A Simple and Environmentally Benign Synthetic Protocol of Indeno-Fused Pyrido[2,3-*d*]pyrimidines

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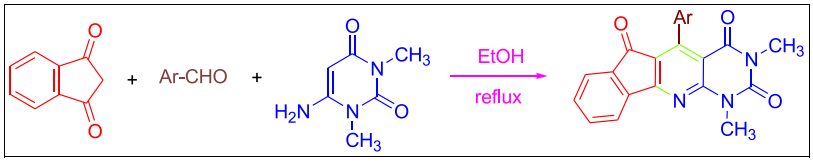

An efficient and environmentally benign protocol for the synthesis of indeno [2 ,1 :5,6] pyrido[2,3-*d*] pyrimidines has been developed. The synthesis of these pharmacologically important compounds can be achieved by the one-pot three-component condensation of 6-amino-1,3-dimethyluracil, aromatic aldehydes, and 1,3-indandione in ethanol without using catalyst and oxidizing agent. This protocol has the advantages of easier work-up, milder reaction conditions, and an environmentally benign procedure compared with other methods.

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INTRODUCTION

One aspect of multicomponent reactions that has received relatively little attention is their development in green environments [1]. Ethanol is an inexpensive solvent, miscible with water, and environmentally friendly and shows good reactivity and selectivity in comparison with conventional organic solvents [2,3]. For these reasons, the development of synthetically useful multicomponent reactions using ethanol as the green medium has earned considerable interest.

Organic compounds containing pyrido pyrimidine skeleton are some of the most important type of chemical compounds for their diverse range of extraordinary biological and pharmaceutical activities [4] such as anti-folate [5], anti-bacterial [6], tyrosine kinase inhibitors [7], antimicrobial [8], calcium channel antagonist [9], anti-inflammatory [10], analgesic [10], anti-leishmania [11], tuberculostatic [12], anti-convulsant [13], diuretic and potassium-sparing [14], anti-aggressive activities [15], and its dihydro form exhibit central nervous system (CNS) depressant activities [16].

For example, Palbociclib has been reported as a drug for the treatment of estrogen receptor-positive and HER2-negative breast cancer. This drug is a selective inhibitor of the kinase [17,18]. Pemirolast (INN) used as an anti-allergy drug treatment [19]. Pipemidic acid is a component of antibacterial drugs [20]. Tasosartan is an angiotensin II receptor antagonist (Fig. 1) [21,22].

In 2011, Evdokimov and coworkers reported that flat pyridines [23] inhibit topoisomerase enzyme activity and lead to growth inhibition and cell death. They have been studied pyrido pyrimidine with the desired structure and its dihydropyrido[2,3-*d*]pyrimidines form, as a starting point for the discovery of anti-cancer drugs [23].

Previous synthetic methods for producing these compounds are reported as follows: in 2005, Agarwal et al. have reported solid supported synthesis of dihydropyrido [2,3-*d*]pyrimidines using microwave irradiation [16]. In 2008, Shi et al. reported synthesis of pyrimidine derivatives in ionic liquid [bmim]Br with 75–93% yields [24]. In 2011, these products were synthesized in two stages; in the first stage, three components refluxed in a mixture of acetic acid and ethylene glycol, leading to dihydropyridine form; then, dihydropyridines was oxidized to the corresponding indenopyridine by chloranil as an excellent oxidizing agent in dimethylformamide at reflux [23]. In 2012, this reaction also reported in water promoted by *p*-toluenesulfonic acid (20 mol%) with an efficiency of 60–90% [25]. In 2012, Khurana et al. described a method for the synthesis of these systems using 20 mol% $InCl_3$ (20 mol%) as catalyst in water, and the products were obtained with 87–90% yields [26]. In 2013, these products were synthesized in the presence of 10 mol% of $Zr(HSO_4)_4$ as a catalyst in solvent-free condition [27]. Gilbertson et al. evaluated some of these pyridopyrimidine derivatives for their ability to inhibit cyclic nucleotide synthesis in the presence of stable toxin [28]. Almost all of these procedures suffer from certain drawbacks such as expensive catalysts, harsh reaction conditions, or toxic solvents.

RESULTS AND DISCUSSION

Owing to the importance of this pharmacophore, we became interested in the synthesis of indeno[2 ,1 :5,6]

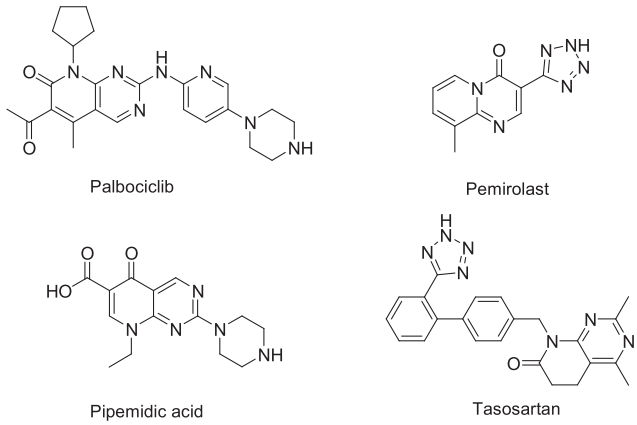
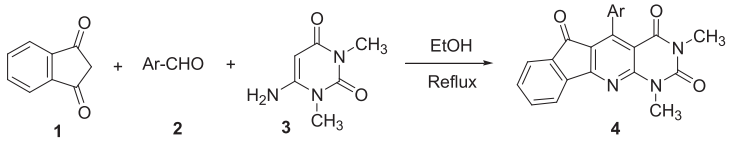


Figure 1. Selected chemical compounds containing pyrido pyrimidine skeleton.

pyrido[2,3-*d*]pyrimidine derivatives from readily available electron-rich amino heterocycles like 6-amino-1,3-dimethyl uracil in new and efficient routes. We now report a method for the synthesis of indeno[2 ,1 :5,6] pyrido[2,3-*d*]pyrimidine derivatives **4** by one-pot three-component condensation of 1,3-indandione (**1**), aromatic aldehydes (**2**), and 6-amino-1,3-dimethyl uracil (**3**) without any catalyst and oxidizing agent in EtOH at reflux (Scheme 1).

The reaction was completed after 3–8 h to afford corresponding heterocyclic systems **4a**–**4h**, in moderate to good yields (54–96%). ^{1}H and ^{13}C NMR spectra of crude product clearly indicated the formation of pyrido [2,3-*d*]pyrimidine **4**. The structures of the products **4a**–**4l** were deduced from their IR, ^{1}H, and ^{13}C NMR spectra. The IR spectrum of **4a** displayed characteristic carbonyl bands (1717 and 1668 cm^{-1}). The ^{1}H NMR spectrum of **4a** consisted of two single sharp lines for methyl groups (δ = 3.36 and 3.91 ppm). The AB system is observed for aromatic protons (δ = 7.13 and 7.23 ppm), along with multiplets for the indenone aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 23 sharp signals in agreement with proposed structure. The key signals are the two methyl carbons (δ = 28.4 and 30.6 ppm) and three signals (δ = 155.4, 159.8, and

Scheme 1. Synthesis of pyrido pyrimidines.



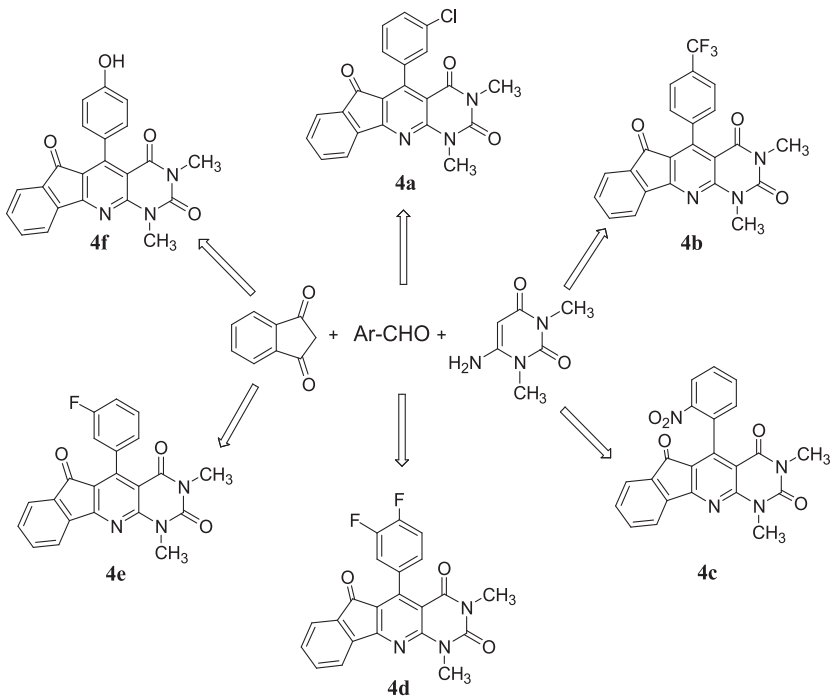
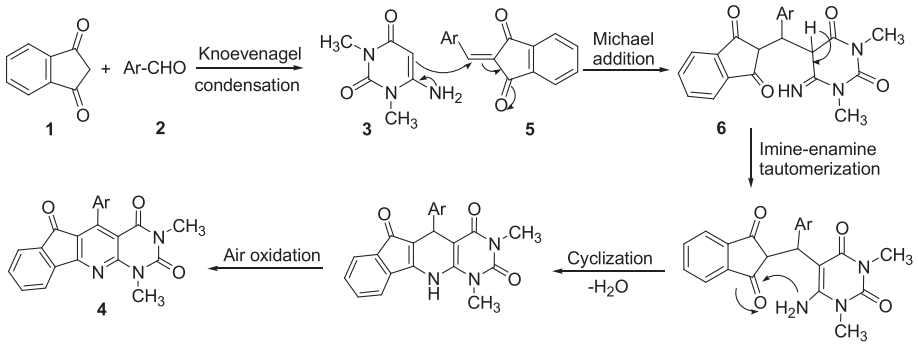


Figure 2. The structure of novel pyrimidine annulated heterocyclic compounds.

Scheme 2. Proposed mechanism for the formation of compound **4**.



188.3 ppm) for three carbon atoms of carbonyl groups. Partial assignments of these resonances are given in the Experimental section (See supporting information). The ^{1}H and ^{13}C NMR spectra of **4b**–**4l** were similar to those of **4a** except for the aryl moieties, which exhibited characteristic resonances in appropriate regions of the spectrum. The product **4a**–**4f** are novel compounds that have not been reported in the literatures (Fig. 2).

A plausible mechanism for the reaction is shown in Scheme 2. The formation of these heterocycles can be rationalized by initial formation of a conjugated electron-deficient heterodiene by Knoevenagel condensation of 1,3-indandione **1** and aldehyde **2** to generate adduct **5**, followed by a Michael-type addition reaction with 6-amino-1,3-dimethyl uracil **3** to afford **6**. Then, nucleophilic addition of the amino group to the carbonyl group leads to the formation of dihydropyridine, which is then oxidized to product **4** (Scheme 2) [26].

The product **4** is insoluble in ethanol, so easily be purified by filtration and washing with ethanol, and column chromatography is unnecessary. As shown in Table 1, several functionalities present in the aryl moiety such as halogen, hydroxyl, and nitro group, which were tolerated. The aromatic aldehydes substituted by electron-affinity groups in *ortho* or *para* position did work well. But the aromatic aldehydes with electron withdrawing groups such as 2,6-dichlorobenzaldehyde was examined, but it did not give the corresponding product **4** (entry **4l**). The results on the synthesis of pyrido[2,3-*d*]pyrimidines **4** are given in Table 1.

Table 1

Synthesis of pyrido[2,3-*d*]pyrimidines **4a**–**4k.**

Entry	Ar	Time (h)	Yield (%)	Mp (°C)
4a	3-ClC_6H_4	5	75	326–328
4b	4-$CF_3C_6H_4$	8	54	294–296
4c	2-$NO_2C_6H_4$	4	82	329–330
4d	3,4-$F_2C_6H_3$	6	60	277–279
4e	3-FC_6H_4	7	65	327–329
4f	4-OHC_6H_4	8	58	368–369
4g	4-ClC_6H_4	4	82	309–311 [25]
4h	4-BrC_6H_4	5	84	299–301 [25]
4i	4-$NO_2C_6H_4$	3	96	261–263 [25]
4j	4-FC_6H_4	6	69	286–288 [25]
4k	4-$OMeC_6H_4$	8	75	266–268 [25]
4l	2,6-$Cl_2C_6H_3$	–	No reaction	–

CONCLUSION

In summary, we have developed an easy, green, and efficient one-pot method for the synthesis of pyrimidine annulated heterocyclic systems without using any catalyst in ethanol. The advantages of this method include operational simplicity, mild reaction conditions, high yield, easy isolation of products, and does not involve any purification techniques like column chromatography.

EXPERIMENTAL

General. The 6-amino-1,3-dimethyl uracil, 1,3-indandione, aromatic aldehydes, and other reagents and solvents used in this work were obtained from Aldrich (St. Louis, MO) and Merck Chemical Co. (Germany) and used without further purification. IR spectra were recorded on Bruker Tensor 27 Fourier transform infrared instrument (Germany). NMR spectra were recorded with a Bruker DRX-300 Avance instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) with $CDCl_3$ and DMSO as solvents. Chemical shifts are given in ppm (δ) relative to internal tetramethylsilane, and coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded with an Agilent 5975C VL MSD (USA) with Triple-Axis Detector (Santa Clara, CA) operating at an ionization potential of 70 eV. Melting points were measured with an electrothermal 9100 apparatus (England).

General procedure for the synthesis of indeno-fused pyrido pyrimidine compound 4a. A mixture of 1,3-indandione (1 mmol, 0.146 g) and 3-chlorobenzaldehyde (1 mmol, 0.150 g) in ethanol (6 mL) in a 25 mL round-bottomed flask fitted with a reflux condenser was heated with stirring in an oil-bath maintained at 80°C for the appropriate time as mentioned in Table 1. After complete appearance of the yellow solid, the 6-amino-1,3-dimethyluracil (1 mmol, 0.155 g) in 4 mL ethanol was added. The initial deposit disappeared, and product reprecipitated. The reaction mixture was cooled to room temperature, and resulting solid product was filtered, washed with ethanol, and dried to obtain the pure product **4a** in good yield (75%) and analyzed by ^{1}H NMR and ^{13}C NMR.

5-(3-Chloro-phenyl)-1,3-dimethyl-1H-indeno[2′,1′:5,6]pyrido [2,3-d]pyrimidine-2,4,6-trione (4a). Yellow powder: mp 326–328°C, 0.290 g, yield 75%; IR (KBr) ($\bar{\upsilon}_{max}$ /cm^{-1}): 3066, 2946, 1716, 1668, 1567, 1492, 1367, 1286, 1166, 1088,786, 738. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (3H, s, CH_3), 3.91 (3H, s, CH_3), 7.13 (1H, d, $^3J_{HH}$ = 8.5 Hz, ArH), 7.22–7.26 (1H, m, ArH), 7.40–7.47 (2H, m, ArH and $CH_{ind.}$), 7.57 (1H, d, $^3J_{HH}$ = 6.8 Hz, ArH), 7.65–7.70 (2H, m, ArH and $CH_{ind.}$), 7.96 (1H, d, $^3J_{HH}$ = 8.8 Hz, $CH_{ind.}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4 (CH_3), 30.6 (CH_3), 106.8 (**C**─C═N), 120.9 ($C_{ind.}$), 122.0 ($CH_{ind.}$), 123.7 ($CH_{ind.}$), 125.2, 126.9, 128.0, 128.9, 132.8 (Ar), 132.9 ($C_{ind.}$), 133.3 ($CH_{ind.}$), 135.1 ($C_{ind.}$), 136.2 ($CH_{ind.}$), 136.3 (C_{ipso} Ar), 140.5 ($C_{ind.}$), 150.4 (C-Ar), 150.7 ($C_{3ind.}$), 155.4, 159.8 (2C═O) 168.4 (N═C─N), 188.2 (C═O). MS (EI, 70 eV): *m/z* (%) = 403 (63) [M + 1]+, 402 (80) [M]+, 289 (51), 256 (33), 227 (81), 214 (72), 200 (77), 187 (40), 138 (43), 114 (55), 100 (100), 74 (77), 56 (67), 50 (44). *Anal.* Calcd (%) for $C_{23}H_{15}ClN_2O_3$: C, 68.58; H, 3.75; N, 6.95. Found C, 68.7; H, 3.9; N, 6.8.

5-(4-Trifluoromethyl-phenyl)-1,3-dimethyl-1H-indeno[2′,1′:5,6] pyrido[2,3-d]pyrimidine-2,4,6-trione (4b). Yellow powder: mp 294–296°C, 0.229 g, yield 54%; IR (KBr): ($\bar{\upsilon}_{max}$ /cm^{-1}): 3391, 3058, 2956, 1719, 1667, 1571, 1499, 1322, 1245, 1162, 1114, 1066, 834, 786. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (3H, s, CH_3), 3.92 (3H, s, CH_3), 7.34 (2H, d, $^3J_{HH}$ = 9 Hz, ArH), 7.56 (1H, d, $^3J_{HH}$ = 8.4 Hz, $CH_{ind.}$), 7.65–7.69 (2H, m, $CH_{ind.}$), 7.73 (2H, d, $^3J_{HH}$ = 9 Hz, ArH), 7.99 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH_{ind}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.6 (CH_3), 30.8 (CH_3), 106.9 (C─C═N), 121.8 (CF_3), 122.4 (C_{ind}), 124.0 (CH_{ind}), 124.9 (CH_{ind}), 125.9, 130.1 (C_{ind}), 127.35, 130.54 (Ar), 133.1 (CH_{ind}), 135.2 (C_{ind}), 136.5 (CH_{ind}), 138.4 (C_{ipso} Ar), 140.7 (C_{ind}), 150.9 (C-Ar), 151.1 (C_{3ind}), 155.7, 160.2 (2C═O), 168.8 (N═C─N), 188.5 (C═O). MS (EI, 70 eV): *m/z* (%) = 437 (67) [M + 1]+, 436 (68) [M]+, 323 (56), 256 (24), 227 (40), 214 (44), 200 (38), 130 (31), 102 (62), 76 (77), 69 (100), 56 (88). *Anal.* Calcd (%) for $C_{24}H_{15}F_3N_2O_3$: C, 66.06; H, 3.46; N, 6.42. Found C, 66.3; H, 3.6; N, 6.5.

5-(2-Nitro-phenyl)-1,3-dimethyl-1H-indeno[2′,1′:5,6]pyrido [2,3-d]pyrimidine-2,4,6-trione (4c). Yellow powder: mp 329–330°C, 0.329 g, yield 82%; IR (KBr): ($\bar{\upsilon}_{max}$ /cm^{-1}): 3392, 3067, 2948, 1716, 1666, 1573, 1513, 1355, 1286, 1166, 788. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.32 (3H, s, CH_3), 3.92 (3H, s, CH_3), 7.23 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.56 (1H, d, $^3J_{HH}$ = 7.2 Hz, $CH_{ind.}$), 7.60–7.77 (4H, m, ArH and CH_{ind}), 7.99 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH_{ind}), 8.42 (1H, d, $^3J_{HH}$ = 8.4 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5 (CH_3), 30.7 (CH_3), 106.5 (C─C═N), 120.3 (C_{ind}), 122.2 (Ar), 124.0 (CH_{ind}), 124.8 (CH_{ind}), 129.0 (C_{ind}), 129.1, 129.3 (Ar), 131.8 (CH_{ind}), 132.9 (C_{ind}), 133.7 (CH_{ind}), 135.2 (C_{ipso} Ar), 136.48 (Ar), 141.0 (C_{ind}), 146.5 (Ar), 149.6 (C-Ar), 150.9 (C_{3ind}), 155.6, 160.4 (2C═O), 168.9 (N═C─N), 188.8 (C═O). MS (EI, 70 eV): *m/z* (%) = 414 (5) [M]+, 368 (100), 324 (21), 312 (10), 227 (9), 169 (12). *Anal.* Calcd (%) for $C_{23}H_{15}N_3O_5$: C, 66.83; H, 3.66; N, 10.16. Found C, 66.7; H, 3.5; N, 10.1.

5-(3,4-Difluoro-phenyl)-1,3-dimethyl-1H-indeno[2′,1′:5,6] pyrido[2,3-d]pyrimidine-2,4,6-trione (4d). Yellow powder: mp 277–279°C, 0.235 g, yield 60%; IR (KBr): ($\bar{\upsilon}_{max}$ /cm^{-1}): 3390, 3071, 2962, 1718, 1671, 1572, 1508, 1278, 1170, 760. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (3H, s, CH_3), 3.91 (3H, s, CH_3), 6.93–6.98 (1H, m, ArH), 7.03–7.10 (1H, m, ArH), 7.23–7.32 (1H, m, CH_{ind}), 7.54–7.59 (1H, m, CH_{ind}), 7.69 (2H, d, $^3J_{HH}$ = 7.5 Hz, CH_{ind}, ArH), 7.99 (1H, d, $^3J_{HH}$ = 8.2 Hz, CH_{ind}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.6 (CH_3), 30.8 (CH_3), 107.0 (C─C═N), 116.9 (Ar), 121.2 (Ar), 122.1 (C_{ind}), 123.4 (CH_{ind}), 124.0 (CH_{ind}), 130.9 (C_{ind}), 131.0 (Ar), 131.1 (CH_{ind}), 133.1 (C_{ind}), 135.2 (CH_{ind}), 136.5 (C_{ipso} Ar), 148.5 (Ar), 140.6 (C_{ind}), 150.2 (C-Ar), 150.9 (C_{3ind}), 151.7 (Ar), 155.7, 160.0 (2C═O), 169.0 (N═C─N), 188.7 (C═O). MS (EI, 70 eV): *m/z* (%) = 405 (62) [M + 1]+, 404 (93) [M]+, 291 (46), 287 (100), 263 (31), 250 (31), 235 (27), 202 (33), 140 (29), 118 (30), 102 (42), 77 (27), 58 (44). *Anal.* Calcd (%) for $C_{23}H_{14}F_2N_2O_3$: C, 68.32; H, 3.49; N, 6.93. Found C, 68.5; H, 3.3; N, 6.7.

5-(3-Fluoro-phenyl)-1,3-dimethyl-1H-indeno[2′,1′:5,6]pyrido [2,3-d]pyrimidine-2,4,6-trione (4e). Light orange powder: mp 327–329°C, 0.243 g, yield 65%. IR (KBr): ($\bar{\upsilon}_{max}$ /cm^{-1}): 3392, 3075, 2954, 1717, 1669, 1570, 1497, 1292, 1169, 786. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (3H, s, CH_3), 3.91 (3H, s, CH_3), 6.96–7.02 (2H, m, ArH), 7.17–7.26 (1H, m, CH_{ind}), 7.43–7.50 (1H, m, CH_{ind}), 7.54 (1H, d, $^3J_{HH}$ = 6.9 Hz, CH_{ind}), 7.69 (2H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.98 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH_{ind}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5 (CH_3), 30.7 (CH_3), 106.9 (C─C═N), 114.4 (Ar), 119.7 (Ar), 121.1 (C_{ind}), 121.4 (Ar), 122.6 (CH_{ind}), 123.8 (CH_{ind}), 131.0 (CH_{ind}), 131.54 (Ar), 132.9 (C_{ind}), 135.1 (CH_{ind}), 136.4 (C_{ipso} Ar), 140.6 (C_{ind}), 150.87 (C-Ar), 151.0 (C_{3ind}), 155.7,

160.0 (2C═O), 162.1 (Ar), 168.9 (N═C─N), 188.6 (C═O). MS (EI, 70 eV): *m/z* (%) = 387 (61) [M + 1]+, 386 (75) [M]+, 268 (37), 302 (30), 294 (52), 273 (78), 246 (64), 232 (65), 218 (57), 193 (100), 137 (45), 130 (47), 109 (54), 102 (63), 75 (48), 44 (30). *Anal.* Calcd (%) for $C_{23}H_{15}FN_2O_3$: C, 71.50; H, 3.91; N, 7.25. Found C, 71.8; H, 4.1; N, 7.1.

5-(4-Hydroxy-phenyl)-1,3-dimethyl-5,11-dihydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione (4f). Yellow powder: mp 368–369°C, 0.228 g, yield 58%. IR (KBr): ($\bar{\upsilon}_{max}$ /cm^{-1}): 3379, 3048, 2956, 1710, 1660, 1571, 1506, 1367, 1277, 1207 749. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.37 (3H, s, CH_3), 3.90 (3H, s, CH_3), 6.95 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.15 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.65–7.72 (2H, m, CH_{ind}), 7.90 (1H, d, $^3J_{HH}$ = 7.9 Hz, CH_{ind}), 7.98 (1H, d, $^3J_{HH}$ = 8.7 Hz, CH_{ind}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4 (CH_3), 30.5 (CH_3), 107.1 (C─C═N), 114.7 (Ar), 121.1 (C_{ind}), 121.7 (CH_{ind}), 123.5 (CH_{ind}), 124.5 (CH_{ind}), 128.8 (Ar), 132.6 (C_{ipso} Ar), 134.8 (CH_{ind}), 136.4 (C_{ind}), 140.5 (C_{ind}), 150.9 (C-Ar), 153.5 (C_{3ind}), 155.5, 160.0 (2C═O), 157.6 (Ar), 168.4 (N═C─N), 188.6 (C═O). MS (EI, 70 eV): *m/z* (%) = 384 (100), 271 (12), 192 (10). *Anal.* Calcd (%) for $C_{23}H_{16}N_2O_4$: C, 71.87; H, 4.20; N, 7.29. Found C, 71.7; H, 4.3; N, 7.1.

5-(4-Chloro-phenyl)-1,3-dimethyl-5,11-dihydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione (4g). Yellow powder: mp 309–311°C, 0.320 g, yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (3H, s, CH_3), 3.91 (3H, s, CH_3), 7.18 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.47 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.55 (1H, d, $^3J_{HH}$ = 6.9 Hz, CH_{ind}), 7.65–7.70 (2H, m, CH_{ind}), 7.98 (1H, d, $^3J_{HH}$ = 7.2 Hz, CH_{ind}).

5-(4-Bromo-phenyl)-1,3-dimethyl-5,11-dihydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione (4h). Yellow powder: mp 299–301°C, 0.366 g, yield 84%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (3H, s, CH_3), 3.90 (3H, s, CH_3), 7.11 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.57 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH_{ind}), 7.62 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.63–7.70 (2H, m, CH_{ind}), 7.98 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH_{ind}).

5-(4-Nitro-phenyl)-1,3-dimethyl-5,11-dihydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione (4i). Orange powder: mp 261–263°C, 0.386 g, yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.35 (3H, s, CH_3), 3.92 (3H, s, CH_3), 7.42 (2H, d, $^3J_{HH}$ = 8.7 Hz, ArH), 7.57 (1H, d, $^3J_{HH}$ = 7.2 Hz, CH_{ind}), 7.66–7.70 (2H, m, CH_{ind}), 7.99(1H, d, $^3J_{HH}$ = 7.5 Hz, CH_{ind}), 8.37 (2H, d, $^3J_{HH}$ = 8.7 Hz, ArH).

5-(4-Fluoro-phenyl)-1,3-dimethyl-5,11-dihydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione (4j). Yellow powder: mp 286–288°C, 0.258 g, yield 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (3H, s, CH_3), 3.91 (3H, s, CH_3), 7.15–7.26 (4H, m, ArH, CH_{ind}), 7.55 (1H, d, $^3J_{HH}$ = 6.6 Hz, CH_{ind}), 7.67 (2H, d, $^3J_{HH}$ = 7.2 Hz, ArH), 7.98 (1H, d, $^3J_{HH}$ = 7.2 Hz, CH_{ind}).

5-(4-Methoxy-phenyl)-1,3-dimethyl-5,11-dihydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione (4k). Yellow powder: mp 266–268°C, 0.290 g, yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (3H, s, CH_3), 3.89 (3H, s, OMe), 3.90 (3H, s, CH_3), 7.04 (2H, d, $^3J_{HH}$ = 8.5 Hz, ArH), 7.20 (2H, d, $^3J_{HH}$ = 8.5 Hz, ArH), 7.54 (1H, d, $^3J_{HH}$ = 7.2 Hz, CH_{ind}), 7.64–7.68 (2H,m, CH_{ind}), 7.95 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH_{ind}).

REFERENCES AND NOTES

[1] Kumaravel, K.; Vasuki, G. Curr Org Chem 2009, 13, 1820.

[2] Noyori, R. Chem Commun 2005, 14, 1807.

[3] Talaviya, S.; Majmudar, F. J Med Sci 2012, 1, 7.

[4] Khurana, J. M.; Chaudhary, A.; Nand, B.; Lumb, A. Tetrahedron Lett 2012, 53, 3018.

[5] Rosowsky, A.; Mota, C. E.; Queener, S. F. J Heterocyclic Chem 1995, 32, 335.

[6] Nargund, L. V. G.; Reddy, Y. S. R.; Jose, R. Indian Drugs 1991, 29, 45.

[7] Thompson, A. M.; Bridges, A. J.; Fry, D. W.; Kraker, A. J.; Denny, W. A. J Med Chem 1995, 38, 3780.

[8] Donkor, I. O.; Klien, C. L.; Liang, L.; Zhu, N.; Bradley, E.; Clark, A. M. J. J Pharm Sci 1995, 84, 661.

[9] Pastor, A.; Alajarin, R.; Vaquero, J. J.; Alvarez-Builla, J.; Faude Casa-Juana, M.; Alvarez-Builla, J.; Sunkel, C.; Priego, J. G.; Fonseca, I.; Sanz-Aparicio, J. Tetrahedron 1994, 50, 8085.

[10] Kolla, V. E.; D-Eyanov, A. B.; Nazmedinov, F. Y.; Kashina, Z. N.; Rovosekova, L. P. Khim Farm Zh 1991, 27, 29.

[11] Satti, N. K.; Suri, K. A.; Sun, O. P.; Kapil, A. Indian J Chem Sec B 1993, 32, 978.

[12] Bystryakove, I. D.; Burova, I. A.; Chelysheva, G. M.; Zhilinkova, S. V.; Smirnova, N. M.; Safonova, T. S.; Safonova, T. S. Khim Farm Zh 1991, 25, 31.

[13] Deyanov, A. B.; Niyazov, R. K.; Nazmetdinov, F. Y.; Syropyatov, B. Y.; Kolla, V. E.; Konshin, M. E. Khim Farm Zh 1991, 25, 26.

[14] Monge, A.; Martinez-Merino, V.; Sanmartin, C.; Fernamdez, F. J.; Ochoa, M. C.; Berllver, C.; Artigas, P.; Fernandez-Alvarez, E. Eur J Med Chem 1989, 24, 209.

[15] Saladowwska, H.; Bartoszko-Malik, A.; Zawisza, T. Farmacol 1990, 45, 101.

[16] Agarwal, A.; Chauhan, P. M. S. Tetrahedron Lett 2005, 46, 1345.

[17] Finn, R. S.; Dering, J.; Conklin, D.; Kalous, O.; Cohen, D. J.; Desai, A. J.; Ginther, C.; Atefi, M. Breast Cancer Res 2009, 11, 77.

[18] Rocca, A.; Farolfi, A.; Bravaccini, S.; Schirone, A.; Amadori, D. Expert Opin Pharmacother 2014, 15, 407.

[19] Tinkelman, D. G.; Berkowitz, R. B. Ann Allergy 1991, 66, 162.

[20] Iacovino, R.; Rapuano, F.; Caso, J. V.; Russo, A.; Lavorgna, M.; Russo, C.; Isernia, C. Int J Mol Sci 2013, 14, 13022.

[21] Atkinson, A. J. Jr.; Huang, S. M.; Lertora, J. J.; Markey, S. P. Principles of Clinical Pharmacology; Academic Press, 2012.

[22] Dina, R.; Jafari, M. Am J Health Syst Pharm 2000, 57, 1231.

[23] Evdokimov, N. M.; Van Slambrouck, S.; Heffeter, P.; Tu, L.; Le Calve, B.; Lamoral-Theys, D.; Steelant, W. F. J Med Chem 2011, 54, 2012.

[24] Ji, S. J.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Shi, D. Q. J Heterocycl Chem 2008, 45, 693.

[25] Verma, G. K.; Raghuvanshi, K.; Kumar, R.; Singh, M. S. Tetrahedron Lett 2012, 53, 399.

[26] Khurana, J. M.; Chaudhary, A.; Nand, B.; Lumb, A. Tetrahedron Lett 2012, 53, 3018.
[27] Abdolmohammadi, S.; Balalaie, S.; Barari, M.; Rominger, F. Comb Chem High Throughput Screen 2013, 16, 150.
[28] Tanifum, E. A.; Kots, A. Y.; Choi, B. K.; Murad, F.; Gilbertson, S. R. Bioorg Med Chem Lett 2009, 19, 3067.

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