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Green and Efficient Synthesis of a Novel Series of Indeno-Fused Pyrido [2,3-d] Pyrimidines Using Choline Hydroxide as Eco-Friendly Catalyst in Water

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ABSTRACT
A series of 13 aryl indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-(3H,5H,11H)-triones, 8 of which are new, were synthesized regioselectively in high yields by a three-component reaction of 1,3-indanedione, an araldehyde and 6-aminopyrimidin-2,4(1H,3H)-dione in the presence of choline hydroxide as catalyst in water. The reaction conditions were mild and did not require additional catalysts. Given the inexpensive, nontoxic, and recyclable nature of the choline hydroxide, these reaction conditions are simple to carry out and environmentally friendly.

Keywords: three-component reaction (3CR), aromatic aldehydes, 1,3-indanedione, 6-aminopyrimidin-2,4(1H,3H)-dione, choline hydroxide

INTRODUCTION

The elimination of volatile and toxic organic solvents in chemical processes represents very powerful procedures for green chemical technology from both the economic and synthetic points of view [1]. They have many advantages, such as reduced pollution, lower cost, and simplicity in processing, which are beneficial to the industry as well as to the environment.

In multicomponent approaches, complex products and biologically active molecules are synthesized from readily available starting materials in a single step process. From this point of view, MCRs have emerged as green and powerful tools in organic synthesis and drug discovery [2, 3]. Also, in MCRs, by selecting the different starting materials, a new class of compounds can be synthesized which may show interesting properties [4].

Pyridopyrimidines are nitrogen-bearing heterocyclic compounds which have various pharmaceutical applications. In particular, pyrido[2,3-*d*]pyrimidine derivatives show variable biological activities such as anticancer agents inhibiting dihydrofolate reductases or tyrosine kinases, [5-7] antitumor, [8, 9] antiviral, [10] antihistaminic, [11] anti-inflammatory, [12] antibacterial, [13-17] and also act as cyclin-dependent kinase 4 inhibitors [18]. This structural moiety is present in ramastine (anti-allergic) [19] and pirenperone (tranquilizer) [20]. As a result, the compounds of this class have attracted considerable interests for research. Several MCR methods have been reported for the synthesis of pyrido[2,3-d]pyrimidines [21-26]. Although most of these methods offer distinct advantages, some of them still have their own limitations in terms of yields, longer reaction times and difficult work-up. In some cases, the catalysts used are harmful to environment and cannot be reused. Therefore, an efficient method for the preparation of pyrido [2,3-*d*]pyrimidine derivatives is still desirable.

In continuation of our ongoing program for the synthesis of heterocyclic compounds, [27-33] herein, we report an efficient approach for one-pot regioselectively synthesis of Indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,11*H*)-trione derivatives 4.

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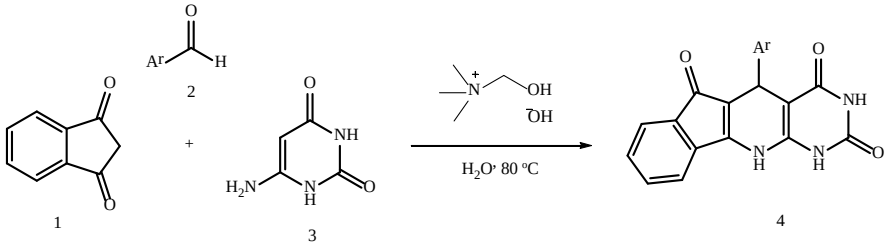

Figure 1. Component Scheme

Table 1. Conditions

Entry	Conditions	Time (min)	Yield (%)
1	ChOH/(1 mmol)-H_2O (5ml)	15	95
2	Et_3N (50 mol%)- H_2O (5 ml)	70	62
3	Piperine (50 mol%)- H_2O (5 ml)	80	59
4	L-Proline (50 mol%)- H_2O (5 ml)	65	36
5	DBU (50 mol%)- H_2O (5 ml)	55	53
6	DABCO (50 mol%)- H_2O (5 ml)	90	70
7	$(EtOH)_3N$ (50 mol%)- H_2O (5 ml)	60	29

Table 2. Product

Entry	Ar group	Product	Time (min)	Yield (%)[b]	Melting Point m.p. (°C)/Lit. m.p. (°C) [Ref]
1	4-OCH_3 C_6H_4	4a	40	89	323-325/324-326[37]
2	4-NO_2 C_6H_4	4b	25	95	325-327/328-330[37]
3	4-Br C_6H_4	4c	30	92	328-330/327-329[37]
4	2,4-Cl C_6H_3	4d	30	92	320-322/this work
5	3-NO_2 C_6H_4	4e	35	91	318-320/320-322[37]
6	3-Cl-4-NO_2 C_6H_3	4f	28	90	333-335/this work
7	4-F C_6H_4	4g	37	88	327-329/325-327[37]
8	2-OH-3-OCH_3 C_6H_3	4h	55	87	319-321/this work
9	4-OH C_6H_4	4i	45	85	320-322/this work
10	2-Br C_6H_4	4j	40	89	315-317/this work
11	4-CN C_6H_4	4k	35	91	326-328/this work
12	2-OH-5-NO_2 C_6H_3	4l	42	89	331-333/this work
13	2-OH-5-Br C_6H_3	4m	50	90	314-316/this work

RESULTS AND DISCUSSION

Our proposed route to the pentacyclic target compounds 4 involved a base-catalyzed condensation between 1,3-indanedione 1, an araldehyde 2 and 6-aminopyrimidin-2,4(1H,3H)-dione 3, a 3-component reaction we hoped would occur in one pot (Scheme 1). Initially, the yields of a model 3-component reaction using 4-bromobenzaldehyde (2; Ar = 4-Br-C6H4) in reaction with 1,3-indanedione 1 and 6-aminopyrimidin-2,4(1H,3H)-dione 3 catalyzed by various base/solvent combinations at 80 °C were determined and the results are shown in **Table 1**.

When the reaction was carried out in the presence of choline hydroxide/water, the product was the desired pentacyclic compound (4c; Ar = 4-Br-C_6H_4) and the reaction had occurred in excellent yield (95%) (entry1). None of the other catalysts (entries 2-7) gave equivalent yields, the best giving only 70% (entry 6). It was thus clear that our one-pot method had worked very well and the choline hydroxide catalyst was thus adopted as the optimum catalyst.

Using the optimum conditions, 12 other aldehydes 2 were reacted with 1,3-indanedione 1 and 6-aminopyrimidin-2,4(1H,3H)-dione 3 to afford the corresponding aryl indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H,5H,11H)-trione derivatives (4a,c-m) and the results are shown in **Table 2**.

As can be seen, very good yields of products were obtained for aldehydes bearing either electron-withdrawing or electron donating groups.

The structures of products were deduced from their IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and CHN analysis data. For example, the IR spectrum of 4a showed absorptions at 3173-3485 cm^{-1} for NH groups and 1708, 1672 cm^{-1} for carbonyl groups, indicating the presence of these functional groups in the proposed structure. The ^{1}H NMR

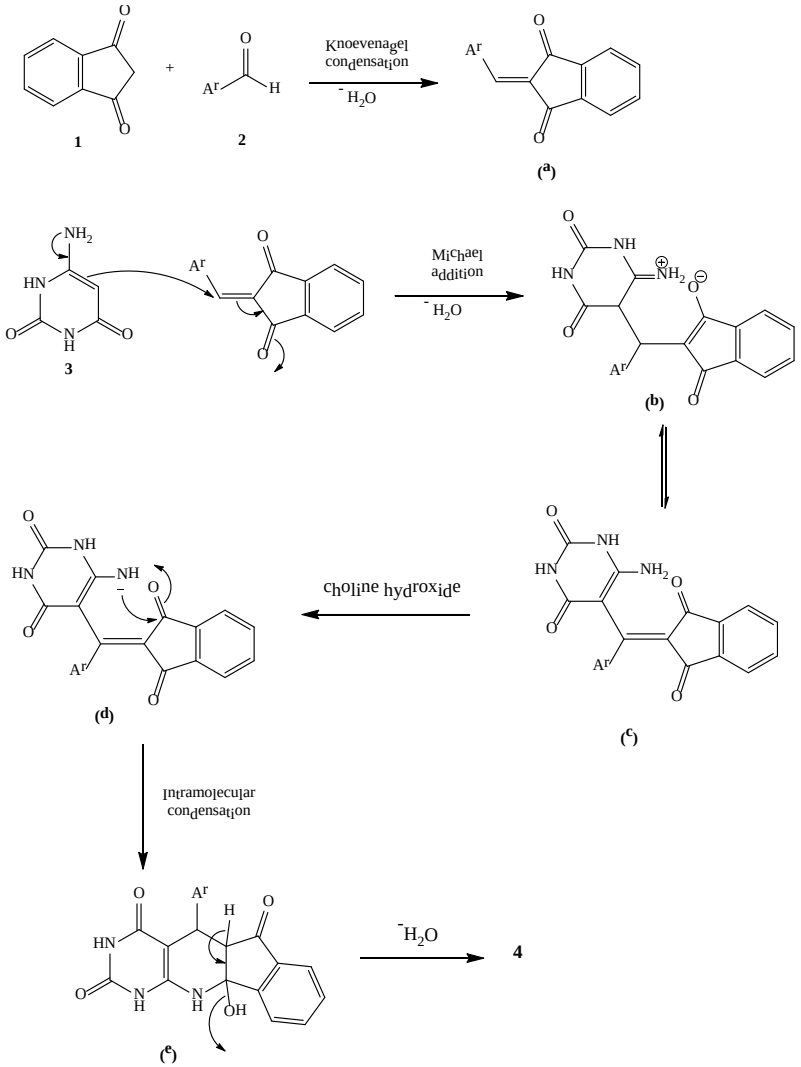

Figure 2. Mechanism for the reaction

spectrum of 4a exhibited a singlet for the (OCH_3) group at δ = 3.84 ppm; also a singlet at δ = 4.85 for the methine group in dihydropyridine are observable. Two doublets at δ = 6.92 and 6.95 ($^3J_{HH}$ = 12 H_z) and multiplet signals at 7.61-7.88 ppm for the aromatic hydrogens. Finally, three singlet signals at δ = 10.27-11.25 ppm for NH hydrogen atoms. The ^1H decoupled ^{13}C NMR spectrum of 4a showed 19 resonances. Elemental analysis confirmed the amounts of C, H, and N in the final product. Compounds 4a-m gave M^+ ions, as expected.

We proposed the following mechanism for the reaction (Scheme 2). On the basis of this mechanism, choline hydroxide is an effective catalyst for the formation of intermediate (a), which readily prepares in situ from Knoevenagel condensation of aldehyde 2 with indandion 1. Then, 6-aminopyrimidin-2,4(1H,3H)-dione 3 attacks the intermediate (a) and affords intermediate (c) *via* Michael addition. The intermediate (d) in the precence of choline hydroxide undergoes intramolecular cyclization with participation of the amino function and one of the 1,3-indandione carbonyl group to form (e). Then the removal of water from (e) forms the aryl indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,11*H*)-trione derivatives (4a-m) as the targeted molecules.

In this report, we have developed a rapid, efficient, and versatile procedure for the synthesis of indeno fused pyrido[2,3-*d*]pyrimidine derivatives 4a–m in a regiochemical manner by using an eco-friendly and biodegradable catalyst based on choline hydroxide. The advantages of this method are operational simplicity, green medium, short reaction times and high yields.

EXPERIMENTAL

All melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser at the analytical laboratory of Islamic Azad University, Yazd branch. Mass spectra were recorded on a Finnigan-Mat 8430 mass spectrometer operating at an ionization potential of 70

eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. NMR spectra were obtained on a Bruker DRX-400 Avance spectrometer (^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) in DMSO-d_6 using TMS as an internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

GENERAL PROCEDURE:

1,3-indanedione, (0.25 mmol), an aromatic aldehyde (0.25 mmol), and 6-aminopyrimidin-2,4(1H,3H)-dione (0.25 mmol) were added to choline hydroxide (0.25 mmol). The resulting mixture was stirred in water for the specified time (**Table 2**) at 80 °C. After reaction completion, (TLC, ethyl acetate/n-hexane, 2:1), the reaction mixture was filtered and the solid residue recrystallized from ethanol to obtain the pure product. All the products identified by IR, ^{1}H NMR and ^{13}C NMR spectral data and by comparison of their melting points with literature reports.

5-(4-methoxyphenyl)-5,11-dihydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4a).**

Red powder (89%), m.p. 323-325°C; IR (KBr) (ν_{max}, cm^{-1}): 3485, 3370, 3173 (3NH), 1708, 1680, 1672 (3C=O). ^{1}H NMR: δ 3.84 (3H, s, OCH_3), 4.85 (1H, s, CH), 6.92, 6.95 (4H, 2d, $^3J_{HH}$ = 12 Hz, aromatic), 7.61-7.88 (4H, m, aromatic), 10.27-11.25 (3H, s, 3NH) ppm; ^{13}C NMR: δ 28.9 (CH), 55.2 (OCH_3), 91.9, 110.6, 115.1, 115.6, 121.2, 128.9, 129.8, 130.7, 132.5, 133.1, 133.3, 136.2, 136.3, 144.7, 150.3, 153.5, (aromatic and olefinic carbons), 156.1, 163.3, 191.4 (3C=O) ppm; MS (m/z, %): 373 (34); Analyses: Calcd. for $C_{21}H_{15}N_3O_4$: C, 67.56; H, 4.05; N, 11.25; Found: C, 67.44; H, 3.99; N, 11.36; %.

5-(4-nitrorophenyl)-5,11-dihydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4b).**

Red powder (95%), m.p. 325-327 °C; IR (KBr) (ν_{max}, cm^{-1}): 3465, 3220, 3130 (N-H), 1700,1663, 1539, 1336 (NO_2) cm^{-1}; ^{1}H NMR: δ 4.84 (1H, s, CH), 7.30-7.52 (4H, m, aromatic) 7.58, 8.12 (4H, 2d, $^3J_{HH}$ = 12 Hz, aromatic), 10.42-11.01 (3H, 3s, 3NH); ^{13}C NMR: 34.5 (CH), 90.5, 108.6, 119.8, 122.8, 123.7, 129.5, 129.6, 130.8, 131.0, 132.7, 132.8, 136.1, 145.6, 146.4, 150.2, 153.0 (aromatic and olefinic carbons), 154.4, 163.3, 191.0 (3C=O) ppm; MS (m/z, %): 388 (38); Analyses: Calcd. for $C_{20}H_{12}N_4O_5$: C, 61.86; H, 3.11; N, 14.43. Found C, 61.83; H, 3.09; N, 14.41; %.

5-(4-bromophenyl)-5,11-dihydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4c).**

Red powder (92%), m.p. 328-330°C; IR (KBr) (ν_{max}, cm^{-1}): 3420, 3215, 3135 (NH), 1698, 1668, 1657 (C=O) cm^{-1}. ^{1}H NMR: δ 4.67 (1H, s, CH), 7.24, 7.44 (2H, 2d, $^3J_{HH}$ = 12 Hz, aromatic), 7.28-7.66 (4H, m, aromatic), 10.27-10.97 (3H, s, 3NH) ppm; ^{13}C NMR: 33.8 (CH), 91.0, 109.4, 119.6, 121.3, 130.4, 130.9, 131.0, 131.3, 132.6, 132.9, 133.4, 135.9, 136.4, 145.0, 145.2, 150.2 (aromatic and olefinic carbons), 154.0, 163.3, 191.2 (3C=O) ppm; MS (m/z, %): 388 (38); Analyses: Calcd. for $C_{20}H_{12}N_3O_3Br$: C, 56.89; H, 2.86; N, 9.95. Found C, 56.80; H, 2.59; N, 10.03; %.

5-(2,4-dichlorophenyl)-5,11-dihydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4d).**

Red powder (92%), m.p. 320-322°C; IR (KBr) (ν_{max}, cm^{-1}): 3450, 3165, 3150(NH), 1703, 1687, 1627(C=O) cm^{-1}. ^{1}H NMR: δ 5.08 (1H, s, CH), 7.34 (1H, s, aromatic), 7.48 (1H, dd, J_{HH} = 8.4 Hz, J_{HH} = 2.0 Hz, aromatic), 7.64 (1H, s, aromatic), 7.66 (1H, s, aromatic), 7.70 (1H, d, J = 2.0 Hz, 1H), 7.79 (1H, dt, J = 8.2 Hz, J = 2 Hz, aromatic), 7.87 (1H, s, aromatic), 7.96 (1H, s, aromatic), 10.38-10.92 (3H, s, 3NH) ppm; ^{13}C NMR: 29.2 (CH), 90.7, 107.2, 119.6, 124.1, 128.6, 128.8, 130.8, 131.0, 132.1, 132.6, 132.9, 133.4, 136.4, 141.9, 142.1, 150.2 (aromatic and olefinic carbons), 154.4, 163.0, 190.9 (3C=O) ppm; MS (m/z, %): 411 (33); Analyses: Calcd. for $C_{20}H_{11}N_3O_3Cl_2$: C, 58.27; H, 2.69; N, 10.19. Found C, 58.23; H, 2.65; N, 10.16; %.

5-(3-nitrophenyl)-5,11-dihydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4e).**

Red powder (91%), m.p. 318-320°C; IR (KBr) (ν_{max}, cm^{-1}): 3510, 3330, 3180 (NH), 1711, 1655, 1617 (C=O), 1519, 1339 (NO_2) cm^{-1}; ^{1}H NMR: δ 4.86 (1H, s, CH), 7.29 (1H, d, J = 7.2 Hz, aromatic), 7.38 (1H, dt, J = 7.2 Hz, J = 1.6 Hz, aromatic), 7.49 (1H, s, aromatic), 7.56 (1H, t, J = 8.0 Hz, aromatic), 7.78 (1H, t, J = 8.0 Hz, aromatic), 8.04 (1H, dd, J = 8.0 Hz, J = 1.2 Hz, aromatic), 8.09 (1H, s, aromatic), 10.35-11.01(3H, s, 3NH) ppm; ^{13}C NMR: 34.3 (CH), 90.6, 108.7, 119.8, 121.0, 121.8, 122.6, 130.0, 131.1, 132.7, 132.8, 133.5, 135.1, 136.4, 145.5, 147.6, 150.2 (aromatic and olefinic carbons), 154.4, 163.3, 191.2 (3C=O) ppm; MS (m/z, %): 388 (35); Analyses: Calcd. for $C_{20}H_{12}N_4O_5$: C, 61.86; H, 3.11; N, 14.43 Found C, 61.77; H, 3.08; N, 14.52; %.

5-(4-chloro-3-nitrophenyl)-5,11-dihydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4f).**

Red powder (90%), m.p. 333-335°C; IR (KBr) (ν_{max}, cm^{-1}): 3445, 3215, 3165(NH), 1706, 1684, 1663 (C=O), 1526, 1337 (NO_2) cm^{-1}; ^{1}H NMR: δ 4.83 (1H, s, CH), 7.30-7.95 (7H, aromatic), 10.44-11.01 (3H, s, 3NH) ppm; ^{13}C NMR: 30.5 (CH), 90.1, 108.2, 119.9, 124.9, 127.6, 131.1, 131.4, 132.7, 132.9, 133.7, 136.0, 136.5, 142.1, 146.5, 147.9, 150.2 (aromatic and olefinic carbons), 154.5, 163.3, 191.2 (3C=O) ppm; MS (m/z, %): 422 (30); Analyses: Calcd. for; $C_{20}H_{11}N_4O_5Cl$: C, 56.82; H, 2.62; N, 13.25 Found C, 56.70; H, 2.55; N, 13.33; %.

5-(4-fluorophenyl)-5,11-dihydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4g).**

Red powder (88%), m.p. 327-329°C; IR (KBr) (ν_{max}, cm^{-1}): 3440, 3220, 3125(NH), 1697, 1673, 1659(C=O) cm^{-1}; ^{1}H NMR: 4.70 (1H, s, CH), 7.07 (2H, t, J=8.4Hz, aromatic), 7.22 (1H, d, J = 8.8 Hz, aromatic), 7.36 (1H, t, J=8.4Hz, aromatic), 7.44 (2H, d, J = 8.0 Hz, aromatic), 7.65 (1H, d, J = 7.2 Hz, aromatic), 10.23-10.96 (3H, s, 3NH) ppm; ^{13}C NMR: 33.4 (CH), 91.3, 109.8, 115.2 (J_{CF} = 21 Hz, C^{ortho}), 119.6, 129.9, 129.9, 130.5 (J_{CF} = 9 Hz, C^{meta}), 130.9, 132.6, 133.4,

136.2, 140.6 (J_{CF} = 2 H_Z, C^{ortho}), 145.1, 150.2, 157.9 (J_{CF} = 246 H_Z, C^{ipso}), (aromatic and olefinic carbons), 153.9, 163.3, 191.3 (3C=O) ppm; MS (m/z, %): 361 (41); Analyses: Calcd. for; $C_{20}H_{12}N_3O_3F$: C, 66.48; H, 3.35; N, 11.63 Found C, 66.41; H, 3.29; N, 11.59; %.

5-(2-hydroxy-3-methoxyphenyl)-5,11-dihydro-1H-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4h).**

Red powder (87%), m.p. 319-321°C; IR (KBr) (ν_{max}, cm^{-1}): 3485, 3275, 3185 (NH), 3215 (OH), 1704, 1674, 1657 (C=O) cm^{-1}; ^1H NMR: δ 4.88 (1H, s, CH), 6.65 (2H, d, *J*=7.6H_Z, aromatic), 6.73 (1H, t, *J* = 8.8 H_Z, aromatic), 7.27 (1H, d, *J* = 8.8 H_Z, aromatic), 7.37 (1H, dt, *J* = 7.2 H_Z, *J* = 1.2 H_Z, aromatic), 7.49 (3H, m, aromatic), 8.78 (1H, br, OH), 10.24-11.04 (3H, s, 3NH) ppm; ^{13}C NMR: 28.9 (CH), 91.4, 109.6, 110.4, 119.3, 119.3, 121.2, 121.8, 130.7, 132.4, 132.5, 133.1,136.4, 144.3, 145.5, 148.7, 150.0 (aromatic and olefinic carbons), 154.6, 164.4, 191.2 (C=O) ppm; MS (m/z, %): 389 (44); Analyses: Calcd. For $C_{21}H_{15}N_3O_5$: C, 64.78; H, 3.88; N, 10.79 Found C, 64.89; H, 3.79; N, 10.68; %.

5-(4-hydroxyphenyl)-5,11-dihydro-1H-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4i).**

Red powder (85%), m.p. 320-322°C; IR (KBr) (ν_{max}, cm^{-1}): 3470, 3281, 3150(NH), 3211 (OH), 1707, 1682, 1645(C=O) cm^{-1}; ^1H NMR: δ 4.57 (1H, s, CH), 6.62 (2H, d, *J* = 12 H_Z, aromatic), 7.11 (2H, d, *J* = 12 H_Z, aromatic), 7.28 (2H, d, *J* = 6.8 H_Z, aromatic), 7.37 (1H, dt, *J* = 8.8 H_Z, *J* = 0.8 H_Z, aromatic), 7.40 (1H, d, *J*=6.8H_Z, aromatic), 7.47 (1H, dt, *J* = 8.8 H_Z, *J* = 0.8 H_Z, aromatic), 9.19 (1H, s, OH), 10.12-10.91 (3H, s, 3NH) ppm; ^{13}C NMR: 32.9 (CH), 91.9, 110.6, 115.1, 115.6, 121.2, 129.0, 129.9, 130.7, 132.6, 133.0, 133.2, 136.3, 136.4, 144.7, 150.3, 153.5 (aromatic and olefinic carbons), 156.2, 163.3, 191.4 (C=O) ppm; MS (m/z, %): 359 (43); Analyses: Calcd. For $C_{20}H_{13}N_3O_4$: C, 66.85; H, 3.65; N, 11.69. Found C, 66.71; H, 3.59; N, 11.73; %.

5-(2-bromophenyl)-5,11-dihydro-1H-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4j).**

Red powder (89%), m.p. 315-317°C; IR (KBr) (ν_{max}, cm^{-1}): 3441, 3215, 3185 (NH), 1708, 1680, 1659 (C=O) cm^{-1}; ^1H NMR: δ 5.10 (1H, s, CH), 7.07-7.54 (8H, m, aromatic), 10.24-10.88 (3H, s, 3NH) ppm; ^{13}C NMR: 35.0 (CH), 91.4, 107.2, 119.5, 124.1, 127.4, 128.0, 129.9, 130.9, 131.8, 132.6, 132.8, 133.6, 136.4, 140.7, 145.4, 150.2 (aromatic and olefinic carbons), 161.2, 163.0, 190.9 (3C=O) ppm; MS (m/z, %): 421 (41); Analyses: Calcd. For $C_{20}H_{12}N_3O_3Br$: C, 56.89; H, 2.86; N, 9.95 Found C, 56.77; H, 2.82; N, 10.02; %.

5-(4-cyanophenyl)-5,11-dihydro-1H-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4k).**

Red powder (91%), m.p. 326-328°C; IR (KBr) (ν_{max}, cm^{-1}): 3473, 3232, 3151 (NH), 2224 (CN), 1703, 1679, 1650 (C=O) cm^{-1}. ^1H NMR: δ 4.78 (1H, s, CH), 7.23-7.71 (4H, m, aromatic), 7.72, 7.87 (4H, 2dm, *J* = 12H_Z, aromatic), 10.38-10.99 (3H, s, 3NH) ppm; ^{13}C NMR: 34.6 (CH), 90.5, 107.0, 109.4, 119.5, 119.7 (CN), 129.3, 130.6, 131.0, 131.5, 132.5, 132.7, 132.9, 133.5, 136.4, 145.5, 149.6, 150.2 (aromatic and olefinic carbons), 154.4, 163.3, 191.1 (3C=O) ppm; MS (m/z, %): 368 (37); Analyses: Calcd. For $C_{21}H_{12}N_4O_3$: C, 68.48; H, 3.28; N, 15.21. Found C, 68.37; H, 3.22; N, 15.30; %.

5-(2-hydroxy-5-nitrophenyl)-5,11-dihydro-1H-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4l).**

Red powder (89%), m.p. 331-333°C; IR (KBr) (ν_{max}, cm^{-1}): 3480, 3270, 3110 (NH), 2216 (OH), 1708, 1662, 1621(C=O), 1540, 1340 (NO_2) cm^{-1}. ^1H NMR: δ 4.60 (1H, s, CH), 7.62-8.33 (7H, m, aromatic), 10.93 (1H, s, OH), 11.45-12.36 (3H, s, 3NH) ppm; ^{13}C NMR: 19.0 (CH), 96.6, 107.2, 121.0, 122.1, 123.2, 124.0, 124.5, 129.2, 129.8, 130.6, 133.5, 136.4, 140.5, 147.3, 150.2, 161.8 (aromatic and olefinic carbons), 157.9, 168.7, 188.7 (C=O) ppm; MS (m/z, %): 404 (33); Analyses: Calcd. For $C_{20}H_{12}N_4O_6$: C, 59.41; H, 2.99; N, 13.86 Found C, 59.31; H, 3.07; N, 13.74; %.

5-(5-bromo-2-hydroxyphenyl)-5,11-dihydro-1H-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione **(4m).**

Red powder (90%), m.p. 314-316°C; IR (KBr) (ν_{max}, cm^{-1}): 3475, 3290, 3117(NH), 3214 (OH), 1699, 1674, 1644 (C=O) cm^{-1}; ^1H NMR: 4.85 (1H, s, CH), 6.69 (1H, d, *J* = 8.4 H_Z, aromatic), 7.03 (1H, m, aromatic), 7.11 (1H, dd, *J* = 8.4 H_Z, *J* = 2.8 H_Z aromatic), 7.25 (1H, d, *J* = 6.8 H_Z, aromatic), 7.37 (1H, dt, *J* = 8.8 H_Z, *J* = 0.8 H_Z, aromatic), 7.43 (1H, dt, *J* = 8.8 H_Z, *J* = 0.8 H_Z, aromatic), 7.64 (1H, m, aromatic), 9.26 (1H, s, OH), 10.62- 11.12 (3H, s, 3NH) ppm; ^{13}C NMR: 29.1 (CH), 90.4, 107.8, 111.3, 117.3, 119.3, 122.0, 124.6, 130.0, 130.4, 131.9, 133.4, 135.9, 136.4, 140.7, 150.2, 157.7 (aromatic and olefinic carbons), 154.7, 161.3,188.6 (3C=O) ppm; MS (m/z, %): 437 (35); Analyses: Calcd. For $C_{20}H_{12}N_3O_4Br$: C, 54.82; H, 2.76; N, 9.59 Found C, 54.72; H, 2.67; N, 9.63; %.

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