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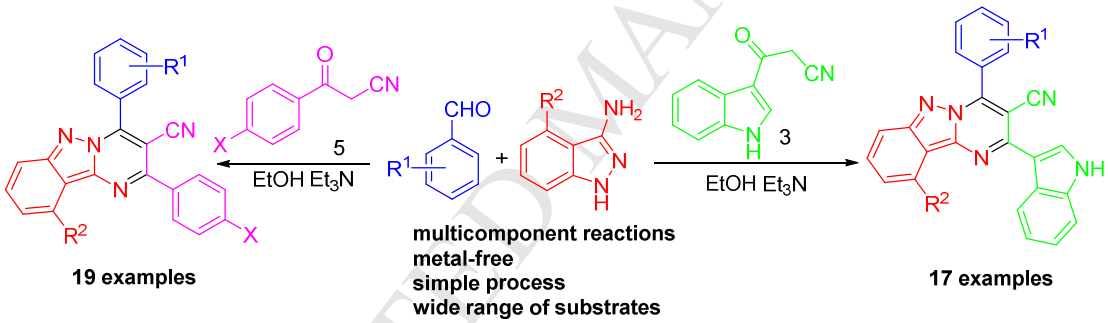

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Abstract An efficient metal-free cascade reaction to synthesize novel pyrimido[1,2-*b*]indazole-3-carbonitrile derivatives was reported. The reaction starts from aromatic aldehydes, 1*H*-indazol-3-amine (4-chloro-1*H*-indazol-3-amine), and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile or 3-oxo-3-arylpro-panenitrile in the presence of ethanol and triethylamine under plain laboratory conditions. The reaction was easy to operate with good tolerance to substrates in high yield.

Keywords Pyrimido[1,2-*b*]indazole, Indole, 1*H*-indazol-3-amine, Triethylamine, Multicomponent reactions

1. Introduction

Multicomponent reactions (MCRs) mean that the three or more reactants react and convert them into the diversity molecules with one-pot process.[1-7] More attention has been paid on this synthetic method because of simple set-up, atom economy, and high yield. Recently, various MCRs have efficiently constructed nitrogen-bearing heterocyclic compounds which have biological and pharmacoligical activities.[8-10] The nucleus structure of 3-substituted indole is prevalent in natural products and is very important in medicinal chemistry also.[11,12] Compounds with these structures have many important bioactivities, such as anticancer, anti-tumour,[13] anti-inflammatory, decreasing hypoglycemic, analgesic effective and anti-pyretic effects.[14] The pyrazolo[1,5-*a*]pyrimidine derivatives show antimicrobial, antibacterial, antitrichomonal,

antischistosomal, anticancer, and antitumor properties.[15] Several marketed drugs, such as divaplon, taniplon, and fasiplon, have pyrazolo[1,5-*a*]pyrimidine motifs in their main core structure (Fig. 1)[16].

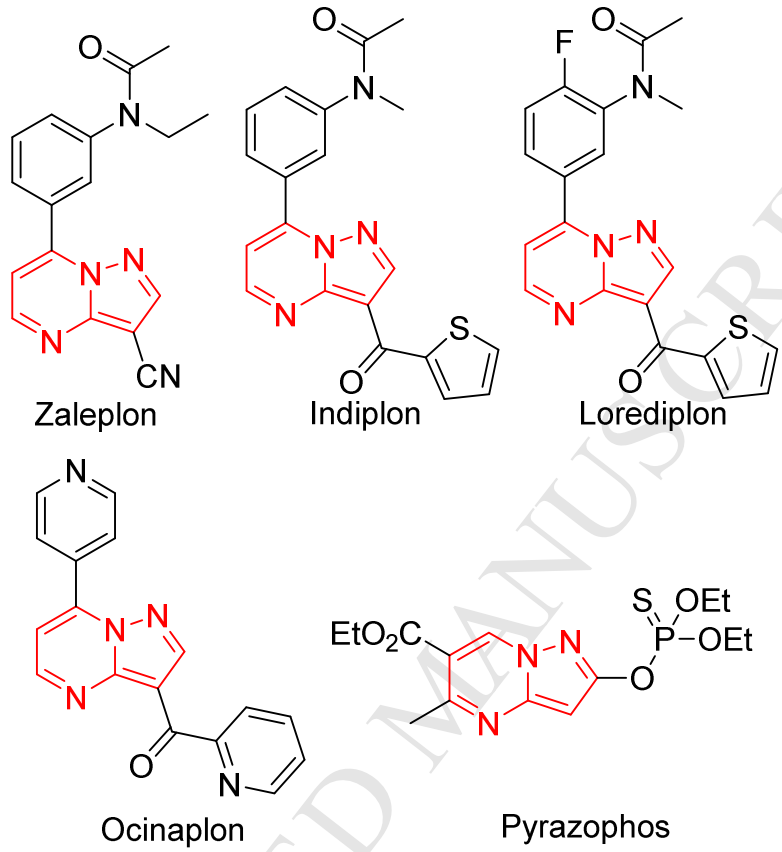


Figure 1. The active compounds with pyrazolo[1,5-*a*]pyrimidine nucleus.

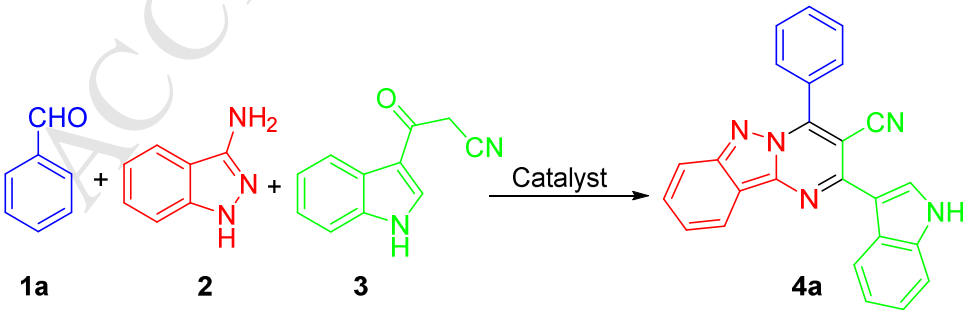
Pyrimido[1,2-*b*]indazole scaffolds being like pyrazolo[1,5-*a*]pyrimidine nucleus in their central motifs are the important nitrogen-bearing heterocyclic compounds. These compounds also have some interesting biological properties, for examples, they can be used as anticancer and protein kinase inhibitors. Some medicines with the main structures of pyrimido[1,2-*b*] indazole can treat a variety of ailments.[17]

It was found that 1*H*-indazol-3-amine was an efficient reagent for the synthesis of pyrimido[1,2-*b*]indazole derivatives. As far as we know, only two research groups have synthesized some pyrimido[1,2-*b*]indazole derivatives from 1*H*-indazol-3-amine, successfully. Jeong's group has synthesized pyrimido[1,2-*b*]indazole derivatives from a three-component reaction of 1*H*-indazol-3-amine, aldehydes, and malononitrile.[18] They used 1*H*-indazol-3-amine, aldehydes and 1,3-dicarbonyl staring material to give the similar compounds.[19] Recently, the

reaction of 4-hydroxy-2*H*-chromen-2-one, isatin, and 1*H*-indazole-3-amine was also reported by this group.[20] Palaniraja's group published three papers about the reaction making pyrimido[1,2-*b*]indazole derivatives.[21] Considering the importance of 3-substituted indole and pyrimido[1,2-*b*]indazole, we plan to synthesize novel compounds with both pyrimido[1,2-*b*]indazole and 3-substituted indole scaffolds from aromatic aldehydes, 1*H*-indazol-3-amine, and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile.

2. Results and Discussion

At the beginning of this research, we employed benzaldehyde (**1a**), 1*H*-indazol-3-amine (**2**), and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **3** as the substrates to optimize this reaction conditions (Scheme **1**). First, proton acid hydrated p-toluene sulphonic acid (PTSA·H_2O) and Lewis acid ($FeCl_3$) were selected to evaluate the acidic catalysts on the model reaction. Showing different from the reported methods,[19] acidic catalysts have no catalytic effect (Table 1, entries 1-2). Next, we tested the base catalysts. Organic base (DBU, piperidine, DMAP, Et_3N) and inorganic base (such as KOH, NaOH, K_2CO_3, and Na_2CO_3) was used. The results showed that the organic alkalis had a good catalytic effect (Table 1, entries 3-6), while the inorganic strong bases (KOH, NaOH) had a weak catalytic effect (Table 1, entries 7-8). However, the inorganic weak bases (K_2CO_3, Na_2CO_3) could not provide target product (Table 1, entries 9-10). Of all the catalysts, triethylamine had the best catalytic capacity. Next, the influence of the reaction time, temperature, and catalyst loading were investigated (Table 1, entries 11-18). Finally, the optimum condition was obtained as follows: EtOH as solvent, 20 mol % catalyst loading, 80 ^{o}C, and about 5 h reaction time (Table 1, entry 16). The results were listed in Table **1**.



Scheme 1. The model reaction of benzaldehyde, 1*H*-indazol-3-amine, and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile.

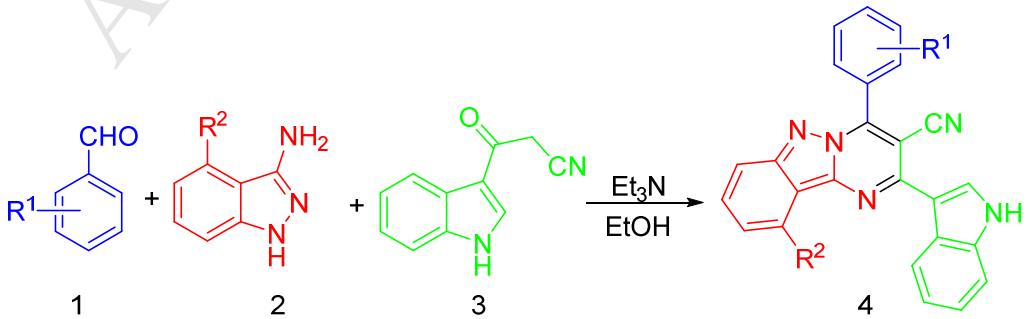
Table 1 Condition optimization for the reaction between benzaldehyde, 1*H*-indazol-3-amine, and

3-(1*H*-indol-3-yl)-3-oxopropanenitrile[a].

Entry	Solvent	Catalyst (mol%)	Temp. °C	Time (h)	Yields (%)[b]
1	CH_3CN	PTSA H_2O (30)	80	3	0
2	CH_3CN	$FeCl_3$ (30)	80	3	0
3	CH_3CN	DBU (30)	80	3	30
4	CH_3CN	Piperidine (30)	80	3	41
5	CH_3CN	DMAP (30)	80	3	15
6	CH_3CN	Et_3N (30)	80	3	76
7	CH_3CN	KOH (30)	80	3	25
8	CH_3CN	NaOH (30)	80	3	28
9	CH_3CN	K_2CO_3 (30)	80	3	trace
10	CH_3CN	Na_2CO_3 (30)	80	3	trace
11	CH_3OH	Et_3N (30)	80	3	56
12	EtOH	Et_3N(30)	80	3	85
13	THF	Et_3N (30)	80	3	42
14	EtOH	Et_3N (20)	80	3	82
15	EtOH	Et_3N (10)	80	3	67
16	EtOH	Et_3N (20)	80	5	91
17	EtOH	Et_3N (20)	80	7	90
18	EtOH	Et_3N (20)	60	7	52

[a]Reaction condition: Reagent: benzaldehyde **1a** (1 mmol), 1*H*-indazol-3-amine **2** (1 mmol), and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **3** (1 mmol), solvent (8 mL).
[b]Isolated Yields

With the optimized reaction conditions in hand, we next expanded the model reaction of different aromatic aldehydes with 1*H*-indazol-3-amines and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (Scheme **2**). It was found that both electron-donating (OH, Me, MeO) and electron-withdrawing (F, Cl, Br, NO_2) substituents of aromatic aldehydes worked well, giving the desired compounds **4a**−**4l** in good yields. 4-Pyridylformaldehyde could be applied to this method too, and the corresponding product **4m** was obtained in 85% yield. In addition, 4-chloro-1*H*-indazol-3- amine was also explored, and the corresponding products **4n**-**4q** were obtained with high yields. The results were summarized in Table **2**.



Scheme 2. The reactions of aromatic aldehydes, (substituted) 1*H*-indazol-3-amine, and

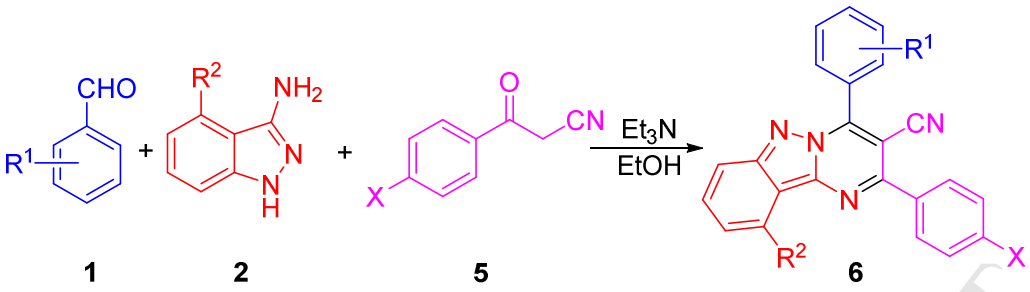
3-(1*H*-indol-3-yl)-3-oxopropanenitrile.

Table 2 Three-component reactions of aromatic aldehydes, (substituted) 1*H*-indazol-3-amine, and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile[a].

Entry	R^1	R^2	Compounds	Yields (%)[b]
1	1-H	H	**4a**	91
2	4-F	H	**4b**	90
3	4-Cl	H	**4c**	89
4	3,4-Cl_2	H	**4d**	90
5	4-Br	H	**4e**	88
6	4-NO_2	H	**4f**	92
7	4-OH	H	**4g**	91
8	4-CH_3	H	**4h**	87
9	3-CH_3O	H	**4i**	89
10	4-CH_3O	H	**4j**	90
11	3,4-OCH_2O	H	**4k**	86
12	3,4,5-$(CH_3O)_3$	H	**4l**	87
13	4-pyridyl	H	**4m**	85
14	4-F	Cl	**4n**	82
15	4-OH	Cl	**4o**	89
16	4-CH_3	Cl	**4p**	85
17	4-CH_3O	Cl	**4q**	88

[a]Reaction method: aromatic aldehydes (1 mmol), 1*H*-indazol-3-amine (4-chloro-1*H*-indazol-3-amine) (1 mmol), and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (1 mmol), EtOH (8 mL), Et_3N (0.2 mmol), 80 ^oC, reaction time (3-5 h) (monitored reactions by TLC).
[b]Isolated Yields

In order to obtain more pyrimido[1,2-*b*]indazole derivatives, 3-oxo-3-arylpropanenitrile was also applied in our synthesis. Under screened conditions, the reactions of different aromatic aldehydes,1*H*-indazol-3-amine and 3-oxo-3-arylpropanenitrile were performed very well and the 2,4-diaryl-3,4-dihydropyrimido[1,2-*b*]indazole-3-carbonitrile products **6a**-**6p** were obtained with high yields (Scheme **3**). Simultaneously, this reaction was also effective to the staring material of 4-chloro-1*H*-indazol-3-amine, and the corresponding products **6q**-**6s** were synthesized under screened conditions. The results were listed in Table **3**.



Scheme 3. The reactions of aromatic aldehydes, (substituted) 1*H*-indazol-3-amine, and 3-oxo-3-arylpropanenitrile.

Table 3 Three-component reactions of aromatic aldehydes, (substituted) 1*H*-indazol-3-amine, and 3-oxo-3-arylpropanenitrile[a]

Entry	R^1	R^2	X	Compounds	Yields (%)[b]
1	H	H	H	**6a**	86
2	3-CH_3	H	H	**6b**	89
3	4-CH_3	H	H	**6c**	87
4	3,4-$(CH_3)_2$	H	H	**6d**	83
5	4-OH	H	H	**6e**	90
6	4-CH_3O	H	H	**6f**	89
7	3,4,5-$(CH_3O)_3$	H	H	**6g**	86
8	3,4-Cl_2	H	H	**6h**	83
9	4-OH	H	F	**6i**	88
10	4-CH_3	H	F	**6j**	81
11	4-OH	H	Cl	**6k**	87
12	3-CH_3	H	Cl	**6l**	80
13	4-CH_3	H	Cl	**6m**	84
14	3-CH_3O	H	Cl	**6n**	88
15	4-CH_3O	H	Cl	**6o**	83
16	3,4,5-$(CH_3O)_3$	H	Cl	**6p**	80
17	4-OH	Cl	H	**6q**	91
18	4-CH_3	Cl	H	**6r**	88
19	4-CH_3O	Cl	H	**6s**	89

[a]Reaction method: aromatic aldehydes (1 mmol), 1*H*-indazol-3-amine (4-chloro-1*H*-indazol-3-amine) (1 mmol), and 3-oxo-3-arylpropanenitrile (1 mmol), EtOH (8 mL), Et_3N (0.2 mmol), 80 ^oC, reaction time (3-5 h) (monitored reactions by TLC).
[b]Isolated Yields

The products structures were determined by IR, ^{1}HNMR, and ^{13}C NMR, and HRMS analysis (see in Supporting Information). In their IR, the signal of cyano group (-CN) were found, but the signal of amino group (-NH_2) (Supporting information, Fig. 75) disappeared, which means the products are different from that data of literature.[18] In accordance with the result, a possible mechanism was provided in Figure **2**. Firstly, the Knoevenagel product **A** of aldehyde and

3-(1*H*-indol-3-yl)-3-oxopropanenitrile was formed in EtOH with Et_3N as a catalyst. Then, it maybe has two approaches to reacting with 1*H*-indazol-3-amine. In path **a**, the amino group of 1*H*-indazol-3-amine reacted with the carbonyl group of **A** to give imine intermediate **B**. Intermediate **C** is the tautomer of **B**, and then, **D** was formed from the intramolecular cyclization of intermediate **C**. At last, products **4** were obtained after an oxidation reaction. If the reaction was operated as path **b**, it could give a structure similar to that of the literature.[18] However, we did not find this structure.

In order to test our hypothesis, the reaction of benzaldehyde **4a** and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **3** were first performed and the condensation product **7** (Supporting information, Fig. 73, 74) was obtained. Then, the reaction of **7** and 1*H*-indazol-3-amine was carried out under screened condition. As expected, the product **4a** could be successfully obtained with 90% yield (Scheme **4**). The results fully proved our proposed mechanism.

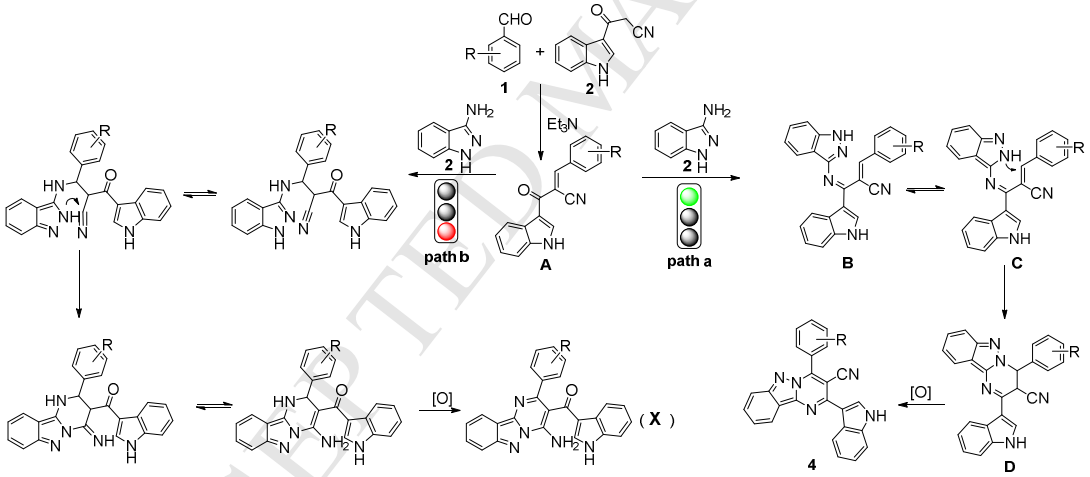
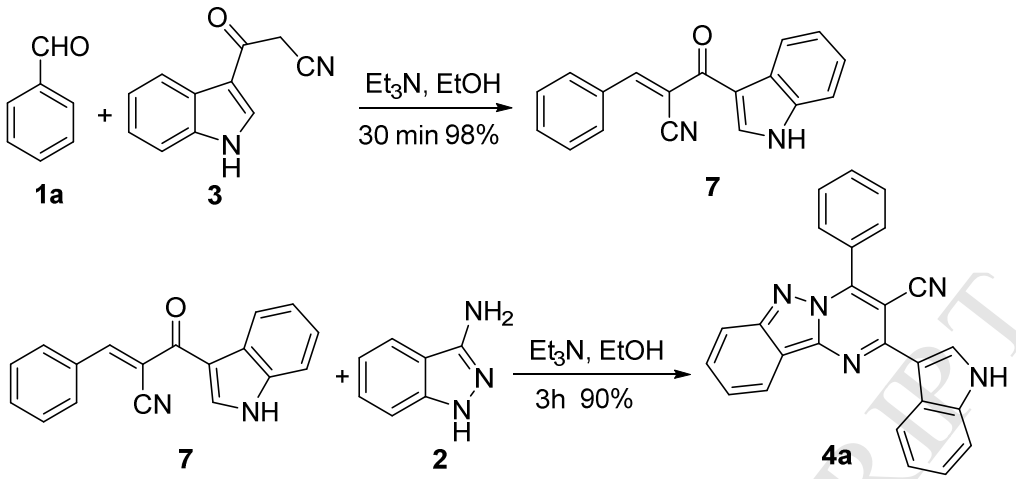


Figure 2. The possible reaction mechanism.



Scheme 4. The controlled reaction of **4a**.

3. Conclusion

In conclusion, we have reported a facile and efficient cascade reactions for the synthesis of pyrimido[1,2-*b*]indazole-3-carbonitrile derivatives from aromatic aldehyde, 1*H*-indazol-3-amine (4-chloro-1*H*-indazol-3-amine), and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile or 3-oxo-3-arylpropanenitrile under metal-free conditions. It was a very successful process for the construction of pyrimido[1,2-*b*]indazole compounds under plain laboratory conditions. This synthetic path was novel as compared to the reported literature. This reaction has the advantages of simple operation, high yields, easy isolation and wide scope substrates.

4. Experimental

4.1 General methods

All reagents were purchased from the Merck and Sigma-Aldrich chemical companies and used without further purification. Melting points were determined on XT-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a FT Bruker Tensor 27 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained from solution in DMSO-d_6 (or $CDCl_3$ or DMSO-d_6 : $CDCl_3$ = 9:1) using a Bruker-400 spectrometer. HRMS spectra were obtained with a Bruker microTOF-Q 134 instrument.

4.2 General procedure for the synthesis of pyrimido[1,2-*b*]indazole-3-carbonitrile dericatives

The mixture of aromatic aldehyde (1 mmol), 1*H*-indazol-3-amine (4-chloro-1*H*-indazol-3-amine) (1 mmol), and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile or 3-oxo-3-arylpropanenitrile (1 mmol), 95% EtOH (8 mL), Et_3N (0.2 mmol) was put in a reaction

flask under 80 ^{o}C about 3–5 h (monitored by TLC). After the completion of the reaction, the reaction mixture was cooled to room temperature and the products could be precipitated out from solvent. Then, compound **4** and **6** were recrystallized from DMF or EtOH.

*4.2.1 2-(1H-indol-3-yl)-4-phenylpyrimido[1,2-b]indazole-3-carbonitrile (**4a**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.42 (s, 1H), 8.62 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 1,2 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.76 – 7.60 (m, 6H), 7.37 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 154.5, 151.9 147.5, 143.2, 136.8, 136.2, 133.4, 131.0, 130.4, 129.4, 128.5, 125.2, 122.6, 122.2, 121.8, 121.1, 120.6, 117.4, 116.8, 113.4, 112.6, 103.5, 95.6; IR (KBr): 3362, 2923, 2226, 1636, 1541, 1522, 1458, 1401, 1260, 1158, 1079, 1028, 938, 859, 755, 733, 699, 610, 580, 530 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{25}H_{15}N_5Na$: 408.1225, found: 408.1231.

*4.2.2 4-(4-fluorophenyl)-2-(1H-indol-3-yl)pyrimido[1,2-b]indazole-3-carbonitrile (**4b**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.43 (s, 1H), 8.62 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.17 (dd, J = 8.0, 5.6 Hz, 2H), 7.82 (d, J = 8.8 Hz, 1H), 7.79 – 7.64 (m, 3H), 7.51 (t, J = 8.8 Hz, 2H), 7.40 – 7.29 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 162.2, 153.5, 151.9, 147.4, 143.1, 136.2, 133.5, 133.3, 131.8 (d, $J_{C\text{-}F}$ = 8.9 Hz), 131.0, 125.1, 122.6, 122.3, 121.8, 121.1, 120.7, 117.4, 116.8, 115.6 (d, $J_{C\text{-}F}$ = 11.8 Hz), 113.4, 112.6, 103.4, 95.5; IR (KBr): 3405, 2924, 2223, 1639, 1541, 1518, 1507, 1401, 1239, 1159, 1079, 1028, 948, 839, 755, 738, 708, 669, 577, 528 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{25}H_{14}FN_5Na$: 426.1131, found: 426.1148.

*4.2.3 4-(4-chlorophenyl)-2-(1H-indol-3-yl)pyrimido[1,2-b]indazole-3-carbonitrile (**4c**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.44 (s, 1H), 8.62 (s, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.78 – 7.71 (m, 3H), 7.58 (d, J = 8.4 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 160.6, 153.3, 151.9, 147.4, 143.1, 136.2, 135.6, 135.4, 133.5, 132.6, 131.2, 130.0, 129.1, 128.7, 125.1, 122.3, 120.7, 116.8, 113.5, 112.6, 103.4, 95.5; IR (KBr):3422, 2925, 2224, 1645, 1604, 1568, 1550, 1488, 1400, 1370, 1160, 1079, 1029, 976, 930, 845, 730, 734, 670, 585, 529 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{25}H_{14}ClN_5Na$: 442.0835, found: 442.0828.

*4.2.4 4-(3,4-dichlorophenyl)-2-(1H-indol-3-yl)pyrimido[1,2-b]indazole-3-carbonitrile (**4d**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.47 (s, 1H), 8.65 (s, 1H), 8.37-8.35 (m, 2H), 8.10 (dd, J = 2.4 Hz, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.76 – 7.66 (m, 3H), 7.40 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 : $CDCl_3$ = 9:1) (δ, ppm): 151.8, 147.3, 143.0, 137.1, 136.2, 133.6, 133.3, 131.4, 131.1, 130.8, 129.5, 125.1, 122.6, 122.3, 122.0, 121.1, 120.7, 117.2, 116.8, 113.6, 112.6, 103.3, 95.3; IR (KBr): 3421, 2925, 2222, 1636, 1522, 1458, 1400, 1241, 1158, 1080, 1029, 939, 903, 856, 755, 737, 610, 577, 530 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{25}H_{13}Cl_2N_5Na$: 476.0446, found: 476.0470.

*4.2.5 4-(4-bromophenyl)-2-(1H-indol-3-yl)pyrimido[1,2-b]indazole-3-carbonitrile (**4e**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.43 (s, 1H), 8.62 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.8 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 153.4, 151.9, 147.4, 143.1, 136.3, 135.9, 133.6, 132.0, 131.6, 131.5, 131.0, 130.2, 125.1, 124.2, 122.7, 122.3, 121.9, 121.1, 120.7, 117.4, 116.8, 113.5, 112.6, 103.4, 95.4; IR (KBr): 3420, 2924, 2230, 1636, 1541, 1522, 1399, 1242, 1158, 1079, 1028, 947, 755, 739, 669, 577, 530 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{25}H_{14}BrN_5Na$: 486.0330, found: 486.0351.

*4.2.6 2-(1H-indol-3-yl)-4-(4-nitrophenyl)pyrimido[1,2-b]indazole-3-carbonitrile (**4f**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.46 (s, 1H), 8.64 (s, 1H), 8.51 (d, J = 8.4 Hz, 2H), 8.41 – 8.32 (t, J = 9.2 Hz, 3H), 7.87 (d, J = 8.8 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 152.3, 152.0, 148.4, 147.4, 143.0, 142.7, 136.3, 133.7, 131.2, 130.9, 129.6, 125.1, 124.1, 123.7, 122.7, 122.3, 121.1, 120.7, 117.2, 116.9, 113.7, 112.7, 103.3, 95.6; IR (KBr):3400, 2924, 2222, 1649, 1534, 1518, 1507, 1397, 1230, 1150, 1079, 1028, 930, 830, 755, 737, 708, 670, 550, 535 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{25}H_{14}N_6NaO_2$: 453.1076, found: 453.1062.

*4.2.7 4-(4-hydroxyphenyl)-2-(1H-indol-3-yl)pyrimido[1,2-b]indazole-3-carbonitrile (**4g**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.39 (s, 1H), 10.14 (s, 1H), 8.59 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.8 Hz, 1H), 7.71 – 7.61 (m, 3H), 7.34 – 7.29 (m, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 159.8, 154.5, 151.9, 147.5, 143.3, 136.2, 133.4, 131.2, 130.9, 127.4, 125.2, 122.6, 122.2, 121.4, 121.2, 120.6, 117.8, 116.6, 115.4, 113.2, 112.6, 103.5, 95.1; IR (KBr): 3405, 2925, 2234, 1634, 1568, 1539, 1488, 1401, 1369, 1158, 1079, 1029, 948, 841, 749, 734, 669, 578 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{25}H_{15}N_5NaO$: 424.1174, found: 424.1189.

*4.2.8 2-(1H-indol-3-yl)-4-(p-tolyl)pyrimido[1,2-b]indazole-3-carbonitrile (**4h**)*

Yellow solid; m.p. >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.40 (s, 1H), 8.60 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.8 Hz, 1H), 7.72 – 7.62 (m, 3H), 7.46 (d, J = 8.0 Hz, 2H), 7.38 – 7.28 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 154.5, 151.9, 147.4, 143.2, 140.3, 136.2, 133.9, 133.4, 130.9, 129.3, 129.1, 125.2, 122.6, 122.2, 121.6, 121.1, 120.6, 117.5, 116.7, 113.3, 112.6, 103.5, 95.5, 21.0; IR (KBr): 3405, 2923, 2223, 1637, 1522, 1401, 1242, 1158, 1080, 1028, 948, 847, 754, 737, 669, 650, 610, 577, 530 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{26}H_{17}N_5Na$: 422.1382, found: 422.1380.

*4.2.9 2-(1H-indol-3-yl)-4-(3-methoxyphenyl)pyrimido[1,2-b]indazole-3-carbonitrile (**4i**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.41 (s, 1H), 8.61 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.73 – 7.62 (m, 5H), 7.57 (t, J = 8.0 Hz, 1H), 7.39 – 7.28 (m, 2H), 7.22 (t, J = 8.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 159.1, 154.2, 151.9, 147.4, 143.1, 138.0, 136.2, 133.4, 131.0, 129.7, 125.2, 122.6, 122.3, 121.8, 121.7, 121.2, 120.6, 117.4, 116.8, 115.8, 115.0, 113.4, 112.6, 103.5, 95.7, 55.4; IR (KBr): 3405, 2925, 2219, 1634, 1527, 1488, 1402, 1385, 1246, 1158, 1080, 1029, 948, 853, 750, 705, 577, 530 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{26}H_{17}N_5NaO$: 438.1331, found: 438.1345.

*4.2.10 2-(1H-indol-3-yl)-4-(4-methoxyphenyl)pyrimido[1,2-b]indazole-3-carbonitrile (**4j**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.40 (s, 1H), 8.60 (s, 1H), 8.29 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.0 Hz,

1H), 7.67 – 7.61 (m, 2H), 7.34 -7.34 (m, 2H), 7.25 - 7.20 (m, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 161.1, 154.1, 151.9, 147.5, 143.2, 136.2, 133.4, 131.1, 130.9, 129.0, 125.2, 122.6, 122.2, 121.5, 121.1, 120.6, 117.7, 116.6, 114.0, 113.2, 112.6, 103.5, 95.2, 55.5; IR (KBr): 3343, 2926, 2223, 1637, 1609, 1567, 1548, 1519, 1486, 1465, 1437, 1377, 1297, 1256, 1178, 1159, 1128, 1080, 1033, 939, 900, 832, 754, 678, 654, 617, 594, 518, 438, 426 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^+$ calculated for $C_{26}H_{17}N_5NaO$: 438.1331, found: 438.1339.

*4.2.11 4-(benzo[d][1,3]dioxol-5-yl)-2-(1H-indol-3-yl)pyrimido[1,2-b]indazole-3-carbonitrile (**4k**)*

Yellow solid; m.p. >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.43 (s, 1H), 8.61 (s, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.67 – 7.67 (m, 4H), 7.33 -7.30 (m, 2H), 7.23 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 6.19 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 153.9, 151.9, 149.3, 147.5, 143.1, 136.2, 133.5, 130.6, 125.2, 124.3, 122.6, 122.3, 121.2, 120.7, 116.7, 113.3, 112.6, 109.4, 108.4, 103.5, 101.8, 95.4; IR (KBr): 3420, 2924, 2225, 1668, 1636, 1528, 1489, 1441, 1385, 1339, 1246, 1211, 1157, 1079, 1030, 935, 912, 858, 746, 709, 619, 576, 520 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^+$ calculated for $C_{26}H_{15}N_5NaO_2$: 452,1123, found: 452.1136.

*4.2.12 2-(1H-indol-3-yl)-4-(3,4,5-trimethoxyphenyl)pyrimido[1,2-b]indazole-3-carbonitrile (**4l**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.40 (s, 1H), 8.60 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.70 -7.64 (m, 3H), 7.44 (s, 2H), 7.39 – 7.34 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 3.93 (s, 6H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 : $CDCl_3$ = 9:1) (δ, ppm): 153.8, 152.7, 151.9, 147.4, 142.9, 139.4, 136.2, 133.1, 131.7, 130.8, 125.1, 122.4, 122.3, 121.5, 121.1, 120.5, 117.4, 116.6, 113.3, 112.5, 107.0, 103.5, 95.4, 60.2, 56.1; IR (KBr):3407, 2924, 2219, 1634, 1527, 1488, 1452 1402, 1385, 1246, 1210, 1158, 1080, 1053 1029, 948, 923 853, 750, 732, 705, 577, 530 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^+$ calculated for $C_{28}H_{21}N_5NaO_3$: 498.1542, found: 498.1561.

*4.2.13 2-(1H-indol-3-yl)-4-(pyridin-4-yl)pyrimido[1,2-b]indazole-3-carbonitrile (**4m**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.47 (s, 1H), 8.89 (d, J = 5.6 Hz, 2H), 8.63 (s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 5.2 Hz, 2H), 7.87 (d, J = 8.8 Hz, 1H), 7.72 (t, J = 7.6 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 : $CDCl_3$ = 9:1) (δ, ppm): 162.2,

151.8, 150.0, 147.4, 143.8, 143.0, 136.3, 133.5, 131.0, 125.1, 123.4, 122.6, 122.2, 121.0, 120.7, 116.9, 113.6, 112.6, 103.3, 95.2; IR (KBr):3240, 2924, 2221, 1635, 1507, 1490, 1400, 1262, 1158, 1080, 1028, 948, 842, 755, 736, 708, 611, 580, 531 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{24}H_{14}N_6Na$: 409.1178, found: 409.1175.

*4.2.14 10-chloro-4-(4-fluorophenyl)-2-(1H-indol-3-yl)pyrimido[1,2-b]indazole-3-carbonitrile (**4n**)*

Yellow solid; m.p. > 280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.48 (s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.28 (d, J = 8.8 Hz, 1H), 8.22 – 8.15 (m, 2H), 8.12 (d, J = 0.8 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 2H), 7.45 (dd, J = 8.8, 1.6 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 154.6, 152.3, 147.7, 143.4, 136.2, 133.6, 133.1, 132.0, 131.9, 125.0 (d, J_{CF} = 14.0 Hz), 124.5, 123.2, 122.7, 122.3, 120.7, 118.9, 117.3, 115.6 (d, J_{CF} = 14.0 Hz), 112.6, 112.2, 103.3, 96.1; IR (KBr):3413, 3222, 2225, 1703, 1636, 1567, 1521, 1482, 1456, 1384, 1221, 1162, 1030, 958, 783, 732, 640 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{25}H_{13}ClFN_5Na$: 460.0741, found: 460.0752.

*4.2.15 10-chloro-4-(4-hydroxyphenyl)-2-(1H-indol-3-yl)pyrimido[1,2-b]indazole-3-carbonitrile (**4o**)*

Yellow solid; m.p. > 280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.41 (s, 1H), 10.19 (s, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.07 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.64 (ddd, J = 15.9, 11.1, 7.6 Hz, 3H), 7.37 (d, J = 7.2 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 160.0, 154.8, 152.5, 147.7, 142.8, 136.2, 133.4, 131.2, 131.0, 127.2, 126.9, 125.2, 122.6, 122.2, 121.3, 120.4, 117.6, 115.6, 115.4, 112.5, 110.6, 103.4, 95.4; IR (KBr): 3448, 2923, 2225, 1653, 1636, 1559, 1541, 1522, 1507, 1498, 1474, 1458, 1399, 1385, 1339, 1160,1029 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{25}H_{14}ClN_5NaO$: 458.0785, found: 458.0783.

*4.2.16 10-chloro-2-(1H-indol-3-yl)-4-(p-tolyl)pyrimido[1,2-b]indazole-3-carbonitrile (**4p**)*

Yellow solid; m.p. > 280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.43 (s, 1H), 8.59 (s, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.72 – 7.57 (m, 3H), 7.48 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 7.2 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 155.0, 152.5, 147.7, 142.7, 140.6, 136.2, 133.9, 133.5, 131.1,

129.3, 129.2, 126.8, 125.2, 122.6, 122.3, 121.6, 120.7, 117.5, 115.7, 112.6, 110.8, 103.4, 95.9, 21.1; IR (KBr): 3448, 3227, 2223, 1636, 1567, 1542, 1521, 1482, 1384, 1162, 1029, 958, 786, 733, 669 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{26}H_{16}ClN_5Na$: 456.0992, found: 456.0983.

4.2.17 10-chloro-2-(1H-indol-3-yl)-4-(4-methoxyphenyl)pyrimido[1,2-b]indazole-3-carbonitrile ***(4q)***

Yellow solid; m.p. > 280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.41 (s, 1H), 8.59 (s, 1H), 8.18 – 8.12 (m, 2H), 7.75 (d, J = 8.8 Hz, 1H), 7.70 -7.59 (m, 3H), 7.37 (d, J = 7.2 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.24 -7.21 (m, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 161.3, 154.6, 152.6, 147.8, 142.8, 136.2, 133.4, 131.1, 128.9, 126.8, 125.2, 122.6, 122.2, 121.5, 120.7, 117.6, 115.7, 114.1, 112.6, 110.6, 103.4, 95.6, 55.5; IR (KBr): 3448, 2224, 1637, 1560, 1517, 1482, 1384, 1252, 1036, 736 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{26}H_{16}ClN_5NaO$: 472.0941, found: 472.0950.

4.2.18 2,4-diphenylpyrimido[1,2-b]indazole-3-carbonitrile ***(6a)***

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.38 (d, J = 8.4 Hz, 1H), 8.16 – 8.09 (m, 2H), 8.01 (t, J = 3.6 Hz, 2H), 7.84 (d, J = 8.8 Hz, 1H), 7.72(d, J = 2.0 Hz, 2H), 7.71 (s, 1H), 7.66 (t J = 7.6 Hz, 1H), 7.62-7.60 (m, 3H), 7.37 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 154.4, 153.5, 151.5, 144.1, 136.4, 132.5, 131.6, 130.9, 130.3, 129.4, 129.2, 129.0, 128.7, 122.5, 121.5, 117.3, 116.2, 114.2, 97.1; IR (KBr): 3422, 2926, 2220, 1636, 1482, 1458, 1401, 1158, 1079, 1028, 948, 856, 757, 734, 692, 668, 609, 578, 532 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{23}H_{14}N_4NaO$: 369.1116, found: 369.1127.

4.2.19 2-phenyl-4-(m-tolyl)pyrimido[1,2-b]indazole-3-carbonitrile ***(6b)***

Yellow solid; m.p. 276 - 278°C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.35 (d, J = 8.0 Hz, 1H), 8.05 – 7.98 (m, 2H), 7.87 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.74 – 7.69 (m, 4H), 7.54 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 154.1, 152.3, 151.3, 143.2, 138.0, 136.3, 131.7, 131.1, 130.2, 129.6, 129.0, 128.6, 128.5, 126.3, 122.1, 121.1, 116.7, 116.2, 113.2, 97.8, 21.0; IR (KBr): 3421, 2924, 2222, 1636, 1507, 1401, 1158, 1080, 1028, 947, 757, 692, 587, 531 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{24}H_{16}N_4NaO_2$: 383.1273, found: 383.1289.

*4.2.20 2-phenyl-4-(p-tolyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6c**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.37 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 8.01 – 7.89 (m, 3H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 2H), 7.70 (s, 1H), 7.65 (t, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* =7.6 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 154.5, 153.5, 151.5, 144.1, 141.3, 133.7, 132.4, 131.5, 130.3, 129.7, 129.3, 129.2, 128.7, 122.4, 121.6, 117.3, 116.3, 114.1, 97.0, 21.7; IR (KBr): 3416, 2924, 2218, 1637, 1401, 1158, 1080, 1028, 758, 733, 642, 577, 531 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{24}H_{16}N_4NaO$: 383.1273, found: 383.1299.

*4.2.21 4-(3,4-dimethylphenyl)-2-phenylpyrimido[1,2-b]indazole-3-carbonitrile (**6d**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, $CDCl_3$) (*δ*, ppm): 8.38 (d, *J* = 8.4 Hz, 1H), 8.00 (t, *J* = 3.6 Hz, 2H), 7.88 (s, 1H), 7.84 (t, *J* = 9.2 Hz, 2H), 7.71 (d, *J* = 2.4 Hz, 2H), 7.70 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 154.7, 153.5, 151.4, 144.1, 140.0, 137.4, 134.0, 132.4, 131.5, 130.4, 130.3, 130.2, 129.2, 128.7, 126.8, 122.3, 121.6, 117.2, 116.4, 114.1, 97.1, 20.1, 20.0; IR (KBr): 3412, 2924, 2218, 1636, 1566, 1481, 1401, 1373, 1158, 1079, 1029, 948, 758, 730, 695, 669, 610, 581, 528 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{25}H_{18}N_4Na$: 397.1429, found: 397.1451.

*4.2.22 4-(4-hydroxyphenyl)-2-phenylpyrimido[1,2-b]indazole-3-carbonitrile (**6e**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (*δ*, ppm): 10.19 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.01-7.95 (m, 4H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.73 – 7.70 (m, 3H), 7.66 (t, *J* = 8.4 Hz 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) (*δ*, ppm): 159.9, 153.8, 152.3, 151.3, 143.3, 131.6, 131.1, 131.0, 130.3, 129.2, 128.6, 127.0, 121.7, 121.1, 116.6, 116.5, 115.5, 113.0, 97.2; IR (KBr): 3420, 2925, 2220, 1636, 1611, 1567, 1550, 1513, 1401, 1371, 1281, 1242, 1157, 1080, 1029, 948, 834, 757, 735, 617, 577, 531 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{23}H_{14}N_4NaO$: 385.1065, found: 385.1078.

*4.2.23 4-(4-methoxyphenyl)-2-phenylpyrimido[1,2-b]indazole-3-carbonitrile (**6f**)*

Yellow solid; m.p. > 280°C; ^{1}H NMR (400 MHz, DMSO-d_6) (*δ*, ppm): 8.33 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 8.03 – 8.01 (m, 2H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.74 – 7.72 (m, 3H), 7.69 (d, *J* =8.8 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (100

MHz, DMSO-d_6) (δ, ppm): 161.7, 153.9, 152.8, 143.8, 132.1, 131.7, 131.3, 130.7, 129.6, 129.1, 122.4, 121.6, 117.2, 117.0, 114.6, 113.5, 97.9, 56.0; IR (KBr):3416, 2924, 2220, 1636, 1512, 1402, 1384, 1298, 1253, 1158, 1079, 1028, 948, 840, 755, 689, 612, 578, 532 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{24}H_{16}N_4NaO$: 399.1222, found: 399.1243.

*4.2.24 2-phenyl-4-(3,4,5-trimethoxyphenyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6g**)*

Yellow solid; m.p. > 280°C; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.36 (d, J = 8.4 Hz, 1H), 8.04 - 8.02 (m, 2H), 7.84 (d, J = 8.8 Hz, 1H), 7.74 - 7.69 (m, 4H), 7.42 – 7.42 (m, 3H), 3.91 (s, 6H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$-d) (δ, ppm): 153.9, 153.6, 153.5, 151.6, 143.9, 140.5, 132.5, 131.6, 131.4, 130.2, 129.2, 128.6, 122.5, 121.6, 117.3, 116.4, 114.1, 106.9, 96.9, 61.2, 56.5; IR (KBr): 3419, 2927, 2222, 1635, 1506, 1458, 1404, 1384, 1244, 1158, 1122, 1080, 1028, 947, 853, 743, 705, 577, 528 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{26}H_{20}N_4NaO_3$: 459.1433, found: 459.1427.

*4.2.25 4-(3,4-dichlorophenyl)-2-phenylpyrimido[1,2-b]indazole-3-carbonitrile (**6h**)*

Yellow solid; m.p. > 280°C; ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.37 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.99 (t, J = 3.6 Hz, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.72 – 7.71 (m, 2H), 7.68 (t, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 : $CDCl_3$: = 9:1) (δ, ppm): 152.8, 152.1, 150.7, 143.2, 136.3, 134.2, 131.8, 131.0, 130.1, 129.6, 128.4, 127.9, 122.0, 120.7, 116.6, 115.4, 113.5, 96.1; IR (KBr): 3420, 2923, 2220, 1636, 1399, 1339, 1158, 1029, 938, 753, 687, 610, 578, 529 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{23}H_{12}Cl_2N_4Na$: 437.0337, found: 437.0351.

*4.2.26 2-(4-fluorophenyl)-4-(4-hydroxyphenyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6i**)*

Yellow solid; m.p. > 280 °C; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 10.22 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.16 – 8.06 (m, 2H), 8.03 – 7.91 (m, 2H), 7.80 (d, J = 8.8 Hz, 1H), 7.68 (t, J = 5.2 Hz, 1H), 7.59 (t, J = 8.8 Hz, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.03 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 159.9, 153.7, 152.3, 150.4, 143.3, 133.1 (d, $J_{C\text{-}F}$ = 9.0 Hz), 130.9, 126.9, 125.5, 121.8, 121.1, 116.6, 116.5, 115.8 (d, $J_{C\text{-}F}$ = 22.0 Hz), 115.5, 113.0, 97.3; IR (KBr): 3448, 2921, 2226, 1643, 1601, 1507, 1454, 1428, 1384, 1333,1265, 1238, 1165, 1108, 918, 861, 762 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{23}H_{13}FN_4NaO$: 403.0971, found: 403.0975.

*4.2.27 2-(4-fluorophenyl)-4-(p-tolyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6j**)*

Yellow solid; m.p. > 280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.33 (d, J = 8.4 Hz, 1H), 8.14 -8.10 (m, 2H), 7.96 (dd, J = 17.6, 8.0 Hz, 2H), 7.83 (d, J = 8.8 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.63 – 7.45 (m, 4H), 7.38 (d, J = 8.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 153.8, 152.3, 150.4, 143.3, 140.6, 133.5, 133.2 (d, $J_{C\text{-}F}$ = 9.0 Hz), 131.7, 131.3, 130.3, 129.2, 129.1, 125.4, 122.1, 121.1, 116.7, 116.3, 116.0, 115.7 (d, $J_{C\text{-}F}$ = 22.0 Hz), 113.2, 97.7, 21.0; IR (KBr): 3447, 2923, 2224, 1637, 1559, 1522, 1507, 1489, 1458, 1384, 1236, 1163, 1030, 743 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{24}H_{15}FN_4Na$: 401.1178, found: 401.1185.

*4.2.28 2-(4-chlorophenyl)-4-(4-hydroxyphenyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6k**)*

Yellow solid; m.p. > 280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 10.21 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 7.83 -7.78 (m, 3H), 7.67 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 159.9, 153.7, 152.3, 150.2, 143.3, 136.5, 132.3, 131.2, 130.9, 128.8, 128.0, 126.9, 121.8, 121.1, 116.6, 116.5, 115.5, 113.0, 97.2; IR (KBr): 3439, 2227, 1637, 1611, 1592, 1592, 1576, 1551, 1509, 1478, 1368, 1169, 1114, 1095, 1027, 830, 743 cm^{-1}; HRMS (ESI-TOF) m/z calculated for $C_{23}H_{13}ClN_4NaO$: 419.0676, found [M+Na]$^{+}$: 419.0679.

*4.2.29 2-(4-chlorophenyl)-4-(m-tolyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6l**)*

Yellow solid; m.p. 274 -276 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.34 (d, J = 8.4 Hz, 1H), 8.10 – 8.03 (m, 2H), 7.86 - 7.82 (m, 5H), 7.71 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 153.9, 152.3, 150.2, 143.2, 138.0, 136.6, 136.2, 132.3, 131.3, 131.2, 129.6, 128.9, 128.6, 127.9, 126.3, 122.2, 121.1, 116.7, 116.2, 113.2, 97.8, 21.1; IR (KBr): 3447, 2923, 2223, 1638, 1636, 1593, 1507, 1479, 1457, 1398, 1373, 1167, 1095, 1030, 829, 757, 742, 701, 646, 582 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{24}H_{15}ClN_4Na$: 417.0883, found: 417.0896.

*4.2.30 2-(4-chlorophenyl)-4-(p-tolyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6m**)*

Yellow solid; m.p. >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.34 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.4 Hz, 3H), 7.71 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 : $CDCl_3$ = 9:1) (δ, ppm): 153.6, 152.3, 150.0, 143.2, 140.4, 136.7, 133.3, 132.1, 131.1, 129.1, 129.0,

128.7, 127.6, 121.9, 120.9, 116.6, 113.2, 97.4, 21.0; IR (KBr):3348, 2224, 1637, 1593, 1479, 1369, 1187, 1170, 1116, 1094, 827, 774, 744, 669, 649, 618 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{24}H_{15}ClN_4Na$: 417.0883, found: 417.0886.

*4.2.31 2-(4-chlorophenyl)-4-(3-methoxyphenyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6n**)*

Yellow solid; m.p. 254 - 256 °C; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.35 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 3H), 7.72 (t, J = 7.6 Hz, 1H), 7.66 – 7.55 (m, 3H), 7.40 (t, J = 7.6 Hz, 1H), 7.23 (dd, J = 8.0, 2.0 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 159.2, 153.4, 152.3, 150.1, 143.1, 137.5, 136.7, 132.3, 131.3, 129.9, 128.9, 127.8, 122.2, 121.4, 121.1, 116.7, 116.1, 114.7, 113.2, 97.8, 55.4; IR (KBr): 3347, 2923, 2226, 1637, 1483, 1425, 1384, 1252, 1169, 1116, 1092, 1032, 851, 828, 773, 738, 698 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{24}H_{15}ClN_4NaO$: 433.0832, found: 433.0840.

*4.2.32 2-(4-chlorophenyl)-4-(4-methoxyphenyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6o**)*

Yellow solid; m.p. >280 °C; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.32 (d, J = 8.4 Hz, 1H), 8.08 – 8.04 (m, 4H), 7.84 (s, 1H), 7.83 – 7.78 (m, 2H), 7.69 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 161.3, 153.4, 152.3, 150.2, 143.3, 136.6, 132.3, 131.3, 130.9, 128.8, 128.5, 127.9, 122.0, 121.1, 116.7, 116.4, 114.2, 113.1, 97.4, 55.5; IR (KBr):3334, 2225, 1637, 1608, 1593, 1550, 1511, 1479, 1370, 1306, 1258, 1170, 1134, 1115, 1092, 1040, 1024, 1012, 904, 830, 802, 742, 620, 555, 531 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{24}H_{15}ClN_4NaO$: 433.0832, found: 433.0846.

*4.2.33 2-(4-chlorophenyl)-4-(3,4,5-trimethoxyphenyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6p**)*

Yellow solid; m.p. > 280 °C; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.37 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.8 Hz, 3H), 7.73 (t, J = 8.8 Hz, 1H), 7.45 – 7.38 (m, 3H), 3.92 (s, 6H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 153.4, 152.9, 152.3, 150.1, 143.1, 139.6, 136.7, 132.3, 131.4, 131.3, 128.9, 127.8, 122.2, 121.2, 116.7, 116.3, 113.2, 106.9, 97.8, 60.3, 56.2; IR (KBr): 3347, 2920, 2220, 1717, 184, 1669, 1653, 1647, 1636, 1559, 1540, 1457, 1399, 1029, 743, 569 cm^{-1}; HRMS (ESI-TOF) m/z $[M+Na]^+$ calculated for $C_{26}H_{19}ClN_4NaO_3$: 493.1043, found: 493.1051.

*4.2.34 10-chloro-4-(4-hydroxyphenyl)-2-phenylpyrimido[1,2-b]indazole-3-carbonitrile (**6q**)*

Yellow solid; m.p. > 280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 10.25 (s, 1H), 8.06 – 8.01 (m, 2H), 8.00 – 7.95 (m, 2H), 7.79 – 7.69 (m, 4H), 7.64 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.07 – 7.01 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 160.1, 154.2, 152.9, 151.7, 142.8, 131.6, 131.3, 131.0, 130.2, 129.1, 128.6, 126.9, 126.8, 121.7, 116.4, 115.6, 115.6, 110.4, 97.5; IR (KBr): 3348, 2229, 1735, 1654, 1636, 1560, 1544, 1534, 1508, 1447, 1458, 1437, 1399, 1375, 1158, 1030, 737,698 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{23}H_{13}ClN_4NaO$: 419.0676, found: 419.0686.

*4.2.35 10-chloro-2-phenyl-4-(p-tolyl)pyrimido[1,2-b]indazole-3-carbonitrile (**6r**)*

Yellow solid; m.p.165–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.02 (dd, J = 8.0, 1.6 Hz, 2H), 7.89 – 7.84 (m, 2H), 7.69 – 7.59 (m, 2H), 7.49 (t, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 160.1, 145.4, 139.0, 136.5, 135.6, 133.1, 131.9, 129.7, 129.4, 128.9, 128.4, 126.6, 126.1, 125.4, 113.7, 95.7, 20.9; IR (KBr):3348, 2923, 2237, 1654, 1648, 1559, 1542, 1501, 1447, 1385, 1030, 899, 734, 692, 678, 603 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{24}H_{15}ClN_4Na$: 417.0883, found: 417.0895.

*4.2.36 10-chloro-4-(4-methoxyphenyl)-2-phenylpyrimido[1,2-b]indazole-3-carbonitrile (**6s**)*

Yellow solid; m.p. 163–165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.04 – 7.98 (m, 2H), 7.88 – 7.82 (m, 2H), 7.70 – 7.59 (m, 3H), 7.51 -7.46 (m, 3H), 7.03 – 6.97 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 160.1, 145.2, 136.6, 135.6, 133.0, 131.9, 131.1, 129.7, 129.4, 128.4, 126.6, 126.1, 120.3, 113.8, 95.7, 55.3; IR (KBr): 3448, 2923, 2235, 1647, 1502, 1384, 1253, 1027, 850, 830, 742 cm^{-1}; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{24}H_{15}ClN_4NaO$: 433.0832, found: 433.0836.

*4.2.37 2-(1H-indole-3-carbonyl)-3-phenylacrylonitrile (**7**)*

Yellow solid; m.p. 233-235 °C; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.32 (s, 1H, NH), 8.47 (s, 1H, CH), 8.25 (s, 1H, CH), 8.19 (d, J = 12.0 Hz, 1H), 8.07 – 8.05 (m, 2H), 7.62-7.61 (m, 3H), 7.56 (d, J = 8.0 Hz, 1H), 7.29 (q, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 181.4, 152.1, 136.7, 136.1, 132.5, 132.3, 130.3, 129.1, 126.1, 123.6, 122.4, 121.3, 117.6, 113.6, 112.5, 111.5; HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calculated for $C_{18}H_{12}N_2NaO$: 295.0847, found: 295.0849.

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Supplementary Material ^{1}H NMR and ^{13}C NMR spectra for all compounds are available free of charge via the Internet.

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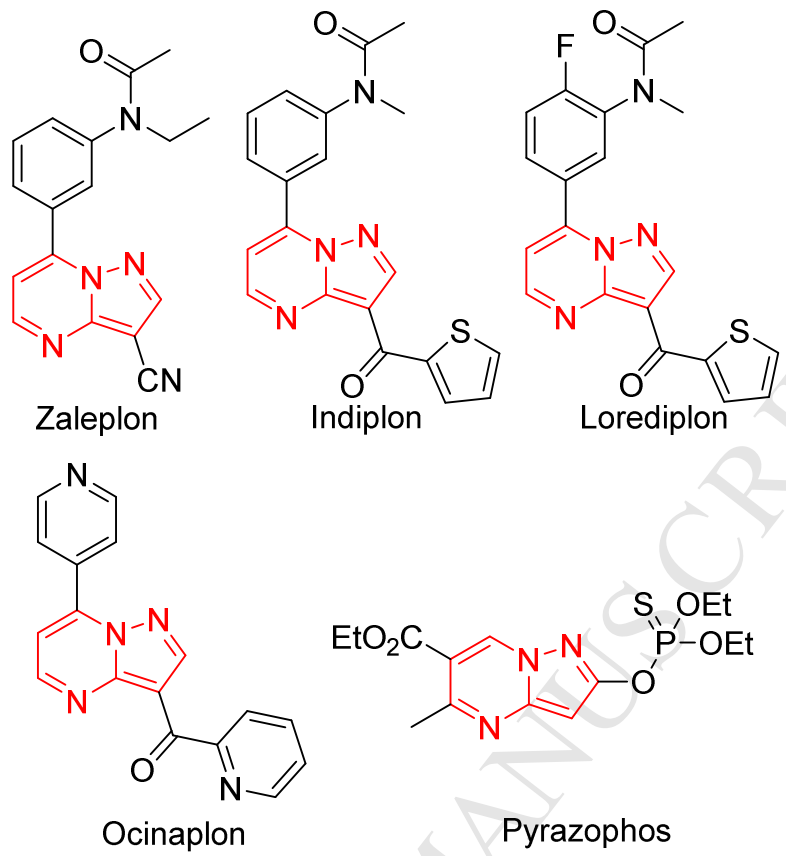
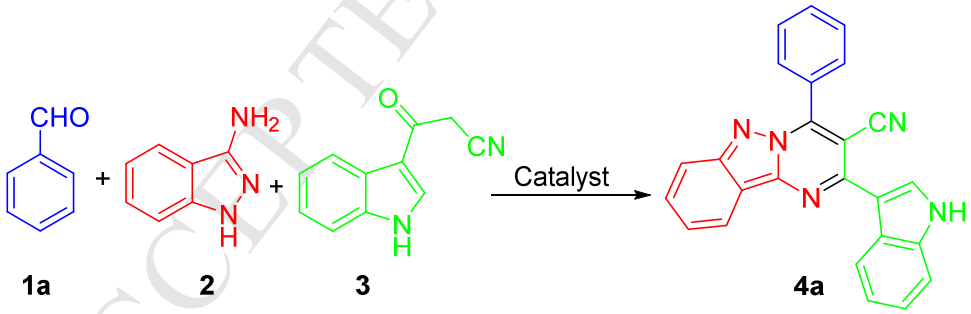


Figure 1. The active compounds with pyrazolo[1,5-*a*]pyrimidine nucleus.



Scheme 1. The model reaction of benzaldehyde, 1*H*-indazol-3-amine, and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile.

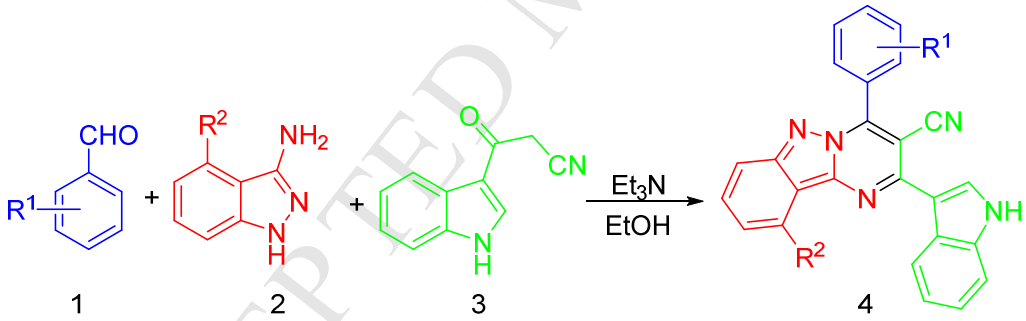
Table 1 Condition optimization for the reaction between benzaldehyde, 1*H*-indazol-3-amine, and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile[a].

Entry	Solvent	Catalyst (mol%)	Temp. °C	Time (h)	Yields (%)[b]
1	CH_3CN	PTSA·H_2O (30)	80	3	0
2	CH_3CN	$FeCl_3$ (30)	80	3	0

3	CH_3CN	DBU (30)	80	3	30
4	CH_3CN	Piperidine (30)	80	3	41
5	CH_3CN	DMAP (30)	80	3	15
6	CH_3CN	Et_3N (30)	80	3	76
7	CH_3CN	KOH (30)	80	3	25
8	CH_3CN	NaOH (30)	80	3	28
9	CH_3CN	K_2CO_3 (30)	80	3	trace
10	CH_3CN	Na_2CO_3 (30)	80	3	trace
11	CH_3OH	Et_3N (30)	80	3	56
12	EtOH	Et_3N(30)	80	3	85
13	THF	Et_3N (30)	80	3	42
14	EtOH	Et_3N (20)	80	3	82
15	EtOH	Et_3N (10)	80	3	67
16	EtOH	Et_3N (20)	80	5	91
17	EtOH	Et_3N (20)	80	7	90
18	EtOH	Et_3N (20)	60	7	52

[a]Reaction condition: Reagent: benzaldehyde **1a** (1 mmol), 1*H*-indazol-3-amine **2** (1 mmol), and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **3** (1 mmol), solvent (8 mL).

[b]Isolated Yields



Scheme 2. The reactions of aromatic aldehydes, (substituted) 1*H*-indazol-3-amine, and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile.

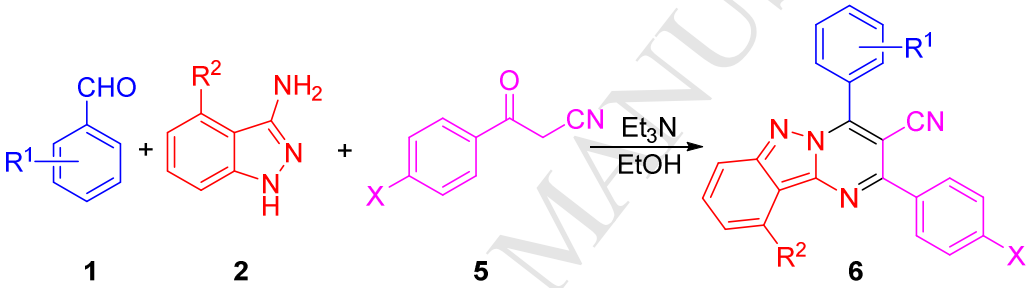
Table 2 Three-component reactions of aromatic aldehydes, (substituted) 1*H*-indazol-3-amine, and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile[a].

Entry	R^1	R^2	Compounds	Yields (%)[b]
1	1-H	H	**4a**	91
2	4-F	H	**4b**	90
3	4-Cl	H	**4c**	89
4	3,4-Cl_2	H	**4d**	90
5	4-Br	H	**4e**	88
6	4-NO_2	H	**4f**	92
7	4-OH	H	**4g**	91
8	4-CH_3	H	**4h**	87
9	3-CH_3O	H	**4i**	89

10	4-CH_3O	H	**4j**	90
11	3,4-OCH_2O	H	**4k**	86
12	3,4,5-$(CH_3O)_3$	H	**4l**	87
13	4-pyridyl	H	**4m**	85
14	4-F	Cl	**4n**	82
15	4-OH	Cl	**4o**	89
16	4-CH_3	Cl	**4p**	85
17	4-CH_3O	Cl	**4q**	88

[a]Reaction method: aromatic aldehydes (1 mmol), 1*H*-indazol-3-amine (4-chloro-1*H*-indazol-3-amine) (1 mmol), and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (1 mmol), EtOH (8 mL), Et_3N (0.2 mmol), 80 °C, reaction time (3-5 h) (monitored reactions by TLC).

[b]Isolated Yields



Scheme 3. The reactions of aromatic aldehydes, (substituted) 1*H*-indazol-3-amine, and 3-oxo-3-arylpropanenitrile.

Table 3 Three-component reactions of aromatic aldehydes, (substituted) 1*H*-indazol-3-amine, and 3-oxo-3-arylpropanenitrile[a]

Entry	R^1	R^2	X	Compounds	Yields (%)[b]
1	H	H	H	**6a**	86
2	3-CH_3	H	H	**6b**	89
3	4-CH_3	H	H	**6c**	87
4	3,4-$(CH_3)_2$	H	H	**6d**	83
5	4-OH	H	H	**6e**	90
6	4-CH_3O	H	H	**6f**	89
7	3,4,5-$(CH_3O)_3$	H	H	**6g**	86
8	3,4-Cl_2	H	H	**6h**	83
9	4-OH	H	F	**6i**	88
10	4-CH_3	H	F	**6j**	81
11	4-OH	H	Cl	**6k**	87
12	3-CH_3	H	Cl	**6l**	80
13	4-CH_3	H	Cl	**6m**	84
14	3-CH_3O	H	Cl	**6n**	88
15	4-CH_3O	H	Cl	**6o**	83

16	3,4,5-$(CH_3O)_3$	H	Cl	**6p**	80
17	4-OH	Cl	H	**6q**	91
18	4-CH_3	Cl	H	**6r**	88
19	4-CH_3O	Cl	H	**6s**	89

[a]Reaction method: aromatic aldehydes (1 mmol), 1*H*-indazol-3-amine (4-chloro-1*H*-indazol-3-amine) (1 mmol), and 3-oxo-3-arylpropanenitrile (1 mmol), EtOH (8 mL), Et_3N (0.2 mmol), 80 °C, reaction time (3-5 h) (monitored reactions by TLC).

[b]Isolated Yields

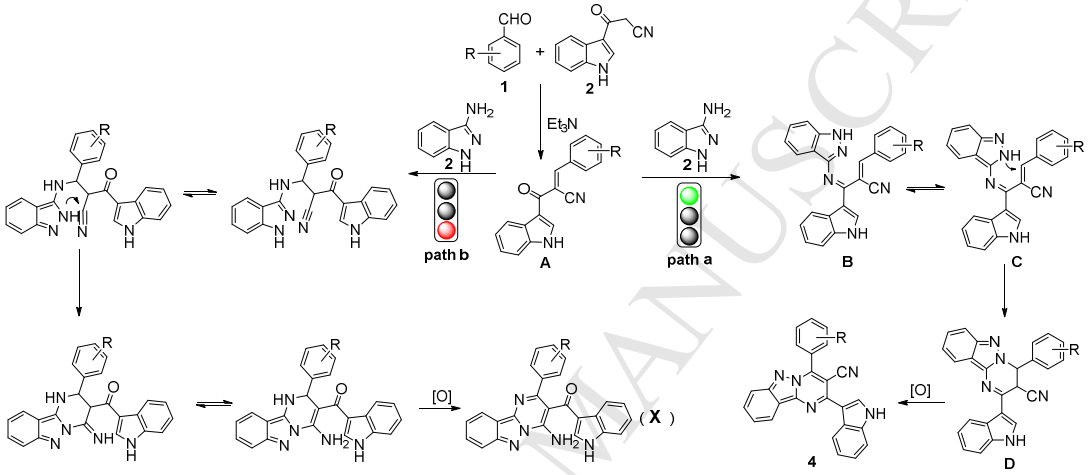
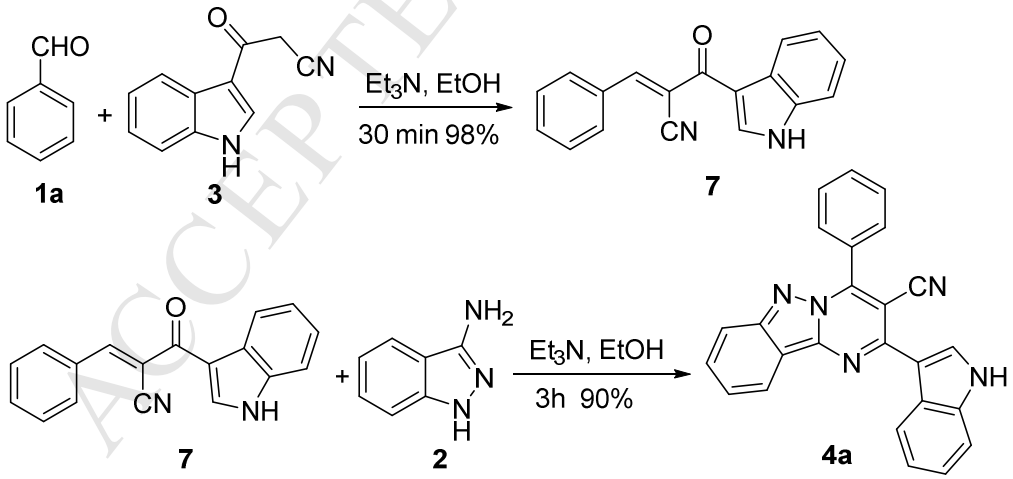


Figure 2. The possible reaction mechanism.



Scheme 4. The controlled reaction of **4a**.