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# Regioselective, one-pot, multi-component, green synthesis of substituted benzo[*c*]pyrazolo[2,7] naphthyridines†

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An efficient and environmentally benign synthetic protocol has been developed for the synthesis of benzo [c]pyrazolo[2,7]naphthyridine derivatives through regioselective multi-component "on-water" reaction of isatin, malononitrile and 3-aminopyrazole. The Knoevenagel condensation of isatin with malononitrile resulted in the formation of arylidene, which subsequently underwent Michael addition with 3-aminopyrazole followed by basic hydrolysis, cyclization, decarboxylation and aromatization to give the target naphthyridines in good to excellent yields. The one-pot multi-component protocol was also employed to obtain the said naphthyridines in a lower yield (10–15%) than obtained by basic hydrolysis of spiro-intermediates. The present study shows attractive features such as the use of water as a green solvent, short reaction time, reduced waste products and transition metal free *C*–*C* and *C*–*N* bond formation. The structures of the synthesized derivatives were established through FTIR, $^{1}$H-NMR, $^{13}$C-NMR spectroscopy and ESI-mass spectrometry.

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## Introduction

The diversity of oriented synthesis has inspired advances in drug design and the synthesis of stereochemical and structural variants of special molecular motifs resembling natural product skeletons.[1] 2,7-Naphthyridine scaffolds, known as small bispyridine structures, have recently gained attention in novel drug development. Out of the six isomeric forms of naphthyridines, benzo[*c*][2,7] naphthyridines are found in a number of biologically important alkaloids[2,3] such as subarine **1**,[4] amphimedine **2**,[5] perlolidine **3**,[6] meridine **4** (ref. 7) and PDK-I inhibitor **5**,[8] as shown in Fig. 1.

1,2 Pyrazole derivatives are an important class of nitrogen-containing heterocycles and have gained much interest in the fields of agriculture research and drug discovery.[9] The pyrazole containing natural products including L-α-amino-β-(pyrazolyl-*N*)-propanoic acid,[10] withasomnine,[11] pyrazofurin,[12] formycin,[13] oxoformycin B,[14] nostocine[15,16] and so on, are scaffolds that exhibit a wide range of importance in medicinal chemistry.

Studies in the literature reveal that many of the benzo[*c*][2,7] naphthyridine derivatives[17–21] have been synthesized employing new strategies to investigate the potential of fused five membered heterocycles such as isoxazolo-,[22] cyclopenta-,[23] pyrazolo-,[24] imidazo-[25] and furo-[26,27] annulated 2,7-naphthyridines. Numerous reported elegant reactions that often involved multistep harsh reaction conditions using organic solvents and homogenous or heterogeneous catalysts.[28,29]

In particular, transition metal free synthesis is an ideal synthetic route starting from simple and easily available raw materials and carried out under green and standard reaction conditions with a single operation and excellent tolerance of multifunctional groups for further derivatization. The use of green solvents is well accepted and an effective solution for not having to use multistep harsh reaction conditions. Water is the most often used green solvent for organic syntheses and is the first choice of organic chemists as it is nontoxic, readily available, inexpensive, has valuable effects on reaction rates and selectivity of organic transformations.[30] Various terminologies such as "on-water," "in-water", "in the presence of water" have evolved for when water is used as a reaction medium. Insolubility of several organic reactants in water make the reaction mixture heterogeneous which may cause difficulties in the use of water as a solvent.[31] It has been observed that many organic reactions proceed faster in heterogeneous mixtures rather than in homogeneous mixtures. The in-water (homogeneous mixture) reactions usually accelerate the rate *via* an enforced polarity effect, hydrophobic and hydrogen bonding interactions, whereas in the case of on-water (heterogeneous mixture) reactions, the acceleration of reaction rates has been observed due to the presence of free OH groups on the organic-water

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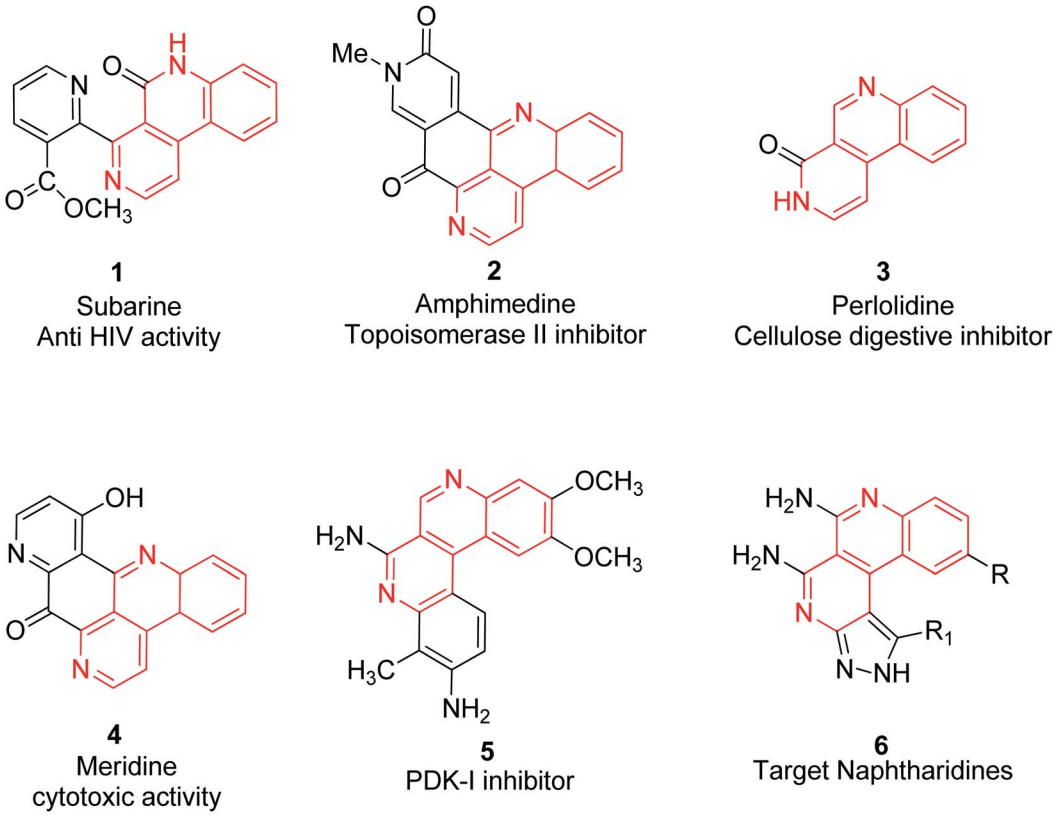



Fig. 1 Naturally occurring naphthyridine scaffolds and the target molecule.

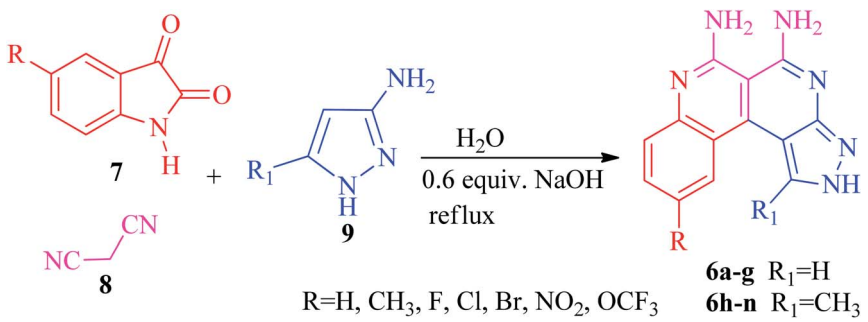
interface.[32,33] Herein, the development of new eco-friendly and efficient routes for the solid–liquid phase heterogeneous synthesis of benzo[*c*]pyrazolo[2,7]naphthyridines *via* an on-water multi-component reaction in the presence of NaOH, are described. Although, as far as is known, 2,7-naphthyridines fused with benzo at side-*c* and with pyrazole at side-*f* depicted as naphthyridine **6** (Fig. 1) are hitherto unknown. So this paper reports an on-water green synthetic methodology of benzo[*c*] naphthyridine derivatives fused with a pyrazole moiety.

## Results and discussion

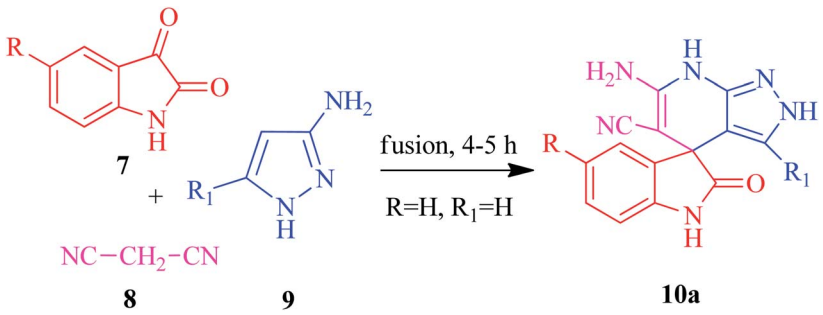
### Synthesis of benzo[*c*]pyrazolo[2,7]naphthyridines

The current research points towards the exploitation of the innate reactivity of substituted benzo[*c*]pyrazolo[2,7] naphthyridines **6**. An effective strategy for the regioselective synthesis of benzo[*c*]pyrazolo[2,7]naphthyridines **6a–n** was established through a one-pot multi-component synthesis in comparison with a two-step synthetic procedure. The one-pot multi-component synthesis of the respective compounds was carried out by using $H_2O$ as the solvent. For the said purpose, isatin **7**, malononitrile **8** and 3-aminopyrazole **9** were fused, refluxed in $H_2O$ for 4–5 h and charged with NaOH for a further 2–3 h to afford the formation of the benzo[*c*]pyrazolo[2,7] naphthyridines **6a–n** (Scheme 1).

The synthesis of benzo[*c*]pyrazolo[2,7]naphthyridines was also established through a two-step procedure *via* the formation of an intermediate, spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine] followed by alkaline hydrolysis and intramolecular cyclization. Previously, spiroindoline scaffolds were synthesized by the use




Scheme 1 One-pot multi-component protocol for synthesis of benzo[c]pyrazolo[2,7]naptharidines **6a–n**.




Scheme 2 Synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine] **10a**.

of various catalysts in different solvents,[34] whereas in the present study the scaffolds were synthesized by a catalyst free, on-water fusion method. For this, initially the one-pot, three component reaction of isatins **7**, malanonitrile **8** and 3-amino-pyrazole **9** was performed by fusing them on a sand bath for an appropriate time without a catalyst to afford the formation of the intermediate, spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine] **10a** (Scheme 2).

In order to evaluate the substrate scope, the syntheses of various (un)substituted spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridines] **10a–n** were accomplished with excellent yields under optimized reaction conditions (Table 1).

The benzo[*c*]pyrazolo[2,7]naphthyridines **6a–n** were subsequently synthesized by an efficient and eco-friendly protocol involving basic hydrolysis of the synthesized spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridines] **10a–n**. The solvent also played a significant role in determining the reaction rates and isolated yields so to investigate the efficiency of the basic hydrolysis of the spiroindoline scaffold **10a**, the model reaction was carried out using the solvent free grindstone method as well as in various polar and non-polar solvents, *i.e.*, $CH_2Cl_2$, DMSO, EtOH, MeOH, and THF. From the data listed in Table 2, water emerged as the best solvent for the basic hydrolysis of isatin, as its structure did not leave free water molecules due to the strong intramolecular hydrogen bonding. It also increased the concentration of hydroxide ions in the medium which enhanced the rate of the hydrolysis of isatin[35–38] to form the product with a maximum yield in a shorter reaction time (Scheme 3).

Furthermore, the reaction was also performed in the presence and absence of different potential bases such as piperidine, DABCO and NaOH to evaluate the efficiency of the basic hydrolysis of the spiroindoline scaffold. The NaOH (0.6 equiv.) was found to be the best to obtain the target naphthyridine **6a** (Table 2, entry 6). The optimized reaction conditions were utilized for the required transformations to afford the benzo[*c*]pyrazolo[2,7]naphthyridines **6a–n** in excellent yields. The presence of electron withdrawing and electron donating groups on the isatin ring had an obvious effect on the yields of the products. The yields were higher for the electron withdrawing groups rather than the electron donating groups. The substrate scope reaction results are summarized in Fig. 2.

Table 1 Spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridines] **10a–n**[a]

| Product | R | $R_1$ | Equiv. $H_2O$ | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| **10a** | H | H | 2 | 5 | 90 |
| **10b** | $CH_3$ | H | 2 | 4 | 81 |
| **10c** | F | H | 4 | 3 | 78 |
| **10d** | Cl | H | 5 | 3.5 | 79 |
| **10e** | Br | H | 5 | 3 | 81 |
| **10f** | $NO_2$ | H | 5 | 2 | 84 |
| **10g** | $OCF_3$ | H | 4 | 1 | 85 |
| **10h** | H | $CH_3$ | 2 | 4 | 93 |
| **10i** | $CH_3$ | $CH_3$ | 2 | 3 | 85 |
| **10j** | F | $CH_3$ | 3 | 2.5 | 82 |
| **10k** | Cl | $CH_3$ | 5 | 2.5 | 84 |
| **10l** | Br | $CH_3$ | 5 | 2.5 | 86 |
| **10m** | $NO_2$ | $CH_3$ | 5 | 2 | 85 |
| **10n** | $OCF_3$ | $CH_3$ | 4 | 1.5 | 87 |

[a] Reaction conditions: isatin **7** (2 mmol), malononitrile **8** (2 mmol), 3-amino-5-methylpyrazole/3-aminopyrazole **9** (2 mmol) and water (2–5 equiv.), fusion at 110 °C. [b] Isolated yield.

Table 2 Optimization of the reaction conditions for the model molecule **10a**

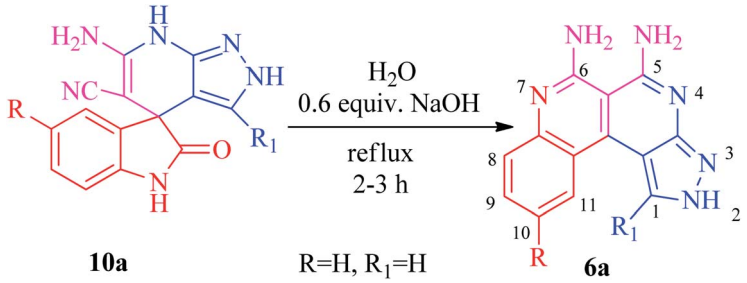
| Entry | Solvent | Base (equiv.) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $H_2O$ | — | 12 | — |
| 2 | $H_2O$ | NaOH (0.2) | 3 | 42 |
| 3 | $H_2O$ | NaOH (0.3) | 3 | 54 |
| 4 | $H_2O$ | NaOH (0.4) | 3 | 68 |
| 5 | $H_2O$ | NaOH (0.5) | 3 | 76 |
| 6 | $H_2O$ | NaOH (0.6) | 3 | 87 |
| 7 | $H_2O$ | Piperidine (0.6) | 3 | 40 |
| 8 | $H_2O$ | DABCO (0.6) | 3 | 32 |
| 9 | Neat | NaOH (0.6) | 3 | 62 |
| 10 | MeOH | NaOH (0.6) | 5 | 30 |
| 11 | EtOH | NaOH (0.6) | 5 | 28 |
| 12 | THF | NaOH (0.6) | 6 | 35 |
| 13 | DMSO | NaOH (0.6) | 5 | 79 |
| 14 | $CH_2Cl_2$ | NaOH (0.6) | 6 | 21 |

[a] Isolated yield.

## Comparison of reaction sequences

In order to explore the reaction sequences, the control experiment was performed with two different pathways and the same products were obtained with a variation in yields (Scheme 4).




Scheme 3 Synthesis of benzo[c]pyrazolo[2,7]naphthyridines **6a**.

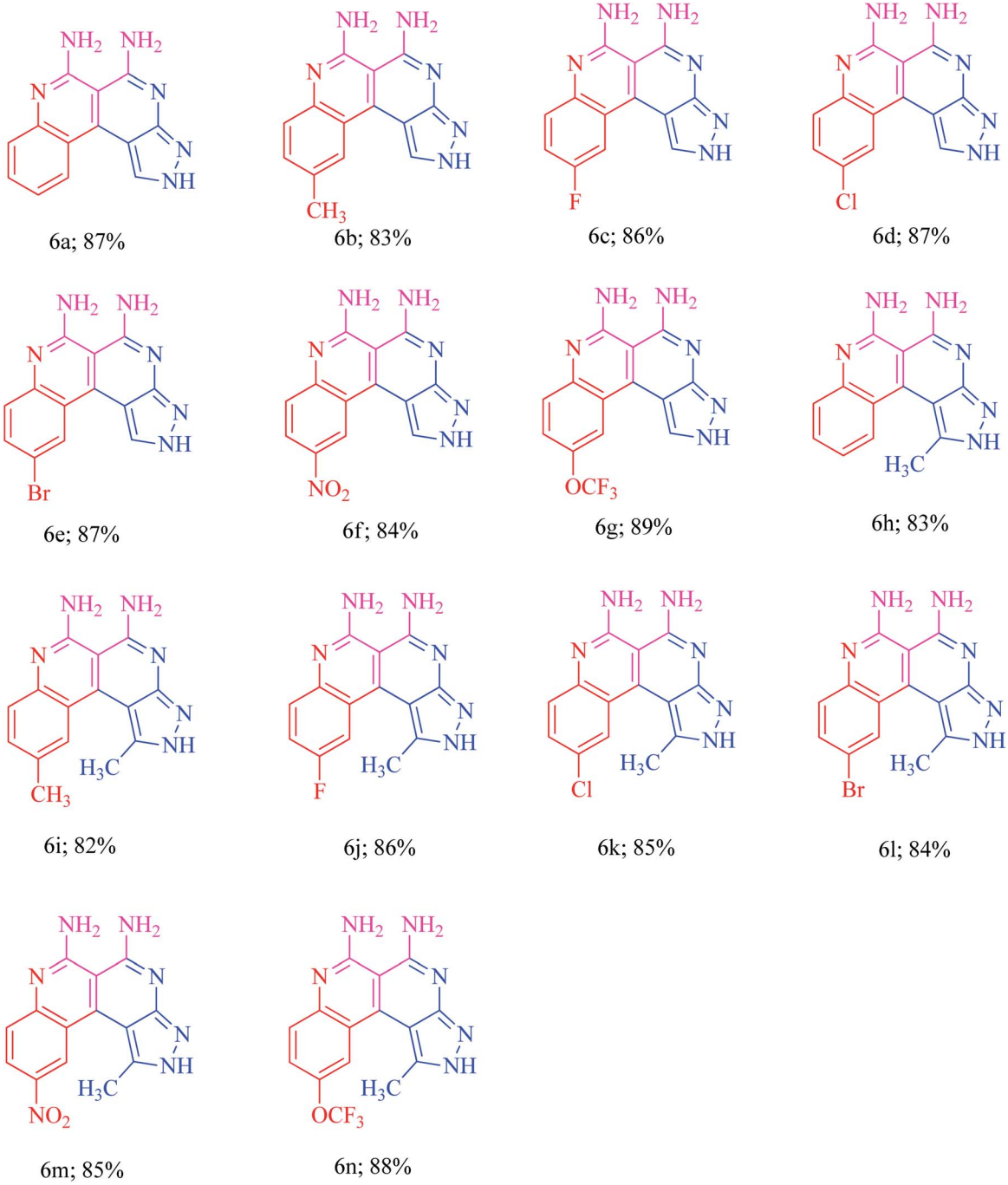
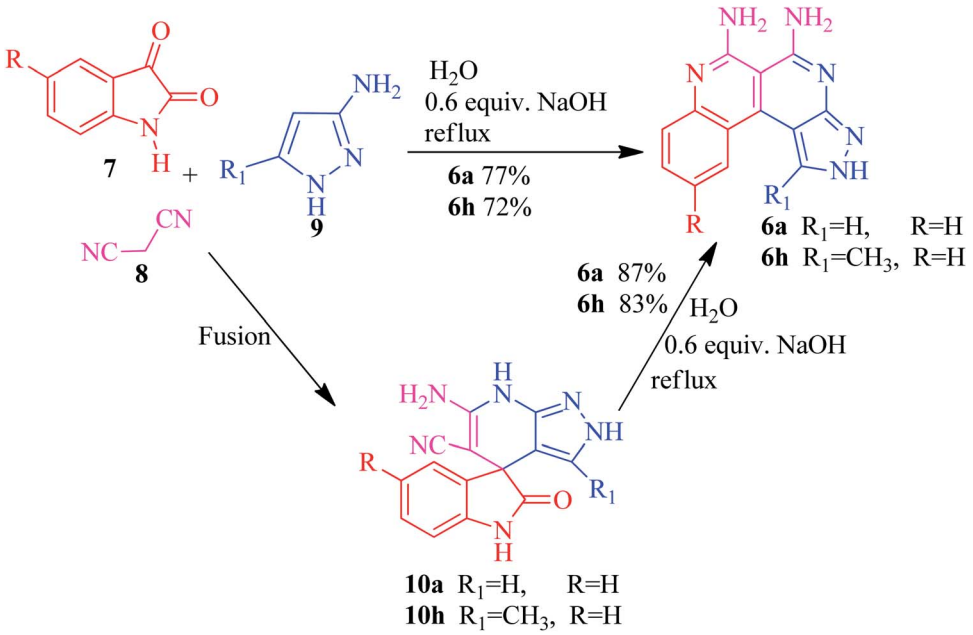
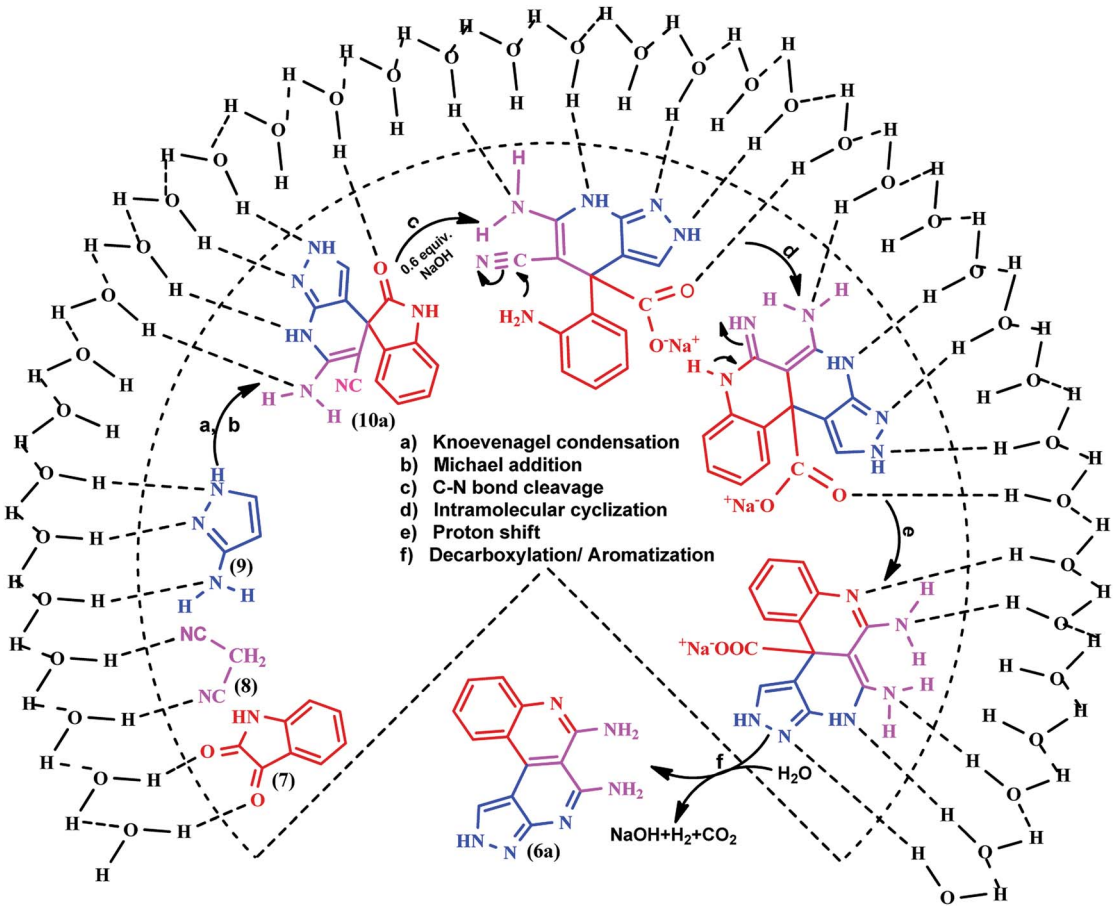


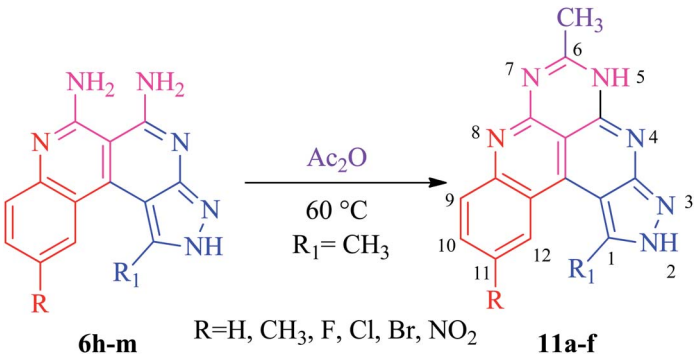

Fig. 2 Substrate scope with different benzo[c]pyrazolo[2,7]naphthyridines **6a–n**. Reaction conditions: spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine] **10a–n** (2 mmol), $H_2O$ (5 ml), NaOH (0.6 equiv.), reflux (2–3 h).




Scheme 4 Control experiments of the three component reaction.




Scheme 5 Plausible mechanism for the synthesis of benzo[c]pyrazolo[2,7]naptharidines **6a**.




Scheme 6 Synthesis of benzo[*c*]pyrazolo[4,3-*f*]pyrimido[4,5,6-*ij*][2,7]naphthyridines **11a–f**.

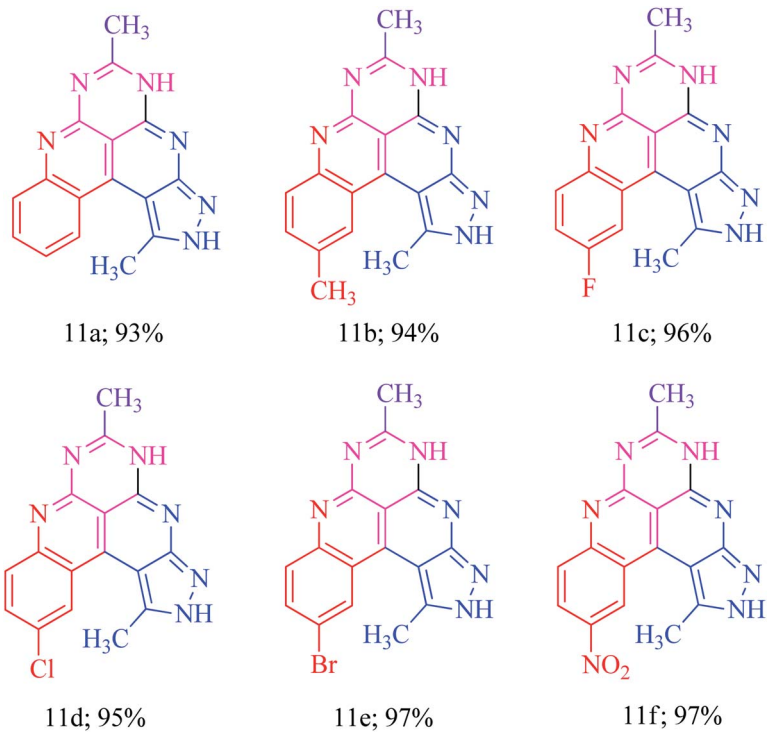



Fig. 3 Substrate scope with different benzo[*c*]pyrazolo[4,3-*f*]pyrimido[4,5,6-*ij*][2,7]naphthyridines **11a–f**. Reaction conditions: benzo[*c*]pyrazolo [2,7]naphthyridines **6h–m** (2 mmol), acetic anhydride (6 ml), heat 60 °C (2–3 h).

The overall yields of substituted benzo[*c*]pyrazolo[2,7]naphthyridines **6a–n** through one-pot synthesis, were found to have a lower yield (10–15%) than that obtained using hydrolysis of the spiro-intermediate **10a–n.**

### Reaction mechanism using the Jung and Marcus model

The Jung and Marcus model[39] was used to explain the efficiency and rate acceleration for the on-water synthesis of benzo[*c*] pyrazolo[2,7]naphthyridines. The experimental results suggested a tentative mechanistic interpretation that the reaction was initiated at the solid–liquid phase water boundary and stabilized by the hydrogen bonding interactions of the free OH groups of water molecules to deliver the product with an excellent yield. Knoevenagel condensation of isatin **7** with malononitrile **8** form an arylidine intermediate with the loss of a water molecule, followed by Michael addition of pyrazole **9** with arylidine resulted in the formation of the spiroindoline scaffold **10a.** The intermediate **10a** undergoes ring opening from the amide linkage by basic hydrolysis, followed by ring closure, tautomerization, decarboxylation and aromatization to produce the targeted heterocycle **6a** (Scheme 5).

### Ring annulation of benzo[*c*]pyrazolo[2,7]naphthyridines

The basis of the synthesis of the benzo[*c*]pyrazolo[2,7]naphthyridines was the additional ring annulation by using amino groups present at 5 and 6 positions. The treatment of derivatives **6h–m** with excess acetic anhydride offered benzo[*c*]pyrazolo[4,3-*f*]pyrimido[4,5,6-*ij*][2,7]naphthyridines **11a–f** with a quantitative

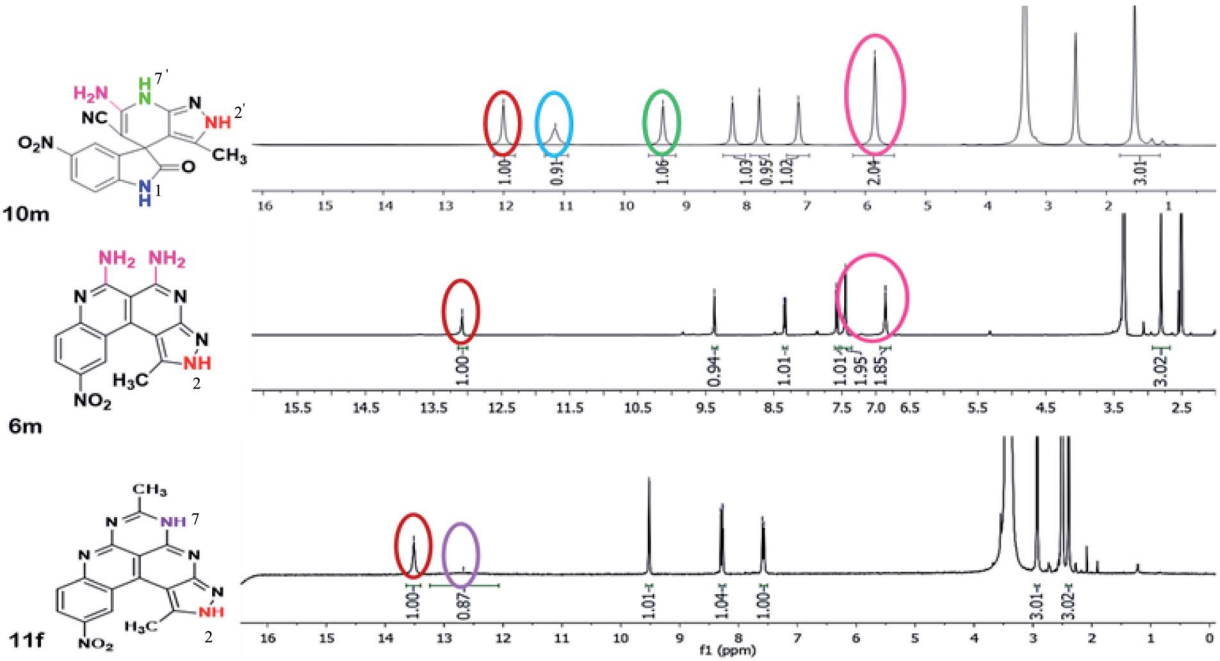



Fig. 4 Comparison of the $^{1}$H-NMR spectra of **10m**, **6m** and **11f**.

yield (Scheme 6). The substrate scope reaction results are summarized in Fig. 3.

### Application of benzo[*c*]pyrazolo[2,7]naphthyridines as a cationic chemosensor (6a–n)

In recent years, great attention has been devoted to the detection of metal ions in environmental or biological systems. For this purpose, different types of chemosensors have been synthesized and shown to display high selectivity for the detection of targeted metals in a pool of different metal ions. Among the various transition metal ions, $Ni^{2+}$ is an essential nutrient for living organisms and is involved in different biological processes such as metabolism, biosynthesis and respiration. The deficiency and extensive use of nickel, affects the life of prokaryotic and eukaryotic organisms.[40]

The synthesized compounds **6a–n** represent a new class of chemosensors with the presence of benzo[*c*]pyrazolo[2,7]naphthyridines as a chromophore and two amino groups as binding sites for selective detection of metals by UV-visible spectroscopy. The UV-visible spectra of compound **6a** in DMSO : $H_2O$ (1 : 5 v/v) were recorded on addition of different metal cations ($Al^{3+}$, $Cd^{2+}$, $Co^{2+}$, $Cr^{3+}$, $Cu^{2+}$, $Fe^{2+}$, $Hg^{2+}$, $Mn^{2+}$, $Ni^{2+}$, $Sn^{2+}$ and $Sr^{2+}$). The spectra of model compound **6a** (Fig. S1, ESI†) showed a bathochromic shift of bands at 537 nm upon the addition of $Ni^{2+}$ ions and no shifting of bands was observed for other competing cations. The initial spectroscopic studies of benzo[*c*]pyrazolo[2,7]naphthyridines showed a selective colorimetric response for $Ni^{2+}$ ions.

### Characterization of the synthesized compounds

The structures of the synthesized compounds **10a–n**, **6a–n** and **11a–f** were established on the basis of their spectroscopic data, *i.e.*, IR, $^{1}$H-NMR, $^{13}$C-NMR spectroscopy, and mass spectrometry (MS). The physical and spectral data of spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine] derivatives **10h–i**, and **10k–m** were in agreement with previously reported data.[34]

### Characterization by IR and NMR

The IR spectra of benzo[*c*]pyrazolo[2,7]naphthyridines **6a–n** showed N–H stretching of the pyrazole and amino groups in the 3421–3088 $cm^{-1}$ regions. The $^{1}$H-NMR spectra showed $NH_2$ moieties which resonated at 6.50–7.45 ppm and exhibited a singlet pyrazole $N^2$–H at $\delta$ 12.82–13.32 ppm in the naphthyridine derivatives. Similarly, the $^{13}$C-NMR spectra of compounds **6a–n** also agreed with the IR and $^{1}$H-NMR results. The IR spectra of benzo[*c*]pyrazolopyrimido[2,7]naphthyridines **11a–f** showed N–H stretching of pyrazole in the 3394–3048 $cm^{-1}$ region. The $^{1}$H-NMR spectra exhibited a broad singlet for pyrimido $N^5$–H at 12.41–12.67 ppm and a singlet for pyrazolo $N^2$–H at 13.38–13.65 ppm in the benzo[*c*]pyrazolopyrimido[2,7]naphthyridines derivatives. The $^{13}$C-NMR spectra of the compounds **11a–f** were also in agreement with the IR and $^{1}$H-NMR results.

### Characterization by MS (ESI)

The electron-spray ionization (ESI) spectra of all these novel heterocyclic compounds exhibited molecular ions of varied intensity which authenticated their molecular weights. The MS/MS spectra of **6a–n** showed the loss of ammonia ($NH_3$) and nitrogen ($N_2$) as the main fragmentation pathway due to the breakage of C–NH, NH bonds that validated the formation of benzo[*c*]pyrazolo[2,7]naphthyridines. The MS/MS spectra of **11a–f** showed the loss of $N_2$ as a main fragmentation pathway. The proposed fragmentation pattern of **6k** is illustrated Fig. S2 (ESI†).

### Comparison of $^1$H-NMR and $^{13}$C-NMR spectra

A comparison of the $^1$H-NMR spectra of the synthesized compounds **10m**, **6m**, **11f** is shown in Fig. 4. The $^1$H-NMR spectra of spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine] **10m** has four separate singlets of protons attached to four different nitrogen atoms at $\delta$ 5.84 ppm for $NH_2$, $\delta$ 9.36 ppm for pyridine $N^{7\prime}$–H, 11.14 ppm for indole $N^1$–H and $\delta$ 12.00 ppm for pyrazole $N^{2\prime}$–H protons, respectively. After the formation of benzo[*c*] pyrazolo[2,7]naphthyridine **6m**, the two peaks of the protons attached to pyridine $N^{7\prime}$–H and indole $N^1$–H disappeared and new peaks of $NH_2$ moieties appeared at 6.86 ppm and 7.45 ppm and the downfield shifting of signals for pyrazole $N^2$–H at $\delta$ 13.08 ppm was observed. After ring expansion of benzo[*c*] pyrazolo[2,7]naphthyridine **6m** to benzo[*c*]pyrazolopyrimido [2,7]naphthyridine **11f**, the peaks of the $NH_2$ moieties in **6m** disappeared and a new peak of pyrimido $N^5$–H was observed at 12.67 ppm. More downfield shifting of signals for pyrazole $N^2$–H at $\delta$ 13.51 ppm was also observed.

The $^{13}$C-NMR spectra of the spiroindoline scaffold **10m** showed the peaks of CN, C–$NH_2$ and C=O groups at 110.31, 155.27 and 180.16 ppm, respectively, which disappeared in **6m** and **11f** due to the transformation of these functionalities into new *C–C* and *C–N* bond (Fig. S3, ESI†).

## Conclusion

A novel multi-component, efficient and eco-friendly strategy was established using $H_2O$ as the solvent, in the absence of a transition metal catalyst, which exhibited enhanced efficiency and rate of reaction to synthesize the spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine] derivatives which were further transformed by basic hydrolysis into new benzo[*c*][2,7] naphthyridines as the target products. The chemical modification involved in the new *C–C* and *C–N* bond formation was achieved by Knoevenagel condensation, Michael addition, intramolecular cyclization, decarboxylation and aromatization sequences. These hitherto unknown compounds were not only prepared by multi-component reactions but a one-pot multi-component protocol was also employed to synthesize the required naphthyridines. The scope of the reaction was further enhanced by additional ring expansion of benzo[*c*][2,7]naphthyridine to form benzo[*c*]pyrazolopyrimido[2,7]naphthyridine. The resulting benzo[*c*]pyrazolo[2,7]naphthyridine heterocycles have a number of potent functionalities for further chemical modifications to develop new precursors as medically important heterocycles.

## Experimental

### General

All the chemicals were used as received from Sigma-Aldrich. All the melting points were determined using a Fisher-Johns melting point apparatus and were uncorrected. The IR spectra were recorded using KBr pellets on a Shimadzu Prestige-21 spectrophotometer. The $^1$H-NMR and $^{13}$C-NMR spectra were recorded on Bruker Avance spectrometer at 300 MHz and 500 MHz, respectively, using DMSO-$d_6$. The mass spectra were recorded on a Thermo Scientific LTQ XL system fitted with an ESI source, a Jeol 600 MS Route, and a Jeol HX-110 high-resolution mass spectrometer (EI-HR). Pre-coated aluminum sheets of silica gel 60 $GF_{254}$ (Merck) were used as TLC plates to check the purity of compounds.

### General procedure for the synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine] (10a–n)

A mixture of isatin **7** (2 mmol), malononitrile **8** (2 mmol), 3-amino-5-methylpyrazole/3-aminopyrazole **9** (2 mmol) and water (2–5 equiv.) were fused under stirring for an appropriate time (4–5 h) in a sand bath at 110 °C. After cooling, the products were washed with hot water/ethanol (1 : 1) to give the desired product **10a–n**. Further purification was done by recrystallization in methanol.

**6′-Amino-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10a).** White solid, yield: 90% (500 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3427, 3350, 3245 (NH), 2171 (C≡N), 1693 (C=O), 1643, 1623, 1589, 1506, 1471, 937, 923, 748, 727; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 5.68 (s, 2H, $NH_2$), 6.85 (d, $J$ = 7.80 Hz, 1H, indole $C_7$–H), 6.93 (d, $J$ = 7.20 Hz, 1H, indole $C_4$–H), 6.99 (t, $J$ = 6.90 Hz, 1H, indole $C_5$–H), 7.05 (s, 1H, pyrazole $C_3^{'}$ – H), 7.18 (t, $J$ = 6.60 Hz, 1H, indole $C_6$–H), 9.29 (s, 1H, pyridine NH), 10.25 (s, 1H, indole NH), 12.14 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 48.98 (C), 54.08 (C–CN), 101.78 (C), 109.94 (C≡N), 121.52 (C), 122.58 (CH), 124.93 (CH), 125.21 (CH), 128.61 (CH), 136.78 (CH), 141.54 (C), 146.85 (C), 155.17 (C–$NH_2$), 180.33 (C=O) ppm; MS (ESI) *m*/*z*: 277.08 $[M - H]^-$. Anal. calcd for $C_{14}H_{10}N_6O$ (%): C, 60.43; H, 3.62; N, 30.20; found (%): C, 60.36; H, 3.59; N, 30.17.

**6′-Amino-5-methyl-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10b).** White solid, yield: 81% (473 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3468, 3292, 3232, 3196 (NH), 2167 (C≡N), 1687 (C=O), 1642, 1620, 1580, 1503, 1426, 1321, 1195, 1144, 1072, 1049, 922, 818, 708, 634; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 2.21 (s, 3H, $C_5$–$CH_3$), 5.68 (s, 2H, $NH_2$), 6.73 (d, $J$ = 7.5 Hz, 1H, indole, $C_7$–H), 6.97 (d, $J$ = 7.5 Hz, 1H, indole, $C_6$–H), 6.81 (s, 1H, indole, $C_4$–H), 7.04 (s, 1H, pyrazole $C_3^{'}$ – H), 9.28 (s, 1H, pyridine NH), 10.15 (s, 1H, indole NH), 12.14 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 21.10 ($CH_3$), 49.03 (C), 54.24 (C–CN), 101.88 (C), 109.68 (C≡N), 121.61 (C), 125.26 (CH), 125.45 (C), 128.89 (CH), 131.36 (CH), 137.01 (C), 139.00 (CH), 146.76 (C), 155.09 (C–$NH_2$), 180.31 (C=O) ppm; MS (ESI) *m*/*z*: 291.17 $[M - H]^-$. Anal. calcd for $C_{15}H_{12}N_6O$ (%): C, 61.64; H, 4.14; N, 28.75; found (%): C, 61.55; H, 4.09; N, 28.71.

**6′-Amino-5-fluoro-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10c).** White solid, yield: 78% (462 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3473, 3299, 3263 (NH), 2171 (C≡N), 1708 (C=O), 1642, 1622, 1581, 1504, 1485, 1178, 788, 711; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 5.74 (s, 2H, $NH_2$), 6.84 (dd, $J$ = 9 Hz, 3.9 Hz, 1H, indole $C_7$–H), 6.87 (d, $J$ = 2.7 Hz, 1H, indole $C_4$–H), 7.02 (td, $J$ = 9 Hz, 2.7 Hz, 1H, indole $C_6$–H), 7.12 (s, 1H, pyrazole $C_3^{'}$ – H), 9.33 (s, 1H, pyridine NH), 10.28 (s, 1H, indole NH), 12.19 (s, 1H, pyrazole NH) ppm; $^{13}$C-

NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 49.56 (C), 53.56 (C–CN), 101.22 (C), 110.74 (CH), 110.84 (CH), 112.32 (CH), 112.64 (CH), 114.92 (CH), 115.23 (CH), 121.41 (C≡N), 125.32 (C), 137.77 (CH), 138.31 (C), 138.41 (C), 146.80 (C), 155.27 (C–$NH_2$), 157.30 (C), 160.45 (C), 180.36 (C=O) ppm; MS (ESI) $m/z$: 295.25 $[M - H]^-$. Anal. calcd for $C_{14}H_9FN_6O$ (%): C, 56.76; H, 3.06; N, 28.37; found (%): C, 56.79; H, 3.06; N, 28.39.

**6′-Amino-5-chloro-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10d).** Brown solid, yield: 79% (493 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3461, 3299, 3228 (NH), 2169 (C≡N), 1693 (C=O), 1639, 1623, 1581, 1504, 1475, 1431, 1217, 819, 723; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 5.77 (s, 2H, $NH_2$), 6.87 (d, $J$ = 8.1 Hz, 1H, indole $C_7$–H), 7.00 (d, $J$ = 1.8 Hz, 1H, indole $C_4$–H), 7.15 (s, 1H, pyrazole $C_3^{'}$ – H), 7.24 (dd, $J$ = 8.1 Hz, 2.1 Hz, 1H, indole $C_6$–H), 9.35 (s, 1H, pyridine NH), 10.41 (s, 1H, indole NH), 12.22 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 49.35 (C), 53.41 (C–CN), 101.03 (C), 111.53 (C≡N), 121.40 (C), 124.91 (CH), 125.39 (C), 126.51 (CH), 128.65 (CH), 138.74 (CH), 140.51 (C), 146.77 (C), 155.27 (C–$NH_2$), 180.03 (C=O) ppm; MS (ESI) $m/z$: 311.17 $[M - H]^-$. Anal. calcd for $C_{14}H_9ClN_6O$ (%): C, 53.77; H, 2.90; N, 26.87; found (%): C, 53.69; H, 2.90; N, 26.89.

**6′-Amino-5-bromo-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10e).** White solid, yield: 81% (576 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3454, 3206, 3071 (NH), 2174 (C≡N), 1692 (C=O), 1613, 1589, 1508, 1473, 1412, 1301, 1221, 1161, 1077, 1023, 823, 717, 689; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 5.77 (s, 2H, $NH_2$), 6.83 (d, $J$ = 8.4 Hz, 1H, indole, $C_7$–H), 7.10 (s, 1H, indole, $C_4$–H), 7.15 (s, 1H, pyrazole $C_3^{'}$ – H), 7.36 (d, $J$, 8.1 Hz, 1H, indole, $C_6$–H), 9.36 (s, 1H, pyridine NH), 10.42 (s, 1H, indole NH), 12.22 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 49.31 (C), 5342 (C–CN), 101.00 (C), 112.09 (C≡N), 114.21 (C), 121.41 (CH), 125.43 (C), 127.59 (CH), 131.49 (CH), 139.16 (C), 140.91 (CH), 146.72 (C), 155.26 (C–$NH_2$), 179.76 (C=O) ppm; MS (ESI) $m/z$: 355.08 $[M - H]^-$. Anal. calcd for $C_{14}H_9BrN_6O$ (%): C, 47.08; H, 2.54; N, 23.53; found (%): C, 47.02; H, 2.51; N, 23.50.

**6′-Amino-5-nitro-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10f).** Yellow solid, yield: 84% (543 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3452, 3321, 3199 (NH), 2171 (C≡N), 1717 (C=O), 1643, 1625, 1581, 1504, 1342, 1217, 715; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 5.90 (s, 2H, $NH_2$), 7.09 (d, $J$ = 8.7 Hz, 1H, indole $C_7$–H), 7.22 (s, 1H, pyrazole $C_3^{'}$ – H), 7.77 (d, $J$ = 2.4 Hz, 1H, indole $C_4$–H), 8.19 (dd, $J$ = 8.7 Hz, 2.4 Hz, 1H indole $C_6$–H), 9.52 (s, 1H, pyridine NH), 11.03 (s, 1H, indole NH), 12.30 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 49.22 (C), 52.73 (C–CN), 100.20 (C), 110.50 (C≡N), 120.20 (CH), 121.20 (C), 125.70 (CH), 126.18 (CH), 137.74 (CH), 143.08 (C), 146.72 (C), 148.25 (C), 155.49 (C–$NH_2$), 180.69 (C=O) ppm; MS (ESI) $m/z$: 322.25 $[M - H]^-$. Anal. calcd for $C_{14}H_9N_7O_3$ (%): C, 52.02; H, 2.81; N, 30.33; found (%): C, 51.97; H, 2.79; N, 30.29.

**6′-Amino-2-oxo-5-(trifluoromethoxy)-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10g).** Light yellow solid, yield: 85% (615 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3438, 3355, 3205 (NH), 2183 (C≡N), 1767 (C=O), 1699, 1623, 1585, 1530, 1488, 1280, 1269, 1166, 925, 725; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 5.78 (s, 2H, $NH_2$), 6.94 (s, 1H, indole $C_4$–H), 6.96 (s, 1H, pyrazole $C_3^{'}$ – H), 7.16 (s, 1H, indole $C_7$–H), 7.20 (dd, $J$ = 8.1 Hz, 1.2 Hz, 1H, indole $C_6$–H), 9.36 (s, 1H, pyridine NH), 10.47 (s, 1H, indole NH), 12.22 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 49.50 (C), 53.31 (C–CN), 100.97 (C), 110.92 (C≡N), 118.40 (CH), 118.92 (CH), 121.28 (C), 122.03 (CH), 122.30 (CH), 125.41 (CH), 138.33 (CH), 140.80 (C), 144.02 (C), 144.04 (C), 146.79 (C), 155.30 (C–$NH_2$), 180.36 (C=O) ppm; MS (ESI) $m/z$: 361.25 $[M - H]^-$. Anal. calcd for $C_{15}H_9F_3N_6O_2$ (%): C, 49.73; H, 2.50; N, 23.20; found (%): C, 49.79; H, 2.53; N, 23.23.

**6′-Amino-3′-methyl-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10h).** White solid, yield: 93% (543 mg), mp > 300 °C literature,[34] mp > 300 °C; IR (KBr, $cm^{-1}$): 3450, 3348, 3220 (NH), 2236 (C≡N), 1702 (C=O), 1640, 1580, 1470, 936, 835, 746, 720. Anal. calcd for $C_{15}H_{12}N_6O$ (%): C, 61.64; H, 4.14; N, 28.75; found (%): C, 61.59; H, 4.12; N, 28.71.

**6′-Amino-3′,5-dimethyl-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10i).** White solid, yield: 85% (516 mg), mp > 300 °C literature,[34] mp > 300 °C; IR (KBr, $cm^{-1}$): 3469, 3265, 3156 (NH), 2165 (C≡N), 1680 (C=O), 1640, 1588, 1500, 1420, 1190, 1075, 925, 801, 708, 630. Anal. calcd for $C_{16}H_{14}N_6O$ (%): C, 62.74; H, 4.61; N, 27.44; found (%): C, 62.70; H, 4.57; N, 27.39.

**6′-Amino-5-fluoro-3′-methyl-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10j).** White solid, yield: 82% (508 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3440, 3362, 3225 (NH), 2170 (C≡N), 1705 (C=O), 1620, 1520, 1480, 1439, 818, 740, 726; $^1$H-NMR (DMSO-$d_6$, 500 MHz): $\delta$ = 1.51 (s, 3H, $C_3^{'}$–$CH_3$), 5.70 (s, 2H, $NH_2$), 6.86 (s, 2H, indole $C_4$–H, $C_7$–H), 7.03 (s, 1H, indole $C_6$–H), 9.22 (s, 1H, pyridine NH), 10.39 (s, 1H, indole NH), 11.90 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 9.13 ($CH_3$), 49.66 (C), 53.62 (C–CN), 98.10 (C), 110.61 (CH), 110.67 (CH), 112.46 (CH), 112.65 (CH), 115.08 (CH), 115.27 (CH), 121.41 (C≡N), 134.57 (C), 137.19 (C), 137.25 (C), 137.82 (C), 146.98 (C), 155.10 (C–$NH_2$), 158.02 (C), 159.91 (C), 179.79 (C=O) ppm; MS (ESI) $m/z$: 309.17 $[M - H]^-$. Anal. calcd for $C_{15}H_{11}FN_6O$ (%): C, 58.06; H, 3.57; N, 27.08; found (%): C, 58.01; H, 3.58; N, 27.03.

**6′-Amino-5-chloro-3′-methyl-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10k).** White solid, yield: 84% (548 mg), mp > 300 °C, literature,[34] mp > 300 °C; IR (KBr, $cm^{-1}$): 3440, 3360, 3260 (NH), 2160 (C≡N), 1703 (C=O), 1620, 1520, 1479, 1440, 818, 748, 727; $^1$H-NMR (DMSO-$d_6$, 500 MHz): $\delta$ = 1.52 (s, 3H, $C_3^{'}$–$CH_3$), 5.72 (s, 2H, $NH_2$), 6.88 (d, $J$ = 10 Hz, 1H, indole $C_7$–H), 6.98 (s, 1H, indole $C_4$–H), 7.25 (d, $J$ = 10 Hz, 1H, indole $C_6$–H), 9.23 (s, 1H, pyridine NH), 10.52 (s, 1H, indole NH), 11.92 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 9.17 ($CH_3$), 49.43 (C), 53.49 (C–CN), 97.96 (C), 111.36 (C≡N), 121.39 (C), 124.99 (CH), 126.69 (C), 128.75 (CH), 134.57 (C), 137.56 (CH), 140.52 (C), 146.95 (C), 155.10 (C–$NH_2$), 179.47 (C=O) ppm; anal. calcd for $C_{15}H_{11}ClN_6O$ (%): C, 55.14; H, 3.39; N, 25.72; found (%): C, 55.19; H, 3.42; N, 25.78.

**6′-Amino-5-bromo-3′-methyl-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10l).** White solid, yield: 86% (638 mg), mp > 300 °C, literature,[34] mp >

300 °C; IR (KBr, $cm^{-1}$): 3445, 3209, 3185 (NH), 2172 (C≡N), 1702, 1613, 1575, 1470, 132, 1215, 1160, 1066, 1021, 715, 679. Anal. calcd for $C_{15}H_{11}BrN_6O$ (%): C, 48.54; H, 2.99; N, 22.64; found (%): C, 48.48; H, 2.97; N, 22.59.

**6′-Amino-3′-methyl-5-nitro-2-oxo-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10m).** Yellow solid, yield: 85% (566 mg), mp > 300 °C, literature,[34] mp > 300 °C; IR (KBr, $cm^{-1}$): 3443, 3364, 3230 (NH), 2180 (C≡N), 1708 (C=O), 1610, 1513, 1502, 1340, 1130; $^1$H-NMR (DMSO-$d_6$, 500 MHz): $\delta$ = 1.53 (s, 3H, $C_3^{'}$–$CH_3$), 5.84 (s, 2H, $NH_2$), 7.11 (s, 1H, indole $C_7$–H), 7.76 (s, 1H, indole $C_4$–H), 8.20 (s 1H, indole $C_6$–H), 9.36 (s, 1H, pyridine NH), 11.15 (s, 1H, indole NH), 12.00 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 9.25 ($CH_3$), 49.30 (C), 52.86 (C–CN), 97.20 (C), 110.31 (C≡N), 120.31 (CH), 121.15 (C), 126.24 (CH), 134.74 (C), 136.56 (CH), 143.26 (C), 146.97 (C), 148.03 (C), 155.27 (C–$NH_2$), 180.16 (C=O) ppm; anal. calcd for $C_{15}H_{11}N_7O_3$ (%): C, 53.41; H, 3.29; N, 29.07; found (%): C, 53.36; H, 3.27; N, 29.03.

**6′-Amino-3′-methyl-2-oxo-5-(trifluoromethoxy)-2′,7′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-5′-carbonitrile (10n).** Light yellow solid, yield: 87% (654 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3436, 3353, 3220 (NH), 2181 (C≡N), 1711 (C=O), 1623, 1586, 1514, 1488, 1269, 1166, 734; $^1$H-NMR (DMSO-$d_6$, 500 MHz): $\delta$ = 1.48 (s, 3H, $C_3^{'}$–$CH_3$), 5.74 (s, 2H, $NH_2$), 6.95 (s, 1H, indole $C_4$–H), 6.97 (s, 1H, indole $C_7$–H), 7.22 (dd, $J$ = 7.5 Hz, 2.1 Hz, 1H, indole $C_6$–H), 9.25 (s, 1H, pyridine NH) 10.57 (s, 1H, indole NH), 11.93 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 9.06 ($CH_3$), 49.54 (C), 53.34 (C–CN), 97.86 (C), 110.79 (C≡N), 118.53 (CH), 119.61 (CH), 121.28 (CH), 121.64 (CH), 122.14 (C), 134.55 (C), 137.04 (C), 140.88 (C), 144.15 (C), 144.16 (C), 147.02 (C), 155.19 (C–$NH_2$), 179.82 (C=O) ppm; MS (ESI) $m/z$: 375.17 $[M - H]^-$. Anal. calcd for $C_{16}H_{11}F_3N_6O_2$ (%): C, 51.07; H, 2.95; N, 22.33; found (%): C, 51.10; H, 2.97; N, 22.37.

### General procedure for one-pot multi-component synthesis of naphthyridines (6a–n)

A mixture of isatin **7** (2 mmol), malononitrile **8** (2 mmol), 3-amino-5-methylpyrazole/3-aminopyrazole **9** (2 mmol) were fused, refluxed in 5 ml of $H_2O$ for an appropriate time (4–5 h) to form intermediate spiroindoline scaffolds. The progress of the reaction was monitored by TLC. After consumption of the reactant, as indicated by TLC, NaOH (0.6 equiv.) was added to the crude product. The reaction mixture was further refluxed for 2–3 h. The reaction was allowed to cool down to room temperature. The precipitate formed was filtered by suction and washed thoroughly with water/ethanol (1 : 1) to obtain the crude product. The resulting residue was recrystallized in methanol to obtain pure heterocycles **6a–n**.

### General procedure for the synthesis of naphthyridines (6a–n) from spiroindolines (10a–n)

To the suspension of spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine] **10a–n** (2 mmol) in 5 ml of $H_2O$, NaOH (0.6 equiv.) was added and the mixture was refluxed for (2–3 h). The progress of the reaction was monitored by TLC. After completion of the reaction as indicated by TLC, the reaction mixture was allowed to cool at room temperature, the precipitate formed was filtered by suction and washed thoroughly with water/ethanol (1 : 1) to obtain the crude product. The resulting residue was recrystallized in methanol to obtain pure heterocycles **6a–n**.

**2*H*-Benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6a).** Light green solid, yield: 87% (435 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3392, 3303, 3213, 3111 (NH), 1609, 1578, 1501, 1418, 1370, 1332, 1284, 1249, 1135, 1032, 966, 842, 731, 642; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 6.65 (s, 2H, $NH_2$), 6.91 (s, 2H, $NH_2$), 7.37 (s, 1H, $C_8$–H), 7.62 (t, $J$ = 7.5 Hz, 2H, $C_9$–H, $C_{10}$–H), 8.67 (d, $J$ = 7.8 Hz, 1H, $C_{11}$–H), 8.74 (s, 1H, pyrazole $C_1$–H), 13.27 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 100.17 (C), 102.83 (C), 120.35 (C), 126.93 (CH), 131.20 (CH), 134.89 (CH), 138.64 (CH), 145.61 (C), 149.61 (CH), 151.69 (C), 156.55 (C–$NH_2$), 158.38 (C–$NH_2$) ppm; MS (ESI) $m/z$: 251.08 $[M + H]^+$. Anal. calcd for $C_{13}H_{10}N_6$ (%): C, 62.39; H, 4.03; N, 33.58; found (%): C, 62.34; H, 4.00; N, 33.53.

**10-Methyl-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6b).** Yellow solid, yield: 83% (439 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3394, 3314, 3213, 3113 (NH), 1577, 1507, 1425, 1375, 1341, 1286, 1212, 1144, 1106, 948, 811, 749, 697; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 2.54 (s, 3H, $C_{10}$–$CH_3$), 6.50 (s, 2H, $NH_2$), 6.92 (s, 2H, $NH_2$), 7.48 (s, 2H, $C_8$–H, $C_9$–H) 8.42 (s, 1H, $C_{11}$–H), 8.79 (s, 1H, pyrazole $C_1$–H), 13.20 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 21.48 ($CH_3$), 100.45 (C), 102.74 (C), 119.25 (C), 120.92 (C), 123.57 (C), 125.89 (CH), 132.92 (CH), 136.95 (CH), 138.24 (C), 145.73 (CH), 153.70 (C), 156.03 (C–$NH_2$), 158.48 (C–$NH_2$) ppm; MS (ESI) $m/z$: 265.17 $[M + H]^+$. Anal. calcd for $C_{14}H_{12}N_6$ (%): C, 63.62; H, 4.58; N, 31.80; found (%): C, 63.68; H, 4.60; N, 31.83.

**10-Fluoro-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6c).** Yellow solid, yield: 86% (461 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3394, 3322, 3212, 3117 (NH), 1615, 1567, 1508, 1479, 1426, 1374, 1254, 1166, 1097, 850, 822, 746; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 6.61 (s, 2H, $NH_2$), 6.96 (s, 2H, $NH_2$), 7.57 (m, 2H, $C_8$–H, $C_9$–H), 8.33 (d, $J$ = 9.6 Hz, 1H, $C_{11}$–H), 8.77 (s, 1H, pyrazole $C_1$–H), 13.29 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 100.42 (C), 102.59 (C), 112.07 (CH), 119.94 (CH), 120.24 (C), 128.30 (CH), 128.77 (CH), 134.54 (C), 141.18 (C), 144.17 (CH), 152.68 (C), 156.23 (C), 158.33 (C–$NH_2$), 158.51 (C–$NH_2$) ppm; MS (ESI) $m/z$: 267.08 $[M - H]^-$. Anal. calcd for $C_{13}H_9FN_6$ (%): C, 58.21; H, 3.38; N, 31.33; found (%): C, 58.16; H, 3.34; N, 31.27.

**10-Chloro-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6d).** Orange solid, yield: 87% (494 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3325, 3213, 3117 (NH), 1596, 1575, 1498, 1423, 1369, 1280, 1249, 966, 847, 699; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 6.79 (s, 2H, $NH_2$), 6.92 (s, 2H, $NH_2$), 7.57 (d, $J$ = 9.3 Hz, 1H, $C_8$–H), 7.65 (dd, $J$ = 9 Hz, 1.5 Hz, 1H, $C_9$–H), 8.53 (s, 1H, $C_{11}$–H), 8.68 (s, 1H, pyrazole $C_1$–H), 13.32 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 100.128 (C), 102.54 (C), 120.82 (C), 125.34 (CH), 126.73 (CH), 128.12 (C), 131.39 (CH), 134.57 (C), 144.11 (C), 146.06 (CH), 150.18 (C), 156.94 (C–$NH_2$), 158.27 (C–$NH_2$) ppm; MS (ESI) $m/z$: 285.17 $[M + H]^+$. Anal. calcd for $C_{13}H_9ClN_6$ (%): C, 54.84; H, 3.19; N, 29.52; found (%): C, 54.75; H, 3.17; N, 29.48.

**10-Bromo-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6e).** Orange yellow solid, yield: 87% (571 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3390, 3321, 3204, 3119 (NH), 1617, 1590, 1497, 1426, 1112, 1077, 1061, 964, 820, 743; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 6.82 (s, 2H, $NH_2$), 6.93 (s, 2H, $NH_2$), 7.51 (d, $J$ = 8.7 Hz, 1H, $C_8$–H), 7.76 (d, $J$ = 7.8 Hz, 1H, $C_9$–H), 8.64 (s, 2H, $C_{11}$–H, pyrazole $C_1$–H), 13.32 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 100.19 (C), 102.49 (C), 114.63 (C), 121.38 (C), 124.36 (C), 128.33 (CH), 134.03 (CH), 134.40 (CH), 137.40 (C), 146.31 (CH), 151.59 (C), 157.01 (C–$NH_2$), 158.25 (C–$NH_2$) ppm; MS (ESI) $m/z$: 329.17 $[M + H]^+$. Anal. calcd for $C_{13}H_9BrN_6$ (%): C, 47.44; H, 2.76; N, 25.53%; found: C, 47.50; H, 2.73; N, 25.47.

**10-Nitro-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6f).** Orange solid, yield: 84% (496 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3392, 3321, 3091 (NH), 1611, 1578, 1490, 1430, 1316, 1248, 1147, 1085, 949, 890, 733, 641; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 7.08 (s, 4H, $NH_2$, $NH_2$), 8.34 (dd, $J$ = 9 Hz, 1.2 Hz, 1H, $C_8$–H), 8.41 (d, $J$ = 8.1 Hz, 1H, $C_9$–H), 8.52 (s, 1H, pyrazole $C_1$–H), 9.31 (s, 1H, $C_{11}$–H), 13.26 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 100.18 (C), 102.56 (C), 118.24 (C), 123.48 (CH), 125.31 (CH), 126.10 (C), 133.86 (CH), 138.56 (CH), 141.17 (C), 144.20 (C), 151.92 (C), 158.36 (C–$NH_2$), 159.12 (C–$NH_2$) ppm; MS (ESI) $m/z$: 294.33 $[M - H]^-$. Anal. calcd for $C_{13}H_9N_7O_2$ (%): C, 52.88; H, 3.07; N, 33.21; found (%): C, 52.84; H, 3.06; N, 33.18.

**10-(Trifluoromethoxy)-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6g).** Yellow solid, yield: 89% (581 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3400, 3340, 3170 (NH), 1605, 1457, 1282, 1150, 1133, 1008, 854, 711, 689, 611; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 6.88 (s, 4H, $NH_2$, $NH_2$), 7.65 (s, 2H, $C_8$–H, $C_9$–H), 8.47 (s, 1H, $C_{11}$–H), 8.67 (s, 1H, pyrazole $C_1$–H), 13.29 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 100.32 (C), 102.53 (C), 118.58 (C), 119.14 (CH), 119.82 (CH), 122.53 (C), 124.88 (CH), 128.08 (CH), 134.26 (C), 137.98 (C), 143.27 (CH), 146.19 (C), 151.73 (C), 157.12 (C–$NH_2$), 158.31 (C–$NH_2$) ppm; MS (ESI) $m/z$: 335.17 $[M + H]^+$. Anal. calcd for $C_{14}H_9F_3N_6O$ (%): C, 50.31; H, 2.71; N, 25.14; found (%): C, 50.27; H, 2.68; N, 25.10.

**1-Methyl-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6h).** Yellow solid, yield: 83% (439 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3419, 3299, 3109 (NH), 1615, 1546, 1384, 1317, 842, 748; $^1$H-NMR (DMSO-$d_6$, 500 MHz): $\delta$ = 2.70 (s, 3H, $C_1$–$CH_3$), 6.60 (s, 2H, $NH_2$), 6.80 (s, 2H, $NH_2$), 7.32 (t, $J$ = 7.5 Hz, 1H, $C_9$–H), 7.56 (d, $J$ = 8 Hz, 1H, $C_8$–H), 7.62 (t, $J$ = 7.5 Hz, 1H, $C_{10}$–H), 8.39 (d, $J$ = 8 Hz, 1H, $C_{11}$–H), 12.90 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 19.46 ($CH_3$), 100.51 (C), 102.43 (C), 119.49 (C), 121.41 (CH), 125.58 (CH), 128.78 (CH), 130.96 (CH), 141.33 (C), 141.76 (C), 147.70 (C), 152.93 (C), 156.65 (C–$NH_2$), 157.82 (C–$NH_2$) ppm; MS (ESI) $m/z$: 265.17 $[M + H]^+$. Anal. calcd for $C_{14}H_{12}N_6$ (%): C, 63.62; H, 4.58; N, 31.80; found (%): C, 63.57; H, 4.55; N, 31.74.

**1,10-Dimethyl-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6i).** Yellow solid, yield: 82% (456 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3420, 3294, 3207, 3109 (NH), 1611, 1572, 1506, 1381, 1319, 1103, 1004, 844, 749, 702, 666, 606; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 2.47 (s, 3H, $C_{10}$–$CH_3$), 2.71 (s, 3H, $C_1$–$CH_3$), 6.50 (s, 2H, $NH_2$), 6.83 (s, 2H, $NH_2$), 7.44 (s, 2H, $C_8$–H, $C_9$–H), 8.18 (s, 1H, $C_{11}$–H), 12.87 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 19.50 ($CH_3$), 21.15 ($CH_3$), 100.87 (C), 102.34 (C), 119.17 (C), 123.17 (C), 128.06 (C), 130.34 (CH), 132.53 (CH), 140.99 (CH), 141.47 (C), 148.26 (C), 153.06 (C), 156.18 (C–$NH_2$), 157.88 (C–$NH_2$) ppm; MS (ESI) $m/z$: 279.17 $[M + H]^+$. Anal. calcd for $C_{15}H_{14}N_6$ (%): C, 64.73; H, 5.07; N, 30.20; found: C, 64.65; H, 5.02; N, 30.16.

**10-Fluoro-1-methyl-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6j).** Yellow solid, yield: 86% (485 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3416, 3334, 3089 (NH), 1620, 1601, 1550, 1498, 1388, 1242, 1170, 979, 848, 822, 755; $^1$H-NMR (DMSO-$d_6$, 500 MHz): $\delta$ = 2.73 (s, 3H, $C_1$–$CH_3$), 6.59 (s, 2H, $NH_2$), 6.86 (s, 2H, $NH_2$), 7.52 (td, $J$ = 8.5 Hz, 2.5 Hz, 1H, $C_9$–H), 7.59 (dd, $J$ = 8.5 Hz, 6.0 Hz, 1H, $C_8$–H), 8.14 (dd, $J$ = 10.5 Hz, 2.50 Hz, 1H, $C_{11}$–H), 12.95 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 19.54 ($CH_3$), 100.83 (C), 102.24 (C), 112.73 (CH), 112.92 (CH), 119.54 (CH), 119.66 (CH), 119.73 (C), 127.62 (C), 127.69 (CH), 140.61 (C), 141.17 (C), 144.57 (C), 156.07 (C), 156.37 (C), 157.83 (C–$NH_2$), 157.96 (C–$NH_2$) ppm; MS (ESI) $m/z$: 283.17 $[M + H]^+$. Anal. calcd for $C_{14}H_{11}FN_6$ (%): C, 59.57; H, 3.93; N, 29.77; found (%): C, 59.51; H, 3.90; N, 29.73.

**10-Chloro-1-methyl-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6k).** Yellow solid, yield: 85% (507 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3416, 3324, 3100 (NH), 1622, 1570, 1542, 1386, 821, 702; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 2.71 (s, 3H, $C_1$–$CH_3$), 6.86 (s, 4H, $NH_2$, $NH_2$), 7.53 (d, $J$ = 8.7 Hz, 1H, $C_8$–H), 7.61 (dd, $J$ = 8.7 Hz, 2.1 Hz, 1H, $C_9$–H), 8.39 (d, $J$ = 1.8 Hz, 1H, $C_{11}$–H), 12.82 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 19.46 ($CH_3$), 100.74 (C), 102.22 (C), 120.14 (C), 120.17 (C), 125.05 (CH), 127.45 (CH), 130.91 (CH), 140.23 (C), 141.09 (C), 146.21 (C), 153.15 (C), 157.07 (C–$NH_2$), 157.81 (C–$NH_2$) ppm; MS (ESI) $m/z$: 299.17 $[M + H]^+$; MS (ESI), $m/z$ (relative intensity, %) 298 ($M^+$, 100), 282 (2.4), 263 (6.7), 246 (2.6), 219 (3.5), 190 (2.2), 179 (3.3), 149 (4.8), 63 (1.6), 42 (1.4); HRMS (EI-HR) $m/z$ calcd for $C_{14}H_{11}ClN_6$ (%); 298.0734, found 298.0734. Anal. calcd for $C_{14}H_{11}ClN_6$ (%): C, 56.29; H, 3.71; N, 28.13; found (%): C, 56.32; H, 3.73; N, 28.1.

**10-Bromo-1-methyl-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6l).** Yellow solid, yield: 84% (575 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3416, 3322, 3159, 3088 (NH), 1629, 1596, 1568, 1496, 1452, 1385, 1324, 1280, 1105, 1071, 936, 820, 745, 666; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 2.70 (s, 3H, $C_1$–$CH_3$), 6.81 (s, 2H, $NH_2$), 6.86 (s, 2H, $NH_2$), 7.47 (d, $J$ = 8.7 Hz, 1H, $C_8$–H), 7.71 (d, $J$ = 8.4 Hz, 1H, $C_9$–H), 8.52 (s, 1H, $C_{11}$–H), 12.99 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) $\delta$ = 19.48 ($CH_3$), 100.61 (C), 102.20 (C), 112.89 (C), 120.83 (C), 127.64 (CH), 130.43 (C), 133.49 (CH), 140.09 (CH), 141.31 (C), 146.60 (C), 152.98 (C), 157.16 (C–$NH_2$), 157.79 (C–$NH_2$) ppm; MS (ESI) $m/z$: 343.08 $[M + H]^+$. Anal. calcd for $C_{14}H_{11}BrN_6$ (%): C, 49.00; H, 3.23; N, 24.49; found (%): C, 48.95; H, 3.20; N, 24.44.

**1-Methyl-10-nitro-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6m).** Yellow solid, yield: 85% (524 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3421, 3315 (NH), 1620, 1573, 1543, 1478, 1315, 1151, 1000, 839, 739; $^1$H-NMR (DMSO-$d_6$, 500 MHz): $\delta$ = 2.80 (s, 3H, $C_1$–$CH_3$), 6.86 (s, 2H, $NH_2$), 7.45 (s, 2H,

$NH_2$), 7.57 (d, $J$ = 9.5 Hz, 1H, $C_8$–H), 8.33 (dd, $J$ = 9.0 Hz, 2.5 Hz, 1H, $C_9$–H), 9.37 (s, 1H, $C_{11}$–H), 13.08 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 19.50 ($CH_3$), 100.19 (C), 102.46 (C), 117.96 (C), 125.01 (CH), 125.84 (C), 126.08 (CH), 130.15 (CH), 140.28 (C), 141.50 (C), 152.38 (C), 153.19 (C), 157.87 (C–$NH_2$), 159.50 (C–$NH_2$) ppm; MS (ESI) $m/z$: 308.08 $[M - H]^-$. Anal. calcd for $C_{14}H_{11}N_7O_2$ (%): C, 54.37; H, 3.58; N, 31.70; found (%): C, 54.32; H, 3.55; N, 31.66.

**1-Methyl-10-(trifluoromethoxy)-2*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridine-5,6-diamine (6n).** Yellow solid, yield: 88% (613 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3407, 3305, 3111 (NH), 1612, 1547, 1389, 1205, 1149, 826, 699; $^1$H-NMR (DMSO-$d_6$, 500 MHz): $\delta$ = 2.70 (s, 3H, $C_1$–$CH_3$), 6.80 (s, 2H, $NH_2$), 6.85 (s, 2H, $NH_2$), 7.61 (m, 2H, $C_8$–H, $C_9$–H), 8.30 (s, 1H, $C_{11}$–H), 12.98 (s, 1H, pyrazole NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 19.30 ($CH_3$), 100.57 (C), 102.21 (C), 119.41 (CH), 119.88 (CH), 120.49 (CH), 121.91 (CH), 124.79 (C), 127.46 (C), 140.66 (C), 141.26 (C), 142.15 (C), 146.68 (C), 152.98 (C), 157.32 (C–$NH_2$), 157.83 (C–$NH_2$) ppm; MS (ESI) $m/z$: 349.17 $[M + H]^+$. Anal. calcd for $C_{15}H_{11}F_3N_6O$ (%): C, 51.73; H, 3.18; N, 24.13; found (%): C, 51.66; H, 3.15; N, 24.09.

### General procedure for the synthesis of benzo[*c*]pyrazolo[4,3-*f*]pyrimido[4,5,6-*ij*][2,7]naphthyridines (11a–f)

A solution of benzo[*c*]pyrazolo[2,7]naphthyridines **6h–m** (2 mmol) in acetic anhydride (6 ml) was heated at 60 °C for 2–3 h. The completion of the reaction was indicated by TLC, the precipitate formed was filtered and washed with water. The crude product was recrystallized in methanol to obtain pure heterocycles **11a–f**.

**1,6-Dimethyl-2,5-dihydrobenzo[*c*]pyrazolo[4,3-*f*]pyrimido[4,5,6-*ij*][2,7]naphthyridine (11a).** Yellow green solid, yield: 93% (537 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3344, 3245, 3048 (NH), 1637, 1587, 1535, 1439, 1402, 1277, 1243, 1162, 1116, 1089, 892, 739, 689, 655, 606; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 2.43 (s, 3H, $C_6$–$CH_3$), 2.95 (s, 3H, $C_1$–$CH_3$), 7.52 (m, 1H, $C_{11}$–H), 7.76 (d, $J$ = 8.1 Hz, 2H, $C_9$–H, $C_{10}$–H), 8.80 (d, $J$ = 8.4 Hz, 1H, $C_{12}$–H), 12.41 (brs, 1H, pyrimido NH), 13.43 (s, 1H, pyrazolo NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 20.122 ($CH_3$), 22.00 ($CH_3$), 66.34 (C), 102.43 (C), 104.73 (C), 119.76 (C), 125.16 (C), 126.55 (CH), 128.09 (CH), 132.75 (CH), 136.25 (CH), 141.37 (C), 147.69 (C), 151.34 (C), 153.56 (C), 155.76 (C) ppm; MS (ESI) $m/z$: 289.25 $[M + H]^+$. Anal. calcd for $C_{16}H_{12}N_6$ (%): C, 66.66; H, 4.20; N, 29.15; found (%): C, 66.69; H, 4.23; N, 29.19.

**1,6,11-Trimethyl-2,5-dihydrobenzo[*c*]pyrazolo[4,3-*f*]pyrimido[4,5,6-*ij*][2,7]naphthyridine (11b).** Yellow solid, yield: 94% (574 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3252, 3131, 3056 (NH), 1637, 1587, 1541, 1437, 1279, 1010, 895, 823, 770, 684; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 1.22 (s, 3H, $C_6$–$CH_3$), 2.40 (s, 3H, $C_{11}$–$CH_3$), 2.92 (s, 3H, $C_1$–$CH_3$), 7.55 (d, $J$ = 7.8 Hz, 1H, $C_9$–H), 7.60 (d, $J$ = 7.2 Hz, $C_{10}$–H), 8.54 (s, 1H, $C_{12}$–H), 12.51 (brs, 1H, pyrimido NH), 13.39 (s, 1H, pyrazolo NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 20.01 ($CH_3$), 22.11 ($CH_3$), 23.45 ($CH_3$), 66.18 (C), 102.27 (C), 104.18 (C), 119.61 (C), 122.18 (C), 125.39 (C), 128.55 (CH), 130.72 (CH), 140.82 (CH), 143.69 (C), 148.73 (C), 154.35 (C), 157.49 (C), 158.82 (C) ppm; MS (ESI) $m/z$: 303.25 $[M + H]^+$. Anal. calcd for $C_{17}H_{14}N_6$ (%): C, 67.54; H, 4.67; N, 27.80; found (%): C, 67.49; H, 4.63; N, 27.77.

**11-Fluoro-1,6-dimethyl-2,5-dihydrobenzo[*c*]pyrazolo[4,3-*f*]pyrimido[4,5,6-*ij*][2,7]naphthyridine (11c).** Greenish yellow solid, yield: 96% (588 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3181, 3135, 3076 (NH), 1639, 1620, 1594, 1547, 1438, 1278, 1247, 1176, 1160, 1113, 1019, 985, 897, 776, 686; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 2.41 (s, 3H, $C_6$–$CH_3$), 2.97 (s, 3H, $C_1$–$CH_3$), 7.69 (td, $J$ = 9.3 Hz, 3 Hz, 1H, $C_{10}$–H), 7.81 (m, 1H, $C_9$–H), 8.55 (dd, $J$ = 11.1 Hz, 2.7 Hz, 1H, $C_{12}$–H), 12.48 (brs, 1H, pyrimido NH), 13.48 (s, 1H, pyrazolo NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 20.56 ($CH_3$), 22.66 ($CH_3$), 66.72 (C), 102.84 (C), 104.66 (C), 112.15 (CH), 112.92 (CH), 120.91 (C), 127.22 (CH), 127.99 (CH), 132.56 (C), 137.58 (CH), 143.40 (C), 146.62 (C), 154.35 (C), 156.15 (C), 156.62 (C), 157.08 (C), 157.63 (C) ppm; MS (ESI) $m/z$: 307.25 $[M + H]^+$. Anal. calcd for $C_{16}H_{11}N_6F$ (%): C, 62.74; H, 3.62; N, 27.44; found (%): C, 62.69; H, 3.60; N, 27.40.

**11-Chloro-1,6-dimethyl-2,5-dihydrobenzo[*c*]pyrazolo[4,3-*f*]pyrimido[4,5,6-*ij*][2,7]naphthyridine (11d).** Yellow green solid, yield: 95% (614 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3137, 3058 (NH), 1641, 1586, 1536, 1272, 1242, 1168, 1132, 1088, 947, 842, 715, 657; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 2.46 (s, 3H, $C_6$–$CH_3$), 2.92 (s, 3H, $C_1$–$CH_3$), 7.69 (d, $J$ = 8.7 Hz, 1 Hz, 1H, $C_9$–H), 7.79 (dd, $J$ = 9 Hz, 2.1 Hz, 1H, $C_{10}$–H), 8.75 (d, $J$, 1.8 Hz, 1H, $C_{12}$–H), 12.53 (brs, 1H, pyrimido NH), 13.65 (s, 1H, pyrazolo NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 20.50 ($CH_3$), 22.47 ($CH_3$), 66.03 (C), 102.78 (C), 104.69 (C), 120.95 (C), 127.34 (C), 128.49 (C), 129.27 (CH), 132.51 (CH), 137.68 (CH), 143.27 (C), 146.82 (C), 150.15 (C), 154.42 (C), 156.57 (C) ppm; MS (ESI) $m/z$: 323.17 $[M + H]^+$. Anal. calcd for $C_{16}H_{11}N_6Cl$ (%): C, 59.54; H, 3.44; N, 26.04; found (%): C, 59.51; H, 3.42; N, 26.00.

**11-Bromo-1,6-dimethyl-2,5-dihydrobenzo[*c*]pyrazolo[4,3-*f*]pyrimido[4,5,6-*ij*][2,7]naphthyridine (11e).** Yellow green solid, yield: 97% (718 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3255, 3186, 3057 (NH), 1639, 1585, 1536, 1484, 1335, 1272, 1197, 1014, 937, 896, 705, 643; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 2.41 (s, 3H, $C_6$–$CH_3$), 2.93 (s, 3H, $C_1$–$CH_3$), 7.63 (d, $J$ = 8.1 Hz, 1H, $C_9$–H), 7.84 (dd, $J$ = 9 Hz, 2.1 Hz, 1H, $C_{10}$–H), 8.94 (d, $J$ = 1.8 Hz, 1H, $C_{12}$–H), 12.54 (brs, 1H, pyrimido NH), 13.50 (s, 1H, pyrazolo NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 20.48 ($CH_3$), 22.54 ($CH_3$), 66.33 (C), 102.33 (C), 104.28 (C), 120.97 (C), 126.22 (C), 128.57 (C), 130.53 (CH), 133.66 (CH), 140.96 (CH), 142.24 (C), 147.30 (C), 153.06 (C), 156.56 (C), 158.33 (C) ppm; MS (ESI) $m/z$: 367.17 $[M + H]^+$. Anal. calcd for $C_{16}H_{11}N_6Br$ (%): C, 52.33; H, 3.02; N, 22.89; found (%): C, 52.36; H, 3.05; N, 22.92.

**1,6-Dimethyl-11-nitro-2,5-dihydrobenzo[*c*]pyrazolo[4,3-*f*]pyrimido[4,5,6-*ij*][2,7]naphthyridine (11f).** Yellow solid, yield: 97% (646 mg), mp > 300 °C; IR (KBr, $cm^{-1}$): 3394, 3178, 3058 (NH), 1640, 1614, 1542, 1516, 1490, 1448, 1378, 1333, 1256, 1130, 999, 893, 804, 712, 638; $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 2.39 (s, 3H, $C_6$–$CH_3$), 2.93 (s, 3H, $C_1$–$CH_3$), 7.58 (d, $J$ = 9.3 Hz, 1H, $C_9$–H), 8.28 (dd, $J$ = 9 Hz, 2.4 Hz, 1H, $C_{10}$–H), 9.52 (d, $J$ = 2.1 Hz, 1H, $C_{12}$–H), 12.67 (brs, 1H, pyrimido NH), 13.51 (s, 1H, pyrazolo NH) ppm; $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) $\delta$ = 20.57 ($CH_3$), 22.56 ($CH_3$), 66.90 (C), 102.51 (C), 104.71 (C), 118.75 (C), 126.97 (C), 129.59 (CH), 130.95 (CH), 137.37 (CH), 141.46 (C), 143.84 (C), 149.14 (C), 151.79 (C), 155.26 (C), 157.66 (C) ppm; MS (ESI) $m/z$:

332.08 $[M - H]^-$. Anal. calcd for $C_{16}H_{11}N_7O_2$ (%): C, 57.66; H, 3.33; N, 29.42; found (%): C, 57.63; H, 3.31; N, 29.38.

## Conflicts of interest

There are no conflicts to declare.

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