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Research Article

THE REACTIONS OF CINNAMONITRILE DERIVATIVES WITH ACTIVE HYDROGEN

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ABSTRACT

Naphthopyrans, naphthodipyrans and benzodipyrans were synthesized by the reaction of α-cyanocinnamonitriles with substituted naphthol and orcinol; polysubstituted benzopyranopyrimidines were also prepared.

Keywords: Naphthopyran, benzodipyran, benzopyranopyrimidine.

INTRODUCTION

Pyran and fused 4H-pyran derivatives have a fertiled source of biological important molecules possessing a wide spectrum of biological and pharmocological activities[1-5] such as, inhibition of influenza,, virus sialidases[6], mutagenic activity[7], activity as antiviral[8], and antiproliferation agents[9], sexheromones[10] and antitumor[11] and anti-inflammatory agent[12]. Naturally occurring naphthopyrans have a variety of interesting biological activities and physiological properties[13,14]. Pyrano[2,3-h] benzopyran has been used as the key intermediate for the synthesis of urea and thiourea derivatives, thioxo-imidazolidinedione, dithioxo-diazetidine and schiff's bases[15] and pharmacological activity[16-18]

EXPERIMENTAL

Melting points were taken on Gallen Kamp melting apparatus and are uncorrected. Infrared were obtained on Nexus 470-670-870. ^{1}H NMR spectra and ^{13}C run on JEOL-400 MHz. the mass spectra were recorded on Ms-δ5988 operating at 70 ev. 2400 CHN analyser.

General procedure for synthesis(3_{a-e}), (4_{a-h}), (5_{a-d})

A solution of substituted naphthol or orcinol (0.01 mol) in ethanol (30 ml) was treated with cinnamonitriles (0.01 mol) and piperidine (0.5 ml). the reactioin mixture was heated until completed precipitation [reactions times range 15 min-120 min.] The solid product which formed was collected by filtrations and recrystallized from a suitable solvent to give (3_{a-e}), (4_{a-h}) and 5_{a-d} (40-70%).

2-Amino-4-(2-thienyl)-6-chloro-3-thioamid-4H-naphtho [1,2-b] pyran-3a. Brown powder (dioxan); yield 60%, m.p. 195-197°C; IR (cm^{-1}) 3433, 3322 (2NH_2), 3055 (CH–aromatic), 1590 (C=C), 1110 (C=S), ^{1}H NMR δ_H: 5.22 (s, 1H, pyran CH), 6.18 (br, 4H,2 NH_2 exchangeable by D_2O), 7.80-7.16 (m, 8H-Ar–H); ^{13}C NMR δ_C (ppm): 29.8 (pyran C_4), 57.2 (pyran C_2), 116.8 (pyran C_5), 117.12-144.50 (Ar–C), 147.7 (pyran C_6) 160.7 (pyran C_2) 205.17 (C=S); Anal. Calcd. For $C_{18}H_{13}ClN_2OS_2$ (372.5): C, 57.98; H, 3.48; N, 7.51; S,17.18; found: C, 57.32 ; H, 3.50; N, 8.00; S, 17.50.

2-Amino-4-(p-chlorophenyl)-6-chloro-3-thioamid-4-H-naphtho [1,2-b] pyran 3b. Buff powder; yield 65% . m.p. 260-262°C; IR (cm^{-1}) 3400, 3318 (2NH_2), 3052 (CH–aromatic), 1112 (C=S), 1600 (C=C); ^{1}H NMR δ_H: 4.98 (s, 1H, pyran CH), 5.80 (s, 4H,2 NH_2, exchangeable by D_2O), 7.75-7.17 (m 9H, Ar–H). Anal. Calcd. For $C_{20}H_{14}Cl_2N_2OS$ (401): C, 59.85; H, 3.49; N, 6.98; S, 7.98; Found: C, 60.00; H, 3.40, N, 6.90, S,7.44.

2-Amino-3-benzoyl-6-chloro-4-(2-thienyl)-4H-naphtho[1,2-b]pyran 3c. Black crystal (ethanol); yield 60%; m.p. 210-212°C; IR (cm^{-1}) 3410, 3393 (NH_2), 3010 (CH–aromatic) 1680 (C=O), 1580 (C=C); ^{1}H NMR δ_H (ppm) 5.80 (s, 1H, pyran CH), 5.00 (s, 2H, NH_2 exchangeable by D_2O), 7.48-7.18 (m, 13H, Ar-

H); ^{13}C NMR δ_C (ppm): 30.11 (pyran C_4) 50.11 (pyran C_3), 117.80 (pyran C_5), 125.40 (C≡N), 114.20-148.11 (Ar–C), 148.12 (pyran C_6). 162.80 (pyran C_2), 200.07 (C=O). Anal. Calcd. For $C_{24}H_{16}ClNO_2$ S (417.5): C, 68.98; H, 3.83; N, 3.35; S,7.66 Found: C, 68.30; H, 4.00; N, 3.80;S,7.16.

2-Amino-3-benzoyl-6-chloro-4-(p-choloro phenyl) 4H-naphtho[1,2-b] pyran 3d. Black powder (ethanol); yield 62%; m.p. 150-152°C; IR (cm^{-1}) 3400, 3338 (NH_2), 3055 (CH–aromatic), 1685 (C=O), 1592 (C=C); ^{1}H NMR δ_H (ppm) 4.80 (s, 1H, pyran CH), 5.68 (s, 2H, NH_2 exchangeable by D_2O) 7.88-7.32 (m, 9H, ArH); Anal. Calcd. for: $C_{26}H_{17}Cl_2NO_2$ (446): C, 69.95; H, 3.81; N, 3.13; Found: C, 70.00; H, 3.33; N, 3.50.

Ethyl-2-amino-6-chloro-4-(2-thienyl)-4H-naphtha [1,2-b] pyran-3-carboxylate 3e. Brown crystal (ethanol) 70%; m.p. 135-137°C IR (cm^{-1}): 3330, 3350 (NH_2) 3020 (CH–aromatic), 2944 (CH–aliphatic), 1700 (C=O), 1580 (C=C) ^{1}H NMR δ_H (ppm): 1.21 (t, 3H, CH_3, J = 7.1 Hz), 4.04 (q, 2H, CH_2, J = 7.55 Hz), 5.42 (s, 1H, pyran CH), 6.22 (s, 2H, NH_2 exchangeable by D_2O), 7.28-7.86 (m, 8H, Ar–H), Anal. Calcd. for: $C_{20}H_{16}ClNO_3$ S (385.5) C, 62.25, H, 4.15; N, 3.63;S,8.30 . Found: C,62.50; H, 4.50; N, 4.00;S,8.00.

2,7-Diamino-4,5-di (2-thieny)-3,6-dithioamid 1,8-dihydronaphtho [2,1-b: 7,8-b'] dipyran 4a. Black crystal (ethanol); 60%; m.p. 170-172°C; IR (cm^{-1}): 3400, 3338 ($4NH_2$) 3055 (CH–aromatic), 1599 (C=C), 1112 (C=S); ^{1}H NMR δ_H (ppm): 4.88, 4.80 (2s, 4H, $2NH_2$) 5.52, 6.20 (2s, 4H, 2(S= C-NH2), 5.35, 5.22 (2s, 2H, pyran CH), 7.11-7.98 (m, 10H, ArH); m/z 548 (M^+, 13%), 237 (100%); Anal. Calcd. for $C_{26}H_{20}N_4O_2S_4$(548), C, 56.93; H, 3.64; N, 10.21; S, 23.35; Found : C, 57.00; H, 3.85; N, 10.00; S, 23.38.

2,7-Diamino-4,5-di(p-chlorophenyl)-3,6-dithioamid-1,8-dihydronaphtho [2,1-b: 7,8-b'] dipyran 4b; Buff powder (ethanol); yield, 65%; m.p. 200-202°C; IR (cm^{-1}): 3420, 3400 ($4NH_2$), 3100 (CH–aromatic) 1580 (C=C),1110(C=S); ^{1}H NMR δ_H (ppm): 4.88, 5.00(2s, 4H, $2NH_2$), 5.11, 5.32 (2s, 4H, 2NH2), 5.80, 6.01 (2s, 2H, pyran CH) 7.82-7.14 (m, 12H, Ar–H); m/z 605 (M^+, 3.00%), 237 (100%)' Anal. Calcd. for $C_{30}H_{22}Cl_2N_4O_2S_2$ (605), C, 59.50; H, 3.63; N, 9.25; S, 10.57; Found: C, 59.20; H, 3.60; N, 9.11; S, 10.55.

2,7-Diamino-3,6-di(benzoyl)-4,5-di(2-thienyl)-1,8-dihydronaphtho [2,1-b: 7,8-b'] dipyran 4_C. black crystal (methanol) yield 55%; m.p. 135-137°C, IR (cm^{-1}): 3400, 3330 (NH_2), 3055 (CH–aromatic) 1690 (C=O) 1550 (C=C); ^{1}H NMR δ_H (ppm) 4.42, 4.88 (2s, 4H, 2 NH_2), 5.80, 6.20 (2s, 2H, pyran CH) 7.00-7.48 (m, 20H, Ar–H); ^{13}C NMR δ_C (ppm) 114.00-147.11 (Ar–C), 205.00,218.00 (2C=O); m/z 638 (M^+ 0.3%), 284 (100%) Anal. Calcd. for : $C_{38}H_{26}N_2O_4S_2$ (638), C, 71.47; H, 4.07; N, 4.38, S, 10.03. Found: C, 71.00, H, 4.30, N, 4.40, S, 10.00.

2,7-Diamino-3,6-di(benzoyl)-4,5-di(p-chloro phenyl)-1,8-dihydro-naphtho [2,1-b: 7,8-b'] dipyran 4d. black powder (ethanol), yield 50%; m.p. 150-152°C; Ir (cm^{-1}) 3442, 3380 ($2NH_2$), 30100 (CH–aromatic) 1688 (2C=O), 1580 (C=C); ^{1}H NMR δ_H (ppm): 4.00, 4.32 (2s, 4H, 2 NH_2), 5.55, 6.11 (2s, 2H, pyran CH), 7.88-7.18 (m, 22H, Ar–H); Anal. Calcd. for: $C_{42}H_{28}Cl_2N_2O_4$ (695), C, 72.51; H, 4.02; N, 4.02;Found:C,72.30;H,4.00;N,3.88.

2,7-Diamino-4,5-di(2-thienyl)-1,8-dihydronaphtho[2,1-b:7,8-b']-3,6-dicarboxylate 4e. yellow crystal (ethanol); yield 66%; m.p. 175-177°C; IR (cm^{-1}), 3440, 3380 ($2NH_2$), 3010 (CH–aromatic), 1710 (2C=O); ^{1}H NMR δ_H (ppm): 1.30 (t, 6H,2 CH_3, J=7.97, Hz), 3.80 (q, 4H, $2CH_2$ J = 9.11 Hz), 4.20 (s, 4H, 2 NH_2), 5.11, 5.80 (2s, 2H, pyran CH), 7.84-7.17 (m, 10H, Ar–H); ^{13}C δ_C (ppm): 13.10 (CH_3–ester), 28.4 (C–4) 62.11 (CH_2-ester), 118.11-158.00 (Ar–C) 168.10,180.00(2C=O); m/z (574) (M^+, 3.18%) 230 (100). Anal cold. For: $C_{30}H_{26}N_2O_6S_2$ (574), C, 62.71; H, 4.52; N, 4.87; S, 11.14; Found : C, 62.33; H, 4.12; N, 4.42; S, 11.00.

2,7-Diamino-4,5-di(p-chlorophenyl)-1,8 dihydro naphtho [2,1-b: 7,8-b']-3,6-dicarboxylate 4f. buff powder (methanol); yield, 55%; m.p. 100-102°C; IR (cm^{-1}) 4438, 4400 ($2NH_2$), 30100 (CH-aromatic), 2900-2848(CH-aliphatic), 1710 (2C=O); ^{1}H NMR δ_H(ppm) 1.13 (t, 6H,2 CH_3 , j = 7.00 Hz), 4.84(q, 4H,2 CH_2, J = 11.12Hz), 5.44, 5.20 (2s, 4H, $2NH_2$), 6.02, 6.11 (2s, 2H, pyran CH), 7.88-7.13 (m, 12H, Ar–H); m/z 631 (M^+, 0.8) (237) (100%). Anal. Calcd. for: $C_{34}H_{28}Cl_2N_2O_6$ (631), C, 64.65; H, 4.43; N, 4.43; Found: C, 64.60; H, 4.40, N, 4.00.

2,7-Diamino-4,5-di(2-thienyl)-1,8-dihydro naphtho [2,1-b: 7,8-b']-3,6-dicarbonitrile 4g. yellow crystal (ethanol); yield, 55%; m.p. 135-137°C, IR (cm^{-1}): 4333, 4280, 4110 ($2NH_2$), 3010 (CH-aromatic), 2222 (2C≡N), 1558 (C=C); ^{1}H NMR δ_H (ppm): 4.44, 4.52 (2s, 4H, $2NH_2$) 7.11-7.48 (m, 10H, Ar–H) m/z 480 (M^+, 11.14) (217) (100%); Anal. Calcd. for: $C_{26}H_{16}N_4O_2S_2$ (480); C, 65.00; H, 3.33; N, 11.66; S, 13.33. Found : C, 65.30; H, 3.30; N, 11.50; S, 13.00.

2,7-Diamino-4,5-di(p-chlorophenyl)-1,8-dihydronaptho [2,1-b: 7,8-b']-3,6-dicarbonitrile 4h. Brown powder (ethanol); yield, 60%; m.p. 110-112°C. IR (cm^{-1}): 4442, 4320 ($2NH_2$), 3100 (CH-aromatic) 2218 (2C≡N), 1580

(C=C), ^{1}H NMR δ_H (ppm): 4.23, 4.44 (2s, 4H, $2NH_2$) 7.48-7.88 (m, 12H, Ar–H); m/z 537 (M^+, 8.20) 237 (100%)' Anal. Calcd. for $C_{30}H_{18}Cl_2N_4O_2$ (537), C, 67.03 H, 3.35; N, 10.42; Found: C, 67.50; H, 3.11; N, 10.50.

2,8-Diamino-4,10-di(p-chlorophenyl)-5-methyl-1, 7-dihydropyrano [2,3-h] benzopyran-3,9-dicarbonitrile 5a. Brown crystal (ethanol); yield 60%; m.p. 220-222°C; IR (cm^{-1}): 3405-3318 ($2NH_2$), 3070 (CH-aromatic) 2900 (CH-aliphatic), 2218 (2C≡N), 1580 (C=C); ^{1}H NNR δ_H (ppm): 1.13 (s, 3H, CH_3), 4.33 (s, 4H, $2NH_2$), 5.20 (s, 2H, CH-pyran), 7.28-7.82 (m, 8H, Ar–H); m/z 501 (M^+ 3.01%) 77 (100%); Anal. Calcd for $C_{27}H_{18}Cl_2O_2N_4$ (501): C, 64.67, H, 3.59; N, 11.17; Found: C, 64.30; H, 3.50; N, 11.00.

2,8-Diamino,4,10-di (p-methoxyphenyl)-5-methyl-1,7-dihydro-pyrano [2,3-h] benzo pyran-3,9-dicarboxylate 5_b brown powder (ethanol); yield 48%; m.p. 160-162°C; IR (cm^{-1}): 3370, 3264 ($2NH_2$), 3100 (CH-aromatic) 2900-2884 (CH-aliphatic) 1710 (2C=O), 1590 (C=C); ^{1}H NMR δ_H (ppm): 1.13 (t, 6H, $2CH_3$, J = 9.18 Hz), 1.88 (s, 3H, CH_3), 3.33 (s, 6H, $2(OCH_3)$), 4.20 (q, 2H, CH_2, J = 11.2 Hz), 4.20, (q, 2H, CH_2, J = 11.2 Hz), 4.80, 5.00 (2s, 4H, $2NH_2$, exchangeable by D_2O), 5.40, 5.22 (2s, 2H, two (CH) two pyran ring) 7.11-7.48 (m, 9H, Ar–H); m/z (M^+, 586) 78 (100%). Anal. Calcd for: $C_{33}H_{34}O_8N_2$ (586): C, 67.57; H, 5.80; N, 4.77; Found: C, 67.11, H, 5.90; N, 4.90.

2,8-Diamino-4,10-di(2-furyl)-5-methyl-1,7-dihydropyrano[2,3-h]benzo pyrano-3,9-dicarboxylate 5_C. black crystal (ethanol, Benzene; m.p. 360-362°C; IR (cm^{-1}) 3440, 3382 ($2NH_2$), 3032 (CH–aromatic), 2995-2883 (CH-aliphatic), 1720 (2C=O), ^{1}H NMR δ_H (ppm) : 1.18 (t, 6H, $2CH_3$, J = 7.11 Hz) 1.82 (s, 1H, CH_3), 4.00 (q, 4H, $2CH_2$, J = 11.08Hz), 4.20, 4.58 (2s, 4H, $2NH_2$), 5.48 (s, 2H, 2(CH) two pyran ring), 7.20-7.78 (m, 7H, Ar–H); m/z 506 (M^+, 3H) 77 (100%); Anal. Calcd. for: $C_{27}H_{26}O_8N_2$ (506): C, 64.03; H, 5.13; N, 5.53; Found: C, 64.00; H, 5.50; N, 5.80.

2,8-Diamino 3,9-di(benzoyl)-5-methyl-4,10-di(2- pyrrol) 1,7-dihydro pyrano [2,3-h] benzo pyran 5d. black powder (ethanol), m.p. 190-192°C; IR (cm^{-1}): 4000, 3620 ($2NH_2$), 3240 (2NH pyrrol) 3035 (CH-aromatic), 1690 (C=O), 1580 (C=C); ^{1}H NMR δ_H (ppm): 1.18 (s, 3H, CH_3), 4.50 (s, 4H, $2NH_2$), 5.55 (s, 2H, 2 (CH) two pyran ring), 5.76 (s, 2H, two pyrrol ring), 7.11-7.86 (m, 9H, Ar–H); m/z 568 (M^+ , 0.35%) 78 (100%); Anal. Calcd. for: $C_{35}H_{28}O_4N_4$ (568): C, 73.94; H, 4.92; N, 9.85; Found : C, 74.50; H, 4.80; N, 9.01.

2,8-Diamino-4,5,10, -trimethyl-pyrano [2,3-h] benzopyran-3,9-dicarbonitrile 6. Buff crystal (ethanol) yield 50%; m.p. 270-272°C; IR (cm^{-1}): 3900-3333 ($2NH_2$), 3033 (CH–aromatic), 2995-2870 (CH–aliphatic), 2222 (2C≡N); ^{1}H NMR (δ_H (ppm): 1.18, 2.28(2s, 9H, $3CH_3$), 6.82 (s, 4H, $2NH_2$), 5.80, 6.00 (2s, 2H, 2(CH) pyran ring), 7.48 (s, 1H, Ar–H); m/z (308) (M^+, 0.80) 77 (100%); Anal. Calcd. for: $C_{17}H_{16}O_2N_4$ (308): C, 66.23; H, 5.19; N, 18.18; Found: C, 66.00; H, 5.50; N, 18.10.

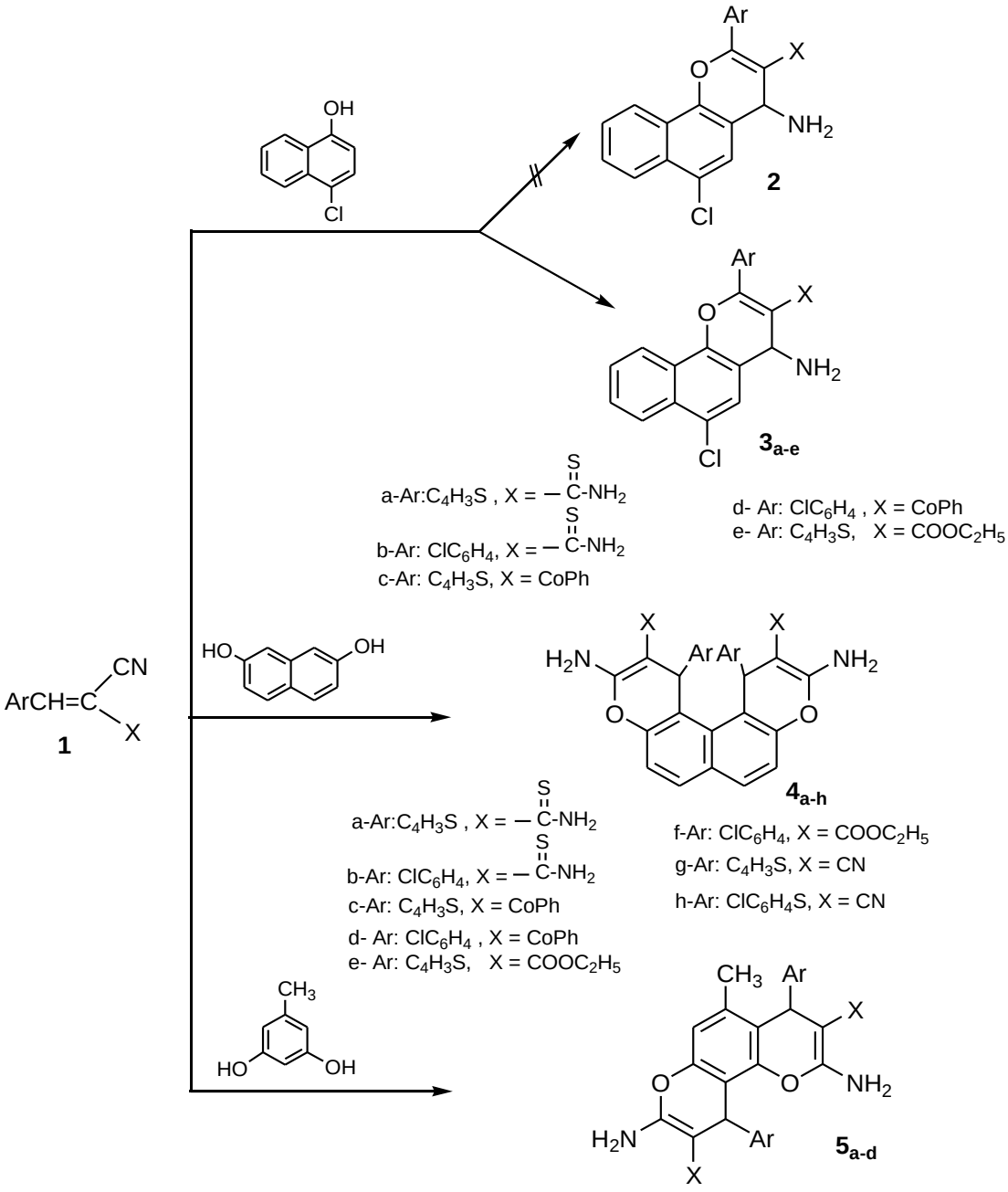
General procedure for compounds 7_a ,8_a

A mixture of 5_a (0.01) in formic acid (20 ml) or in formamide (20 ml) was refluxed for 8h. the solvent was removed under reduced pressure and the obtained solid was recrystallized from ethanol to give compound **7_a** and 8_a compound **7_a**: Brown crystal (ethanol); m.p. 120-122°C; IR (cm^{-1}): 4220 (2OH), 3280 (2NH), 3090 (CH-aromatic), 2920 (CH-alipatic), 1680 (2C=O); ^{1}H NMR δ_H (ppm): 1.13 (s, 3H, CH_3), 5.58, 5.20 (2s, 2H, 2(CH) two pyran ring), 7.11-7.48 (m, 9H, Ar–H), 8.11 (s, 2H, CH-two pyrimidine ring) 11.80 (s, 2H, 2NH, exchangeable by D_2O); m/z (557) M^+, 0.81%) 77(100%); Anal. Calcd. for: $C_{29}H_{18}Cl_2O_4N_4$(557):C, 62.47; H, 3.23; N, 10.05; Found: C, 62.30; H, 3.30; N, 10.00.

Compound **8_a**: Brown crystal (ethanol), yield 52%; m.p. 180-182°C; IR (cm^{-1}): 4220, 3380 ($2NH_2$), 3080 (CH–aromatic), 2992 (CH–aliphatic), 1648 (C=N), 1560 (C=C). ^{1}H NMR δ_H (ppm): 1.32 (s, 3H, CH_3). 3.80, 4.11 (2s, 4H, $2NH_2$), 5.11, 5.40 (2s, 2H, 2(CH) two pyran ring)7.48-7.18 (m,9H, Ar-H), 8.44, 8.69(2s, 2H, 2(CH) two pyrimidine rings) m/z 555 (M^+ 1.18%) (78) (100%); Anal. Calcd. for : $C_{29}H_{20}Cl_2O_2N_6$ (555), C, 62.70; H, 3.60; N, 15.13; found: C, 62.12; H, 3.40; N, 15.50.

RESULTS AND DISCUSSION

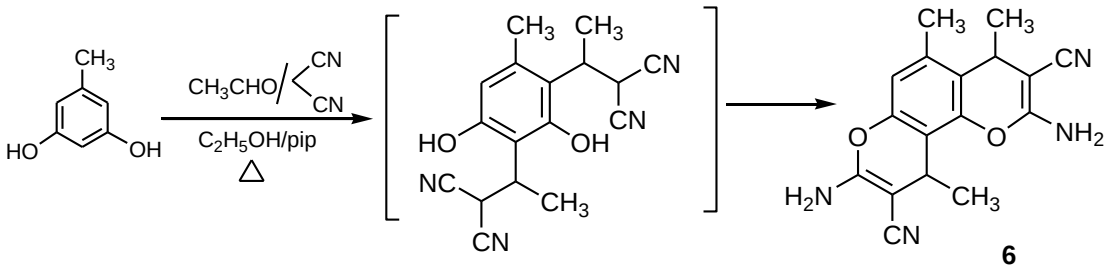
The reaction of cinnamonitriles with active hydrogen reagents has been utilized extensively in the synthesis of 4H-pyran[19]. Thus condensation of various substituted α-cyanocinnam nitriles with 4-chloro-1-naphthol in ethanolic piperidine afforded 1:1 adducts. On the basis of analytical and ^{1}H NMR data, structure **2** was excluded[19]. Structure 3 was established on the basis of the ^{1}H NMR spectra, each of which revealed a one proton singlet at δ 5.25-4.85 corresponding to the pyran C–H proton in 4H naphtho [1,2-b] pyran derivatives **3_{a-e}**. ^{13}C NMR spectrum of **3_a** showed **18** distinct resonance in agreement with the proposed structure (scheme 1).



Scheme. (1):

Reaction of naphthalene-2,7-diol or orcinol in the molar ratio 1:1 under reflux with cinnamonitriles afforded 2:1 adducts the naphtha [2,1-b: 7,8-b'] dipyran **4**$_{a-h}$ and pyrano [2,3-h] benzopyran derivatives **5**$_{a-d}$. Structures **4**$_{a-h}$ and 5$_{a-d}$ were established on the basis of spectral data.

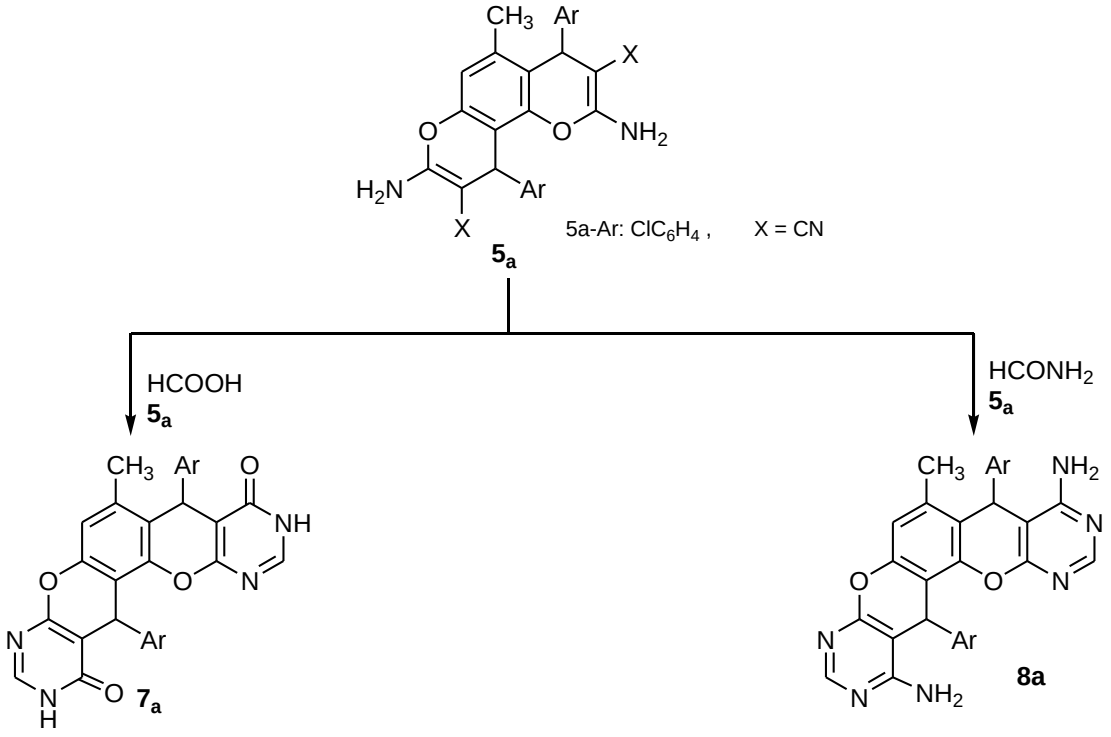
The synthesis of pyrano [2,3-h] benzopyran via multicomponent reaction has attracted significant interest because of their biological and pharmacological activities[20]. Subsequently, the multicomponent reactions of orcinol, malononitrile and acetaldehyde in presence of piperidine in refluxing ethanol gave a new dihydropyrans fused with benzene nucleus 6 (scheme 2).



Scheme (2)

The structures of the products were deduced from their IR and ^{1}H NMR spectral data. The ^{1}H NMR spectral of **6** exhibited singlets identified as methyl groups (δ = 1.18, δ = 2.28), 5.80, 6.00 (2 s, 2H, 2 (CH) two pyran rings.

When $\mathbf{5_{a,b}}$ were refluxed with formic acid or formamide, they afforded benzodipyrano [2,3-d] pyrimidine derivatives $\mathbf{7_a}$ and $\mathbf{8_a}$. The structure of $\mathbf{7_a}$ and $\mathbf{8_a}$ were determined from their correct elemental analysis and spectral data. Both $\mathbf{7_a}$ or $\mathbf{8_a}$ showed the absence of (C≡N) in IR spectrum. The ^{1}H NMR spectrum of 7a exhibited broad singlet identified as (2NH) groups at (δ = 11.80) while compound 8_a exhibited two singlet identified as (NH_2) groups at (δ = 3.80, 4.11).



Scheme. (3):

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