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Fluorescence Studies of Novel Pyrazolopyridinone Fused Imidazopyridine Conjugates

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ABSTRACT: In a continuing effort towards the development of novel pyrazole based architectures with better pharmacological profile, fluorescence characteristics of novel pyrazolopyridinone fused imidazopyridine conjugates were investigated. During the fluorescence studies of these derivatives, different parameters like contact time, solvent system, concentration and effect of different substituents were examined for obtaining the desirable fluorescence results. SARs associated with different points of diversity of these derivatives have also been discussed. Derivatives 3fE and 3eE emerged as most fluorescent derivatives in the present series with fluorescence intensity of 427 a.u. and 399 a.u., respectively.

Keywords: Pyrazole, Imidazo[1,2-*a*]pyridines, Fluorescence, SARs

I. INTRODUCTION

Pyrazole is a privileged class of nitrogen containing heterocyclic compounds and represent an interesting template for the design, synthesis and development of biologically active molecules or drugs in the field of medicinal chemistry [1]. This unique nucleus is gifted with a wide spectrum of biological activities such as anticancer, antitumor, antibacterial, anti-inflammatory, antiviral, anti-HIV, antifungal, antidepressant and anticonvulsant [2]. Figure 1 summarizes some examples of biologically active pyrazole derivatives. Additionally, several drugs occupy pyrazole nucleus in their structure and some of these have been approved by FDA during past years. Drugs like sildenafil, zometapin, celebrex, and rimonabant have been commercialized successfully and are enlisted among the most selling drugs supporting the significance of pyrazole and its derivatives [3].

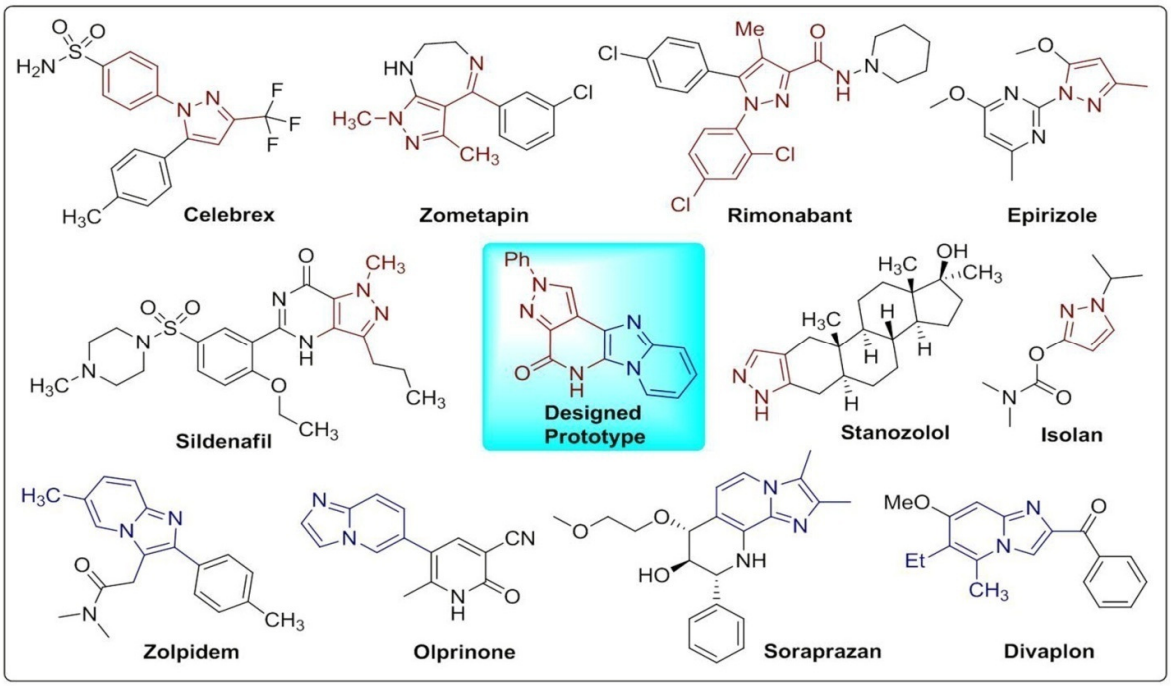


Fig. 1. Some examples of pyrazole and imidazo[1,2-*a*]pyridine based bioactive compounds and drugs.

Consequently, the syntheses of pyrazole embedded derivatives have caught the considerable attention of synthetic chemists working in this area. Similarly, imidazo[1,2-*a*]pyridine is a biologically rich nucleus belonging to family of nitrogen containing heterocyclic compounds and is decorated with widespread biological applications [4]. It is also prevalent in numerous commercial drugs such as zolpidem, soraprazan and olprinone (Fig. 1) [5] and it is worth while to mention that medicinal attributes of imidazo[1,2-*a*]pyridine derivatives have been comprehensively reviewed by our research group recently [6]. Therefore, inspired by their rich biological profile, these two pharmacophores (*i. e.* pyrazole and imidazo[1,2-*a*]pyridine nucleus) were amalgamated to construct a new molecular hybrid i.e. pyrazolopyridinone fused imidazopyridines as described in our previous report [7]. During the synthesis, these novel pyrazole based conjugates were observed to display fluorescence properties and therefore it was envisaged to further investigate their fluorescence characteristic. Here, in the present report, we have reported the results of fluorescence studies of pyrazolopyridinone fused imidazopyridines conjugates which involved the optimization of different parameters like contact time, concentration, solvent and effect of substituent. SARs related to different points of diversity have also been investigated.

II. MATERIALS AND METHODS

Fluorescence emission spectra for pyrazolopyridinone fused imidazopyridine derivatives were recorded on Agilent's Cary Eclipse Fluorescence spectrophotometer. Anhydrous solvent ($CHCl_3$) utilized in the studies was dried and freshly distilled before use. However, commercial anhydrous DMF, DMSO and MeOH (Spectrochem make) were used as such without further distillation.

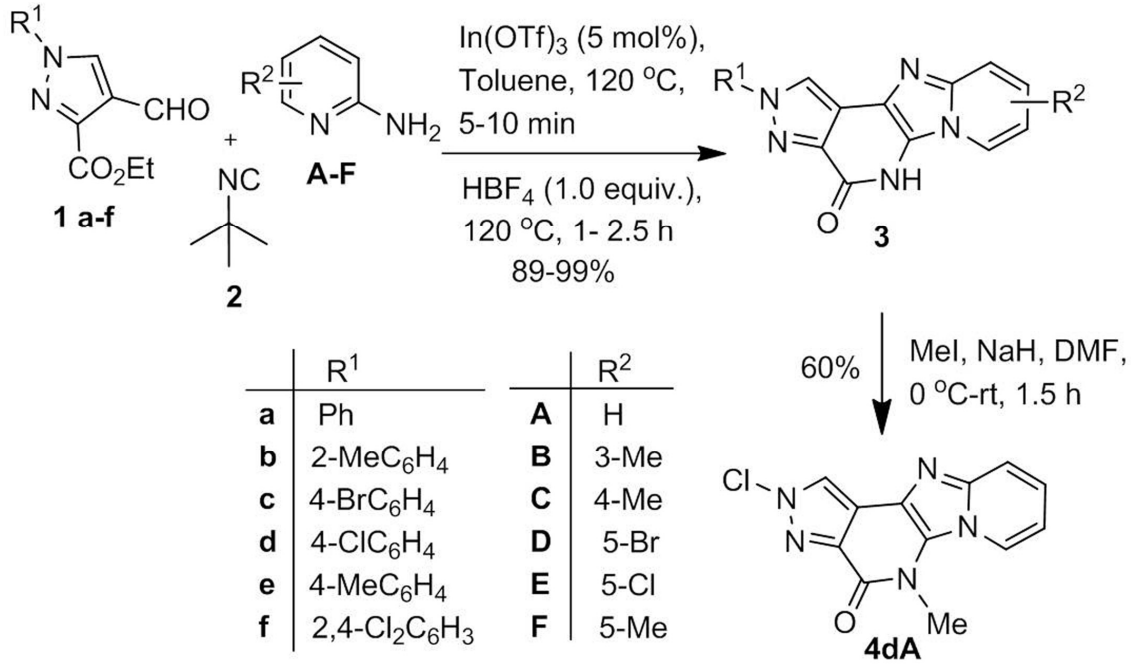
III. RESULTS AND DISCUSSION

A. Chemistry

Synthesis of desired pyrazolopyridinone fused imidazopyridine conjugates (**3**) was acheived from 4-formyl-1*H*-pyrazole-3-carboxylates (**1**), pyridin-2-amines (**A-F**) and *tert*-butyl isonitrile (**2**) *via* one pot $In(OTf)_3$ assisted Groebke-Blackburn-Bienayme (GBB) multicomponent reaction generating *N*-fused imidazo[1,2-*a*]pyridine scaffolds followed by HBF_4 mediated dealkylation and tandem intramolecular condensation as described in our previous report (Scheme 1) [7]. All the products were obtained in excellent yield (89-99%) and were characterized by NMR, FTIR and mass spectrometry. Formation of amide bond in derivatives **3** was further suppourted by carrying out the *N*-methylation of the product **3dA** and **4dA** was successfully obtained in 60% yield.

B. Fluorescence Studies

During the synthesis of pyrazolopyridinone fused imidazopyridines (**3** and **4**), these derivatives were observed to exhibit fluorescence properties. Therefore, it was decided to investigate the fluorescence properties of these derivatives. For obtaining the best fluorescence results, different parameters were optimized like contact time, solvent and concentration using **3aA** as model substrate.



	R^1
a	Ph
b	2-MeC_6H_4
c	4-BrC_6H_4
d	4-ClC_6H_4
e	4-MeC_6H_4
f	2,4-$Cl_2C_6H_3$

	R^2
A	H
B	3-Me
C	4-Me
D	5-Br
E	5-Cl
F	5-Me

Scheme 1. Synthesis of various pyrazolopyridinone fused imidazopyridine conjugates (**3** and **4).**

Fluorescence emission spectra for optimizing the contact time were recorded in 50% methanol in chloroform solution at different intervals of time (5 min, 15 min, 30 min, 45 min and 1 h) at 1×10^{-3} M concentration. It was revealed from the study that **3Aa** displayed maximum fluorescence intensity after 45 minutes of sample preparation. Further, solutions of **3aA** in different organic solvents *i.e.* DMF and DMSO were prepared for optimizing the solvent for obtaining the best fluorescence results. Fluorescence spectra were recorded after 45 minutes of sample preparation in 1×10^{-3} M concentration and fluorescence intensity was observed to be in the following order: 50% MeOH in $CHCl_3$>DMSO>DMF. After optimizing the contact time and solvent parameters, fluorescence emission profile of **3aA** was recorded in 50% MeOH in $CHCl_3$ at different concentrations *viz.* 1×10^{-3} M, 2×10^{-3} M, 3×10^{-3} M, 4×10^{-3} M and 5×10^{-3} M and the obtained results indicated that fluorescence intensity displayed fluctuating behavior. In general, it was found to decrease with increase in concentration. Results of optimization studies are presented in Fig. 2 and it was concluded from the studies that pyrazolopyridinone fused imidazopyridine derivative **3Aa** displayed the maximum fluorescence intensity in 50% MeOH in $CHCl_3$ at 1×10^{-3} M concentration after 45 minutes of sample preparation.

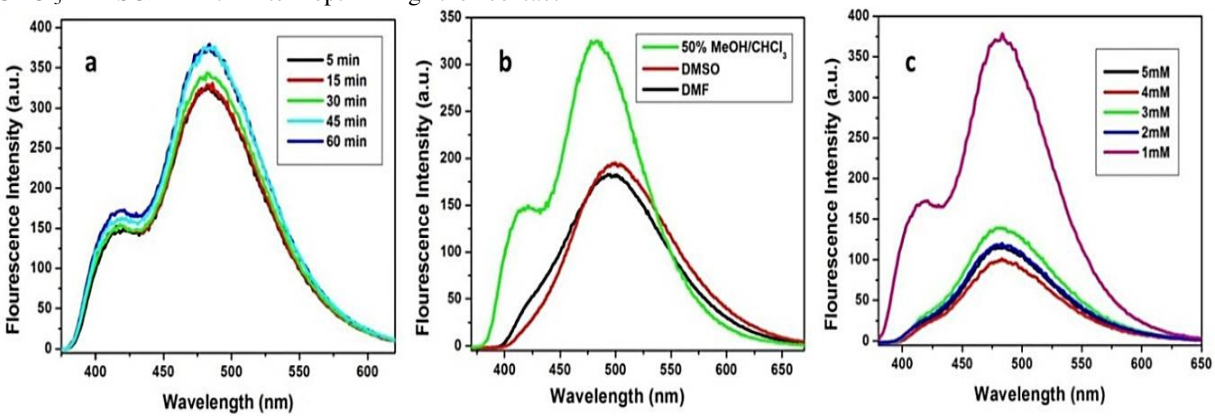


Fig. 2. Optimization results: a) Contact time; b) Solvent; c) Concentration.

Therefore, fluorescence studies of all the other derivatives were studied according to these optimized parameters *i.e.* time: 45 min; solvent: 50% MeOH in $CHCl_3$; concentration: 1×10^{-3} M. Results of fluorescence studies of all the pyrazolopyridinone fused imidazopyridine derivatives (**3** and **4**) are presented in Table 1.

Table 1: Results of fluorescence studies of 3 and 4.

S. No.	Compound No.	R^1	R^2	R^3	λ_{Ex} (nm)	λ_{Em}(nm)	Flourescence Intensity (a.u.)
1	**3aA**	Ph	H	H	236	484	379
2	**3aB**	Ph	3-Br	H	237	481	258
3	**3aC**	Ph	4-Me	H	272	486	221
4	**3aD**	Ph	5-Br	H	242	456	280
5	**3aE**	Ph	5-Cl	H	**Not fluorescent**		
6	**3aF**	Ph	5-Me	H	322	484	120
7	**3bA**	2-MeC_6H_4	H	H	236	485	258
8	**3bE**	2-Me-C_6H_4	5-Cl	H	246	473	240
9	**3cA**	4-Br-C_6H_4	H	H	238	486	277
10	**3cC**	4-Br-C_6H_4	4-Me	H	384	472	273
11	**3cD**	4-Br-C_6H_4	5-Br	H	402	467	171
12	**3cE**	4-Br-C_6H_4	5-Cl	H	246	481	222
13	**3cF**	4-Br-C_6H_4	5-Me	H	310	481	238
14	**3dA**	4-Cl-C_6H_4	H	H	304	483	251
15	**3dE**	4-Cl-C_6H_4	5-Cl	H	246	471	242
16	**3eA**	4-Me-C_6H_4	H	H	234	480	265
17	**3eC**	4-Me-C_6H_4	4-Me	H	236	483	252
18	**3eD**	4-Me-C_6H_4	5-Br	H	322	477	53
19	**3eE**	4-Me-C_6H_4	5-Cl	H	296	439	399
20	**3fA**	2,4-Cl_2-C_6H_3	H	H	270	486	258
21	**3fE**	2,4-Cl_2-C_6H_3	5-Cl	H	274	434	427
22	**4dA**	4-Cl-C_6H_4	H	Me	238	467	316

Derivatives **3fE** and **3eE** were the most fluorescent compound in the present series with fluorescence intensity of 427 a.u. and 399 a.u., respectively while compound **3aE** was not fluorescent at all. **3aA** also exhibited good fluorescent characteristic with fluorescence intensity of 379 a.u.

C. Structure-activity relationships

From the results presented in Table 1, some structure-fluorescence activity relationship was concluded which is outlined in Fig. 3. It was revealed from the structure-fluorescence activity relationship of pyrazolopyridinone fused imidazopyridine derivatives (**3** and **4**) that compounds with substituted phenyl group at R^1 position (**3aA, 3bA, 3cA** and **3dA**) were more fluorescent when R^2 = H with negligible effect on $\lambda_{emission}$. With exception, **3eE** and **3fE** were two most fluorescent derivatives where R^1 = 4-MeC_6H_4 or 2,4-$Cl_2C_6H_4$ and R^2 = 5-Cl. H substituent at R^2 position was more tolerated than other substituents except when R^1 = 4-MeC_6H_4 or 2,4-$Cl_2C_6H_4$ where 5-Cl group was more tolerated (**3eE** and **3fE**). Introduction of methyl group at R^3 position was found to enhance the fluorescence intensity (**3dA** and **4dA**) with a slight blue shift in $\lambda_{emission}$.

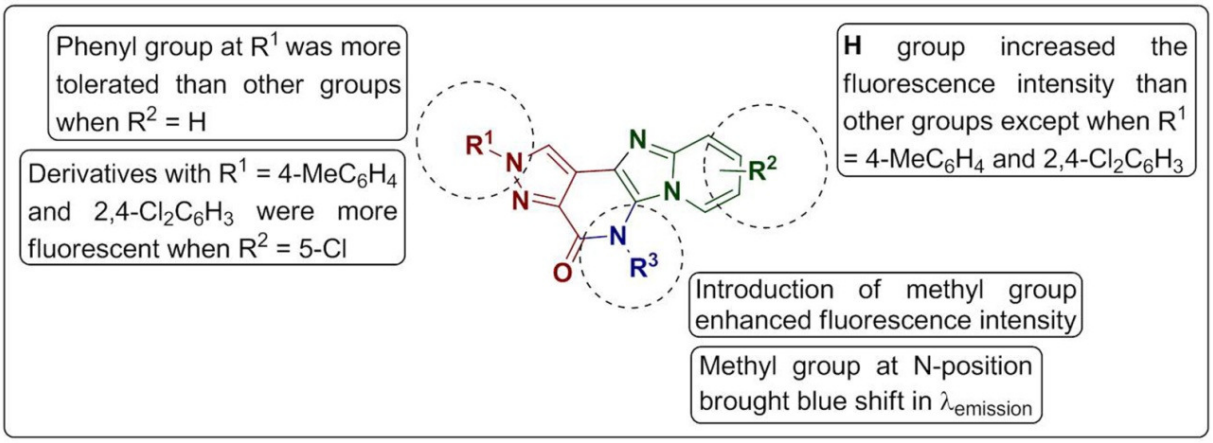


Fig. 3. Pictorial representation of structure-fluorescence activity relationship of pyrazolopyridinone fused imidazopyridine derivatives (**3** and **4**).

IV. CONCLUSION

Moderate to good fluorescence characteristic was displayed by pyrazolopyridinone fused imidazopyridines. Optimization of different parameters led to the conclusion that the best fluorescence results were obtained at 1×10^{-3} M concentration in 50% MeOH/$CHCl_3$ solution after 45 minutes of sample preparation. Derivatives **3fE** and **3eE** emerged as two most fluorescent compounds in the present series and displayed the fluorescence intensity of 427 a.u. and 399 a.u., respectively while compound **3aE** did not exhibited any fluorescent character. **3aA** also exhibited good fluorescent characteristic with fluorescence intensity of 379 a.u. Additionally, SARs investigation revealed that H, 5-Cl substituent at R^2 position were more tolerated groups comparatively and further it was observed that introduction of methyl group at R^3 position enhanced the fluorescence intensity (**3dA** and **4dA**). Furthermore, antimicrobial evaluation of the similar conjugates is underway and will be reported in due course. It is envisaged here that fluorescence characteristic of pyrazolopyridinone fused imidazopyridine conjugates will help them in emerging as a better pharmacophore.

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