Synthesis of Tetrahydropyrimidino[4,3-a]isoquinolines *via* Regiospecific N-Alkylation-Annulation of 4-Aryldihydropyrimidinones

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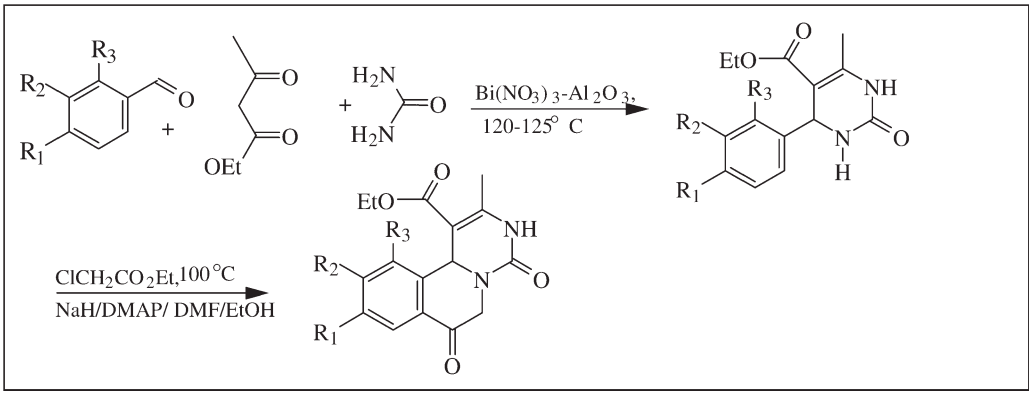

4-Aryldihydropyrimidinones were obtained in excellent yields via solid-phase Biginelli reaction of arylaldehydes, β-ketoester and urea, using bismuth nitrate, immobilized on Al_2O_3 as catalyst. Subsequently, the products were converted into corresponding tetrahydropyrimidino[4,3-a]isoquinolines (69–73% yield) by one-pot regiospecific N-alkylation-annulation reaction using sodium hydride and dimethylaminopyridine.

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INTRODUCTION

The concept of privileged structural types [1], incorporating one or more moieties of proven bioactive compounds, has immensely helped in offering lead compounds for drug discovery [2]. Therefore, the interest in the synthesis of new privileged chemo-types and development of new methodologies for their synthesis [3] is growing unabatedly. Pyrimidoisoquinolines also incorporate two structural moieties and exhibit a wide range of pharmacological properties, such as antihypertensive [4], bronchodilatory [5], inhibitors of platelet phosphodiesterase and platelet aggregation [6]. These structural scaffolds have been usually prepared by the ring closure of tetrahydroisoquinolines [7] or N-phenylethylamides [8]. Despite their attractiveness, many of the known methods have several limitations such as the involvement of multistage laborious processes, long reaction times and stringent reaction conditions. Therefore, the development of a simple and efficient methodology to synthesize pyrimidoisoquinolines, with the requisite structural features for the calcium channel regulatory activity [9–11], would be quiet useful because of their high therapeutic potential.

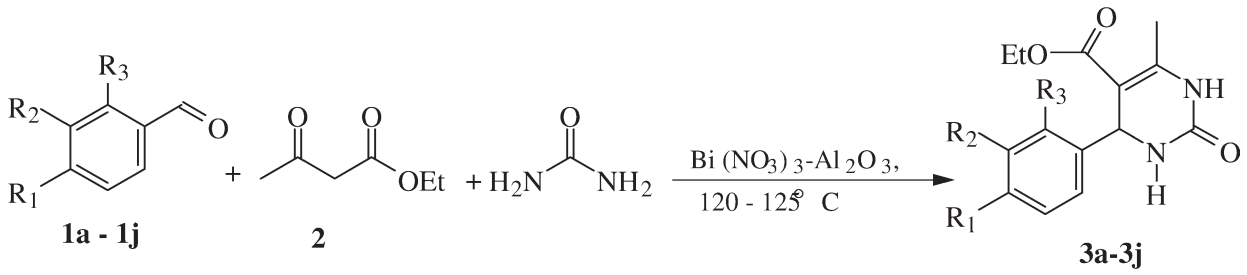
This article describes the synthesis of 4-aryl-3,4-dihydropyrimidinones via solid-phase Biginelli reaction, using bismuth nitrate, immobilized on neutral alumina, as catalyst and their one-pot base catalysed transformation to 4,6,7,11b-tetrahydropyrimido[4,3-a]isoquinolines, using ethyl chloroacetate as N-alkylating agent.

RESULTS AND DISCUSSION

Our strategy for the synthesis of 4, 6, 7, 11b-tetrahydropyrimido[4,3-a]isoquinolines **4a**-**4j** involved regiospecific N-alkylation of 4-aryl-dihydropyrimidinones **3a**-**3j** with readily available ethyl chloroacetate so that the ester group in the products could provide a site for the annulation with aromatic ring.

Several methodologies, each aiming at the improvement of the percent yield, have been documented for the preparation of 4-aryl-3,4-dihydropyrimidinones from arylaldehydes, β-ketoester and urea via Biginelli reaction [12]. These include the use of Lewis acids [13], neat or in combination with protic solvents, solid-supports [14] and microwave irradiation [15]. Our interest in exploring the efficiency of bismuth salts [16] in the solid-phase synthesis of nitrogen heterocyclic compounds, led us to assess the utility of immobilized bismuth nitrate in the preparation of 4-aryl-3, 4-dihydropyrimidinones **3a-3j** (Scheme 1), which were needed for the preparation of the title compounds **4a-4j**.

Scheme 1



1a/3a: $R_1 = R_2 = R_3 = H$
1b/3b: $R_1 = -OCH_3$; $R_2 = R_3 = H$
1c/3c: $R_1 = -NO_2$; $R_2 = R_3 = H$
1d/3d: $R_1 = Cl$; $R_2 = R_3 = H$
1e/3e: $R_1 = F$; $R_2 = R_3 = H$
1f/3f: $R_1 = R_2 = H$; $R_3 = Cl$
1g/3g: $R_1 = R_3 = Cl$; $R_2 = H$
1h/3h: $R_1 = C_4H_9$; $R_2 = R_3 = H$
1i/3i: $R_1 = H$; $R_2 = NO_2$; $R_3 = H$
1j/3j: $R_1 = Br$; $R_2 = R_3 = H$

4-Aryl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin-2-ones **3a-3j** (Scheme 1) were prepared by modified Biginelli reaction of equimolar mixture of aryl aldehydes **1a-1j**, ethylacetoacetate **2** and urea, using bismuth nitrate, immobilized on neutral alumina, as catalyst, in the absence of a solvent. The reactions were carried out at 120–125°C, in a hot air oven. On completion of reactions (3–3.5 hrs) the products were extracted with hot $CHCl_3$, and purified to give products **3a-3j** in high yield (Table 1).The compounds were characterized by spectral methods (ms, IR, ^{1}H-NMR and ^{13}C-NMR). The spectral data was in conformity with the refs. 17 and 18.

The reaction was optimized with respect to the concentration of the catalyst and temperature. The optimum concentration of bismuth nitrate was found to be 0.5 mol % on neutral alumina which was taken in proportion of 1.5 times the weight of aldehyde. No additives were required for promoting the reaction. The optimum temperature for the reaction was 120–125°C; higher temperature led to the formation of multicomponent mixture, with decomposition of the products to form a black mass. At temperatures below 90°C, the reaction did not proceed satisfactorily, even on prolonged heating. Neat bismuth nitrate has been used as catalyst in solution-phase Biginelli reaction [19,20], using acetonitrile as solvent. However, in the absence of the solvent disappointing results were obtained when neat bismuth nitrate or alumina was used as catalyst.

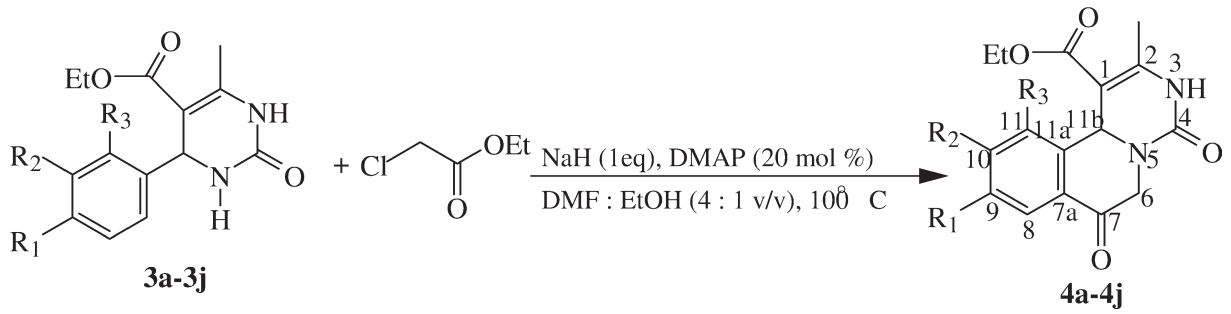
Table 1
Percent yield of **3a–3j**.

Product	R_1	R_2	R_3	Reaction time (h)	% yield
3a	H	H	H	3	90
3b	OCH_3	H	H	3.5	92
3c	NO_2	H	H	3.0	96
3d	Cl	H	H	3.5	88
3e	F	H	H	3.5	83
3f	H	H	Cl	3.5	86
3g	Cl	H	Cl	3.0	84
3h	C_4H_9	H	H	3.5	82
3i	H	NO_2	H	3.5	91
3j	Br	H	H	3.5	87

Earlier [16], our group observed that $Bi(NO_3)_3$-Al_2O_3 is an efficient catalyst for Michael addition. In analogy with this it seems that the present reaction may be proceeding through the initial Perkin-type condensation followed by Michael addition [16] and subsequent heteroannulation rather than through the formation of imine intermediate [21].

Although, in 4-aryl-3,4-dihydropyrimidin-2-ones **3a-3j**, N-3 is more nucleophilic than N-1, the alkylation at N-3 does not occur easily. Earlier [22], N-alkylation with ethyl chloroacetate has been achieved with n-BuLi at very low temperature (−78°C). Our initial attempts to carry out N-alkylation of dihydropyrimidinones with ethyl chloroacetate, using Li_2CO_3, K_2CO_3 and Cs_2CO_3 in neat Me_2CO, DMF, CH_3CN and EtOH or mixture of these solvents failed to give the desired results, even on prolonged refluxing. Therefore, we resorted to organomolecular catalysis and observed that the addition of DMAP to the reaction mixture in the presence of K_2CO_3 and DMF, promoted the reaction, albeit in low yield of product. Encouraged by this observation and after several trials we attempted N – alkylation of **3a** with ethyl chloroacetate in the presence of NaH (1.5 eq) and DMAP, (20 mol %) using DMF-EtOH (4 : 1 v/v) as solvent (Scheme 2). The reaction proceeded well at 100°C.

Scheme 2



After usual work up, chromatographic purification and spectral analysis, we observed that the reaction directly afforded compound **4a** via one-pot regiospecific N-alkylation-annulation. The optimization of the reaction conditions revealed that the optimum concentration of NaH and DMAP was 1.5-equivalent of 4-aryl-3,4-dihydropyrimidinones and 20 mol %, respectively. The optimum proportion of the solvents in the solvent mixtures DMF : EtOH was found to be 4 : 1 v/v.

To study the scope and limitations of the reaction, the reaction of **3b-3j** and ethyl chloroacetate was carried out under optimized reaction conditions when **4b-4j** were obtained in 46–73% yield (Table 2).

Compounds, **4a-4j** were characterized by spectral methods (IR, ^{1}H-NMR, ^{13}C-NMR, DEPT 135°, HMQC and MS) and elemental analysis. The compounds **4a-4j** displayed IR bands characteristic for N-H (3215–3270 cm^{-1}), ester carbonyl (1710–1730 cm^{-1}), amide carbonyl (1610–1660 cm^{-1}) and aryl —CO—CH_2 (1660–1680 cm^{-1}), in addition to the expected aromatic absorption bands. The ^{1}H-NMR spectra of **4a-4j** accounted for aromatic protons, one less than the parent compound **3a-3j** and did not contain the resonance signal due to NH proton nearδ 7.60. The spectra exhibited a lone N-H resonance signal near δ 7.90–8.20 (s, br, 1H). The resonance signal due to H-11b appeared as a singlet near δ 5.56. The spectra displayed two additional resonance signals at δ 4.22–4.38 (d, J = 12.6 Hz, 1H; H_{ax}-6) and 4.38–4.62 (d, J = 12.6 Hz, 1H; H_{eq}- 6), attributable to the geminal methylene protons at position 6, in addition to the expected characteristic signals due to ester and vinylic methyl groups. The ^{13}C-NMR and DEPT 135° of the compounds confirmed the presence of two methylenes carbons, δ_c 58.5–59.5 (C-6) and 59.5 – 59.9 (OCH_2CH_3). The mass spectra of the compounds showed molecular ion peak as the base peak and ms fragmentation agreed well with the assigned structure.

Table 2

Percent yield of **4a–4j**.

Product	R_1	R_2	R_3	% Yield
4a	H	H	H	62
4b	OCH_3	H	H	68
4c	NO_2	H	H	66
4d	Cl	H	H	73
4e	F	H	H	71
4f	H	H	Cl	69
4g	Cl	H	Cl	73
4h	C_4H_9	H	H	71
4i	H	NO_2	H	46
4j	Br	H	H	67

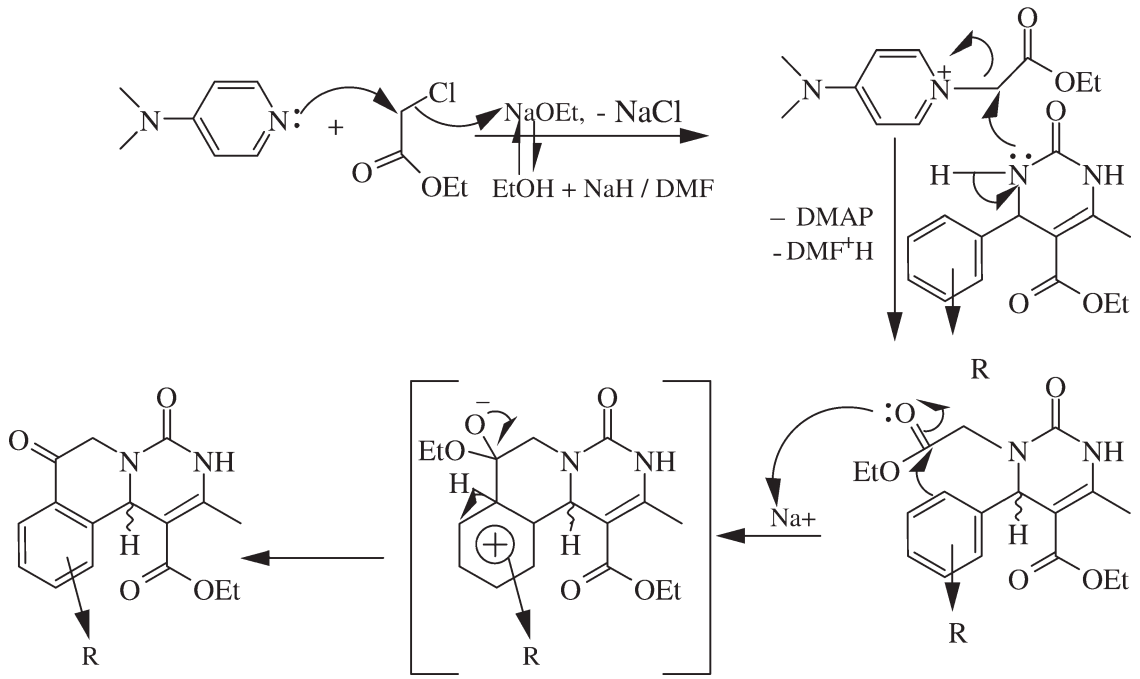
The probable mechanism of the reaction is charted out in Scheme 3. NaH is expected to react faster with ethanol than with carbamide to form sodium ethoxide. Therefore, it was presumed that sodium ethoxide may be the actual base driving the reaction forward. For this reason, we attempted the reaction of **3a-3c** and ethyl chloroacetate in the presence of Na in dry EtOH (10 mL). However, surprisingly, this reaction yielded the compounds **4a-4c** in low yield and most of the substrate pyrimidinones **3a-3c** were recovered unreacted by column chromatography. This also indicated that the presence of DMAP was necessary for the reaction Although the exact mechanistic implications of the solvent mixture are not clear, it seems that DMF, due to its basic character, may be facilitating the reaction by facile removal of proton from the N – 3 of pyrimidinone ring.

The nature of the substituents on the 4-aryl groups of the 4-aryldihydropyrimidin-2-ones seems to have a substantial impact on the annulation process. As expected the presence of deactivating groups, such as nitro group at *ortho* and *para* position, does not favor facile annulation reaction and products are obtained in low yield.

CONCLUSION

Bismuth nitrate, immobilized on neutral alumina, efficiently catalyzes the solid-phase Biginelli reaction of arylaldehyde, acetoacetic ester and urea, to afford ethyl-4-aryl-6-methyl-3,4-dihydro-pyrimidin-2-one-5-carboxylate in high yield. The nontoxic nature of the heterocatalyst mixture $Bi(NO_3)_3$-Al_2O_3 is an added advantage of

Scheme 3



the reaction. We have developed a simple and efficient methodology for the one-pot regiospecific N-alkylation-annulation of 4-aryl-pyrimidin-2-ones to afford corresponding novel tetrahydropyrimido[4,3-a]isoquinolines in moderate to high yield, under mild reaction conditions. Moreover, this methodology is eco-friendly does not need any specialized reaction conditions.

EXPERIMENTAL

General. Melting points were determined on Perfit melting point apparatus and are uncorrected. IR in KBr discs were recorded on Brucker 4800 IR spectrometer. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (50.3 MHz) were obtained on Varian Gemini-300 MHz instrument, using TMS as an internal standard. hrms were recorded at 70 eV, using JEOL D-300 mass spectrometer. CHN analysis was performed on Leco 932, using Helium gas. TLC was done on 0.5 mm thick plates, using BDH silica gel-G adsorbent. Column chromatography was performed on silica gel (Sisco Research Lab., Mumbai), using graded solvent systems of pet.ether (b.p. 40–60°C, pet.ether-CH_2Cl_2, pet.ether-$CHCl_3$ and $CHCl_3$-EtOAc. The calculated mass values are based on the values obtained by Chem.4D Draw (Chem innovations) software.

Preparation of Bi $(NO_3)_3$-Al_2O_3 catalyst. A solution of bismuth nitrate (2.5 g) in methanol (30 mL) and neutral alumina (47.5 g) was stirred, at room temperature, for 12 hrs. The mixture was air dried and then heated at 110°C ± 5°C, in a thermostatic hot air oven, for 6 hrs. The activated bismuth nitrate-alumina mixture was cooled and preserved in a dessicator. The catalyst was reactivated at 110°C ± 5°C for 0.5 hrs every time, before use.

General procedure for the preparation of 4-aryl-5-carboethoxy-6-methyl-3,4-dihydropyrimidine-2(1H)-ones, 3a-3j. A mixture of ethylacetoacetate **2** (20 mmol), aldehyde **1a-1j** (20 mmol), urea (20 mmol) and catalyst Bi$(NO_3)_3$-Al_2O_3 (in proportion by 1.5 times the weight of aldehyde) was charged into conical flask. The reaction mixture was heated at 120–125°C, in a thermostatically controlled hot air oven. Simultaneously, separate experiments were run, to monitor the reaction by TLC of the chloroform extracts of the aliquots drawn out at 0.5 hr intervals of time. On completion of the reaction (3–3.5 hr), the reaction mixture was cooled and products were extracted with hot $CHCl_3$, in a soxhlet extractor. The organic solution was washed with water, dried over anhydrous Na_2SO_4 and freed from the solvent. The residue was crystallized twice from $CHCl_3$-pet. ether (b.p. 40–60°C). The products, **3a-3j,** were characterized by spectral methods and comparison of the spectral data with ref. 20.

General method for the preparation of tetrahydropyrimido[6,1a]isoquinolines, 4a-4j. The pyrimidone **3a-3j** (1×10^{-3} moles) was dissolved in DMF (8 mL) and EtOH (2 mL). The solution was cooled in an ice-bath and NaH (1.5 eq), in DMF (5 mL), was added slowly to the reaction flask. The reaction mixture was stirred for 0.5 h in ice-bath, using $CaCl_2$ guard tube. Subsequently ethyl chloroacetate (1×10^{-3} mol) and DMAP (20 mol %) was introduced into the reaction flask and stirring was continued for another 1.0–1.5 h. The reaction was monitored by t.l.c, using CH_2Cl_2-EtOAc (19 : 1 v/v) solvent system. On consumption of the substrates, the ice-bath was removed and the reaction mixture was brought to room-temperature. Subsequently, the reaction mixture was heated with stirring on a water bath, under anhydrous conditions. After completion of the reaction (2.5–3 hr), the mixture was diluted with EtOH (15 mL) and H_2O (2×15 mL). The product was extracted with $CHCl_3$ (3×20 mL). The $CHCl_3$ layer

was washed with brine (10%), H_2O (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated. The crude mixture was purified by column chromatography using graded solvent systems of petroleum-$CHCl_3$ and petroleum-EtOAc. The products were crystallized from MeOH- pet.ether (b.p. 40–60°C).

Ethyl 2-methyl-4,7-dioxo-4,6,7,11b-tetrahydro-3H-pyrimido[4,3-a]isoquinoline-1-carbo xylate, (4a). Colorless cubes, mp 197–198°C; IR: υ_{max} cm^{-1} 3287, 3020, 1730, 1682, 1660, 1410, 1250, 1145, 1050, 990, 940. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.30 (t, J = 7.1 Hz, 3H), 2.13 (s, 3H), 4.12 (q, J = 7.2 Hz, 2H), 4.24 (d, J = 12.3 Hz, 1H), 4.36 (d, J = 12.3 Hz,1H), 5.40 (s, 1H), 7.18–7.36 (m, 3H), 7.68 (m, 1H), 8.28 (s, br, exch. D_2O, 1H); ^{13}C-NMR ($CDCl_3$): δ_c 13.4, 17.5, 45.1, 58.5, 59.9, 115.4, 126.7, 128.0, 128.4, 132.7, 136.5, 137.3, 137.5, 157.8, 167.5, 196.5; hrms: *m/z* (rel. int.): 300.1116 (100) (M^+) (calc. for $C_{16}H_{16}N_2O_4$, 300.1110), 272 (22), 258 (40), 145 (61), 141 (32), 129 (35), 117 (4), 101 (41), 91 (73), 76 (11), 70 (73). Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.95; H, 5.38; N, 9.33.

Ethyl 9-methoxy-2-methyl-4,7-dioxo-4,6,7,11b-tetrahydro-3H-pyrimido[4,3-a]isoquino line-1-carboxylate, (4b). Colorless needles, mp 210–211°C; IR: υ_{max} cm^{-1} 3295, 3030, 1720, 1680, 1665, 1525, 1510, 1480, 1415, 1240, 1135, 1042, 1050, 980, 920; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H), 2.23 (s, 3H), 3.82 (s, 3H), 4.10 (q, J = 7.2 Hz, 2H), 4.28 (d, J =12.3 Hz, 1H,), 4.38 (d, J =12.3 Hz, 1H), 5.42 (s, 1H), 6.84 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.32 (s, 1H), 8.01 (s, br, 1H); ^{13}C-NMR ($CDCl_3$): δ_c 13.7, 17.2, 45.1, 56.0, 58.5, 59.5, 106.2, 115.2, 118.3, 128.7, 130.9, 138.9, 139.3, 157.8, 159.3, 165.3, 198.6; hrms: *m/z* (rel. int.): 330.1220 (calc. for $C_{17}H_{18}N_2O_5$, 330.1216) (100) (M^+), 302 (26), 229 (44), 176 (67), 147 (50), 142 (35), 130 (40), 110 (75), 106 (12), 102 (40), 70 (77). Anal. Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.83; H, 5.45; N, 8.43.

Ethyl 2-methyl-9-nitro-4,7-dioxo-4,6,7,11b-tetrahydro-3H-pyrimido[4,3-a]isoquinoline-1-carboxylate, (4c). Colorless plates, mp185°C; IR: υ_{max} cm^{-1} 3290, 3030, 2956, 1710, 1685, 1662, 1590, 1480, 1370, 1245, 1150, 1045, 980, 820; ^{1}H-NMR (300MHz, $CDCl_3$): 1.13 (t, J = 7.1 Hz, 3H), 2.20 (s, 3H), 4.10 (q, J = 7.1 Hz, 2H), 4.34 (d, J = 12.4 Hz, 1H), 4.52 (d, J = 12.4 hz, 1H), 5.69 (s, 1H), 7.50 (d, J = 8.2 Hz, 1H), 8.20 (s, br, 1H), 8.23 (dd, J = 8.2, 1.9 Hz, 1H), 8.54 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ_c 14.1, 17.8, 50.3, 58.8, 58.9, 109.5, 129.1, 134.3, 138.6, 144.6, 146.7, 147.0, 149.3, 157.2, 165.3, 199.4; hrms: *m/z* (rel. int.): 345.0968 (100) (M^+) (calcd. for $C_{16}H_{15}N_3O_6$, 345.0961), 317 (28), 303 (41), 189 (62), 141 (38), 162 (52), 136 (73), 129 (33), 121 (10), 101 (44), 70 (78). Anal. Calcd. for $C_{16}H_{15}N_3O_6$: C, 55.65; H, 4.38; N, 12.17. Found: C, 55.67; H, 4.33; N, 12.18.

Ethyl 9-chloro-2-methyl-4,7-dioxo-4,6,7,11b-tetrahydro-3H-pyrimido[4,3-a]isoquinoline-1-carboxylate, (4d). Colorless needles, mp 230–231°C. IR: υ_{max} cm^{-1} 3260, 3035, 1730, 1685, 1660, 1585, 1490, 1470, 1405, 1260, 1180, 1040, 990, 820; ^{1}H-NMR (200 MHz,$CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H), 2.23 (s, 3H), 4.01 (q, J = 7.2 Hz, 2H), 4.38 (d, J = 12.6 Hz, 1H), 4.49 (d, J = 12.6 Hz, 1H), 5.56 (s, 1H), 7.11 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.75 (s, 1H), 8.10 (s, br, 1H); ^{13}C-NMR ($CDCl_3$): δ_c 13.7, 17.3, 47.4, 58.5, 59.5, 106.4, 129.1, 129.4, 132.1, 133.4, 135.6, 138.4, 139.6, 157.8, 165.3, 198.2; hrms: *m/z* (rel. int.): 336.0704 (70), 334.0699 (100) (M^+) (calcd. for $C_{16}H_{15}ClN_2O_4$, 334.0720), 306 (28), 292 (42), 179 (61), 151 (55), 141 (38), 129 (37), 125 (70).110 (14), 70 (75). Anal. Calcd. for $C_{16}H_{15}ClN_2O_4$: C, 57.41; H, 4.52; N, 8.37. Found: C, 57.49; H, 4.51; N, 8.36.

Ethyl 9-fluoro-2-methyl-4,7-dioxo-4,6,7,11b-tetrahydro-3H-pyrimido[4,3-a]isoquinolin e-1-carboxylate, (4e). Colorless needles mp 178–179°C; IR: υ_{max} cm^{-1} 3291, 3020, 1723, 1682, 1660, 1595, 1495, 1460, 1410, 1346, 1265, 1050, 980, 860, 720; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H), 2.21 (s, 3H), 4.10 (q, J = 7.2 Hz, 2H), 4.26 (d, J = 12.6 Hz, 1H), 4.38 (d, J = 12.6 Hz,1H), 5.54 (s, 1H), 7.00 (d, J = 8.1 Hz, 1H), 7.13 (dd, J = 8.1, 1.9 Hz, 1H), 7.56 (d, J = 1.9 Hz, 1H), 7.89 (s, br, 1H); ^{13}C-NMR ($CDCl_3$): δ_c 13.7, 20.9, 49.6, 58.5, 60.0, 106.4, 127.9, 129.1, 133.4, 134.3, 135.9, 136.7, 139.3, 158.1, 165.5, 198.2; hrms: *m/z* (rel. int.): 318.1023 (100) (M^+) (calcd. for $C_{16}H_{15}FN_2O_4$, 318.1016), 290 (24), 276 (42), 163 (62), 141 (36), 135 (53), 129 (35), 109 (71), 101 (41), 94 (14), 70 (74). Anal. Calcd. for $C_{16}H_{15}FN_2O_4$: C, 60.37; H, 4.75; N,8.80. Found: C, 60.38; H, 4.72; N, 8.81.

Ethyl 11-chloro-2-methyl-4,7-dioxo-4,6,7,11b-tetrahydro-3H-pyrimido[4,3-a]isoquinolin e-1-carboxylate, (4f). Colorless needles, mp 165°C; IR: υ_{max} cm^{-1} 3295, 3058, 1730, 1684, 1663, 1545, 1510, 1460, 1420, 1230, 1050, 980, 780; ^{1}H-NMR (200 MHz,$CDCl_3$): δ 1.30 (t, J = 7.1 Hz, 3H), 1.71 (s, 3H), 4.10 (q, J = 7.1 Hz, 2H), 4.39 (d, J = 12.5 Hz, 1H), 4.56 (d, J = 12.5 Hz, 1H), 5.50 (s, 1H), 7.12 (m, 1H), 7.34 (m, 1H), 7.62 (m, 1H), 8.02 (s, br, 1H); ^{13}C-NMR ($CDCl_3$): δ_c 13.7, 17.2, 38.3, 58.5, 59.9, 106.4, 126.5, 128.1, 131.3, 137.1, 138.4, 139.3, 139.8, 157.8, 165.0, 196.5; hrms: *m/z* (rel. int.): 336.0699, 334.0689 (100) (M^+) (calcd. for $C_{16}H_{15}ClN_2O_4$, 334.0720), 306 (23), 292 (43), 179 (162), 151 (56), 141 (34), 129 (38), 125 (71), 110 (14), 70 (74). Anal. Calcd. for $C_{16}H_{15}ClN_2O_4$: C, 57.41; H, 4.52; N, 8.37. Found: C, 57.44; H, 4.59; N, 8.32.

Ethyl 9,11-dichloro-2-methyl-4,7-dioxo-4,6,7,11b-tetrahydro-3H-pyrimido[4,3-a]isoquin oline-1-carboxylate, (4g). Colorless crystals, mp 235–236°C; IR: cm^{-1} 3286, 3010, 1730, 1685, 1660, 1410, 1395, 1380, 1255, 1190, 980, 720; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.17 (t, J = 7.1 Hz, 3H), 2.34 (s, 3H), 4.05 (q, J = 7.1 Hz, 2H), 4.58 (d, J = 12.6, 1H), 4.58 (d, J = 12.6,1H), 5.36 (s, 1H), 7.35 (s, 1H), 7.63 (s, 1H), 7.93 (s, br, 1H); ^{13}C-NMR ($CDCl_3$): δ_c 14.1, 18.6, 40.1, 59.1, 59.6, 101.6, 127.6, 133.9, 134.7, 134.9, 135.2, 139.3, 139.8, 159.2, 167.2, 198.2; hrms: *m/z* (rel. int.): 372.0284 (37), 368.0276 (100) (M^+) (calcd. for $C_{16}H_{14}Cl_2N_2O_4$, 368.0331), 369 (100), 341 (23), 327 (46), 214 (70), 186 (48), 160 (76), 145 (13), 141 (37), 129 (34), 101 (41), 70 (72). Anal. Calcd. for $C_{16}H_{14}Cl_2N_2O_4$: C, 52.05; H, 3.82; N,7.59. Found: C, 52.09; H, 3.80; N, 7.63.

Ethyl 9-*n*-butyl-2-methyl-4,7-dioxo-4,6,7,11b-tetrahydro-3H-pyrimido[4,3-a]isoquinolin e-1-carboxylate, (4h). Colorless crystals, mp 163°C; IR: υ_{max} cm^{-1} 3230, 2998, 1725, 1675, 1662, 1580, 1490, 1370, 1245, 1055, 1040, 985, 780; ^{1}H-NMR ($CDCl_3$): δ 0.96 (t, J = 6.9 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.33–1.62 (m, 4H) 2.26 (s, 3H), 2.55 (m, 2H), 4.01 (q, J = 7.1 Hz, 2H), 4.12 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 5.43 (s, 1H), 6.98 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 7.79 (s, br, 1H), 8.09 (d, J = 2.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$): δ_c 13.7, 14.0, 17.5, 22.7, 34.6, 35.5, 58.3, 59.8, 59.9, 103.5, 128.2, 132.5, 132.9, 134.5, 136.8, 139.5, 137.1, 158.0,

165.3, 197.8; hrms: *m*/*z* (rel. int.): 356.1740 (100) (M^+) (calcd. for $C_{20}H_{24}N_2O_4$, 356.1736), 314 (23), 328 (43), 201 (59), 173 (46), 147 (74), 141 (34), 132 (13), 129 (37), 101 (43), 70 (70). Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N,7.86. Found: C, 67.48; H, 6.76; N, 7.81.

Ethyl 2-methyl-10-nitro-4,7-dioxo-4,6,7,11b-tetrahydro-3H-pyrimido[4,3-a]isoquinolin e-1-carboxylate, (4i). Colorless cubes, m.p. 189°C; IR: υ_{max} cm^{-1} 3315, 3020, 1730,1680, 1675, 1595, 1580, 1510, 1465, 1450, 1380, 1290, 1170, 1040, 980, 710; ^{1}H-NMR ($CDCl_3$): δ 1.36 (t, J = 7.1 Hz, 3H), 2.13 (s, 3H), 4.10 (q, J = 7.1 Hz, 2H), 4.21 (d, J = 12.6 Hz, 1H), 4.43 (d, J = 12.6 Hz, 1H), 5.47 (s, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 8.08 (s br, 1H), 8.18 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ_c 14.1, 17.3, 46.4, 59.5, 59.9, 103.5, 122.5, 123.7, 125.2, 131.2, 134.2, 139.2, 152.6, 155.3, 165.2, 198.6; hrms: *m*/*z* (rel. int.): 345.0969 (100) (M^+), (calcd. for $C_{16}H_{15}N_3O_6$, 345.0961), 317 (26), 303 (41), 189 (62), 162 (50), 141 (38), 136 (74), 129 (34), 121 (10), 101 (43), 70 (71). Anal. Calcd. for $C_{16}H_{15}N_3O_6$: C, 55.65; H, 4.38; N, 12.17. Found: C, 55.67; H, 4.33; N, 12.15.

Ethyl 9-bromo-2-methyl-4,7-dioxo-4,6,7,11b-tetrahydro-3H-pyrimido[4,3-a]isoquinolin e-1-carboxylate, (4j). Colorless cubes, mp 201–202°C; IR: υ_{max} cm^{-1} 3265, 3015, 1730, 1685, 1662, 1490, 1410, 1395, 1386, 1240, 1060, 980, 720; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.17 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 4.10 (q, J = 7.2 Hz, 2H), 4.46 (d, J = 12.5 Hz, 1H), 4.67 (d, J = 12.5 Hz, 1H), 5.36 (s, 1H), 7.34 (dd, J = 8.1, 2.3 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 8.01 (s, br, 1H), 8.22 (d, J = 2.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$): δ_c 13.9, 17.9, 45.8, 59.1, 60.01, 103.2, 122.3, 130.2, 132.3, 136.5, 136.8, 139.1, 146.2, 158.2, 165.3, 197.9; hrms: *m*/*z* (rel. int.): 380.0201 (40) 378.0810 (100) (M^+) (calcd. for $C_{16}H_{15}BrN_2O_4$, 380.0215, 378.0215), 351 (29), 337 (43), 224 (64), 196 (50), 170 (74), 155 (14), 141 (30), 129 (31), 101 (44), 70 (76). Anal. Calcd. for $C_{16}H_{15}BrN_2O_4$: C, 50.68; H, 3.99; N, 7.39. Found: C, 50.64; H, 3.92; N, 7.41.

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