Novel Synthetic Route for 5-Substituted 6-Arylmethylluracils from 2,4,6-Trichloropyrimidines

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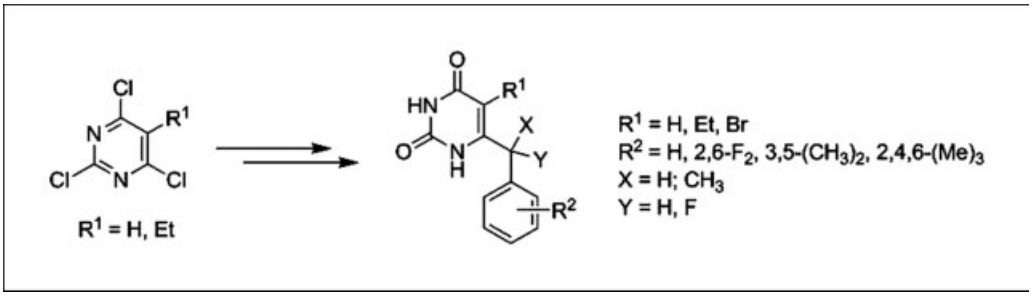

Treatment of 2,4,6-trichloropyrimidines (**1a,b**) with the sodium salt of benzyl cyanide derivatives (**2a,b**) afforded 5-substituted 4-aryl(cyanomethyl)-2,6-dichloropyrimidines (**3a–f**). Compounds **3a,b** were alkylated with methyl iodide to furnish 4-(1-aryl-1-cyanoethyl)-2,6-dichloropyrimidines (**4a,b**). Compounds **3a–f** and **4a,b** were hydrolyzed with concentrated hydrochloric acid to afford 5-substituted 6-arylalkyluracils **5a–h**. 5-Bromo-6-arymethylluracils (**6a–d**) were synthesized by bromination of 6-arylmethylluracils (**5a–d**) with *N*-bromosuccinimide (NBS). Refluxing 2-(2,6-dichloro-5-ethylpyrimidin-4-yl)-2-(3,5-dimethylphenyl)acetonitrile (**3f**) with sodium methoxide followed by oxidation afforded (3,5-dimethylphenyl)(5-ethyl-2,6-dimethoxypyrimidin-4-yl)methanone (**7**). Addition of methylmagnesium bromide to compound **7** gave the tertiary alcohol derivative **8** which was fluorinated by diethylaminosulfurtrifluoride and deprotected by trimethylsilyl iodide to furnish 6-(1-(3,5-dimethylphenyl)-1-fluoroethyl)-5-ethylpyrimidine-2,4(1*H*,3*H*)-dione (**12**).

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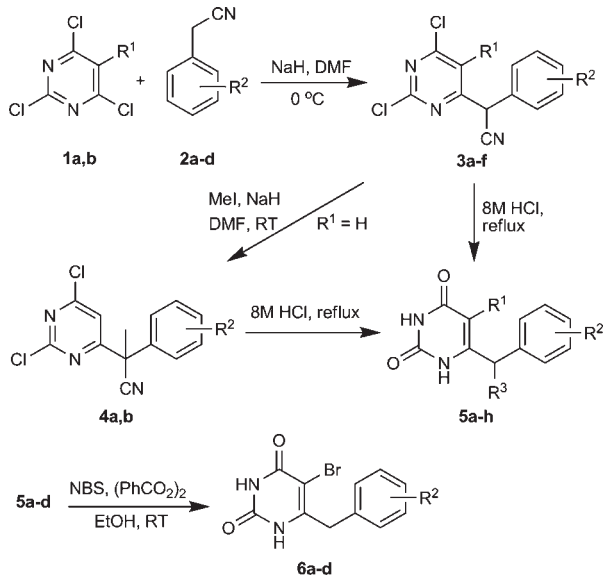
INTRODUCTION

5-Substituted 6-arylmethyluracils are important intermediates for the synthesis of many biologically active compounds. 5-Alkyl-6-arylmethyluracils are used for the synthesis of 6-benzyl-1-ethoxymethyl-5-isopropyluracil (MKC-442) [1–3] analogs as human immunodeficiency virus type 1 (HIV-1) nonnucleoside reverse transcriptase inhibitors (NNRTIs) [4–10]. 5-Bromo-6-arylmethyluracils were used as inhibitors of thymidine phosphorylase [11–13]. Uracil derivatives are known to be synthesized by refluxing the corresponding thiouracils with 10% aqueous chloroacetic acid [14–21]. Thiouracils are synthesized by the condensation of the appropriate β-ketoester with thiourea in strong basic medium [14–21]. Lee and Kim [22] have reported the synthesis of 5-alkyl-6-benzyluracil derivatives by the reaction of 5-alkyl-2,4,6-trichloropyrimidines with various arylmethyl magnesium halides to afford the regioselectively 6-arylmethyl-2,4-dichloropyrimidines as the major products. The dichloropyrimidine derivatives were refluxed with sodium methoxide to afford the dimethoxy derivatives which were refluxed with 37% hydrochloric acid to give 5-alkyl-6-benzyluracil derivatives [22]. El-Brollosy *et al*. [23] have synthesized some of 6-arylmethyluracils by the treatment of Grignard reagents of the corresponding benzyl halides with 4-chloro-5-ethyl-2,6-dimethoxypyrimidine. Hydrolysis of the Grignard products with 4 *M* hydrochloric acid afforded 6-benzyluracil derivatives [23]. In the present work, a novel synthetic route for 5-substituted 6-arylmethyluracils is reported.

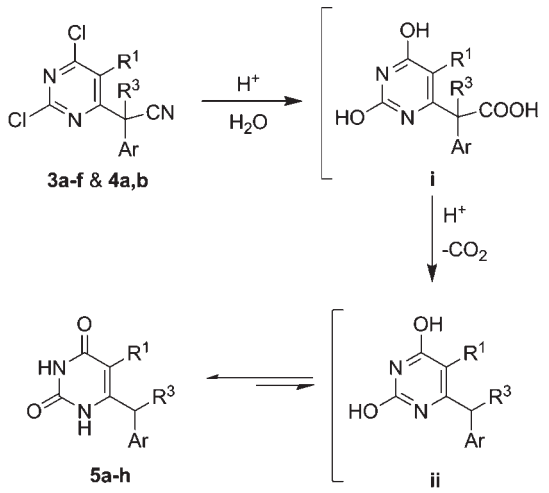
RESULTS AND DISCUSSION

Treatment of the sodium salt of arylacetonitriles (**2a–d**) with 2,4,6-trichloropyrimidine (**1a**) and/or 2,4,6-trichloro-5-ethylpyrimidine (**1b**) afforded 2-aryl-2-(2,6-dichloropyrimidin-4-yl)acetonitrile (**3a–d**) and 2-aryl-2-(2,6-dichloro-5-ethylpyrimidin-4-yl)acetonitriles (**3a,f**), respectively as sole products. No coupling at the 2-position of the pyrimidine ring was observed. As reported,

Scheme 1



Scheme 2



the 4- or 6-position (4-position is equivalent to 6-position in **1a,b**) in chloropyrimidines is more reactive than the 2-position in the nucleophilic substitution reaction [22,24,25]. Coupling at the 4-position of the pyrimidine ring was confirmed by nuclear Overhauser effect (NOE). On irradiation of CH—CN of compound **3c**, 1.29 NOE was detected with H5 which showed 2.0 NOE with CH—CN when irradiated. Compounds **3a,b** were methylated by stirring their sodium salts with methyl iodide in dry dimethylformamide to furnish 2-(2,6-dichloropyrimidin-4-yl)-2-arylacetonitriles **4a,b**. 6-Arylalkyluracils **5a–h** were obtained by refluxing of each compound of **3a–f** and **4a,b** with concentrated hydrochloric acid (Scheme 1). The mechanism for the synthesis of **5a–h** from **3a–f** and **4ab** is postulated as described by Smith and March [26]. The mechanism proceeds through acid hydrolysis of compounds **3a–f** and **4a,b** to their corresponding 2-(2,4-dihydroxypyrimidin-6-yl)-ethanoic acid derivatives **i** as intermediates. The intermediates **i** were decarboxylated in strong acidic medium to afford 6-arylpyrimidine-2,4-diols **ii** which are the enol forms of compounds **5a–h** (Scheme 2). Compounds **5a,b,f** have previously been prepared through desulfurization of the corresponding 2-thiouracil derivatives [14–16]. Compounds **5a–d** were brominated with *N*-bromosuccinimide in absolute ethanol in the presence of benzoyl peroxide at room temperature to give the 5-bromouracil derivatives **6a–d** (Scheme 1). Previously, Johnson and Ambelang [14] has synthesized compound **6a** through attacking compound **5a** with bromine in glacial acetic acid at 40–50°C.

2-(2,6-Dichloro-5-ethylpyrimidin-4-yl)-2-(3,5-dimethylphenyl)acetonitrile (**3f**) was refluxed with sodium methoxide in methanol followed by oxidation with a stream of oxygen at room temperature to furnish (3,5-dimethylphenyl)(5-ethyl-2,6-dimethoxypyrimidin-4-yl)methanone (**7**). Grignard reaction was applied on compound **7** by the treatment with methylmagnesium bromide to give 1-(3,5-dimethylphenyl)-1-(5-ethyl-2,6-dimethoxypyrimidin-4-yl)ethanol (**8**). Treatment of compound **8** with diethylaminosulfurtrifluoride (DAST) furnished two different compounds. One of them is dehydrated compound **9** in 28% yield and the other one is the fluoro derivative **10** in 37% yield. Compound **10** was deprotected by refluxing with trimethylsilyl iodide (TMSI) in dry chloroform to afford 6-[1-(3,5-dimethylphenyl)-1-fluoroethyl]-5-ethylpyrimidine-2,4(1*H*,3*H*)-dione (**11**) (Scheme 3; Table 1).

Scheme 3

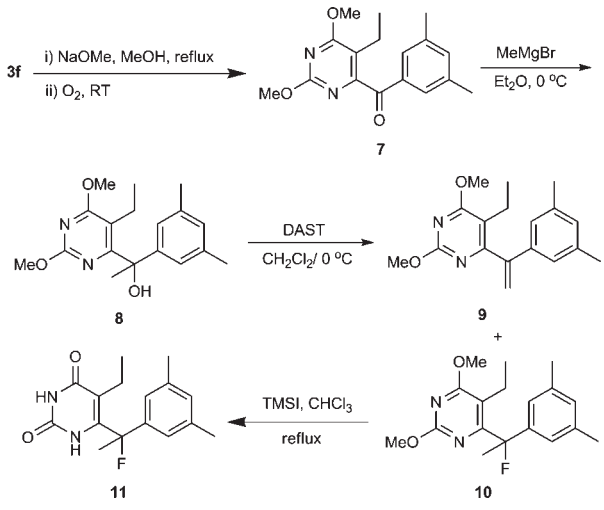


Table 1

Yields and physical data for compounds **3a-f**, **4a,b**, **5a–h,** and **6a–d**.

Compound	R^1	R^2	R^3	Yield (%)	mp (°C)
3a	H	H		71	66–68
3b	H	2,6-(F_2)		72	115–117
3c	H	3,5-($Me)_2$		79	150–151
3d	H	2,4,6-($Me)_3$		56	148–150
3e	Et	2,6-(F_2)		84	91–93
3f	Et	3,5-($Me)_2$		81	108–110
4a		H		72	76–78
4b		3,5-($Me)_2$		75	84–86
5a	H	H	H	82	261–262[a]
5b	H	2,6-(F_2)	H	83	283–284[b]
5c	H	3,5-($Me)_2$	H	87	280–282
5d	H	2,4,6-($Me)_3$	H	78	>300
5e	Et	2,6-(F_2)	H	87	220–221
5f	Et	3,5-($Me)_2$	H	80	218–220[c]
5g	H	H	Me	74	182–184
5h	H	3,5-($Me)_2$	Me	72	219–220
6a		H		77	232–233[d]
6b		2,6-(F_2)		79	259–260
6c		3,5-($Me)_2$		81	263–264
6d		2,4,6-($Me)_3$		72	251–252

[a] mp 260–262°C [14].
[b] mp > 300°C (AcOH) [15].
[c] mp 216–218°C [16].
[d] mp 230–232°C [14].

Novel and facile synthetic route for uracil derivatives starting with the commercially available 2,4,6-trichloropyrimidines and arylmethyl cyanides was achieved. One pot reaction was carried out by the hydrolysis of compounds **3a–f** and **4a,b** followed by decarboxylation of the resultant intermediates in strong acidic medium. The novel synthesized uracil derivatives can be used for the synthesis of NNRTIs and also N1-nucleosides.

EXPERIMENTAL

NMR spectra were recorded on Varian Gemini 2000 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) and a Bruker AVANCE III 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) with TMS as an internal standard. Electron impact mass spectra were recorded on a Finnigan MAT SSQ 710. MALDI spectra were recorded on a 4.7 T Ultima Fourier transform Mass spectrometer (IonSpec, Irvine, CA). Melting points were determined in a Büchi melting point apparatus. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck. Microanalyses were carried out at Chemical Laboratory II, University of Copenhagen, Denmark.

General procedure for the synthesis of 2-aryl-2-(2,6-dichloropyrimidin-4-yl)acetonitriles (3a–f). Sodium hydride (1.1 g, 25 mmol, and 55% suspension in paraffin oil) was added portionwise to a stirred solution of **1a,b** (10 mmol) and the appropriate benzyl cyanide (**2a–d**) (11 mmol) in dry dimethylformamide (20 mL) at 0°C. The mixture was allowed to reach room temperature gradually and left to be stirred for 3 h. The mixture was poured on the ice-cold water and stirred for 1 h. The solid product formed was filtered off and washed with cold water. The solid was purified by stirring with methanol (15 mL), filtered off, washed with methanol, and dried to afford the pure compounds **3b–f**. Only compound **3a** was extracted with ether (3 × 20 mL) from the aqueous mixture. The ether phase was dried and evaporated under reduced pressure. The residual material was purified by silica gel column chromatography using petroleum ether:ether (1:1, v/v) as eluent.

2-(2,6-Dichloropyrimidin-4-yl)-2-phenylacetonitrile (3a). This compound was obtained as white crystals; ^{1}H nmr ($CDCl_3$, 400 MHz): δ 5.22 (s, 1H, CH—CN), 7.41 (s, 1H, H5), 7.42–7.47 ppm (m, 5H, H_{arom}); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 44.36 (*C*H—CN), 116.67 (CN), 117.81 (C5), 127.81, 129.47, 129.74, 131.65 (C_{arom}), 161.10 (C6), 163.91 (C2), 167.61 ppm (C4); ms: (70 eV, electron impact) *m/z* 51 (100%), 263, (39%, $C_{12}H_7{}^{35}Cl_2N_3$, M^+), 265 (20%, $C_{12}H_7{}^{35}Cl^{37}ClN_3$, M^++2), 267 (4%, $C_{12}H_7{}^{37}Cl^{37}ClN_3$, M^++4). Anal. Calcd. for $C_{12}H_7Cl_2N_3$ (264.11): C,54.57; H, 2.67; N, 15.91. Found: C, 55.02; H, 2.59; N, 15.74.

2-(2,6-Dichloropyrimidin-4-yl)-2-(2,6-difluorophenyl)acetonitrile (3b). This compound was obtained as white crystals; ^{1}H nmr ($CDCl_3$, 400 MHz): δ 5.60 (s, 1H, CH—CN), 7.03 (t, 2H, J = 8.4 Hz, H_{arom}), 7.43–7.47 (m, 1H, H_{arom}), 7.66 ppm (s, 1H, H5); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 32.70 (t, J = 3.3 Hz, *C*H—CN), 108.95 (t, J = 17.2 Hz, C_{arom}), 112.34 (dd, J = 2.8, 22 Hz, C_{arom}), 114.60 (CN), 117.73 (C5), 132.11 (t, J = 10.1 Hz, C_{arom}), 160.38 (dd, J = 6.0, 252.4 Hz, C_{arom}), 161.17 (C6), 164.08 (C2), 165.50 ppm (C4); ms: (70 eV, electron impact) *m/z* 125 (100%), 299 (56%, $C_{12}H_5{}^{35}Cl_2F_2N_3$, M^+), 301 (27%, $C_{12}H_5{}^{35}Cl^{37}ClF_2N_3$, M^++2), 303 (6%, $C_{12}H_5{}^{37}$

$Cl_2F_2N_3$, M^++4). Anal. Calcd. for $C_{12}H_5Cl_2F_2N_3$ (300.09): C, 48.03; H, 1.68; N, 14.00. Found: C, 48.15; H, 1.58; N, 13.93.

2-(2,6-Dichloropyrimidin-4-yl)-2-(3,5-dimethylphenyl)acetonitrile (3c). This compound was obtained as white crystals; ^{1}H nmr ($CDCl_3$, 400 MHz) δ: 2.33 (s, 6H, $(CH_3)_2N$), 5.12 (s, 1H, CH—CN), 7.03 (s, 3H, H_{arom}), 7.39 ppm (s, 1H, H5); ^{13}C nmr ($CDCl_3$, 100 MHz) δ: 21.21 [$(CH_3)_2N$], 44.31 (*C*H—CN), 116.87 (C5), 117.87 (CN), 125.46, 131.10, 131.41, 139.64 (C_{arom}), 161.02 (C4), 163.78 (C2), 167.91 (C4) ppm; ms: (70 eV, electron impact) *m/z* 144 (100%), 291 (86%, $C_{14}H_{11}{}^{35}Cl_2N_3$, M^+), 293 (51%, $C_{14}H_{11}{}^{35}Cl^{37}ClN_3$, M^++2), 295 (6%, $C_{14}H_{11}{}^{37}Cl_2N_3$, M^++4). *Anal*. Calcd. for $C_{14}H_{11}Cl_2N_3$ (292.16): C, 57.55; H, 3.79; N, 14.38. Found: C, 58.11; H, 3.85; N, 14.14.

(2,6-Dichloropyrimidin-4-yl)(mesityl)acetonitrile (3d). This compound was obtained as yellow crystals ^{1}H nmr ($CDCl_3$, 300 MHz): δ 2.30 (s, 6H, $3CH_3$), 5.62 (CH—CN), 6.95 (s, 2H, H_{arom}), 7.14 ppm (s, 1H, H5); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 20.67 [$(CH_3)_2$Ar], 20.90 (CH_3Ar), 38.52 (*C*H—CN), 115.96 (CN), 117.20 (C5), 125.74, 130.57, 136.92, 139.53 (C_{arom}), 161.19 (C4), 163.60 (C2), 167.86 ppm (C6); ms: (70 eV, electron impact) *m/z* 32 (100%), 305 (78%, $C_{15}H_{13}{}^{35}Cl_2N_3$, M^+), 307 (55%, $C_{15}H_{13}{}^{35}Cl^{37}ClN_3$, M^++2), 309 (9%, $C_{15}H_{13}{}^{37}Cl_2N_3$, M^++4). Anal. Calcd. for $C_{15}H_{13}Cl_2N_3$ (306.19): C, 58.84; H, 4.28; N, 13.72. Found: C, 58.96; H, 4.05; N, 13.75.

2-(2,6-Dichloro-5-ethylpyrimidin-4-yl)-2-(2,6-difluorophenyl) acetonitrile (3e). This compound was obtained as yellow crystals; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 1.09 (t, 3H, J = 7.2 Hz, C*H*$_3$CH$_2$), 2.81 (q, 2H, J = 7.2 Hz, CH$_3$C*H*$_2$), 5.72 (s, 1H, CH—CN), 7.03 (t, 2H, J = 8.4 Hz, H_{arom}), 7.26–7.44 ppm (m, 1H, H_{arom}); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 11.76 (*C*H$_3$CH$_2$), 21.54 (CH$_3$*C*H$_2$), 31.66 (t, J = 2.6 Hz, CH—CN), 105.87 (C5), 108.81 (t, J = 16.9 Hz, C_{arom}), 112.27 (dd, J = 3.2, 22.3 Hz, C_{arom}), 114.69 (CN), 131.96 (t, J = 10.4 Hz, C_{arom}), 157.54 (C2), 158.84 (d, J = 6.1 Hz, C_{arom}), 161.95 (C4), 162.19 (d, J = 6.2 Hz, C_{arom}), 163.72 ppm (C6); ms: (70 eV, electron impact) *m/z* 308 (100%), 327 (69%, $C_{14}H_9{}^{35}Cl_2F_2N_3$, M^+), 329 (36%, $C_{14}H_9{}^{35}Cl^{37}ClF_2N_3$, M^++2), 331 (7%, $C_{14}H_9{}^{37}Cl_2F_2N_3$, M^++4). Anal. Calcd. for $C_{14}H_9Cl_2F_2N_3$ (328.14): C, 51.24; H, 2.76; N, 12.81. Found: C, 51.31; H, 2.26; N, 12.71.

2-(2,6-Dichloro-5-ethylpyrimidin-4-yl)-2-(3,5-dimethylphenyl) acetonitrile (3f). This compound was obtained as white crystals; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 1.01 (t, 3H, J = 7.6 Hz, C*H*$_3$CH$_2$), 2.31 [s, 6H, (C*H*$_3$)$_2$Ar], 2.75 (q, 2H, J = 7.6 Hz, CH$_3$C*H*$_2$), 5.35 (s, 1H, CH—CN), 6.98 ppm (s, 3H, H_{arom}); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 11.91 (*C*H$_3$CH$_2$), 21.21 (CH$_3$*C*H$_2$), 21.67 [$(CH_3)_2$Ar], 116.94 (CN), 125.43, 130.87, 131.67, 139.45 (C_{arom}), 132.04 (C5), 157.57 (C2), 163.98 (C4), 164.58 ppm (C6); hrms: (maldi) *m/z* calcd. for $C_{16}H_{16}Cl_2N_3$ (MH^+) 320.0716, found 320.0719.

Synthesis of 2-aryl-2-(2,6-dichloropyrimidin-4-yl)propanenitriles (4a,b). To a solution of **3a,b** (2 mmol) in dry dimethylformamide (10 mL) sodium hydride (131 mg, 3 mmol, 55% suspension in paraffin oil) was added portionwise at 0°C. The mixture was stirred for 1 h and then methyl iodide (0.19 mL, 3 mmol) was added at 0°C. The reaction mixture was stirred for 6 h at room temperature then poured on ice-cold water (100 mL). The mixture was extracted with ether (2 × 20 mL) and the combined ether phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residual material was purified by a silica gel column chromatography using petroleum ether:ether (1:1, v/v) as eluent to afford compounds **4a,b**.

2-(2,6-Dichloropyrimidin-4-yl)-2-phenylpropanenitrile (4a). This compound was obtained as colorless prisms; ^{1}H nmr ($CDCl_3$, 400 MHz): δ 2.18 (s, 3H, CH_3), 7.36–7.45 (m, 3H, H_{arom}), 7.47 (s, 1H, H5), 7.49–7.51 ppm (m, 2H, H_{arom}); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 25.80 (CH_3), 48.30 (*C*—CN), 117.63 (CN), 120.61 (C5), 126.19, 129.01, 129.41, 137.11 (C_{arom}), 160.93 (C4), 163.68 (C2), 171.49 ppm (C6); ms: (70 eV, electron impact) *m/z* 77 (100%), 277 (52%, $C_{13}H_9{}^{35}Cl_2N_3$, M^+), 279 (30%, $C_{13}H_9{}^{35}Cl^{37}ClN_3$, M^++2), 281 (6%, $C_{13}H_9{}^{37}Cl_2N_3$, M^++4). Anal. Calcd. for $C_{13}H_9Cl_2N_3$ (278.14): C, 56.14; H, 3.26; N, 15.11. Found: C, 56.70; H, 3.22; N, 15.11.

2-(2,6-Dichloropyrimidin-4-yl)-2-(3,5-dimethylphenyl)propanenitrile (4b). This compound was obtained as colorless prisms; ^{1}H nmr ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H, CH_3), 2.33 [s, 6H, (C*H*$_3$)$_2$Ar], 6.99 (s, 1H, H_{arom}), 7.06 (s, 2H, H_{arom}), 7.43 ppm (s, 1H, H5); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 21.36 [$(CH_3)_2$Ar], 25.65 (CH_3), 48.16 (*C*—CN), 117.77 (CN), 120.85 (C5), 123.87, 130.64, 136.99, 139.21 (C_{arom}), 160.85 (C4), 163.53 (C2), 171.80 ppm (C6); ms: (70 eV, electron impact) *m/z* 158 (100%), 305 (47%, $C_{15}H_{13}{}^{35}Cl_2N_3$, M^+), 307 (47%, $C_{15}H_{13}{}^{35}Cl^{37}ClN_3$, M^++2), 309 (9%, $C_{15}H_{13}{}^{37}Cl_2N_3$, M^++4). Anal. Calcd. for $C_{15}H_{13}Cl_2N_3$ (306.19): C, 58.84; H, 4.28; N, 13.72. Found: C, 58.71; H, 4.23; N, 13.57.

General procedure for synthesis of 6-arylalkylpyrimidine-2,4(1*H*,3*H*)-dione derivatives 5a–h. Each compound of **3a–f** and **4a,b** (5 mmol) was refluxed in a mixture of concentrated hydrochloric acid (30 mL) and acetic acid (5 mL) for 50 h. The reaction mixture was cooled to room temperature and the solid product formed was filtered off, washed with water, and dried to furnish compounds **5a–h**.

6-(2,6-Difluorobenzyl)pyrimidine-2,4(1H,3H)-dione (5b). This compound was obtained as a white solid; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 3.75 (s, 2H, CH_2), 4.78 (s, 1H, H5), 7.18 (t, J = 8.0 Hz, 2H, H_{arom}), 7.44–7.51 (m, 1H, H_{arom}), 11.09 ppm (bs, 2H, 2NH) ; ^{13}C nmr (DMSO-d_6, 100 MHz): δ 24.42 (CH_2), 97.41 (C5), 110.80 (t, J = 20.2 Hz, C_{arom}), 111.69 (dd, J = 18.7, 6.2 Hz, C_{arom}), 130.21 (t, J = 10.3Hz, C_{arom}), 151.31 (C6), 153.54 (C2), 160.76 (dd, J = 246.8, 7.7 Hz, C_{arom}), 163.79 ppm (C4); ms: (70 eV, electron impact) *m/z* 68 (100%), 238 (79%, M^+). Anal. Calcd. for $C_{11}H_8F_2N_2O_2.0.4H_2O$ (245): C, 53.93; H, 3.46; N, 11.43. Found: C, 53.82; H, 3.15; N, 11.33.

6-(3,5-Dimethylbenzyl)pyrimidine-2,4(1H,3H)-dione (5c). This compound was obtained as a white solid; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 2.25 (s, 6H, (C*H*$_3$)$_2$Ar)), 3.54 (s, 2H, CH_2), 5.23 (s, 1H, H5), 6.90 (s, 1H, H_{arom}), 6.93 (s, 2H, H_{arom}), 10.93 ppm (s, 2H, 2NH); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 20.75 [$(CH_3)_2$Ar], 37.30 (CH_2), 98.70 (C5), 126.65, 128.29, 135.82, 137.44 (C_{arom}), 151.53 (C6), 155.61 (C2), 164.02 ppm (C4); ms: (70 eV, electron impact) *m/z* 187 (100%), 230 (49%, M^+). Anal. Calcd. for $C_{13}H_{14}N_2O_2{\cdot}0.25\ H_2O$ (232.07): C, 67.28; H, 6.17; N, 12.07. Found: C, 67.15; H, 6.13; N, 12.08

6-(Mesitylmethyl)pyrimidine-2,4(1H,3H)-dione (5d). This compound was obtained as a white solid; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 2.15 (s, 6H, $2CH_3$), 2.23 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 4.40 (s, 1H, H5), 6.89 (s, 2H, H_{arom}), 10.98 ppm (bs, 2H, 2NH); ^{13}C nmr (DMSO-d_6, 75 MHz): δ 19.32 ($2CH_3$), 20.47 (CH_3), 30.94 (CH_2), 96.55 (C5), 128.68, 128.76, 136.00, 136.61 (C_{arom}), 151.47 (C4), 155.18 (C2), 163.97 ppm

(C6); hrms: (maldi) *m/z* Calcd. for $C_{14}H_{17}N_2O_2$ (MH^+) 245.1285, found 245.1294.

6-(2,6-Difluorobenzyl)-5-ethylpyrimidine-2,4(1H,3H)-dione (5e). This compound was obtained as a white solid; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.60 (t, 3H, J = 7.4 Hz, CH_3CH$_2$), 2.12 (q, 2H, J = 7.4 Hz, CH$_3$CH_2), 3.82 (s, 2H, CH_2Ar), 7.11 (t, 2H, J = 8.3 Hz, H_{arom}), 7.37–7.43 (m, 1H, H_{arom}), 10.78 (s, 1H, NH), 11.04 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 75 MHz): δ 12.54 (*C*H$_3$CH$_2$), 17.30 (CH$_3$*C*H$_2$), 23.72 (*C*H$_2$Ar), 111.23 (C5), 111.67 (dd, J = 7.5, 17.7 Hz, C_{arom}), 129.54 (t, J = 10.5 Hz, C_{arom}), 147.50 (C2), 150.73 (C6), 159.09 (d, J = 8.5 Hz, C_{arom}), 162.36 (d, J = 8.1 Hz, C_{arom}), 164.27 ppm (C4); ms: (70 eV, electron impact) *m/z* 266 (100%, M^+). Anal. Calcd. for $C_{13}H_{12}F_2N_2O_2$ (266.24): C, 58.65; H, 4.54; N, 10.52. Found: C, 58.68; H, 4.23; N, 10.38.

6-(1-Phenylethyl)pyrimidine-2,4(1H,3H)-dione (5g). This compound was obtained as a white solid; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.48 (d, 3H, J = 7.3 Hz, CH_3CH), 3.80 (q, 1H, J = 7.3 Hz, CH$_3$C*H*), 5.41 (s, 1H, H5), 7.25–7.50 (m, 5H, H_{arom}), 10.83 (s, 1H, NH), 10.96 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 180.60 (CH$_3$), 41.27 (CH), 97.18 (C5), 126.98, 127.42, 128.44, 141.54 (C_{arom}), 151.55 (C6), 159.45 (C2), 164.15 ppm (C4); ms: (70 eV, electron impact) *m/z* 216 (100%, M^+). Anal. Calcd. for $C_{12}H_{12}N_2O_2.0.6H_2O$ (227.05): C, 63.48; H, 5.86; N, 12.34. Found: C, 63.46; H, 5.24; N, 12.57.

6-[1-(3,5-Dimethylphenyl)ethyl]pyrimidine-2,4(1H,3H)-dione (5h). This compound was obtained as a white solid; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.44 (d, 3H, J = 7.3 Hz, CH_3CH), 2.25 [s, 6H, (CH_3)$_2$Ar], 3.70 (q, 1H, J = 7.3 Hz, CH$_3$C*H*), 5.39 (s, 1H, H5), 6.89 (s, 1H, H_{arom}), 6.95 (s, 2H, H_{arom}), 10.77 (s, 1H, NH), 10.94 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 18.59 (*C*H$_3$CH), 20.85 [(*C*H$_3$)$_2$Ar], 41.18 (CH$_3$*C*H), 97.06 (C5), 125.13, 128.38, 137.36, 141.35 (C_{arom}), 151.53 (C6), 159.59 (C2), 164.17 ppm (C4); ms: (70 eV, electron impact) *m/z* 158 (100%), 244 (86%, M^+). Anal. Calcd. for $C_{14}H_{16}N_2O_2$ (244.3): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.35; H, 6.54; N, 11.62.

Synthesis of 6-arylmethyl-5-bromopyrimidine-2,4(1*H*, 3*H*)-diones (6a–d). A suspension of **5a–d** (2 mmol), *N*-bromosuccinimide (0.4 g, 2.25 mmol) and benzoyl peroxide (10 mg) in absolute ethanol (15 mL) was stirred for 5 h at room temperature. The solid product was filtered off, washed with ethanol (5 mL) and dried to afford compounds **6a–d**.

6-Benzyl-5-bromopyrimidine-2,4(1H,3H)-dione (6a). This compound was obtained as a white solid; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 3.90 (s, 2H, CH$_2$), 7.25–7.37 (m, 5H, H_{arom}), 11.50 (s, 1H, NH), 11.53 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 400 MHz): δ 37.96 (CH$_2$), 96.01 (C5), 126.95, 128.30, 128.58, 135.13 (C_{arom}), 150.31 (C6), 152.41 (C2), 160.15 ppm (C4); ms: (70 eV, electron impact) *m/z* 201 (100%), 280 (13%, $C_{11}H_9{}^{79}BrN_2O_2$, M^+), 282 (19%, $C_{11}H_9{}^{81}BrN_2O_2$, M^++2). Anal. Calcd. for $C_{11}H_9BrN_2O_2$ (281): C, 47.00; H, 3.23; N, 9.97. Found: C, 46.99; H, 3.12; N, 9.86.

5-Bromo-6-(2,6-difluorobenzyl)pyrimidine-2,4(1H,3H)-dione (6b). This compound was obtained as a white solid; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 3.93 (s, 2H, CH$_2$); 7.11 (t, 2H, J = 8.3 Hz, H_{arom}), 7.37–7.44 (m, 1H, H_{arom}), 11.58 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 400 MHz): δ 26.98 (CH$_2$), 95.72 (C5), 110.96 (t, J = 19.1 Hz, C_{arom}), 111.55 (dd, J = 18.8, 6.2 Hz, C_{arom}), 129.67 (t, J =10.6 Hz, C_{arom}), 150.20 (C6), 151.28 (C2), 159.97 (C4), 160.41 ppm (dd, J =247.2, 8.1 Hz, C_{arom}); ms: (70 eV, electron impact) *m/z* 127 (100%), 316 (28%, $C_{11}H_7{}^{79}BrF_2N_2O_2$, M^+), 318 (23%, $C_{11}H_7{}^{81}BrF_2N_2O_2$, M^++2). Anal. Calcd. for $C_{11}H_7BrF_2N_2O_2$ (318.09): C, 41.67; H, 2.23; N, 8.83. Found: C, 41.46; H, 2.03; N, 8.64.

5-Bromo-6-(3,5-dimethylbenzyl)pyrimidine-2,4(1H,3H)-dione (6c). This compound was obtained as a white solid; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 2.24 (s, 6H, 2CH$_3$), 3.82 (s, 2H, CH$_2$), 6.89 (s, 1H, H_{arom}), 6.93 (s, 2H, H_{arom}), 11.42 (s, 1H, NH), 11.51 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 20.82 (2CH$_3$), 37.81 (CH$_2$), 95.95 (C5), 125.96, 128.33, 134.90, 137.51 (C_{arom}), 150.28 (C6), 152.45 (C2), 160.13 ppm (C4); ms: (70 eV, electron impact) *m/z* 158 (100%) 308 (22%, $C_{13}H_{13}{}^{79}BrN_2O_2$, M^+), 310 (20%, $C_{13}H_{13}{}^{81}BrN_2O_2$, M^++2). Anal. Calcd. for $C_{13}H_{13}BrN_2O_2$ (309.2): C, 50.50; H, 4.24; N, 9.06. Found: C, 50.78; H, 4.12; N, 8.97.

5-Bromo-6-(2,4,6-trimethylbenzyl)pyrimidine-2,4(1H,3H)-dione (6d). This compound was obtained as a white solid; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 2.19 (s, 6H, 2CH$_3$), 2.21 (s, 3H, CH$_3$), 3.90 (s, 2H, CH$_2$), 6.83 (s, 2H, H_{arom}), 10.60 (s, 1H, NH), 11.51 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 20.26 (2CH$_3$), 20.38 (CH$_3$), 95.65 (C5), 128.46, 128.88, 135.77, 137.20 (C_{arom}), 150.14 (C6), 152.61 (C2), 159.87 ppm (C4); ms: (70 eV, electron impact) *m/z* 243 (100%), 322 (21%, $C_{14}H_{15}{}^{79}BrN_2O_2$, M^+), 324 (19%, $C_{14}H_{15}{}^{81}BrN_2O_2$, M^++2). Anal. Calcd. for $C_{14}H_{15}BrN_2O_2$ (323.19): C, 52.03; H, 4.68; N, 8.67. Found: C, 51.93; H, 4.63; N, 8.49.

(3,5-Dimethylphenyl)(5-ethyl-2,6-dimethoxypyrimidin-4-yl) methanone (7). Sodium (0.3 g, 13 mmol) was dissolved in anhydrous methanol (15 mL) at 0°C. Compound **3f** (1 g, 3.1 mmol) was added and the mixture was refluxed for 20 h. Stream of oxygen was pumped through the solution at room temperature for 2 h, the solvent was concentrated to 5 mL under reduced pressure. Water (30 mL) was added to the mixture and the solid product formed was filtered off and dried to give 0.85 g (91%) of **7** as a white solid; mp 99–100°C, 97–99°C [27].

Synthesis of 1-(3,5-dimethylphenyl)-1-(5-ethyl-2,6-dimethoxypyrimidin-4-yl)ethanol (8). Under stream of nitrogen, a solution of MeMgBr (4 mL, 12 mmol, and 3 *M* in Et$_2$O) was added dropwise to a stirred solution of compound **7** (3.0 g, 10 mmol) in diethyl ether (20 mL) at –20°C, the reaction was left to reach room temperature with stirring for 2 h. The reaction was quenched by a saturated solution of ammonium chloride (10 mL). Water (10 mL) was added to the mixture and was extracted with ether (2 × 15 mL). The combined ether phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using ether:petroleum ether (1:10, v/v) as eluent to afford 2.9 g of **8** as a colorless prisms; yield 92%; mp 73–75°C; ^{1}H nmr (CDCl$_3$, 300 MHz): δ 0.59 (t, 3H, J = 7.0 Hz, CH_3CH$_2$), 1.89 (s, 3H, CH_3—C—OH), 2.24 (q, 2H, J = 7.0 Hz, CH$_3$CH_2), 2.27 (s, 6H, (CH_3)$_2$Ar) 3.99 (s, 3H, OCH$_3$), 4.08 (s, 3H, OCH$_3$), 6.29 (s, 1H, OH), 6.88 (s, 1H, H_{arom}), 6.94 ppm (s, 2H, H_{arom}); ^{13}C nmr (CDCl$_3$, 75 MHz): δ 11.87 (*C*H$_3$CH$_2$), 18.56 (CH$_3$*C*H$_2$), 21.32 [(*C*H$_3$)$_2$Ar], 27.29 (*C*H$_3$—C—OH), 54.27, 54.67 (2 OCH$_3$), 74.41 (C—OH), 113.21 (C5), 124.17, 128.93, 137.58, 145.17 (C_{arom}), 161.08 (C6), 169.89 (C2), 171.33 ppm (C4); ms: (70 eV, electron impact) *m/z* 316 (100%, M^+).

Fluorination of 8: Synthesis of compounds 9 and 10. A solution of DAST (0.5 mL, 3.8 mmol) in 1 mL dichloromethane was added dropwise at –5°C to a solution of compound

8 (0.7 g, 2.5 mmol) in dichloromethane (10 mL) under argon at –5°C. The solution was stirred and left to reach room temperature for 4 h. The reaction was quenched by addition of 1 mL saturated solution of sodium carbonate with stirring. Water (10 mL) was added to the mixture and extracted with dichloromethane (2 × 10 mL). The combined dichloromethane phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed by a silica gel column using petroleum ether:ether (2:1, v/v) as eluent to give compounds **9** and **10**.

4-[1-(3,5-Dimethylphenyl)vinyl]-5-ethyl-2,6-dimethoxypyrimidine (9). This compound was obtained as a white solid; yield 37%; mp 112–114°C; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 0.93 (t, 3H, J = 7.4 Hz, C*H*$_3$CH$_2$), 2.27 [s, 6H, (C*H*$_3$)$_2$Ar], 2.38 (q, 2H, J = 7.4 Hz, CH$_3$C*H*$_2$), 3.96 (s, 3H, OCH$_3$), 4.03 (s, 3H, OC*H*$_3$), 5.27, 5.81 (2s, 2H, CH$_2$=C), 6.92 ppm (s, 3H, H$_{arom}$); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 13.59 (*C*H$_3$CH$_2$), 18.88 (CH$_3$*C*H$_2$), 21.26 [(*C*H$_3$)$_2$Ar], 53.90, 54.53 (2 OCH$_3$), 114.78 (C5), 115.54 (*C*H$_2$=C), 124.16, 129.65, 137.72, 146.43 (C$_{arom}$), 138.46 (CH$_2$=*C*), 162.83 (C2), 166.92 (C6), 171.12 ppm (C4); ms: (70 eV, electron impact) m/z 298 (100%, M^+). Anal Calcd. for $C_{18}H_{22}N_2O_2$ (298.38): Calcd: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.42; H, 7.53; N, 9.38.

4-[1-(3,5-Dimethylphenyl)-1-fluoroethyl]-5-ethyl-2,6-dimethoxypyrimidine (10). This compound was obtained as an oil; yield 28%; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 0.86 (t, 3H, J = 7.3 Hz, C*H*$_3$CH$_2$), 2.00 (d, 3H, $J_{H,F}$ = 24.0 Hz, C*H*$_3$—C—F), 2.27 [s, 6H, (C*H*$_3$)$_2$Ar], 2-39–2.47 (m, 2H, CH$_3$C*H*$_2$), 3.97 (s, 1H, OCH$_3$), 4.02 (s, 3H, OCH$_3$), 6.88 (s, 1H, H$_{arom}$), 6.93 ppm (s, 2H, H$_{arom}$); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 13.31 (d, J = 1.9 Hz, *C*H$_3$CH$_2$), 18.24 (d, J = 6.7 Hz, CH$_3$*C*H$_2$), 21.36 [(*C*H$_3$)$_2$Ar], 29.22 (d, J = 25.4 Hz, *C*H$_3$—C—F), 54.08 (OCH$_3$), 54.48 (OCH$_3$), 99.52 (d, J = 174.8 Hz, C—F), 115.68 (C5), 121.79 (d, J = 7.2 Hz, C$_{arom}$), 129.05 (C$_{arom}$), 137.66 (d, J = 1.3 Hz, C$_{arom}$), 143.99 (d, J = 23.7 Hz, C$_{arom}$), 161.88 (C2), 166.28 (d, J = 23.7 Hz, C4), 171.26 ppm (C6); hrms: (MALDI) m/z Calcd. for $C_{18}H_{24}FN_2O_2$ (MH^+) 319.1816, found 319.1808.

6-[1-(3,5-Dimethylphenyl)-1-fluoroethyl]-5-ethylpyrimidine-2,4(1*H*,3*H*)-dione (11). Under stream of nitrogen, a mixture of TMSI (0.16 mL, 1.1 mmol) and compound **10** (160 mg, 0.5 mmol) in dry chloroform (15 mL) was refluxed for 2 h and the mixture was left to reach room temperature. The reaction was quenched with 5% aqueous sodium bicarbonate solution (2 mL), water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with chloroform (2 × 10 mL). The chloroform phases were dried using sodium sulfate and evaporated under reduced pressure. The residual material was chromatographed on a silica gel column using ether as eluent to give 60 mg of **11** as a white solid; yield 63%; mp 200–202°C; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 0.69 (t, 3H, J = 7.2 Hz, C*H*$_3$CH$_2$), 2.07 (q, 2H, J = 7.2 Hz, CH$_3$C*H*$_2$), 2.08 (d, 3H, $J_{H,F}$ = 24 Hz, CH$_3$—C—F), 2.34 [s, 6H, (C*H*$_3$)$_2$Ar], 7.04 (s, 3H, H$_{arom}$), 8.61 (s, 1H, NH), 9.72 ppm (s, 1H, NH); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 12.29 (*C*H$_3$CH$_2$), 18.62 (CH$_3$*C*H$_2$), 21.30 [(*C*H$_3$)$_2$Ar], 24.30 (d, J = 26.5 Hz, *C*H$_3$—C—F), 95.29 (d, J = 174.5 Hz, C—F), 111.63 (C5), 123.97 (d, J = 5.1 Hz, C$_{arom}$), 131.50 (d, J = 3.3 Hz, C$_{arom}$), 138.59 (d, J = 2.1 Hz, C$_{arom}$), 138.18 (d, J = 20.8 Hz, C$_{arom}$), 149.93 (d, J = 43.5 Hz, C6), 150.29 (C2), 164.79 ppm (C4); hrms: (maldi) m/z Calcd. for $C_{16}H_{19}FNaN_2O_2$ (MNa^+) 313.1323, found 313.1323. Anal. Calcd. for $C_{16}H_{19}FN_2O_2 \cdot 0.7H_2O$ (302.95): C, 63.44; H, 6.79; N, 9.25. Found: C, 63.26; H, 6.51; N, 8.82.

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