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Design and synthesis of new naphtho[2,1-*b*]pyrano [2,3-*d*]pyrimidinones under classical and microwave conditions

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Abstract: A fast and efficient method for the synthesis of naphthopyranopyrimidinones derivatives in excellent yields was developed through cyclocondensation reaction between previously prepared pyrimidinic hydrazides and some electrophilic species such as 2,4-pentanedione, 2,5-hexanedione, cyclic anhydrides, and phenylthioisocyanate under microwave irradiation. Compared to the conventional methods applied, it was found that better yields and shorter reaction times were achieved using microwave-assisted synthesis. Structures of all synthesized compounds were established on the basis of spectroscopic methods including ¹H NMR, ¹³C NMR, and HRMS-ES.

Key words: Pyrimidinic hydrazides, cyclocondensation, naphthopyranopyrimidinones derivatives, conventional synthesis, microwave-assisted synthesis

1. Introduction

Pyrimidinone and its derivatives have been studied due to their chemical and biological significance.^{1–4} A literature survey revealed that fused pyrimidinones, and especially pyranopyrimidinone derivatives, are known to exhibit potential antitubercular,⁵ anticancer,⁶ and antioxidant activities.⁷ Therefore, they gained much attention as important pharmacophores and privileged structures in medicinal chemistry. On the other hand, five-membered ring systems, such as pyrrole, pyrrolidinedione, pyrazole, or oxadiazolidinethione substructures, proved to be promising drug candidates. Pyrroles and their derivatives exhibit different important biological activities like antimicrobial,⁸ cytotoxic⁹, and antiinflammatory activities.¹⁰ Furthermore, 2,5-pyrrolidinediones are core structural units found in natural products and also in some approved drugs and clinical drug candidates.^{11,12} Moreover, pyrazolic compounds exhibit a broad spectrum of biological activities such as antiinflammatory,¹³ antitumor,¹⁴ antifungal,¹⁵ and antiviral activities,¹⁶ whereas oxadiazolidinethione and their derivatives are extensively used in medicine due to their pharmacological properties such as anticandidal,¹⁷ antiviral, and antitumor activity.¹⁸

Microwave-assisted organic synthesis is one of the high-speed techniques and efficient synthetic tools¹⁹ that have attracted a substantial amount of attention in recent years, since the first reports by Gedye et al. and Giguere et al. in 1986.^{20,21} It is well known to induce a reduction in the time of various reactions, yield enhancement, and cleaner chemistry. Many reactions have proven to result in higher yield and/or selectivity

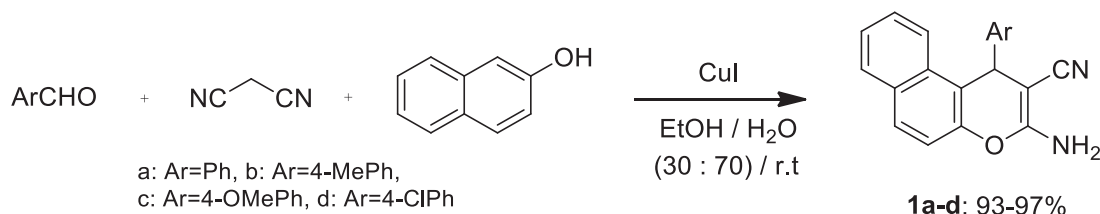
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under microwave irradiation compared with conventional heating.^{22,23} Keeping in view the above and in continuation of our efforts directed toward the synthesis of new heterocyclic compounds with anticipated biological activities,^{24–26} we wish to report herein a comparative study of microwave-assisted synthesis and conventional heating for the preparation of some new hybrid compounds combining naphthopyrano[3,2-*d*]pyrimidinone and pyrrole, pyrrolidinedione, pyrazole, or oxadiazolidinethione rings.

2. Results and discussion

2.1. Synthesis

The 2-aminonaphthopyrano-3-carbonitriles **1a–1d** served as key starting material. They were prepared in high to excellent yields via a one-pot, three-component reaction of arylaldehyde, malononitrile, and β -naphthol in aqueous ethanol using CuI, which is emerging as an effective Lewis acid catalyst for various organic transformations.^{27–30} The structures of these precursors were established on the basis of their spectroscopic data according to our previous work (Scheme 1).³¹



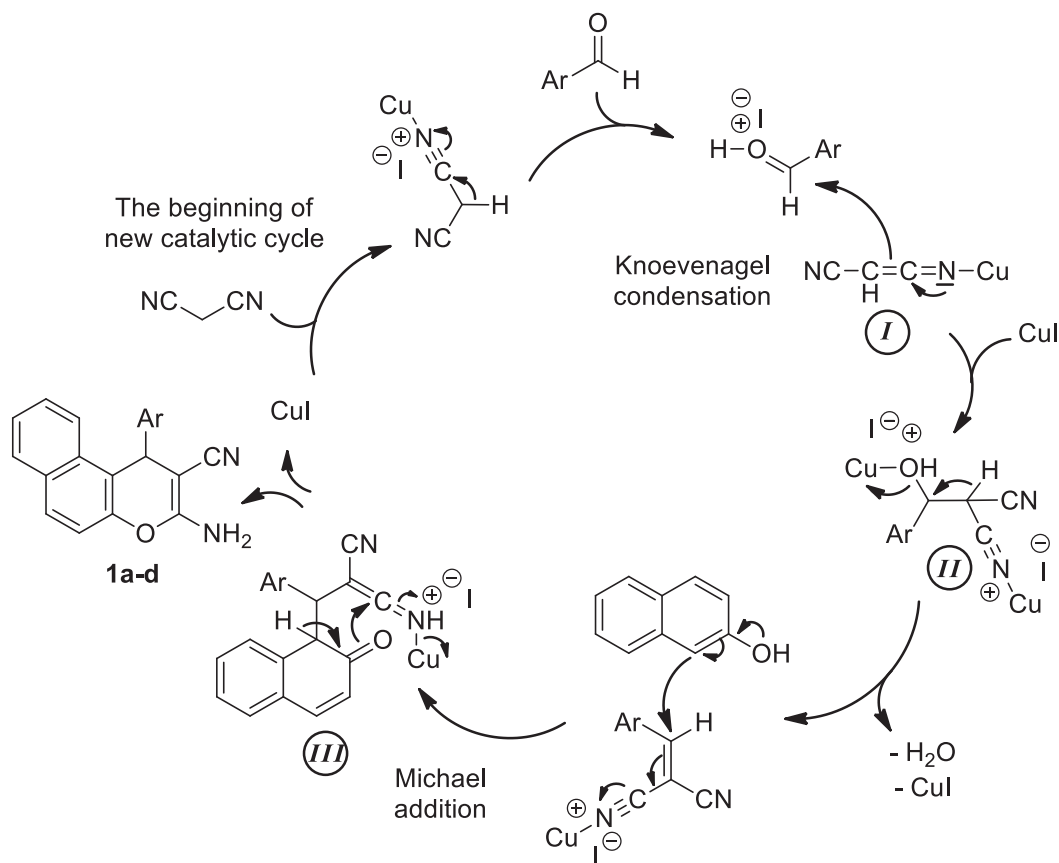
Scheme 1. Synthetic pathway to 2-aminonaphthopyrano-3-carbonitriles **1a–1d**.

Mechanistically, the reaction starts with Knoevenagel condensation between the enol form of malononitrile (**I**) and arylaldehyde in the presence of CuI as a catalyst to give the intermediate (**II**), which is immediately transformed into another intermediate (**III**) as a result of the Michael addition of β -naphthol at the conjugated C=C bond of (**II**), which leads to precursors **1a–1d** in good yields by intramolecular concerted cyclization (Scheme 2).

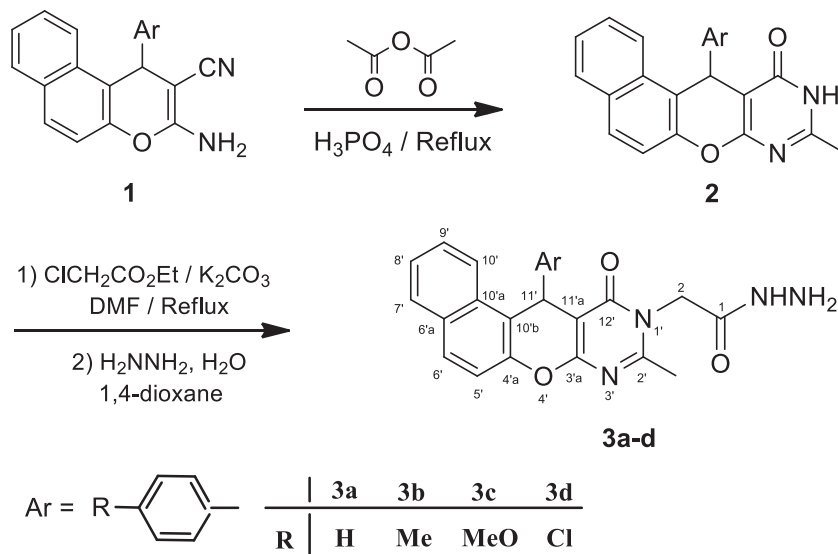
Our approach to the target hybrid molecules **4–9** first started by the synthesis of precursor **3** via condensation reaction of 2-aminonaphthopyrano-3-carbonitrile **1** with acetic anhydride in the presence of a catalytic amount of polyphosphoric acid (PPA) under reflux for 1 h. The obtained pyranopyrimidinones **2** were *N*-alkylated by reaction with ethylchloroacetate to give the corresponding esters, which were subsequently hydrazinolized by hydrazine hydrate (Scheme 3).

In the abovementioned precursors **3**, the hydrazide moiety made them valuable key precursors for the formation of several heterocyclic compounds^{32–34} and aroused our interest to explore them in order to obtain the desired hybrid compounds **4–9**. Thus, we performed the cyclocondensation of pyrimidinic precursors **3** with some electrophilic species, namely 2,4-pentanedione, 2,5-hexanedione, cyclic anhydrides, and phenylthioisocyanate, under both microwave irradiation and classical heating conditions.

This part of our work was initiated with the reaction between pyrimidinic hydrazides **3** and 2,5-hexanedione (Scheme 4). First, this reaction was carried out in a domestic microwave oven (Samsung MW71C, 800 W output power) under solvent-free conditions and was monitored by TLC. In order to determine the best conditions for the preparation of new pyranopyrimidinones **4**, we examined the reaction under various conditions by changing the irradiation power and reaction time. We found that the best yields (87%–96%, Table 1) were



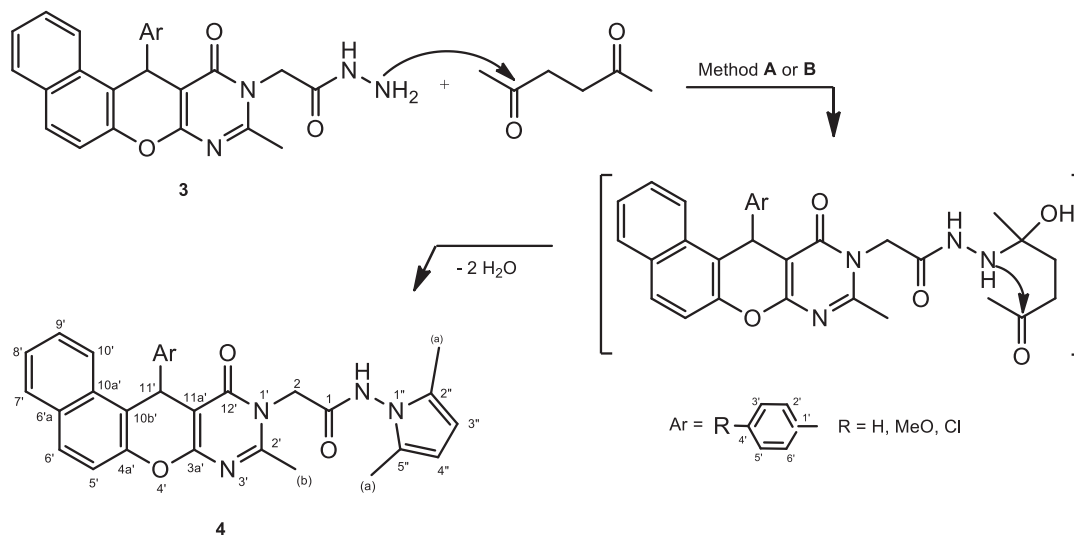
Scheme 2. Proposed mechanism for the formation of compounds **1a-1d**.



Scheme 3. Synthetic pathway to pyrimidinic hydrazides **3a-3d**.

obtained after 3 min of irradiation at 300 W of an equimolar mixture of precursors **3** and 2,5-hexanedione. To compare the microwave-assisted synthesis method with classical heating methods, the synthesis of pyranopy-

rimidinones **4** was also performed under reflux in dioxane without catalyst (method **A**). Related experimental results are shown in Table 1. It is clear that in all cases much shorter reaction times and higher yields were achieved under microwave irradiation compared with classical heating. For example, with conventional heating, pyrrolic derivative **4b** was obtained in 57% yield in 12 h (method **A**), whereas under microwave conditions (method **B**), after 3 min the yield of the reaction was 96%.



Scheme 4. Synthetic pathway to pyrrolic derivatives **4a–4c**.

Table 1. Comparison between the conventional procedure (method **A**) and microwave irradiation (method **B**) for the synthesis of compounds **4**, **5**, **7**, and **8**.

Entry	R	Method A		Method B	
		Time (h)	Yield (%) ^a	Time (min)	Yield (%) ^a
4a	H	12	45	3	87
4b	MeO	12	57	3	96
4c	Cl	12	52	3	92
5a	H	12	52	3	88
5b	Me	12	58	3	92
5c	MeO	12	64	3	96
7a	H	12	43	5	86
7b	Me	12	47	5	92
7c	MeO	12	60	5	88
8a	H	12	45	5	94
8b	Me	12	55	5	96
8c	MeO	12	58	5	95

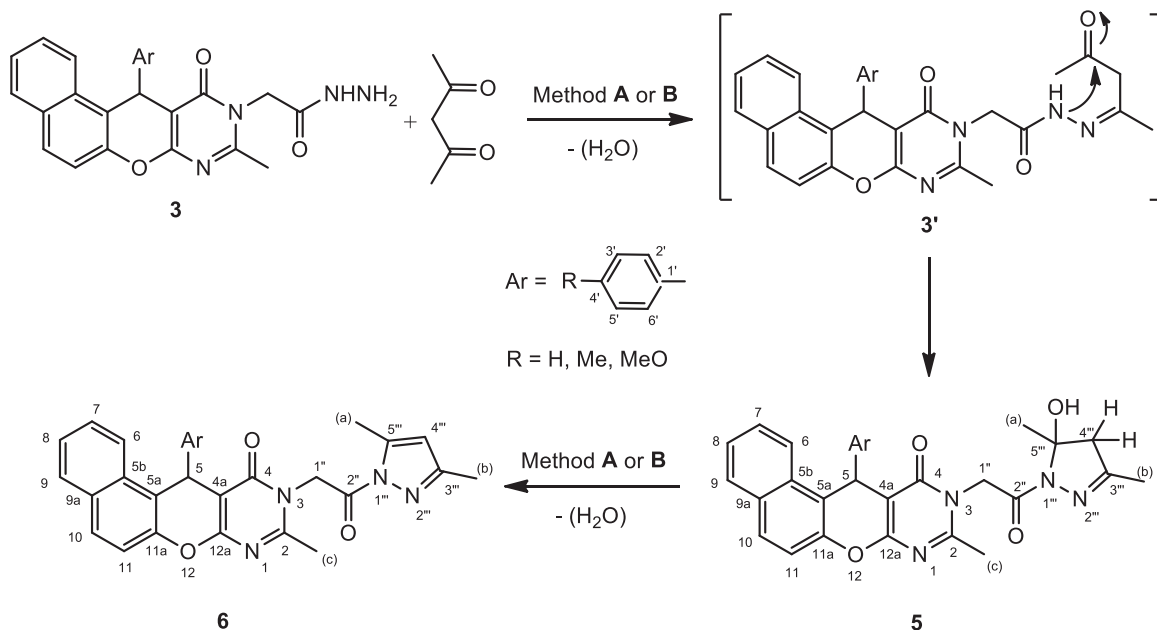
^aIsolated yields.

The thus-formed new compounds **4** were characterized essentially by ¹H NMR spectra showing, in addition to the signals corresponding to the protons introduced by the naphthopyranopyrimidinone moiety, the

presence of a singlet at δ_H 10.88–11.12 due to the NH group and one signal relative to methyl groups at δ_H 1.93–1.99 and ethylene protons at δ_H 4.74–4.82 and 4.90–4.96, for which chemical shifts and multiplicities were in good agreement with the proposed structure.

Encouraged by this success, we became interested in applying this protocol for 2,4-pentanedione, two cyclic anhydrides, and phenylthioisocyanate. Thus, cyclocondensation of pyrimidinic hydrazides **3** and 2,4-pentanedione, in the same solvent-free reaction conditions (method **B**: 3 min of irradiation at 300 W), afforded the new hydroxylated pyrazolic derivatives **5** (88%–96% yield, Table 1). Alternatively, compounds **5** were obtained in yields ranging from 52% to 64% (Table 1) when an equimolar mixture of hydrazides **3** and pentane-2,4-dione was heated under reflux with dioxane for 12 h (method **A**) (Table 1).

A plausible mechanism explaining the formation of these compounds is shown in Scheme 5. This mechanism results in the nonisolable hydrazone intermediate **3'**, obtained by the nucleophilic attack of hydrazide **3** followed by dehydration, which develops an intramolecular cyclization to afford compounds **5**.



Scheme 5. Synthetic pathway to pyrazolic derivatives **5a–5c** and **6a–6b**.

We note that the possibility of formation of a pseudo-six-membered ring, inducing a strong hydrogen bond, may explain why the reaction has not evolved to compounds **6** under the same experimental conditions that allowed access to compounds **4** (Figure).

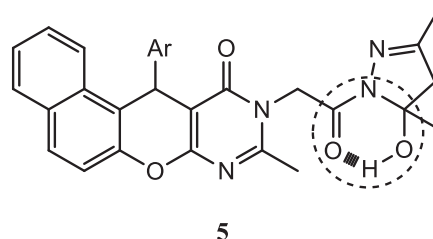


Figure. Possibility of formation of hydrogen bonding in compounds **5**.

Conventional heating of compounds **5** in dioxane in the presence of a catalytic amount of acetic acid

afforded pyrazolic derivatives **6** in 48%–54% yield in 12 h (method **A**) due to a second dehydration. The same reaction conducted for 10 min in DMF with microwave assistance at 300 W in the presence of a catalytic amount of acetic acid (method **B**) afforded the same products, **6a** and **6b**, in yields ranging from 90% to 97% (Scheme 5; Table 2).

Table 2. Comparison between the conventional procedure (method **A**) and microwave irradiation (method **B**) for the synthesis of compounds **6**.

Entry	R	Method A		Method B	
		Time (h)	Yield (%) ^a	Time (min)	Yield (%) ^a
6a	H	12	48	10	90
6b	Me	12	54	10	97

^aIsolated yields.

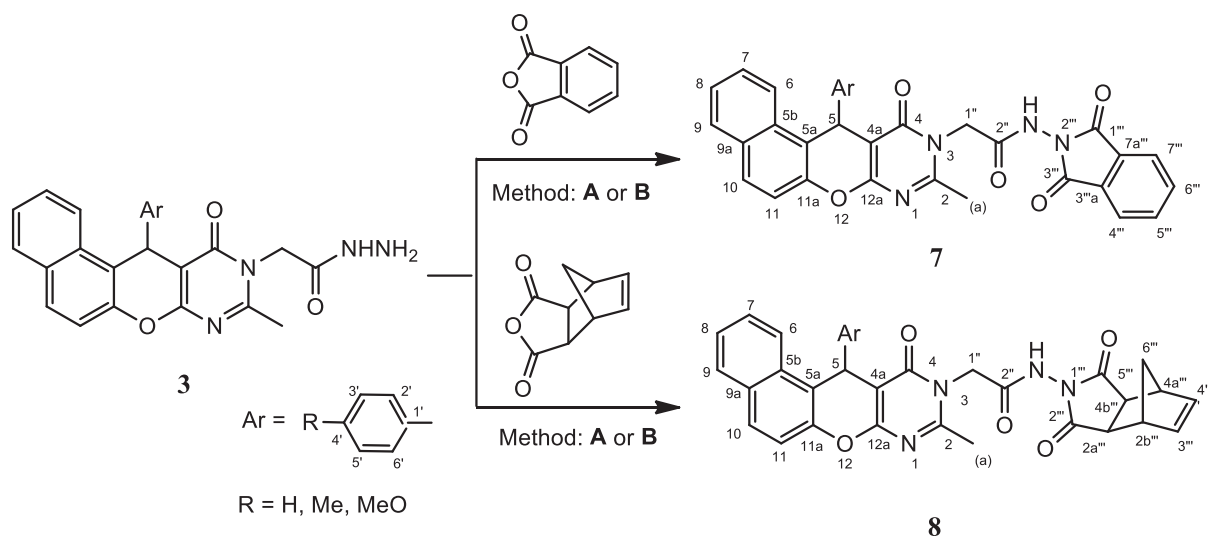
The structures of new compounds **5** have been assigned from their analytical data and mass spectroscopy (HR-ES-MS). Furthermore, the ¹H NMR spectra of compounds **5** showed the duplication of some signals confirming the obtaining of two nonseparable diastereoisomers due to the presence of two stereocenters C-5 at δ_C (35.2–36.1) and C-5''' at δ_C (90.6–90.7); therefore, the second dehydration, which in principle leads to compounds **6**, had not occurred. The ¹H NMR spectra of these compounds indicate essentially the presence of characteristic signals based on their chemical shifts, readily assigning the protons of the methylene group (H-1''), which was found as a pair of two doublets at δ_H 4.91–5.18 ($J = 17.4$ and 17.7 Hz), and also the presence of two singlets at δ_H 5.68–5.77 due to the H-5 proton and two broad D₂O-exchangeable singlets at δ_H 6.49–6.54 due to the OH group in the two diastereoisomers. Unambiguous proof for obtained products **5a–5c** arose from their ¹³C NMR data (see Section 3).

Similarly, the structures of isolated products **6** were confirmed on the basis of their spectral data. In the ¹H NMR spectrum, we note essentially the disappearance of the two doublets assigning the protons of the methylene group (H-4''') and the two broad singlets due to the OH group and the appearance of a new singlet at δ_H 6.02 relative to the proton H-4''' due to the formation of the double bond after the second dehydration. The ¹³C NMR spectrum of this compound showed essentially the appearance of new signals at 111.6–111.7 and 144.6 ppm attributable to the ethylenic carbons C-4''' and C-5''', respectively.

On the other hand, heating pyrimidinic precursors **3** under reflux for 12 h with phthalic or tricyclic anhydrides in glacial acetic acid (method **A**) furnished the corresponding new pyrrolidinediones **7a–7c** and **8a–8c** in 43%–60% yield. The same reaction conducted for 5 min under microwave assistance at 300 W in DMF (method **B**) afforded the same products **7a–7c** and **8a–8c** in yields ranging from 86% to 96% (Scheme 6, Table 1).

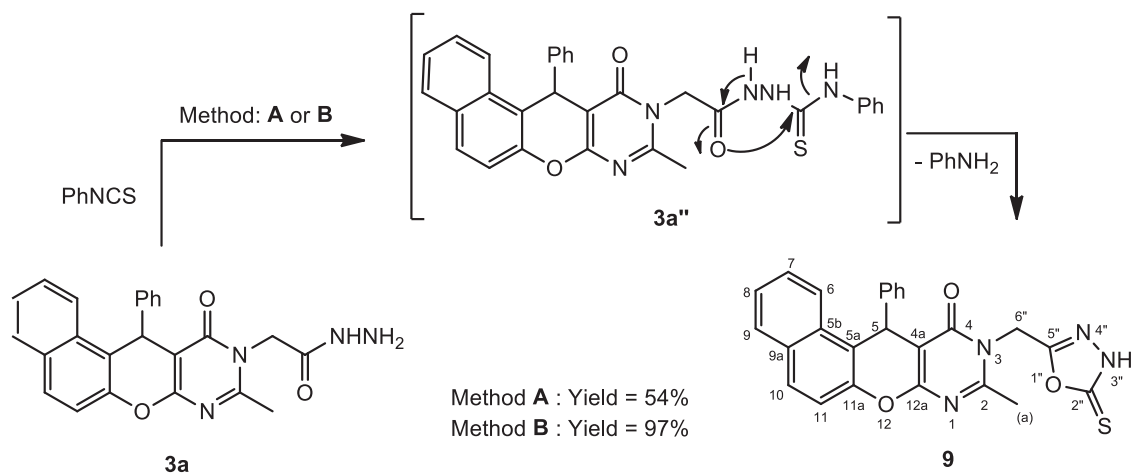
The structures of all new synthesized compounds **7** and **8** have been assigned from their analytical data and IR, ¹H NMR, ¹³C NMR, and mass spectroscopy (HRMS-ES).

Finally, our attention was focused on the reaction of hydrazide **3a** with phenylisothiocyanate. However, after 3 min of solvent-free irradiation at 300 W of an equimolar mixture of precursor **3a** and phenylthioisocyanate we obtained the new oxadiazolidinethione derivative **9** in 97% yield (method **B**). When the reaction was carried out under refluxing dioxane for 6 h (method **A**), product **9** was yielded in 54% (Scheme 7). Mechanistically, phenylisothiocyanate reacted with hydrazide **3a** to give the nonisolable intermediate **3a''**, which yields to



Scheme 6. Synthetic pathway to derivatives **7a-7c** and **8a-8c**.

the formation of oxazolidinethione **9** via intramolecular cyclization followed by elimination of a molecule of phenylamine.



Scheme 7. Synthetic pathway to oxathiazolidinethione **9**.

The structure of newly synthesized compound **9** was characterized by ¹H NMR and ¹³C NMR, which show the absence of signals of the phenyl group, proving the elimination of a molecule of phenylamine and the access to compound **9**. Furthermore, the HRMS-ES mass spectra showed essentially the pseudomolecular ion peaks [M+H]⁺, which were in good agreement with the assigned structures.

2.2. Conclusions

In summary, a straightforward, efficient, and cost-effective method was achieved for the preparation of some new hybrid molecules combining pyranopyrimidinones with pyrrole, pyrrolidine, pyrazole, or oxazolidinethione (**4-9**) with the assistance of microwave irradiation from hydrazides **3** and some electrophilic species via cyclocondensation reactions. The method offers several advantages including good to high yields, cleaner products, and

particularly a reduction in reaction time. In this study, the use of microwave irradiation reduced the reaction time from 3–12 h to 3–5 min with better yields than those obtained by conventional methods, which makes this method particularly attractive.

3. Experimental

3.1. General experimental procedures

All reactions were monitored by TLC using aluminum sheets of SDS silica gel 60 F₂₅₄, 0.2 mm. Melting temperatures were determined on an Electrothermal 9002 apparatus and were reported uncorrected. NMR spectra were recorded on a Bruker AC-300 spectrometer at 300 MHz (¹H) and 75 MHz (¹³C). All chemical shifts were reported as δ values (ppm) relative to residual nondeuterated solvent. Mass spectra were acquired with an LCT Premier XE mass spectrometer (Waters, ESI technique, positive mode). Starting materials **2** and **3** were prepared according to the literature.^{35,36} Microwave irradiation was performed in a domestic microwave oven (Samsung MW71C, 800 W output power).

3.2. Synthesis

3.2.1. General procedure for the synthesis of 2-amino-3-cyanonaphthopyranes **1a–1d**

A solution of aromatic aldehyde (10 mmol), malononitrile (10 mmol), β -naphthol (10 mmol), and CuI (0.37 g, 20 mol%) in 50 mL of ethanol and water (30:70 v/v) was stirred at room temperature for 1 h. The precipitated solid was separated and purified by recrystallization in ethanol to give compounds **1a–1d** in good yields (93%–97%). Their spectral data were detailed in our previous work.³¹

3.2.2. General procedure for the synthesis of hydrazides **3a–3d**

Acetic anhydride (20 mL) was added to 2-amino-3-cyanonaphthopyranes **1** (10 mmol), and then orthophosphoric acid (5 mL) was added carefully and the resulting hot mixture was refluxed for 3 h. After cooling, the mixture was diluted with cold water, and the formed solid was collected by filtration, washed several times with cold water, and subjected to crystallization from ethanol to afford compounds **2**. In the second step, a mixture of **2** (10 mmol), ethyl chloroacetate (11 mmol), and anhydrous potassium carbonate (10.5 g) in dry DMF (100 mL) was refluxed for 8 h. The reaction mixture was allowed to cool and then it was poured in water. The thus-formed resultant solid was filtered off, dried, and crystallized from ethanol; then it was treated with hydrazine hydrate (15 mmol) under reflux with 1,4-dioxane (50 mL) for 6 h. The excess of solvent was removed and the product was crystallized from ethanol, giving the desired hydrazides **3**.

3.2.2.1. 2-(2-Methyl-12-oxo-11-phenyl-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-3-yl)acetohydrazide (**3a**)

White solid, yield 72%, mp 262–264 °C (ethanol), ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.45 (s, 3H, CH₃), 4.20 (s, 2H, NH₂), 4.57 (d, 1H, H₂, *J* = 16.2 Hz), 4.72 (d, 1H, H₂, *J* = 16.2 Hz), 5.77 (s, 1H, H_{11'}), 7.06 (t, 1H, *J* = 7.2 Hz, ArH), 7.15–7.52 (m, 7H, ArH), 7.90–7.99 (m, 3H, ArH), 9.22 (s, 1H, -NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 22.3 (-CH₃), 36.2 (C_{11'}), 44.9 (C₂), 100.1 (C_{11'a}), 116.5 (C_{10'b}), 117.3 (C_{5'}), 123.3 (C_{10'}), 124.9 (C_{8'}), 126.4 (C_{9'}), 127.1 (C_{2''},_{6''}), 128.1 (C_{7'}), 128.2 (C_{6'}), 128.5 (C_{3''},_{5''}), 129.4 (C_{6'a}),

130.6 (C_{13'a}), 131.1 (C_{4''}), 144.1 (C_{1''}), 147.9 (C_{4'a}), 159.2 (C_{2'}), 159.7 (C_{3'a}), 161.5 (C_{12'}), 165.6 (C₁); HRMS-ES calculated for [M+H]⁺ C₂₄H₂₁N₄O₃: 413.1502; found: 413.1510.

3.2.2.2. 2-(2-Methyl-11-(*p*-methylphenyl)-12-oxo-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-3-yl)acetohydrazide (3b)

White solid, yield 68%, mp 258–260 °C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.45 (s, 3H, CH₃), 2.51 (s, 3H, CH₃), 4.30 (s, 2H, NH₂), 4.55 (d, 1H, H₂, *J* = 16.2 Hz), 4.69 (d, 1H, H₂, *J* = 16.2 Hz), 5.67 (s, 1H, H_{11'}), 6.73 (d, 2H, *J* = 8.7 Hz, ArH), 7.21 (d, 2H, *J* = 8.7 Hz, ArH), 7.40–7.52 (m, 3H, ArH), 7.91–7.97 (m, 3H, ArH), 9.41 (s, 1H, -NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 22.3 (CH₃-Ar), 22.5 (-CH₃), 35.2 (C_{11'}), 44.8 (C₂), 100.2 (C_{11'a}), 116.6 (C_{10'b}), 117.3 (C_{5'}), 123.4 (C_{10'}), 124.9 (C_{8'}), 127.1 (C_{9'}), 128.5 (C_{2'',6''}), 129.1 (C_{7'}), 129.4 (C_{6'}), 130.4 (C_{3'',5''}), 131.1 (C_{6'a}), 136.2 (C_{13'a}), 147.6 (C_{1''}), 157.7 (C_{4'a}), 158.8 (C_{2'}), 159.7 (C_{3'a}), 161.5 (C_{12'}), 165.6 (C₁); HRMS-ES calculated for [M+H]⁺ C₂₅H₂₃N₄O₃: 427.1623; found: 427.1617.

3.2.2.3. (2-Methyl-11-(*p*-methoxyphenyl)-12-oxo-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-3-yl)acetohydrazide (3c)

White solid, yield 64%, mp 274–276 °C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.45 (s, 3H, CH₃), 3.62 (s, 3H, OCH₃), 4.30 (s, 2H, NH₂), 4.56 (d, 1H, H₂, *J* = 16.5 Hz), 4.69 (d, 1H, H₂, *J* = 16.5 Hz), 5.67 (s, 1H, H_{11'}), 6.74 (d, 2H, *J* = 8.4 Hz, ArH), 7.21 (d, 2H, *J* = 8.4 Hz, ArH), 7.40–7.52 (m, 3H, ArH), 7.91–7.97 (m, 3H, ArH), 9.42 (s, 1H, -NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 22.5 (-CH₃), 35.2 (C_{11'}), 44.8 (C₂), 54.9 (-OCH₃), 100.2 (C_{11'a}), 113.6 (C_{3'',5''}), 116.5 (C_{10'b}), 117.3 (C_{5'}), 123.4 (C_{10'}), 124.9 (C_{8'}), 127.2 (C_{9'}), 128.5 (C_{7'}), 129.2 (C_{2'',6''}), 129.3 (C_{1''}), 130.4 (C_{6'}), 131.1 (C_{6'a}), 136.2 (C_{1''}), 147.6 (C_{4''}), 157.7 (C_{4'a}), 158.8 (C_{2'}), 159.7 (C_{3'a}), 161.4 (C_{12'}), 165.8 (C₁); HRMS-ES calculated for [M+H]⁺ C₂₅H₂₃N₄O₄: 443,1521; found: 443,1513.

3.2.2.4. (2-Methyl-11-(*p*-chlorophenyl)-12-oxo-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-3-yl)acetohydrazide (3d)

White solid, yield 63%, mp 282–284 °C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.46 (s, 3H, CH₃), 4.21 (s, 2H, NH₂), 4.58 (d, 1H, H₂, *J* = 15.9 Hz), 4.64 (d, 1H, H₂, *J* = 15.9 Hz), 5.79 (s, 1H, H_{11'}), 7.22–7.53 (m, 7H, ArH), 7.61–7.99 (m, 3H, ArH), 9.30 (s, 1H, -NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 22.3 (-CH₃), 35.7 (C_{11'}), 45.0 (C₂), 99.6 (C_{11'a}), 115.9 (C_{10'b}), 117.3 (C_{5'}), 123.3 (C_{10'}), 125.0 (C_{8'}), 127.2 (C_{9'}), 128.1 (C_{3'',5''}), 128.5 (C_{7'}), 129.7 (C_{6'}), 129.9 (C_{2'',6''}), 130.5 (C_{6'a}), 131.1 (C_{13'a}), 131.2 (C_{4''}), 142.9 (C_{1''}), 147.9 (C_{4'a}), 159.1 (C_{2'}), 159.9 (C_{3'a}), 161.3 (C_{12'}), 165.5 (C₁); HRMS-ES calculated for [M+H]⁺ C₂₄H₂₀ClN₄O₃: 447,1146; found: 447,1152.

3.2.3. General procedure for synthesis of 2-(2-methyl-12-oxo-11-aryl-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-1-yl)-N-(2,5-dimethylpyrrol-1-yl) acetamides 4

Method A (conventional method): A mixture of appropriate hydrazide **3** (1 mmol) and 2,5-hexanedione (1 mmol) was stirred under reflux with dry dioxane. After 12 h, the reaction mixture was cooled to room

temperature, the dioxane was removed in vacuo, and the residue was purified by silica gel chromatography (chloroform and ethyl acetate, 70:30) to give compounds **4**.

Method **B** (microwave-assisted): An open 25-mL flask containing hydrazide **3** (1 mmol) and 2,5-hexanedione (1 mmol) was introduced in a domestic microwave oven (Samsung MW71C, 800 W output power) and irradiated for 3 min (300 W). The reaction was monitored by TLC, and after completion the flask was cooled and the obtained residue was recrystallized from ethanol to give compounds **4**.

3.2.4. 2-(2-Methyl-12-oxo-11-phenyl-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-1-yl)-N-(2,5-dimethylpyrrol-1-yl) acetamide (**4a**)

White solid, mp 246–248 °C (ethanol), ¹H NMR (300 MHz, DMSO-*d*₆) δ = 1.93 (s, 6H, 2CH₃^(a)), 2.46 (s, 3H, CH₃^(b)), 4.74 (d, 1H, H₂, *J* = 16.5 Hz), 4.90 (d, 1H, H₂, *J* = 16.5 Hz), 5.57 (s, 2H, H_{3''},_{4''}), 5.73 (s, 1H, H_{11'}), 7.02 (t, 1H, *J* = 7.2 Hz, ArH), 7.11–7.50 (m, 7H, ArH), 7.87–7.95 (m, 3H, ArH), 11.05 (s, 1H, -NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 10.7 (C_a), 22.6 (C_b), 35.9 (C_{11'}), 45.3 (C₂), 100.0 (C_{11'a}), 103.1 (C_{3''},C_{4''}), 116.2, 117.3, 123.4, 125.0, 126.5, 126.7 (C_{2''}), 127.2, 128.1 (C_{3'''},_{5'''}), 128.2 (C_{2'''},_{6'''}), 128.5, 129.5, 130.4, 131.1, 143.9, 147.7 (C_{4'a}), 158.9, 159.5, 161.3 (C_{12'}), 166.1 (C₁); HRMS-ES calculated for [M+H]⁺ C₃₀H₂₇N₄O₃: 491,2005; found: 491,2012.

3.2.5. 2-(2-Methyl-12-oxo-11-(*p*-methoxyphenyl)-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-1-yl)-N-(2,5-dimethylpyrrol-1-yl) acetamide (**4b**)

White solid, mp 252–254 °C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.99 (s, 6H, 2CH₃^(a)), 2.51 (s, 3H, CH₃^(b)), 3.63 (s, 3H, OCH₃), 4.81 (d, 1H, H₂, *J* = 16.5 Hz), 4.96 (d, 1H, H₂, *J* = 16.5 Hz), 5.63 (s, 2H, H_{3''},_{4''}), 5.75 (s, 1H, H_{11'}), 6.73 (d, 2H, *J* = 8.4 Hz, ArH), 7.22 (d, 2H, *J* = 8.4 Hz, ArH), 7.49–7.52 (m, 3H, ArH), 7.91–7.98 (m, 3H, ArH), 11.12 (s, 1H, -NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 10.9 (C_a, C_b), 22.5 (C_c), 35.1 (C_{11'}), 45.8 (C₂), 54.9 (C_d), 100.3 (C_{11'a}), 103.1 (C_{3''},C_{4''}), 113.6 (C_{3'''},_{5'''}), 116.4, 117.3, 124.9, 126.8 (C_{2''}), 127.1, 128.2, 128.5, 129.1 (C_{2'''},_{6'''}), 129.5, 130.4, 131.1, 136.1, 147.6 (C_{4'a}), 157.7, 158.8, 159.4, 161.3 (C_{12'}), 166.1 (C₁); HRMS-ES calculated for [M+H]⁺ C₃₁H₂₉N₄O₄: 521,2189; found: 521,2197.

3.2.6. 2-(2-Methyl-12-oxo-11-(*p*-chlorophenyl)-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-1-yl)-N-(2,5-dimethylpyrrol-1-yl) acetamide (**4c**)

White solid, mp 264–266 °C (ethanol), ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.98 (s, 6H, 2 CH₃^(a)), 2.15 (s, 3H, CH₃^(c)), 2.53 (s, 3H, CH₃^(b)), 4.82 (d, 1H, H₂, *J* = 16.5 Hz), 4.96 (d, 1H, H₂, *J* = 16.5 Hz), 5.62 (s, 2H, H_{3''},_{4''}), 5.81 (s, 1H, H_{11'}), 7.21 (d, 2H, *J* = 8.4 Hz, ArH), 7.34 (d, 2H, *J* = 8.4 Hz, ArH), 7.46–7.51 (m, 3H, ArH), 7.91–7.98 (m, 3H, ArH), 10.88 (s, 1H, -NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 10.7 (C_a, C_b), 20.5 (C_d), 22.4 (C_c), 35.6 (C_{11'}), 45.4 (C₂), 99.7 (C_{11'a}), 103.2 (C_{3''},C_{4''}), 115.7, 117.3, 123.3, 124.9, 126.9 (C_{2''}), 127.2, 128.1 (C_{3'''},_{5'''}), 128.5, 129.7, 129.9 (C_{2'''},_{6'''}), 130.4, 131.1, 131.2, 142.8, 147.9 (C_{4'a}), 159.2, 159.7, 161.4 (C_{12'}), 165.9 (C₁). HRMS-ES calculated for [M+H]⁺ C₃₀H₂₆ClN₄O₃: 525,2139; found: 525,2148.

3.3. General procedure for the synthesis of 3-(2-(4,5-dihydro-5-hydroxy-3,5-dimethylpyrazol-1-yl)-2-oxoethyl)-2-methyl-5-aryl-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-4(5H)-ones 5

Method **A** (conventional method): A mixture of appropriate hydrazide **3** (1 mmol) and 2,4-pentanedione (1 mmol) was stirred under reflux with dry dioxane. After 12 h, the reaction mixture was cooled to room temperature, and the dioxane was removed in vacuo and the residue was purified by silica gel chromatography (chloroform and ethyl acetate, 60:40) to yield compounds **5**.

Method **B** (microwave-assisted): An open 25-mL flask containing hydrazide **3** (1 mmol) and 2,4-pentanedione (1 mmol) was introduced in a domestic microwave oven (Samsung MW71C, 800 W output power) and irradiated for 3 min (300 W). The reaction was monitored by TLC, and after completion the flask was cooled and the obtained residue was recrystallized from ethanol to give compounds **5**.

3.3.1. 3-(2-(4,5-Dihydro-5-hydroxy-3,5-dimethylpyrazol-1-yl)-2-oxoethyl)-2-methyl-5-phenyl-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-4(5H)-one (5a,a')

White solid, mp: 251–253 °C (ethanol), ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.73 (s, 6H, CH_{3(5a)}^(a) and CH_{3(5a')}^(a)), 2.01 (s, 6H, CH_{3(5a)}^(b) and CH_{3(5a')}^(b)), 2.40 (s, 6H, CH_{3(5a)}^(c) and CH_{3(5a')}^(c)), 2.82 (d, 2H, H_{4'''_a(5a,a')}, *J* = 18.4 Hz), 2.97 (d, 2H, H_{4'''_b(5a,a')}, *J* = 18.4 Hz), 4.91–5.16 (4d, 4H, *J* = 17.4 Hz, *J* = 17.7 Hz, H_{1''(5a)} and H_{1''(5a')}), 5.75 and 5.77 (2s, 2H, H_{5(5a)} and H_{5(5a')}), 6.49 and 6.54 (2s, 2H, OH_(5a) and OH_(5a')), 7.07 (t, 2H, *J* = 6.9 Hz, ArH), 7.19 (t, 4H, *J* = 7.2 Hz, ArH), 7.32 (d, 4H, *J* = 7.2 Hz, ArH), 7.42–7.55 (m, 6H, ArH), 7.93–7.99 (m, 6H, ArH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 15.8 (C_{b(5a)} and C_{b(5a')}), 22.3 (C_{c(5a)} and C_{c(5a')}), 25.6 and 25.7 (C_{a(5a)} and C_{a(5a')}), 36.1 (C_{5(5a)} and C_{5(5a')}), 46.2 and 46.3 (C_{1''(5a)} and C_{1''(5a')}), 52.0 (C_{4'''(5a)} and C_{4'''(5a')}), 90.6 and 90.7 (C_{5'''(5a)} and C_{5'''(5a')}), 99.9 and 100.0 (C_{4a(5a)} and C_{4a(5a')}), 116.4, 117.3, 123.4, 125.0, 126.5, 127.2, 128.1, 128.2, 128.5, 129.5, 130.4, 131.1, 144.1 (C_{arom.}), 147.7 (C_{11a(5a)} and C_{11a(5a')}), 156.2 and 156.3 (C_{3'''(5a)} and C_{3'''(5a')}), 159.0, 159.8 (C_{arom.}), 161.3 (C_{4(5a)} and C_{4(5a')}), 163.1 and 163.3 (C_{2''(5a)} and C_{2''(5a')}); HRMS-ES calculated for [M+H]⁺ C₂₉H₂₇N₄O₃: 495,1954; found: 495,1947.

3.3.2. 3-(2-(4,5-Dihydro-5-hydroxy-3,5-dimethylpyrazol-1-yl)-2-oxoethyl)-2-methyl-5-(*p*-methylphenyl)-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-4(5H)-one (5b,b')

White solid, mp 248–250 °C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.73 (s, 6H, CH_{3(5b)}^(a) and CH_{3(5b')}^(a)), 2.01 (s, 6H, CH_{3(5b)}^(b) and CH_{3(5b')}^(b)), 2.14 (s, 6H, CH_{3(5b)}^(d) and CH_{3(5b')}^(d)), 2.39 (s, 6H, CH_{3(5b)}^(c) and CH_{3(5b')}^(c)), 2.81 (d, 2H, H_{4'''_a(5a,a')}, *J* = 18.6 Hz), 2.96 (d, 2H, H_{4'''_b(5a,a')}, *J* = 18.6 Hz), 4.91–5.13 (4d, 4H, *J* = 17.4 Hz, *J* = 17.7 Hz, H_{1''(5b)} and H_{1''(5b')}), 5.68 and 5.70 (2s, 2H, H_{5(5b)} and H_{5(5b')}), 6.50 and 6.53 (2s, 2H, OH_(5b) and OH_(5b')), 6.98 (d, 4H, *J* = 7.8 Hz, ArH), 7.19 (d, 4H, *J* = 7.8 Hz, ArH), 7.40–7.53 (m, 6H, ArH), 7.91–7.98 (m, 6H, ArH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 15.8 (C_{b(5b)} and C_{b(5b')}), 20.4 (C_{d(5b)} and C_{d(5b')}), 22.3 (C_{c(5b)} and C_{c(5b')}), 25.6 and 25.7 (C_{a(5b)} and C_{a(5b')}), 35.6 (C_{5(5b)} and C_{5(5b')}), 46.2 and 46.3 (C_{1''(5b)} and C_{1''(5b')}), 51.9 (C_{4'''(5b)} and C_{4'''(5b')}), 90.6 and 90.7 (C_{5'''(5b)} and C_{5'''(5b')}), 100.2 and 100.3 (C_{4a(5b)} and C_{4a(5b')}).

$C_{4(5b')}$), 116.5, 117.3, 123.4, 124.9, 127.1, 128.0, 128.5, 128.8, 129.4, 130.4, 131.0, 135.6, 141.2 ($C_{arom.}$), 147.6 ($C_{11a(5b)}$ and $C_{11a(5b')}$), 156.2 and 156.3 ($C_{3'''(5b)}$ and $C_{3'''(5b')}$), 158.9, 159.7 ($C_{arom.}$), 161.3 ($C_{4(5b)}$ and $C_{4(5b')}$), 163.2 and 163.3 ($C_{2''(5b)}$ and $C_{2''(5b')}$), HRMS-ES calculated for $[M+H]^+$ $C_{30}H_{29}N_4O_4$: 509.2111, found: 509.2102.

3.3.3. 3-(2-(4,5-Dihydro-5-hydroxy-3,5-dimethylpyrazol-1-yl)-2-oxoethyl)-2-methyl-5-(*p*-methoxyphenyl)-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-4(5H)-one (5c,c')

White solid, mp 244–246 °C (ethanol); 1H NMR (300 MHz, DMSO- d_6) δ = 1.74 (s, 6H, $CH_{3(5c)}^{(a)}$, and $CH_{3(5c')}^{(a)}$), 2.01 (s, 6H, $CH_{3(5c)}^{(b)}$ and $CH_{3(5c')}^{(b)}$), 2.44 (s, 6H, $CH_{3(5c)}^{(c)}$ and $CH_{3(5c')}^{(c)}$), 2.78 (d, 2H, $H_{4'''a(5a,a')}$, J = 18.6 Hz), 2.97 (d, 2H, $H_{4'''b(5a,a')}$, J = 18.6 Hz), 3.63 (s, 6H, $OCH_{3(5c)}$ and $OCH_{3(5c')}$), 4.98–5.18 (4d, 4H, J = 17.4 Hz, J = 17.7 Hz, $H_{1''(5c)}$ and $H_{1''(5c')}$), 5.68 and 5.69 (2s, 2H, $H_{5(5c)}$ and $H_{5(5c')}$), 6.50 and 6.54 (2s, 2H, $OH_{(5c)}$ and $OH_{(5c')}$), 6.74 (d, 4H, J = 8.7 Hz, ArH), 7.22 (d, 4H, J = 8.7 Hz, ArH), 7.40–7.53 (m, 6H, ArH), 7.91–7.99 (m, 6H, ArH); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 15.8 ($C_{b(5c)}$ and $C_{b(5c')}$), 22.3 ($C_{c(5c)}$ and $C_{c(5c')}$), 25.7 and 25.8 ($C_{a(5c)}$ and $C_{a(5c')}$), 35.2 ($C_{5(5b)}$ and $C_{5(5b')}$), 46.2 and 46.3 ($C_{1''(5a)}$ and $C_{1''(5a')}$), 51.9 ($C_{4'''(5c)}$ and $C_{4'''(5c')}$), 54.9 ($OCH_{3(5c)}$ and $OCH_{3(5c')}$), 90.6 and 90.7 ($C_{5'''(5c)}$ and $C_{5'''(5c')}$), 100.1 and 100.2 ($C_{4a(5c)}$ and $C_{4(5c')}$), 113.6, 116.5, 117.3, 123.4, 124.9, 127.1, 128.5, 129.1, 129.4, 130.4, 131.0, 136.2 ($C_{arom.}$), 147.6 ($C_{11a(5c)}$ and $C_{11a(5c')}$), 156.2 and 156.3 ($C_{3'''(5c)}$ and $C_{3'''(5c')}$), 157.7, 158.9, 159.6 ($C_{arom.}$), 161.3 ($C_{4(5c)}$ and $C_{4(5c')}$), 163.2 and 163.3 ($C_{2''(5c)}$ and $C_{2''(5c')}$). HRMS-ES calculated for $[M+H]^+$ $C_{30}H_{29}N_4O_5$: 525.2138; found: 525.2148.

3.4. General procedure for the synthesis of pyrrolidinedione derivatives 6

Method **A** (conventional method): Compound **5** (1 mmol) was stirred under reflux with dioxane in the presence of a catalytic amount of glacial acetic acid. After 12 h, the reaction mixture was cooled to room temperature, and the dioxane was removed in vacuo and the residue was purified by silica gel chromatography (chloroform and ethyl acetate, 80:20) to yield compounds **6**.

Method **B** (microwave-assisted): An open 25-mL flask containing compounds **5** (1 mmol) dissolved in a minimum amount of DMF (2 mL) in the presence of a catalytic amount of acetic acid was irradiated in a domestic microwave oven (Samsung MW71C, 800 W output power) for 10 min at 300 W. The reaction was monitored by TLC, and after completion the flask was cooled and the obtained residue was purified by silica gel chromatography (chloroform and ethyl acetate, 80:20) to yield compounds **6**.

3.4.1. 3-(2-(4,5-Dihydro-3,5-dimethylpyrazol-1-yl)-2-oxoethyl)-2-methyl-5-(phenyl)-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-4(5H)-one (6a)

White solid, mp 234–236 °C; 1H NMR (300 MHz, DMSO- d_6) δ = 2.25 (s, 3H, $CH_3^{(c)}$), 2.51 (s, 6H, $2CH_3^{(a,b)}$), 5.32 (d, 1H, $H_{1''}$, J = 18.3 Hz), 5.77 (d, 1H, $H_{1''}$, J = 18.3 Hz), 5.87 (s, 1H, H_5), 6.02 (s, 1H, $H_{4'''}$), 7.15 (d, 2H, J = 8.4 Hz, ArH), 7.35 (d, 2H, J = 8.4 Hz, ArH), 7.39–7.48 (m, 4H, ArH), 7.80–7.84 (m, 3H, ArH). ^{13}C NMR (75 MHz, DMSO- d_6): δ = 13.6 and 13.7 ($C_{a,b}$), 22.7 (C_c), 36.3 (C_5), 47.5 ($C_{1''}$), 100.0 (C_{4a}),

111.7 (C_{4'''}), 116.0, 117.5, 123.5, 125.0, 127.1, 128.4, 128.5, 129.6, 129.8, 131.0, 131.6, 132.4, 142.2, 144.6, 148.2, 153.5, 158.5, 159.7, 162.1 (C₄), 166.1 (C₂); HRMS-ES calculated for [M+H]⁺ C₂₉H₂₅N₄O₃: 477,1848; found: 477,1853.

3.4.2. 3-(2-(4,5-Dihydro-3,5-dimethylpyrazol-1-yl)-2-oxoethyl)-2-methyl-5-(*p*-methylphenyl)-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-4(5H)-one (6b)

White solid, mp 237–239 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ = 2.22 (s, 3H, CH₃^(d)), 2.31 (s, 3H, CH₃^(c)), 2.52 (s, 6H, 2CH₃^(a,b)), 5.30 (d, 1H, H_{1''}, *J* = 18 Hz), 5.83 (d, 1H, H_{1''}, *J* = 18.3 Hz), 5.88 (s, 1H, H₅), 6.02 (s, 1H, H_{4'''}), 7.01 (d, 2H, *J* = 7.8 Hz, ArH), 7.29–7.49 (m, 5H, ArH), 7.81 (d, 2H, *J* = 7.8 Hz, ArH), 7.95 (d, 1H, *J* = 8.1 Hz, ArH). ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 13.6 and 13.7 (C_{a,b}), 20.8 (C_d), 22.6 (C_c), 36.4 (C₅), 47.4 (C_{1''}), 101.6 (C_{4a}), 111.6 (C_{4'''}), 116.8, 117.4, 123.7, 124.8, 126.9, 128.3, 128.4, 129.0, 129.2, 131.2, 131.6, 136.1, 140.9, 144.6, 148.2, 153.5, 158.1, 159.7, 162.2 (C₄), 166.2 (C₂); HRMS-ES calculated for [M+H]⁺ C₃₀H₂₇N₄O₃: 491,2038; found: 491,2024.

3.5. General procedure for the synthesis of pyrrolidinedione derivatives 7 and 8(a–c)

Method A (conventional method): A mixture of appropriate hydrazide **3** (1 mmol) and cyclic anhydride (1 mmol) was stirred under reflux with glacial acetic acid. After 12 h, the reaction mixture was allowed to cool to room temperature and then was poured in water; the precipitate formed was filtered off, washed with water, dried, and crystallized from ethanol to give the pyrrolidinediones **7** and **8**.

Method B (microwave-assisted): An equimolar mixture of the appropriate hydrazide **3** (1 mmol) and cyclic anhydride (1 mmol) was dissolved in a minimum amount of DMF (2 mL) and irradiated in a domestic microwave oven (Samsung MW71C, 800 W output power) for 5 min at 300 W. The reaction was monitored by TLC, and after completion the flask was cooled and the obtained residue was recrystallized from ethanol to afford compounds **7** and **8**.

3.5.1. 2-(2-Methyl-4-oxo-5-phenyl-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-3(5H)-yl)-N-(1,3-dioxoisoindolin-2-yl) acetamide (7a)

White solid, mp 278–280 °C (ethanol), ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.60 (s, 3H, CH₃^(a)), 5.01 (d, 1H, H_{1''}, *J* = 17.7 Hz), 5.21 (d, 1H, H_{1''}, *J* = 17.7 Hz), 5.88 (s, 1H, H₅), 7.18 (t, 1H, *J* = 6.9 Hz, ArH), 7.29 (t, 2H, *J* = 7.2 Hz, ArH), 7.43 (d, 2H, *J* = 7.2 Hz, ArH), 7.47–7.64 (m, 3H, ArH), 8.02–8.13 (m, 7H, ArH), 11.12 (s, 1H, -NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 22.2 (C_a), 35.1 (C₅), 44.5 (C_{1''}), 100.1 (C_{4a}), 116.3, 117.2, 123.4, 123.7 (C_{4'''},_{7'''}), 124.9, 126.5, 127.2, 128.1 (C_{3'},_{5'}), 128.2 (C_{2'},_{6'}), 128.5, 129.5 (C_{3'''},_{a,7'''}), 130.4, 131.0, 135.3 (C_{5'''},_{6'''}), 135.7, 141.0, 147.5 (C_{11a}), 158.9 (C_{3'''}), 159.5, 161.3 (C₄), 164.7 (C_{2''}), 166.3 (C_{1'''},_{3'''}); HRMS-ES calculated for [M+H]⁺ C₃₂H₂₃N₄O₅: 543.1590; found: 543.1601.

3.5.2. 2-(2-Methyl-4-oxo-5(*p*-methylphenyl)-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-3(5H)-yl)-N-(1,3-dioxoisoindolin-2-yl) acetamide (7b)

White solid, mp 278–280 °C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.14 (s, 3H, CH₃^(b)), 2.49 (s, 3H, CH₃^(a)), 4.89 (d, 1H, H_{1''}, *J* = 17.4 Hz), 5.12 (d, 1H, H_{1''}, *J* = 17.4 Hz), 5.71 (s, 1H, H₅), 6.98 (d, 2H,

$J = 7.8$ Hz, ArH), 7.20 (d, 2H, $J = 7.8$ Hz, ArH), 7.40–7.51 (m, 3H, ArH), 7.90–7.99 (m, 7H, ArH), 11.26 (s, 1H, -NH); ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 20.45$ (C_b), 22.2 (C_a), 35.6 (C_5), 44.3 ($\text{C}_{1''}$), 100.2 (C_{4a}), 116.4, 117.3, 123.4, 123.7 ($\text{C}_{4''',7''}$), 124.9, 127.1, 128.0 ($\text{C}_{3',5'}$), 128.5, 128.8 ($\text{C}_{2',6'}$), 129.4, 129.5 ($\text{C}_{3''',a,7''a}$), 130.4, 131.0, 135.2 ($\text{C}_{5''',6''}$), 135.6, 141.0, 147.5 (C_{11a}), 158.9 ($\text{C}_{3''}$), 159.5, 161.1 (C_4), 164.8 ($\text{C}_{2''}$), 166.3 ($\text{C}_{1''',3''}$); HRMS-ES calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{33}\text{H}_{25}\text{N}_4\text{O}_5$: 557.1747, found: 557.1738.

3.5.3. 2-(2-Methyl-4-oxo-5(*p*-methoxyphenyl)-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-3(5H)-yl)-N-(1,3-dioxoisindolin-2-yl) acetamide (7c)

White solid, mp 274–276 °C (ethanol), ^1H NMR (300 MHz, DMSO- d_6): $\delta = 2.49$ (s, 3H, $\text{CH}_3^{(a)}$), 3.56 (s, 3H, $\text{CH}_3^{(b)}$), 4.89 (d, 1H, $\text{H}_{1''}$, $J = 17.4$ Hz), 5.12 (d, 1H, $\text{H}_{1''}$, $J = 17.4$ Hz), 5.71 (s, 1H, H_5), 6.74 (d, 2H, $J = 7.8$ Hz, ArH), 7.22 (d, 2H, $J = 7.8$ Hz), 7.42–7.51 (m, 3H, ArH), 7.90–7.99 (m, 7H, ArH), 11.30 (s, 1H, -NH); ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 22.2$ (C_a), 35.2 (C_5), 44.3 ($\text{C}_{1''}$), 54.9 (C_b), 100.2 (C_{4a}), 113.6 ($\text{C}_{3',5'}$), 116.5, 117.3, 123.4, 123.7 ($\text{C}_{4''',7''}$), 124.9, 127.1, 128.5, 129.1 ($\text{C}_{2',6'}$), 129.4, 129.5 ($\text{C}_{3''',a,7''a}$), 130.4, 131.1, 135.2 ($\text{C}_{5''',6''}$), 136.1, 147.5 (C_{11a}), 157.8 ($\text{C}_{3''}$), 159.4, 159.6, 161.2 (C_4), 164.8 ($\text{C}_{2''}$), 166.3 ($\text{C}_{1''',3''}$); HRMS-ES calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{33}\text{H}_{25}\text{N}_4\text{O}_6$: 573.1783, found: 573.1791.

3.5.4. 2-(2-Methyl-4-oxo-5-phenyl-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-3(5H)-yl)-N-(1,3-dioxopyrrolidino[3,4-*d*]hept[2.2.1]-5-en-2-yl) acetamide (8a)

White solid, mp 260–262 °C (ethanol); ^1H NMR (300 MHz, DMSO- d_6): $\delta = 1.54$ (d, 1H, $\text{H}_{6''}$, $J = 9$ Hz), 1.74 (d, 1H, $\text{H}_{6''}$, $J = 9$ Hz), 2.43 (s, 3H, $\text{CH}_{(a)}$), 3.28 (m, 2H, $\text{H}_{2''',a,4''b}$), 3.44 (m, 2H, $\text{H}_{2''',b,4''a}$), 4.71 (d, 1H, $\text{H}_{1''}$, $J = 17.1$ Hz), 4.96 (d, 1H, $\text{H}_{1''}$, $J = 17.1$ Hz), 5.71 (s, 1H, H_5), 6.05 (m, 2H, $\text{H}_{3''}$, $\text{H}_{4''}$), 7.08 (t, 1H, $J = 7.2$ Hz, ArH), 7.19 (t, 2H, $J = 7.2$ Hz, ArH), 7.42 (d, 2H, $J = 7.2$ Hz, ArH), 7.46–7.54 (m, 3H, ArH), 7.92–8.00 (m, 3H, ArH), 10.94 (s, 1H, -NH); ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 22.1$ ($\text{CH}_{3(a)}$), 36.1 (C_5), 43.6 ($\text{C}_{2''',b,4''a}$), 44.2 ($\text{C}_{2''',a,4''b}$), 44.4 ($\text{C}_{6''}$), 51.2 ($\text{C}_{1''}$), 100.0 (C_{4a}), 116.3, 117.3, 123.4, 124.9, 126.5, 127.2, 128.1, 128.2 ($\text{C}_{3',5'}$), 128.5 ($\text{C}_{2',6'}$), 129.5, 130.4, 131.1, 134.5 ($\text{C}_{3''',4''}$), 143.9, 147.7 (C_{11a}), 159.1 (C_{12a}), 159.6, 161.4 (C_4), 164.9 ($\text{C}_{2''}$), 173.6 ($\text{C}_{2''',5''}$); HRMS-ES calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{33}\text{H}_{27}\text{N}_4\text{O}_5$: 559.1903, found: 559.1911.

3.5.5. 2-(2-Methyl-4-oxo-5(*p*-methylphenyl)-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-3(5H)-yl)-N-(1,3-dioxopyrrolidino[3,4-*d*]hept[2.2.1]-5-en-2-yl)acetamide (8b)

White solid, mp 265–267 °C (ethanol); ^1H NMR (300 MHz, DMSO- d_6): $\delta = 1.53$ (d, 1H, $\text{H}_{6''}$, $J = 9$ Hz), 1.74 (d, 1H, $\text{H}_{6''}$, $J = 9$ Hz), 2.19 (s, 3H, $\text{CH}_{(b)}$), 2.58 (s, 3H, $\text{CH}_{(a)}$), 3.31 (m, 2H, $\text{H}_{2''',a,4''b}$), 3.42 (m, 2H, $\text{H}_{2''',b,4''a}$), 4.29 (d, 1H, $\text{H}_{1''}$, $J = 17.1$ Hz), 4.98 (d, 1H, $\text{H}_{1''}$, $J = 17.1$ Hz), 5.69 (s, 1H, H_5), 6.16 (m, 2H, $\text{H}_{3''}$, $\text{H}_{4''}$), 6.98 (d, 2H, $J = 7.8$ Hz, ArH), 7.25 (d, 2H, $J = 7.8$ Hz, ArH), 7.38–7.42 (m, 3H, ArH), 7.76–7.94 (m, 3H, ArH), 10.48 (s, 1H, -NH); ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 20.5$ ($\text{CH}_{3(b)}$), 22.4 ($\text{CH}_{3(a)}$), 35.9 (C_5), 43.8 ($\text{C}_{2''',b,4''a}$), 44.5 ($\text{C}_{2''',a,4''b}$), 45.6 ($\text{C}_{6''}$), 51.1 ($\text{C}_{1''}$), 101.0 (C_{4a}), 115.9,

116.9, 123.2, 124.5, 126.6, 127.2, 128.0 (C_{3',5'}), 128.6 (C_{2',6'}), 128.9, 130.4, 131.1, 134.2 (C_{3'''',4'''}), 135.7, 140.4, 147.2 (C_{11a}), 158.2 (C_{12a}), 159.3, 161.1 (C₄), 164.2 (C_{2''}), 173.0 (C_{2''',5'''}); HRMS-ES calculated for [M+H]⁺ C₃₄H₂₉N₄O₅: 573.2138, found: 573.2155.

3.5.6. 2-(2-Methyl-4-oxo-5(*p*-methoxyphenyl)-4H-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidin-3(5H)-yl)-N-(1,3-dioxopyrrolidino[3,4-*d*]hept[2.2.1]-5-en-2-yl)acetamide (8c)

White solid, mp 266–268 °C (ethanol), ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.54 (d, 1H, H_{6'''}, *J* = 9 Hz), 1.73 (d, 1H, H_{6'''}, *J* = 9 Hz), 2.42 (s, 3H, CH_{3(a)}), 3.28 (m, 2H, H_{2'''a,4'''b}), 3.44 (m, 2H, H_{2'''b,4'''a}), 3.57 (s, 3H, OCH_{3(b)}), 4.72 (d, 1H, H_{1''}, *J* = 17.1 Hz), 4.97 (d, 1H, H_{1''}, *J* = 17.1 Hz), 5.69 (s, 1H, H₅), 6.05 (m, 2H, H_{3'''}, H_{4'''}), 6.74 (d, 2H, *J* = 8.4 Hz, ArH), 7.21 (d, 2H, *J* = 8.4 Hz, ArH), 7.41–7.52 (m, 3H, ArH), 7.91–7.99 (m, 3H, ArH), 10.94 (s, 1H, -NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 22.2 (CH_{3(a)}), 35.1 (C₅), 43.7 (C_{2'''b,4'''a}), 44.6 (C_{2'''a,4'''b}), 45.4 (C_{6'''}), 51.8 (C_{1''}), 55.4 (CH_{3(b)}), 101.0 (C_{4a}), 113.6 (C_{3',5'}), 116.5, 117.3, 123.4, 124.9, 127.2, 128.2, 128.5, 129.1 (C_{2',6'}), 129.4, 130.4, 131.1, 134.5 (C_{3'''',4'''}), 136.1, 147.5 (C_{11a}), 157.7 (C_{12a}), 158.8, 161.1 (C₄), 164.3 (C_{2''}), 173.7 (C_{2''',5'''}); HRMS-ES calculated for [M+H]⁺ C₃₄H₂₉N₄O₆: 589.2009, found: 589.2015.

3.6. Synthesis of 3-((4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl)-2-methyl-5-phenyl-4H-naphtho[2,1-*b*]pyrano [2,3-*d*] pyrimidin-4(5H)-one 9

Method **A** (conventional method): A mixture of hydrazide **3a** (1 mmol) and phenylthioisocyanate (1 mmol) was stirred under reflux with dry dioxane. After 6 h, the reaction mixture was cooled to room temperature, and the dioxane was removed in vacuo and the residue was purified by silica gel chromatography (chloroform and ethyl acetate, 60:40) to give compound **9**.

Method **B** (microwave-assisted): An open 25-mL flask containing hydrazide **3a** (1 mmol) and phenylthioisocyanate (1 mmol) was introduced in a domestic microwave oven (Samsung MW71C, 800 W output power) and irradiated for 3 min (300 W). The reaction was monitored by TLC, and after completion the flask was cooled and the obtained residue was recrystallized from ethanol to give compound **9**.

3.6.1. 3-((4,5-Dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl)-2-methyl-5-phenyl-4H-naphtho[2,1-*b*]pyrano[2,3-*d*] pyrimidin-4(5H)-one (9)

Yellow solid, mp 248–250 °C (ethanol), ¹H NMR (300 MHz, DMSO-*d*₆) δ = 2.58 (s, 3H, CH₃), 5.22 (d, 1H, H_{6''}, *J* = 17.1 Hz), 5.36 (d, 1H, H_{6''}, *J* = 17.1 Hz), 5.77 (s, 1H, H₅), 7.06 (t, 1H, *J* = 7.2 Hz, ArH), 7.14 (t, 2H, *J* = 7.2 Hz, ArH), 7.32 (d, 2H, *J* = 7.2 Hz, ArH), 7.46–7.54 (m, 4H, ArH+NH) 7.91–7.98 (m, 3H, ArH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 22.5 (CH₃), 35.9 (C₅), 39.0 (C_{6''}), 100.2 (C_{4a}), 116.2, 117.3, 123.4, 125.0, 126.6, 127.2, 128.1 (C_{3',5'}), 128.2 (C_{2',6'}), 128.5, 129.6, 130.3, 131.1, 143.8, 147.5 (C_{11a}), 158.7 (C_{2''}), 159.1 (C_{12a}), 159.5, 160.9 (C₄), 177.8 (C_{5''}); HRMS-ES calculated for [M+H]⁺ C₂₅H₁₉N₄O₃S: 455.1100, found: 455.1108.

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