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SHORT COMMUNICATION

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Three-component synthesis of arene-linked pyrazolo[1,5-*a*]pyrimidines

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Abstract

In this study, we aimed to establish an efficient method for synthesizing two new series of arene-linked pyrazolo[1,5-*a*]pyrimidines. This was achieved by reacting 1*H*-pyrazole-3,5-diamines with the respective acetophenones and benzaldehydes in a 1:1:1 ratio. To optimize this three-component reaction, various bases, and solvents were investigated. Use of two equivalents of KOH in ethanol at reflux for 4–6 h resulted in 89%–96% yields of the desired products. Structure of new products was elucidated by considering their elemental and spectral data.

1 | INTRODUCTION

The pyrimidine nucleus can be found in a wide range of nucleic acids and nucleotides in nature. Scaffolds containing pyrimidine units have a wide range of bioactivity, such as antibacterial [1], antifungal [2], antiviral [3], and antimalarial properties [4]. Furthermore, pyrimidines showed promising antitumor activity against different carcinoma cell lines [5]. For the fusion of biodynamic hetero systems, the synthesis of fused pyrimidines is very interesting [6]. This has been extremely beneficial in the development of new molecular structures for drug candidates with various pharmaceutical properties.

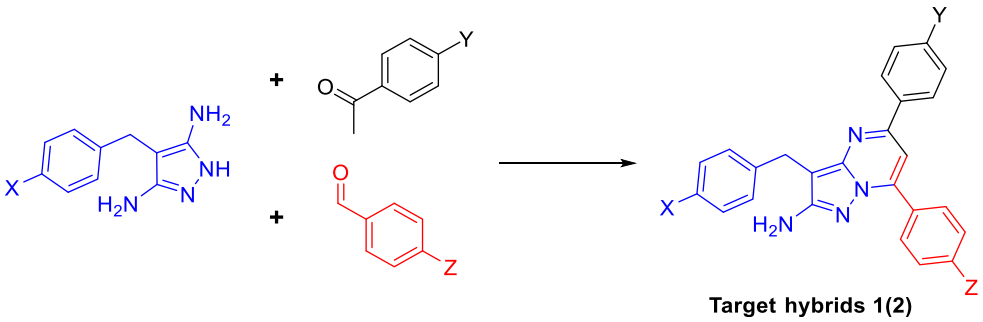
Pyrimidine-fused scaffolds are a rapidly growing area of heterocyclic chemistry research [7, 8]. This is due to their distinct structures, which have numerous applications in medicinal chemistry [9, 10]. Pyrazolo[1,5-*a*] pyrimidine scaffolds are purine analogs with a wide range of biological properties. They have an effect on the central nervous system because they can be used as benzodiazepine receptor ligands [11], and antitubercular agents [12]. Additionally, they demonstrate important antitumor activity [13], as well as their promising ability to inhibit several kinases that are used as effective targets in chemotherapy, such as Src family (*c*-Src, Lck, and CHK) [14], B-Raf [15], and pim kinases [16]. Also, they exhibit interesting antibacterial [17], and antifungal activity [18]. Figure S1 depicts some promising pyrazolo [1,5-*a*]pyrimidine-based drugs (see electronic supplementary file) [19–21].

Several publications have described the synthesis of pyrazolo[1,5-*a*]pyrimidines by reacting 3(5)-aminopyrazoles **I** with a variety of 1,3-bielectrophilic reagents, including enaminones [22, 23], α,β-unsaturated nitriles [24, 25], 1,3-diketones [26, 27], and β-ketoesters [9, 28]. Repeating the previous reaction with α,β-unsaturated ketones **II** in the presence of hydroxide salts produced products **III**, not **IV** (see Scheme S1, electronic supplementary file) [18, 29]. We pointed herein to develop a facile protocol to prepare new two series of arene-linked pyrazolo[1,5-*a*]pyrimidines.

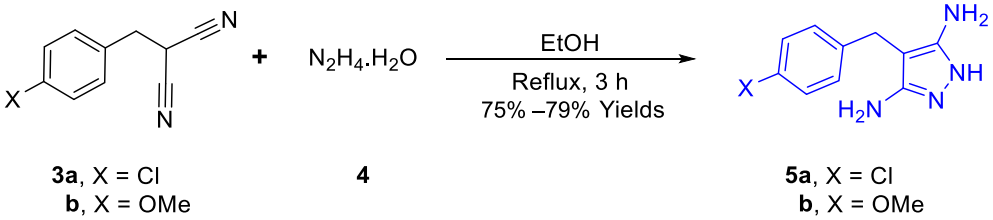
2 | RESULTS AND DISCUSSION

We present a facile three-component protocol for the synthesis of arene-linked pyrazolo[1,5-*a*]pyrimidines in excellent yields. The reaction involved reacting the respective acetophenones, benzaldehydes, and 1*H*-pyrazole-3,5-diamines in the presence of an efficient base (see Scheme 1).

Initially, the 1*H*-pyrazole-3,5-diamines used in this study were prepared using previously published procedures [30, 31]. As a result, the respective 2-(4-substituted benzyl)malononitriles **3a,b** were reacted with hydrazine



SCHEME 1 Schematic diagram for the tandem synthesis of the target arene-linked pyrazolo[1,5-*a*]pyrimidines.



SCHEME 2 Synthesis of the intermediates 4-(4-substituted benzyl)-1*H*-pyrazole-3,5-diamines **5a**,**b**.

TABLE 1 Optimization of the synthesis of the target pyrazolo [1,5-*a*]pyrimidine **1a**.

Entry[a]	Base	Solvent[b]	Time (h)	Yield (%)[c]
1	NaOH	Dioxane	6	66
2	NaOH	DMF	6	52
3	NaOH	EtOH	6	69
4	$Ba(OH)_2$	Dioxane	6	52
5	$Ba(OH)_2$	DMF	6	44
6	$Ba(OH)_2$	EtOH	6	49
7	KOH	Dioxane	6	72
8	KOH	DMF	6	67
9	KOH	EtOH	6	62
10	KOH	EtOH	6	83
11	KOH	EtOH	5	90

[a]All reactions are mediated using 2.5 equivalents of the appropriate base.
[b]All reactions are carried out at reflux except entries 9 and 10, which are carried out at 40°C and 60°C, respectively.
[c]All reactions were tracked down by TLC analyses.

hydrate **4** in ethanol at reflux for 3 h to afford good yields of 4-(4-substituted benzyl)-1*H*-pyrazole-3,5-diamines **5a,b** (see Scheme 2).

After that, we examined the utility of the precursors **5** in the one-pot synthesis of the desired fused pyrimidines **1(2)**. Therefore, the reaction of 1*H*-pyrazole-3,-5-diamine **5a** with acetophenone **6a** and benzaldehyde **7a** in a molar ratio of 1:1:1 in dioxane was performed. The reaction was carried out using 2.5 equivalents of sodium hydroxide. After heating the reaction mixture at reflux for 6 h, a sole product was produced, in 66% yield, as detected by the TLC analyses (Table 1 and Entry 1). Its ^{1}H-NMR spectrum revealed three singlet signals at δ 4.00, 5.73, and 7.40 owing to CH_2, NH_2, and H6 protons, respectively, in addition to a multiplet signal at the range from δ 7.18 to δ 8.29 owing to 14 aromatic protons (see "Experimental Section"). The prior product was identified as 5,7-diphenylpyrazolo[1,5-*a*]pyrimidin-2-amine **1a** (see Scheme 3) [32, 33].

Taking the synthesis of **1a** as a representative example, different bases, solvents, temperatures, and reaction times were investigated to achieve the best yields of the desired products (see Table 1). All reactions were carried out using 2.5 equivalents of the respective base and monitored by TLC analyses. Repeating the one-pot reaction in DMF or ethanol in the presence of NaOH gave **1a** in 52% and 69% yields, respectively (Table 1 and Entries 2 and 3). Next, we investigate the utility of barium hydroxide to conduct the above reaction in dioxane, DMF, or ethanol. The previous base afforded the target **1a** in yields ranging from 44% to 52% (Table 1 and Entries 4–6). We also carried out the potassium hydroxide-mediated reaction protocol. Using dioxane or DMF at reflux for 6 h yielded **1a** in 72% and 67%, respectively (Table 1 and Entries 7 and 8). Furthermore, ethanol was examined as an efficient solvent to give **1a** at different reaction temperatures (see Table 1, Entries 9–11). Best yield of **1a**, 90%, was obtained by conducting the previous reaction in ethanol at reflux for 5 h (see Table 1, Entry 11).

Next, we examined the optimized amount of potassium hydroxide to mediate the above one-pot reaction. All reactions were carried out in ethanol at reflux for 5–8 h and using amounts of KOH ranging from 1.5 to 2.5 equivalents. TLC analyses were used to monitor all trials. The results in Table 2 demonstrates that the best conditions for the previous reaction were using 2.0 equivalents

SCHEME 3 Three-component synthesis of the target pyrazolo[1,5-*a*] pyrimidine **1a**.

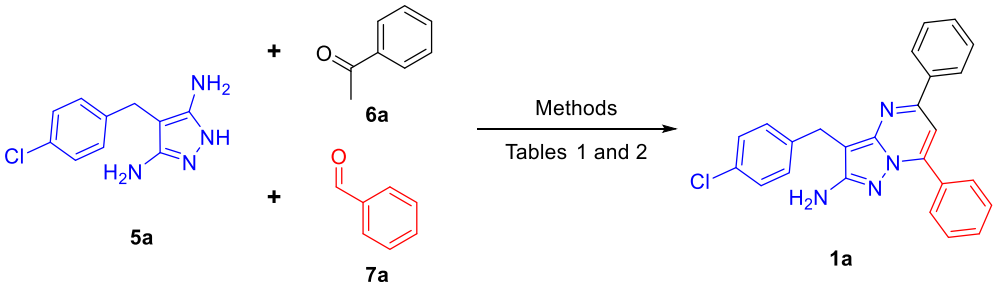


TABLE 2 Optimizing the yield of KOH-mediated synthesis of pyrimidine **1a**.

Entry[a]	No. of equivalents	Time (h)	Yield (%)[b]
1	1.5	8	72
2	1.75	6	81
3	1.75	8	83
4	2.0	5	94
5	2.0	6	93
6	2.2	5	92
7	2.2	6	91
8	2.5	5	90

[a]All reactions are KOH-mediated ones and are conducted in ethanol at reflux.
[b]All reactions were tracked down by TLC analyses.

of KOH in ethanol at reflux for 5 h. It afforded **1a** in 94% yield (Table 2 and Entry 4).

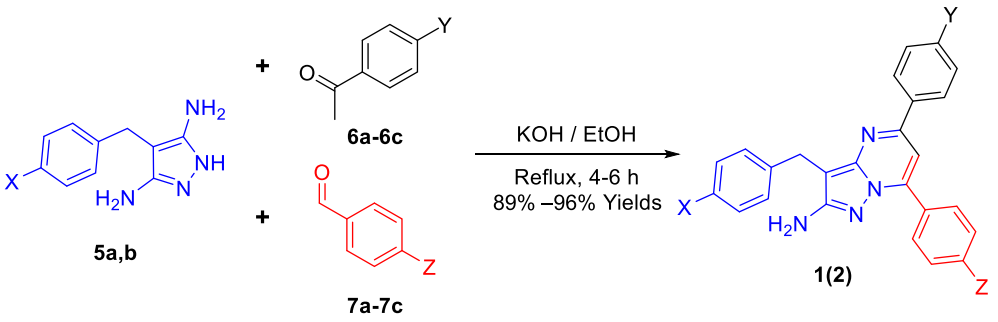
Using the above optimal conditions, a new series of pyrazolo[1,5-*a*]pyrimidines **1b–1i** were prepared in 89%–96% yields via the one-pot reaction of 1*H*-pyrazole-3,-5-diamines **5a** with the respective acetophenones **6a–6c** and benzaldehydes **7a–7c** (see Scheme 4 and Table 3). The proposed structure of pyrazolo[1,5-*a*]pyrimidines **1** are in agreement with Palaniraja's single-crystal X-ray studies on the structure of pyrimidine analogs [34]. Instead of **5a**, use of 1*H*-pyrazole-3,5-diamine **5b** afforded a second series of pyrazolo[1,5-*a*]pyrimidines **2a–2i** in 90–96% yields via a similar one-pot protocol (see Scheme 4 and Table 3).

The structure of the above pyrimidines **1(2)** was confirmed by their independent synthesis by another route. Therefore, the reaction of **5b** with prop-2-en-1-one **8b** in ethanol in the presence of one equivalent of potassium hydroxide at reflux for 4 h was conducted. The previous reaction afforded such a product that found completely identical in all aspects to pyrimidine **2b** not **2d**. Additionally, product **2d** was obtained by repeating the previous reaction using enone **8d** instead of **8b** (see Scheme 5).

The reaction may begin with a potassium hydroxide-mediated condensation between acetophenones **6** and benzaldehydes **7** to produce the enones **8**. The previous intermediates were reacted with **5** via successive acyl nucleophilic and aza-Michael additions of NH_2 and pyrazole-NH functions in **5** to the electrophilic enone-CO function and olefinic-C3 in enones **8** to afford the adduct **10** through the intermediate **9**. The isolable products **1(2)** were obtained from the intermediate **10** by successive removal of one molecule of water and hydrogen (see Scheme 6) [35]. The proposed structure of the previous products is consistent with our recent study on pyrimidine analogs using activation energy calculations, natural atomic charge calculations, Fukui indexes derived from density functional theory, MM2, and MMFF94 calculations [36].

To obtain an additional evidence for the structure of the above pyrazolo[1,5-*a*]pyrimidines **1(2)**, the reaction between 1*H*-pyrazole-3,5-diamine **5** with enone **8** was investigated in glacial acetic acid. The use of acetic acid as an efficient dual solvent and mediator is also investigated. As shown in Scheme 7, the reaction of **5b** with enone **8b** was carried out in glacial acetic acid at reflux for 6 h to give the *N*-(pyrazolo[1,5-*a*]pyrimidin-2-yl)acetamide **11** (see "Experimental Section"). The prior upon alkaline hydrolysis using ethanolic potassium hydroxide solution at reflux for 4 h gave an identical product to pyrimidine **2d** in all aspects. This result is in agreement with previous results reported by El-Hashash et al. on pyrimidine analogs [37].

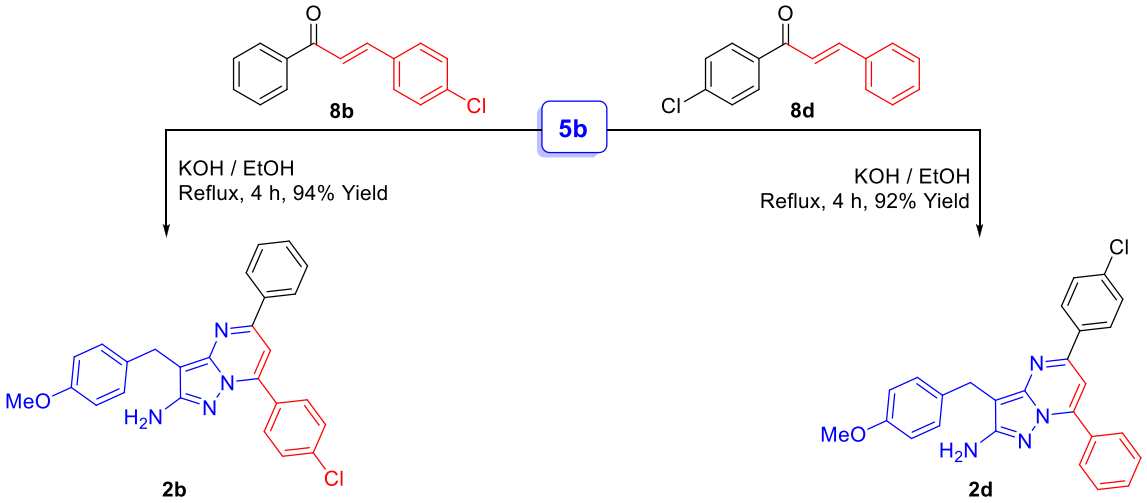
The formation of pyrimidine **11** may proceed by an initial protonation of the enone **8b**, followed by tautomerism to give intermediate **13** through **12**. Next, **13** was reacted with **5** in acetic acid by an initial nucleophilic addition of an amino function in **5** to the most electrophilic enone-C3, followed by successive acetylation, cyclocondensation, and autooxidation to give **11** through intermediates **14–16** (see Scheme 8). This mechanism is consistent with the findings previously reported by Manachou et al. [38] The previous study investigated into the mechanism of pyrazolo[1,5-*a*]azines formation in the presence of acetic acid. The authors used theoretical calculations of activation energy, natural atomic charge, and Fukui indexes derived from DFT.



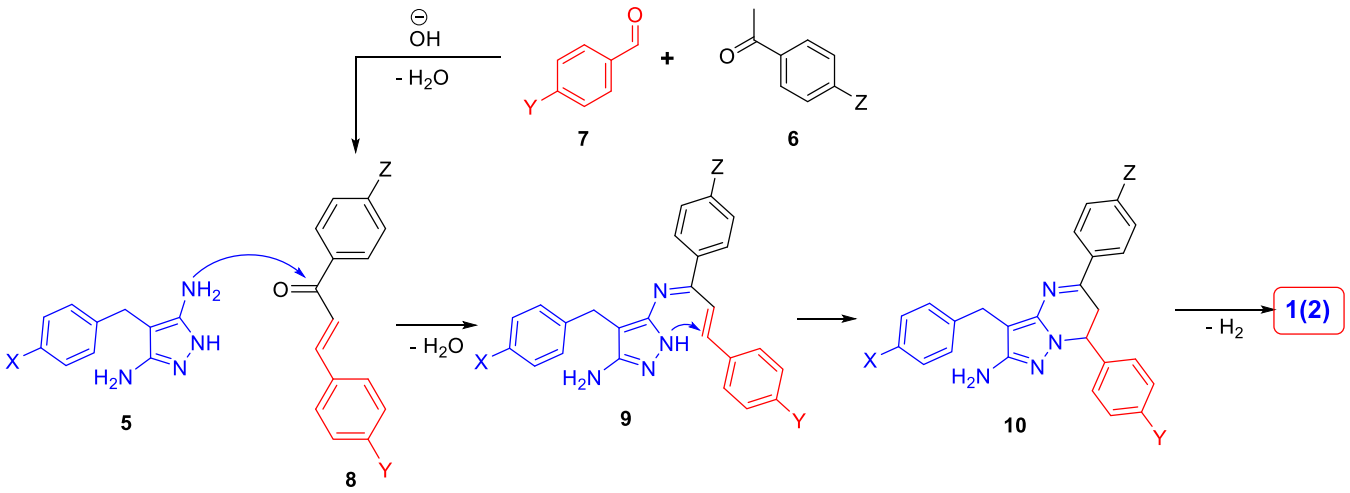
SCHEME 4 One-pot synthesis of the target pyrazolo[1,5-*a*]pyrimidines **1(2)**.

TABLE 3 The isolated yields of the target pyrazolo[1,5-*a*]pyrimidines **1(2)**.

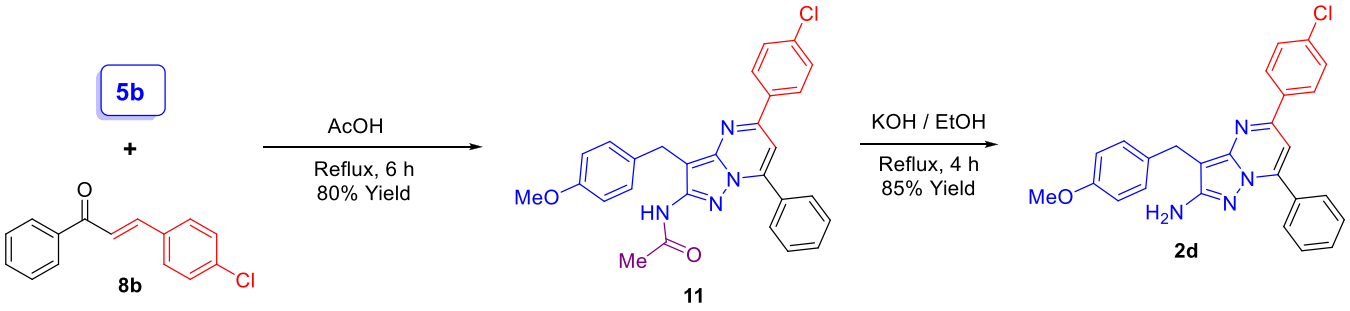
Entry	Product	X	Y	Z	Time (h)	Yield (%)
1	**1a**	Cl	H	H	5	94
2	**1b**	Cl	H	Cl	6	93
3	**1c**	Cl	H	OMe	6	90
4	**1d**	Cl	Cl	H	5	89
5	**1e**	Cl	Cl	Cl	6	91
6	**1f**	Cl	Cl	OMe	6	92
7	**1g**	Cl	Me	H	5	95
8	**1h**	Cl	Me	Cl	6	92
9	**1i**	Cl	Me	OMe	5	96
10	**2a**	OMe	H	H	4	91
11	**2b**	OMe	H	Cl	5	90
12	**2c**	OMe	H	OMe	4	92
13	**2d**	OMe	Cl	H	5	93
14	**2e**	OMe	Cl	Cl	6	91
15	**2f**	OMe	Cl	OMe	5	92
16	**2g**	OMe	Me	H	4	93
17	**2h**	OMe	Me	Cl	5	96
18	**2i**	OMe	Me	OMe	4	95



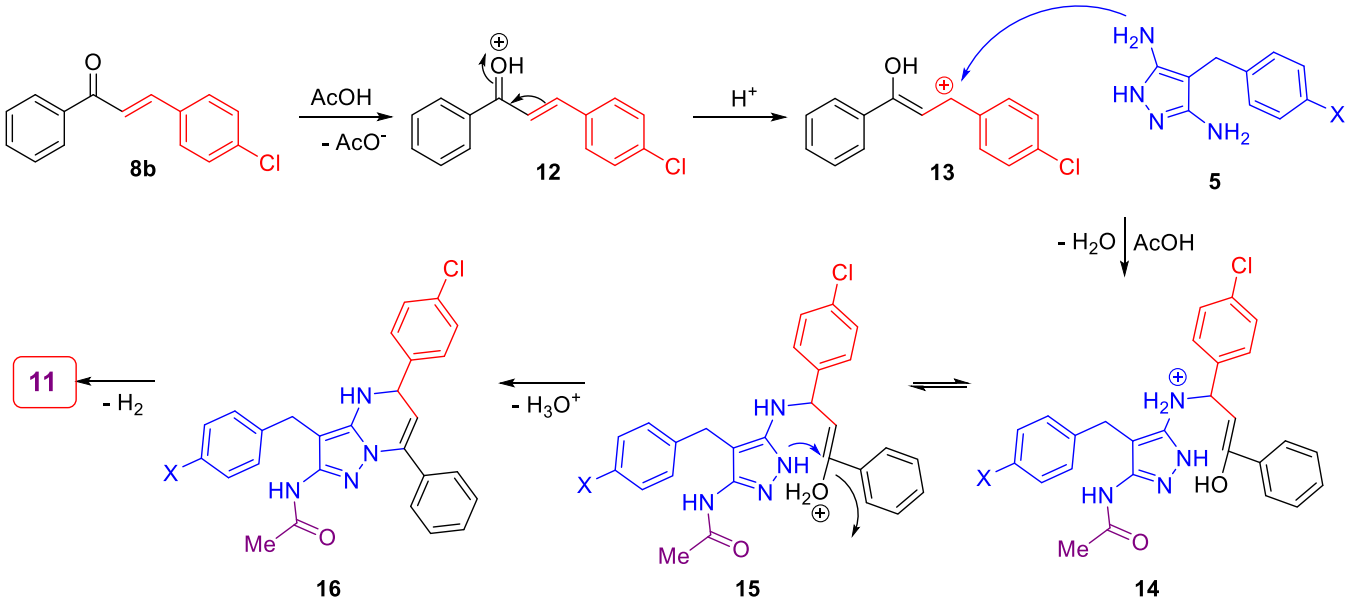
SCHEME 5 Synthesis of fused-pyrimidines **2b** and **2d**.



SCHEME 6 Proposed mechanism for the formation of fused-pyrimidines **1(2)**.



SCHEME 7 Alternative synthesis of fused-pyrimidine **2d**.



SCHEME 8 Proposed mechanism for the formation of **11**.

3 | CONCLUSION

In this study, an efficient method was established to synthesize two new series of arene-linked pyrazolo[1,5-*a*]pyrimidines. The new products were prepared, in good yields, by reacting the appropriate 1*H*-pyrazole-3,5-diamines with different acetophenones and benzaldehydes in ethanolic potassium hydroxide solution.

4 | EXPERIMENTAL SECTION

4.1 | Materials

All solvents were acquired from commercial sources. All other chemicals were acquired from Merck and used without further purification. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile attenuated total reflectance sampling accessory on the Nicolet iS10 FT-IR spectrometer. NMR spectra were recorded on Bruker Avance III 400 MHz spectrophotometer DMSO-d_6 as a solvent, whereas chemical shifts were expressed as δ ppm units. Mass spectra were recorded on a GC-MS-QP1000EX spectrometer using inlet type at 70 eV. Elemental analyses were carried out on a EuroVector instrument C, H, N analyzer EA3000 Series. For full characterization data of new products, see electronic supplementary file.

4.2 | General procedure for the three-component synthesis of arene-linked pyrazolo[1,5-*a*]pyrimidines 1(2)

A mixture of 1*H*-pyrazole-3,5-diamines **5a,b** (5 mmol), the appropriate acetophenones **6a–6c** (5 mmol), benzaldehydes **7a–7c** (5 mmol), and potassium hydroxide (10 mmol) was heated in ethanol (15 mL) at reflux for 5 h. The reaction mixture was cooled and the obtained product was collected by filtration, washed with cold ethanol, dried, and recrystallized from the appropriate solvent.

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No acknowledgment is available.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

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