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A novel one-pot and rapid synthesis of polyfunctionalized benzo[a]pyrimido[5',4':5,6] pyrido[2,3-c]phenazine derivatives under microwave irradiation

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Abstract: A one-pot, environmentally friendly, and efficient protocol for the synthesis of novel polyfunctionalized benzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine derivatives has been reported by a one-pot, four-component sequential reaction between 2-hydroxynaphthalene-1,4-dione, benzene-1,2-diamines, benzaldehydes, and 6-amino-1,3-dimethyluracil in the presence of *p*-TSA as a nontoxic, inexpensive, ecofriendly, and efficacious solid acid catalyst. Two C-C bonds, two C=N bonds, and one C-N bond, as well as two new rings, were formed in this reaction. Through this procedure, compounds with substantial biological and pharmaceutical properties are generated in a single operation. Factors such as high yields, less reaction time, operational simplicity, and lack of any dangerous reagents/solvents have made this process a green one.

Key words: Multicomponent reactions, microwave irradiation, *p*-TSA, benzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine.

1. Introduction

In recent years, due to increased attention to the environment, creating compounds with a significant framework and virtues was considered via the design of green chemical processes by the maximum structural complexity and the least number of synthetic stages.[1]

In this direction, multicomponent reactions are highly efficient processes that construct complex molecules from simple substances. This kind of method has become valued in organic chemistry because of many advantages such as structural variety, straightforward processes, being low-priced, facile performance, ecofriendliness, reducing chemical waste in synthesis, atom economy, excellent selectivity, and minimal reaction stages with excellent yields.[2]

In addition, microwave-assisted organic synthesis has been introduced as a revolution in the preparation of heterocyclic compounds. This nonclassic heating has resulted in the development of efficient synthetic methods for producing drugs. The significant advantages of this technique are high yields with maximum optimal use of the reactants and short time span of protocol.[3]

Pyridopyrimidines as fused pyrimidines are important for pharmaceutical exponents.[4] Some of them are found in a number of natural compounds like DNA, RNA, and cofactors.[5–8] Many studies showed that these compounds display various bioactivities such as anticancer, cyclin-dependent kinase 4 (CDK4) inhibition,[9,10] insecticidal,[11] antihistaminic,[12] antibacterial,[13] and antiinflammatory activities.[14]

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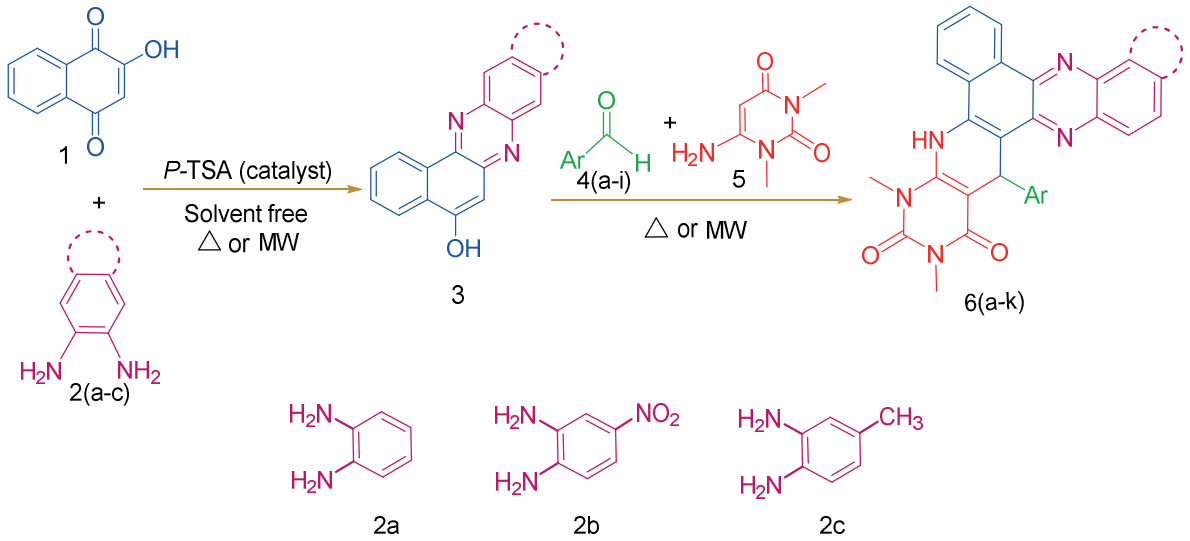
Moreover, phenazines are a worthy kind of annulated pyrazines that are produced naturally by many bacteria[15] and they have attracted much interest due to their pharmacological and biological characteristics[16] including chemopreventive, insecticidal, antibiotic, antimalarial, antiparasitic, and fungicidal activities.[17–21]

Considering the abovementioned points and as part of our research on the development of environmentally friendly methods for the synthesis of heterocyclic compounds[22–25], we would like to describe a highly effectual and precipitous process through the four-component sequential condensation reaction between 2-hydroxynaphthalene-1,4-dione **1**, benzene-1,2-diamines **2**, benzaldehyde compounds **4**, and 6-amino-1,3-dimethyluracil **5** in the presence of *p*-TSA as a green catalyst for the synthesis of novel benzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine derivatives **6** under conventional heating or microwave irradiation (Scheme 1).



Scheme 1. Synthesis of benzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine derivatives. Structures of **4a**–**4i** are listed in Table 2.

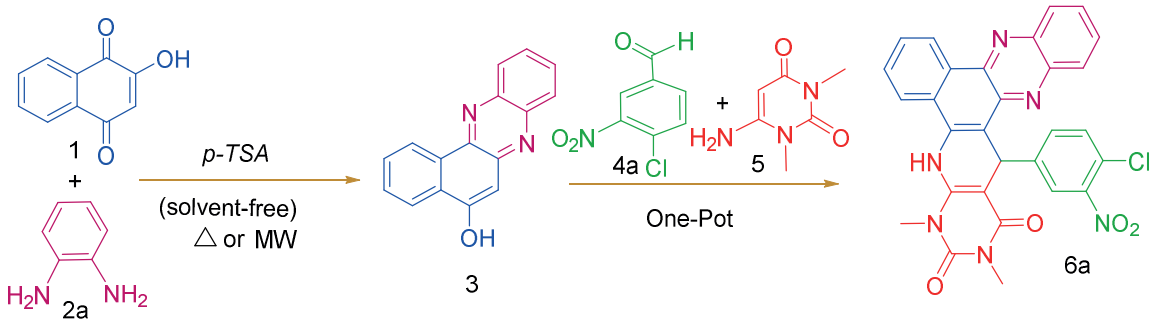
2. Results and discussion

In order to determine the suitable catalyst for the synthesis of pyridopyrimidine compounds, a one-pot, four-component condensation reaction was carried out utilizing 2-hydroxy-1,4-naphthoquinone (**1**) (1 mmol), benzene-1,2-diamine (**2a**) (1 mmol), 4-chloro-3-nitrobenzaldehyde (**4a**) (1 mmol), and 6-amino-1,3-dimethyluracil (**5**) (1 mmol) in the presence of Lewis acids, protic liquid acids, and solid acids (Scheme 2).

Initially, in order to increase the efficiency and reduce byproducts, 2-hydroxy-1,4-naphthoquinone (**1**) and benzene-1,2-diamine (**2a**) were blended in the presence of various catalysts for the synthesis of benzo[a]phenazin-5-ol (**3**). In the next step, 4-chloro-3-nitrobenzaldehyde (**4a**) and 6-amino-1,3-dimethyluracil (**5**) were mixed with a 1:1 ratio for the synthesis of novel 16-(4-chloro-3-nitrophenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine-1,3(2*H*,4*H*)-dione (**6a**). As indicated in Table 1, the best efficiency and yields were achieved with 20% mol of *p*-TSA under solvent-free conditions.

The reaction was repeated for the synthesis of **6a**–**6k** in the presence of *p*-TSA as a suitable catalyst. As expected, the products were obtained with high yields (Table 2).

Heterocyclic compounds **6a**–6**k** were confirmed by IR, ^{1}H and ^{13}C NMR, elemental analysis, and mass spectrometry. The structure of product **6a** is discussed as a representative spectrum with the NMR spectroscopy



Scheme 2. Synthesis of 16-(4-chloro-3-nitrophenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine-1,3(2*H*,4*H*)-dione (**6a**).

Table 1. Optimization of the four-component sequential reaction conditions of 2-hydroxy-1,4-naphthoquinone, benzene-1,2-diamine, 4-chloro-3-nitrobenzaldehyde, and 6-amino-1,3-dimethyluracil in the case of various catalysts under different thermal conditions.

		Conventional heating[a]			Microwave irradiation[a]		
Entry	Catalyst (mol%)	T (°C)	Time (min)	Yield (%)[b]	Power (W)[c]	Time (min)	Yield (%)[b]
1	None	100	40	-	300	15	-
2	$FeCl_3$ (15)	100	30	56	300	10	62
3	$ZnCl_2$ (15)	100	30	48	300	10	57
4	HCl (15)	100	30	65	300	10	68
5	CH_3CO_2 (15)	100	30	77	300	10	80
6	CF_3CO_2H (15)	100	30	62	300	10	67
7	*p*-TSA (15)	100	30	88	300	10	94
8	*p*-TSA (15)	70	40	67	180	15	75
9	*p*-TSA (20)	100	30	88	300	10	92
10	*p*-TSA (10)	100	30	79	300	10	83
11	*p*-TSA (15)	140	30	87	450	10	90

[a] The reaction was achieved through thermal (Δ) and microwave irradiation (MW) under solvent-free conditions.
[b] Isolated yields.
[c] The reaction was conducted at various microwave powers (180–450 W) at 70–140 °C.

data. The ^{1}H NMR spectrum of **6a** displayed two singlets at $\delta = 3.34$ and 3.49 ppm for the two methyl groups, one singlet for the allylic methine at $\delta = 5.33$ ppm, and another one at $\delta = 10.08$ ppm for the NH group, which was exhibited through the absorption of IR at 3430 cm^{-1}. In addition, when isobutyraldehyde as an aliphatic aldehyde was mixed with **3** and **5**, reaction between these three materials did not occur.

For a better perception of the process presented, a suggested mechanism for the sequential one-pot synthesis of benzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazines is proposed in Scheme 3. First, the organization of benzo[*a*]phenazin-5-ol (**3a**) can be explained via a condensation of 4-hydroxy-1,2-naphthoquinone (**1**) and benzene-1,2-diamine (**2a**). Then the efficient Knoevenagel condensation of benzo[a]phenazin-5-ol (**3a**) and aryladehyde **4** created product **8**. Lastly, compound **6a** was offered by a sequence of facile Michael addition/cyclization/dehydration reactions between **8** and 6-amino-1,3-dimethyluracil **5** (Scheme 3).[2,26]

In conclusion, we have developed a novel highly efficient synthesis of pyrimidine-based pyrido[2,3-*c*]phenazine derivatives through the one-pot, four-component sequential reaction of 2-hydroxynaphthalene-1,4-

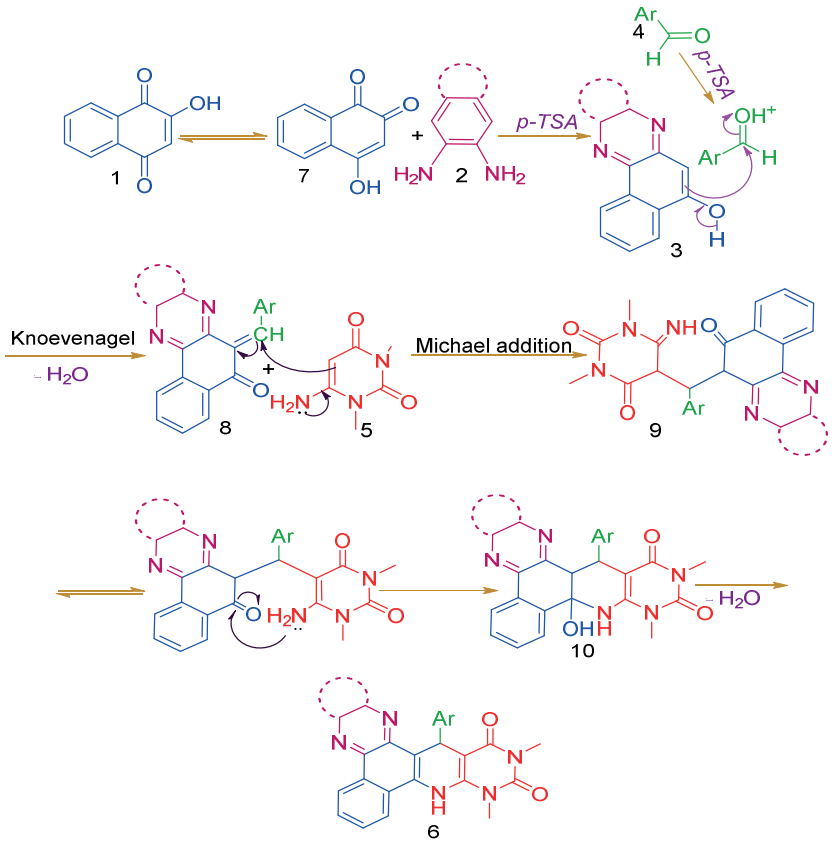
Table 2. Synthesis of benzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine derivatives.

Entry	Ar	Diamine	Product	Time (min)		Yield (%)[a]	
				Δ^b	MW[c]	Δ^b	MW[c]
1	4-Cl-3-$NO_2C_6H_3$	2a	**6a**	30	10	88	94
2	2-BrC_6H_4	2a	**6b**	30	10	82	86
3	3-$CH_3OC_6H_4$	2a	**6c**	40	15	76	81
4	2-OH-3-$CH_3OC_6H_3$	2a	**6d**	50	15	74	78
5	2-$CH_3OC_6H_4$	2a	**6e**	40	15	80	84
6	2,4-$Cl_2C_6H_3$	2a	**6f**	30	10	85	90
7	2-OH-5-$NO_2C_6H_4$	2a	**6g**	40	10	81	85
8	2-OHC_6H_4	2a	**6h**	40	15	79	84
9	2-ClC_6H_4	2a	**6i**	30	10	84	89
10	2,4-$Cl_2C_6H_3$	2b	**6j**	30	10	72	76
11	2,4-$Cl_2C_6H_3$	2c	**6k**	30	10	87	93

[a]Isolated yields.

[b]The times and yields of reactions under thermal (Δ) conditions at 100 °C.

[c]The times and yields of reactions under microwave irradiation (300 W, 100 °C) conditions.



Scheme 3. Suggested mechanism for the one-pot synthesis of benzo[*a*] pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazines.

dione, benzene-1,2-diamine, arylaldehyde, and 6-amino-1,3-dimethyluracil in the presence of p-TSA as a green catalyst under microwave irradiation conditions. Novelty, available materials, operational simplicity, use of inexpensive and nontoxic catalyst without any byproduct in solvent-free conditions, and most importantly the existence of heterocyclic frames with high biological properties in the product are features of this method.

3. Experimental

3.1. General procedures

All materials utilized including solvents and reactants were obtained from Aldrich and Merck, which did not require purification. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer. IR spectra were recorded on a Shimadzu IR-470 spectrometer. Mass spectra were recorded on an Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV. Melting points were measured on an Electrothermal 9100 apparatus. ^{1}H NMR and ^{13}C NMR were determined on Bruker 400 MHz spectrometer in $CDCl_3$ as the solvent. All reactions were carried out using a laboratory microwave oven (MicroSYNTH, Milestone Company, Italy). Thin-layer chromatography (TLC) was performed on silica-gel Polygram SILG/UV 254 plates.

3.2. General procedure for the synthesis of benzo[*a*]pyrimido[5,4':5,6]pyrido[2,3-*c*] phenazine derivatives

At the beginning, a mixture of equimolar amounts of 2-hydroxynaphthalene-1,4-dione (**1**) (1 mmol), benzene-1,2-diamine **2** (1 mmol), and p-TSA (20 mol%) was stirred under solvent-free microwave irradiation (300 W for 100 °C) or conventional heating (100 °C) conditions. The reaction was completed in less than 6 min with the formation of orange solid **3**. Then arylaldehyde **4** (1 mmol) and 6-amino-1,3-dimethyluracil **5** (1 mmol) were added to orange product **3** under microwave irradiation or conventional heating at the right temperature and appropriate time as illustrated in Table 2. The creation of product **6** was confirmed by TLC and the reaction mixture was cooled, washed with ethanol (10 mL), filtered, and dried to obtain solid pure powder **6**.

3.2.1. 16-(4-Chloro-3-nitrophenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido [2,3-*c*]phenazine-1,3(2*H*,4*H*)-dione (Table 2, entry 1)

Red powder, yield under Δ: 0.484 g (88%), under MW: 0.517 g (94%), mp 271–273 °C; IR (KBr) (ν_{max}, cm^{-1}): 3430, 3035, 2900, 1685, 1652, 1585, 1559, 1526, 1498, 1351, 1275, 1145, 1058, 761; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (s, 3H, NCH_3), 3.81 (s, 3H, NCH_3), 5.33 (s, 1H, CH), 7.29–7.44 (m, 1H, ArH), 7.51–7.57 (m, 1H, ArH), 7.62 (d, J = 8.0 Hz, 1H, ArH), 7.67 (d, J = 8.0 Hz, 1H, ArH), 7.84–8.18 (m, 1H, ArH), 8.34 (d, J = 8.0 Hz, 1H, ArH), 8.38–8.42 (m, 1H, ArH), 8.45 (d, J = 8.4 Hz, 1H, ArH), 8.52–8.74 (m, 1H, ArH), 9.06–9.12 (m, 1H, ArH), 9.34–9.42 (m, 1H, ArH), 10.08 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.6, 30.6 ($2CH_3$), 35.7 (CH), 86.7, 117, 124.0, 124.5, 125.1, 125.9, 126.4, 128.5, 129.1, 129.5, 129.8, 130.0, 130.4, 130.6, 130.7, 131.3, 132.6, 137.0, 139.4, 140.3, 142.6, 143.6, 150.6, 154.9 ($C_{olefinic}$ and C_{arom}), 157.5, 161.5 (2C=O) ppm; MS (m/z, %): 550 (M^+, 4); Anal. Calcd for $C_{29}H_{19}ClN_6O_4$: C, 63.22; H, 3.48; N, 15.25 %. Found: C, 63.41; H, 3.32; N, 15.19 %.

3.2.2. 16-(2-Bromophenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine-1,3(2*H*,4*H*)-dione (Table 2, entry 2)

Dark orange powder, yield under Δ: 0.451 g (82%), under MW: 0.473 g (86%), mp 249–250 °C; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3365, 3035, 2905, 1686, 1657, 1586, 1560, 1499, 1452, 1344, 1266, 1130, 1046, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.38 (s, 3H, NCH_3), 3.73 (s, 3H, NCH_3), 5.33 (s, 1H, CH), 7.11–7.28 (m, 1H, ArH), 7.51–7.62 (m, 5H, ArH), 7.83–7.90 (m, 1H, ArH), 8.37 (d, J = 8.0 Hz, 1H, ArH), 8.50–8.52 (m, 1H, ArH), 8.60–8.62 (m, 1H, ArH), 9.09–9.10 (m, 1H, ArH), 9.39–9.42 (m, 1H, ArH), 10.39 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ28.5, 29.6 ($2CH_3$), 36.6 (CH), 87.8, 116.9, 123.8, 124.8, 125.0, 126.0, 127.1, 127.2, 127.9, 128.3, 128.7, 128.9, 129.6, 129.8, 130.2, 130.5, 130.8, 131.3, 131.6, 133.0, 135.1, 137.8, 145.7, 154.4 ($C_{olefinic}$ and C_{arom}), 157.7, 163.8 (2C=O) ppm; MS (m/z, %): 549 (M^+, 2); Anal. Calcd for $C_{29}H_{20}BrN_5O_2$: C, 63.28; H, 3.66; N, 12.27 %. Found: 63.45; H, 3.52; N, 12.31 %.

3.2.3. 16-(3-Methoxyphenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine-1,3(2*H*,4*H*)-dione (Table 2, entry 3)

Brown powder, yield under Δ: 0.381 g (76%), under MW: 0.406 g (81%), mp 223–225 °C; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3375, 3020, 2915, 1685, 1656, 1578, 1490, 1441, 1356, 1250, 1137, 1041, 757; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (s, 3H, NCH_3), 3.67 (s, 3H, OCH_3), 3.72 (s, 3H, NCH_3), 5.32 (s, 1H, CH), 7.03–7.29 (m, 1H, ArH), 7.43–7.58 (m, 1H, ArH), 7.65 (t, J = 7.6 Hz, 1H, ArH), 7.70–7.96 (m, 3H, ArH), 8.04 (d, J = 8.0 Hz, 1H, ArH), 8.16–8.30 (m, 1H, ArH), 8.36 (d, J = 7.6 Hz, 1H, ArH), 8.43 (d, J = 8.0 Hz, 1H, ArH), 8.54–8.56 (m, 1H, ArH), 9.12–9.34 (m, 1H, ArH), 10.00 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ28.6, 30.4 ($2CH_3$), 35.2 (CH), 58.3 (OCH_3), 87.4, 110.2, 112.2, 118.1, 119.3, 121.5, 123.6, 124.6, 124.8, 125.2, 126.0, 128.9, 129.3, 129.6, 130.2, 131.2, 131.7, 131.9, 134.2, 139.1, 140.5, 143.1, 150.9, 153.2 ($C_{olefinic}$ and C_{arom}), 159.5, 168.1 (2C=O) ppm; MS (m/z, %): 501 (M^+, 6); Anal. Calcd for $C_{30}H_{23}N_5O_3$: C, 71.84; H, 4.62; N, 13.96 %. Found: C, 71.98; H, 4.73; N, 13.91 %.

3.2.4. 16-(2-Hydroxy-3-methoxyphenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine-1,3(2*H*,4*H*)-dione (Table 2, entry 4)

Green powder, yield under Δ: 0.383 g (74%), under MW: 0.403 g (78%), mp 225–226 °C; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3460, 3025, 2900, 1693, 1645, 1580, 1451, 1405, 1369, 1334, 1278, 1088, 1027, 745; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.30 (s, 3H, NCH_3), 3.72 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 5.88 (s, 1H, CH), 6.81–9.35 (m, 11H, ArH), 9.74 (s, 1H, OH), 10.90 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ28.2, 31.0 ($2CH_3$), 36.4 (CH), 58.4 (OCH_3), 84.5, 110.3, 120.8, 122.9, 124.6, 125.2, 126.2, 128.1, 128.5, 128.6, 129.1, 129.2, 129.6, 129.7, 130.0, 131.0, 132.3, 138.5, 140.6, 141.6, 142.4, 148.5, 150.9, 153.2 ($C_{olefinic}$ and C_{arom}), 162.1, 165.7 (2C=O) ppm; MS (m/z, %): 517 (M^+, 2); Anal. Calcd for $C_{30}H_{23}N_5O_4$: C, 69.62; H, 4.48; N, 13.53 %. Found: C, 69.85; H, 4.35; N, 13.48 %.

3.2.5. 16-(2-Methoxyphenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*] phenazine-1,3(2*H*,4*H*)-dione (Table 2, entry 5)

Brown powder, yield under Δ: 0.401 g (80%), under MW: 0.421 g (84%), mp 188–190 °C; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3430, 3030, 2915, 1698, 1665, 1578, 1545, 1491, 1407, 1362, 1249, 1045, 745; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.33 (s, 3H, NCH_3), 3.66 (s, 3H, OCH_3), 3.72 (s, 3H, NCH_3), 5.20 (s, 1H, CH), 7.06 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, ArH), 7.06 (d, J = 8.0 Hz, 1H, ArH), 7.13–7.23 (m, 1H, ArH), 7.29–7.33 (m, 1H, ArH), 7.46–7.52 (m, 1H, ArH), 7.84–7.90 (m, 2H, ArH), 8.33–8.37 (m, 1H, ArH), 8.51–8.60 (m, 1H, ArH), 8.71–8.95 (m, 1H, ArH), 9.18–9.34 (m, 1H, ArH), 9.40 (d, J = 7.6 Hz, 1H, ArH), 10.52 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ28.6, 30.3 ($2CH_3$), 35.3 (CH), 55.7 (OCH_3), 83.9, 105.3, 110.3,116.7, 120.7, 122.2, 124.3, 126.9, 127.4, 127.8, 128.2, 128.8, 128.9, 129.0, 129.4, 129.6, 129.7, 129.9, 130.3, 130.9, 131.6, 140.6, 151.0, 153.3 ($C_{olefinic}$ and C_{arom}), 157.5, 159.0 (2C=O) ppm; MS (m/z, %): 501 (M^+, 5); Anal. Calcd for $C_{30}H_{23}N_5O_3$: C, 71.84; H, 4.62; N, 13.96 %. Found: C, 71.61; H, 4.80; N, 14.02 %.

3.2.6. 16-(2,4-Dichlorophenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*] phenazine-1,3(2*H*,4*H*)-dione (Table 2, entry 6)

Dark red powder, yield under Δ: 0.459 g (85%), under MW: 0.486 g (90%), mp 231–232 °C; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3350, 3040, 2895, 1667, 1638, 1584, 1560, 1499, 1452, 1361, 1277, 1140, 1057, 757; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.38 (s, 3H, NCH_3), 3.82 (s, 3H, NCH_3), 5.33 (s, 1H, CH), 7.29–7.41 (m, 1H, ArH), 7.52–7.62 (m, 1H, ArH), 7.75 (d, J = 8.0 Hz, 1H, ArH), 7.82–7.92 (m, 2H, ArH), 8.12–8.14 (m, 1H, ArH), 8.30 (t, J = 8.0 Hz, 1H, ArH), 8.37 (d, J = 9.2 Hz, 1H, ArH), 8.50–8.65 (m, 1H, ArH), 8.73 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H, ArH), 9.22–9.29 (m, 1H, ArH), 10.43 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ28.7, 29.6 ($2CH_3$), 34.3 (CH), 87.2, 112.2, 122.6, 124.7, 125.0, 126.0, 126.4, 127.3, 128.9, 129.4, 129.7, 129.8, 130.0, 130.2, 130.8, 131.4, 131.7, 138.5, 140.8, 141.3, 145.6, 146.6, 150.7, 153.9 ($C_{olefinic}$ and C_{arom}), 154.0, 165.2 (2C=O) ppm; MS (m/z, %): 539 (M^+, 7); Anal. Calcd for $C_{29}H_{19}Cl_2N_5O_2$: C, 64.46; H, 3.54; N, 12.96 %. Found: C, 64.70; H, 3.68; N, 12.90 %.

3.2.7. 16-(2-Hydroxy-5-nitrophenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido [2,3-*c*]phenazine-1,3(2*H*,4*H*)-dione (Table 2, entry 7)

Red powder, yield under Δ: 0.431 g (81%), under MW: 0.452 g (85%), mp: 235–237 °C; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3350, 3050, 2925, 1686, 1585, 1558, 1521, 1443, 1335, 1274, 1147, 1056, 763; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.39 (s, 3H, NCH_3), 3.75 (s, 3H, NCH_3), 5.33 (s, 1H, CH), 7.15 (d, J = 8.0 Hz, 1H, ArH), 7.36 (t, J = 8.4 Hz, 1H, ArH), 7.44 (t, J = 7.6 Hz, 1H, ArH), 7.54 (d, J = 8.8 Hz, 1H, ArH), 7.60 (t, J = 6.8 Hz, 1H, ArH), 7.80-8.18 (m, 3H, ArH), 8.27–8.53 (m, 1H, ArH), 9.12–9.18 (m, 1H, ArH), 9.32–9.41 (m, 1H, ArH), 10.15 (s, 1H, NH), 10.89 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ28.6, 30.5 ($2CH_3$), 35.1 (CH), 86.9, 117.0, 125.4, 126.0, 126.5, 128.4, 128.9, 129.1, 129.8, 130.2, 130.3, 130.5, 131.4, 131.8, 136.9, 140.1, 140.6, 141.0, 141.7, 144.8, 145.5, 148.7, 150.7, 155.0 ($C_{olefinic}$ and C_{arom}), 157.5, 164.7 (2C=O) ppm; MS (m/z, %): 532 (M^+, 2); Anal. Calcd for $C_{29}H_{20}N_6O_5$: C, 65.41; H, 3.79; N, 15.78 %. Found: C, 65.23; H, 3.92; N, 15.74 %.

3.3. 16-(2-Hydroxyphenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phe- nazine-1,3(2*H*,4*H*)-dione (Table 2, entry 8)

Orange powder, yield under Δ: 0.386 g (79%), under MW: 0.410 g (84%), mp 244–246 °C; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3495, 3025, 2900, 1696, 1644, 1581, 1485, 1444, 1401, 1327, 1283, 1145, 1052, 755; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.35 (s, 3H, NCH_3), 3.71 (s, 3H, NCH_3), 5.89 (s, 1H, CH), 6.87 (td, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.14 (dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.26 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.68–7.71 (m, 1H, ArH), 7.80–7.92 (m, 4H, ArH), 8.18–8.20 (m, 1H, ArH), 8.33–8.40 (m, 1H, ArH), 8.60 (dd, J_1 = 8.6 Hz, J_2 = 0.8 Hz, 1H, ArH), 9.28 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H, ArH), 10.42 (s, 1H, NH), 10.60 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ28.5, 30.9 ($2CH_3$), 36.5 (CH), 89.1, 115.1, 119.1, 124.2, 124.9, 125.1, 125.2, 127.9, 128.0, 128.3, 128.6, 129.3, 129.4, 129.8, 129.9, 130.1, 131.3, 139.7, 140.7, 141.5, 143.4, 150.3, 151.4, 154.0 ($C_{olefinic}$ and C_{arom}), 154.6, 165.1 (2C=O) ppm; MS (m/z, %): 487 (M^+, 3); Anal. Calcd for $C_{29}H_{21}N_5O_3$: C, 71.45; H, 4.34; N, 14.37 %. Found: C, 71.20; H, 4.45; N, 14.41 %.

3.3.1. 16-(2-Chlorophenyl)-2,4-dimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyri- do[2,3-*c*]phe- nazine-1,3(2*H*,4*H*)-dione (Table 2, entry 9)

Red powder,yield under Δ: 0.424 g (84%), under MW: 0.449 g (89%), mp 251–252 °C; IR (KBr): 3365, 3040, 2915, 1688, 1665, 1585, 1559, 1529, 1499, 1356, 1267, 1123, 1046, 748; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.35 (s, 3H, NCH_3), 3.73 (s, 3H, NCH_3), 5.33 (s, 1H, CH), 7.06 (td, J_1 = 8.2 Hz, J_2 = 1.6 Hz, 1H, ArH), 7.11–7.29 (m, 1H, ArH), 7.39 (dd, J_1 = 8.8 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.43–7.62 (m, 2H, ArH), 7.82–7.89 (m, 2H, ArH), 8.13 (d, J = 8.0 Hz, 1H, ArH), 8.30 (t, J= 8.4, 1H, ArH), 8.37 (d, J = 7.6 Hz, 1H, ArH), 9.08–9.10 (m, 1H, ArH), 9.38–9.41 (m, 1H, ArH), 10.52 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ28.5, 30.5 ($2CH_3$), 35.0 (CH), 88.0, 116.8, 124.3, 124.8, 124.9, 126.0, 126.8, 127.1, 127.7, 128.2, 129.8, 130.2, 130.3, 130.4, 131.3, 131.6, 133.6, 135.0, 136.4, 137.0, 140.0, 145.8, 150.9, 154.0 ($C_{olefinic}$ and C_{arom}), 157.8, 163.9 (2C=O) ppm; MS (m/z, %): 505 (M^+, 2); Anal. Calcd for $C_{29}H_{20}ClN_5O_2$: C, 68.84; H, 3.98; N, 13.84 %. Found: C, 68.58; H, 3.83; N, 13.93 %.

3.3.2. 16-(2,4-Dichlorophenyl)-2,4-dimethyl-12-nitro-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyri- do[2,3-*c*]phenazine-1,3(2*H*,4*H*)-dione (Table 2, entry 10)

Brown powder, yield under Δ: 0.421 g (72%), under MW: 0.445 g (76%), mp 236–238 °C; IR (KBr): 3430, 3050, 2900, 1666, 1617, 1582,1555, 1512, 1451, 1331,1144, 1048, 774; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.37 (s, 3H, NCH_3), 3.82 (s, 3H, NCH_3), 5.36 (s, 1H, CH), 6.99 (d, 1H, J= 8.4 HZ), 7.05–7.29 (m, 2H, ArH), 7.38–7.42 (m, 1H, ArH), 7.46–7.60 (m, 1H, ArH), 7.90–7.96 (m, 1H, ArH), 8.40–8.62 (m, 2H, ArH), 8.96–9.39 (m, 2H, ArH), 10.45 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 30.5 ($2CH_3$), 37.9 (CH), 84.6, 117.0, 124.6, 125.8, 126.7, 127.6, 128.8, 129.0, 130.2, 130.3, 130.6, 131.3, 131.6, 132.1, 133.2, 133.7, 134.4, 135.7, 137.3, 139.3, 140.8, 143.0, 148.4, 150.8 ($C_{olefinic}$ and C_{arom}), 158.9, 163.5 (2C=O) ppm; MS (m/z, %): 584 (M^+, 6); Anal. Calcd for $C_{29}H_{18}Cl_2N_6O_4$: C, 59.50; H, 3.10; N, 14.36 %. Found: C, 59.41; H, 3.26; N, 14.46 %.

3.3.3. 16-(2,4-Dichlorophenyl)-2,4,13-trimethyl-5,16-dihydrobenzo[*a*]pyrimido[5',4':5,6]pyrido[2,3-*c*]phenazine-1,3(2*H*,4*H*)-dione (Table 2, entry 11)

Dark orange powder, yield under Δ: 0.482 g (87%), under MW: 0.515 g (93%), mp: 216–218 °C; IR (KBr): 3425, 3025, 2900, 1666, 1584, 1556, 1522, 1498, 1340, 1141, 1063, 769; ^{1}H NMR (400 MHz, $CDCl_3$): δ2.67 (s, 3H, CH_3), 3.31 (s, 3H, NCH_3), 3.75 (s, 3H, NCH_3), 6.18 (s, 1H, CH), 7.29–7.48 (m, 2H, ArH), 7.65–8.52 (m, 5H, ArH), 8.08–9.32 (m, 3H, ArH), 10.06 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ22.0 (CH_3), 28.7, 30.5 ($2CH_3$), 34.8 (CH), 88.8, 124.0, 124.4, 124.5, 124.7, 124.9, 125.9, 129.0, 129.2, 129.8, 130.1, 130.3, 131.1, 131.2, 131.5, 131.7, 132.0, 132.8, 133.8, 140.4, 140.6, 147.9, 150.6, 153.5 ($C_{olefinic}$ and C_{arom}), 156.9, 164.6 (2C=O) ppm ; MS (m/z, %): 553 (M^+, 7); Anal. Calcd for $C_{30}H_{21}Cl_2N_5O_2$: C, 59.50; H, 3.10; N, 14.36 %. Found: C, 59.36; H, 3.28; N, 14.42 %.

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References

1. Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195-206.
2. Yazdani-Elah-Abadi, A.; Mohebat, R.; Maghsoodlou, M. T. *RSC Adv.* **2016**, *6*, 84326-84333.
3. Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629-639.
4. Satasia, S. P.; Kalaria, P. N.; Raval, D. K. *Org. Biomol. Chem.* **2014**, *12*, 1751-1758.
5. Blaney, J. M.; Hansch, C.; Silipo, C.; Vittoria, A. *Chem. Rev.* **1984**, *84*, 333-407.
6. Castle, R.; Phillips, S.; Katritzky, A.; Rees, C.; Boulton, A.; McKillop, A. *Comprehensive Heterocyclic Chemistry, Vol. 3*; Pergamon Press: Oxford, UK, 1984.
7. Gut, J. *Adv. Heterocycl. Chem.* **1963**, *1*, 189-251.
8. Ribble, W.; Hill, W. E.; Ochsner, U. A.; Jarvis, T. C.; Guiles, J. W.; Janjic, N.; Bullard, J. M. *Antimicrob. Agents Chemother.* **2010**, *54*, 4648-4657.
9. Duan, S.; Place, D.; Perfect, H. H.; Ide, N. D.; Maloney, M.; Sutherland, K.; Price Wiglesworth, K. E.; Wang, K.; Olivier, M.; Kong, F. *Org. Process Res. Dev.* **2016**, *20*, 1191-1202.
10. VanderWel, S. N.; Harvey, P. J.; McNamara, D. J.; Repine, J. T.; Keller, P. R.; Quin, J.; Booth, R. J.; Elliott, W. L.; Dobrusin, E. M.; Fry, D. W. *J. Med. Chem.* **2005**, *48*, 2371-2387.
11. Singh, G.; Singh, G.; Yadav, A. K.; Mishra, A. *Indian J. Chem.* **2002**, *41B*, 430-432.
12. Quintela, J.; Peinador, C.; Botana, L.; Estévez, M.; Riguera, R. *Bioorgan. Med. Chem.* **1997**, *5*, 1543-1553.
13. Bazgir, A.; Khanaposhtani, M. M.; Soorki, A. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5800-5803.
14. El-Gazzar, A. R. B.; Hafez, H. N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3392-3397.
15. Laursen, J. B.; Nielsen, J. *Chem. Rev.* **2004**, *104*, 1663-1686.
16. Hafez, H.; Hegab, M.; Ahmed-Farag, I.; El-Gazzar, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4538-4543.
17. Cimmino, A.; Evidente, A.; Mathieu, V.; Andolfi, A.; Lefranc, F.; Kornienko, A.; Kiss, R. *Nat. Prod. Rep.* **2012**, *29*, 487-501.
18. Ligon, J. M.; Hill, D. S.; Hammer, P. E.; Torkewitz, N. R.; Hofmann, D.; Kempf, H. J.; Pée, K. H. V. *Pest Manag. Sci.* **2000**, *56*, 688-695.

19. Makgatho, M. E.; Anderson, R.; O'Sullivan, J. F.; Egan, T. J.; Freese, J. A.; Cornelius, N.; van Rensburg, C. E. *Drug Dev. Res.* **2000**, *50*, 195-202.

20. Nishanth Kumar, S.; Nisha, G.; Sudaresan, A.; Venugopal, V.; Sree Kumar, M.; Lankalapalli, R. S.; Dileep Kumar, B. *Med. Mycol.* **2014**, *52*, 482-490.

21. Wang, J.; Zhi, X.; Yu, X.; Xu, H. *J. Agric. Food. Chem.* **2013**, *61*, 6336-6343.

22. Mohebat, R.; Yazdani Elah Abadi, A.; Maghsoodlou, M. T.; Mohammadi, M. *Res. Chem. Intermed.* **2016**, *42*, 5915-5926.

23. Yazdani-Elah-Abadi, A.; Maghsoodlou, M. T.; Mohebat, R.; Heydari; R. *Chin. Chem. Lett.* **2017**, *28*, 446-452.

24. Mohebat, R.; Yazdani-Elah-Abadi, A. *Chin. Chem. Lett.* **2017**, *28*, 1340-1344.

25. Mohebat, R.; Yazdani-Elah-Abadi, A.; Maghsoodlou, M. T.; Hazeri, N. *Chin. Chem. Lett.* **2017**, *28*, 943-948.

26. Ji, S. J.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S.; Shi, D. Q. *J. Heterocyclic Chem.* **2008**, *45*, 693-702.