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A simple protocol for the green synthesis of a new series of pyrimido[4,5-*b*][1,6]naphthyridines in the presence of silver nanoparticles (AgNPs)

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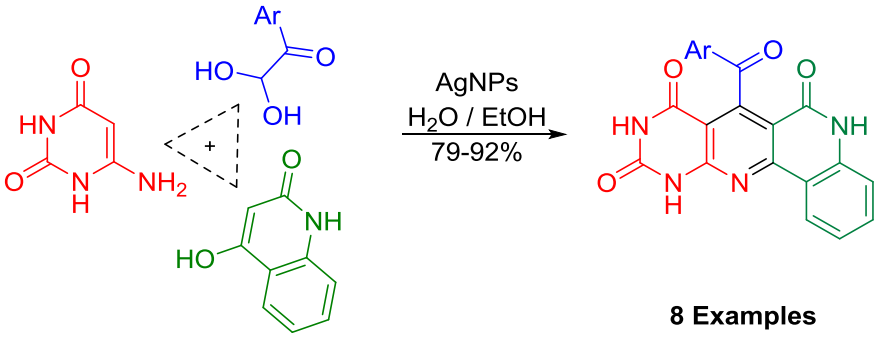
Abstract

Eight polyfunctionalized pyrimidonaphthyridine derivatives has been synthesized, in 79-92% yields, via the one-pot, three-component reaction of aryl glyoxal monohydrates, 6-aminouracil and 4-hydroxyquinolin-2(1*H*)-one in H_2O/EtOH in the presence of AgNPs under mild conditions. In this work colloidal AgNPs acts as an efficient, economical, green nanocatalyst, leading to a simple method of preparation.



Keywords: Aryl glyoxal hydrates, 6-aminouracil, AgNPs, 4-hydroxyquinolin-2(1*H*)-one, pyrimidonaphthyridines

Introduction

Nitrogen-containing fused heterocycles have stimulated the interest of chemists because of their wide range of biological, medicinal and therapeutic properties,[1] such as anti-cancer,[2] anti-HIV[3,4] anti-microbial,[5,6] anti-tumor[7] and anti-bacterial.[8] As such, their synthesis via the combination various hetero scaffolds is of interest in medicinal chemistry and developing more fused nitrogen-containing ring systems is worthwhile.

Both pyrimidine and 1,6-naphthyridine scaffolds are important structural motifs in chemistry, so preparing pyrimidonaphthyridine derivatives, in which these scaffolds are merged, could, tentatively, provide compounds that exhibit simultaneously the biological properties of each moiety.[9,10]

The green synthesis of silver nanoparticles (AgNPs) using *Ferula latisecta* leaf extracts has been reported.[11] Ghahremanzadeh *et al.* reported a one-pot, three component synthesis of spiro- furo- pyrido- pyridimidine-indolines using highly active magnetically reusable nano catalysts in water.[12]

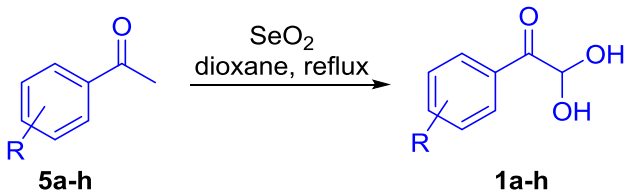
As part of our on-going work on the synthesis of fused heterocycles by one-pot multicomponent reactions,[13-21] we report herein, a one-pot, three component approach for accessing fused pyrimido-naphthyridines by reaction of aryl glyoxals, 6-aminouracil and 4-hydroxyquinolin-2(1*H*)-one in the presence of AgNPs under mild conditions in high yields.

Results and Discussion

The reaction of 4-methylphenyl glyoxal monohydrate (**1e**), 6-aminouracil (**2**) and 4-hydroxyquinolin-2(1*H*)-one (**3**) was chosen as a trial reaction (Table 1). The reaction mixture was stirred using various catalysts and two disparate green solvent systems. A solid precipitate separated out in 50-92% yields, which was characterized by its spectral data to be the desired substituted pyrimido[4,5-*b*][1,6]naphthyridine (**4e**).

The highest yield (91%) was achieved when the reaction was performed using 10 ppm of AgNPs as a nanocatalyst in H_2O/EtOH (1:1) after 3 h of reaction time (Table 1, entry 6). To investigate the effect of catalyst amount, the reaction was repeated in the presence of various amounts of AgNPs. Increasing the amount of catalyst did not affect the reaction yield significantly.

To find the most appropriate solvent for this reaction, the reaction was then repeated using various green solvent systems such as H_2O, EtOH, EtOH/H_2O (1:1), EtOH/H_2O (1:2), and AcOH (Table 1); EtOH/H_2O (1:1) was the best choice of solvent for this reaction. Acidic catalysts such as *p*-TSA and *L*-proline provided lower yields (Table 1). The aryl glyoxal monohydrates **1a-h** were obtained by oxidation of similar acetophenones **5a-h** with SeO_2 by literature methods[22] (Scheme 1).

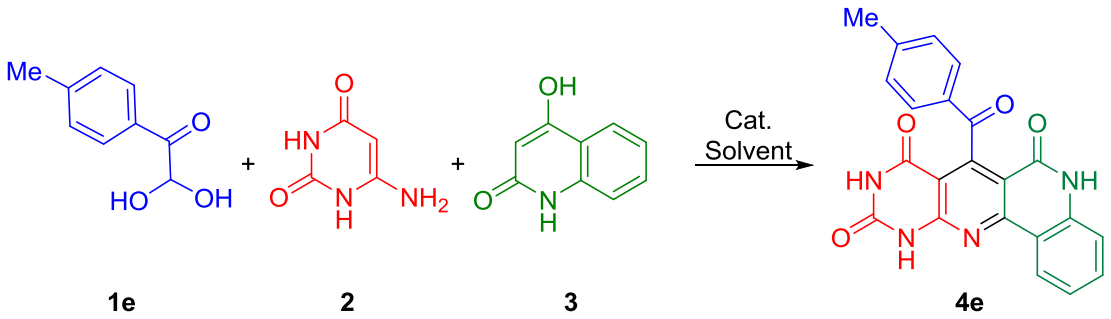


5a-h **1a-h**

R = H, 4-Cl, 4-Br, 4-F, 4-Me, 4-MeO, 3-MeO-4-OH, 3,4-$(MeO)_2$

Scheme 1. The preparation of aryl glyoxal monohydrates **1a-h.**

Table 1. Optimization of the reaction conditions



1e **2** **3** **4e**

Entry	Solvent	Temp. (°C)	Catalyst (mol %)	Time (h)	Yield 4e (%)
1	EtOH/H_2O (1:1)	Reflux	*L*-proline (20 mol%)	7	52
2	EtOH	Reflux	*L*-proline (20 mol%)	7	58
3	EtOH	Reflux	*p*-TSA (20 mol%)	6	57
4	EtOH/H_2O (1:1)	Reflux	*p*-TSA (20 mol%)	6	50
5	EtOH/H_2O (1:1)	60	AgNPs (5 ppm)	3	74
6	**EtOH/H_2O (1:1)**	**60**	**AgNPs (10 ppm)**	**3**	**91**
7	EtOH/H_2O (1:1)	60	AgNPs (20 ppm)	3	92
8	EtOH/H_2O (2:1)	60	AgNPs (10 ppm)	2	91
9	H_2O	60	AgNPs (10 ppm)	24	-
10	AcOH	70	*L*-proline (20 mol%)	10	79
11	AcOH	Reflux	*L*-proline (20 mol%)	10	70

The AgNPs was prepared via minor modifications of the literature method.[23,24] The SEM image and EDX spectrum of the nanocatalyst used are shown in Figures 1 and 2, respectively.

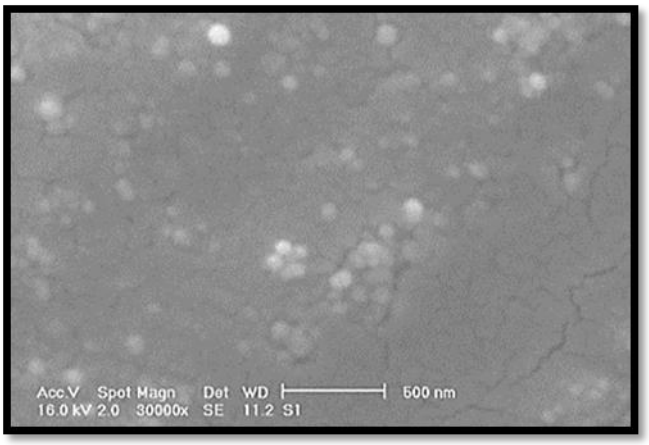


Figure 1. SEM images of AgNPs.

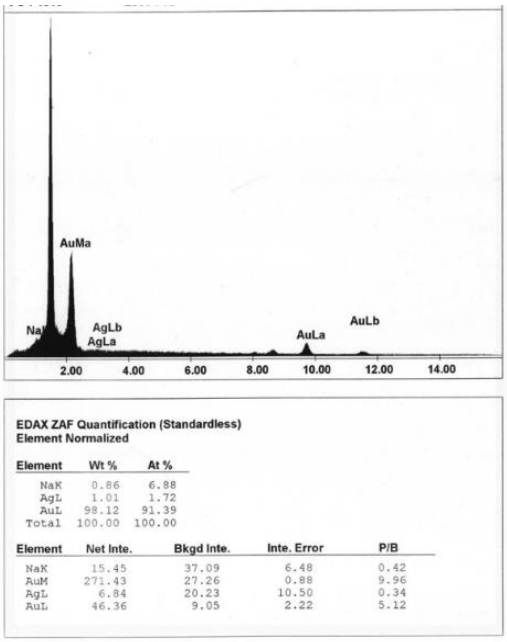
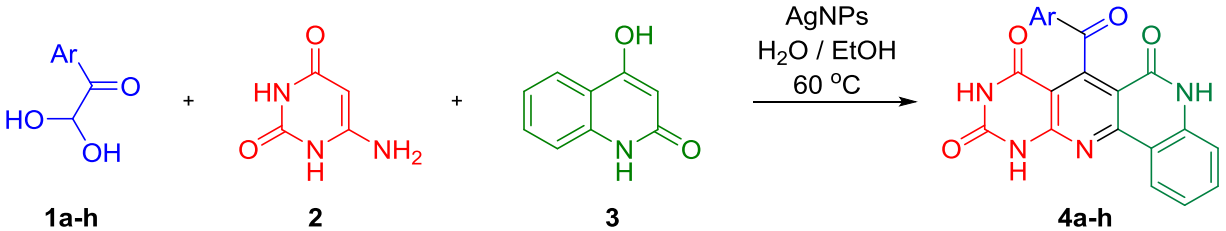


Figure 2. EDX spectrum of AgNPs.

The one-pot, three-component reaction of aryl glyoxal monohydrates **1a-h**, 6-aminouracil (**2**) and 4-hydroxyquinolin-2(1*H*)-one (**3**) in the presence of AgNPs (10 ppm) in H_2O/EtOH (1:1) afforded the desired pyrimido[4,5-*b*][1,6]naphthyridines **4a-h** in high yields (Table 2). The substituted pyrimido[4,5-*b*][1,6]naphthyridines **4a-h** were characterized using FT-IR, ^{1}H and ^{13}C NMR spectral data and microanalysis.

In the ^{1}H NMR spectra of products **4a-h**, the characteristic broad singlets at around δ_H 10.33-11.78, ascribed to the NH groups, was present in all new products. In the ^{13}C NMR spectra, signals located around δ_C 159.8-173.3 were attributed to the three different carbonyl groups. In the FT-IR (KBr) spectra, the characteristic absorptions bands at 3302-3438 and 1649-1718 cm^{-1} could be assigned to the vibrations of NH and different carbonyl groups, respectively.

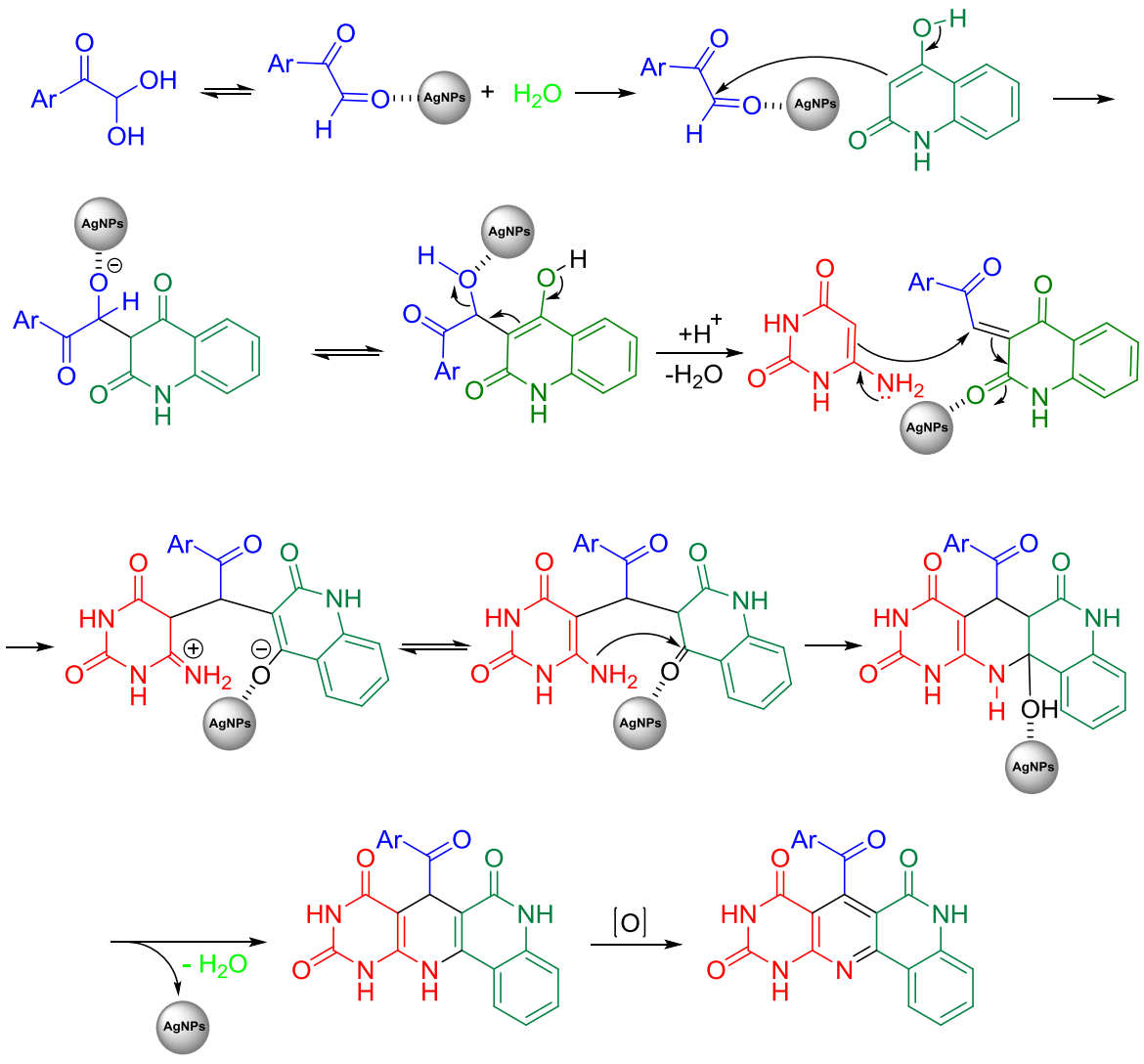
Table 2. The synthesis of pyrimido[4,5-*b*][1,6]naphthyridines **4a-h**.



1a-h **2** **3** **4a-h**

Entry	Ar	Time (min)	Yields (%)
1	Ph	300	**4a** (79)
2	4-BrC_6H_4	240	**4b** (88)
3	4-ClC_6H_4	270	**4c** (82)
4	4-FC_6H_4	240	**4d** (87)
5	4-Tol	180	**4e** (91)
6	4-MeOC_6H_4	150	**4f** (92)
7	3-MeO-4-HOC_6H_3	180	**4g** (89)
8	3,4-(MeO)$_2C_6H_3$	210	**4h** (90)

The proposed mechanism of this reaction involves the initial condensation of aryl glyoxals with 4-hydroxyquinolin-2(1*H*)-one to give an intermediate that reacts with 6-aminouracil to form the expected products through intramolecular condensation and further oxidation (Scheme 2).



Scheme 2. The proposed mechanism for synthesis of compounds **4a-h** in the presence of nanocatalyst.

Conclusions

We have developed a one-pot, three-component synthesis of pyrimido[4,5-*b*][1,6]naphthyridine derivatives in the presence of AgNPs as a nanocatalyst. This protocol has the advantages of using a green solvent system, a low nanocatalyst loading (10 ppm), high yields and a simple work up procedure.

Experimental Section

General. Melting points were measured on a Philip Harris C4954718 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer at 300 and 75.5 MHz, respectively. Chemical shifts were measured in DMSO-d_6 using TMS as the internal standard. Fourier

Transform Infrared (FTIR) spectra were recorded on a Thermo-Nicolet Nexus 670-FT-IR instrument. Elemental analyses were performed using a Leco Analyzer 932. The scanning electron microscopy (SEM) image of nanoparticles was obtained from Philips XL30. The EDX analysis of nanoparticles was obtained using the BAL-TEC SCDOOS apparatus.

Preparation of AgNPs as nanocatalyst. A solution of glucose (1% w/v) (1 mL) and a solution of sodium citrate (1×10^{-3} M) (2 mL) were added to a solution of silver nitrate (1×10^{-3} M) (1 mL). The resulting solution was heated at 60 ^{o}C for an hour when the color of the mixture changed from pale yellow to orange.[23,24] In this work the colloidal form of AgNPs we used, but freeze-dried nanoparticals were also satisfactory.[25]

General procedure for synthesis of new pyrimido[4,5-*b*][1,6]naphthyridines 4a-h. The aryl glyoxal monohydrate (1 mmol) was dissolved in H_2O/EtOH (1:1) (6 mL), then 6-aminouracil (1 mmol), 4-hydroxyquinolin-2(1*H*)-one (1 mmol) and AgNPs (10 ppm) were added to the reaction mixture. The reaction mixture was heated at 60 °C for different periods of time according to Table 2. Thin layer chromatography (TLC), was used to determine the reaction completion using (EtOAc/hexane, 2:3) as eluent. The obtained precipitate was filtered and then rinsed with distilled water. The products, recrystallized from EtOH, were obtained as pale yellow to brown powders, in yields of 79-92%.

7-Benzoylbenzo[*h*]pyrimido[4,5-*b*][1,6]naphthyridine-6,8,10(5*H*,9*H*,11*H*)-trione (4a). Yield 79% (303 mg), light brown powder, mp 347 ^{o}C (dec). IR (KBr, ν_{max}, cm^{-1}): 3357, 3190, 3001, 2872, 1718, 1643, 1608, 1510, 1462, 1428, 1279, 1215, 1146, 819, 765. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.69 (1H, s, D_2O exchanged, NH), 11.26 (1H, s, D_2O exchanged, NH), 10.38 (1H, s, D_2O exchanged, NH), 7.78 (1H, d, *J* 8.1 Hz, Ar), 7.47 (1H, dd, *J* 7.5, 7.5 Hz, Ar), 7.39 (2H, d, *J* 7.5 Hz, Ar), 7.30-7.21 (3H, m, Ar), 7.13 (2H, dd, *J* 7.5, 7.5 Hz, Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ_C 163.3, 159.9, 159.8, 158.9, 151.5, 143.2, 140.5, 138.8, 138.7, 132.6, 132.5, 130.0, 129.6, 129.5, 128.5, 127.7, 127.5, 125.7, 125.4, 122.3. Anal. calcd for $C_{21}H_{12}N_4O_4$: C, 65.62; H, 3.15; N, 14.58. Found: C, 65.44; H, 3.02; N, 14.69%. HRMS: Found: *m/z* 384.0871 $[M]^+$. $C_{21}H_{12}N_4O_4$ requires: M = 384.0859.

7-(4-Bromobenzoyl)benzo[*h*]pyrimido[4,5-*b*][1,6]naphthyridine-6,8,10(5*H*,9*H*,11*H*)-trione (4b). Yield 88% (406 mg), pale yellow powder, mp 337 ^{o}C (dec). IR (KBr, ν_{max}, cm^{-1}): 3434, 3166, 3029, 2879, 1692, 1612, 1493, 1447, 1256, 1129, 1007. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.78 (1H, s, D_2O exchanged, NH), 11.28 (1H, s, D_2O exchanged, NH), 10.37 (1H, s, D_2O exchanged, NH), 7.78 (1H, d, *J* 7.8 Hz, Ar), 7.53-7.40 (3H, m, Ar), 7.37 (1H, d, *J* 8.4 Hz, Ar), 7.29 (2H, d, *J* 8.1 Hz, Ar), 7.14 (1H, dd, *J* 7.8, 7.8 Hz, Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ_C 163.5, 163.2, 160.0, 159.0, 152.8, 151.6, 150.9, 140.7, 140.5, 138.8, 132.6, 131.9, 131.8, 130.7, 130.4, 129.4, 127.4, 127.3, 119.9. Anal. calcd for $C_{21}H_{11}BrN_4O_4$: C, 54.45; H, 2.39; N, 12.09. Found: C, 54.27; H, 2.22; N, 12.26%. HRMS: Found: *m/z* 463.9956 $[M+2]^+$, 461.9951 $[M]^+$. $C_{21}H_{11}BrN_4O_4$ requires: M = 463.9943, 461.9964.

7-(4-Chlorobenzoyl)benzo[*h*]pyrimido[4,5-*b*][1,6]naphthyridine-6,8,10(5*H*,9*H*,11*H*)-trione (4c). Yield 82% (343 mg), light brown powder, mp 340 ^{o}C (dec). IR (KBr, ν_{max}, cm^{-1}): 3438, 3181, 3087, 2892, 1709, 1609, 1501, 1440, 1249, 1137, 1097, 1011. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.73 (1H, s, D_2O exchanged, NH), 11.28 (1H, s, D_2O exchanged, NH), 10.40 (1H, s, D_2O exchanged, NH), 7.78 (1H, d, *J* 8.1 Hz, Ar), 7.50 (1H, dd, *J* 8.1, 8.1 Hz, Ar), 7.42 (2H, dd, *J* 8.1, 8.1 Hz, Ar), 7.26 (1H, d, *J* 8.7 Hz, Ar), 7.20-7.01 (3H, m, Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ_C 166.2, 163.3, 159.9, 159.0, 151.6, 140.4, 138.7, 129.2, 129.1, 127.8, 127.7, 124.6, 122.3, 116.6, 116.3, 116.2, 116.1, 115.6, 114.8. Anal. calcd for $C_{21}H_{11}ClN_4O_4$: C, 60.23; H, 2.65; N, 13.38. Found: C, 60.09; H, 2.78; N, 13.24%. HRMS: Found: *m/z* 420.0447 $[M+2]^+$, 418.0472 $[M]^+$. $C_{21}H_{11}ClN_4O_4$ requires: M = 420.0439, 418.0469.

7-(4-Fluorobenzoyl)benzo[*h*]pyrimido[4,5-*b*][1,6]naphthyridine-6,8,10(5*H*,9*H*,11*H*)-trione (4d). Yield 87% (350 mg), brown powder, mp 339 ^{o}C (dec). IR (KBr, ν_{max}, cm^{-1}): 3302, 3150, 3037, 2890, 1680, 1509, 1439, 1239, 1152, 1019. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.66 (1H, s, D_2O exchanged, NH), 11.29 (1H, s, D_2O exchanged, NH), 10.42 (1H, s, D_2O exchanged, NH), 7.78 (1H, d, *J* 8.7 Hz, Ar), 7.53-7.30 (6H, m, Ar), 7.15 (1H,

dd, *J* 7.8, 7.8 Hz, Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ_C 163.6, 163.2, 159.9, 159.8, 152.8, 151.6, 150.9, 140.6, 140.5, 138.8, 131.6, 131.1, 129.7, 129.3, 129.1, 127.9, 127.5, 127.4, 124.7. Anal. calcd for $C_{21}H_{11}FN_4O_4$: C, 62.69; H, 2.76; N, 13.93. Found: C, 62.40; H, 2.65; N, 14.19%. HRMS: Found: *m/z* 402.0770 $[M]^+$. $C_{21}H_{11}FN_4O_4$ requires: M = 402.0764.

7-(4-Methylbenzoyl)benzo[*h*]pyrimido[4,5-*b*][1,6]naphthyridine-6,8,10(5*H*,9*H*,11*H*)-trione (4e). Yield 91% (362 mg), pale orange powder, mp 333 °C (dec). IR (KBr, ν_{max}, cm^{-1}): 3420, 3175, 3034, 1709, 1672, 1636, 1503, 1436, 1399, 1241, 1140, 1018. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.61 (1H, s, D_2O exchanged, NH), 11.24 (1H, s, D_2O exchanged, NH), 10.36 (1H, s, D_2O exchanged, NH), 7.78 (1H, d, *J* 7.5 Hz, Ar), 7.47 (1H, dd, *J* 7.5, 7.5 Hz, Ar), 7.35 (2H, d, *J* 7.8 Hz, Ar), 7.12-7.33 (1H, m, Ar), 7.11 (1H, dd, *J* 7.2, 7.2 Hz, Ar), 7.05 (2H, d, *J* 7.5 Hz, Ar), 2.26 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ_C 173.3, 163.6, 160.0, 158.8, 152.7, 151.6, 150.9, 140.3, 140.2, 138.8, 136.1, 135.9, 130.0, 129.8, 128.7, 127.5, 127.4, 125.6, 125.5, 18.6. Anal. calcd for $C_{22}H_{14}N_4O_4$: C, 66.33; H, 3.54; N, 14.06. Found: C, 66.19; H, 3.40; N, 14.28%. HRMS: Found: *m/z* 398.1003 $[M]^+$. $C_{22}H_{14}N_4O_4$ requires: M = 398.1015.

7-(4-Methoxybenzoyl)benzo[*h*]pyrimido[4,5-*b*][1,6]naphthyridine-6,8,10(5*H*,9*H*,11*H*)-trione (4f). Yield 92% (381 mg), pale yellow powder, mp 335 °C (dec). IR (KBr, ν_{max}, cm^{-1}): 3410, 3183, 3069, 2857, 1685, 1634, 1517, 1448, 1244, 1190, 1131, 1020. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.58 (1H, s, D_2O exchanged, NH), 11.25 (1H, s, D_2O exchanged, NH), 10.33 (1H, s, D_2O exchanged, NH), 7.78 (1H, d, *J* 7.5 Hz, Ar), 7.44 (1H, dd, *J* 8.4, 8.4 Hz, Ar), 7.40-7.20 (3H, m, Ar), 7.12 (1H, dd, *J* 7.8, 7.8 Hz, Ar), 6.83 (2H, d, *J* 8.1 Hz, Ar), 3.73 (3H, s, OCH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ_C 163.7, 163.4, 160.0, 152.7, 151.6, 151.0, 140.2, 140.0, 139.0, 128.9, 128.5, 127.0, 125.2, 122.3, 122.2, 115.7, 115.6, 107.0, 100.5, 27.5. Anal. calcd for $C_{22}H_{14}N_4O_5$: C, 66.77; H, 3.41; N, 13.52. Found: C, 66.52; H, 3.39; N, 13.68%. HRMS: Found: *m/z* 414.0989 $[M]^+$. $C_{22}H_{14}N_4O_5$ requires: M = 414.0964.

7-(4-Hydroxy-3-methoxybenzoyl)benzo[*h*]pyrimido[4,5-*b*][1,6]naphthyridine-6,8,10(5*H*,9*H*,11*H*)-trione (4g). Yield 89% (383 mg), brown powder, mp 297 °C (dec). IR (KBr, ν_{max}, cm^{-1}): 3348, 3188, 2996, 2877, 1710, 1638, 1511, 1436, 1277, 1217, 1148, 1022, 816, 770. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.47 (1H, s, D_2O exchanged, NH), 11.27 (1H, s, D_2O exchanged, NH), 10.33 (1H, s, D_2O exchanged, NH), 8.94 (1H, s, D_2O exchanged, OH), 7.83-7.78 (1H, m, Ar), 7.47-7.32 (1H, m, Ar), 7.31-7.25 (1H, m, Ar), 7.13-7.00 (2H, m, Ar), 6.71 (1H, d, *J* 7.2 Hz, Ar), 6.70 (1H, d, *J* 7.5 Hz, Ar), 3.52 (3H, s, OCH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ_C 166.2, 163.5, 159.9, 158.9, 154.1, 151.6, 150.3, 147.5, 145.8, 140.0, 138.7, 129.7, 128.9, 123.9, 122.2, 122.1, 120.6, 115.6, 114.2, 114.1, 112.1, 16.3. Anal. calcd for $C_{21}H_{12}N_4O_5$: C, 63.00; H, 3.02; N, 13.99. Found: C, 62.85; H, 2.92; N, 14.14%. HRMS: Found: *m/z* 430.0934 $[M]^+$. $C_{21}H_{12}N_4O_5$ requires: M = 430.0913.

7-(3,4-Dimethoxybenzoyl)benzo[*h*]pyrimido[4,5-*b*][1,6]naphthyridine-6,8,10(5*H*,9*H*,11*H*)-trione (4h). Yield 90% (400 mg), brown powder, mp 361 °C (dec). IR (KBr, ν_{max}, cm^{-1}): 3368, 3208, 2933, 2857, 1649, 1512, 1455, 1250, 1219, 1148, 1020. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.55 (1H, s, D_2O exchanged, NH), 11.29 (1H, s, D_2O exchanged, NH), 10.36 (1H, s, D_2O exchanged, NH), 7.78 (1H, d, *J* 7.5 Hz, Ar), 7.47 (1H, dd, *J* 7.8, 7.8 Hz, Ar), 7.26 (1H, d, *J* 7.8 Hz, Ar), 7.13 (1H, dd, *J* 7.2, 7.2 Hz, Ar), 7.04 (1H, s, Ar), 6.94 (1H, d, *J* 7.5 Hz, Ar), 6.62 (1H, d, *J* 8.7 Hz, Ar), 3.67 (3H, s, CH_3), 3.53 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ_C 167.9, 163.5, 162.3, 159.8, 151.4, 148.6, 148.0, 144.2, 139.7, 138.3, 130.3, 128.5, 125.1, 125.0, 124.5, 124.4, 119.3, 118.5, 116.2, 115.4, 113.4, 25.2, 21.7. Anal. calcd for $C_{23}H_{16}N_4O_6$: C, 62.16; H, 3.63; N, 12.61. Found: C, 61.99; H, 3.53; N, 12.80%. HRMS: Found: *m/z* 444.1061 $[M]^+$. $C_{23}H_{16}N_4O_6$ requires: M = 444.1070.

Acknowledgements

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