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Synthesis of 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles via a four-component condensation reaction

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ABSTRACT

A direct and efficient approach for the synthesis of a new series of 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles has been developed through a sequential one-pot, four-component condensation reaction of easily available aromatic aldehydes, toluene-4-sulfonylmethyl isocyanide ($TsCH_2NC$), and 5-amino-1*H*-pyrazole-4-carbonitrile. The reaction was performed in the presence of *p*-toluenesulfonic acid as a catalyst at room temperature in acetonitrile as a solvent. Products were obtained in moderate to high yields.

1. Introduction

Imidazopyrazoles, as one of the most important fused heterocyclic compounds, are attractive for 'drug discovery'; since many compounds incorporating these scaffolds exhibit a wide range of biological, medicinal, and pharmaceutical activities, such as anti-tumor,[1] anti-inflammatory,[2] antiviral in Herpes Simplex Virus type-1,[3] and anti-neoplastic with L1210 leukemia-cells.[4] In addition, some of these compounds have shown inhibitor effects, such as deoxyribonucleic acid synthesis,[5] MAP kinase,[2] L1220 tumor-derived ribonucleotide reductase[6] and ribonucleoside diphosphate reductase,[7] synchronization of human lymphoid cells, and HeLa cells.[8,9] Additionally, some others, which are nonsteroidal agonists and antagonists of androgen receptor modulators have been shown to be useful in the treatment of a variety of diseases.[10]

Very recently, a new series of anti-inflammatory agents, with all imidazopyrazole structure, have been synthesized and accordingly, biological evaluation showed dual inhibition activity in both fMLP-OMe and IL8-induced chemotaxis.[11] Therefore, providing good synthetic methods, as well as new derivatives with this structure, is important in organic synthesis. Although several methods have been reported for the synthesis of imidazo[1,2-*b*]pyrazoles,[12] many of these methods are based on multi-step syntheses, and the range of compounds that can be prepared is limited.

Multi-component reactions (MCRs), are chemical transformations in which three or more different starting materials are combined together in a single reaction flask and generate a final complex product.[13] These reactions, because of their productivity, simplicity, convergence, facile execution, environmental concerns, atom economy, and ability to generate large libraries of compounds are one of the most powerful synthetic tools in medicinal chemistry, combinatorial chemistry, drug discovery, organic synthesis, and materials science.[13] Therefore, the use of MCRs has raised great attention from research groups working in these areas. Isocyanides are valuable synthons with interesting chemical properties,[14] and have been used widely in MCRs.[15] A subclass of MCR with an isocyanide base is known as the isocyanide multi-component reaction (IMCRs).[15] One IMCR, which was used to produce imidazo[1,2-*b*]azines using isocyanides, aldehydes, and 2-aminoazines and/or aminoazoles in the presence of acid catalysts was first reported by the Groebke, Blackburn, and Bienayme groups simultaneously in 1998.[16] The methodologies for this reaction have been developed by various groups, using different Bronsted and Lewis acid catalysts.[17] Also, various aminoazole rings, such as 2-aminobenzimidazole, 2-aminobenzthiazole, 2-aminothiadiazole, 2-aminothiadiazole, 3-aminotriazole, and 3-aminopyrazoles have been utilized for production of a wide range of products.[16c,18] Mikhail Krasavin, who has worked carefully on this reaction, proved that products of the reaction between of benzyl isocyanides, with 3-amino-1,2,4-triazole

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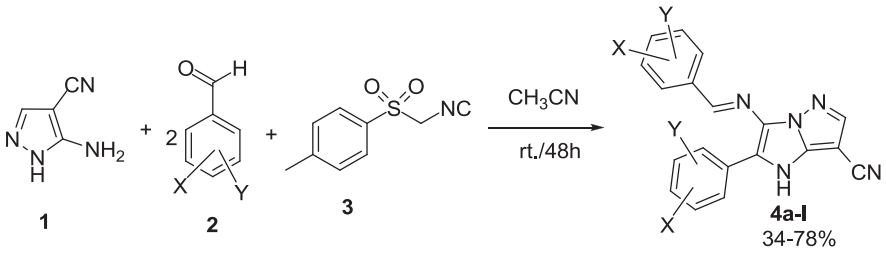
and aromatic aldehydes is different from others due to the oxidation of the product.[19] In addition, in another report he has showed that in the presence of trifluoroacetic acid (TFA), *N*-alkyl imidazo[1,2-*b*] azines are produced instead of *N*-acyl imidazo[1,2-*b*]azines.[20]

Recently, we have reported the synthesis of a new series of 5*H*-imidazo[1,2-*b*]pyrazoles using various aminopyrazoles, aromatic aldehydes, and isocyanides by the Groebke–Blackburn–Bienayme three-component reaction.[21] Our efforts in the continuation of this work, led to superior results, and we synthesized a novel series of these fused ring systems. By this method, we have developed an efficient method for the synthesis of 3-(benzylideneamino)-2-aryl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles (**4a**–**l**). In our work, a one-pot four-component condensation reaction was performed between 5-amino-1*H*-pyrazole-4-carbonitrile (**1**), 2 equiv of an aldehyde (**2**) and toluene-4-sulfonylmethyl isocyanide **3** using acetonitrile as solvent and *p*-toluenesulfonic acid as catalyst at room temperature (Scheme 1).



Scheme 1. Synthesis of 3-(arylideneamino)-2-aryl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles **4a**–**l**.

2. Results and discussions

Firstly, 5-amino-1*H*-pyrazole-4-carbonitrile (1 equiv) was treated with benzaldehyde (1 equiv) in acetonitrile in the presence of *p*-toluenesulfonic acid catalyst (10 mol %) at room temperature for 24 h. Then, 1 equiv of $TsCH_2NC$ (**3**) was added. After 48 h, monitoring of the reaction showed that a new product had been generated. Separation was performed by column chromatography and the yield of reaction was 23%. Spectroscopic data indicated that 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile **4a** was synthesized in a four-component reaction. In another reaction (in one-pot form) it was found that a good yield (54%) was obtained after 48 h. Next, various experiments were designed to optimize the reaction conditions.

To optimize the conditions for this four-component reaction, 5-amino-1*H*-pyrazole-4-carbonitrile (**1**), benzaldehyde (**2a**), and $TsCH_2NC$ (**3**) were selected as model reactants. Initially, different solvents in the presence and absence of *p*-TsOH at room temperature were utilized for investigation of solvent and catalytic effects (Table 1). The reactions were also performed under solvent free conditions (Table 1, entry 14). The results indicated that in solvent free conditions no yield was obtained, and among the different solvents acetonitrile was found to be the best solvent at room temperature (Table 1). The presence of the catalyst for this transformation was also found to be necessary (column 4, Table 1).

Next, in order to determine the best catalyst, a number of Lewis and Bronsted acids (10 mol %) were screened. The employed catalysts are listed in Table 2. The experiments showed that the highest yields were obtained using *p*-TsOH as catalyst. The optimum catalyst amount was next investigated by studying the reaction with different amounts of *p*-TsOH at room temperature. The best results were obtained in the presence of 20 mol % of *p*-TsOH. Results show that by reducing the amount of catalyst from 20 mol %, yields were decreased, while increasing the amount of *p*-TsOH did not have any effect on the yield of the reaction. The reaction was then repeated at various temperatures (entry 6, Table 2) in acetonitrile. The results showed that the best yields of reaction were obtained at room temperature.

To find out the scope and limitations of the reaction, we extended the procedure to use various substituted benzaldehydes in the presence of 3-amino-4-pyrazolecarbonitrile and toluene-4-sulfonylmethyl isocyanide (Table 3). The reactions proceeded with electron-withdrawing and electron-donating substituents in the *ortho*, *meta*, and *para* positions of the benzaldehydes.

It's worthy to note, when 2-hydroxybenzaldehyde was used, it was expected that a seven membered ring is formed. But, ^{1}H NMR and ^{13}C NMR spectra demonstrate that no seven membered ring has been produced. Both phenolic OH groups have been appeared in H NMR spectra while the formation of a seven membered ring product results in the appearance of one of them. Furthermore, not observation of the signal of amine group protons in H NMR and signal of a sp^3 carbon atom, which linked to oxygen and nitrogen in ^{13}C NMR are strong evidences for no formation of seven membered ring.

Table 1
Optimization of solvent type and effect of catalyst in synthesis of 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile[a]

Entry	Solvent	Yield[b,c] (%)	Yield[b,c,d] (%)
1	Water	0	0
2	Methanol	0	20
3	Ethanol	0	20
4	DMSO	0	18
5	DMF	0	21
6	Dioxane	0	50
7	THF	0	51
8	Acetonitrile	0	54
9	Ethyl acetate	0	18
10	Chloroform	0	10
11	Toluene	0	Trace
12	[bmim]Br	0	30
13	$[bmim]BF_4$	0	30
14	Solvent-free	0	0

[a] Benzaldehyde (2 mmol), $TsCH_2NC$ (1 mmol), 5-amino-1*H*-pyrazole-4-carbonitrile (1 mmol) in solvent (5 mL), 48 h.
[b] Isolated yield.
[c] Room temperature.
[d] In the presence of *p*-TsOH catalyst (10 mol %).

The structures of **4a**–**l** were deduced from their IR, ^{1}H NMR, ^{13}C NMR, Mass spectra, and elemental analyses. For example, the IR spectrum of **4g** showed absorptions at 3298 (NH), 2939 (CH_3), 2217 (CN), 1606 (C=N), 1509 (C=C), 1430 (bending CH_3), 1289 (C–N), 1269, and 1269 (C–N) cm^{-1}, indicating the presence of these functional groups in the proposed structure. The ^{1}H NMR spectrum of **4g** exhibited three singlets for the CH of imine group, the NH, and the CH on the pyrazole ring at δ=9.87, 12.45, and 8.24 ppm, respectively. Four doublets corresponding to the four aromatic hydrogen atoms appeared at δ=6.63 and 7.78 with *J* 8.8 Hz and at δ=6.73 and 7.86 with *J* 8.4 Hz as well as two singlets at δ=6.66 and 6.74 for the aromatic hydrogens. Four singlets at 3.91, 3.88, 3.86, and 3.84 ppm were identified as the methoxy groups in the aromatic rings. The ^{1}H decoupled ^{13}C NMR spectrum of **4g** showed 23

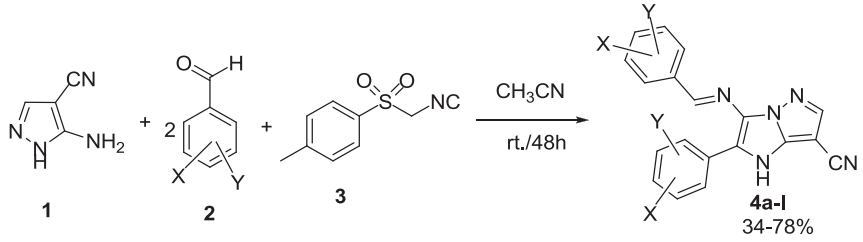
Table 2
Effects of catalyst types and catalyst amount in synthesis of 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile[a]

Entry	Catalyst	Amount (%)	Time (h)	Yield[b] (%)
1	AcOH	10 mol	48	38
2	CF_3CO_2H	10 mol	48	44
3	H_3PO_4 85%	10 mol	48	29
4	H_2SO_4 88%	10 mol	48	39
5	*p*-TsOH	40 mol	72	65
		20 mol	48	65
		20 mol	24	48
		20 mol	18	21
		20 mol	12	10
		20 mol	6	—
		10 mol	48	54
		5 mol	48	20
		3 mol	48	<5
6	*p*-TsOH	20 mol	48	<5[c]
		20 mol	48	Trace[d]

[a] Benzaldehyde (2 mmol), $TsCH_2NC$ (1 mmol), 5-amino-1*H*-pyrazole-4-carbonitrile (1 mmol) in acetonitrile (5 mL), rt.
[b] Isolated yield.
[c] Isolated yield 50 °C.
[d] Isolated yield reflux.

A proposed mechanism for the formation of the product **4** is provided in Scheme 3. It is reasonable to assume that the protonated Schiff base **5** is formed by adding benzaldehyde to the aminopyrazole solution in the presence of *p*-toluenesulfonic acid. Then, compound **6** is produced by a nonconcerted [4+1] cycloaddition reaction between protonated Schiff base **5** and isocyanide **3**, followed by tautomerization.[16] After that, intermediate **7** was obtained via oxidation of **6**.[19] After this stage, it is likely that imine group in intermediate **7** was protonated by *p*-toluenesulfonic acid and consequently intermediate **8** was generated. Following, by quenching with water, hemiaminal **9** was produced. Then, second hemiaminal **10** was generated via hydrolysis of hemiaminal **9**. Subsequently, by elimination of formaldehyde from hemiaminal **10**, 3-amino-2-phenyl-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile **11** is generated. Finally, the other benzaldehyde reacts with the amine group and generates the final product 3-(4-nitrobenzylidene amino)-2-(4-nitrophenyl)-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile **4**. We could not detect compound **10**, because this compound was converted to *p*-toluenesulfonic acid via an unknown mechanism; this subject was confirmed by an increase in the amount of catalyst at the end of reaction.

Table 3
Synthesis of 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles



Entry	X	Y	Product	Yield[a]	Mp (°C)
1	–H	–H	**4a**	65	195–196
2	4-CH_3	–H	**4b**	67	202–203
3	4-*iso*-Pr	–H	**4c**	34	232–233
4	4-OCH_3	–H	**4d**	76	220–221
5	3-OCH_3	–H	**4e**	65	223–224
6	2-OH	–H	**4f**	60	209–210
7	2-OCH_3	4-OCH_3	**4g**	61	251–252
8	3-OCH_3	4-OCH_3	**4h**	54	254–255
9	4-Cl	–H	**4i**	68	225–226
10	3-Br	–H	**4j**	76	266–267
11	3-NO_2	–H	**4k**	78	236–237
12	2-Cl	4-Cl	**4l**	69	254–255

[a] Isolated yield.

distinct resonances, in agreement with the suggested structures. Mass spectrum of **4g** showed the expected molecular-ion peak. Elemental analysis faithfully confirmed the amounts of C, H, and N in the final product. The spectral data for **4g** and other compounds are given in the Experimental section.

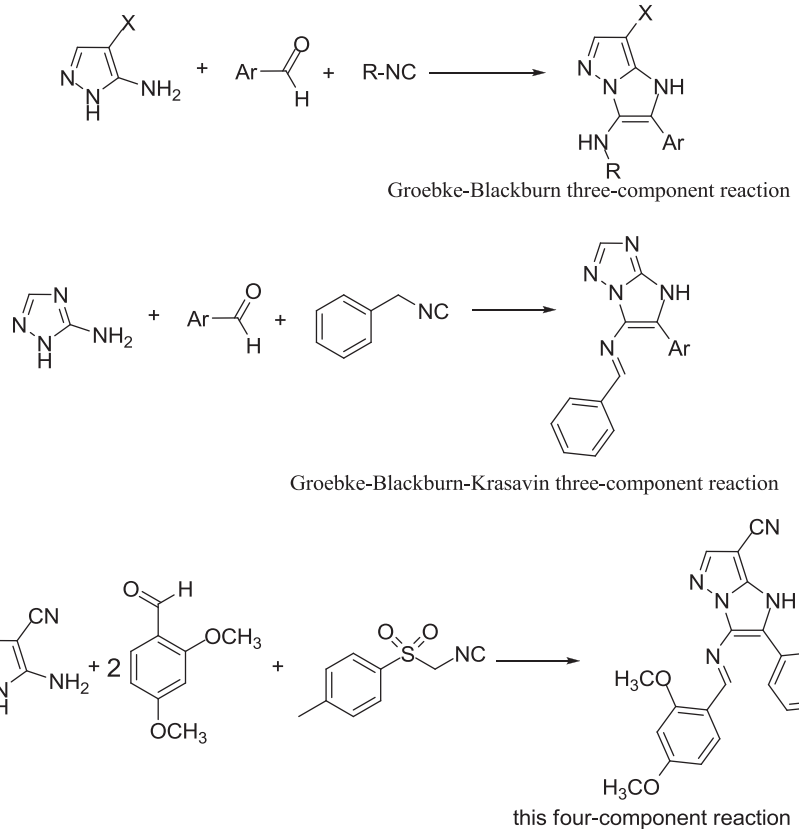
This work was done in continuation of the Groebke–Blackburn–Bienayme and Krasavin three-component reactions, and the products were similar to those reported by Krasavin (Scheme 2). This new isocyanide-based four-component strategy provides an efficient, simple, convenient, and applicable way for the synthesis of different types of 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazoles. In this synthetic method, readily available starting materials were used. Also inexpensive and unpleasant benzyl isocyanides have been replaced with $TsCH_2NC$ that is a solid isocyanide. Additionally, an imine group was generated, which could be important for other transformations.

In conclusion, a convenient and efficient one-pot four-component synthesis of 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles is reported from readily available and inexpensive starting materials, such as aldehydes, 3-amino-4-pyrazolecarbonitrile, and tosmic isocyanide. The 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles obtained in this study could also serve as valuable synthons for further elaboration into more complex compounds.

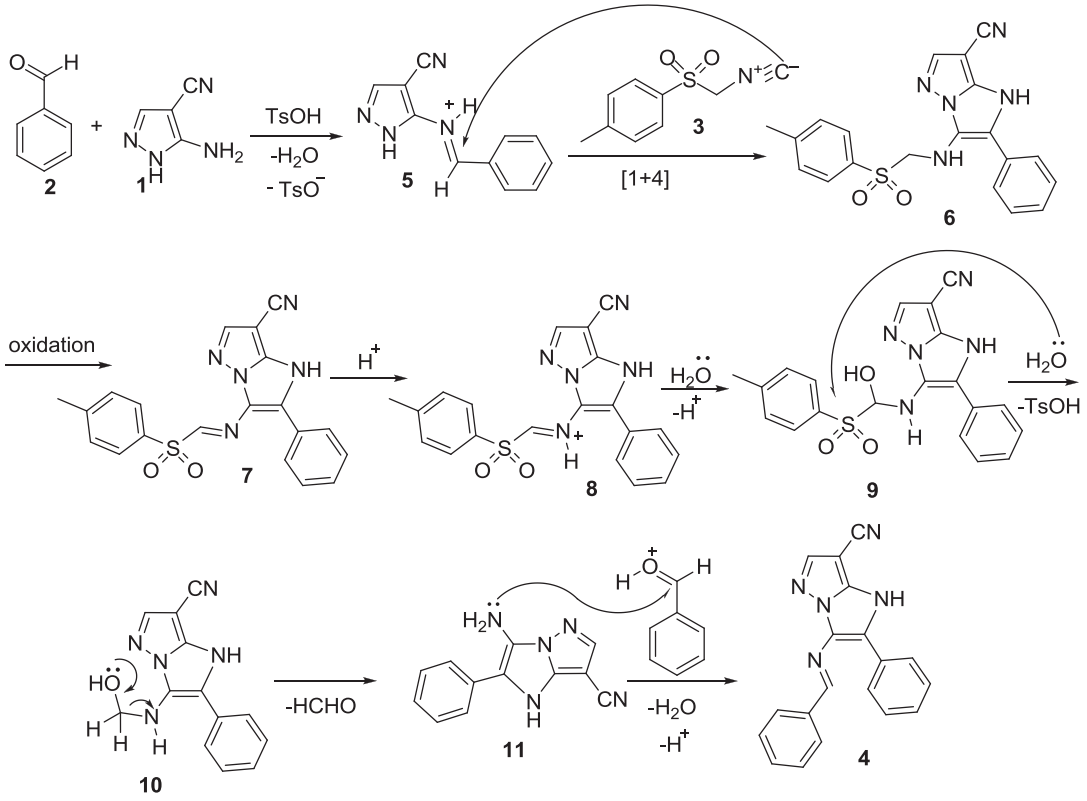
3. Experimental

3.1. General procedure

All chemicals were purchased from Acros and/or Alfa-Aesar companies and used without any further purification. Melting points were determined on an Electrothermal 9100 apparatus. IR



Scheme 2. Comparing this reaction with previous similar reports.



Scheme 3. Mechanism of the four-component reaction.

spectra were recorded on a FT Infrared Spectroscope instrument JASCO, FT/IR-6300 model as KBr discs. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-AVANCE 400 MHz NMR instrument using DMSO-d_6 as solvent. Mass spectra were recorded on a Shimadzu QP 1100 EX mass-Spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHNS Rapid analyzer.

3.2. General procedure for the synthesis of 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazoles (4a–l)

A solution of aldehyde (2 mmol), 3-aminopyrazole (1 mmol), and *p*-toluenesulfonic acid catalyst (20 mol %) in MeCN (5 mL) was magnetically stirred for 24 h in room temperature. Next $TsCH_2NC$ (1 mmol) was added and the reaction mixture was stirred for 24 h in room temperature. After completion of the reaction, which was followed by TLC EtOAc/petroleum ether 4:1, the reaction mixture was filtered, and the precipitate washed with methanol. Finally pure solid product was obtained by column chromatography.

3.3. Compounds characterization data

*3.3.1. 3-(Benzylideneamino)-2-phenyl-1H-imidazo[1,2-b]pyrazole-7-carbonitrile (**4a**).* Yellow powder (0.202 g, 65%); mp 195–196 °C; R_f (20% petroleum ether/EtOAc) 0.55; ν_{max} (KBr) 3242, 3197, 3057, 2224, 1623, 1483, 1197 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.12–8.16 (10H, m, 10CH$_{arom}$), 8.31 (1H, s, CH$_{pyrazole}$), 9.71 (1H, s, CH$_{imine}$), 13.19 (1H, s, NH$_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 66.48, 114.58, 125.47, 126.77, 127.18, 128.82, 129.05, 129.41, 129.55, 131.27, 135.20, 136.54, 139.49, 146.52, 155.76 ppm; *m*/*z* (EI, 70 eV) 311 (M$^+$, 87%); Anal. Found: C, 73.09; H, 4.09; N, 22.38. $C_{19}H_{13}N_5$ requires C, 73.30; H, 4.21; N, 22.49.

*3.3.2. 3-(4-Methylbenzylideneamino)-2-p-tolyl-5H-imidazo[1,2-b]pyrazole-7-carbonitrile (**4b**).* Cream powder (0.220 g, 65%); mp 202–203 °C; R_f (20% petroleum ether/EtOAc) 0.60; ν_{max} (KBr) 3242, 3171, 3055, 2918, 2223, 1620, 1480, 1196, 818 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.37 (6H, s, 2CH$_3$), 7.31 (2H, d, ^3J 8.0 Hz, 2CH$_{arom}$), 7.35 (2H, d, ^3J 8.0 Hz, 2CH$_{arom}$), 7.77 (2H, d, ^3J 8.0 Hz, 2CH$_{arom}$), 8.00 (2H, d, ^3J 8.0 Hz, 2CH$_{arom}$), 8.31 (1H, s, CH$_{pyrazole}$), 9.70 (1H, s, CH$_{imine}$), 13.03 (1H, s, NH$_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 20.85, 21.17, 66.33, 114.62, 124.80, 126.06, 126.69, 126.99, 128.02, 129.35, 129.61, 134.02, 138.08, 139.29, 141.29, 146.26, 155.24 ppm; *m*/*z* (EI, 70 eV) 339 (M$^+$, 44%). Anal. Found: C, 74.49; H, 5.09; N, 20.80. $C_{21}H_{17}N_5$ requires C, 74.32; H, 5.05; N, 20.63.

*3.3.3. 3-(4-Isopropylbenzylideneamino)-2-(4-isopropylphenyl)-5H-imidazo[1,2-b]pyrazole-7-carbonitrile (**4c**).* Orange powder (0.134 g, 34%); mp 232–233 °C; R_f (20% petroleum ether/EtOAc) 0.60; ν_{max} (KBr) 3269, 3214, 2981, 2223, 1628, 1597, 1509, 1480, 1339 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.27 (6H, d, ^3J 7.2 Hz, 2CH$_3$), 1.31 (6H, d, ^3J 7.2 Hz, 2CH$_3$), 2.93–3.02 (2H, m, 2CH), 7.41 (2H, d, ^3J 8.2 Hz, 2CH$_{arom}$), 7.45 (2H, d, ^3J 8.2 Hz, 2CH$_{arom}$), 7.88 (2H, d, ^3J 8.2 Hz, 2CH$_{arom}$), 8.07 (2H, d, ^3J 8.2 Hz, 2CH$_{arom}$), 8.27 (1H, s, 1CH$_{pyrazole}$), 9.65 (1H, s, CH$_{imine}$), 13.08 (1H, br s, NH$_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 23.58, 23.68, 33.27, 33.47, 66.32, 114.76, 124.87, 126.66, 126.74, 127.04, 127.12, 128.17, 134.54, 139.53, 146.32, 148.85, 151.95, 154.97; *m*/*z* (EI, 70 eV) 395 (M$^+$, 100%); Anal. Found: C, 76.05; H, 6.29; N, 17.80. $C_{25}H_{25}N_5$ requires C, 75.92; H, 6.37; N, 17.71.

*3.3.4. 3-(4-Methoxybenzylideneamino)-2-(4-methoxyphenyl)-5H-imidazo[1,2-b]pyrazole-7-carbonitrile (**4d**).* Yellow powder (0.282 g, 76%); mp 221–221 °C; R_f (20% petroleum ether/EtOAc) 0.53; ν_{max} (KBr) 3243, 3173, 2932, 2223, 1612, 1507, 1253, 1181, 1166, 1035, 837 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.84 (6H, s, 2OMe), 7.07 (2H, d, ^3J 7.6 Hz, 2CH$_{arom}$), 7.13 (2H, d, ^3J 7.6 Hz, 2CH$_{arom}$), 7.86 (2H, d, ^3J 7.6 Hz, 2CH$_{arom}$), 8.08 (2H, d, ^3J 7.6 Hz, 2CH$_{arom}$), 8.24 (1H, s, CH$_{pyrazole}$), 9.58 (1H, s, CH$_{imine}$), 12.93 (1H, s, NH$_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 55.26, 55.38, 66.20, 114.31, 114.53, 114.76, 121.44, 124.47, 126.04, 128.41, 129.50, 129.79, 139.10, 146.12, 154.41, 159.31, 161.70 ppm; *m*/*z* (EI, 70 eV) 371 (M$^+$, 74%); Anal. Found: C, 67.80; H, 4.59; N, 18.92. $C_{21}H_{17}N_5O_2$ requires C, 67.91; H, 4.61; N, 18.86.

*3.3.5. 3-(3-Methoxybenzylideneamino)-2-(3-methoxyphenyl)-5H-imidazo[1,2-b]pyrazole-7-carbonitrile (**4e**).* Yellow powder (0.241 g, 65%); mp 223–224 °C; R_f (20% petroleum ether/EtOAc) 0.53; ν_{max} (KBr) 3253, 3170, 2938, 2230, 1630, 1569, 1489, 1468, 1280, 1241, 1207, 1040, 778 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.83 (3H, s, OMe), 3.86 (3H, s, OMe), 6.98–7.77 (8H, m, CH$_{arom}$), 8.27 (1H, s, CH$_{pyrazole}$), 9.60 (1H, s, CH$_{imine}$), 13.13 (1H, s, NH$_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 55.08, 55.20, 66.45, 111.88, 112.20, 114.53, 114.57, 117.52, 119.35, 120.94, 125.02, 126.73, 129.88, 129.99, 130.13, 138.01, 139.44, 146.54, 155.46, 159.35, 159.64 ppm; *m*/*z* (EI, 70 eV) 371 (M$^+$, 90%); Anal. Found: C, 67.79; H, 4.58; N, 18.88. $C_{21}H_{17}N_5O_2$ requires C, 67.91; H, 4.61; N, 18.86.

*3.3.6. 3-(2-Hydroxybenzylideneamino)-2-(2-hydroxyphenyl)-5H-imidazo[1,2-b]pyrazple-7-carbonitrile (**4f**).* Cream powder (0.206 g, 60%); mp 209–210 °C; R_f (20% petroleum ether/EtOAc) 0.45; ν_{max} (KBr) 3270, 3099, 2224, 1622, 1596, 1485, 1457, 1193, 746 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.91–7.66 (8H, m, CH$_{arom}$), 8.31 (1H, s, CH$_{pyrazole}$), 9.77 (1H, s, CH$_{imine}$), 10.50 (1H, s, OH), 11.67 (1H, s, OH), 12.96 (1H, s, NH$_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 66.35, 114.71, 115.09, 116.42, 116.55, 117.17, 119.26, 119.46, 119.57, 120.67, 129.18, 130.13, 130.77, 132.73, 136.41, 146.42, 154.98, 155.18, 158.72 ppm; *m*/*z* (EI, 70 eV) 343 (M$^+$, 91%); Anal. Found: C, 66.53; H, 3.80; N, 20.29. $C_{19}H_{13}N_5O_2$ requires C, 66.47; H, 3.82; N, 20.40.

*3.3.7. 3-(2,4-Dimethoxybenzylideamino)-2-(2,4-dimethoxyphenyl)-5H-imidazo[1,2-b]pyrazole-7-carbonitrile (**4g**).* Yellow powder (0.263 g, 61%); mp 251–252 °C; R_f (20% petroleum ether/EtOAc) 0.50; ν_{max} (KBr) 3414, 3298, 2939, 2835, 2217, 1606, 1508, 1267, 1211, 1030 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.84 (3H, s, OMe), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 3.91 (3H, s, OMe), 6.63–6.74 (4H, m, 4CH$_{arom}$), 7.78 (1H, d, ^3J 8.4 Hz, 1CH$_{arom}$), 7.86 (1H, d, ^3J 8.8 Hz, 1CH$_{arom}$), 8.24 (1H, s, CH$_{pyrazole}$), 9.87 (1H, s, CH$_{imine}$), 12.45 (1H, s, NH$_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 55.42, 55.48, 55.71, 55.83, 65.87, 97.95, 98.50, 105.32, 106.77, 109.70, 115.02, 118.03, 123.89, 125.68, 127.21, 132.96, 138.25, 146.17, 149.84, 157.95, 160.38, 161.27, 163.26 ppm; *m*/*z* (EI, 70 eV) 431 (M$^+$, 100%); Anal. Found: C, 64.16; H, 4.96; N, 16.31. $C_{23}H_{21}N_5O_4$ requires C, 64.03; H, 4.91; N, 16.23.

*3.3.8. 3-(3,4-Dimethoxybenzylideamino)-2-(3,4-dimethoxyphenyl)-5H-imidazo[1,2-b]pyrazole-7-carbonitrile (**4h**).* Yellow powder (0.233 g, 54%); mp 254–255 °C; R_f (20% petroleum ether/EtOAc) 0.50; ν_{max} (KBr) 3253, 3202, 2939, 2833, 2226, 1630, 1507, 1483, 1264, 1232, 1023 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.84 (6H, s, 2OMe), 3.89 (3H, s, OMe), 3.89 (3H, s, OMe), 7.10 (1H, d, ^3J 8.4 Hz, CH$_{arom}$), 7.14 (1H, d, ^3J 8.5 Hz, CH$_{arom}$), 7.46 (1H, dd, ^3J 8.4 Hz, ^4J 1.4 Hz, CH$_{arom}$), 7.49 (1H, d, ^4J 1.4 Hz, CH$_{arom}$), 7.70 (1H, dd, ^3J 8.5 Hz, ^4J 1.8 Hz, CH$_{arom}$), 7.83 (1H, d, ^4J 1.8 Hz, CH$_{arom}$), 8.25 (1H, s, CH$_{pyrazole}$), 9.60 (1H, s, CH$_{imine}$), 12.95 (1H, s, NH$_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 55.32, 55.48, 55.55, 55.63, 66.16, 109.13, 110.34, 111.63, 111.84, 114.77, 119.66, 121.54, 122.88, 124.61, 129.58, 139.10, 146.12, 148.65, 149.03, 149.12, 151.66, 154.87 ppm; *m*/*z* (EI, 70 eV) 431 (M$^+$, 3%); Anal. Found: C, 64.19; H, 4.93; N, 16.19. $C_{23}H_{21}N_5O_4$ requires C, 64.03; H, 4.91; N, 16.23.

*3.3.9. 3-(4-Chlorobenzylideneamino)-2-(4-chlorophenyl)-5H-imidazo[1,2-b]pyrazole-7-carbonitrile (**4i**).* Yellow powder (0.254 g, 67%); mp 225–226 °C; R_f (20% petroleum ether/EtOAc) 0.55; ν_{max}

(KBr) 3271, 3221, 3051, 2224, 1623, 1501, 1486, 1268, 1132, 815 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.43 (2H, d, ^3J 7.3 Hz, $2CH_{arom}$), 7.47 (2H, d, ^3J 7.3 Hz, $2CH_{arom}$), 7.72 (2H, d, ^3J 7.2 Hz, $2CH_{arom}$), 7.98 (2H, d, ^3J 7.3 Hz, $2CH_{arom}$), 8.15 (1H, s, $CH_{pyrazole}$), 9.40 (1H, s, CH_{imine}), 13.05 (1H, s, $NH_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 67.02, 114.85, 125.37, 126.31, 127.93, 128.96, 129.11, 129.34, 129.93, 133.55, 135.57, 136.18, 139.85, 146.84, 154.79 ppm; *m*/*z* (EI, 70 eV) 383 (M^++4, 1), 381 (M^++2, 4), 379 (M^+, 7%); Anal. Found: C, 60.21; H, 2.96; N, 18.38. $C_{19}H_{11}Cl_2N_5$ requires C, 60.02; H, 2.92; N, 18.42.

*3.3.10. 3-(3-Bromobenzylideamino)-2-(3-bromophenyl)-5H-imidazo [1,2-b]pyrazole-7-carbonitrile (**4j**).* Yellow powder (0.356 g, 76%); mp 266–267 °C; R_f (20% petroleum ether/EtOAc) 0.55; ν_{max} (KBr) 3236, 3183, 3057, 2226, 1619, 1449, 1194, 774, 672 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.44–8.26 (8H, m, $3CH_{arom}$), 8.37 (1H, s, $CH_{pyrazole}$), 9.49 (1H, s, CH_{imine}), 13.30 (1H, br s, $NH_{pyrazole}$) ppm. δ_C (100 MHz, DMSO-d_6) 66.66, 114.38, 122.01, 122.45, 125.04, 125.65, 125.89, 127.49, 129.63, 129.76, 130.81, 130.85, 131.01, 131.10, 133.73, 138.65, 139.73, 146.70, 154.13 ppm; *m*/*z* (EI, 70 eV) 471 (M^++4, 1), 469 (M^++2, 2), 467 (M^+, 1%); Anal. Found: C, 48.41; H, 2.35; N, 14.87. $C_{19}H_{11}Br_2N_5$ requires C, 48.64; H, 2.36; N, 14.93.

*3.3.11. 3-(3-Nitrobenzylideamino)-2-(3-nitrophenyl)-5H-imidazo [1,2-b]pyrazole-7-carbonitrile (**4k**).* Yellow powder (0.313 g, 78%); mp 236–237 °C; R_f (20% petroleum ether/EtOAc) 0.48; ν_{max} (KBr) 3236, 3109, 2239, 1622, 1529, 1354, 1182, 808, 678 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.51–8.18 (8H, m, $8CH_{arom}$), 8.24 (1H, s, $CH_{pyrazole}$), 9.20 (1H, s, CH_{imine}), 13.08 (1H, br s, $NH_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 66.70, 113.97, 120.93, 121.48, 122.30, 124.93, 125.16, 129.77, 129.86, 130.26, 131.57, 133.71, 137.34, 139.54, 146.63, 147.48, 147.94, 153.38 ppm; *m*/*z* (EI, 70 eV) 371 (M^+−30, 1%); Anal. Found: C, 56.99; H, 2.78; N, 24.34. $C_{19}H_{11}N_7O_4$ requires C, 56.86; H, 2.76; N, 24.43.

*3.3.12. 3-(2,4-Dichlorobenzylideamino)-2-(2,4-dichlorophenyl)-5H-imidazo[1,2-b]pyrazole-7-carbonitrile (**4l**).* Yellow powder (0.310 g, 69%); mp 254–255 °C; R_f (20% petroleum ether/EtOAc) 0.58; ν_{max} (KBr) 3219, 3172, 3099, 2234, 1617, 1589, 1436, 1102, 864 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.52 (1H, dd, ^3J 8.6 Hz, ^4J 1.8 Hz, CH_{arom}), 7.66 (1H, dd, ^3J 8.4 Hz, ^4J 2.0 Hz, CH_{arom}), 7.76 (1H, d, ^4J 2.0 Hz, CH_{arom}), 7.77 (1H, d, ^3J 8.4 Hz, CH_{arom}), 7.90 (1H, d, ^4J 1.8 Hz, CH_{arom}), 7.65 (1H, d, ^3J 8.6 Hz, CH_{arom}), 8.37 (1H, s, $CH_{pyrazole}$), 9.93 (1H, s, CH_{imine}), 13.50 (1H, br s, $NH_{pyrazole}$) ppm; δ_C (100 MHz, DMSO-d_6) 66.75, 114.33, 126.18, 127.57, 128.15, 128.37, 129.59, 129.63, 132.23, 134.09, 134.79, 135.29, 135.35, 136.33, 138.80, 139.60, 146.89, 150.58 ppm; *m*/*z* (EI, 70 eV) 455 (M^++8, 1), 453 (M^++6, 19), 451 (M^++4, 79) 449 (M^++2, 97), 447 (M^+, 90%); Anal. Found: C, 50.63; H, 2.00; N, 15.64. $C_{19}H_9Cl_4N_5$ requires C, 50.81; H, 2.02; N, 15.59.

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