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Aqueous hydrotropic solution: green reaction medium for synthesis of pyridopyrimidine carbonitrile and spiro-oxindole dihydroquinazolinone derivatives

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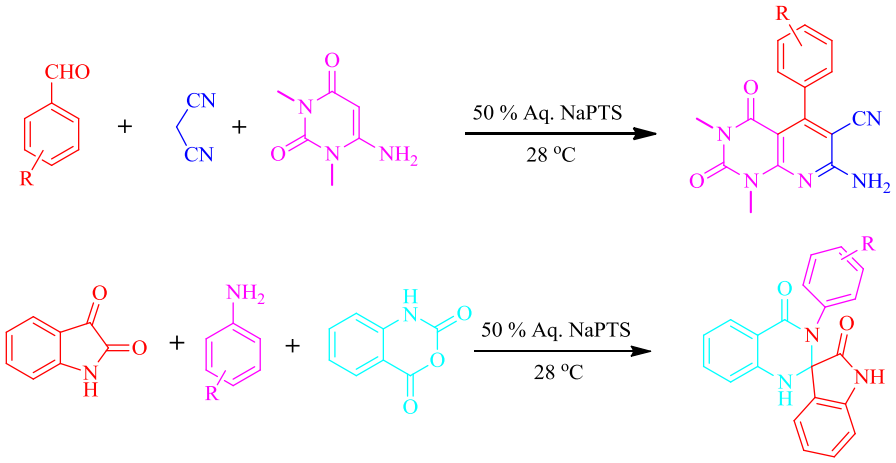
Abstract

From the green chemistry point of view, water is one of the most sustainable solvents for chemical transformations, but there are some limitations to its use as a reaction medium due to the lack of solubility of organic compounds. To overcome this difficulty, we used aqueous hydrotropic solution, which increases the solubility of organic compounds in water by 200-fold. We report an environmentally efficient method for synthesis of pyridopyrimidine carbonitriles and spiro-oxindole dihydroquinazolinones by using 50 % aqueous sodium *p*-toluene sulfonate (NaPTS) solution at ambient reaction condition. The merits of the present protocol include short reaction time, excellent product yield with high purity, easy workup procedure and reusability of reaction medium.

Graphical abstract



Keywords Multicomponent reaction · Hydrotropic solution · Dihydroquinazolinone · Green reaction medium · Spiro-oxindole

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Introduction

Multicomponent reactions (MCRs) play an important role in synthetic medicinal and organic chemistry [1]. Due to their high atom economy and short reaction time, they are one of the most powerful tools in the modern drug discovery process [2]. These reactions proceed in one pot to form complex structures in a single operation by formation of new C–C and C–N bonds [3]. Recently, a number of researchers have synthesized various heterocyclic molecules by using green methodologies [4, 5].

From the green chemistry prospective, carrying out organic transformations in aqueous medium remains a great challenge. As a universal solvent, it is desirable to use water as a reaction medium due to its safe, harmless and environmentally benign nature [6], but most organic compounds are insoluble in water. To overcome this difficulty, we have carried out reactions in hydrotropes [7]. The term "hydrotropes" refers to a class of water-soluble surface-active compounds with amphiphilic character and hydrophobic regions that enhance the solubility of organic reactants and nonpolar compounds in aqueous phase at higher concentration [8]. They can increase the solubility of organic compounds up to 200-fold in water [9]. They usually comprise hydrophilic and hydrophobic moieties, with the latter typically being too small to induce micelle formation [10, 11].

Pyrido[2,3-*d*]pyrimidine and spiro-oxindole derivatives are an important class of heterocyclic compounds [12], being the main components of some naturally occurring products. These compounds have attracted increasing interest in recent years due to their useful biological and pharmacological properties [13, 14]. Pyrido[2,3-*d*]pyrimidine and spiro-oxindole derivatives exhibit intriguing biological activities such as antitumor, antiallergic, antifolate, antimicrobial, antibacterial [15], antiinflammatory [16], analgesic, antihypertensive [17], tuberculostatic and anticonvulsant [18] effects. In addition, pyridopyrimidines is very important class of annelated uracils (Fig. 1) [19] with biological significance because of their connection with the purine pyridine system [20, 21].

Dihydroquinazolin-4(3*H*)-ones exhibit a broad spectrum of biological and pharmaceutical activities [22]. Spiro-oxindole fused quinazolinone compounds show antimalarial, antibacterial, anticancer and antimycobacterial activities [23, 24]. The heterocyclic spiro-oxindole ring system is a widely distributed structural framework [25] that is present in a number of pharmaceuticals (Fig. 2) and natural products, including cytostatic alkaloids such as spirotryprostatins A and B and strychnophylline [26, 27].

Due to the versatile biological activities of pyridopyrimidine carbonitrile and spiro-oxindole derivatives, they have become important targets of synthetic organic chemistry. In this context, a number of methods have been reported for synthesis of these fused heterocycles [28]. Recently reported methods for synthesis of pyrido[2,3-*d*]pyrimidine carbonitrile include use of triethanolamine in water at 80 °C [29], glycerol [30], in dimethylformamide (DMF) under microwave irradiation [31], nanocrystalline MgO in water [32], sulfonic acid-functionalized SBA-15 [33], 1,4-diazabicyclo[2.2.2]octane (DABCO)-functionalized

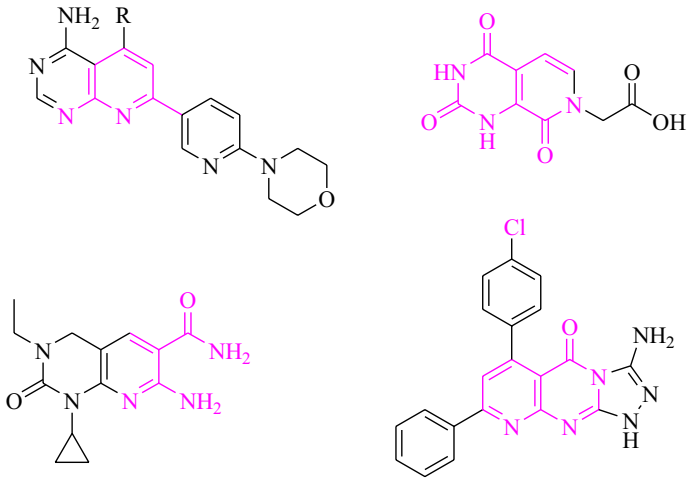


Fig. 1 Biologically active pyridopyrimidine derivatives

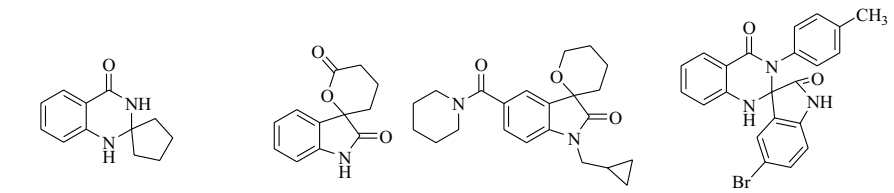
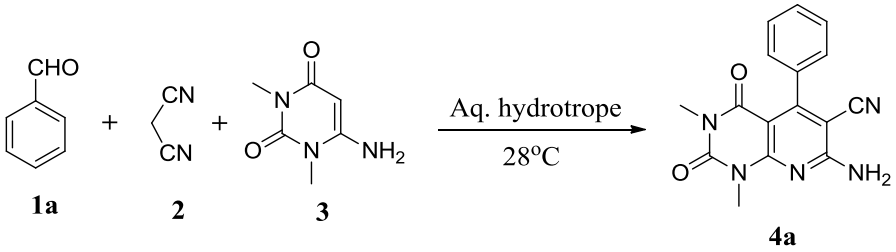


Fig. 2 Biologically active spiro-oxindole quinazolinone molecules

ionic liquid [34], Fe_3O_4 nanoparticles in EtOH at 40 °C [35] and Al-HMS-20 in EtOH at room temperature [36]. Meanwhile, synthesis of spiro-oxindole derivatives has been reported using different catalytic systems, such as alum in ethanol [37], $SnCl_2{\cdot}H_2O$ in ethanol under reflux condition [38], ethylenediamine in water under reflux condition [39], $[HMIm]HSO_4$ at 100 °C [40], bentonite under ultrasound irradiation [23], nano-CuO in ethanol [24], acetic acid under microwave irradiation [41], $Fe_3O_4GO–SO_3H$ in solvent-free condition at 100 °C [42], nano-CeO_2 in water–ethanol (1:1) system [22] and cetyltrimethylammonium bromide (CTAB) in water [26] based on the cosolvent effect [43–46]. However, reported methods suffer from one or more limitations such as use of volatile solvents or homogeneous catalysts, long reaction time and unsatisfactory yield. To overcome these difficulties and in continuation of our interest in the synthesis of bioactive molecules [47–51], we developed and describe herein one-pot three-component synthesis of pyrido[2,3-*d*]pyrimidine carbonitrile by reaction of aldehyde, malononitrile and 6-amino-1,3-dimethyluracil and spiro-oxindole dihydroquinazolinone using isatin, aniline and isatoic anhydride in 50 % aqueous hydrotropic medium at 28 °C.



1a 2 3 4a

Scheme 1 Synthesis of pyrido[2,3-*d*]pyrimidine carbonitrile

Table 1 Optimization of various hydrotropes

Entry	Hydrotrope	Time (min)	Yield[a] (%)
1	Sodium benzene sulfonate (NaBS)	120	56
2	Sodium *p*-xylene sulfonate (NaXS)	90	65
3	**Sodium *p*-toluene sulfonate (NaPTS)**	**25**	**92**
4	Sodium cumene sulfonate (NaCS)	70	70

Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol) and 6-amino-1,3-dimethyluracil (1 mmol) in 5 mL aq. hydrotropic solution (50 % w/v) stirred at 28 °C

[a]Isolated product yield

Results and discussion

Initially, to optimize the reaction conditions, including temperature, solvent and catalyst, we carried out the reaction of benzaldehyde (**1a**), malononitrile (**2**) and 6-amino-1,3-dimethyluracil (**3**) as model reaction (Scheme 1). To identify a suitable hydrotrope for synthesis of pyrido[2,3-*d*]pyrimidine carbonitrile, we carried out the model reaction using different hydrotropes such as sodium benzene sulfonate (NaBS), sodium *p*-xylene sulfonate (NaXS), sodium *p*-toluene sulfonate (NaPTS) and sodium cumene sulfonate (NaCS). Comparatively, higher activity was observed with NaPTS based on the results presented in Table 1, due to its overall planar structure and presence of more balanced hydrophobic and hydrophilic regions generating microunits.

Based on the reaction time and product yield, we considered that the sodium salt *p*-toluene sulfonate (NaPTS) was the best hydrotrope for synthesis of pyrido[2,3-*d*]pyrimidine carbonitrile. After choosing the suitable hydrotrope, we screened the model reaction using different concentrations of aqueous NaPTS hydrotropic solution (Table 2, entries 1–8), noting that 50 % aqueous NaPTS gave the maximum yield of the pyridopyrimidine derivative **4a**. Further increase in the concentration of NaPTS above 50 % failed to increase the product yield. After optimization of the concentration of NaPTS, we carried out the reaction at different temperatures (Table 2, entries 9–12), observing the maximum product yield at 28 °C. At higher temperature, rate of micelle formation decreses which inturn result in product yield decrement.

Table 2 Optimization of reaction conditions for synthesis of pyridopyrimidine derivatives

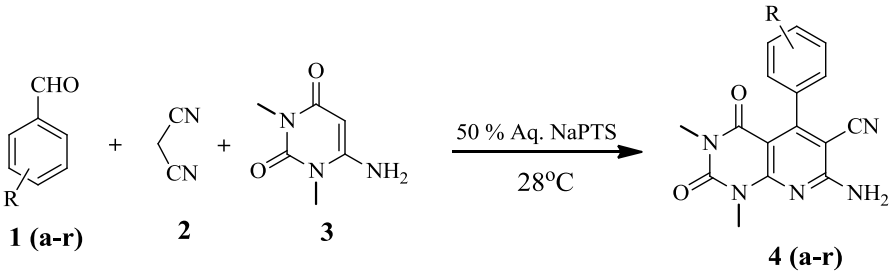
Entry	Hydrotrope concentration (% *w/v*)	Temperature (°C)	Time (min)	Yield[a] (%)
1	H_2O	28	150	–
2	5 % NaPTS	28	120	40
3	10 % NaPTS	28	100	54
4	20 % NaPTS	28	80	66
5	30 % NaPTS	28	65	75
6	40 % NaPTS	28	50	80
7	**50 % NaPTS**	**28**	**25**	**92**
8	60 % NaPTS	28	30	90
9	50 % NaPTS	40	30	88
10	50 % NaPTS	60	30	84
11	50 % NaPTS	80	30	80
12	50 % NaPTS	100	30	78

Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol) and 6-amino-1,3-dimethyluracil (1 mmol) in 5 mL aq. hydrotropic solution (% w/v) stirred at various temperatures

[a]Isolated product yield

After optimization of the reaction conditions, we explored the scope of the reaction for different substituted aldehydes (Scheme 2; Table 3, entries 1–18). It was observed that aldehydes bearing electron-withdrawing as well as electron-releasing groups underwent the reaction smoothly to afford desired pyridopyrimidine derivatives in excellent yield.

Our next task was to explore the scope of NaPTS for synthesis of spiro-oxindole dihydroquinazolinone derivatives. For this purpose, we reacted isatoic anhydride (**5**) and isatin (**6**) with various structurally diverse anilines **7a–o** to obtain a series of spiro-oxindole dihydroquinazolinone derivatives **8a–o** (Scheme 3; Table 4). It was found that various anilines with electron-releasing and electron-withdrawing substituents gave corresponding spiro-oxindole dihydroquinazolinone derivatives in good to excellent yield. However, in case of nitroaniline,



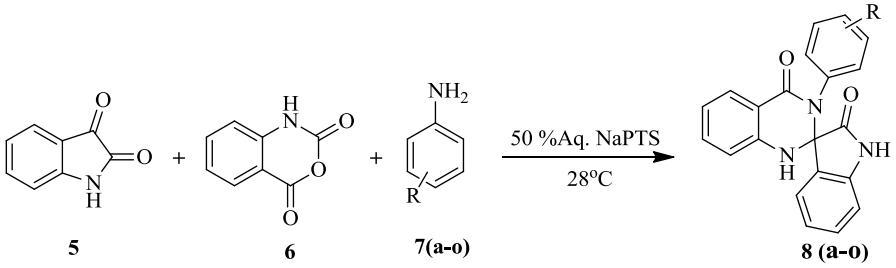
Scheme 2 General reaction for synthesis of pyridopyrimidine carbonitrile derivatives

Table 3 Synthesis of pyrido[2,3-*d*]pyrimidine carbonitrile derivatives

Entry	Aldehyde	Product	Time (min)	Yield[a] (%)	M.p. (°C) obs. [lit.] [Ref.]
1	R = H	**4a**	25	92	240–243 [242–245] [30]
2	R = 4-CH_3	**4b**	25	92	226–228 [227–229] [30]
3	R = 3-CH_3	**4c**	25	88	221–224 [221–223] [33]
4	R = 2-CH_3	**4d**	25	90	216–218 [215–217] [33]
5	R = 4-$N(CH_3)_2$	**4e**	25	86	261–162 [160–162] [30]
6	R = 4-OCH_3	**4f**	25	95	226–228 [225–227] [33]
7	R = 3-OCH_3	**4g**	25	94	221–224 [221–223] [30]
8	R = 2-OCH_3	**4h**	25	92	216–218 [215–217] [33]
9	R = 3-NO_2	**4i**	25	88	302 [> 300] [30]
10	R = 4-NO_2	**4j**	25	90	281–282 [280–281] [33]
11	R = 4-F	**4k**	25	86	244–246 [245–247] [30]
12	R = 2-Cl	**4l**	25	85	242–244 [241–243] [30]
13	R = 4-Cl	**4m**	25	88	235–237 [234–236] [33]
14	R = 4-Br	**4n**	25	89	236–238 [235–237] [30]
15	R = 4-CN	**4o**	25	86	266–268 [229–230] [33]
16	R = 2-OH	**4p**	25	91	198–200 [197–199] [30]
17	R = 3-OH	**4q**	25	88	291–292 [290–292] [33]
18	R = 4-OH	**4r**	25	92	266–268 [229–230] [30]

Reaction conditions: aldehyde (1 mmol), malononitrile (1 mmol), and 6-amino-1,3-dimethyluracil (1 mmol) in 5 mL aq. NaPTS solution (50 % w/v) stirred at 28 °C

[a]Isolated product yield



Scheme 3 General reaction for synthesis of spiro-oxindole dihydroquinazolinone derivatives

no product formation was observed, which might be due to the strong electron-withdrawing character of nitro group (Table 4, entry 9).

Recyclability

Recovery and reuse of catalysts is highly preferable for a green process. Thus, the reusability of the catalyst was investigated using the reaction of benzaldehyde, malononitrile and 6-amino-1,3-dimethyluracil as model reaction (Scheme 1). After reaction

Table 4 Synthesis of spiro-oxindole dihydroquinazolinone derivatives

Entry	Aniline	Product	Time (min)	Yield[a] (%)	M.p. (°C) obs. [lit.] [Ref.]
1	R = H	**8a**	30	88	250–252 [251–253] [37]
2	R = 2-CH_3	**8b**	30	87	278–280 [280–282] [37]
3	R = 3-CH_3	**8c**	30	86	272–276 [274–276] [39]
4	R = 4-CH_3	**8d**	30	90	270–272 [271–273] [37]
5	R = 2-OCH_3	**8e**	30	89	276–280 [278–280] [43]
6	R = 3-OCH_3	**8f**	30	86	275–276 [274–276] [43]
7	R = 4-OCH_3	**8g**	30	92	268–270 [269–271] [37]
8	R = 4-CH_2CH_3	**8h**	30	88	294–296 [295–297] [40]
9	R = 2-NO_2	**8i**	–	–	–
10	R = 2-Cl	**8j**	30	86	248–252 [250–252] [40]
11	R = 3-Cl	**8k**	30	82	292–294 [293–295] [40]
12	R = 4-Cl	**8l**	30	88	262–264 [264–266] [37]
13	R = 4-F	**8m**	30	84	294–298 [295–296] [39]
14	R = 4-Br	**8n**	30	89	212–214 [213–215] [37]
15	R = benzylamine	**8o**	30	85	190–194 [190–192] [37]

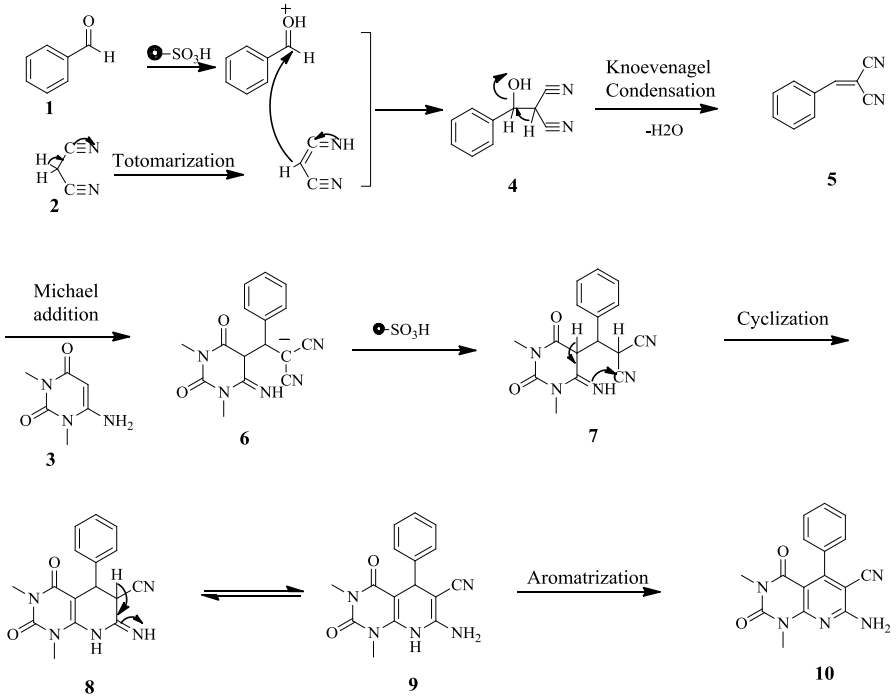
Reaction conditions: isatoic anhydride (1 mmol), isatin(1 mmol) and aniline (1 mmol) in 5 mL of aq. NaPTS solution (50 % w/v) stirred at 28 °C

[a]Isolated product yield

completion, the reaction mixture was filtered and the filtrate was washed with ethyl acetate; the obtained NaPTS, after evaporating the aqueous layer, was reused directly in the next run. It was found that the catalyst could be recycled five times with only a slight decrease in product yield.

Plausible reaction mechanism

A plausible reaction mechanism for the synthesis of pyrido[2,3-*d*]pyrimidine carbonitrile derivatives is shown in Scheme 4. The SO_3H group of NaPTS donates a proton to the carbonyl carbon of aldehyde and increases the electrophilicity of the carbonyl carbon and activates the aldehyde **1**. This aldehyde reacts with malononitrile **2** to form intermediate **4**, followed by Knoevenagel condensation to produce benzylidene malononitrile **5**. Michael addition of 6-amino-1,3-dimethyluracil **3** with intermediate **5** gives intermediate **6**. NaPTS donates another proton to intermediate **6** to form intermediate **7**, which undergoes cyclization to form intermediate **8**, followed by aromatization to give the desired product **10**.



Scheme 4 Plausible reaction mechanism

Conclusions

We describe a protocol based on an efficient multicomponent domino approach for synthesis of pyridopyrimidine and spiro-oxindole dihydroquinazolinone derivatives by one-pot reaction in aqueous NaPTS medium. The reactions show broad substrate scope with no side-product observed. This green synthesis shows various attractive features such as environmentally friendly reaction medium, fast reaction rate which enables the reaction to complete within 25–30 min and convenient workup procedure requiring only simple filtration.

Experimental

General

The different substrates used for synthesis of various derivatives were purchased from both Sigma-Aldrich and Alfa Aesar and used without any further purification. TLC was carried out using silica gel G 60 F_{254} plates (Merck). The melting points of products were determined in open capillary tubes and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and distortionless enhancement by polarization transfer (DEPT)-135 spectra were recorded on a Bruker-Avance 300 MHz and 75 MHz

spectrometer using tetramethylsilane (TMS) as internal standard and $CDCl_3$/dimethyl sulfoxide (DMSO)-d_6 as solvent.

General procedure for synthesis of pyridopyrimidine carbonitrile derivatives

In a round-bottomed flask, a mixture of 2.5 g sodium salt *p*-toluene sulfonic acid and 5 mL water was stirred for 15 min at 28 °C to obtain 50 % aq. NaPTS solution. Then, substituted aldehyde (1 mmol), malononitrile (1 mmol) and 6-amino-1,3-dimethyluracil (1 mmol) were added to 50 % aq. NaPTS solution and stirred for required time as indicated in Table 3. Reaction progress was monitored by thin-layer chromatography (TLC). After reaction completion, 10 mL water was added to the reaction mixture and solid product was separated by filtration. The obtained product was washed with water and recrystallized from ethanol to yield pyridopyrimidine carbonitrile derivatives. The synthesized compounds were identified by comparison of physical and spectral data (^{1}H NMR, ^{13}C NMR, MS and FT-IR).

General procedure for synthesis of spiro-oxindole dihydroquinazolinone

In a round-bottomed flask, a mixture of 2.5 g sodium salt *p*-toluene sulfonic acid and 5 mL water was stirred for 15 min at 28 °C to obtain 50 % aq. NaPTS solution. Then, various substituted aniline (1 mmol), isatoic anhydride (1 mmol) and isatin (1 mmol) were added to 50 % aq. NaPTS solution and stirred for required time as indicated in Table 4. Reaction progress was monitored by thin-layer chromatography (TLC). After reaction completion, 10 mL water was added to the reaction mixture and solid product was separated by filtration. The obtained product was washed with water and recrystallized from ethanol to yield pyridopyrimidine carbonitrile derivatives. The synthesized compounds were identified by comparison of physical and spectral data (^{1}H NMR, ^{13}C NMR, MS and FT-IR).

Spectral data of selected compounds

7-Amino-1,3-dimethyl-2,4-dioxo-5-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*] pyrimidine-6-carbonitrile (**4a**)

White solid; m.p.: 240–243 °C (lit. 242–245 °C) [30]; IR (KBr, ν_{max}/cm^{-1}): 3350.72, 3190.42, 3117.30, 2158.16, 1689.55, 1371.18, 1252.64 and 1174.04. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 3.08 (s, 3H), 3.38 (s, 3H), 7.12-7.28 (m, 5H), 7.38 (s, 2H-NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.43, 158.40, 151.42, 149.94, 144.70, 130.44, 129.49, 128.82, 127.66, 126.36, 119.58, 29.14, 28.42 ppm. MS: $C_{16}H_{13}N_5O_2$, $m^+ = 307$.

7-Amino-5-(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4f)

White solid; m.p.: 226–228 °C (lit. 225–227 °C) [33]; IR (KBr, ν_{max}/cm^{-1}): 3342.72, 3286.38, 3172.12, 2956.20 2191.70, 1684.79, 1648.30, 1361.98, 1248.04 and 1054.14. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 3.10 (s, 3H), 3.42 (s, 3H), 3.92 (s, 3H), 6.85 (d, 2H, $J=6.3$ Hz), 7.16 (d, 2H, $J=6.0$ Hz) 7.32 (s, 2H–NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.14, 159.31, 158.15, 151.02, 150.72, 137.24, 129.35, 119.33, 114.06, 59.58 30.18, 28.76 ppm. MS: $C_{17}H_{15}N_5O_3$, $m^+=337$.

7-Amino-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4i)

White solid; m.p.: >300 °C (lit. >300 °C) [30]; IR (KBr, ν_{max}/cm^{-1}): 3373.85, 3306.68, 3184.42, 2196.46, 1683.76, 1391.18, 1232.64 and 1194.04. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 3.48 (s, 3H), 3.78 (s, 3H), 5.92 (s, 2H-NH_2), 7.23-8.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.80, 158.01, 157.15, 154.82, 150.02, 147.94, 137.70, 132.14, 127.45, 124.02, 122.66, 114.56, 30.28, 28.26 ppm. MS: $C_{16}H_{12}N_6O_4$, $m^+=352$.

7-Amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4m)

White solid; m.p.: 235–237 °C (lit. 234–236 °C) [33]; IR (KBr, ν_{max}/cm^{-1}): 3393.05, 3326.28, 3198.47, 2205.76, 1688.71, 1399.88, 1252.61, 1194.04 and 850.23. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 3.16 (s, 3H), 3.52 (s, 3H), 7.29 (d, 2H, $J=6.6$ Hz), 7.51 (d, 2H, $J=6.0$ Hz), 7.88 (s, 2H-NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.09, 160.98, 159.11, 158.78, 152.92, 150.43, 135.91, 132.01, 130.11, 128.07, 118.22, 101.52, 89.35, 31.42, 29.62 ppm. MS: $C_{16}H_{12}ClN_5O_2$, $(m+2)=341$.

3′-Phenyl-1′*H*-spiro[indoline-3,2′-quinoline]-2,4′(3′*H*)-dione (8a)

White solid; m.p.: 250–252 °C (lit. 251-253 °C) [37]; IR (KBr, ν_{max}/cm^{-1}): 3690.18, 3225.30, 2840.20, 1721.12, 1615.36, 1480.70, 1340.30 and 750.25. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.43 (s, 1H), 7.72–7.54 (m, 2H), 7.31 (t, 1H, $J=6.3$ Hz), 7.19 (t, 2H, $J=7.5$ Hz and 5.1 Hz) 7.14 (d, 1H, $J=6.9$ Hz), 7.00–6.90 (m, 4H), 6.77(d, 1H, $J=7.2$ Hz), 6.70 (d, 2H, $J=8.1$ Hz), 6.63 (d, 1H, $J=7.8$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.05, 162.02, 146.60, 141.65, 138.00, 133.64, 130.79, 127.60, 126.61, 126.59, 126.46, 126.26, 126.00, 122.14, 117.65, 114.51, 110.08, 76.35. MS: $C_{21}H_{15}N_3O_2$, $m^+=341$.

3′-(*p*-Tolyl)-1′*H*-spiro[indoline-3,2′-quinoline]-2,4′(3′*H*)-dione (8d)

White solid; m.p.: 270–272 °C (lit. 271–273 °C) [37]; IR (KBr, ν_{max}/cm^{-1}): 3830.40, 3640.26, 3148.52, 1723.24, 1630.51, 1515.80, 1468.70, 1340.78, 1176.28

and 548.97. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.44 (s, 1H), 7.73 (d, 1H, J=7.8 Hz), 7.63 (s, 1H), 7.58 (d, 1H, J=7.2 Hz), 7.35 (t, 1H, J=7.8 Hz), 7.27 (t, 1H, J=7.8 Hz), 7.05 (d, 2H, J=8.2 Hz), 6.98 (t, 1H, J=7.5 Hz), 6.93 (d, 2H, J=7.8 Hz), 6.82–6.70 (m, 2H), 6.65 (d, 1H, J=7.8 Hz), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.74, 165.43, 149.90, 145.63, 139.82, 137.44, 134.59, 130.70, 127.45, 126.40, 122.20, 117.62, 114.35, 110.10, 72.45, 22.56; MS: $C_{22}H_{17}N_3O_2$, m^+=355.

3′-(4-Methoxyphenyl)-1′*H*-spiro[indoline-3,2′-quinoline]-2,4′(3′*H*)-dione (**8g**)

White solid; m.p.: 268–270 °C (lit. 269–271 °C) [37]; IR (KBr, ν_{max}/cm^{-1}): 3650.40, 3289.42, 1720.30, 1589.34, 1350.04, 1240.08 and 748.25. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.40 (s, 1H), 7.68–7.62 (m, 1H), 7.57 (s, 1H), 7.55 (d, 1H, J=7.2 Hz), 7.32–7.24 (m, 1H), 7.12 (d, 1H, J=1.2 Hz), 6.93 (d, 1H, J=0.9 Hz), 6.88 (d, 2H, J=7.2 Hz), 6.76–6.72 (m, 3H), 6.70 (d, 1H, J=7.8 Hz), 6.65 (d,1H, J=7.5 Hz), 3.60 (s, 3H): ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.84, 172.45, 161.21, 157.12, 146.09, 140.59, 133.57, 130.60, 127.50, 126.53, 122.43, 115.03, 76.05, 54.43; MS: $C_{22}H_{17}N_3O_3$, m^+=371.

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