A Step-wise Facile approach to Synthesis of Pyrido[1,2-a]pyrimidines and their transformation to 3-(3-arylpyrazolo)-2,3-dihydropyrido[1,2-a]pyrimidine-2,4-diones.

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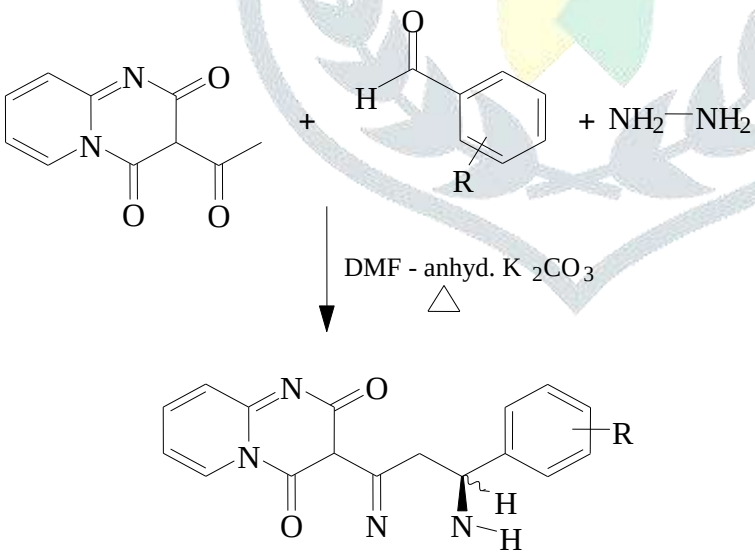
ABSTRACT

The synthesis of Pyridipyrimidines has been an area of intrest for many a workers due to its potential phoarmacological activity as lead compound in many formulations. A simple methodology has been formulated to the synthesis of Pyrido[1,2-a]pyrimidines and have been converted into their 3-(3-arylpyrazolo)-2,3-dihydropyrido[1,2-a]pyrimidine-2,4-diones using mild and easy one pot Bigenelli condensation in the final step.



INTRODUCTION

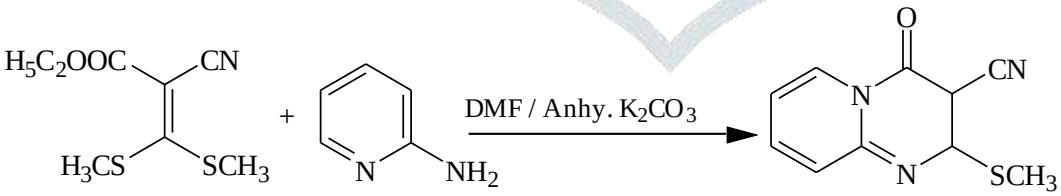
Pyrido[1,2-a]pyrimidines moiety is an important structural moiety of many alkaloids, These alkaloids display multiple pharmacological properties. Batzelladine-A and B are reported to inhibit the bindingof HIV gp-120 to CD_4cells. Therefore, these compounds are potential new lead compounds for drug development[1]. Several marine alkaloids whose structures are charted out below have been found to contain five membered imidazoline moiety.

Nortopsentin D, has been characterized from Indo-Pacific sponge *Dragmacidon* species. Although, as such this alkaloid is not cytotoxic but it does metabolise to a highly cytotoxic product[2]. A series of 2,5-bisquinoline-imidazoline alkaloids, namely Nortopsentins, have been characterized from *Spongosorites ruetzleri*.[3] These alkaloids were found to display strong anti-fungal activity. (10E)-Hymenialdisine and (10E)-debromohymenialdisine have been reported from *Stylotella aurantium*.[4]The compounds possessing pyrazoline moiety joined to a pyrido[1,2-a]pyrimidine nucleus,[5] are expected to display interesting biological activities.[6-8] Such compounds may exhibit anti hypertensive,[9,10] antibacterial,[11] antimicrobial,[12] anti-inflammatory,[13] analgesic,[13] antileishmanial,[14]antitumor,[15] antiallergic,[16] antioxidant[17] activity and also HIV-1 integrase inhibitor activity.[18-20] Our effort was the development of an efficient methodology for the synthesis of new 3-arylpyrazolo-2,3-dihydropyrido[1,2-a]pyrimidinones which may prove useful analogues of marine derived imidazolines.

Earlier Approaches

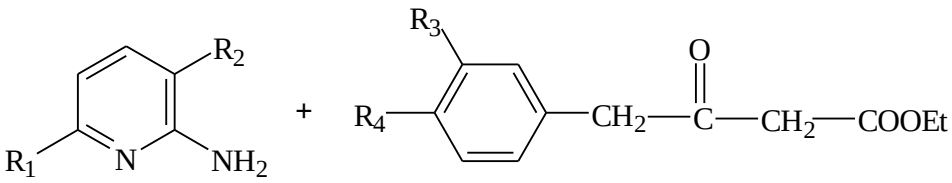
A number of methods have been reported for the development of pyridopyrimidine derivatives.[21-29]They have been synthesized by the cyclization of 2-aminopyridine with ethylcyanoacetate, at 80-100°C and 14 Kbar;[30] by cyclization of 2-aminopyridine with Vilsmeier-Haack reagent, [31] Pyrido[2,3-d]pyrimidin-4-ones have been prepared by a three-component reaction of *α,β*-unsaturated ketone, α-methylketones and ammonium acetate, adsorbed on the surface of solid support like acidic alumina or montmorillonite K-10 clay and subjected to microwave irradiation [32]

Pyrido[1,2-a]pyrimidines have been prepared by treating acrylate with 2-aminopyridine, using DMF and anhydrous potassium carbonate[33] (Scheme 2).



Scheme 2

Pyrido[1,2-a]pyrimidines have also been synthesized by the condensation-annulation reaction of the appropriate 2-aminopyridine and suitable *β*-ketoester, in the presence of polyphosphoric acid (PPA) at 100°C (Scheme 3).[34,35] In practice this reaction gives poor yield and the reaction leads to the formation of multi-component mixture.



R_1, R_2 = H, OH

Scheme 3

The methods described so far for the preparation of pyrido[1,2-a]pyrimidine ring system involve two general routes: (a) formation of the pyridine ring by cyclization of suitable substituents of a pyrimidine compound and (b) formation of the pyrimidine ring by cyclization of a suitably substituted pyridine derivative.[36-40]

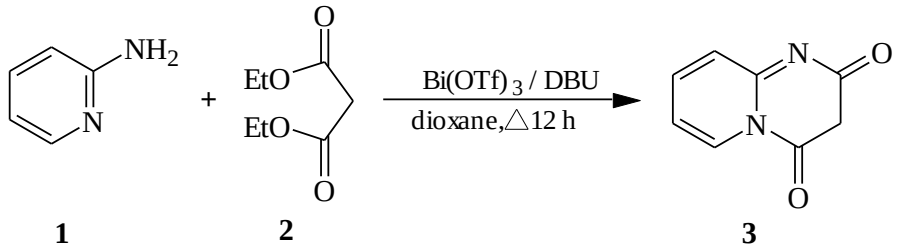
Results and Discussions

Synthesis of 3-(3-arylpyrazolo)-2,3-dihydropyrido[1,2-a]pyrimidine-2,4-diones.

Our strategy for the preparation of arylpyrazole substituted pyrido[1,2-a] pyrimidines involved the synthesis of 3-acetyl-2,3-dihydo pyrido[1,2-a] pyrimidine-2,4-diones from which the synthesis of the target compounds was conceived by one-pot Bigenelli reaction.

Synthesis of 2,3-dihydropyrido[1,2-a]pyrimidine-2,4-diones.

Initially, 2,3-dihydropyrido[1,2-a]pyrimidine-2,4-diones were synthesised from 2-aminopyridine and diethyl malonate. Earlier,[41] this reaction has been carried out in the presence of strong acids, at refluxing temperatures, and the products revealed that the reaction proceeds with enolisation which was likely to hinder the desired acetylation at position 3 of the pyrido[1,2-a]pyrimidine. The use of $POCl_3$ in the reaction also was not suitable option as this also effects both enolisation and halogenation of the carbonyl groups. Therefore, a search for a suitable catalyst for the preparation of 2,3-dihydropyrido[1,2-a]pyrimidine-2,4-dione was imperative. Since, the departure of ethoxy function from an ester is facilitated by acids, the use of Lewis acid catalyst seemed to be an appropriate proposition. Since, bismuth ions are mild acids, an attempt was made to condense 2-aminopyridine and diethyl malonate in the presence of $BiCl_3$, $Bi(NO_3)_3$ and $Bi(OTf)_3$. These reagents afforded the desired pyridopyrimidines in low yield and major product was an amide ester. This suggested that Lewis acids were not effective in bringing about the annulations which needed removal of the proton from the amide nitrogen. It was proposed that simultaneous use of a base may facilitate the reaction. Infact, the use of the catalytic amounts of DBU and the solvent dioxane improved not only the yield of pyridopyrimidine but also reduced the reaction time. Optimisation of the reaction conditions revealed that for the best performance (80% yield), the optimum concentration of bismuth triflate was 20 mol percent and that of DBU was 30 mol percent (Scheme 4). The reaction was carried out by heating on a water bath for 12 hours. After usual work up, the compound **3** was crystallized from hot ethanol.



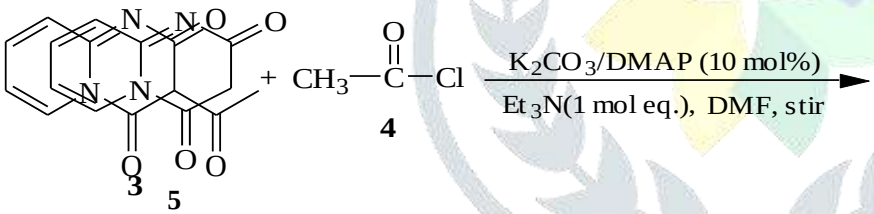
1 **2** **3**

Scheme 4

The IR spectrum of the compound **3** exhibited, two amide carbonyl signals at υ_{max} 1660 and 1673 cm^{-1}, in addition to aromatic absorption bands. The ^{1}H-NMR spectrum contained two proton resonance signal at δ 3.67 (s). The spectrum displayed resonance signals due to the hetero aromatic protons at δ 6.97 (d, J = 8.9 Hz, 2H), 7.45 (d, J = 8.9 Hz, 1H) and 8.30 (d, J = 8.9 Hz, 1H). The ^{13}C-NMR and DEPT 135° revealed the presence of one methylene carbon, δ_C 59.4, and two carbonyl groups, δ_C 159.4 and 160.8. Other ^{13}C-NMR signals were displayed at δ_C 110.1, 120.9, 121.5, 123.4 and 126.5.

Acetylation of compound 3

The next step involved acetylation of compound **3** which was achieved with quantitative yield by reacting the compound with acetyl chloride in the presence of potassium carbonate, triethylamine and dimethylaminopyridine. The reaction was best carried out at room temperature using dimethyl formamide as solvent (Scheme 5).



3 **4** **5**

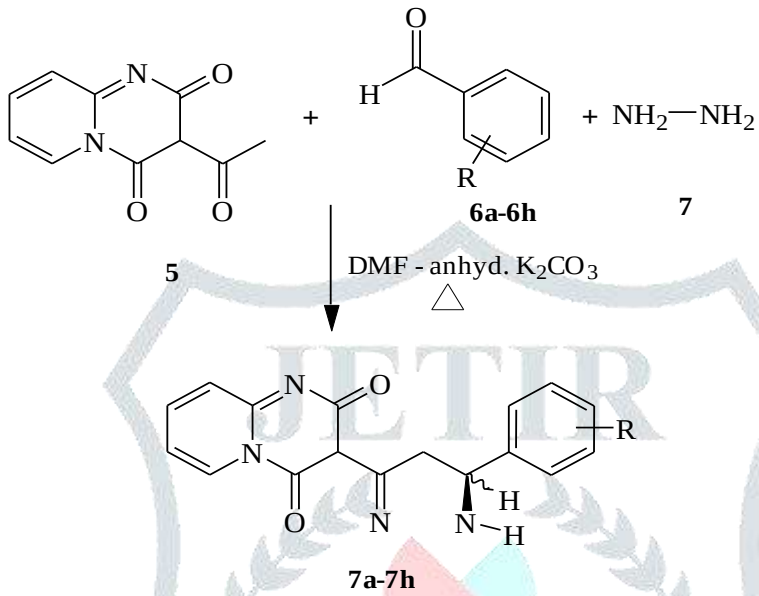
Scheme 5

The ^{1}H-NMR spectrum of the acetyl derivative **5** displayed the characteristic signal for acetoxyl methyl at δ 2.01 (s, 3H), δ_C 12.5. A single proton resonance signal at δ 5.16 (s, 1H) was attributed to C-3 carbinylic proton. The three carbonyl signals were observed at δ 150.8, 164.3 and 167.2. Using the optimized conditions, 2-acetyl-2,3-dihydropyrido[1,2-a]pyrimidine-2,4-dione was prepared quantitatively by batch wise process. The synthesis of 3-pyrazolo-2,3-dihydropyrido[1,2-a]pyrimidine-2,4-dione was envisaged *via* Michael addition-condensation of α,β-unsaturated ketones, which were likely to be formed *in situ* by the reaction of 3-acetyl-2,3-dihydropyrido[1,2-a]pyrimidine-2,4-dione **5** and aryl aldehyde, in the presence of a catalyst.

Synthesis of 3-(3-arylpyrazolo)-2,3-dihydropyrido[1,2-a]pyrimidine-2,4-diones.

An equimolar mixture of 3-acetyl-2,3-dihydropyrido[1,2-a]pyrimidine-2,4-dione **5**, an aryl aldehyde **6a-6h**, in N, N/-dimethyl formamide, was stirred for 4-8 h, at room temperature, in the presence of anhydrous K_2CO_3. The reaction was monitored by tlc and on disappearance of the aldehyde in the reaction mixture, hydrazine hydrate in equimolar proportion was added to the reaction flask. Since, further reaction was sluggish at room temperature, the reaction flask was heated on

water bath. On completion of the reaction (6-10 h), the reaction mixture was cooled to room temperature and triturated with water, when pale yellow precipitates were obtained (Scheme 6) (Table 1). The solid products were separated by filtration and were crystallized from DMF-ethanol to afford colourless compounds **7a-7h**. The compounds were characterized by spectral methods and elemental analysis (See experimental).



7a-7h

6a/7a. R = Ph
6b/7b. R = (4- OMe) Ph
6c/7c. R = (4 - Cl) Ph
6d/7d. R = (3 - Cl) Ph
6e/7e. R = (3,4 - O - CH_2 - O) Ph
6f/7f. R = (3,4 - OMe) Ph
6g/7g. R = (4 - Br) Ph
6h/7h. R = (4 - NO_2) Ph

Scheme 6

Table 1: Percentage yield of Products **7a-7h**

Compound	% Yield	Compound	% Yield
7a	65	**7e**	61
7b	68	**7f**	62
7c	67	**7g**	68
7d	61	**7h**	62

Experimental

General

Melting points are uncorrected and were determined on Perfit melting point apparatus. IR spectra were recorded on Brucker 4800 IR spectrometer. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50.3 MHz) spectra were recorded using a Brucker AcDPX-200 spectrometer; some spectra were recorded on Varian Gemini 300 MHz instrument, using TMS as standard. HRMS were recorded at 70 eV on JEOL D-300 mass spectrometer; CHN analysis was done on Fison Model EA 1108 elemental analyzer. TLC was performed on 0.5 mm thick plates, using silica gel-G (BDH) adsorbent. Column chromatography was performed on silica gel (mesh size 60-120 BDH). The calculated mass values are based on the values obtained by Chem 4-D Draw (chem. innovation) software.

Procedure for the preparation of 2,3-dihydropyrido[1,2-a]pyrimidine-2,4-dione

2-aminopyridine (1 x 10^{-3} moles) and ethyl acetoacetate (1 x 10^{-3} moles) were taken in dioxane (10 mL). To this solution $Bi(OTf)_3$ (20 mol percent) and DBU (30 mol percent) were added, with constant stirring. The reaction mixture was then heated on a water bath and monitored by tlc. On completion of the reaction (12 h), the reaction mixture was cooled and the solvent evaporated, under reduced pressure. Subsequently, water (20 mL) was added to the reaction flask and the product, extracted with ethylacetate (50 mL). The organic layer was washed successively with brine and water (15 mL) (2-3 times) and dried over anhydrous sodium sulphate. After filteration the solution was freed from the solvent. The residue was purified by column chromatography, on silica gel, using graded solvents of CH_2Cl_2-EtOAc. The compound was recrystallized from hot ethanol.

Procedure for acetylation of 2,3-dihydropyrido[1,2-a]pyrimidine-2,4-diones, 3.

Compound **3** (5 x 10^{-2} moles) was dissolved in DMF and K_2CO_3, DMAP (10 mol percent), Et_3N (1 mol. eq.) was added to the solution while stirring. The mixture was stirred for another 15 minutes. Subsequently, acetyl chloride (5.5 x 10^{-2} moles) was added dropwise to the reaction mixture. The mixture was stirred, at room temperature. On completion of the reaction (tlc), the solvent was concentrated and the reaction mixture triturated with water when the acetate **5** precipitated out. The solid residue was recovered by filtration, dried in air and extracted with chloroform (50 mL). The solution was freed from the solvent, under reduced pressure and the solid mass recrystallized from chloroform-ethanol to afford tlc pure compound **5**.

Procedure for the preparation of 3-(3-arylpyrazolo)-2,3-dihydropyrido[1,2-a]pyrimidine-2,4-diones.

3-Acetyl-2,3-dihydropyrido[1,2-a]pyrimidine-2,4-dione (1 x 10^{-3} moles) was dissolved in DMF. To this solution was added an aryl aldehyde (1 x 10^{-3} moles) **6a-6h** and anhydrous potassium carbonate (1 mol eq.). The reaction mixture was stirred for 4-8 h at room temperature. Subsequently, hydrazine hydrate (1 x 10^{-3} moles) was added to the reaction mixture. The reaction flask was heated on water bath. On completion of the reaction (6-10 h), the reaction mixture was cooled to room temperature and triturated with water when pale yellow precipitate was obtained. The contents of the flask were filtered and the solid residue washed with water (2-3 times). The solid products thus obtained were crystallized from DMF-ethanol to afford colourless compounds **7a-7h**.

Conclusion : A simple approach involving preparation of 2,3-dihydropyrido[1,2-a]pyrimidine-2,4-dione in the first step followed by its acetylation and then conversion of this acetyl derivative into 3-(3-arylpyrazolo)-2,3-

dihydropyrido[1,2-a]pyrimidine-2,4-diones by condensing it with aldehyde and hydrazine in presence of K_2CO_3 under mild conditions has been achieved.

Spectral data of compounds

***3H*-pyrido[1,2-a]pyrimidine-2,4-dione, (3)** Colorless crystals, m.p. 174°C. IR (KBr): υ_{max} 2998, 1710, 1670, 1665, 1640, 1535, 1473, 1152, 1045, 1017, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 4.54 (s, 2H), 7.10 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.28 (d, *J* = 9.6, 1.5 Hz, 2H), 8.14 (dd, *J* = 9.6, 1.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ_C 55.3, 117.1, 125.8, 127.8, 136.4, 152.1, 162.6, 166.4. HRMS: *m/z* (rel. int.) 162.0422 (100) (M^+), (calc. for $C_8H_6N_2O_2$, 162.0429), 134 (65), 106 (71). Anal.: CHN (%): Found; C, 59.22; H, 3.71; N, 17.29; Calc.; C, 59.26; H, 3.73; N, 17.28.

3-acetyl-*3H*-pyrido[1,2-a]pyrimidine-2,4-dione, (5) Colorless crystals, m.p. 182°C. IR (KBr): υ_{max} 2998, 1715, 1672, 1665, 1643, 1530, 1472, 1154, 1045, 1017, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.01 (s, 3H), 6.23 (s, 1H), 7.16 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.25 (dd, *J* = 9.6, 1.5 Hz, 2H), 8.10 (dd, *J* = 9.6, 1.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ_C 12.5, 79.4, 117.4, 125.1, 127.6, 136.0, 153.0, 166.8, 168.4, 203.6. HRMS: *m/z* (rel. int.) 204.0538 (100) (M^+), (calc. for $C_{10}H_8N_2O_3$, 204.0535), 162 (59), 134 (67), 106 (75). Anal.: CHN (%): Found; C, 58.80; H, 3.97; N, 13.72; Calc.; C, 58.82; H, 3.97; N, 13.72.

3-(4,5-dihydro-5-phenyl-*1H*-pyrazol-3-yl)-2-hydroxy-*4H*-pyrido[1,2-a]pyrimidin-4-one,(7a) Colorless crystals, m.p. 189°C. IR (KBr): υ_{max} 3430 (OH), 3236 (NH), 2930, 1695 (-C-OH), 1670 (C = O), 1640 (NH), 1530, 1470, 1410, 1150, 1040, 1015, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.13 (dd, *J* = 8.1, 4.0 Hz, 1H), 3.24 (dd, *J* = 8.0, 4.1 Hz, 1H), 5.20 (dd, *J* = 4.0, 4.1 Hz, 1H), 7.03 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.20 (dd, *J* = 9.6, 1.5 Hz, 2H), 7.28-7.30 (m, 5H), 8.78 (dd, *J* = 9.6, 1.5 Hz, 1H), 10.54 (s br, exch. D_2O, 1H), 11.36 (s br, exch. D_2O, 1H). ^{13}C-NMR ($CDCl_3$): δ_C 44.3, 52.8, 117.5, 126.4, 127.6, 127.8, 128.1, 128.2, 128.4, 128.6, 133.4, 137.3, 148.1, 153.3, 157.8, 163.4, 176.2. HRMS: *m/z* (rel. int.) 306.1113 (100) (M^+), (calc. for $C_{17}H_{14}N_4O_2$, 306.1117), 304 (58), 278 (69), 228 (40), 173 (36), 162 (46), 159 (50). Anal.: CHN (%): Found; C, 66.68; H, 4.65; N, 18.27; Calc.; C, 66.66; H, 4.61; N, 18.29.

3-(4,5-dihydro-5-(4-methoxyphenyl)-*1H*-pyrazol-3-yl)-2-hydroxy-*4H*-pyrido[1,2-a]pyrimidin-4-one, (7b) Colorless crystals, m.p. 192°C. IR (KBr): υ_{max} 3435 (OH), 3233 (NH), 2932, 1696 (-C-OH), 1670 (C = O), 1645 (NH), 1532, 1470, 1414, 1150, 1041, 1015, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.16 (dd, *J* = 8.1, 4.0 Hz, 1H), 3.26 (dd, *J* = 8.0, 4.1 Hz, 1H), 3.73 (s, 3H), 5.33 (dd, *J* = 4.0, 4.1 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 2H), 7.03 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.20 (dd, *J* = 9.6, 1.5 Hz, 2H), 8.78 (dd, *J* = 9.5, 1.7 Hz, 1H), 10.54 (s br, exch. D_2O, 1H), 11.36 (s br, exch. D_2O, 1H). ^{13}C-NMR ($CDCl_3$): δ_C 44.3, 53.7, 56.08, 113.0, 113.8, 117.5, 126.4, 127.6, 127.7, 127.8, 133.4, 137.3, 148.1, 153.8, 157.6, 157.8, 163.4, 176.3. HRMS: *m/z* (rel. int.) 336.1226 (100) (M^+), (calc. for $C_{18}H_{16}N_4O_3$, 336.1222), 334 (51), 308 (70), 228 (46), 173 (38), 162 (44), 159 (43). Anal.: CHN (%): Found; C, 64.25; H, 4.71; N, 16.62; Calc.; C, 64.28; H, 4.79; N, 16.66.

3-(5-(4-chlorophenyl)-4,5-dihydro-*1H*-pyrazol-3-yl)-2-hydroxy-*4H*-pyrido [1,2-a]pyrimidin-4-one, (7c) Colorless crystals, m.p. 190°C. IR (KBr): υ_{max} 3432 (OH), 3230 (NH), 2936, 1690 (-C-OH), 1672 (C=O), 1640 (NH), 1536, 1473, 1414, 1152, 1040, 1015, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.10 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.16 (dd, *J* = 8.0, 4.1 Hz, 1H), 5.26 (dd, *J* = 4.0, 4.1 Hz, 1H), 7.03 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.20 (dd, *J* = 9.6, 1.5 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 8.78 (dd, *J* = 9.5, 1.8 Hz, 1H), 10.54 (s br, exch. D_2O, 1H), 11.36 (s br, exch. D_2O, 1H). ^{13}C-NMR ($CDCl_3$): δ_C 45.5, 54.9, 117.6, 126.4, 127.7, 128.7, 129.0, 129.1, 129.3, 133.7, 137.3, 138.9, 148.2, 153.3, 157.6, 163.5, 176.5. HRMS: *m/z* (rel. int.) 340.0729 (100) (M^+), (calc. for $C_{17}H_{13}ClN_4O_2$, 340.0727), 338 (53),

312 (62), 228 (45), 173 (38), 162 (43), 159 (48). Anal.: CHN (%): Found; C, 59.90; H, 3.81; N, 16.40; Calc.; C, 59.92; H, 3.85; N, 16.44.

3-(5-(2-chlorophenyl)-4,5-dihydro-*1H*-pyrazol-3-yl)-2-hydroxy-*4H*-pyrido [1,2-a]pyrimidin-4-one, (7d) Colorless crystals, m.p. 182°C. IR (KBr): υ_{max} 3432 (OH), 3235 (NH), 2934, 1692 (-C-OH), 1674 (C=O), 1648 (NH), 1530, 1478, 1414, 1150, 1041, 1015, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.15 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.23 (dd, *J* = 8.0, 4.1 Hz, 1H), 5.30 (dd, *J* = 4.1, 4.0 Hz, 1H), 7.03 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.14 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.20 (dd, *J* = 9.6, 1.5 Hz, 2H), 7.22 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.35 (dd, *J* = 8.3, 1.95 Hz, 1H), 7.58 (dd, *J* = 8.3, 2.0 Hz, 1H), 8.78 (dd, *J* = 9.6, 1.5 Hz, 1H), 10.54 (s br, exch. D_2O, 1H), 11.36 (s br, exch. D_2O, 1H). ^{13}C-NMR ($CDCl_3$): δ_C 45.2, 57.0, 117.5, 120.1, 126.4, 127.6, 128.4, 128.7, 129.0, 129.3, 130.3, 137.3, 148.3, 153.3, 157.5, 163.5, 176.4. HRMS: *m/z* (rel. int.) 340.0722 (100) (M^+), (calc. for $C_{17}H_{13}ClN_4O_2$, 340.0727), 338 (51), 312 (65), 228 (44), 173 (36), 162 (40), 159 (47). Anal.: CHN (%): Found; C, 59.96; H, 3.84; N, 16.43; Calc.; C, 59.92; H, 3.85; N, 16.44.

3-(5-(benzo[d][1,3]dioxol-6-yl)-4,5-dihydro-*1H*-pyrazol-3-yl)-2-hydroxy-*4H*-pyrido [1,2-a]pyrimidin-4-one,(7e) Colorless crystals, m.p. 187°C. IR (KBr): υ_{max} 3433 (OH), 3233 (NH), 2936, 1694 (-C-OH), 1675 (C = O), 1642 (NH), 1530, 1478, 1414, 1150, 1046, 1015, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.18 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.28 (dd, *J* = 8.0, 4.1 Hz, 1H), 5.30 (dd, *J* = 4.1, 4.0 Hz, 1H), 6.01 (s, 2H), 6.70 (s, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.94 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.04 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.20 (dd, *J* = 9.6, 1.5 Hz, 2H), 8.78 (dd, *J* = 9.6, 1.5 Hz, 1H), 10.54 (s br, exch. D_2O, 1H), 11.36 (s br, exch. D_2O, 1H). ^{13}C-NMR ($CDCl_3$): δ_C 46.3, 58.1, 100.7, 115.6, 117.4, 123.9, 126.4, 127.4, 127.5, 133.2, 137.3, 148.5, 149.5, 149.8, 153.3, 157.4, 163.5, 176.3. HRMS: *m/z* (rel. int.) 350.1012 (100) (M^+), (calc. for $C_{18}H_{14}N_4O_4$, 350.1015), 348 (54), 322 (66), 228 (39), 173 (34), 162 (45), 159 (48). Anal.: CHN (%): Found; C, 61.75; H, 4.08; N, 15.92; Calc.; C, 61.71; H, 4.03; N, 15.99.

3-(4,5-dihydro-5-(3,4-dimethoxyphenyl)-*1H*-pyrazol-3-yl)-2-hydroxy-*4H*-pyrido[1,2-a]pyrimidin-4-one, (7f) Colorless crystals, m.p. 178°C. IR (KBr): υ_{max} 3438 (OH), 3230 (NH), 2935, 1694 (-C-OH), 1672 (C = O), 1643 (NH), 1536, 1472, 1418, 1152, 1048, 1015, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.20 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.30 (dd, *J* = 8.0, 4.1 Hz, 1H), 3.75 (s, 3H), 3.78 (s, 3H), 5.36 (dd, *J* = 4.0, 4.1 Hz, 1H), 6.38 (s, 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 6.64 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.04 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.23 (dd, *J* = 9.6, 1.5 Hz, 2H), 8.72 (dd, *J* = 9.6, 1.7 Hz, 1H), 10.50 (s br, exch. D_2O, 1H), 11.6 (s br, exch. D_2O, 1H). ^{13}C-NMR ($CDCl_3$): δ_C 47.3, 56.3, 57.1, 57.3, 114.9, 115.3, 117.4, 126.4, 127.5, 127.6, 135.2, 137.3, 148.3, 153.2, 156.3, 157.7, 158.5, 163.5, 176.2. HRMS: *m/z* (rel. int.) 366.1322 (100) (M^+), (calc. for $C_{19}H_{18}N_4O_4$, 366.1328), 364 (52), 338 (63), 228 (41), 173 (35), 162 (47), 159 (46). Anal.: CHN (%): Found; C, 62.25; H, 4.98; N, 15.29; Calc.; C, 62.29; H, 4.95; N, 15.29.

3-(5-(4-bromophenyl)-4,5-dihydro-*1H*-pyrazol-3-yl)-2-hydroxy-*4H*-pyrido [1,2-a]pyrimidin-4-one, (7g) Colorless crystals, m.p. 171°C. IR (KBr): υ_{max} 3436 (OH), 3230 (NH), 2938, 1694 (-C-OH), 1670 (C=O), 1643 (NH), 1535, 1472, 1410, 1152, 1041, 1015, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.10 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.21 (dd, *J* = 8.0, 4.1 Hz, 1H), 5.42 (dd, *J* = 4.0, 4.1 Hz, 1H), 7.05 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.20 (dd, *J* = 9.6, 1.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 8.71 (dd, *J* = 9.6, 1.7 Hz, 1H), 10.50 (s br, exch. D_2O, 1H), 11.16 (s br, exch. D_2O, 1H). ^{13}C-NMR ($CDCl_3$): δ_C 43.4, 51.5, 117.4, 126.4, 127.6, 128.1, 128.3, 128.9, 129.6, 129.8, 137.2, 148.1, 153.2, 157.3, 163.2, 176.2. HRMS: *m/z* (rel. int.) 384.0228 (100) (M^+), (calc. for $C_{17}H_{13}BrN_4O_2$, 384.0222), 382 (55), 356 (60), 228 (41), 173 (36), 162 (48), 159 (52). Anal.: CHN (%): Found; C, 53.02; H, 3.48; N, 14.55; Calc.; C, 53.00; H, 3.40; N, 14.54.

3-(4,5-dihydro-5-(4-nitrophenyl)-*1H*-pyrazol-3-yl)-2-hydroxy-*4H*-pyrido [1,2-a]pyrimidin-4-one, (7h) Colorless crystals, m.p. 201°C. IR (KBr): υ_{max} 3432 (OH), 3236 (NH), 2935, 1692 (-C-OH), 1670 (C=O), 1645 (NH), 1530, 1475, 1414, 1150, 1041, 1015, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.21 (dd, *J* =

8.0, 4.0 Hz, 1H), 3.27 (dd, *J* = 8.0, 4.1 Hz, 1H), 5.60 (dd, *J* = 4.0, 4.1 Hz, 1H), 7.05 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.24 (dd, *J* = 9.6, 1.5 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 8.16 (d, *J* = 8.0 Hz, 2H), 8.70 (dd, *J* = 9.6, 1.7 Hz, 1H), 10.50 (s br, exch. D_2O, 1H), 11.6 (s br, exch. D_2O, 1H). ^{13}C-NMR ($CDCl_3$): δ_C 48.5, 58.2, 117.4, 122.8, 123.6, 123.9, 126.4, 127.6, 133.4, 133.7, 137.3, 148.1, 153.1, 157.8, 163.5, 176.2. HRMS: *m/z* (rel. int.) 351.0962 (100) (M^+), (calc. for $C_{17}H_{13}N_5O_4$, 351.0968), 349 (56), 323 (65), 228 (41), 173 (38), 162 (45), 159 (52). Anal.: CHN (%): Found; C, 58.10; H, 3.78; N, 19.95; Calc.; C, 58.12; H, 3.73; N, 19.93.

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