

2H, ArH), 7.17 (d, 2H, ArH), 6.79 (s, 2H, NH_2), 6.41 (s, 1H, ArH), 6.19 (s, 1H, ArH), 4.74 (s, 1H, 4-H), 4.01-4.04 (q, 3H, CH_2CH_3), 2.10 (s, 3H, CH_3), 1.17-1.22(t, 2H, CH_2CH_3); MS: m/z 359(M^+), 361(M+2), 313, 298, 278, 248, 211, 144, 91, 77, 66.; Elemental Analysis for $C_{19}H_{18}ClNO_4$: Calculated: C, 63.42; H, 5.04; N, 3.89; %. Found: C, 63.41; H, 5.0; N, 3.80; %.

Ethyl-2-amino-4-(3-chlorophenyl)-7-hydroxy-5-methyl-4H-chromene-3-carboxylate (3b10)
Yield: 78%; MP: 130-132^{0}C; IR (KBr, cm^{-1}): 3445 (O-H), 3340 (amine N-H str), 3049 (aromatic C–H str), 1666 (Ester C=O Str), 1290 (amine C-N Str), 782 (C-Cl Str); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.48 (s, 1H, OH), 7.34-7.38 (m, 4H, ArH), 6.70 (s, 2H, NH_2), 6.41 (s, 1H, ArH), 6.19 (s, 1H, ArH), 4.70 (s, 1H, 4-H), 4.04-4.06 (q, 3H, CH_2CH_3), 1.95 (s, 3H, CH_3), 1.17-1.22 (t, 2H, CH_2CH_3); MS: m/z 359(M^+), 361(M+2), 313, 298, 278, 248, 211, 144, 91, 77, 66.; Elemental Analysis for $C_{19}H_{18}ClNO_4$: Calculated: C, 63.42; H, 5.04; N, 3.89; %. Found: C, 63.38; H, 5.01; N, 3.80; %.

Biological Evolution

Antimicrobial Screening

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards [17]. Serial dilutions of the test compounds and reference drugs were prepared in Muellere-Hinton agar. Drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL). Further progressive dilutions with melted Muellere-Hinton agar were performed to obtain the required concentrations.

In primary screening 1000 μg mL^{-1}, 500 μg mL^{-1} and 250 μg mL^{-1} concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution at 200 μg mL^{-1}, 100 μg mL^{-1}, 50 μg mL^{-1}, 25 μg mL^{-1}, 12.5 μg mL^{-1}, and 6.25 μg mL^{-1} concentration against all microorganisms.

Table-2 Minimal inhibitory concentration (MIC) of all synthesized compounds

Code	S.a.	S.p.	E.c.	P.a.	C.a.	A.n.	A.c.
3a1	200	100	100	100	250	1000	250
3a2	200	500	62.5	500	1000	500	500
3a3	100	200	500	500	250	>1000	>1000
3a4	250	62.5	250	500	>1000	>1000	>1000
3a5	500	100	100	125	500	>1000	1000
3a6	100	200	62.5	125	500	>1000	>1000
3a7	500	500	250	500	500	>1000	1000
3a8	500	62.5	250	250	250	200	200
3a9	500	500	100	250	500	500	>1000
3a10	500	500	100	250	250	1000	250
3b1	200	500	250	500	1000	500	>1000
3b2	500	100	62.5	100	500	500	>1000
3b3	250	500	500	500	200	500	200
3b4	200	100	100	500	500	1000	200
3b5	500	62.5	62.5	100	250	1000	1000
3b6	250	250	250	250	500	500	1000
3b7	250	500	500	500	250	>1000	>1000
3b8	500	100	500	250	1000	>1000	1000
3b9	500	500	1000	1000	500	1000	1000
3b10	500	250	500	500	1000	1000	1000

RESULTS AND DISCUSSION

2-benzylidenemalononitrial **2a** and ethyl-2-cyano-3-phenylacrylate **2b** were prepared in good yield according to the literature procedure. [16] The synthesis of new chromenes containing amino, cyano and ester functional groups as shown in reaction scheme. The reaction of orcinol with 2-benzylidenemalononitrial **2a** and ethyl-2-cyano-3-phenylacrylate **2b** in presence of anhydrous potassium carbonate using ethanol solvent to obtain 2-amino-7-hydroxy-5-methyl-4-substitute phenyl-4H-chromene-3-carbonitrile **3a1-10** and ethyl-2-amino-4-substuted iphenyl-7-hydroxy-5-methyl-4H-chromene-3-carboxylate **3b1-10**. All the compounds were obtained in good yield. These compounds were characterized on the basis of elemental and spectral analyses.

IR spectra of each compound showed a band for O–H stretching vibrations for intermolecular hydrogen bonding near 3430-3445 cm^{-1} while primary amine, nitrial and carbonyl of ester stretching shown at 3340 cm^{-1} , 2180 cm^{-1} and 1660 cm^{-1} respectively. In the case of 1H-NMR shown the chemical shift value of OH at near 9.48 δppm and primary amine was shown at near 6.70 δppm. All the title compounds showed [M+] of 100% intensity as the molecular ion peak. Compound containing chlorine showed isotopic peak at [M+2] of about 33% intensity to that of parent ion peak whereas bromo derivative showed isotopic peak at [M+2] of about equal intensity. The results of elemental analyses were found in good agreement with the calculated values.

CONCLUSION

Present study describes the synthesis of a series of 2-amino-7-hydroxy-5-methyl-4-substitute phenyl-4H-chromene-3-carbonitrile and ethyl-2-amino-4-substuted iphenyl-7-hydroxy-5-methyl-4H-chromene-3-carboxylate starting from the 2-benzylidenemalononitrial and ethyl-2-cyano-3-phenylacrylate. The compounds were characterized by modern analytical techniques such as CHN analyses, IR, Mass and proton NMR spectra. All the title compounds were screened for their in vitro antibacterial and antifungal activity against Streptococcus pyogenes, Staphylococcus aureus (Gram positive) and Escherichia coli, Pseudomonas aeruginosa (Gram negative) and three antifungal strains Candida albicans, Aspergillus Niger, Aspergillus clavatus taking ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin, and greseofulvin as standard drugs. Their minimum inhibitory concentrations (MIC) were determined. The results of antibacterial activity showed that compounds 3a2, 3a6, 3b2 and 3b5 give the good activity against gram negative bacteria of Escherichia coli using the ampiciline standard drug. 3a4, 3a8 and 3b5 give the good activity against gram positive bacteria of Streptococcus pyogenes using the ampiciline standard drug. Now in antifungal activity compounds 3a1, 3a3, 3a8, 3a10, 3b3, 3b5 and 3b7 give good activity against Candida albicans using the greseofulvin standard drug.

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