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RAPID COMMUNICATION

An efficient Synthesis and Photophysical Properties of 1*H*-pyrazolo-[3,4-*b*]pyridine and pyrazolo[3,4-*b*][1,8] naphthyridines

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Abstract A novel synthon 6-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridine-5-carbaldehyde **4** was synthesized by multistep process. Then Friedlander condensation of this synthon with reactive methylenes was performed to achieve interesting tricyclic **6a**-**b**, tetracyclic **6d** and pentacyclic **6c** N-heterocycles in excellent yield. The absorption and emission spectra of compounds **1**–**4** and **6** were measured and observed that the absorption and emission depends on the substituent at C-6 and C-7 position of pyridine ring in naphthyridines skeleton **6**.

Keywords 6-amino-3(4-methoxyphenyl)-1-phenyl-1*H*--pyrazolo[3,4-*b*]pyridine-5-carbaldehyde · pyrazolo[3,4-*b*][1,8]naphthyridines · 3-(4-methoxyphenyl)-1-phenyl-6,7,8,9-tetrahydro-1*H*-benzo[b]pyrazolo[4,3-*b*][1,8]naphthyridines · Absorption and emission spectra · Fluorescence · Quantum yield

Introduction

Development of novel fluorescent molecules as chemosensors for the detection of chemically, biologically, and environmentally important functional molecules has received much attention in recent years [1–4]. The first naphthyridine derivatives were prepared in 1893 by Reissert who suggested the name naphthyridine [5]. From literature it was also noted that 1,8-naphthyridine derivatives were not only use as luminescence materials in molecular recognition because of their rigid planer structure [6–8], possess antibacterial [9], antymicobacterial [10], antitumoral [11], anti-inflammatory [12], antiplatelet [13], gastric antisecretary [14], antiallergic [15] and local anaesthetic [16]. Recently, our research group reported systematic studies about the fluorescence properties of differently substituted pyrazolofused heterocycles [17–22] and benzo naphthyridines [23–26]. Annulation reactions with hetrocyclic aminoaldehydes provides synthectic entry into hetrocyclic systems, fused to a pyridine or pyrimidine nucleus by Friedlander condensation reactions with reactive methylenes. Thus a suitable blue-emitting material with high brightness and good thermal stability still remains to be developed. These literature reports and our ongoing research in this area prompted us to synthesize new pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4-*b*][1,8]naphthyridines.

Results and Discussion

The key starting material 6-amino-3-(3-bromo-4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide **1** (Scheme 1) containing two bifunctional groups was prepared by Friedlander condensation of 5-amino-3-(3-bromo-4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-cabaldehyde with cyanoacetamide [27].

Our initial aim in this work was to design a short and efficient synthetic strategy for synthesis of 6-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde **4**. For preparing pyrazolo[3,4-*b*]pyridine was used a known synthetic sequence, typically via reaction the 5-aminopyrazole with diethyl ethoxy methylenemalonate. This is general, easy and extensible technology for the

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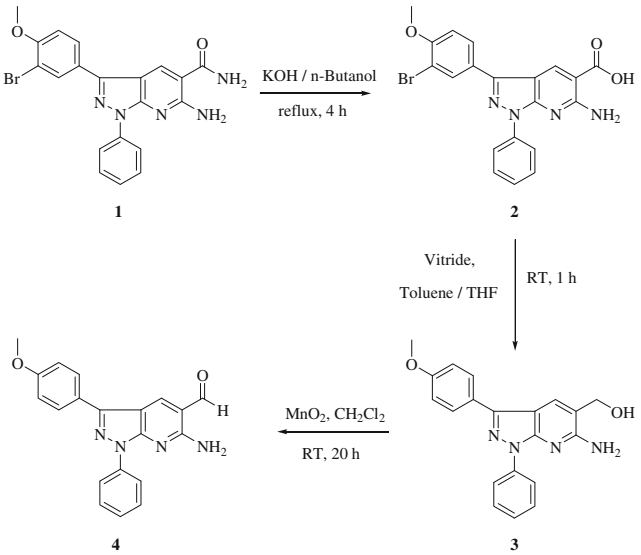


Scheme 1 Synthesis of 6-amino-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbaldehyde

construction of this heterocycles system [28–32]. A convenient route was successfully developed for the synthesis of novel synthon **4** with amino and aldehyde functionality adjacent to each other which is depicted in (Scheme 1).

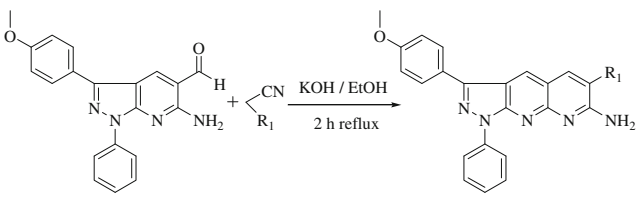
The synthesis begins with *o*-aminocarboxamide **1**. The hydrolysis of *o*-aminocarboxamide **1** is difficult in low boiling alcoholic solvents because of low solubility. We had tried hydrolysis in methanol, ethanol, isopropanol and tert-butanol. Hydrolysis of *o*-aminocarboxamide compound **1** under reflux conditions in n-butanol was successful and gave colourless solid with 93 % yield. The obtained solid was characterized by spectral and analytical data and assigned 6-amino-3-(3-bromo-4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*-]pyridine-5-carboxylic acid **2**.

Compound **3** was obtained by reduction of acid **2** using vitride in 93 % yield in which unexpected debromination was observed (Reductive dehalogenation). The same reduction was also carried out by using different reducing agents such as Lithium aluminium hydride ($LiAlH_4$), Diisobutylaluminium hydride (DIBAL-H), but starting material was not consumed. After completion of reaction, Al-complex was hydrolysed with aqueous ammonium acetate solution. Inorganic salts were filtered through celite. Aqueous layer was extracted with ethyl acetate, the organic solvent was evaporated under reduced pressure and furnished a pale yellow solid. It was crystallized from methanol and characterized by spectral and analytical data and assigned (6-amino-3-(4-methoxy-phenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl) methanol **3**.

Then the target synthon **4** was achieved by oxidation of primary alcohol to aldehyde is a useful reaction in organic chemistry. A variety of reagents are reported for the oxidation of primary alcohol to aldehyde this conversion several oxidizing agents are known such as pyridinium dichromate (PDC), pyridinium chlorochromate (PCC) and Dess-Martin periodonate. Oxidation of alcohol to aldehyde is partial oxidation; aldehydes are further oxidized to carboxylic acid. Hence, we have carried out oxidation at room temperature for 24 h. Then the dark brown colored solution was filtered through celite. The solvent was removed from the colourless filtrate which yielded a colourless solid. It was crystallized from methanol and characterized by spectral and analytical data and assigned 6-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde **4**. Thus versatile synthon was utilized for the synthesis of pyrazolo[3,4-*b*][1,8]naphthyridines **6**.

For the annulations of heterocyclic system *o*-aminoaldehyde has wide applicability. From literature it was noted that *o*-aminoaldehyde such as **4** has wide applicability. The first and best known member of this class of compounds has been utilized for synthesis of various heterocycles [33–37]. Recently, we have applied Friedlander reaction to 5-aminopyrazole-4-carbaldehyde and found that reactions with active methylene compounds are useful for the synthesis of pyrazolo[3,4-*b*]pyridines [27]. On the extension of this reaction we wish to describe synthesis of pyrazolo[3,4-*b*]- [1,8]naphthyridines **6** a tricyclic heterocycles with four or more nitrogen atoms. The Friedlander reaction is initiated by attack of a carbanion formed from an active methylene or methyl neighbouring to the carbonyl function on the formyl carbon atom of *o*-aminoaldehyde **4** followed by cyclization to afford the pyrazolo[3,4-*b*]- [1,8]naphthyridine skeleton such as **6**.

Thus, the Friedlander condensation of 6-aminopyrazolo[3,4-*b*]pyridine-5-carbaldehyde **4** with reactive methylenes was studied. Initially condensation was performed with cyanoacetamide **5a** in refluxing ethanolic potassium hydroxide solution for 2 hours (Scheme 2). It was observed that the solid crystallized out from the yellow colored reaction mass at reflux temperature itself, which was cooled to room temperature and isolated by filtration. The obtained solid was purified by crystallization from ethanol as yellow colored solid in 88 % yield. The obtained solid was characterized by spectral and analytical data and assigned as 7-amino-3-(4-methoxyphenyl)-1-phenyl-



5, 6	R_1
a	$CONH_2$
b	CN

Scheme 2 7-amino-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazolo- [3,4-b][1,8]naphthyridine derivatives **6a** and **6b**

1*H*-pyrazolo[3,4-*b*][1,8]naphthyridine-6-carboxamide **6a**. Analogously, malononitrile was condensed with *o*-aminoaldehyde **4** under similar reaction conditions to yield 7-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo- [3,4-*b*][1,8]naphthyridine-6-carbonitrile **6b** and characterized by spectral and analytical data.

After successful condensation of cyanoacetamide and malononitrile we extend our strategy towards cyclic ketone. We performed condensation of 6-aminopyrazolo- [3,4-*b*-]pyridine-5-carbaldehyde **4** with 1-indanone **5c** (Scheme 3) which yielded yellowish brown solid under similar reaction condition described for synthesis of **6a-b**. The obtained solid was purified characterized by spectral and analytical methods and assigned 3-(4-methoxyphenyl)-1-phenyl-1,6-dihydroindeno[1,2-*b*]pyrazolo- [4,3-*g*][1,8]naphthyridine **6c**. Thus we can achieve synthesis of polycyclic heterocycles using ketones as condensation partner.

Analogously cyclohexanone **5d** was condensed with *o*-aminoaldehyde **4** to achieve tetracyclic heterocycles **6d** (Scheme 4). It was also characterized by spectral and analytical methods and assigned 3-(4-methoxyphenyl)-1-phenyl-6,7,8,9-tetrahydro-1*H*-benzo[b]pyrazolo[4,3-*g*][1,8]naphthyridine **6d**.

Further the condensation of *o*-aminoaldehyde **4** was studied with acetophenones and alkyl ketones in ethanolic potassium hydroxide yielded pyrazolo naphthyridine derivatives **6e-j** in good yield (Scheme 5). Allthese compounds were characterized by spectral and analytical data.

We tried the Friedlander reaction using various organic bases such as pyridine, triethylamine, di-isopropylamine as well as inorganic bases such as sodium carbonate, potassium carbonate but it was observed that no product formation in the reaction that may be due to weak basicity of organic and inorganic bases. So further we planned reaction in strong bases such as NaOH, KOH and potassium tert-butoxide. Among all the strong bases KOH found to be effective for this condensation and gave better yield. Moreover, we found that the yield of product was decreased when reaction was carried out using NaOH and potassium tert-butoxide gave unwanted product. Friedlander reactions were carried out using potassium hydroxide under reflux in absolute ethanol. The use of 2 % of ethanolic potassium hydroxide solution was sufficient to promote the reaction with excellent yield.

Photophysical Properties

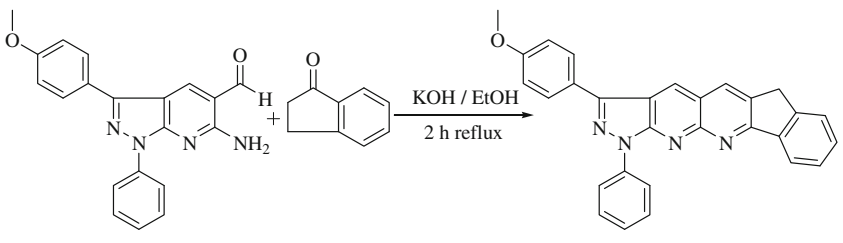
To the best of our knowledge, fused polycycle especially the fused heterocycles has efficient luminescence. All of our products **1**, **2**, **3**, **4** and **6a-j** exhibit strong fluorescence which can be distinguished by our eyes readily in DMSO or under UV light (360 nm), so the fluorescence properties of the synthesized compounds were evaluated, and the relationship between the observed fluorescence and the substitution pattern on the naphthyridine ring were deduced. Usually naphthyridine compounds are highly fluorescent after excitation to the locally exited state and some of the naphthyridine derivatives show interesting photo-induced properties. Therefore, we have tried to measure the absorption and fluorescence emission spectral properties of all pyrazolopyridines on Shimadzu's RF-3100 Spectrophotometer and Spectrofluorometer respectively, for $1x10^{-3}$M concentration in polar aprotic solvent DMSO. The results obtained are summarized in Table 1. The photophysical properties of compounds **1**, **2**, **3**, **4** and **6a-j** were determined with respect to quinine sulphate, which were used as a reference standard for the present study. We have calculated their fluorescence quantum yield and are listed in Table 1.

Calculation of the Fluorescence Quantum Yield

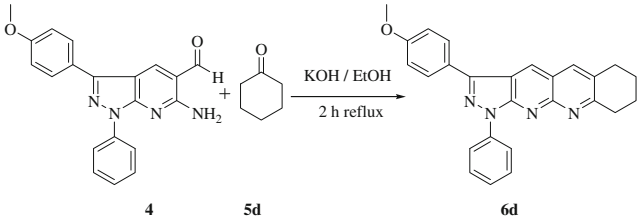
The fluorescence quantum yield is the important characteristic of fluorophores. The quantum yield (Φ_F) is the number of emitted photons relative to the number of absorbed photons. Substances with largest quantum yields, near to unity, such as rhodamines, display the brightest emission. The measurement of absolute quantum yields requires more sophisticated instrumentation. It is easier to determine relative quantum yields of fluorophores by comparing it with reference standard. The most commonly used reference standards are cresyl violet, fluorescein, quinine sulphate, tryptophan, L-tyrosine etc. Herein, we used quinine sulphate as a reference standard and calculated the quantum yields of pyrazolo[3,4-*b*][1,8]naphthyridines derivatives **6a-j** by using equation,

$$Q = Q_R \frac{I}{I_R} \frac{OD_R}{OD} \frac{n^2}{n_R^2}$$

Scheme 3 3-(4-methoxyphenyl)-1-phenyl-1,6-dihydroindeno[1,2-b]pyrazolo- [4,3-g][1,8]naphthyridine **6c**



4 **5c** **6c**



4 5d 6d

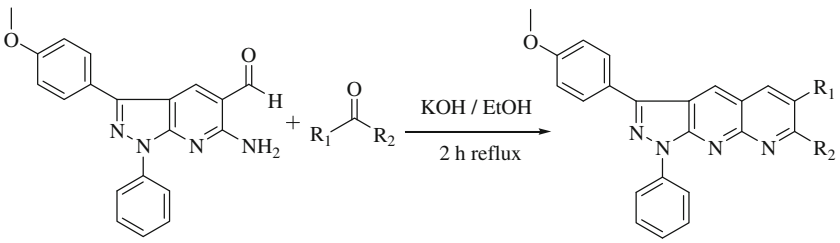
Scheme 4 3-(4-methoxyphenyl)-1-phenyl-6,7,8,9-tetrahydro-1H-benzo[b]pyrazolo[4,3-g][1,8]naphthyridine **6d**

Where *Q* is the quantum yield, *I* is the integrated intensity, *n* is the refractive index, and *OD* is the optical density. The subscript R refers to the reference fluorophore of known quantum yield. It was noted that the incorporation of constituent on to the pyrazolo[3,4-*b*]- [1,8]naphthyridines **6a-j** in the aryl ring at C_6 and C_7 position of pyridine nucleus has profound influence on the absorption and emission properties Fig. 1. These findings reveal that pyrazolo[3,4-*b*][1,8]naphthyridines **6a-j** substituted with electron donating substituent's such as alkyl group in the aryl ring at C_6 and C_7 of pyridine, enhanced the UV absorption in the range of 467–476 nm and fluorescence maxima in the range of 545–559 nm as well as quantum yields in the range of 0.30-0.34. Dialkyl substituted pyrazolo[3,4-*b*][1,8]naphthyridines **6 g-h** showed comparatively slight less fluorescence than mono alkyl substituted pyrazolo[3,4-*b*][1,8]naphthyridines **6i-j**. When the substituents is electron withdrawing such as aryl ring in the pyrazolo[3,4-*b*][1,8]naphthyridines **6e,f** reduces the UV absorption in the range of 441 and 444 nm and fluorescence maxima in the range of 513 and 516 nm along with quantum yields in the range of 0.28 and 0.29 respectively. Quantum yield results are summarized in Table 1 indicates that compound **6a-j** shown high quantum efficiency as compared to compound **1**–**4** may be due to conjugation through aromatic system. The comparative absorption and emission spectra of **6a-j** are graphically represented in Fig. 2.

Conclusion

In conclusion, we have described simple and efficient approach for the synthesis of highly functionalized 6-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbaldehyde **4** and it was utilized as synthon for Friedlander condensation with active methylenes to obtained novel tetracyclic or pentacyclic heterocycles i.e., pyrazolo[3,4-*b*][1,8]naphthyridines **6a-j**. The synthesis of new 6-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde **4** was carried out through a three stage process which involves the hydrolysis of *o*-amino carboxamide **1** followed by the reduction of carboxylic acid compound **2** with vitride to gave *o*-amino alcohol **3** and further oxidation with MnO_2 yielded the important key synthon i.e., *o*-aminoaldehyde **4**. All synthesized compounds were characterized by spectral and analytical data. It was observed that the pyrazolo[3,4-*b*]-[1,8]naphthyridines **6a-j** showed strong fluorescence, so we further studied the photophysical properties of these compounds in organic polar aprotic solvent DMSO. Potential correlations between structure and optical properties are discussed. The spectroscopic data are compiled and the quantum yields calculated are impressive. All these compounds emit high blue, yellow and green fluorescence with 0.17–0.34 quantum yields. All these findings reveal that pyrazolo[3,4-*b*][1,8]naphthyridine **6a-j** are very useful because of their stability and their photophysical properties. Moreover, these strongly fluorescent compounds may find

Scheme 5 6,7-disubstituted pyrazolo [3,4-b][1,8]naphthyridine derivatives **6e-j**



4 5e-j 6e-j

5	R_1	R_2
e	3-OMe-C_6H_4	CH_3
f	C_4H_3S(2-yl)	CH_3
g	CH_3CH_2	CH_3CH_2
h	CH_3	CH_3CH_2
i	CH_3	$CH(CH_3)_2$
j	CH_3	CH_3

6	R_1	R_2
e	3-OMe-C_6H_4	H
f	C_4H_3S(2-yl)	H
g	CH_3	CH_3CH_2
h	CH_3	CH_3
i	H	$CH(CH_3)_2$
j	H	CH_3

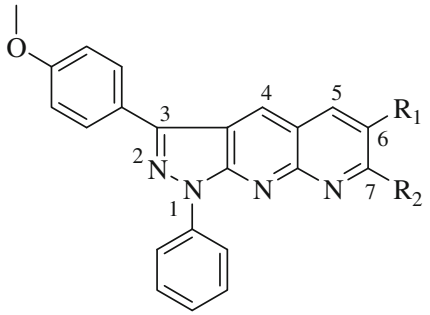


Fig. 1 Representative structure of compounds **6**

application in opto-electronic devices and are addition in the library of new heterocyclic compounds.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus, Model MFB595 in open capillary tubes and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS), and multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Infrared spectra were recorded as KBr pellets on a Shimadzu FTIR-408 spectrophotometer. Mass spectra were recorded on a Shimadzu LC-MS: EI QP 2010A mass spectrometer with ionization potential 70 eV. Elemental analyses were performed on Thermo Quest Flash 1112 Series EA analyzer. Reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60 F254 (Merck) plates using UV light (254 and 366 nm) for detection and compounds were purified by column chromatography by using silica gel of 5–20 μm (Merck, 60–120 mesh). Column dimension 39× 2 cm and elution volume used is about 200–400 mL for each product. Common reagent grade chemicals are either commercially available and were used without further purification or were prepared by standard literature procedures.

Synthesis of 6-amino-3-(3-bromo-4-methoxyphenyl) -1-phenyl-1*H*-pyrazolo- [3,4-*b*]pyridine-5-carboxylic acid, 2

A solution of amide **1** (15 g, 34.22 mmol) in n-butanol (150 ml) was refluxed with potassium hydroxide (15 g, 267.3 mmol in 15 ml water) for 4 h. The reaction mixture was stirred for about 4 hours at reflux empeature. After completion of the reaction as indicated by TLC (eluent chloroform/methanol, 9:1), and concentrated under reduced pressure. The reaction mixture was left to cool at room temperature; water (300 ml) was added to the solid residue to get clear solution. It was then acidified with hydrochloric acid to pH of about 2, solid obtained was filtered, washed with water to furnished **2**.

Colorless solid; (Yield=14 g, 93 %); mp 308-312 °C; IR (KBr, cm^{-1}): 3470, 3342, 1618, 1499; ^{1}H NMR (DMSO-d_6) δ: 13.26 (s, 1H), 8.76 (s, 1H), 8.32 (d, 2H, *J*=7.84 Hz), 8.15 (d, 1H, *J*=2.04 Hz), 7.97 (dd, 1H, *J*=8.56 Hz), 7.77 (s, 2H), 7.52 (t, 2H, *J*=7.84 Hz), 7.31 (m, 2H), 3.94 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 168.31, 159.16, 156.14, 152.44, 143.86, 139.14, 136.26, 131.05, 129.17 (2C), 127.93, 125.89, 125.87, 120.66 (2C), 113.29, 111.47, 107.21, 104.76, 56.57;

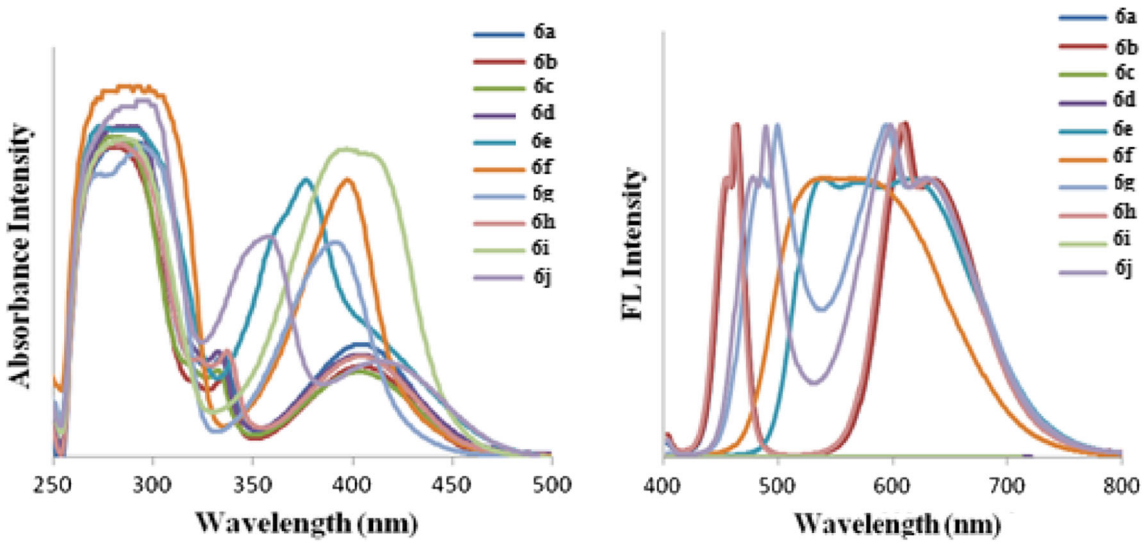


Fig. 2 The comparative absorption and fluorescence spectra of compounds 6a–j

Table 1 The Photophysical data for electronic absorption ($\lambda_{abs.\ max.}$), Fluorescence ($\lambda_{em.\ max.}$) and quantum yield (Φ_f) of pyrazolo[3,4-*b*][1,8]naphthyridines

Comp.	UV λ . Max/nm	Em λ. Max/nm	Quantum yield (Φ_f)
1	384	475	0.23
2	361	460	0.22
3	348	418	0.17
4	371	465	0.20
6a	456	537	0.33
6b	462	541	0.34
6c	439	507	0.27
6d	470	538	0.27
6e	441	513	0.29
6f	444	516	0.31
6 g	467	545	0.31
6 h	476	546	0.30
6i	473	551	0.32
6j	470	559	0.34

MS (EI): m/z=440 (M^{+1}). Anal. Calcd. for $C_{20}H_{15}BrN_4O_3$: C, 54.69; H, 3.44; N, 12.75. Found: C, 54.70; H, 3.28; N, 12.63.

Synthesis of (6-amino-3-(4-methoxyphenyl) -1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl) methanol, 3

To a solution of acid **2** (13 g, 29.61 mmol) in toluene, Vitride (52 ml) was charged at room temperature in one lot, with vigorous stirring, leads to an exothermic reaction. And the reaction mixture was stirred for one hour. Ammonium acetate solution in water (30 %) was added to quench the reaction mixture. Solid obtained was filtered through celite and washed with toluene. Filtrate transferred in seperatory funnel, aqueous layer was extracted with ethyl acetate (3×20 ml). Then the combined organic layers were washed with water (3×20 ml), dried over anhydrous sodium sulfate and concentrated in vacuum to furnished **3** pale yellow solid.

Pale yellow solid; (Yield=7.5 g, 73 %); mp 194-197 °C; IR (KBr, cm^{-1}): 3450, 3348, 1622, 1494; ^{1}H NMR (DMSO-d_6) δ: 8.39 (d, 2H, *J*=6.80 Hz), 8.15 (s, 1H), 7.95 (d, 2H, *J*= 6.80 Hz), 7.53 (m, 2H), 7.26 (m, 1H), 7.12 (d, 2H, *J*=6.80), 6.52 (s, 2H), 5.34 (t, 1H, *J*=5.20), 4.51 (d, 2H *J*=5.20), 3.85 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 159.95, 157.91, 151.13, 143.77, 140.36, 129.35 (2C), 128.86, 128.48 (2C), 125.96, 125.27, 120.38 (2C), 119.05, 114.87 (2C), 107.15, 60.72, 55.71; MS (EI): m/z=347 (M^{+1}), 369 (Na^+). Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.27; H, 5.30; N, 16.12.

Synthesis of 6-amino-3-(4-methoxyphenyl) -1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridine-5-carbaldehyde, 4

To the solution of **3** (7 g, 20.23 mmol) in dichloromethane (35 ml) was added Manganese (IV) dioxide (5.27 g, 60.59 mmol) at room temperature. The reaction mixture was stirred for 24 h at room temperature. After completion of the reaction as indicated by TLC (eluent ethylacetate/hexane, 1:1), the reaction mixture was filtered through celite and evaporated dichloromethane under reduced pressure. The crude product obtained was purified by crystallization from methanol to furnished **4** as pale yellow solid.

Pale yellow solid; (Yield=6.2 g, 89 %); mp 196-197 °C; IR (KBr, cm^{-1}): 3415, 3348, 1657, 1506; ^{1}H NMR (DMSO-d_6) δ: 9.95 (s, 1H), 8.90 (s, 1H), 8.29 (t, 2H, *J*=7.68 Hz), 8.00 (dd, 2H, *J* =1.84 Hz), 7.93 (s, 2H), 7.52 (m, 2H, *J*=7.68), 7.32 (d, 1H, *J*=7.40 Hz), 7.10 (d, 2H, *J*=8.84), 3.84 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 193.18, 160.20, 158.09, 158.02, 152.17, 145.71, 142.97, 139.05, 129.11, 128.54 (2C), 125.89, 124.25, 120.77 (2C), 114.58, 112.62, 112.59, 108.03, 55.39; MS (EI): m/z=345 (M^{+1}). Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.88; H, 4.73; N, 16.60.

Synthesis of 3-(4-methoxyphenyl) -1-phenyl-1*H*-pyrazolo[3,4-*b*][1,8]- naphthyridine derivatives, 6a–j

General Procedure

To a solution of 6-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]- pyridine-5-carbaldehyde **4** (2 mmol), aliphatic or aromatic ketones or cyclic ketones **(5a–j)** (2 mmol) was added ethanolic potassium hydroxide solution (10 ml, 2 %). The reaction mixture was refluxed for 2 h. After completion of the reaction as indicated by TLC (eluent ethylacetate/hexane, 1:1), the reaction mixture was cooled to room temperature. The precipitated solid was collected by filtration, washed with ethanol, dried and crystallized from ethanol.

7-amino-3-(4-methoxyphenyl) -1-phenyl-1*H*-pyrazolo[3,4-*b*][1,8] naphthyridine-6-carboxamide, 6a

This compound was synthesized by using cyanoacetamide; yellow solid (Yield=0.52 g, 88 %); mp>315 °C; IR (KBr, cm^{-1}): 3074, 3004, 1610, 1492; ^{1}H NMR (DMSO-d_6) δ: 9.00 (s, 1H), 8.73 (s, 1H), 8.51 (d, 2H, *J*=7.76 Hz), 8.26 (s, 1H), 8.11 (d, 2H, *J*=8.76 Hz), 7.87 (s, 2H), 7.69 (s, 1H), 7.58 (t, 2H, *J*=8.28 Hz), 7.31 (t, 1H, *J*=7.36 Hz), 7.17 (d, 2H, *J*= 8.80 Hz), 3.88 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 168.93,

160.14, 160.09, 156.14, 152.72, 144.48, 140.84, 139.38, 133.71, 129.02 (2C), 128.48 (2C), 125.21, 124.29, 119.95 (2C), 114.61 (2C), 114.54, 113.32, 112.64, 55.33. MS (EI): m/z=411 (M^{+1}). Anal. Calcd. for $C_{23}H_{18}N_6O_2$: C, 67.31; H, 4.42; N, 20.48. Found: C, 67.36; H, 4.27; N, 20.29.

7-amino-3-(4-methoxyphenyl) -1-phenyl-1*H*-pyrazolo[3,4-*b*][1,8] naphthyridine-6-carbonitrile, 6b

This compound was synthesized by using malononitrile; yellow solid (Yield=0.48 g, 86 %); mp>315 °C; IR (KBr, cm^{-1}): 3336, 3247, 2212, 1656, 1552; ^{1}H NMR (DMSO-d_6) δ: 9.16 (s, 1H), 8.91 (s, 1H), 8.47 (d, *J*=7.88 Hz, 2H), 8.10 (d, *J*= 8.68 Hz, 2H), 7.67 (s, 2H), 7.59 (t, *J*=7.62 Hz, 2H), 7.48 (s, 1H), 7.18 (d, *J*=8.76 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 165.35, 160.60, 153.24, 156.92, 150.67, 145.81, 141.10, 139.33, 131.84, 129.47 (2C), 128.54 (2C), 125.21, 124.29, 120.26 (2C), 116.37, 115.11, 114.54 (2C), 81.36, 25.82. MS (EI): m/z=393 (M^{+1}). Anal. Calcd. for $C_{23}H_{16}N_6O$: C, 70.40; H, 4.11; N, 21.42. Found: C, 70.51; H, 4.35; N, 21.33.

3-(4-methoxyphenyl) -1-phenyl-1,6-dihydroindeno[1,2-*b*]pyrazolo[4,3-*g*] [1,8]- naphthyridine, 6c

This compound was synthesized by using indanone; yellowish brown solid (Yield=0.47 g, 74 %); mp 310–312 °C; IR (KBr, cm^{-1}): 3469, 3327, 1642, 1509; ^{1}H NMR (DMSO-d_6) δ: 8.17 (s, 2H), 7.87 (d, 2H, *J*=8.15 Hz), 7.91 (m, 2H), 7.37 (m, 2H), 7.31 (m, 4H), 7.28 (dd, 1H, *J*=8.40 Hz), 7.16 (m, 2H) 3.88 (s, 2H), 3.75 (s, 3H).^{13}C NMR (DMSO-d_6) δ:160.35, 158.42, 155.12, 149.11, 145.98, 140.46, 139.33, 137.80, 135.74, 133.21, 131.96, 129.65, 129.40 (2C), 128.61 (2C), 127.44, 127.83, 126.05 (2C), 125.74, 120.19, 120.88 (2C), 114.67, 114.80 (2C), 55.62, 36.08; MS (EI): m/z=441 (M^{+1}). Anal. Calcd. for $C_{29}H_{20}N_4O$: C, 79.07; H, 4.58; N, 12.72. Found: C, 78.94; H, 4.37; N, 12.07.

3-(4-methoxyphenyl) -1-phenyl-6,7,8,9-tetrahydro-1*H*-benzo[b] pyrazolo[4,3-*g*]- [1,8]naphthyridine, 6d

This compound was synthesized by using cyclohexanone; yellow solid (Yield=0.49 g, 84 %); mp 246–249 °C; IR (KBr, cm^{-1}): 3439, 3340, 1611, 1496; ^{1}H NMR (DMSO-d_6) δ: 8.62 (s, 2H), 8.42 (d, 2H, *J*=8.00 Hz), 8.24 (d, 1H, *J*= 6.00 Hz), 7.91 (m, 2H), 7.52 (t, 2H, *J*=4.40 Hz), 7.27 (m, 1H), 7.01 (dd, 1H, *J*=8.40 Hz), 3.96 (s, 3H), 3.09 (m, 2H). 2.95 (m, 2H), 1.91 (m, 4H).^{13}C NMR (DMSO-d_6) δ: 160.91, 156.33, 156.02, 149.64, 146.95, 139.22, 135.10, 134.00, 132.87, 129.14 (2C), 128.35 (2C), 126.94, 125.30, 124. 17, 120.96 (2C), 114.28, 114.02 (2C), 55.48, 31.90, 31.88, 23.74 (2C); MS (EI): m/z=407 (M^{+1}). Anal. Calcd. for $C_{26}H_{22}N_4O$: C, 76.83; H, 5.46; N, 13.78. Found: C, 76.82; H, 5.81; N, 13.40.

7-(3-methoxyphenyl)-3-(4-methoxyphenyl) -1-phenyl-1*H*-pyrazolo[3,4-*b*][1,8]- naphthyridine, 6e

This compound was synthesized by using 3-methoxy acetophenone; yellow solid (Yield=0.54 g, 82 %); mp 214–217 °C; IR (KBr, cm^{-1}): 3476, 3321, 1609, 1502; ^{1}H NMR (DMSO-d_6) δ: 8.45 (d, 2H, *J*=7.60 Hz), 8.43 (s, 1H), 8.22 (m, 2H), 8.08 (m, 2H), 7.89 (s, 1H), 7.61 (dd, 1H, *J*=4.40), 7.52 (m, 2H), 7.27 (m, 2H), 6.99 (m, 3H), 3.94 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 162.32, 160.57, 160.20, 154.85, 152.42, 144.73, 140.14, 139.56, 139.33, 131.98, 129.79, 129.14 (2C), 128.82 (2C), 125.73, 124.82, 121.23 (2C), 120.67, 118.20, 118.01, 117.04, 116.98, 114.62 (2C), 112.93, 55.46, 30.94; MS (EI): m/z=459 (M^{+1}). Anal. Calcd. for $C_{29}H_{22}N_4O_2$: C, 75.97; H, 4.84; N, 12.22. Found: C, 75.91; H, 4.95; N, 12.10.

3-(4-methoxyphenyl)-1-phenyl-7-(thiophen-2-yl) -1*H*-pyrazolo[3,4-*b*][1,8]- naphthyridine, 6f

This compound was synthesized by using 2-acetyl thiophene; yellow solid (Yield=0.53 g, 85 %); mp 298–301 °C; IR (KBr, cm^{-1}): 3453, 3320, 1631, 1491; ^{1}H NMR (DMSO-d_6) δ: 9.18 (s, 1H), 8.55 (d, 2H, *J*=8.42 Hz), 8.47 (s, 1H), 8.22 (m, 2H), 7.71 (m, 2H), 7.60 (m, 1H), 7.30 (m, 2H), 7.28 (m, 1H), 7.11 (d, 1H, *J*=7.68 Hz), 7.03 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 160.52, 158.94, 152.06, 146.88, 148.87, 139.90, 139.33, 135.88, 135.27, 129.61 (2C), 128.41 (2C), 128.11, 127.95, 126.36 (2C), 125.89, 124.66, 121.47, 120.44 (2C), 115.72, 114.93 (2C), 55.74; MS (EI): m/z=435 (M^{+1}). Anal. Calcd. for $C_{26}H_{18}N_4OS$: C, 71.87; H, 4.18; N, 12.89. Found: C, 71.75; H, 4.39; N, 12.91.

7-ethyl-3-(4-methoxyphenyl) -6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*][1,8]- naphthyridine, 6 g

This compound was synthesized by using 3-pentanone; green solid (Yield=0.42 g, 75 %); mp 217–219 °C; IR (KBr, cm^{-1}): 3430, 3355, 1667, 1495; ^{1}H NMR (DMSO-d_6) δ: 9.35 (s, 1H), 8.52 (d, 2H, *J*=8.52 Hz), 8.36 (s, 1H), 8.17 (m, 2H), 7.63 (m, 2H), 7.36 (m, 1H), 7.18 (m, 2H), 3.89 (s, 3H), 3.02 (q, 2H),

2.57 (s, 3H), 2.52 (s, 3H), 1.37 (t, 3H, *J*=7.40 Hz). ^{13}C NMR (DMSO-d_6) δ: 161.42, 157.98, 154.90, 149.62, 145.77, 139.01, 135.44, 132.91, 131.80, 130.96, 128.31, 126.55, 125.78, 122.03, 120.58 (2C), 114.60, 114.04 (2C), 53.84, 25.37, 19.44, 15.60; MS (EI): m/z=395 (M^{+1}). Anal. Calcd. for $C_{25}H_{22}N_4O$: C, 76.12; H, 5.62; N, 14.20. Found: C, 76.46; H, 5.81; N, 14.57.

3-(4-methoxyphenyl) -6,7-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*][1,8]-naphthyridine, 6 h

This compound was synthesized by using methyl ethyl ketone; yellowish green solid (Yield=0.43 g, 78 %); mp 237–239 °C; IR (KBr, cm^{-1}): 3447, 3315, 1640, 1494; ^{1}H NMR (DMSO-d_6) δ: 8.77 (s, 1H), 8.62 (d, 2H, *J*=8.40 Hz), 8.06 (m, 2H), 8.02 (s, 1H), 7.54 (m, 2H), 7.27 (s, 1H), 7.10 (dd, 2H, *J*= 6.80, 4.80 Hz), 3.93 (s, 3H), 2.82 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 183.49, 165.17, 160.10, 151.42, 144.01, 139.38, 137.34, 132.14, 129.12, 128.83 (2C), 128.45 (2C), 125.06, 120.02 (2C), 118.06, 115.47, 114.38 (2C), 55.15, 30.54, 23.92, 18.80; MS (EI): m/z=381 (M^{+1}). Anal. Calcd. for $C_{24}H_{20}N_4O$: C, 75.77; H, 5.30; N, 14.73. Found: C, 75.90; H, 5.28; N, 14.55.

7-isopropyl-3-(4-methoxyphenyl) -1-phenyl-1*H*-pyrazolo[3,4-*b*][1,8]- naphthyridine, 6i

This compound was synthesized by using 3-methyl-2-butanone; yellowish green solid (Yield=0.45 g, 80 %); mp 180–183 °C; IR (KBr, cm^{-1}): 3450, 3338, 1626, 1491; ^{1}H NMR (DMSO-d_6) δ: 8.89 (s, 1H), 8.61 (dd, 2H, *J*= 8.40 Hz), 8.34 (d, 1H, *J*=8.40 Hz), 8.09 (dd, 2H, *J*=10, 7.20 Hz), 7.56 (t, 2H, *J*=7.60 Hz), 7.45 (d, 1H, *J*=8.80 Hz), 7.27 (s, 1H), 7.12 (dd, 2H, *J*=6.80, 4.80 Hz), 3.94 (s, 3H), 3.46 (m, 1H), 1.47 (d, 6H, *J*=7.20 Hz). ^{13}C NMR (DMSO-d_6) δ: 173.10, 162.45, 153.94, 151.50, 144.18, 139.44, 139.20, 133.40, 128.90 (2C), 128.50 (2C), 125.29, 124.11, 120.34 (2C), 118.74, 117.57, 115.67, 114.40 (2C), 55.16, 37.01, 21.96; MS (EI): m/z=395 (M^{+1}). Anal. Calcd. for $C_{25}H_{22}N_4O$: C, 76.12; H, 5.62; N, 14.20. Found: C, 76.03; H, 5.84; N, 14.18.

3-(4-methoxyphenyl) -7-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*][1,8] -naphthyridine, 6j

This compound was synthesized by using acetone; green solid (Yield=0.46 g, 88 %); mp 233–235 °C; IR (KBr, cm^{-1}): 3472, 3319, 1644, 1502; ^{1}H NMR (DMSO-d_6) δ: 8.35 (s, 1H), 8.62 (d, 2H, *J*=7.6), 8.24 (d, 1H, *J*=8.40), 8.06 (d, 2H, *J*=8.80), 7.55 (t, 2H, *J*=7.60), 7.27 (m, 2H), 7.10 (d, 2H, *J* =8.80), 3.92 (s, 3H), 2.88 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 160.47, 158.13, 157.08, 149.77, 145.30, 139.28, 135.11, 134.06, 129.99 (2C), 128.37 (2C), 126.61, 125.92, 124.26, 121.55, 120.55 (2C), 114.73, 114.09 (2C), 55.40, 24.68; MS (EI): m/z=367 (M^{+1}). Anal. Calcd. for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29. Found: C, 75.69; H, 4.70; N, 15.52.

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