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Synthesis of 2-substituted 6-(5-oxo-1-phenylpyrrolidin-3-yl)pyrimidin-4(3*H*)-ones

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ABSTRACT

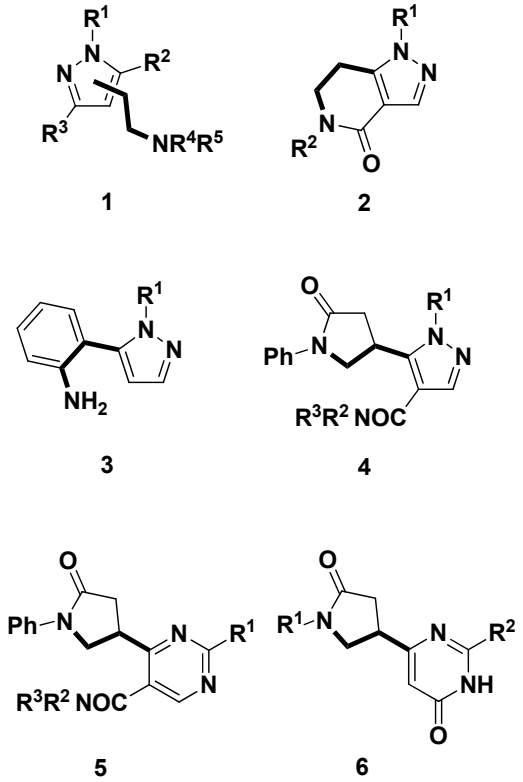
2-Substituted 6-(5-oxo-1-phenylpyrrolidin-3-yl)pyrimidin-4(3*H*)-ones were synthesized in three steps from itaconic acid derivatives via cyclization with primary amines followed by Masamune-Claisen condensation, and cyclization of the newly formed *β*-keto esters with amidines. Preparation and/or isolation of β-keto esters with polar *N*-substituents failed, but the corresponding final products were obtained in a different way. 6-(1-(3-Hydroxypropyl)-5-oxopyrrolidin-3-yl)-2-phenylpyrimidin-4(3*H*)-one was obtained by hydrogenolytic o-deprotection of its *o*-benzyl derivative. Depending on reaction conditions, further mesylation of 6-(1-(3-(benzyloxy)propyl)-5-oxopyrrolidin-3-yl)-2-phenylpyrimidin-4(3*H*)-one followed by treatment with pyrrolidine gave either the monoaminated- or the diaminated product. The structures of novel compounds were determined by NMR.

1. Introduction

Histamine, dopamine, tryptamine, serotonin, and melatonin are representative chemical messengers playing a crucial role in biological processes [1]. Various 2-[(hetero)aryl]ethylamines are analogues of the above chemical messengers and, consequently, such 2-ethylamino-functionalized heterocyclic compounds represent attractive synthetic targets. In this context, the preparation of novel synthetic analogues of naturally occurring 2-((hetero)aryl)ethylamines is of particular interest in medicinal, synthetic organic, and combinatorial chemistry [2-9]. In the last decade, the synthesis of aminoethyl functionalized heterocycles has represented an important part of our research studies. Within this context, we have been so far focused on the synthesis of two types of 2-(heteroaryl) ethylamines: a) the open-chain analogues of histamine, **1**, [10-13] and bicyclic conformationally constrained analogues of histamine, **2**-**4**, [14-16] and b) 2-substituted 6-(5-oxo-1-phenylpyrrolidin-3-yl)pyrimidine-5-carboxamides, **5**, as 2-aminoethyl-functionalized pyrimidines [17]. In continuation, we have focused our attention on 2-substituted 6-(5-oxo-1-phenylpyrrolidin-3-yl)pyrimidin-4(3*H*)-ones, **6**, as novel type of 2-aminoethyl-functionalized pyrimidines (Scheme 1).

2. Experimental

[1,1'-Biphenyl]-4-carboxamidine hydrochloride (**11d**), and 4-((pyrrolidin-1-yl)methyl)benzamidine dihydrochloride (**11e**) were purchased from Ukrorgsyntez Ltd. 5-Oxo-1-phenylpyrrolidine-3-carboxylic acid (**9a**) [18], methyl 3-oxo-3-(5-oxo-1-phenylpyrrolidin-3-yl)propanoate (**10a**) [16], and 3-(benzyloxy)propylamine (**8b**) [19] were prepared according to the literature procedures. All other compounds were purchased from Sigma-Aldrich.



Scheme 1

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2.1. Instrumentation

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting point system. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus. All NMR measurements were performed with TMS as the internal standard. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS spectrometer. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrophotometer. Microwave irradiations were performed on CEM Discover Laboratory Microwave Oven. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II on the Faculty of Chemistry and Chemical Technology, University of Ljubljana. Flash column chromatography (FC) and column chromatography (CC) were performed on silica gel (Fluka, Silica gel 60, particle size 0.035-0.070 mm). Medium pressure liquid chromatography (MPLC) was performed on a Büchi Flash Chromatography System (Büchi Fraction Collector C-660, Büchi Pump Module C-605, Büchi Control Unit C-620) on silica gel (LiChroprep® Si 60, 15-25 μm), column dimensions: 26×460 mm, backpressure: 10 Bar, detection: UV (254 nm).

2.2. Synthesis

2.2.1. Synthesis of 1-(3-(substituted)propyl)-5-oxopyrrolidine-3-carboxylic acids (9c,d)

Compounds **9c** and **9d** were prepared following modified literature procedure [18]. A mixture of itaconic acid (**7a**) (1.30 g, 10 mmol), water (4 mL), and 3-amino-1-propanol (**8c**) (751 mg, 10 mmol) or 3-(dimethylamino)propanamine (**8d**) (1.021 g, 10 mmol) was heated in a sealed vessel under microwave irradiation (300 W, 120 °C, ~3 bar) for 1 h. The reaction mixture was evaporated in vacuum and the residual water was removed by repetitive co-evaporation in vacuum with ethyl acetate (3×20 mL) and dichloromethane (3×20 mL) to give the crude oily compounds **9c** and **9d**, which were used in the following step without purification (Scheme 2).

1-(3-(Hydroxy)propyl)-5-oxopyrrolidine-3-carboxylic acid (**9c**): Yield: 100% of brownish oil. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.57 (p, 2H, J = 6.8 Hz, $CH_2CH_2CH_2$), 2.38-2.43 (m, 2H, 4-CH_2), 2.93-3.04 (m, 1H, 3-H), 3.19 (dt, 2H, J = 4.0, 7.1 Hz, $CH_2CH_2CH_2N$), 3.37 (t, 2H, J = 6.3 Hz, $CH_2CH_2CH_2O$), 3.44-3.50 (m, 2H, 2-CH_2), OH and COOH exchanged.

1-(3-(Dimethylamino)propyl)-5-oxopyrrolidine-3-carboxylic acid (**9d**): Yield: 100% of brownish oil. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.60 (p, 2H, J = 7.2 Hz, $CH_2CH_2CH_2$), 2.21 (s, 6H, NMe_2), 2.26-2.34 (m, 2H, $CH_2CH_2CH_2NMe_2$), 2.38-2.44 (m, 2H, 4-CH_2), 2.95-3.06 (m, 1H, 3-H), 3.09-3.24 (m, 2H, $CH_2CH_2CH_2N$), 3.44-3.50 (m, 2H, 2-CH_2), COOH exchanged.

2.2.2. Synthesis of methyl 1-(3-(benzyloxy)propyl)-5-oxopyrrolidine-3-carboxylate (12)

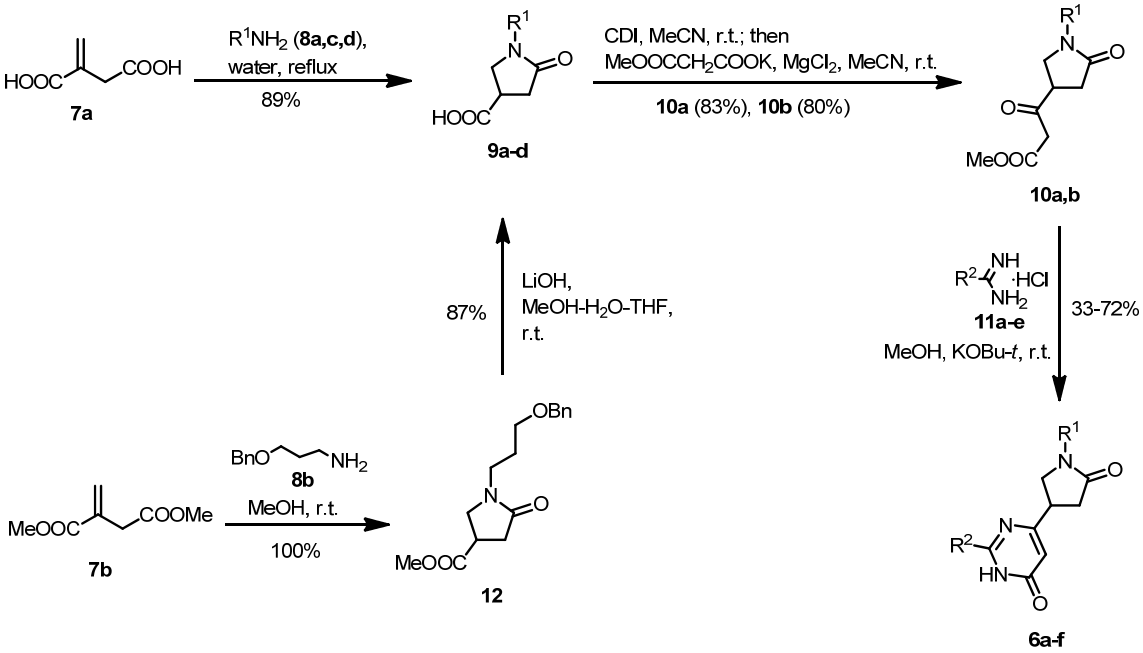
This compound was prepared following a slightly modified literature procedure [20]. A solution of 3-(benzyloxy)propan-1-amine (**8b**) (2.484 g, 15 mmol) in methanol (20 mL) was added drop wise to a stirred solution of dimethyl itaconate (**7b**) (2.378 g, 15 mmol) in methanol (70 mL) at room temperature (r.t.) and the mixture was stirred at r.t. for 24 h. The solvent was removed in vacuum to give the crude oily **12**, which was used in the following step without further purification (Scheme 2). Yield: 100% of yellowish oil. FT-IR (KBr, cm^{-1}): 3029 ν(CH) (br, alkyl), 2948 ν(CH) (br, alkyl), 2860 ν(CH) (br, alkyl), 1733 ν(C=O) (ester), 1683 ν(C=O) (br, amide), 1493, 1452, 1434, 1362, 1265, 1199, 1178, 1098, 1026, 937, 848, 737, 698, 609. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.84 (tt, 2H, J = 7.2, 6.1 Hz, $CH_2CH_2CH_2$), 2.61 (dd, 1H, J = 17.1, 9.6 Hz, 4-Ha), 2.68 (dd, 1H, J = 17.1, 7.6 Hz, 4-Hb), 3.12-3.24 (m, 1H, 3-H), 3.40 (td, 2H, J = 2.7; 7.0 Hz, $CH_2CH_2CH_2N$), 3.50 (t, 2H, J = 6.2 Hz, $CH_2CH_2CH_2O$), 3.55-3.65 (m, 2H, 2-CH_2), 3.73 (s, 3H, CO_2Me), 4.49 (s, 2H, $PhCH_2O$), 7.27-7.38 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ, ppm): 27.0, 33.5, 35.4, 39.4, 48.6, 51.7, 67.2, 72.4, 127.0, 127.1, 127.8, 137.9, 171.7, 172.7. HRMS (EI): m/z found for $C_{16}H_{21}NO_4$: m/z = 292.1544 (MH^+); calcd.: m/z = 292.1549 (MH^+).

2.2.3. Synthesis of 1-(3-(Benzyloxy)propyl)-5-oxopyrrolidine-3-carboxylic acid (9b)

$LiOH·H_2O$ (839 mg, 20 mmol) was added to a solution of the ester **12** from the above experiment (15 mmol) in a mixture of THF (7 mL), H_2O (7 mL), and MeOH (7 mL). The resulting mixture was stirred at r.t. for 1 h. MeOH and THF were removed by evaporation in vacuum at 50 mbar/35 °C, the aqueous residue was diluted with H_2O (20 mL), and washed with CH_2Cl_2 (3×100 mL). The aqueous phase was acidified with aq. HCl (1M, 22 mL) and the product was extracted with EtOAc (3×100 mL). The combined organic phase was dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated in vacuum to give compound **9b** (Scheme 2). Yield: 87% of yellowish oil. FT-IR (NaCl, cm^{-1}): 2926 ν(CH) (alkyl), 1731 ν(C=O) (ester), 1650 ν(C=O) (amide), 1496, 1454, 1366, 1199, 1105, 745, 700. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.84 (p, 2H, J = 6.9 Hz, $CH_2CH_2CH_2$), 2.67 (dd, 1H, J = 17.3, 9.7 Hz, 4'-Ha), 2.75 (dd, 1H, J = 17.2, 7.2 Hz, 4'-Hb), 3.11-3.27 (m, 1H, 3'-H), 3.41 (td, 2H, J = 7.2, 2.5 Hz, $CH_2CH_2CH_2N$), 3.50 (t, 2H, J = 6.1 Hz, $CH_2CH_2CH_2O$), 3.58 (dd, 1H, J = 10.1, 8.5 Hz, 2'-Ha), 3.66 (dd, 1H, J = 10.1, 6.1 Hz, 2'-Hb), 4.48 (s, 2H, $PhCH_2O$), 6.91 (br s, 1H, COOH), 7.23-7.43 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 27.4, 34.2, 36.0, 40.4, 49.6, 67.7, 73.1, 127.8, 127.9, 128.5, 138.2, 173.9, 175.7. HRMS (EI): m/z found for $C_{15}H_{19}NO_4$: 278.1379 (MH^+); calcd.: m/z = 278.1392 (MH^+).

2.2.4. Synthesis of methyl 3-(1-(3-(benzyloxy)propyl)-5-oxopyrrolidin-3-yl)-3-oxopropanoate (10b)

This compound was prepared following the literature procedure for the synthesis of closely related compounds [2,3]. Under argon, 1,1'-carbonyldiimidazole (CDI) (2.69 g, 16.59 mmol) was added to a stirred solution of carboxylic acid **9b** (3.63 g, 13.1 mmol) in anh. THF (60 mL) at r.t. and the resulting mixture was stirred at r.t. for 1 h. During this time CO_2 evolved, therefore the reaction flask was not completely sealed. A solid powdered mixture of $MgCl_2$ (1.21 g, 12.71 mmol) and potassium monomethyl malonate (3.07 g, 19.65 mmol) was added under a blanket of argon in one portion via a powder funnel, which was then rinsed with anh. THF (20 mL), and the resulting suspension was stirred under argon at r.t. for 12 h. Volatile components were evaporated in vacuum, aq. $NaHSO_4$ (1M, 100 mL) was added to the residue, and the product was extracted with EtOAc (3×100 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and the filtrate were evaporated in vacuum and the crude oily reside was purified by CC (EtOAc). Fractions containing the product were combined and volatile components were evaporated in vacuum to give compound **10b** (Scheme 2). Yield: 3.50 g (80%) of yellowish oil. FT-IR (NaCl, cm^{-1}): 2952 ν(CH) (alkyl), 2866 ν(CH) (alkyl), 1747 ν(C=O) (ester), 1715 ν(C=O) (ketone), 1682 ν(C=O) (amide), 1495, 1454, 1362, 1317, 1268, 1100, 1027, 743, 700. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.85 (p, 2H, J = 7.0, 6.6 Hz, $CH_2CH_2CH_2$), 2.50-2.72 (m, 2H, 4'-CH_2), 3.36-3.45 (m, 1H, 3'-H), 3.40 (td, 2H, J = 7.0, 2.0 Hz, $CH_2CH_2CH_2N$), 3.46-3.54 (m, 5H, $CH_2CH_2CH_2O$, CH_2COOMe, and 2'-Ha), 3.64 (dd, 1H, J = 9.5, 5.9 Hz, 2'-Hb), 3.75 (s, 3H, COOMe), 4.48 (s, 2H, $PhCH_2O$), 7.23-7.40 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ, ppm): 27.4, 33.3, 40.2, 42.9, 47.5, 47.9, 52.5, 67.8, 73.1, 127.6, 127.7, 128.4, 138.3, 167.0, 171.9, 200.9. HRMS (EI): m/z found for $C_{18}H_{23}NO_5$: m/z = 334.1658 (MH^+); calcd.: m/z = 334.1654 (MH^+).



8a-10a: R^1 = Ph
8b-10b: R^1 = -$(CH_2)_3$OBn
8c, 9c: R^1 = -$(CH_2)_3$OH
8d, 9d: R^1 = -$(CH_2)_3$NMe$_2$

10a+11a → 6a: 33%, R^1 = Ph, R^2 = H
10a+11b → 6b: 49%, R^1 = Ph, R^2 = Me
10a+11c → 6c: 72%, R^1 = Ph, R^2 = Ph
10a+11d → 6d: 72%, R^1 = Ph, R^2 = 1,1'-biphenyl-4-yl
10a+11e → 6e: 37%, R^1 = Ph, R^2 = 4-((pyrrolidin-1-yl)methyl)phenyl
10b+11c → 6f: 58%, R^1 = -$(CH_2)_3$OBn, R^2 = Ph

Scheme 2

2.2.5. General procedure for the synthesis of 2-substituted 6-(5-oxo-1-phenylpyrrolidin-3-yl)pyrimidin-4(3H)-ones (6a-f)

A mixture of β-keto ester **10a**,**b** (1 mmol), MeOH (4 mL), amidine salt **11a-e** (1 mmol), and KOBu-*t* (112 mg, 1 mmol) was stirred at r.t. for 48 h. Then, water (4 mL) was added, the mixture was stirred at r.t. for 1 h, and the precipitate was collected by filtration to give **6a-f**. In this manner, analytically pure compounds **6a-d** were obtained (Scheme 2). Compounds **6e** and **6f** were further purified by FC over silica gel (d = 3 cm, l = 5 cm). Fractions containing the product were combined and evaporated *in vacuo* to give compound **6e** and **6f** (Scheme 2).

6-(5-Oxo-1-phenylpyrrolidin-3-yl)pyrimidin-4(3H)-one (**6a**): Prepared from **10a** (261 mg, 1 mmol), formamidine acetate (**11a**) (104 mg, 1 mmol), and KOBu-*t* (112 mg, 1 mmol). White. Yield: 33%. M.p.: 223-228 °C (with slow decomp. above 200 °C). FT-IR (KBr, cm^{-1}): 2794 ν(OH) (br, alkyl), 1682 ν(C=O) (amide), 1662 ν(C=O) (amide), 1601, 1500, 1488, 1458, 1427, 1398, 1307, 1283, 1242, 1221, 1203, 1176, 1147, 1118, 1022, 979, 946, 916, 896, 877, 805, 773, 752, 721, 685, 661. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.70 (dd, 1H, *J* = 16.8, 7.7 Hz, 4'-Ha), 2.85 (dd, 1H, *J* = 16.8, 9.0 Hz, 4'-Hb), 3.60 (p, 1H, *J* = 8.1 Hz, 3'-H), 3.88 (dd, 1H, *J* = 9.8, 6.5 Hz, 2'-Ha), 4.13 (t, 1H, *J* = 9.1 Hz, 2'-Hb), 6.32 (s, 1H, 5-H), 7.13 (t, 1H, *J* = 7.3 Hz, *p*-Ph), 7.37 (t, 2H, *J* = 7.8 Hz, *m*-Ph), 7.66 (d, 2H, *J* = 8.0 Hz, *o*-Ph), 8.19 (s, 1H, 2-H), 12.44 (s, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6, δ, ppm): 36.7, 37.3, 52.0, 112.3, 119.4, 124.0, 128.7, 139.3, 150.4, 161.2, 167.0, 172.3. Anal. calcd. for $C_{14}H_{13}N_3O_2 \cdot 1¼H_2O$: C, 55.89; H, 4.77; N, 13.97. Found: C, 55.82; H, 4.47; N, 13.68%.

2-Methyl-6-(5-oxo-1-phenylpyrrolidin-3-yl)pyrimidin-4(3H)-one (**6b**): Prepared from **10a** (261 mg, 1 mmol), acetamidine hydrochloride (**11b**)(95 mg, 1 mmol), and KOBu-*t* (112 mg, 1 mmol). White. Yield: 49%. M.p.: 234-237 °C. FT-IR (KBr, cm^{-1}): 2986 ν(CH) (br, alkyl), 1670 ν(C=O) (br, amide), 1591, 1497, 1474, 1450, 1410, 1386, 1355, 1305, 1280, 1230, 1212, 1176, 1128, 1048, 1017, 955, 888, 847, 752, 697, 684, 663. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.28 (s, 3H, 2-Me), 2.72 (dd, 1H, *J* = 16.8, 8.4 Hz, 4'-Ha), 2.81 (dd, 1H, *J* = 16.9, 9.0 Hz, 4'-Hb), 3.55 (qd, 1H, *J* = 8.5, 6.9 Hz, 3'-H), 3.88 (dd, 1H, *J* = 9.7, 7.0 Hz, 2'-Ha), 4.10 (dd, 1H, *J* = 9.7, 8.4 Hz, 2'-Hb), 6.16 (s, 1H, 5-H), 7.03-7.22 (m, 1H, *p*-Ph), 7.28-7.45 (m, 2H, *m*-Ph), 7.60-7.76 (m, 2H, *o*-Ph), 12.38 (s, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6, δ, ppm): 21.3, 36.9, 37.2, 52.0, 109.2, 119.4, 124.0, 128.7, 139.3, 159.7, 162.4, 166.7, 172.3. Anal. calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.60; H, 5.54; N, 15.38%.

6-(5-Oxo-1-phenylpyrrolidin-3-yl)-2-phenylpyrimidin-4(3H)-one (**6c**): Prepared from **10a** (261 mg, 1 mmol), benzamidine hydrochloride (**11c**)(157 mg, 1 mmol), and KOBu-*t* (112 mg, 1 mmol). Yield: 72% of white solid. M.p.: 235-236 °C. FT-IR (KBr, cm^{-1}): 3065 ν(CH) (br, alkyl), 1684 ν(C=O) (amide), 1685 ν(C=O) (amide), 1597, 1542, 1497, 1471, 1444, 1389, 1348, 1301, 1281, 1228, 1180, 1126, 1034, 982, 925, 857, 792, 757, 688, 669, 660, 641, 615. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.82 (dd, 1H, *J* = 16.3, 7.4 Hz, 4'-Ha), 2.90 (dd, 1H, *J* = 16.2, 8.0 Hz, 4-Hb), 3.69 (qd, 1H, *J* = 8.2, 6.5 Hz, 3'-H), 3.98 (dd, 1H, *J* = 9.8, 6.5 Hz, 2'-Ha), 4.20 (dd, 1H, *J* = 9.8, 8.2 Hz, 2'-Hb), 6.36 (s, 1H, 5-H), 7.05-7.20 (m, 1H, *p*-Ph), 7.38 (dd, 2H, *J* = 8.6, 7.3 Hz, *m*-Ph), 7.47-7.61 (m, 3H, *p*-Ph and *m*-Ph), 7.66-7.72 (m, 2H, *o*-Ph), 8.11-8.17 (m, 2H, *o*-Ph), 12.65 (s, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6, δ, ppm): 37.1, 37.4, 52.3, 109.6, 119.5, 124.0, 127.9, 128.6, 128.7, 131.8, 132.5, 139.4, 157.8, 163.6, 167.2,

172.4. Anal. calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.16; H, 5.01; N, 12.54%.

2-([1,1'-Biphenyl]-4-yl)-6-(5-oxo-1-phenylpyrrolidin-3-yl) pyrimidin-4(3H)-one (**6d**): Prepared from **10a** (261 mg, 1 mmol), [1,1'-biphenyl]-4-carboxamidine hydrochloride (**11d**)(232 mg, 1 mmol), and KOBu-*t* (112 mg, 1 mmol). Yield: 72% of white solid. M.p.: 303-308 °C. FT-IR (KBr, cm^{-1}): 2877 ν(CH) (br, alkyl), 1693 ν(C=O) (amide), 1649 ν(C=O) (amide), 1594, 1542, 1519, 1491, 1384, 1356, 1296, 1281, 1223, 1187, 1128, 1040, 1008, 980, m900, 847, 756, 732, 688, 674. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.85 (dd, 1H, *J* = 16.8, 7.9 Hz, 4'-Ha), 2.91 (dd, 1H, *J* = 16.7, 8.8 Hz, 4'-Hb), 3.70 (p, 1H, *J* = 7.8 Hz, 3'-H), 4.00 (dd, 1H, *J* = 9.6, 6.5 Hz, 2'-Ha), 4.21 (dd, 1H, *J* = 9.7, 8.2 Hz, 2'-Hb), 6.37 (s, 1H, 5-H), 7.14 (t, 1H, *J* = 7.3 Hz, *p*-Ph), 7.35-7.45 (m, 3H, *m,p*-Ph), 7.50 (t, 2H, *J* = 7.7 Hz, *m*-Ph), 7.71 (dd, 2H, *J* = 8.3, 1.3 Hz, *m*-C_6H_4), 7.75 (d, 2H, *J* = 7.3 Hz, *o*-Ph), 7.82 (d, 2H, *J* = 8.5 Hz, *o*-C_6H_4), 8.25 (d, 2H, *J* = 8.0 Hz, *o*-Ph), 12.76 (s, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6, δ, ppm): 37.1, 37.3, 52.3, 119.4, 123.8, 126.6, 126.7, 127.9, 128.3, 128.5, 128.8, 139.0, 139.2, 172.1. Anal. calcd. for $C_{26}H_{21}N_3O_2 \cdot \frac{1}{3}H_2O$: C, 75.53; H, 5.28; N, 10.16. Found: C, 75.82; H, 5.23; N, 10.16%.

6-(5-Oxo-1-phenylpyrrolidin-3-yl)-2-(4-((pyrrolidin-1-yl) methyl)phenyl)pyrimidin-4(3H)-one (**6e**): Prepared from **10a** (261 mg, 1 mmol), 4-((pyrrolidin-1-yl)methyl)benzamidine dihydrochloride (**11e**)(232 mg, 1 mmol), and KOBu-*t* (224 mg, 2 mmol); flash chromatography (FC) first EtOAc:EtOH = 10:1 to elute less polar impurities, then EtOAc:EtOH = 3:1 to elute the product **6e**. Yield: 37% of yellowish solid. M.p.: 202-214 °C (with slow decomp. above 200 °C). FT-IR (KBr, cm^{-1}): 2954 ν(br, CH) (alkyl), 2772 ν(CH) (alkyl), 1690 ν(C=O) (amide), 1651 ν(C=O) (amide), 1594, 1541, 1514, 1495, 1476, 1421, 1386, 1358, 1299, 1280, 1219, 1186, 1127, 1042, 981, 861, 756, 690, 673, 661. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm):1.64-1.76 (m, 4H, 2×CH_2 of pyrrolidine), 2.40-2.52 (m, 4H, 2×CH_2 of pyrrolidine), 2.82 (dd, 1H, *J* = 16.7, 7.8 Hz, 4'-Ha), 2.90 (dd, 1H, *J* = 16.7, 8.6 Hz, 4'-Hb), 3.65 (s, 2H, ArCH_2N), 3.66 (p, 1H, *J* = 8.1 Hz, 3'-H), 3.97 (dd, 1H, *J* = 9.7, 6.5 Hz, 2'-Ha), 4.19 (dd, 1H, *J* = 9.8, 8.2 Hz, 2'-Hb), 6.33 (s, 1H, 5-H), 7.13 (t, 1H, *J* = 7.4 Hz, *p*-Ph), 7.38 (dd, 2H, *J* = 8.7, 7.2 Hz, *m*-Ph), 7.43 (d, 2H, *J* = 8.2 Hz, *m*-C_6H_4), 7.70 (dd, 2H, *J* = 8.7, 7.2 Hz, *o*-Ph), 8.09 (d, 2H, *J* = 8.3 Hz, *o*-C_6H_4), 12.56 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz, δ, ppm): 23.1, 37.1, 37.4, 52.3, 53.5, 59.0, 109.2, 119.5, 124.0, 127.8, 128.6, 128.7, 131.3, 139.4, 143.1, 157.8, 163.9, 167.1, 172.4. Anal. calcd. for $C_{25}H_{26}N_4O_2 \cdot H_2O$: C, 69.42; H, 6.53; N, 12.95. Found: C, 69.37; H, 6.31; N, 12.97%.

6-(1-(3-(Benzyloxy)propyl)-5-oxopyrrolidin-3-yl)-2-phenyl pyrimidin-4(3H)-one (**6f**): Prepared from **10b** (261 mg, 1 mmol), benzamidine hydrochloride (**11c**)(157 mg, 1 mmol), and KOBu-*t* (112 mg, 1 mmol); FC first EtOAc to elute less polar impurities, then EtOAc:MeOH = 10:1 to elute the product **6f**. Yield: 58% of yellowish oil. FT-IR (NaCl, cm^{-1}): 3063 ν(CH) (NH) (alkyl, lactam), 2928 ν(CH) (NH) (alkyl, lactam), 2861 ν(CH) (NH) (alkyl, lactam), 1657ν(C=O) (amide), 1603, 1548, 1502, 1444, 1310, 1265, 1102, 982, 850, 697. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.89 (p, 2H, *J* = 6.5 Hz, $CH_2CH_2CH_2$), 2.71 (dd, 1H, *J* = 16.7, 9.0 Hz, 4'-Ha), 2.81 (dd, 1H, *J* = 16.8, 7.8 Hz, 4'-Hb), 3.41-3.50 (m, 1H, 3'-H), 3.46 (t, 2H, *J* = 7.1 Hz, $CH_2CH_2CH_2$N), 3.52 (t, 2H, *J* = 6.2 Hz, $CH_2CH_2CH_2$O), 3.59 (dd, 1H, *J* = 9.6, 6.5 Hz, 2'-Ha), 3.71 (dd, 1H, *J* = 9.6, 8.5 Hz, 2'-Hb), 4.46 (s, 2H, PhCH_2O), 6.29 (s, 1H, 5-H), 7.20-7.34 (m, 5H, Ph), 7.49-7.61 (m, 3H, *m,p*-Ph), 8.16-8.22 (m, 2H, *o*-Ph), 12.73 (s, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6, δ, ppm): 27.7, 36.4, 38.5, 40.1, 51.8, 67.8, 73.1, 110.1, 127.6, 127.7, 127.9, 128.4, 129.0, 131.8, 132.3, 138.3, 157.4, 165.3, 168.6, 173.4. HRMS (EI): *m/z* found for $C_{24}H_{25}N_3O_3$: *m/z* = 404.1967 (MH^+); calcd.: *m/z* = 404.1974 (MH^+).

2.2.6. Synthesis of 6-(1-(3-hydroxypropyl)-5-oxopyrrolidin-3-yl)-2-phenylpyrimidin-4(3H)-one (6g)

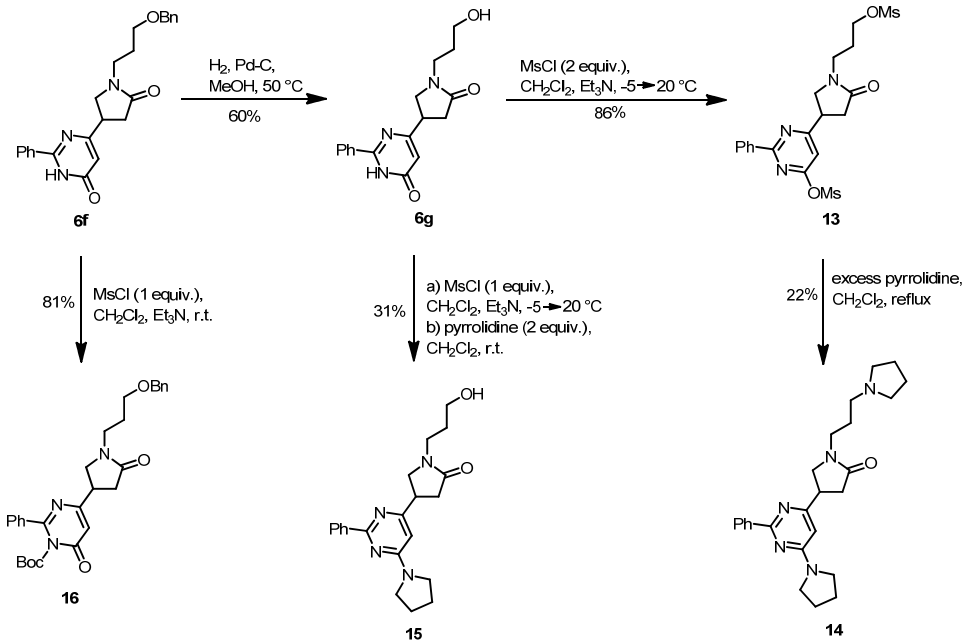
A mixture of **6f** (1 g, 2.48 mmol), MeOH (100 mL), and 10% Pd-C (350 mg) was hydrogenated (P = 60 psi of H_2) at 50 °C for 7 days. The reaction mixture was filtered through a plug of Celite® and thoroughly washed with CH_2Cl_2. Volatile components were evaporated in vacuum and the residue was purified by CC (EtOAc:MeOH; 10:1). Fractions containing the product were combined and volatile components were evaporated in vacuum to give compound **6g**. Yield: 471 mg (60%) of white semi-solid. FT-IR (KBr, cm^{-1}): 3425 ν(OH) (alcohol), 2934 ν(CH) (NH) (alkyl, lactam), 1652 ν(C=O) (amide), 1550, 1496, 1444, 1401, 1308, 1269, 1179, 1058, 983, 853, 756, 694. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.74 (p, 2H, *J* = 6.0 Hz, $CH_2CH_2CH_2$), 2.80 (dd, 1H, *J* = 17.0, 8.9 Hz, 4'-Ha), 2.88 (dd, 1H, *J* = 16.9, 7.3 Hz, 4'-Hb), 3.32-3.44 (m, 1H, 3'-H), 3.44 (dt, 1H, *J* = 14.1, 5.9 Hz, 1H of $CH_2CH_2CH_2$N), 3.52-3.67 (m, 5H, 1H of $CH_2CH_2CH_2$N, $CH_2CH_2CH_2OH$, and 2'-Ha), 3.74 (dd, 1H, *J* = 9.5, 8.5 Hz, 2'-Hb), 6.32 (s, 1H, 5-H), 7.51-7.63 (m, 3H, *m,p*-Ph), 8.11-8.17 (m, 2H, *o*-Ph), 12.15 (br s, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6, δ, ppm): 29.6, 36.2, 38.2, 39.1, 51.8, 58.5, 110.0, 127.7, 128.8, 131.6, 132.2, 157.4, 165.0, 168.2, 174.3. HRMS (EI): *m/z* found for $C_{17}H_{19}N_3O_3$: *m/z* = 314.1499 (MH^+); calcd.: *m/z* = 314.1505 (MH^+).

2.2.7. Synthesis of 3-(4-(6-((methylsulfonyl)oxy)-2-phenyl-pyrimidin-4-yl)-2-oxopyrrolidin-1-yl)propyl methane sulfonate (13)

To a cooled (-5 °C) stirred solution of compound **6g** (250 mg, 0.80 mmol) in anh. CH_2Cl_2 (5 mL) was added anh. Et_3N (280 μL, 2 mmol) followed by addition of methanesulfonyl chloride (131 μL, 1.7 mmol) and the resulting mixture was stirred at -5 °C for 20 min. and at r.t. for 30 min. The reaction mixture was directly (without previous evaporation) purified by FC (EtOAc). Fractions containing the product were combined and volatile components were evaporated in vacuum to give compound **13** (Scheme 3). Yield: 326 mg (86%) of white semi-solid. FT-IR (KBr, cm^{-1}): 2936 ν(CH) (alkyl), 1682 ν(C=O) (amide), 1592, 1574, 1556, 1496, 1370, 1317, 1190, 1040, 929, 802, 776, 701. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.02 (p, 2H, *J* = 6.4 Hz, $CH_2CH_2CH_2$), 2.83 (d, 2H, *J* = 7.7 Hz, 4'-CH_2), 3.00 (s, 3H, NSO_2Me), 3.48 (t, 2H, *J* = 6.8 Hz, $CH_2CH_2CH_2$N), 3.65 (s, 3H, OSO_2Me), 3.68-3.87 (m, 3H, 3'-H and 2'-CH_2), 4.24 (t, 2H, *J* = 6.1 Hz, $CH_2CH_2CH_2$O), 6.86 (s, 1H, 5-H), 7.44-7.55 (m, 3H, *m,p*-Ph), 8.34-8.39 (m, 2H, *o*-Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ, ppm): 26.9, 36.6, 37.1, 38.5, 39.0, 41.4, 51.7, 67.8, 106.9, 128.4, 128.7, 131.8, 135.8, 164.88, 164.91, 173.1, 174.2.

2.2.8. Synthesis of 4-(2-phenyl-6-(pyrrolidin-1-yl)pyrimidin-4-yl)-1-(3-(pyrrolidin-1-yl)propyl)pyrrolidin-2-one (14)

To a solution of compound **13** (300 mg, 0.638 mmol) in anh. CH_2Cl_2 (5 mL) under argon was added pyrrolidine (700 μL, 8.3 mmol) and the mixture was stirred under reflux for 19 h. Volatile components were evaporated in vacuum and the residue was purified by FC (EtOAc:MeOH:Et_3N, 10:1:1). Fractions containing the product were combined and volatile components were evaporated in vacuum to give compound **14** (Scheme 3). Yield: 60 mg (22%) of colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.73-1.90 (m, 6H, $CH_2CH_2CH_2$ and 2×CH_2 of pyrrolidine), 1.98-2.12 (m, 4H, 2×CH_2 of pyrrolidine), 2.49-2.60 (m, 6H, 3×CH_2N of pyrrolidine), 2.73 (dd, 1H, *J* = 16.7, 9.1 Hz, 4'-Ha), 2.90 (dd, 1H, *J* = 16.7, 7.4 Hz, 4'-Hb), 3.19-3.61 (m, 7H, 3'-H, CH_2N of pyrrolidine, $CH_2CH_2CH_2$N, and $CH_2CH_2CH_2$O), 3.67 (dd, 1H, *J* = 9.7, 6.4 Hz, 2'-Ha), 3.74 (dd, 1H, *J* = 9.7, 8.7 Hz, 2'-Hb), 6.05 (s, 1H, 5-H), 7.38-7.46 (m, 3H, *m,p*-Ph); 8.39-8.47 (m, 2H, *o*-Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ, ppm): 23.5, 25.4, 26.6, 37.1, 38.8, 40.8, 46.5, 52.5, 53.7, 54.2, 98.9, 128.3, 128.3, 130.2, 138.8, 160.8, 163.7, 167.6, 174.2. ESI: *m/z* found for $C_{25}H_{33}N_5O$: *m/z* = 420.2745 (MH^+); calcd.: *m/z* = 420.2763 (MH^+).



Scheme 3

2.2.9. Synthesis of 1-(3-hydroxypropyl)-4-(2-phenyl-6-(pyrrolidin-1-yl)pyrimidin-4-yl)pyrrolidin-2-one (15)

To a cooled (-5 °C) solution of compound **6g** (471 mg, 1.503 mmol) in anh. CH_2Cl_2 (5 mL) was added anh. Et_3N (252 μL, 1.804 mmol) followed by addition of methanesulfonyl chloride (116 μL, 1.503 mmol) and the resulting mixture was stirred at -5 °C for 20 min. and then at r.t. for 1 h. The reaction mixture was directly (without previous evaporation) purified by FC (EtOAc). Fractions containing the intermediate mono-mesylate were combined, evaporated in vacuum, and the residue was dried under high vacuum (r.t./0.1 Torr). The residue was dissolved in anhydrous CH_2Cl_2 (5 mL) under argon followed by addition of pyrrolidine (253 μL, 3 mmol), the mixture was stirred at r.t. for two days, and evaporated in vacuum. The residue was purified by FC (EtOAc:MeOH, 10:1). Fractions containing the product were combined, volatile components were evaporated *in vacuo*, and the residue was purified by MPLC (EtOAc:MeOH, 10:1). Fractions containing the product were combined and volatile components were evaporated in vacuum to give compound **15** (Scheme 3). Yield: 174 mg (31%) of white solid. M.p.: 101-105 °C (white solid). FT-IR (KBr, cm^{-1}): 3406 ν(CH) (alcohol), 2942 ν(CH) (alkyl), 2872 ν(CH) (alkyl), 1668 ν(C=O) (amide), 1596, 1536, 1505, 1455, 1381, 1347, 1168, 1062, 1028, 700. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.64 (p, 2H, *J* = 6.8 Hz, $CH_2CH_2CH_2$), 1.97 (br s, 4H, 2×CH_2 of pyrrolidine), 2.63 (d, 2H, *J* = 8.1 Hz, 4'-CH_2), 3.21-3.36 (m, 2H, $CH_2CH_2CH_2N$), 3.36-3.46 (m, 5H, 2×CH_2N of pyrrolidine and 3'-H), 3.50-3.66 (m, 3H, $CH_2CH_2CH_2O$ and 2'-Ha), 3.73 (t, 1H, *J* = 7.5 Hz, 2'-Hb), 4.43 (br s, 1H, OH), 6.35 (s, 1H, 5-H), 7.43-7.48 (m, 3H, *m,p*-Ph), 8.29-8.42 (m, 2H, *o*-Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ, ppm): 25.2, 29.6, 36.9, 38.7, 39.0, 46.3, 52.7, 58.5, 98.8, 128.1, 128.2, 130.1, 138.6, 160.7, 163.6, 167.3, 175.0. HRMS (EI): *m/z* found for $C_{21}H_{26}N_4O_2$: *m/z* = 367.2122 (MH^+); calcd.: *m/z* = 367.2134 (MH^+).

2.2.10. Synthesis of tert-butyl 4-(1-(3-(benzyloxy)propyl)-5-oxopyrrolidin-3-yl)-6-oxo-2-phenylpyrimidine-1(6H)-carboxylate (16)

To a solution of compound **6f** (360 mmol 0.89 mmol) in anh. THF (5 mL) was added Et_3N (63 mL, 0.45 mmol) and DMAP (56 mg, 0.45 mmol) followed by addition of $(Boc)_2O$ (397 mg, 1.78 mmol) and the mixture was stirred at r.t. for 3 h. The reaction mixture was diluted with EtOAc (200 mL) and washed with water (2×50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components were evaporated in vacuum. The residue was purified by CC (EtOAc). Fractions containing the product were combined and volatile components were evaporated in vacuum to give compound **16** (Scheme 3). Yield: 365 mg (81%) of light yellowish oil. FT-IR (NaCl, cm^{-1}): 2930 ν(CH) (alkyl), 1767 ν(C=O) (ester), 1693 ν(C=O) (amide), 1590, 1573, 1558, 1494, 1455, 1386, 1246, 1132, 1057, 852, 698. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.60 (s, 9H, *t*-Bu), 1.90 (dq, 2H, *J* = 7.5, 6.2 Hz, $CH_2CH_2CH_2$), 2.73-2.94 (m, 2H, 4'-CH_2), 3.48 (t, 2H, *J* = 7.1 Hz, $CH_2CH_2CH_2N$), 3.53 (t, 2H, *J* = 6.1 Hz, $CH_2CH_2CH_2O$), 3.61-3.84 (m, 3H, 3'-H and 2'-CH_2), 4.46 (s, 2H, $PhCH_2O$), 6.93 (s, 1H, 5-H), 7.21-7.36 (m, 5H, Ph), 7.42-7.54 (m, 3H, *m,p*-Ph), 8.39-8.46 (m, 2H, *o*-Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 27.8, 27.9, 37.1, 39.1, 40.4, 52.4, 68.0, 73.3, 85.3, 107.6, 127.8, 128.0, 128.6, 128.7, 131.6, 136.6, 138.5, 149.6, 165.6, 165.8, 173.3. HRMS (EI): *m/z* found for $C_{29}H_{33}N_3O_5$: *m/z* = 504.2478 (MH^+); calcd.: *m/z* = 504.2498 (MH^+).

3. Results and discussion

First, methyl 3-oxo-3-(5-oxo-1-phenylpyrrolidin-3-yl) propanoate (**10a**) was prepared in two steps form itaconic acid (**7a**) following the literature procedure [16]. Treatment of the β-keto ester **10a** with formamidine acetate (**11a**), acetamidine hydrochloride (**11b**), benzamidine hydrochloride (**11c**), [1,1'-biphenyl]-4-carboxamidine hydrochloride (**11d**), and 4-((pyrrolidin-1-yl)methyl)benzamidine dihydrochloride (**11e**) in methanol in the presence of potassium *tert*-butoxide at room temperature afforded the corresponding 2-substituted 6-(5-oxo-1-phenylpyrrolidin-3-yl)pyrimidin-4(3*H*)-ones **6a**-**e** in 33-72% yields (Scheme 2). Next, we tried to prepare the analogues of **6a**-**e** bearing polar substituents at the pyrrolidine nitrogen

atom following the above synthetic route. Though treatment of itaconic acid (**7a**) with 3-amino-1-propanol (**8c**) and 3-(dimethylamino)propanamine (**8d**) in water under reflux [18] did afford the corresponding 5-oxopyrrolidin-3-carboxylic acids **9c** and **9d**, further carboxymethylation under Masamune-Claisen conditions did not give the desired β-keto esters. This was not really surprising, since carboxylic acids bearing highly polar and/or basic substituents are usually difficult substrates for Masamune-Claisen condensations [13]. On the other hand, condensation of dimethyl itaconate (**7b**) with 3-(benzyloxy) propylamine (**8b**) [19] in methanol at room temperature proceeded smoothly to afford methyl 1-(3-(benzyloxy)propyl)-5-oxopyrrolidine-3-carboxylate (**12**) in quantitative yield. Hydrolysis of the ester **12** then gave the carboxylic acid **9b** in 87% yield. Quite expectedly, Masamune-Claisen homologation of the carboxylic acid **9b** with protected OH functionality at the side chain led to the corresponding β-keto ester **10b**, which was cyclized with benzamidine (**11c**) to furnish 6-(1-(3-(benzyloxy)propyl)-5-oxopyrrolidin-3-yl)-2-phenylpyrimidin-4(3*H*)-one (**6f**) in 46% yield over two steps (Scheme 2).

Finally, some transformations and derivatizations using functionalized pyrimidinone **6f** as a starting material were carried out. Catalytic hydrogenation under 3 bar of hydrogen in the presence of 10% Pd-C resulted in removal of the O-benzyl group to afford the N'-(3-hydroxypropyl)-substituted analogue **6g** in 60% yield. Subsequent mesylation of **6g** with two equivalents of mesyl chloride at -5 °C → 20 °C produced the *bis-o*-mesylate **13** in 86% yield, while further treatment of **13** with excess pyrrolidine in refluxing dichloromethane for 19 h did not proceed to completion and furnished 4-(2-phenyl-6-(pyrrolidin-1-yl)pyrimidin-4-yl)-1-(3-(pyrrolidin-1-yl)propyl) pyrrolidin-2-one (**14**) along with several by-products. Upon chromatographic workup, the bis-substitution product **14** was isolated in 22% yield. To obtain the mono-aminated compound as well, the pyridone **6g** was treated first with one equivalent of mesyl chloride at -5 °C → 20 °C and the intermediate mono-mesylate was treated further with two equivalents of pyrrolidine in dichloromethane at room temperature for 48 h. Subsequent chromatographic workup afforded 1-(3-hydroxypropyl)-4-(2-phenyl-6-(pyrrolidin-1-yl)pyrimidin-4-yl) pyrrolidin-2-one (**15**) in 31% yield. It is noteworthy, that low yields of the amination products **14** and **15** were due to incomplete conversion and competitive formation of by-products upon treatment of the mesylates with excess pyrrolidine. Further, low yield of the mono-aminated product **15** could also be explained by lack of chemoselectivity in the mesylation step, since formation of the bis-mesylate **13** as the by-product was detected by TLC. Acylation of pyrimidone **6f** with Boc_2O in the presence of 4-dimethylaminopyridine (DMAP) proceeded smoothly to furnish the *N*-acylated pyrimidone **16** in 81% yield (Scheme 3).

The structures of newcompounds **9b**, **10b**, **6a-g**, and **12-16** were determined by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, HRMS) and by elemental analyses for C, H, and N. Compounds **9b**, **10b**, **6f**,**g**, and **12-16** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C NMR and HRMS. Spectral data for compounds novel compounds **9b**, **10b**, **6a-g**, and **12-16** were in agreement with the data for closely related known compounds [16,17]. Structural assignment of 1-(3-hydroxypropyl)-4-(2-phenyl-6-(pyrrolidin-1-yl)pyrimidin-4-yl)pyrrolidin-2-one (**15**) was based on ^{1}H NMR data. A broad singlet at 4.43 ppm was in agreement with the aliphatic OH group, whereas the regioisomeric 6-(5-oxo-1-(3-(pyrrolidin-1-yl)propyl)pyrrolidin-3-yl)-2-phenylpyrimidin-4(3*H*)-one should exhibit a broad signal at ~12 ppm corresponding to the pyridone NH group.

4. Conclusion

In conclusion, s simple three step synthesis of 6-(5-oxo-1-phenylpyrrolidin-3-yl)pyrimidin-4(3*H*)-ones **6a-f** from comercially available itaconic acid (**7a**) was developed. The synthesis comprises cyclisation of **7a** with a primary amine **8**, Masamune-Claisen homologation of 5-pyrrolidone-3-carboxylic acid **9**, and cyclisation of the so formed β-keto ester with an amidine **11**. Unfortunately, polar *N*-substituents bearing basic or acidic functional groups are not compatible with the Masamune-Claisen condensation; however, this problem can be circumvented by suitable protection of these functional groups or by transformation of the *N*-substituents after the pyrimidine ring formation.

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